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### Title

I, Studies directed towards the total synthesis of nocathiacin III : II, the development of a new synthetic technology for the construction of N-hydroxyindoles and synthesis of nocathiacin model systems ; III, the development of a mild and selective...

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- I.** Studies Directed Towards the Total Synthesis of Nocathiacin III.
- II.** The Development of a New Synthetic Technology for the Construction of *N*-Hydroxyindoles and Synthesis of Nocathiacin Model Systems.
- III.** The Development of a Mild and Selective Method for the Hydrolysis of Esters with Trimethyltin Hydroxide.
- IV.** Contributions Towards the Total Synthesis of Thiostrepton

A dissertation submitted in partial satisfaction of the  
Requirements for the Degree of Philosophy

in

Chemistry

by

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2008

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Chair

University of California, San Diego

2008

## **DEDICATION**

This work is dedicated to the memories of Celia Estrada, Donald and Emma Roe, and  
Candice Green.

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## LIST OF SYMBOLS AND ABBREVIATIONS

Ac	acetyl
Ac <sub>2</sub> O	acetic anhydride
AcOH	acetic acid
All	allyl
Alloc	allyloxycarbonyl
Bn	benzyl
Boc	<i>tertiary</i> -butoxycarbonyl
br	broad
Bu	butyl
<i>t</i> Bu	<i>tertiary</i> -butyl
°C	Celsius
ca.	calculated
$\delta$	chemical shift in ppm
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	diisobutylaluminum hydride
4-DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide

DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
equiv	equivalents
Et	ethyl
Et <sub>2</sub> O	diethyl ether
EtOAc	ethyl acetate
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
Fm	9-fluorenylmethyl
Fmoc	9-fluorenylmethoxycarbonyl
g	gram
h	hour
hept	heptet
HRMS	high-resolution mass spectroscopy
HATU	<i>O</i> -(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
HBTU	<i>O</i> -(Benzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	1-hydroxybenzotriazole
Hz	Hertz
Imid	imidazole
<i>i</i> Pr	isopropyl

IR	infrared
$J$	coupling constant in Hertz
kg	kilogram
L	liter(s)
M	molar
m	multiplet
MALDI	matrix-assisted laser-desorption ionization
Me	methyl
mg	milligram
MHz	megahertz
min	minutes
$\mu\text{L}$	microliters
mL	milliliters
$\mu\text{M}$	micromolar
mM	millimolar
mmol	millimole
MOM	methoxymethyl
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
MS	molecular sieves
NMR	nuclear magnetic resonance
$\nu$	frequency
Nu	nucleophile

Pd/C	palladium on carbon
Ph	phenyl
PMB	4-methoxybenzyl
pyr	pyridine
PRSP	penicillin-resistant <i>Streptococcus pneumoniae</i>
PTLC	preparatory thin layer chromatography
PyBOP	benzotriazol-1-yl- <i>N</i> -oxy-tris(pyrrolidino) phosphonium hexafluorophosphate
q	quartet
quin	quintuplet
$R_f$	retention factor
rsm	recovered starting material
s	singlet
SEM	2-(trimethylsilyl)ethoxymethyl
sep	septet
sext	sextet
SiO <sub>2</sub>	silica gel
t	triplet
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	<i>tert</i> -butyldimethylsilyl
TES	triethylsilane

TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
Tf <sub>2</sub> O	trifluoromethanesulfonic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilane
TLC	thin layer chromatography
TMSE	2-trimethylsilylethanol
<i>p</i> TsOH	<i>para</i> -toluenesulfonic acid
UV	ultraviolet
VRE	vancomycin-resistant enterococci
[Zn]	activated zinc

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## Publications

1. Total Synthesis of Thiostrepton, Part 1: Construction of the Dehydropiperidine/Thiazoline-Containing Macrocyclic. K.C. Nicolaou, Brian S. Safina, Mark Zak, Anthony A. Estrada, Sang Hyup Lee, *Angew. Chem. Int. Ed.* **2004**, *43*, 5087–5092.
2. Total Synthesis of Thiostrepton, Part 2: Construction of the Quinaldic Acid Macrocyclic and Final Stages of the Synthesis. K.C. Nicolaou, Mark Zak, Brian S. Safina, Sang Hyup Lee, Anthony A. Estrada, *Angew. Chem. Int. Ed.* **2004**, *43*, 5092–5097.
3. A Mild and Selective Method for the Hydrolysis of Esters with Trimethyltin Hydroxide. K.C. Nicolaou, Anthony A. Estrada, Mark Zak, Sang Hyup Lee, Brian S. Safina, *Angew. Chem. Int. Ed.* **2005**, *44*, 1378–1382.
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  8. Synthesis of Highly Substituted *N*-Hydroxyindoles by 1,5-Addition of Carbon Nucleophiles to Unsaturated Nitrones. K.C. Nicolaou, Anthony A. Estrada, Sang Hyup Lee, Graeme C. Freestone, *Angew. Chem. Int. Ed.* **2006**, *45*, 5364–5368.
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## ABSTRACT OF THE DISSERTATION

- I. Studies Directed Towards the Total Synthesis of Nocathiacin III.
- II. The Development of a New Synthetic Technology for the Construction of *N*-Hydroxyindoles and Synthesis of Nocathiacin Model Systems.
- III. The Development of a Mild and Selective Method for the Hydrolysis of Esters with Trimethyltin Hydroxide.
- IV. Contributions Towards the Total Synthesis of Thiostrepton

by

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Doctor of Philosophy in Chemistry

University of California, San Diego, 2008

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The nocathiacins are a family of three thiopeptide antibiotics that possess remarkable biological activity and operate with a mechanism of action that involves

binding to rRNA and disrupting the elongation step of bacterial protein synthesis. Chapter 1 details the retrosynthetic strategy and synthesis of advanced tetrasilylated nocathiacin III intermediate **1.45**. The highlights of the synthesis include the efficient construction of the 3-hydroxypyridine core (**1.9**) via a hetero-Diels–Alder reaction and a novel transannular *N*-hydroxyindole/macroetherification reaction which accomplishes bicycle and *N*-hydroxyindole formation in a one-pot cascade process.

Chapter 2 outlines the development of a new synthetic method for the construction of 3-substituted *N*-hydroxyindoles via 1,5-nucleophilic addition to highly reactive nitron species. The described chemistry provides a versatile entry into substituted *N*-hydroxyindoles carrying O-, S-, and carbon nucleophilic moieties, creating a diverse library of potentially biologically active and synthetically useful compounds. Furthermore, the method was applied to the successful synthesis of nocathiacin model systems through inter- and intramolecular etherification processes.

Chapter 3 describes the discovery of a mild and selective method for the hydrolysis of esters employing trimethyltin hydroxide, which has found broad applicability in total synthesis since our publication. The overall scope and generality of the protocol is demonstrated as well as the remarkable sensitivity of this reagent upon exposure to highly epimerization sensitive substrates such as thiazolines and dichlorinated aryl glycine moieties. The propensity of Me<sub>3</sub>SnOH to selectively hydrolyze methyl esters over other esters is also shown.

Chapter 4 reveals the significant contributions made towards the total synthesis of the thiopeptide antibiotic thiostrepton (**4.1**), which was completed in 2004. These



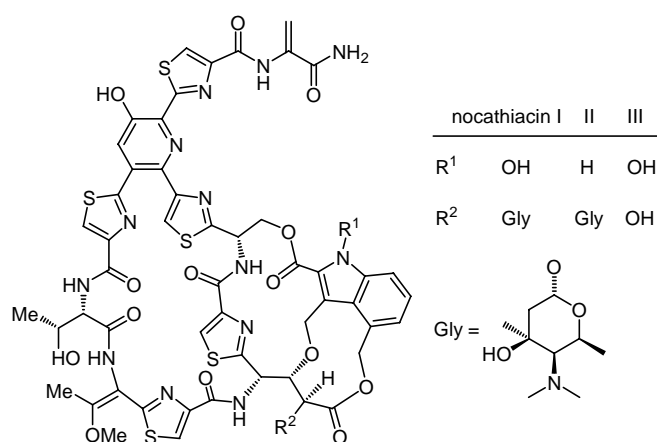
include the concise, multi-gram scale synthesis of bis-dehydroalanine tail fragment **4.4**, and the elucidation of the *C5/C6* dehydropiperidine core stereochemistry.

**Chapter 1: Studies Directed Towards the Total Synthesis of  
Nocathiacin III: Synthesis of the 3-Hydroxypyridine Core and  
Construction of an Advanced Nocathiacin III Intermediate**

## A. Introduction

### 1. Isolation and Biological Activity of the Nocathiacins

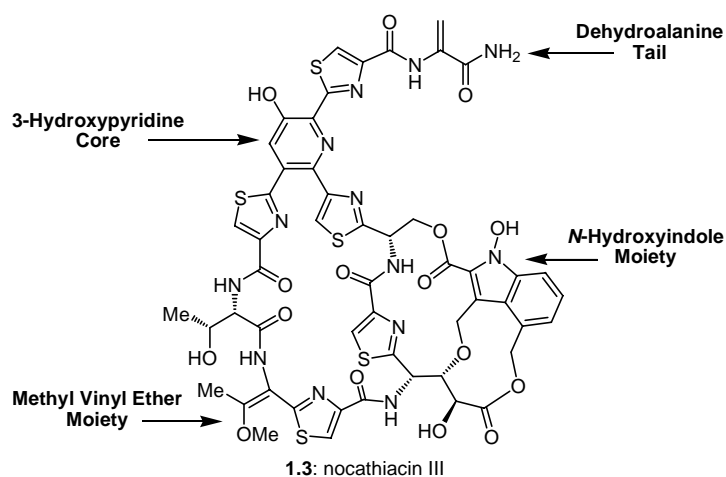
Nocathiacin I (**1.1**, Figure 1.1) and its naturally occurring analogs, nocathiacin II (**1.2**) and III (**1.3**), are members of the thiopeptide class of antibiotics.<sup>1</sup> Isolated from *Amicolaptosis* sp. in 1998,<sup>2</sup> and subsequently from *Nocardia* sp. (ATCC-202099) in 2002,<sup>3</sup> they exhibit strikingly potent activity *in vitro* (nanomolar potency) against a wide spectrum of Gram-positive bacteria (including multiple-drug resistant pathogens such as MRSA, VRE and PRSP) as well as excellent *in vivo* efficacy in a systemic *S. aureus* infection mice model, with potency comparable to that of vancomycin in the same study.<sup>3</sup> Their use in humans, however, has thus far been impractical due to pharmacokinetic and solubility issues. The mechanism of action of the nocathiacins, similar to that of thiostrepton, involves binding to the 23S rRNA of the 50S ribosomal subunit at the same site as the L11 ribosomal protein, thereby stalling translation and affecting the elongation step of bacterial protein synthesis.<sup>4</sup>



**Figure 1.1** Molecular structure of nocathiacin I (**1.1**), II (**1.2**) and III (**1.3**).

## 2. Structural Features and Retrosynthetic Analysis of Nocathiacin III

From a synthetic perspective, nocathiacin III (**1.3**) presents a formidable challenge. Its densely functionalized architecture, including hydroxypyridine and *N*-hydroxyindole moieties, and numerous ester and amide bonds, require the use of several orthogonal protecting groups, whose installation and timely release necessitate careful planning and constant adaptation. Furthermore, the sensitive nature of the *N*-hydroxyindole and methyl vinyl ether moieties required late stage assembly, which added an increased risk factor to the existing synthetic challenges posed by this highly complex natural product.

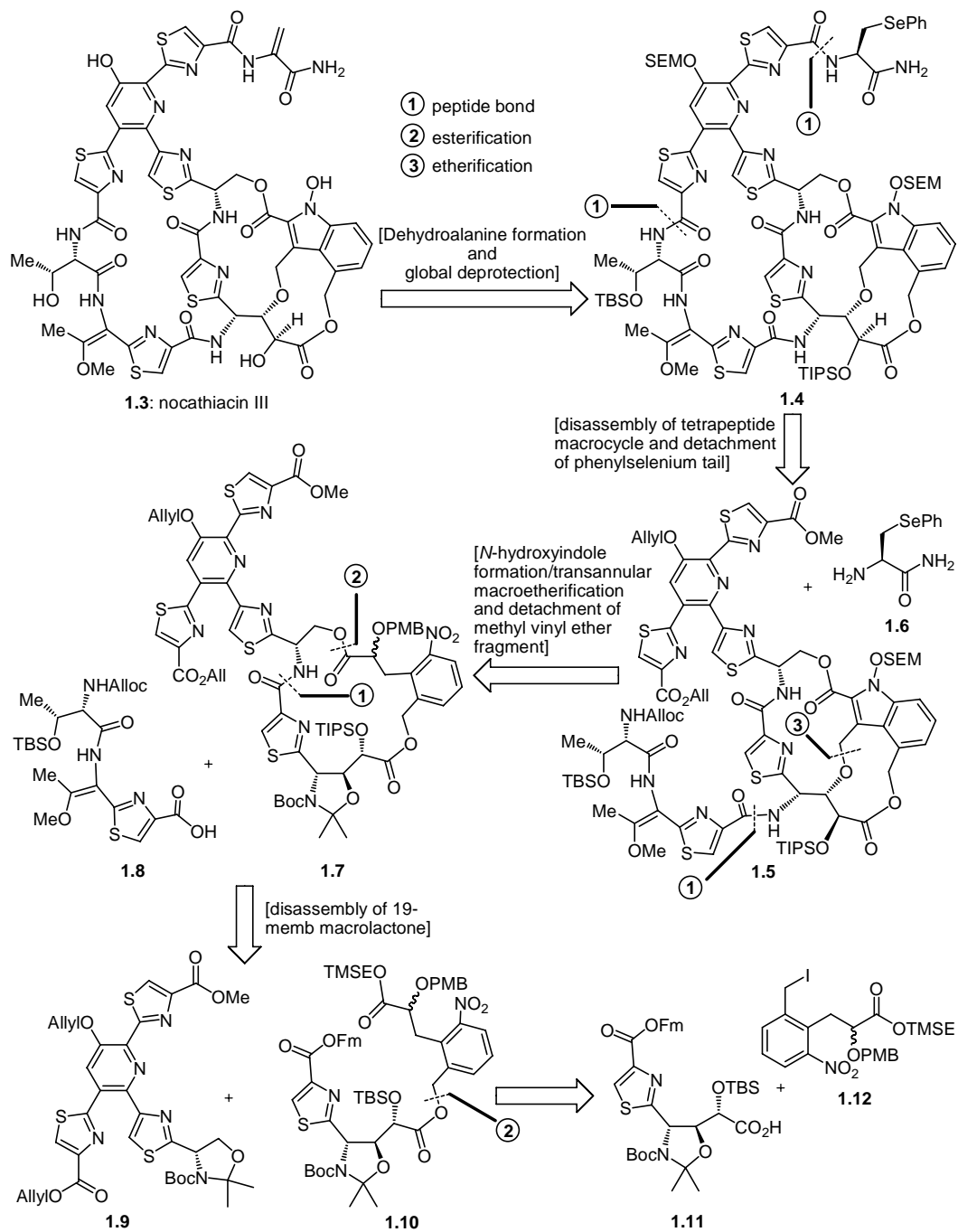


**Figure 1.2** Important structural features of nocathiacin III (**1.3**).

Structurally, nocathiacin III (**1.3**, Figure 1.2) encompasses 6 stereogenic centers (three of which do not arise from amino acids), 11 rings, an *E*-tetrasubstituted double bond, and a tail comprised of a dehydroalanine residue. Among its rings are five thiazoles, a central 3-hydroxypyridine, a novel *N*-hydroxyindole, a 26-membered

tetrapeptide ring, and two complex macrocyclic (15- and 10-membered) domains bridged by an ether linkage. The current retrosynthetic analysis, shown in Figure 1.3, reveals the five major building blocks: hydroxypyridine core **1.9**, methyl vinyl ether subunit **1.8**, tail precursor **1.6**, *N*-hydroxyindole precursor **1.12**, and amino diol subunit **1.11**.

Thus, nocathiacin III (**1.3**, Figure 1.3) is expected to arise from its protected form **1.4** through dehydroalanine formation and global deprotection. Proceeding in the reverse direction, known tail fragment **1.6**<sup>5</sup> is excised from nocathiacin precursor **1.4**, and the 26-membered macrocyclic domain is disassembled at the indicated carbon–nitrogen bond to give advanced intermediate **1.5**. Further retrosynthetic simplification is accomplished by rupturing the indicated carbon–oxygen bond creating the 19-membered provisional macrocycle **1.7**, and detachment of methyl vinyl ether acid **1.8** through an amide bond disconnection. The resulting macrocycle (**1.7**) is dismantled through rupture of the indicated ester bond to give, after further peptide bond disconnection, 3-hydroxypyridine core **1.9** and ester **1.10**. Finally, scission of the indicated ester bond reveals building blocks **1.11** and **1.12**.



**Figure 1.3** Retrosynthetic analysis of nocathiacin III (1.3) and definition of key building blocks 1.6, 1.8, 1.9, 1.11, and 1.12.

## B. 3-Hydroxypyridine Core

### 1. 3-Hydroxypyridine Core Retrosynthetic Analysis

The retrosynthetic strategy and design for the central 3-hydroxypyridine core (**1.9**) is depicted in Figure 1.4. Retrosynthetic simplification reveals diester **1.13**, whose construction via a carefully planned oxazole hetero-Diels–Alder reaction<sup>6</sup> differed from the standard aza-Diels–Alder dimerization strategy commonly employed for several thiopeptide antibiotics.<sup>1c</sup> The SEM oxazole diene **1.14** could then be further dissected to give acid **1.15** and diethyl aminomalonate.

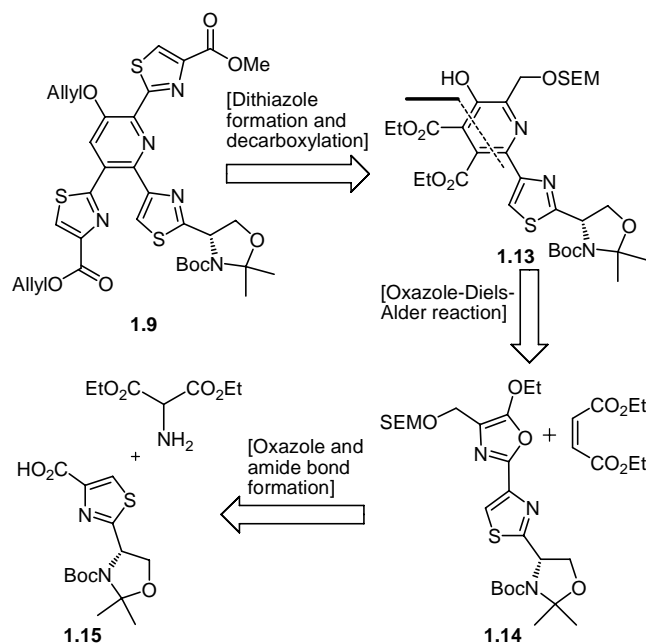


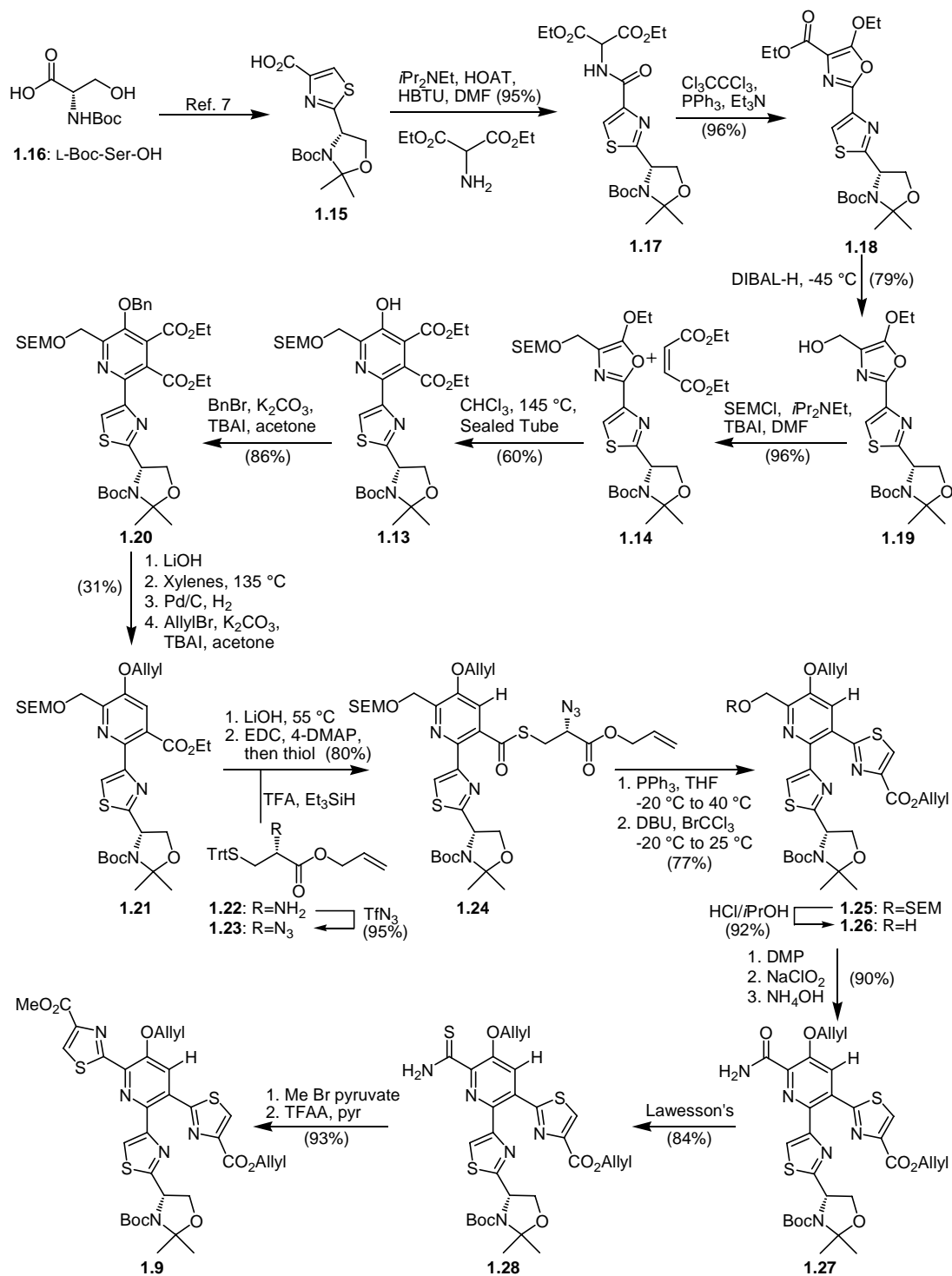
Figure 1.4 Retrosynthetic analysis of 3-hydroxypyridine core **1.9**.

### 2. Synthesis of the 3-Hydroxypyridine Core

Scheme **1.1** summarizes the synthesis of hydroxypyridine core **1.9**, which commences with the peptide coupling of known thiazole acid **1.15**<sup>7</sup>, derived from L-

Boc-Ser-OH (**1.16**), and commercially available diethyl aminomalonate to give diester **1.17** (HBTU, HOAt, *i*Pr<sub>2</sub>NEt) in 95% yield. A Robinson-Gabriel-type cyclodehydration using Morwick's mild conditions (Cl<sub>3</sub>CCCl<sub>3</sub>, Ph<sub>3</sub>P, Et<sub>3</sub>N, 96%)<sup>8</sup> followed by DIBAL-H reduction (79%) of the remaining ethyl ester and protection of the resulting primary alcohol as the SEM ether (SEMCl, *i*Pr<sub>2</sub>NEt, TBAI, 96%) furnished SEM oxazole **1.14** in 72% yield over three steps. A hetero-Diels–Alder reaction between SEM oxazole **1.14** and diethyl maleate conducted in a sealed tube at 145 °C yielded the desired 3-hydroxypyridine **1.13** in 60% yield, whose phenolic moiety was then capped as a benzyl ether (**1.20**, BnBr, K<sub>2</sub>CO<sub>3</sub>, TBAI, 18-crown-6, 86%). Selective LiOH monohydrolysis, thermal decarboxylation of the resulting monoacid (xylenes, 135 °C), hydrogenolysis (Pd/C, H<sub>2</sub>) and subsequent allylation (AllylBr, K<sub>2</sub>CO<sub>3</sub>, TBAI, 18-crown-6) provided monoester **1.21** in 31% yield over four steps. Hydrolysis of the remaining ester under more forcing conditions (LiOH, 55 °C), and thioester formation (**1.24**, EDC, 4-DMAP, 80% from **1.21**) utilizing the free thiol derived from azido-cysteine **1.23** gave us the opportunity to utilize Arndt's recently published aza-Wittig thiazole synthesis.<sup>9</sup> Thus, reduction of the azide (**1.24**) with PPh<sub>3</sub> followed by oxidation/aromatization with DBU and BrCCl<sub>3</sub> furnished thiazole allyl ester **1.25** in 77% yield over two steps. SEM removal (HCl/*i*PrOH, 92%) yielded primary alcohol **1.26**, which was then subjected to DMP and Pinnick oxidation<sup>10</sup>, followed by exposure to NH<sub>4</sub>OH to give amide **1.27** in 90% yield over three steps. Finally, subjection to Lawesson's reagent generated thioamide **1.28** (84%),





**Scheme 1.1** Synthesis of 3-hydroxypyridine core **1.9**.

whose conversion to hydroxypyridine core **1.9** was smoothly carried out via the Hantzsch protocol<sup>11</sup> (methyl bromopyruvate, then TFAA, 93% over two steps).

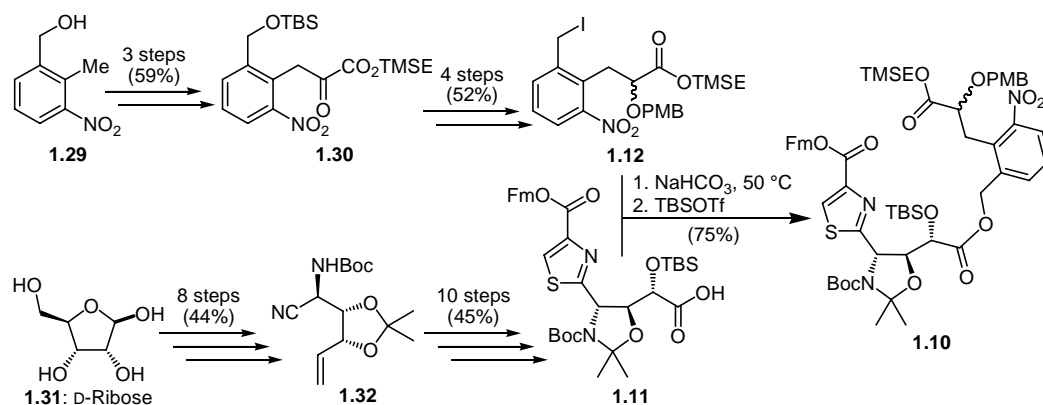
### 3. Conclusion

The successful gram scale synthesis of the orthogonally protected, central 3-hydroxypyridine core (**1.9**) of the nocathiacins stood as a significant achievement in several ways. The key ring forming process was conducted in a novel fashion rather than resorting to the previously employed aza-Diels–Alder dimerization. Additionally, the final fragment (**1.9**) was poised to undergo selective manipulation of the two thiazole ester protecting groups (C2 and C5, pyridine numbering) allowing for increased flexibility in the fragment assembly process. Furthermore, with the most synthetically challenging fragment completed, the possibility of completing the synthesis of the targeted natural products became much more of a reality.

## C. Construction of an Advanced Nocathiacin III Intermediate

### 1. Concurrent Work from These Laboratories

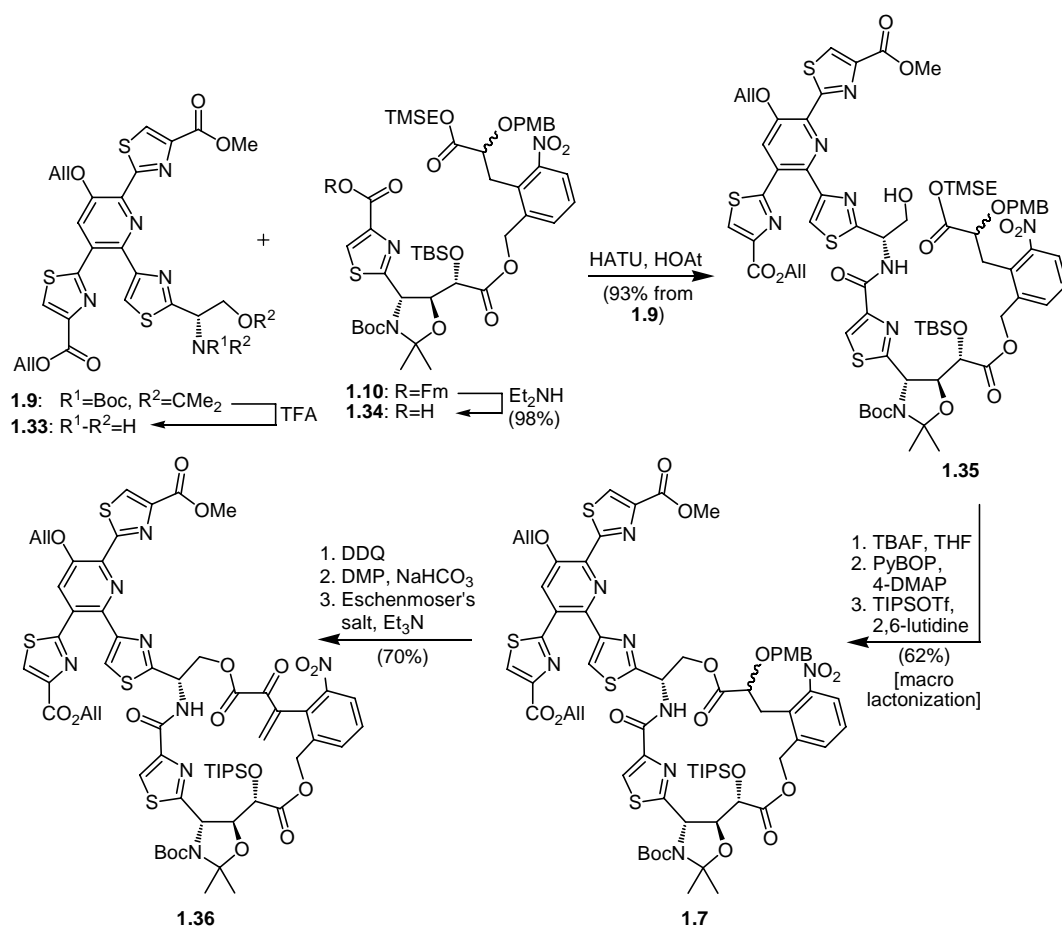
The synthesis and union of *N*-hydroxyindole precursor **1.12** and amino diol subunit **1.11** (Scheme 1.2) was accomplished primarily by post doctoral research associate Dr. Graeme Freestone, and therefore, highlights will only be presented here. *N*-Hydroxyindole precursor **1.12** was generated from commercially available 2-methyl-3-nitrobenzyl alcohol (**1.29**) through the intermediacy of TMSE ester **1.30** in 31% yield over 7 steps. Coupling partner **1.11** was furnished in 20% overall yield (18 steps) from D-ribose (**1.31**) via nitrile intermediate **1.32**, whose amine bearing stereocenter was installed through a Yb(OTf)<sub>3</sub> chelation controlled diastereoselective Strecker-type addition.<sup>12</sup> The coupled fragment **1.10** was formed through esterification of iodide **1.12** and acid **1.11** (NaHCO<sub>3</sub>, DMF, 50 °C) and reprotection of the exposed secondary alcohol (TBSOTf, 75% over two steps). The latter was necessary because during the esterification, the TBS group underwent silyl migration to form an  $\alpha$ -hydroxy silyl ester that was liberated to the corresponding  $\alpha$ -hydroxy acid in solution.



**Scheme 1.2** Synthesis of *N*-hydroxyindole precursor-amino diol subunit **1.10**.

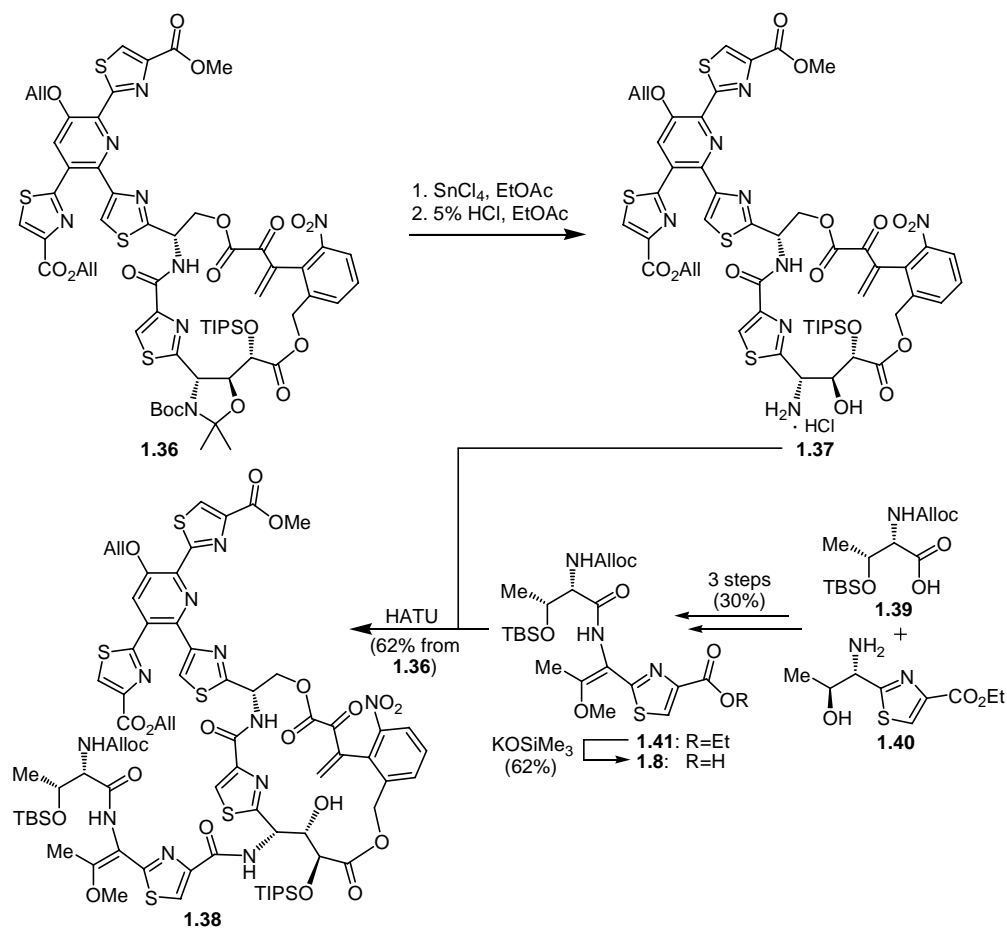
## 2. Fragment Assembly Process

The fragment assembly process (Scheme 1.3) commences with Et<sub>2</sub>NH mediated fluorenylmethyl ester removal and isopropylidene acetal/*N*-Boc deprotection with TFA to produce peptide coupling partners **1.34** (98% yield) and **1.33** respectively, whose union in the presence of HATU and HOAt proved very efficient (**1.35**, 93% from **1.9**). The TMSE ester and TBS ether were then removed simultaneously with TBAF and the resulting dihydroxy acid underwent regioselective macrolactonization under the influence of PyBOP and excess 4-DMAP. The



**Scheme 1.3** Synthesis of advanced  $\alpha,\beta$ -unsaturated ketoester intermediate **1.36**.

remaining alcohol was then resilylated with TIPSOTf and 2,6-lutidine to afford macrolactone **1.7** in 62% yield over 3 steps. The PMB ether was then removed through the action of DDQ to furnish a diastereomeric mixture of secondary alcohols, which underwent oxidation with DMP/NaHCO<sub>3</sub> and subsequent methylene insertion with Eschenmoser's Salt<sup>13</sup> to provide the  $\alpha,\beta$ -unsaturated ketoester **1.36** in 70% yield over three steps.

