The First Total Synthesis of (–)-Lemonomycin

and

Progress Toward the Total Synthesis of (+)-Cyanocycline A

Thesis by

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To the wonderful people who support me

and the great minds that taught me

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ABSTRACT

The first total synthesis of (–)-lemonomycin has been accomplished in an efficient and convergent manner. The synthesis features a highly diastereoselective, auxiliary-controlled dipolar cycloaddition that forms the bicyclic core and set the absolute stereochemistry of the natural product. The resulting diazabicycle was advanced by Suzuki coupling, diastereoselective hydrogenation, and a highly convergent, completely diastereoselective Pictet-Spengler cyclization with a glycosyloxy-acetaldehyde. The Pictet-Spengler product was then converted to (–)-lemonomycin in three steps. The glycosyl portion of lemonomycin was synthesized diastereoselectively from D-threonine.

The synthesis of (+)-cyanocycline A has been approached along two synthetic routes. Progress along a silyl ether route led to the discovery of a new diastereoselective hydrogenation of an unsaturated diazabicyclic to set the C(4) stereochemistry of cyanocycline A. The product of this reduction was advanced through a convergent Stille coupling reaction to an enamide that contains all but six of the heavy atoms of cyanocycline A with the correct stereochemistry at each of the stereogenic carbons. Further, the enamide functionality is an ideal precursor for installation of the C(13b) amino group.

Progress along an oxazoline route has led to the development of a novel dipolar cycloaddition of an alkynyl oxazoline. The resulting diazabicycle was advanced through a convergent Stille coupling reaction and diastereoselective hydrogenation to a late stage intermediate that contains all but three of the heavy atoms of cyanocycline A and has the correct relative stereochemistry for cyanocycline A.

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List of Abbreviations

$[\alpha]_D$	specific rotation a wavelength of sodium D line
A	adenine
Ac	acetyl
ACN	acetonitrile
Ala	alanine
app	apparent
aq	aqueous
Ar	aryl group
atm	atmosphere
BBN	borabicyclo[3.3.1]nonane
BHT	2,6-di-*tert*-butyl-4-methylphenol
Bn	benzyl
BOC	*tert*-butoxycarbonyl
BOM	benzyloxymethyl
br	broad
BSA	*N*,*O*-bis(trimethylsilyl)acetamide
Bu	butyl
n-Bu	butyl
t-Bu	*tert*-butyl
Bz	benzoyl
c	concentration for optical rotation measurement
^{13}C	carbon 13, isotope

/C	supported on activated carbon
°C	degrees Celsius
calc'd	calculated
CAM	ceric ammonium molybdate stain
CAN	ammonium cerium(IV) nitrate
CBZ	benzyloxycarbonyl
CCDC	Cambridge Crystallographic Data Centre
C	cytosine
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
d	doublet
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMS	dimethylsulfide
DMSO	dimethylsulfoxide

DNA	deoxyribonucleic acid
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
DTT	dithiothreitol
ee	enantiomeric excess
E	entgegen olefin geometry
EI	electrospray ionization
equiv	equivalent(s)
Et	ethyl
EtOAc	ethyl acetate
FAB	fast atom bombardment
g	gram
G	guanine
Gly	glycine
[H]	reduction
h	hour(s)
^{1}H	proton
^{3}H	tritium
HETCOR	heteronuclear correlation (^{1}H-^{13}C)
HMDS	hexamethyldisilazide or hexamethyldisilizane
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy

Hz	hertz
IC_{50}	concentration required for 50% growth inhibition
IR	infrared spectroscopy
J	coupling constant
kcal	kilocalories
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
L	liter
LUMO	lowest unoccupied molecular orbital
m	meta
m	multiplet or milli
μ	micro
M	mega
m/*z*	charge to mass ratio
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MIC	minimal inhibitory concetration
min	minute(s)
M	metal of molar
mol	mole(s)
mp	melting point
Ms	methanesulfonyl
MS	molecular sieves

NBS	*N*-bromosuccinimide
NMO	4-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
o	ortho
[O]	oxidation
p	para
PDC	pyridinium dichromate
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
ppm	parts per million
Pr	propyl
i-Pr	isopropyl
psi	pounds per square inch
pyr	pyridine
q	quartet
R	alkyl group
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
R_F	retention factor
RNA	ribonucleic acid
s	singlet
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenyl silyl

TBS	*tert*-butyldimethylsilyl
temp	temperature
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
TROC	trichloroethoxycarbonyl
t	triplet
T	thymine
Ts	*p*-toluenesulfonyl
UV	ultraviolet
Vis	visual wavelength
v/v	volume per volume
w/v	weight per volume
X	halide or trifluoromethanesulfonate
Z	zusammen olefin geometry

CHAPTER ONE

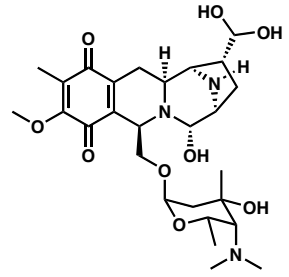
An Historical and Contextual Introduction to Lemonomycin and Cyanocycline A

1.1 The Tetrahydroisoquinoline Antitumor Antibiotics

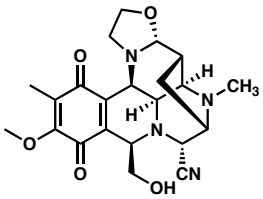
Representative Structures

Lemonomycin and cyanocycline A belong to a class of natural products known as the tetrahydroisoquinoline antitumor antibiotics.[1] These compounds are structurally characterized by a tetrahydroisoquinoline ring system fused to a diazabicyclic core with either a two- (**1**-**3**) or three-carbon (**4**-**6**) bridge (Figure 1.1). Variations of oxidation states, substitution patterns, and the presence of additional fragments distinguish several subfamilies of natural products. Of the two-carbon bridged subfamilies, lemonomycin (**1**) is distinguished by the presence of a unique glycosyl unit and an aldehyde hydrate. Cyanocycline A (**2**) and several closely related compounds exhibit an oxazolidine ring that connects the bridging carbons to the tetrahydroisoquinoline ring system. Quinocarcin (**3**) is characterized by an anisole ring in place of the typical quinone and a carboxylic acid attached to the two-carbon bridge. Among the subfamilies with a three-carbon bridge, the saframycins (e.g., saframycin A **4**) are bisquinone-containing compounds with a glyoxamide side chain. The renieramycins (e.g., renieramycin C **5**) manifest an angelate ester in place of the glyoxamide unit. The ecteinascidins (e.g., ecteinascidin 743 **6**) present a bridging thioether ring and an additional tetrahydroisoquinoline unit, as well as oxygenated aromatic rings in place of the typical quinones.

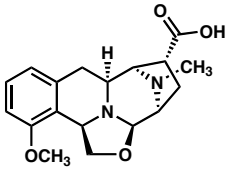
Figure 1.1 Representative Tetrahydroisoquinoline Antitumor Antibiotics



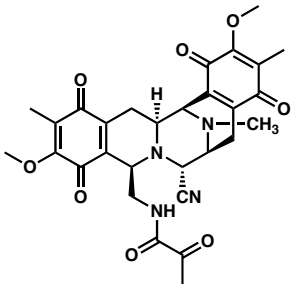
Lemonomycin (1)



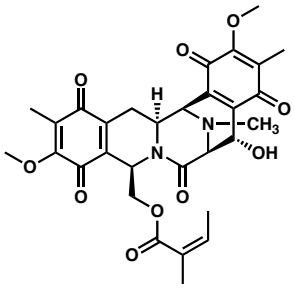
Cyanocycline A (2)



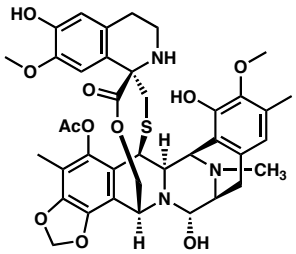
Quinocarcin (3)



Saframycin A (4)



Renieramycin C (5)

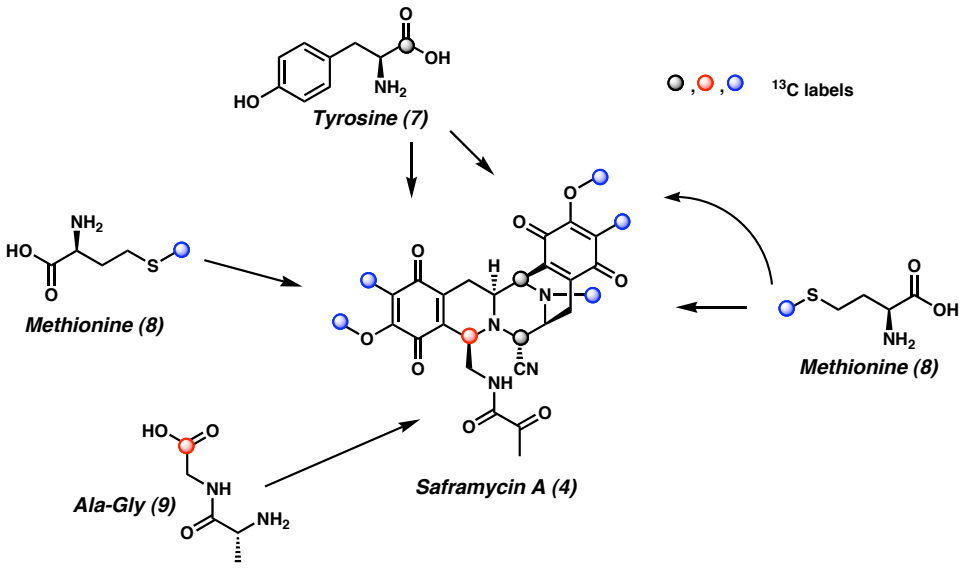


Ecteinascidin 743 (6)

Tetrahydroisoquinoline Biosynthesis

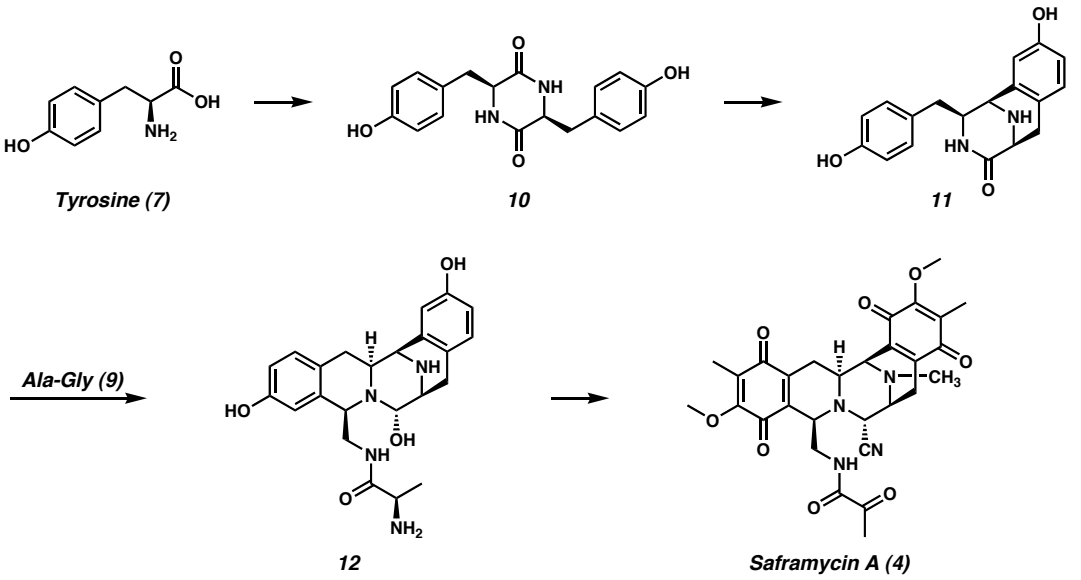
The tetrahydroisoquinoline antitumor antibiotics are biosynthetically derived from amino acids. The most intensely studied biosynthetic pathways are those leading to saframycin A and naphthyridinomycin (*vide infra*). The biosynthetic origins of saframycin A have been elucidated by the use of isotopically labeled substrates (Figure 1.2).[2] In this manner it has been determined that the central piperazine core and the two quinone rings are derived from two molecules of tyrosine (**7**), while the side chain and the remaining carbon of the tetrahydroisoquinoline system begin as the dipeptide Ala-Gly (**9**). The four methyl groups on the quinones and the *N*-methyl group arise from the *S*-methyl of methionine (**8**).

Figure 1.2 Labeling Studies on Saframycin A



The likely biosynthetic pathway begins with the dimerization of tyrosine to form diketopiperazine **10** (Scheme 1.1).[3] Amide reduction followed by iminium ion cyclization provides the diazabicyclic core structure (**11**). Reduction of the remaining amide and incorporation of Ala-Gly produces tetrahydroisoquinoline **12**. Subsequent arene oxidation and methylation yield saframycin A.[4] The biosyntheses of the renieramycins, safracins, and ecteinascidins are expected to proceed through similar pathways. Comparatively, the biosynthetic pathways leading to lemonomycin, quinocarcin, and the naphthyridinomycin (e.g., cyanocycline A) likely proceed through a similar diketopiperazine intermediate derived from tyrosine and either glutamic acid or an ornithine residue (*vide infra*).

Scheme 1.1 Biosynthetic Pathway of Saframycin A



Biological Activity of the Tetrahydroisoquinoline Antitumor Antibiotics

As befits the name, the tetrahydroisoquinoline antitumor antibiotics are generally potent, broad-spectrum cytotoxins effective against mammalian and bacterial cells. It is likely that these compounds are the end product of a cellular defense mechanism, and the wide variation of structures within the family may be indicative of a kind of microbial arms race. The various structures support several modes of action, of which three major categories have been proposed and studied.[1] The most common mode of action is DNA alkylation, which seems to be operative whenever carbinolamine or aminonitrile functionality is present. Oxidative degradation of DNA via the generation of superoxide from either semiquinone intermediates or α-amino radical intermediates is a second important pathway. Lastly, a unique mode of action involving interruption of the DNA excision repair system leading to double strand DNA cleavage has been observed for ecteinascidin 743.[5]

1.2 Lemonomycin

Isolation and Biological Activity

Lemonomycin was isolated in 1964 from a fermentation broth of the soil bacteria *Streptomyces candidus* as a mixture with two other minor-component antibiotic compounds.[6,7] In total, 4 g of lemonomycin hydrochloride were purified from 2,000 L of broth. The free base was prepared by treatment of the hydrochloride salt with aqueous sodium hydroxide and extraction into chloroform. This free base was precipitated from aqueous acetone "as lemon-yellow spheres," leading to the name of lemonomycin. The isolation chemists were not able to fully determine the structure of lemonomycin, but based on ^{1}H NMR and IR spectroscopy they were able to establish the presence of a quinone and of *N*-methyl and *O*-methyl functionality. Degradation experiments were found to liberate dimethyl amine. Potentiometric titration indicated that lemonomycin contained two basic sites.

The isolation chemists found lemonomycin to be a potent, broad-spectrum antibiotic with activity comparable or superior to penicillin G and erythromycin (Table ch1A). Both gram-positive and gram-negative bacteria were susceptible to the antibiotic. The authors note further that lemonomycin, administered either orally or subcutaneously, protects mice from staphylococcal and streptococcal infections. Unfortunately, the antibiotic was found to be lethal at levels only slightly higher than the therapeutic dose.

Table 1.1: Minimal Inhibitory Concentrations (μg/mL)

Organism	Lemonomycin	Tetracycline	Penicillin G	Erythromycin
Staphylococcus aureus (Lederle 4050B-122-7)	0.08	10	>100	1.5
S. aureus (Lederle 4050B-122-10)	0.15	>100	>100	3
S. aureus (Lederle 4050B-122-13)	0.15	2.5	0.08	3
S. aureus (Lederle 4050B-122-14)	0.15	>100	0.04	3

S. aureus Rose ATCC 14154	0.15	>100	>100	12.5
S. aureus Smith	0.04	2.5	0.8	1.5
Streptococcus faecalis ATCC 8043	0.4	2.5	2.5	0.4
S. pyogenes C203	<0.005	1.2	0.001	0.2
S. pyogenes (Lederle 8053B-40-2)	0.01	25	0.01	0.4
S. pyogenes (Lederle 8053B-40-3)	0.01	100	0.01	0.4
S. pyogenes NY5	<0.005	2.5	0.01	0.2
Streptococcus sp. λ-Strep. 11	5.0	>100	2.5	1.5
Streptococcus sp. β-Strep. 80	2.5	>100	2.5	1.5
Mycobacterium smegmatis ATCC 607	6.2			
Staphylococcus aureus ATCC 6548P	0.2			
Bacillus subtilis ATCC 6633	0.05			
Pseudomonas fluorescens ATCC 12633	1.6			
Proteus vulgaris ATCC 9484	0.4			
Escherichia coli ATCC9637	1.6			
Salmonella gallinarum (Lederle 604)	0.8			
Clostridium sporogenes ATCC7955	>100			

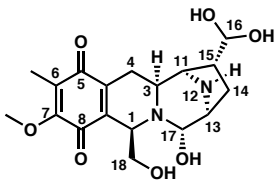
Structural Elucidation of Lemonomycin

The study of lemonomycin became dormant until 2000, when chemists at Wyeth-Ayerst Research reinvestigated the compound as part of a program aimed at testing older antibiotic compounds against newly-evolved, highly antibiotic-resistant bacterial strains.[8] These chemists found that lemonomycin is active against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium* with minimal inhibitory concentrations of 0.4 and 0.2 μg/mL, respectively. The natural product also exhibited in vitro activity against a human colon tumor cell line (HCT116) with an IC_{50} of 0.36 μg/mL.

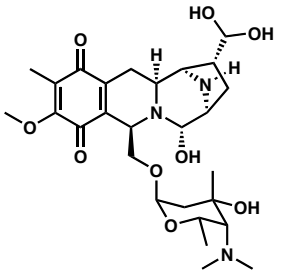
In addition to reinvestigating lemonomycin's biological activity, the Wyeth-Ayerst team determined the connectivity and relative stereochemistry of the natural product by NMR spectroscopic methods. The complex alkaloid exhibits a quinone portion reminiscent of the saframycin subfamily and a 3,8-diazabicyclo[3.2.1]octane core similar to quinocarcin (Figure 1.3). Contrastingly, lemonomycin is unique among the nearly 60 natural products and hundreds of synthetic analogues in this family in that it

bears glycosylation at C(18). This is particularly surprising in light of the extensive work toward derivatization of this position in the ecteinascidins,[9] saframycins, and quinocarcins. Furthermore, the 2,6-dideoxy-4-amino sugar (**14**) is rare in nature, having been isolated only as a substituent on glycothiohexide α,[10] nocathiacin I,[11] and MJ347-81F4 A,[12] and, in an oxidized form, as a substituent of the saccharocarcins.[13] All of these natural products are potent antibiotics, indicating that lemonose (**14**)[14] may be important to their biological activity.

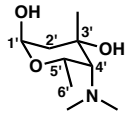
Figure 1.3 The Structure and Numbering of Lemonomycin



Lemonomycin Aglycon (13)



Lemonomycin (1)



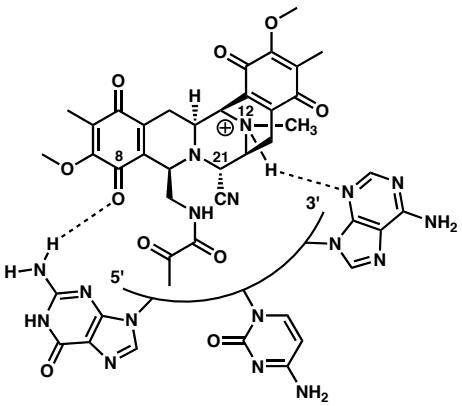
Lemonose (14)

In addition to the unique nature of the lemonose glycosylation, lemonomycin bears an aldehyde hydrate at C(16) that is unprecedented in the tetrahydroisoquinoline antitumor antibiotics. One OH group of the aldehyde hydrate likely forms an intramolecular hydrogen bond to N(12), in effect existing as a covalently bound water molecule. The incorporation of this hydrogen bond could affect the basicity of N(12), which might be important to lemonomycin's biological mode of action.

Proposed Mode of Action

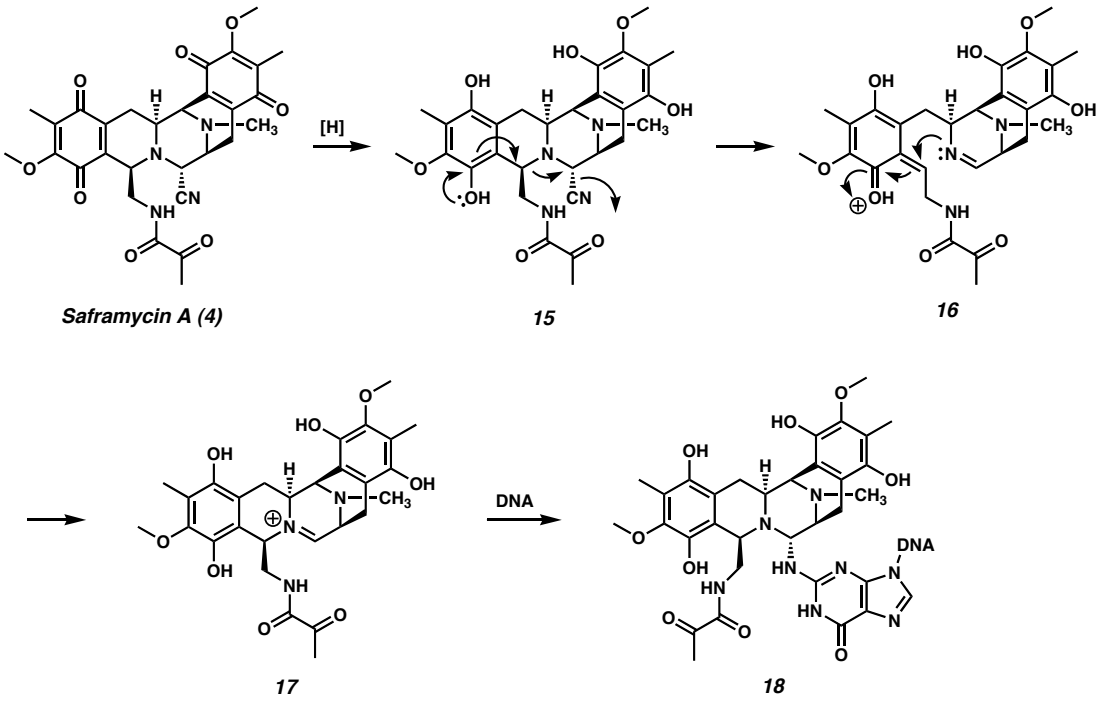
No studies have been reported concerning the mode of action responsible for the toxicity of lemonomycin. However, the structural similarities between lemonomycin and saframycin A, which has been extensively studied in this regard, indicate that the modes of action also may be similar. The toxicity of saframycin A occurs as a result of the natural product's interactions with DNA. Under mildly acidic conditions (pH 5-6), saframycin A exhibits non-covalent binding to the minor groove of DNA.[15] Calculations on the interaction of saframycin A with the DNA duplex oligomer d(GATGCATC)$_2$ have indicated that this binding is enforced by hydrogen bonding interactions of an N(12) ammonium proton with N(3) of adenine and of the C(8) oxygen with the NH_2 of an upstream guanine (Figure 1.4).[16] Additional hydrogen bonding interactions are available to the reduced (hydroquinone) form of saframycin A, which exhibits concomitantly stronger binding.

Figure 1.4 Hydrogen Bonding Interactions of Saframycin A with DNA



Saframycin A is also able to form covalent adducts with DNA. In vitro studies showed that reduction to the hydroquinone (**15**) was necessary to potentiate the alkylation activity of saframycin A (Scheme 1.2).[17] The fact that the saframycins are active in vivo without prior reduction indicates that saframycin A may undergo spontaneous conversion to hydroquinone **15** under the mild reducing conditions inside cells. Once formed, the hydroquinone readily loses HCN from C(21), generating iminium ion **17** via the intermediacy of quinone methide **16**. When bound to DNA, this iminium alkylates N(2) of guanine to form covalent complex **18**, thereby inhibiting RNA and DNA synthesis.[17]

Scheme 1.2 DNA Alkylation by Saframycin A



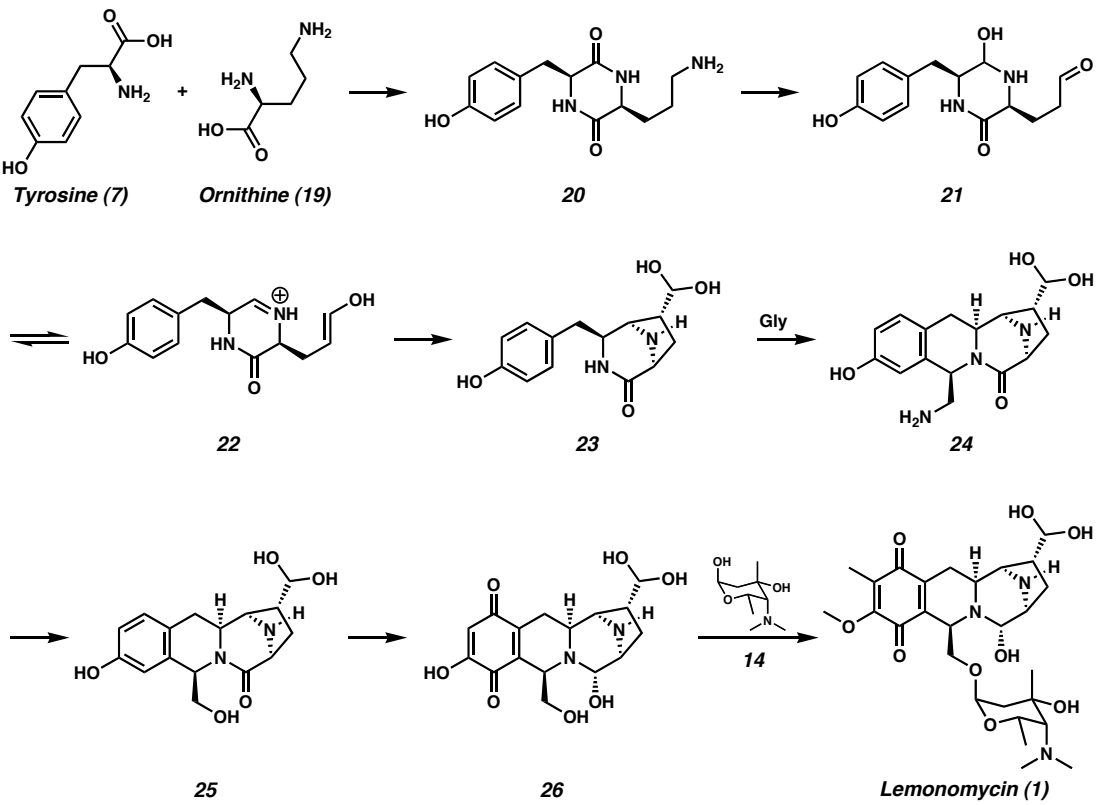
The saframycins also cause oxidative degradation of DNA via the production of oxygen radicals.[15,18] Hydroquinone **15** can undergo one electron oxidation to a

semiquinone, which reacts with dissolved oxygen to produce superoxide. Under protic conditions, superoxide rapidly disproportionates to form hydrogen peroxide and molecular oxygen.[19] Hydrogen peroxide then reacts with adventitious divalent iron to produce hydroxyl radical, which in turn causes oxidative single strand DNA cleavage.[15,20]

Biosynthetic Proposal for Lemonomycin

The biosynthesis of lemonomycin has not been studied. We expect, however, that it proceeds similarly to the biosynthesis of saframycin A (*vide supra*) and naphthyridinomycin (*vide infra*). Therefore, we propose that lemonomycin arises by the dimerization of tyrosine with ornithine to produce diketopiperazine **20** (Scheme 1.3).[21] Oxidation of the primary amine and reduction of one amide leads to carbinolamine **21**, which cyclizes to form diazabicyclooctane **23** through the intermediacy of iminium ion **22**. Incorporation of glycine generates tetrahydroisoquinoline **24**, the primary amine of which is converted to an alcohol by oxidation, hydrolysis, and reduction to produce **25**. Subsequent aromatic oxidation, methylation, and glycosylation with lemonose (**14**) yield lemonomycin. The biosynthesis of lemonose also has not been studied, but the sugar is likely derived from a common polyketide hexose by deoxygenation and amination.[22]

Scheme 1.3 Biosynthetic Proposal for Lemonomycin

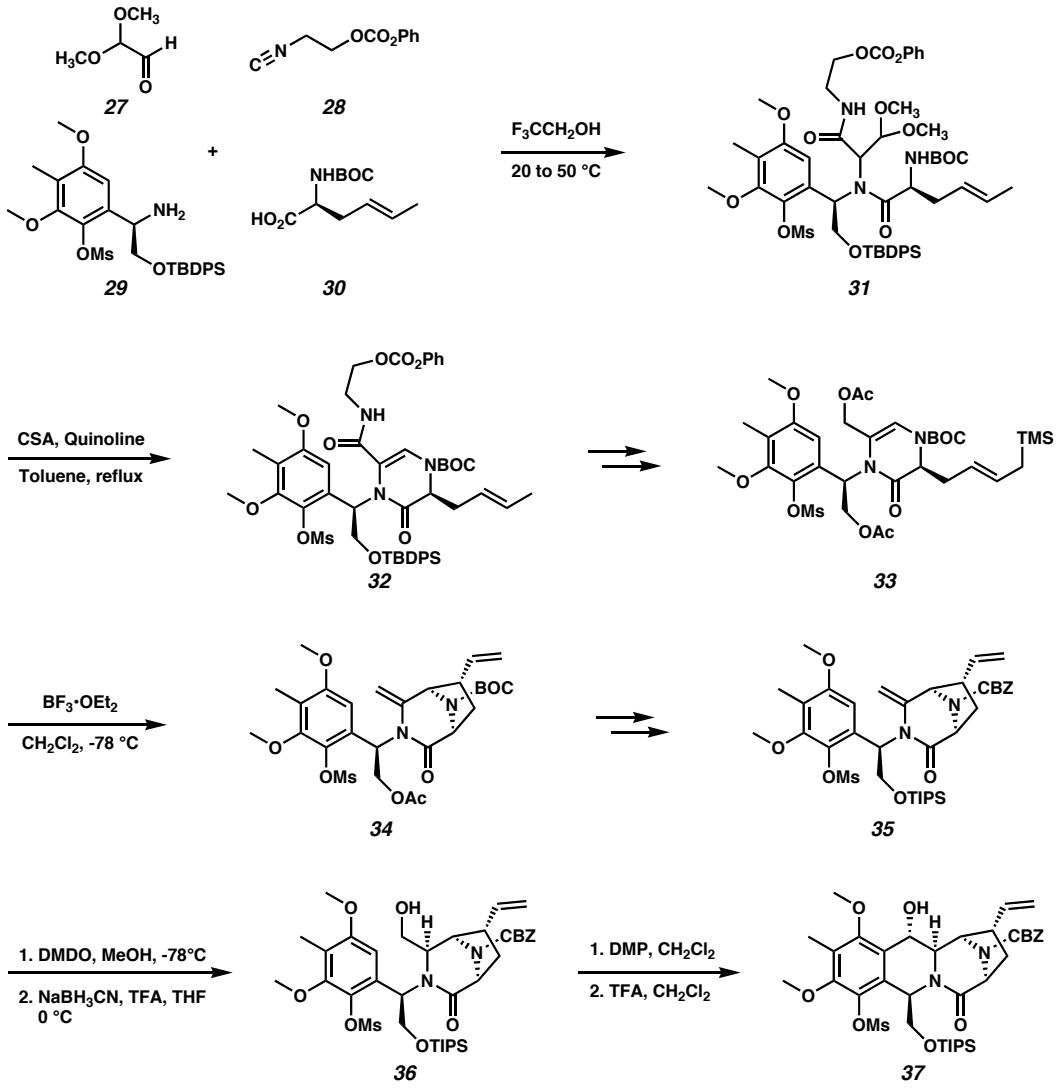


Synthetic Approaches to Lemonomycin

No synthetic work on lemonomycin was reported before our published total synthesis.[23] Subsequent to our work, however, two partial synthetic approaches were reported. The first, by the Fukuyama research group, features an Ugi four-component coupling reaction to form amide **31** (Scheme 1.4).[24] Acid catalyzed cyclization produces tetrahydroketopyrazine **32**, which is readily advanced to allylic acetate **33**. Under Lewis acidic conditions, acetate elimination followed by allyl silane cyclization provides enamide **34**. Protecting group manipulation followed by oxidation with dimethyldioxirane and reduction with sodium cyanoborohydride yields alcohol **36**, which

can be oxidized to the aldehyde and cyclized to tetrahydroisoquinoline **37** under acidic conditions. Further advancement of **37** has not been reported.

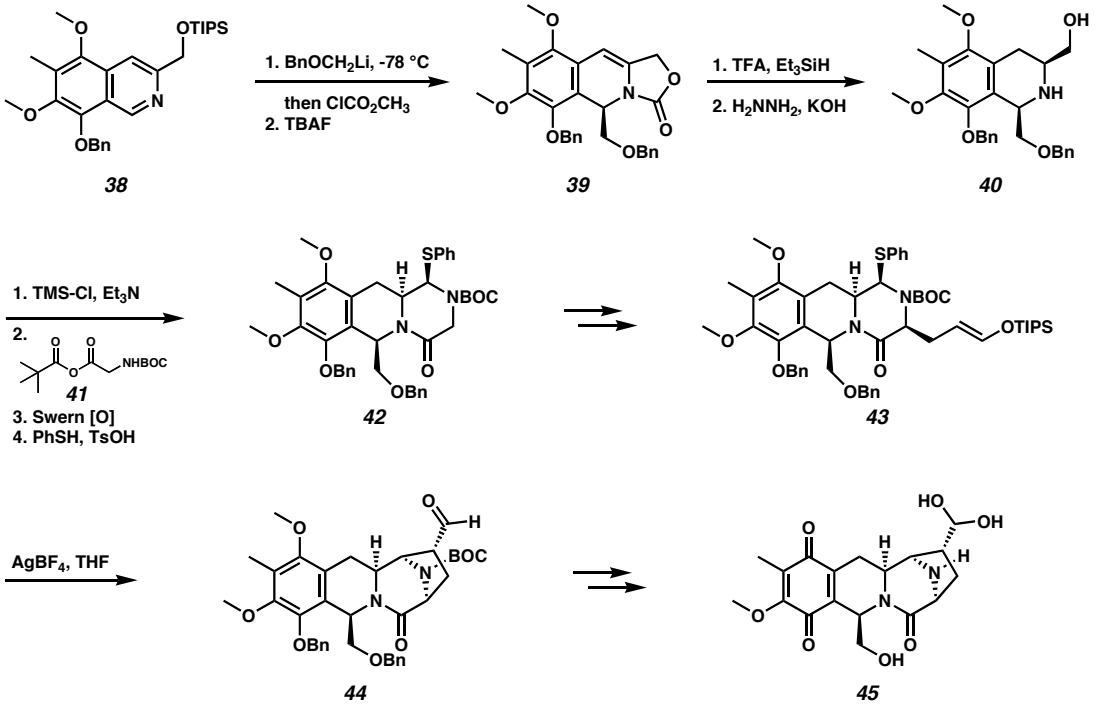
Scheme 1.4 Fukuyama's Approach Toward Lemonomycin



A similarly stepwise approach toward the bicyclic core of lemonomycin has been reported by Magnus et al. (Scheme 1.5).[25] Beginning from isoquinoline **38**,[26] alkyl lithium addition, acylation, and treatment with TBAF yielded racemic styrene **39**. Ionic

reduction and cleavage of the oxazolidinone provided cis-disubstituted tetrahydroisoquinoline **40**, which was advanced to α-thioamine **42** via acylation with *N*-BOC glycine equivalent **41** followed by oxidation and treatment with thiophenol. Lactam **42** was converted to silyl enol ether **43** by a five-step sequence involving a key alkylation and epimerization to the desired stereochemistry. Subsequent iminium ion cyclization mediated by silver tetrafluoroborate provided tetracycle **44**, which was uneventfully advanced to quinone **45**. Further work with **45** has not been reported.

Scheme 1.5 Magnus' Approach Toward Lemonomycin

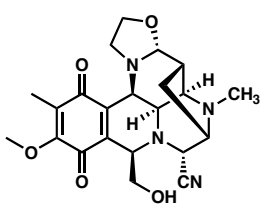


1.3 Cyanocycline A

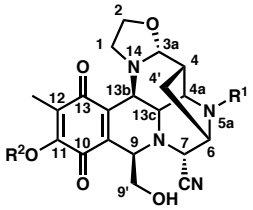
Isolation and Closely Related Compounds

Cyanocycline A (**2**, Figure 1.5) was isolated in 1982 from cultures of the soil bacterium *Streptomyces flavogriseus*.[27] The antibiotic was collected by Amberlite XAD-2 column chromatography of the culture filtrate followed by adjustment to pH 8.5 and extraction into ethyl acetate. The crude compound was purified by extensive chromatography followed by precipitation from chloroform with acetone to provide 65 mg of cyanocycline A from 150 L of culture broth. The structure was originally characterized spectroscopically by IR, UV, and NMR and was ultimately proven by X-ray analysis of single crystals obtained by recrystallization from acetone or ethanol.[28] Cyanocycline A exhibits a similar core structure to lemonomycin with a 3,8-diazabicyclo[3.2.1]octane moiety fused to a quinone-bearing tetrahydroisoquinoline ring system. However, the stereochemistry at C(4) is inverted, and the C(3a) aldehyde oxidation state is condensed into an oxazolidine ring. The oxazolidine nitrogen is bound to C(13b), forming a polycyclic, caged structure. Additionally, cyanocycline A bears its namesake cyano group as a C(7) aminonitrile, and the C(9') hydroxyl is unsubstituted.

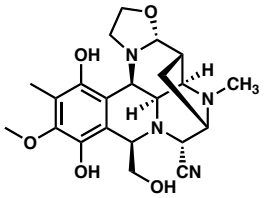
Figure 1.5 The Cyanocyclines, Bioxalomycins, and Naphthyridinomycin



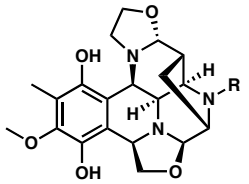
Cyanocycline A (2)



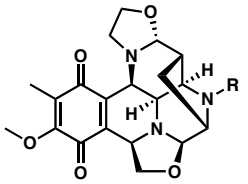
R^1=H, R^2=CH_3 Cyanocycline B (46)
R^1=CH_3, R^2=H Cyanocycline F (47)



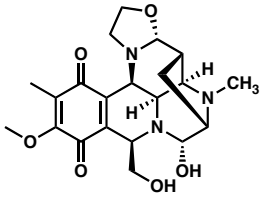
Cyanocycline C (48)



R=H Bioxalomycin α1 (49)
R=CH_3 Bioxalomycin α2 (50)



R=H Bioxalomycin β1 (51)
R=CH_3 Bioxalomycin β2 (52)



Naphthyridinomycin (53)

Prior to the discovery of cyanocycline A, a closely related structure was isolated from *Streptomyces lusitanus* AY B-1026, a species of soil bacteria collected on Easter Island.[29] This structure, named naphthyridinomycin, differs from cyanocycline A only in the presence of a carbinolamine in place of the C(7) aminonitrile. Almost simultaneously with the disclosure of the natural isolation of cyanocycline A, its structure was produced synthetically by treatment of naphthyridinomycin with sodium cyanide.[30] Later, in 1994, several closely related compounds were isolated from *Streptomyces viridostaticus* ssp. litoralis and named the bioxalomycins.[31,32] These compounds differ from the cyanocycline and naphthyridinomycin core structures only in that the C(9') hydroxyl is cyclized onto C(7) in the form of an oxazolidine ring. The isolation procedures utilized for the isolation of the bioxalomycins were milder than those utilized in the original isolation of naphthyridinomycin. When these milder procedures were applied to the

isolation of antibiotics from *Streptomyces lusitanus*, only bioxalomycin β2 was isolated, with no naphthyridinomycin being found. Synthetically, it was shown that bioxalomycin β2 could be converted to cyanocycline A upon treatment with potassium cyanide. The reverse reaction has also been accomplished by treating cyanocycline A with aqueous silver nitrate.[33] The interconversion of cyanocycline A and bioxalomycin β2, as well as the ready conversion of naphthyridinomycin to cyanocycline A, indicates that the naturally occurring form of all three natural products may in fact be the same.[34] The available evidence, however, does not allow a determination of which structure is the natural form.

Biological Activity of Cyanocycline A

Cyanocycline A exhibits potent, broad-spectrum antibiotic activity against both gram-positive and gram-negative bacteria (Table 1.2).[27] Cyanocycline A was found to have activity similar to naphthyridinomycin against several strains of bacteria and against Hela tumor cells, for which concentrations as low as 1 μg/mL were sufficient to prevent an increase in cell numbers for 48 hours.[30] Cyanocycline A is also active against Meth A cells in vitro and when grown as an ascites tumor.[35]

Table 1.2 Minimal Inhibitory Concentrations for Cyanocycline A

Test Organism	MIC (μg/mL)	Test Organism	MIC (μg/mL)
Bacillus subtilis PCI-219	0.005	*Proteus mirabilis* 1287	0.31
Bacillus cereus T-1	0.62	*Proteus mirabilis* 9'	0.31
Micrococcus luteus B	0.0025	*Serratia marcescens* TO-50	0.62
Staphylococcus epidermidis TO-3	0.005	*Serratia marcescens* FU-111	0.62
Staphylococcus aureus 209P	0.005	*Pseudomonas aeruginosa* J-272	0.62
Escherichia coli NIHJ	0.08	*Pseudomonas aeruginosa* NGB75	0.62
Escherichia coli 11	0.15	*Pseudomonas aeruginosa* M-57740	0.31

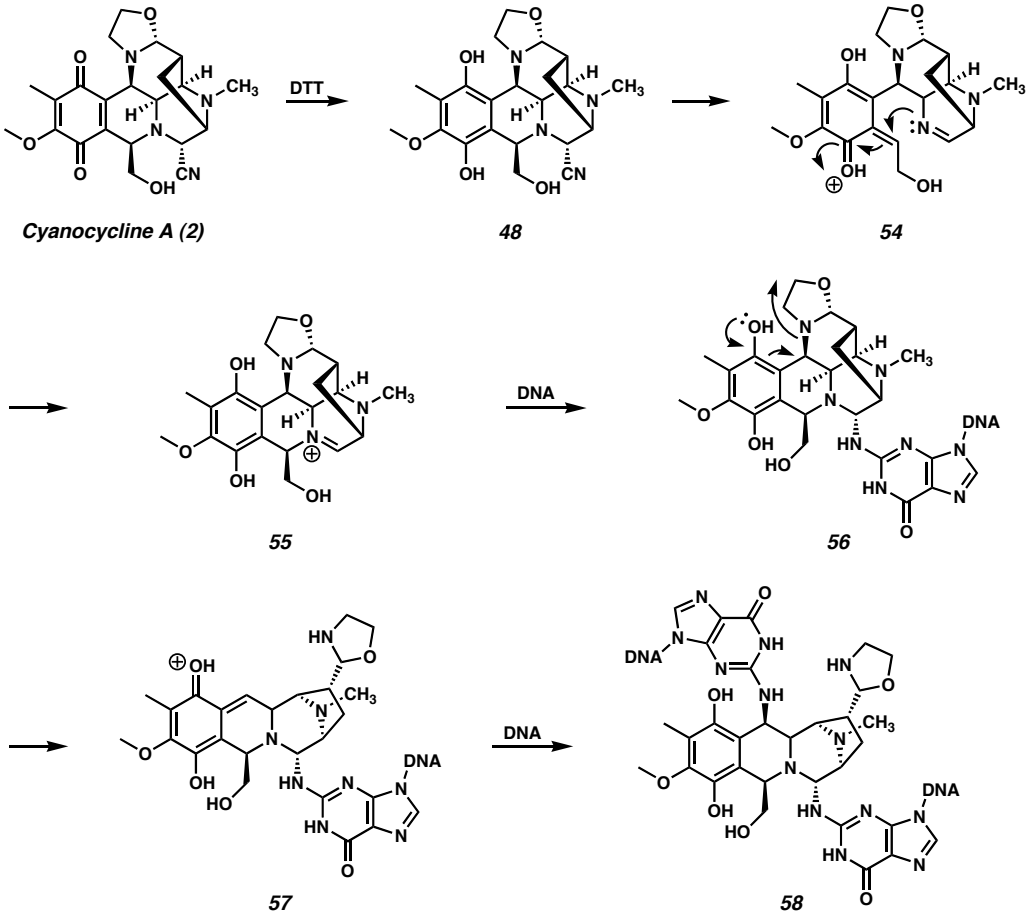
Salmonella enteritidis T-1	0.08	*Pseudomonas aeruginosa* J-162	0.31
Salmonella typhi Tanaka	0.04	*Pseudomonas aeruginosa* Ps-4	0.15
Klebsiella pneumoniae 3K25	0.31	*Candida albicans* IAM4888	50
Klebsiella pneumoniae 15C	0.31	*Saccharomyces cerevisiae* IAM4804	50
Shigella flexneri 2b TO-1	0.08	*Penicillium chrysogenum* IAM7305	50
Shigella sonnei TO-1	0.15	*Aspergillus niger* IAM2020	100

Cyanocycline A causes cell death by inhibiting the synthesis of DNA, RNA, and proteins.[35] This activity was found to be attenuated by the addition of exogenous DNA, indicating that DNA binding is the primary mode of action. In support of this indication, Zmijewski, et al. have shown that ^{3}H labeled naphthyridinomycin forms a covalent complex with DNA, and that this covalent complex is a poor substrate for DNA translation and transcription enzymes.[36]

Arora, et al. have used molecular modeling studies to analyze the binding mode of cyanocycline A and naphthyridinomycin with DNA.[37] These authors considered covalent binding of C(7) of the antibiotic to N(2) of guanine in either a groove-binding mode or a partially intercalated mode. The groove-binding conformation places the antibiotic in the minor groove of DNA with an edge-on approach, such that the carbonyl of C(10) and the C(9') hydroxyl form hydrogen bonds to DNA, while C(7) is covalently bound in the *R* configuration. This model was found to be substantially favored over the partially intercalated model, which places the quinone ring intercalated into DNA with C(7) again covalently bound in the *R* configuration. A similar study was carried out by Remers, et al., who considered DNA alkylation by both the C(7) aminonitrile and the C(3a) oxazolidine.[38] Both sites of alkylation were considered feasible, but the geometries of the bound complexes were not suitable for crosslinking duplex DNA. Instead, a crosslink between DNA and protein was proposed.

It was later determined, however, that both bioxalomycin α2 and cyanocycline A are capable of forming crosslinks with duplex DNA (cyanocycline A required prior reduction with dithiothreitol).[39] The crosslink was formed with $^{5'}CG^{3'}$ specificity, indicating alkylation of two guanine bases on N(2) in the minor groove. The authors report that preliminary molecular modeling studies support the covalent binding of C(7) and C(13b) to DNA with partial intercalation of the hydroquinone ring into the DNA helix. A mechanism for this crosslinking has been proposed (Scheme 1.6).

Scheme 1.6 DNA Crosslinking by Cyanocycline A

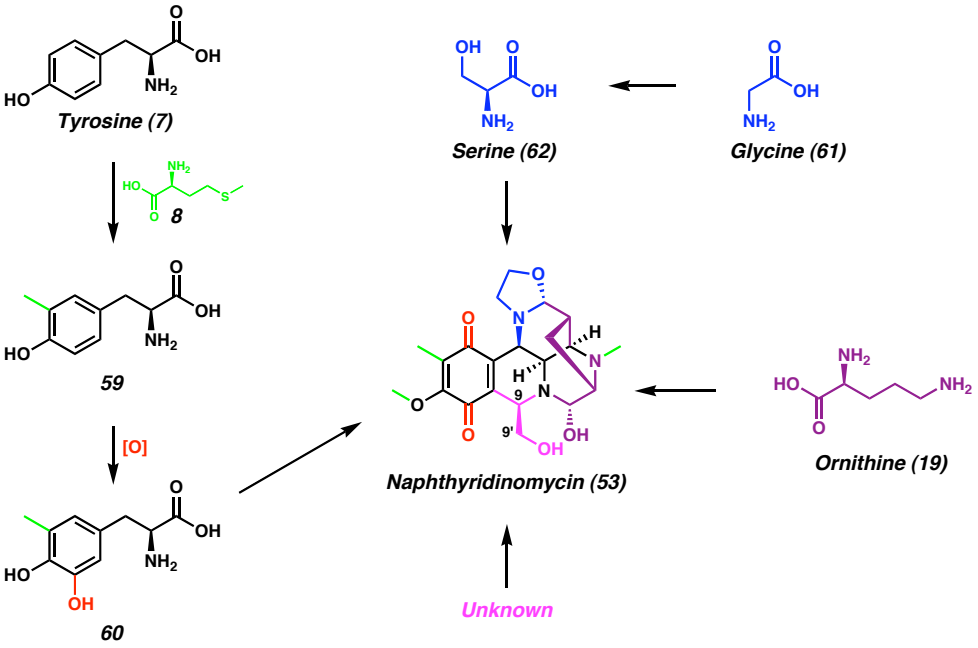


Biosynthesis of Cyanocycline A

While the biosynthesis of cyanocycline A has not been directly investigated, several studies have appeared regarding the biosynthesis of naphthyridinomycin. The close structural similarities of these two compounds indicate that the biosynthesis is likely the same for both antibiotics (*vide supra*). The biosynthesis of naphthyridinomycin by *Streptomyces lusitanus* NRRL 8034 was first investigated by feeding studies with labeled amino acids and other potential precursors.[40] This work showed that carbons C(13b), C(13c), and C(4a), as well as the quinone ring, were derived from tyrosine (Scheme 1.7). Labeled glycine was incorporated at C(1) and C(2), while the C(5'), C(11'), and C(12') methyl groups were labeled by *S*-$^{13}CH_3$ methionine. Ornithine was incorporated into the natural product, while glutamate, acetate, glucose, and dihydroxyphenylalanine were not incorporated.

It was later determined that glycine is converted to serine prior to incorporation into the natural product and that N(14) is derived from that serine.[41] The remaining carbons of the bicyclooctane moiety (3a, 4, 4', 6, and 7) are derived from ornithine. A final study determined that, while dihydroxyphenylalanine was not incorporated into naphthyridinomycin, 3'-methyltyrosine (**59**) and 5'-methyldihydroxyphenylalanine (**60**) were incorporated.[42] This information allowed the authors to propose that tyrosine is first methylated and then hydroxylated in the early stages of the biosynthetic pathway. The significant mystery that remains is the origin of C(9) and C(9').

Scheme 1.7 Biosynthesis of Naphthyridinomycin



Previous Syntheses of Cyanocycline A

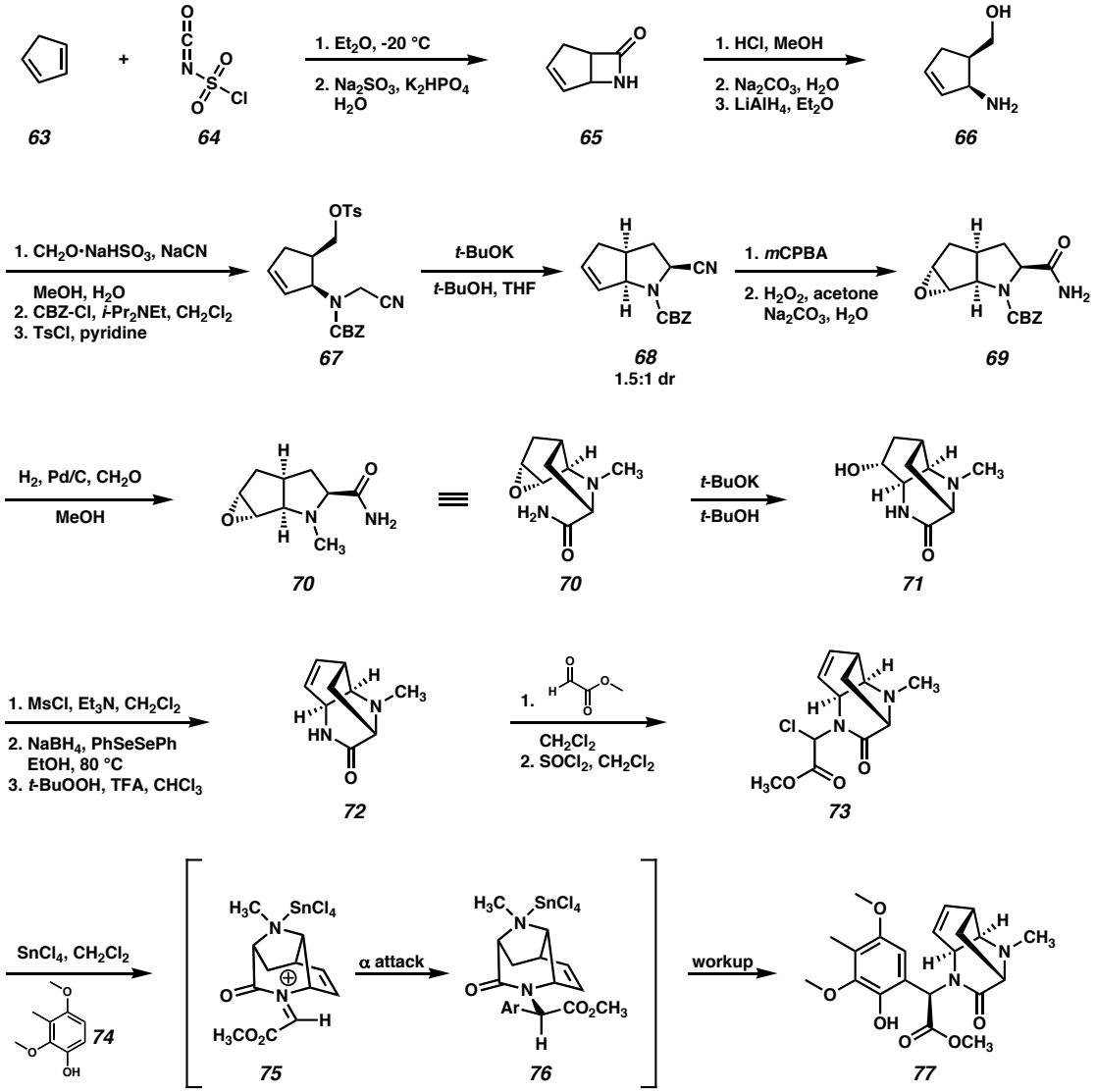
Several partial syntheses of the cyanocycline and naphthyridinomycin structures have been reported.[43] However, only two completed total syntheses have been reported, one by the Evans research group and one by the Fukuyama research group. Both of these synthetic efforts were originally targeted toward naphthyridinomycin, but were later focused on cyanocycline in light of the greater stability of the C(7) aminonitrile compared with the C(7) carbinolamine of naphthyridinomycin. Both syntheses were originally performed along racemic pathways, although each group was later able to develop an asymmetric route to cyanocycline A.

Evans' Total Synthesis of Cyanocycline A

The Evans synthesis of cyanocycline A began with the cycloaddition of cyclopentadiene and chlorosulfonyl isocyanate to yield β-lactam **65** (Scheme 1.8).[44] Methanolysis and reduction provided amino alcohol **66**, which was readily advanced to tosylate **67**. Treatment of the tosylate with potassium *tert*-butoxide allowed facile 5-exo cyclization to pyrrole **68**. The poor diastereocontrol in the formation of **68** could be partially addressed by separation of the diastereomers and epimerization of the undesired isomer under basic conditions, providing 58% yield of the pure desired isomer after one cycle. Epoxidation followed by hydrolysis of the nitrile produced amide **69**. The benzyl carbamate was replaced by a methyl group in a single step by hydrogenolysis in the presence of formaldehyde. The resulting epoxy amide (**70**) underwent facile *tert*-butoxide mediated 6-exo cyclization to generate ketopiperazine **71**,[45] which could be converted to alkene **72** by a three-step protocol.

To set up one of the key steps of the synthesis, amide **72** was condensed with methyl glyoxylate and then converted to α-chloroamine **73** with thionyl chloride. Under Lewis acidic conditions, the chloride was eliminated to form putative iminium ion **75**, which underwent Friedel-Crafts alkylation of arene **74** with high stereoselectivity and complete regiocontrol. The origin of the stereo- and regioselectivity is not completely clear, but Evans proposes that the *Z*-iminium ion is selectively formed, and the steric encumbrance of a Lewis acid coordinated to the amine of **75** prevents alkylation on the β face. The surprising regiocontrol may result from chelation of the ester carbonyl to an intermediate tin phenoxide.[46]

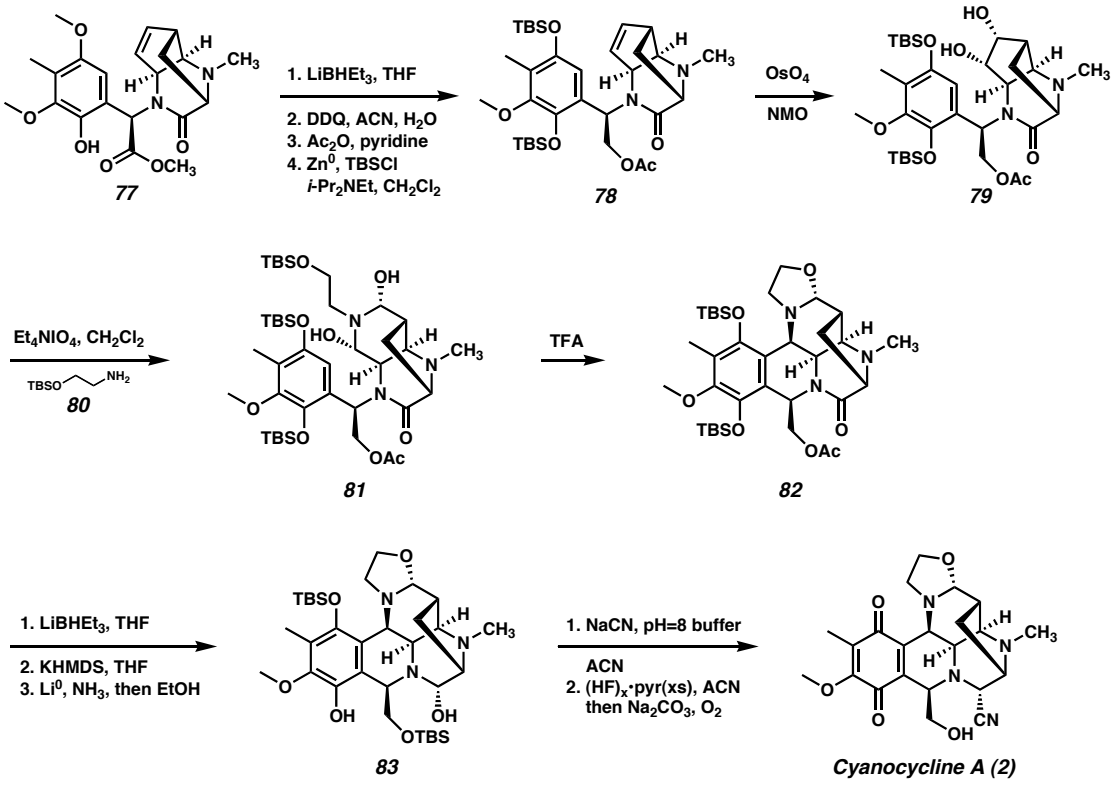
Scheme 1.8 Evans' Synthesis of Cyanocycline A



The key Friedel-Crafts alkylation product **77** was readily progressed to acetate **78**, which was converted to diol **79** under standard conditions (Scheme 1.9). The next challenge of the synthesis was the cleavage of this diol to an expected dialdehyde intermediate followed by incorporation of an ethanolamine unit. Unfortunately, this reaction was complicated by rapid hydration of the dialdehyde. The resulting dihydroxytetrahyropyran resisted all attempts to incorporate an ethanolamine unit. It was

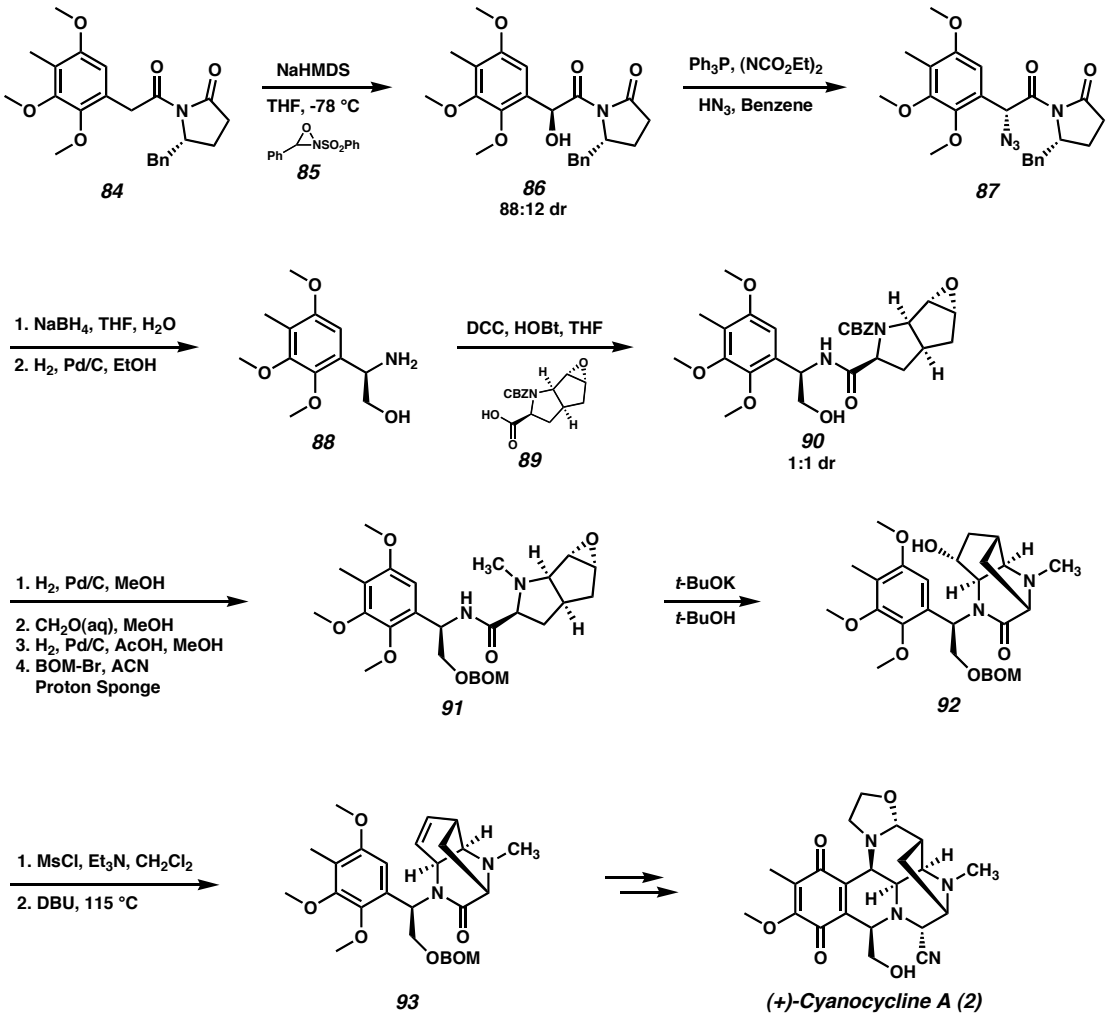
eventually discovered, however, that anhydrous cleavage of the diol with tetraethylammonium periodate in the presence of amine **80** yielded dihydroxypiperidine **81**. Treatment of this compound with neat trifluoroacetic acid potentiated an iminium ion cascade cyclization to hexacycle **82**. Amide reduction also proved challenging, and it was discovered that deacetylation of the C(9') hydroxyl and migration of a TBS group to this position was necessary before the amide could be reduced. Dissolving metal conditions were then employed for the generation of carbinolamine **83**. Incorporation of cyanide, desilylation, and oxidation provided cyanocycline A, which was identical to a natural sample in all respects other than optical rotation.

Scheme 1.9 Completion of the Evans Synthesis



The Evans group was later able to impart asymmetry to their synthesis through the use of a phenylalaninol-derived oxazolidinone chiral auxiliary (Scheme 1.10).[47] Oxidation of the sodium enolate of enantiopure **84** with Davis oxaziridine **85** delivered alcohol **86**, from which the minor diastereomer could be chromatographically removed. Mitsunobu inversion to azide **87** followed by two-step reduction yielded amino alcohol **88**. The amine of **88** could be coupled to racemic acid **89**[48] to provide a separable mixture of **90** and the diastereomer arising from the opposite enantiomer of **89**. Protecting group exchange revealed amide **91**, which was readily cyclized to tetracycle **92** under basic conditions. Elimination of the alcohol to alkene **93** was effected by mesylation and heating with neat DBU. This alkene was then advanced to (+)-cyanocycline A by a route thematically similar to that used in the racemic case, although the minor differences between alkene **93** and alkene **77** caused several technical challenges.

Scheme 1.10 Evans' Asymmetric Synthesis

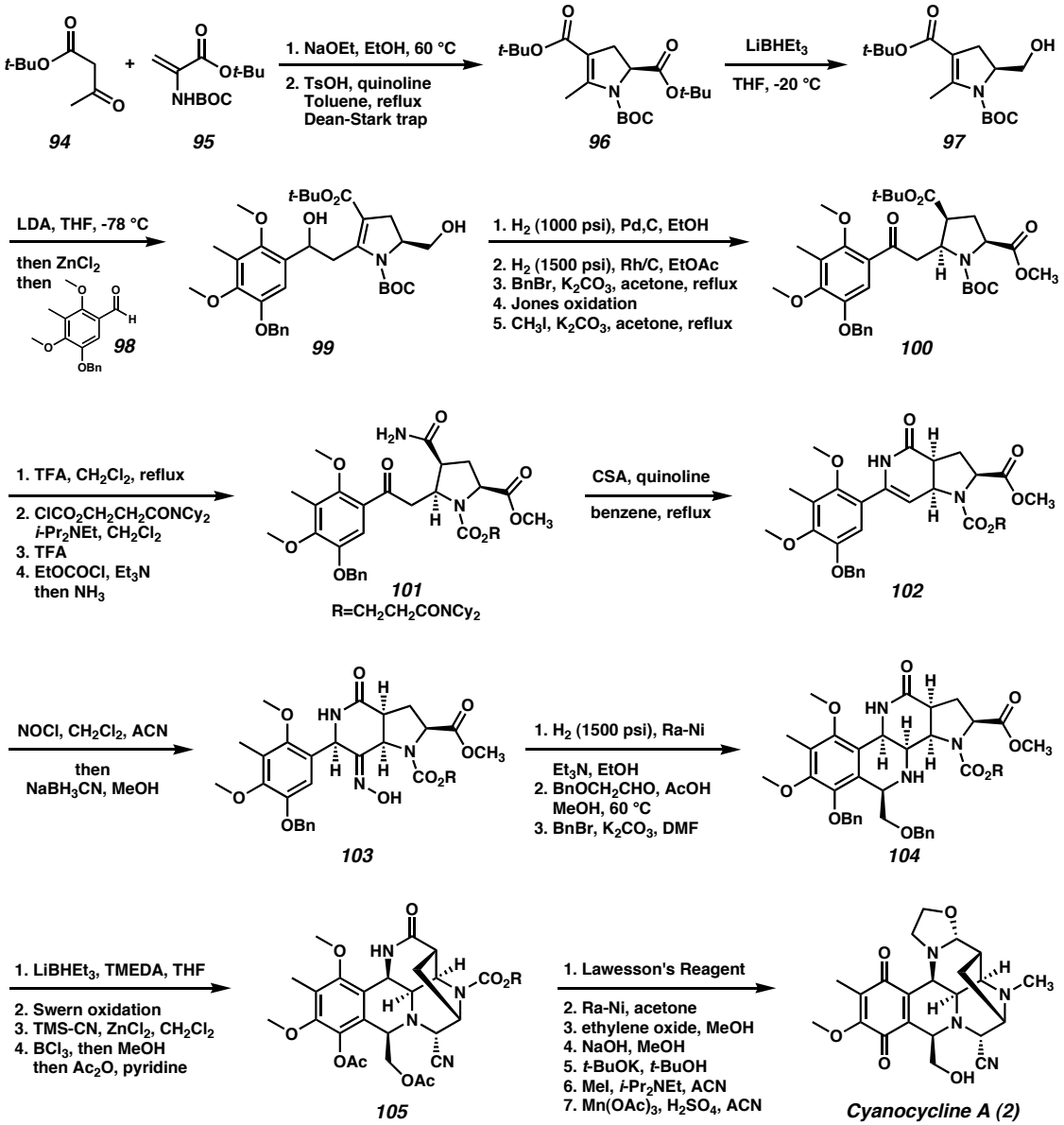


Fukuyama's Total Synthesis of Cyanocycline A

Fukuyama's synthesis of cyanocycline A began with the condensation of *tert*-butyl acetoacetate with dehydroalanine derivative **95** to provide pyrrolidine ring synthon **96** (Scheme 1.11).[49] Reduction followed by vinylogous aldol generated benzylic alcohol **99**, the enamide of which was diastereoselectively reduced to yield diester **100** after oxidation and methylation. This diester was selectively converted to monoamide **101**, which could then be condensed to enamide **102**. Nitrosylation and stereoselective

reduction supplied oxime **103**. Subsequent reduction of the oxime to an amine followed by Pictet-Spengler cyclization then generated key tetracycle **104**.

Scheme 1.11 Fukuyama's Total Synthesis of Cyanocycline A

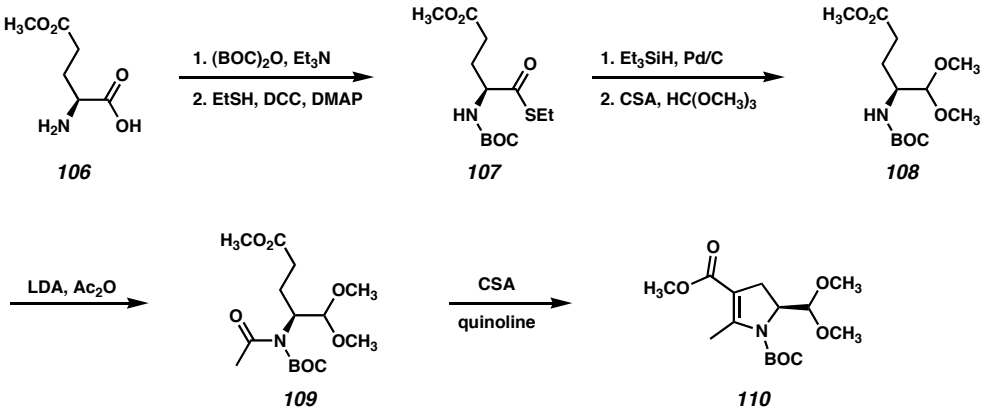


The ester of **104** was adjusted to the aldehyde oxidation state by superhydride reduction and Swern oxidation. The intermediate aldehyde underwent partial

condensation with the secondary amine and was trapped as the aminonitrile upon treatment with TMS-CN, producing pentacycle **105** after protecting group interchange. The remaining amide was converted to the oxazolidine by a three-step procedure consisting of conversion to the thioamide with Lawesson's reagent, Raney nickel reduction to the iminium ion, and reaction with ethylene oxide. Deprotection and oxidation then furnished racemic cyanocycline A.

The Fukuyama synthesis was rendered asymmetric by construction of dihydropyrrole **110** from L-glutamic acid methyl ester **106** (Scheme 1.12).[33] Reaction with di-*tert*-butyl-dicarbonate followed by coupling with ethanethiol provided thioester **107**, which could be reduced with palladium and triethylsilane to the aldehyde oxidation state and trapped as the dimethyl acetal (**108**). Acylation of the urethane nitrogen followed by condensative cyclization yielded dihydropyrrole **110**, which could be converted to (+)-cyanocycline A by the established route.

Scheme 1.12 Fukuyama's Asymmetric Route



1.4 Conclusion

The tetrahydroisoquinoline antitumor antibiotics are a structurally diverse, chemically interesting, and biologically active class of natural products isolated from bacterial and marine sources. The determined investigations of many chemists and biologists have elucidated the many structures, biosynthetic pathways, and modes of biological activity native to these compounds. Additionally, extensive synthetic work has led to the total syntheses of many of these complex natural products, particularly those characterized by their 3,9-diazabicyclo[3.3.1]nonane core. Cyanocycline A, as a representative of the subfamily characterized by a 3,8-diazabicyclo[3.2.1]octane core, has also garnered substantial synthetic attention, leading to two total syntheses. Lemonomycin, as the most recently characterized member of this family, had not been synthesized prior to our work.

1.5 Notes and Citations

(1) For a comprehensive review of the chemistry and biology of the tetrahydroisoquinoline antitumor antibiotics, see: Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669-1730.

(2) (a) Mikami, Y.; Takahashi, K.; Yazawa, K.; Arai, T.; Namikoshi, M.; Iwasaki, S.; Okuda, S. *J. Biol. Chem.* **1985**, *260*, 344-348. (b) Arai, T.; Yazawa, K.; Takahashi, K.; Maeda, A.; Mikami, Y. *Antimicrob. Agents Chemother.* **1985**, *28*, 5-11.

(3) Diketopiperizine **10** was shown to be a viable intermediate in the biosynthesis of ecteinascidin 743, see: Jeedigunta, S.; Krenisky, J. M.; Kerr, R. G. *Tetrahedron* **2000**, *56*, 3303-3307.

(4) The exact order of steps leading from diketopiperazine **10** to saframycin A has not been established.

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(46) It is also possible that an aryl ether intermediate rearranges to yield **77**, see reference 44d.

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CHAPTER TWO

The First Total Synthesis of (–)-Lemonomycin

2.1 Synthetic Planning for (–)-Lemonomycin

Structure and Synthetic Challenges

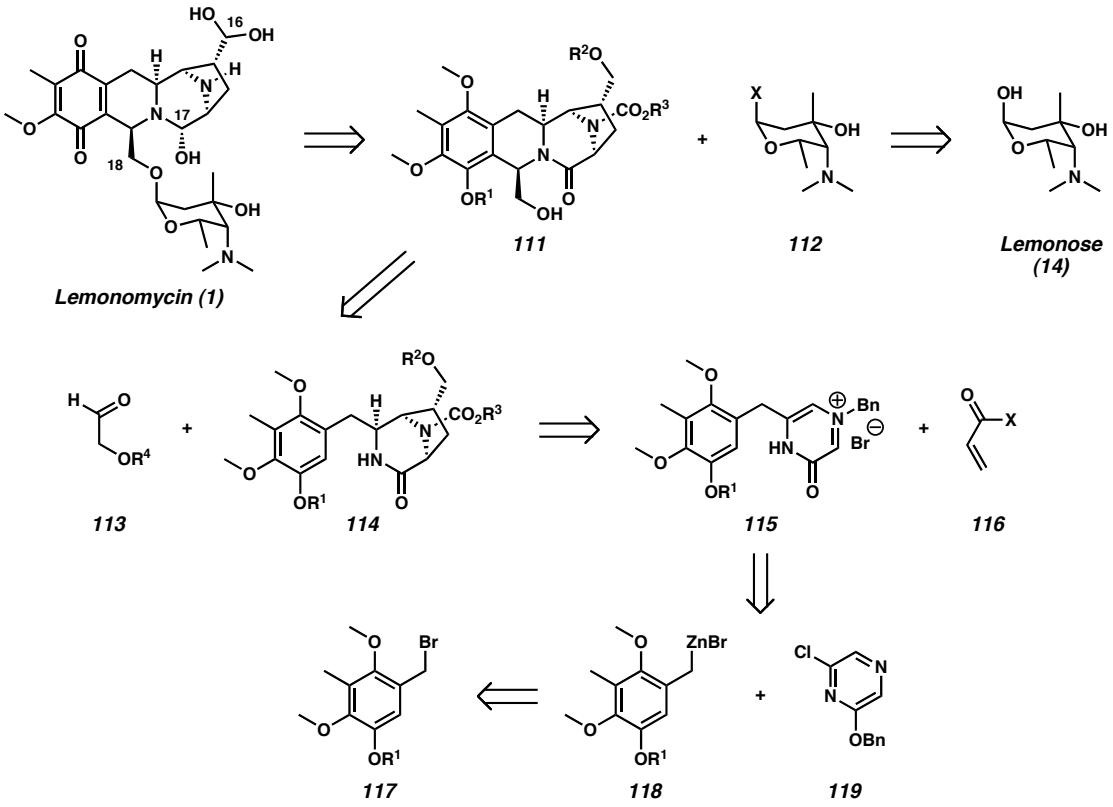
Lemonomycin (**1**, Scheme 2.1) presents an array of challenges to the synthetic chemist.[1] The natural product incorporates a stereochemically dense tetracyclic core bound through the C(18) oxygen to a complex 2,6-dideoxy-4-aminopyranose. The compound contains a total of ten stereocenters, including two sets of three contiguous stereogenic carbons. Lemonomycin also displays a variety of chemically sensitive groups, including one secondary and two tertiary amines, as well as quinone, carbinolamine, aldehyde hydrate, acetal, and tertiary alcohol functionality. Additionally, no reports concerning synthetic routes toward lemonomycin had appeared in the literature prior to our work,[2] so the potential pitfalls of any synthetic plan were unknown.

Original Retrosynthesis

In our analysis of lemonomycin, we envisioned the natural product arising from alcohol **111** by late stage glycosylation with a lemonose synthon such as **112** followed by adjustment of the oxidation states of the arene, C(16), and C(17) (Scheme 2.1). Alcohol **111** would in turn be derived from amide **114** and aldehyde **113** by a Pictet-Spengler cyclization.[3,4] We then recognized the diazabicyclooctane moiety as a retron for a dipolar cycloaddition transform, revealing dipole precursor **115** and acrylate **116**. Potentially, asymmetry could be introduced in this step through the use of either a chiral Lewis acid

catalyst or a chiral auxiliary on the acrylate fragment. Dipole precursor **115** was simplified by a Negishi coupling transform to unveil benzylic zinc bromide **118** and chloropyrazine **119**. The organozinc reagent was expected to be readily accessible from benzylic bromide **117**.

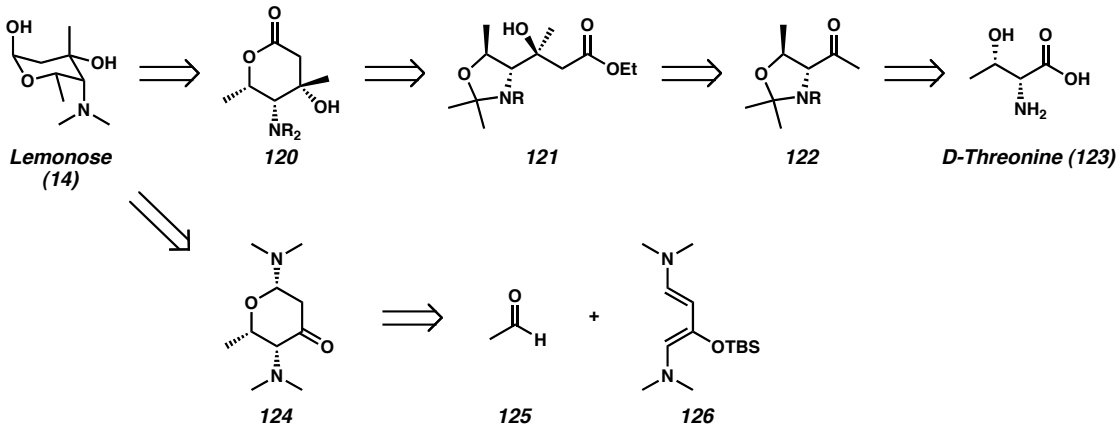
Scheme 2.1 Retrosynthetic Analysis of Lemonomycin



We anticipated that a glycosyl precursor (**112**) could be readily synthesized from lemonose (**14**). Lemonose could be generated by diastereoselective reduction of lactone **120**, which could in turn arise by hydrolysis and cyclization from ester **121** (Scheme 2.2). Application of a Felkin-Ahn-controlled diastereoselective aldol transform to ester **121** revealed methyl ketone **122**, which was expected to be available from D-threonine (**123**).[5]

A second possible strategy for the synthesis of lemonose (**14**) involves hetero-Diels-Alder chemistry. Lemonose could be derived by methyl anion addition and hydrolysis from aminopyranone **124**. This pyranone could be simplified by the application of a catalytic asymmetric hetero-Diels-Alder transform to reveal diene **126** and acetaldehyde (**125**) as starting materials.[6]

Scheme 2.2 Retrosynthetic Analysis of Lemonose



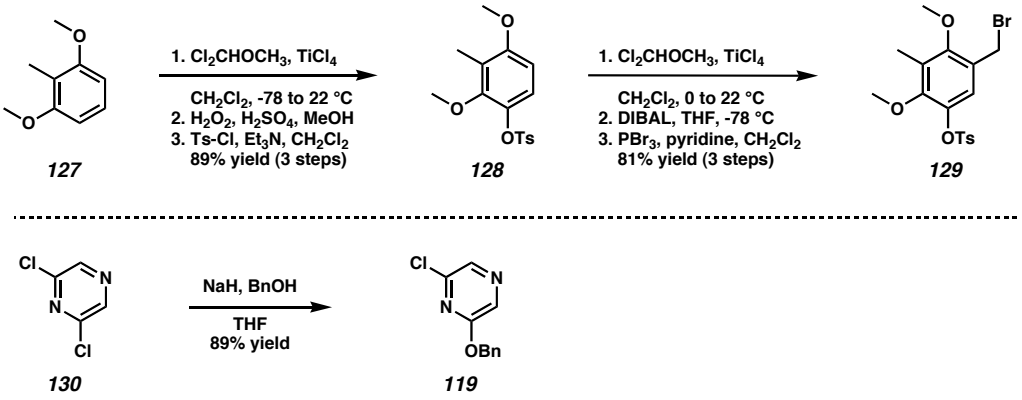
2.2 Early Synthetic Work

Dipole Synthesis

Our first targets thus became the reagents for the Negishi coupling reaction, specifically benzylic bromide **129** and chloropyrazine **119** (Scheme 2.3). The synthesis of **129** began with 2,6-dimethoxytoluene (**127**), which was converted to tosylate **128** by a formylation, Baeyer-Villiger oxidation under hydrolytic conditions, and reaction with tosyl chloride.[7] Recrystallization of **128** proved to be the only necessary purification in this sequence. Tosylate **128** was then converted to benzylic bromide **129** by a three-step procedure of formylation, DIBAL reduction to the alcohol, and treatment with

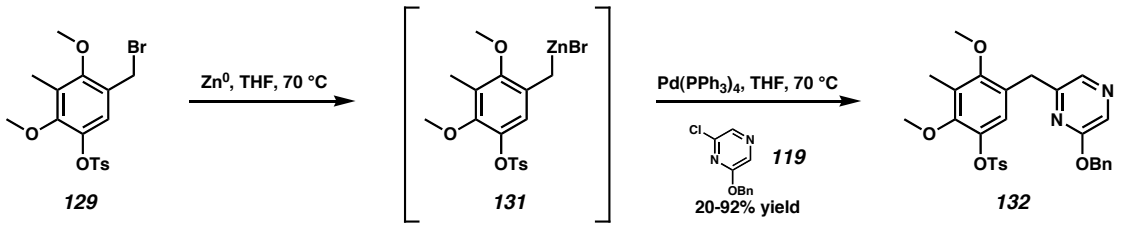
phosphorus tribromide and pyridine. The only necessary purification along this route was a rapid silica gel filtration of the final reaction mixture. Chloropyrazine **119** was readily synthesized from commercially available 2,6-dichloropyrazine (**130**) by selective mono substitution with in situ generated sodium benzyloxide.[8]

Scheme 2.3 Synthesis of the Negishi Coupling Partners



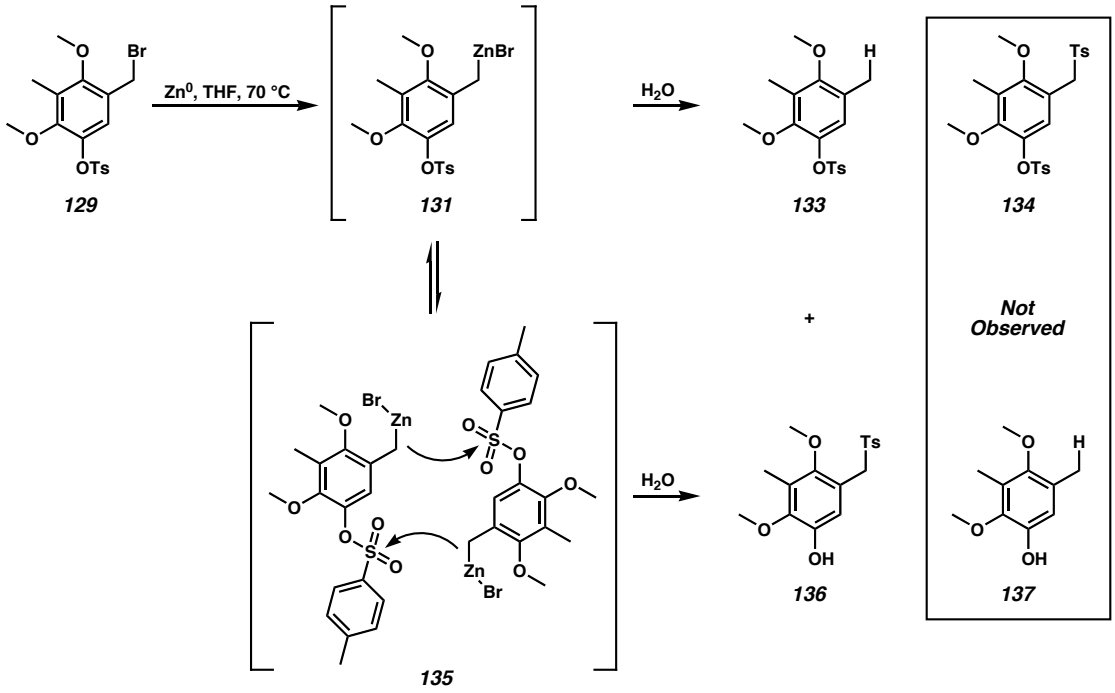
With the coupling partners in hand, we turned our attention to the Negishi reaction (Scheme 2.4). It was quickly discovered that reaction of bromide **129** with zinc dust[9] in tetrahydrofuran followed by addition of chloropyrazine **119** and a palladium(0) catalyst effected facile coupling to bisarene **132**.[10] The results of this reaction, unfortunately, were highly inconsistent, providing yields that varied between 20% and 92%. After extensive investigation, it was found that reproducibility could not be attained despite adjustments to the solvent, temperature, catalyst, or catalyst loading of the palladium-catalyzed step.

Scheme 2.4 Negishi Coupling Reaction



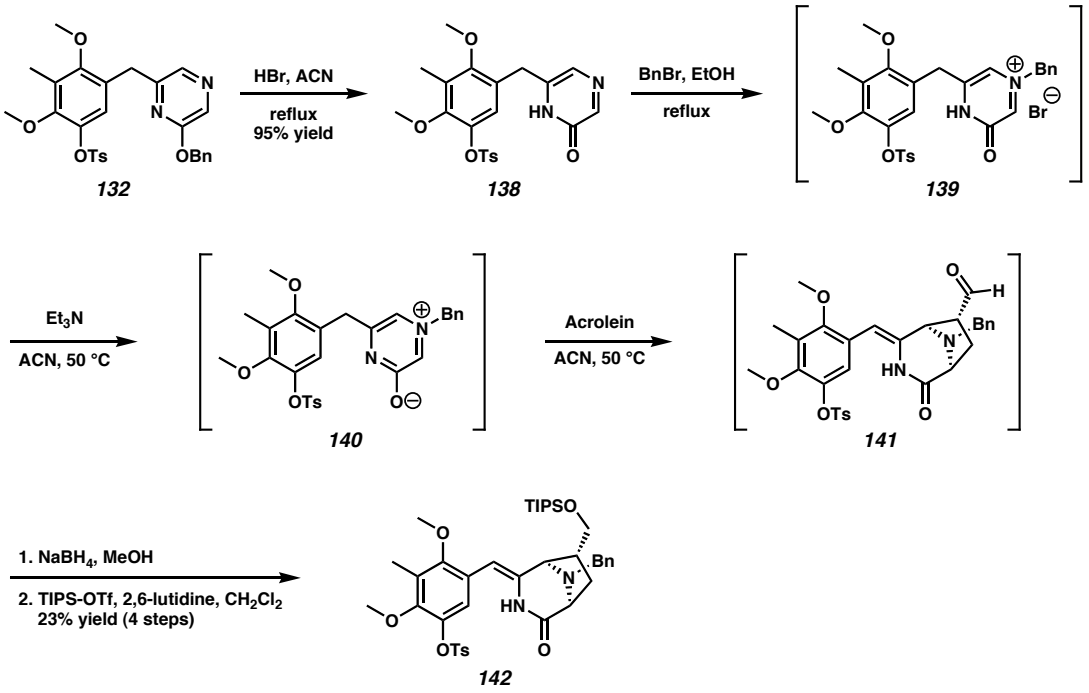
The zinc-insertion step of the Negishi sequence was therefore investigated by treating bromide **129** with zinc dust, heating the solution to 70 °C, and quenching the reaction with water (Scheme 2.5). This reaction provided the expected desbromo toluene **133**, which is generated by protonolysis of putative benzylic zinc intermediate **131**. To our surprise, however, a sulfonyl-transfer product (**136**) was also isolated in amounts that varied unpredictably over several reaction trials. Importantly, neither disulfonyl arene **134** nor the fully desulfonylated product (**137**) was isolated. We therefore propose that **136** must arise through a multimeric complex such as **135**, wherein the two sulfonyl-transfer events occur more rapidly than dissociation of the complex.[11,12] The association of organometallic **131** into a complex such as **135** could occur through π-stacking forces, coordination of the sulfonyl oxygen atoms to cationic zinc centers, or bridging Zn-Br-Zn interactions. Unfortunately, attempts to control the extent of sulfonyl transfer by the use of alternative solvent, the introduction of aromatic cosolvent to impede π-stacking, the presence or absence of oxygen, and the use of different batches of starting material and reagents failed to induce or prevent sulfonyl transfer in any consistent way. We were therefore unable to improve the reliability of the Negishi coupling sequence.

Scheme 2.5 Unexpected Sulfonyl Transfer Reaction



Despite the inconsistency of the Negishi coupling reaction, gram quantities of bisarene **132** could be produced. This compound was advanced by acidic benzyl ether cleavage to pyrazinone **138** (Scheme 2.6). Alkylation of the pyrazinone with benzyl bromide provided oxidopyrazinium **139** as an unstable oil. Treatment of this salt with triethylamine and acrolein generated an inseparable mixture of cycloadducts **141** through the intermediacy of dipole **140**.[13,14,15] After reduction and silylation, diazabicyclooctane **142** could be isolated as a single isomer. Unfortunately, due to the instability of **139** and **140** and the formation of isomers in the cycloaddition reaction, the yield of **142** could not be improved beyond 23% over the four steps.

Scheme 2.6 Dipolar Cycloaddition

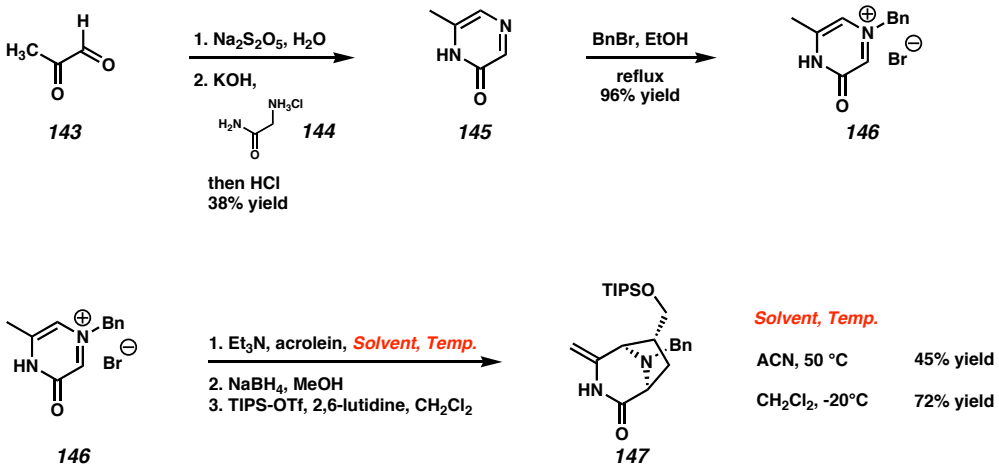


Optimization of the Dipolar Cycloaddition

In light of the difficulty in synthesizing pyrazinone **138** and the unstable nature of oxidopyrazinium salt **139**, we decided to optimize the dipolar cycloaddition with the simple oxidopyrazinium salt **146**.[16] Oxidopyrazinium **146** was readily synthesized by known procedures. Thus, cyclocondensation of glycinamide hydrochloride (**144**) with pyruvaldehyde (**143**) followed by alkylation of the resulting pyrazinone **145** with benzyl bromide provided **146** as a bench-stable powder (Scheme 2.7).[17] When this compound was treated with triethylamine and acrolein in acetonitrile at 50 °C, a mixture of inseparable cycloadducts again resulted, with a single isomer (**147**) available in 45% yield after reduction and silylation. Gratifyingly, the yield of silyl ether **147** could be

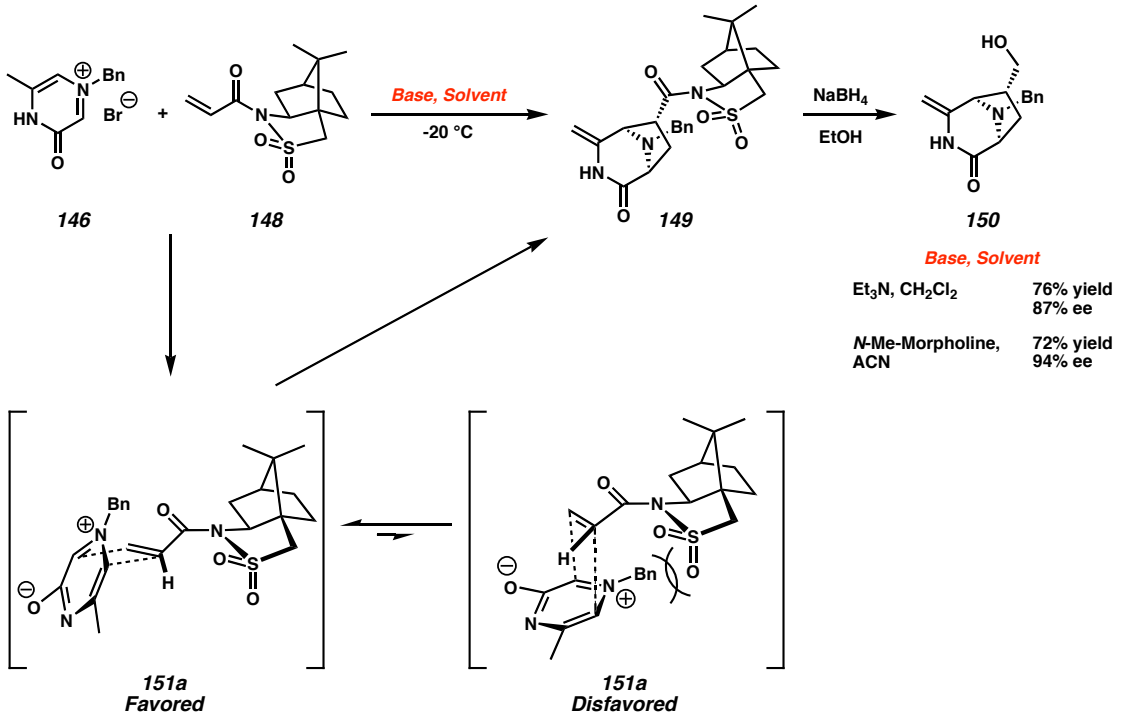
increased to 72% by performing the cycloaddition reaction in dichloromethane at –20 °C. The increased yield was primarily due to the minimization of other cycloadduct isomers.

Scheme 2.7 Cycloaddition Optimization with a Simple Dipole



Having developed optimized conditions for the dipolar cycloaddition of **146** with acrolein, we investigated the use of chiral auxiliaries for the production of enantioenriched diazabicyclic compounds. The acrylamide of Oppolzer's sultam (**148**)[18] was tested due to its well-precedented use in dipolar cycloadditions of nitrile oxides, silyl nitronates, and azomethine ylides.[19,20] To our delight, under the conditions utilized for our racemic cycloaddition, this acrylamide provided good diastereocontrol in the production of **149**, such that alcohol **150** could be isolated in 87% ee after reductive cleavage of the auxiliary (Scheme 2.8). After a screen of conditions, it was found that **150** could be produced with 94% ee if *N*-methyl morpholine was utilized as the base and acetonitrile as the solvent.[21]

Scheme 2.8 Asymmetric Dipolar Cycloaddition



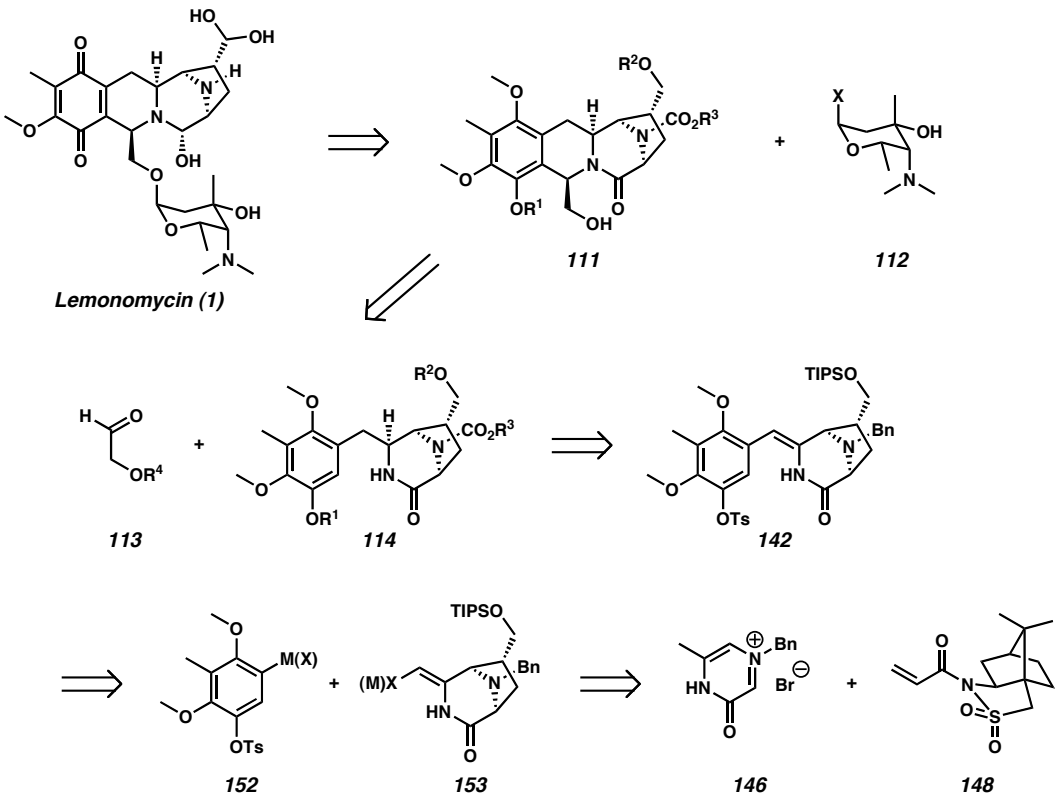
In analogy to proposed models,[19] the cycloaddition of **146** with **148** is expected to occur through transition state **151**. The conformation of the acrylamide is controlled by lone pair repulsion and by the steric influence of the amide. Lone pair repulsion causes the carbonyl oxygen to rotate away from the sulfonamide oxygen atoms, placing the C-O double bond and the N-S bond in an *s-trans* orientation. The steric influence of the amide forces the acrylamide olefin and carbonyl into an *s-cis* geometry. In this conformation, the pseudoaxial sulfonamide oxygen blocks the lower face of the alkene. Cycloaddition across the top face of the alkene yields **149**.

2.3 Second Generation Approach to (–)-Lemonomycin

Revised Synthetic Plan

Our success in developing an asymmetric, high-yielding route to alcohol **150** encouraged us to utilize this compound as an intermediate in the synthesis of (–)-lemonomycin. We therefore revised our retrosynthetic plan to include the early-stage asymmetric dipolar cycloaddition (Scheme 2.9). It was still expected that the natural product could be derived from **114** by a Pictet-Spengler cyclization and late-stage glycosylation (*vide supra*). However, lactam **114** was now simplified by the application of a diastereoselective hydrogenation transform and protecting group manipulations to reveal styrene **142**, which contains a retron for a palladium catalyzed coupling reaction.[22] Application of this transform unveiled arene **152** with either a halide or metallic substituent and enamide **153** with the opposite functionality. The enamide was expected to be readily accessible from oxidopyrazinium **146** and acrylamide **148** through our dipolar cycloaddition protocol.

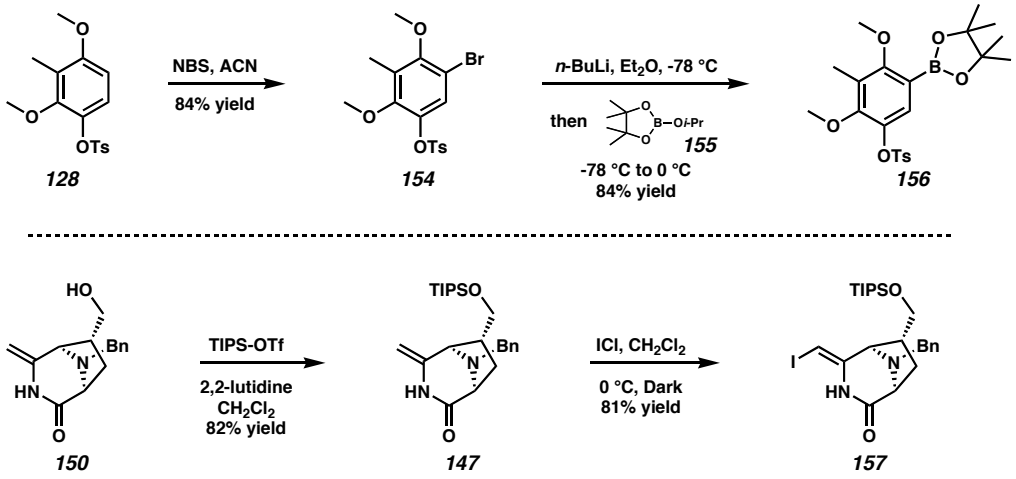
Scheme 2.9 Revised Retrosynthesis of (–)-Lemonomycin



Styrene Synthesis

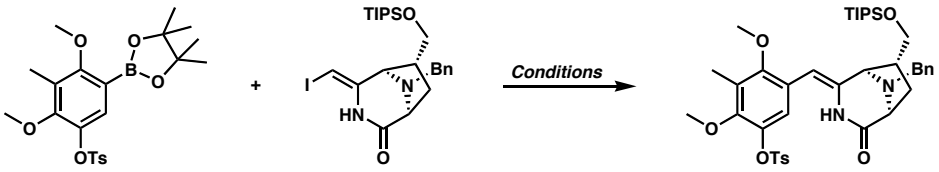
With a new synthetic plan in mind, we investigated the synthesis of styrene **142**. To this end, arene **128** was cleanly brominated to provide **154**, which could be converted to boronic ester **156** by lithium-bromide exchange and quenching with boronate **155** (Scheme 2.10). Alcohol **150** was converted to silyl ether **147** under standard conditions. Attempts to convert the enamide of **147** to an organometallic reagent by either hydroboration or mercuration were unsuccessful, but the enamide was readily iodinated with iodine monochloride to provide vinyl iodide **157**. Boronate **156** and iodide **157** were expected to be useful substrates for a Suzuki coupling reaction.[23]

Scheme 2.10 Synthesis of the Suzuki Substrates



With boronic ester **156** and vinyl iodide **157** in hand, we investigated the Suzuki coupling reaction (Table 1).[24] A variety of standard conditions gave poor results, but we were pleased to find that reaction with catalytic tetrakis(triphenylphosphine)palladium(0) and aqueous sodium carbonate provided a moderate yield of styrene **142** (Entry 5). The use of lithium carbonate as the stoichiometric base was less effective (Entry 4), but improved yields of coupled product were obtained when either potassium or cesium carbonate was employed as the base (Entries 6 and 7). Moreover, these reactions required only 5 mol% palladium for efficient catalysis. Importantly, the coupling reaction with potassium carbonate as base was effective on multigram scale, although a slight drop in yield was observed (Entry 8).

Table 2.1 Suzuki Coupling



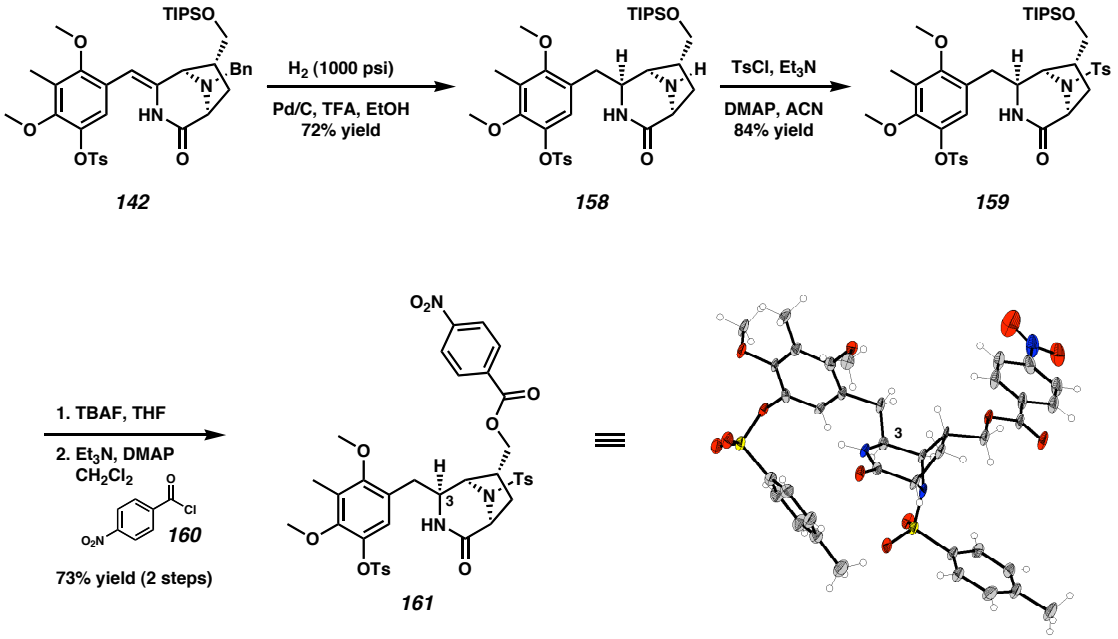
Entry	*Conditions*		*Yield*
1	$PdCl_2(dppf)\cdot CH_2Cl_2$ (10 mol%), KOAc, DMSO, 80 °C		0%
2	$PdCl_2(dppf)\cdot CH_2Cl_2$ (20 mol%), K_3PO_4, DME, 85 °C		trace
3	$Pd(PPh_3)_4$ (10 mol%), $Ba(OH)_2$, DME, H_2O, 75 °C		49%
4	$Pd(PPh_3)_4$ (10 mol%), Li_2CO_3 (aq), Benzene, MeOH, 70 °C		44%
5	$Pd(PPh_3)_4$ (10 mol%), Na_2CO_3 (aq), Benzene, MeOH, 70 °C		63%
6	*$Pd(PPh_3)_4$ (5 mol%), K_2CO_3 (aq), Benzene, MeOH, 70 °C*		*73%*
7	$Pd(PPh_3)_4$ (5 mol%), Cs_2CO_3 (aq), Benzene, MeOH, 70 °C		73%
8	*$Pd(PPh_3)_4$ (5 mol%), K_2CO_3 (aq), Benzene, MeOH, 70 °C*	*3.1g Scale*	*69%*

Diastereoselective Reduction of the Enamide

The next challenge was hydrogenation of styrene **142** with necessary control of stereochemistry (Scheme 2.11). After substantial experimentation, it was discovered that carbon-supported palladium(0) in ethanol with an acidic cosolvent was uniquely effective for the reduction of **142**, although significant conversion (with concomitant benzyl amine hydrogenolysis) was observed only at high hydrogen pressures.[25] Use of trifluoroacetic acid as the acidic cosolvent provided lactam **158** as single diastereomer, while the use of acetic acid led to a mixture of **158** and an apparently diastereomeric compound.[26] To prove the stereochemistry of **158**, a crystalline substance was required.[27] Toward this end, treatment of amine **158** with tosyl chloride produced tosamide **159**. Silyl ether cleavage followed by acylation with 4-nitrobenzoyl chloride then provided ester **161** as a highly crystalline solid. X-ray diffraction analysis of a single crystal of **161** showed that

the stereochemistry at C(3)[28] matched the stereochemistry reported for the natural product.

