THE ADAPTIVE NATURE OF PALLADIUM REACTIVITY IN SYNTHESIS

Thesis by

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To my family

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ABSTRACT

Both Pd(0) and Pd(II) have had, and continue to have, far-reaching impacts on organic synthesis. The versatile nature of palladium, in conjunction with the mechanistic understanding and predictive models that have been elucidated, has permitted a wealth of exploration into the seemingly endless potential of this metal. The utility of palladium is described in the context of the syntheses of the pharmaceutical agents Prozac® and Singulair®, as well as the natural products dragmacidin F and telomestatin.

First, the palladium-catalyzed aerobic oxidative kinetic resolution for the enantioselective preparation of a variety of pharmaceutical substances, including Prozac® and Singulair®, is described. In this regard, the versatility of this resolution is further demonstrated by the diversity of the substrates chosen for this study, and for the first time this work extends the utility of the resolution to include amino alcohol derivatives and highly functionalized benzylic alcohols.

Secondly, an enantiodivergent strategy for the total chemical synthesis of both (+)- and (–)-dragmacidin F from a single enantiomer of quinic acid has been developed and successfully implemented. Although unique, the synthetic routes to these antipodes share a number of key features, including novel Pd(0) reductive isomerization reactions, Pd(II)-mediated oxidative carbocyclization reactions, halogen-selective Suzuki couplings, and high-yielding late-stage Neber rearrangements.

Finally, progress toward the total synthesis of the potent telomerase inhibitor telomestatin is described. Palladium-mediated cross-coupling reactions are employed to assemble oligooxazole intermediates from oxazole building blocks. Additionally, this strategy utilizes a minimum number of protecting groups, and proposes a unique aryl–aryl macrocyclization as the last step of the synthesis. In addition to the biological relevance of the desired target, a successful total synthesis of telomestatin would also enable rapid access to the preparation of telomestatin analogs. This would allow for the investigation of key interactions between telomestatin and the G-quadruplex.

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LIST OF ABBREVIATIONS

Å	Ångstrom
$[\alpha]_D$	specific rotation at wavelength of sodium D line
Ac	acetyl, acetate
app.	apparent
aq.	aqueous
Ar	aryl
atm	atmosphere
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOXAX	2,2'-Bis(oxazolyl)-1,1'-binaphthyl
bp	boiling point
BQ	benzoquinone
br	broad
Bu	butyl
n-Bu	butyl
t-Bu	*tert*-Butyl
c	concentration for specific rotation measurements
°C	degrees Celsius
calc'd	calculated
cat.	catalytic
Cbz	carbobenzyloxy
CCDC	Cambridge Crystallographic Data Centre
CDI	1,1'-carbonyldiimidazole
CI	chemical ionization

comp.	complex
Cy	cyclohexyl
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
dba	dibenzylideneacetone
dec.	decomposition
dppb	1,4-bis(diphenylphosphino)butane
dppf	1,1'-bis(diphenylphosphino)ferrocene
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DNA	(deoxy)ribonucleic acid
dr	diastereomeric ratio
EC_{50}	median effective concentration (50%)
EDC	*N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide
ee	enantiomeric excess
EI	electron impact
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
FAB	fast atom bombardment
g	gram(s)
GC	gas chromatography
gCOSY	gradient-selected correlation spectroscopy
h	hour(s)

HIV	human immunodeficiency virus
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
HSV	herpes simplex virus
$h\nu$	light
Hz	hertz
IC_{50}	median inhibition concentration (50%)
IR	infrared (spectroscopy)
J	coupling constant
λ	wavelength
L	liter
m	multiplet or milli
m	meta
m/z	mass to charge ratio
μ	micro
M	metal or molar
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s)
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
n	nano
N	normal

nbd	norbornadiene
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
Nu	nucleophile
[O]	oxidation
o	ortho
p	para
PDC	pyridinium dichromate
Pin	pinacolato
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
PhH	benzene
ppm	parts per million
PPTs	pyridinium *p*-toluenesulfonate
Pr	propyl
i-Pr	isopropyl
Py	pyridine
q	quartet
ref	reference
R_f	retention factor
rt	room temperature
s	singlet or strong or selectivity factor
sat.	saturated
SEM	(trimethylsilyl)ethoxymethyl

SET	single electron transfer
sp	species or (–)-sparteine
t	triplet
TBAF	tetrabutylammonium fluoride
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TCNE	tetracyanoethylene
Tf	trifluoromethanesulfonyl (trifyl)
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMS	trimethylsilyl
TON	turnover number
Tr	trityl
Ts	*p*-toluenesulfonyl (tosyl)
UV	ultraviolet
w	weak
w/*v*	weight to volume
v/*v*	volume to volume
X	anionic ligand or halide

CHAPTER ONE

Palladium in Organic Synthesis

1.1 Background

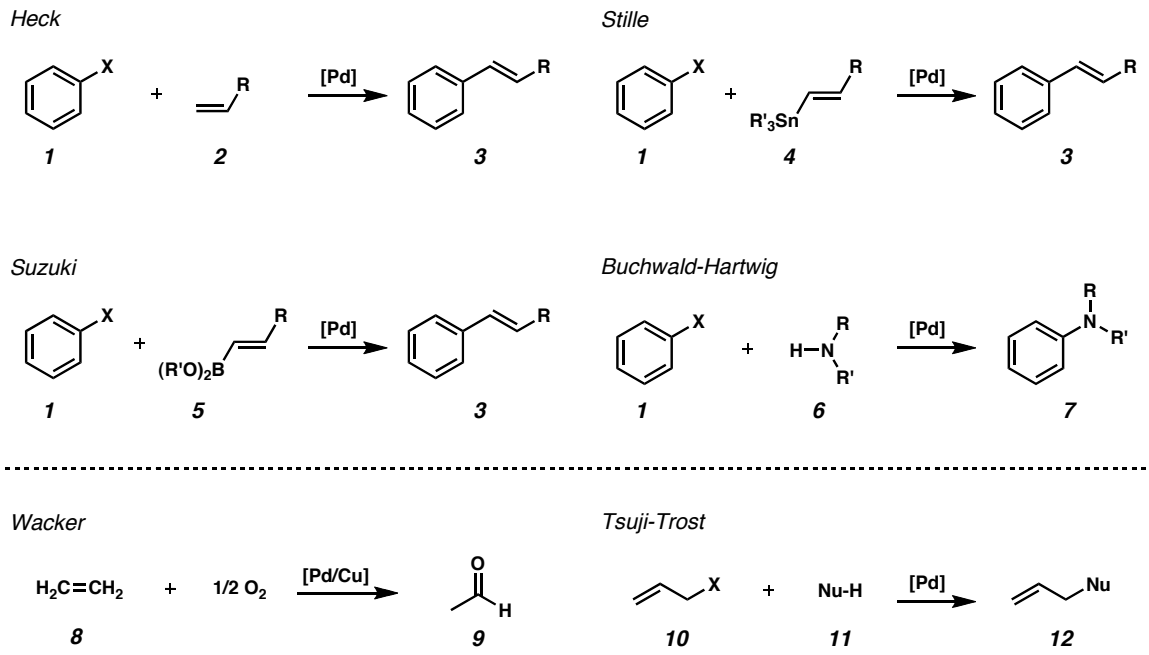
1.1.1 Introduction

Palladium (Pd), named after the asteroid Pallas, is arguably the most versatile and ubiquitous metal in modern organic synthesis.[1,2] Palladium-mediated processes have become essential tools, spanning countless applications in the syntheses of natural products, polymers, agrochemicals, and pharmaceuticals. In part, this far-reaching scope is due to palladium's ability to participate in catalytic transformations, as well as its high functional group tolerance. Nearly every area of organic synthesis has been impacted by this versatile transition metal, which has fundamentally changed the way retrosynthetic analysis is approached.

Palladium can be used to conduct myriad transformations with organic molecules. In fact, there are a number of well-known name reactions that feature this metal, including the Heck, Suzuki, Stille, and Buchwald-Hartwig cross-couplings; the Wacker process;[3] and the Tsuji-Trost allylation (Scheme 1.1.1).[1,2] In addition, Pd also enables hydrogenation; hydrogenolysis; carbonylation; the formation of C–C, C–O, C–N, and C–S bonds; cycloisomerization; and even pericyclic reactions.[1,2] Palladium-based methods often proceed under mild conditions affording high yields, with excellent levels of stereo-, regio-, and chemoselectivity. Domino catalysis, where multiple Pd-catalyzed

transformations are carried out in a single operation, is also a powerful extension of this chemistry.[1u]

Scheme 1.1.1



1.2 Palladium(0) and Palladium(II)

1.2.1 Oxidation States of Palladium

Although palladium can exist in a number of different oxidation states, useful organic methods are dominated by the use of Pd(0) and Pd(II),[1,2] although the utility of Pd(IV)[4] has been steadily emerging in its own right. The remaining oxidation states have not, as of yet, found practical applications, and their observation remains rare.[5] The increased stability of the even-numbered oxidation states (e.g., 0, +2, +4) can be rationalized by the low tendency of palladium to undergo one-electron or radical processes; conversely, it readily participates in two-electron oxidation or reduction.[2a]

Palladium's ability to undergo facile and reversible two-electron operations has contributed to its widespread use as a catalyst, since each oxidation state can yield different chemistry (see Figure 1.2.1 for examples of reaction classes). Reactions such as cross-couplings and olefin hydrogenation are common to the Pd(0) platform, while transformations such as alcohol oxidation and cycloisomerization can be achieved using Pd(II).

Figure 1.2.1

Types of Transformations

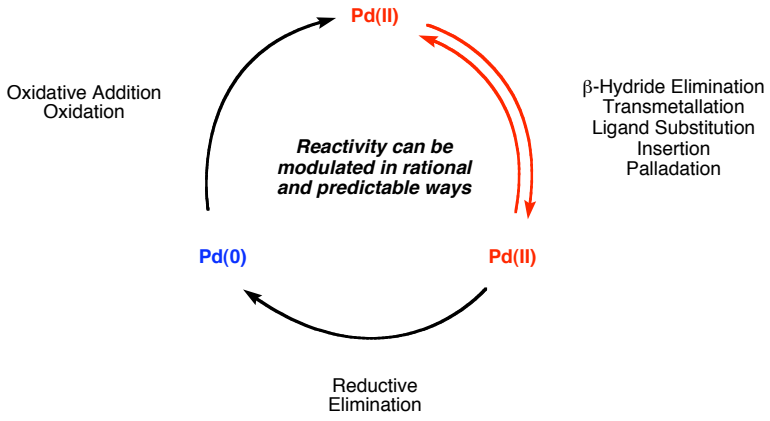
Pd^0	Pd^{II}
Cross-couplings	Wacker Process
Allylic Alkylation	Cycloisomerization
Hydrogenation	Alcohol Oxidation
Hydrogenolysis	Allylic Oxidation
Carbonylation	Allylic Rearrangements

1.2.2 General Reactivity

The bulk of the organopalladium literature is centered on the use of Pd(0) and Pd(II). Although many reports do not clearly delineate the active catalyst (e.g., Pd(II) precatalysts can be used to generate Pd(0) in situ), in general, palladium-catalyzed reactions proceed through the simplified cycle presented in Figure 1.2.2. Pd(0) can undergo either oxidation or oxidative addition, which affords a Pd(II) complex. Pd(II) complexes can generate new Pd(II) complexes via processes such as β-hydride elimination, transmetallation, ligand substitution, insertion, or palladation. Finally, reductive elimination converts the Pd(II) complex back to Pd(0). This mechanistic understanding, combined with the ability of ligands and reaction parameters to modulate

the reactivity of palladium, has allowed for a substantial amount of rational design in this field.

Figure 1.2.2



1.2.3 Palladium(0) Reactivity

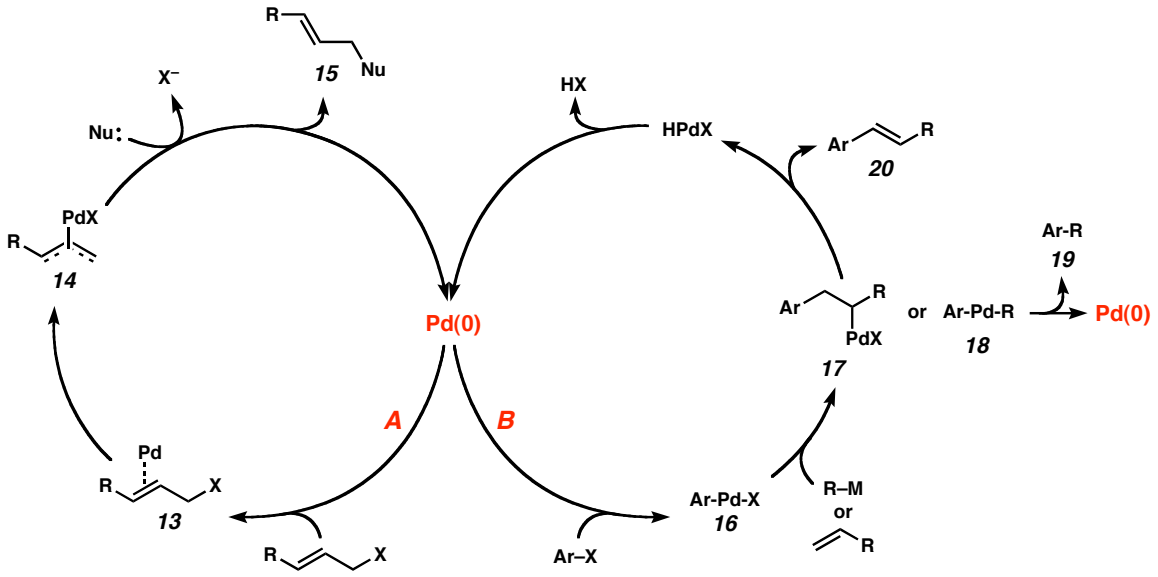
Palladium(0) catalysis has been the focal point of palladium research over the past several decades. A popular method of preparing Pd(0) complexes is via an in situ reduction of a Pd(II) species by reagents such as alkenes, alcohols, amines, phosphines, or metal hydrides. Considered to be nucleophilic, Pd(0) complexes contain a d^{10} palladium, and they are easily oxidized to the Pd(II) state; thus most of the catalytic processes using Pd(0) generally begin with oxidative addition. In general, increasing the electron density on palladium promotes oxidative addition.

One frequent mode of reactivity characteristic of Pd(0) involves the complexation of an olefin with an allylic leaving group, and subsequent oxidative addition (e.g., Pd(0) → **13** → **14**) to generate a Pd(II) π-allyl complex (**14**, Path A, Scheme 1.2.1). Subsequent

nucleophilic attack, which occurs predominately at the less-hindered carbon of the palladium π-allyl complex, affords the product (**15**) and regenerates the Pd(0) catalyst.

Another common reaction pathway for Pd(0) is regularly observed in cross-coupling chemistry. Specifically, oxidative addition to a molecular bond (e.g., Ar–X) forms an electrophilic Pd(II) complex (e.g., **16**, Path B). At this juncture, any number of Pd(II) reactions can take place, such as olefin insertion (**16** → **17**) or transmetallation (**16** → **18**). Pd(0) is eventually regenerated by a reductive elimination sequence; β-hydride elimination of **17** produces **20** and HPdX, which becomes Pd(0) and HX upon reductive elimination. Similarly, reductive elimination of **18** affords the product (**19**) and Pd(0) directly.

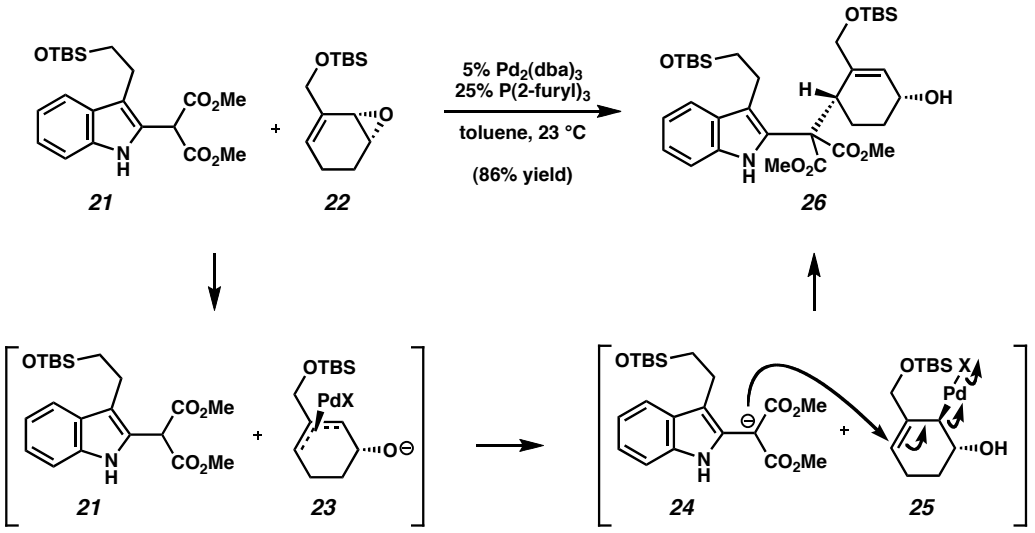
Scheme 1.2.1



Fukuyama recently carried out a relevant example of Pd(0) catalysis in the early steps of his total synthesis of (–)-strychnine.[6] Indole malonate **21** and vinyl epoxide **22**

were treated with Pd(0) at room temperature (Scheme 1.2.2). Initial oxidative addition to the vinyl epoxide produced Pd(II) π-allyl complex **23**, and the resulting alkoxide was quenched by malonate **21** to form **24**. The malonate anion (**24**) then attacked the electrophilic palladium(II) complex (**25**) in a stereo- and regioselective manner to yield the product (**26**). This product is an intermediate in the synthesis of (–)-strychnine, and was subsequently carried forward to complete the total synthesis.

Scheme 1.2.2



1.2.4 Palladium(II) Reactivity

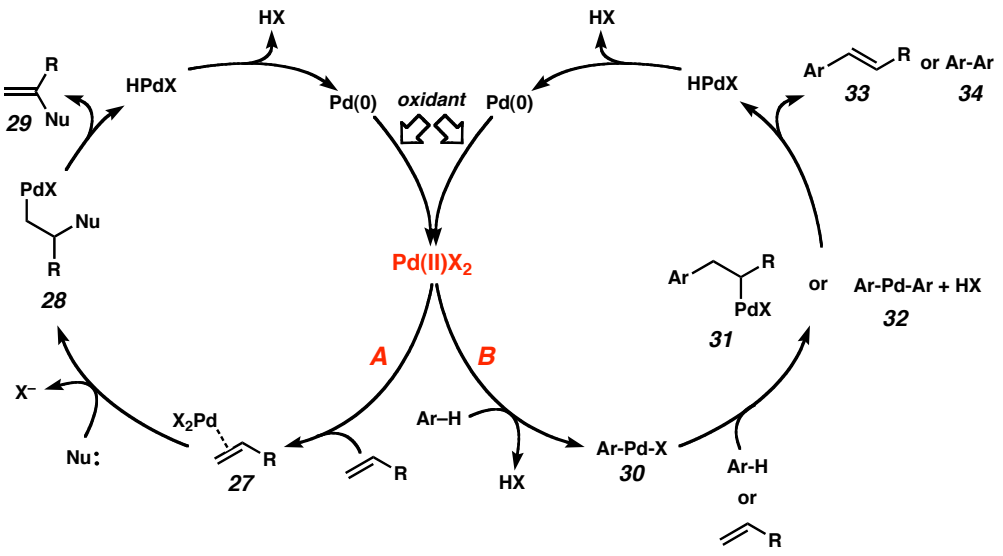
Palladium(II) catalysis, in contrast to palladium(0), has received significantly less attention from the synthetic community in the past, although there has been a revitalized interest within the last several years.[1i–k] Pd(II) complexes are typically electrophilic and air stable, and thus usually interact with electron-rich functionalities such as olefins, alkynes, and arenes. The lack of Pd(II) research may initially seem surprising, considering that Pd(II) also promotes useful modes of reactivity (see Figure 1.2.1).

However, one of the main complications that has been problematic in the development of Pd(II) methodology is the difficulty of reoxidizing Pd(0) → Pd(II). Completion of the catalytic cycle to regenerate Pd(II) requires the presence of a stoichiometric oxidant, such as $CuCl_2$, $Cu(OAc)_2$, benzoquinone, *tert*-butyl hydroperoxide (TBHP), MnO_2, HNO_3, and most recently O_2. Not unexpectedly, the addition of these oxidants to a reaction has often interfered with the catalyst/ligand system (or the substrates themselves), and has led to complications in maintaining chemo- or stereoselective processes.

A typical reaction with electrophilic Pd(II) commences with the complexation of an olefin by Pd(II) (**27**, Path A, Scheme 1.2.3). An intermolecular or intramolecular nucleophilic attack on the resulting olefin complex can then occur, generally at the more substituted position of the olefin (**28**, Path A—Wacker-type mechanism). Although any number of Pd(II) processes can occur at this stage (see Figure 1.2.2), the final product typically results from β-hydride elimination (e.g., **28** → **29**). The resultant palladium hydride, HPdX, then undergoes a reductive elimination–oxidation sequence to regenerate the active Pd(II) catalyst.[7]

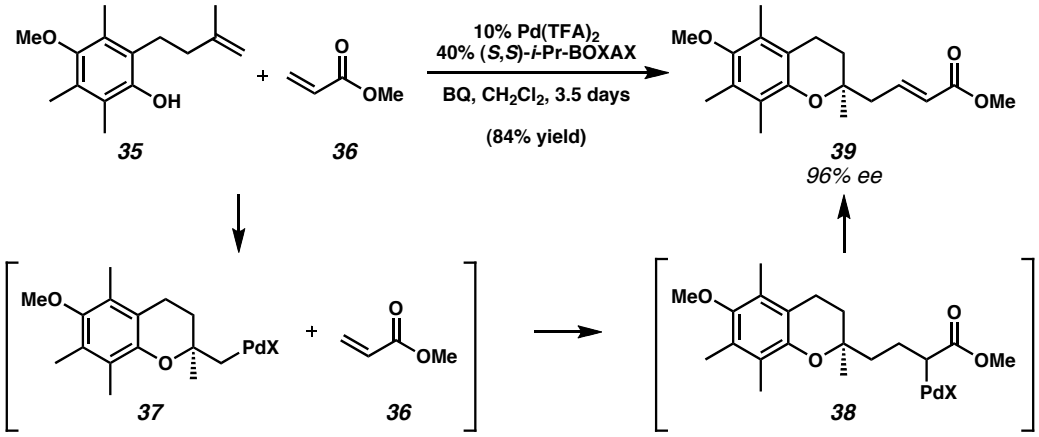
Alternatively, a pathway involving direct attack of the $Pd(II)X_2$ complex by a nucleophile (e.g, an arene) is also possible (**30**, Path B—Friedel-Crafts-type mechanism).[8] In a similar fashion, this complex (**30**) can then participate in traditional Pd(II) pathways such as a successive Friedel-Crafts type attack to form **31**, or olefin insertion to form **32**. Although different processes may be observed, β-hydride elimination and reductive elimination sequences are likely to be the final steps in the cycle prior to reoxidation of palladium.

Scheme 1.2.3



A recent report disclosed by Tietze pertaining to the synthesis of vitamin E highlights the synthetic utility of Pd(II).[9] Tietze's synthetic route relied upon a critical cyclization event, in which phenol **35** and methyl acrylate (**36**) were exposed to a chiral Pd(II) salt where (*S,S*)-*i*-Pr-BOXAX served as the ligand (Scheme 1.2.4). Enantiofacial coordination of the palladium to the olefin of phenol **35**, followed by oxypalladation, results in the formation of the key tertiary stereogenic center, which then leaves palladium(II) intermediate **37** without an accessible β-hydride. Without a competing β-hydride elimination pathway, intermediate **37** is able to react further, and underwent a Heck coupling with methyl acrylate (**36**) to afford Pd(II) complex **38**. Restoration of the enoate through β-hydride elimination then generated the product (**39**), as well as a Pd(II) hydride, X–Pd–H. Reductive elimination to liberate HX then afforded a Pd(0) species, which could be reoxidized to Pd(II) using benzoquinone. The chroman product (**39**) obtained by Tietze was later elaborated to furnish vitamin E.

Scheme 1.2.4



1.3 Conclusion

In summary, both Pd(0) and Pd(II) have had, and continue to have, far-reaching impacts on organic synthesis. The versatile nature of palladium, in conjunction with the mechanistic understanding and predictive models that have been elucidated, has permitted a wealth of exploration into the seemingly endless potential of this metal. Additionally, deficiencies in the Pd(II) and Pd(IV) literature are likely to be remedied as greater control over the oxidation of palladium(0) is achieved.

1.4 Notes and References

(1) (a) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, 107, 5318–5365. (b) Muzart, J. *J. Mol. Catal. A: Chem.* **2007**, *276*, 62–72. (c) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644–4680. (d) Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. *Adv. Synth. Catal.* **2006**, *348*, 23–39. (e) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873–2920. (f) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285–2309. (g) Muzart, J. *Tetrahedron* **2005**, *61*, 5955–6008. (h) Muzart, J. *Tetrahedron* **2005**, *61*, 9423–9463. (i) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400–3420. (j) Sigman, M. S.; Schultz, M. J. *Org. Biomol. Chem.* **2004**, *2*, 2551–2554. (k) Stoltz, B. M. *Chem. Lett.* **2004**, *33*, 362–367. (l) Tietze, L. F.; Ila, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453–3516. (m) Nishimura, T.; Uemura, S. *Synlett* **2004**, 201–216. (n) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2963. (o) Agrofoglio, L. A.; Gillaizeau, I.; Saito, Y. *Chem. Rev.* **2003**, *103*, 1875–1916. (p) Negishi, E.-I.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979–2017. (q) Kiss, G. *Chem. Rev.* **2001**, *101*, 3435–3456. (r) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066. (s) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067–3125. (t) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314–321. (u) Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959–5989. (v) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (w) Tsuji, J. *Synthesis* **1990**, 739–749.

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(3) For a recent review, see: Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev.* **2005**, *105*, 2329–2365 and references therein.

(4) For recent examples of Pd(IV) transformations, see the following references and references therein: (a) Desai, L. V.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5737–5740. (b) Yu, J. Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041–4047. (c) Daugulis, O.; Zaitsev, V. G.; Shabasov, D.; Pham, O.-N.; Lazareva, A. *Synlett* **2006**, 3382–3388. (d) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148–13149.

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(6) Kaburagi, Y.; Tokuyama, T.; Fukuyama, T. *J. Am. Chem. Soc*. **2004**, *126*, 10246–10247.

(7) The pathway for reoxidation of Pd may not necessarily proceed through Pd(0); rather, it may involve the direct insertion of O_2 into a Pd hydride. For recent discussions concerning the mechanistic details of Pd oxidation by molecular oxygen, see: (a) Gligorich, K. M.; Sigman, M. S. *Angew. Chem., Int. Ed*. **2006**, *45*, 6612–6615. (b) Popp, B. V.; Stahl, S. S. *J. Am. Chem. Soc*. **2007**, *129*, 4410–4422. (c) Chowdhury, S.; Rivalta, I.; Russo, N.; Sicilia, E. *Chem. Phys. Lett*. **2007**, *443*, 183–189. (d) Keith, J. M.; Goddard, W. A., III; Oxgaard, J. *J. Am. Chem. Soc*. **2007**, *129*, 10361–10369.

(8) Pd(II) complexes such as **30** can also be generated via transmetallation (e.g., Pd(II)X_2 + Ar–M → Ar–Pd–X + MX). For a recent example, see: Lindh, J.; Enquist, P.-A.; Pilotti, Å.; Nilsson, P.; Larhed, M. *J. Org. Chem.* **2007**, *72*, 7957–7962 and references therein.

(9) (a) Tietze, L. F.; Sommer, K. M.; Zinngrebe, J.; Stecker, F. *Angew. Chem., Int. Ed.* **2005**, *44*, 257–259. For a recent synthetic application of a Pd(II) heterocyclization from our group, see: (b) Liu, Q.; Ferreira, E. M.; Stoltz, B. M. *J. Org. Chem.* **2007**, *72*, 7352–7358.

CHAPTER TWO

The Resolution of Important Pharmaceutical Building Blocks by Palladium-Catalyzed Aerobic Oxidation of Secondary Alcohols

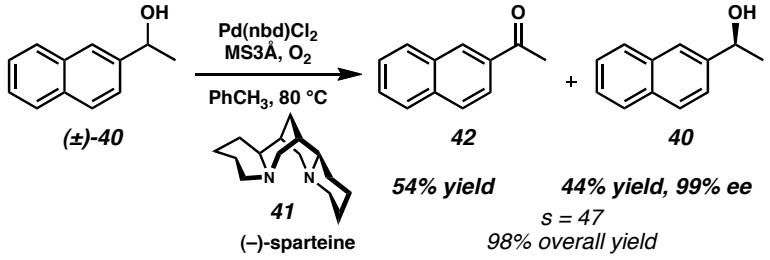
2.1 Background

2.1.1 Introduction

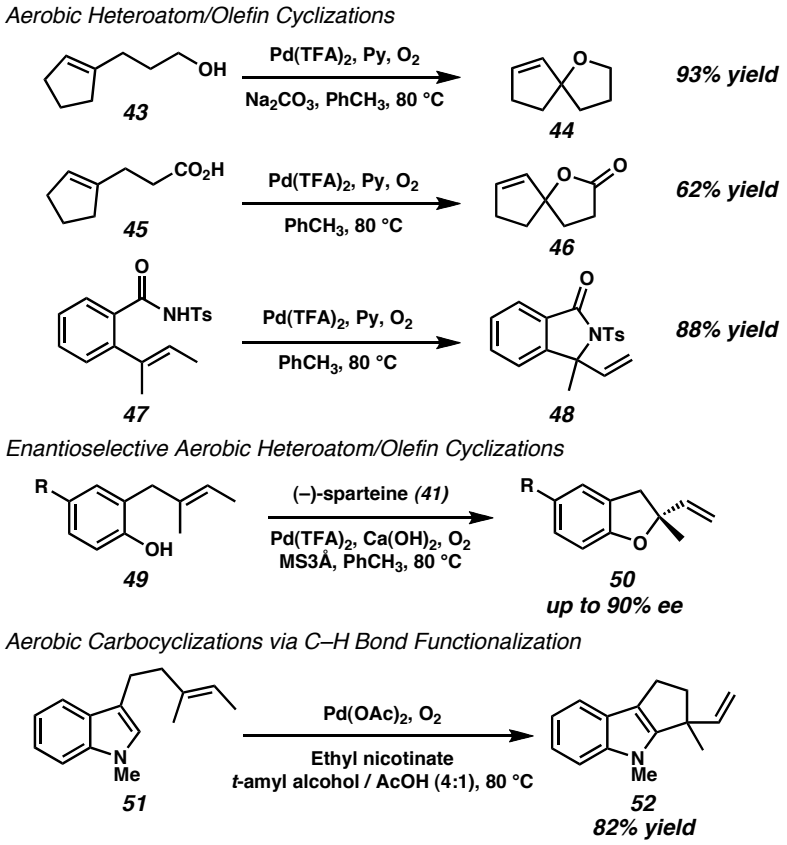
As part of a general program initiated in the area of asymmetric dehydrogenation chemistry, our laboratory recently reported the oxidative kinetic resolution of secondary alcohols. Our method employs a simple palladium dichloride catalyst precursor [Pd(nbd)Cl_2] in conjunction with (–)-sparteine (**41**), which serves as both ligand and base, and molecular oxygen as the stoichiometric oxidant (Scheme 2.1.1).[1,2,3] In this resolution, one enantiomer of a secondary alcohol (e.g., (±)-**40**) is preferentially oxidized to the ketone (e.g., **42**), leaving behind the other, slower-reacting enantiomer of the alcohol (e.g., **40**). The relative reaction rates of each enantiomer, referred to as *selectivity* (k_{rel} or s), can be computed from the enantiomeric excess of the alcohol at a given conversion.[4]

This palladium/sparteine system proved useful for the resolution of simple benzylic and allylic alcohols, as well as the desymmetrization of meso-diols, with selectivities ranging from 6.6–47.1 (Scheme 2.1.1).[4] Additionally, the use of dehydrogenative Pd(II) catalysis has been extended to oxidative cyclizations including both heterocyclizations and carbocyclizations (Scheme 2.1.2).[5]

Scheme 2.1.1



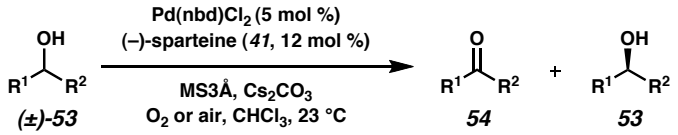
Scheme 2.1.2



Since the initial report,[1a] a number of conceptual improvements to the original oxidative kinetic resolution system have been made that allow a range of secondary alcohols (e.g., **40**) to be resolved with a variety of differing experimental procedures depending on the substrate.[1b,1c] A second method was developed employing Cs_2CO_3 and *t*-

BuOH as additives, which provided generally higher selectivities and shorter reaction times under lower reaction temperatures (Table 2.1.1).[1b] Additionally, a third iteration of our reaction replaced toluene with chloroform, which enabled us to run these transformations at room temperature using ambient air as the stoichiometric oxidant (Table 2.1.2).[1c]

Table 2.1.1



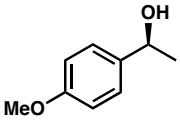
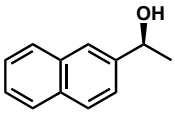
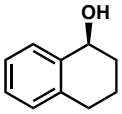
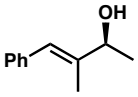
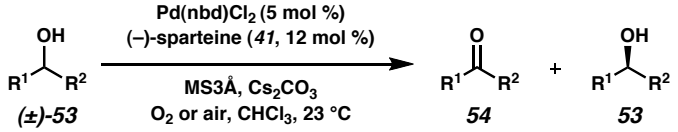
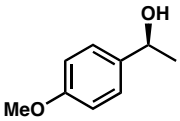
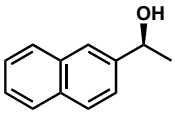
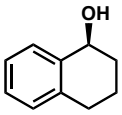
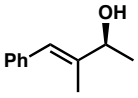
entry	unreacted alcohol, major enantiomer	O_2 source	time	conversion (%)	ee ROH (%)	*s*
1	 ***55***	O_2	48 h	62.6	99.9	27.1
		air	24 h	62.3	99.8	25.4
2	 ***40***	O_2	48 h	59.3	99.6	31.1
		air	24 h	55.5	98.0	37.3
3	 ***56***	O_2	24 h	57.5	98.0	27.6
		air	16 h	60.2	99.6	28.0
4	 ***57***	O_2	48 h	62.6	98.7	17.9
		air	44 h	64.7	98.9	15.7

Table 2.1.2

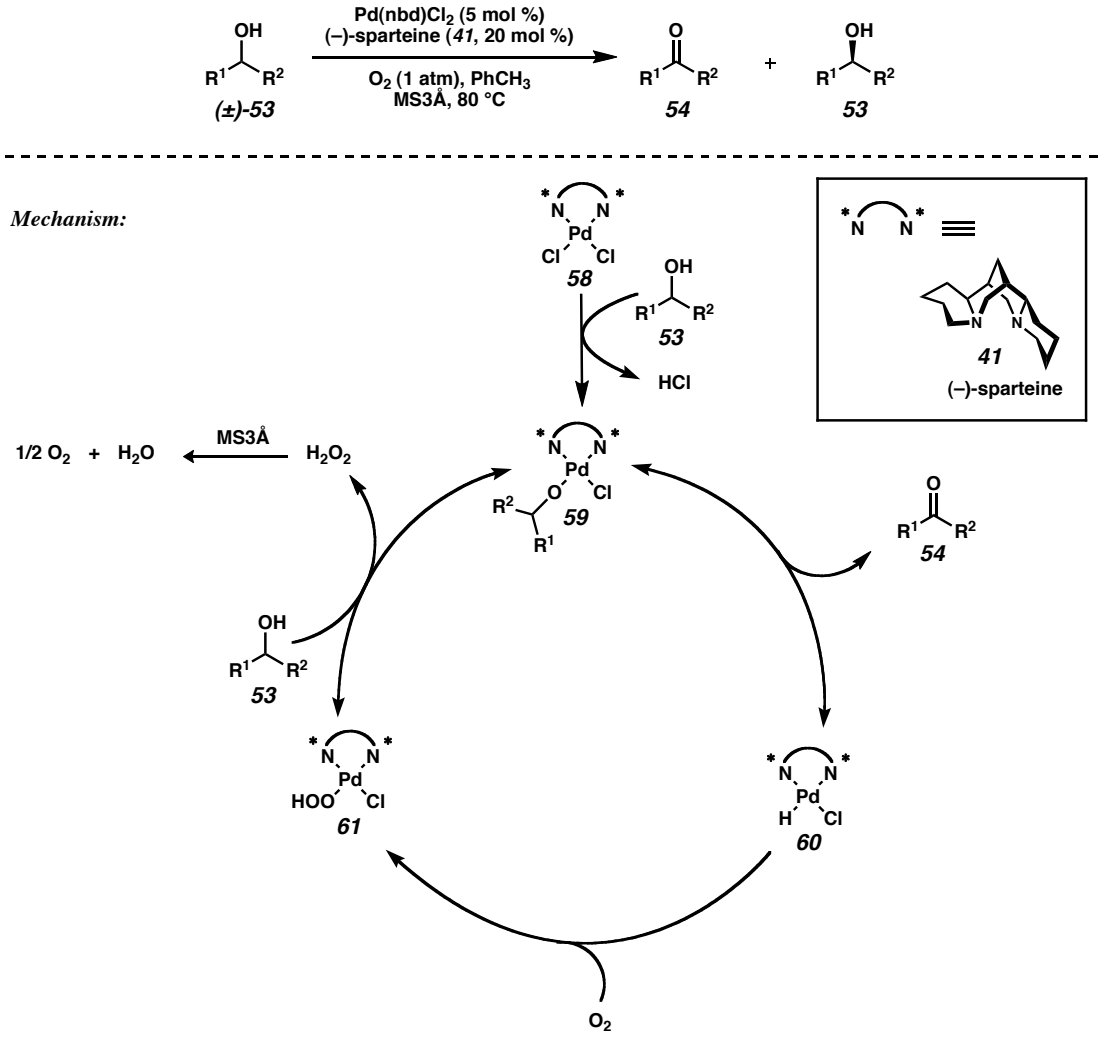


entry	unreacted alcohol, major enantiomer	atm	time	conversion (%)	ee ROH (%)	*s*
1	 ***55***	O_2	48 h	62.6	99.9	27.1
		air	24 h	62.3	99.8	25.4
2	 ***40***	O_2	48 h	59.3	99.6	31.1
		air	24 h	55.5	98.0	37.3
3	 ***56***	O_2	24 h	57.5	98.0	27.6
		air	16 h	60.2	99.6	28.0
4	 ***57***	O_2	48 h	62.6	98.7	17.9
		air	44 h	64.7	98.9	15.7

2.1.2 Mechanism of the Pd-Catalyzed Oxidative Kinetic Resolution

The general mechanism envisioned for this reaction is outlined in Scheme 2.1.3.[6] Starting with a palladium(II)-ligand complex (**58**), ligand substitution with a chiral substrate molecule (**53**) affords Pd(II) alkoxide **59**. This complex (**59**) can undergo β-hydride elimination to afford palladium hydride **60**, and generate oxidized substrate molecule **54**. Oxidation of the palladium with molecular oxygen then gives rise to **61**,[7] which can undergo ligand substitution with another substrate molecule (**53**) and continue the catalytic cycle. Finally, the hydrogen peroxide that is produced in the final step is proposed to be disproportionated into oxygen and water via the action of MS3Å.[3]

Scheme 2.1.3



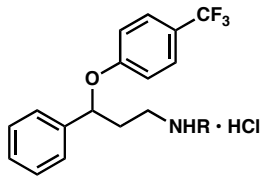
2.2 The Oxidative Kinetic Resolution of Pharmaceutical Building Blocks

2.2.1 Pharmaceutical Targets

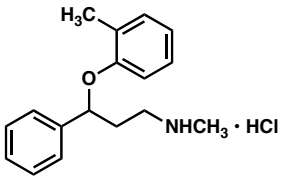
Although this oxidative kinetic resolution system had been optimized and studied in detail, it had primarily only been tested with simple, commercially-available benzylic alcohols. To demonstrate the potential synthetic utility of our palladium-catalyzed enantioselective alcohol oxidation, we investigated the oxidative kinetic resolution of a diverse set of small molecules representing key building blocks of bioactive,

pharmaceutically relevant materials (Figure 2.2.1).[8] These pharmaceutical substances included A) the antidepressants fluoxetine hydrochloride (Prozac®, **62**), norfluoxetine (**63**), tomoxetine (**64**), and nisoxetine (**65**),[9] and B) the orally active leukotriene receptor antagonist montelukast sodium (Singulair®, **66**).[10,11] These compounds were specifically chosen due to the inclusion of a key benzylic or allylic alcohol in the known synthetic routes (i.e., **67**–**70**, Table 2.2.1). We believed that these pharmaceutical agents would represent an ideal testing ground for our new asymmetric methodology.

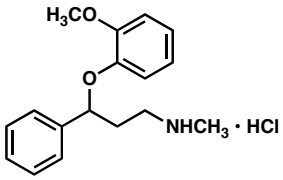
Figure 2.2.1



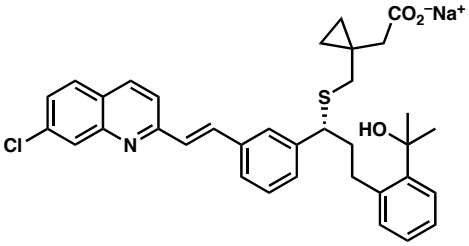
R = CH_3, Fluoxetine·HCl (Prozac®, 62)
R = H, Norfluoxetine·HCl (63)



Tomoxetine (64)



Nisoxetine (65)



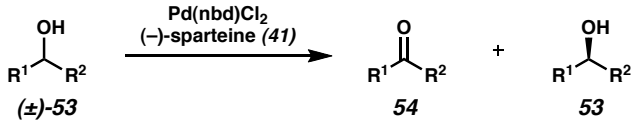
Montelukast Sodium (Singulair®, 66)

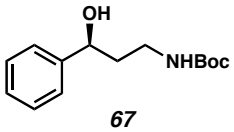
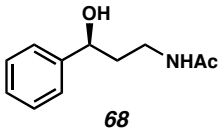
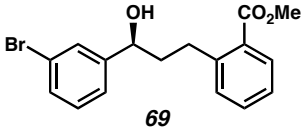
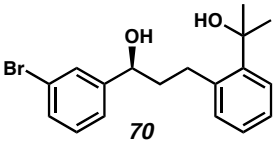
2.2.2 Resolution of Pharmaceutical Intermediates

To this end, we prepared a number of key intermediates by literature procedures and subjected them to kinetic resolution using a variety of our palladium-catalyzed aerobic conditions.[12] To our delight, all of the intermediates were resolved to high enantiomeric excess and with good-to-excellent selectivity (*s*) between the *R* and *S* enantiomers (*s* = 9.0–17.9).[4] As shown in Table 2.2.1, the amino alcohol derivatives **67** and **68**, relevant to the antidepressants **62**–**65**, could be resolved under our original conditions, employing $Pd(nbd)Cl_2$, (–)-sparteine (**41**), and O_2.[1a] While acetamide **68** was reasonably selective (*s* = 9), the more synthetically versatile Boc derivative **67** could be resolved with a selectivity factor of nearly 18.

Notably, carbamate **67** could be easily converted to *N*-methyl derivative **71** by reduction with $LiAlH_4$ (78% yield) or to primary amine **72** by treatment with TFA (68% yield), and ketone **73** could be recycled to (±)-**67** by quantitative reduction with $NaBH_4$ (Scheme 2.2.1). Amino alcohol intermediates **71** and **72** could then be converted to pharmaceutically-relevant compounds **62**–**65** using known procedures.[9]

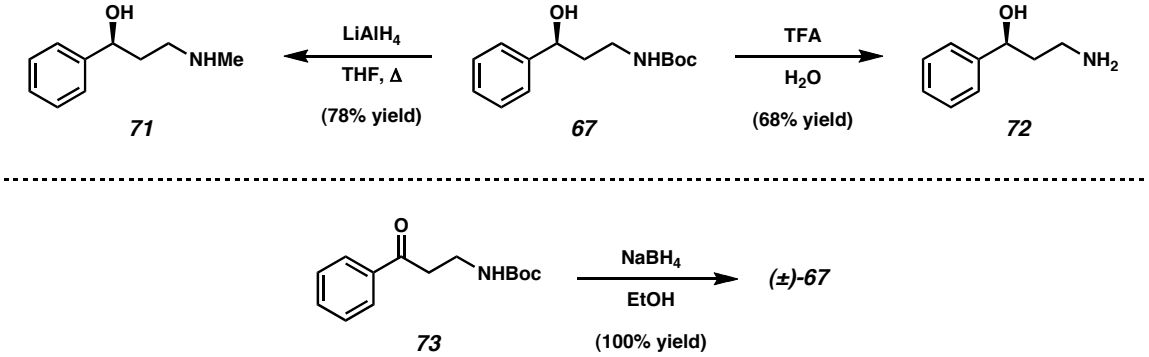
Table 2.2.1



entry	unreacted alcohol, major enantiomer	method[a]	time	conversion (%)	ee ROH (%)[e]	*s*
1	 **67**	A	24 h	57.5[c]	93.1	17.9
2	 **68**	A	14.5 h	70.0[c]	97.0	9.0
3	 **69**	B[b]	4.5 h	62.5[d]	92.9	11.2
4	 **70**	B[b]	4.5 h	70.6[c]	99.9	15.3

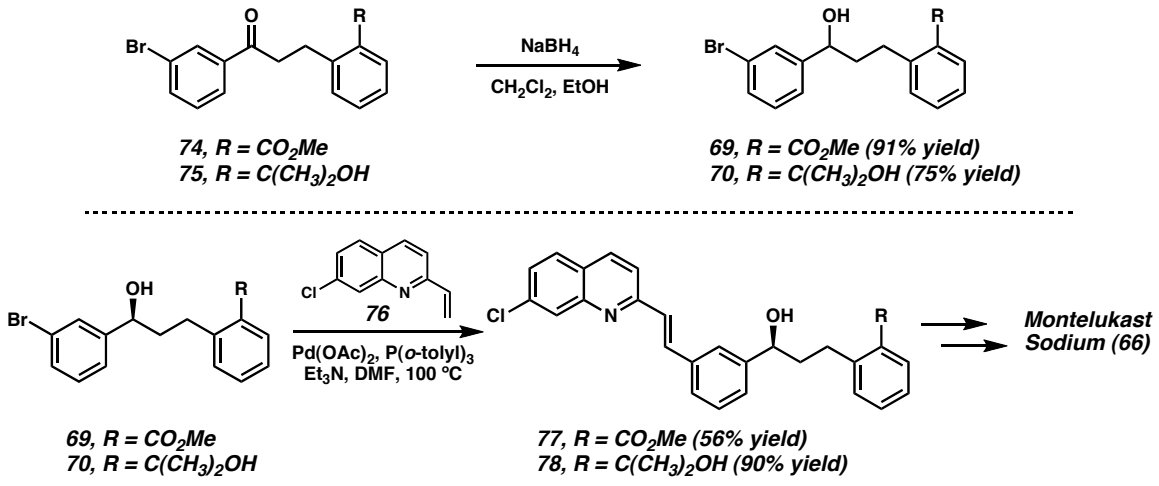
[a] Method A: 5 mol % $Pd(nbd)Cl_2$, 20 mol % (–)-sparteine (**41**), MS3Å, O_2 (1 atm), 0.1 M in $PhCH_3$, 80 °C. Method B: 5 mol % $Pd(nbd)Cl_2$, 20 mol % (–)-sparteine (**41**), 0.5 equiv Cs_2CO_3, 1.5 equiv *t*-BuOH, MS3Å, O_2 (1 atm), 0.25 M in $PhCH_3$, 60 °C. [b] Performed at 80 °C. [c] Conversion determined by isolated yield. [d] Conversion determined by ^1H NMR. [e] Enantiomeric excess (ee) determined by chiral HPLC. Total mass recovery in all cases was greater than 85%.

Scheme 2.2.1



The molecules relevant to the Singulair® system also resolved quite efficiently under our conditions (Table 2.2.1, entries 3 and 4). In order to minimize the experimental time involved for the resolution of compounds **69** and **70**, we chose to employ our recently described base-accelerated conditions.[1b] Smooth and rapid kinetic resolution was observed for both substrates (4.5 h) leading to production of the relevant enantiomer en route to Singulair®. Importantly, these resolutions provide a notable example of the functional group compatibility of the rate-accelerated system, as both aryl bromides and benzoate esters are tolerated in the oxidation. Again, the corresponding ketones **74** and **75** could be easily recycled via borohydride reduction. Furthermore, intermolecular Heck reaction of both **69** and **70** provided access to elaborated benzylic alcohols **77** and **78**, intermediates used in the production of montelukast sodium (Scheme 2.2.2).

Scheme 2.2.2



2.3 Conclusion

In conclusion, we have employed the palladium-catalyzed aerobic oxidative kinetic resolution of secondary alcohols for the enantioselective preparation of a variety

of pharmaceutical substances including Prozac® (**62**) and Singulair® (**66**). These examples demonstrate the power and utility of the methods to overcome many subtleties of substrate functionality. In this regard, the versatility of this resolution is further demonstrated by the diversity of the substrates chosen for this study, and for the first time this work extends the utility of the resolution to include amino alcohol derivatives and highly functionalized benzylic alcohols. Efforts to develop new catalyst systems and expand the utility and generality of asymmetric aerobic dehydrogenations continue.

2.4 Experimental Section

2.4.1 Materials and Methods

Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (either freshly distilled or passed through activated alumina columns). All commercially obtained reagents were used as received. Reaction temperatures were controlled using an IKAmag temperature modulator. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates, (0.25 mm) and visualized using a combination of UV, anisaldehyde, and potassium permanganate staining. ICN silica gel (particle size 0.032–0.063 mm) was used for flash column chromatography. Analytical chiral HPLC was performed on a Chiralcel® OJ or Chiralpak® AD column (each is 4.6 mm x 250 mm) obtained from Daicel Chemical Industries, Ltd. Analytical achiral GC was performed using an Agilent DB-WAX (30.0 m x 0.25 mm) column. ^{1}H NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz) 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. ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 75 MHz) and are reported relative to Me_4Si (δ 0.0). 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}). Optical rotations were measured with a Jasco P-1010 polarimeter. High-resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility. Chemicals were purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI.

2.4.2 Methods of Determination for Enantiomeric Excess and % Conversion

Table 2.4.1. Methods for determination of enantiomeric excess

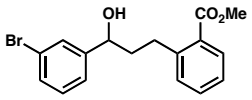
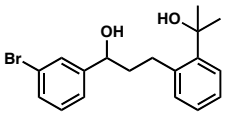
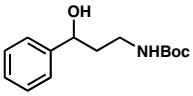
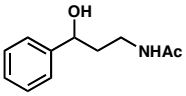
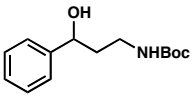
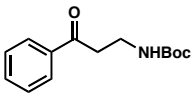
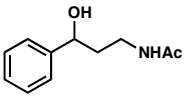
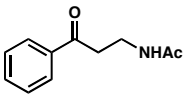
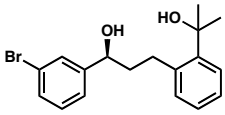
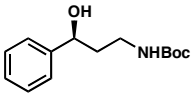
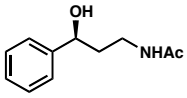
Entry	Substrate	HPLC Assay	Conditions	Retention Time (min)	
				(*R*)-isomer	(*S*)-isomer
1	 ***69***	Chiralpak® AD	5% EtOH/hexanes 1.0 mL/min 254 nm	15.8	17.1
2	 ***70***	Chiralcel® OJ	5% EtOH/hexanes 1.0 mL/min 210 nm	17.8	15.0
3.	 ***67***	Chiralcel® OJ	8% 2-propanol/hexanes 1.0 mL/min 210 nm	10.5	20.1
4	 ***68***	Chiralpak® AD	6% 2-propanol/hexanes 1.0 mL/min 210 nm	27.9	23.8

Table 2.4.2. Methods for determination of % conversion

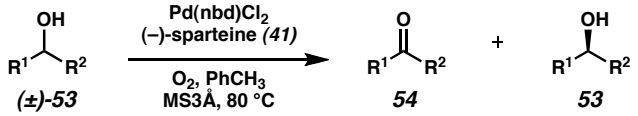
Entry	Substrate	Ketone	GC Conditions	Retention Time (min)	
				Alcohol	Ketone
1	 ***67***	 ***73***	70 °C, 15 min; 7 °C/min to 240 °C; hold 20 min 1.0 mL/min carrier gas flow	48.1	42.2
2	 ***68***	 ***81***	70 °C, 15 min; 7 °C/min to 240 °C; hold 20 min 1.0 mL/min carrier gas flow	53.5	45.1

2.4.3 Optical Rotations of New Compounds

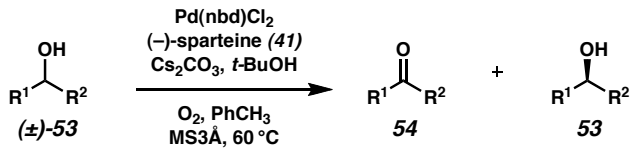
Table 2.4.3. Optical rotations (refer to Table 2.2.1 for relevant % enantiomeric excess)

Entry	Substrate	Rotation
1	 ***70***	$[\alpha]^{26}_{D}$ –31.7° (*c* 1.0, benzene)[13]
2	 ***67***	$[\alpha]^{25}_{D}$ –15.4° (*c* 1.0, $CHCl_3$)[13]
3	 ***68***	$[\alpha]^{25}_{D}$ –23.6° (*c* 1.3, $CHCl_3$)[14]

2.4.4 Representative Procedures for Oxidative Kinetic Resolution

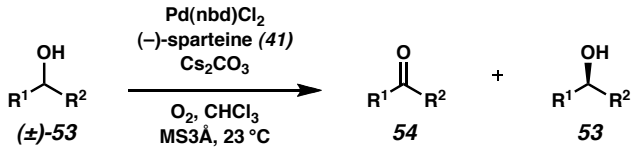


Kinetic Resolution Conditions A: "Original Conditions."[1a] To an oven-dried reaction tube with stir bar was added oven-dried powdered 3Å molecular sieves (250 mg). After cooling, $Pd(nbd)Cl_2$ (6.7 mg, 0.025 mmol) followed by toluene (2.5 mL) and then (–)-sparteine (**41**, 23.4 mg, 23 μL, 0.10 mmol) were added. The reaction tube was then vacuum evacuated and purged with O_2 (3x), and the tube was heated to 80 °C with vigorous stirring under O_2 atmosphere (1 atm) for 20 min. A solution of alcohol **53** (0.50 mmol) in toluene (2.5 mL) was added, and the reaction was allowed to proceed under O_2 atmosphere (1 atm) at 80 °C. Aliquots were filtered through a small plug of silica gel (Et_2O eluent), evaporated, and analyzed. Purification of ketone **54** and enantioenriched alcohol **53** was accomplished by direct chromatography of the crude reaction mixture.



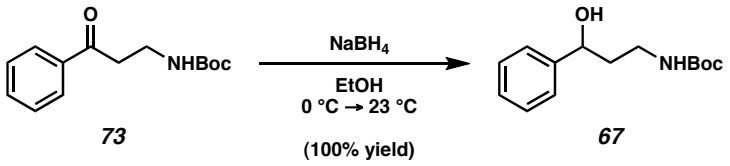
Kinetic Resolution Conditions B: "Rate-Accelerated Conditions."[1b] To an oven-dried reaction tube with stir bar was added oven-dried powdered 3Å molecular sieves (500 mg). After cooling, $Pd(nbd)Cl_2$ (13.5 mg, 0.05 mmol), followed by toluene (2 mL) and then (–)-sparteine (**41**, 46.9 mg, 46 μL, 0.20 mmol) were added. The reaction tube was then vacuum evacuated and purged with O_2 (3x), and the tube was heated (60 °C) with vigorous stirring under O_2 atmosphere (1 atm) for 20 min. Finely powdered

anhydrous Cs_2CO_3 (162.9 mg, 0.50 mmol) was added, followed by a solution of alcohol **53** (1.0 mmol), *t*-butanol (111.2 mg, 143 μL, 1.5 mmol) and toluene (2 mL). The reaction was allowed to proceed under O_2 atmosphere (1 atm) at 60 °C. Aliquots were filtered through a small plug of silica gel (Et_2O eluent), evaporated, and analyzed. Purification of ketone **54** and enantioenriched alcohol **53** was accomplished by direct chromatography of the crude reaction mixture.



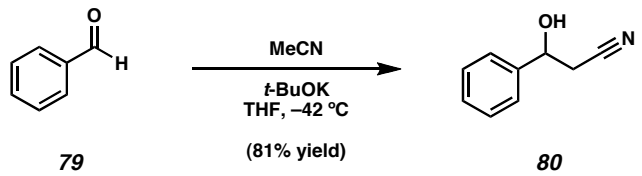
Kinetic Resolution Conditions C: "Chloroform Conditions."[1c] To an oven-dried reaction tube with stir bar was added oven-dried powdered 3Å molecular sieves (500 mg). After cooling, $Pd(nbd)Cl_2$ (13.5 mg, 0.05 mmol), followed by chloroform (2 mL, stabilized with amylenes) and then (–)-sparteine (**41**, 28.1 mg, 27.6 μL, 0.12 mmol) were added. The reaction tube was then vacuum evacuated and purged with O_2 (3x), and the reaction was stirred vigorously at 23 °C under O_2 atmosphere (1 atm) for 15 min. Finely powdered anhydrous Cs_2CO_3 (130.3 mg, 0.40 mmol) was added, followed by a solution of alcohol **53** (1.0 mmol) in chloroform (2 mL). The reaction was allowed to proceed under O_2 atmosphere (1 atm) at 23 °C. Aliquots were filtered through a small plug of silica gel (Et_2O eluent), evaporated, and analyzed. Purification of ketone **54** and enantioenriched alcohol **53** was accomplished by direct chromatography of the crude reaction mixture.

2.4.5 Representative Procedure for Ketone Recycling

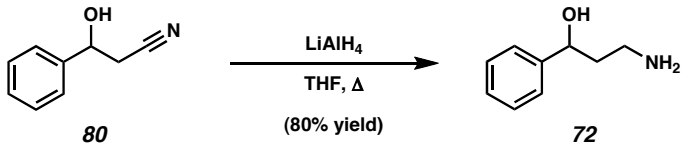


Carbamate 67. To keto-carbamate **73** (113.3 mg, 0.45 mmol) in EtOH (2.0 mL) was added $NaBH_4$ (40.0 mg, 1.0 mmol) at 0 °C. After stirring for 3 h and allowing the reaction to warm to 23 °C, saturated aq. NH_4Cl was added dropwise at 0 °C. The mixture was diluted with EtOAc (1 mL) and H_2O (1 mL) and the phases were partitioned. The aqueous phase was extracted with EtOAc (3 x 1 mL). The organic extracts were combined and passed over a small plug of silica gel (EtOAc eluent). The solvent was removed in vacuo to afford carbamate **67** (113.8 mg, 100% yield).

2.4.6 Preparative Procedures

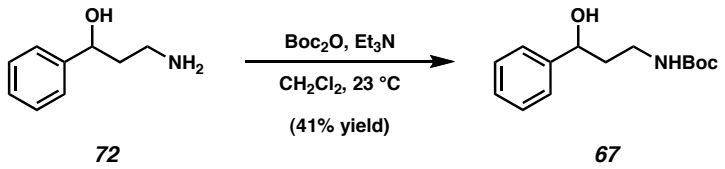


Nitrile 80.[9c] A flask charged with THF (100 mL) and acetonitrile (3.2 mL, 57.1 mmol) was cooled to –42 °C and treated dropwise with a solution of *t*-BuOK (7.1 g, 63.3 mmol) in THF (25 mL). After stirring for 45 min, freshly distilled benzaldehyde (**79**, 5.7 mL, 56.4 mmol) was added dropwise. The reaction was allowed to warm to –15 °C over a 4 h period, and then was quenched by slow addition of saturated aq. NH_4Cl (35 mL). The layers were partitioned, and the aqueous phase was extracted with Et_2O (2 x 100 mL). The combined organics were washed with H_2O (2 x 20 mL) and saturated aq. NaCl (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was flash chromatographed (1:1 Et_2O:hexanes eluent) to give nitrile **80** (6.69 g, 81% yield) as a colorless oil. R_f 0.16 (1:1 Et_2O:hexanes); characterization data for this compound have been previously reported.[9a]



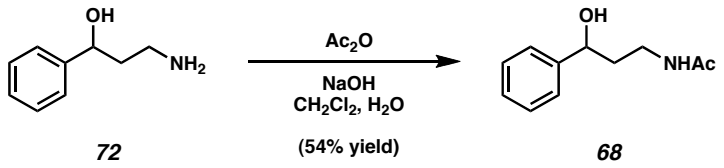
Amino alcohol 72. A flask was charged with a suspension of $LiAlH_4$ (2.92 g, 77.0 mmol) in THF (100 mL). After cooling to 0 °C, the suspension was treated with nitrile **80** (4.54 g, 30.9 mmol) dropwise, and the resulting brown mixture was heated to reflux for 5 h. The reaction was cooled to 0 °C, and quenched by slow addition of H_2O (3

mL), followed by 15% *w/v* aq. NaOH (3 mL), and finally by H_2O (9 mL). The crude green sludge was vacuum filtered and washed well with Et_2O. The filtrate was concentrated under reduced pressure to a green oil, and partitioned between EtOAc (100 mL) and 15% *w/v* aq. NaOH (30 mL). The aqueous phase was extracted with EtOAc (2 x 100 mL), and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated in vacuo to afford amino alcohol **72** (3.74 g, 80% yield) as a dark orange oil, which was used without further purification. R_f 0.0 (1:1 EtOAc:hexanes); characterization data for this compound have been previously reported.[9a]

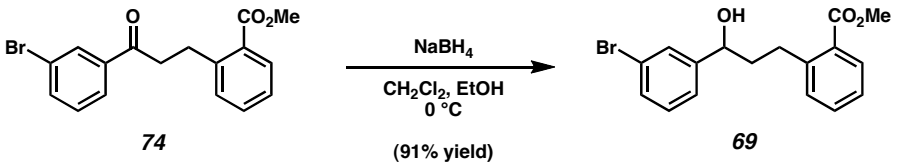


Carbamate 67. To amino alcohol **72** (2.14 g, 14.1 mmol) in CH_2Cl_2 (25 mL) was added Et_3N (2.8 mL, 20.1 mmol) over 1–2 min at 23 °C, followed by Boc_2O (3.09 g, 14.2 mmol). The reaction was stirred for 2 h, then quenched by addition of saturated aq. NH_4Cl (15 mL). The phases were partitioned, and the aqueous phase was extracted with CH_2Cl_2 (2 x 30 mL). The organic extracts were combined, washed with saturated aq. $NaHCO_3$ (15 mL), H_2O (15 mL), and saturated aq. NaCl (15 mL), and dried over $MgSO_4$. The crude product was concentrated in vacuo, and passed over a short plug of silica gel (20:1 CH_2Cl_2:MeOH eluent). A solid was precipitated from the residue by treatment with hexanes:Et_2O (10:1, 10 mL), and the solvent was evaporated in vacuo. This material was then recrystallized from hexanes:Et_2O (10:1, 10 mL), filtered, and rinsed with ice-cold pentane (3 x 5 mL) to afford carbamate **67** (1.44 g, 41% yield) as a white solid. R_f 0.60 (7:1 CH_2Cl_2:MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.23 (m, 5H), 4.84 (br s, 1H),

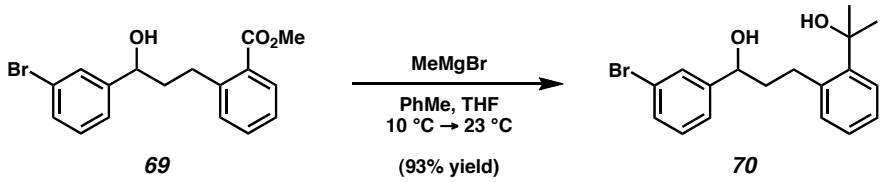
4.77–4.69 (m, 1H), 3.55–3.36 (m, 1H), 3.22–3.09 (m, 1H), 2.94 (br s, 1H), 1.88–1.80 (m, 2H), 1.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 144.5, 128.6, 127.6, 125.8, 79.8, 71.9, 39.8, 37.8, 28.6; IR (film) 3360 (br), 1688, 1515, 1281, 1252, 1170 cm^{-1}; HRMS-FAB *m/z*: [M + H]$^+$ calc'd for $C_{14}H_{22}NO_3$, 252.1600; found, 252.1600.



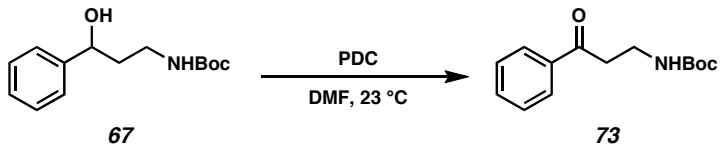
Acetamide 68. To amino alcohol **72** (1.61 g, 10.6 mmol) in CH_2Cl_2 (17 mL) and aq. 1.4 N NaOH (17 mL, 23.8 mmol) was added acetic anhydride (1.3 mL, 13.8 mmol) at 23 °C. After the biphasic reaction was stirred for 5 h, the layers were partitioned, and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organics were washed with H_2O (15 mL) and saturated aq. NaCl (15 mL), then dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the crude material was passed over a short plug of silica gel (20:1 CH_2Cl_2:MeOH eluent). After concentrating to a yellow oil, hexanes:Et_2O (10:1, 10 mL) was added, which precipitated a yellow solid. The solvent was evaporated in vacuo, and the yellow solid was triturated with pentane:Et_2O (12:1), and collected by vacuum filtration to afford acetamide **68** (1.10 g, 54% yield) as a pale yellow solid. R_f 0.50 (9:1 CH_2Cl_2:MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.24 (m, 5H), 5.96 (br s, 1H), 4.72 (dd, J = 7.4, 5.8 Hz, 1H), 3.73–3.59 (m, 1H), 3.28–3.14 (m, 1H), 3.19 (br s, 1H), 1.97 (s, 3H), 1.90–1.81 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 144.4, 128.6, 127.5, 125.8, 72.0, 39.0, 37.0, 23.3; IR (film): 3295 (br), 1651, 1556 cm^{-1}; HRMS-FAB (*m/z*): [M + H]$^+$ calc'd for $C_{11}H_{16}NO_2$, 194.1181; found, 194.1190.



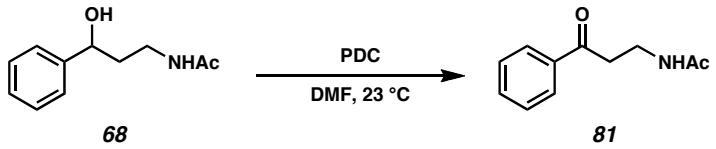
Bromo Methyl Ester 69. To 2-[3-(3-bromophenyl)-3-oxopropyl]benzoic acid methyl ester[15] (**74**, 1.763 g, 5.08 mmol), previously described by Larsen, et al.,[10a] in EtOH (12 mL) and CH_2Cl_2 (12 mL), was added $NaBH_4$ (208.8 mg, 5.52 mmol) portionwise over a 5-min period at 0 °C. The reaction was stirred for 3.5 h at 0 °C, then quenched by slow addition of 0.1 N HCl (45 mL). After stirring 30 min, the mixture was poured over CH_2Cl_2 (75 mL) and the phases were partitioned. The aqueous phase was extracted with CH_2Cl_2 (75 mL), and the organic extracts were combined, washed with H_2O (15 mL) and brine (15 mL), and dried over $MgSO_4$. The solvent was evaporated in vacuo, and the crude product was chromatographed (7:1 hexanes:EtOAc eluent) to provide the product as a viscous oil. The residual solvent was removed by lyophilization from benzene to afford bromo methyl ester **69** (1.61 g, 91% yield) as a white-to-off-white solid. R_f 0.44 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (app. dd, J = 8.1, 1.5 Hz, 1H), 7.50 (app. t, J = 1.7 Hz, 1H), 7.46–7.33 (m, 2H), 7.28–7.14 (m, 4H), 4.64 (app. t, J = 6.2 Hz, 1H), 3.87 (s, 3H), 3.16–2.97 (m, 3H), 2.06–1.97 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 147.2, 143.7, 132.4, 131.2, 130.9, 130.3, 130.0, 129.2, 129.0, 126.2, 124.5, 122.6, 72.6, 52.5, 41.6, 30.4; IR (film) 3460 (br), 1722, 1263, 1083 cm^{-1}; HRMS-EI m/z: $[M - H]^+$ calc'd for $C_{17}H_{16}BrO_3$, 347.0283; found, 347.0274.



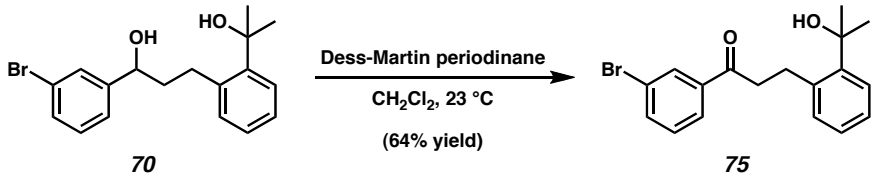
Bromo Diol 70. To bromo methyl ester **69** (1.502 g, 4.30 mmol) in THF (9 mL) and toluene (9 mL) was added MeMgBr (2.78 M in Et_2O, 8.5 mL, 23.4 mmol) in a rapid dropwise fashion at 10 °C. The solution was stirred at 23 °C for 3.5 h after the addition was complete, then quenched by slow addition of saturated aq. NH_4Cl. The resulting mixture was poured over Et_2O (50 mL) and brine (25 mL). The organic phase was dried over $MgSO_4$, and chromatographed (7:1 hexanes:EtOAc → 3:1 hexanes:EtOAc). The fractions containing the methyl ketone (slightly higher R_f than the desired product) were concentrated in vacuo and resubjected to the initial reaction conditions. After purification in the same manner described above, all of the product containing fractions were combined and evaporated in vacuo. The viscous oil was lyophilized from benzene to provide bromo diol **70** (1.39 g, 93% combined yield) as a white-to-off-white solid. R_f 0.33 (3:2 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (app. s, 1H), 7.37–7.31 (m, 2H), 7.26–7.09 (m, 5H), 4.61 (dd, J = 8.6, 4.1 Hz, 1H), 3.26–3.14 (m, 1H), 3.12–3.01 (m, 1H), 2.21 (br s, 1H), 2.15–1.95 (m, 3H), 1.67 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.2, 144.9, 140.0, 131.4, 130.3, 130.0, 129.1, 127.4, 125.8, 125.6, 124.5, 122.6, 74.5, 72.5, 42.2, 32.4, 32.3, 29.7; IR (film) 3356 (br), 1069 cm^{-1}; HRMS-EI *m/z*: $[M - H]^+$ calc'd for $C_{18}H_{20}BrO_2$, 349.0628; found, 349.0631.



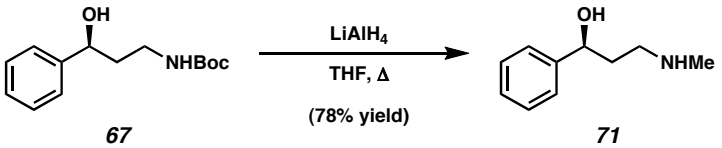
Keto-Carbamate 73. To carbamate **67** (27.5 mg, 0.11 mmol) in DMF (2 mL) was added pyridinium dichromate (237 mg, 0.63 mmol) at 23 °C. After 10 h, the reaction mixture was diluted in Et_2O (5 mL) and brine (5 mL), and the phases were partitioned. The aqueous phase was extracted with Et_2O (2 x 5 mL), and the organic extracts were combined, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed (20:1 → 10:1 hexanes:EtOAc eluent) to afford keto-carbamate **73** as a solid, which was used as an authentic standard to confirm the oxidative kinetic resolution product of carbamate **67**. R_f 0.50 (1:1 EtOAc:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97–7.90 (m, 2H), 7.61–7.51 (m, 1H), 7.49–7.39 (m, 2H), 5.13 (br s, 1H), 3.53 (q, J = 5.9 Hz, 2H), 3.19 (t, J = 5.5 Hz, 2H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4, 156.1, 136.7, 133.6, 128.8, 128.1, 79.3, 38.8, 35.6, 28.5; IR (film) 1682, 1506, 1172 cm^{-1}; HRMS-FAB *m/z*: $[M + H]^+$ calc'd for $C_{14}H_{20}NO_3$, 250.1443; found, 250.1441.



Keto-Acetamide 81. Compound **81** was prepared in an analogous manner to keto-carbamate **73**. The characterization data for this compound have been previously reported by Knochel.[16]

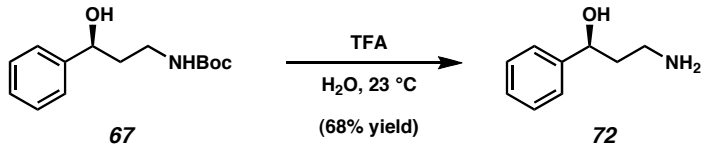


Bromo Hydroxy Propanone 75. To bromo diol **70** (51.6 mg, 0.15 mmol) in CH_2Cl_2 (2.5 mL) was added Dess-Martin periodinane (70.7 mg, 0.17 mmol). The mixture was stirred for 3 h at 23 °C, and then chromatographed directly (1:1 Et_2O:pentane eluent) to provide bromo hydroxy propanone **75** (33.0 mg, 64% yield) as a solid. This product was used as an authentic standard to confirm the oxidative kinetic resolution product of bromo diol **70**. R_f 0.60 (3:2 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6) δ 8.06 (app. t, *J* = 1.7 Hz, 1H), 7.86–7.81 (m, 1H), 7.57 (app. ddd, 1H, *J* = 7.7, 1.6, 1.1 Hz, 1H), 7.25–7.20 (m, 1H), 7.11–6.98 (m, 3H), 6.65 (app. td, *J* = 10.8, 3.9 Hz), 3.43 (app. t, *J* = 7.7 Hz, 2H), 2.98–2.91 (m, 2H), 1.44–1.41 (m, 6H); ^{13}C NMR (75 MHz, C_6D_6) δ 198.1, 146.4, 140.5, 139.5, 136.0, 132.2, 131.8, 130.6, 127.7, 127.1, 126.4, 126.4, 123.4, 73.8, 42.4, 32.6 (2C), 29.2; IR (film) 3452 (br), 1684, 1198 cm^{-1}; HRMS-FAB *m/z*: $[M + H]^+$ for $C_{18}H_{20}O_2Br$ calc'd, 347.0647; found, 347.0632.

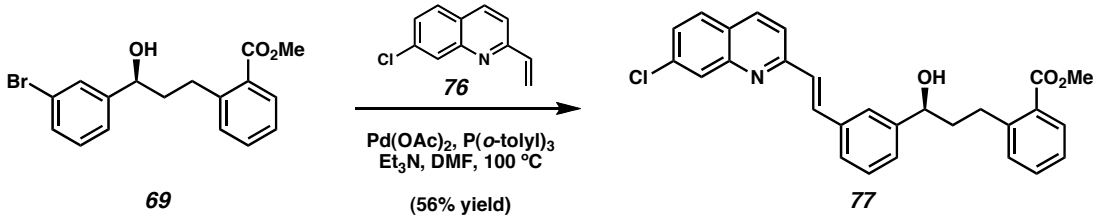


(*S*)-Methyl Amine 71. To a suspension of $LiAlH_4$ (56.8 mg, 1.5 mmol) in THF (1.5 mL) was added enantioenriched carbamate **67** (47.5 mg, 0.19 mmol). The reaction was heated to reflux for 5.5 h, and then quenched at 0 °C by slow addition of H_2O (50 μL), followed by 15% *w/v* aq. NaOH (50 μL), and finally by H_2O (150 μL). The mixture was filtered, and the filter cake was rinsed well with Et_2O. The filtrate was evaporated

under reduced pressure, diluted in CH_2Cl_2 (1 mL), washed with saturated aq. NaCl (0.5 mL), and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, which provided methyl amine **71** (24.5 mg, 78% yield) as an oil. $[\alpha]^{26}_D$ –33.7° (*c* 0.81, $CHCl_3$). lit[17]: $[\alpha]^{23}_D$ –37.4° (*c* 1%, $CHCl_3$).

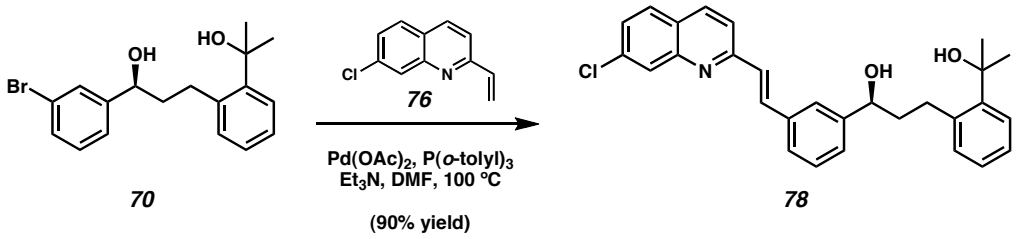


(*S*)-Amino Alcohol 72. To enantioenriched carbamate **67** (25.2 mg, 0.1 mmol) was added a mixture of trifluoroacetic acid (1.0 mL) and H_2O (0.2 mL). The solution was stirred at 23 °C for 48 h, and then the volatiles were removed in vacuo. The aqueous residue was made basic using 5 N aq. NaOH (1 mL), and extracted with CH_2Cl_2 (3 x 1 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to afford title compound **72** (10.2 mg, 68% yield) as a solid. Characterization data for this compound have been previously reported.[9a] $[\alpha]^{25}_D$ –40.5 ° (*c* 0.5, MeOH). lit:[9a] $[\alpha]^{25}_D$ –43.65° (*c* 1, MeOH).



(*S*)-Chloroquinoline Methyl Ester 77.[10b,18] To enantioenriched bromo methyl ester **69** (83.8 mg, 0.24 mmol) was added $Pd(OAc)_2$ (3.0 mg, 0.013 mmol), P(*o*-tolyl)$_3$ (12.7 mg, 0.042 mmol), 2-ethenyl-7-chloroquinoline[10a] (**76**, 47.0 mg, 0.25 mmol), and

DMF (0.7 mL). The dark mixture was degassed three times using the freeze-pump-thaw technique, and then Et_3N (93 μL, 0.67 mmol) was added. The reaction was heated to 100 °C for 3 h, then cooled to 23 °C. The crude mixture was diluted with EtOAc (2 mL) and H_2O (2 mL). The phases were partitioned, and the aqueous phase was extracted with EtOAc (3 x 2 mL). The combined organic extracts were dried by passage over a short plug of silica gel (EtOAc eluent), and the solvent was evaporated in vacuo. The residue was purified by flash chromatography (5:1 hexanes:EtOAc eluent). Desired chloroquinoline methyl ester **77** (62.0 mg, 56% yield) was obtained as a solid after evaporation of solvent under reduced pressure, and lyophilization from benzene. R_f 0.21 (3:2 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6) 8.35 (app. d, J = 1.6 Hz, 1H), 7.92–7.85 (m, 2H), 7.68 (s, 1H), 7.43–7.36 (m, 3H), 7.29–6.89 (m, 8H), 4.67 (t, J = 5.8 Hz, 1H), 3.43 (s, 3H), 3.30–3.10 (m, 2H), 2.65 (br s, 1H), 2.11 (m, 2H); ^{13}C NMR (75 MHz, C_6D_6, 27/28 C) 168.5, 157.5, 149.7, 146.9, 145.1, 137.2, 136.1, 136.0, 132.7, 131.9, 131.5, 130.2, 129.3, 129.3, 129.1, 128.9, 127.3, 127.1, 126.7, 126.5, 126.2, 125.7, 120.6, 73.6, 52.0, 42.5, 31.2; IR (film) 3407 (br), 1719, 1607, 1497, 1258 cm^{-1}; HRMS-FAB m/z: [M + H]$^+$ calc'd for $C_{28}H_{25}NO_3Cl$, 458.1523; found, 458.1517. lit (R)-**77**:[10b] $[\alpha]^{22}_D$ +28.3° (99.5% ee, c 1, $CHCl_3$). The absolute configuration of **77** was determined by optical rotation and chiral HPLC,[19] and no degradation of enantiopurity was observed in the conversion of starting material (**69**) to product (**77**).



(*S*)-Chloroquinoline Diol 78.[18,19] To enantioenriched bromo diol **70** (41.6 mg, 0.12 mmol) was added $Pd(OAc)_2$ (1.9 mg, 0.008 mmol), P(*o*-tolyl)$_3$ (10.8 mg, 0.035 mmol), 2-ethenyl-7-chloroquinoline[10a] (**76**, 23.9 mg, 0.12 mmol), and DMF (0.35 mL). The dark mixture was degassed three times using the freeze-pump-thaw technique, and then Et_3N (40 μL, 0.29 mmol) was added. The reaction was heated to 100 °C for 3 h, then cooled to 23 °C. The crude mixture was chromatographed directly (9:1 hexanes:EtOAc → 3:1 hexanes:EtOAc eluent). Desired chloroquinoline diol **78** (49.2 mg, 90% yield) was obtained as a solid after evaporation of solvent under reduced pressure and lyophilization from benzene. R_f 0.11 (3:2 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6) 8.32 (app. d, J = 1.6 Hz, 1H), 7.82 (app. d, J = 16.5 Hz, 1H), 7.69 (app. s, 1H), 7.42–7.31 (m, 4H), 7.29–7.00 (m, 8H), 4.68 (dd, J = 8.2, 4.4 Hz, 1H), 3.97 (br s, 1H), 3.45–3.32 (m, 1H), 3.21–3.10 (m, 1H), 2.96 (br s, 1H), 2.23–2.09 (m, 2H), 1.50 (s, 1H), 1.48 (s, 1H); ^{13}C NMR (75 MHz, C_6D_6, 28/29 C) 157.5, 149.5, 146.8, 146.1, 141.1, 137.1, 136.2, 136.0, 135.9, 132.2, 129.3, 129.3, 129.0, 129.0, 128.9, 127.8, 127.3, 126.8, 126.3, 126.2, 125.8, 120.4, 74.3, 73.4, 43.0, 32.6, 32.4, 30.4; IR (film) 3361 (br), 1607, 1498 cm^{-1}; HRMS-FAB *m/z*: $[M + H]^+$ calc'd for $C_{29}H_{29}NO_2Cl$, 458.1887; found, 458.1886. The absolute configuration of **78** was determined by chiral HPLC,[19] and no degradation of enantiopurity was observed in the conversion of starting material (**70**) to product (**78**).

2.5 Notes and References

(1) (a) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001**, *123*, 7725–7726. (b) Bagdanoff, J. T.; Ferreira, E. M.; Stoltz, B. M. *Org. Lett.* **2003**, *5*, 835–837. (c) Bagdanoff, J. T.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 353–357.

(2) Simultaneous to our publication, a related system was reported; see: Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc.* **2001**, *123*, 7475–7476.

(3) The kinetic resolutions in references 1 and 2 were based on a non-asymmetric alcohol oxidation employing $Pd(OAc)_2$, pyridine, and O_2, see: Nishimura, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750–6755.

(4) The selectivity factor (s) was determined using the equation: $s = k_{rel}$(fast/slow) = ln[(1 - C)(1 - ee)]/ln[(1 - C)(1 + ee)], where C = conversion. For an excellent discussion of kinetic resolutions, see: Kagan, H. B.; Fiaud, J. C. In *Topics in Stereochemistry*; Eliel, E. L., Ed.; Wiley & Sons: New York, 1988; Vol. 18, pp 249–330.

(5) (a) Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2892–2895. (b) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578–9579.

(6) A model for the observed stereochemistry was recently proposed: (a) Trend, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 4482–4483. (b) Nielsen, R. J.; Keith, J. M.; Stoltz, B. M.; Goddard, W. A., III *J. Am. Chem. Soc.* **2004**, *126*, 7967–7974.

(7) For recent discussions concerning the mechanistic details of Pd oxidation by molecular oxygen, see: (a) Gligorich, K. M.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 6612–6615. (b) Popp, B. V.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 4410–4422. (c) Chowdhury, S.; Rivalta, I.; Russo, N.; Sicilia, E. *Chem. Phys. Lett.* **2007**, *443*, 183–189. (d) Keith, J. M.; Goddard, W. A., III; Oxgaard, J. *J. Am. Chem. Soc.* **2007**, *129*, 10361–10369.

(8) Portions of this chapter are reproduced in part, with permission, from: Caspi, D. D.; Ebner, D. C.; Bagdanoff, J. T.; Stoltz, B. M. *Adv. Synth. Catal.* **2004**, *346*, 185–189 (Copyright 2004 Wiley-VCH Verlag GmbH & Co.KGaA).

(9) (a) Mitchell, D.; Koenig, T. M. *Synth. Commun.* **1995**, *25,* 1231–1238. (b) Kumar, A.; Ner, D. H.; Dike, S. Y. *Tetrahedron Lett.* **1991**, *32*, 1901–1904. (c) Koenig, T. M.; Mitchell, D. *Tetrahedron Lett.* **1994**, *35*, 1339–1342. (d) Ali, I. S.; Sudalai, A. *Tetrahedron Lett.* **2002**, *43,* 5435–5436. (e) Kumar, A.; Ner, D. H.; Dike, S. Y. *Ind. J. Chem.* **1992***, 31B*, 803–809 and references therein.

(10) (a) Larsen, R. D.; Corley, E. G.; King, A. O.; Carroll, J. D.; Davis, P.; Verhoeven, T. R.; Reider, P. J.; Labelle, M.; Gauthier, J. Y.; Xiang, Y. B.; Zamboni, R. J. *J. Org. Chem.* **1996**, *61*, 3398–3405. (b) King, A. O.; Corley, E. G.; Anderson, R. K.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J.; Xiang, Y. B.; Belley, M.; Leblanc, Y.; Labelle, M.; Prasit, P.; Zamboni, R. J. *J. Org. Chem.* **1993**, *58*, 3731–3735. (c) Bhupathy, M.; McNamara, J. M.; Sidler, D. R.; Volante, R. P.; Bergan, J. J. (Merck & Co., Inc.). WO 95/18107, 1995. (d) Bhupathy, M.; McNamara, J. M.; Sidler, D. R.; Volante, R. P.; Bergan, J. (Merck & Co., Inc.), U.S. Patent 5,614,632, 1997, and references therein.

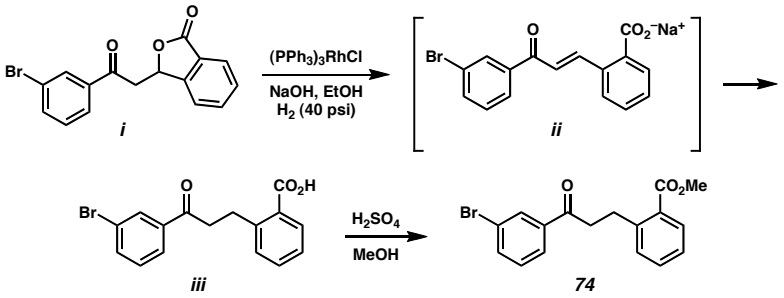
(11) (a) Kuethe, J. T.; Wong, A.; Wu, J.; Davies, I. W.; Dormer, P. G.; Welch, C. J.; Hillier, M. C.; Hughes, D. L.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 5993–6000. (b) Desai, R. C.; Cicala, P.; Meurer, L. C.; Finke, P. E. *Tetrahedron Lett.* **2002**, *43*, 4569–4570 and references therein.

(12) Substrates were tested under all of the available oxidative kinetic resolution protocols (see reference 1), and the best results are reported.

(13) The absolute configurations of **67** and **70** were assigned by conversion to known compounds (**67** → **72** and **70** → **78**).

(14) The absolute configuration of **68** was assigned by analogy to known compounds.

(15) In our hands, the reported benzofuranone reduction with Wilkinson's catalyst[10a] (**i** → **ii** → **iii**) did not proceed as described unless the starting material was further purified. This could be accomplished by filtering benzofuranone **i** in boiling EtOAc to remove insoluble impurities. Additionally, the product obtained after the benzofuranone reduction did not match the reported values for benzoic acid **iii**; however, brief exposure to acidic MeOH (conditions for the subsequent esterification reaction, **iii** → **74**) quantitatively converted it to the reported compound (**iii**).



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(17) Robertson, D. W.; Krushinski, J. H.; Fuller, R. W.; Leander, J. D. *J. Med. Chem.* **1988**, *31*, 1412–1417.

(18) The NMR characterization data have been previously reported in $CDCl_3$. In our hands, these compounds slowly decomposed in $CDCl_3$, so we have reported these data in C_6D_6.

(19) O'Brien, T.; Crocker, L.; Thompson, R.; Thompson, K.; Toma, P. H.; Conlon, D. A.; Feibush, B.; Moeder, C.; Bicker, G.; Grinberg, N. *Anal. Chem.* **1997**, *69*, 1999–2007.

APPENDIX ONE

Spectra Relevant to Chapter Two:

The Resolution of Important Pharmaceutical Building Blocks by Palladium-Catalyzed Aerobic Oxidation of Secondary Alcohols

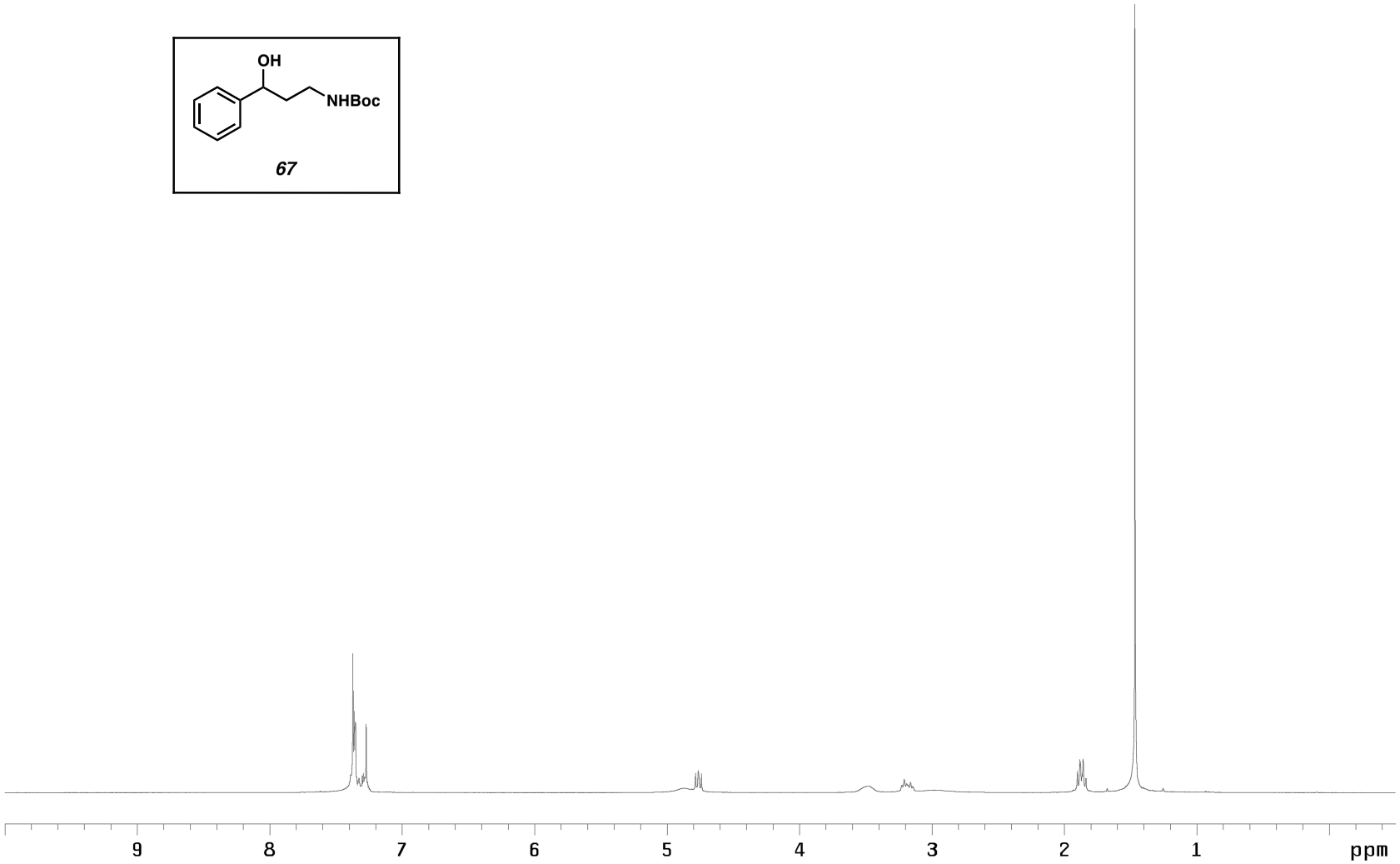


Figure A1.1 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **67**

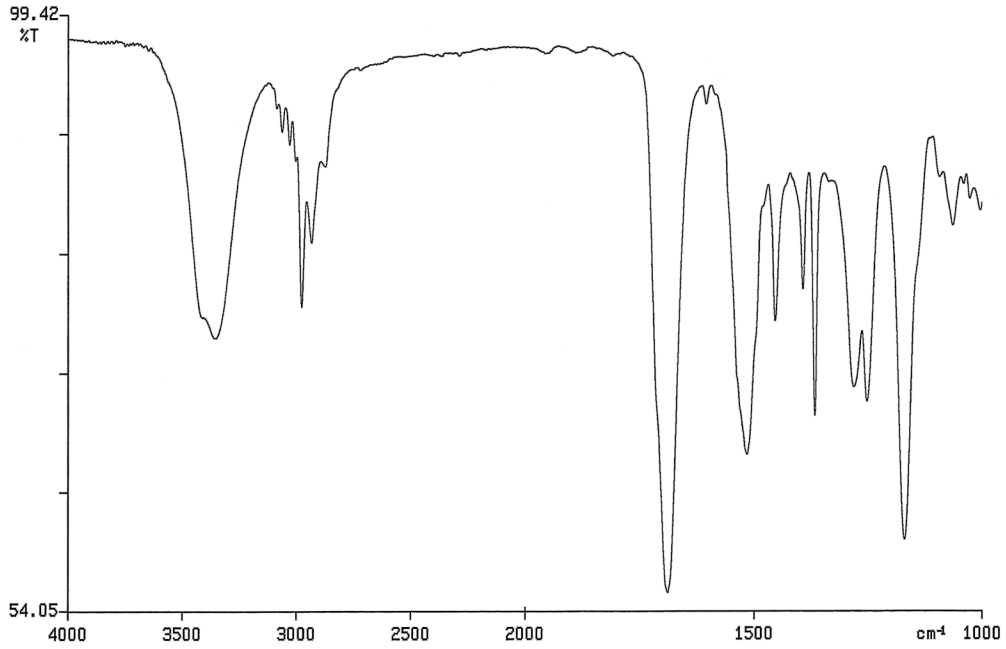


Figure A1.2 Infrared spectrum (thin film/NaCl) of compound **67**

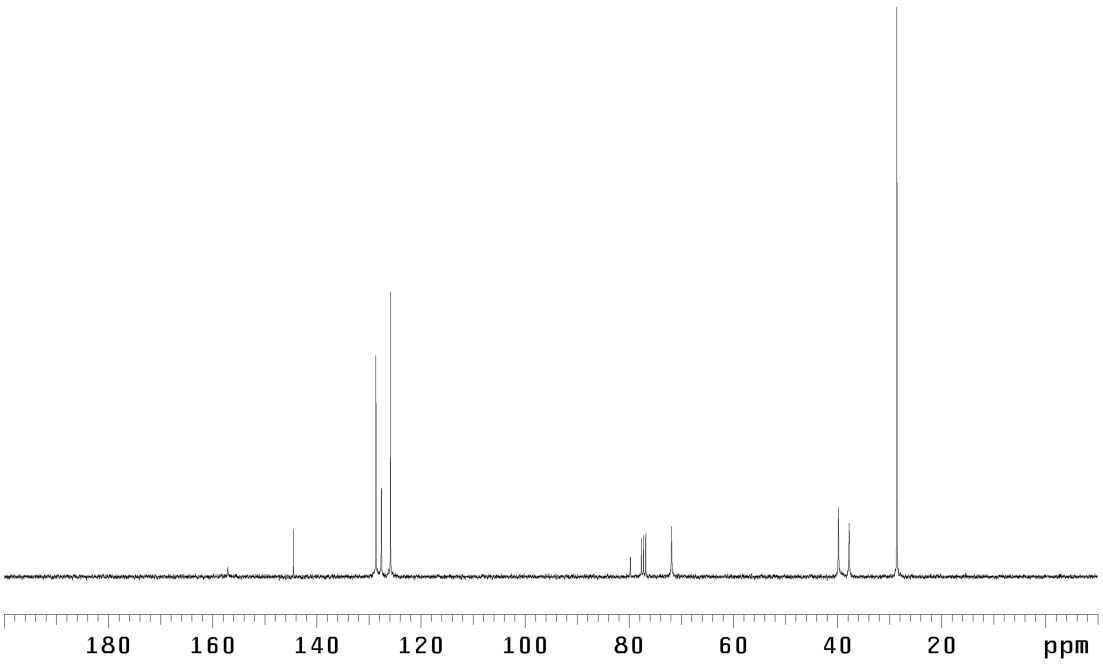


Figure A1.3 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **67**

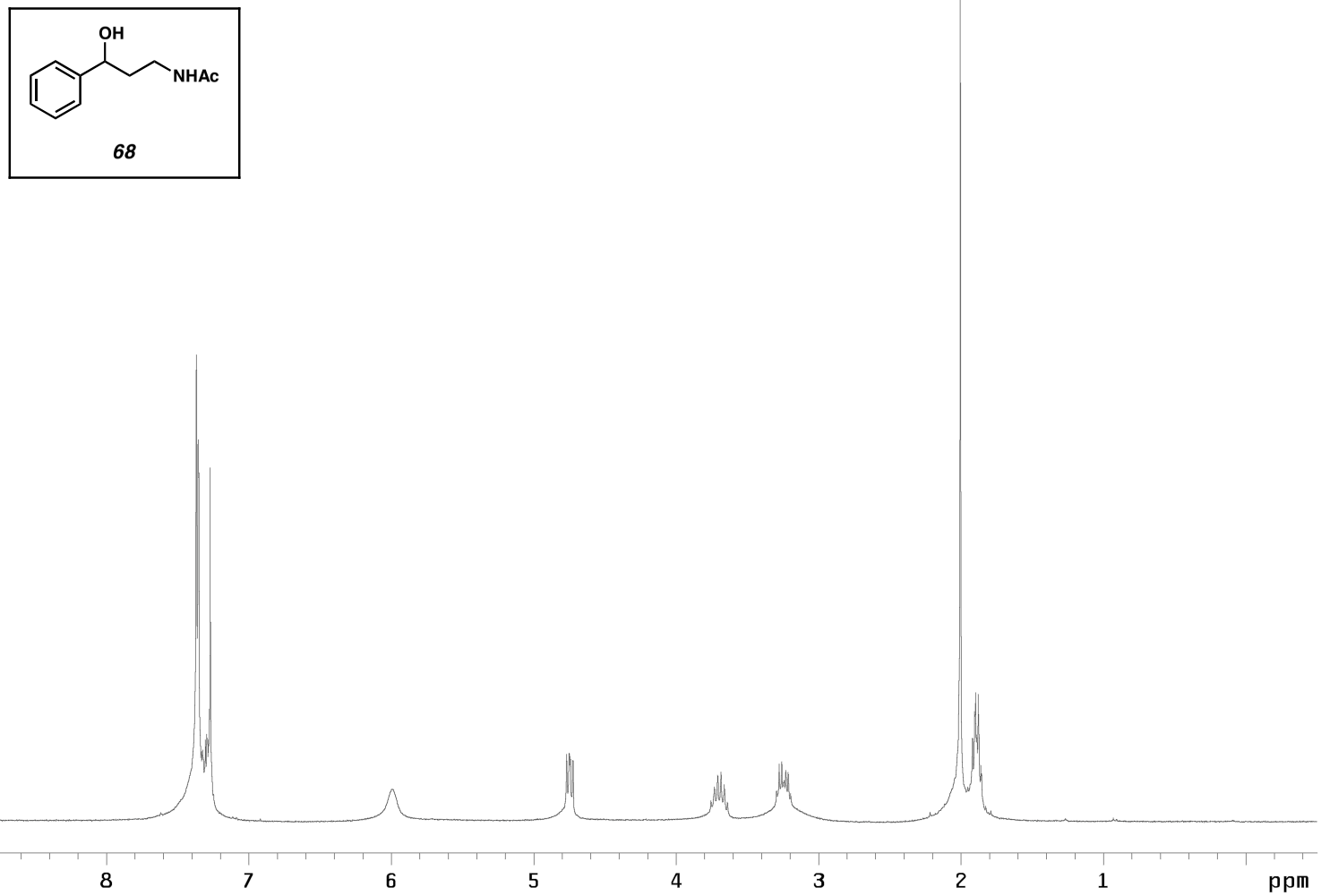


Figure A1.4 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **68**

Figure A1.5 Infrared spectrum (thin film/NaCl) of compound **68**

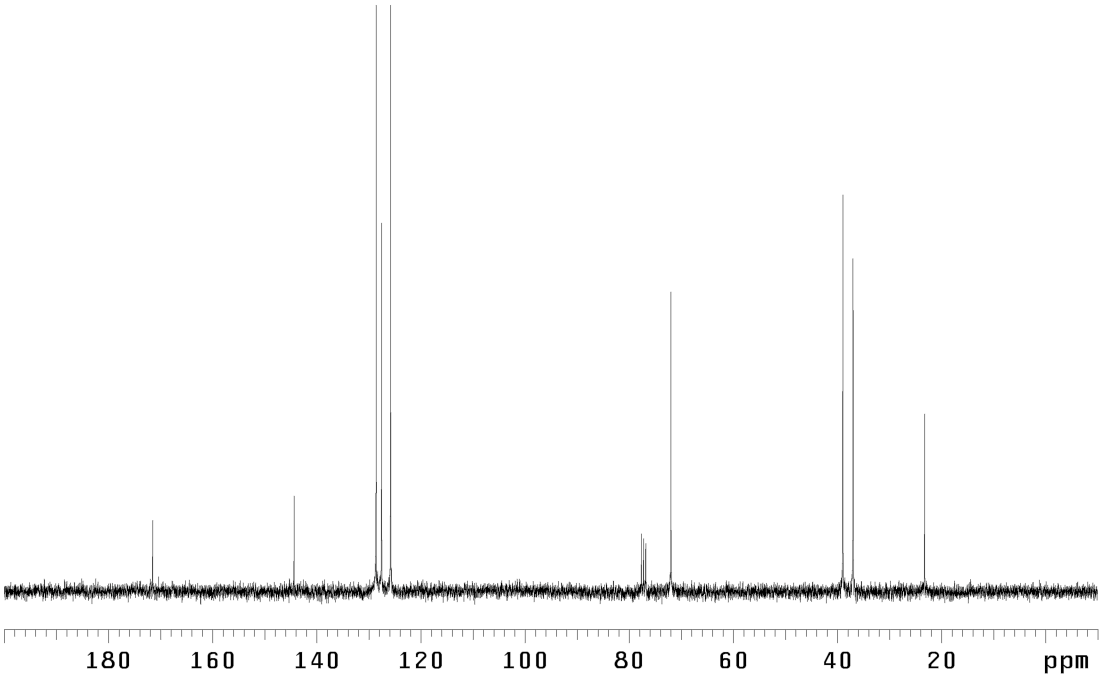


Figure A1.6 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **68**

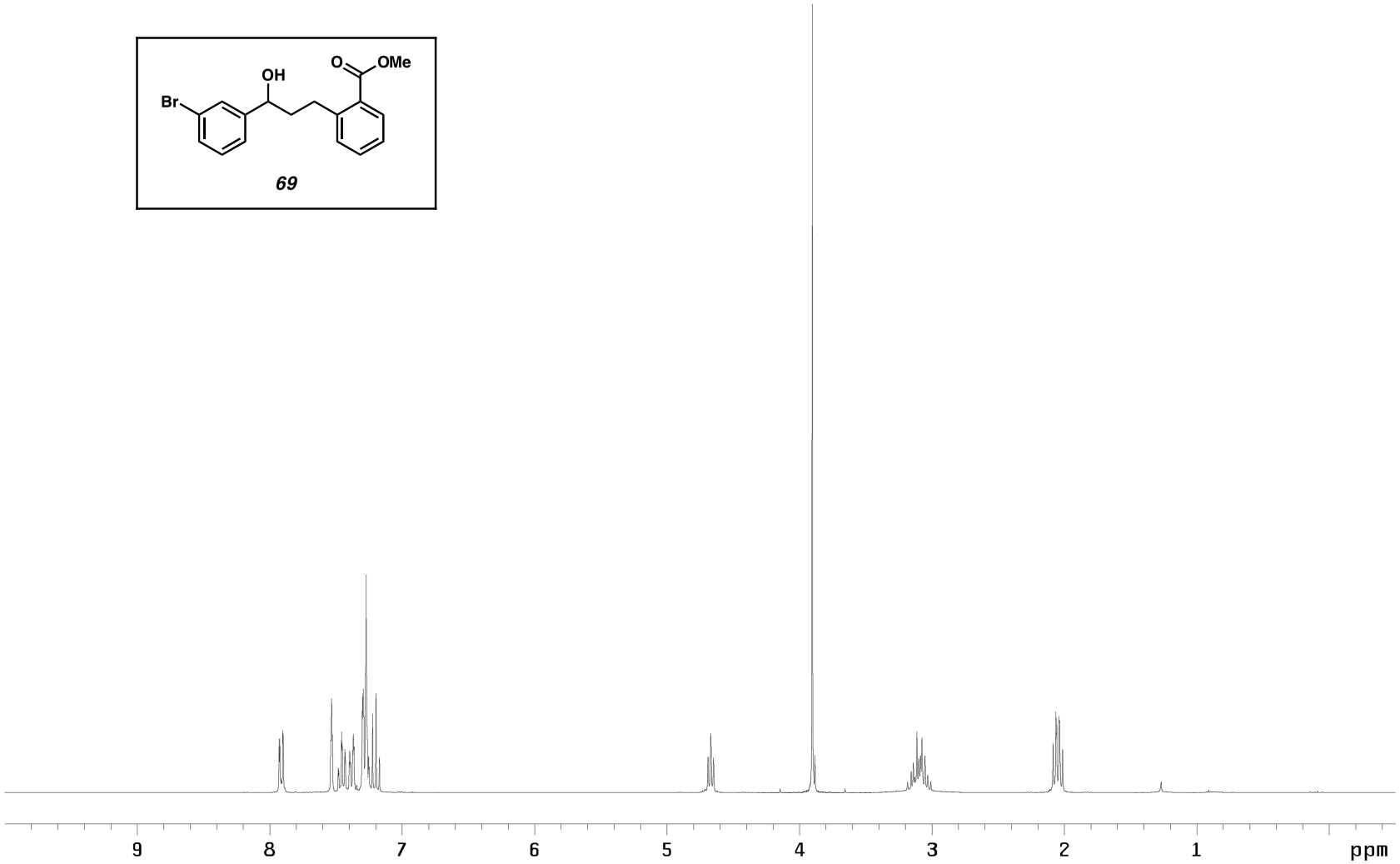


Figure A1.7 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **69**

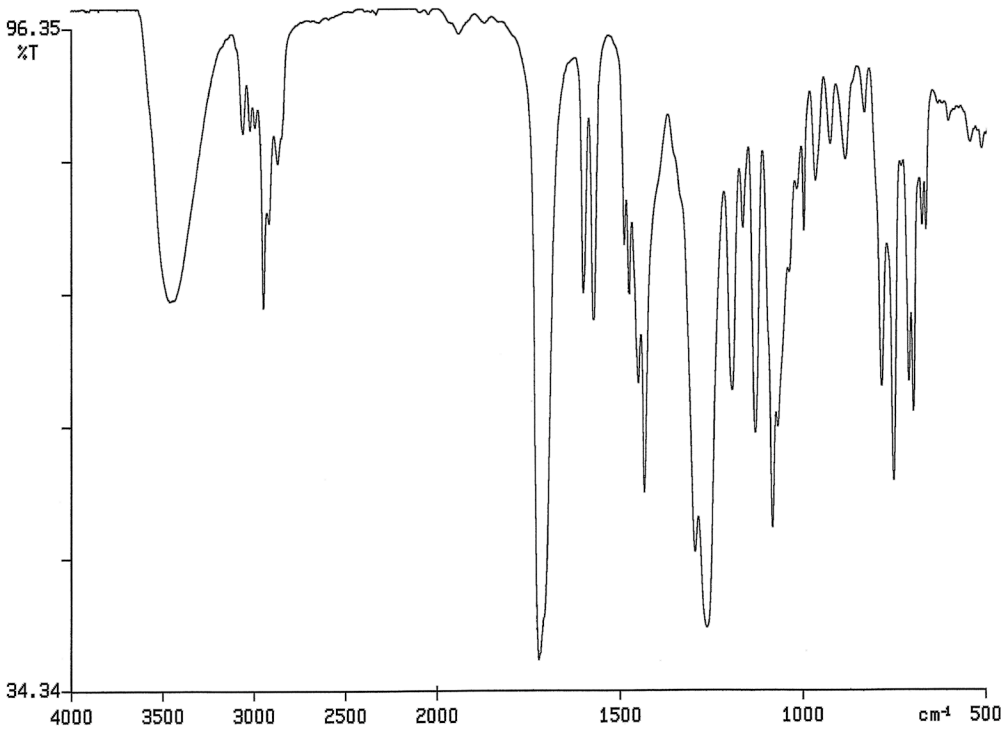


Figure A1.8 Infrared spectrum (thin film/NaCl) of compound **69**

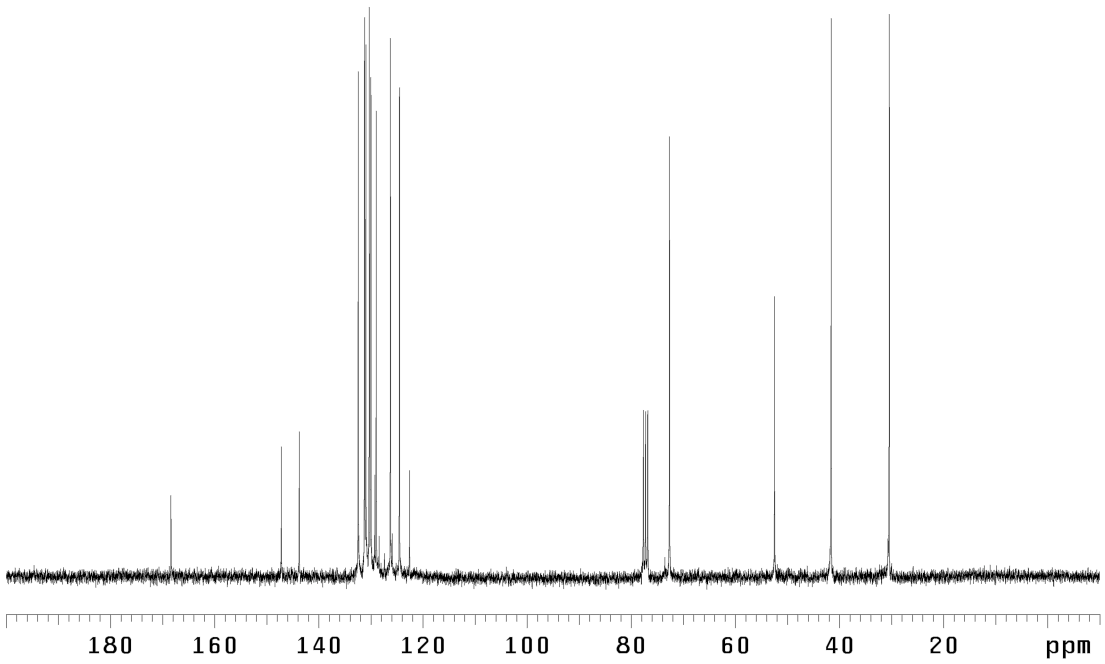


Figure A1.9 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **69**

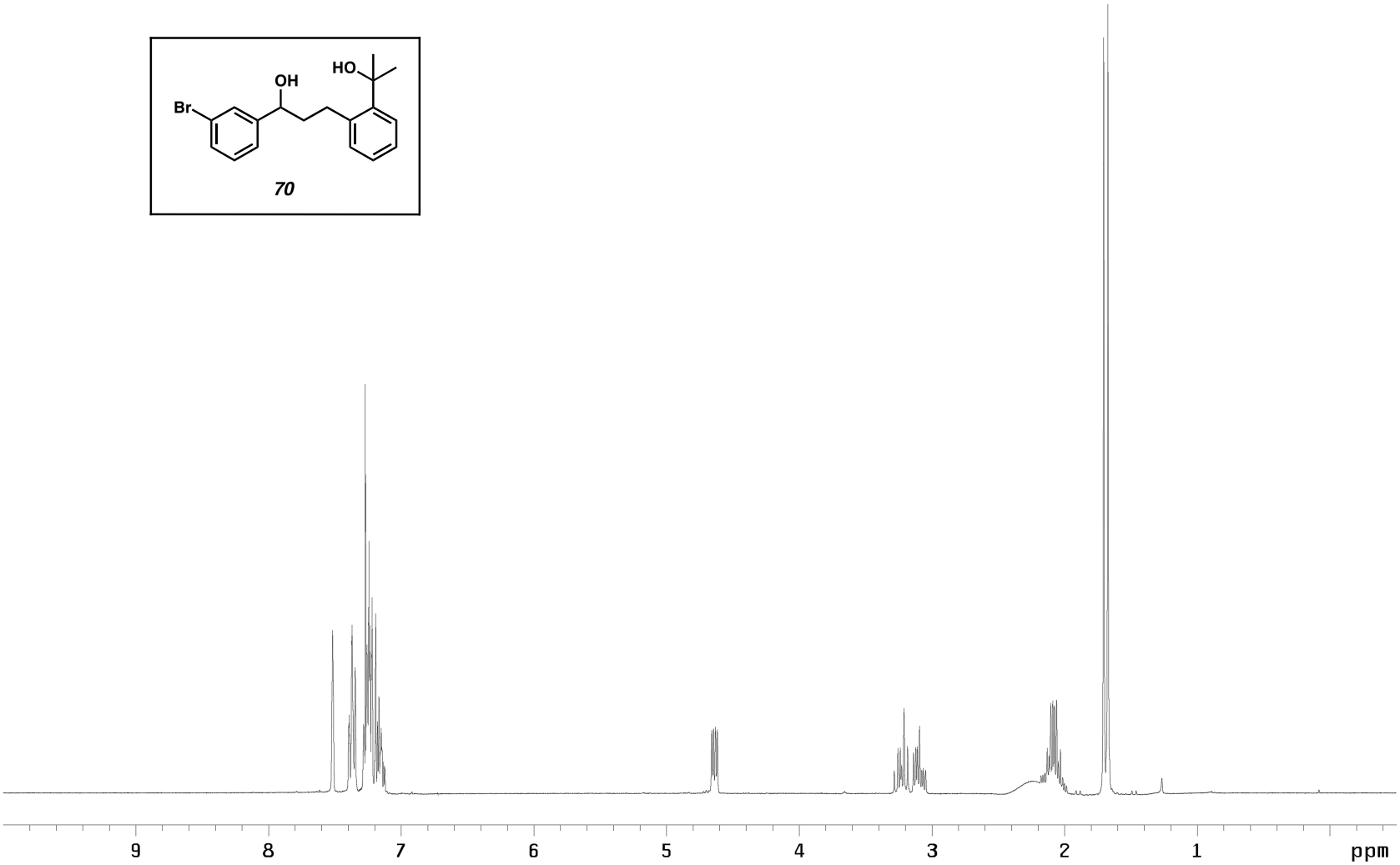


Figure A1.10 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **70**

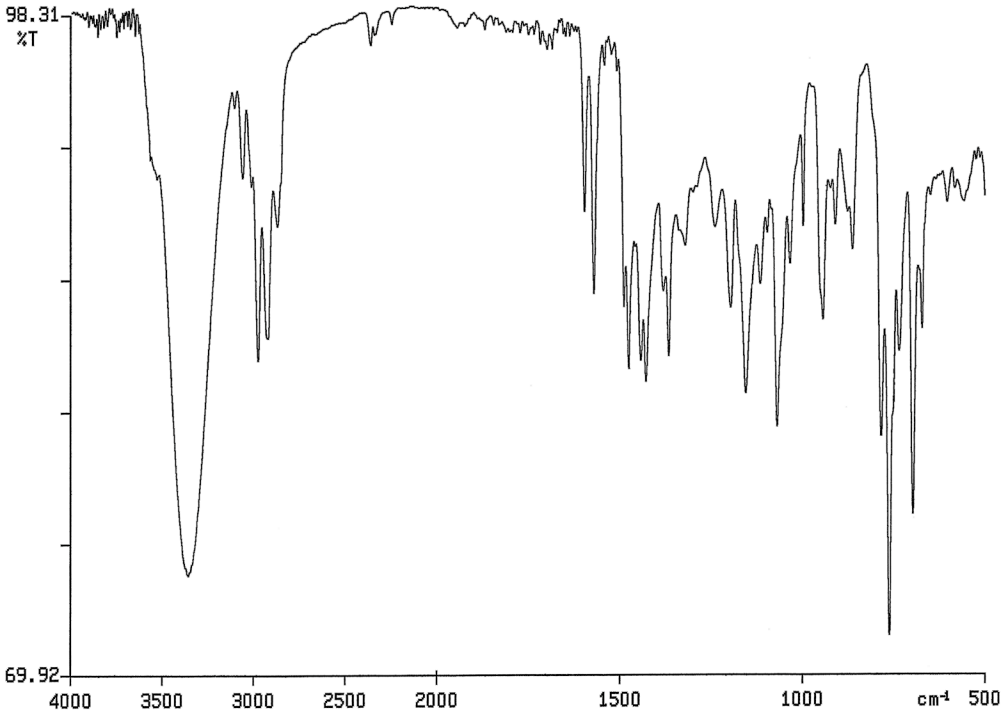


Figure A1.11 Infrared spectrum (thin film/NaCl) of compound **70**

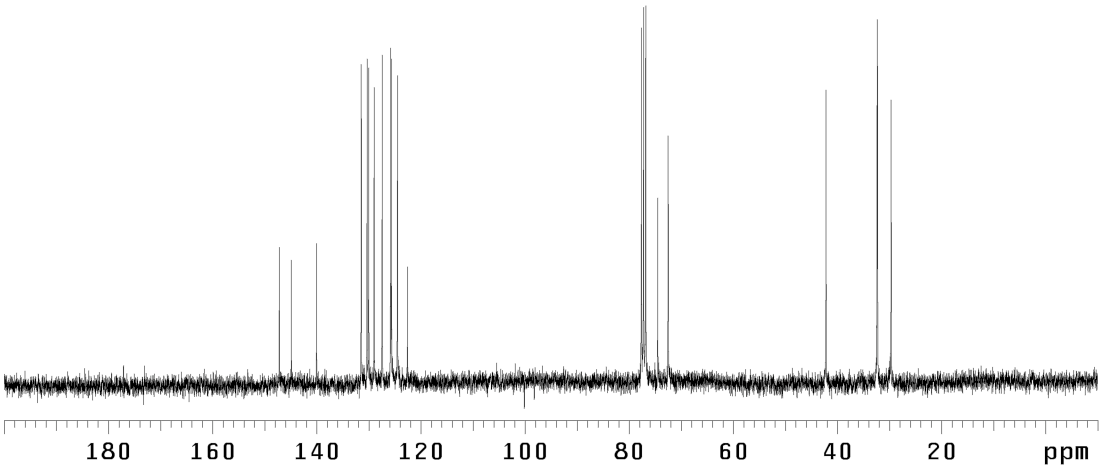


Figure A1.12 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **70**

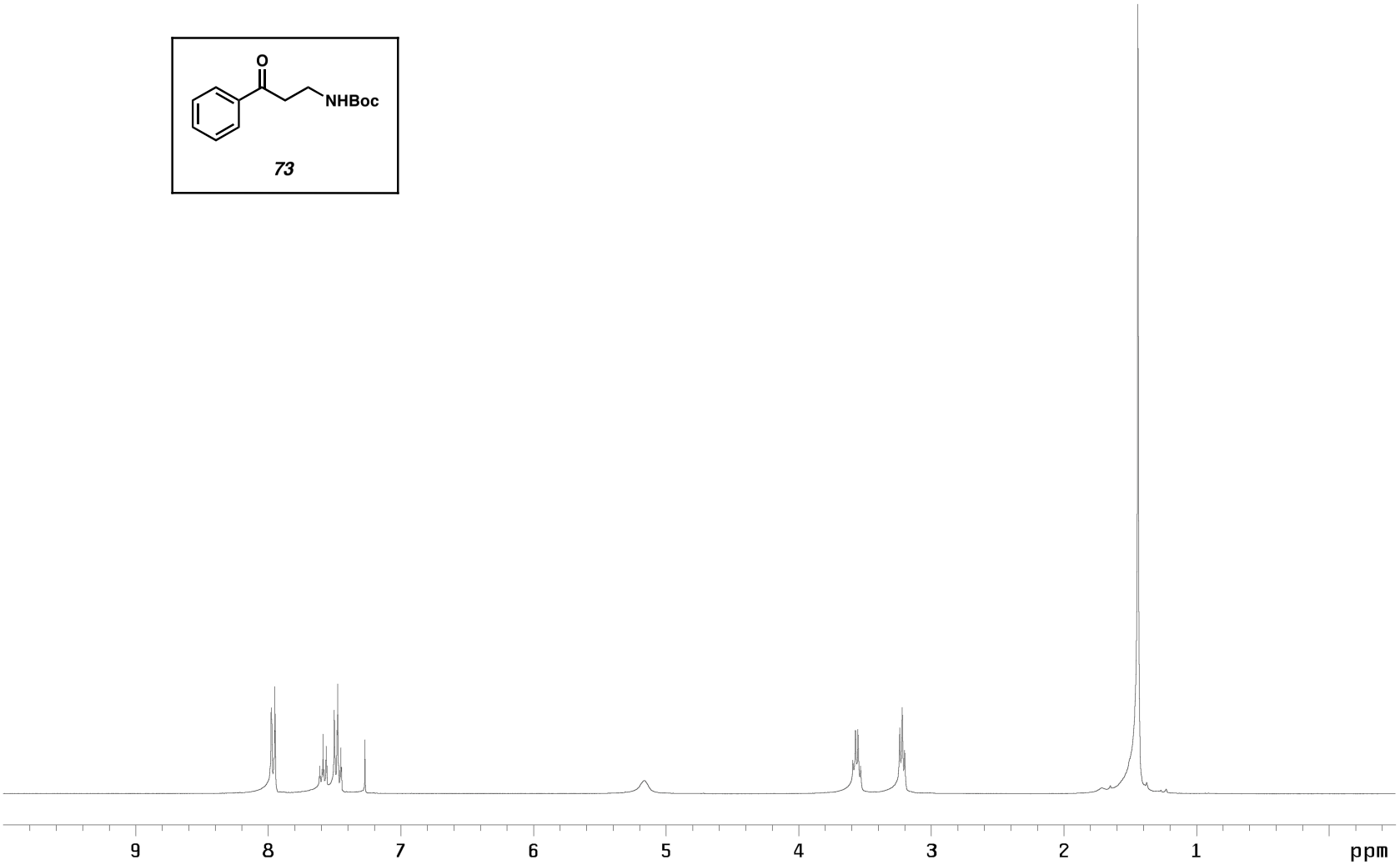


Figure A1.13 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **73**

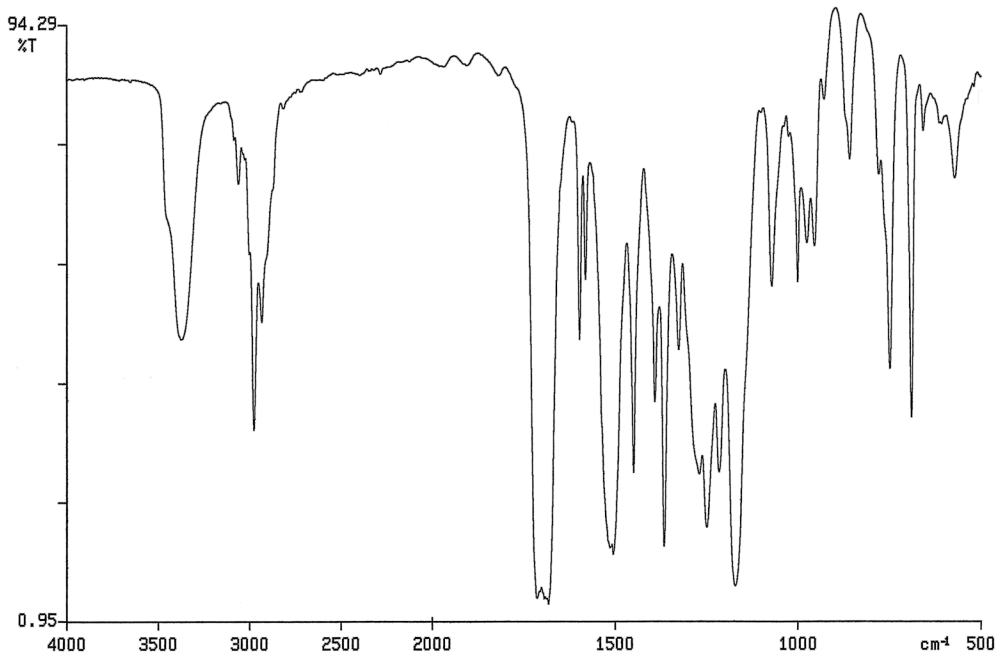


Figure A1.14 Infrared spectrum (thin film/NaCl) of compound **73**

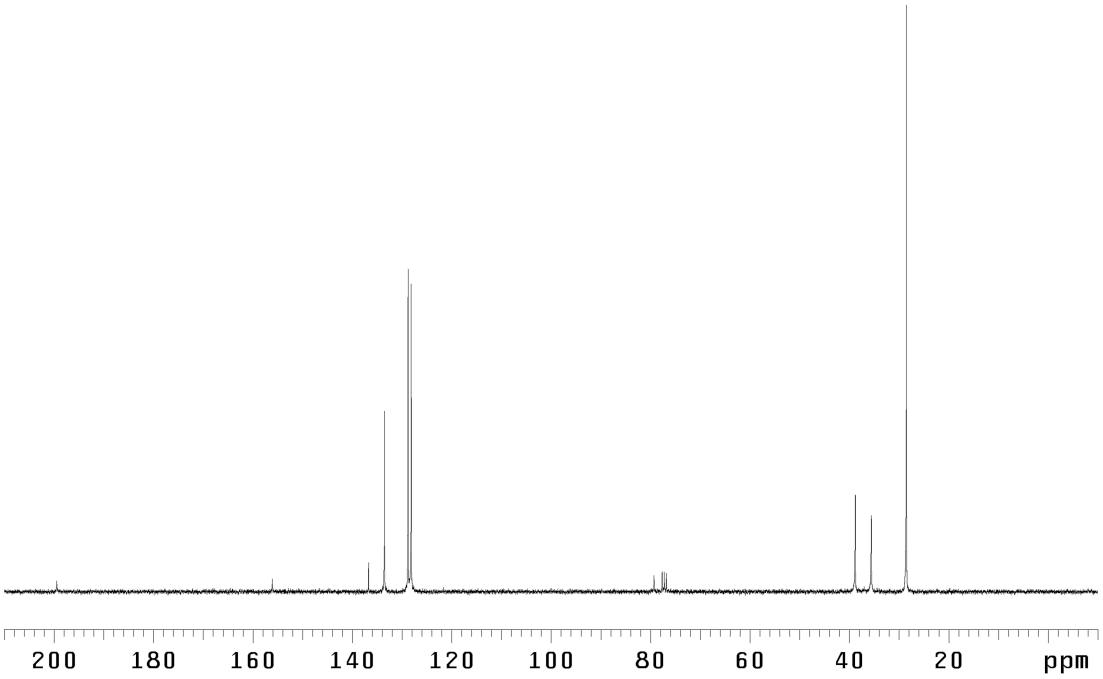


Figure A1.15 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **73**

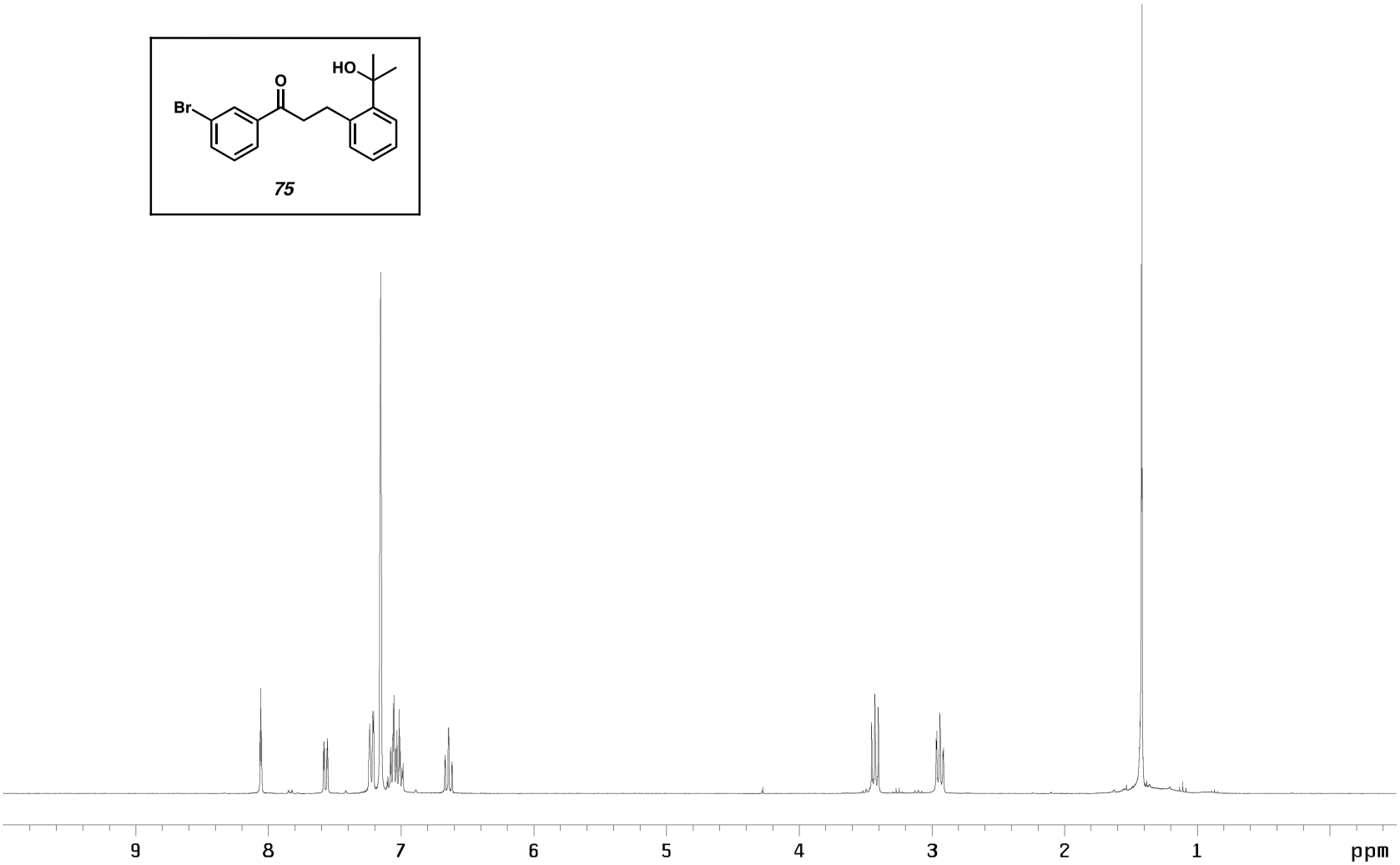


Figure A1.16 ^{1}H NMR (300 MHz, C_6D_6) of compound **75**

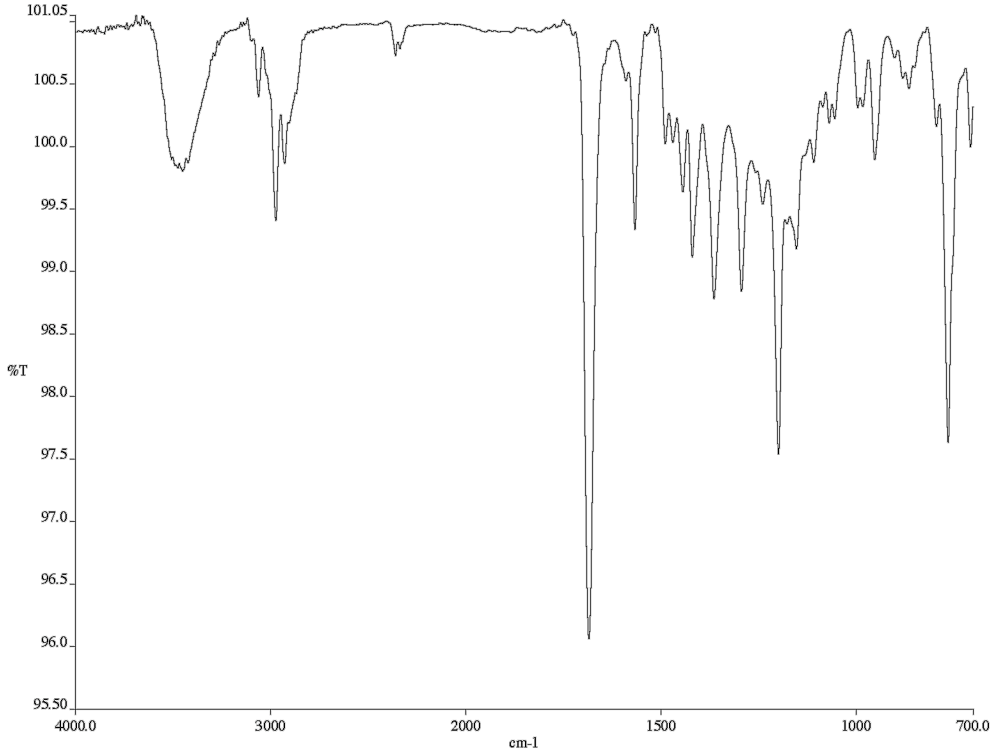


Figure A1.17 Infrared spectrum (thin film/NaCl) of compound **75**

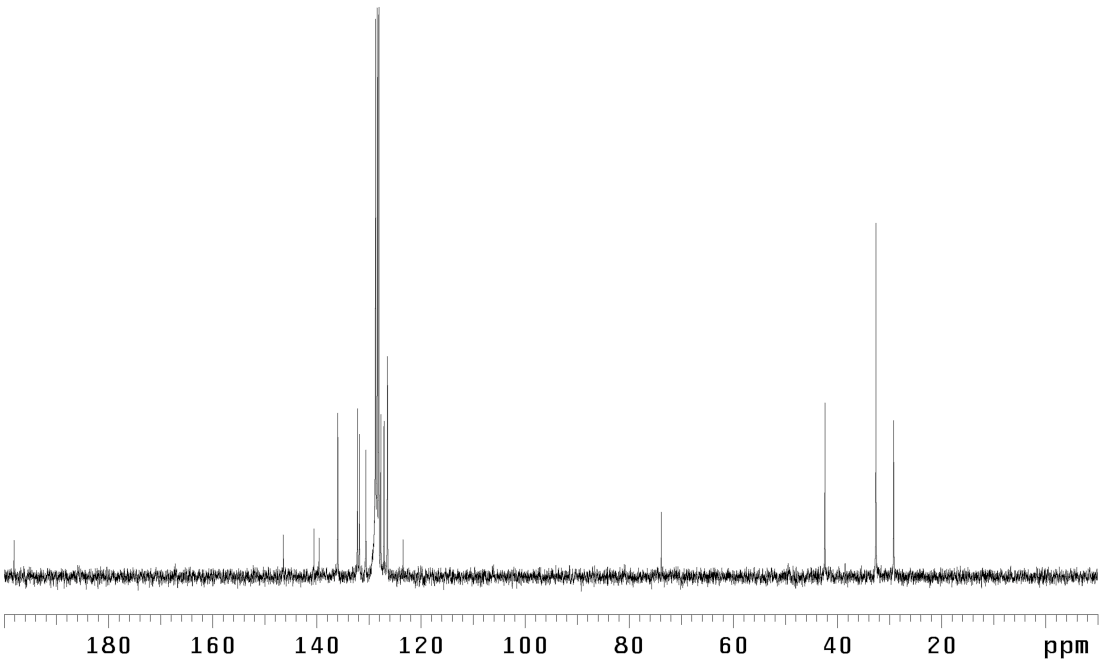


Figure A1.18 ^{13}C NMR (75 MHz, C_6D_6) of compound **75**

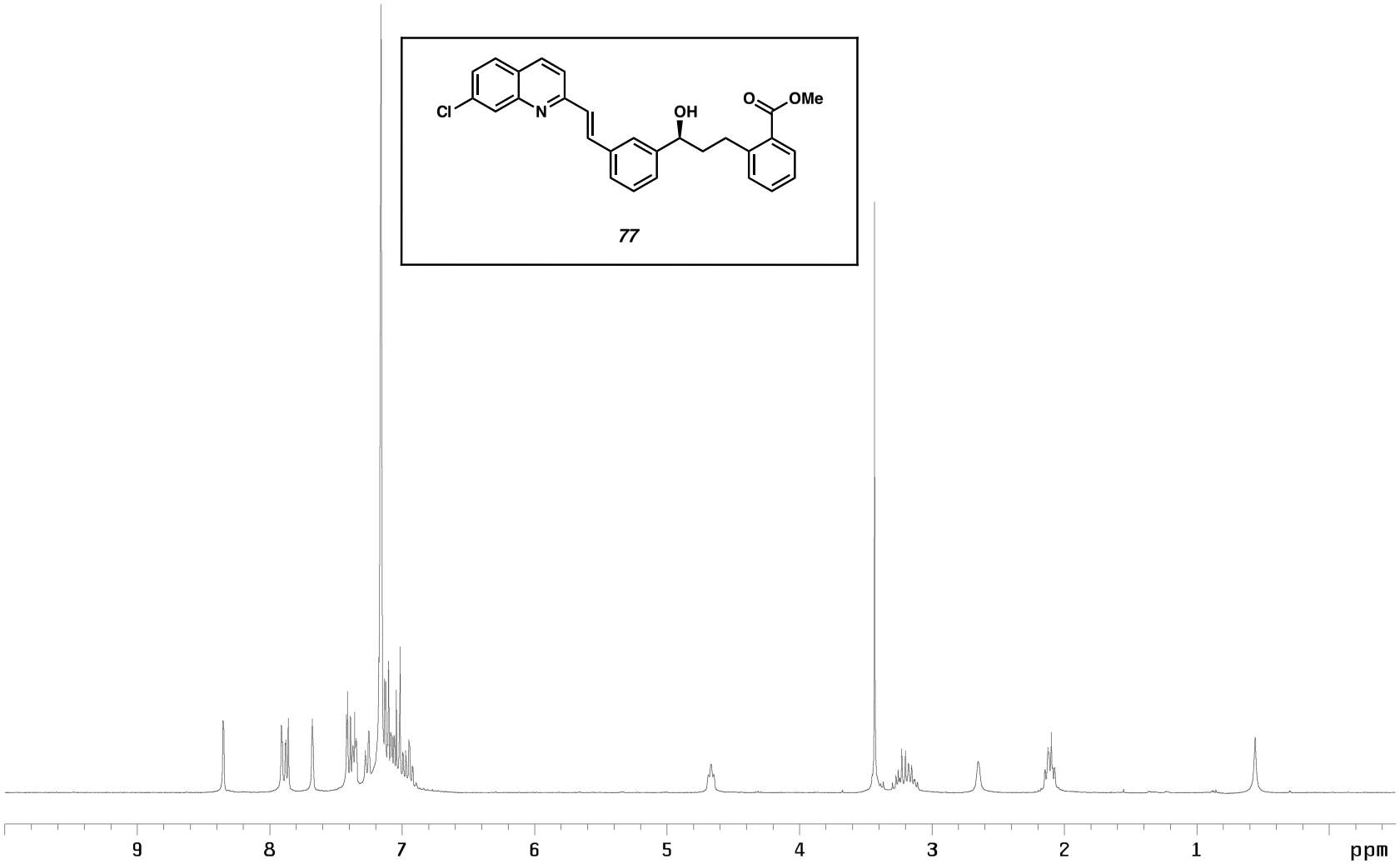


Figure A1.19 ^{1}H NMR (300 MHz, C_6D_6) of compound **77**

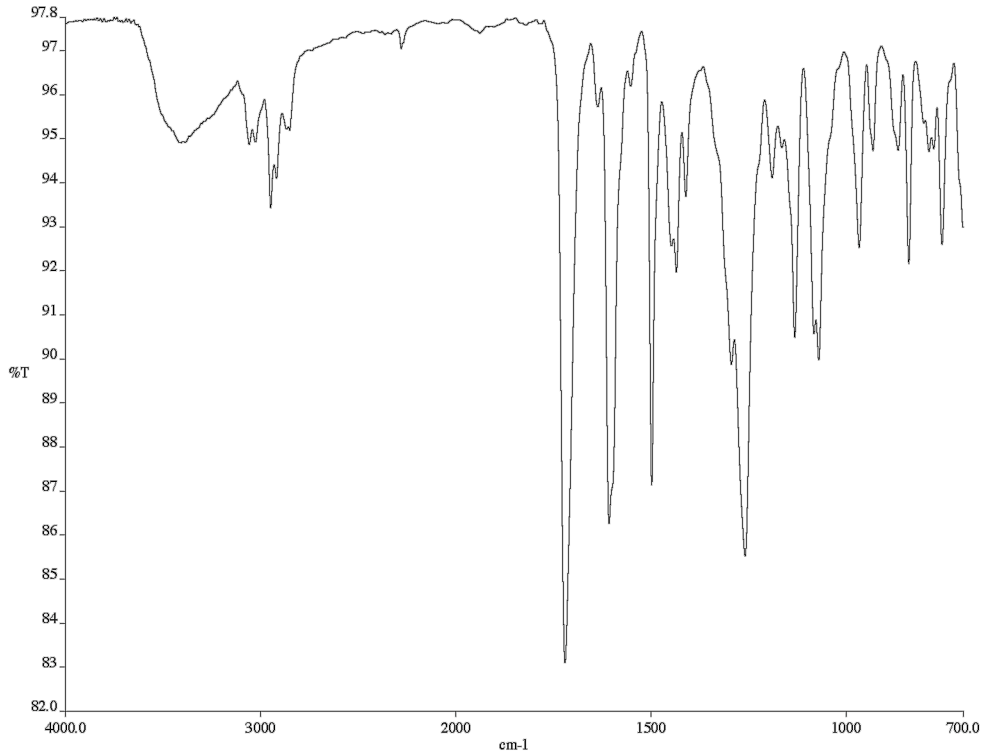


Figure A1.20 Infrared spectrum (thin film/NaCl) of compound **77**

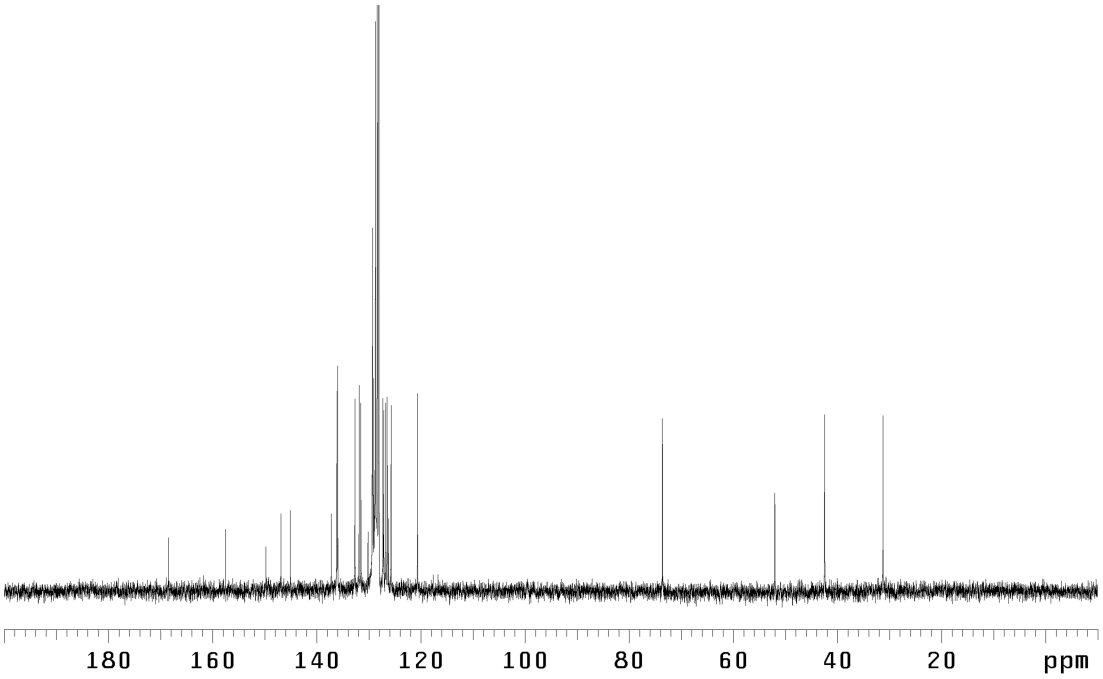


Figure A1.21 ^{13}C NMR (75 MHz, C_6D_6) of compound **77**

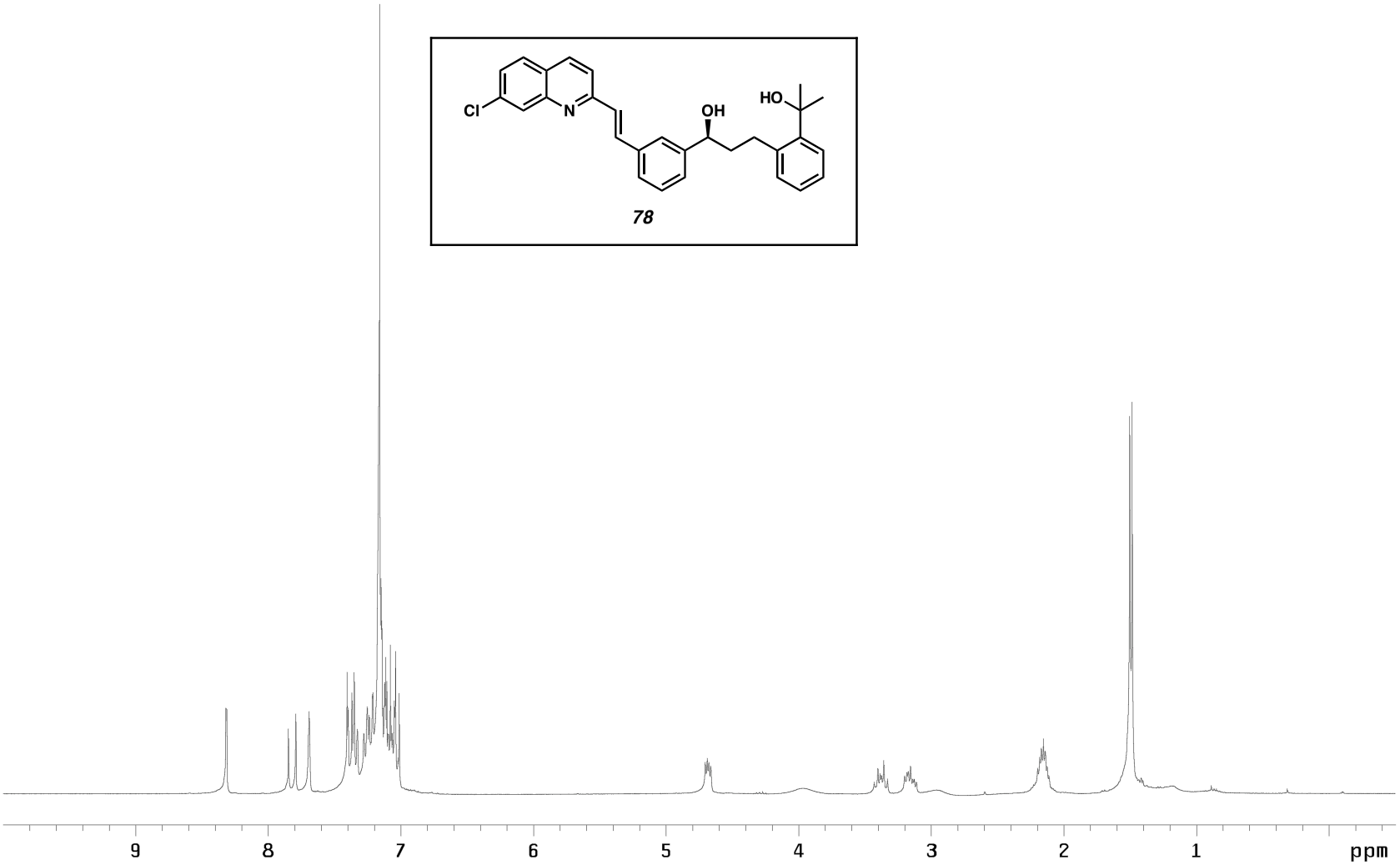


Figure A1.22 ^{1}H NMR (300 MHz, C_6D_6) of compound **78**

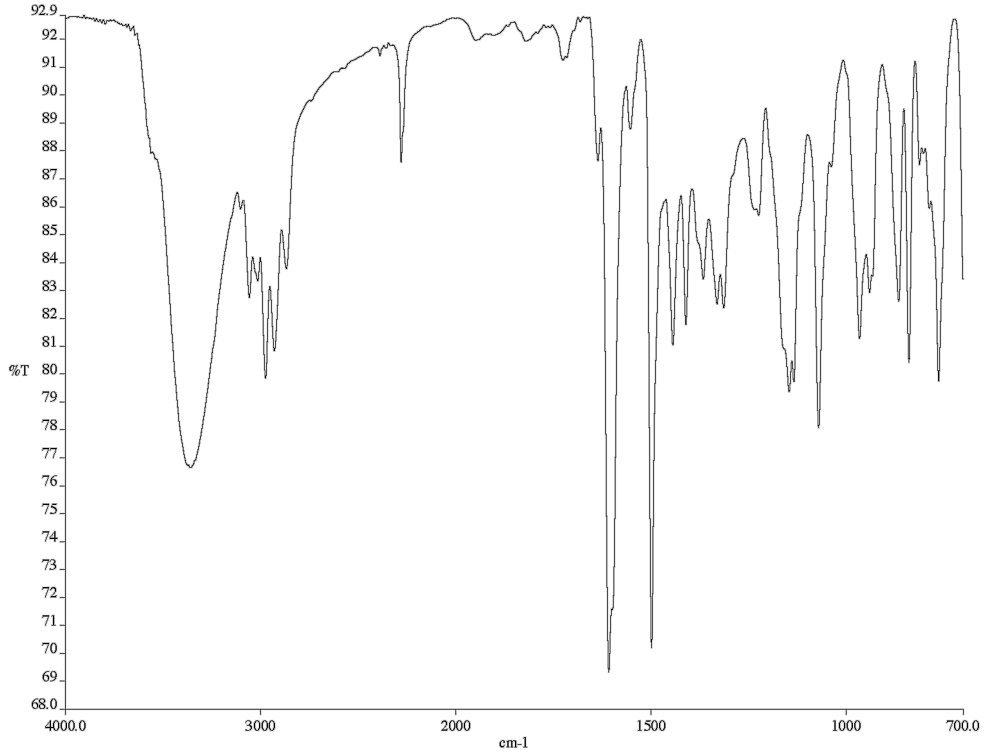


Figure A1.23 Infrared spectrum (thin film/NaCl) of compound **78**

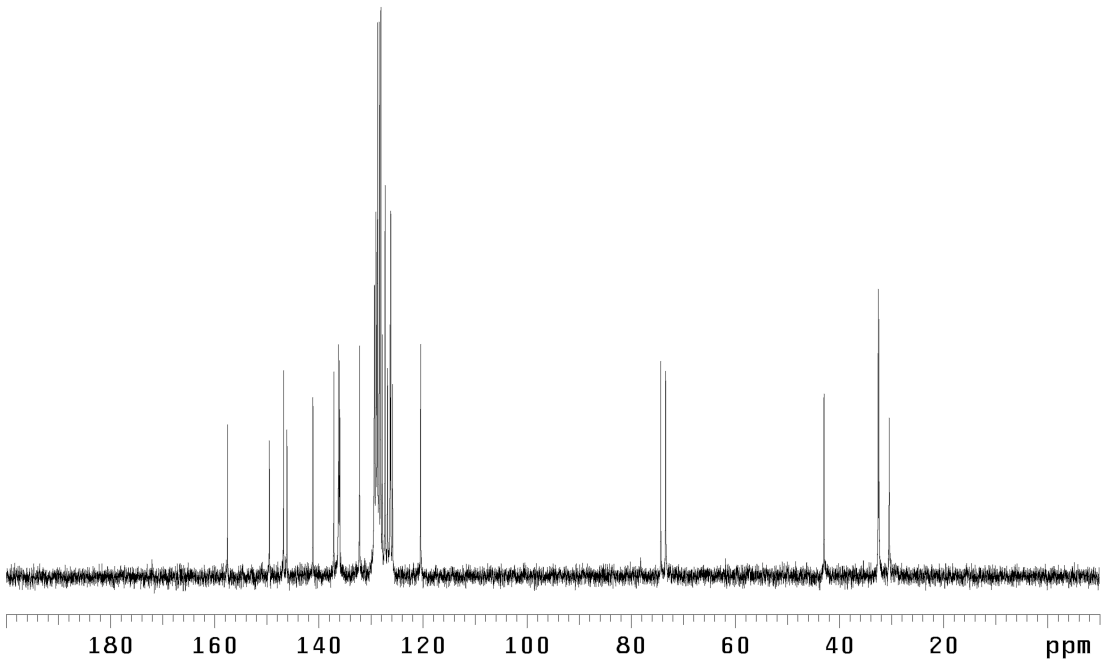


Figure A1.24 ^{13}C NMR (75 MHz, C_6D_6) of compound **78**

CHAPTER THREE

The Total Syntheses of (+)- and (–)-Dragmacidin F[†]

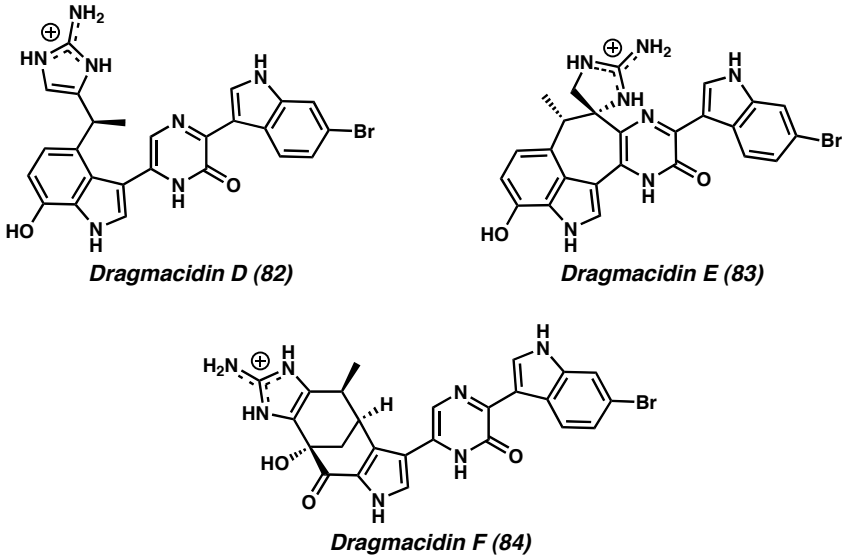
3.1 Background

3.1.1 Introduction

Over the past several decades, the search for natural products in marine environments has led to the discovery of a number of biologically active bis(indole) alkaloids.[1] These compounds, as well as their unnatural analogs, have shown promise as leads for the development of novel therapeutics, particularly in the area of cancer.[2] Of the many bis(indole) alkaloids found in nature, the dragmacidins have received considerable attention from the scientific community over the past decade due to their broad range of biological activity and complex structures.[3,4,5] This structurally elaborate class of bromoindole marine alkaloids was isolated from a variety of deep-water sponges including *Dragmacidon*, *Halicortex*, *Spongosorites*, and *Hexadella,* and the tunicate *Didemnum candidum.* As part of a research program geared toward the synthesis of complex heterocyclic natural products, our laboratory initiated an effort in the fall of 2000 to synthesize those dragmacidins that possess a pyrazinone core, namely, dragmacidins D, E, and F (Figure 3.1.1, **82**–**84**).[4]

[†] This work was performed in collaboration with Neil K. Garg, a graduate student in the Stoltz group (Ph.D. 2005).

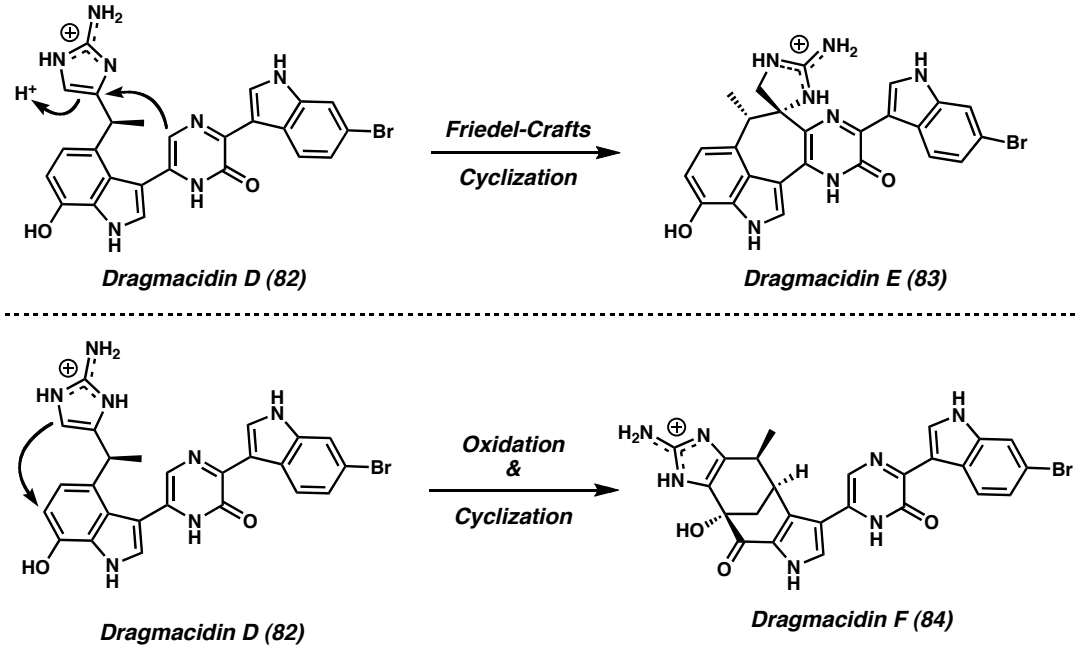
Figure 3.1.1



3.1.2 Biosynthesis

Dragmacidin D (**82**),[4a,b] was selected as a primary target predominantly because it was believed to be the biosynthetic precursor to dragmacidins E (**83**) and F (**84**).[4c] (Scheme 3.1.1). Dragmacidins D (**82**) and E (**83**) are related via a Friedel-Crafts cyclization between the pyrazinone and aminoimidazole groups of dragmacidin D, which occurs in order to construct the seven-membered ring of dragmacidin E (i.e., **82** → **83**). Although **84** does not contain a bis(indole) framework, it is presumed to be derived biosynthetically from dragmacidin D (**82**) via an oxidative de-aromatization/cyclization process (i.e., **82** → **84**). Related oxidation pathways for tryptophan derivatives have been observed in nature.[6] Furthermore, dragmacidin D (**82**) seemed to be the least structurally complex of the pyrazinone-containing dragmacidin family members, and therefore a suitable entry point into this class.

Scheme 3.1.1

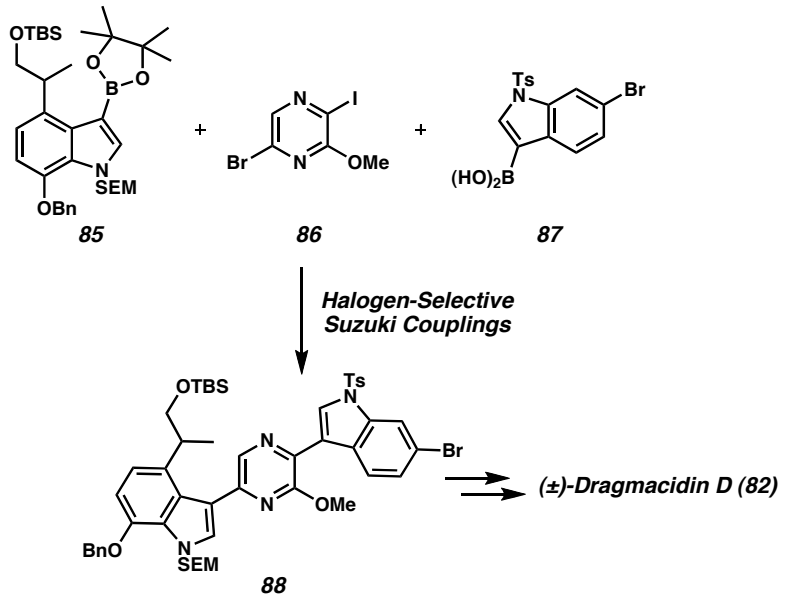


3.1.3 Previous Synthetic Studies

In 2002, our laboratory reported the total synthesis of (±)-dragmacidin D (**82**), the first of any of these three unique dragmacidin alkaloids to be prepared.[7] The highly convergent approach to **82** relied on a series of halogen-selective Suzuki cross-couplings of **85**, **86**, and **87** to build the bis(indole)pyrazine skeleton (**88**) of the natural product (Scheme 3.1.2). In addition, the appropriate selection and cleavage sequence of protecting groups proved to be of critical importance, as only highly specific arrangements permitted successful late-stage manipulations. We hypothesized that this general synthetic strategy could also be applied to the other pyrazinone-containing members of the dragmacidin family. Having developed a strategy to construct the bis(indole)pyrazinone core of dragmacidin D (**82**), we set out to extend the scope of our halogen-selective Suzuki coupling methodology to the synthesis of related natural

products. We reasoned that our approach could be amenable to the preparation of the antiviral agent dragmacidin F (**84**),[4c] which is perhaps the most daunting target of the dragmacidin natural products.[8,9]

Scheme 3.1.2



3.1.4 Isolation and Bioactivity of Dragmacidin F

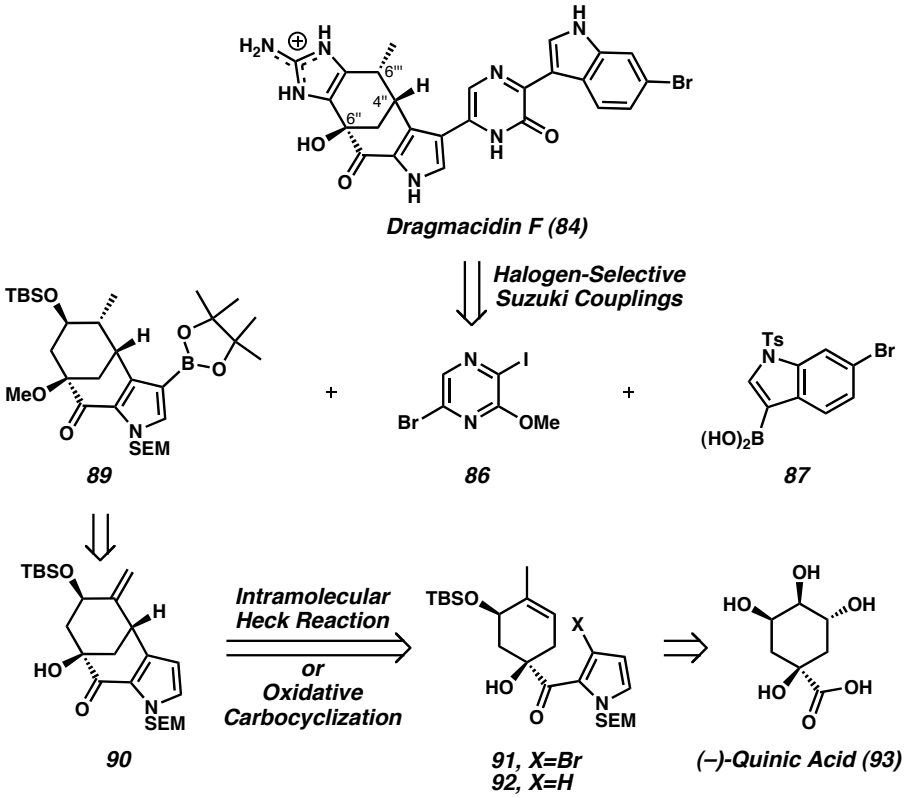
Dragmacidin F (**84**) was isolated in 2000 from the ethanol extracts of the Mediterranean sponge *Halicortex* sp. This marine natural product exhibits in vitro antiviral activity against herpes simplex virus (HSV-I; EC_{50} = 95.8 μM) and human immunodeficiency virus (HIV-I; EC_{50} = 0.91 μM),[4c] and thus is an attractive target from a biological perspective. In addition, dragmacidin F (**84**) possesses a variety of structural features that make it an attractive target for total synthesis. These synthetic challenges include the differentially substituted pyrazinone, the bridged [3.3.1] bicyclic ring system, which is fused to both the trisubstituted pyrrole and aminoimidazole heterocycles, and the

installation and maintenance of the 6-bromoindole fragment. Given the limited supply of dragmacidin F (**84**) available from natural sources, a successful synthetic approach to **84** could also facilitate the production of sufficient quantities of material needed for advanced biological studies.