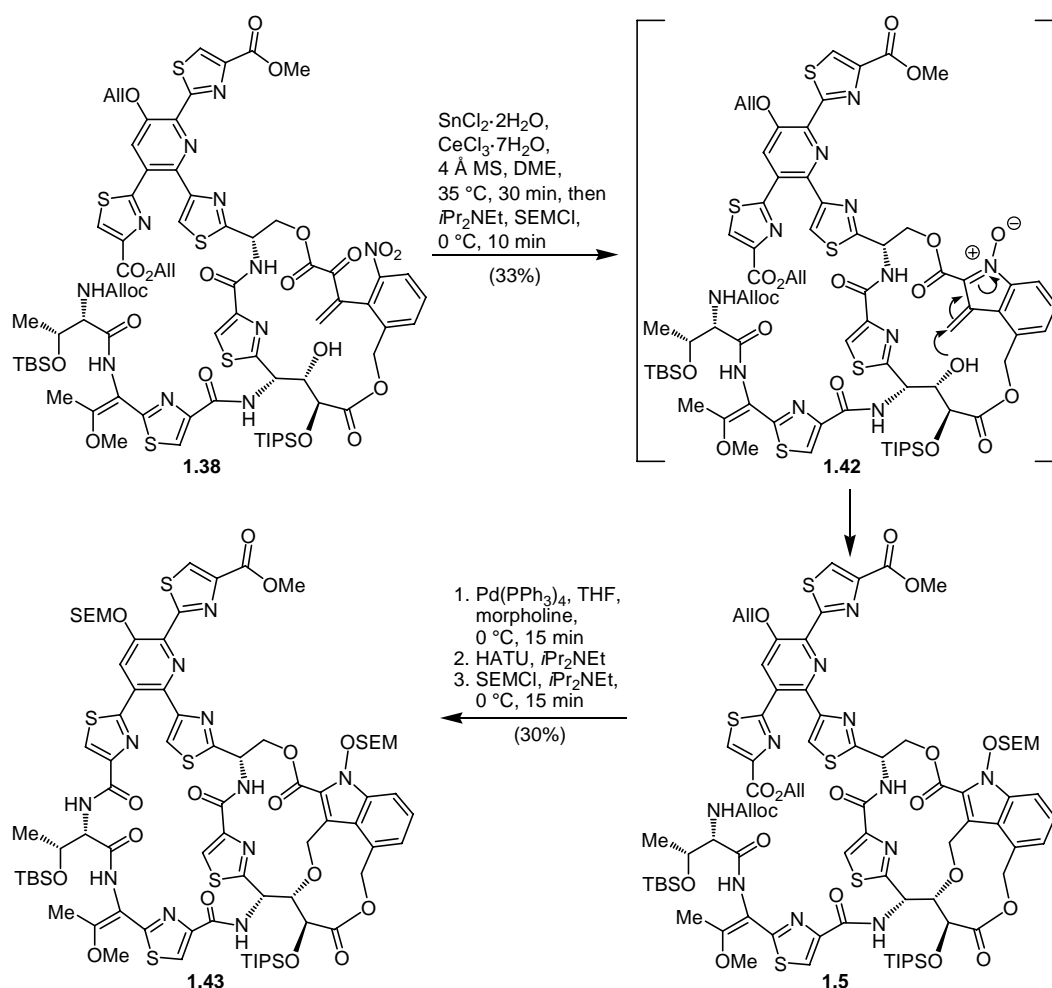


**Scheme 1.4** Synthesis of methyl vinyl ether subunit **1.8** and key reaction precursor **1.38**.

Scheme 1.4 depicts the elaboration of ketoester **1.36** into key reaction precursor **1.38** and highlights the synthesis of methyl vinyl ether fragment **1.8**, which was constructed by Dr. Graeme Freestone. Thus, after unsuccessful attempts to remove the *t*-butyl carbamate and acetonide protecting groups in one-pot, the *N*-Boc group was mildly and chemoselectively removed with anhydrous SnCl<sub>4</sub><sup>14</sup> and the remaining *N*-O acetal was deprotected by exposure to 5% HCl in dry EtOAc. The methyl vinyl ether acid **1.8**, synthesized from derivatized L-Thr building blocks **1.39** and **1.40** (19% over four steps), was then coupled to amino alcohol·HCl salt **1.37** (HATU, *i*Pr<sub>2</sub>NEt) to generate tripeptide **1.38** in 62% yield from **1.36** (three steps).

Applying our *N*-hydroxyindole synthetic methodology and utilizing the experience gained with the successfully designed model systems discussed in Chapter 2,<sup>15</sup> the transannular macroetherification/*N*-hydroxyindole formation of **1.38** was accomplished in one fell swoop (SnCl<sub>2</sub>·2H<sub>2</sub>O, 4 Å molecular sieves, CeCl<sub>3</sub>·7H<sub>2</sub>O, DME, 35 °C) to gratifyingly produce *N*-hydroxyindole **1.5**, after *in situ* SEM protection (SEMCl, *i*Pr<sub>2</sub>NEt, TBAI) in 33% yield (Scheme 1.5). This transformation is aided by the close proximity of the nitron and secondary alcohol reaction partners as depicted by proposed intermediate **1.42** (verified by manual molecular modeling). Additionally, the formation of the accompanying 1,4-addition by-product<sup>15</sup> (see Scheme 2.4, Chapter 2), that arises from hydroxylamine condensation onto the Michael acceptor rather than the ketone, is suppressed by the addition of CeCl<sub>3</sub>·7H<sub>2</sub>O to the reaction mixture. This optimization, however, could not be successfully applied to the more simplified systems presented in Chapter 2. Removal of the allyl ether,

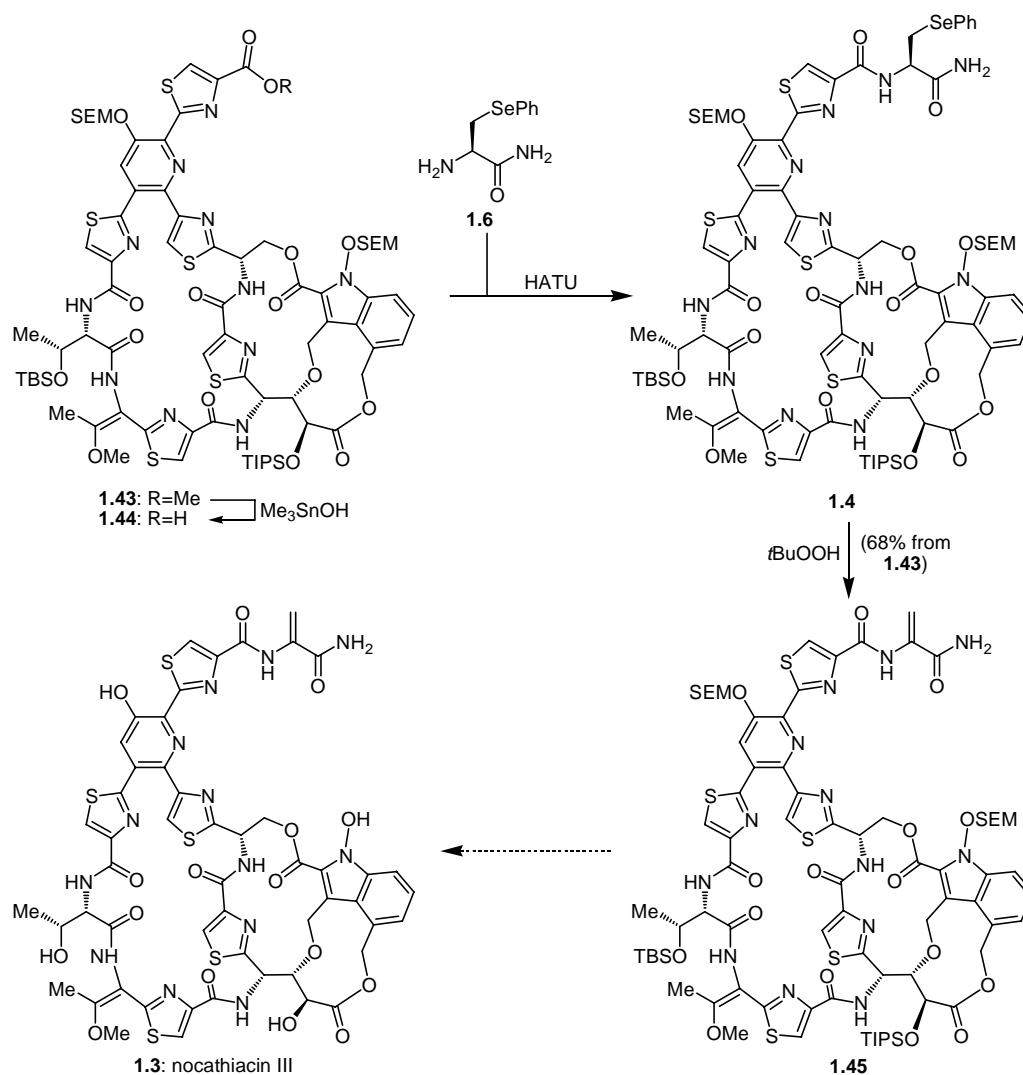
ester, and carbamate protecting groups in bicycle **1.5** [ $\text{Pd}(\text{PPh}_3)_4$ , morpholine, THF] was followed by macrolactamization (HATU,  $i\text{Pr}_2\text{NEt}$ ) and SEM protection (SEMCl,  $i\text{Pr}_2\text{NEt}$ , TBAI, 30% over three steps) of the free phenol to afford macrolactam **1.43**, which possesses the entire macrocyclic framework of the nocathiacins.



**Scheme 1.5** *N*-hydroxyindole formation via transannular etherification and synthesis of macrolactam **1.43**.

The selective hydrolysis of the methyl ester in the presence of the two lactone moieties in macrolactam **1.43** was accomplished through the mild action of  $\text{Me}_3\text{SnOH}$

(1,2-dichloroethane, 70 °C), which was developed in our laboratory and is discussed in detail in Chapter 3,<sup>16</sup> to yield acid **1.44**. Subsequent coupling with tail precursor **1.6** was achieved in the presence of *i*Pr<sub>2</sub>NEt and HATU to give tail coupled product **1.4**. Oxidation/elimination (*t*BuOOH) of the phenylselenium protecting group then proceeded efficiently to afford the tetrasilylated form (**1.45**, 68% from **1.43**) of nocathiacin III (**1.3**). All attempts to remove the silyl groups have unfortunately, thus far, been unsuccessful.



**Scheme 1.6** Synthesis of nocathiacin III precursor **1.45**.



### 3. Conclusion

In synthesizing advanced nocathiacin III tetrasilylated intermediate **1.45**, the ability to successfully incorporate all 5 synthetic building blocks in a convergent fragment assembly process has been demonstrated. This accomplishment encompassed the application of our *N*-hydroxyindole synthetic methodology to construct the bicyclic and *N*-hydroxyindole moieties in a cascade process, as well as the utilization of the Me<sub>3</sub>SnOH reagent to selectively hydrolyze a methyl ester, enabling the attachment of tail precursor **1.6** at a late stage juncture. As is the case with several complex total synthesis endeavors, the mild removal of protecting groups is commonly the final hurdle which must be overcome to release the natural product in its isolated form. With the lessons learned from recent attempts and the flexible approach adopted for the assembly process, optimism remains that the total synthesis of nocathiacin III (**1.3**) will be completed in the near future.

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## E. Experimental Section

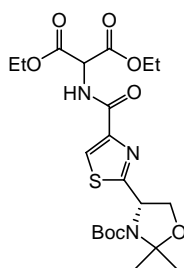
### 1. General Techniques

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, 1,2-dimethoxyethane (DME), and methylene chloride ( $\text{CH}_2\text{Cl}_2$ ) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically ( $^1\text{H}$  NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an ethanolic solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F<sub>254</sub>). Optical rotations were recorded on a Perkin–Elmer 343 polarimeter. NMR spectrum was recorded on Bruker DRX-600, DRX-500, AMX-500 or AMX-400 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s=singlet, d=doublet, t=triplet, q=quartet,  $\frac{1}{2}\text{ABq}=\frac{1}{2}\text{AB}$  quartet, m=multiplet, quin=quintuplet, sext=sextet, sep=septet, hept=heptet, br=broad. IR spectra were recorded on a Perkin–Elmer 1600 or Spectrum 100 series FTIR spectrometer.

Electrospray ionization (ESI) mass spectrometry (MS) experiments were performed on an API 100 Perkin–Elmer SCIEX single quadrupole mass spectrometer at 4000 V emitter voltage. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer using MALDI (matrix-assisted laser-desorption ionization) or ESI (electrospray ionization).

## 2. Preparation of Compounds

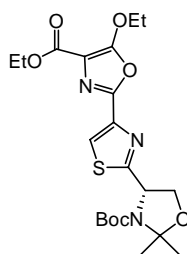
**1.17**: Known thiazole acid **1.15**<sup>7</sup> (4.43 g, 13.49 mmol) was dissolved in anhydrous DMF (67 mL) and cooled to 0 °C. *i*Pr<sub>2</sub>NEt (4.7 mL, 26.98 mmol), diethyl aminomalonate hydrochloride (2.86g, 13.49 mmol), HBTU (5.6 g, 14.84 mmol) and HOAt (2.0 g, 14.84 mmol) were then added and the reaction mixture was allowed to stir for 10 min at 0 °C and 2 h at 25 °C. The mixture was then diluted with EtOAc (100 mL), washed with H<sub>2</sub>O (150 mL), aqueous 5% HCl solution (50 mL), brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. Purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes, 30:70→40:60) afforded diester **1.17** (6.23 g, 95%) as a yellow oil.



**1.17**:  $R_f=0.59$  (silica gel, EtOAc/hexanes, 1:1);  $[\alpha]_D^{34} -31.6$  ( $c$  3.49, CH<sub>2</sub>Cl<sub>2</sub>); IR (film)  $\nu_{\max}$  3406, 2982, 2938, 2881, 1758, 1742, 1696, 1680, 1535, 1478, 1365, 1247,

1166, 1088, 1052, 848, 768  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ , 66  $^\circ\text{C}$ )  $\delta$  8.08 (s, 1H), 8.03 (br s, 1H), 5.26 (dd,  $J=6.3, 1.9$  Hz, 1H), 5.18 (d,  $J=6.6$  Hz, 1H), 4.34 (dd,  $J=9.2, 6.2$  Hz, 1H), 4.31–4.24 (m, 4H), 4.15 (dd,  $J=9.2, 1.8$  Hz, 1H), 1.72 (s, 3H), 1.58 (s, 3H), 1.39 (br s, 9H), 1.29–1.26 (m, 6H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  174.1, 166.1, 160.5 (2C), 151.3, 148.4, 124.2, 69.0, 68.5, 62.6 (2C), 60.3, 59.1 (2C), 56.3, 28.1 (3C), 26.4, 13.9 (2C); HRMS (ESI-TOF) calcd for  $\text{C}_{21}\text{H}_{32}\text{N}_3\text{O}_8\text{S}^+$   $[\text{M}+\text{H}^+]$  486.1905, found 486.1908.

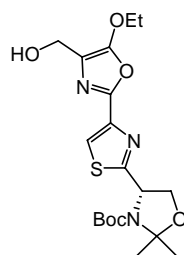
**1.18**:  $\text{PPh}_3$  (101.6 g, 0.39 mol) and  $\text{Cl}_3\text{CCCl}_3$  (91.7 g, 0.39 mol) were dissolved in  $\text{CH}_2\text{Cl}_2$  (1800 mL) and  $\text{Et}_3\text{N}$  (108 mL, 0.77 mol) was added dropwise at 0  $^\circ\text{C}$  followed by cannula addition of diester **1.17** (94 g, 0.19 mol) in  $\text{CH}_2\text{Cl}_2$  (200 mL). After 10 min at 0  $^\circ\text{C}$  and 5 h at 25  $^\circ\text{C}$ , the reaction mixture was poured into 900 mL  $\text{H}_2\text{O}$ , separated, and the organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. Purification of the residue by flash column chromatography (silica gel,  $\text{EtOAc}/\text{hexanes}$ , 20:80 $\rightarrow$ 50:50) afforded oxazole **1.18** (87.2 g, 96%) as a light yellow foam.



**1.18**:  $R_f=0.43$  (silica gel,  $\text{EtOAc}/\text{hexanes}$ , 1:1);  $[\alpha]_{\text{D}}^{34} -37.1$  ( $c$  3.41,  $\text{CH}_2\text{Cl}_2$ ); IR (film)  $\nu_{\text{max}}$  2981, 2937, 2881, 1701, 1622, 1598, 1364, 1264, 1203, 1168, 1088, 1055, 847, 733  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ , 66  $^\circ\text{C}$ )  $\delta$  7.91 (s, 1H), 5.27 (dd,  $J=6.5,$

1.7 Hz, 1H), 4.56 (q,  $J=7.0$  Hz, 2H), 4.34 (dd,  $J=9.2, 6.6$  Hz, 1H), 4.31 (q,  $J=7.0$  Hz, 2H), 4.15 (dd,  $J=9.2, 1.3$  Hz, 1H), 1.72 (s, 3H), 1.57 (s, 3H), 1.46 (t,  $J=7.0$  Hz, 3H), 1.39 (br s, 9H), 1.34 (t,  $J=7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  176.8, 162.6, 162.5, 152.8, 148.0, 143.7, 121.1, 109.3, 71.8, 70.1, 69.6, 63.9, 61.5 (2C), 60.6 (2C), 28.7 (3C), 15.6, 15.0; HRMS (ESI-TOF) calcd for  $\text{C}_{21}\text{H}_{30}\text{N}_3\text{O}_7\text{S}^+$   $[\text{M}+\text{H}^+]$  468.1799, found 468.1802.

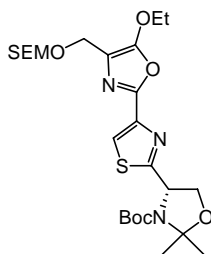
**1.19:** Oxazole ethyl ester **1.18** (87 g, 0.19 mol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (930 mL) and cooled to  $-45$  °C. DIBAL-H (465 mL, 0.47 mol, 1.0 M in  $\text{CH}_2\text{Cl}_2$ ) was then added dropwise with an addition funnel over 20 min and after stirring at  $-45$  °C for 3 h, the reaction mixture was quenched with MeOH (7.0 mL) and stirred for 12 h with saturated aqueous sodium potassium tartrate solution (500 mL). The mixture was extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 100\text{mL}$ ) and the combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. Purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes, 40:60  $\rightarrow$  acetone/hexanes, 80:20) afforded primary alcohol **1.19** (62.5 g, 79%) as a light yellow foam.



**1.19:**  $R_f=0.17$  (silica gel, EtOAc/hexanes, 8:2);  $[\alpha]_{\text{D}}^{34} -1.46$  ( $c$  1.89,  $\text{CH}_2\text{Cl}_2$ ); IR (film)  $\nu_{\text{max}}$  3355, 2981, 2936, 2886, 1700, 1655, 1365, 1252, 1168, 1089, 1053, 847,

733  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ , 66  $^\circ\text{C}$ )  $\delta$  7.82 (s, 1H), 5.27–5.26 (m, 1H), 4.41 (s, 2H), 4.34–4.30 (m, 3H), 4.14–4.13 (m, 1H), 1.72 (s, 3H), 1.57 (s, 3H), 1.42–1.38 (m, 12H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  176.5, 156.1, 153.6, 152.8, 149.5, 144.7, 119.8, 118.9, 72.1, 70.1, 69.6, 60.5 (2C), 60.4, 57.5, 55.7, 28.7 (3C), 15.6; HRMS (ESI-TOF) calcd for  $\text{C}_{19}\text{H}_{28}\text{N}_3\text{O}_6\text{S}^+$   $[\text{M}+\text{H}^+]$  426.1693, found 426.1696.

**1.14:** Primary alcohol **1.19** (58 g, 0.14 mol) was dissolved in DMF (650 mL) and cooled to 0  $^\circ\text{C}$ . *i*Pr<sub>2</sub>NEt (71.8 mL, 0.41 mol), SEMCl (48.6 mL, 0.27 mol), and TBAI (507 mg, 1.4 mmol) were then added and after stirring at 25  $^\circ\text{C}$  for 3 h, the reaction mixture was diluted with EtOAc (300 mL) and the organic layer was washed with H<sub>2</sub>O (500 mL), aqueous 5% HCl solution (100 mL), brine (100 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. Purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes, 20:80→50:50) afforded SEM oxazole **1.14** (72.7 g, 96%) as a light yellow oil.

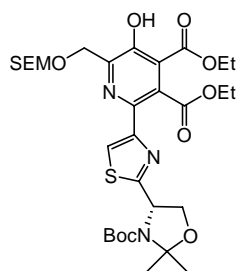


**1.14:**  $R_f=0.67$  (silica gel, EtOAc/hexanes, 6:4);  $[\alpha]_D^{34} -42.4$  (*c* 1.67,  $\text{CH}_2\text{Cl}_2$ ); IR (film)  $\nu_{\text{max}}$  2977, 2952, 2881, 1705, 1654, 1365, 1249, 1170, 1089, 1053, 1033, 838, 735  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ , 66  $^\circ\text{C}$ )  $\delta$  7.82 (s, 1H), 5.26 (dd,  $J=6.5, 1.7$  Hz, 1H), 4.70 (s, 2H), 4.42 (s, 2H), 4.35–4.31 (m, 3H), 4.14–4.13 (m, 1H), 3.67–3.65 (m,



2H), 1.72 (s, 3H), 1.57 (s, 3H), 1.41–1.39 (m, 12H), 0.96–0.93 (m, 2H), 0.03 (s, 9H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  176.5, 157.2, 152.8, 149.6, 144.7, 119.8, 115.9, 94.9, 72.1, 70.1, 69.6, 66.1, 62.0, 60.6 (3C), 60.4, 59.9, 28.7 (3C), 19.0, 15.7, –0.96 (3C); HRMS (ESI-TOF) calcd for  $\text{C}_{25}\text{H}_{42}\text{N}_3\text{O}_7\text{SSi}^+$  [ $\text{M}+\text{H}^+$ ] 556.2507, found 556.2511.

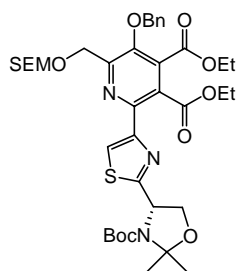
**1.13:** SEM oxazole **1.14** (34 g, 61.35 mmol) was dissolved in  $\text{CHCl}_3$  (61 mL) in a sealed tube and diethyl maleate (139 mL, 0.86 mol) was added. After stirring at 140 °C for 43 h, the volatiles were removed in vacuo and the remaining solution was purified by flash column chromatography (silica gel, EtOAc/hexanes, 5:95→40:60) to afford 3-hydroxypyridine **1.13** (25 g, 60%) as an orange oil.



**1.13:**  $R_f=0.40$  (silica gel, EtOAc/toluene, 2:8);  $[\alpha]_{\text{D}}^{36} -16.2$  ( $c$  2.88,  $\text{CH}_2\text{Cl}_2$ ); IR (film)  $\nu_{\text{max}}$  2980, 2946, 2886, 1735, 1703, 1365, 1247, 1223, 1166, 1096, 1053, 1039, 836, 768  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ , 66 °C)  $\delta$  10.22 (br s, 1H), 7.87 (s, 1H), 5.22 (dd,  $J=6.3, 1.5$  Hz, 1H), 4.83 (s, 2H), 4.82 (s, 2H), 4.45 (q,  $J=7.0$  Hz, 2H), 4.35–4.30 (m, 3H), 4.12 (dd,  $J=9.2, 1.9$  Hz, 1H), 3.68–3.65 (m, 2H), 1.71 (s, 3H), 1.57 (s, 3H), 1.41 (br s, 9H), 1.37 (t,  $J=7.0$  Hz, 3H), 1.28 (t,  $J=7.4$  Hz, 3H), 0.91–0.87 (m, 2H), 0.01 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ , 66 °C)  $\delta$  169.1, 168.0, 154.9, 153.8, 150.7, 150.3, 141.4, 127.8, 121.8, 120.0, 115.3, 96.8, 70.4, 70.3, 68.3, 66.9, 64.9, 63.3, 62.6,

61.2 (2C), 61.1, 29.4 (3C), 19.6, 15.1, 15.0, -0.50 (3C); HRMS (ESI-TOF) calcd for  $C_{31}H_{48}N_3O_{10}SSi^+$   $[M+H]^+$  682.2824, found 682.2824.

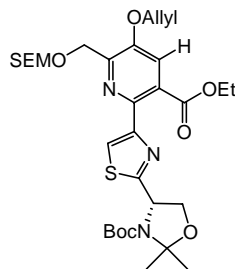
**1.20:** To 3-hydroxypyridine **1.13** (75 g, 0.11 mol) dissolved in acetone (550 mL) was added benzyl bromide (52.3 mL, 0.44 mol), 18-crown-6 (2.9 g, 11.0 mmol),  $K_2CO_3$  (69.1 g, 0.50 mol), and TBAI (4.1 g, 11.0 mmol). After refluxing for 12 h, the reaction mixture was cooled to 25 °C, filtered through celite and concentrated. Purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes, 10:90→20:80) afforded benzyl ether **1.20** (73 g, 86%) as a yellow oil.



**1.20:**  $R_f=0.56$  (silica gel, EtOAc/hexanes, 3:7);  $[\alpha]_D^{36} -16.2$  ( $c$  2.22,  $CH_2Cl_2$ ); IR (film)  $\nu_{max}$  2980, 2946, 2886, 1736, 1704, 1365, 1249, 1170, 1100, 1053, 849, 836, 733  $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $CD_3CN$ , 66 °C)  $\delta$  8.00 (s, 1H), 7.49–7.33 (m, 5H), 5.24 (br d,  $J=5.0$  Hz, 1H), 5.14 (s, 2H), 4.79 (s, 2H), 4.80 (s, 2H), 4.36–4.27 (m, 5H), 4.16 (dd,  $J=9.0, 1.5$  Hz, 1H), 3.66–3.63 (m, 2H), 1.72 (s, 3H), 1.58 (s, 3H), 1.44 (br s, 9H), 1.30 (t,  $J=7.0$  Hz, 3H), 1.25 (t,  $J=7.0$  Hz, 3H), 0.89–0.86 (m, 2H), -0.01 (s, 9H);  $^{13}C$  NMR (125 MHz,  $CD_3CN$ , 66 °C)  $\delta$  167.7, 166.4, 155.9, 154.8, 151.0, 146.7, 144.8, 138.5, 137.3, 130.3, 130.2, 129.9, 129.5, 128.5, 127.8, 121.2, 96.8, 79.9, 70.4, 70.3, 68.0, 67.0, 65.8, 64.2, 63.6, 63.1, 61.2, 61.1 (2C), 29.5 (3C), 19.6, 15.2, 15.1, -

0.3 (3C); HRMS (ESI-TOF) calcd for  $C_{38}H_{54}N_3O_{10}SSi^+$   $[M+H^+]$  772.3294, found 772.3282.

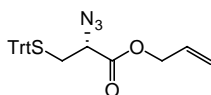
**1.21:** To benzyl ether **1.20** (71 g, 91.9 mmol) dissolved in THF (540 mL), EtOH (180 mL) and H<sub>2</sub>O (180 mL) was added LiOH (5.51 g, 230 mmol) at 0 °C. The reaction mixture was allowed to warm to 25 °C and after stirring for 16 h, aqueous 5% HCl solution (50 mL) was added and the volatiles were removed in vacuo. The resulting solution was diluted with EtOAc (300 mL), separated, washed with brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. Purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes, 20:80 → MeOH/CH<sub>2</sub>Cl<sub>2</sub> 15:85) afforded monoacid with a slight amount of diacid byproduct. The mixture was dissolved in xylenes (1537 mL), warmed to 130 °C, stirred for 6 h and concentrated. The crude residue was then dissolved in EtOH (174 mL) and Pd/C (2.45 g, 10% on activated carbon) was added. After purging with H<sub>2</sub> gas and stirring for 64 h at 25 °C under H<sub>2</sub>, the reaction mixture was filtered through celite and concentrated. To the crude mixture dissolved in acetone (300 mL) was added K<sub>2</sub>CO<sub>3</sub> (11.8 g, 85 mmol), allyl bromide (6.0 mL, 68 mmol) and 18-crown-6 (900 mg, 3.4 mmol) at 0 °C. After stirring for 12 h at 25 °C, the mixture was filtered through celite and concentrated. Purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes, 15:85→60:40) afforded allyl ether **1.21** (18.5 g, 31% over four steps) as a white foam.



**1.21:**  $R_f=0.46$  (silica gel, EtOAc/hexanes, 3:7);  $[\alpha]_D^{35} -32.0$  ( $c$  2.41,  $\text{CH}_2\text{Cl}_2$ ); IR (film)  $\nu_{\text{max}}$  2977, 2952, 2875, 1724, 1702, 1364, 1325, 1247, 1169, 1089, 1053, 1038, 859, 834, 734  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ , 66 °C)  $\delta$  7.79 (s, 1H), 7.44 (s, 1H), 6.13–6.05 (m, 1H), 5.46 (dq,  $J=17.5, 1.5$  Hz, 1H), 5.32 (dq,  $J=17.5, 1.5$  Hz, 1H), 5.21 (br d,  $J=5.5$  Hz, 1 H), 4.78 (s, 2H), 4.76 (s, 2H), 4.68 (dt,  $J=5.0, 1.5$  Hz, 2H), 4.32–4.25 (m, 3H), 4.13 (dd,  $J=9.0, 2.0$  Hz, 1H), 3.67–3.64 (m, 2H), 1.70 (s, 3H), 1.56 (s, 3H), 1.42 (br s, 9H), 1.23 (t,  $J=7.0$  Hz, 3H), 0.91–0.88 (m, 2H), 0.01 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ , 66 °C)  $\delta$  169.5, 156.2, 155.7, 154.0, 150.8, 134.6, 130.1, 127.9, 121.3, 119.2, 119.1, 96.7, 71.3, 70.5, 70.4, 67.6, 66.7, 63.1, 61.7, 61.1 (3C), 29.4 (3C), 19.6, 15.2,  $-0.5$  (3C); HRMS (ESI-TOF) calcd for  $\text{C}_{31}\text{H}_{48}\text{N}_3\text{O}_8\text{SSi}^+$   $[\text{M}+\text{H}^+]$  650.2926, found 650.2931.

**1.23:** Trifluoromethanesulfonic anhydride (109 mL, 647 mmol) was added dropwise to sodium azide (84 g, 1.29 mol) in water (215 mL) and  $\text{CH}_2\text{Cl}_2$  (215 mL) at 0 °C. The resulting mixture was stirred for 2 h at 0 °C, then saturated aqueous  $\text{NaHCO}_3$  solution (300 mL) was added. The layers were separated and the aqueous layer was re-extracted with  $\text{CH}_2\text{Cl}_2$  (2×160 mL). The combined organic layers were then washed with saturated aqueous  $\text{NaHCO}_3$  solution (100 mL). This trifluoromethanesulfonyl

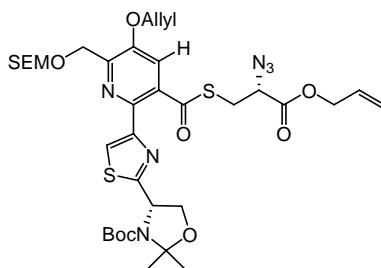
azide solution in  $\text{CH}_2\text{Cl}_2$  was added to a solution of H-L-STr-Cys-OAllyl (**1.22**, 87 g, 215 mmol) in EtOH (1700 mL) and  $\text{H}_2\text{O}$  (535 mL), followed by addition of  $\text{Et}_3\text{N}$  (120 mL, 860 mmol) and  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  (2.7 g, 10.8 mmol) at 25 °C. The reaction mixture was stirred for 1.5 h at 25 °C, and then the volatiles were removed in vacuo. The residual blue aqueous layer was extracted with EtOAc (3×200 mL) and the combined organic layers were washed with brine (100 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. Purification of the residue by flash column chromatography (silica gel, Et<sub>2</sub>O/hexanes, 20:80→50:50) afforded azide **1.23** (88 g, 95%) as an orange oil.



**1.23**:  $R_f=0.64$  (silica gel, EtOAc/hexanes, 2:8);  $[\alpha]_D^{35} -14.6$  ( $c$  4.35,  $\text{CH}_2\text{Cl}_2$ ); IR (film)  $\nu_{\text{max}}$  3386, 3279, 3058, 3027, 2109, 1742, 1489, 1445, 1265, 1186, 1153, 937, 740, 699  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.47–7.45 (m, 6H), 7.33–7.30 (m, 6H), 7.26–7.23 (m, 3H), 5.91–5.83 (m, 1H), 5.30 (dq,  $J=17.0$ , 1.5 Hz, 1H), 5.26 (dq,  $J=10.5$ , 1.0 Hz, 1H), 4.61 (dq,  $J=6.0$ , 1.5 Hz, 2H), 3.24 (dd,  $J=8.0$ , 6.0 Hz, 1H), 2.71 (dd,  $J=13.5$ , 6.0 Hz, 1H), 2.59 (dd,  $J=13.0$ , 8.0 Hz, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  168.8, 144.4 (3C), 131.3, 129.7 (3C), 128.8 (3C), 128.3 (3C), 128.3 (3C), 127.1 (3C), 119.2, 76.9, 66.5, 61.6, 33.3; HRMS (ESI-TOF) calcd for  $\text{C}_{25}\text{H}_{23}\text{N}_3\text{O}_2\text{SNa}^+$   $[\text{M}+\text{Na}^+]$  452.1403, found 452.1391.

**1.24**: Azide **1.23** (31.8 g, 74 mmol) dissolved in  $\text{CH}_2\text{Cl}_2$  (150 mL) and  $\text{Et}_3\text{SiH}$  (47.8 mL, 296 mmol) was cooled to 0 °C and TFA (150 mL) was added dropwise. After stirring for 30 min at 0 °C the reaction mixture was concentrated (careful of volatility

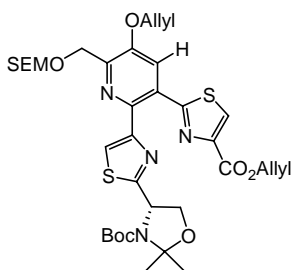
of product) and the residue was purified by flash column chromatography (silica gel, Et<sub>2</sub>O/hexanes, 5:95→10:90). The free thiol was concentrated until only a slight amount of solvent remained (due to volatility of product) and was used as such in the esterification reaction. The acid coupling partner was prepared by dissolving allyl ether **1.21** (18.4 g, 28 mmol) and LiOH (1.36 g, 56 mmol) in THF (169 mL), EtOH (56 mL) and H<sub>2</sub>O (56 mL), and stirring at 55 °C for 2 h. After cooling to 25 °C the reaction mixture was diluted with EtOAc (200 mL), acidified with aqueous 5% HCl solution (100 mL) and separated. The aqueous layer was extracted with EtOAc (3×50 mL) and the combined organic layers were washed with brine (100 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. To the crude acid, dissolved in CH<sub>2</sub>Cl<sub>2</sub> (280 mL), was added EDC (5.97 g, 31 mmol), 4-DMAP (690 mg, 5.6 mmol) and thiol obtained above at 0 °C. After 10 min the reaction mixture was warmed to 25 °C and 4-DMAP was added portionwise until the reaction pH was neutral (careful of adding too much 4-DMAP as this will facilitate disulfide formation). After stirring for 12 h at 25 °C the mixture was concentrated and purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes, 10:90→20:80) afforded thioester **1.24** (17.9 g, 80% over two steps) as a yellow foam.