Scheme 2.11 Diastereoselective Reduction of the Enamide

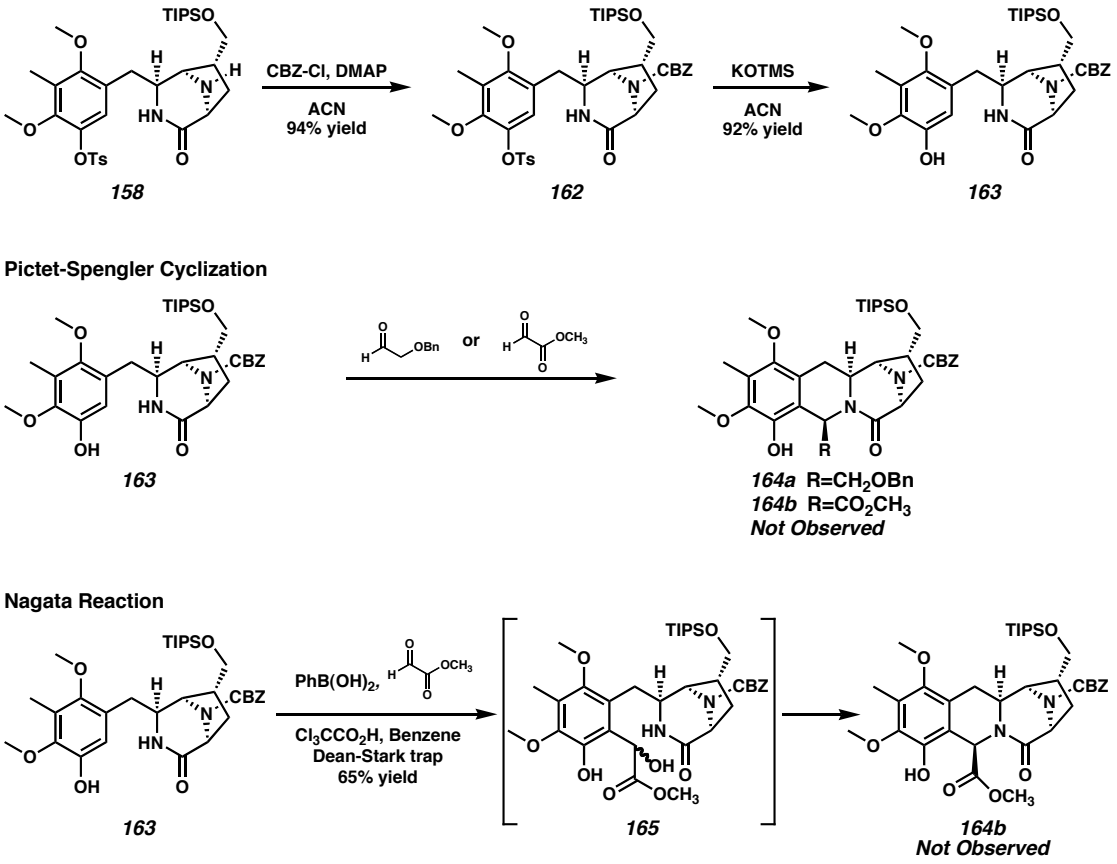


Pictet-Spengler Cyclization

Amide **158** was advanced synthetically by conversion of the amine to a urethane with CBZ-Cl and DMAP in acetonitrile (Scheme 2.12). Cleavage of the tosylate was effected with potassium trimethylsilanoate to provide phenol **163**, which was expected to be an effective substrate for Pictet-Spengler cyclization to tetrahydroisoquinoline **164**. Unfortunately, treatment of **163** with benzyloxyacetaldehyde under a variety of conditions failed to provide any cyclized product. In analogy to the protocol utilized by Evans for the synthesis of cyanocycline A,[29] we then attempted to condense **163** with

monomeric methyl glyoxylate. Unfortunately, these conditions also failed to cause any conversion of the starting material.

Scheme 2.12 Pictet-Spengler and Nagata Attempts



The proposed Pictet-Spengler cyclization would mechanistically form a carbon-nitrogen bond followed by a carbon-carbon bond. Due to the failure of the Pictet-Spengler protocols, we searched for a reaction that would allow for direct carbon-carbon bond formation. In this regard, phenol **163** was treated with phenyl boronic acid, methyl glyoxylate, and catalytic trichloroacetic acid according to the procedure of Nagata.[30] This reaction provided an inseparable mixture of diastereomeric alcohols **165** (dr = 4:3), the

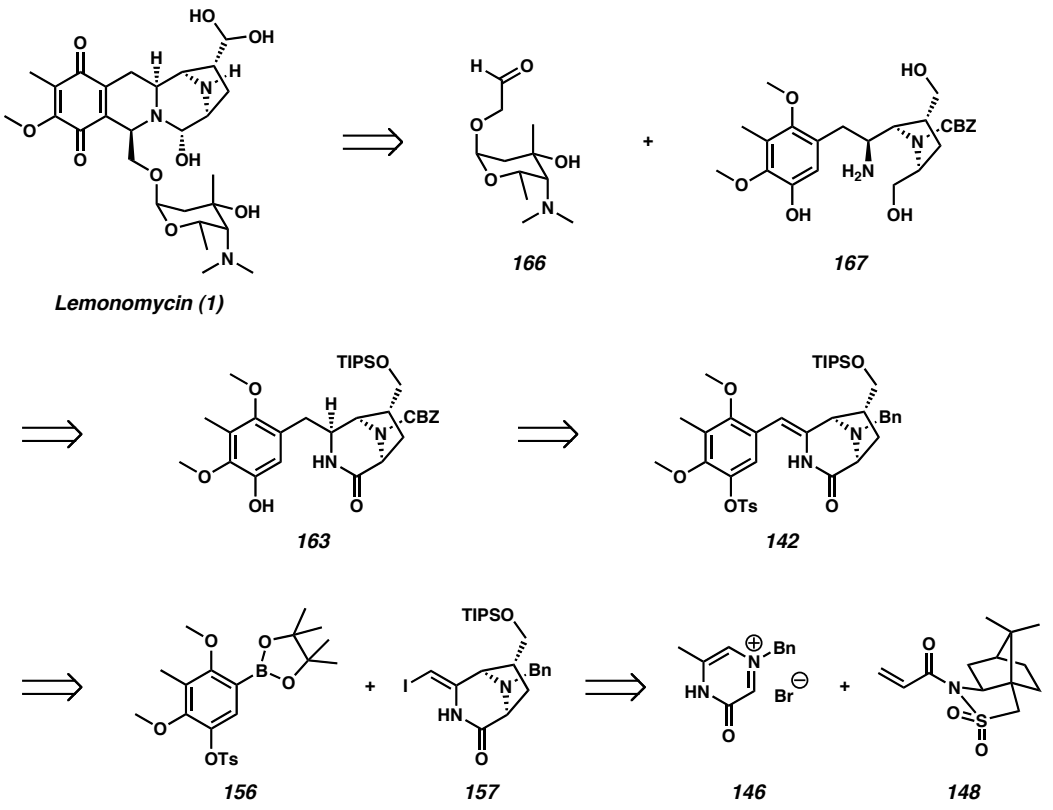
structures of which were assigned by ^{1}H NMR and mass spectral data. Unfortunately, cyclization of this compound to tetrahydroisoquinoline **164b** could not be induced under protic or Lewis acidic conditions, nor by conversion of the alcohol to a better leaving group.[31]

2.4 Final Synthetic Approach to (–)-Lemonomycin

Final Synthetic Plan

The failure of phenol **163** to cyclize to the tetrahydroisoquinoline was likely due to insufficient nucleophilicity of the amide nitrogen. To solve this problem, we altered our retrosynthetic analysis of lemonomycin to incorporate a Pictet-Spengler cyclization with primary amine **167** as its substrate (Scheme 2.13).[32] We also made a strategic decision to incorporate the lemonose unit on the aldehyde substrate (**166**), thus avoiding late stage glycosylation and protecting group manipulations. Aminotriol **167** would arise by reduction and silyl ether cleavage from tricycle **163**, the synthesis of which had already accomplished.

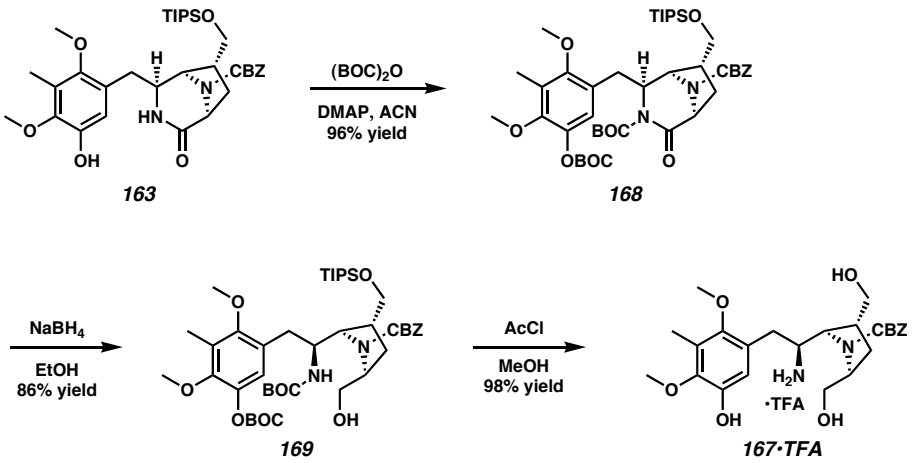
Scheme 2.13 Final Retrosynthetic Analysis of (–)-Lemonomycin



Synthesis of the Aminotriol

Due to the difficulty of direct reduction of amides to amino alcohols, lactam **163** was activated by conversion to imide **168** (Scheme 2.14). Reduction of **168** with excess sodium borohydride in ethanol then cleaved the lactam to protected amino alcohol **169**. Treatment of this compound with in situ-generated methanolic hydrochloric acid effected cleavage of the silyl ether and both BOC groups to provide aminotriol **167**, which was isolated as the trifluoroacetate salt after preparative HPLC purification. In model Pictet-Spengler reactions with a variety of α-hydroxyacetaldehyde derivates, **167** typically generated diastereomerically pure tetrahydroisoquinoline products.[33]

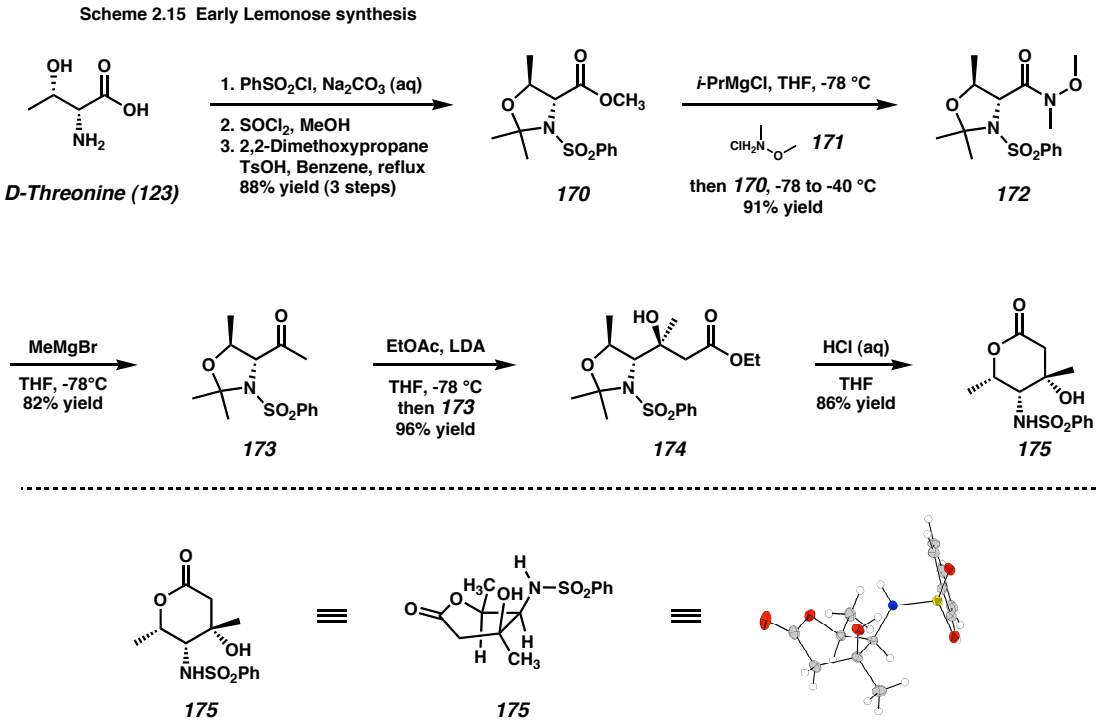
Scheme 2.14 Aminotriol Synthesis



Synthesis of Lemonose

With an effective amine substrate for the Pictet-Spengler reaction in hand, we began the synthesis of an aldehyde-appended lemonose fragment (i.e., **166**) as the Pictet-Spengler coupling partner.[34] After considering our two retrosynthetic analyses of lemonose (Scheme 2.2), we chose to pursue the better-precedented[5] route beginning with threonine. In this regard, D-threonine (**123**) was advanced to methyl ester **170** following known procedures (Scheme 2.15).[35,36] The methyl ester was converted to Weinreb amide **172** with the magnesium salt of *N,O*-dimethylhydroxylamine.[37] Treatment of **172** with methylmagnesium bromide cleanly yielded ketone **173**, which was expected to be an excellent substrate for Felkin-Ahn-controlled diastereoselective addition of nucleophiles.[38] Thus, addition of the lithium ketene acetal of ethyl acetate to ketone **173** generated tertiary alcohol **174** as a single diastereomer. Cleavage of the oxazolidine ring under acidic conditions proceeded with concomitant lactonization to provide lactone **175**, the relative stereochemistry of which was proven by X-ray diffraction analysis of a single crystal.[39]

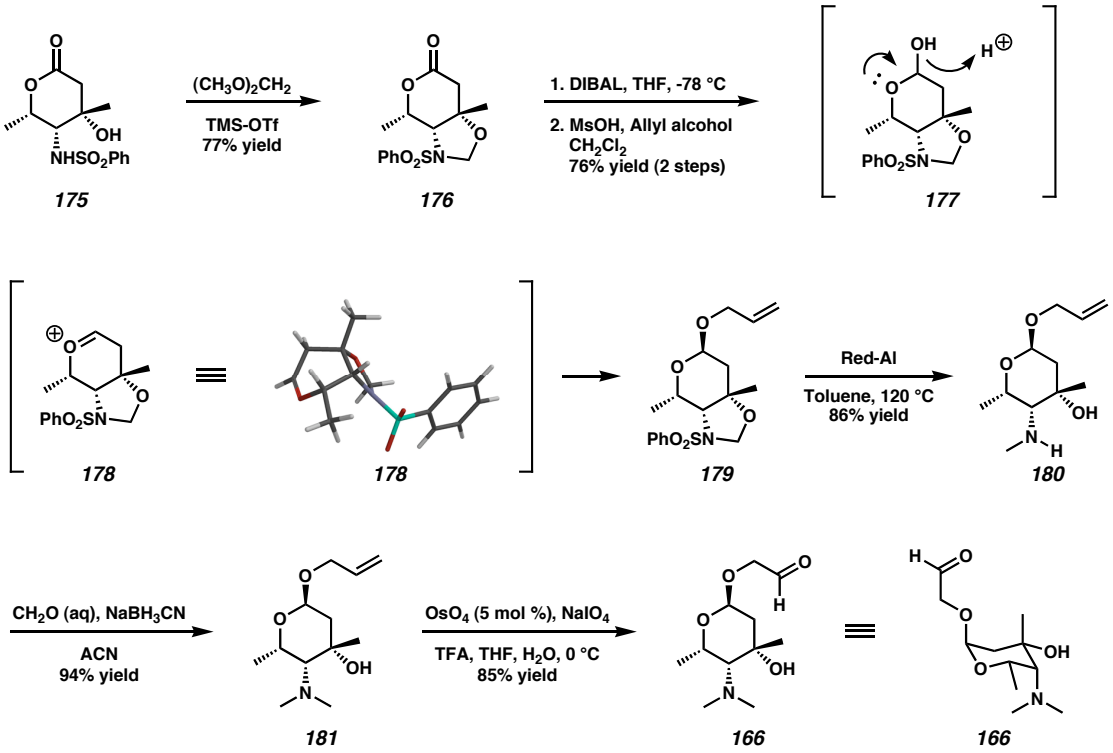
Scheme 2.15 Lemonose Synthesis: Preparation of a Key δ-Lactone



Lactone **175** was converted to oxazolidine **176** with dimethoxymethane and trimethylsilyl triflate (Scheme 2.16). The oxazolidine moiety served two important functions. First, the oxazolidine methylene acts as a latent methyl group for eventual conversion to the dimethylamine substituent. Second, the *cis*-fused bicyclic structure of oxazolidine **176** allowed for the highly diastereoselective introduction of an allyloxy group by reduction with DIBAL followed by treatment with allyl alcohol and methanesulfonic acid. Diastereoselectivity arose from the cup-shaped structure of intermediate oxocarbenium **178**.[40] Attack from the convex face of **178** provided allyl glycoside **179** with trace (<5%) amounts of the easily separable anomer.[41] Red-Al reduction removed the benzenesulfonyl group and cleaved the oxazolidine ring to yield secondary amine **180**, which was readily converted to the tertiary amine by reductive

methylation. Oxidative cleavage of the allyl group was then effected by catalytic dihydroxylation in the presence of sodium periodate, leading directly to glycosyloxy acetaldehyde **166**.[42]

Scheme 2.16 Synthesis of Lemonose

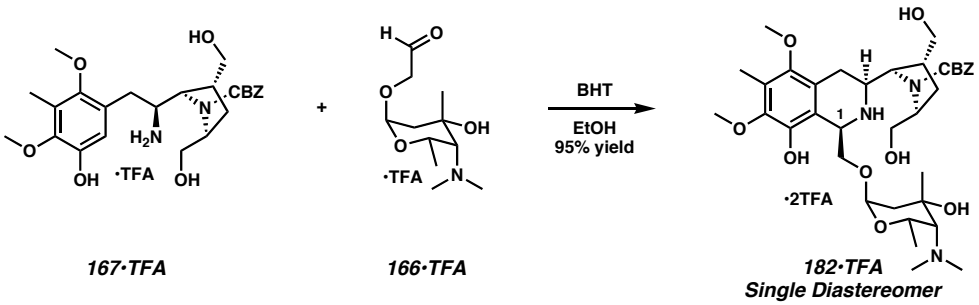


Completion of (–)-Lemonomycin

With the Pictet-Spengler substrates **166** and **167** in hand, we began the final campaign toward lemonomycin. To our delight, we discovered that simply mixing the trifluoroacetate salts of **166** and **167** in ethanol at room temperature provided 95% yield of tetrahydroisoquinoline **182** as a single diastereomer at C(1) (Scheme 2.17).[43] This reaction marked one of the first examples of a Pictet-Spengler cyclization employing a complex α-glycosyloxy aldehyde as a substrate.[44] The high yielding and completely

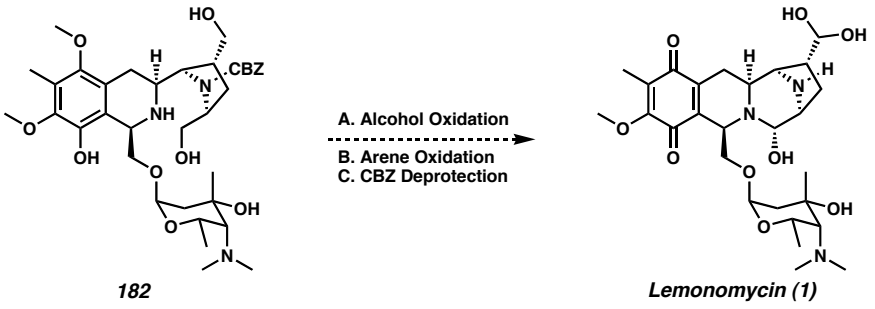
diastereoselective reaction also accomplished a highly convergent strategy for the synthesis of the lemonomycin core structure.

Scheme 2.17 Pictet-Spengler Cyclization



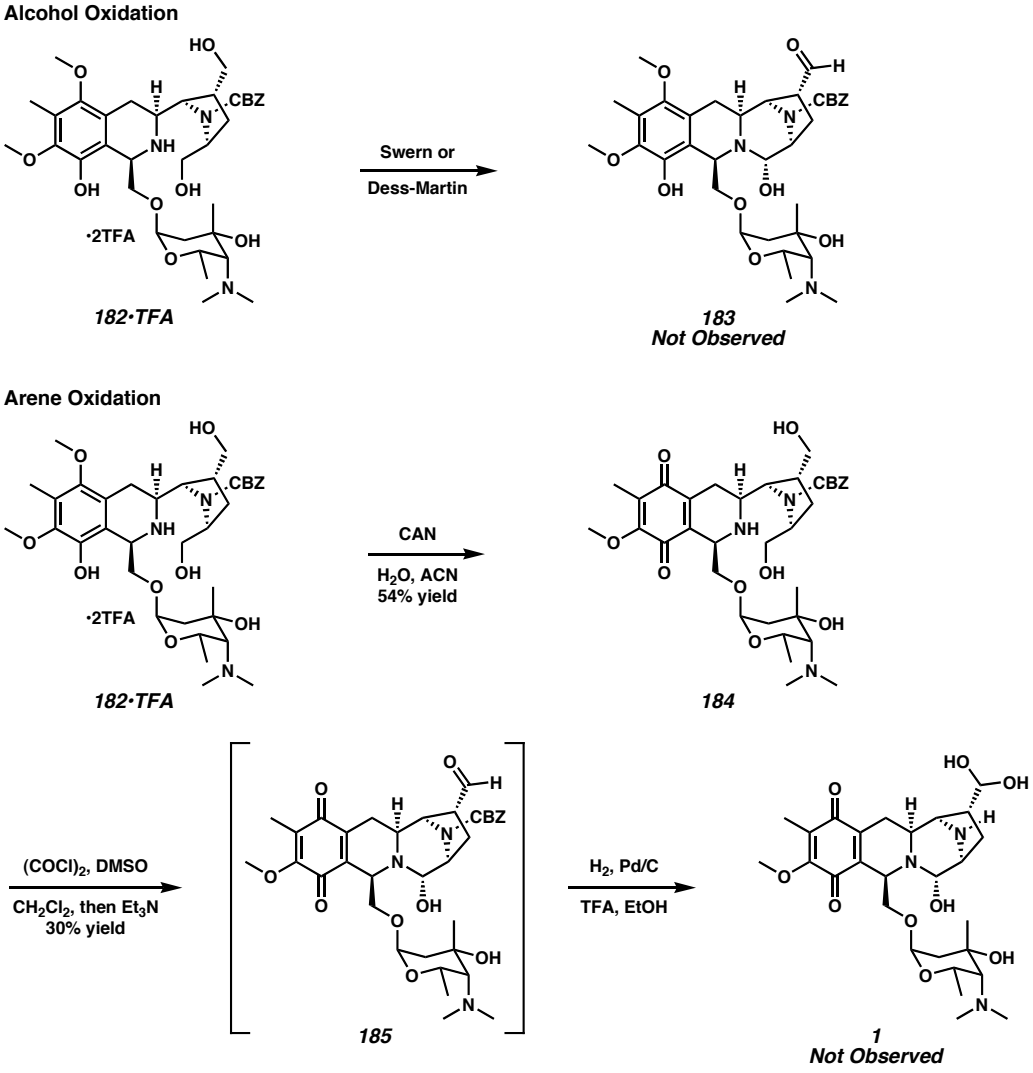
The remaining challenges for converting tetrahydroisoquinoline **182** to lemonomycin were threefold and deceptively simple (Scheme 2.18). The oxidation of the phenol to a quinone was required. The two alcohols were to be oxidized to the carbinolamine and aldehyde hydrate, respectively. It was expected that the two alcohol oxidations would be accomplished in a single reaction. Lastly, the carbamate protecting group had to be removed.

Scheme 2.18 Endgame Challenges



We first attempted to advance **182** by alcohol oxidation, but standard conditions for conversion to the bisaldehyde (Swern oxidation, Dess-Martin periodinane, etc.) failed on this compound (Scheme 2.19). We then tried the aromatic oxidation as the first of the three steps. This oxidation was achieved with ammonium cerium(IV) nitrate, yielding quinone **184** in moderate yield. Alcohol oxidation then was accomplished under Swern oxidation conditions, providing a compound with ^{1}H NMR and mass spectral data consistent with alcohol **185**.[45] Unfortunately, attempts to remove the CBZ group under hydrogenolytic or acidic conditions generated an array of unidentifiable decomposition products.

Scheme 2.19 Alcohol and Arene Oxidation Routes



Faced with the difficulties of routes beginning with either of the oxidations, we decided to first remove the CBZ group (Scheme 2.20). Thus, hydrogenolysis of **182** provided triaminotetraol **186** in good yield. Ammonium cerium (IV) nitrate oxidation then yielded quinone **187**, again bringing us within a single step of the natural product. Unfortunately, alcohol oxidation utilizing Dess-Martin periodinane,[46] Swern, Moffatt,

DMS/NBS,[47] Uemura,[48] Larock,[49] pyridinium dichromate, or TPAP/NMO[50] failed to yield even a trace of lemonomycin (**1**).

We therefore turned to the only path still available, which would require alcohol oxidation of triaminotetraol **186**. Despite the presence of confounding functionality in the form of the phenol, tertiary alcohol, and two secondary amines, we discovered that carefully controlled Swern oxidation conditions with DMSO present in cosolvent quantities effected the oxidation of **186** (Scheme 2.20). The oxidation was complicated by the formation of intermediate methylthiomethyl ether or amine groups,[51] but this problem was mitigated by treatment of the crude reaction mixture with aqueous hydrochloric acid, yielding clean phenol **188** in 52% yield along with two monooxidized compounds in 33% and 13% yield.[52] The completion of the synthesis was then accomplished by cerium(IV) oxidation of the phenol to provide (–)-lemonomycin. Our synthetic sample was identical to a natural sample by all spectroscopic and chromatographic methods, including ^{1}H NMR, ^{13}C NMR, IR, UV/Vis, HRMS, optical rotation, TLC, and HPLC coinjection.[53]

Scheme 2.20 Completion of (–)-Lemonomycin

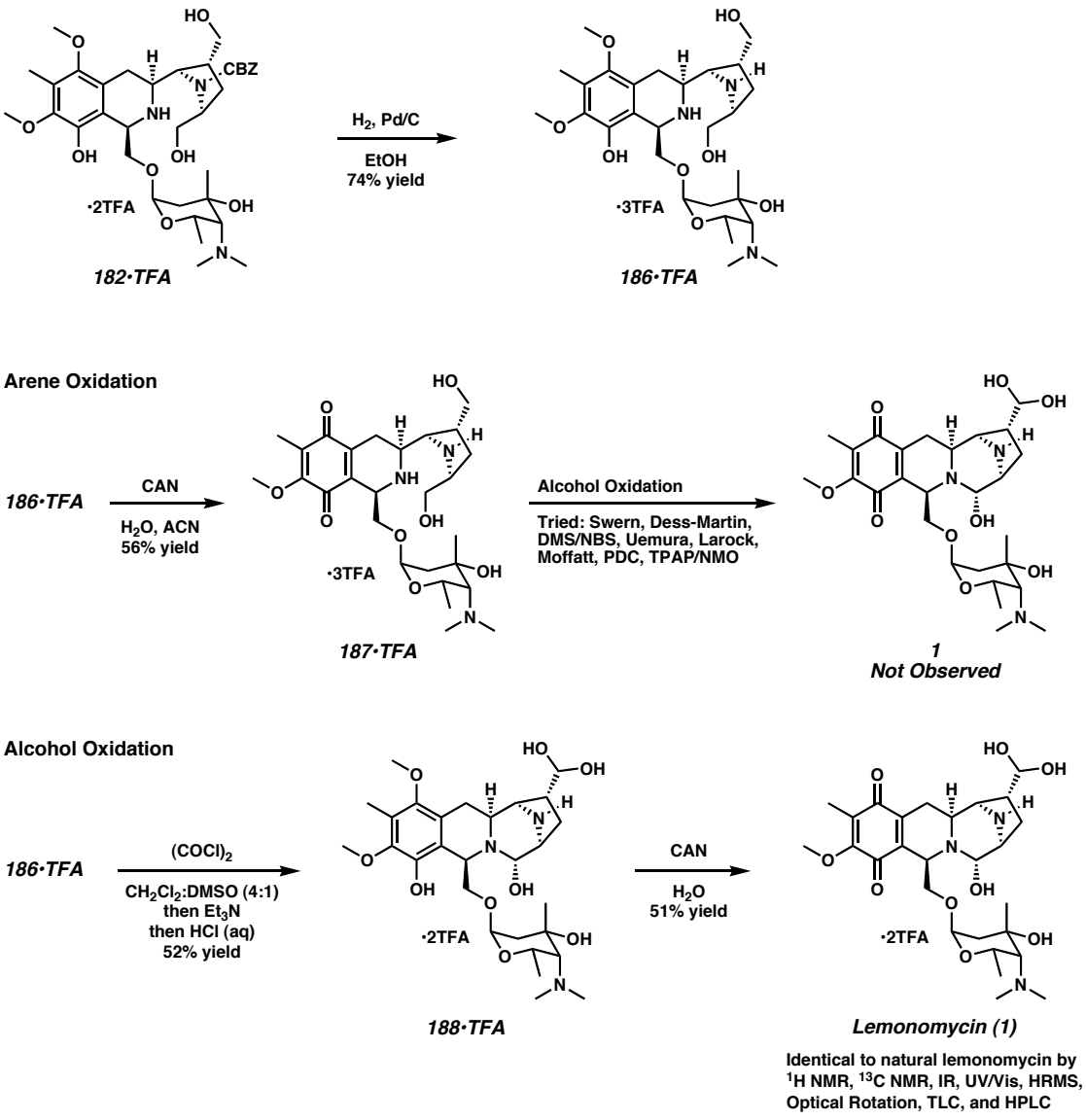
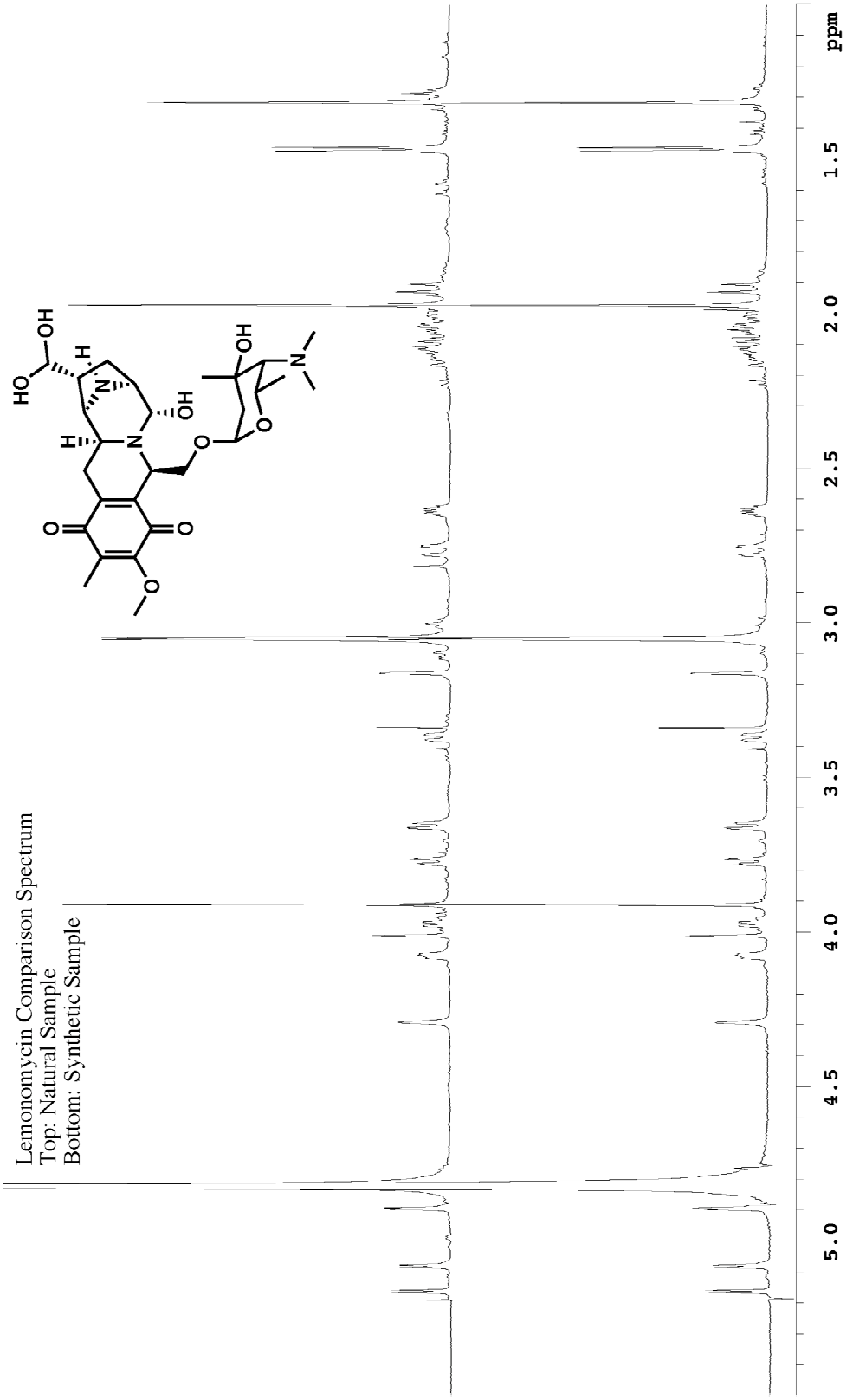


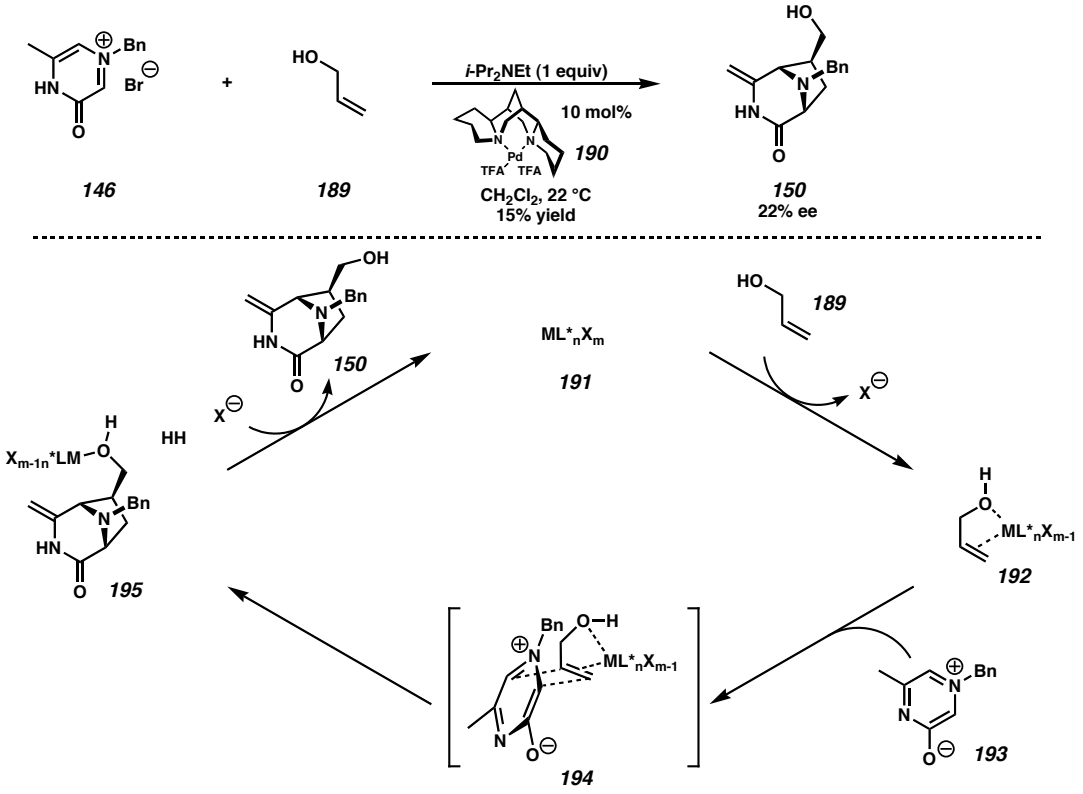
Figure 2.1 Comparison ^{1}H NMR Spectra of Natural and Synthetic (–)-Lemonomycin



2.5 Progress Toward a Catalytic Asymmetric Dipolar Cycloaddition

The reaction of oxidopyrazinium **146** with acrylamide **148** (Scheme 2.8) provided a route to enantiopure (–)-lemonomycin. While highly effective, this reaction required the use of a chiral auxiliary to induce asymmetry. A potentially more efficient and cost effective method of generating enantioenriched **150** would be the cycloaddition of **146** with allyl alcohol (**189**) catalyzed by a high oxidation state late transition metal coordinated by chiral ligands (e.g., **191**, Scheme 2.21).[54,55] We expected that this reaction would proceed mechanistically by π-coordination of allyl alcohol to the catalyst, producing intermediate **192**. It was hoped that the influence of the chiral ligands would cause the metal to bind only one prochiral face of the olefin. The LUMO of the bound olefin should be lowered relative to free allyl alcohol, such that the dipole will react selectively with complex **192**.[56] Cycloaddition onto the olefin face opposite from the metal catalyst through transition state **194** would produce bound diazabicycle **195**, which would dissociate to form enantioenriched **150** and the free metal catalyst.

Scheme 2.21 Catalytic Asymmetric Dipolar Cycloaddition



We first attempted the catalytic asymmetric cycloaddition of **146** with allyl alcohol in the presence of (–)-sparteine $Pd(TFA)_2$ complex **190**. We were pleased to find that these initial conditions provided diazabicycle **150** in 15% yield and 22% ee. Unfortunately, attempts to optimize this reaction by employing alternative ligands (diamines, bisphosphines, phosphinooxazolines,[57] pyridine/amidine ligands,[58] phenol/ oxazoline ligands,[59] and dienes[60]), metals ($NiBr_2$, $Pd(OAc)_2$, $PdCl_2$, $PdBr_2$, $PtCl_2$, PtI_2, $CuCl_2$, $CuBr_2$, $ZnCl_2$, $ZnBr_2$, $RhCl_3$, $IrCl_3$, and $RuCl_3$), bases, and solvents, as well as allyl ethers in place of allyl alcohol, provided no increase in either yield or enantioselectivity.

2.6 Concluding Remarks

The first total synthesis of (–)-lemonomycin has been accomplished in an efficient and highly convergent manner. Our synthetic planning evolved significantly during the project. Our original plan featured a Negishi coupling, subsequent dipolar cycloaddition, and a proposed amide Pictet-Spengler cyclization. After making significant progress along this route, we discovered a highly diastereoselective, auxiliary controlled dipolar cycloaddition with a simple dipole precursor. We therefore altered our synthetic plan to include this reaction followed by a key Suzuki coupling reaction and a diastereoselective enamide hydrogenation. After completing this hydrogenation, our planning was confounded by the poor reactivity of the resulting lactam. We circumvented this problem by reducing the lactam to a primary amine, which proved to be an excellent substrate for the unprecedented, highly convergent, high yielding, and completely diastereoselective Pictet-Spengler cyclization with the lemonose appended hydroxyacetaldehyde. Advancement of the Pictet-Spengler product to (–)-lemonomycin then was accomplished in three steps that notably only succeeded in the order of deprotection, alcohol oxidation, and final arene oxidation. The synthesis contains thirty-five total reactions from commercially available materials. The longest linear sequence is seventeen steps, counted from either glycinamide hydrochloride or D-threonine. The total yield of (–)-lemonomycin is 1.2% from glycinamide hydrochloride and 4.1% from D-threonine.

With the completion of the total synthesis of (–)-lemonomycin, the major goal of this project has been accomplished. Two areas of research, however, could warrant further attention. First, the synthesis of lemonose from D-threonine, though effective, is somewhat lengthy. A much shorter synthesis might be achieved if efficient and

enantioselective conditions can be developed for the hetero-Diels-Alder reaction proposed in Scheme 2.2. Second, our synthesis of lemonose has been applied to both enantiomeric series, thus providing (+)-*O*-oxoethyl-lemonose in addition to the (–)-*O*-oxoethyl-lemonose utilized for the synthesis (–)-lemonomycin. Use of (+)-*O*-oxoethyl-lemonose in an analogous Pictet-Spengler cyclization followed by the deprotection and oxidation steps would lead to a diastereomer of lemonomycin that might have improved biological activity. In a broader investigation, this strategy could be used for the incorporation of many different glycosyl units into the lemonomycin structure, leading to a library of potential antineoplastic agents and antibiotics with improved efficacy against highly resistant strains.

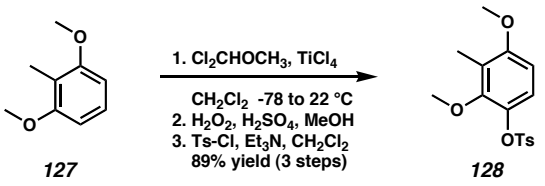
2.7 Experimental Procedures

Materials and Methods

Unless otherwise stated, reactions were performed at ambient temperature (typically 20 to 22 °C) in flame-dried glassware under a nitrogen or argon atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Acrolein was distilled under nitrogen immediately prior to use. All other commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV, anisaldehyde, permanganate, or CAM staining. ICN Silica gel (particle size 0.032-0.063 mm) was used for flash chromatography. Preparatory reversed-phase HPLC was performed on a Waters HPLC with a Waters Delta-Pak 25 x 100 mm, 15 μm C_{18} column equipped with a guard, utilizing a flow rate of 10 mL/min and a ramp of 1% B/min (A eluent = 95:5:0.05 water:acetonitrile:trifluoroacetic acid, B eluent = 5:95:0.01 water:acetonitrile:trifluoroacetic acid) with visualization at 270 nm. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a chiralcel AD column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd., with visualization at 254 nm. Optical rotations were measured with a Jasco P-1010 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on either a Varian Mercury 300 (at 300 MHz and 75 MHz respectively), Varian Mercury 500 (at 500 MHz and 125 MHz respectively), or a Varian Mercury 600 (600 MHz for proton only) spectrometer and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm),

multiplicity, coupling constant (Hz), and integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). UV spectra were measured on a Beckman-Coulter DU 7400 spectrophotometer. High-resolution mass spectra were obtained from the Caltech Mass Spectral Facility. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number (see individual structures for deposition number).

Preparation of Compounds



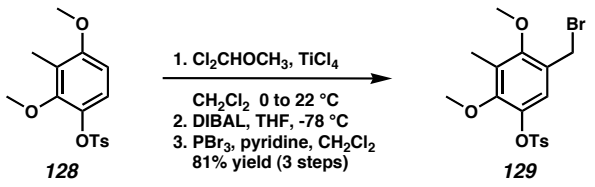
127 *128*

Tosyl Arene 128

To a –78 °C solution of 2,6-dimethoxytoluene (10.0 g, 65.7 mmol) and dichloromethyl methyl ether (7.7 mL, 85.4 mmol) in dichloromethane (65.7 mL) was added titanium tetrachloride (14.4 mL, 131 mmol) dropwise over 5 min. The reaction mixture was warmed to 20 °C over 30 min. The reaction mixture was then poured onto crushed ice (approximately 50 mL). After the ice had thawed, the mixture was extracted with dichloromethane (2 x 200 mL). The combined organics were dried over sodium sulfate and concentrated to provide the crude aldehyde (11.35 g, 96% yield).

To a solution of the crude aldehyde (11.35 g, 63 mmol) in methanol (90 mL) were added hydrogen peroxide (30% w/w in water, 9.3 mL, 82.0 mmol) and sulfuric acid (875 μL, 15.75 mmol). After 10 min, the reaction was quenched into a mixture of saturated aqueous sodium bicarbonate (100 mL) and water (100 mL). The mixture was extracted into dichloromethane (2 x 250 mL). The combined organics were dried over sodium sulfate and concentrated to yield the crude phenol (10.55 g, 97% yield).

To a solution of the phenol (10.15 g, 60.4 mmol) in dichloromethane (60 mL) were added triethylamine (8.4 mL, 60.4 mmol) and *p*-toluenesulfonyl chloride (11.5 g, 60.4 mmol). The reaction mixture was maintained at 20 °C for 3.5 h, after which acetonitrile (80 mL) and saturated aqueous sodium bicarbonate (50 mL) were added. After an additional hour the volatiles were removed in vacuo, and the residue was diluted with water (350 mL) and extracted into dichloromethane (2 x 250 mL). The combined organics were dried over magnesium sulfate, concentrated, and purified by flash chromatography on silica gel (10:90 to 20:80 ethyl acetate:hexanes eluent) to provide **128** (18.64 g, 96% yield) as a white solid. Alternatively, **128** could be obtained directly by recrystallization from ether with hexanes: R_F 0.67 (30:70 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 2H), 6.87 (d, *J* = 9.3 Hz, 1H), 6.49 (d, *J* = 8.7 Hz, 1H), 3.77 (s, 3H), 3.68 (s, 3H), 2.43 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 151.2, 145.1, 136.4, 133.2, 129.6, 128.4, 121.4, 120.4, 105.2, 60.9, 55.8, 21.9, 9.3; IR (NaCl/film) 2941, 1597, 1483, 1371, 1177, 1111 cm^{-1}; HRMS (FAB) calc'd for $[C_{16}H_{18}O_5S+H]^+$: *m/z* 323.0953, found 323.0965.



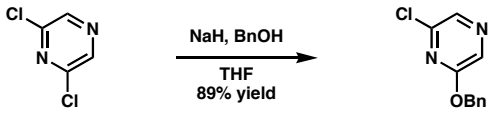
Benzylic Bromide 129

To a 0 °C solution of **128** (12.2 g, 37.8 mmol) and dichloromethyl methyl ether (6.8 mL, 75.7 mmol) in dichloromethane (75 mL) was added titanium tetrachloride (12.5 mL, 113.6 mmol). The solution was allowed to warm to 22 °C for 3 h, after which the reaction was quenched into ice water (500 mL). The mixture was extracted into dichloromethane (2 x 250 mL). The combined organics were dried over sodium sulfate and concentrated to provide the crude aldehyde (13.22 g, 99.7% yield).

To a –78 °C solution of the aldehyde (13.22 g, 37.7 mmol) in tetrahydrofuran (75 mL) was added DIBAL (8.07 mL, 45.3 mmol) dropwise over 5 min. The reaction mixture was maintained at –78 °C for 15 min, after which additional DIBAL (3.35 mL, 18.9 mmol) was added. After an additional 15 min, aqueous sodium potassium tartrate (200 mL) was added. The reaction mixture was allowed to warm to 22 °C with vigorous stirring for 1.5 h. The mixture was extracted with diethyl ether (3 x 200 mL). The combined organics were dried over magnesium sulfate and concentrated to provide the crude alcohol (13.05 g, 98% yield).

To a 0 °C solution of the alcohol (13.05 g, 37.1 mmol) and pyridine (2.99 mL, 37.1 mmol) in dichloromethane (37 mL) was added a solution of phosphorus tribromide (2.99 mL, 31.5 mmol) in dichloromethane (37 mL) dropwise over 7 min. After 10 min, the reaction mixture was filtered through silica gel with dichloromethane. The filtrate

was concentrated to yield analytically pure bromide **129** (12.65 g, 82.5% yield) as a white powder: R_F 0.55 (30:70 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 6.6, 1.8 Hz, 2H), 7.33 (d, *J* = 7.8 Hz, 2H), 6.88 (s, 1H), 4.43 (s, 2H), 3.82 (s, 3H), 3.74 (s, 3H), 2.46 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 152.5, 145.6, 138.9, 133.1, 129.9, 128.7, 127.2, 126.9, 122.9, 61.3, 61.1, 27.8, 21.9, 10.1; IR (NaCl/film) 2943, 1598, 1482, 1374, 1191, 1177, 991, 843, 769 cm^{-1}; HRMS (FAB+) calc'd for $[C_{17}H_{19}O_5SBr]^{\bullet+}$: *m/z* 414.0136, found 414.0145.

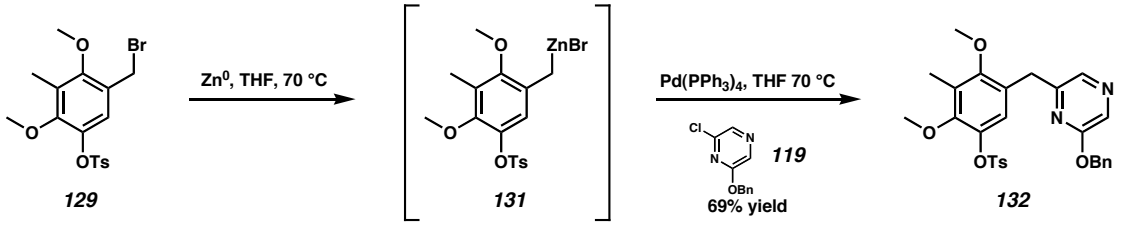


130 *119*

Chloropyrazine 119

To a suspension of sodium hydride (60% suspension in mineral oil, 1.47 g, 36.85 mmol) in tetrahydrofuran (67 mL) was added benzyl alcohol (3.47 mL, 33.56 mmol) (caution: hydrogen evolution). After 15 min, 2,6-dichloropyrazine (5.0 g, 33.56 mmol) was added in portions over 5 min (caution: exotherm). After 5.5 h, the reaction mixture was diluted with diethyl ether (250 mL) and washed with water (250 mL) followed by saturated aqueous sodium chloride (100mL). The organics were dried over magnesium sulfate, concentrated, and purified by flash chromatography on silica gel (3:97 to 7:93 ethyl acetate:hexanes eluent) to provide **119** as a white solid: R_F 0.38 (10:90 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (s, 1H), 8.17 (s, 1H), 7.48-7.35 (comp m, 5H), 5.39 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 145.6, 135.7, 135.6,

133.5, 128.8, 128.7, 128.6, 69.1; IR (NaCl/film) 1565, 1523, 1408, 1361, 1305, 1175, 1002 cm^{-1}; HRMS (EI+) calc'd for $[C_{11}H_9N_2OCl]^{\bullet+}$: *m/z* 220.0403, found 220.0408.



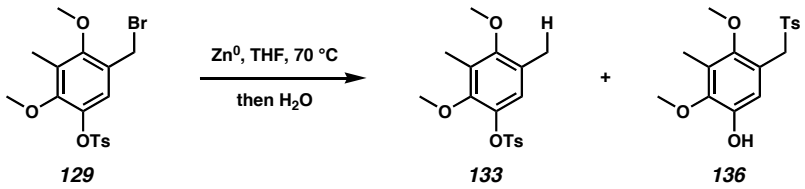
Bisarene 132

The yield of this reaction varied unpredictably from trial to trial. The following procedure is a representative example.

To a suspension of zinc dust (1.57 g, 24 mmol) in THF (4 mL) was added ethereal hydrogen chloride (2 M, 60 μL, 120 μmol). After 20 min, the mixture was cooled to –78 °C and evacuated to 1 torr for 20 min to effect deoxygenation. The suspension was then heated to reflux.

To the refluxing suspension of zinc dust was added a degassed solution of bromide **129** (500 mg, 1.20 mmol) in tetrahydrofuran (4 mL) via cannula. After 10 min, the reaction mixture was cooled to 22 °C and passed through a schlenk filter into a solution of chloropyrazine **119** (265 mg, 1.2 mmol) and tetrakis(triphenylphosphine)palladium(0) (69 mg, 60 μmol) in tetrahydrofuran (4 mL). The reaction mixture was heated to reflux for 5 h, cooled to 22 °C, and diluted with water (100 mL). The mixture was extracted with ethyl acetate (2 x 50 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (20:80 to 25:75 ethyl acetate:hexanes eluent) to provide

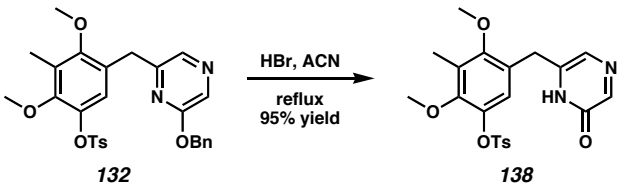
bisarene **132** (430.5 mg, 69% yield) as an off-white foam: R_F 0.25 (30:70 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.94 (s, 1H), 7.72 (d, *J* = 8.7 Hz, 2H), 7.42-7.31 (comp m, 5H), 7.24 (d, *J* = 8.1 Hz, 2H), 6.84 (s, 1H), 5.34 (s, 2H), 3.96 (s, 2H), 3.72 (s, 3H), 3.63 (s, 3H), 2.42 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4155.9, 152.0, 150.6, 145.3, 138.9, 136.6, 135.8, 133.4, 133.3, 129.7, 128.6, 128.5, 128.4, 128.2, 127.3, 126.7, 122.6, 67.9, 61.0, 60.9, 34.9, 21.8, 10.1; IR (NaCl/film) 2941, 1536, 1482, 1416, 1371, 1191, 1177, 1008 cm^{-1}; HRMS (FAB+) calc'd for $[C_{28}H_{28}N_2O_6S+H]^+$: *m/z* 521.1746, found 521.1722.



Toluene 133 and Phenol 136

To a refluxing suspension of zinc dust (653.7 mg, 10.0 mmol) in tetrahydrofuran (2.5 mL) was added ethereal hydrogen chloride (2 M, 25 μL, 50 μmol). After 10 min, a solution of bromide **129** (207.7 mg, 500 μmol) in tetrahydrofuran (2.5 mL) was added dropwise over 5 min. After an additional 10 min, the reaction was quenched with water (1 mL), cooled to 22 °C, diluted with diethyl ether (35 mL), and washed with water (50 mL) followed by saturated aqueous sodium chloride (25 mL). The organic layer was dried over magnesium sulfate, concentrated, and purified by flash chromatography on silica gel (15:85 to 30:70 ethyl acetate:hexanes eluent) to yield toluene **133** (59.7 mg, 36% yield) and phenol **136** (92.4 mg, 55% yield). Characterization of **133**: R_F 0.45

(30:70 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 6.79 (s, 1H), 3.67 (s, 3H), 3.64 (s, 3H), 2.45 (s, 3H), 2.18 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 149.6, 145.3, 138.7, 133.6, 129.8, 128.6, 126.9, 126.3, 122.5, 60.9, 60.1, 21.9, 16.0, 9.9; IR (NaCl/film) 2938, 1483, 1371, 1191, 1176, 1022, 844, 570, 551 cm^{-1}; HRMS (EI+) calc'd for $[C_{17}H_{20}O_5S]^{\bullet+}$: *m/z* 336.1031, found 336.1027. Characterization of **136**: R_F 0.18 (30:70 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (br s, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 6.97 (s, 1H), 4.93 (s, 2H), 3.73 (s, 3H), 3.71 (s, 3H), 2.45 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 152.3, 145.6, 138.8, 133.3, 129.9, 128.6, 127.1, 124.8, 122.9, 73.8, 62.0, 61.0, 21.9, 9.9; IR (NaCl/film) 3439 (br), 2943, 1483, 1371, 1191, 1176, 1110, 551 cm^{-1}; HRMS (EI+) calc'd for $[C_{17}H_{20}O_5S\text{-}H]^+$: *m/z* 335.0953, found 335.0946.

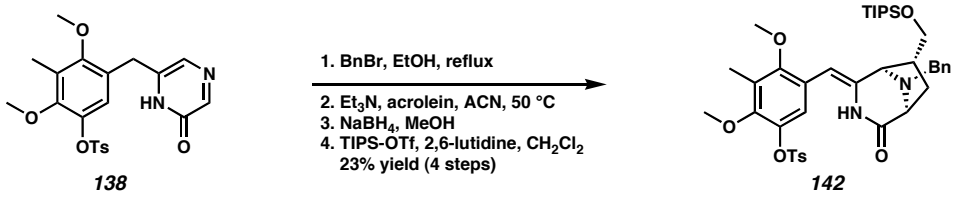


132 *138*

Pyrazinone 138

To a solution of pyrazine **132** (200 mg, 384 μmol) in acetonitrile (3.8 mL) was added aqueous hydrobromic acid (870 μL, 7.68 mmol). The reaction mixture was heated to reflux for 1 h, cooled to 22 °C, and quenched into a solution of saturated aqueous sodium bicarbonate (40 mL), saturated aqueous sodium thiosulfate (3 mL), and water (30 mL). The mixture was extracted with ethyl acetate (2 x 35 mL). The combined organics

were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (0:100 to 2:98 methanol:chloroform eluent) to yield pyrazinone **138** (156.8 mg, 95% yield) as a light yellow plastic: R_F 0.43 (50:50 acetone:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.19 (br s, 1H), 8.00 (s, 1H), 7.75 (d, *J* = 8.7 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.13 (s, 1H), 6.85 (s, 1H), 3.75 (s, 2H), 3.73 (s, 3H), 3.69 (s, 3H), 2.44 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 155.8, 151.7, 146.7, 145.6, 139.11, 139.10, 133.2, 129.9, 128.5, 127.3, 124.3, 123.7, 122.5, 61.0, 31.5, 21.9, 10.3; IR (NaCl/film) 2934, 1656, 1607, 1481, 1372, 1177, 994 cm^{-1}; HRMS (FAB+) calc'd for $[C_{21}H_{22}N_2O_6S+H]^+$: *m/z* 431.1277, found 431.1281.



138 *142*

Diazabycycle 142 from Pyrazinone 138

To a solution of pyrazinone **138** (343.5 mg, 799 μmol) in anhydrous ethanol (4 mL) was added benzyl bromide (925 μL, 7.99 mmol). The reaction mixture was heated to reflux for 20 h, cooled to 22 °C, concentrated to approximately 1 mL volume, and filtered through silica gel (0:100 to 20:80 methanol:chloroform eluent). Fractions containing the oxidopyrazinium (R_F 0.05, 5:95 methanol:chloroform) were concentrated to a violet oil that was used immediately.

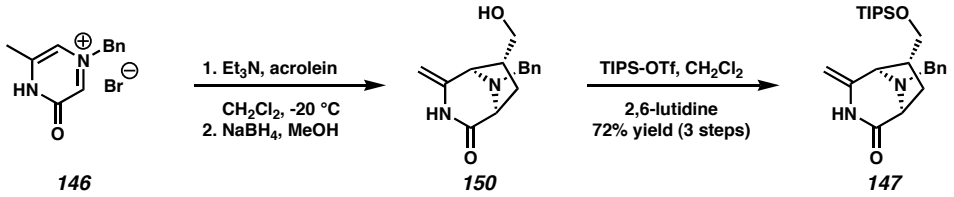
To a 50 °C solution of the oxidopyrazinium in acetonitrile (4 mL) were added triethylamine (122 μL, 879 μmol) and acrolein (59 μL, 879 μmol). After 2 h, the

reaction mixture was cooled to 22 °C, diluted with water (50 mL), and extracted into ethyl acetate (3 x 50 mL). The combined organics were dried over sodium sulfate and concentrated to provide the crude cycloadducts.

To a solution of the crude cycloadducts in methanol (8 mL) was added sodium borohydride (303 mg, 7.99 mmol) in portions over 10 min. After an additional 10 min, hydrochloric acid (1 M in water, 15 mL) was added. After an additional 10 min, the mixture was diluted with saturated aqueous sodium bicarbonate (100 mL) and extracted into ethyl acetate (3 x 50 mL). The combined organics were dried over sodium sulfate and concentrated to yield the crude alcohols.

To a solution of the crude mixture of alcohols in dichloromethane (8 mL) were added 2,6-lutidine (102 μL, 879 μmol) and triisopropylsilyl trifluoromethanesulfonate (236 μL, 879 μmol). After 1 h, additional 2,6-lutidine (46.4 μL, 400 μmol) and triisopropylsilyl trifluoromethanesulfonate (107 μL, 400 μmol) were added. After an additional 30 min, the reaction mixture was diluted with dichloromethane (100 mL) and washed with saturated aqueous sodium bicarbonate (50 mL). The organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (20:80 ethyl acetate:hexanes eluent) to provide diazabicyle **142** (135.5 mg, 23% yield) as a yellow oil: R_F 0.37 (30:70 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (br s, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.35-7.19 (comp m, 7H), 6.75 (s, 1H), 5.17 (s, 1H), 3.79 (d, *J* = 13.2 Hz, 1H), 3.72-3.58 (comp m, 4H), 3.67 (s, 3H), 3.64 (s, 3H), 3.52 (d, *J* = 7.2 Hz, 1H), 2.41 (s, 3H), 2.35 (m, 1H), 2.14 (s, 3H), 2.09 (dd, *J* = 12.6, 9.0 Hz, 1H), 1.69 (ddd, *J* = 12.6, 7.2, 6.0 Hz, 1H), 1.01 (br s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 153.9, 150.6, 145.5, 139.2, 138.3, 137.4, 135.1, 133.4, 129.9, 128.9, 128.6, 127.6,

127.5, 123.8, 122.2, 100.2, 66.0, 63.8, 62.8, 61.2, 60.3, 52.8, 47.4, 32.6, 22.1, 18.4, 12.3, 10.2; IR (NaCl/film) 2942, 2865, 1694, 1661, 1378, 1178, 1110, 993, 551 cm^{-1}; HRMS (FAB) calc'd for $[C_{40}H_{54}N_2O_7SSi+H]^+$: *m/z* 735.3499, found 735.3508.



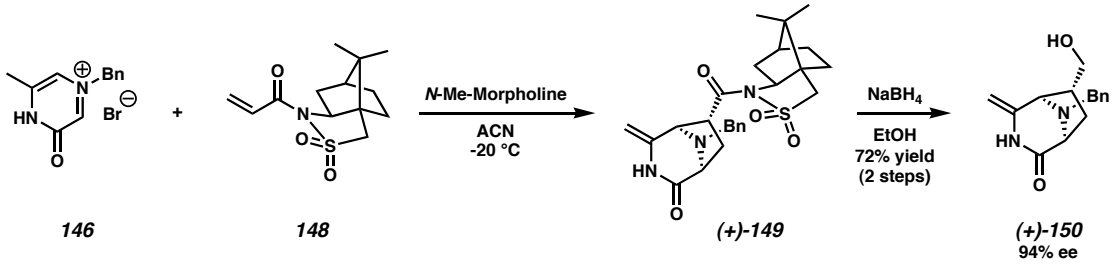
146 *150* *147*

Silyl Ether 147 by Racemic Dipolar Cycloaddition

To a suspension of oxidopyrazinium bromide **146** (10.0 g, 35.6 mmol) in dichloromethane (119 mL) was added triethylamine (14.9 mL, 107 mmol), affording a clear solution that was cooled to -20 °C over 15 min. Acrolein (7.15 mL, 107 mmol) was then added dropwise over 5 min. The reaction mixture was maintained at -20 °C for 74 h, then warmed to 0 °C and diluted with methanol (71 mL). Sodium borohydride (5.4 g, 142 mmol) was added in portions over 15 min. After an additional 15 min, the reaction mixture was warmed to room temperature, quenched with saturated aqueous ammonium chloride (200 mL) and water (300 mL), and extracted into dichloromethane (200 mL, 250 mL). The combined organics were dried over sodium sulfate, concentrated, and dried aziotropically from benzene (50 mL) to provide racemic **150**, which was used without further purification.

To a solution of crude **150** in dichloromethane (71 mL) were added 2,6-lutidine (4.57 mL, 39.2 mmol) and triisopropylsilyl trifluoromethanesulfonate (10.5 mL, 39.2 mmol). After 75 min the reaction was quenched with water (500 mL) and extracted into

dichloromethane (100 mL, 150 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (15:85 ethyl acetate:hexanes eluent) to provide racemic **147** (10.65 g, 72% yield) as a white solid: R_F 0.41 (30:70 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.21 (comp m, 6H), 4.21 (s, 1H), 4.08 (s, 1H), 3.77 (d, *J* = 12.9 Hz, 1H), 3.71 (d, *J* = 13.2 Hz, 1H), 3.65 (s, 1H), 3.63-3.54 (comp m, 2H), 3.51 (d, *J* = 6.9 Hz, 1H), 2.34 (app ddd, *J* = 14.3, 9.3, 5.3 Hz, 1H), 2.09 (dd, *J* = 13.4, 9.5 Hz, 1H), 1.69 (ddd, *J* = 13.2, 7.2, 5.2 Hz, 1H), 1.02 (br s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 142.7, 138.4, 128.8, 128.3, 127.2, 90.6, 65.9, 63.2, 61.2, 52.5, 47.1, 32.3, 18.3, 12.2; IR (NaCl/film) 3195, 2943, 2866, 1687, 1650, 1105 cm^{-1}; HRMS (FAB) calc'd for $[C_{24}H_{38}N_2O_2Si+H]^+$: *m/z* 415.2781, found 415.2786.



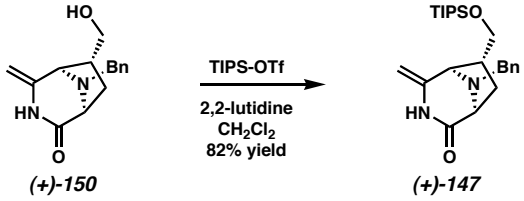
Diazabicycles (+)-149 and (+)-150

To a chilled (-20 °C) suspension of **146** (421.5 mg, 1.5 mmol) in acetonitrile (15 mL) were added **148** (485 mg, 1.8 mmol) and *N*-methylmorpholine (495 μL, 4.5 mmol), affording a clear solution. The reaction mixture was maintained at -20 °C for 72 h, after which ethanol (15 mL) and sodium borohydride (570 mg, 15 mmol) were added. The reaction mixture was warmed to 20 °C for 4.5 h, after which additional sodium

borohydride (570 mg, 15 mmol) was added. After an addition 1.5 h the reaction was quenched with saturated aqueous ammonium chloride (125 mL) and extracted with ethyl acetate (100 mL, 50 mL). The organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (40:60 to 85:15 ethyl acetate:hexanes eluent) to provide **(+)-150** (278 mg, 72% yield, 94.7% ee) as a colorless oil: R_F 0.11 (70:30 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (br s, 1H), 7.38-7.25 (comp m, 5H), 4.32 (d, *J* = 1.2 Hz, 1H), 4.15 (br s, 1H), 3.81 (d, *J* = 13.2 Hz, 1H), 3.73 (m, 1H), 3.72 (d, *J* = 12.9 Hz, 1H), 3.60 (d, *J* = 6.0 Hz, 1H), 3.57 (m, 1H), 3.56 (s, 1H), 2.81 (br s, 1H), 2.37 (m, 1H), 2.21 (dd, *J* = 12.9, 9.0 Hz, 1H), 2.09 (ddd, *J* = 13.2, 7.3, 5.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 141.7, 137.7, 129.0, 128.7, 127.8, 91.2, 66.2, 63.2, 63.0, 52.6, 45.5, 32.9; IR (NaCl/film) 3354, 3210, 2936, 1676, 1317 cm^{-1}; HRMS (FAB) calc'd for $[C_{15}H_{18}N_2O_2+H]^+$: *m/z* 259.1447, found 259.1457; $[\alpha]_D^{23}$ +44.2° (*c* 0.5, $CHCl_3$). HPLC analysis (Chiracel AD column, 10:90 2-propanol:hexanes, 1 mL/min, λ = 254 nm) showed the product to be of 94.7% ee (t_{fast} = 17.95 min, major; t_{slow} = 22.28 min, minor).

An analytical sample of the intermediate cycloadduct **(+)-149** was prepared by flash chromatography on silica gel (20:20:60 acetone:dichloromethane:hexanes eluent): R_F 0.33 (25:25:50 acetone:dichloromethane:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (br s, 1H), 7.32-7.22 (comp m, 5H), 4.37 (d, *J* = 1.2 Hz, 1H), 4.32 (d, *J* = 0.6 Hz, 1H), 3.94 (d, *J* = 13.2 Hz, 1H), 3.89 (dd, *J* = 8.1, 4.8 Hz, 1H), 3.75 (br d, *J* = 7.2 Hz, 1H), 3.68 (br s, 1H), 3.59 (dd, *J* = 8.7, 4.2 Hz, 1H), 3.57 (d, *J* = 13.2 Hz, 1H), 3.41 (s, 2H), 3.06 (ddd, *J* = 13.2, 7.8, 3.9 Hz, 1H), 2.15 (dd, *J* = 13.5, 9.0 Hz, 1H), 2.06 (dd, *J* = 13.5, 7.8 Hz, 1H), 1.96-1.79 (comp m, 4H), 1.46-1.30 (comp m, 2H), 0.92 (s, 3H), 0.75 (s, 3H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 171.3, 170.9, 139.2, 138.1, 128.8, 128.5, 127.5, 93.8, 65.8, 63.4, 63.3, 53.3, 52.1, 49.1, 48.5, 47.9, 44.8, 38.5, 33.0, 31.3, 26.6, 20.7, 20.0; IR (NaCl/film) 3313, 3199, 2958, 1695, 1653, 1330, 1211, 1133 cm^{-1}; HRMS (FAB) calc'd for $[C_{25}H_{31}N_3O_4S+H]^+$: *m/z* 470.2114, found 470.2127; $[\alpha]_D^{25}$ +137.3° (*c* 0.5, acetone).

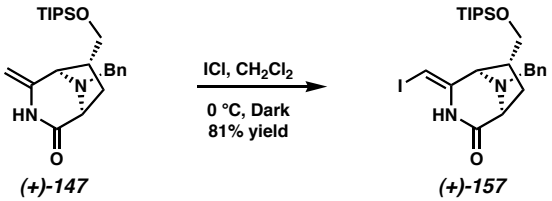


(+)-150 *(+)-147*

Silyl ether (+)-147

To a solution of **(+)-150** (1.9 g, 7.36 mmol) in dichloromethane (25 mL) were added 2,6-lutidine (1.03 mL, 8.83 mmol) and triisopropylsilyl trifluoromethanesulfonate (2.37 mL, 8.83 mmol). After 15 min, the reaction was quenched with water (150 mL) and extracted with dichloromethane (50 mL, 30 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (15:85 to 30:70 ethyl acetate:hexanes eluent) to provide **(+)-147** (2.50 g, 82% yield) as a colorless oil: R_F 0.41 (30:70 ethyl acetate:hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.21 (comp m, 6H), 4.21 (s, 1H), 4.08 (s, 1H), 3.77 (d, *J* = 12.9 Hz, 1H), 3.71 (d, *J* = 13.2 Hz, 1H), 3.65 (s, 1H), 3.63-3.54 (comp m, 2H), 3.51 (d, *J* = 6.9 Hz, 1H), 2.34 (app ddd, *J* = 14.3, 9.3, 5.3 Hz, 1H), 2.09 (dd, *J* = 13.4, 9.5 Hz, 1H), 1.69 (ddd, *J* = 13.2, 7.2, 5.2 Hz, 1H), 1.02 (br s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 142.7, 138.4, 128.8, 128.3, 127.2, 90.6, 65.9, 63.2, 61.2, 52.5, 47.1, 32.3, 18.3, 12.2; IR (NaCl/film) 3195, 2943,

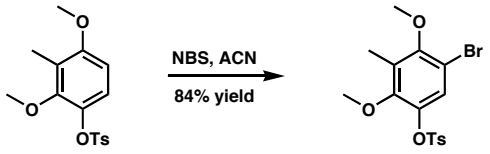
2866, 1687, 1650, 1105 cm^{-1}; HRMS (FAB) calc'd for $[C_{24}H_{38}N_2O_2Si+H]^+$: *m / z* 415.2781, found 415.2786; $[\alpha]_D^{23}$ +25.7° (*c* 1.5, acetone).



Iodoenamide (+)-157

(Note: reaction run in a foil-wrapped flask to exclude light.) To a cooled (0 °C) solution of **(+)-147** (10.65 g, 25.7 mmol) in dichloromethane (128 mL) was added a cooled (0 °C) solution of iodine monochloride (6.26 g, 38.6 mmol) in dichloromethane (38.6 mL) via cannula over 5 min. After 30 min, additional iodine monochloride (1.25 g, 7.7 mmol) in dichloromethane (7.7 mL) was added. After an additional 15 min, the reaction was quenched with saturated aqueous sodium bisulfite (100 mL) followed by saturated aqueous sodium bicarbonate (100 mL). After stirring vigorously for 15 min (caution: gas evolution) the reaction mixture was diluted with water (150 mL) and the phases were separated. The aqueous phase was extracted with dichloromethane (150 mL), and the combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (10:90 ethyl acetate:hexanes eluent) to provide **(+)-157** (11.32 g, 82% yield) as a colorless oil: R_F 0.65 (30:70 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (br s, 1H), 7.33-7.24 (comp m, 5H), 4.98 (s, 1H), 3.85 (s, 1H), 3.75 (d, *J* = 13.2 Hz, 1H), 3.63 (d, *J* = 13.2 Hz, 1H), 3.64-3.54 (comp m, 2H), 3.52 (d, *J* = 7.2 Hz, 1H), 2.33 (m, 1H), 2.09 (dd, *J* = 13.2, 9.3 Hz, 1H),

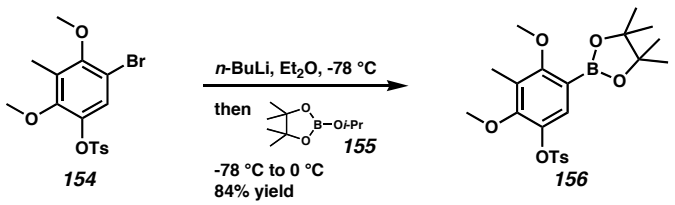
1.69 (ddd, J = 13.2, 7.2, 5.5 Hz, 1H), 1.02 (br s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 144.1, 137.7, 128.7, 128.5, 127.5, 65.7, 63.5, 62.8, 52.6, 46.6, 32.1, 18.3, 12.2; IR (NaCl/film) 2941, 2864, 1703, 1632, 1280, 1104, 683 cm^{-1}; HRMS (FAB) calc'd for $[C_{24}H_{37}IN_2O_2Si+H]^+$: m/z 541.1748, found 541.1755; $[\alpha]_D^{25}$ +47.3° (c 1.0, acetone).



128 *154*

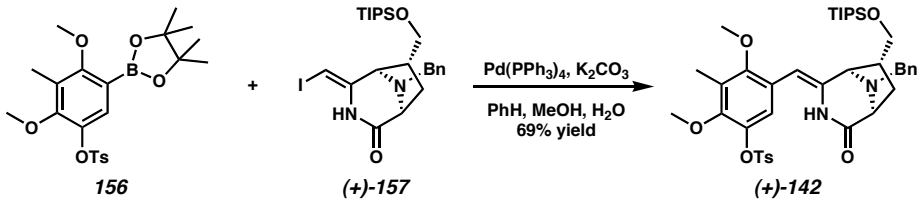
Aryl Bromide 154

To a solution of arene **128** (1.0 g, 3.1 mmol) in acetonitrile (10 mL) was added *N*-bromosuccinimide (580 mg, 3.2 mmol). After 10.5 h the reaction mixture was diluted with ethyl acetate (150 mL), washed with saturated aqueous sodium bicarbonate (100 mL), dried over sodium sulfate, concentrated, and filtered through a pad of silica gel (30:70 ethyl acetate:hexanes eluent) to provide **154** (1.04 g, 84% yield) as a white solid: R_F 0.67 (30:70 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 7.8 Hz, 2H), 7.15 (s, 1H), 3.77 (s, 3H), 3.69 (s, 3H), 2.47 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 151.1, 145.6, 139.1, 132.9, 129.8, 128.5, 128.2, 124.7, 110.9, 61.1, 60.6, 22.0, 10.7; IR (NaCl/film) 2940, 1469, 1377, 1177, 554 cm^{-1}; HRMS (FAB) calc'd for $[C_{16}H_{17}BrO_5S+H]^+$: m/z 401.0058, found 401.0045.



Arylboronic ester 156

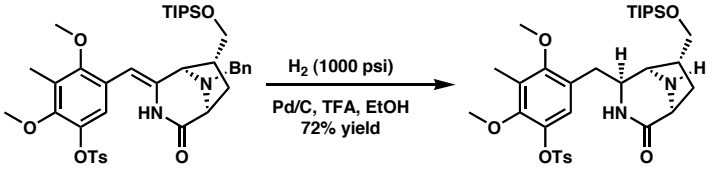
To a chilled (-78 °C) solution of **154** (2.5 g, 6.23 mmol) in anhydrous diethyl ether (62 mL) was added *n*-butyllithium (4.3 mL, 2.5M solution in hexanes, 10.9 mmol) dropwise over 5 min. After 20 min a solution of 2-isopropoxy-4,4,5,5-tetramethyldioxaborolane (**155**, 2.5 mL, 12.5 mmol) in anhydrous diethyl ether (41 mL) was added via cannula over 5 min. The reaction mixture was then warmed to -40 °C over 20 min and quenched with saturated aqueous ammonium chloride (50 mL). After warming to 20 °C, the mixture was diluted with water (100 mL) and extracted with diethyl ether (2 x 100 mL). The combined organics were dried over magnesium sulfate, concentrated, and purified by flash chromatography on silica gel (10:90 to 20:80 ethyl acetate:hexanes eluent) to provide **156** (2.35 g, 84% yield) as a colorless oil: R_F 0.65 (30:70 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.22 (s, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 2.46 (s, 3H), 2.13 (s, 3H), 1.32 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 154.0, 145.0, 138.2, 133.0, 129.5, 128.3, 128.1, 126.2, 83.6, 62.1, 60.7, 24.8, 21.7, 9.5; IR (NaCl/film) 2979, 2935, 1597, 1358, 1178, 1143 cm^{-1}; HRMS (FAB) calc'd for $[C_{22}H_{29}BO_7S+H]^+$: m/z 449.1805, found 449.1819.



Styrene (+)-142

To a solution of aryl boronic ester **156** (3.1 g, 6.9 mmol) and iodoenamide **(+)-157** (3.75 g, 6.9 mmol) in benzene (138 mL) were added methanol (27.6 mL), aqueous potassium carbonate (2.0 M, 13.8 mL, 27.6 mmol) and tetrakis(triphenylphosphine)-palladium (399 mg, 345 μmol, 5 mol%). The reaction mixture was deoxygenated by twice freezing under vacuum, flushing with argon, and melting. The reaction mixture was then sealed under argon and heated to 70 °C for 3.5 h. The mixture was then cooled to 23 °C, diluted with water (50 mL) and saturated aqueous sodium chloride (50 mL), and extracted with ethyl acetate (100 mL) followed by dichloromethane (100 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (15:85 to 20:80 ethyl acetate:hexanes eluent) to provide **(+)-142** (3.47 g, 69% yield) as a yellow oil: R_F 0.37 (30:70 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (br s, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.35-7.19 (comp m, 7H), 6.75 (s, 1H), 5.17 (s, 1H), 3.79 (d, *J* = 13.2 Hz, 1H), 3.72-3.58 (comp m, 4H), 3.67 (s, 3H), 3.64 (s, 3H), 3.52 (d, *J* = 7.2 Hz, 1H), 2.41 (s, 3H), 2.35 (m, 1H), 2.14 (s, 3H), 2.09 (dd, *J* = 12.6, 9.0 Hz, 1H), 1.69 (ddd, *J* = 12.6, 7.2, 6.0 Hz, 1H), 1.01 (br s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 153.9, 150.6, 145.5, 139.2, 138.3, 137.4, 135.1, 133.4, 129.9, 128.9, 128.6, 127.6, 127.5, 123.8, 122.2, 100.2, 66.0, 63.8, 62.8, 61.2, 60.3, 52.8, 47.4, 32.6, 22.1, 18.4, 12.3, 10.2; IR (NaCl/film) 2942, 2865, 1694, 1661, 1378,

1178, 1110, 993, 551 cm^{-1}; HRMS (FAB) calc'd for $[C_{40}H_{54}N_2O_7SSi+H]^+$: *m/z* 735.3499, found 735.3508; $[\alpha]_D^{25}$ +40.1° (*c* 0.5, acetone).

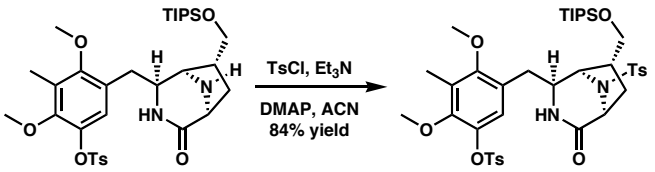


(+)-142 *(–)-158*

Lactam (–)-158

To an ethanol (58 mL) solution of **(+)-142** (2.13 g, 2.90 mmol) were added trifluoroacetic acid (4.5 mL, 58 mmol) and palladium on carbon (10% w/w, 4.26 g). The reaction mixture was pressurized to 1000 psi with hydrogen in a stainless steel reaction vessel for 28 h. The reaction mixture was then diluted with a mixture of water (175 mL), saturated aqueous sodium bicarbonate (175 mL), and saturated aqueous sodium chloride (175 mL), and extracted with ethyl acetate (150 mL, 2 x 100 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (0:100 to 5:95 triethylamine:chloroform eluent) to provide **(–)-158** (1.345 g, 72% yield) and a colorless oil: R_F 0.52 (10:90 methanol:chloroform); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 6.76 (s, 1H), 5.30 (s, 1H), 3.79-3.68 (comp m, 6H), 3.67 (s, 3H), 3.59 (app q, *J* = 8.5 Hz, 1H), 3.47 (s, 1H), 2.69 (dd, *J* = 14.0, 4.0 Hz, 1H), 2.63-2.49 (comp m, 2H), 2.47 (s, 3H), 2.23-2.04 (comp m, 2H), 2.15 (s, 3H), 1.62 (ddd, *J* = 12.8, 6.6, 6.6 Hz, 1H), 1.07 (br s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 156.1, 150.9, 145.5, 138.9, 133.2, 129.9, 128.5, 127.3, 125.7, 122.2, 66.3, 61.0, 60.8, 60.3, 60.0, 58.8, 38.6, 35.2, 33.0, 22.1, 18.4, 12.2,

10.3; IR (NaCl/film) 2943, 2866, 1678, 1483, 1377, 1178, 1109, 1008 cm^{-1}; HRMS (FAB) calc'd for $[C_{33}H_{50}N_2O_7SSi+H]^+$: *m/z* 647.3186, found 647.3183; $[\alpha]_D^{23}$ -15.9° (*c* 1.0, acetone).

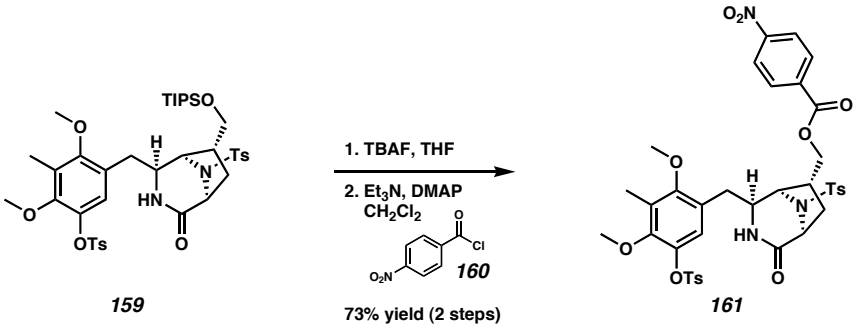


158 *159*

Tosamide 159

To a solution of **158** (200 mg, 310 μmol) in acetonitrile (6.2 mL) were added triethylamine (130 μL, 930 μmol), *N,N*-dimethylaminopyridine (19 mg, 155 μmol), and *p*-toluenesulfonyl chloride (88.7 mg, 465 μmol). The reaction mixture was maintained at 20 °C for 1.5 h, diluted with ethyl acetate (100 mL), washed with saturated aqueous ammonium chloride (50 mL) followed by saturated aqueous sodium chloride (50 mL), dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (40:60 to 50:50 ethyl acetate:hexanes) to provide **159** (208 mg, 84% yield) as a colorless oil: R_F 0.30 (50:50 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.4 Hz, 2H), 7.77 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 7.8 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 6.72 (s, 1H), 5.19 (s, 1H), 4.35 (s, 1H), 4.18 (d, *J* = 6.6 Hz, 1H), 3.89 (m, 1H), 3.70 (s, 3H), 3.67 (s, 3H), 3.61 (dd, *J* = 9.8, 5.6 Hz, 1H), 3.49 (app t, *J* = 9.9 Hz, 1H), 2.72-2.53 (comp m, 3H), 2.48 (s, 3H), 2.40 (s, 3H), 2.17 (dd, *J* = 12.9, 8.7 Hz, 1H), 2.16 (s, 3H), 1.67 (ddd, *J* = 12.9, 6.6, 6.3 Hz, 1H), 1.10 (br s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 156.3, 155.7, 151.3, 145.7, 144.4, 139.1, 137.1, 133.3, 130.1, 130.0, 128.6, 127.6,

125.0, 122.1, 65.0, 61.1, 61.0, 60.8, 60.4, 56.9, 39.8, 34.3, 32.3, 22.0, 21.8, 18.3, 12.1, 10.3; IR (NaCl/film) 3334, 3200, 2943, 2866, 1687, 1483, 1376, 1176, 1182, 1107, 1007, 995, 664, 551 cm^{-1}; HRMS (FAB) calc'd for $[C_{40}H_{56}N_2O_9S_2Si+H]^+$: *m/z* 801.3275, found 801.3296.



159 161

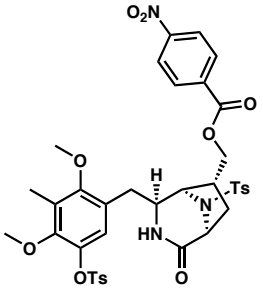
Nitrobenzoate 161

To a solution of **159** (175 mg, 219 μmol) in tetrahydrofuran (4.4 mL) was added tetrabutylammonium fluoride (1 M in tetrahydrofuran, 328 μL, 328 μmol). After 10 min, the reaction mixture was diluted with ethyl acetate (50 mL), washed with water (50 mL) followed by saturated aqueous sodium chloride (35 mL), dried over sodium sulfate, concentrated, and filtered through a pad of silica gel (ethyl acetate eluent) to provide the alcohol (140 mg, 99% yield), which was used without further purification.

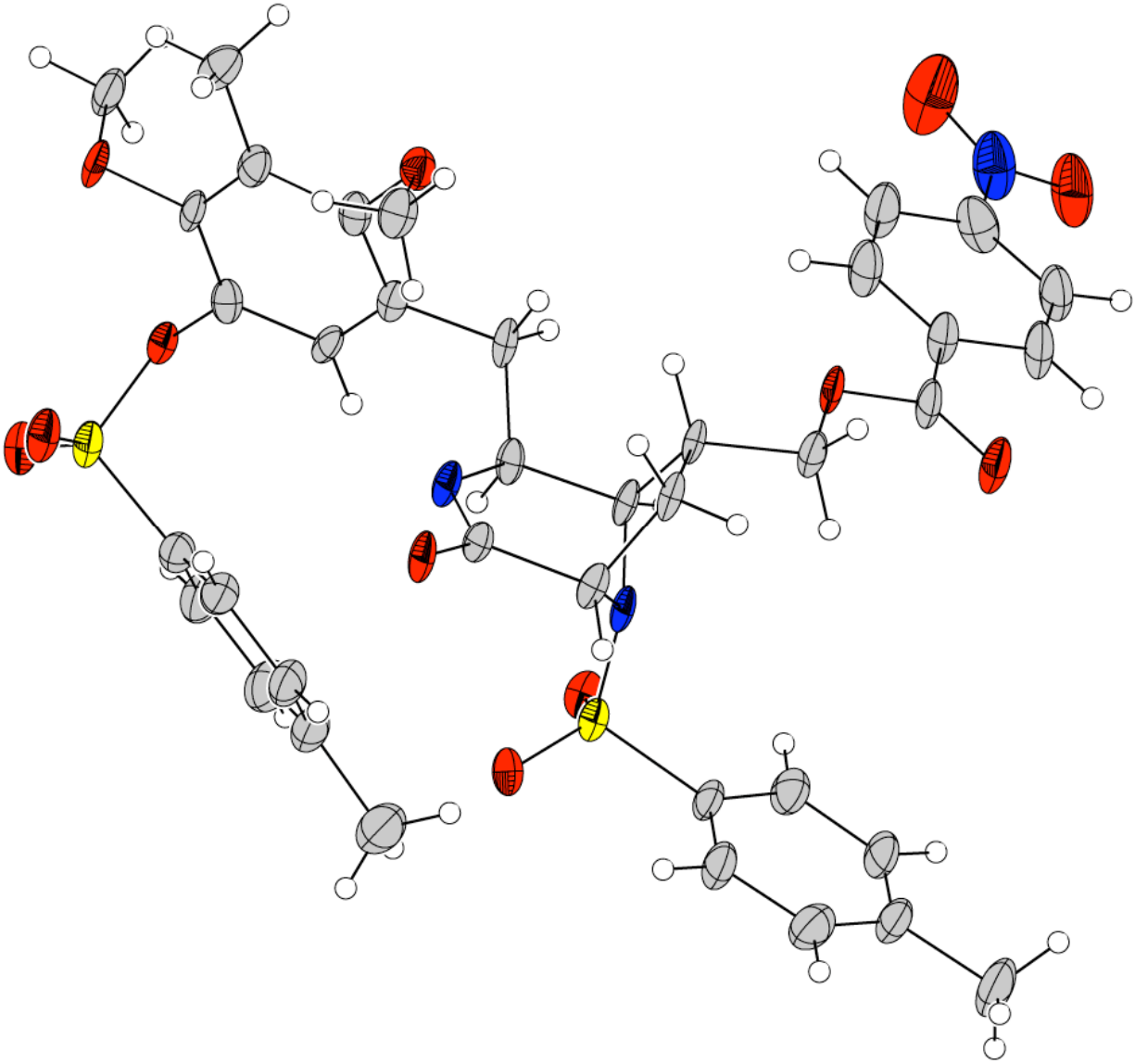
To a solution of the alcohol (60 mg, 93 μmol) in dichloromethane (1.9 mL) were added *N,N*-dimethylaminopyridine (5.7 mg, 46.5 μmol), triethylamine (25.9 μL, 186 μmol), and 4-nitrobenzoyl chloride (25.9 mg, 139.5 μmol). After 10 min the reaction mixture was diluted with dichloromethane (35 mL), washed with water (35 mL), dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel

(60:40 ethyl acetate:hexanes eluent) to provide **161** (54.5 mg, 74% yield) as a white, crystalline solid. Crystals of sufficient quality for X-ray analysis were grown from acetone:water by slow evaporation: m.p. 156.5-158 °C (corrected for benzanilide, mp. 163-163.5 °C); R_F 0.47 (85:15 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.7 Hz, 2H), 8.21 (d, *J* = 8.7 Hz, 2H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.79 (d, *J* = 9.3 Hz, 2H), 7.36 (d, *J* = 9.0 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 6.85 (s, 1H), 5.22 (s, 1H), 4.43 (dd, *J* = 11.1, 6.6 Hz, 1H), 4.38-4.28 (comp m, 2H), 4.26 (d, *J* = 6.6 Hz, 1H), 3.93 (ddd, *J* = 8.4, 4.4, 4.1 Hz, 1H), 3.67 (s, 3H), 3.65 (s, 3H), 3.00 (ddd, *J* = 14.3, 7.7, 6.9 Hz, 1H), 2.69 (dd, *J* = 13.7, 5.0 Hz, 1H), 2.59 (dd, *J* = 13.8, 8.7 Hz, 1H), 2.46 (s, 3H), 2.42 (s, 3H), 2.37 (dd, *J* = 13.2, 9.0 Hz, 1H), 2.11 (s, 3H), 2.02 (ddd, *J* = 13.2, 6.6, 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 164.6, 156.1, 151.3, 151.0, 145.8, 144.8, 139.1, 136.6, 135.2, 133.2, 131.0, 130.3, 130.0, 128.6, 127.6, 127.5, 124.1, 124.0, 122.2, 67.1, 61.0, 60.94, 60.91, 60.4, 56.7, 36.0, 35.2, 32.2, 22.0, 21.8, 10.3; IR (NaCl/film) 3338, 3207, 2944, 1726, 1688, 1528, 1349, 1275, 1176, 1161, 1105, 1003, 721 cm^{-1}; HRMS (FAB) calc'd for $[C_{38}H_{39}N_3O_{12}S_2+H]^+$: *m/z* 794.2054, found 794.2047.

Crystal structure of 161



161



Crystal data and structure refinement for 161 (CCDC 219709).

Empirical formula	$C_{38}H_{38}N_3O_{12}S_2 \cdot C_3H_6O$
Formula weight	850.91
Crystallization Solvent	Acetone
Crystal Habit	Blade
Crystal size	0.59 x 0.21 x 0.07 mm^3
Crystal color	Colorless

Data Collection

Preliminary Photos	Rotation	
Type of diffractometer	Bruker SMART 1000	
Wavelength	0.71073 Å MoKa	
Data Collection Temperature	100(2) K	
q range for 4790 reflections used in lattice determination	2.31 to 27.48°	
Unit cell dimensions	a = 11.907(2) Å	a= 66.875(2)°
	b = 13.420(2) Å	b= 69.845(3)°
	c = 14.819(3) Å	g = 75.856(3)°
Volume	2028.1(6) $Å^3$	
Z	2	
Crystal system	Triclinic	
Space group	P-1	
Density (calculated)	1.393 Mg/m^3	

F(000)	894
Data collection program	Bruker SMART v5.054
q range for data collection	1.56 to 28.18°
Completeness to q = 28.18°	88.5 %
Index ranges	$-15 \leq h \leq 15$, $-17 \leq k \leq 17$, $-19 \leq l \leq 18$
Data collection scan type	ω scans at 3 ϕ settings
Data reduction program	Bruker SAINT v6.022
Reflections collected	17713
Independent reflections	8831 [R_{int}= 0.1081]
Absorption coefficient	0.202 mm^{-1}
Absorption correction	None
Max. and min. transmission (predicted)	0.9860 and 0.8903

Structure solution and Refinement

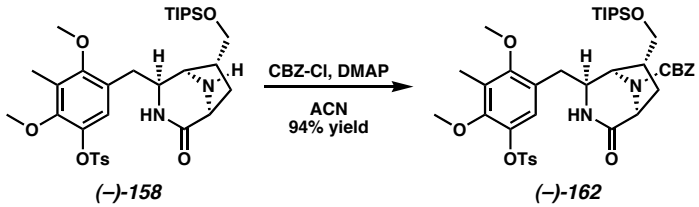
Structure solution program	SHELXS-97 (Sheldrick, 1990)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Geometric positions
Structure refinement program	SHELXL-97 (Sheldrick, 1997)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	8831 / 5 / 517
Treatment of hydrogen atoms	Riding
Goodness-of-fit on F^2	1.605

Final R indices [I>2s(I), 4683 reflections]	R1 = 0.0784, *w*R2 = 0.1558
R indices (all data)	R1 = 0.1543, *w*R2 = 0.1704
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma 2(Fo2)$
Max shift/error	0.001
Average shift/error	0.000
Largest diff. peak and hole	1.430 and -0.784 e.Å^{-3}

Special Refinement Details

Refinement of F2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F2, conventional R-factors (R) are based on F, with F set to zero for negative F2. The threshold expression of F2 > 2σ(F2) is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

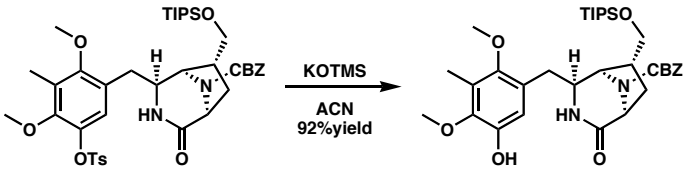
All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.



(–)-158 *(–)-162*

Carbamate (–)-162

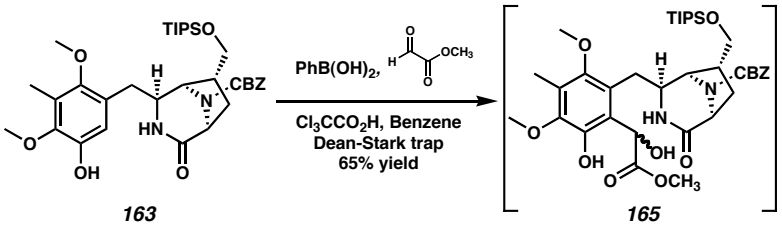
To a solution of **(–)-158** (700 mg, 1.08 mmol) in acetonitrile (21.6 mL) were added *N,N*-dimethylaminopyridine (463 mg, 3.8 mmol) and benzyl-chloroformate (543 μL, 3.8 mmol). After 40 min, the reaction was quenched into saturated aqueous ammonium chloride (150 mL) and extracted into ethyl acetate (3 x 50 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (25:25:50 ethyl acetate:dichloromethane:hexanes eluent) to provide **(–)-162** (794 mg, 94% yield) as a white foam: R_F 0.46 (70:30 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$, 50°C) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.35-7.23 (comp m, 7H), 6.74 (s, 1H), 5.36 (s, 1H), 5.17 (d, *J* = 12.3 Hz, 1H), 5.08 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 6.6 Hz, 1H), 4.33 (s, 1H), 3.93 (m, 1H), 3.69 (s, 3H), 3.64 (s, 3H), 3.62 (m, 1H), 3.48 (app t, *J* = 9.5 Hz, 1H), 2.70 (dd, *J* = 14.0, 3.5 Hz, 1H), 2.65-2.54 (comp m, 2H), 2.42 (s, 3H), 2.15 (dd, *J* = 12.6, 8.7 Hz, 1H), 2.13 (s, 3H), 1.65 (ddd, *J* = 12.8, 6.6, 6.0 Hz, 1H), 1.05 (br s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$, 50 °C) δ 170.9, 156.2, 153.8, 151.2, 145.4, 139.0, 136.3, 133.5, 129.8, 128.6, 128.5, 128.2, 128.0, 127.3, 125.1, 122.1, 67.5, 65.7, 60.9, 60.7, 59.1, 58.8, 56.4, 39.1, 34.0, 32.6, 21.9, 18.3, 12.3, 10.3; IR (NaCl/film) 2943, 2866, 1709, 1685, 1378, 1178, 1109 cm^{-1}; HRMS (FAB) calc'd for $[C_{41}H_{56}N_2O_9SSi+H]^+$: *m/z* 781.3554, found 781.3528; $[\alpha]_D^{25}$ -20.8° (*c* 1.0, acetone).



(–)-162 *(–)-163*

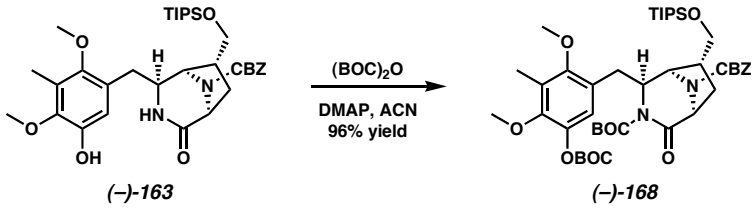
Phenol (–)-163

To a solution of **(–)-162** (1.0 g, 1.28 mmol) in acetonitrile (25 mL) was added potassium trimethylsilanoate (90% grade, 1.82 g, 12.8 mmol). The reaction mixture was maintained at 20 °C for 1.5 h, quenched with saturated aqueous ammonium chloride (25 mL), and stirred vigorously for 10 min. The mixture was diluted with saturated aqueous sodium chloride (150 mL), acidified to pH 5 with concentrated hydrochloric acid, and extracted with ethyl acetate (3 x 100 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (50:50 to 80:20 ethyl acetate:hexanes eluent) to provide **(–)-163** (735 mg, 92% yield) as a white foam: R_F 0.42 (70:30 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$, 50 °C) δ 7.37-7.29 (comp m, 5H), 6.59 (s, 1H), 6.03 (s, 1H), 5.66 (s, 1H), 5.19 (d, *J* = 12.3 Hz, 1H), 5.10 (d, *J* = 12.3 Hz, 1H), 4.52 (d, *J* = 6.6 Hz, 1H), 4.39 (s, 1H), 4.05 (br s, 1H), 3.77 (s, 3H), 3.69-3.61 (comp m, 4H), 3.52 (m, 1H), 2.76 (dd, *J* = 13.8, 3.9 Hz, 1H), 2.71-2.61 (comp m, 2H), 2.23 (s, 3H), 2.20 (dd, *J* = 13.2, 8.7 Hz, 1H), 1.67 (ddd, *J* = 12.8, 6.6, 6.0 Hz, 1H), 1.08 (br s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$, 50 °C) δ 171.3, 154.0, 150.5, 145.9, 145.5, 136.4, 128.6, 128.2, 128.0, 125.5, 125.2, 114.2, 67.5, 65.8, 60.8, 59.0, 56.6, 39.3, 34.1, 32.7, 18.3, 12.3, 10.2; IR (NaCl/film) 3306, 2943, 2865, 1709, 1679, 1457, 1418, 1307, 1112 cm^{-1}; HRMS (FAB) calc'd for $[C_{34}H_{50}N_2O_7Si+H]^+$: *m/z* 627.3465, found 627.3469; $[\alpha]_D^{24}$ -30.5° (*c* 1.0, acetone).



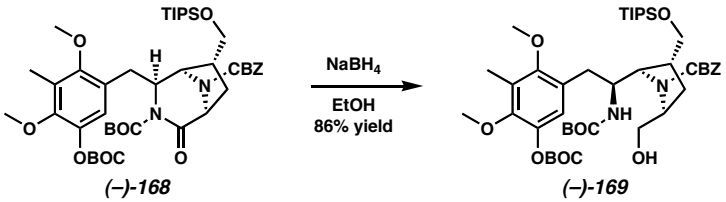
Ester 165

To a solution of phenol **163** (25 mg, 40 μmol) in benzene (2 mL) were added trichloroacetic acid (6.5 mg, 40 μmol), phenylboronic acid (10 mg, 80 μmol), and methyl glyoxylate (25 μL, approximately 280 μmol). The reaction mixture was heated to reflux with removal of water by a Dean-Stark trap for 48 h. After cooling, the mixture was diluted with ethyl acetate (50 mL) and washed with a mixture of saturated aqueous sodium bicarbonate (25 mL) and saturated aqueous sodium chloride (25 mL). The organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (80:20:0 to 80:20:3 ethyl acetate:hexanes:methanol eluent) to provide ester **165** (18 mg, 65% yield) as a 4:3 mixture of diastereomers: R_F 0.27 (70:30 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$, peaks of the major diastereomer) δ 7.39-7.28 (comp m, 5H), 5.90 (br s, exchangeable, 1H) 5.35 (s, 1H), 5.19 (d, *J* = 12.6 Hz, 1H), 5.08 (d, *J* = 12.0 Hz, 1H), 4.52-4.43 (comp m, 2H), 4.03 (s, 1H), 3.98 (app dd, *J* = 5.1, 2.1 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.78-3.60 (comp m, 5H), 2.99-2.61 (comp m, 3H), 2.25 (s, 3H), 2.22-2.14 (m, 1H), 1.68-1.59 (m, 1H), 1.55 (br s, exchangeable, 1H), 1.16-1.01 (comp m, 21H); MS (APCI) calc'd for $[C_{37}H_{54}N_2O_{10}Si+H]^+$: *m/z* 715.4, found 715.4.



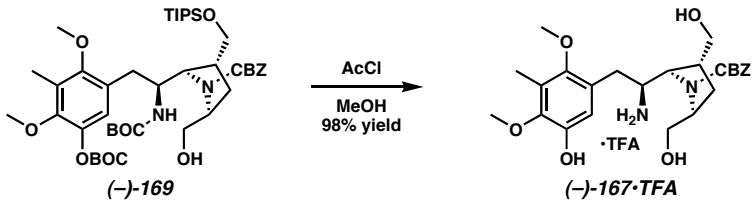
Imide (–)-168

To a solution of **(–)-163** (960 mg, 1.53 mmol) in acetonitrile (15.3 mL) were added *N,N*-dimethylaminopyridine (935 mg, 7.66 mmol) and di-*tert*-butyl dicarbonate (1.67 g, 7.66 mmol). The reaction mixture was maintained at 20 °C for 25 min, diluted with water (150 mL), and extracted with ethyl acetate (2 x 75 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (10:90 to 20:80 ethyl acetate:hexanes) to provide **(–)-168** (1.22 g, 96% yield) as an off-white foam: R_F 0.63 (30:70 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$, 50°C) δ 7.40-7.22 (comp m, 5H), 6.86 (s, 1H), 5.16 (d, *J* = 12.8 Hz, 1H), 5.04 (d, *J* = 12.8 Hz, 1H), 4.64 (app d, *J* = 6.6 Hz, 2H), 3.93 (d, *J* = 4.5 Hz, 1H), 3.81 (s, 3H), 3.68 (s, 3H), 3.61 (br s, 1H), 3.28 (dd, *J* = 9.3, 7.8 Hz, 1H), 3.10 (dd, *J* = 13.7, 4.4 Hz, 1H), 2.84-2.70 (comp m, 2H), 2.21 (s, 3H), 2.17 (dd, *J* = 13.8, 8.7 Hz, 1H), 2.05 (m, 1H), 1.57 (s, 9H), 1.54 (s, 9H), 0.99 (br s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$, 50 °C) δ 169.8, 155.2, 153.4, 152.4, 151.8, 150.1, 140.7, 136.3, 128.6, 128.1, 127.9, 126.2, 124.8, 121.2, 84.1, 83.4, 79.4, 67.4, 65.8, 60.7, 60.1, 57.1, 38.5, 32.9, 30.6, 28.6, 28.2, 28.0, 18.2, 12.2, 10.2; IR (NaCl/film) 2943, 2866, 1762, 1717, 1275, 1234, 1154 cm^{-1}; HRMS (FAB) calc'd for $[C_{44}H_{66}N_2O_{11}Si+H]^+$: *m/z* 827.4515, found 827.4498; $[\alpha]_D^{23}$ -26.2° (*c* 1.0, $CHCl_3$).



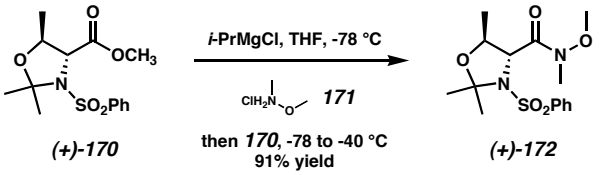
Protected aminotriol (–)-169

To a solution of **(–)-168** (1.22 g, 1.47 mmol) in ethanol (14.7 mL) was added sodium borohydride (1.12 g, 29.5 mmol). The reaction mixture was maintained at 20 °C for 1 h 45 min, then quenched slowly (caution: gas evolution) with saturated aqueous ammonium chloride (100 mL), diluted with water (20 mL), and extracted with dichloromethane (50 mL, 2 x 25 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (25:75 to 35:65 ethyl acetate:hexanes eluent) to provide **(–)-169** (1.05 g, 86 % yield) as a white foam: R_F 0.27 (30:70 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$, 50 °C) δ 7.43-7.29 (comp m, 5H), 6.73 (s, 1H), 5.18 (s, 2H), 4.10 (m, 1H), 3.97-3.85 (comp m, 2H), 3.80 (dd, *J* = 11.6, 2.9 Hz, 1H), 3.75 (s, 3H), 3.63 (dd, *J* = 11.7, 6.6 Hz, 1H), 3.59-3.47 (comp m, 5H), 2.84 (br d, *J* = 11.7 Hz, 1H), 2.46 (br t, *J* = 11.6 Hz, 1H), 2.35 (m, 1H), 2.20 (s, 3H), 2.02-1.86 (comp m, 2H), 1.56 (s, 9H), 1.26 (s, 9H), 1.06 (br s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$, 50 °C) δ 157.5, 155.9, 155.2, 151.9, 149.6, 140.4, 136.5, 128.6, 128.3, 128.2, 127.2, 125.5, 121.6, 83.2, 79.2, 67.9, 67.2, 65.8, 65.3, 61.3, 60.7, 60.6, 55.0, 42.4, 33.1, 29.3, 28.5, 28.0, 18.3, 12.3, 10.1; IR (NaCl/film) 3353, 2943, 2866, 1761, 1698, 1275, 1233, 1156 cm^{-1}; HRMS (FAB) calc'd for $[C_{44}H_{70}N_2O_{11}Si+H]^+$: *m/z* 831.4828, found 831.4827; $[\alpha]_D^{24}$ -7.6° (*c* 1.0, acetone).



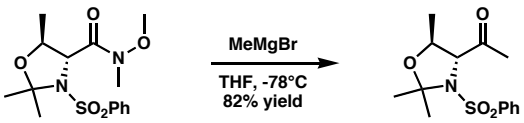
Aminotriol (–)-167

To a cooled (0 °C) solution of **(–)-169** (250 mg, 300 μmol) in methanol (6 mL) was added acetyl chloride (427 μL, 6 mmol) dropwise over 30 seconds. The reaction mixture was warmed to 20 °C for 9 h, concentrated, and purified by preparative HPLC to provide **(–)-167** trifluoroacetate (175 mg, 98% yield) as a colorless, highly viscous oil: R_F 0.11 (10:90 methanol:chloroform); ^{1}H NMR (300 MHz, CD_3OD, 50 °C) δ 7.32 (br s, 5H), 6.63 (s, 1H), 5.12 (br s, 2H), 4.11-4.01 (comp m, 2H), 3.99 (app t, *J* = 3.0 Hz, 1H), 3.90 (app td, *J* = 7.4, 2.4 Hz, 1H), 3.74 (s, 3H), 3.64 (s, 3H), 3.59-3.46 (comp m, 3H), 2.92 (br s, 1H), 2.75 (m, 1H), 2.50 (ddd, *J* = 13.8, 6.3, 3.7 Hz, 1H), 2.19 (s, 3H), 2.17 (dd, *J* = 15.3, 7.8 Hz, 1H), 2.02 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6, 75 °C) δ 154.7, 149.2, 145.8, 145.4, 136.3, 128.0, 127.4, 127.0, 124.0, 123.3, 115.2, 66.1, 63.0, 62.1, 60.9, 59.9, 59.1, 58.5, 54.6, 30.3, 28.4, 9.2; IR (NaCl/film) 3272, 2946, 2896, 1694, 1674, 1418, 1204, 1134 cm^{-1}; HRMS (FAB) calc'd for $[C_{25}H_{34}N_2O_7+H]^+$: *m/z* 475.2444, found 475.2445; $[\alpha]_D^{24}$ -11.4° (*c* 0.48, methanol).



Amide (+)-172

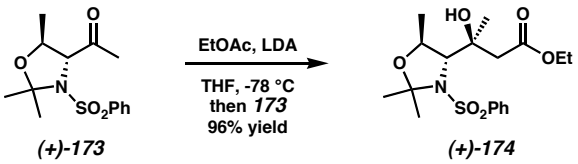
To a –40 °C suspension of *N,O*-dimethylhydroxylamine hydrochloride (**171**) (2.75 g, 28.3 mmol) in tetrahydrofuran (94 mL) was added a solution of isopropylmagnesium chloride in tetrahydrofuran (2 M, 28.2 mL, 56.4 mmol). After 15 min, a solution of ester **(+)-170** (5.90 g, 18.8 mmol) in tetrahydrofuran (37.7 mL) was added. The mixture was maintained at –40 °C for 3.5 h and then quenched with saturated aqueous ammonium chloride (200 mL). The phases were separated, and the aqueous layer was extracted with ethyl acetate (100 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (80:20 to 60:40 hexanes:ethyl acetate eluent) to provide amide **(+)-172** (5.88 g, 91% yield) as a white solid: R_F 0.27 (50:50 hexanes:ethyl acetate eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05-8.01 (comp m, 2H), 7.63-7.51 (m, 3H), 4.66 (d, *J* = 7.0 Hz, 1H), 4.26 (m, 1H), 3.80 (s, 3H), 3.23 (s, 3H), 1.54 (s, 3H), 1.49 (s, 3H), 1.35 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.8, 128.8, 128.0, 97.3, 74.8, 64.2, 61.4, 27.4, 18.8; IR (NaCl/film) 2982, 1677, 1447, 1344 cm^{-1}; HRMS (FAB) *m/z* calc'd for $[C_{15}H_{22}N_2O_5S+H]^+$: 343.1328, found 343.1312; $[\alpha]_D^{25}$ +71.9° (*c* 1.0, $CHCl_3$).