3.1.5 Retrosynthetic Analysis of Dragmacidin F

Our retrosynthetic analysis for dragmacidin F (**84**) is shown in Scheme 3.1.3. On the basis of our experience with dragmacidin D (**82**), we reasoned that the aminoimidazole moiety would best be incorporated at a late stage in the synthesis.[7] The carbon skeleton of the natural product would then arise via a series of halogen-selective Suzuki cross-coupling reactions (**89** + **86** + **87**). Pyrazine **86** and indoloboronic acid **87** were both readily accessible,[7] while pyrroloboronic ester **89** perhaps could be derived from pyrrole-fused bicycle **90**, our key retrosynthetic intermediate. We then targeted bicycle **90** from two related directions: a Pd(0)-mediated intramolecular Heck reaction[10] of bromopyrrole **91**, and a Pd(II)-promoted oxidative carbocyclization[11] involving *des*-bromopyrrole **92**. The successful implementation of the latter method was particularly attractive since it is closely aligned with our interest in Pd(II)-catalyzed dehydrogenation reactions.[12] Both of the cyclization substrates (**91** and **92**) could be prepared from commercially available (–)-quinic acid (**93**).[13] At the time of this synthetic effort, the absolute stereochemistry of natural dragmacidin F (**84**) was not known; thus, the absolute stereochemistry of our target (**84**) was chosen arbitrarily.

Scheme 3.1.3



3.2 The Total Synthesis of (+)-Dragmacidin F

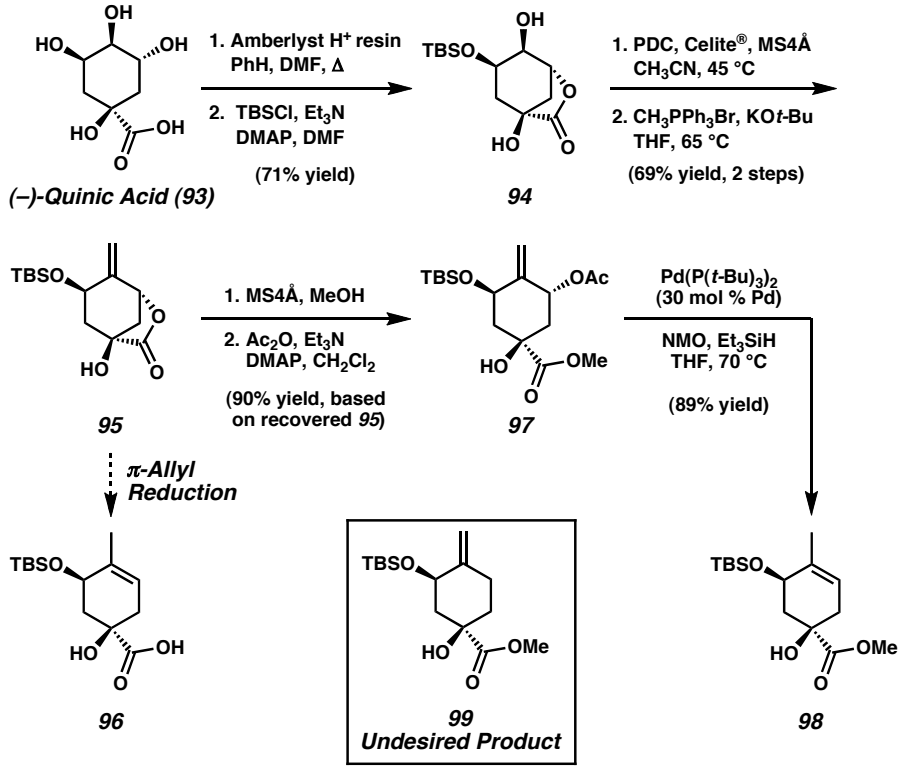
3.2.1 Synthesis of Cyclization Substrates

Our synthesis of dragmacidin F (**84**) began with a known two-step protocol involving lactonization and silylation of (–)-quinic acid (**93**) to afford bicyclic lactone **94** (Scheme 3.2.1).[14] Subsequent oxidation and Wittig olefination of **94** produced exo-methylene lactone **95** in good yield. Initially, we envisioned the direct conversion of lactone **95** to unsaturated carboxylic acid **96** by executing a homogeneous Pd(0)-catalyzed π-allyl hydride addition reaction.[15] Despite considerable experimentation, however, exposure of lactone **95** to a variety of Pd and hydride sources under standard conditions[15] led to the formation of complex product mixtures. As a result, a more

stepwise approach was tried. Methanolysis of lactone **95** followed by acetylation of the resulting 2° alcohol[16] gave rise to allylic acetate **97**, another potential substrate for π-allyl reduction chemistry. Although **97** did react under most literature protocols, undesired exocyclic olefin **99** was typically the major product observed, and **98** could not be isolated by conventional purification techniques. This was not an altogether unexpected outcome; in fact, overcoming the practical problem of regioselectivity (e.g., **98** vs. **99**) in nucleophilic addition to π-allylpalladium complexes has been the subject of intense study.[17]

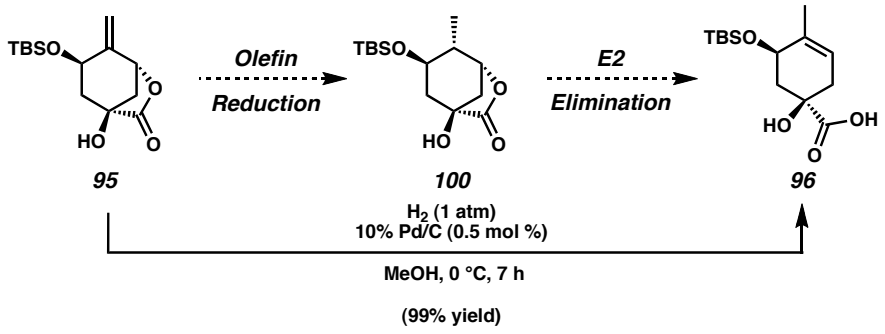
After substantial optimization, we were able to access **98** as the major product by employing stoichiometric $Pd(P(t\text{-}Bu)_3)_2$[18] in the presence of triethylsilane as a reductant. Further refinements designed to facilitate catalysis led to a reduced Pd loading (30 mol %) when *N*-methylmorpholine-*N*-oxide (NMO) was used as an additive.[19] Under these conditions, cyclohexene **98** was obtained in 89% yield as a single olefin regioisomer. Unfortunately, this transformation often gave inconsistent results and was particularly sensitive to oxygen, water, and the quality of Et_3SiH. These difficulties coupled with the high catalyst loading resulted in substantial material throughput problems. We therefore sought yet another method to prepare cyclohexene **98**, or a closely related derivative thereof (i.e., **96**), in a more facile and preparative manner.

Scheme 3.2.1



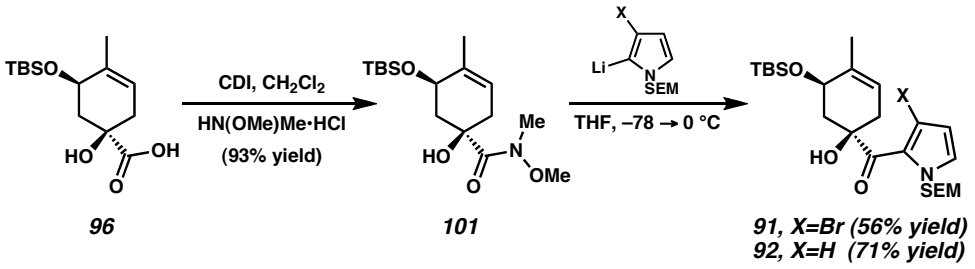
In our revised plan, we conceived a two-step route to obtain carboxylic acid **96** via diastereoselective reduction of olefin **95** followed by base-promoted elimination of the carboxylate functionality of **100** (Scheme 3.2.2). The first part of this sequence was attempted by exposing olefin **95** to standard catalytic hydrogenation conditions (Pd/C, 1 atm H_2). Surprisingly, these conditions led to the production of a compound that was more polar than we expected for simple olefin hydrogenation (i.e., **100**). To our delight, the product was identified as unsaturated carboxylic acid **96**. Under our optimized reaction conditions (0.5 mol % Pd/C, 1 atm H_2, MeOH, 0 °C), essentially quantitative reductive isomerization to **96** was observed.[20,21]

Scheme 3.2.2



With facile access to cyclohexene carboxylic acid **96**, preparation of the key cyclization precursors proceeded without difficulty. Activation of acid **96** with CDI followed by the addition of HN(OMe)Me•HCl afforded Weinreb amide **101** (Scheme 3.2.3). The Weinreb amide functionality was then displaced with the appropriate lithiopyrrole[22] reagent to produce Heck cyclization substrate **91**[23] and oxidative cyclization substrate **92**.

Scheme 3.2.3

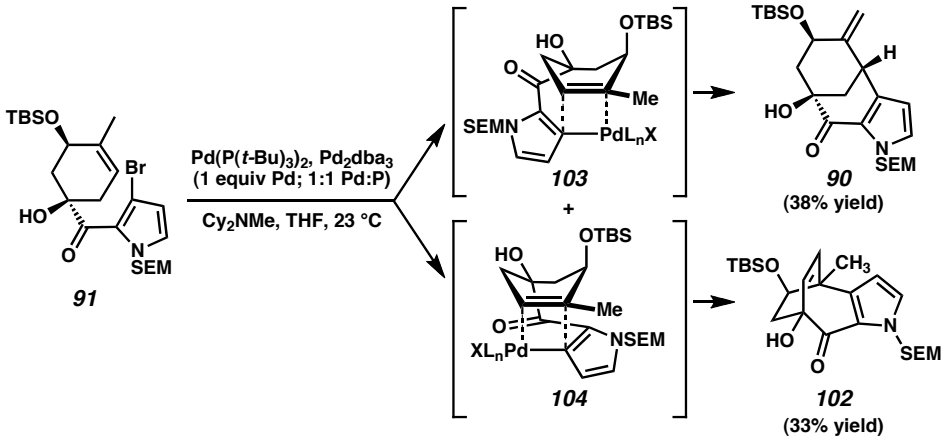


3.2.2 Intramolecular Heck Cyclization

With the pyrrole-fused cyclohexene substrates in hand, Neil Garg carried out extensive studies in order to achieve the intramolecular Heck cyclization of bromopyrrole

91. Attempts to utilize standard procedures were unsuccessful,[10] likely due to the thermal instability of the bromopyrrole moiety. However, implementation of the room-temperature conditions developed by Fu[24] provided the desired [3.3.1] bicyclic product (**90**), albeit in low yield (Scheme 3.2.4). Unfortunately, the formation of **90** was hampered by competitive production of [3.2.2] bicycle **102**. Although efforts to optimize temperature, solvent, base, and concentration were not met with success, it was found that increased quantities of Pd improved the ratio of the desired [3.3.1] bicycle (**90**) to the undesired [3.2.2] bicycle (**102**). In addition, the ratio of **90** to **102** decreased over time,[25] suggesting that the active catalytic species varied during the course of the reaction or that selectivity changed as the concentration of $R_3NH^+Br^-$ increased.

Scheme 3.2.4

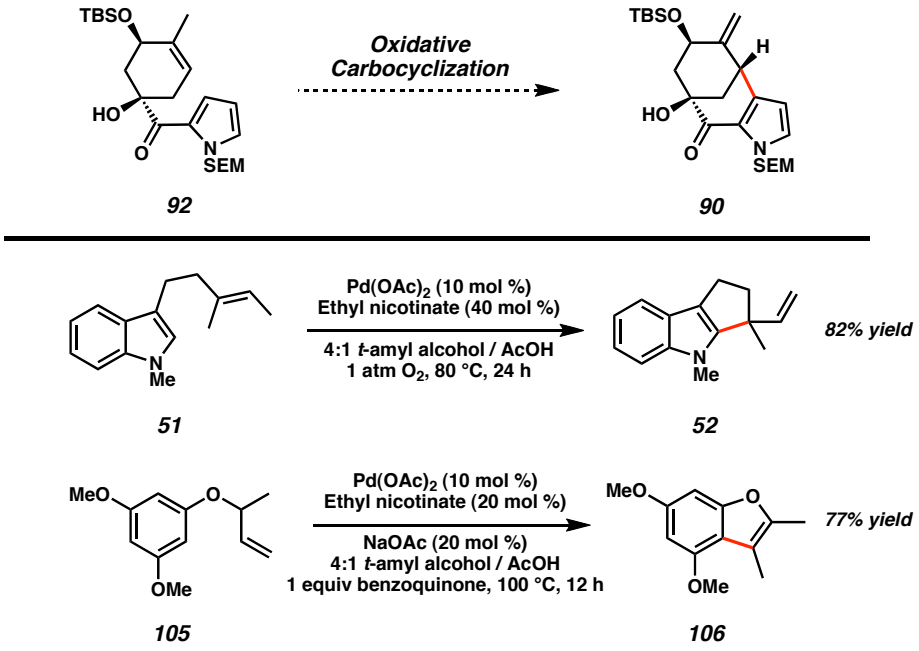


3.2.3 Intramolecular Oxidative Cyclization

Although the Heck reaction was useful for preparing reasonable quantities of bicycle **90**, an alternative and potentially more selective route to **90** was desired. In conjunction with ongoing research in our group,[12] we turned to the Pd(II)-mediated C–C

bond forming approach. In this scenario, C(3)-unsubstituted pyrrole **92** would undergo intramolecular carbocyclization to afford **90** (Scheme 3.2.5). Previously in our laboratories, indoles (e.g., **51**) and electron-rich aryl ethers (e.g., **105**) had been shown to be competent cyclization substrates. However, pyrrole heterocycles had never been tested in this regard, especially not to form bridged bicycles.

Scheme 3.2.5

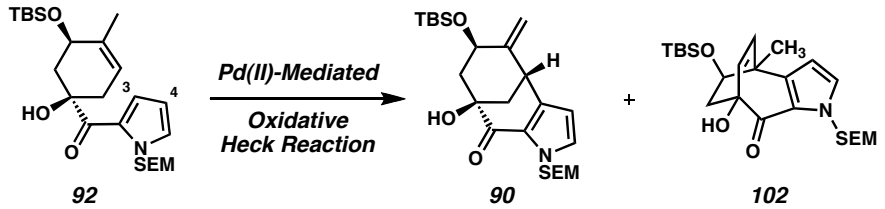


As a starting point, stoichiometric Pd(II) was employed for the oxidative cyclization reaction to eliminate the need for a co-oxidant, which could complicate preliminary studies. Catalytic methods could, in theory, be devised once these stoichiometric conditions were optimized. Protocols reported by our group were initially tried, however, these conditions did not afford any of desired bicycle **90** (Table 3.2.1, entry 1). Indeed, initial experimentation revealed that neither pyridine, ethyl nicotinate,

nor triphenylphosphine were effective ligands for promoting cyclization in the presence of $Pd(OAc)_2$.[12c,d]

Although these initial conditions failed, a control experiment omitting the ligand did produce a trace amount of desired bicycle **90** (entry 2). Interestingly, a number of byproducts were also discovered in the reaction pot of entry 2, which appeared to be caused by *t*-amyl alcohol incorporation into the starting material and product.[26] Thus, substituting *t*-butyl alcohol for *t*-amyl alcohol as solvent (entry 3) and conducting the reaction under an atmosphere of dioxygen led to the consumption of all starting material and production of desired bicycle **90** as the major product by crude ^{1}H NMR in 15% isolated yield.[27]

Table 3.2.1



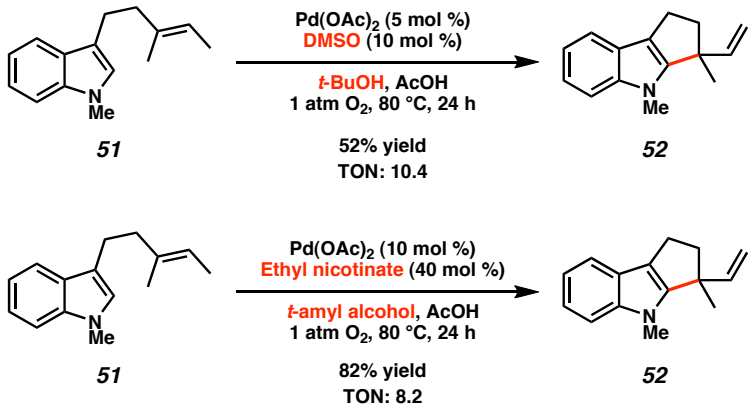
entry	conditions	result	
1	$Pd(OAc)_2$ (stoichiometric or cat w/ O_2) ethyl nicotinate, pyridine or PPh_3 *t*-amyl OH, AcOH, 80 °C	no reaction, starting material recovered	
2	$Pd(OAc)_2$ (1 equiv) *t*-amyl OH, AcOH, 80 °C	***90*** *trace*	***102*** *not observed*
3	$Pd(OAc)_2$ (1 equiv) *t*-BuOH, AcOH, 80 °C, O_2	***90*** 15% yield	***102*** *not observed*
4	$Pd(OAc)_2$ (stoichiometric or cat w/ O_2) ethyl nicotinate, pyridine or PPh_3 *t*-BuOH, AcOH, 80 °C	no reaction, starting material recovered	
5	$Pd(OAc)_2$ (1 equiv), DMSO *t*-BuOH, AcOH, 80 °C, 2 h	***90*** 56% yield	***102*** *not observed*
6	$Pd(OAc)_2$ (1 equiv), DMSO dioxane, AcOH, 80 °C, 7.5 h	***90*** 41% yield	***102*** *not observed*
7	$Pd(OAc)_2$ (1 equiv), DMSO *t*-BuOH, AcOH, 60 °C, 10 h	***90*** 74% yield	***102*** *not observed*

Upon learning that the use of *t*-amyl alcohol was deleterious to this cyclization, both pyridine and phosphine-based ligands were reinvestigated with *t*-butanol (entry 4). Unfortunately, however, the desired transformation was rendered inactive under these conditions. On the basis of these results, we hypothesized that an ideal ligand would be sufficient to stabilize the palladium complex without being overly coordinating as to halt the reactivity in the cyclization.[28] Thus, a focused investigation of possible ligands was undertaken. A marked improvement was realized when DMSO was employed;[29] the desired cyclization product could be obtained in 56% yield (entry 5). Dioxane was also competent as a *t*-butanol substitute, though a diminished yield of product was obtained (entry 6). Subsequent optimization of temperature, solvent, and reaction time led to an ideal set of conditions whereby the desired [3.3.1] bicycle (**90**) was isolated as the sole product in 74% yield (entry 7). This transformation is particularly noteworthy since it results in functionalization of the electronically deactivated and sterically congested C(3) position of acyl pyrrole **92**.[30,31] Importantly, the undesired [3.2.2] bicycle (**102**) seen as a byproduct in the classical Heck reaction has never been observed as a product of the oxidative Heck cyclization of substrate **92**.

Despite considerable experimentation, we were unable to render the conversion of acyl pyrrole **92** to bicycle **90** catalytic in Pd in the presence of a stoichiometric oxidant (e.g., O_2 or benzoquinone). This difficulty has been attributed to the extreme sensitivity of both the starting material and desired product to oxidative decomposition.[32,33] This hypothesis is corroborated by related catalytic pyrrole cyclizations that were described after the report of this work,[34] as well as an unoptimized study that we conducted in the conversion of **51** → **52** (Scheme 3.2.6). Applying our DMSO-based conditions in the

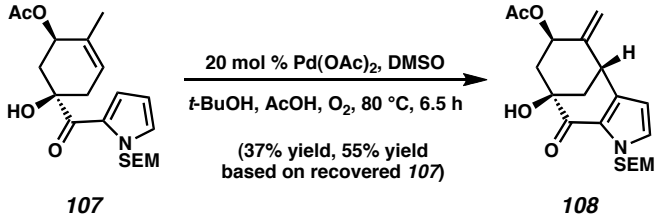
same cyclization yields a similar turnover number (10.4) to the one initially reported (8.2).[12c] These collective results suggest that palladium is capable of reoxidation under these conditions, and thus in principle, is also able to function in a catalytic manner.

Scheme 3.2.6



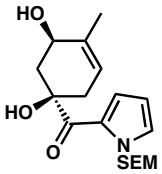
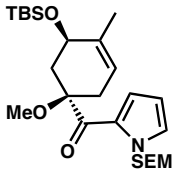
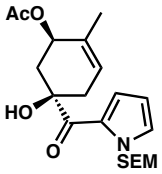
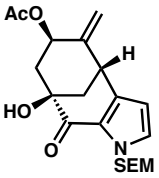
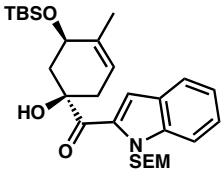
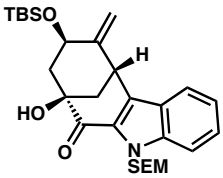
Notably, we have observed some catalysis in the cyclization of a closely related substrate, acetate **107** (Scheme 3.2.7). In this case, oxidative Heck cyclization using 20 mol % $Pd(OAc)_2$, under 1 atm of O_2, afforded [3.3.1] bicycle **108** in 37% yield (55% based on recovered **107**). As isolated yields and catalyst turnover for this process were low, and bicycle **108** was not directly useful for our total synthesis goals, we elected to utilize the stoichiometric Pd-mediated oxidative Heck reaction (**92** → **90**) as a means to advance material en route to dragmacidin F.

Scheme 3.2.7



We also explored the Pd(II)-mediated carbocyclization of a number of substrates related to TBS ether **92** (Table 3.2.2, entry 1). For instance, the TIPS ether analog (entry 2) underwent cyclization, albeit in lower yield with respect to the parent TBS compound. However, if the 2° alcohol was left unprotected altogether (entry 3)[35] or the substrate possessed a 3° methyl ether (entry 4)[36], formation of the desired bicyclic products was not observed. Interestingly, the acetate derivative readily participated in the cyclization reaction (entry 5). As previously described, exposure of the acetate substrate to catalytic conditions (20 mol % Pd, 1 atm O_2) also led to the formation of the desired product, although in modest yield with a TON of 1.9 (entry 6). It was also possible to annulate C(3) of related indole substrates under our standard conditions (entry 7).

Table 3.2.2[a]

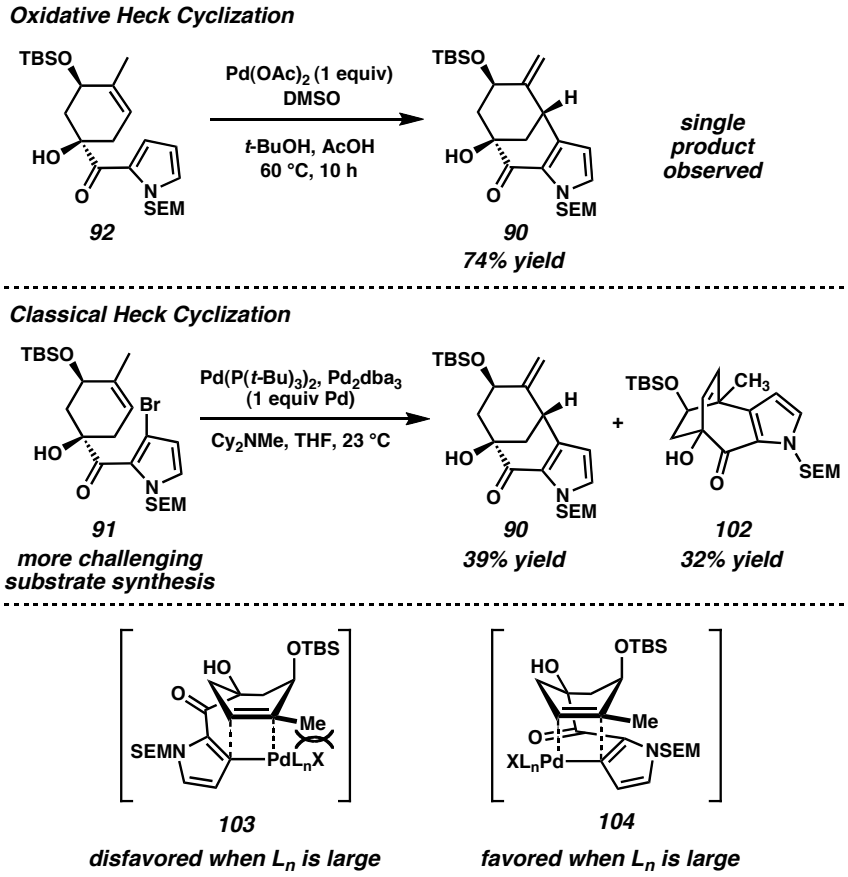
entry	substrate	product	temp (°C)	time	yield[b]
1	 **92**	 **90**	60	10 h	74%
2	 **109**	 **110**	60	13.5 h	51% (63%)
3	 **111**	—	80	*complex mixture*	
4	 **112**	—	80	*no reaction*	
5	 **107**	 **108**	80	1.8 h	53% (66%)
6			80[c]	6.5 h	37% (55%)
7	 **113**	 **114**	80	2.5 h	49%

[a] Standard Conditions: 1 equiv $Pd(OAc)_2$, 2 equiv DMSO, *t*-BuOH:AcOH (4:1, 0.01 M). [b] Isolated Yield. Number in parentheses represents the yield based on recovered starting material. [c] 20 mol % $Pd(OAc)_2$, 40 mol % DMSO, *t*-BuOH:AcOH (4:1, 0.01 M), O_2 (1 atm)

In the context of our total synthesis objective, the oxidative Heck reaction strategy is advantageous compared to the classical Heck route for preparing [3.3.1] bicycle **90** on

the basis of several factors (Scheme 3.2.8): a) the oxidative Heck approach does not require the synthesis of a halogenated starting material (i.e., **91**), which can sometimes be significantly challenging;[23,37] b) using identical palladium loadings, the oxidative Heck cyclization provides bicycle **90** in nearly twice the chemical yield as the classical Heck reaction; c) the oxidative Heck reaction furnishes bicycle **90** as a single product, whereas the classical Heck reaction requires a more tedious chromatographic separation of the undesired [3.2.2] bicycle (**102**). Although more detailed mechanistic studies are pending, we partially attribute the differences in product distribution between the two strategies to the effects of ligands. More specifically, the use of bulky $P(t\text{-Bu})_3$ ligands in the classical Heck cyclization could favor olefin insertion transition state **104** over **103**, as it would place the large PdL_nX away from the more substituted position of the olefin undergoing insertion.

Scheme 3.2.8

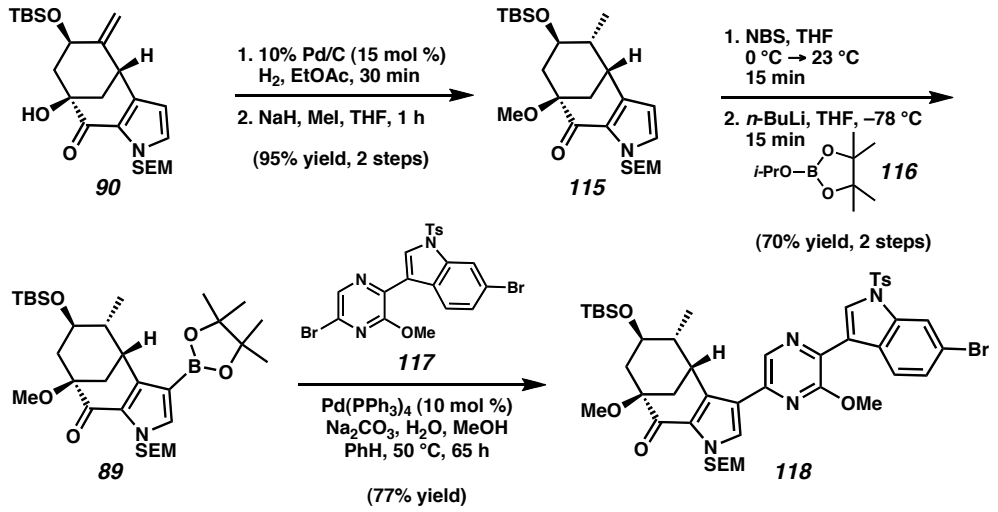


3.2.4 Assembling the Carbon Skeleton of Dragmacidin F

With the [3.3.1] bicyclic framework in hand (i.e., **90**), we focused our attention on constructing the full carbon skeleton of dragmacidin F (**118**, Scheme 3.2.9). The final stereocenter present in the natural product was installed via catalytic hydrogenation of olefin **90**, and was followed by methylation of the 3° alcohol to produce bis(ether) **115**. The methyl protecting group was selected initially for its robustness[16] and would presumably allow for the exploration of late-stage chemistry in the form of a model system.[38] Methyl ether **115** was then elaborated via regioselective bromination of the pyrrole and metalation to boronic ester **89**. In the critical halogen-selective Suzuki

fragment coupling, pyrroloboronic ester **89** was reacted with dibromide **117** (prepared from **86** + **87**)[7] under Pd(0) catalysis. By analogy to our dragmacidin D studies,[7] we were pleased to find that at 50 °C, the desired C–C bond forming reaction took place to afford the fully coupled product (**118**) in 77% yield. Importantly, the indolylbromide moiety was maintained under these reaction conditions.

Scheme 3.2.9

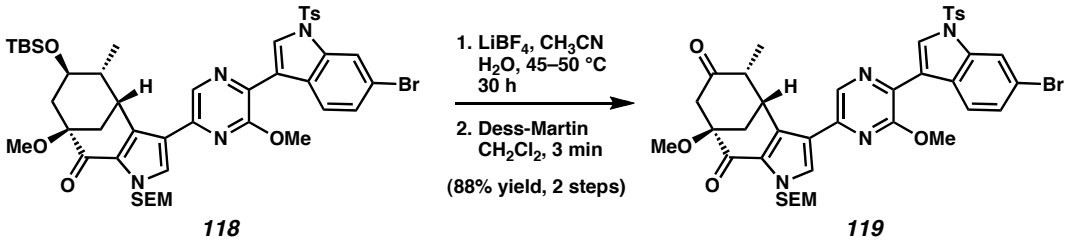


3.2.5 End-Game: Total Synthesis of (+)-Dragmacidin F

With the carbon framework completed, few tasks remained in order to finish the total synthesis of dragmacidin F (**84**), namely, removal of all protecting groups and installation of the aminoimidazole unit. Of particular note is the similarity of these synthetic challenges to those encountered in our total synthesis of dragmacidin D (**82**).[7] Not surprisingly, we decided to utilize the methods that were already familiar to us in order to elaborate **118** to the desired natural product (**84**). To this end, we anticipated that the presence of an amino group α to the ketone would allow for eventual introduction of

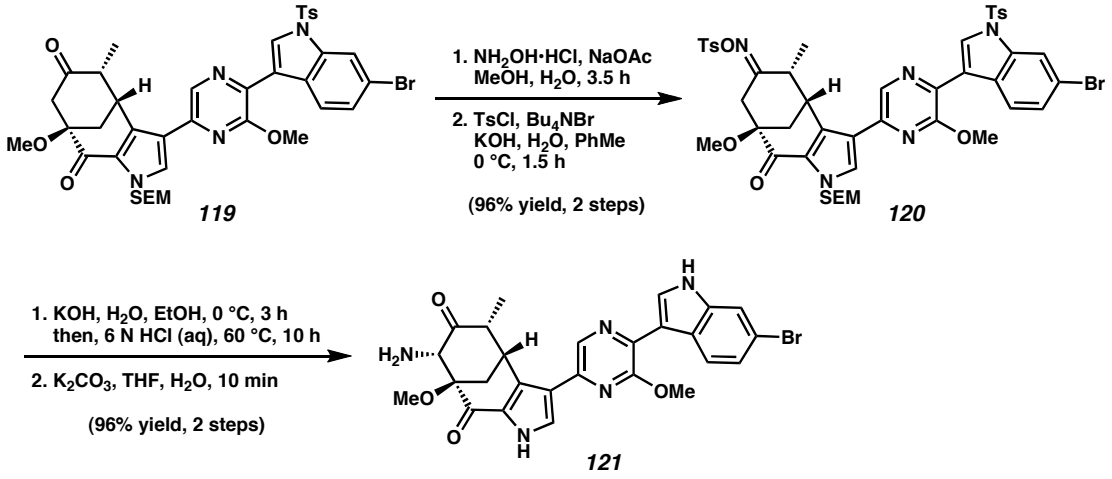
the aminoimidazole moiety. Therefore, selective cleavage of silyl ether **118**, followed by oxidation with Dess-Martin periodinane, produced ketone **119** (Scheme 3.2.10).

Scheme 3.2.10



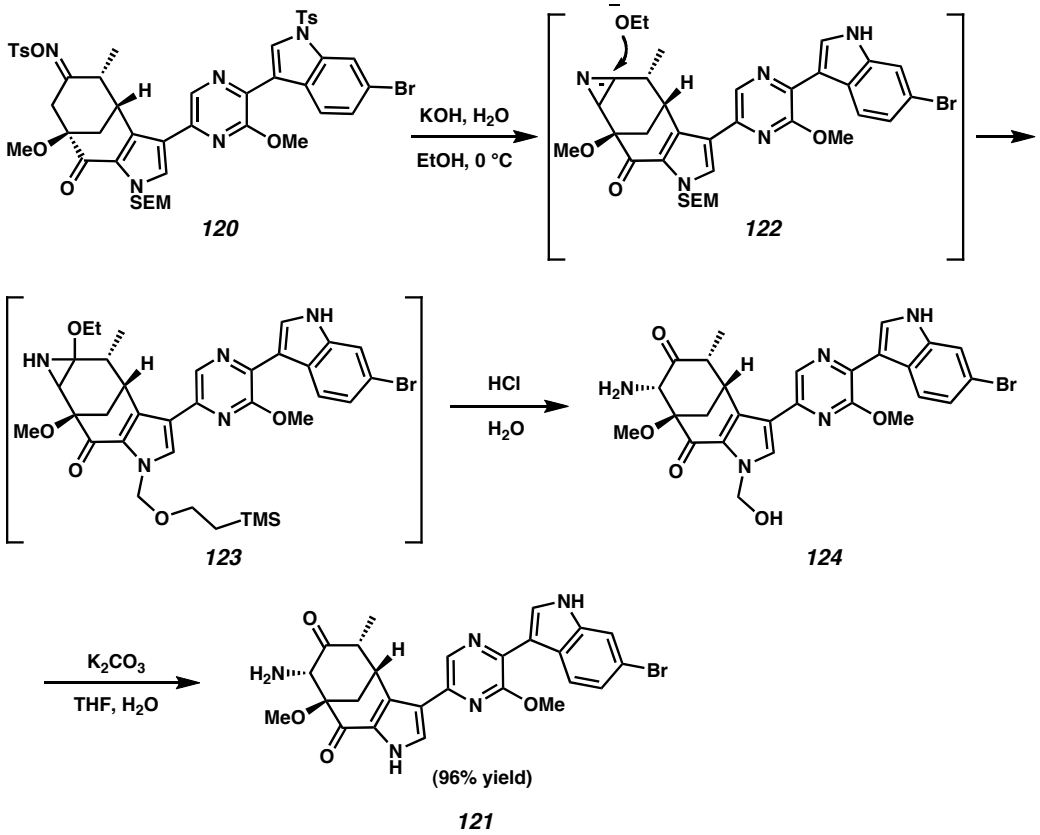
Although attempts to introduce the necessary α-amino group failed under numerous literature protocols,[8b] Neil Garg skillfully managed the installation of this substituent using a Neber rearrangement.[39,40] In this scenario, an activated oxime derivative would undergo alkoxide-promoted rearrangement to furnish an α-amino ketone. Thus, ketone **119** was converted to tosyloxime **120** via standard conditions (Scheme 3.2.11). Gratifyingly, exposure of substrate **120** to aqueous KOH in ethanol led to Neber rearrangement. After optimization, we found that simply exposing tosyloxime **120** to i) KOH, ii) HCl, and iii) K_2CO_3 produced α-amino ketone **121** as a single regio- and stereochemical isomer in excellent yield.[41,42,43] Furthermore, under these reaction conditions, both the tosyl and SEM protective groups were quantitatively removed from their corresponding heterocycles. To the best of our knowledge, this is the first example of a successful Neber rearrangement in the context of natural product synthesis.[44]

Scheme 3.2.11



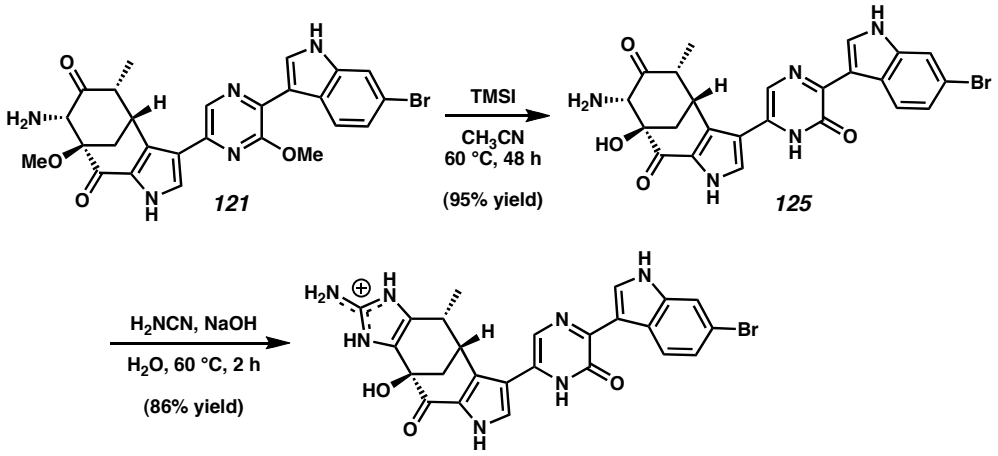
A more detailed look at the possible mechanism of the Neber rearrangement/deprotection sequence is shown in Scheme 3.2.12. Exposure of tosyloxime **120** to KOH in ethanol likely leads to the formation of detosylated azirine **122**, which is attacked by ethoxide to afford ethoxyaziridine **123**.[40a,45] Following acid-mediated hydrolysis, the amino ketone moiety is installed with concomitant partial cleavage of the SEM protective group (**123** → **124**).[41b,46] Finally, treatment of hemiaminal **124** with K_2CO_3 removes the remaining portion of the SEM group, thus giving rise to the deprotected amino ketone (**121**).

Scheme 3.2.12



In order to unveil the masked pyrazinone functionality, Neber rearrangement product **121** was treated with TMSI at 60 °C (Scheme 3.2.13).[16] Fortuitously, both the pyrazinone and the 3° alcohol functionalities were revealed simultaneously (**121** → **125**). In the final step of the synthesis, the penultimate amino ketone (**125**) was subjected to cyanamide and aqueous NaOH to produce enantiopure dragmacidin F (**84**).[7,47] Our efficient and enantiospecific route allows access to **84** in 7.8% overall yield in just 21 steps from (–)-quinic acid (**93**).

Scheme 3.2.13

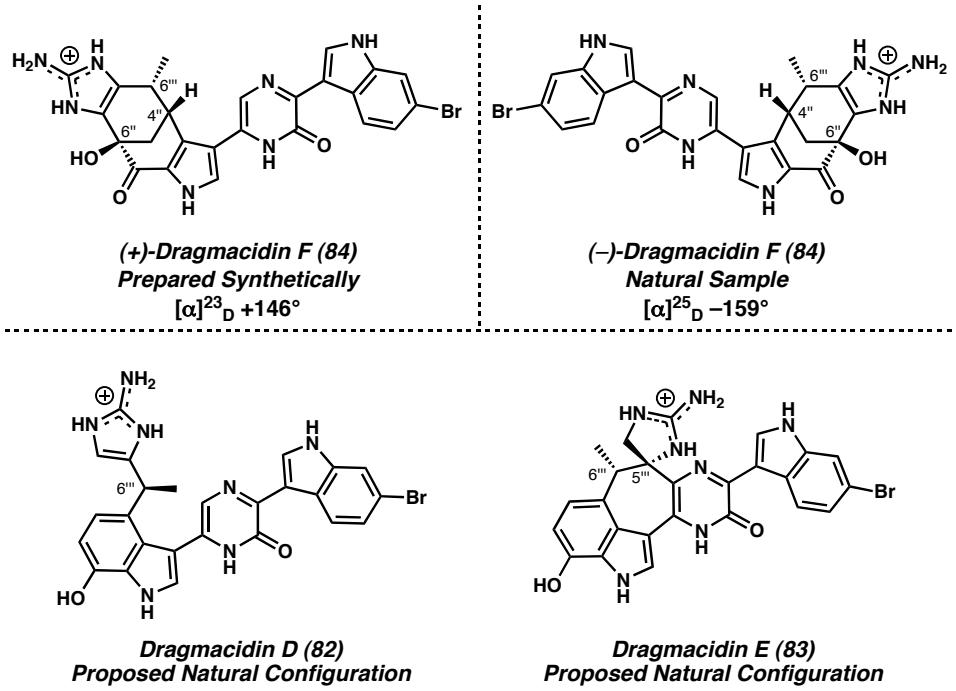


(+)-Dragmacidin F (84)

3.3 The Absolute Stereochemistry of the Pyrazinone-Containing Dragmacidins.

Synthetic dragmacidin F (**84**) was spectroscopically identical (^{1}H NMR, ^{13}C NMR, IR, UV, HPLC) to a sample obtained from natural sources,[3f] with the exception of the sign of rotation (natural: $[\alpha]^{25}_D$ –159° (*c* 0.4, MeOH); synthetic: $[\alpha]^{23}_D$ +146° (*c* 0.45, MeOH)). Thus, our synthesis from (–)-quinic acid (**93**) established, for the first time, the absolute configuration of natural dragmacidin F (**84**) to be (4”*S*, 6”*S*, 6’”*S*) as shown in Figure 3.3.1.[48] On the basis of the hypothesis that dragmacidins D, E, and F are biosynthetically related, it is likely that the absolute stereochemical configurations of natural dragmacidins D (**82**) and E (**83**) are (6’”*S*) and (5’”*R*, 6’”*S*), respectively. Having developed a route to the unnatural antipode of dragmacidin F ((+)-**84**), we set out to extend our approach to the total synthesis of (–)-**84**.

Figure 3.3.1



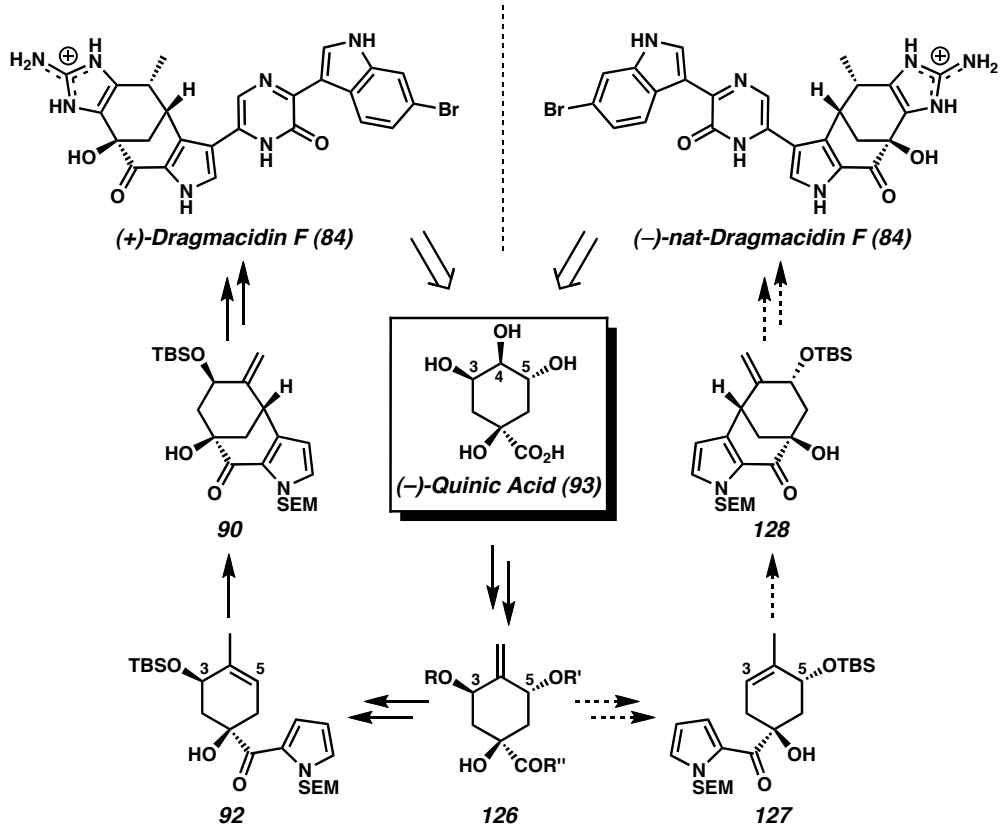
3.4 The Total Synthesis of (–)-Dragmacidin F

3.4.1 An Enantiodivergent Strategy for the Preparation of (–)-Dragmacidin F

As described above, naturally occurring and readily available (–)-quinic acid (**84**)[13] had served as the starting material for our synthetic approach to (+)-**84**. Unfortunately, the (+)-enantiomer of **93** is not easily accessible,[49] and we were confronted with the possibility that our synthesis would not be amenable to the preparation of our new target molecule, (–)-dragmacidin F ((–)-**84**). We reasoned, however, that it might be possible to exploit (–)-quinic acid (**93**) in an enantiodivergent manner that would allow access to both (+)- and (–)-**84** (Scheme 3.4.1).[50] For such an approach to succeed, (–)-quinic acid (**93**) would be elaborated via selective manipulation of the C(3), C(4), and C(5) hydroxyl groups to a pseudo-C_2-symmetric[51] derivative (**126**) en route to pyrrolocyclohexene **127**, the diastereomer of which (i.e., **92**) was employed in our

synthesis of (+)-**84**. Analogous to our approach to (+)-**84** (i.e., **92** → **90**), we anticipated that **127** could undergo oxidative carbocyclization to afford annulated pyrrole **128**. Bicycle **128** would then be elaborated to (–)-dragmacidin F ((–)-**84**). Of the key transformations outlined in Scheme 3.4.1, we were familiar with the Pd-mediated oxidative carbocyclizations and the late-stage manipulations of related compounds; however, the successful preparation of (–)-dragmacidin F ((–)-**84**) would rely heavily on the identification of a suitable quinic acid derivative (**126**), the facile synthesis of that compound, and the rapid conversion of **126** to the requisite cyclization substrate (**92**).

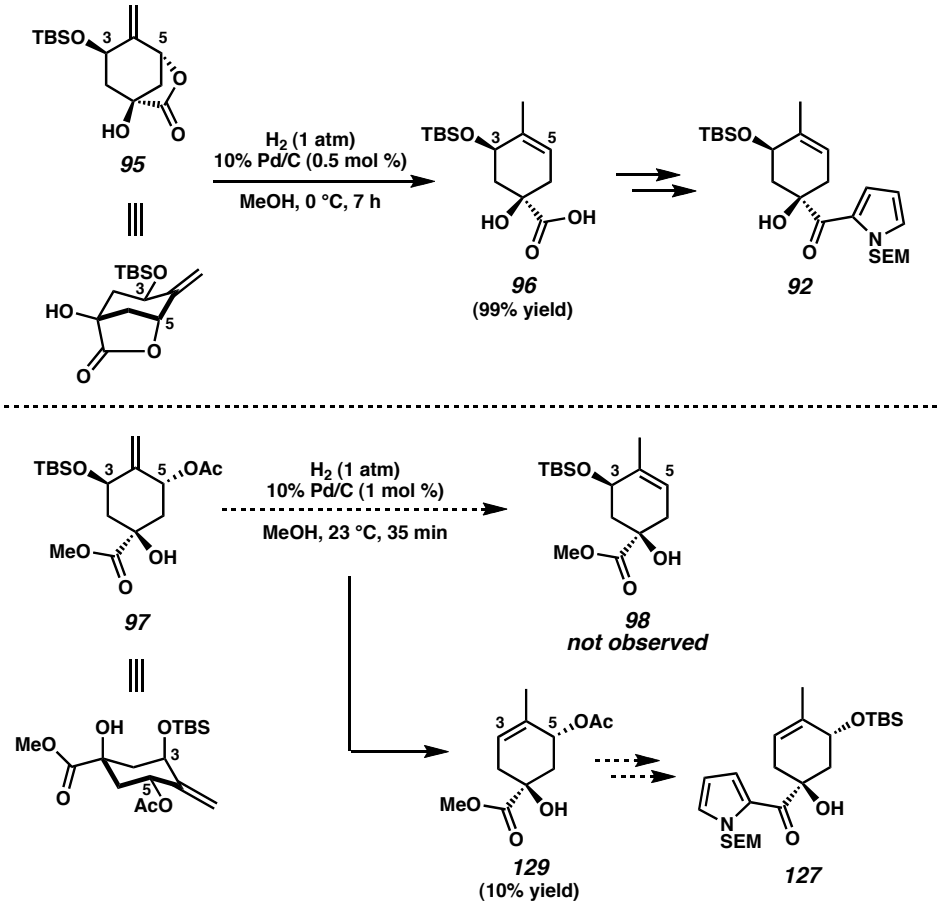
Scheme 3.4.1



3.4.2 The Development of a Reductive Isomerization Reaction

Fortunately, potential solutions to these problems had become apparent during our studies of a novel reductive isomerization reaction discovered in our synthesis of (+)-dragmacidin F ((+)-**84**). Two critical results are shown in Scheme 3.4.2. In the first experiment, treatment of lactone **95** with Pd/C and H_2 in methanol at 0 °C furnished carboxylic acid **96** in essentially quantitative yield via reductive loss of the C(5) carboxylate with concomitant olefin migration (i.e., net S_N2' reduction). In the second experiment, a closely related derivative (**97**) was exposed to similar reaction conditions.[52] Surprisingly, the reductive isomerization reaction proceeded with loss of the C(3) silyl ether rather than the C(5) acetate, thus producing small quantities of allylic acetate **129** instead of the anticipated product (**98**).[53] The observation that (t-Bu)Me_2SiO^- was preferentially ejected from compound **97** despite the clear superiority of AcO^- as a leaving group led us to consider that the C(3) silyl ether moiety was positioned in an axial orientation, thereby facilitating its elimination.[54] This preferred conformation of **97** represents a cyclohexane ring-flip with respect to lactone **95**, and thus gives rise to the reductive isomerization product (**129**) possessing a $\Delta_{3,4}$ olefin. Importantly, the possibility existed that the unexpected product obtained from this reaction (i.e., **129**) could be converted to cyclization substrate **127** (diastereomeric to **92**).

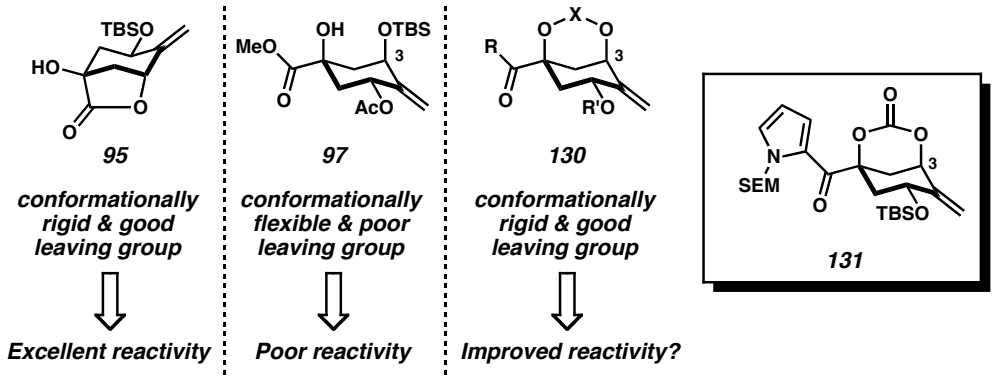
Scheme 3.4.2



Our efforts to optimize the reductive isomerization of **97** to **129** were hampered by competitive hydrogenation of the olefin moiety of **97**, a complication not observed in the high-yielding conversion of **95** to **96**. Although both processes presumably involve the elimination of an axially disposed leaving group,[54] we reasoned that the successful conversion of **95** to **96** was due to the carboxylate being conformationally restricted to an axial orientation, while substrate **97** possessed a poorer leaving group (*t*-Bu)Me_2SiO^-) and was free to adopt alternate conformations (Figure 3.4.1). We hypothesized that derivatives of **97** containing an axially-locked leaving group at C(3) (e.g., **130**) would be more suitable substrates for the reductive isomerization reaction. Thus, carbonate **131**

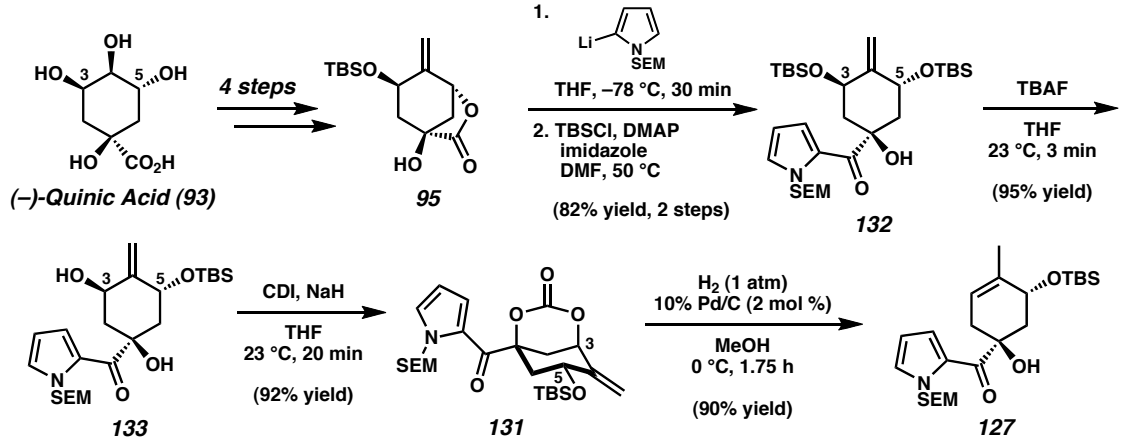
was identified as the key (–)-quinic acid derived intermediate en route to the desired cyclization substrate (**127**), and became the focus of our efforts.

Figure 3.4.1



Our synthesis of carbonate **131** began with bicyclic lactone **95**, a derivative of (–)-quinic acid (**93**) that was used in our total synthesis of (+)-**84** (Scheme 3.4.3). Addition of 2-lithio-SEM-pyrrole[22] followed by TBS protection afforded bis(silylether) **132** in good yield. This pseudo-C_2-symmetric compound then underwent rapid diastereoselective mono-desilylation upon treatment with TBAF in THF to produce the *syn* 1,3-diol **133**.[55] Importantly, this desymmetrization proceeded with complete selectivity and allowed us to efficiently differentiate the C(3) and C(5) positions of the cyclohexyl moiety. Diol **133** was smoothly converted to bicyclic carbonate **131** in the presence of CDI, effectively restricting the C(3) substituent to an axial disposition. Gratifyingly, exposure of carbonate **131** to our reductive isomerization conditions (2 mol % Pd/C, H_2, MeOH, 0 °C) led to the selective formation of the desired cyclization substrate (**127**) in 90% yield.[56]

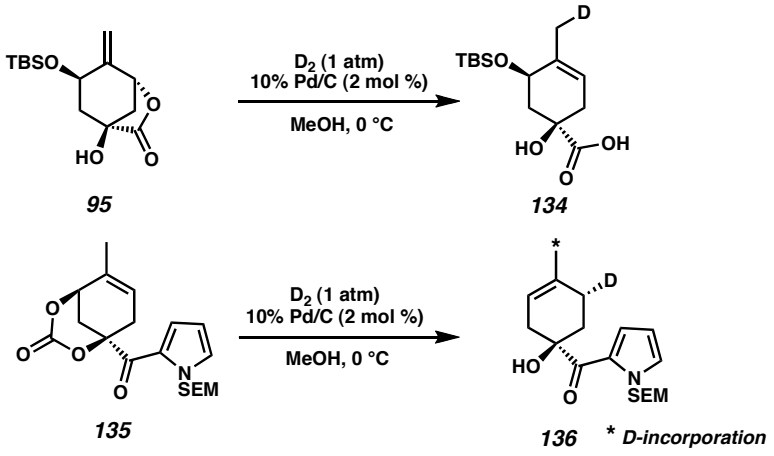
Scheme 3.4.3



3.4.3 The Scope and Mechanism of the Reductive Isomerization Reaction

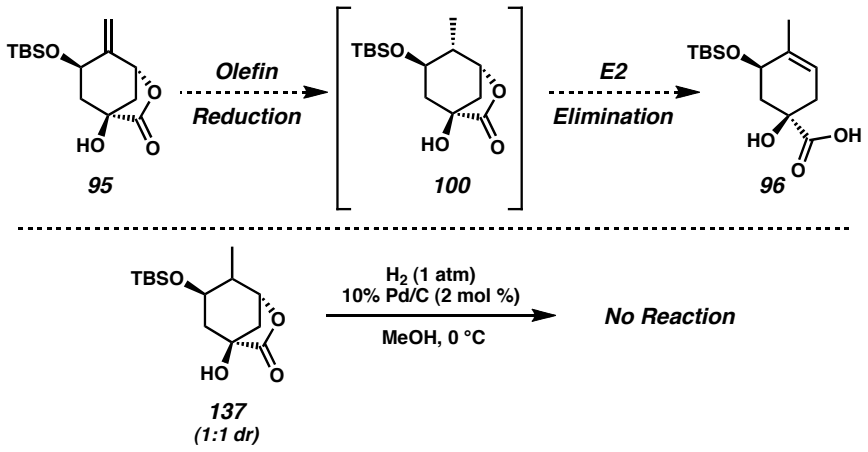
On the basis of these results, we set out to examine the unusual reactivity of the heterogeneous palladium system.[57] Intrigued by our initial results (**95** → **96** and **131** → **127**), we began a more detailed study of this reductive isomerization by examining the origin of the hydrogen atom in the newly formed C-H bond. Experiments employing D_2 indicate that the deuterium delivered at the allylic positions of **134** and **136** originates from D_2, whereas no C-D incorporation was observed by using CD_3OD (Scheme 3.4.4).[58] Furthermore, deuterium incorporation occurs with complete stereoselectivity (**135** → **136**), with additional incorporation at the exocyclic methyl group.[59]

Scheme 3.4.4



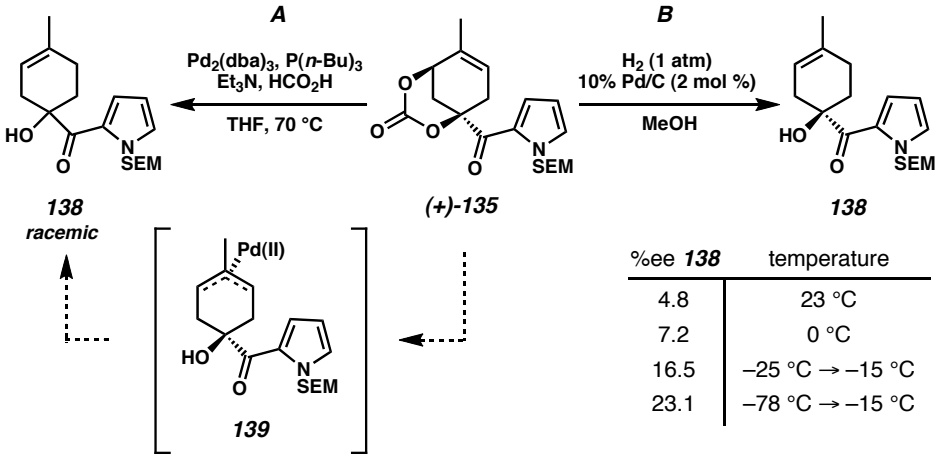
In terms of mechanism, we considered the simple possibility that our transformation could be proceeding in a tandem fashion via hydrogenation of the olefin followed by E2 elimination (e.g., **95** → **100** → **96**, Scheme 3.4.5). However, subjection of an independently prepared sample of saturated lactone **137** (1:1 dr) to the identical reaction conditions (10% Pd/C, H_2, MeOH, 0 °C) led to no reaction, allowing us to dismiss its potential as a viable intermediate.[60]

Scheme 3.4.5



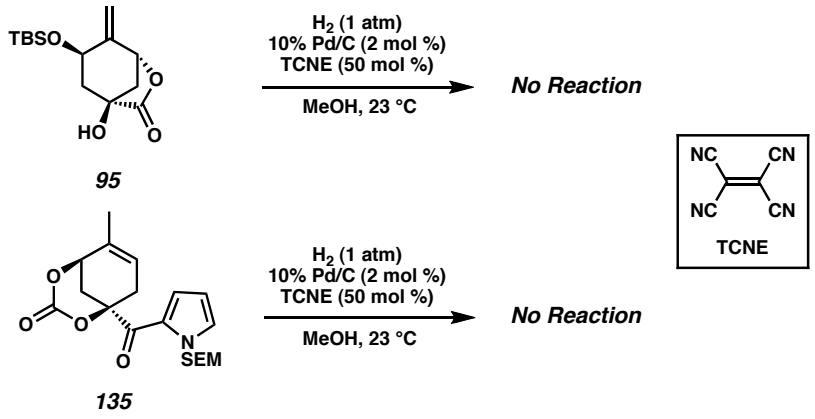
A π-allyl mechanism could be probed by using carbonate-bearing trisubstituted olefin **135**. Under π-allyl hydrogenolysis conditions, racemic **138** was obtained (Scheme 3.4.6A).[41b] Interestingly, analysis by chiral HPLC revealed that, under our reductive isomerization conditions at 0 °C, cyclohexene **138** was produced in 7.2% ee (Scheme 3.4.6B). In fact, by lowering the reaction temperature, up to 23.1% ee could be achieved.[41b] Although complete optical purity was not maintained in the product, this result suggests a reaction pathway that does not solely involve a meso-π-allylpalladium complex (e.g., **139**).[61]

Scheme 3.4.6



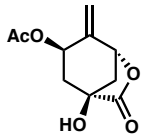
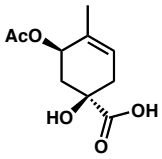
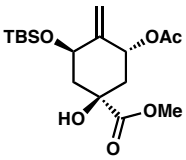
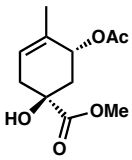
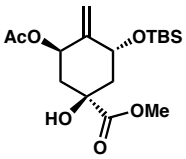
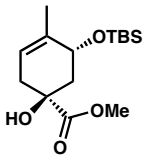
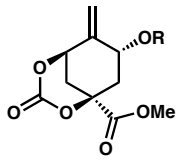
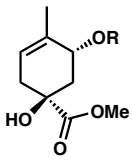
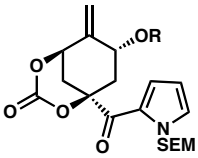
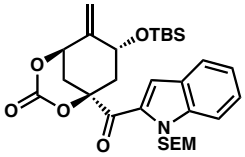
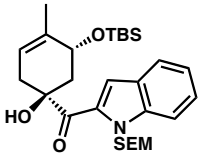
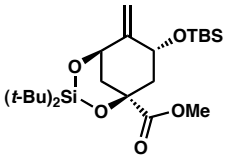
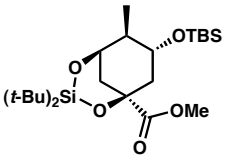
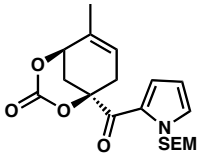
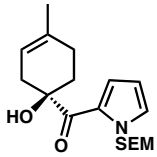
Recently, both Sajiki and Hara have invoked a single-electron transfer (SET) mechanism for other transformations involving the use of 10% Pd/C and MeOH.[62] In accordance with this hypothesis, exposing either lactone **95** or carbonate **135** to our standard conditions in the presence of tetracyanoethylene (TCNE) as a SET inhibitor completely halts all reactivity, even at 23 °C (Scheme 3.4.7).[63]

Scheme 3.4.7



We prepared a number of substrates to assess the generality of this reaction (Table 3.4.1).[64] As a starting point, a simple variant of lactone **95** bearing an acetate on the secondary allylic alcohol was synthesized (i.e., **140**). We were pleased to see that **140** could be converted to carboxylic acid **141** in good yield (entry 1). The use of allylic acetate **97** as a substrate (entry 2), on the other hand, led to an unexpected result. We anticipated that methyl ester **98** would be the observed product because acetate is a superior leaving group to silanolate (see Scheme 3.4.2, vide supra). However, the compound obtained (i.e., **129**) resulted from a net loss of the OTBS group.[65] Notably, none of the byproducts formed under homogeneous π-allyl protocols were observed under these heterogeneous conditions (**98**, **99**, **iv**[20], see Scheme 3.2.1, vide supra). In order to probe this result further, a version of **97** with exchanged protecting groups on the secondary alcohols was prepared (**142**, entry 3). In this case, elimination of acetate occurred.[65]

Table 3.4.1[a]

entry	substrate	product	time	yield[b]
1	 ***140***	 ***141***	15 min	71%
2[c]	 ***97***	 ***129***	1 h 35 min	3%[d] 10%[e,f]
3[c,e]	 ***142***	 ***143***	1.5 h	27%
4	 ***144***	 ***129*** **R = Ac**	1 h	81%
5	***145***	***143*** **R = TBS**	8 min	94%
6	 ***146***	 ***147*** **R = Ac**	20 min	94%
7	***148***	***149*** **R = H**	15 min	80%
8	 ***150***	 ***151***	4 h	90%
9	 ***152***	 ***153***	1 h	68%
10[g]	 ***135***	 ***138***	1.3 h	91%

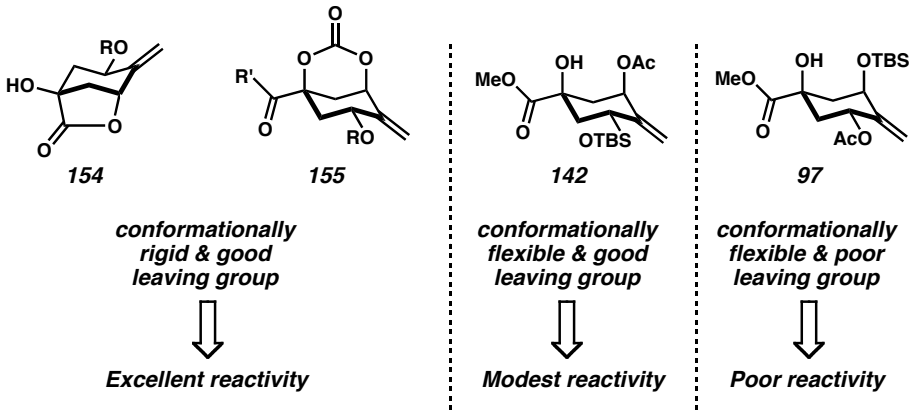
[a] Standard conditions: H_2 (balloon, 1 atm), 10% Pd/C (2 mol % Pd), MeOH, 0 °C. [b] Isolated yield. [c] Yield based on ^{1}H NMR integration. [d] 10% Pd/C (0.5 mol % Pd). [e] 10% Pd/C (1 mol % Pd). [f] Reaction performed at 23 °C. [g] Product formed in 7.2% ee.

Due to the success of the rigid bicyclic lactone framework in this reaction, we reasoned that the reactivity of **97** and **142** might be improved by restricting them as bicyclic carbonates (**144** and **145**). These carbonate-containing substrates were well tolerated and led to competent production of the corresponding methyl esters (entries 4 and 5). Additionally, carbonates with adjacent heterocyclic moieties such as pyrrole (**146** and **148**) and indole (**150**) could be converted into their reductively isomerized counterparts in excellent yields (entries 6–8 and 10). The use of an acetate protecting group on the secondary allylic alcohol (entries 1, 4, and 6), or an unprotected alcohol altogether (entry 7), did not significantly influence the overall reaction efficiency. Interestingly, replacement of the carbonate moiety with a dioxasilyl linkage led solely to diastereoselective hydrogenation of the olefin (entry 9).[66] Somewhat surprisingly, reductive isomerization using a trisubstituted olefin was also quite facile (entry 10, cf. Scheme 3.4.6).[67]

A model to rationalize some of these anomalous differences in reactivity is presented in Figure 3.4.2, which is an extended version of the model conceived in our initial hypothesis (see Figure 3.4.1, vide supra). An examination of the three-dimensional structures of the starting materials in Table 3.4.1 reveals that the leaving group is positioned preferentially in an axial orientation with respect to the six-membered ring.[68] Furthermore, structurally rigid bicyclic lactones and carbonates with locked axial leaving groups (e.g., **154** and **155**) exhibited enhanced yields relative to their more flexible monocyclic counterparts (**142** and **97**). The difference in yield between substrates **142** and **97** can be attributed to leaving group ability (i.e. $AcO^- > Me_2(t\text{-Bu})SiO^-$). This leaving group effect was also observed when the carbonate functionality was replaced

with a dioxasilyl moiety (entry 9), in which case only direct olefin hydrogenation occurred.

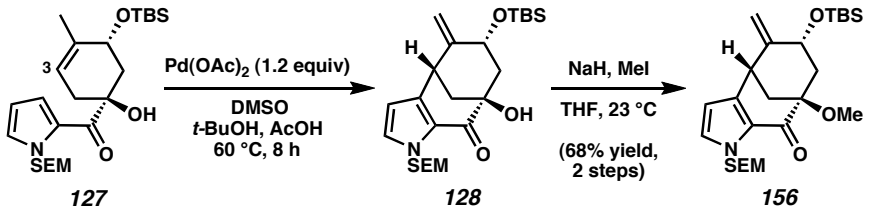
Figure 3.4.2



3.4.4 Constructing the [3.3.1] Bicycle En Route to (–)-Dragmacidin F

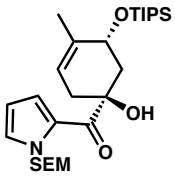
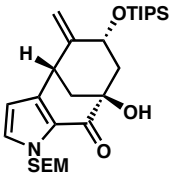
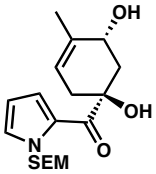
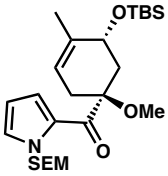
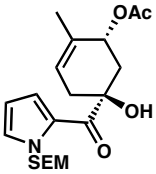
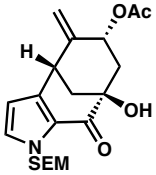
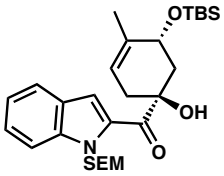
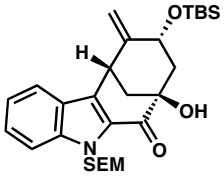
After assembling target substrate **127**, we turned our attention to the key Pd(II)-mediated cyclization reaction (Scheme 3.4.8). Substrate **127** was treated with 1.2 equiv of $Pd(OAc)_2$ under conditions similar to those described earlier, at which point, the desired pyrrole-fused bicycle (**128**) formed as a single regio- and stereoisomer. Notably, bond formation between the pyrrole functionality and C(3) of **127** occurred even in the presence of the bulky C(5) silyl ether group positioned syn to the acyl pyrrole subunit. Following protection of the 3° alcohol, [3.3.1] bicycle **156** was obtained in 68% yield for the two-step process.

Scheme 3.4.8



We also explored the Pd(II)-mediated carbocyclization of a number of substrates related to the diastereomeric counterpart (**127**) of TBS ether **92** (cf. Table 3.2.2, vide supra). The TIPS ether analog underwent smooth cyclization (Table 3.4.2, entry 1), while the use of the hydroxy derivative[35] (entry 2) or the 3° methyl ether derivative[36] (entry 3) did not lead to any product formation. Additionally, the substrates bearing acetate (entry 4) and indole (entry 5) moieties participated in the cyclization reaction. In general, the results of this study (Table 3.4.2) mirrored the results of their diastereomeric counterparts in Table 3.2.2, albeit in lower yields. This decrease in reactivity could be attributed, at least in part, to the steric repulsion between the newly forming bond at C(3) and the protected alcohol at C(5).

Table 3.4.2[a]

entry	substrate	product	temp (°C)	time	yield[b]
1	 ***157***	 ***158***	80	2.3 h	51% (70%)
2	 ***149***	—	80	*complex mixture*[c]	
3	 ***159***	—	80	*no reaction*	
4	 ***147***	 ***160***	60[d]	11 h	10%[e]
5	 ***151***	 ***161***	80	2.3 h	34%

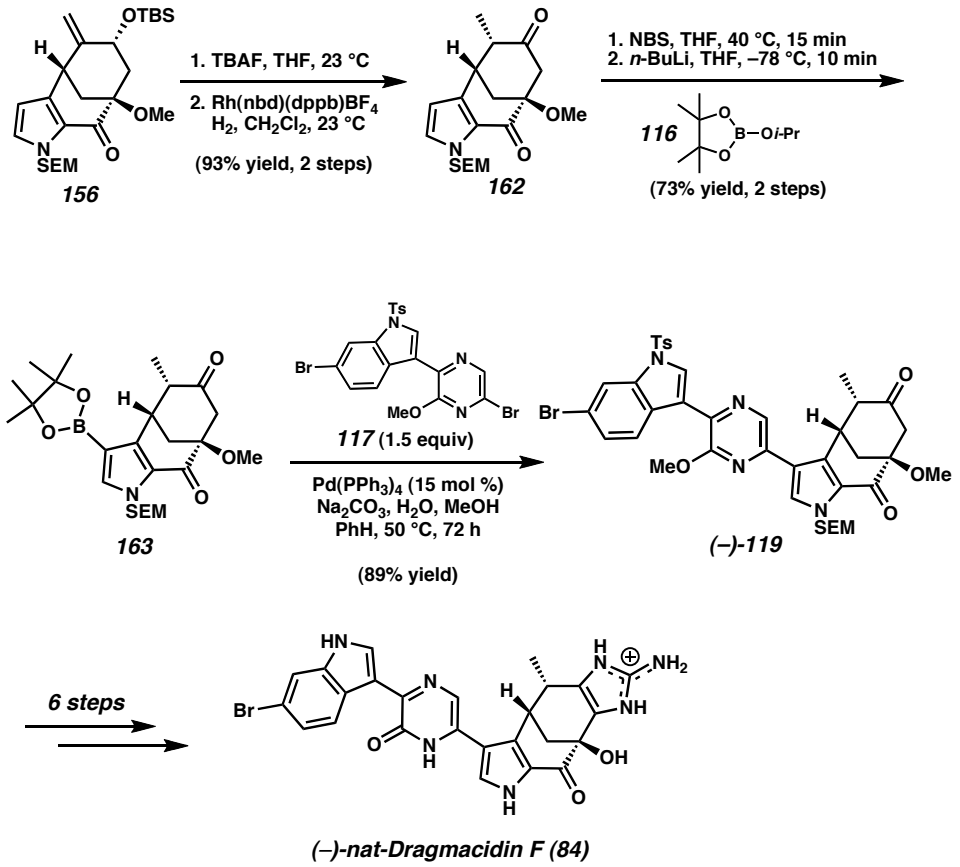
[a] Standard Conditions: 1 equiv $Pd(OAc)_2$, 2 equiv DMSO, *t*-BuOH:AcOH (4:1, 0.01 M). [b] Isolated Yield. Number in parentheses represents the yield based on recovered starting material. [c] Trace product may have formed in this reaction, but could not be isolated. [d] At 80 °C, trace product formation and substantial decomposition were observed.

3.4.5 End-Game: Total Synthesis of (–)-Dragmacidin F

Despite the similarity of **156** to its diastereomeric counterpart (**115**, Scheme 3.2.9) employed in the synthesis of (+)-dragmacidin F (**84**), attempts to carry out similar elaborations using previously developed protocols were unsuccessful. Thus, a slightly

modified end-game route was conceived and carried out by Neil Garg. Cleavage of the TBS ether of **156** using TBAF in THF, followed by a tandem olefin isomerization/tautomerization process using Brown's cationic rhodium catalyst[69] Rh(nbd)(dppb)BF_4 and H_2, formed ketone **162** as a single diastereomer in 93% yield over two steps (Scheme 3.4.9).[70] Position-selective bromination and low-temperature metalation of the pyrrole in the presence of two ketones gave rise to boronic ester **163**. Subsequent halogen-selective cross-coupling of **163** with dibromide **117** afforded the desired Suzuki adduct (–)-**119** (89% yield), the enantiomer of which had been employed in the synthesis of (+)-dragmacidin F. Finally, Suzuki adduct (–)-**119** was converted to (–)-dragmacidin F ((–)-**84**) via our previously described six-step protocol (vide supra). Synthetic and natural (–)-**84**[3f] were spectroscopically identical, including the sign of optical rotation (natural (–)-**84**: $[\alpha]^{25}_{D}$ –159° (*c* 0.4, MeOH); synthetic (–)-**84**: $[\alpha]^{23}_{D}$ –148° (*c* 0.2, MeOH)).[41b]

Scheme 3.4.9



3.5 Conclusion

In summary, we have developed an enantiodivergent strategy to access both antipodes of dragmacidin F (**84**) from a single enantiomer of readily available (–)-quinic acid (**93**). Our highly efficient syntheses provide (+)-**84** in 7.8% overall yield and (–)-**84** in 9.3% overall yield beginning from **93**. The routes that we have developed to (+)- and (–)-**84** are concise and feature a number of key transformations, namely: a) highly efficient functionalizations of (–)-**93** to differentiate C(3) and C(5), b) novel reductive isomerization reactions, c) sterically demanding Pd(II)-mediated oxidative carbocyclizations, d) halogen-selective Suzuki cross-coupling reactions, and e) high-

yielding late-stage Neber rearrangements. Advanced biological testing of both synthetic antipodes of dragmacidin F is currently underway.

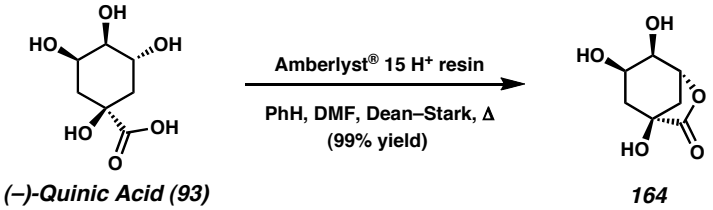
3.6 Experimental Section

3.6.1 Materials and Methods

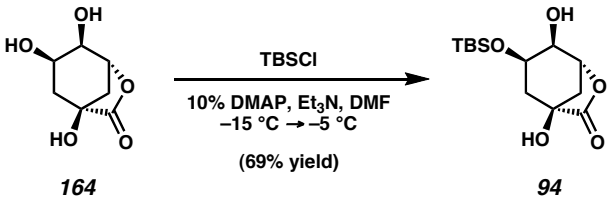
Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (either freshly distilled or passed through activated alumina columns). 10% Pd/C was purchased from Aldrich Chemical Company, Inc. (20,569-9). All commercially obtained reagents were used as received. Reaction temperatures were controlled using an IKAmag temperature modulator. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm) and visualized using a combination of UV, anisaldehyde, ceric ammonium molybdate, and potassium permanganate staining. ICN silica gel (particle size 0.032–0.063 mm) was used for flash column chromatography. Disposable Sep-Pak C_{18} Vac Cartridges were purchased from Waters and used for all reversed-phase filtrations. HPLC analysis was performed on a Beckman Gold system using a Rainin C_{18}, Microsorb MV, 5 μm, 300 x 4.6 mm reversed-phased column in 0.1% (*w*/*v*) TFA with acetonitrile/H_2O as eluent and a flow rate of 1.0 mL/min, gradient elution of 1.25% acetonitrile/min. Preparatory reversed-phase HPLC was performed on a Beckman HPLC with a Waters DeltaPak 25 x 100 mm, 100 μm C_{18} column equipped with a guard, 0.1% (*w*/*v*) TFA with acetonitrile/H_2O as eluent, and gradient elution of 0.50% acetonitrile/min. For all reversed-phase purifications, H_2O (18MΩ) was obtained from a Millipore MiliQ water purification system and TFA from Halocarbon, Inc. ^{1}H NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz), a Varian Inova 500 (at 500 MHz), or a Varian Inova 600 (at 600 MHz) 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. ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 75 MHz), or a Varian Inova 500 (at 125 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer or a Perkin Elmer Spectrum BXII spectrometer and are reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-1010 polarimeter. High-resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility. Analytical chiral HPLC was performed on a Chiralpak® AD column (4.6 mm x 250 mm) obtained from Daicel Chemical Industries, Ltd.

3.6.2 Preparative Procedures

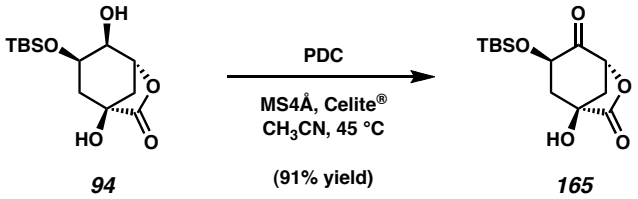


Lactone 164. A mixture of D-(–)-quinic acid (**93**) (50.0 g, 260.2 mmol), Amberlyst® 15 ion-exchange resin (7 g, 35 mmol), benzene (500 mL), and DMF (125 mL) was refluxed under a Dean-Stark trap for 16 h. The reaction mixture was cooled to 23 °C and filtered over a pad of Celite®. The filtrate was then evaporated under reduced pressure to afford a thick oil, which was diluted with CH_2Cl_2 (150 mL). Hexanes (250 mL) was added and the resulting mixture was allowed to sit at 23 °C for 2 h. The product was collected by vacuum filtration and was further dried in vacuo to afford lactone **164** (44.9 g, 99% yield) as a white powder. R_f 0.40 (3:1 EtOAc:acetone); characterization data for this compound have been previously reported.[14a]



TBS Lactone 94. To a mixture of lactone **164** (90.0 g, 517 mmol), DMAP (6.31 g, 51.7 mmol), triethylamine (90 mL, 646 mmol), and DMF (345 mL) at –15 °C was added TBSCl (84.9 g, 563 mmol) in 3 equal portions over 30 min. The temperature was maintained between –20 °C and –15 °C during the addition. The reaction mixture was allowed to warm to –5 °C over 3 h, quenched by the addition of 5% aq. citric acid (120 mL), and then warmed to 23 °C. The solvent was removed in vacuo, and the crude

product was diluted with 5% aq. citric acid (350 mL) and extracted with Et_2O (1 x 500 mL, 2 x 400 mL). The combined organic layers were washed with H_2O (2 x 400 mL) and brine (400 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The product was triturated with hexanes (750 mL) and collected by vacuum filtration. It was further dried under vacuum to afford TBS lactone **94** (102.8 g, 69% yield) as a dry white solid. R_f 0.48 (1:1 hexanes:EtOAc); R_f 0.28 (2:1 Et_2O:hexanes); characterization data for this compound have been previously reported.[14b]

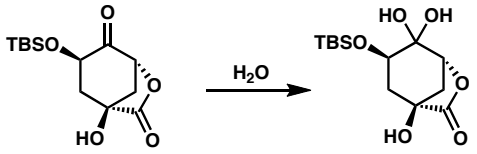


Keto Lactone 165. A mixture of TBS lactone **94** (3.72 g, 12.90 mmol), powdered 4Å activated molecular sieves (2.79 g), Celite® (2.79 g), pyridinium dichromate (12.13 g, 32.2 mmol), and acetonitrile (185 mL) was heated to 45 °C for 24 h. The reaction was allowed to cool to 23 °C, and then was filtered over a plug of silica gel topped with Celite® (EtOAc eluent). The solvent was removed under reduced pressure to afford a brown oil, which was further purified by passage over a plug of silica gel (1:1 hexanes:EtOAc eluent). Evaporating the solvent in vacuo afforded keto lactone **165** (3.35 g, 91% yield) as a pale yellow oil.

Alternate Procedure. Powdered 4Å activated molecular sieves (184.6 g) were agitated and flame-dried under vacuum for approximately 30 min until a fine, powder-like consistency was obtained. Upon cooling to 23 °C, CH_2Cl_2 (540 mL) was introduced, and the slurry was cooled to 0 °C. Freshly prepared pyridinium dichromate[71] (148.7 g,

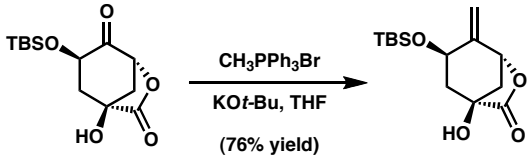
395.3 mmol) was added, and the resulting heterogeneous orange mixture was treated with TBS lactone **94** (70.04 g, 242.8 mmol) portionwise over 4 min. After the addition was complete, the reaction was stirred for 5 min and then freshly distilled AcOH (49.0 mL, 856.0 mmol) was added dropwise over a 20-min period. The reaction temperature was maintained at 0 °C for 15 min after the addition was complete, and the mixture was then stirred at 23 °C. After 10 h, the reaction was judged complete by ^{1}H NMR. The dark mixture was evenly divided into 3 portions, each of which was filtered over a pad of silica gel (10 cm diameter x 7.5 cm height, EtOAc eluent). The filtrates were combined and evaporated in vacuo to afford a dark liquid, and this residue was further coevaporated with toluene (3 x 150 mL). The crude product was diluted in a mixture of hexanes:EtOAc (10:1; 250 mL) and filtered over a pad of powdered Na_2SO_4 to remove insoluble impurities. The filtrate was evaporated, and dried in vacuo, to afford keto lactone **165** (55.27 g, 80% yield) as a brown, waxy solid. This material was used immediately in the next step without further purification. *Unstable to TLC conditions*; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.71 (d, *J* = 6.6 Hz, 1H), 4.52 (dd, *J* = 10.3, 8.9 Hz, 1H), 2.95 (s, 1H), 2.88–2.79 (m, 1H), 2.57–2.47 (m, 1H), 2.39 (d, *J* = 12.4 Hz, 1H), 2.13 (dd, *J* = 12.4 Hz, 10.5 Hz, 1H), 0.88 (s, 9H), 0.11 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.6, 177.4, 79.0, 72.0, 70.6, 43.2, 42.6, 25.8 (3C), 18.5, –4.6, –5.3; IR (film): 3444 (br), 2931, 2858, 1799, 1753, 1254, 1144, 1111 cm^{-1}; HRMS-FAB (*m*/*z*): $[M + H]^+$ calc'd for $C_{13}H_{23}O_5Si$, 287.1315; found, 287.1316; $[\alpha]^{19}_{D}$ –96.47° (*c* 1.0, C_6H_6).

*NOTE: Exposure of keto lactone **165** to water (e.g., aqueous workup, or prolonged exposure to silica gel) led to the formation of hydrate **166**, as a white powder.*



165 *166*

Hydrate 166. *Unstable to TLC conditions*; mp 104–6 °C; ^{1}H NMR (300 MHz, CD_3OD): δ 4.46 (d, *J* = 5.8 Hz, 1H), 3.75 (dd, *J* = 10.7, 7.0 Hz, 1H), 2.48–2.31 (comp. m, 2H), 2.10–2.00 (m, 1H), 1.76 (app. t, *J* = 11.4 Hz, 1H), 0.93 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD): δ 179.4, 93.2, 81.8, 73.0, 72.3, 41.5, 40.9, 26.5 (3C), 19.1, –4.3, –4.7; IR (KBr): 3440 (br), 3374 (br), 2929, 2858, 1782, 1256, 1108, 1070 cm^{-1}; HRMS-CI (*m/z*): $[M + H]^+$ calc'd for $C_{13}H_{24}O_6Si$, 304.1342; found, 304.1336; $[\alpha]^{19}_{D}$ –54.29° (*c* 1.0, MeOH).



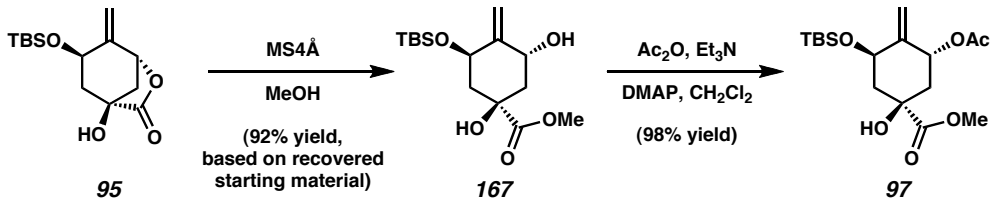
165 *95*

Methylene Lactone 95. To CH_3PPh_3Br (105 mg, 0.293 mmol) in THF (2.8 mL) at 0 °C was added potassium *t*-butoxide (31.3 mg, 0.279 mmol). The mixture was warmed to 23 °C and stirred for an additional 10 min. Keto lactone **165** (40 mg, 0.140 mmol) in THF (1 mL) was added and stirring was continued at 23 °C for 15 min. The reaction mixture was then refluxed for 2 h and cooled to 23 °C. The solvent was removed under reduced pressure, and the residue was partitioned between Et_2O (3 mL) and brine (1.5 mL). The layers were separated, and the aqueous layer was further extracted with Et_2O (3 x 1 mL). The combined organic layers were washed with brine (1.5 mL), dried by passage over a plug of silica gel (Et_2O eluent, then 2:1 hexanes:EtOAc eluent), and

evaporated under reduced pressure. The crude product was purified by flash chromatography (2:1 hexanes:EtOAc eluent) to afford methylene lactone **95** (30 mg, 76% yield) as a white solid.

Alternate Procedure. To CH_3PPh_3Br (82.9 g, 232.1 mmol) in THF (1.10 L) at 23 °C was added potassium *t*-butoxide (23.8 g, 212.1 mmol) in one portion. The mixture was stirred for 2 h, then cooled to 0 °C. Keto lactone **165** (54.5 g, 190.3 mmol) in THF (240 mL) was added dropwise over a 30 min period. The reaction was allowed to warm slowly to 23 °C over 9 h, then quenched by the addition of ice-cold 15% aq. NH_4Cl (500 mL). The solvent was evaporated under reduced pressure, and the residue was partitioned between Et_2O (500 mL) and H_2O (100 mL). The aqueous phase was extracted with Et_2O (3 x 250 mL), and the combined organics were washed with H_2O (100 mL) and brine (100 mL) and dried over $MgSO_4$. Evaporation of the solvent afforded a crude yellow oil, which was filtered over a plug of silica gel (4:1 pentane:Et_2O → 3:2 pentane:Et_2O eluent). After evaporating the solvent in vacuo, the residue was triturated with ice-cold pentane (40 mL). The white solid was filtered and washed with ice-cold pentane (2 x 2 mL). A second crop was collected from the filtrate after concentrating its volume to 15 mL. Drying the collected material in vacuo afforded methylene lactone **95** (22.1 g, 41% yield) as a white solid. R_f 0.59 (1:1 hexanes:EtOAc); mp 87–88 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.25–5.23 (m, 1H), 5.13–5.10 (m, 1H), 5.07 (d, J = 6.0 Hz, 1H), 4.38–4.29 (m, 1H), 2.85 (s, 1H), 2.67–2.59 (m, 1H), 2.31–2.21 (m, 1H), 2.09 (d, J = 11.5 Hz, 1H), 1.86 (app. t, J = 11.3 Hz, 1H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.1, 144.8, 111.0, 79.4, 73.1, 67.1, 44.7, 44.7, 26.0 (3C), 18.5, –4.5, –4.7; IR (film): 3426 (br),

2956, 2931, 2858, 1791, 1254, 1120, 1071 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+$ calc'd for $C_{14}H_{25}O_4Si$, 285.1522; found, 285.1519; $[\alpha]^{19}_D$ –101.71° (*c* 1.0, $CHCl_3$).

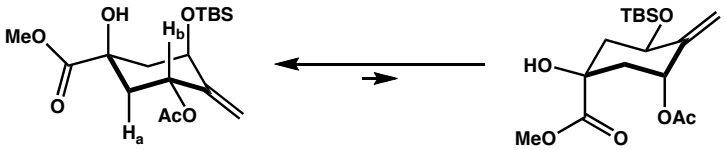


Methyl Ester 97. To lactone **95** (420 mg, 1.477 mmol) and activated oven-dried 4Å molecular sieves (100 mg) was added MeOH (15 mL). The reaction mixture was stirred at 23 °C for 5.5 h, then filtered over a short plug of Celite® (EtOAc eluent). After evaporation of the reaction mixture under reduced pressure, the residue was purified by flash column chromatography (2:1 hexanes:EtOAc eluent) to afford starting material lactone **95** (82 mg, 20% yield) and siloxy diol **167** (345 mg, 74% yield, 92% yield based on recovered starting material), which was used directly in the subsequent reaction.

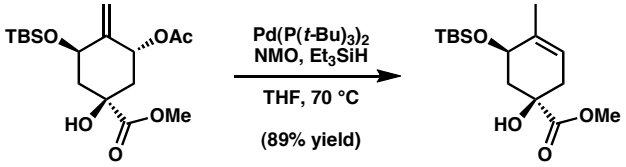
To siloxy diol **167** (80.0 mg, 0.253 mmol) in CH_2Cl_2 (1.5 mL) was added Et_3N (71 μL, 0.506 mmol), DMAP (3 mg, 0.0253 mmol), followed by Ac_2O (31 μL, 0.329 mmol). The reaction mixture was stirred at 23 °C for 10 min, quenched with saturated aq. $NaHCO_3$ (5 mL), and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were filtered over a plug of silica gel (CH_2Cl_2 eluent, then EtOAc eluent) and evaporated under reduced pressure. The crude product was purified by flash chromatography (3:1 hexanes:EtOAc eluent) to afford methyl ester **97** (89.0 mg, 98% yield) as a colorless oil. R_f 0.50 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.90–5.81 (m, 1H), 4.96 (br s, 1H), 4.94 (br s, 1H), 4.91–4.89 (m, 1H), 4.67 (app. t, *J* = 3.2 Hz, 1H), 3.74 (s, 3H), 2.38 (ddd, *J* = 12.7, 5.2, 2.2 Hz, 1H), 2.19–2.03 (comp. m, 2H), 2.09 (s, 3H), 1.93 (app. t,

J = 12.1 Hz, 1H), 0.87 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.7, 169.6, 146.3, 108.5, 76.5, 75.1, 68.0, 52.9, 42.7, 41.2, 25.8 (3C), 21.1, 18.1, –4.6, –5.2; IR (film) 3464 (br), 2954, 2932, 2858, 2888, 1739 (br), 1369, 1233 (br), 1124, 1098, 1072, 1036 cm^{-1}; HRMS-FAB (m/z): $[M + H]^+$ calc'd for $C_{17}H_{31}O_6Si$, 359.1890; found, 359.1900; $[\alpha]^{26}_D$ –26.61° (c 1.0, C_6H_6).

The stable chair conformer of methyl ester **97** was determined using homodecoupling NMR experiments. The coupling constant between H_a and H_b was measured as J_{ab} = 10.7 Hz.



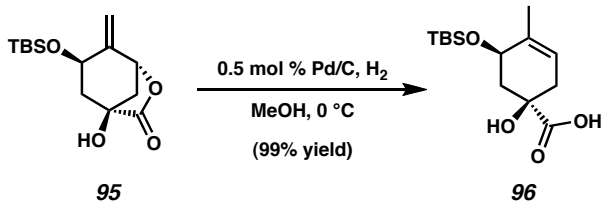
97-favored *97-disfavored*



97 *98*

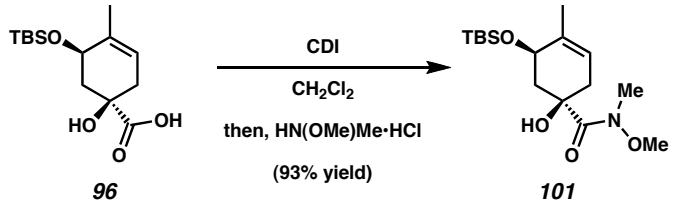
Siloxycyclohexene 98. Methyl ester **97** (94 mg, 0.262 mmol), $Pd(P(t\text{-}Bu_3)_2)$ (40.2 mg, 0.0786 mmol), anhydrous *N*-methylmorpholine *N*-oxide (307 mg, 2.52 mmol), THF (5.2 mL), and freshly distilled Et_3SiH (1.67 mL, 10.5 mmol) were combined under a glovebox atmosphere. The reaction mixture was immediately removed from the glovebox and placed in a 70 °C oil bath. After 3.5 h, the reaction mixture was cooled to 0 °C, and the volatiles were removed under reduced pressure. Saturated aq. NH_4Cl (15 mL) was added, and the mixture was extracted with Et_2O (3 x 25 mL). The combined organic

layers were washed with brine (15 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (5:1 hexanes:EtOAc eluent) to afford siloxycyclohexene **98** (70 mg, 89% yield) as a pale yellow oil. R_f 0.55 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.49–5.42 (m, 1H), 4.62 (s, 1H), 4.18–4.12 (m, 1H), 3.76 (s, 3H), 2.45–2.38 (comp. m, 2H), 2.16–2.10 (comp. m, 2H), 1.79–1.74 (m, 3H), 0.88 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.3, 133.7, 120.9, 73.0, 68.7, 52.6, 38.4, 36.9, 25.9 (3C), 21.4, 18.0, –4.3, –4.7; IR (film) 3478 (br), 2955, 2858, 1740, 1451, 1253, 1217, 1111, 1065, 1037 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+$ calc'd for $C_{15}H_{19}O_4Si$, 301.1835; found, 301.1835; $[\alpha]^{24}_D$ +77.62° (*c* 0.47, $CHCl_3$).

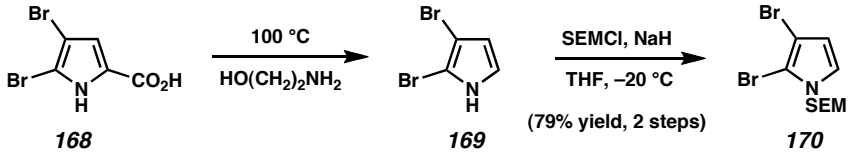


Acid 96. A mixture of methylene lactone **95** (4.0 g, 14.1 mmol) and 10% Pd/C (80 mg, 0.075 mmol) in methanol (120 mL) was cooled to 0 °C. The reaction vessel was evacuated and back-filled with H_2 (3x). After 7 h at 0 °C, the mixture was filtered over a pad of Celite® (MeOH eluent), and the solvent was evaporated under reduced pressure to afford a colorless oil. Residual solvent was removed by holding the crude product under vacuum for 10 h, providing acid **96** (4.0 g, 99% yield), which was used immediately without further purification. R_f 0.28 (1:1 hexanes:EtOAc; 1% acetic acid); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.88 (s, 1H), 5.53–5.48 (m, 1H), 4.16–4.11 (m, 1H), 2.71–2.60 (m, 1H), 2.36–2.22 (m, 1H), 2.18 (dd, *J* = 14.3, 3.9 Hz, 1H), 2.08–2.01 (m, 1H), 1.79–1.76 (m,

3H), 0.89 (s, 9H), 0.15–0.13 (comp. m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.4, 133.2, 121.1, 73.6, 68.6, 37.9, 35.9, 25.8 (3C), 21.4, 18.0, –4.5, –4.7; IR (film): 3356 (br), 2956, 2931, 2858, 1768 (br), 1718 (br), 1255, 1063 cm^{-1}; HRMS-FAB (*m/z*): [M + H]$^+$ calc'd for $C_{14}H_{27}O_4Si$, 287.1679; found, 287.1675; $[\alpha]^{19}_D$ +37.58° (*c* 1.0, C_6H_6).



Weinreb Amide 101. To acid **96** (4.0 g, 14.1 mmol) in CH_2Cl_2 (70 mL) at 23 °C was added 1,1'-carbonyldiimidazole (3.65 g, 22.5 mmol) in equal portions over 15 min. After the final addition, stirring was continued for 10 min, then *N,O*-dimethylhydroxylamine • HCl (3.43 g, 35.16 mmol) was added in one portion. The reaction was allowed to stir at 23 °C for 3 h. Et_2O was added (50 mL), and the reaction mixture was filtered. The filtrate was evaporated, diluted with Et_2O (125 mL), washed with 5% aq. citric acid (2 x 50 mL) and brine (50 mL), and dried over $MgSO_4$. The crude product was purified by flash chromatography (3:1 hexanes:EtOAc eluent) to afford Weinreb amide **101** (4.29 g, 93% yield) as a colorless oil. R_f 0.42 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.43 (m, 1H), 4.72 (s, 1H), 4.17–4.11 (m, 1H), 3.71 (s, 3H), 3.22 (s, 3H), 2.59–2.24 (comp. m, 3H), 2.03 (dd, *J* = 14.6, 4.1 Hz, 1H), 1.75–1.71 (m, 3H), 0.86 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 15/16 C): δ 133.5, 121.5, 74.3, 69.4, 61.2, 38.1, 35.9, 26.0, 25.9 (3C), 21.3, 18.1, –4.3, –4.7; IR (film): 3463 (br), 2956, 2932, 2858, 1655, 1362, 1254 cm^{-1}; HRMS-EI (*m/z*): [M + H]$^+$ calc'd for $C_{16}H_{32}NO_4Si$, 330.2101; found, 330.2085; $[\alpha]^{19}_D$ +41.13° (*c* 1.0, $CHCl_3$).

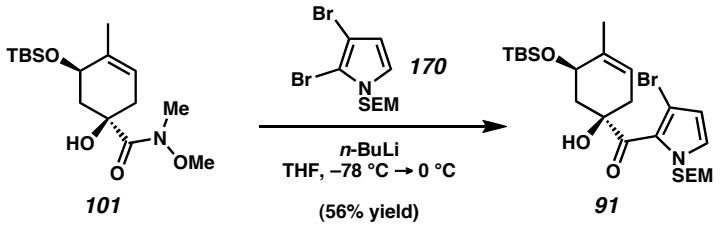


Dibromopyrrole 170. A solution of 4,5-dibromopyrrole carboxylic acid (**168**)[72] (6.05 g, 22.5 mmol) in ethanolamine (36 mL) was heated to 100 °C for 2 h, cooled to 23 °C, and poured into a mixture of Et_2O (200 mL) and 0.5 N aq. HCl (300 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 250 mL). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, and concentrated to 100 mL. The solution was diluted with hexanes (100 mL), filtered over a plug of silica gel (2:1 hexanes:Et_2O eluent), and concentrated to 150 mL. THF (100 mL) was added, and the solution was concentrated to 100 mL. This solvent exchange procedure was repeated 2 additional times (2 x 100 mL THF) to afford 2,3-dibromopyrrole (**169**) as a solution in THF, which was used immediately in the subsequent reaction.

*CAUTION: Concentrating the above described solutions to dryness or near-dryness leads to rapid decomposition of 2,3-dibromopyrrole (***169***).*[37]

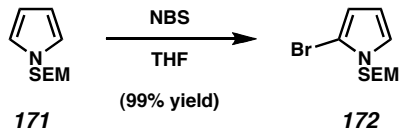
To 2,3-dibromopyrrole (**169**) in THF at –20 °C was added NaH (60% dispersion in mineral oil, 1.51 g, 37.8 mmol) in 3 equal portions over 3 min. After 10 min at –20 °C, SEMCl (4.8 mL, 27.1 mmol) was added dropwise over 1 min. The reaction mixture was allowed to warm to –8 °C over 40 min and was then quenched with saturated aq. NH_4Cl (30 mL). After warming to 23 °C, the reaction mixture was diluted with Et_2O (75 mL) and H_2O (20 mL), and the layers were separated. The aqueous layer was further extracted

with Et_2O (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (6:1 hexanes:CH_2Cl_2, then 4:1 hexanes:CH_2Cl_2 eluent) to afford dibromopyrrole **170** (6.25 g, 79% yield) as a yellow oil. R_f 0.17 (6:1 hexanes:CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.82 (d, *J* = 3.6 Hz, 1H), 6.25 (d, *J* = 3.3 Hz, 1H), 5.21 (s, 2H), 3.48 (t, *J* = 8.1 Hz, 2H), 0.88 (t, *J* = 8.1 Hz, 2H), –0.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 123.1, 112.3, 103.7, 99.8, 77.8, 66.2, 17.9, –1.2 (3C); IR (film): 2953, 2896, 1514, 1470, 1279, 1250, 1109, 1084 cm^{-1}; HRMS-EI (*m/z*): $[M + H]^+$ calc'd for $C_{10}H_{17}NOSiBr_2$, 352.9446; found, 352.9435.



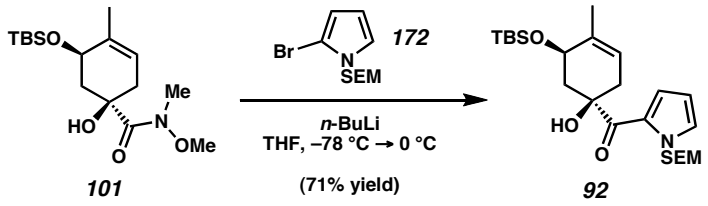
Bromo Acyl Pyrrole 91. To dibromopyrrole **170** (6.02 g, 17.06 mmol) in THF (114 mL) at –78 °C was added *n*-BuLi (2.5 M in hexanes, 6.7 mL, 16.8 mmol) dropwise over 1 min. After 10 min at –78 °C, Weinreb amide **101** (1.58 g, 4.80 mmol) in THF (15 mL) was added dropwise over 30 seconds. The reaction vessel was immediately warmed to 0 °C, stirred for 90 min, and cooled to –78 °C. The reaction was quenched with saturated aq. NH_4Cl (15 mL), then warmed to 23 °C. The volatiles were removed in vacuo, and the residue was partitioned between Et_2O (75 mL) and H_2O (30 mL). The layers were separated, and the aqueous layer was further extracted with Et_2O (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash

chromatography (11:9 CH_2Cl_2:hexanes eluent) to afford bromo acyl pyrrole **91** (1.47 g, 56% yield) as a colorless oil. R_f 0.29 (11:9 hexanes:CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.77 (d, *J* = 2.9 Hz, 1H), 6.20 (d, J= 2.7 Hz, 1H), 5.53–5.47 (m, 1H), 5.35 (d, *J* = 10.4 Hz, 1H), 5.29 (d, *J* = 10.4 Hz, 1H), 4.72 (s, 1H), 4.18–4.14 (m, 1H), 3.31 (t, *J* = 8.2 Hz, 2H), 2.65–2.53 (m, 1H), 2.53–2.41 (m, 1H), 2.32 (dt, *J* = 14.3, 1.7 Hz, 1H), 2.15 (dd, *J* = 14.2 Hz, 4 Hz, 1H), 1.79–1.76 (m, 3H), 0.87 (s, 9H), 0.81 (t, *J* = 8.2 Hz, 2H), 0.12 (s, 6H), –0.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.9, 133.2, 129.6, 125.0, 121.6, 112.5, 101.8, 78.9, 78.6, 68.9, 66.2, 38.6, 37.4, 26.0 (3C), 21.5, 18.1, 17.8, –1.2 (3C), –4.1, –4.7; IR (film): 3477 (br), 2953, 1664 (br), 1400, 1253, 1101 cm^{-1}; HRMS-EI (*m/z*): [M + H]$^+$ calc'd for $C_{24}H_{43}NO_4Si_2Br$, 544.1914; found, 544.1903; $[\alpha]^{19}_D$ +1.64° (*c* 1.0, $CHCl_3$).



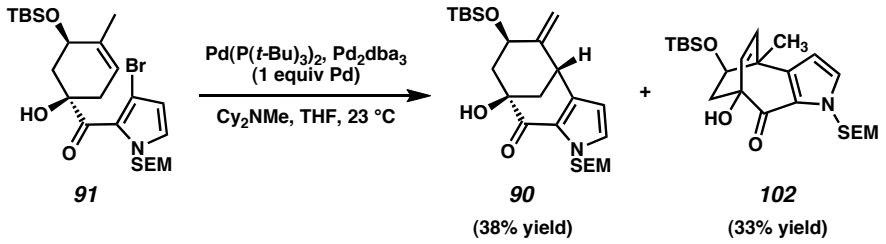
Bromopyrrole 172. To SEM pyrrole **171**[22] (1.25 g, 6.33 mmol) in THF (125 mL) at 23 °C was added freshly recrystallized NBS (1.127 g, 6.33 mmol) in one portion. After stirring for 5 min, additional NBS was added (15 mg, 0.084 mmol), and the reaction was immediately judged complete by TLC. The reaction mixture was poured into saturated aq. $NaHCO_3$ (100 mL) and extracted with Et_2O (1 x 100 mL, 2 x 50 mL). The combined organic layers were washed with brine (75 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by passage over a plug of silica gel (CH_2Cl_2 eluent) to afford bromopyrrole **172** (1.73 g, 99% yield) as a pale yellow oil. R_f 0.53 (1:1 CH_2Cl_2:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.83 (app. t, *J* = 2.5 Hz, 1H),

6.18–6.16 (comp. m, 2H), 5.22 (s, 2H), 3.53–3.46 (m, 2H), 0.92–0.85 (m, 2H), –0.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 122.9, 111.9, 110.1, 102.0, 76.7, 66.0, 17.9, –1.2 (3C); IR (film): 2953, 2895, 1264, 1249, 1108, 1085 cm^{-1}; HRMS-EI (*m*/*z*): [M + H]$^+$ calc'd for $C_{10}H_{18}NOSiBr$, 275.0341; found, 275.0331.



Acyl Pyrrole 92. To bromopyrrole **172** (1.73 g, 6.26 mmol) in THF (42 mL) at –78 °C was added *n*-BuLi (2.25 M in hexanes, 2.7 mL, 6.16 mmol) dropwise over 1 min. After 10 min at –78 °C, Weinreb amide **101** (655 mg, 1.99 mmol) in THF (5 mL) was added dropwise over 1 min. The reaction vessel was immediately warmed to 0 °C, stirred for 25 min, and cooled to –78 °C. The reaction mixture was quenched with saturated aq. NH_4Cl (10 mL), then warmed to 23 °C. The volatiles were removed under reduced pressure. The residue was partitioned between Et_2O (75 mL) and H_2O (50 mL), and the layers were separated. The aqueous layer was further extracted with Et_2O (2 x 40 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (23:1 hexanes:EtOAc, then 15:1 hexanes:EtOAc eluent) to afford acyl pyrrole **92** (656 mg, 71% yield) as a colorless oil. R_f 0.30 (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (dd, *J* = 4.0, 1.7 Hz, 1H), 7.06 (dd, *J* = 2.5, 1.7 Hz, 1H), 6.19 (dd, *J* = 4.0, 2.5 Hz, 1H), 5.71 (d, *J* = 10.4 Hz, 1H), 5.67 (d, *J* = 10.0 Hz, 1H), 5.52–5.47 (m, 1H), 4.90 (s, 1H), 4.19 (app. t, *J* = 3.1 Hz, 1H), 3.51 (t, *J* = 8.3 Hz, 2H), 2.52–2.46

(comp. m, 2H), 2.19–2.16 (comp. m, 2H), 1.80–1.78 (m, 3H), 0.92–0.88 (comp. m, 11H), 0.13 (s, 6H), –0.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 22/24 C): δ 193.7, 133.5, 129.9, 128.0, 123.8, 121.7, 109.0, 78.2, 69.4, 66.3, 38.6, 38.3, 26.0 (3C), 21.5, 18.1, –1.2 (3C), –4.2, –4.7; IR (film): 3476, 2954, 2931, 2859, 1639, 1412, 1310, 1251, 1085 cm^{-1}; HRMS-EI (*m/z*): $[M + H]^+$ calc'd for $C_{24}H_{44}NO_4Si_2$, 466.2809; found, 466.2822; $[\alpha]^{19}_D$ +34.25° (*c* 1.0, C_6H_6).



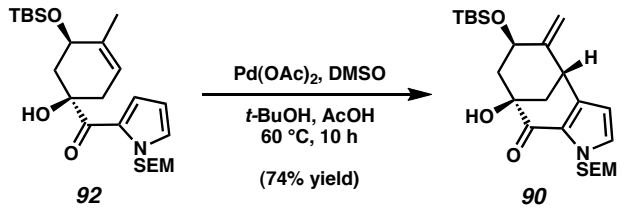
[3.3.1] Bicycle 90. Bromo acyl pyrrole **91** (52.0 mg, 0.0955 mmol), Pd_2dba_3 (21.9 mg, 0.0239 mmol), $Pd(P(t\text{-}Bu)_3)_2$ (24.4 mg, 0.0477 mmol), THF (1.2 mL), and Cy_2NMe (24.3 μL, 0.115 mmol) were combined under a glovebox atmosphere and stirred at 23 °C for 10 h. The reaction vessel was removed from the glovebox, diluted with 3:1 hexanes:EtOAc (2 mL), and filtered over a plug of silica gel topped with Celite® (3:1 hexanes:EtOAc eluent). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (CH_2Cl_2, then 3:1 hexanes:EtOAc eluent). The crude product was further purified by flash chromatography (6:1 hexanes:EtOAc eluent) to afford [3.3.1] bicycle **90** (16.7 mg, 38% yield) and [3.2.2] bicycle **102** (14.4 mg, 33% yield), both as pale yellow oils.

[3.3.1] Bicycle 90: R_f 0.20 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.07 (d, *J* = 2.7 Hz, 1H), 6.05 (d, *J* = 2.7 Hz, 1H), 5.71 (d, *J* = 9.9 Hz, 1H), 5.58 (d, *J* = 9.9 Hz,

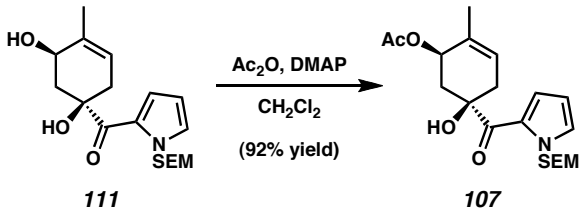
1H), 5.09–5.05 (m, 2H), 4.00 (s, 1H), 3.99–3.90 (m, 1H), 3.84 (app. t, *J* = 3.0 Hz, 1H), 3.55–3.47 (m, 2H), 2.39 (app. dt, *J* = 7.4, 3.8 Hz, 1H), 2.13–2.03 (comp. m, 2H), 1.73 (app. t, *J* = 11.8 Hz, 1H), 0.98–0.76 (comp. m, 11H), –0.04 (s, 9H), –0.11 (s, 6H); ^{1}H NMR (300 MHz, C_6D_6): δ 6.53 (d, *J* = 2.5 Hz, 1H), 5.77 (d, *J* = 2.8 Hz, 1H), 5.55 (d, *J* = 10.2 Hz, 1H), 5.32 (app. t, *J* = 1.9 Hz, 1H), 5.26 (d, *J* = 10.2 Hz, 1H), 5.01–4.97 (m, 1H), 4.29 (s, 1H), 4.27–4.19 (m, 1H), 3.59–3.47 (comp. m, 3H), 2.45–2.31 (comp. m, 2H), 2.16 (dd, *J* = 12.1, 3.0 Hz, 1H), 2.07 (app. t, *J* = 11.8 Hz, 1H), 0.92–0.89 (comp. m, 11H), 0.01 (s, 9H), –0.06 (s, 3H), –0.07 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6): δ 191.5, 149.4, 141.8, 132.0, 125.5, 108.5, 107.4, 76.8, 75.8, 68.4, 66.3, 48.9, 45.5, 40.7, 26.3 (3C), 18.8, 18.2, –0.8 (3C), –4.4, –4.7; IR (film): 3480, 2953, 2858, 1651, 1420, 1318, 1251, 1100, 1077 cm^{-1}; HRMS-FAB (*m/z*): $[M]^+$ calc'd for $C_{24}H_{41}NO_4Si_2$, 463.2574; found, 463.2577; $[\alpha]^{23}_{D}$ –275.07° (*c* 1.0, $CHCl_3$).

[3.2.2] Bicycle 102: R_f 0.42 (5:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 6.55 (d, *J* = 2.7 Hz, 1H), 6.23 (d, *J* = 8.8 Hz, 1H), 5.96 (d, *J* = 3.3 Hz, 1H), 5.94 (d, *J* = 9.2 Hz, 1H), 5.59 (d, *J* = 10.4 Hz, 1H), 5.40 (d, *J* = 9.9 Hz, 1H), 5.32 (s, 1H), 3.82–3.75 (m, 1H), 3.46 (t, *J* = 7.7 Hz, 2H), 2.46 (dd, *J* = 13.7, 7.7 Hz, 1H), 2.25 (dd, *J* = 13.7, 1.6 Hz, 1H), 1.52 (s, 3H), 0.92 (s, 9H), 0.82 (t, *J* = 8.0 Hz, 2H), –0.03 (s, 3H), –0.08 (s, 3H), –0.09 (s, 9H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.98 (d, *J* = 2.7 Hz, 1H), 6.15 (d, *J* = 2.7 Hz, 1H), 6.02 (d, *J* = 9.3 Hz, 1H), 5.98 (d, *J* = 8.8 Hz, 1H), 5.69 (d, *J* = 9.9 Hz, 1H), 5.62 (d, *J* = 9.9 Hz, 1H), 4.93 (s, 1H), 3.81 (d, *J* = 7.7 Hz, 1H), 3.50 (t, *J* = 8.0 Hz, 2H), 2.36 (dd, *J* = 14.3, 7.7 Hz, 1H), 1.94 (dd, *J* = 14.3, 1.6 Hz, 1H), 1.55 (s, 3H), 0.91–0.83 (comp. m, 11H), 0.02 (s, 3H), 0.01 (s, 3H), –0.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.7,

144.1, 139.4, 134.5, 129.1, 121.8, 107.7, 78.2, 77.8, 73.3, 66.4, 45.7, 45.0, 26.0 (3C), 22.2, 18.2, 18.0, –1.25 (3C), –4.1, –4.6; IR (film): 3432, 2955, 2858, 1645, 1250, 1081 cm^{-1}; HRMS-EI (*m/z*): $[M + H]^+$ calc'd for $C_{24}H_{42}NO_4Si_2$, 464.2652; found, 464.2665; $[\alpha]^{19}_D$ +19.22° (*c* 1.0, C_6H_6).

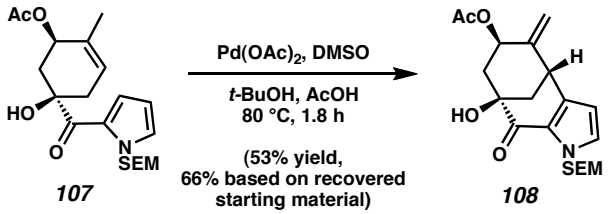


Alternate Procedure. To acyl pyrrole **92** (106.0 mg, 0.227 mmol) was added $Pd(OAc)_2$ (51.1 mg, 0.227 mmol), DMSO (32.3 μL, 0.455 mmol), *t*-BuOH (18.2 mL), and AcOH (4.5 mL). The mixture was heated to 60 °C for 10 h, cooled to 23 °C, and filtered over a plug of silica gel (3:1 hexanes:EtOAc eluent). The solvent was evaporated, and the residue was again filtered over a plug of silica gel (3:1 hexanes:EtOAc eluent). After removal of solvent in vacuo, the product was purified by flash chromatography on silica gel (6:1 hexanes:EtOAc eluent) to afford [3.3.1] bicycle **90** (78.4 mg, 74% yield) as a pale yellow oil.



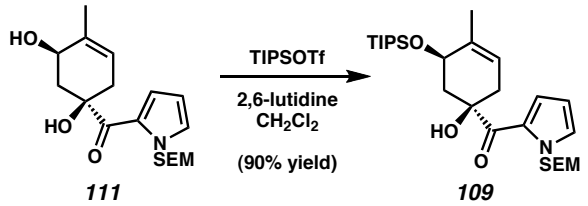
Allylic Acetate 107. To allylic alcohol **111**[73] (131.0 mg, 0.37 mmol) in CH_2Cl_2 (7.5 mL) at 23 °C was added DMAP (68.1 mg, 0.56 mmol) followed by Ac_2O (53 μL, 0.56 mmol). After stirring for 50 min, the reaction was quenched by the addition of

saturated aq. $NaHCO_3$ (10 mL). Et_2O (30 mL) was added, the phases were partitioned, and the aqueous phase was extracted with Et_2O (3 x 30 mL). The combined organics were washed successively with H_2O (10 mL) and brine (10 mL), dried over $MgSO_4$, and evaporated in vacuo. Flash chromatography of the crude product (7:3 hexanes:Et_2O eluent) provided allylic acetate **107** (134.4 mg, 92%) as a colorless oil. R_f 0.21 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.71 (dd, *J* = 3.9, 1.7 Hz, 1H), 6.76 (dd, *J* = 2.6, 1.8 Hz, 1H), 6.10 (dd, *J* = 4.0, 2.6 Hz, 1H), 5.63 (d, *J* = 10.2 Hz, 1H), 5.57 (d, *J* = 9.9 Hz, 1H), 5.50–5.45 (m, 1H), 5.32–5.26 (m, 1H), 3.45 (t, *J* = 7.8 Hz, 2H), 3.39 (s, 1H), 2.69–2.58 (m, 1H), 2.51–2.35 (comp. m, 2H), 2.28 (app. dt, *J* = 8.6, 5.0 Hz, 1H), 1.60–1.57 (comp. m, 6H), 0.84 (t, *J* = 7.8 Hz, 2H), –0.07 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 193.4, 169.9, 131.2, 130.6, 128.3, 124.6, 124.0, 109.2, 78.5, 77.6, 69.7, 66.4, 38.4, 38.3, 20.9, 20.8, 18.3, –1.0 (3C); IR (film) 3458 (br), 2924, 1734, 1641, 1314, 1372, 1247, 1085 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+$ calc'd for $C_{20}H_{32}NO_5Si$, 394.2050; found, 394.2030; $[\alpha]^{27}_D$ +22.38° (*c* 1.0, C_6H_6).



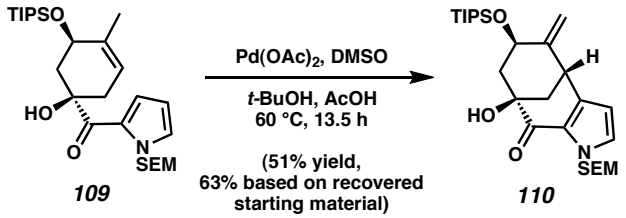
Allylic Acetate 108. For representative procedures, see oxidative cyclization of **92** → **90** or **113** → **114**. Purified by preparative thin-layer chromatography (4:1 CH_2Cl_2:Et_2O eluent). *Note:* Table 3.2.2, Entry 5 was performed in a round-bottom flask fitted with reflux condenser and an O_2 balloon. R_f 0.56 (4:1 CH_2Cl_2:Et_2O); ^{1}H NMR (300 MHz, C_6D_6): δ 6.52 (d, *J* = 2.7 Hz, 1H), 5.76 (d, *J* = 2.7 Hz, 1H), 5.51–5.41 (m, 1H), 5.46

(d, J = 10.4 Hz, 1H), 5.27 (d, J = 10.4 Hz, 1H), 4.93 (app. t, J = 1.7 Hz, 1H), 4.91–4.88 (m, 1H), 4.35 (s, 1H), 3.56 (t, J = 7.7 Hz, 2H), 3.47 (app. t, J = 3.1 Hz, 1H), 2.49–2.36 (comp. m, 2H), 2.17–2.09 (m, 1H), 1.94 (app. t, J = 12.0 Hz, 1H), 1.55 (s, 3H), 0.96–0.86 (m, 2H), –0.01 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 190.6, 169.2, 145.5, 141.0, 132.4, 125.4, 108.6, 106.8, 76.8, 75.4, 69.0, 66.5, 45.3, 44.5, 40.9, 20.6, 18.2, –0.9 (3C); IR (film) 3469 (br), 2952, 1743, 1651, 1237, 1093, 1037 cm^{-1}; HRMS-FAB (m/z): $[M+H]^+$ calc'd for $C_{20}H_{30}NO_5Si$, 392.1893; found, 392.1886; $[\alpha]^{27}_D$ –389.72° (c 0.6, C_6H_6).

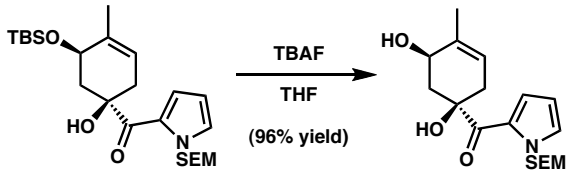


TIPS Ether 109. To allylic alcohol **111**[73] (50.7 mg, 0.14 mmol) in CH_2Cl_2 (5 mL) at 23 °C was added 2,6-lutidine (34 μL, 0.29 mmol), followed by TIPSOTf (44 μL, 0.16 mmol). After stirring 5 min, saturated aq. NH_4Cl (5 mL) was added to quench the reaction. The phases were partitioned, and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine (5 mL), and dried over $MgSO_4$. Following evaporation of the solvent in vacuo, the crude product was purified by flash chromatography (9:1 hexanes:EtOAc eluent) to provide TIPS ether **109** (65.8 mg, 90%) as a colorless oil. R_f 0.58 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 8.12 (dd, J = 3.9, 1.6 Hz, 1H), 6.77 (dd, J = 2.5, 1.6 Hz, 1H), 6.15 (dd, J = 3.9, 2.5 Hz, 1H), 5.69 (d, J = 10.1 Hz, 1H), 5.65 (d, J = 9.6 Hz, 1H), 5.34–5.29 (m, 1H), 5.00 (s, 1H), 4.24–4.19 (m, 1H), 3.49 (t, J = 7.8 Hz, 2H), 2.69–2.63 (comp. m, 2H), 2.50–2.42 (m, 1H), 2.40–2.32 (m, 1H), 1.78–1.74 (m, 3H), 1.09–0.97 (comp. m, 21H), 0.85 (t, J =

7.8 Hz, 2H), –0.06 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 194.1, 133.8, 130.3, 129.0, 124.7, 122.8, 109.2, 78.9, 78.5, 70.5, 66.3, 39.6, 39.4, 22.0, 18.7 (3C), 18.7 (3C), 18.4, 13.3 (3C), –0.9 (3C); IR (film) 3472 (br), 2947, 2868, 1639, 1413, 1310, 1249, 1084 cm^{-1}; HRMS-FAB (*m*/*z*): [M + H]$^+$ calc'd for $C_{27}H_{50}NO_4Si_2$, 508.3278; found, 508.3273; $[\alpha]^{27}_D$ +29.49° (*c* 1.0, C_6H_6).



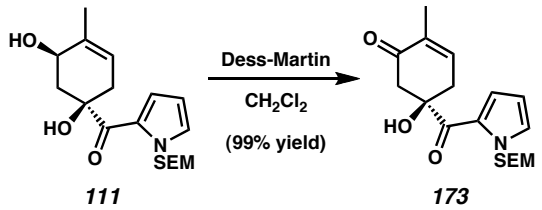
TIPS Ether 110. For representative procedures, see oxidative cyclization of **92** → **90** or **113** → **114**. Purified by preparative thin-layer chromatography (4:1 hexanes:EtOAc eluent). R_f 0.29 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 6.54 (d, *J* = 2.7 Hz, 1H), 5.78 (d, *J* = 2.7 Hz, 1H), 5.52 (d, *J* = 10.1 Hz, 1H), 5.41 (app. t, *J* = 2.1 Hz, 1H), 5.32 (d, *J* = 10.1 Hz, 1H), 5.02 (app. t, *J* = 2.3 Hz, 1H), 4.38–4.29 (m, 1H), 4.25 (s, 1H), 3.59–3.45 (comp. m, 3H), 2.50–2.38 (comp. m, 2H), 2.21–2.04 (comp. m, 2H), 1.09–0.78 (comp. m, 23H), –0.01 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 191.5, 149.6, 141.7, 131.8, 125.6, 108.5, 107.5, 76.9, 75.9, 68.6, 66.5, 49.2, 40.7, 18.6 (3C) 18.6 (3C), 18.2, 13.1 (3C), –0.9 (3C); IR (film) 3478 (br), 2946, 2867, 1650, 1100, 1080 cm^{-1}; HRMS-EI (*m*/*z*): [M]$^+$ calc'd for $C_{27}H_{47}NO_4Si_2$, 505.3044; found, 505.3041; $[\alpha]^{27}_D$ –207.44° (*c* 0.6, C_6H_6).



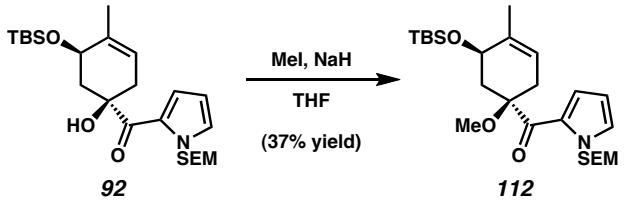
92 *111*

Allylic Alcohol 111. To allylic silyl ether **92** (100.0 mg, 0.21 mmol) in THF (5 mL) at 23 °C was added TBAF (1.0 M in THF, 250 μL, 0.25 mmol). After stirring 5 min, the reaction mixture was quenched by the addition of saturated aq. NH_4Cl (5 mL). The reaction was poured into Et_2O (5 mL) and H_2O (5 mL), and the phases were partitioned. The aqueous phase was extracted with Et_2O (4 x 3 mL), and the combined organic extracts were dried by passage over a plug of SiO_2 gel (Et_2O eluent). The solvent was evaporated in vacuo, and the residue was passed over another plug of SiO_2 gel (Et_2O eluent) to afford allylic alcohol **111** (72.8 mg, 96% yield) as a colorless oil. R_f 0.38 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.01 (dd, *J* = 4.1, 1.7 Hz, 1H), 6.70 (dd, *J* = 2.5, 1.7 Hz, 1H), 5.99 (dd, *J* = 4.1, 2.8 Hz, 1H), 5.52 (d, *J* = 10.0 Hz, 1H), 5.49 (d, *J* = 10.2 Hz, 1H), 5.31–5.25 (m, 1H), 4.95 (s, 1H), 3.93–3.84 (m, 1H), 3.60 (app. d, *J* = 9.6 Hz, 1H), 3.41 (t, *J* = 7.8 Hz, 2H), 2.77–2.65 (m, 1H), 2.27–2.16 (comp. m, 3H), 1.93–1.89 (m, 3H), 0.82 (t, *J* = 7.7 Hz, 2H), –0.08 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 194.0, 136.2, 131.0, 126.9, 123.5, 120.0, 109.5, 78.8, 77.8, 68.1, 66.6, 41.0, 38.7, 21.7, 18.3, –1.0 (3C); IR (film) 3388 (br), 2953, 1632, 1412, 1309, 1249, 1086 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+$ calc'd for $C_{18}H_{30}NO_4Si$, 352.1944; found, 352.1941; $[\alpha]^{27}_D$ +31.11° (*c* 1.0, C_6H_6).

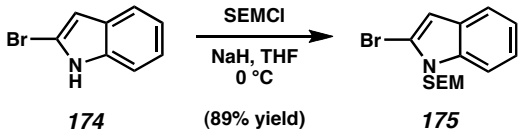
*For entry 2 (Table 3.2.2) and entry 8 (Table 3.4.2), small quantities of enone **173** were observed. An authentic sample was prepared as follows:*



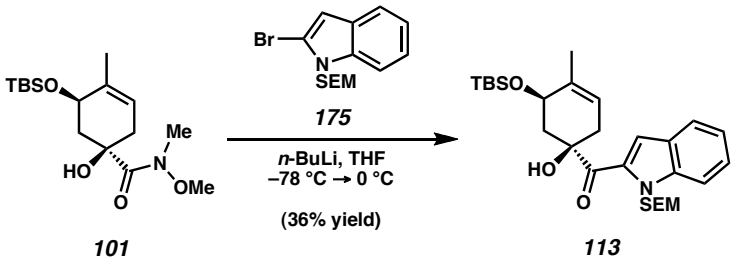
Enone 173. To allylic alcohol **111** (11.4 mg, 0.032 mmol) in CH_2Cl_2 (1 mL) was added Dess-Martin periodinane (31.4 mg, 0.074 mmol). After stirring for 20 min, a solution of saturated $Na_2S_2O_3$: saturated $NaHCO_3$ (1:1, 1 mL) was added to quench the reaction. The phases were partitioned, and the aqueous phase was extracted with Et_2O (1 x 4 mL). The combined organics were dried by passage over a plug of SiO_2, and the solvent was evaporated in vacuo. The residue was purified by preparative thin layer chromatography (1:1 hexanes:EtOAc eluent) to furnish enone **173** (11.4 mg, 99% yield) as a pale yellow oil. R_f 0.40 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.03 (dd, *J* = 4.1, 1.4 Hz, 1H), 6.68 (dd, *J* = 2.5, 1.6 Hz, 1H), 5.97 (dd, *J* = 4.1, 2.7 Hz, 1H), 5.92–5.87 (m, 1H), 5.48 (d, *J* = 9.6 Hz, 1H), 5.43 (d, *J* = 9.6 Hz, 1H), 3.40 (t, *J* = 7.8 Hz, 2H), 3.25 (s, 1H), 2.98 (d, *J* = 16.0 Hz, 1H), 2.83–2.73 (m, 1H), 2.66 (dd, *J* = 16.3, 1.6 Hz, 1H), 2.25–2.14 (m, 1H), 1.84–1.81 (m, 3H), 0.82 (t, *J* = 7.8 Hz, 2H), –0.08 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 195.2, 191.4, 138.9, 135.8, 131.1, 126.7, 123.5, 109.5, 80.3, 78.7, 66.6, 49.5, 38.4, 18.3, 16.4, –1.0 (3C); IR (film) 3424 (br), 2953, 1677, 1639, 1412, 1249, 1085 cm^{-1}; HRMS-FAB (*m/z*): [M + H]$^+$ calc'd for $C_{18}H_{28}NO_4Si$, 350.1788; found, 350.1784; $[\alpha]^{27}_D$ –21.94° (*c* 1.0, C_6H_6).



Methyl Ether 112. To allylic silyl ether **92** (55.0 mg, 0.12 mmol) in THF (2 mL) at 23 °C was added NaH (60% dispersion in mineral oil, 95.5 mg, 2.39 mmol). After stirring for 5 min, MeI (200 μL, 3.21 mmol) was added. After stirring for 30 min, saturated aq. NH_4Cl (2 mL) was added dropwise over 1 min to quench the reaction. EtOAc (1 mL) was added, and the phases were partitioned. The aqueous phase was extracted with EtOAc (2 x 1 mL), and the combined organic extracts were washed with brine (1 mL) and dried over $MgSO_4$. After evaporation of the solvent in vacuo, the residue was purified by flash chromatography (9:1 hexanes:EtOAc eluent) to afford methyl ether **112** (21.1 mg, 37% yield). R_f 0.53 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.76 (dd, *J* = 3.9, 1.6 Hz, 1H), 6.69 (dd, *J* = 2.5, 1.5 Hz, 1H), 6.08 (dd, *J* = 3.9, 2.5 Hz, 1H), 5.64 (d, *J* = 9.6 Hz, 1H), 5.45 (d, *J* = 10.1 Hz, 1H), 5.35–5.30 (m, 1H), 4.52–4.43 (m, 1H), 3.45 (t, *J* = 7.8 Hz, 2H), 3.10 (s, 3H), 2.99–2.85 (comp. m, 2H), 2.36–2.25 (m, 1H), 2.22 (dd, *J* = 12.4, 9.2 Hz, 1H), 1.82–1.79 (m, 3H), 0.98 (s, 9H), 0.88–0.82 (m, 2H), 0.09 (s, 3H), 0.07 (s, 3H), –0.05 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6, 24/25 C): δ 193.2, 136.5, 130.0, 122.2, 120.7, 109.2, 84.6, 78.2, 70.1, 66.4, 51.7, 42.4, 35.0, 26.4 (3C), 20.3, 18.6, 18.4, –1.0 (3C), –3.7, –4.4; IR (film) 2954, 1645, 1412, 1250, 1079 cm^{-1}; HRMS-FAB (*m*/*z*): $[M + H]^+$ calc'd for $C_{25}H_{46}NO_4Si_2$, 480.2965; found, 480.2958; $[\alpha]^{27}_D$ +43.57° (*c* 1.0, C_6H_6).

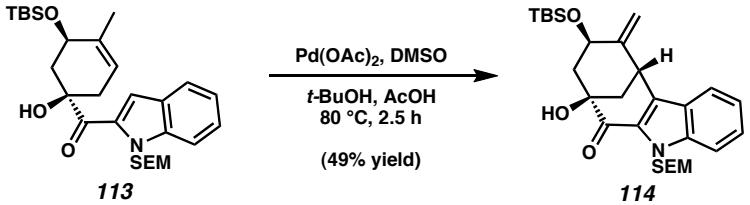


2-Bromo SEM Indole (175). To a solution of 2-bromoindole[74] (**174**, 500.0 mg, 2.55 mmol) in THF (25 mL) cooled to 0 °C was added NaH (60% dispersion in mineral oil, 145.2 mg, 3.63 mmol). After H_2 evolution ceased (3 min), SEMCl (500.0 μL, 2.82 mmol) was added dropwise over 1 min. The reaction was stirred for 10 min, and was quenched by the addition of saturated aq. NH_4Cl (20 mL). Et_2O (50 mL) was added, the phases were partitioned, and the aqueous phase was extracted with Et_2O (2 x 75 mL). The combined organic extracts were washed with brine (15 mL) and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was purified by flash chromatography (9:1 hexanes:Et_2O eluent) to afford 2-bromo SEM indole (**175**, 741.3 mg, 89% yield) as a colorless oil. R_f 0.60 (4:1 hexanes:EtOAc).



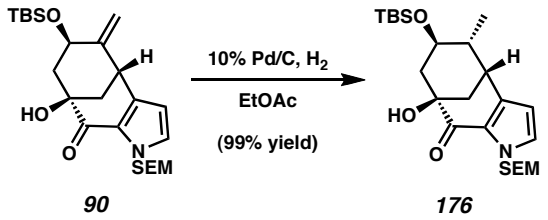
Indole 113. To 2-bromo SEM indole (**175**, 482.6 mg, 1.48 mmol) in THF (7 mL) cooled to –78 °C was added *n*-BuLi (2.5 M in hexanes, 590 μL, 1.48 mmol). The solution was stirred for 10 min, and was then treated dropwise over 1 min with a solution of Weinreb amide **101** (161.5 mg, 0.49 mmol) in THF (2 mL). The solution was immediately warmed to 0 °C and stirred for 30 min. The reaction was quenched at –78 °C with saturated aq. NH_4Cl (10 mL), and was allowed to thaw slowly to 23 °C. Et_2O (50

mL) was added, the phases were partitioned, and the aqueous phase was extracted with Et_2O (2 x 75 mL). The combined organic extracts were washed successively with H_2O (15 mL) and brine (15 mL), and dried over $MgSO_4$. Following evaporation of the solvent in vacuo, the crude product was purified by flash chromatography (19:1 hexanes:EtOAc eluent) to furnish indole **113** (92.2 mg, 36% yield) as a colorless oil. R_f 0.48 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 8.41 (s, 1H), 7.64–7.60 (m, 1H), 7.50–7.46 (m, 1H), 7.28–7.21 (m, 1H), 7.10–7.04 (m, 1H), 6.03–5.95 (m, 2H), 5.35–5.30 (m, 1H), 5.23 (s, 1H), 3.96–3.92 (m, 1H), 3.58 (t, J = 7.8 Hz, 2H), 2.77–2.57 (comp. m, 2H), 2.42–2.35 (m, 1H), 2.35–2.28 (m, 1H), 1.70–1.67 (m, 3H), 0.93–0.81 (m, 2H), 0.89 (s, 9H), 0.00 (s, 3H), –0.02 (s, 3H), –0.10 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 196.9, 141.0, 133.7, 132.8, 127.5, 126.8, 124.1, 122.3, 121.9, 117.8, 112.2, 79.3, 74.1, 69.9, 66.0, 39.3, 39.3, 26.2 (3C), 21.6, 18.4, 18.3, –0.9 (3C), –4.3, –4.6; IR (film) 3466 (br), 2954, 1655, 1250, 1072 cm^{-1}; HRMS-EI (m/z): $[M]^+$ calc'd for $C_{28}H_{45}NO_4Si_2$, 515.2887; found, 515.2893; $[\alpha]^{27}_D$ –12.17° (c 1.0, C_6H_6).



Indole 114. To indole **113** (23.5 mg, 0.05 mmol) was added $Pd(OAc)_2$ (10.2 mg, 0.05 mmol), DMSO (6.5 μL, 0.09 mmol), t-BuOH (3.6 mL), and AcOH (0.9 mL). The mixture was heated at 80 °C for 2.5 h, cooled to 23 °C, and filtered over a plug of silica gel (EtOAc eluent). The solvent was evaporated, and the crude product was purified by flash chromatography on silica gel (19:1 hexanes:EtOAc eluent) to afford pure [3.3.1]

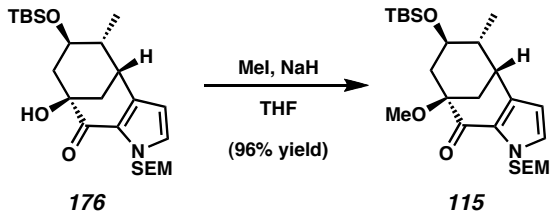
bicycle. R_f 0.33 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.52–7.46 (m, 1H), 7.37–7.32 (m, 1H), 7.20–7.14 (m, 1H), 7.05–6.97 (m, 1H), 5.97 (d, *J* = 10.9 Hz, 1H), 5.73 (d, *J* = 10.9 Hz, 1H), 5.39 (app. t, *J* = 2.1 Hz, 1H), 5.11 (app. t, *J* = 2.0 Hz, 1H), 4.24–4.15 (m, 1H), 4.18 (s, 1H), 3.85 (app. t, *J* = 3.2 Hz, 1H), 3.69–3.52 (m, 2H), 2.47 (app. dt, *J* = 7.5, 3.9 Hz, 1H), 2.40–2.31 (m, 1H), 2.29–2.22 (m, 1H), 2.11 (app. t, *J* = 11.8 Hz, 1H), 1.01–0.77 (m, 2H), 0.83 (s, 9H), –0.05 (s, 9H), –0.17 (s, 3H), –0.24 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6, 27/28 C): δ 194.9, 148.1, 141.6, 133.8, 129.1, 125.0, 122.2, 122.1, 112.6, 108.3, 76.5, 73.6, 68.3, 66.1, 48.6, 45.4, 38.7, 26.2 (3C), 18.7, 18.2, –0.9 (3C), –4.5, –4.8; IR (film) 3485, 2953, 1657, 1250, 1106, 1073 cm^{-1}; HRMS-FAB (*m/z*): [M]$^+$ calc'd for $C_{28}H_{43}NO_4Si_2$, 513.2731; found, 513.2719; $[\alpha]^{27}_D$ –281.78° (*c* 0.3, C_6H_6).



Reduced [3.3.1] Bicycle 176. [3.3.1] Bicycle **90** (360 mg, 0.78 mmol), 10% Pd/C (130 mg, 0.12 mmol), and EtOAc (8 mL) were combined, and the reaction vessel was evacuated and back-filled with H_2 (1 atm). The reaction mixture was stirred under H_2 for 30 min, then filtered over a plug of silica gel topped with Celite® (EtOAc eluent) to afford reduced [3.3.1] bicycle **176** as a colorless oil (358 mg, 99% yield). R_f 0.28 (5:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 6.55 (d, *J* = 2.5 Hz, 1H), 5.74 (d, *J* = 2.5 Hz, 1H), 5.56 (d, *J* = 10.2 Hz, 1H), 5.30 (d, *J* = 10.2 Hz, 1H), 4.27 (s, 1H), 3.59–3.45 (m, 2H), 3.19 (ddd, *J* = 12.9, 7.7, 3.3 Hz, 1H), 2.58 (dd, *J* = 6.5, 3.2 Hz, 1H), 2.37–2.20

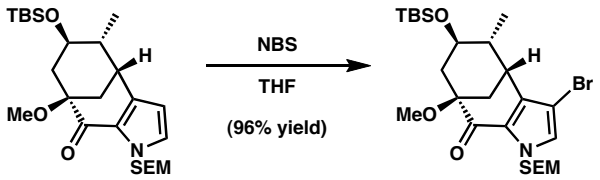
(comp. m, 2H), 2.06–1.90 (comp. m, 2H), 1.63–1.50 (m, 1H), 1.00 (d, J = 6.6 Hz, 3H), 0.94–0.89 (comp. m, 11H), –0.02 (s, 9H), –0.06 (s, 3H), –0.09 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6): δ 190.8, 140.4, 131.3, 125.2, 110.1, 76.6, 75.6, 71.8, 66.1, 46.8, 44.3, 40.0, 37.3, 25.9 (3C), 18.1, 17.9, 16.5, –1.2 (3C), –4.0, –4.6; IR (film): 3473 (br), 2953, 2931, 2857, 1651, 1420, 1249, 1079 cm^{-1}; HRMS-EI (m/z): $[M + H]^+$ calc'd for $C_{24}H_{44}NO_4Si_2$, 466.2809; found, 466.2804; $[\alpha]^{19}_D$ –166.30° (c 1.0, C_6H_6).

NOTE: In some instances, trace phosphine contaminants from the Heck reaction (i.e., ***91*** *→* ***90****) prevented the reduction from occurring. Simply working up the reaction and re-exposing it to the identical reaction conditions (as described above) allowed the reduction to proceed.*



Methyl Ether 115. To reduced [3.3.1] bicycle **176** (358 mg, 0.77 mmol) in THF (7.7 mL) at 23 °C was added NaH (60% dispersion in mineral oil, 123 mg, 3.08 mmol). After stirring for 2 min at 23 °C, MeI was added (335 μL, 5.38 mmol). The resulting mixture was stirred for 1 h, cooled to 0 °C, and quenched with saturated aq. NH_4Cl (4 mL), then warmed to 23 °C. Et_2O (10 mL) and H_2O (5 mL) were added, and the layers were separated. The aqueous layer was further extracted with Et_2O (2 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash

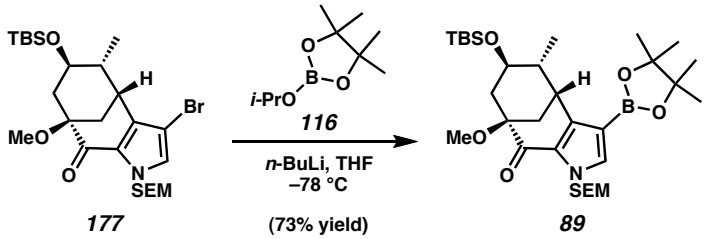
chromatography (4:1 hexanes:EtOAc eluent) to afford methyl ether **115** (354 mg, 96% yield) as a colorless oil. R_f 0.34 (5:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 6.58 (d, *J* = 2.8 Hz, 1H), 5.78 (d, *J* = 2.5 Hz, 1H), 5.57 (d, *J* = 10.2 Hz, 1H), 5.54 (d, *J* = 10.2 Hz, 1H), 3.65–3.50 (m, 2H), 3.37 (s, 3H), 3.22 (ddd, *J* = 12.9, 7.9, 3.1 Hz, 1H), 2.68 (dd, *J* = 6.5, 3.2 Hz, 1H), 2.59–2.49 (comp. m, 2H), 1.86 (dd, *J* = 12.4 Hz, 11.3 Hz, 1H), 1.72–1.56 (m, 2H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.93–0.85 (comp. m, 11H), –0.02 (s, 9H), –0.07 (s, 3H), –0.10 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6, 24/25 C): δ 189.4, 138.3, 130.4, 109.7, 81.9, 76.9, 72.4, 66.2, 51.8, 45.9, 41.3, 41.2, 37.6, 26.4 (3C), 18.5, 18.3, 17.0, –0.9 (3C), –3.6, –4.4; IR (film): 2954, 1657, 1421, 1250, 1085 cm^{-1}; HRMS-EI (*m/z*): [M + H]$^+$ calc'd for $C_{25}H_{46}NO_4Si_2$, 480.2965; found, 480.2970; $[\alpha]^{19}_D$ –172.9° (*c* 1.0, C_6H_6).



115 *177*

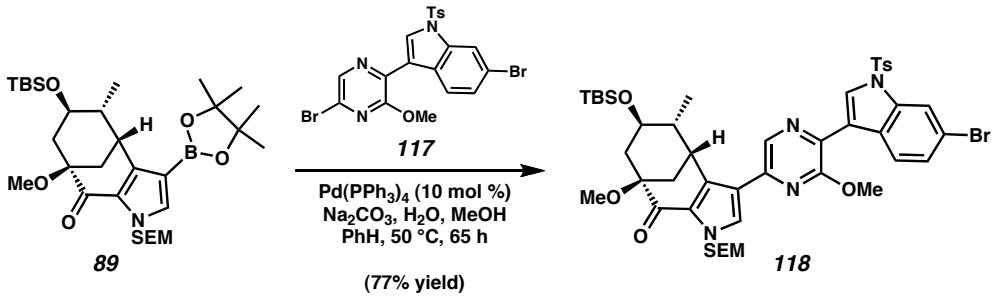
Bromide 177. To methyl ether **115** (305 mg, 0.64 mmol) in THF (6 mL) at 0 °C was added freshly recrystallized NBS (147 mg, 0.83 mmol). After stirring for 10 min at 0 °C, the reaction mixture was warmed to 23 °C, and additional NBS (30 mg, 0.17 mmol) was added. After 5 min, the reaction was quenched with saturated aq. $Na_2S_2O_3$, diluted with H_2O (15 mL), and extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (5:1 hexanes:EtOAc eluent) to afford bromide **177** (340 mg, 96% yield) as a colorless oil. R_f 0.55 (3:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 6.57 (s, 1H), 5.46 (d, *J* = 10.2 Hz, 1H),

5.34 (d, J = 10.2 Hz, 1H), 3.57–3.41 (m, 2H), 3.32–3.20 (m, 4H), 2.88 (dd, J = 6.5, 3.2 Hz, 1H), 2.46 (ddd, J = 12.2, 5.1, 2.5 Hz, 1H), 2.28 (app. dt, J = 7.4, 4.0 Hz, 1H), 1.78 (app. t, J = 11.8 Hz, 1H), 1.69–1.57 (m, 1H), 1.52 (dd, J = 11.8, 3.0 Hz, 1H), 1.19 (d, J = 6.9 Hz, 3H), 0.91–0.80 (comp. m, 11H), –0.05 (s, 9H), –0.09 (s, 3H), –0.12 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6): δ 189.6, 147.2, 137.2, 130.1, 98.4, 81.8, 77.0, 72.1, 66.6, 51.8, 45.8, 42.4, 41.0, 35.9, 26.3 (3C), 18.5, 18.3, 17.8, –0.9 (3C), –3.7, –4.3; IR (film): 2954, 2930, 1664, 1249, 1089 cm^{-1}; HRMS-EI (m/z): [M + H]$^+$ - H_2 calc'd for $C_{25}H_{43}NO_4Si_2Br$, 556.1914; found, 556.1928; $[\alpha]^{19}_D$ –98.22° (c 1.0, C_6H_6).



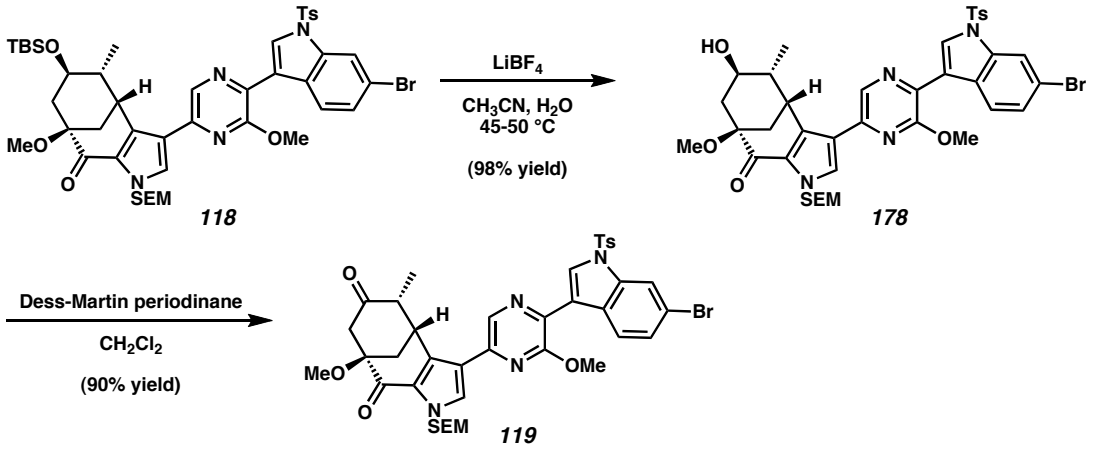
Boronic Ester 89. To bromide **177** (116 mg, 0.21 mmol) and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**116**) (847 μL, 4.15 mmol) in THF (10.4 mL) at –78 °C was added n-BuLi (2.3 M in hexanes, 1.35 mL, 3.11 mmol) dropwise over 2 min. After stirring for 15 min at –78 °C, the reaction mixture was quenched with saturated aq. NH_4Cl, warmed to 23 °C, and diluted with H_2O (10 mL). The mixture was extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (4:1 hexanes:EtOAc with 0.5% Et_3N eluent) to afford boronic ester **89** (92 mg, 73% yield) as a white powder, which was used immediately in the next step. R_f 0.50 (3:1 hexanes:EtOAc); mp 143–145 °C; ^{1}H NMR (300 MHz, C_6D_6): δ 7.42 (s, 1H), 5.55 (d, J = 10.1 Hz, 1H), 5.51 (d, J = 9.8 Hz, 1H), 3.74–3.68 (m, 1H), 3.60–3.50 (m,

2H), 3.43–3.36 (m, 1H), 3.33 (s, 3H), 2.65–2.53 (comp. m, 2H), 1.91 (app. t, J = 11.8 Hz, 1H), 1.89–1.80 (m, 1H), 1.68 (dd, J = 11.8, 2.8 Hz, 1H), 1.34 (d, J = 6.6 Hz, 3H), 1.15 (s, 6H), 1.14 (s, 6H), 0.94–0.81 (comp. m, 11H), –0.04 (s, 3H), –0.05 (s, 9H), –0.07 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6, 30/31 C): δ 190.1, 145.1, 139.3, 130.2, 83.5 (2C), 82.0, 77.2, 72.6, 66.5, 51.7, 46.1, 42.0, 41.6, 36.8, 26.4 (3C), 25.4 (2C), 25.2 (2C), 18.5, 18.3, 16.9, –0.9 (3C), –3.6, –4.3; IR (film): 2953, 2931, 2858, 1658, 1543, 1249, 1141, 1085 cm^{-1}; HRMS-FAB (m/z): [M + H]$^+$ calc'd for $C_{31}H_{57}BNO_6Si_2$, 606.3818; found, 606.3805; $[\alpha]^{19}_D$ –98.84° (c 1.0, C_6H_6).



Suzuki Adduct 118. Bromopyrazine **117** (46.5 mg, 0.087 mmol), boronic ester **89** (35 mg, 0.058 mmol), benzene (1.15 mL), methanol (231 μL), 2 M aq. Na_2CO_3 (96 μL), and tetrakis(triphenylphosphine)palladium(0) (6.7 mg, 0.0058 mmol) were combined and deoxygenated by sparging with argon for 5 min. The reaction vessel was evacuated, purged with N_2, sealed, heated to 50 °C for 65 h, cooled to 23 °C, then quenched by the addition of Na_2SO_4 (200 mg). Following filtration over a pad of silica gel (2:1 hexanes:EtOAc eluent) and evaporation to dryness under reduced pressure, the remaining residue was purified by flash chromatography (3:1 hexanes:EtOAc eluent) to afford Suzuki adduct **118** (41.5 mg, 77% yield) as a yellow oil. R_f 0.43 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.61 (d, J = 8.5 Hz, 1H), 8.45 (s, 1H),

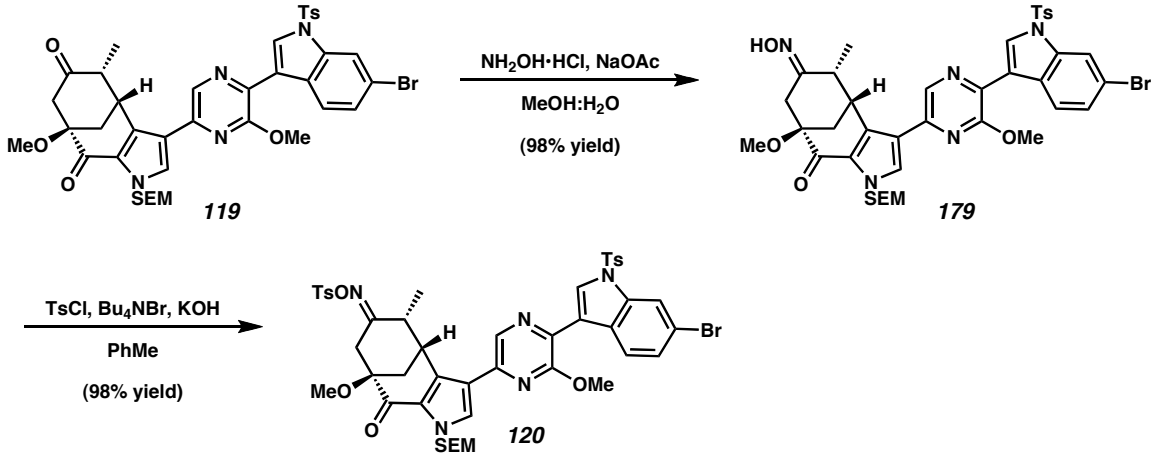
8.44 (s, 1H), 8.16 (d, J = 1.5 Hz, 1H), 7.80 (d, J = 8.5 Hz, 2H), 7.59 (s, 1H), 7.40 (dd, J = 8.5, 1.8 Hz, 1H), 7.23 (d, J = 7.9 Hz, 2H), 5.85 (d, J = 10.0 Hz, 1H), 5.78 (d, J = 10.0 Hz, 1H), 4.27–4.21 (m, 1H), 4.19 (s, 3H), 3.72–3.59 (m, 2H), 3.34 (s, 3H), 3.13–3.02 (m, 1H), 2.87–2.77 (m, 1H), 2.32 (s, 3H), 2.22–2.12 (m, 1H), 1.98–1.89 (m, 1H), 1.82–1.72 (m, 1H), 1.67 (app. t, J = 11.7 Hz, 1H), 1.04–0.83 (m, 2H), 0.78 (s, 9H), 0.72 (d, J = 6.7 Hz, 3H), –0.02 (s, 9H), –0.09 (s, 3H), –0.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 44/45 C): δ 190.0, 156.2, 145.7, 143.6, 136.9, 135.7, 135.5, 135.0, 132.7, 130.3 (2C), 130.2, 129.3, 128.8, 128.5, 127.3, 127.1 (2C), 125.3, 120.5, 119.0, 116.9, 116.4, 81.3, 77.2, 71.4, 66.7, 54.3, 51.6, 44.8, 41.8, 40.2, 34.8, 25.9 (3C), 21.8, 18.1, 16.1, –1.1 (3C), –4.0, –4.7; IR (film): 2952, 1660, 1555, 1372, 1372, 1190, 1140, 1089 cm^{-1}; HRMS-FAB (m/z): $[M]^+$ calc'd for $C_{45}H_{59}N_4O_7Si_2SBr$, 934.2826; found, 934.2829; $[\alpha]^{21}_D$ +51.73° (c 1.0, $CHCl_3$).



Ketone 119. Suzuki adduct **118** (113 mg, 0.121 mmol), $LiBF_4$ (113 mg, 1.21 mmol), acetonitrile (6 mL), and water (600 μL) were heated to 45–50 °C. After 9 h, additional $LiBF_4$ (30 mg, 0.32 mmol) was introduced, and heating was continued. After 6 h, additional $LiBF_4$ (35 mg, 0.32 mmol) was introduced, and heating was continued for 16 h. The reaction mixture was cooled to 23 °C, quenched with 10% aq. citric acid (10

mL), and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by flash chromatography (3:1 EtOAc:hexanes eluent) to yield alcohol **178** (96.9 mg, 98% yield) as a yellow oil, which was used in the subsequent step without further purification. R_f 0.44 (3:1 EtOAc:hexanes).

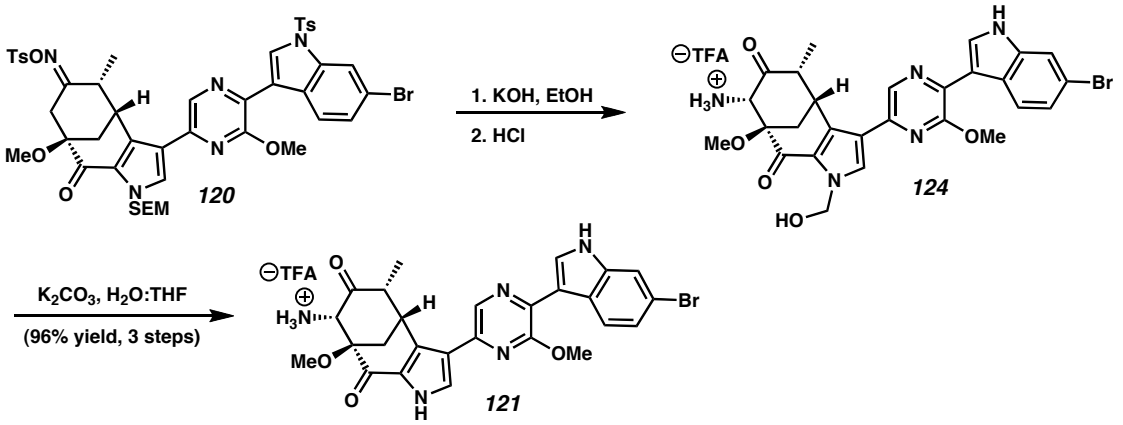
To alcohol **178** (96 mg, 0.117 mmol) in CH_2Cl_2 (2.0 mL) at 23 °C was added Dess-Martin periodinane (74.3 mg, 0.175 mmol). The mixture was stirred for 3 min, quenched with a solution of saturated aq. $NaHCO_3$ and saturated aq. $Na_2S_2O_3$ (1:1, 5 mL), stirred for 5 min, and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (1:1 hexanes:EtOAc eluent) to yield ketone **119** (86 mg, 90% yield) as a yellow foam. R_f 0.48 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.61 (d, *J* = 8.5 Hz, 1H), 8.45 (s, 1H), 8.42 (s, 1H), 8.18 (d, *J* = 1.7 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.56 (s, 1H), 7.42 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.25 (d, *J* = 7.7 Hz, 2H), 5.77 (d, *J* = 10.5 Hz, 1H), 5.72 (d, *J* = 10.2 Hz, 1H), 4.62–4.56 (m, 1H), 4.20 (s, 3H), 3.57 (app. dt, *J* = 8.2, 1.8 Hz, 2H), 3.43 (s, 3H), 3.14–3.06 (m, 1H), 2.91–2.81 (m, 1H), 2.74 (s, 2H), 2.40 (dd, *J* = 12.5, 2.9 Hz, 1H), 2.34 (s, 3H), 0.96–0.88 (m, 2H), 0.78 (d, *J* = 6.6 Hz, 3H), –0.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 37/39 C): δ 207.2, 188.0, 156.1, 145.7, 143.2, 136.3, 135.7, 134.9, 132.6, 130.7, 130.3 (2C), 128.8, 128.4, 127.3, 127.1 (2C), 125.4, 120.5, 119.0, 116.8, 116.3, 82.4, 77.1, 66.9, 54.3, 52.2, 52.0, 49.2, 40.2, 35.2, 21.8, 18.1, 12.2, –1.2 (3C); IR (film): 2950, 1716, 1664, 1557, 1373, 1190, 1178, 1090 cm^{-1}; HRMS-FAB (*m/z*): $[M]^+$ calc'd for $C_{39}H_{43}N_4O_7SiSBr$, 818.1805; found, 818.1836; $[\alpha]^{21}_D$ +71.61° (*c* 1.0, $CHCl_3$).