**1.24:**  $R_f=0.47$  (silica gel, EtOAc/hexanes, 3:7);  $[\alpha]_D^{35} -21.5$  ( $c$  1.58,  $\text{CH}_2\text{Cl}_2$ ); IR (film)  $\nu_{\text{max}}$  2977, 2952, 2875, 2116, 1745, 1699, 1373, 1366, 1264, 1170, 1102, 1054, 859, 836, 735, 703  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ , 66 °C)  $\delta$  7.84 (s, 1H), 7.35 (s, 1H), 6.13–6.05 (m, 1H), 6.03–5.95 (m, 1H), 5.47 (dq,  $J=17.5, 1.5$  Hz, 1H), 5.41–5.37 (m, 1H), 5.33 (dq,  $J=10.5, 1.0$  Hz, 1H), 5.30–5.27 (m, 1H), 5.20–5.19 (m, 1H), 4.79 (s, 2H), 4.77 (s, 2H), 4.72 (dt,  $J=5.5, 1.5$  Hz, 2H), 4.69 (dt,  $J=5.0, 1.5$  Hz, 2H), 4.39 (dd,  $J=7.5, 5.5$  Hz, 1H), 4.30–4.26 (m, 1H), 4.14–4.12 (m, 1H), 3.66–3.63 (m, 2H), 3.58 (dd,  $J=13.5, 5.0$  Hz, 1H), 3.39–3.32 (m, 1H), 1.69 (s, 3H), 1.56 (s, 3H), 1.42 (br s, 9H), 0.90–0.87 (m, 2H), 0.00 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ , 66 °C)  $\delta$  173.8, 170.5, 153.9, 142.0, 139.4, 137.4, 135.1, 134.6, 134.4, 133.6, 133.3, 120.3, 120.0, 119.4, 96.8, 71.4, 70.4, 70.3, 68.1, 67.6, 66.7, 63.2, 63.1, 61.0 (2C), 32.8, 29.4 (3C), 19.6,  $-0.49$  (3C); HRMS (ESI-TOF) calcd for  $\text{C}_{35}\text{H}_{51}\text{N}_6\text{O}_9\text{S}_2\text{Si}^+$   $[\text{M}+\text{H}^+]$  791.2923, found 791.2934.

**1.25:** To thioester **1.24** (14.2 g, 17.9 mmol) dissolved in THF (400 mL) was added  $\text{PPh}_3$  (8.0 g, 30.5 mmol) in THF (150 mL) via cannula over 10 min at  $-20$  °C. The reaction mixture was allowed to warm to 25 °C, heated to 40 °C, and stirred for 12 h. After concentration in vacuo, purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes, 10:90→60:40) afforded a thiazoline intermediate, which was immediately dissolved in  $\text{CH}_2\text{Cl}_2$  (307 mL) and cooled to  $-20$  °C. DBU (4.37 mL, 29.2 mmol) was then added and after 5 min,  $\text{BrCCl}_3$  (2.16 mL, 21.9 mmol) was added and the reaction mixture stirred for 10 min at  $-20$  °C and 30

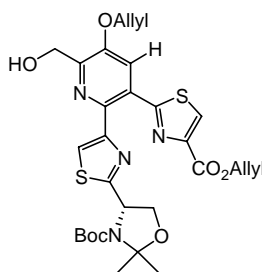
min at 25 °C. The mixture was washed with aqueous 5% HCl solution (100 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. Purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes, 30:70→50:50) afforded thiazole allyl ester **1.25** (10.3 g, 77% over two steps) as a yellow foam.



**1.25**:  $R_f=0.44$  (silica gel, EtOAc/hexanes, 35:65);  $[\alpha]_D^{35} -3.2$  ( $c$  0.89,  $\text{CH}_2\text{Cl}_2$ ); IR (film)  $\nu_{\text{max}}$  2977, 2951, 2881, 1734, 1702, 1373, 1364, 1247, 1204, 1168, 1089, 1053, 991, 859, 835, 752  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ , 66 °C)  $\delta$  8.28 (s, 1H), 7.71 (s, 1H), 7.70 (s, 1H), 6.23–6.12 (m, 2H), 5.57 (dq,  $J=17.0$ , 1.5 Hz, 1H), 5.51 (dq,  $J=17.0$ , 1.5 Hz, 1H), 5.41 (dq,  $J=11.0$ , 1.5 Hz, 1H), 5.38 (dq,  $J=10.5$ , 1.5 Hz, 1H), 5.16–5.11 (m, 1H), 4.91 (dt,  $J=6.0$ , 1.5 Hz, 2H), 4.90 (s, 2H), 4.89 (s, 2H), 4.81 (dt,  $J=5.0$ , 1.5 Hz, 2H), 4.23 (dd,  $J=9.0$ , 6.5 Hz, 1H), 3.97 (br d,  $J=9.0$  Hz, 1H), 3.78–3.75 (m, 2H), 1.71 (s, 3H), 1.61 (s, 3H), 1.49 (br s, 9H), 1.02–0.99 (m, 2H), 0.11 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ , 66 °C)  $\delta$  167.5, 162.5, 154.5, 154.3, 150.6, 148.3, 144.6, 134.5, 134.3, 131.6, 130.1, 122.6, 121.3, 119.5, 119.2, 96.7, 71.3, 70.3, 70.2, 67.6, 67.1, 66.7, 60.8 (3C), 29.4 (3C), 19.6,  $-0.42$  (3C); HRMS (ESI-TOF) calcd for  $\text{C}_{35}\text{H}_{49}\text{N}_4\text{O}_8\text{S}_2\text{Si}^+$   $[\text{M}+\text{H}^+]$  745.2755, found 745.2725.



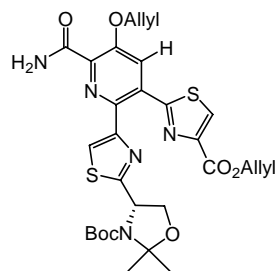
**1.26:** To thiazole allyl ester **1.25** (11 g, 14.8 mmol) dissolved in *i*PrOH (370 mL) at 0 °C was added 1M HCl in Et<sub>2</sub>O (370 mL) dropwise with an addition funnel. After stirring for 1 h at 0 °C, the reaction mixture was allowed to warm to 25 °C and stirred for 3 h. The mixture was then quenched with Et<sub>3</sub>N (55 mL), concentrated, and diluted with CH<sub>2</sub>Cl<sub>2</sub> (200 mL) and H<sub>2</sub>O (200 mL). The organic layer was washed with aqueous 5% HCl solution (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. Purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes, 40:60→95:5) afforded primary alcohol **1.26** (8.35 g, 92%) as a yellow oil.



**1.26:**  $R_f=0.50$  (silica gel, EtOAc/hexanes, 60:40);  $[\alpha]_D^{35} -3.1$  ( $c$  2.35, CH<sub>2</sub>Cl<sub>2</sub>); IR (film)  $\nu_{\max}$  3458, 2981, 2936, 2881, 1701, 1365, 1264, 1206, 1169, 1089, 1054, 991, 733, 703 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>CN, 66 °C)  $\delta$  8.29 (s, 1H), 7.81 (s, 1H), 7.66 (s, 1H), 6.14–6.03 (m, 2H), 5.48–5.40 (m, 2H), 5.32 (dq,  $J=10.5, 1.0$  Hz, 1H), 5.29 (dq,  $J=10.5, 1.5$  Hz, 1H), 5.03 (dd,  $J=6.0, 1.5$  Hz, 1H), 4.82 (dt,  $J=5.5, 1.5$  Hz, 2H), 4.78 (d,  $J=5.0$  Hz, 2H), 4.72 (dt,  $J=5.0, 1.5$  Hz, 2H), 4.13 (dd,  $J=9.0, 6.5$  Hz, 1H), 3.86 (dd,  $J=9.0, 1.5$  Hz, 1H), 3.81 (br t,  $J=4.0$  Hz, 1H), 1.61 (s, 3H), 1.51 (s, 3H), 1.39 (br s, 9H); <sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>CN, 66 °C)  $\delta$  168.6, 159.0, 154.9, 153.9, 151.6, 151.3, 150.4, 147.2, 144.0, 134.4, 134.3, 131.8, 131.6, 121.5, 119.4 (2C), 119.2, 71.2,

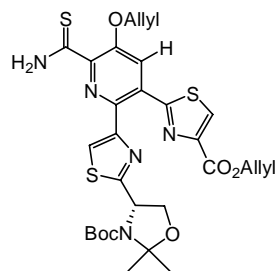
71.1, 70.3 (2C), 67.1, 61.8, 60.8, 29.4 (3C); HRMS (ESI-TOF) calcd for  $C_{29}H_{35}N_4O_7S_2^+$   $[M+H^+]$  615.1942, found 615.1948.

**1.27:** To primary alcohol **1.26** (9.5 g, 15.4 mmol) dissolved in  $CH_2Cl_2$  (150 mL) was added  $NaHCO_3$  (6.5 g, 77.2 mmol) and DMP (16.4 g, 38.6 mmol) at 25 °C. After stirring for 2 h at 25 °C, the reaction mixture was quenched with saturated aqueous  $NaHCO_3/Na_2S_2O_3$  solution ( $2 \times 100$  mL), and the organic layer was dried ( $Na_2SO_4$ ) and concentrated. To the crude aldehyde, dissolved in *t*BuOH (124 mL) and  $H_2O$  (31 mL), was added 2-Me-2-butene (82 mL, 773 mmol),  $NaH_2PO_4$  (9.3 g, 77.3 mmol) and  $NaClO_2$  (7.0 g, 77.3 mmol) at 25 °C. After stirring for 1 h, the reaction mixture was diluted with EtOAc (200 mL), washed with pH 7 buffer (50 mL) and brine (50 mL), dried ( $Na_2SO_4$ ) and concentrated. To the crude acid, dissolved in THF (150 mL) at 0 °C, was added  $Et_3N$  (2.37 mL, 17.0 mmol) and ethyl chloroformate (1.62 mL, 17.0 mmol) and the reaction mixture stirred for 45 min at 0 °C and 1 hr at 25 °C. The mixture was then cooled to 0 °C and  $NH_4OH$  (10.5 mL, 154 mmol) was added and stirring continued at 25 °C for 12 h. After removing the THF in vacuo, the mixture was diluted with EtOAc (200 mL), washed with aqueous 5% HCl solution (100 mL), dried ( $Na_2SO_4$ ) and concentrated. Purification of the residue by flash column chromatography (silica gel, acetone/hexanes, 30:70→75:25) afforded amide **1.27** (8.73 g, 90% over three steps) as a yellow foam.



**1.27:**  $R_f=0.35$  (silica gel, acetone/hexanes, 50:50);  $[\alpha]_D^{35} -2.8$  ( $c$  2.00,  $\text{CH}_2\text{Cl}_2$ ); IR (film)  $\nu_{\text{max}}$  3463, 3332, 2981, 2936, 2875, 1689, 1364, 1229, 1206, 1168, 1089, 1053, 991, 768, 735  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  8.21 (br s, 1H), 7.98 (br s, 1H), 7.65 (br s, 1H), 7.60–7.57 (m, 1H), 6.11–6.01 (m, 2H), 5.58–5.55 (m, 1H), 5.43–5.40 (m, 1H), 5.38–5.36 (m, 1H), 5.31–5.29 (m, 1H), 5.20–5.06 (m, 1H), 4.86 (d,  $J=5.4$  Hz, 2H), 4.81 (d,  $J=4.8$  Hz, 2H), 4.15 (dd,  $J=9.0, 6.0$  Hz, 1H), 4.08–3.99 (m, 1H), 1.73 (br s, 3H), 1.55 (br s, 3H), 1.50 (br s, 9H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  173.7, 165.5, 164.5, 160.8, 154.0, 152.2, 152.0, 151.4, 146.7, 142.4, 138.8, 131.7, 131.4, 129.6, 123.8, 120.2, 119.2, 119.0, 70.3, 69.1, 68.5, 66.1, 66.0, 59.1 (3C), 28.3 (3C); HRMS (ESI-TOF) calcd for  $\text{C}_{29}\text{H}_{34}\text{N}_5\text{O}_7\text{S}_2^+$   $[\text{M}+\text{H}^+]$  628.1894, found 628.1904.

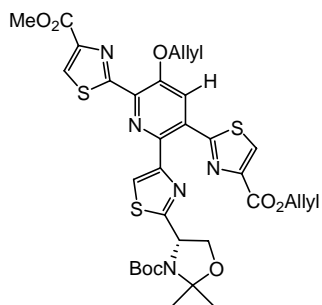
**1.28:** To amide **1.27** (6.25 g, 9.95 mmol) dissolved in DME (50 mL) was added Lawesson's reagent (2.85 g, 6.97 mmol) and after stirring for 5 h at 25 °C, the reaction mixture was concentrated and purification of the residue by flash column chromatography (silica gel, acetone/hexanes, 20:80→60:40) afforded thioamide **1.28** (5.38 g, 84%) as an orange foam.



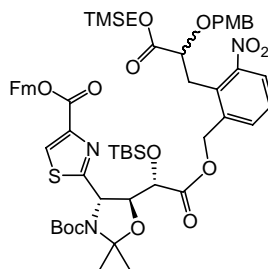
**1.28:**  $R_f=0.58$  (silica gel, acetone/hexanes, 50:50);  $[\alpha]_D^{35} -0.6$  ( $c$  1.93,  $\text{CH}_2\text{Cl}_2$ ); IR (film)  $\nu_{\text{max}}$  3291, 3179, 2980, 2941, 2881, 1698, 1365, 1263, 1206, 1168, 1091, 1053, 991, 734  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  8.80–8.62 (m, 1H), 8.19 (br s, 1H), 7.98 (br d,  $J=24.6$  Hz, 1H), 7.87 (br s, 1H), 7.68 (br s, 1H), 6.10–6.02 (m, 2H), 5.59–5.56 (m, 1H), 5.44–5.41 (m, 1H), 5.35–5.29 (m, 2H), 5.15–5.05 (m, 1H), 4.87–4.86 (m, 2H), 4.76 (br s, 2H), 4.14 (dd,  $J=9.0, 6.6$  Hz, 1H), 4.00 (dd,  $J=25.2, 8.4$  Hz, 1H), 1.71 (br s, 3H), 1.55 (br s, 3H), 1.50 (br s, 9H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  196.0, 164.8, 160.8, 152.3, 152.1, 151.4, 146.6, 143.2, 141.9, 141.8, 131.7, 131.4, 130.3, 129.6, 123.8, 120.5, 119.1, 118.9, 70.3, 70.2, 69.1, 68.4, 66.1, 59.1 (3C), 28.3 (3C); HRMS (ESI-TOF) calcd for  $\text{C}_{29}\text{H}_{34}\text{N}_5\text{O}_6\text{S}_3^+$   $[\text{M}+\text{H}^+]$  644.1666, found 644.1663.

**1.9:** To thioamide **1.28** (5.1 g, 8.07 mmol) dissolved in DME (40 mL) at 0 °C was added  $\text{NaHCO}_3$  (5.43 g, 64.6 mmol) and methyl bromopyruvate (1.72 mL, 16.1 mmol). After stirring for 12 h at 25 °C, the reaction mixture was concentrated and the residue was diluted with EtOAc (100 mL), washed with  $\text{H}_2\text{O}$  (50 mL) and brine (50 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. To the crude orange syrup dissolved in DME (40 mL) at 0 °C was added pyridine (5.9 mL, 72.6 mmol) and TFAA (4.56 mL, 32.3 mmol). After stirring for 40 min at 0 °C,  $\text{Et}_3\text{N}$  (5 mL) was added and the reaction

mixture was concentrated and purification of the residue by flash column chromatography (silica gel, acetone/hexanes, 25:85→60:40) gave trithiazole **1.9** (5.37 g, 93%) as an orange foam.

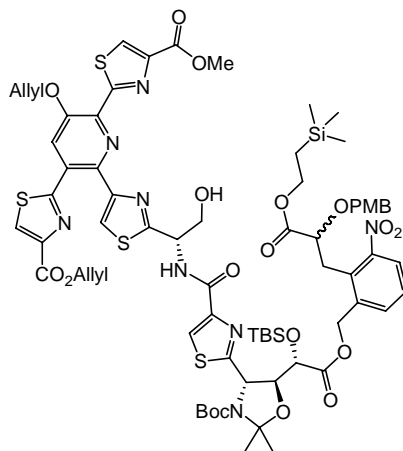


**1.9**:  $R_f=0.37$  (silica gel, acetone/hexanes, 40:60);  $[\alpha]_D^{35} -2.7$  ( $c$  2.13,  $\text{CH}_2\text{Cl}_2$ ); IR (film)  $\nu_{\text{max}}$  2982, 2946, 2886, 1700, 1364, 1241, 1206, 1168, 1089, 1052, 990, 734, 702  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ , 66 °C)  $\delta$  8.39 (s, 1H), 8.32 (s, 1H), 7.98 (s, 1H), 7.82 (s, 1H), 6.22–6.15 (m, 1H), 6.12–6.04 (m, 1H), 5.77 (dq,  $J=15.8, 1.9$  Hz, 1H), 5.43 (dq,  $J=17.3, 1.5$  Hz, 1H), 5.39 (dq,  $J=10.6, 1.5$  Hz, 1H), 5.30 (dq,  $J=10.6, 1.5$  Hz, 1H), 5.09 (dd,  $J=6.2, 1.8$  Hz, 1H), 4.90 (dt,  $J=5.2, 1.9$  Hz, 2H), 4.84 (dt,  $J=5.9, 1.5$  Hz, 2H), 4.17 (dd,  $J=8.8, 6.3$  Hz, 1H), 3.94 (s, 3H), 3.94–3.92 (m, 1H), 1.63 (s, 3H), 1.54 (s, 3H), 1.42 (br s, 9H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  173.4, 165.8, 165.1, 162.1, 160.8, 152.4, 151.5, 151.4, 148.0, 146.6, 143.2, 139.7, 131.8, 131.2, 129.8, 129.7, 129.5, 124.6, 122.7, 120.3, 119.0, 118.4, 70.0, 69.1, 68.4, 66.1, 66.0, 59.1 (3C), 52.3, 28.3 (3C); HRMS (ESI-TOF) calcd for  $\text{C}_{33}\text{H}_{35}\text{N}_5\text{O}_8\text{S}_3^+$   $[\text{M}+\text{H}^+]$  726.1720, found 726.1731.



**1.10:** [ca. 1:1 mixture of inseparable diastereomers]  $R_f=0.53$  (silica gel, EtOAc/hexanes, 30:70);  $[\alpha]_D^{35} -13.6$  ( $c$  2.07, CH<sub>2</sub>Cl<sub>2</sub>); IR (film)  $\nu_{\max}$  2954, 2931, 2896, 2858, 1734, 1709, 1531, 1513, 1451, 1365, 1248, 1202, 1170, 1098, 1035, 837, 757, 739, 702 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>CN, 66 °C)  $\delta$  8.06 (s, 1H), 8.05 (s, 1H), 7.84–7.82 (m, 2+2H), 7.72–7.68 (m, 3+3H), 7.55–7.50 (m, 1+1H), 7.43–7.31 (m, 5+5H), 6.88–6.87 (m, 2+2H), 6.71–6.70 (m, 2+2H), 5.34–5.09 (m, 3+3H), 4.64–4.59 (m, 3+3H), 4.56 (t,  $J=3.5$  Hz, 1+1H), 4.43 (dd,  $J=11.5, 3.0$  Hz, 1+1H), 4.35 (br t,  $J=6.5$  Hz, 1+1H), 4.23–4.17 (m, 2+2H), 4.14 (d,  $J=11.5$  Hz, 1+1H), 4.06–4.02 (m, 1+1H), 3.72 (s, 3+3H), 3.34–3.27 (m, 2+2H), 1.64 (s, 3+3H), 1.63 (s, 3+3H), 1.31 (br s, 9+9H), 0.99–0.93 (m, 2+2H), 0.90–0.89 (m, 9+9H), 0.10–0.04 (m, 15+15H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$  171.6, 169.9, 161.0, 160.9, 159.1, 150.8, 150.8, 143.6, 143.5, 141.3, 141.2, 138.2, 138.1, 133.8, 130.7, 130.6, 129.5, 129.4, 129.4, 129.4, 128.8, 127.8, 127.4, 127.2, 127.1, 125.3, 125.3, 124.5, 124.4, 119.9, 113.5, 82.5, 77.2, 76.9, 72.3, 72.1, 67.1, 64.4, 64.3, 63.6, 59.2 (2C), 55.1, 46.7, 30.7, 28.2 (3C), 25.6 (3C), 17.4, (2C), -1.5 (3C), -5.1, -5.2; HRMS (ESI-TOF) calcd for C<sub>59</sub>H<sub>76</sub>N<sub>3</sub>O<sub>14</sub>S<sub>3</sub>Si<sub>2</sub><sup>+</sup> [M+H<sup>+</sup>] 1138.4581, found 1138.4578.

**1.35:** To Fm ester **1.10** (5.2 g, 4.57 mmol) dissolved in CH<sub>2</sub>Cl<sub>2</sub> (398 mL) at 0 °C was added Et<sub>2</sub>NH (61 mL) and the reaction mixture was allowed to warm to 25 °C over 3 h. Toluene (150 mL) was then added and the mixture was concentrated. Purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes, 10:90 → MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 10:90) afforded acid **1.34** (4.3 g, 98%) as a white foam, which was immediately used in the peptide coupling reaction. The amine coupling partner was obtained by dissolving trithiazole **1.9** (3.4 g, 4.68 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (23 mL), cooling to 0 °C, and adding TFA (23 mL). After stirring for 50 min at 25 °C, the reaction mixture was quenched with saturated aqueous NaHCO<sub>3</sub> solution (25 mL), separated, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2×30 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated and the crude amine (**1.33**) was used immediately in the coupling reaction. Thus, a solution of the acid obtained above in DMF (40 mL) was added via cannula to the crude amine at 0 °C, followed by the addition of *i*Pr<sub>2</sub>NEt (1.39 mL, 7.96 mmol), HATU (1.66 g, 4.38 mmol), and HOAt (596 mg, 4.38 mmol). After stirring for 1 h at 0 °C the mixture was diluted with EtOAc (50 mL) and the organic layer was washed with H<sub>2</sub>O (50 mL) and aqueous 5% HCl solution (25 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. Purification of the residue by flash column chromatography (silica gel, acetone/hexanes, 30:70→60:40) gave secondary amide **1.35** (6.65 g, 93% from **1.9**) as a yellow foam.



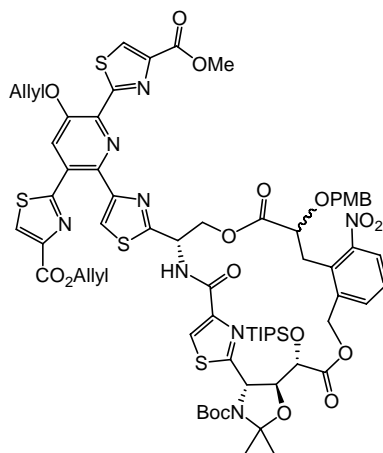
**1.35:** [ca. 1:1 mixture of inseparable diastereomers]  $R_f=0.42$  (silica gel, acetone/hexanes, 40:60);  $[\alpha]_D^{35} -12.9$  ( $c$  2.47,  $\text{CH}_2\text{Cl}_2$ ); IR (film)  $\nu_{\text{max}}$  3402, 3118, 2953, 2926, 2855, 1716, 1673, 1532, 1366, 1263, 1249, 1210, 1171, 1097, 990, 837, 733, 702  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  8.32 (s, 1+1H), 8.31 (s, 1+1H), 8.00 (s, 2+2H), 7.87–7.83 (m, 2+2H), 7.71–7.69 (m, 1+1H), 7.49–7.44 (m, 1+1H), 7.31–7.27 (m, 1+1H), 6.82–6.79 (m, 2+2H), 6.64–6.63 (m, 2+2H), 6.19–6.13 (m, 1+1H), 6.06–6.01 (m, 1+1H), 5.92–5.89 (m, 1+1H), 5.45–5.39 (m, 3+3H), 5.30–5.28 (m, 3+3H), 5.14 (br dd,  $J=16.2, 13.2$  Hz, 1+1H), 4.86 (br s, 4+4H), 4.53–4.48 (m, 2+2H), 4.38 (br s, 1+1H), 4.24–4.21 (m, 2+2H), 4.12–4.10 (m, 2+2H), 3.96 (s, 3+3H), 3.79–3.77 (m, 1+1H), 3.73–3.72 (m, 1+1H), 3.72 (s, 3+3H), 3.30–3.29 (m, 2+2H), 1.62 (br s, 6+6H), 1.42 (br s, 9+9H), 1.02–0.99 (m, 2+2H), 0.82 (s, 9H), 0.80 (s, 9H), 0.04–0.06 (m, 15+15H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  171.7, 171.6, 169.9, 169.9, 169.6, 169.5, 165.8, 165.8, 165.1, 165.0, 162.0, 160.8, 160.7, 160.5, 159.1, 152.1, 151.3, 150.8, 150.8, 150.7, 148.5, 148.0, 146.8, 142.8, 142.8, 142.7, 139.6, 138.1, 138.0, 133.9, 131.8, 131.1, 130.6, 129.8, 129.5, 129.4, 128.7, 127.5, 127.5, 127.4, 124.7, 124.6, 124.6, 124.3, 123.0, 123.0, 121.2, 121.1, 119.9, 118.9, 118.4, 113.6, 113.5, 77.2, 76.9,



72.4, 72.4, 72.3, 72.2, 70.0, 66.1, 64.4, 64.3, 63.9, 63.7, 59.4, 59.1 (2C), 55.1, 52.3, 38.6, 30.7, 28.1 (3C), 25.5 (3C), 25.5 (3C), 17.4 (2C), -1.6 (3C), -5.1, -5.3; HRMS (ESI-TOF) calcd for  $C_{70}H_{87}N_8O_{19}S_4Si_2^+$   $[M+H^+]$  1527.4503 found 1527.4505.

**1.7:** To the secondary amide **1.35** (6.6 g, 4.32 mmol) dissolved in THF (115 mL) at 0 °C was added TBAF (9.52 mL, 12.96 mmol, 1 M solution in THF) and the reaction mixture was allowed to warm to 25 °C over 4 h. The reaction mixture was concentrated and purification of the residue by flash column chromatography (silica gel, acetone/hexanes, 60:40 → MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 15:85) afforded the dihydroxy acid, which was immediately used in the subsequent macrolactonization. The dihydroxy acid dissolved in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) was added via syringe pump to a solution of PyBOP (22.4 g, 43.2 mmol) and 4-DMAP (15.8 g, 130 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1970 mL) over 12 h at 25 °C. The mixture was allowed to stir for a further 4 h at 25 °C, then washed with aqueous 5% HCl solution (100 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. Purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes, 80:20→90:10) gave the cyclized product, which was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (43 mL) and cooled to 0 °C. 2,6-Lutidine (11 mL, 95 mmol) and TIPSOTf (17.5 mL, 64.8 mmol) were then added and stirring was continued for 24 h at 0 °C. The reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed with saturated aqueous NaHCO<sub>3</sub> solution (100 mL) and aqueous 5% HCl solution (100 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. Purification of the residue by flash column chromatography (silica

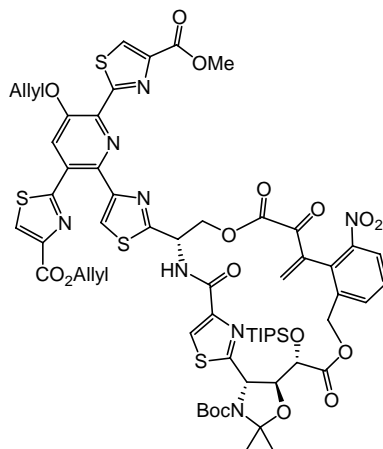
gel, EtOAc/hexanes, 50:50→90:10) afforded macrocycle **1.7** (3.84 g, 62% over three steps) as a yellow foam.



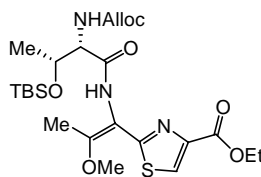
**1.7**: [ca. 1:1 mixture of inseparable diastereomers]  $R_f=0.67$  (silica gel, EtOAc/hexanes, 80:20);  $[\alpha]_D^{36} -9.7$  ( $c$  1.97,  $\text{CH}_2\text{Cl}_2$ ); IR (film)  $\nu_{\text{max}}$  3392, 2944, 2867, 1715, 1533, 1366, 1247, 1211, 1168, 1100, 991, 844, 756, 684  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  8.35–8.30 (m, 2+2H), 8.15–8.13 (m, 1+1H), 8.01–7.86 (m, 1+1H), 7.81–7.60 (m, 2+2H), 7.46–7.44 (m, 1+1H), 7.34–7.28 (m, 2+2H), 6.88–6.70 (m, 2+2H), 6.65–6.58 (m, 2+2H), 6.20–6.14 (m, 1+1H), 6.08–6.04 (m, 1+1H), 5.88–5.83 (m, 1+1H), 5.46–5.43 (m, 3+3H), 5.33–5.30 (m, 2+2H), 4.91–4.85 (m, 5+5H), 4.72 (br s, 1+1H), 4.65–4.60 (m, 2+2H), 4.47–4.44 (m, 2+2H), 4.28–4.26 (m, 1+1H), 4.18–4.14 (m, 1+1H), 3.99–3.96 (m, 4+4H), 3.73–3.71 (m, 4+4H), 3.60–3.53 (m, 1+1H), 1.66–1.60 (m, 3+3H), 1.46–1.42 (m, 3+3H), 1.42–1.26 (m, 9+9H), 1.01–0.90 (m, 21+21H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  170.6, 170.5, 170.1, 169.7, 165.1, 165.0, 164.9, 161.9, 160.8, 159.2, 159.1, 159.1, 151.7, 151.3, 151.3, 151.2, 150.5, 147.9, 146.7, 142.9, 142.8, 142.7, 142.6, 140.1, 139.5, 131.8, 131.1, 130.4, 130.1, 129.7, 129.6, 129.5, 128.6, 128.4, 127.6, 127.4, 126.3, 126.1, 125.1, 125.0, 124.9, 124.8, 123.2, 123.1,

123.0, 121.1, 119.1, 119.0, 118.7, 118.7, 117.0, 113.5, 113.5, 76.6, 76.5, 73.8, 73.0, 72.7, 72.0, 70.1, 70.1, 66.2, 66.2, 66.0, 65.8, 65.4, 64.9, 64.3, 58.2 (2C), 55.2, 53.4, 52.4, 52.4, 50.1, 50.0, 28.3 (3C), 28.2, 17.6 (3C), 17.7 (3C), 12.3, 12.2, 12.1; HRMS (ESI-TOF) calcd for  $C_{68}H_{79}N_8O_{18}S_4Si^+$   $[M+H^+]$  1451.4159 found 1451.4153.

**1.36:** To macrocycle **1.7** (3.8 g, 2.62 mmol) dissolved in  $CH_2Cl_2$  (118 mL) and  $H_2O$  (13 mL) at 0 °C was added DDQ (2.38 g, 10.5 mmol) and the reaction mixture was allowed to warm to 25 °C over 12 h. The reaction mixture was washed with saturated aqueous  $NaHCO_3$  solution (100 mL) and the aqueous layer was extracted with  $CH_2Cl_2$  (3×50 mL). The combined organic layers were dried ( $Na_2SO_4$ ), concentrated, and the residue was purified by flash column chromatography (silica gel,  $Et_2O$ /hexanes, 50:50 →  $EtOAc$ /hexanes, 95:5) to afford a diastereomeric mixture of secondary alcohols. This mixture was immediately dissolved in  $CH_2Cl_2$  (24 mL) and  $NaHCO_3$  (1 g, 12 mmol) and DMP (4 g, 12 mmol) were added. After 1 h at 25 °C, the reaction mixture was washed with saturated aqueous  $NaHCO_3/Na_2S_2O_3$  solution (25 mL), and the organic layer was dried ( $Na_2SO_4$ ) and concentrated. To the crude ketoester dissolved in  $CH_2Cl_2$  (24 mL) was added *N,N*-dimethylmethyleniminium chloride (1.12 g, 12 mmol), and after stirring for 10 min at 25 °C,  $Et_3N$  (1.67 mL, 12 mmol) was added dropwise. Stirring was continued for 45 min and then the reaction mixture was purified directly by flash column chromatography (silica gel,  $EtOAc$ /hexanes, 60:40→100:0) to afford  $\alpha,\beta$ -unsaturated ketoester **1.36** (2.46 g, 70% over three steps) as a white foam.



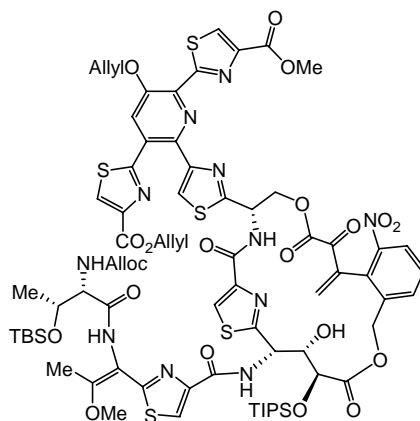
**1.36:**  $R_f=0.58$  (silica gel, EtOAc/hexanes, 70:30);  $[\alpha]_D^{36} -21.7$  ( $c$  1.72,  $\text{CH}_2\text{Cl}_2$ ); IR (film)  $\nu_{\text{max}}$  3392, 3118, 2945, 2867, 1713, 1534, 1478, 1366, 1211, 1155, 1098, 1069, 991, 881, 757, 733, 683  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  8.34–8.28 (m, 2H), 8.15–8.00 (m, 2H), 7.92–7.88 (m, 2H), 7.78–7.72 (m, 1H), 7.54–7.44 (m, 2H), 6.67 (br d,  $J=17.4$  Hz, 1H), 6.17–6.15 (m, 2H), 6.07–6.00 (m, 1H), 5.92–5.89 (m, 1H), 5.77–5.76 (m, 1H), 5.46–5.41 (m, 3H), 5.32–5.29 (m, 2H), 5.06–5.03 (m, 1H), 4.87–4.80 (m, 5H), 4.67–4.52 (m, 2H), 3.97–3.94 (m, 4H), 1.70 (br s, 3H), 1.48 (br s, 3H), 1.30 (br s, 9H), 1.04–0.95 (m, 21H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  183.6, 182.3, 169.8, 169.5, 169.3, 166.8, 164.9, 162.1, 162.0, 161.8, 160.8, 160.7, 153.1, 151.4, 148.8, 148.7, 148.1, 147.9, 146.7, 146.5, 142.6, 139.6, 139.6, 131.8, 131.2, 130.1, 129.9, 129.5, 129.4, 124.9, 124.6, 122.9, 121.3, 119.1, 119.0, 118.5, 72.2, 70.0, 66.2, 66.1, 65.6, 65.4, 62.8, 60.4, 57.3 (2C), 52.3, 49.7, 47.1, 28.3 (3C), 17.8 (3C), 17.8 (3C), 12.2 (3C); HRMS (ESI-TOF) calcd for  $\text{C}_{61}\text{H}_{69}\text{N}_8\text{O}_{17}\text{S}_4\text{Si}^+$   $[\text{M}+\text{H}^+]$  1341.3427 found 1341.3448.



**1.41:**  $R_f=0.41$  (silica gel, EtOAc/hexanes, 50:50);  $[\alpha]_D^{34} -2.9$  ( $c$  2.77,  $\text{CH}_2\text{Cl}_2$ ); IR (film)  $\nu_{\text{max}}$  3317, 2951, 2930, 2856, 1719, 1500, 1383, 1321, 1237, 1209, 1096, 1038, 836, 779  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  8.18 (br s, 1H), 8.10 (s, 1H), 5.98–5.89 (m, 2H), 5.32 (dd,  $J=17.5, 1.5$  Hz, 1H), 5.19 (dq,  $J=10.5, 1.0$  Hz, 1H), 4.56–4.55 (m, 2H), 4.41–4.37 (m, 1H), 4.30–4.25 (3H), 3.90 (s, 3H), 1.96 (s, 3H), 1.33–1.30 (m, 6H), 0.83 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  170.6, 163.6, 162.9, 161.0, 157.5, 146.5, 134.7, 128.2, 118.1, 112.2, 70.1, 66.7, 62.1, 61.4, 57.0, 26.5 (3C), 20.2, 18.9, 15.1, 14.6,  $-4.0, -4.3$ ; HRMS (ESI-TOF) calcd for  $\text{C}_{24}\text{H}_{40}\text{N}_3\text{O}_7\text{SSi}^+$   $[\text{M}+\text{H}^+]$  542.2351 found 542.2357.