(+)-172 *(+)-173*

Ketone (+)-173

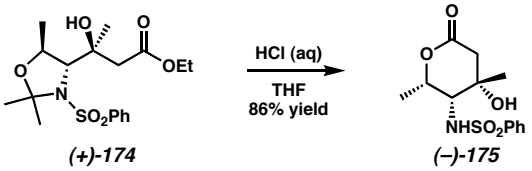
To a –78 °C solution of amide **(+)-172** (1.64 g, 4.79 mmol) in tetrahydrofuran (20 mL) was added methylmagnesium bromide (1.8 mL, 5.4 mmol). After 45 min, additional methylmagnesium bromide (1.8 mL, 5.4 mmol) was added. The solution was allowed to warm to 22 °C. The reaction mixture was quenched with saturated aqueous ammonium chloride (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organics were dried over sodium sulfate and evaporated. The residue was purified by flash chromatography on silica gel (4:1 to 1:1 hexanes:ethyl acetate eluent) to yield ketone **(+)-173** (1.30 g, 82% yield) as a white solid: R_F 0.38 (70:30 hexanes:ethyl acetate eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (m, 2H), 7.64-7.51 (comp m, 3H), 4.22 (m, 1H), 3.70 (d, *J* = 8.0 Hz, 1H), 2.42 (s, 3H), 1.69 (s, 3H), 1.49 (s, 3H), 1.26 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5, 139.7, 133.1, 129.2, 127.8, 98.2, 74.6, 72.8, 28.8, 25.8, 25.0, 17.9; IR (NaCl/film) 2987, 1716, 1344, 1157 cm^{-1}; HRMS (FAB) *m/z* calc'd for $[C_{14}H_{19}NO_4S+H]^+$: 298.1113, found 298.1101; $[\alpha]_D^{26}$ +148.0° (*c* 1.0, $CHCl_3$).



Ester (+)-174

To a 0 °C solution of diisopropylamine (11.3 mL, 80.9 mmol) in tetrahydrofuran (77 mL) was added *n*-butyllithium (30 mL, 76 mmol). After 20 min, the solution was cooled to -78 °C, and a solution of ethyl acetate (7.5 mL, 77 mmol) in tetrahydrofuran (154 mL) was added dropwise over 5 min. After 1 h, a solution of ketone **(+)-173** (4.83 g, 16.2 mmol) in tetrahydrofuran (81 mL) at -78 °C was added via cannula. After 2.5 h the reaction mixture was quenched with saturated aqueous ammonium chloride (100 mL). The mixture was allowed to warm to 22 °C and partitioned between water (100 mL) and ethyl acetate (50 mL). The aqueous phase was extracted with ethyl acetate (50 mL), and the combined organics were dried over magnesium sulfate. Solvent was evaporated and the residue was purified by flash chromatography on silica gel (10:10:80 to 15:15:70 ethyl acetate:dichloromethane:hexanes eluent) to provide aldol adduct **(+)-174** (6.01 g, 96% yield) as a colorless oil: R_F 0.61 (50:25:25 hexanes:dichloromethane:ethyl acetate eluent); ^{1}H NMR (300 MHz, C_6D_6) δ 7.92-7.89 (comp m, 2H), 6.93-6.90 (m, 3H), 4.52 (dq, *J* = 6.6, 2.0 Hz, 1H), 4.12 (d, *J* = 2.4 Hz, 1H), 4.08-3.90 (comp m, 2H), 3.30 (d, *J* = 17.0 Hz, 1H), 2.47 (d, *J* = 17.0 Hz, 1H), 1.62 (s, 3H), 1.49 (s, 3H), 1.33 (s, 3H), 0.96 (t, *J* = 7.0 Hz, 3H), 0.69 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 140.6, 133.2, 129.1, 128.6, 99.8, 74.9, 72.8, 72.0, 61.0, 42.9, 31.2, 28.8, 24.4, 22.5, 14.4; IR

(NaCl/film) 3480, 2986, 1710, 1447, 1346, 1204 cm^{-1}; HRMS (FAB) *m/z* calc'd for $[C_{18}H_{27}NO_6S+H]^+$: 386.1637, found 386.1637; $[\alpha]_D^{26}$ +64.0° (*c* 2.0, acetone).

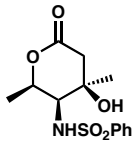


(+)-174 *(–)-175*

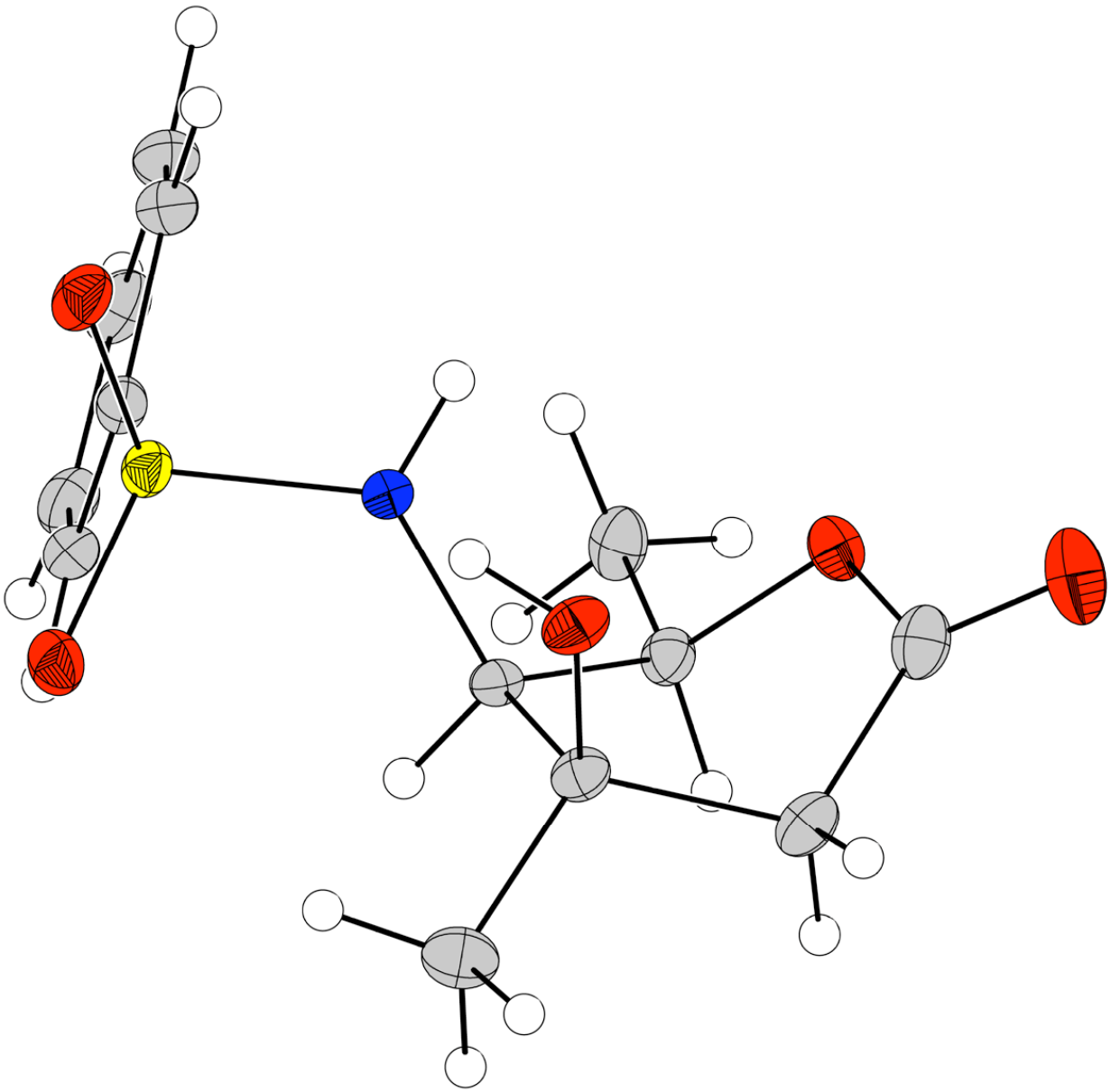
Lactone (–)-175

To a solution of ester **(+)-174** (0.467g, 1.21 mmol) in tetrahydrofuran (12 mL) was added aqueous hydrochloric acid (1 M, 0.242 mL, 0.242 mmol). After 13 h, the reaction was quenched with saturated aqueous sodium bicarbonate (50 mL), extracted with ethyl acetate (2 x 30 mL), and dried over sodium sulfate. Solvent was evaporated and the residue was purified by flash chromatography on silica gel (25:25:50 to 30:30:40 acetone:dichloromethane:hexanes eluent) to afford lactone **(–)-175** (0.312 g, 86% yield) as a white solid. Crystals of sufficient quality for X-ray analysis of lactone **(+)-175** (prepared analogously from L-threonine) were grown from dichloromethane by slow evaporation: uncorrected mp. 164-165 °C; R_F 0.20 (50:25:25 hexanes:dichloromethane: acetone eluent); ^{1}H NMR (300 MHz, acetone-d_6) δ 8.01-7.90 (comp m, 2H), 7.68-7.56 (comp m, 3H), 4.61 (dq, *J* = 6.6 , 4.5 Hz, 1H), 3.66 (d, *J* = 4.0 Hz, 1H), 2.76 (d, *J* = 16.0 Hz, 1H), 2.50 (d, *J* = 16.0 Hz, 1H), 1.20 (d, *J* = 6.6 Hz, 3H), 1.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 140.7, 133.2, 129.4, 127.3, 76.0, 69.9, 59.3, 43.2, 27.5, 16.6; IR (NaCl/film) 3496, 3289, 2996, 1738, 1448, 1337 cm^{-1}; HRMS (FAB) *m/z* calc'd for $[C_{13}H_{17}NO_5S+H]^+$: 300.0906, found 300.0909; $[\alpha]_D^{26}$ -74.2° (*c* 1.0, $CHCl_3$).

Crystal Structure of (+)-175



(+)-175



Crystal data and structure refinement for (+)-175 (CCDC 217756).

Empirical formula	$C_{13}H_{17}NO_5S$
Formula weight	299.34
Crystal Habit	Prism
Crystal size	0.35 x 0.31 x 0.26 mm^3
Crystal color	Colorless

Data Collection

Preliminary Photos	Rotation
Type of diffractometer	Bruker SMART 1000
Wavelength	0.71073 Å MoKa
Data Collection Temperature	100(2) K
q range for 21790 reflections used	
in lattice determination	2.77 to 28.06°
Unit cell dimensions	a = 8.0871(4) Å
	b = 8.2042(4) Å
	c = 20.6350(10) Å
Volume	1369.09(12) $Å^3$
Z	4
Crystal system	Orthorhombic
Space group	P212121
Density (calculated)	1.452 Mg/m^3
F(000)	632
Data collection program	Bruker SMART v5.054

q range for data collection	1.97 to 28.28°
Completeness to q = 28.28°	96.1 %
Index ranges	$-10 \leq h \leq 10$, $-10 \leq k \leq 10$, $-26 \leq l \leq 26$
Data collection scan type	ω scans at 7 ϕ settings
Data reduction program	Bruker SAINT v6.022
Reflections collected	27404
Independent reflections	3217 [R_{int}= 0.0507]
Absorption coefficient	0.255 mm^{-1}
Absorption correction	None
Max. and min. transmission (predicted)	0.9366 and 0.9159

Structure solution and Refinement

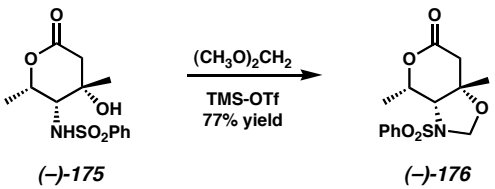
Structure solution program	SHELXS-97 (Sheldrick, 1990)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Difference Fourier map
Structure refinement program	SHELXL-97 (Sheldrick, 1997)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	3217 / 0 / 249
Treatment of hydrogen atoms	Unrestrained
Goodness-of-fit on F^2	2.819
Final R indices [$I>2\sigma(I)$, 3121 reflections]	R1 = 0.0288, *w*R2 = 0.0590
R indices (all data)	R1 = 0.0298, *w*R2 = 0.0591

Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.001
Average shift/error	0.000
Absolute structure parameter	0.02(5)
Largest diff. peak and hole	0.449 and -0.350 e.$Å^{-3}$

Special Refinement Details

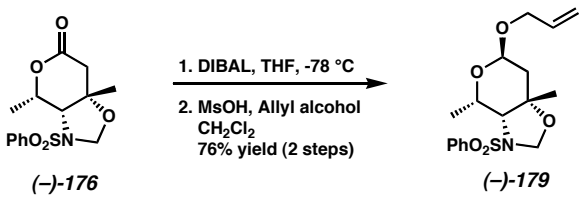
Refinement of F^2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.



Oxazolidine (–)-176

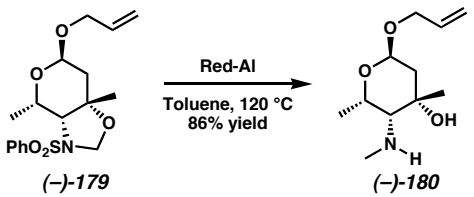
To a suspension of lactone **(–)-175** (2.92 g, 9.75 mmol) in dimethoxymethane (49 mL) at 0 °C was added trimethylsilyl trifluoromethanesulfonate (5.3 mL, 29 mmol) dropwise over 3 min. After 20 min, the reaction was quenched with saturated aqueous sodium bicarbonate (100 mL). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (75 mL). The combined organics were dried over magnesium sulfate, concentrated, and purified by flash chromatography on silica gel (15:15:70 to 30:30:40 acetone:dichloromethane:hexanes eluent) to provide oxazolidine **(–)-176** (2.34 g, 77% yield) as a white solid: R_F 0.46 (50:25:25 hexanes: dichloromethane:acetone eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95-7.90 (comp m, 2H), 7.75-7.58 (comp m, 3H), 5.23 (d, *J* = 7.2 Hz, 1H), 4.69 (d, *J* = 7.2 Hz, 1H), 4.49 (dq, *J* = 6.3 , 2.7 Hz, 1H), 3.80 (d, *J* = 2.7 Hz, 1H), 2.74 (d, *J* = 16.0 Hz, 1H), 2.54 (d, *J* = 16.0 Hz, 1H), 1.61 (d, *J* = 6.3 Hz, 3H), 0.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 137.8, 134.1, 129.8, 128.3, 82.0, 81.7, 75.0, 65.2, 40.9, 25.6, 17.3; IR (NaCl/film) 3430, 2902, 1765, 1446 cm^{-1}; HRMS (FAB) *m/z* calc'd for $[C_{14}H_{17}NO_5S+H]^+$: 312.0906, found 312.0909; $[\alpha]_D^{25}$ -151.0° (*c* 1.0, $CHCl_3$).



Bicycle (–)-179

To a –78 °C solution of oxazolidine **(–)-176** (1.94 g, 6.23 mmol) in tetrahydrofuran (62 mL) was added diisobutylaluminum hydride (2.2 mL, 12 mmol) dropwise over 1 min. After 30 min, the reaction was quenched with aqueous sodium potassium tartrate (1 M, 100 mL). Organics were extracted with ethyl acetate (2 x 50 mL), dried over magnesium sulfate, and concentrated. The residue was further dried by azeotropic removal of water with benzene. The crude residue was dissolved in dichloromethane (62 mL), and allyl alcohol (6.35 mL, 93.4 mmol) and methanesulfonic acid (0.81 mL, 1.2 mmol) were added. After 18 h, the reaction was quenched with saturated aqueous sodium bicarbonate (100 mL). The mixture was extracted with dichloromethane (50 mL), dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10:90 to 15:85 ethyl acetate:hexanes eluent) to afford bicycle **(–)-179** (1.67 g, 76% yield) as a colorless oil: R_F 0.17 (85:15 hexanes:ethyl acetate eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91-7.87 (comp m, 2H), 7.65-7.51 (comp m, 3H), 5.87 (m, 1H), 5.25 (appt. ddd, *J* = 17.1, 3.3, 1.8 Hz, 1H), 5.29-5.12 (comp m, 2H), 4.84 (dd, *J* = 8.1, 6.0 Hz, 1H), 4.81 (d, *J* = 5.7 Hz, 1H), 4.20 (ddt, *J* = 13.2, 5.7, 1.8 Hz, 1H), 4.04 (dq, *J* = 6.6, 2.7 Hz, 1H), 3.96 (ddt, *J* = 11.7, 5.1, 1.2 Hz, 1H), 3.53 (d, *J* = 2.4 Hz, 1H), 2.17 (dd, *J* = 15.6, 6.3 Hz, 1H), 1.64 (dd, *J* = 15.3, 8.4 Hz, 1H), 1.34 (d, *J* = 6.6 Hz, 3H), 0.65 (s, 3H); ^{13}C NMR (75

MHz, $CDCl_3$) δ 138.7, 134.8, 133.6, 129.5, 128.1, 117.1, 95.9, 81.4, 81.0, 68.4, 65.7, 65.6, 37.8, 26.3, 17.4; IR (NaCl/film) 2981, 1447, 1353, 1166 cm^{-1}; HRMS (FAB) *m/z* calc'd for $[C_{17}H_{23}NO_5S+H]^+$: 354.1375, found 354.1373; $[\alpha]_D^{26}$ -140.5° (*c* 1.00, $CHCl_3$).

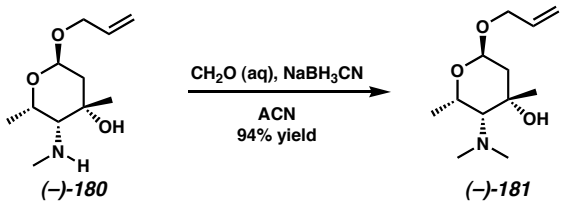


(–)-179 *(–)-180*

Glycoside (–)-180

To a solution of bicycle **(–)-179** (0.554 g, 1.57 mmol) in toluene (16 mL) was added Red-Al (65% w/w in toluene, 3.53 mL, 11.7 mmol). The mixture was heated to reflux for 2 h 45 min and cooled to 0 °C. Celite (1.0 g) and saturated aqueous sodium sulfate (1.0 mL) were added, in that order. The mixture was allowed to warm to 22 °C and filtered. The solids were washed with ethyl acetate (50 mL) and saturated aqueous sodium chloride (15 mL). The combined filtrates were phase-separated, and the aqueous phase was extracted with ethyl acetate (2 x 25 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (90:10:0.1:0.5 to 90:10:2:0.5 chloroform:ethyl acetate:methanol:triethylamine eluent) to provide glycoside **(–)-180** (0.290 g, 86% yield) as a colorless oil: R_F 0.09 (95:5 dichloromethane:methanol eluent); ^1H NMR (300 MHz, $CDCl_3$) δ 5.88 (m, 1H), 5.24 (appt. ddd, *J* = 17.7, 3.3, 1.5 Hz, 1H), 5.15 (appt. ddd, *J* = 10.5, 3.3, 1.8 Hz, 1H), 4.79 (d, *J* = 4.2 Hz, 1H), 4.16 (dq, *J* = 5.7, 0.9 Hz, 1H), 4.10 (ddt, *J* = 13.2, 4.8, 1.8 Hz, 1H), 3.89 (ddt, *J* = 13.2, 6.0, 1.5 Hz, 1H), 2.59 (s, 3H), 2.02 (s, 1H), 1.72 (appt. d, *J* = 14.1 Hz, 1H),

1.59 (dd, *J* = 13.8, 4.5 Hz, 1H), 1.41 (s, 3H), 1.26 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.7, 116.6, 90.0, 68.2, 68.0, 67.7, 64.9, 40.0, 38.7, 26.1, 18.5; IR (NaCl/flim) 3345, 2932, 1118 cm^{-1}; HRMS (FAB) *m/z* calc'd for $[C_{11}H_{20}NO_3+H]^+$: 216.1600, found 216.1603; $[\alpha]_D^{26}$ -185.3° (*c* 1.00, $CHCl_3$).

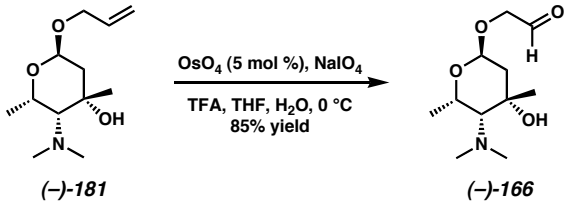


(–)-180 *(–)-181*

***N,N*-Dimethyl pyranose (–)-181**

To a solution of amine **(–)-180** (0.430 g, 2.00 mmol) in acetonitrile (20 mL) was added sodium cyanoborohydride (0.377 g, 6.00 mmol). After 5 min, aqueous formaldehyde (37% w/w in water, 0.75 mL, 10 mmol) was added. The mixture was stirred vigorously for 2 h, and the reaction was quenched with glacial acetic acid (0.86 mL). After concentrating to 5 mL volume, the solution was diluted with aqueous sodium hydroxide (1 M, 15 mL) and saturated aqueous sodium chloride (40 mL). The mixture was extracted with ethyl acetate (3 x 100 mL). The combined organics were dried over sodium sulfate and concentrated. The residue was purified by flash chromatography on silica gel (90:10:0.1:0.5 to 90:10:1.5:0.5 chloroform:ethyl acetate:methanol:triethylamine eluent) to yield dimethylamino pyranose **(–)-181** (0.429 g, 94% yield) as a colorless oil: R_F 0.45 (90:10 chloroform:methanol eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89 (m, 1H), 5.35-5.10 (comp m, 2H), 5.14 (appt. dd, *J* = 10.5, 1.8 Hz, 1H), 4.93 (t, *J* = 2.7 Hz, 1H), 4.25 (dq, *J* = 7.2, 2.7 Hz, 1H), 4.09 (ddt, *J* = 13.2, 5.1, 0.9 Hz, 1H), 3.91 (ddt, *J* = 13.2,

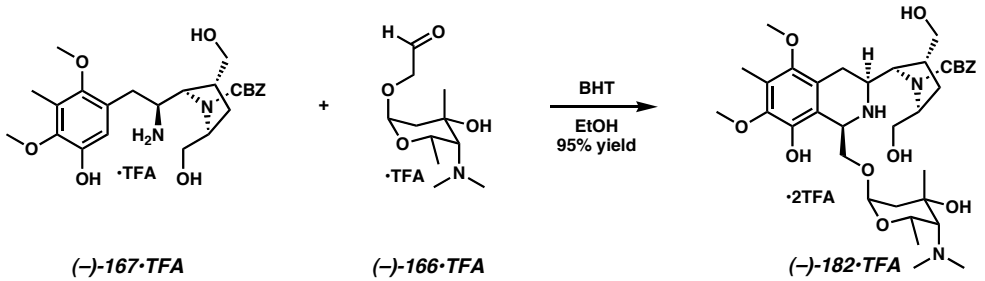
5.7, 1.5 Hz, 1H), 2.68 (s, 3H), 2.21 (d, *J* = 2.7 Hz, 1H), 1.88 (d, *J* = 2.7 Hz, 2H), 1.43 (s, 3H), 1.38 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.5, 116.3, 97.0, 69.4, 67.9, 66.2, 62.2, 45.0, 41.0, 29.5, 19.0; IR (NaCl/film) 3288, 2937, 1395, 1119 cm^{-1}; HRMS (FAB) *m/z* calc'd for $[C_{12}H_{22}NO_3 + H]^+$: 230.1756, found 230.1754; $[\alpha]_D^{24}$ -158.5° (*c* 1.0, acetone).



Glycosyloxyacetaldehyde (–)-166

To a 0 °C solution of glycoside **(–)-181** (0.060 g, 0.26 mmol) in tetrahydrofuran (4.8 mL) and water (0.48 mL) were added trifluoroacetic acid (0.10 mL, 1.3 mmol), osmium tetroxide (3.3 mg, 0.013 mmol), and sodium periodate (0.14 g, 0.65 mmol). The reaction mixture was maintained at 0 °C for 16 h and then quenched with aqueous potassium hydroxide (10 M, 0.13 mL). After diluting with ethanol (5 mL), the mixture was filtered through a pad of silica gel, concentrated, and purified by preparative thin layer chromatography (15:85 methanol:chloroform eluent) to afford aldehyde **(–)-166** as its trifluoroacetate salt (50.1 mg, 55% yield) and aldehyde **(–)-166** as the free base (18.4 mg, 30% yield): R_F 0.25 (10:90 methanol:chloroform eluent); ^{1}H NMR (300 MHz, CD_3OD) δ 4.90 (d, *J* = 4.5 Hz, 1H), 4.62 (appt. dt *J* = 8.4, 5.7 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 1H), 3.47 (m, 1H), 3.38 (m, 1H), 2.68 (s, 6H), 2.30 (s, 1H), 1.88 (dd, *J* = 13.8, 4.5 Hz, 1H), 1.78 (d, *J* = 14.4 Hz, 1H), 1.39 (s, 3H), 1.35 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75

MHz, CD_3OD) δ 97.8, 96.7, 69.7, 69.6, 69.2, 67.2, 65.5, 43.9, 40.4, 28.7, 18.0; IR (NaCl/film) 3290, 2937, 2836, 1682, 1127 cm^{-1}; $[\alpha]_D^{25}$ -122.5° (*c* 0.45, CH_2Cl_2).

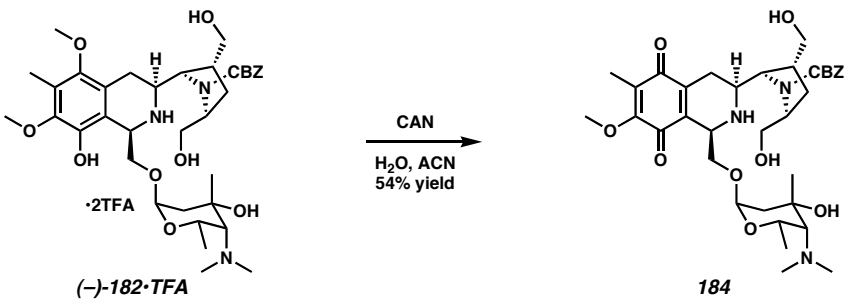


(–)-167·TFA *(–)-166·TFA* *(–)-182·TFA*

Tetrahydroisoquinoline (–)-182

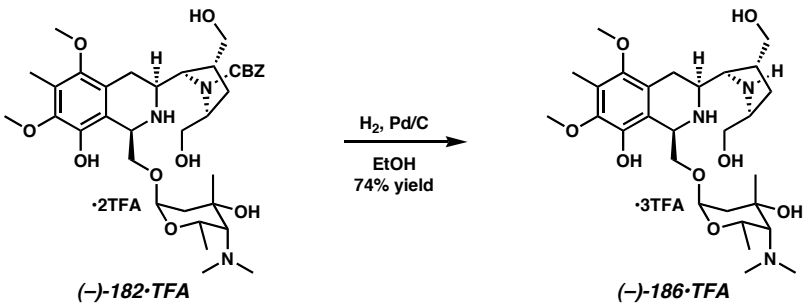
To neat **(–)-167** trifluoroacetate (50 mg, 85 μmol) were added 2,6-di-*tert*-butyl-4-methyl phenol (9.3 mg, 42.5 μmol) and a solution of **(–)-166** trifluoroacetate (50 mg, 144.7 μmol) in ethanol (1.7 mL). The reaction mixture was sealed under argon in a foil-wrapped vial at 20 °C. After 36 h, additional **(–)-166** (5 mg, 21.6 μmol) was added. After 63 h, the reaction mixture was concentrated and purified by preparative HPLC to provide **(–)-182** bis-trifluoroacetate (74 mg, 95% yield) as a colorless, highly viscous oil: R_F 0.27 (10:90 methanol:chloroform); ^1H NMR (300 MHz, CD_3OD, 45 °C) δ 7.43-7.32 (comp m, 5H), 5.29 (d, *J* = 12.0 Hz, 1H), 5.21 (d, *J* = 12.0 Hz, 1H), 5.12 (d, *J* = 3.3 Hz, 1H), 4.97 (s, 1H), 4.51 (br d, *J* = 7.8 Hz, 1H), 4.18 (m, 1H), 4.02 (br d, *J* = 8.7 Hz, 1H), 3.83 (app d, *J* = 9.9 Hz, 1H), 3.80-3.57 (comp m, 6H), 3.73 (s, 3H), 3.64 (s, 3H), 3.36 (d, *J* = 6.6 Hz, 1H), 3.04 (s, 6H), 3.01 (s, 1H), 2.62-2.46 (comp m, 2H), 2.21 (s, 3H), 2.13-2.01 (comp m, 3H), 1.93 (ddd, *J* = 21.9, 11.3, 10.8 Hz, 1H), 1.44 (d, *J* = 6.9 Hz, 3H), 1.19 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD, 50 °C) δ 159.5, 150.1, 146.8, 144.4, 137.4, 129.7, 129.4, 128.9, 126.0, 124.0, 115.5, 98.1, 72.1, 69.5, 67.9, 66.8, 64.9, 64.5, 63.9,

63.5, 61.7, 61.3, 61.2, 57.5, 55.4, 44.8, 39.9, 30.8, 30.5, 21.9, 18.6, 10.0; IR (NaCl/film) 3307, 3064, 2945, 1682, 1204, 1180, 1131 cm^{-1}; HRMS (FAB) calc'd for $[C_{36}H_{53}N_3O_{10}+H]^+$: *m/z* 688.3809, found 688.3835; $[\alpha]_D^{26}$ -71.3° (*c* 0.5, methanol).



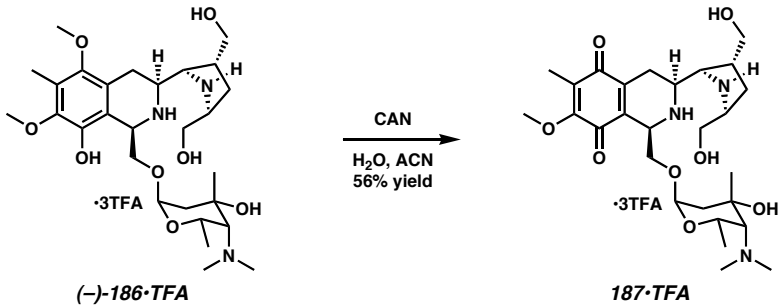
Quinone 184

To a 0 °C solution of **(–)-182** bis-trifluoroacetate (10 mg, 10.9 μmol) in acetonitrile (953 μL) was added a solution of ammonium cerium(IV) nitrate (14.9 mg, 27.2 μmol) in water (136 μL). After 10 min, the reaction was quenched into a mixture of saturated aqueous sodium bicarbonate (10 mL) and saturated aqueous sodium chloride (10 mL) and extracted into ethyl acetate (3 x 15 mL). The organics were dried over sodium sulfate, concentrated, and purified by preparative thin-layer chromatography on silica gel (15:85 methanol:chloroform eluent) to provide **184**: R_F 0.35 (10:90 methanol:chloroform); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.33 (comp m, 5H), 5.19 (d, *J* = 12.6 Hz, 1H), 5.13 (d, *J* = 12.3 Hz, 1H), 4.86 (br s, 1H), 4.29 (app d, *J* = 7.5 Hz, 1H), 4.18-4.10 (m, 1H), 3.99 (s, 3H), 3.84 (dd, *J* = 7.2, 2.7 Hz, 1H), 3.75-3.67 (m, 1H), 3.65-3.47 (comp m, 5H), 2.69 (d, *J* = 2.5 Hz, 1H), 2.64 (s, 6H), 2.45-2.36 (m, 1H), 2.08 (d, *J* = 2.7 Hz, 1H), 1.95 (s, 3H), 1.92-1.77 (comp m, 3H), 1.42-1.34 (comp m, 2H), 1.29 (d, *J* = 7.2 Hz, 3H), 1.15 (s, 3H).



Tetrahydroisoquinoline (–)-186

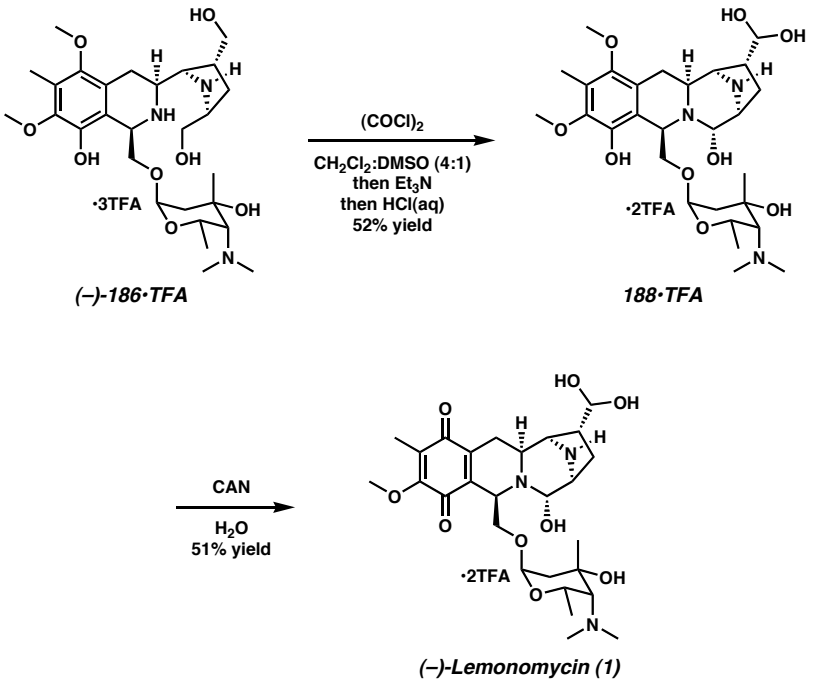
To a solution of **(–)-182** bis-trifluoroacetate (74 mg, 80.7 μmol) in ethanol (8 mL) was added palladium on carbon (10% w/w, 15 mg). The reaction mixture was purged and flushed with hydrogen, then maintained under a balloon of hydrogen for 30 min. The mixture was filtered through celite, concentrated, and purified by preparative HPLC to provide **(–)-186** tris-trifluoroacetate (53.5 mg, 74% yield) as a colorless, highly viscous oil: R_F 0.25 (10:90 methanol: chloroform, eluted twice); ^{1}H NMR (300 MHz, D_2O) δ 5.17 (s, 1H), 5.11 (d, *J* = 3.9 Hz, 1H), 4.66 (dd, *J* = 10.8, 3.3 Hz, 1H), 4.01-3.85 (comp m, 4H), 3.82-3.61 (comp m, 5H), 3.77 (s, 3H), 3.71 (s, 3H), 3.34 (dd, *J* = 16.8, 2.4 Hz, 1H), 3.04 (s, 6H), 3.00 (s, 1H), 2.89 (dd, *J* = 16.5, 12.6 Hz, 1H), 2.75 (m, 1H), 2.24 (s, 3H), 2.22-1.93 (comp m, 3H), 1.89 (d, *J* = 15.0 Hz, 1H), 1.52 (d, *J* = 7.2 Hz, 3H), 0.95 (s, 3H); ^{13}C NMR (125 MHz, D_2O) δ 148.2, 145.0, 142.9, 125.6, 122.3, 114.1, 96.2, 70.2, 67.2, 64.2, 64.0, 62.5, 62.1, 61.1, 61.0, 60.9, 60.1, 55.6, 54.2, 47.2, 43.5, 41.9, 37.3, 28.5, 27.9, 24.8, 17.5, 9.1; IR (NaCl/film) 3296, 2947, 1682, 1468, 1417, 1204, 1131, 1054, 1004, 800, 723 cm^{-1}; HRMS (FAB) calc'd for $[C_{28}H_{47}N_3O_8+H]^+$: *m/z* 554.3441, found 554.3463; $[\alpha]_D^{24}$ -83.1° (*c* 0.25, methanol).



(–)-186·TFA *187·TFA*

Quinone 187

To a 0 °C solution of **(–)-186** tris-trifluoroacetate (6.3 mg, 7.0 μmol) in acetonitrile (525 μL) and water (100 μL) was added a solution of ammonium cerium(IV) nitrate (9.6 mg, 17.5 μmol) in water (75 μL). After 15 min, the reaction mixture was diluted with water (3 mL) and purified by preparative HPLC to provide **187** tris-trifluoroacetate: R_F 0.25 (10:90 methanol:chloroform, eluted twice); ^{1}H NMR (600 MHz, D_2O) δ 5.15 (d, *J* = 6.0 Hz, 1H), 4.30 (dd, *J* = 10.8, 6.0 Hz, 1H), 4.01 (app q, *J* = 10.8 Hz, 1H), 3.91 (s, 3H), 3.96-3.89 (m, 1H), 3.87-3.81 (comp m, 2H), 3.80-3.73 (comp m, 2H), 3.61 (dd, *J* = 12.0, 10.8 Hz, 1H), 3.52-3.45 (m, 1H), 3.23-3.17 (comp m, 2H), 3.10-3.04 (comp m, 7H), 2.70-2.63 (m, 1H), 2.57 (app ddd, *J* = 18.0, 12.0, 3.6 Hz, 1H), 2.15-1.93 (comp m, 5H), 1.98 (s, 3H), 1.56 (d, *J* = 10.8 Hz, 1.37 (s, 3H); MS (APCI) calc'd for $[C_{27}H_{44}N_3O_8]^+$: *m/z* 538.4, found 538.7.



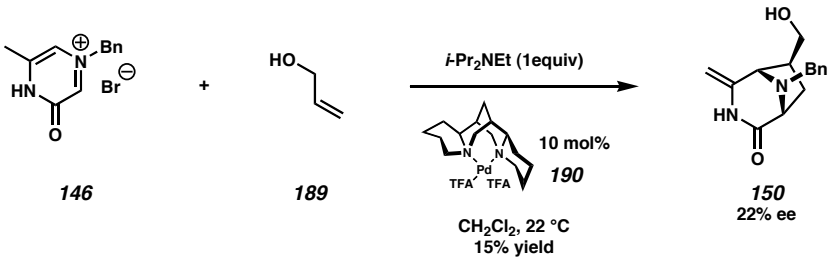
(–)-186·TFA *188·TFA* *(–)-Lemonomycin (1)*

188 and (–)-Lemonomycin (1)

To a -78 °C solution of dimethyl sulfoxide (7.9 μL, 111.6 μmol) in dichloromethane (744 μL) was added oxalyl chloride (4.9 μL, 55.8 μmol). After 30 min, this solution was added via cannula to a -78 °C solution of **(–)-186** tris-trifluoroacetate (10.0 mg, 11.16 μmol) in 4:1 dichloromethane:dimethyl sulfoxide (560 μL). The reaction mixture was maintained at -78 °C for 1h, after which triethylamine (23.3 μL, 167.4 μmol) was added. After an additional 15 min, the reaction mixture was warmed to 0 °C over 10 min. The reaction mixture was extracted into 1M aqueous hydrochloric acid (2 x 1 ml) and warmed to 20 °C for 41 h. The mixture was then purified by preparative HPLC to provide **188** bis-trifluoroacetate (4.6 mg, 52% yield) as a colorless film, which was used immediately in the next reaction.

To a cooled (0 °C) solution of **188** bis-trifluoroacetate (4.6 mg, 5.78 μmol) in water (1.16 mL) was added cerium(IV) ammonium nitrate (7.9 mg, 14.5 μmol). After 10

min, the reaction mixture was purified by preparative HPLC to provide (–)-lemonomycin (**1**, 2.3 mg, 51% yield) as a bright yellow film: ^{1}H NMR (600 MHz, D_2O) δ 5.16 (d, *J* = 4.8 Hz, 1H), 5.08 (d, *J* = 4.8 Hz, 1H), 4.90 (d, *J* = 3.6 Hz, 1H), 4.29 (s, 1H), 4.08 (dd, *J* = 6.6, 2.4 Hz, 1H), 4.01 (s, 1H), 3.98 (br q, *J* = 7.2 Hz, 1H), 3.91 (s, 3H), 3.77 (dd, *J* = 10.8, 2.4 Hz, 1H), 3.66 (dd, *J* = 10.2, 1.5 Hz, 1H), 3.37 (br d, *J* = 9.6 Hz, 1H), 3.16 (s, 1H), 3.054 (s, 3H), 3.048 (s, 3H), 2.77 (dd, *J* = 17.4, 2.4 Hz, 1H), 2.64 (ddd, *J* = 9.6, 4.8, 4.8 Hz, 1H), 2.17-1.98 (comp m, 4H), 1.97 (s, 3H), 1.92 (d, *J* = 14.4 Hz, 1H), 1.47 (d, *J* = 7.2 Hz, 3H), 1.32 (s, 3H); ^{13}C NMR (125 MHz, D_2O) δ 190.3, 184.6, 158.2, 144.6, 140.6, 133.4, 99.8, 92.9, 81.3, 72.6, 71.3, 69.7, 64.9, 64.1, 63.3, 62.8, 54.4, 52.4, 49.7, 44.4, 43.4, 40.6, 31.3, 28.5, 26.5, 19.9, 11.0; IR (NaCl/film) 3249, 3094, 2943, 1673, 1611, 1443, 1387, 1329, 1207, 1137, 802, 724 cm^{-1}; UV-Vis (methanol) λ_{max} 272, 363 nm; HRMS (FAB) calc'd for $[C_{27}H_{41}N_3O_9\text{-}OH]^+$: *m/z* 534.2815, found 534.2839; $[\alpha]_D^{23}$ -124.2° (*c* 0.1, H_2O).



Alcohol 150 by Catalytic Asymmetric Dipolar Cycloaddition

To a suspension of **146** (20 mg, 71.1 μmol) in dichloromethane (711 μL) was added diisopropylethylamine (12.4 μL, 71.1 μmol), affording a clear solution. After 10 min, palladium complex **190** (4.0 mg, 7.1 μmol) and allyl alcohol (14.5 μL, 213.3 μmol)

were added. After 96 h, the reaction mixture was purified by preparative thin-layer chromatography on silica gel to yield alcohol **150** (2.7 mg, 15% yield) as a colorless oil. The spectral data of this compound matched with samples generated by non-catalyzed cycloadditions. HPLC analysis (Chiracel AD column, 10:90 2-propanol:hexanes, 1 mL/min, λ = 254 nm) showed the product to be of 22% ee (t_{fast} = 17.95 min, minor; t_{slow} = 22.28 min, major).

2.8 Notes and Citations

(1) For the isolation of lemonomycin, see: (a) Whaley, H. A.; Patterson, E. L.; Dann, M.; Shay, A. J.; Porter, J. N. *Antimicrob. Agents Chemother.* **1964**, *8*, 83-86. For the structural determination of lemonomycin, see: (b) He, H.; Shen, B.; Carter, G. T. *Tetrahedron Lett.* **2000**, *41*, 2067-2071.

(2) Our total synthesis of (–)-lemonomycin has been communicated, see: Ashley, E. R.; Cruz, E. G.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 15000-15001.

(3) (a) Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030-2036. For a recent review of the Pictet-Spengler cyclization, see: (b) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797-1842.

(4) Pictet-Spengler cyclizations have been utilized for the synthesis of several tetrahydroisoquinoline antitumor antibiotics. For a comprehensive review of the chemistry and biology of these compounds, see: Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669-1730.

(5) This synthetic route is precedented by a similar series of reactions leading to L-callipeltose, see: Evans, D. A.; Hu, E.; Tedrow, J. S. *Org. Lett.* **2001**, *3*, 3133-3136.

(6) For recent examples of catalytic asymmetric hetero-Diels-Alder reactions, see: (a) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146. (b)

Thadani, A. N.; Stankovic, A. R.; Rawal, V. H. *Proc. Nat'l. Acad. Sci.* **2004**, *101*, 5846-5850. (c) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398-2400. (d) Schaus, S. E.; Brnalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403-405.

(7) The formylation and Baeyer-Villiger oxidation follow known procedures, see: (a) Kaliakoudas, D.; Eugster, C. H.; Ruedi, P. *Helv. Chim. Acta* **1990**, *73*, 48-62. (b) Nikaido, M.; Aslanian, R.; Scavo, F.; Helquist, P.; Åkermark, B.; Bäckvall, J.-E. *J. Org. Chem.* **1984**, *49*, 4740-4741.

(8) The selective substitution of 2,6-dichloropyrazine with sodium benzyloxide is known, see: Cheeseman, G. W. H.; Törzs, E. S. G. *J. Chem. Soc.* **1965**, 6681-6688.

(9) The zinc was preactivated with ethereal hydrogen chloride, and excess zinc was removed by filtration prior to the palladium catalyzed coupling step.

(10) For Negishi coupling of benzylic zinc reagents with chloropyridines, see: (a) Shiota, T.; Yamamor, T. *J. Org. Chem.* **1999**, *64*, 453-457. (b) Minato, A.; Tamao, K.; Hayashi, T.; Suzuki, K.; Kumada, M. *Tetrahedron Lett.* **1980**, *21*, 845-848. For a general review of the Negishi reaction, see: (c) Negishi, E.; Zeng, X.; Tan, Z.; Qian, M.; Hu, Q.; Huang, Z. Palladium- or Nickel-catalyzed Cross-coupling with Organometals Containing Zinc, Aluminum, and Zirconium: The Negishi Coupling.

Metal-Catalyzed Cross-Coupling Reactions, 2nd ed.; Wiley-VHC: Weinheim, 2004; 2, 815-889.

(11) For examples of multimeric organozinc enolate complexes, see: (a) van der Steen, F. H.; Boersma, J.; Spek, A. L.; Van Koten, G. *Organometallics* **1991**, *10*, 2467-2480. (b) Dekker, J.; Budzelaar, P. H. M. Boersma, J.; van der Kerk, G. J. M.; Spek, A. L. *Organometallics* **1984**, *3*, 1403-1407.

(12) Since an excess of insoluble zinc metal is present throughout the reaction, the unusual product distribution may be the result of complex surface chemistry.

(13) The reaction protocol for this dipolar cycloaddition is based on the pioneering work of Joule, see: (a) Kiss, M.; Russell-Maynard, J.; Joule, J. A. *Tetrahedron Lett*. **1987**, *28*, 2187-2190. (b) Allway, P. A.; Sutherland, J. K.; Joule, J. A. *Tetrahedron Lett*. **1990**, *31*, 4781-4782. (c) Yates, N. D.; Peters, D. A.; Allway, P. A.; Beddeoes, R. L.; Scopes, D. I. C.; Joule, J. A. *Heterocycles* **1995**, *40*, 331-347.

(14) Williams has developed an oxidative dipolar cycloaddition for the synthesis of related natural products, see: Scott, J. D.; Williams, R. M. *J. Am. Chem. Soc*. **2002**, *124*, 2951-2956 and references therein.

(15) Due to their instability, oxidopyrazinium **139** was characterized only by ^{1}H NMR, and no attempt was made to characterize dipole **140**. Due to the inseparability of

the various cycloadducts **141**, none were fully characterized before advancement to silyl ether **142**.

(16) Oxidopyrazinium **146** was reported by Joule as a substrate for dipolar cycloaddition with a variety of electron poor olefins, although not with acrolein, see reference 13.

(17) Lutz, W. B.; Lazarus, S.; Klutchko, S.; Meltzer, R. I. *J. Org. Chem.* **1964**, *29*, 415-418.

(18) Thom, C.; Kocienski, P. *Synthesis* **1992**, 582-586.

(19) For a review of thermal reactions utilizing Oppolzer's sultam, see: Kim. B. H.; Curran, D. P. *Tetrahedron* **1993**, *49*, 293-318.

(20) Garner utilized the acrylamide of Oppolzer's sultam for a related dipolar cycloaddition that led to the total synthesis of (–)-quinocarcin, see: Garner, P.; Ho, W.B.; Shin, H. *J. Am. Chem. Soc.* **1993**, *115*, 10742-10753.

(21) The ee of **150** could be raised to >98% by chromatographic purification of **149** prior to the cleavage of the auxiliary.

(22) For reviews of transition metal-catalyzed coupling reactions, see: (a) Diederich, F.; Stang, P. J.; Eds.; *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH:

Weinheim, 1998. (b) Geissler, H. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 2.10, pp 158. (c) Tsuji, J. In *Transition Metal Reagents and Catalysts*; Wiley: Chichester, 2000; Chapter 3, pp 27.

(23) Heck coupling reactions between bromide **154** (and the analogous aryl iodide) and enamides such as **147** were also extensively investigated, but these reactions were universally unsuccessful.

(24) For reviews of Suzuki coupling reactions, see: (a) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147-168. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483.

(25) Hydrogenolysis of the benzyl amine proceeded at a rate that was competitive with the rate of olefin hydrogenation. Under conditions with lower hydrogen pressures, a debenzylated compound with the styrene intact could be isolated.

(26) The second product from the hydrogenation in the presence of acetic acid reaction was not fully characterized.

(27) Due to the overlap of key signals in the ^{1}H NMR spectrum, the stereochemistry of **158** was recalcitrant to NOE analysis.

(28) Lemonomycin numbering, see Figure 1.3, Chapter 1.

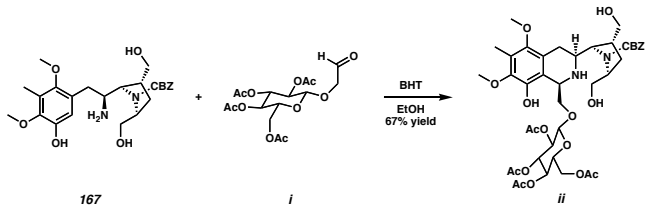
(29) (a) Evans, D. A.; Biller, S. A. *Tetrahedron Lett*. **1985**, *26*, 1907-1910. (b) Evans, D. A.; Biller, S. A. *Tetrahedron Lett*. **1985**, *26*, 1911-1914. (c) Evans, D. A.; Illig, C. R.; Saddler, J. C. *J. Am. Chem. Soc*. **1986**, *108*, 2478-2479. (d) Biller, S. A. An Approach to the Total Synthesis of (±)-Naphthyridinomycin A. Ph.D. Thesis, California Institute of Technology, Pasadena, CA, 1982.

(30) Nagata, W.; Okada, K.; Aoki, T. *Synthesis* **1979**, *5*, 365-368.

(31) Treatment of **165** with trifluoroacetic acid, trimethylsilyl iodide, palladium(0) catalysts, or triphenyl phosphine and carbon tetrabromide failed to yield any cyclized product.

(32) A similar strategy involving reduction of an amide to a primary amine before Pictet-Spengler cyclization was utilized in the Fukuyama synthesis of Saframycin A, see: Fukuyama, T.; Yang, L.; Ajeck, K. L.; Sachleben, R. A. *J. Am. Chem. Soc*. **1990**, *112*, 3712-3713.

(33) *O*-Silyl and *O*-benzyl hydroxyacetaldehyde derivatives were utilized to test the Pictet-Spengler cyclization. As proof of principle for our eventual incorporation of lemonose during the Pictet-Spengler reaction, we also tested the reaction of aminotriol **167** with glucose-derived aldehyde **i**, which provided tetrahydroisoquinoline **ii** in 67% yield.



167 *i* *ii*

(34) The synthesis of lemonose was accomplished in collaboration with Ernie Cruz, a graduate student in the Stoltz research group.

(35) (a) Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1988**, *53*, 2367-2371. (b) Szechner, B.; Achmatowicz, O.; Galdecki, Z.; Fruzinski, A. *Tetrahedron* **1994**, *50*, 7611-7624.

(36) This synthetic route was also performed with L-threonine as the starting material, such that both enantiomers of each compound in Scheme 2.15 and Scheme 2.16 have been prepared.

(37) For the synthesis of Weinreb amides from esters with *N*,*O*-dimethylhydroxylamine hydrochloroide and isopropylmagnesium chloride, see: Williams, J. M.; Jobson, R.

B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett*. **1995**, *36*, 5461-5464.

(38) (a) Chérest, M.; Felkin, H. *Tetrahedron Lett*. **1968**, 2205-2208. (b) Anh, N. T. *Top. Curr. Chem*. **1980**, *88*, 145-162. (c) Reetz, T. M. *Chem. Rev*. **1999**, *99*, 1121-1162.

(39) The crystal structure shown in Scheme 2.15 was obtained from crystals of *ent*-**175**, which was synthesized from L-threonine. For clarity in this scheme, the obtained structure was inverted to depict the absolute stereochemistry of **175** derived from D-threonine.

(40) The conformation of **178** was minimized by AM1 semiempirical calculations utilizing Spartan '02 v1.0.8 (Wavefunction, Inc.).

(41) An analogous reduction and allyloxy group installation in the absence of the oxazolidine ring provided minimal diastereocontrol over the anomeric center.

(42) For the use of periodate and catalytic osmium tetroxide for the production of carbonyls from alkenes, see: Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem*. **1956**, *21*, 478-479.

(43) Tetrahydroisoquinoline **182** was the only compound recovered from the Pictet-Spengler cyclization. Any trace (<3%) diastereomeric compound arising from the

minor enantiomer of **167** (94% ee) must be removed during HPLC purification of **182**.

(44) The use of glycosyloxy aldehydes in a Pictet-Spengler cyclization is precedented only by our work (see endnote 33). Typical Pictet-Spengler studies have utilized only simple, commercially available aldehydes, see reference 3b.

(45) The mass spectral data of **185** agrees with the proposed structure ($[M+H]^+ = 668.2$), and the ^1H NMR shows an aldehyde peak at 9.65 ppm. However, the compound could not be purified sufficiently to obtain full NMR characterization.

(46) For a review of hypervalent iodine reagents for alcohol oxidation, including the Dess-Martin periodinane, see: Tohma, H.; Kita, Y. *Adv. Synth. Catal.* **2004**, *346*, 111-124.

(47) For reviews of alcohol oxidation with activated DMSO reagents, including the Swern, Moffatt, and DMS/NBS oxidations, see: (a) Tidwell, T. T. *Synthesis* **1990**, 857-870. (b) Tidwell, T. T. *Org. React.* **1990**, *39*, 297-572.

(48) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750-6755.

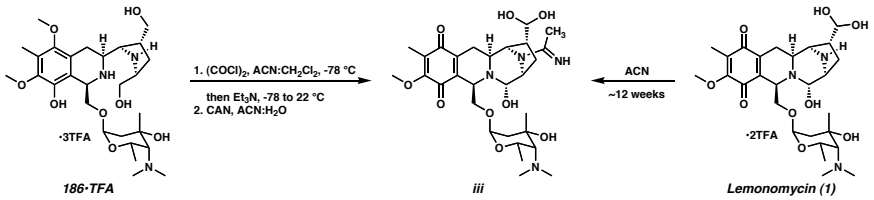
(49) Peterson, K. P.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 3185-3189.

(50) For a review of tetrapropylammonium perruthenate catalized alcohol oxidation, see: Ley, S. V.; Norman, J. N.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639-666.

(51) Mass spectrometry analysis of the crude reaction mixtures showed M+61 and M+121 in addition to M+H, indicating the presence of one or two methylthiomethyl groups.

(52) In principle, these monooxidized compounds could be resubmitted to the Swern oxidation to yield additional **188**. However, these reactions were not attempted.

(53) In addition to the spectroscopic matching of natural and synthetic (–)-lemonomycin, our synthetic intermediates were chemically correlated with the natural product through a serendipitous discovery. Specifically, Swern oxidation of **186** with acetonitrile as the cosolvent followed by CAN oxidation yielded amidine **iii**, wherein the secondary amine had attacked an equivalent of acetonitrile. Amidine **iii** was also produced when natural (–)-lemonomycin was stored as a solution in acetonitrile for a period of several weeks.



(54) Chiral Lewis acid catalysis has been used for asymmetric dipolar cycloadditions of enal and enoate derivatives. Although this remains an active area of research, we

felt that the use of π-acid catalysis would be more interesting. For recent examples, see: (a) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 11926-11927. (b) Desimoni, G.; Faita, G.; Mortoni, A.; Righetti, P. *Tetrahedron Lett.* **1999**, *40*, 2001-2004. (c) Kodama, H.; Ito, J.; Hori, K.; Ohta, T.; Furukawa, I. *J. Organomet. Chem.* **2000**, *603*, 6-12. (d) Iwasa, S.; Tsushima, S.; Shimada, T.; Nishiyama, H. *Tetrahedron Lett.* **2001**, *42*, 6715-6717. (e) Suga, H.; Nakajima, T.; Itoh, K.; Kakehi, A. *Org. Lett.* **2005**, *7*, 1431-1434. (f) Carmona, D.; Lamata, M. P.; Viguri, F.; Rodriguez, R.; Oro, L. A.; Balana, A. I.; Lahoz, F. J.; Tejero, T.; Merino, P.; Franco, S.; Montesa, I. *J. Am. Chem. Soc.* **2004**, *126*, 2716-2717.

(55) Organocatalytic nitrone dipolar cycloadditions with enals have also been reported, see: Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874-9875. These conditions failed to catalyze the cycloaddition of **146** with acrolein.

(56) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions;* John Wiley & Sons: New York, 1978.

(57) (a) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1993**, *32*, 566-568. (b) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769-1772. (c) Dawson, G. J.; Frost, C. G.; Coote, S. J.; Williams, J. M. J. *Tetrahedron Lett.* **1993**, *34*, 3149-3150.

(58) Davenport, A. J.; Davies, D. L.; Fawcett, J.; Russell, D. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, *13*, 1500-1503.

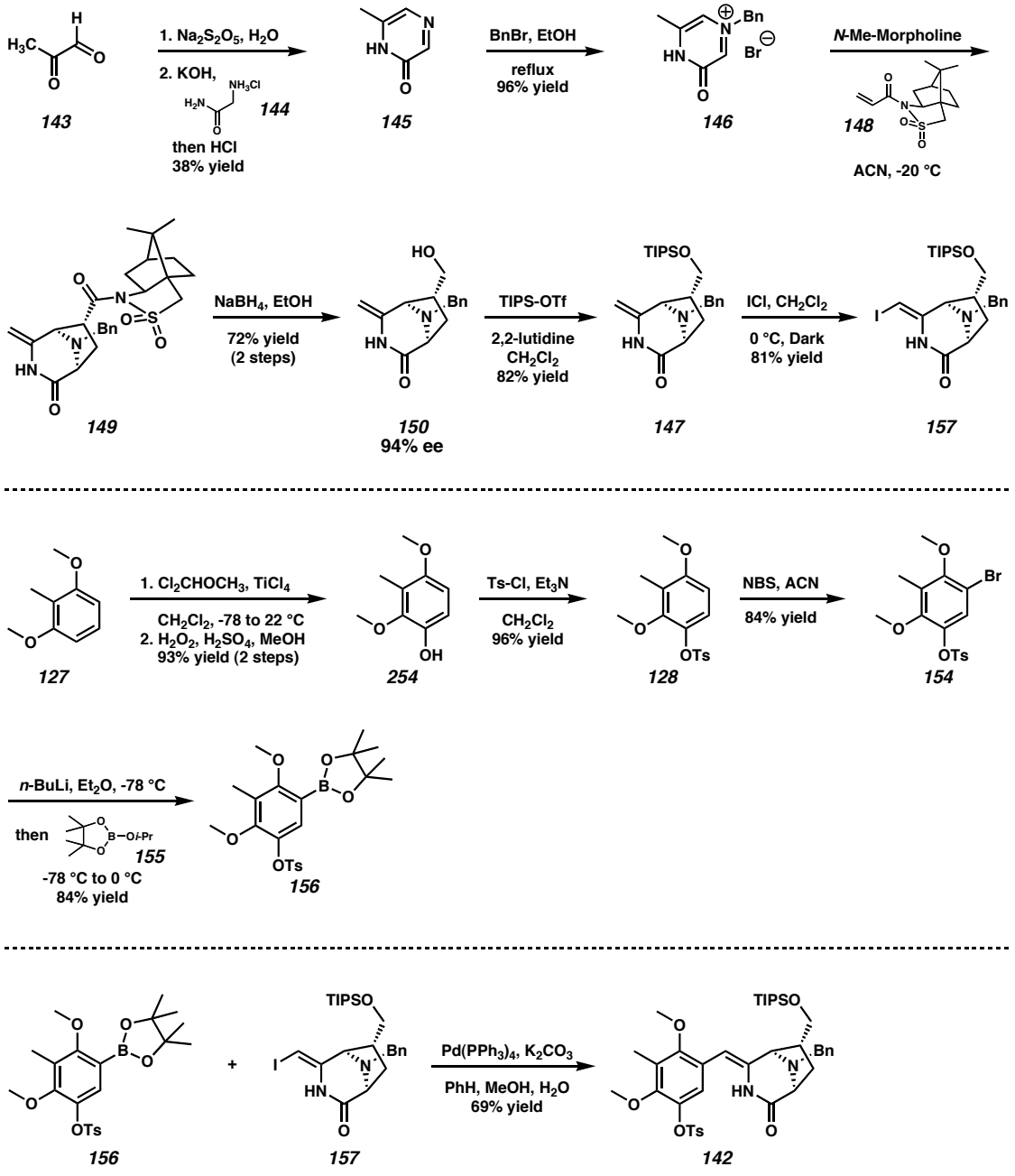
(59) Scheurer, A.; Mosset, P.; Bauer, W.; Saalfrank, R. W. *Eur. J. Org. Chem.* **2001**, *16*, 3067-3074.

(60) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628-1629.

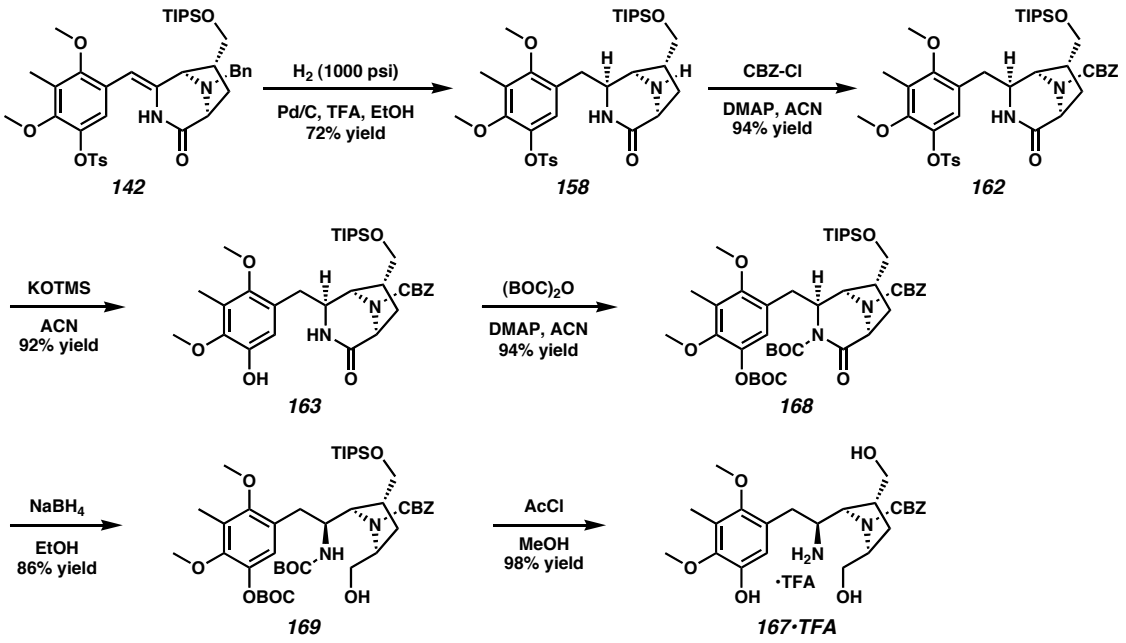
APPENDIX ONE

Synthetic Summary for (–)-Lemonomycin

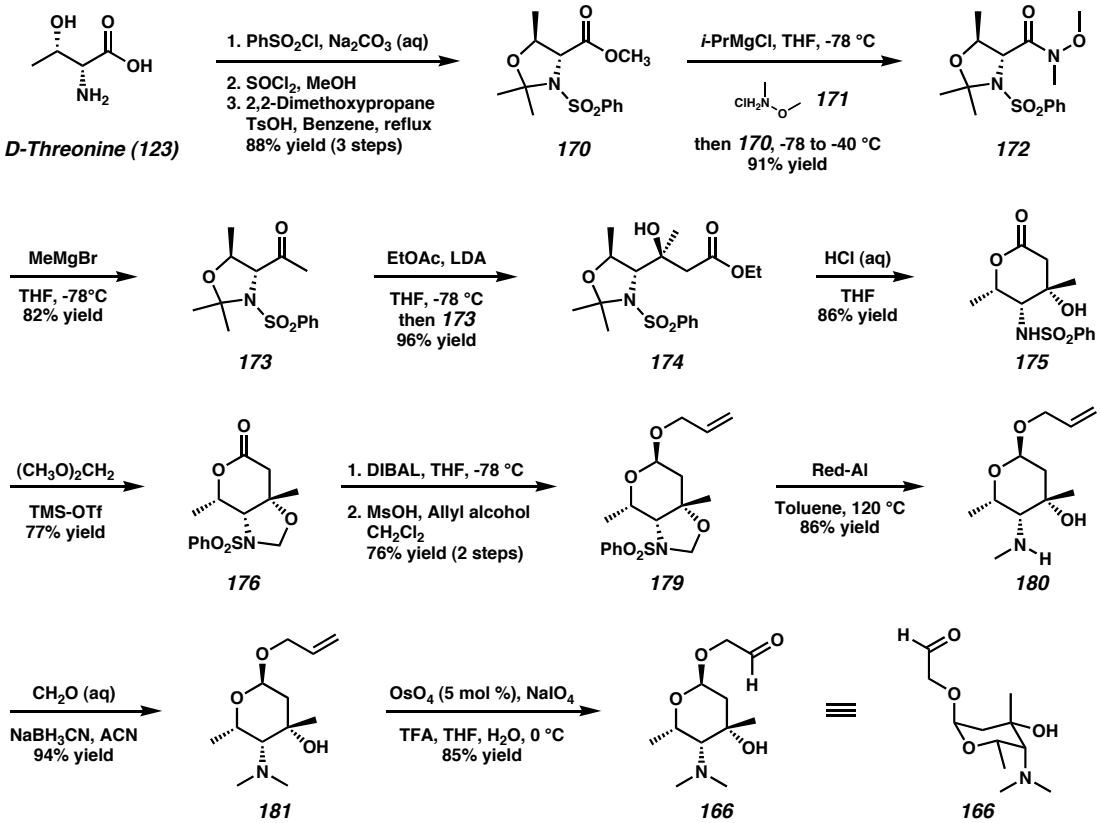
Scheme A1.1 Synthesis and Coupling of the Suzuki Substrates



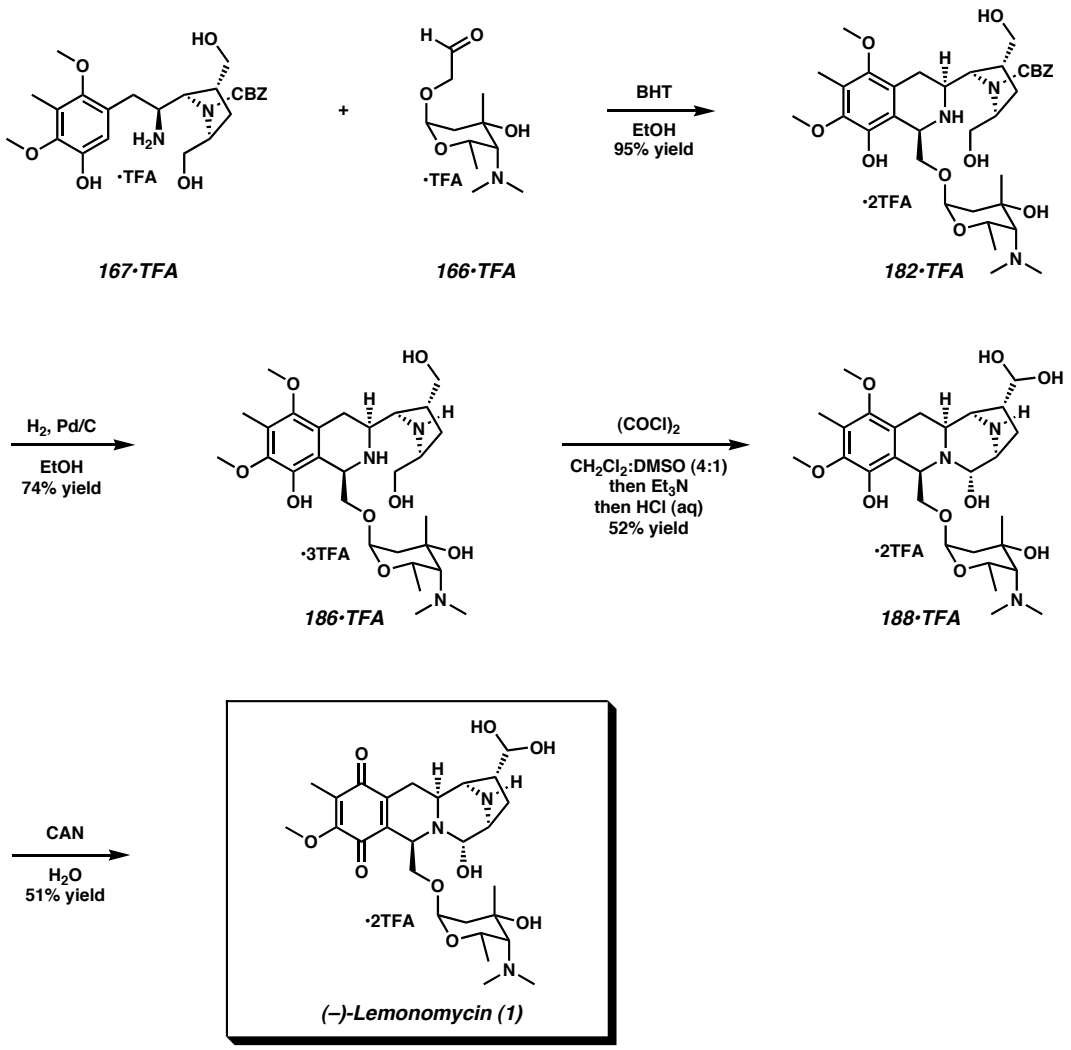
Scheme A1.2 Synthesis of the Aminotriol



Scheme A1.3 Synthesis of Lemonose



Scheme A1.4 Completion of (–)-Lemonomycin



APPENDIX TWO

Spectra of Compounds in Chapter Two

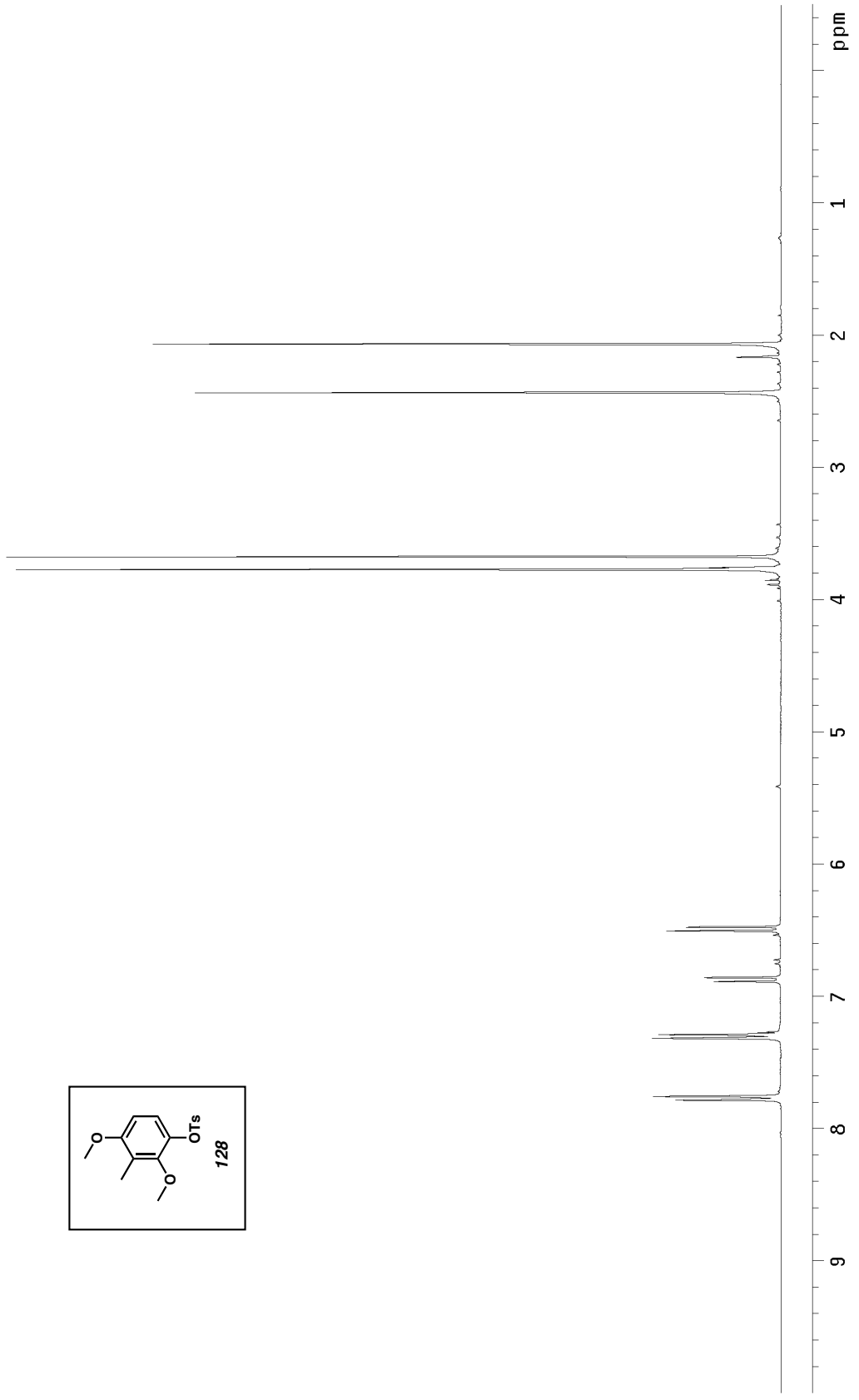


Figure A2.1 ^{1}H NMR of compound **128** (300 MHz, $CDCl_3$)

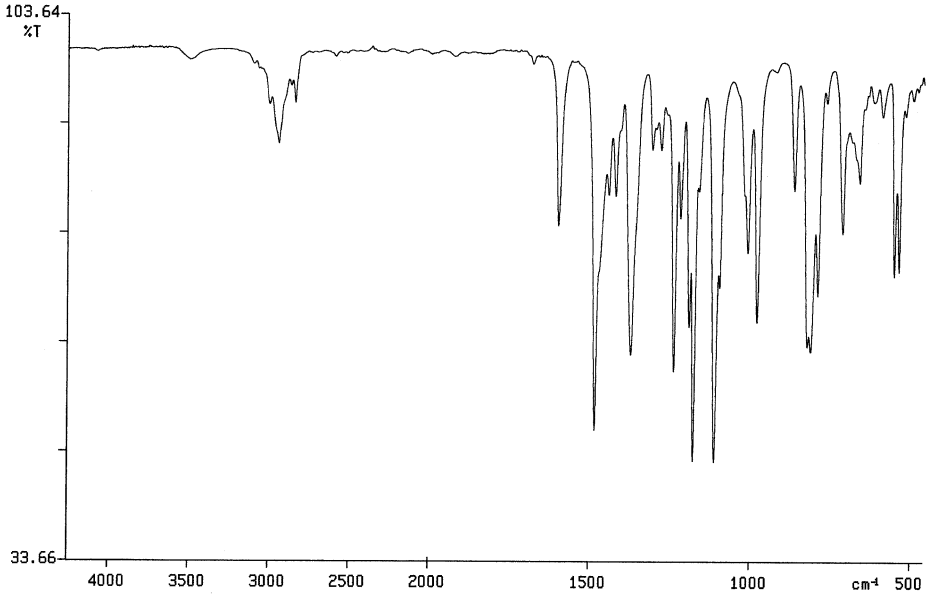


Figure A2.2 IR of compound **128** (NaCl/film)

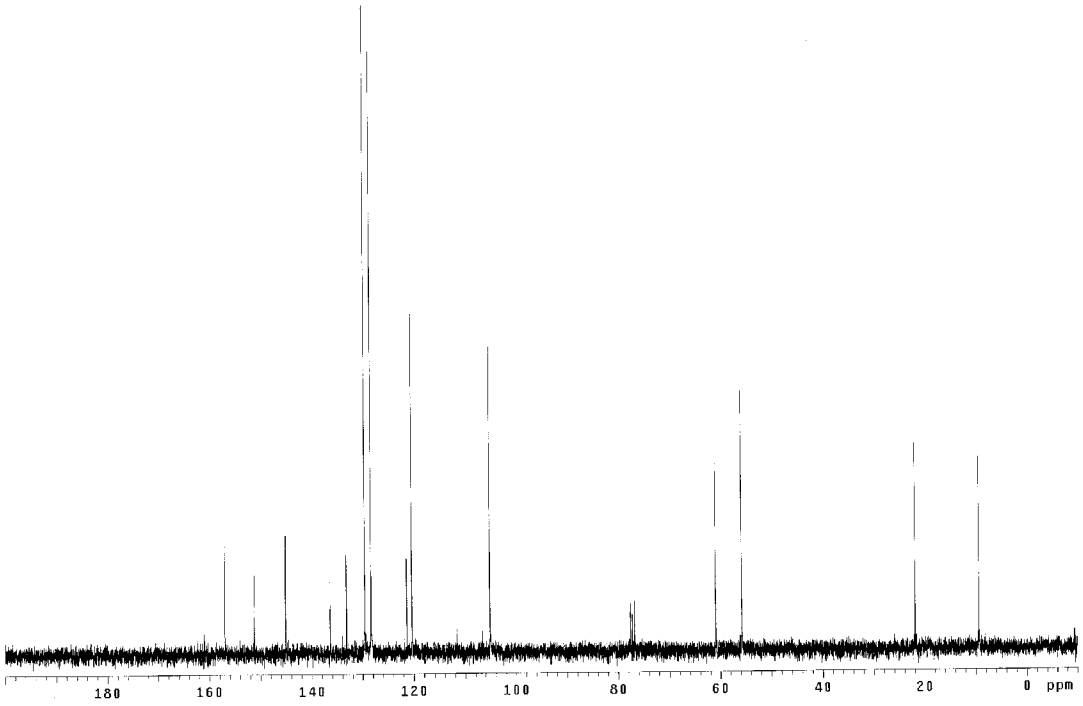


Figure A2.3 ^{13}C NMR of compound **128** (75 MHz, $CDCl_3$)

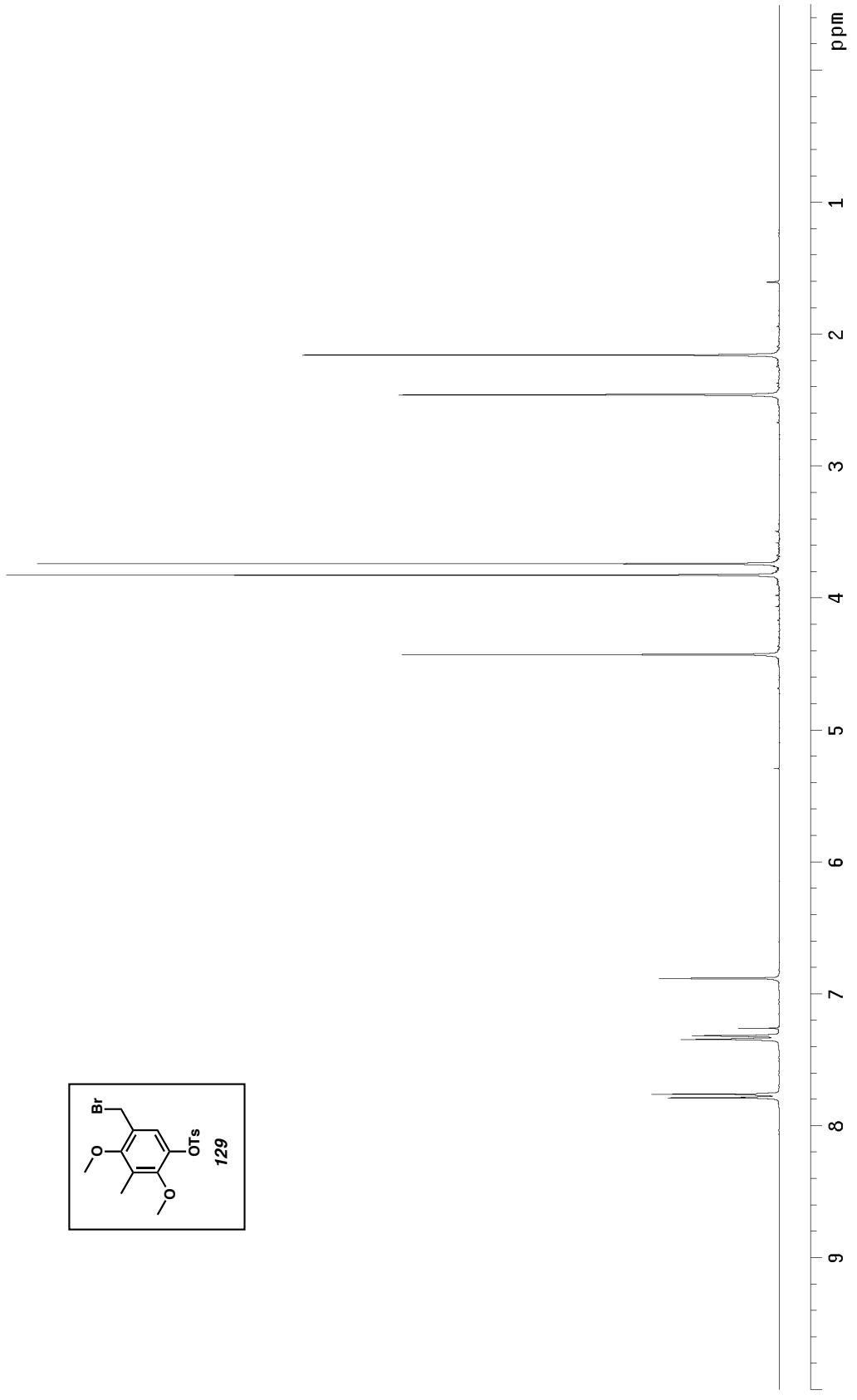


Figure A2.4 ^{1}H NMR of compound **129** (300 MHz, $CDCl_3$)

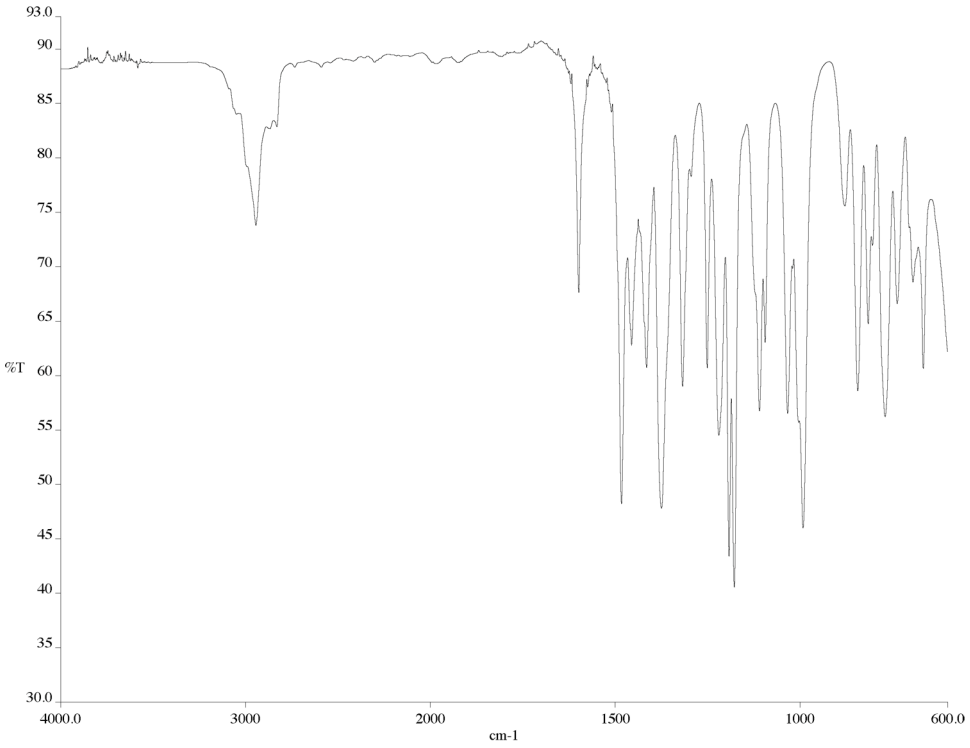


Figure A2.5 IR of compound **129** (NaCl/film)

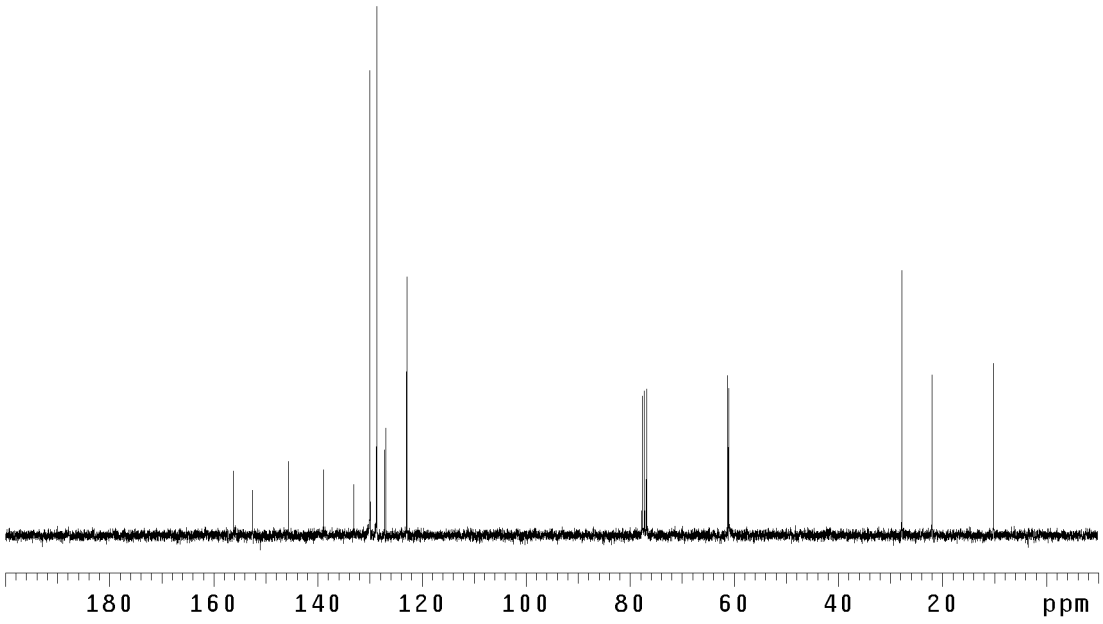


Figure A2.6 ^{13}C NMR of compound **129** (75 MHz, $CDCl_3$)

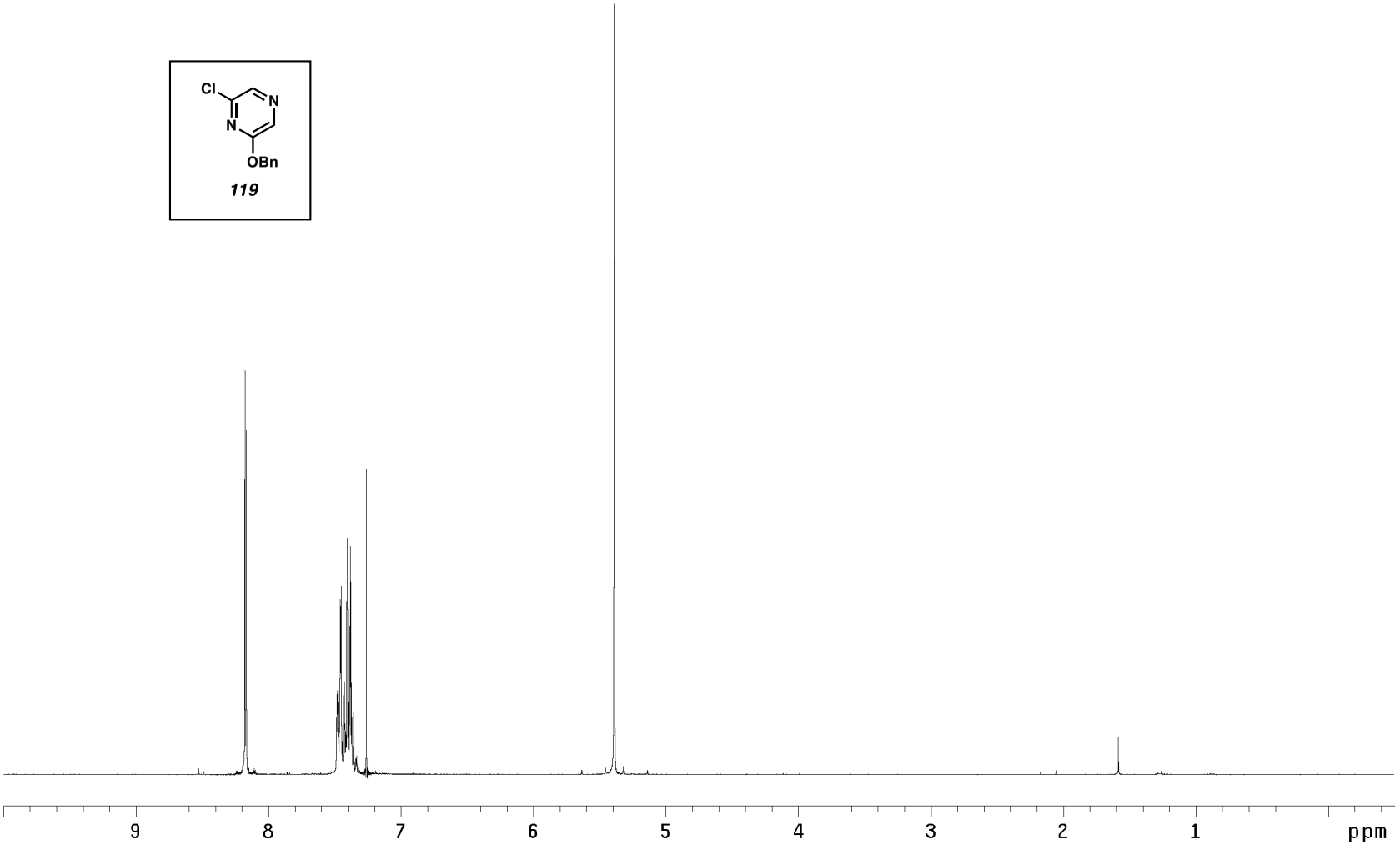


Figure A2.7 ^{1}H NMR of compound **119** (300 MHz, $CDCl_3$)

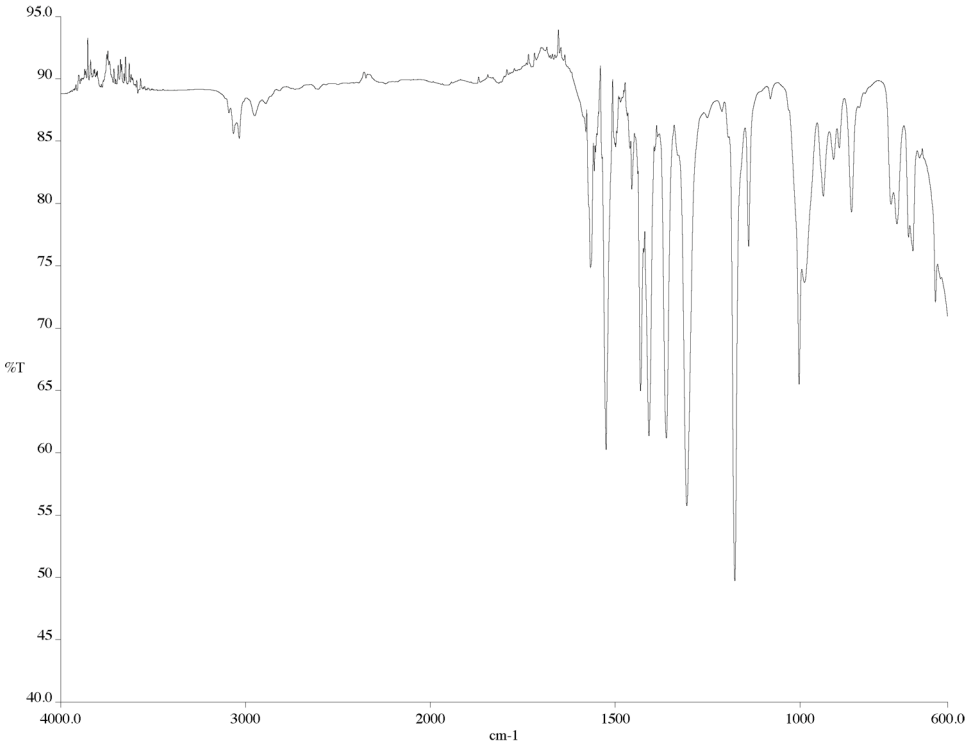


Figure A2.8 IR of compound **119** (NaCl/film)

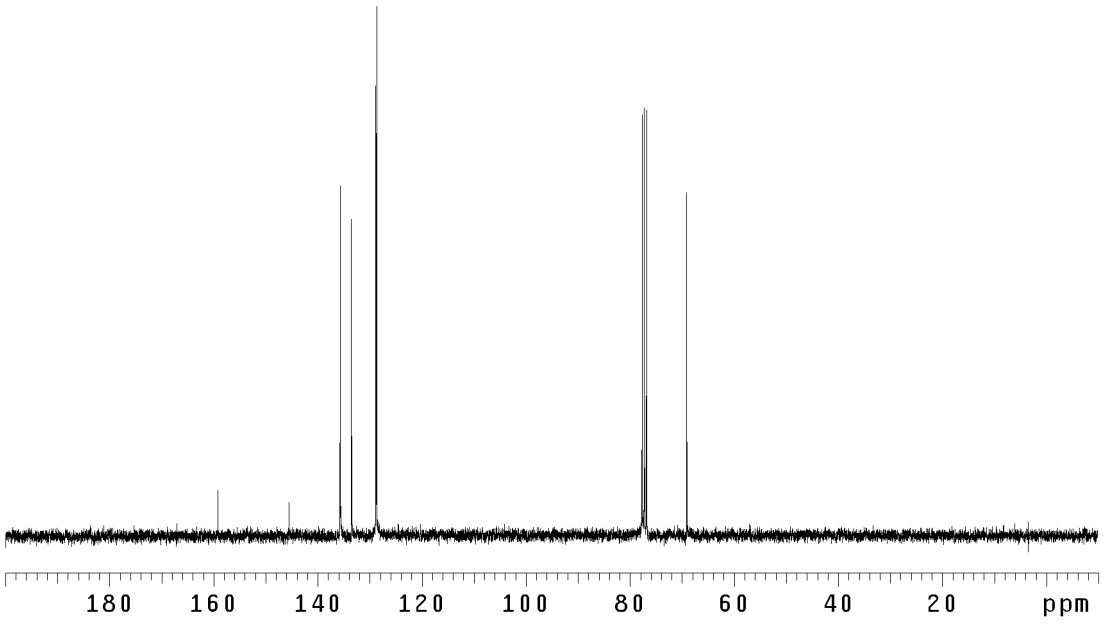


Figure A2.9 ^{13}C NMR of compound **119** (75 MHz, $CDCl_3$)

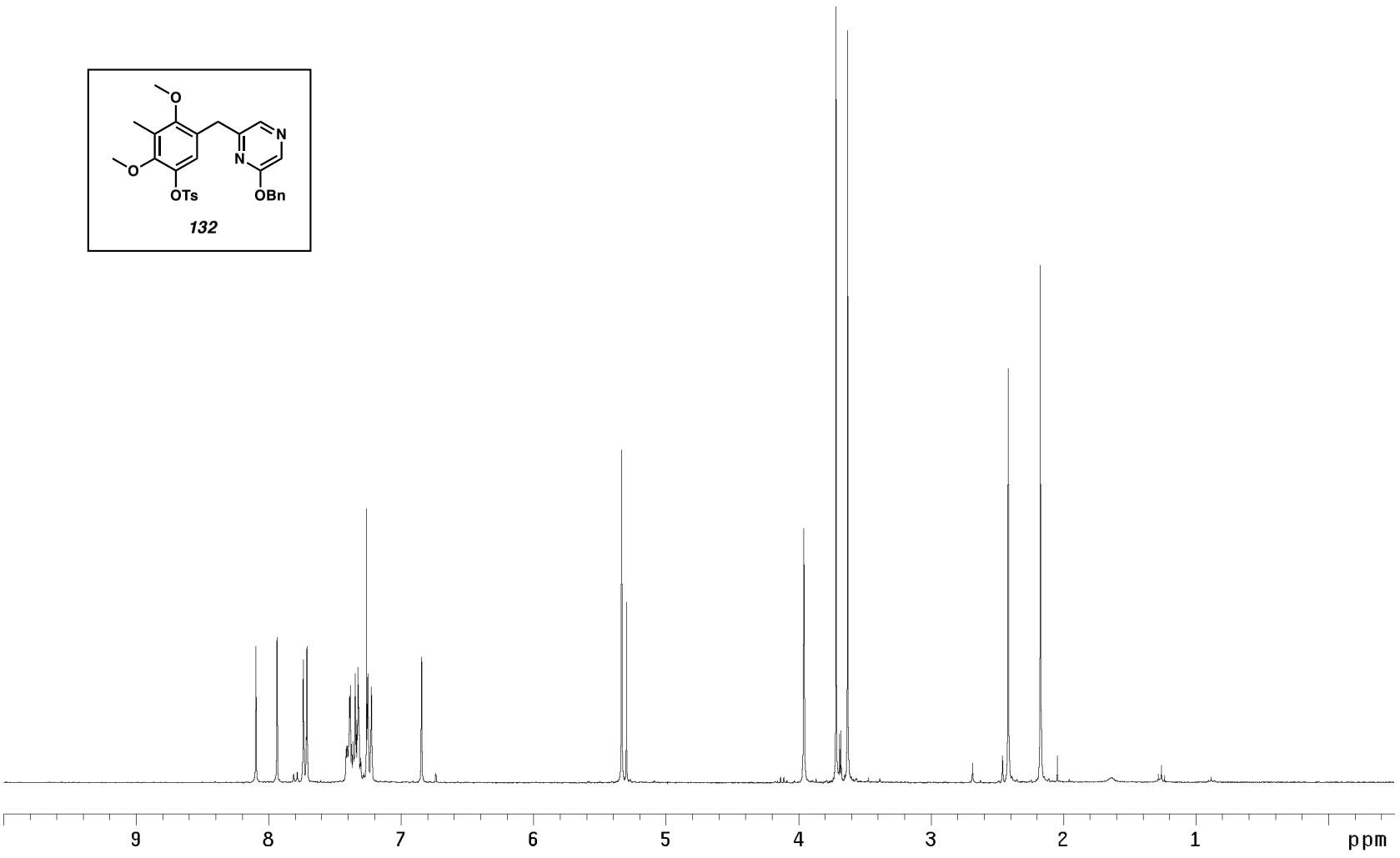


Figure A2.10 ^{1}H NMR of compound **132** (300 MHz, $CDCl_3$)

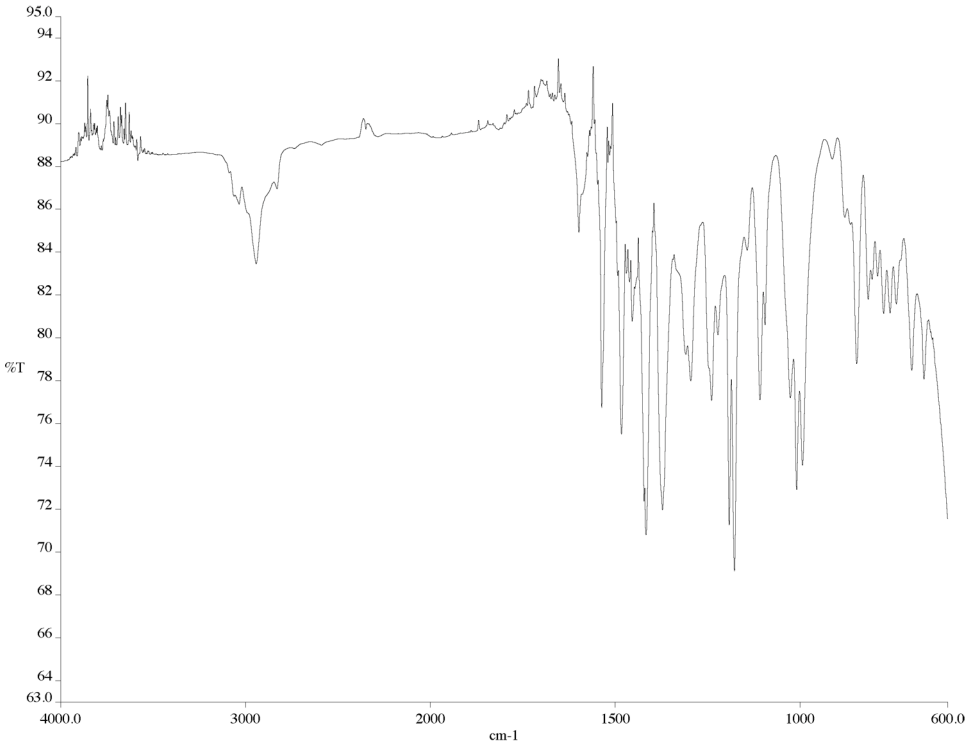


Figure A2.11 IR of compound **132** (NaCl/film)

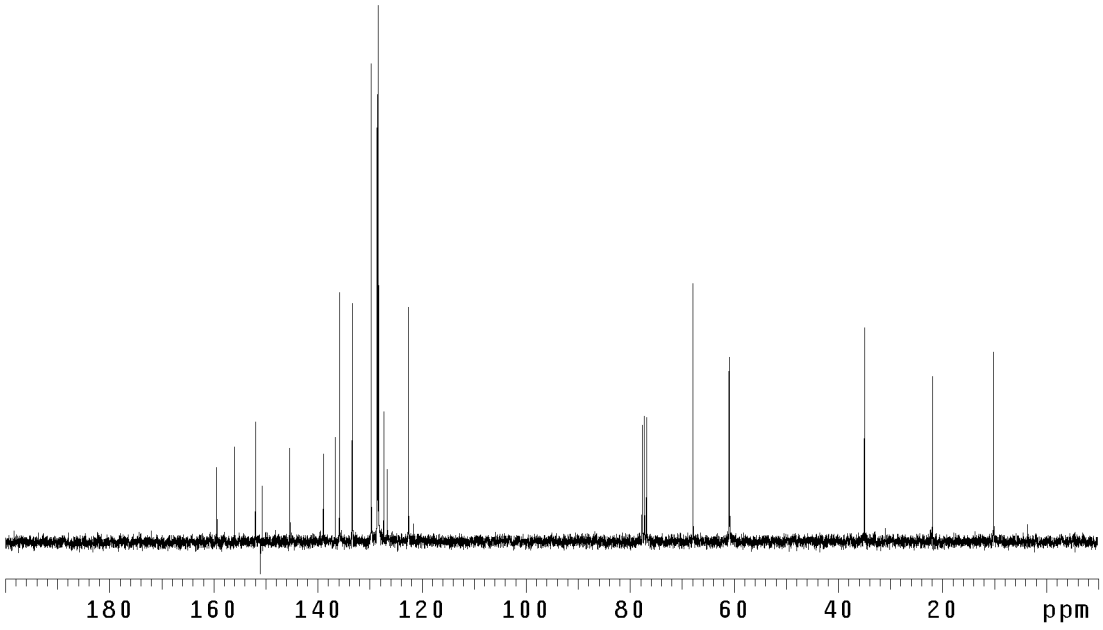


Figure A2.12 ^{13}C NMR of compound **132** (75 MHz, $CDCl_3$)

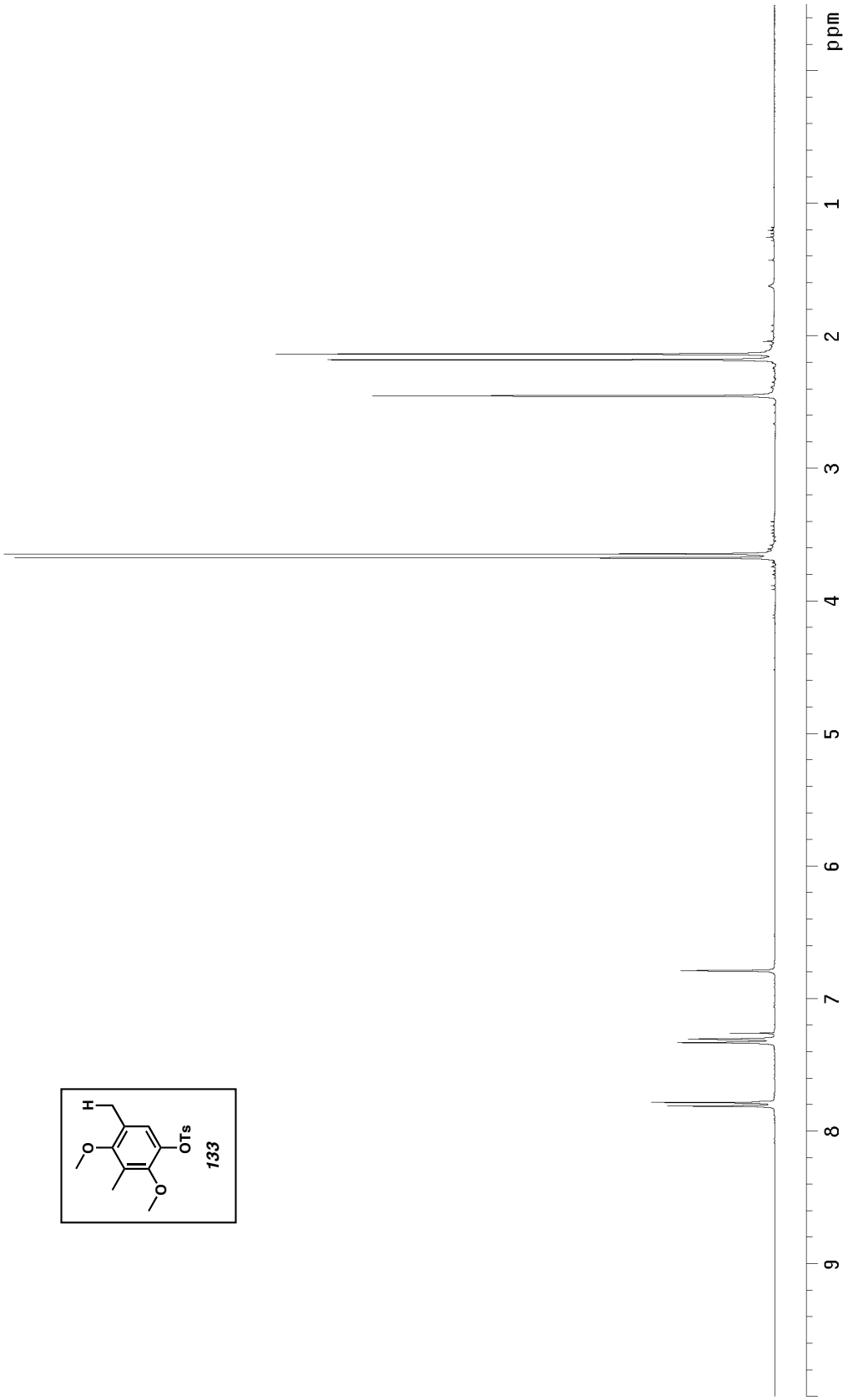


Figure A2.13 ^{1}H NMR of compound **133** (300 MHz, $CDCl_3$)

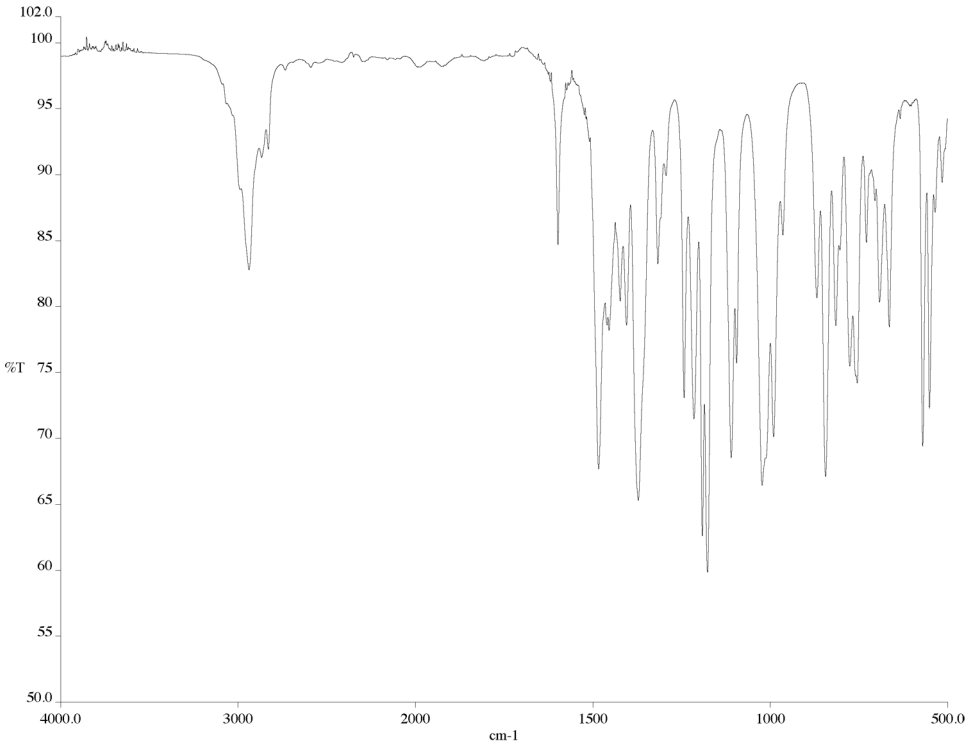


Figure A2.14 IR of compound **133** (NaCl/film)