Tosyl Oxime 120. To ketone **119** (50.0 mg, 0.061 mmol), NH_2OH•HCl (85 mg, 1.22 mmol), and NaOAc•$3H_2O$ (125 mg, 0.915 mmol) was added methanol (2.5 mL), followed by H_2O (350 μL), then additional methanol (5 mL). The homogeneous solution was stirred at 23 °C for 8 h, and the solvent was removed under reduced pressure. H_2O (15 mL) was added, and the resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was further purified by filtration over a plug of silica gel (EtOAc eluent) to yield oxime **179** (50.1 mg, 98% yield) as a yellow foam, which was used without purification in the subsequent reaction. R_f 0.46 (1:1 hexanes:EtOAc).

To a solution of oxime **179** (20.0 mg, 0.0240 mmol), TsCl (14.0 mg, 0.0734 mmol), and Bu_4NBr (1.0 mg, 0.0031 mmol) in toluene (2.0 mL) at 0 °C was added 50% aq. KOH (310 μL). The reaction mixture was stirred at 0 °C for 2 h, quenched with ice-cold H_2O (1.5 mL) and extracted with ice-cold EtOAc (5 x 1 mL). The combined organic layers were washed with brine (1 mL), dried by passage over a plug of silica gel (EtOAc eluent), and evaporated under reduced pressure. The crude product was purified by flash

chromatography (1:1 hexanes:EtOAc eluent) to yield tosyl oxime **120** (23.3 mg, 98% yield) as a yellow foam. R_f 0.48 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.63 (d, *J* = 8.5 Hz, 1H), 8.46 (s, 1H), 8.41 (s, 1H), 8.19 (d, *J* = 1.4 Hz, 1H), 7.81 (d, *J* = 8.3 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.51 (s, 1H), 7.44 (dd, *J* = 8.7, 1.5 Hz, 1H), 7.28–7.19 (comp. m, 4H), 5.87 (d, *J* = 10.2 Hz, 1H), 5.42 (d, *J* = 10.2 Hz, 1H), 4.45–4.43 (m, 1H), 4.20 (s, 3H), 3.67–3.53 (comp. m, 3H), 3.38 (s, 3H), 2.98–2.89 (m, 1H), 2.87–2.77 (m, 1H), 2.42 (s, 3H), 2.35 (s, 3H), 2.12 (d, *J* = 14.0 Hz, 2H), 1.05–0.85 (m, 2H), 0.78 (d, *J* = 6.6 Hz, 3H), –0.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.2, 165.8, 156.3, 145.8, 144.8, 143.5, 135.8, 135.7, 135.3, 135.0, 132.9, 132.6, 130.4 (2C), 129.9, 129.4 (2C), 129.1 (2C), 128.9, 128.4, 128.0, 127.5, 127.2 (2C), 125.3, 120.3, 119.2, 116.8, 116.5, 80.8, 77.4, 67.2, 54.4, 52.2, 42.5, 40.3, 36.5, 36.2, 21.9, 21.9, 18.1, 13.7, –1.1 (3C); IR (film): 2946, 1665, 1555, 1373, 1191, 1178, 1140 cm^{-1}; HRMS-FAB (*m*/*z*): $[M]^+$ calc'd for $C_{46}H_{50}N_5O_9SiS_2Br$, 987.2002; found, 987.2038; $[\alpha]^{20}_D$ +139.01° (*c* 1.0, $CHCl_3$).

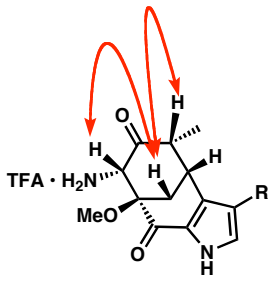


Aminoketone 121. To a stirred solution of tosyl oxime **120** (23.3 mg, 0.0236 mmol) in EtOH (3.5 mL) at 0 °C was added 50% aq. KOH (450 μL) dropwise over 1 min. The reaction mixture was stirred at 0 °C for 3 h, then 6 N aq. HCl (5 mL) was added. The reaction mixture was heated to 60 °C for 10 h, cooled to 23 °C, and purified by reversed-phase filtration through a Sep-Pak column: loaded with water containing 0.1% (*w*/*v*) TFA, washed with 15% acetonitrile:water containing 0.1% (*w*/*v*) TFA to remove salts, then 70% acetonitrile:water containing 0.1% (*w*/*v*) TFA to collect the crude product. The solvents were removed under reduced pressure to afford hemiaminal **124**, which was used immediately in the subsequent reaction. Although hemiaminal **124** is typically used in crude form, it has been observed by ^{1}H NMR. ^{1}H NMR (600 MHz, CD_3OD): δ 8.61 (d, *J* = 8.2 Hz, 1H), 8.52 (s, 1H), 8.24 (s, 1H), 7.94 (s, 1H), 7.60 (s, 1H), 7.25 (d, *J* = 9.2 Hz, 1H), 5.72 (d, *J* = 10.1 Hz, 1H), 5.65 (d, *J* = 10.1 Hz, 1H), 4.85–4.82 (m, 1H), 4.49 (s, 1H), 4.21 (s, 3H), 3.47 (s, 3H), 3.36–3.30 (m, 1H), 3.26 (dd, *J* = 12.8, 2.7 Hz, 1H), 2.61 (dd, *J* = 12.8, 2.7 Hz, 1H), 0.85 (d, *J* = 7.3 Hz, 3H).

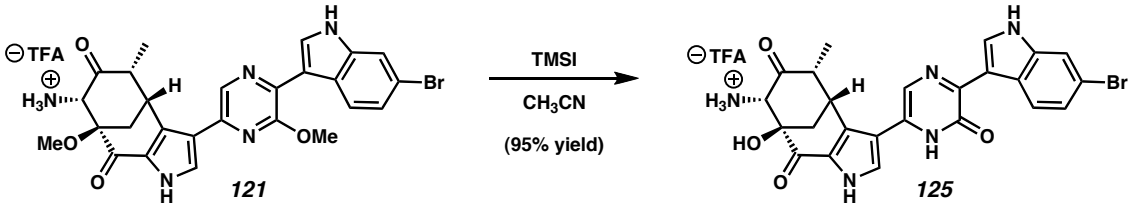
To hemiaminal **124** and K_2CO_3 (60 mg, 0.434 mmol) in THF (2 mL) at 23 °C was added H_2O (200 μL). The reaction mixture was stirred for 10 min, then purified by reversed-phase filtration through a Sep-Pak column: loaded with water containing 0.1%

(*w*/*v*) TFA, washed with 10% acetonitrile:water containing 0.1% (*w*/*v*) TFA to remove salts, then 70% acetonitrile:water containing 0.1% (*w*/*v*) TFA to collect the crude product. After removal of solvents under reduced pressure, the crude material was further purified by reversed-phased HPLC. Concentration under reduced pressure provided aminoketone **121** (15.0 mg, 96% yield) as an orange/red oil. ^{1}H NMR (300 MHz, CD_3OD): δ 8.60 (d, *J* = 8.5 Hz, 1H), 8.53 (s, 1H), 8.23 (s, 1H), 7.81 (s, 1H), 7.61 (d, *J* = 1.4 Hz, 1H), 7.25 (dd, *J* = 8.7, 1.8 Hz, 1H), 4.82–4.78 (m, 1H), 4.46 (s, 1H), 4.21 (s, 3H), 3.47 (s, 3H), 3.41–3.30 (m, 1H), 3.26 (dd, *J* = 12.9, 3.9 Hz, 1H), 2.61 (dd, *J* = 12.9, 3.0 Hz, 1H), 0.88 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD, 25/26 C): δ 203.5, 183.3, 156.8, 142.4, 139.9, 139.1, 136.3, 133.4, 130.7, 129.9, 129.6, 126.9, 125.5, 124.5, 123.1, 116.9, 115.4, 112.6, 84.3, 66.0, 54.5, 52.9, 40.4, 36.6, 12.2; IR (film): 3156 (br), 2935, 1674, 1531, 1447, 1409, 1203, 1135 cm^{-1}; HRMS-FAB (*m*/*z*): $[M + H]^+$ calc'd for $C_{26}H_{25}N_5O_4Br$, 550.1090; found, 550.1071; $[\alpha]^{20}_{D}$ +99.19° (*c* 0.87, MeOH).

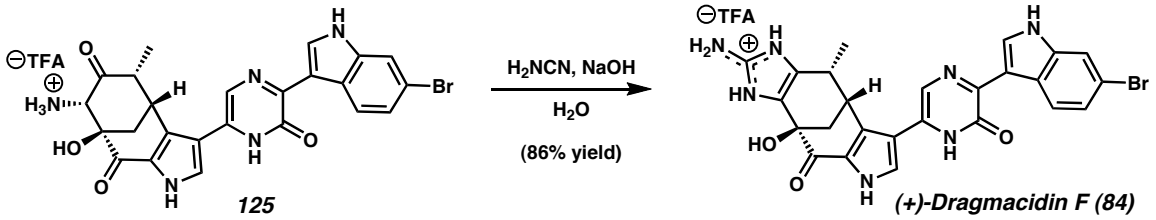
The relative stereochemistry of deprotected aminoketone **121** was determined by NOE experiments. Medium-strength NOE interactions were observed as indicated below.[75] Analogous NOE interactions were observed for hemiaminal **124** and deprotected aminoketone **125**.



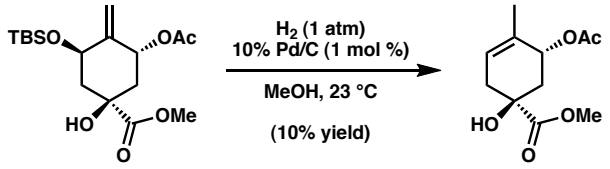
121



Deprotected Aminoketone 125. To a stirred solution of aminoketone **121** (7.5 mg, 0.0113 mmol) in MeCN (1 mL) at 0 °C was added TMSI (500 μL, 3.51 mmol) dropwise over 30 sec. The reaction mixture was heated to 60 °C for 48 h, cooled to 0 °C, then transferred dropwise into a chilled solution (0 °C) of saturated aqueous sodium metabisulfite (5 mL). The mixture was diluted with 6 N HCl (15 mL), stirred at 0 °C for 20 min, then purified by reversed-phase filtration through a Sep-Pak column: loaded with water containing 0.1% (*w*/*v*) TFA, washed with 1 N HCl, 10% acetonitrile:water containing 0.1% (*w*/*v*) TFA to remove salts, then 60% acetonitrile:water containing 0.1% (*w*/*v*) TFA to collect the crude product. After removal of solvents under reduced pressure, the crude material was further purified by reversed-phase HPLC. Concentration under reduced pressure provided deprotected aminoketone **125** (6.8 mg, 95% yield) as an orange/red oil. ^{1}H NMR (300 MHz, CD_3OD): δ 8.69 (s, 1H), 8.59 (d, *J* = 8.5 Hz, 1H), 7.69 (s, 1H), 7.61 (d, *J* = 1.7 Hz, 1H), 7.57 (s, 1H), 7.27 (dd, *J* = 8.5, 1.7 Hz, 1H), 4.40 (s, 1H), 4.06–3.98 (m, 1H), 3.31–3.21 (m, 1H), 2.87 (dd, *J* = 13.2, 3.3 Hz, 1H), 2.79 (dd, *J* = 13.1, 2.9 Hz, 1H), 0.85 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD, 23/24 C): δ 203.4, 186.0, 157.4, 139.1, 136.3, 132.5, 132.4, 130.2, 130.1, 128.2, 126.7, 126.7, 125.6, 124.9, 117.1, 115.4, 113.6, 79.3, 67.1, 49.6, 45.5, 36.7, 12.3; IR (film): 3164 (br), 2927, 1674, 1451, 1207, 1143 cm^{-1}; HRMS-FAB (*m*/*z*): $[M + H]^+$ calc'd for $C_{24}H_{21}N_5O_4Br$, 522.0777; found, 522.0783; $[\alpha]^{22}_D$ +86.88° (*c* 0.33, MeOH).



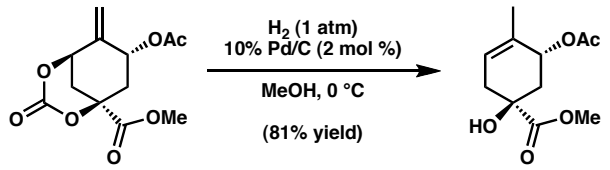
(+)-Dragmacidin F (84). To deprotected aminoketone **125** (3.6 mg, 0.0056 mmol) and cyanamide (120 mg, 2.86 mmol) in H_2O (2 mL, degassed by sparging with argon) at 23 °C was added 10% aq. NaOH (80 μL). The reaction mixture was heated to 60 °C for 2 h, cooled to 23 °C, then purified by reversed-phase filtration through a Sep-Pak column: loaded with water containing 0.1% (*w*/*v*) TFA, washed with 10% acetonitrile:water containing 0.1% (*w*/*v*) TFA to remove salts, then 60% acetonitrile:water containing 0.1% (*w*/*v*) TFA to collect the crude product. After removal of solvents under reduced pressure, the product was further purified by reversed-phase HPLC. Concentration under reduced pressure afforded (+)-dragmacidin F (**84**, 3.2 mg, 86% yield) as an orange/red oil. ^{1}H NMR (600 MHz, CD_3OD): δ 8.69 (s, 1H), 8.59 (d, *J* = 8.7 Hz, 1H), 7.68 (s, 1H), 7.60 (s, 1H), 7.47 (s, 1H), 7.26 (d, *J* = 8.7 Hz, 1H), 4.12 (br s, 1H), 3.40–3.34 (m, 1H), 2.73 (dd, *J* = 12.0, 2.9 Hz, 1H), 2.45 (d, *J* = 11.6 Hz, 1H), 0.92 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD, 22/25 C): δ 188.5, 157.5, 149.6, 139.1, 132.6, 132.4, 128.5, 128.4, 126.7, 126.2, 125.6, 124.9, 124.8, 123.3, 117.1, 115.4, 113.7, 72.8, 45.3, 36.9, 33.3, 15.9; IR (film): 3175 (br), 2925, 1679, 1637, 1205, 1141 cm^{-1}; UV (MeOH) λ_{max} 283, 389 nm; HRMS-FAB (*m*/*z*): $[M + H]^+$ calc'd for $C_{25}H_{21}N_7O_3Br$, 546.0889; found, 546.0883; $[\alpha]^{23}_D$ +146.21° (*c* 0.45, MeOH).



97 *129*

Acetoxycyclohexene 129. A mixture of methyl ester **97** (50.0 mg, 0.140 mmol) and 10% Pd/C (1.5 mg, 0.0014 mmol) in MeOH (1.3 mL) was stirred under an H_2 atmosphere at 23 °C. After 35 min, the reaction mixture was filtered over a Celite® plug (MeOH eluent), and the solvent was evaporated in vacuo. ^{1}H NMR integration showed that acetoxycyclohexene **129** was formed in approximately 10% yield.

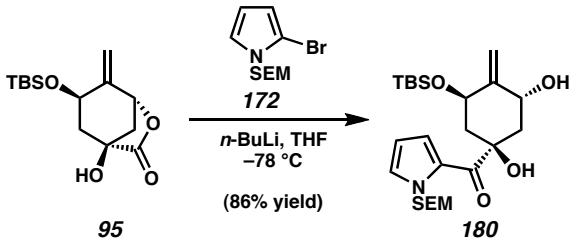
Alternate Procedure. A mixture of methyl ester **97** (21.4 mg, 0.06 mmol) and 10% Pd/C (0.3 mg, 0.0003 mmol) in MeOH (1.5 mL) was cooled to 0 °C. The reaction vessel was then evacuated and back-filled with H_2 (4x). After 1 h, the reaction mixture was filtered over a Celite® plug (MeOH eluent), and the solvent was evaporated in vacuo. ^{1}H NMR integration showed that acetoxycyclohexene **129** was formed in approximately 3% yield. An analytical sample of **129** was prepared via an alternate route as follows:



144 *129*

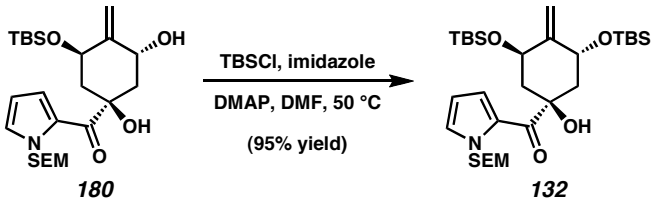
A mixture of acetoxycarbonate **144**[76] (18.5 mg, 0.07 mmol) and 10% Pd/C (1.4 mg, 0.001 mmol) in MeOH (1.3 mL) was cooled to 0 °C. The reaction vessel was then evacuated and back-filled with H_2 (3x). After 1 h at 0 °C, the reaction mixture was filtered over a Celite® plug (MeOH eluent), and the solvent was evaporated in vacuo. The residue was purified by flash chromatography (1:1 EtOAc:hexanes eluent) to afford

acetoxycyclohexene **129** (12.6 mg, 81% yield) as a colorless oil. R_f 0.46 (2:1 EtOAc:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.57–5.48 (comp. m, 2H), 3.77 (s, 3H), 3.06 (br s, 1H), 2.69–2.58 (m, 1H), 2.29–2.20 (m, 1H), 2.16–1.91 (comp. m, 2H), 2.05 (s, 3H), 1.69–1.66 (m, 3H);^{13}C NMR (75 MHz, $CDCl_3$): δ 176.1, 170.9, 132.7, 122.0, 73.8, 70.7, 53.2, 37.1, 35.3, 21.3, 19.2; IR (film) 3477 (br), 2953, 1736, 1239 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+$ calc'd for $C_{11}H_{17}O_5$, 229.1076; found 229.1066; $[\alpha]^{25}_D$ –3.31° (*c* 0.6, $CHCl_3$).



***Anti*-diol 180.** To 2-bromo SEM pyrrole (**172**, 4.66 g, 16.87 mmol) in THF (112 mL) at –78 °C was added *n*-BuLi (2.5 M in hexanes, 6.04 mL, 15.09 mmol) dropwise over 1 min. After 7 min at –78 °C, lactone **95** (1.26 g, 4.44 mmol) in THF (10 mL) was added dropwise over 1 min. The reaction vessel was immediately warmed to –42 °C, stirred for 30 min, and cooled to –78 °C. The reaction mixture was quenched with saturated aq. NH_4Cl (50 mL), then warmed to 23 °C. The volatiles were removed under reduced pressure. The residue was partitioned between Et_2O (125 mL) and H_2O (100 mL), and the layers were separated. The aqueous layer was further extracted with Et_2O (2 x 125 mL). The combined organic layers were washed with brine (75 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (4:1 hexanes:EtOAc eluent) to afford *anti*-diol **180** (1.84 g, 86% yield) as a pale yellow foam. R_f 0.48 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 8.11

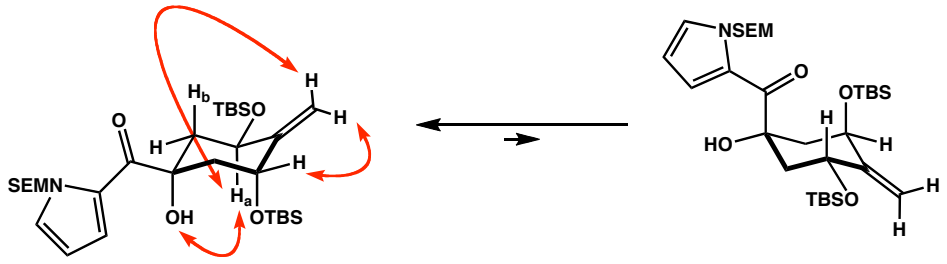
(dd, J = 4.1, 1.7 Hz, 1H), 6.78 (app. t, J = 2.1 Hz, 1H), 6.15 (dd, J = 4.0, 2.6 Hz, 1H), 5.71 (d, J = 9.9 Hz, 1H), 5.58 (d, J = 10.2 Hz, 1H), 5.26 (s, 1H), 5.17 (app. t, J = 1.8 Hz, 1H), 4.92–4.82 (m, 1H), 4.76–4.73 (m, 1H), 4.45 (app. t, J = 3.0 Hz, 1H), 3.47 (t, J = 7.7 Hz, 2H), 2.66 (ddd, J = 12.4, 5.2, 2.5 Hz, 1H), 2.39 (dd, J = 14.4, 2.9 Hz, 1H), 2.20 (app. dt, J = 8.7, 4.8 Hz, 1H), 1.92 (app. t, J = 12.0 Hz, 1H), 0.88–0.80 (comp. m, 12H), –0.04 (s, 3H), –0.06 (s, 3H), –0.06 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 192.8, 151.6, 130.5, 128.6, 124.8, 109.3, 108.3, 83.0, 78.5, 76.7, 66.4, 66.2, 48.5, 42.1, 26.1 (3C), 18.4, 18.4, –0.9 (3C), –4.4, –5.1; IR (film): 3456 (br), 2953, 1637, 1406, 1250, 1091 cm^{-1}; HRMS-FAB (m/z): [M + H]$^+$ calc'd for $C_{24}H_{44}NO_5Si_2$, 482.2758; found, 482.2751; $[\alpha]^{28}_D$ –21.18° (c 1.0, C_6H_6).



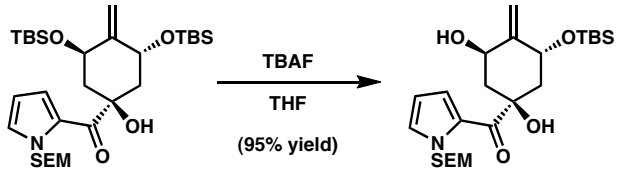
Bis(silylether) 132. To a solution of *anti*-diol **180** (253.1 mg, 0.53 mmol), imidazole (147.1 mg, 2.16 mmol), and DMAP (23.5 mg, 0.19 mmol) in DMF (5.0 mL), was added TBSCl (152.5 mg, 1.01 mmol). The solution was warmed to 50 °C for 70 min, cooled to 0 °C, then quenched by the addition of 10% (w/v) aq. citric acid (10 mL). Et_2O (40 mL) was added, and the layers were partitioned. The aqueous phase was further extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (9:1 hexanes:EtOAc eluent) to provide bis(silylether) **132** (296.0 mg, 95% yield) as a colorless oil that solidified under reduced

pressure. R_f 0.61 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 8.17 (dd, *J* = 4.0, 1.8 Hz, 1H), 6.76 (dd, *J* = 2.5, 1.7 Hz, 1H), 6.14 (dd, *J* = 4.0, 2.6 Hz, 1H), 5.68 (d, *J* = 9.9 Hz, 1H), 5.62 (d, *J* = 10.2 Hz, 1H), 5.37 (s, 1H), 5.32 (app. t, *J* = 2.1 Hz, 1H), 5.22–5.14 (m, 1H), 4.77 (app. t, *J* = 1.9 Hz, 1H), 4.50 (app. t, *J* = 3.0 Hz, 1H), 3.47 (t, *J* = 7.8 Hz, 2H), 2.82 (ddd, *J* = 12.7, 5.1, 2.6 Hz, 1H), 2.45 (dd, *J* = 14.6, 2.8 Hz, 1H), 2.27–2.18 (comp. m, 2H), 0.99 (s, 9H), 0.88 (s, 9H), 0.82 (t, *J* = 7.8 Hz, 2H), 0.17 (s, 3H), 0.14 (s, 3H), 0.00 (s, 3H), –0.04 (s, 3H), –0.07 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6, 29/30 C): δ 192.6, 151.6, 130.4, 124.5, 109.3, 108.6, 83.2, 78.5, 76.8, 67.4, 66.3, 49.3, 42.1, 26.4 (3C), 26.1 (3C), 18.9, 18.4, 18.3, –0.9 (3C), –4.3, –4.4, –4.5, –5.1; IR (film): 3464 (br), 1953, 2929, 1640, 1405, 1309, 1251, 1094 cm^{-1}; HRMS-FAB (*m/z*): [M + H]$^+$ calc'd for $C_{30}H_{58}NO_5Si_3$, 596.3623; found, 596.3594; $[\alpha]^{27}_D$ –7.16° (*c* 1.0, C_6H_6).

The stable chair conformer of bis(silylether) **132** was determined using a combination of NOESY-1D, gCOSY, and homodecoupling NMR experiments. Medium-strength NOE interactions were observed as indicated below.[75] The coupling constant between H_a and H_b was measured as J_{ab} = 11.0 Hz.

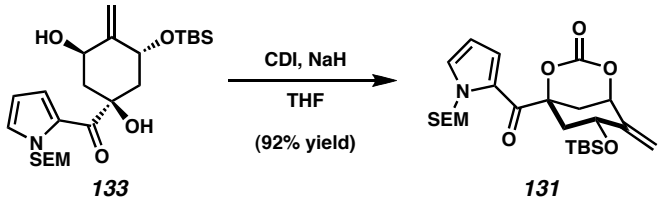


132-favored *132-disfavored*

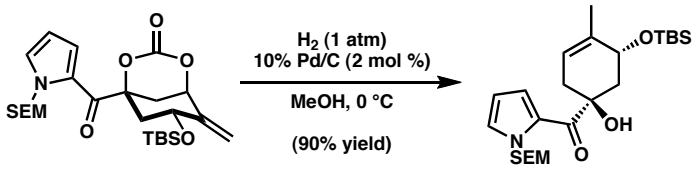


132 *133*

***Syn*-diol 133.** To bis(silylether) **132** (113.9 mg, 0.19 mmol) in THF (10.0 mL) was added TBAF (1.0 M in THF, 195 μL, 0.20 mmol) in a dropwise fashion over 1 min. The reaction mixture was stirred for 2 min, quenched with saturated aq. NH_4Cl (15 mL), then poured into EtOAc (40 mL). The layers were partitioned, and the aqueous layer was further extracted with EtOAc (2 x 40 mL). The combined organic extracts were successively washed with H_2O (15 mL) and brine (15 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash chromatography (7:1 hexanes:EtOAc eluent) to furnish *syn*-diol **133** (87.5 mg, 95% yield) as a pale yellow oil. R_f 0.29 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.09 (dd, J = 4.1, 1.4 Hz, 1H), 6.63 (dd, J = 2.3, 1.5 Hz, 1H), 5.89 (dd, J = 4.1, 2.5 Hz, 1H), 5.51–5.39 (comp. m, 4H), 5.27–5.19 (m, 1H), 5.01 (app. t, J = 2.1 Hz, 1H), 4.52–4.46 (m, 1H), 3.86 (d, J = 8.0 Hz, 1H), 3.37 (t, J = 7.7 Hz, 2H), 2.45–2.23 (comp. m, 3H), 2.04 (app. dt, J = 8.4, 4.9 Hz, 1H), 0.99 (s, 9H), 0.79 (t, J = 7.8 Hz, 2H), 0.14 (s, 3H), 0.11 (s, 3H), –0.09 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 191.6, 152.9, 131.4, 126.4, 124.0, 109.8, 108.5, 81.2, 78.8, 74.7, 67.4, 66.6, 49.0, 43.3, 26.4 (3C), 18.9, 18.3, –1.0 (3C), –4.5, –4.5; IR (film): 3363 (br), 2954, 1631, 1410, 1314, 1250, 1101 (br) cm^{-1}; HRMS-FAB (m/z): $[M + H]^+$ calc'd for $C_{24}H_{44}NO_5Si_2$, 482.2758; found, 482.2780; $[\alpha]^{27}_D$ –27.06° (c 1.0, C_6H_6).

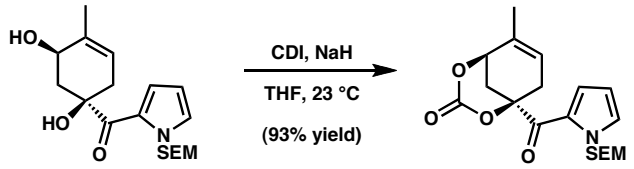


Carbonate 131. To *syn*-diol **133** (68.2 mg, 0.14 mmol) and 1,1'-carbonyldiimidazole (37.0 mg, 0.23 mmol) in THF (2.6 mL) was added NaH (60% dispersion in mineral oil, 21.9 mg, 0.55 mmol) in one portion. The reaction was stirred for 20 min at 23 °C, then quenched by addition of saturated aq. NH_4Cl (20 mL). The reaction mixture was poured into EtOAc (30 mL), the layers were partitioned, and the aqueous layer was further extracted with EtOAc (2 x 30 mL). The combined organic extracts were successively washed with H_2O (10 mL) and brine (10 mL), dried over $MgSO_4$, and evaporated under reduced pressure. Purification of the residue by flash chromatography (6:1 hexanes:EtOAc eluent) afforded carbonate **131** (65.8 mg, 92% yield) as a colorless oil. R_f 0.29 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.91 (dd, *J* = 4.1, 1.7 Hz, 1H), 6.68 (dd, *J* = 2.8, 1.7 Hz, 1H), 6.02 (dd, *J* = 4.3, 2.6 Hz, 1H), 5.51 (d, *J* = 9.9 Hz, 1H), 5.43 (d, *J* = 9.9 Hz, 1H), 5.24 (app. t, *J* = 1.9 Hz, 1H), 4.84–4.75 (m, 1H), 4.69 (app. t, *J* = 1.8 Hz, 1H), 4.46 (dd, *J* = 3.9, 1.9 Hz, 1H), 3.39 (t, *J* = 7.7 Hz, 2H), 2.78 (ddd, *J* = 13.5, 6.1, 2.5 Hz, 1H), 2.12–1.98 (comp. m, 2H), 1.92–1.85 (m, 1H), 0.86 (s, 9H), 0.81 (t, *J* = 7.8 Hz, 2H), –0.07 to –0.08 (comp. m, 12H), –0.10 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6): δ 185.9, 147.2, 146.4, 132.1, 126.7, 125.0, 112.2, 110.3, 87.9, 80.3, 78.8, 66.8, 66.5, 46.1, 33.7, 26.2 (3C), 18.6, 18.3, –1.0 (3C), –4.7, –5.0; IR (film): 2954, 1764, 1641, 1413, 1354, 1251, 1173, 1089 cm^{-1}; HRMS-FAB (*m*/*z*): $[M + H]^+$ calc'd for $C_{25}H_{42}NO_6Si_2$, 508.2551; found, 508.2560; $[\alpha]^{27}_D$ –54.78° (*c* 1.0, C_6H_6).



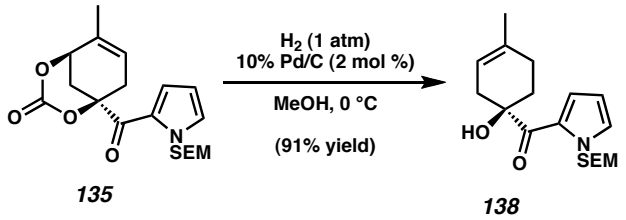
131 *127*

Pyrrolocyclohexene 127. A mixture of carbonate **131** (40.0 mg, 0.08 mmol) and 10% Pd/C (1.7 mg, 0.002 mmol) in MeOH (1.0 mL) was cooled to 0 °C. The reaction vessel was then evacuated and back-filled with H_2 (3x). After 1.75 h at 0 °C, the reaction mixture was filtered over a Celite® plug (MeOH eluent), and the solvent was evaporated in vacuo. The residue was purified by flash chromatography (9:1 hexanes:EtOAc eluent) to afford pyrrolocyclohexene **127** (33.1 mg, 90% yield) as a colorless oil. R_f 0.53 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 6.94 (dd, *J* = 4.1, 1.4 Hz, 1H), 6.64 (dd, *J* = 2.6, 1.5 Hz, 1H), 5.89 (dd, *J* = 4.0, 2.6 Hz, 1H), 5.54 (d, *J* = 10.2 Hz, 1H), 5.45 (d, *J* = 10.2 Hz, 1H), 5.39–5.33 (m, 1H), 4.87–4.78 (m, 1H), 4.78 (s, 1H), 3.40 (t, *J* = 7.8 Hz, 2H), 2.97–2.85 (m, 1H), 2.48 (dd, *J* = 12.5, 9.8 Hz, 1H), 2.34–2.26 (m, 1H), 2.21–2.08 (m, 1H), 1.95–1.90 (m, 3H), 0.96 (s, 9H), 0.81 (t, *J* = 7.8 Hz, 2H), 0.06 (s, 3H), 0.03 (s, 3H), –0.08 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 193.8, 138.5, 131.0, 126.4, 123.1, 120.1, 109.7, 78.8, 78.2, 69.6, 66.5, 44.7, 38.9, 26.4 (3C), 20.6, 18.6, 18.3, –1.0 (3C), –3.8, –4.5; IR (film): 3431 (br), 2954, 1634, 1414, 1250, 1089 (br) cm^{-1}; HRMS-FAB (*m/z*): [M + H]$^+$ calc'd for $C_{24}H_{44}NO_4Si_2$, 466.2809; found, 466.2804; $[\alpha]^{28}_D$ +26.19° (*c* 1.0, C_6H_6).



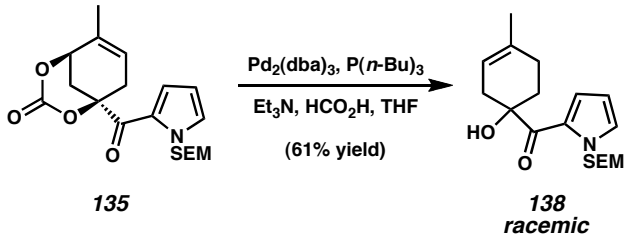
111 *135*

Pyrrolocarbonate 135. To diol **111** (114.5 mg, 0.33 mmol) in THF (6 mL) at 23 °C was added 1,1'-carbonyldiimidazole (86.9 mg, 0.54 mmol) followed by NaH (60% dispersion in mineral oil, 55.2 mg, 1.38 mmol). After stirring for 40 min at 23 °C, saturated aq. NH_4Cl (10 mL) was added to quench the reaction and EtOAc (50 mL) was added. The phases were partitioned, and the aqueous layer was further extracted with EtOAc (2 x 75 mL). The combined organic layers were successively washed with H_2O (15 mL) and brine (15 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash chromatography (4:1 hexanes:EtOAc eluent) to provide pyrrolocarbonate **135** (114.3 mg, 93% yield) as a pale yellow oil. R_f 0.53 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.85 (dd, *J* = 4.1, 1.4 Hz, 1H), 6.70 (dd, *J* = 2.7, 1.8 Hz, 1H), 6.04 (dd, *J* = 4.1, 2.7 Hz, 1H), 5.52 (d, *J* = 9.9 Hz, 1H), 5.48 (d, *J* = 10.0 Hz, 1H), 4.91–4.86 (m, 1H), 3.78 (app. t, *J* = 3.0 Hz, 1H), 3.41 (t, *J* = 7.8 Hz, 2H), 2.42–2.37 (comp. m, 2H), 1.97 (ddd, *J* = 14.1, 3.3, 1.0 Hz, 1H), 1.83 (dd, *J* = 14.2, 2.3 Hz, 1H), 1.40 (app. q, *J* = 2.0 Hz, 3H), 0.83 (t, *J* = 7.8 Hz, 2H), –0.07 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 187.6, 147.5, 132.6, 131.9, 127.1, 125.1, 122.6, 110.2, 85.9, 78.7, 73.8, 66.5, 37.9, 30.4, 21.0, 18.3, –1.0 (3C); IR (film) 2952, 1751, 1643, 1413, 1178, 1093 cm^{-1}; HRMS-EI (*m/z*): $[M]^+$ calc'd for $C_{19}H_{27}NO_5Si$, 377.1658; found, 377.1655; $[\alpha]^{24}_D$ +2.72° (*c* 1.0, C_6H_6).

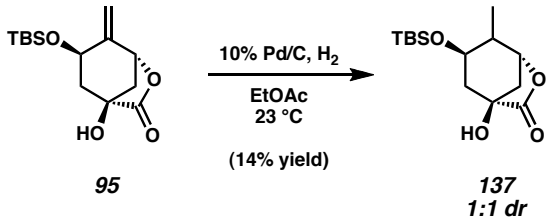


Trisubstituted Olefin 138. A mixture of pyrrolocarbonate **135** (41.6 mg, 0.11 mmol) and 10% Pd/C (2.3 mg, 0.002 mmol) in MeOH (2.0 mL) was cooled to 0 °C. The reaction vessel was then evacuated and back-filled with H_2 (3x). After 1.3 h at 0 °C, the reaction mixture was filtered over a Celite® plug (MeOH eluent) and the solvent was evaporated in vacuo. The residue was purified by preparative thin-layer chromatography (13:4:3 hexanes:EtOAc:CH_2Cl_2 eluent) to afford pyrrolocyclohexene **138** (33.5 mg, 91% yield) as a colorless oil. R_f 0.64 (13:7 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.16 (dd, *J* = 4.0, 1.5 Hz, 1H), 6.72 (dd, *J* = 2.7, 1.6 Hz, 1H), 6.02 (dd, *J* = 4.0, 2.7 Hz, 1H), 5.56 (s, 2H), 5.35–5.28 (m, 1H), 3.98 (s, 1H), 3.43 (t, *J* = 7.8 Hz, 2H), 2.98–2.85 (m, 1H), 2.51–2.33 (m, 1H), 2.24–2.10 (comp. m, 2H), 1.88–1.73 (comp. m, 2H), 1.67–1.63 (m, 3H), 0.82 (t, *J* = 7.8 Hz, 2H), –0.08 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 195.5, 134.0, 130.6, 127.3, 123.1, 118.5, 109.3, 78.7, 76.8, 66.5, 38.4, 34.2, 27.2, 24.1, 18.3, –1.0 (3C); IR (film) 3441 (br), 2957, 1727, 1632, 1413, 1084 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+$ calc'd for $C_{18}H_{30}NO_3Si$, 336.1995; found, 336.1993; $[\alpha]^{24}_D$ –0.02° (*c* 1.0, C_6H_6); 7.2% ee as measured by chiral HPLC (2% EtOH:hexanes eluent). Retention times: 13.9 min, 15.6 min.

A racemic sample was prepared as follows:

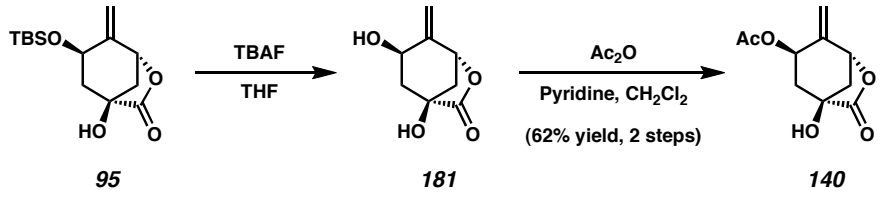


To carbonate **135** (9.9 mg, 0.03 mmol) and $Pd_2(dba)_3$ (2.7 mg, 0.003 mmol) was added THF (800 μL) followed by P(*n*-Bu)$_3$ (2.8 μL, 0.011 mmol), Et_3N (5.2 μL, 0.04 mmol) and formic acid (1.6 μL, 0.04 mmol).[77] The solution was stirred at 23 °C for 3 h, and was then heated to 70 °C for 70 min. The reaction was cooled to 23 °C and purified directly by preparative thin-layer chromatography (4:1 hexanes:EtOAc eluent). The crude product was then re-purified by preparative thin-layer chromatography (13:4:3 hexanes:EtOAc:CH_2Cl_2 eluent) to provide an a racemic, analytical sample of **138** (5.4 mg, 61% yield).



Reduced Lactone 137. A mixture of methylene lactone **95** (63.1 mg, 0.22 mmol) and 10% Pd/C (39.8 mg, 0.04 mmol) in EtOAc (2 mL) was evacuated and back-filled with H_2 (3x). After 7 min at 23 °C, the mixture was filtered over a pad of Celite® (EtOAc eluent) and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography (2:1 hexanes:EtOAc eluent) to provide reduced lactone **137** (8.7 mg, 14% yield) as a white amorphous solid and a 1:1 mixture of diastereomers. R_f 0.59 (1:1

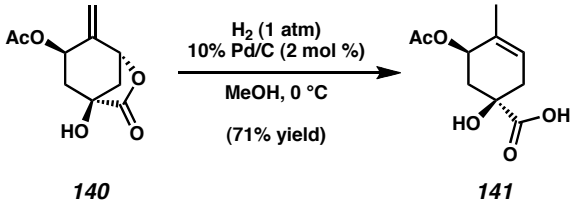
hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$, 1:1 mixture of diastereomers): δ 4.68–4.63 (m, 1H), 4.51 (d, *J* = 6.4 Hz, 1H), 4.04–3.94 (m, 1H), 3.45 (ddd, *J* = 12.9, 6.2, 4.1 Hz, 1H), 2.63 (app. d, *J* = 10.1 Hz, 1H), 2.49 (ddd, *J* = 11.2, 6.4, 3.2 Hz, 1H), 2.44–2.33 (m, 1H), 2.29–2.22 (comp. m, 2H), 2.14 (ddd, *J* = 12.1, 6.6, 2.9 Hz, 1H), 2.08 (app. d, *J* = 11.2 Hz, 1H), 2.00–1.82 (comp. m, 3H), 1.65–1.54 (comp. m, 2H), 1.12 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 7.4 Hz, 3H), 0.86 (s, 9H), 0.85 (s, 9H), 0.03–0.02 (comp. m, 6H), 0.02–0.01 (comp. m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 1:1 mixture of diastereomers): δ 178.5, 178.2, 80.4, 80.0, 73.5, 72.8, 71.4, 67.0, 44.8, 43.6, 41.9, 41.4, 37.4, 35.9, 25.9 (6C), 18.2, 18.1, 16.1, 10.7, –4.0, –4.6, –4.6, –4.8; IR (film) 3424 (br), 2930, 1787, 1099 cm^{-1}; HRMS-EI (*m*/*z*): $[M]^+$ calc'd for $C_{14}H_{26}O_4Si$, 286.1600; found, 286.1612; $[\alpha]^{25}_D$ –64.48° (*c* 1.0, C_6H_6).



Acetoxylactone 140. To lactone **95** (510.1 mg, 1.80 mmol) in THF (25 mL) and freshly distilled AcOH (300 μL, 5.24 mmol) was added TBAF (1.0 M in THF, 4.0 mL, 4.0 mmol) in a dropwise fashion over 3 min. The reaction was stirred for 16 h, and then the solvent was evaporated in vacuo to afford hydroxylactone **181**, which was used immediately in the subsequent reaction. Although hydroxylactone **181** is typically used in crude form, it has been observed by ^{1}H NMR. R_f 0.25 (3:1 EtOAc:hexanes). ^{1}H NMR (300 MHz, CD_3OD): δ 5.27 (dd, *J* = 2.4, 1.1 Hz, 1H), 5.20–5.17 (m, 1H), 5.11 (d, *J* = 6.1

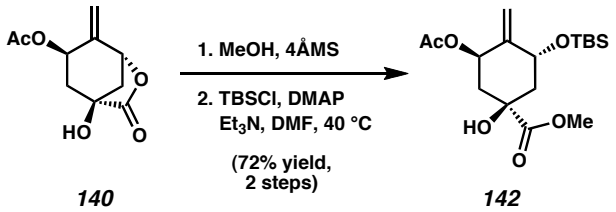
Hz, 1H), 4.26 (app ddt, J = 10.7, 7.5, 2.4 Hz, 1H), 2.63 (ddd, J = 11.3, 6.1, 3.1 Hz, 1H), 2.34 (ddd, J = 11.4, 7.4, 3.3 Hz, 1H), 1.98 (d, J = 11.4 Hz, 1H), 1.72 (t, J = 11.3, 1H).

Hydroxylactone **181** was dissolved in CH_2Cl_2 (17 mL) and pyridine (1.02 mL, 12.6 mmol) was added. A solution of Ac_2O (355 μL, 3.76 mmol) in CH_2Cl_2 (355 μL) was added via syringe pump at a rate of 170 μL/h. After the addition was complete, the reaction was quenched by the addition of 10% *(w/v)* aq. citric acid (35 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (3:2 hexanes:EtOAc eluent) to provide acetoxylactone **140** (235 mg, 62% yield, 2 steps) as a white crystalline solid. R_f 0.52 (3:1 EtOAc:hexanes); mp 87–89 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.54–5.44 (m, 1H), 5.16 (d, J = 2.4 Hz, 1H), 5.09–5.04 (comp. m, 2H), 3.26 (br s, 1H), 2.70 (ddd, J = 11.4, 6.1, 2.9 Hz, 1H), 2.52–2.42 (m, 1H), 2.14–2.08 (m, 1H), 2.12 (s, 3H), 1.87 (dd, J = 12.0, 10.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.7, 169.9, 140.4, 111.6, 79.2, 72.9, 67.4, 44.2, 40.3, 21.0; IR (film) 3441 (br), 1790, 1743, 1240, 1128, 1042 cm^{-1}; HRMS-EI (*m/z*): [M + H]$^+$ calc'd for $C_{10}H_{13}O_5$, 213.0763; found, 213.0769; $[\alpha]^{25}_D$ –229.70° (*c* 1.0, C_6H_6).



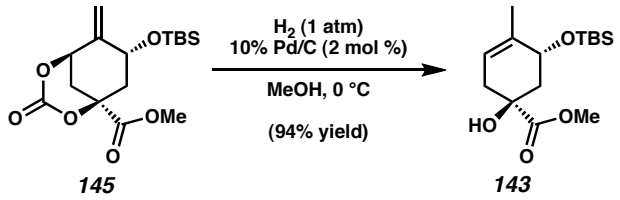
Acid 141. For representative procedures, see reductive isomerization of **131** → **127** or **135** → **138**. Purified by preparative thin-layer chromatography (19:1:1

EtOAc:MeOH:AcOH eluent). R_f 0.53 (19:1:1 EtOAc:MeOH:AcOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (br s, 1H), 5.66–5.60 (m, 1H), 5.39–5.32 (m, 1H), 2.68–2.54 (m, 1H), 2.39–2.23 (comp. m, 2H), 2.14–2.00 (m, 1H), 2.06 (s, 3H), 1.74–1.69 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.9, 170.7, 130.8, 123.7, 72.5, 68.9, 36.6, 35.7, 21.4, 20.6; IR (film) 3440 (br), 2938, 1728, 1242 cm^{-1}; HRMS-FAB (*m/z*): [M + Na]$^+$ calc'd for $C_{10}H_{14}O_5Na$, 237.0739; found, 237.0744; $[\alpha]^{25}_D$ +83.74° (*c* 1.0, $CHCl_3$).

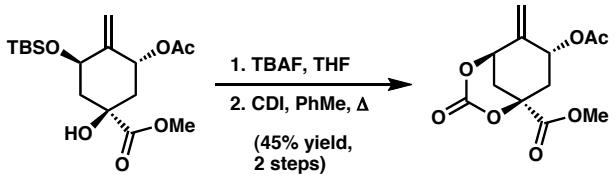


Methyl Ester 142. To acetoxylactone **140** (310 mg, 1.46 mmol) and oven-dried powdered 4ÅMS (220 mg) was added MeOH (20 mL). The suspension was stirred for 1 h, and then filtered over Celite® (EtOAc eluent). The filtrate was evaporated in vacuo, and was subsequently passed over a plug of SiO_2 gel (EtOAc eluent). Following evaporation of the solvent under reduced pressure, this material was used in the next step without further purification. R_f 0.33 (3:1 EtOAc:hexanes). To this crude material in DMF (7.3 mL) was added Et_3N (1.63 mL, 11.7 mmol) and DMAP (17.8 mg, 0.15 mmol). TBSCl (880 mg, 5.84 mmol) was added, and the solution was warmed to 40 °C. After stirring for 1 h, the solution was allowed to cool to 23 °C and quenched by the addition of 10% (*w/v*) aq. citric acid (10 mL). The reaction mixture was poured over H_2O (10 mL) and Et_2O (40 mL), and the phases were partitioned. The aqueous phase was extracted with Et_2O (2 x 30 mL), and the combined organic extracts were washed with brine (15 mL) and dried over $MgSO_4$. Following evaporation of the solvent in vacuo, the crude

product was purified by flash chromatography (2:1 hexanes:EtOAc eluent) to afford methyl ester **142** (376 mg, 72% yield, 2 steps) as a white solid. R_f 0.53 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.62 (app. t, *J* = 3.7 Hz, 1H), 5.24 (app. t, *J* = 1.9 Hz, 1H), 5.10 (app. t, *J* = 1.7 Hz, 1H), 4.73–4.63 (m, 1H), 3.74 (s, 3H), 3.16 (br s, 1H), 2.14 (dd, *J* = 14.9, 4.3 Hz, 1H), 2.09–2.00 (comp. m, 2H), 2.03 (s, 3H), 1.90 (dd, *J* = 12.5, 10.6 Hz, 1H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.5, 170.2, 146.6, 111.7, 75.3, 74.0, 66.8, 53.2, 45.7, 38.8, 26.0 (3C), 21.5, 18.4, –4.8, –4.9; IR (film) 3481 (br), 2955, 2930, 2858, 1734 (br), 1372, 1251, 1237, 1124, 1108, 1069, 1016 cm^{-1}; HRMS-FAB (*m*/*z*): [M + H]$^+$ calc'd for $C_{17}H_{31}O_6Si$, 359.1890; found, 359.1894; $[\alpha]^{26}_D$ –7.32° (*c* 1.0, $CHCl_3$).

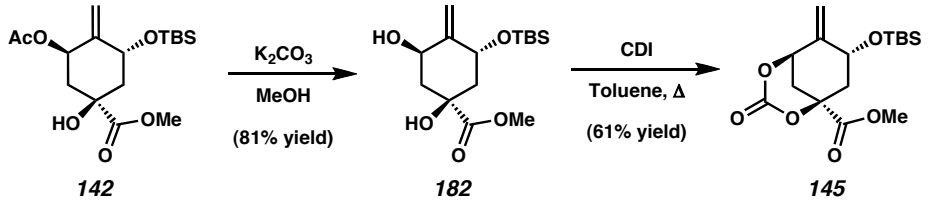


Methyl Ester 143. For representative procedures, see reductive isomerization of **131 → 127** or **135 → 138**. Purified by flash chromatography (7:3 hexanes:EtOAc eluent). R_f 0.62 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.38–5.31 (m, 1H), 4.44–4.34 (m, 1H), 3.78 (s, 3H), 3.10 (br s, 1H), 2.65–2.53 (m, 1H), 2.08–1.89 (comp. m, 3H), 1.74–1.70 (m, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.9, 137.2, 119.0, 74.5, 68.2, 53.2, 40.8, 35.8, 26.1 (3C), 20.1, 18.3, –4.1, –4.6; IR (film) 3492 (br), 2954, 2857, 1730, 1249, 1095 cm^{-1}; HRMS-FAB (*m*/*z*): [M + H]$^+$ calc'd for $C_{15}H_{29}O_4Si$, 301.1835; found, 301.1841; $[\alpha]^{24}_D$ +29.49° (*c* 1.0, C_6H_6).



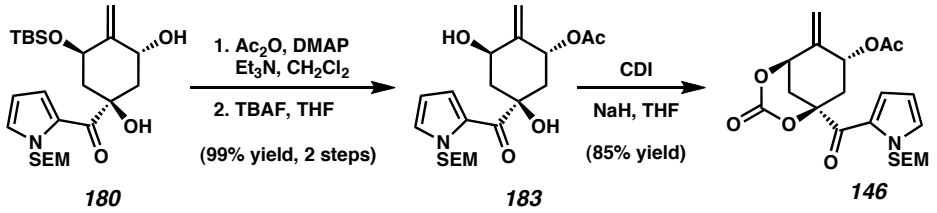
97 *144*

Acetoxycarbonate 144. To a solution of methyl ester **97** (44.8 mg, 0.12 mmol) in THF (2 mL) was added TBAF (1.0 M in THF, 140 μL, 0.14 mmol). After 3 min of stirring, the reaction was quenched by the addition of saturated aq. NH_4Cl (2 mL). EtOAc (4 mL) was added, and the phases were partitioned. The aqueous phase was further extracted with EtOAc (2 x 2 mL). The combined organic layers were successively washed with H_2O (1 mL) and brine (1 mL), and dried over $MgSO_4$. The solvent was evaporated in vacuo, and the residue was dissolved in toluene (4 mL). 1,1'-carbonyldiimidazole (82.1 mg, 0.51 mmol) was added, and the mixture was heated at reflux for 2 h. After cooling to 23 °C, the crude reaction mixture was directly purified by flash column chromatography (3:2 hexanes:EtOAc eluent) to afford pure acetoxycarbonate **144** (16.9 mg, 45% yield, 2 steps). R_f 0.15 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.70–5.62 (m, 1H), 5.25 (app. d, *J* = 2.5 Hz, 1H), 5.19 (app. d, *J* = 2.5 Hz, 1H), 5.16 (dd, *J* = 4.1, 1.9 Hz, 1H), 3.81 (s, 3H), 2.84 (ddd, *J* = 13.4, 6.4, 2.7 Hz, 1H), 2.55–2.48 (m, 1H), 2.32–2.26 (m, 1H), 2.12 (s, 3H), 1.96 (dd, *J* = 13.3, 11.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.3, 168.3, 146.6, 140.2, 113.7, 81.6, 79.5, 66.4, 53.7, 39.3, 32.7, 20.9; IR (film) 1763 (br), 1230, 1180, 1120 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+$ calc'd for $C_{12}H_{15}O_7$, 271.0818; found, 271.0810; $[\alpha]^{25}_D$ –154.53° (*c* 1.0, C_6H_6).



TBS Carbonate 145. To methyl ester **142** (201 mg, 0.56 mmol) in MeOH (5 mL) was added powdered K_2CO_3 (150 mg, 1.09 mmol). After stirring 10 min, the MeOH was evaporated in vacuo and the residue was diluted in Et_2O (50 mL) and saturated aq. NH_4Cl (25 mL). The layers were partitioned, and the aqueous phase was extracted with Et_2O (25 mL). The combined organics were successively washed with H_2O (15 mL) and brine (15 mL), and dried over $MgSO_4$. The solvent was evaporated in vacuo, and *syn*-diol **182** (143.9 mg, 81% yield) was carried on to the next step without further purification. R_f 0.38 (1:1 hexanes:EtOAc).

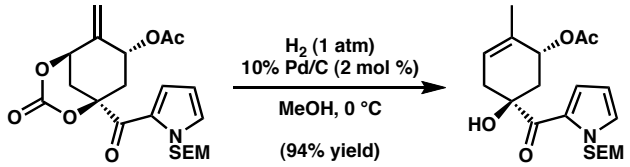
To *syn*-diol **182** (48.9 mg, 0.15 mmol) in toluene (3 mL) was added 1,1'-carbonyldiimidazole (80 mg, 0.50 mmol), and the reaction mixture was heated to reflux for 2.5 h. After cooling to 23 °C, the residue was chromatographed directly (7:3 hexanes:EtOAc eluent) to afford TBS carbonate **145** (32.2 mg, 61% yield). R_f 0.47 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.34 (dd, J = 2.2, 1.1 Hz, 1H), 5.21–5.19 (m, 1H), 5.15 (dd, J = 4.0, 1.8 Hz, 1H), 4.55–4.47 (m, 1H), 3.82 (s, 3H), 2.62 (ddd, J = 13.6, 6.2, 2.6 Hz, 1H), 2.45 (ddd, J = 14.2, 4.1, 2.7 Hz, 1H), 2.26 (dd, J = 14.2, 1.8 Hz, 1H), 1.92 (dd, J = 13.5, 10.7 Hz, 1H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.6, 147.2, 144.9, 113.4, 82.1, 79.9, 65.7, 53.6, 43.5, 33.0, 25.9 (3C), 18.3, –4.7, –4.9; IR (film) 2957, 2930, 2857, 1748 (br), 1254, 1178, 1103, 1054 cm^{-1}; HRMS-FAB (m/z): [M + H]$^+$ calc'd for $C_{16}H_{27}O_6Si$, 343.1577; found, 343.1592; $[\alpha]^{26}_D$ –81.11° (c 1.0, C_6H_6).



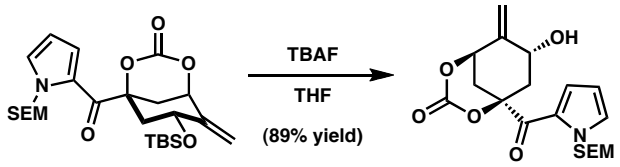
Acetoxycarbonate 146. To *anti*-diol **180** (1.77 g, 3.68 mmol) in CH_2Cl_2 (25 mL) at 23 °C was added Et_3N (1.28 mL, 9.19 mmol) and DMAP (45 mg, 0.368 mmol), followed by Ac_2O (451 μL, 4.78 mmol). The reaction mixture was stirred for 5 min, and then additional Ac_2O (125 μL, 1.32 mmol) was added. Stirring was continued for 5 min, and then another portion of Ac_2O (100 μL, 1.06 mmol) was added. After 5 min, the reaction mixture was quenched with saturated aq. $NaHCO_3$ (15 mL). The volatile solvents were removed under reduced pressure. The residue was diluted with H_2O (30 mL) and extracted with EtOAc (3 x 70 mL). The combined organic layers were dried over $MgSO_4$, and evaporated under reduced pressure. Subsequent filtration over a short plug of silica gel afforded the crude product, which was used immediately in the following reaction. R_f 0.63 (2:1 hexanes:EtOAc).

To the crude product in THF (25 mL) was added TBAF (1.0 M in THF, 3.85 mL, 3.85 mmol). After 2 min of stirring, the reaction was quenched by the addition of saturated aq. NH_4Cl (30 mL) and the volatile solvents were removed under reduced pressure. The residue was diluted with H_2O (50 mL) and extracted with EtOAc (3 x 60 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (3:2 hexanes:EtOAc eluent) to afford acetoxycyclohexene **183** (1.49 g, 99% yield, 2 steps) as a colorless oil. R_f 0.23 (2:1 hexanes:EtOAc).

To acetoxycyclohexene **183** (222 mg, 0.542 mmol) and 1,1'-carbonyldiimidazole (132 mg, 0.813 mmol) in THF (10.8 mL) at 23 °C was added NaH (60% dispersion in mineral oil, 54 mg, 1.35 mmol). After 2 min of stirring, the reaction was quenched by the addition of saturated aq. NH_4Cl (10 mL) and the volatile solvents were removed under reduced pressure. The residue was diluted with H_2O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (2:1 hexanes:EtOAc eluent) to afford acetoxycarbonate **146** (200.1 mg, 85% yield) as a colorless oil. R_f 0.25 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.75 (dd, *J* = 4.3, 1.5 Hz, 1H), 6.74 (dd, *J* = 2.5, 1.7 Hz, 1H), 6.03 (dd, *J* = 4.3, 2.6 Hz, 1H), 5.89–5.79 (m, 1H), 5.47 (s, 2H), 4.90 (d, *J* = 2.2 Hz, 1H), 4.73 (d, *J* = 1.9 Hz, 1H), 4.54 (dd, *J* = 3.9, 1.9 Hz, 1H), 3.40 (t, *J* = 7.8 Hz, 2H), 2.82 (ddd, *J* = 13.4, 6.3, 2.3 Hz, 1H), 2.03 (dd, *J* = 14.6, 1.9 Hz, 1H), 1.95 (ddd, *J* = 14.6, 3.8, 2.4 Hz, 1H), 1.81 (dd, *J* = 13.2, 11.3 Hz, 1H), 1.63 (s, 3H), 0.81 (t, *J* = 7.8 Hz, 2H), –0.08 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 185.4, 168.9, 146.8, 141.6, 132.3, 126.4, 125.4, 112.6, 110.4, 87.4, 80.0, 78.7, 67.3, 66.5, 41.7, 33.3, 20.5, 18.3, –1.0 (3C); IR (film) 2953, 1764, 1643, 1413, 1356, 1234, 1177, 1129, 1106, 1086, 1048 cm^{-1}; HRMS-FAB (*m*/*z*): $[M + H]^+$ calc'd for $C_{21}H_{30}NO_7Si$, 436.1792; found, 436.1807; $[\alpha]^{27}_D$ –112.57° (*c* 1.0, C_6H_6).

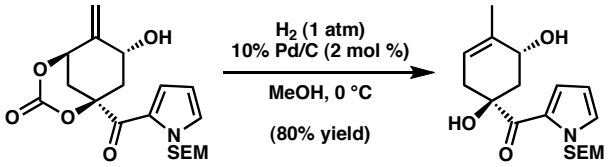


Allylic Acetate 147. A mixture of acetoxycarbonate **146** (734 mg, 1.69 mmol) and 10% Pd/C (36 mg, 0.03 mmol) in MeOH (17 mL) was cooled to 0 °C. The reaction vessel was then evacuated and back-filled with H_2 (3x). After 20 min at 0 °C, the reaction mixture was filtered over a Celite® plug (MeOH eluent) and the solvent was evaporated in vacuo. The residue was purified by flash chromatography (3:1 hexanes:EtOAc eluent) to afford allylic acetate **147** (625 mg, 94% yield). R_f 0.56 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.05 (dd, *J* = 4.1, 1.7 Hz, 1H), 6.69 (dd, *J* = 2.2, 1.4 Hz, 1H), 6.07–5.98 (m, 1H), 5.95 (dd, *J* = 3.9, 2.8 Hz, 1H), 5.53 (d, *J* = 9.9 Hz, 1H), 5.47 (d, *J* = 9.9 Hz, 1H), 5.36–5.30 (m, 1H), 4.09 (br s, 1H), 3.42 (t, *J* = 7.8 Hz, 2H), 2.80 (ddd, *J* = 18.0, 5.2, 2.6 Hz, 1H), 2.43 (ddd, *J* = 12.6, 6.1, 1.7 Hz, 1H), 2.34 (dd, *J* = 12.4, 9.6 Hz, 1H), 2.17–2.06 (m, 1H), 1.72–1.69 (m, 3H), 1.68 (s, 3H), 0.82 (t, *J* = 7.8 Hz, 2H), –0.08 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 193.3, 170.4, 133.8, 130.9, 126.9, 123.1, 122.7, 109.5, 78.7, 78.3, 71.9, 66.6, 39.6, 38.2, 21.0, 19.4, 18.3, –1.0 (3C); IR (film) 3438 (br), 2951, 1735, 1717, 1636, 1413, 1370, 1241, 1082, 1024 cm^{-1}; HRMS-FAB (*m*/*z*): [M + H]$^+$ calc'd for $C_{20}H_{32}NO_5Si$, 394.2050; found, 394.2031; $[\alpha]^{27}_D$ –9.91° (*c* 1.0, C_6H_6).



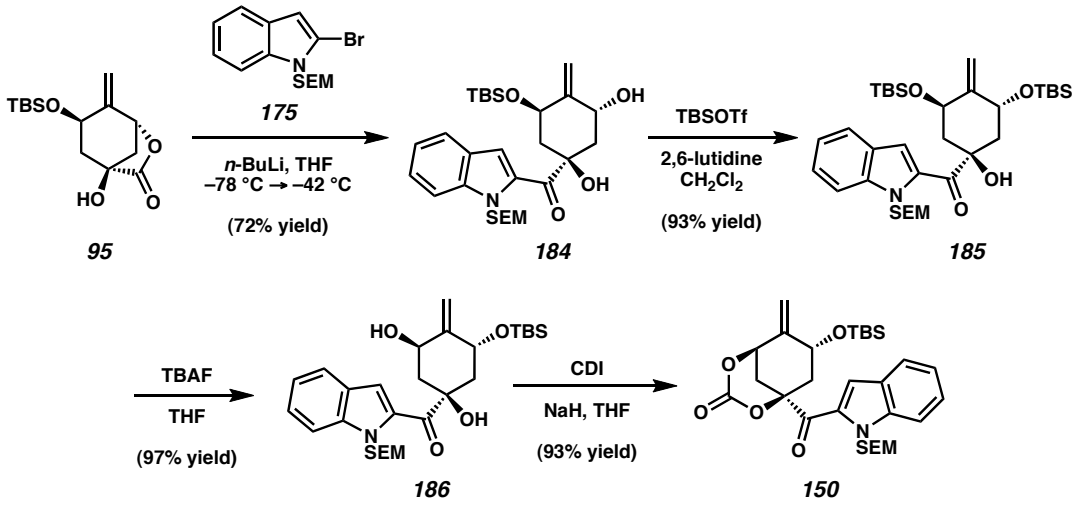
131 *148*

Hydroxycarbonate 148. To carbonate **131** (41.8 mg, 0.08 mmol) in THF (1 mL) was added TBAF (1.0 M in THF, 85 μL, 0.085 mmol) at 23 °C. After stirring 3 min, the reaction was quenched by the addition of saturated aq. NH_4Cl (1 mL). EtOAc (1 mL) was added, the phases were partitioned, and the aqueous phase was extracted with EtOAc (3 x 1 mL). The combined organics were washed successively with H_2O (1 mL) and brine (1 mL), and dried over $MgSO_4$. The solvent was evaporated in vacuo, and the crude product was purified by flash chromatography (1:1 hexanes:EtOAc eluent) to provide hydroxycarbonate **148** (28.7 mg, 89% yield) as a colorless oil. R_f 0.29 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.77 (dd, *J* = 4.1, 1.4 Hz, 1H), 6.72 (app. t, *J* = 2.1 Hz, 1H), 6.08 (dd, *J* = 4.1, 2.3 Hz, 1H), 5.48 (d, *J* = 10.1 Hz, 1H), 5.42 (d, *J* = 10.1 Hz, 1H), 5.29 (app. t, *J* = 1.6 Hz, 1H), 4.78–4.75 (m, 1H), 4.52–4.42 (comp. m, 2H), 3.40 (t, *J* = 8.0 Hz, 2H), 2.67 (ddd, *J* = 13.4, 6.1, 2.6 Hz, 1H), 2.47 (app. d, *J* = 5.5 Hz, 1H), 2.00 (dd, *J* = 14.4, 1.6 Hz, 1H), 1.91–1.81 (comp. m, 2H), 0.83 (t, *J* = 7.8 Hz, 2H), –0.07 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 185.8, 147.9, 145.9, 132.0, 126.6, 125.1, 112.2, 110.2, 88.1, 80.6, 78.7, 66.6, 65.4, 45.2, 33.4, 18.2, –1.0 (3C); IR (film) 3455 (br), 2953, 2895, 1756, 1644, 1414, 1360, 1250, 1179, 1082 (br) cm^{-1}; HRMS-FAB (*m/z*): [M + H]$^+$ calc'd for $C_{19}H_{28}NO_6Si$, 394.1686; found, 394.1690; $[\alpha]^{26}_D$ –77.69° (*c* 1.0, C_6H_6).



148 *149*

Allylic alcohol 149. A mixture of hydroxycarbonate **148** (34.2 mg, 0.09 mmol) and 10% Pd/C (1.5 mg, 0.001 mmol) in MeOH (1.4 mL) was cooled to 0 °C. The reaction vessel was then evacuated and back-filled with H_2 (3x). After 15 min at 0 °C, the reaction mixture was filtered over a Celite® plug (MeOH eluent) and the solvent was evaporated in vacuo. The residue was purified by flash chromatography (3:1 hexanes:EtOAc eluent) to afford allylic alcohol **149** (24.3 mg, 80% yield) as a colorless oil. R_f 0.33 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.19 (dd, *J* = 4.0, 1.6 Hz, 1H), 6.69 (dd, *J* = 2.4, 1.6 Hz, 1H), 5.98 (dd, *J* = 4.1, 2.5 Hz, 1H), 5.50 (d, *J* = 10.1 Hz, 1H), 5.46 (d, *J* = 9.8 Hz, 1H), 5.27–5.21 (m, 1H), 4.45–4.34 (m, 1H), 3.99 (s, 1H), 3.41 (t, *J* = 7.8 Hz, 2H), 2.91–2.79 (m, 1H), 2.26 (dd, *J* = 12.9, 8.1 Hz, 1H), 2.20–2.03 (comp. m, 3H), 1.87–1.83 (m, 3H), 0.82 (t, *J* = 7.8 Hz, 2H), –0.08 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 194.3, 137.9, 130.9, 126.9, 123.5, 119.9, 109.5, 78.7, 78.4, 68.4, 66.6, 43.9, 38.8, 19.9, 18.3, –1.0 (3C); IR (film) 3407 (br), 2953, 2920, 1629, 1412, 1309, 1250, 1081 cm^{-1}; HRMS-FAB (*m*/*z*): [M + H]$^+$ calc'd for $C_{18}H_{30}NO_4Si$, 352.1944; found, 352.1931; $[\alpha]^{25}_D$ +21.44° (*c* 1.0, C_6H_6).



Indolocarbonate 150. To 2-bromo SEM indole (**175**, 345.0 mg, 1.06 mmol) in THF (7 mL) cooled to –78 °C was added *n*-BuLi (2.5 M in hexanes, 380 μL, 0.95 mmol) dropwise over 1 min. The reaction was stirred for 7 min, and then a solution of lactone **95** (80.8 mg, 0.28 mmol) in THF (1 mL) was added dropwise over 2 min. The solution was warmed to –42 °C, and stirred for 1 h. The reaction was quenched at –78 °C by the addition of saturated aq. NH_4Cl (3 mL), and was allowed to thaw slowly to 23 °C. Et_2O (50 mL) and H_2O (10 mL) were added, the phases were partitioned, and the aqueous phase was extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed with brine (15 mL) and dried over $MgSO_4$. Following evaporation of the solvent in vacuo, the crude product was purified by flash chromatography (9:1 hexanes:EtOAc eluent) to afford *anti*-diol **184** (108.9 mg, 72% yield) as a pale yellow foam. R_f 0.40 (4:1 hexanes:EtOAc).

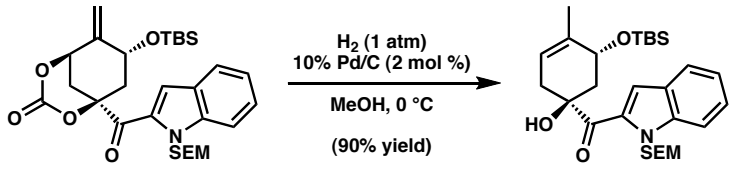
To *anti*-diol **184** (762.8 mg, 1.43 mmol) in CH_2Cl_2 (20 mL) at 23 °C was added 2,6-lutidine (360 μL, 3.09 mmol). The solution was treated with TBSOTf (480 μL, 2.09 mmol), and was stirred for 10 min. The reaction was quenched by the addition of saturated aq. NH_4Cl (50 mL). The phases were partitioned, and the aqueous phase was

extracted with CH_2Cl_2 (4 x 50 mL). The combined organic extracts were washed with brine (15 mL) and dried over $MgSO_4$. Following evaporation of the solvent in vacuo, the crude product was purified by flash chromatography (9:1 hexanes:EtOAc eluent) to afford bis(silylether) **185** (859.6 mg, 93% yield) as a white solid. R_f 0.48 (4:1 hexanes:EtOAc).

To bis(silylether) **185** (859.6 mg, 1.33 mmol) in THF (34 mL) at 23 °C was added TBAF (1.0 M in THF, 1.40 mL, 1.40 mmol) in a dropwise fashion over 1 min. After stirring 5 min, the reaction was quenched by the addition of saturated aq. NH_4Cl (50 mL). Et_2O (50 mL) was added, the phases were partitioned, and the aqueous phase was extracted with Et_2O (75 mL x 2). The combined organics were washed with brine (25 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash chromatography (9:1 hexanes:EtOAc → 4:1 hexanes:EtOAc eluent) to afford *syn*-diol **186** (687.1 mg, 97% yield) as a pale yellow foam. R_f 0.28 (4:1 hexanes:EtOAc).

To *syn*-diol **186** (687.1 mg, 1.29 mmol) in THF (30 mL) at 23 °C was added NaH (60% dispersion in mineral oil, 167.0 mg, 4.18 mmol). When H_2 evolution ceased (3 min), 1,1'-carbonyldiimidazole (331.3 mg, 2.04 mmol) was added in one portion. The reaction was quenched after 30 min of stirring with saturated aq. NH_4Cl (50 mL). Et_2O (50 mL) was added, the phases were partitioned, and the aqueous phase was extracted with Et_2O (75 mL x 2). The combined organics were washed with brine (25 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash chromatography (9:1 hexanes:EtOAc eluent) to furnish indolocarbonate **150** (668.9 mg, 93% yield) as a white foam. R_f 0.37 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ

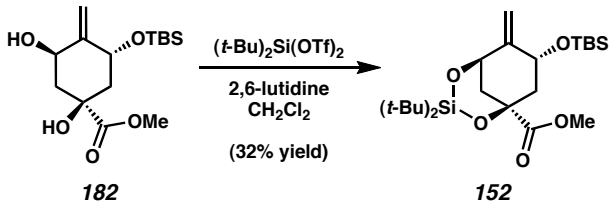
8.24 (d, J = 0.8 Hz, 1H), 7.45 (app. dt, J = 4.5, 2.8 Hz, 1H), 7.38–7.34 (m, 1H), 7.24–7.18 (m, 1H), 7.03–6.97 (m, 1H), 5.86 (d, J = 10.6 Hz, 1H), 5.77 (d, J = 10.4 Hz, 1H), 5.26 (dd, J = 2.0, 1.5 Hz, 1H), 4.88–4.79 (m, 1H), 4.74 (app. t, J = 1.7 Hz, 1H), 4.54 (dd, J = 3.9, 2.0 Hz, 1H), 3.51–3.44 (m, 2H), 2.86 (ddd, J = 13.5, 6.0, 2.3 Hz, 1H), 2.11–1.92 (comp. m, 3H), 0.87 (s, 9H), 0.80 (t, J = 7.7 Hz, 2H), –0.05 (s, 3H), –0.07 (s, 3H), –0.12 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 188.9, 147.0, 146.2, 141.5, 130.7, 127.9, 127.3, 124.7, 122.4, 118.2, 112.5, 111.9, 88.3, 80.2, 74.1, 66.7, 66.2, 46.1, 33.6, 26.2 (3C), 18.6, 18.3, –1.0 (3C), –4.7, –4.9; IR (film) 2954, 1765, 1656, 1355, 1170, 1086 cm^{-1}; HRMS-EI (m/z): [M]$^+$ calc'd for $C_{29}H_{43}NO_6Si_2$, 557.2629; found, 557.2632; $[\alpha]^{23}_D$ –34.29 (c 1.0, C_6H_6).



150 *151*

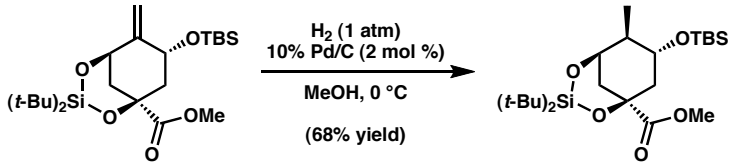
Acyl Indole 151. A mixture of indolocarbonate **150** (230.2 mg, 0.41 mmol) and 10% Pd/C (8.8 mg, 0.008 mmol) in MeOH (10 mL) was cooled to 0 °C. The reaction vessel was then evacuated and back-filled with H_2 (3x). After 4 h at 0 °C, the reaction mixture was filtered over a Celite® plug (MeOH eluent) and the solvent was evaporated in vacuo. The residue was purified by flash chromatography (9:1 hexanes:EtOAc eluent) to afford acyl indole **151** (192.2 mg, 90% yield) as a pale yellow oil. R_f 0.48 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.43–7.42 (m, 1H), 7.42–7.39 (m, 1H), 7.39–7.37 (m, 1H), 7.24–7.17 (m, 1H), 7.07–7.01 (m, 1H), 5.90 (d, J = 10.6 Hz, 1H), 5.82 (d, J = 10.6 Hz, 1H), 5.41–5.35 (m, 1H), 4.87–4.77 (m, 1H), 4.29 (s, 1H), 3.51 (t, J

= 7.8 Hz, 2H), 3.03–2.92 (m, 1H), 2.66–2.57 (m, 1H), 2.43–2.35 (m, 1H), 2.23–2.11 (m, 1H), 1.95–1.92 (m, 3H), 0.96 (s, 9H), 0.82 (t, J = 7.8 Hz, 2H), 0.08 (s, 3H), 0.06 (s, 3H), –0.12 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 197.1, 141.0, 138.7, 130.7, 127.4, 127.0, 124.0, 122.3, 119.9, 116.1, 112.2, 79.3, 74.2, 69.5, 66.2, 44.4, 38.8, 26.4 (3C), 20.6, 18.6, 18.3, –1.0 (3C), –3.8, –4.5; IR (film) 3449 (br), 2954, 1643, 1249, 1092 cm^{-1}; HRMS-EI (m/z): $[M]^+$ calc'd for $C_{28}H_{45}NO_4Si_2$, 515.2887; found, 515.2875; $[\alpha]^{27}_D$ –27.67° (c 1.0, C_6H_6).



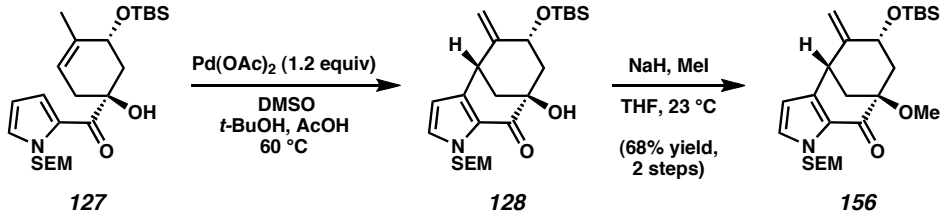
Dioxasilylcyclohexane 152. To *syn*-diol **182** (19.3 mg, 0.06 mmol) in CH_2Cl_2 (1.2 mL) was added 2,6-lutidine (30 μL, 0.26 mmol) followed by rapid dropwise addition of $(t\text{-Bu})_2Si(OTf)_2$ (30 μL, 0.08 mmol) over 1 min. The reaction was stirred for 16 h at 23 °C, and then quenched by the addition of saturated aq. NH_4Cl (1 mL). The phases were partitioned, and the aqueous phase was extracted with CH_2Cl_2 (3 x 1 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo. Purification by preparative thin-layer chromatography (11:2 hexanes:EtOAc eluent) afforded dioxasilylcyclohexane **152** (9.0 mg, 32% yield) as a colorless oil. R_f 0.50 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.17 (app. t, J = 1.9 Hz, 1H), 5.14–5.06 (comp. m, 2H), 4.78 (dd, J = 3.8, 2.1 Hz, 1H), 3.73 (s, 3H), 2.71 (app. dt, J = 9.1, 4.9 Hz, 1H), 2.42 (ddd, J = 13.1, 7.2, 2.9 Hz, 1H), 2.00–1.80 (comp. m, 2H), 1.08 (s, 9H), 1.07 (s, 9H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 150.2, 110.6,

76.8, 74.9, 66.6, 52.6, 45.4, 39.1, 29.2 (3C), 28.7 (3C), 26.0 (3C), 21.7, 21.6, 18.3, –4.3, –4.5; IR (film) 2937, 2860, 1758, 1739, 1473, 1243, 1112 cm^{-1}; HRMS-EI (*m/z*): $[M]^+$ calc'd for $C_{23}H_{44}O_5Si_2$, 456.2727; found, 456.2740; $[\alpha]^{21}_D$ –47.35° (*c* 1.0, C_6H_6).



152 *153*

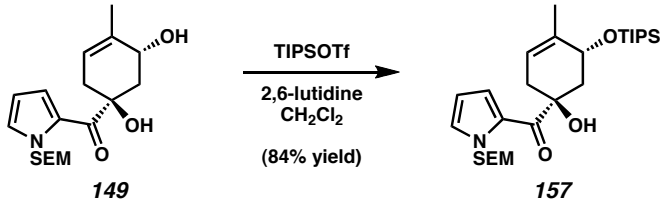
Reduced Dioxasilylcyclohexane 153. For representative procedures, see reductive isomerization of **131** → **127** or **135** → **138**. Purified by preparative thin-layer chromatography (4:1 hexanes:EtOAc eluent). R_f 0.82 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.30–4.19 (comp. m, 2H), 3.73 (s, 3H), 2.64 (ddd, *J* = 14.5, 4.0, 3.1 Hz, 1H), 2.29 (ddd, *J* = 13.4, 5.9, 2.9 Hz, 1H), 1.88–1.72 (comp. m, 2H), 1.53–1.43 (m, 1H), 1.15 (d, *J* = 6.6 Hz, 3H), 1.09 (s, 9H), 1.06 (s, 9H), 0.86 (s, 9H), 0.02 (s, 3H), 0.02 (s, 3H); ^{1}H NMR (300 MHz, C_6D_6): δ 4.47 (app. dt, *J* = 9.9, 5.6 Hz, 1H), 3.97–3.92 (m, 1H), 3.32 (s, 3H), 2.71–2.58 (comp. m, 2H), 1.99 (dd, *J* = 13.3, 10.3 Hz, 1H), 1.63 (dd, *J* = 14.4, 1.7 Hz, 1H), 1.44–1.31 (m, 1H), 1.28 (d, *J* = 6.4 Hz, 3H), 1.20 (s, 9H), 1.19 (s, 9H), 1.00 (s, 9H), 0.14 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6): δ 173.7, 77.6, 74.1, 70.1, 52.1, 45.9, 44.8, 38.6, 29.8 (3C), 29.4 (3C), 26.4 (3C), 22.2, 22.1, 18.5, 15.9, –3.2, –3.8; IR (film) 2954, 2936, 2895, 2860, 1757, 1739, 1258, 1146, 1100, 1081 cm^{-1}; HRMS-EI (*m/z*): $[M]^+$ calc'd for $C_{23}H_{46}O_5Si_2$, 458.2884; found, 458.2886; $[\alpha]^{25}_D$ –52.92° (*c* 1.0, $CHCl_3$).



[3.3.1] Bicycle 128. To pyrrolocyclohexene **127** (40.0 mg, 0.0859 mmol) was added $Pd(OAc)_2$ (23.0 mg, 0.103 mmol), DMSO (14.6 μL, 0.206 mmol), *t*-BuOH (6.9 mL), and AcOH (1.7 mL). The mixture was heated to 60 °C for 8 h, cooled to 23 °C, and filtered over a plug of silica gel (2:1 hexanes:EtOAc eluent). The solvent was evaporated, and the product was purified by flash chromatography on silica gel (8:1 hexanes:EtOAc eluent) to afford [3.3.1] bicycle **128** contaminated with a trace amount of pyrrolocyclohexene **127**. Although this material was carried on to the subsequent step without further purification, an analytical sample of **128** was obtained by flash chromatography on silica gel (12:1 hexanes:EtOAc eluent) as a colorless oil. R_f 0.64 (3:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 6.64 (d, *J* = 2.5 Hz, 1H), 6.25 (d, *J* = 10.2 Hz, 1H), 5.84 (d, *J* = 2.8 Hz, 1H), 5.07 (d, *J* = 9.9 Hz, 1H), 4.79 (br s, 1H), 4.66 (br s, 1H), 4.24–4.19 (m, 1H), 4.19 (s, 1H), 3.68–3.51 (m, 2H), 3.43–3.38 (m, 1H), 2.61 (app. dt, *J* = 7.3, 3.9 Hz, 1H), 2.21–2.10 (m, 2H), 2.06–1.98 (m, 1H), 0.99–0.77 (m, 2H), 0.72 (s, 9H), –0.04 (s, 9H), –0.11 (s, 3H), –0.24 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6): δ 192.0, 148.6, 142.7, 130.5, 126.3, 113.2, 108.3, 77.0, 73.4, 73.0, 66.6, 48.5, 45.5, 40.2, 26.1 (3C), 18.4, 18.3, –1.0 (3C), –4.4, –5.1; IR (film): 3468 (br), 2951, 1648, 1422, 1250, 1094, 1062 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+$ calc'd for $C_{24}H_{42}NO_4Si_2$, 464.2652; found, 464.2661; $[\alpha]^{27}_D$ +319.22° (*c* 1.0, C_6H_6).

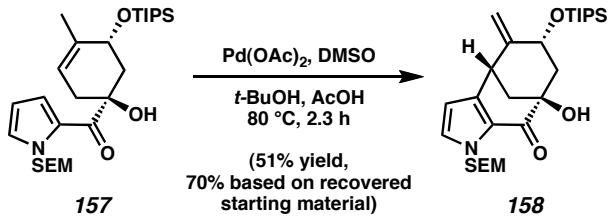
Methyl Ether 156. The crude mixture of **127** and **128** obtained from the previous step was dissolved in THF (1.5 mL) at 23 °C, and NaH (60% dispersion in mineral oil, 17

mg, 0.429 mmol) was added. After stirring for 1 min at 23 °C, MeI was added (53 μL, 0.859 mmol). The resulting mixture was stirred for 1.5 h, quenched with saturated aq. NH_4Cl (1.5 mL), and extracted with Et_2O (4 x 1 mL). The combined organic layers were washed with brine (1 mL), dried by passage over a plug of silica gel (EtOAc eluent), and evaporated under reduced pressure. The crude product was purified by flash chromatography (10:1 hexanes:EtOAc eluent) to afford methyl ether **156** (28.2 mg, 68% yield, 2 steps) as a colorless oil. R_f 0.43 (5:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 6.62 (d, *J* = 2.6 Hz, 1H), 6.43 (d, *J* = 10.3 Hz, 1H), 5.86 (d, *J* = 2.6 Hz, 1H), 5.06 (d, *J* = 10.0 Hz, 1H), 4.84 (d, *J* = 1.5 Hz, 1H), 4.69 (d, *J* = 1.5 Hz, 1H), 4.29–4.22 (m, 1H), 3.42–3.52 (m, 2H), 3.45 (app. t, *J* = 2.8 Hz, 1H), 3.39 (s, 3H), 2.79 (app. dt, *J* = 7.4, 3.8 Hz, 1H), 2.49 (app. dt, *J* = 8.1, 4.4 Hz, 1H), 1.96 (dd, *J* = 13.8, 4.7 Hz, 1H), 1.70 (dd, *J* = 11.7, 3.2 Hz, 1H), 0.96–0.82 (m, 2H), 0.73 (s, 9H), –0.06 (s, 9H), –0.11 (s, 3H), –0.23 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6): δ 189.2, 149.2, 140.9, 129.6, 128.9, 112.9, 107.6, 79.0, 77.3, 72.7, 66.6, 51.5, 46.3, 41.7, 39.9, 26.1 (3C), 18.4, 18.4, –1.0 (3C), –4.4, –5.1; IR (film): 2951, 1661, 1426, 1250, 1113, 1066; HRMS-FAB (*m/z*): $[M + H]^+$ calc'd for $C_{25}H_{44}NO_4Si_2$, 478.2809; found, 478.2815; $[\alpha]^{27}_D$ +312.37° (*c* 1.0, C_6H_6).



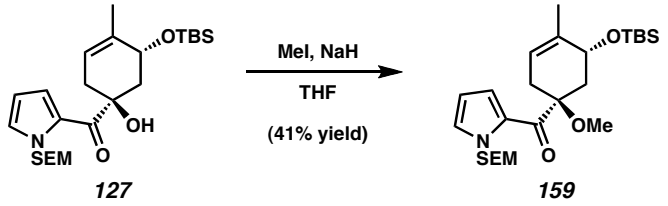
TIPS Ether 157. To allylic alcohol **149** (48.5 mg, 0.14 mmol) in CH_2Cl_2 (5 mL) at 23 °C was added 2,6-lutidine (32 μL, 0.27 mmol), followed by TIPSOTf (42 μL, 0.16 mmol). After stirring 5 min, saturated aq. NH_4Cl (5 mL) was added to quench the

reaction. The phases were partitioned, and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine (5 mL), and dried over $MgSO_4$. Following evaporation of the solvent in vacuo, the crude product was purified by flash chromatography (19:1 hexanes:EtOAc → 9:1 hexanes:EtOAc eluent) to provide TIPS ether **157** (58.5 mg, 84%) as a colorless oil. R_f 0.48 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 6.98 (dd, *J* = 4.1, 1.4 Hz, 1H), 6.64 (dd, *J* = 2.5, 1.6 Hz, 1H), 5.91 (dd, *J* = 4.1, 2.7 Hz, 1H), 5.50 (d, *J* = 10.0 Hz, 1H), 5.46 (d, *J* = 10.0 Hz, 1H), 5.39–5.33 (m, 1H), 5.07–4.98 (m, 1H), 4.79 (s, 1H), 3.39 (t, *J* = 7.8 Hz, 2H), 2.97–2.85 (m, 1H), 2.55–2.46 (m, 1H), 2.44–2.36 (m, 1H), 2.20–2.08 (m, 1H), 2.05–2.00 (m, 3H), 1.16–1.02 (comp. m, 21H), 0.80 (t, *J* = 7.8 Hz, 2H), –0.08 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 193.9, 139.1, 131.0, 126.3, 123.0, 119.9, 109.7, 78.8, 78.2, 70.1, 66.6, 44.9, 38.9, 20.8, 18.9 (3C), 18.8 (3C), 18.3, 13.5 (3C), –1.0 (3C); IR (film) 3431 (br), 2946, 2866, 1631, 1413, 1382, 1250, 1094 cm^{-1}; HRMS-FAB (*m*/*z*): [M + H]$^+$ calc'd for $C_{27}H_{50}NO_4Si_2$, 508.3278; found, 508.3264; $[\alpha]^{27}_D$ +14.46° (*c* 1.0, C_6H_6).



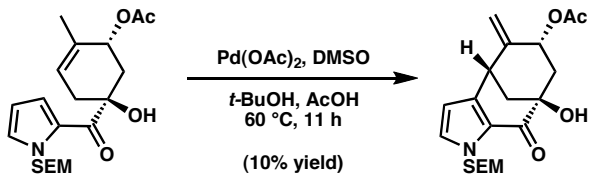
TIPS Ether 158. For representative procedures, see oxidative cyclization of **92** → **90** or **113** → **114**. Purified by preparative thin-layer chromatography (9:1 CH_2Cl_2:Et_2O eluent). R_f 0.48 (4:1 hexanes:EtOAc); R_f 0.65 (4:1 Et_2O:CH_2Cl_2); ^{1}H NMR (300 MHz, C_6D_6): δ 6.62 (d, *J* = 2.7 Hz, 1H), 6.26 (d, *J* = 10.1 Hz, 1H), 5.86 (d, *J* = 2.7 Hz, 1H), 5.06 (d, *J* = 10.1 Hz, 1H), 4.84 (app. d, *J* = 1.6 Hz, 1H), 4.73 (app. d, *J* = 1.6 Hz, 1H),

4.39–4.33 (m, 1H), 4.24 (s, 1H), 3.67–3.50 (m, 2H), 3.42 (app. t, J = 3.1 Hz, 1H), 2.62 (app. dt, J = 7.4, 4.1 Hz, 1H), 2.30 (app. dt, J = 8.1, 4.7 Hz, 1H), 2.15 (dd, J = 11.8, 3.1 Hz, 1H), 2.06 (dd, J = 14.0, 4.9 Hz, 1H), 0.98–0.71 (comp. m, 23H), –0.04 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 192.0, 148.3, 142.6, 130.6, 126.1, 113.8, 108.6, 77.0, 73.5, 72.9, 66.6, 48.6, 45.9, 40.3, 18.6 (3C), 18.6 (3C), 18.2, 12.8 (3C), –1.0 (3C); IR (film) 3475 (br), 2945, 1648, 1094, 1057 cm^{-1}; HRMS-EI (m/z): [M]$^+$ calc'd for $C_{27}H_{47}NO_4Si_2$, 505.3044; found, 505.3040; $[\alpha]^{23}_D$ +253.79° (c 0.7, C_6H_6).



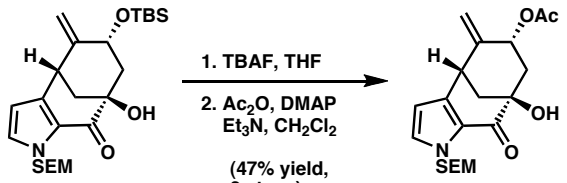
Methyl Ether 159. To allylic silyl ether **127** (10 mg, 0.02 mmol) in THF (1 mL) at 23 °C was added NaH (60% dispersion in mineral oil, 17 mg, 0.43 mmol). After stirring for 5 min, MeI (37 μL, 0.59 mmol) was added, and the reaction was stirred for 30 min. Saturated aq. NH_4Cl (2 mL) was added slowly to quench the reaction mixture, and Et_2O (1 mL) was added. The phases were partitioned, and the aqueous phase was extracted with Et_2O (2 x 1 mL). The combined organic extracts were dried over $MgSO_4$, evaporated in vacuo, and purified by flash chromatography (19:1 hexanes:EtOAc eluent) to afford methyl ether **159** (4.2 mg, 41% yield). R_f 0.51 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.78 (dd, J = 4.1, 1.7 Hz, 1H), 6.73 (dd, J = 2.5, 1.7 Hz, 1H), 6.10 (dd, J = 4.0, 2.6 Hz, 1H), 5.64 (d, J = 9.9 Hz, 1H), 5.59 (d, J = 9.9 Hz, 1H), 5.29–5.23 (m, 1H), 4.62–4.53 (m, 1H), 3.47 (t, J = 2.8 Hz, 2H), 3.14 (s, 3H), 2.77 (ddd, J = 13.7, 5.4, 2.4 Hz, 1H), 2.70–2.58 (m, 1H), 2.53–2.41 (m, 1H), 2.32 (dd, J = 13.8, 9.9 Hz, 1H),

1.84–1.80 (m, 3H), 0.97 (s, 9H), 0.84 (t, J = 7.8 Hz, 2H), 0.09 (s, 6H), –0.08 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 193.7, 137.6, 130.4, 129.2, 122.4, 119.8, 109.5, 85.8, 78.3, 69.6, 66.4, 52.6, 38.8, 34.9, 26.4 (3C), 20.3, 18.6, 18.3, –1.0 (3C), –3.8, –4.4; IR (film) 2953, 2930, 2857, 1644, 1412, 1250, 1078 cm^{-1}; HRMS-EI (m/z): [M]$^+$ calc'd for $C_{25}H_{45}NO_4Si_2$, 479.2887; found, 479.2887; $[\alpha]^{27}_D$ +7.38° (c 0.6, C_6H_6).



147 *160*

[3.3.1] Bicycle 160. For representative procedures, see oxidative cyclization of **92** → **90** or **113** → **114**. A 10% yield of **160** was obtained based on ^{1}H NMR integration relative to benzothiazole as an internal standard. An analytical sample of **160** was prepared as follows:



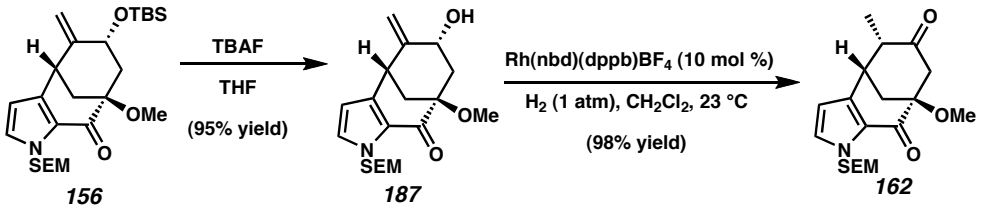
128 *160*

To silyl ether **128** (10.4 mg, 0.02 mmol) in THF (1 mL) was added TBAF (1.0 M in THF, 75 μL, 0.075 mmol) dropwise over 1 min at 23 °C. After 23 h, the reaction was quenched by the addition of saturated aq. NH_4Cl (1 mL). The aqueous layer was extracted with EtOAc (4 x 1 mL), and the combined organics were dried over $MgSO_4$ and evaporated in vacuo. Purification of the crude product by preparative thin-layer

chromatography (1:1 hexanes:EtOAc eluent) afforded the crude diol, which was used in the subsequent reaction. R_f 0.09 (7:3 hexanes:EtOAc).

To a vial containing the crude diol in CH_2Cl_2 (1.1 mL) was added DMAP (2.2 mg, 0.02 mmol) and Et_3N (31 μL, 0.22 mmol), followed by Ac_2O (31 μL, 0.33 mmol). The vial was sealed and heated at 50 °C for 40 min. The reaction was allowed to cool to 23 °C, and saturated aq. $NaHCO_3$ (1 mL) was added. The aqueous layer was extracted with EtOAc (4 x 1 mL), and the combined organics were dried over $MgSO_4$ and evaporated in vacuo. Purification of the residue by preparative thin-layer chromatography (7:3 hexanes:EtOAc) afforded [3.3.1] bicycle **160** (4.1 mg, 47% yield, 2 steps) as a colorless oil. R_f 0.22 (7:3 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 6.53 (d, *J* = 2.3 Hz, 1H), 5.73 (d, *J* = 2.3 Hz, 1H), 5.53 (d, *J* = 10.1 Hz, 1H), 5.49–5.45 (m, 1H), 5.39 (d, *J* = 10.1 Hz, 1H), 5.12 (d, *J* = 1.4 Hz, 1H), 4.92 (d, *J* = 1.8 Hz, 1H), 4.20 (s, 1H), 3.67–3.52 (m, 2H), 3.33–3.29 (m, 1H), 2.50 (app. dt, *J* = 7.7, 4.0 Hz, 1H), 2.12 (ddd, *J* = 14.7, 2.7, 1.8 Hz, 1H), 2.04 (dd, *J* = 12.1, 3.0 Hz, 1H), 1.96 (dd, *J* = 14.7, 5.5 Hz, 1H), 1.35 (s, 3H), 0.91–0.85 (m, 2H), –0.04 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6): δ 191.4, 169.0, 143.6, 142.3, 131.2, 126.1, 117.5, 108.2, 76.8, 73.1, 72.9, 66.7, 44.5, 44.0, 40.0, 20.8, 18.3, –1.0 (3C); IR (film) 3471 (br), 2951, 1738, 1650, 1231, 1094 cm^{-1}; HRMS-EI (*m*/*z*): $[M]^+$ calc'd for $C_{20}H_{29}NO_5Si$, 391.1815; found, 391.1800; $[\alpha]^{24}_D$ +396.32° (*c* 0.5, C_6H_6).

[3.3.1] Bicycle 161. For representative procedures, see oxidative cyclization of **92** → **90** or **113** → **114**. Purified by preparative thin-layer chromatography (4:1 hexanes:EtOAc eluent). R_f 0.55 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.51–7.48 (m, 1H), 7.48–7.46 (m, 1H), 7.27–7.21 (m, 1H), 7.08–7.02 (m, 1H), 6.63 (d, *J* = 10.7 Hz, 1H), 5.59 (d, *J* = 10.7 Hz, 1H), 4.89 (app. d, *J* = 1.4 Hz, 1H), 4.68 (app. d, *J* = 1.7 Hz, 1H), 4.20–4.15 (m, 1H), 4.13 (s, 1H), 3.79–3.58 (comp. m, 3H), 2.69 (app. dt, *J* = 7.6, 4.0 Hz, 1H), 2.23 (dd, *J* = 11.8, 3.0 Hz, 1H), 2.20–2.12 (m, 1H), 2.09–2.01 (m, 1H), 1.03–0.79 (m, 2H), 0.51 (s, 9H), –0.07 (s, 9H), –0.25 (s, 3H), –0.69 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6, 27/28 C): δ 195.3, 147.4, 141.4, 134.7, 129.8, 127.8, 121.8, 121.6, 113.8, 112.4, 74.1, 73.7, 72.9, 66.2, 48.6, 45.2, 38.1, 25.7 (3C), 18.2, 18.1, –1.0 (3C), –5.0, –5.3; IR (film) 3475 (br), 2951, 1656, 1250, 1061 cm^{-1}; HRMS-EI (*m*/*z*): $[M]^+$ calc'd for $C_{28}H_{43}NO_4Si_2$, 513.2731; found, 513.2730; $[\alpha]^{24}_D$ +216.18° (*c* 0.25, C_6H_6).

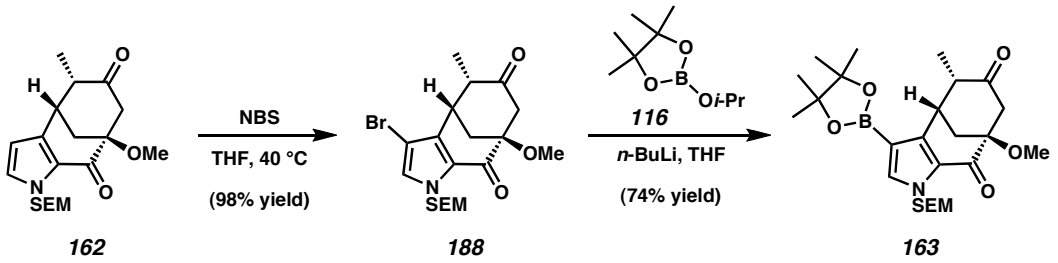


Ketone 162. To methyl ether **156** (120 mg, 0.25 mmol) in THF (12.5 mL) was added TBAF (1.0 M in THF, 750 μL, 0.75 mmol). The reaction mixture was stirred for 4 h, quenched with saturated aq. NH_4Cl (10 mL), diluted with H_2O (5 mL), and extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with brine (15

mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash chromatography (1:1 hexanes:EtOAc eluent) to furnish allylic alcohol **187** (86 mg, 95% yield) as a pale yellow oil. R_f 0.12 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 6.60 (d, *J* = 2.8 Hz, 1H), 5.81 (d, *J* = 2.8 Hz, 1H), 5.64 (d, *J* = 10.2 Hz, 1H), 5.58 (d, *J* = 10.2 Hz, 1H), 4.80 (d, *J* = 1.7 Hz, 1H), 4.64 (d, *J* = 1.7 Hz, 1H), 4.15–4.09 (m, 1H), 3.68–3.59 (m, 2H), 3.42 (t, *J* = 3.2 Hz, 1H), 3.36 (s, 3H), 2.72 (app. dt, *J* = 7.4, 3.9 Hz, 1H), 2.58 (app. dt, *J* = 8.1, 4.9 Hz, 1H), 1.89 (dd, *J* = 14.2, 5.1 Hz, 1H), 1.65 (dd, *J* = 11.6, 3.0 Hz, 1H), 0.97–0.88 (m, 2H), 0.59 (d, *J* = 3.9 Hz, 1H), –0.03 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6, 18/19 C): δ 189.4, 149.4, 140.6, 130.4, 113.8, 107.4, 78.9, 76.7, 72.0, 66.2, 51.6, 44.3, 41.1, 39.5, 18.4, –0.9 (3C); IR (film): 3460 (br), 2951, 1659, 1424, 1248, 1111, 1023 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+$ calc'd for $C_{19}H_{30}NO_4Si$, 364.1944; found, 364.1942; $[\alpha]^{24}_D$ +330.71° (*c* 1.0, C_6H_6).

Allylic alcohol **187** (44.0 mg, 0.121 mmol) and freshly prepared Rh(nbd)(dppb)BF_4 (8.6 mg, 0.0121 mmol)[69] were combined under a glovebox atmosphere. The reaction vessel was carefully sealed and removed from the glovebox. CH_2Cl_2 (12.0 mL) was added, and a balloon of H_2 (1 atm) was applied without purging. After 3 h of stirring, the reaction mixture was filtered over a plug of silica gel (CH_2Cl_2, then 2:1 hexanes:EtOAc eluent) to afford ketone **162** (43.0 mg, 98% yield) as a colorless oil. R_f 0.30 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 6.53 (d, *J* = 2.5 Hz, 1H), 5.66 (d, *J* = 2.5 Hz, 1H), 5.50 (d, *J* = 10.5 Hz, 1H), 5.36 (d, *J* = 10.2 Hz, 1H), 3.57–3.38 (m, 2H), 3.34 (s, 3H), 2.98 (dd, *J* = 14.3, 2.5 Hz, 1H), 2.70–2.64 (m, 1H), 2.57–2.47 (m, 1H), 2.43 (d, *J* = 14.3 Hz, 1H), 2.11–1.99 (m, 1H), 1.69 (dd, *J* = 12.2, 2.6 Hz, 1H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.84 (t, *J* = 8.0 Hz, 2H), –0.03 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6): δ

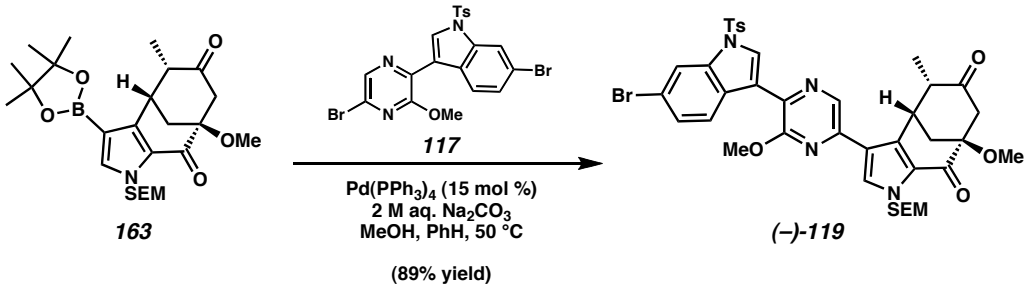
205.7, 187.9, 137.5, 131.1, 126.6, 109.7, 82.9, 76.8, 66.4, 52.7, 52.3, 48.1, 41.0, 37.7, 18.3, 13.0, –1.0 (3C); IR (film): 2952, 2931, 1716, 1660, 1421, 1123, 1097, 1076 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+$ - H_2 calc'd for $C_{19}H_{28}NO_4Si$, 362.1788; found, 362.1778; $[\alpha]^{27}_D$ +163.23° (*c* 1.0, C_6H_6).



Boronic Ester 163. A flask wrapped in aluminum foil at 23 °C was charged with ketone **162** (25 mg, 0.0689 mmol), THF (5 mL), and freshly recrystallized NBS (37.5 mg, 0.211 mmol). The reaction vessel was placed in a 40 °C oil bath, stirred for 15 min, then cooled to 0 °C. The reaction was quenched with saturated aq. $Na_2S_2O_3$ (10 mL), diluted with H_2O (5 mL), and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and evaporated under reduced pressure to afford the crude product. Further purification by flash column chromatography (3:1 hexanes:EtOAc eluent) afforded bromide **188** (29.9 mg, 98% yield) as a colorless oil. R_f 0.45 (2:1 hexanes:EtOAc).

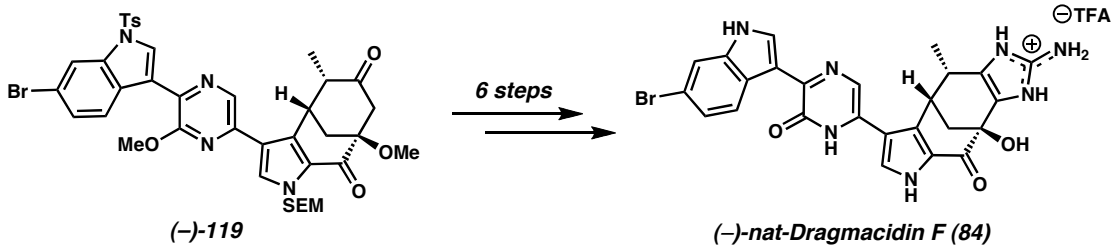
To bromide **188** (27 mg, 0.061 mmol) and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**116**, 510 μL, 2.5 mmol) in THF (7 mL) at –78 °C was added *n*-BuLi (2.5 M in hexanes, 730 μL, 0.183 mmol) dropwise over 3 min. After stirring for an additional 10 min at –78 °C, the reaction mixture was quenched with saturated aq. NH_4Cl (7 mL), warmed to 23 °C, diluted with H_2O (10 mL), and extracted with EtOAc (3 x 20

mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$ and evaporated under reduced pressure to afford the crude product. Further purification by flash column chromatography (3:1 hexanes:EtOAc eluent) afforded boronic ester **163** (22 mg, 74% yield) as a colorless oil. R_f 0.42 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.37 (s, 1H), 5.46 (d, *J* = 10.2 Hz, 1H), 5.33 (d, *J* = 10.2 Hz, 1H), 3.77–3.72 (m, 1H), 3.49–3.38 (m, 2H), 3.31 (s, 3H), 3.03 (dd, *J* = 14.0, 2.8 Hz, 1H), 2.61–2.53 (m, 1H), 2.47 (d, *J* = 13.8 Hz, 1H), 2.36–2.25 (m, 1H), 1.78 (dd, *J* = 12.4, 3.0 Hz, 1H), 1.24 (d, *J* = 6.6 Hz, 3H), 1.12 (s, 12H), 0.84–0.77 (m, 2H), –0.05 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6, 23/25 C): δ 206.4, 188.3, 144.6, 140.0, 83.6 (2C), 83.1, 77.1, 66.5, 52.9, 52.3, 49.0, 41.4, 37.1, 25.3 (2C), 25.2 (2C), 18.3, 13.0, –0.9 (3C); IR (film) 2977, 2951, 1718, 1664, 1543, 1399, 1322, 1263, 1145, 1092, 1074; HRMS-FAB (*m*/*z*): [M + H]$^+$ calc'd for $C_{25}H_{41}NO_6SiB$, 490.2796; found, 490.2800; $[\alpha]^{29}_D$ +50.77° (*c* 0.4, C_6H_6).



Pyrazine (–)-119. A vial charged with bromopyrazine **117** (29.6 mg, 0.055 mmol), boronic ester **163** (18 mg, 0.0368 mmol), and tetrakis(triphenylphosphine)palladium(0) (6.4 mg, 0.0055 mmol) was evacuated and purged with N_2. Deoxygenated benzene (735 μL), deoxygenated methanol (150 μL), and deoxygenated 2 M aq. Na_2CO_3 (61 μL) were then added. The reaction vessel was sealed, heated to 50 °C for 72 h, cooled to 23 °C, then quenched by the addition of Na_2SO_4 (200

mg). Following filtration over a pad of silica gel (3:1 EtOAc:hexanes eluent) and evaporation to dryness under reduced pressure, the residue was purified by flash column chromatography (2:1 → 1:1 hexanes:EtOAc eluent) to afford pyrazine (–)-**119** (26.8 mg, 89% yield) as a yellow foam. R_f, ^{1}H NMR, ^{13}C NMR, HRMS, and IR characterization data for (+)-**119** are reported earlier in this section. $[\alpha]^{27}_D$ –72.92° (*c* 1.0, $CHCl_3$).



(–)-Dragmacidin F (84). Pyrazine (–)-**119** was converted to (–)-dragmacidin F (**84**) by methods described earlier in this section. ^{1}H NMR, ^{13}C NMR, HRMS, and IR characterization data for (+)-**84** are also reported above. $[\alpha]^{29}_D$ –148.33° (*c* 0.20, MeOH). For comparison, natural (–)-dragmacidin F (**84**): $[\alpha]^{25}_D$ –159° (*c* 0.40, MeOH).[4c]

3.7 Notes and References

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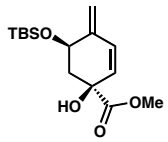
from loss of $^{-}$OAc. In stark contrast, exposure of **97** to heterogeneous reductive isomerization conditions did not produce any of these compounds (see Scheme 3.4.2).



iv

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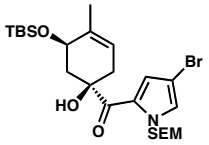
(22) For the discovery and use of SEM pyrrole, see: (a) Edwards, M. P.; Ley, S. V.; Lister, S. G.; Palmer, B. D. *J. Chem. Soc., Chem. Commun*. **1983**, 630–633. (b) Muchowski, J. M.; Solas, D. R. *J. Org. Chem*. **1984**, *49*, 203–205. (c) Edwards, M. P.; Ley, S. V.; Lister, S. G.; Palmer, B. D.; Williams, D. J. *J. Org. Chem*. **1984**, *49*, 3503–3516. (d) Edwards, M. P.; Doherty, A. M.; Ley, S. V.; Organ, H. M. *Tetrahedron* **1986**, *42*, 3723–3729.

(23) During the conversion of **101** to **91**, 2,4-disubstituted pyrrole **v** was formed as a byproduct.

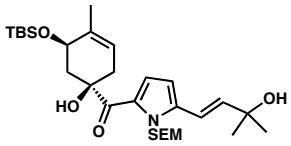


v

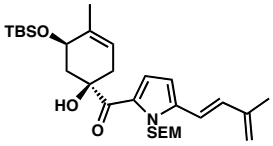
(24) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989–7000.

(25) By conducting reactions in THF-d_8, it was possible to monitor Heck reactions by ^{1}H NMR.

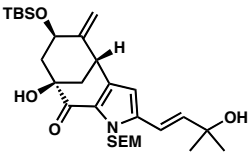
(26) The use of *t*-amyl alcohol in the cyclization of **92** → **90** led to the formation of byproducts such as **vi**, **vii**, and **viii**. Additionally, simply re-exposing **90** to the *t*-amyl alcohol-based reaction conditions, led to the formation of **viii**.



vi



vii



viii

(27) This reaction was performed using stoichiometric $Pd(OAc)_2$. The atmosphere of dioxygen seemed to enhance the overall conversion, but this reaction also proceeded under an inert atmosphere. In either case, the formation of Pd black was observed.

(28) Although pyridine and ethyl nicotinate failed to perform in this cyclization, employing more electron-deficient pyridines (such as 3,4,5–trihalogenated pyridines) led to production of desired bicycle **90**.

(29) DMSO has commonly been employed in oxidative Pd(II) chemistry. See: (a) Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298–5300. (b) Van Benthem, R. A. T. M.; Hiemstra, H.; Michels, J. J.; Speckamp, W. N. *J. Chem. Soc., Chem. Commun.* **1994**, 357–359. (c) Rönn, M.; Bäckvall, J.-E.; Andersson, P. G. *Tetrahedron Lett.* **1995**, *36*, 7749–7752. (d) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346–1347. (e) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400–3420. See also references therein.

(30) Gilow, H. M.; Hong, Y. H.; Millirons, P. L.; Snyder, R. C.; Casteel, W. J., Jr. *J. Heterocycl. Chem.* **1986**, *23*, 1475–1480.

(31) Reactions conducted in the presence of acetic acid-*d* led to deuterium incorporation in the pyrrole ring of both the starting material (**92**) and the product (**90**), mostly at C(4).

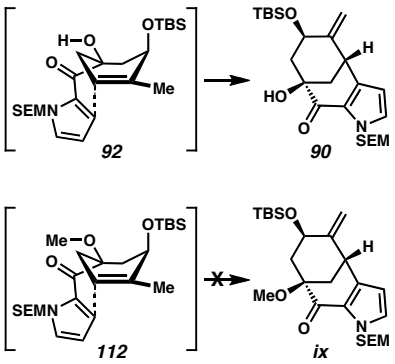
(32) The instability of pyrroles to oxidants is well known. See: (a) Ciamician, G.; Silber, P. *Chem. Ber.* **1912**, *45*, 1842–1845. (b) Bernheim, F.; Morgan, J. E. *Nature* **1939**, *144*, 290. (c) Chierici, L.; Gardini, G. P. *Tetrahedron* **1966**, *22*, 53–56.

(33) The instability of the starting material and product to oxidation was confirmed by a series of control experiments wherein aliquots of reactions were carefully monitored by ^{1}H NMR analysis using benzothiazole as an internal standard. In the presence of oxidants, substantial non-specific decomposition readily occurred.

(34) Recently, related oxidative cyclizations of pyrrole substrates have been reported. See: (a) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Paladino, G. *Tetrahedron* **2005**, *61*, 1077–1082. (b) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528–2529.

(35) Direct oxidation of starting material to the corresponding enone was observed.

(36) The lack of reactivity of the 3° methyl ether substrate (**112**) vs. **92** may be due to the transition state. In order to form bicycle **90**, a nearly coplanar arrangement between the tertiary alcohol and the carbonyl of **92** is required, which may also be facilitated via an intramolecular hydrogen bond. In the case of the tertiary methyl ether (**112**), the additional steric bulk of the methyl group may disfavor this orientation.



(37) The Heck route required the use of 2,3-dibromopyrrole, an extremely unstable compound. For a discussion regarding the instability of bromopyrroles, see: Audebert, P.; Bidan, G. *Synthetic Metals* **1986**, *15*, 9–22.

(38) In preliminary investigations, late-stage chemistry in the presence of a reactive 3° alcohol was unsuccessful.

(39) Neber, P. W.; Friedolsheim, A. V. *Justus Liebigs Ann. Chem.* **1926**, *449*, 109–134.

(40) (a) For a review, see: O'Brien, C. *Chem. Rev.* **1964**, *64*, 81–89. (b) For a recent study involving the Neber rearrangement, see: Ooi, T.; Takahashi, M.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2002**, *124*, 7640–7641.

(41) (a) Purified by reversed-phase chromatography using trifluoroacetic acid in the eluent. (b) See *3.6 Experimental Section* for details.

(42) Derivatives of **120** bearing a free 3° alcohol or a TMS-protected 3° alcohol produced complex mixtures of products when subjected to Neber rearrangement conditions.

(43) Acid-promoted dimerization of the amino ketone functionalities was not observed.

(44) (a) Woodward reported a Neber rearrangement during synthetic studies involving lysergic acid. Unfortunately, the Neber rearrangement product could not be further utilized in the synthesis. See: Kornfeld, E. C.; Fornefeld, E. J.; Kline, G. B.; Mann, M. J.; Morrison, D. E.; Jones, R. G.; Woodward, R. B. *J. Am. Chem. Soc.* **1956**, *78*, 3087–3114. (b) For the use of the Neber rearrangement in drug discovery, see: Chung, J. Y. L.; Ho, G.-J.; Chartrain, M.; Roberge, C.; Zhao, D.; Leazer, J.; Farr, R.; Robbins, M.; Emerson, K.; Mathre, D. J.; McNamara, J. M.; Hughes, D. L.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **1999**, *40*, 6739–6743.

(45) The intermediacy of azirines in Neber rearrangements is well accepted. These azirines presumably arise from transient nitrenes. See: (a) House, H. O.; Berkowitz, W. F. *J. Org. Chem.* **1963**, *28*, 307–311. (b) House, H. O.; Berkowitz, W. F. *J. Org. Chem.* **1963**, *28*, 2271–2276.

(46) Hemiaminal **124** has been isolated and characterized by ^{1}H NMR.

(47) Boehm, J. C.; Gleason, J. G.; Pendrak, I.; Sarau, H. M.; Schmidt, D. B.; Foley, J. J.; Kingsbury, W. D. *J. Med. Chem.* **1993**, *36*, 3333–3340.

(48) Dragmacidin numbering convention, see reference 4c.

(49) (a) (+)-Quinic acid ((+)-**93**) is commercially available in limited quantities from Interbioscreen Ltd. (50 mg/$305 USD). (b) (+)-Quinic acid ((+)-**93**) potentially

could be prepared via multistep synthesis by applying methods used for the preparation of (–)-quinic acid (**93**). See: Rapado, L. P.; Bulugahapitiya, V.; Renaud, P. *Helv. Chim. Acta* **2000**, *83*, 1625–1632 and references therein. (c) Enantiopure (–)-quinic acid (**93**) can also be racemized. See: Grewe, R.; Lorenzen, W.; Vining, L. *Chem. Ber.* **1954**, *87*, 793–802.

(50) Surprisingly, despite its widespread use in natural product synthesis and its near symmetry, (–)-quinic acid (**93**) has rarely been used in an enantiodivergent manner. For examples, see: (a) Ulibarri, G.; Nadler, W.; Skrydstrup, T.; Audrain, H.; Chiaroni, A.; Riche, C.; Grierson, D. S. *J. Org. Chem.* **1995**, *60*, 2753–2761. (b) Ulibarri, G.; Audrain, H.; Nadler, W.; Lhermitte, H.; Grierson, D. S. *Pure Appl. Chem.* **1996**, *68*, 601–604. (c) Barros, M. T.; Maycock, C. D.; Ventura, M. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 166–173.

(51) If R = R', **126** is considered to be pseudo-C_2-symmetric. Pseudo-C_2-symmetric molecules are those that would be C_2-symmetric if they did not contain a central chirotopic, nonstereogenic center. For discussions, see: (a) Schreiber, S. L. *Chem. Scr.* **1987**, *27*, 563–566. (b) Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9–17. (c) Magnuson, S. R. *Tetrahedron* **1995**, *51*, 2167–2213. (d) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1994.

(52) Olefin **97** was also exposed to the reaction conditions used for the reductive isomerization of **95** to **96**. Only trace quantities of **129** were produced under those conditions.[41b,53b]

(53) (a) Yield determined based on ^{1}H NMR integration. (b) The material isolated was predominantly a mixture of diastereomeric olefin hydrogenation products.

(54) The favored conformation of **97** depicted in Scheme 3.4.2 is consistent with ^{1}H NMR studies.[41b]

(55) ^{1}H NMR experiments show that the C(3) silyl ether of **132** is axially disposed.[41b] For similar examples of axial-selective TBS cleavage promoted by TBAF, see: (a) Craig, B. N.; Janssen, M. U.; Wickersham, B. M.; Rabb, D. M.; Chang, P. S.; O'Leary, D. J. *J. Org. Chem.* **1996**, *61*, 9610–9613. (b) Meier, R.-M.; Tamm, C. *Helv. Chim. Acta*, **1991**, *74*, 807–818.

(56) For a classic example involving the use of conformational analysis to solve stereochemical problems in total synthesis, see: Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *Tetrahedron* **1958**, *2*, 1–57.

(57) Isolated examples of similar reactivity using Pd/C, H_2 and a protic solvent have been reported in the literature, see: (a) Paulson, D. R.; Gilliam, L. S.; Terry, V. O.; Farr, S. M.; Parker, E. J.; Tang, F. Y. N.; Ullman, R.; Ribar, G. *J. Org. Chem.* **1978**,

43, 1783–1787. (b) Dauben, W. G.; Hance, P. D. *J. Am. Chem. Soc.* **1955**, *77*, 2451–2453. (c) Dauben, W. G.; Hayes, W. K.; Schwarz, J. S. P.; McFarland, J. W. *J. Am. Chem. Soc.* **1960**, *82*, 2232–2238.

(58) Complete deuterium incorporation was observed at the internal allylic positions by ^{1}H and ^{2}H NMR (See Scheme 3.4.4). Although nearly complete deuterium incorporation was observed at the exocyclic methyl group, this may only be occurring after initial reductive isomerization. See reference 59.

(59) Control experiments demonstrate that the deuterium incorporation at the exocyclic methyl group can happen after the reductive isomerization has occurred. The stereochemistry of the deuterium in **136** was elucidated by ^{1}H NMR homonuclear decoupling and NOESY-1D experiments.

(60) Conducting this experiment in the presence of **95** did not lead to consumption of **137**.

(61) Few examples of heterogeneous Pd/C-mediated allylic substitution have been reported, see: (a) Bergbreiter, D. E.; Chen, B. *J. Chem. Soc, Chem. Commun.* **1983** 1238–1239. (b) Felpin, F.-X.; Landais, Y. *J. Org. Chem.* **2005**, *70*, 6441–6446.

(62) (a) Sajiki, H.; Kume, A.; Hattori, K.; Hirota, K. *Tetrahedron Lett.* **2002**, *43*, 7247–7250. (b) Ishizaki, M.; Yamada, M.; Watanabe, S.-i.; Hoshino, O.; Nishitani, K.; Hayashida, M.; Tanaka, A.; Hara, H. *Tetrahedron* **2004**, *60*, 7973–7981.

(63) Simple control experiments suggest that the presence of TCNE does not prevent the direct reduction of olefins from occurring.

(64) With the exception of **138** (entry 10), all of the compounds in Table 3.4.1 are enantiopure.

(65) The major product in this reaction resulted from direct hydrogenation of the olefin moiety and was formed as a mixture of diastereomers.

(66) No reductive isomerization product could be isolated from this reaction.

(67) The absolute stereochemistry of **138** (entry 10) depicted is shown by analogy to the other products in Table 3.4.1.

(68) The three-dimensional conformations of **97** and **142** were ascertained by ^{1}H NMR homonuclear decoupling and NOESY-1D experiments.

(69) Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190–203.

(70) Bergens, S. H.; Bosnich, B. *J. Am. Chem. Soc.* **1991**, *113*, 958–967.

(71) Xiao, W. *Huaxue Shiji* **1992**, *14*, 363–366.

(72) Bailey, D. M.; Johnson, R. E. *J. Med. Chem.* **1973**, *16*, 1300–1302.

(73) The synthesis of allylic alcohol **111** is described on p. 96.

(74) (a) Liu, Y.; Gribble, G. W. *J. Nat. Prod.* **2002**, *65*, 748–749. (b) Bergman, J.; Venemalm, L. *J. Org. Chem.* **1992**, *57*, 2495–2497.

(75) Claridge, T. D. W. in *High-Resolution NMR Techniques in Organic Chemistry*; Pergamon: Amsterdam, 1999; pp. 320–326.

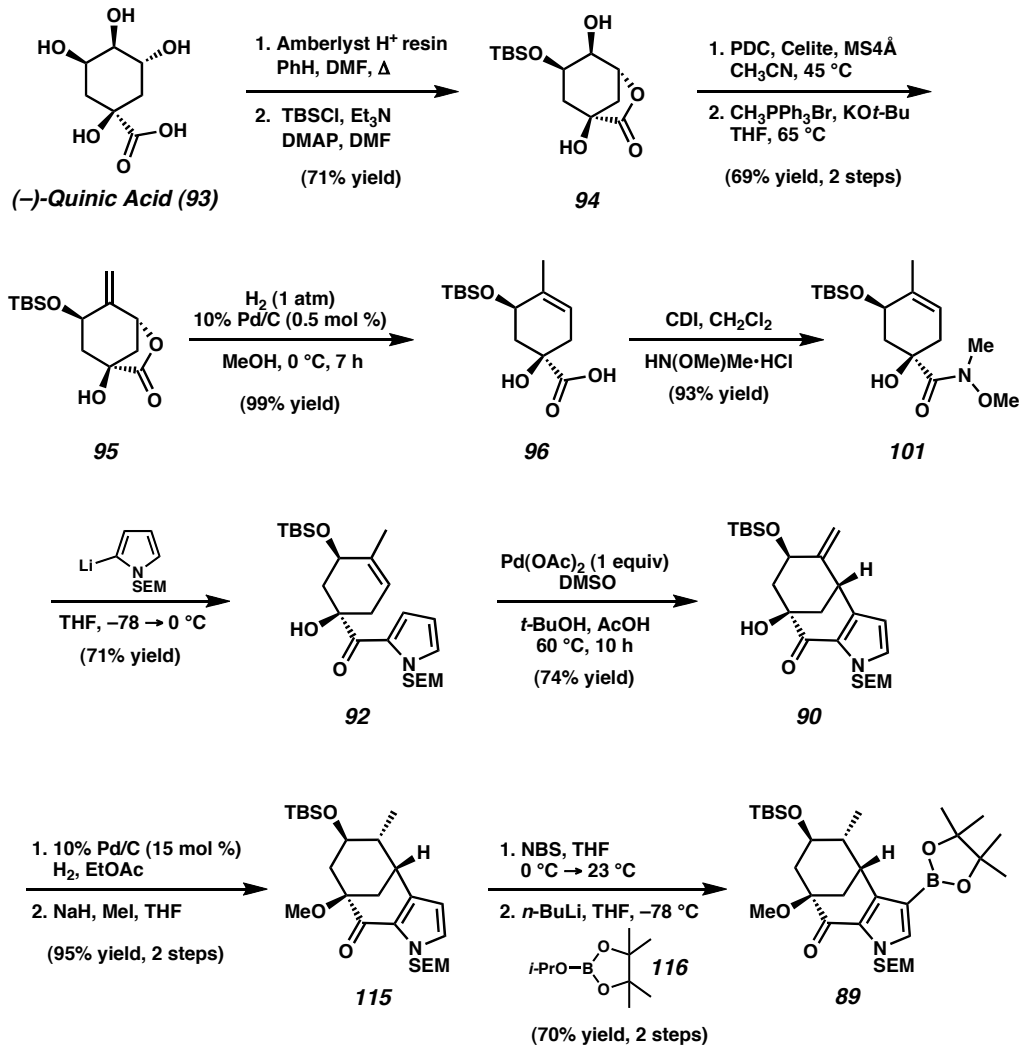
(76) The synthesis of acetoxycarbonate **144** is described on p. 96.

(77) Tsuji, J; Minami, I; Shimizu, I. *Synthesis* **1986**, 623–627.

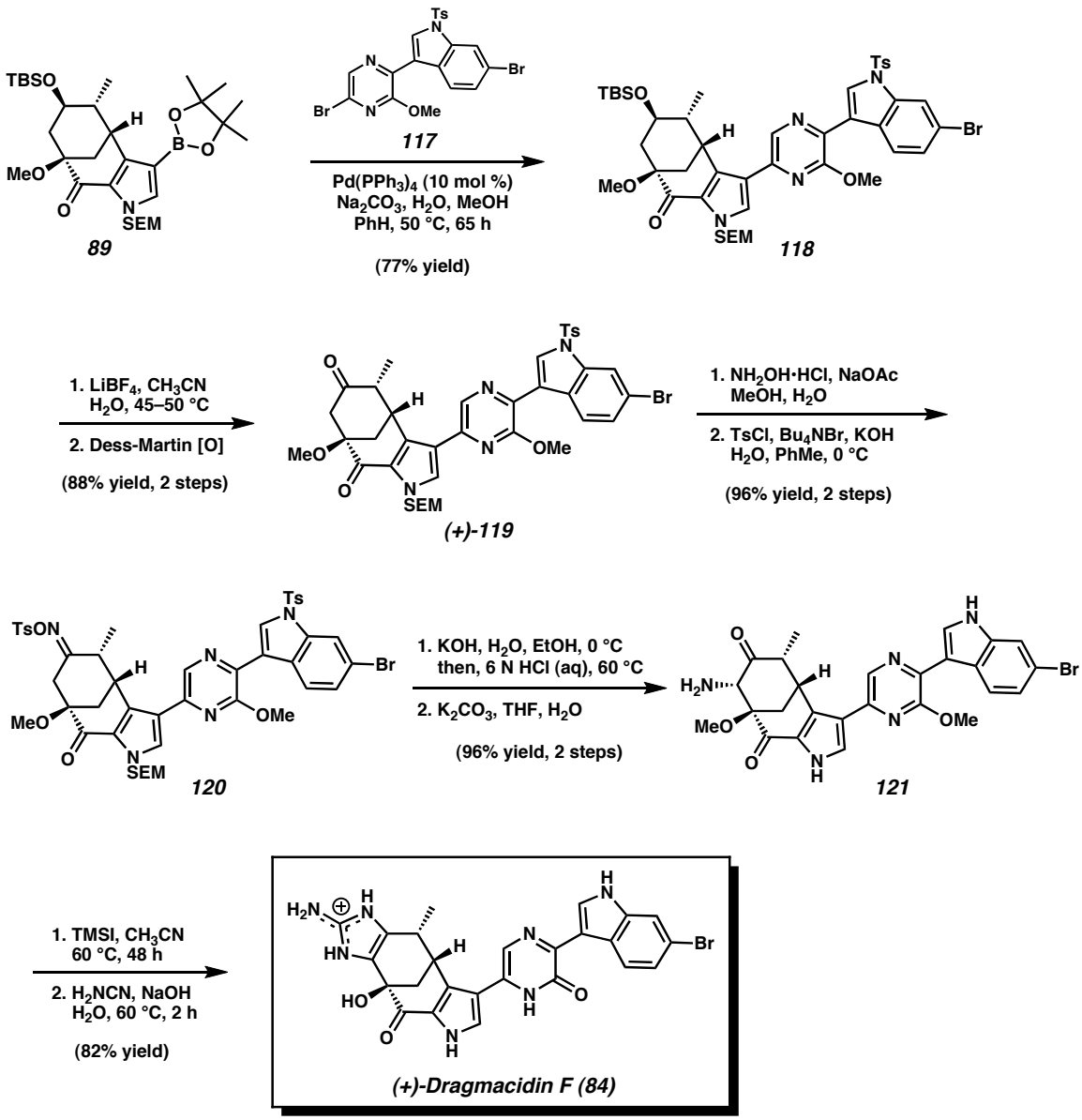
APPENDIX TWO

Synthetic Summary for (+)- and (–)-Dragmacidin F (84)

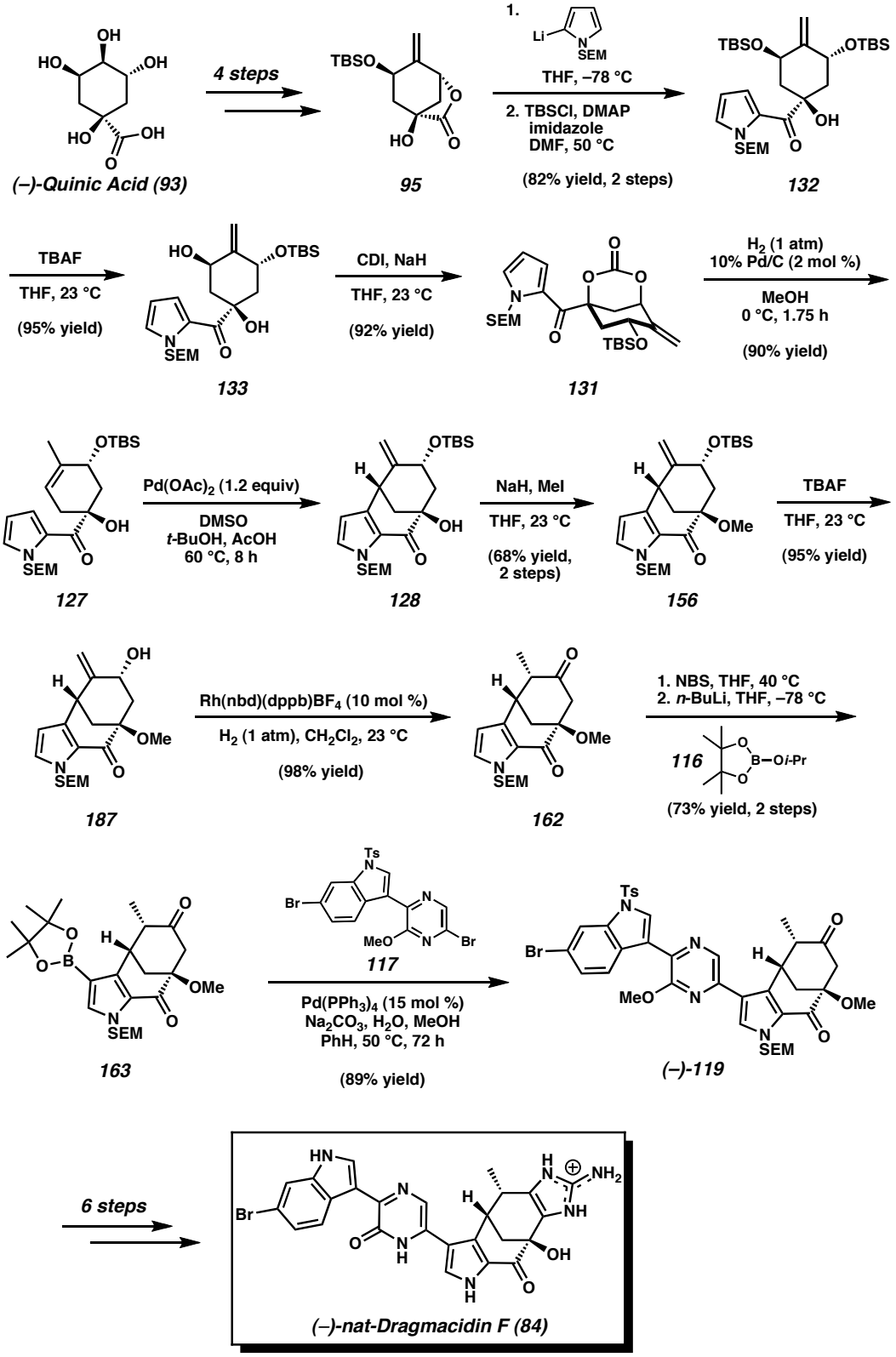
Scheme A2.1 The synthesis of boronic ester **89**



Scheme A2.2 The synthesis of (+)-dragmacidin F (**84**)



Scheme A2.3 The synthesis of (–)-dragmacidin F (**84**)



APPENDIX THREE

Spectra Relevant to Chapter Three:

The Total Syntheses of (+)- and (–)-Dragmacidin F

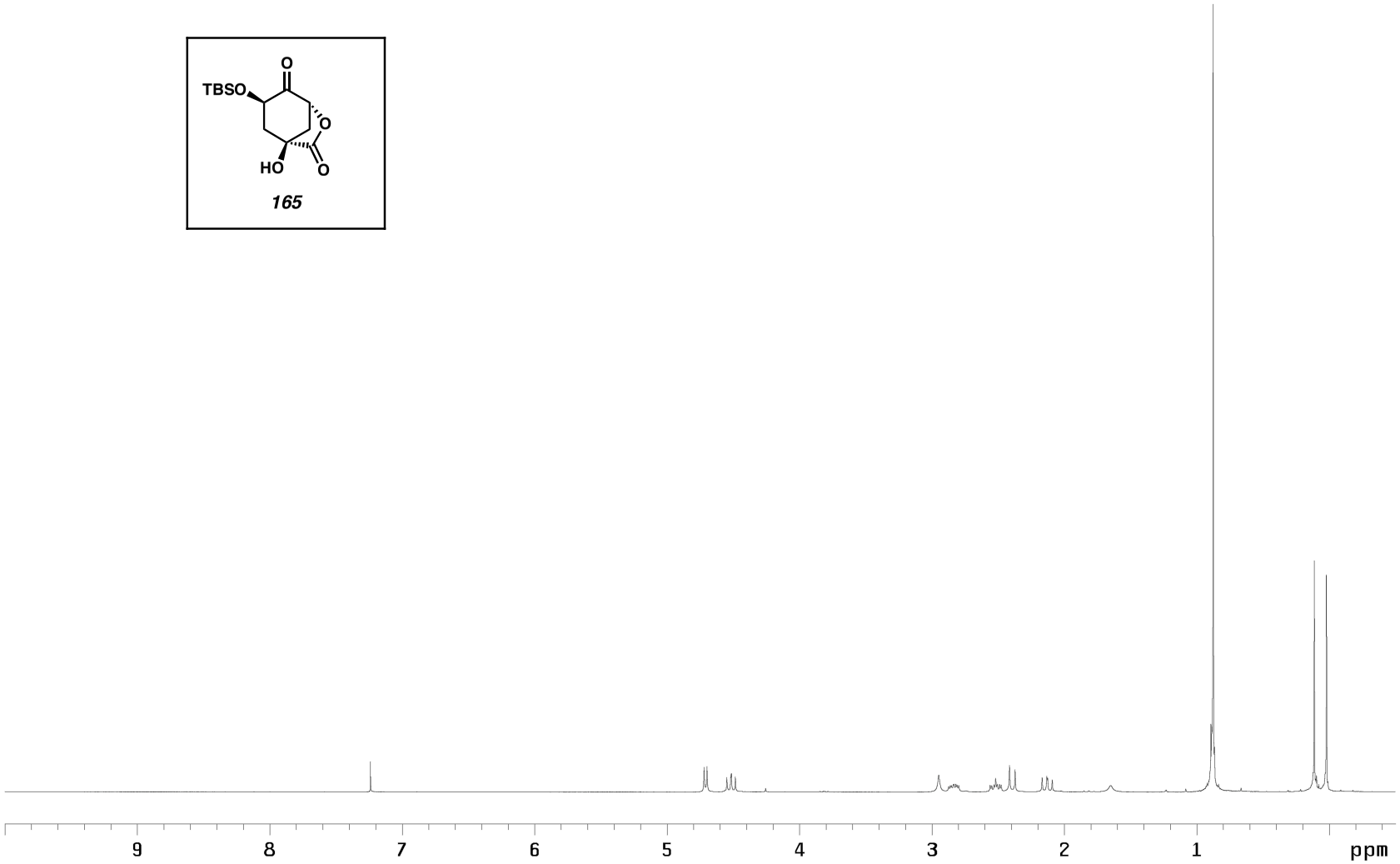


Figure A3.1 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **165**

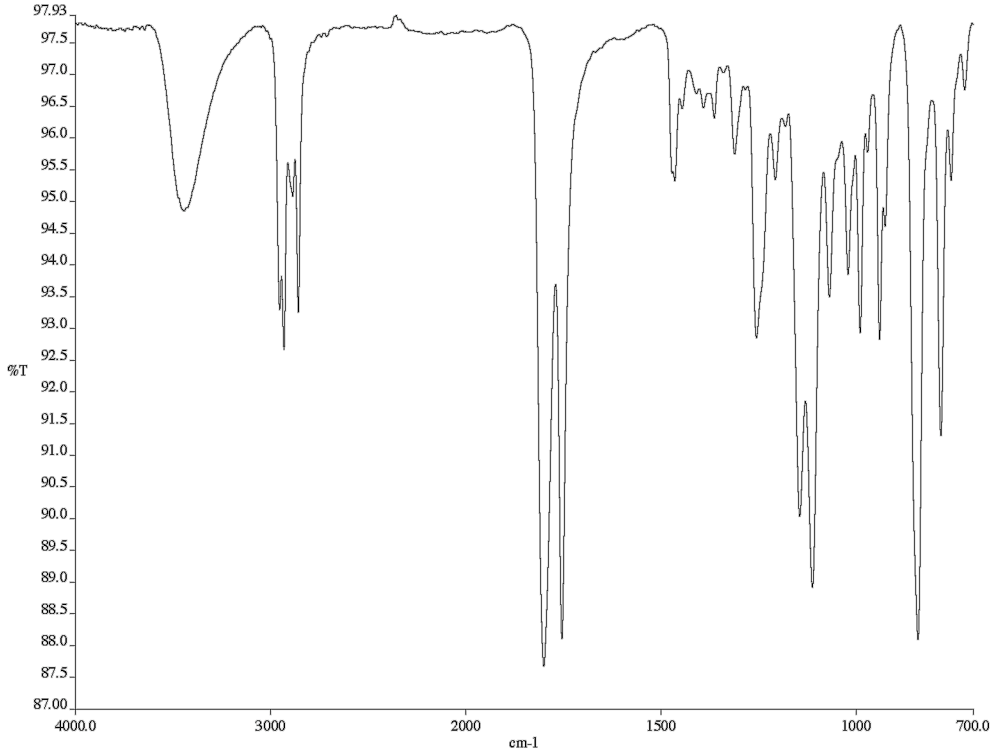


Figure A3.2 Infrared spectrum (thin film/NaCl) of compound **165**

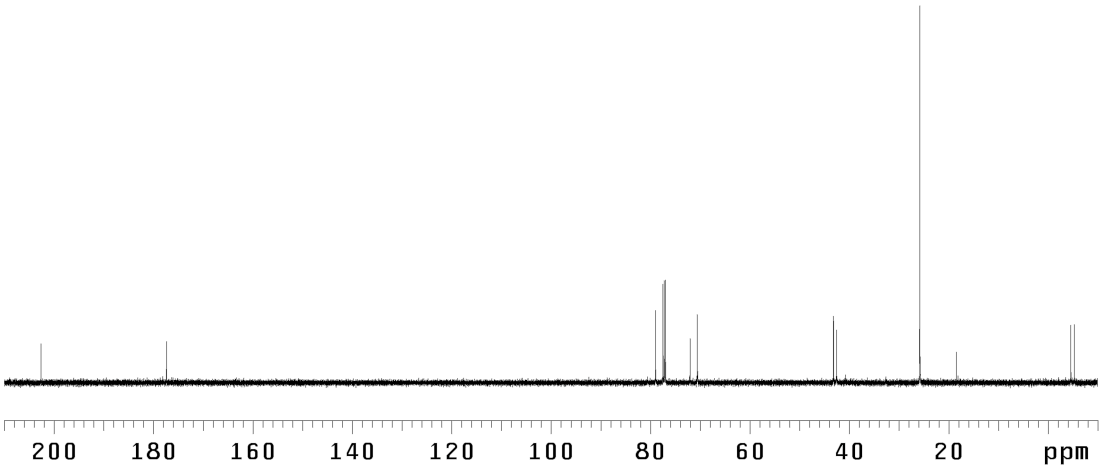


Figure A3.3 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **165**

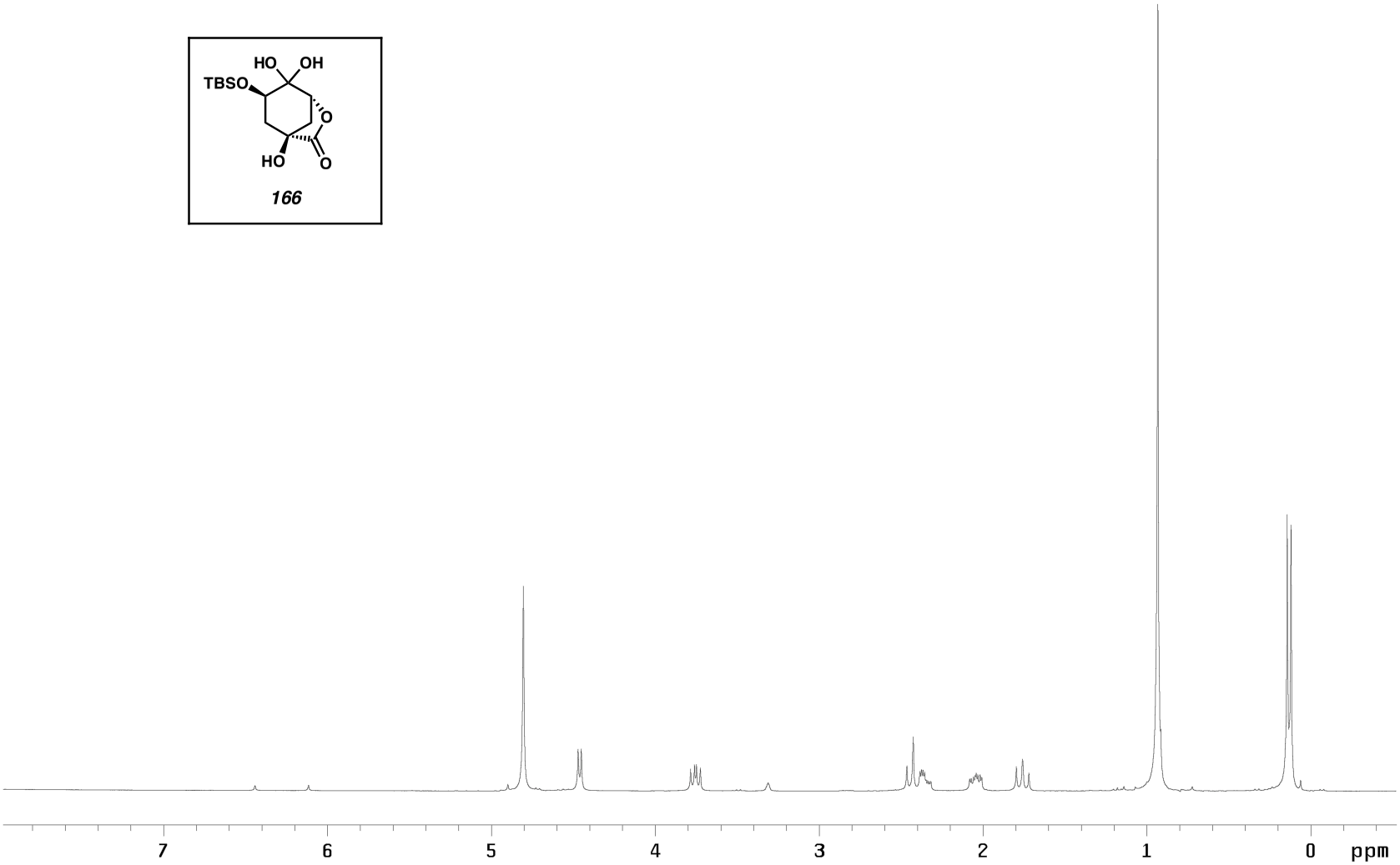


Figure A3.4 ^{1}H NMR (300 MHz, CD_3OD) of compound **166**

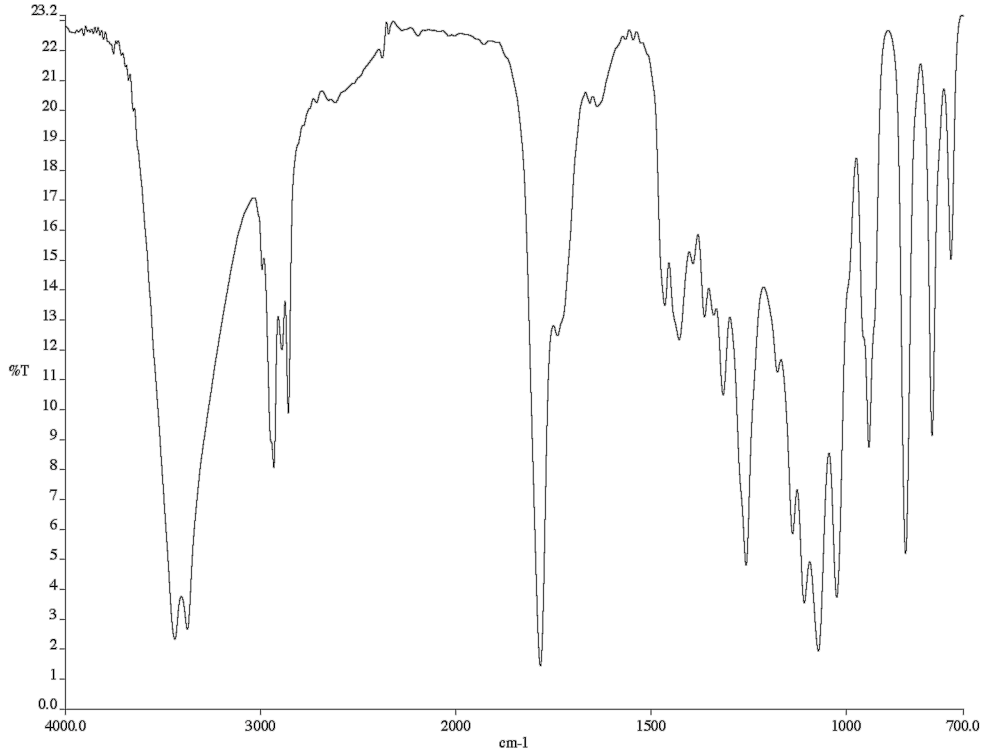


Figure A3.5 Infrared spectrum (KBr pellet) of compound **166**

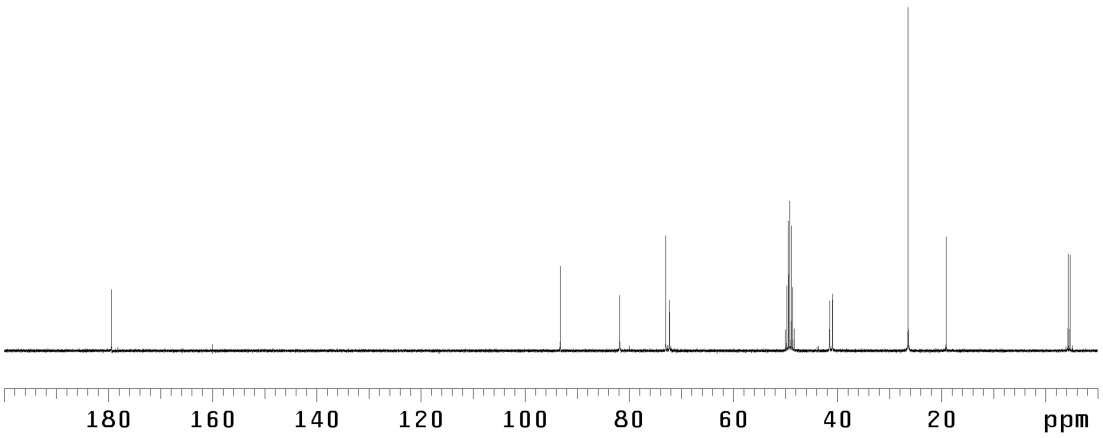


Figure A3.6 ^{13}C NMR (75 MHz, CD_3OD) of compound **166**

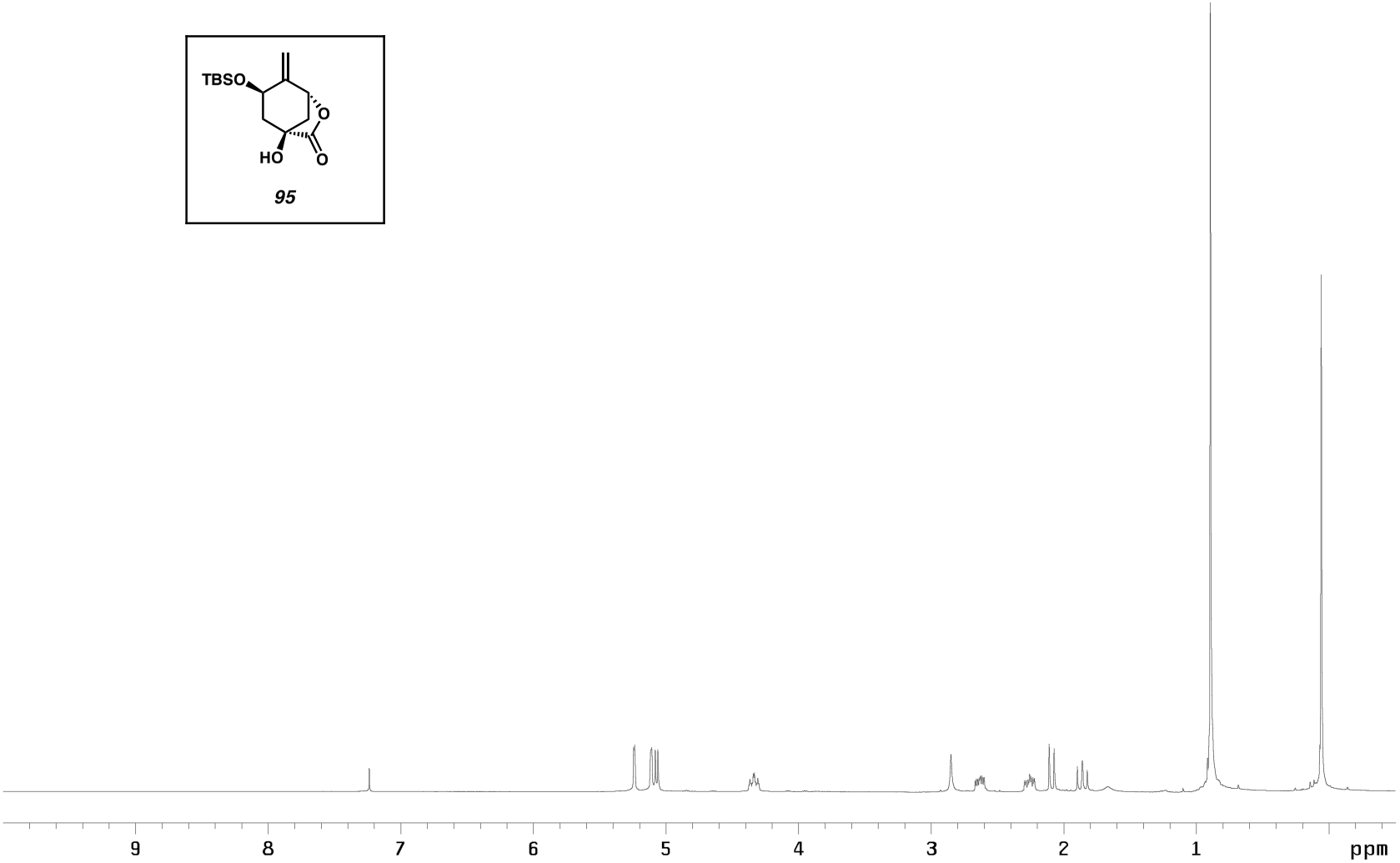


Figure A3.7 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **95**

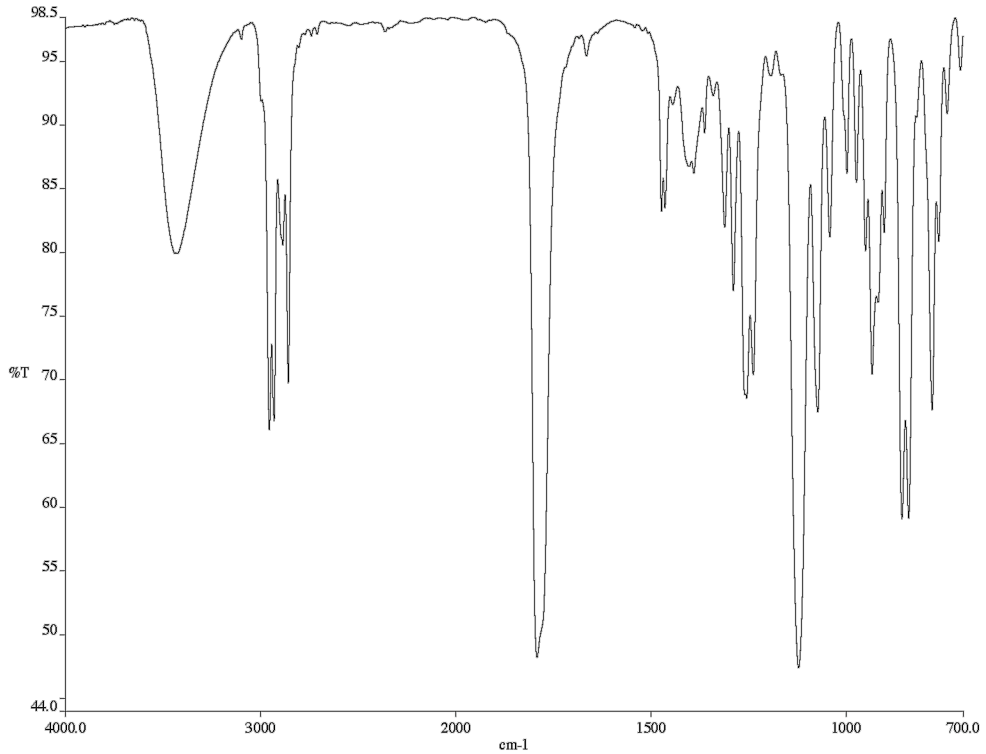


Figure A3.8 Infrared spectrum (thin film/NaCl) of compound **95**

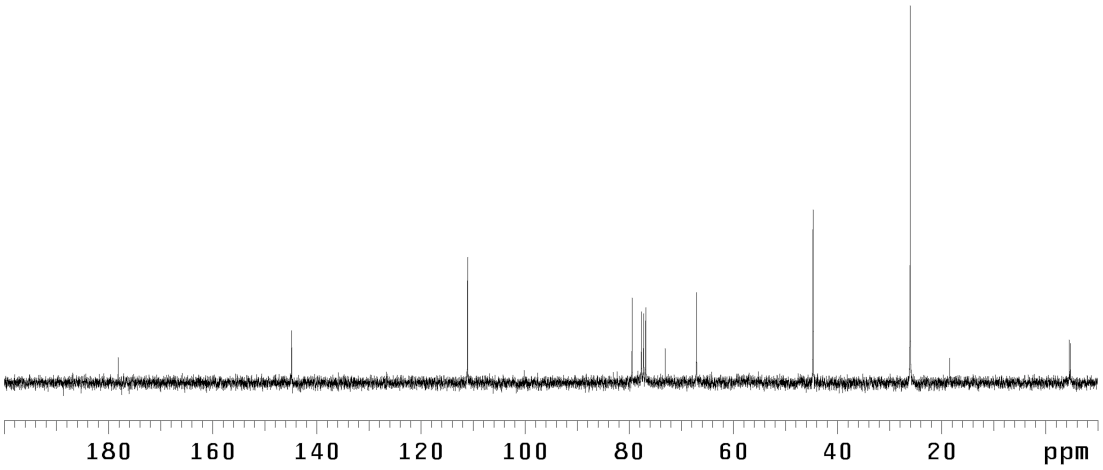


Figure A3.9 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **95**

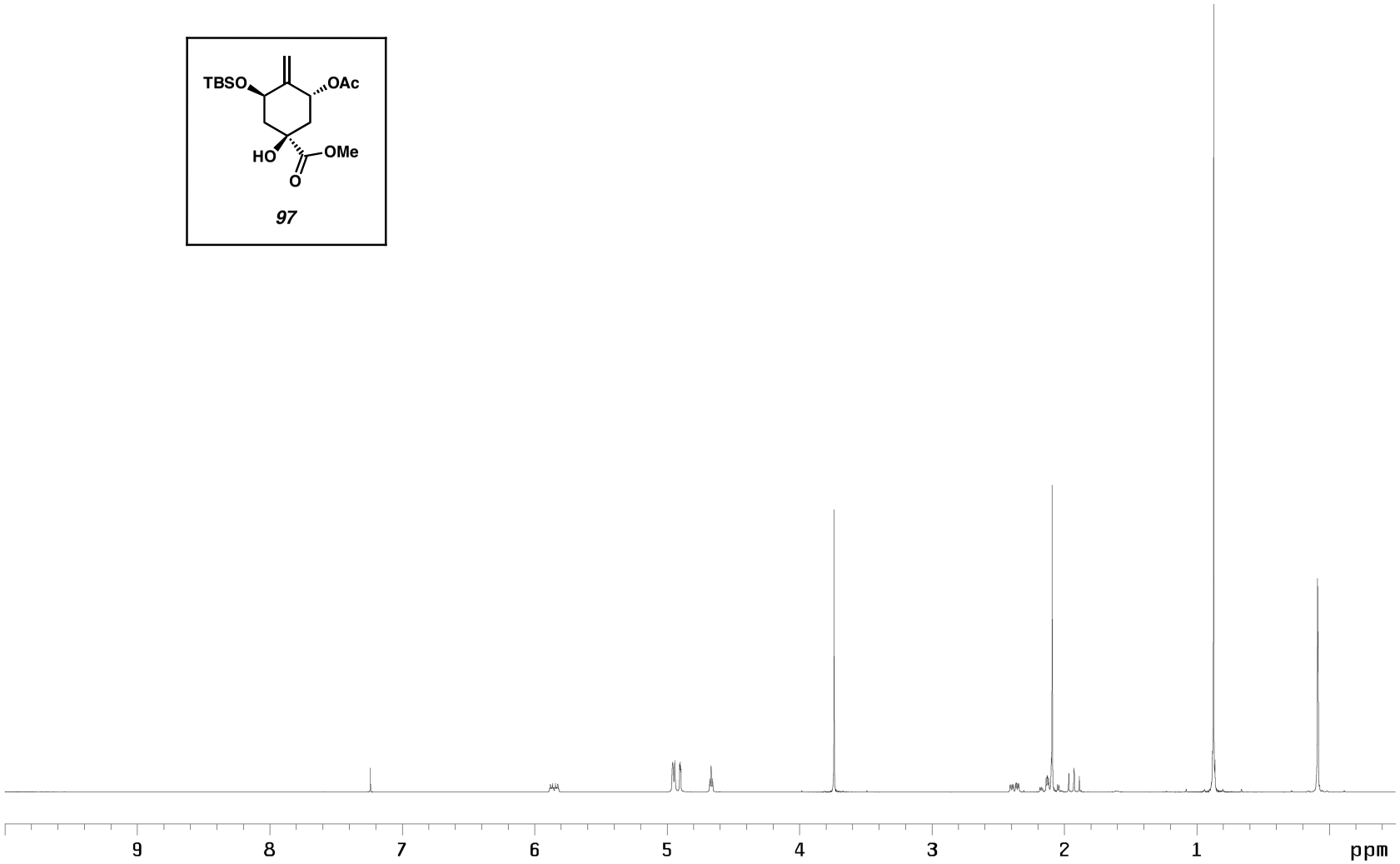


Figure A3.10 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **97**

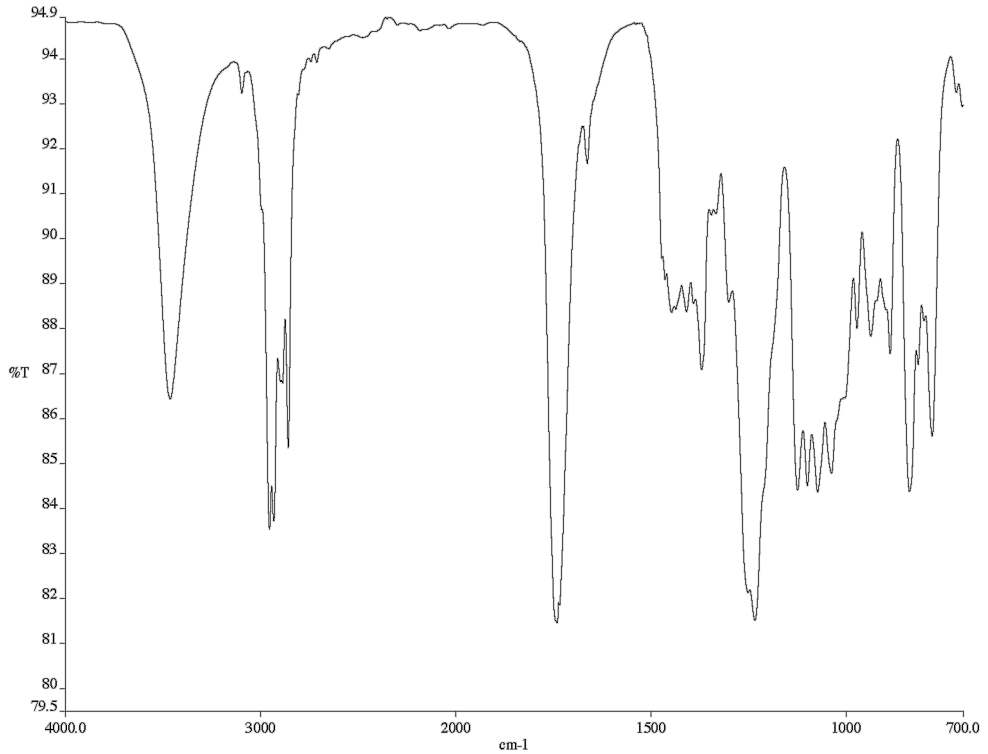


Figure A3.11 Infrared spectrum (thin film/NaCl) of compound **97**

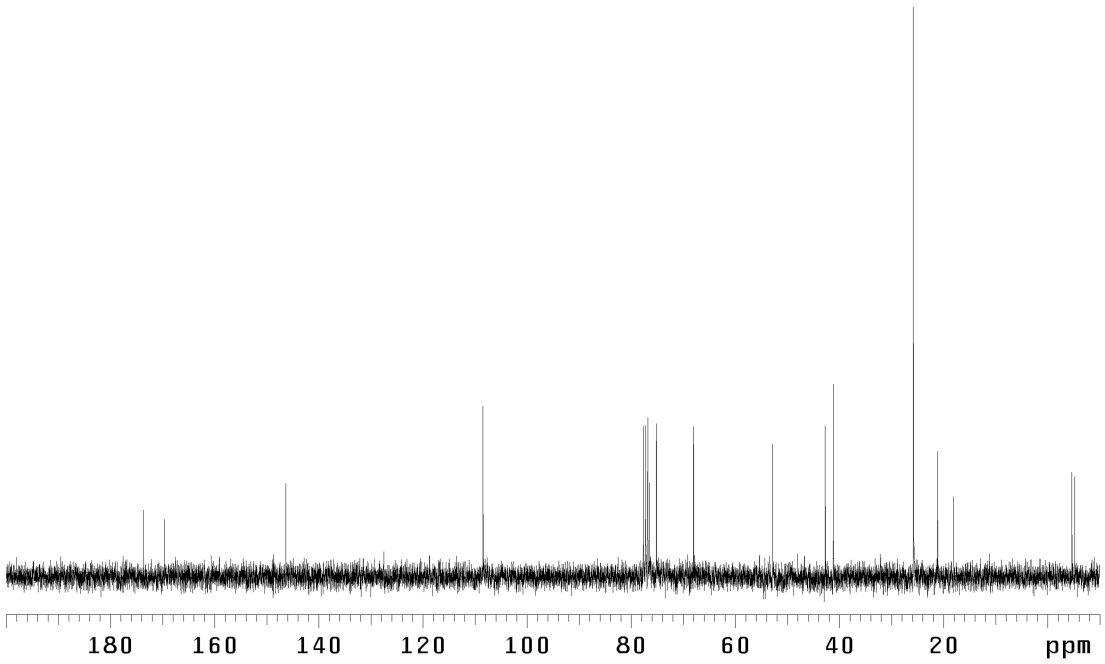


Figure A3.12 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **97**

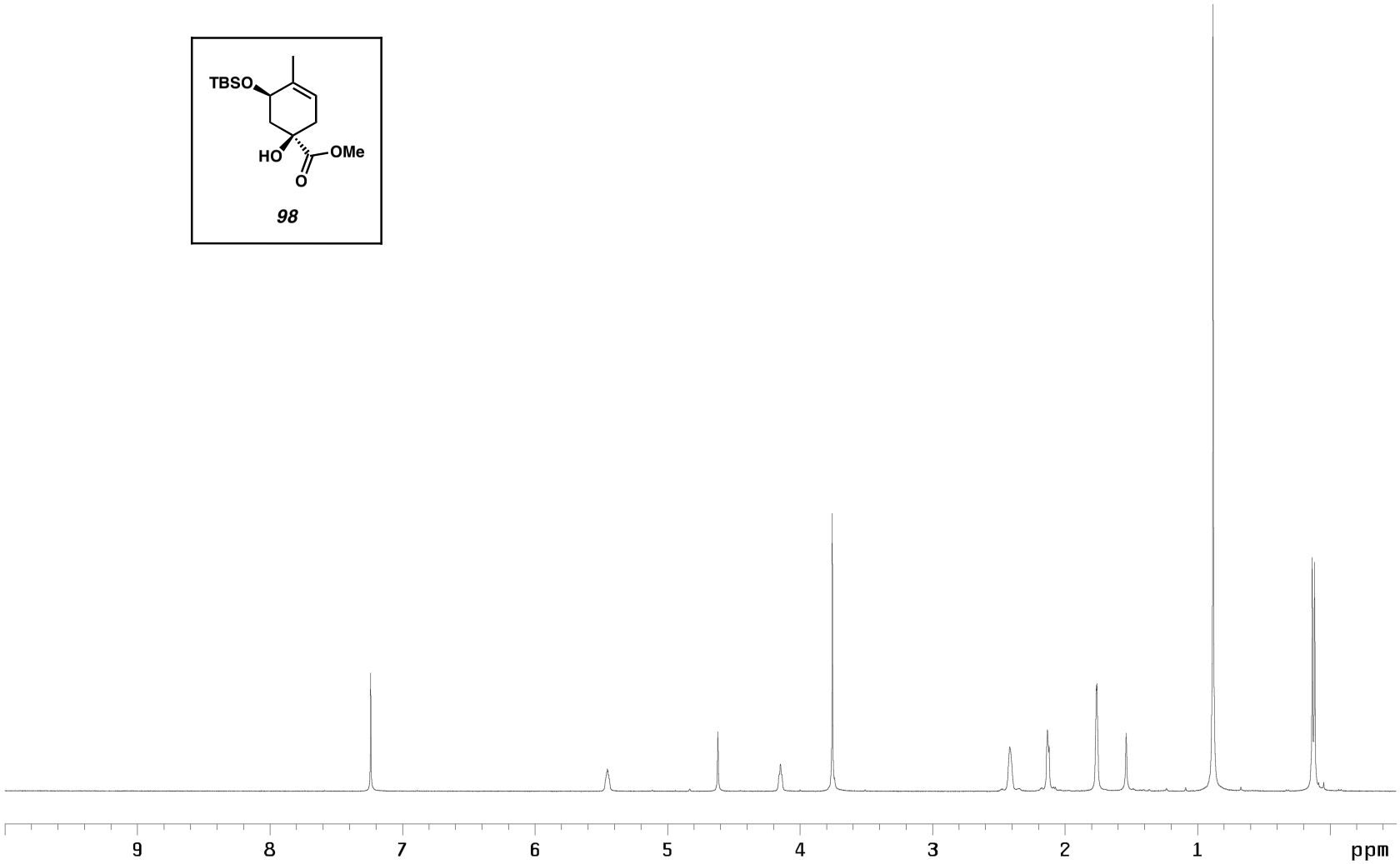


Figure A3.13 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **98**

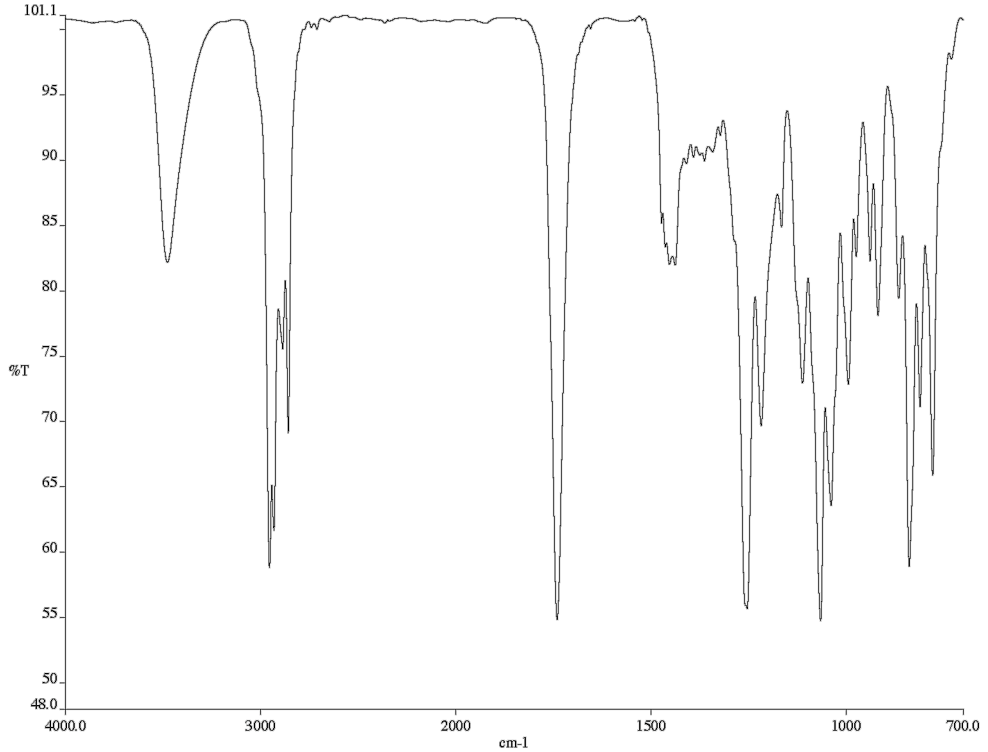


Figure A3.14 Infrared spectrum (thin film/NaCl) of compound **98**

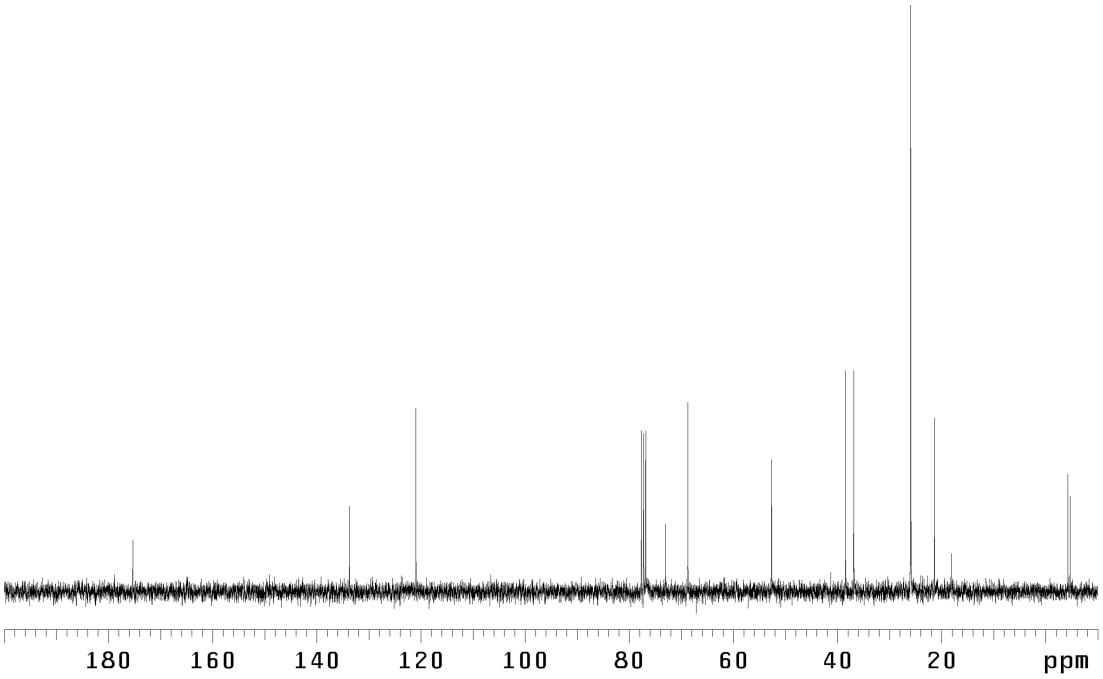


Figure A3.15 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **98**

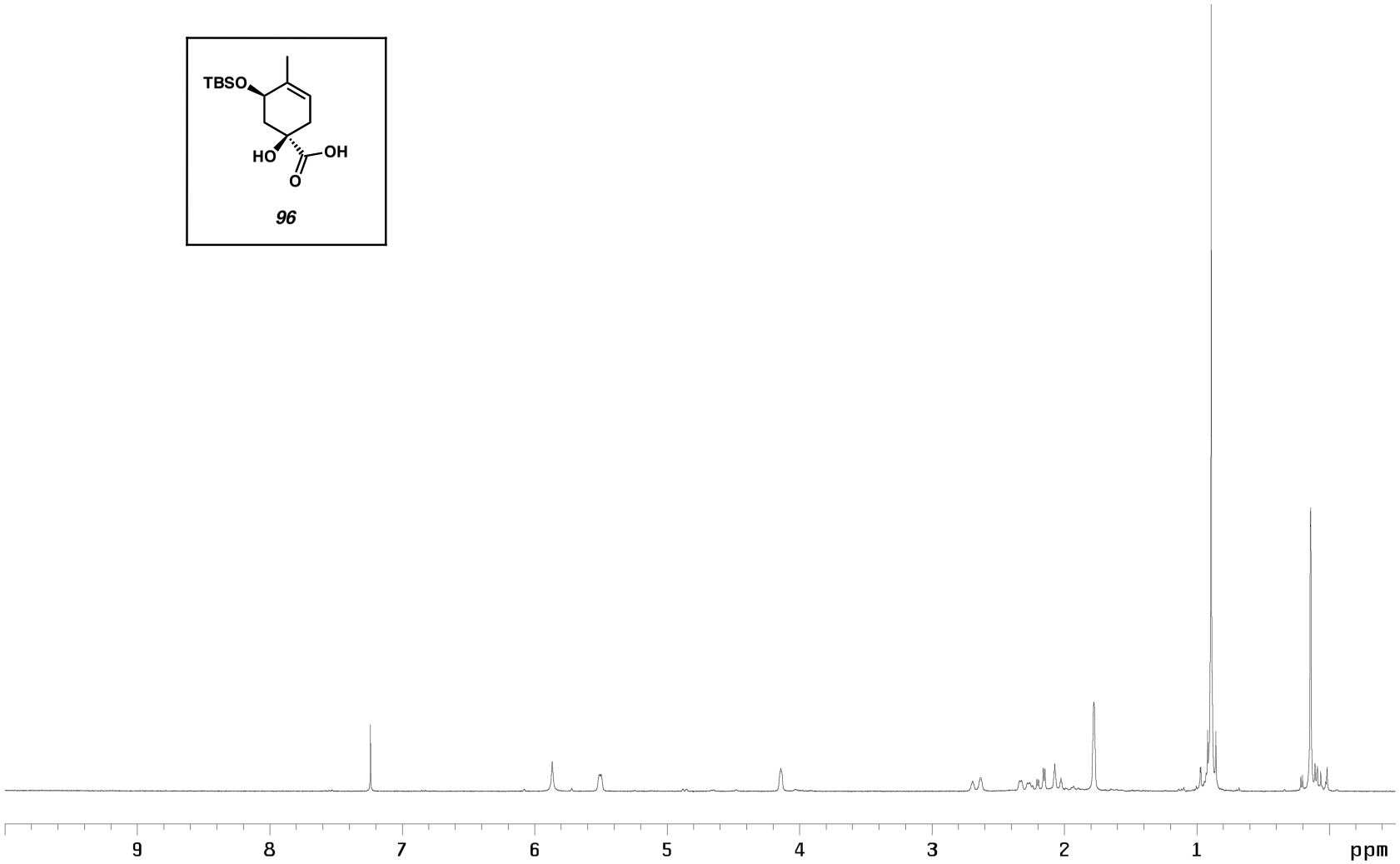


Figure A3.16 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **96**

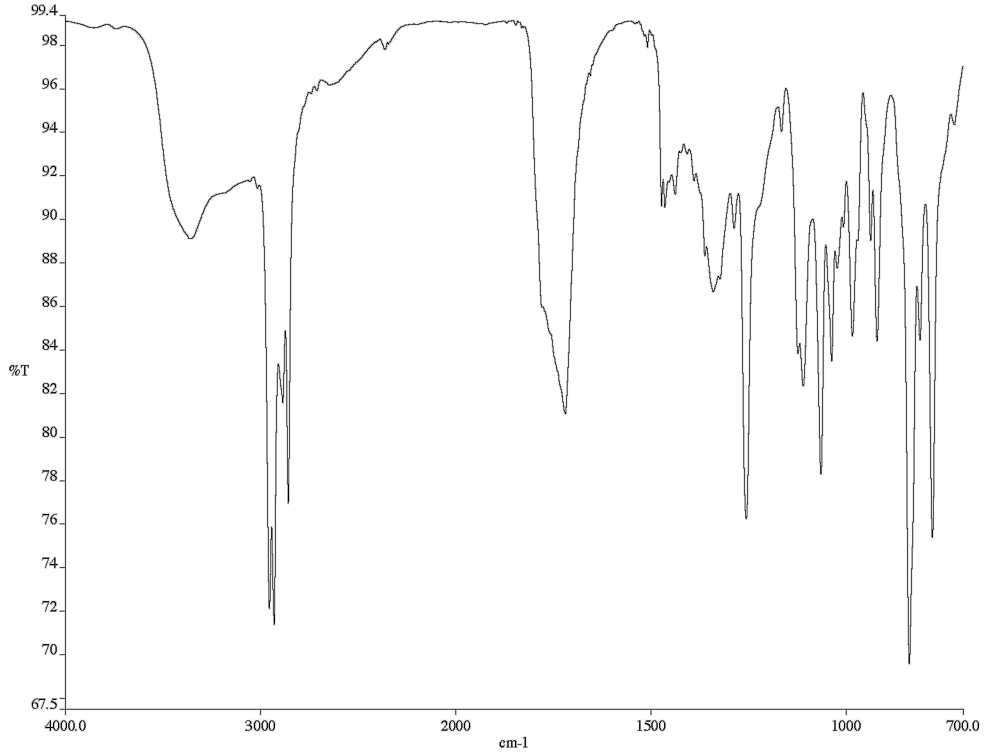


Figure A3.17 Infrared spectrum (thin film/NaCl) of compound **96**

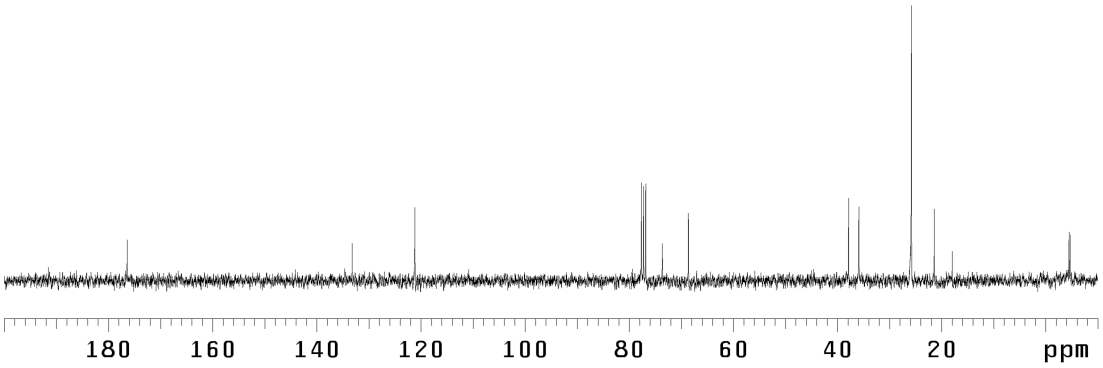


Figure A3.18 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **96**

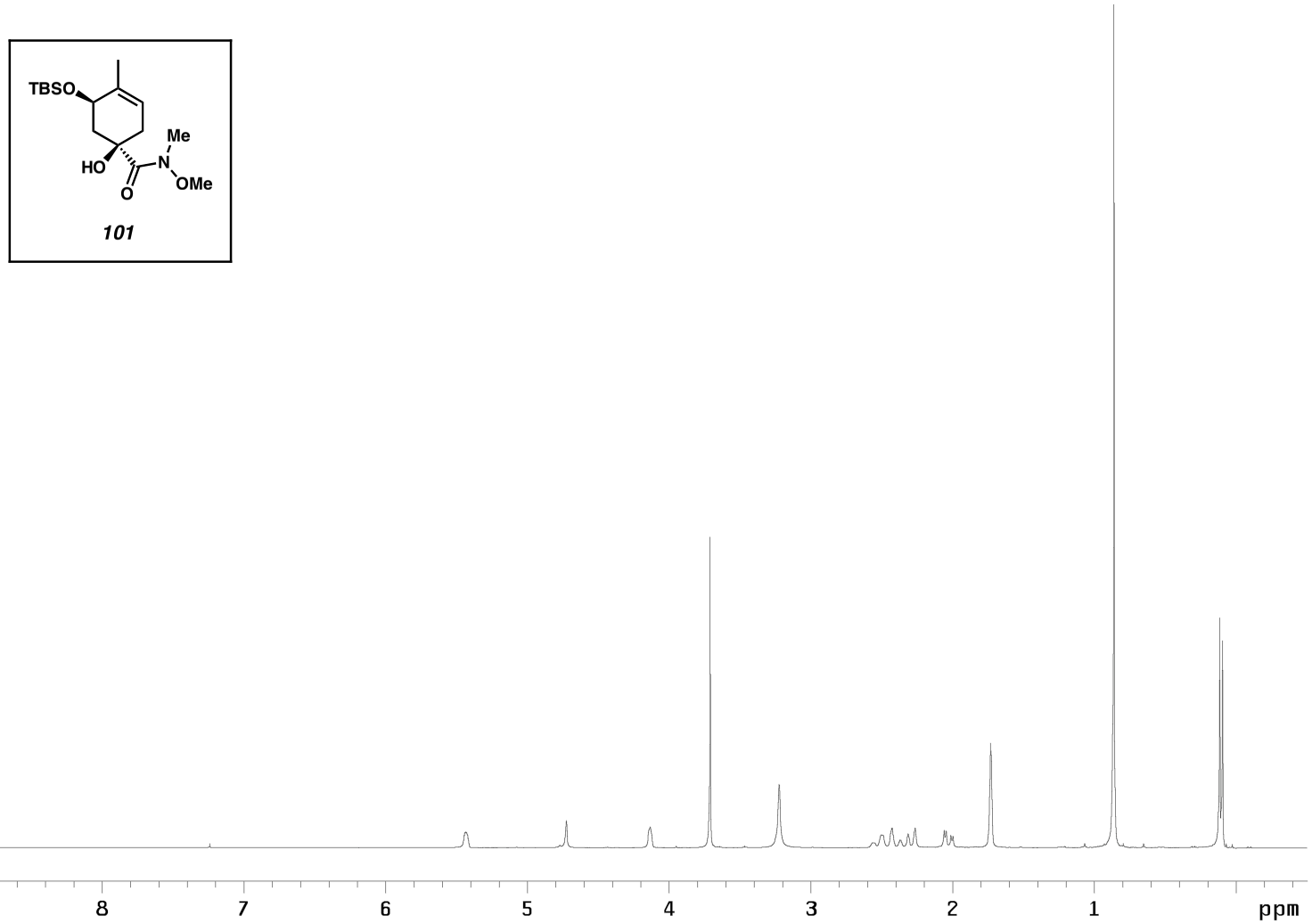


Figure A3.19 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **101**

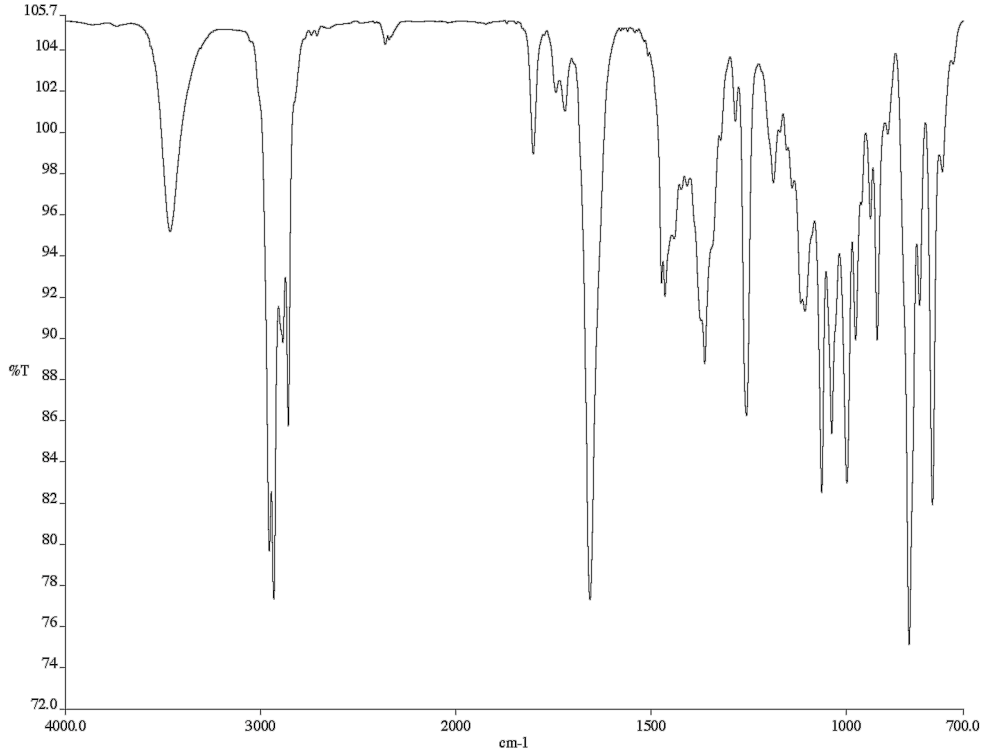


Figure A3.20 Infrared spectrum (thin film/NaCl) of compound **101**

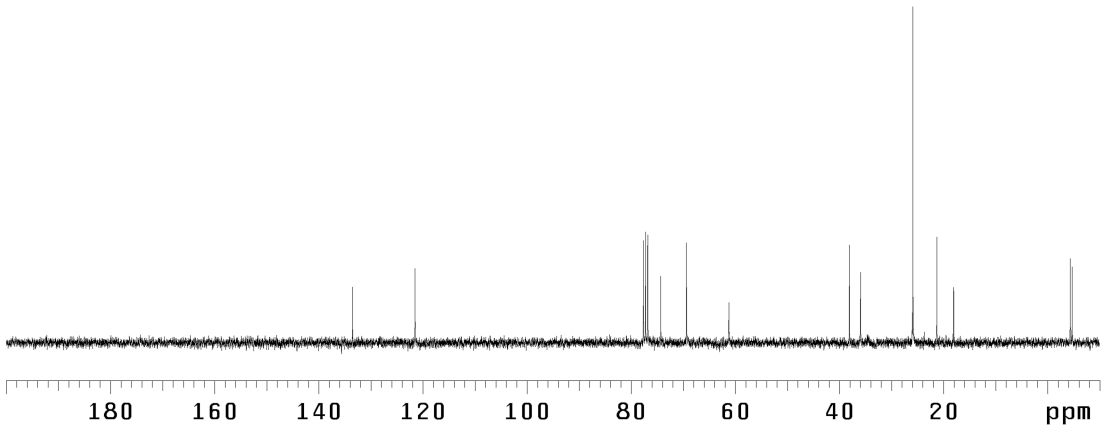


Figure A3.21 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **101**

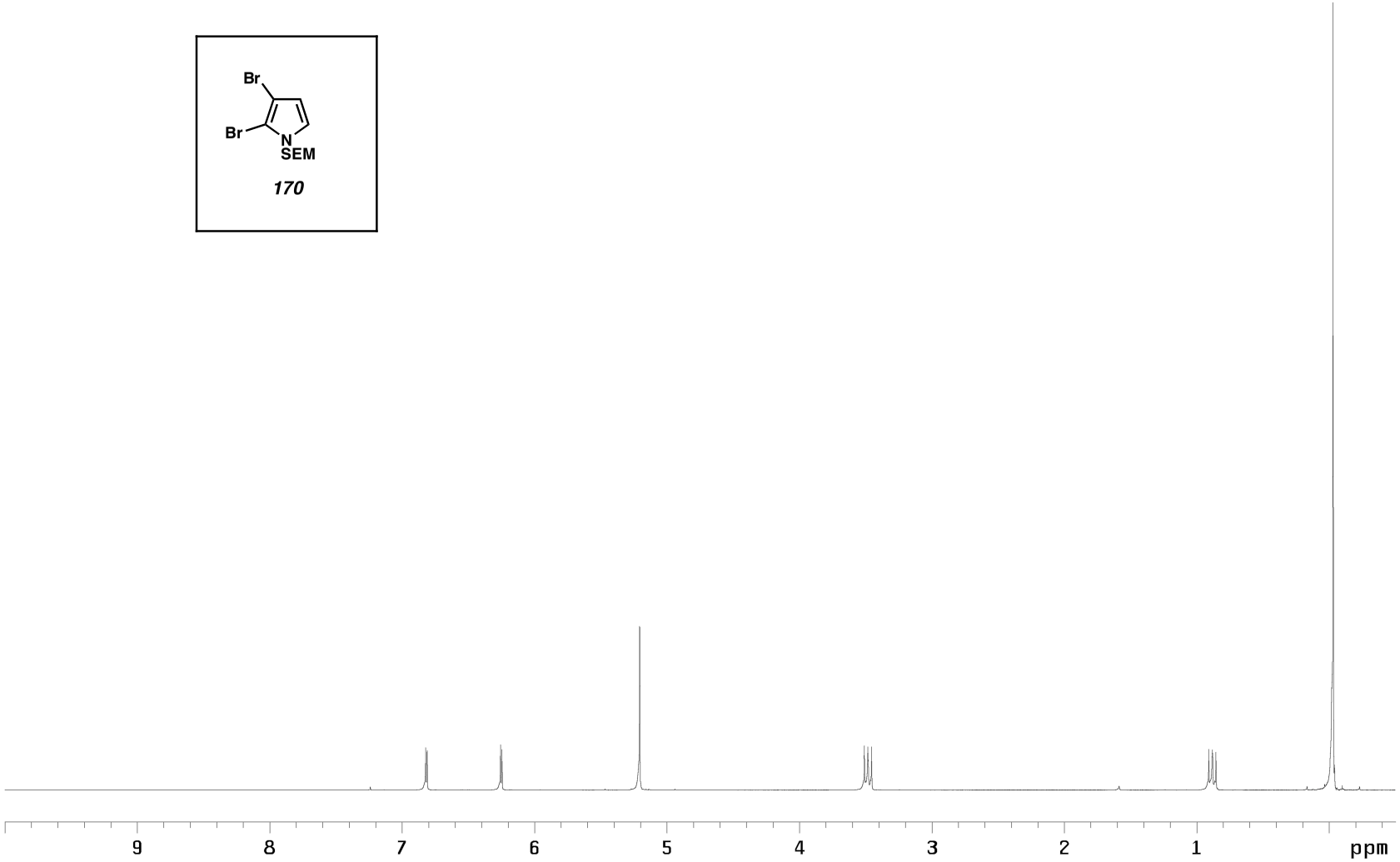


Figure A3.22 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **170**

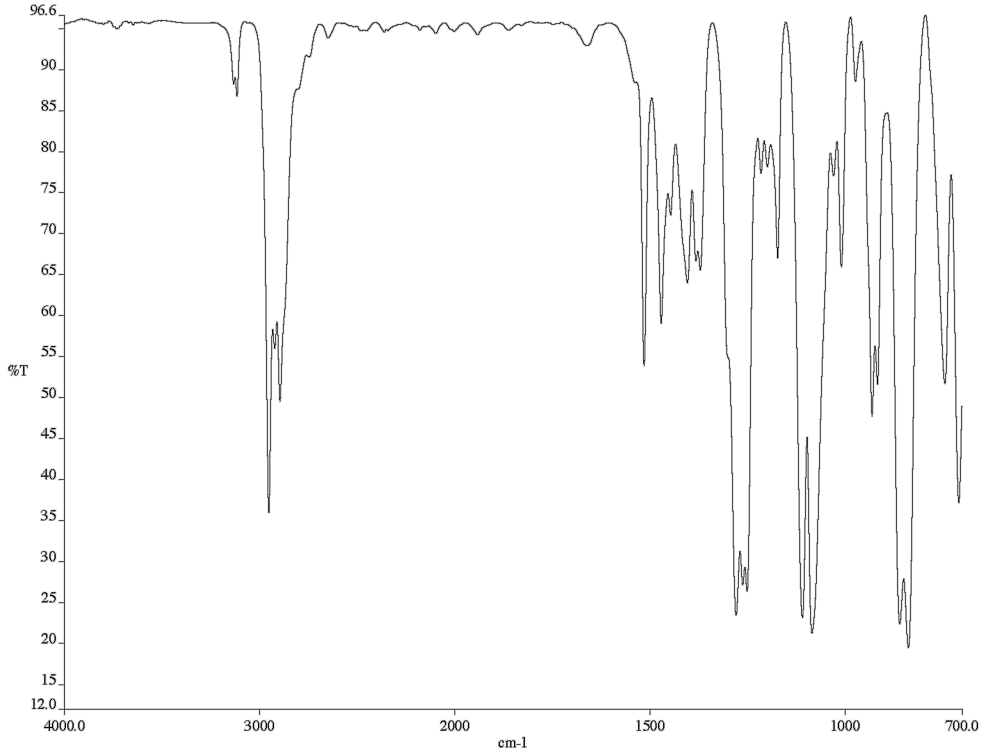


Figure A3.23 Infrared spectrum (thin film/NaCl) of compound **170**

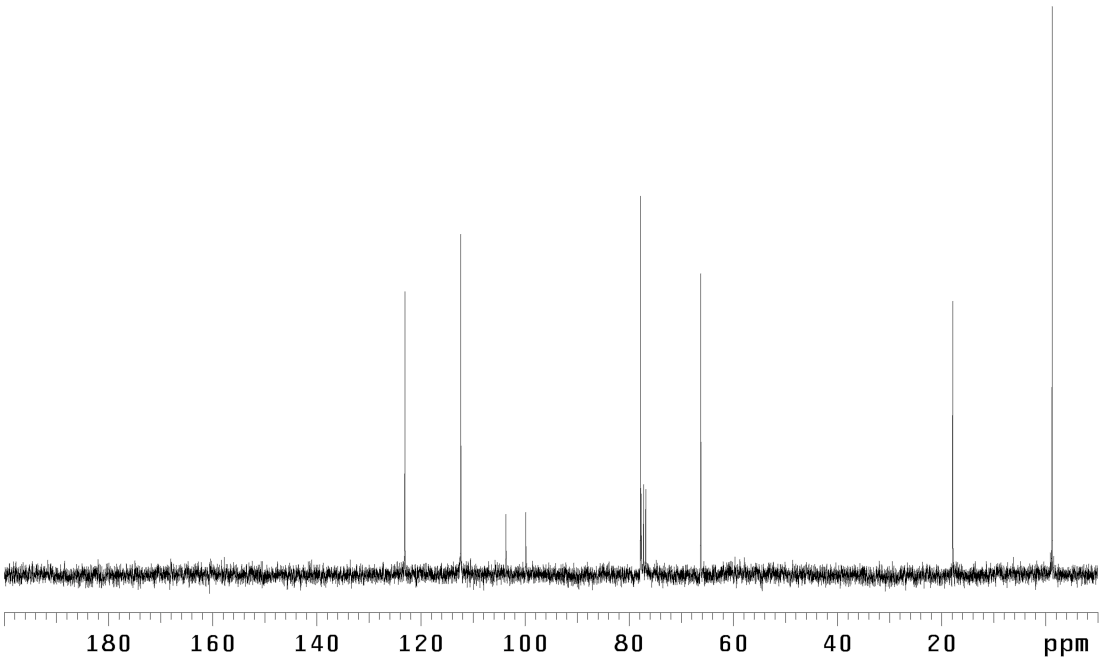


Figure A3.24 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **170**

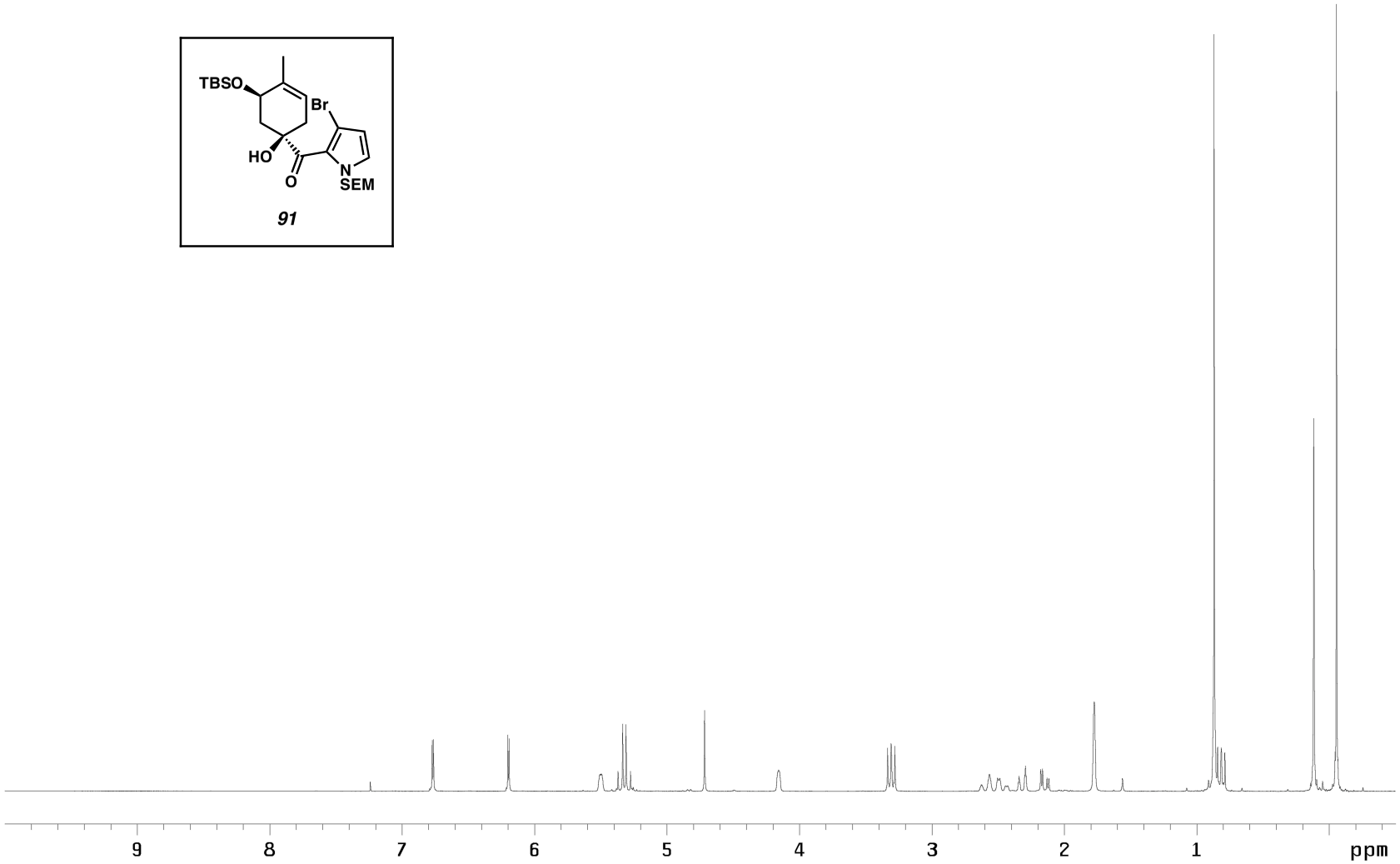


Figure A3.25 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **91**

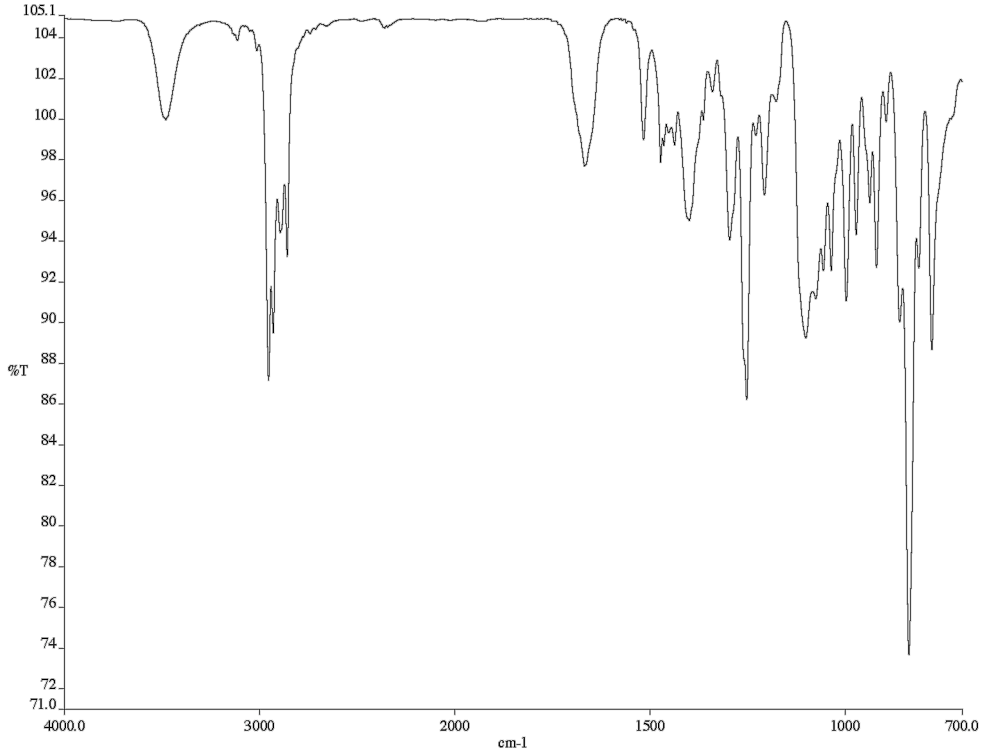


Figure A3.26 Infrared spectrum (thin film/NaCl) of compound **91**

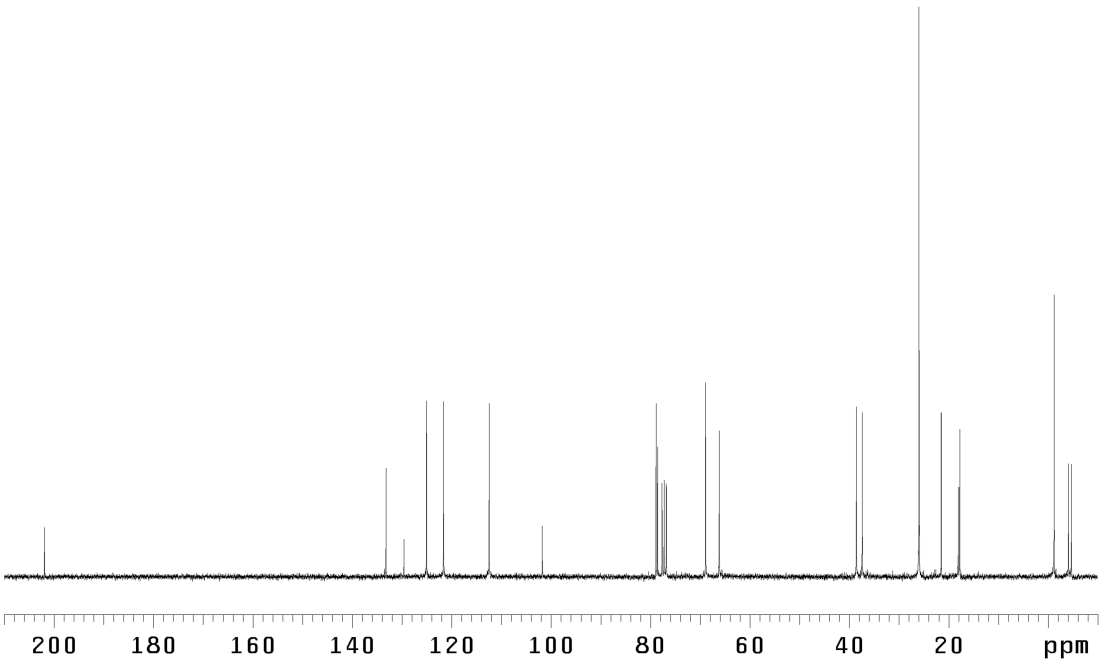


Figure A3.27 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **91**

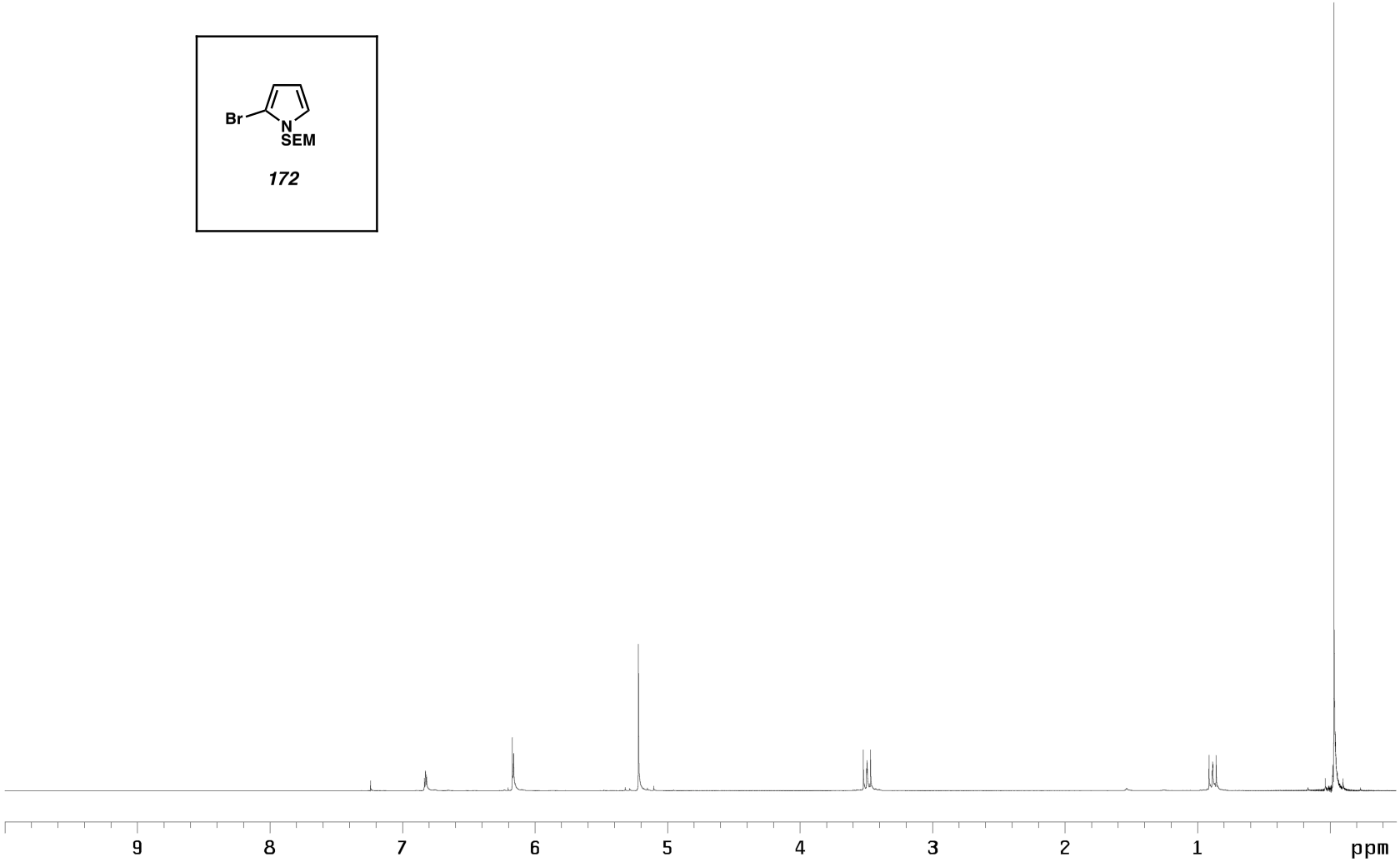


Figure A3.28 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **172**

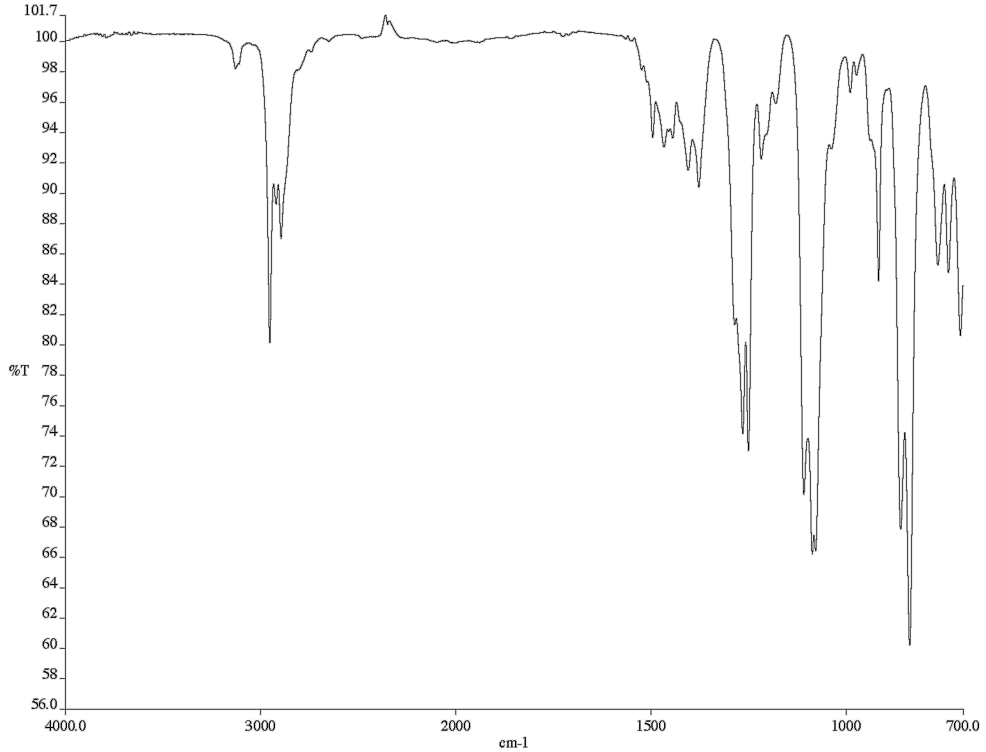


Figure A3.29 Infrared spectrum (thin film/NaCl) of compound **172**

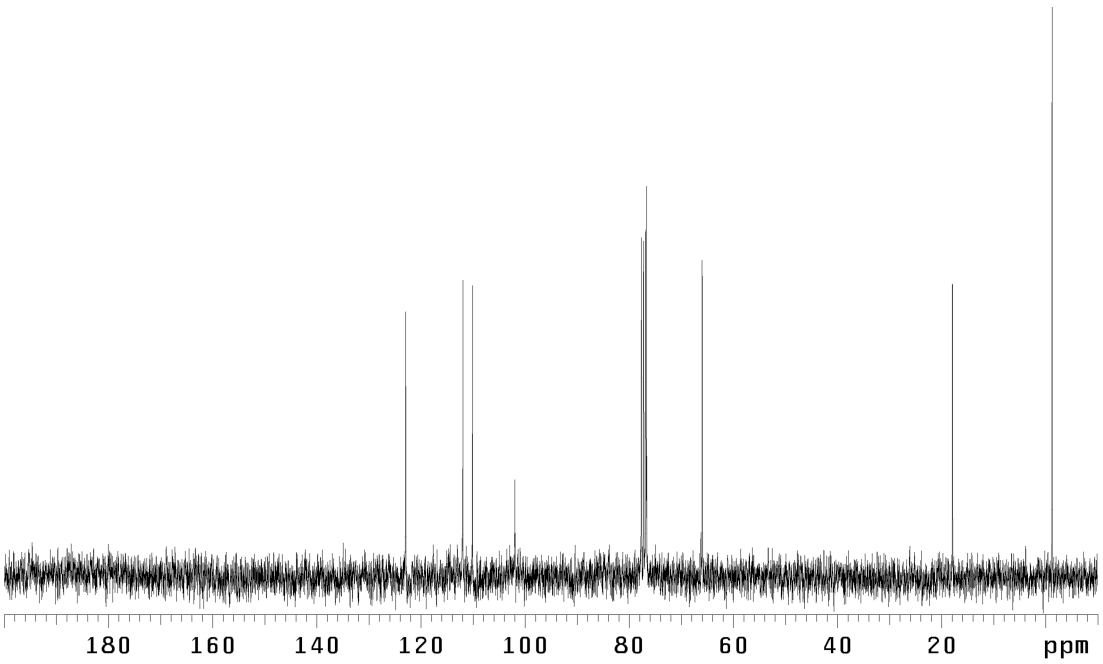


Figure A3.30 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **172**

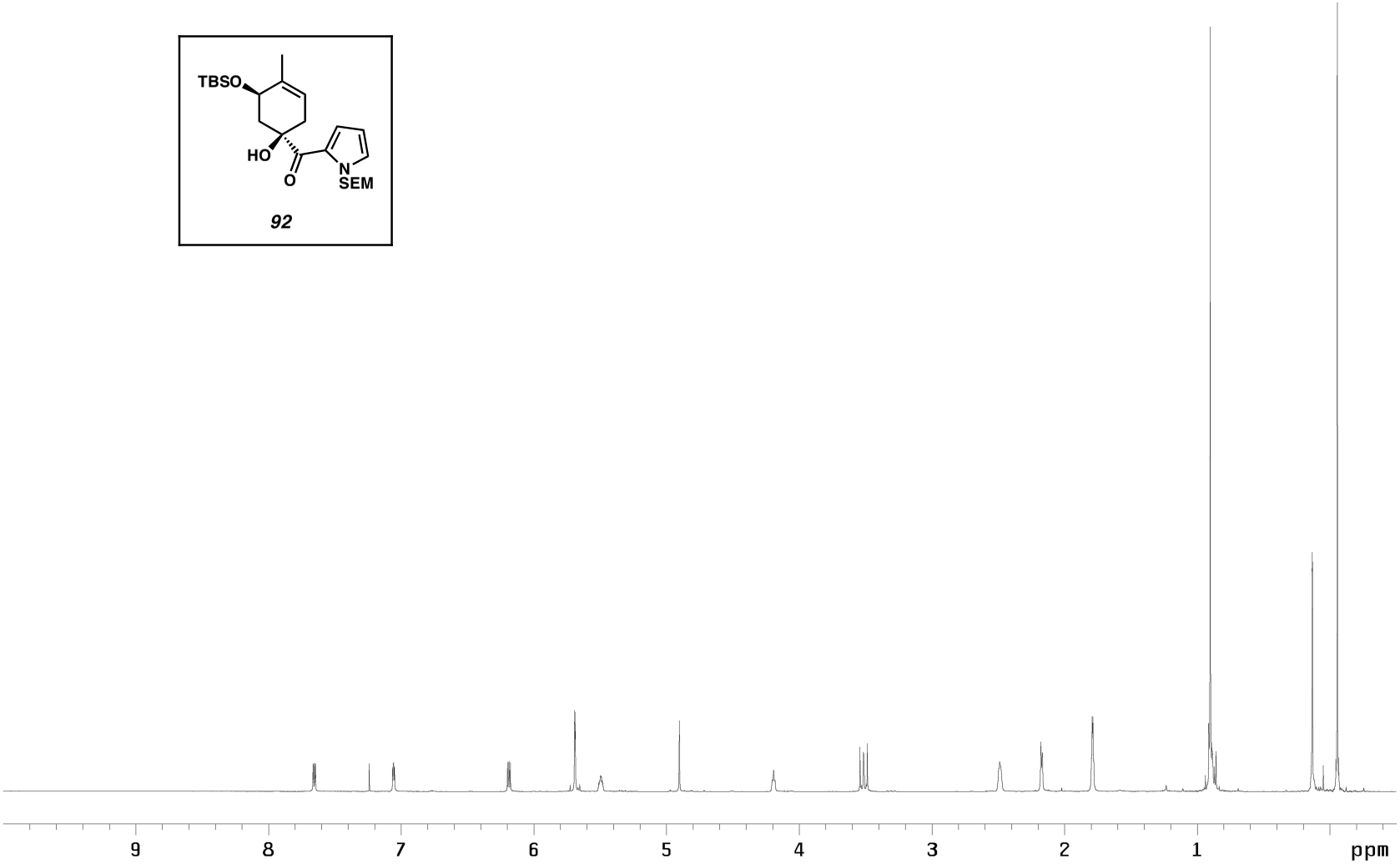


Figure A3.31 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **92**

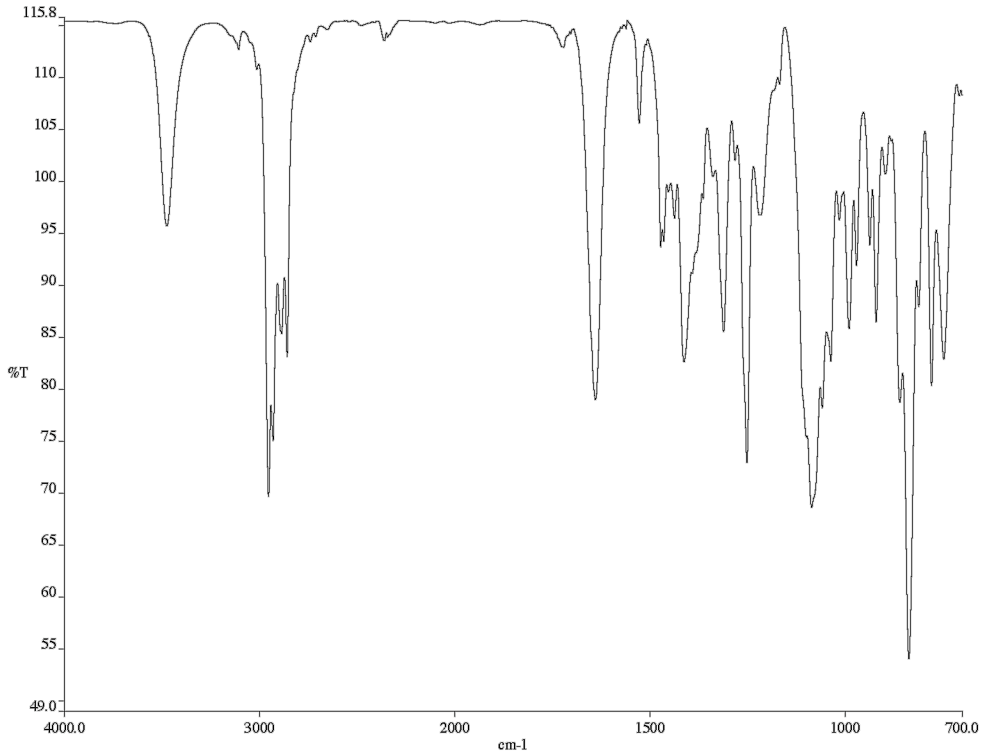


Figure A3.32 Infrared spectrum (thin film/NaCl) of compound **92**

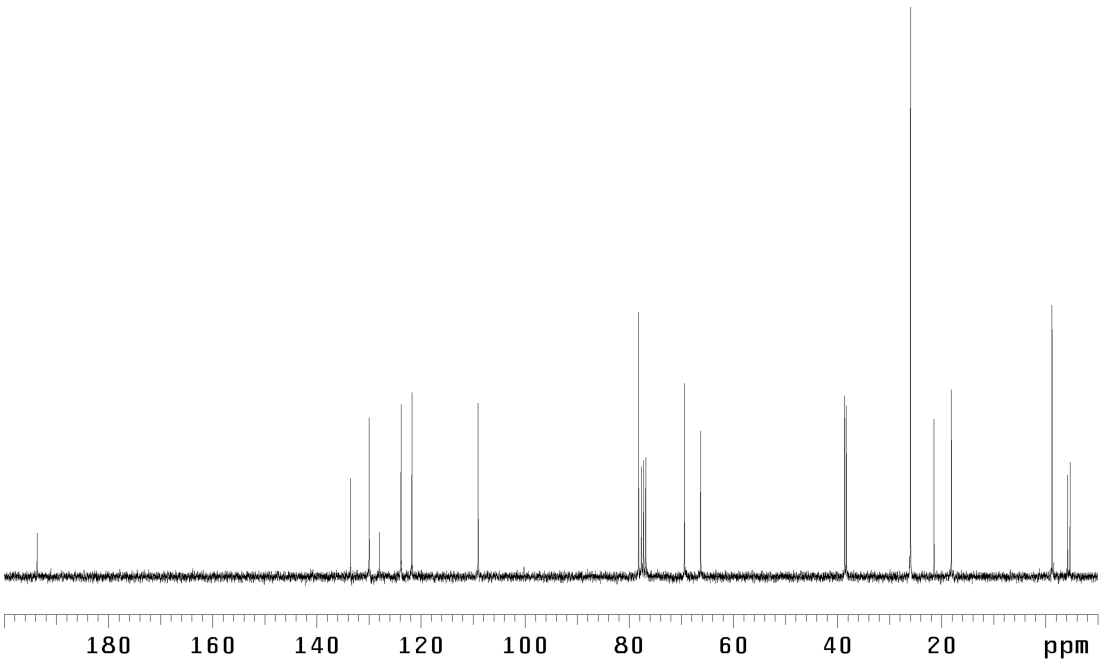


Figure A3.33 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **92**

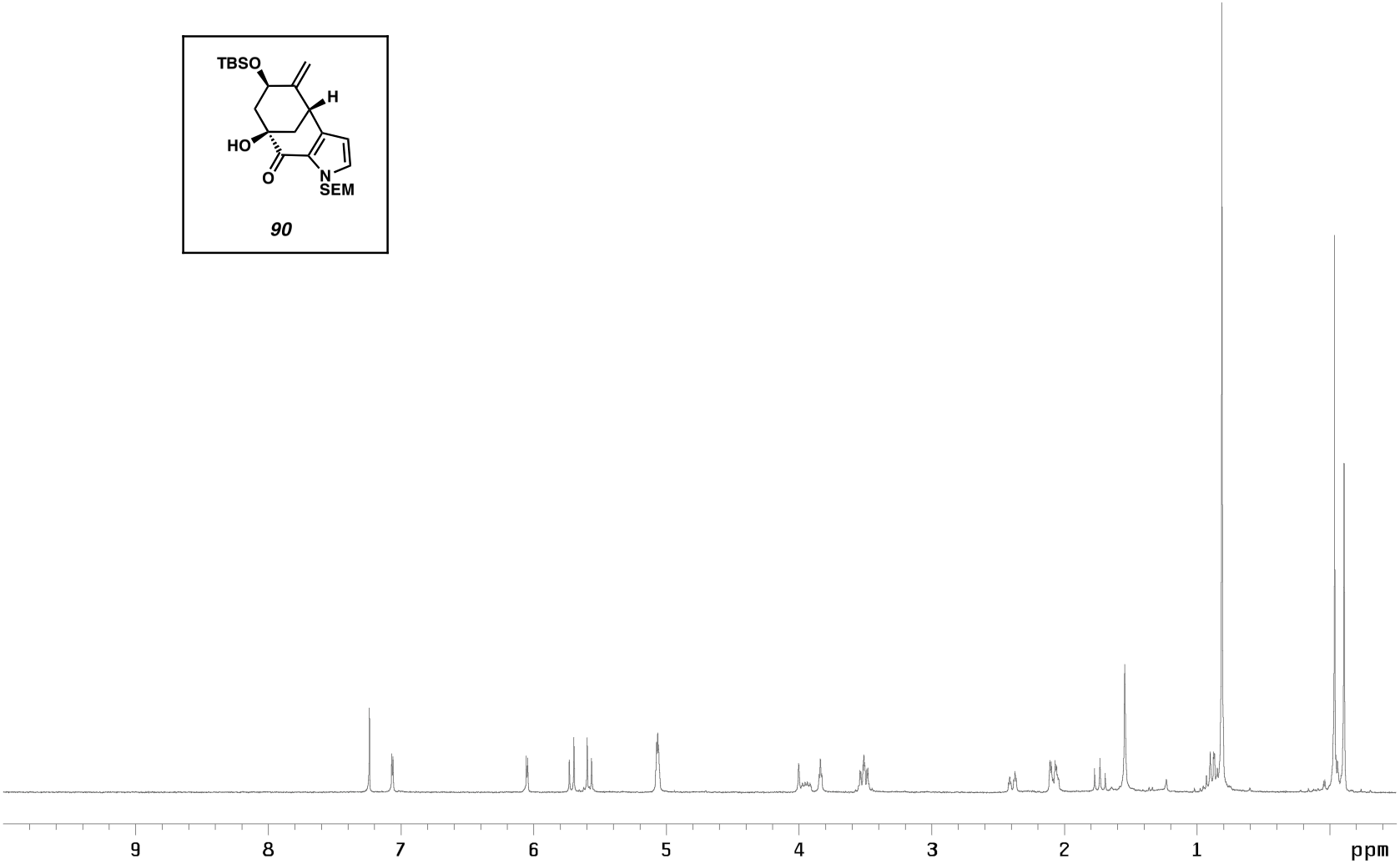


Figure A3.34 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **90**

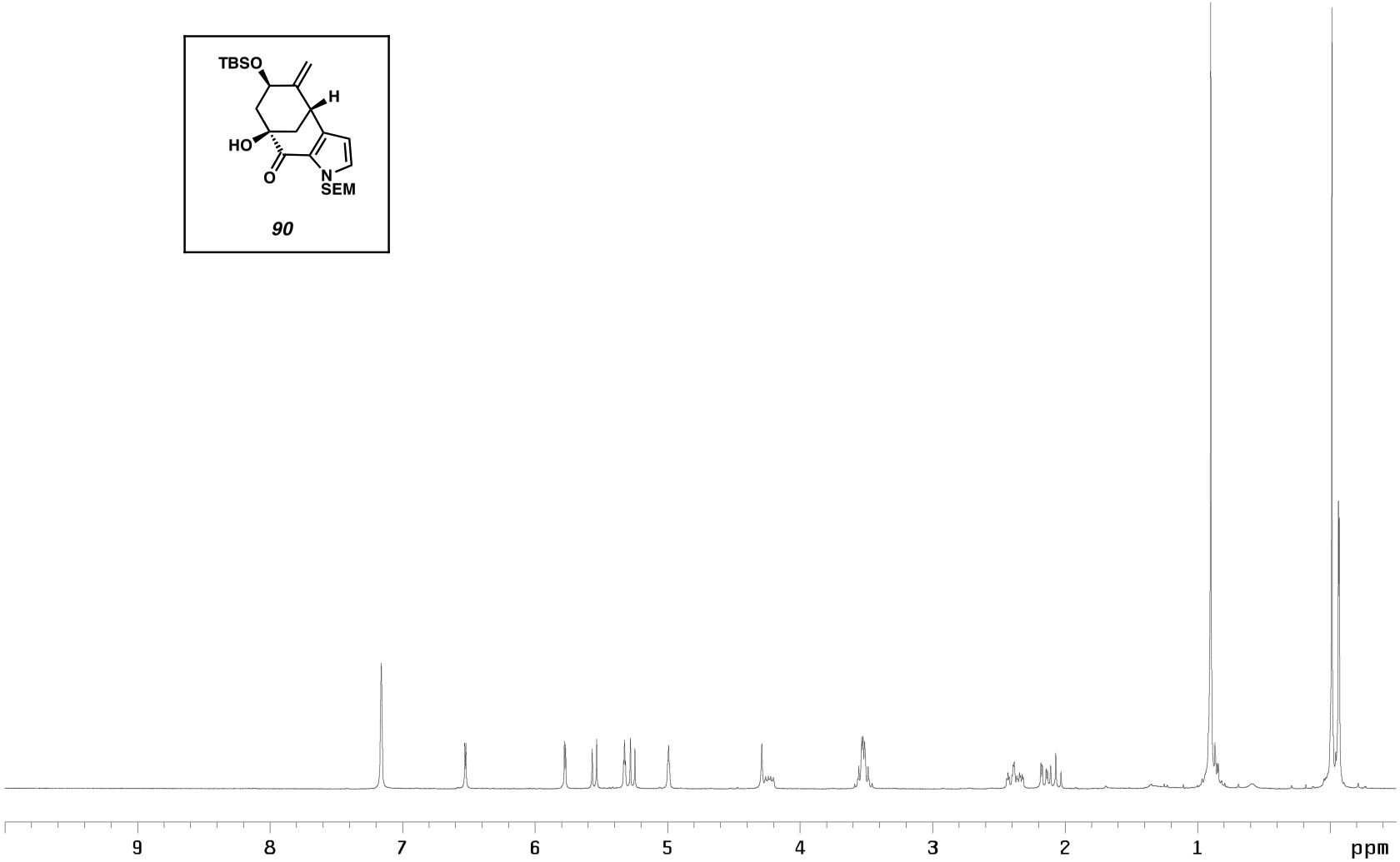


Figure A3.35 ^{1}H NMR (300 MHz, C_6D_6) of compound **90**

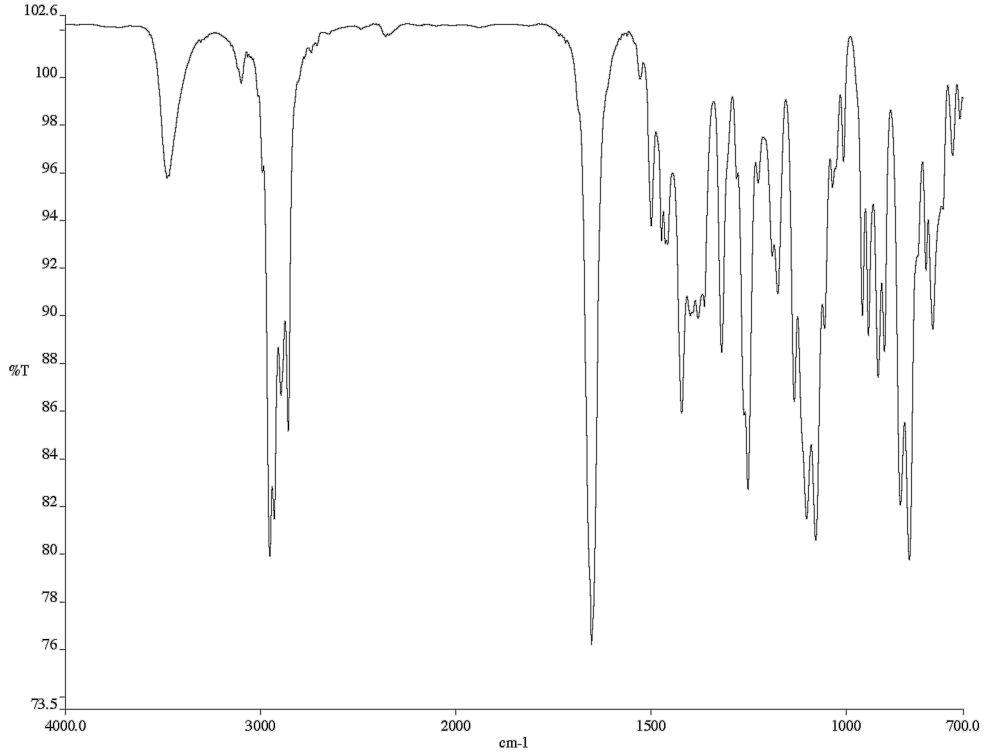


Figure A3.36 Infrared spectrum (thin film/NaCl) of compound **90**

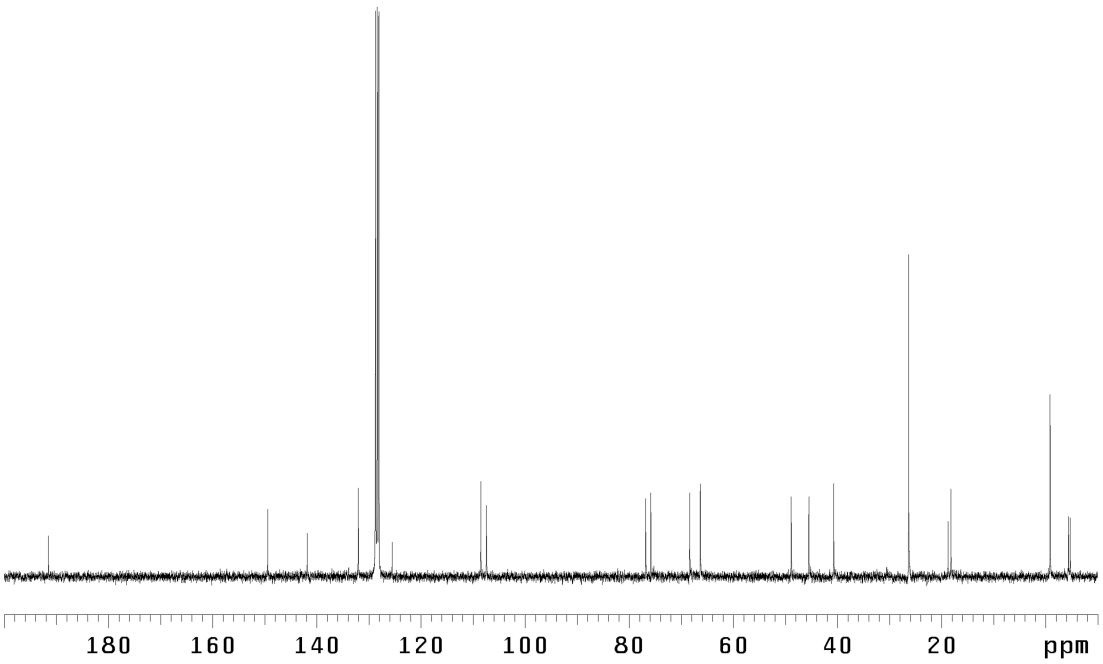


Figure A3.37 ^{13}C NMR (75 MHz, C_6D_6) of compound **90**

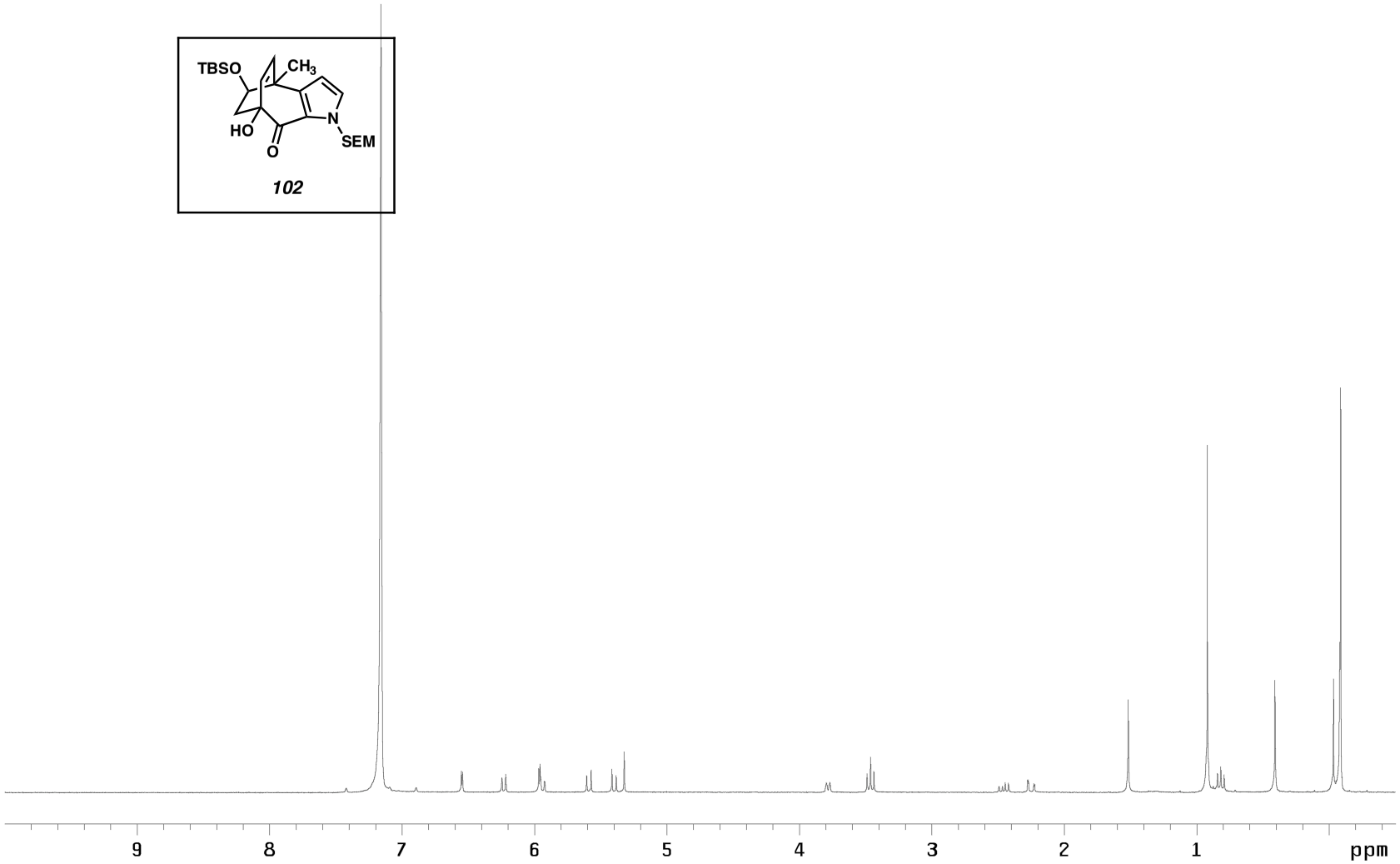


Figure A3.38 ^{1}H NMR (300 MHz, C_6D_6) of compound **102**

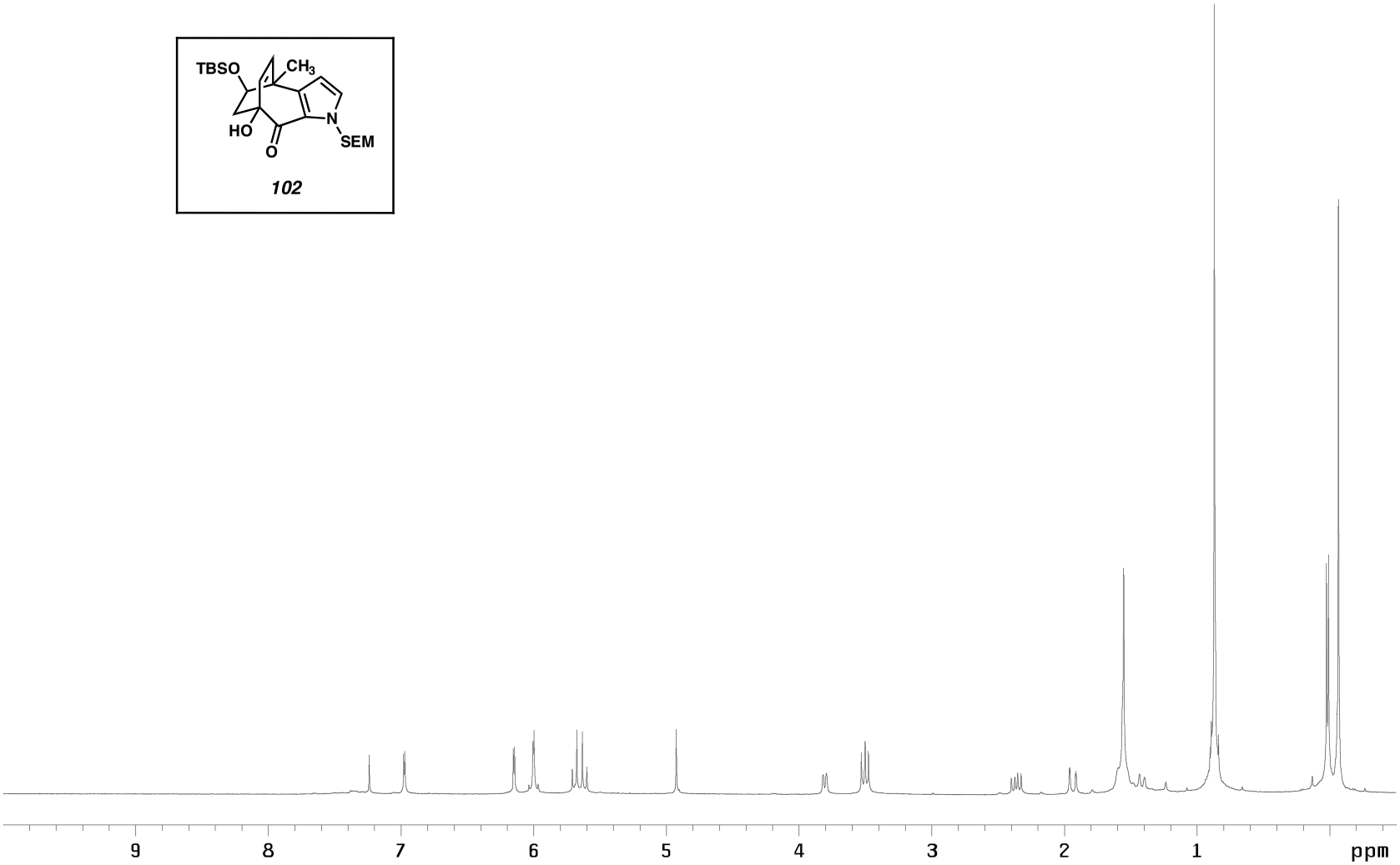


Figure A3.39 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **102**

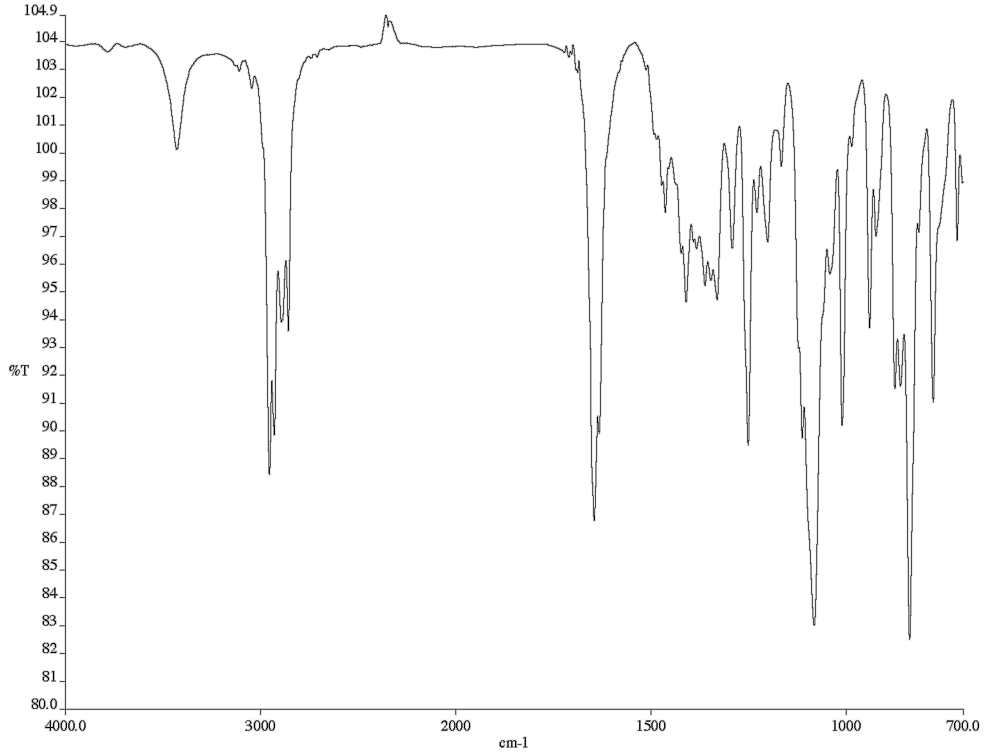


Figure A3.40 Infrared spectrum (thin film/NaCl) of compound **102**

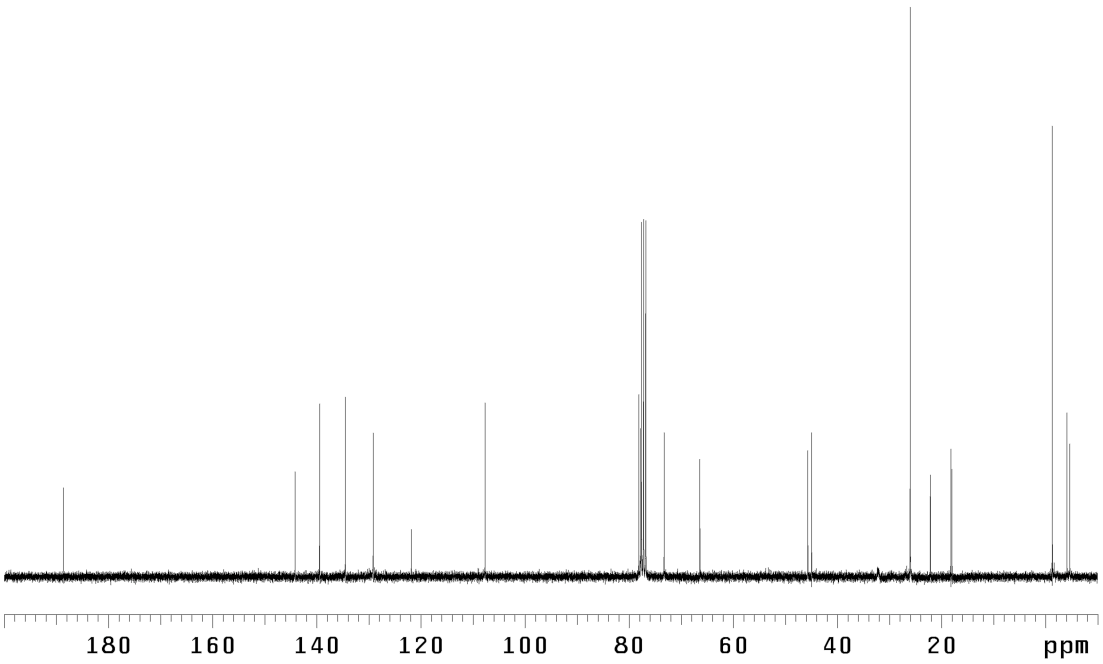


Figure A3.41 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **102**

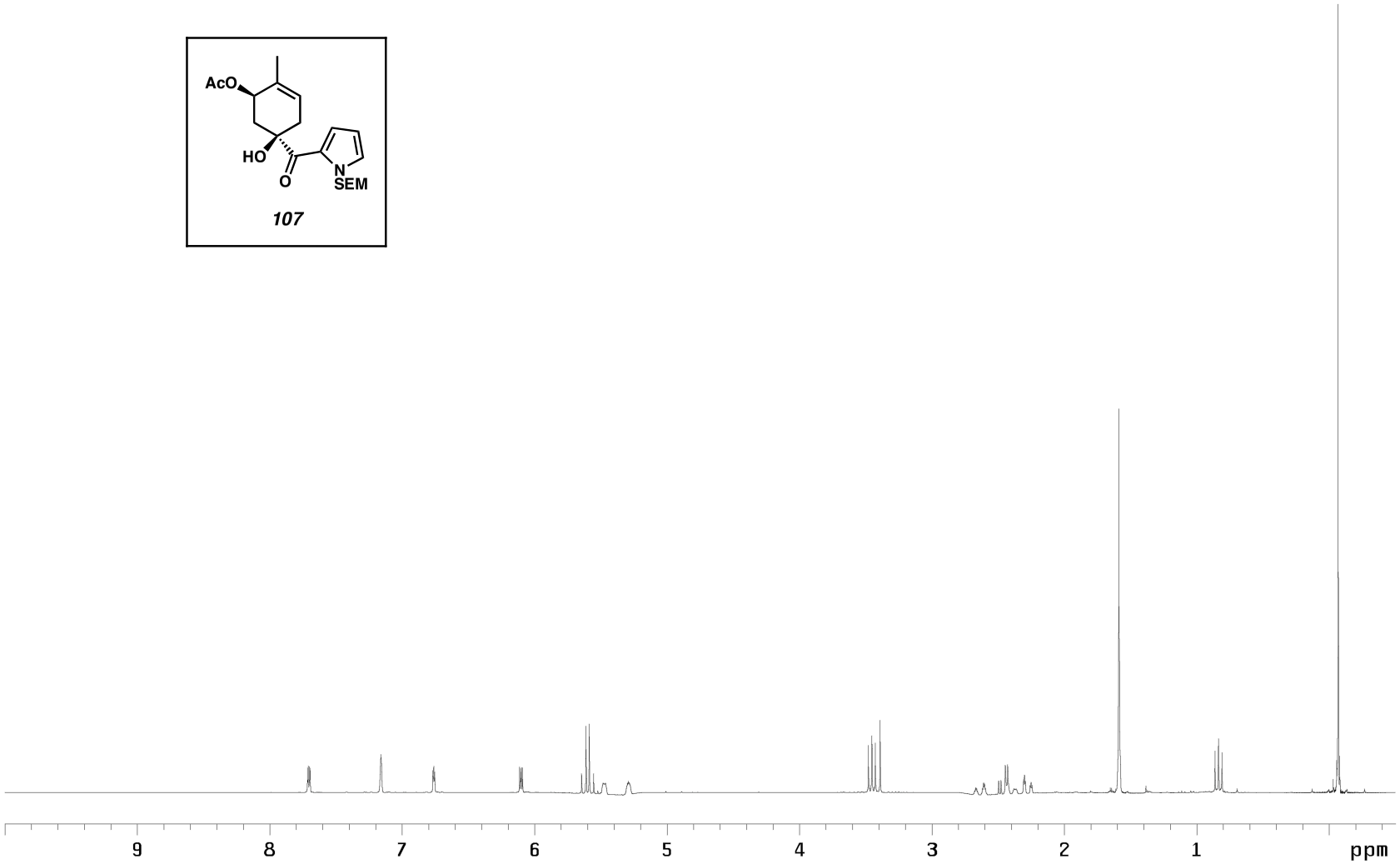


Figure A3.42 ^{1}H NMR (300 MHz, C_6D_6) of compound **107**

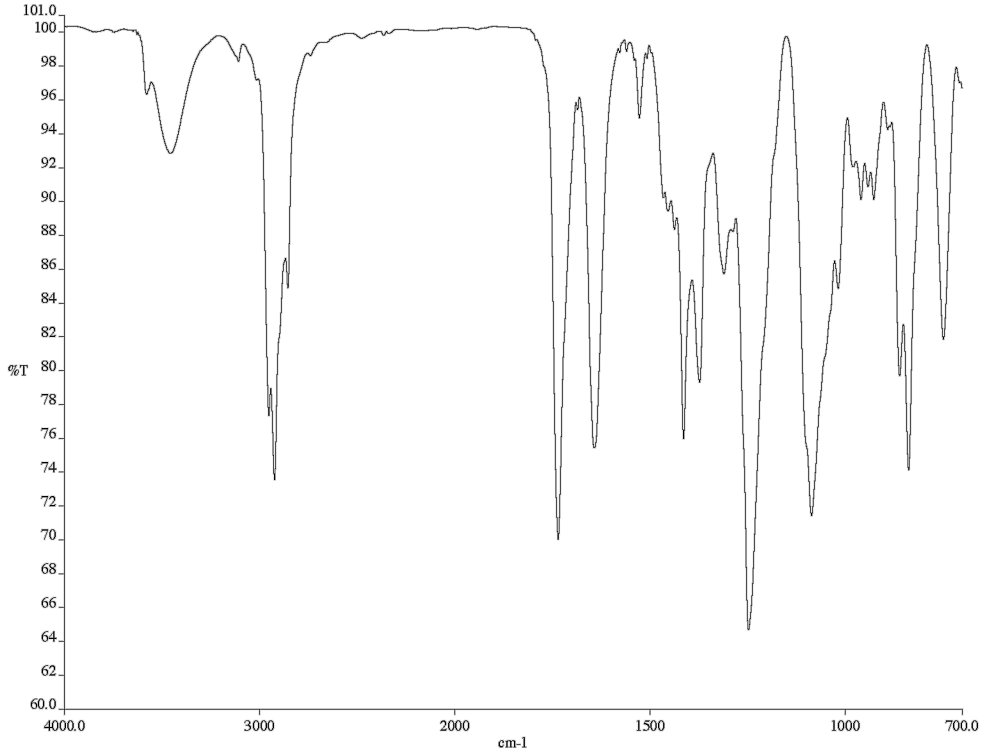


Figure A3.43 Infrared spectrum (thin film/NaCl) of compound **107**

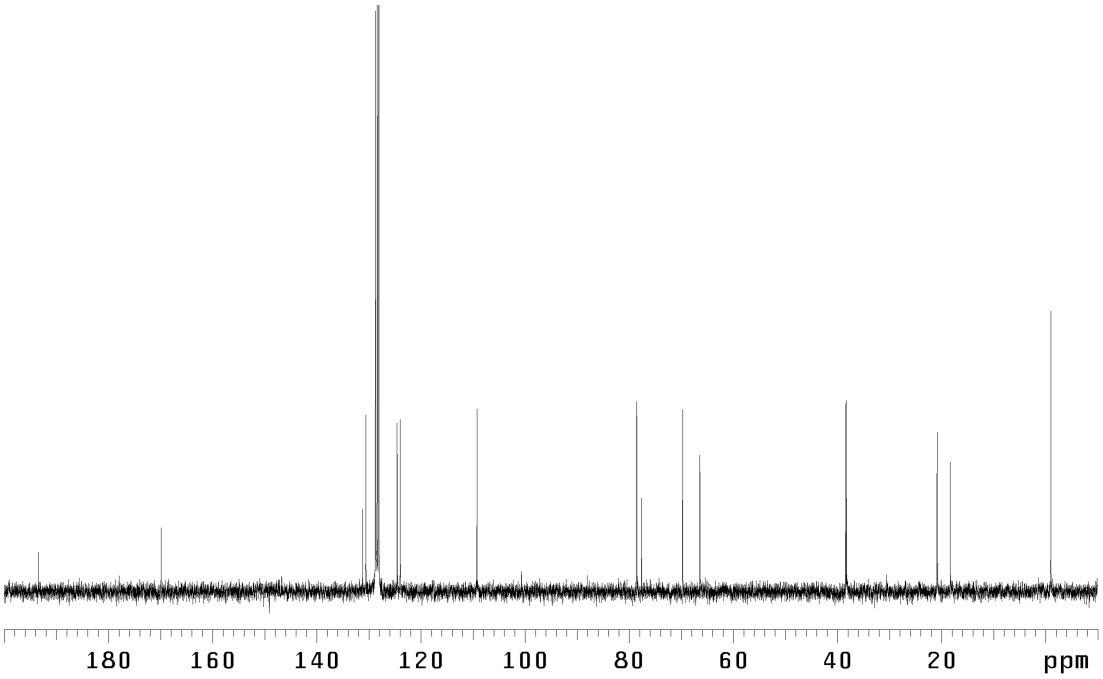


Figure A3.44 ^{13}C NMR (75 MHz, C_6D_6) of compound **107**

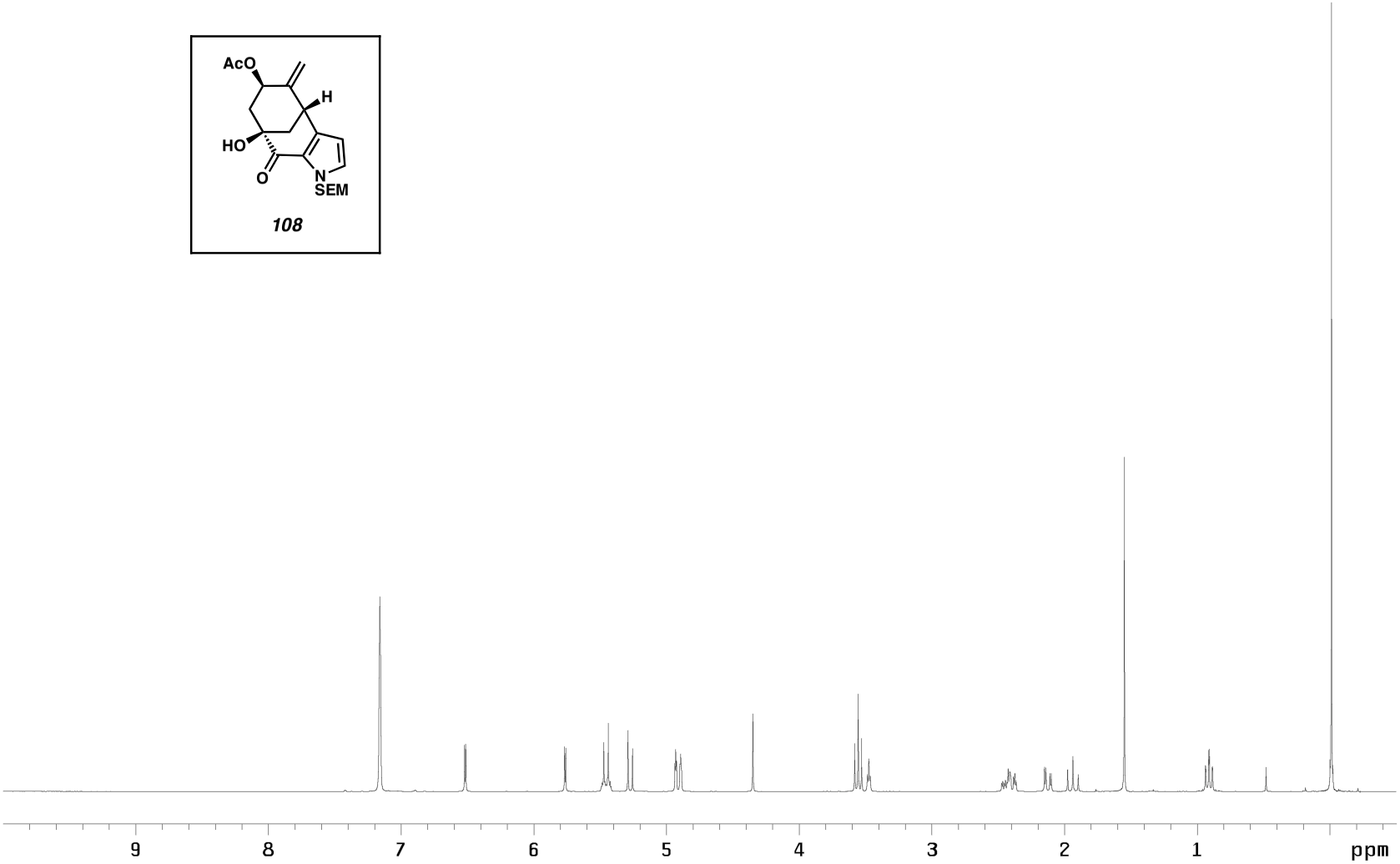


Figure A3.45 ^{1}H NMR (300 MHz, C_6D_6) of compound **108**

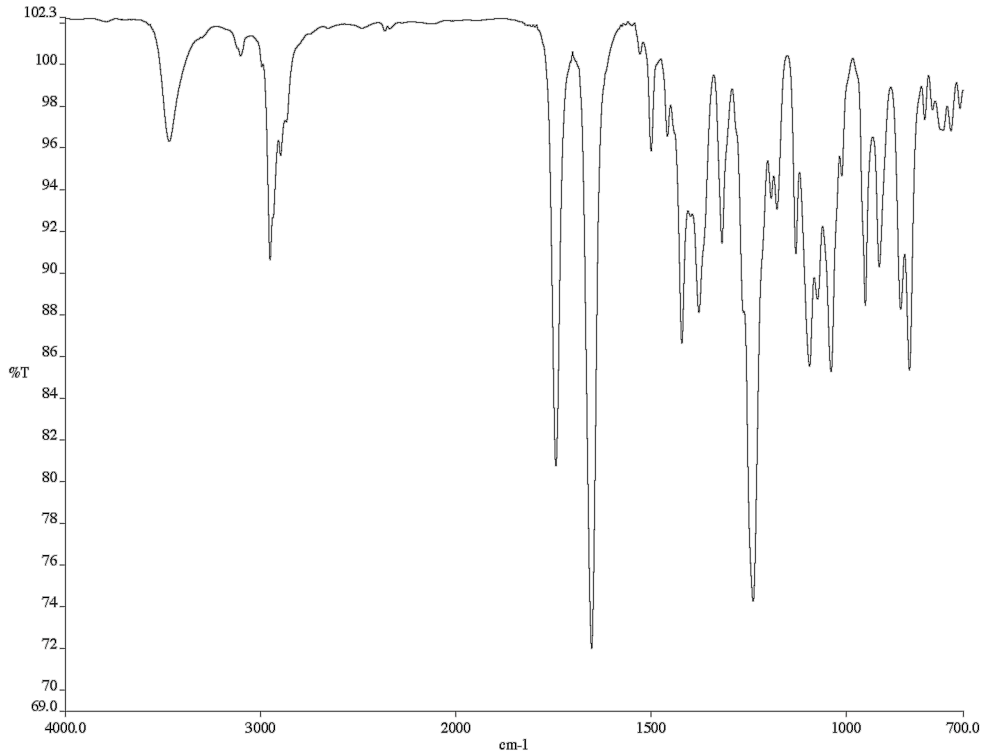


Figure A3.46 Infrared spectrum (thin film/NaCl) of compound **108**

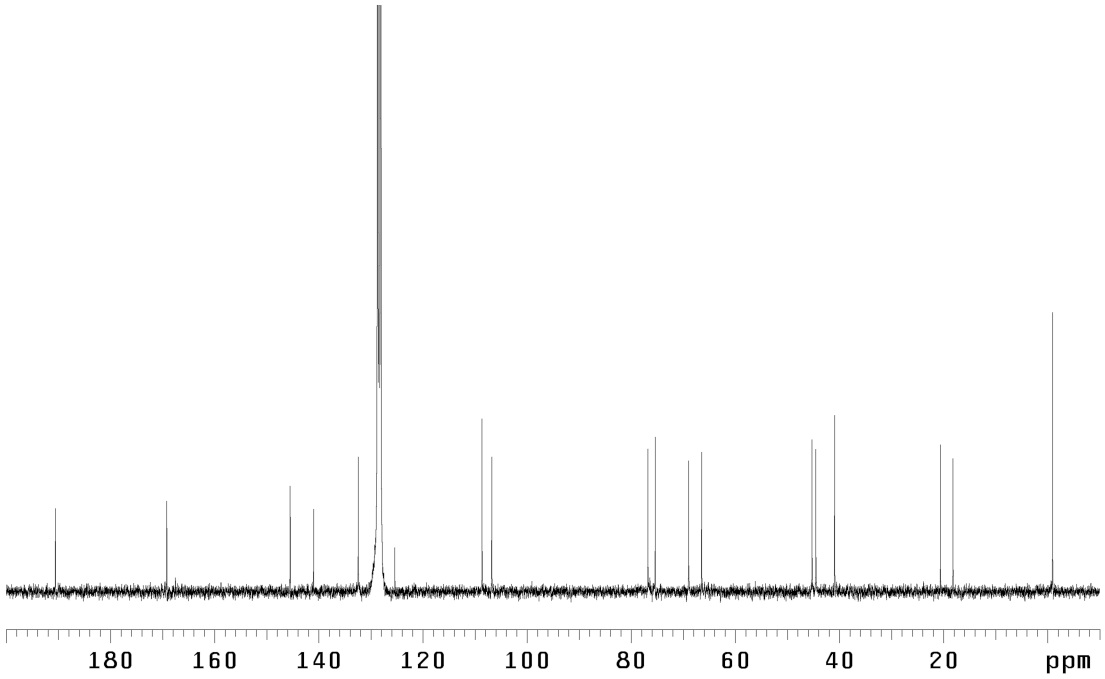


Figure A3.47 ^{13}C NMR (75 MHz, C_6D_6) of compound **108**

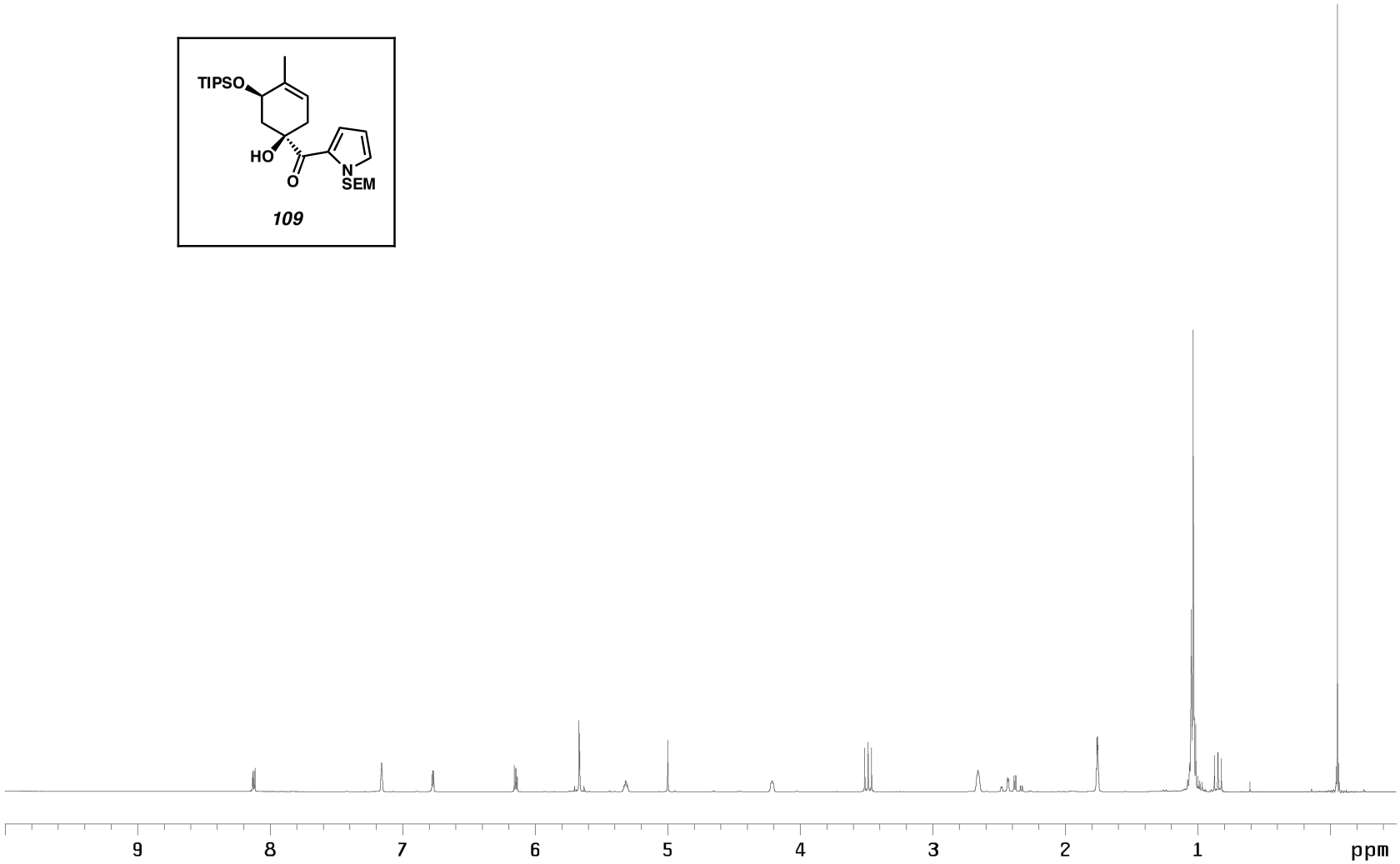


Figure A3.48 ^{1}H NMR (300 MHz, C_6D_6) of compound **109**

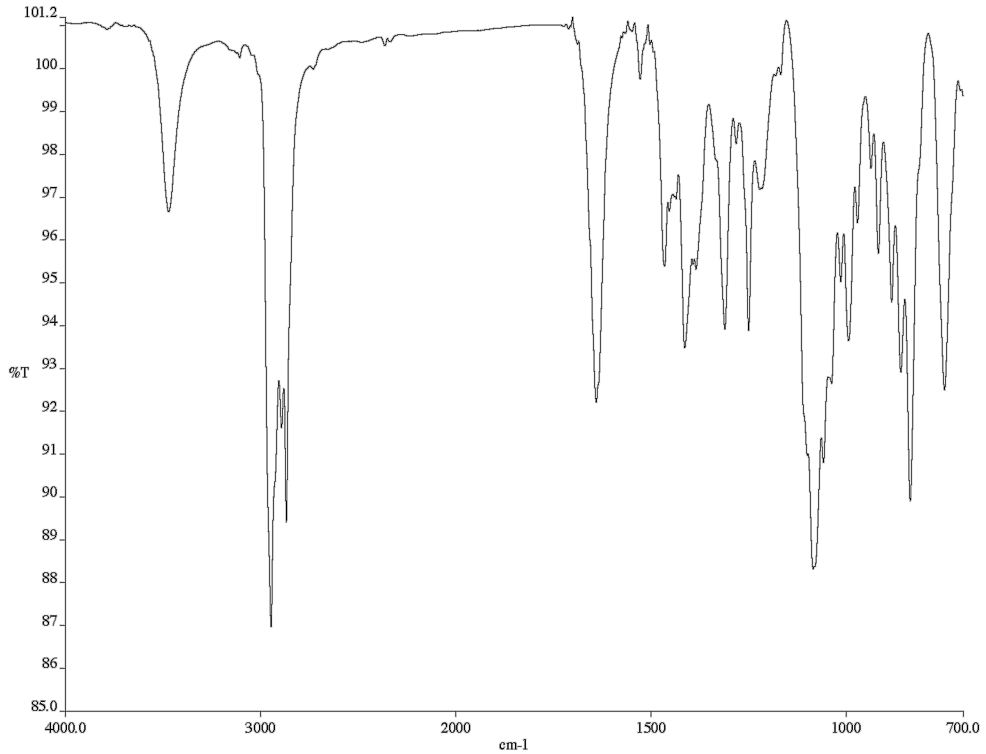