**1.38:** To ethyl ester **1.41** (1.24 g, 2.29 mmol) dissolved in  $\text{Et}_2\text{O}$  (23 mL) at 0 °C was added  $\text{KOSiMe}_3$  (734 mg, 5.7 mmol) and the reaction mixture was stirred at 25 °C for 35 min. The organic layer was then washed with aqueous 5% HCl solution (20 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. Purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes, 70:30  $\rightarrow$  MeOH/ $\text{CH}_2\text{Cl}_2$ , 10:90) afforded the acid (**1.8**, 729 mg, 62%) as a white foam, which was immediately used in the peptide coupling reaction described below. The amine coupling partner was obtained by dissolving  $\alpha,\beta$ -unsaturated ketoester **1.36** (2.0 g, 1.49 mmol) in anhydrous EtOAc (57 mL), and adding  $\text{SnCl}_4$  (14.9 mL, 14.9 mmol, 1 M solution in  $\text{CH}_2\text{Cl}_2$ ). After stirring for 30 min at 25 °C, the reaction mixture was quenched with saturated aqueous

NaHCO<sub>3</sub> solution (25 mL), diluted with EtOAc (100 mL), separated, and the aqueous layer was extracted with EtOAc (2×30 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated and the crude *N*-Boc deprotected secondary amine was immediately dissolved in anhydrous EtOAc (24.8 mL), cooled to 0 °C, and aqueous 5% HCl solution (24.8 mL) was added. After stirring for 3 h at 25 °C, the two layers were separated and the organic layer was azeotroped with toluene (2×15 mL). The crude amine hydrochloride salt was then dissolved in DMF (8 mL), cooled to –20 °C, and *i*Pr<sub>2</sub>NEt (519 μL, 2.98 mmol) was added followed by cannula addition of the acid obtained above in DMF (7 mL) and HATU (560 mg, 1.56 mmol). After stirring for 40 min at –20 °C the mixture was diluted with EtOAc (50 mL) and the organic layer was washed with H<sub>2</sub>O (30 mL) and aqueous 0.01 M KHSO<sub>4</sub> solution (25 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. Purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes, 60:40→100:0) gave secondary alcohol **1.38** (1.57 g, 62% over three steps) as a white foam.

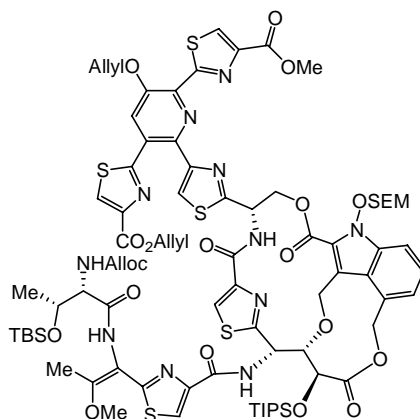


**1.38**:  $R_f=0.55$  (silica gel, EtOAc/hexanes, 90:10);  $[\alpha]_D^{34} -12.9$  ( $c$  1.03, CH<sub>2</sub>Cl<sub>2</sub>); IR (film)  $\nu_{\max}$  3386, 3113, 2948, 2886, 2860, 1722, 1673, 1532, 1490, 1383, 1247, 1133,

1098, 991, 842, 780  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  8.39–8.34 (m, 2H), 8.26–8.21 (m, 2H), 8.12–7.95 (m, 4H), 7.86–7.75 (m, 2H), 7.67–7.50 (m, 2H), 6.77–6.57 (m, 1H), 6.53–6.36 (m, 1H), 6.17–6.12 (m, 1H), 6.06–6.00 (m, 1H), 5.95–5.87 (m, 2H), 5.81–5.77 (m, 2H), 5.41–5.12 (m, 6H), 4.94–4.72 (m, 7H), 4.56–4.43 (m, 5H), 4.39–4.20 (m, 3H), 3.92–3.86 (m, 6H), 2.11 (s, 3H), 1.26 (d,  $J=6.6$  Hz, 3H), 0.94–0.77 (m, 30H), 0.10–0.07 (m, 6H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  170.5, 169.3, 164.9, 162.0, 161.9, 161.8, 161.2, 160.9, 160.8, 158.9, 156.6, 156.5, 151.4, 148.8, 148.7, 148.6, 147.7, 147.0, 146.9, 146.7, 143.9, 142.8, 142.7, 140.0, 139.5, 139.4, 139.4, 136.8, 136.3, 135.3, 132.4, 132.3, 131.8, 131.1, 129.8, 129.6, 126.2, 125.6, 125.3, 123.7, 123.2, 119.1, 118.4, 118.0, 110.8, 74.3, 74.0, 73.5, 70.2, 67.9, 66.3, 66.1, 64.1, 63.7, 60.4, 59.7, 55.8, 52.5, 25.8 (3C), 25.7, 25.6, 17.9, 17.8 (3C), 17.7 (3C), 12.3, 12.2, 12.1, –5.0, –5.2; HRMS (ESI-TOF) calcd for  $\text{C}_{75}\text{H}_{90}\text{N}_{11}\text{O}_{21}\text{S}_5\text{Si}_2^+$   $[\text{M}+\text{H}^+]$  1696.4449 found 1696.4430.

**1.5:** To secondary alcohol **1.38** (87 mg, 0.051 mmol) dissolved in DME (700  $\mu\text{L}$ ) at 25  $^\circ\text{C}$  was added 4 Å molecular sieves (17.4 mg, 20 wt%),  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  (21 mg, 0.056 mmol) and  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  (34.7 mg, 0.154 mmol) and the reaction mixture was stirred at 35  $^\circ\text{C}$  for 25 min. The crude reaction mixture was then cooled to 0  $^\circ\text{C}$  and *i* $\text{Pr}_2\text{NEt}$  (31  $\mu\text{L}$ , 0.179 mmol), SEMCl (36  $\mu\text{L}$ , 0.204 mmol), and TBAI (1.9 mg, 0.005 mmol) were added sequentially. After stirring for 15 min at 0  $^\circ\text{C}$  the reaction mixture was filtered through cotton with the aid of  $\text{CH}_2\text{Cl}_2$  (5 mL), concentrated, and the residue was

purified directly by PTLC (silica gel, acetone/hexanes, 45:55) to afford the SEM protected *N*-hydroxyindole **1.5** (30 mg, 33% over two steps) as a white foam.

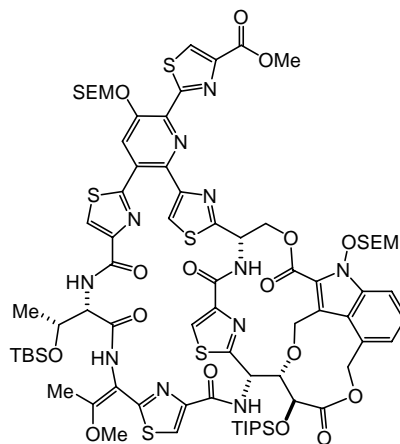


**1.5:**  $R_f=0.60$  (silica gel, acetone/hexanes, 45:55);  $[\alpha]_D^{34} -35.6$  ( $c$  1.76, CH<sub>2</sub>Cl<sub>2</sub>); IR (film)  $\nu_{\max}$  3396, 3113, 2926, 2854, 1721, 1676, 1531, 1488, 1464, 1259, 1249, 1213, 1127, 1099, 992, 836, 734, 702 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN)  $\delta$  9.49 (br s, 1H), 8.58 (br s, 1H), 8.32 (s, 1H), 8.09–8.08 (m, 2H), 8.05 (s, 1H), 8.04 (s, 1H), 7.90 (s, 1H), 7.87 (s, 1H), 7.59 (d,  $J=8.4$  Hz, 1H), 7.36 (t,  $J=7.2$  Hz, 1H), 7.17 (d,  $J=7.2$  Hz, 1H), 6.14–6.09 (m, 1H), 5.93–5.81 (m, 3H), 5.62–5.61 (m, 1H), 5.55–5.53 (m, 1H), 5.42–5.29 (m, 5H), 5.24–5.10 (m, 4H), 5.05–5.03 (m, 1H), 4.89–4.83 (m, 5H), 4.69–4.67 (m, 1H), 4.58–4.55 (m, 1H), 4.45–4.41 (m, 5H), 4.31 (d,  $J=9.0$  Hz, 1H), 4.10 (dd,  $J=7.8, 2.4$  Hz, 1H), 3.92 (s, 3H), 3.87 (s, 3H), 3.49–3.42 (m, 2H), 2.11 (s, 3H), 1.15 (d,  $J=6.6$  Hz, 3H), 0.94–0.78 (m, 32H), –0.00–0.10 (m, 15H); <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>CN)  $\delta$  171.9, 171.6, 171.5, 166.4, 166.0, 163.8, 163.1, 163.0, 161.9, 161.8, 161.7, 160.5, 158.2, 154.3, 153.0, 152.7, 150.3, 149.0, 148.0, 147.6, 147.5, 144.2, 140.7, 138.2, 134.3, 133.7, 133.3, 132.0, 131.7, 131.4, 130.1, 127.3, 126.9, 126.8, 126.3, 125.1, 124.3, 122.7, 121.1, 119.1, 118.9, 118.2, 113.4, 112.1, 103.6, 76.2, 74.2, 73.6,



71.1, 69.7, 69.4, 67.1, 66.8, 64.6, 62.0, 61.3, 57.1, 55.9, 53.1, 50.7, 26.6 (3C), 21.5, 19.2, 18.9, 18.6 (6C), 14.9, 13.4 (3C), -1.0 (3C), -3.9, -4.3; HRMS (ESI-TOF) calcd for  $C_{81}H_{104}N_{11}O_{20}S_5Si_3^+$   $[M+H^+]$  1794.5365 found 1794.5325.

**1.43:** To *N*-hydroxyindole **1.5** (8.5 mg, 0.004 mmol) dissolved in THF (200  $\mu$ L) at 0 °C was added  $Pd(PPh_3)_4$  (1.7 mg, 0.001 mmol) and morpholine (15  $\mu$ L, 0.166 mmol). After stirring for 15 min at 0 °C,  $H_2O$  (2 mL), aqueous 5% HCl solution (500  $\mu$ L) and  $CH_2Cl_2$  (5 mL) were added and after separation, the aqueous layer was extracted with  $CHCl_3$  (5 mL). The combined organic layers were dried ( $Na_2SO_4$ ) and concentrated. The crude reaction mixture, dissolved in  $CH_2Cl_2$  (1.28 mL) and DMF (320  $\mu$ L), was cooled to 0 °C and *i*Pr<sub>2</sub>NEt (8.4  $\mu$ L, 0.047 mmol) and HATU (9.1 mg, 0.024 mmol) were added. After stirring for 30 min at 0 °C and 22 h at 25 °C, the mixture was diluted with  $CHCl_3$  (5 mL), washed with  $H_2O$  (5 mL) and aqueous 5% HCl solution (2 mL), dried ( $Na_2SO_4$ ) and concentrated. The crude residue, dissolved in  $CH_2Cl_2$  (200  $\mu$ L), was then cooled to 0 °C and *i*Pr<sub>2</sub>NEt (3.3  $\mu$ L, 0.019 mmol), SEMCl (2.5  $\mu$ L, 0.014 mmol), and TBAI (0.9 mg, 0.002 mmol) were added sequentially. After stirring for 15 min at 0 °C the reaction mixture was purified directly by PTLC (silica gel, acetone/hexanes, 45:55) to afford macrolactam **1.43** (2.5 mg, 30% over three steps) as a clear oil.

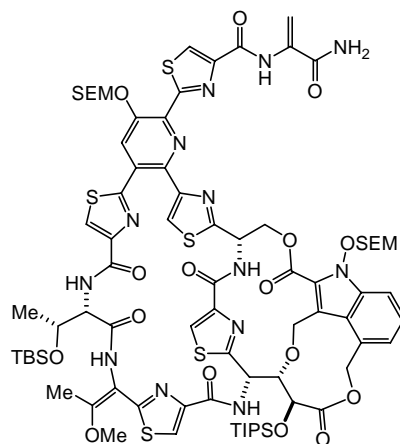


**1.43:**  $R_f=0.43$  (silica gel, acetone/hexanes, 40:60);  $[\alpha]_D^{34} -6.38$  ( $c$  0.13,  $\text{CH}_2\text{Cl}_2$ ); IR (film)  $\nu_{\text{max}}$  3392, 2924, 2845, 1724, 1663, 1532, 1484, 1464, 1249, 1102, 834, 748  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  9.63 (d,  $J=9.0$  Hz, 1H), 8.93 (d,  $J=9.0$  Hz, 1H), 8.34 (s, 1H), 8.12 (s, 1H), 8.11 (s, 3H), 8.05 (s, 1H), 8.00 (d,  $J=7.2$  Hz, 1H), 7.98 (s, 1H), 7.89 (s, 1H), 7.84 (br s, 1H), 7.56 (d,  $J=8.4$  Hz, 1H), 7.29 (t,  $J=8.4$  Hz, 1H), 7.06 (d,  $J=7.2$  Hz, 1H), 6.11–6.09 (m, 1H), 5.89 (d,  $J=10.2$  Hz, 1H), 5.80 (br s, 2H), 5.60–5.55 (m, 3H), 5.40 (1/2Abq,  $J=7.2$  Hz, 1H), 5.35 (1/2Abq,  $J=7.2$  Hz, 1H), 5.34–5.33 (m, 1H), 4.90–4.86 (m, 2H), 4.84–4.82 (m, 1H), 4.72–4.71 (m, 1H), 4.63 (dd,  $J=11.4$ , 4.2 Hz, 1H), 4.36 (d,  $J=9.6$  Hz, 1H), 3.96 (s, 3H), 3.92 (s, 3H), 3.72–3.62 (m, 4H), 2.11 (s, 3H), 1.04 (d,  $J=6.6$  Hz, 3H), 0.95–0.82 (m, 34H), 0.10–0.06 (m, 24H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  169.2, 168.4, 168.0, 167.6, 166.6, 165.5, 163.5, 162.0, 161.4, 161.0, 159.7, 156.7, 153.0, 150.8, 150.3, 148.3, 147.9, 147.0, 146.5, 145.8, 145.3, 143.8, 140.2, 138.4, 138.2, 137.0, 135.1, 132.6, 132.1, 132.0, 131.3, 130.0, 126.1, 125.4, 121.9, 121.1, 112.1, 102.5, 94.1, 74.9, 72.9, 71.7, 68.9, 67.7, 66.3, 64.1, 63.1, 60.8, 55.8, 52.4, 52.3, 50.4, 45.8, 25.8 (3C), 24.7, 22.7, 18.3, 18.0 (3C), 17.9

(3C), 14.1 (3C), 12.3, -1.4 (3C), -1.5 (3C), -4.8 (2C); HRMS (ESI-TOF) calcd for  $C_{77}H_{103}N_{11}O_{18}S_5Si_4^+$   $[M+H^+]$  1742.5236 found 1742.5236.

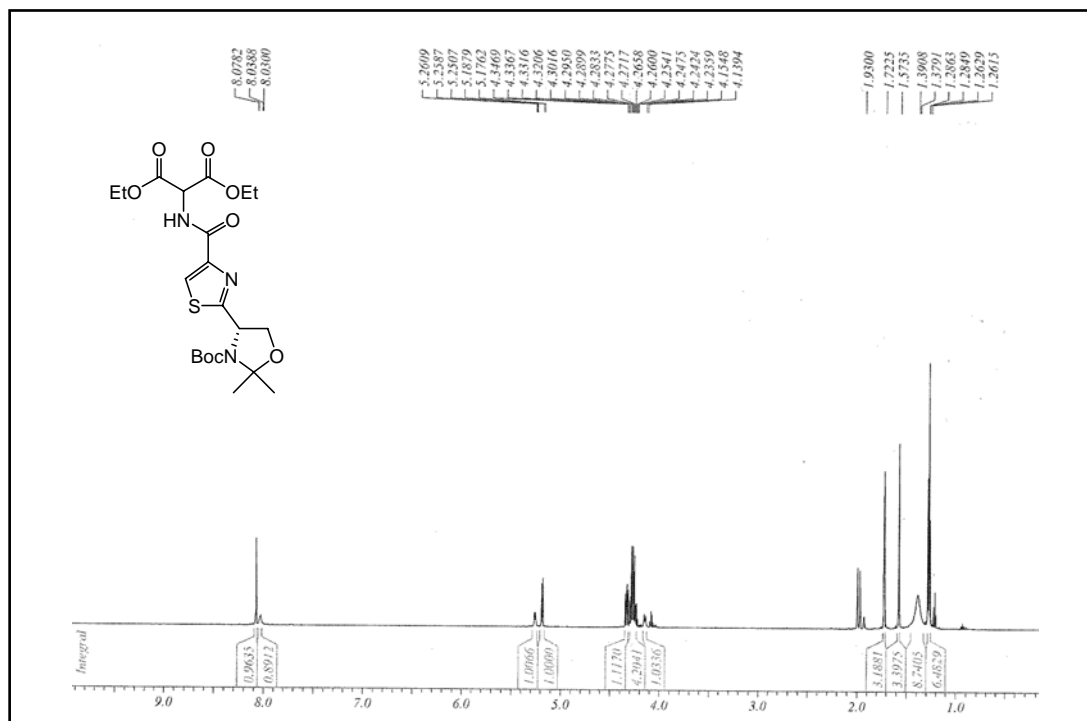
**1.45:** To macrolactam methyl ester **1.43** (3.3 mg, 0.002 mmol) dissolved in 1,2-dichloroethane (250  $\mu$ L) at 25 °C was added  $Me_3SnOH$  (3.4 mg, 0.019 mmol). After stirring for 1 h at 65 °C, another 3.4 mg of  $Me_3SnOH$  was added and the reaction mixture stirred for an additional 3 h at 65 °C. After cooling to 25 °C the mixture was diluted with  $CHCl_3$  (5 mL), washed with aqueous 0.01 M  $KHSO_4$  solution (5 mL), dried ( $Na_2SO_4$ ) and concentrated. The crude residue, dissolved in DMF (200  $\mu$ L), was cooled to 0 °C and  $iPr_2NEt$  (1.0  $\mu$ L, 0.006 mmol), tail fragment **1.6** (1.4 mg, 0.004 mmol), and HATU (0.9 mg, 0.002 mmol) were added. After stirring for 30 min at 0 °C and 30 min at 25 °C, the mixture was diluted with  $CHCl_3$  (5 mL), washed with  $H_2O$  (5 mL) and aqueous 5%  $HCl$  solution (2 mL), dried ( $Na_2SO_4$ ) and concentrated. The crude residue was purified by PTLC (silica gel, acetone/hexanes, 50:50) to afford the tail coupled product **1.4**, which was immediately submitted to oxidation/elimination conditions. Thus, to **1.4** dissolved in  $CH_2Cl_2$  (300  $\mu$ L) at 0 °C was added  $NaHCO_3$  (4.6 mg, 0.055 mmol) and  $tBuOOH$  (33  $\mu$ L, 0.184 mmol, ~ 5.5 M in decane). After stirring for 5 min at 0 °C and 55 min at 25 °C, another 33  $\mu$ L of  $tBuOOH$  was added and the reaction mixture stirred for an additional 1 h.  $CHCl_3$  (5 mL) and aqueous  $NaHCO_3/Na_2S_2O_3$  solution (5 mL) were then added and after separation, the aqueous layer was extracted with  $CHCl_3$  (5 mL). The combined organic layers were dried

(Na<sub>2</sub>SO<sub>4</sub>), concentrated, and purified by PTLC (silica gel, MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 8:92) to afford tetrasilylated nocathiacin III **1.45** (2.3 mg, 68% over three steps) as a clear oil.

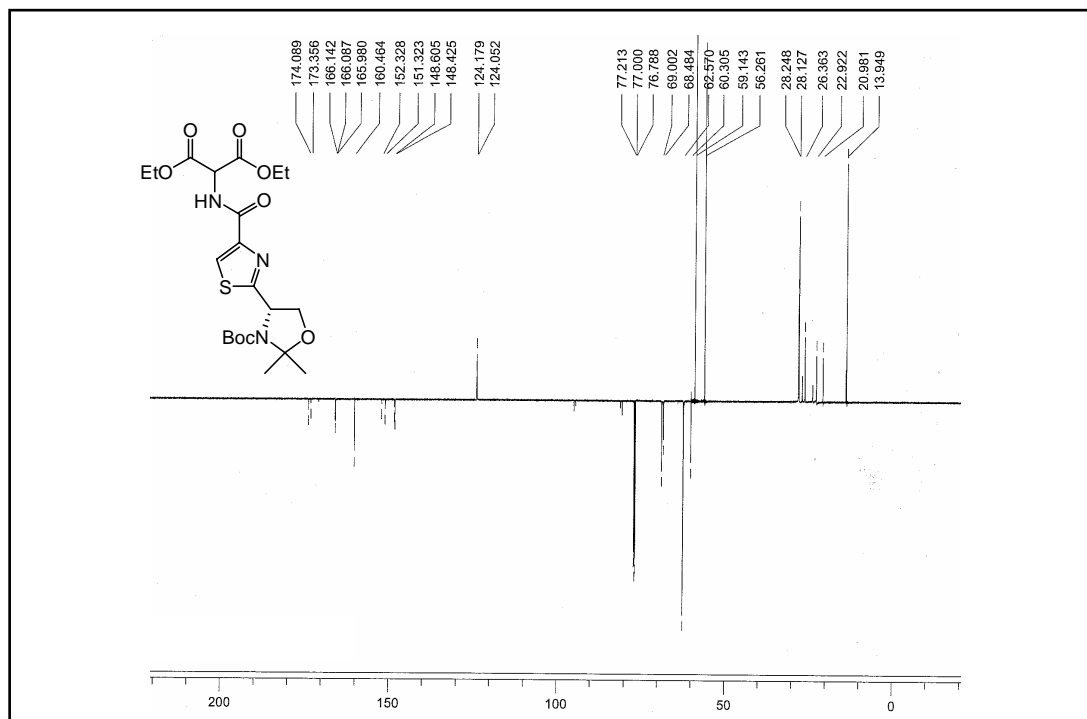


**1.45**:  $R_f=0.42$  (silica gel, MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 10:90);  $[\alpha]_D^{34} -1.03$  ( $c$  0.23, CH<sub>2</sub>Cl<sub>2</sub>); IR (film)  $\nu_{\max}$  3351, 2923, 2852, 1713, 1663, 1529, 1461, 1264, 1249, 1100, 1041, 859, 837, 741 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$  9.66 (d,  $J=9.6$  Hz, 1H), 9.14 (d,  $J=10.8$  Hz, 1H), 9.12 (br s, 1H), 8.27 (s, 1H), 8.16 (s, 1H), 8.11 (s, 1H), 8.07 (s, 1H), 8.03 (d,  $J=7.2$  Hz, 1H), 7.98 (s, 1H), 7.87 (s, 1H), 7.72 (br s, 1H), 7.55 (d,  $J=8.4$  Hz, 1H), 7.28 (t,  $J=7.8$  Hz, 1H), 7.07 (d,  $J=6.6$  Hz, 1H), 6.19 (br s, 2H), 6.09–6.07 (m, 1H), 5.96 (br s, 1H), 5.93 (d,  $J=10.8$  Hz, 1H), 5.63 (s, 2H), 5.60–5.58 (m, 1H), 5.41–5.37 (m, 2H), 5.35–5.34 (m, 2H), 5.18–5.13 (m, 1H), 4.95–4.91 (m, 1H), 4.87–4.85 (m, 1H), 4.70–4.69 (m, 1H), 4.62 (dd,  $J=12.6, 4.8$  Hz, 1H), 4.40 (d,  $J=9.0$  Hz, 1H), 3.90 (s, 3H), 3.70–3.60 (m, 4H), 2.09 (s, 3H), 0.96 (d,  $J=7.2$  Hz, 3H), 0.92–0.69 (m, 34H), 0.08–0.10 (m, 24H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$  178.5, 171.2, 166.8, 165.3, 164.4, 163.3, 161.3, 161.0, 160.8, 159.9, 159.8, 158.3, 151.0, 150.4, 148.3, 148.1, 146.9, 144.3, 140.6, 139.9, 139.0, 137.1, 136.0, 133.6, 132.1, 132.1, 130.0, 129.6, 128.6, 128.5, 128.2, 127.9, 125.2, 125.1, 122.9, 120.4, 120.0, 112.3, 112.1, 103.1, 102.4,

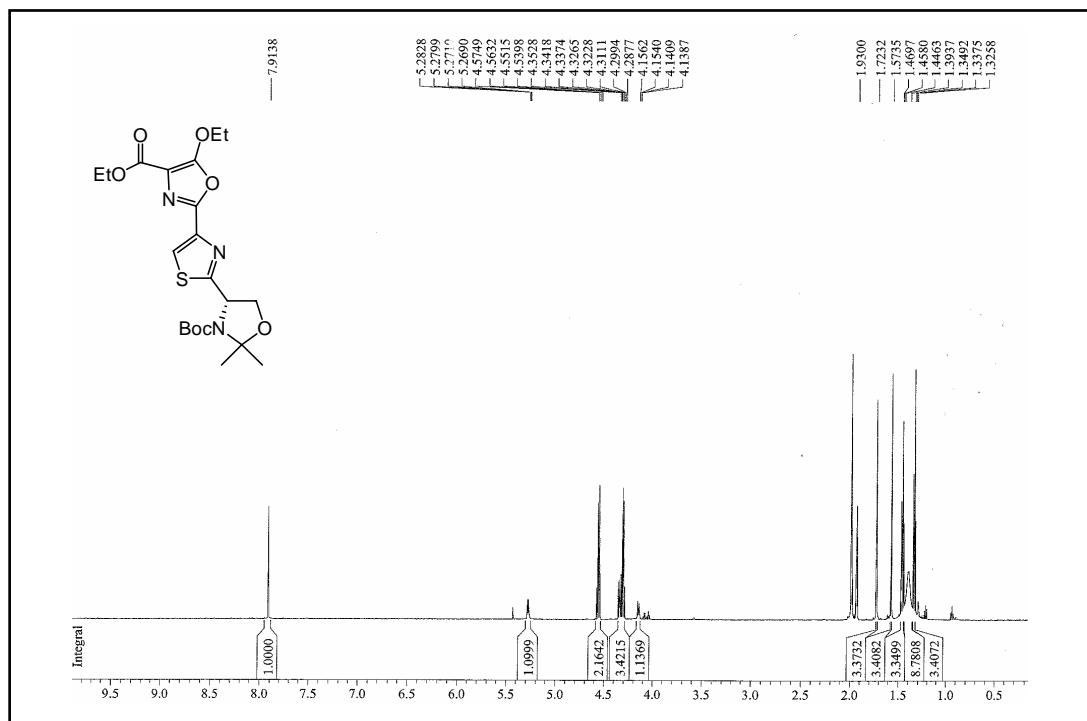
93.5, 74.9, 73.2, 71.9, 70.5, 68.7, 67.4, 66.4, 63.9, 63.1, 60.8, 55.8, 48.3, 45.8, 25.7 (3C), 24.7, 22.7, 21.1 (6C), 19.1, 18.0, 14.2 (3C), -1.4 (3C), -1.5 (3C), -4.8 (2C); HRMS (ESI-TOF) calcd for  $C_{79}H_{105}N_{13}O_{18}S_5Si_4^+$   $[M+H^+]$  1796.5454 found 1796.5464.



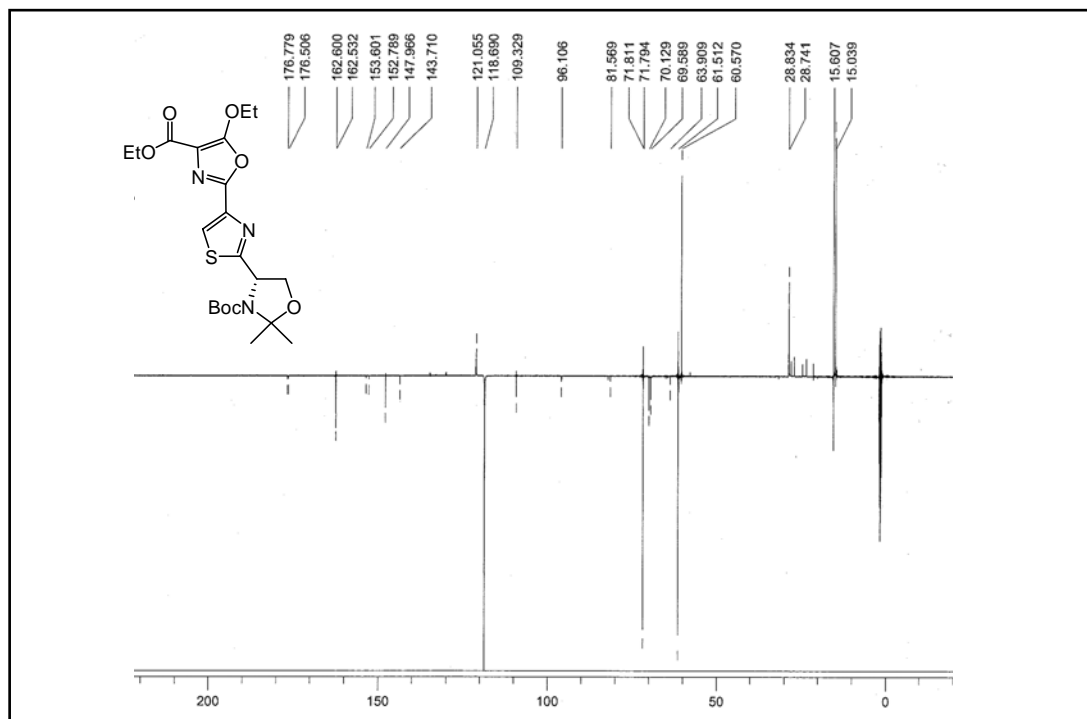
**Spectrum 1.1** <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>CN, 66 °C) spectrum of compound 1.17.



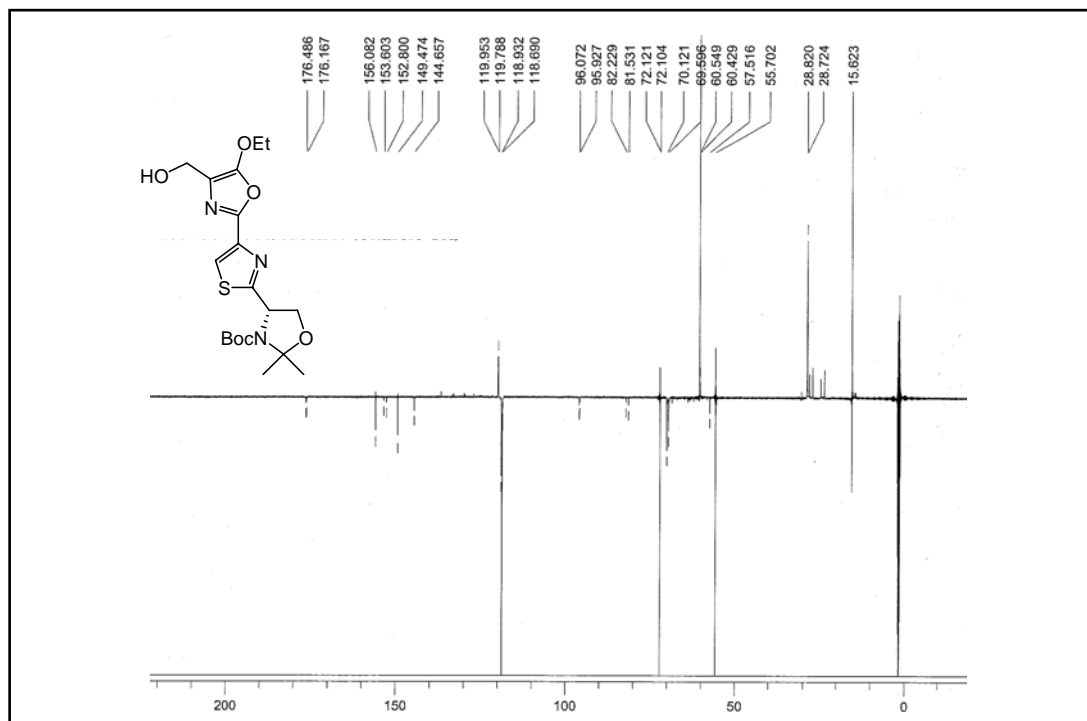
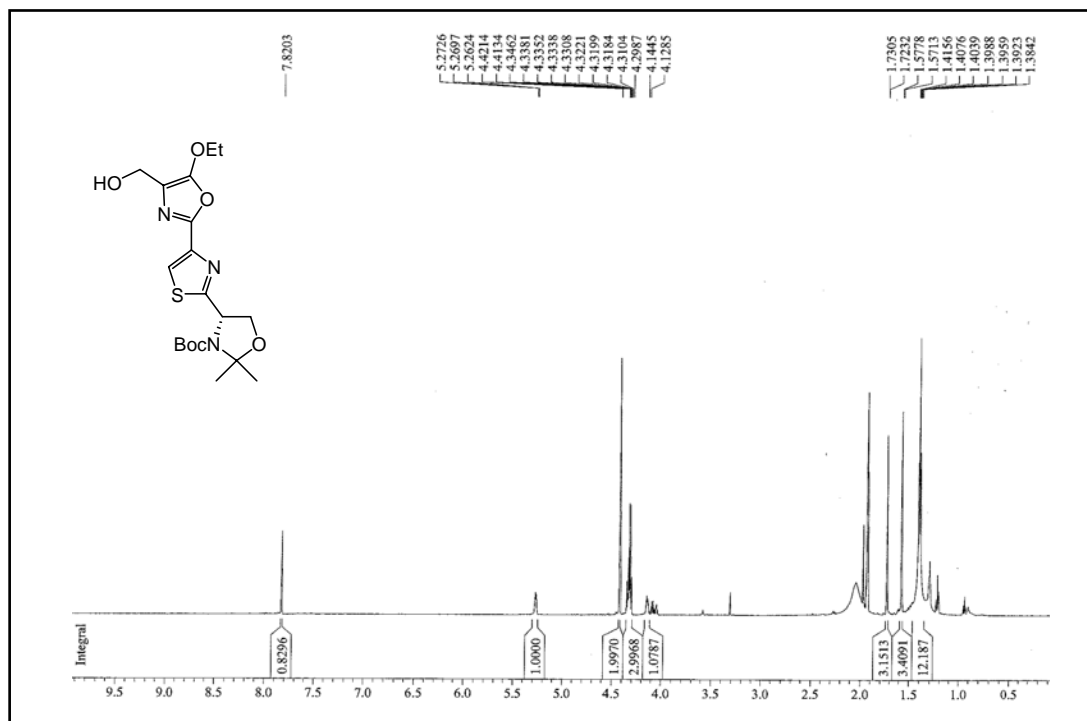
**Spectrum 1.2** <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) spectrum of compound 1.17.