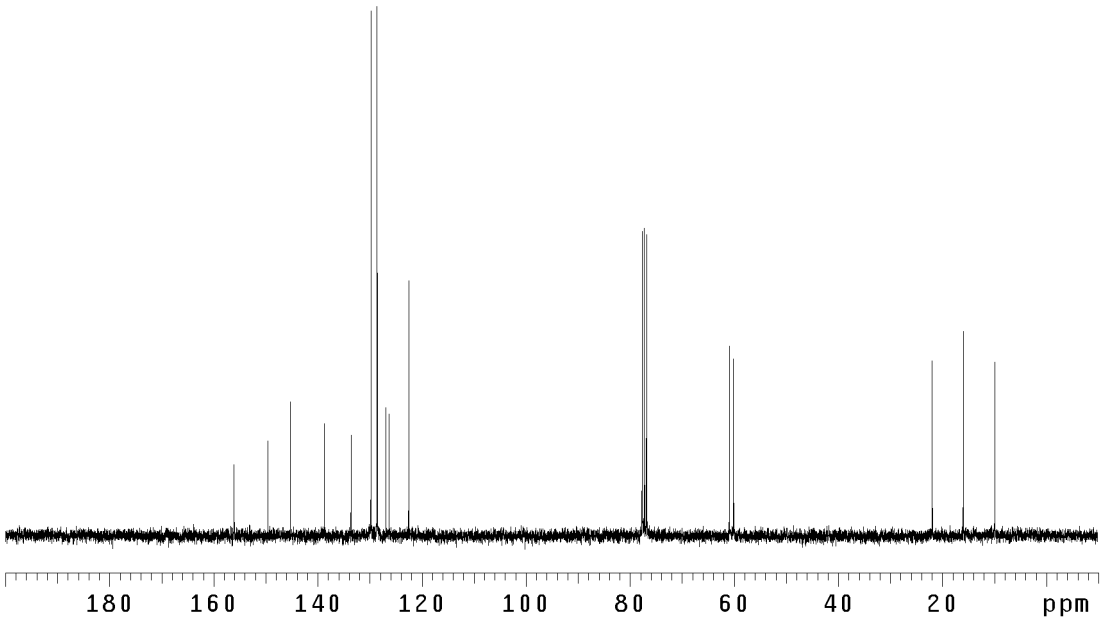


Figure A2.15 ^{13}C NMR of compound **133** (75 MHz, $CDCl_3$)

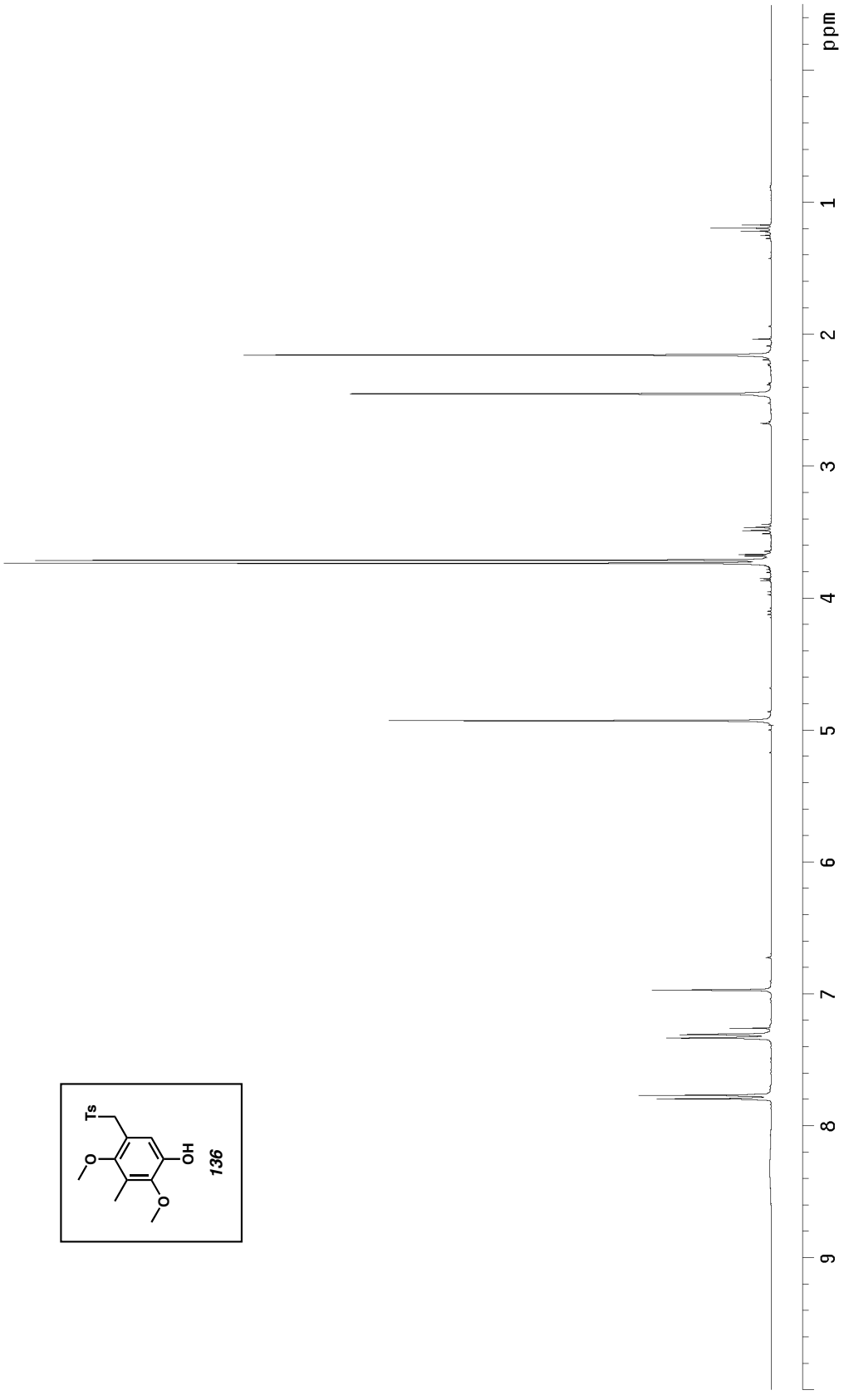


Figure A2.16 ^{1}H NMR of compound **136** (300 MHz, $CDCl_3$)

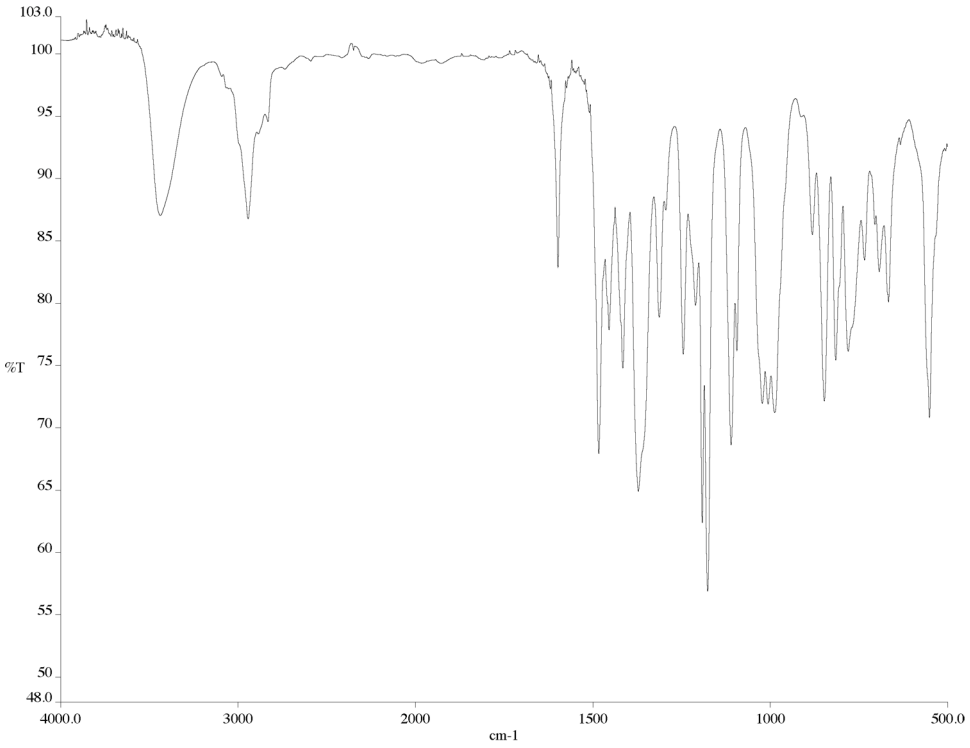


Figure A2.17 IR of compound **136** (NaCl/film)

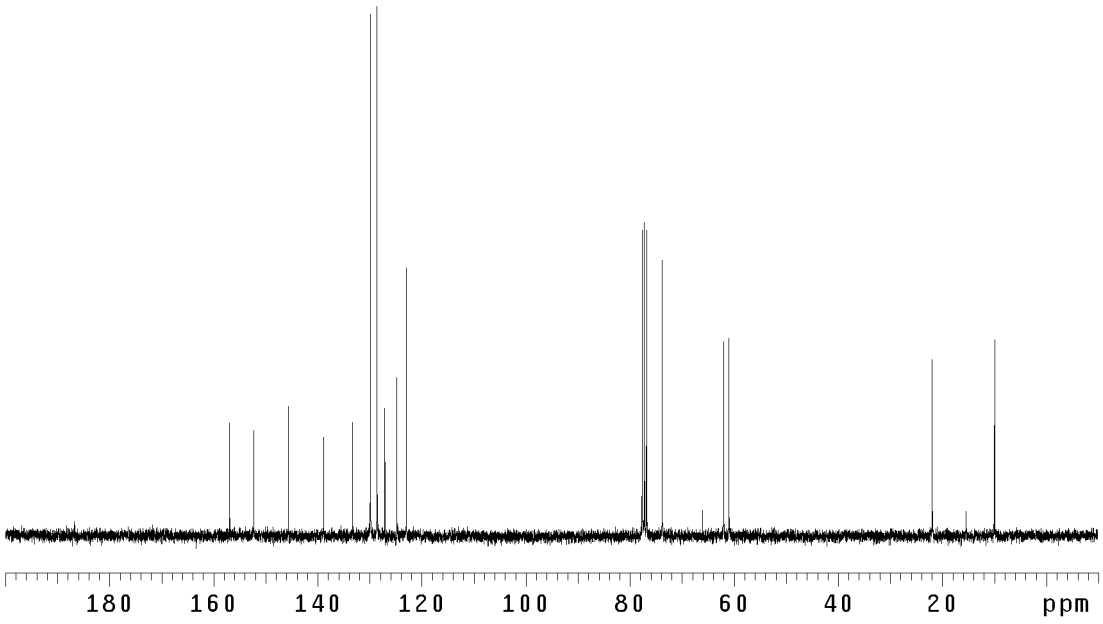


Figure A2.18 ^{13}C NMR of compound **136** (75 MHz, $CDCl_3$)

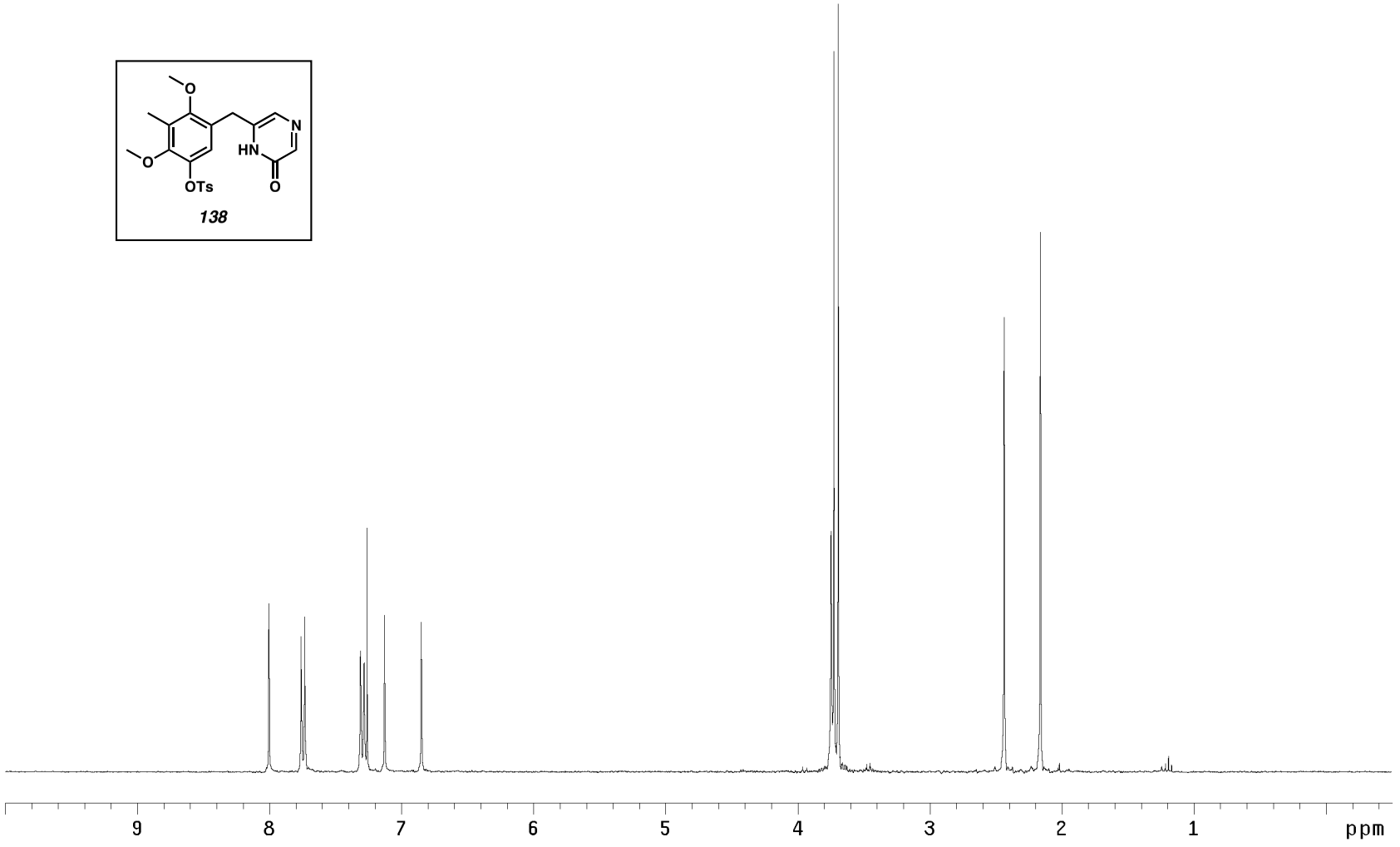


Figure A2.19 ^{1}H NMR of compound **138** (300 MHz, $CDCl_3$)

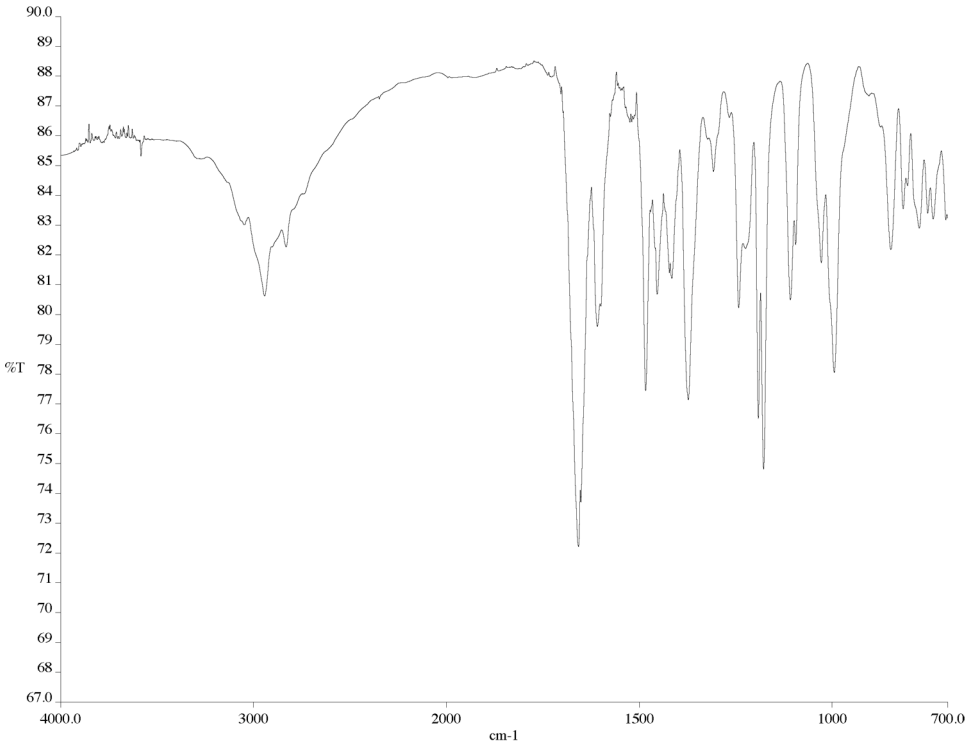


Figure A2.20 IR of compound **138** (NaCl/film)

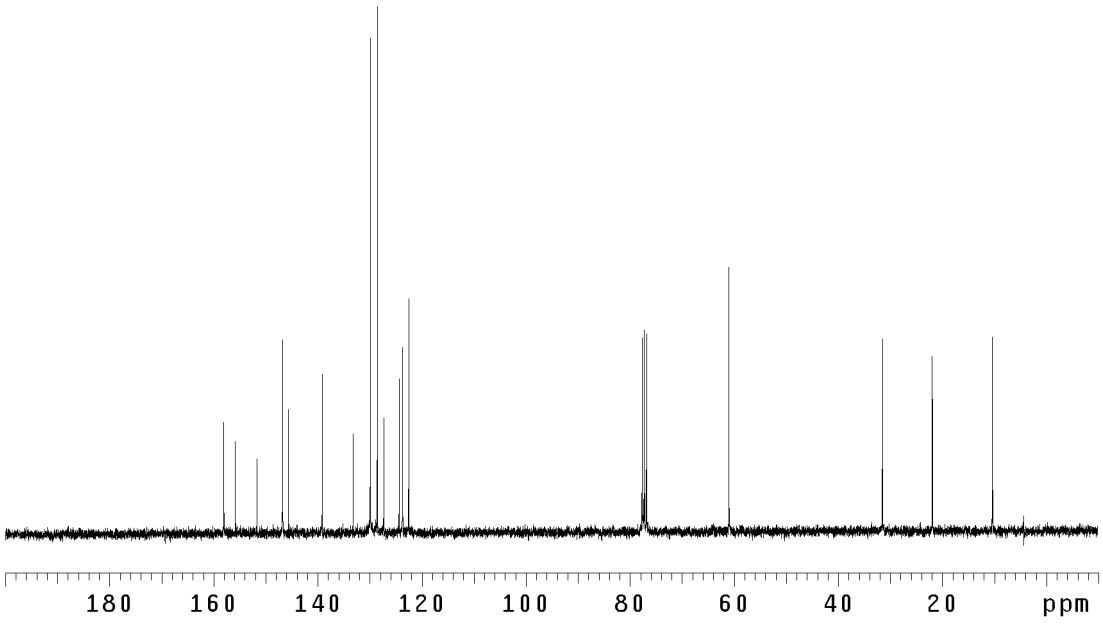


Figure A2.21 ^{13}C NMR of compound **138** (75 MHz, $CDCl_3$)

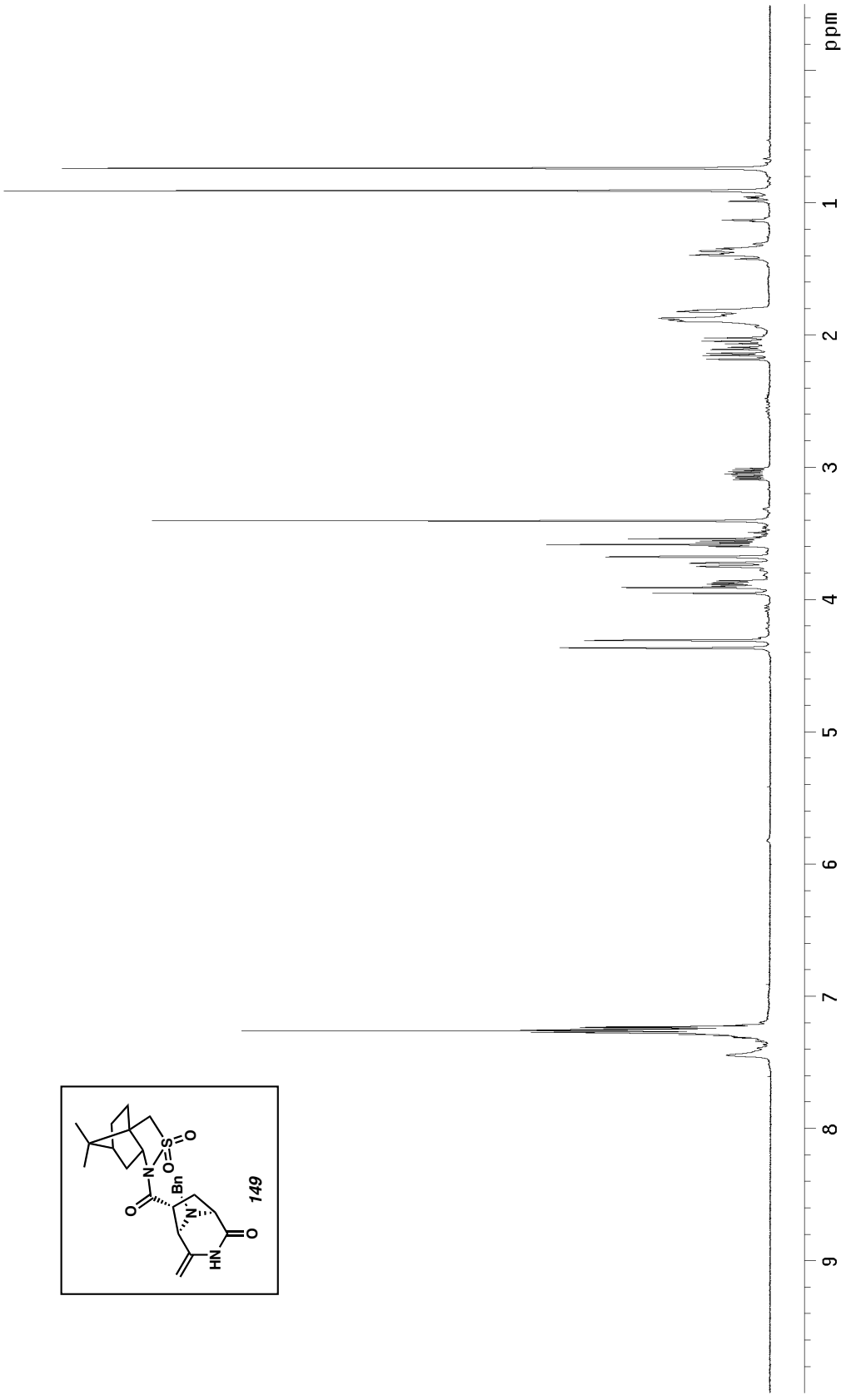


Figure A2.22 ^{1}H NMR of compound **149** (300 MHz, $CDCl_3$)

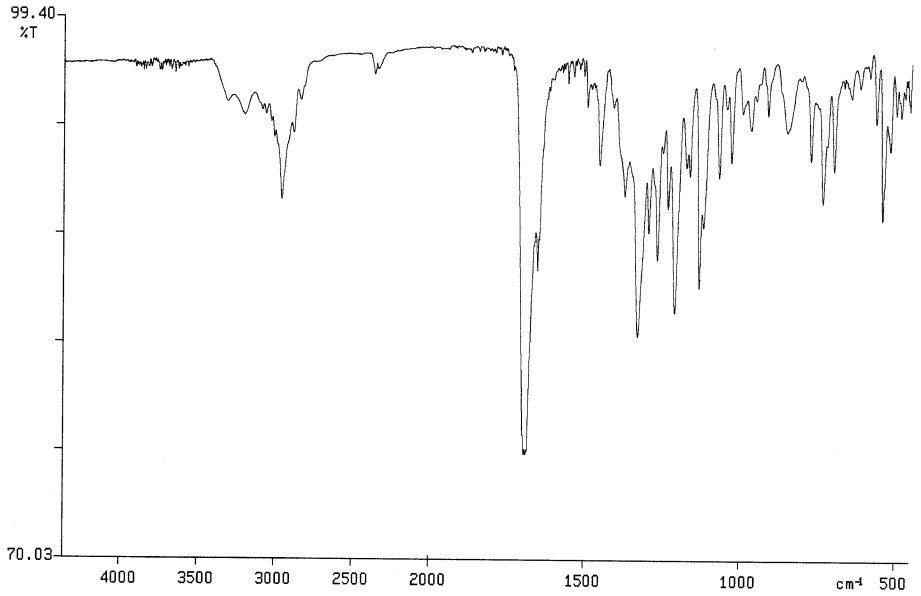


Figure A2.23 IR of compound **149** (NaCl/film)

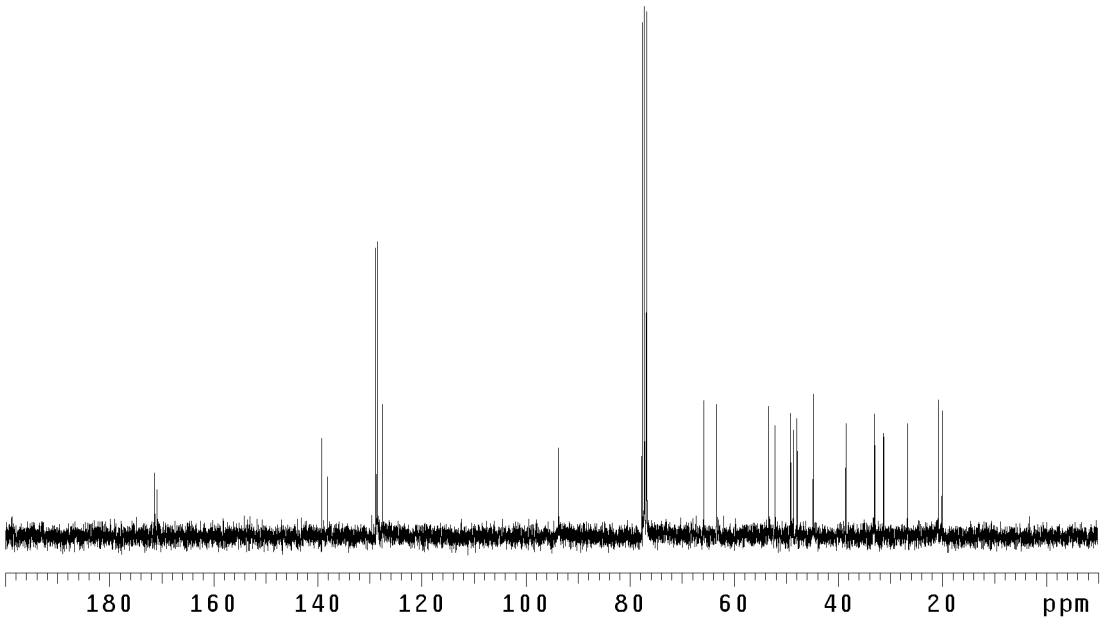


Figure A2.24 ^{13}C NMR of compound **149** (75 MHz, $CDCl_3$)

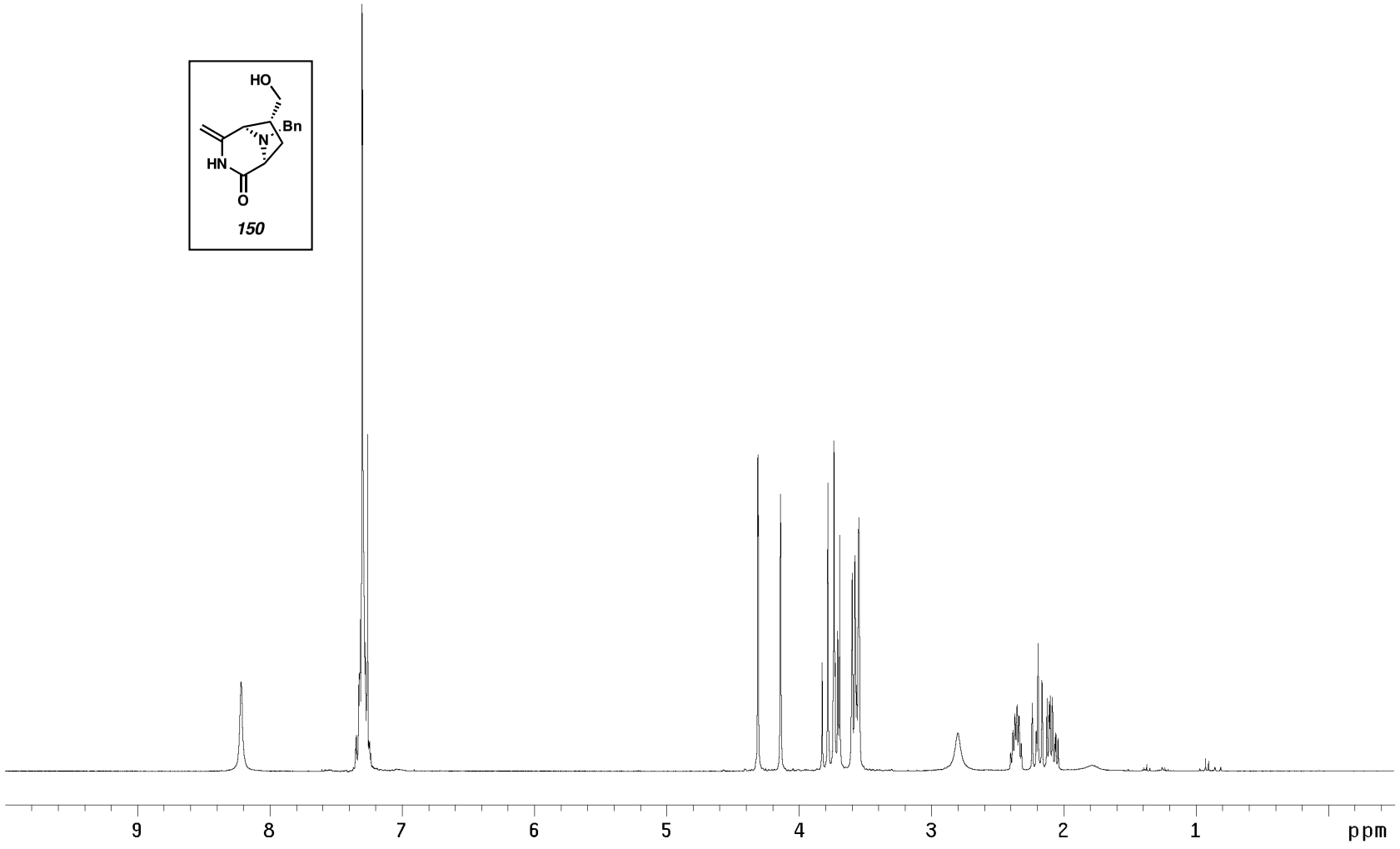


Figure A2.25 ^{1}H NMR of compound **150** (300 MHz, $CDCl_3$)

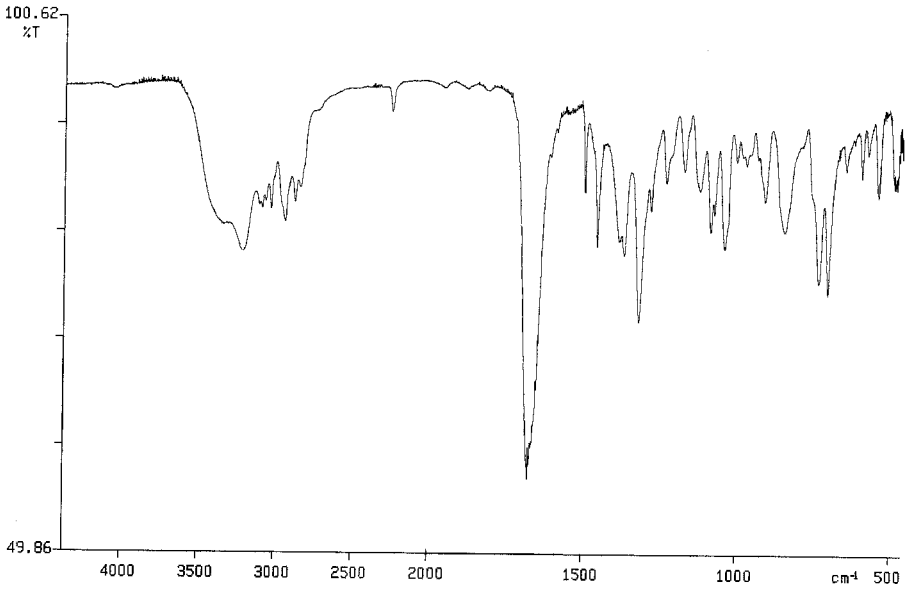


Figure A2.26 IR of compound **150** (NaCl/film)

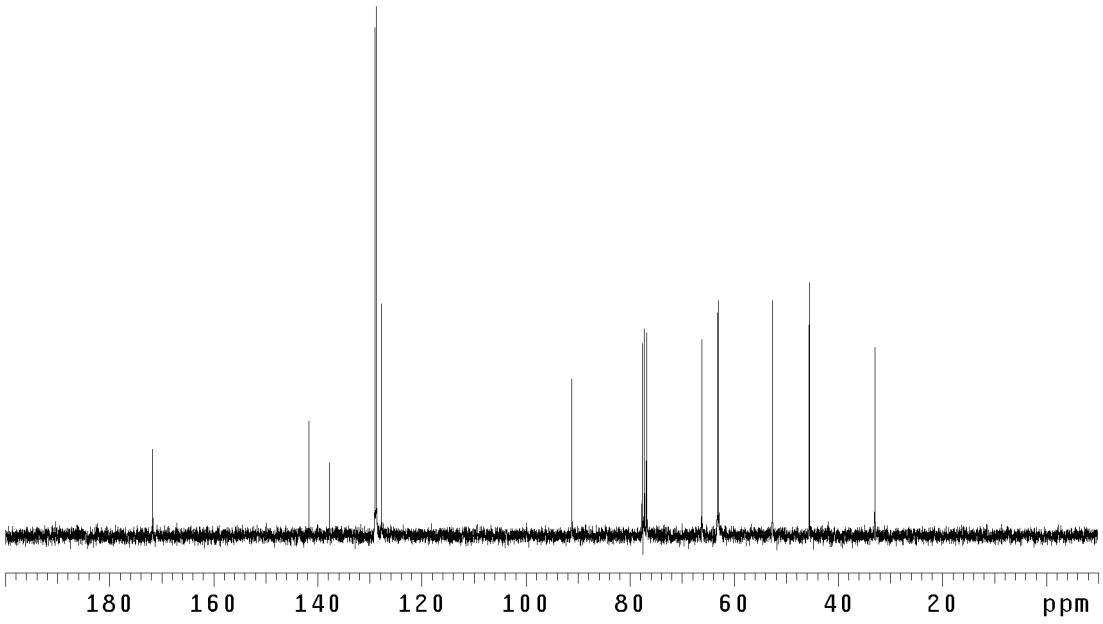


Figure A2.27 ^{13}C NMR of compound **150** (75 MHz, $CDCl_3$)

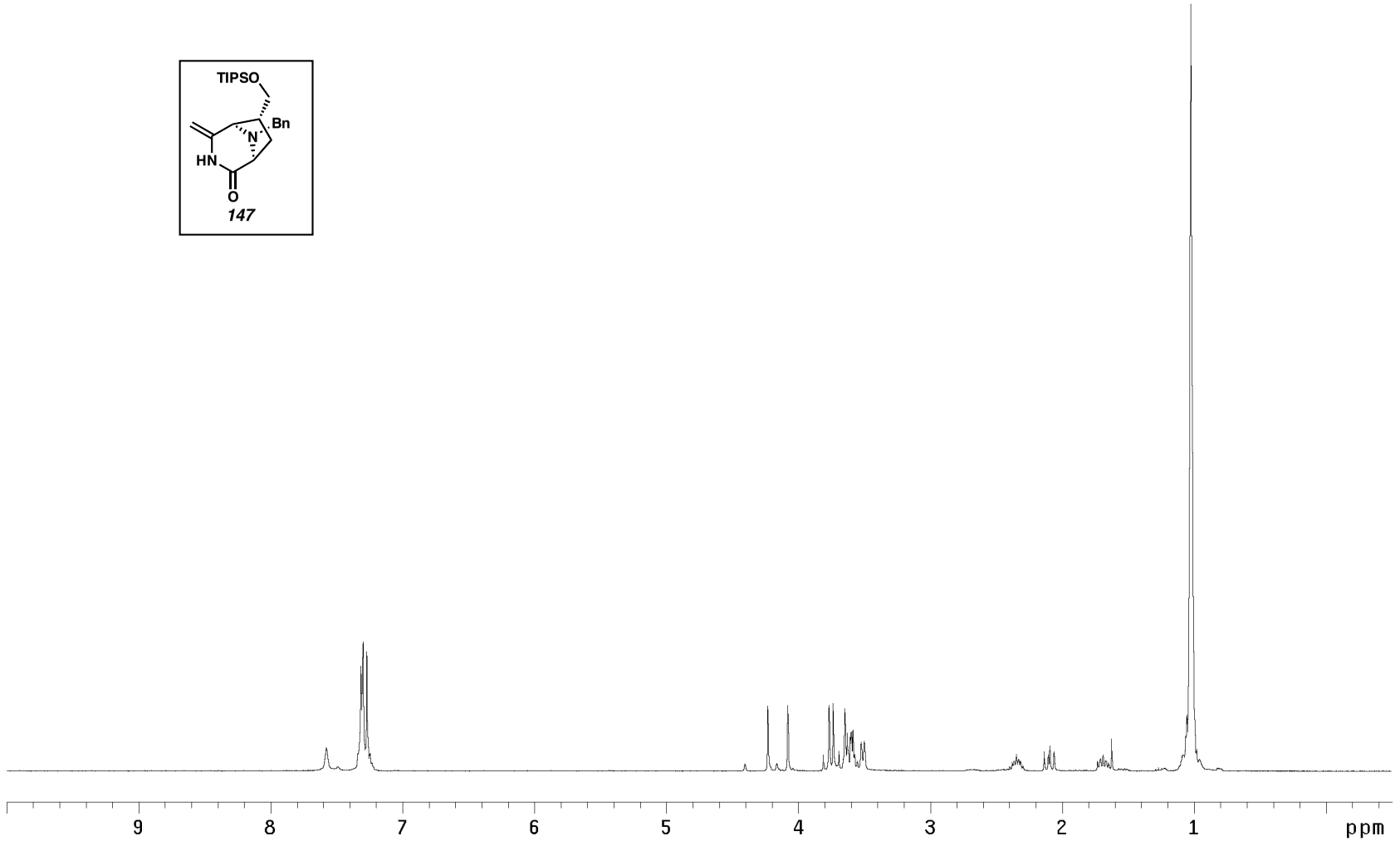


Figure A2.28 ^{1}H NMR of compound **147** (300 MHz, $CDCl_3$)

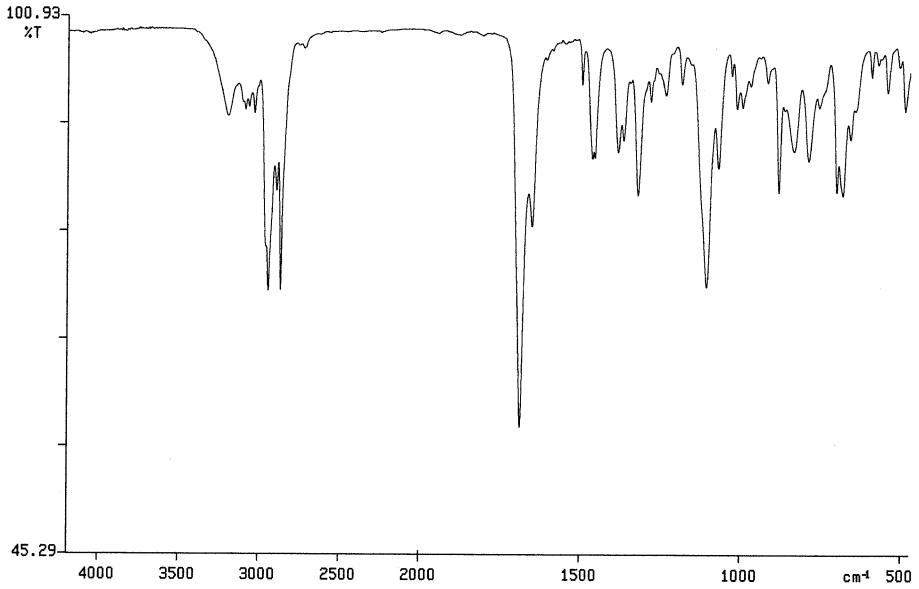


Figure A2.29 IR of compound **147** (NaCl/film)

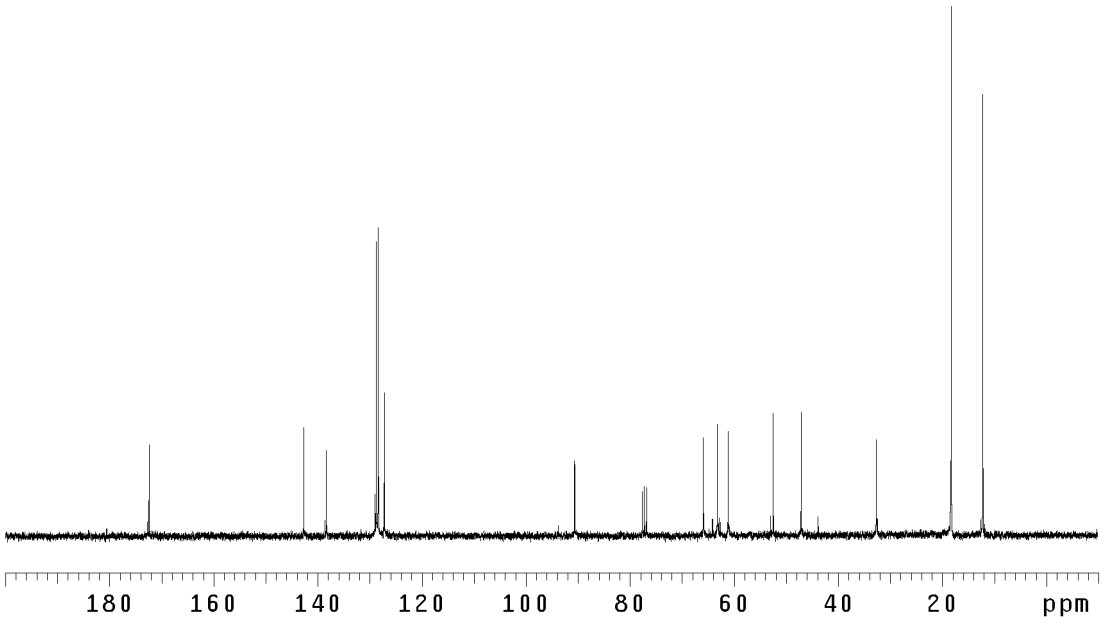


Figure A2.30 ^{13}C NMR of compound **147** (75 MHz, $CDCl_3$)

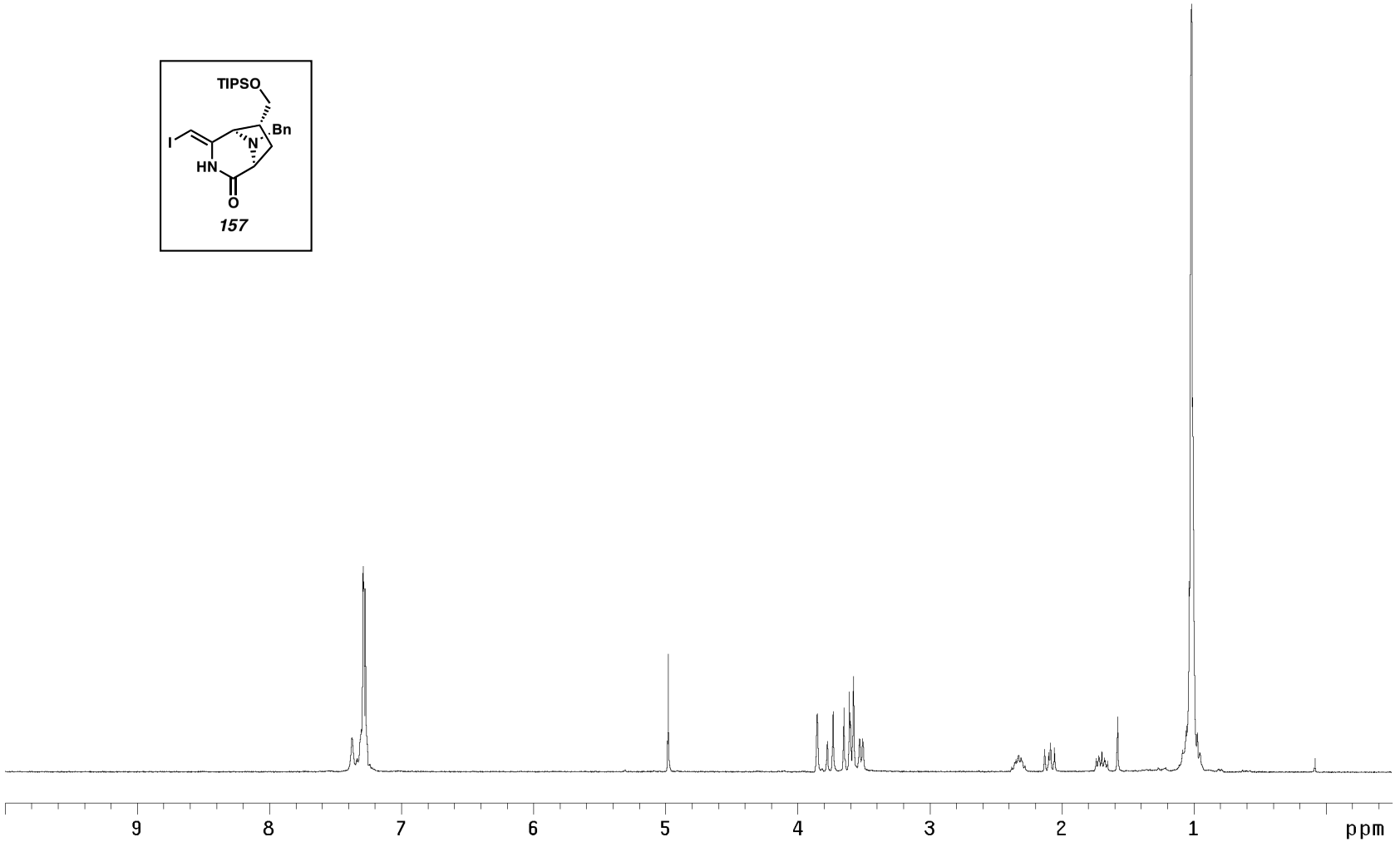


Figure A2.31 ^{1}HNMR of compound **157** (300 MHz, $CDCl_3$)

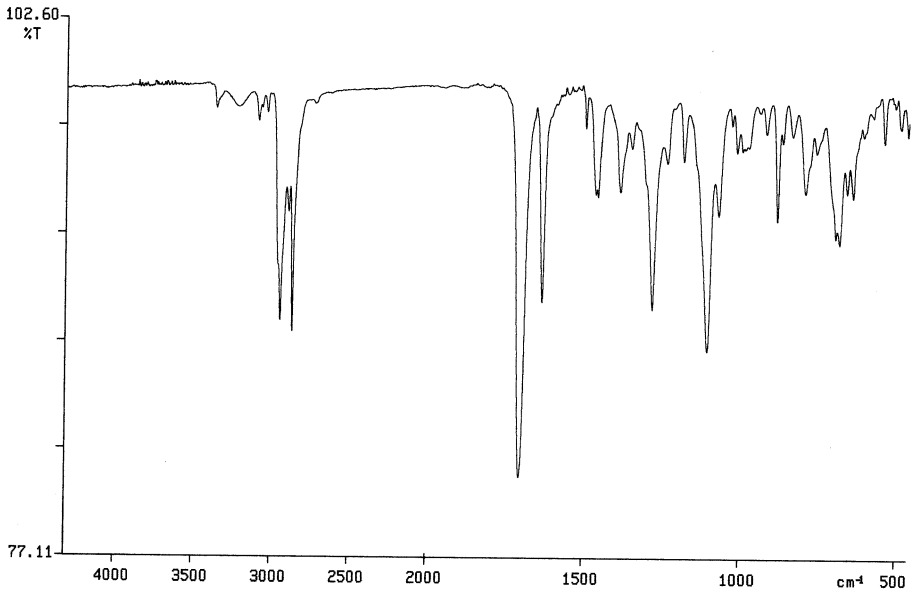


Figure A2.32 IR of compound **157** (NaCl/film)

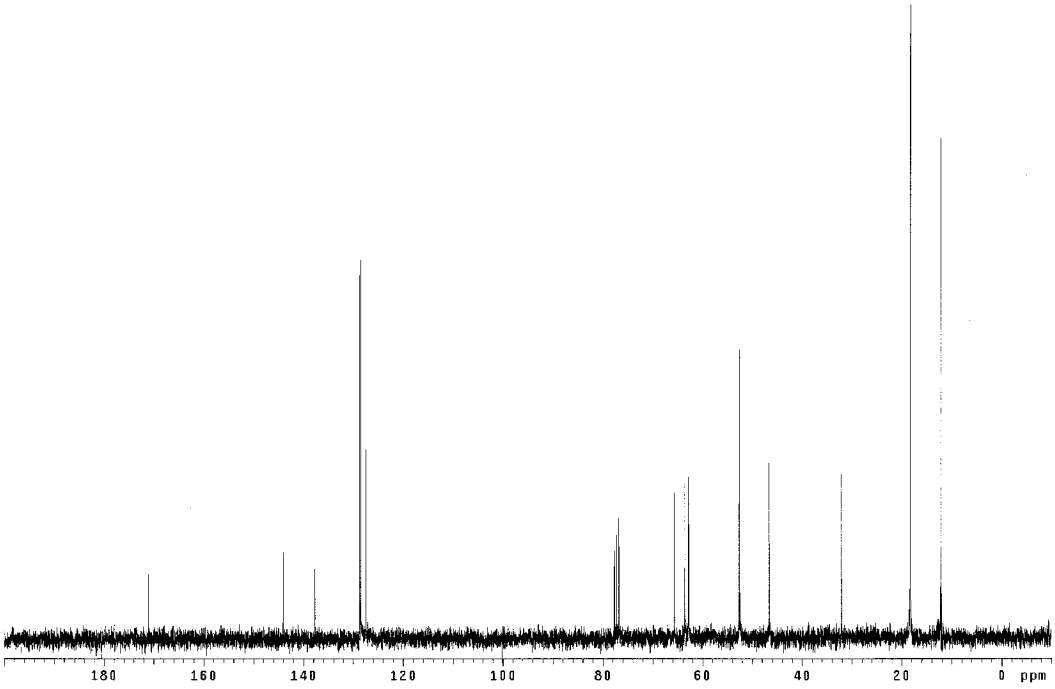


Figure A2.33 ^{13}C NMR of compound **157** (75 MHz, $CDCl_3$)

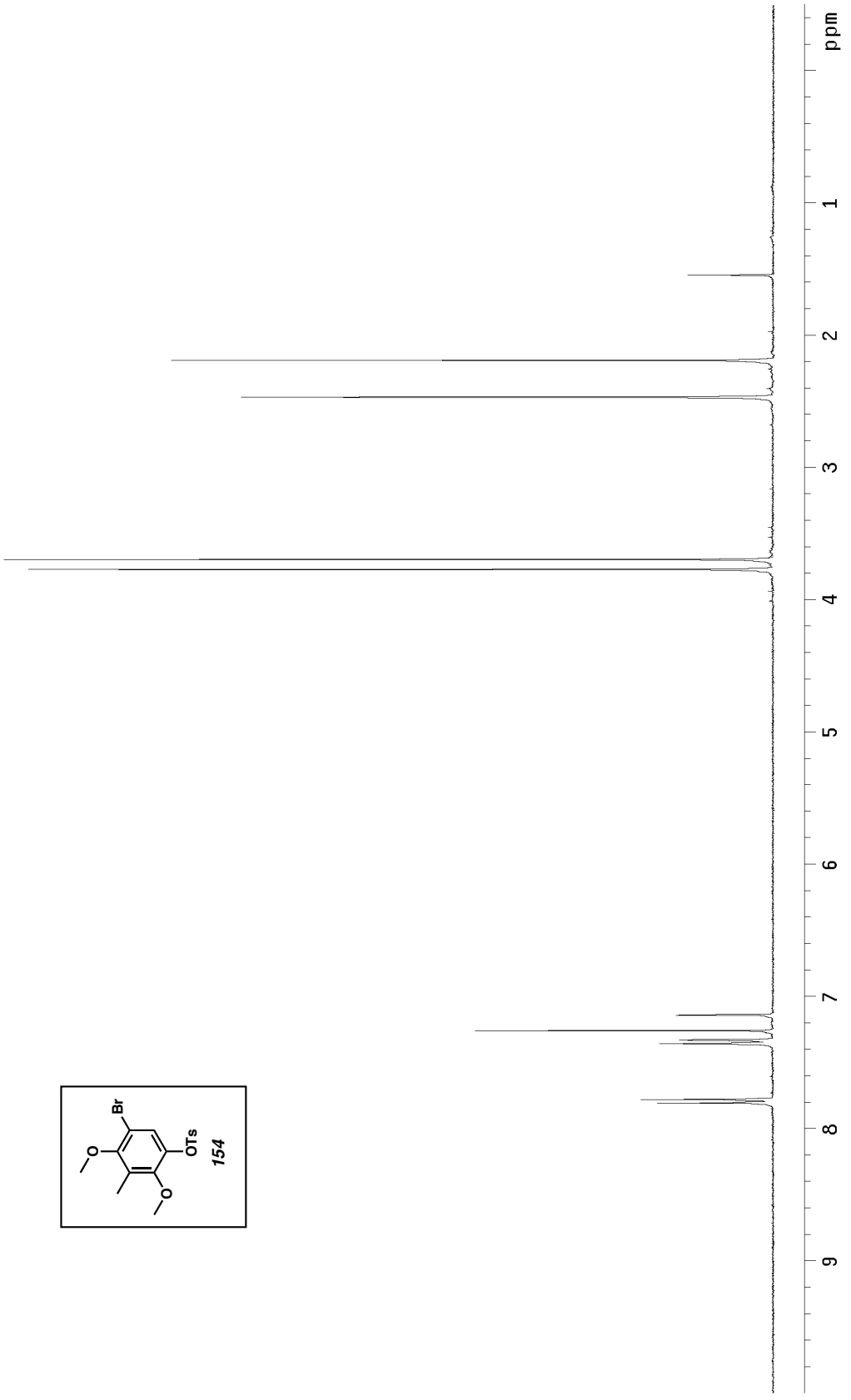


Figure A2.34 ^{1}H NMR of compound **154** (300 MHz, $CDCl_3$)

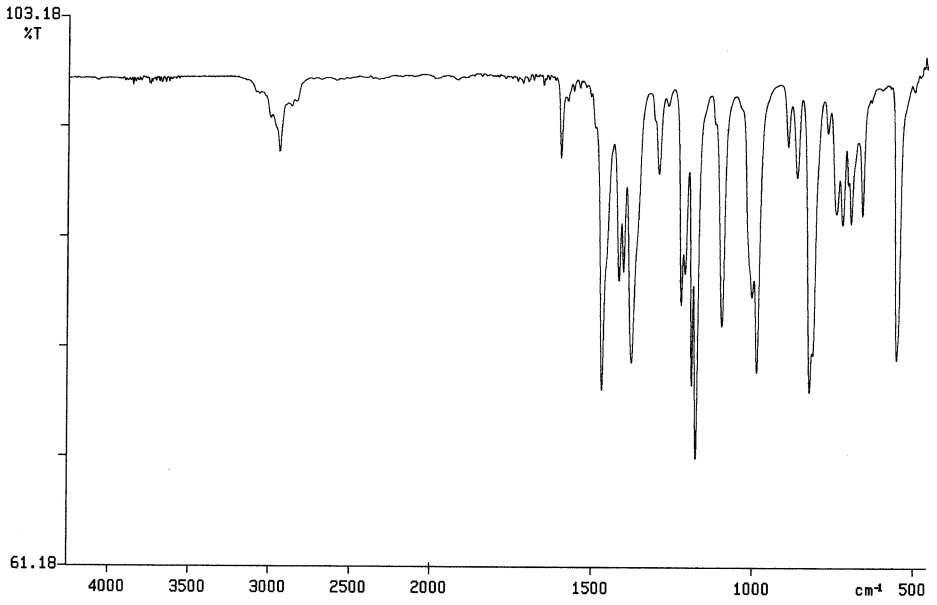


Figure A2.35 IR of compound **154** (NaCl/film)

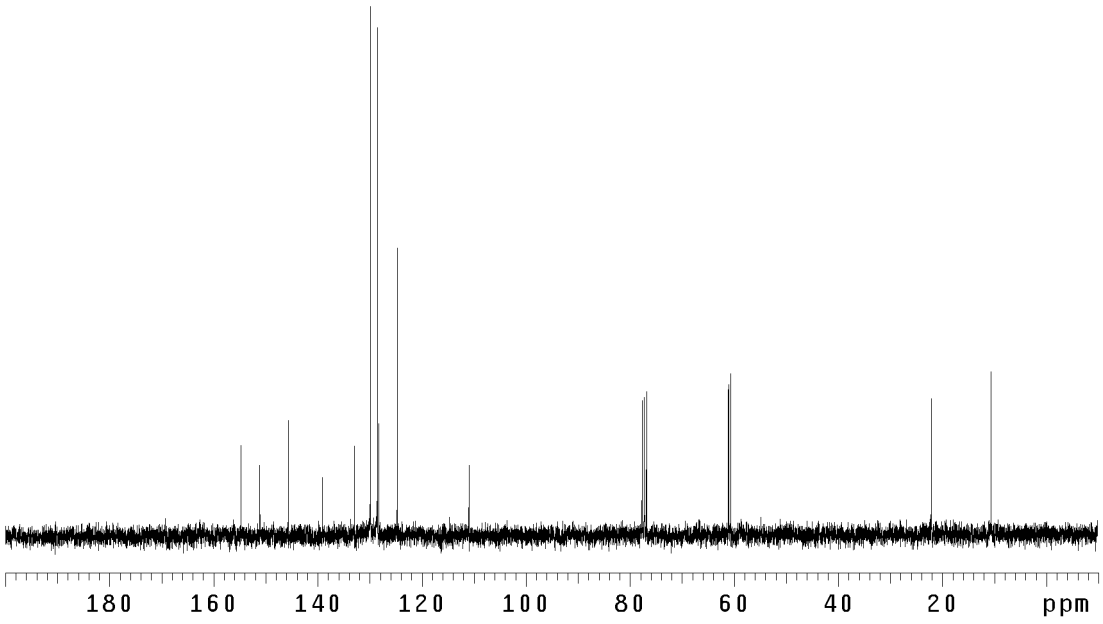


Figure A2.36 ^{13}C NMR of compound **154** (75 MHz, $CDCl_3$)

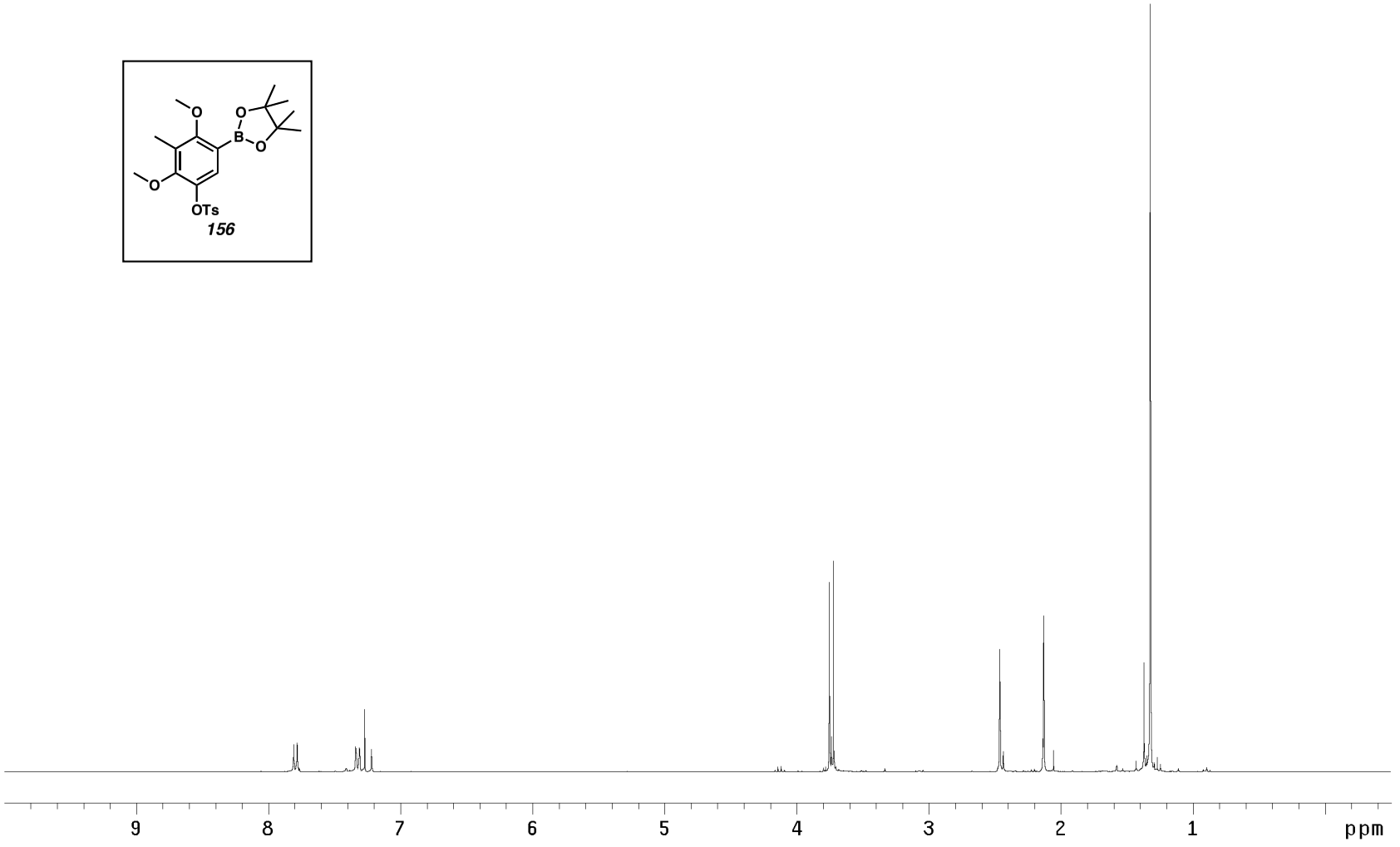


Figure A2.37 ^{1}H NMR of compound **156** (300 MHz, $CDCl_3$)

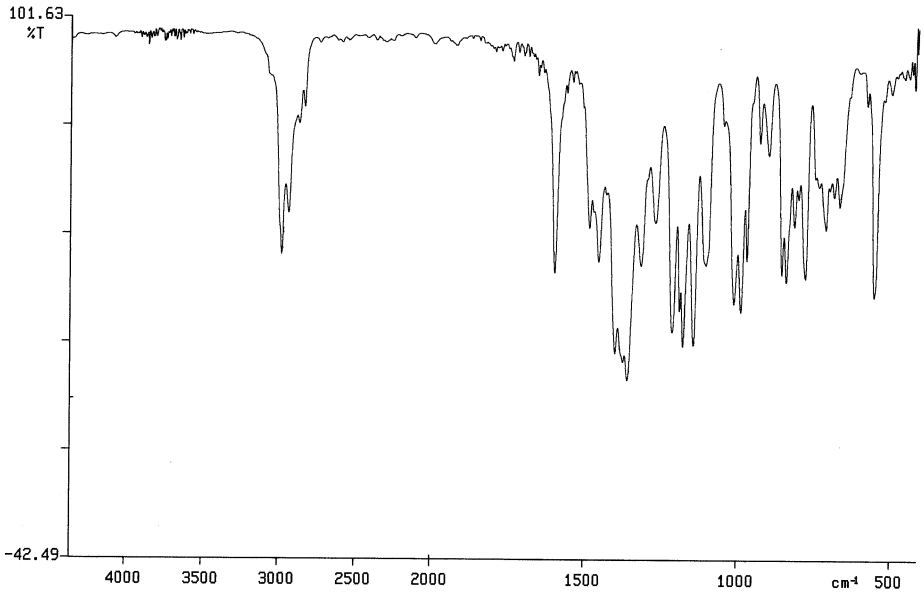


Figure A2.38 IR of compound **156** (NaCl/film)

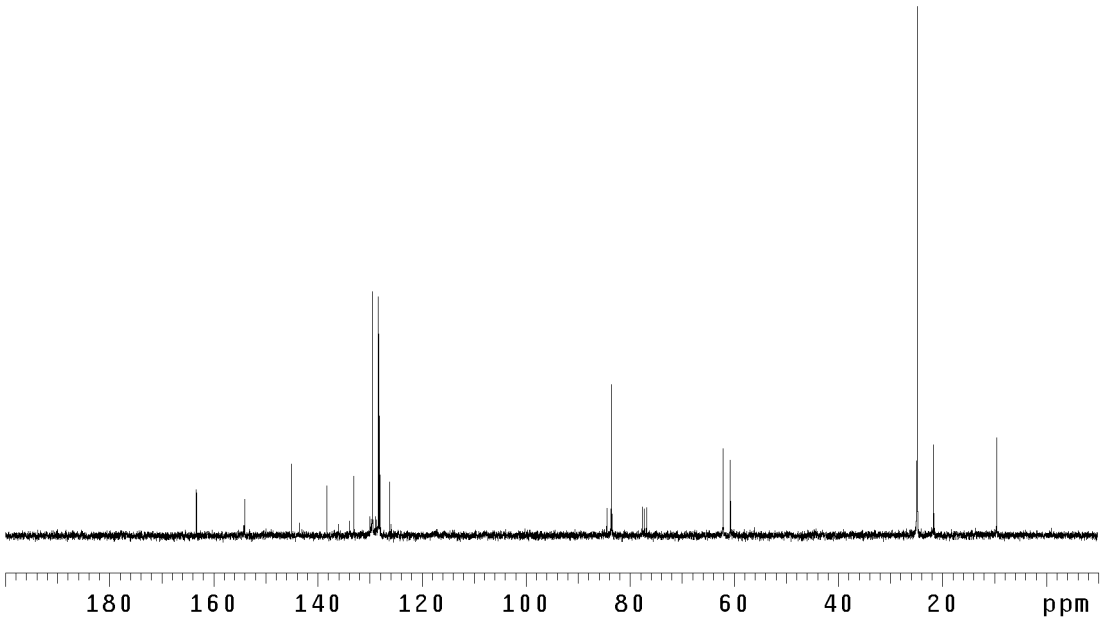


Figure A2.39 ^{13}C NMR of compound **156** (75 MHz, $CDCl_3$)

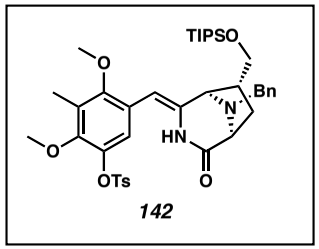


Figure A2.40 ^{1}H NMR of compound **142** (300 MHz, $CDCl_3$)

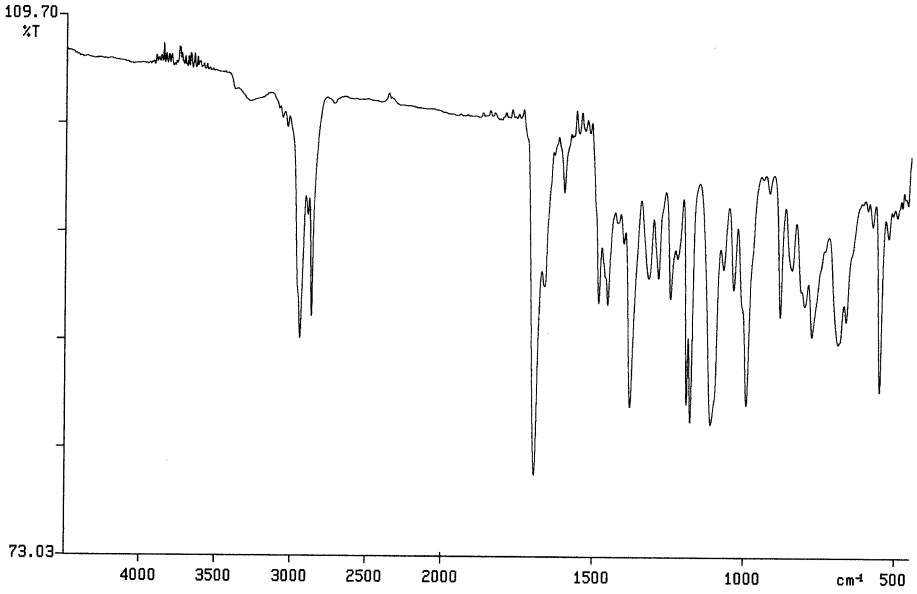


Figure A2.41 IR of compound **142** (NaCl/film)

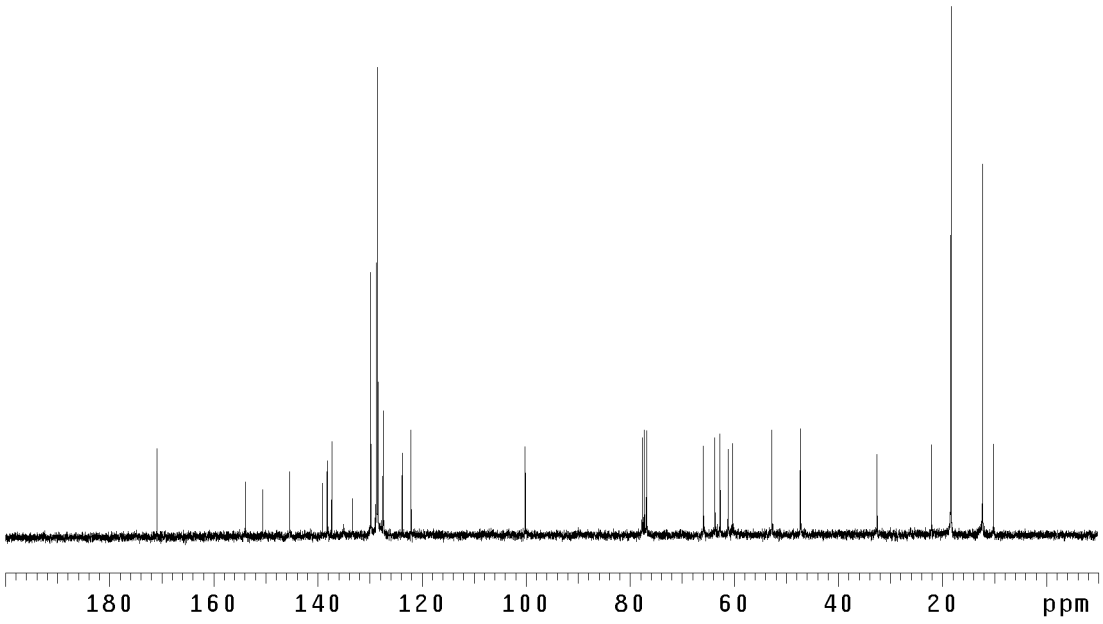


Figure A2.42 ^{13}C NMR of compound **142** (75 MHz, $CDCl_3$)

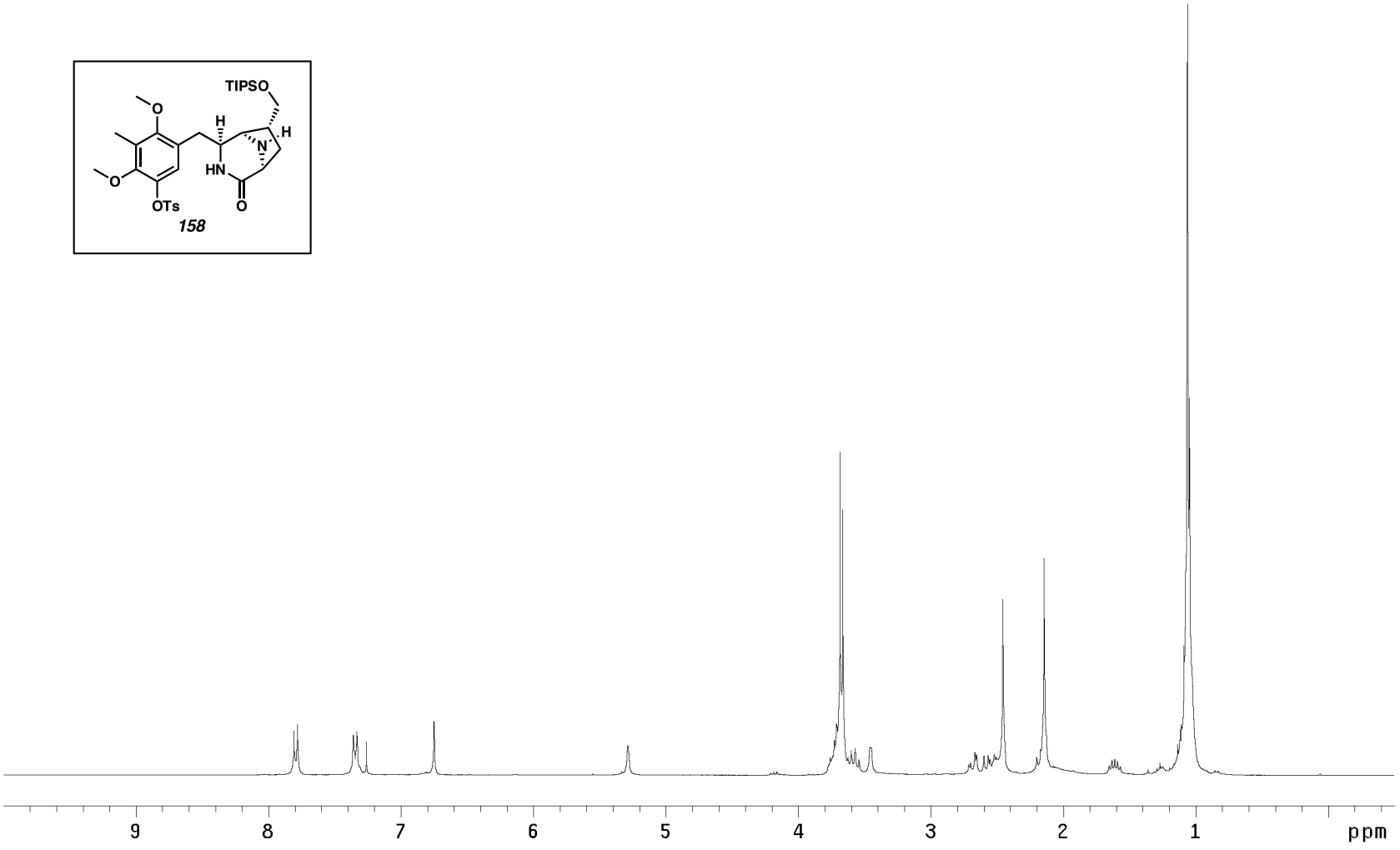


Figure A2.43 ^{1}H NMR of compound **158** (300 MHz, $CDCl_3$)

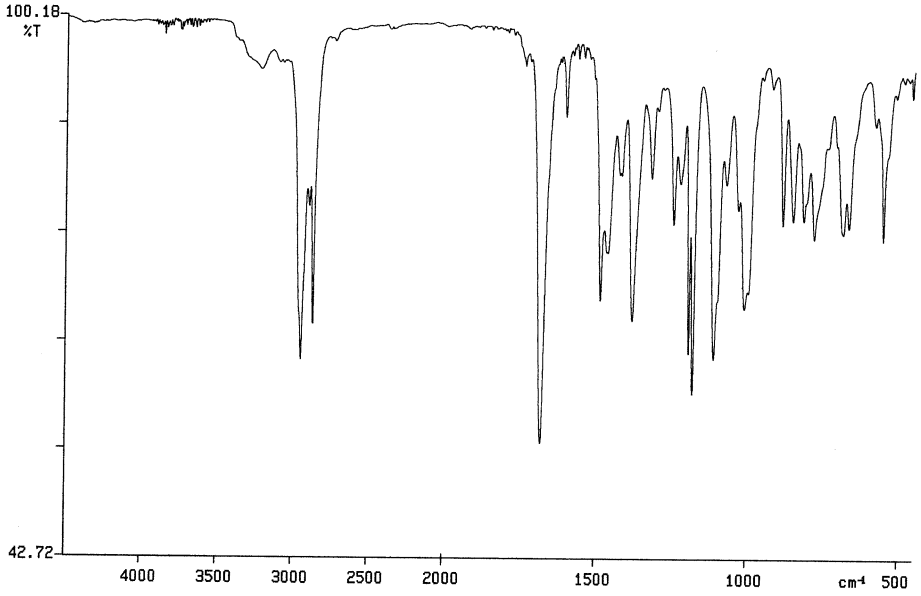


Figure A2.44 IR of compound **158** (NaCl/film)

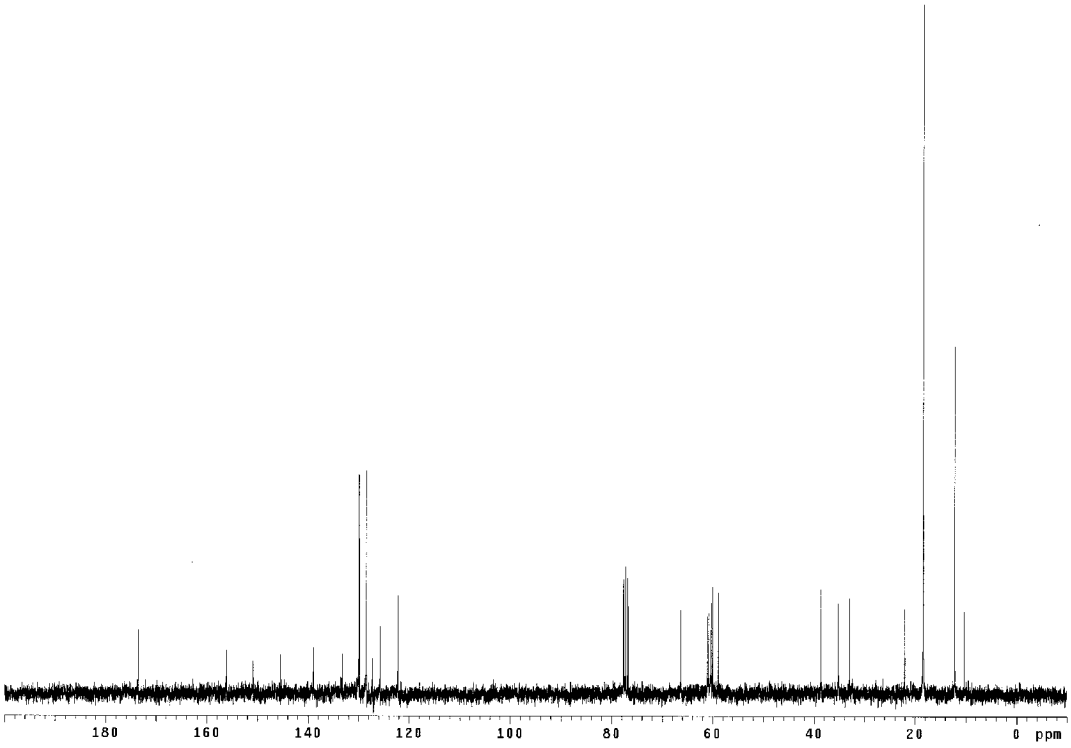


Figure A2.45 ^{13}C NMR of compound **158** (75 MHz, $CDCl_3$)

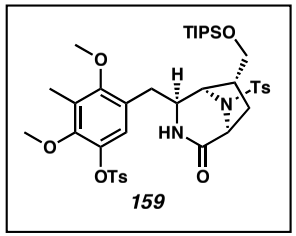


Figure A2.46 ^{1}H NMR of compound **159** (300 MHz, $CDCl_3$)

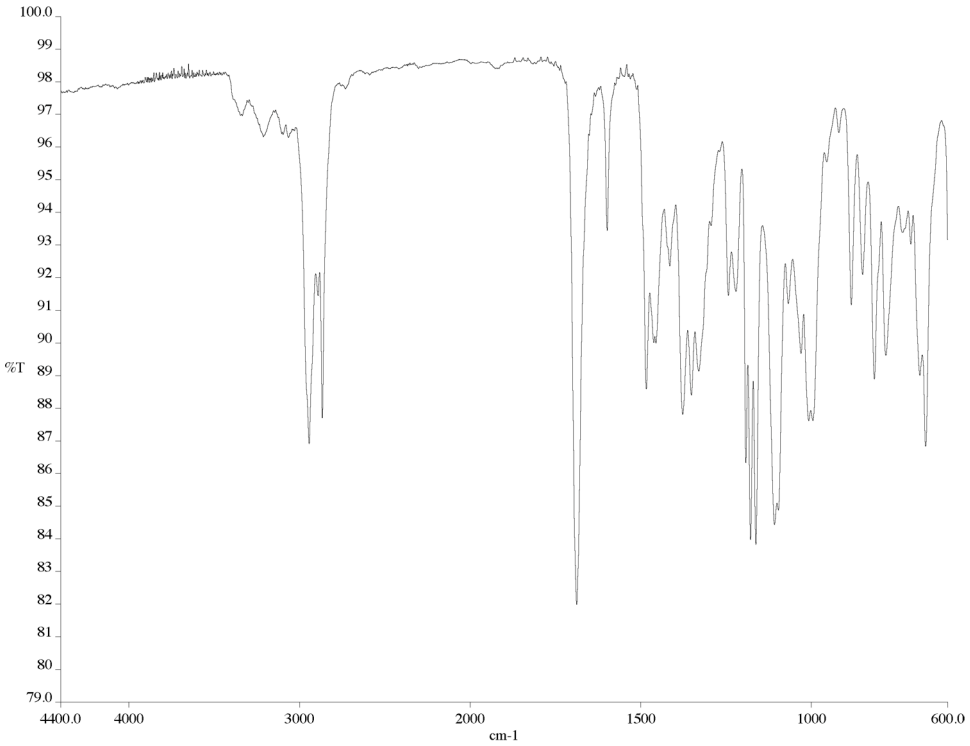


Figure A2.47 IR of compound **159** (NaCl/film)

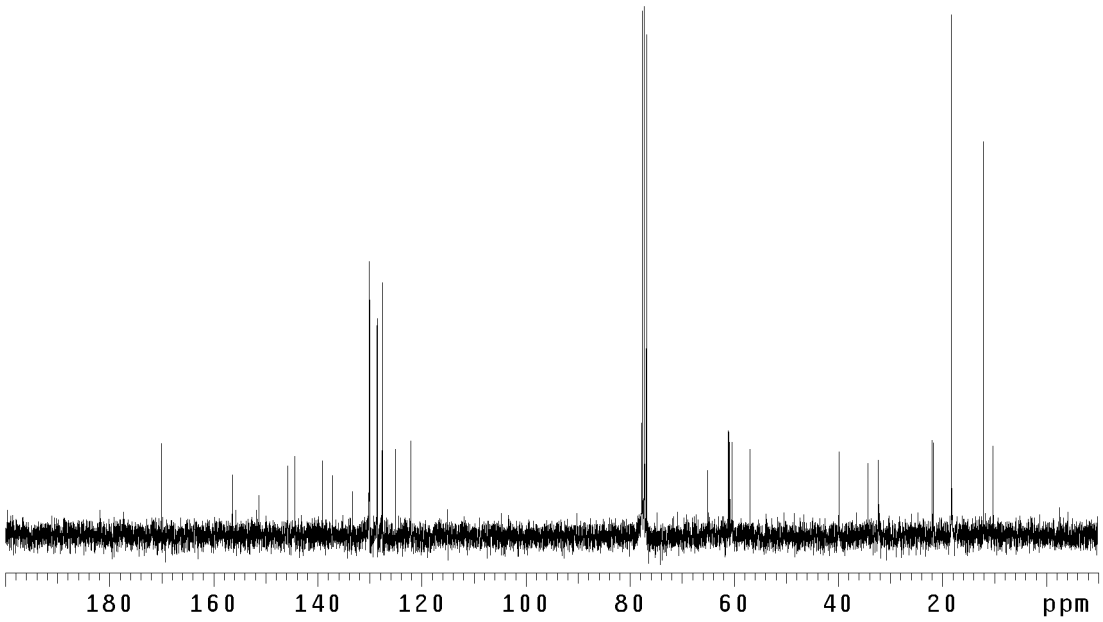


Figure A2.48 ^{13}C NMR of compound **159** (75 MHz, $CDCl_3$)

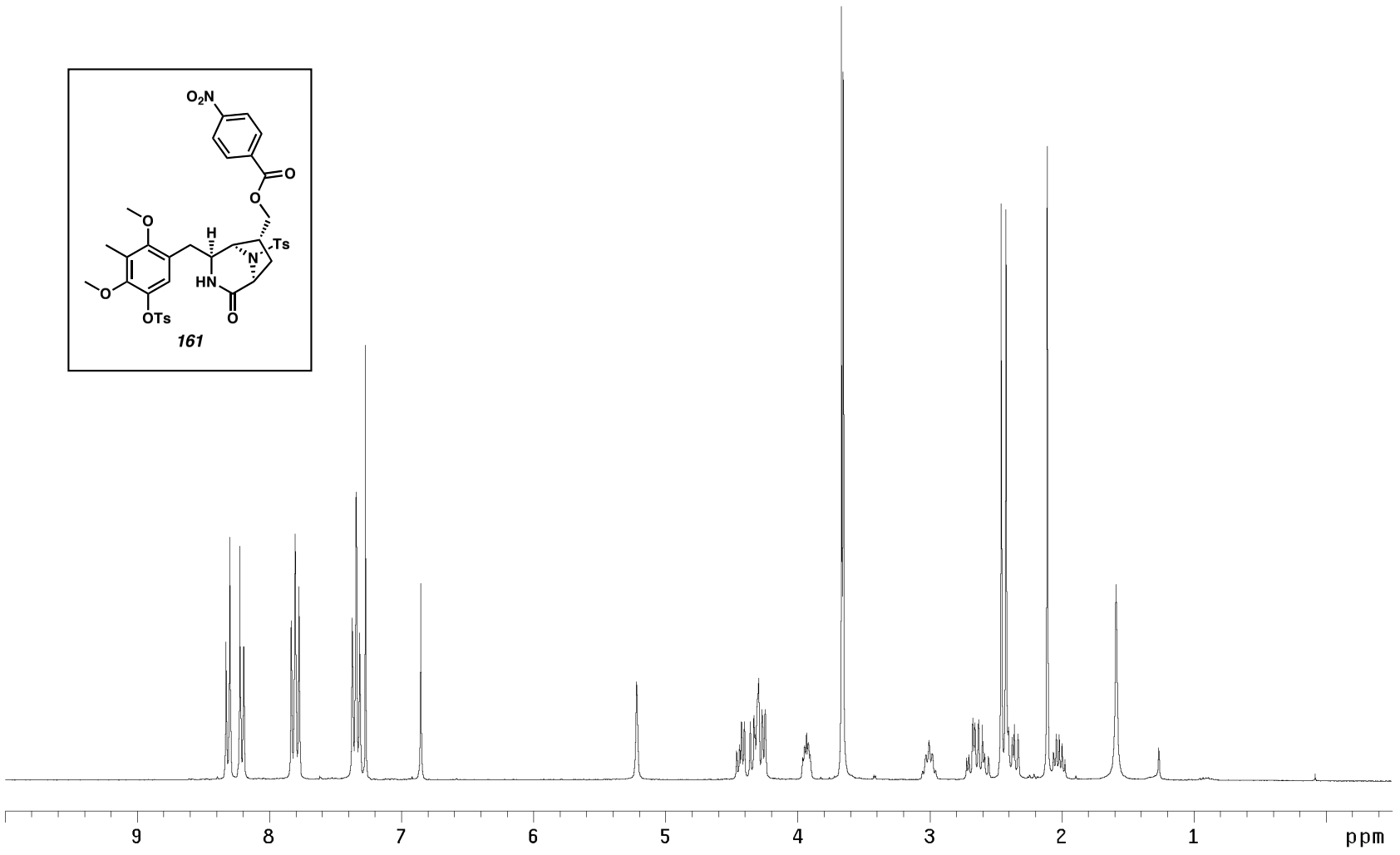


Figure A2.49 ^{1}H NMR of compound **161** (300 MHz, $CDCl_3$)

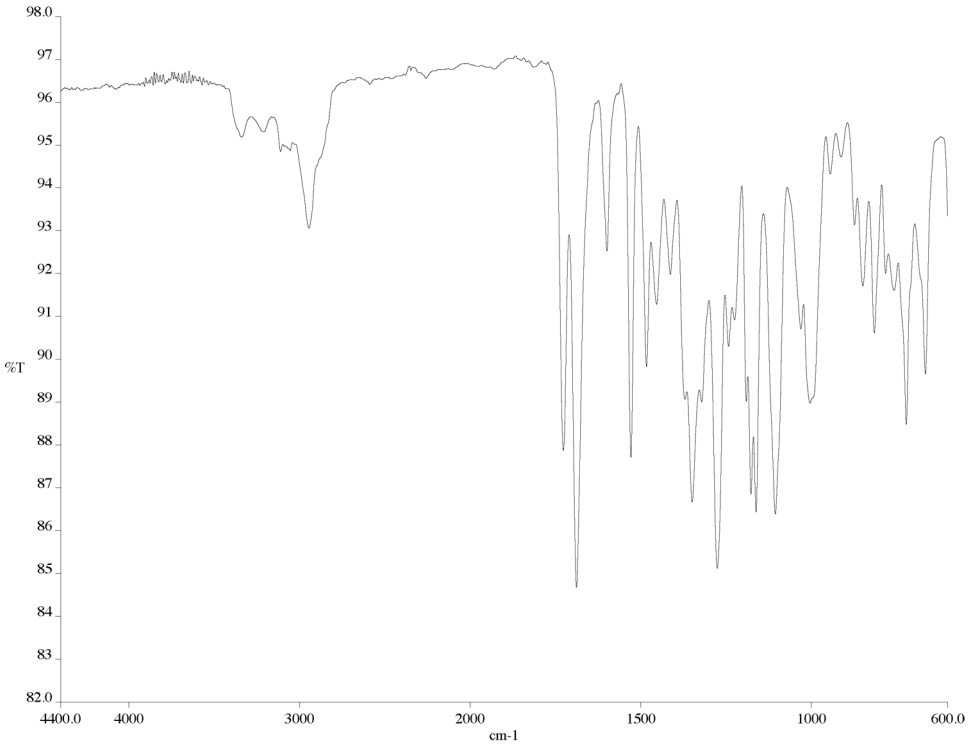


Figure A2.50 IR of compound **161** (NaCl/film)

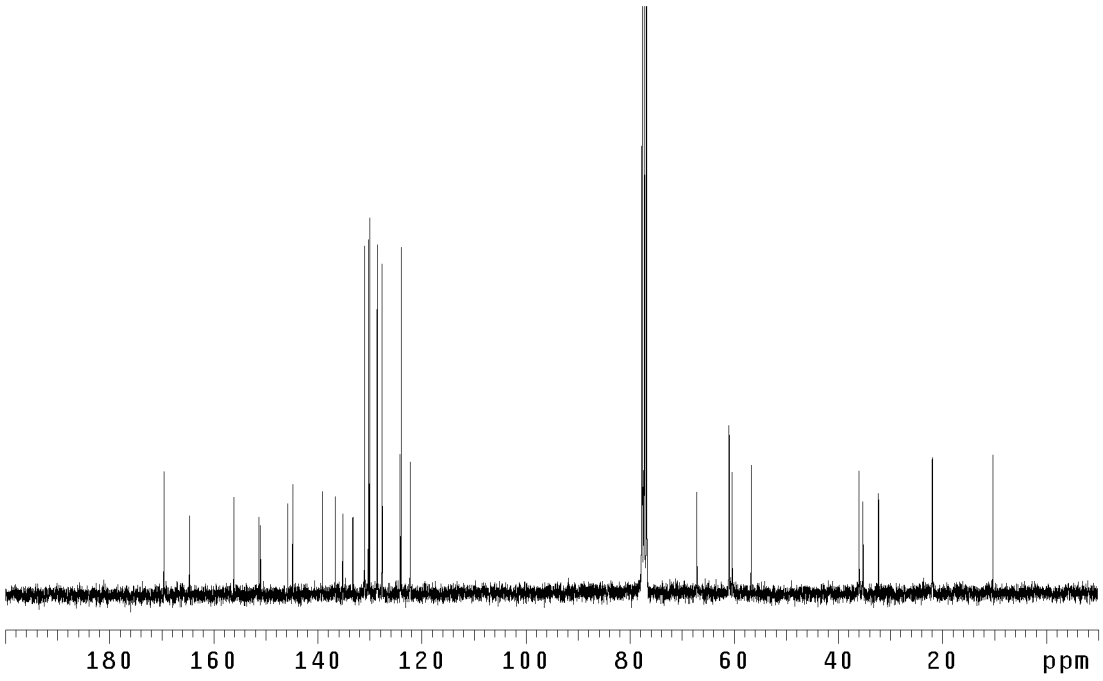


Figure A2.51 ^{13}C NMR of compound **161** (75 MHz, $CDCl_3$)

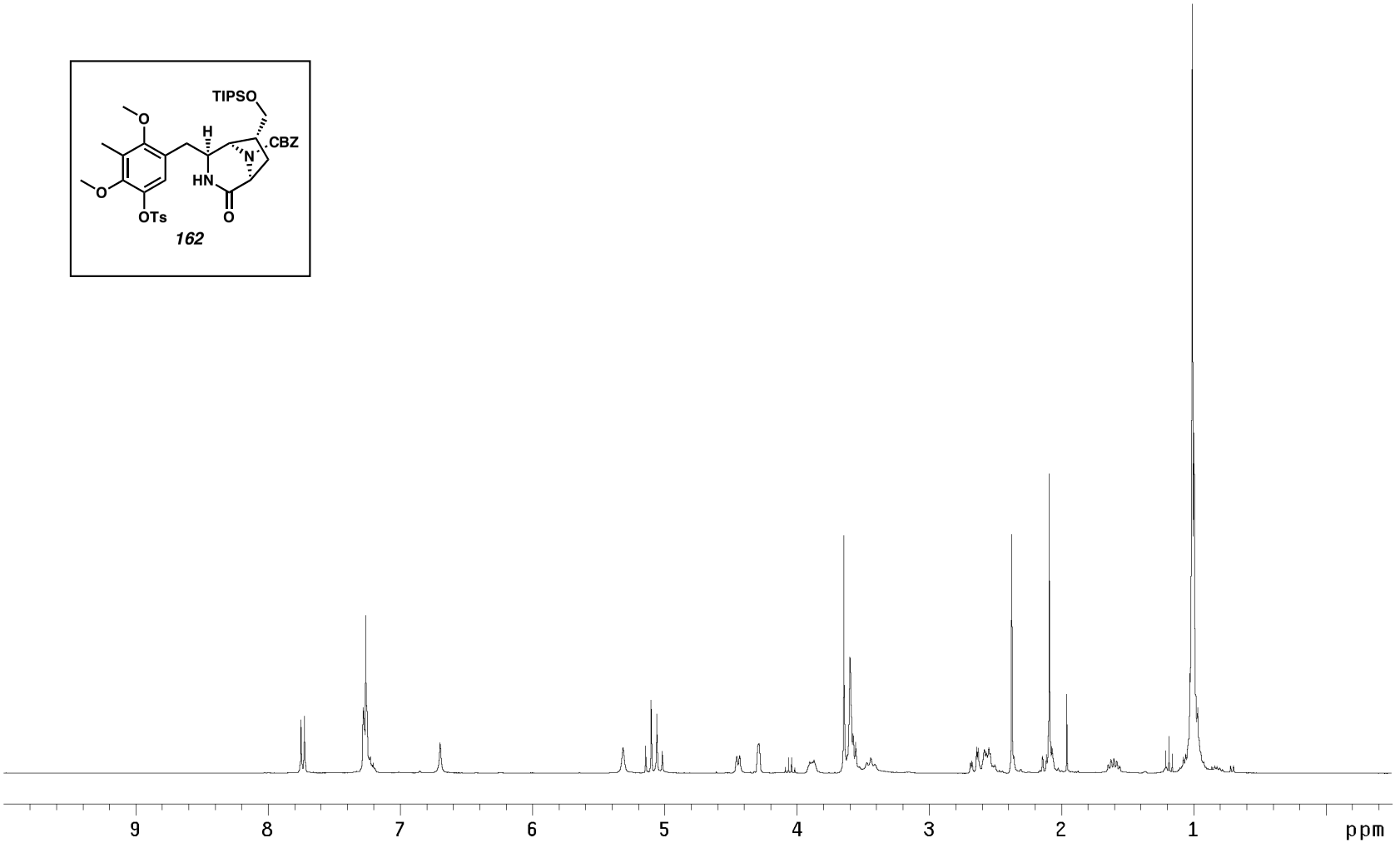


Figure A2.52 ^{1}H NMR of compound **162** (300 MHz, $CDCl_3$, 50 °C)

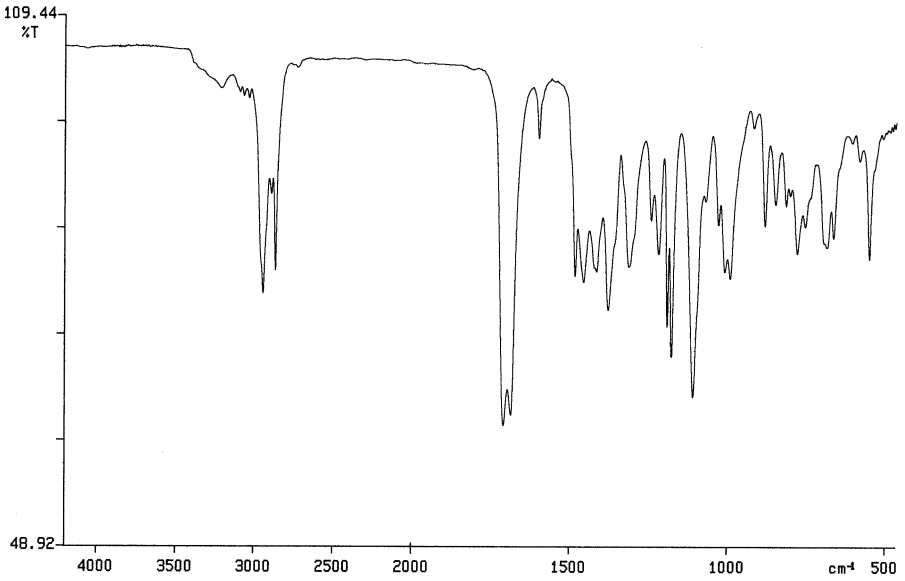


Figure A2.53 IR of compound **162** (NaCl/film)

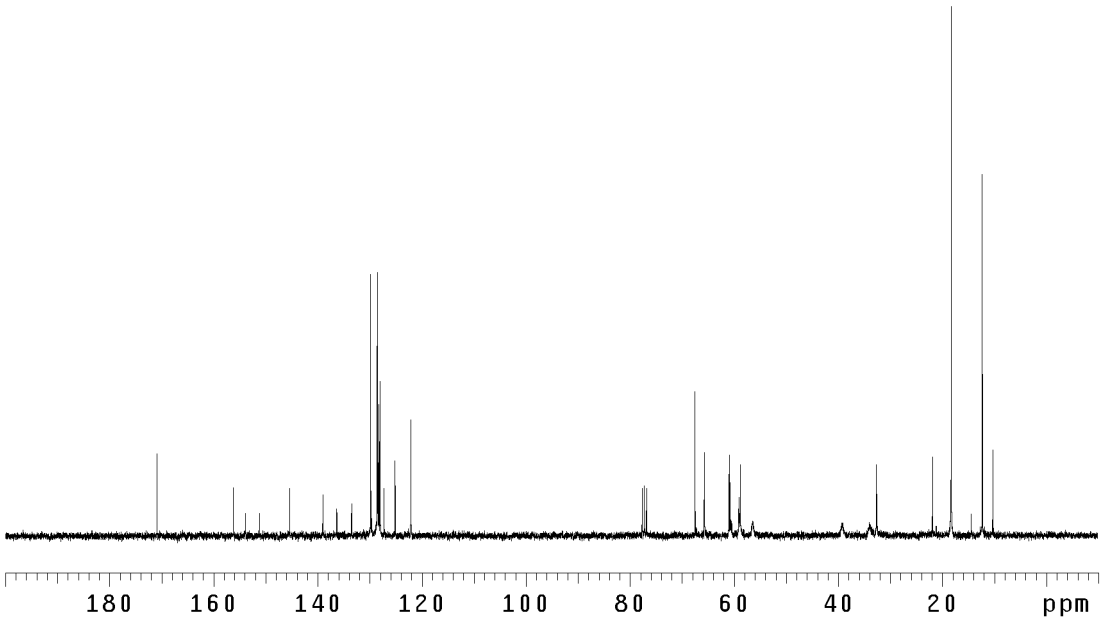


Figure A2.54 ^{13}C NMR of compound **162** (75 MHz, $CDCl_3$, 50 °C)

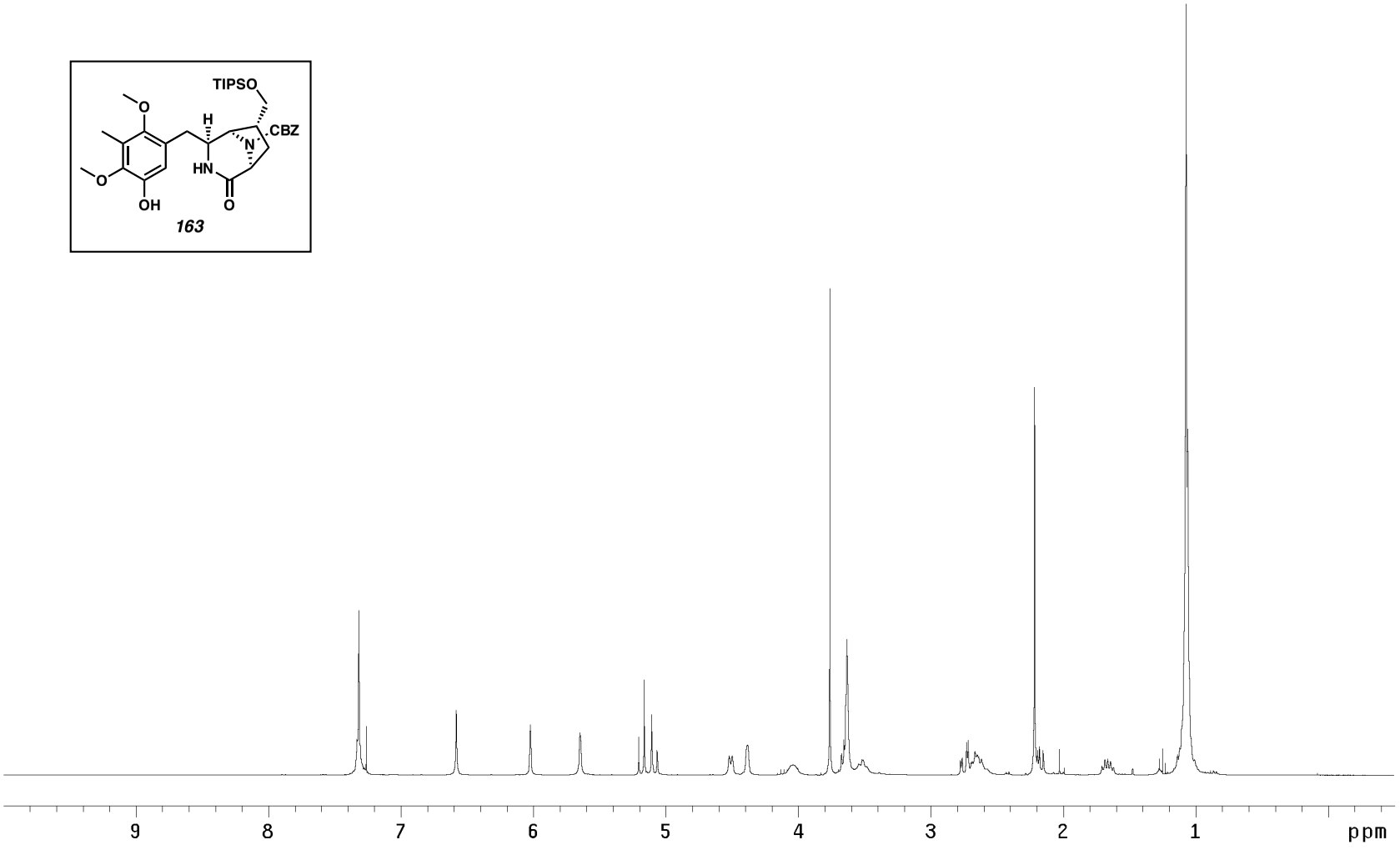


Figure A2.55 ^{1}H NMR of compound **163** (300 MHz, $CDCl_3$, 50 °C)

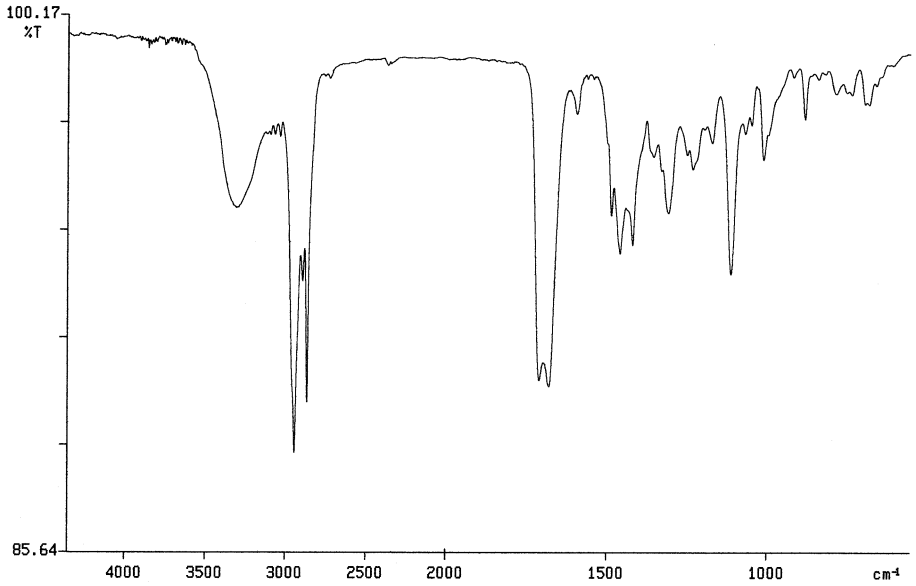


Figure A2.56 IR of compound **163** (NaCl/film)

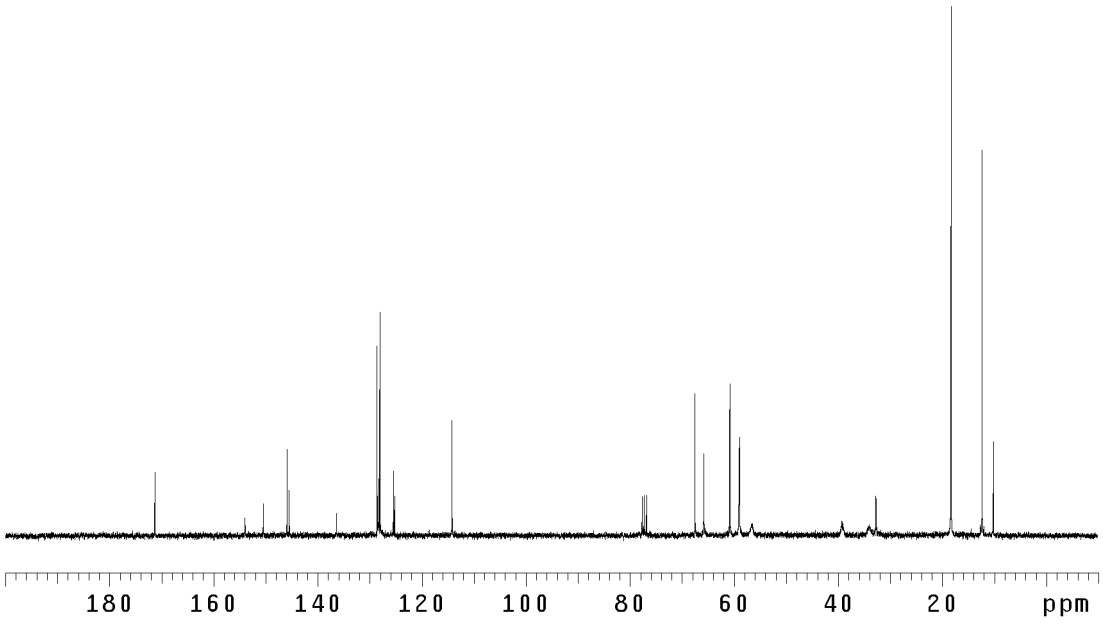
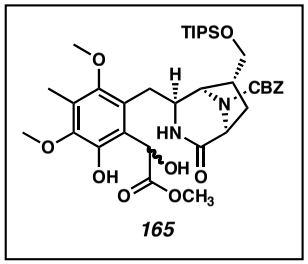


Figure A2.57 ^{13}C NMR of compound **163** (75 MHz, $CDCl_3$, 50 °C)



165

Figure A2.58 ^{1}H NMR of compound **165** (300 MHz, $CDCl_3$, 57 °C)