Figure A3.49 Infrared spectrum (thin film/NaCl) of compound **109**

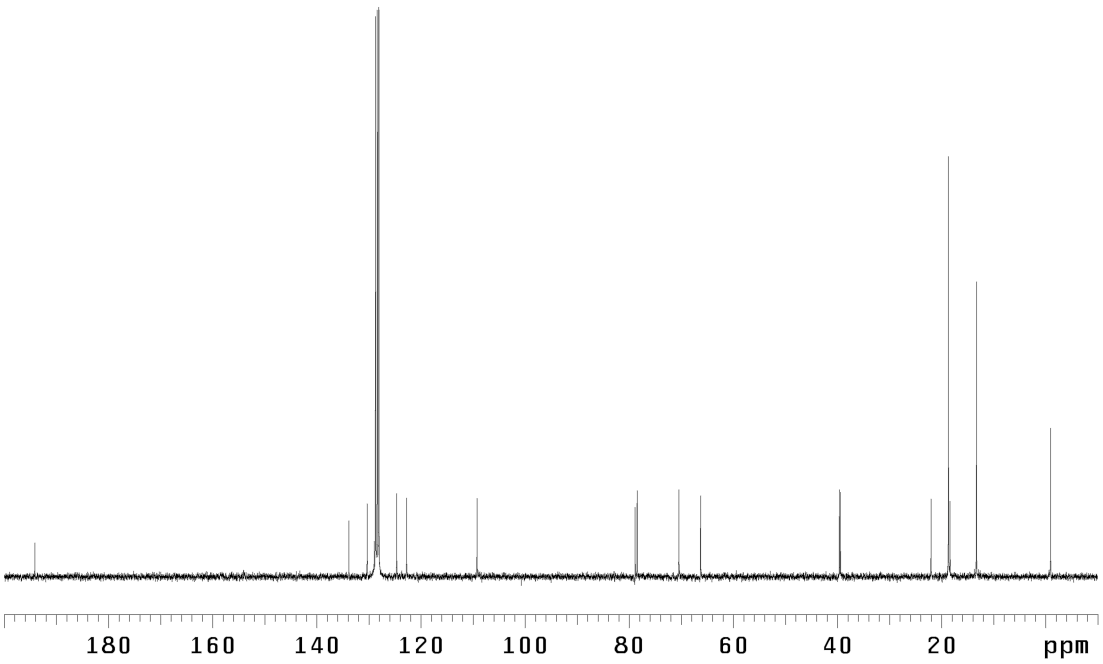


Figure A3.50 ^{13}C NMR (75 MHz, C_6D_6) of compound **109**

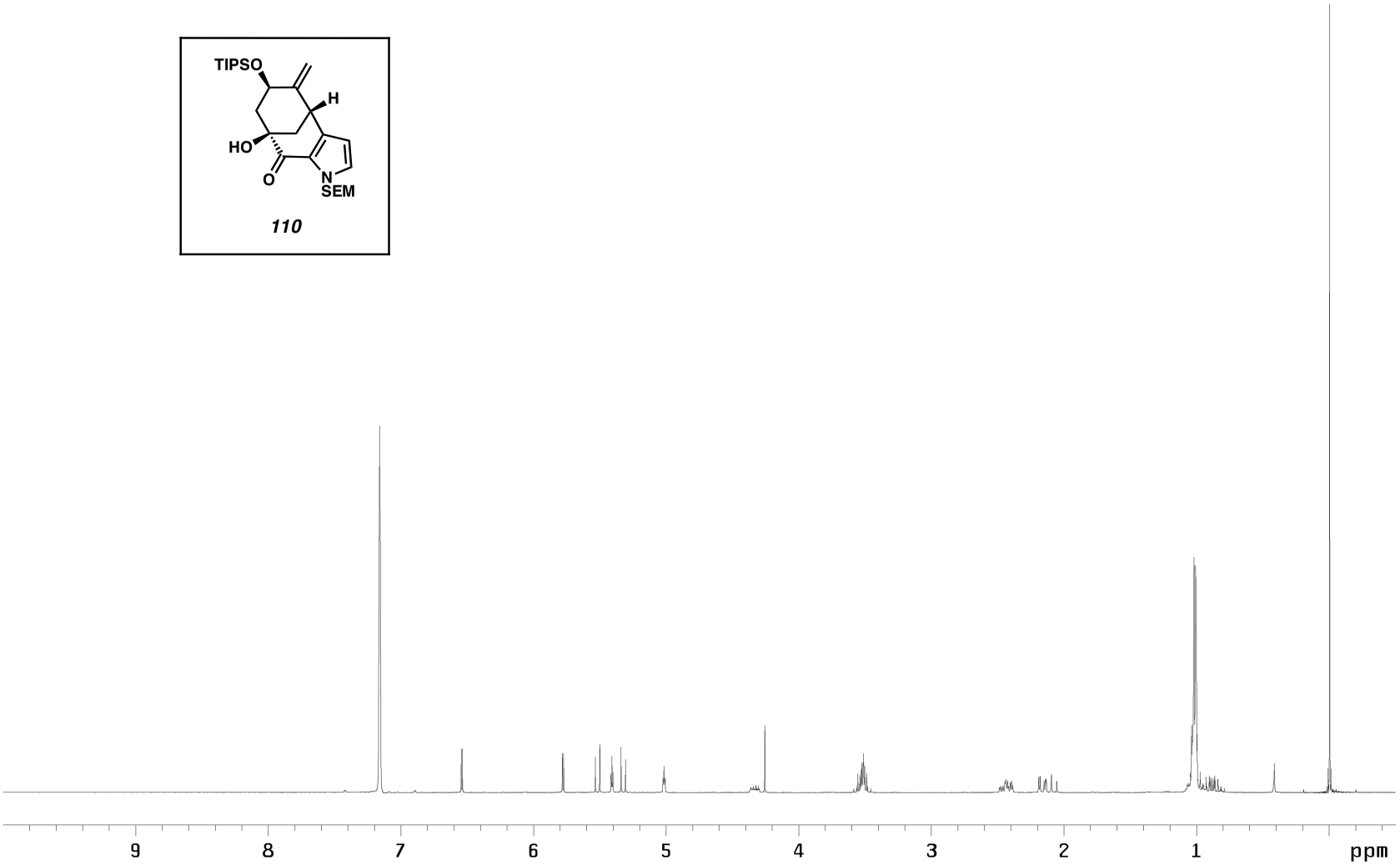


Figure A3.51 ^{1}H NMR (300 MHz, C_6D_6) of compound **110**

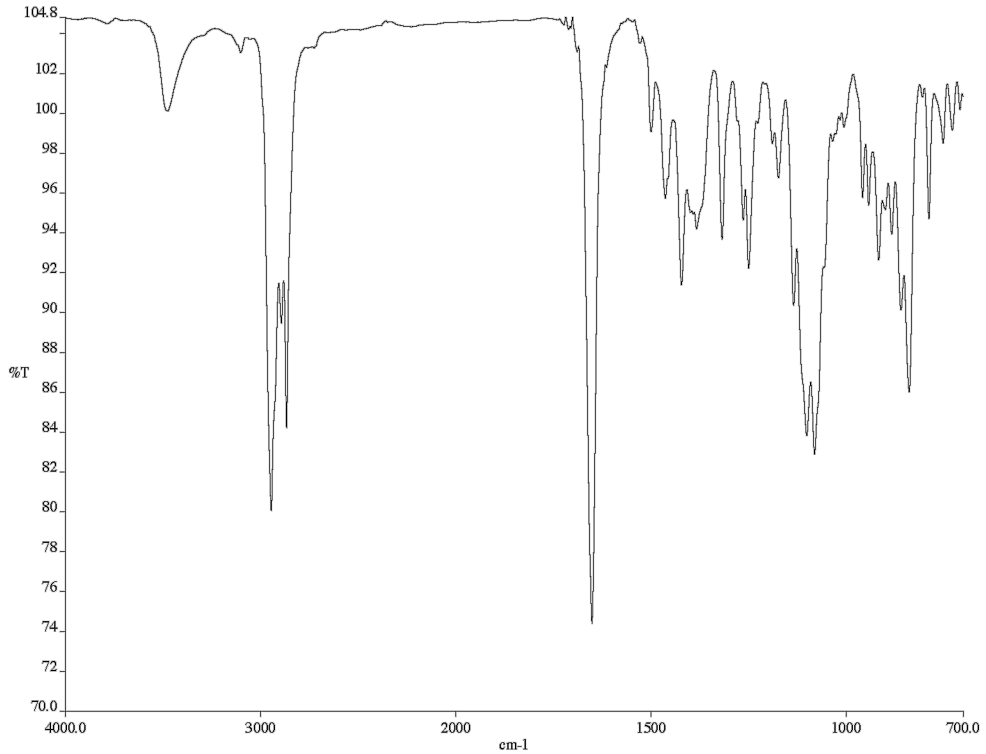


Figure A3.52 Infrared spectrum (thin film/NaCl) of compound **110**

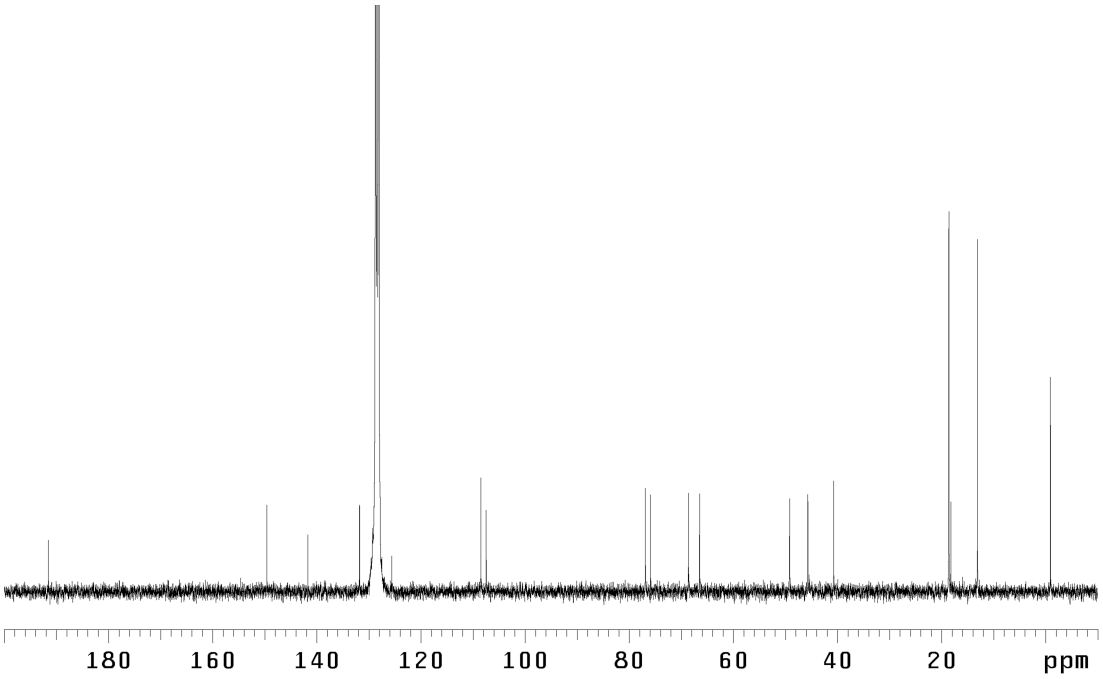


Figure A3.53 ^{13}C NMR (75 MHz, C_6D_6) of compound **110**

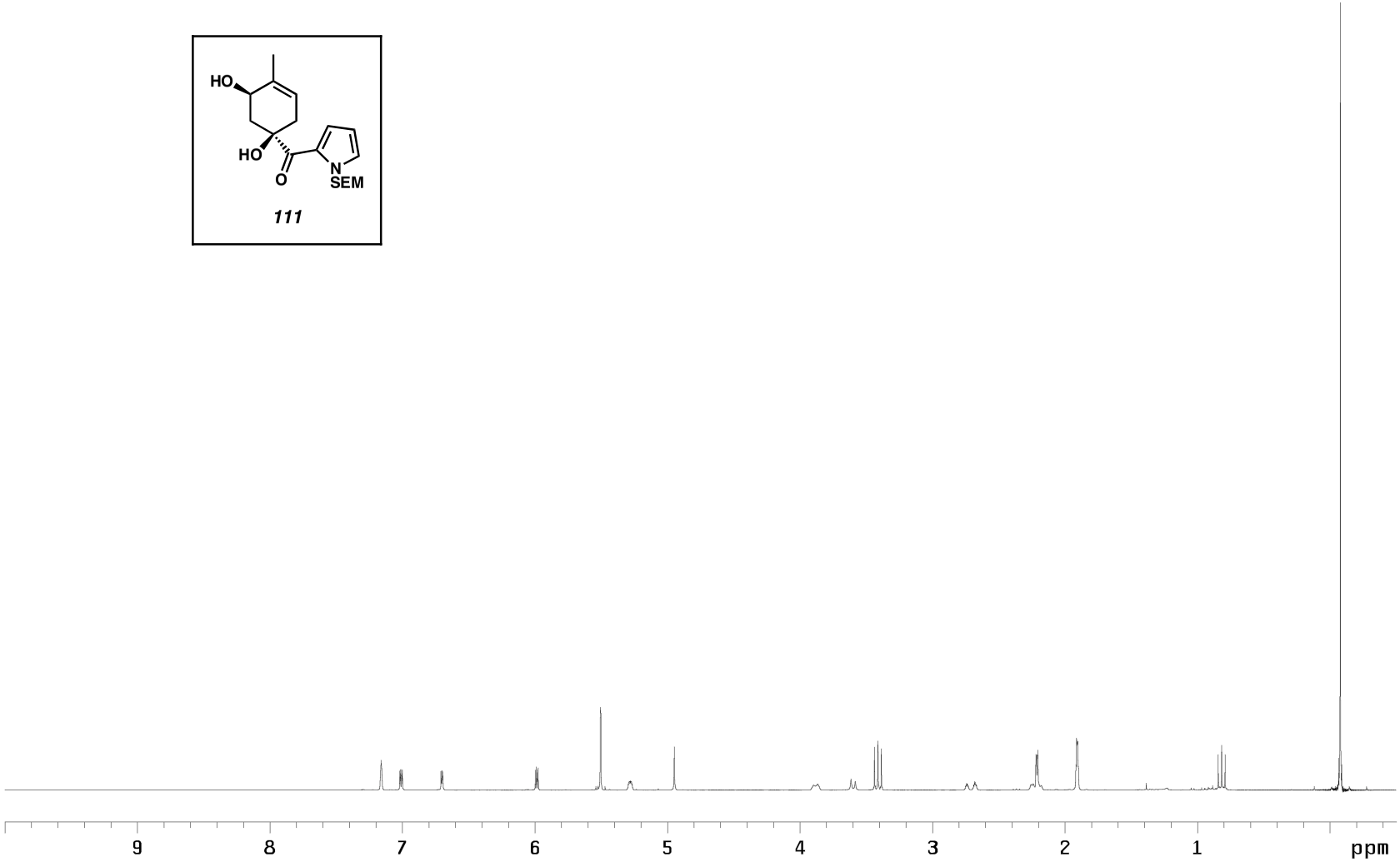


Figure A3.54 ^{1}H NMR (300 MHz, C_6D_6) of compound **111**

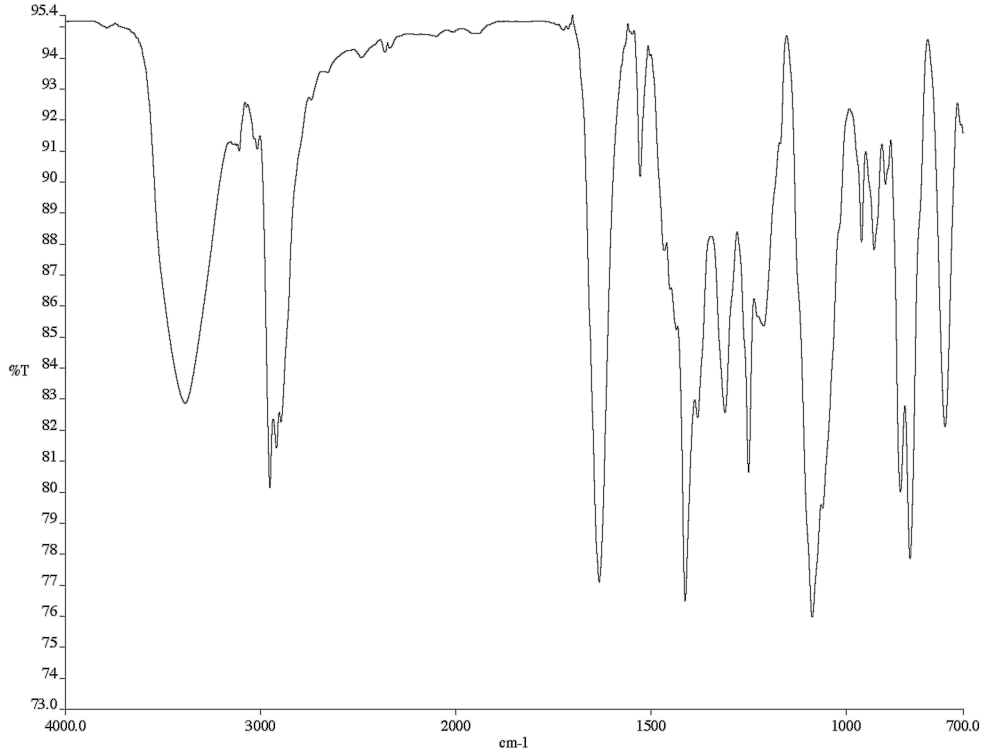


Figure A3.55 Infrared spectrum (thin film/NaCl) of compound **111**

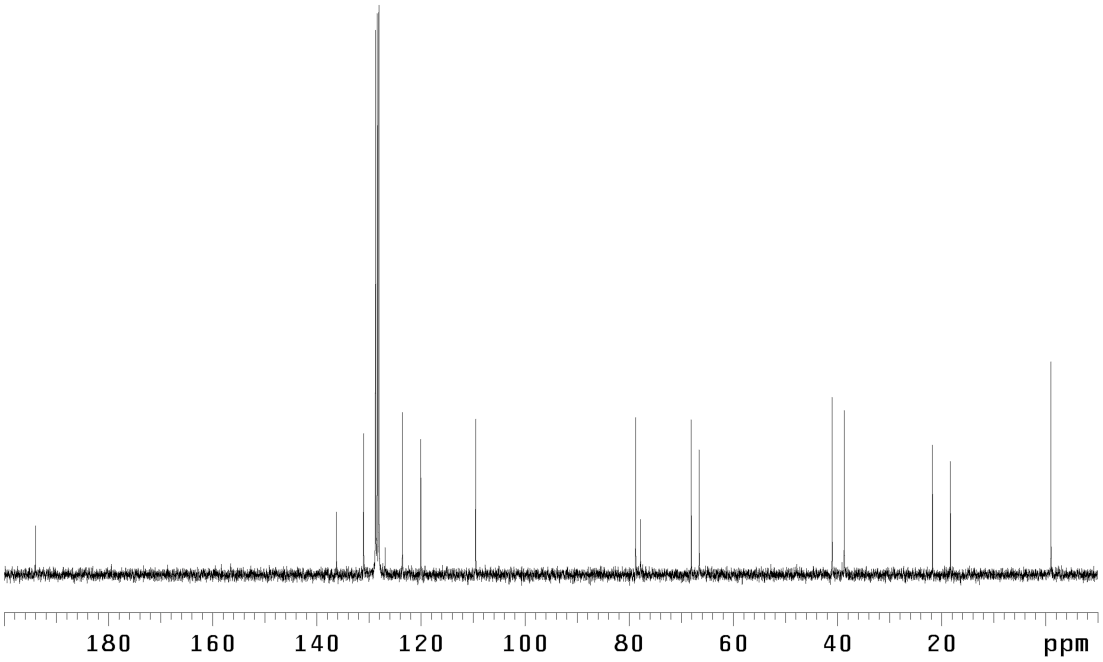


Figure A3.56 ^{13}C NMR (75 MHz, C_6D_6) of compound **111**

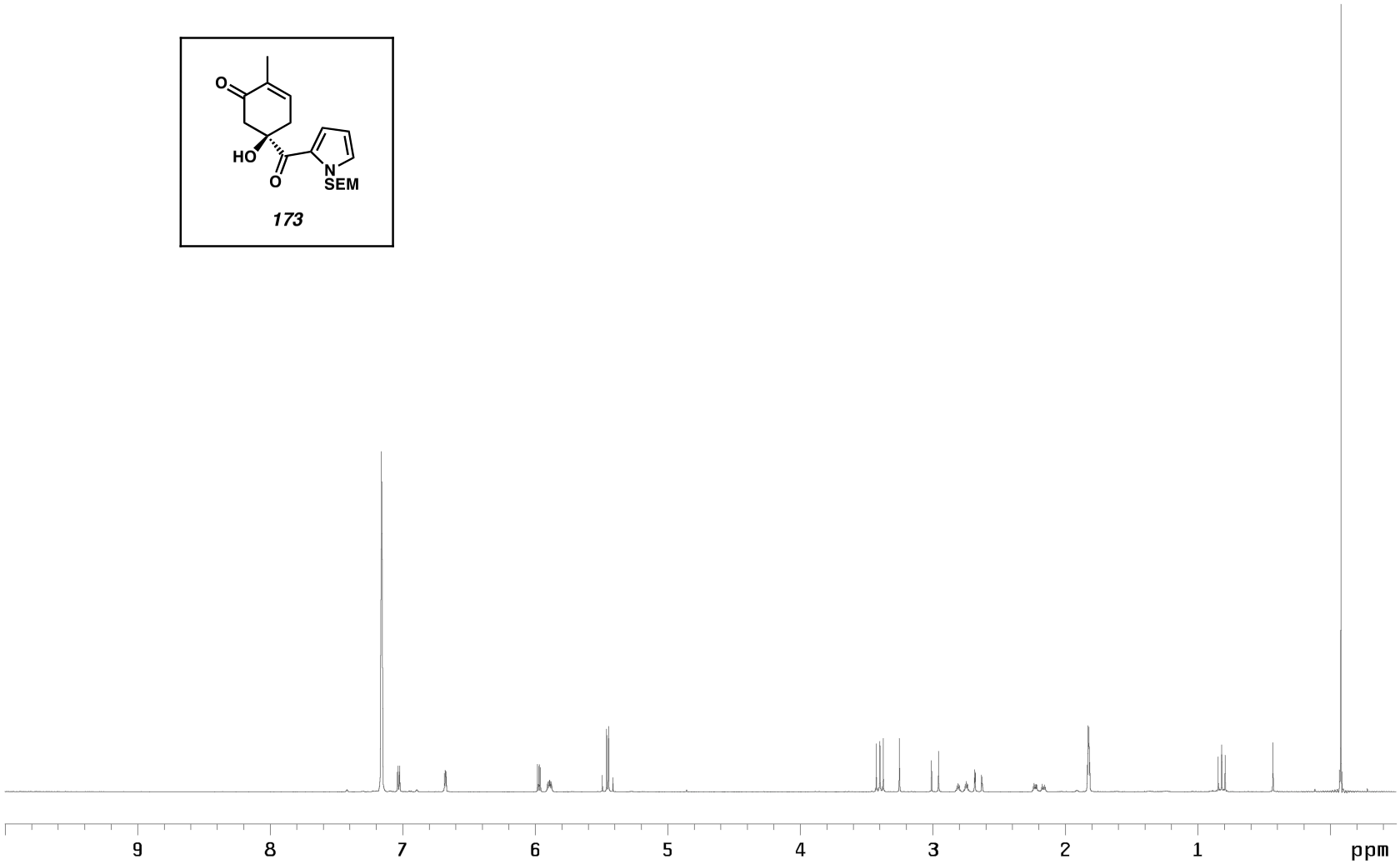


Figure A3.57 ^{1}H NMR (300 MHz, C_6D_6) of compound **173**

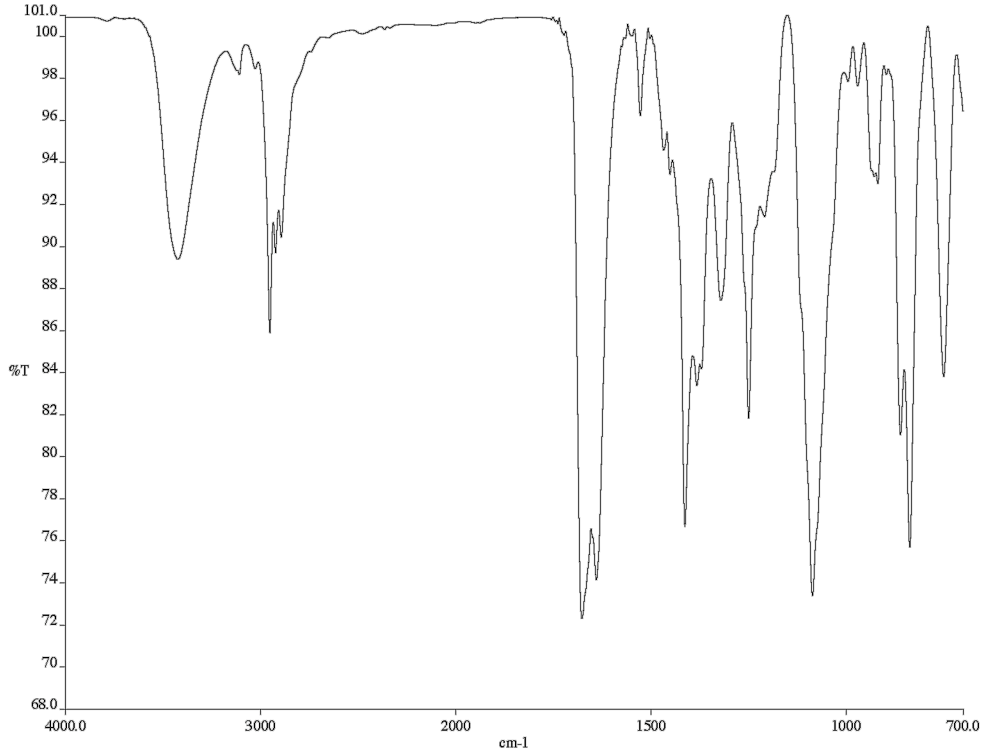


Figure A3.58 Infrared spectrum (thin film/NaCl) of compound **173**

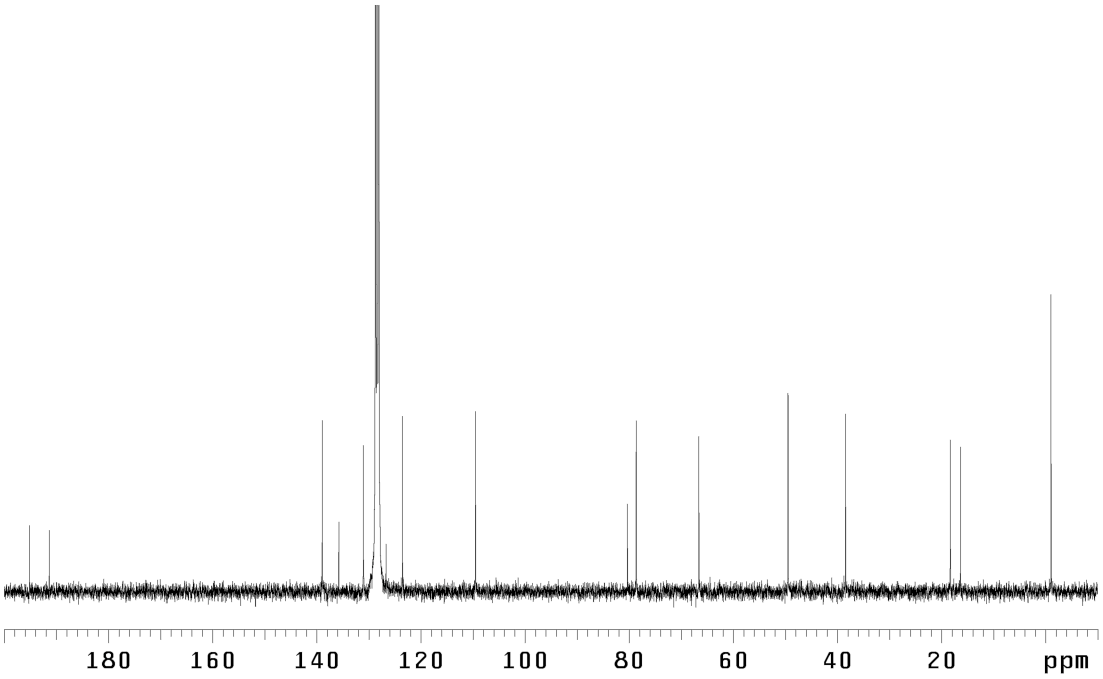


Figure A3.59 ^{13}C NMR (75 MHz, C_6D_6) of compound **173**

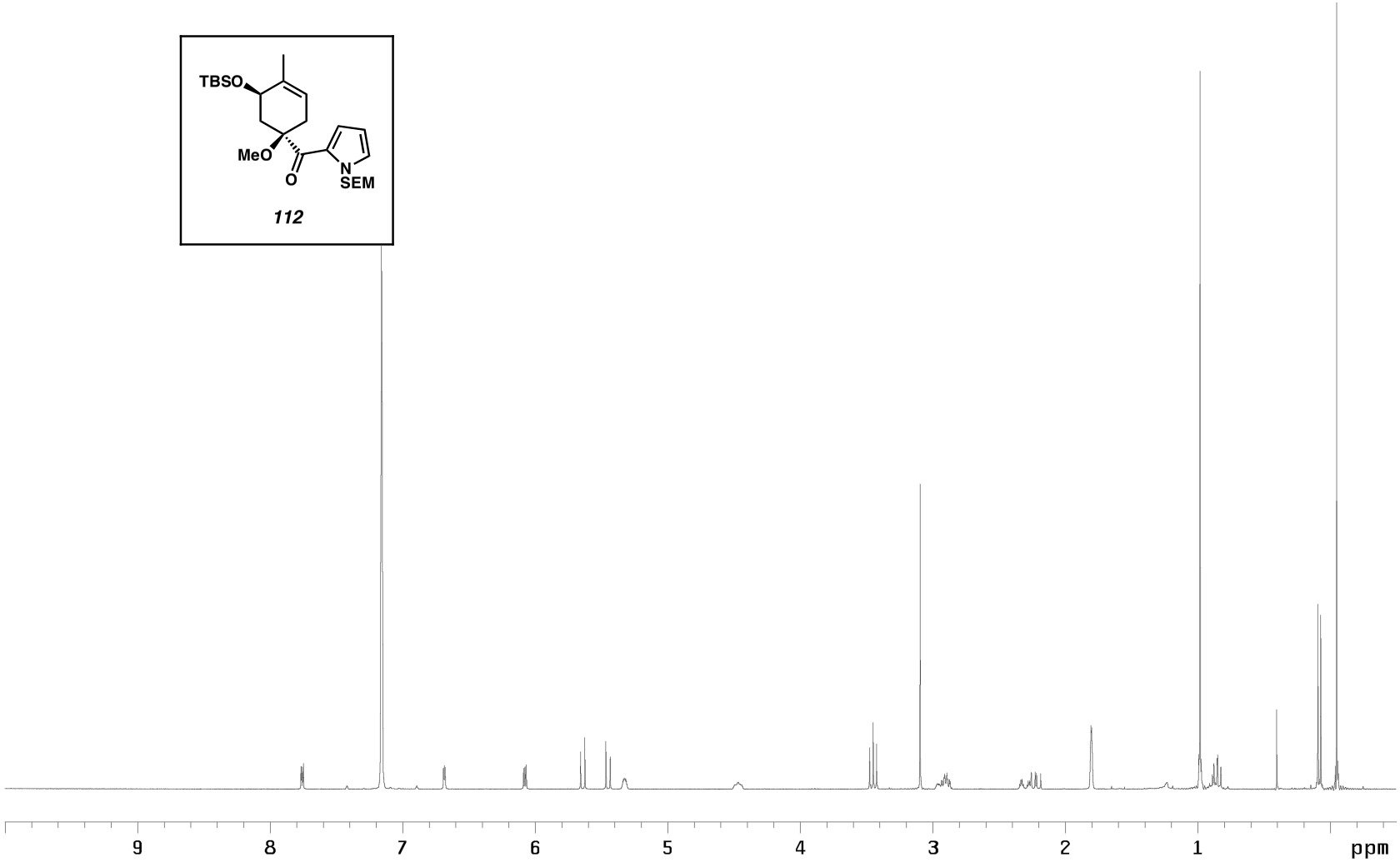


Figure A3.60 ^{1}H NMR (300 MHz, C_6D_6) of compound **112**

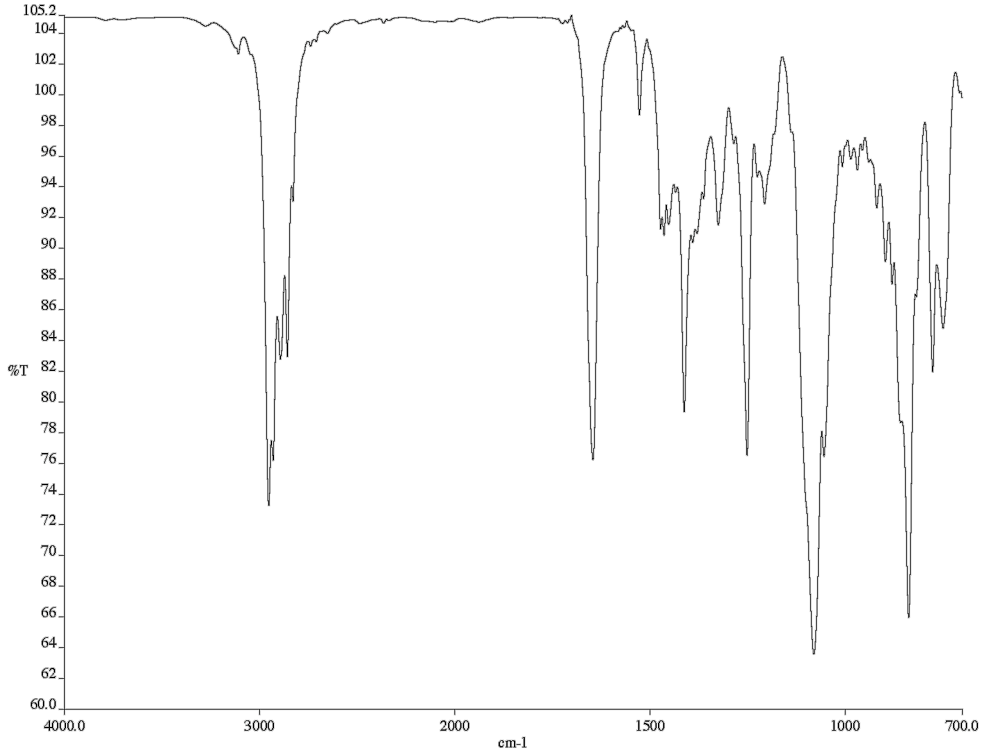


Figure A3.61 Infrared spectrum (thin film/NaCl) of compound **112**

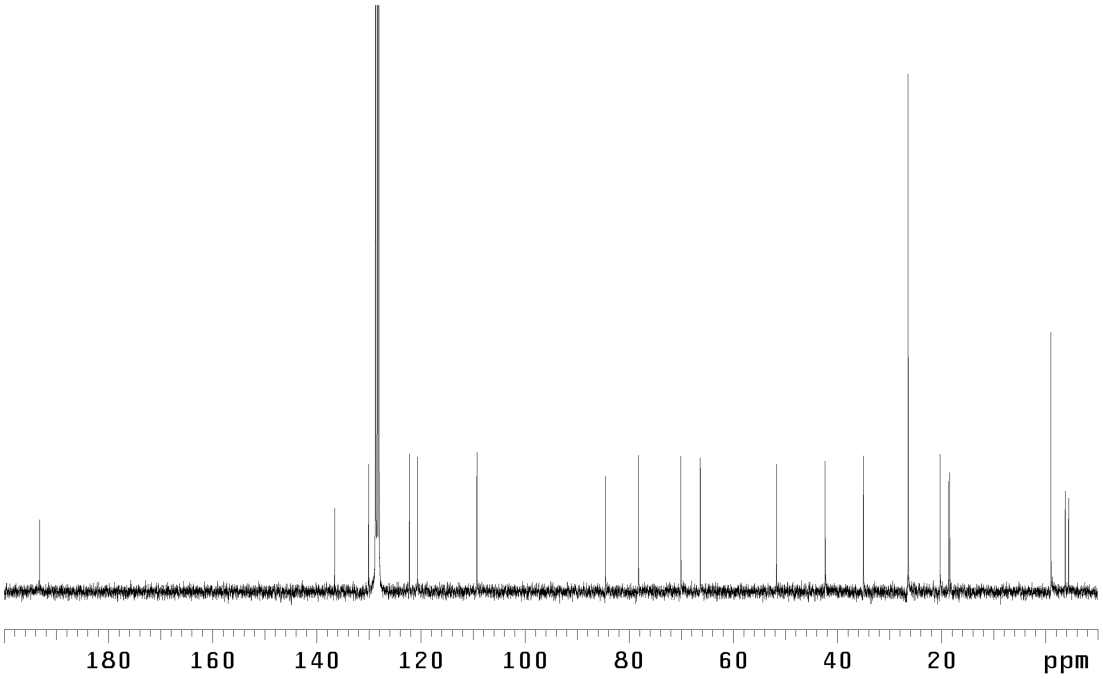


Figure A3.62 ^{13}C NMR (75 MHz, C_6D_6) of compound **112**

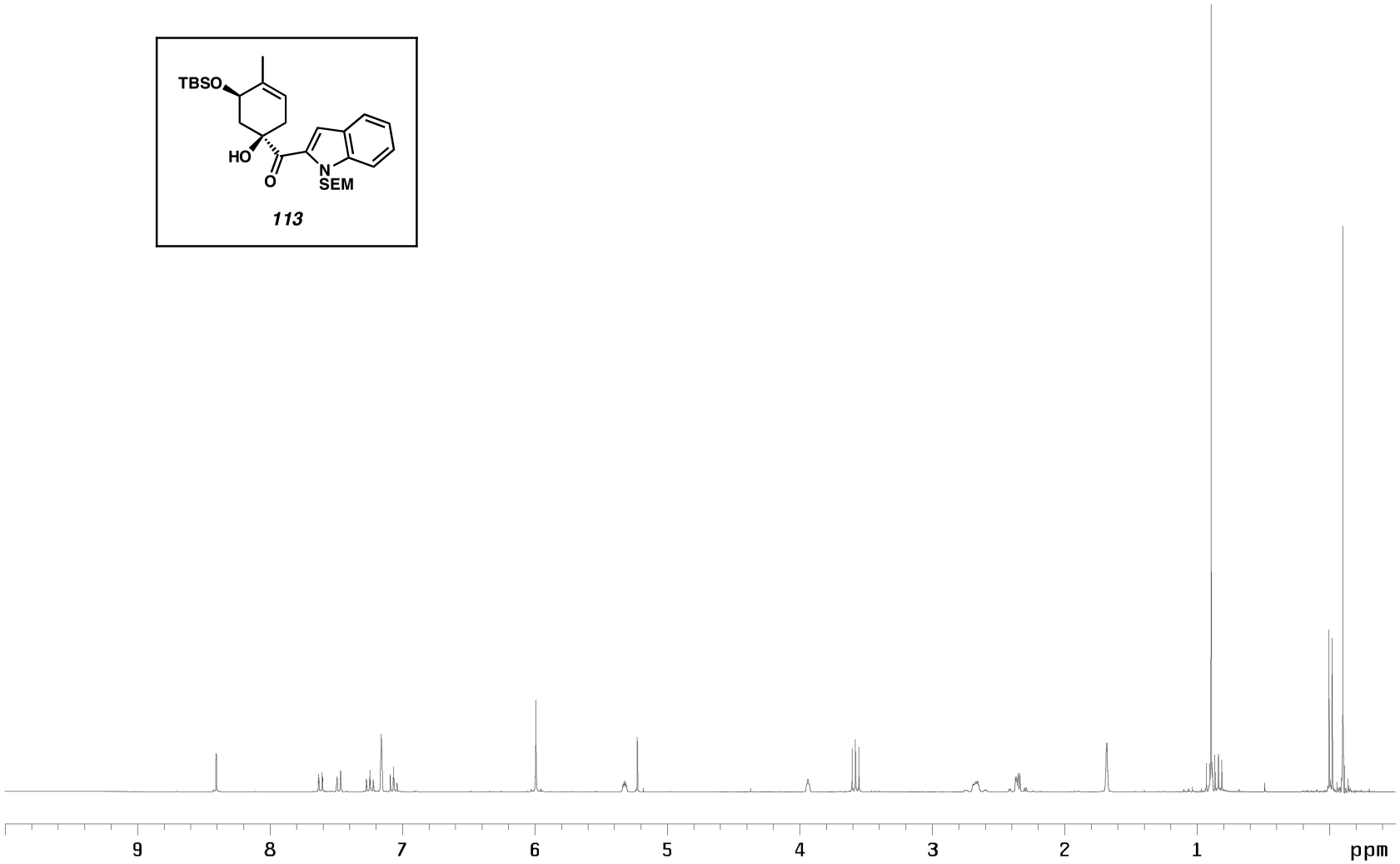


Figure A3.63 ^{1}H NMR (300 MHz, C_6D_6) of compound **113**

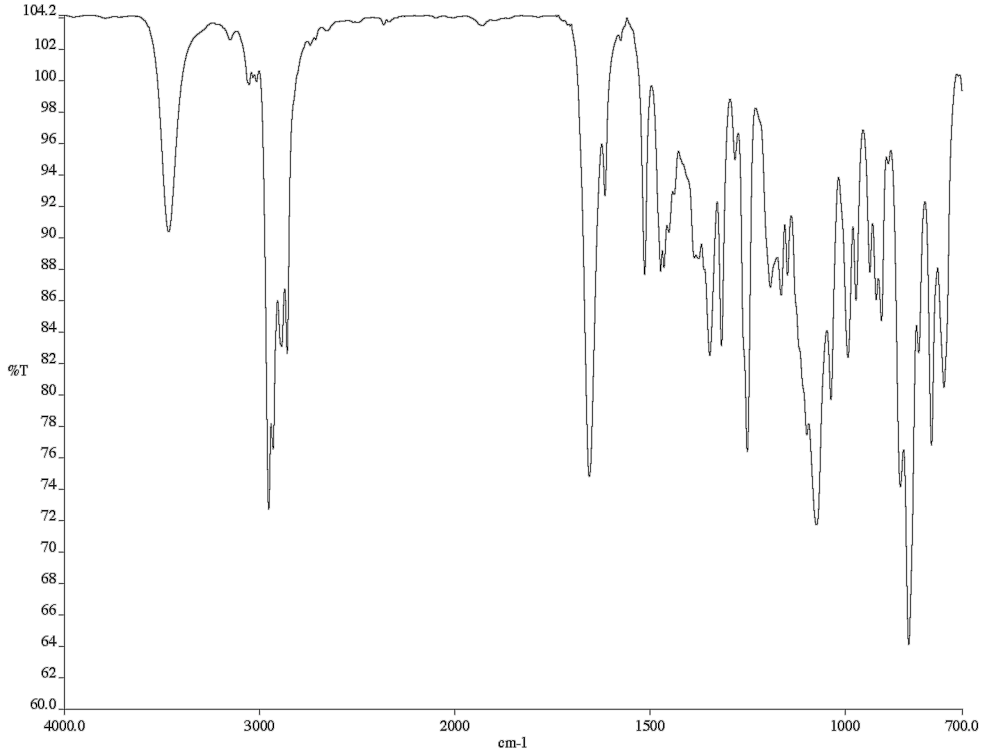


Figure A3.64 Infrared spectrum (thin film/NaCl) of compound **113**

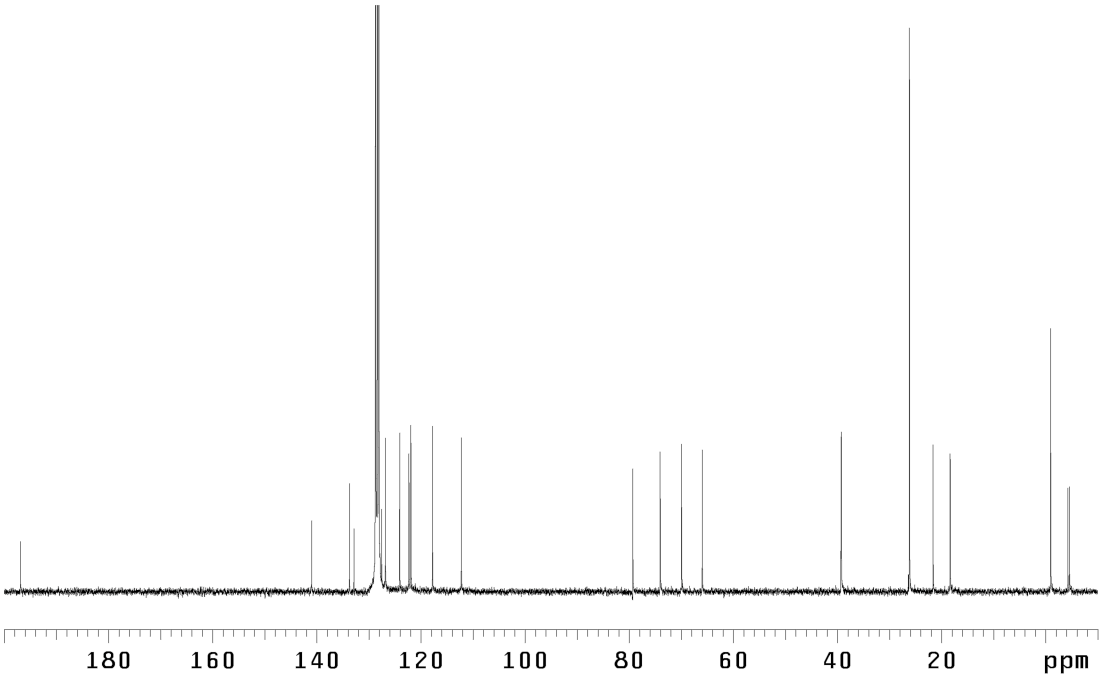


Figure A3.65 ^{13}C NMR (75 MHz, C_6D_6) of compound **113**

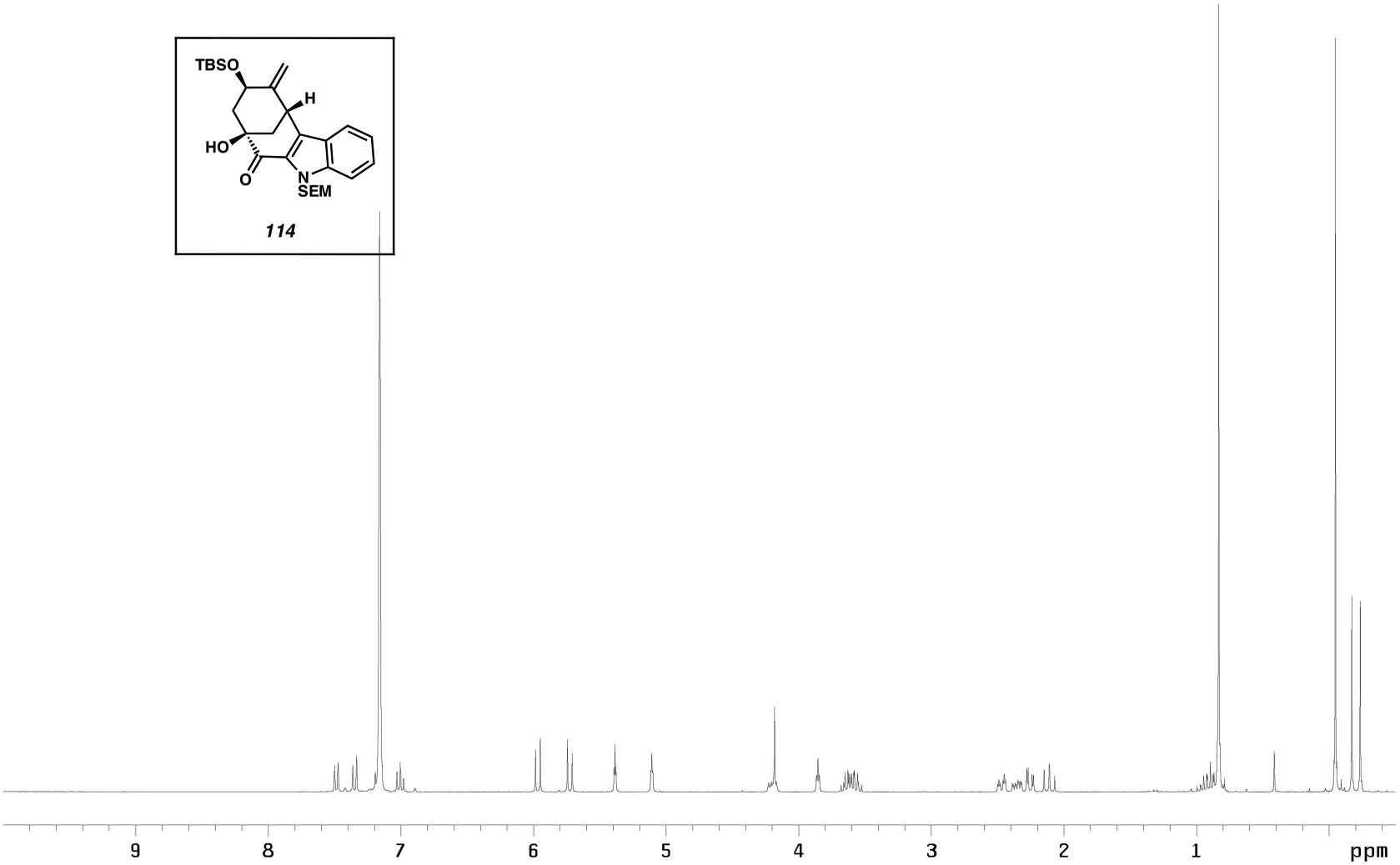


Figure A3.66 ^{1}H NMR (300 MHz, C_6D_6) of compound **114**

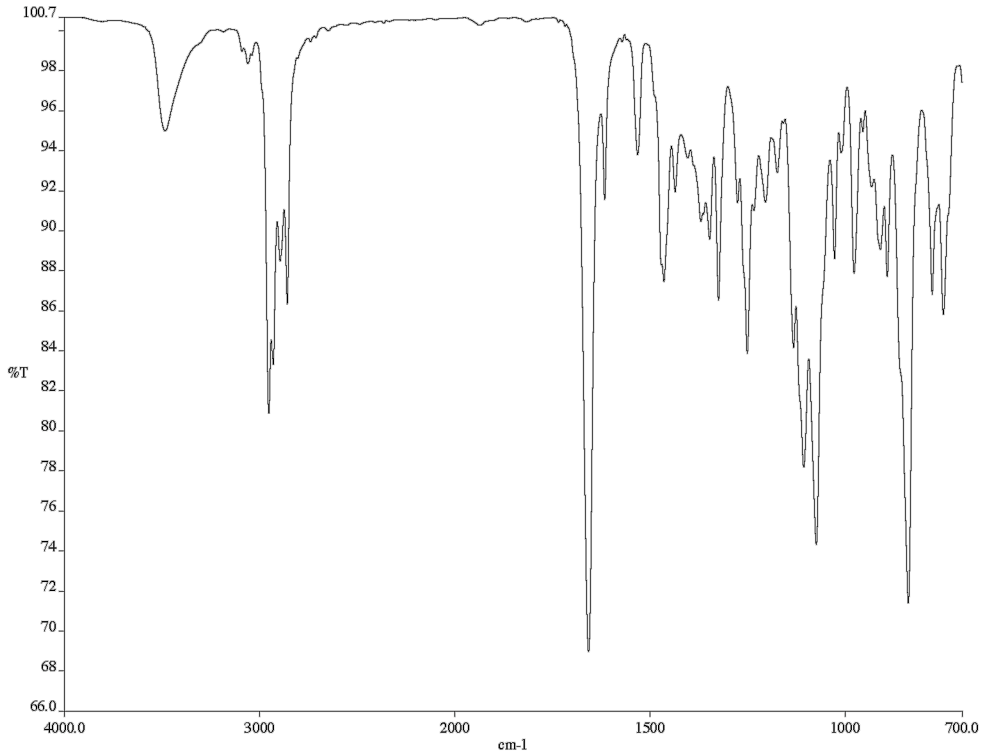


Figure A3.67 Infrared spectrum (thin film/NaCl) of compound **114**

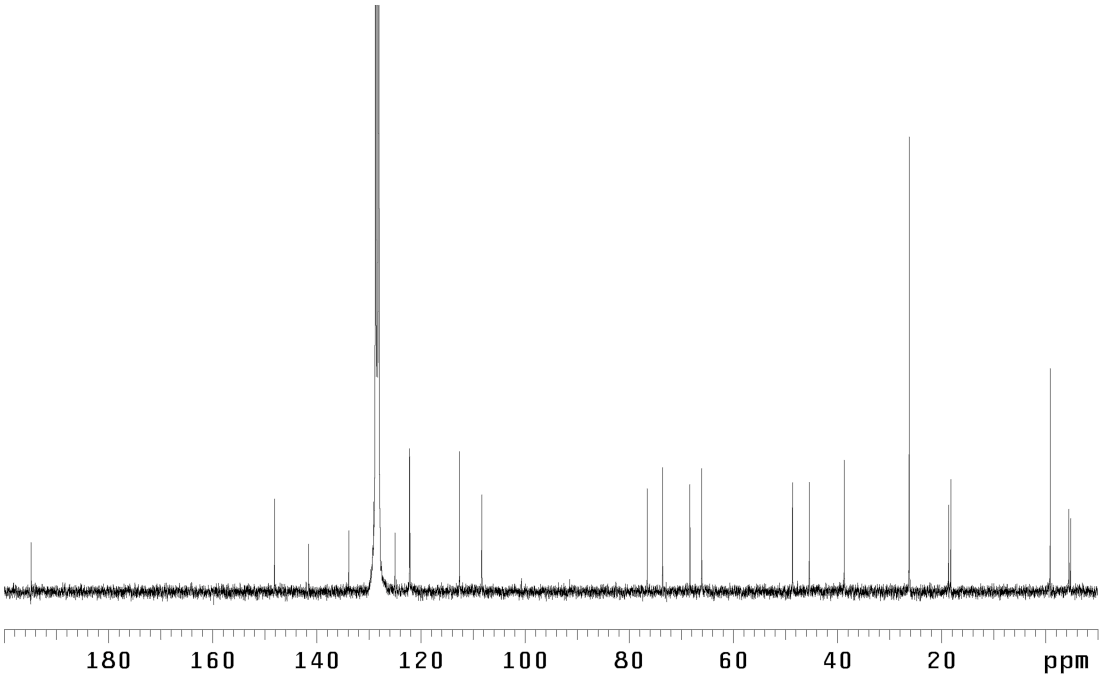


Figure A3.68 ^{13}C NMR (75 MHz, C_6D_6) of compound **114**

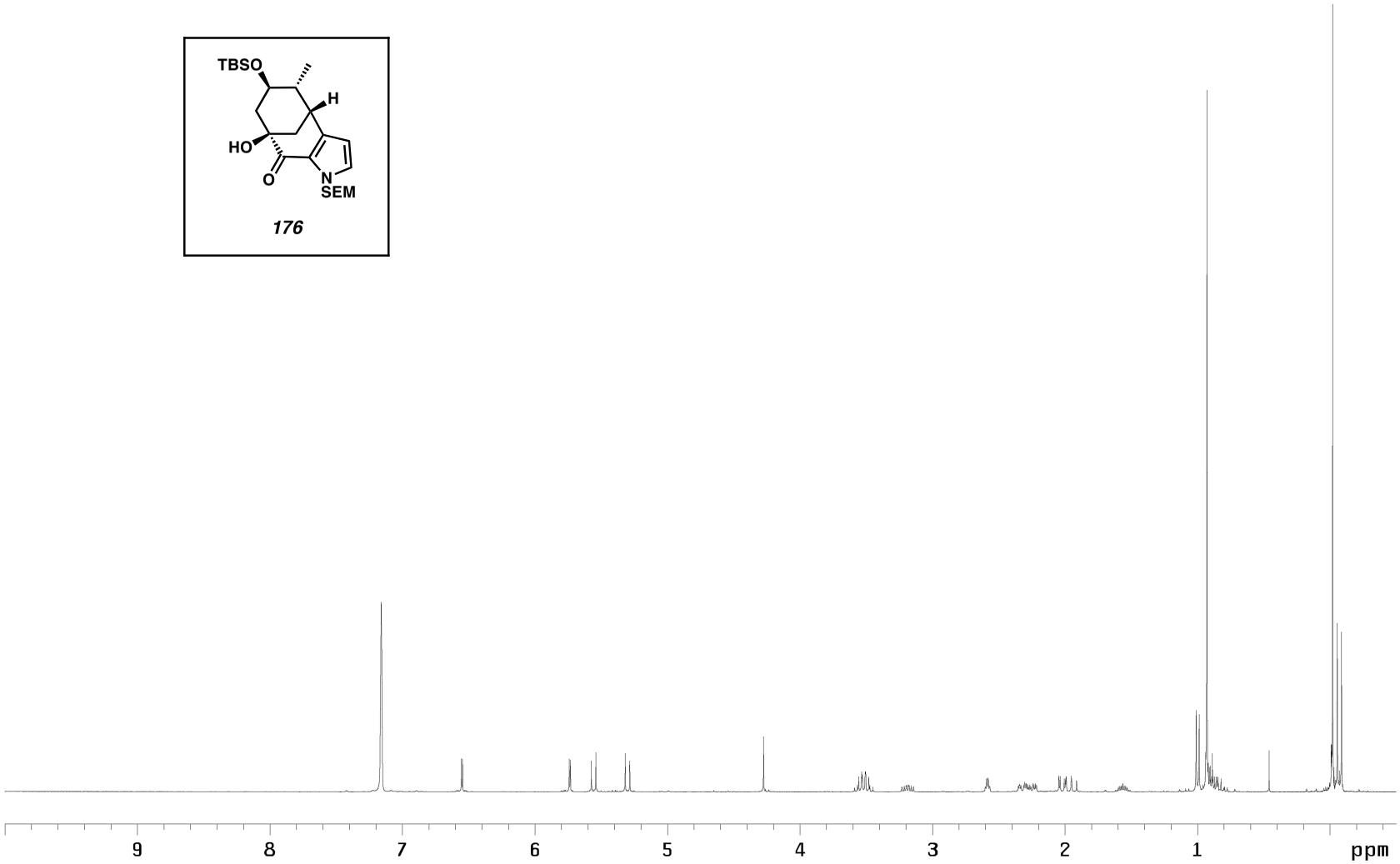


Figure A3.69 ^{1}H NMR (300 MHz, C_6D_6) of compound **176**

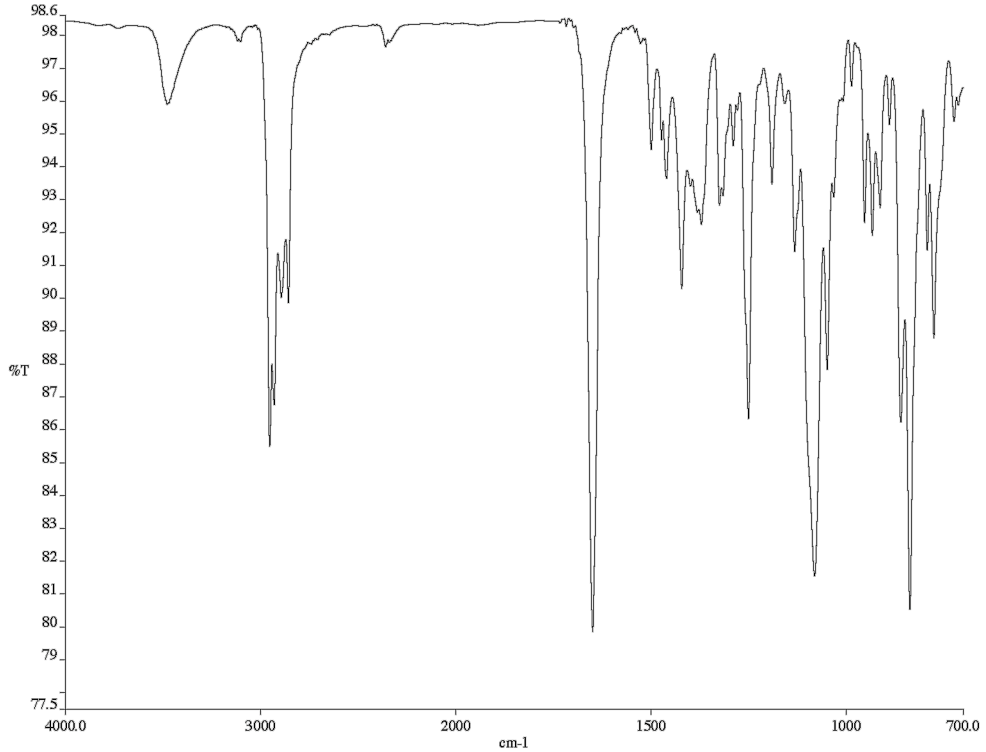


Figure A3.70 Infrared spectrum (thin film/NaCl) of compound **176**

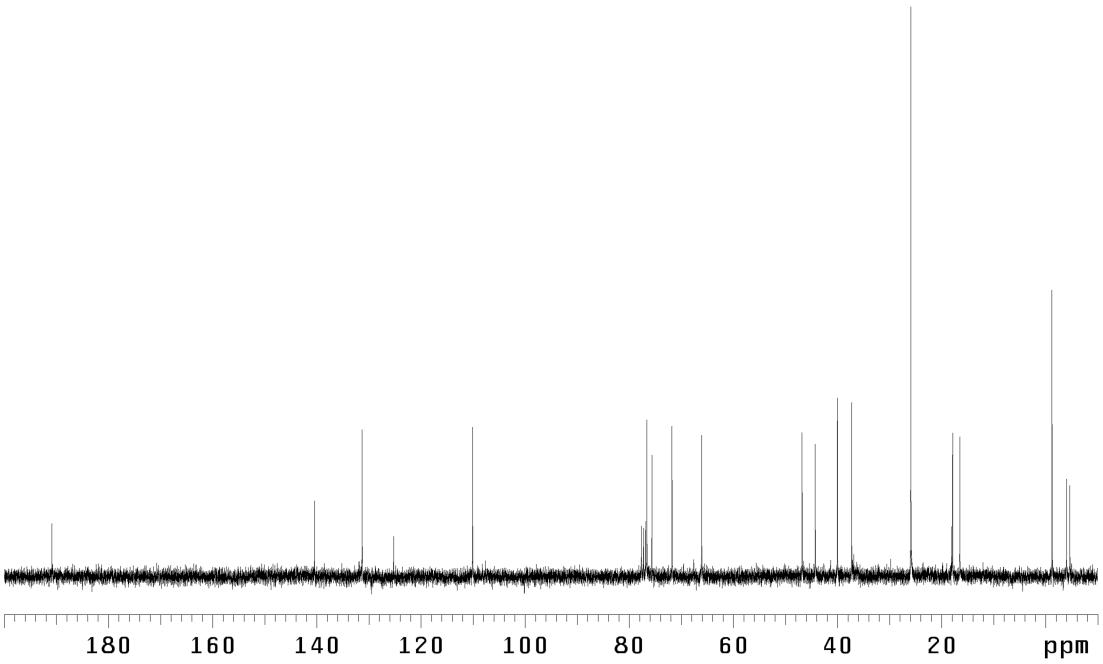


Figure A3.71 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **176**

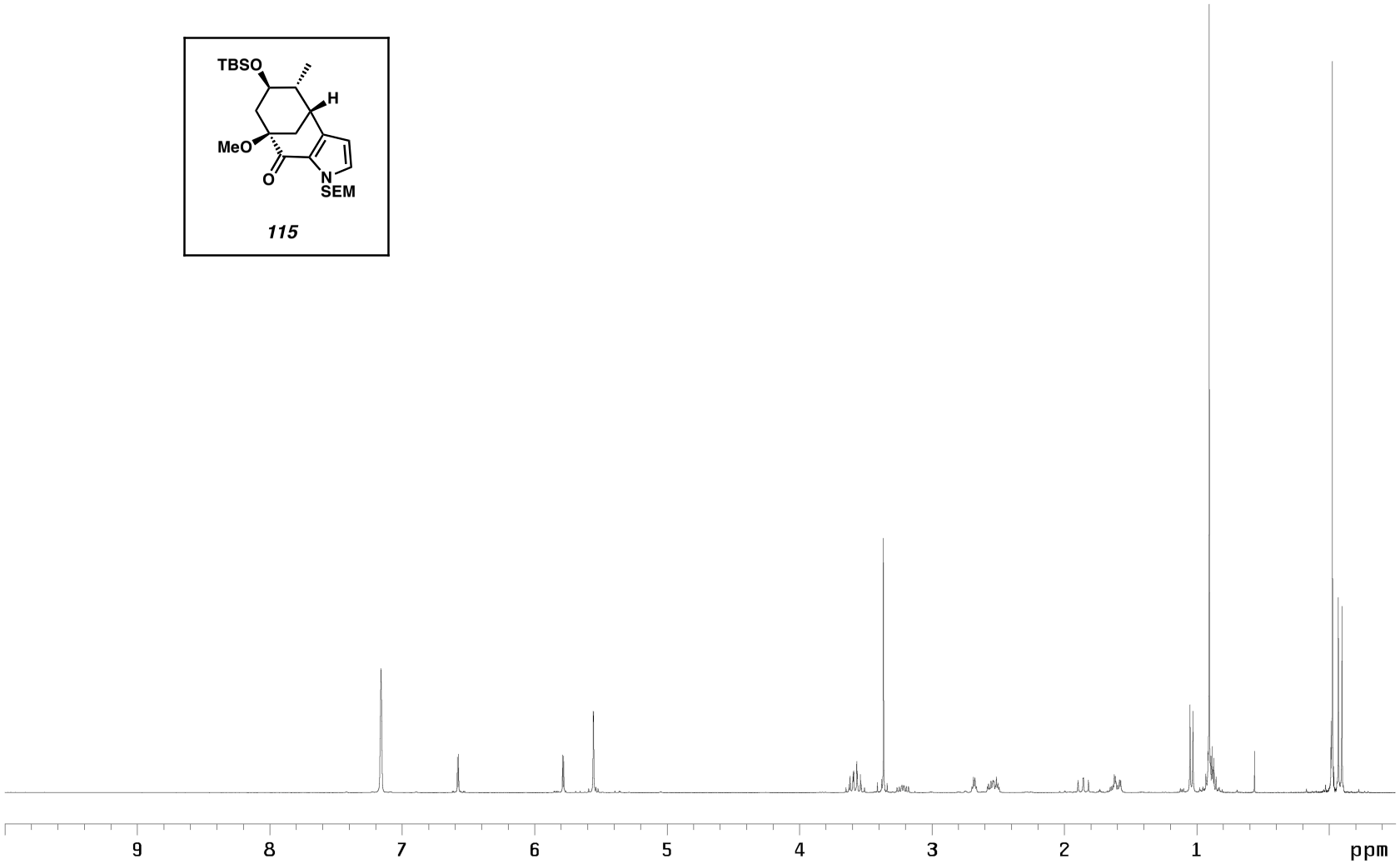


Figure A3.72 ^{1}H NMR (300 MHz, C_6D_6) of compound **115**

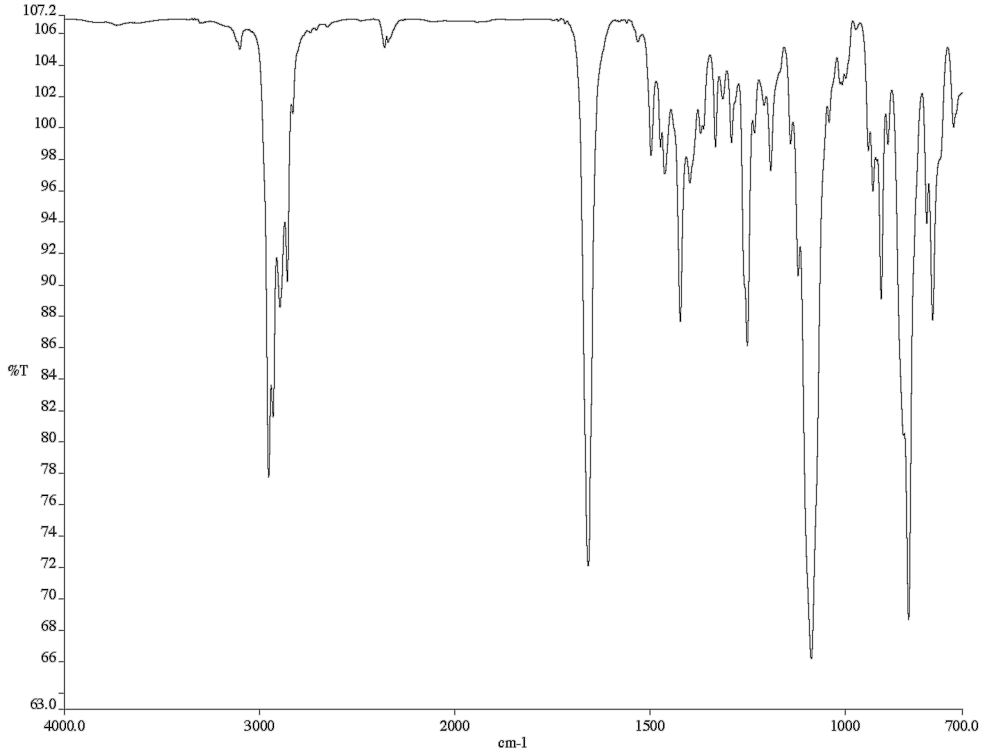


Figure A3.73 Infrared spectrum (thin film/NaCl) of compound **115**

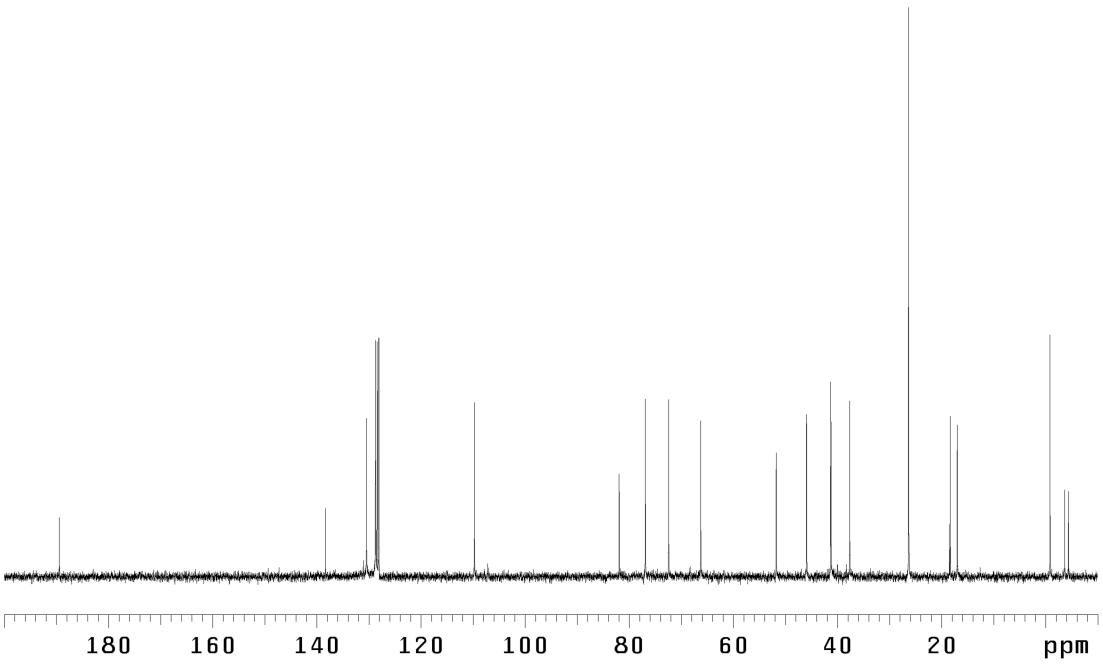


Figure A3.74 ^{13}C NMR (75 MHz, C_6D_6) of compound **115**

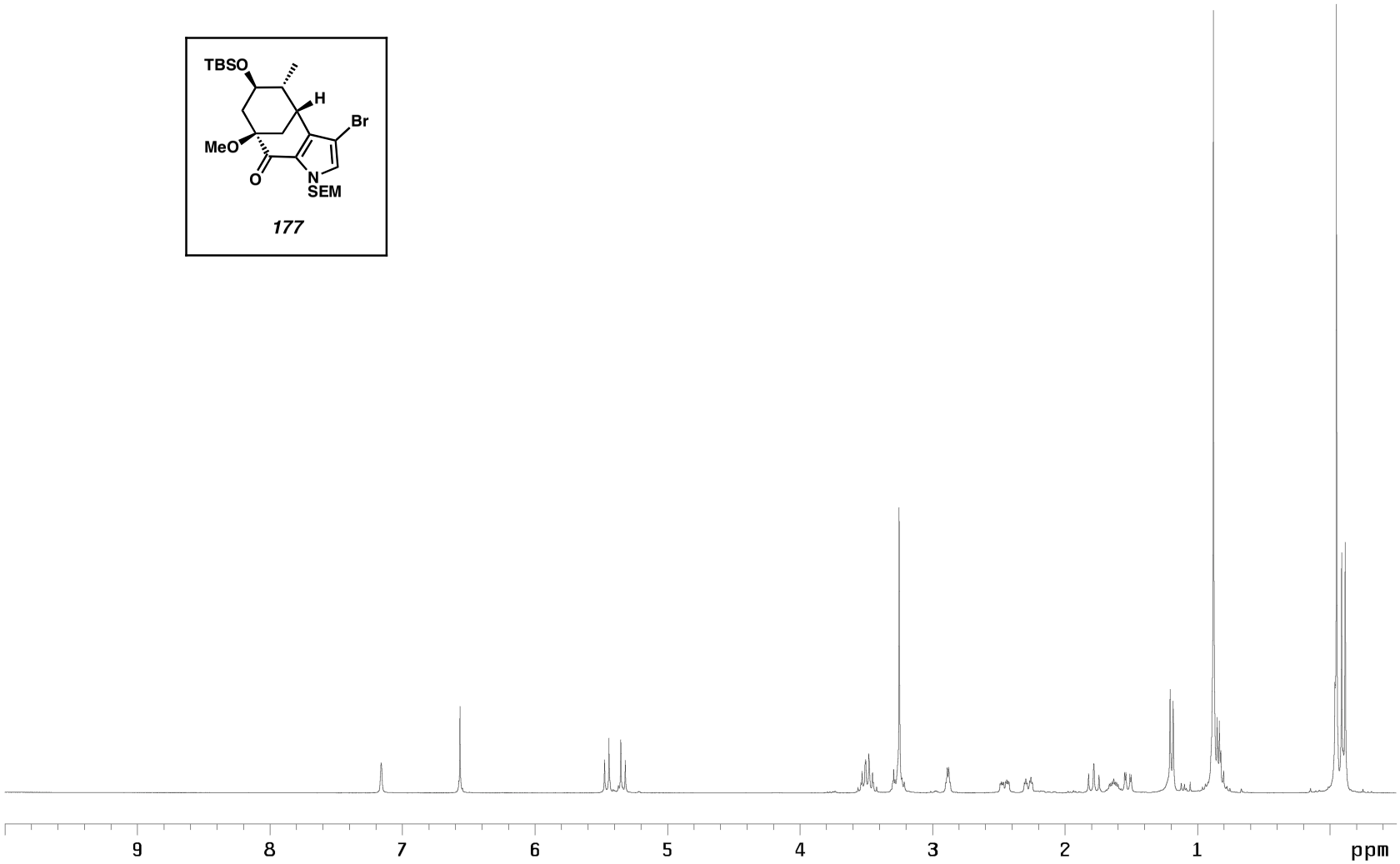


Figure A3.75 ^{1}H NMR (300 MHz, C_6D_6) of compound **177**

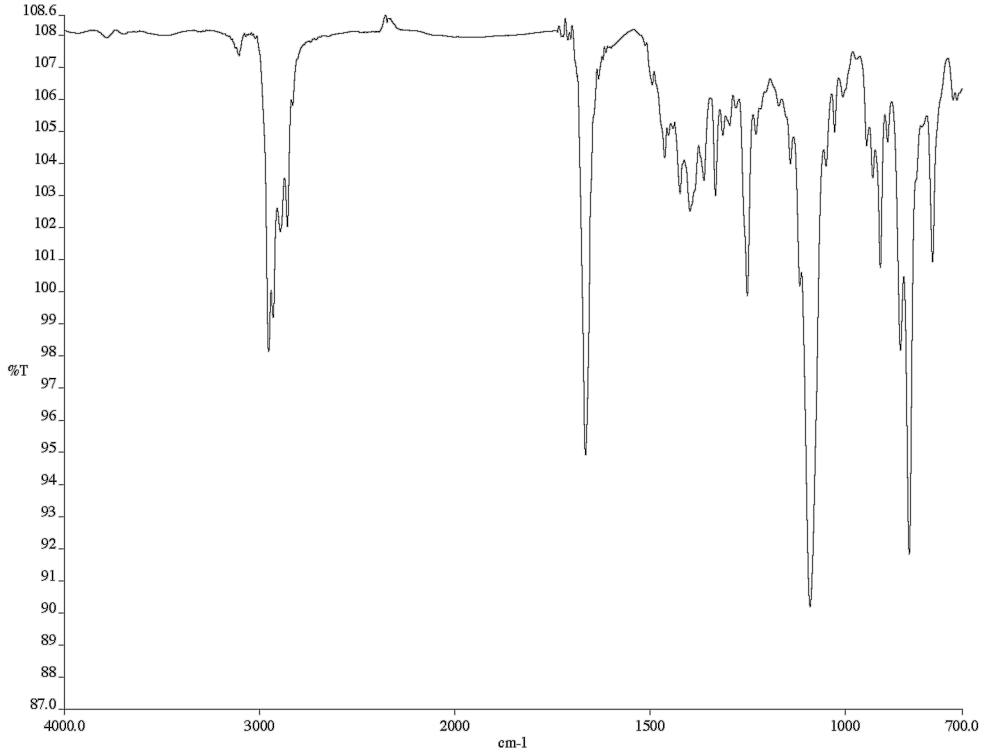


Figure A3.76 Infrared spectrum (thin film/NaCl) of compound **177**

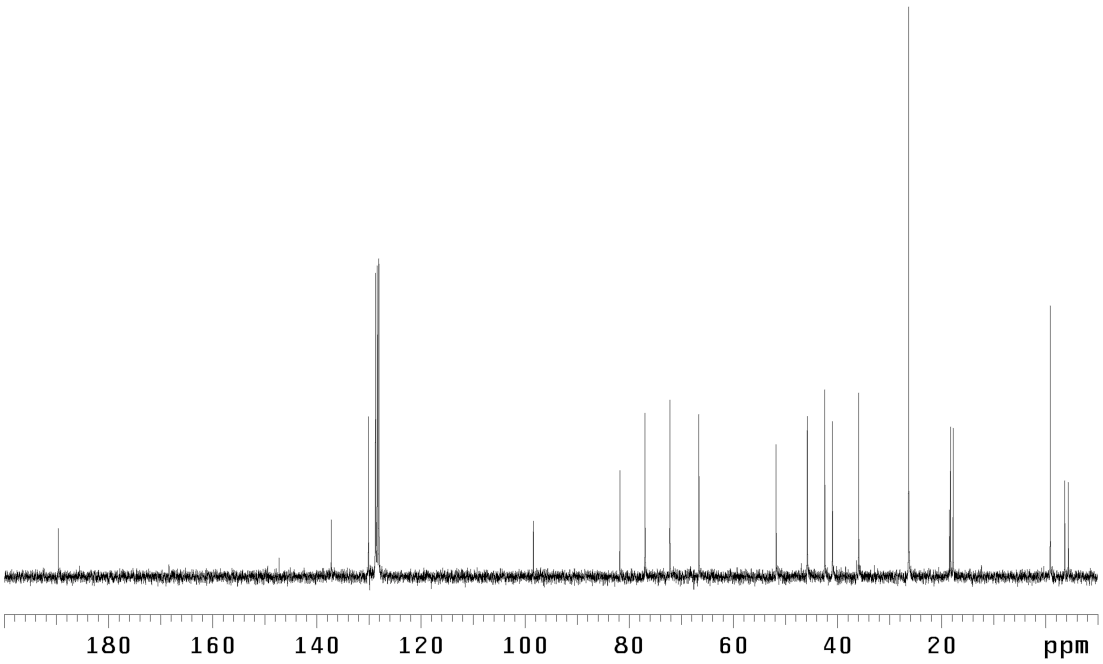


Figure A3.77 ^{13}C NMR (75 MHz, C_6D_6) of compound **177**

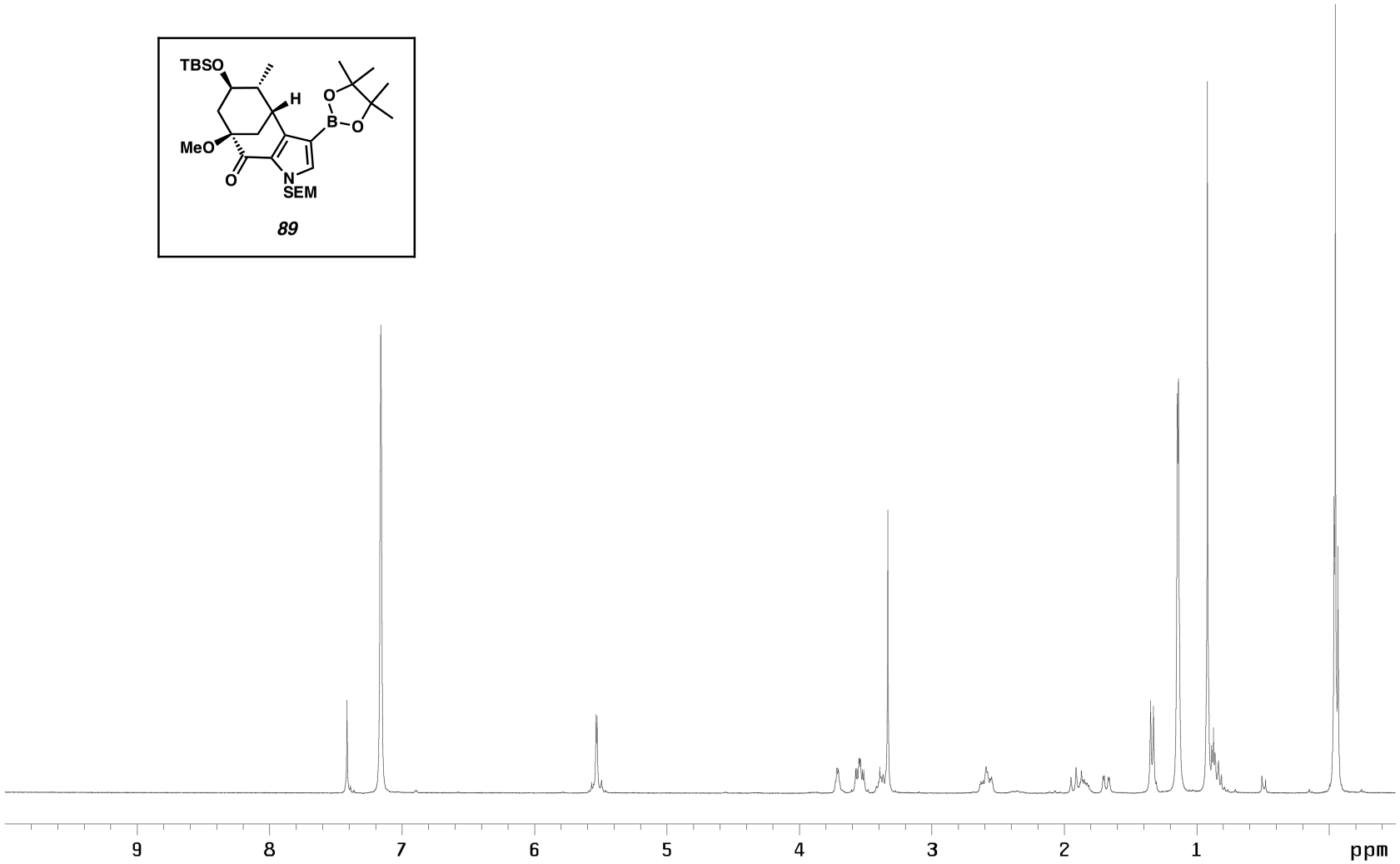


Figure A3.78 ^{1}H NMR (300 MHz, C_6D_6) of compound **89**

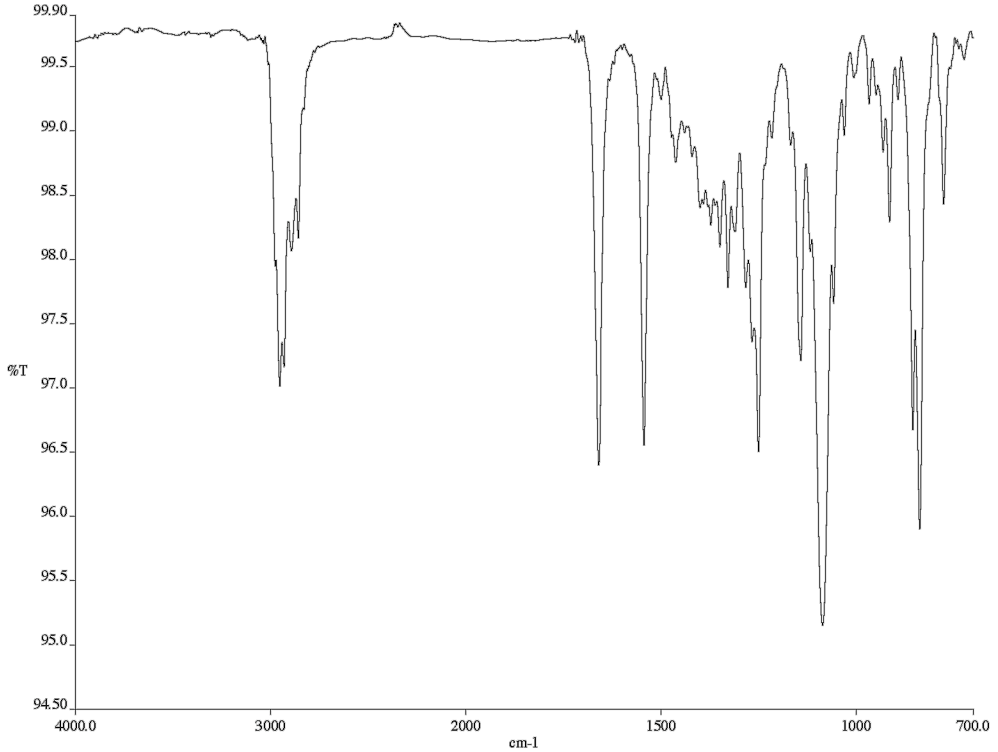


Figure A3.79 Infrared spectrum (thin film/NaCl) of compound **89**

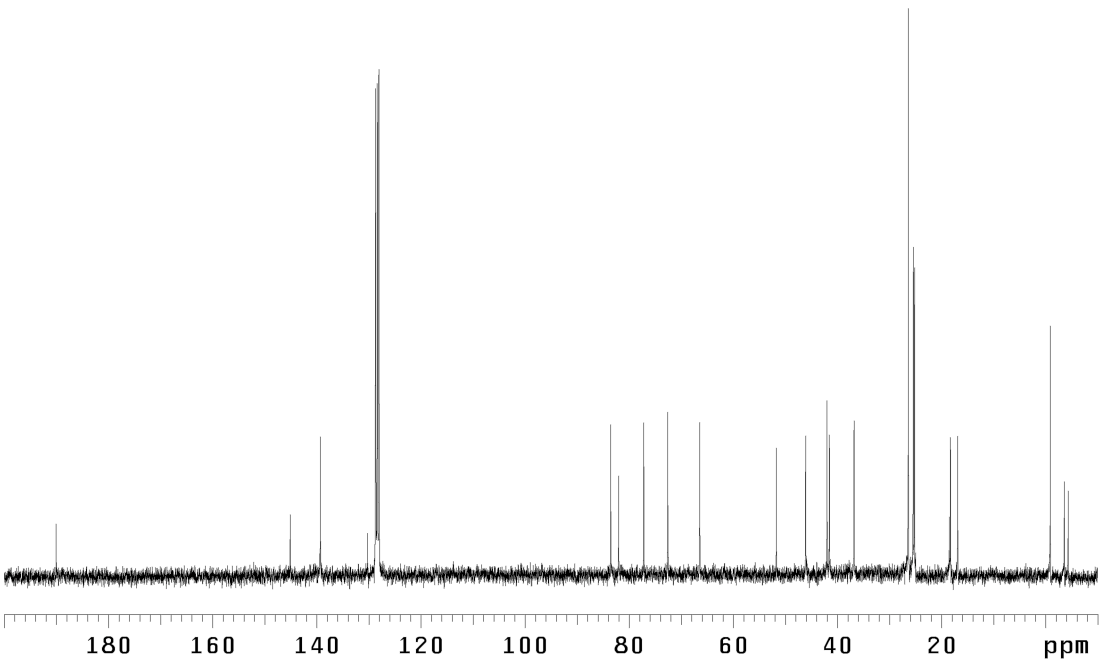


Figure A3.80 ^{13}C NMR (75 MHz, C_6D_6) of compound **89**

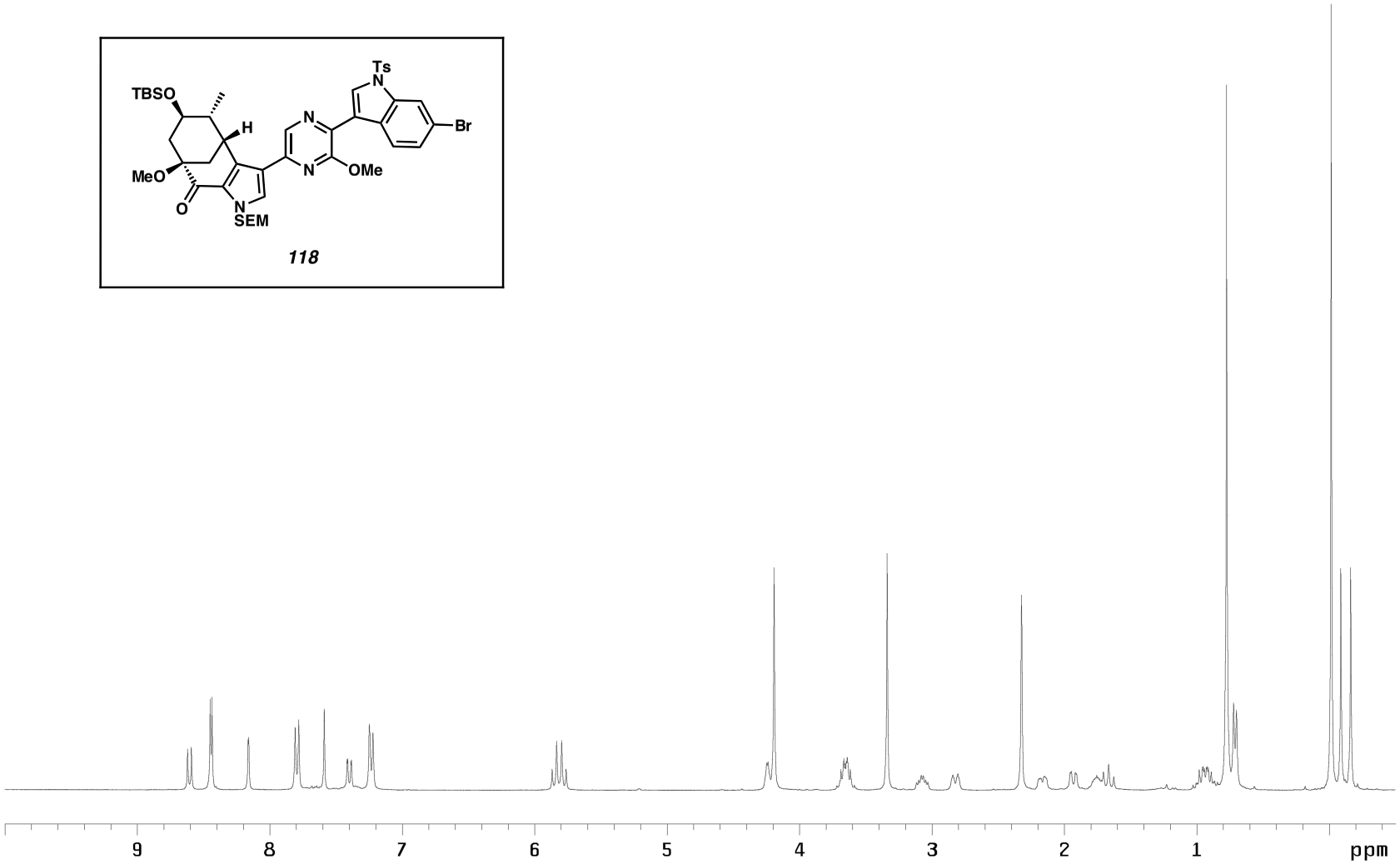


Figure A3.81 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **118**

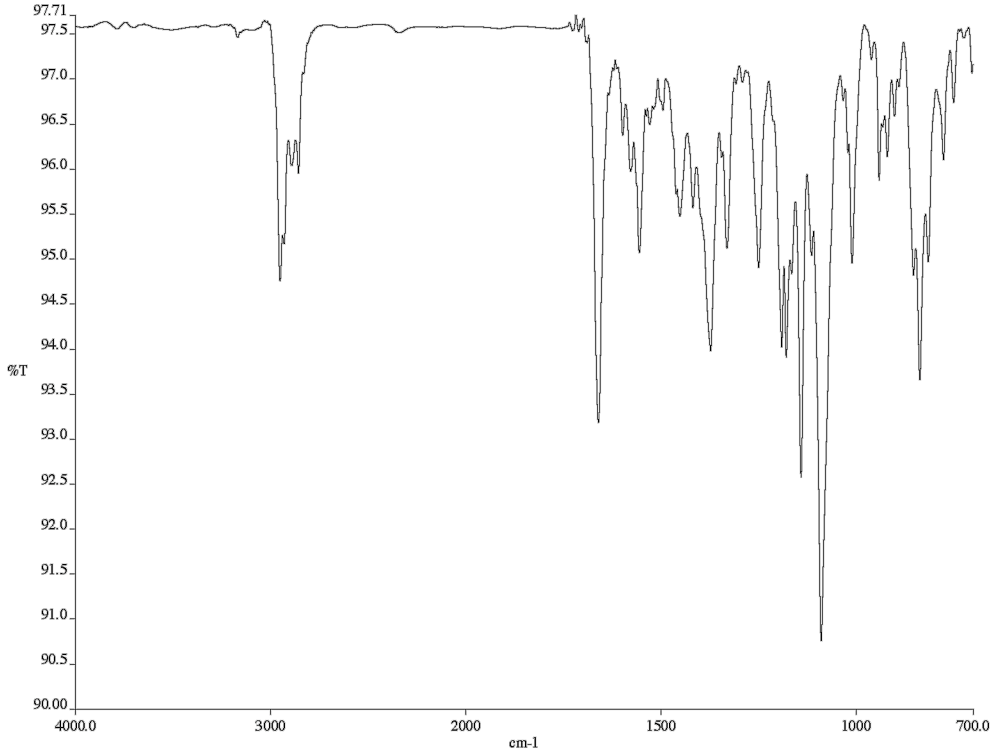


Figure A3.82 Infrared spectrum (thin film/NaCl) of compound **118**

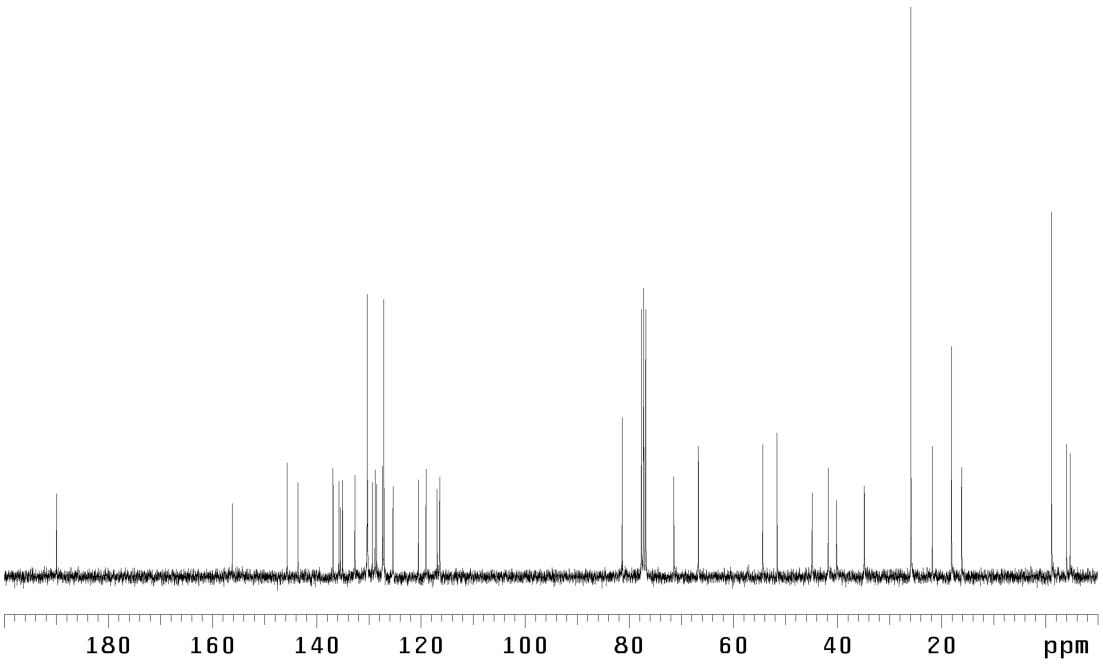


Figure A3.83 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **118**

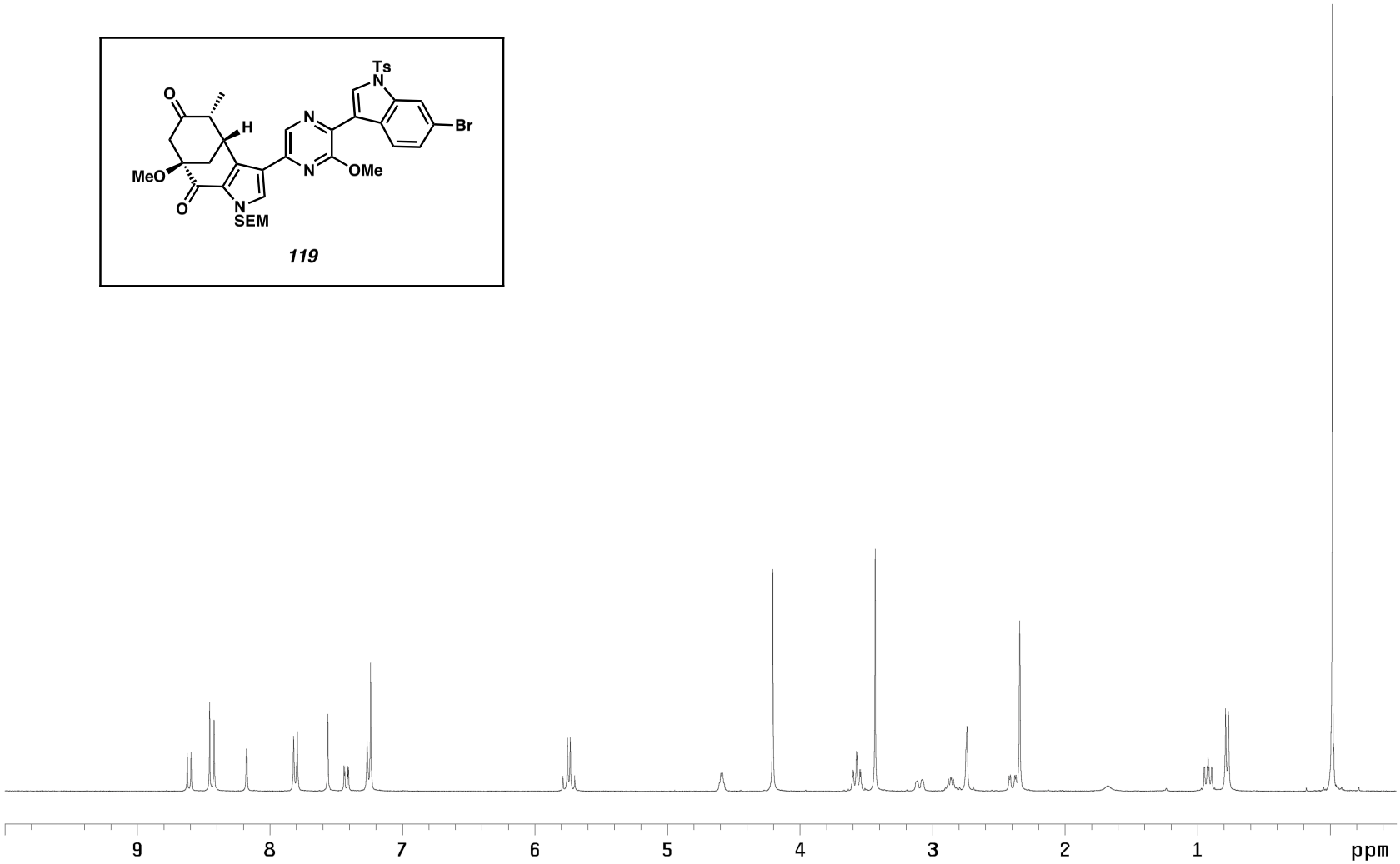


Figure A3.84 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **119**

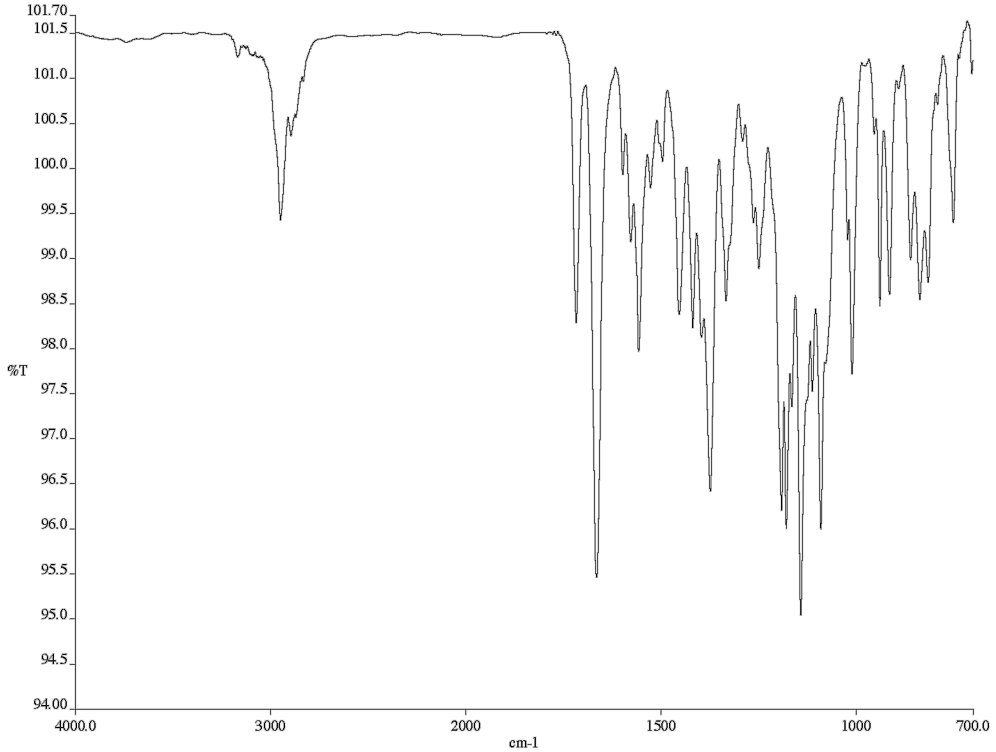


Figure A3.85 Infrared spectrum (thin film/NaCl) of compound **119**

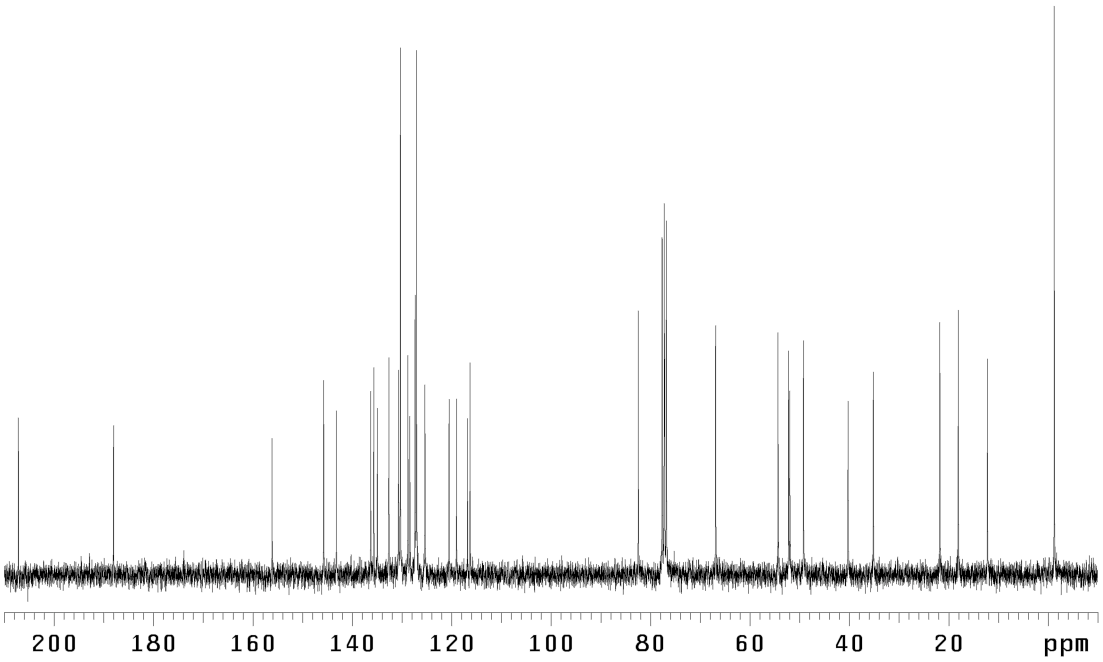


Figure A3.86 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **119**

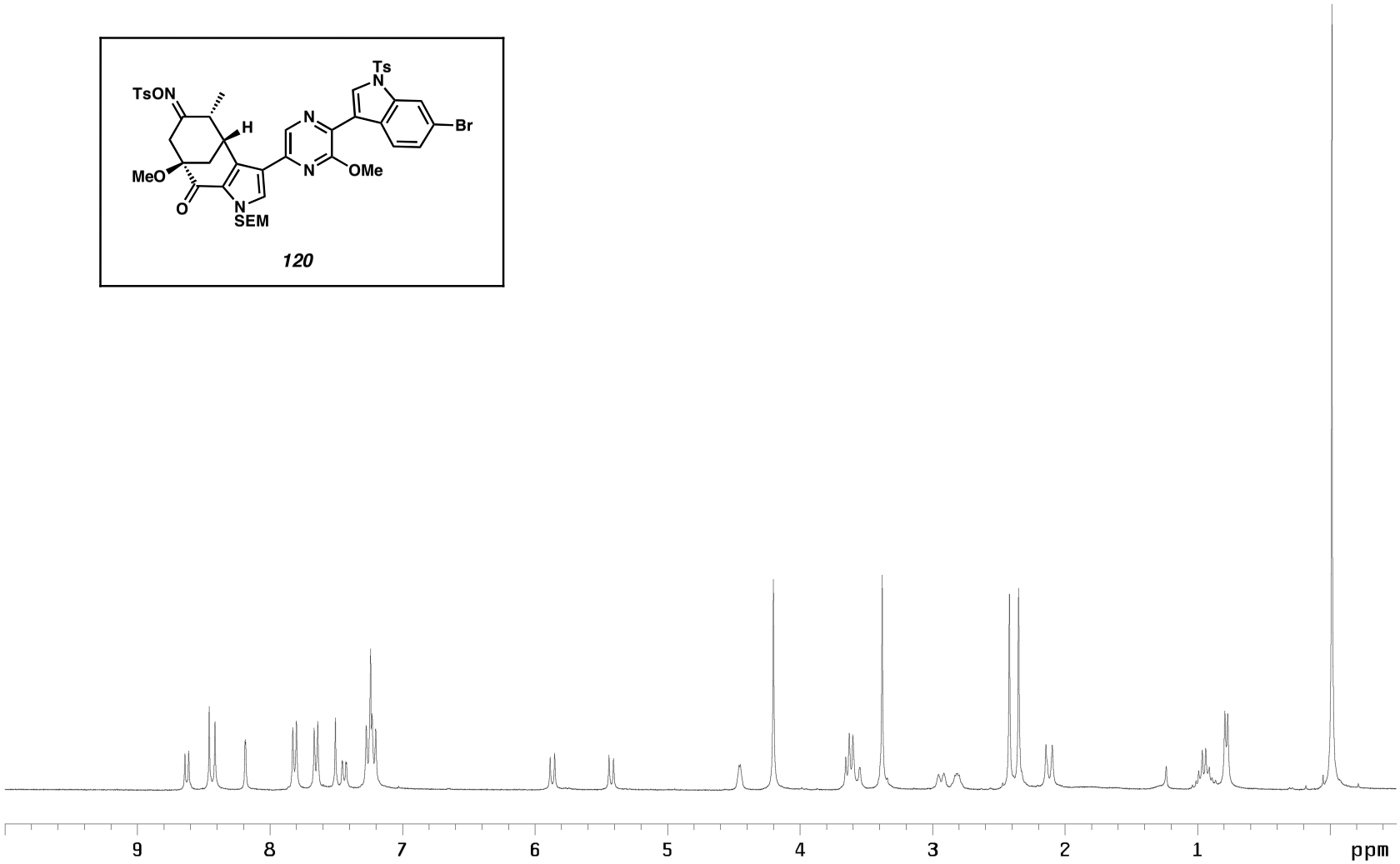


Figure A3.87 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **120**

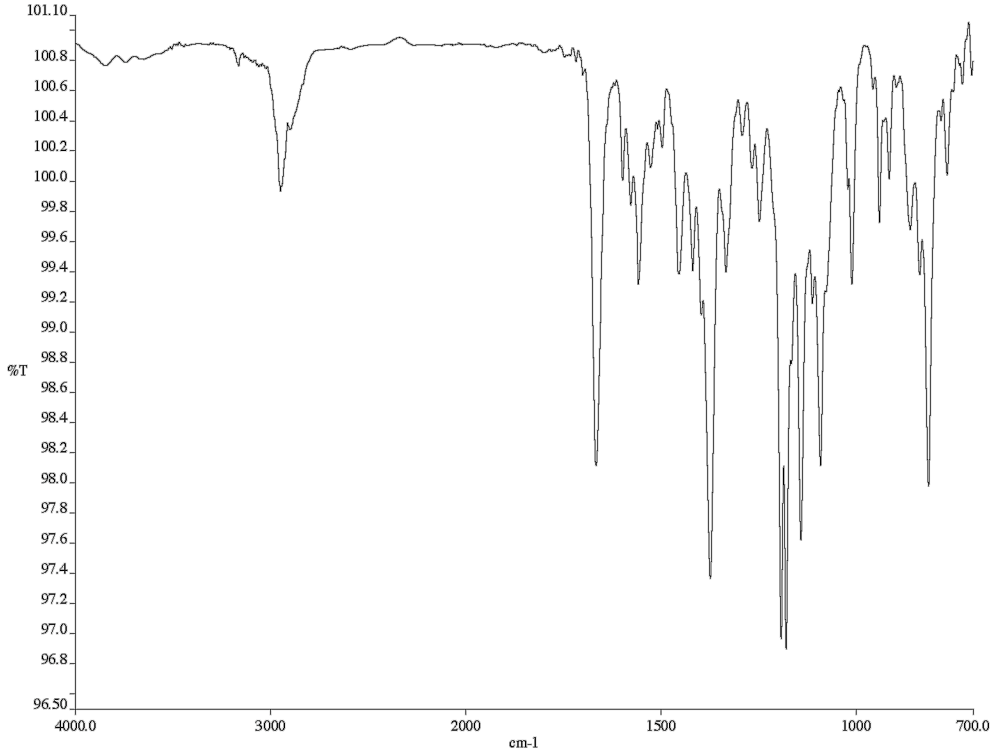


Figure A3.88 Infrared spectrum (thin film/NaCl) of compound **120**

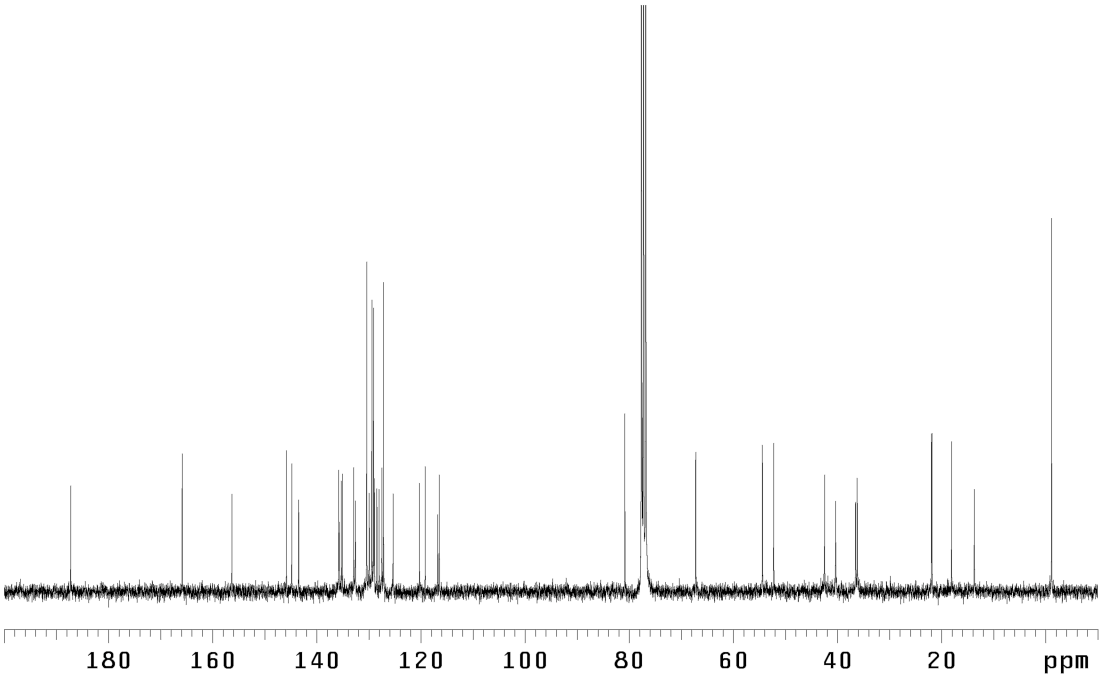


Figure A3.89 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **120**

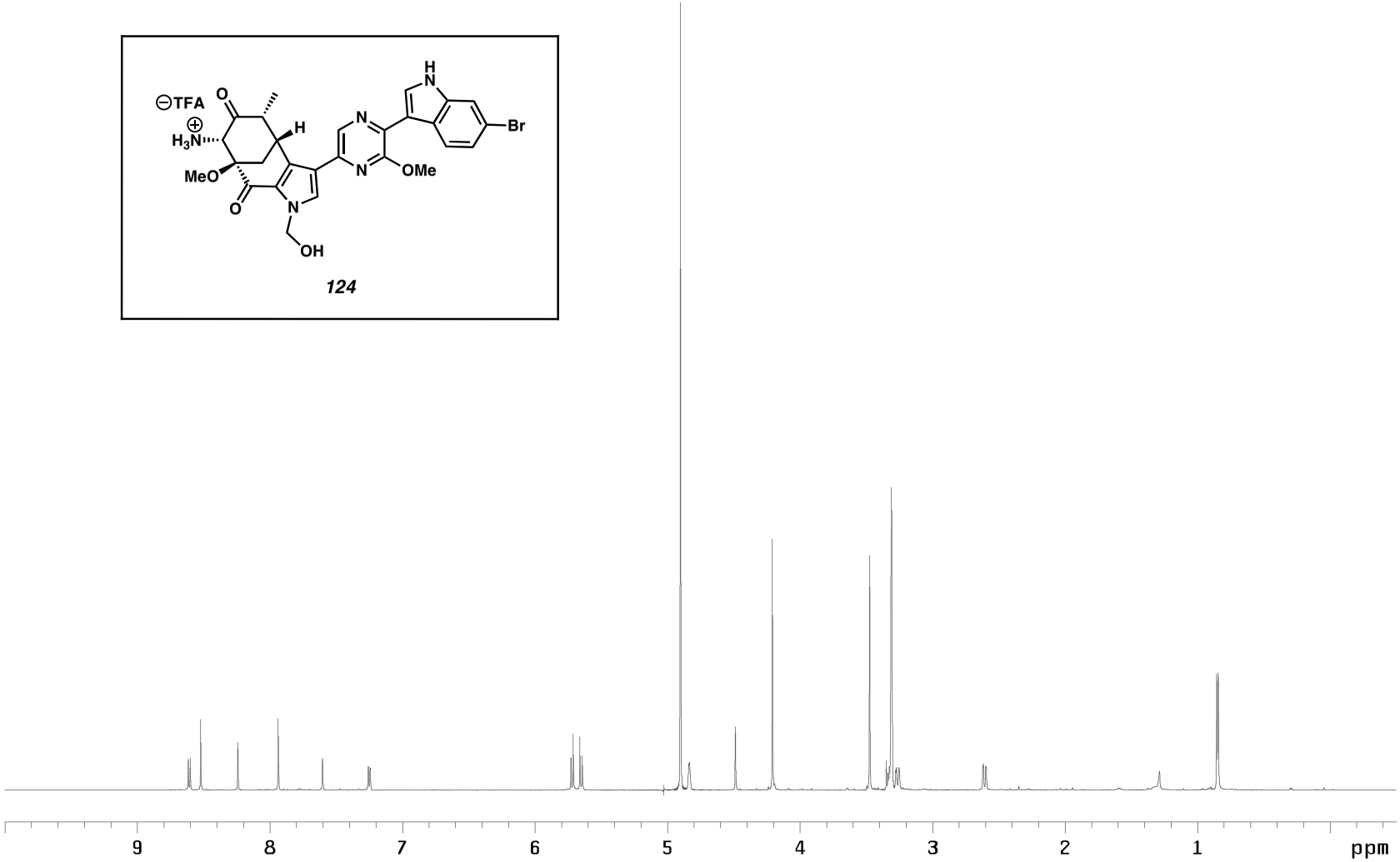


Figure A3.90 ^{1}H NMR (600 MHz, CD_3OD) of compound **124**

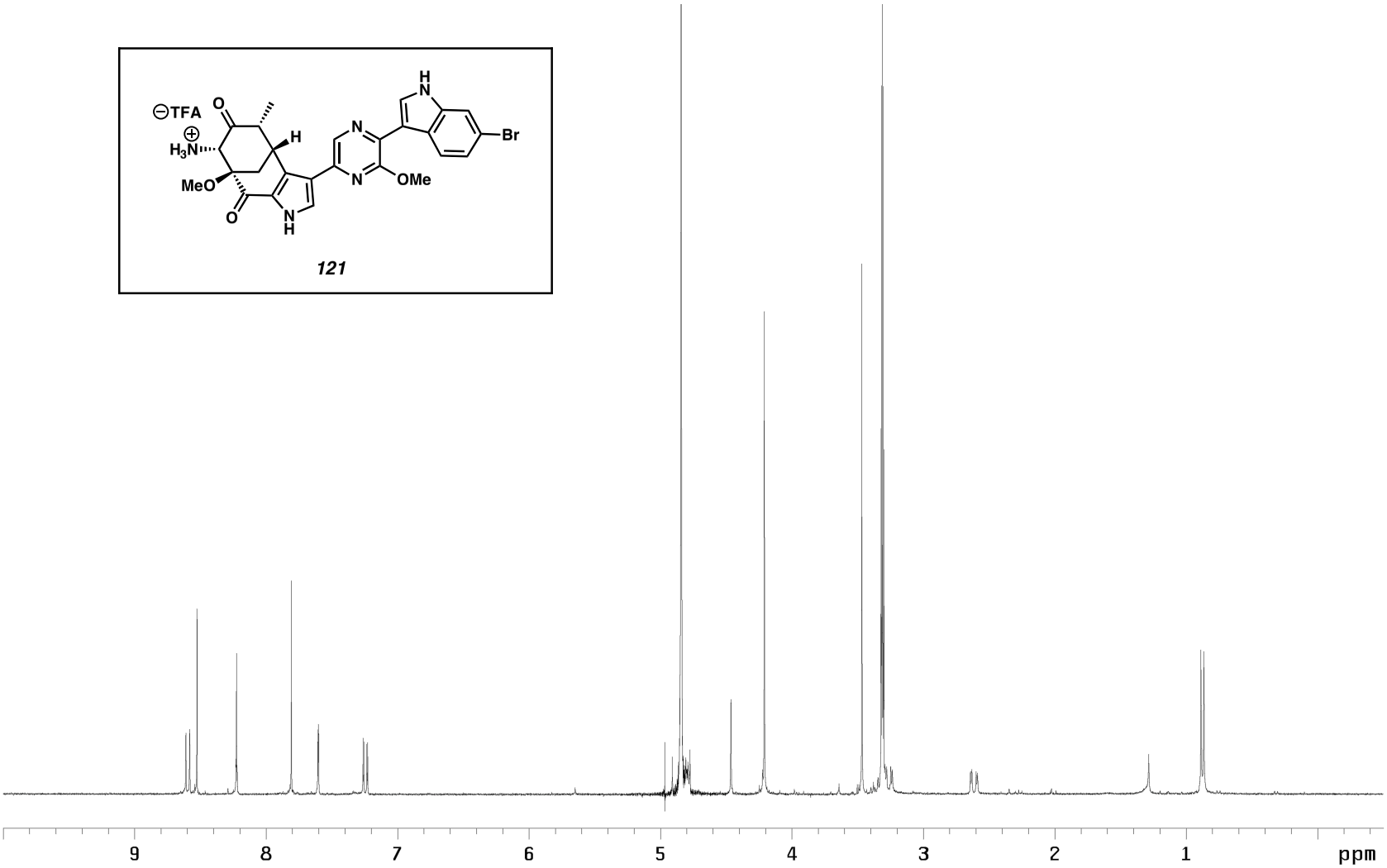


Figure A3.91 ^{1}H NMR (300 MHz, CD_3OD) of compound **121**

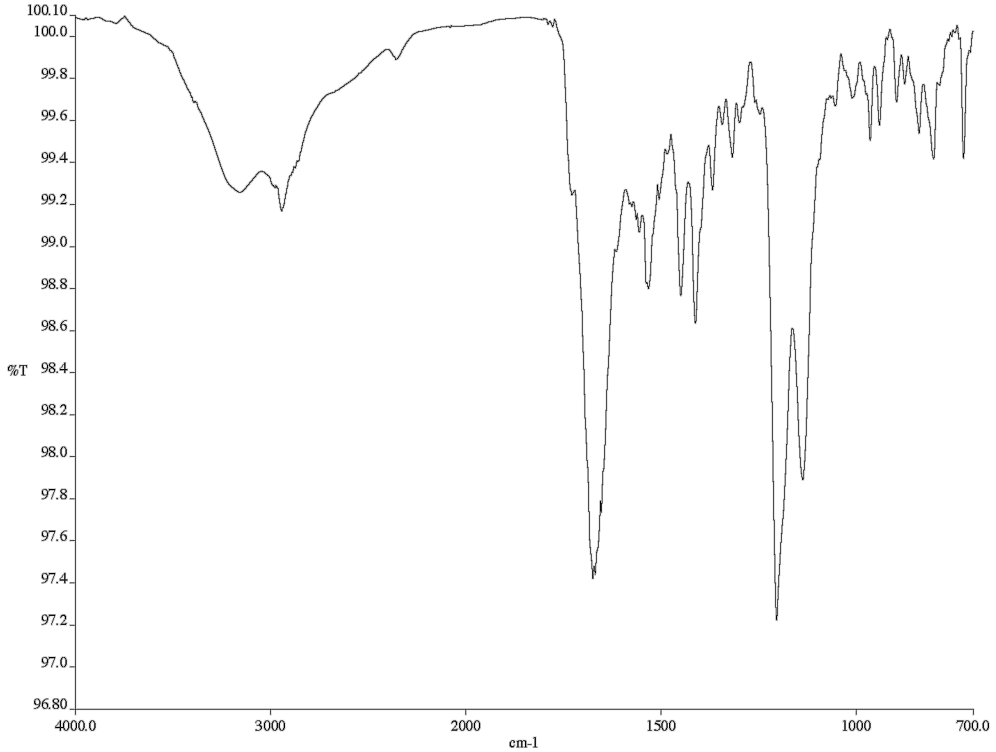


Figure A3.92 Infrared spectrum (thin film/NaCl) of compound **121**

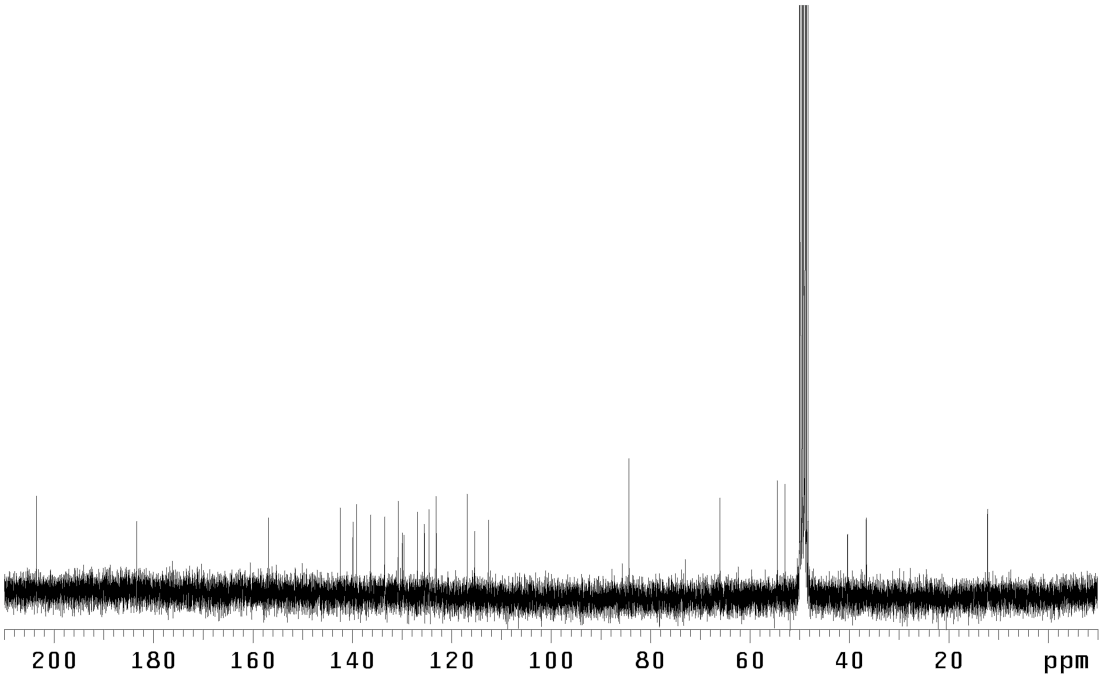


Figure A3.93 ^{13}C NMR (75 MHz, CD_3OD) of compound **121**

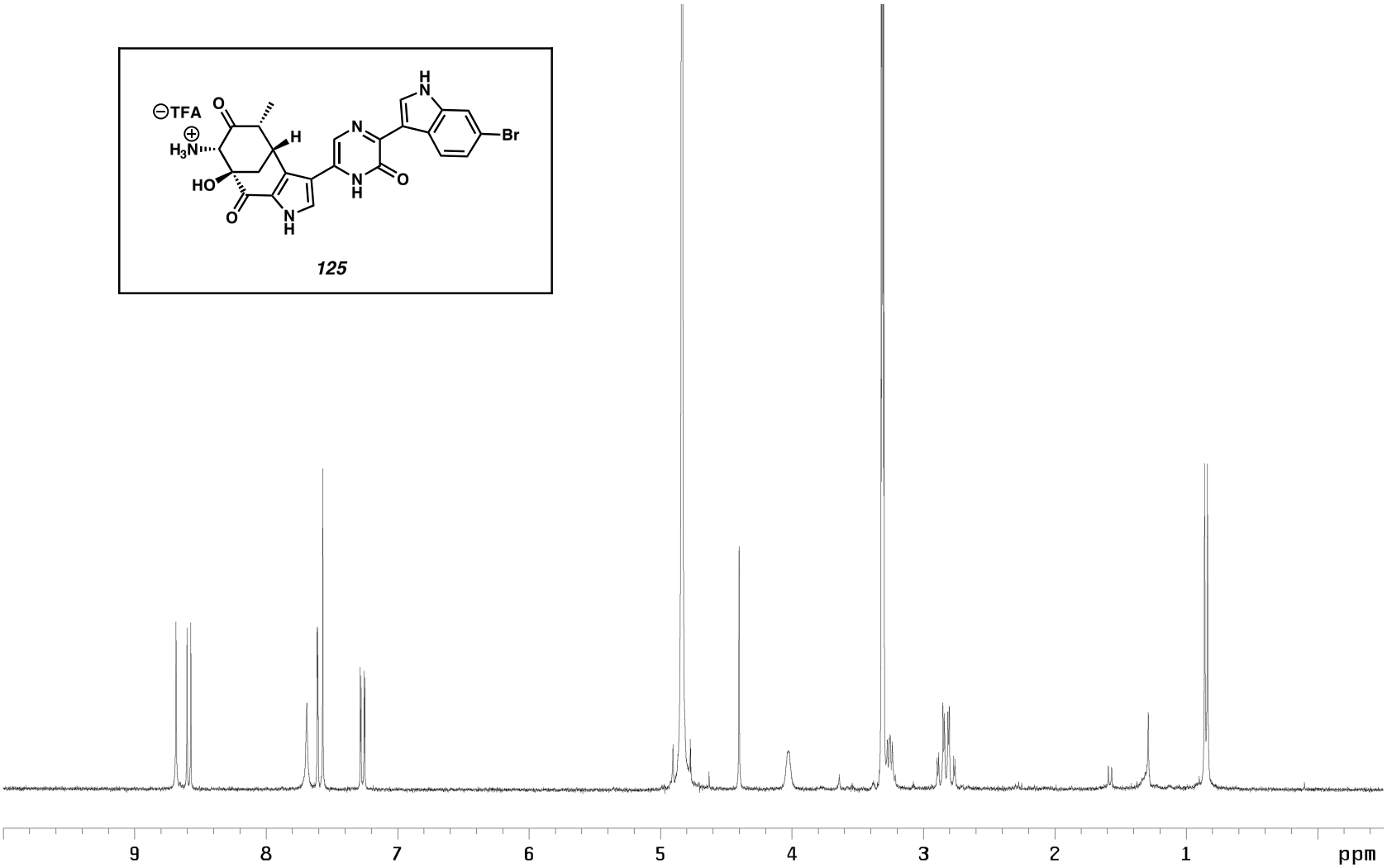


Figure A3.94 ^{1}H NMR (300 MHz, CD_3OD) of compound **125**

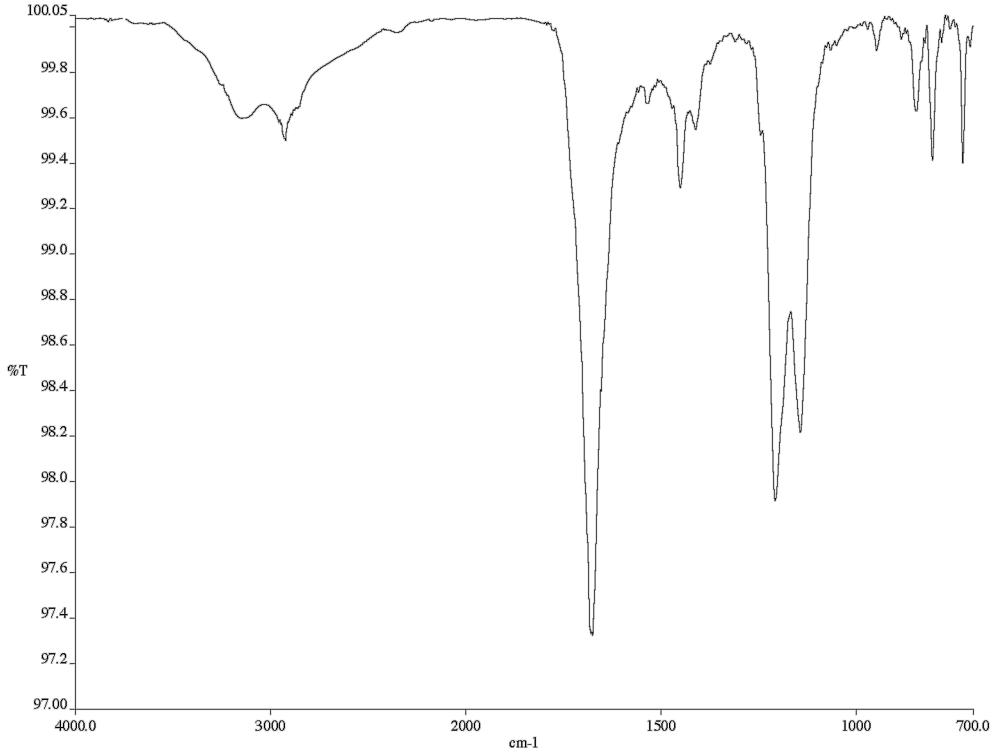


Figure A3.95 Infrared spectrum (thin film/NaCl) of compound **125**

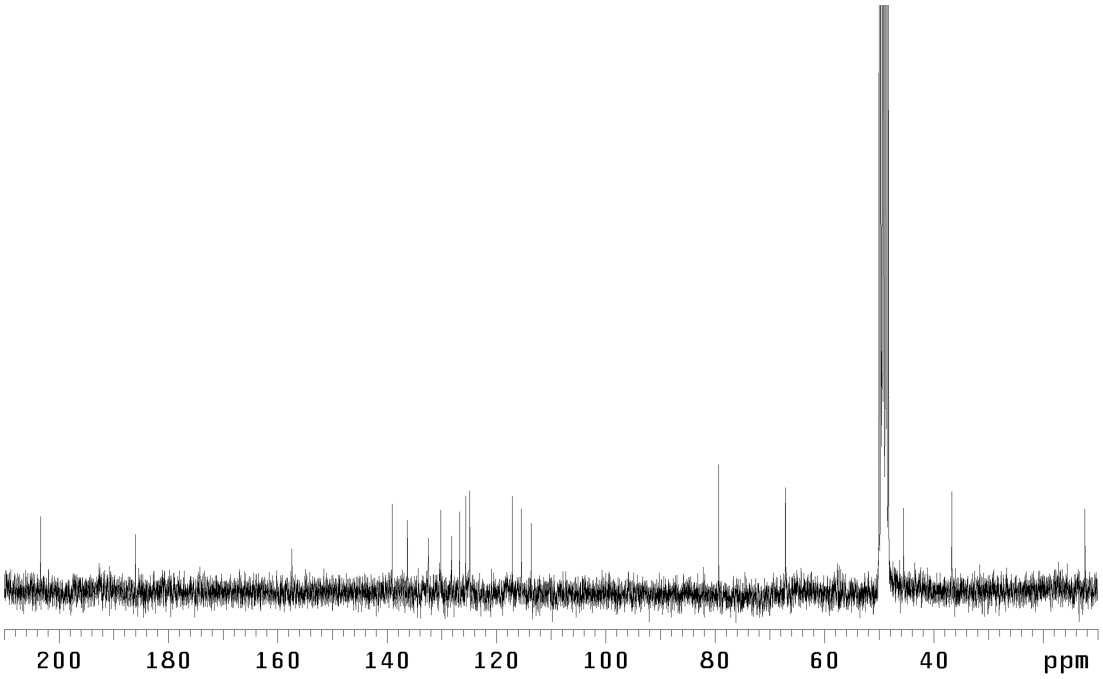


Figure A3.96 ^{13}C NMR (75 MHz, CD_3OD) of compound **125**

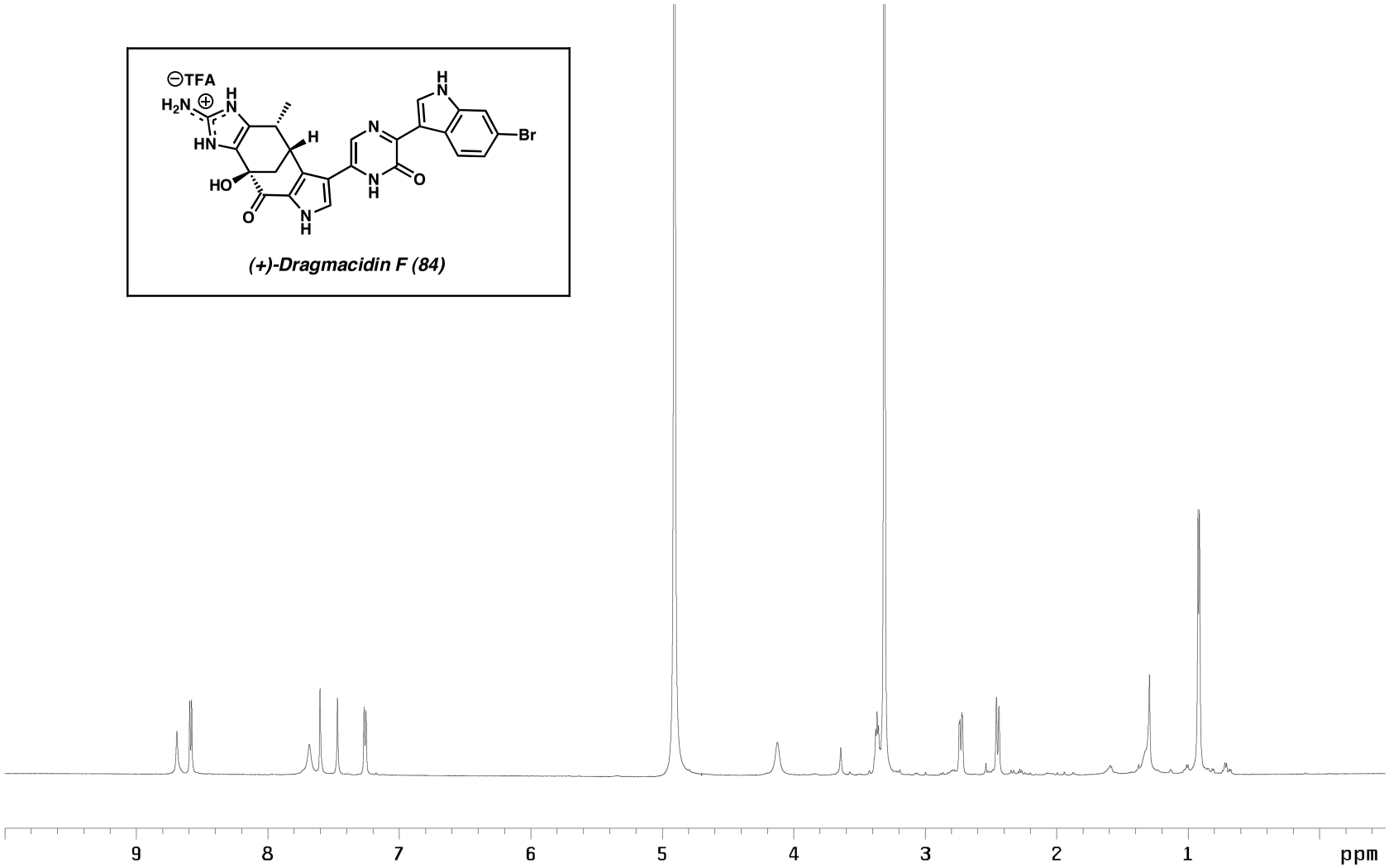


Figure A3.97 ^{1}H NMR (600 MHz, CD_3OD) of (+)-dragmacidin F (**84**)

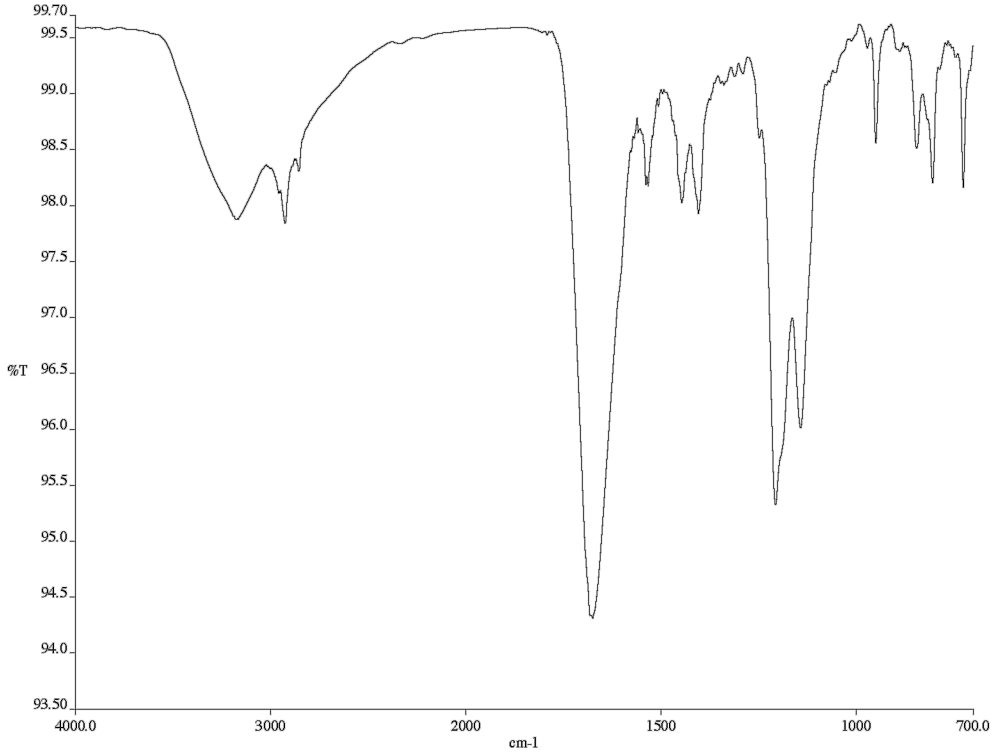


Figure A3.98 Infrared spectrum (thin film/NaCl) of (+)-dragmacidin F (**84**)

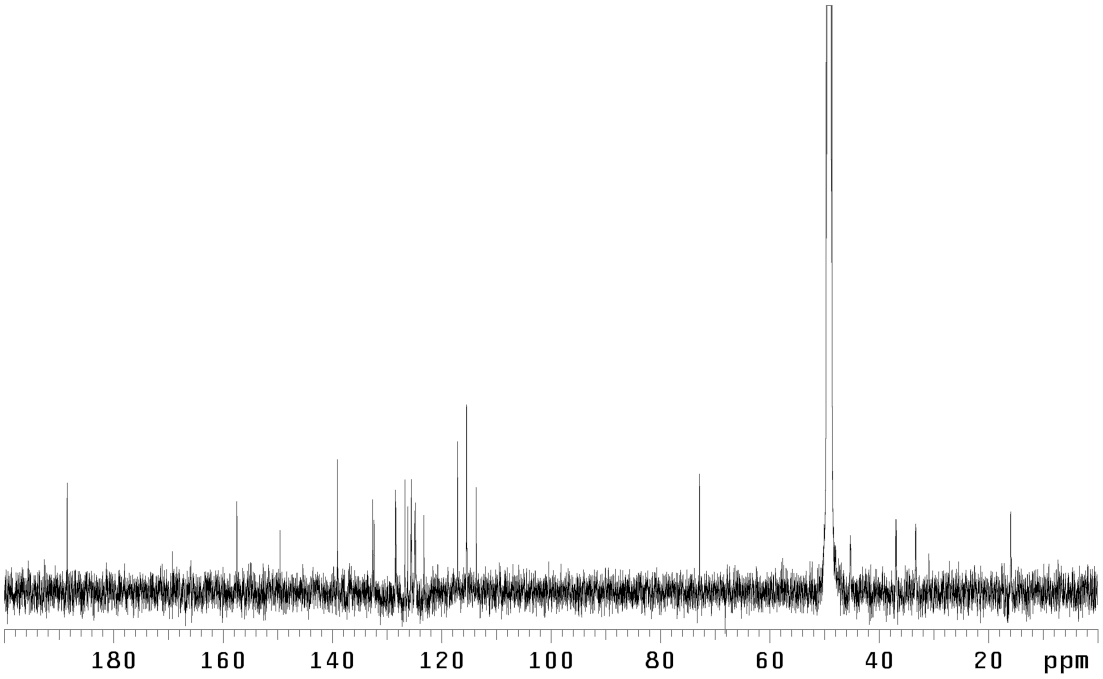


Figure A3.99 ^{13}C NMR (125 MHz, CD_3OD) of (+)-dragmacidin F (**84**)