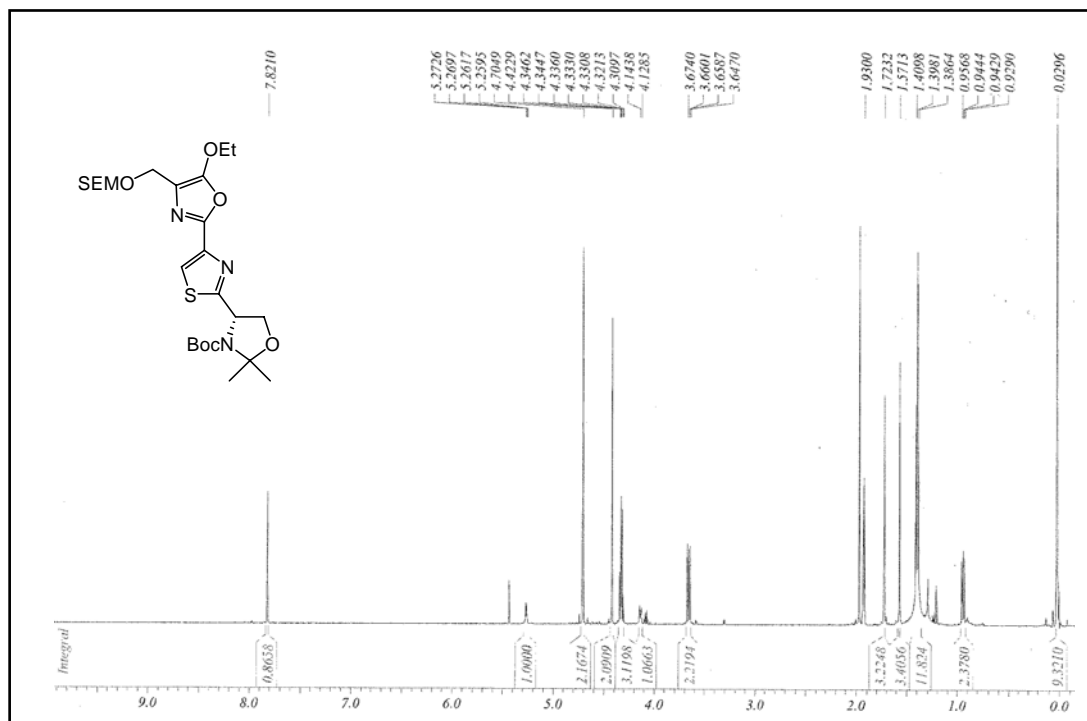
**Spectrum 1.3**  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ , 66 °C) spectrum of compound **1.18**.



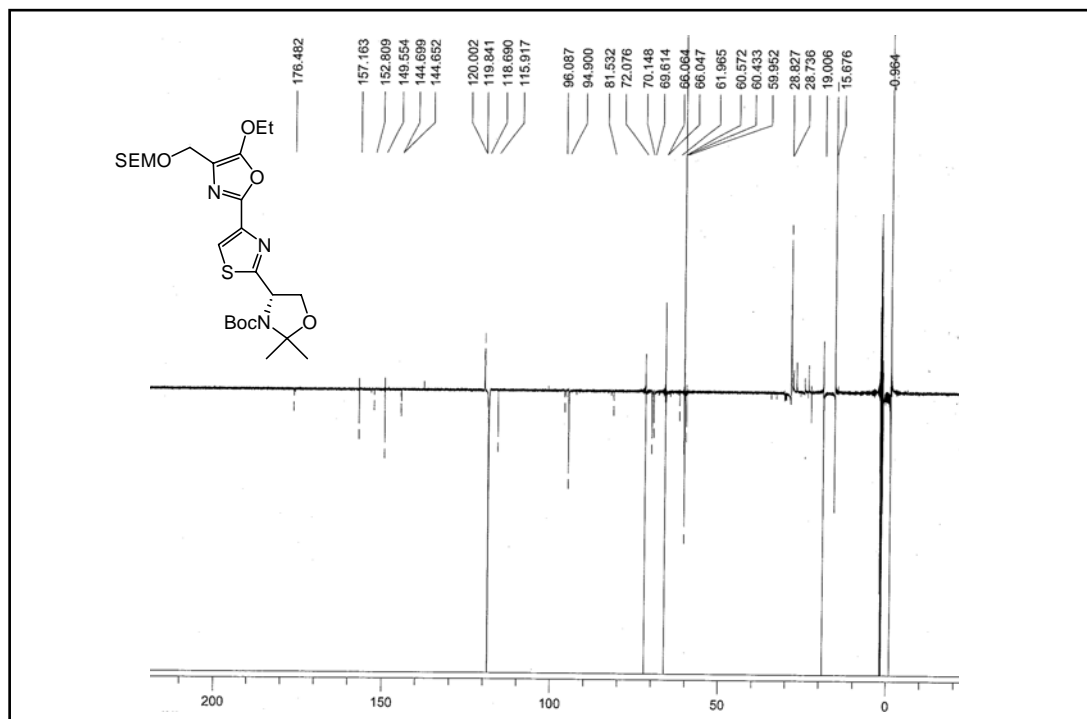
**Spectrum 1.4**  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **1.18**.



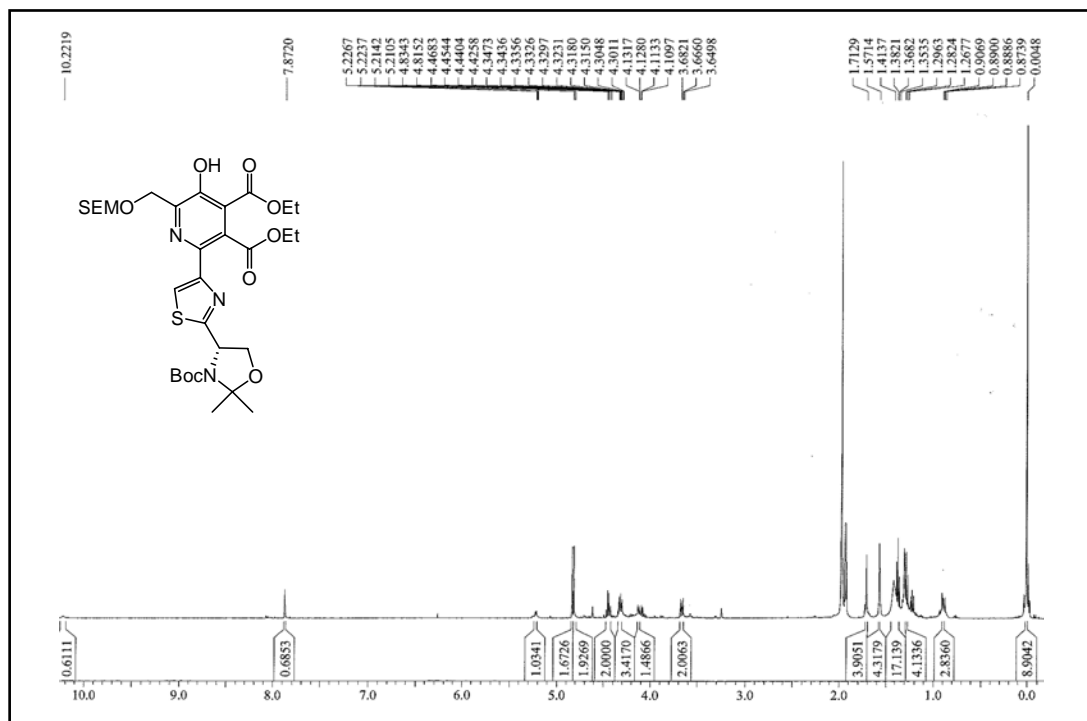




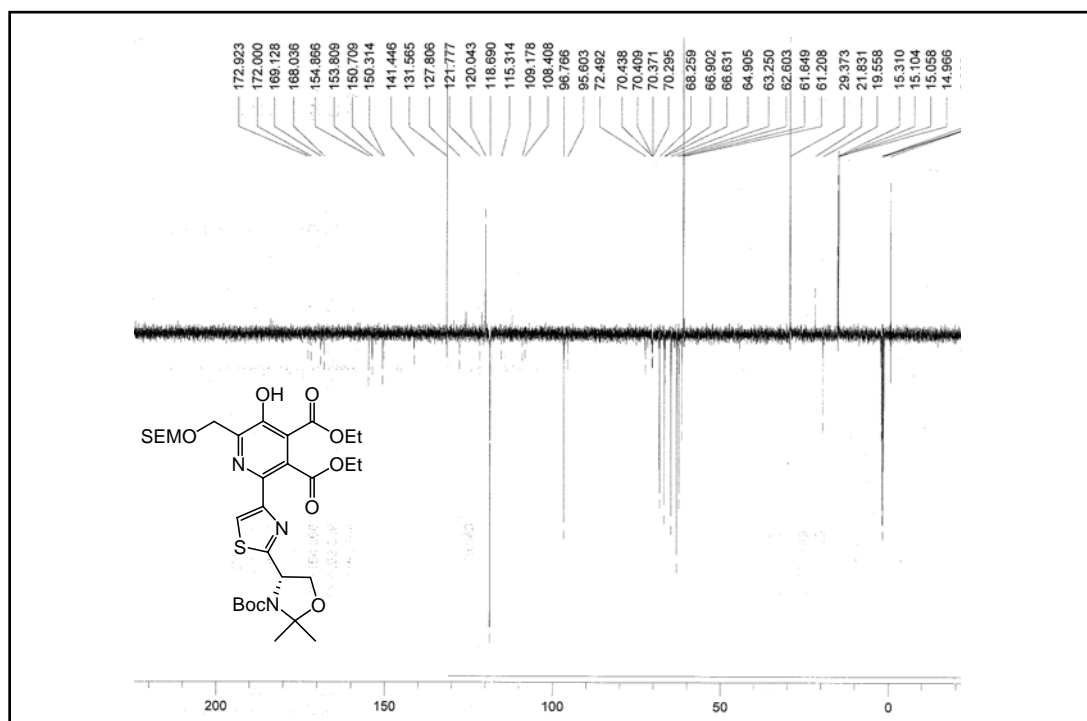
**Spectrum 1.7**  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ , 66 °C) spectrum of compound **1.14**.



**Spectrum 1.8**  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **1.14**.



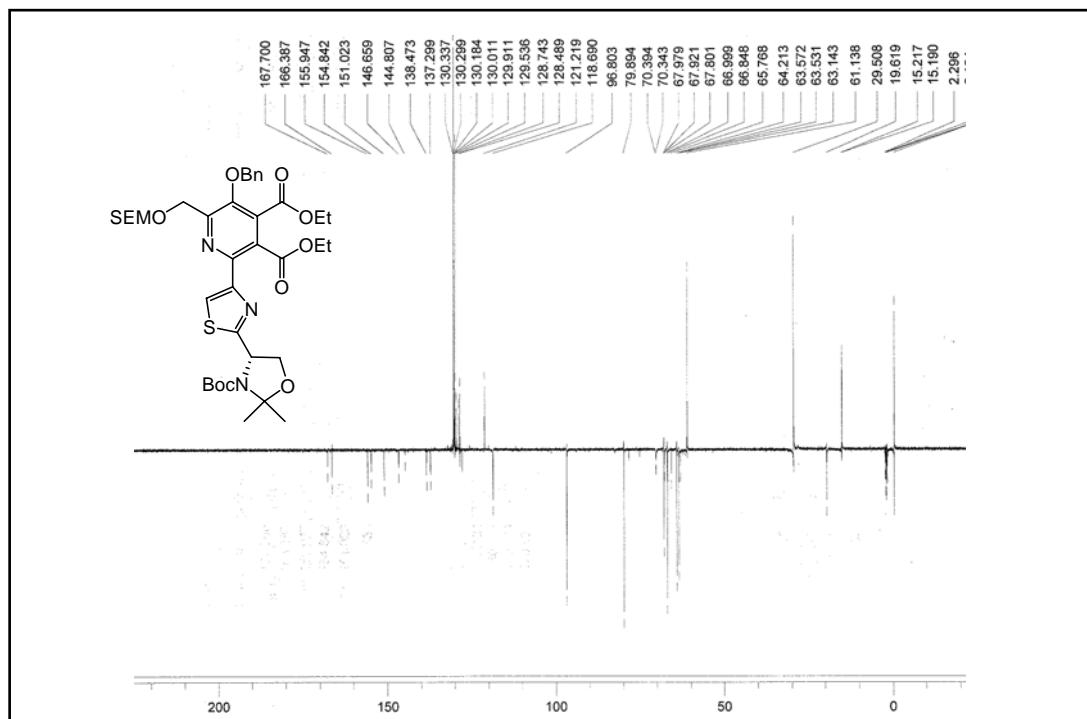
**Spectrum 1.9**  $^1\text{H NMR}$  (500 MHz,  $\text{CD}_3\text{CN}$ , 66 °C) spectrum of compound 1.13.



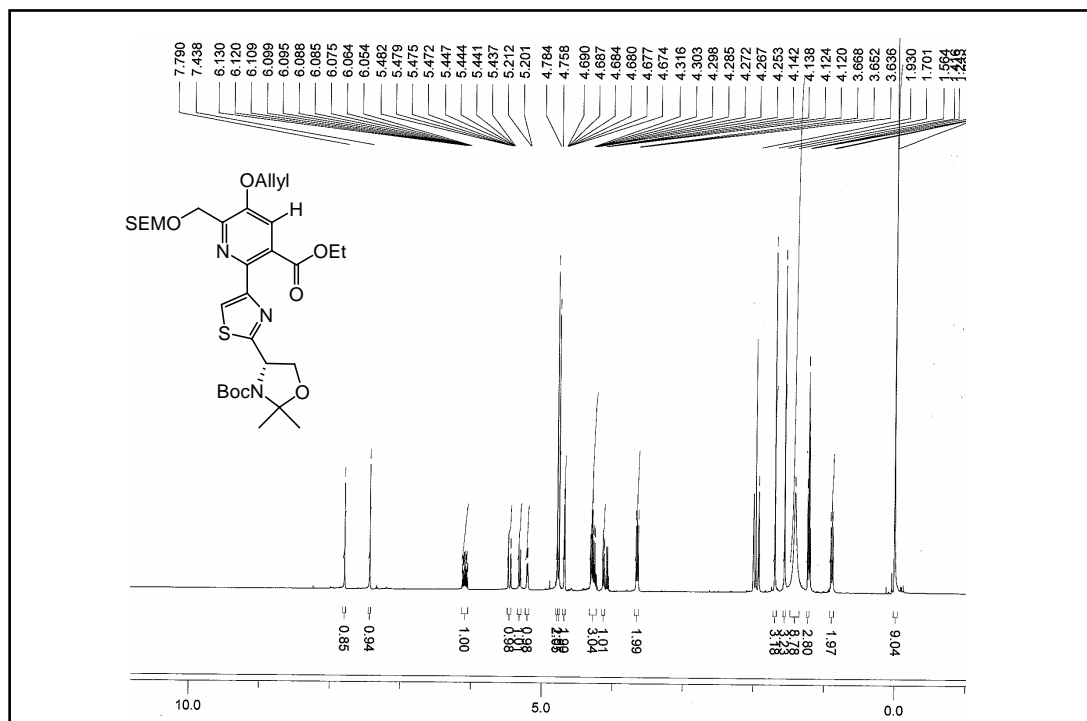
**Spectrum 1.10**  $^{13}\text{C NMR}$  (125 MHz,  $\text{CD}_3\text{CN}$ , 66 °C) spectrum of compound 1.13.



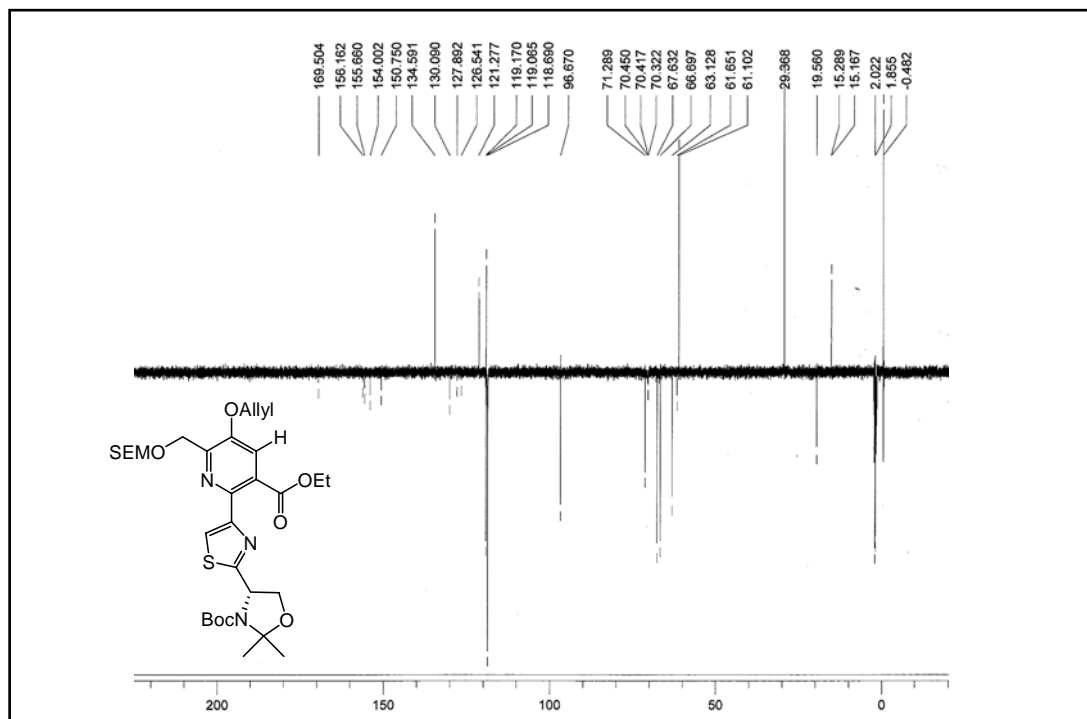
**Spectrum 1.11** <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>CN, 66 °C) spectrum of compound 1.20.



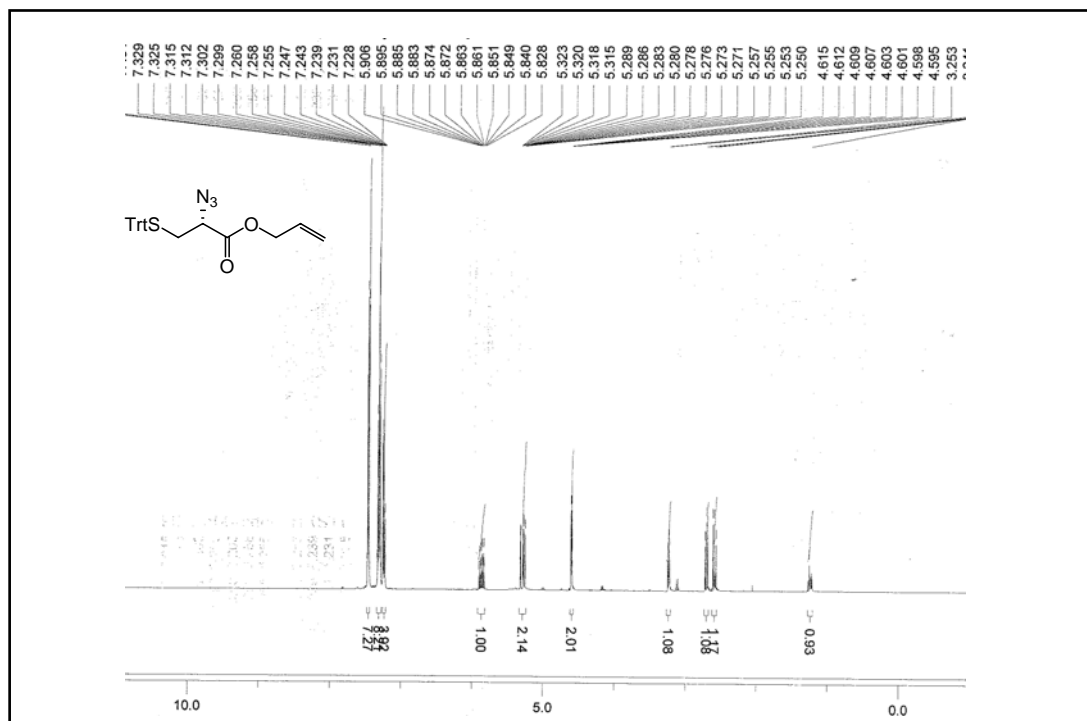
**Spectrum 1.12** <sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>CN, 66 °C) spectrum of compound 1.20.



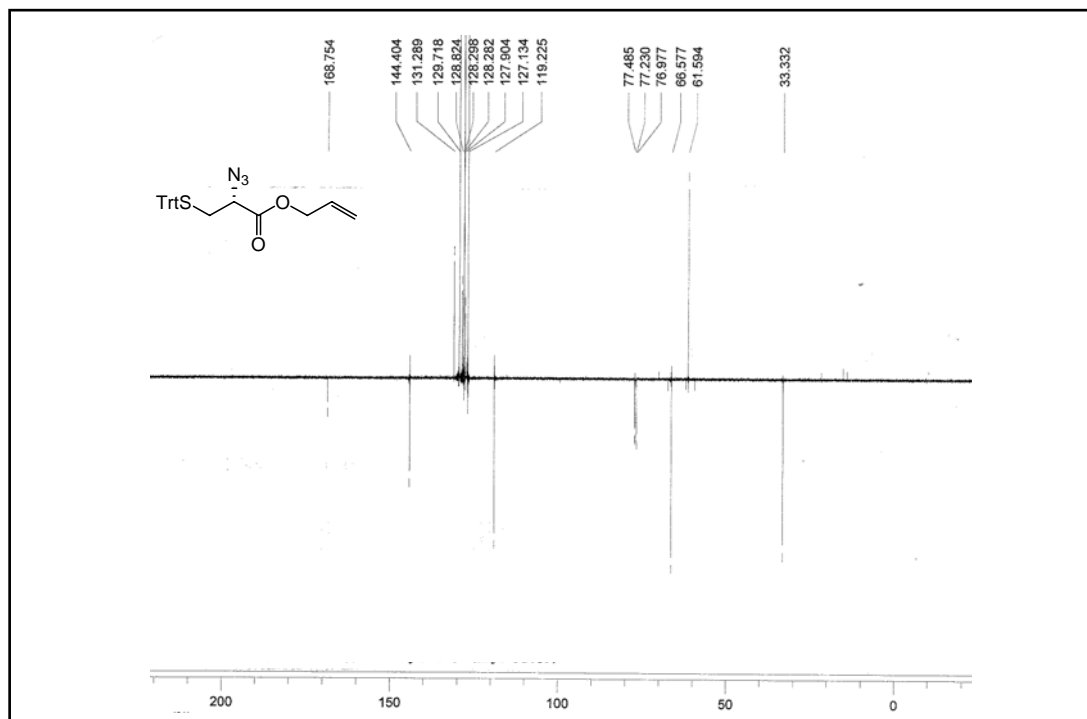
**Spectrum 1.13**  $^1\text{H NMR}$  (500 MHz,  $\text{CD}_3\text{CN}$ , 66 °C) spectrum of compound 1.21.



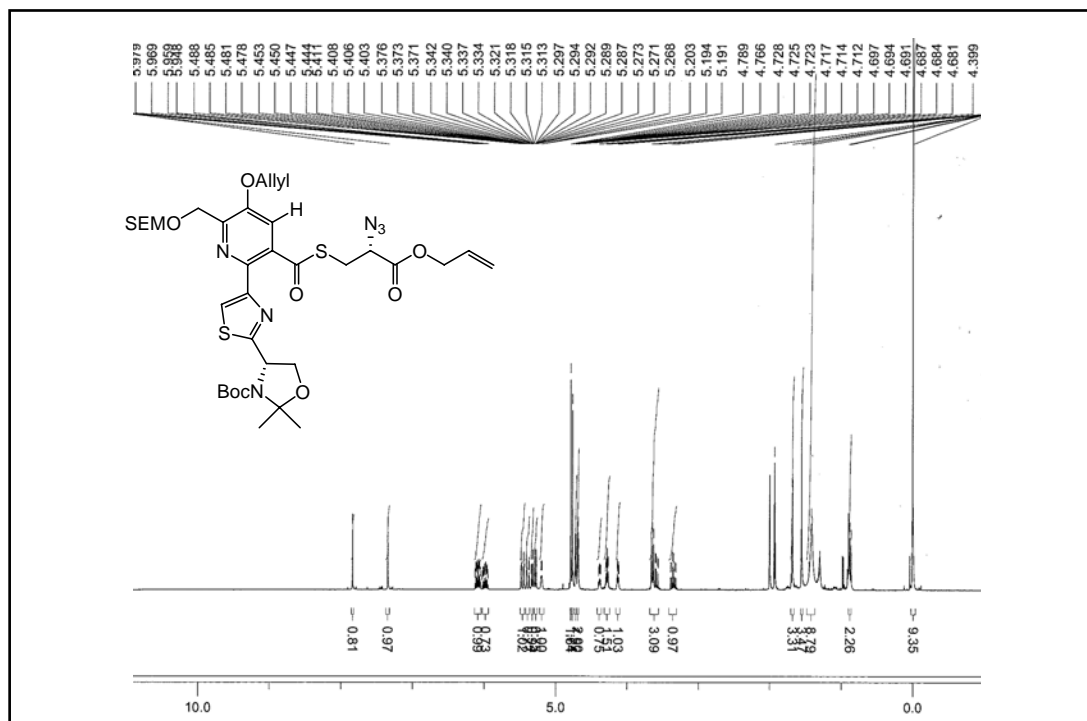
**Spectrum 1.14**  $^{13}\text{C NMR}$  (125 MHz,  $\text{CD}_3\text{CN}$ , 66 °C) spectrum of compound 1.21.



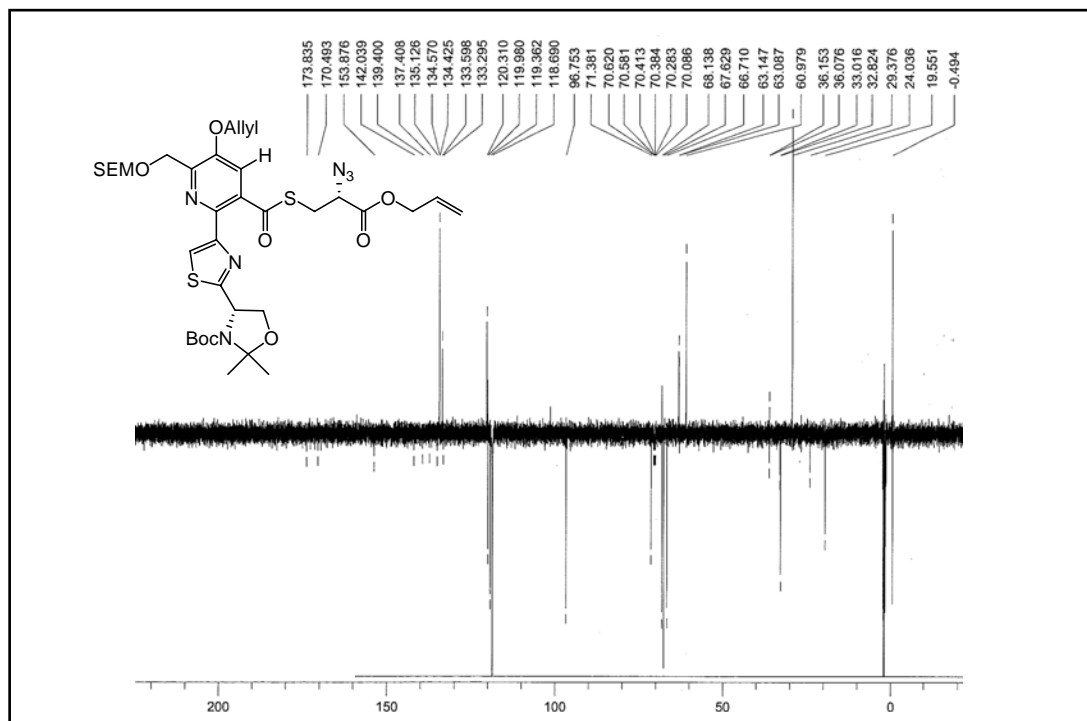
**Spectrum 1.15**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) spectrum of compound **1.23**.



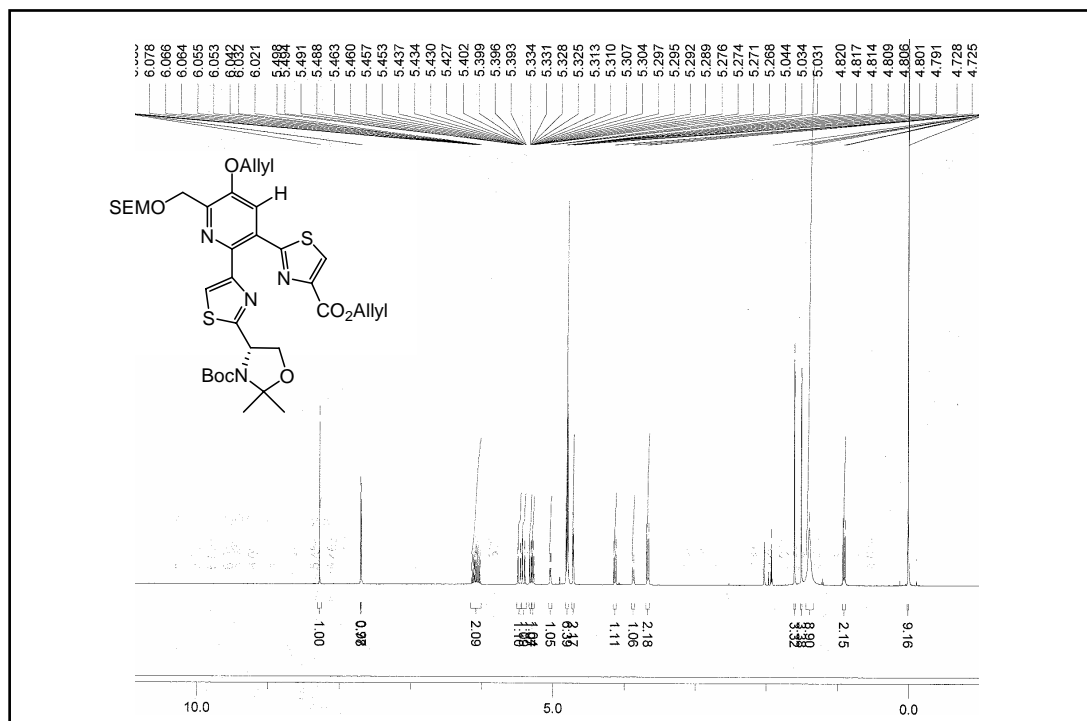
**Spectrum 1.16**  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) spectrum of compound **1.23**.



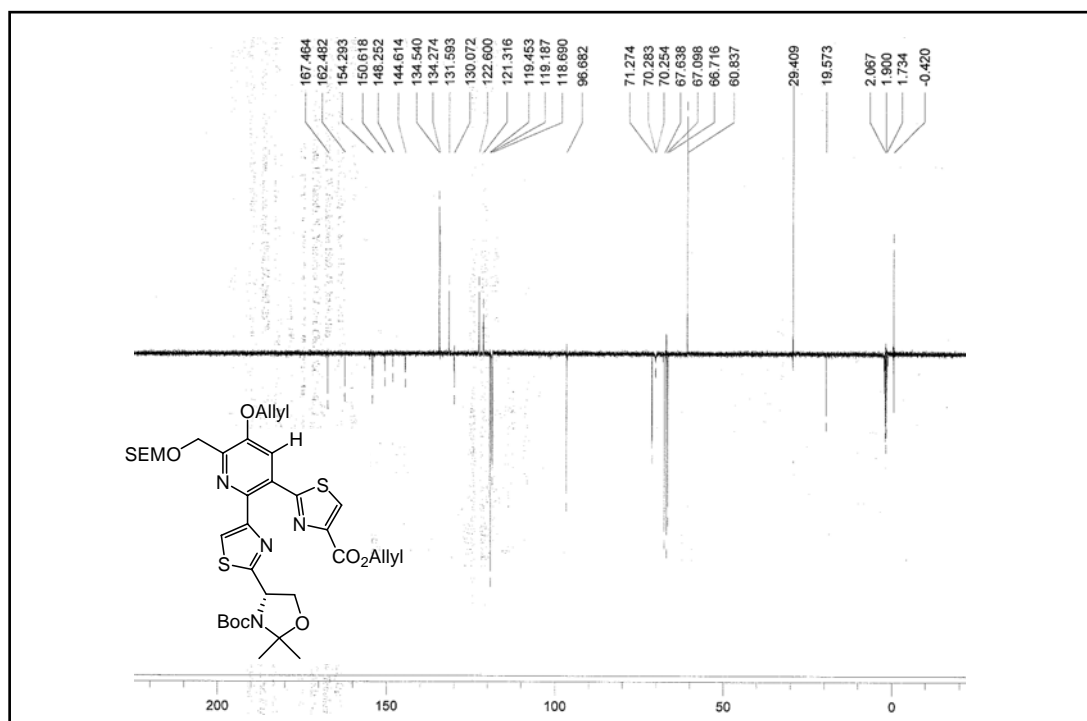
**Spectrum 1.17**  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ , 66 °C) spectrum of compound **1.24**.



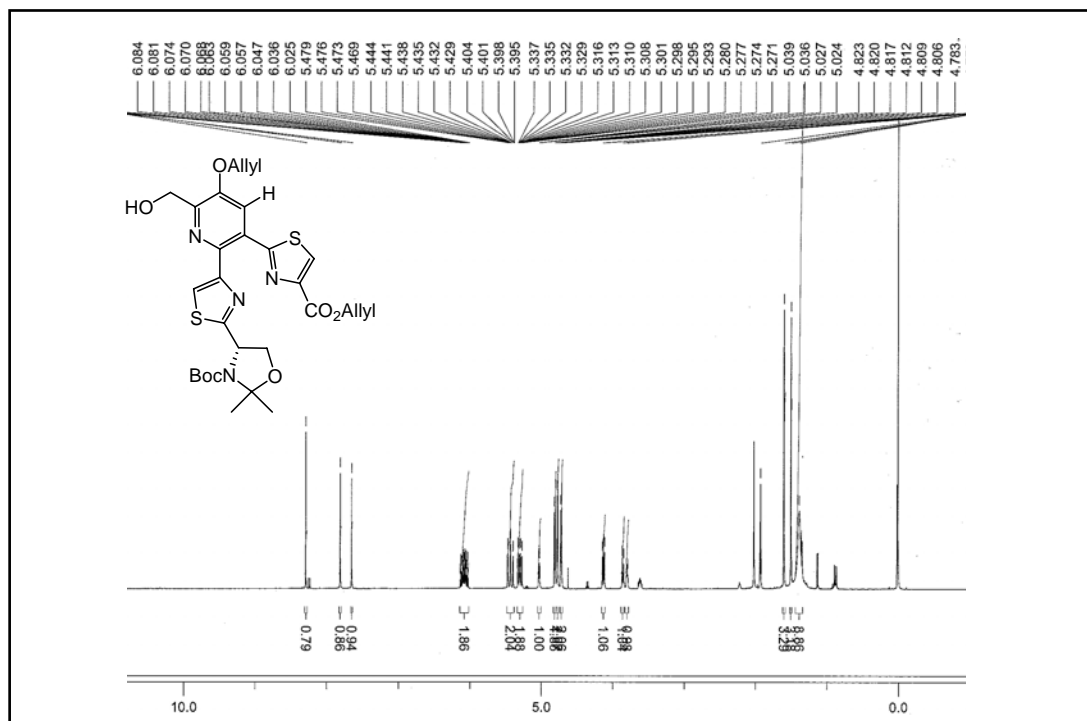
**Spectrum 1.18**  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ , 66 °C) spectrum of compound **1.24**.



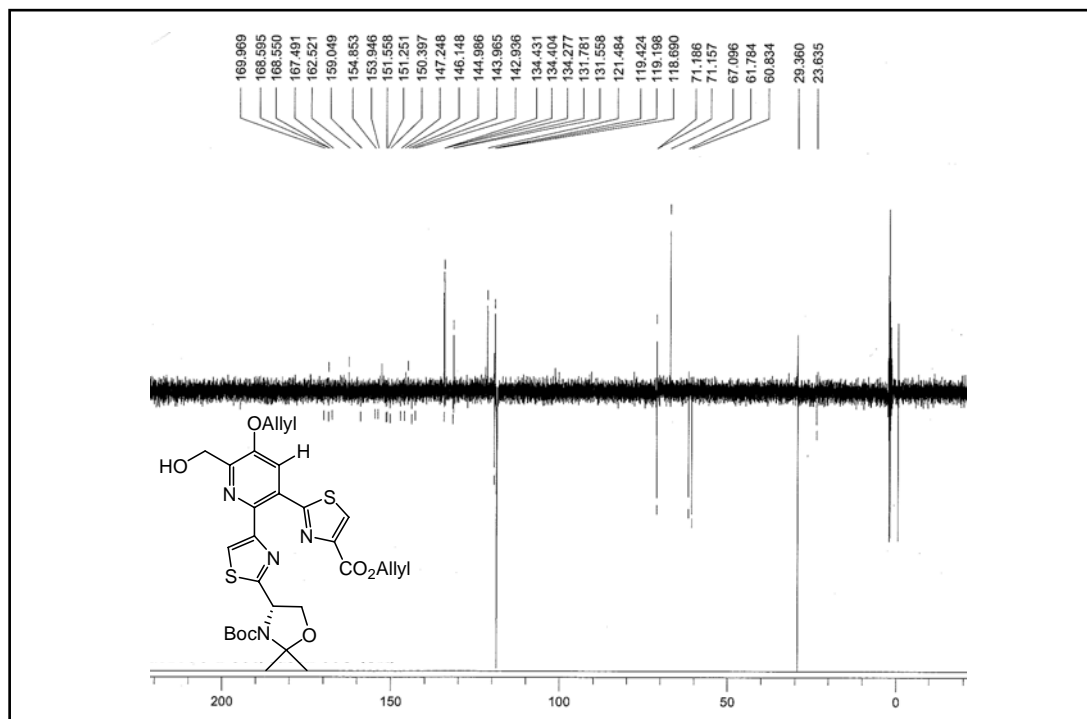
**Spectrum 1.19** <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>CN, 66 °C) spectrum of compound 1.25.