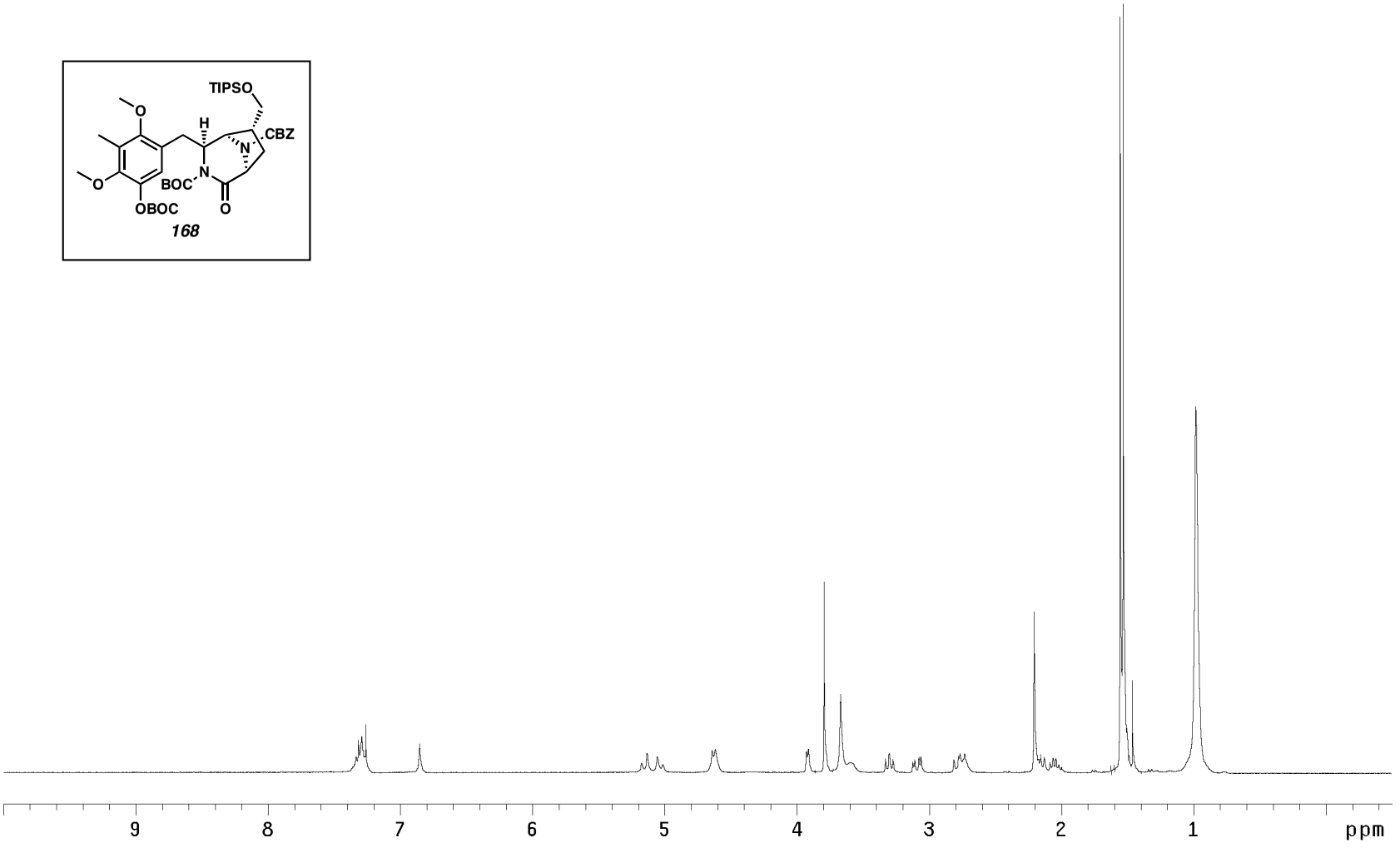


Figure A2.59 ^{1}H NMR of compound **168** (300 MHz, $CDCl_3$, 50 °C)

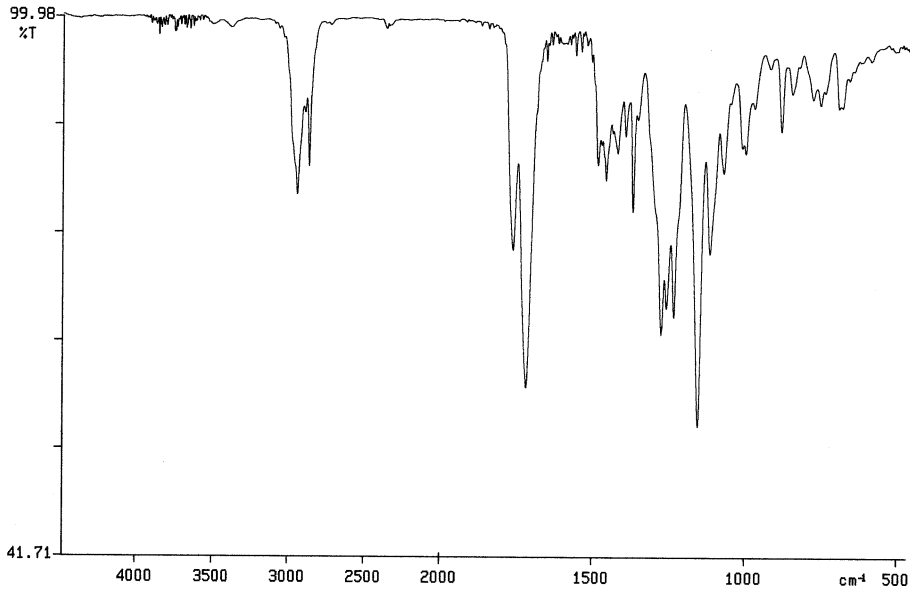


Figure A2.60 IR of compound **168** (NaCl/film)

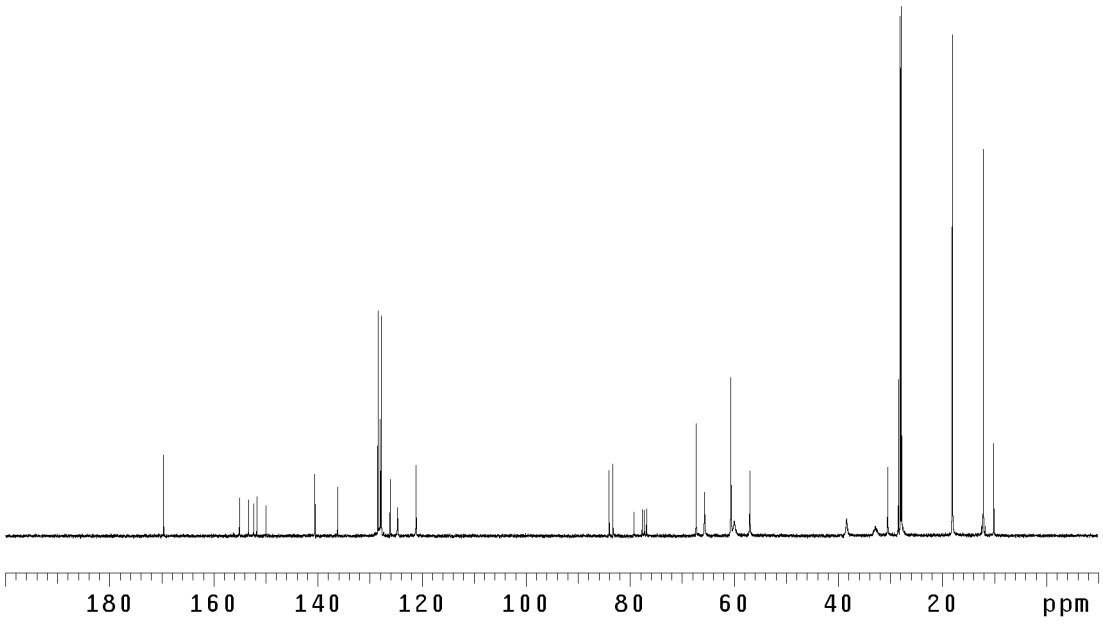


Figure A2.61 ^{13}C NMR of compound **168** (75 MHz, $CDCl_3$, 50 °C)

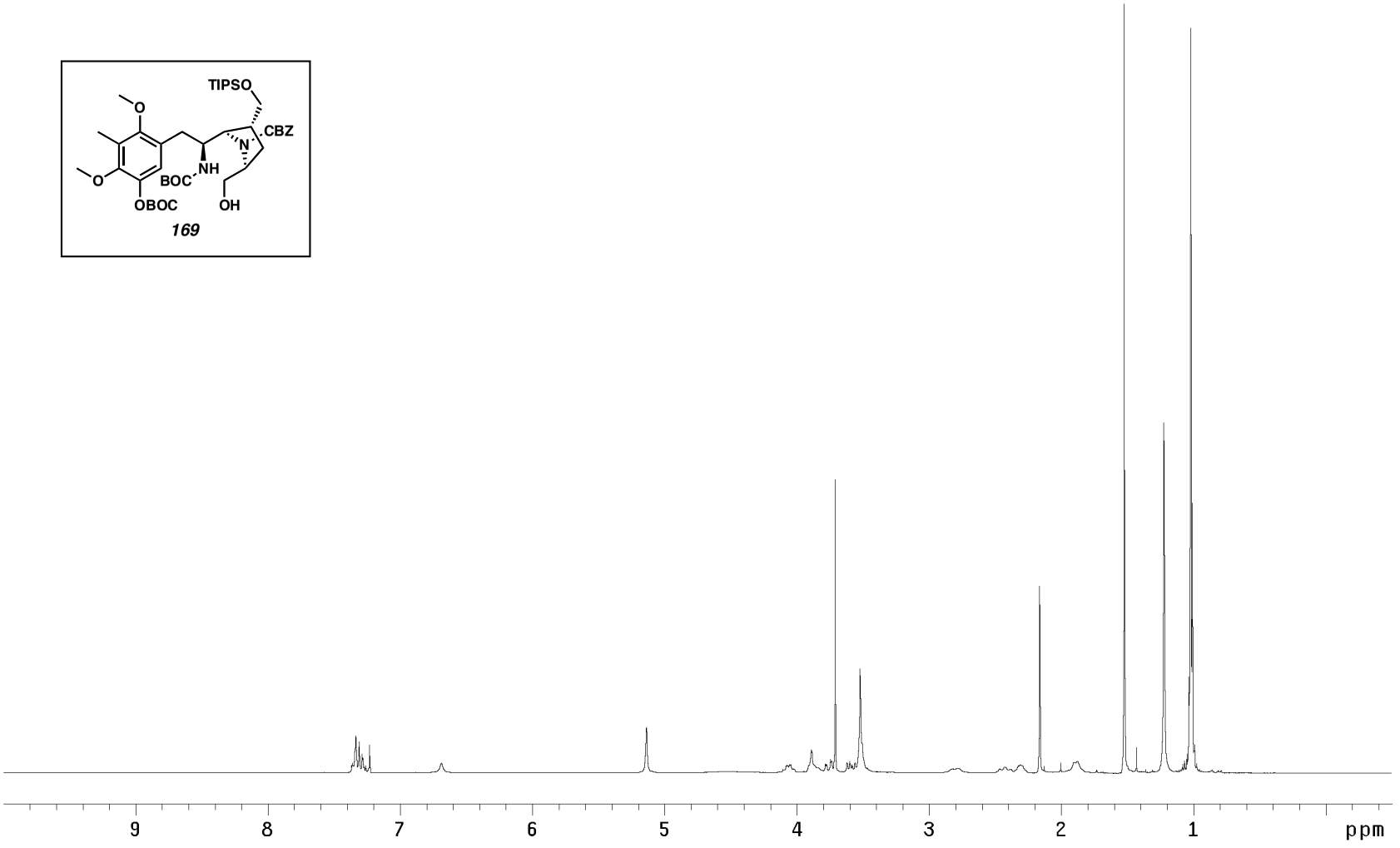


Figure A2.62 ^{1}H NMR of compound **169** (300 MHz, $CDCl_3$, 50 °C)

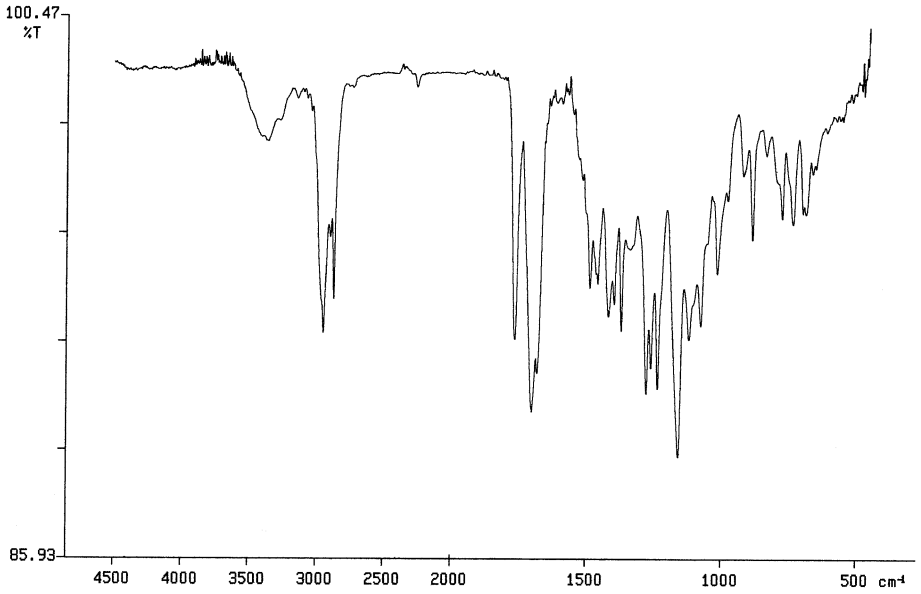


Figure A2.63 IR of compound **169** (NaCl/film)

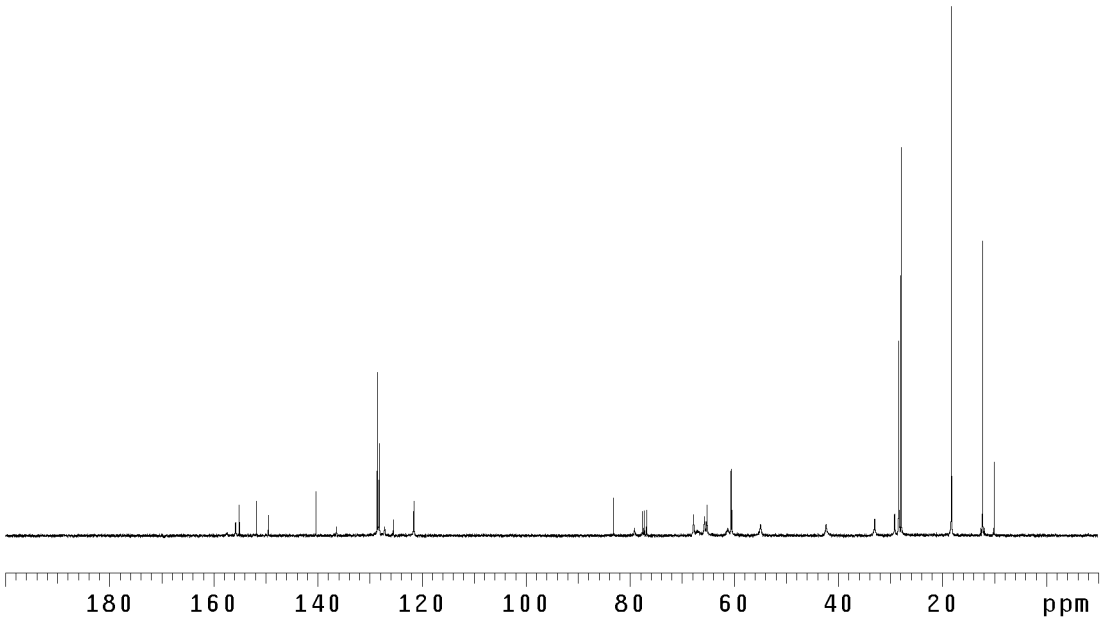


Figure A2.64 ^{13}C NMR of compound **169** (75 MHz, $CDCl_3$, 50 °C)

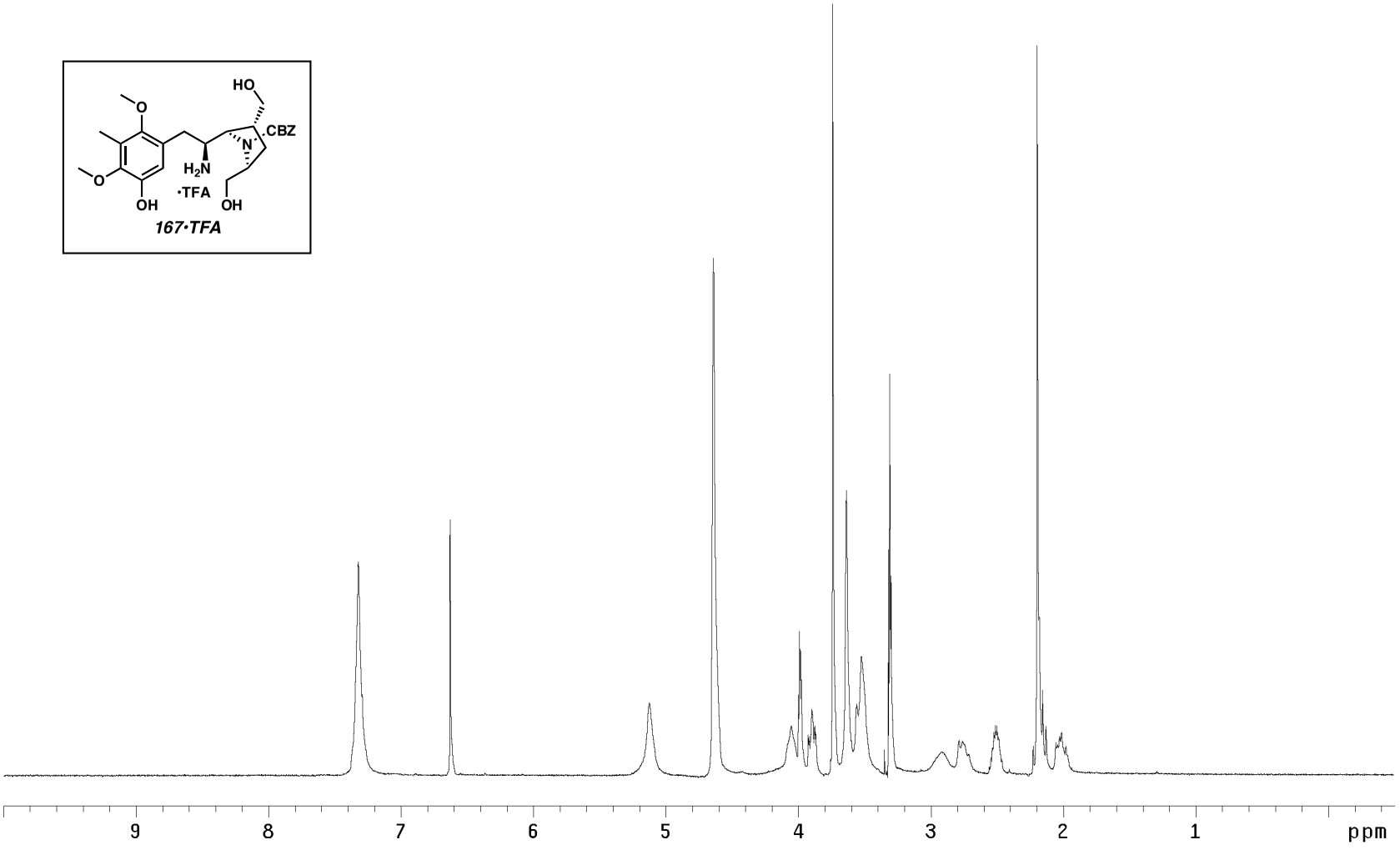


Figure A2.65 ^{1}H NMR of compound **167** (300 MHz, CD_3OD, 50 °C)

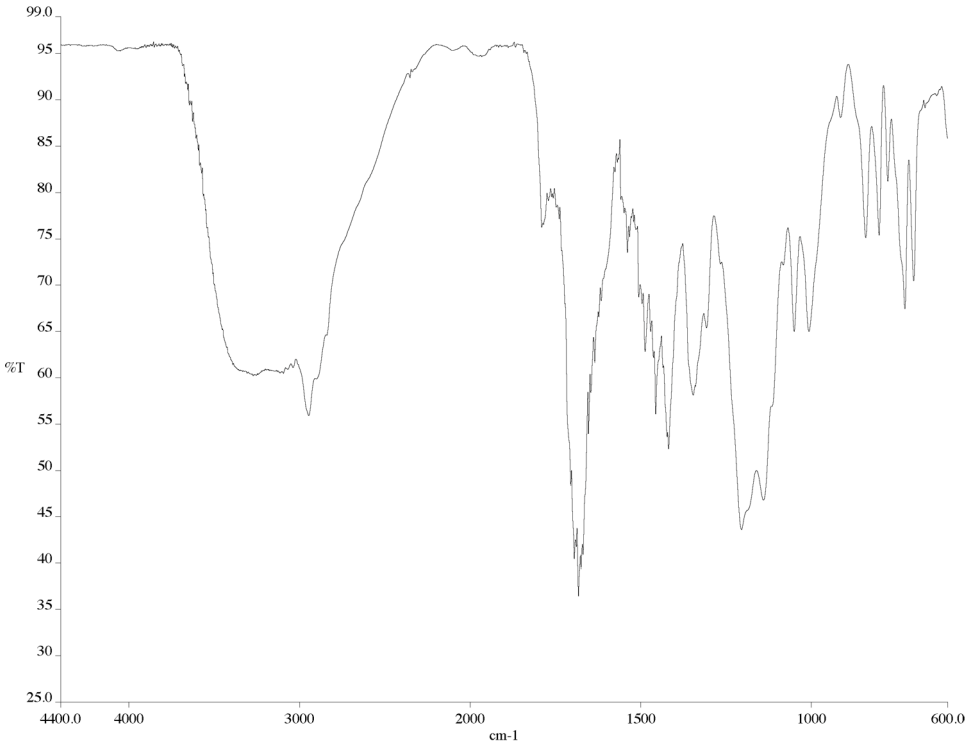


Figure A2.66 IR of compound **167** (NaCl/film)

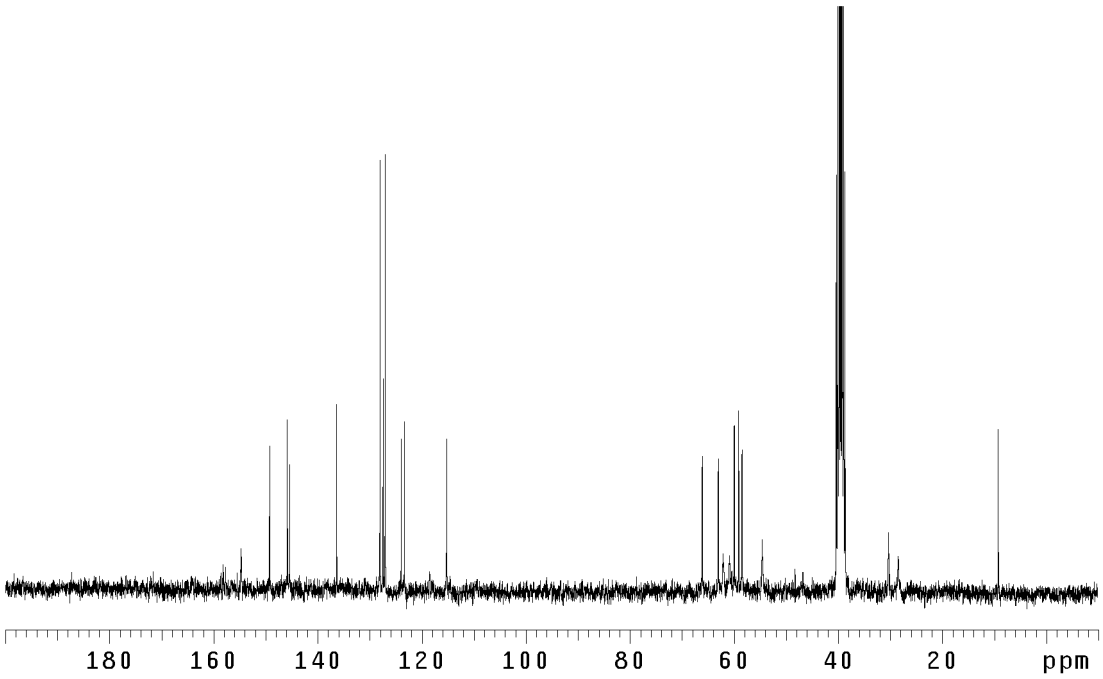


Figure A2.67 ^{13}C NMR of compound **167** (75 MHz, DMSO-d_6, 75 °C)

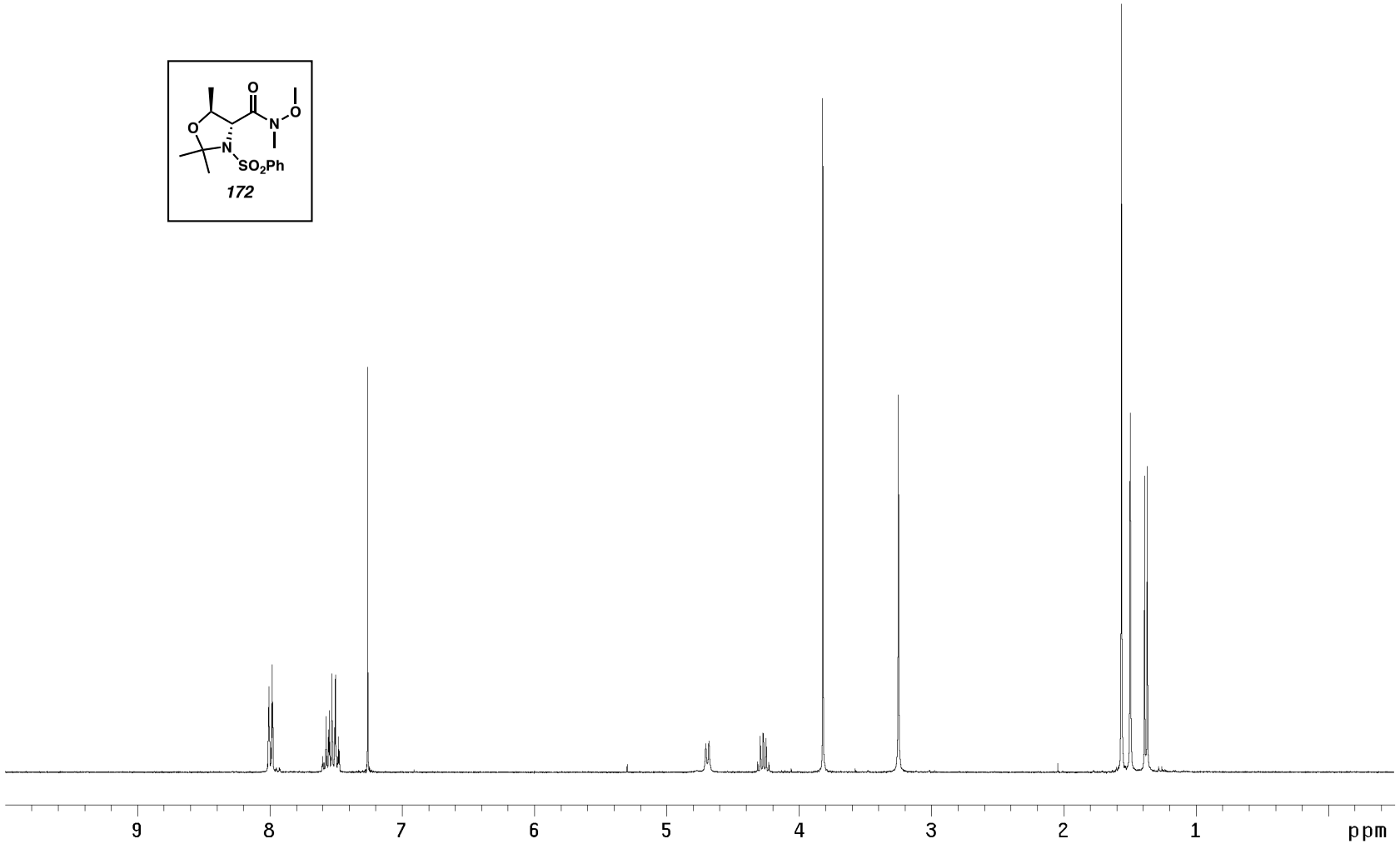


Figure A2.68 ^{1}H NMR of compound **172** (300 MHz, $CDCl_3$)

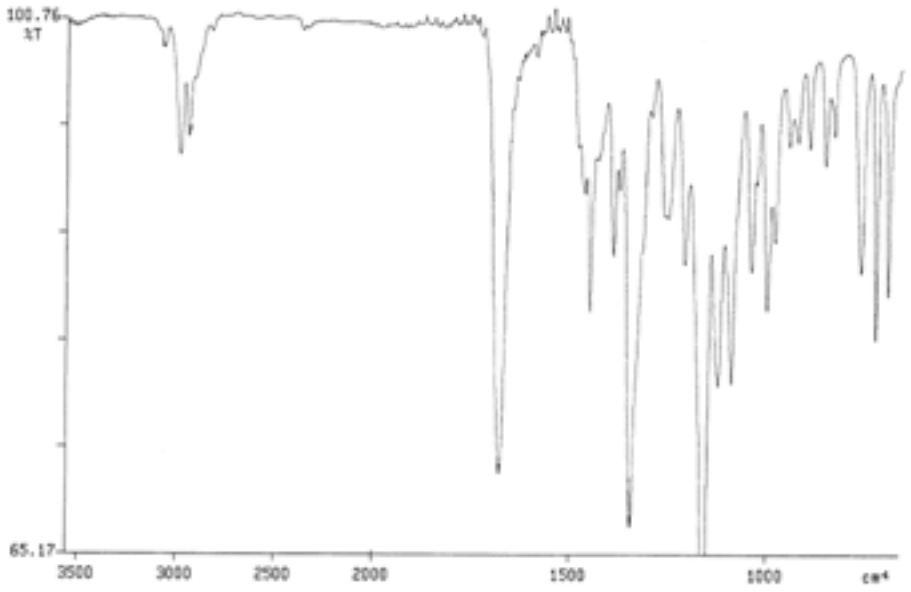


Figure A2.69 IR of compound **172** (NaCl/film)

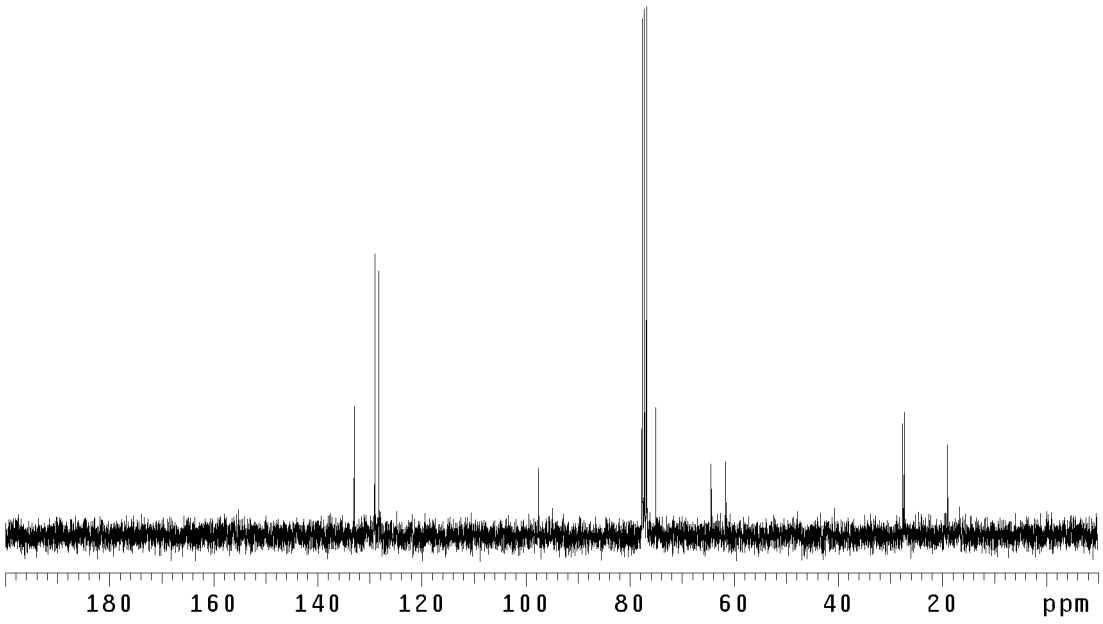


Figure A2.70 ^{13}C NMR of compound **172** (75 MHz, $CDCl_3$)

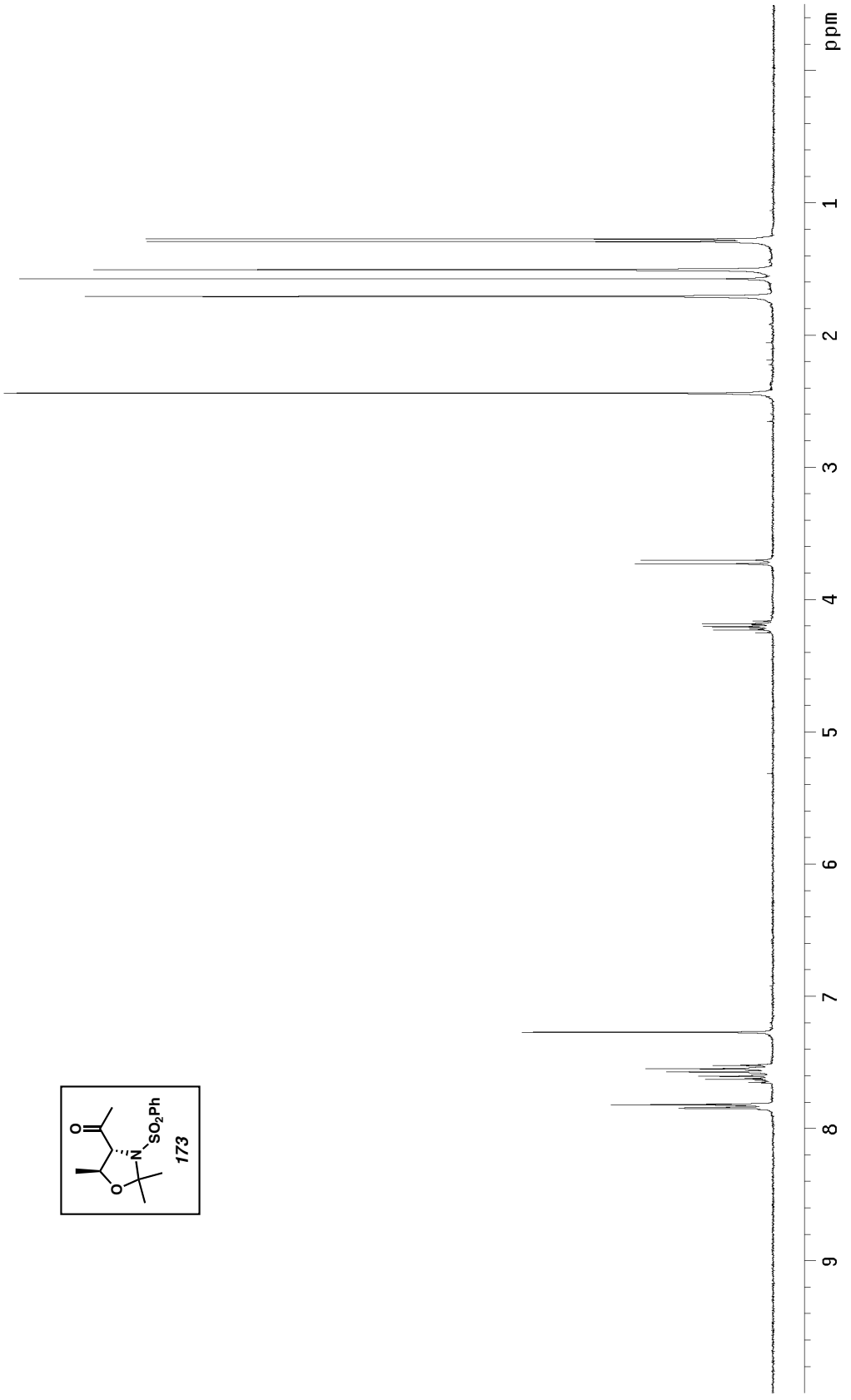


Figure A2.71 ^{1}H NMR of compound **173** (300 MHz, $CDCl_3$)

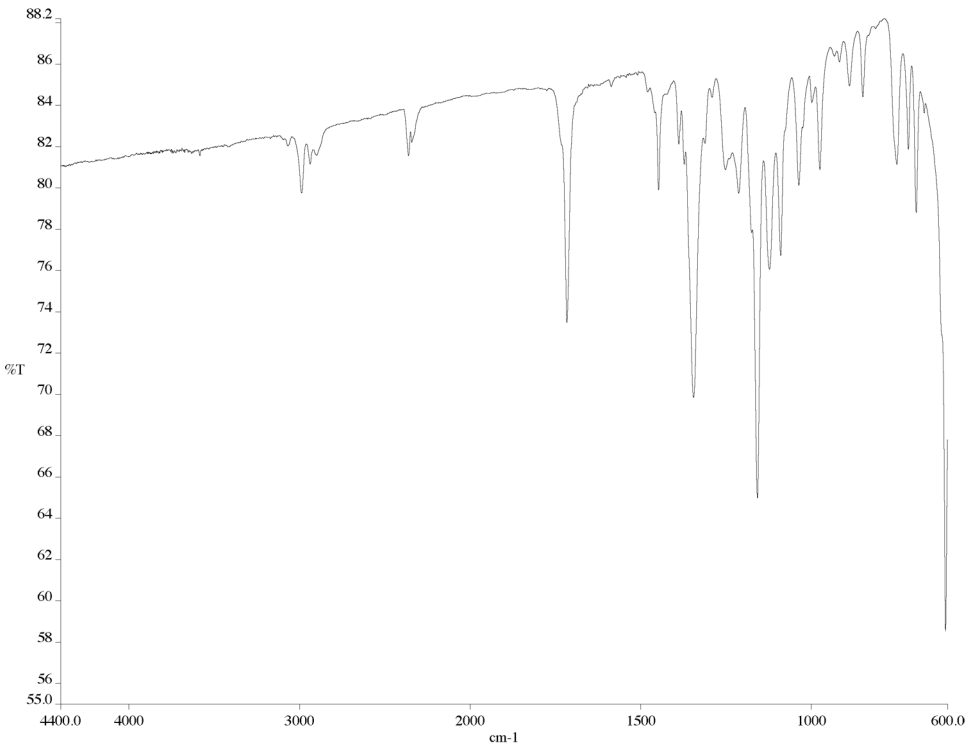


Figure A2.72 IR of compound **173** (NaCl/film)

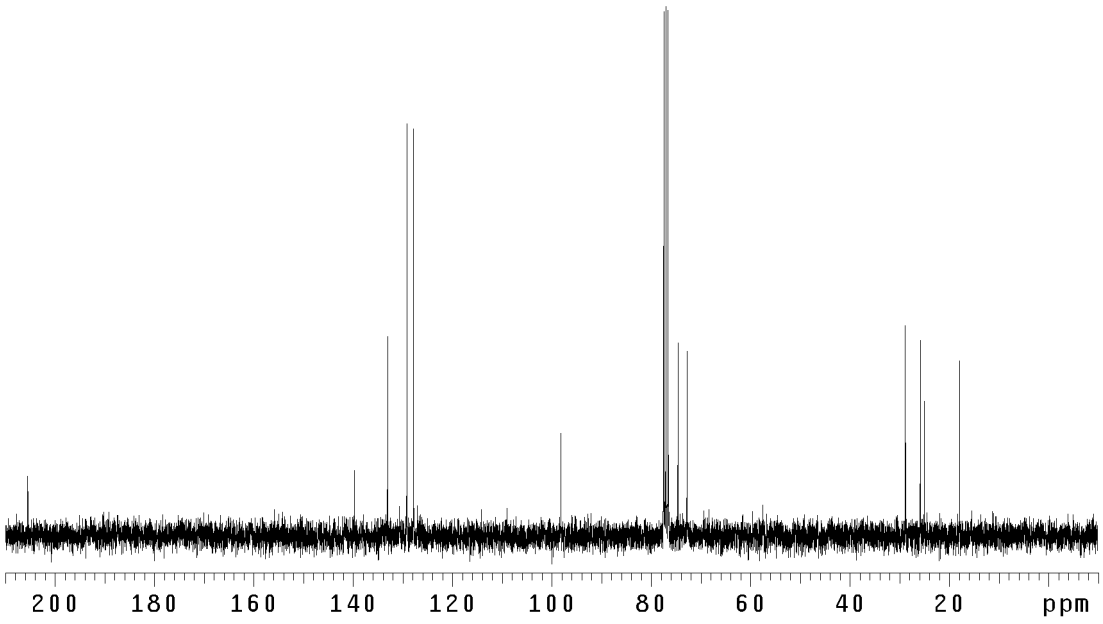


Figure A2.73 ^{13}C NMR of compound **173** (75 MHz, $CDCl_3$)

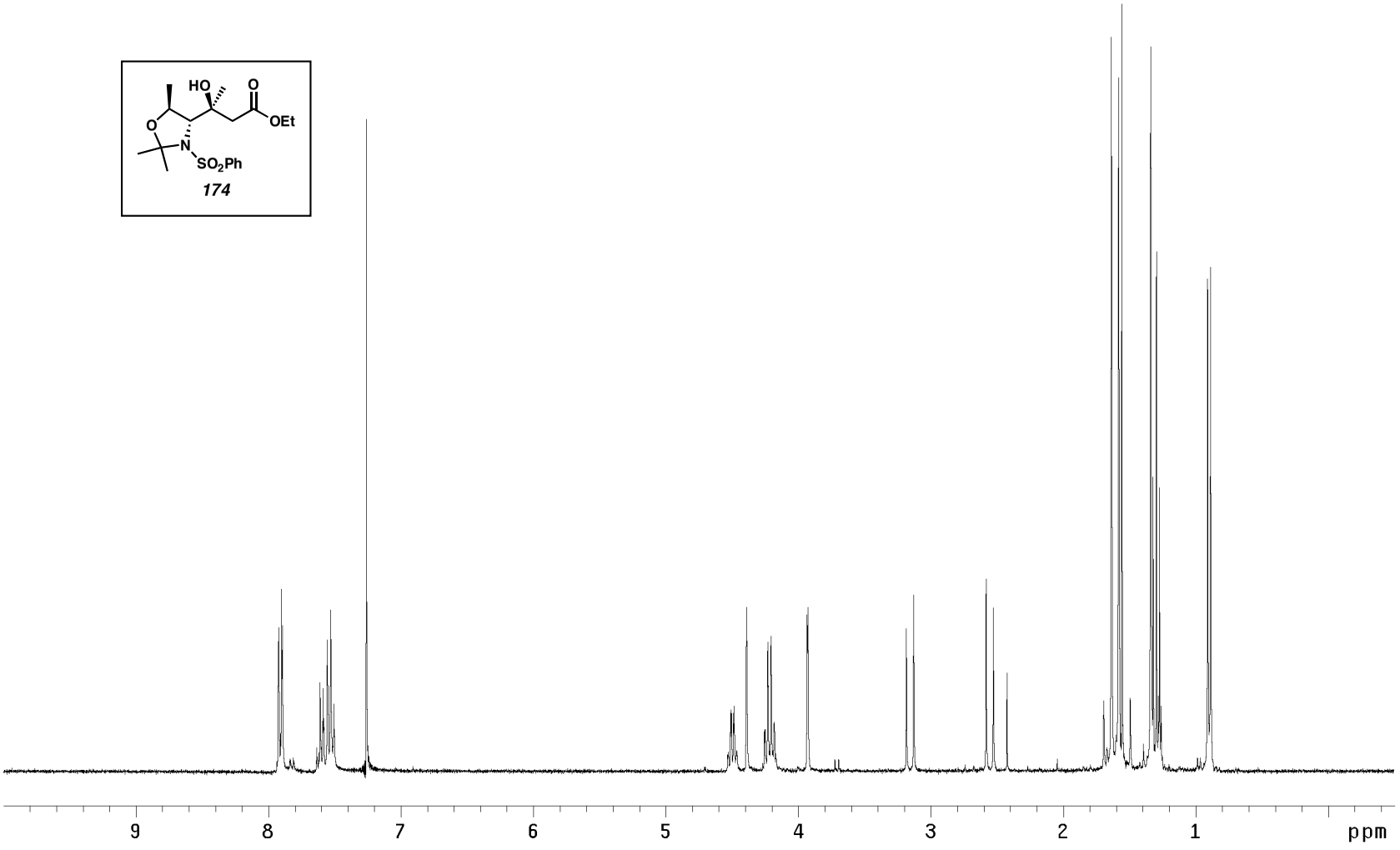


Figure A2.74 ^{1}H NMR of compound **174** (300 MHz, $CDCl_3$)

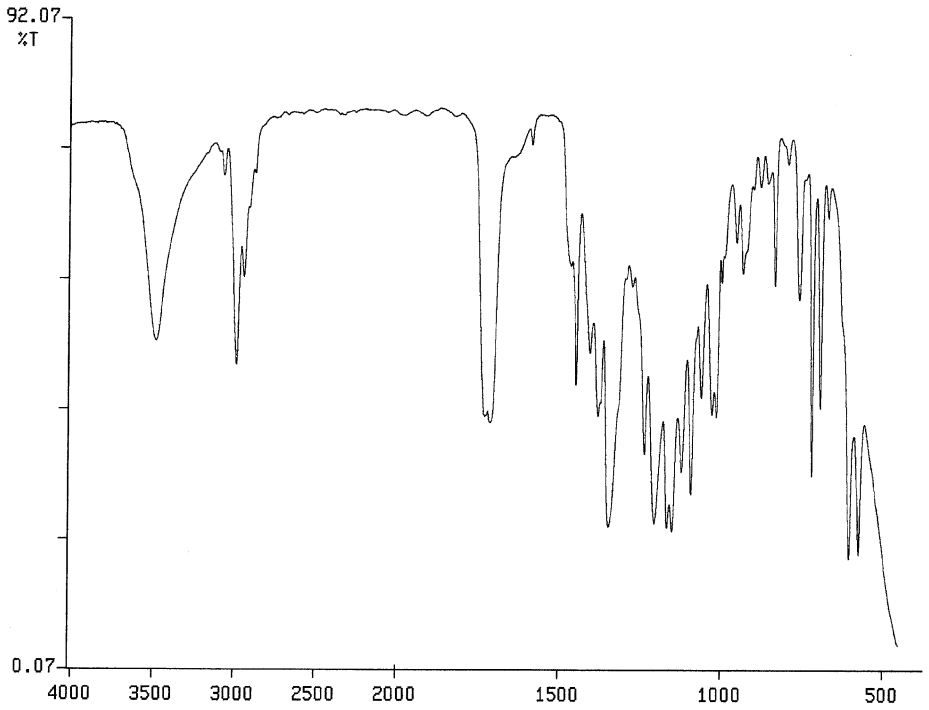


Figure A2.75 IR of compound **174** (NaCl/film)

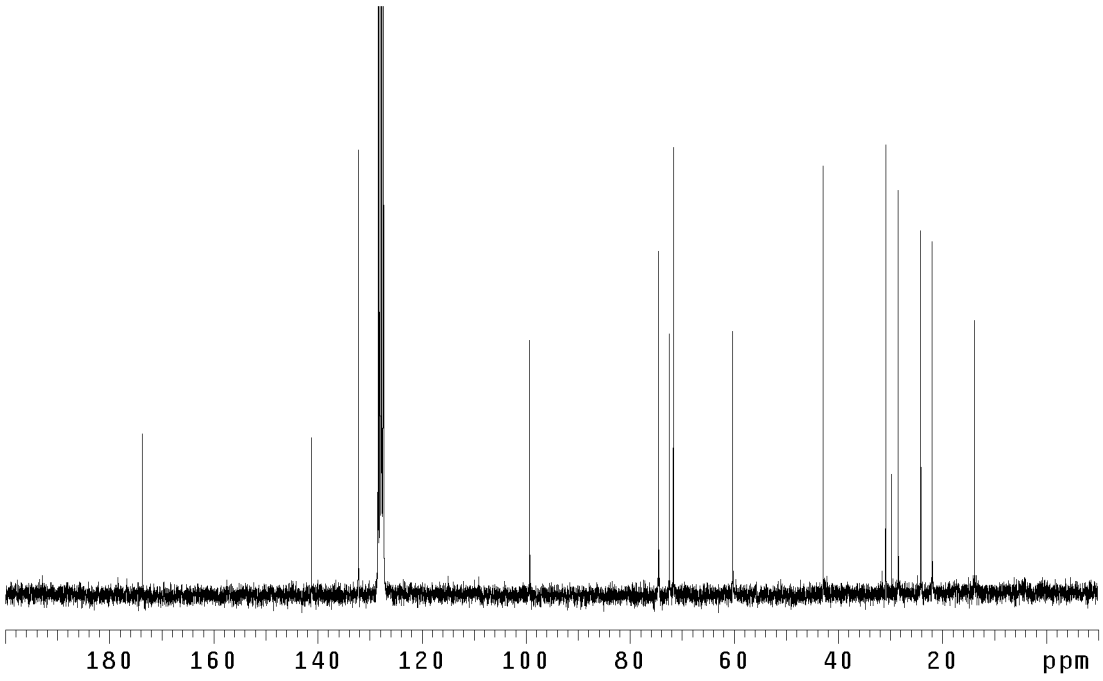


Figure A2.76 ^{13}C NMR of compound **174** (75 MHz, C_6D_6)

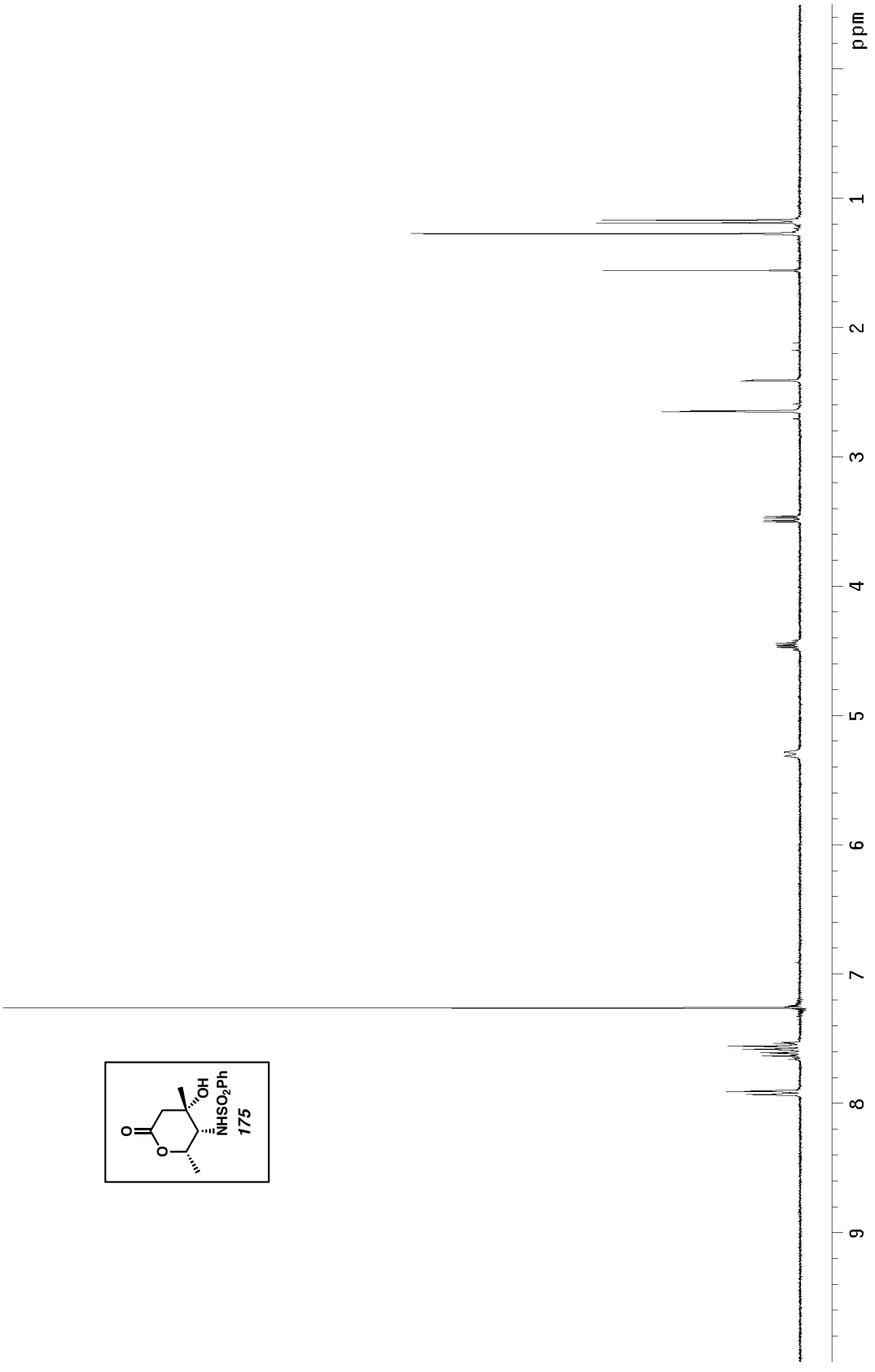


Figure A2.77 ^{1}H NMR of compound **175** (300 MHz, $CDCl_3$)

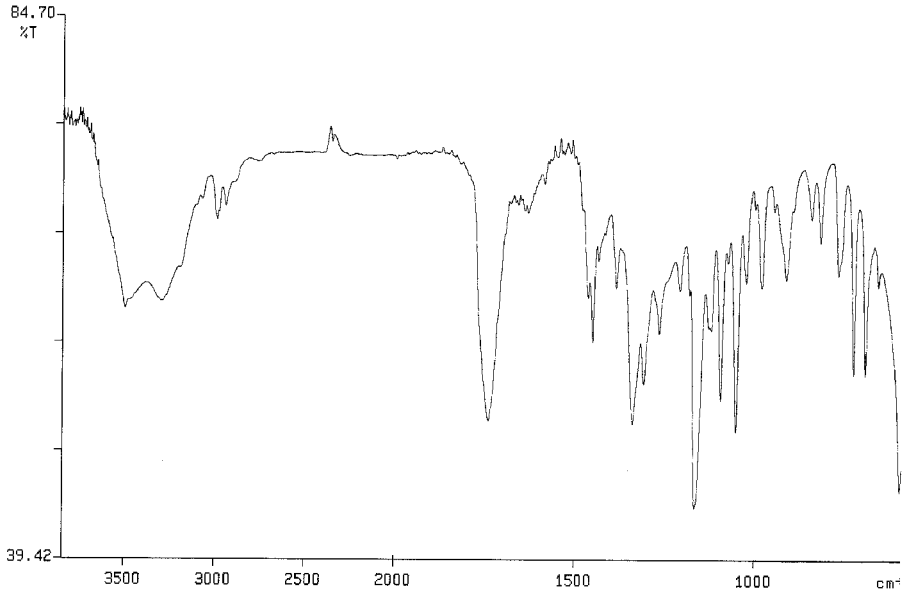


Figure A2.78 IR of compound **175** (NaCl/film)

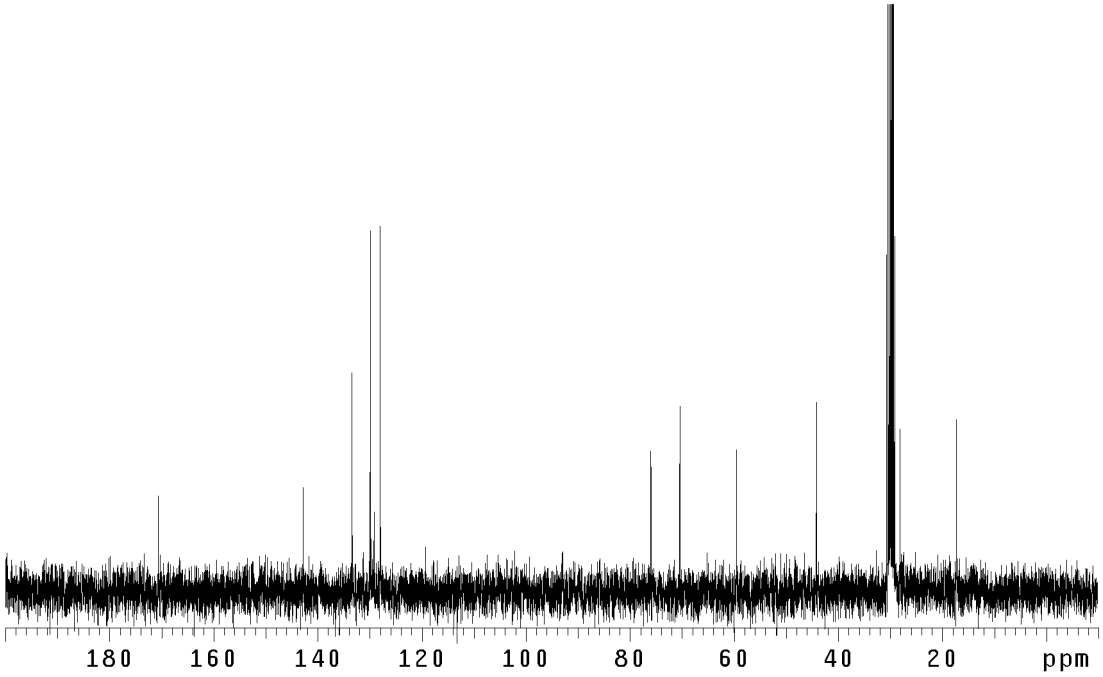


Figure A2.79 ^{13}C NMR of compound **175** (75 MHz, Acetone-d_6)

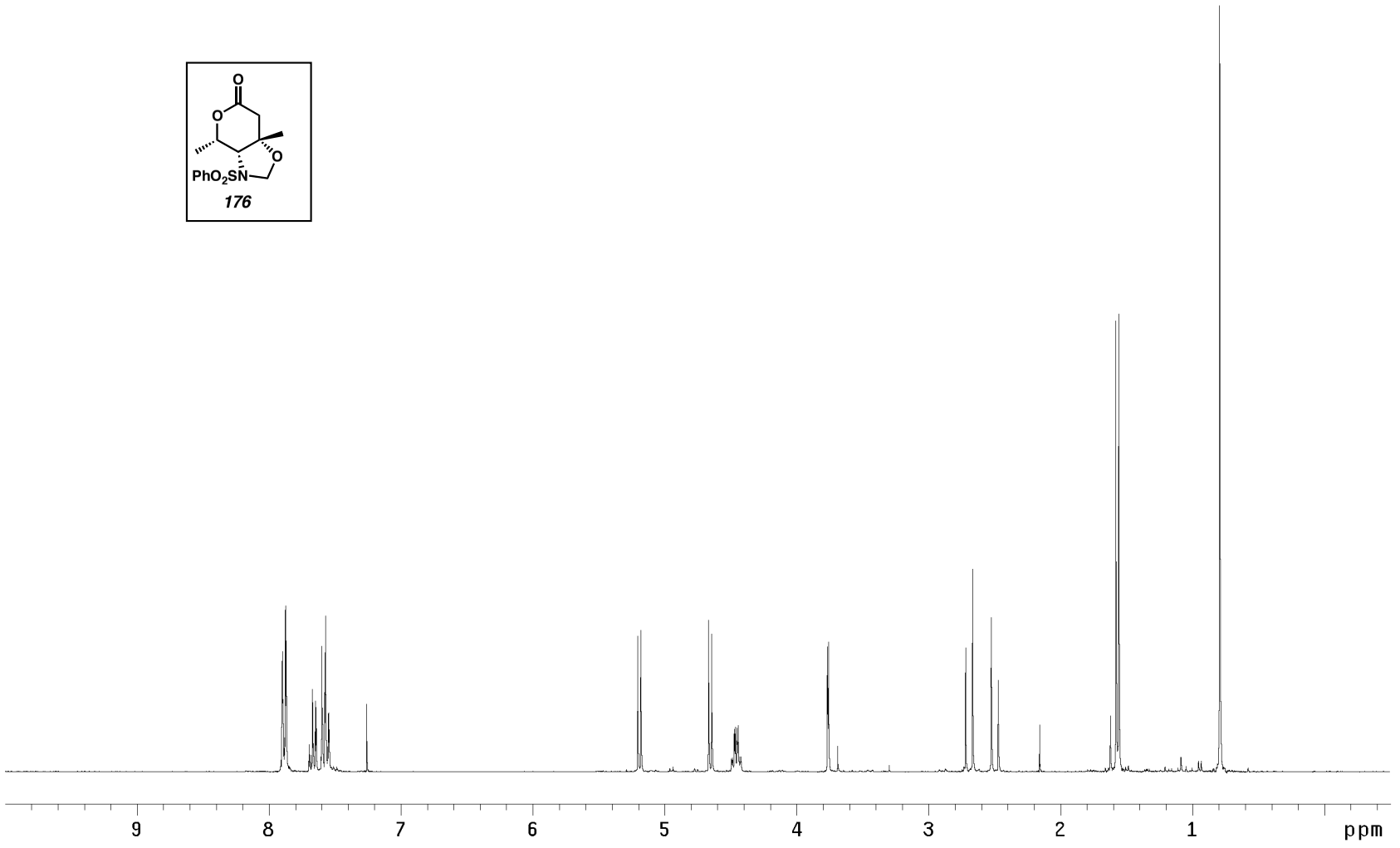


Figure A2.80 ^{1}H NMR of compound **176** (300 MHz, $CDCl_3$)

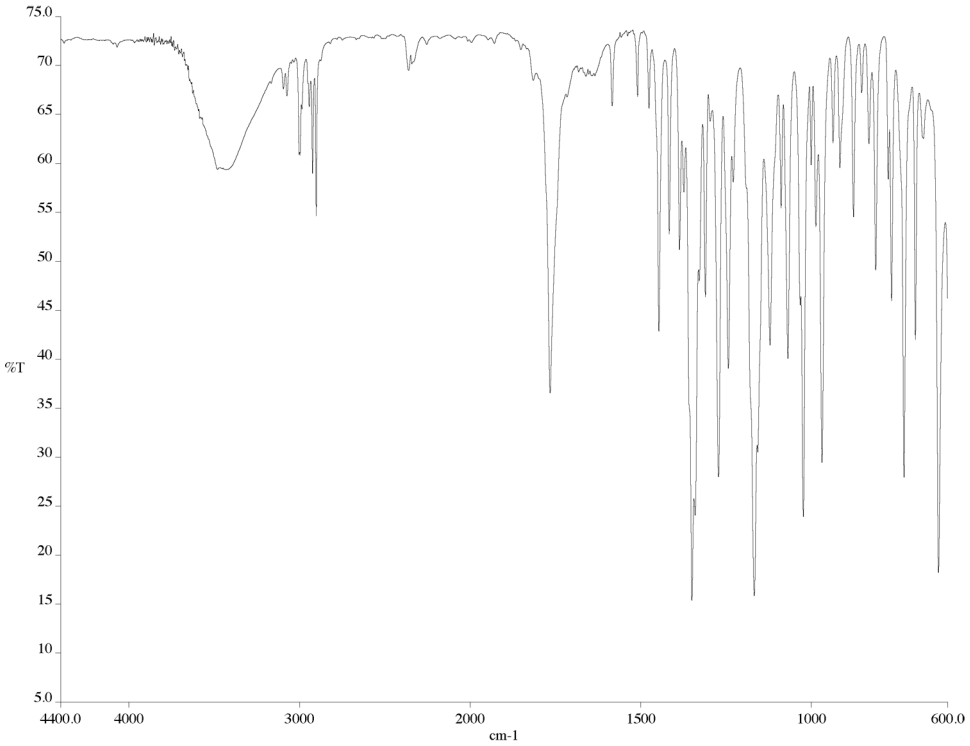


Figure A2.81 IR of compound **176** (NaCl/film)

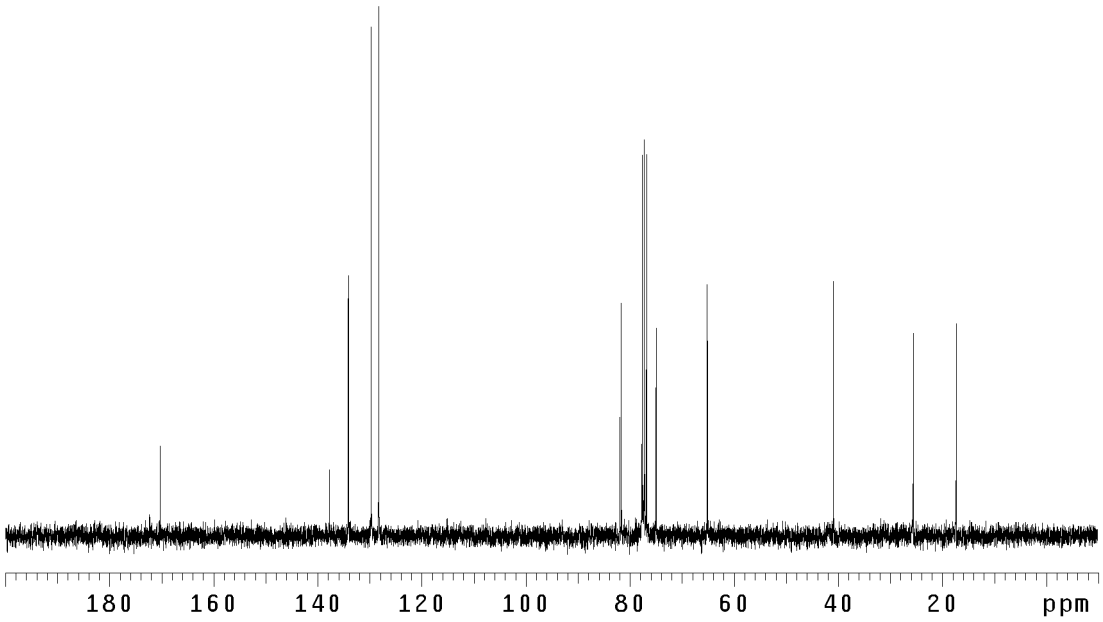


Figure A2.82 ^{13}C NMR of compound **176** (75 MHz, $CDCl_3$)

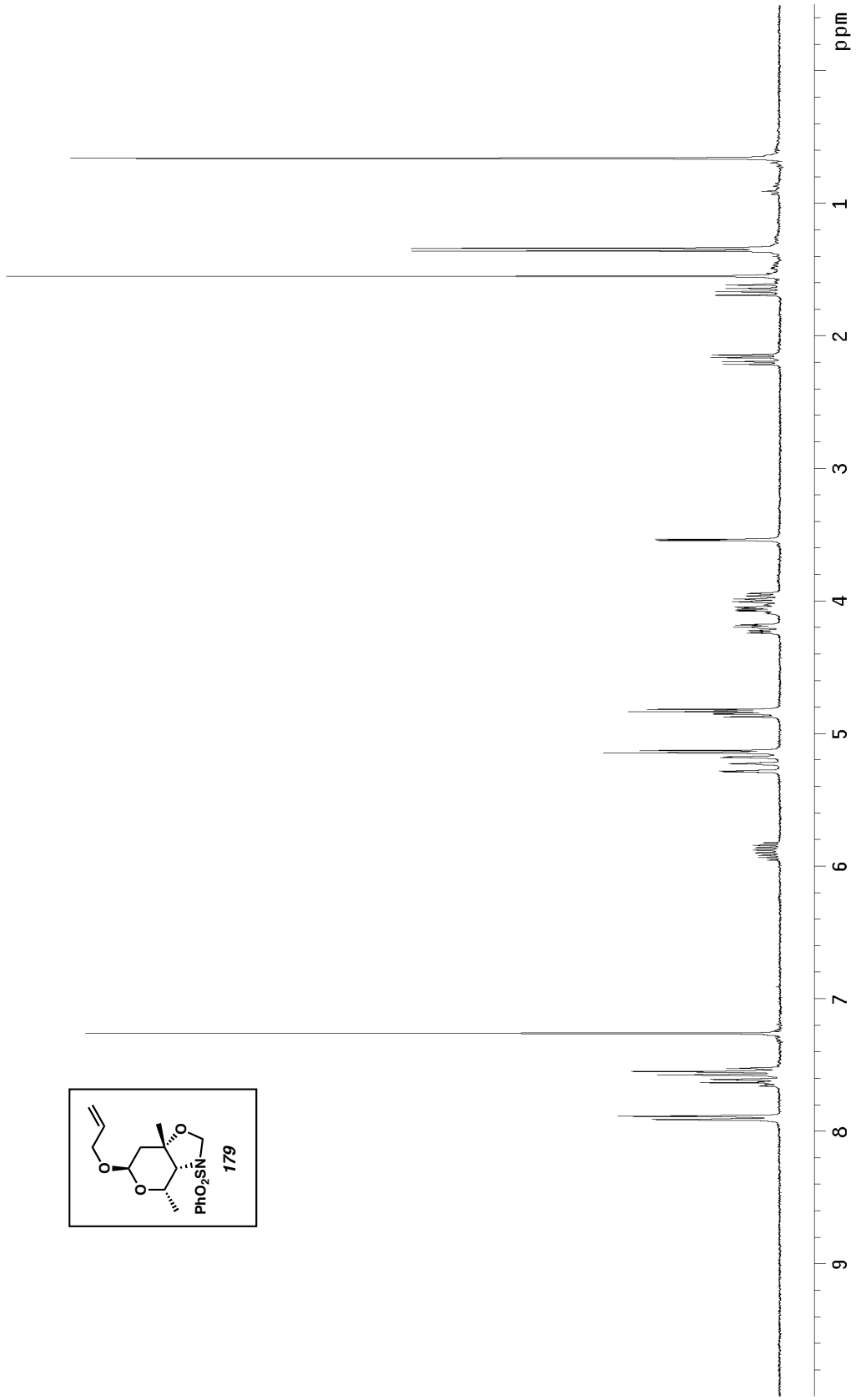


Figure A2.83 ^{1}H NMR of compound **179** (300 MHz, $CDCl_3$)

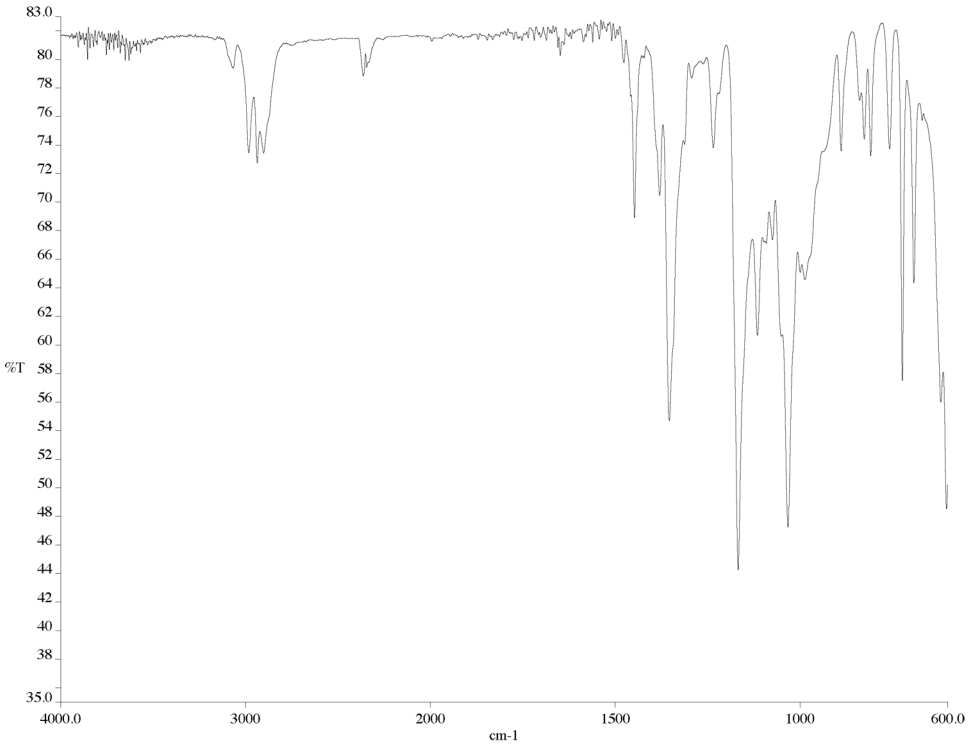


Figure A2.84 IR of compound **179** (NaCl/film)

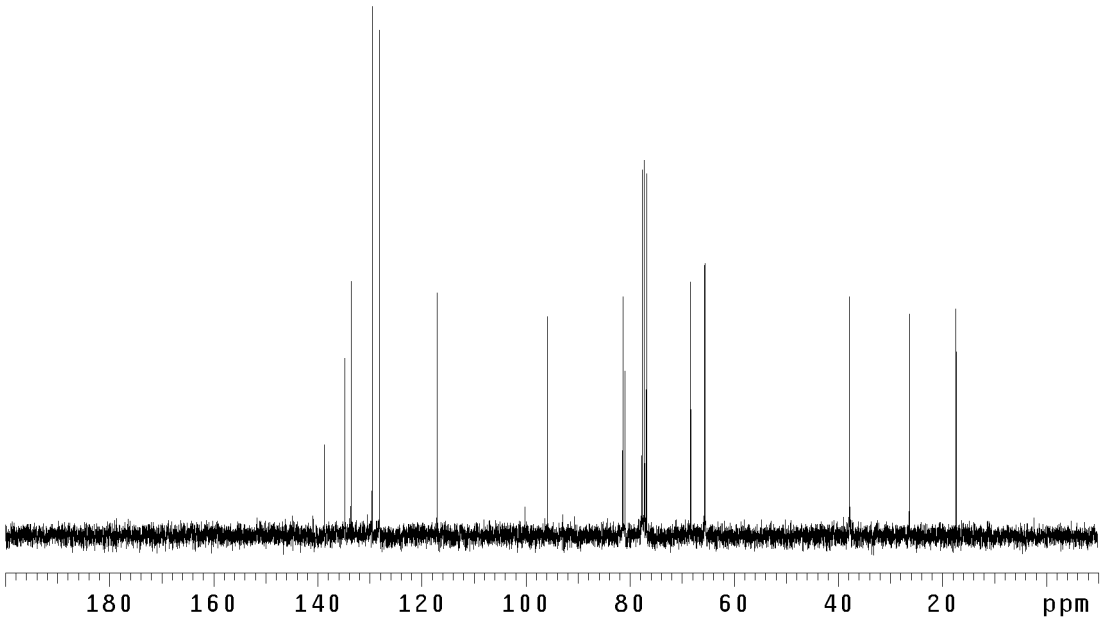


Figure A2.85 ^{13}C NMR of compound **179** (75 MHz, $CDCl_3$)

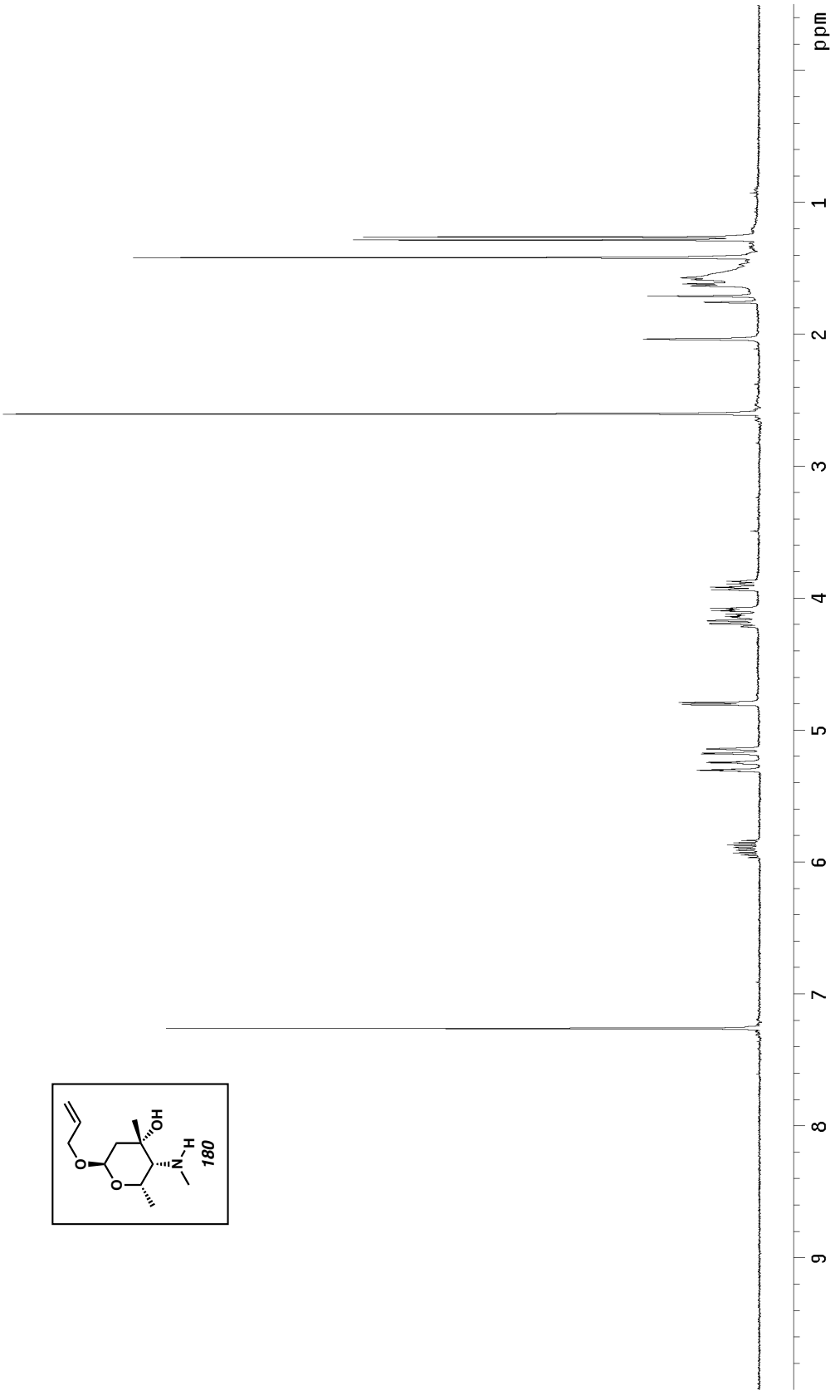


Figure A2.86 ^{1}H NMR of compound **180** (300 MHz, $CDCl_3$)

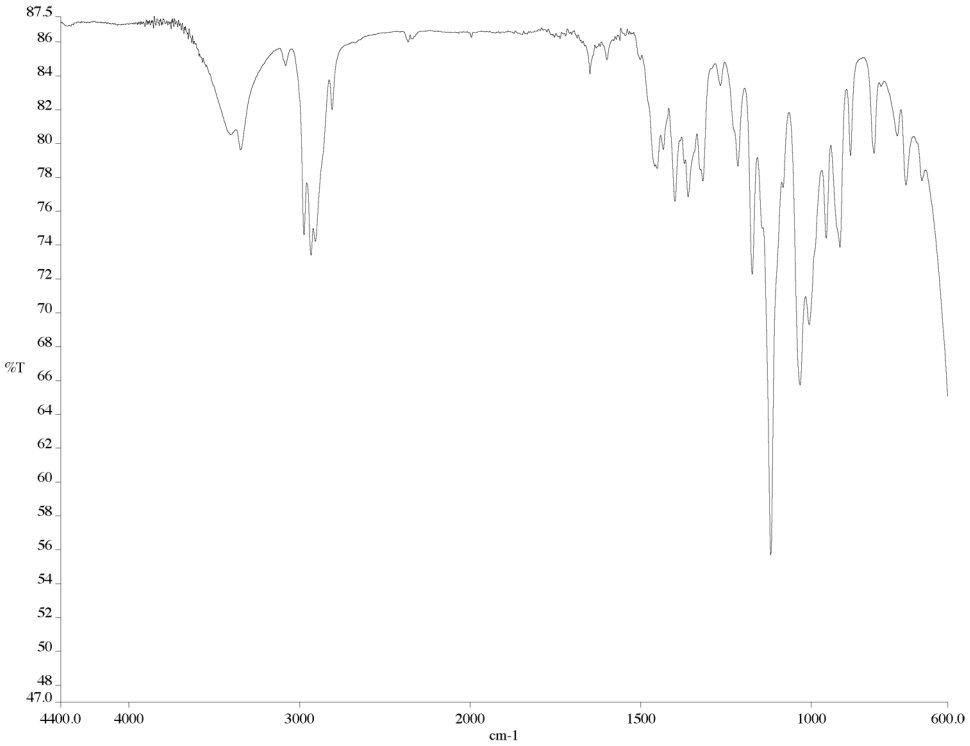


Figure A2.87 IR of compound **180** (NaCl/film)

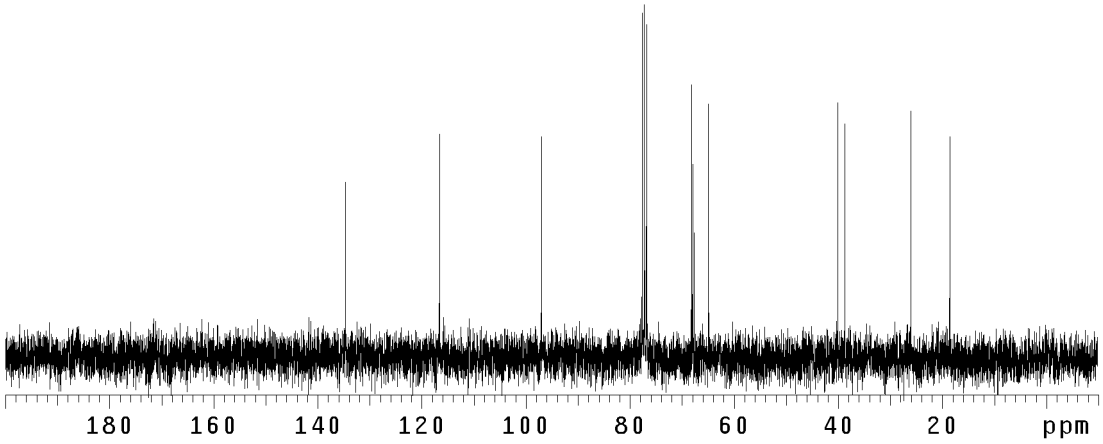


Figure A2.88 ^{13}C NMR of compound **180** (75 MHz, $CDCl_3$)

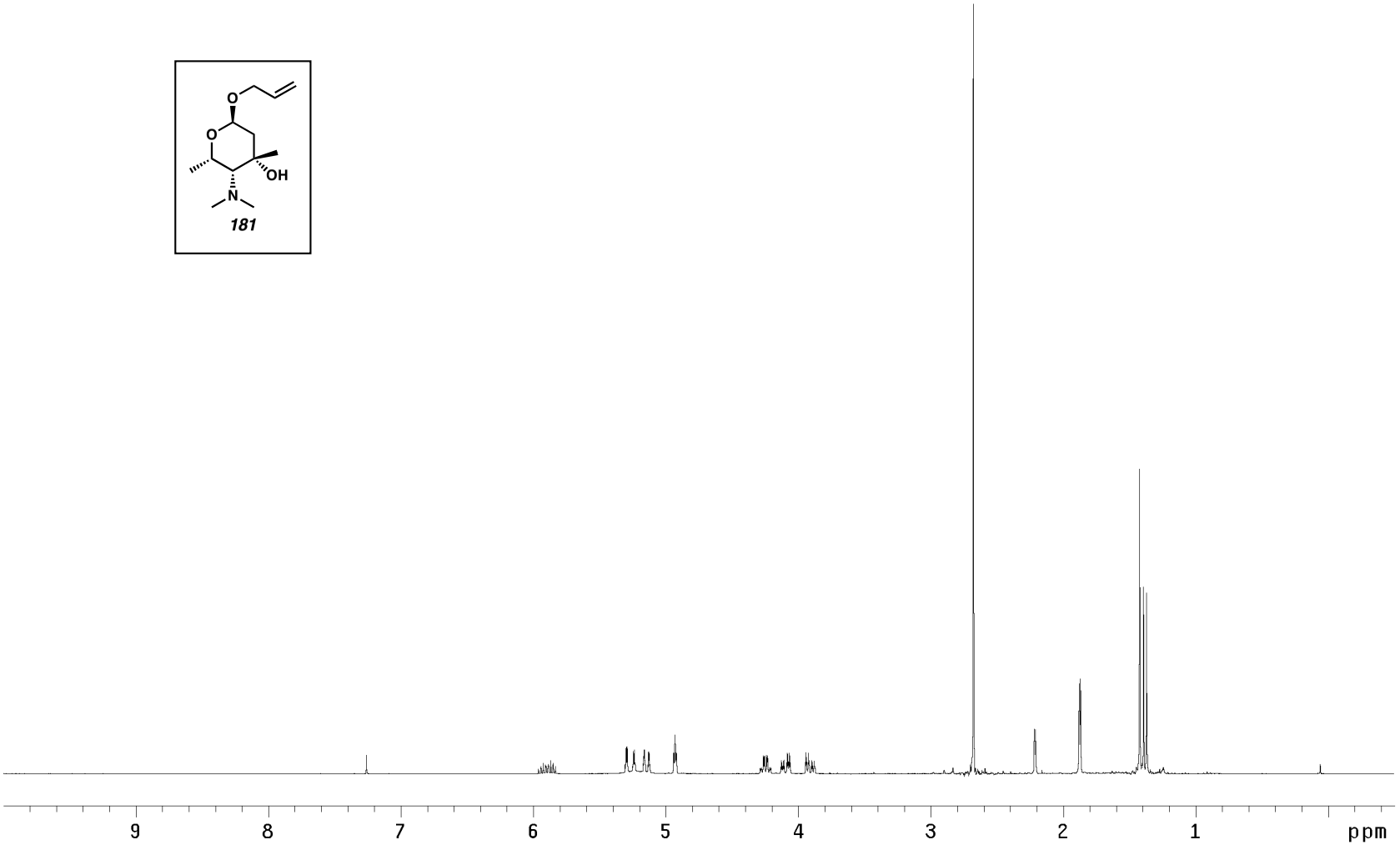


Figure A2.89 ^{1}H NMR of compound **181** (300 MHz, $CDCl_3$)

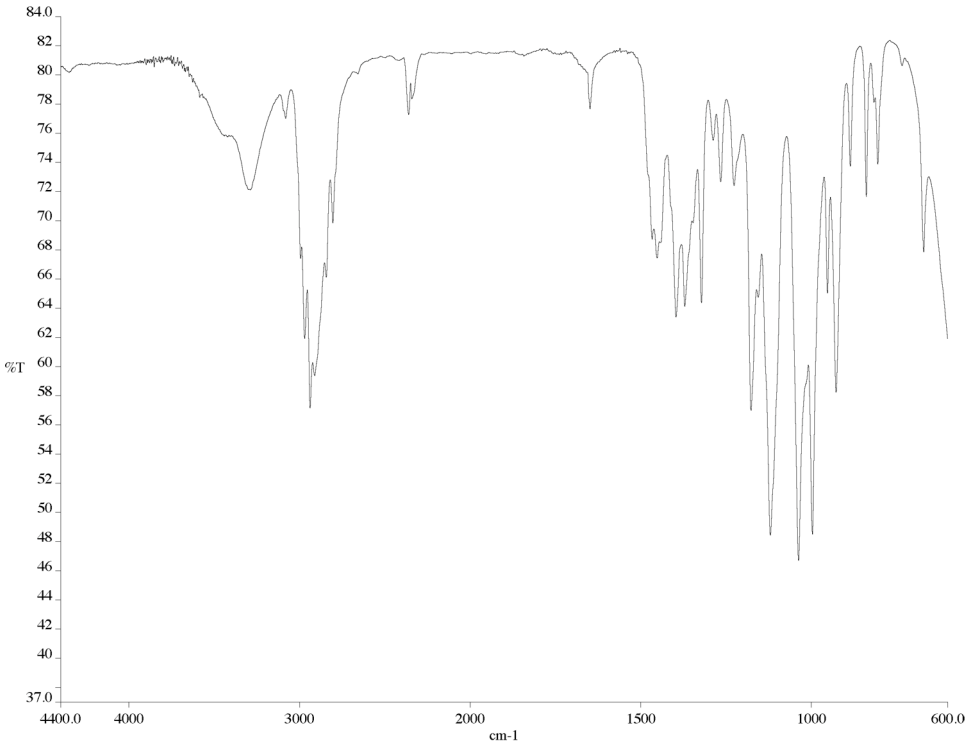


Figure A2.90 IR of compound **181** (NaCl/film)

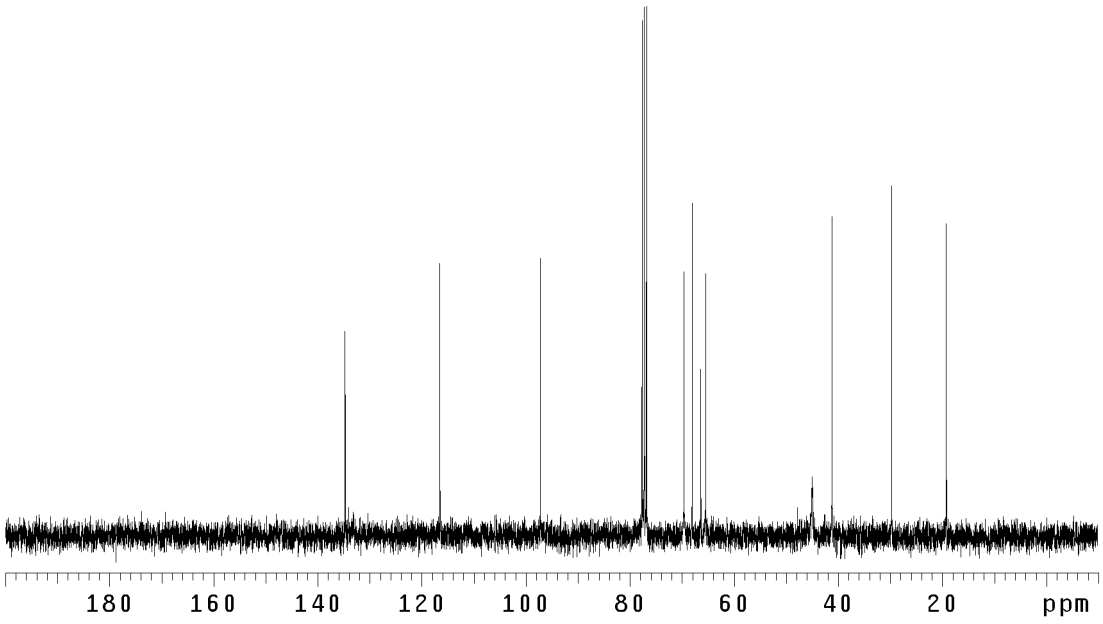


Figure A2.91 ^{13}C NMR of compound **181** (75 MHz, $CDCl_3$)

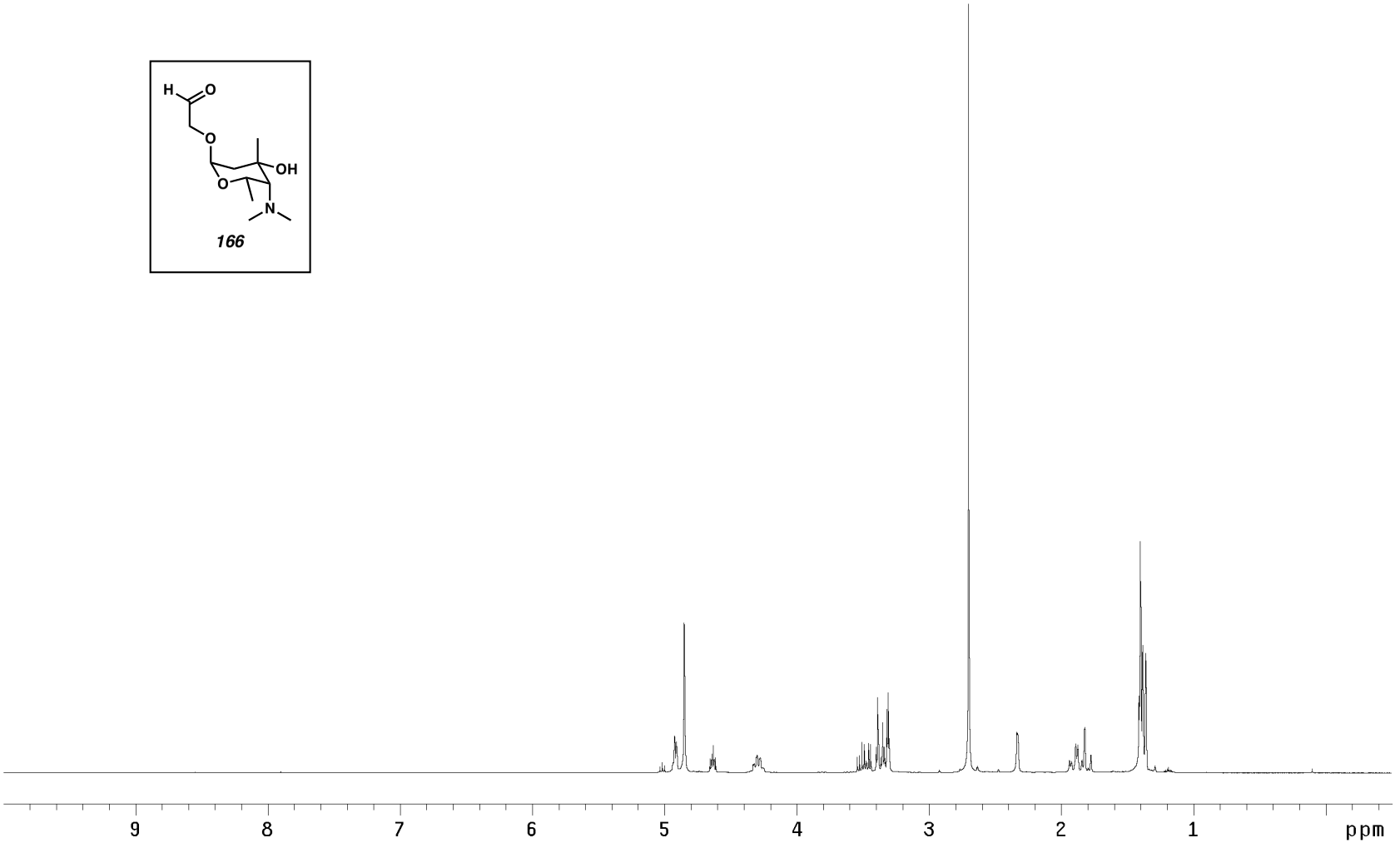


Figure A2.92 ^{1}H NMR of compound **166** (300 MHz, CD_3OD)

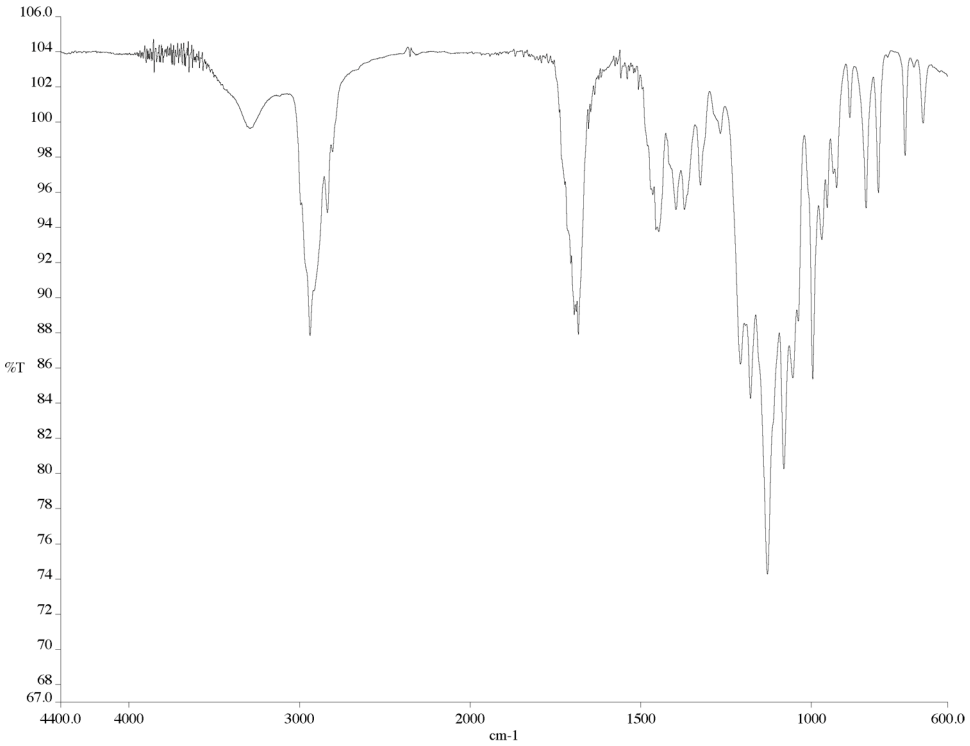


Figure A2.93 IR of compound **166** (NaCl/film)

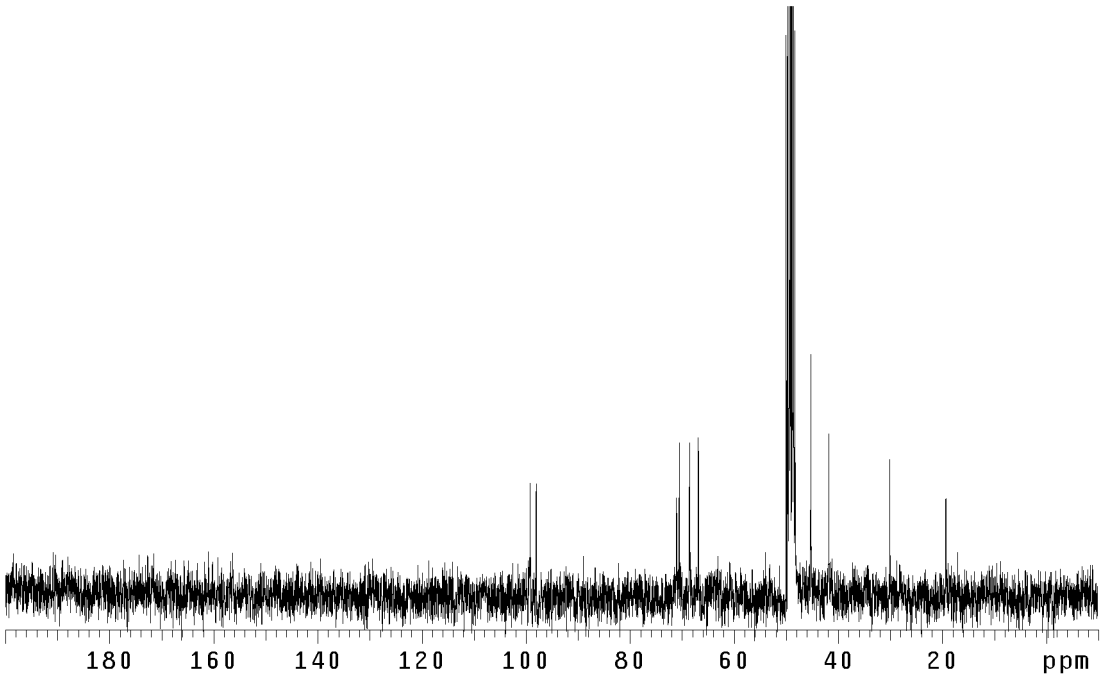


Figure A2.94 ^{13}C NMR of compound **166** (75 MHz, CD_3OD)

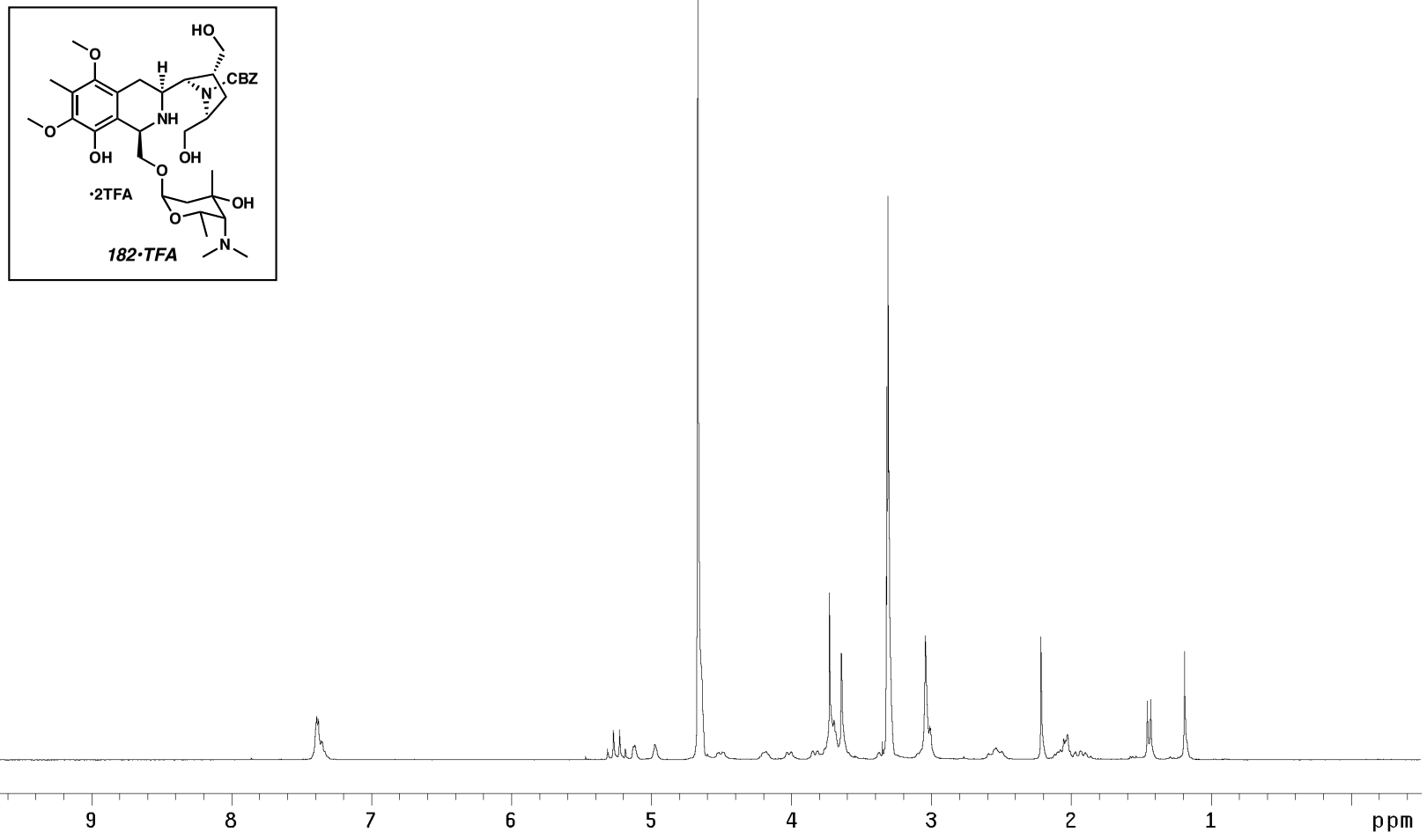


Figure A2.95 ^{1}H NMR of compound **182** (300 MHz, CD_3OD, 45 °C)

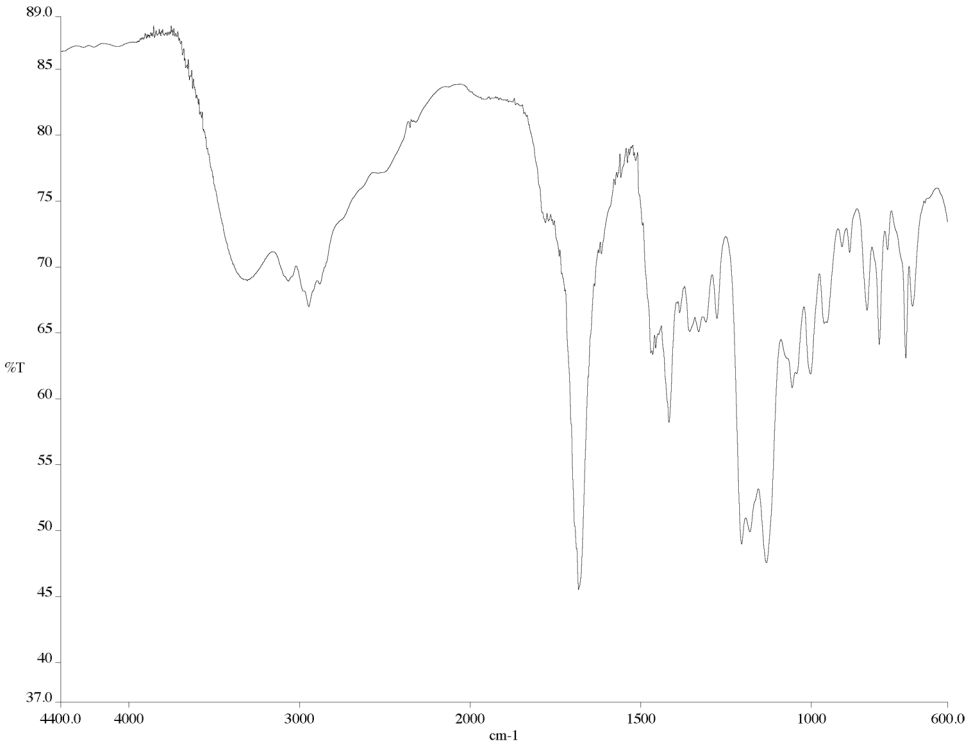


Figure A2.96 IR of compound **182** (NaCl/film)

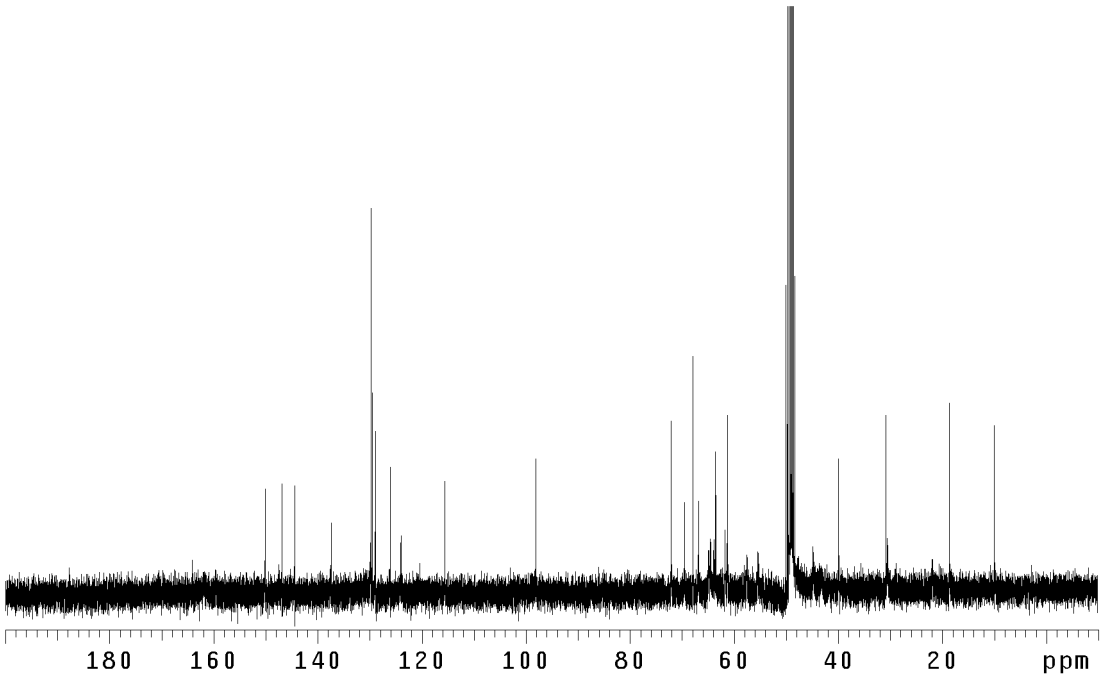


Figure A2.97 ^{13}C NMR of compound **182** (75 MHz, CD_3OD, 50 °C)

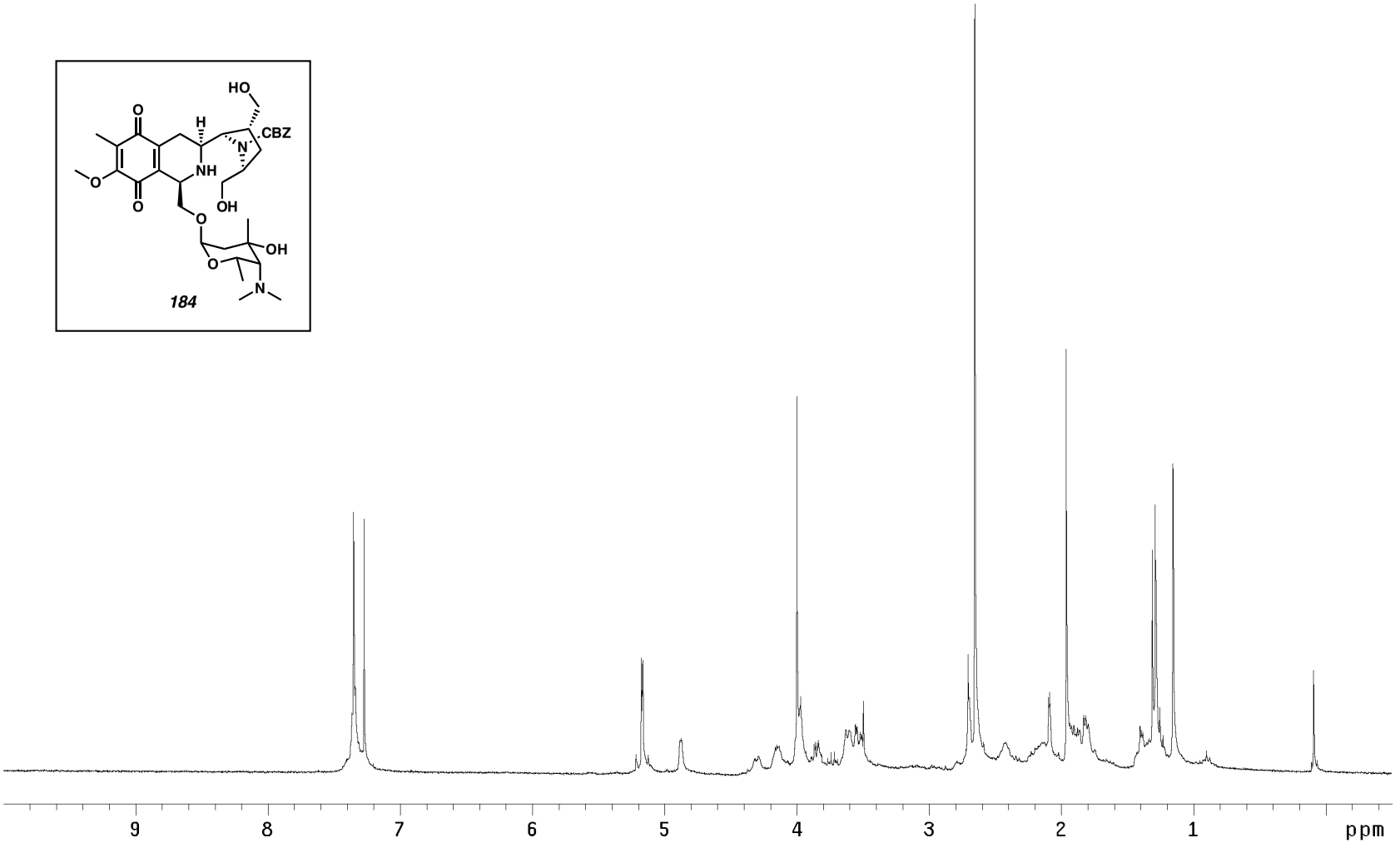


Figure A2.98 ^{1}H NMR of compound **184** (300 MHz, $CDCl_3$, 50 °C)