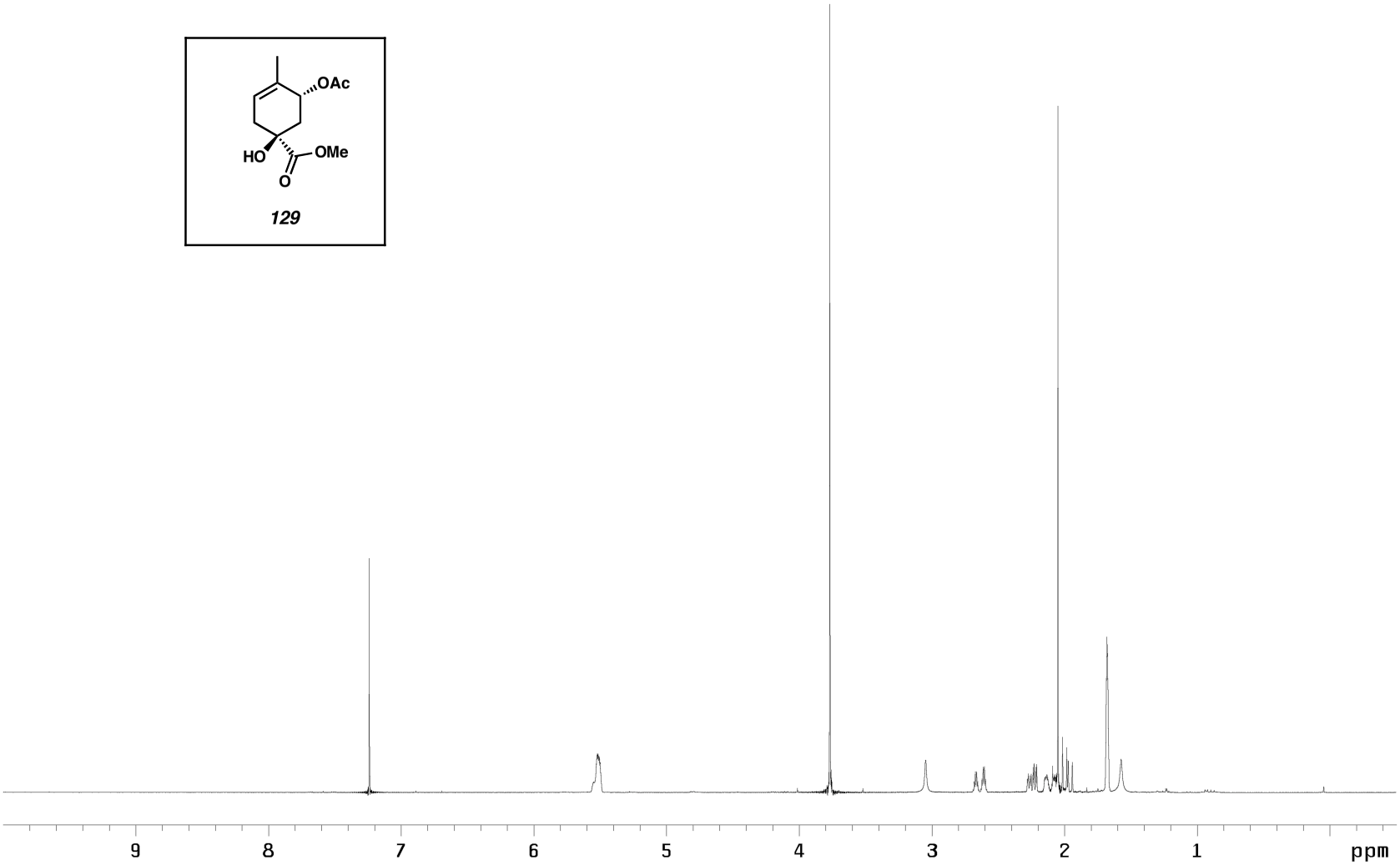


Figure A3.100 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **129**

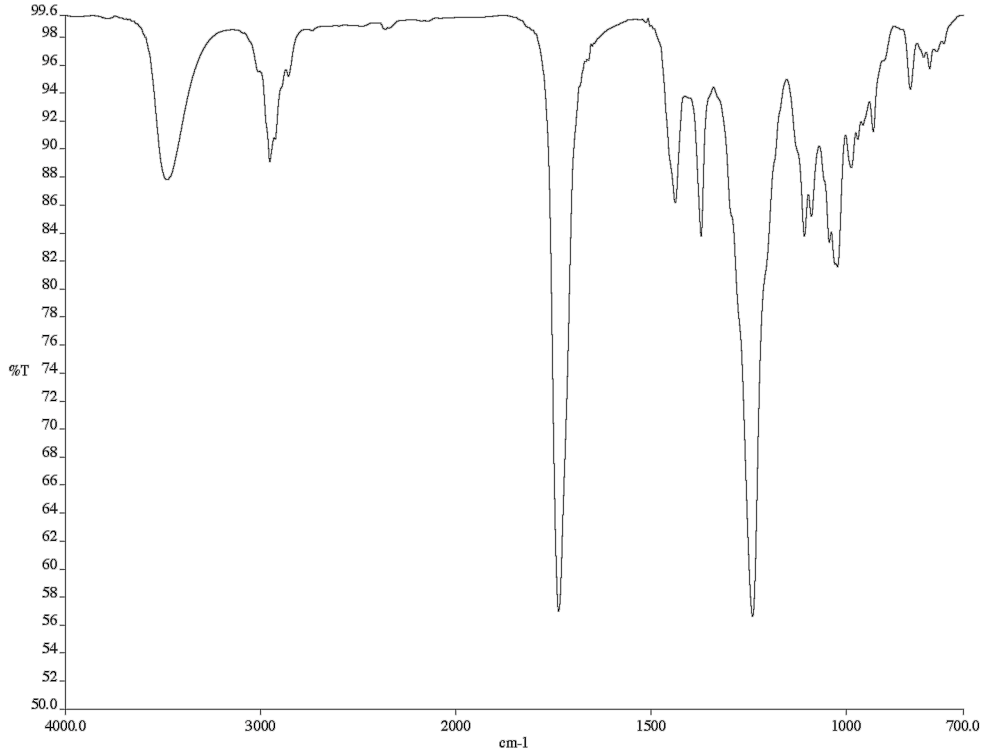


Figure A3.101 Infrared spectrum (thin film/NaCl) of compound **129**

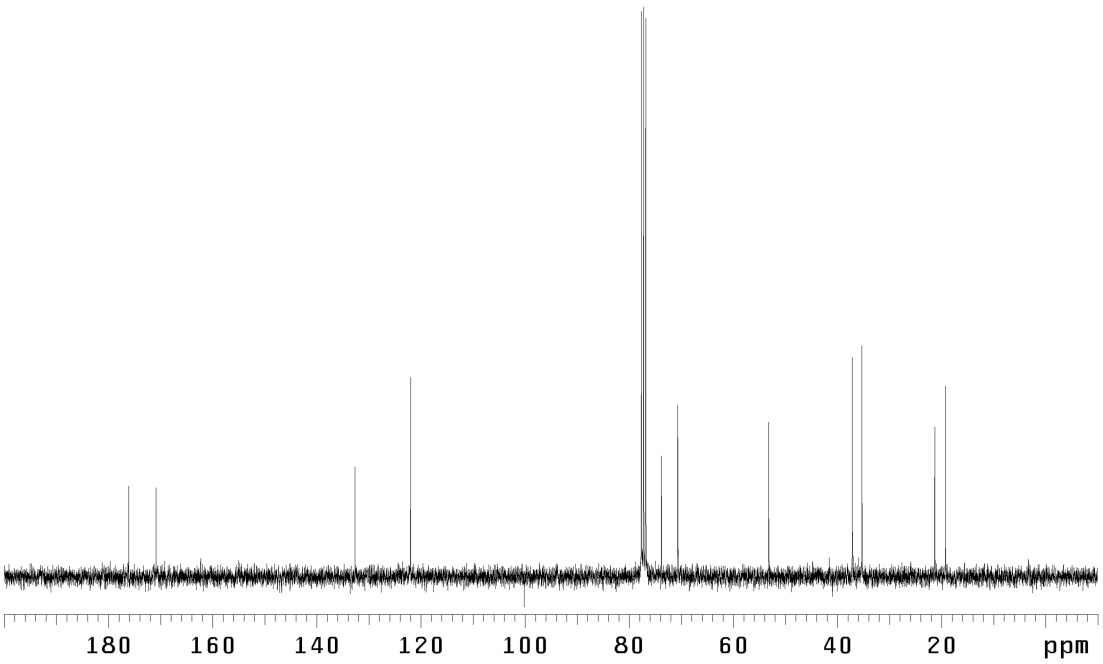


Figure A3.102 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **129**

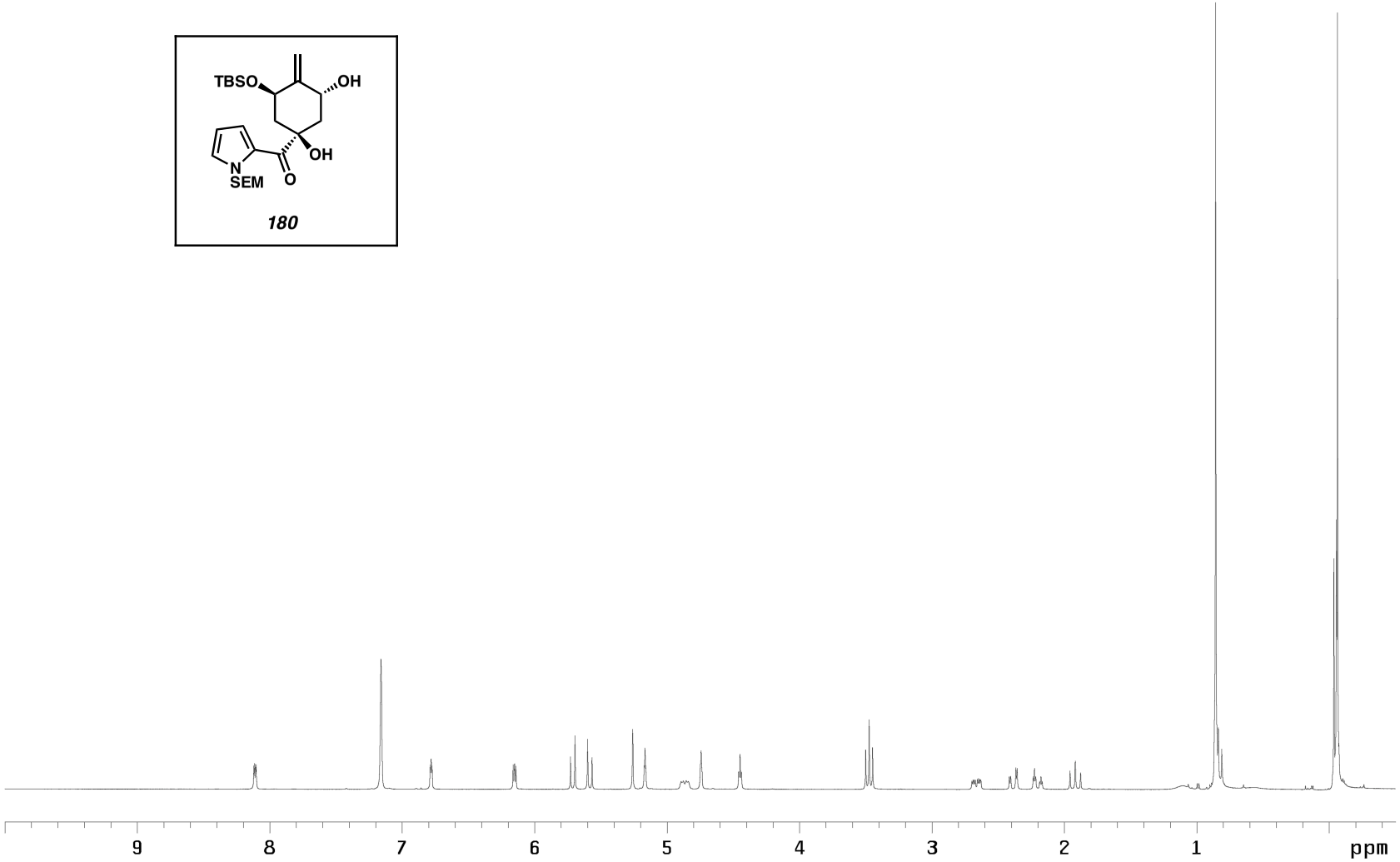


Figure A3.103 ^{1}H NMR (300 MHz, C_6D_6) of compound **180**

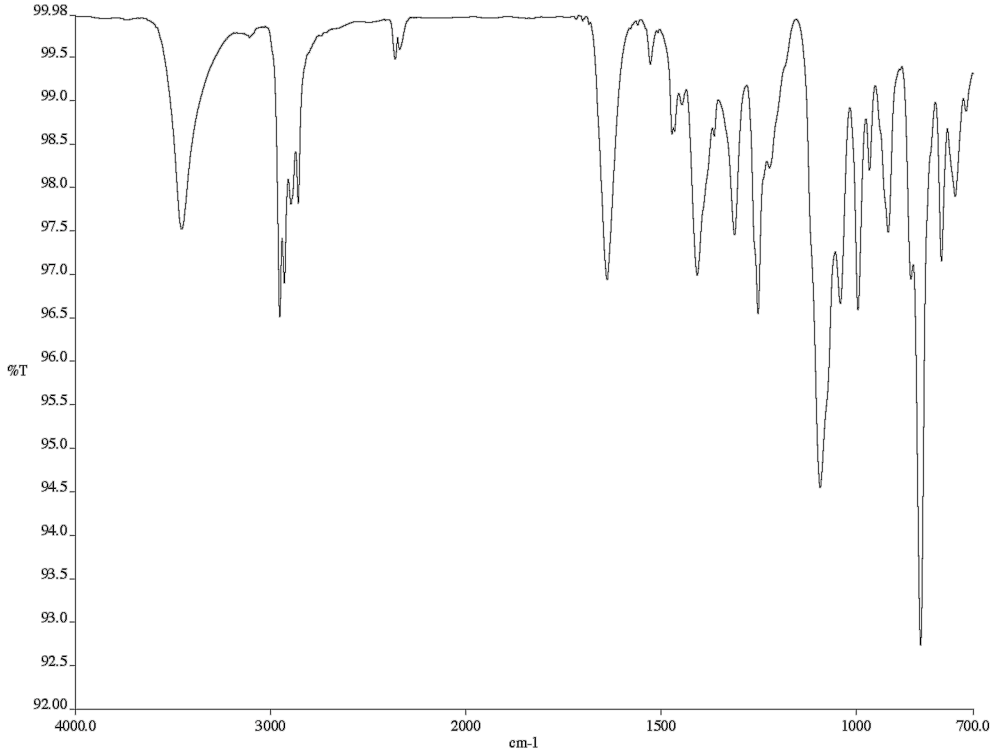


Figure A3.104 Infrared spectrum (thin film/NaCl) of compound **180**

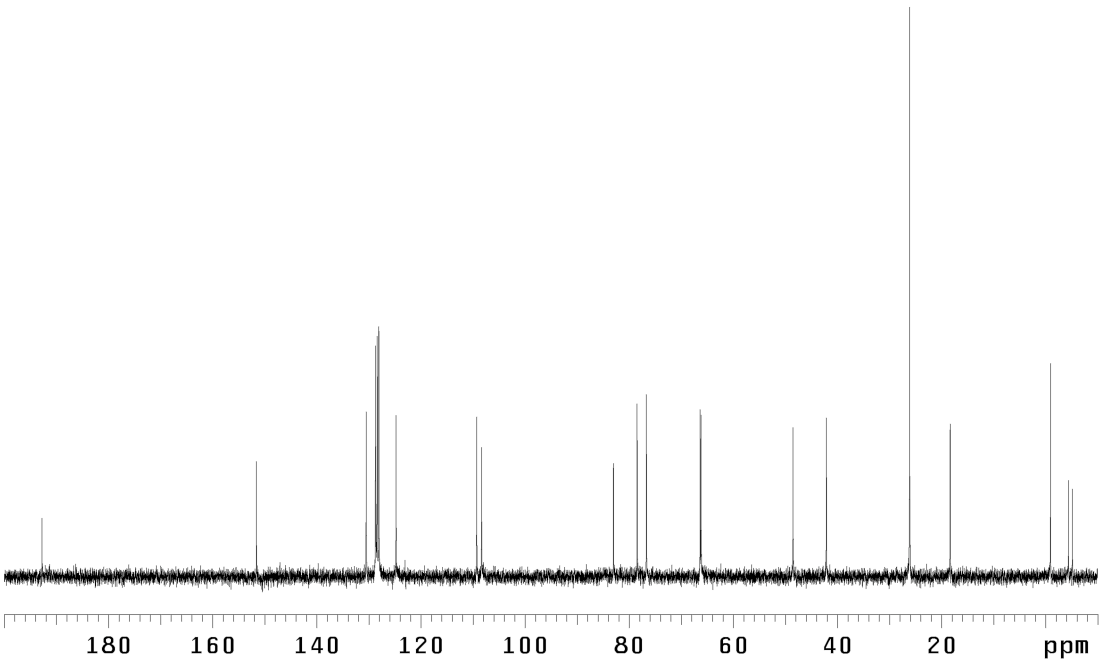


Figure A3.105 ^{13}C NMR (75 MHz, C_6D_6) of compound **180**

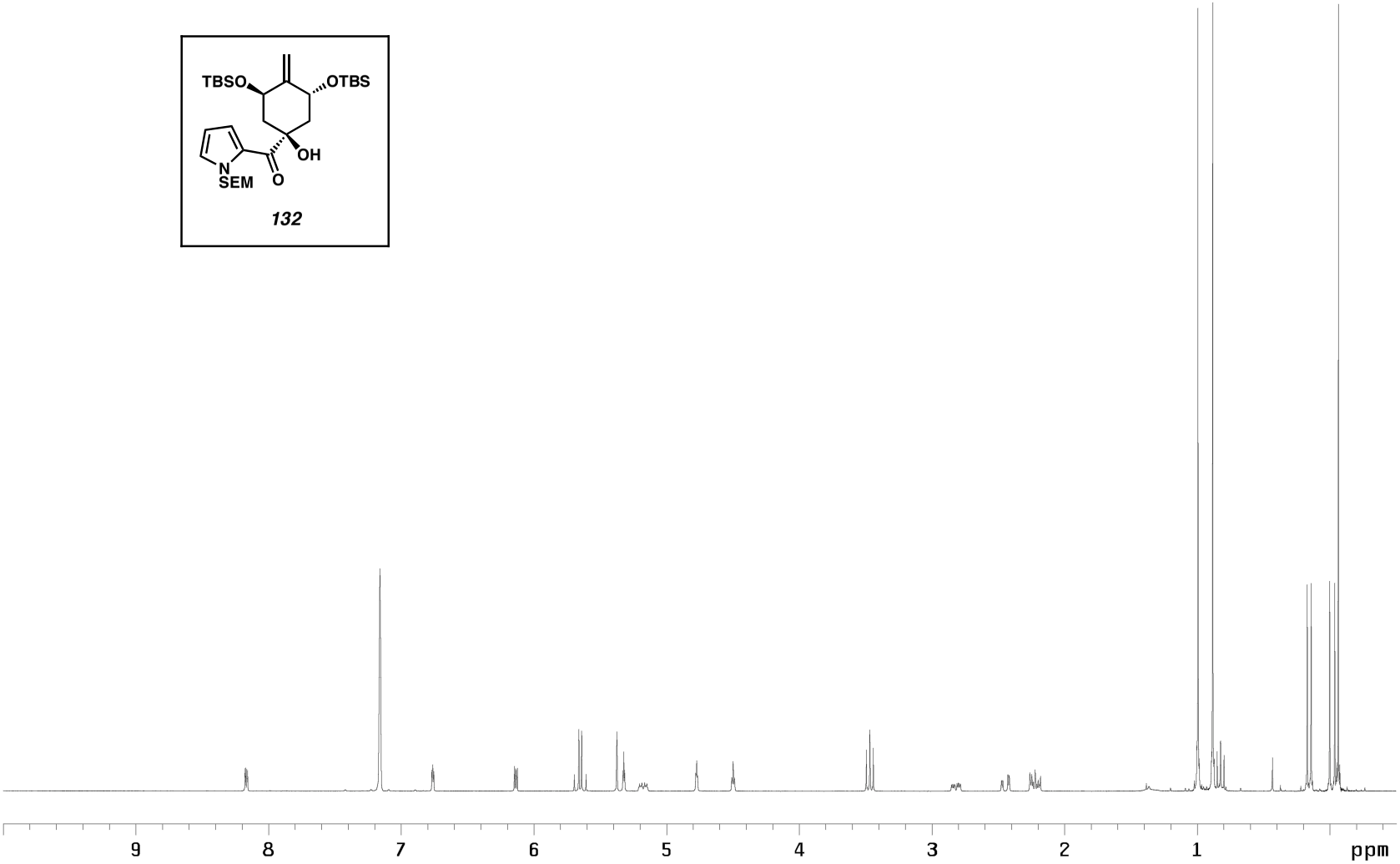


Figure A3.106 ^{1}H NMR (300 MHz, C_6D_6) of compound **132**

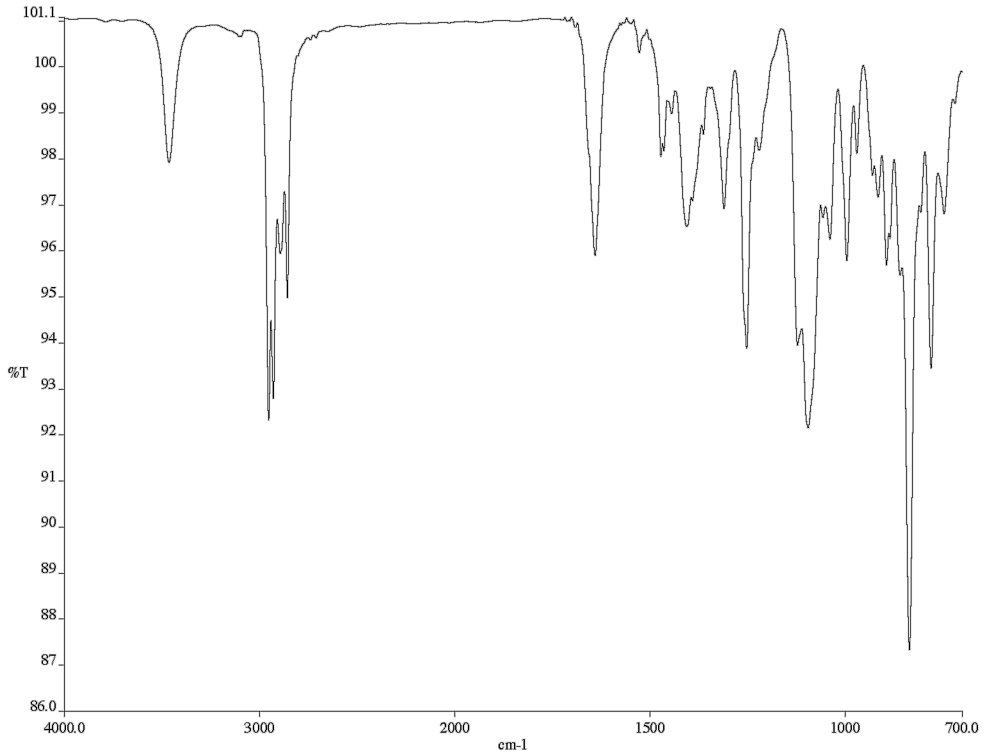


Figure A3.107 Infrared spectrum (thin film/NaCl) of compound **132**

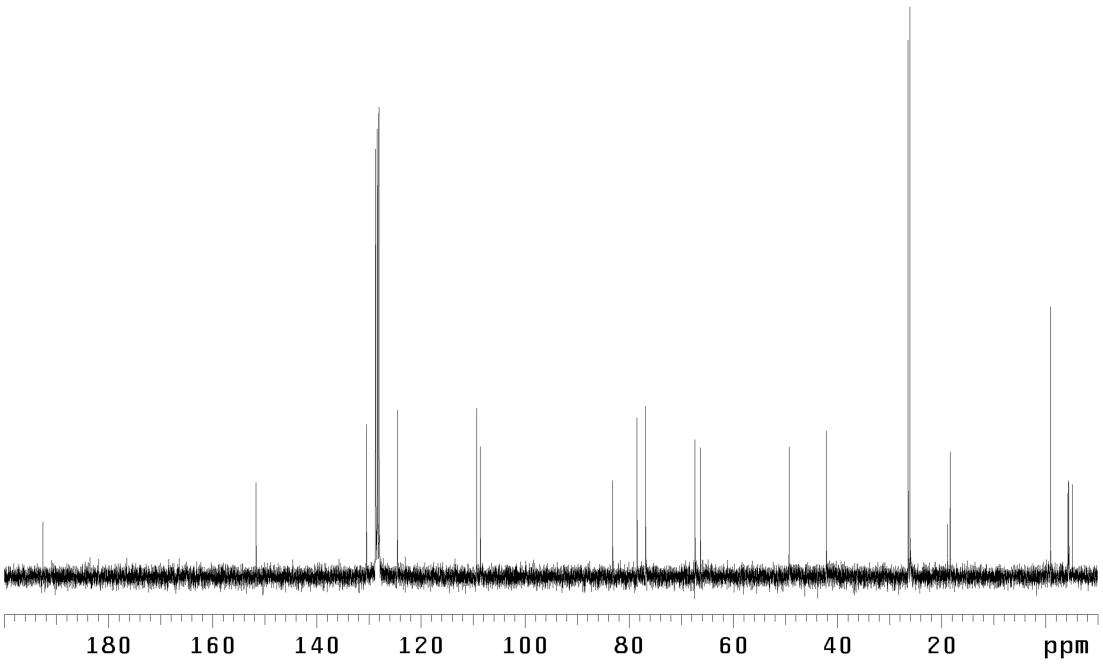


Figure A3.108 ^{13}C NMR (75 MHz, C_6D_6) of compound **132**

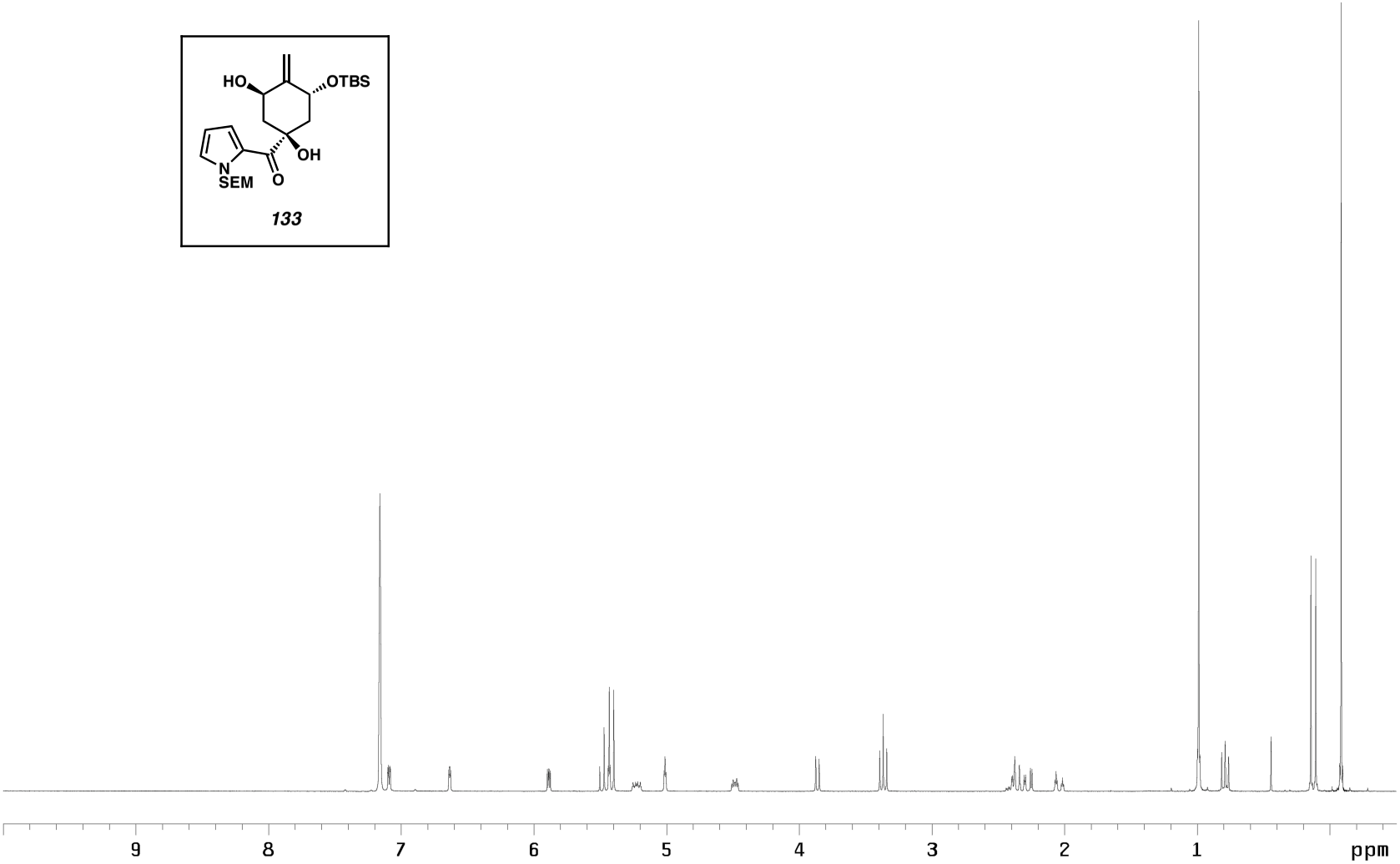


Figure A3.109 ^{1}H NMR (300 MHz, C_6D_6) of compound **133**

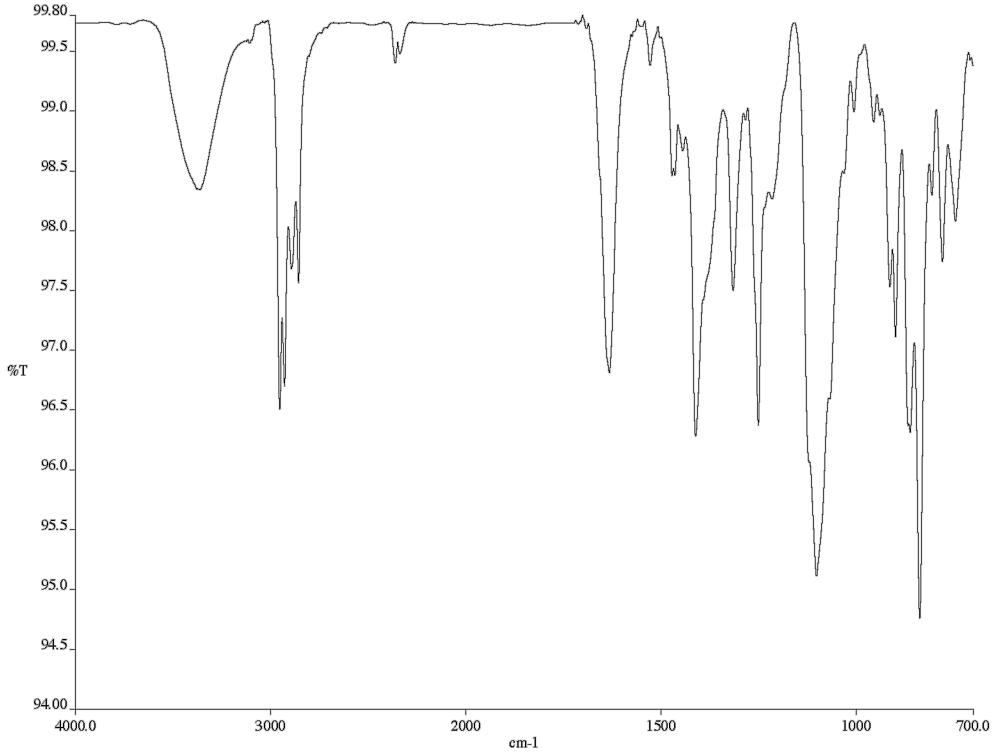


Figure A3.110 Infrared spectrum (thin film/NaCl) of compound **133**

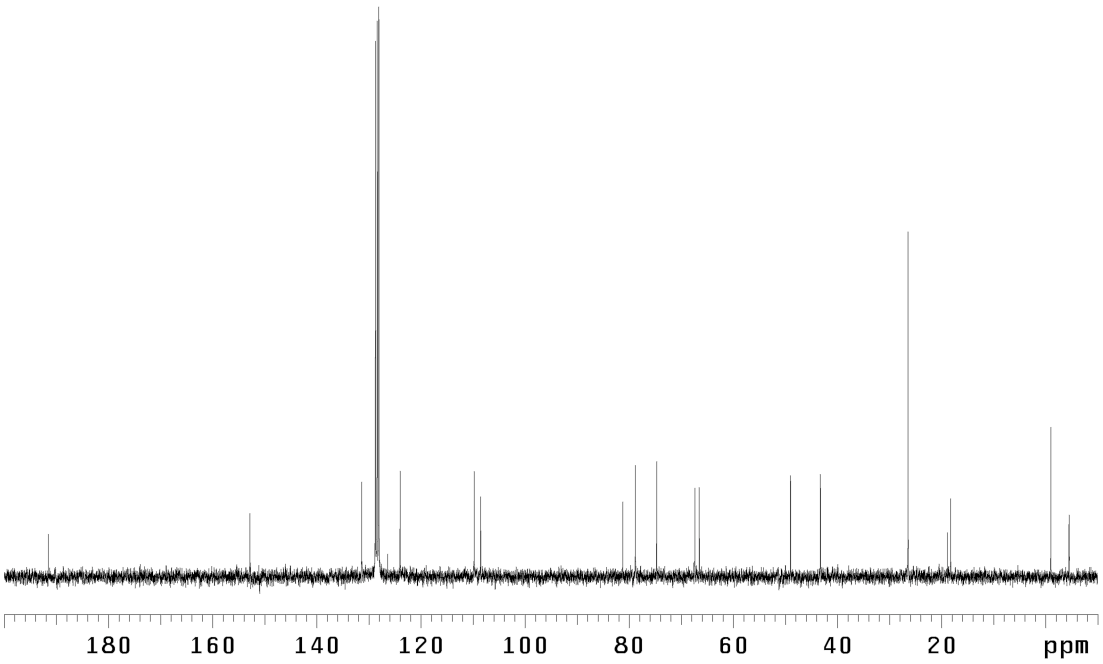


Figure A3.111 ^{13}C NMR (75 MHz, C_6D_6) of compound **133**

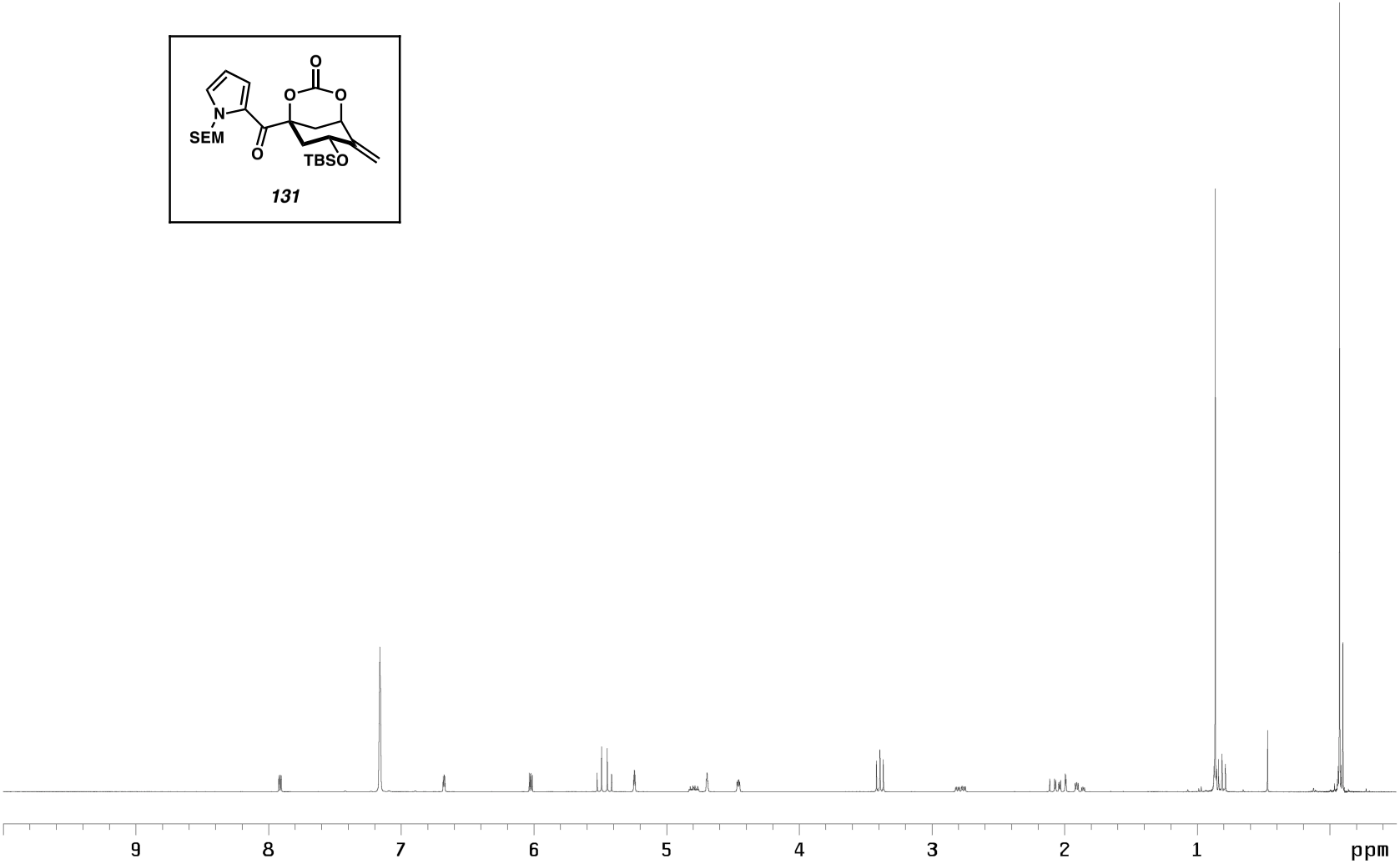


Figure A3.112 ^{1}H NMR (300 MHz, C_6D_6) of compound **131**

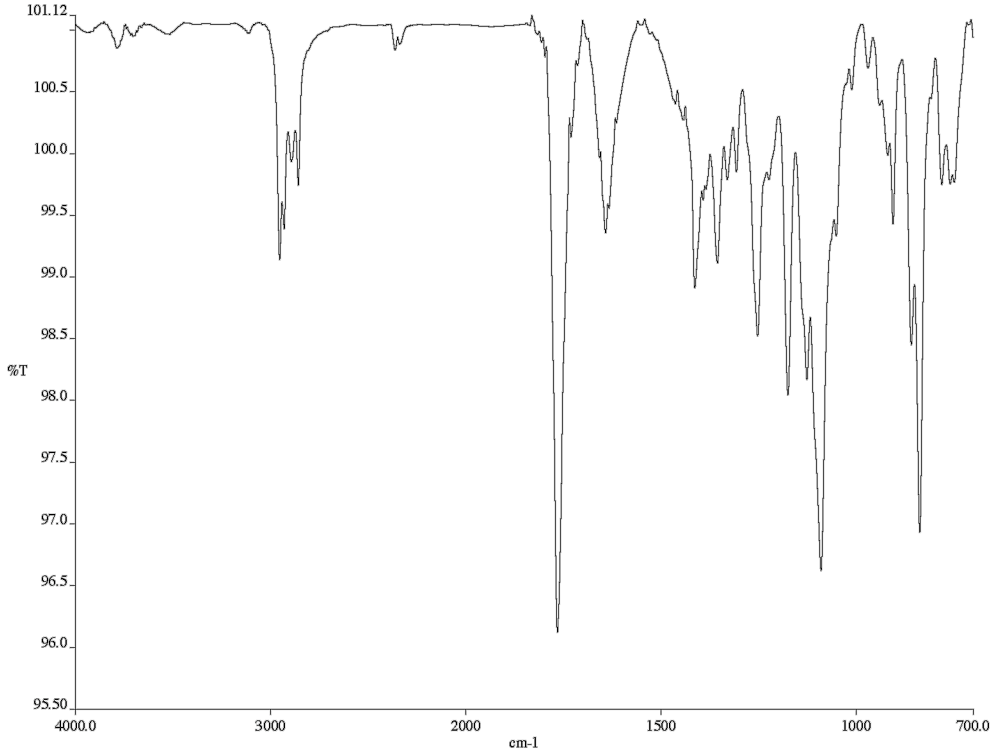


Figure A3.113 Infrared spectrum (thin film/NaCl) of compound **131**

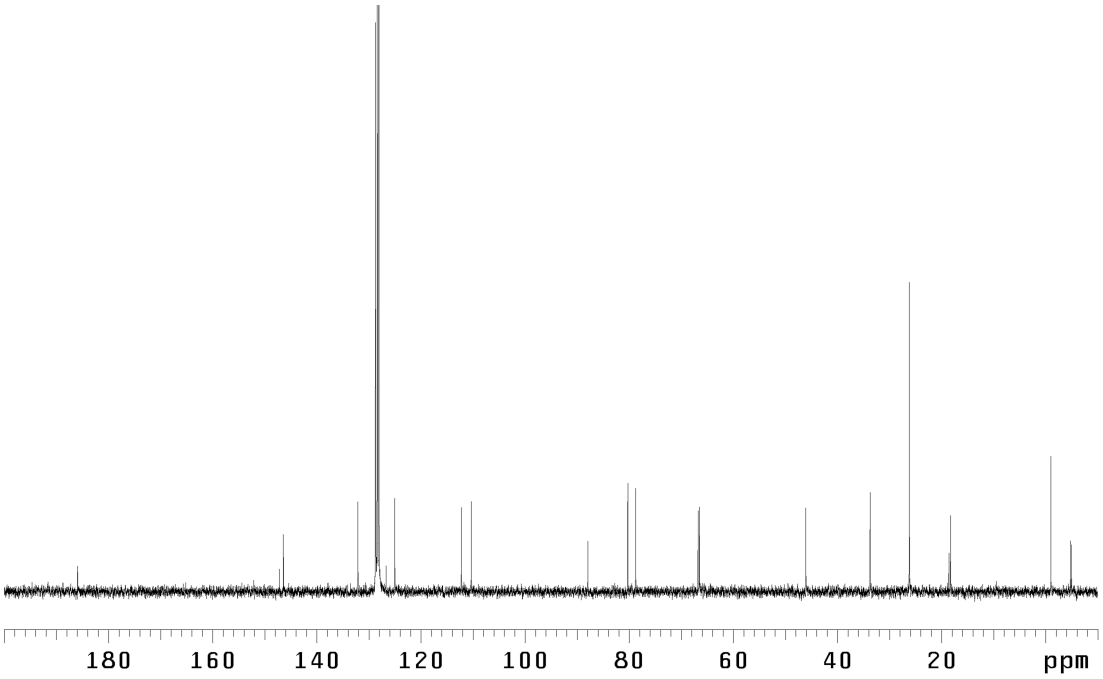


Figure A3.114 ^{13}C NMR (75 MHz, C_6D_6) of compound **131**

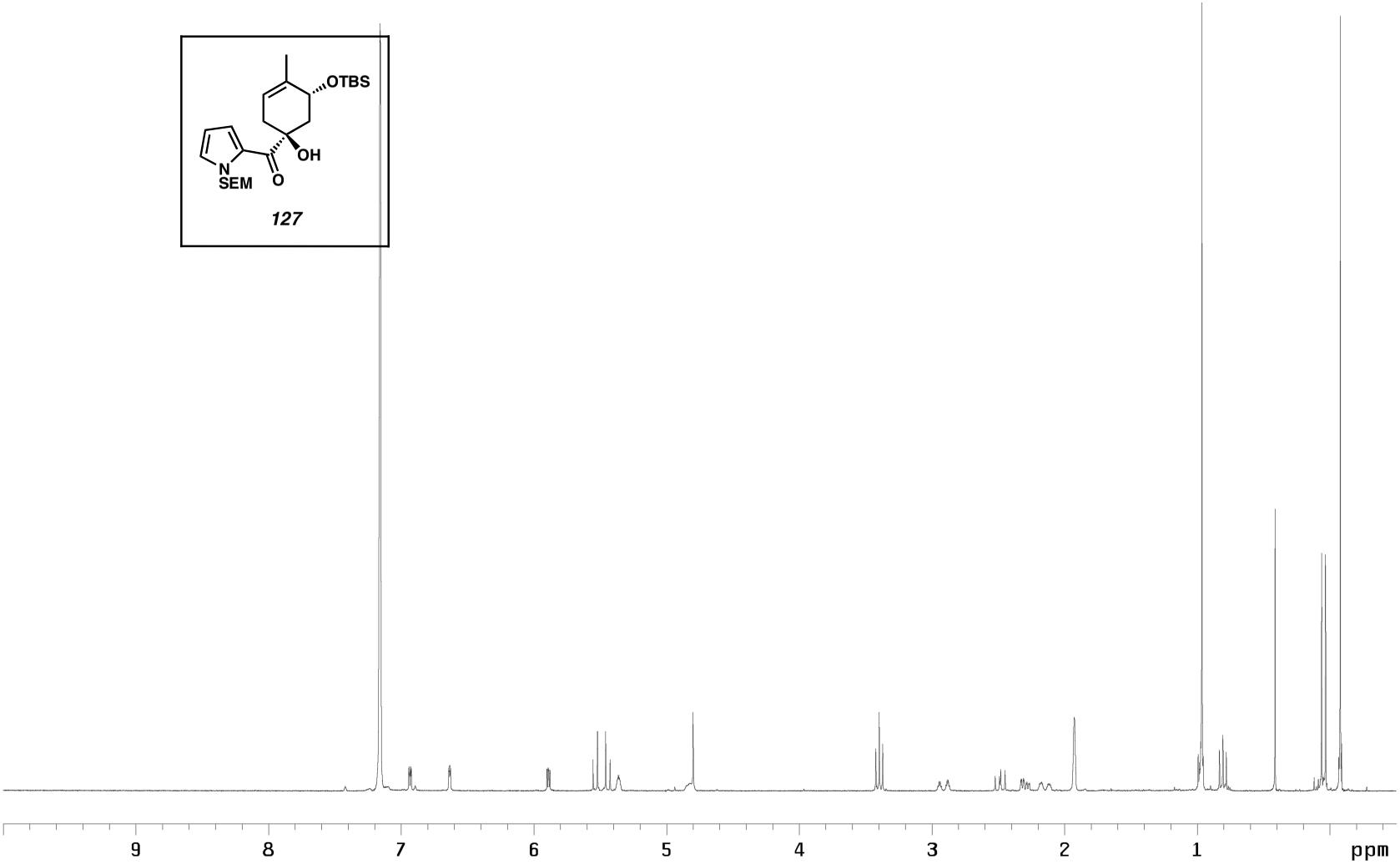


Figure A3.115 ^{1}H NMR (300 MHz, C_6D_6) of compound **127**

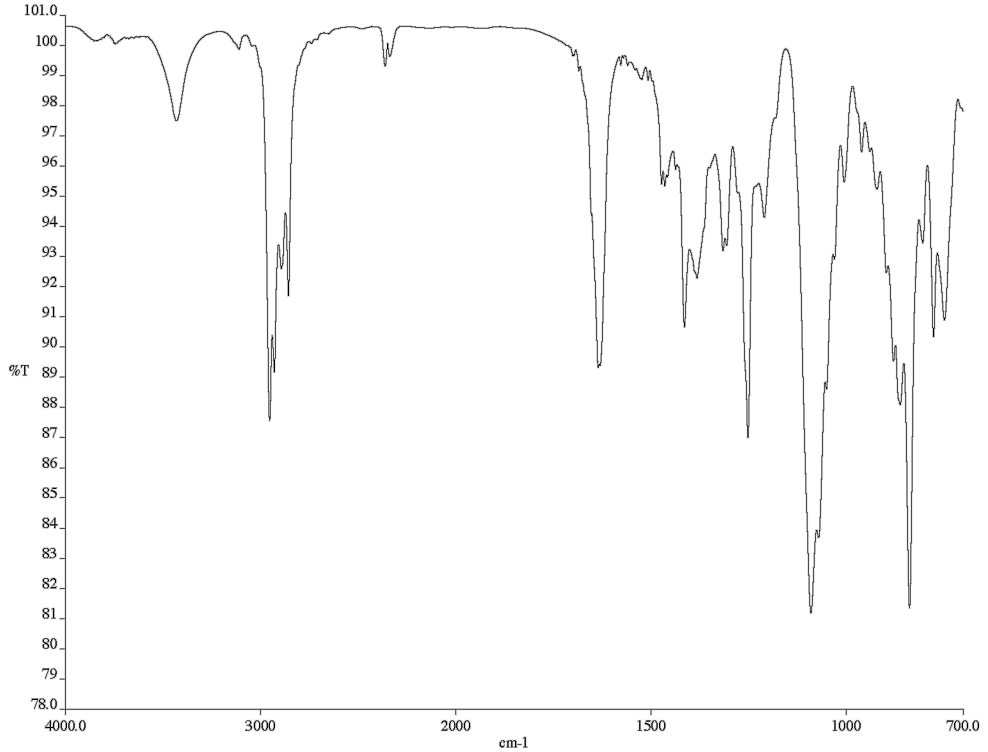


Figure A3.116 Infrared spectrum (thin film/NaCl) of compound **127**

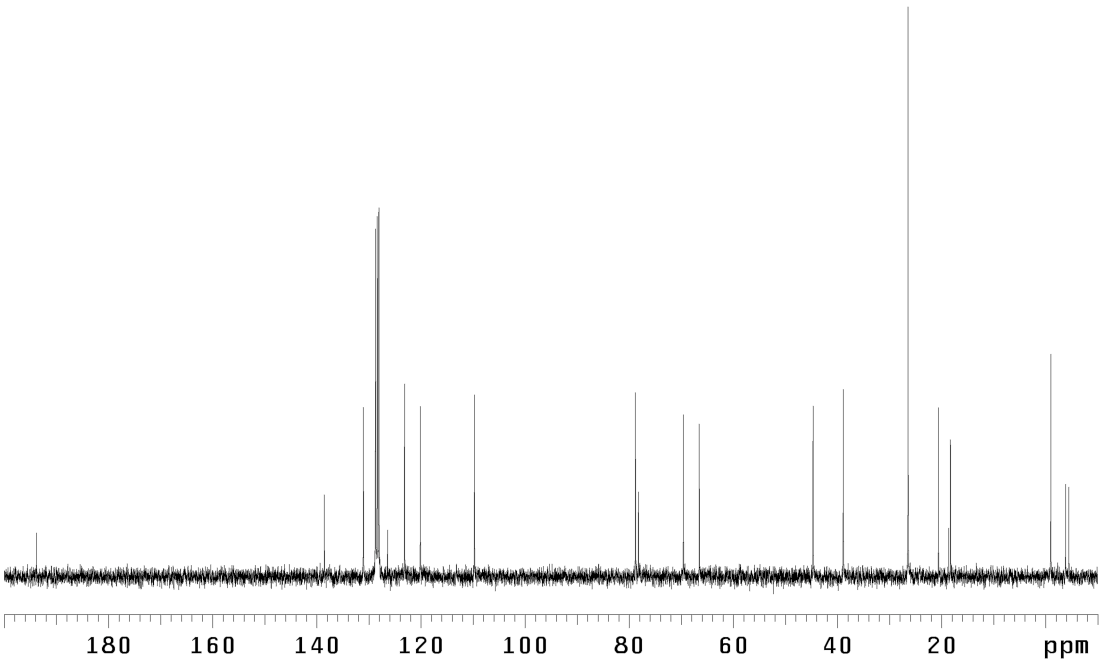


Figure A3.117 ^{13}C NMR (75 MHz, C_6D_6) of compound **127**

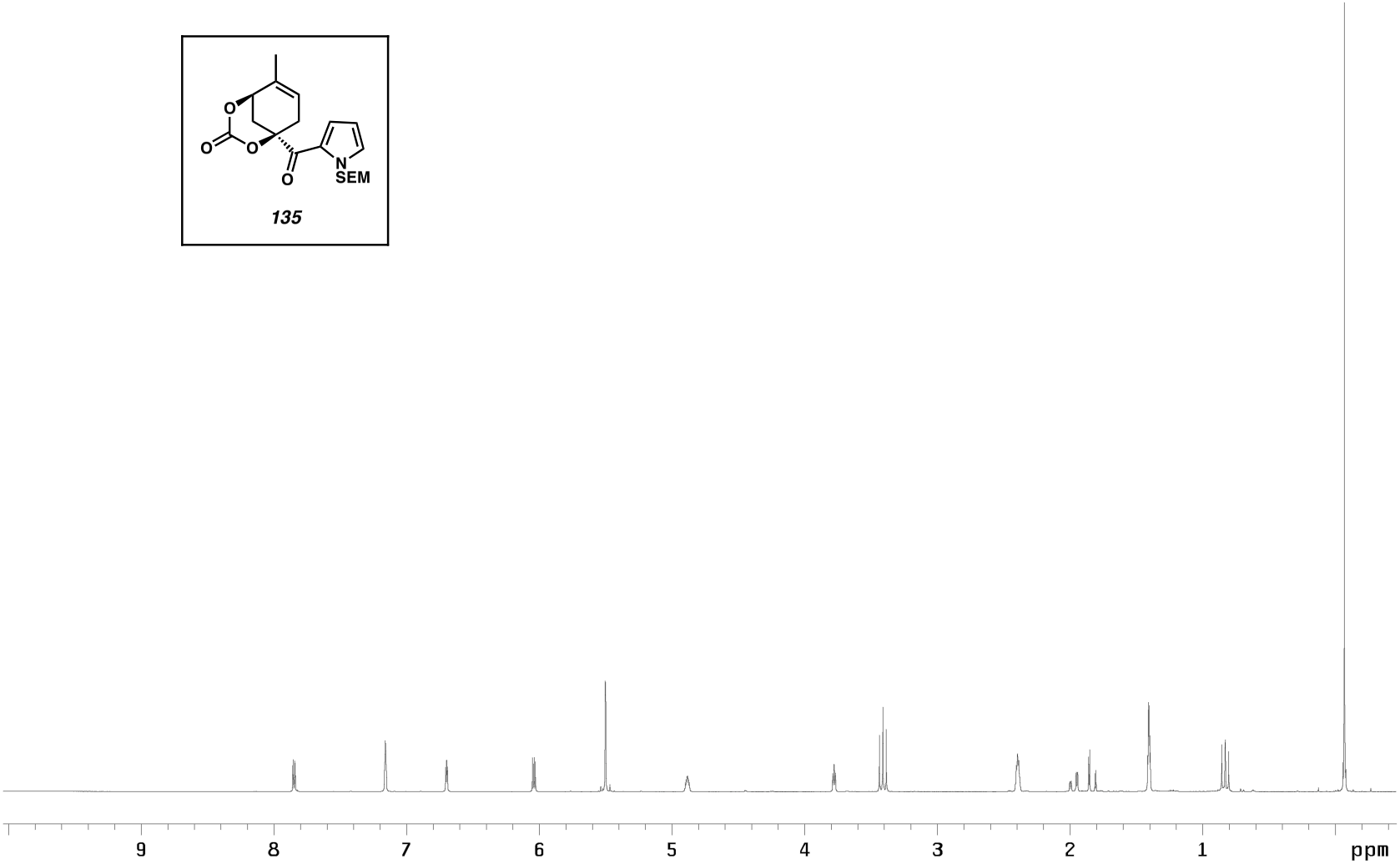


Figure A3.118 ^{1}H NMR (300 MHz, C_6D_6) of compound **135**

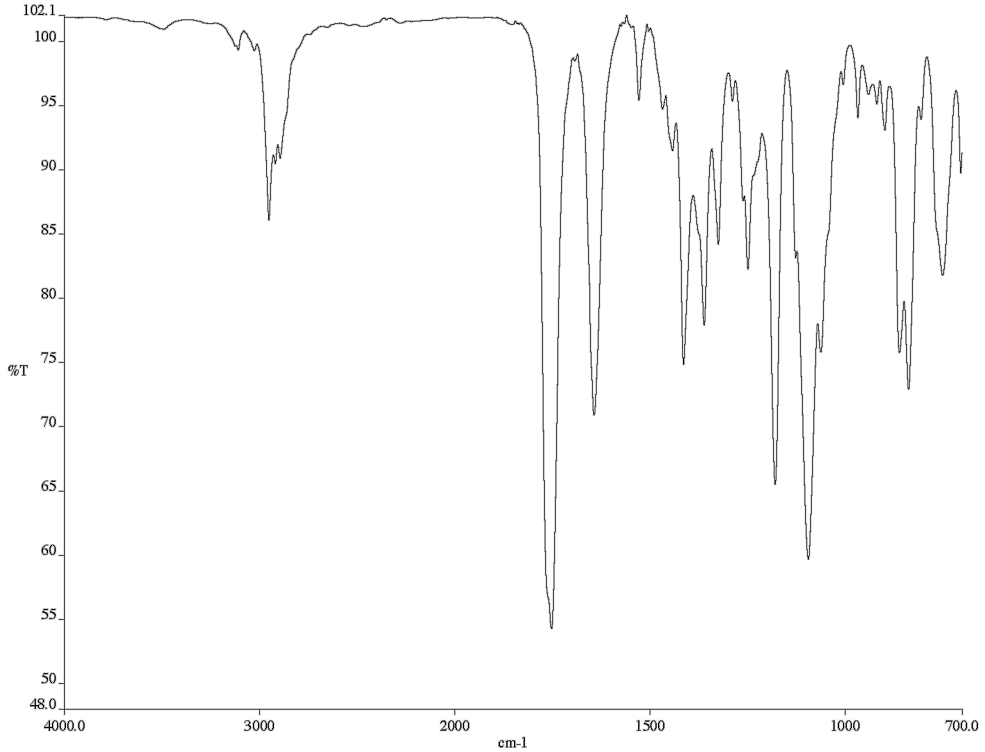


Figure A3.119 Infrared spectrum (thin film/NaCl) of compound **135**

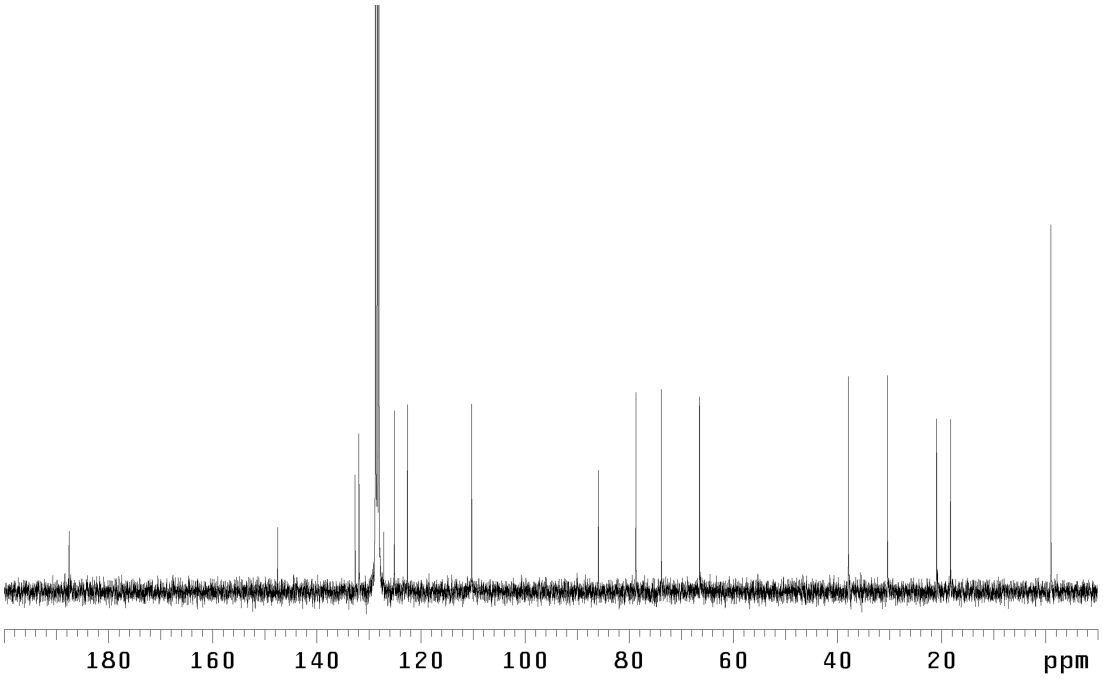


Figure A3.120 ^{13}C NMR (75 MHz, C_6D_6) of compound **135**

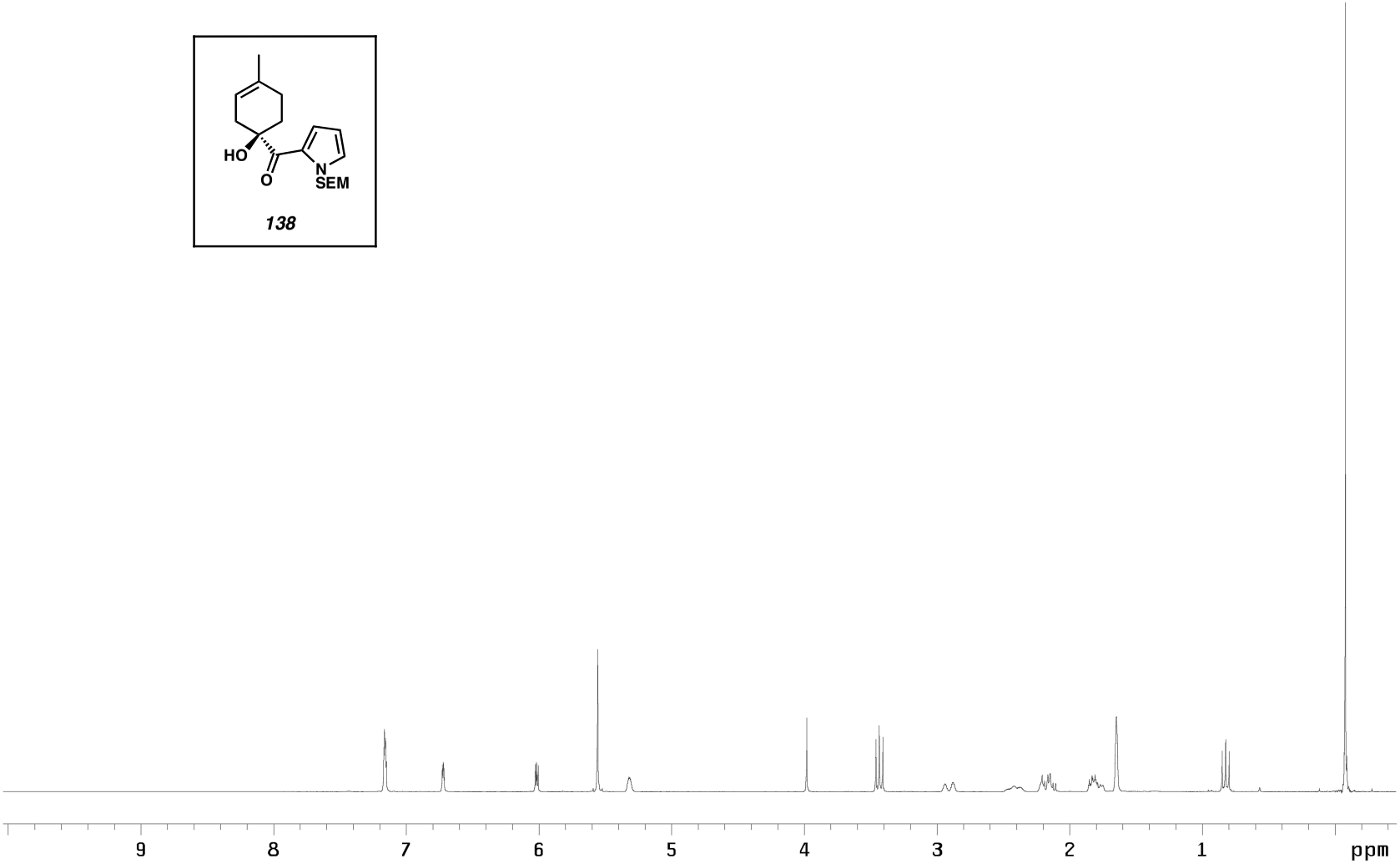


Figure A3.121 ^{1}H NMR (300 MHz, C_6D_6) of compound **138**

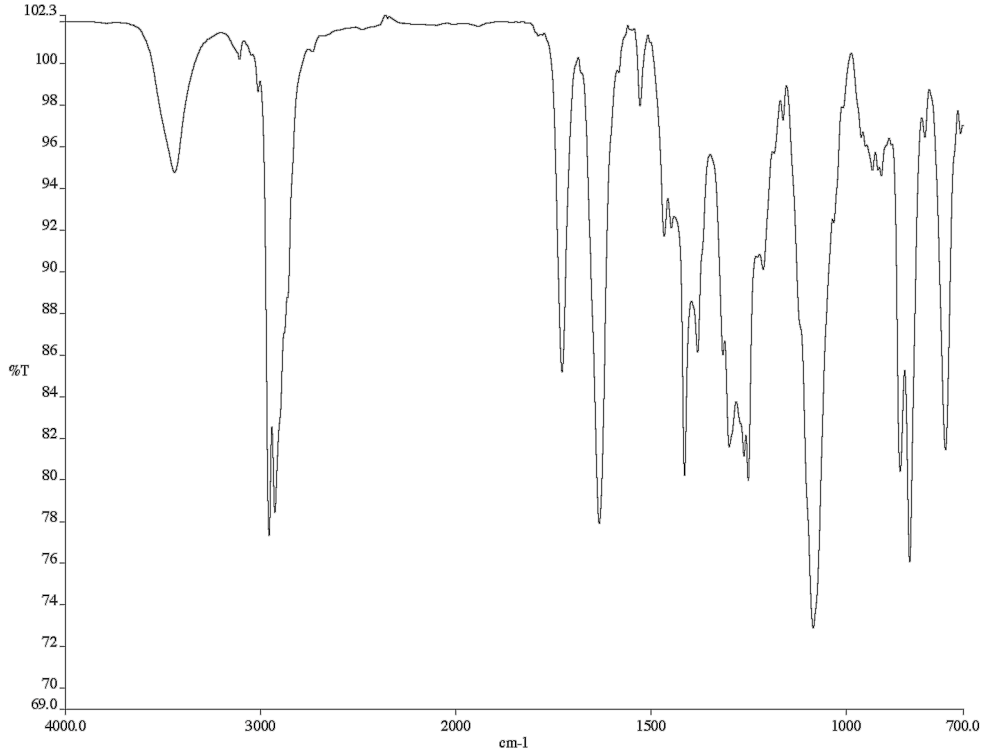


Figure A3.122 Infrared spectrum (thin film/NaCl) of compound **138**

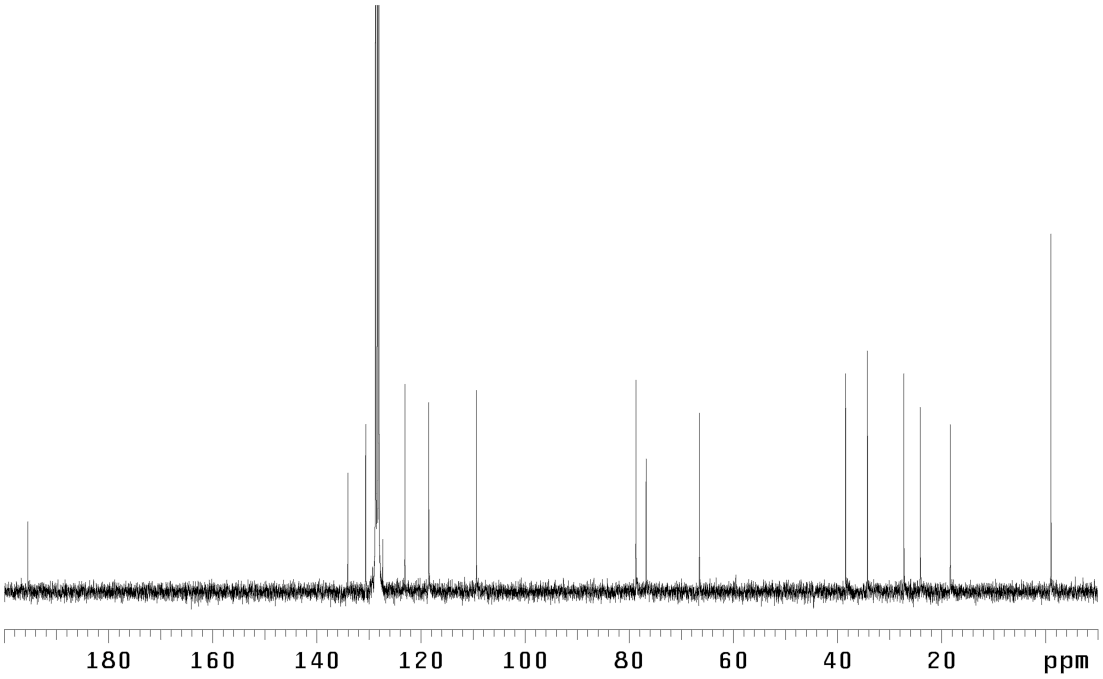


Figure A3.123 ^{13}C NMR (75 MHz, C_6D_6) of compound **138**

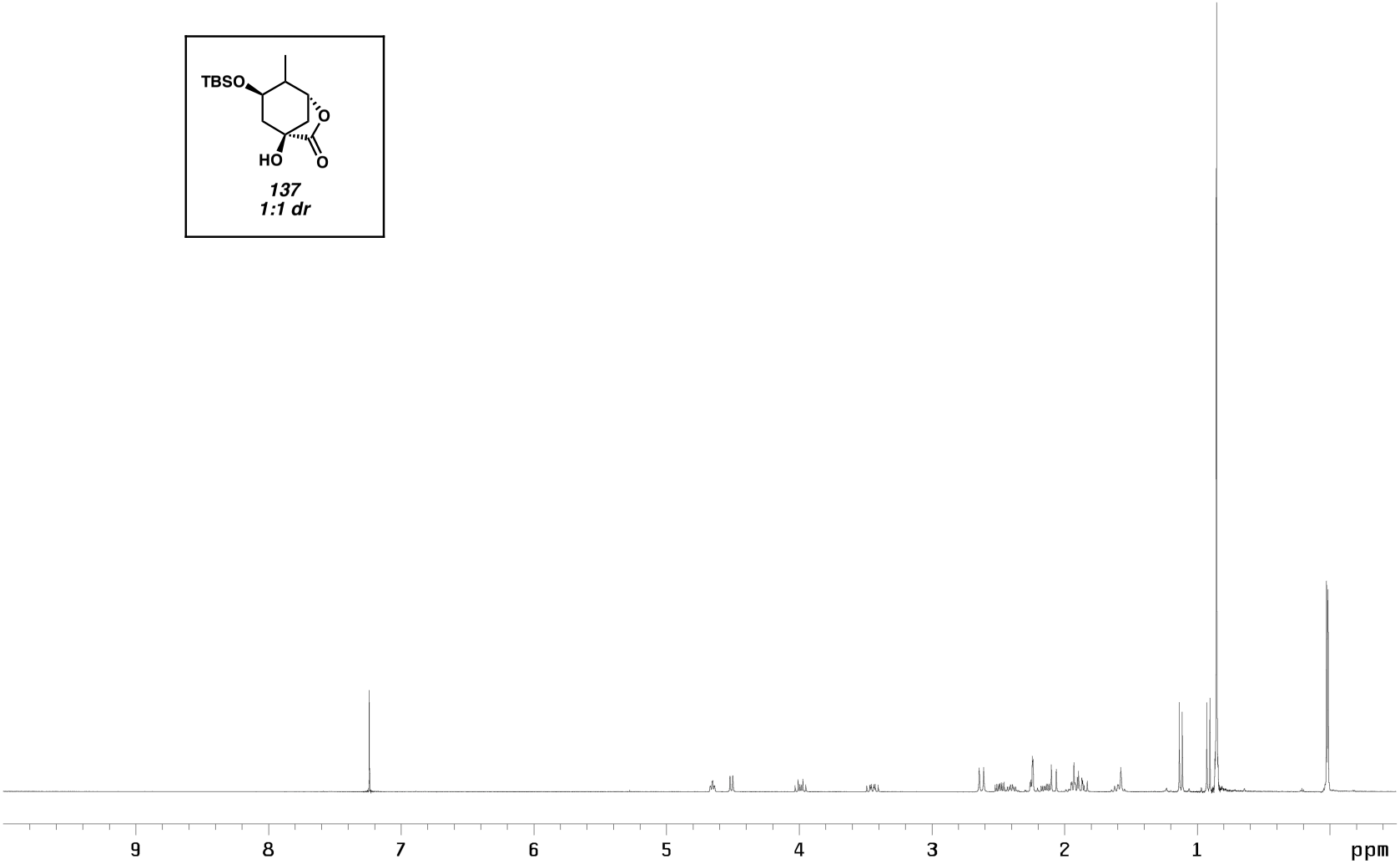


Figure A3.124 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **137**

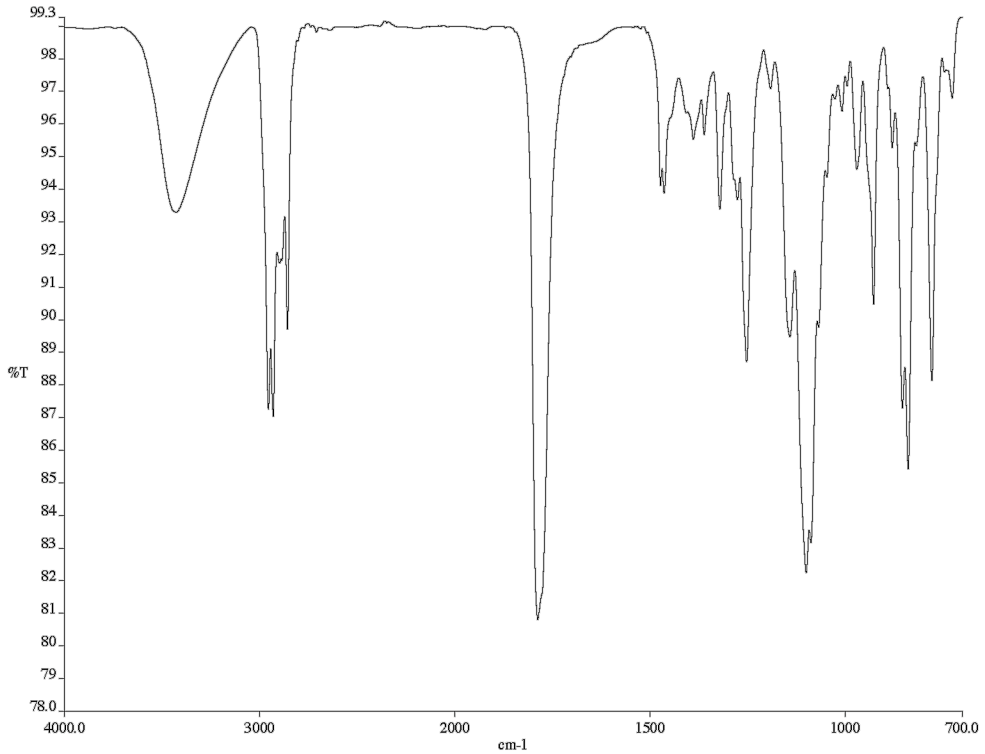


Figure A3.125 Infrared spectrum (thin film/NaCl) of compound **137**

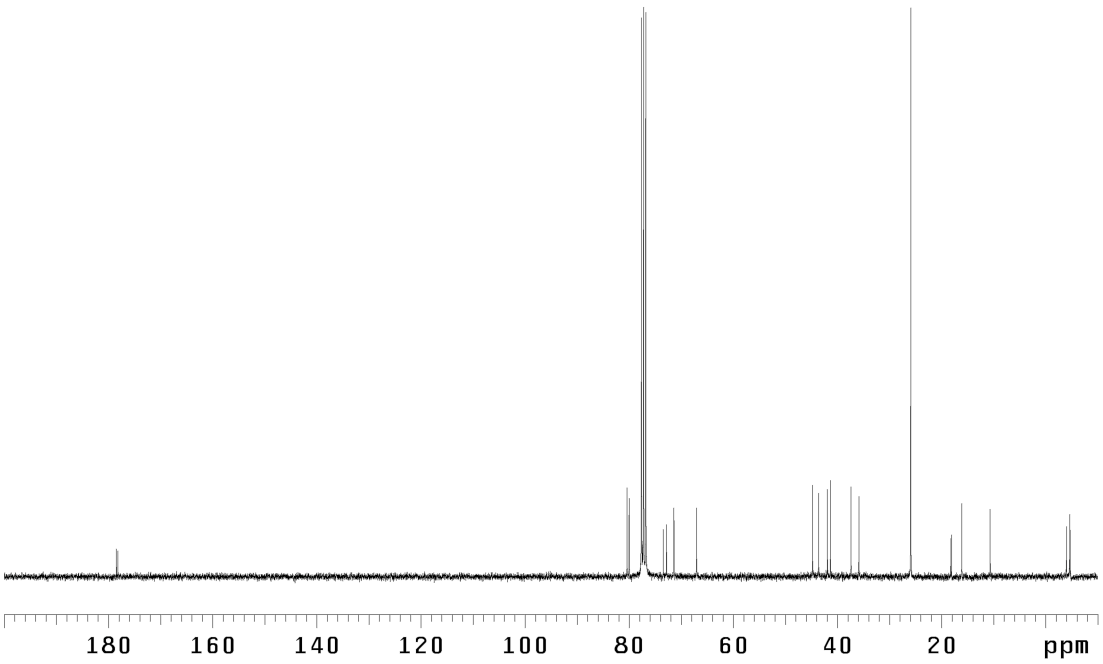


Figure A3.126 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **137**

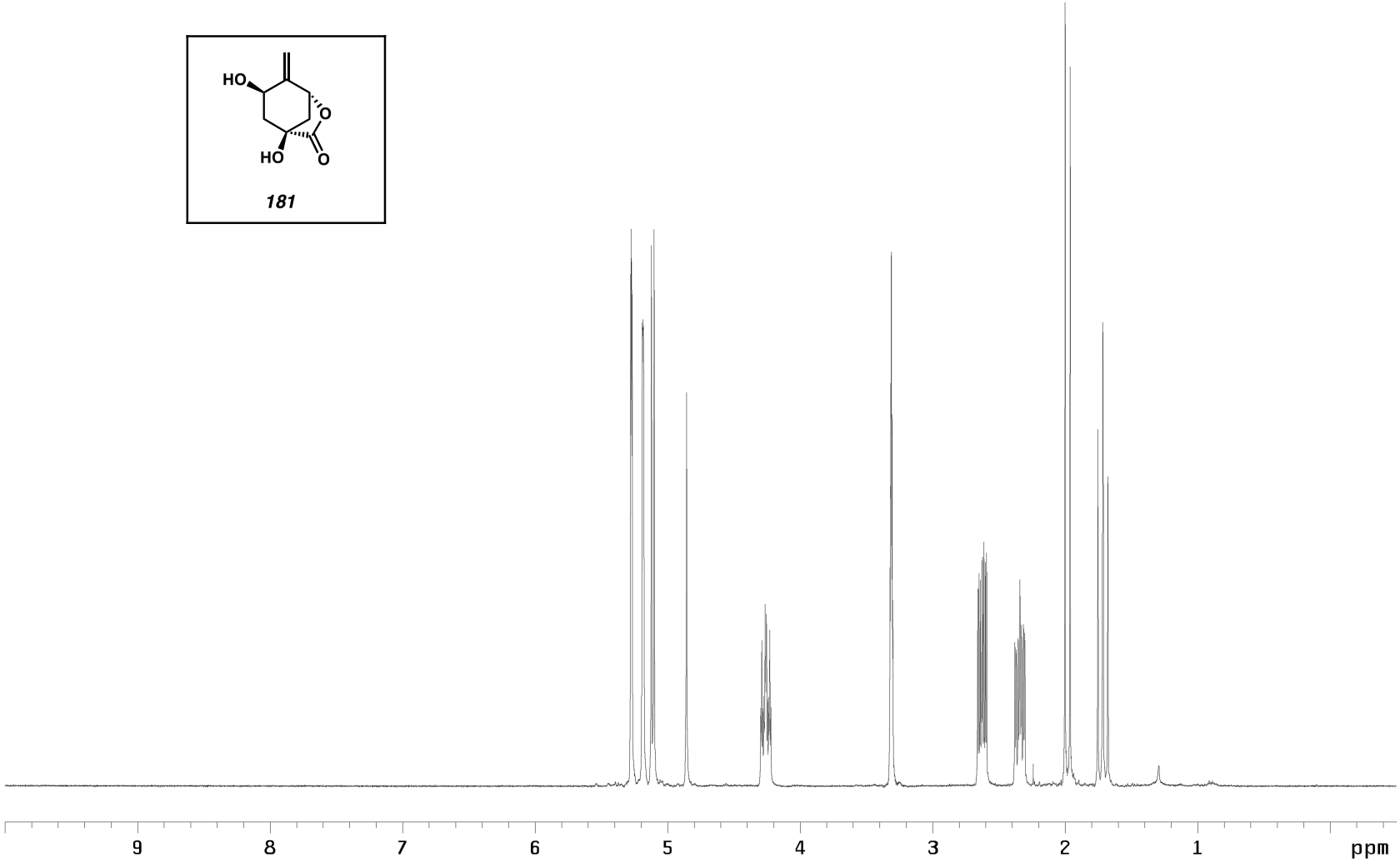


Figure A3.127 ^{1}H NMR (300 MHz, CD_3OD) of compound **181**

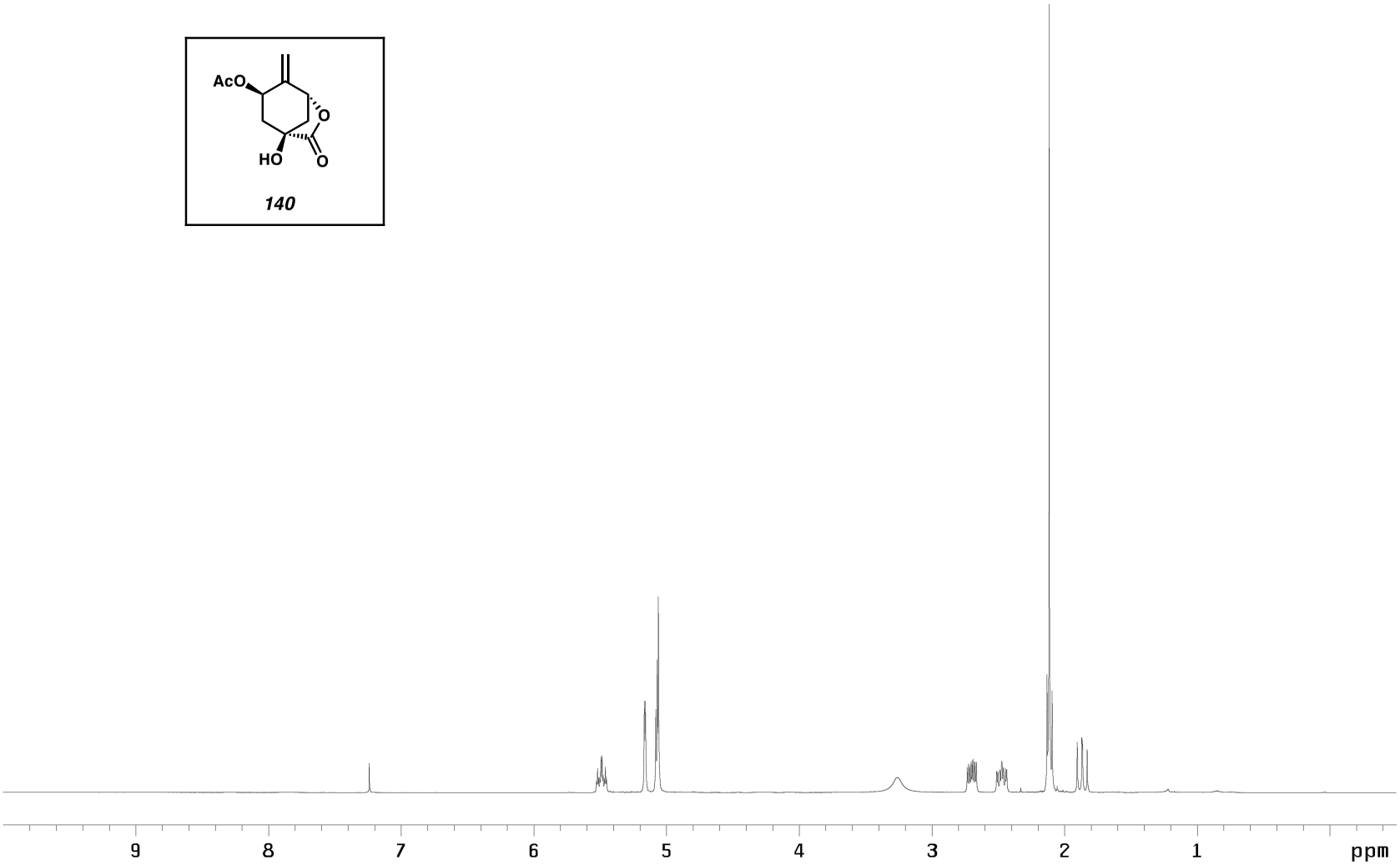


Figure A3.128 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **140**

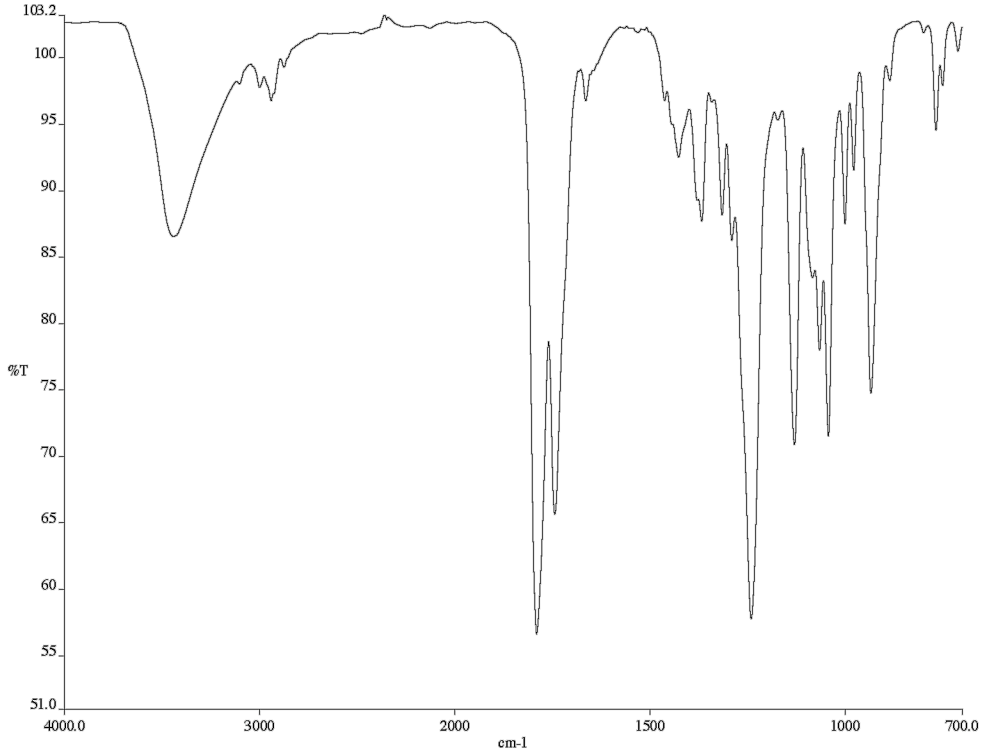


Figure A3.129 Infrared spectrum (thin film/NaCl) of compound **140**

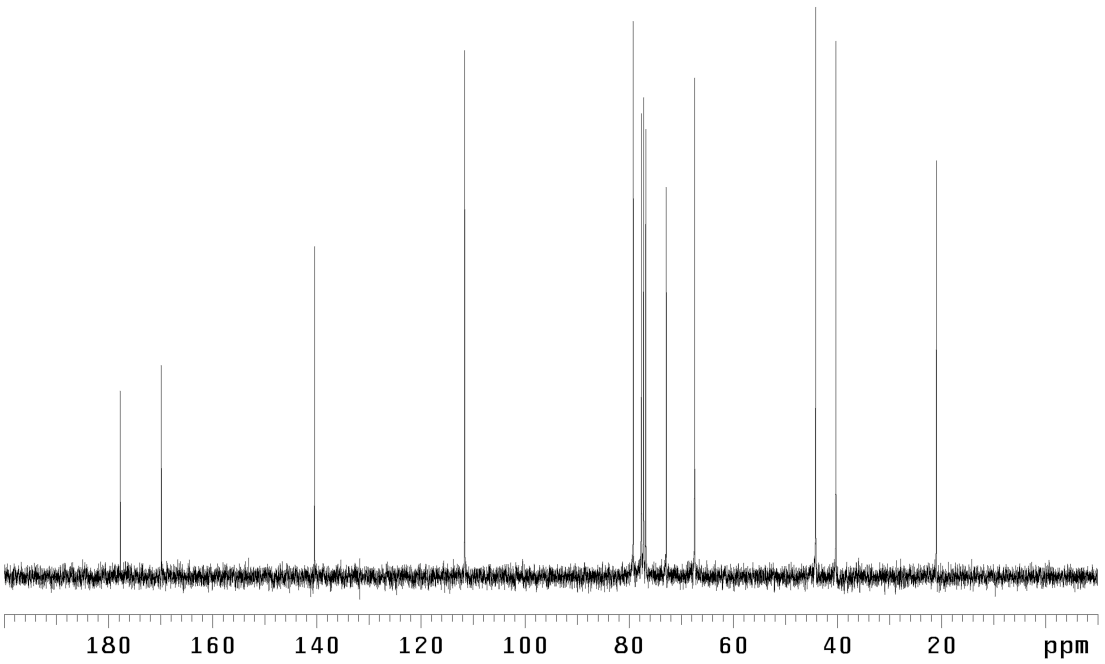


Figure A3.130 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **140**

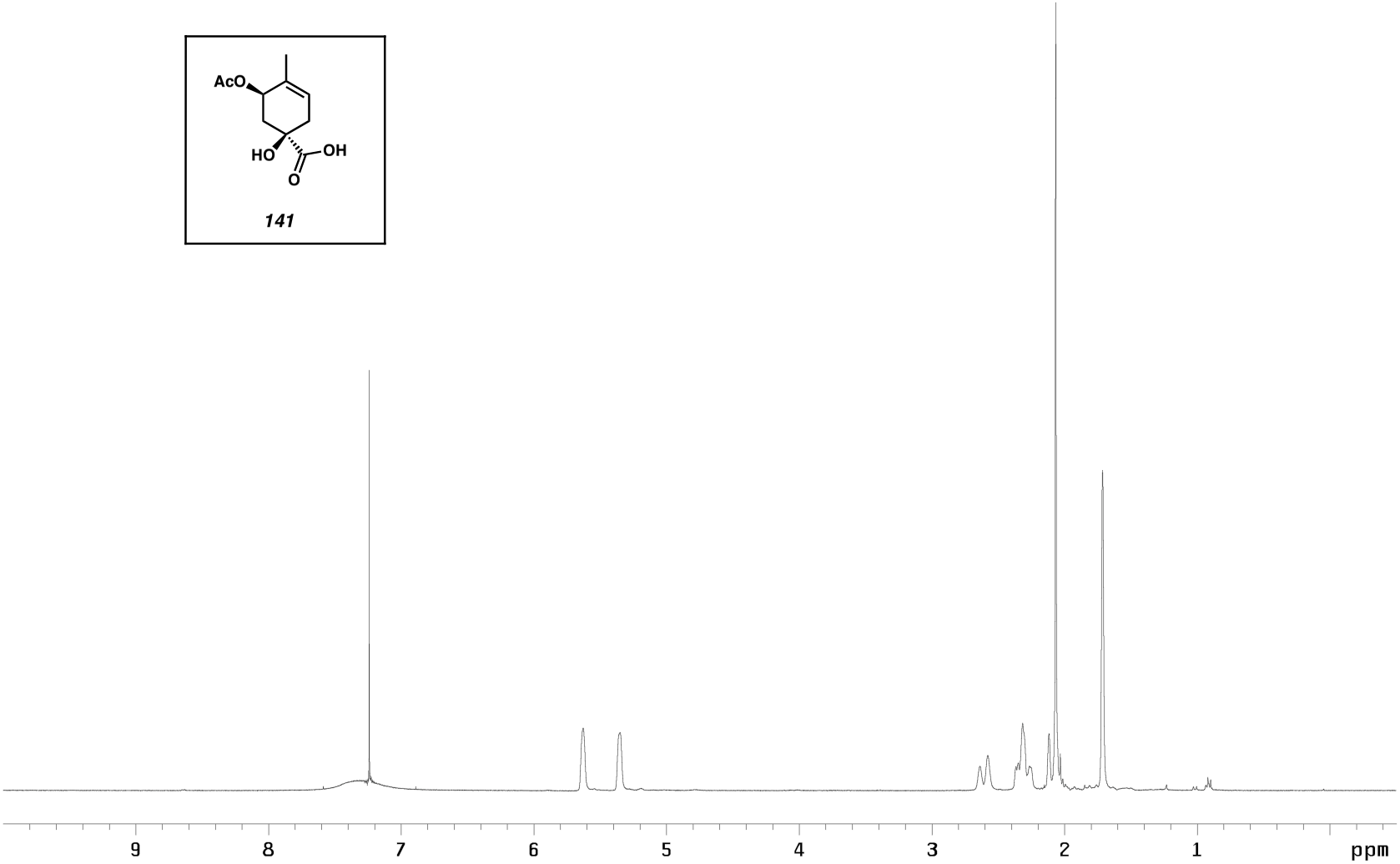


Figure A3.131 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **141**

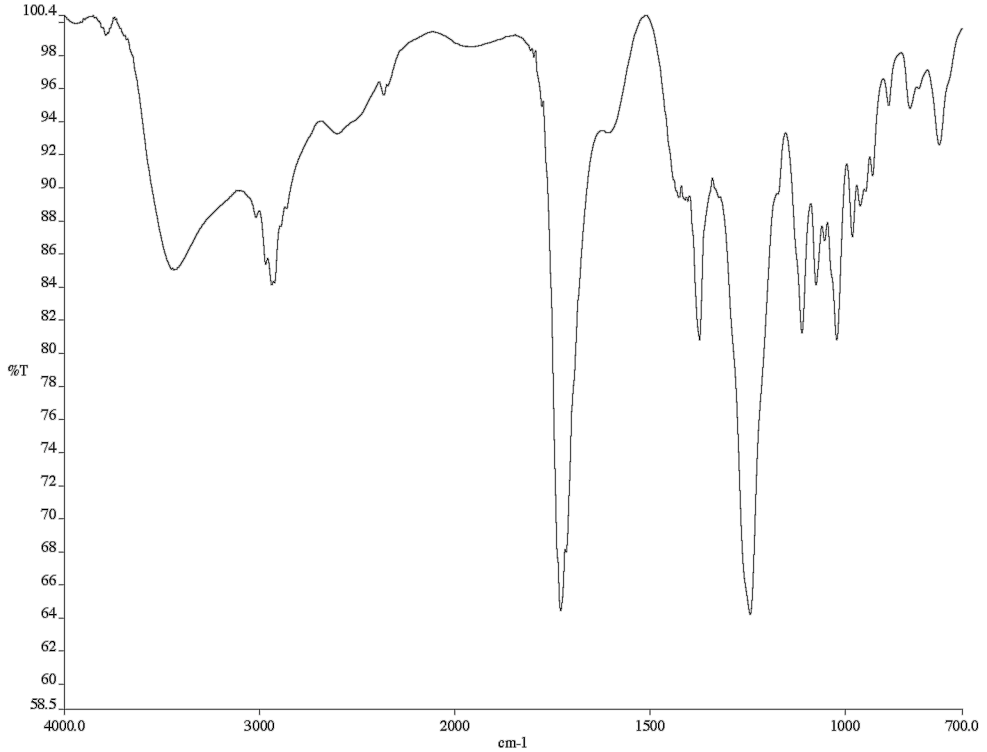


Figure A3.132 Infrared spectrum (thin film/NaCl) of compound **141**

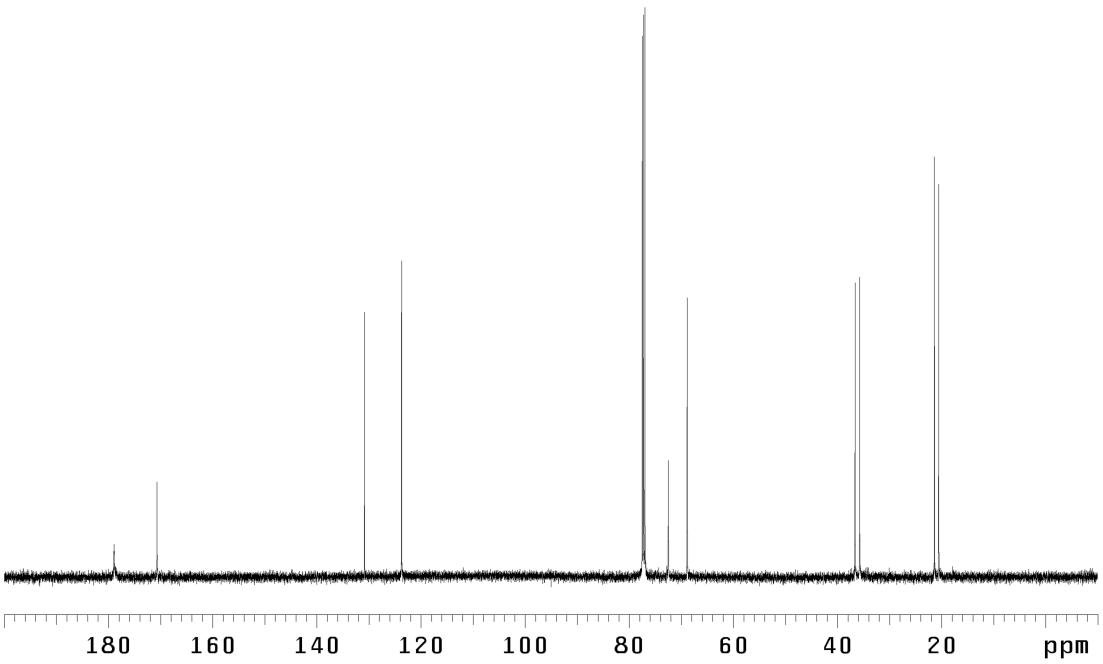


Figure A3.133 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **141**

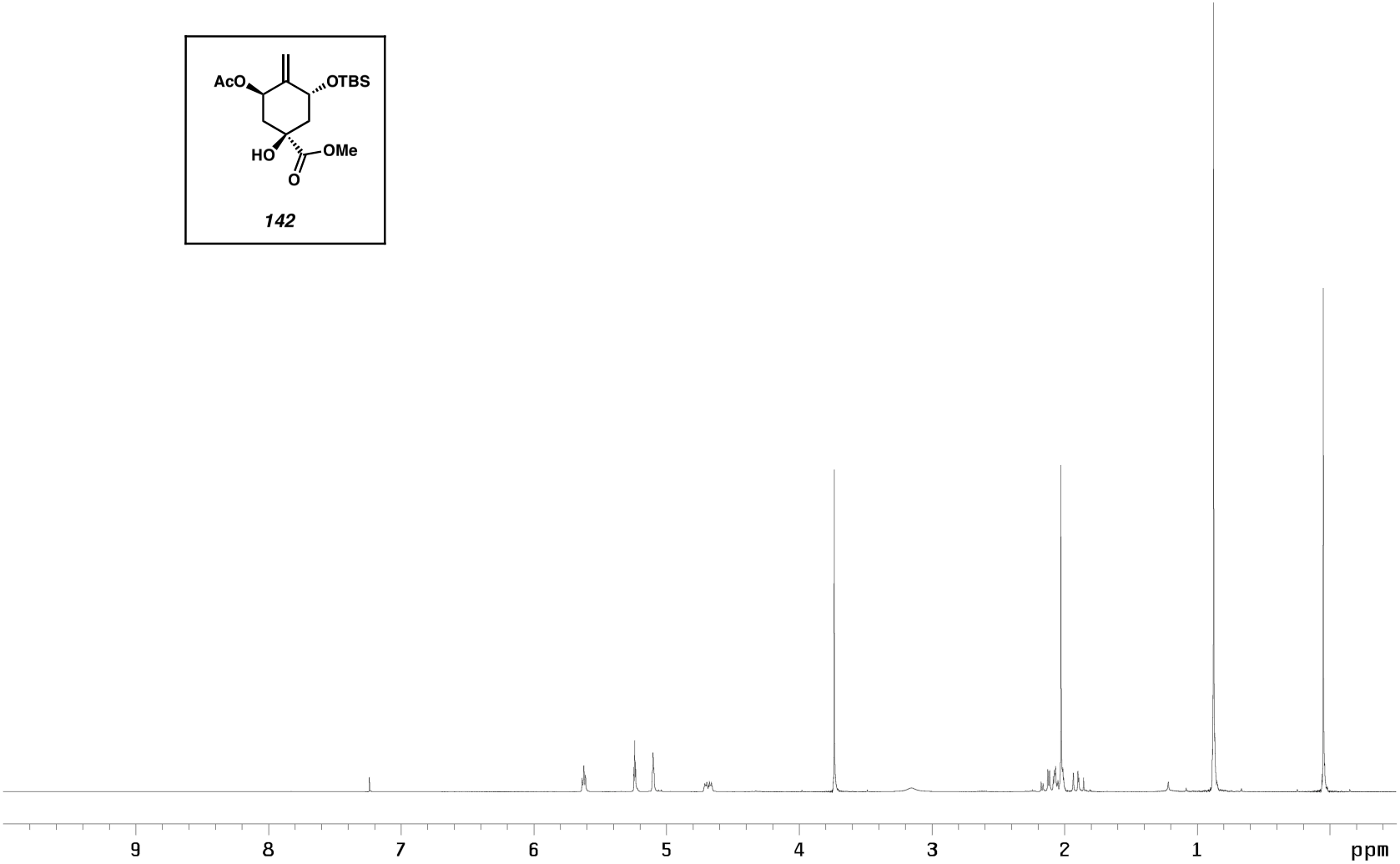


Figure A3.134 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **142**

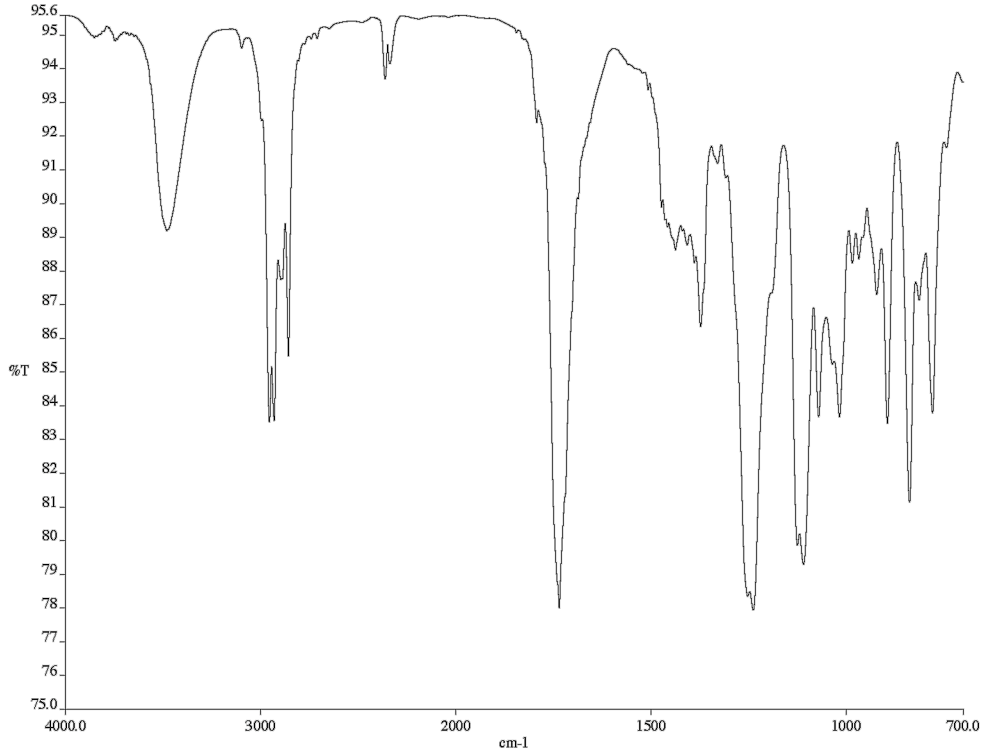


Figure A3.135 Infrared spectrum (thin film/NaCl) of compound **142**

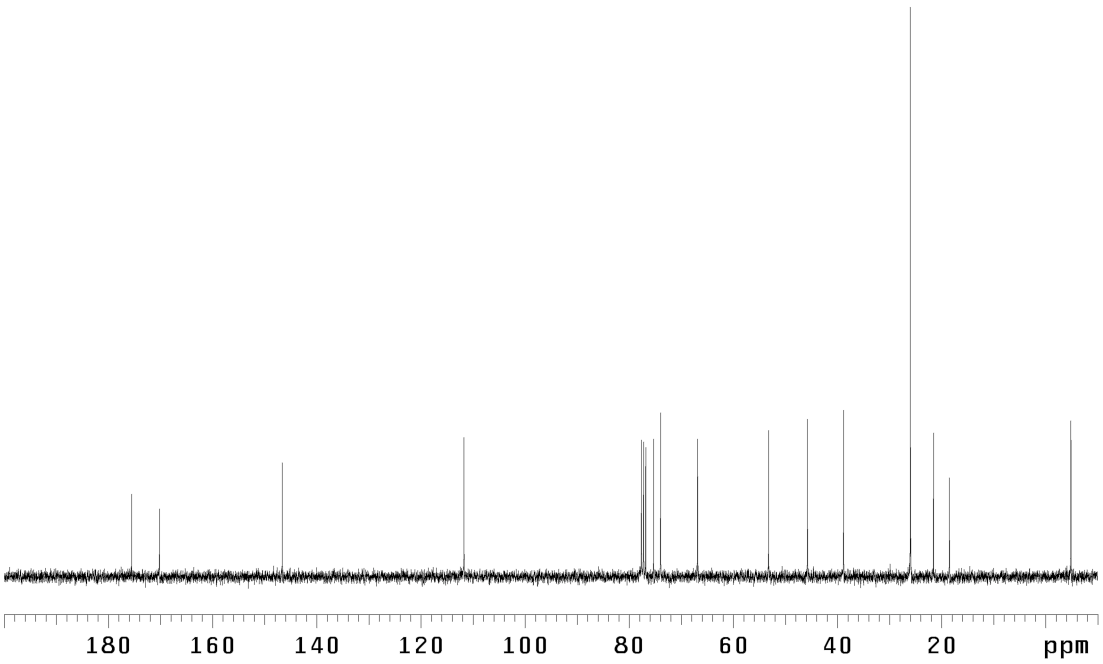


Figure A3.136 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **142**

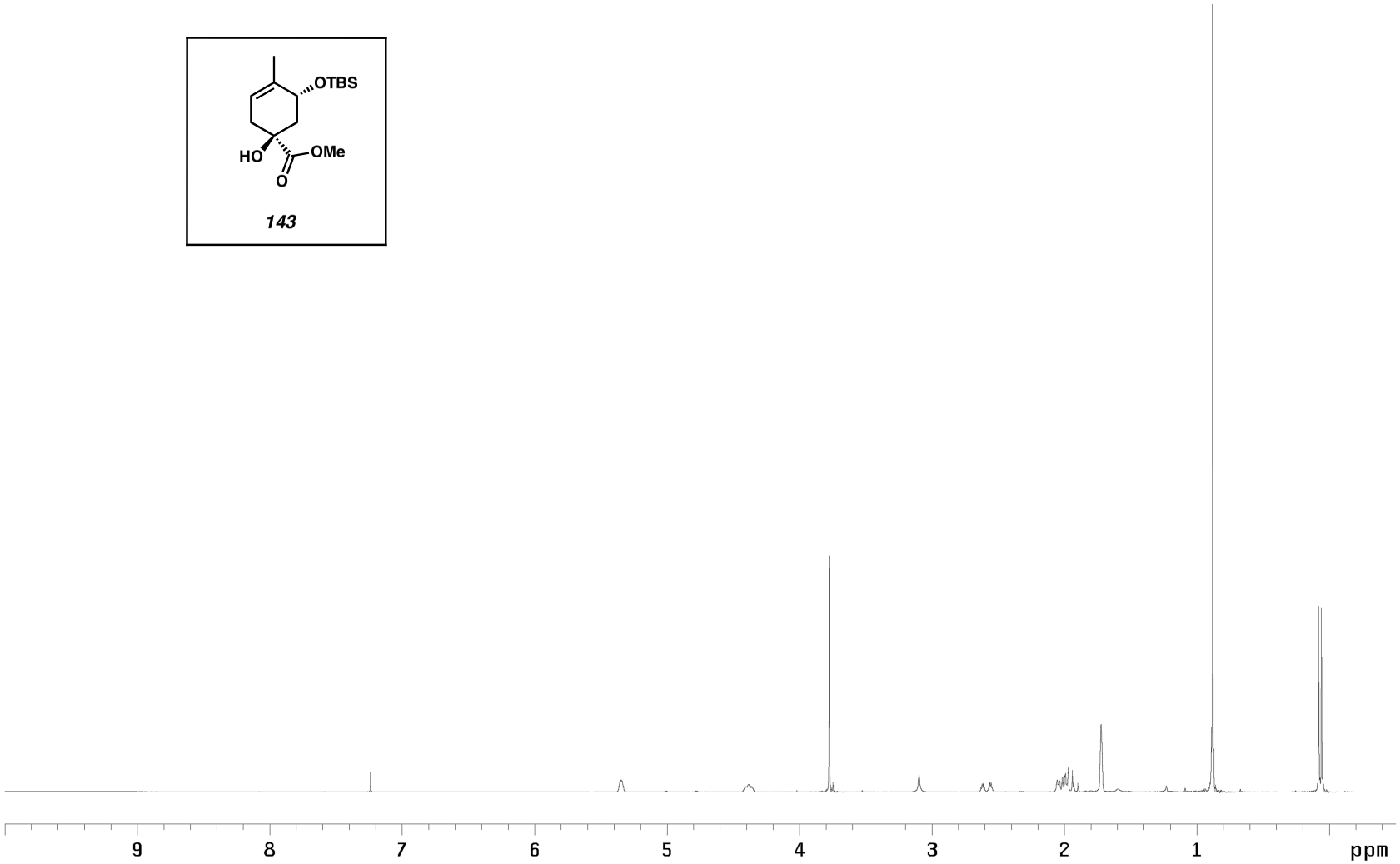


Figure A3.137 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **143**

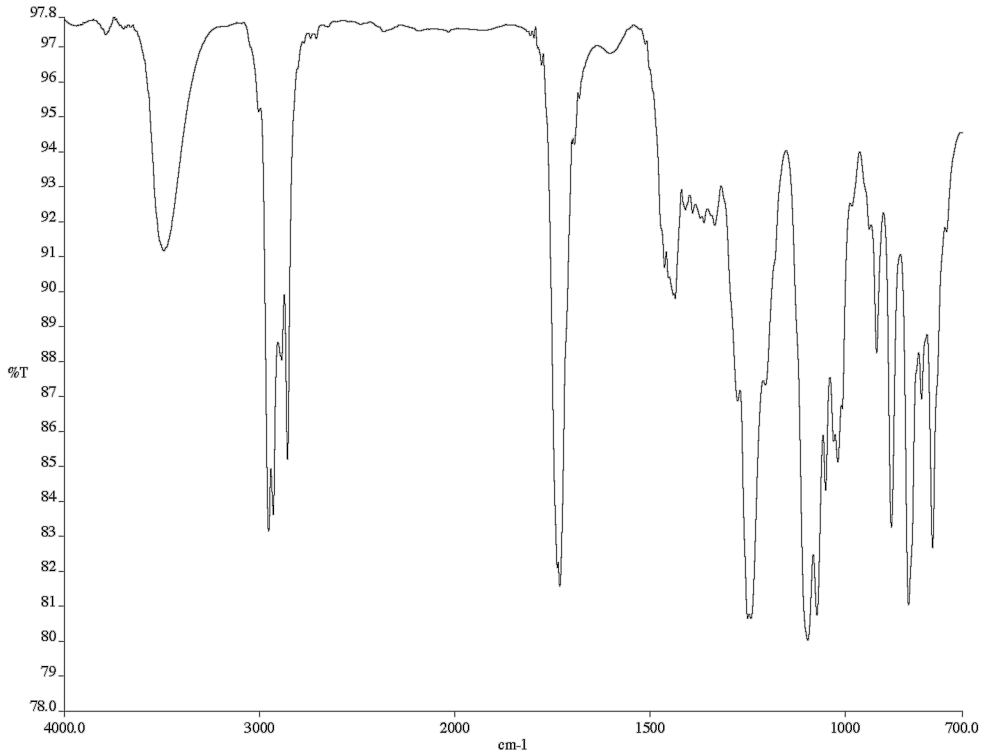


Figure A3.138 Infrared spectrum (thin film/NaCl) of compound **143**

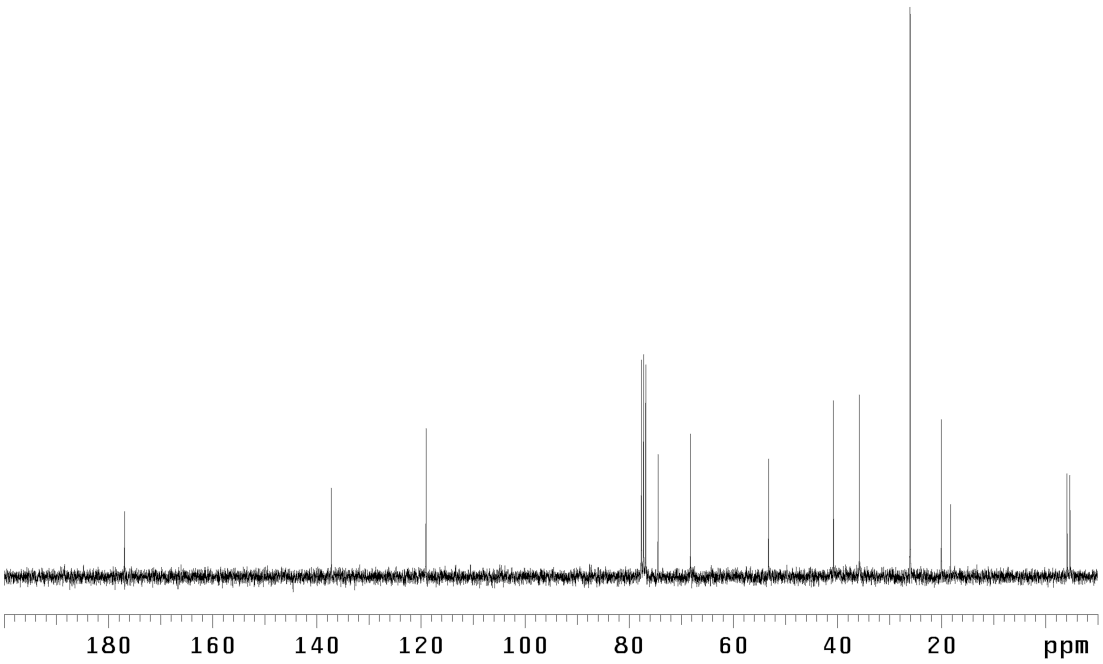


Figure A3.139 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **143**

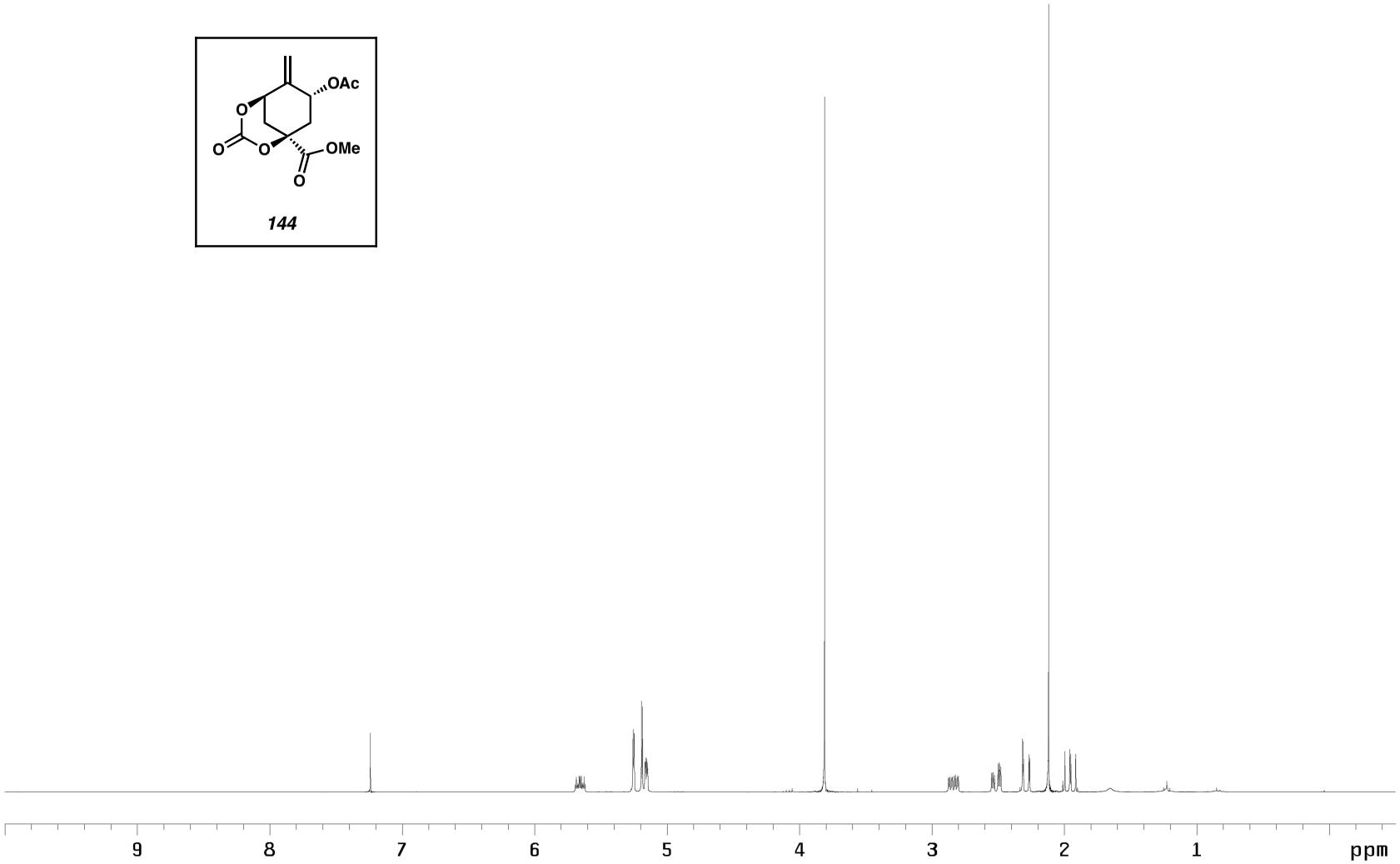


Figure A3.140 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **144**

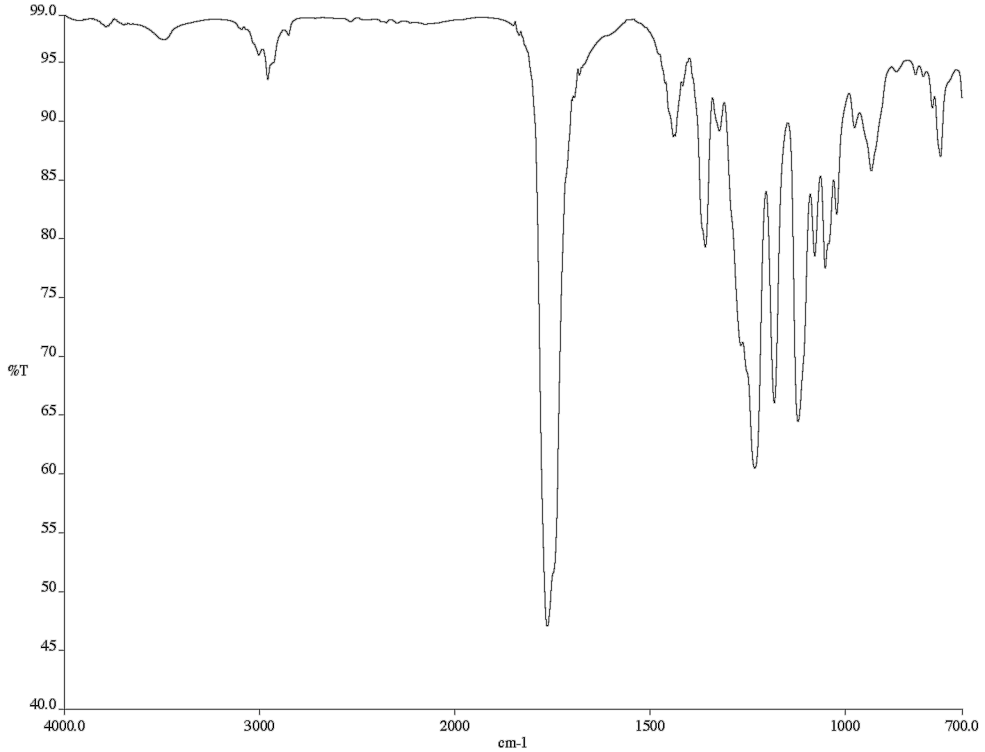


Figure A3.141 Infrared spectrum (thin film/NaCl) of compound **144**

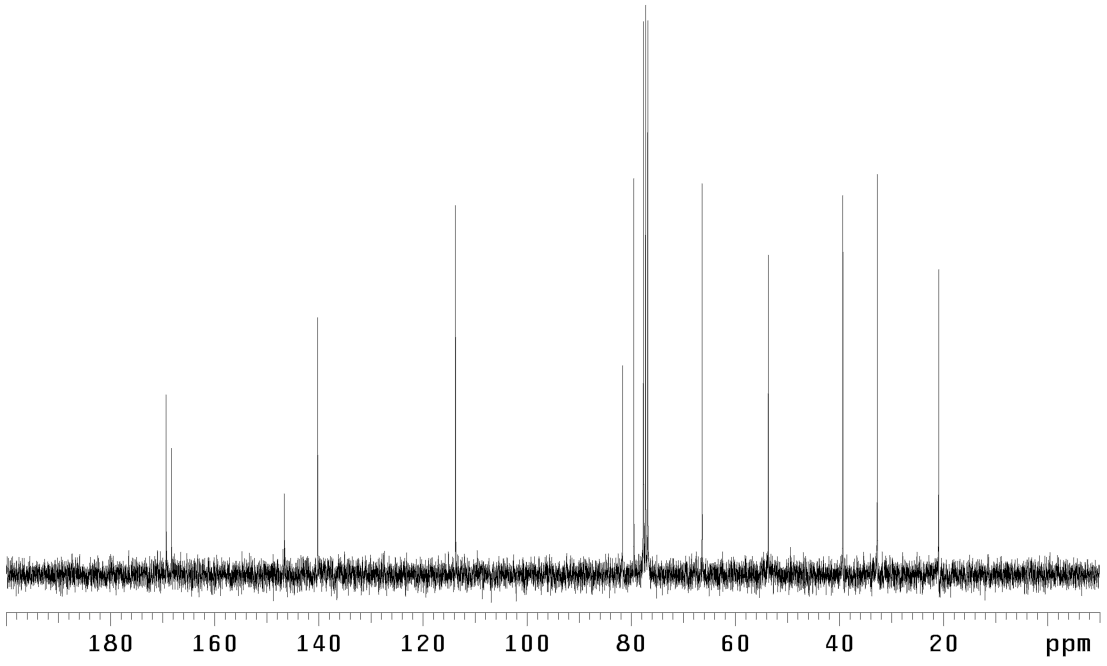


Figure A3.142 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **144**

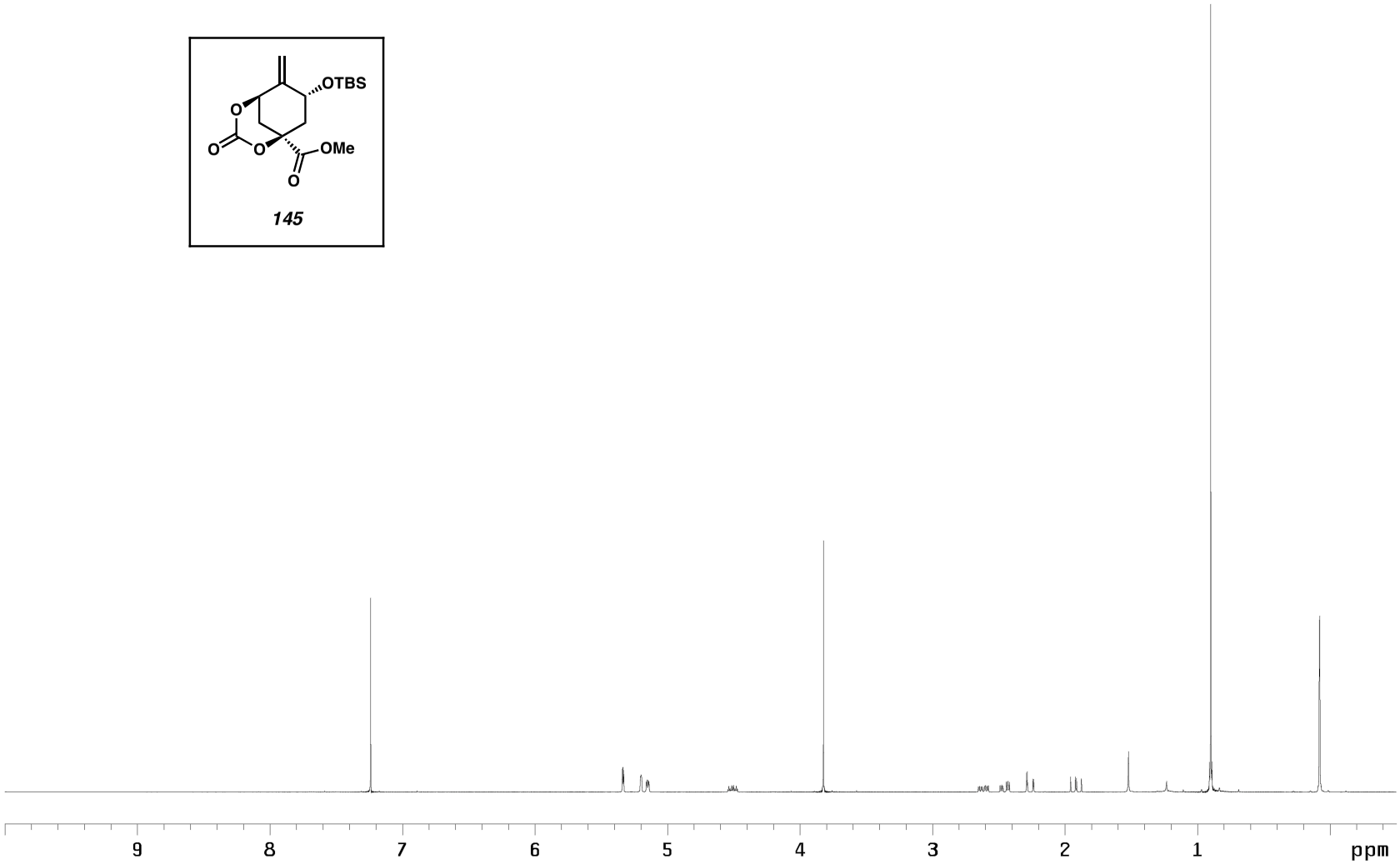


Figure A3.143 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **145**

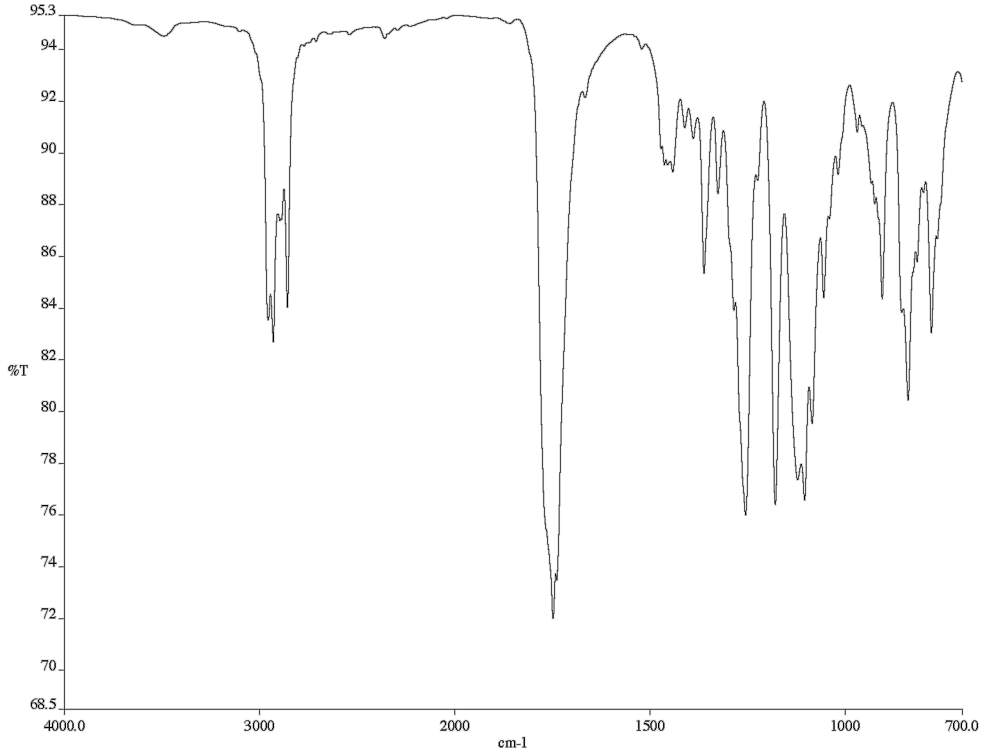


Figure A3.144 Infrared spectrum (thin film/NaCl) of compound **145**

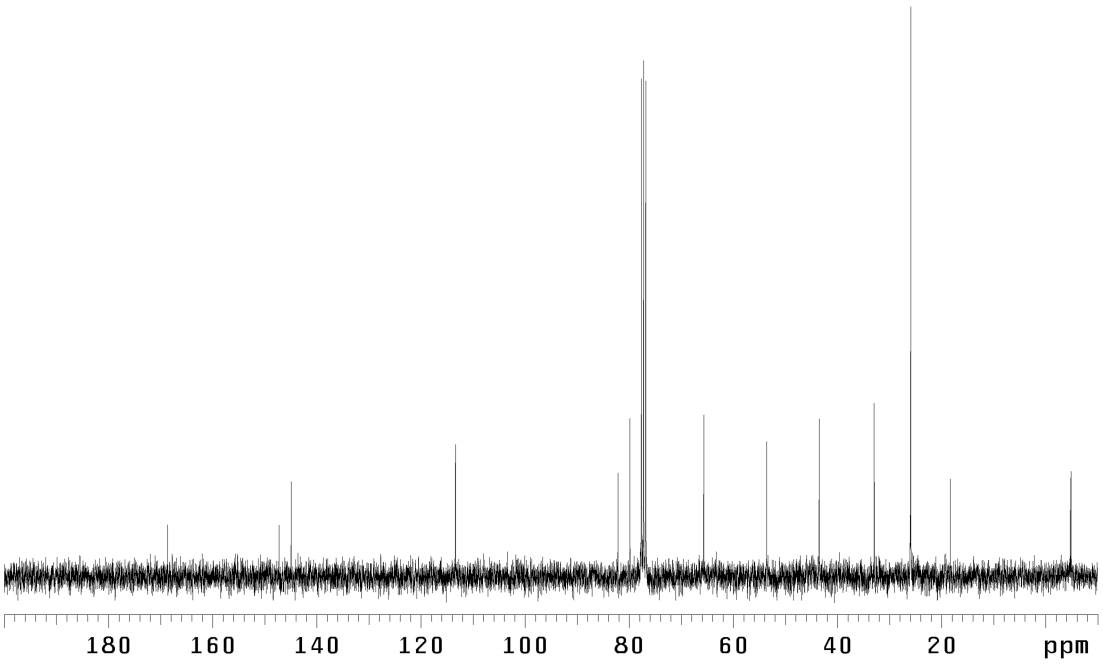


Figure A3.145 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **145**

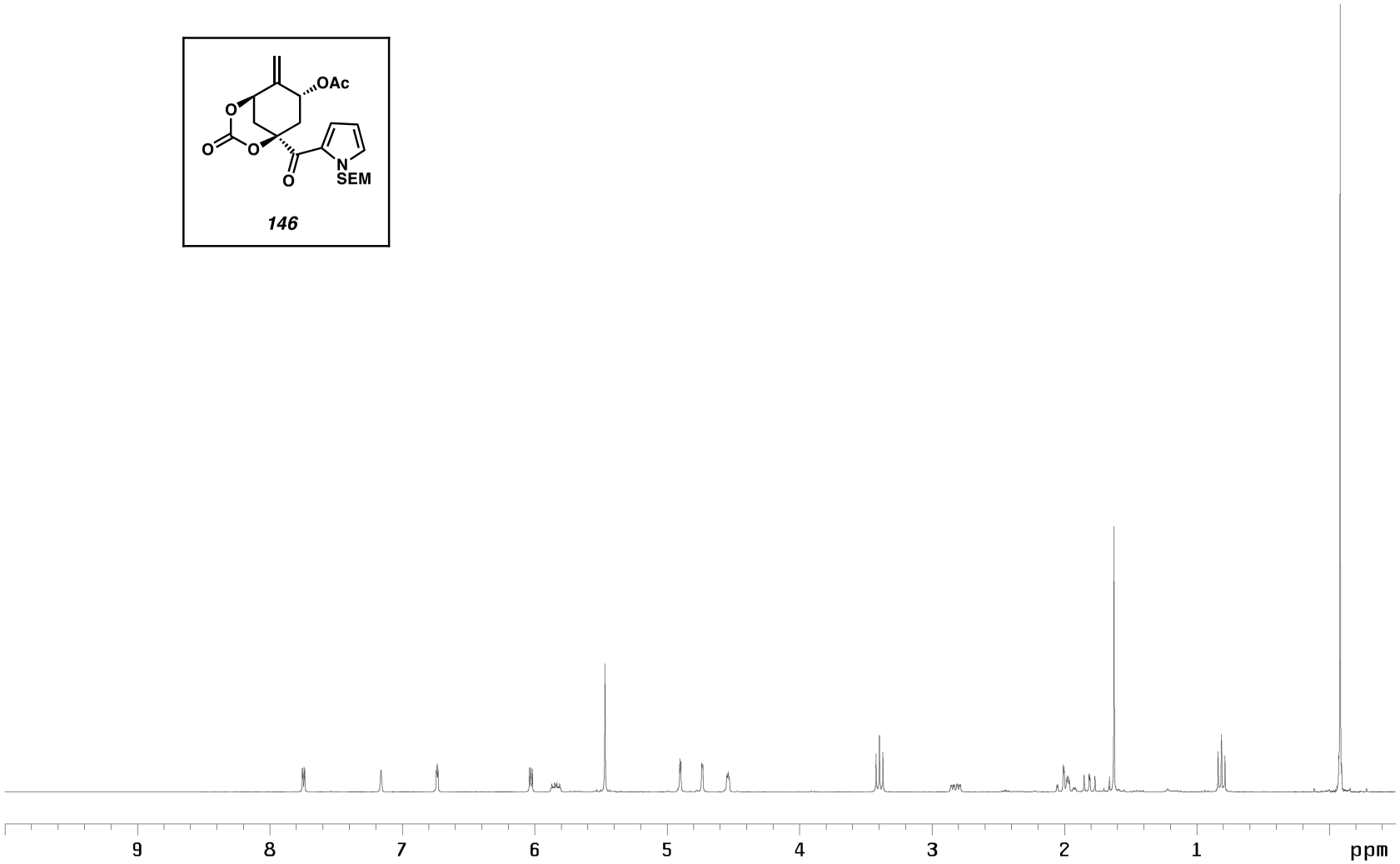


Figure A3.146 ^{1}H NMR (300 MHz, C_6D_6) of compound **146**

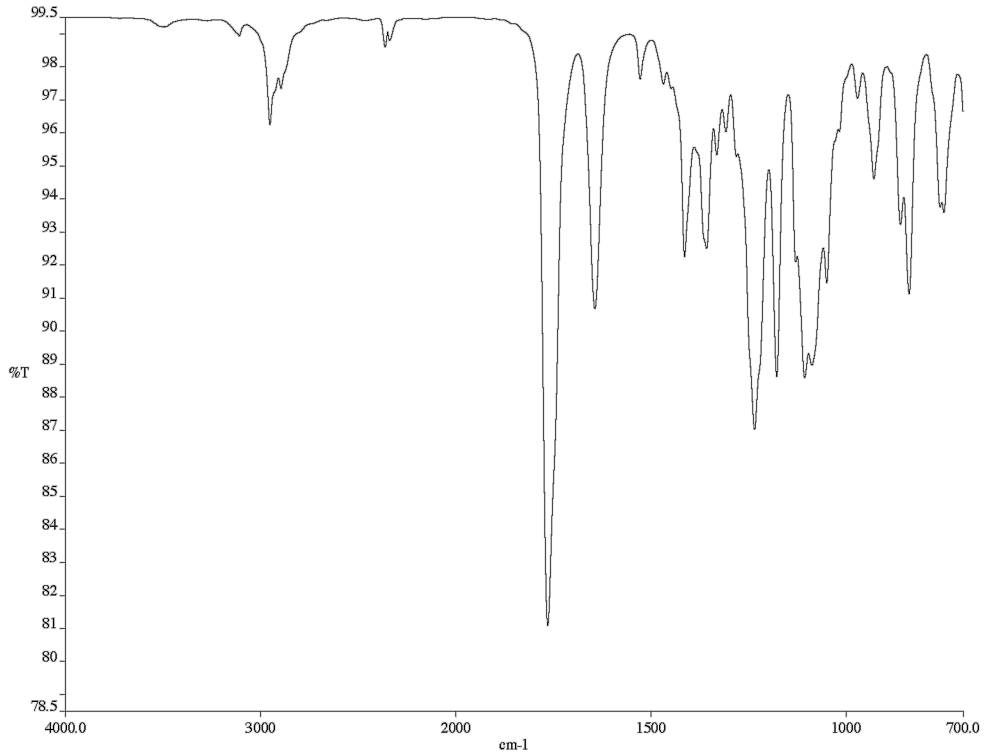


Figure A3.147 Infrared spectrum (thin film/NaCl) of compound **146**

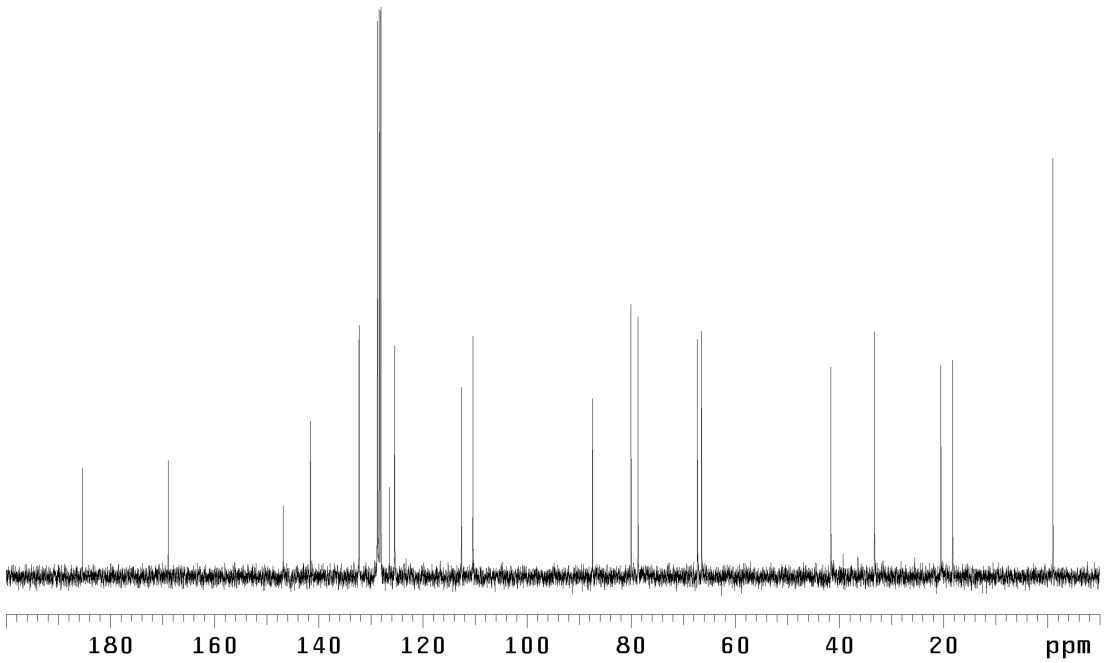


Figure A3.148 ^{13}C NMR (75 MHz, C_6D_6) of compound **146**

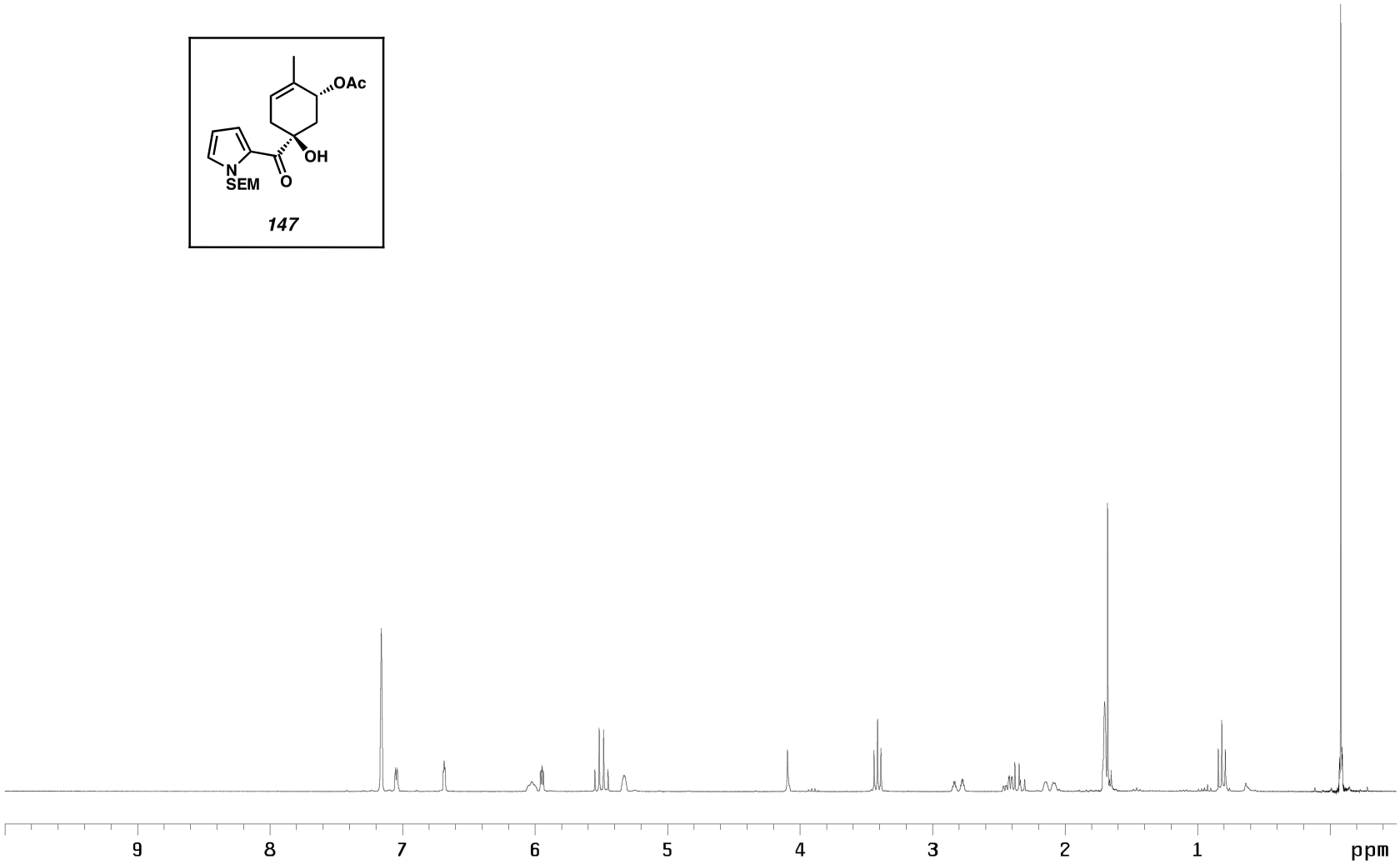


Figure A3.149 ^{1}H NMR (300 MHz, C_6D_6) of compound **147**

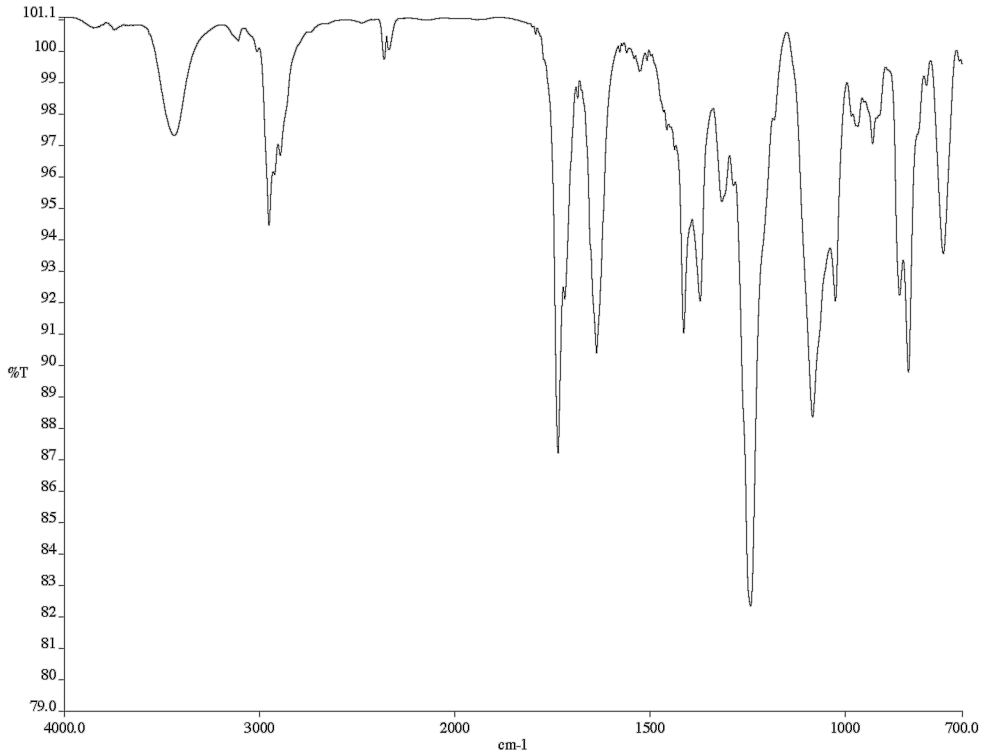


Figure A3.150 Infrared spectrum (thin film/NaCl) of compound **147**

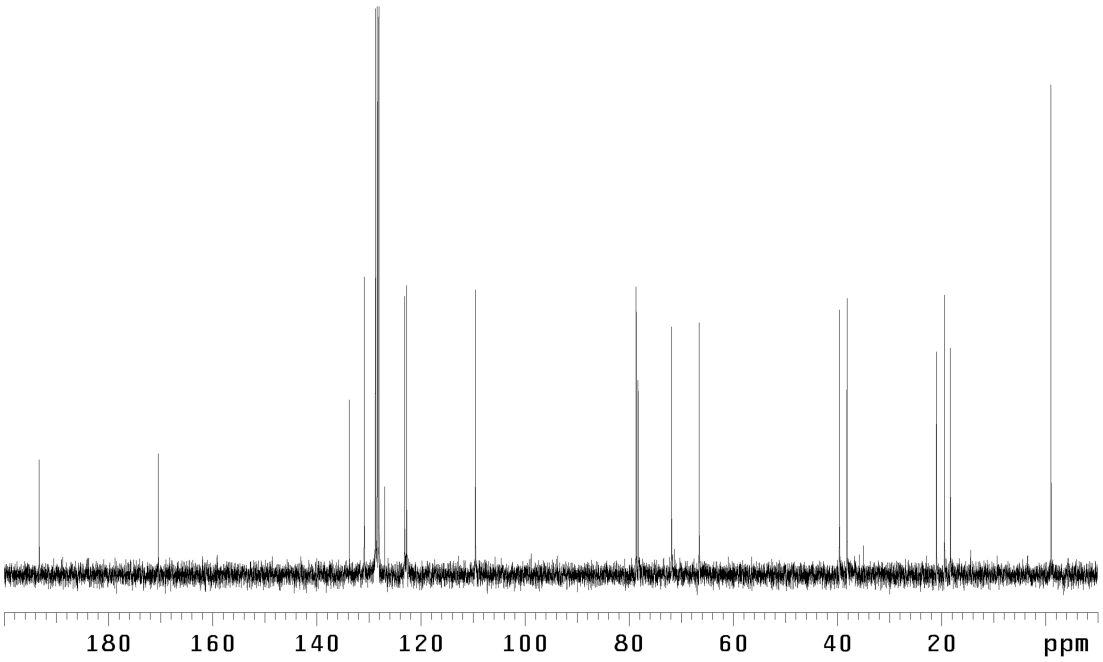


Figure A3.151 ^{13}C NMR (75 MHz, C_6D_6) of compound **147**

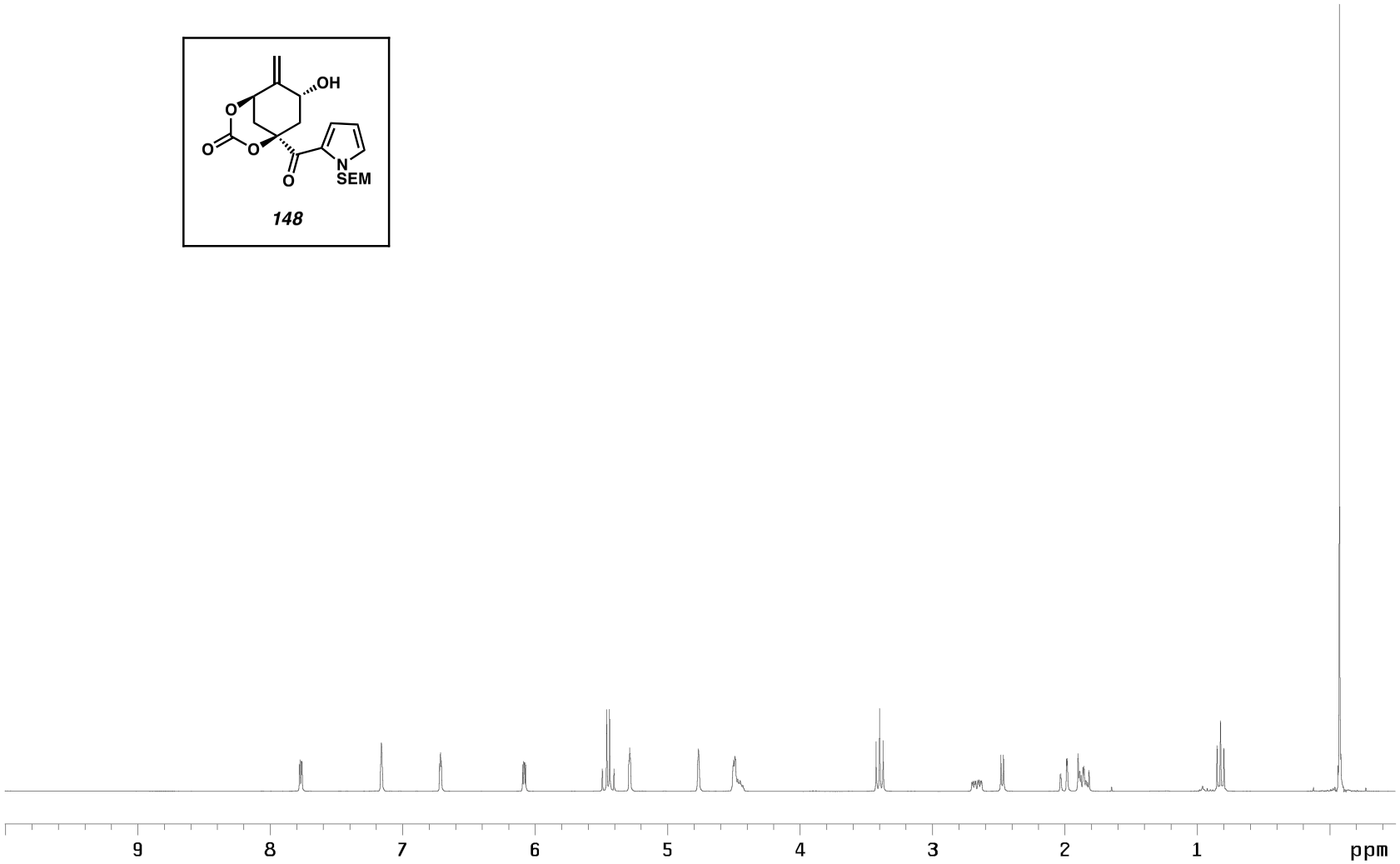


Figure A3.152 ^{1}H NMR (300 MHz, C_6D_6) of compound **148**

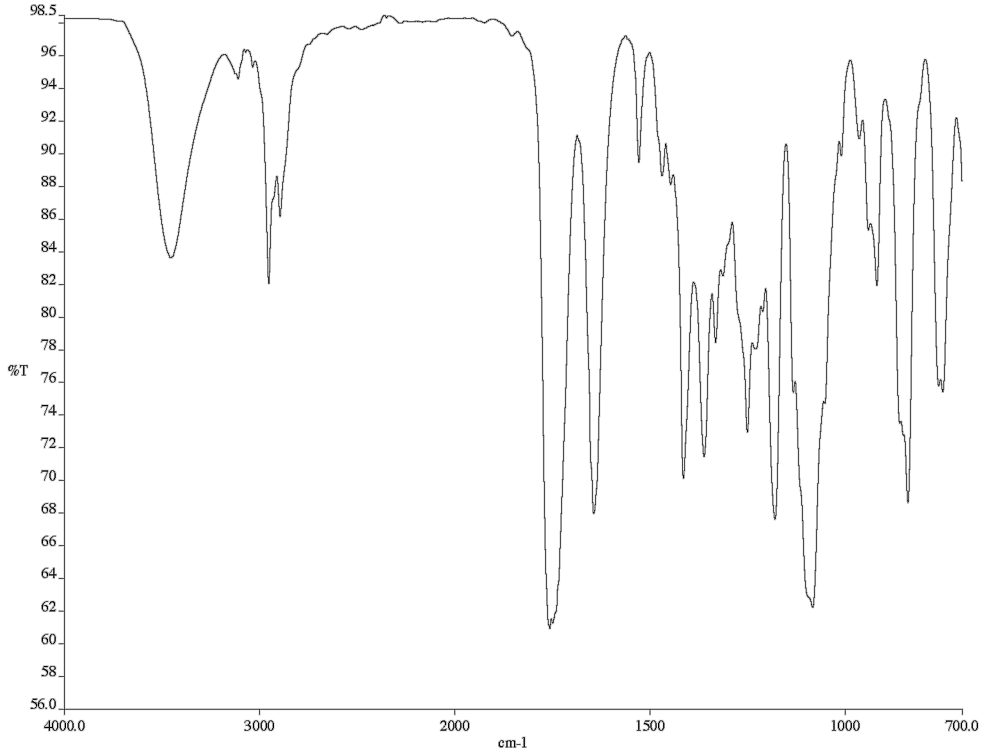


Figure A3.153 Infrared spectrum (thin film/NaCl) of compound **148**

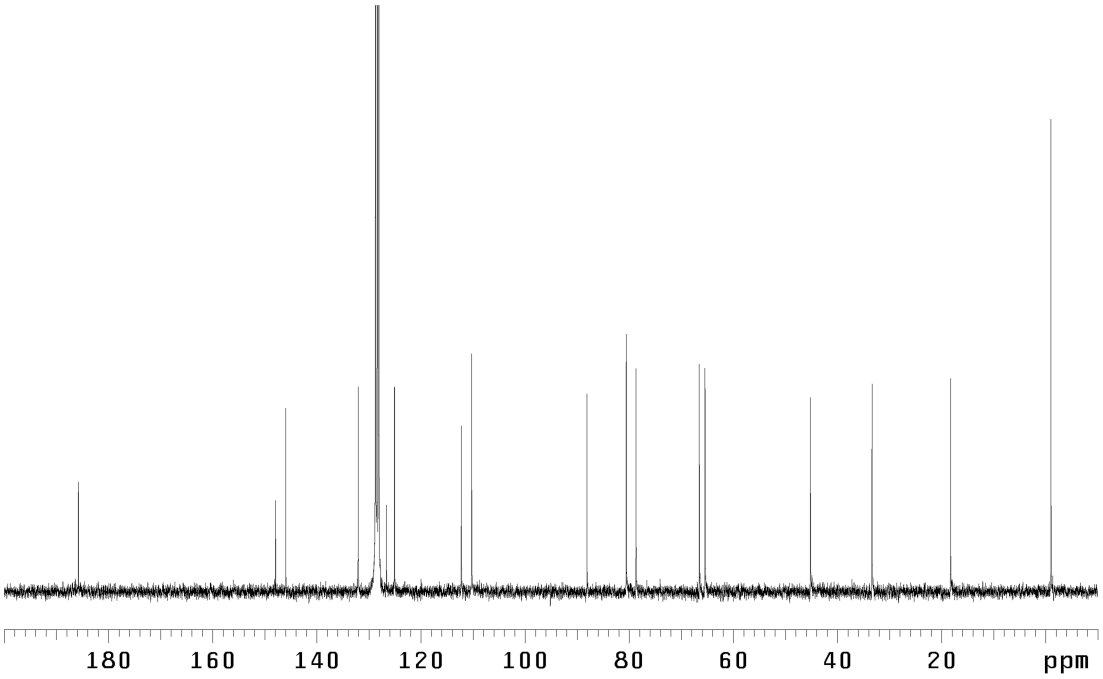


Figure A3.154 ^{13}C NMR (75 MHz, C_6D_6) of compound **148**

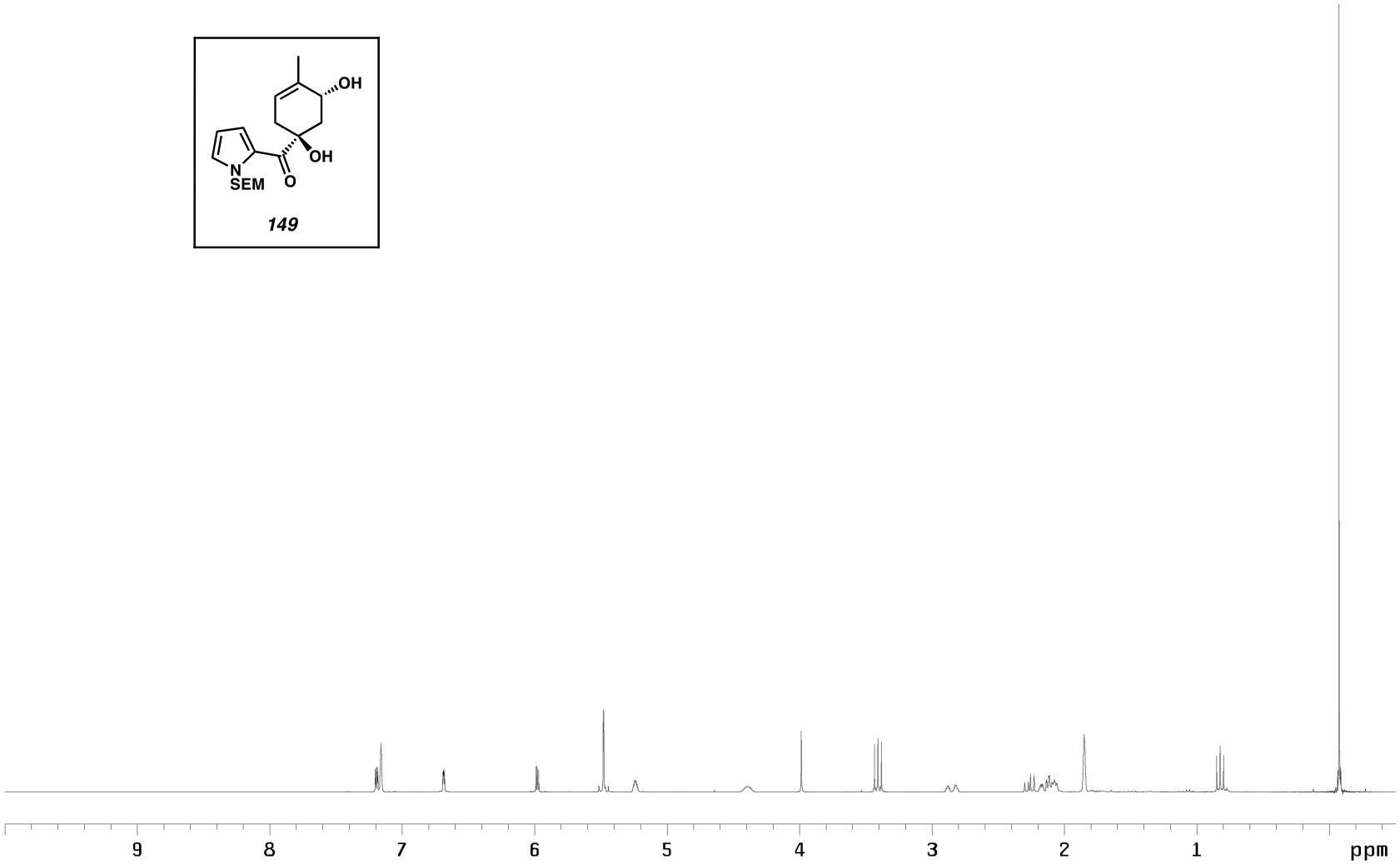


Figure A3.155 ^{1}H NMR (300 MHz, C_6D_6) of compound **149**

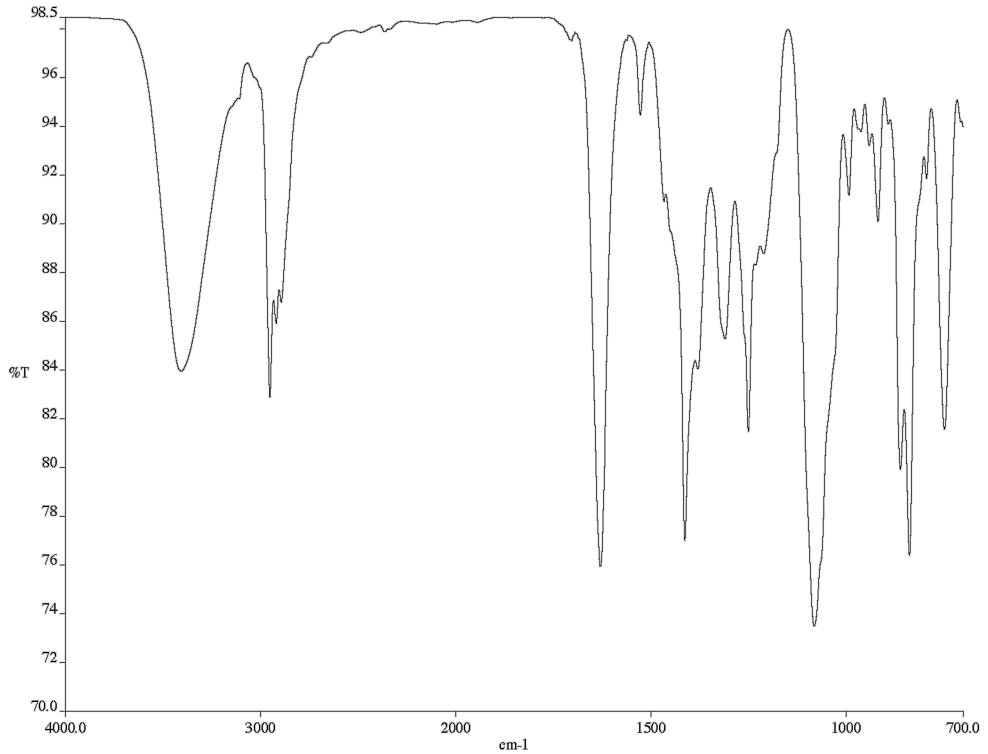


Figure A3.156 Infrared spectrum (thin film/NaCl) of compound **149**

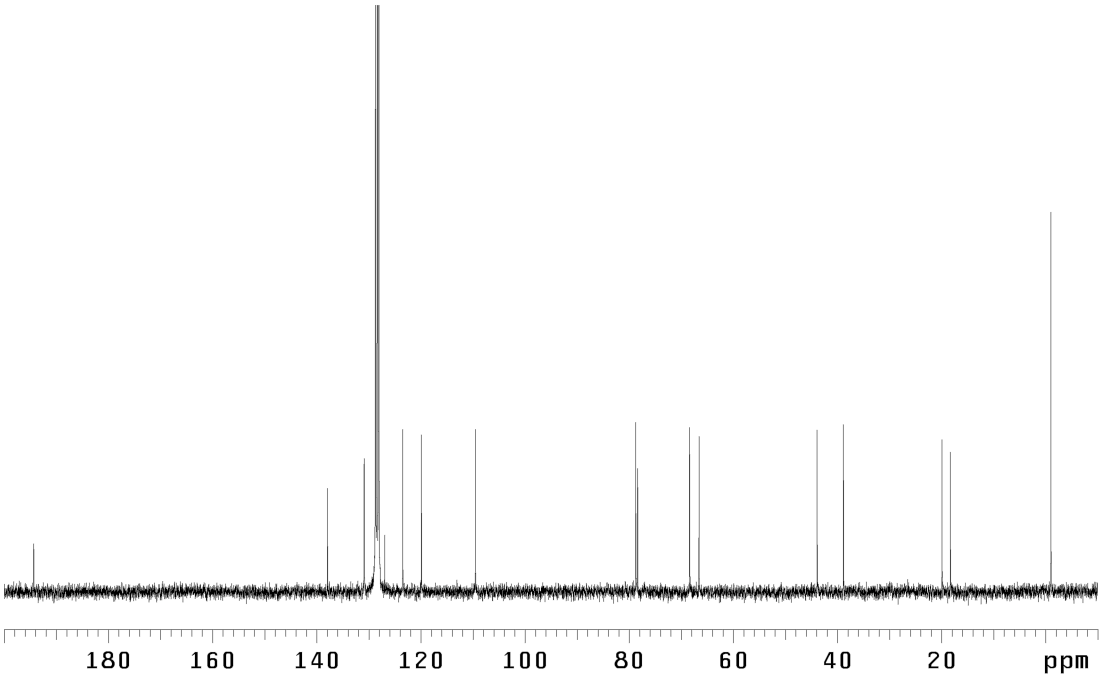


Figure A3.157 ^{13}C NMR (75 MHz, C_6D_6) of compound **149**

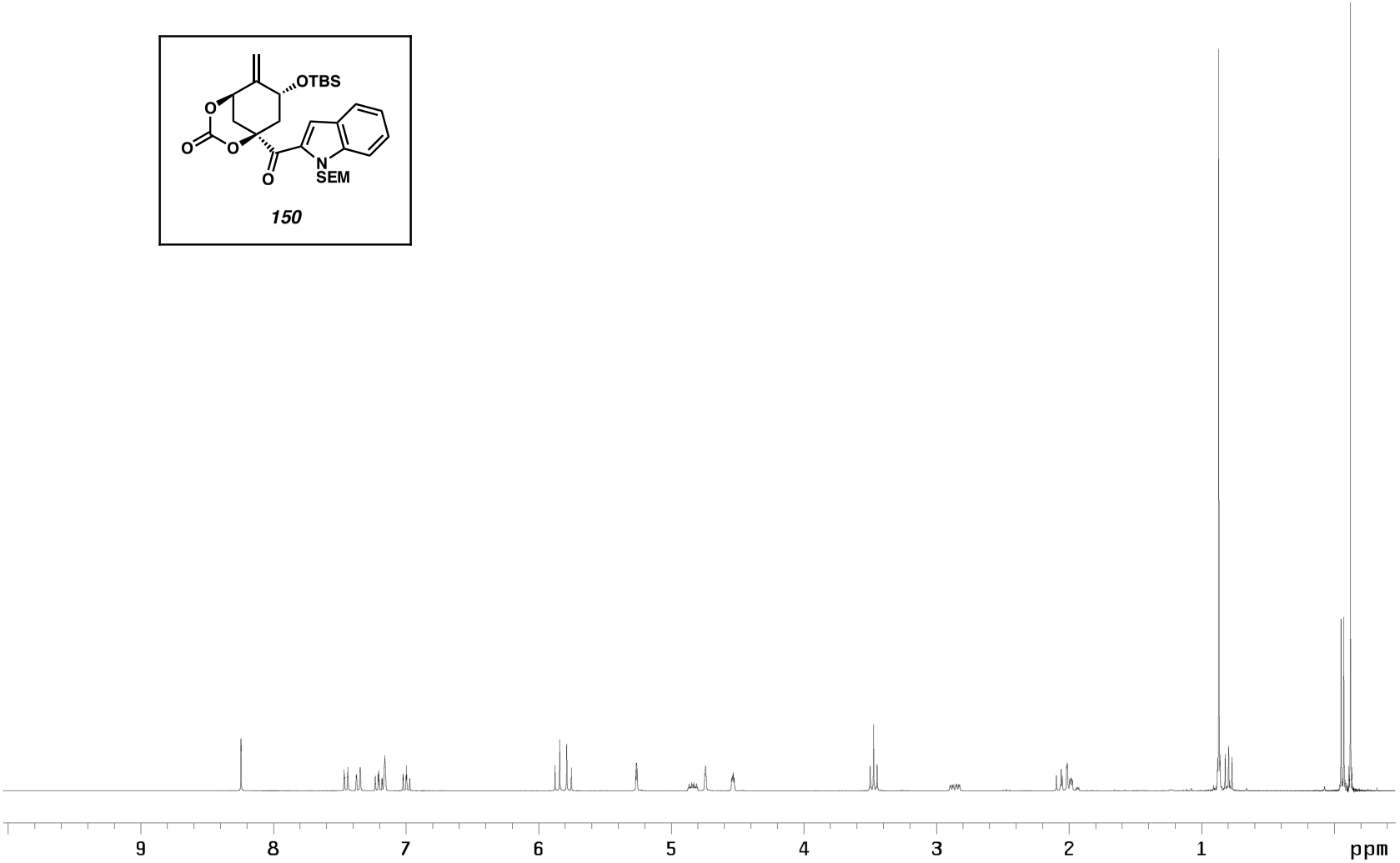


Figure A3.158 ^{1}H NMR (300 MHz, C_6D_6) of compound **150**

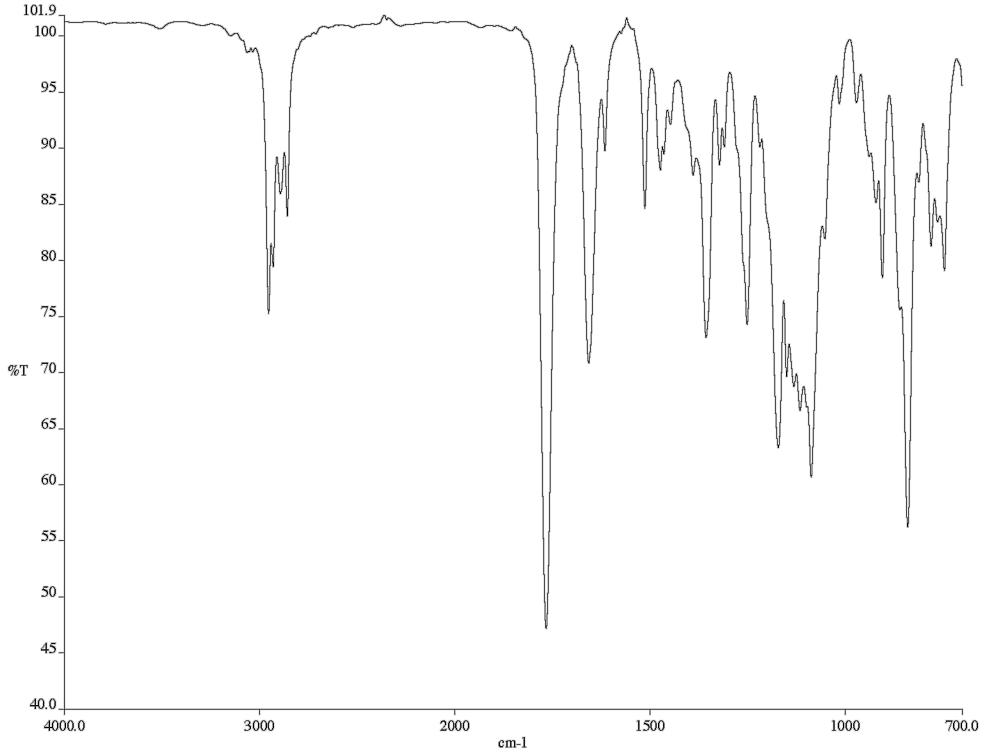


Figure A3.159 Infrared spectrum (thin film/NaCl) of compound **150**

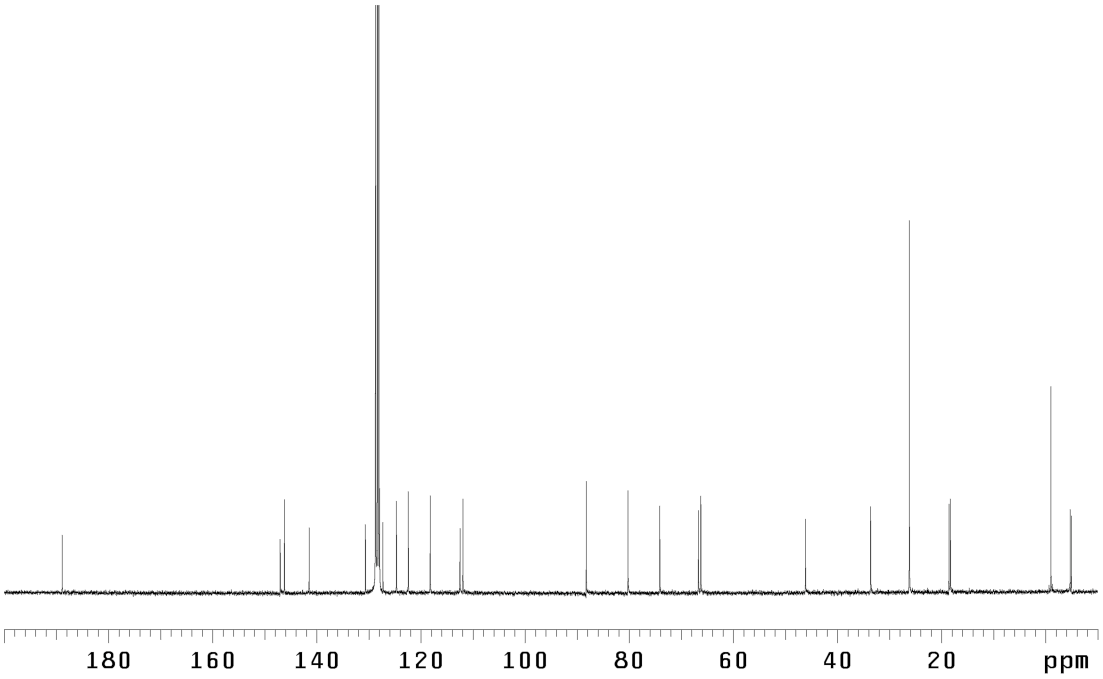


Figure A3.160 ^{13}C NMR (75 MHz, C_6D_6) of compound **150**

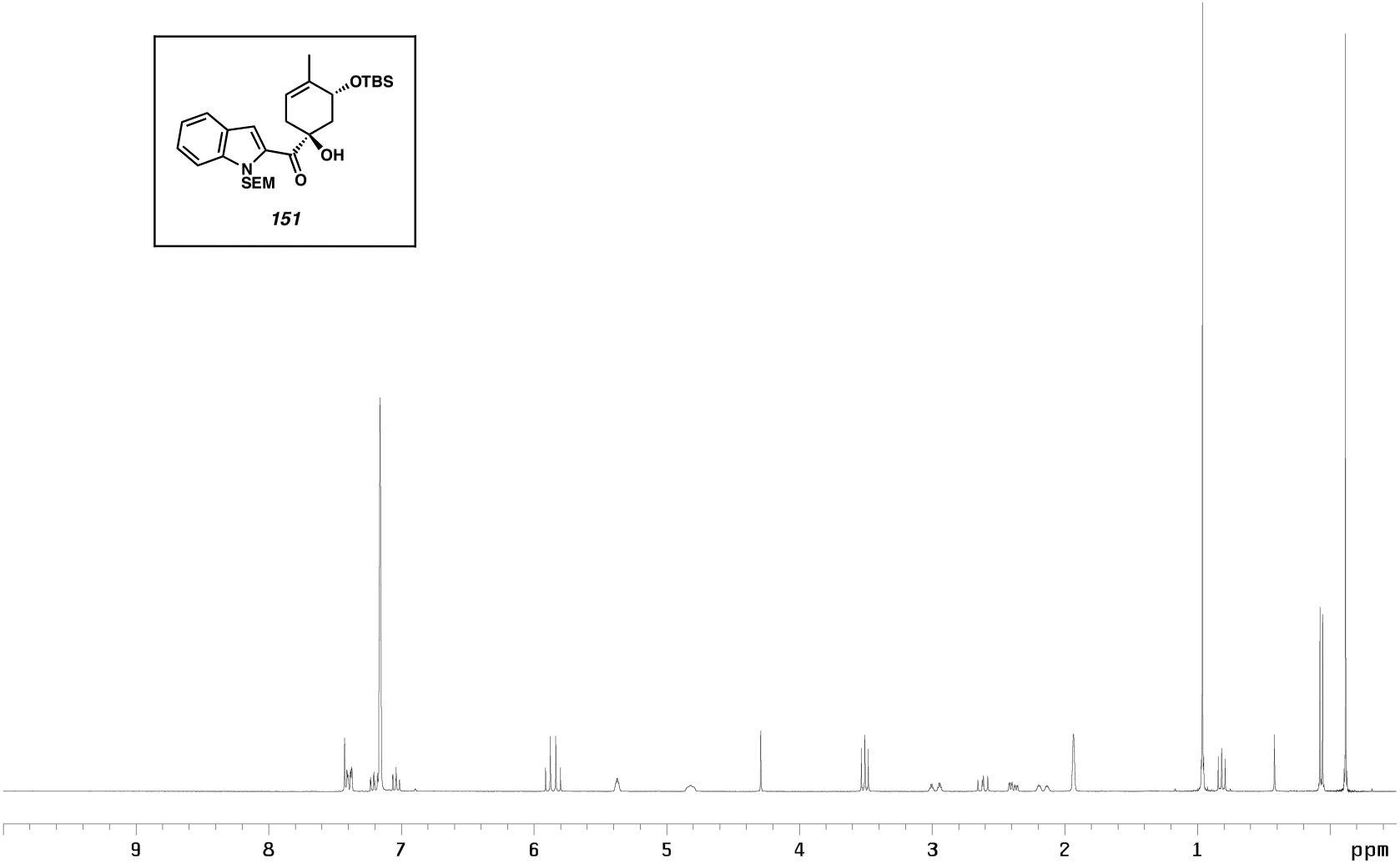


Figure A3.161 ^{1}H NMR (300 MHz, C_6D_6) of compound **151**

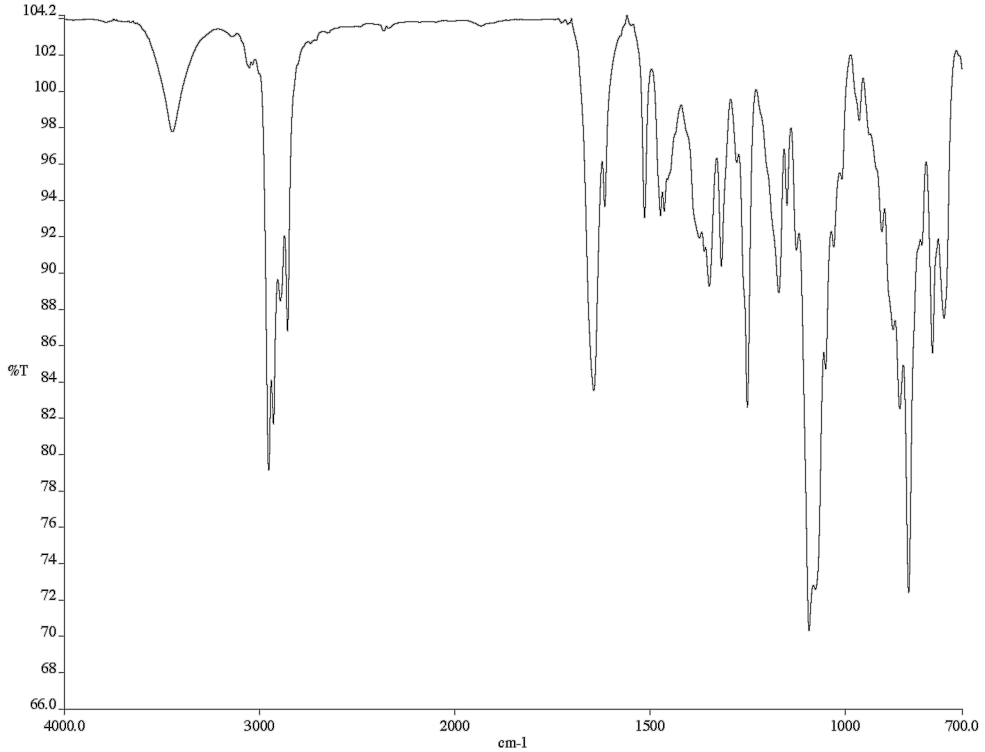


Figure A3.162 Infrared spectrum (thin film/NaCl) of compound **151**

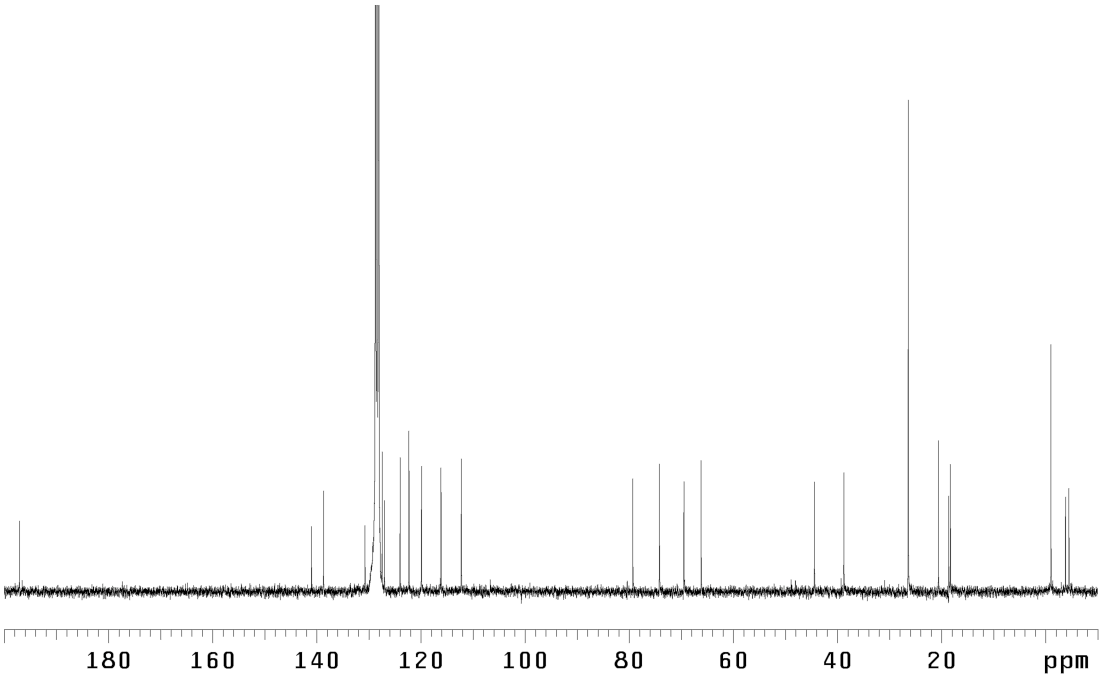


Figure A3.163 ^{13}C NMR (75 MHz, C_6D_6) of compound **151**

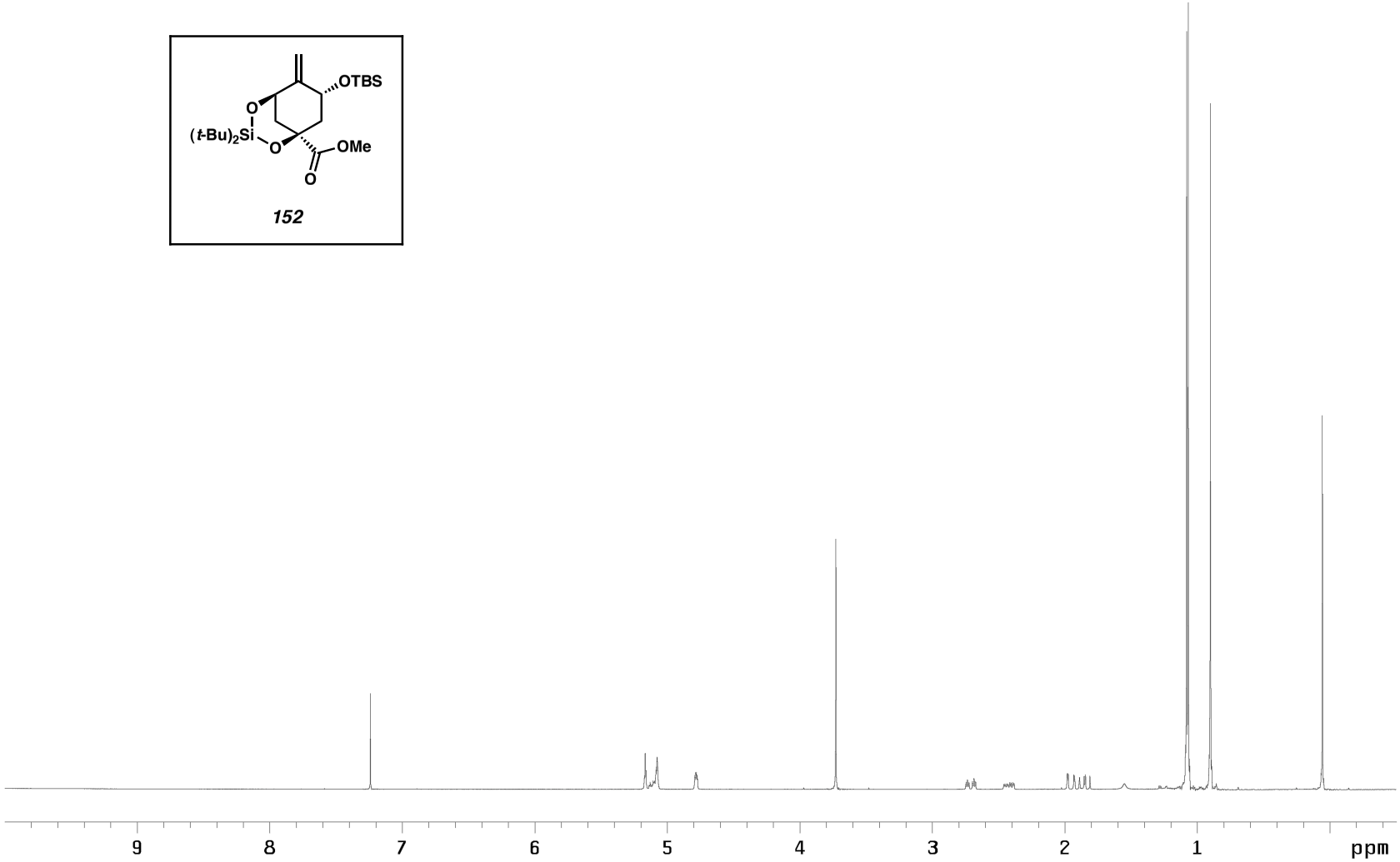


Figure A3.164 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **152**

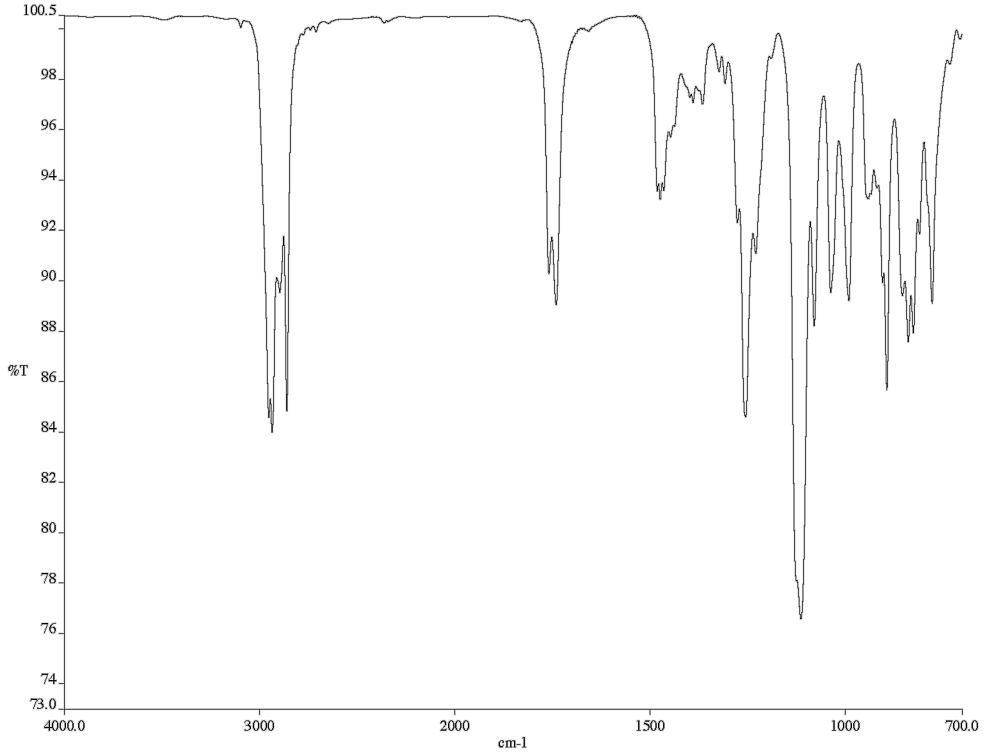


Figure A3.165 Infrared spectrum (thin film/NaCl) of compound **152**

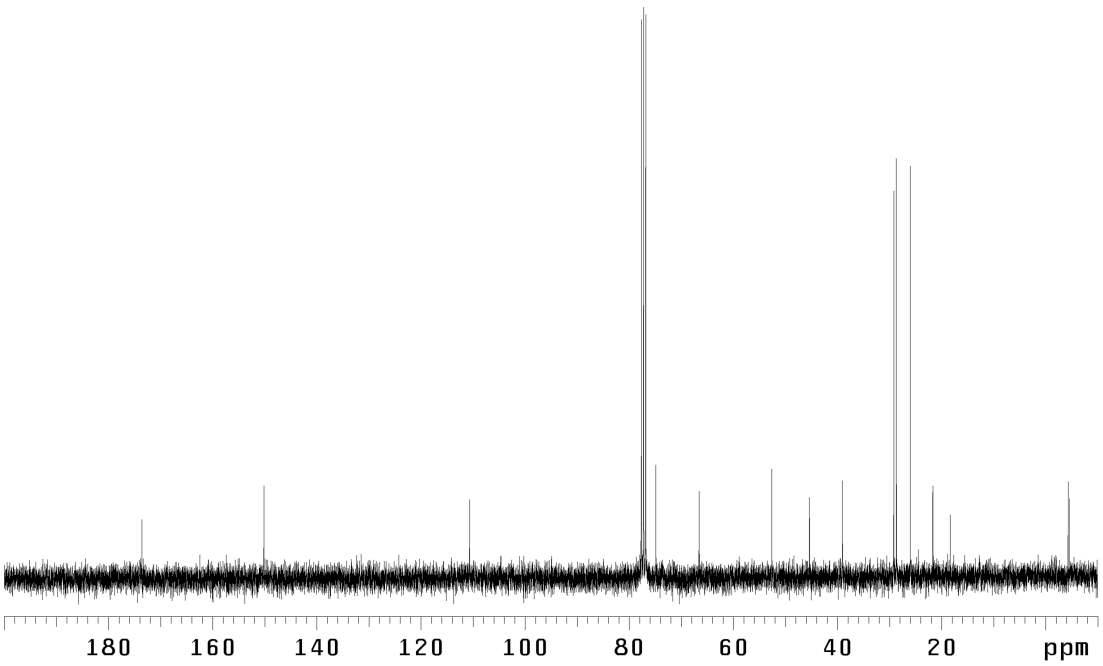


Figure A3.166 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **152**

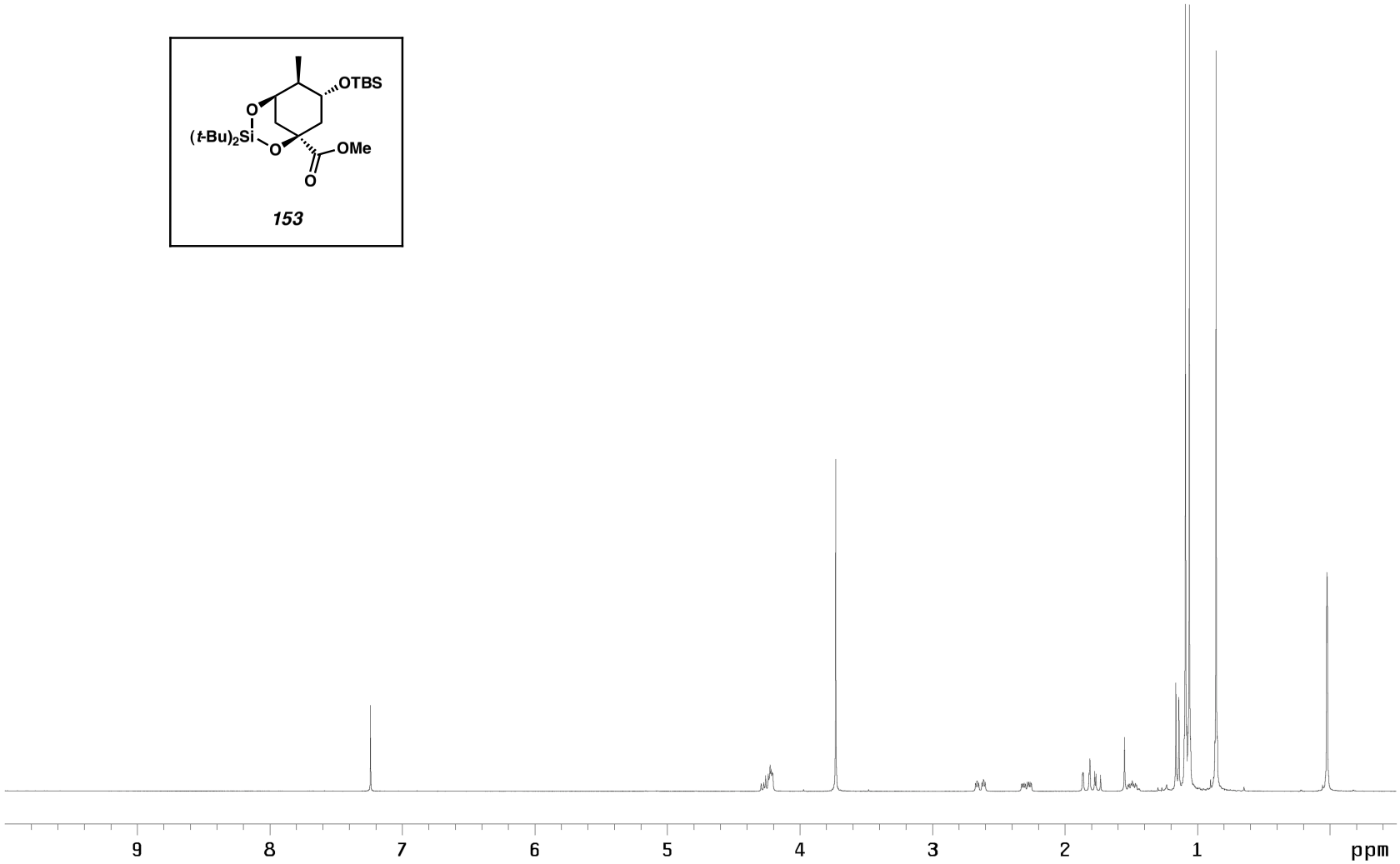


Figure A3.167 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **153**

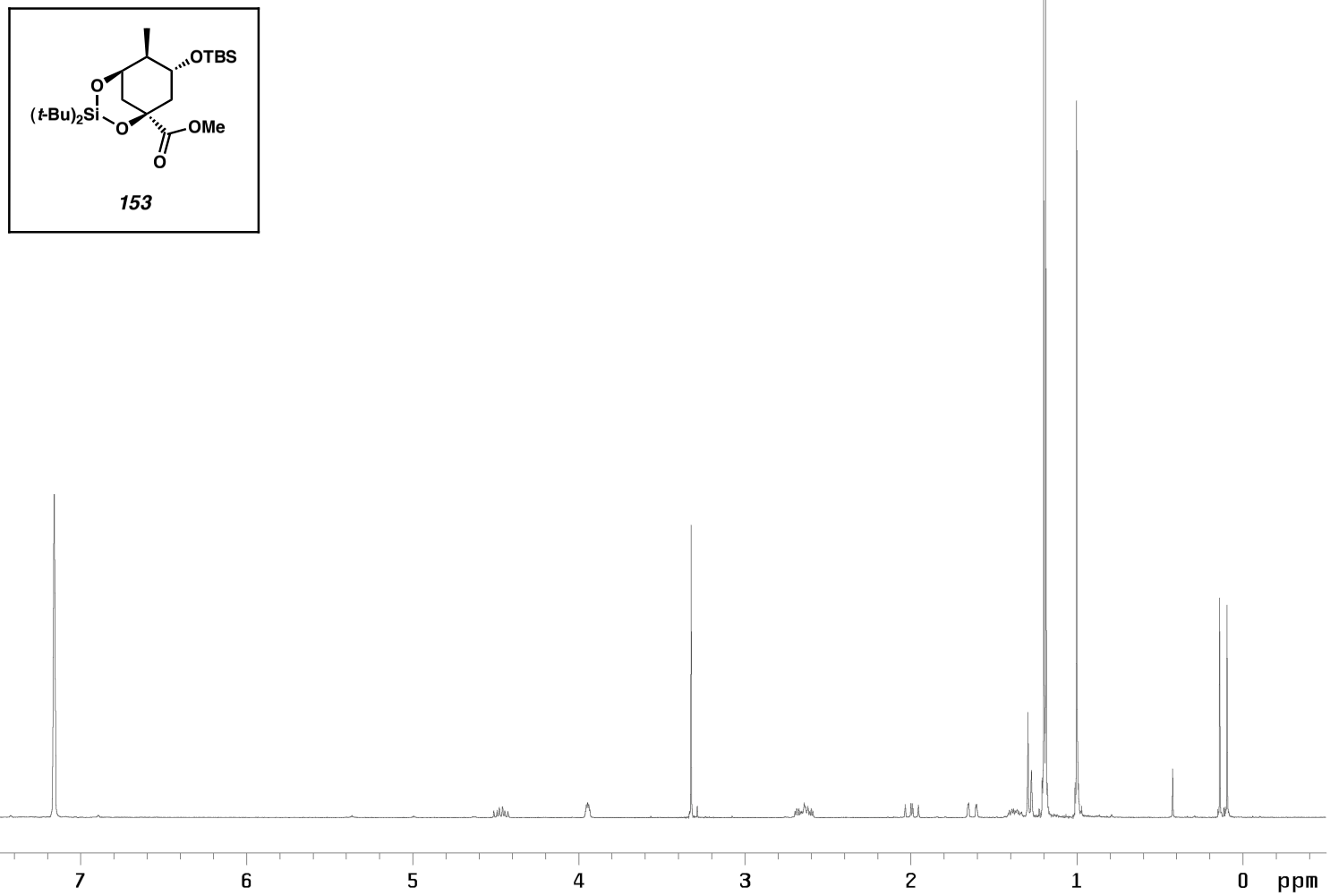


Figure A3.168 ^{1}H NMR (300 MHz, C_6D_6) of compound **153**

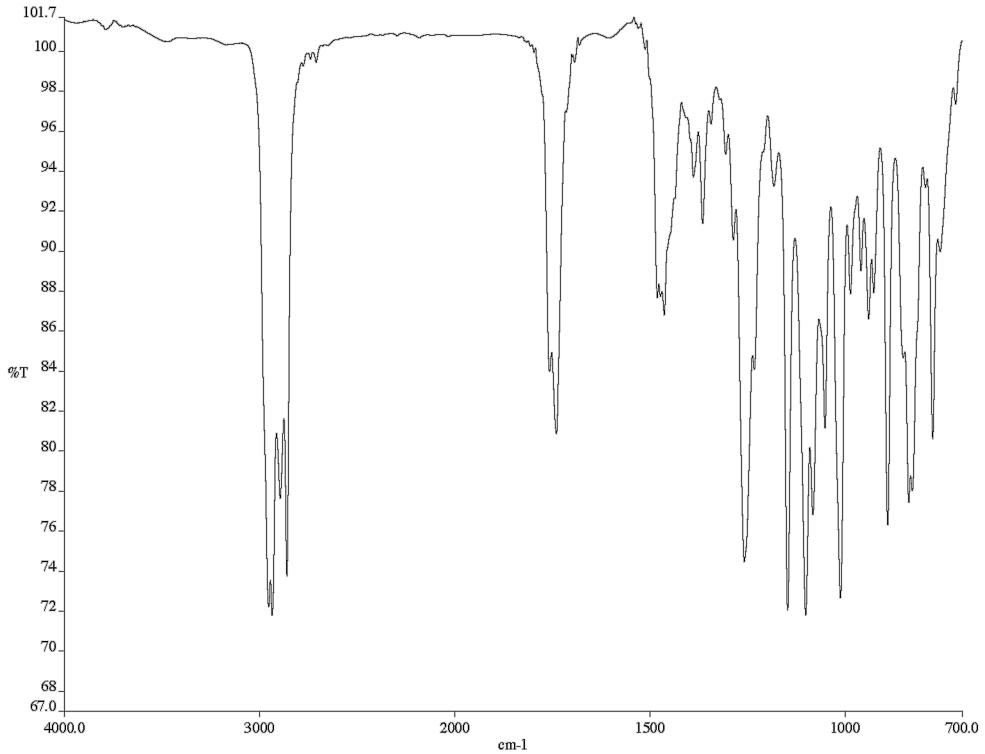


Figure A3.169 Infrared spectrum (thin film/NaCl) of compound **153**

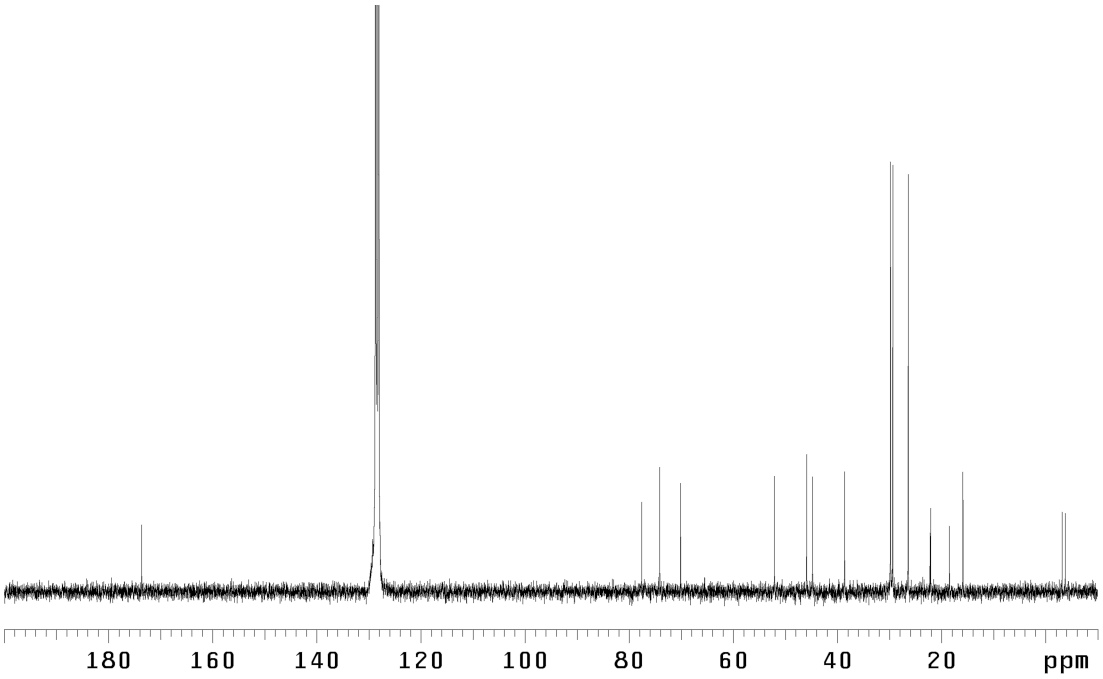


Figure A3.170 ^{13}C NMR (75 MHz, C_6D_6) of compound **153**

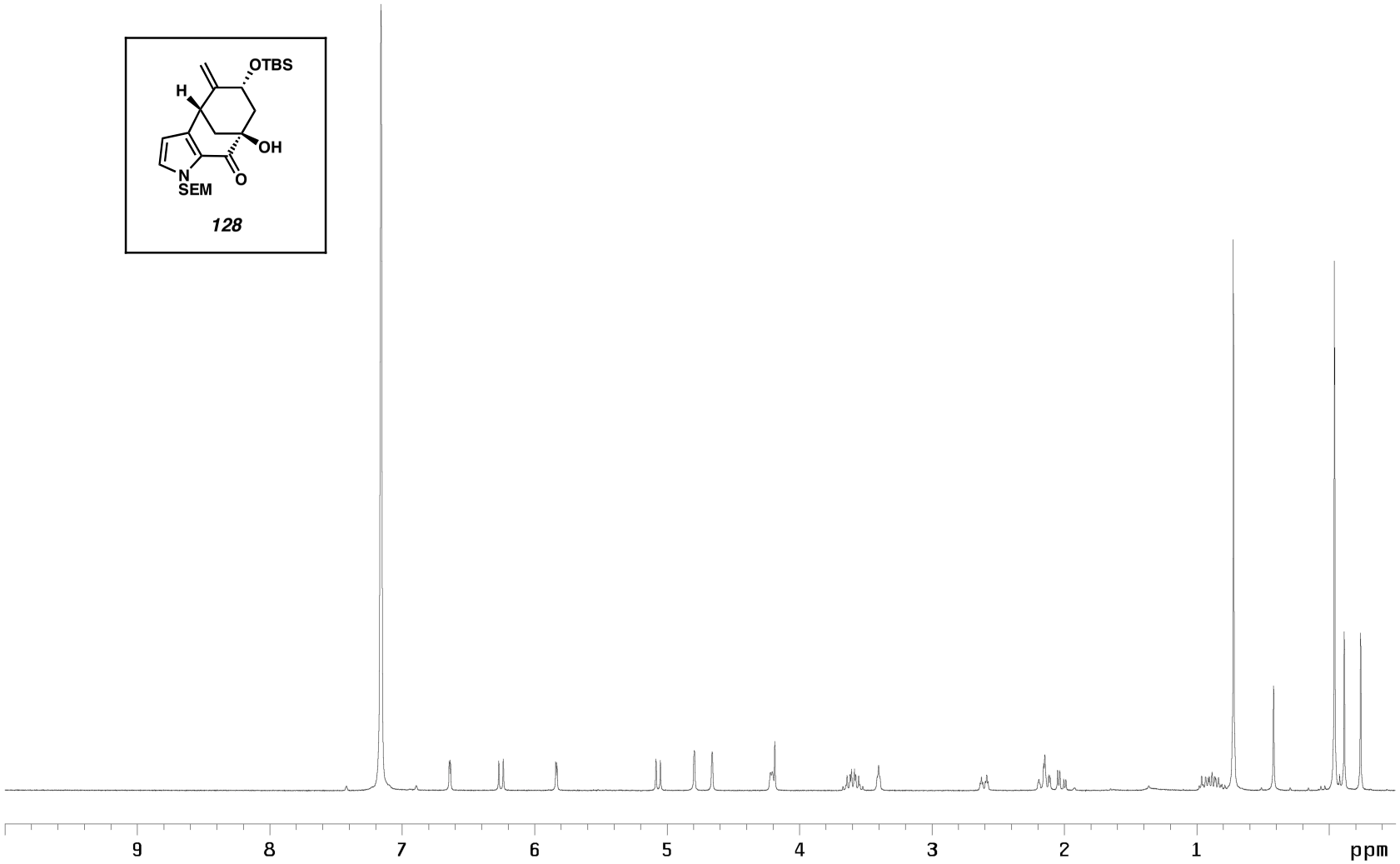


Figure A3.171 ^{1}H NMR (300 MHz, C_6D_6) of compound **128**

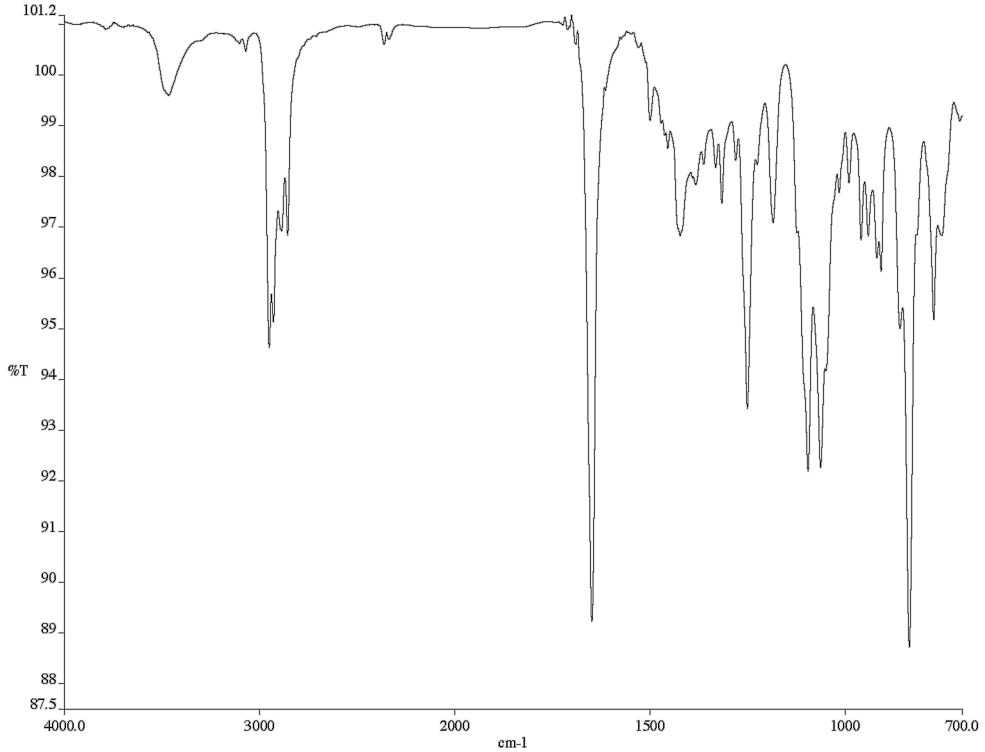


Figure A3.172 Infrared spectrum (thin film/NaCl) of compound **128**

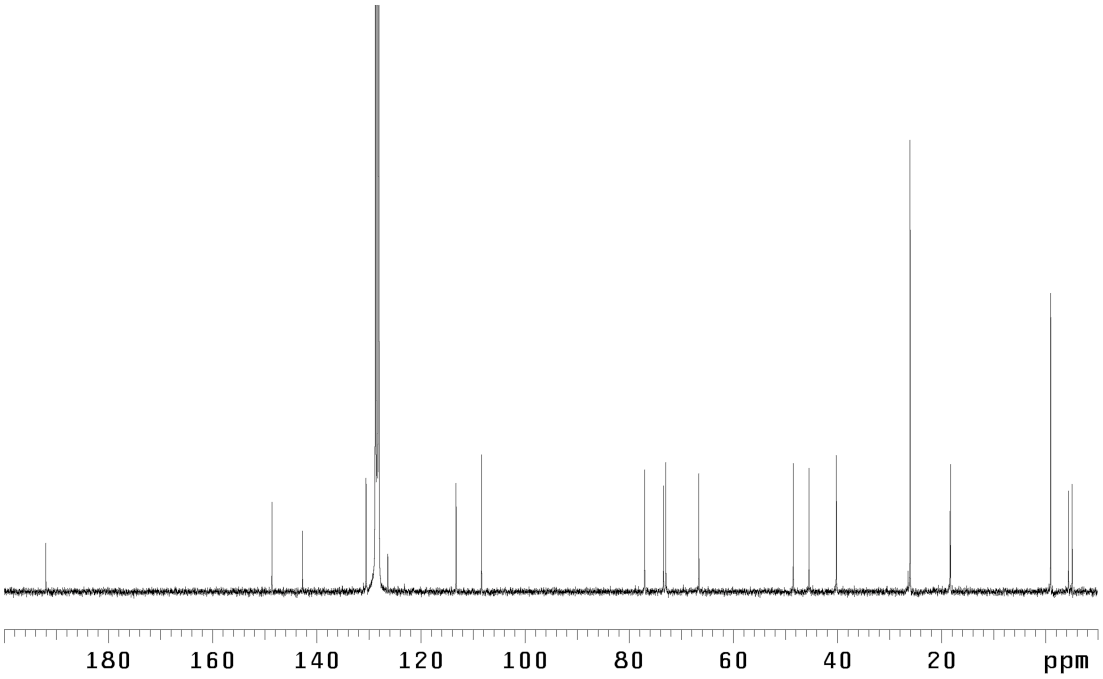


Figure A3.173 ^{13}C NMR (75 MHz, C_6D_6) of compound **128**

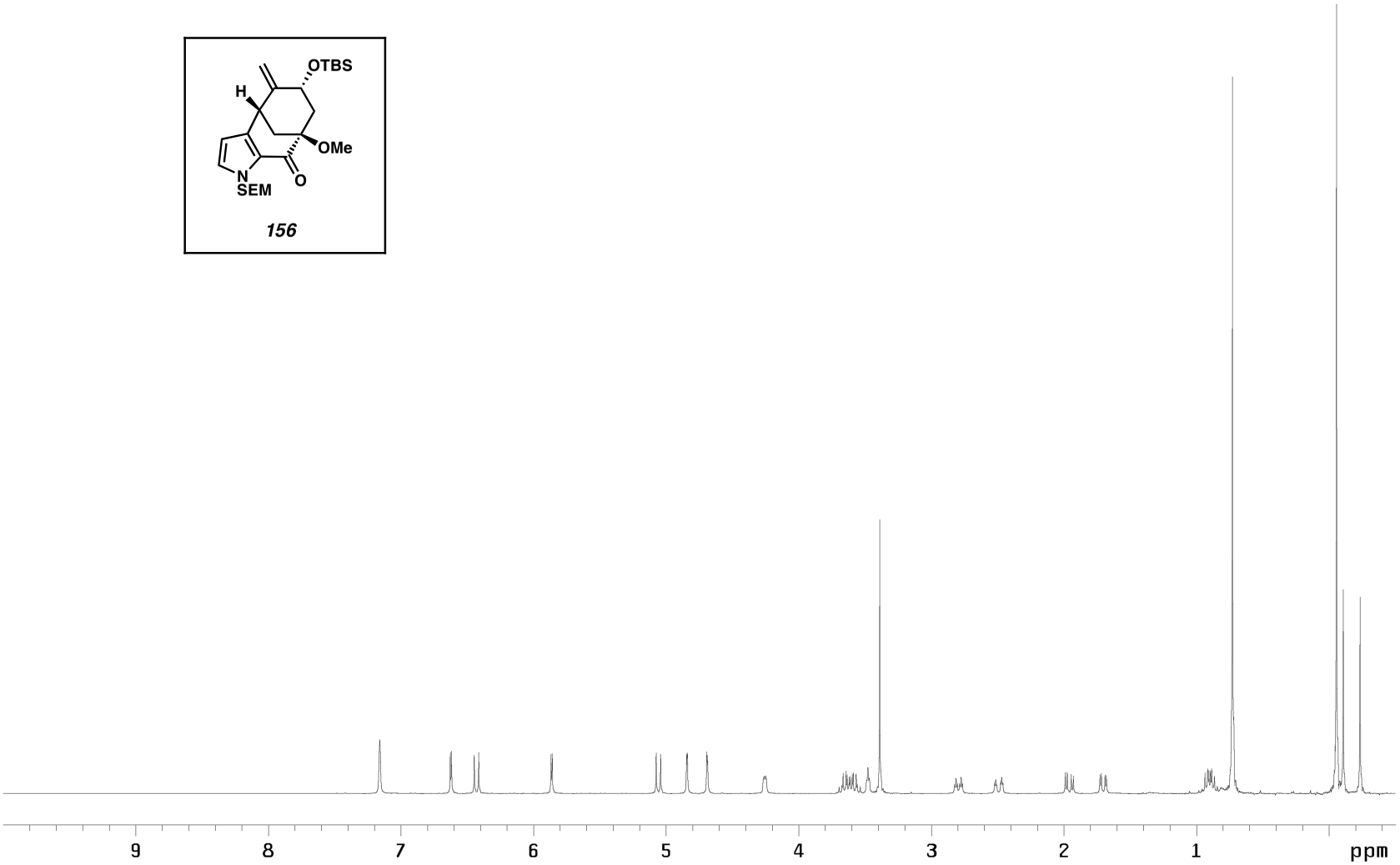


Figure A3.174 ^{1}H NMR (300 MHz, C_6D_6) of compound **156**

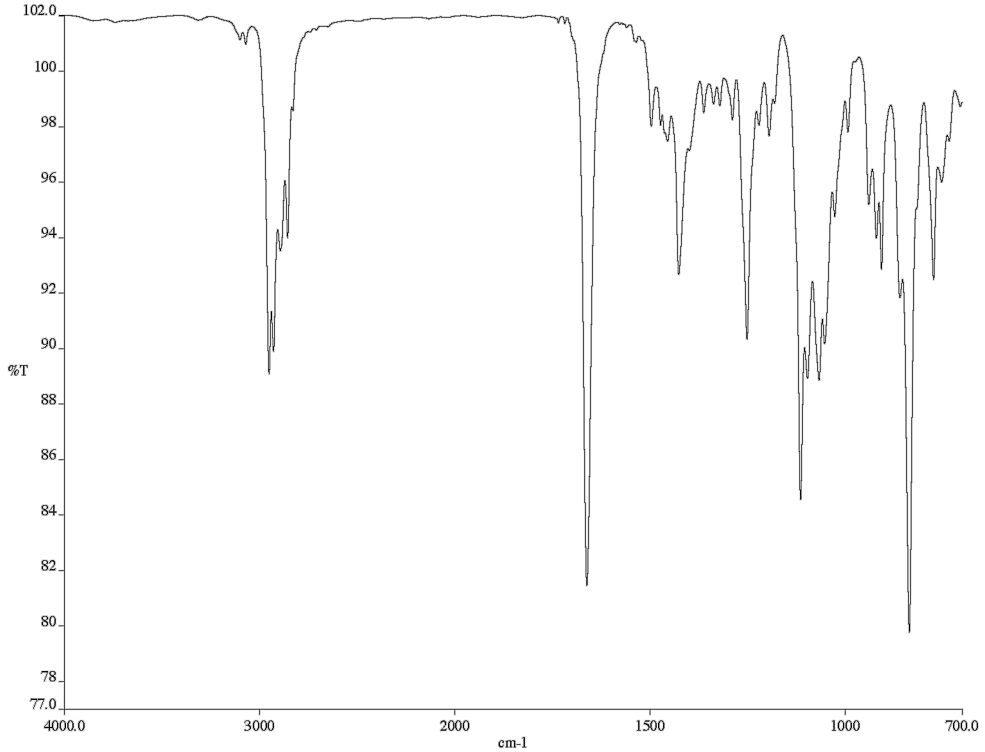


Figure A3.175 Infrared spectrum (thin film/NaCl) of compound **156**

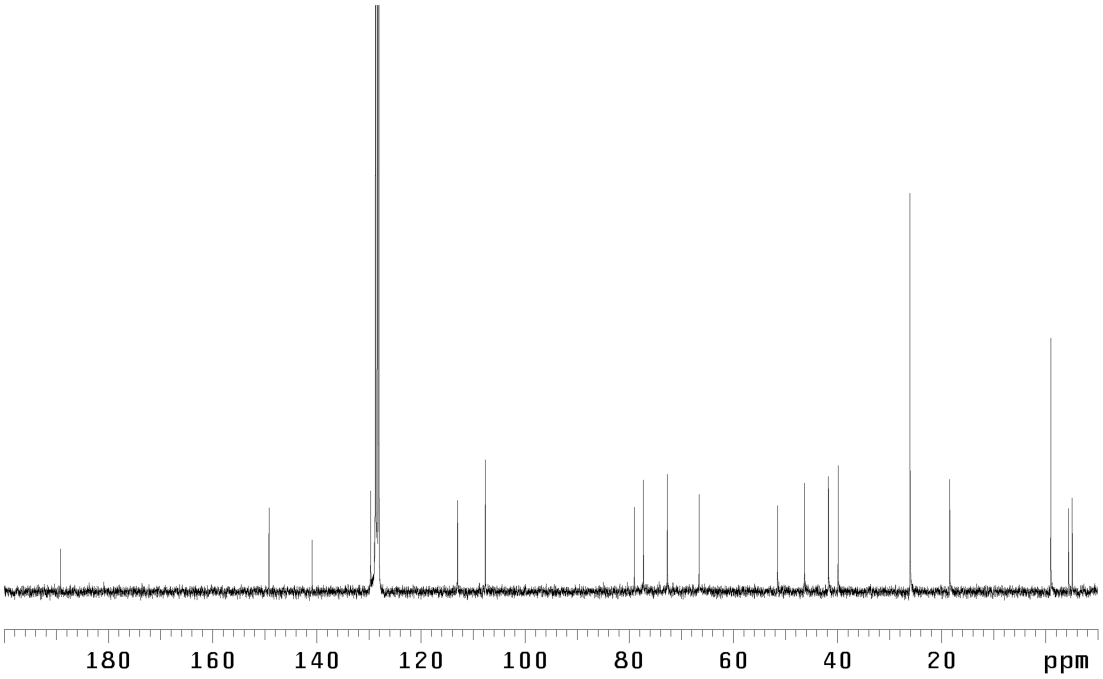


Figure A3.176 ^{13}C NMR (75 MHz, C_6D_6) of compound **156**

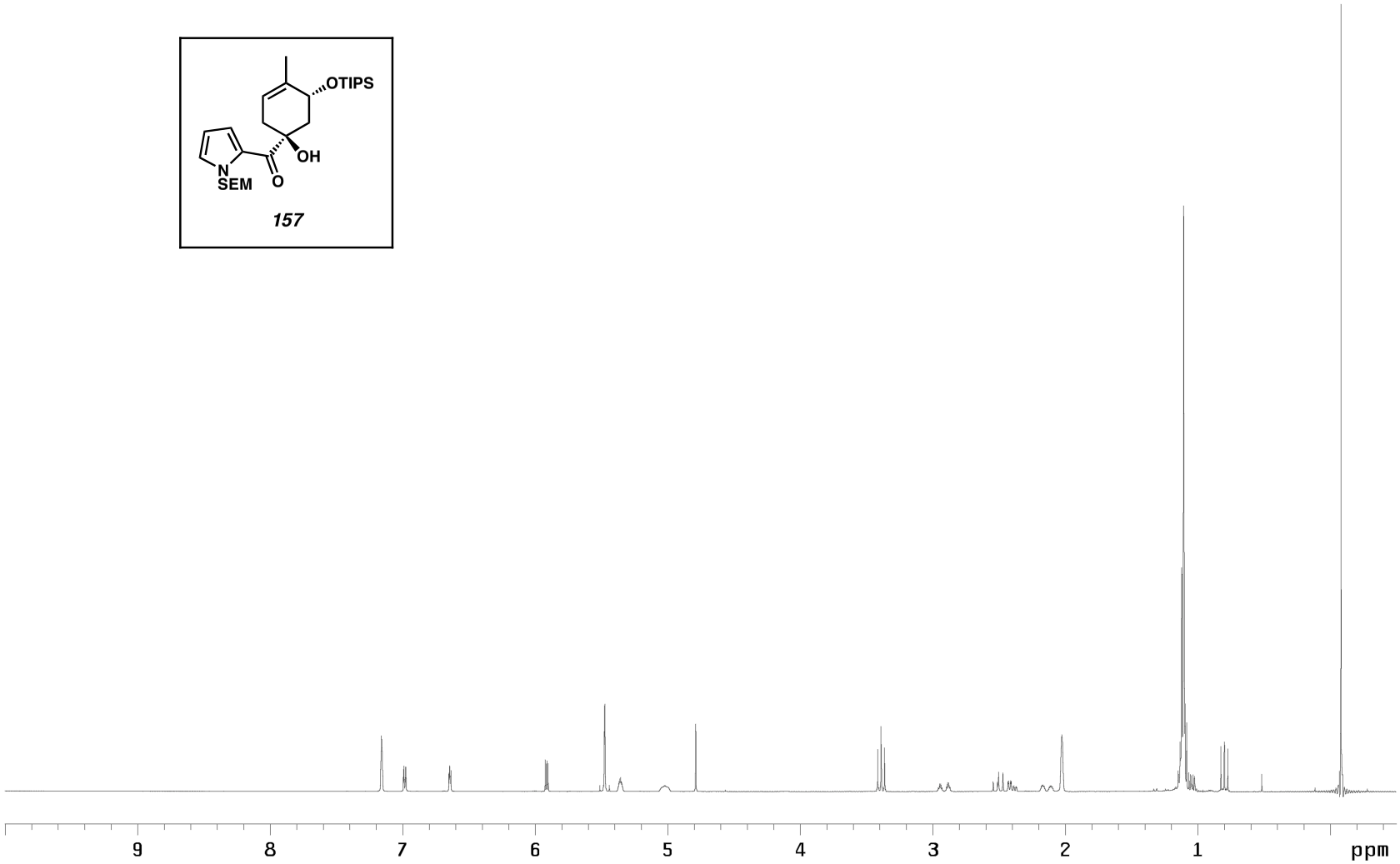


Figure A3.177 ^{1}H NMR (300 MHz, C_6D_6) of compound **157**

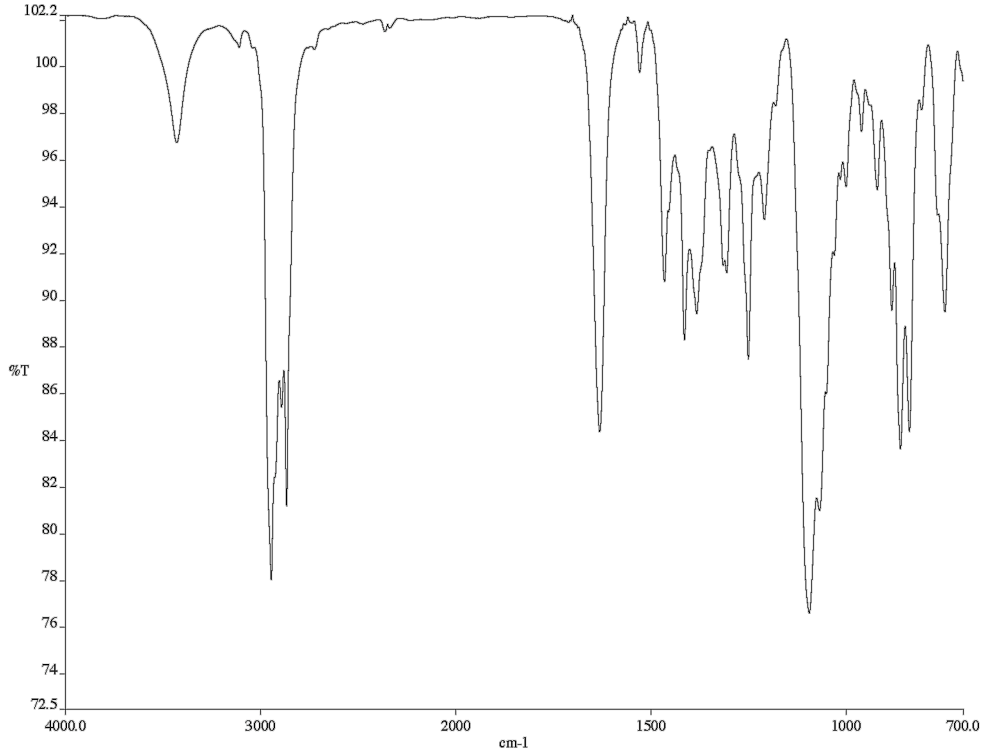


Figure A3.178 Infrared spectrum (thin film/NaCl) of compound **157**

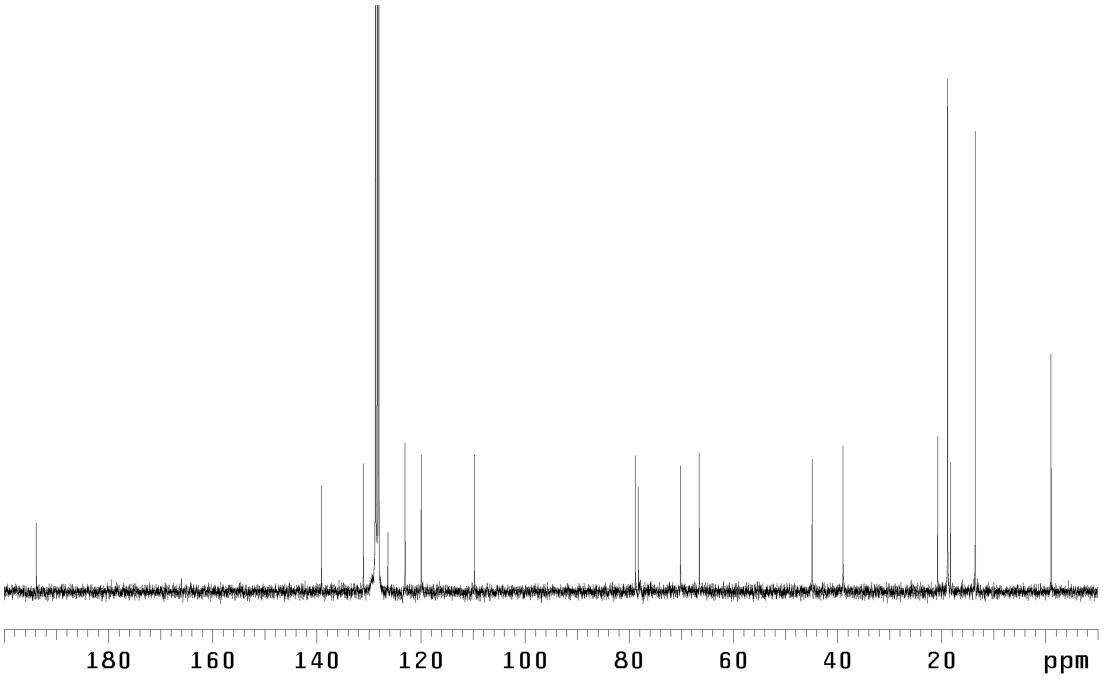


Figure A3.179 ^{13}C NMR (75 MHz, C_6D_6) of compound **157**

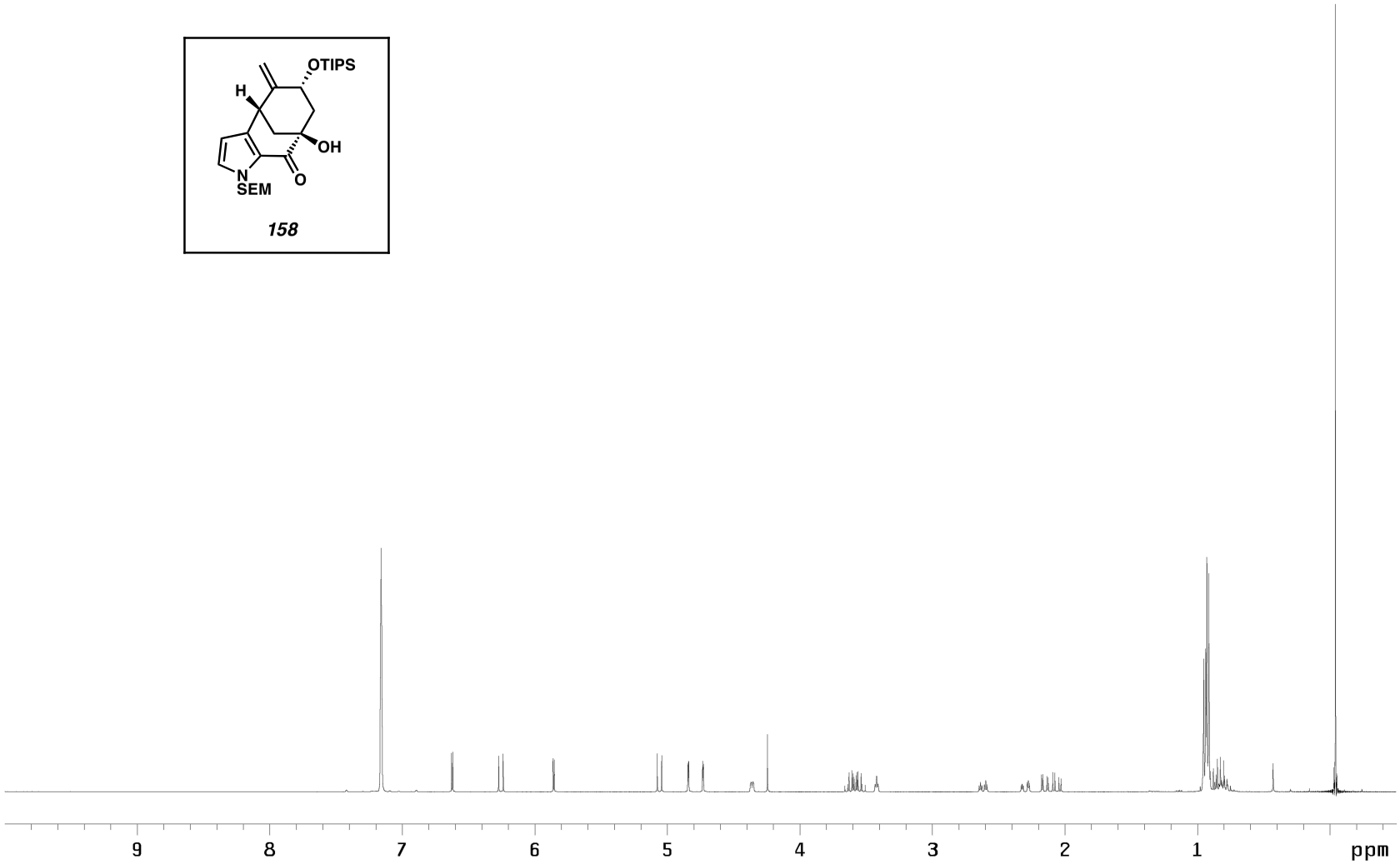


Figure A3.180 ^{1}H NMR (300 MHz, C_6D_6) of compound **158**

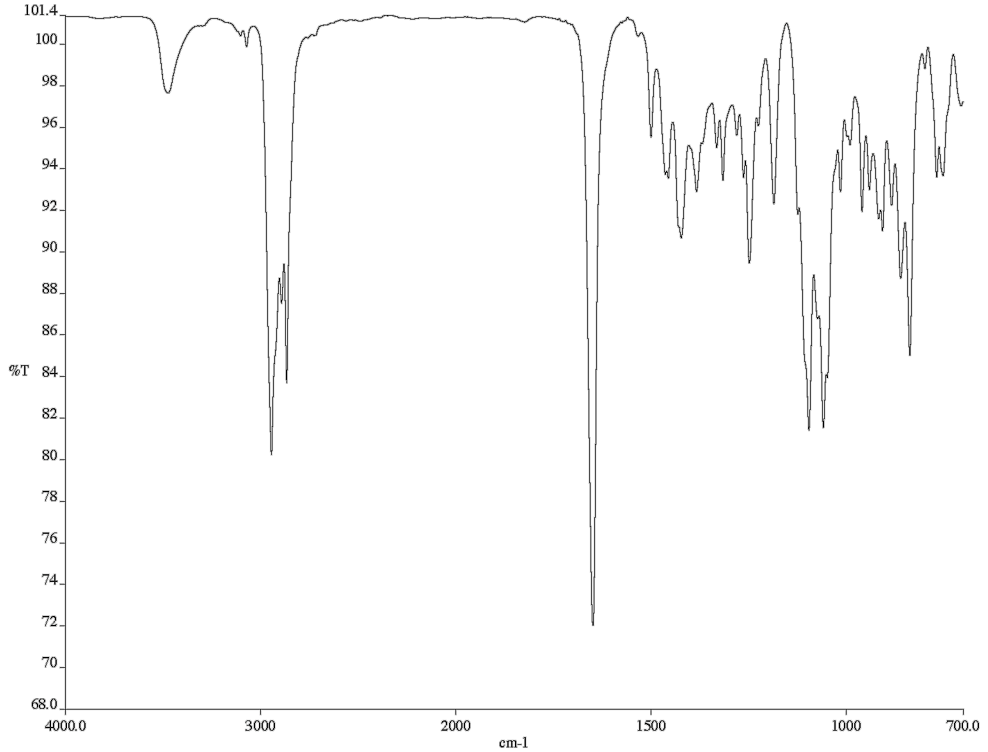


Figure A3.181 Infrared spectrum (thin film/NaCl) of compound **158**

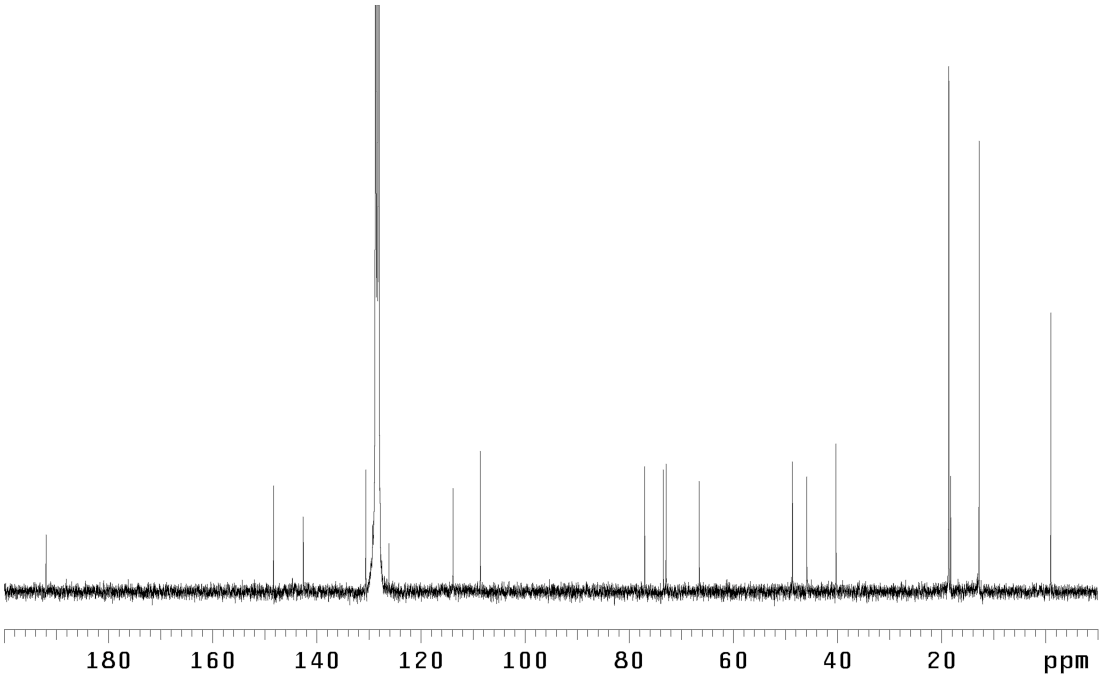


Figure A3.182 ^{13}C NMR (75 MHz, C_6D_6) of compound **158**

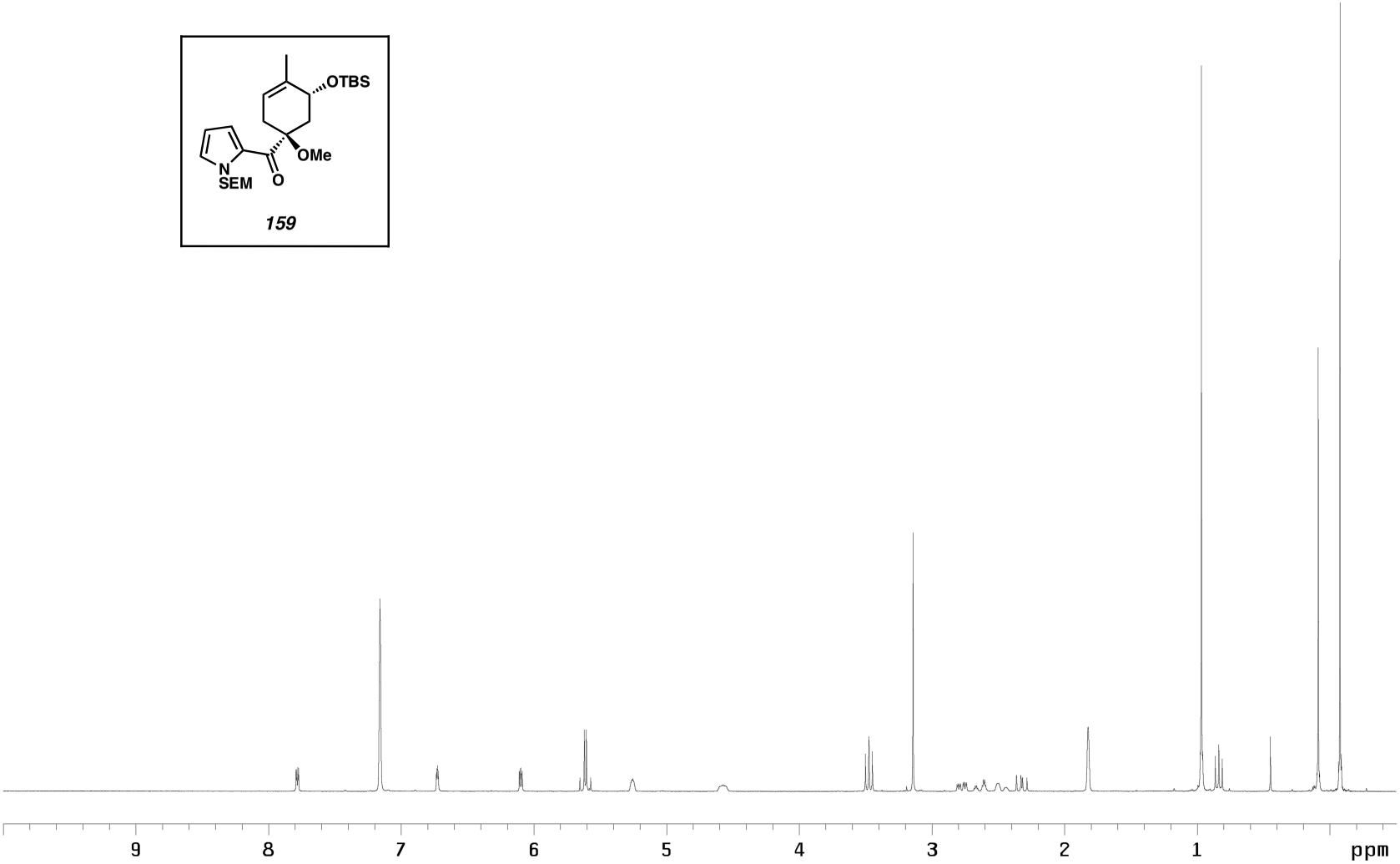


Figure A3.183 ^{1}H NMR (300 MHz, C_6D_6) of compound **159**

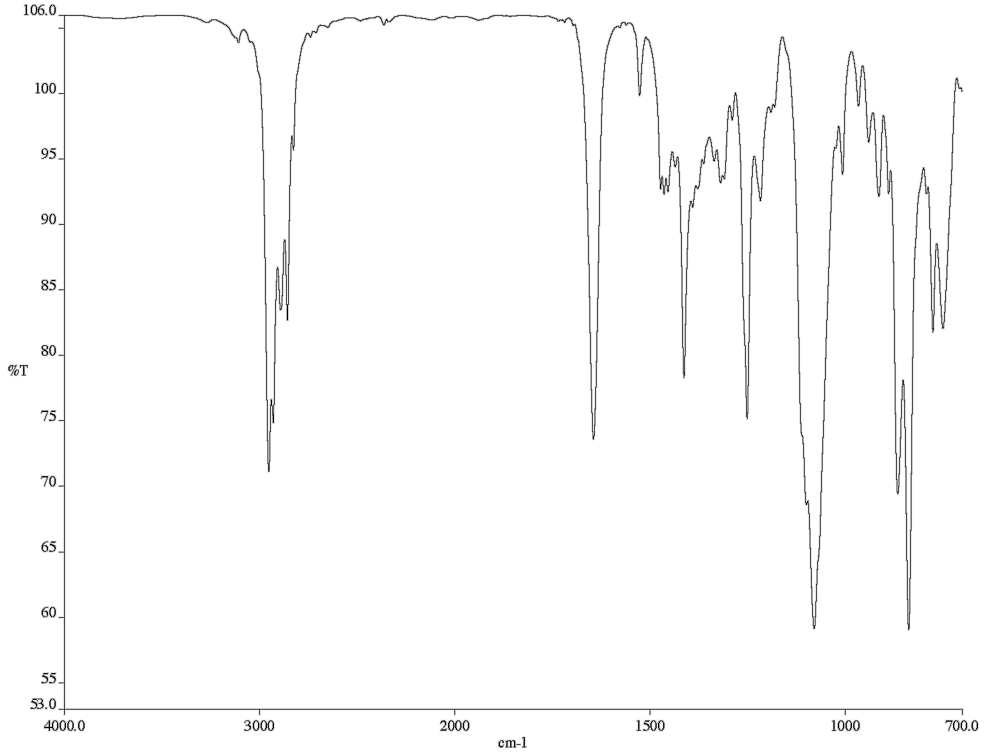


Figure A3.184 Infrared spectrum (thin film/NaCl) of compound **159**

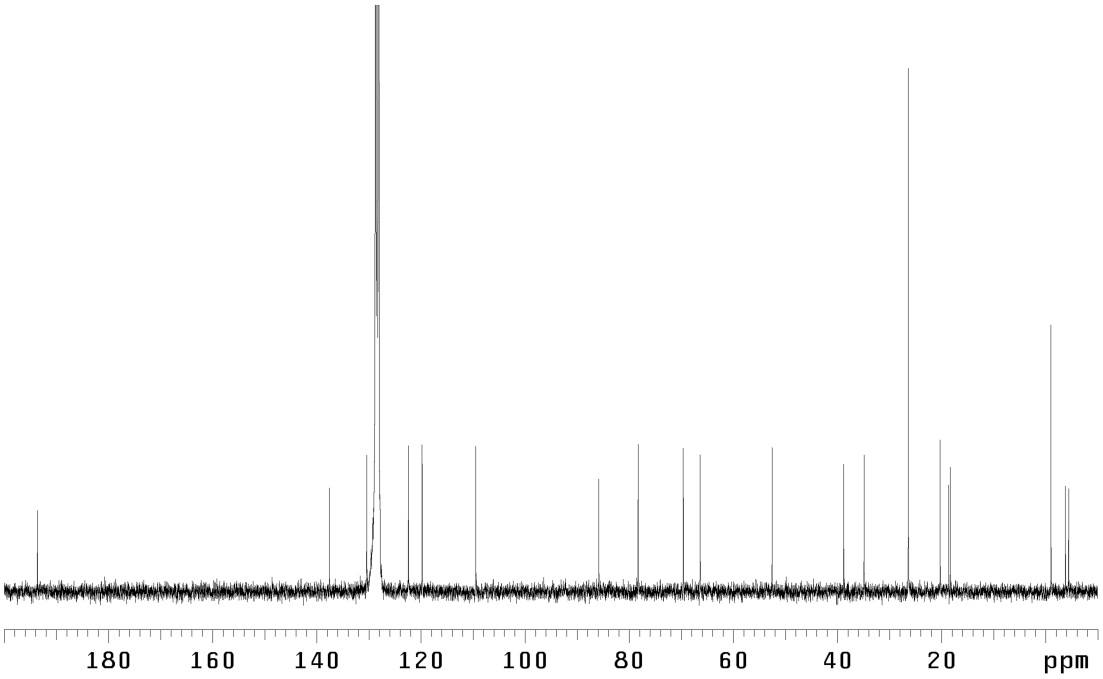


Figure A3.185 ^{13}C NMR (75 MHz, C_6D_6) of compound **159**

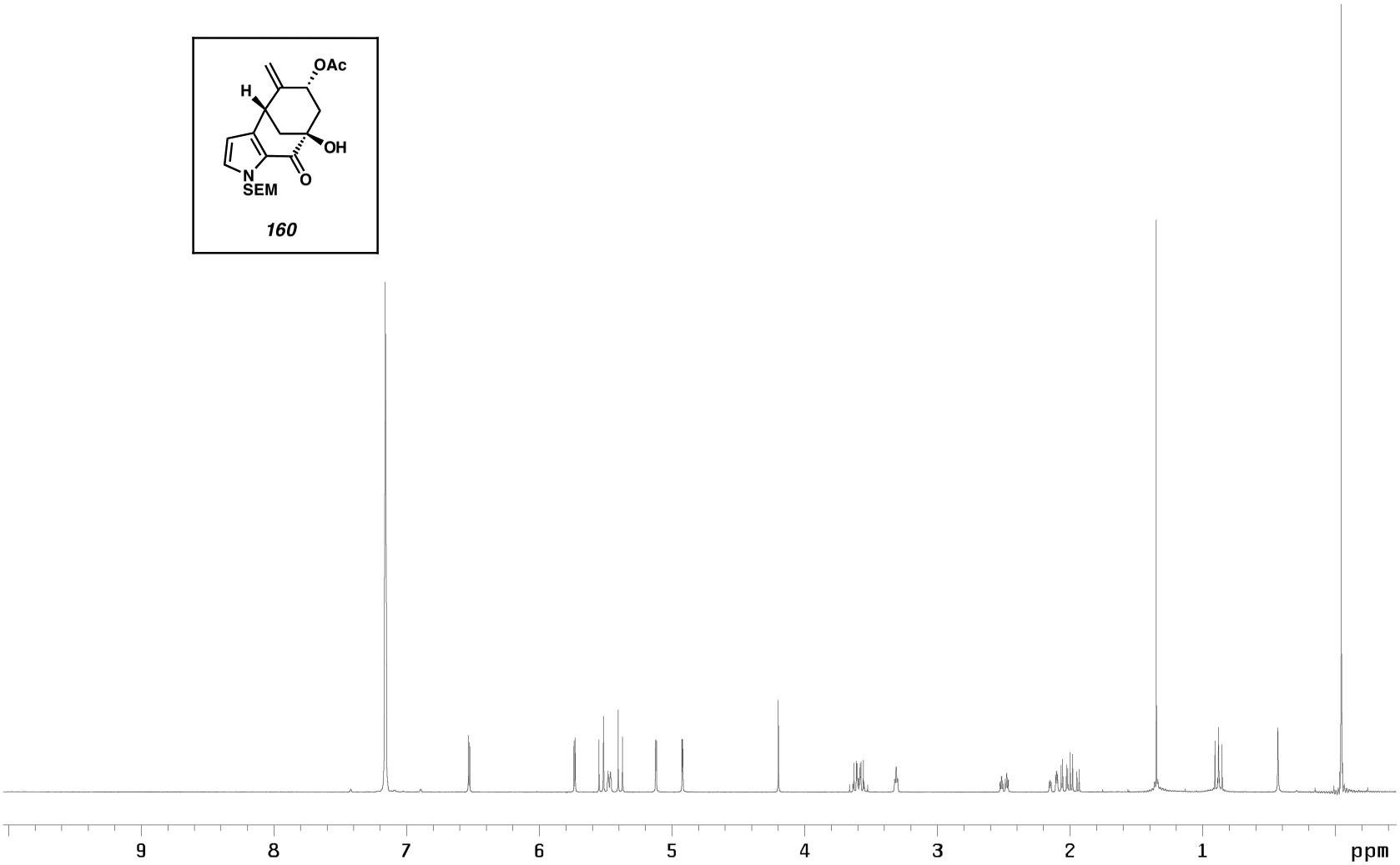


Figure A3.186 ^{1}H NMR (300 MHz, C_6D_6) of compound **160**

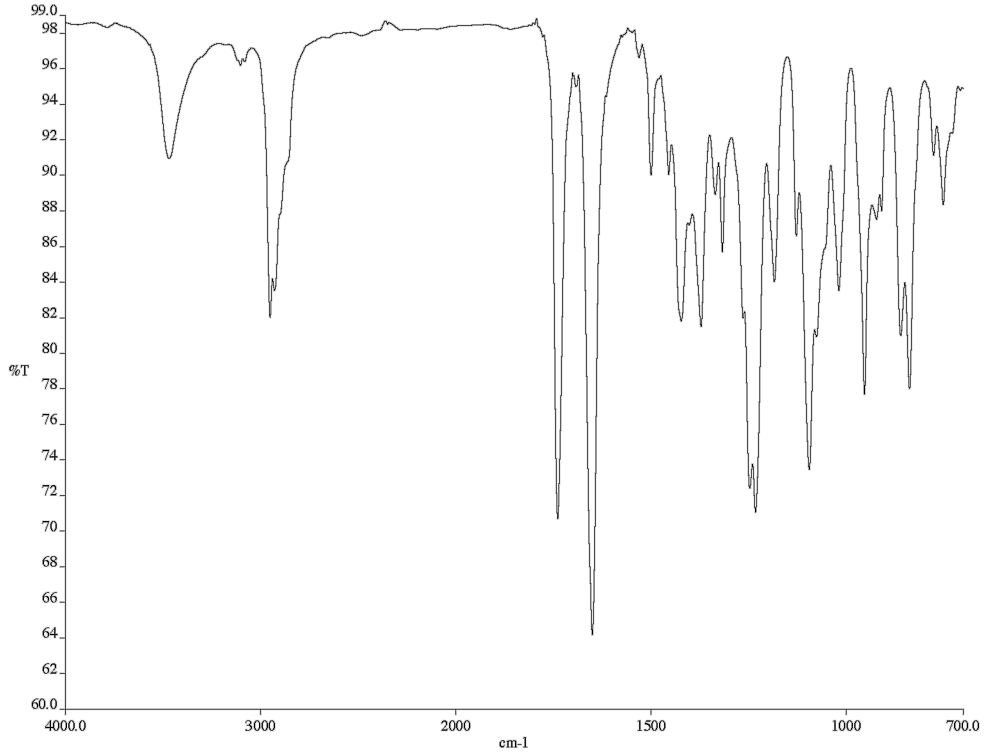


Figure A3.187 Infrared spectrum (thin film/NaCl) of compound **160**

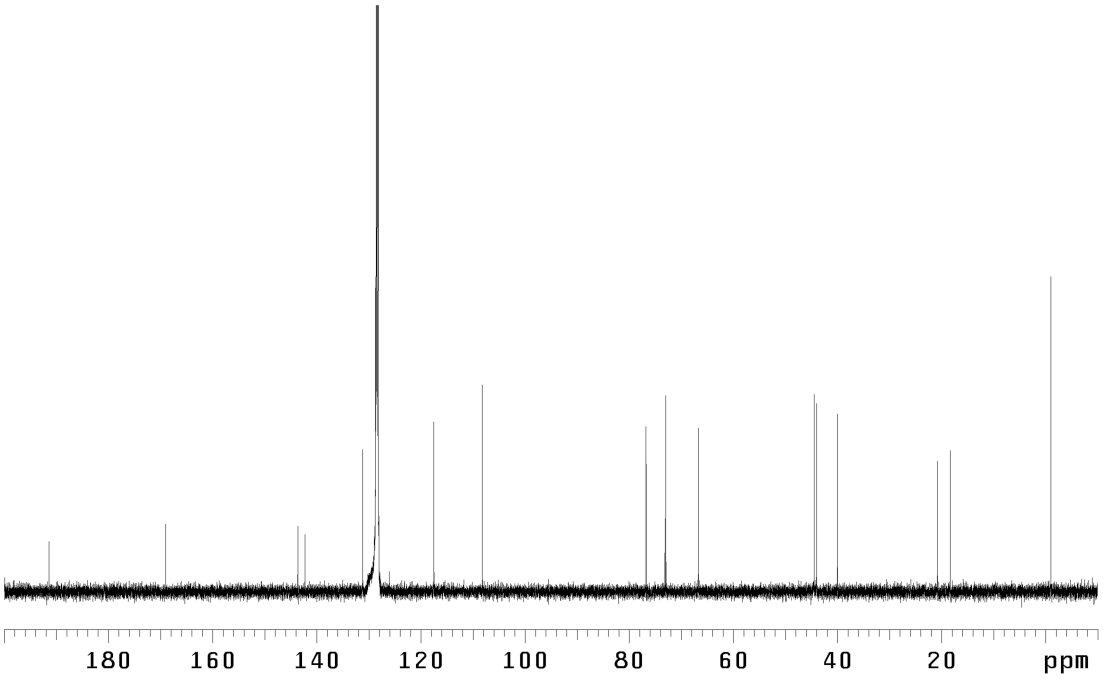


Figure A3.188 ^{13}C NMR (125 MHz, C_6D_6) of compound **160**

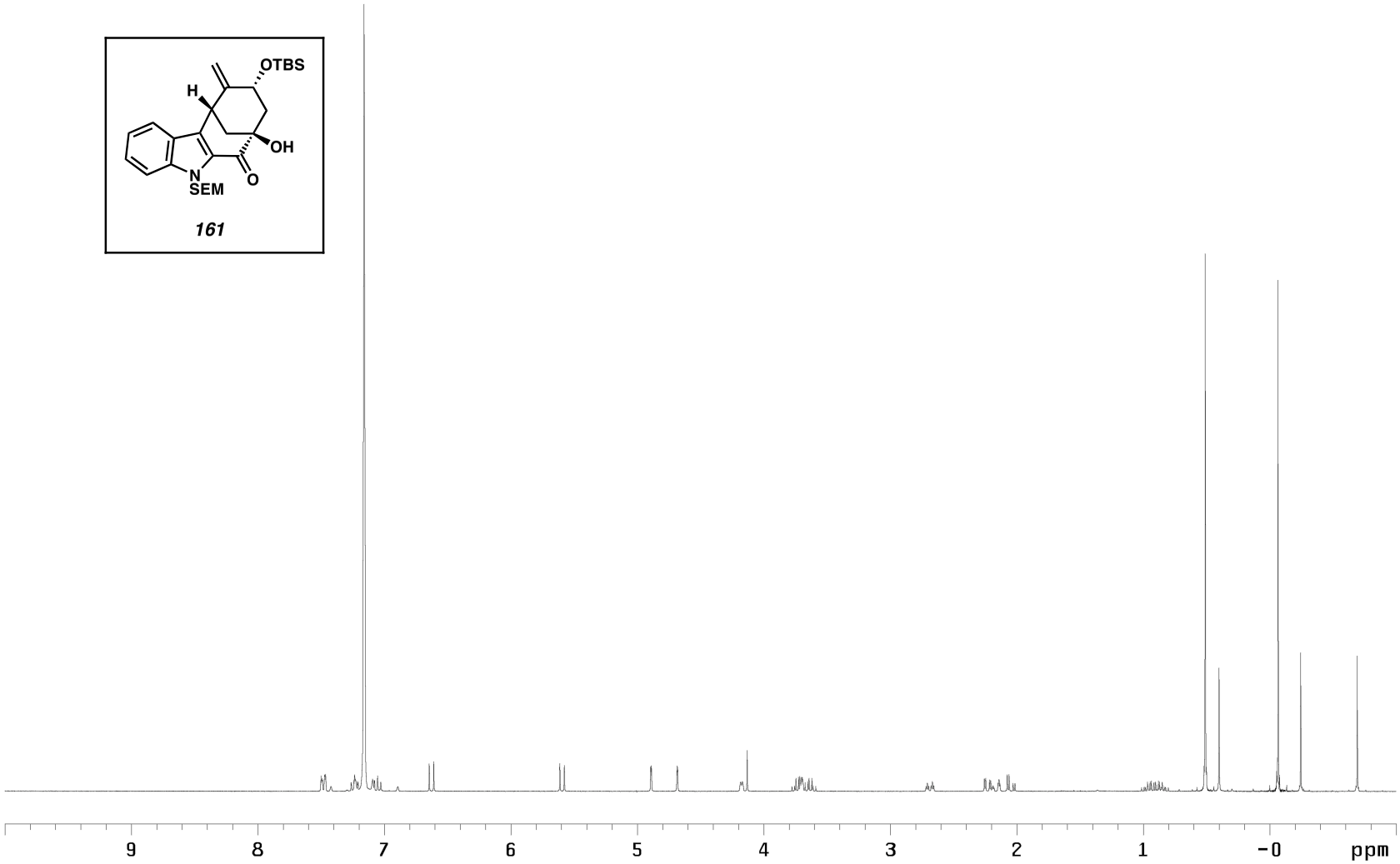


Figure A3.189 ^{1}H NMR (300 MHz, C_6D_6) of compound **161**

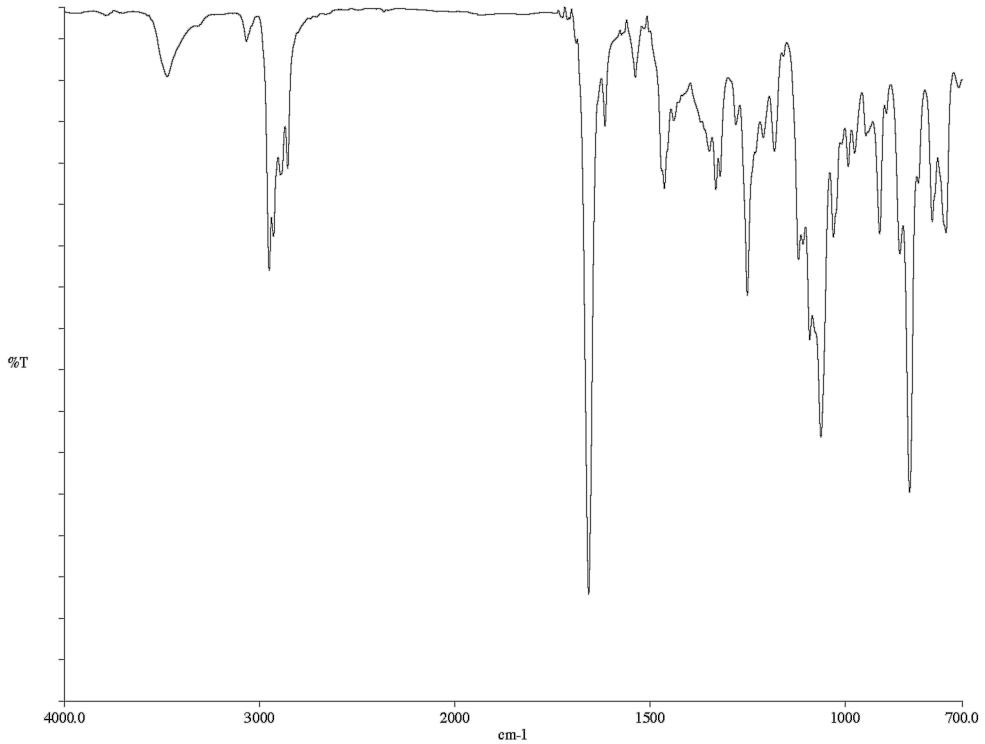


Figure A3.190 Infrared spectrum (thin film/NaCl) of compound **161**

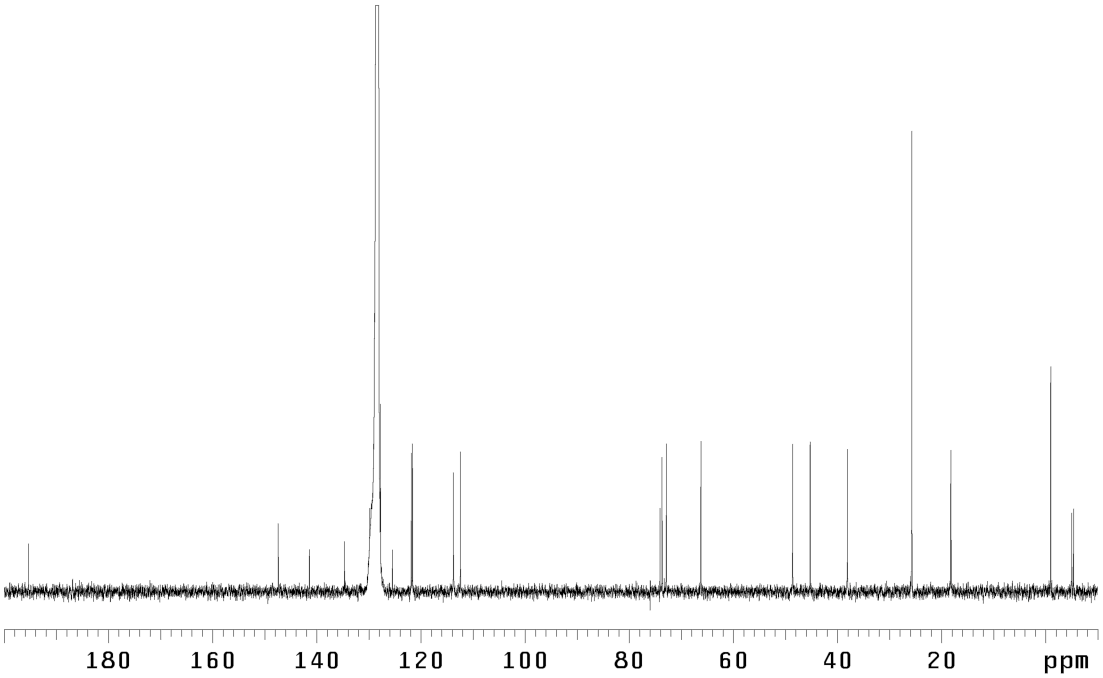


Figure A3.191 ^{13}C NMR (125 MHz, C_6D_6) of compound **161**

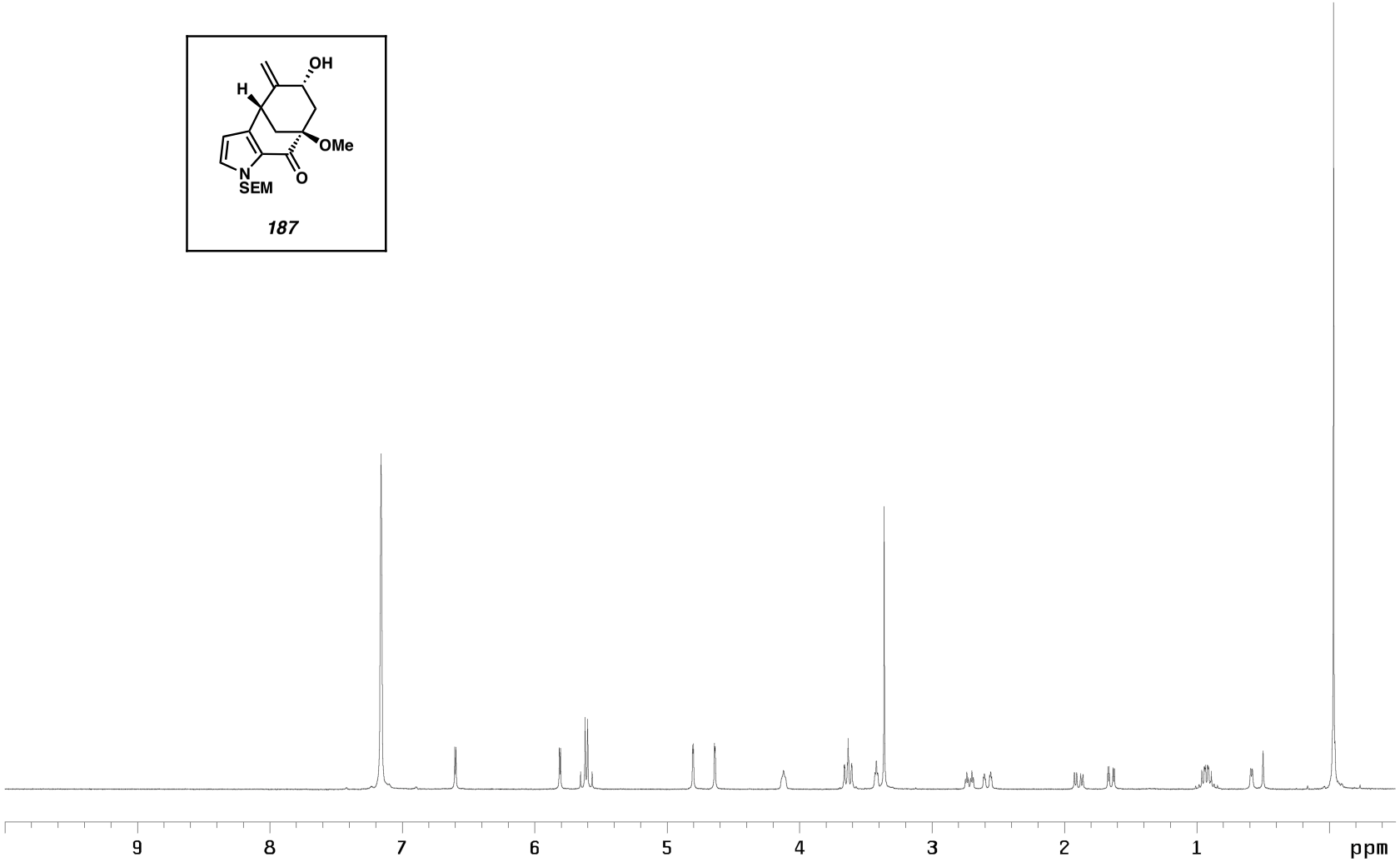


Figure A3.192 ^{1}H NMR (300 MHz, C_6D_6) of compound **187**

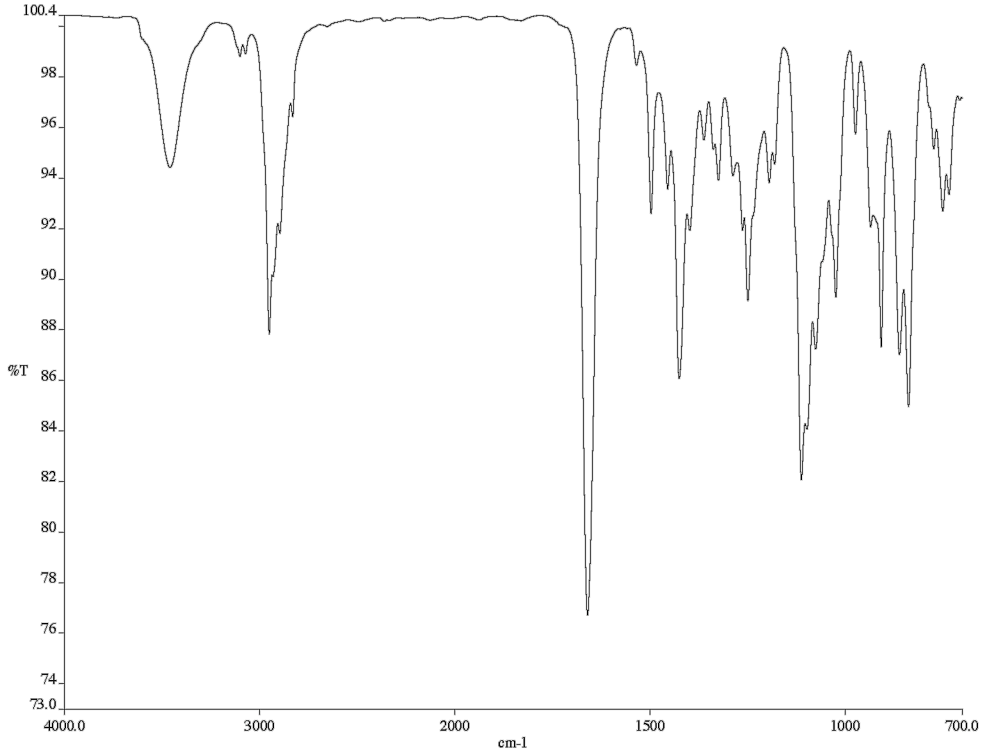


Figure A3.193 Infrared spectrum (thin film/NaCl) of compound **187**

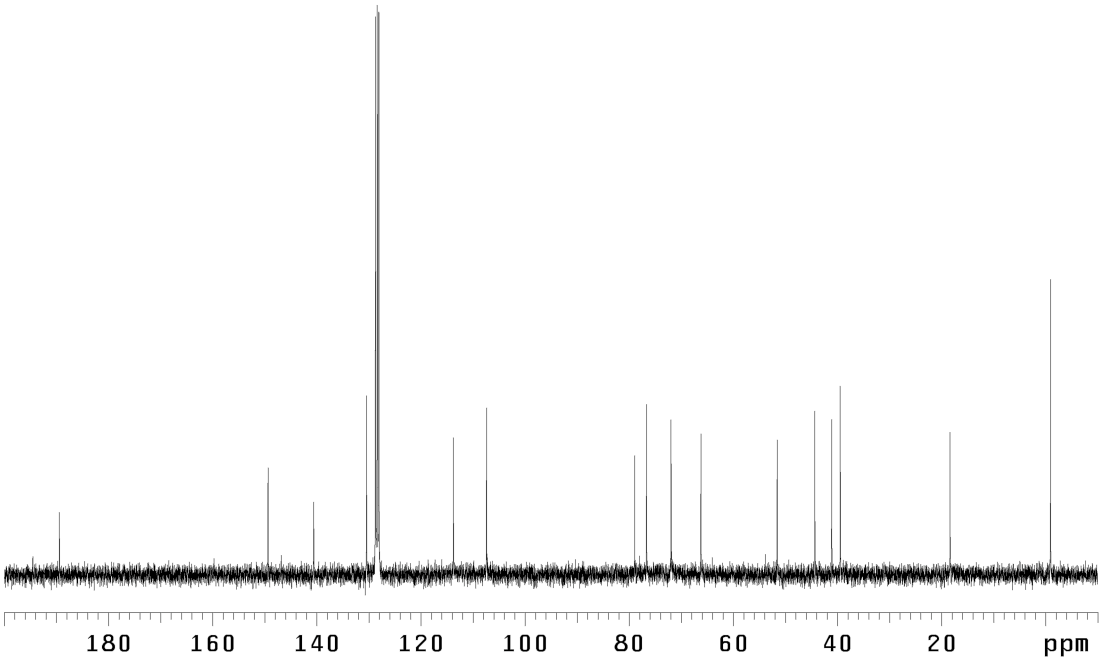


Figure A3.194 ^{13}C NMR (75 MHz, C_6D_6) of compound **187**

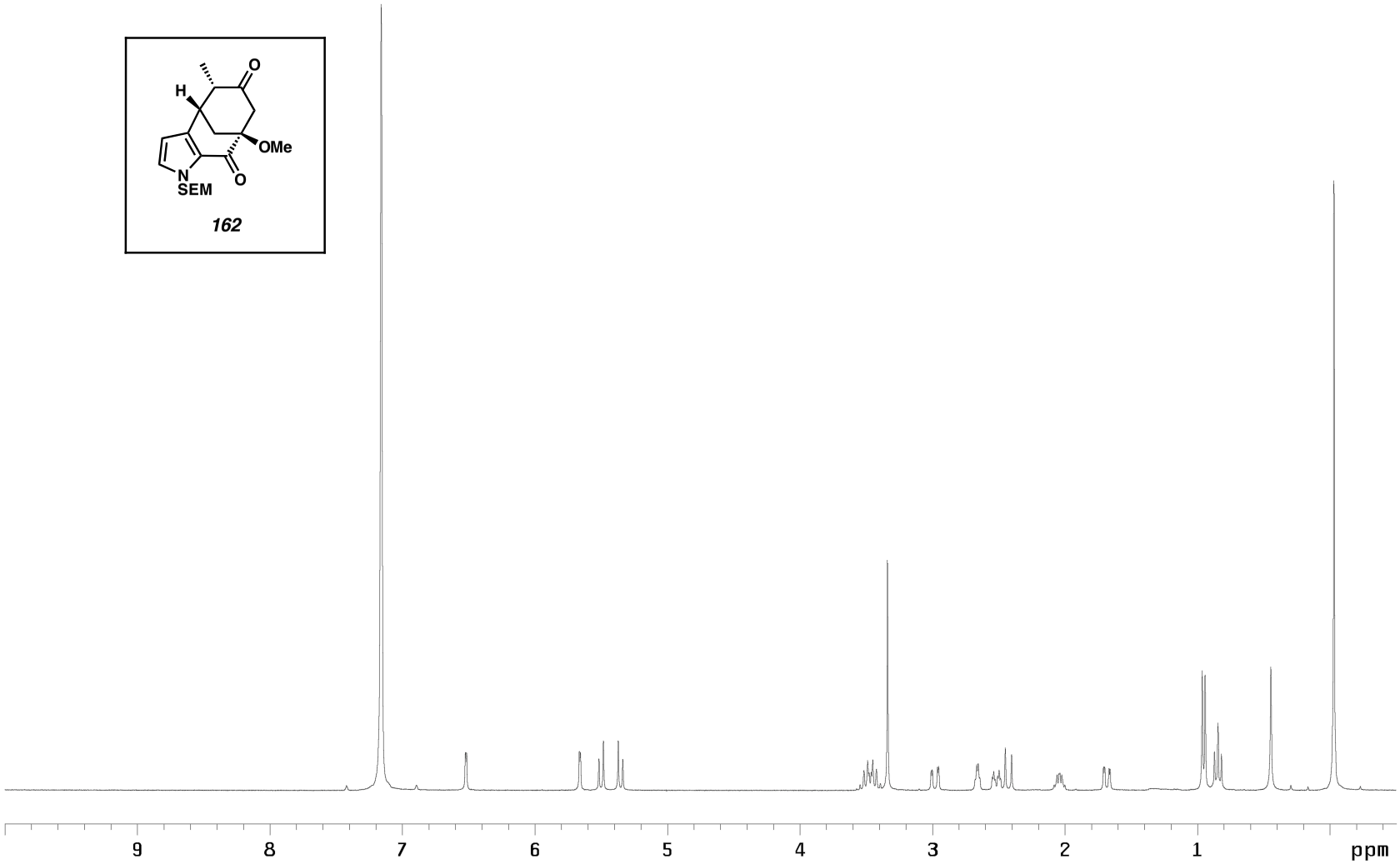


Figure A3.195 ^{1}H NMR (300 MHz, C_6D_6) of compound **162**

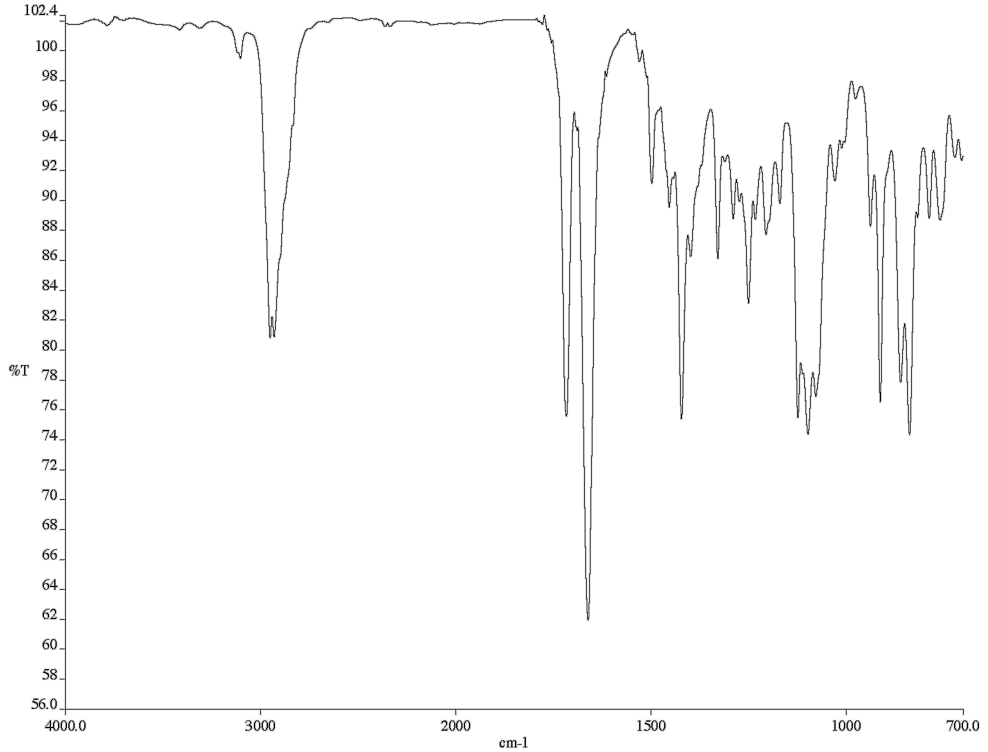


Figure A3.196 Infrared spectrum (thin film/NaCl) of compound **162**

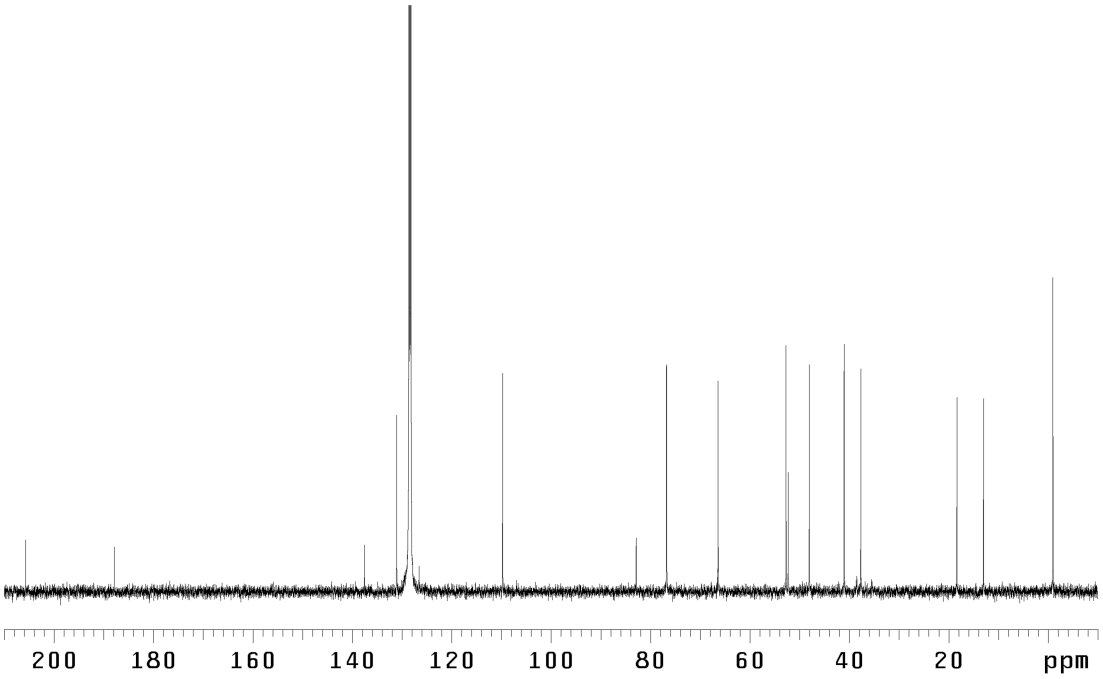


Figure A3.197 ^{13}C NMR (125 MHz, C_6D_6) of compound **162**

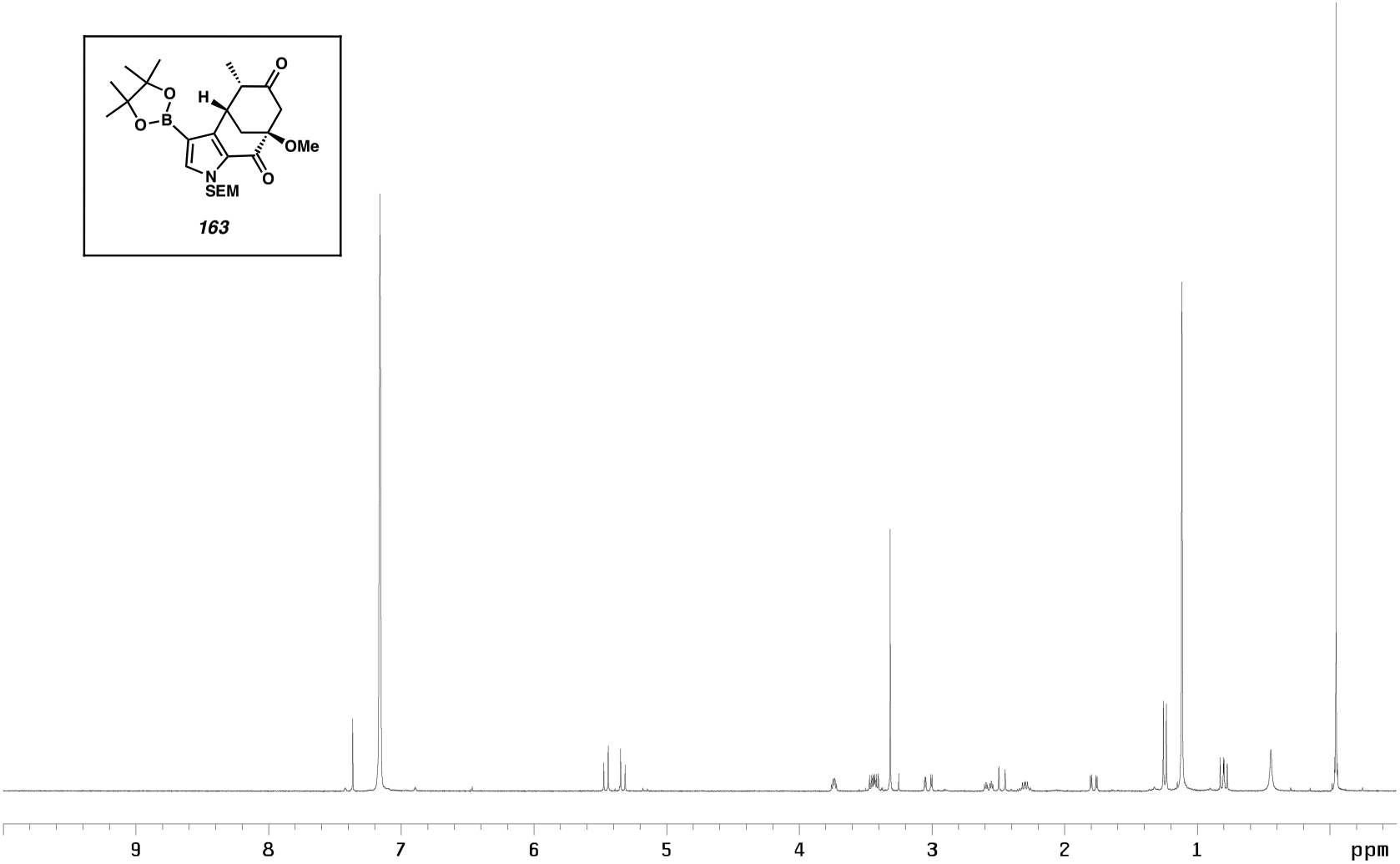


Figure A3.198 ^{1}H NMR (300 MHz, C_6D_6) of compound **163**

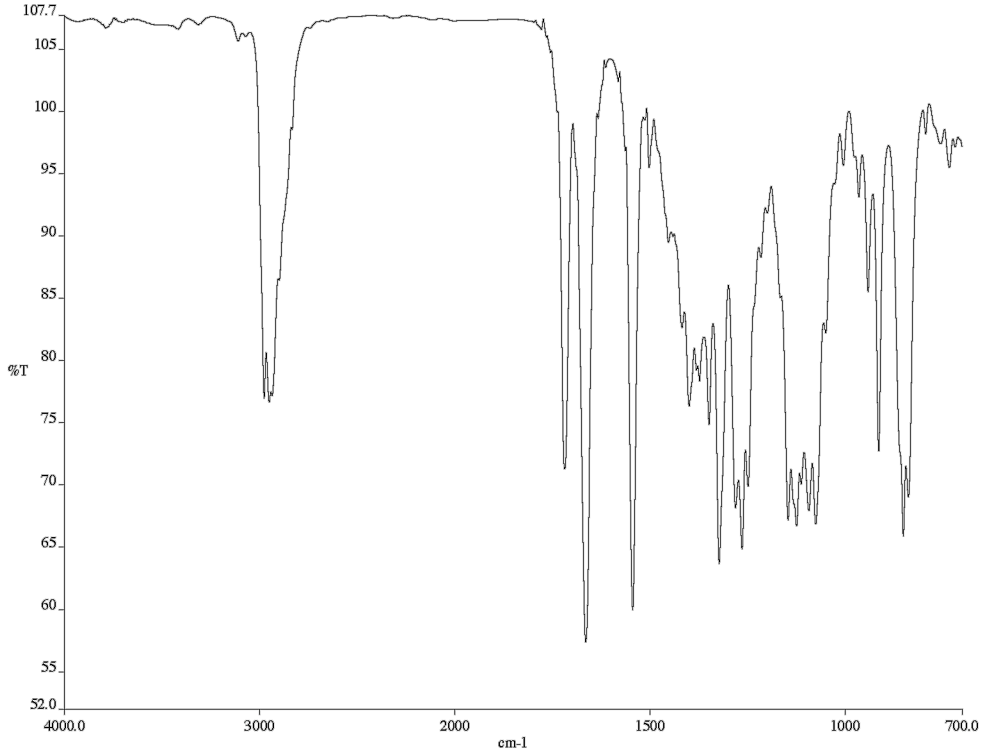


Figure A3.199 Infrared spectrum (thin film/NaCl) of compound **163**

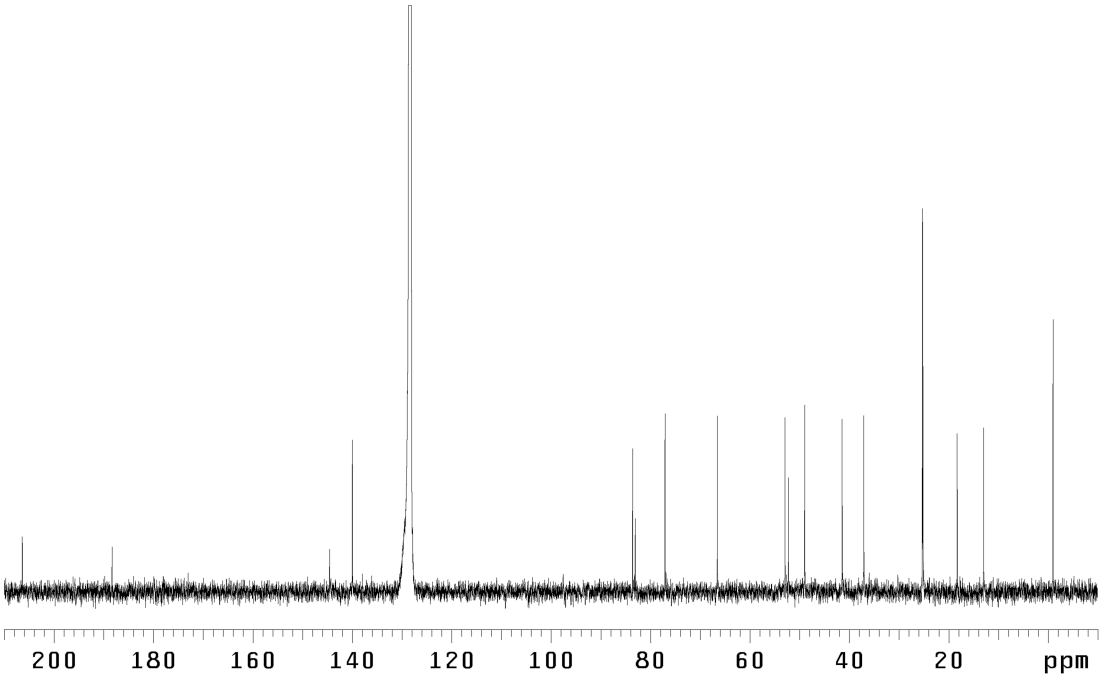


Figure A3.200 ^{13}C NMR (125 MHz, C_6D_6) of compound **163**

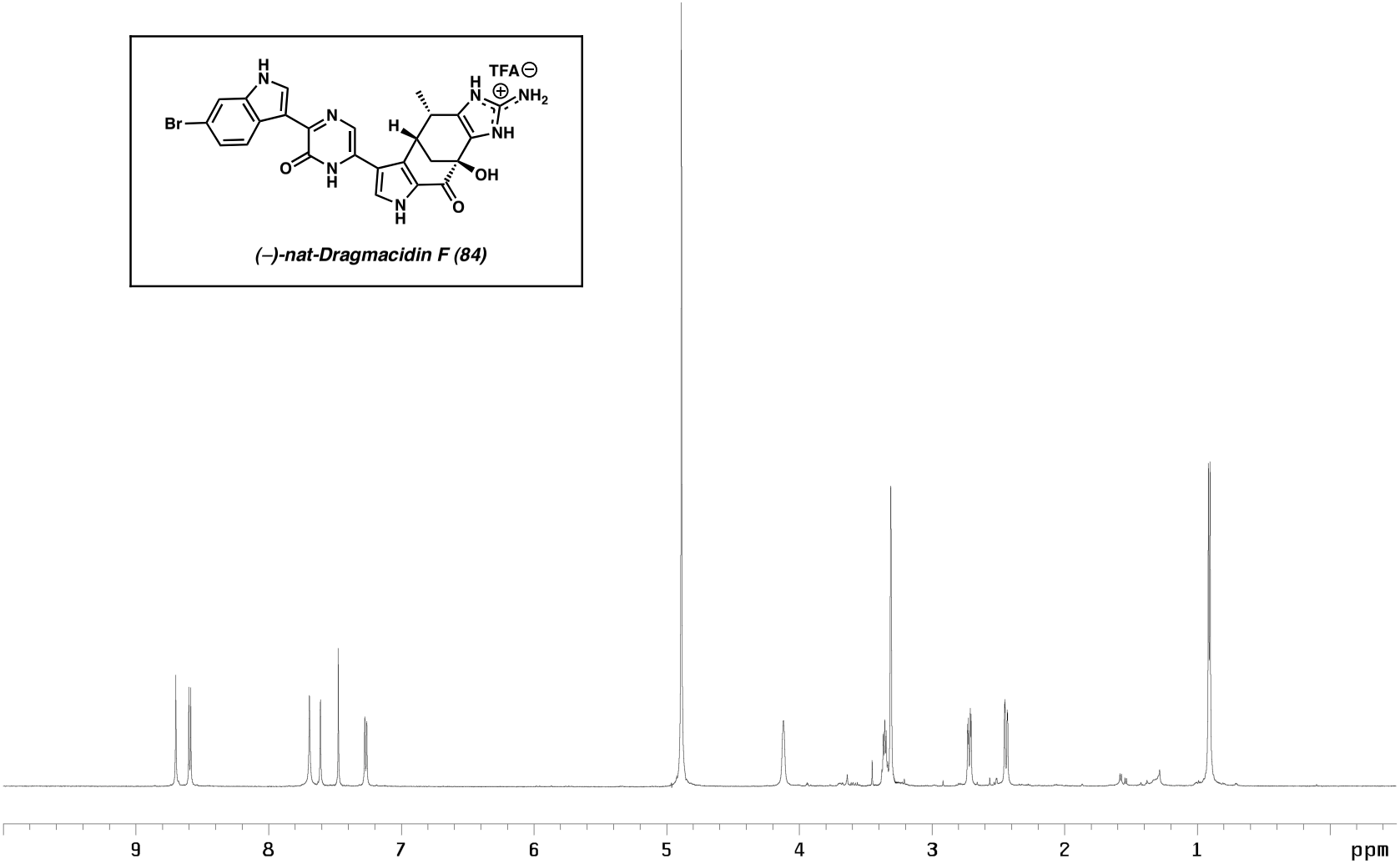


Figure A3.201 ^{1}H NMR (600 MHz, CD_3OD) of (–)-dragmacidin F (**84**)

CHAPTER FOUR

Progress Toward The Total Synthesis of (*R*)–Telomestatin[†]

4.1 Background

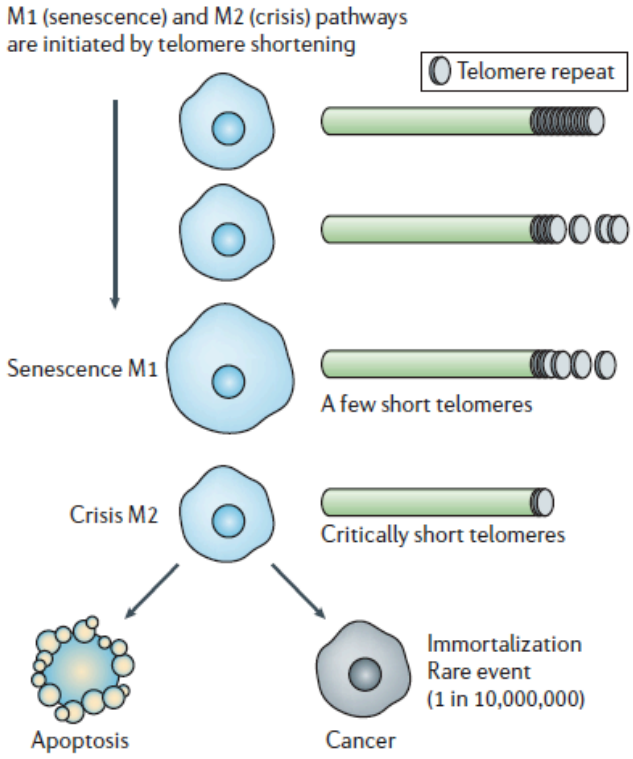
4.1.1 Telomeres and Telomerase

The ends of eukaryotic chromosomes consist of specialized DNA nucleoprotein complexes known as telomeres.[1] Telomeres safeguard the integrity of chromosomes and protect them from base-pair loss, comparable to the small plastic at the end of a shoelace that prevents the twine from unraveling. The human telomere is composed of tandem repeats of the guanine-rich hexanucleotide sequence d(TTAGGG). With the exception of the single-stranded 3´ overhang, most telomeric DNA is double stranded.

In human cells, telomere length erodes naturally with each cell division cycle, since DNA polymerase is unable to fully replicate the ends – a phenomenon known as the "end replication problem". Thus, telomeres are thought to effectively function as cellular clocks, keeping record of how many times a cell divides. Telomeres progressively shorten until a critically short length of telomeric DNA is reached, at which point cells undergo replicative senescence (mortality stage 1 (M1), see Figure 4.1.1), losing their ability to divide.[1] This can be followed by cell crisis (mortality stage 2 ((M2)) and apoptosis.

[†] This work was performed in collaboration with Dr. Haiming M. Zhang, a postdoctoral scholar in the Stoltz group, and Justin T. Mohr, a graduate student in the Stoltz group.

Figure 4.1.1 (reprinted with permission from (2); © 2006, Macmillan Publishers Ltd.)

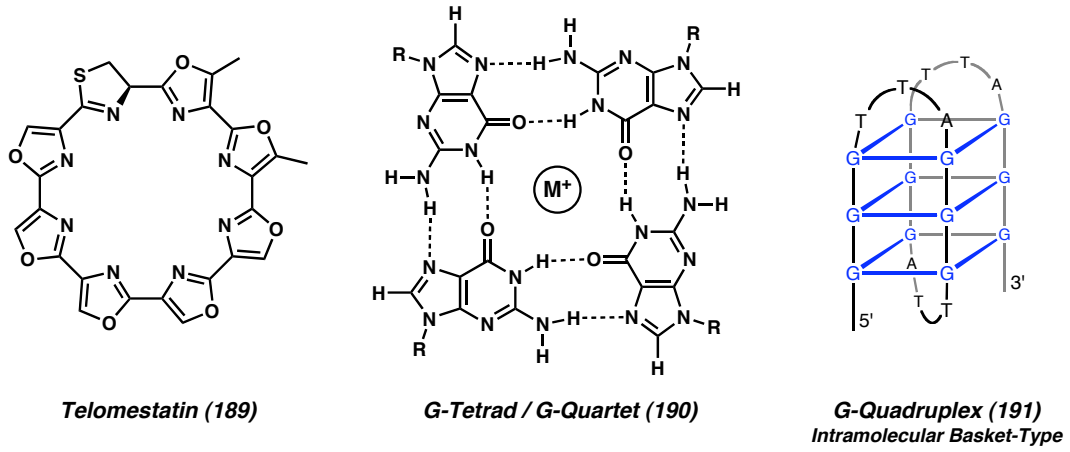


A mechanism for telomere maintenance is provided by a specialized cellular ribonucleoprotein enzyme complex called telomerase.[1,2,3,4,5] Discovered by Carol Greider in 1984, telomerase is involved in telomere capping and in the DNA-damage response, and has been implicated in aging and genetic diseases.[2,3] In human cells, telomerase functions as a reverse transcriptase to add multiple copies of the TTAGGG motif to the end of the G-strand of the telomere. Telomerase activity is usually absent from normal cells; however, in the majority of tumor cells (85-90%) this enzyme is overexpressed, contributing to the immortalization of human tumor cells by protecting against telomere loss during replication.[6] Because telomerase is necessary for the immortality of so many cancer types, telomerase inhibition has become an important target for the development of new anticancer agents.[3]

4.1.2 Isolation and Biological Activity

In 2001, a team of Japanese scientists conducted a screen for telomerase inhibitors, and isolated and characterized telomestatin (**189**, Figure 4.1.2) from the metabolites of microorganism *Streptomyces anulatus* 3533-SV4.[7,8,9,10] The structure of telomestatin (**189**) consists of a macrocyclic arrangement of five oxazoles, two methyloxazoles, and one thiazoline ring.[11] Telomestatin (**189**) is the strongest and most specific telomerase inhibitor identified to date, with an IC_{50} value of 0.005 μM (5 nM).[7] Further studies on this natural product demonstrated that it is able to inhibit the activity of telomerase without affecting DNA polymerases or reverse transcriptases.[7]

Figure 4.1.2



Telomestatin (189) ***G-Tetrad / G-Quartet (190)*** ***G-Quadruplex (191)***
Intramolecular Basket-Type

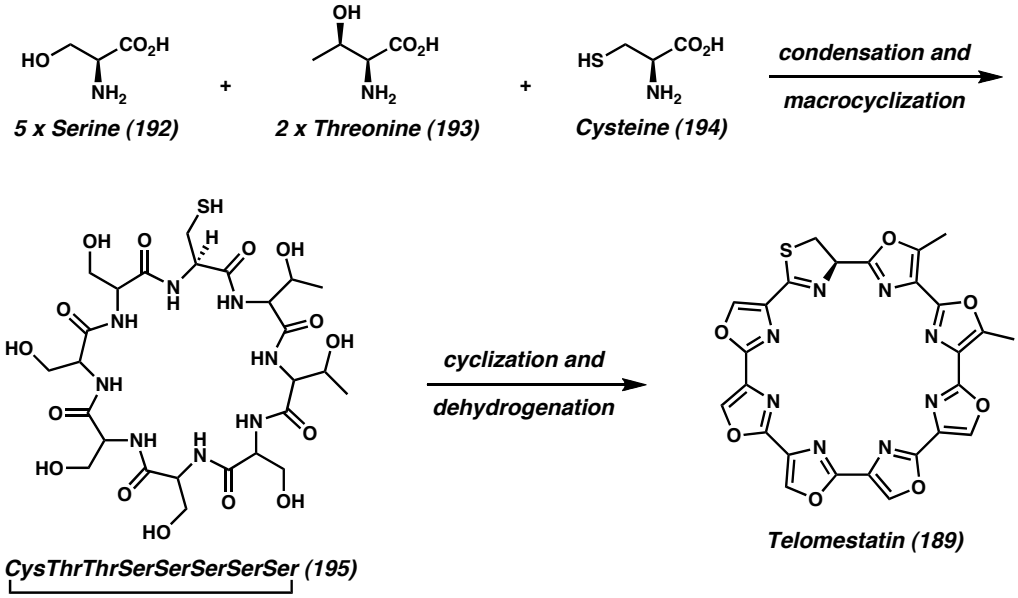
G-quadruplex structures (e.g., **191**) are formed in vivo from the guanine-rich $d(TTAGGG)_n$ repeat sequences of human telomeres, which are stacked layers of G-tetrads (also known as G-quartets, **190**).[12] Previous research has shown that the formation of such G-quadruplex structures (e.g., **191**) sequesters the single-stranded $d(TTAGGG)_n$ primer molecules required for telomerase activity, thus preventing the action of

telomerase.[13] While direct catalytic inhibition of telomerase by telomestatin (**189**) cannot be ruled out, evidence suggests that telomestatin (**189**) facilitates the formation of or stabilizes G-quadruplex structures (e.g., **191**), thereby inhibiting telomerase activity indirectly.[9b,14] Indeed, modeling studies on the binding interactions of telomestatin (**189**) and the G-quadruplex (e.g., **191**) demonstrated that sources of stable interactions include hydrogen bonding between the nitrogens of the guanine bases and the oxygens of the oxazole rings, stacking interactions with the G-tetrad, as well as electrostatic interactions between the ring nitrogens and the guanine bases.[9b]

4.1.3 Biosynthesis

The biosynthesis of telomestatin (**189**), although not yet reported in the literature, probably involves the intermediacy of octapeptide **195** generated from the condensation and macrocyclization of eight amino acids—five serine (**192**), two threonine (**193**), and one cysteine (**194**) (Scheme 4.1.1).[15,16] Cyclodehydration and oxidation of **195** would then generate the final product (**189**). Although telomestatin (**189**) is almost certainly derived from the abovementioned amino acids, there is no evidence to suggest that the all of the peptide bonds must be formed prior to the heterocyclization steps.[15a]

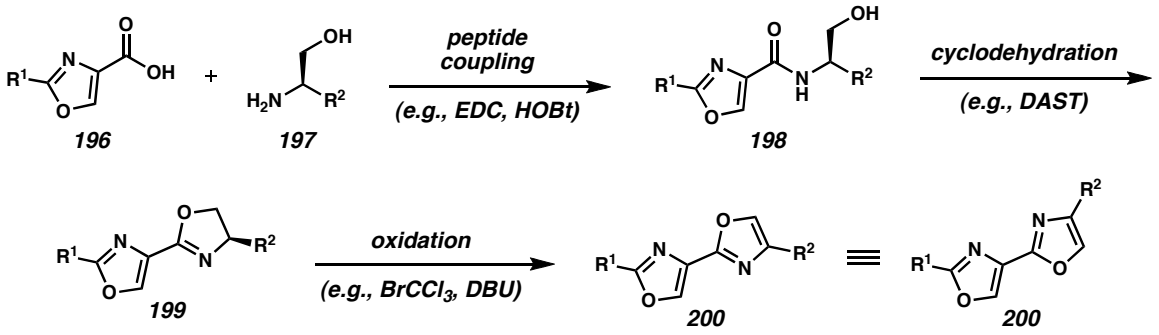
Scheme 4.1.1



4.1.4 Previous Synthetic Studies

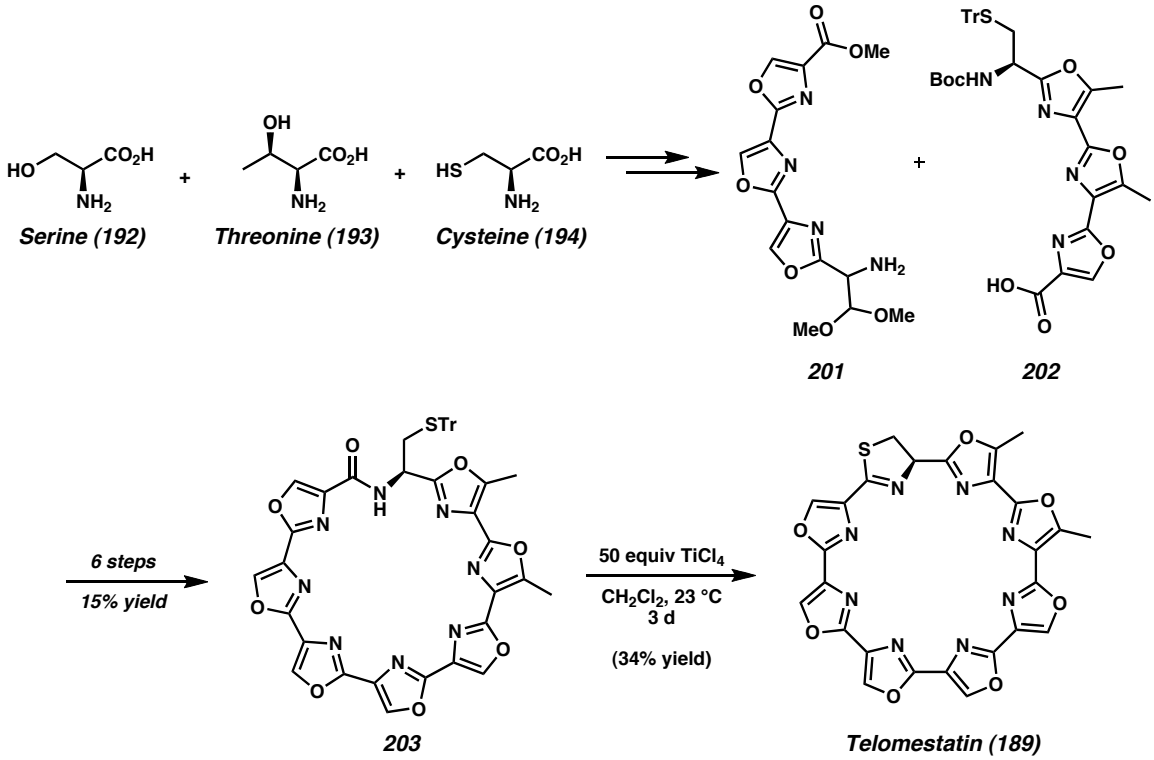
There are two published total syntheses of telomestatin (**189**) in the literature,[17] as well as a handful of syntheses en route to the natural product.[10,18,19] Despite the amount of synthetic attention that this molecule has garnered, however, every one of the reported approaches relies heavily on the use of amino acid precursors, as well as linear, repeated peptide-bond formation–cyclization–oxidation sequences to form the oxazole rings (**196** + **197** → **198** → **199** → **200**, Scheme 4.1.2). In fact, this sequence bears resemblance to the proposed telomestatin (**189**) biosynthesis (Scheme 4.1.1, vide infra). Not surprisingly, the use of these methods typically also requires multiple protection and deprotection steps. While the described routes are usually reasonably convergent, the use of this inefficient design strategy (i.e., Scheme 4.1.2) renders them lengthy and impractical—especially for analog synthesis.

Scheme 4.1.2



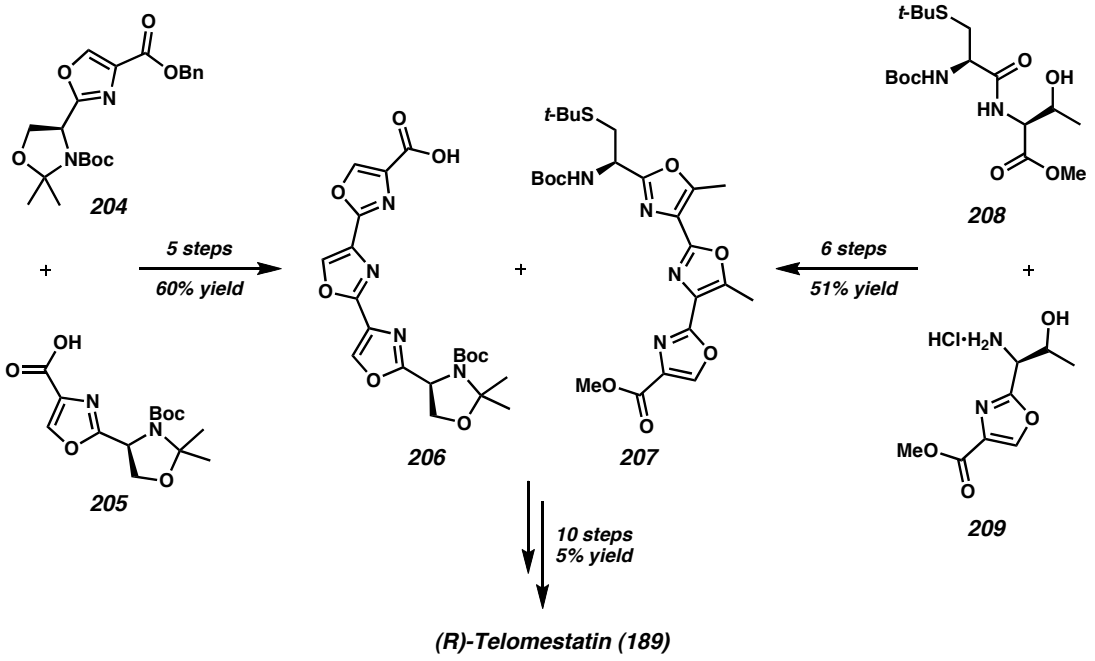
The first total synthesis of telomestatin (**189**) appeared in the literature in a 2002 patent reported by the Japanese company Taiho Pharmaceutical (Scheme 4.1.3).[17a] While experimental details are limited, they achieved the synthesis of **201** and **202** in unreported yields via the use of peptide bond formation–cyclization–oxidation sequences beginning from amino acid precursors (**192–194**, see Scheme 4.1.2, vide infra). Trisoxazole ester **201** and trisoxazole acid **202** were then stitched together in a similar manner over 6 steps to form **203**, and $TiCl_4$-mediated thiazoline closure produced the natural product (**189**). Advancing the two key trisoxazole fragments (**201** and **202**) to the end required 7 total steps in 5% overall yield, with 10 mg of the natural product reported.

Scheme 4.1.3



During the course of our synthetic endeavors, a Japanese group led by Doi and Takahashi also reported a total synthesis of telomestatin (**189**), and definitively confirmed the absolute stereochemistry of the natural product as (*R*)-telomestatin (**189**).[17b] Although the details of the Taiho Pharmaceutical synthesis are incomplete,[17a] both of these routes appear to be fundamentally similar (Scheme 4.1.4). Amino-acid-derived building blocks **204**, **205**, **208**, and **209** were readily available in less than 5 steps, and could be advanced to key trisoxazole fragments **206** and **207** using the cyclization protocol previously described (see Scheme 4.1.2, vide infra). These two key fragments (**206** and **207**) were then advanced over 10 subsequent steps to provide the natural product in 5% overall yield from these intermediates.

Scheme 4.1.4



In addition to the aforementioned synthetic efforts, a handful of novel poly-oxazole methodologies have also been published. These methods include a two-stage iterative oxazole synthesis by Vedejs,[20a] as well as a series of palladium-catalyzed Suzuki coupling approaches by Greaney and Inoue.[20b–d] While these approaches seem promising, to date they have not been resulted in a completed total synthesis of telomestatin (**189**).

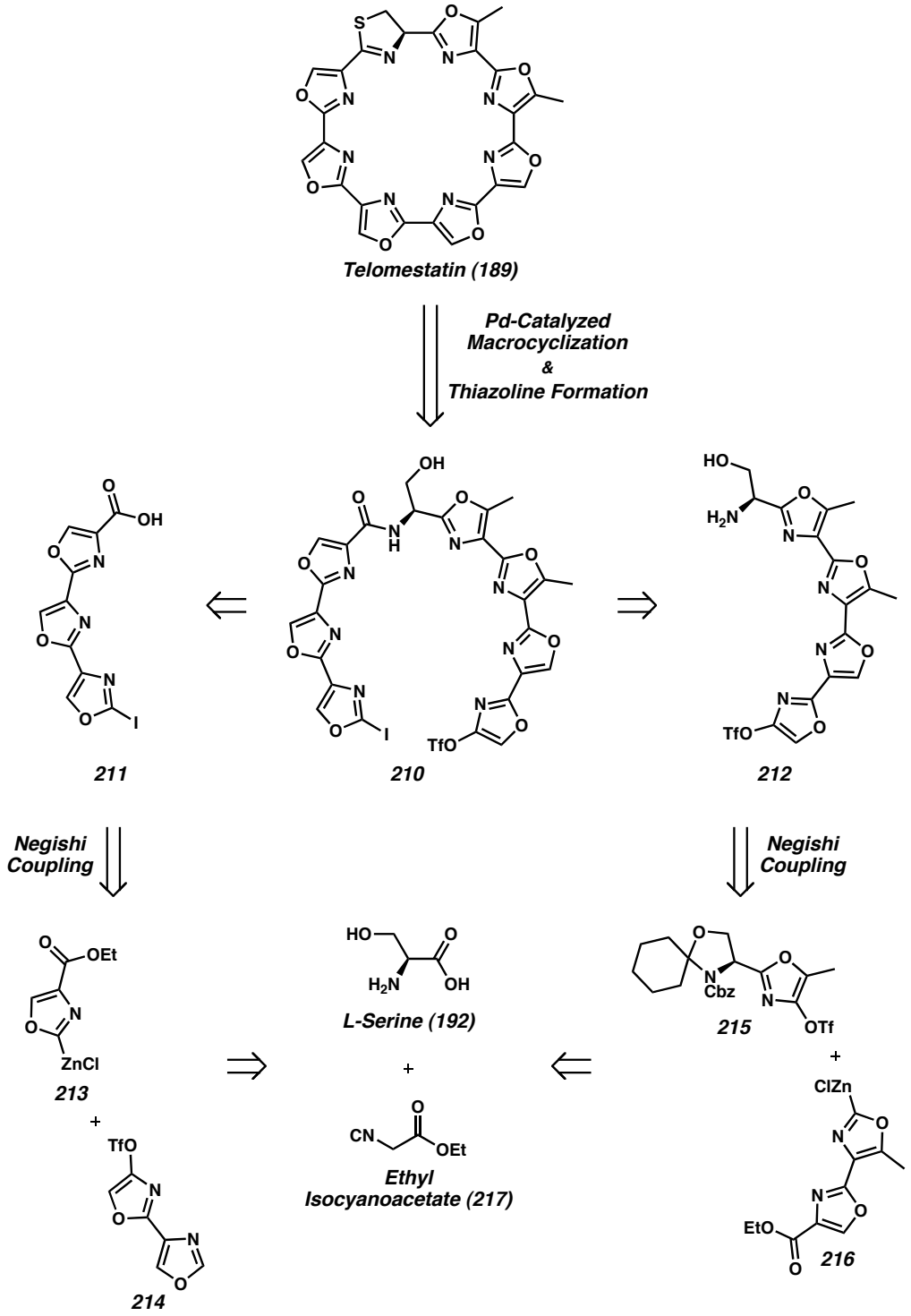
Given the significant anticancer therapeutic potential of telomestatin (**189**),[9,10] as well as the lengthy and low-yielding preparations to date,[17] a successful synthesis of this molecule would not only deliver the natural product in an efficient manner, but would also be readily amenable to analog synthesis for further biological testing.

4.1.5 Retrosynthetic Analysis of Telomestatin

Our retrosynthetic analysis for telomestatin (**189**) is shown in Scheme 4.1.5. On the basis of the reported telomestatin (**189**) syntheses,[17] as well as the potential for sulfur to oxidize or poison metal catalysts, we envisioned a late-stage installation of the sulfur moiety and the thiazoline ring. Additionally, in order to maximize synthetic efficiency, we sought to complete the final aryl–aryl linkage of **210** and induce macrocyclization using a palladium-catalyzed cross-coupling.[21,22] This maneuver would also allow for a high degree of convergency by dividing the molecule into two roughly equal halves.[23] Disconnection across the amide bond in **210** then reveals trisoxazole iodo acid **211** and tetrakisoxazole amino alcohol **212**.

Iodo acid **211** would be targeted by way of a palladium-catalyzed Negishi cross-coupling between zinc reagent **213** and bisoxazole triflate **214**. Amino alcohol **212**, in turn, would also be assembled using a Negishi cross-coupling between triflate **215** and zinc reagent **216**. All of the achiral oxazole building blocks (**213**, **214**, **216**) would be obtained from ethyl isocyanoacetate (**217**), and chiral triflate **215** would be derived from the natural amino acid *L*-serine (**192**).

Scheme 4.1.5

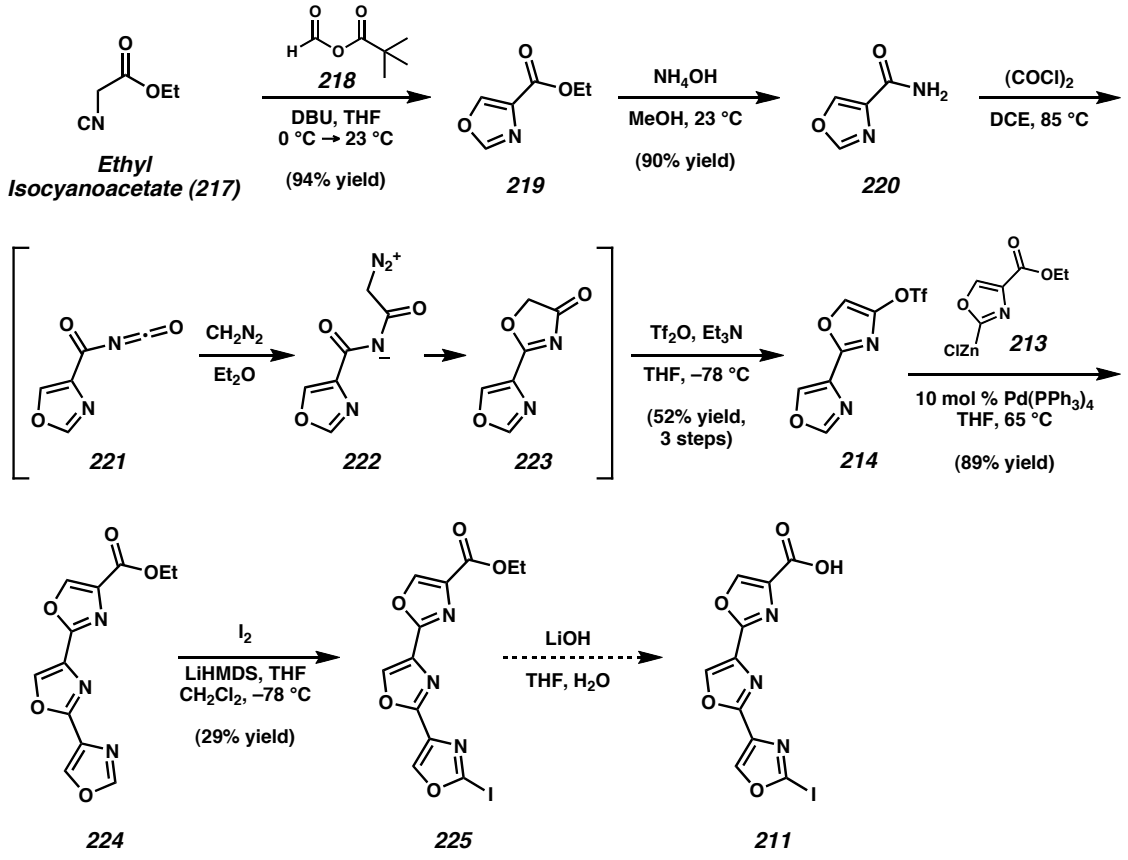

Telomestatin (189)
Pd-Catalyzed
Macrocyclization
&
Thiazoline Formation
211
210
212
Negishi
Coupling
Negishi
Coupling
213
214
L-Serine (192)
Ethyl
Isocyanoacetate (217)
215
216

4.2 Progress Toward The Total Synthesis of Telomestatin

4.2.1 Synthesis of Left-hand Trisoxazole Iodo Acid

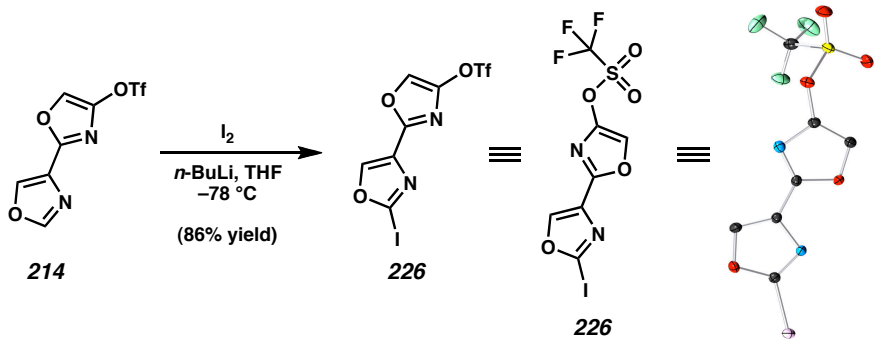
Our synthesis of the left-hand trisoxazole portion (**211**) of telomestatin (**189**) began with the preparation of known oxazole ester **219**. Exposure of ethyl isocyanoacetate (**217**) to mixed anhydride **218**[24] and DBU led to a high yield of oxazole ester **219**,[25] which was smoothly converted to amide **220** by the action of aqueous ammonia in methanol (Scheme 4.2.1). Conversion to bisoxazole triflate **214** was achieved by means of a three-step sequence, which commenced by heating amide **220** in the presence of oxalyl chloride to give rise to acyl isocyanate **221**.

Scheme 4.2.1



Subjection of acyl isocyanate **221** to anhydrous, alcohol-free diazomethane dried over sodium metal[26] led to in situ production of **222**, which rapidly cyclized with loss of nitrogen to form oxazolone **223**.[27] Treatment of this intermediate with Tf_2O and amine base produced bisoxazole triflate **214** in 52% yield over 3 steps.[28] Although NMR techniques were initially used for characterization, further confirmation of the structural identity was achieved by single crystal X-ray diffraction upon conversion to the iodo derivative (**214** → **226**, Scheme 4.2.2).[29]

Scheme 4.2.2



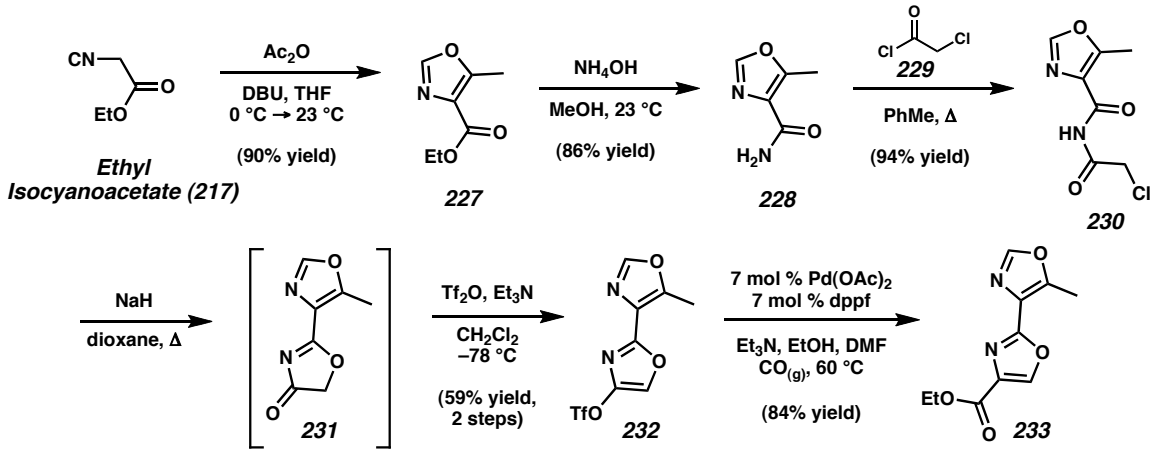
A wide range of cross-couplings of appropriate mono and bisoxazole subunits were investigated to prepare the desired trisoxazole fragment (**224**), including Stille, Suzuki, and Negishi protocols.[30,31] Ultimately, the Negishi approach proved to be the most robust to accomplish this union.[30] The necessary zinc reagent (**213**) for this reaction could be prepared from **219** via a deprotonation/quenching event with LiHMDS and $ZnCl_2$, furnishing trisoxazole **224** after successful aryl fusion with bisoxazole **214**.[32] Installation of the heteroaryl iodide could be realized at this juncture, since incorporating the iodide earlier in the synthesis would likely interfere with the Negishi cross-coupling

of **214** + **213**.[33] Deprotonation of trisoxazole **224** using LiHMDS, in an optimized solvent mixture of THF and dichloromethane,[34] followed by quenching with iodine produced **225**.[32] Finally, it is anticipated that hydrolysis of ester **225** would lead to the desired acid (**211**).

4.2.2 Synthesis of Right-hand Tetrakisoxazole Amino Alcohol

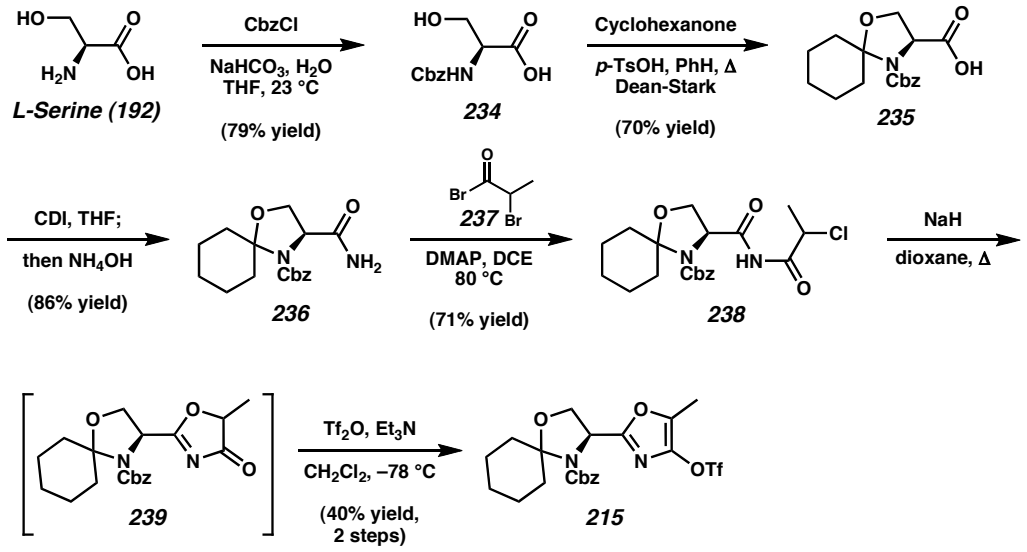
Assembly of the tetrakisoxazole amino alcohol subunit (**212**) begins with the preparation of methylbisoxazole ester **233**. The synthesis of this fragment is adapted from the route to bisoxazole triflate **214** (see Scheme 4.2.1, vide infra). Following a reported two-step procedure, mixing ethyl isocyanoacetate (**217**) with acetic anhydride and DBU led to the formation of methyloxazole ester **227**,[35] which was treated with ammonium hydroxide to generate amide **228** (Scheme 4.2.3). Acetylation with chloroacetyl chloride (**229**) gave rise to imide **230**, which could be converted to triflate **232** via oxazolone **231**. A Pd-catalyzed carbonylation reaction of triflate **232** with ethanol led to the production of desired ester **233** in 84% yield.

Scheme 4.2.3



With ester **233** now in hand, preparation of the triflate coupling partner (**215**) could proceed. Protection of *L*-serine (**192**) as the *N*-Cbz carbamate (**234**) was accomplished using published procedures (Scheme 4.2.4).[36] Refluxing **234** under Dean-Stark conditions with cyclohexanone and a catalytic amount of *p*-toluenesulfonic acid afforded cyclohexylidene **235**.[37] Acid **235** was then activated with CDI, and displaced with NH_4OH to produce amide **236**. Reaction of amide **236** with **237** led to imide cyclization precursor **238**, which was treated with NaH to form oxazolone **239**. Finally, oxazole triflate **215** was accessed from oxazolone **239** via triflation.

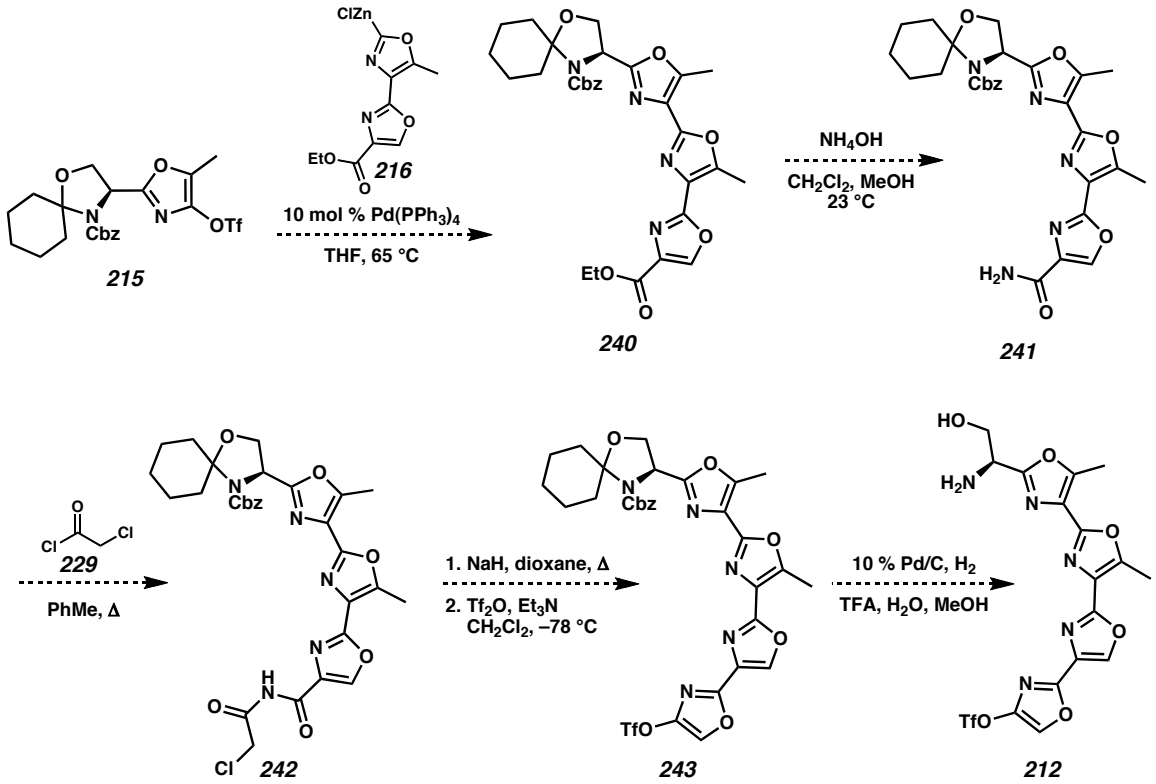
Scheme 4.2.4



With the ready availability of the key coupling partners (**215** and **233**), the Negishi cross-coupling was attempted. It is anticipated that exposure of triflate **215** to the Negishi reagent (**216**) of ester **233** under palladium catalysis would lead to the assembly of trisoxazole **240** (Scheme 4.2.5).[38] Installation of the final oxazole ring present in

desired tetrakisoxazole **212** could then be initiated via conversion to amide **241**. Acylation of amide **241** would then be executed to prepare imide **242**, which could be cyclized and treated with Tf_2O to furnish tetrakisoxazole triflate **243**.[39] Cleavage of both the benzyl carbamate and cyclohexylidene protecting groups would then occur under the action of Pd/C, H_2, and TFA in wet methanol, ultimately affording amino alcohol **212**.[40]

Scheme 4.2.5

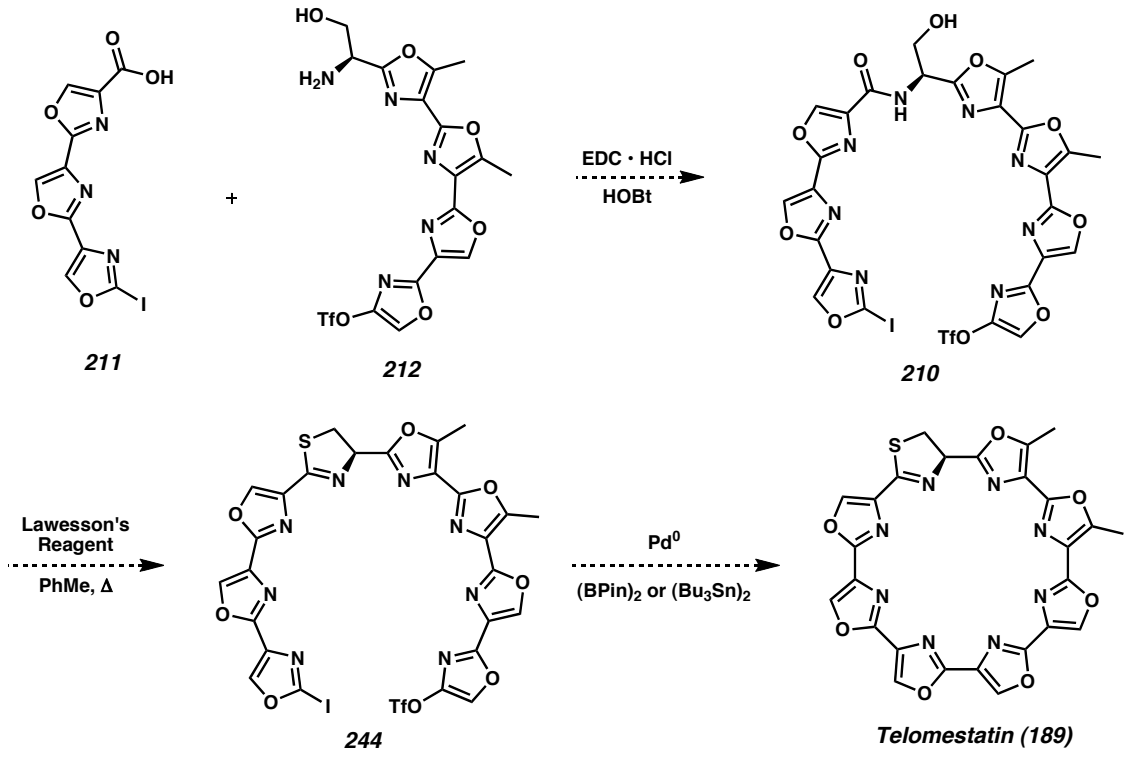


4.2.3 Late-Stage and Proposed Endgame

With the assembly of the two major fragments completed (**211** and **212**), amide bond formation would then be initiated (Scheme 4.2.6). Successful coupling of these two partners would afford hydroxyamide **210**. Treatment of **210** with Lawesson's reagent is

then anticipated to lead to closure of the thiazoline ring to form **244**.[41] Finally, an intramolecular Pd-catalyzed cross-coupling of the iodide and triflate moieties of **244** would complete the macrocycle, as well as the total synthesis of telomestatin (**189**).[21,42,43,44]

Scheme 4.2.6



4.3 Conclusion

In conclusion, we have developed an extremely promising route to deliver the potent telomerase inhibitor (*R*)-telomestatin (**189**) from readily available ethyl isocyanoacetate (**217**) and *L*-serine (**192**). Our convergent synthesis employs palladium-mediated cross-coupling reactions to assemble oligooxazole intermediates from oxazole

building blocks. Additionally, this strategy utilizes a minimum number of protecting groups, and proposes a unique aryl–aryl macrocyclization as the last step of the synthesis.

In addition to the biological relevance of the desired target, a successful total synthesis of telomestatin using our approach would also enable rapid access to the preparation of telomestatin analogs. This would allow for the investigation of key interactions between telomestatin and the G-quadruplex, as well as the examination of the predictions generated by previous computer modeling studies, especially the still unresolved question of whether telomestatin actually facilitates the formation of the G-quadruplex, stabilizes the G-quadruplex, or does both.

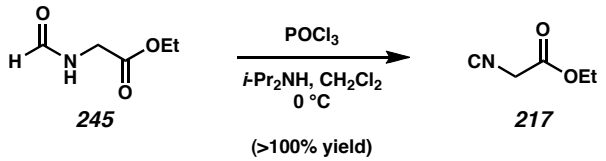
4.4 Experimental Section

4.4.1 Materials and Methods

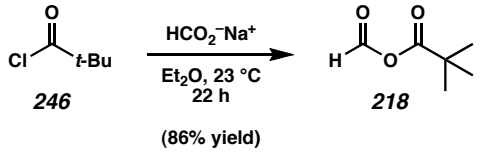
Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (either freshly distilled or passed through activated alumina columns). All commercially obtained reagents were used as received. Reaction temperatures were controlled using an IKAmag temperature modulator. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm) and visualized using a combination of UV, anisaldehyde, ceric ammonium molybdate, and potassium permanganate staining. ICN silica gel (particle size 0.032–0.063 mm) or SiliCycle Silia*Flash* P60 Academic silica gel (particle size 0.040–0.063 mm; pore diameter 60 Å) was used for flash column chromatography. ^{1}H NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz), or a Varian Inova 500 (at 500 MHz) 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. ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 75 MHz), or a Varian Inova 500 (at 125 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{13}C NMR spectra are reported in terms of chemical shift (δ ppm) and coupling constant (^{19}F, Hz). ^{19}F NMR spectra were recorded on a Varian Mercury 300 (at 282 MHz) and are reported relative to external F_3CCO_2H standard (δ –76.53). Data for ^{19}F NMR spectra are reported in terms of chemical shift (δ ppm). IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer or a Perkin Elmer Spectrum BXII spectrometer and are reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-1010 polarimeter. High-resolution mass spectra were obtained

from the California Institute of Technology Mass Spectral Facility. X-Ray crystallographic data were obtained from the California Institute of Technology Beckman Institute X-Ray Crystallography Laboratory.

4.4.2 Preparative Procedures

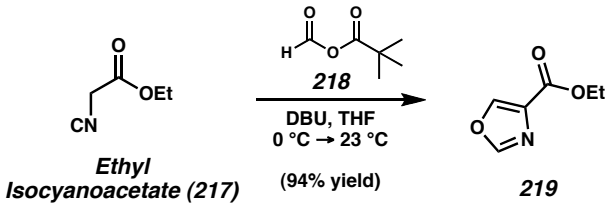


Ethyl Isocyanoacetate (217). To a solution of *N*-formylglycine ethyl ester (**245**, 52.9 mL, 403.4 mmol) in CH_2Cl_2 (330 mL) at 0 °C was added *i*-Pr_2NH (142 mL, 1.013 mol). $POCl_3$ (41.0 mL, 447.9 mmol) was added dropwise over 1 h (1 drop/s addition rate). The reaction was stirred for 3 h at 0 °C, then quenched by slow addition of Na_2CO_3 (90.0 g in 400 mL H_2O), keeping the internal temperature below 15 °C. After the addition was complete, the reaction was stirred for 2 h at 23 °C. CH_2Cl_2 (500 mL) and H_2O (400 mL) were added, and the phases were partitioned. The aqueous layer was further extracted with CH_2Cl_2 (2 x 250 mL). The organic layers were combined, washed with H_2O (200 mL), dried over $MgSO_4$, filtered, and evaporated in vacuo to furnish ethyl isocyanoacetate (**217**, 46.2 g, 45.6 g theoretical, >100% yield) as an orange oil. This crude material was used without any further purification. R_f 0.61 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27 (q, J = 7.1 Hz, 2H), 4.20 (s, 2H), 1.31 (t, J = 7.2 Hz, 3H). This compound is also commercially available from Aldrich (226319).