**Spectrum 1.20** <sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>CN, 66 °C) spectrum of compound 1.25.

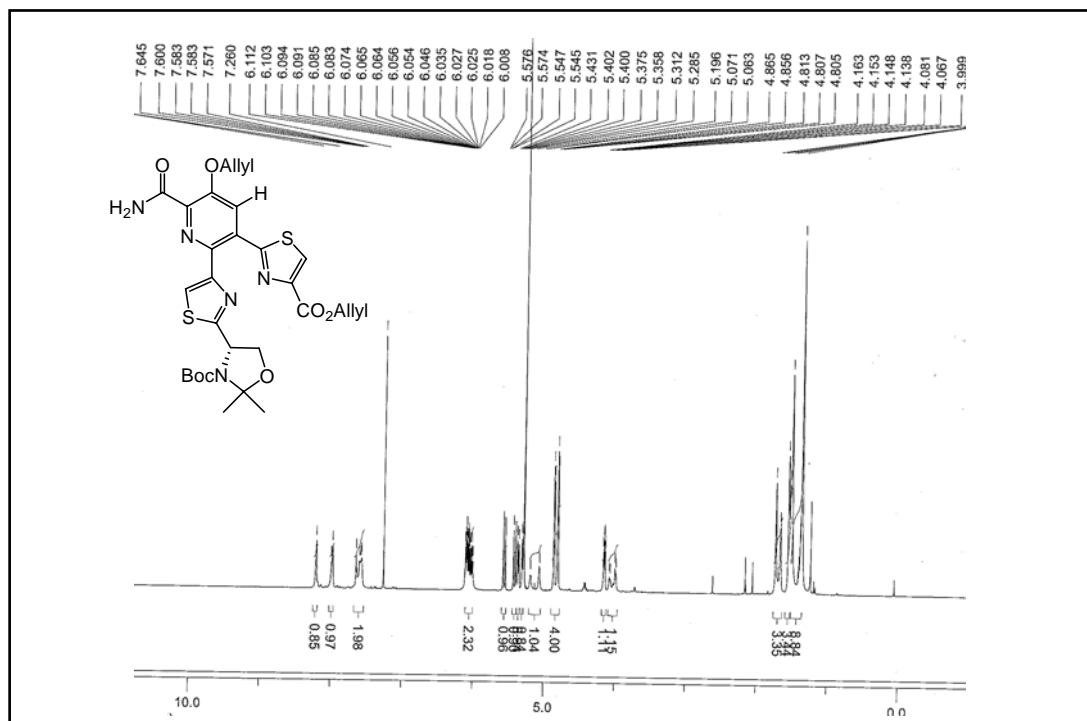


Spectrum 1.21 <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>CN, 66 °C) spectrum of compound 1.26.

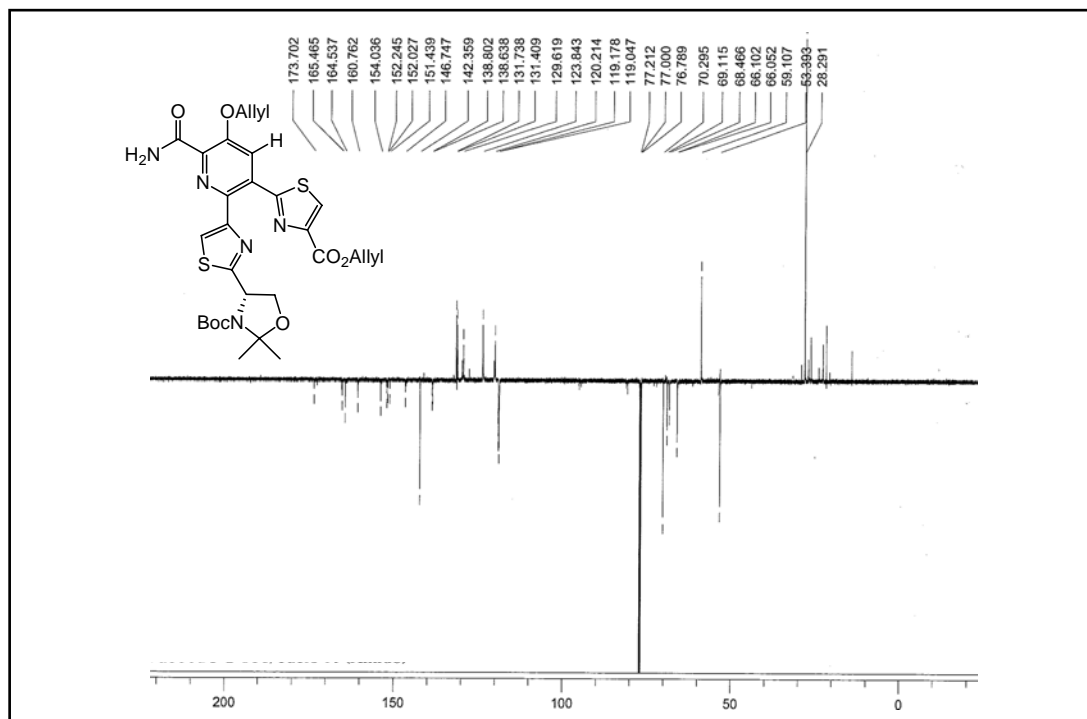


Spectrum 1.22 <sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>CN, 66 °C) spectrum of compound 1.26.

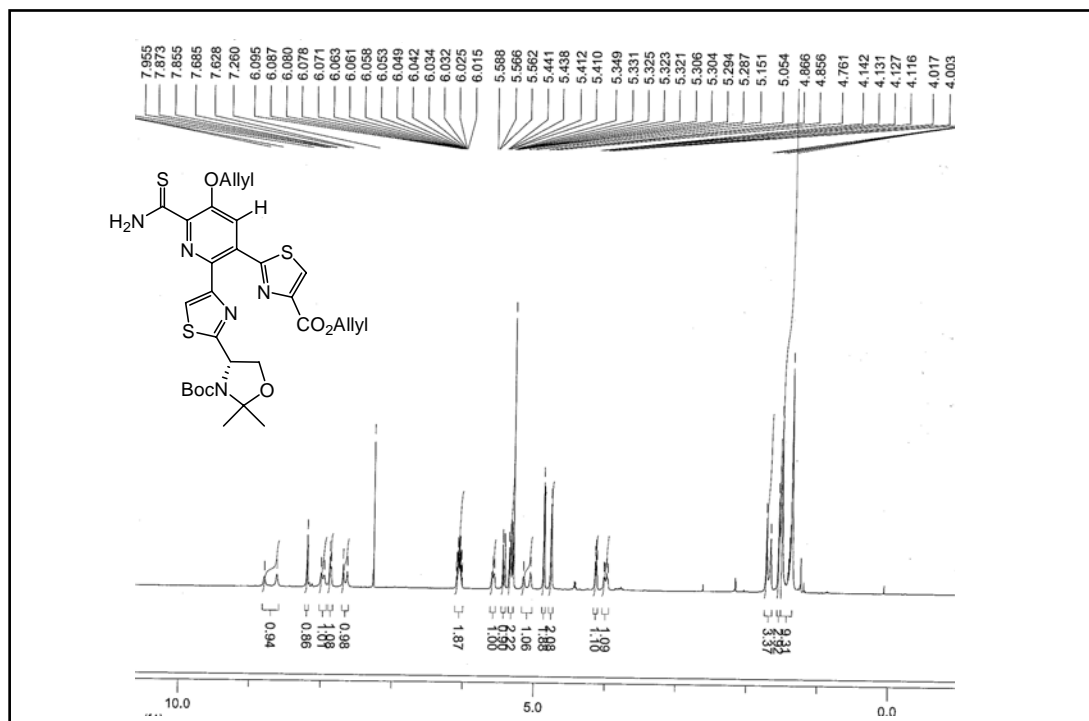




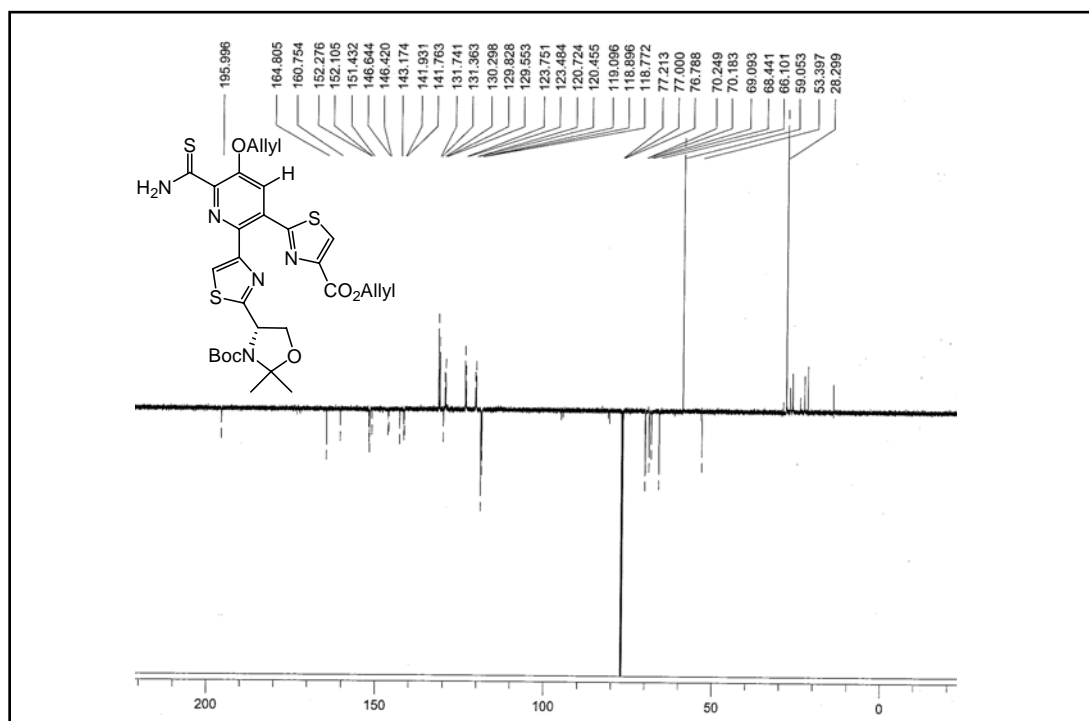
**Spectrum 1.23**  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ) spectrum of compound 1.27.



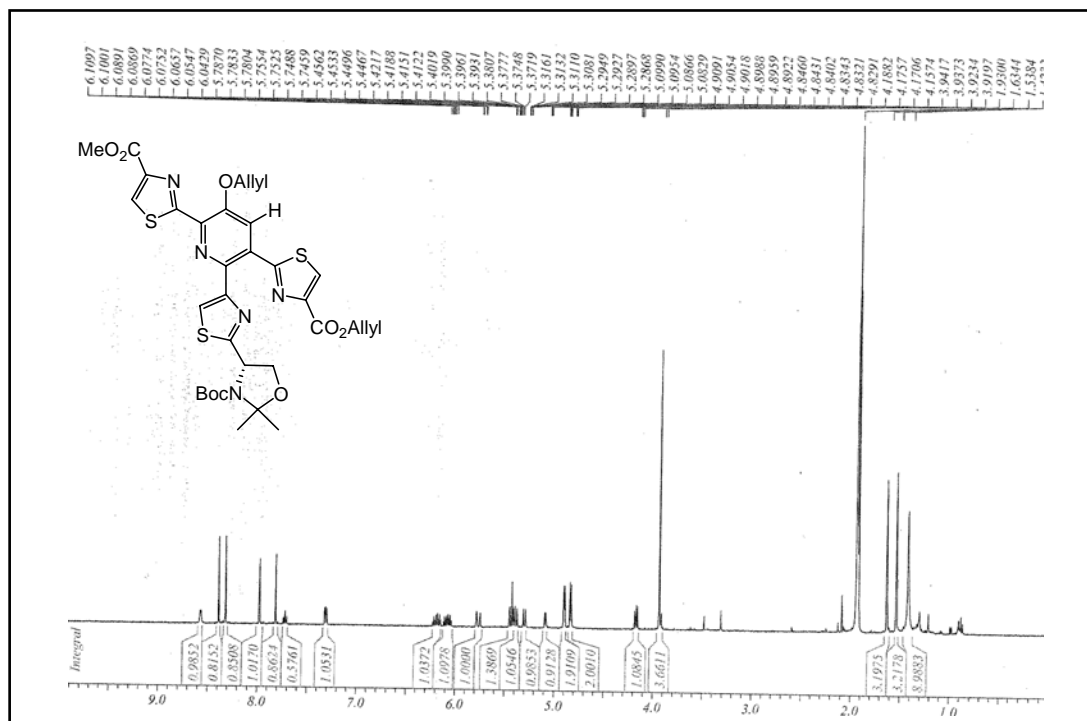
**Spectrum 1.24**  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ) spectrum of compound 1.27.



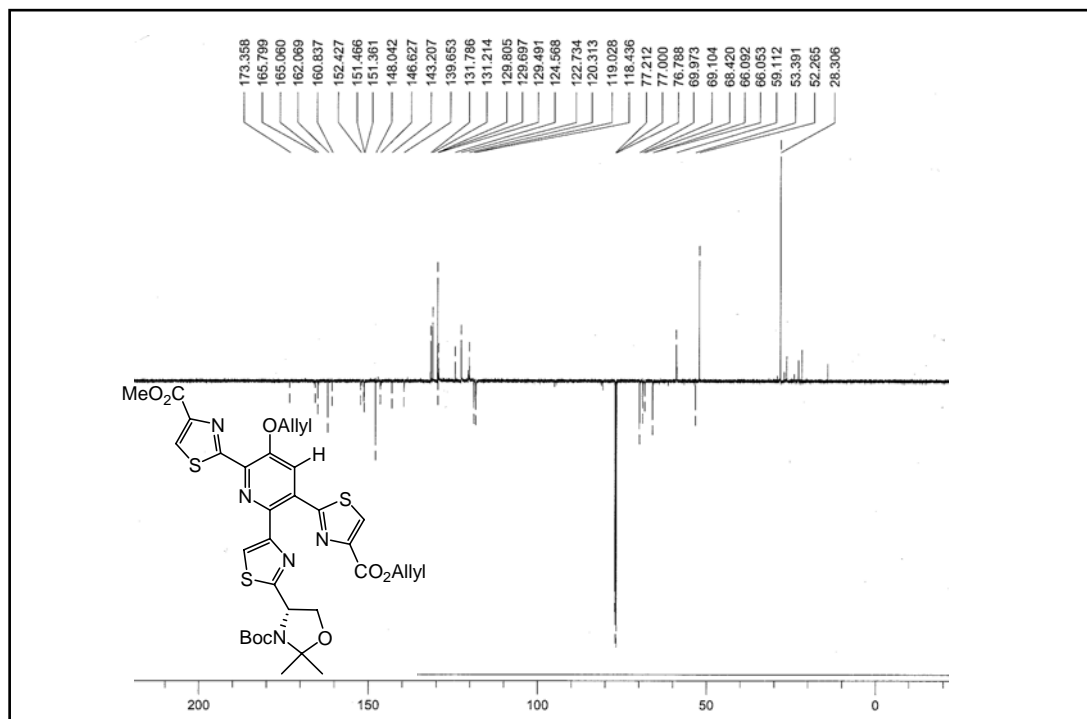
Spectrum 1.25  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ) spectrum of compound 1.28.



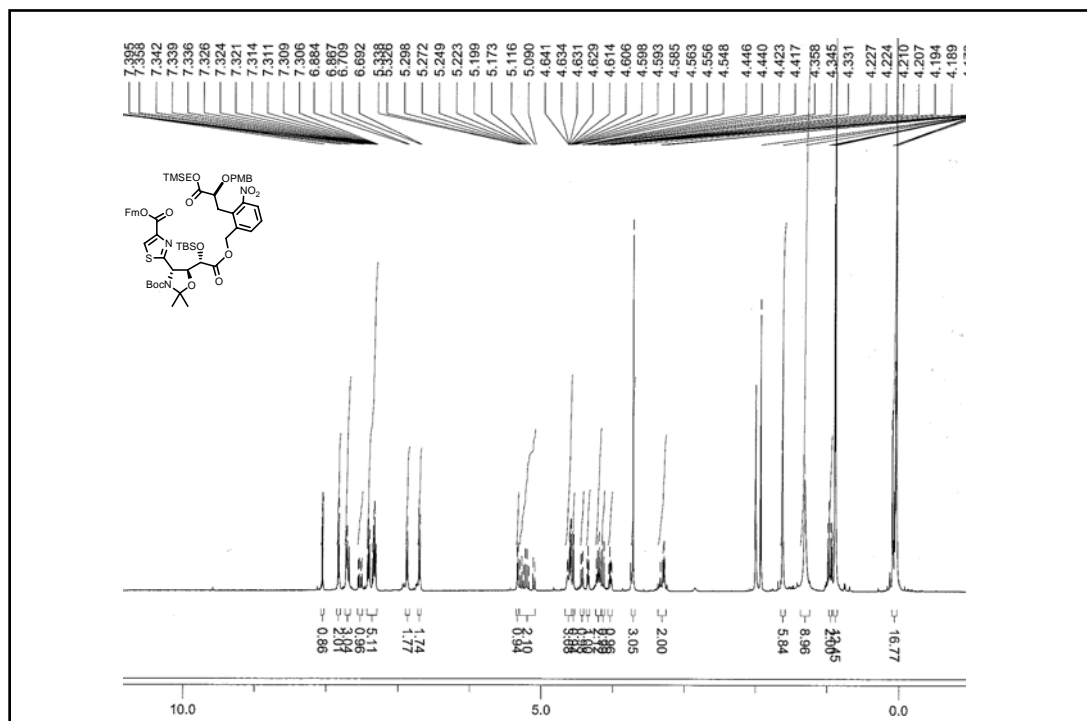
Spectrum 1.26  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ) spectrum of compound 1.28.



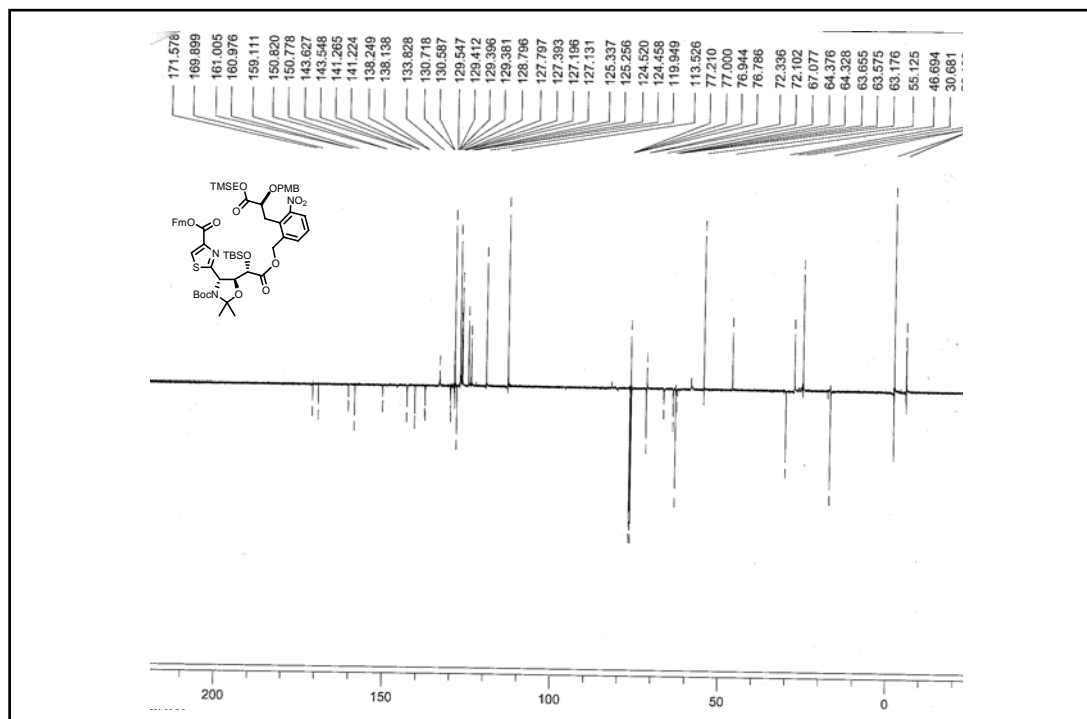
**Spectrum 1.27** <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>CN, 66 °C) spectrum of compound **1.9**.



**Spectrum 1.28** <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) spectrum of compound **1.9**.

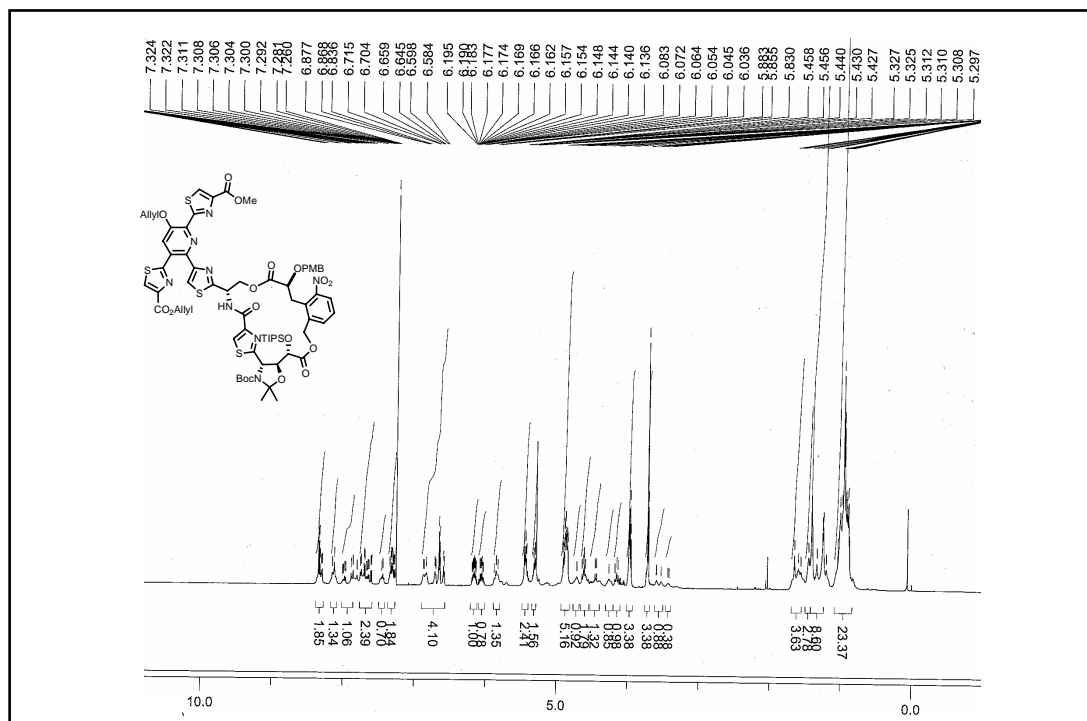


Spectrum 1.29  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ , 66 °C) spectrum of compound 1.10.

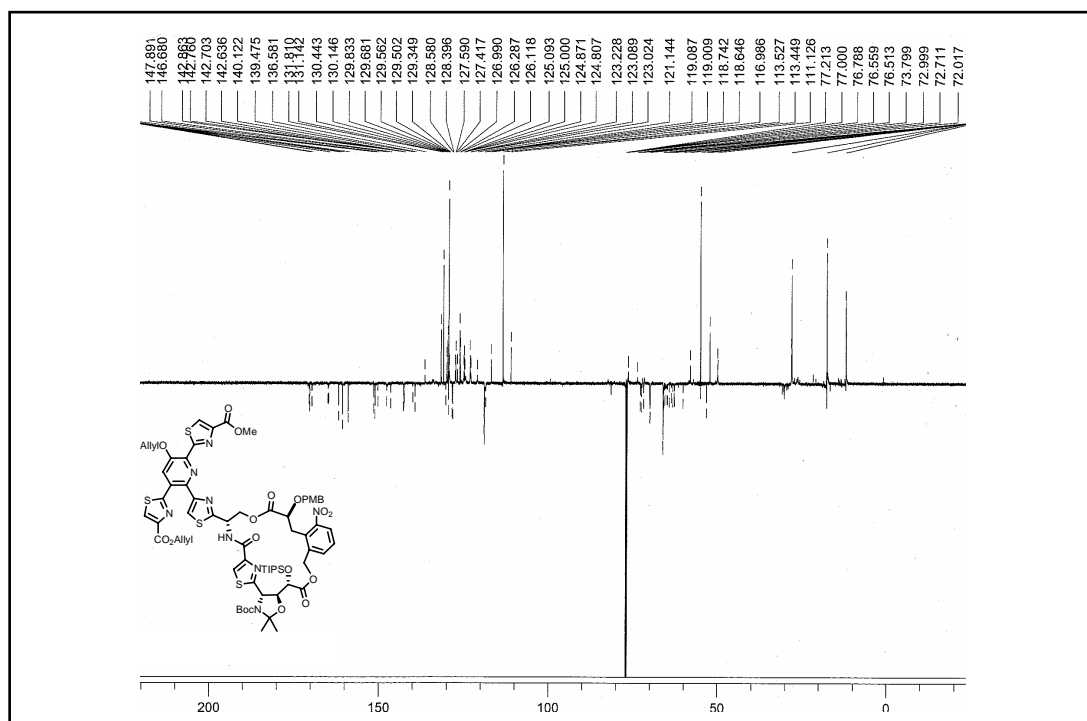


Spectrum 1.30  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ) spectrum of compound 1.10.





Spectrum 1.33 <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) spectrum of compound 1.7.

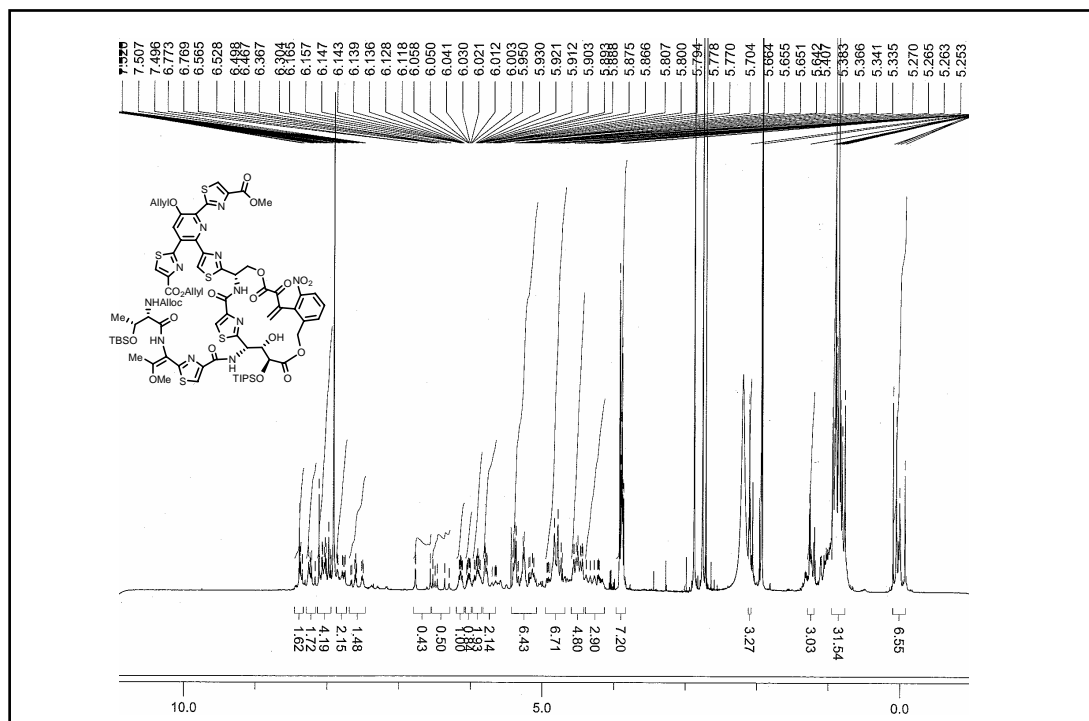


Spectrum 1.34 <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) spectrum of compound 1.7.

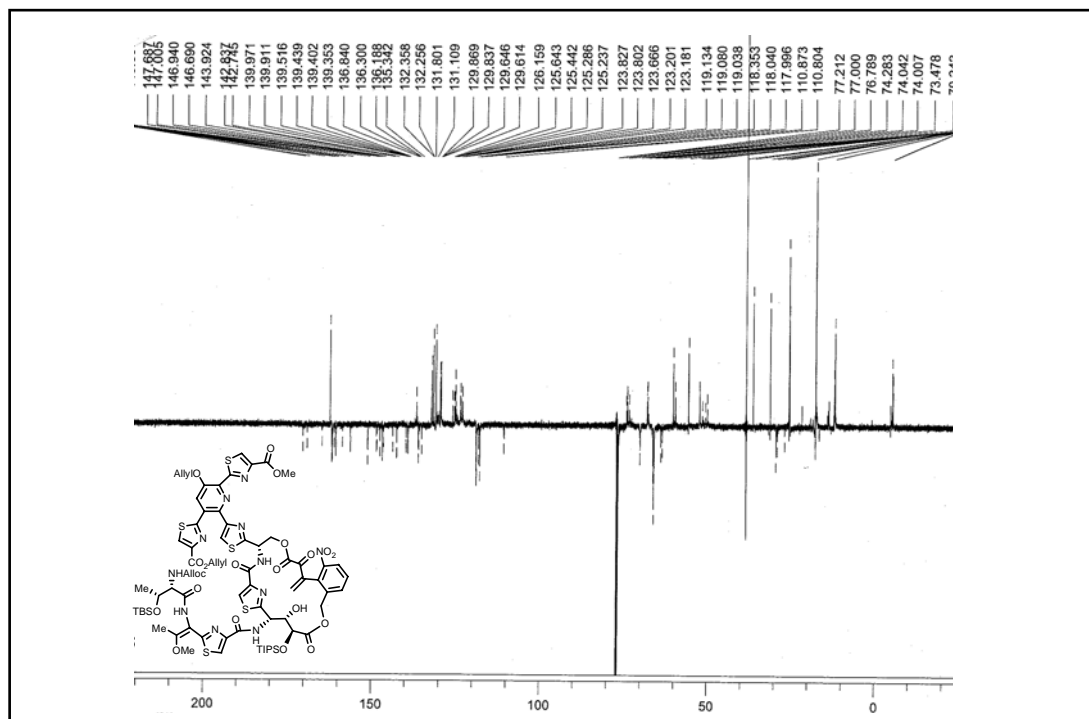


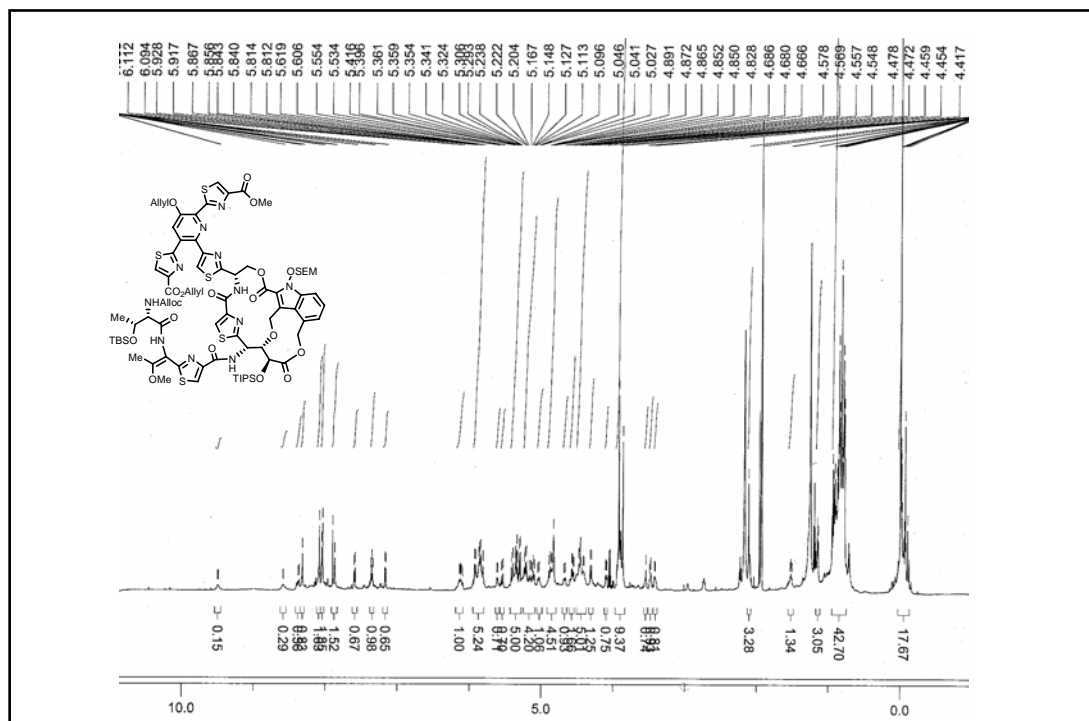




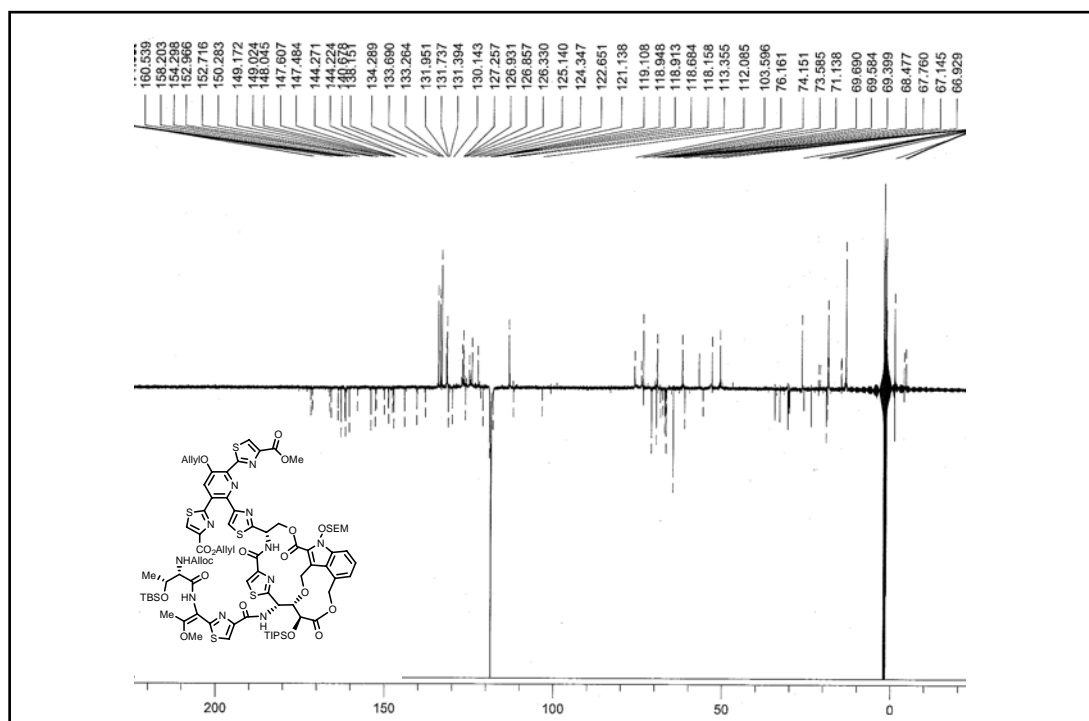


**Spectrum 1.39**  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **1.38**.

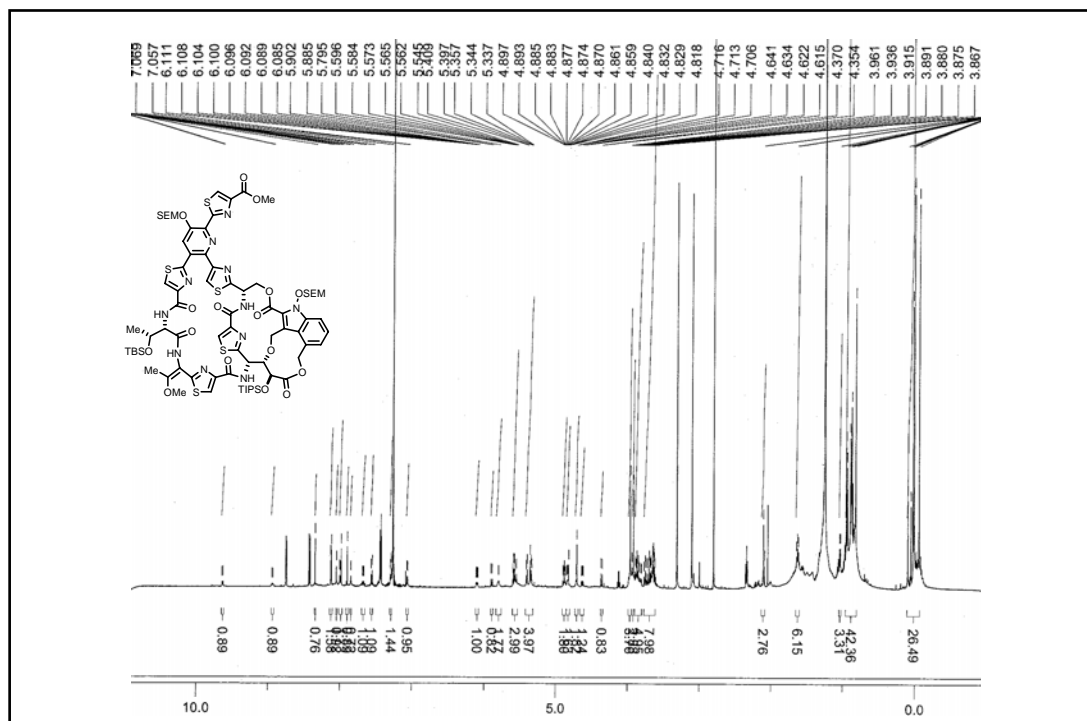




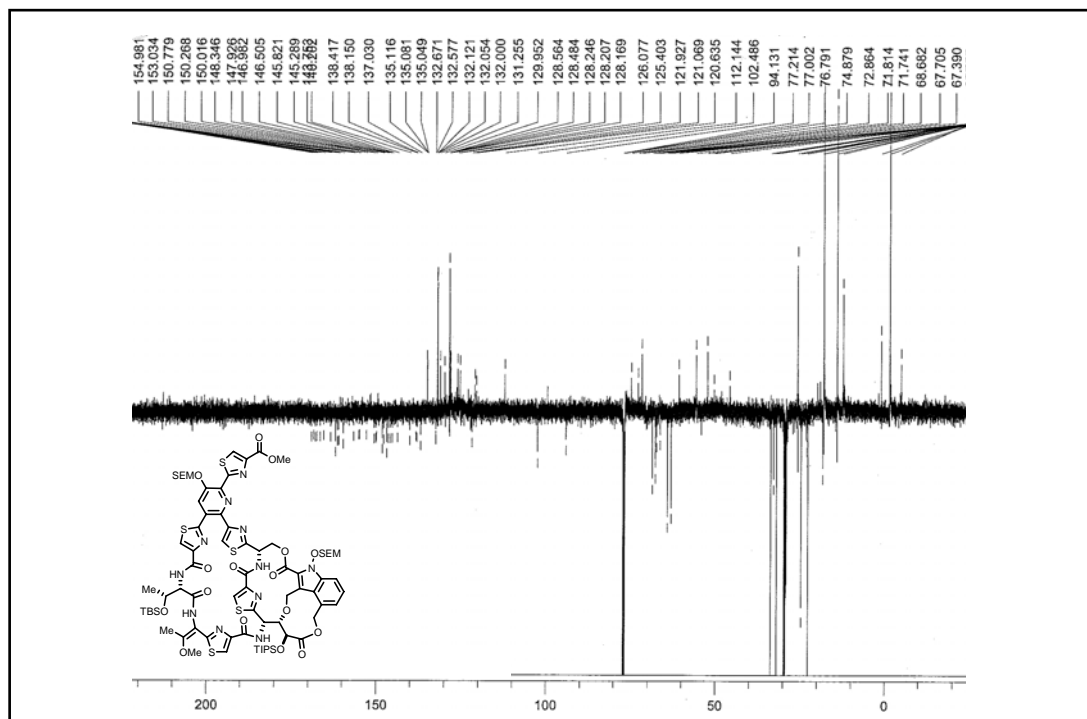
Spectrum 1.41 <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN) spectrum of compound 1.5.