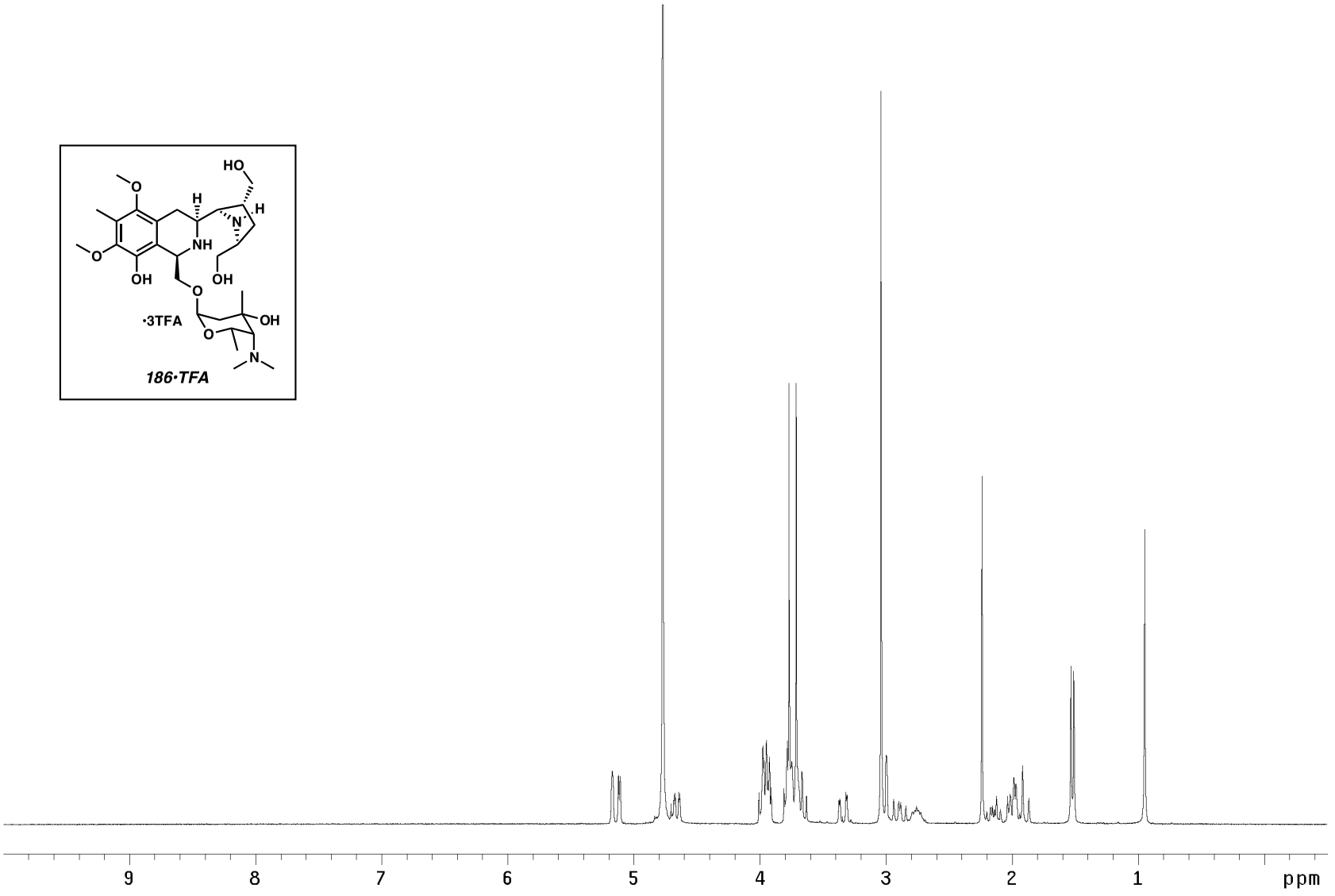


Figure A2.99 ^{1}H NMR of compound **188** (300 MHz, D_2O)

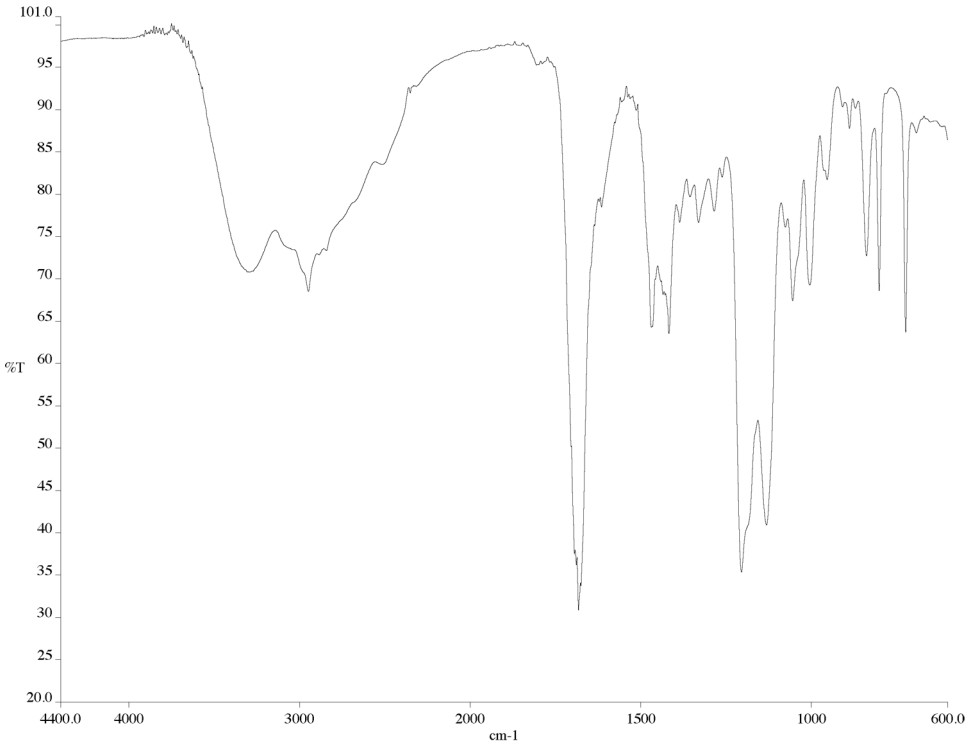


Figure A2.100 IR of compound **186** (NaCl/film)

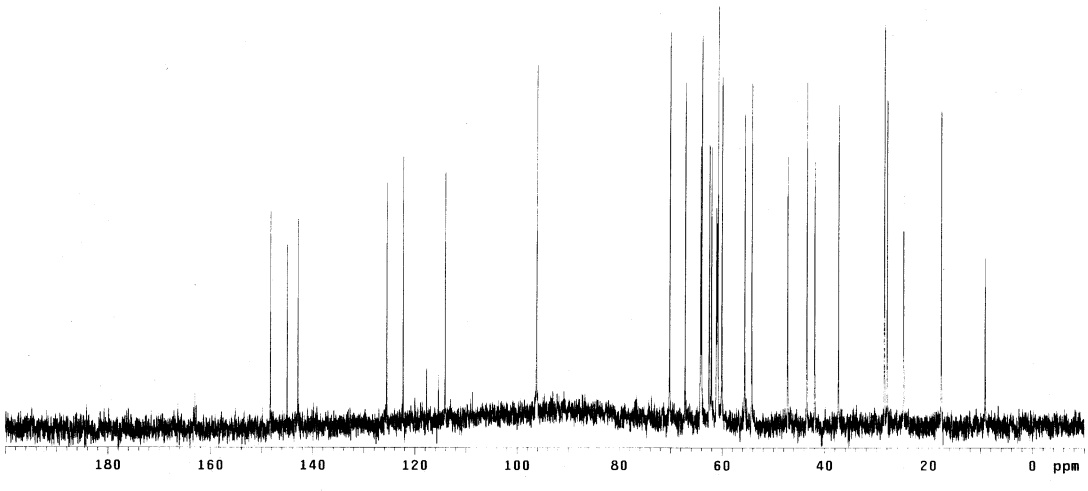


Figure A2.101 ^{13}C NMR of compound **186** (125 MHz, D_2O)

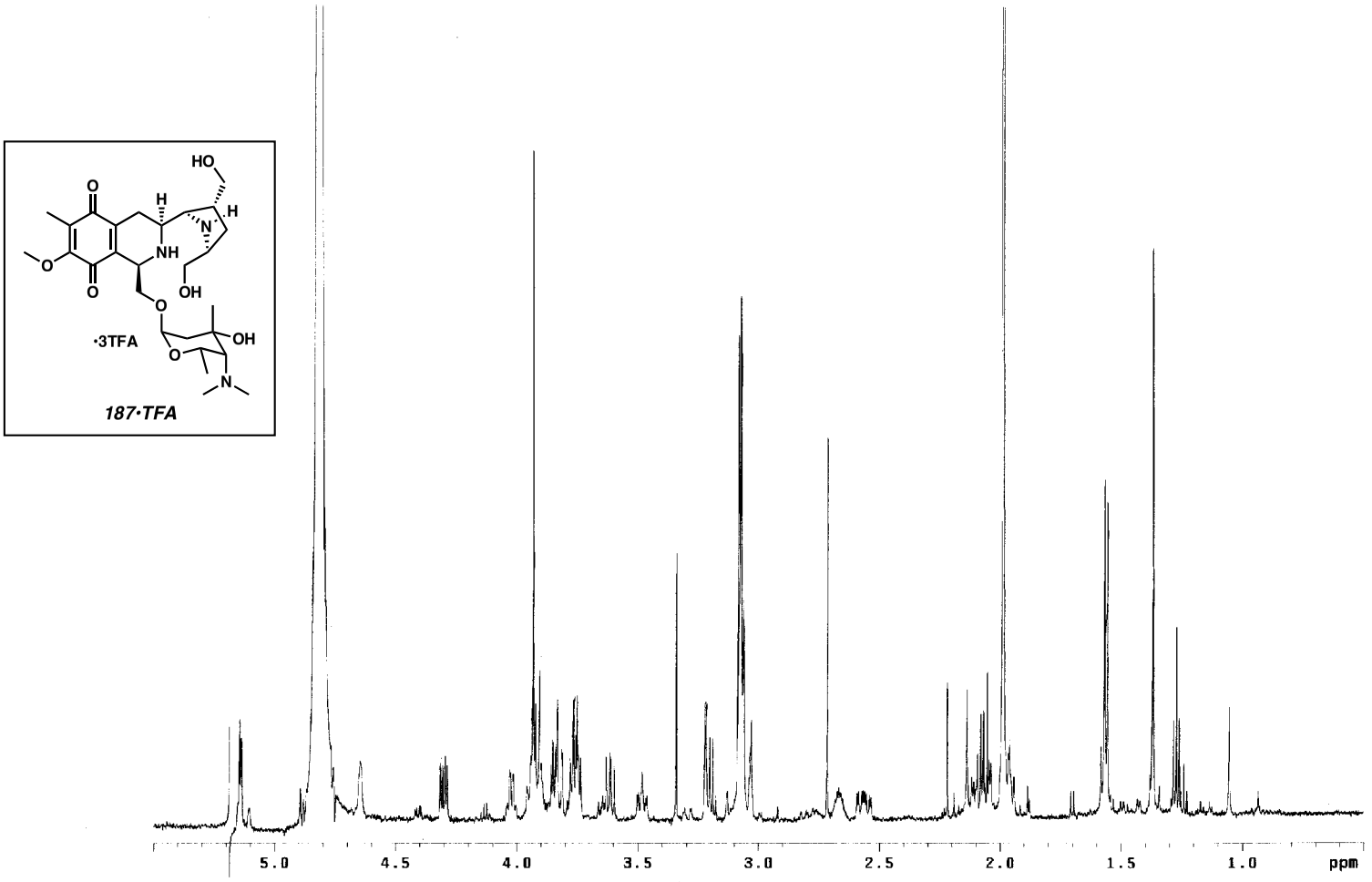


Figure A2.102 ^{1}H NMR of compound **187** (600 MHz, D_2O)

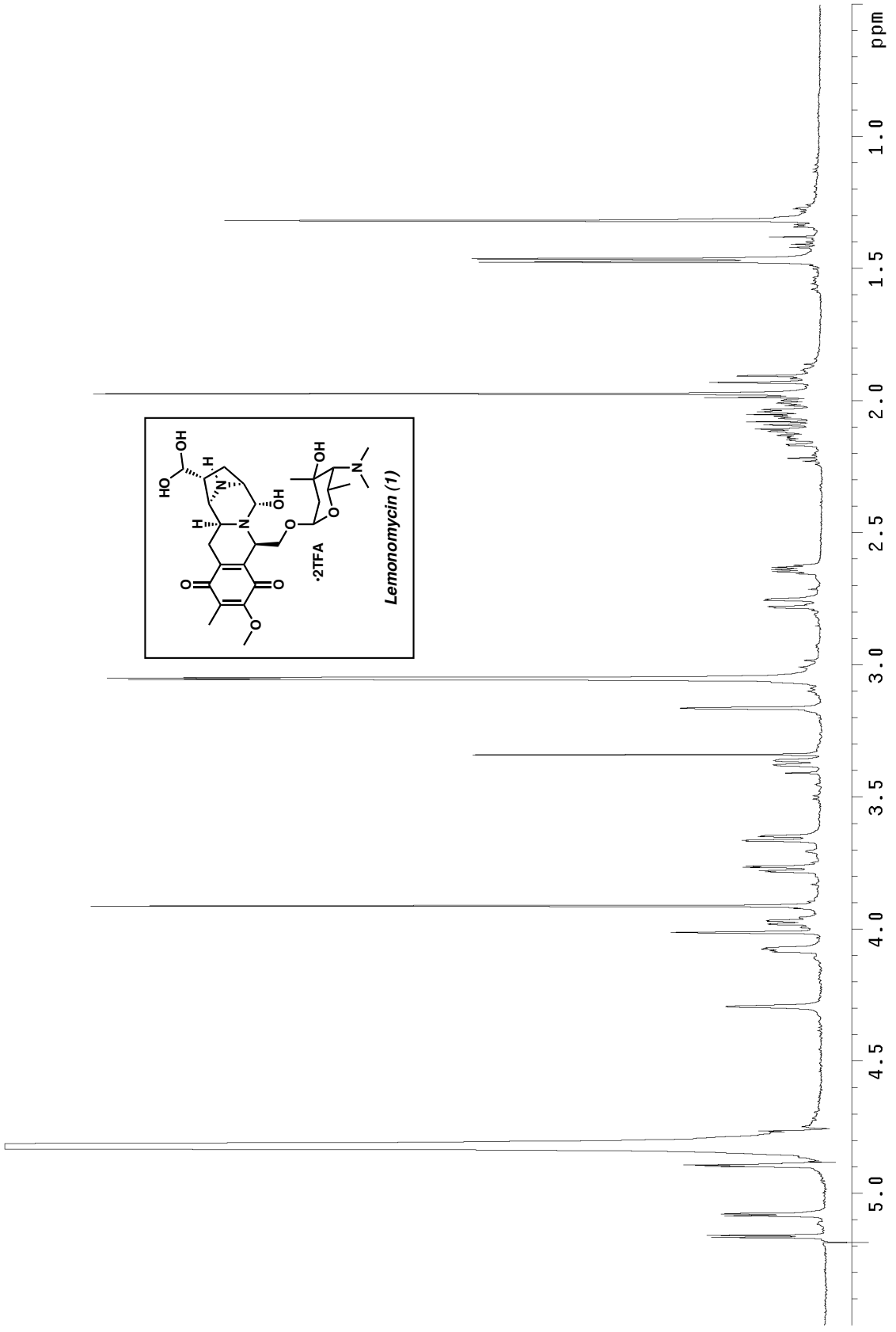


Figure A2.103 ^{1}H NMR of (–)-Lemonomycin (**1**) (600 MHz, D_2O)

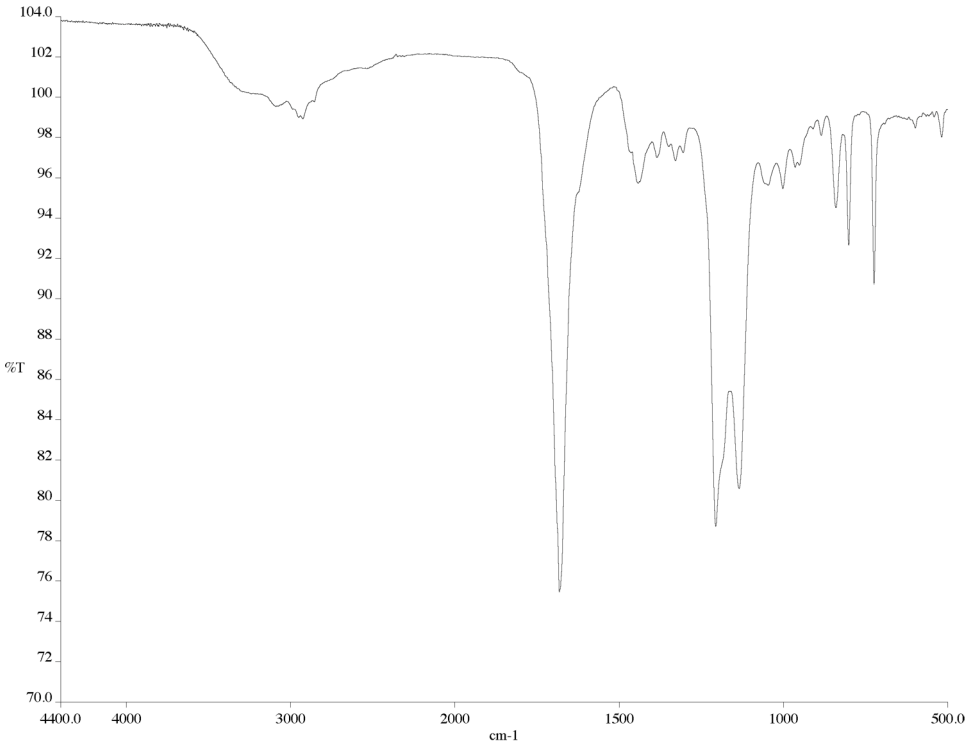


Figure A2.104 IR of (–)-Lemonomycin (**1**) (NaCl/film)

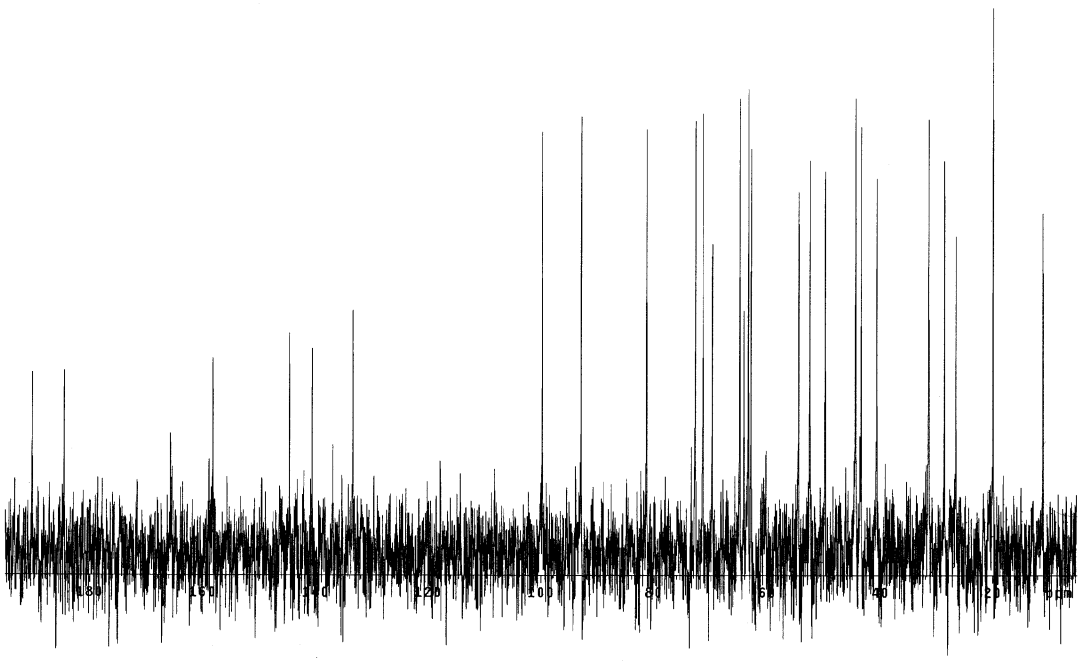


Figure A2.105 ^{13}C NMR of (–)-Lemonomycin (**1**) (125 MHz, D_2O)

CHAPTER THREE

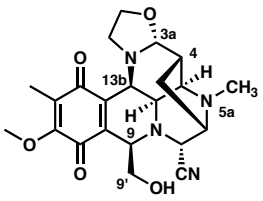
Progress Toward the Synthesis of (+)-Cyanocycline A

3.1 First Generation Approach Toward (+)-Cyanocycline A

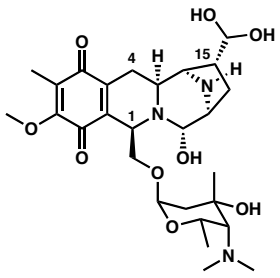
Synthetic Challenges and Structural Comparison to (–)-Lemonomycin

Cyanocycline A (**2**) presents the synthetic chemist with a host of challenges, including polar groups, sensitive functionality, and difficult stereochemical arrays (Figure 3.1).[1,2] The hexacyclic, caged structure contains eight stereocenters, including five contiguous stereogenic carbons around the piperidine ring. Three basic amines and a primary alcohol contribute polarity and sensitivity to oxidative conditions, while the quinone, aminonitrile, and oxazolidine are vulnerable to both reduction and hydrolysis.

Figure 3.1 Structural Comparison of Cyanocycline A and Lemonomycin



Cyanocycline A (2)



Lemonomycin (1)

Structurally, cyanocycline A bears both striking similarities to and important differences from lemonomycin (**1**).[3] Both compounds contain a tetrahydroisoquinoline-5,8-dione ring system fused to a 3,9-diazabicyclo[3.2.1]octane core. Additionally, both compounds exhibit hydroxymethyl functionality at C(1) of the tetrahydroisoquinoline (C(9) by cyanocycline numbering), and the absolute and relative stereochemistry around

much of the core structure is identical. However, cyanocycline A is distinguished from lemonomycin by the presence of a bridging oxazolidine ring that incorporates C(3a) and connects to C(13b) of the tetrahydroisoquinoline. To allow this connection, the stereochemistry at C(4) is epimeric to that at C(15) of lemonomycin, and C(13b) is one oxidation state higher than C(4) of lemonomycin. Conspicuously absent in cyanocycline A is the glycosyl unit of lemonomycin, as the C(9') hydroxyl is unsubstituted. Further, cyanocycline A bears a methyl group at N(5a), which is absent from lemonomycin, and has an aminonitrile in place of the carbinolamine of lemonomycin.

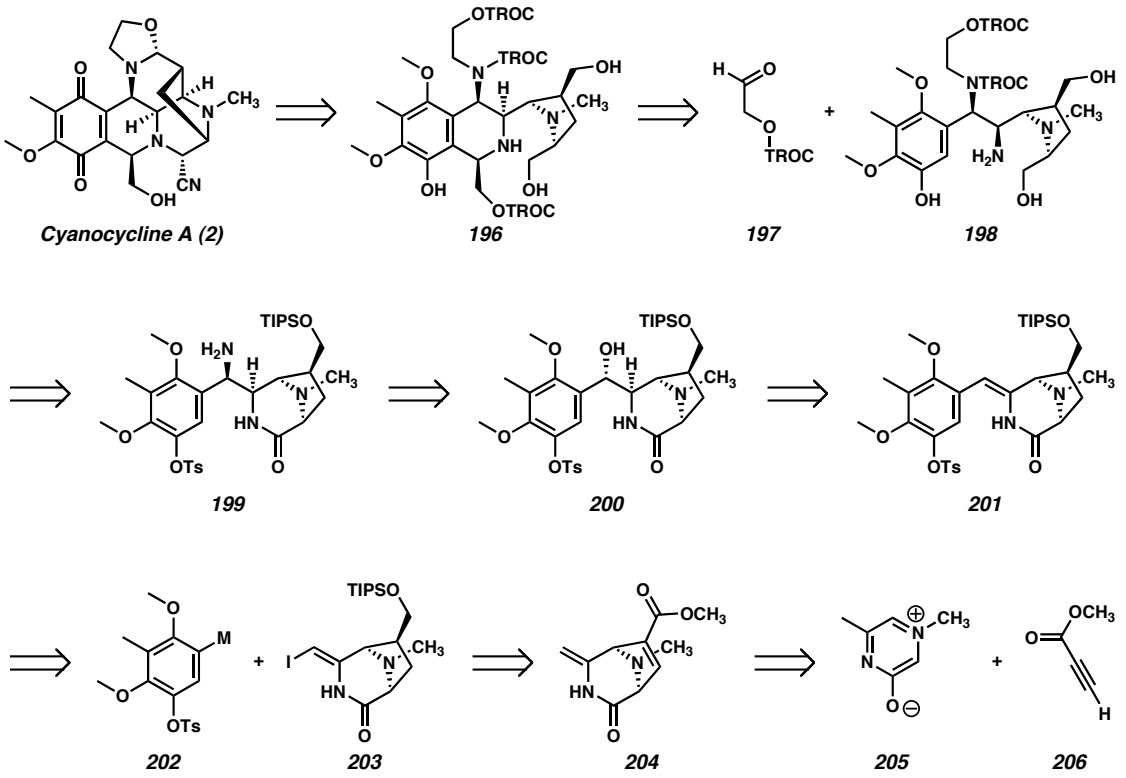
Retrosynthetic Analysis: Silyl Ether Route

To address the synthetic challenges of cyanocycline A, we planned to draw heavily on the knowledge garnered in our total synthesis of (–)-lemonomycin.[4] We therefore planned to utilize a dipolar cycloaddition, a palladium-catalyzed coupling reaction, and a Pictet-Spengler cyclization as the major carbon-carbon bond-forming reactions. However, the synthetic plan had to be altered to account for the differences between the cyanocycline and lemonomycin structures. To solve these challenges, we developed and pursued two strategies for the synthesis cyanocycline A.

Our first retrosynthetic analysis simplified cyanocycline A by deprotection and oxidation transforms to tetrahydroisoquinoline **196** (Scheme 3.1). Retro-Pictet-Spengler cyclization then revealed aminotriol **198** and protected hydroxyacetaldehyde **197**. Aminotriol **198** was disconnected through retrosynthetic reductive amination and amide reduction to amine **199**. This amine was expected to be available by Mitsunobu displacement from alcohol **200**, which could in turn be simplified to enamide **201** by

application of epoxidation and reduction transforms.[5] Enamide **201** was further simplified by retrosynthetic palladium coupling to unveil arene **202** and iodoenamide **203**. We planned to synthesize iodide **203** by stereoselective reduction,[6] protection, and iodination from diazabicycle **204**. Lastly, implementation of a dipolar cycloaddition transform led to dipole **205** and methyl propiolate as starting materials for the synthesis.

Scheme 3.1 Retrosynthetic Analysis of Cyanocycline A



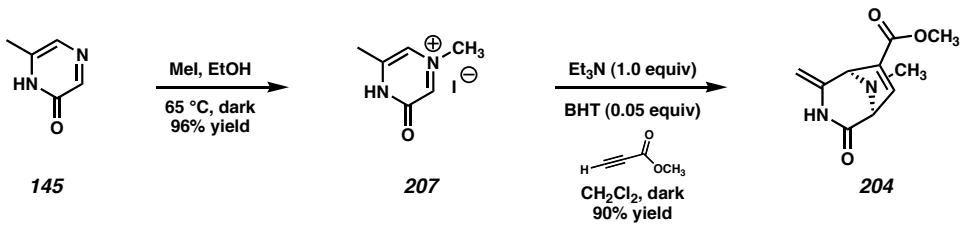
This retrosynthetic analysis addresses the differences between cyanocycline A and lemonomycin through both the use of alternative starting materials and unique transformations. The N(5a) methyl group appears as the *N*-methyl of dipole **205**, while the use of aldehyde **197** in the Pictet-Spengler cyclization resolves absence of lemonose

from the cyanocycline framework. The problem of the epimeric relationship between C(4) of cyanocycline and C(15) of lemonomycin is rectified through a diastereoselective olefin reduction of diazabicycle **204**. Lastly, the sequence of enamide oxidation, Mitsunobu inversion, and reductive amination installs the correct oxidation state at C(13b) and provides the necessary atoms for the oxazolidine ring.

Synthetic Progress Along the Silyl Ether Route

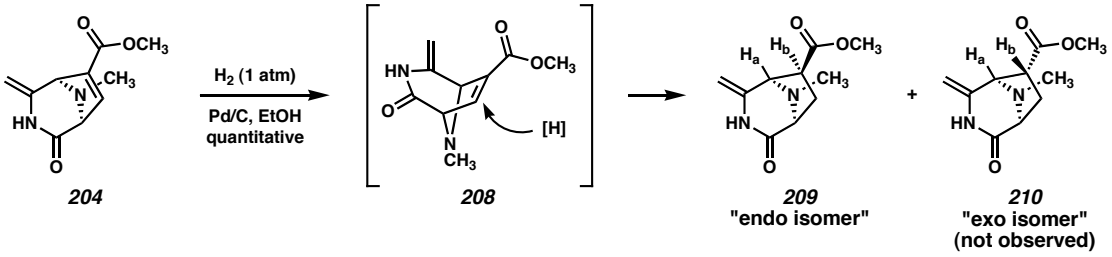
We began our synthetic efforts toward cyanocycline A with the synthesis of an appropriate *N*-methyl dipole precursor. Thus, pyrazinone **145**[7] was alkylated with iodomethane in ethanol to provide oxidopyrazinium salt **207** (Scheme 3.2). Gratifyingly, **207** proved to be an excellent substrate for the dipolar cycloaddition with methyl propiolate, providing diazabicycle **204** in high yield. The significant difference between this reaction and our previous dipolar cycloaddition conditions[4] concerns the amount of base. Since free triethylamine causes the decomposition of methyl propiolate, precisely one equivalent of triethylamine was used to deprotonate oxidopyrazinium **207**. Further, the addition of a small amount of BHT (0.05 equiv) was found to be beneficial, likely due to a buffering effect of the mildly acidic phenol proton.

Scheme 3.2 Dipolar Cycloaddition with Methyl Propiolate



The next challenge of the synthesis was the reduction of diazabicycle **204** to saturated alcohol **211** (Scheme 3.3). This conversion was accomplished through a two-step sequence. First, catalytic hydrogenation of **204** provided saturated ester **209** as a single diastereomer in quantitative yield. The desired diastereomer results from hydrogenation on the convex face of the diazabicycle in transition state **208**, wherein the enamide blocks the top face of the olefin. The relative stereochemistry of the product was determined by ^{1}H NMR. In the desired "endo" product (**209**), the C-H_a and C-H_b bonds are nearly parallel, such that H_a appears in the ^{1}H NMR as a clean doublet. Comparatively, in "exo" compounds such as **210**, the C-H_a and C-H_b bonds are nearly perpendicular, such that H_a is a clear singlet by ^{1}H NMR.[8,9]

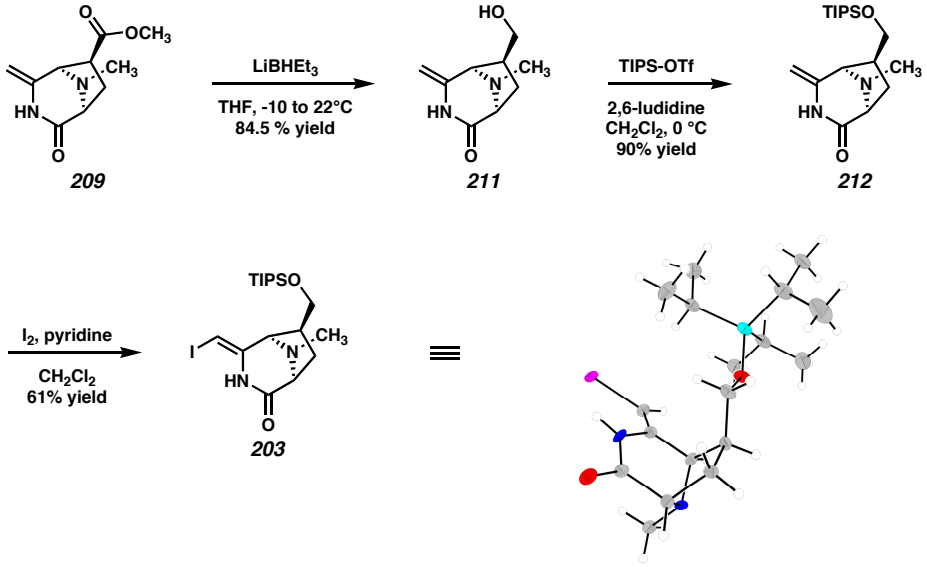
Scheme 3.3 Stereoselective Reduction of the Unsaturated Diazabicycle



We then turned our attention to the reduction of ester **209** to alcohol **211** under conditions that would prevent epimerization of the potentially labile α-stereocenter.[10] This reaction was satisfactorily completed by the treatment of **209** with superhydride, which provided **211** with minimal epimerization (Scheme 3.4). Silylation of the alcohol under standard conditions yielded ether **212**, which was iodinated with molecular iodine to generate iodoenamide **203**. To our delight, iodide **203** was highly crystalline, which

allowed the stereochemistry and olefin geometry of **203** to be proven by X-ray analysis of a single crystal. The crystallographic evidence confirmed the stereochemical assignment of **209** derived from ^{1}H NMR coupling data.

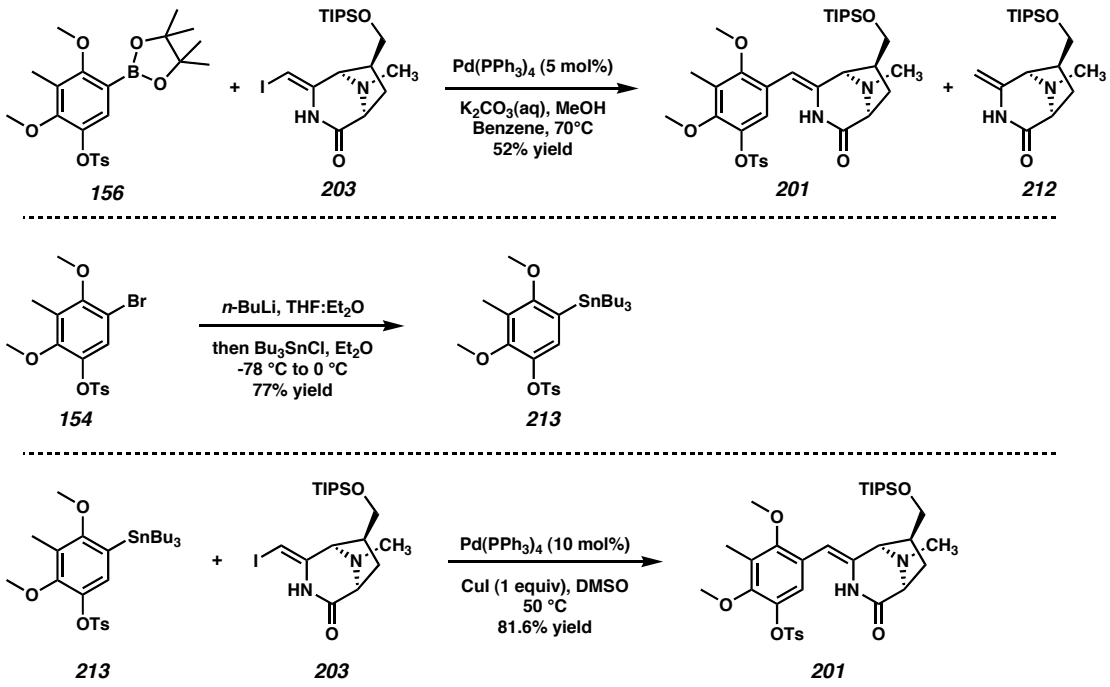
Scheme 3.4 Advancement to the Iodoenamide



The palladium-catalyzed coupling of iodide **203** with arylmetal reagents was then investigated.[11] It was found that Suzuki coupling of the vinyl iodide (**203**) with aryl boronic ester **156** under the conditions optimized for the lemonomycin substrates[4] provided styrene **201** in moderate yield (Scheme 3.5). Unfortunately, this reaction was complicated by competitive reduction of iodide **203** to enamide **212**.

We therefore investigated the potential Stille coupling of **203** to provide **201**. To facilitate this coupling, aryl stannane **213** was synthesized from aryl bromide **154** in good yield. Stille coupling in the presence of copper iodide then cleanly yielded styrene **201** in good yield with only trace amounts of the vinyl iodide reduction product (**212**).[12]

Scheme 3.5 Styrene Synthesis

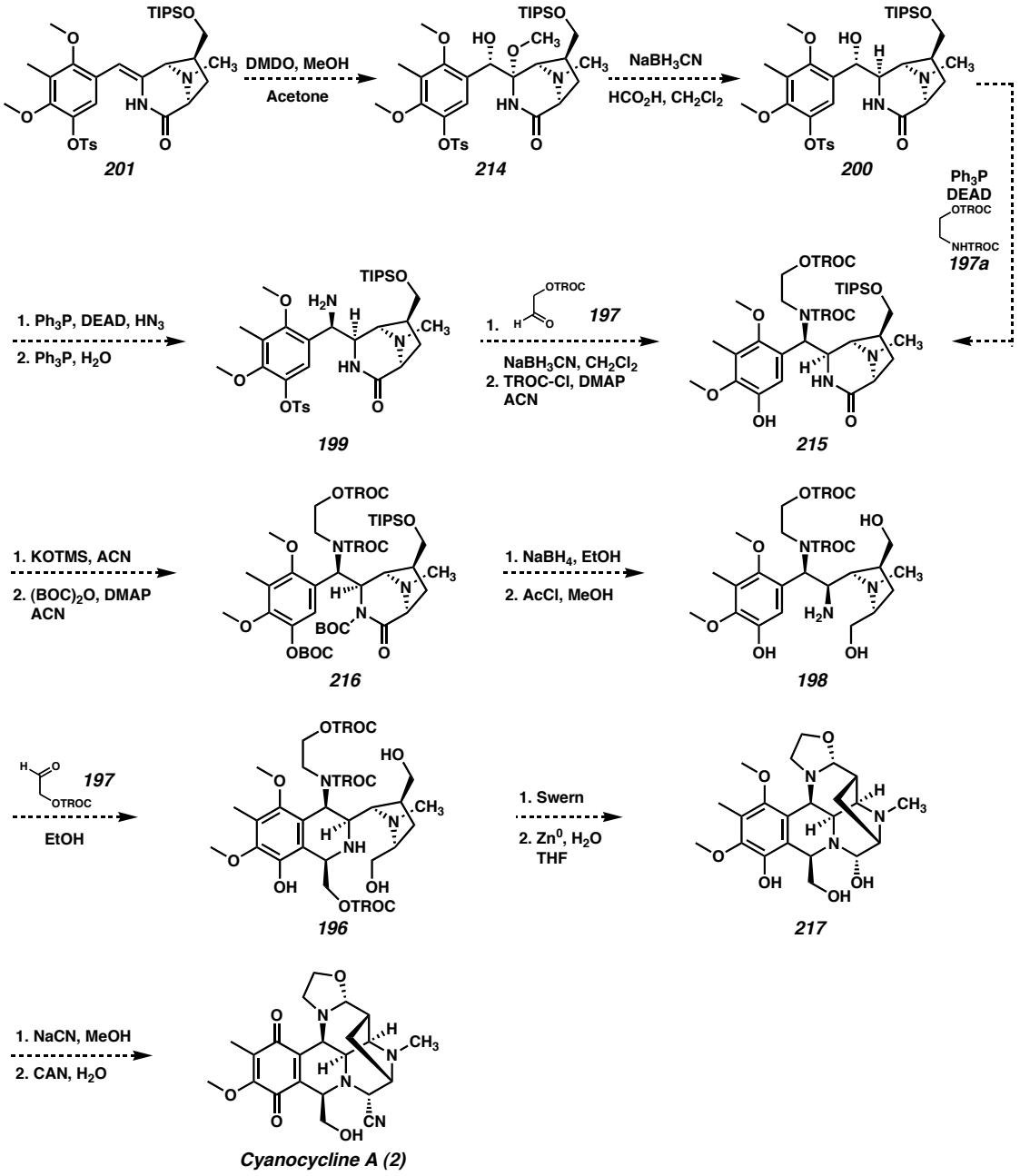


Proposal for Completion of the Silyl Ether Route

We expect that styrene **201** will be amenable to conversion to cyanocycline A (Scheme 3.6). Following the procedure of Fukuyama, we expect that oxidation of styrene **201** with dimethyldioxirane in methanol will yield aminol **214**.[5] Reduction with sodium cyanoborohydride should generate alcohol **200**, which will be advanced to amine **199** by Mitsunobu inversion followed by azide reduction. Reductive amination with aldehyde **197** followed by acylation of the resulting amine will provide protected amino alcohol **215**. Alternatively, **215** may be directly accessible by a Mitsunobu inversion of **200** with carbamate **197a**. Detosylation of the phenol and activation of the lactam with di-*tert*-butyldicarbonate is expected to produce imide **216**, which will be converted to aminotriol **198** by reduction and acidic deprotection. Pictet-Spengler cyclization with aldehyde **197** will synthesize tetrahydroisoquinoline **196**.[13] Swern oxidation followed by zinc mediated

cleavage of the TROC groups should generate oxazolidine **217**, which will be converted to cyanocycline A (**2**) by treatment with sodium cyanide and cerium(IV) oxidation.

Scheme 3.6 Planned Completion of the Silyl Ether Route



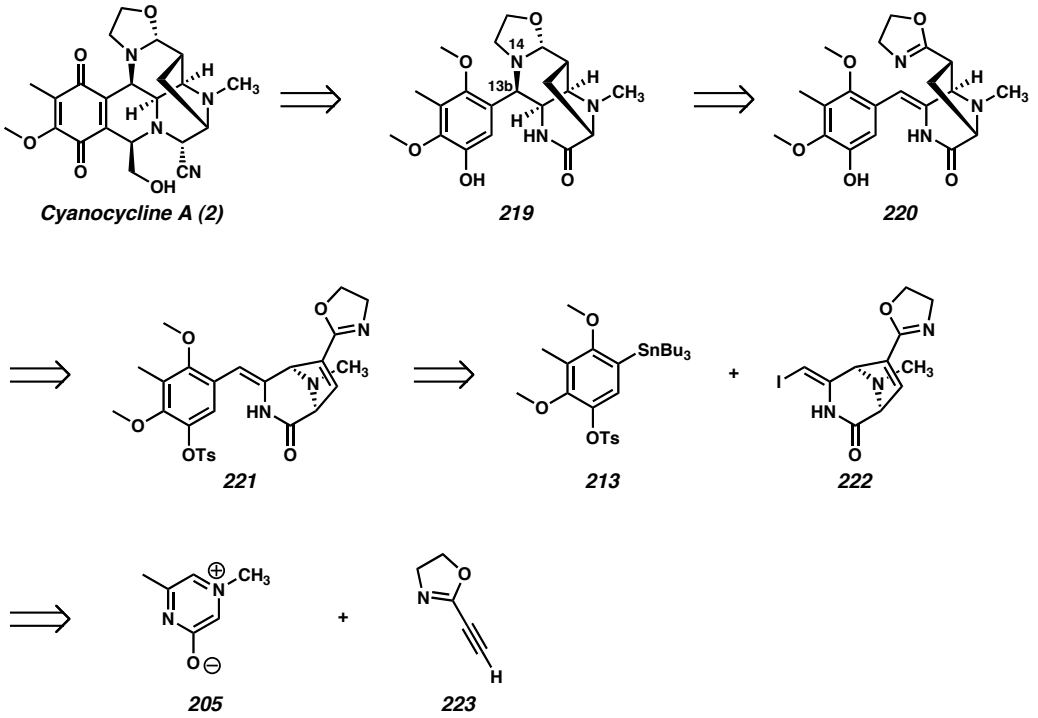
3.2 Second Generation Approach Toward (+)-Cyanocycline A

Retrosynthetic Analysis: Oxazoline Route

Our first generation route toward cyanocycline A is thematically conservative and therefore likely to provide a total synthesis of the natural product. We also wished, however, to approach cyanocycline A from a daring angle that might lead to a more efficient and intellectually valuable synthesis of the natural product. We therefore developed and pursued a second generation synthetic route featuring a proposal for an unprecedented reductive cyclization of an oxazoline with an alkene.

We expected that cyanocycline A (**2**) would be accessible by a glyoxalate Pictet-Spengler cyclization and oxidation state adjustment from lactam **219** (Scheme 3.7). Disconnection of the C(13b)-N(14) bond by retrosynthetic application of our proposed reductive cyclization reaction simplified **219** to oxazoline **220**. Retrosynthetic hydrogenation led to alkene **221**, and a subsequent Stille coupling transform revealed aryl stannane **213** and iodoenamide **222**. We expected to synthesize enamide **222** from dipole **205** and alkynyl oxazoline **223** by a dipolar cycloaddition reaction.

Scheme 3.7 Second Generation Retrosynthesis of Cyanocycline A



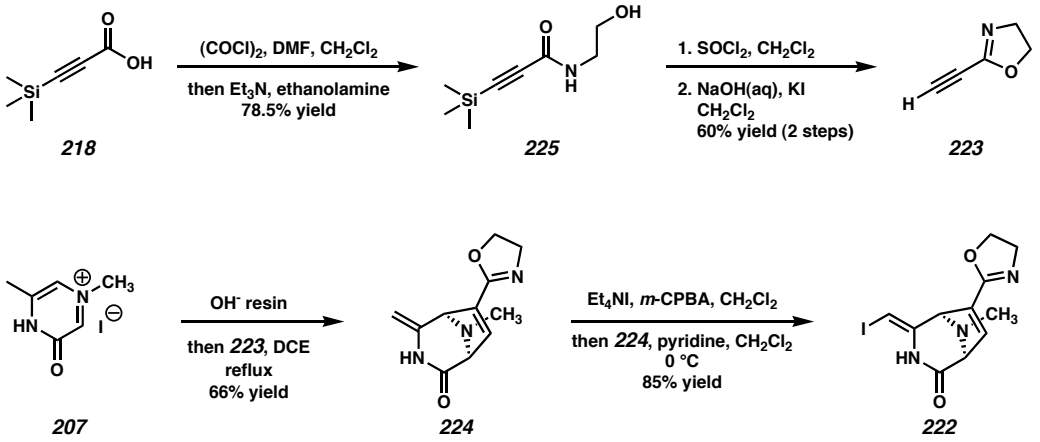
Our second-generation retrosynthesis resolves the differences between lemonomycin and cyanocycline A through reactions both similar to and substantially different from our first generation route. In analogy to our first generation route, the N(5a) methyl group is derived from the *N*-methyl dipole **205**, and the C(4) stereochemistry is again planned to be set by a diastereoselective hydrogenation reaction. Contrastingly, we now plan to address the oxazolidine ring and the C(13b) oxidation state directly by the cyclization of the oxazoline and enamide moieties of **220**.

Synthetic Progress Along the Oxazoline Route

The first challenge of the oxazoline route was the synthesis of alkynyl oxazoline **223** (Scheme 3.8). We began this synthesis with acid **218**, which was smoothly

converted to hydroxyamide **225** via the intermediate acid chloride. Subsequent chlorination with thionyl chloride followed by treatment with sodium hydroxide and potassium iodide cleanly provided alkyne **223**.[14]

Scheme 3.8 Dipolar Cycloaddition with the Alkynyl Oxazoline

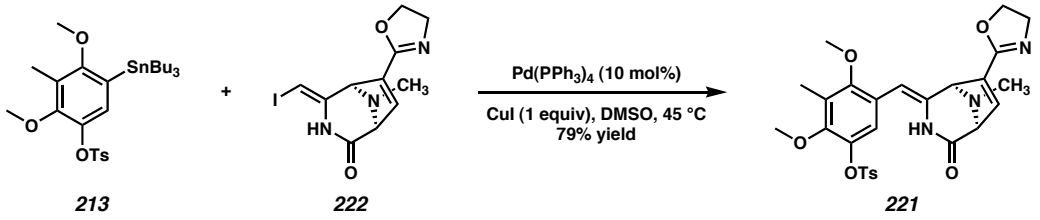


With **223** in hand, we investigated the dipolar cycloaddition with oxidopyrazinium **207**. Unfortunately, the amine-mediated conditions that had proven useful for our earlier substrates provide only low yields (< 46%) of diazabicycle **224**. We therefore turned to a modification of the original conditions reported by Joule,[15] in which oxidopyrazinium **207** is deprotonated with ion exchange resin, isolated as the salt-free dipole (**205**), and then reacted with a dipolarophile. After optimization of these conditions, we found that diazabicycle **224** could be produced in moderate yield by performing the dipolar cycloaddition at elevated temperature in dichloroethane. Despite the moderate yield, this reaction represents a substantial advancement of this type of cycloaddition to the use of a weakly activated acetylenic dipolarophile. Iodination of **224** also proved difficult, but good yields of iodide **222** could be obtained under modified Sha

conditions employing *meta*-chloroperbenzoic acid and tetraethylammonium iodide in pyridine-buffered dichloromethane.[16]

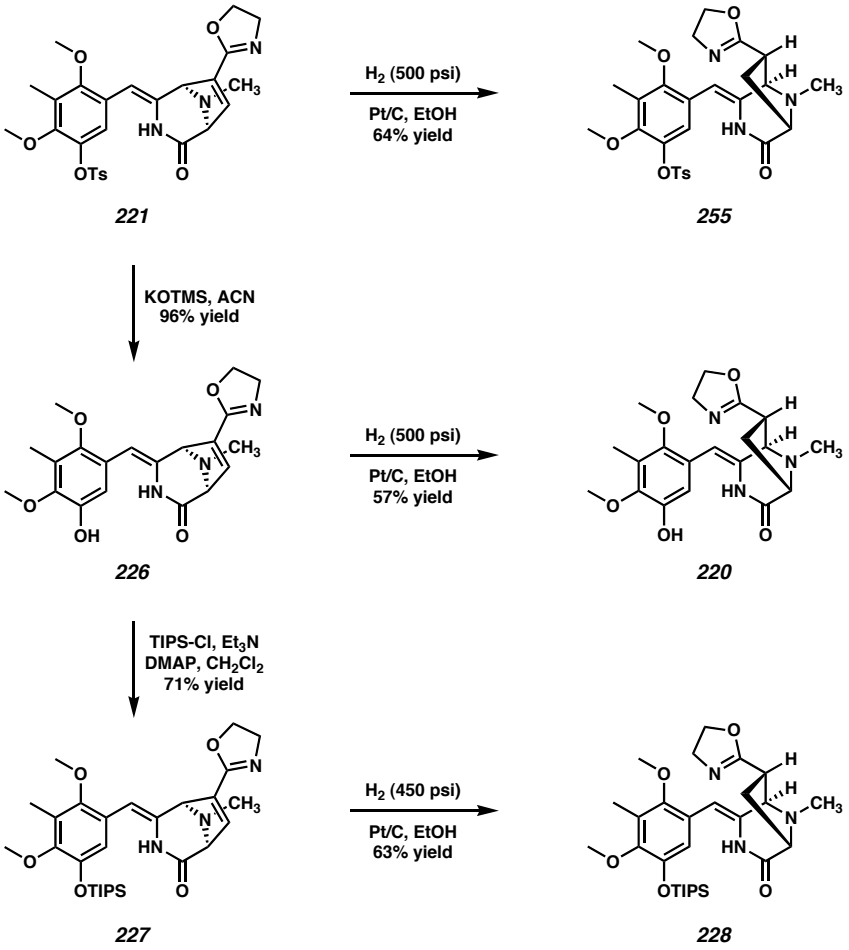
Having developed a synthesis for the diazabicyclic fragment, we investigated the Stille coupling of iodide **222** with stannane **213** (Scheme 3.9).[17] Several simple conditions (Pd(0) source, ligand, solvent) failed to provide the styrene. However, a hit was discovered by application of Corey's cuprous chloride accelerated conditions, which yielded the coupled product (**221**) in 52% yield.[18,12] Further experimentation with copper(I) accelerated conditions led to an optimized protocol that employed stoichiometric cuprous iodide and catalytic tetrakis(triphenylphosphine)palladium(0) in dimethylsulfoxide, which generated styrene **221** in good yield.[19]

Scheme 3.9 Stille Coupling



Styrene **221** was then advanced to three electronically differentiated substrates for the reductive cyclization reaction (Scheme 3.10). Immediate hydrogenation provided oxazoline **255**, while detosylation followed by hydrogenation yielded phenol **220**. Silyl ether **228** was produced by silylation of phenol **226** with triisopropylsilyl chloride followed by catalytic hydrogenation with carbon-supported platinum.[20]

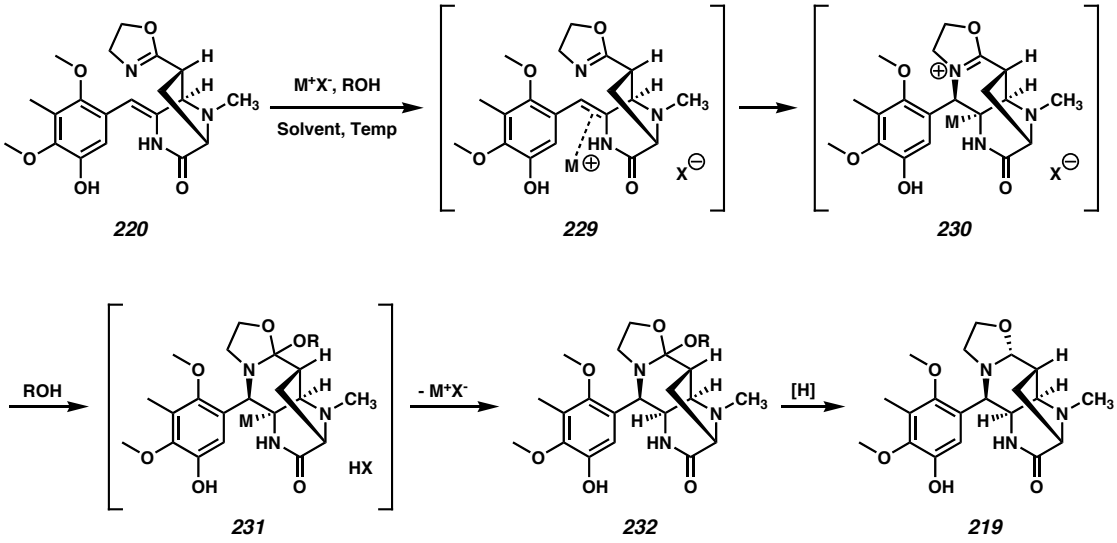
Scheme 3.10 Cyclization Substrate Synthesis



Two strategies toward the desired oxazoline/olefin cyclization have been pursued. The first involved the use of high-oxidation state late transition metal π-acids (Scheme 3.11). It was hoped that activation of the olefin by the metal in intermediate **229** would lead to attack of the oxazoline nitrogen, providing cationic intermediate **230**. Quenching of the cation with an alcohol nucleophile would generate complex **231**, from which protonolysis of the metal-carbon bond would yield piperidine **232** and the regenerated metal catalyst. It was expected that **232** would be amenable to hydride reduction to oxazolidine **219**. Unfortunately, attempts to conduct this reaction with a variety of

platinum(II) and cationic gold(I) catalysts led only to oxazoline hydrolysis and epimerization of the C(4) stereocenter.

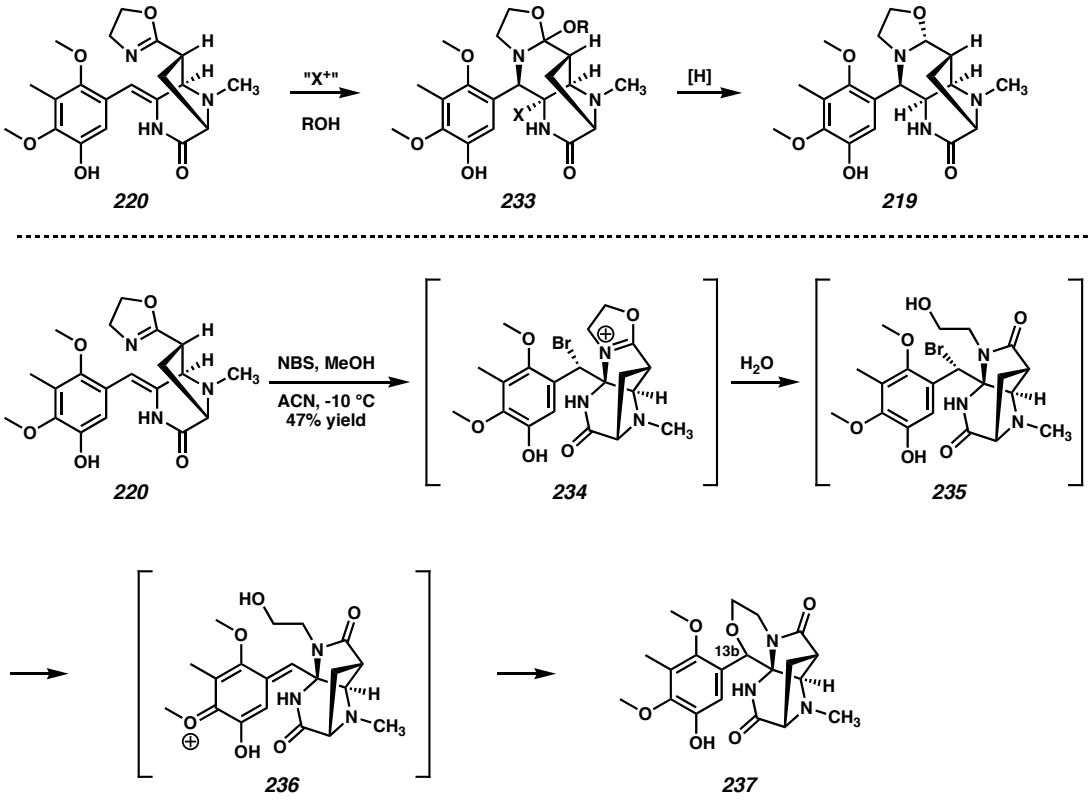
Scheme 3.11 Proposed Cyclization by π-Acid Activation



We then turned to oxidation of olefin **220** with halogenation reagents (Scheme 3.12). It was hoped that activation of **220** by a halogen source in the presence of an alcohol nucleophile would lead to piperidine **233** through a mechanism similar to that shown in Scheme 3.11. It was then expected that reduction of **233** with an appropriate hydride source would remove both the halide and the alkoxide substituents to yield oxazolidine **219**. In attempting this reaction, we quickly discovered that *N*-bromosuccinimide was uniquely effective for the oxidation of **220**. However, the isolated product proved to be pyrrolidinone **237** rather than the desired piperidine (**233**). Although the mechanism of this oxidative cyclization reaction has not been studied, we propose that pyrrolidine **237** results from bromonium-mediated 5-exo cyclization of

oxazoline **220** to cationic intermediate **234**. Rapid hydrolysis of **234** by adventitious water provides hydroxyamide **235**. Loss of bromide forms quinone-methide cation **236**, which is attacked by the hydroxyl group to generate the morpholine ring. Hydroxyamide **235** could alternatively undergo S_N2 displacement of the bromide to yield **237** directly.[21]

Scheme 3.12 *N*-Bromosuccinimide Mediated Cyclization



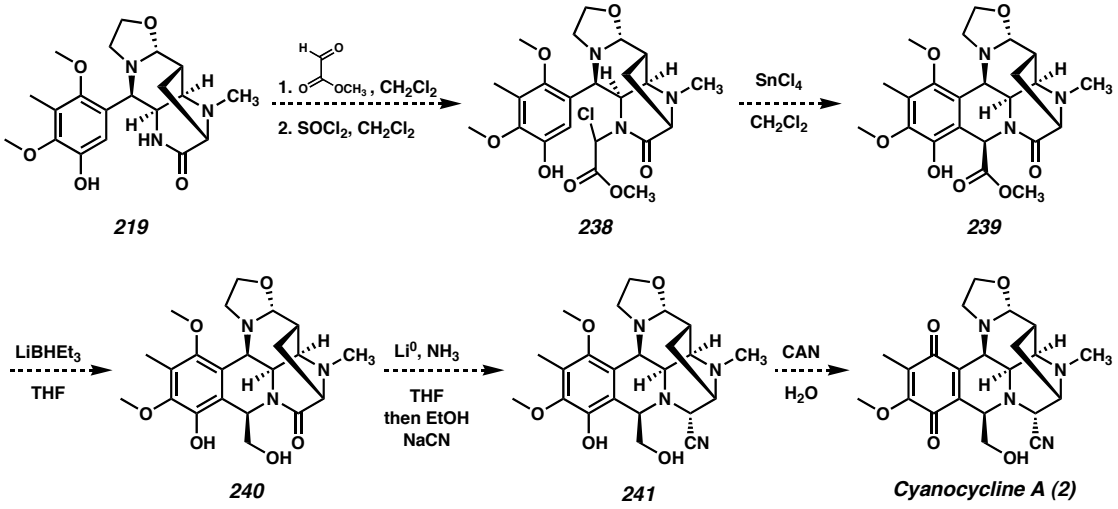
The structure of **237** was assigned on the basis of the NMR resonances of the benzylic carbon and attached proton, the HETCOR correlation of these two resonances, and the resonance of the aminal carbon. The ^{1}H NMR exhibits a sharp singlet at 5.43 ppm that is assigned as the benzylic proton attached to C(13b). A HETCOR spectrum[22] shows a correlation between this proton and a carbon at 73.6 ppm, which indicates an

attached oxygen atom rather than an attached nitrogen atom. A second carbon resonance appears at 72.9 ppm, which is in good agreement with the value expected for an aminal carbon. The stereochemistry of the aminal is enforced by the caged ring structure. The benzylic stereochemistry has not been determined.

Proposal for Completion of the Oxazoline Route

While our early investigations into the conversion of oxazoline **220** to piperidine **219** have not been successful, we anticipate that this reaction will eventually be accomplished by radical reduction, an oxidation-reduction sequence, or photolysis in the presence of a hydrogen atom donor. With **219** in hand, we expect that condensation with methyl glyoxalate followed by treatment with thionyl chloride will yield α-chloroamide **238** (Scheme 3.13). Tin(IV) mediated chloride elimination will then trigger an iminium ion cyclization, producing tetrahydroisoquinoline **239**.[23] Reduction under non-Lewis acidic conditions should provide alcohol **240** without reducing the oxazolidine ring. Dissolving metal conditions will reduce the amide to the carbinolamine, which will be trapped as aminonitrile **241**.[23] The natural product will then arise by cerium(IV) oxidation of the phenol.

Scheme 3.13 Proposed Completion of the Oxazoline Route



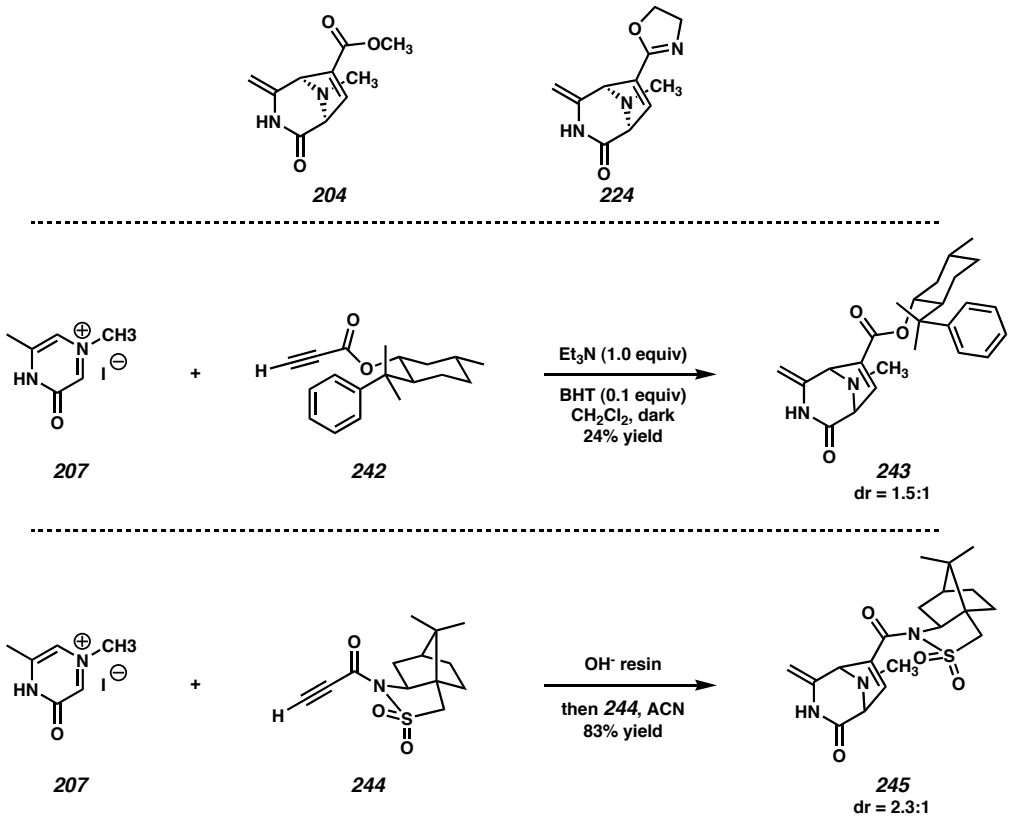
3.3 Progress Toward an Asymmetric Alkyne Dipolar Cycloaddition

Known Chiral Auxiliaries

Our proposed and partially executed syntheses of cyanocycline A utilize a series of diastereoselective reactions, such that all of the stereocenters in the natural product will be set from the stereocenters extant in the early diazabicyclic intermediates (**204** and **224**). Further, it is likely that an ester-appended diazabicycle such as **204** could be readily converted to oxazoline **224**. To render either synthetic route asymmetric, access to an enantiopure ester-appended diazabicycle is required. Such an enantiopure diazabicycle could arise by the dipolar cycloaddition of oxidopyrazinium **207** with an appropriate acylated chiral auxiliary (Scheme 3.14). In this regard, we investigated the dipolar cycloaddition of **207** with the alkynoate of 8-phenylmenthol (**242**)[24] and the alkynamide of Oppolzer's Sultam (**244**).[25] The phenylmenthol-derived alkynoate provided a poor yield of inseparable cycloadducts as a nearly even mixture of diastereomers. The Oppolzer's Sultam-derived alkynamide faired somewhat better,

providing cycloadducts **245** in good yield, but the selectivity is still well below the synthetically useful threshold.[26]

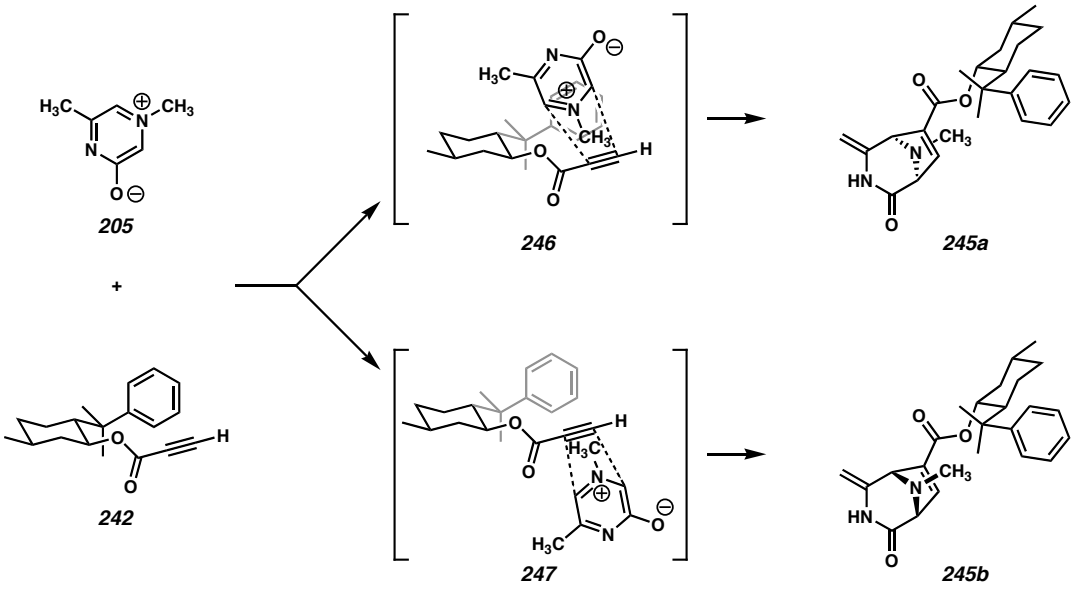
Scheme 3.14 Dipolar Cycloaddition with Known Chiral Auxiliaries



The poor diastereoselectivity of these reactions was initially surprising. The pheylmenthol auxiliary in particular should provide excellent facial bias around the alkyne, allowing the dipole to approach only opposite the phenyl ring (Scheme 3.15). It was soon realized, however, that facial bias around the alkyne is insufficient for diastereoselectivity. For example, reaction of dipole **205** with alkynoate **242** can proceed through transition states **246** and **247**, which both involve approach of the dipole away from the auxiliary's phenyl ring, but which provide opposite diastereomers of product

(**245a** vs. **245b**). To impart diastereocontrol, the auxiliary must therefore control both the facial bias of the alkyne and the orientation of the approaching dipole, differentiating the "endo" approach (e.g., **246**) from the "exo" approach (e.g., **247**).[27]

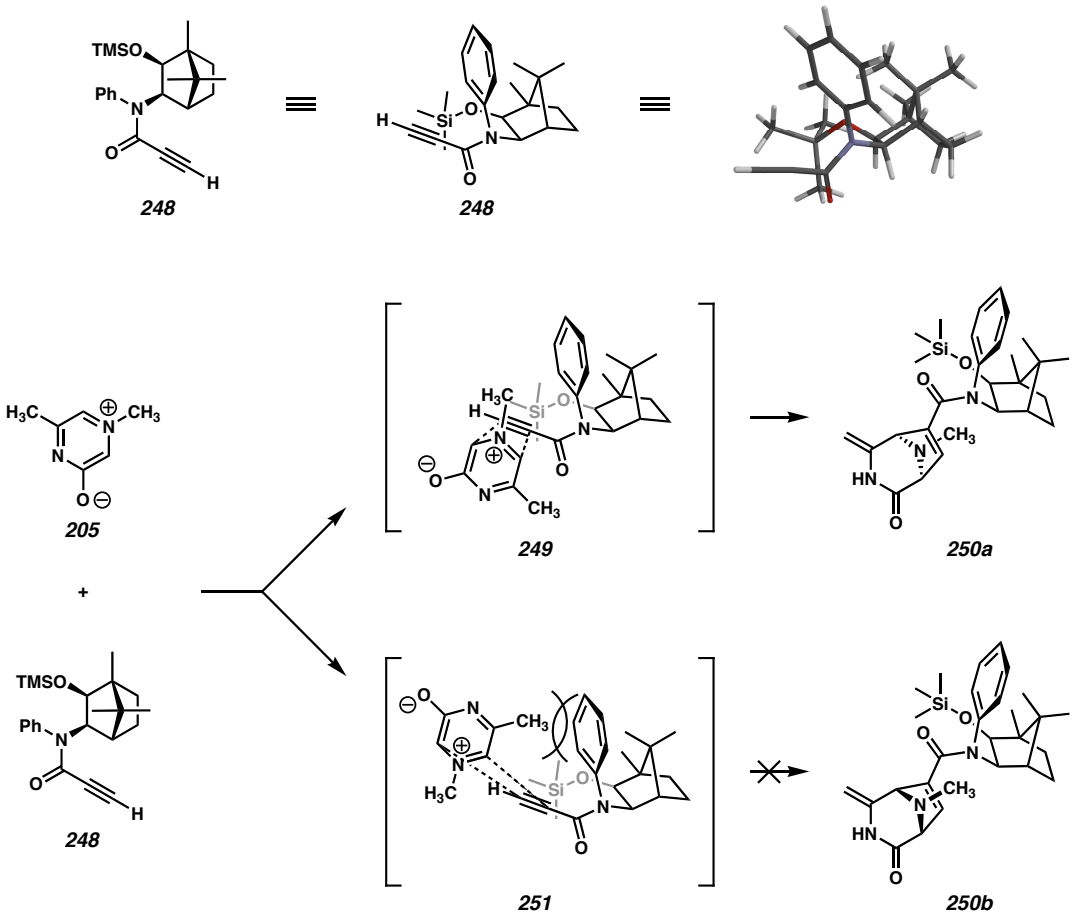
Scheme 3.15 Dipolar Cycloaddition with the Phenylmenthol-derived Auxiliary



Design and Utilization of a New Chiral Auxiliary

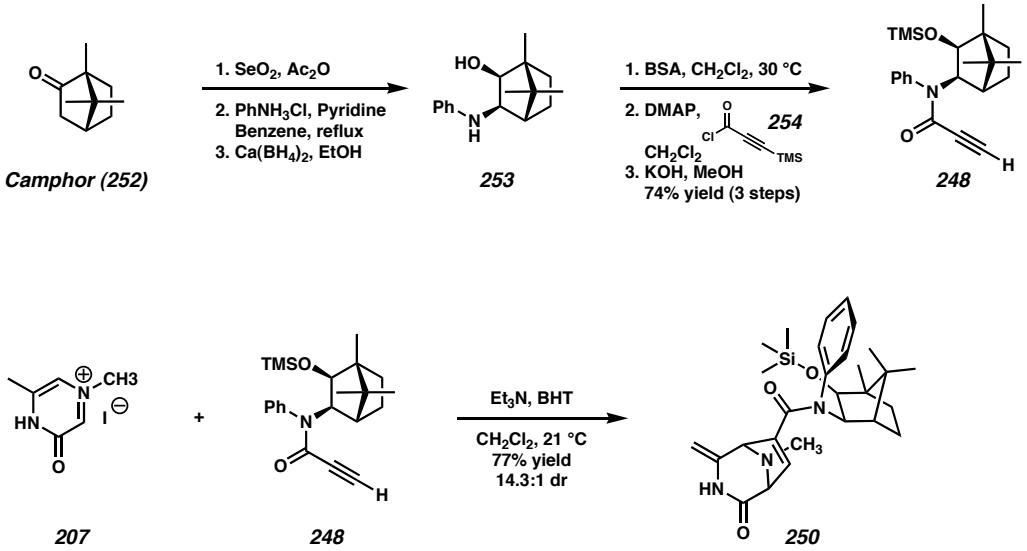
To distinguish the endo and exo orientations of the dipole, auxiliary **248** was designed (Scheme 3.16).[28] In its lowest energy conformation,[29] the phenyl ring of **248** is oriented perpendicularly to the reactive alkyne. This orientation places the steric bulk of the phenyl ring above the alkynoate, while the silyloxy group blocks the back face. Dipole **205** must therefore approach over the front face. In exo transition state **249**, the dipole's *N*-methyl group is accommodated by the auxiliary's phenyl ring. In endo transition state **251**, the phenyl group and the dipole's *C*-methyl group clash extensively, destabilizing this pathway.

Scheme 3.16 Design of a New Chiral Auxiliary



Kevin Allan synthesized the desired alkynoate **248** from camphor (Scheme 3.17). Camphor (**252**) was advanced by known procedures[30] to amino alcohol **253**, which was selectively *O*-silylated with *N*,*O*-bis(trimethysilyl)acetamide. Acylation and alkyne deprotection afforded alkynoate **248**. This alkynoate was then reacted with oxidopyrazinium **207** and triethylamine in dichloromethane to provide cycloadduct **250** with a diastereomeric ratio of 14.3 to 1. Although the relative stereochemistry of **250** has not been confirmed, this reaction represents a major advance in alkyne dipolar cycloaddition chemistry that will lead to an asymmetric synthesis of cyanocycline A.

Scheme 3.17 Synthesis and Utilization of the New Auxiliary



3.4 Conclusion

Substantial progress toward the synthesis of (+)-cyanocycline A has been completed along two synthetic routes. Progress along the silyl ether route led to the discovery of a new diastereoselective hydrogenation of an unsaturated diazabicyclic intermediate to set the C(4) stereochemistry of cyanocycline A. The product of this reduction was advanced through a convergent Stille coupling reaction. The coupled intermediate contains all but six of the heavy atoms of cyanocycline A with the correct stereochemistry at each of the stereogenic carbons. Further, the enamide functionality is an ideal precursor for installation of the C(13b) amino group.

Progress along the oxazoline route has led to the development of a novel dipolar cycloaddition of an alkynyl oxazoline. The resulting diazabicycle was advanced through a convergent Stille coupling reaction and diastereoselective hydrogenation to a late stage intermediate for the synthesis of cyanocycline A. This intermediate contains all but three

of the heavy atoms of cyanocycline A and has the correct relative stereochemistry for advancement to the natural product. Attempted cyclization of this intermediate has not yet been fully successful, although a compound with the correct C(13b) oxidation state was formed by reaction with *N*-bromosuccinimide.

In collaboration with Kevin Allan, a novel chiral auxiliary for the alkynoate dipolar cycloaddition was designed and synthesized. Application of the chiral auxiliary led to the production of cycloadducts with 20:1 diastereoselectivity. It is expected that the major cycloadduct will be readily converted to intermediates in either of our synthetic routes. Advancement of that material eventually will provide an asymmetric synthesis of (+)-cyanocycline A.

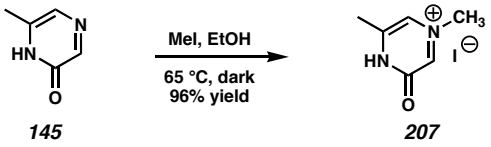
3.5 Experimental Procedures

Materials and Methods

Unless otherwise stated, reactions were performed at ambient temperature (typically 20 to 22 °C) in flame-dried glassware under a nitrogen or argon atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Acrolein was distilled under nitrogen immediately prior to use. All other commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV, anisaldehyde, permanganate, or CAM staining. ICN Silica gel (particle size 0.032-0.063 mm) was used for flash chromatography. Optical rotations were measured with a Jasco P-1010 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on either a Varian Mercury 300 (at 300 MHz and 75 MHz respectively), Varian Mercury 500 (at 500 MHz and 125 MHz respectively), or a Varian Mercury 600 (600 MHz for proton only) spectrometer and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). UV spectra were measured on a Beckman-Coulter DU 7400 spectrophotometer. High-resolution mass spectra were obtained from the Caltech Mass Spectral Facility. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, and copies

can be obtained on request, free of charge, by quoting the publication citation and the deposition number (see individual structures for deposition number).

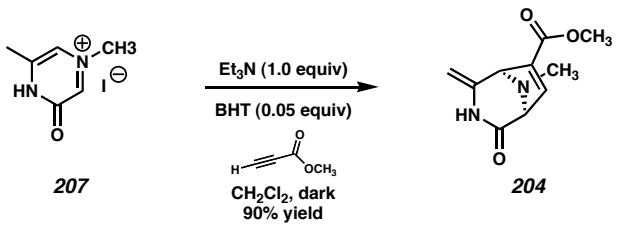
Preparation of Compounds



145 *207*

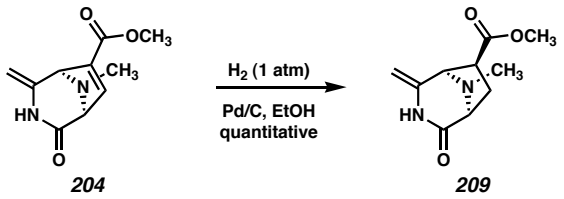
Oxidopyrazinium 207

(Note: the reaction was performed in a foil-wrapped flask equipped with a reflux condenser.) To a suspension of pyrazinone **145** (5.0 g, 45.4 mmol) in anhydrous ethanol (90 mL) was added iodomethane (14.1 mL, 227 mmol). The reaction mixture was degassed by cooling to –78 °C and evacuating to 1 torr for 20 min, then flushing with argon. The mixture was then heated to 65 °C. After 27 h, additional iodomethane (7.05 mL, 113.5 mmol) was added. After 47 h, the reaction was cooled to 0 °C and filtered. The filter cake was washed with cold (0 °C) ethanol (100 mL) and dried under vacuum to yield oxidopyrazinium **207** (11.0 g, 96% yield) as a red-orange powder: ^{1}H NMR (300 MHz, D_2O) δ 8.38 (s, 1H), 7.59 (s, 1H), 4.24 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (75 MHz, D_2O) δ 158.2, 149.4, 142.0, 118.6, 49.3, 16.9; IR (Nujol) 1685, 1635, 1462 cm^{-1}; Elemental Analysis $C_6H_9N_2OI$, calc'd: C, 28.59; H, 3.60; N, 11.11; I, 50.35, found, C, 28.66; H, 3.79; N, 10.90; I, 50.68.



Diazbicycle 204

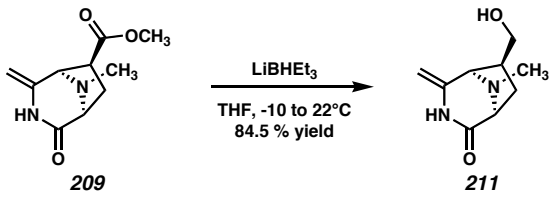
(Note: the reaction was performed in a foil-wrapped flask.) To a suspension of **207** (504 mg, 2.0 mmol) in dichloromethane (6.7 mL) were added BHT (22.0 mg, 100 μmol) and triethylamine (279 μL, 2.0 mmol). After 30 min, methyl propiolate (534 μL, 6.0 mmol) was added. After 5 h 45 min, the mixture was diluted with saturated aqueous ammonium chloride (50 mL) and saturated aqueous sodium bisulfite (5 mL) and extracted into dichloromethane (2 x 25 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (50:50:1 to 80:20:1 ethyl acetate:hexanes:triethylamine) to yield **204** (377 mg, 90% yield): R_F 0.37 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (br s, 1H), 7.10 (d, J = 2.7 Hz, 1H), 4.42 (s, 1H), 4.33-4.28 (comp m, 2H), 3.96 (s, 1H), 3.78 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 163.0, 141.3, 138.7, 136.9, 94.0, 71.0, 66.5, 52.1, 36.6; IR (NaCl/film) 3211, 2951, 1721, 1689, 1299, 1256, 1089 cm^{-1}; HRMS (FAB+) calc'd for $[C_{10}H_{12}N_2O_3]^{\bullet+}$: *m/z* 208.0848, found 208.0851.



204 *209*

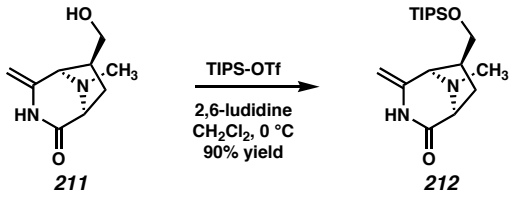
Ester 209

To a solution of **204** (100.0 mg, 480.3 μmol) in ethanol (4.8 mL) was added palladium on carbon (10% w/w, 20 mg). The reaction vessel was purged, flushed with hydrogen, and maintained under 1 atm of hydrogen for 1 h 15 min. The mixture was then filtered directly through a column packed with celite over silica gel (95:5:1 ethyl acetate:ethanol:triethylamine eluent) to provide **209** (100.9 mg, quantitative), which was sufficiently pure for use in the next reaction. An analytically pure sample of **204** was prepared by flash chromatography on silica gel (0:100:1 to 3:97:1 methanol:ethyl acetate: ethyldimethylamine eluent): R_F 0.24 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (br s, 1H), 4.32 (s, 1H), 4.08 (s, 1H), 3.86 (d, *J* = 6.6 Hz, 1H), 3.65 (s, 3H), 3.48 (d, *J* = 7.2 Hz, 1H), 3.47-3.41 (m, 1H), 2.51-2.33 (comp m, 2H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 170.9, 138.8, 93.2, 65.3, 65.0, 52.3, 48.0, 35.7, 31.4; IR (NaCl/film) 3199, 2951, 1740, 1690, 1653, 1322, 1205, 1018, 846 cm^{-1}; HRMS (FAB+) calc'd for $[C_{10}H_{14}N_2O_3]^{\bullet+}$: *m/z* 210.1005, found 210.1010.



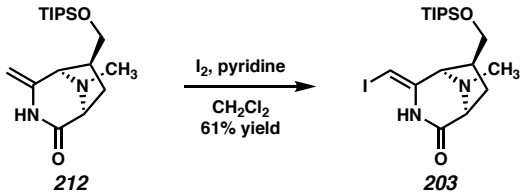
Alcohol 211

To a –10 °C solution of **209** (56 mg, 266 μmol) in tetrahydrofuran (2.7 mL) was added a solution of lithium triethylborohydride in tetrahydrofuran (1 M, 1.33 mL, 1.33 mmol) dropwise over 2 min. After 15 min, the reaction mixture was allowed to warm to 22 °C. After an additional 30 min, the reaction was quenched with ethyl acetate (1 mL). After an additional 5 min, the solution was concentrated and purified by flash chromatography on silica gel (4:96:1 to 13:87:1 methanol:ethyl acetate:triethylamine eluent) to yield **211** (41.0 mg, 84.5% yield): R_F 0.12 (10:90 methanol:ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (br s, 1H), 4.42 (s, 1H), 4.21 (s, 1H), 3.69 (d, *J* = 6.3 Hz, 1H), 3.58 (d, *J* = 7.5 Hz, 2H), 3.43 (d, *J* = 7.5 Hz, 1H), 2.78-2.66 (m, 1H), 2.50-2.38 (m, 1H), 2.45 (s, 3H) 2.36 (br s, 1H), 1.51 (dd, *J* = 13.2, 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 139.2, 93.2, 64.7, 64.6, 63.5, 43.3, 35.6, 32.7; IR (NaCl/film) 3321 br, 3202, 2944, 1682, 1322, 1044 cm^{-1}; HRMS (EI+) calc'd for $[C_9H_{14}N_2O_2]^{\bullet+}$: *m/z* 182.1055, found 182.1059.



Silyl Ether 212

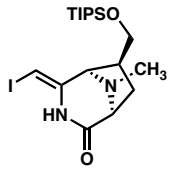
To a 0 °C solution of alcohol **211** (108.2 mg, 593.7 μmol) in dichloromethane (6.0 mL) were added 2,6-lutidine (242.0 μL, 2.08 mmol) and triisopropylsilyl trifluoromethanesulfonate (478.7 μL, 1.78 mmol). After 20 min, the reaction mixture was diluted with ethyl acetate (75 mL) and washed with water (75 mL) followed by saturated aqueous sodium chloride (25 mL). The organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (55:45:1 to 6:35:1 ethyl acetate:hexanes:ethyldimethylamine eluent) to provide silyl ether **212** (181.0 mg, 90% yield): R_F 0.38 (70:30 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (s, 1H), 4.39 (s, 1H), 4.20 (s, 1H), 3.69 (d, *J* = 6.0 Hz, 1H), 3.62 (d, *J* = 7.8 Hz, 2H), 3.44 (d, *J* = 7.5 Hz, 1H), 2.74-2.62 (m, 1H), 2.47 (s, 3H), 2.46-2.36 (m, 1H), 1.50 (dd, *J* = 13.2, 6.0 Hz, 1H), 1.08-0.98 (comp m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 138.4, 93.8, 64.9, 64.6, 64.0, 44.1, 35.6, 32.5, 18.2, 12.1; IR (NaCl/film) 2942, 2865, 1689, 1099, 882, 681 cm^{-1}; HRMS (FAB+) calc'd for $[C_{18}H_{34}N_2O_2Si+H]^+$: *m/z* 339.2468, found 339.2462.



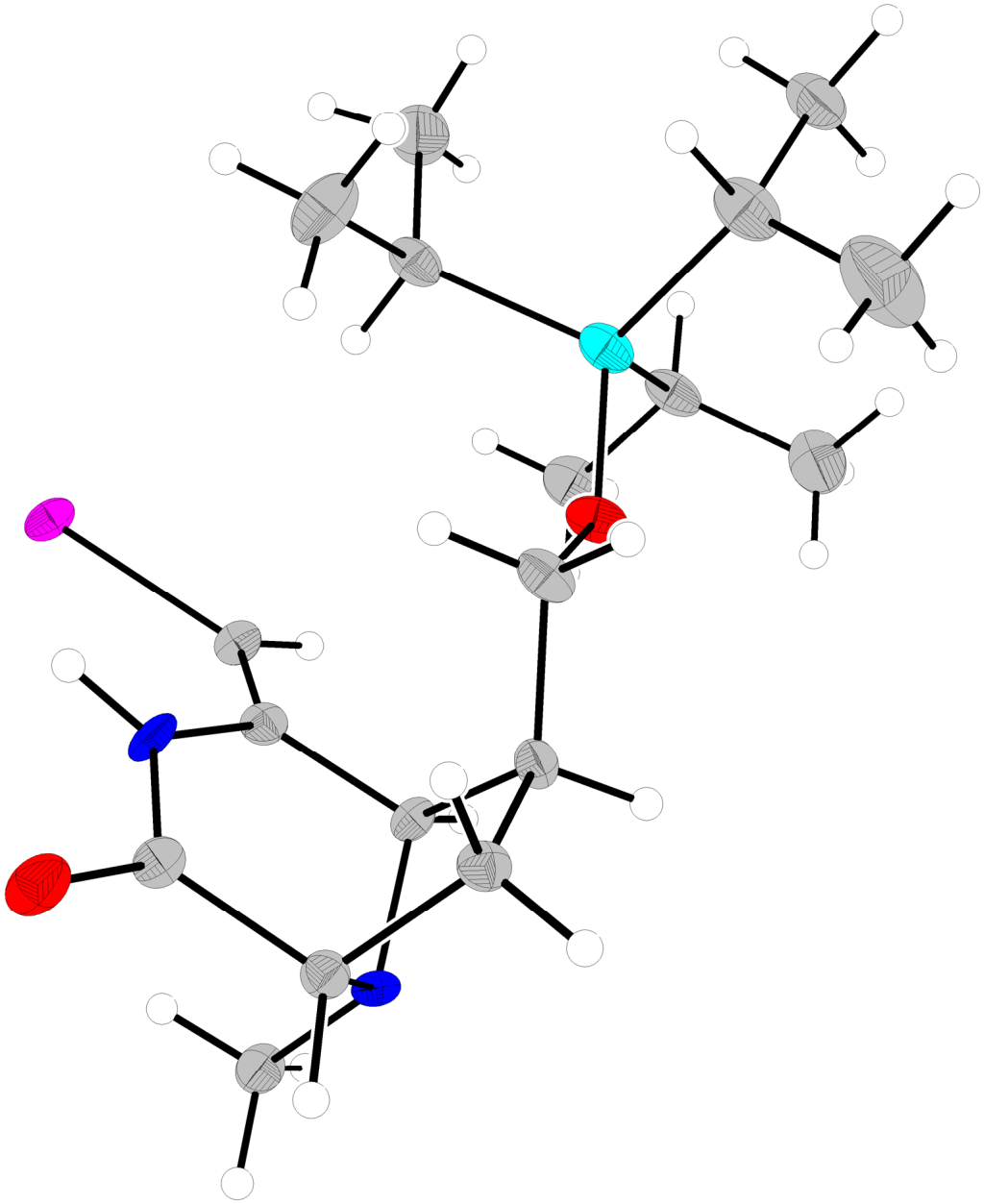
Iodoenamide 203

(Note: the reaction was performed in a foil-wrapped flask.) To a solution of enamide **212** (181.0 mg, 534.6 μmol) in dichloromethane (5.3 mL) were added pyridine (130 μL, 1.60 mmol) and iodine (149.2 mg, 588.0 μmol). After 15 min, the reaction mixture was diluted with ethyl acetate (75 mL) and washed with a mixture of water (100 mL) and saturated aqueous sodium thiosulfate (5 mL) followed by saturated aqueous sodium chloride (25 mL). The organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (20:80:1 to 30:70:1 ethyl acetate:hexanes:ethyldimethlamine eluent) to provide iodide **203** (152.0 mg, 61% yield): R_F 0.77 (70:30 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (br s, 1H), 5.11 (s, 1H), 3.91 (d, *J* = 6.3 Hz, 1H), 3.64 (dd, *J* = 10.2 6.0 Hz, 1H), 3.45 (app t, *J* = 10.2 Hz, 1H), 3.45 (d, *J* = 7.5 Hz, 1H), 2.73-2.61 (m, 1H), 2.47-2.35 (m, 1H), 2.43 (s, 3H), 1.43 (dd, *J* = 13.2, 5.7 Hz, 1H), 1.06-1.01 (comp m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 140.1, 66.7, 65.0, 63.7, 55.1, 44.4, 35.7, 31.8, 18.3, 12.1; IR (NaCl/film) 3217, 2940, 2865, 1700, 1634, 1299, 1109, 1092, 691 cm^{-1}; HRMS (FAB+) calc'd for $[C_{18}H_{33}N_2O_2SiI+H]^+$: *m/z* 465.1435, found 465.1445. A crystal of sufficient quality for X-ray analysis was grown from ethyl acetate:hexanes by slow diffusion.

Crystal Structure of 203



203



Crystal data and structure refinement for 203 (CCDC 286418).

Empirical formula	$C_{18}H_{33}IN_2O_2Si$
Formula weight	464.45
Crystallization Solvent	Ethyl acetate/hexanes
Crystal Habit	Plate
Crystal size	0.26 x 0.18 x 0.01 mm^3
Crystal color	Colorless

Data Collection

Type of diffractometer	Bruker SMART 1000	
Wavelength	0.71073 Å MoKα	
Data Collection Temperature	100(2) K	
θ range for 8013 reflections used		
in lattice determination	2.88 to 29.24°	
Unit cell dimensions	a = 7.4435(5) Å	α= 89.566(4)°
	b = 8.1736(6) Å	β= 81.264(4)°
	c = 19.5349(14) Å	γ = 65.225(3)°
Volume	1064.51(13) $Å^3$	
Z	2	
Crystal system	Triclinic	
Space group	P-1	
Density (calculated)	1.449 Mg/m^3	
F(000)	476	
Data collection program	Bruker SMART v5.630	
θ range for data collection	2.11 to 30.48°	
Completeness to θ = 30.48°	87.5 %	
Index ranges	$-10 \le h \le 10$, $-11 \le k \le 11$, $-26 \le l \le 27$	
Data collection scan type	ω scans at 7 ϕ settings	

Data reduction program	Bruker SAINT v6.45A
Reflections collected	21316
Independent reflections	5678 [R_{int}= 0.0847]
Absorption coefficient	1.573 mm^{-1}
Absorption correction	None
Max. and min. transmission	0.9844 and 0.6852

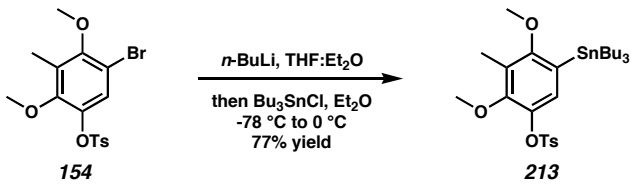
Structure solution and Refinement

Structure solution program	Bruker XS v6.12
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Geometric positions
Structure refinement program	Bruker XL v6.12
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	5678 / 0 / 224
Treatment of hydrogen atoms	Riding
Goodness-of-fit on F^2	1.656
Final R indices [I>2σ(I), 4244 reflections]	R1 = 0.0666, *w*R2 = 0.0849
R indices (all data)	R1 = 0.0972, *w*R2 = 0.0874
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.001
Average shift/error	0.000
Largest diff. peak and hole	1.920 and -3.266 e.$Å^{-3}$

Special Refinement Details

Refinement of F^2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

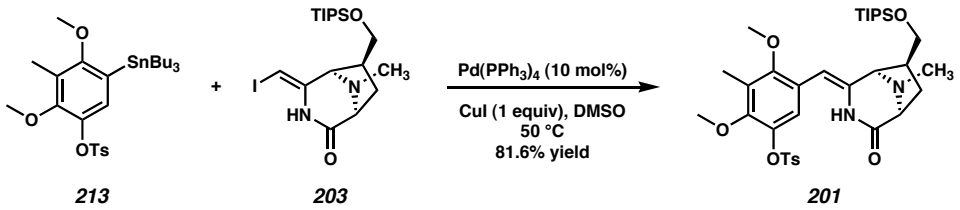
All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.



154 *213*

Stannane 213

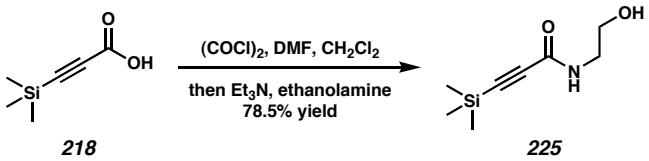
To a –78 °C solution of bromide **154** (1.0 g, 2.5 mmol) in tetrahydrofuran:diethyl ether (1:1, 25 mL) was added a solution of *n*-butyllithium in hexanes (2.5 M, 1.1 mL, 2.75 mmol) dropwise down the flask walls over 45 sec. After 15 min, a –78 °C solution of tributyltin chloride (814 μL, 3.0 mmol) in diethyl ether (6.0 mL) was added via cannula. After an additional 10 min, the reaction mixture was warmed to 0 °C over 10 min, then quenched with water (100 mL). The mixture was extracted into diethyl ether (2 x 25 mL). The combined organics were dried over magnesium sulfate, concentrated, and purified by flash chromatography on silica gel (5:95 to 10:90 ethyl acetate:hexanes eluent) to provide stannane **213** (1.17 g, 77% yield): R_F 0.55 (15:85 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 7.81 (d, *J* = 8.4 Hz, 2H), 7.30 (s, 1H), 6.70 (d, *J* = 8.1 Hz, 2H), 3.56 (s, 3H), 3.35 (s, 3H), 2.06 (s, 3H), 1.83 (s, 3H), 1.68-1.55 (comp m, 6H), 1.44-1.31 (comp m, 6H), 1.14-1.07 (comp m, 6H), 0.93 (t, *J* = 7.2 Hz, 9H); ^{13}C NMR (75 MHz, C_6D_6) δ 163.7, 153.4, 144.9, 140.6, 135.0, 130.0, 129.5, 129.0, 125.7, 100.7, 61.2, 60.9, 29.9, 28.1, 21.6, 14.3, 11.0, 10.8; IR (NaCl/film) 2955, 2926, 1465, 1378, 1188, 1178, 1095, 1010, 988, 825, 812 cm^{-1}; HRMS (FAB+) calc'd for $[C_{28}H_{44}O_5SSn+H]^+$: *m/z* 613.2010, found 613.2023.



Styrene 201

(Note: the reaction was performed in a foil-wrapped vessel.) To a solution of **213** (78.9 mg, 129 μmol) and **203** (30.0 mg, 64.5 μmol) in dimethylsulfoxide were added copper(I) iodide (12.3 mg, 64.5 μmol) and tetrakis(triphenylphosphine)palladium(0) (7.5 mg, 6.45 μmol). The reaction mixture was deoxygenated by twice freezing under vacuum and melting under argon. The reaction mixture was then sealed under argon and heated to 50 °C. After 3 h, the mixture was cooled to 22 °C, diluted with ethyl acetate (50 mL), and washed with a mixture of water (135 mL) and saturated aqueous ammonium hydroxide (15 mL) followed by water (150 mL) followed by saturated aqueous sodium chloride (25 mL). The organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (25:25:50:0.5 to 30:30:40:0.5 ethyl acetate:dichloromethane:hexanes:ethyldimethylamine eluent) to provide styrene **201** (34.7 mg, 81.6% yield): R_F 0.35 (35:35:40 ethyl acetate: dichloromethane:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.80 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 7.8 Hz, 2H), 6.78 (s, 1H), 5.35 (s, 1H), 3.74 (d, *J* = 6.3 Hz, 1H), 3.69 (s, 3H), 3.68-3.66 (comp m, 2H), 3.65 (s, 3H), 3.50 (d, *J* = 7.8 Hz, 1H), 2.84-2.70 (m, 1H), 2.55-2.43 (m, 1H), 2.50 (s, 3H), 2.46 (s, 3H), 2.15 (s, 3H), 1.54 (dd, *J* = 13.5, 5.7 Hz, 1H), 1.04-0.99 (comp m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 153.9, 145.5, 139.2, 133.5, 129.9, 128.5, 127.6, 123.7, 122.3, 103.4, 66.3, 65.0, 64.3, 61.1, 60.4,

45.1, 35.7, 32.7, 22.0, 18.2,, 12.1, 10.0; IR (NaCl/film) 2942, 2865, 1693, 1377, 1191, 1178, 1111, 992 cm^{-1}; HRMS (FAB+) calc'd for $[C_{34}H_{50}N_2O_7SSi+H]^+$: *m/z* 659.3186, found 659.3209.

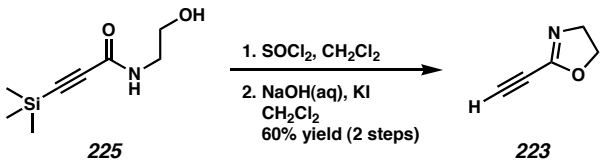


218 ***225***

Amide 225

To a solution of acid **218** (9.5 g, 66.8 mmol) and dimethylformamide (517 μL, 6.68 mmol) in dichloromethane (267 mL) was added oxalyl chloride (6.41 mL, 73.5 mmol) dropwise over 10 min (caution: gas evolution). After 1.5 h, this reaction mixture was added dropwise over 20 min to a solution of ethanolamine (12.1 mL, 200.4 mmol) and triethylamine (18.6 mL, 133.6 mmol) in dichloromethane (200 mL) (caution: exotherm). After an additional 2 h 10 min, the resulting reaction mixture was quenched into aqueous hydrochloric acid (0.5 M, 600 mL). The phases were separated, and the aqueous layer was extracted with dichloromethane (50 mL). The combined organics were dried over magnesium sulfate, concentrated, and purified by flash chromatography on silica gel (50:50 to 80:20 ethyl acetate:hexanes eluent) to provide amide **225** (9.72 g, 78.5% yield): R_F 0.31 (70:30 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (br s, 1H), 3.73 (app t, *J* = 5.4 Hz, 2H), 3.44 (app q, *J* = 5.4 Hz, 2H), 2.99 (br s, 1H), 0.21 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8, 97.5, 92.4, 61.6, 42.6, -0.6; IR (NaCl/film)

3270 br, 3057, 2960, 1632, 1546, 1251, 846 cm^{-1}; HRMS (EI+) calc'd for $[C_8H_{15}NO_2Si]^{\bullet+}$: *m/z* 185.0872, found 185.0877.



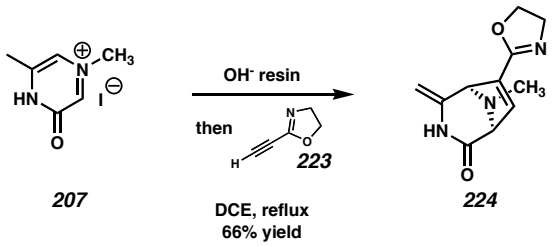
225 ***223***

Oxazoline 223

To a 0 °C solution of amide **225** (9.72 g, 52.46 mmol) in dichloromethane (75 mL) was added thionyl chloride (11.5 mL, 157.38 mmol) dropwise over 5 min. The reaction mixture was then allowed to warm to 23 °C for 8 h, after which water (500 mL) was added (caution: gas evolution). The phases were separated, and the organics were washed with a mixture of water (100 mL) and saturated aqueous sodium chloride (100 mL), dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (15:85 to 25:75 ethyl acetate:hexanes eluent) to provide the alkyl chloride (8.83 g, 83% yield).

To a solution of the chloride (8.83 g, 43.35 mmol) in dichloromethane (87 mL) were added aqueous sodium hydroxide (1 M, 217 mL, 217 mmol) and potassium iodide (3.60 g, 21.68 mmol). The reaction mixture was stirred vigorously for 5.5 h. The mixture was then diluted with saturated aqueous sodium chloride (250 mL) and extracted into dichloromethane (2 x 75 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (35:65 to 70:30 diethyl ether:pentane eluent) to provide oxazoline **223** (2.95 g, 72% yield) as a volatile white solid that must be stored below –20 °C to prevent decomposition and sublimation:

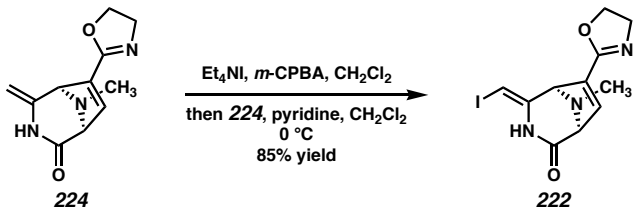
R_F 0.15 (30:70 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 3.61 (t, *J* = 9.9 Hz, 2H), 3.38 (t, *J* = 9.9 Hz, 2H), 2.67 (s, 1H); ^{13}C NMR (75 MHz, C_6D_6) δ 149.7, 78.7, 73.1, 67.6, 55.4; IR (NaCl/film) 3273, 3232, 2128, 1630, 1218, 991, 956, 910, 698 cm^{-1}; HRMS (EI+) calc'd for $[C_5H_5NO]^{\bullet+}$: *m/z* 95.0371, found 95.0368.



Diazabicycle 224

An aqueous solution of **207** (126 mg, 500 μmol) was eluted through a column of Amberlite IRA 400 hydroxide resin (3.95 g, 15 mmol) with 1:1 methanol:water. The UV-active fractions that eluted were collected and concentrated in vacuo. To the resulting semisolid was added a solution of oxazoline **223** (95 mg, 1.0 mmol) in dichloroethane (5 mL). The reaction mixture was heated to reflux for 1 h 15 min, then cooled to 23 °C, diluted with water (55 mL) and saturated aqueous sodium chloride (15 mL), and extracted with dichloromethane (2 x 50 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (20:4:76 to 20:10:70 ethyl acetate:methanol:chloroform eluent) to yield diazabicycle **224** (72.2 mg, 66% yield): R_F 0.30 (10:10:80 ethyl acetate:methanol:chloroform); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (br s, 1H), 6.82 (d, *J* = 2.7 Hz, 1H), 4.44 (d, *J* = 1.5 Hz, 1H), 4.41 (d, *J* = 1.5 Hz, 1H), 4.35-4.24 (comp m, 3H), 4.04-3.94 (comp m, 3H), 2.46 (s,

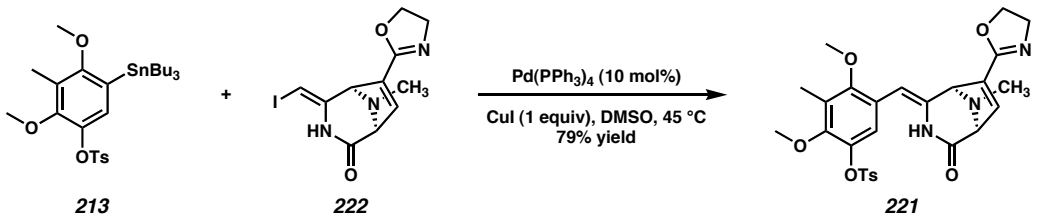
3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 160.0, 137.5, 136.1, 135.1, 93.4, 71.4, 67.8, 67.5, 55.3, 37.1; IR (NaCl/film) 3203, 2977, 2946, 2904, 2873, 1687, 1656, 1290, 1052 cm^{-1}; HRMS (FAB+) calc'd for $[C_{11}H_{13}N_3O_2]^{\bullet+}$: *m/z* 219.1008, found 219.1002.