Mixed Anhydride 218.[24] To a suspension of finely powdered oven-dried sodium formate (63.78 g, 937.9 mmol) in Et_2O (590 mL) was added pivaloyl chloride (**246**, 57.7 mL, 468.7 mmol) over 2 min. The suspension was vigorously stirred at 23 °C for 22 h. The solid was removed by filtration, and the filtrate was evaporated in vacuo at 0 °C, affording mixed anhydride **218** (52.3 g, 86% yield) as a volatile, colorless oil. This material was immediately used in the next step without further purification. Characterization data for this compound have been previously reported.[24]

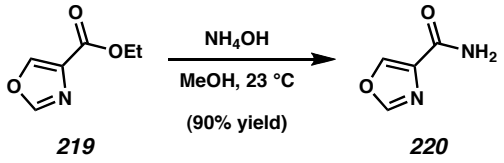
*NOTE: The rate of this heterogeneous reaction seems to be dependent on the particle size of sodium formate as well as the stirring rate. It is highly advised to monitor the reaction by ^{1}H NMR until the pivaloyl chloride (**246**) is consumed.*



Oxazole Ester 219.[25] To a stirring solution of ethyl isocyanoacetate (**217**, 5.74 g, 5.54 mL, 50.7 mmol) in THF (60 mL) at 0 °C was added DBU (15.2 mL, 101.6 mmol), followed by a solution of mixed anhydride **218** (13.2 g, 101.4 mmol) in THF (40 mL) added over 5 min. The mixture was stirred at 0 °C for 30 min, and then at 23 °C for 15 h. The reaction mixture was concentrated, and the crude product was filtered over a plug of silica gel (1:1 hexanes:EtOAc eluent). The solvent was evaporated under reduced

pressure, and the residue was purified by flash chromatography (3:2 hexanes:EtOAc eluent) to afford oxazole ester **219** (6.44 g, 90% yield) as a yellow oil, which solidified upon refrigeration.

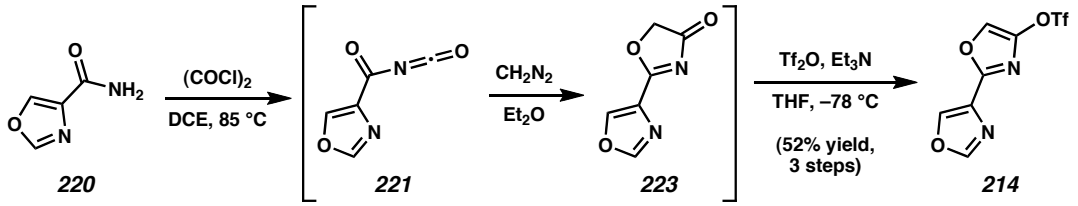
Alternate Procedure. To a solution of ethyl isocyanoacetate (**217**, 22.4 g, 197.6 mmol) in THF (221 mL) at 0 °C was added DBU (60.0 mL, 401.2 mmol), followed by additional THF (30 mL). To this solution was added freshly prepared mixed anhydride **218** (51.7 g, 397.5 mmol) in THF (120 mL) via cannula over 25 min at 0 °C, followed by additional THF (40 mL). The reaction was stirred for 4 h, and the temperature was allowed to increase gradually from 0 °C → 23 °C. EtOAc (255 mL) and H_2O (130 mL) were added, and the phases were partitioned. The aqueous layer was further extracted with EtOAc (3 x 250 mL). The organic layers were combined and washed with 0.5 M HCl (2 x 100 mL), saturated aq. Na_2CO_3 (100 mL), H_2O (100 mL), and brine (100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to yield a dark, orange oil. The crude product was purified by passage over a plug of silica gel (1:1 hexanes:EtOAc eluent) to provide oxazole ester **219** (14.80 g, 53% yield) as a yellow oil. R_f 0.43 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, J = 0.8 Hz, 1H), 7.91 (d, J = 0.8 Hz, 1H), 4.38 (q, J = 7.2 Hz, 2H), 1.37 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.2, 151.6, 144.2, 133.6, 61.5, 14.5; IR (film) 3131, 2983, 1740, 1312, 1148, 1102 cm^{-1}; HRMS-EI (*m*/*z*): $[M]^+$ calc'd for $C_6H_7NO_3$, 141.0426; found, 141.0423.



Oxazole Amide 220. To a solution of oxazole ester **219** (1.41 g, 10.0 mmol) in MeOH (25 mL) was added concentrated ammonium hydroxide (28.0–30.0% in H_2O, 25 mL) in one portion at 23 °C. After stirring at 23 °C for 3 h, the solvent was evaporated in vacuo. The crude product was adsorbed onto silica gel using MeOH as solvent, and purified by flash chromatography (10:1 $CHCl_3$:MeOH eluent) to furnish amide **220** (1.02 g, 90% yield) as a white solid.

Alternate Procedure. To a solution of oxazole ester **219** (28.92 g, 204.9 mmol) in MeOH (134 mL) was added concentrated ammonium hydroxide (28–30%, 127 mL) in one portion at 23 °C. The reaction was stirred for 11 h at 23 °C, and then the solvent was evaporated in vacuo. Following further coevaporation under reduced pressure with acetonitrile (3 x 150 mL), the crude product was dissolved in boiling EtOAc (750 mL). Solid impurities were removed by decantation, and the solution was allowed to cool to 23 °C. Hexanes (1 L) was added, and the solution was cooled to 12 °C and allowed to crystallize. The product was collected by vacuum filtration and dried further under high vac to yield oxazole amide **220** (14.30 g, 62% yield) as a pale yellow solid. The filtrate was concentrated, and the crystallization procedure was repeated to afford a second batch of **220** (3.59 g), which was combined with the first batch to provide oxazole amide **220** (17.89 g, 78% combined yield) as a pale yellow solid. R_f 0.35 (10:1 $CHCl_3$:MeOH); mp 156–158 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.56 (d, J = 1.1 Hz, 1H), 8.48 (d, J = 1.1 Hz, 1H), 7.66 (br s, 1H), 7.51 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.8, 152.2,

142.0, 135.8; IR (KBr) 3379, 3154, 3111, 1664 (br), 1413, 1111 cm^{-1}; HRMS-EI (*m/z*): $[M]^+$ calc'd for $C_4H_4N_2O_2$, 112.0273; found, 112.0271.



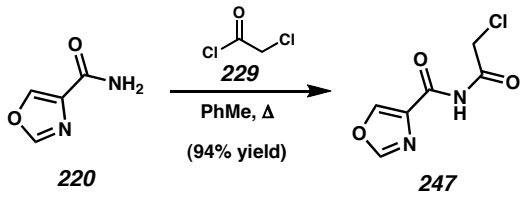
Bisoxazole Triflate 214. To oxazole amide **220** (224.0 mg, 2.0 mmol) and 1,2-dichloroethane (20 mL) in a Schlenk flask at 23 °C was added $(COCl)_2$ (0.720 mL, 8.25 mmol) in a rapid dropwise fashion. The flask was sealed, and the mixture was heated at 85 °C for 2 h. The reaction was allowed to cool to 23 °C, and the solvent was carefully evaporated in vacuo under an inert atmosphere to afford **221** as a pale yellow solid, which was immediately used in the subsequent reaction without further purification.

To crude acylisocyanate **221** dissolved in Et_2O (20 mL) was added a sodium-dried ethanol-free solution of freshly prepared CH_2N_2 in Et_2O[26] (20 mL) in a rapid dropwise fashion. When bubbling ceased, and the solution turned pale yellow, the solvent was carefully concentrated in vacuo under an inert atmosphere to afford crude oxazolone **223** as a yellow solid, which was directly used in the following step.

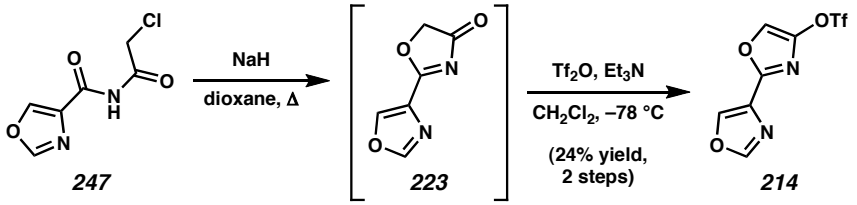
To oxazolone **223** in THF (30 mL) at –78 °C was added Et_3N (0.700 mL, 5.02 mmol), followed by dropwise addition of Tf_2O (0.512 mL, 3.04 mmol). The reaction was stirred at –78 °C for 1 h, and allowed to thaw at 23 °C for 30 min. Et_2O (30 mL) was then added, and the precipitates were removed by vacuum filtration. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography (2:1 hexanes:EtOAc eluent) to afford bisoxazole triflate **214** (298.0 mg, 52% yield, 3 steps) as

a yellow oil, which solidified upon refrigeration. R_f 0.64 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, J = 0.8 Hz, 1H), 8.00 (d, J = 0.8 Hz, 1H), 7.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 152.3, 145.8, 140.0, 129.7, 126.9, 118.8 (q, J_{CF} = 320 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ –73.2; IR (film) 3133, 1585, 1429, 1215, 1131 cm^{-1}; HRMS-EI (*m/z*): $[M]^+$ calc'd for $C_7H_3N_2O_5F_3S$, 283.9715; found, 283.9707.

*Alternate procedure for the preparation of **214**:*



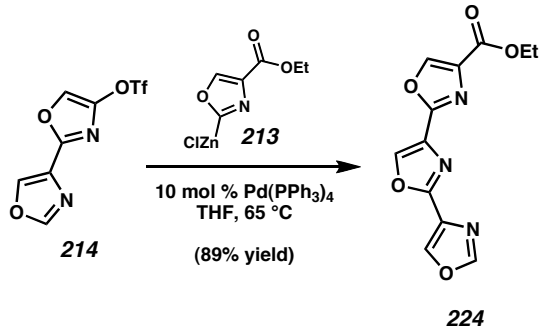
Oxazole Chloro Imide 247. To a suspension of oxazole amide **220** (3.20 g, 28.6 mmol) in toluene (30 mL) was added chloroacetyl chloride (**229**, 3.0 mL, 37.7 mmol) over 30 sec at 23 °C. The flask was fitted with reflux condenser and a drying tube containing Drierite®, and the reaction mixture was heated at 115 °C for 4.5 h under gentle reflux. The reaction was allowed to cool to 23 °C, and hexanes (150 mL) was added. After cooling to 0 °C, the product was collected by vacuum filtration, washed with hexanes (3 x 30 mL), and further dried under high vac to furnish oxazole imide **247** (5.04 g, 94% yield) as a light brown powder. R_f 0.33 (1:1 hexanes:EtOAc); mp 126–128 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.06 (br s, 1H), 8.97 (d, J = 1.1 Hz, 1H), 8.62 (d, J = 1.1 Hz, 1H), 4.73 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.5, 158.9, 152.8, 144.9, 133.9, 45.5; IR (KBr) 3307, 3139, 1734, 1700, 1578, 1471, 1287, 1188, 1095, 1050 cm^{-1}; HRMS-EI (*m/z*): $[M]^+$ calc'd for $C_6H_5N_2O_3Cl$, 187.9989; found, 187.9992.



Bisoxazole Triflate 214. To a whipped suspension of NaH (60% dispersion in mineral oil, 1.81 g, 45.3 mmol) in dioxane (725 mL) at 23 °C was added oxazole imide **247** (8.00 g, 42.4 mmol) portionwise over 1 min. The mixture was stirred at 23 °C for 15 min and then was heated at 110 °C for 40 min. After cooling to 23 °C over 1 h, the reaction mixture was filtered over a pad of Celite® (Et_2O eluent). The filtrate was coevaporated under reduced pressure with heptane (3 x 500 mL) and benzene (300 mL), and was further dried under high vac to provide oxazolone **223** as an orange solid. This material was immediately carried to the subsequent step without further purification. Although oxazolone **223** is typically used in crude form, it has been observed by ^{1}H NMR. ^{1}H NMR (300 MHz, DMSO-d_6) δ (9.31, J = 0.9 Hz, 1H), 8.75 (d, J = 0.9 Hz, 1H), 4.91 (s, 2H).

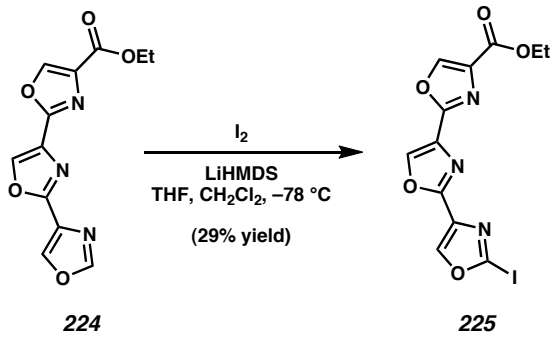
To oxazolone **223** dissolved in CH_2Cl_2 (230 mL) at –78 °C was added Et_3N (12.0 mL, 86.1 mmol) over 1 min, followed by dropwise addition of freshly prepared Tf_2O (8.6 mL, 51.1 mmol) over 2 min. The reaction was held at –78 °C for 45 min, and was then immediately warmed to 0 °C for 15 min. H_2O (100 mL) was added, and the phases were partitioned. The aqueous phase was further extracted with CH_2Cl_2 (2 x 300 mL), and the combined organics were dried over $MgSO_4$ and concentrated under reduced pressure to afford a dark colored syrup. The residue was purified by flash chromatography (7:3 hexanes:CH_2Cl_2 → 1:1 hexanes:CH_2Cl_2 eluent), and the product-containing fractions were collected and concentrated in vacuo. The crude product was further purified by flash

chromatography (4:1 hexanes:EtOAc eluent) to afford bisoxazole triflate **214** (2.927 g, 24% yield, 2 steps) as an off-white solid.



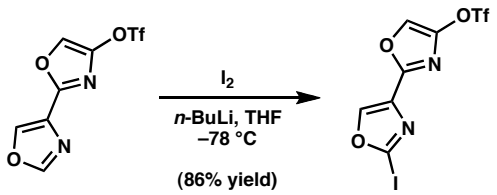
Trisoxazole Ester 224. To oxazole ester **219** (155.2 mg, 1.10 mmol) in THF (9.5 mL) at –78 °C was added LiHMDS (1.0 M in THF, 1.23 mL, 1.23 mmol) in a dropwise fashion. The reaction was stirred at –78 °C for 30 min, and then $ZnCl_2$ (0.5 M in THF, 6.70 mL, 3.35 mmol) was added over 3 min. The solution was kept at –78 °C for an additional 5 min and was then held at 0 °C for 2.5 h to deliver Negishi reagent **213**. In a separate flask was prepared a solution of bisoxazole triflate **214** (267.8 mg, 0.94 mmol), $Pd(PPh_3)_4$ (109.5 mg, 0.09 mmol), and THF (9.5 mL). This freshly prepared solution was then transferred into the flask containing Negishi reagent **213** via cannula, and the resulting mixture was heated at 65 °C for 1.5 h. After cooling to 23 °C, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and filtered over a plug of silica gel (1:1 hexanes:EtOAc → EtOAc eluent). The product containing-fractions were concentrated under reduced pressure, adsorbed onto silica gel using a 1:1 mixture of THF:CH_2Cl_2 as solvent, and purified further by flash chromatography (3:1 hexanes:EtOAc → EtOAc eluent). The product-containing fractions were concentrated in vacuo and redissolved in a minimum of hot CH_2Cl_2:THF (1:1, 4 mL). Hexanes (12 mL) was added, and the

suspension was stirred for 2 h. The solvent was carefully removed, and the solid was triturated with hexanes (2 x 10 mL). The solid was dried under high vac to provide trisoxazole ester **224** (230.4 mg, 89% yield) as a fluffy, white solid. R_f 0.31 (3:1 EtOAc:hexanes); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.10 (s, 1H), 9.05 (d, J = 1.1 Hz, 1H), 8.99 (s, 1H), 8.68 (d, J = 0.8 Hz, 1H), 4.32 (q, J = 7.2 Hz, 2H), 1.31 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.4, 155.6, 154.9, 153.6, 145.6, 141.1, 141.0, 133.5, 130.0, 128.5, 60.8, 14.1; IR (film) 3136, 1721, 1277, 1164 cm^{-1}; HRMS-FAB (m/z): [M + H]$^+$ calc'd for $C_{12}H_{10}N_3O_5$, 276.0620; found, 276.0629.



Trisoxazole Iodo Ester 225. To trisoxazole ester **224** (100.1 mg, 0.37 mmol) in THF (24 mL) and CH_2Cl_2 (13 mL) at –78 °C was added LiHMDS (1.0 M in THF, 440 μL, 0.44 mmol) dropwise. The reaction was stirred for 30 min at –78 °C, and then a solution of I_2 (138.6 mg, 0.55 mmol) in THF (2.0 mL) was added in a rapid dropwise fashion. The solution was allowed to warm slowly to 23 °C over 3 h and then was concentrated in vacuo. The residue was dissolved in a minimum of THF:CH_2Cl_2 (1:1, 7 mL) and was filtered over a plug of silica gel (1:1 EtOAc:CH_2Cl_2 eluent). The product-containing fractions were concentrated and purified by flash chromatography (6:4 CH_2Cl_2:EtOAc eluent). The solid residue was suspended in THF:CH_2Cl_2 (1:1, 4 mL) and

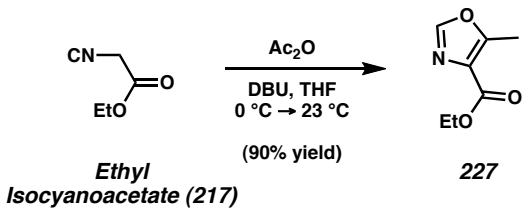
hexanes (10 mL) and vigorously triturated. Further trituration with hexanes (2 x 10 mL) and drying under high vac afforded trisoxazole iodo ester **225** (42.3 mg, 29% yield) as a yellow solid. R_f 0.35 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.12 (s, 1H), 9.10 (s, 1H), 9.00 (s, 1H), 4.32 (q, J = 7.1 Hz, 2H), 1.31 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.4, 154.8, 154.7, 146.2, 145.6, 141.1, 133.5, 131.5, 130.0, 109.3, 60.8, 14.1; IR (film) 3132, 1720, 1133 cm^{-1}; HRMS-EI (*m/z*): [M]$^+$ calc'd for $C_{12}H_8N_3O_5I$, 409.9509; found, 409.9500.



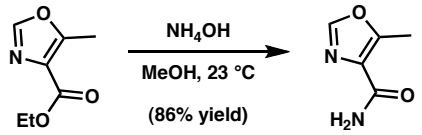
214 *226*

Bisoxazole Iodo Triflate 226. To bisoxazole triflate **214** (41.3 mg, 0.15 mmol) in THF (3.0 mL) at –78 °C was added *n*-BuLi (2.5 M in hexanes, 65 μL, 0.16 mmol) in a dropwise fashion. After stirring at –78 °C for 30 min, a separate solution of I_2 (43.9 mg, 0.17 mmol) in THF (1.0 mL) cooled to –78 °C was added via cannula. Additional THF (0.5 mL) was used to rinse the cannula, which was added to the reaction mixture. The reaction was stirred at –78 °C for 1.5 h, allowed to thaw to 23 °C, and concentrated in vacuo. The residue was purified directly by flash chromatography (3:1 hexanes:EtOAc eluent) to provide bisoxazole iodo triflate **226** (51.5 mg, 86% yield) as a yellow solid. Suitable crystals for X-ray diffraction were obtained by vapor diffusion of heptane into an EtOAc solution of **226** at 23 °C. R_f 0.30 (4:1 hexanes:EtOAc); mp 96–98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.74 (s, 1H), 7.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.0, 145.8, 145.1, 132.9, 127.1, 118.8 (q, J_{CF} = 320 Hz), 103.4; ^{19}F NMR (282 MHz,

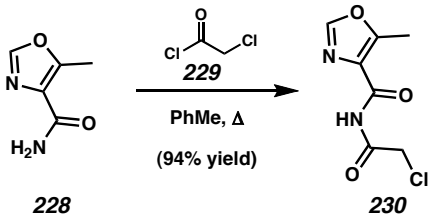
$CDCl_3$) δ –73.2; IR (film) 3451 (br), 1585, 1430, 1221 cm^{-1}; HRMS-EI (*m/z*): $[M]^+$ calc'd for $C_7H_2F_3IN_2O_5S$, 409.8681; found, 409.8693.



Methyl Oxazole Ethyl Ester 227.[35] To a solution of ethyl isocyanoacetate (**217**, 1.13 g, 10.0 mmol) in THF (12 mL) at 0 °C was added DBU (3.0 mL, 20.0 mmol), followed by dropwise addition of a solution of acetic anhydride (1.89 mL, 20.0 mmol) in THF (8 mL). The mixture was stirred at 0 °C for 30 min and then at 23 °C for 12 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography (3:2 hexanes:EtOAc eluent) to give methyl oxazole ethyl ester **227** (1.54 g, 90% yield) as a yellow oil. Characterization data for this compound have been reported previously.[35] R_f 0.47 (1:1 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (s, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 2.62 (s, 3H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 156.6, 149.0, 127.5, 61.2, 14.5, 12.1; IR (film) 3129, 2983, 1716, 1615, 1105 cm^{-1}; HRMS-EI (*m/z*): $[M]^+$ calc'd for $C_7H_9NO_3$, 155.0582; found, 155.0585.

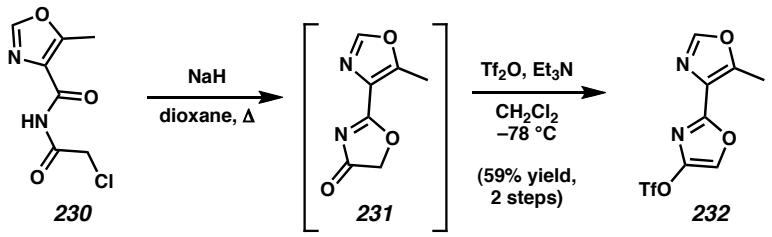


Methyl Oxazole Amide 228. To a solution of methyl oxazole ester **227** (1.55 g, 10 mmol) in MeOH (25 mL) was added concentrated ammonium hydroxide (28–30%, 25 mL) in one portion at 23 °C. The reaction mixture was stirred at 23 °C for 66 h, and then the solvent was evaporated under reduced pressure. The crude product was adsorbed onto silica gel using MeOH as solvent, and purified by flash chromatography (12:1 $CHCl_3$:MeOH eluent) to yield methyl oxazole amide **228** (1.07 g, 86% yield) as a white solid. R_f 0.41 (10:1 $CHCl_3$:MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.29 (s, 1H), 7.48 (br s, 1H), 7.40 (br s, 1H), 2.55 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.1, 152.4, 149.4, 128.6, 11.2; IR (KBr) 3391, 3154, 1690, 1621, 1193, 1121 cm^{-1}; HRMS-EI (*m*/*z*): $[M]^+$ calc'd for $C_5H_6N_2O_2$, 126.0429; found, 126.0435.



Methyl Oxazole Chloro Imide 230. To methyl oxazole amide **228** (732.6 mg, 5.81 mmol) in toluene (6 mL) was added chloroacetyl chloride (**229**, 650 μL, 8.17 mmol) over 30 sec at 23 °C. The flask was fitted with reflux condenser and a drying tube containing Drierite®, and the reaction mixture was heated at 115 °C for 9 h under gentle reflux. The reaction was allowed to cool to 23 °C, and hexanes (50 mL) was added. The suspension was vigorously stirred for 2 h at 23 °C. The product was collected by vacuum

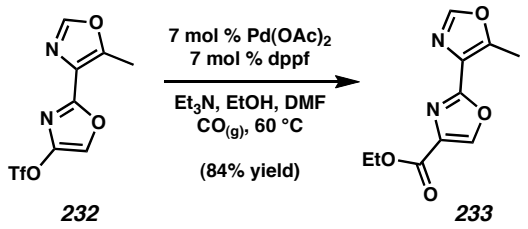
filtration, rinsed with hexanes (3 x 10 mL), and further dried under high vac to afford methyl oxazole chloro imide **230** (1.10 g, 94% yield) as a white solid. R_f 0.50 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.64 (br s, 1H), 8.48 (s, 1H), 4.70 (s, 2H), 2.61 (s, 3H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 166.8, 159.9, 156.3, 150.0, 127.3, 45.0, 11.5; IR (film) 3261, 1732, 1724, 1704, 1614, 1482, 1180 cm^{-1}; HRMS-EI (*m/z*): $[M]^+$ calc'd for $C_7H_7N_2O_3Cl$, 202.0145; found, 202.0142.



Methyl Bisoxazole Triflate 232. To a well-stirred suspension of NaH (60% dispersion in mineral oil, 251.2 mg, 6.28 mmol) in dioxane (90 mL) was slowly added chloro imide **230** (1.096 g, 5.41 mmol) over 1 min at 23 °C. After stirring 15 min at this temperature, the reaction was heated at 110 °C for 40 min and then allowed to cool at 23 °C for 20 min, and then at 10 °C for 30 min. The mixture was filtered over a pad of Celite® (Et_2O eluent), and then evaporated in vacuo, coevaporating with heptane (3 x 100 mL) and benzene (50 mL). Trace volatiles were removed by high vac to afford oxazolone **231**, which was immediately used in the subsequent reaction.

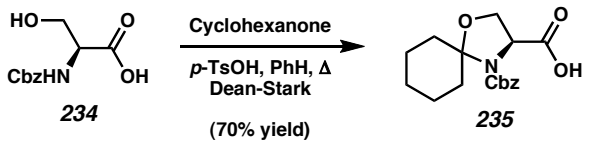
To a solution of oxazolone **231** in CH_2Cl_2 (30 mL) at –78 °C was added Et_3N (1.5 mL, 10.8 mmol) dropwise over 1 min. Freshly prepared Tf_2O (1.1 mL, 6.5 mmol) was then added dropwise over 2 min. After stirring for 45 min at –78 °C, the reaction was immersed in a 0 °C bath for 15 min. The reaction was quenched at 0 °C by the addition of H_2O (100 mL), and the phases were partitioned. The aqueous phase was further extracted

with CH_2Cl_2 (3 x 100 mL). The combined organics were washed with brine (30 mL), dried over $MgSO_4$, and evaporated in vacuo. The crude product was purified by flash chromatography (4:1 hexanes:EtOAc eluent) to afford methyl bisoxazole triflate **232** (955.6 mg, 59% yield, 2 steps) as an orange solid. R_f 0.19 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.73 (s, 1H), 2.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 152.2, 150.3, 145.9, 126.3, 124.4, 118.8 (q, J_{CF} = 321 Hz), 11.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ –73.2; IR (film) 3133, 1647, 1589, 1435, 1229, 1137 cm^{-1}; HRMS-EI (*m/z*): $[M]^+$ calc'd for $C_8H_5N_2O_5F_3S$, 297.9871; found, 297.9862.



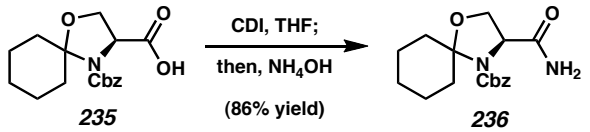
Methyl Bisoxazole Ethyl Ester 233. Methyl bisoxazole triflate **232** (1.46 g, 4.90 mmol), $Pd(OAc)_2$ (77.2 mg, 0.34 mmol), 1,1'-bis(diphenylphosphino)ferrocene (190.9 mg, 0.34 mmol), and DMF (27 mL) were combined in a 250 mL sealable Schlenk flask. EtOH (5.8 mL, 99.3 mmol) and Et_3N (1.9 mL, 13.6 mmol) were rapidly added, and the solution was sparged with carbon monoxide gas for 15 min. The flask was sealed and heated at 60 °C for 12 h. The solution was allowed to cool to 23 °C, and was sparged with argon for 15 min *(Caution: CO gas!)*. EtOAc (300 mL) and H_2O (100 mL) were added, and the phases were separated. The aqueous layer was further extracted with EtOAc (2 x 200 mL). The combined organics were washed with 0.1 M HCl (50 mL), H_2O (50 mL), and brine (50 mL), dried over $MgSO_4$, and evaporated in vacuo. Purification by flash chromatography (7:1 CH_2Cl_2:EtOAc eluent) furnished methyl

bisoxazole ethyl ester **233** (913.5 mg, 84% yield) as a brown-tan solid. R_f 0.35 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.82 (s, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 2.74 (s, 3H), 1.38 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 156.7, 151.7, 149.9, 143.5, 134.7, 124.5, 61.5, 14.5, 11.9; IR (film) 3127, 2983, 1739, 1720, 1576, 1316, 1113 cm^{-1}; HRMS-EI (*m/z*): $[M]^+$ calc'd for $C_{10}H_{10}N_2O_4$, 222.0641; found, 222.0648.

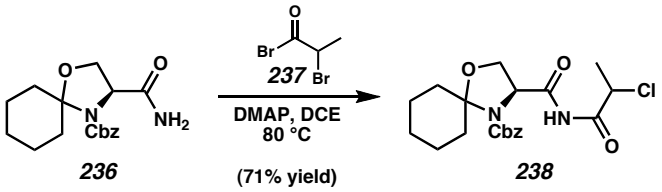


Acid 235. To *N*-Cbz-serine[36] (**234**, 5.0 g, 20.9 mmol) in benzene (150 mL) was added cyclohexanone (3.0 mL, 28.9 mmol) and *p*-toluenesulfonic acid (420 mg, 2.2 mmol). The mixture was heated to reflux under a Dean-Stark trap for 18 h and then was allowed to cool to 23 °C. The reaction mixture was poured over saturated aq. $NaHCO_3$ (100 mL), and the phases were partitioned. The aqueous phase was further extracted with Et_2O (2 x 100 mL), and the combined organics were extracted with saturated aq. $NaHCO_3$ (2 x 100 mL). The aqueous phases were all combined, acidified to pH = 2 using 3 M HCl, and extracted with EtOAc (2 x 150 mL). The combined EtOAc extracts were washed with 1 N HCl (40 mL) and brine (40 mL), dried over $MgSO_4$, and concentrated in vacuo to provide acid **235** (4.64 g, 70% yield) as an off-white foam. R_f 0.24 (1:1 hexanes:EtOAc; 1% acetic acid); ^{1}H NMR (500 MHz, C_6D_6, 70 °C, mixture of rotamers) δ 7.24–7.03 (comp. m, 5H), 5.09 (d, *J* = 12.7 Hz, 1H), 5.02 (d, *J* = 12.4 Hz, 1H), 4.31–4.24 (m, 1H), 3.95–3.80 (m, 1H), 3.65–3.58 (m, 1H), 2.83–1.00 (comp. m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$, major rotamer) δ 177.0, 152.0, 136.5, 128.7 (2C), 128.2,

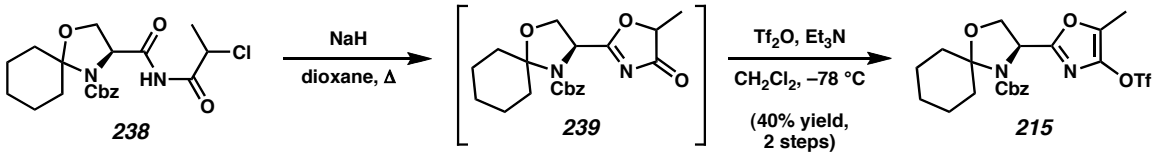
127.9 (2C), 97.2, 67.1, 66.6, 58.8, 33.5, 31.6, 24.8, 23.5, 23.4; IR (film) 2935 (br), 1713 (br), 1415, 1351, 1211, 1085 cm^{-1}; HRMS-EI (*m/z*): $[M]^+$ calc'd for $C_{17}H_{21}O_5N$, 319.1240; found, 319.1435; $[\alpha]^{20}_D$ –26.99° (*c* 1.0, MeOH).



Amide 236. To acid **235** (6.12 g, 19.2 mmol) in THF (80 mL) at 23 °C was added 1,1'-carbonyldiimidazole (6.15 g, 37.9 mmol) in one portion. The reaction was stirred for 15 min, then concentrated ammonium hydroxide (28.0–30.0% in H_2O, 20 mL) was added in a steady stream. After 3 h of additional stirring at 23 °C, the reaction mixture was poured over EtOAc (200 mL) and 10% aq. citric acid (100 mL). The phases were partitioned, and the organic extract was washed with 1 M HCl (5 x 50 mL) until the pH of the aqueous phase was less than 2. The organic phase was further washed with saturated aq. $NaHCO_3$ (50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo to yield amide **236** (5.24 g, 86% yield) as a white foam. R_f 0.42 (3:1 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C, mixture of rotamers) δ 7.37–7.27 (comp. m, 5H), 6.02 (br s, 1H), 5.31 (br s, 1H), 5.18 (d, *J* = 12.2 Hz, 1H), 5.13 (d, *J* = 12.4 Hz, 1H), 4.40 (app. d, *J* = 6.6 Hz, 1H), 4.31–4.20 (m, 1H), 2.05 (app. t, *J* = 7.9 Hz), 2.51–2.33 (m, 1H), 2.24–2.11 (m, 1H), 1.72–1.45 (comp. m, 7H), 1.28–1.10 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ 173.8 (br), 136.1, 128.8 (2C), 128.5, 128.1 (2C), 97.1, 67.4 (br), 67.2 (br), 60.4, 35.4 (br), 29.9 (br), 24.8, 23.5, 23.3; IR (film) 3335, 3197, 2934, 1694 (br), 1410, 1349, 1084 cm^{-1}; HRMS-EI (*m/z*): $[M]^+$ calc'd for $C_{17}H_{22}N_2O_4$, 319.1580; found, 318.1584; $[\alpha]^{19}_D$ –19.56° (*c* 0.5, MeOH).



Chloroimide 238. To amide **236** (0.80 g, 2.51 mmol) in 1,2-dichloroethane (17 mL) at 23 °C was added DMAP (590.9 mg, 4.84 mmol), followed by dropwise addition of 2-bromopropionyl bromide (**237**, 470 μL, 4.49 mmol). The solution was heated at 80 °C for 3 h and was then allowed to cool to 23 °C. The reaction mixture was purified directly by flash chromatography (7:1 hexanes:EtOAc → 4:1 hexanes:EtOAc eluent) to afford chloroimide **238** (0.73 g, 71% yield) as a colorless oil. R_f 0.20 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C, mixture of rotamers) δ 8.86 (br s, 1H), 7.36–7.26 (comp. m, 5H), 5.20–5.05 (m, 2H), 4.92–4.87 (m, 1H), 4.61–4.47 (m, 1H), 4.24–4.08 (comp. m, 2H), 2.55–1.10 (comp. m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers) δ 171.0 (br), 169.2, 136.1, 128.8 (2C), 128.4, 128.1, 128.0, 97.4 (br), 67.4 (br), 61.5 (br), 54.9, 54.7, 34.3 (br), 31.0 (br), 24.8, 23.5, 21.6, 21.5; IR (film) 3275, 3208, 2936, 1743, 1715, 1413, 1348, 1204 cm^{-1}; HRMS-FAB (*m*/*z*): $[M + H]^+$ calc'd for $C_{20}H_{26}N_2ClO_5$, 409.1530; found, 409.1525; $[\alpha]^{20}_D$ –44.89° (*c* 1.0, MeOH).



Methyl Oxazole Triflate 215. To a slurry of NaH (60% dispersion in mineral oil, 105.9 mg, 2.65 mmol) in dioxane (24 mL) at 23 °C was added a solution of chloroimide **238** (1.00 g, 2.45 mmol) in dioxane (13 mL) in a steady stream. Immediately after the

addition, the flask was fitted with a reflux condenser and was heated at 110 °C for 1 h. The flask was then allowed to cool to 23 °C over 2 h and was filtered over a pad of Celite® (CH_2Cl_2 eluent). The filtrate was concentrated to a viscous, colorless oil. Benzene (10 mL) was added, and the volatiles were further evaporated in vacuo to afford oxazolone **239** as a white foam. This crude material was immediately carried to the subsequent step without further purification.

Crude oxazolone **239** was dissolved in CH_2Cl_2 (14 mL), and the resulting colorless solution was cooled to –78 °C. Et_3N (615 μL, 4.41 mmol) was added, followed by dropwise addition of Tf_2O (445 μL, 2.65 mmol). The solution was maintained at –78 °C for 2.5 h, quenched by addition of H_2O (1 mL), and allowed to thaw to 23 °C. Additional H_2O (10 mL) was added, and the phases were separated. The aqueous layer was further extracted with CH_2Cl_2 (5 x 5 mL), and the combined organics were dried over $MgSO_4$, and concentrated to a brown oil. Purification of the crude product by flash chromatography (19:1 hexanes:EtOAc eluent) gave methyl oxazole triflate **215** (499.1 mg, 40% yield, 2 steps) as a white solid. R_f 0.37 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 7.40–7.12 (comp. m, 5H), 5.20–4.90 (comp. m, 3H), 4.19–4.05 (comp. m, 2H), 2.49–1.04 (comp. m, 10H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, major rotamer) δ 158.8, 151.9, 140.6, 138.1, 136.3, 128.6 (2C), 128.3, 128.1 (2C), 118.7 (q, J_{CF} = 321 Hz), 97.2, 67.7, 67.1, 55.1, 33.7, 31.4, 24.7, 23.5, 23.5, 9.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ –73.5; IR (film) 2937, 1715, 1430, 1348, 1226, 1135 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+$ calc'd for $C_{21}H_{24}SN_2O_7F_3$, 505.1256; found, 505.1232; $[\alpha]^{20}_D$ –1.03° (*c* 1.0, MeOH).

4.5 Notes and References

(1) For a recent historical commentary regarding telomeres and telomerase, see: Blackburn, E. H.; Greider, C. W.; Szostak, J. W. *Nature Med.* **2006**, *12*, 1133–1138.

(2) Reprinted, with permission, from: Shay, J. W.; Wright, W. E. *Nat. Rev. Drug Discovery* **2006**, *5*, 577–584 (Copyright 2006 Macmillan Publishers Ltd).

(3) For recent reviews regarding telomerase and cancer therapeutics, see: (a) Incles, C. M.; Schultes, C. M.; Neidle, S. *Curr. Opin. Investig. Drugs* **2003**, *7*, 675–685. (b) Kelland, L. R. *Eur. J. Cancer* **2005**, *41*, 971–979. (c) Olaussen, K. A.; Dubrana, K.; Dornont, J.; Spano, J. P.; Sabatier, L.; Soria, J. C. *Crit. Rev. Oncol. Hematol.* **2006**, *57*, 191–214. (d) Pendino, F.; Tarkanyi, I.; Dudognon, C.; Hillion, J.; Lanotte, M.; Aradi, J.; Segal-Bendirdjian, E. *Curr. Cancer Drug Targets* **2006**, *6*, 147–180. (e) Artandi, S. E. *N. Engl. J. Med.* **2006**, *355*, 1195–1197. (f) Cian, A. D.; Lacroix, L.; Douarre, C.; Temine-Smalli, N.; Trentesaux, C.; Riou, J.-F.; Mergny, J.-L. *Biochimie* **2008**, *90*, 131–155.

(4) The composition of human telomerase has recently been reported, see: Cohen, S.; Graham, M.; Lovrecz, G.; Bache, N.; Robinson, P.; Reddel, R. *Science* **2007**, *315*, 1850–1853.

(5) An X-ray structure of the *N*-terminal domain of telomerase has recently been isolated. See: Jacobs, S. A.; Podell, E. R.; Cech, T. R. *Nat. Struct. Biol.* **2006**, *13*, 218–225.

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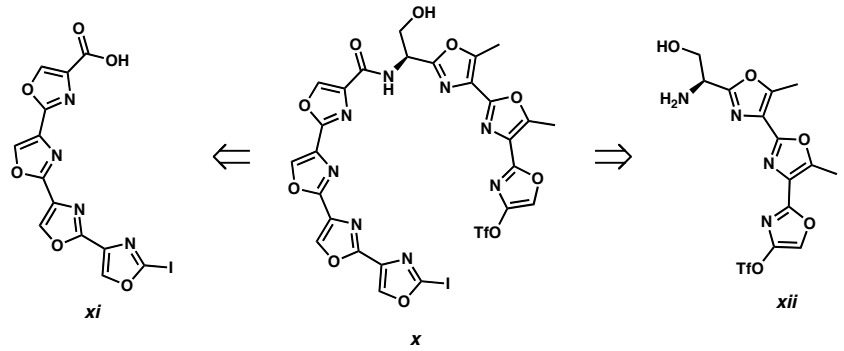

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(28) Although no characterization data or experimental details were provided, the synthesis of compound **214** via a related route was recently reported. See reference 20d.

(29) (a) See Section 4.4 Experimental Section. (b) Iodobisoxazole triflate **226** is shown with 50% probability ellipsoids (Note: Only *Molecule A* is depicted). 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 282586.

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(31) For Negishi cross-couplings of oxazoles, see: (a) Harn, N. K.; Gramer, C. J.; Anderson, B. A. *Tetrahedron Lett.* **1995**, *36*, 9453–9456. (b) Anderson, B. A.; Harn, N. K. *Synthesis* **1996**, 583–585. (c) Anderson, B. A.; Becke, L. M.; Booher, R. N.; Flaugh, M. E.; Harn, N. K.; Kress, T. J.; Varie, D. L.; Wepsiec, J. P. *J. Org. Chem.* **1997**, *62*, 8634–8639. (d) Vedejs, E.; Luchetta, L. M. *J. Org. Chem.* **1999**, *64*, 1011–1014. (e) Reeder, M. R.; Gleaves, H. E.; Hoover, S. A.; Imbordino, H. R.; Pangborn, J. *J. Org. Process Res. Dev.* **2003**, *7*, 696–699.

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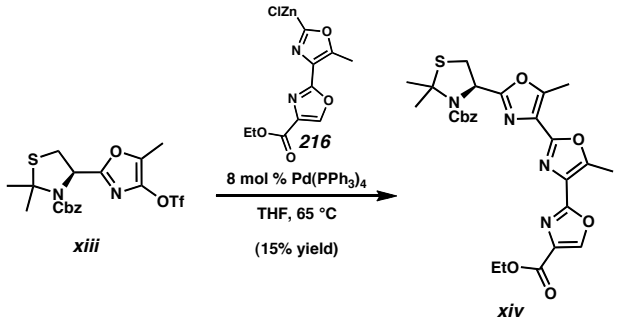
(37) The acetonide protecting group was initially employed instead of a cyclohexylidene moiety, but it was found to be labile in later steps.

(38) Cross-coupling attempts using oxazole triflate **215** and a suitable trisoxazole partner to form tetrakisoxazole triflate **243** directly were not explored, due to the near certainty of competition between the various oxazole triflates. Cross-couplings in a related system to form ester **xiv** were met with limited success.



(39) Preliminary experiments have resulted in the preparation of milligram quantities of tetrakisoxazole triflate **243** using the described route.

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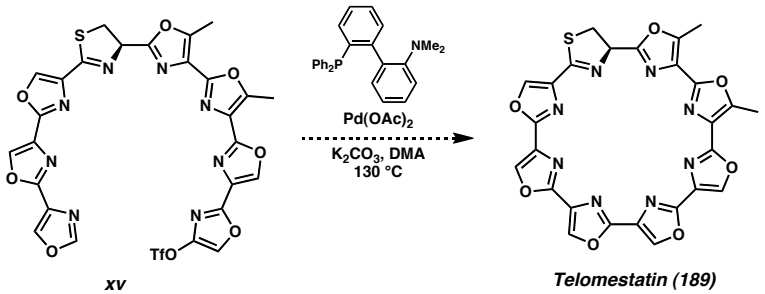
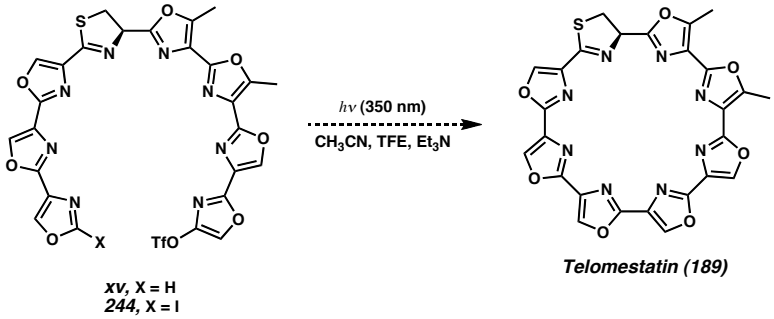
(43) An alternate macrocyclization strategy via direct arylation may also be possible (i.e., **xv** → **189**). For pertinent references, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (b) Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186–9187. (c) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581–590. (d) Miki, Y.; Shirokoshi, H.; Asai, M.; Aoki, Y.; Matsukida, H. *Heterocycles* **2003**, *60*, 2095–2101.