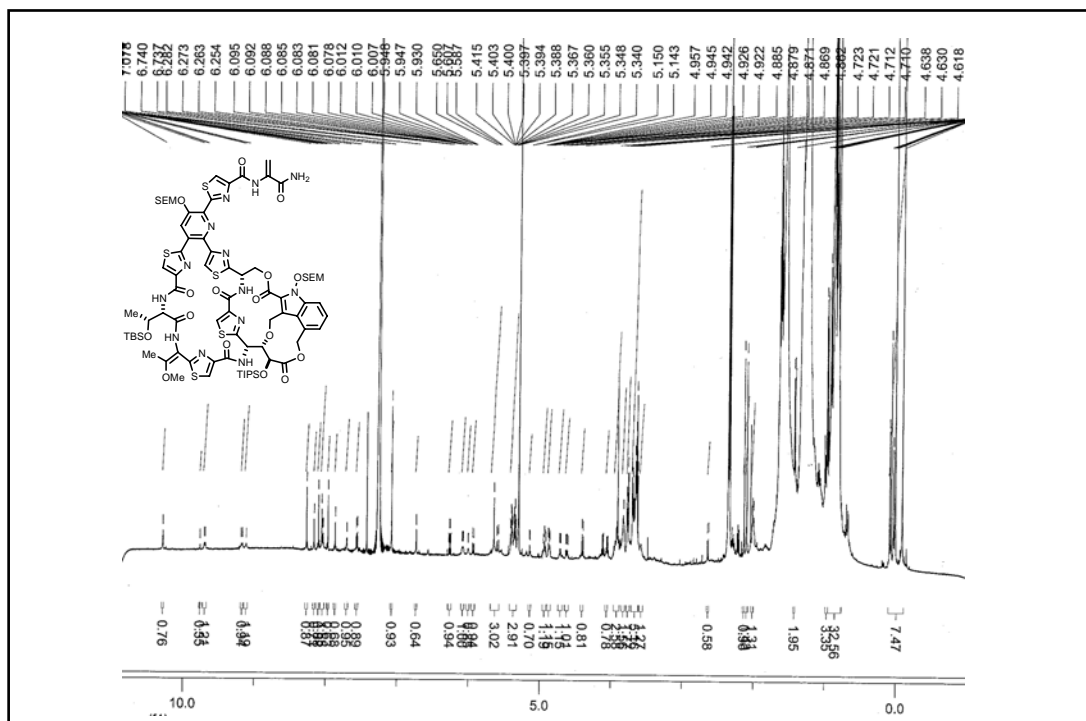
Spectrum 1.42 <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>CN) spectrum of compound 1.5.



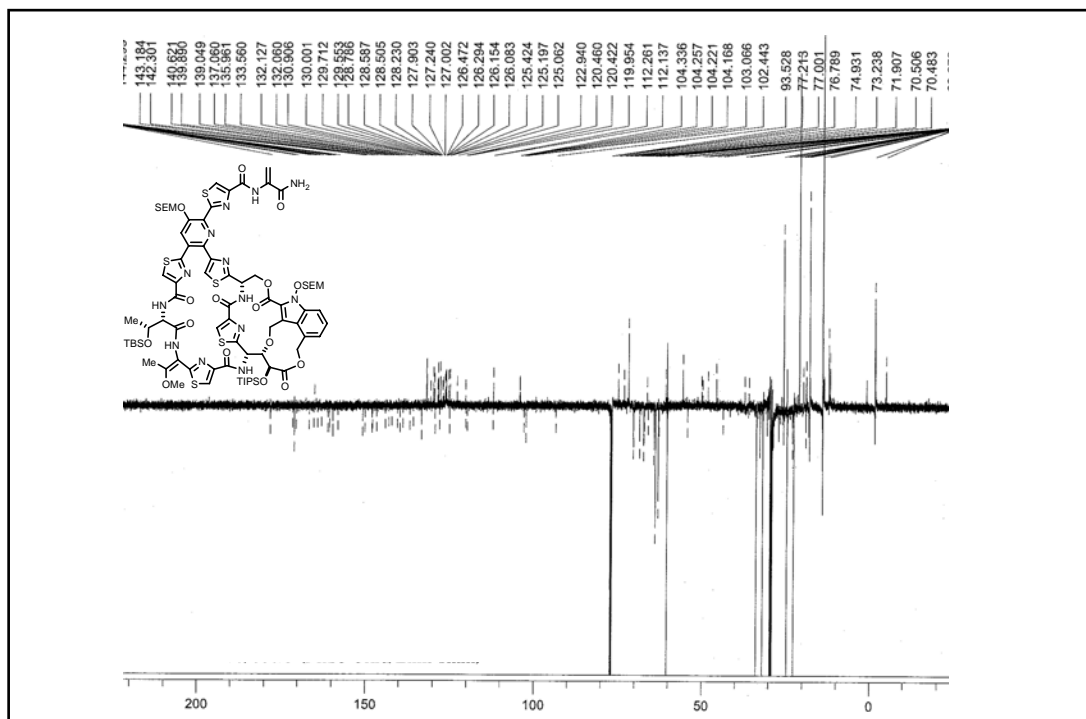
**Spectrum 1.43**  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ) spectrum of compound **1.43**.



**Spectrum 1.44**  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ) spectrum of compound **1.43**.



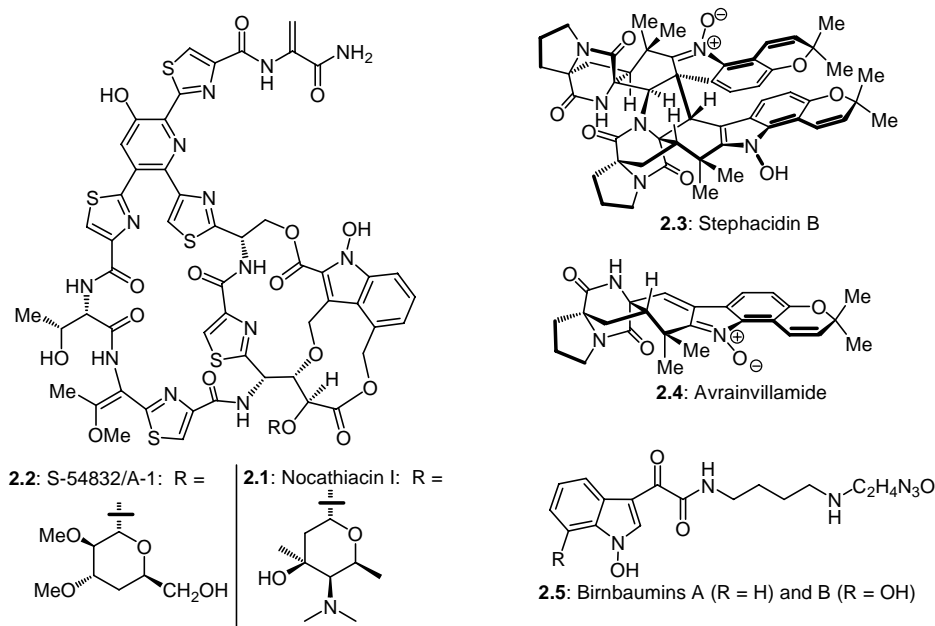
Spectrum 1.45  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ) spectrum of compound 1.45.



**Chapter 2: The Development of a New Synthetic Technology for the  
Construction of *N*-Hydroxyindoles and Synthesis of Nocathiacin  
Model Systems**

## A. Introduction

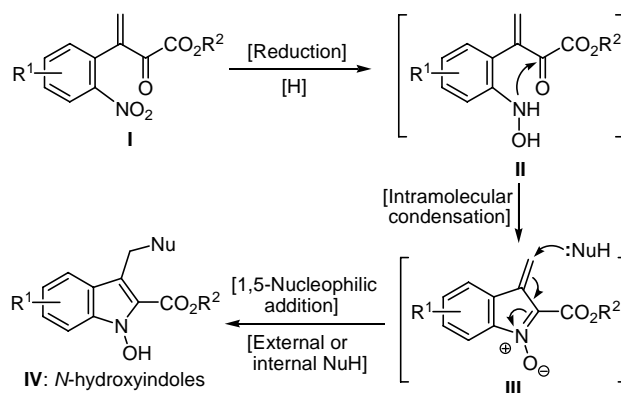
Upon examination of the molecular structure of nocathiacin I (**2.1**, Figure 2.1), it was immediately clear that the construction of the *N*-hydroxyindole structural motif would be one of the most difficult obstacles en route to a total synthesis. *N*-hydroxyindoles are intriguing molecular entities with potentially promising biological roles and previously demonstrated usefulness as synthetic building blocks.<sup>1</sup> Additionally, there are very few *N*-hydroxyindole containing natural products that have been reported from nature (**2.1–2.5**, Figure 2.1), a consequence that is possibly linked to its instability to isolation. Nevertheless, inspired by this challenge and the lack of general methods for *N*-hydroxyindole synthesis,<sup>2</sup> we developed a new synthetic method<sup>3</sup> in efforts to access a wide range of diversely functionalized *N*-hydroxyindoles as well as to construct nocathiacin model systems, which we hoped would ultimately aid us in our total synthesis endeavors.



**Figure 2.1** *N*-Hydroxyindole containing natural products isolated to date.

## B. Background and Mechanistic Rationale

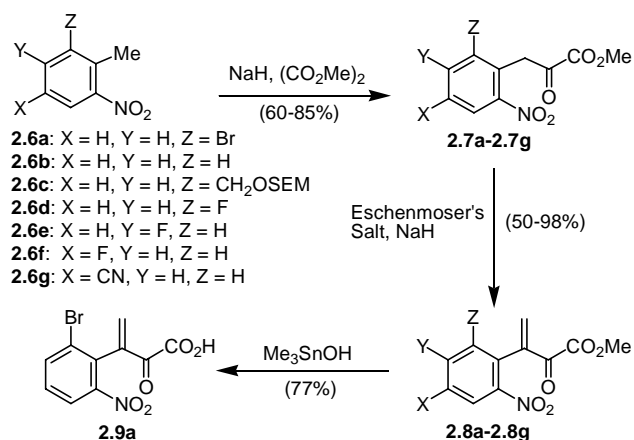
Existing methods for *N*-hydroxyindole construction vary in their efficiency, practicality, and ability to create molecular complexity stemming from the indole nucleus. In developing our own methodology, we sought to establish a mild set of conditions that would be amenable to highly complex systems as well as allow for the introduction of functionality at the 3-position of the newly formed *N*-hydroxyindoles. Furthermore, we wanted to take advantage of the abundant commercial availability of aromatic nitro compounds as our starting materials. Scheme 2.1 illustrates our general route for the construction of 3-substituted *N*-hydroxyindoles (**IV**). Thus, mild and selective reduction of generalized nitro ketoester **I** gives hydroxylamine **II**, which undergoes an intramolecular condensation onto the neighboring ketone to generate the fleeting nitrone species **III**. This reactive intermediate (**III**) can then be engaged in a 1,5-addition by various nucleophiles to form the desired substituted *N*-hydroxyindoles (**IV**).



**Scheme 2.1** General route for the construction of 3-substituted *N*-hydroxyindoles (**IV**).

### C. Generation of Starting Material and Investigation of Reduction Methods

Scheme 2.2 depicts the synthesis of  $\alpha,\beta$ -unsaturated nitro ketoesters **2.8a–g** and acid **2.9a** from commercially available nitro toluene compounds **2.6a–g** [aside from **2.6c** which is made by protection of 2-methyl-3-nitrobenzyl alcohol (SEMCl, *i*Pr<sub>2</sub>NEt, 98%)]. The initial step involves ketoester formation with dimethyl oxalate in the presence of NaH in DMF at 0–25 °C (60–85%). The freshly made ketoesters (**2.7a–g**) are then exposed to Eschenmoser's salt<sup>4</sup> in the presence of NaH in THF at 0–25 °C to furnish the desired  $\alpha,\beta$ -unsaturated nitro ketoesters **2.8a–g** (50–98%) in two facile and efficient transformations. Acid **2.9a** is accessed by applying our Me<sub>3</sub>SnOH synthetic methodology (1,2-dichloroethane, 70 °C, 77%) that will be discussed in detail in Chapter 3.

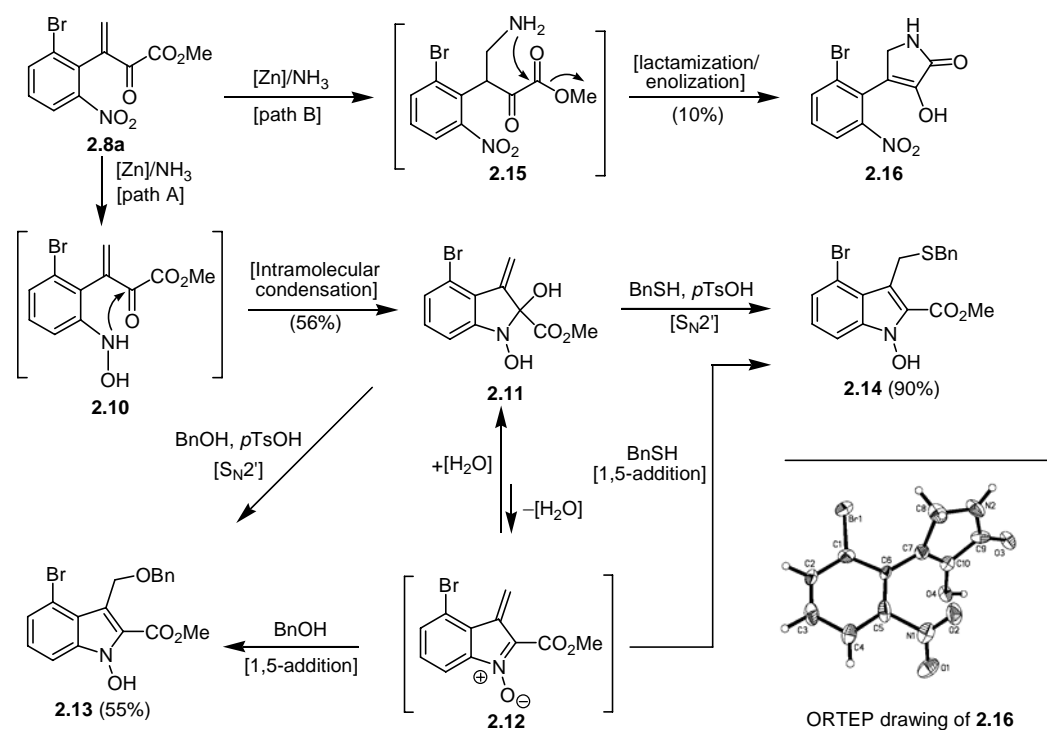


**Scheme 2.2** Synthesis of nitro ketoesters **2.8a–2.8g** and acid **2.9a**

Two sets of experimental conditions utilizing different reduction sources proved successful in generating and trapping  $\alpha,\beta$ -unsaturated nitrones. Scheme 2.3



illustrates the first procedure (method A) which uses activated zinc [Zn] (prepared from zinc dust, 1,2-dibromoethane and TMSCl)<sup>5</sup> as the reducing agent as shown with nitro ketoester **2.8a**. Thus, addition of **2.8a** and aqueous 1 N NH<sub>4</sub>Cl to [Zn] in THF resulted in the formation of tertiary alcohol **2.11** (56%, path A), and hydroxylactam **2.16** (10%, path B, see ORTEP structure).<sup>6</sup> Exposure of tertiary alcohol **2.11** to BnOH

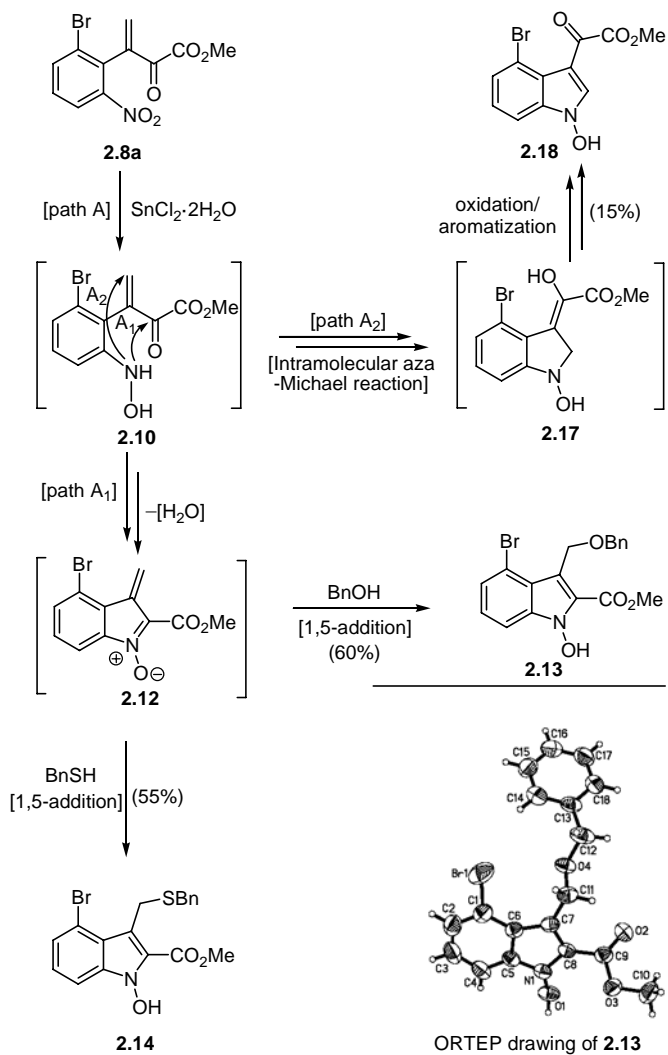


**Scheme 2.3** [Zn]/NH<sub>4</sub>Cl-induced (method A) *N*-hydroxyindole formation. ORTEP drawing of **2.16** drawn at the 50% probability level.

(5.0 equiv) or BnSH (5.0 equiv) in DME at 40 °C in the presence of *p*TsOH furnished *N*-hydroxyindoles **2.13** (55%) and **2.14** (90%) respectively, which can occur via both, or one of two possible mechanistic pathways. The first involves loss of water from indoline **2.11** to form the highly reactive nitrene species **2.12** (elusive to isolation)

which undergoes immediate 1,5-addition in the presence of a capable nucleophile. Alternatively, one could also envision S<sub>N</sub>2'-type displacement directly from **2.11** under the mildly acidic conditions.

In the search of a more direct and convenient method, we decided to use SnCl<sub>2</sub>·2H<sub>2</sub>O as the reduction source (method B). Hence, as depicted in Scheme 2.4, ketoester **2.8a** is treated with SnCl<sub>2</sub>·2H<sub>2</sub>O (2.2 equiv) in the presence of BnOH (5.0 equiv) or BnSH (5.0 equiv) and 4 Å molecular sieves in DME at 40 °C. These conditions gave products **2.13** (60%, see ORTEP structure)<sup>6</sup> and **2.14** (55%) respectively through path A<sub>1</sub>. Accompanying formation of ketoester by-product **2.18** (15%, path A<sub>2</sub>) remains an issue that has yet to be solved. Nonetheless, the SnCl<sub>2</sub>·2H<sub>2</sub>O procedure (method B) was adopted as the preferred method for *N*-hydroxyindole construction. After optimization studies were carried out, in which the effect of reaction parameters such as stoichiometry, temperature, water content, molecular sieves, and solvent were tested, we set out to explore its generality and scope with respect to nucleophiles.



**Scheme 2.4**  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ -induced (method B) *N*-hydroxyindole formation. ORTEP drawing of **2.13** drawn at the 50% probability level.

#### D. *N*-Hydroxyindole Synthesis with Heteroatom Nucleophilic C-3 Substitution

As can be seen in Tables 2.1 and 2.2, primary and secondary alcohols, and thiols participate in these reactions to give the desired 3-substituted *N*-hydroxyindoles in moderate to excellent yields. Additionally, entries 4–9 (Tables 2.1 and 2.2) demonstrate the generality with respect to the  $\alpha,\beta$ -unsaturated nitro ketoester

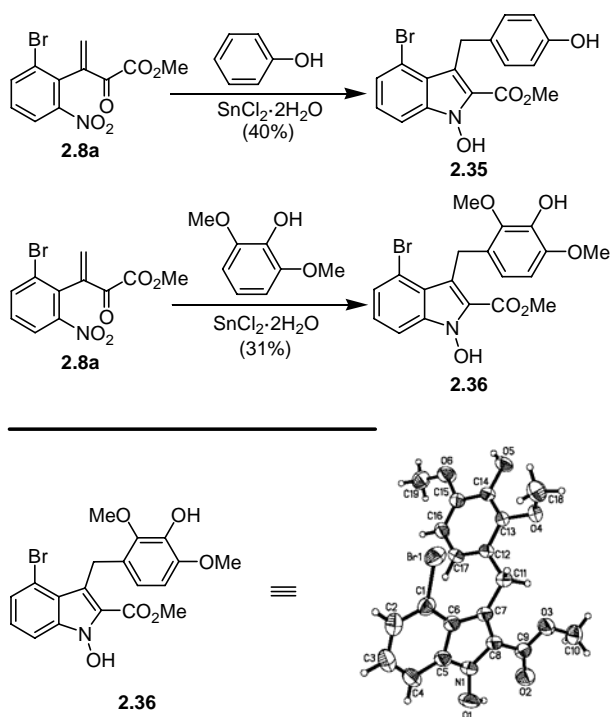
**Table 2.1** Synthesis of 3-substituted-*N*-hydroxyindoles through 1,5-addition of oxygen nucleophiles to substituted  $\alpha,\beta$ -unsaturated nitrones.

Entry	$\alpha,\beta$ -Unsaturated nitro ketoester	NuH	Product VI	Yield [%]
	<p style="text-align: center;"> <math>\text{V} \xrightarrow[\text{DME, 4 \AA MS, 1-3 h, 40 }^\circ\text{C}]{\text{SnCl}_2 \cdot 2\text{H}_2\text{O (2.2 equiv), NuH (5.0 equiv)}} \text{VI}</math> </p>			
1	<b>2.8a</b>		<p style="text-align: center;"><b>2.19</b></p>	54
2	<b>2.8a</b>	EtOH	<p style="text-align: center;"><b>2.20</b></p>	47
3	<b>2.8a</b>		<p style="text-align: center;"><b>2.21</b></p>	41
4	<b>2.8a</b>	BnOH	<p style="text-align: center;"><b>2.13</b></p>	60
5	<b>2.8c</b>	BnOH	<p style="text-align: center;"><b>2.22</b></p>	37
6	<b>2.8d</b>	BnOH	<p style="text-align: center;"><b>2.23</b></p>	87
7	<b>2.8e</b>	BnOH	<p style="text-align: center;"><b>2.24</b></p>	56
8	<b>2.8f</b>	BnOH	<p style="text-align: center;"><b>2.25</b></p>	55
9	<b>2.8g</b>	BnOH	<p style="text-align: center;"><b>2.26</b></p>	47

**Table 2.2** Synthesis of 3-substituted-*N*-hydroxyindoles through 1,5-addition of sulfur nucleophiles to substituted  $\alpha,\beta$ -unsaturated nitrones.

Entry	$\alpha,\beta$ -Unsaturated nitro ketoester	NuH	Product VI	Yield [%]
	<p style="text-align: center;"><b>V</b></p>		<p style="text-align: center;"><b>VI</b></p>	
			$\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (2.2 equiv) $\text{NuH}$ (5.0 equiv) DME, 4 Å MS, 1-3 h, 40 °C	
1	<b>2.8a</b>		<p style="text-align: center;"><b>2.27</b></p>	75
2	<b>2.8a</b>	PhSH	<p style="text-align: center;"><b>2.28</b></p>	68
3	<b>2.8a</b>		<p style="text-align: center;"><b>2.29</b></p>	73
4	<b>2.8a</b>	BnSH	<p style="text-align: center;"><b>2.14</b></p>	55
5	<b>2.8c</b>	BnSH	<p style="text-align: center;"><b>2.30</b></p>	54
6	<b>2.8d</b>	BnSH	<p style="text-align: center;"><b>2.31</b></p>	75
7	<b>2.8e</b>	BnSH	<p style="text-align: center;"><b>2.32</b></p>	60
8	<b>2.8f</b>	BnSH	<p style="text-align: center;"><b>2.33</b></p>	61
9	<b>2.8g</b>	BnSH	<p style="text-align: center;"><b>2.34</b></p>	57

component with benzyl alcohol and benzyl mercaptan as nucleophiles. Amines did not fare nearly as well as capable nucleophiles in the 1,5-addition process, as morpholine and aniline produced the corresponding products in only 27% and 18% yield respectively.<sup>3a,c</sup> Contributing factors to the moderate yields in certain cases include previously mentioned by-product **2.18** (Scheme 2.4) and dimerization/polymerization processes in which the nitron intermediate is captured by the *N*-OH group of the desired product.<sup>1b</sup>



**Scheme 2.5** Initial observations of C-C bond formation via 1,5-addition of phenolic nucleophiles. ORTEP drawing of **2.36** drawn at the 50% probability level.

Phenols were also tested as nucleophiles with the initial expectation that they would deliver the desired oxygen-carbon bonded 1,5-addition products. However,

after testing phenol and 2,6-dimethoxyphenol (Scheme 2.5), we were delighted to discover that they produced the C–C bonded products (**2.35**, 40% and **2.36**, 31%) as seen in Scheme 2.5. An X-ray crystal structure of **2.36** (see ORTEP drawing)<sup>6</sup> further confirmed this outcome. Inspired by these fascinating results, we launched a second phase investigation in which we desired to test a variety of carbon nucleophiles employing the SnCl<sub>2</sub>·2H<sub>2</sub>O (method B) reaction conditions.

### E. *N*-Hydroxyindole Synthesis with Carbon Nucleophilic C-3 Substitution

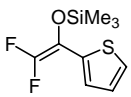
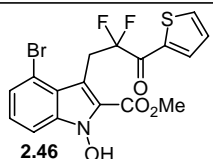

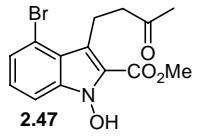
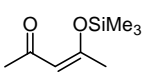
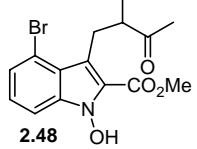
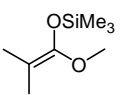
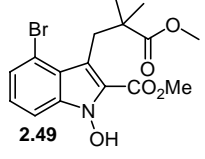

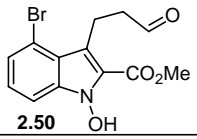
Table 2.3 illustrates the successful use of a variety of cyclic and acyclic silyl enol ethers (as well as ethyl vinyl ether, entry 14) with bromo ketoester **2.8a** to generate 3-substituted *N*-hydroxyindoles with aliphatic, aromatic and heteroaromatic appendages. Additionally, the introduction of ketone (entries 1–12), ester (entry 13), aldehyde (entry 14), and halogen (entries 8–10) functional groups, enhances the synthetic usefulness of these products as they are amenable to further chemical manipulation. The ability to form the desired heterocycles through C–C bond formation was further expanded to the use of silanes, stannanes, and related compounds as nucleophiles (Table 2.4). Thus, allyl silanes (entries 1–4) and stannanes (entries 8 and 9) with varying substituents afforded the desired products in moderate to good yields. Absolute confirmation of *gem*-dimethyl compound **2.57** was obtained by X-ray crystallographic analysis (see ORTEP drawing, Figure 2.2).<sup>6</sup> Interestingly, the use of allyl trimethoxysilane (entry 5) with bromo ketoester **2.8a** generated methoxy

**Table 2.3** Synthesis of 3-alkyl-*N*-hydroxyindoles through 1,5-addition of silyl enol ethers to the substituted  $\alpha,\beta$ -unsaturated nitron derived from **2.8a**.

Entry	Enol ether	Product	Yield [%]
	<p><b>2.8a</b></p>	<p>Product OH</p>	
1		<p><b>2.37</b></p>	61
2		<p><b>2.38</b></p>	70
3		<p><b>2.39</b></p>	66
4		<p><b>2.40</b></p>	73
5		<p><b>2.41</b></p>	60
6		<p><b>2.42</b></p>	63
7		<p><b>2.43</b></p>	68
8		<p><b>2.44</b></p>	75
9		<p><b>2.45</b></p>	75



**Table 2.3** Synthesis of 3-alkyl-*N*-hydroxyindoles through 1,5-addition of silyl enol ethers to the substituted  $\alpha,\beta$ -unsaturated nitron derived from **2.8a** (continued).

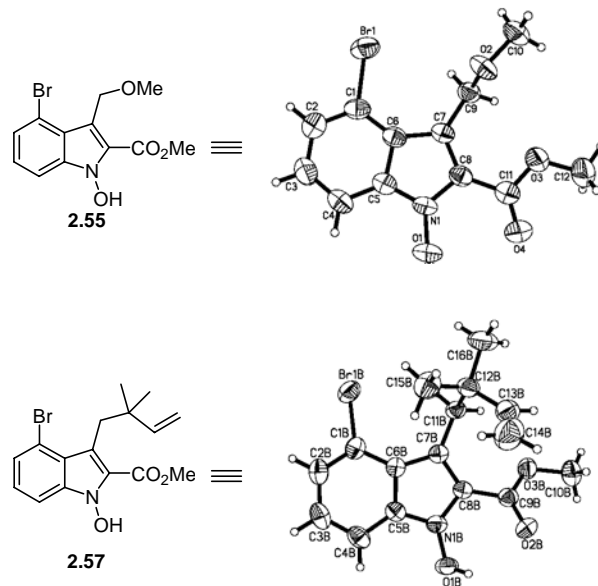
Entry	Enol ether	Product	Yield [%]
10		 <b>2.46</b>	63
11		 <b>2.47</b>	51
12		 <b>2.48</b>	33
13		 <b>2.49</b>	30
14		 <b>2.50</b>	31

substituted *N*-hydroxyindole **2.55** rather than the expected allyl substituted product. The same methoxy indole was also produced with methoxytrimethylsilane as the nucleophile. An X-ray crystal structure (see ORTEP drawing, Figure 2.2)<sup>6</sup> further confirmed these results. 1,5-Reduction of the reactive  $\alpha,\beta$ -unsaturated nitron species could also be accomplished through the use of triethylsilane (entry 7).

Although the versatility of this methodology with respect to the  $\alpha,\beta$ -unsaturated ketoester component has been briefly demonstrated with benzyl alcohol (Table 2.1) and benzyl mercaptan (Table 2.2) heteroatom nucleophiles, we wished to

**Table 2.4** Synthesis of 3-alkyl-*N*-hydroxyindoles through 1,5-addition of silanes and stannanes to the substituted  $\alpha,\beta$ -unsaturated nitrone derived from **2.8a**.