Iodoenamide 222

To a 0 °C suspension of tetraethylammonium iodide (1.04 g, 4.05 mmol) in dichloromethane (27 mL) was added *meta*-chloroperbenzoic acid (466 mg, 2.70 mmol). After 25 min, the resulting dark orange solution was added via cannula to a 0 °C solution of **224** (295 mg, 1.35 mmol) and pyridine (546 μL, 6.75 mmol) in dichloromethane (9.0 mL). After an additional 10 min, the reaction mixture was poured into saturated aqueous sodium bicarbonate (75 mL), and the remaining iodination reagent was quenched by the dropwise addition of saturated aqueous sodium thiosulfate (5 mL) until the red color dissipated. The phases were separated, and the aqueous layer was extracted with dichloromethane (25 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (0:20:80:1 to 2:18:80:1 methanol:ethyl acetate:chloroform:ethyldimethylamine eluent) to provide iodoenamide **222** (398.5 mg, 85% yield): R_F 0.38 (10:10:80 ethyl acetate:methanol:chloroform); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (br s, 1H), 6.80 (d, *J* = 2.7 Hz, 1H), 5.41 (s, 1H), 4.58 (d, *J* = 1.8 Hz, 1H), 4.35-4.26 (comp m, 2H), 4.01-3.92 (comp m, 3H), 2.43 (s, 3H); ^{13}C

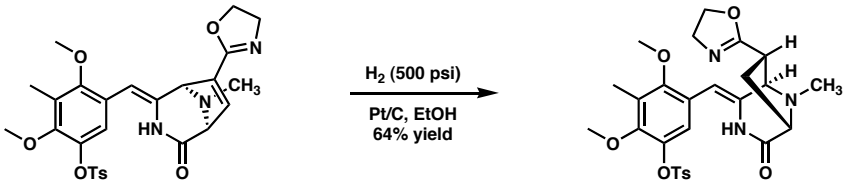
NMR (75 MHz, $CDCl_3$) δ 165.8, 159.6, 138.5, 135.7, 135.1, 71.6, 68.8, 67.6, 56.4, 55.3, 36.9; IR (NaCl/film) 3085, 2971, 2946, 1693, 1658, 1385, 1278, 1052 cm^{-1}; HRMS (FAB+) calc'd for $[C_{11}H_{12}N_3O_2I+H]^+$: *m/z* 346.0053, found 346.0041.



Styrene 221

To a solution of stannane **213** (70.8 mg, 115.8 μmol) and iodoenamide **222** (20 mg, 57.9 μmol) in dimethylsulfoxide (1.2 mL) were added copper(I) iodide (11.0 mg, 57.9 μmol) and tetrakis(triphenylphosphine)palladium(0) (6.7 mg, 5.8 μmol). The reaction mixture was deoxygenated by three times freezing under vacuum and thawing under argon, then sealed under argon and heated to 45 °C. After 24 h, the mixture was cooled to 22 °C, diluted with water (150 mL) and saturated aqueous ammonium hydroxide (10 mL), and extracted into ethyl acetate (50 mL, 35 mL). The organics were washed with half-saturated aqueous sodium chloride (50 mL) followed by saturated aqueous sodium chloride (25 mL), dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (1:99:1 to 5:95:1 ethanol:ethyl acetate: ethyldimethylamine eluent) to provide styrene **221** (24.8 mg, 79% yield): R_F 0.26 (10:90 ethanol:ethyl acetate); ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.77 (s, 1H), 7.33 (d, *J* = 7.8 Hz, 2H), 6.85 (d, *J* = 2.7 Hz, 1H), 6.82 (s, 1H), 5.57 (s, 1H), 4.45 (d, *J* = 1.5 Hz, 1H), 4.30 (app t, *J* = 9.6 Hz, 2H), 4.01-3.92 (comp m, 3H), 3.66 (s, 3H), 3.56

(s, 3H), 2.50 (s, 3H), 2.45 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 160.0, 154.1, 151.0, 145.5, 139.1, 136.0, 135.3, 133.4, 131.6, 129.9, 128.5, 127.5, 123.4, 122.4, 102.9, 71.8, 69.3, 67.5, 61.1, 60.2, 55.4, 37.3, 21.9, 9.9; IR (NaCl/film) 2941, 1692, 1659, 1372, 1191, 1177, 991, 551 cm^{-1}; HRMS (FAB+) calc'd for $[C_{27}H_{29}N_3O_7S+H]^+$: *m/z* 540.1804, found 540.1795.

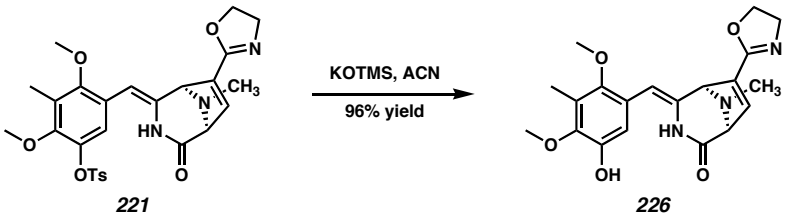


221 ***225***

Oxazoline 255

(Note: the reaction was performed in a stainless steel reaction vessel.) To a solution of styrene **221** (50 mg, 92.6 μmol) in anhydrous ethanol (1.8 mL) was added platinum on carbon (5% w/w, 15 mg). The reaction vessel was pressurized to 500 psi with hydrogen. After 11 h, the mixture was filtered through celite with ethanol eluent, concentrated, and purified by flash chromatography on silica gel (90:5:5 to 80:10:10 ethyl acetate:acetonitrile:methanol eluent) to provide oxazoline **255** (32.0 mg, 64% yield): R_F 0.37 (10:10:80 methanol:ethyl acetate:chloroform); ^{1}H NMR (300 MHz, CD_3OD) δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 6.86 (s, 1H), 5.42 (s, 1H), 4.23 (app td, *J* = 18.0, 9.0 Hz, 2H), 4.03 (d, *J* = 6.6 Hz, 1H), 3.79-3.65 (comp m, 2H), 3.67 (s, 3H), 3.65 (s, 3H), 3.54 (d, *J* = 7.2 Hz, 1H), 3.53-3.46 (m, 1H), 2.64-2.52 (m, 1H), 2.51 (s, 3H), 2.49-2.40 (m, 1H), 2.46 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ

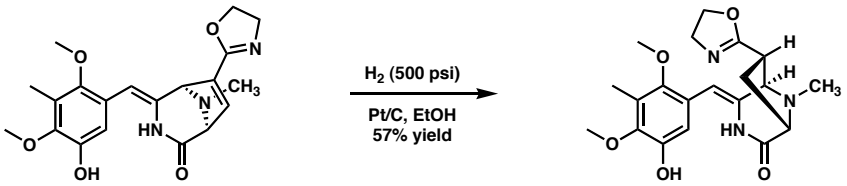
172.5, 169.3, 156.1, 152.1, 147.4, 140.4, 134.6, 134.3, 131.2, 129.6, 128.6, 125.1, 123.0, 104.6, 69.4, 68.0, 66.6, 61.5, 54.8, 43.1, 36.0, 32.7, 21.8, 9.8; IR (NaCl/film) 2944, 1691, 1482, 1372, 1191, 1176, 990 cm^{-1}; HRMS (FAB+) calc'd for $[C_{27}H_{31}N_3O_7S+H]^+$: *m/z* 542.1961, found 542.1971.



Phenol 226

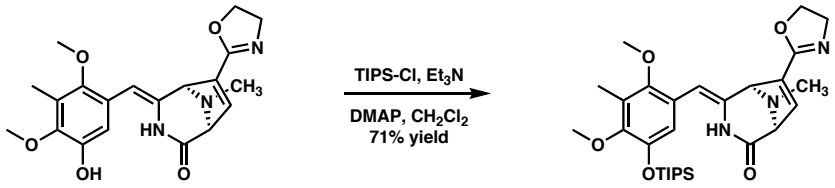
To a solution of tosylate **221** (758 mg, 1.40 mmol) in acetonitrile (14 mL) was added potassium trimethylsilanoate (90% grade, 998 mg, 7.0 mmol). After 1h 15 min, the reaction mixture was hydrolyzed with saturated aqueous ammonium chloride (20 mL) for 10 min. The mixture was diluted with saturated aqueous sodium chloride (150 mL) and extracted into ethyl acetate (75 mL, 50 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (1:20:79:1 to 5:20:75:1 methanol:ethyl acetate:chloroform:ethyldimethylamine eluent) to provide phenol **226** (518 mg, 96% yield): R_F 0.37 (10:10:80 methanol:ethyl acetate:chloroform); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.28 (br s, 1H), 6.84 (d, *J* = 2.7 Hz, 1H), 6.52 (s, 1H), 5.63 (s, 1H), 4.47 (s, 1H), 4.27 (app t, *J* = 9.5 Hz, 2H), 3.99-3.89 (comp m, 3H), 3.71 (s, 3H), 3.49 (s, 3H), 2.46 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 160.2, 148.4, 146.0, 145.9, 136.4, 134.9, 130.0, 125.6, 123.2, 114.4, 104.5, 70.5, 68.8, 67.5, 60.5, 60.3, 55.0, 37.0, 9.7; IR (NaCl/film) 3251 br, 2938,

1389, 1656, 1234, 1051, 1003, 731 cm^{-1}; HRMS (FAB+) calc'd for $[C_{20}H_{23}N_3O_5+H]^+$: *m/z* 386.1716, found 386.1735.



Oxazoline 220

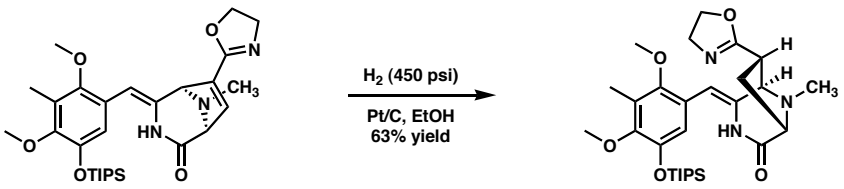
(Note: the reaction was performed in a stainless steel reaction vessel.) To alkene **226** (59.3 mg, 153.8 μmol) in anhydrous ethanol (2 mL) was added platinum on carbon (5% w/w, 23 mg). The reaction vessel was pressurized with hydrogen to 500 psi. After 3 h, the reaction mixture was filtered through celite with ethanol eluent, concentrated, and purified by flash chromatography on silica gel (80:10:10 to 70:15:15 ethyl acetate:acetonitrile:methanol eluent) to provide oxazoline **220** (34.0 mg, 57% yield): R_F 0.26 (70:15:15 ethyl acetate:acetonitrile:methanol); ^{1}H NMR (300 MHz, CD_3OD) δ 6.53 (s, 1H), 5.41 (s, 1H), 4.23-4.15 (comp m, 2H), 4.00 (d, *J* = 6.3 Hz, 1H), 3.81-3.62 (comp m, 2H), 3.76 (s, 3H), 3.61 (s, 3H), 3.52 (d, *J* = 7.2 Hz, 1H), 3.52-3.44 (m, 1H), 2.63-2.52 (m, 1H), 2.51 (s, 3H), 2.48 (app td, *J* = 13.5, 5.7 Hz, 1H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 172.5, 169.4, 149.6, 148.0, 147.5, 132.6, 127.0, 124.4, 115.2, 106.3, 69.4, 68.1, 66.5, 61.1, 60.7, 54.8, 43.1, 36.0, 32.8, 9.9; IR (NaCl/film) 3251 br, 2943, 1666, 1483, 1453, 1325, 1236, 1006 cm^{-1}; HRMS (FAB+) calc'd for $[C_{20}H_{25}N_3O_5+H]^+$: *m/z* 388.1872, found 388.1870.



226 *227*

Silyl Ether 227

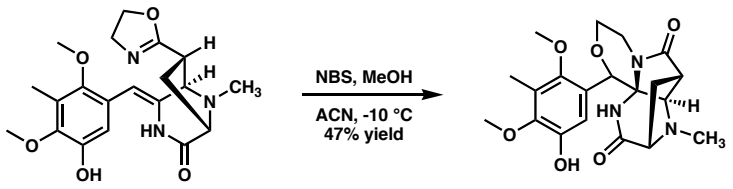
To a solution of phenol **226** (100 mg, 259.4 μmol) in dichloromethane (2.6 mL) were added triethylamine (181 μL, 1.30 mmol), 4-dimethylaminopyridine (7.9 mg, 64.8 μmol), and triisopropylsilyl chloride (167 μL, 778.2 μmol), in that order. After 52 h, the reaction mixture was diluted with water (50 mL) and extracted into dichloromethane (25 mL, 15 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash chromatography on silica gel (0:90:10:1 to 1:99:0:1 methanol:ethyl acetate:hexanes:ethyldimethylamine eluent) to provide silyl ether **227** (99.0 mg, 71% yield): R_F 0.61 (10:90 methanol:ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (s, 1H), 6.85 (d, *J* = 2.7 Hz, 1H), 6.49 (s, 1H), 5.58 (s, 1H), 4.47 (s, 1H), 4.30 (app t, *J* = 9.9 Hz, 2H), 4.02-3.91 (comp m, 3H), 3.76 (s, 3H), 3.53 (s, 3H), 2.52 (s, 3H), 2.17 (s, 3H), 1.32-1.19 (comp m, 3H), 1.10 (d, *J* = 6.9 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 160.2, 149.3, 148.9, 145.9, 136.1, 135.1, 130.2, 126.6, 122.7, 118.7, 104.5, 71.8, 69.3, 67.5, 60.3, 60.2, 55.3, 37.3, 18.1, 13.0, 9.8; IR (NaCl/film) 2944, 2867, 1694, 1659, 1482, 1242, 1064, 882 cm^{-1}; HRMS (FAB+) calc'd for $[C_{29}H_{43}N_3O_5Si+H]^+$: *m/z* 542.3050, found 542.3053.



227 *228*

Oxazoline 228

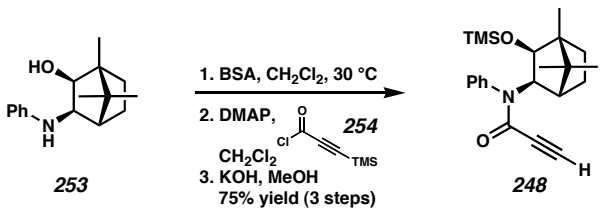
(Note: the reaction was performed in a stainless steel reaction vessel.) To alkene **227** (94.0 mg, 173.6 μmol) in anhydrous ethanol (1.7 mL) was added platinum on carbon (5% w/w, 27 mg, 6.9 μmol). The reaction vessel was pressurized with hydrogen to 450 psi. After 2 h, the reaction mixture was filtered through celite with ethanol eluent, concentrated, and purified by flash chromatography on silica gel (1:99:0.5 to 5:95:0.5 methanol:ethyl acetate:ethyldimethylamine eluent) to provide oxazoline **228** (59.0 mg, 63% yield): R_F 0.34 (10:90 methanol:ethyl acetate); ^{1}H NMR (300 MHz, CD_3OD) δ 6.57 (s, 1H), 5.42 (s, 1H), 4.29-4.15 (comp m, 2H), 4.04 (d, *J* = 6.6 Hz, 1H), 3.77 (s, 3H), 3.76-3.64 (comp m, 2H), 3.36 (s, 3H), 3.53 (d, *J* = 7.5 Hz, 1H), 3.52-3.46 (m, 1H), 2.65-2.53 (m, 1H), 2.52 (s, 3H), 2.46 (app td, *J* = 13.7, 5.6 Hz, 1H), 2.21 (s, 3H), 1.35-1.21 (comp m, 3H), 1.13 (d, *J* = 6.6 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 166.7, 149.3, 149.2, 146.0, 132.1, 126.9, 123.0, 118.1, 104.0, 67.9, 66.9, 65.1, 60.3, 60.2, 54.5, 42.3, 35.7, 32.3, 18.1, 13.0, 9.8; IR (NaCl/film) 2944, 2867, 1696, 1666, 1482, 1241, 1064, 1012, 882 cm^{-1}; HRMS (FAB+) calc'd for $[C_{29}H_{45}N_3O_5Si+H]^+$: *m/z* 544.3207, found 544.3219.



220 *237*

Pyrrolidinone 237

To a –10 °C solution of oxazoline **220** (35.0 mg, 90.3 μmol) and methanol (36.5 μL, 903 μmol) in acetonitrile (903 μL) was added *N*-bromosuccinimide (17.7 mg, 99.3 μmol). After 15 min, the reaction mixture was partially purified by flash chromatography on silica gel (0:0:100 to 15:15:70 methanol:acetonitrile:ethyl acetate eluent). The resulting mixture of products was further purified by flash chromatography on silica gel (0:100:1 to 10:90: methanol:ethyl acetate eluent:ethyldimethylamine eluent) to provide pyrrolidinone **237** (17.0 mg, 47% yield): R_F 0.37 (15:15:70 methanol:acetonitrile:ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (s, 1H), 6.94 (s, 1H), 6.51 (s, 1H), 5.43 (s, 1H), 3.86 (d, *J* = 5.7 Hz, 1H), 3.84 (s, 3H), 3.84-3.77 (comp m, 2H), 3.66 (app td, *J* = 12.0, 5.4 Hz, 1H), 3.52 (d, *J* = 7.2 Hz, 1H), 3.32 (app td, *J* = 13.8, 4.5 Hz, 1H), 3.05-2.97 (m, 1H), 2.57-2.43 (m, 1H), 2.39 (s, 3H), 2.27 (s, 3H), 1.94 (dd, *J* = 13.7, 2.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 172.0, 152.3, 147.1, 145.0, 126.5, 122.3, 113.6, 73.6, 72.9, 65.1, 64.8, 62.5, 60.8, 56.9, 42.9, 37.1, 36.2, 31.0, 10.2; IR (NaCl/film) 3245 br, 2943, 1673, 1453, 1417, 1113, 1008 cm^{-1}; HRMS (EI+) calc'd for $[C_{20}H_{25}N_3O_6]^{\bullet+}$: *m*/*z* 403.1743, found 403.1743.



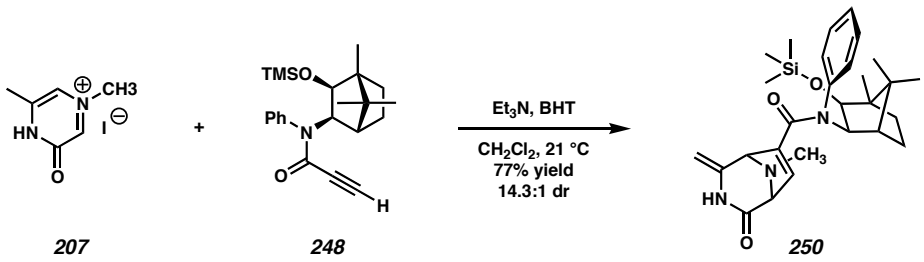
Alkynamide 248

To a 30 °C solution of amino alcohol **253** (1.008 g, 4.10 mmol) in dichloromethane (10.2 mL) was added *N*,*O*-bis(trimethylsilyl)acetamide (4.05 mL, 16.4 mmol). After 15 h, additional *N*,*O*-bis(trimethylsilyl)acetamide (1.01 mL, 4.09 mmol) was added. After an additional 6 h, the reaction mixture was concentrated and purified by flash chromatography on silica gel (4:96 ethyl acetate:hexanes eluent) to provide the silyl ether (1.18 g, 91% yield).

To a solution of trimethylsilyl propynoic acid (247.3 mg, 1.74 mmol) and dimethylformamide (16 μL, 207 μmol) in dichloromethane (1.6 mL) was added oxalyl chloride (156 μL, 1.79 mmol) (caution: gas evolution). After 20 min, a solution of 4-dimethylaminopyridine (147.4 mg, 1.21 mmol) and the step-one silyl ether (152.3 mg, 480 μmol) in dichloromethane (1.6 mL) was added dropwise over 1 min. After an additional 15 min, the reaction mixture was diluted with dichloromethane (25 mL) and washed with saturated aqueous ammonium chloride (2 x 25 mL) followed by saturated aqueous sodium chloride (15 mL). The organics were dried over magnesium sulfate, concentrated, and purified by flash chromatography on silica gel (4:96 ethyl acetate:hexanes eluent) to provide the *C*-trimethylsilyl alkynamide.

To a solution of *C*-trimethylsilyl alkynamide (2.01 g, 4.6 mmol) in methanol (60 mL) was added anhydrous potassium hydroxide (660 mg, 11.8 mmol). After 5 min, the

reaction mixture was diluted in ethyl acetate (100 mL) and washed with saturated aqueous sodium bicarbonate (100 mL). The organics were dried over magnesium sulfate, concentrated, and purified by flash chromatography on silica gel (10:90 ethyl acetate:hexanes eluent) to provide alkynamide **248** (1.54 g, 91% yield) as a pale yellow oil: R_F 0.32 (15:85 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCL_3$) δ 7.45-7.30 (comp m, 4H), 7.14-7.02 (m, 1H) 4.30 (d, *J* = 6.6 Hz, 1H), 4.04 (d, *J* = 6.9 Hz, 1H), 2.72 (s, 1H), 1.94 (d, *J* = 2.1 Hz, 1H), 1.78-1.62 (m, 1H), 1.51-1.36 (m, 1H), 1.28-1.12 (comp m, 2H), 0.82 (s, 3H), 0.58 (s, 3H), 0.50 (s, 3H), 0.19 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 140.6, 133.7, 130.6, 128.4, 128.3, 83.4, 79.5, 66.9, 49.5, 47.3, 47.0, 32.4, 29.0, 21.9, 21.7, 12.9, 0.9; IR (NaCl/thin film) 2960, 2106, 1634, 1594, 1491, 1344, 839 cm^{-1}; HRMS (FAB) *m/z* calc'd for $[C_{22}H_{32}NO_2Si+H]^+$: 370.2202, found 370.2193.



207 *248* *250*

Diazabicycle 250

To a 21 °C suspension of pyrazinone **207** (114.1 mg, 453 μmol) in dichloromethane (2.5 mL) were added alkynamide **248** (500.7 mg, 1.35 mmol) and 2,6-di-*tert*-butyl-4-methylphenol (20.0 mg, 91 μmol). Et_3N (66.0 μL, 474 μmol) was then added in four portions at 2 h intervals. The solution was maintained at 21 °C for an additional 22 h, then diluted with dichloromethane (50 mL) and washed with saturated

aqueous ammonium chloride (2 x 50 mL) followed by brine (50 mL). The organics were dried over magnesium sulfate, concentrated, and purified by flash chromatography on silica gel (50:50 to 75:25 ethyl acetate:hexanes eluent) to yield diazabicycle **250** (173.1 mg, 77% yield, 14.3:1 dr) as a white solid: R_F 0.27 (75:25 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.28 (m, 4H), 7.14-7.02 (m, 1H), 5.55 (d, *J* = 2.7 Hz, 1H), 4.34 (d, *J* = 7.2 Hz, 1H), 4.32 (s, 1H), 4.19 (d, *J* = 1.2 Hz, 1H), 4.04 (d, *J* = 6.9 Hz, 1H), 3.84 (s, 1H), 3.62-3.60 (m, 1H), 2.08 (s, 3H), 1.78-1.62 (m, 1H), 1.50-1.34 (m, 1H), 1.28-1.10 (comp m, 2H), 0.80 (s, 3H), 0.58 (s, 3H), 0.47 (s, 3H), 0.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 164.0, 141.6, 141.2, 137.9, 135.6, 128.8, 128.6, 93.2, 83.9, 71.9, 69.8, 68.2, 49.5, 47.2, 47.1, 37.3, 32.5, 29.5, 22.2, 21.7, 13.0, 1.0; IR (NaCl/thin film) 3224, 2954, 1691, 1634, 1591, 1495, 1349, 903, 839 cm^{-1}; LRMS (APCI) *m/z* calc'd for $[C_{28}H_{39}N_3O_3Si+H]^+$: 494.3, found 494.2.

3.6 Notes and Citations

(1) For the isolation and crystallographic characterization of cyanocycline A, see: (a) Hayashi, T.; Noto, T.; Nawata, Y.; Okazaki, H.; Sawada, M.; Ando, K. *J. Antibiot.* **1982**, *35*, 771-777. (b) Hayashi, T.; Nawata, Y. *J. Chem. Soc. Perkin Trans. II* **1983**, 335-343.

(2) For a comprehensive review of the chemistry and biology of the tetrahydroisoquinoline antitumor antibiotics, including cyanocycline A, see: Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669-1730.

(3) For the isolation of lemonomycin, see: (a) Whaley, H. A.; Patterson, E. L.; Dann, M.; Shay, A. J.; Porter, J. N. *Antimicrob. Agents Chemother.* **1964**, *8*, 83-86. For the structural determination of lemonomycin, see: (b) He, H.; Shen, B.; Carter, G. T. *Tetrahedron Lett.* **2000**, *41*, 2067-2071.

(4) Our synthesis of (–)-lemonomycin is discussed in Chapter 2 of this thesis. See also: Ashley, E. R.; Cruz, E. G.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 15000-15001.

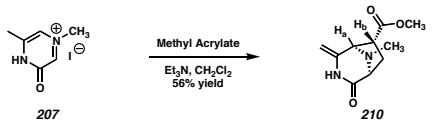
(5) A similar enamide has been advanced stereoselectively to a similar alcohol by epoxidation with dimethyldioxirane followed by reduction with sodium cyanoborohydride, see: Mori, K.; Rikimaru, K.; Kan, T.; Fukuyama, T. *Org. Lett.* **2004**, *6*, 3095-3097.

(6) The diastereoselective hydrogenation of enamide **142** (Scheme 2.11, Chapter 2) provides empirical support for the ability of the diazabicyclic framework to direct reduction to the convex face of **204**.

(7) Lutz, W. B.; Lazarus, S.; Klutchko, S.; Meltzer, R. I. *J. Org. Chem.* **1964**, *29*, 415-418.

(8) This effect was first reported for diazabicyclooctane ring systems by Joule, see: Kiss, M.; Russell-Maynard, J.; Joule, J. A. *Tetrahedron Lett.* **1987**, *28*, 2187-2190.

(9) Diazabicycle **210** was produced by the dipolar cycloaddition of **207** with methyl acrylate. H_a of **210** appears as a sharp singlet at $\delta = 3.99$ in $CDCl_3$.



(10) Semiempirical calculations at the AM1 level indicate that "endo" isomer **209** is 3.1 kcal/mol less stable than "exo" isomer **210**. These calculations were performed with Spartan '02 v1.0.8 (Wavefunction, Inc.).

(11) For reviews of transition metal-catalyzed coupling reactions, see: (a) Diederich, F.; Stang, P. J.; Eds.; *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 1998. (b) Geissler, H. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 2.10, pp 158.

(c) Tsuji, J. In *Transition Metal Reagents and Catalysts*; Wiley: Chichester, 2000; Chapter 3, pp 27.

(12) For examples of copper(I) accelerated Stille reactions, see: (a) Bellina, F.; Carpita, A.; De Santis, M.; Rossi, R. *Tetrahedron* **1994**, *50*, 12029-12046. (b) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc*. **1999**, *121*, 7600-7605. (c) For a review of the Stille reaction including copper(I) accelerated conditions, see: Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1-652.

(13) (a) Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges*. **1911**, *44*, 2030-2036. For a recent review of the Pictet-Spengler cyclization, see: (b) Cox, E. D.; Cook, J. M. *Chem. Rev*. **1995**, *95*, 1797-1842.

(14) This oxazoline synthesis is based on the Bristol-Meyers-Squibb modification of Nishiyama's oxazoline synthesis, see: (a) Totleben, M. J.; Prasad, J. S.; Simpson, J. H.; Chan, S. H.; Vanyo, D. J.; Kuehner, D. E.; Deshpande, R.; Kodersha, G. A. *J. Org. Chem.* **2001**, *66*, 1057-1060. (b) Nishiyama, H.; Yamaguchi, S.; Kondo, M.; Itoh, K. *J. Org. Chem.* **1992**, *57*, 4306-4309.

(15) (a) Allway, P. A.; Sutherland, J. K.; Joule, J. A. *Tetrahedron Lett.* **1990**, *31*, 4781-4782. (b) Yates, N. D.; Peters, D. A.; Allway, P. A.; Beddeoes, R. L.; Scopes, D. I. C.; Joule, J. A. *Heterocycles* **1995**, *40*, 331-347. Also, see reference 8.

(16) (a) Sha, C.-K.; Jean, T.-S.; Wang, D.-C. *Tetrahedron Lett.* **1990**, *31*, 3745-3748.

(b) Sha, C.-K.; Young, J.-J.; Jean, T.-S. *J. Org. Chem.* **1987**, *52*, 3919-3920.

(17) The analogous Suzuki coupling of **222** with aryl boronate **156** provided at best 54% yield of styrene **221**.

(18) These conditions utilized $Pd(PPh_3)_4$ (10 mol%), LiCl (6 equiv), and CuCl (5 equiv) in DMSO at 70 °C, see reference 12b.

(19) This Stille coupling provided good conversion to the styrene on preparative scale. However, difficulties in separating the highly polar product from dimethylsulfoxide resulted in somewhat lower yields (65% yield or better).

(20) The stereochemistry of hydrogenation products **225**, **220**, and **228** was assigned by the appearance of doublets for both bridgehead protons in the ^1H NMR. See the discussion of this effect for **209** (Scheme 3.3).

(21) A second product, apparently diastereomeric to **237**, was isolated from the oxidation of **220** with NBS. Such a diastereomer could easily result from quinone-methide cation **236**, but is less likely to result from S_N2 displacement of bromide **235**. We therefore favor the mechanism involving **236**.

(22) The HETCOR was taken in $CDCl_3$ with decoupling at 300 MHz and observation at 75 MHz.

(23) A similar sequence was utilized in the Evans synthesis of cyanocycline A, see: (a) Evans, D. A.; Biller, S. A. *Tetrahedron Lett*. **1985**, *26*, 1907-1910. (b) Evans, D. A.; Biller, S. A. *Tetrahedron Lett*. **1985**, *26*, 1911-1914. (c) Evans, D. A.; Illig, C. R.; Saddler, J. C. *J. Am. Chem. Soc*. **1986**, *108*, 2478-2479. (d) Biller, S. A. An Approach to the Total Synthesis of (±)-Naphthyridinomycin A. Ph.D. Thesis, California Institute of Technology, Pasadena, CA, 1982.

(24) Fonquerna, S.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron* **1995**, *51*, 4239-4254.

(25) Shi, M.; Wang, C.-J. *J. Chem. Res*. **2004**, *2*, 107-110.

(26) The diastereomeric ratios of **243** and **245** were determined by ^{1}H NMR integrations of the crude reaction mixtures. These compounds were not further purified or characterized.

(27) In this case, orientation of the three-carbon dipole unit over the auxiliary's carbonyl oxygen is termed "endo," while approach of the three-carbon unit over the ester oxygen (or amide nitrogen) is termed "exo."

(28) This work was performed in collaboration with Kevin Allan, a graduate student in the Stoltz research group.

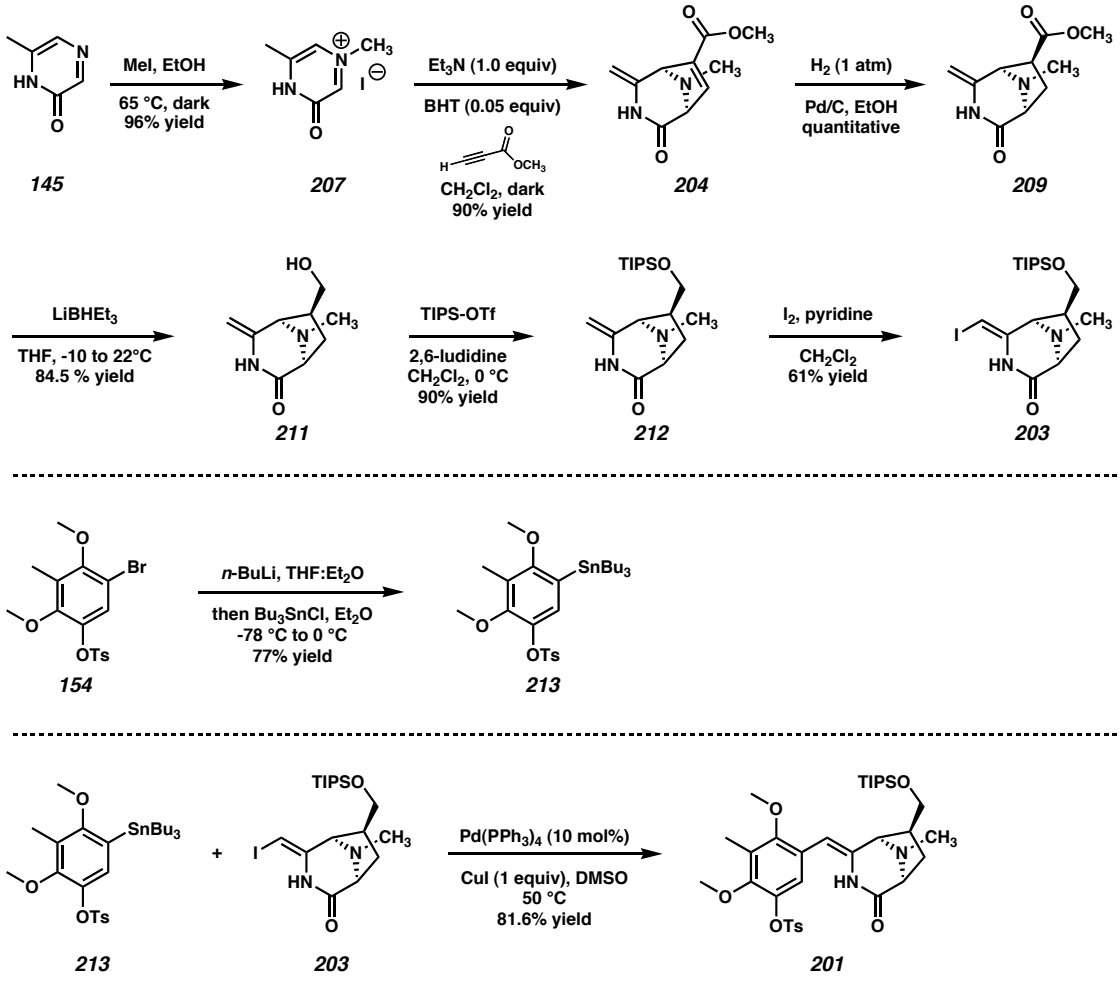
(29) The conformation of **248** was minimized with semiempirical calculations at the AM1 level. These calculations were performed with Spartan '02 v1.0.8 (Wavefunction, Inc.).

(30) Helmchen, G.; Selim, A.; Dorsch, D.; Taufer, I. *Tetrahedron Lett*. **1983**, *24*, 3213-3216.

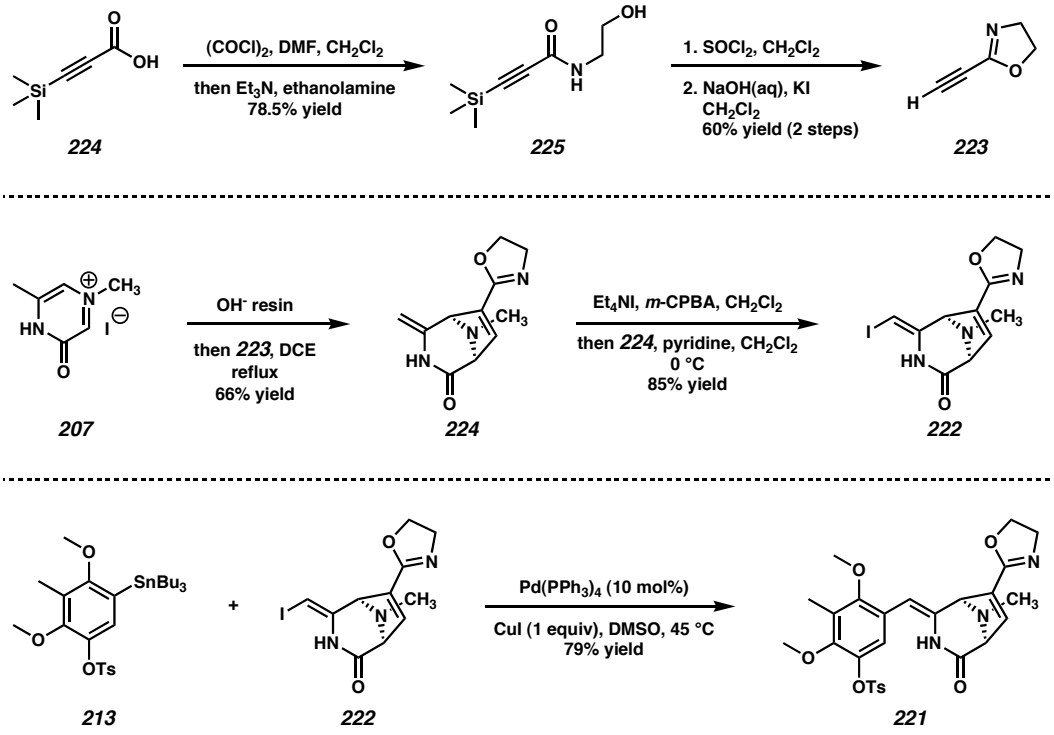
APPENDIX THREE

Summary of Synthetic Progress Toward Cyanocycline A

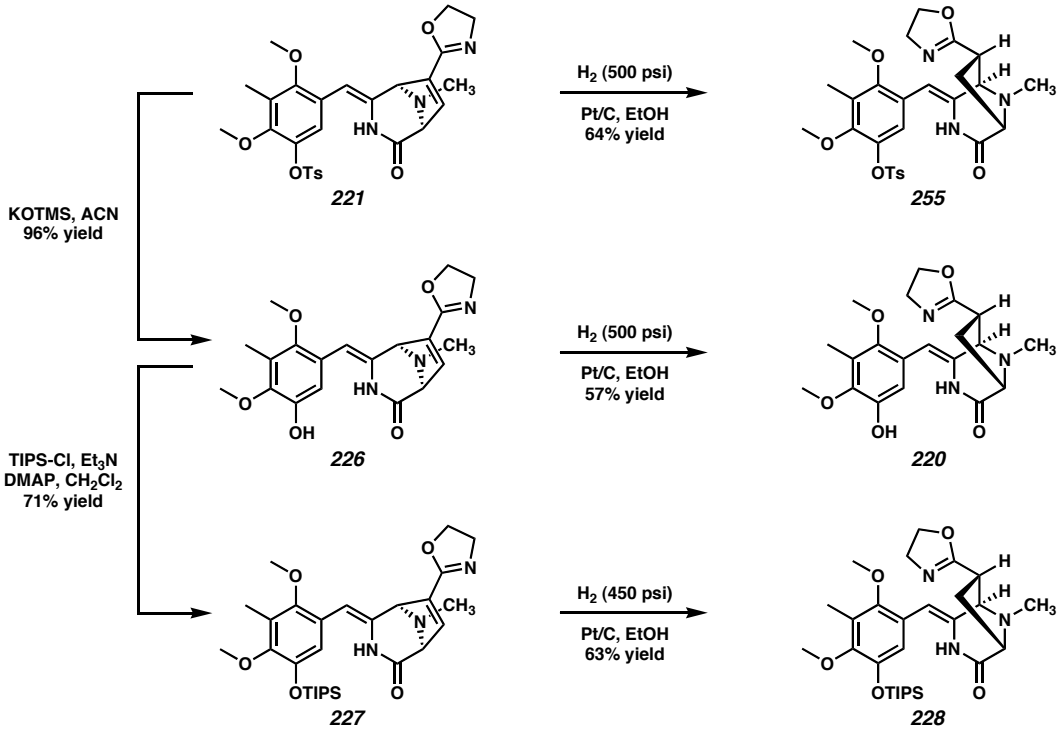
Scheme A3.1 Progress on the Silyl Ether Route



Scheme A3.2 Oxazoline Route: Synthesis of the Styrene



Scheme A3.3 Synthesis of Oxazoline-Olefin Cyclization Substrates



APPENDIX FOUR

Spectra of Compounds in Chapter Three

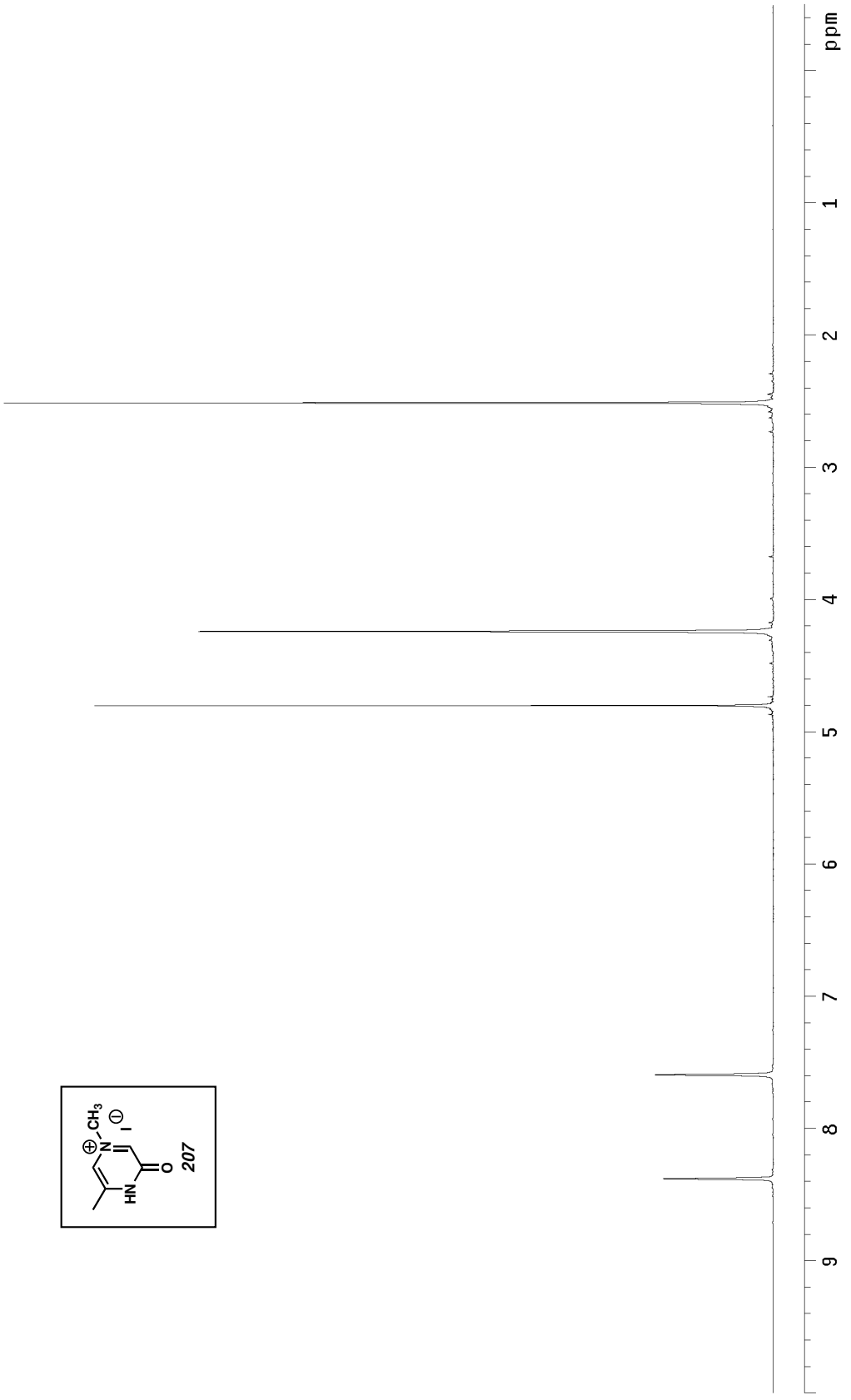


Figure A4.1 ^{1}H NMR of compound **207** (300 MHz, D_2O)

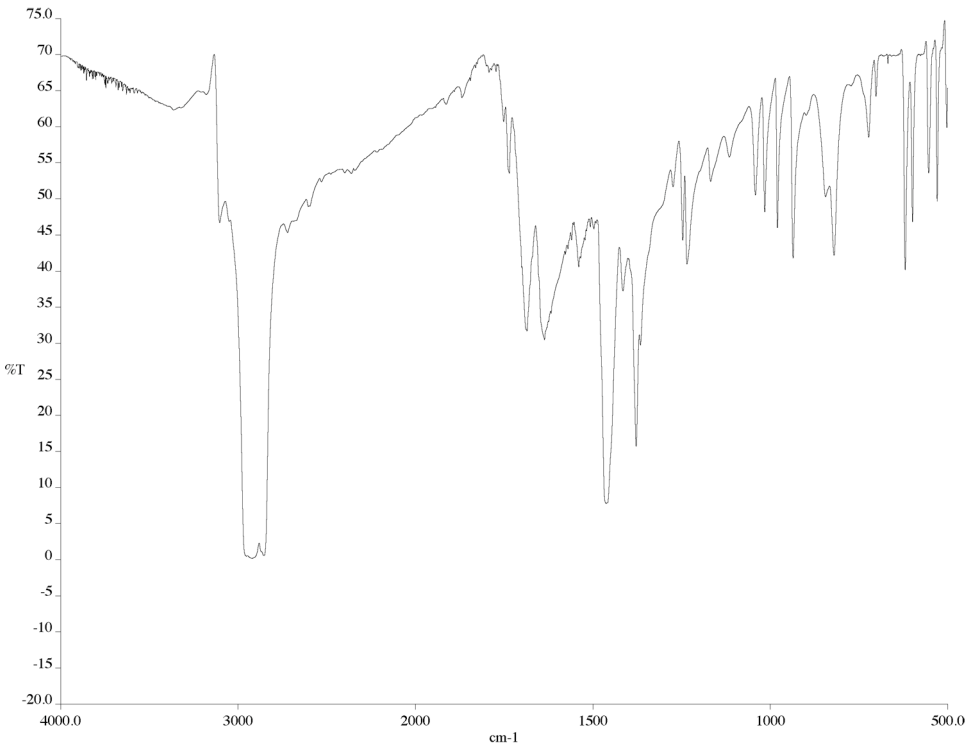


Figure A4.2 IR of compound **207** (Nujol)

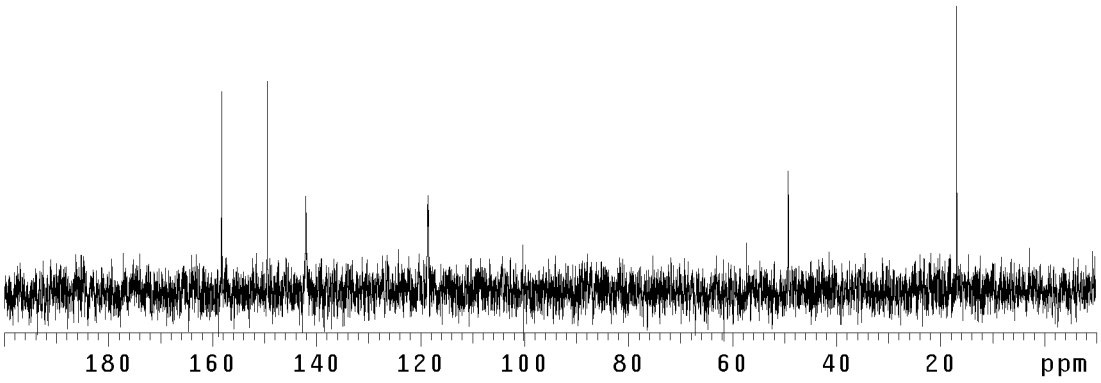


Figure A4.3 ^{13}C NMR of compound **207** (75 MHz, D_2O)

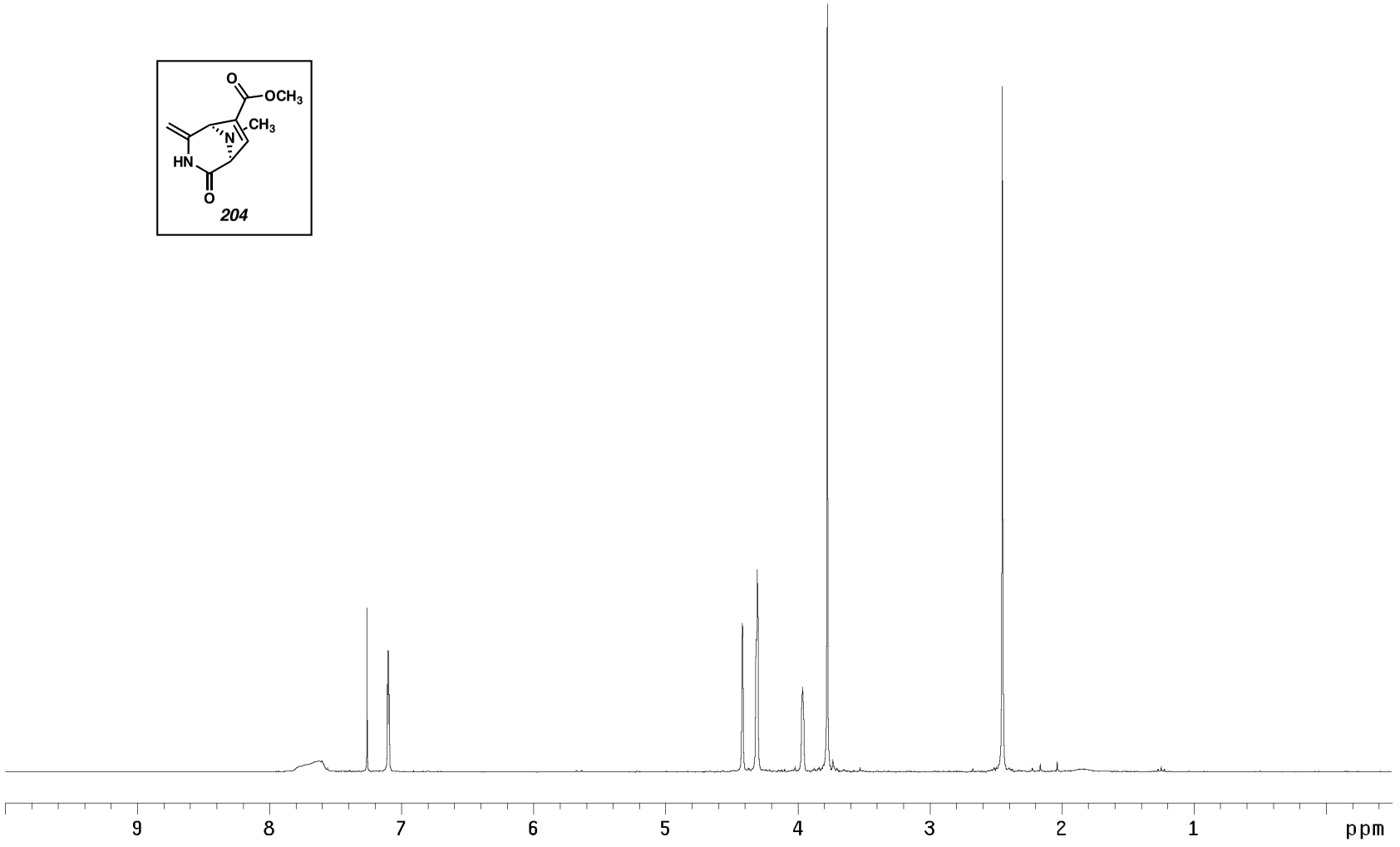


Figure A4.4 ^{1}H NMR of compound **204** (300 MHz, $CDCl_3$)

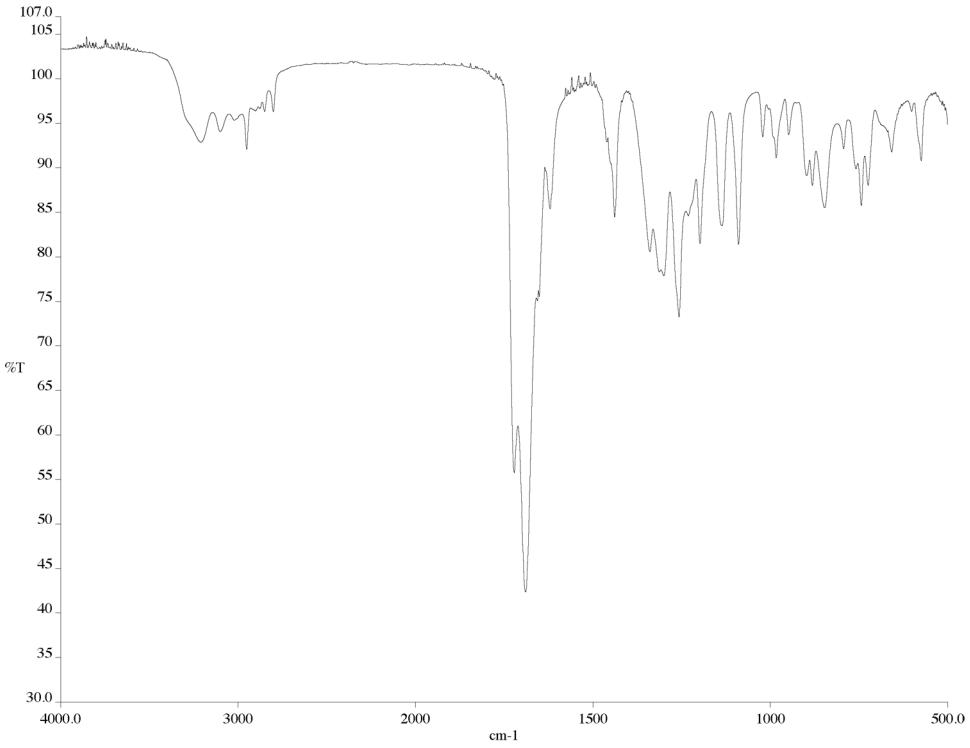


Figure A4.5 IR of compound **204** (NaCl/film)

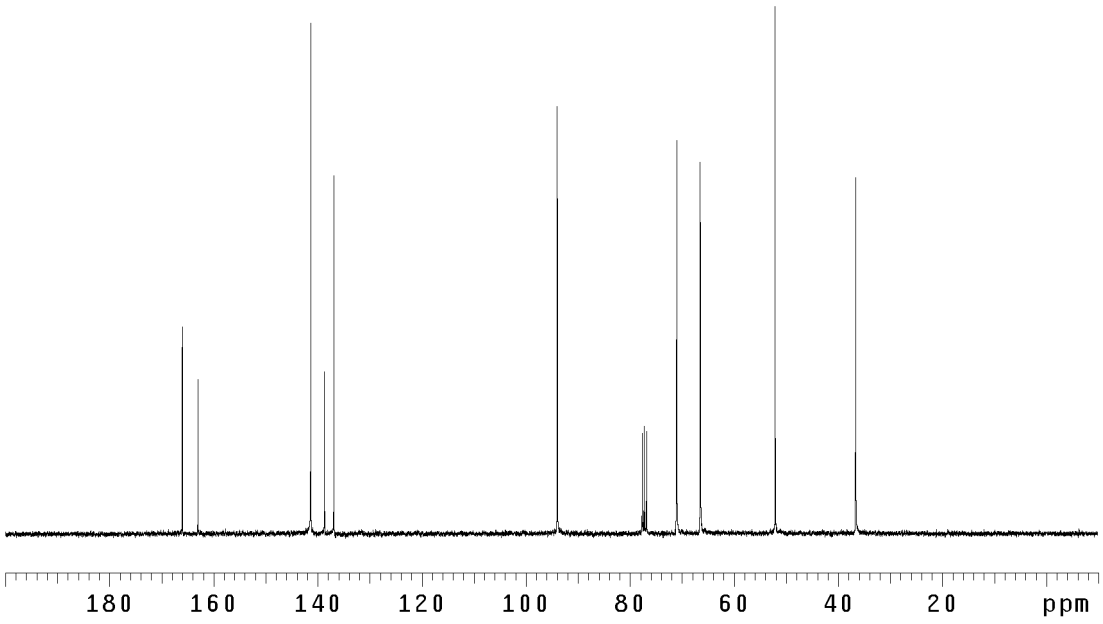


Figure A4.6 ^{13}C NMR of compound **204** (75 MHz, $CDCl_3$)

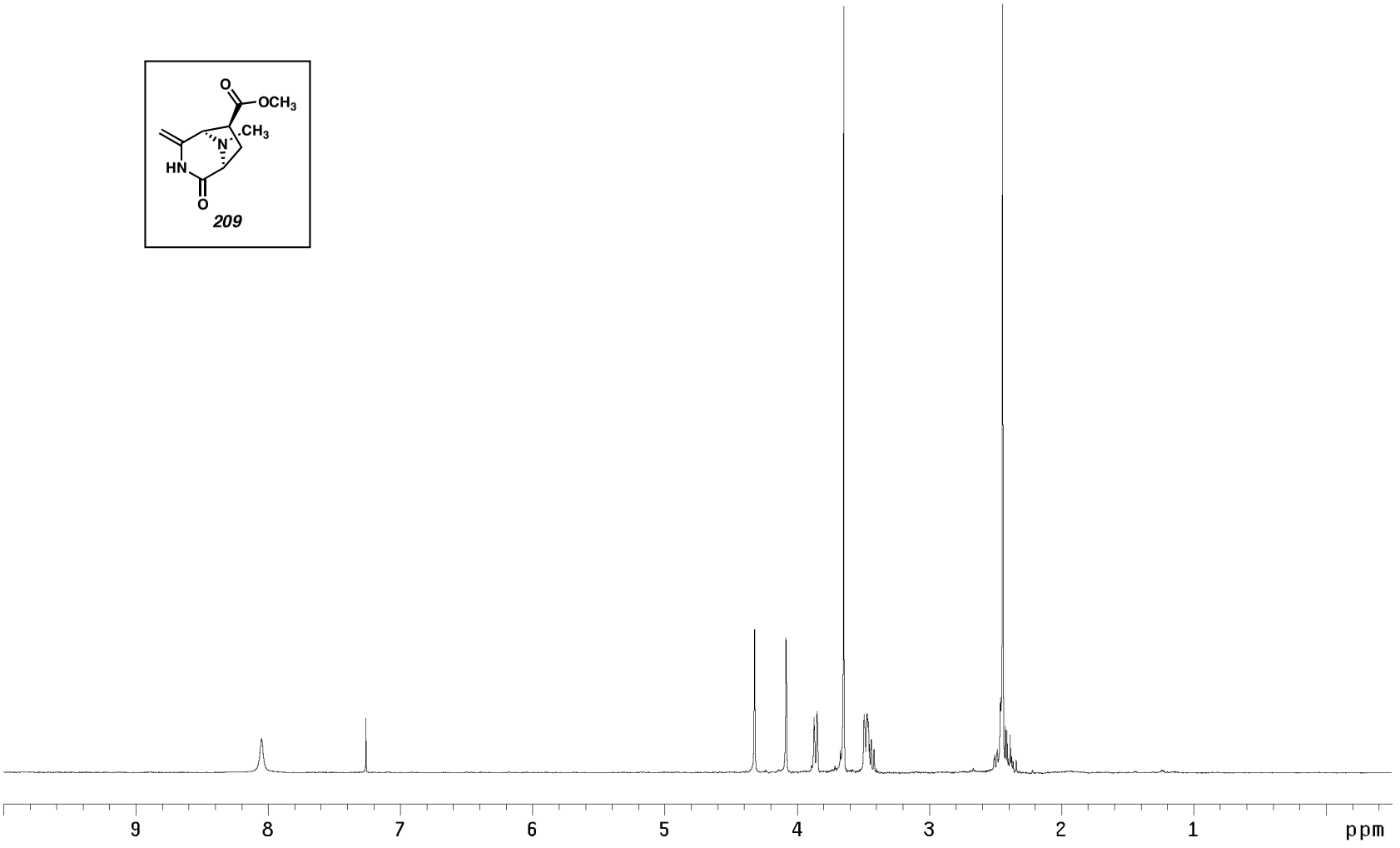


Figure A4.7 ^{1}H NMR of compound **209** (300 MHz, $CDCl_3$)

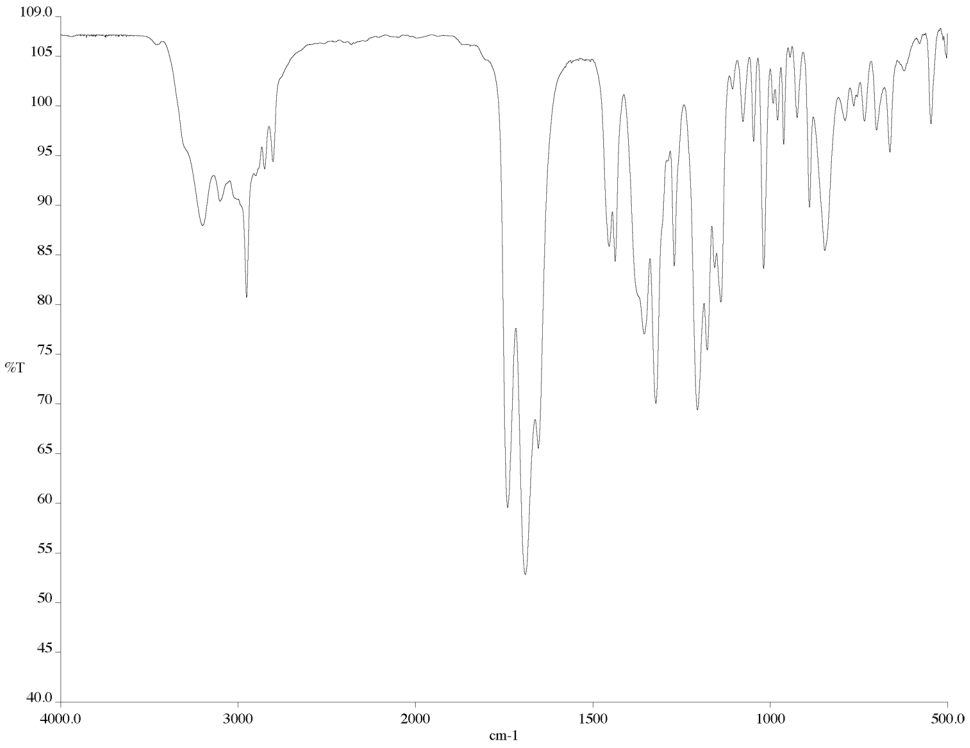


Figure A4.8 IR of compound **209** (NaCl/film)

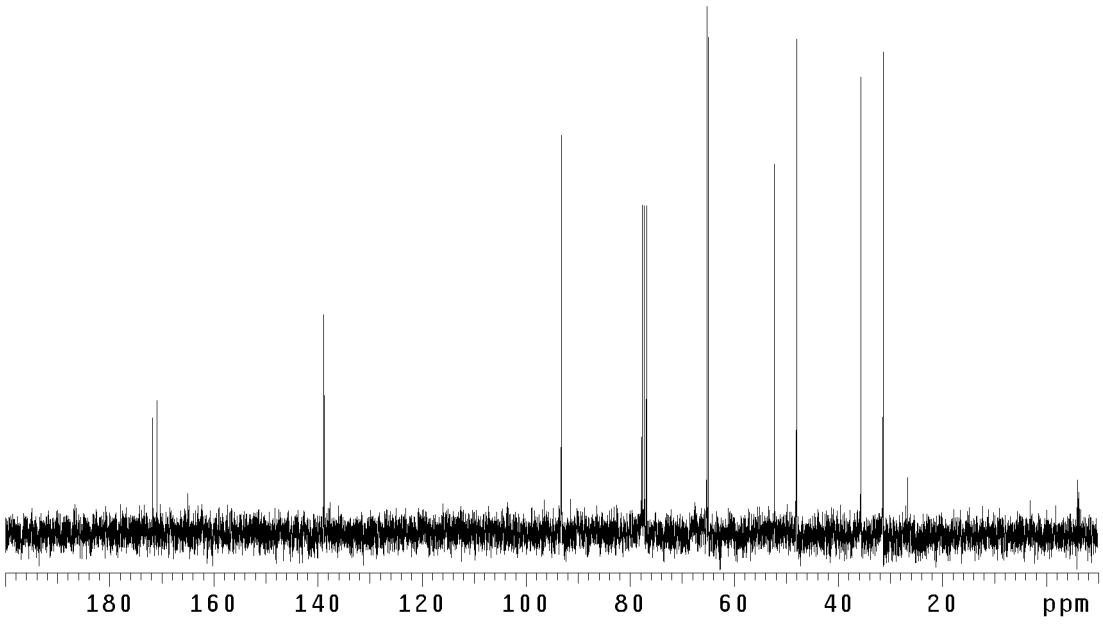


Figure A4.9 ^{13}C NMR of compound **209** (75 MHz, $CDCl_3$)

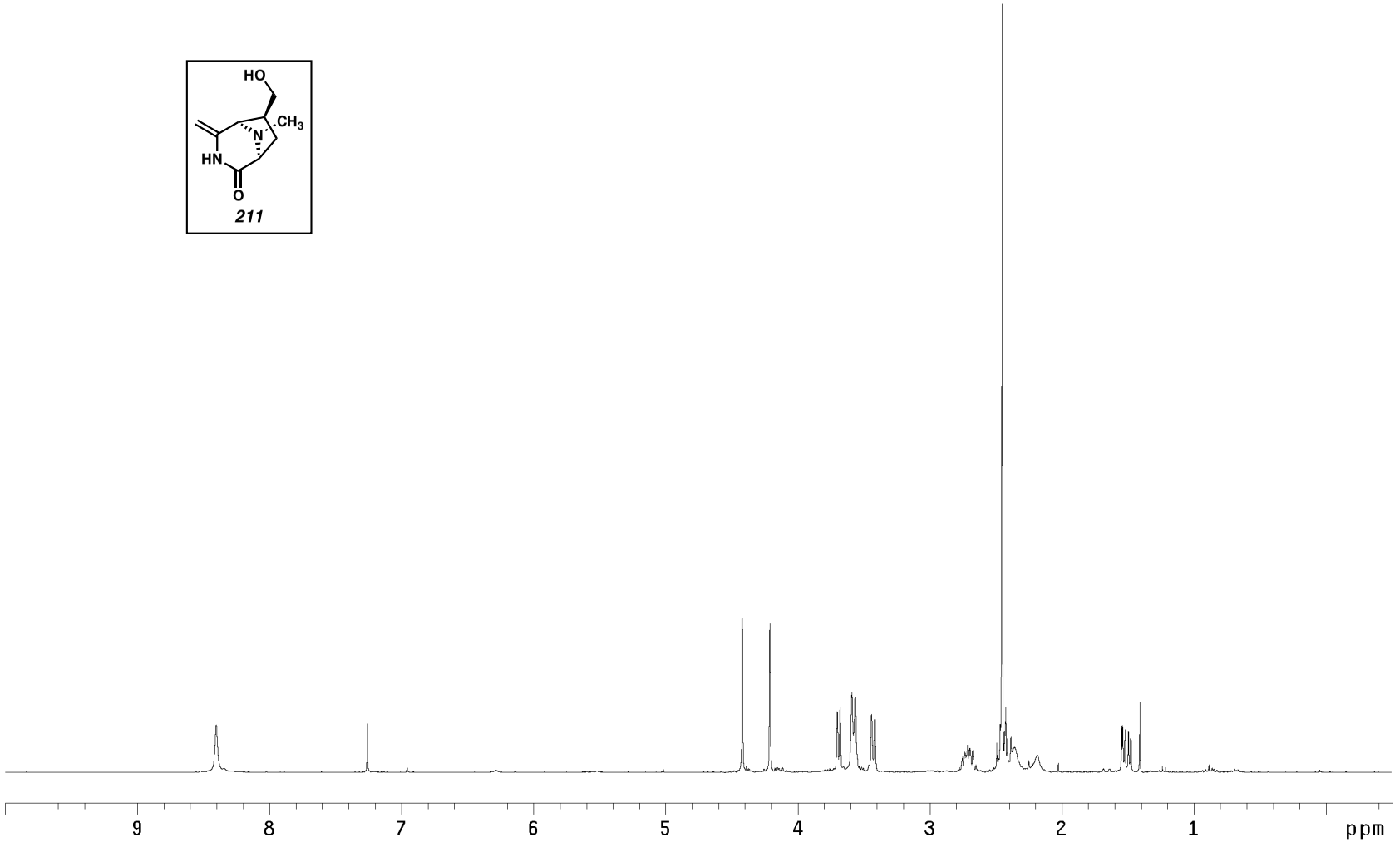


Figure A4.10 ^{1}H NMR for compound **211** (300 MHz, $CDCl_3$)

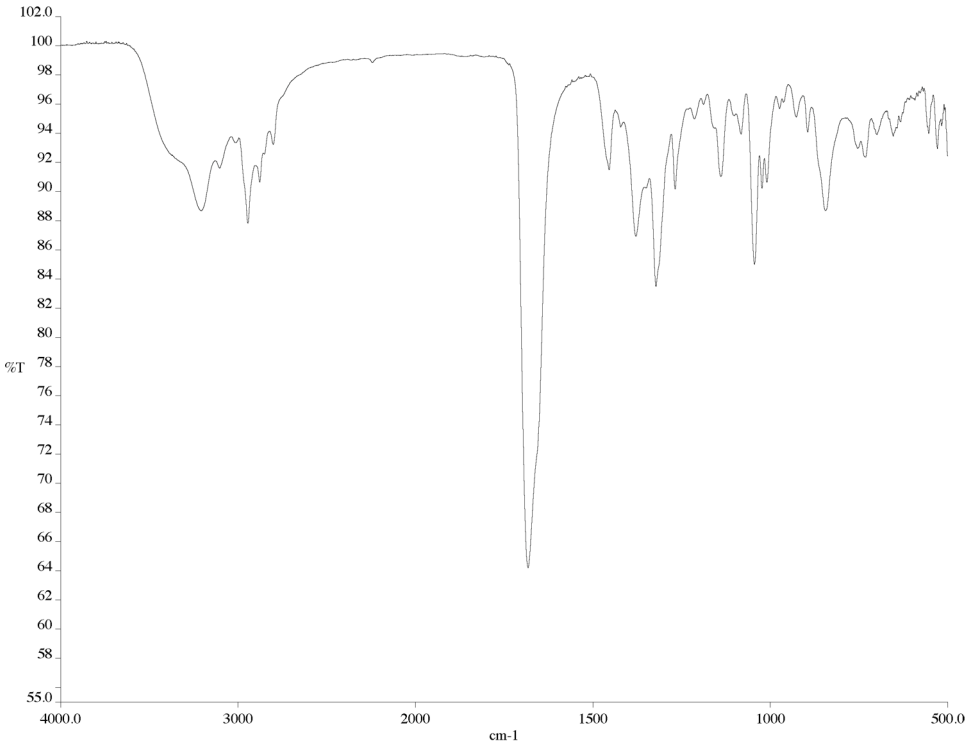


Figure A4.11 IR of compound **211** (NaCl/film)

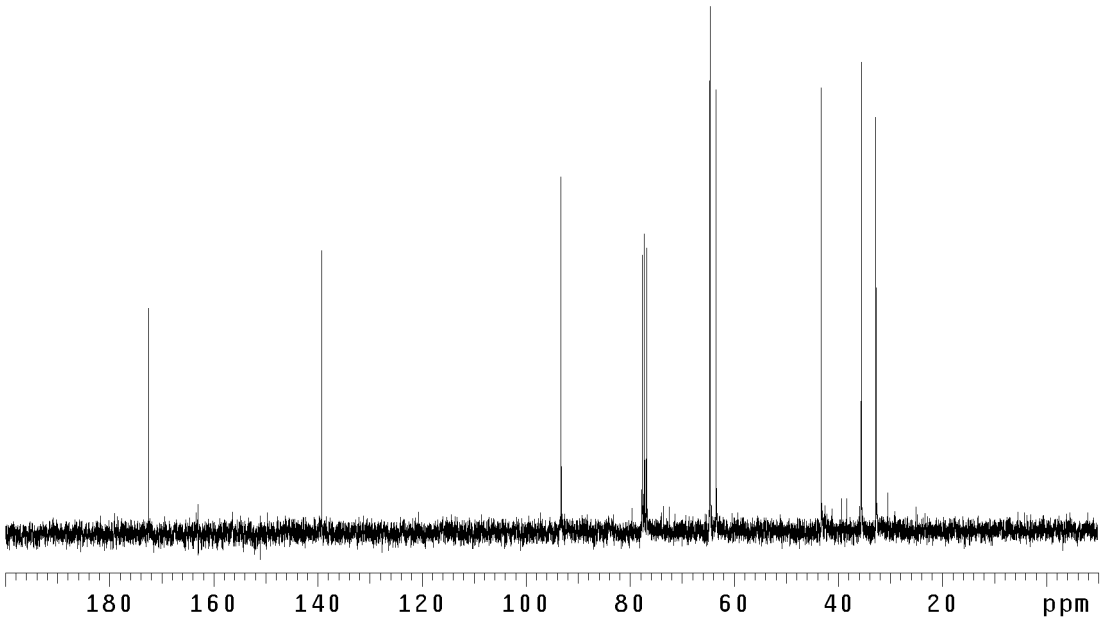


Figure A4.12 ^{13}C NMR of compound **211** (75 MHz, $CDCl_3$)

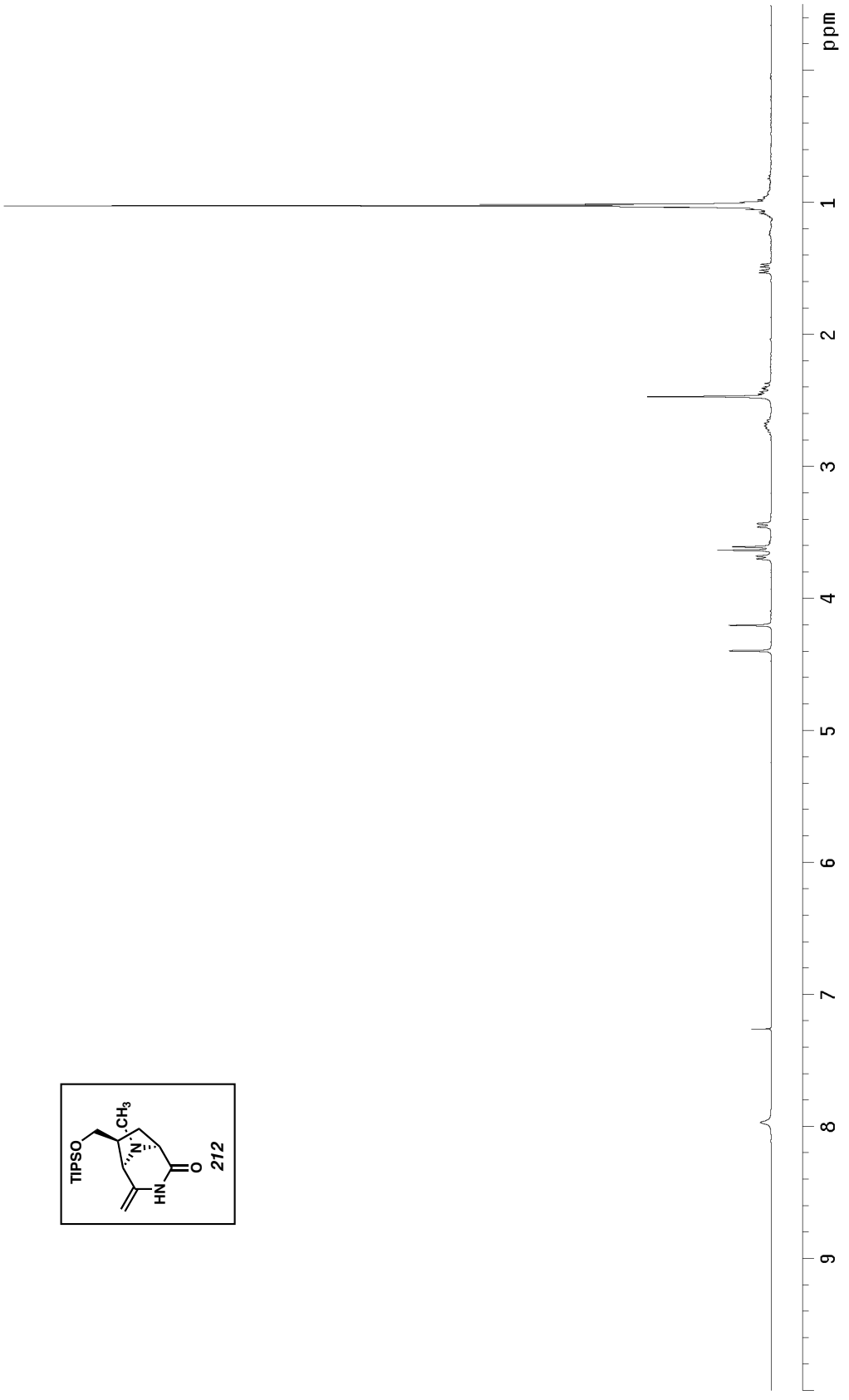


Figure A4.13 ^{1}H NMR of compound **212** (300 MHz, $CDCl_3$)

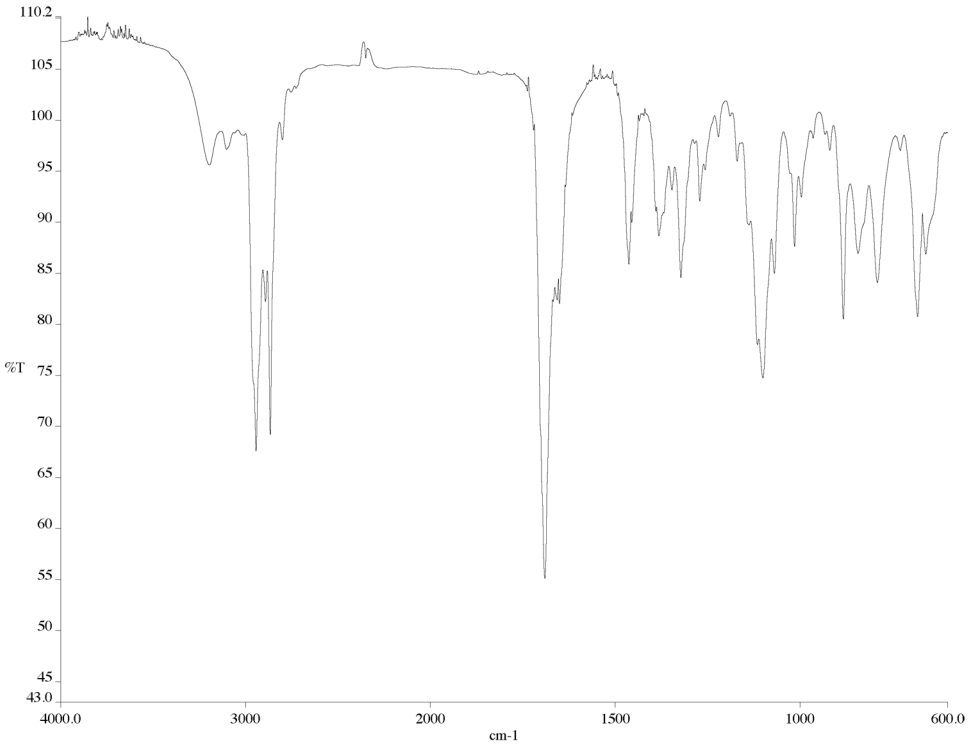


Figure A4.14 IR of compound **212** (NaCl/film)

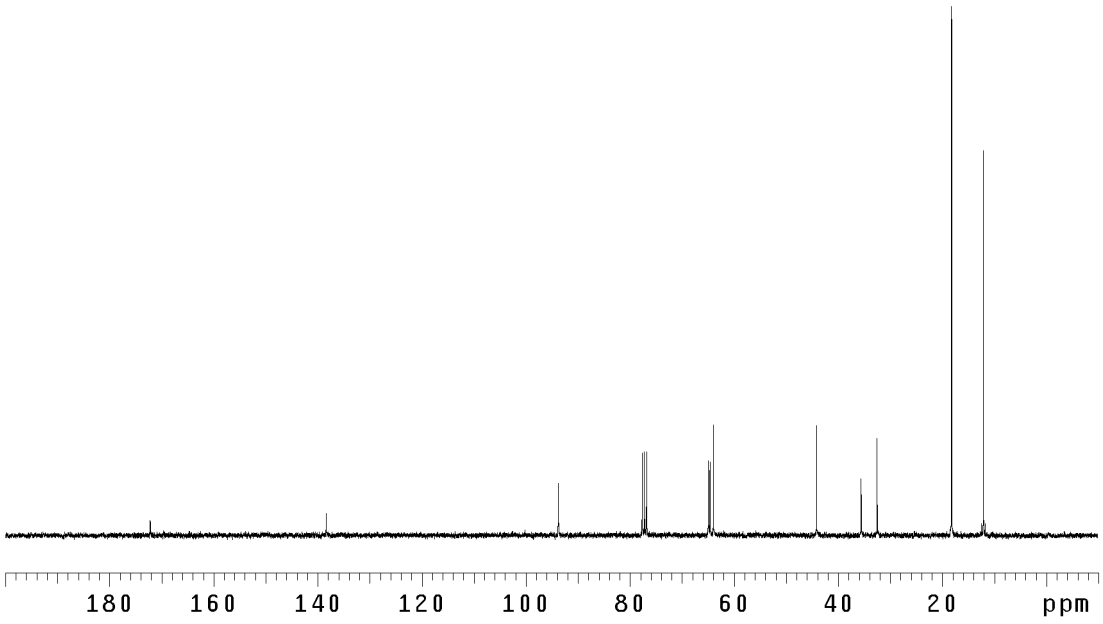


Figure A4.15 ^{13}C NMR of compound **212** (75 MHz, $CDCl_3$)

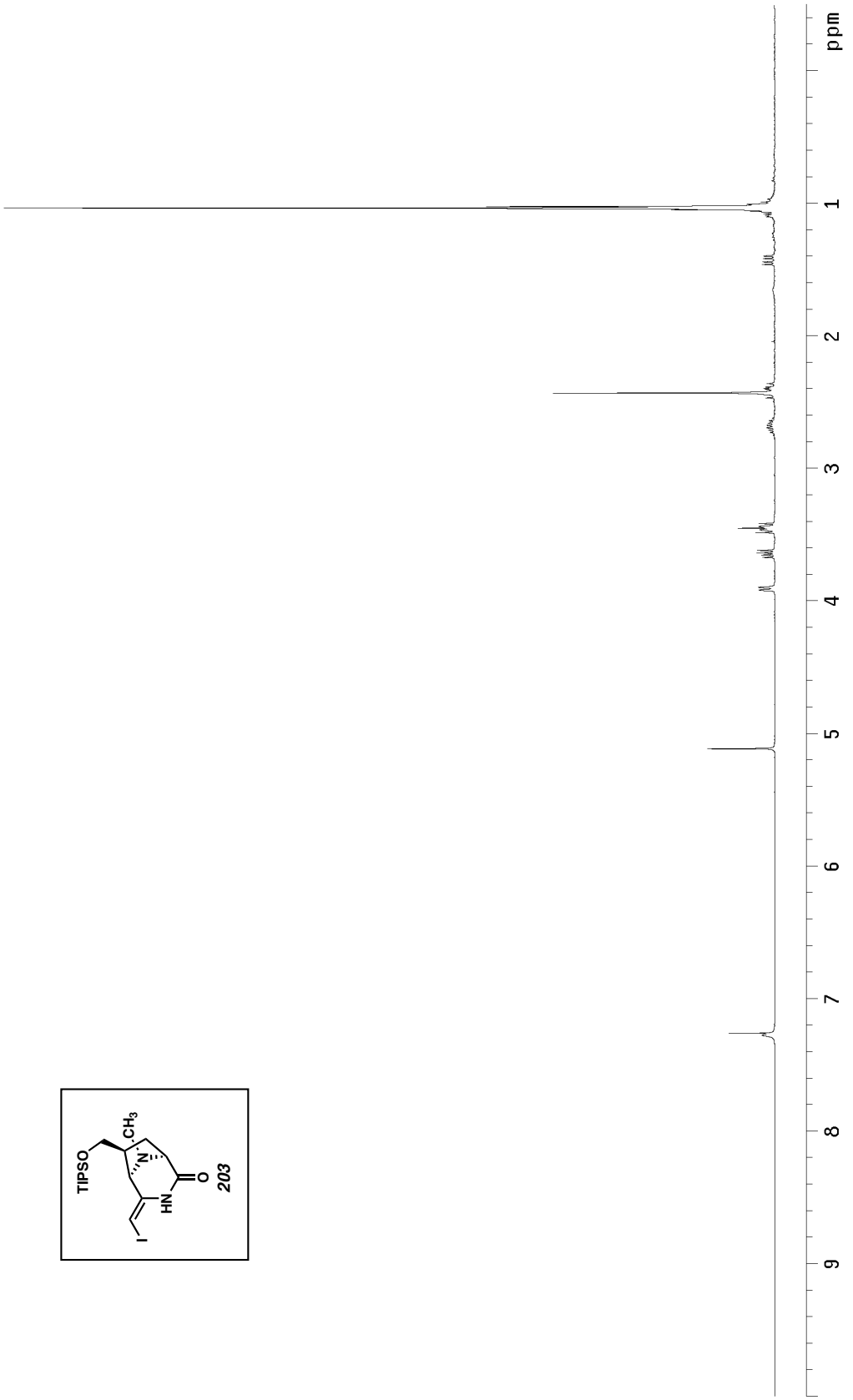


Figure A4.16 ^{1}H NMR of compound **203** (300 MHz, $CDCl_3$)

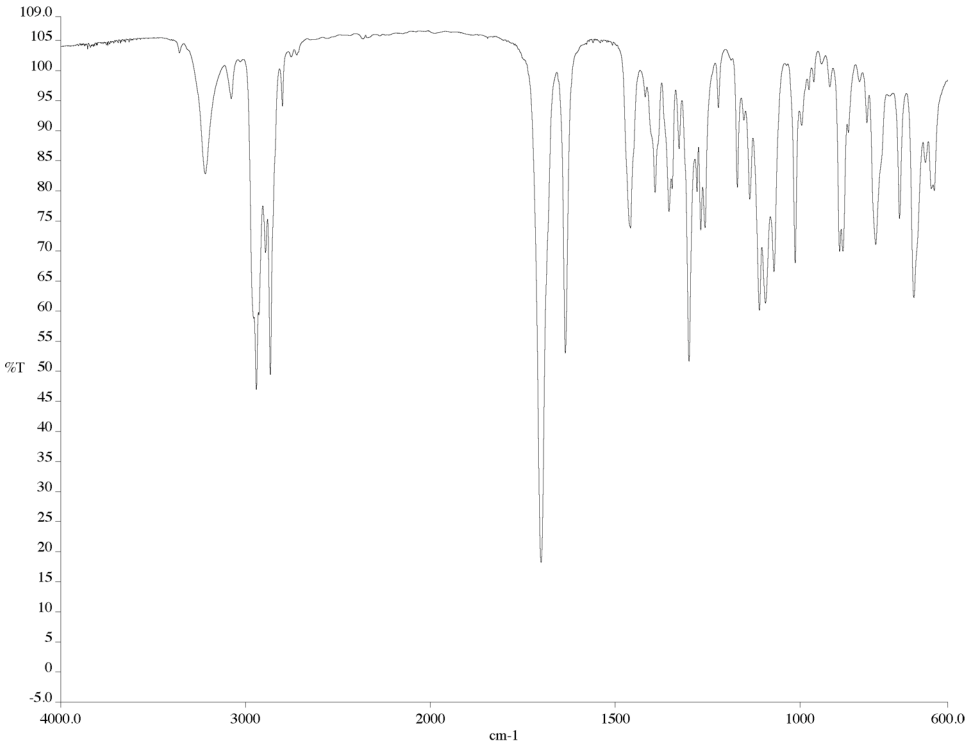


Figure A4.17 IR of compound **203** (NaCl/film)

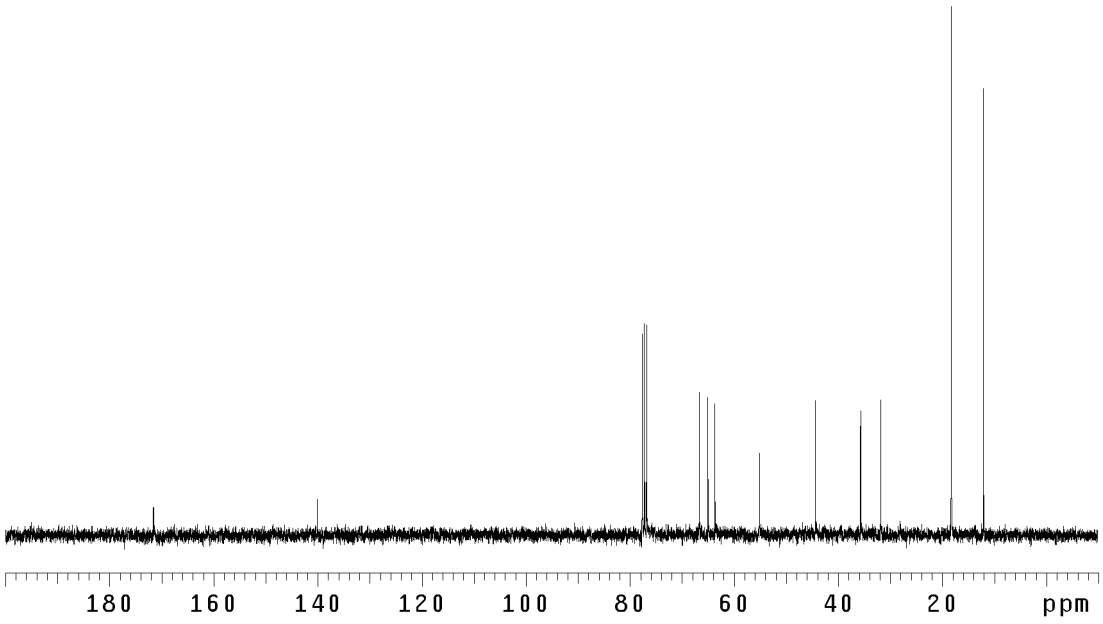


Figure A4.18 ^{13}C NMR of compound **203** (75 MHz, $CDCl_3$)

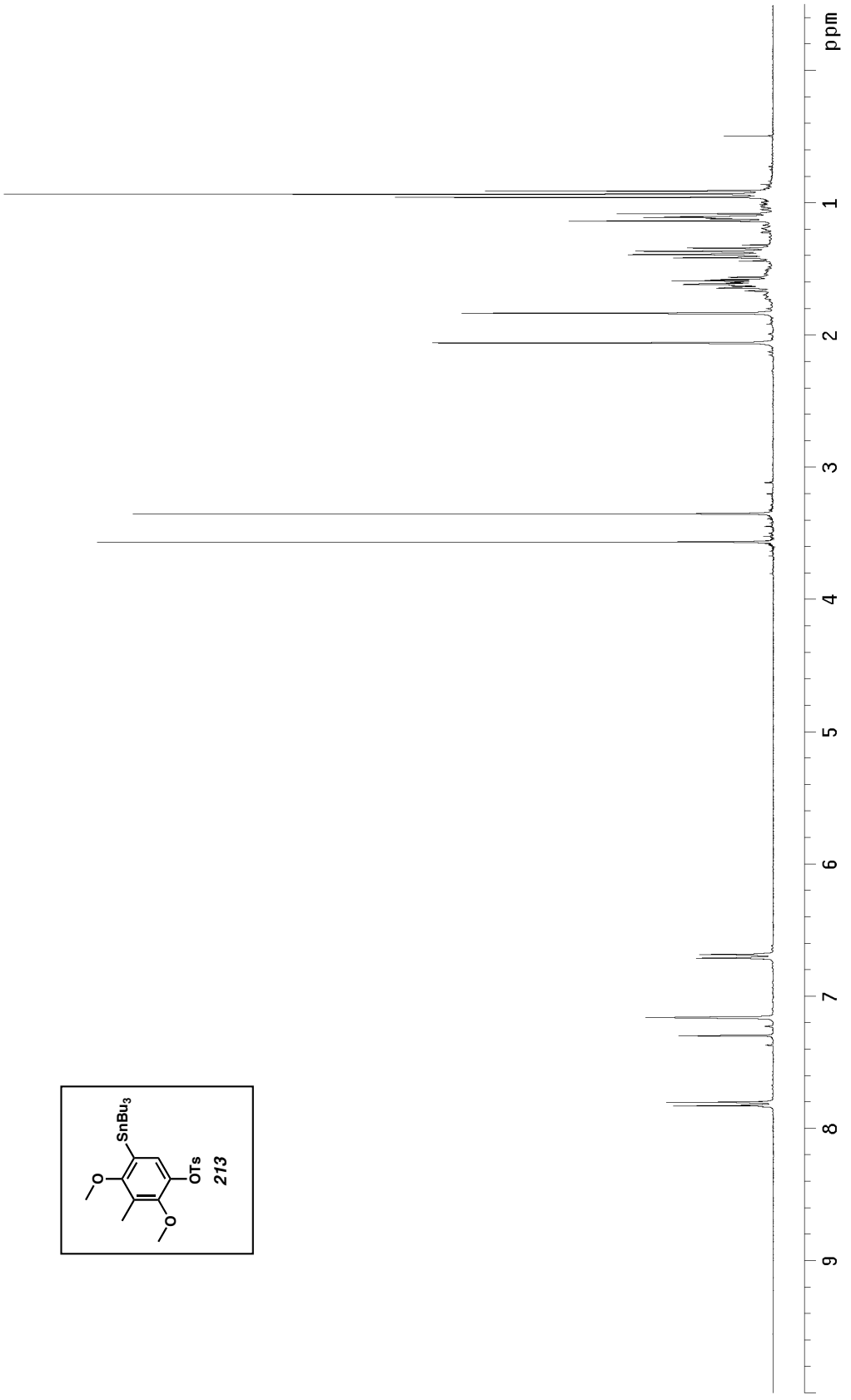


Figure A4.19 ^{1}H NMR of compound **213** (300 MHz, C_6D_6)

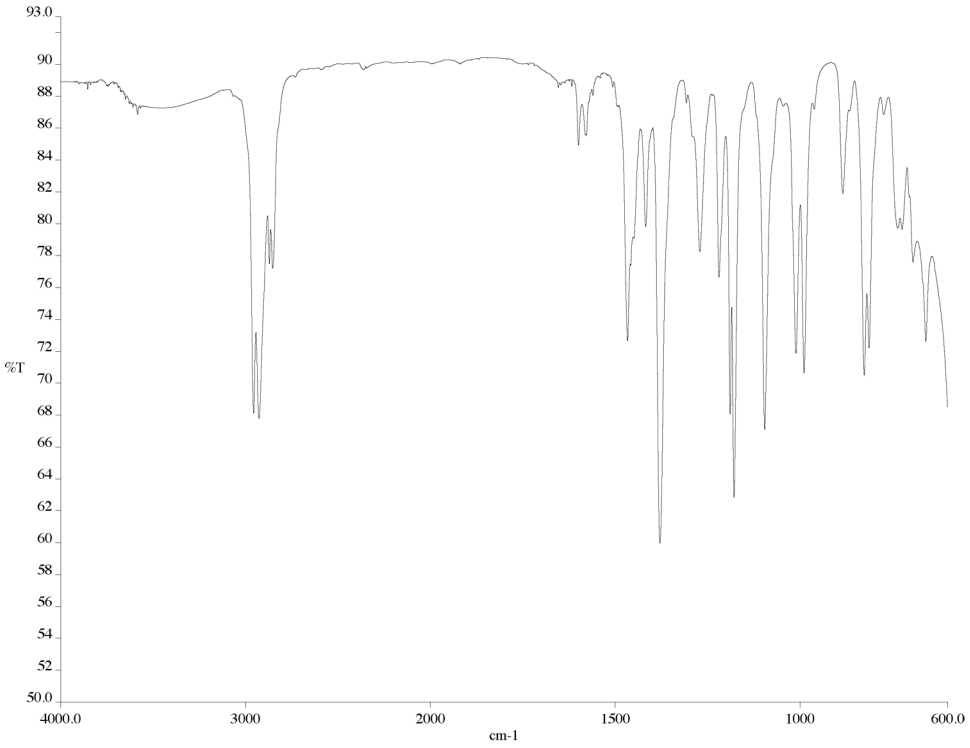


Figure A4.20 IR of compound **213** (NaCl/film)

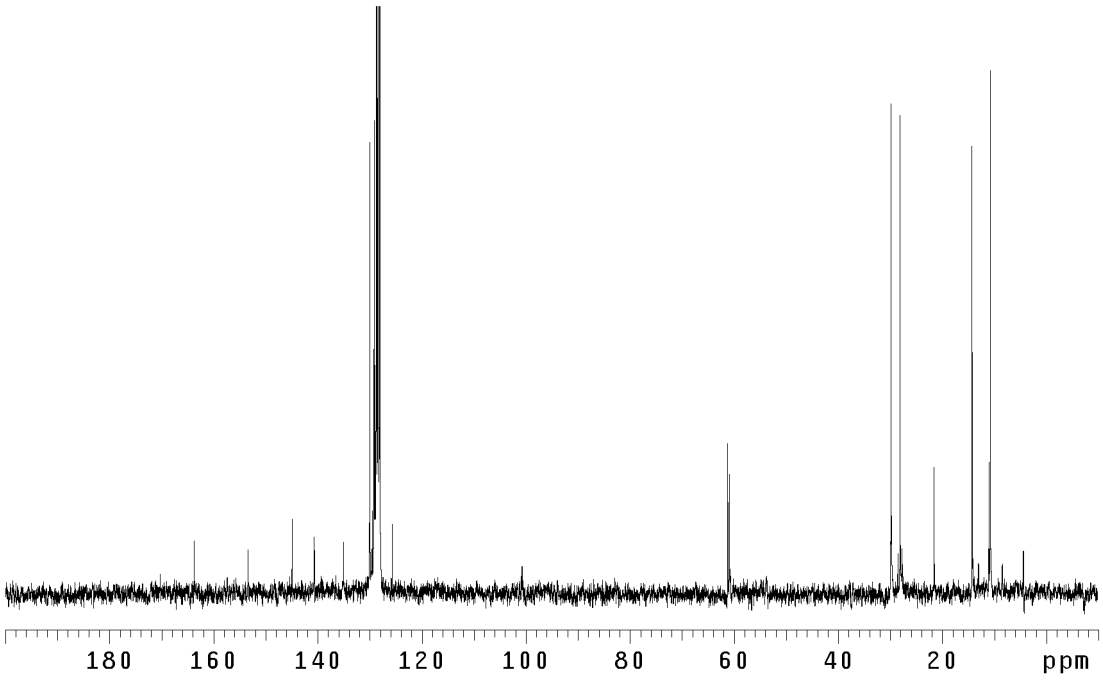


Figure A4.21 ^{13}C NMR of compound **213** (75 MHz, C_6D_6)

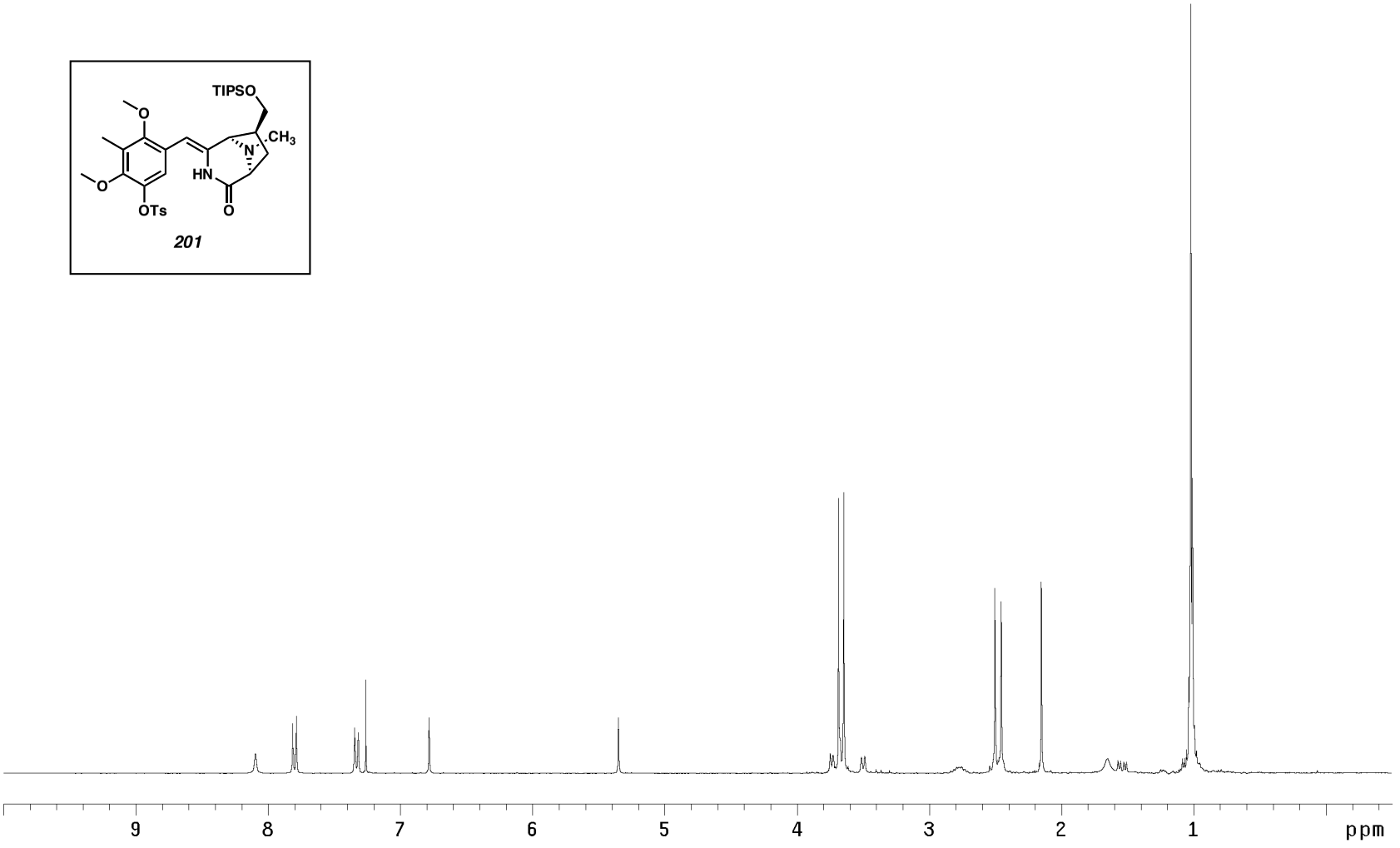


Figure A4.22 ^{1}H NMR of compound **201** (300 MHz, $CDCl_3$)

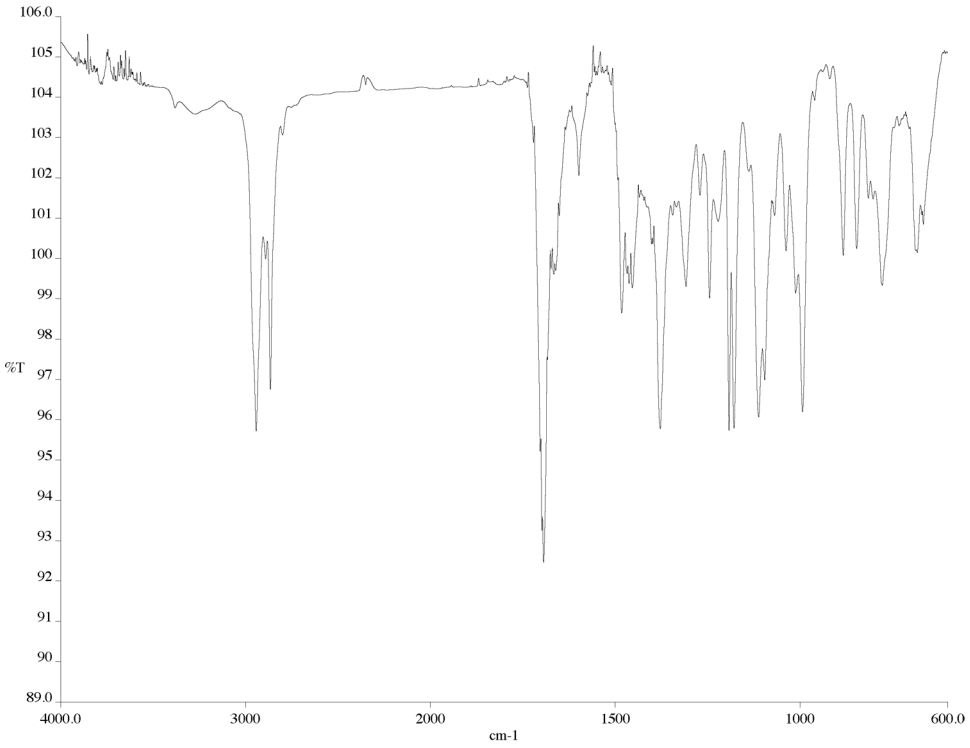


Figure A4.23 IR of compound **201** (NaCl/film)

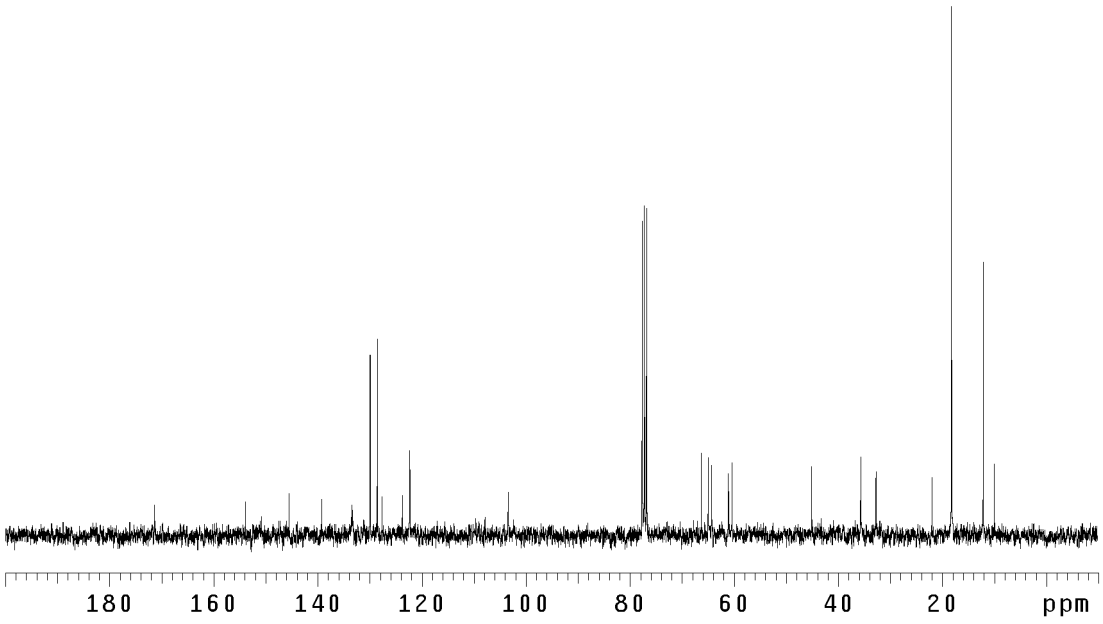


Figure A4.24 ^{13}C NMR of compound **201** (75 MHz, $CDCl_3$)

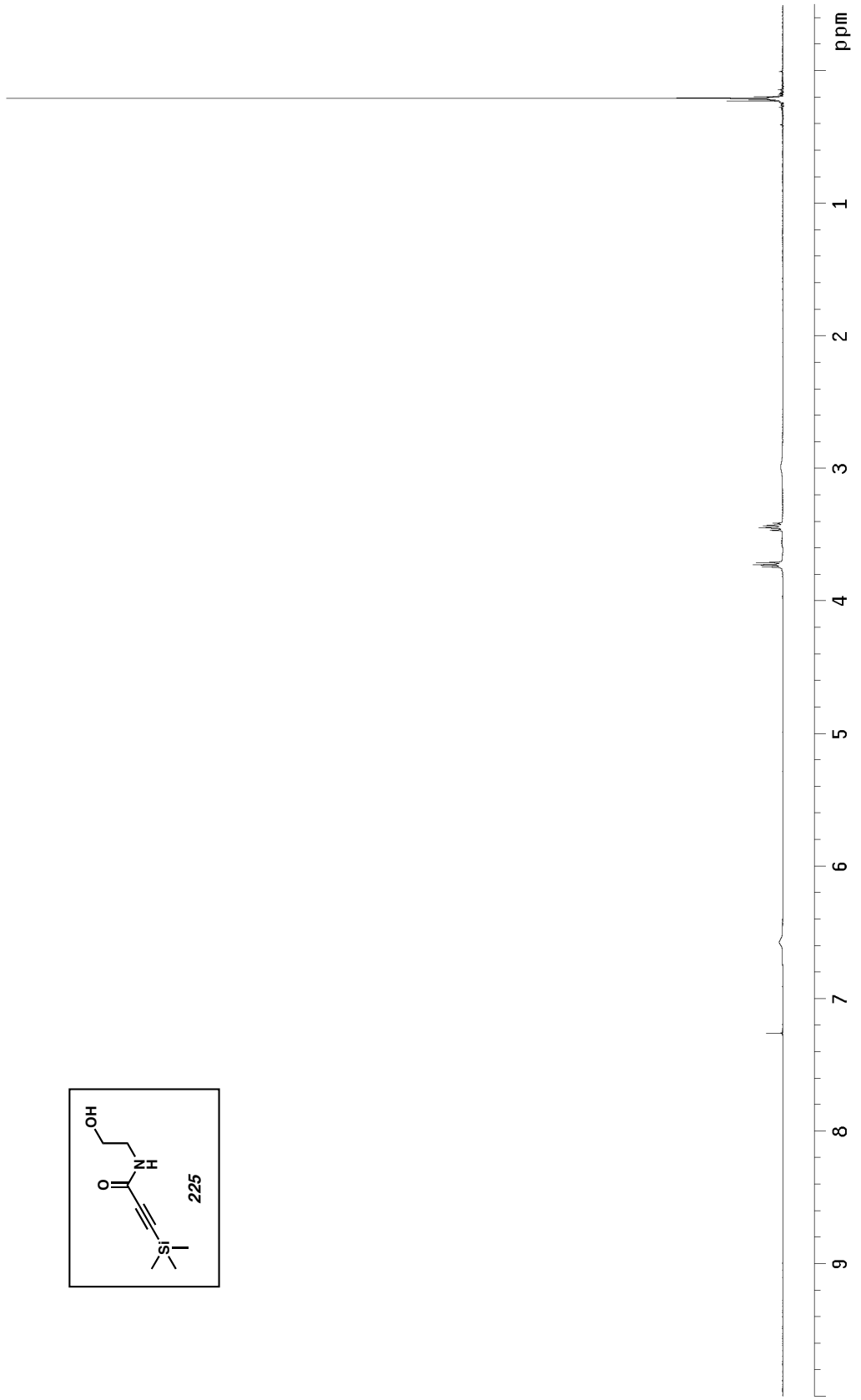


Figure A4.25 ^{1}H NMR of compound **225** (300 MHz, $CDCl_3$)