(44) A final macrocyclization approach involving a Witkop photocyclization would be promising option as well (i.e., **244** or **xv** → **189**). For relevant examples, see: (a) Fagnoni, M.; Albini, A. *Acc. Chem. Res.* **2005**, *38*, 713–721. (b) Burgett, A. W. G.; Li, Q.; Wei, Q.; Harran, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4961–4966. (c) De Carolis, M.; Protti, S.; Fagnoni, M.; Albini, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1232–1236. (d) Freccero, M.; Fagnoni, M.; Albini, A. *J. Am. Chem. Soc.* **2003**, *125*, 13182–13190. (e) Feldman, K. S.; Ngernmeesri, P. *Org. Lett.* **2005**, *7*, 5449–5452. (f) Mangion, I. K. "Development of Organocatalytic Direct Aldol Transformations, Total Syntheses of Brasoside and Littoralisone, and Progress Toward the Total

Synthesis of Diazonamide A." Ph.D. Thesis, California Institute of Technology, 2006. http://resolver.caltech.edu/CaltechETD:etd-05232006-210214



APPENDIX FOUR

Spectra Relevant to Chapter Four:

Progress Toward The Total Synthesis of Telomestatin

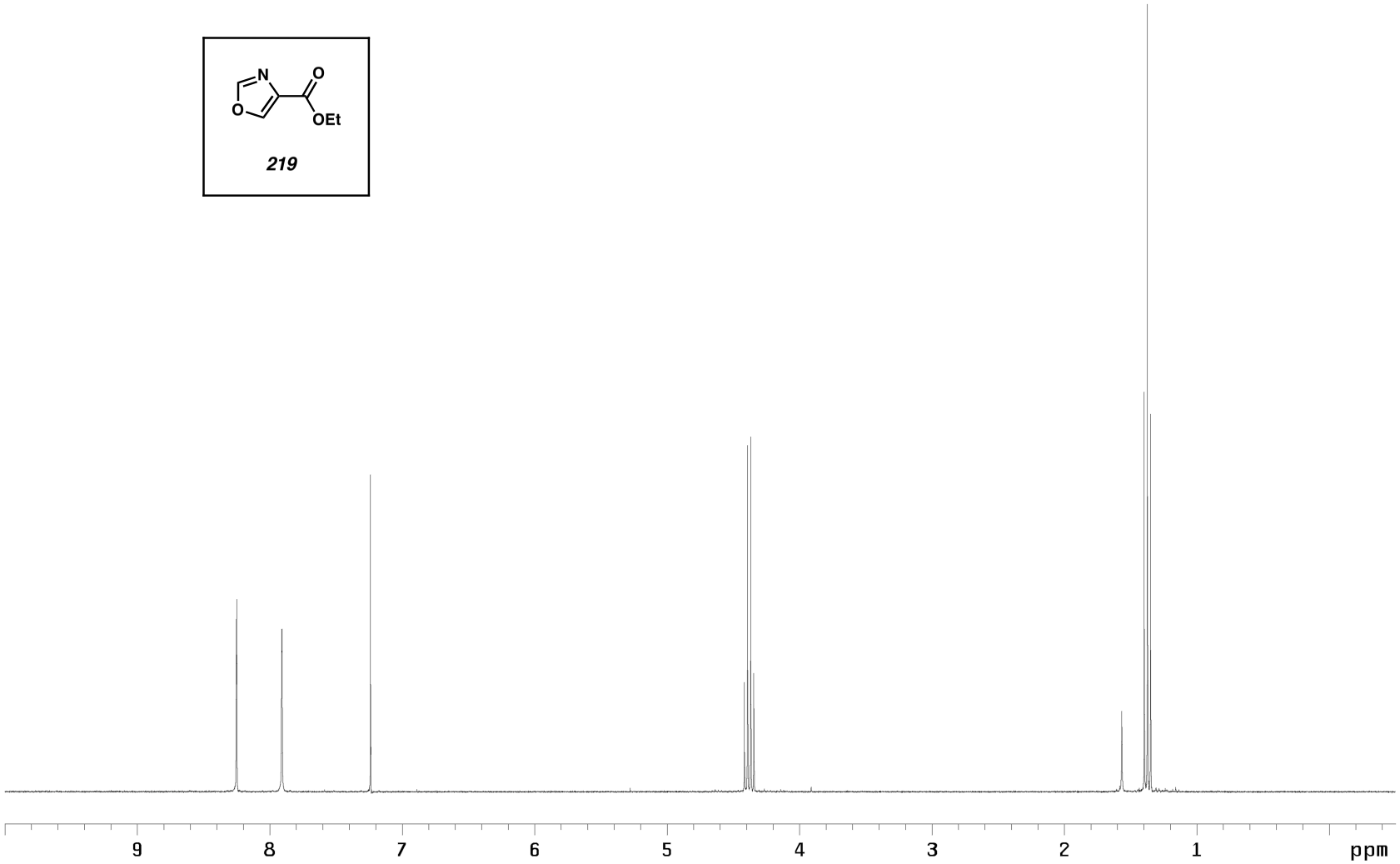


Figure A4.1 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **219**

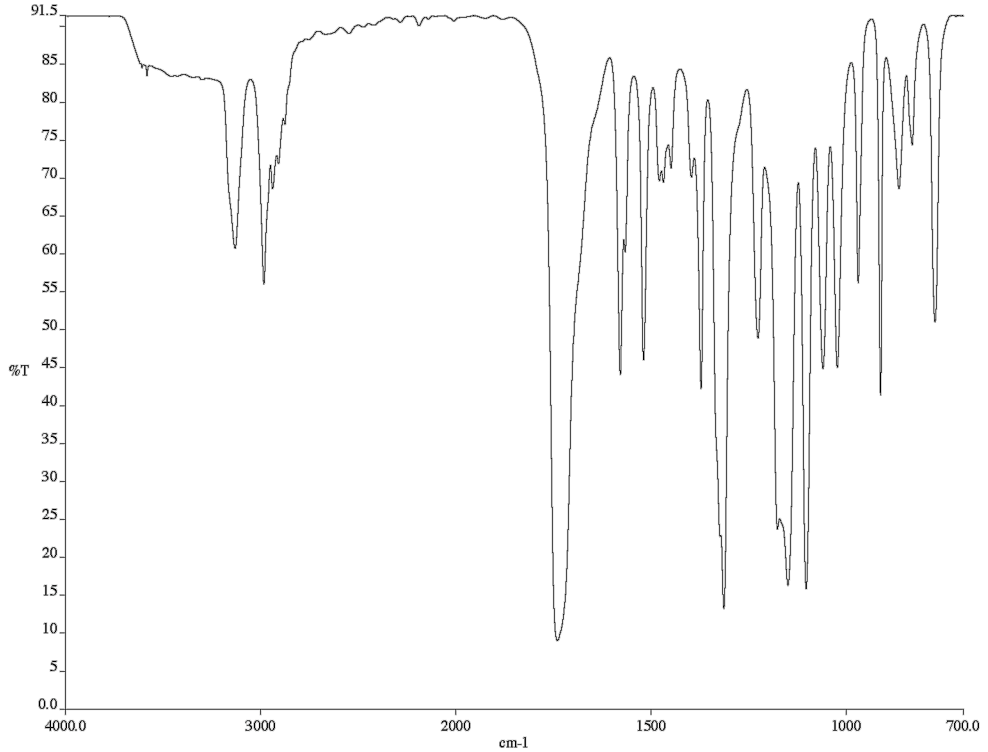


Figure A4.2 Infrared spectrum (thin film/NaCl) of compound **219**

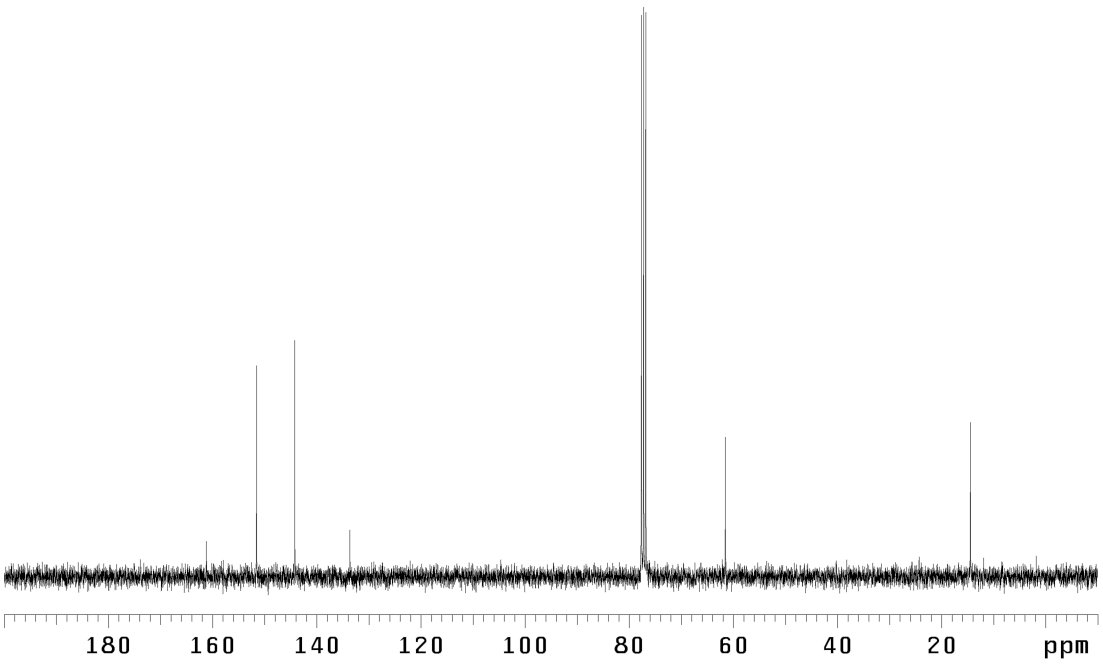


Figure A4.3 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **219**

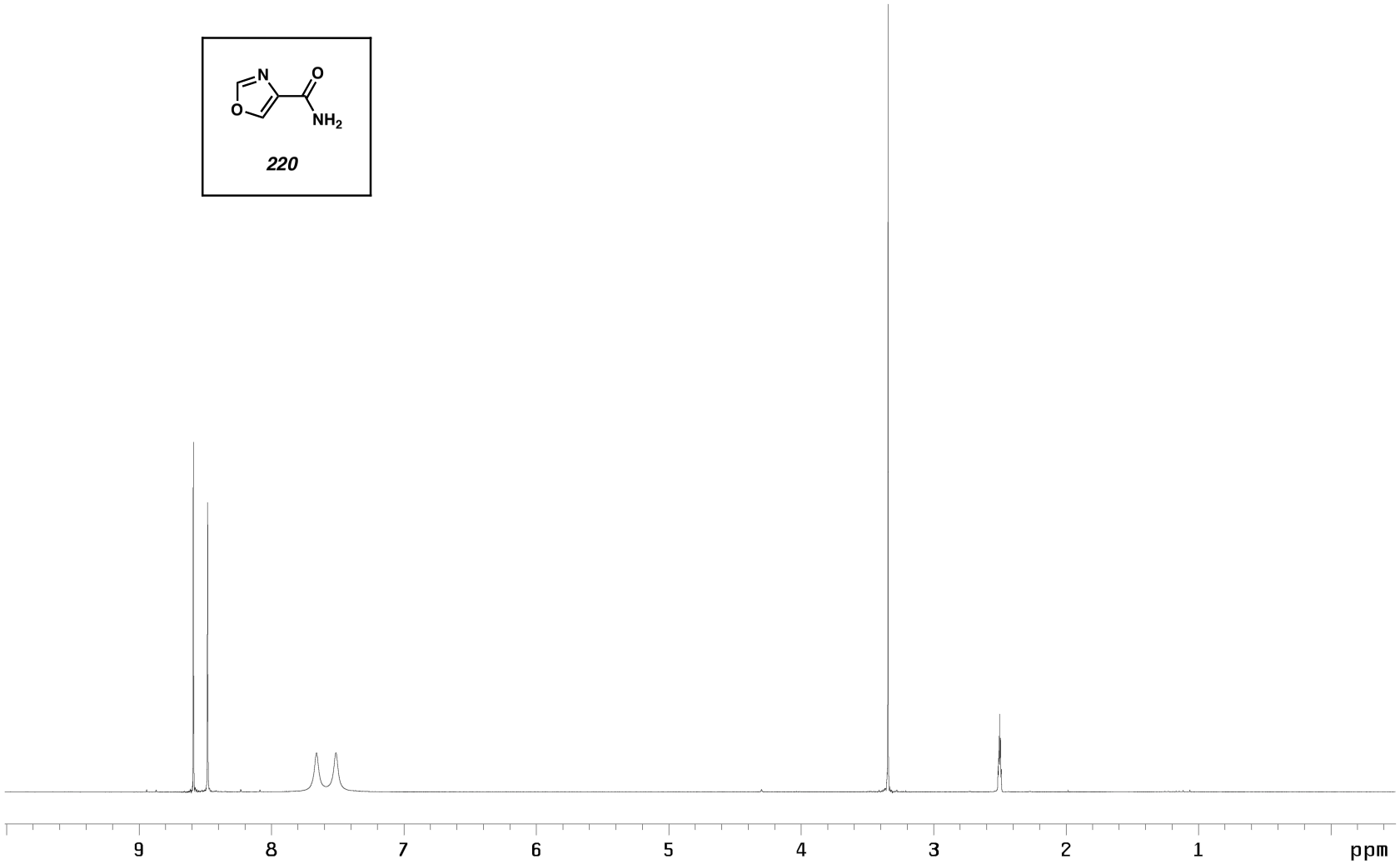


Figure A4.4 ^{1}H NMR (300 MHz, DMSO-d_6) of compound **220**

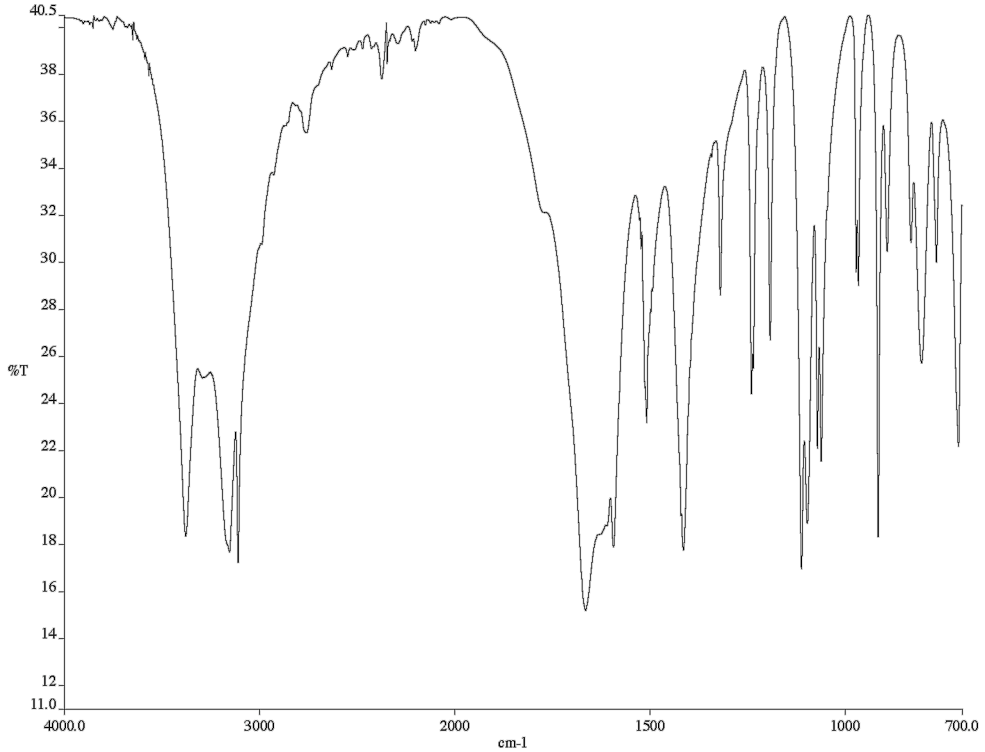


Figure A4.5 Infrared spectrum (KBr pellet) of compound **220**

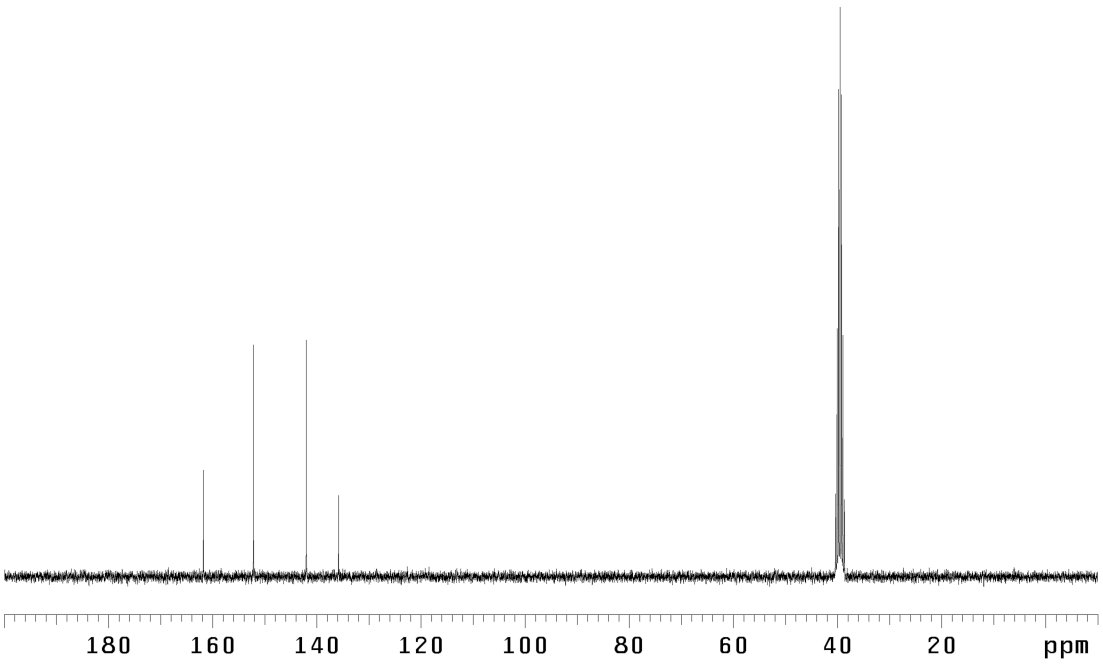


Figure A4.6 ^{13}C NMR (75 MHz, DMSO-d_6) of compound **220**

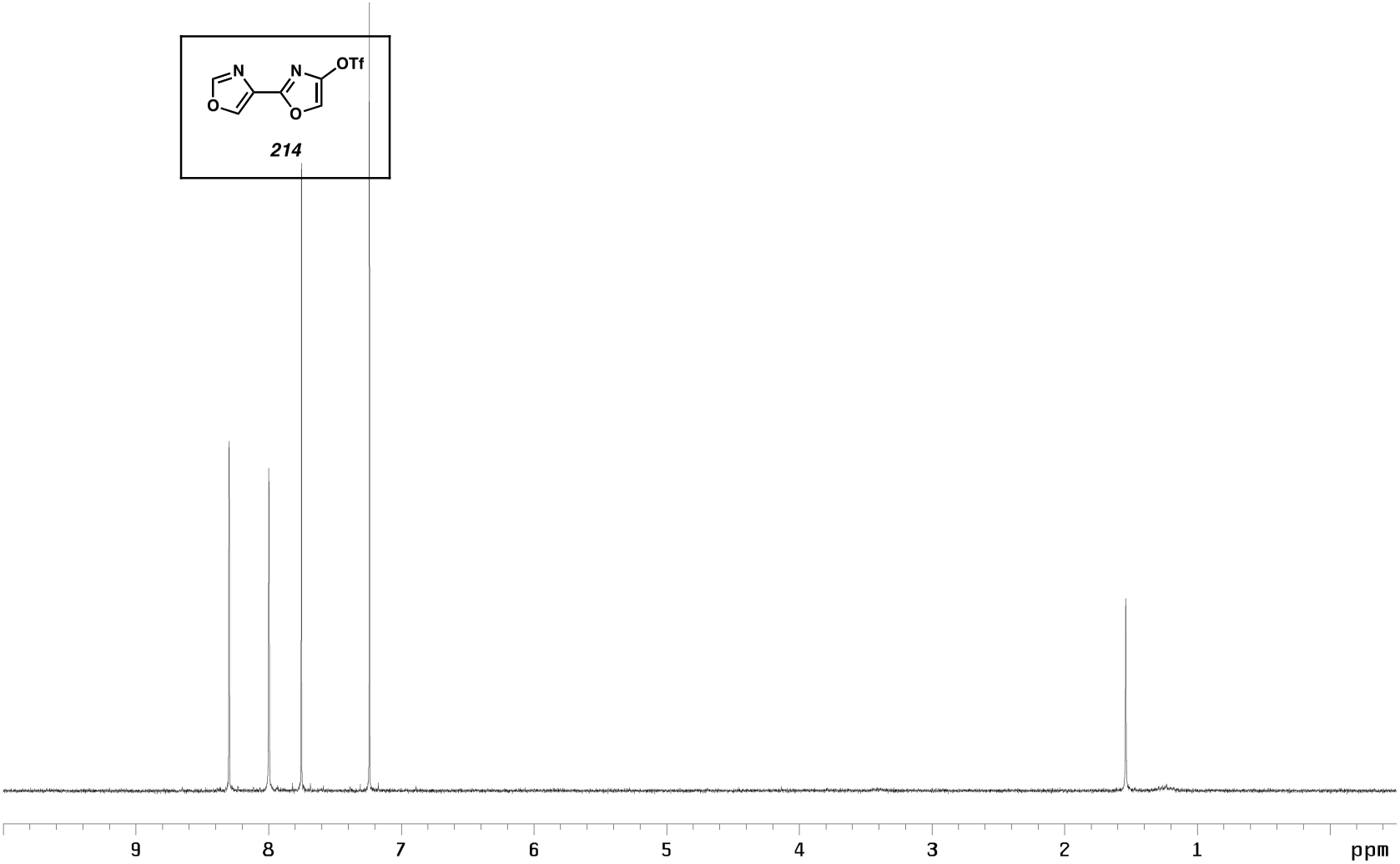


Figure A4.7 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **214**

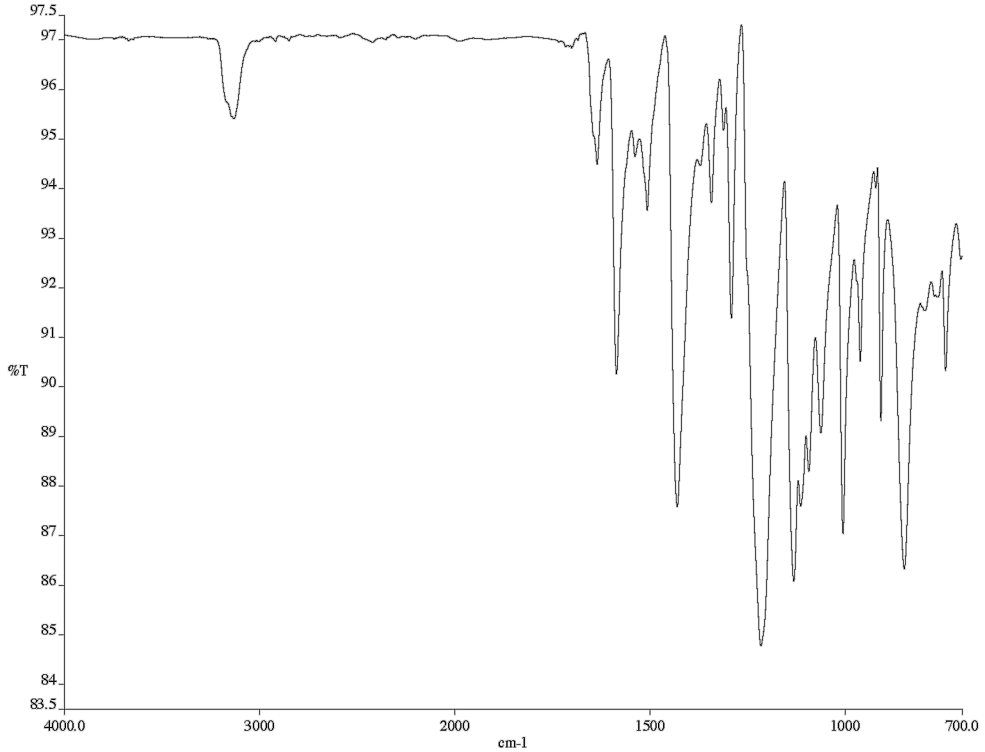


Figure A4.8 Infrared spectrum (thin film/NaCl) of compound **214**

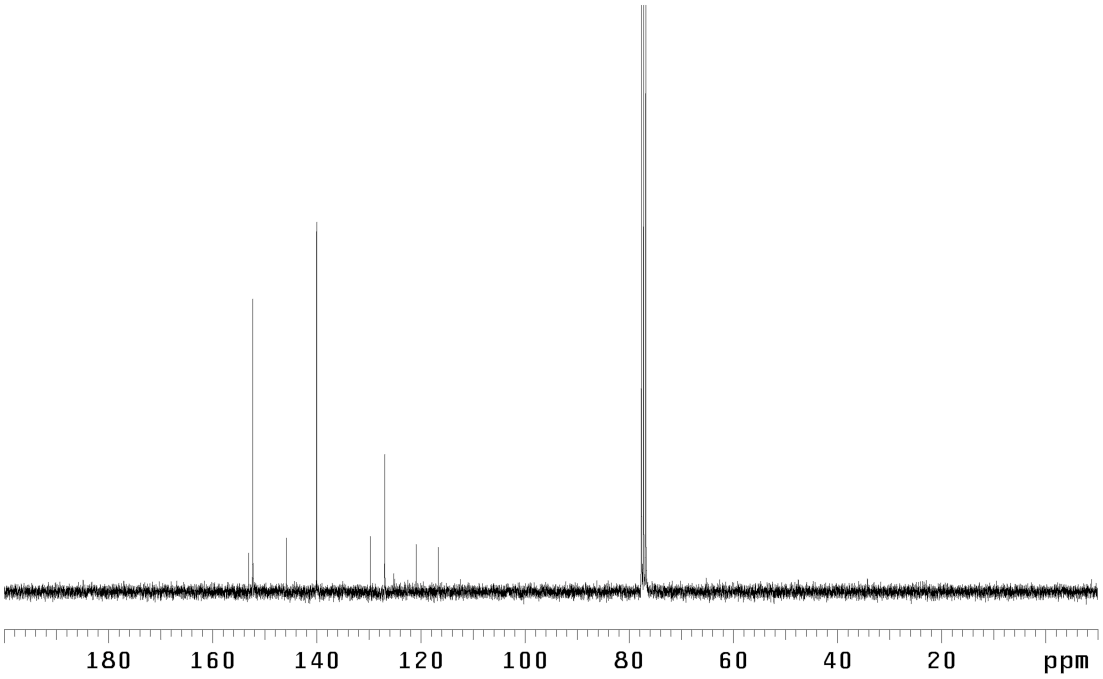


Figure A4.9 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **214**

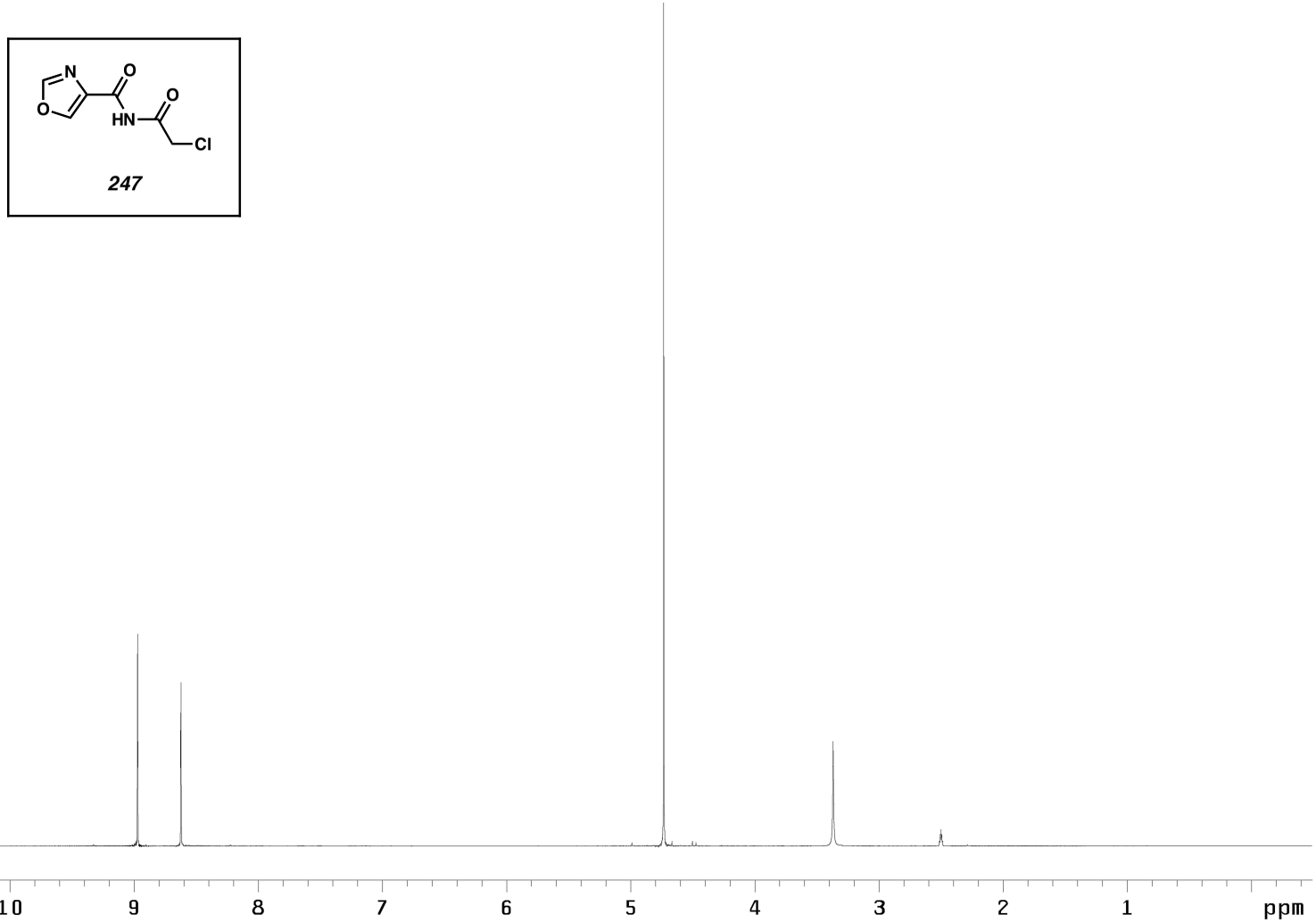


Figure A4.10 ^{1}H NMR (300 MHz, DMSO-d_6) of compound **247**

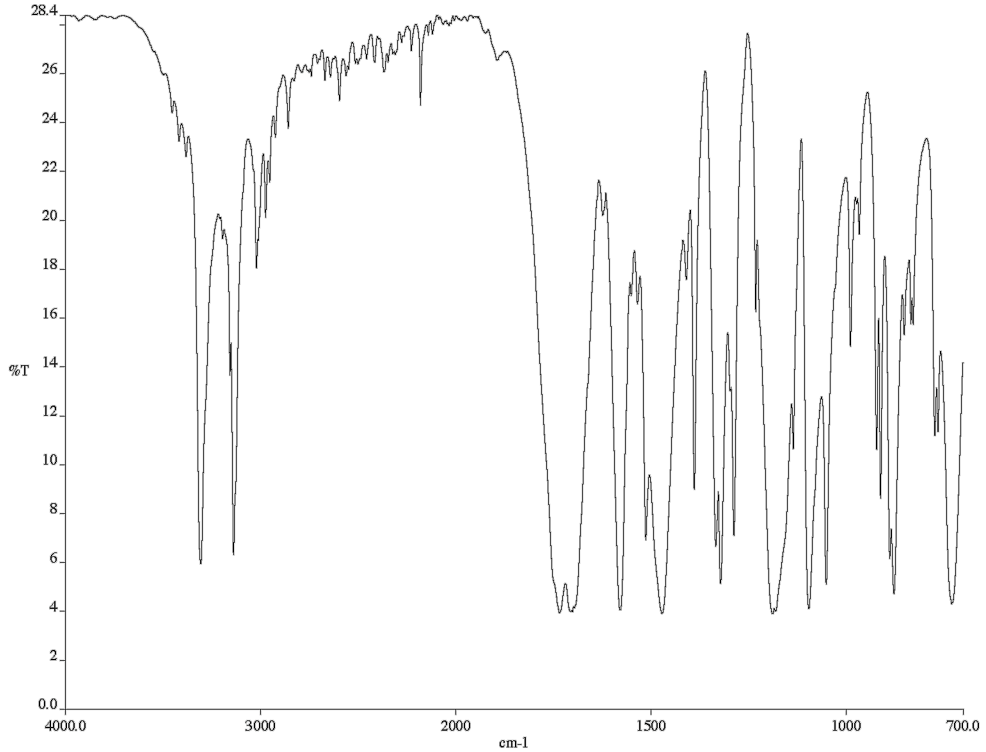


Figure A4.11 Infrared spectrum (KBr pellet) of compound **247**

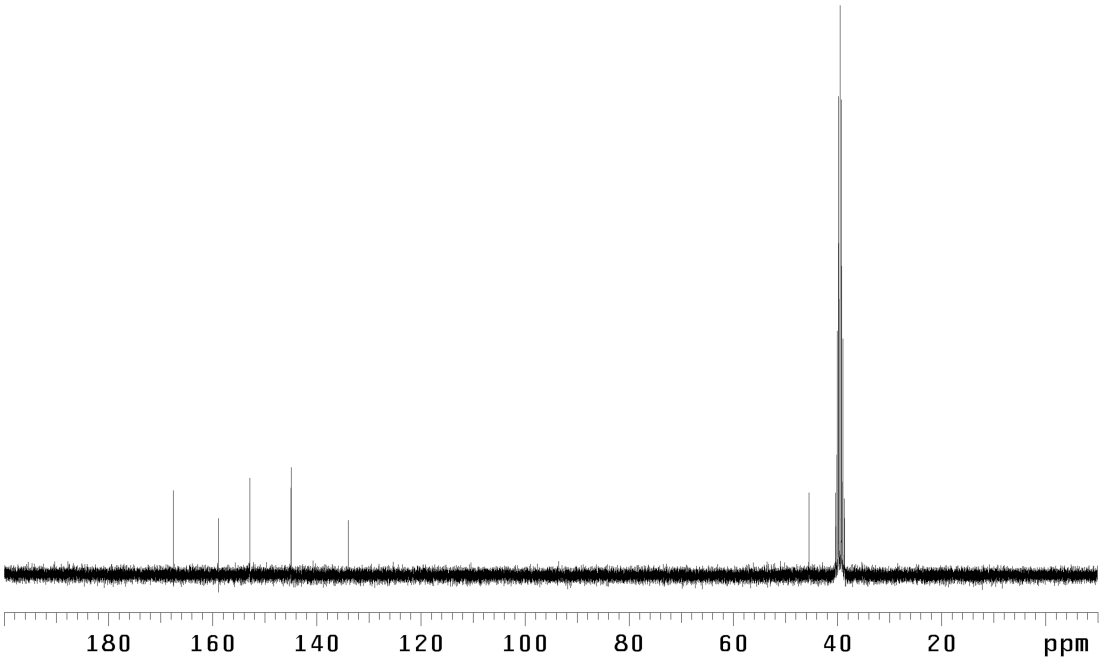


Figure A4.12 ^{13}C NMR (75 MHz, DMSO-d_6) of compound **247**

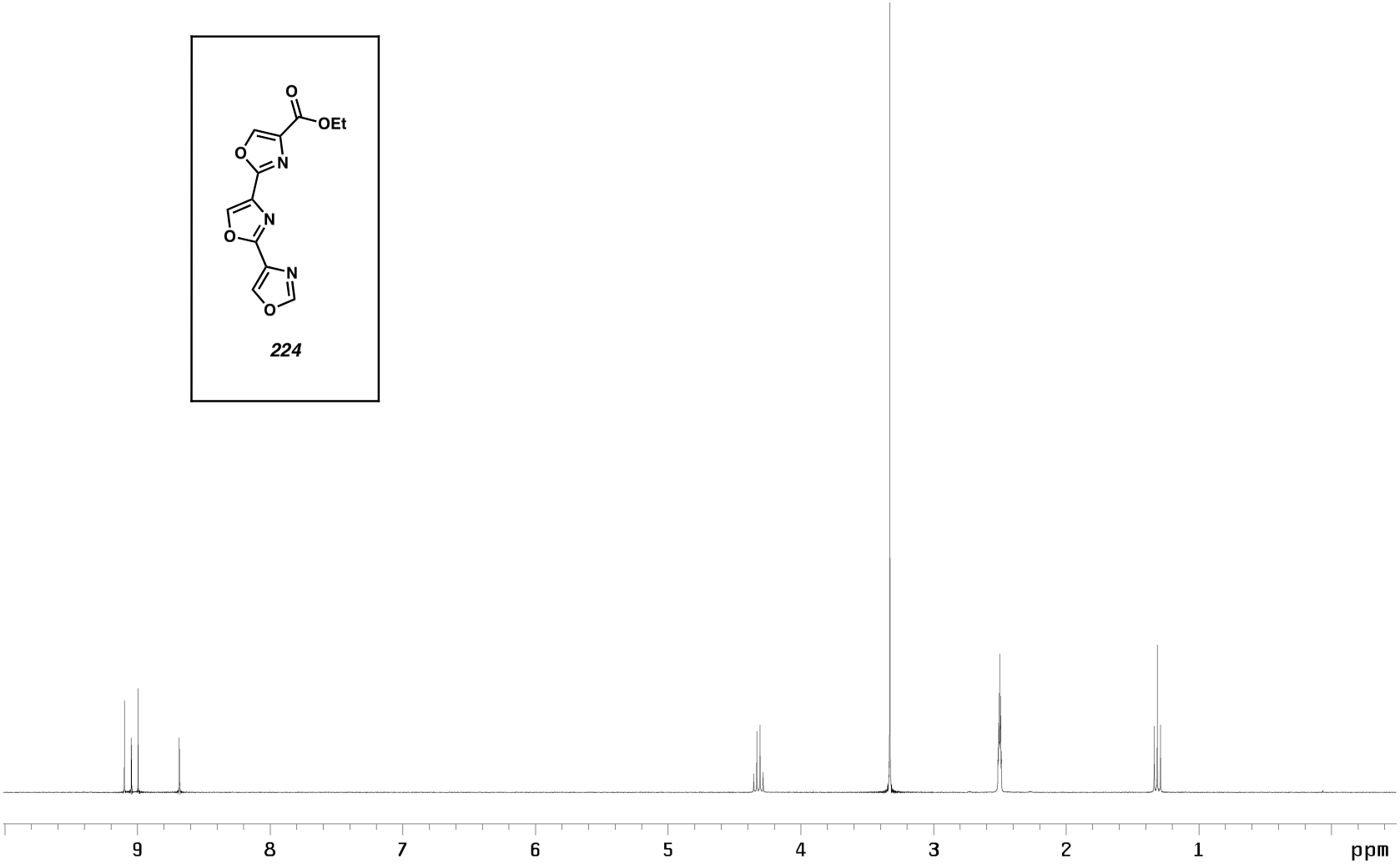


Figure A4.13 ^{1}H NMR (300 MHz, DMSO-d_6) of compound **224**

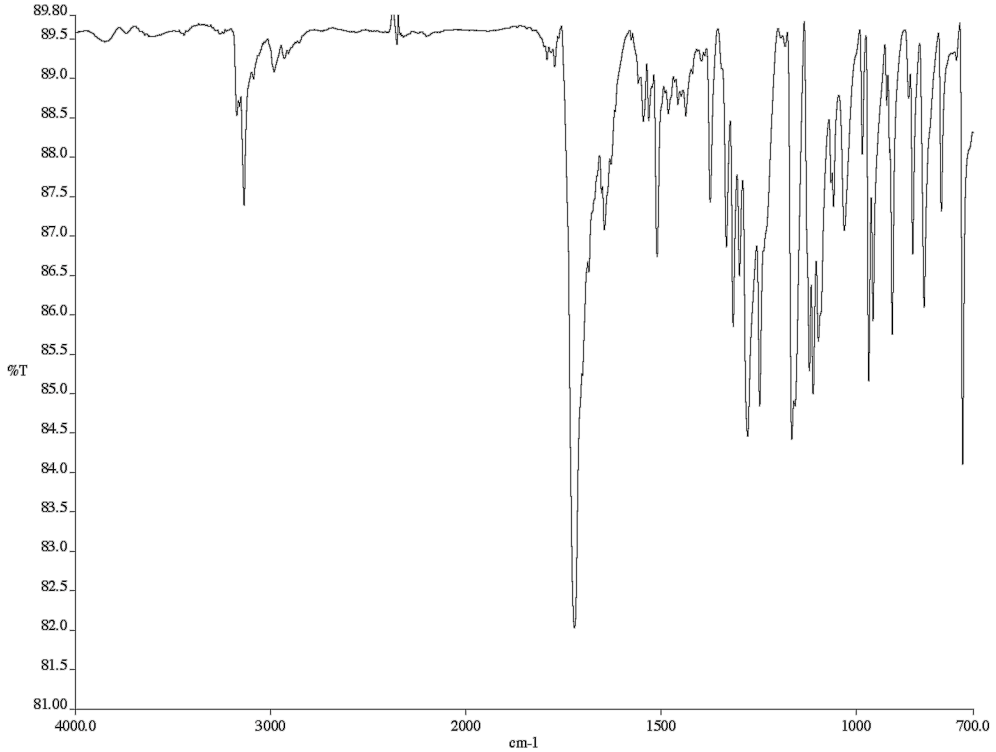


Figure A4.14 Infrared spectrum (thin film/NaCl) of compound **224**

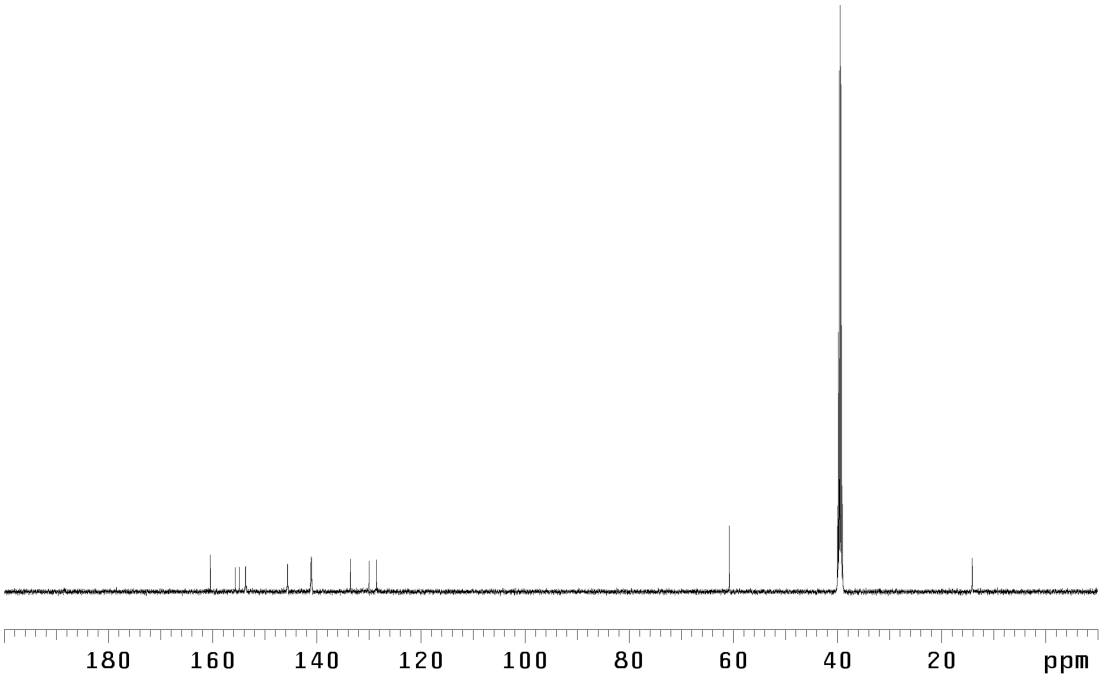


Figure A4.15 ^{13}C NMR (125 MHz, DMSO-d_6) of compound **224**

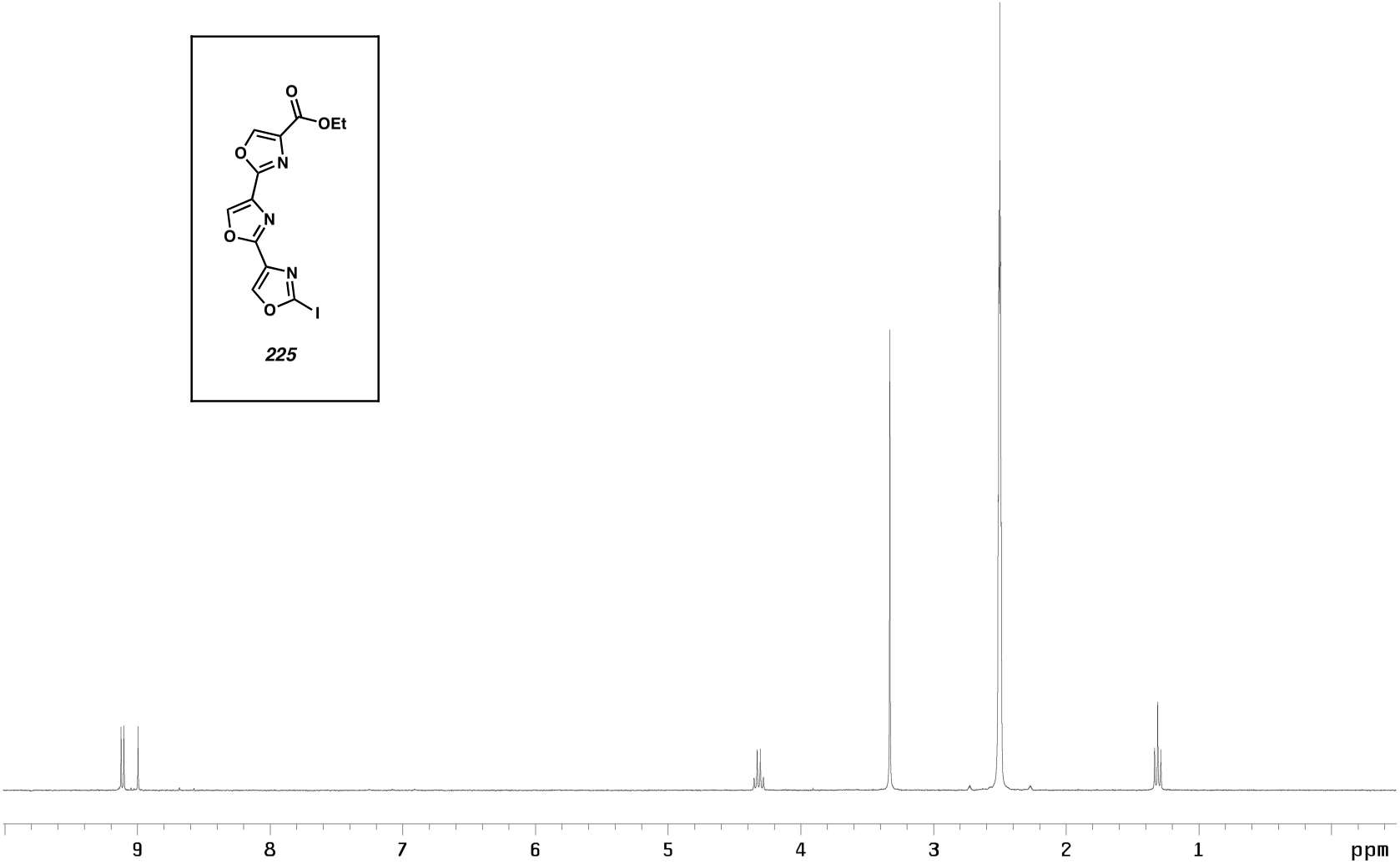


Figure A4.16 ^{1}H NMR (300 MHz, DMSO-d_6) of compound **225**

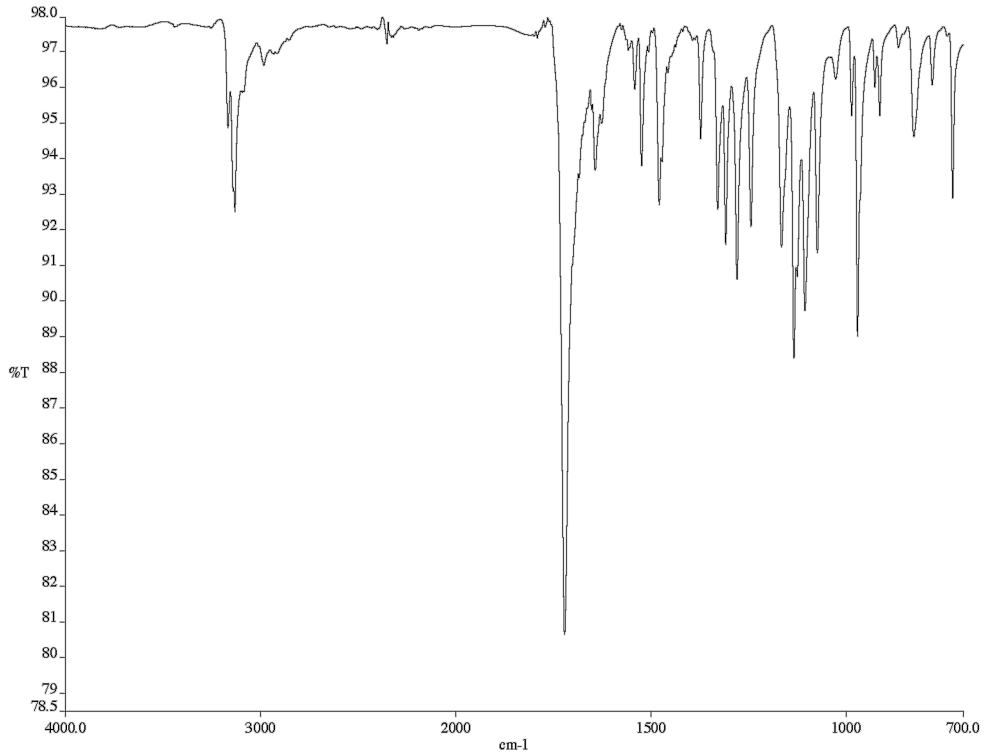


Figure A4.17 Infrared spectrum (thin film/NaCl) of compound **225**

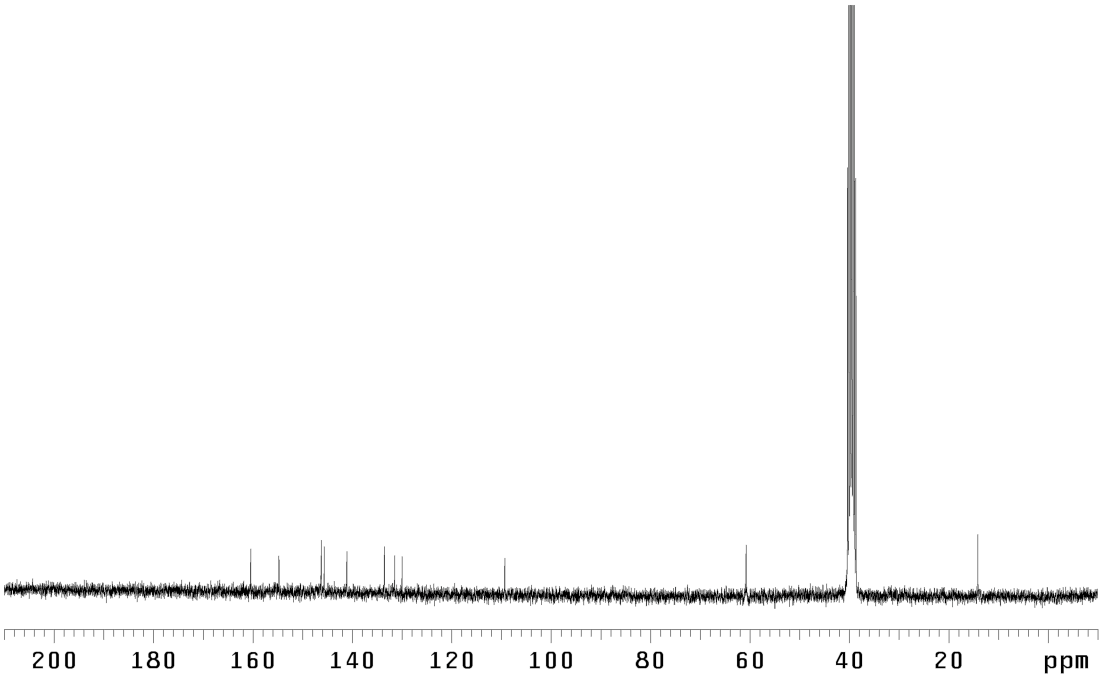


Figure A4.18 ^{13}C NMR (75 MHz, DMSO-d_6) of compound **225**

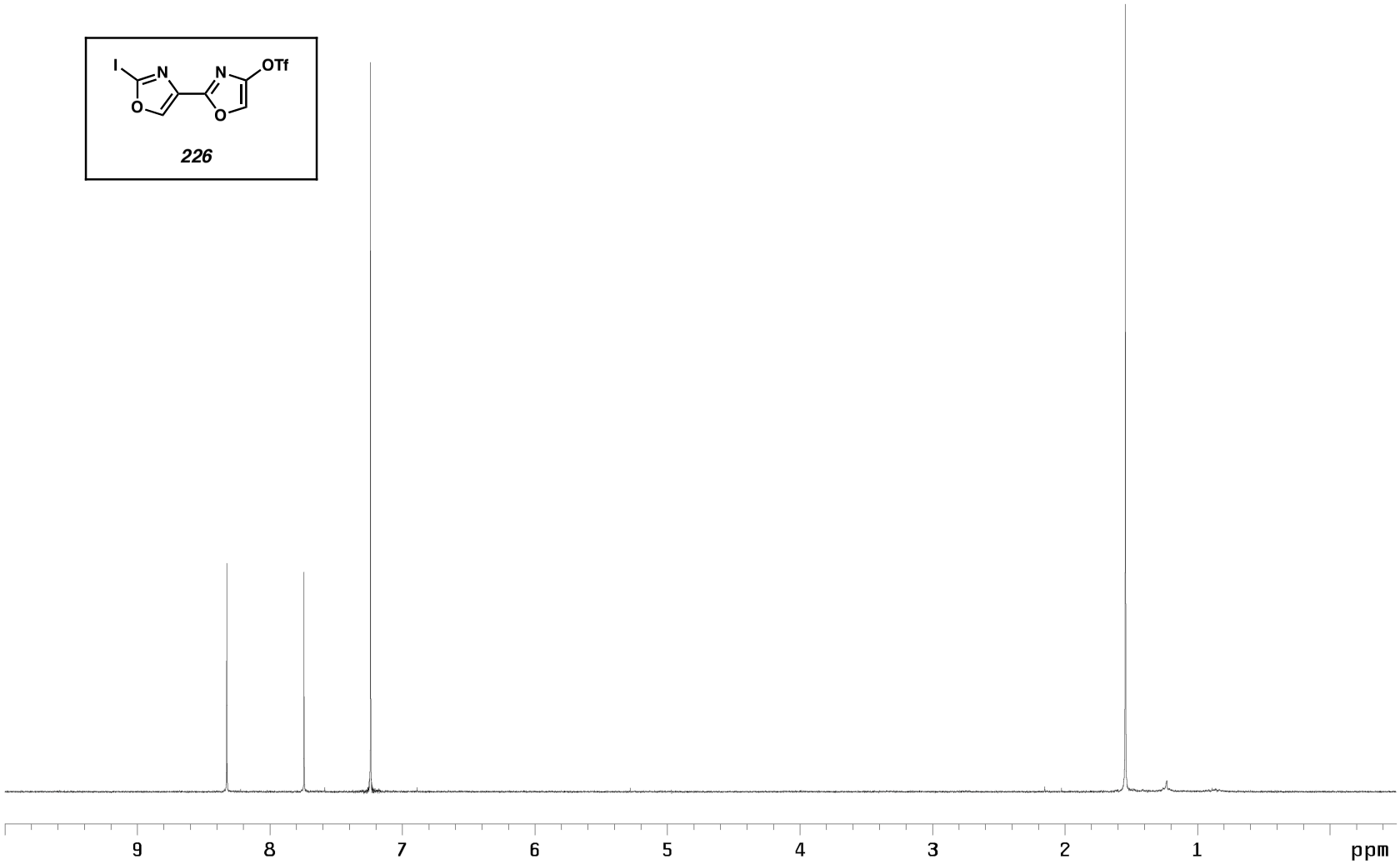


Figure A4.19 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **226**

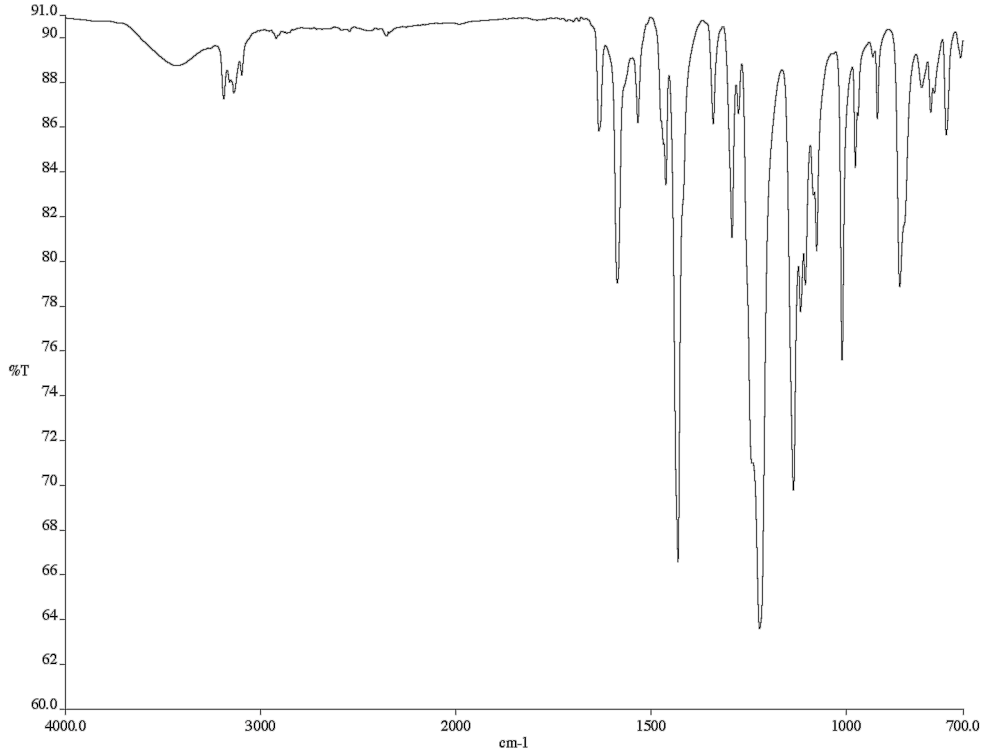


Figure A4.20 Infrared spectrum (thin film/NaCl) of compound **226**

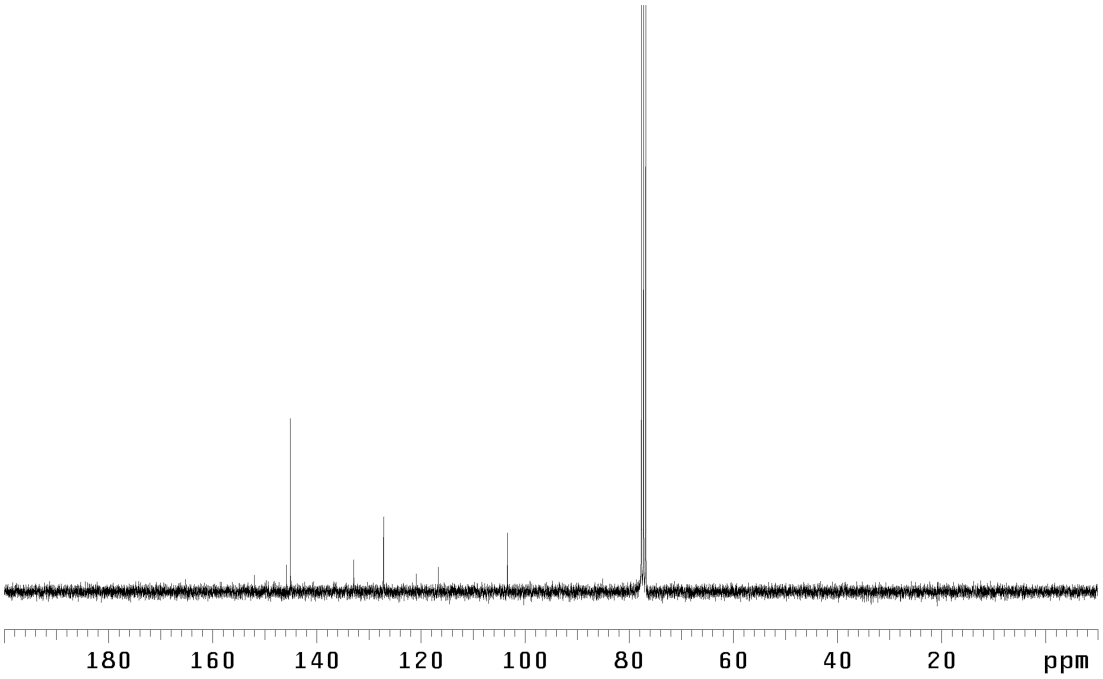


Figure A4.21 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **226**

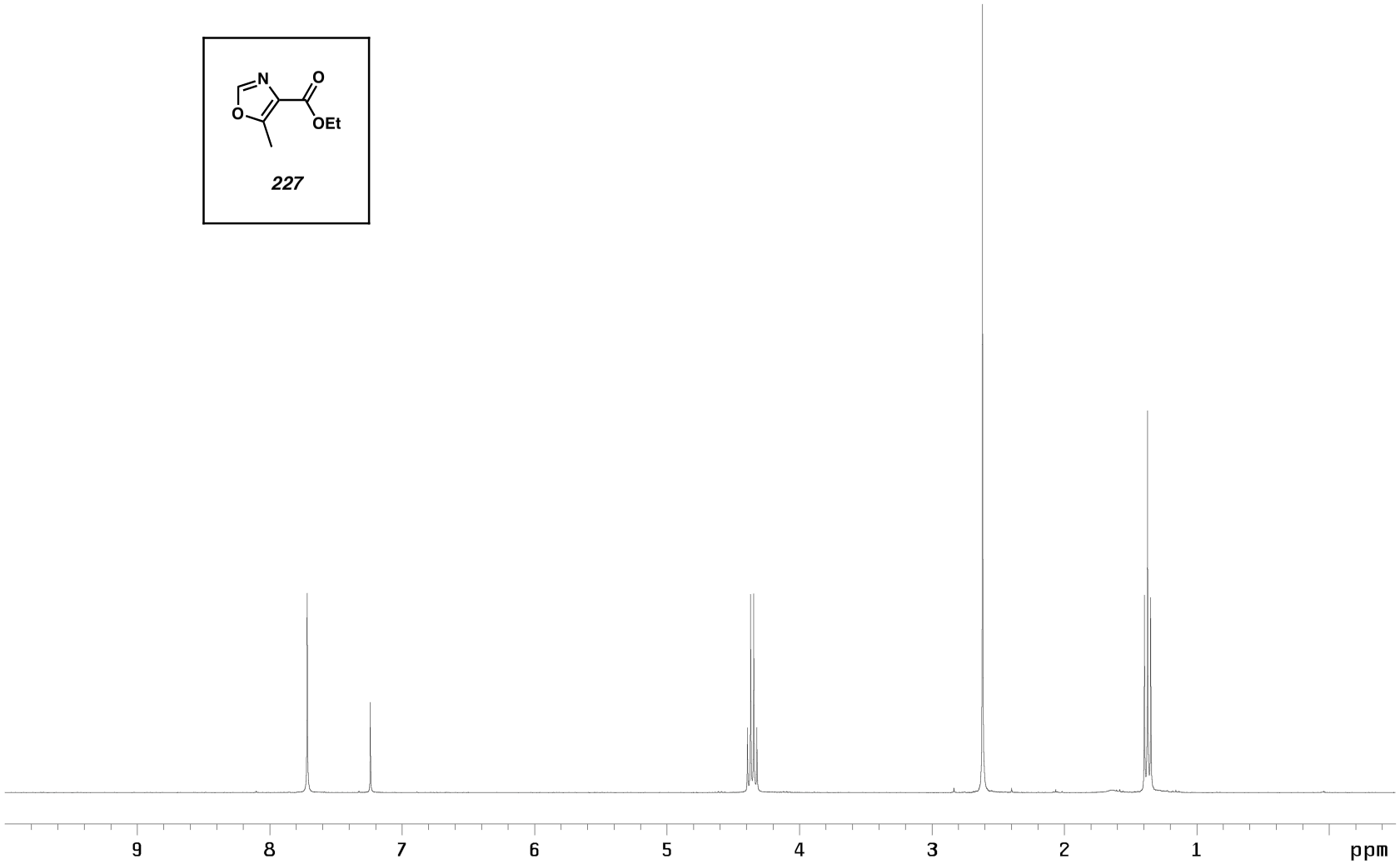


Figure A4.22 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **227**

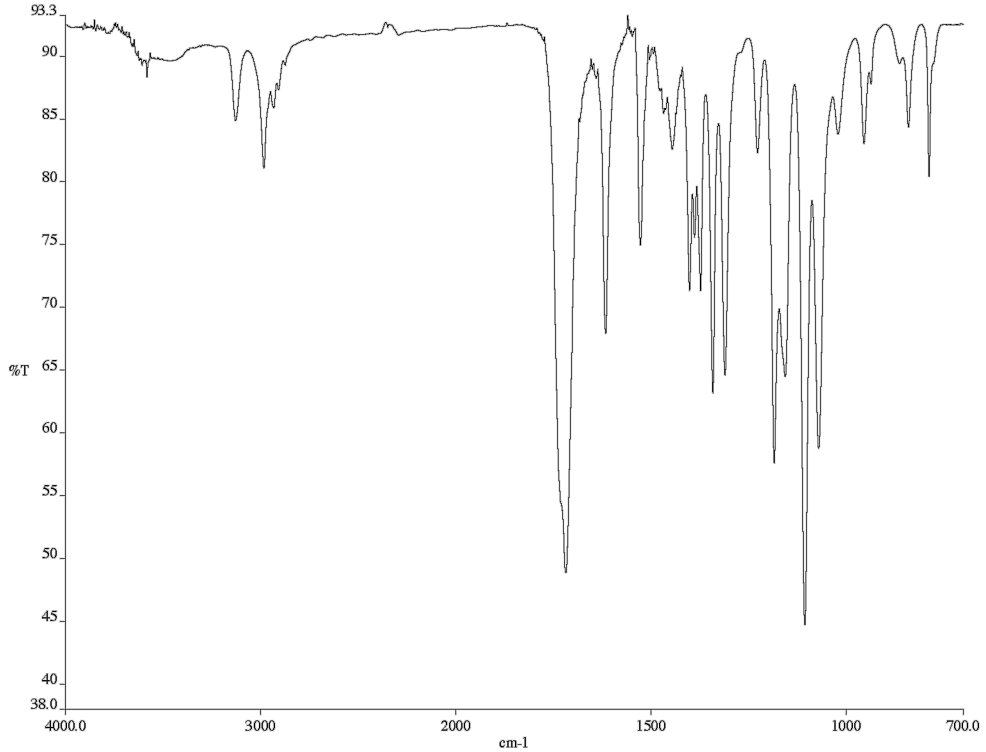


Figure A4.23 Infrared spectrum (thin film/NaCl) of compound **227**

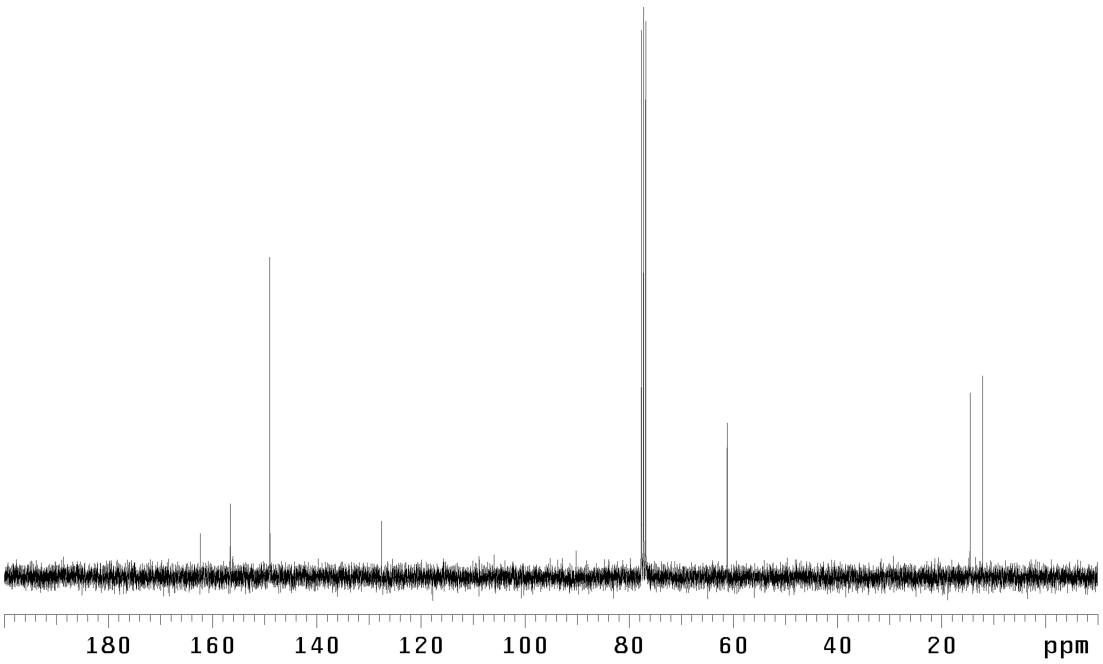


Figure A4.24 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **227**

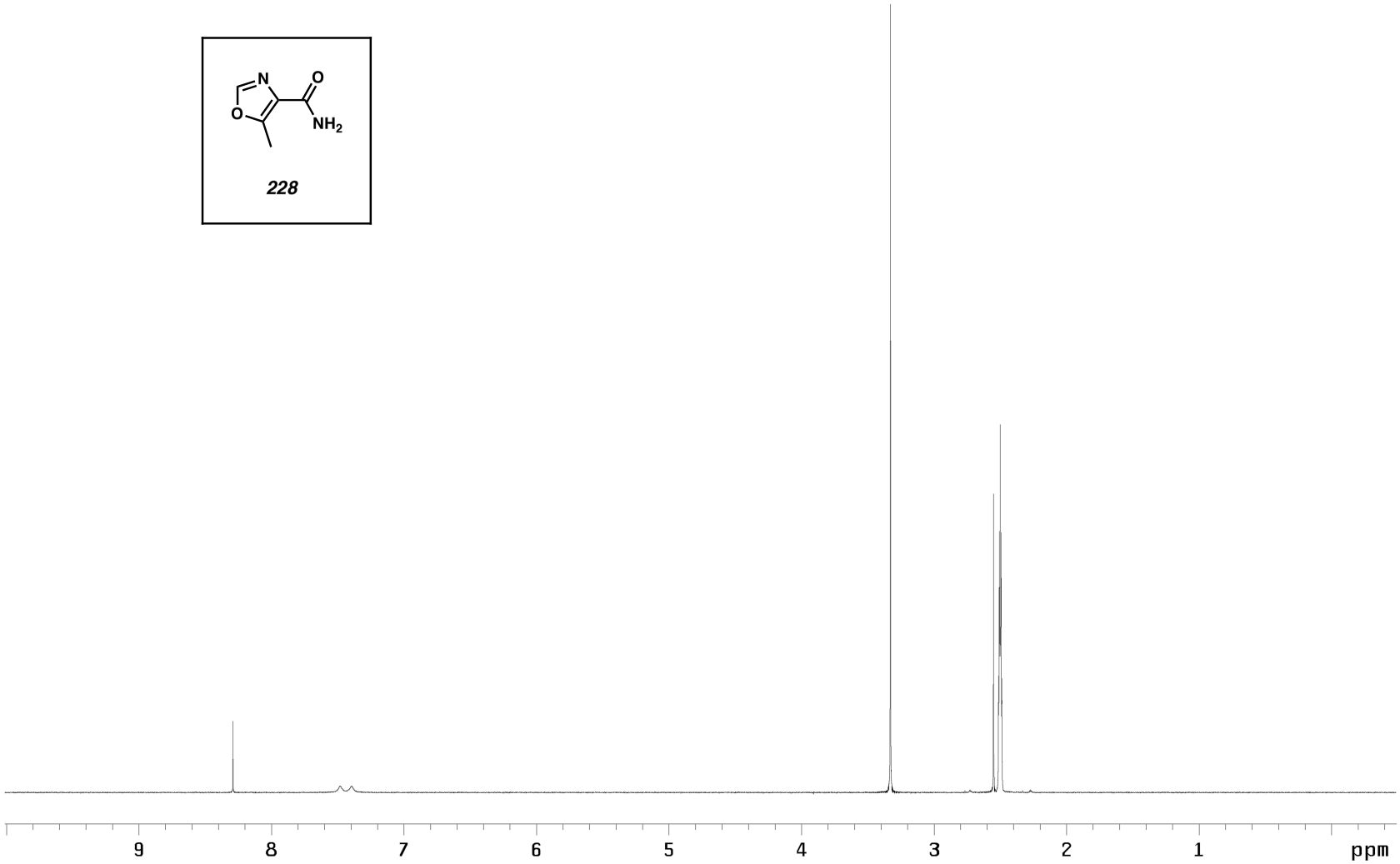


Figure A4.25 ^{1}H NMR (300 MHz, DMSO-d_6) of compound **228**

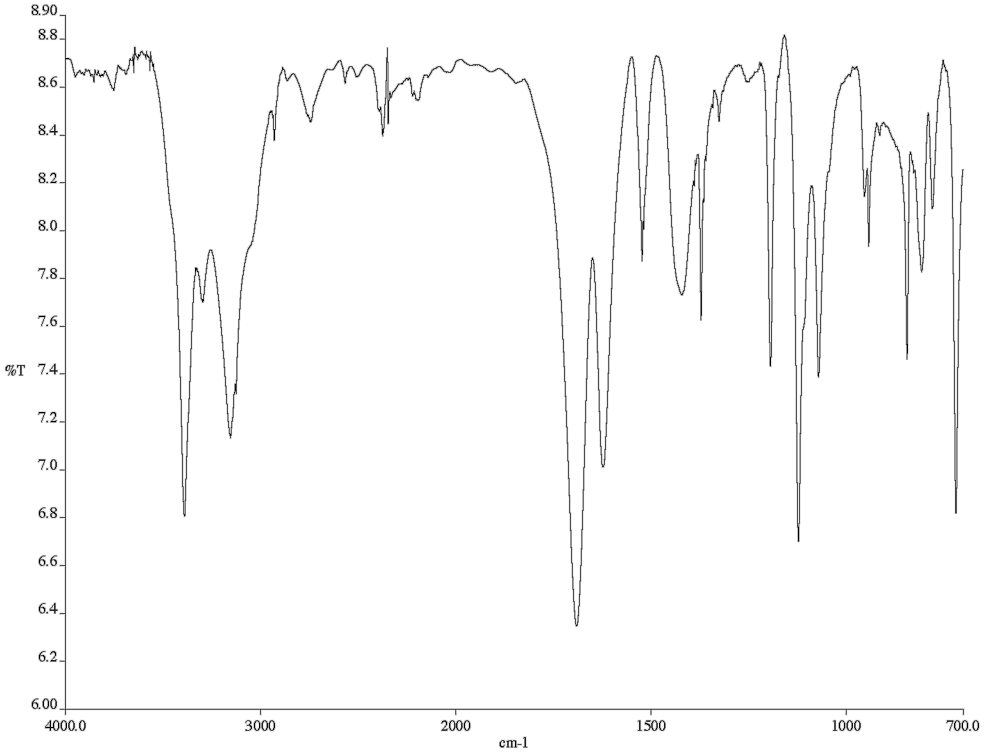


Figure A4.26 Infrared spectrum (KBr pellet) of compound **228**

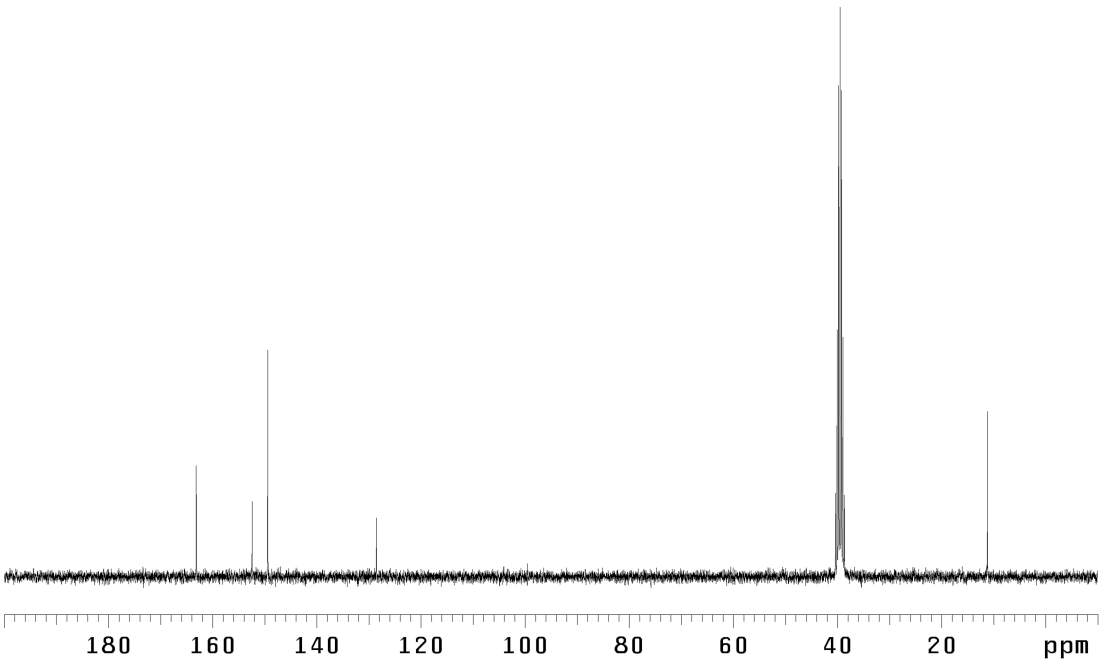


Figure A4.27 ^{13}C NMR (75 MHz, DMSO-d_6) of compound **228**

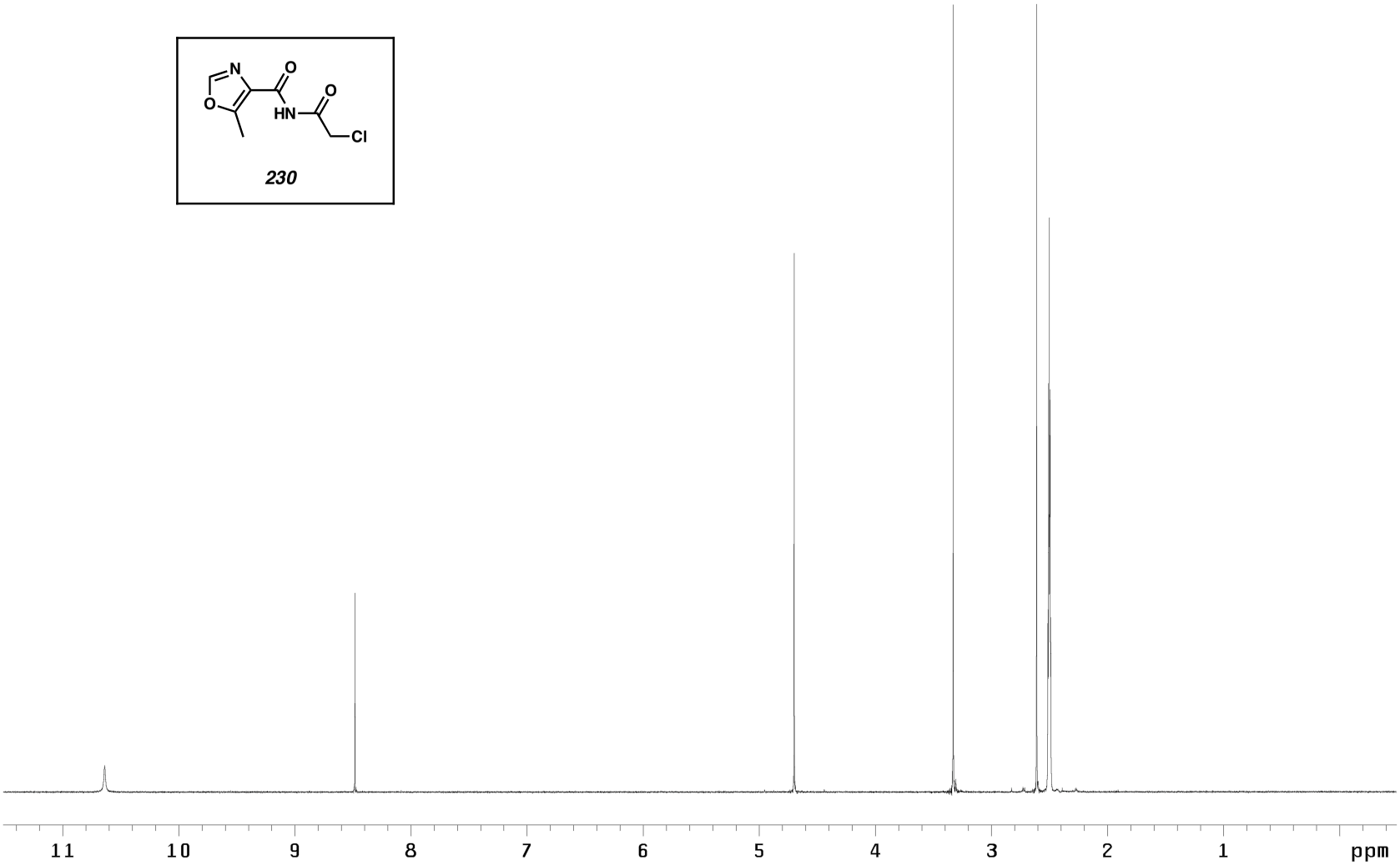


Figure A4.28 ^{1}H NMR (300 MHz, DMSO-d_6) of compound **230**

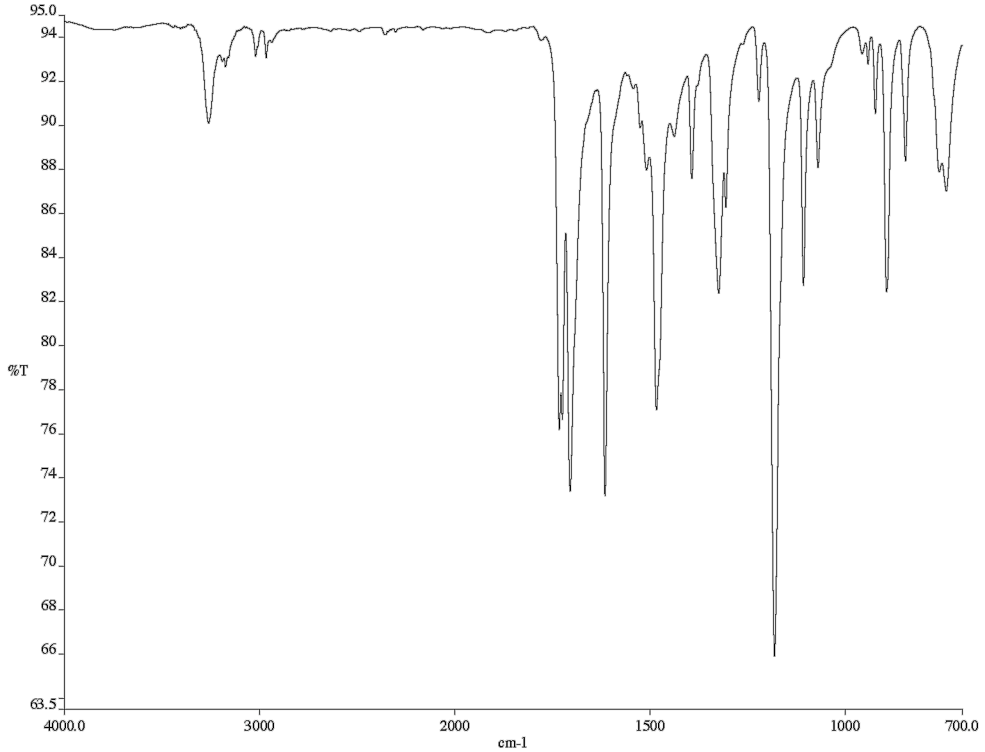


Figure A4.29 Infrared spectrum (thin film/NaCl) of compound **230**

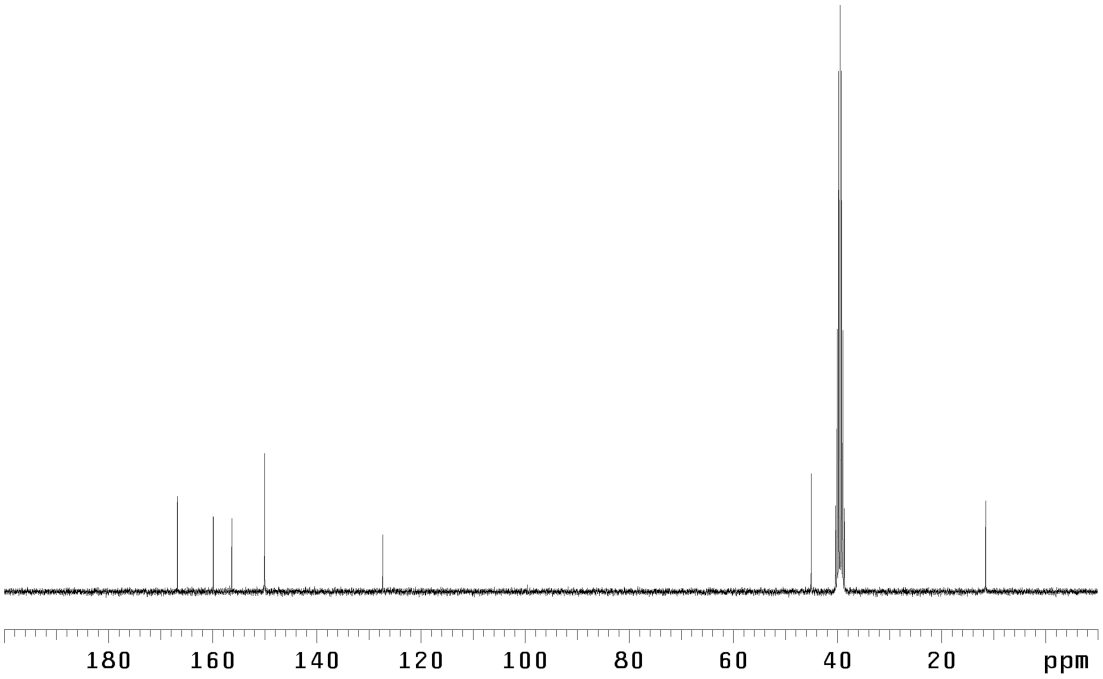


Figure A4.30 ^{13}C NMR (75 MHz, DMSO-d_6) of compound **230**

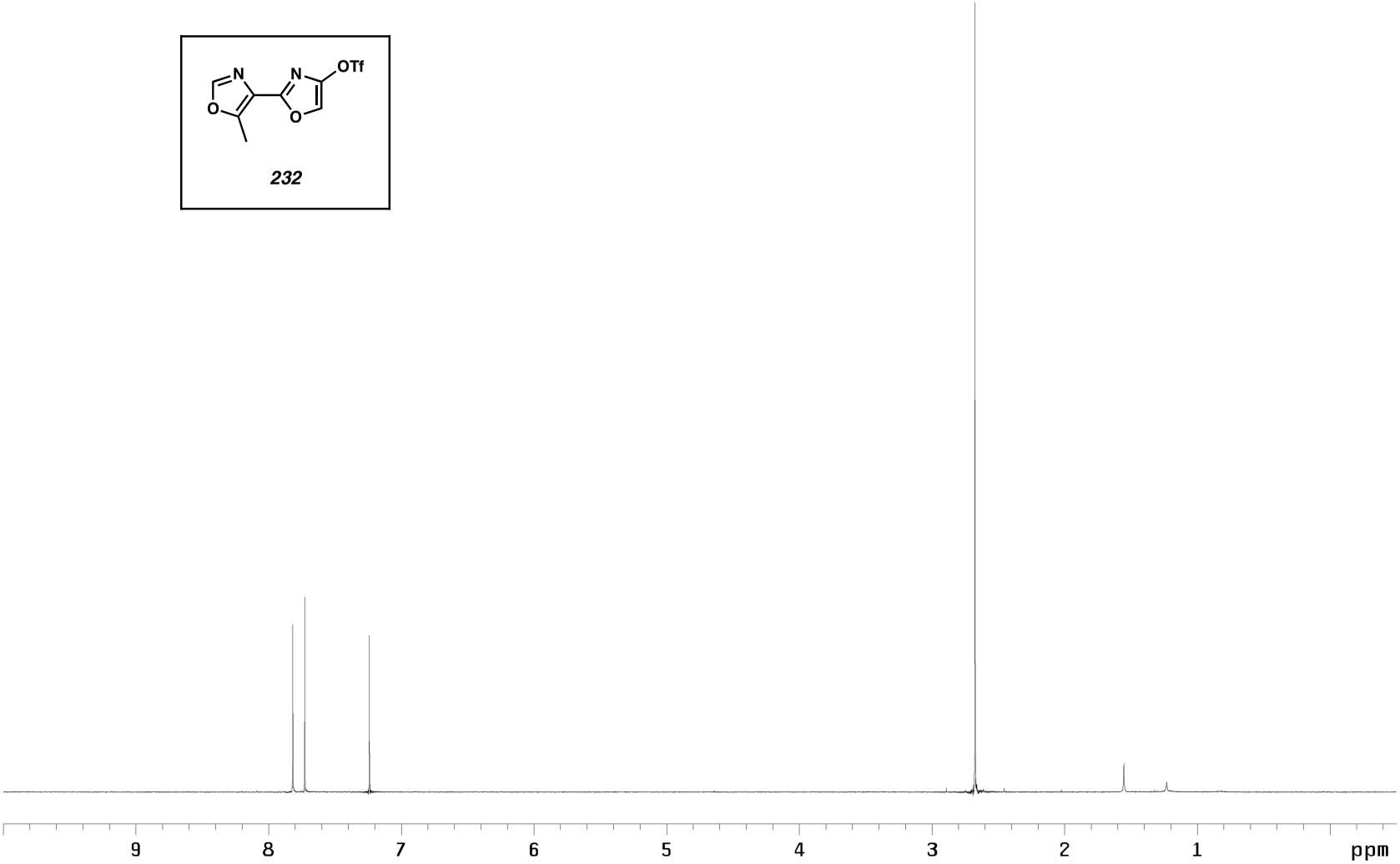


Figure A4.31 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **232**

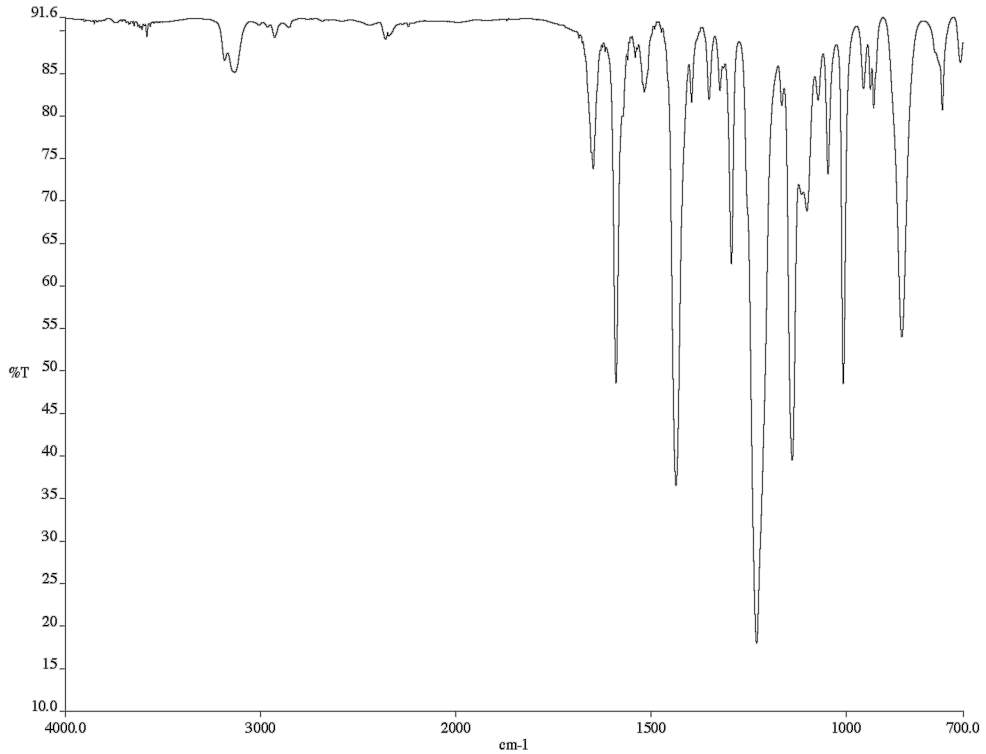


Figure A4.32 Infrared spectrum (thin film/NaCl) of compound **232**

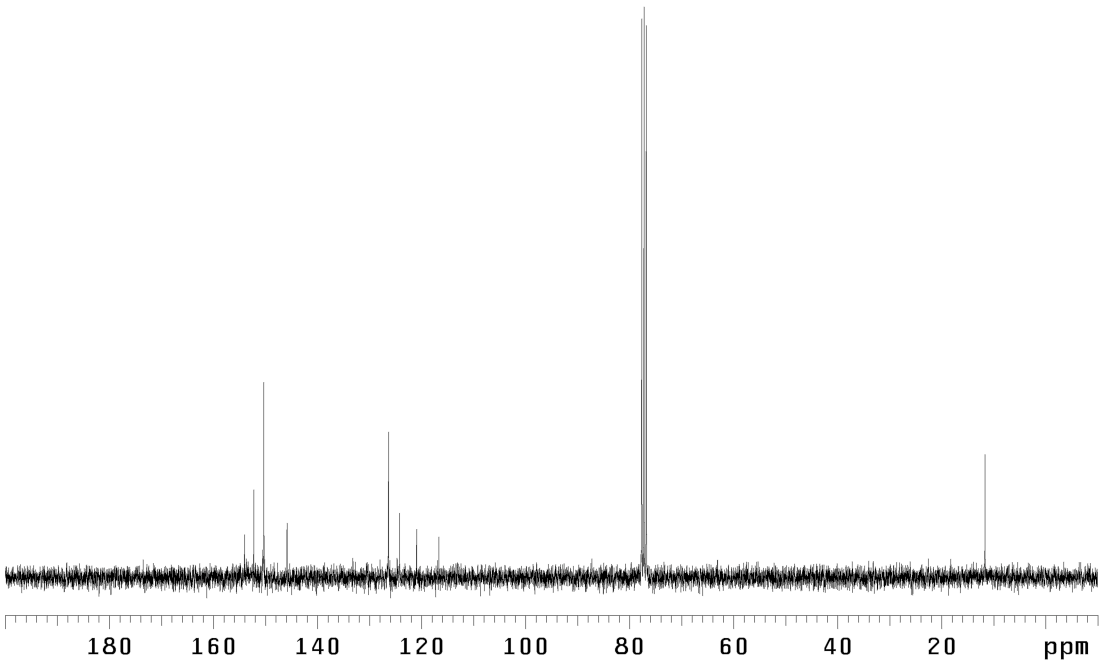


Figure A4.33 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **232**

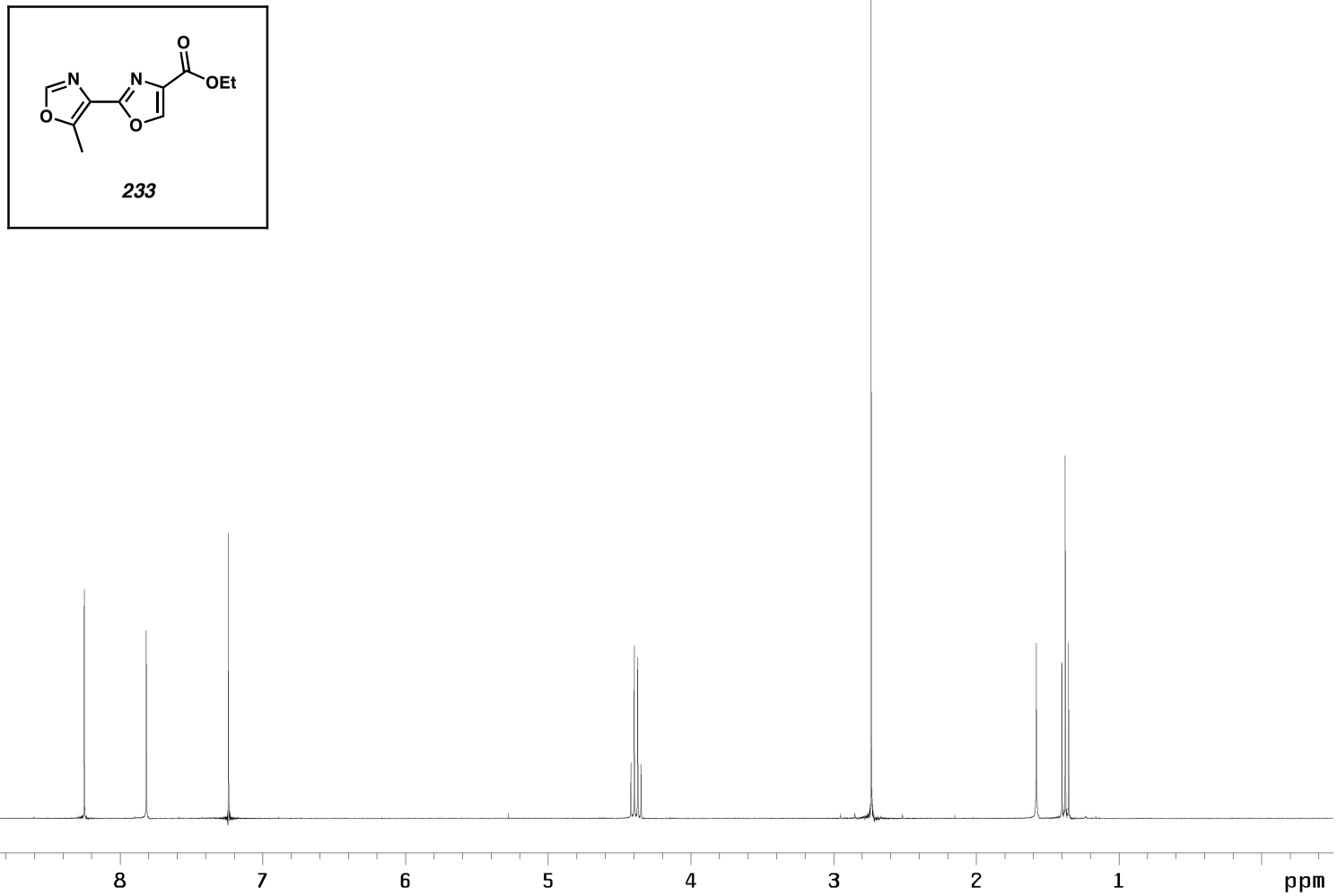


Figure A4.34 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **233**

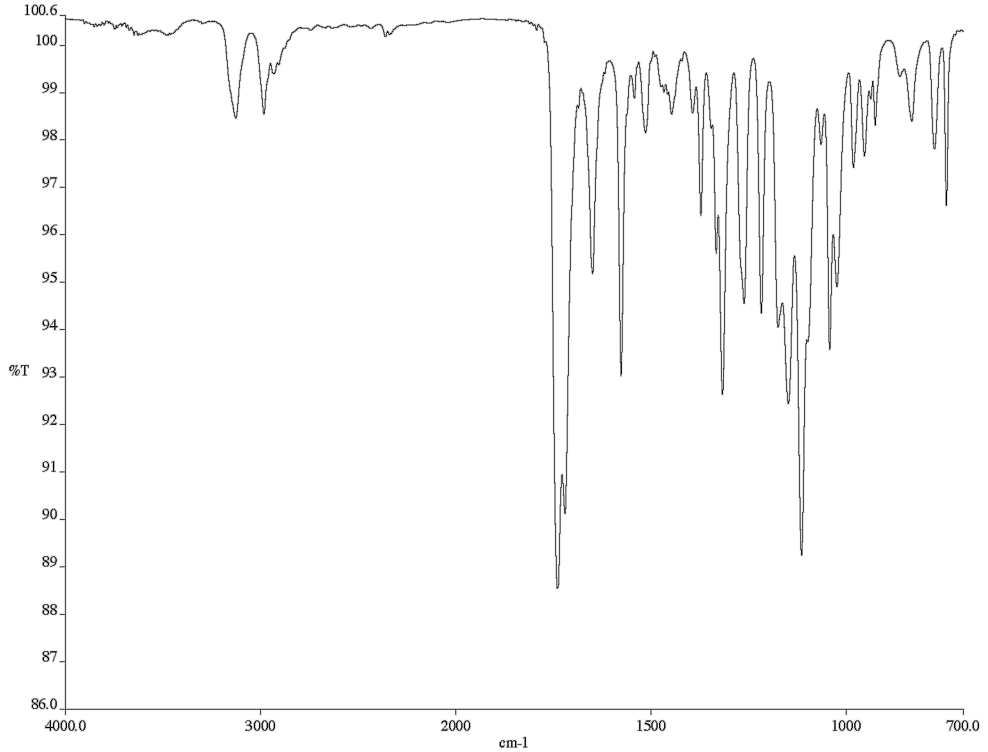


Figure A4.35 Infrared spectrum (thin film/NaCl) of compound **233**

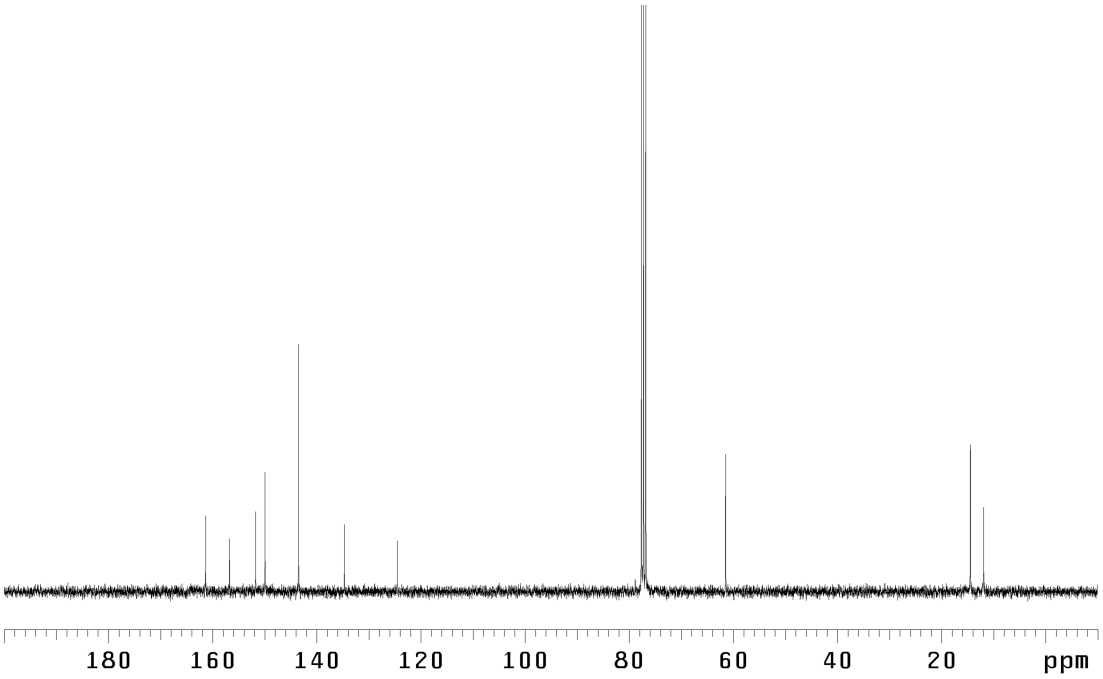


Figure A4.36 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **233**

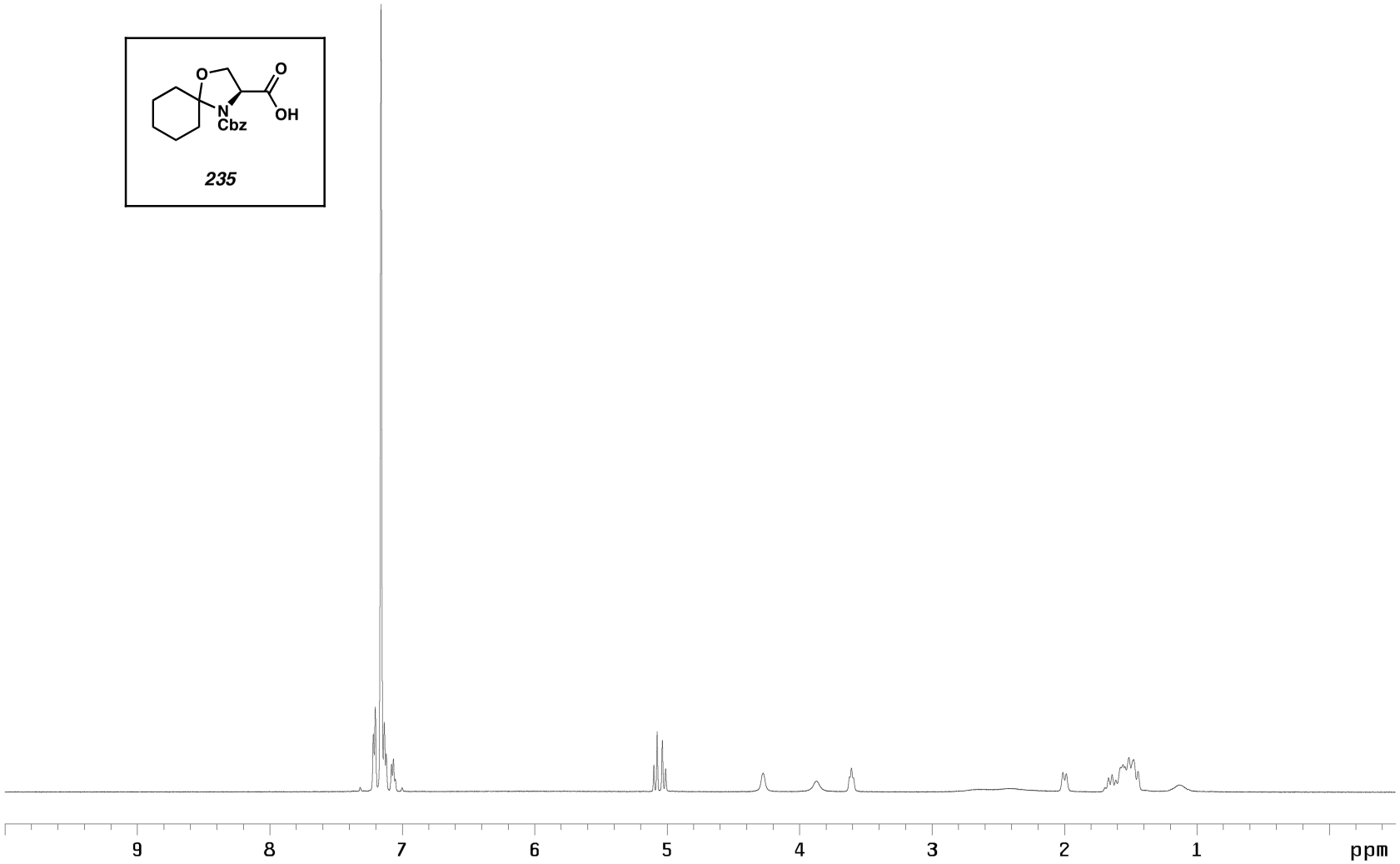


Figure A4.37 ^{1}H NMR (500 MHz, C_6D_6, 70 °C) of compound **235**

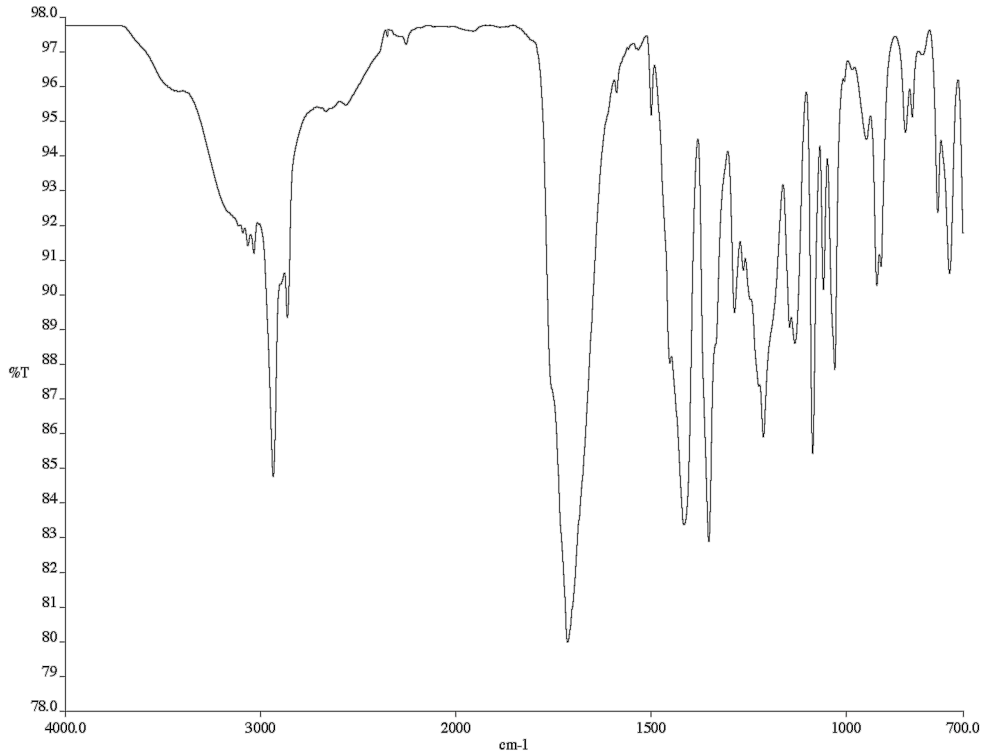


Figure A4.38 Infrared spectrum (thin film/NaCl) of compound **235**

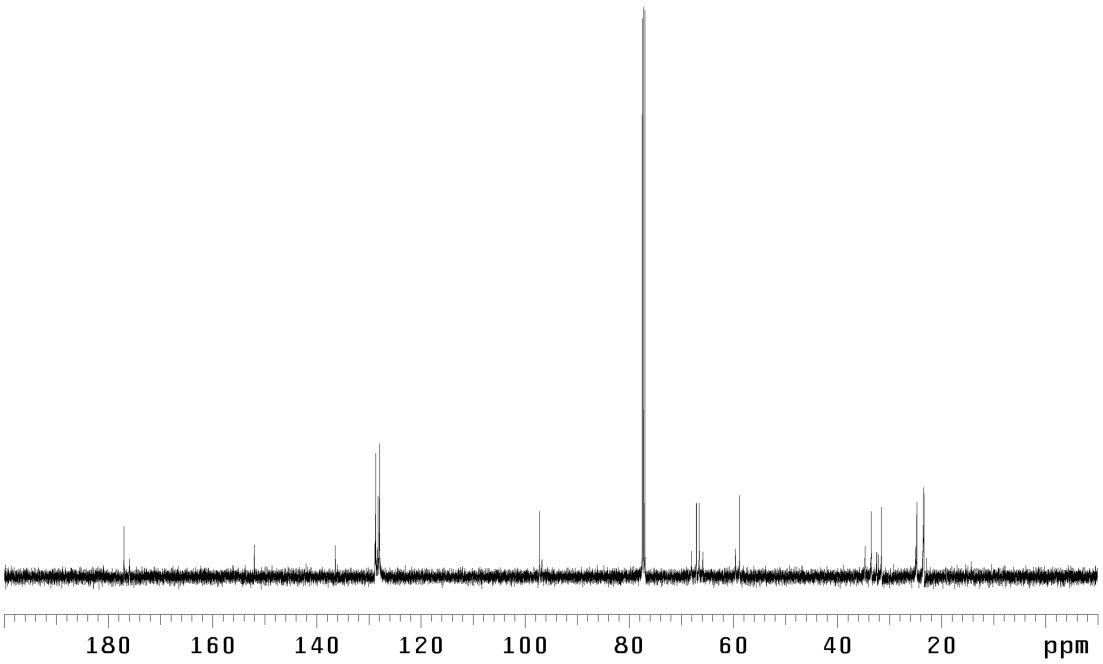


Figure A4.39 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **235**

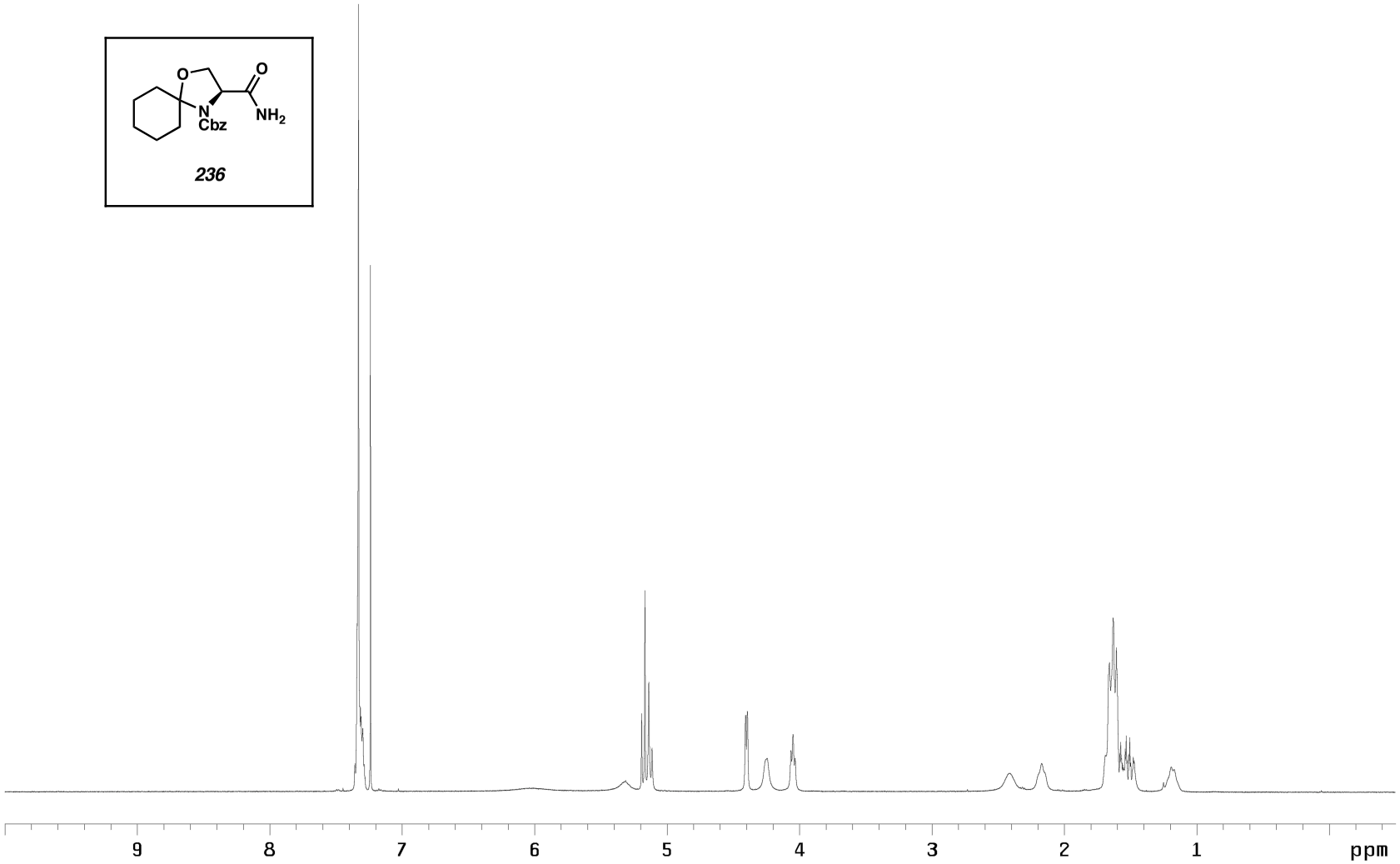


Figure A4.40 ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) of compound **236**

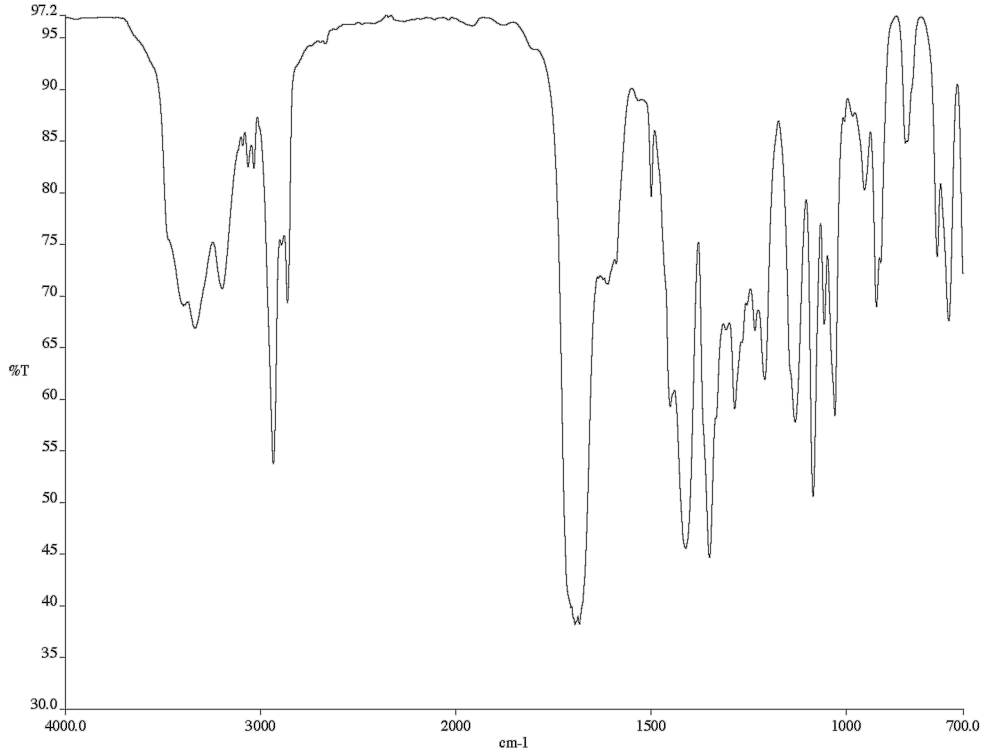


Figure A4.41 Infrared spectrum (thin film/NaCl) of compound **236**

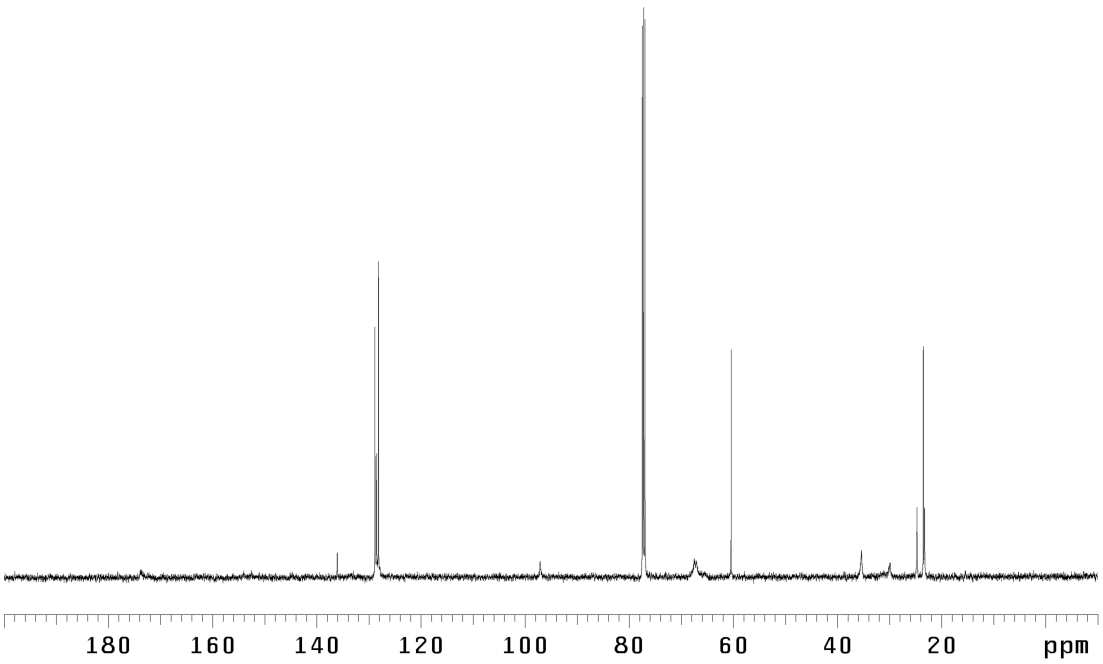


Figure A4.42 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **236**

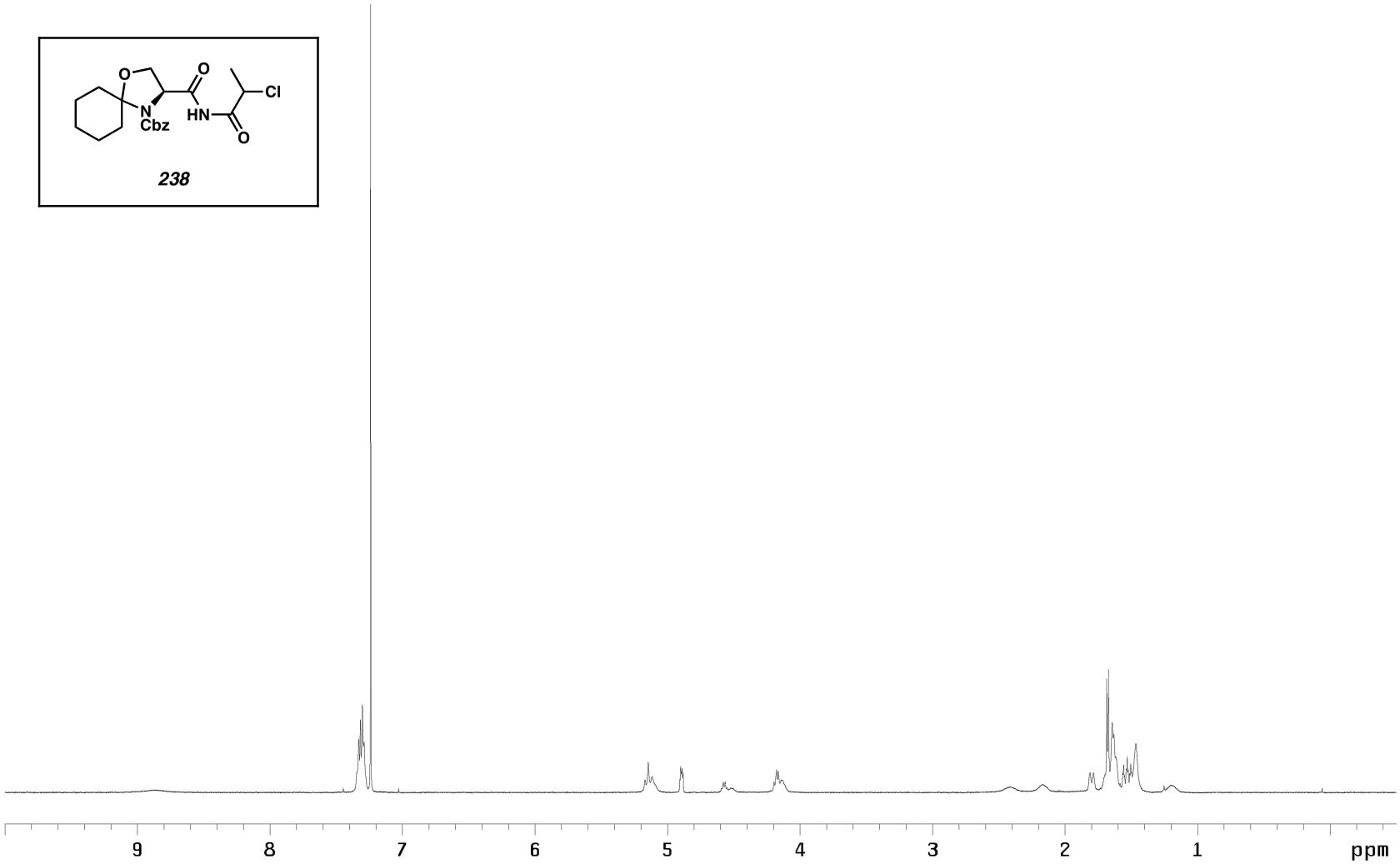


Figure A4.43 ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) of compound **238**

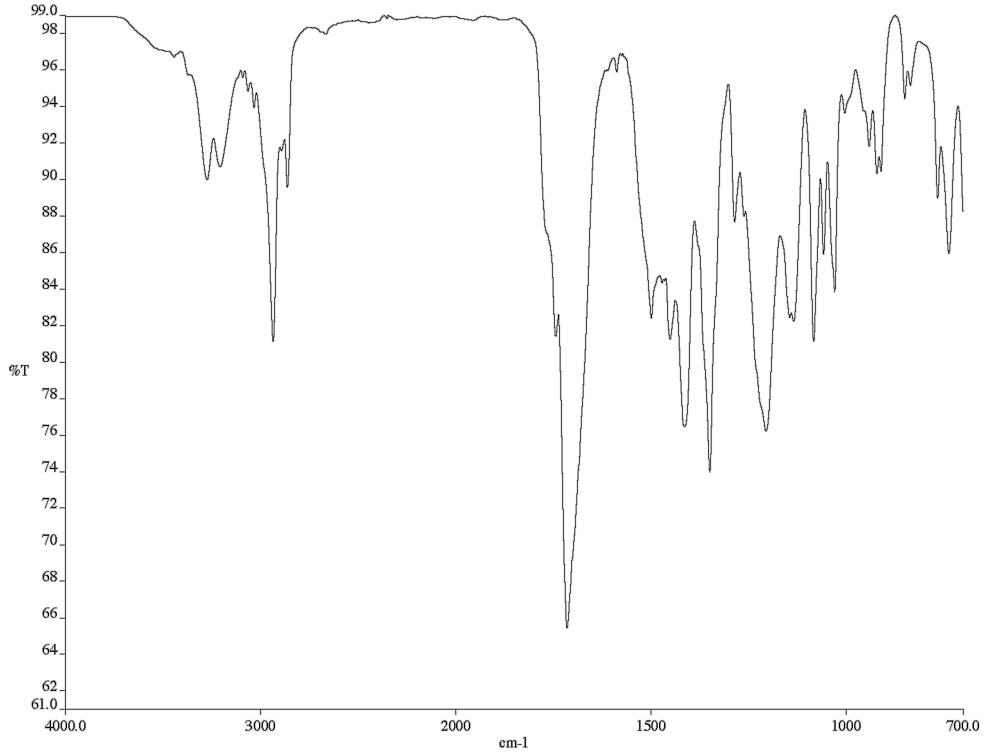


Figure A4.44 Infrared spectrum (thin film/NaCl) of compound **238**

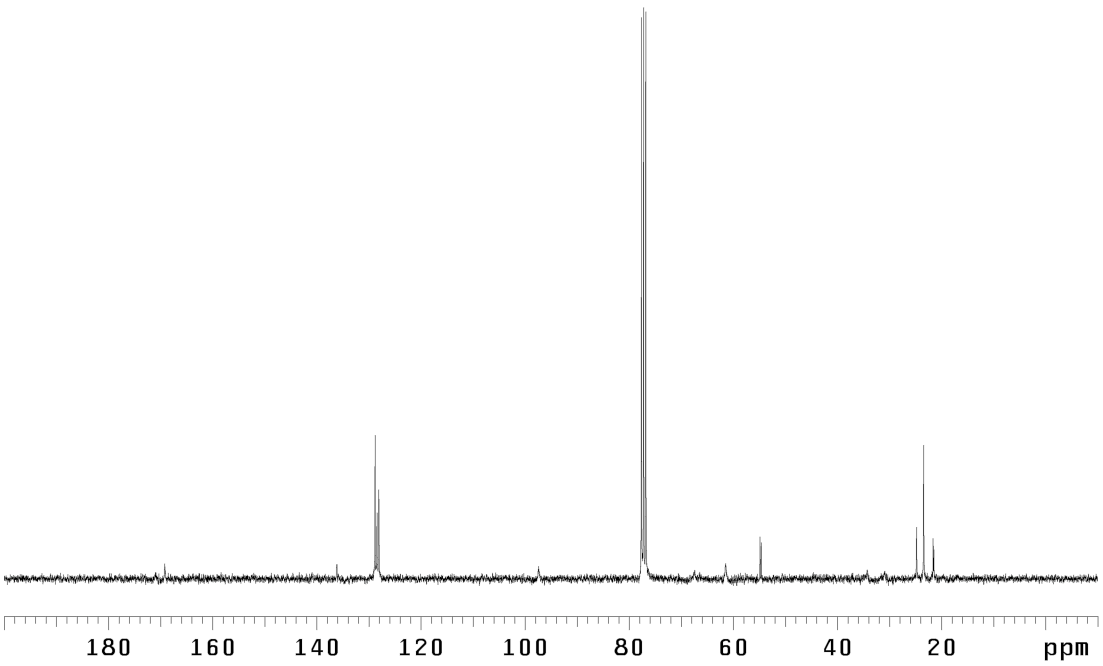


Figure A4.45 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **238**

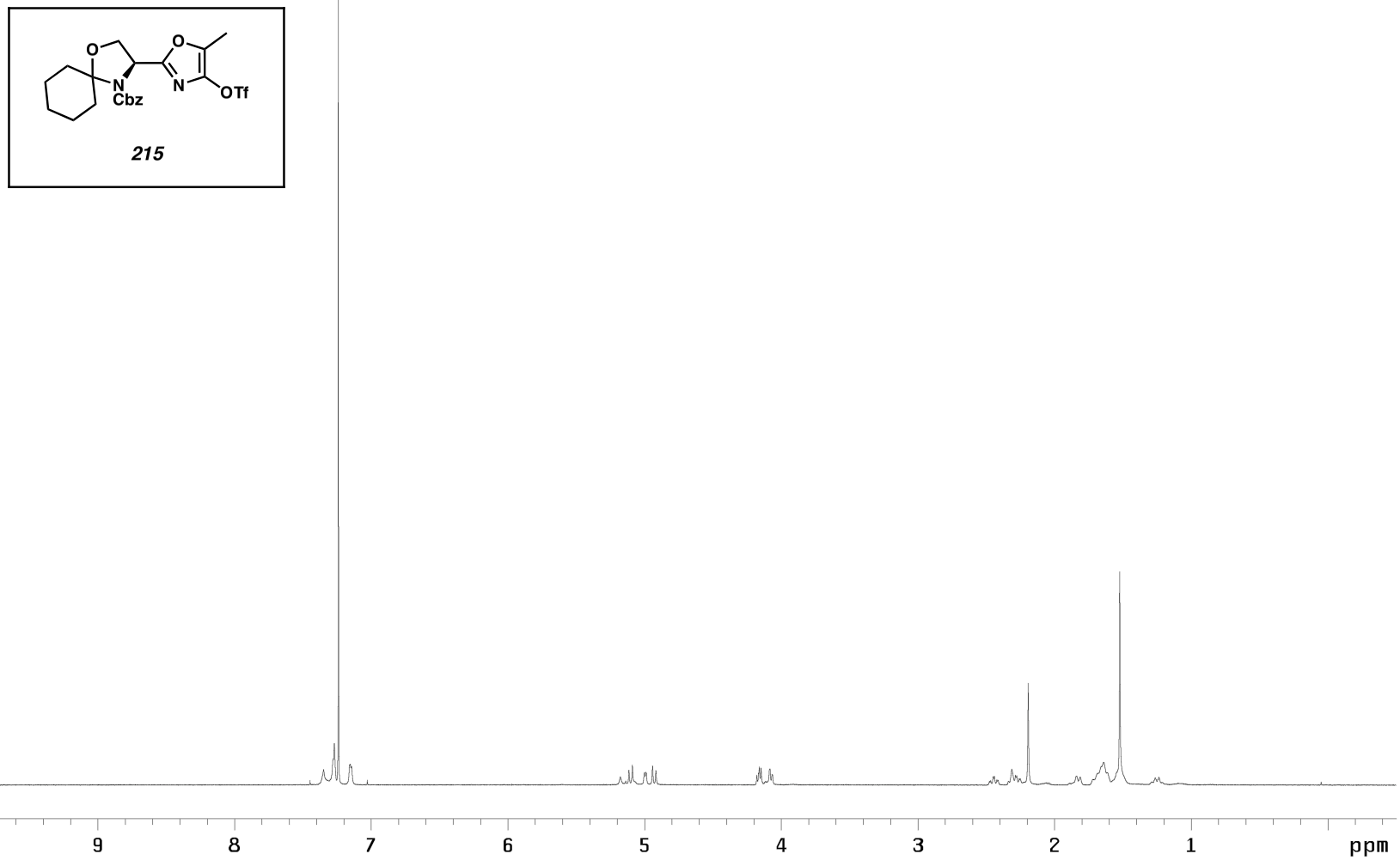


Figure A4.46 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **215**

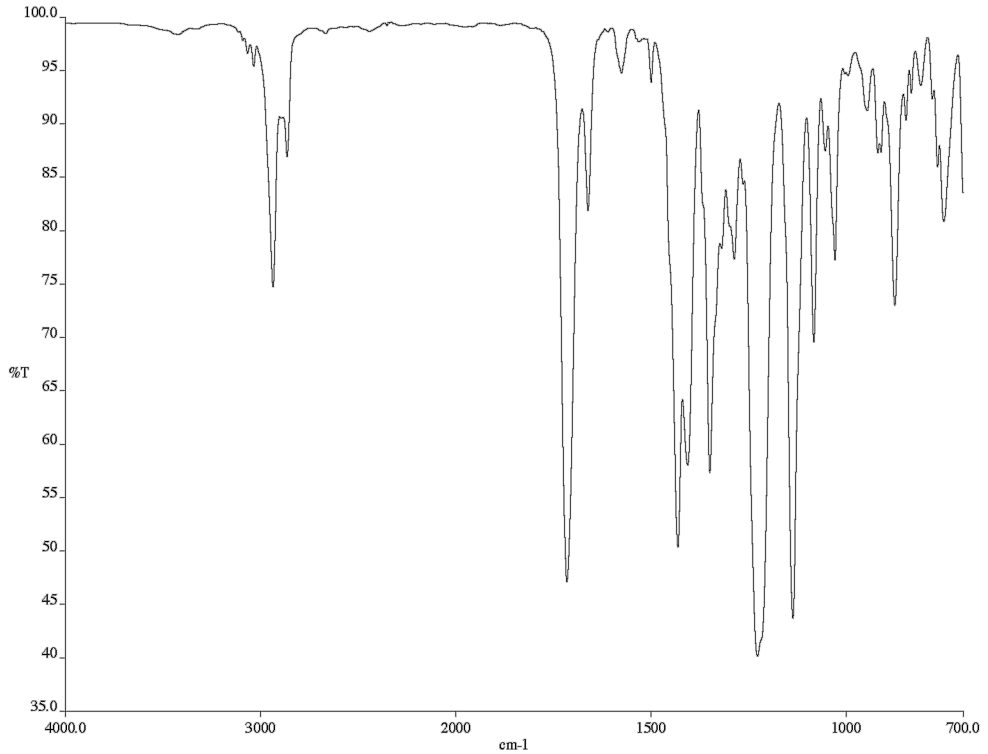


Figure A4.47 Infrared spectrum (thin film/NaCl) of compound **215**

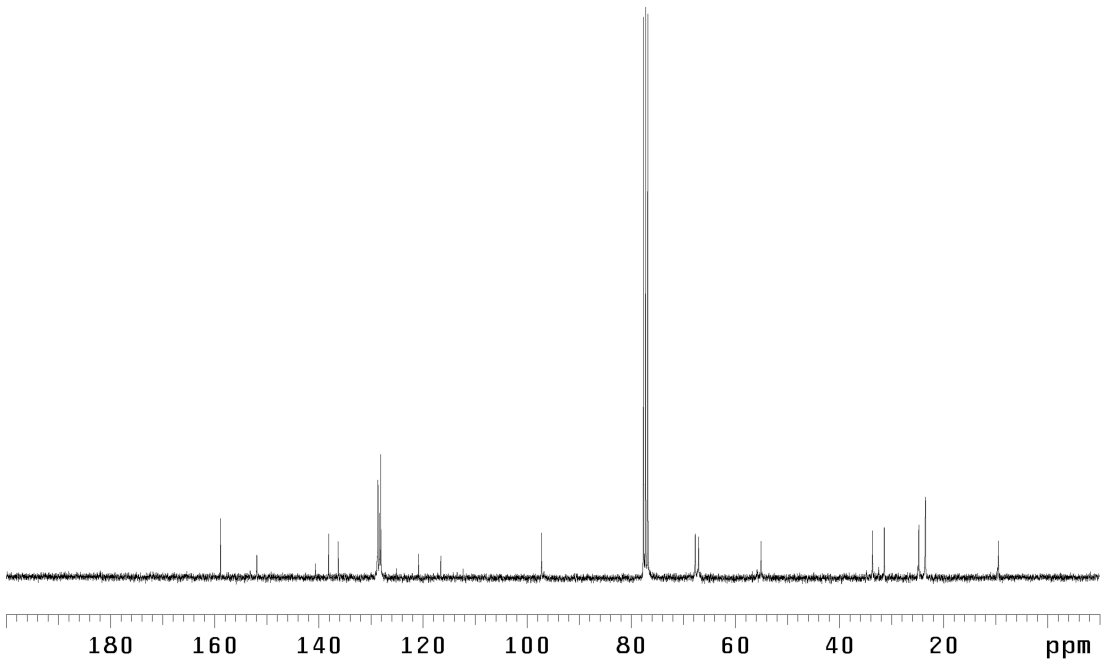


Figure A4.48 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **215**

APPENDIX FIVE

X-Ray Crystallography Reports Relevant to Chapter Four:

Progress Toward The Total Synthesis of Telomestatin

A5.1 Crystal Structure Analysis of 226

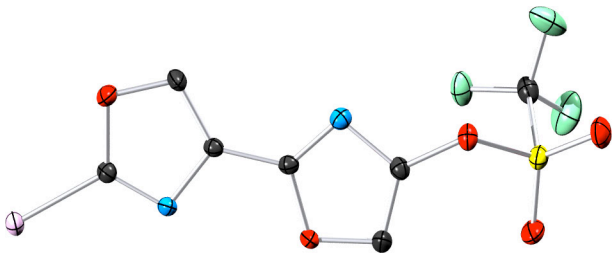


Figure A5.1.1 Iodobisoxazole triflate **226** is shown with 50% probability ellipsoids (Note: Only Molecule A is depicted). Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 282586.

Table A5.1.1 Crystal data and structure refinement for **226** (CCDC 282586)

Empirical formula	$C_7H_2F_3IN_2O_5S$	
Formula weight	410.07	
Crystallization Solvent	Diethylether	
Crystal Habit	Plate	
Crystal size	0.48 x 0.22 x 0.19 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 9170 reflections used in lattice determination	2.74 to 33.18°	
Unit cell dimensions	a = 5.3805(5) Å b = 14.4770(13) Å c = 14.8833(13) Å	α= 92.205(2)° β= 92.046(2)° γ = 90.356(2)°
Volume	1157.68(18) $Å^3$	
Z	4	
Crystal system	Triclinic	
Space group	P-1	
Density (calculated)	2.353 Mg/m^3	
F(000)	776	
Data collection program	Bruker SMART v5.630	
θ range for data collection	1.93 to 33.66°	
Completeness to θ = 33.66°	82.2 %	
Index ranges	$-8 \leq h \leq 7$, $-19 \leq k \leq 20$, $-22 \leq l \leq 22$	
Data collection scan type	ω scans at 5 ϕ settings	
Data reduction program	Bruker SAINT v6.45A	
Reflections collected	19450	
Independent reflections	7576 [R_{int}= 0.0597]	
Absorption coefficient	3.006 mm^{-1}	
Absorption correction	Gaussian	
Max. and min. transmission	0.91449 and 0.56264	

5.1.1 (cont.)

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	7576 / 0 / 359
Treatment of hydrogen atoms	Unrestrained
Goodness-of-fit on F^2	1.034
Final R indices [I>2σ(I), 5482 reflections]	R1 = 0.0311, *w*R2 = 0.0538
R indices (all data)	R1 = 0.0539, *w*R2 = 0.0583
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.002
Average shift/error	0.000
Largest diff. peak and hole	0.827 and -0.793 e.$Å^{-3}$

Special Refinement Details

This molecule crystallizes with two unique conformations in the asymmetric unit, differing from each other by the torsion angles around the C(6*)-O(3*) and the O(3*)-S1* bonds, as illustrated in Figures A5.1.1 thru A5.1.4 and listed in Table A5.1.6. The difference in the environment of these two molecules is illustrated in Figure A5.1.5 and A5.1.6. A short intermolecular contact between the I1 and N(1B), distance = 3.05Å, is **NOT** present between I2 and N(1A).

Another interesting feature observed in this structure are the CH-N and CH-O hydrogen bonds listed in Table A5.1.7. Although these are not the "classical" hydrogen bonds they are not without precedent[1,2] and the values observed herein are consistent with those observed elsewhere[1].

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.

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(1) Rahman, A. N. M. M.; Bishop, R.; Craig, D. C.; Scudder, M. L. *Eur. J. Org. Chem.* **2001**, 863–873.
(2) Jiang, L.; Lai, L. *J. Biol. Chem.* **2002**, 37732–37740.

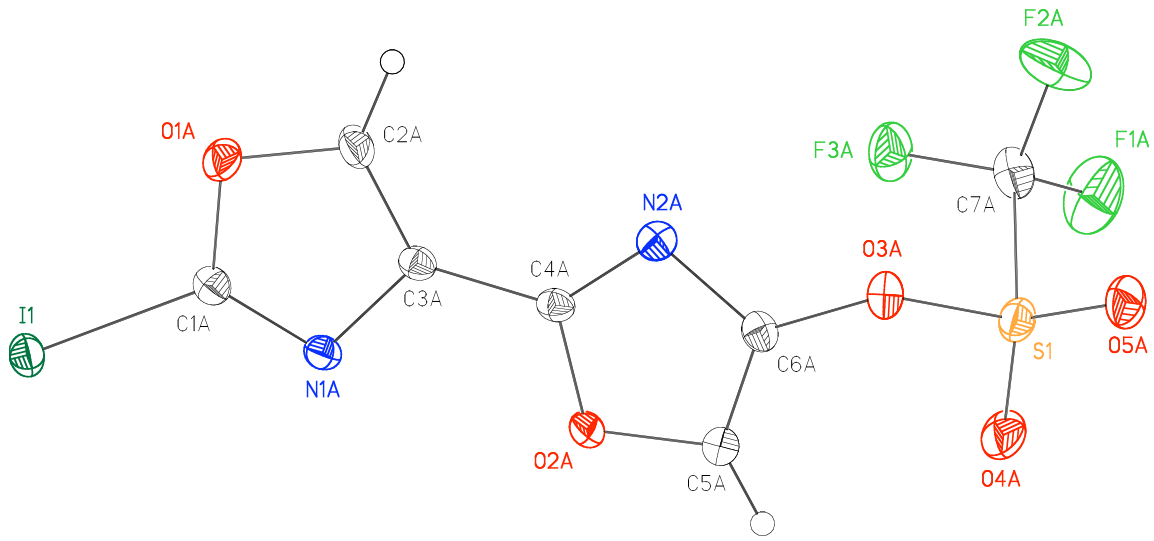

Figure A5.1.2 *Molecule A*

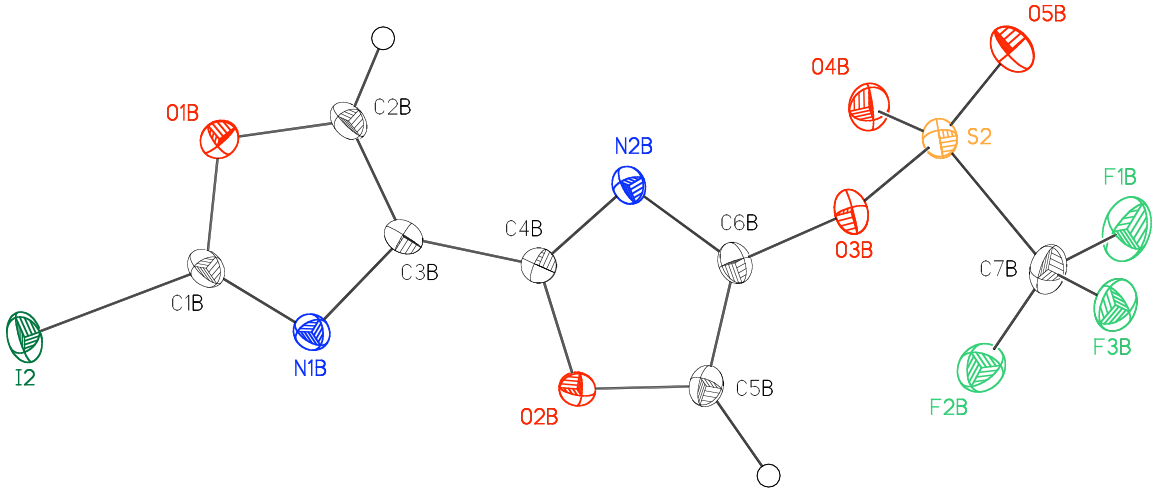

Figure A5.1.3 *Molecule B*

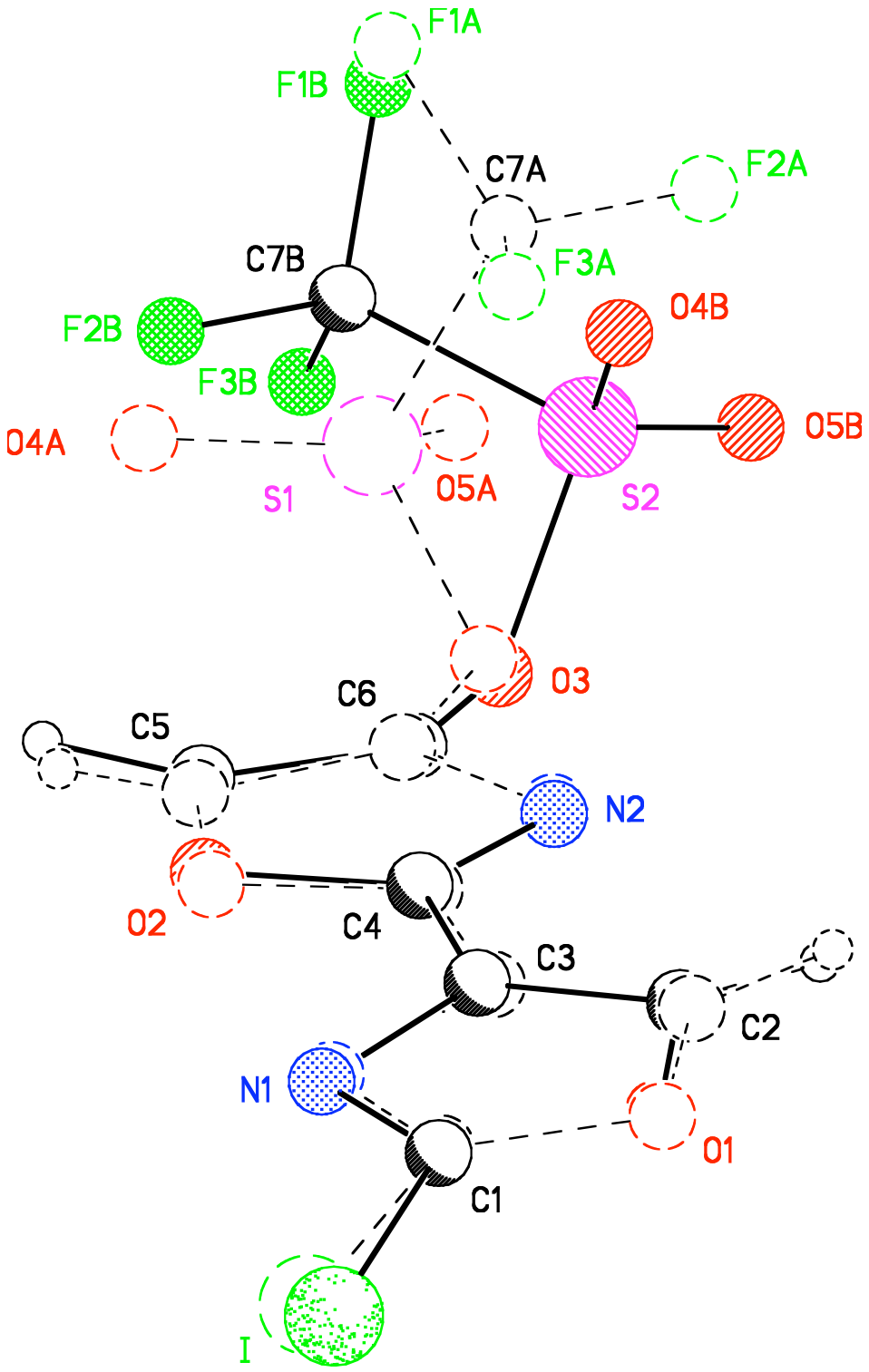

Figure A5.1.4 *Overlap of molecule A and B emphasizing the torsion angle around the C(6)-O(3) bond*

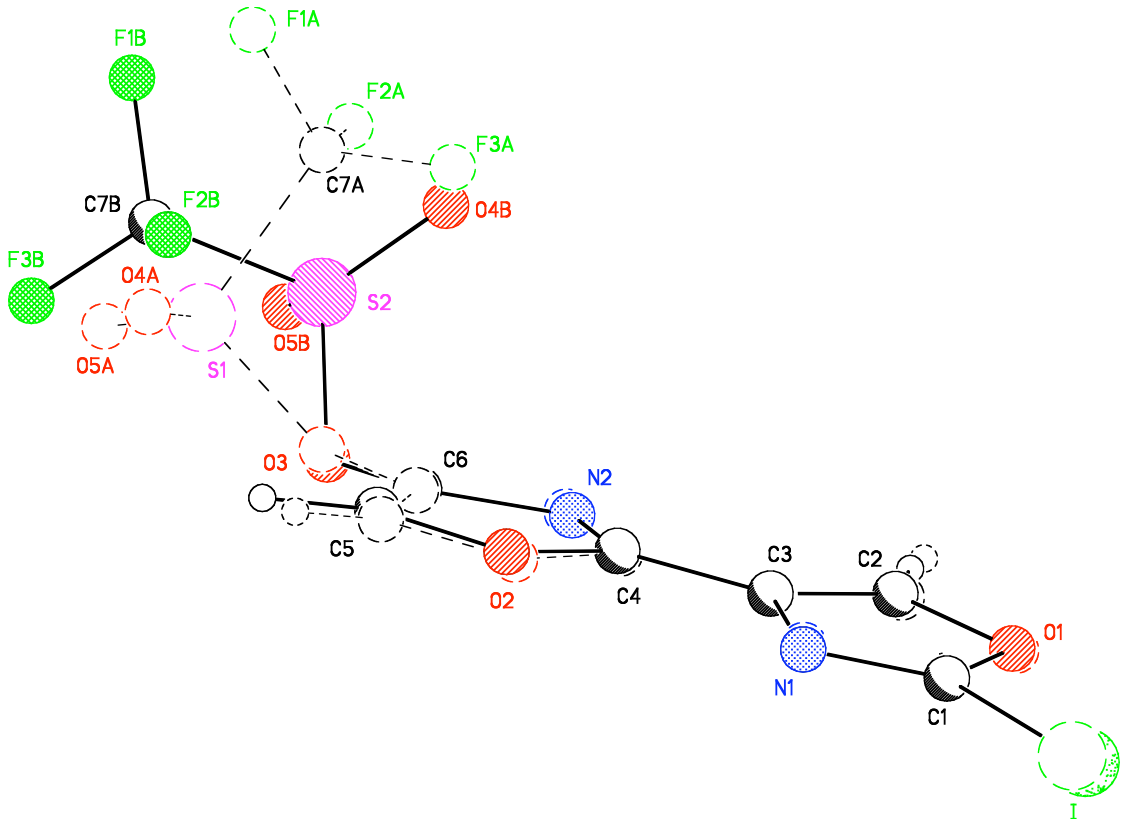

Figure A5.1.5 *Overlap of molecule A and B emphasizing the torsion angle around the O(3)-S bond*

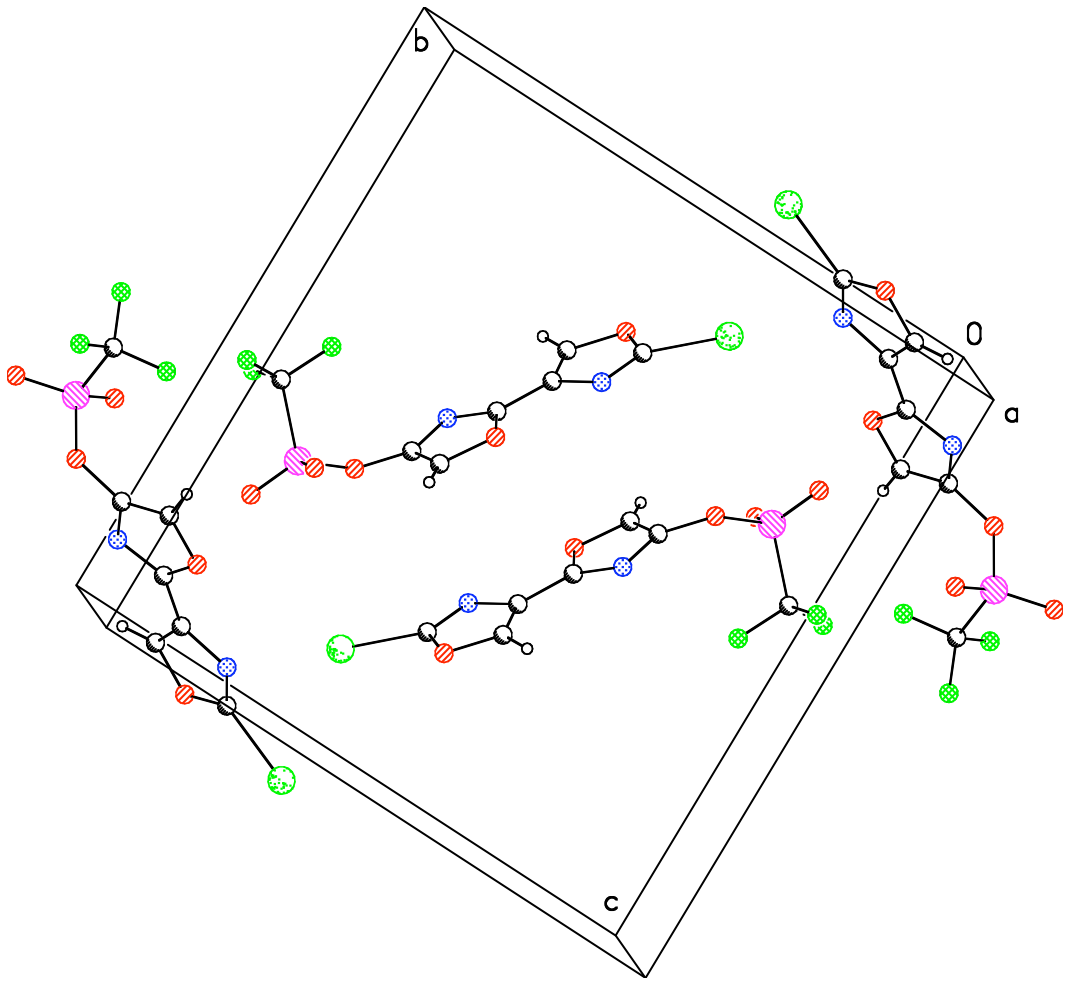

Figure A5.1.6 *Packing in the unit cell with the I(1)-N(1B) interaction emphasized*

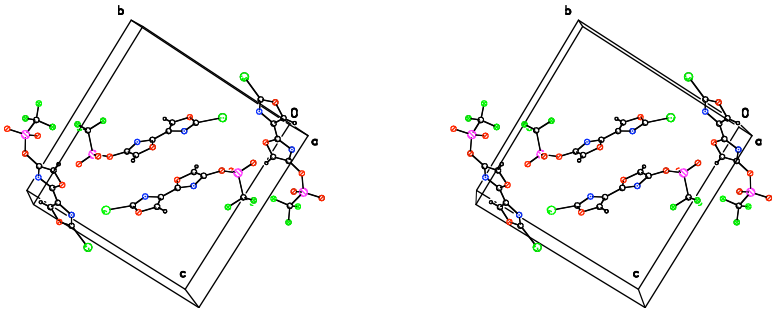

Figure A5.1.7 *Stereo view of the packing in the unit cell with the I(1)-N(1B) interaction emphasized*

Table A5.1.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for **226** (CCDC 282586). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
I(1)	2611(1)	3487(1)	1553(1)	17(1)
S(1)	2125(1)	8201(1)	6603(1)	18(1)
F(1A)	2445(4)	9715(1)	5750(1)	44(1)
F(2A)	-1292(4)	9274(1)	5935(1)	39(1)
F(3A)	903(3)	8577(1)	4943(1)	29(1)
O(1A)	-1301(3)	4609(1)	2445(1)	21(1)
O(2A)	3752(3)	5878(1)	4665(1)	19(1)
O(3A)	701(3)	7278(1)	6286(1)	17(1)
O(4A)	4719(4)	8117(2)	6483(1)	28(1)
O(5A)	1112(4)	8483(1)	7431(1)	25(1)
N(1A)	2396(4)	4804(2)	3161(1)	15(1)
N(2A)	-68(4)	6392(2)	4929(1)	16(1)
C(1A)	1153(5)	4399(2)	2502(2)	15(1)
C(2A)	-1614(5)	5227(2)	3160(2)	20(1)
C(3A)	609(5)	5342(2)	3598(2)	13(1)
C(4A)	1312(5)	5888(2)	4403(2)	13(1)
C(5A)	3925(5)	6421(2)	5442(2)	20(1)
C(6A)	1616(5)	6724(2)	5578(2)	15(1)
C(7A)	954(5)	8991(2)	5757(2)	22(1)
I(2)	2895(1)	5915(1)	10688(1)	27(1)
S(2)	3024(1)	11753(1)	7553(1)	19(1)
F(1B)	3756(3)	12036(2)	5882(1)	39(1)
F(2B)	6039(3)	10962(1)	6438(1)	27(1)
F(3B)	6889(3)	12400(1)	6769(1)	29(1)
O(1B)	596(3)	7723(1)	10466(1)	19(1)
O(2B)	6105(3)	9010(1)	8594(1)	16(1)
O(3B)	4951(3)	11381(1)	8288(1)	18(1)
O(4B)	1164(4)	11076(2)	7332(1)	26(1)
O(5B)	2497(4)	12676(2)	7808(2)	32(1)
N(1B)	4077(4)	7636(2)	9688(1)	15(1)
N(2B)	3301(4)	10062(2)	9005(1)	14(1)
C(1B)	2595(5)	7220(2)	10211(2)	17(1)
C(2B)	865(5)	8548(2)	10051(2)	17(1)
C(3B)	2946(5)	8489(2)	9579(2)	14(1)
C(4B)	4040(5)	9214(2)	9059(2)	13(1)
C(5B)	6713(5)	9817(2)	8192(2)	17(1)
C(6B)	5014(5)	10439(2)	8451(2)	15(1)
C(7B)	5080(5)	11791(2)	6599(2)	23(1)

Table A5.1.3 Bond lengths [Å] and angles [°] for **226** (CCDC 282586)

I(1)-C(1A)	2.074(3)
S(1)-O(5A)	1.4128(19)
S(1)-O(4A)	1.419(2)
S(1)-O(3A)	1.5838(19)
S(1)-C(7A)	1.833(3)
F(1A)-C(7A)	1.317(3)
F(2A)-C(7A)	1.311(3)
F(3A)-C(7A)	1.329(3)
O(1A)-C(1A)	1.357(3)
O(1A)-C(2A)	1.378(3)
O(2A)-C(4A)	1.356(3)
O(2A)-C(5A)	1.373(3)
O(3A)-C(6A)	1.404(3)
N(1A)-C(1A)	1.287(3)
N(1A)-C(3A)	1.404(3)
N(2A)-C(4A)	1.304(3)
N(2A)-C(6A)	1.372(3)
C(2A)-C(3A)	1.348(4)
C(2A)-H(2A)	0.96(3)
C(3A)-C(4A)	1.447(3)
C(5A)-C(6A)	1.340(4)
C(5A)-H(5A)	0.92(3)
I(2)-C(1B)	2.049(3)
S(2)-O(5B)	1.408(2)
S(2)-O(4B)	1.418(2)
S(2)-O(3B)	1.591(2)
S(2)-C(7B)	1.833(3)
F(1B)-C(7B)	1.323(3)
F(2B)-C(7B)	1.325(4)
F(3B)-C(7B)	1.321(3)
O(1B)-C(1B)	1.361(3)
O(1B)-C(2B)	1.374(3)
O(2B)-C(4B)	1.357(3)
O(2B)-C(5B)	1.376(3)
O(3B)-C(6B)	1.394(3)
N(1B)-C(1B)	1.295(3)
N(1B)-C(3B)	1.392(3)
N(2B)-C(4B)	1.298(3)
N(2B)-C(6B)	1.381(3)
C(2B)-C(3B)	1.345(4)
C(2B)-H(2B)	0.95(3)
C(3B)-C(4B)	1.461(4)
C(5B)-C(6B)	1.344(4)
C(5B)-H(5B)	1.14(3)
O(5A)-S(1)-O(4A)	122.97(13)
O(5A)-S(1)-O(3A)	106.06(12)
O(4A)-S(1)-O(3A)	110.99(12)
O(5A)-S(1)-C(7A)	107.22(13)
O(4A)-S(1)-C(7A)	106.61(13)
O(3A)-S(1)-C(7A)	100.73(12)

C(1A)-O(1A)-C(2A)	104.0(2)
C(4A)-O(2A)-C(5A)	105.2(2)
C(6A)-O(3A)-S(1)	119.74(17)
C(1A)-N(1A)-C(3A)	103.7(2)
C(4A)-N(2A)-C(6A)	102.6(2)
N(1A)-C(1A)-O(1A)	115.2(2)
N(1A)-C(1A)-I(1)	125.35(19)
O(1A)-C(1A)-I(1)	119.42(17)
C(3A)-C(2A)-O(1A)	107.7(2)
C(3A)-C(2A)-H(2A)	131.2(19)
O(1A)-C(2A)-H(2A)	120.6(19)
C(2A)-C(3A)-N(1A)	109.4(2)
C(2A)-C(3A)-C(4A)	130.7(2)
N(1A)-C(3A)-C(4A)	119.9(2)
N(2A)-C(4A)-O(2A)	114.1(2)
N(2A)-C(4A)-C(3A)	129.4(2)
O(2A)-C(4A)-C(3A)	116.4(2)
C(6A)-C(5A)-O(2A)	105.6(2)
C(6A)-C(5A)-H(5A)	135(2)
O(2A)-C(5A)-H(5A)	119(2)
C(5A)-C(6A)-N(2A)	112.5(2)
C(5A)-C(6A)-O(3A)	130.0(2)
N(2A)-C(6A)-O(3A)	117.5(2)
F(2A)-C(7A)-F(1A)	108.7(3)
F(2A)-C(7A)-F(3A)	108.9(2)
F(1A)-C(7A)-F(3A)	108.4(2)
F(2A)-C(7A)-S(1)	111.1(2)
F(1A)-C(7A)-S(1)	109.2(2)
F(3A)-C(7A)-S(1)	110.4(2)
O(5B)-S(2)-O(4B)	123.51(14)
O(5B)-S(2)-O(3B)	107.15(13)
O(4B)-S(2)-O(3B)	110.21(11)
O(5B)-S(2)-C(7B)	106.84(14)
O(4B)-S(2)-C(7B)	107.37(13)
O(3B)-S(2)-C(7B)	98.96(12)
C(1B)-O(1B)-C(2B)	104.3(2)
C(4B)-O(2B)-C(5B)	104.9(2)
C(6B)-O(3B)-S(2)	119.66(16)
C(1B)-N(1B)-C(3B)	103.1(2)
C(4B)-N(2B)-C(6B)	102.8(2)
N(1B)-C(1B)-O(1B)	114.9(2)
N(1B)-C(1B)-I(2)	128.2(2)
O(1B)-C(1B)-I(2)	116.89(18)
C(3B)-C(2B)-O(1B)	107.2(2)
C(3B)-C(2B)-H(2B)	131.5(18)
O(1B)-C(2B)-H(2B)	121.3(18)
C(2B)-C(3B)-N(1B)	110.5(2)
C(2B)-C(3B)-C(4B)	126.9(2)
N(1B)-C(3B)-C(4B)	122.5(2)
N(2B)-C(4B)-O(2B)	114.6(2)
N(2B)-C(4B)-C(3B)	127.2(2)
O(2B)-C(4B)-C(3B)	118.2(2)
C(6B)-C(5B)-O(2B)	105.9(2)
C(6B)-C(5B)-H(5B)	131.3(14)

O(2B)-C(5B)-H(5B)	122.7(14)
C(5B)-C(6B)-N(2B)	111.8(2)
C(5B)-C(6B)-O(3B)	128.0(2)
N(2B)-C(6B)-O(3B)	120.0(2)
F(3B)-C(7B)-F(2B)	109.7(2)
F(3B)-C(7B)-F(1B)	109.1(2)
F(2B)-C(7B)-F(1B)	109.2(2)
F(3B)-C(7B)-S(2)	110.4(2)
F(2B)-C(7B)-S(2)	109.83(19)
F(1B)-C(7B)-S(2)	108.5(2)

Table A5.1.4 Anisotropic displacement parameters ($Å^2$ x 10^4) for **226** (CCDC 282586). The anisotropic displacement factor exponent takes the form: $-2\pi^2$ [$h^2 a^{*2} U^{11}$ + ... + 2 h k a* b* U^{12}].

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
I(1)	213(1)	135(1)	163(1)	-16(1)	4(1)	9(1)
S(1)	183(3)	205(4)	153(3)	-35(3)	0(2)	-9(3)
F(1A)	608(14)	276(11)	434(11)	62(9)	-48(10)	-215(10)
F(2A)	367(11)	449(13)	360(10)	124(9)	119(8)	207(9)
F(3A)	441(11)	258(10)	157(8)	-11(7)	8(7)	21(8)
O(1A)	131(10)	257(11)	224(10)	-80(8)	-11(8)	-7(8)
O(2A)	136(9)	185(11)	236(10)	-76(8)	-20(8)	45(8)
O(3A)	206(10)	161(10)	152(9)	-19(7)	26(7)	-28(8)
O(4A)	150(10)	334(13)	327(11)	-115(10)	-19(8)	-27(9)
O(5A)	324(12)	273(12)	146(9)	-47(8)	16(8)	33(9)
N(1A)	124(11)	134(12)	187(11)	-6(9)	-6(8)	15(8)
N(2A)	144(11)	171(12)	151(10)	12(9)	13(8)	-11(9)
C(1A)	140(13)	128(14)	174(12)	9(10)	20(10)	-9(10)
C(2A)	145(14)	194(16)	259(14)	-88(12)	25(11)	18(11)
C(3A)	118(12)	121(13)	160(12)	17(10)	12(9)	3(9)
C(4A)	124(13)	112(13)	164(12)	28(10)	-1(10)	2(9)
C(5A)	195(15)	192(16)	195(13)	-46(11)	-42(11)	41(11)
C(6A)	157(13)	135(14)	164(12)	-2(10)	29(10)	-5(10)
C(7A)	239(15)	191(16)	226(14)	-28(12)	57(11)	-15(12)
I(2)	383(1)	149(1)	293(1)	70(1)	73(1)	31(1)
S(2)	176(3)	178(4)	232(3)	67(3)	23(3)	11(3)
F(1B)	316(11)	599(14)	258(9)	217(9)	-64(8)	-25(9)
F(2B)	304(10)	273(10)	239(8)	-8(7)	55(7)	-9(8)
F(3B)	225(9)	261(10)	377(10)	80(8)	25(8)	-79(7)
O(1B)	205(10)	185(11)	195(9)	21(8)	56(8)	14(8)
O(2B)	177(10)	152(10)	161(9)	11(7)	36(7)	36(7)
O(3B)	237(10)	140(10)	158(9)	28(7)	-17(7)	-3(8)
O(4B)	143(10)	293(12)	344(11)	134(10)	-20(8)	-26(8)
O(5B)	366(13)	186(12)	423(13)	75(10)	110(10)	88(9)
N(1B)	172(12)	139(12)	150(10)	0(9)	7(9)	14(9)
N(2B)	179(12)	122(12)	129(10)	5(8)	-3(8)	5(9)
C(1B)	210(14)	129(14)	160(12)	-2(10)	1(10)	30(10)
C(2B)	222(15)	126(14)	155(12)	4(10)	2(10)	47(11)
C(3B)	145(13)	130(14)	129(11)	-25(10)	-29(9)	18(10)
C(4B)	142(13)	144(14)	106(11)	-9(9)	-12(9)	1(10)
C(5B)	187(14)	150(14)	175(12)	18(10)	18(10)	-29(10)
C(6B)	196(14)	115(14)	145(11)	0(10)	-21(10)	-10(10)
C(7B)	189(15)	260(17)	235(14)	86(12)	-16(11)	-58(12)

Table A5.1.5 Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for **226** (CCDC 282586)

	x	y	z	U_{iso}
H(2A)	-3150(60)	5540(20)	3230(20)	29(9)
H(5A)	5460(60)	6530(20)	5710(20)	31(9)
H(2B)	-260(50)	9040(20)	10145(19)	16(7)
H(5B)	8370(50)	9877(18)	7738(17)	12(7)

Table A5.1.6 Torsion angles [°] for **226** (CCDC 282586)

N(2A)-C(6A)-O(3A)-S(1)	-135.1(2)
N(2B)-C(6B)-O(3B)-S(2)	-81.0(3)
C(6A)-O(3A)-S(1)-C(7A)	81.2(2)
C(6B)-O(3B)-S(2)-C(7B)	-96.8(2)

Table A5.1.7 CH···N hydrogen bonds for **226** (CCDC 282586) [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(2A)-H(2A)...N(1A)#1	0.96(3)	2.61(3)	3.277(4)	127(2)
C(5A)-H(5A)...N(2A)#2	0.92(3)	2.72(3)	3.348(4)	127(2)
C(2B)-H(2B)...N(2B)#3	0.95(3)	2.45(3)	3.334(4)	155(2)
C(5B)-H(5B)...O(5A)#2	1.14(3)	2.54(3)	3.269(3)	120.1(17)
C(5B)-H(5B)...O(4B)#2	1.14(3)	2.40(3)	3.323(3)	136.6(18)

Symmetry transformations used to generate equivalent atoms:
#1 x-1,y,z
#2 x+1,y,z
#3 -x,-y+2,-z+2

APPENDIX SIX

Notebook Cross-Reference

The following notebook cross-reference has been included to facilitate access to the original spectroscopic data obtained for the compounds presented in this thesis. For each compound, both hardcopy and electronic characterization folders have been created that contain copies of the original ^{1}H NMR, ^{13}C NMR, and IR spectra. All notebooks and spectral data are stored in the Stoltz archives.

Table A6.1 Compounds appearing in Chapter 2: The Resolution of Important Pharmaceutical Building Blocks by Palladium-Catalyzed Aerobic Oxidation of Secondary Alcohols

Compound	^{1}H NMR	^{13}C NMR	IR
67	DDC-I-141	DDC-I-141	DDC-I-141
68	DDC-I-137	DDC-I-137	DDC-I-137
69	DDC-II-267-OH	DDC-II-267-OH	DDC-II-267-OH
70	DDC-II-269-OH	DDC-II-269-OH	DDC-II-269-OH
73	DDC-I-163	DDC-I-163	DDC-I-163
75	DDC-I-265	DDC-I-265	DDC-I-265
77	DDC-II-231	DDC-II-231	DDC-II-231
78	DDC-II-169	DDC-II-169	DDC-II-169

Table A6.2 Compounds appearing in Chapter 3: The Total Synthesis of (+)- and (–)-Dragmacidin F

Compound	^{1}H NMR	^{13}C NMR	IR
94	DDC-IV-223	DDC-III-107	DDC-IV-223
166	NKG-XVI-105	NKG-XVI-105	NKG-XVI-105
95	DDC-III-121	DDC-III-121	DDC-III-121
97	DDC-VIII-65	DDC-VIII-65	DDC-VIII-65
98	NKG-XXIII-75	NKG-XIX-133	NKG-XXIII-75
96	NKG-XIX-237	NKG-XIX-131	NKG-XIX-131
101	NKG-XV-123	NKG-XIX-103	NKG-XIX-103
170	DDC-IV-221	DDC-IV-221	DDC-IV-221
91	NKG-XIX-107	NKG-XIX-107	NKG-XIX-107
172	DDC-IV-217	DDC-IV-217	DDC-IV-217
92	DDC-IV-61	DDC-IV-61	NKG-XVIII-63
90	NKG-XIV-301P3 ($CDCl_3$) NKG-XXI-101 (C_6D_6)	NKG-XXI-101	NKG-XIX-112
102	NKG-XVI-295P1	NKG-XVI-295P1	NKG-XVI-295P1
107	DDC-VI-271	DDC-VI-271	DDC-VI-251
108	DDC-VIII-193	DDC-VIII-193	DDC-VIII-193
109	DDC-VIII-167	DDC-VIII-167	DDC-VIII-167
110	DDC-VIII-195	DDC-VIII-195	DDC-VIII-195
111	DDC-VI-269	DDC-VI-269	DDC-VIII-169
173	DDC-VIII-171	DDC-VIII-171	DDC-VIII-171
112	DDC-VIII-173	DDC-VIII-173	DDC-VIII-173
113	DDC-VIII-175	DDC-VIII-175	DDC-VIII-175
114	DDC-VIII-191	DDC-VIII-191	DDC-VIII-191
176	NKG-XIX-118	NKG-XIX-118	NKG-XIX-118
115	NKG-XIX-119	NKG-XIX-119	NKG-XIX-119
177	NKG-XIX-121	NKG-XIX-121	NKG-XIX-121
89	NKG-XIX-123	NKG-XIX-123	NKG-XIX-123
118	NKG-XIX-135	NKG-XIX-135	NKG-XIX-135
119	NKG-XIX-143	NKG-XIX-143	NKG-XIX-143

Compound	^{1}H NMR	^{13}C NMR	IR
120	NKG-XIX-139	NKG-XIX-139	NKG-XIX-139
124	NKG-XIX-37		
121	NKG-XIX-151	NKG-XIX-151	NKG-XIX-151
125	NKG-XIX-163	NKG-XIX-163	NKG-XIX-155
(+)-84	NKG-XIX-227B	NKG-XIX-227	NKG-XIX-227
129	DDC-VIII-143	DDC-VIII-143	DDC-VIII-143
180	NKG-XXII-53	NKG-XXII-53	NKG-XXII-53
132	DDC-VII-201	DDC-VII-195	DDC-VII-195
133	DDC-VII-207	DDC-VII-225	DDC-VII-207
131	DDC-VII-217	DDC-VII-213	DDC-VII-213
127	DDC-VIII-99	NKG-XXII-81	NKG-XXII-81
135	DDC-VIII-291	DDC-VIII-291	DDC-VIII-291
138	DDC-IX-51	DDC-IX-51	DDC-IX-51
137	DDC-IX-111	DDC-IX-111	DDC-IX-111
181	DDC-IX-35		
140	DDC-IX-41	DDC-IX-41	DDC-IX-41
141	DDC-IX-53	DDC-IX-53	DDC-IX-53
142	DDC-VII-67	DDC-VII-67	DDC-VII-67
143	DDC-VIII-121	DDC-VIII-121	DDC-VIII-121
144	DDC-VIII-117	DDC-VIII-117	DDC-VIII-117
145	DDC-VIII-81	DDC-VIII-55	DDC-VIII-81
146	NKG-XXII-41	NKG-XXII-41	NKG-XXII-41
147	NKG-XXII-43	NKG-XXII-43	NKG-XXII-43
148	DDC-VIII-69	DDC-VIII-69	DDC-VIII-69
149	DDC-VII-299	DDC-VII-299	DDC-VII-299
150	DDC-VIII-213	DDC-VIII-213	DDC-VIII-213
151	DDC-VIII-187	DDC-VIII-187	DDC-VIII-187
152	DDC-VIII-225	DDC-VIII-225	DDC-VIII-215-T
153	DDC-VIII-273 ($CDCl_3$) DDC-VIII-249-Prep (C_6D_6)	DDC-VIII-249-Prep	DDC-VIII-273
128	NKG-XXII-116	NKG-XXII-116	NKG-XXII-116
156	NKG-XXII-131	NKG-XXII-131	NKG-XXII-131

Compound	^{1}H NMR	^{13}C NMR	IR
157	DDC-VIII-165	DDC-VIII-165	DDC-VIII-165
158	DDC-VIII-199	DDC-VIII-199	DDC-VIII-199
159	NKG-XXII-97	DDC-VIII-189	DDC-VIII-189
160	DDC-VIII-299	DDC-VIII-299	DDC-VIII-299
161	DDC-VIII-197	DDC-VIII-197	DDC-VIII-197
187	NKG-XXIII-57	NKG-XXIII-57	NKG-XXIII-57
163	NKG-XXII-213	NKG-XXII-213	NKG-XXII-213
162	NKG-XXIII-35	NKG-XXII-209	NKG-XXII-209
(–)-84	NKG-XXIII-179		

Table A6.3 Compounds appearing in Chapter 4: Progress Toward The Total Synthesis of Telomestatin

Compound	^{1}H NMR	^{13}C NMR	IR
219	DDC-XI-191	HMZ-VII-275	HMZ-VII-275
220	TAD-I-137b2	HMZ-X-261	HMZ-X-261
214	DDC-XI-177	DDC-XI-177	DDC-XI-177
247	DDC-X-61	TAD-I-141	TAD-I-139
224	DDC-XIV-89	DDC-XIV-89	DDC-XIV-89
225	DDC-XIV-119	DDC-XIV-91	DDC-XIV-91
226	DDC-IX-291	DDC-XI-275	DDC-XI-275
227	DDC-XIV-87	HMZ-VII-283	HMZ-VII-283
228	DDC-XIII-277	HMZ-XI-235	HMZ-XI-235
230	DDC-XI-193	DDC-XIII-125	DDC-XIII-125
232	DDC-XI-205	DDC-XI-205	HMZ-IX-229
233	DDC-XI-269	DDC-XIII-129	DDC-XIII-129
235	DDC-XIV-115	DDC-XIV-115	DDC-XIV-115
236	DDC-XIV-111	DDC-XIV-111	DDC-XIV-111
238	DDC-XIV-79	DDC-XIV-79	DDC-XIV-79
215	JTM-XIII-247B	JTM-XIII-247B	JTM-XIII-247B

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ABOUT THE AUTHOR

Daniel D. Caspi was born on February 7, 1980, in Berkeley, CA. He was raised by his parents, Susan and Shlomo, and was joined shortly after his second birthday by his younger sister, Sara. Dan's childhood years were spent living in Alameda, CA, a suburb in the Bay Area and a former Naval base. He attended College Preparatory High School in Oakland, CA, where he played piano in the high school jazz band. His enthusiasm for chemistry was ignited by the AP Chemistry course, where he convinced the charismatic Mr. Coakley to add highly explosive laboratory experiments to the course repertoire.

After graduating from high school in 1998, Dan began his undergraduate studies at Revelle College at UC San Diego as a Chemistry major. After completing the organic chemistry lecture and laboratory series, and realizing that he was deeply interested in the subject, he was inspired to further his knowledge outside of the classroom. During the summer after his sophomore year, he began working at a local biotech company, Metabasis Therapeutics, Inc., where he received his first taste of medicinal chemistry research under the guidance of Dr. Jorge Gomez. Dan was also a teaching assistant for an undergraduate chemistry course for non-chemistry majors, where he tried, with limited success, to convert social science majors to the physical sciences.

In 2002, Dan's passion for organic chemistry led him to sunny Pasadena, CA, to pursue doctoral studies with Professor Brian M. Stoltz at the California Institute of Technology. In 2008, he earned his Ph.D. in chemistry for investigations involving the use of palladium in the context of pharmaceutical and natural product synthesis. Dan will join the process group at Abbott Laboratories in North Chicago, IL, in March of 2008.