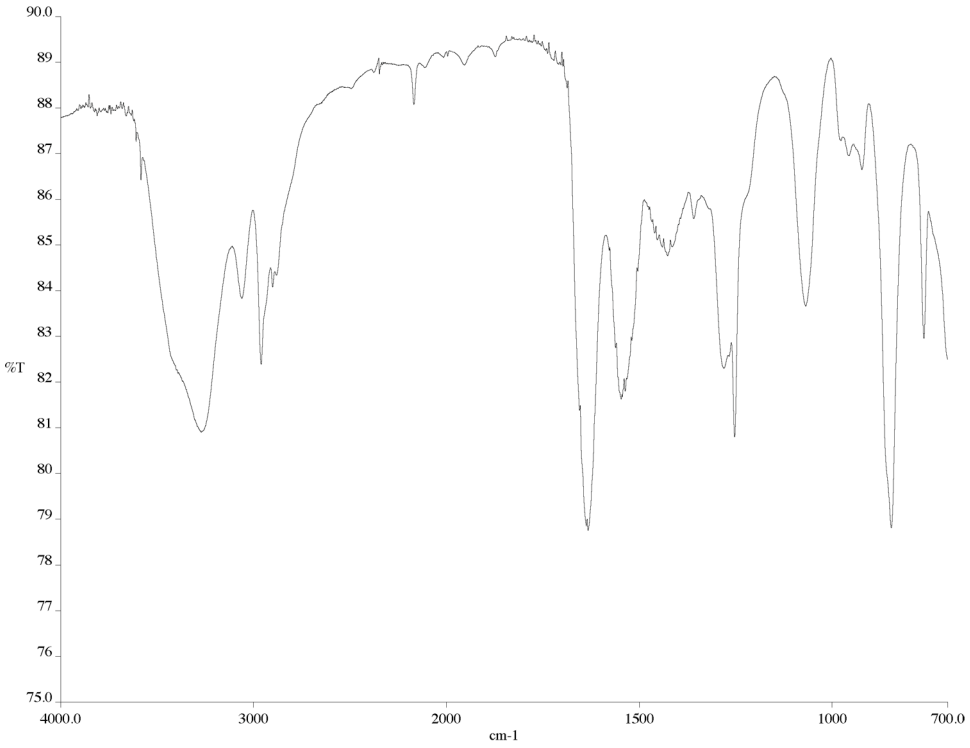


Figure A4.26 IR of compound **225** (NaCl/film)

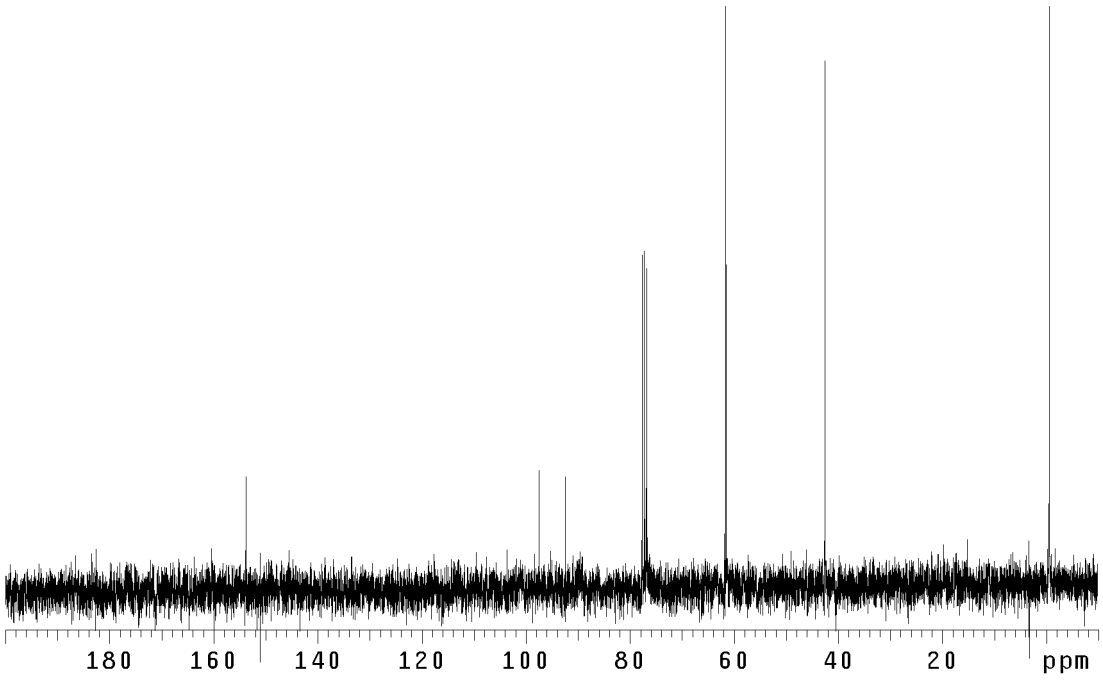


Figure A4.27 ^{13}C NMR of compound **225** (75 MHz, $CDCl_3$)

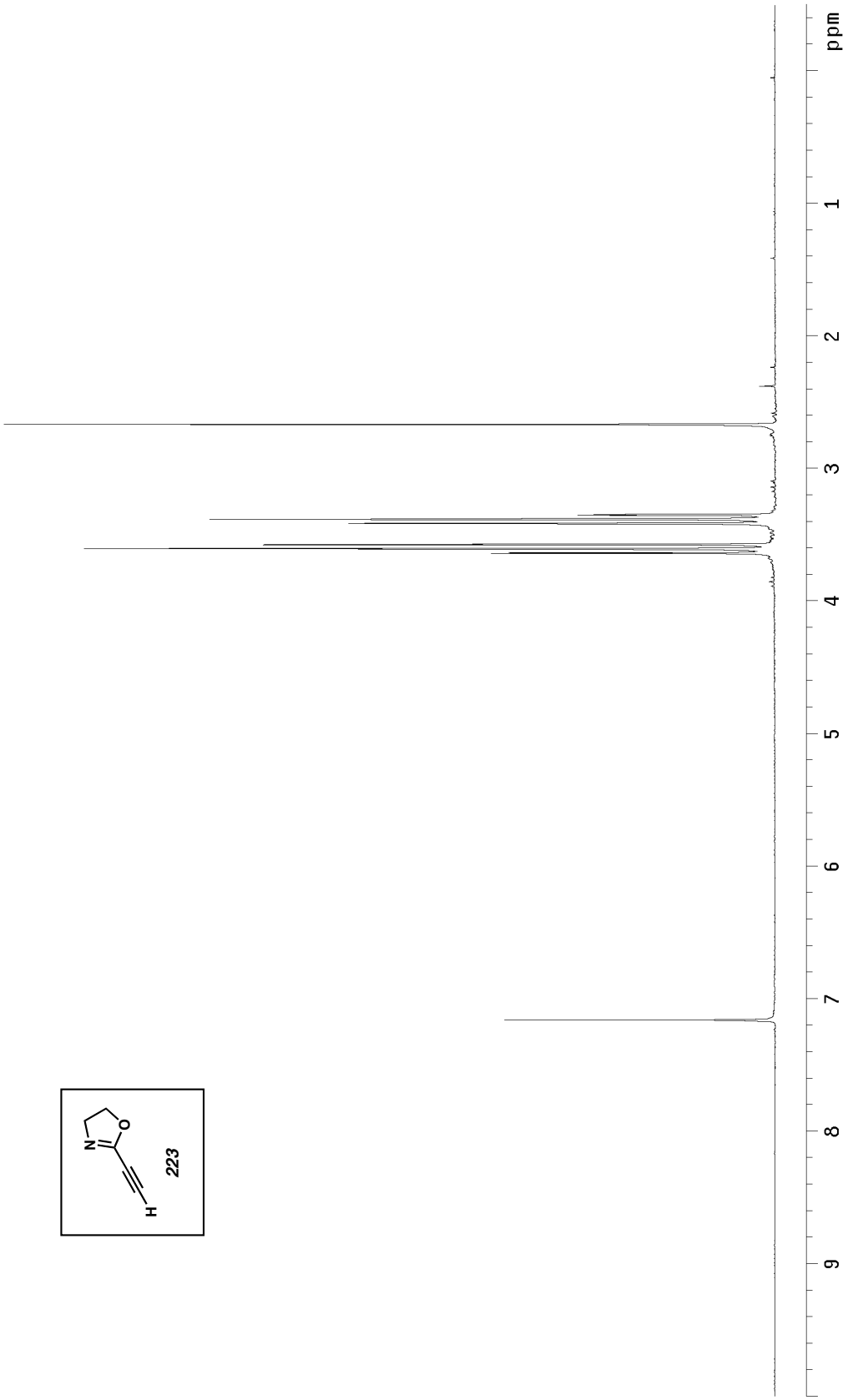


Figure A4.28 ^{1}H NMR of compound **223** (300 MHz, C_6D_6)

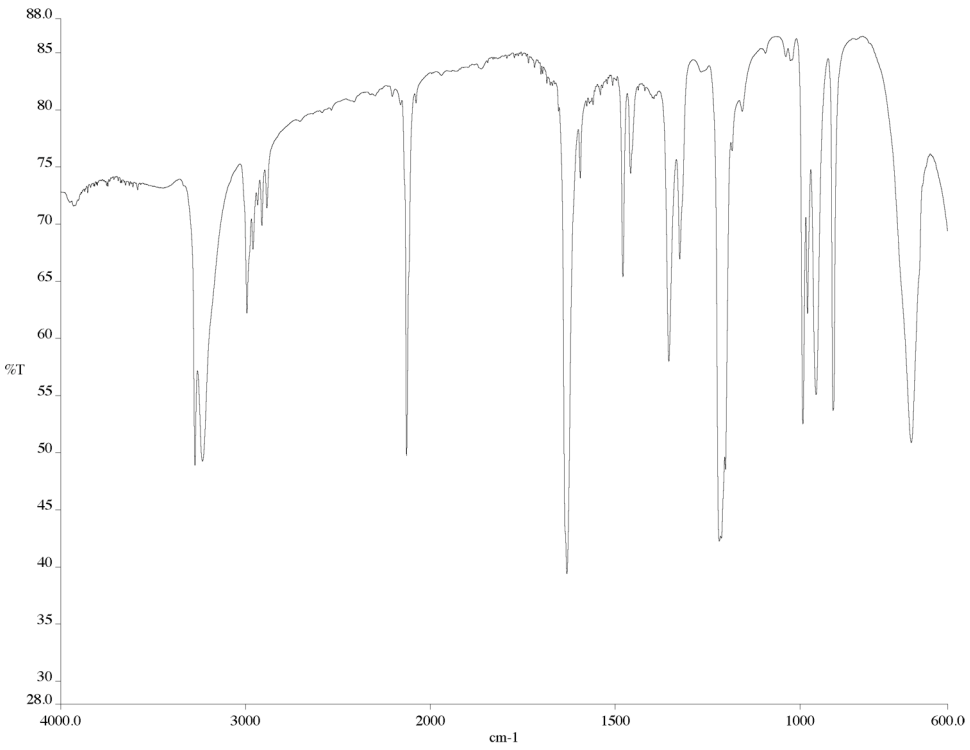


Figure A4.29 IR of compound **223** (NaCl/film)

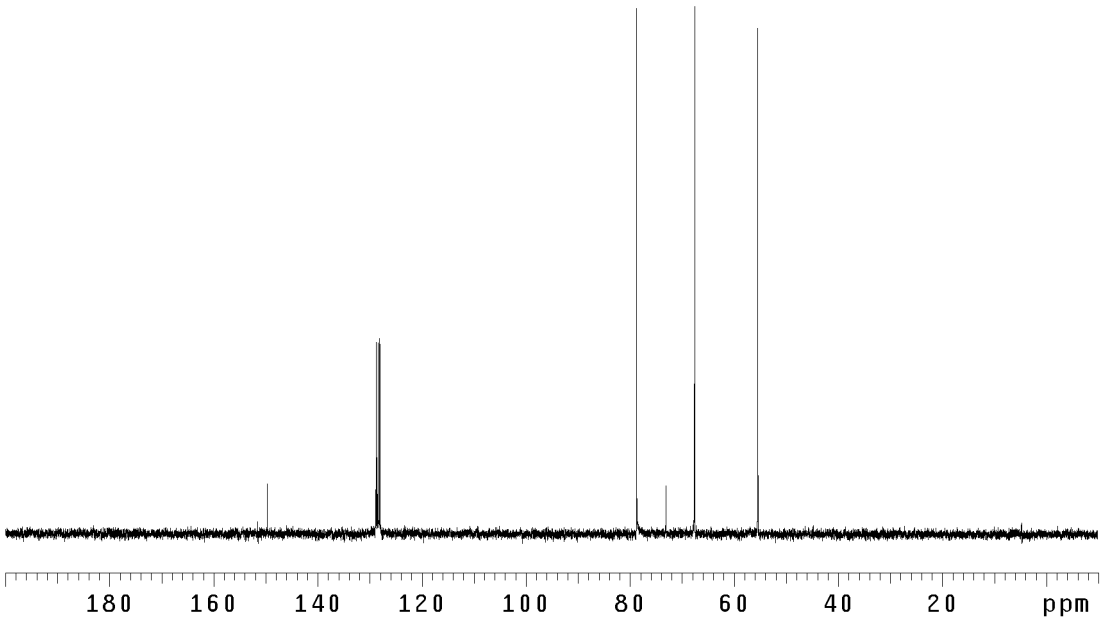


Figure A4.30 ^{13}C NMR of compound **223** (75 MHz, C_6D_6)

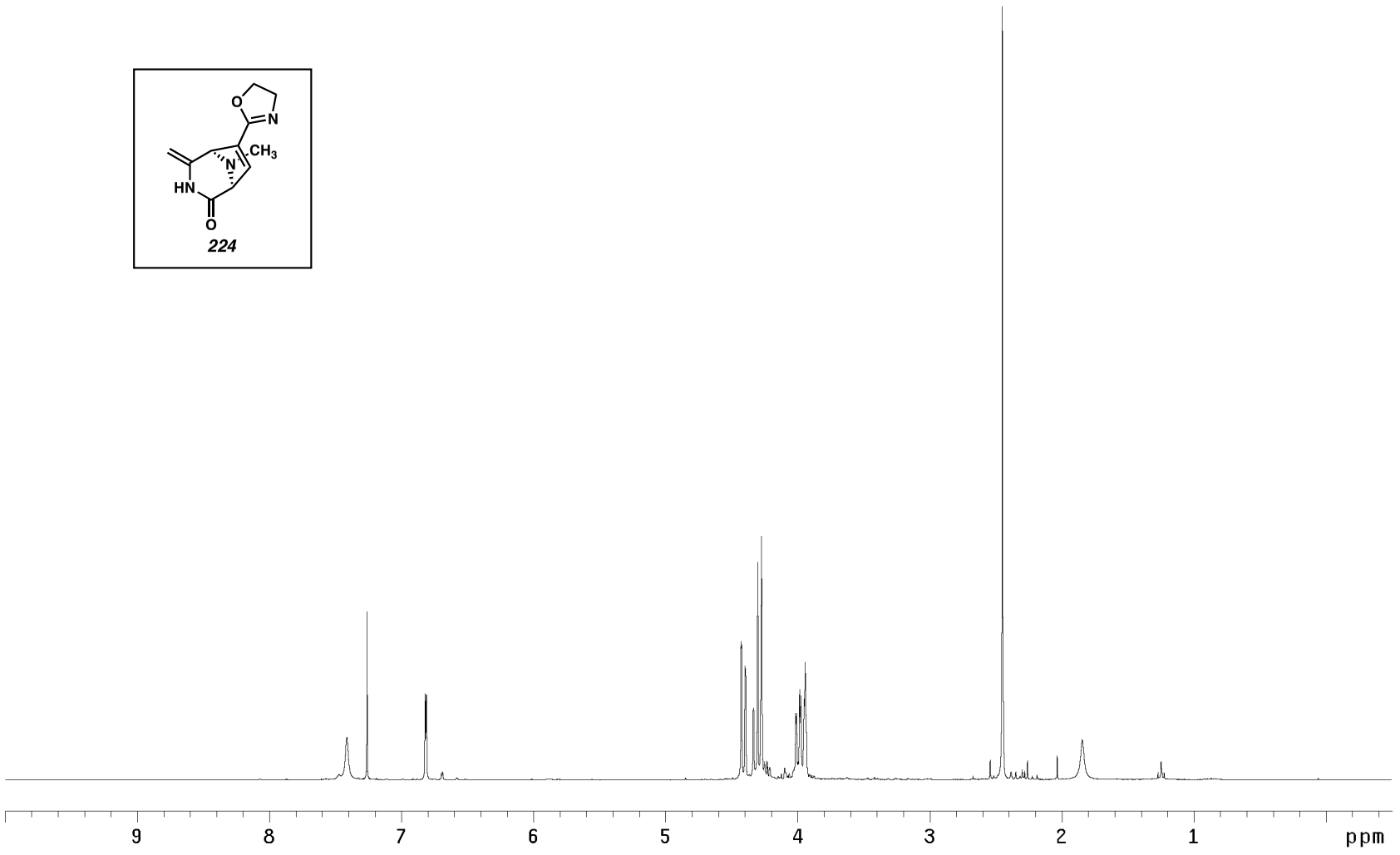


Figure A4.31 ^{1}H NMR of compound **224** (300 MHz, $CDCl_3$)

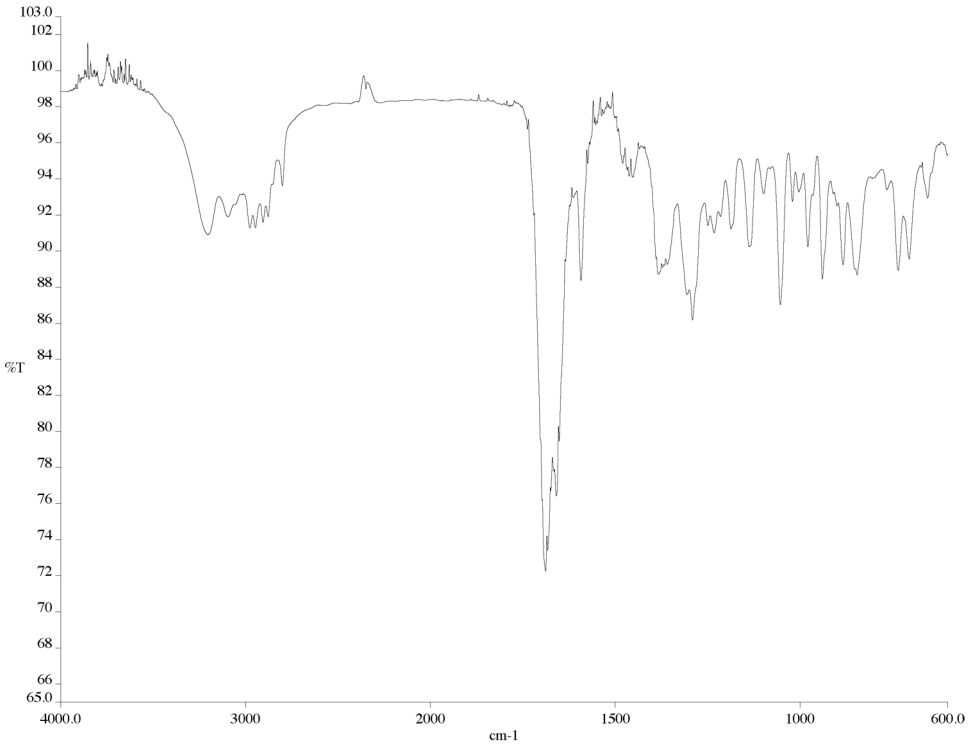


Figure A4.32 IR of compound **224** (NaCl/film)

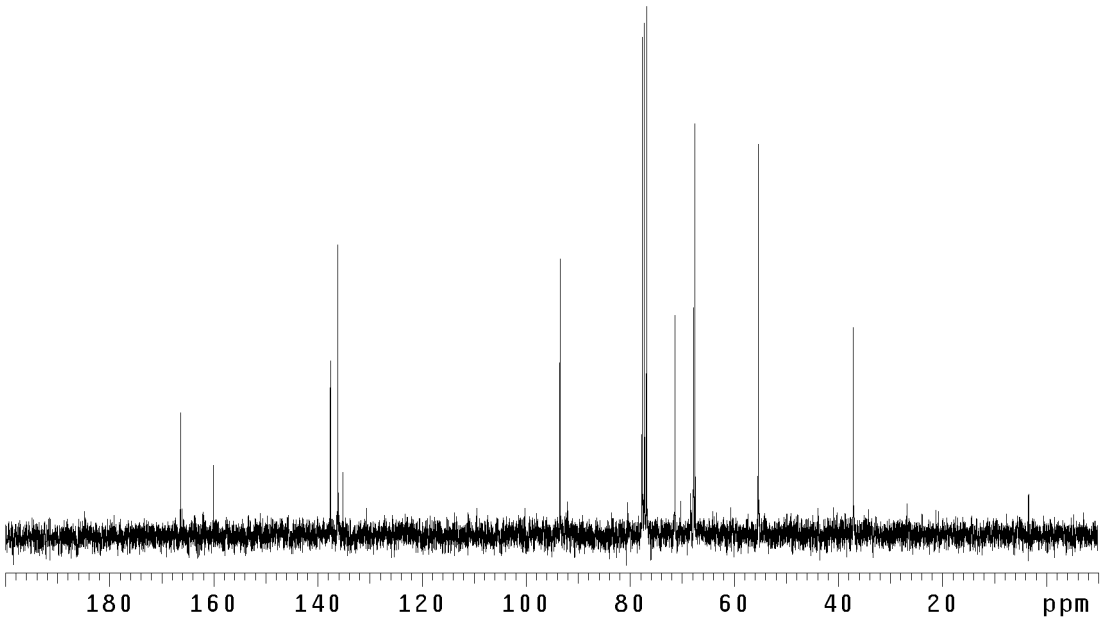


Figure A4.33 ^{13}C NMR of compound **224** (75 MHz, $CDCl_3$)

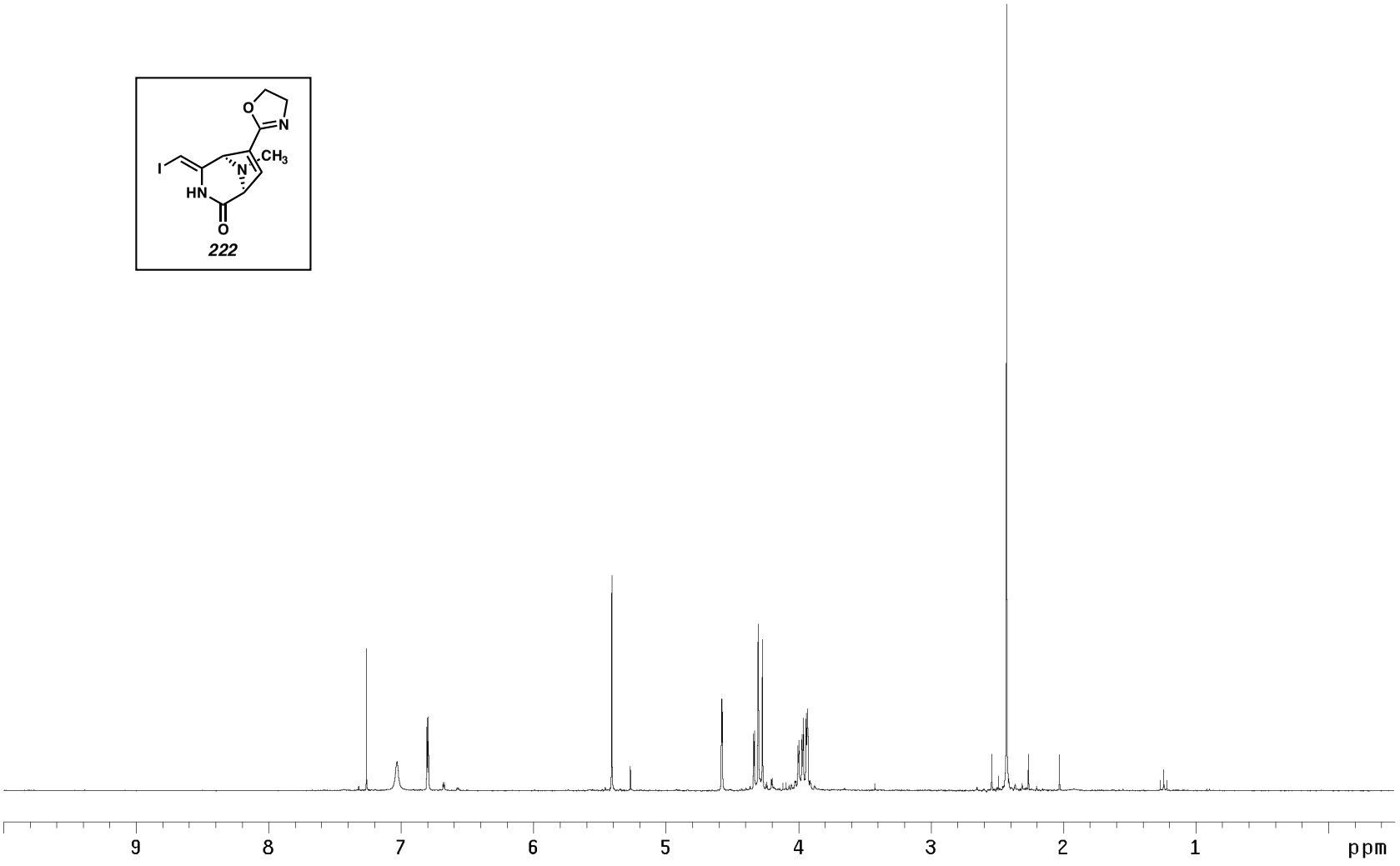


Figure A4.34 ^{1}H NMR of compound **222** (300 MHz, $CDCl_3$)

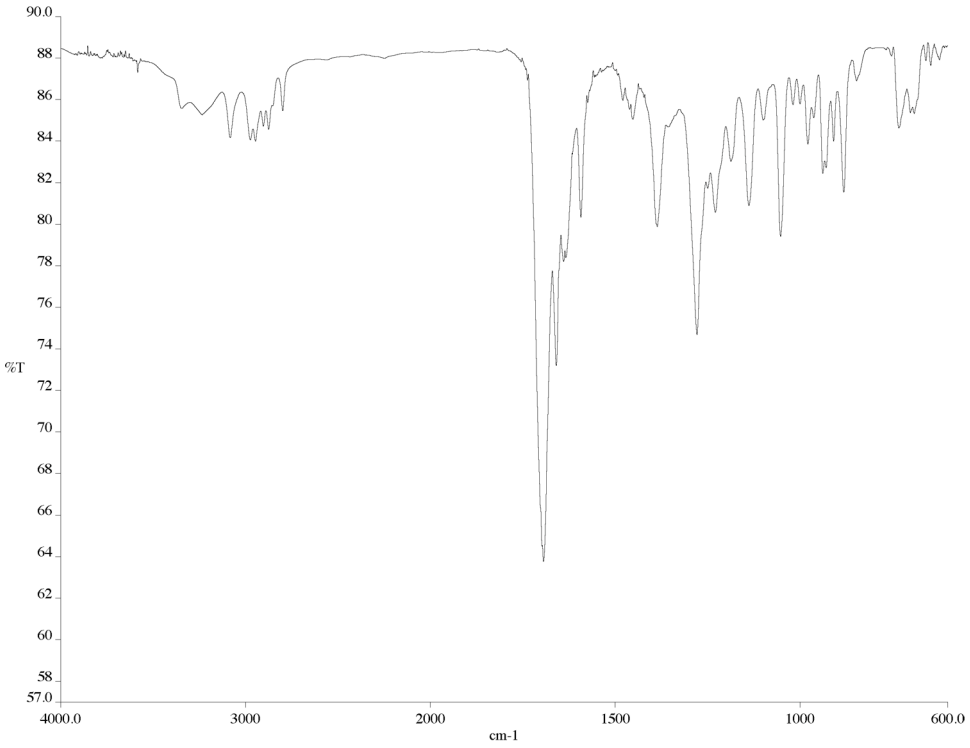


Figure A4.35 IR of compound **222** (NaCl/film)

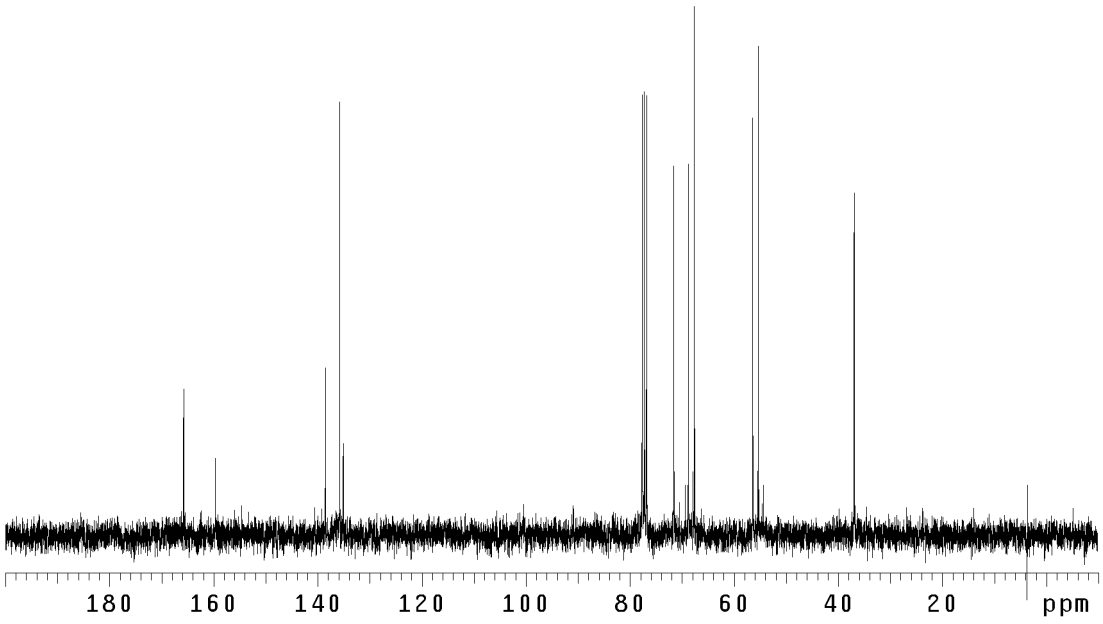


Figure A4.36 ^{13}C NMR of compound **222** (75 MHz, $CDCl_3$)

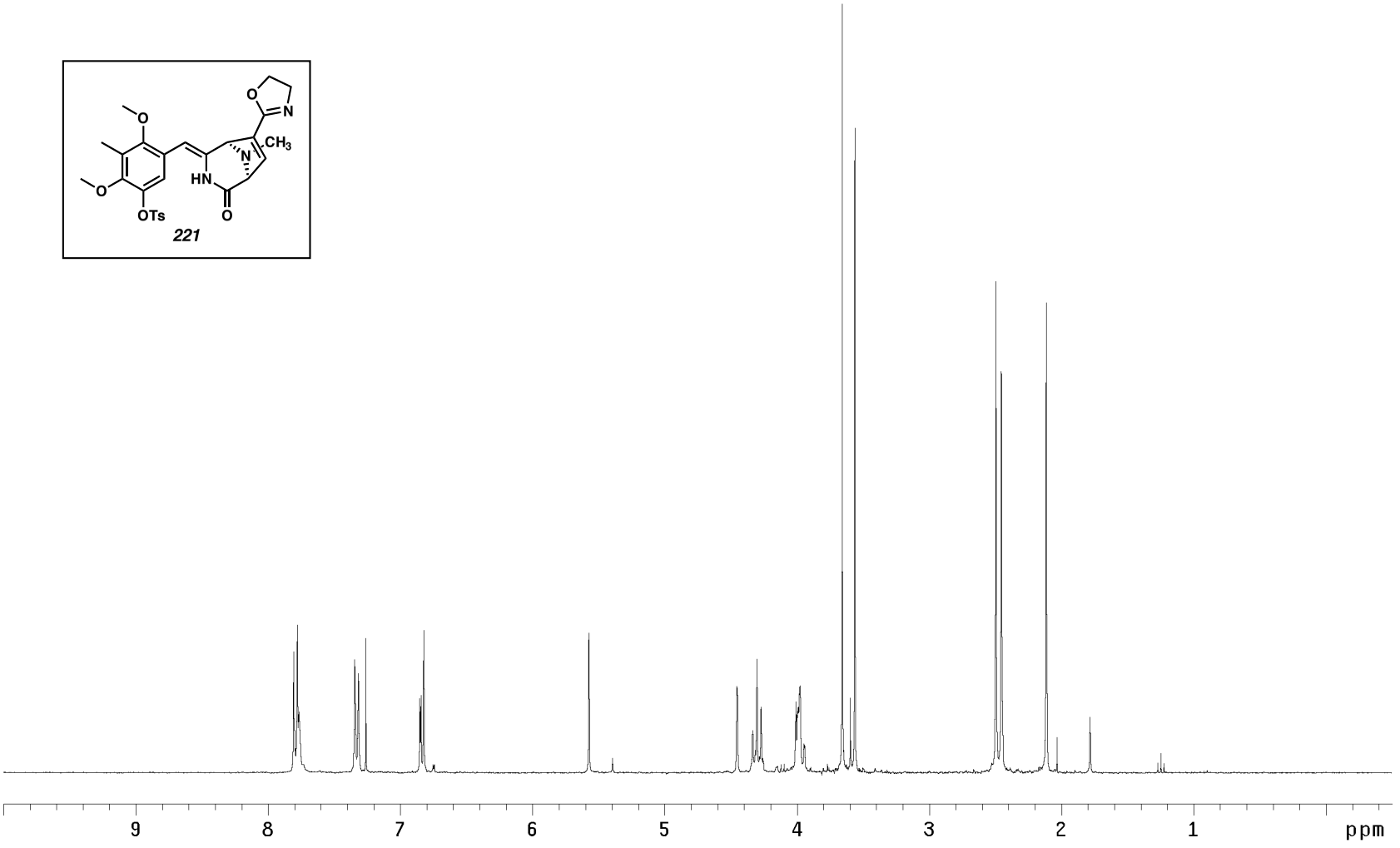


Figure A4.37 ^{1}H NMR of compound **221** (300 MHz, $CDCl_3$)

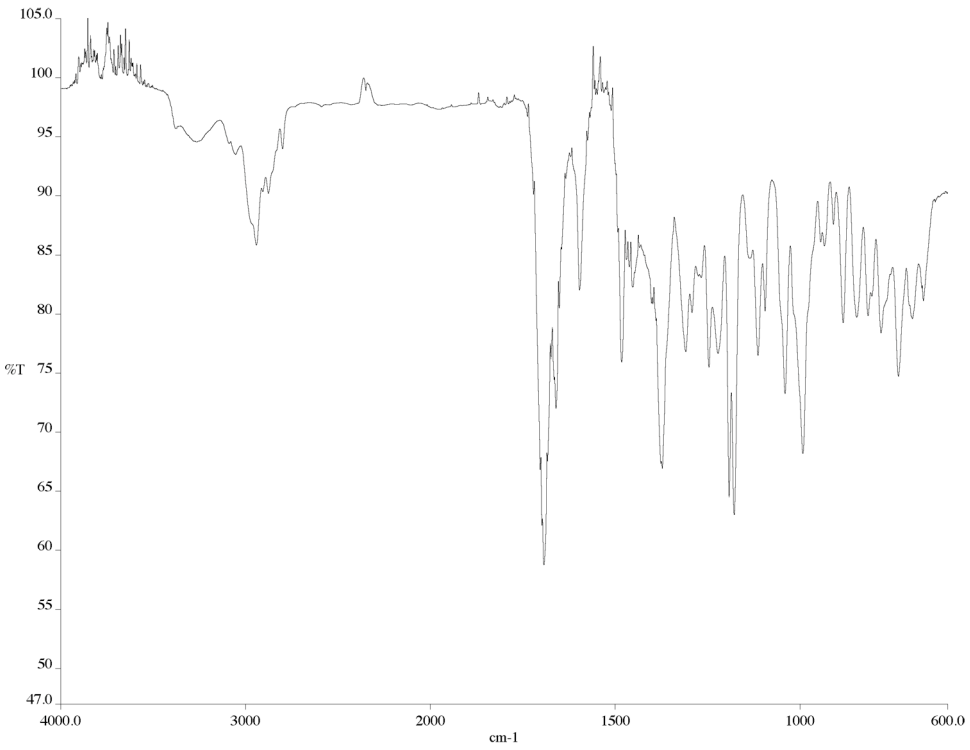


Figure A4.38 IR of compound **221** (NaCl/film)

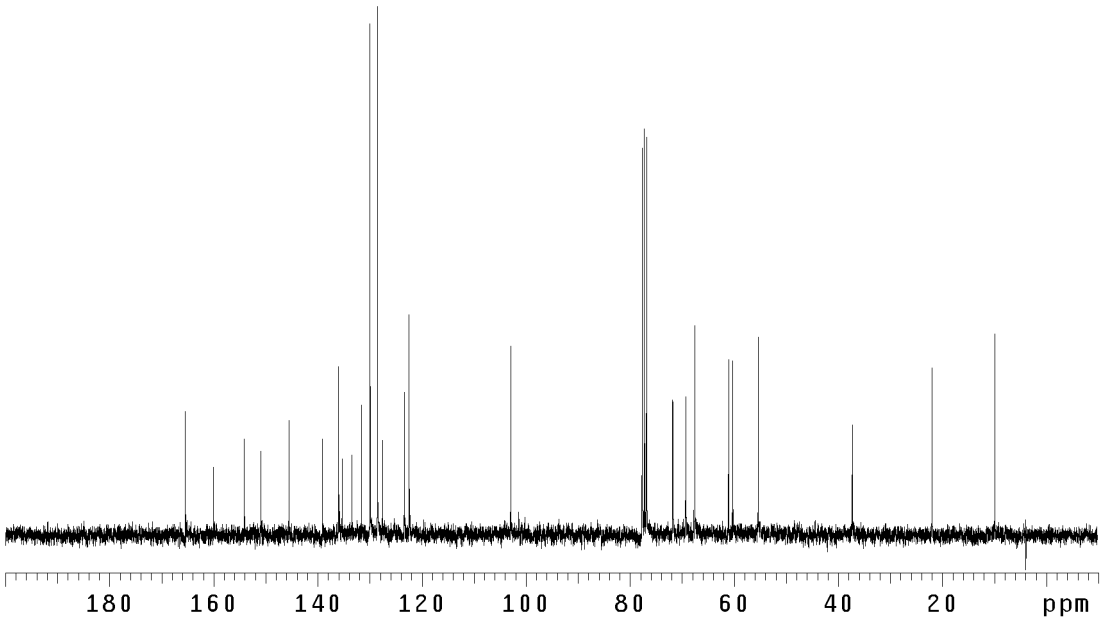


Figure A4.39 ^{13}C NMR of compound **221** (75 MHz, $CDCl_3$)

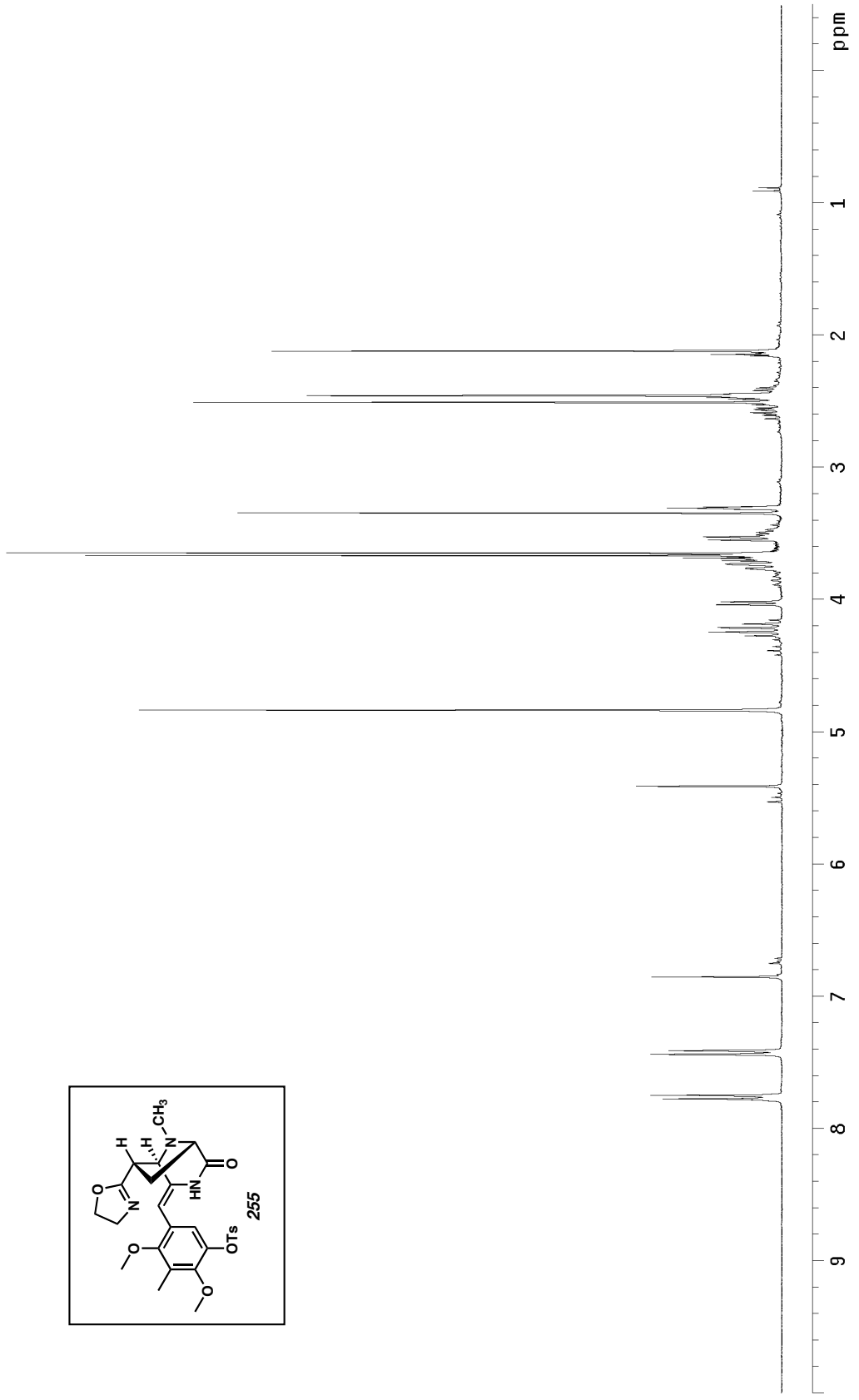


Figure A4.40 ^{1}H NMR of compound **255** (300 MHz, CD_3OD, impurity at 3.35 is CH_3OH)

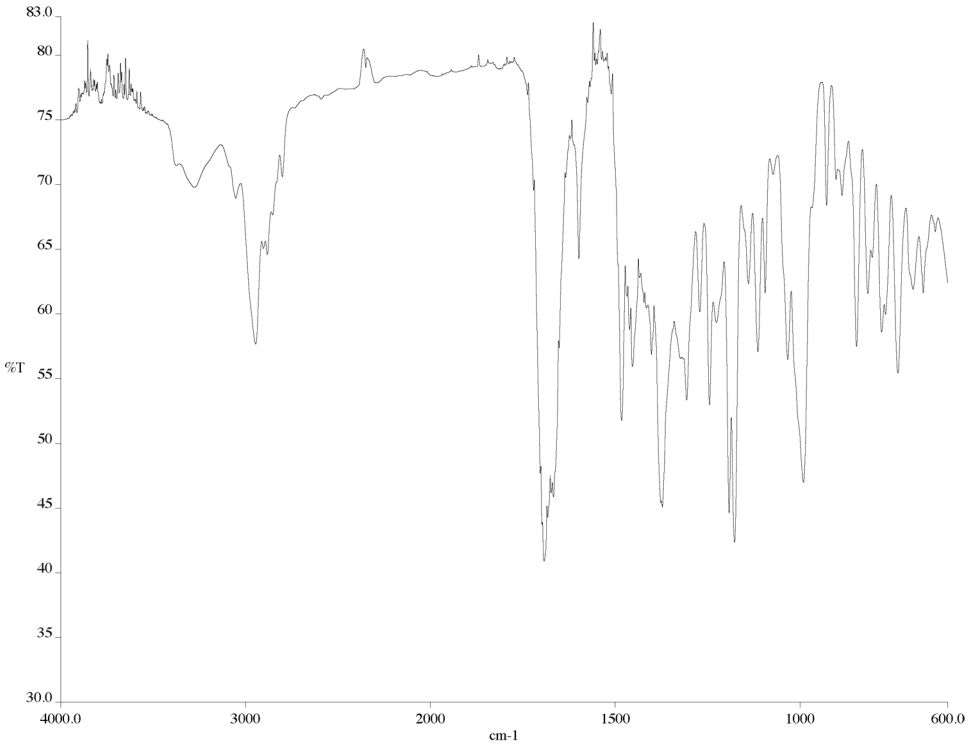


Figure A4.41 IR of compound **255** (NaCl/film)

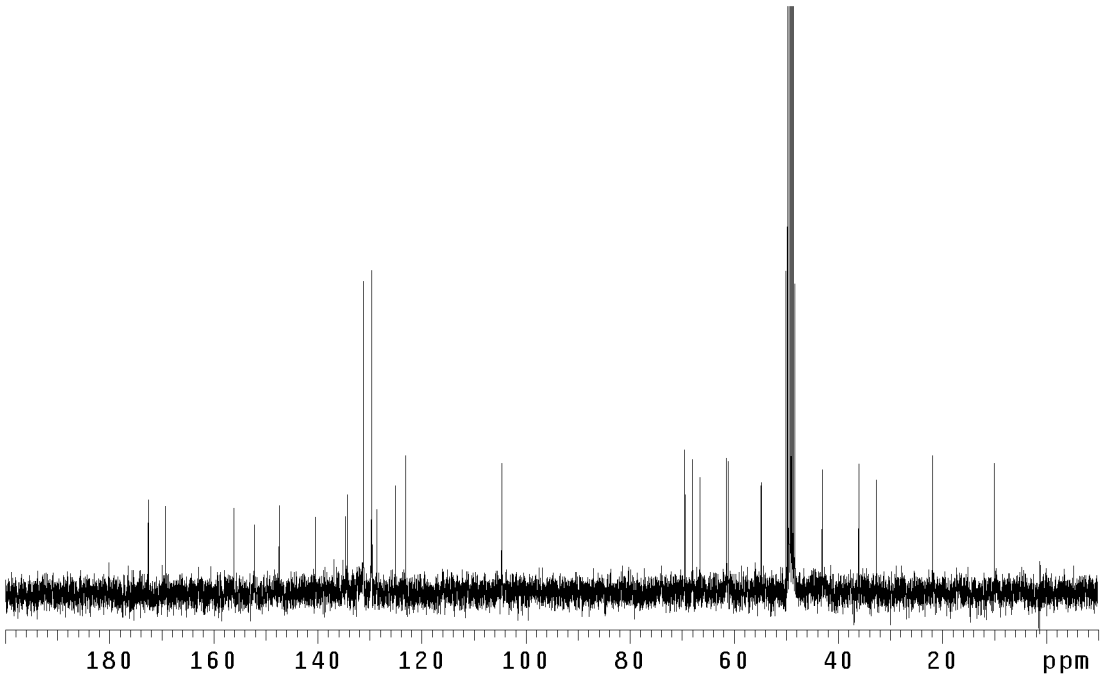


Figure A4.42 ^{13}C NMR of compound **255** (75 MHz, CD_3OD)

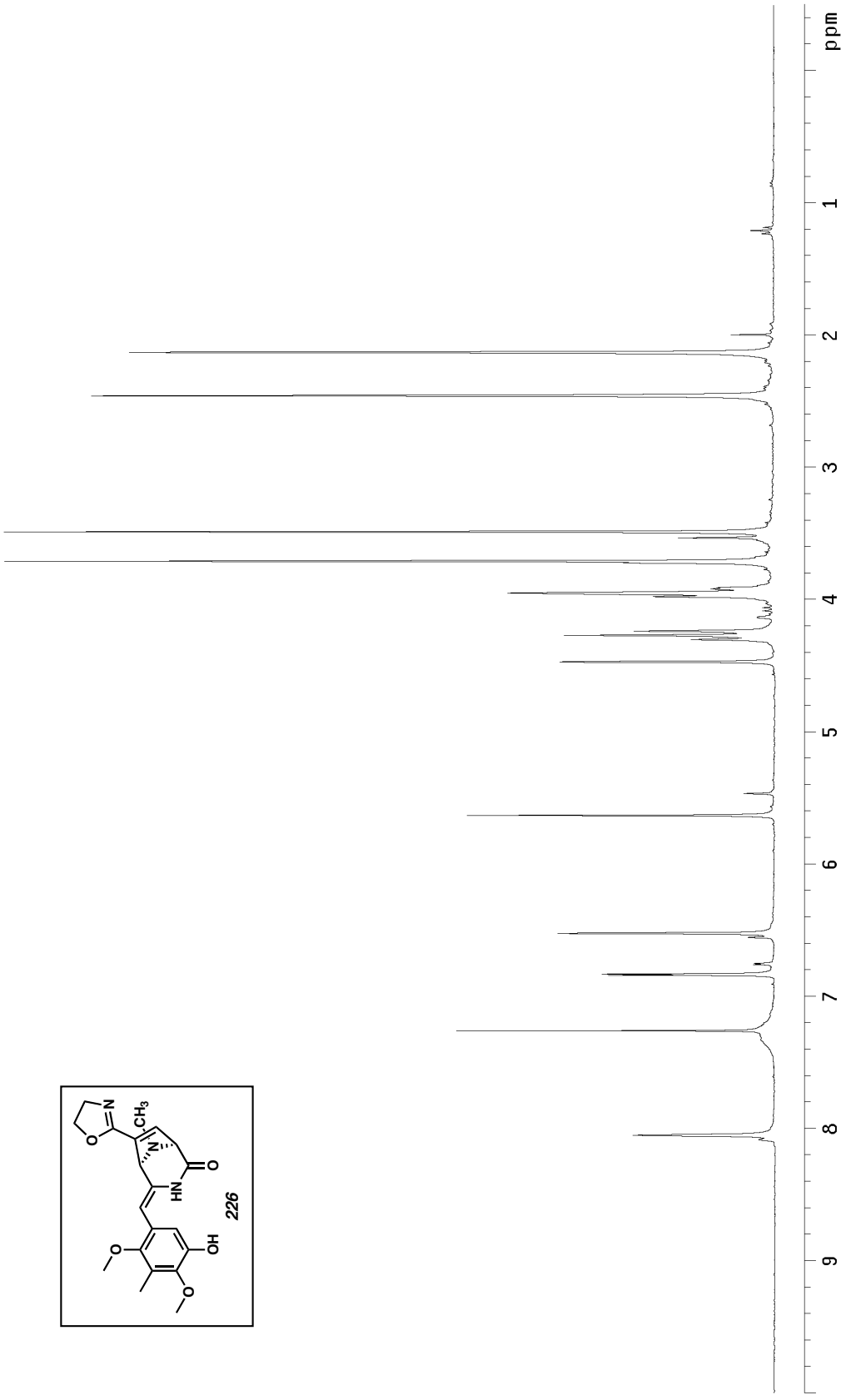


Figure A4.43 ^{1}H NMR of compound **226** (300 MHz, $CDCl_3$)

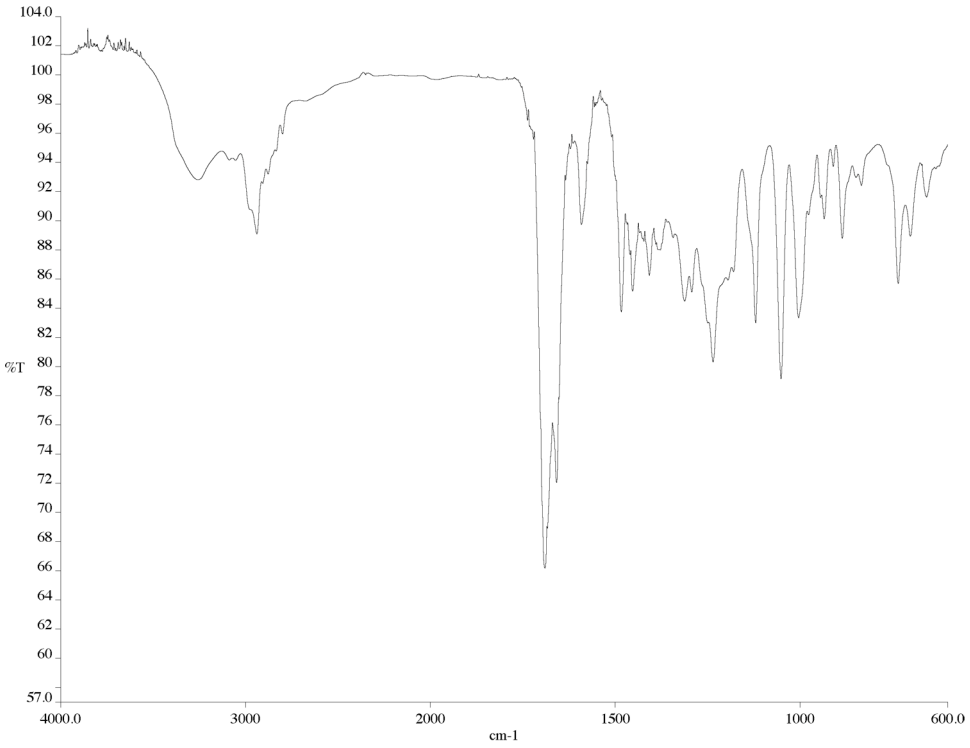


Figure A4.44 IR of compound **226** (NaCl/film)

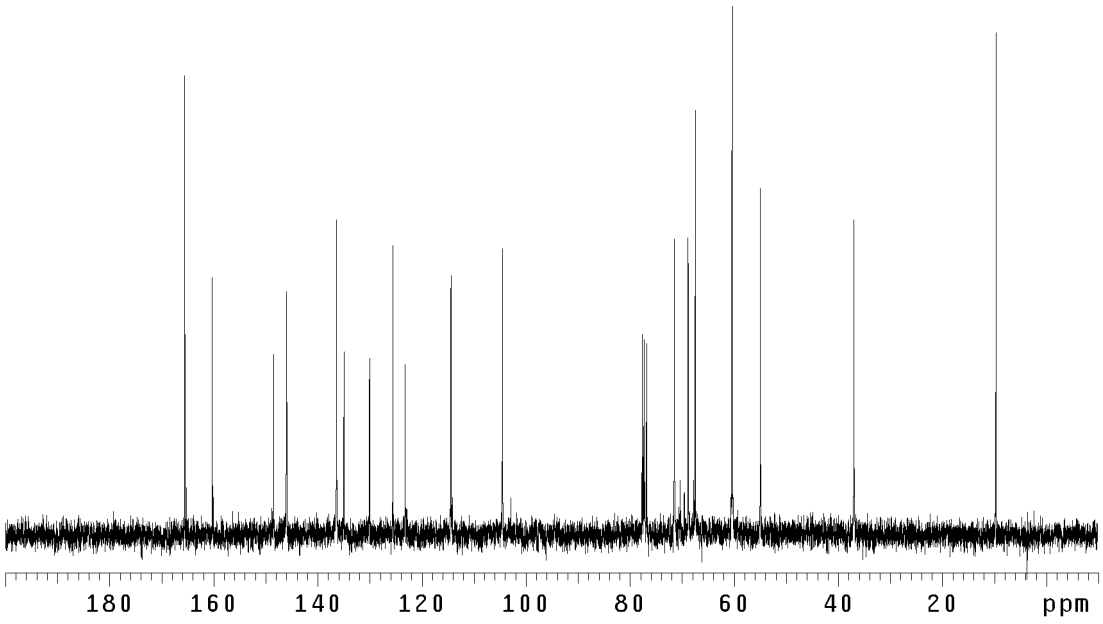


Figure A4.45 ^{13}C NMR of compound **226** (75 MHz, $CDCl_3$)

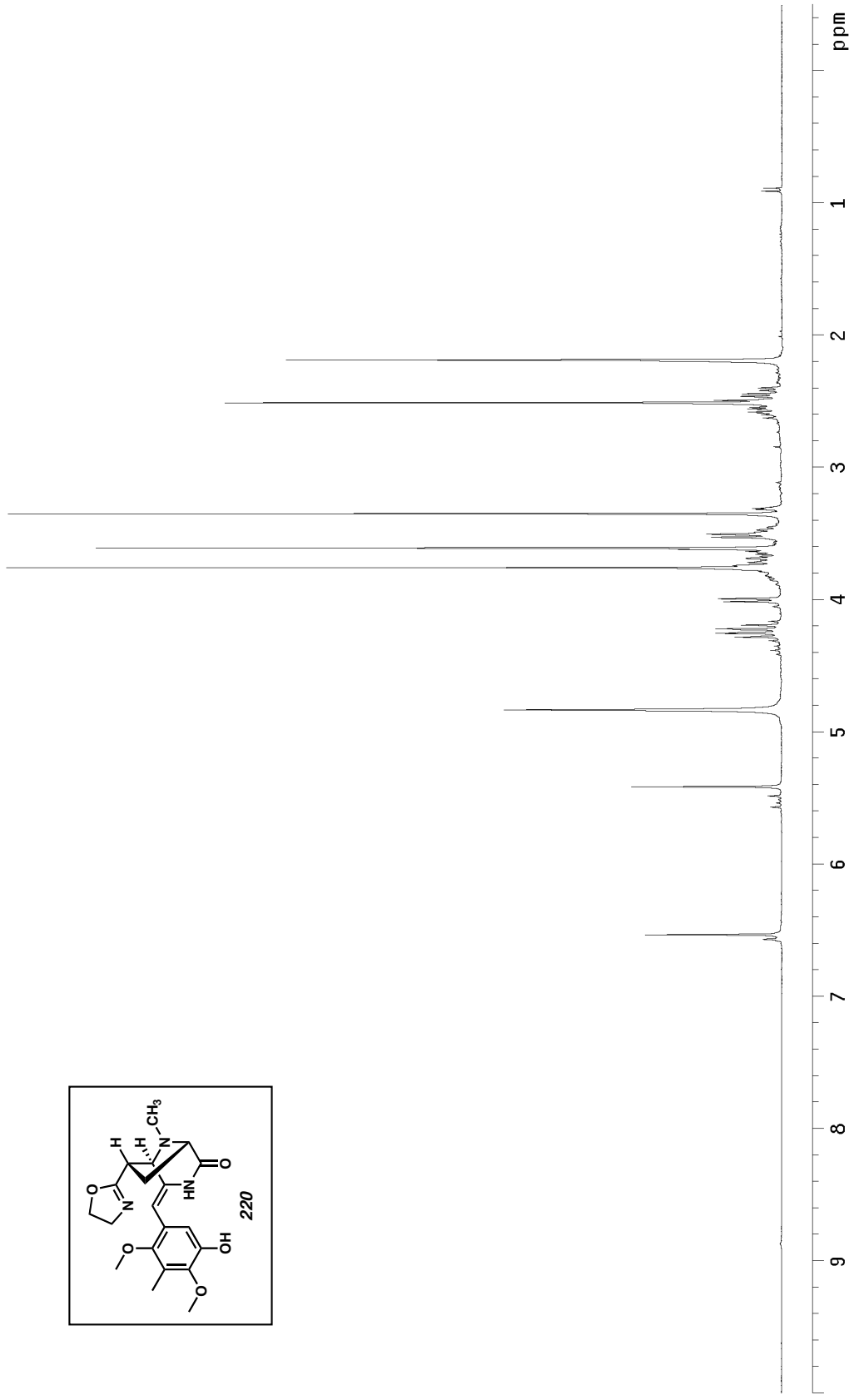


Figure A4.46 ^{1}H NMR of compound **220** (300 MHz, CD_3OD, impurity at 3.35 is CH_3OH)

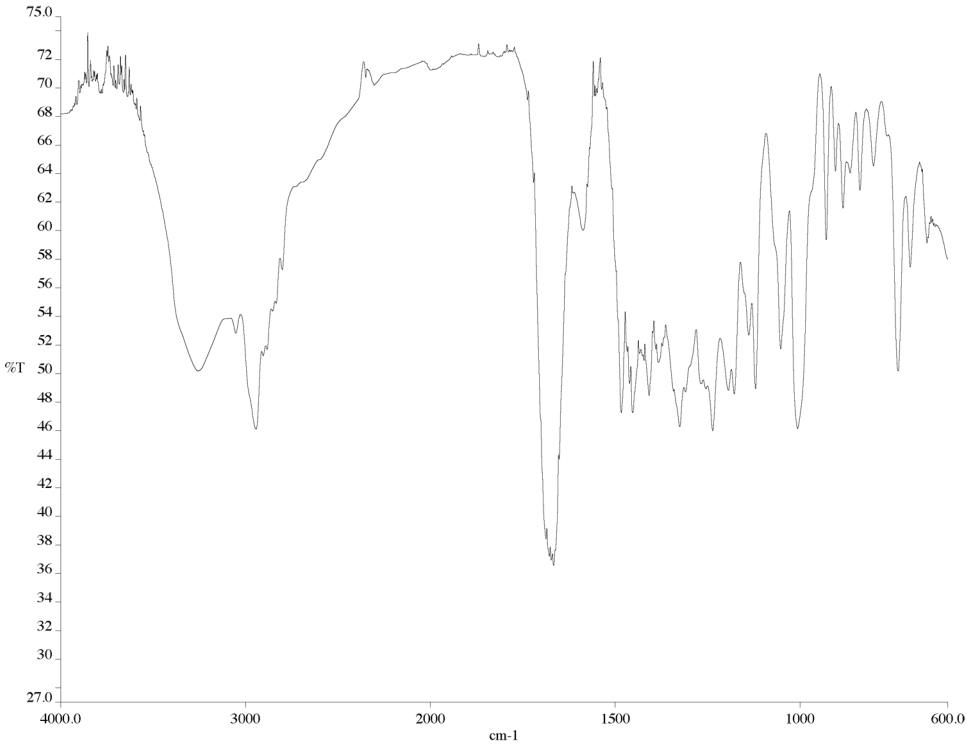


Figure A4.47 IR of compound **220** (NaCl/film)

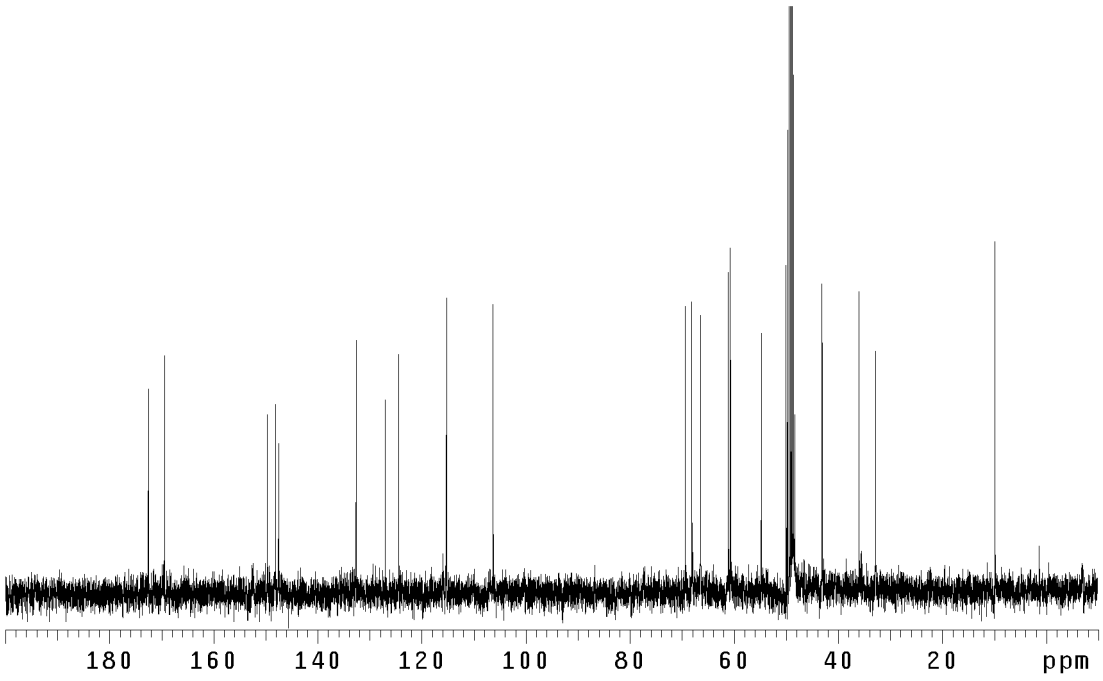


Figure A4.48 ^{13}C NMR of compound **220** (75 MHz, CD_3OD)

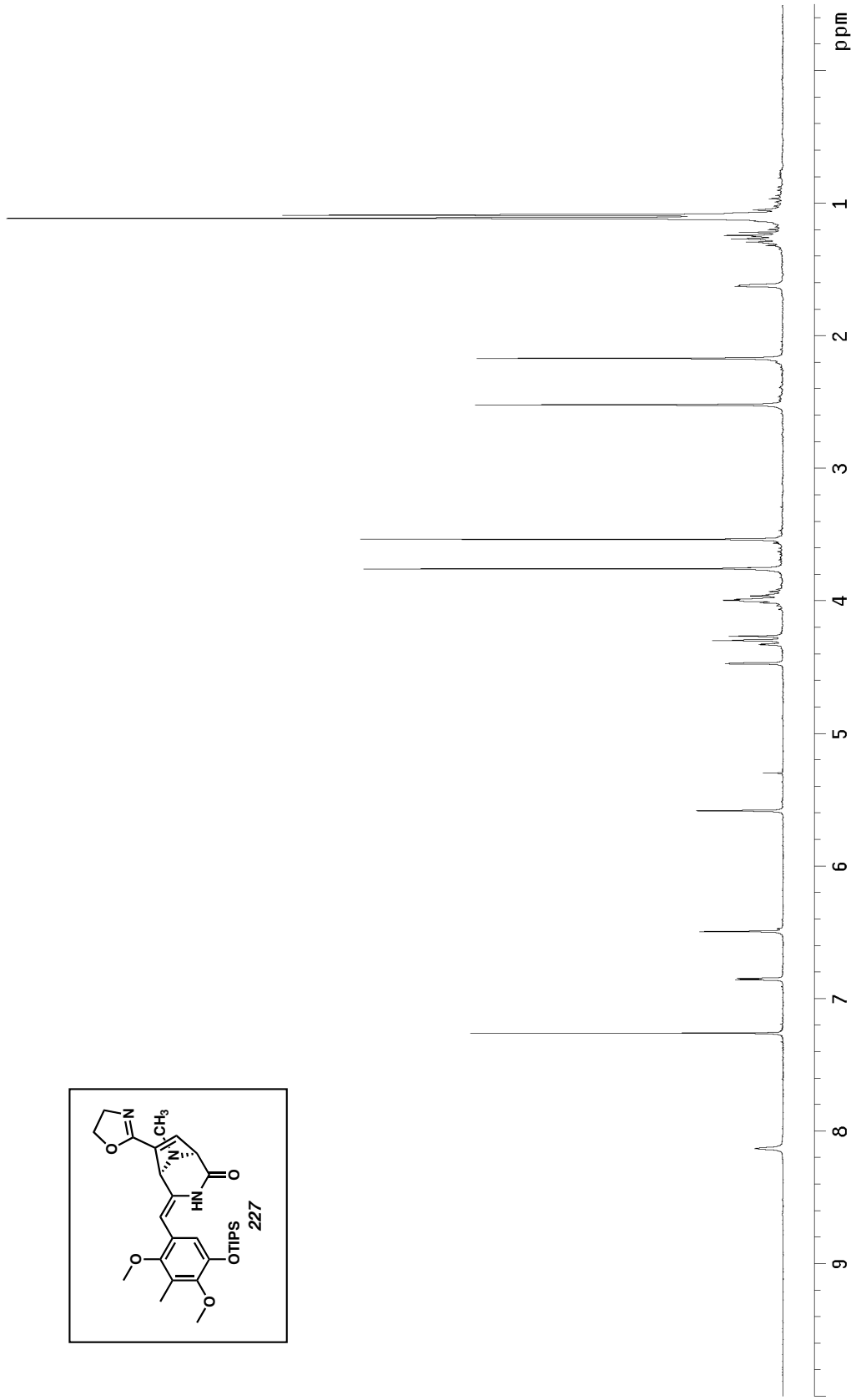


Figure A4.49 ^{1}H NMR of compound **227** (300 MHz, $CDCl_3$)

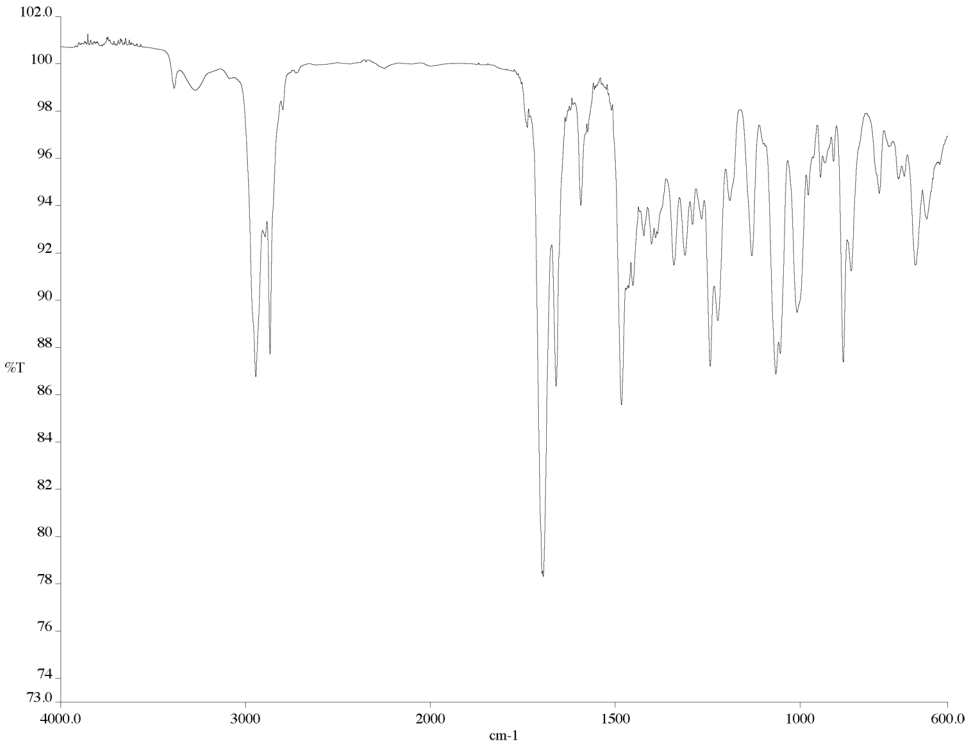


Figure A4.50 IR of compound **227** (NaCl/film)

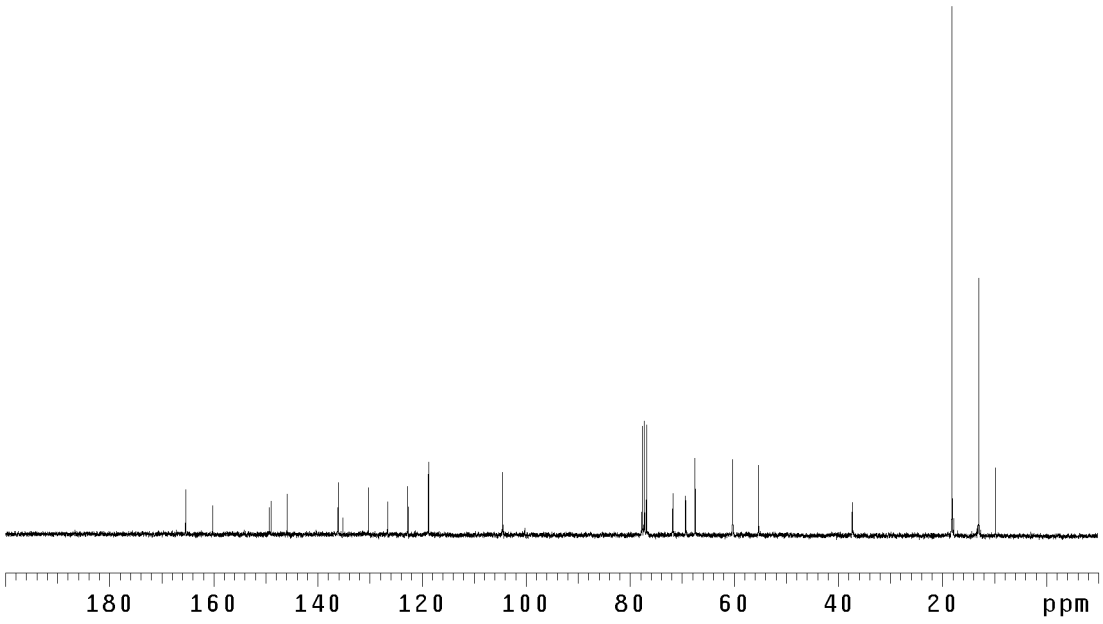


Figure A4.51 ^{13}C NMR of compound **227** (75 MHz, $CDCl_3$)

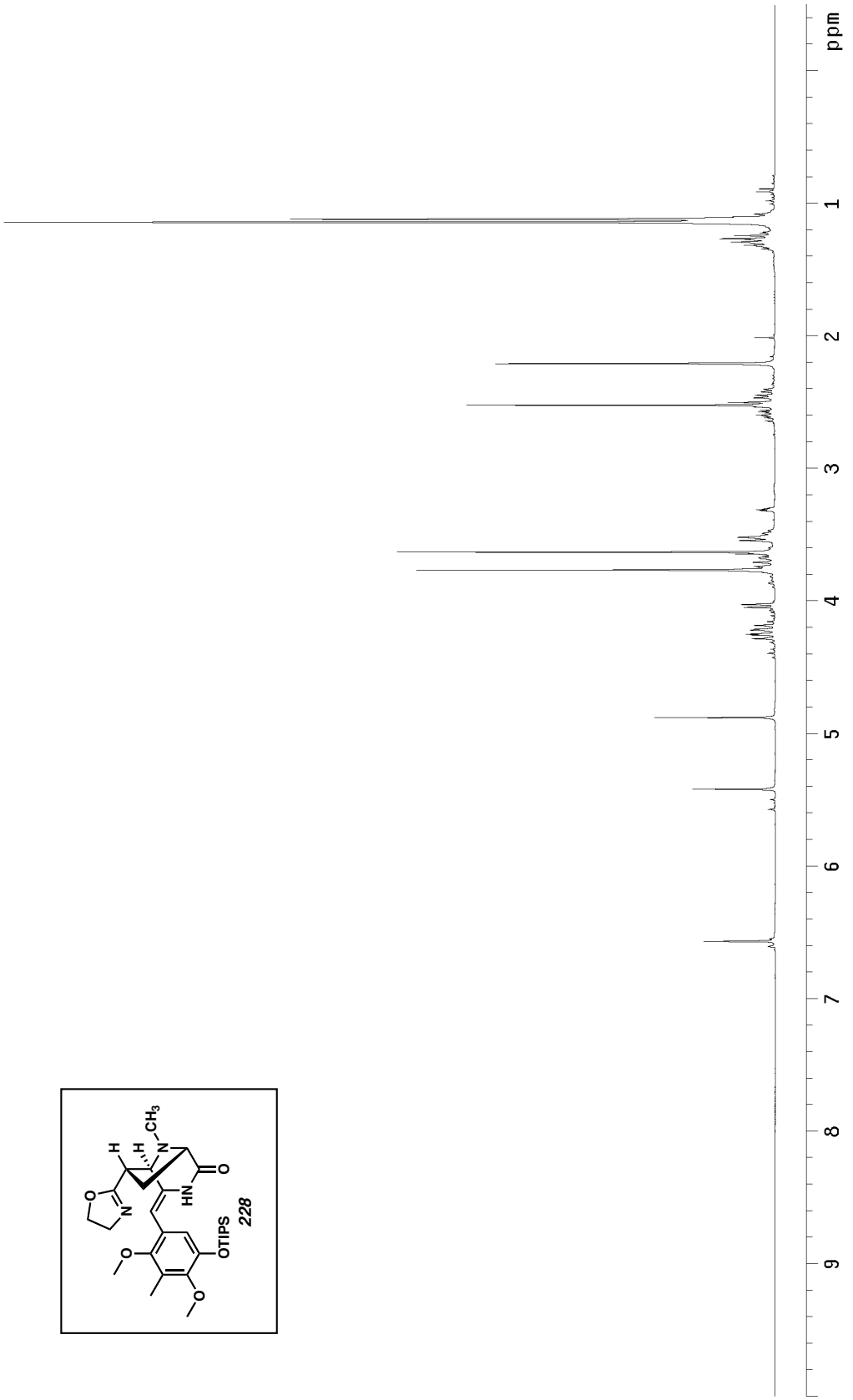


Figure A4.52 ^{1}H NMR of compound **228** (300 MHz, CD_3OD)

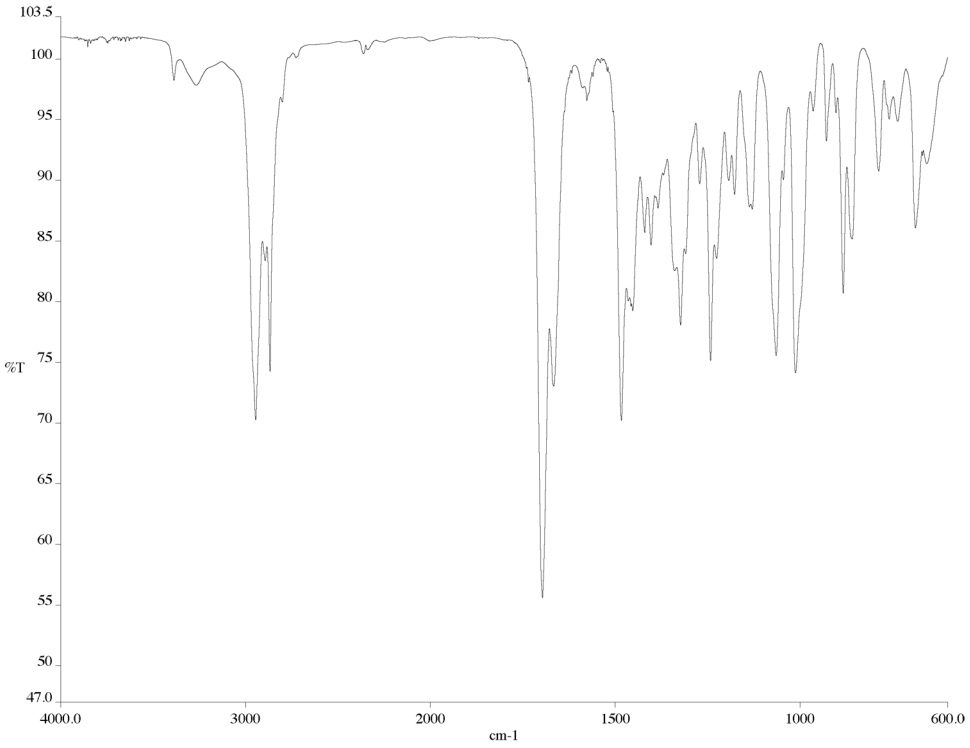


Figure A4.53 IR of compound **228** (NaCl/film)

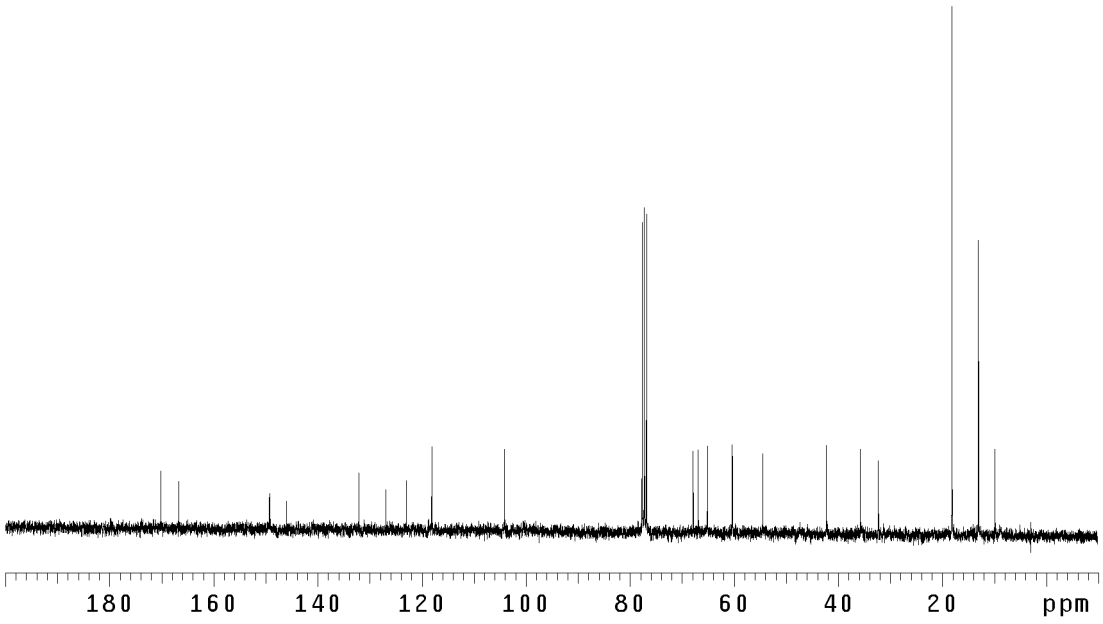


Figure A4.54 ^{13}C NMR of compound **228** (75 MHz, $CDCl_3$)

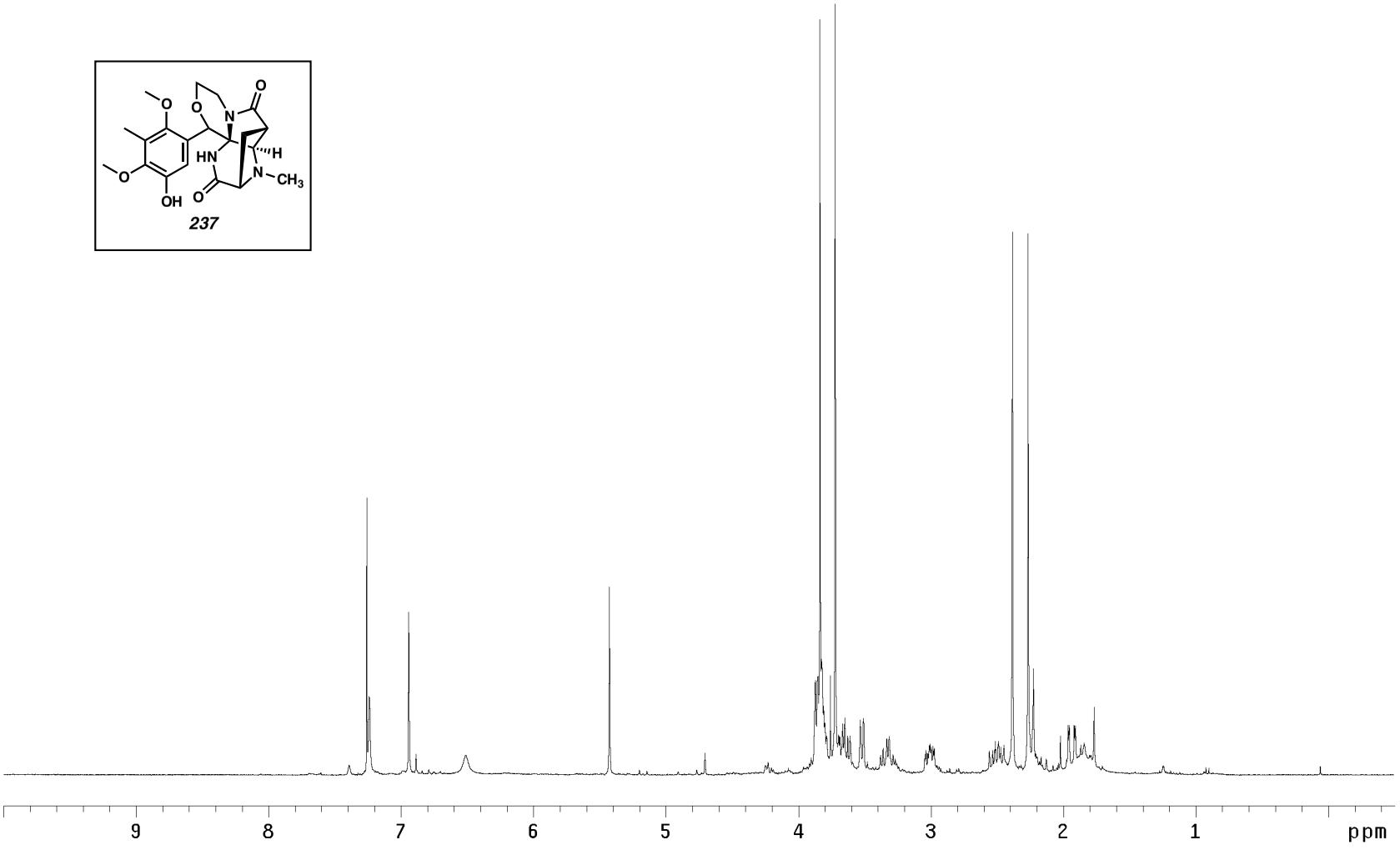


Figure A4.55 ^{1}H NMR of compound **237** (300 MHz, $CDCl_3$)

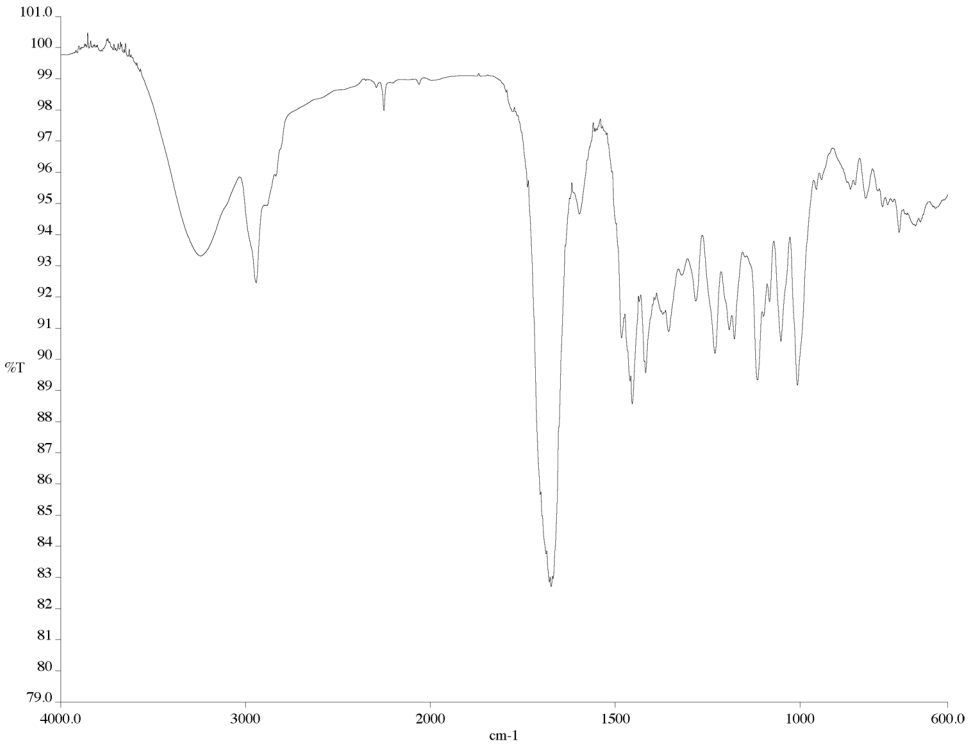


Figure A4.56 IR of compound **237** (NaCl/film)

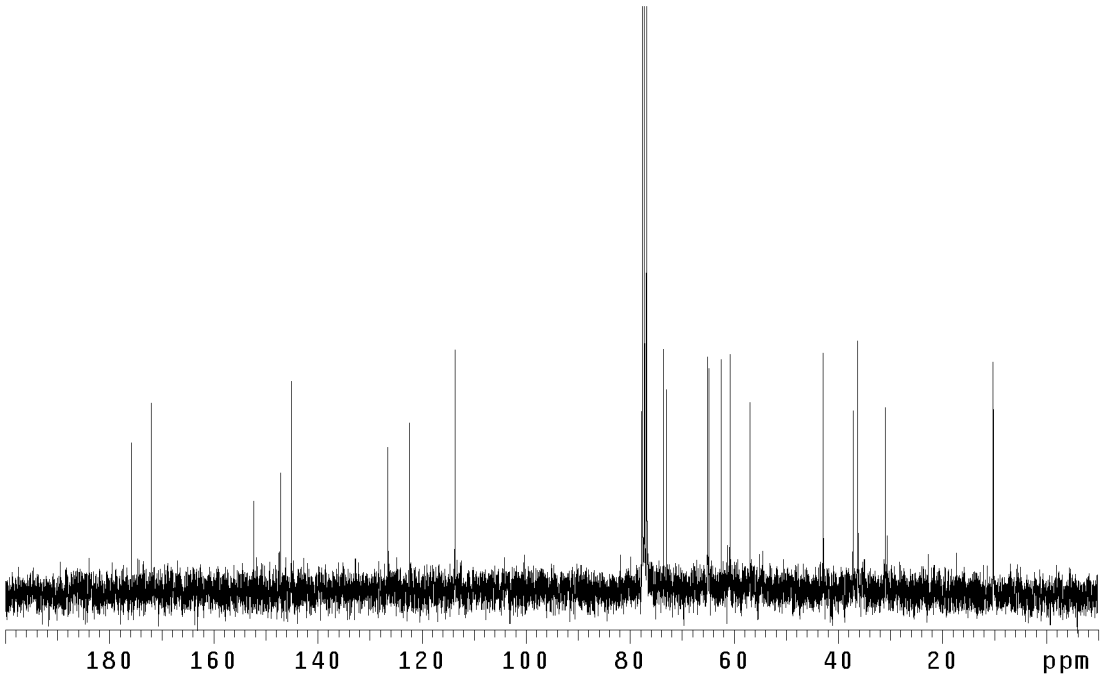


Figure A4.57 ^{13}C NMR of compound **237** (75 MHz $CDCl_3$)

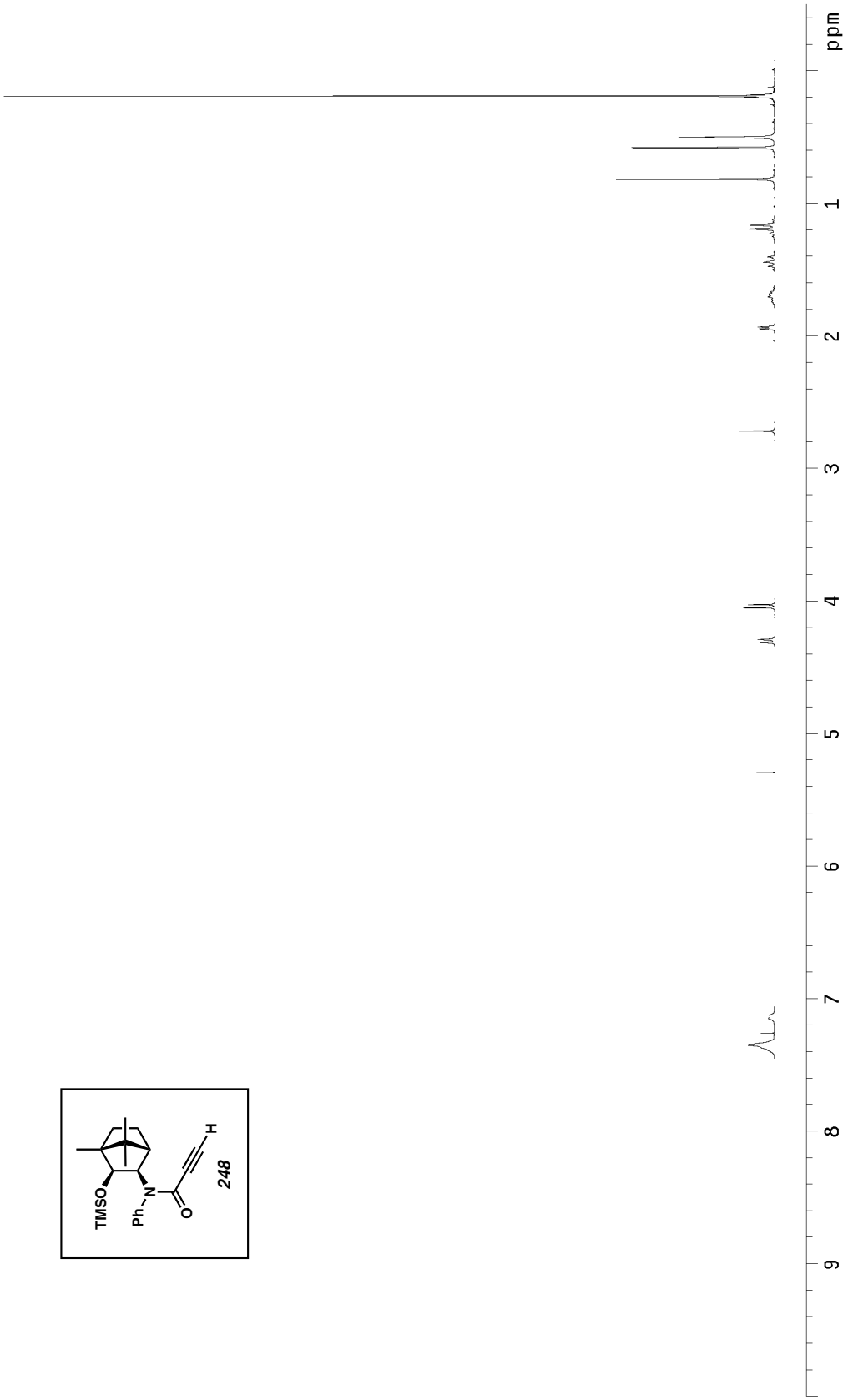


Figure A4.58 ^{1}H NMR of compound **248** (300 MHz, $CDCl_3$)

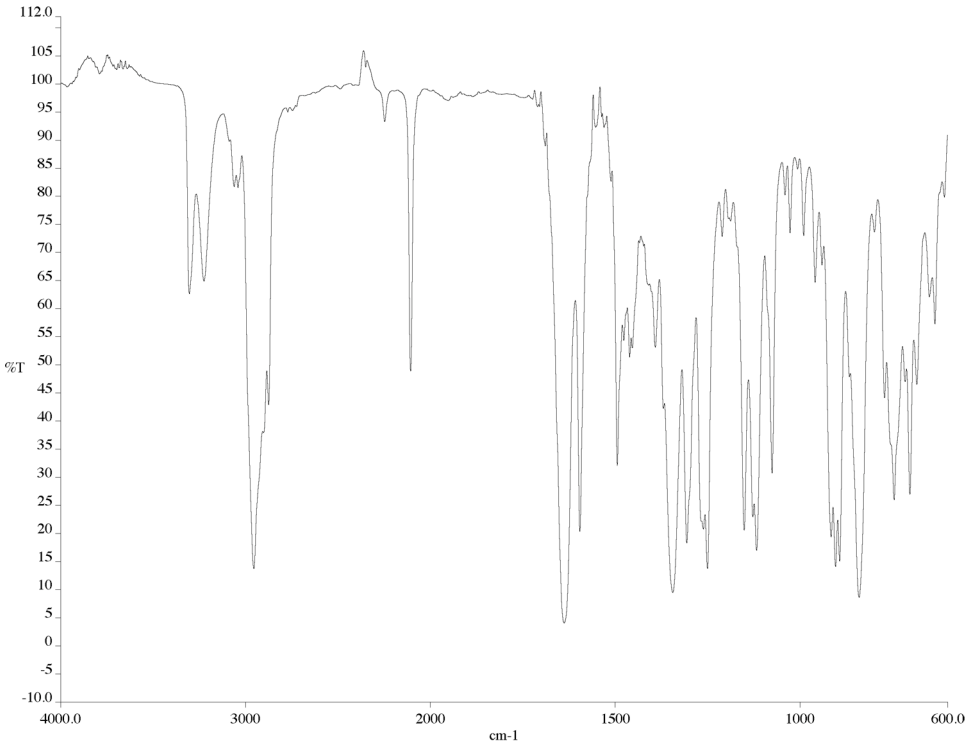


Figure A4.59 IR of compound **248** (NaCl/film)

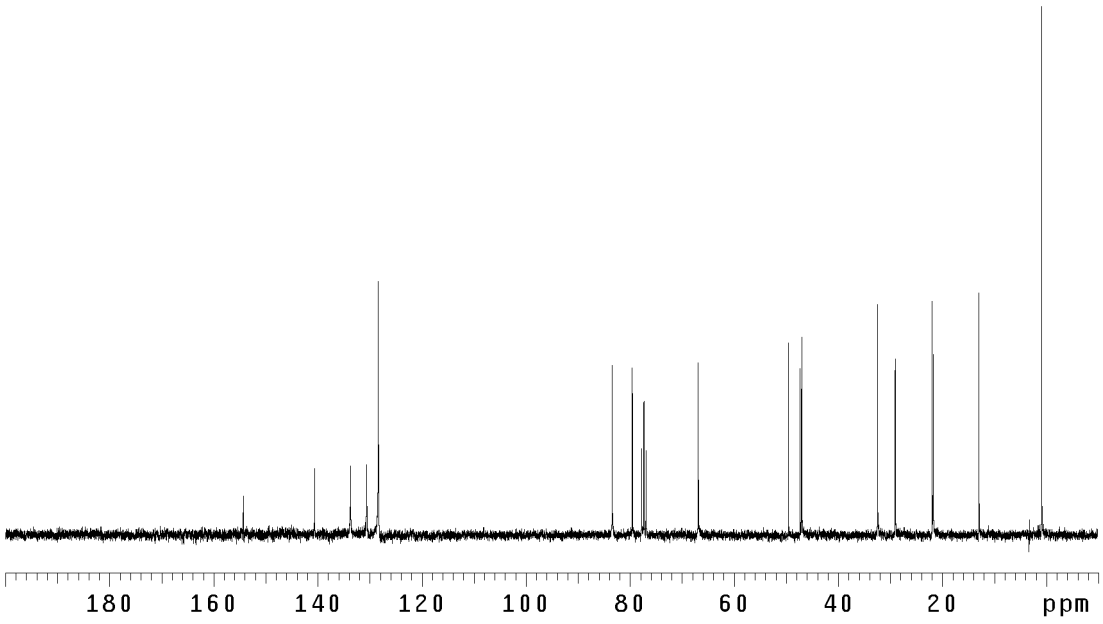


Figure A4.60 ^{13}C NMR of compound **248** (75 MHz, $CDCl_3$)

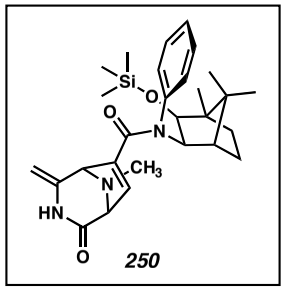


Figure A4.61 ^{1}H NMR of compound **250** (300 MHz, $CDCl_3$)

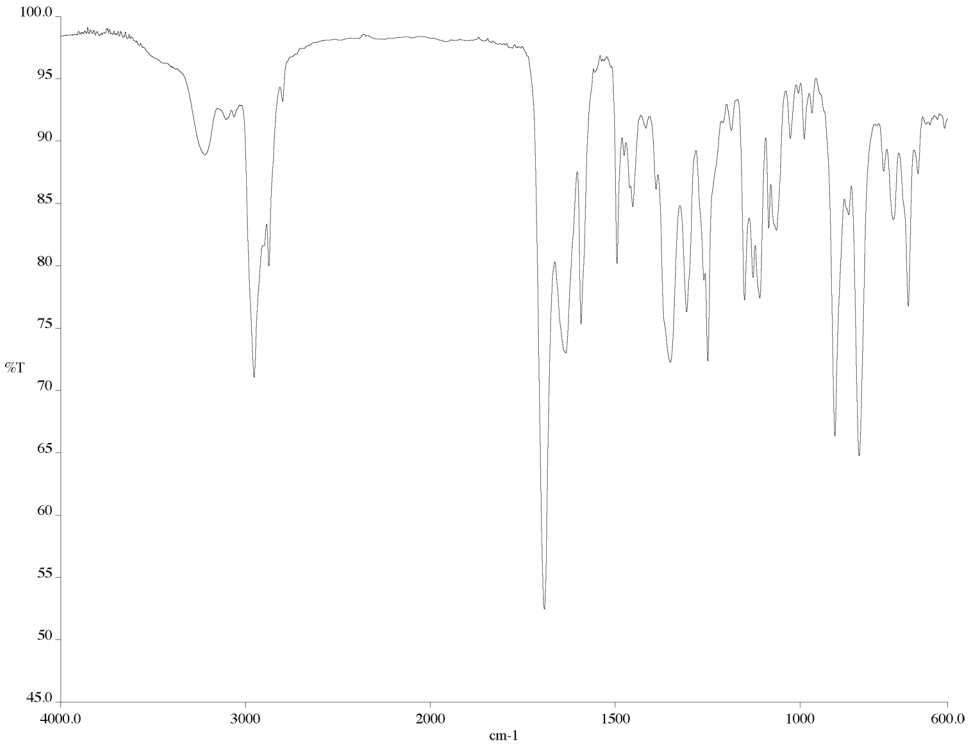


Figure A4.62 IR of compound **250** (NaCl/film)

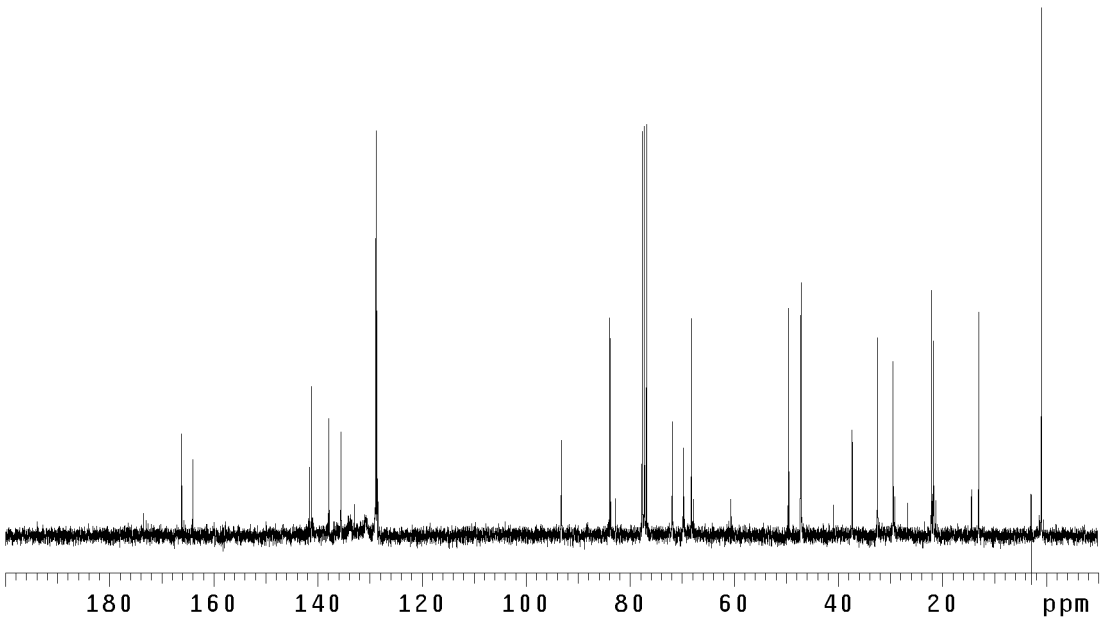


Figure A4.63 ^{13}C NMR of compound **250** (75 MHz, $CDCl_3$)

APPENDIX FIVE

Notebook Cross-Reference for New Compounds†

Table A5.1 Compounds in Chapter Two: The First Total Synthesis of (–)-Lemonomycin

Compound	^{1}H NMR	^{13}C NMR	IR
128	ERA-VIII-59.1	ERA-VIII-59.1	ERA-VIII-59.1
129	ERA-V-33.1	ERA-V-33.1	ERA-V-33.1
119	ERA-XIV-125.1	ERA-XIV-125.1	ERA-XIV-125.1
132	ERA-XIV-129.1	ERA-XIV-129.1	ERA-XIV-129.1
133	ERA-XIV-71.1	ERA-XIV-71.1	ERA-V-37.3
136	ERA-XIV-71.3	ERA-XIV-71.3	ERA-XV-85.1
138	ERA-XIV-133.1	ERA-XIV-133.1	ERA-XIV-133.1
149	ERA-IX-129.1	ERA-IX-129.1	ERA-IX-129.1
150	ERA-IX-201.1	ERA-IX-201.1	ERA-IX-201.1
147	ERA-VIII-35.1	ERA-VIII-35.1	ERA-VIII-35.1
157	ERA-V-223a	ERA-V-223a	ERA-V-223a
154	ERA-V-219.1	TYL-I-179.1	TYL-I-179.1
156	ERA-VIII-135.1	ERA-VIII-135.1	ERA-VIII-135.1
142	ERA-VI-131.1	ERA-VI-131.1	ERA-VI-131.1
158	ERA-VII-139.1a	ERA-VII-139.1a	ERA-VII-139.1a
159	ERA-VIII-249.1	ERA-VIII-249.1	ERA-VIII-249.1
161	ERA-VIII-259.1	ERA-VIII-259.1	ERA-VIII-259.1
162	ERA-VII-221.1	ERA-VII-221.1	ERA-VII-233.1
163	ERA-VII-229.1	ERA-VII-229.1	ERA-VII-229.1
165	ERA-VI-150.2		
168	ERA-VII-269.1	ERA-VII-245.1	ERA-VII-245.1
169	ERA-VII-247.1	ERA-VII-247.1	ERA-VII-247.1
167	ERA-X-249.1	ERA-X-249.1	ERA-X-249.1
172	ERA-IX-151.1	EGC-III-Weinreb	EGC-III-Weinreb
173	ERA-IX-155.1	EGC-II-41	EGC-II-41
174	ERA-IX-153.1	EGC-III-81.3	EGC-III-81.3
175	ERA-IX-177.1	EGC-II-63.1	EGC-II-63.1
176	ERA-IX-251.1	EGC-II-137.2	EGC-III-87.2
179	ERA-IX-273.1	EGC-III-91.1	EGC-III-91.1
180	ERA-IX-299.1	EGC-III-95.2	EGC-III-95.2
181	ERA-IX-275.1	EGC-III-97.1	EGC-III-97.1
166	ERA-X-79.3	EGC-III-99.1	ERA-X-227.1
182	ERA-X-141.1a	ERA-X-81.1	ERA-X-141.1
184	ERA-X-49.1		
186	ERA-X-247.1	ERA-X-247.1	ERA-X-247.1
187	ERA-X-125.1		
1	ERA-X-259.1	ERA-X-259.1	ERA-X-259.1
iii	ERA-X-237.1		

Table A5.2 Compounds in Chapter Three: Progress Toward the Synthesis of (+)-Cyanocycline A

Compound	^{1}H NMR	^{13}C NMR	IR
207	ERA-XIV-167.1	ERA-XIV-167.1	ERA-XIV-167.1
204	ERA-XV-41.1	ERA-XV-41.1	ERA-XV-41.1
209	ERA-XV-43.1	ERA-XV-43.1	ERA-XV-43.1
211	ERA-XV-51.1a	ERA-XV-51.1	ERA-XV-51.1
212	ERA-XV-49.1	ERA-XV-49.1	ERA-XV-49.1
203	ERA-XV-59.1	ERA-XV-59.1	ERA-XV-59.1
213	ERA-XIV-163.1	ERA-XIV-163.1	ERA-XIII-299.1
201	ERA-XV-61.2	ERA-XV-61.2	ERA-XV-61.2
225	ERA-XIV-115.1	ERA-XIV-115.1	ERA-XIV-123.1
223	ERA-XIV-131.1H	ERA-XIV-131.1c2	ERA-XIV-131-1aa
224	ERA-XIII-31.1	ERA-XIV-157.1	ERA-XIV-157.1
222	ERA-XIV-159.1	ERA-XIV-159.1	ERA-XIV-159.1
221	ERA-XIV-165.1	ERA-XIV-165.1	ERA-XIV-165.1
255	ERA-XIV-187.1	ERA-XIV-187.1	ERA-XIV-187.1
226	ERA-XIV-177.1	ERA-XIV-177.1	ERA-XIV-177.1
220	ERA-XIV-185.1	ERA-XIV-185.1	ERA-XIV-185.1
227	ERA-XV-35.1	ERA-XV-35.1	ERA-XV-35.1
228	ERA-XV-63.1	ERA-XV-45.1	ERA-XV-45.1
237	ERA-XIV-271.1a	ERA-XIV-271.1a	ERA-XIV-271.1a
248	KMA-II-279.3	KMA-III-85.1	KMA-III-85.1
250	KMA-III-107.2	KMA-III-105.2c	KMA-III-79.3

† Compounds are listed in the order of appearance in appendices two and four.

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ABOUT THE AUTHOR

Eric Robert Ashley was born in Helena, Montana, on August 20th, 1977, a time when cows still grazed on the lawn outside Saint Peter's Hospital. He is the child of Sandi and David, and the younger brother by two years of Laurie. After a brief stint in Lawrence, Kansas, the Ashley family raised Eric in Montana for his childhood and teenage years. During that time he learned to love the wilderness, hiking, and skiing. Eric became an avid soccer player and an earnest, if ungifted, clarinetist. Eric attended Helena High School and graduated as the salutatorian of his class in the spring of 1996.

Eric then traveled cross-country to Cambridge, Massachusetts, where he attended Harvard College. Eric rowed for the freshman and Winthrop House crews, was an active member of the Catholic Students Association and the Environmental Action Committee, and co-founded the Harvard Chapter of the Sierra Club. After considering a concentration in Folklore and Mythology, Eric chose to study chemistry with a focus on organic synthesis and chemical biology. Eric conducted research on peptide nucleic acids under the advisement of Professor David Liu. He also spent a summer synthesizing petromyzonol sulfate congeners at Cayman Chemical in Ann Arbor, Michigan. Eric graduated Magna cum Laude in June of 2000 with an Arts Baccalaureate in chemistry.

In the late summer of 2000, Eric moved to Pasadena, California, where he began doctoral research with Professor Brian Stoltz at the California Institute of Technology. In July of 2004, Eric married Olivia Ann Tudor. Eric completed his research on the synthesis of tetrahydroisoquinoline natural products in the autumn of 2005, and will receive his Ph.D. at commencement in 2006. Eric will begin postdoctoral studies with Professor Eric Jacobsen at Harvard University in January of 2006.