Entry	Silane/stannane	Product	Yield [%]
<p style="text-align: center;"><b>2.8a</b> <math>\xrightarrow[\text{DME, 4 \AA MS, 1-30 h, 40 }^\circ\text{C}]{\text{SnCl}_2 \cdot 2\text{H}_2\text{O (2.5 equiv), \text{Silane/stannane (5.0 equiv)}}}</math> Product <b>OH</b></p>			
1			57
2			61
3			49
4			57
5			53
6	$\text{Me}_3\text{SiOMe}$		50
7	$\text{Et}_3\text{SiH}$		50
8			25
9			62



**Figure 2.2** ORTEP drawings of compounds **2.55** and **2.57** drawn at the 50% probability level.

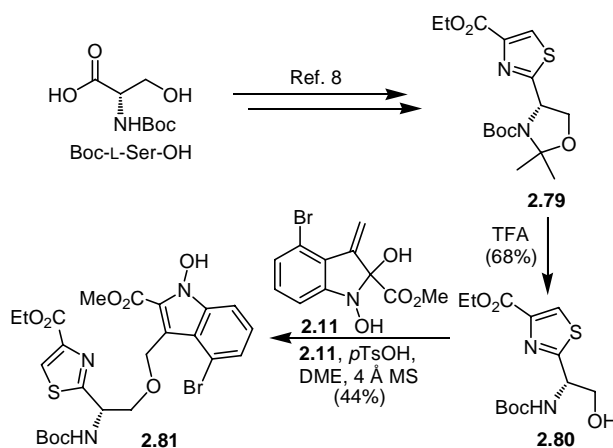
further extend this to C–C bond formation. This was accomplished by exposing ketoesters **2.8a–g**, with varying substitution patterns around the aromatic nuclei, to silyl enol ethers **2.58**, **2.59** and **2.60**<sup>7</sup>, which yielded the desired *N*-hydroxyindoles (Table 2.5). It is worth noting that the survival of the cyano residue (entry 7) can be attributed to the mildness of the combination of reagents employed.

**Table 2.5** Synthesis of 3-alkyl-*N*-hydroxyindoles through 1,5-addition of silyl enol ethers **2.58**, **2.59**, and **2.60** to substituted  $\alpha,\beta$ -unsaturated nitrones.

Entry	ketoester	Product	Yield [%]	Product	Yield [%]	Product	Yield [%]
1	<b>2.8a</b>		61		73		75
2	<b>2.8b</b>		27		33		22
3	<b>2.8c</b>		57		46		50
4	<b>2.8d</b>		44		61		61
5	<b>2.8e</b>		35		44		25
6	<b>2.8f</b>		60		61		34
7	<b>2.8g</b>		43		40		30

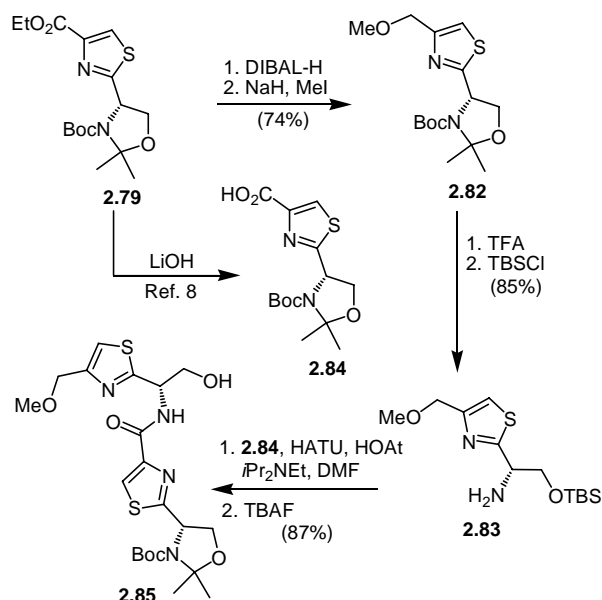
## F. Nocathiacin *N*-Hydroxyindole Model System Construction

With the scope of the current methodology having been developed to a comfortable level of practicality, we set out to apply the newly designed technology to the synthesis of suitable nocathiacin model systems. Scheme 2.6 illustrates the simplest model system constructed (**2.81**), which commences with a selective isopropylidene acetal cleavage of known thiazole ethyl ester **2.79**<sup>8</sup> to give *N*-Boc amino alcohol **2.80** (TFA, MeOH, CH<sub>2</sub>Cl<sub>2</sub>, 68%). The targeted *N*-hydroxyindole model system (**2.81**) is then furnished through intermolecular 1,5-addition or S<sub>N</sub>2'-type displacement of indoline **2.11** with alcohol **2.80** (*p*TsOH, 4 Å molecular sieves, DME, 44%, method A). This initial success served as the springboard for the synthesis of the 15-membered *N*-hydroxyindole containing macrocyclic model systems **2.88a** and **2.88b** (Scheme 2.8), which closely resemble the natural product scaffold.



**Scheme 2.6** Construction of *N*-hydroxyindole nocathiacin model system **2.81**.

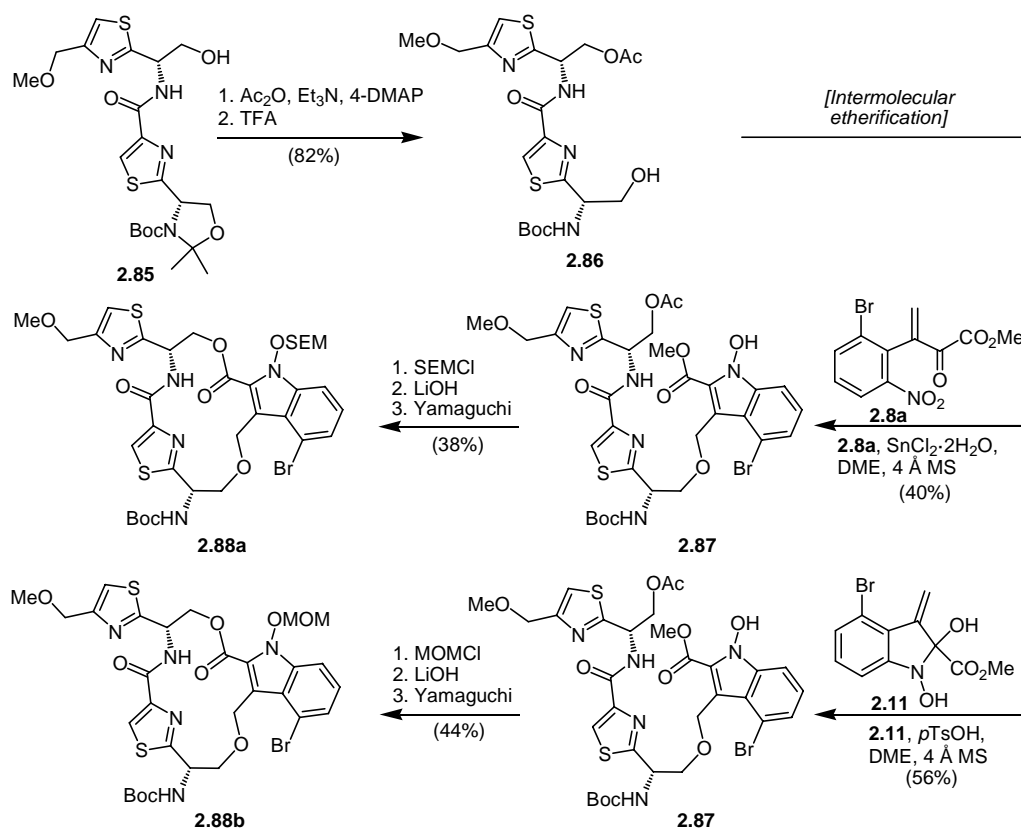
Scheme 2.7 depicts the synthesis of key intermediate **2.85**. Thus, thiazole ethyl ester **2.79**<sup>8</sup> is reduced (DIBAL-H) and methylated (NaH, MeI, 74% over two steps) to give methyl ether **2.82**. Removal of both *N*-Boc and acetal protecting groups (TFA) and selective alcohol silylation (TBSCl) generated amine **2.83** in 85% yield over two steps. Peptide coupling with known acid **2.84**<sup>8</sup> (HATU, HOAt, *i*Pr<sub>2</sub>NEt, DMF) and desilylation (TBAF) occurred smoothly to afford complex alcohol **2.85** in 87% yield over two steps. Acetylation (Ac<sub>2</sub>O, Et<sub>3</sub>N, 4-DMAP) and selective acetal removal



**Scheme 2.7** Synthesis of complex alcohol **2.85**.

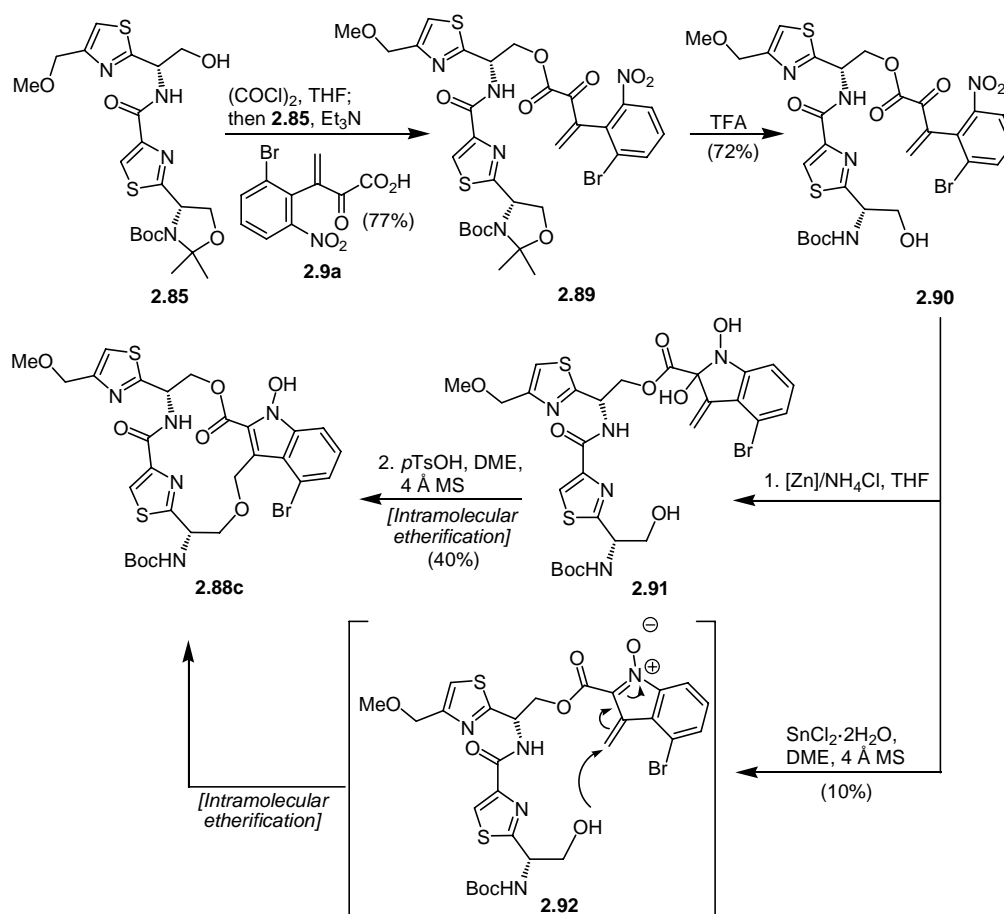
(TFA, MeOH, CH<sub>2</sub>Cl<sub>2</sub>, 82% over two steps) was then carried out to provide hydroxy acetate **2.86** (Scheme 2.8). This substrate served as a capable nucleophile in providing *N*-hydroxyindole **2.87** through an intermolecular etherification process with either nitro ketoester **2.8a** (SnCl<sub>2</sub>·2H<sub>2</sub>O, 4 Å molecular sieves, DME, 40%, method B) or

indoline **2.11** (*p*TsOH, 4 Å molecular sieves, DME, 56%, method A). Completion of model system **2.88a** was accomplished through SEM protection (SEMCl, *i*Pr<sub>2</sub>NEt, TBAI) of the *N*-hydroxy moiety of **2.87** followed by acetate and methyl ester hydrolysis (LiOH), and Yamaguchi macrolactonization<sup>9</sup> (2,4,6-trichlorobenzoyl chloride, Et<sub>3</sub>N, 4-DMAP, 38% over three steps) of the intermediate hydroxy acid to afford the *N*-OSEM protected model system **2.88a**. In addition, after MOM protection of *N*-hydroxyindole **2.87** (MOMCl, *i*Pr<sub>2</sub>NEt, TBAI), the same set of transformations were carried out to construct **2.88b** in 44% yield over three steps.



**Scheme 2.8** Construction of nocathiacin model systems **2.88a** (*N*-OSEM) and **2.88b** (*N*-OMOM) via intermolecular *N*-hydroxyindole formation.

Having successfully applied our methodology to a complex intermolecular process, we now wished to test the feasibility of an intramolecular operation (Scheme 2.9). Thus, key intermediate **2.85** was esterified with the acid chloride of ketoacid **2.9a** [(COCl)<sub>2</sub>, THF, then **2.85**, Et<sub>3</sub>N, 77%] and the resulting ketoester (**2.89**) underwent selective acetal removal (TFA, MeOH, CH<sub>2</sub>Cl<sub>2</sub>, 72%) to provide secondary amine **2.90**. With the primary alcohol nucleophile now tethered to the  $\alpha,\beta$ -unsaturated nitro ketoester moiety, both methods (A and B) were employed to furnish *N*-OH model system **2.88c**. Method A proceeded via a stepwise process in which complex indoline



**Scheme 2.9** Construction of nocathiacin model system **2.88c** (*N*-OH) via intramolecular *N*-hydroxyindole formation.



**2.91** was initially formed ([Zn], NH<sub>4</sub>Cl, THF), followed by intramolecular etherification (*p*TsOH, 4 Å molecular sieves, DME, 40%). Alternatively, method B (SnCl<sub>2</sub>·2H<sub>2</sub>O, 4 Å molecular sieves, DME, 10%) occurs in a one pot process, presumably through reactive intermediate **2.92**, to provide **2.88c**, albeit in lower yield.

## G. Conclusion

The described chemistry provides a versatile entry into substituted *N*-hydroxyindoles carrying O-, S-, and carbon nucleophilic moieties creating a diverse library of synthetic building blocks and potentially biologically active compounds. The process tolerates a variety of functionalities and substituents amenable to further chemical manipulation. Furthermore, the successful construction of nocathiacin model systems **2.81** and **2.88a–c** provided us with the confidence that we would be able to improve upon, and incorporate our methodology into our total synthesis endeavors as described in Chapter 1.

## H. References

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6. Crystallographic data (excluding structure factors) for the structures in this thesis have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-264685 (compound **2.16**), CCDC-264686 (compound **2.13**), CCDC-264687 (compound **2.36**), CCDC-603155 (compound **2.55**), and CCDC-603156 (compound **2.57**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax:+44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
7. a) G. K. S. Prakash, J. Hu, G. A. Olah, *J. Fluorine Chem.* **2001**, *112*, 357–362; b) H. Amii, T. Kobayashi, Y. Hatamoto, K. Uneyama, *Chem. Commun.* **1999**, 1323–1324.
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## I. Experimental Section

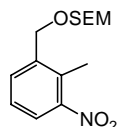
### 1. General Techniques

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, 1,2-dimethoxyethane (DME), and methylene chloride ( $\text{CH}_2\text{Cl}_2$ ) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically ( $^1\text{H}$  NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Difluorosilyl enol ethers were prepared according to the literature procedures.<sup>7</sup> Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an ethanolic solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F<sub>254</sub>). Optical rotations were recorded on a Perkin–Elmer 343 polarimeter. NMR spectrum was recorded on Bruker DRX-600, DRX-500, AMX-500 or AMX-400 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s=singlet, d=doublet, t=triplet, q=quartet,  $\frac{1}{2}\text{ABq}=\frac{1}{2}\text{AB}$  quartet, m=multiplet, quin=quintuplet, sext=sextet, sep=septet, hept=heptet, br=broad. IR spectra were recorded on a Perkin–Elmer 1600

or Spectrum 100 series FTIR spectrometer. Electrospray ionization (ESI) mass spectrometry (MS) experiments were performed on an API 100 Perkin–Elmer SCIEX single quadrupole mass spectrometer at 4000 V emitter voltage. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer using MALDI (matrix-assisted laser-desorption ionization) or ESI (electrospray ionization).

## 2. Preparation of Compounds

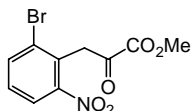
**2.6c:** To 2-methyl-3-nitrobenzyl alcohol (20 g, 120 mmol) in DMF (600 mL) at 25 °C were added *i*Pr<sub>2</sub>NEt (62.5 mL, 359 mmol), SEMCl (42.2 mL, 239 mmol), and TBAI (442 mg, 1.20 mmol). After stirring for 12 h, the reaction mixture was diluted with EtOAc (500 mL), washed with H<sub>2</sub>O (500 mL), brine (500 mL), and dried (Na<sub>2</sub>SO<sub>4</sub>). The resulting solution was concentrated and the residue was subjected to flash column chromatography (silica gel, Et<sub>2</sub>O/hexanes, 20:80→60:40) to afford **2.6c** (35 g, 98%) as a yellow oil.



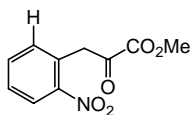
**2.6c:**  $R_f$ =0.60 (silica gel, EtOAc/hexanes, 2:8); IR (film)  $\nu_{\max}$  2953, 2886, 1527, 1465, 1352, 1248, 1189, 1155, 1105, 1057, 1028, 937, 920, 858, 834, 802, 759, 736, 715, 694, 666  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>CN)  $\delta$  7.69 (d,  $J$ =8.0 Hz, 1H), 7.62 (d,  $J$ =8.0 Hz, 1H), 7.34 (t,  $J$ =8.0 Hz, 1H), 4.73 (s, 2H), 4.64 (s, 2H), 3.63 (t,  $J$ =8.5 Hz, 2H), 2.39 (s, 3H), 0.91 (t,  $J$ =8.5 Hz, 2H), 0.01 (s, 9H); <sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>CN)

$\delta$  152.7, 141.2, 134.0, 132.0, 128.0, 124.6, 95.9, 68.5, 66.5, 19.2, 15.1,  $-0.7$  (3C); HRMS (ESI-TOF) calcd for  $C_{14}H_{23}NO_4SiNa^+$   $[M+Na^+]$  320.1288, found 320.1284.

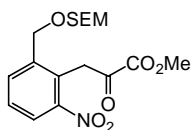
**General procedure for the synthesis of ketoesters 2.7a–2.7g:** To a suspension of NaH (60% dispersion in mineral oil, 4.0 equiv) in DMF (1.67 M) at 0 °C was added a solution of nitrotoluene (3.0–15.0 mmol) in DMF (0.74 M) via cannula. After stirring for 10 min, a solution of dimethyl oxalate (5.0 equiv) in DMF (0.96 M) was added via cannula and after stirring for 1 h at 0 °C, the reaction mixture was allowed to warm to 25 °C and stirring was continued for 12 h. The reaction mixture was then cooled to 0 °C, quenched with saturated aqueous  $NH_4Cl$  solution (5–25 mL), diluted with EtOAc (20–100 mL), washed with  $H_2O$  (5–25 mL), and dried ( $Na_2SO_4$ ). After concentration, the residue was subjected to flash column chromatography to give the ketoesters.



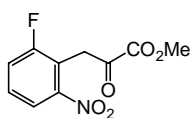
**2.7a:**  $R_f=0.78$  (silica gel, EtOAc/hexanes, 1:1); IR (film)  $\nu_{max}$  3093, 2956, 1735, 1598, 1527, 1436, 1403, 1349, 1274, 1201, 1059, 803, 736, 718  $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $CD_3CN$ )  $\delta$  8.00–7.97 (m, 2H), 7.46 (t,  $J=8.3$  Hz, 1H), 4.67 (s, 2H), 3.89 (s, 3H);  $^{13}C$  NMR (125 MHz,  $CD_3CN$ )  $\delta$  189.6, 161.4, 151.6, 138.7, 130.9, 129.9, 128.4, 125.3, 53.9, 44.3; HRMS (ESI-TOF) calcd for  $C_{10}H_8BrNO_5Na^+$   $[M+Na^+]$  323.9478, found 323.9475.



**2.7b:**  $R_f=0.51$  (silica gel, EtOAc/hexanes, 4:6); IR (film)  $\nu_{\max}$  3441 (br), 2959, 2850, 1732, 1605, 1575, 1514, 1437, 1394, 1346, 1261, 1195, 1057, 966, 858, 786, 725, 664  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  8.10 (d,  $J=8.1$  Hz, 1H), 7.71–7.64 (m, 1H), 7.57–7.51 (m, 1H), 7.42 (d,  $J=7.7$  Hz, 1H), 4.53 (s, 2H), 3.86 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  190.9, 161.7, 149.6, 135.0, 134.8, 130.2, 129.9, 126.1, 53.8, 44.9; HRMS (ESI-TOF) calcd for  $\text{C}_{10}\text{H}_9\text{NO}_5\text{Na}^+$  [ $\text{M}+\text{Na}^+$ ] 246.0373, found 246.0363.

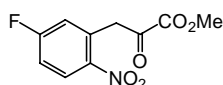


**2.7c:**  $R_f=0.38$  (silica gel, EtOAc/hexanes, 3:7); IR (film)  $\nu_{\max}$  2953, 2892, 1735, 1612, 1528, 1438, 1349, 1247, 1188, 1155, 1104, 1056, 1031, 991, 858, 833, 804, 767, 734, 692  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.02 (d,  $J=8.4$  Hz, 1H), 7.67 (d,  $J=7.2$  Hz, 1H), 7.46 (t,  $J=8.0$  Hz, 1H), 4.63 (s, 2H), 4.61 (s, 2H), 4.59 (s, 2H), 3.94 (s, 3H), 3.59 (t,  $J=8.4$  Hz, 2H), 0.94 (t,  $J=8.4$  Hz, 2H), 0.01 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  189.1, 161.2, 150.3, 140.1, 135.2, 128.8, 128.7, 125.4, 94.1, 67.4, 66.1, 53.7, 39.6, 18.5,  $-1.0$  (3C); HRMS (ESI-TOF) calcd for  $\text{C}_{17}\text{H}_{25}\text{NO}_7\text{SiNa}^+$  [ $\text{M}+\text{Na}^+$ ] 406.1292, found 406.1291.

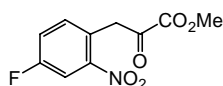


**2.7d:**  $R_f=0.29$  (silica gel, EtOAc/hexanes, 2:8); IR (film)  $\nu_{\max}$  3459 (br), 3107, 2950, 1730, 1531, 1466, 1452, 1429, 1401, 1360, 1332, 1281, 1244, 1226, 1189, 1147, 1064,

971, 837, 800, 763, 735  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  7.91 (d,  $J=7.9$  Hz, 1H), 7.58–7.50 (m, 2H), 4.53 (s, 2H), 3.87 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  189.8, 162.0 (d,  $J=247.3$  Hz), 161.3, 150.4, 130.7 (d,  $J=9.2$  Hz), 121.8 (d,  $J=3.4$  Hz), 121.7 (d,  $J=20.6$  Hz), 118.4 (d,  $J=19.5$  Hz), 53.8, 36.6; HRMS (ESI-TOF) calcd for  $\text{C}_{10}\text{H}_8\text{FNO}_5\text{Na}^+$  [ $\text{M}+\text{Na}^+$ ] 264.0279, found 264.0269.

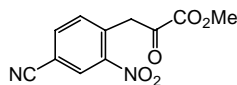


**2.7e:**  $R_f=0.56$  (silica gel, EtOAc/hexanes, 4:6); IR (film)  $\nu_{\text{max}}$  3413 (br), 3083, 2958, 2919, 2849, 1736, 1590, 1525, 1343, 1249, 1062, 840, 751, 613  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  8.20 (dd,  $J=9.2, 4.1$  Hz, 1H), 7.18–7.13 (m, 1H), 7.03 (dd,  $J=8.7, 4.1$  Hz, 1H), 4.51 (s, 2H), 3.90 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  188.4, 164.8 (d,  $J=256.6$  Hz), 160.5, 144.2, 132.5 (d,  $J=9.1$  Hz), 128.3 (d,  $J=10.3$  Hz), 120.5 (d,  $J=22.8$  Hz), 115.8 (d,  $J=22.8$  Hz), 53.5, 44.4; HRMS (ESI-TOF) calcd for  $\text{C}_{10}\text{H}_8\text{FNO}_5\text{Na}^+$  [ $\text{M}+\text{Na}^+$ ] 264.0279, found 264.0276.



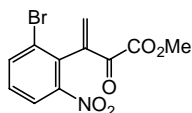
**2.7f:**  $R_f=0.45$  (silica gel, EtOAc/hexanes, 4:6); IR (film)  $\nu_{\text{max}}$  3099, 2959, 1734, 1618, 1532, 1499, 1440, 1398, 1349, 1325, 1235, 1133, 1062, 949, 880, 819, 806, 747, 682  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  7.89 (dd,  $J=8.5, 2.5$  Hz, 1H), 7.47–7.45 (m, 2H), 4.53 (s, 2H), 3.88 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  190.7, 162.4 (d,  $J=247.1$  Hz), 161.6, 150.0 (d,  $J=8.8$  Hz), 136.4 (d,  $J=7.9$  Hz), 126.3 (d,  $J=3.9$  Hz), 121.0 (d,  $J=21.1$  Hz), 113.5 (d,  $J=27.3$  Hz), 53.8, 44.3; HRMS (ESI-TOF) calcd for  $\text{C}_{10}\text{H}_8\text{FNO}_5\text{Na}^+$  [ $\text{M}+\text{Na}^+$ ] 264.0279, found 264.0269.





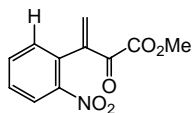
**2.7g:**  $R_f=0.28$  (silica gel, EtOAc/hexanes, 1:1); IR (film)  $\nu_{\max}$  3372 (br), 3088, 2958, 2926, 2237, 1736, 1619, 1535, 1440, 1396, 1352, 1268, 1062, 912, 834, 795, 747, 677  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.44 (d,  $J=8.0$  Hz, 1H), 8.17 (d,  $J=1.6$  Hz, 1H), 7.84 (dd,  $J=8.0, 1.6$  Hz, 1H), 6.96 (d,  $J=1.4$  Hz, 1H), 6.92 (d,  $J=1.4$  Hz, 1H), 3.98 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  161.3, 149.8, 137.8, 136.6, 135.9, 135.3, 129.9, 117.5, 113.7, 102.7, 53.9; HRMS (ESI-TOF) calcd for  $\text{C}_{11}\text{H}_7\text{N}_2\text{O}_5^-$   $[\text{M}-\text{H}]^-$  247.0360, found 247.0369.

**General procedure for the synthesis of  $\alpha,\beta$ -unsaturated ketoesters 2.8a–2.8g:** To a solution of ketoester (0.5–10 mmol) in THF (0.03 M) at 0 °C was added NaH (60% dispersion in mineral oil, 1.1 equiv) and, after stirring for 1 h, *N,N*-dimethylmethyleniminium chloride (3.0 equiv) was added and the reaction mixture stirred for 12 h at 25 °C. After cooling to 0 °C, the reaction mixture was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  solution (1–20 mL), diluted with EtOAc (5–100 mL), washed with  $\text{H}_2\text{O}$  (1–20 mL), and dried ( $\text{Na}_2\text{SO}_4$ ). After concentration, the residue was subjected to flash column chromatography to give the  $\alpha,\beta$ -unsaturated ketoesters.

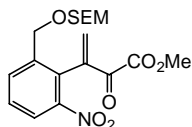


**2.8a:**  $R_f=0.53$  (silica gel, EtOAc/hexanes, 4:6); IR (film)  $\nu_{\max}$  3389 (br), 2954, 2913, 2861, 2355, 1719, 1672, 1526, 1472, 1431, 1349, 1237, 1026  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.02 (dd,  $J=8.4, 1.3$  Hz, 1H), 7.94 (dd,  $J=8.1, 1.3$  Hz, 1H), 7.44

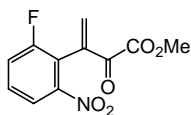
(dd,  $J=8.4, 8.1$  Hz, 1H), 6.79 (s, 1H), 6.17 (s, 1H), 3.93 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  183.1, 162.5, 149.5, 141.8, 137.9, 134.8, 132.5, 130.5, 126.3, 123.8, 53.3; HRMS (ESI-TOF) calcd for  $\text{C}_{11}\text{H}_8\text{BrNO}_5\text{Na}^+$  [ $\text{M}+\text{Na}^+$ ] 335.9478, found 335.9477.



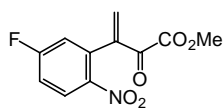
**2.8b:**  $R_f=0.29$  (silica gel, EtOAc/hexanes, 3:7); IR (film)  $\nu_{\text{max}}$  3474 (br), 3404 (br), 2953, 2906, 2849, 1740, 1688, 1601, 1567, 1531, 1514, 1433, 1410, 1341, 1271, 1236, 1132, 1028, 958, 859, 790, 761  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  8.10 (d,  $J=8.3$  Hz, 1H), 7.77–7.74 (m, 1H), 7.65–7.62 (m, 1H), 7.45 (dd,  $J=7.5, 1.3$  Hz, 1H), 6.55 (s, 1H), 6.51 (s, 1H), 3.89 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  186.5, 164.3, 148.7, 144.1, 135.2, 134.7, 133.4, 131.4, 131.1, 125.4, 53.7; HRMS (ESI-TOF) calcd for  $\text{C}_{11}\text{H}_{10}\text{NO}_5^+$  [ $\text{M}+\text{H}^+$ ] 236.0553, found 236.0550.



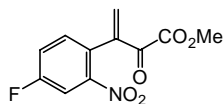
**2.8c:**  $R_f=0.55$  (silica gel, EtOAc/hexanes, 1:1); IR (film)  $\nu_{\text{max}}$  2954, 2884, 1743, 1690, 1525, 1343, 1243, 1131, 1102, 1061, 1032, 938, 861, 832, 761, 732, 691  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  8.03 (d,  $J=8.1$  Hz, 1H), 7.83 (d,  $J=7.8$  Hz, 1H), 7.60 (dd,  $J=8.1, 7.8$  Hz, 1H), 6.63 (s, 1H), 6.26 (s, 1H), 4.62 (s, 2H), 4.46 (d,  $J=3.5$  Hz, 2H), 3.87 (s, 3H), 3.56 (t,  $J=8.3$  Hz, 2H), 0.88 (t,  $J=8.3$  Hz, 2H),  $-0.01$  (s, 9H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  186.2, 164.2, 149.7, 140.8, 140.7, 134.9, 134.6, 130.8, 130.4, 124.7, 95.3, 67.3, 66.0, 53.7, 18.5,  $-1.4$  (3C); HRMS (ESI-TOF) calcd for  $\text{C}_{18}\text{H}_{25}\text{NO}_7\text{SiNa}^+$  [ $\text{M}+\text{Na}^+$ ] 418.1292, found 418.1297.



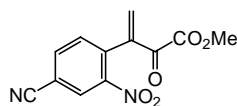
**2.8d:**  $R_f=0.54$  (silica gel, EtOAc/hexanes, 3:7); IR (film)  $\nu_{\max}$  3473 (br), 3371 (br), 3096, 3954, 1738, 1687, 1621, 1524, 1447, 1345, 1294, 1248, 1182, 1121, 1065, 1024, 947, 881, 805, 729, 672  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  8.95 (d,  $J=8.3$  Hz, 1H), 7.67–7.63 (m, 1H), 7.59–7.56 (m, 1H), 6.76 (s, 1H), 6.50 (s, 1H), 3.90 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  186.1, 164.1, 160.7 (d,  $J=247.3$  Hz), 149.8, 137.4 (d,  $J=2.3$  Hz), 136.5, 132.1 (d,  $J=10.3$  Hz), 122.4 (d,  $J=22.9$  Hz), 121.5 (d,  $J=3.4$  Hz), 119.9 (d,  $J=20.6$  Hz), 53.9; HRMS (ESI-TOF) calcd for  $\text{C}_{11}\text{H}_9\text{FNO}_5^+$  [ $\text{M}+\text{H}^+$ ] 254.0459, found 254.0452.



**2.8e:**  $R_f=0.52$  (silica gel, EtOAc/hexanes, 3:7); IR (film)  $\nu_{\max}$  3083, 2959, 1743, 1695, 1585, 1526, 1436, 1347, 1218, 1132, 1036, 948, 843, 727, 611  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  8.24 (dd,  $J=9.2, 5.3$  Hz, 1H), 7.27–7.24 (m, 1H), 7.08 (dd,  $J=8.3, 2.6$  Hz, 1H), 6.64 (s, 1H), 6.29 (s, 1H), 3.93 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  185.3, 165.4 (d,  $J=253.2$  Hz), 163.5, 144.5, 142.7, 134.6, 134.4 (d,  $J=10.3$  Hz), 128.1 (d,  $J=10.3$  Hz), 120.9 (d,  $J=25.1$  Hz), 117.3 (d,  $J=22.8$  Hz), 53.4; HRMS (ESI-TOF) calcd for  $\text{C}_{11}\text{H}_8\text{FNO}_5\text{Na}^+$  [ $\text{M}+\text{Na}^+$ ] 276.0279, found 276.0279.



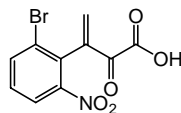
**2.8f:**  $R_f=0.33$  (silica gel, EtOAc/hexanes, 2:8); IR (film)  $\nu_{\max}$  3097, 2958, 1741, 1690, 1537, 1338, 1349, 1271, 1213, 1132, 1034, 947, 882, 812, 674  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.87 (dd,  $J=8.3, 2.6$  Hz, 1H), 7.43–7.40 (m, 1H), 7.37 (dd,  $J=8.9, 5.7$  Hz, 1H), 6.59 (s, 1H), 6.31 (s, 1H), 3.92 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  183.9, 162.6, 161.7 (d,  $J=252.0$  Hz), 147.9 (d,  $J=8.0$  Hz), 142.7, 133.8 (d,  $J=8.0$  Hz), 132.5, 127.4 (d,  $J=3.4$  Hz), 121.2 (d,  $J=20.5$  Hz), 112.5 (d,  $J=27.4$  Hz), 52.9; HRMS (ESI-TOF) calcd for  $\text{C}_{11}\text{H}_8\text{FNO}_5\text{Na}^+$   $[\text{M}+\text{Na}^+]$  276.0279, found 276.0274.



**2.8g:**  $R_f=0.55$  (silica gel, EtOAc/hexanes, 1:1); IR (film)  $\nu_{\max}$  2237, 1742, 1693, 1556, 1537, 1353, 1251, 1140, 1033  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.45 (d,  $J=1.6$  Hz, 1H), 7.98 (dd,  $J=7.8, 1.6$  Hz, 1H), 7.54 (d,  $J=1.6$  Hz, 1H), 6.75 (s, 1H), 6.35 (s, 1H), 3.94 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  185.6, 163.8, 148.8, 142.8, 138.4, 136.3, 135.9, 134.7, 129.4, 117.4, 114.8, 53.9; HRMS (ESI-TOF) calcd for  $\text{C}_{12}\text{H}_8\text{N}_2\text{O}_5\text{Na}^+$   $[\text{M}+\text{Na}^+]$  283.0325, found 283.0325.

**2.9a:** To methyl ester **2.8a** (84 mg, 0.267 mmol) in 1,2-dichloroethane (3.3 mL) was added  $\text{Me}_3\text{SnOH}$  (180 mg, 0.80 mmol) and the resulting mixture was stirred at 70  $^\circ\text{C}$ . After stirring for 1 h, the reaction mixture was diluted with EtOAc (10 mL), washed with aqueous 5% HCl solution (3 $\times$ 5 mL) and dried ( $\text{Na}_2\text{SO}_4$ ). The resulting solution was concentrated and the residue was subjected to flash column chromatography

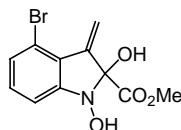
(silica gel, EtOAc/hexanes, 30:70 → MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 20:80) to afford acid **2.9a** (62 mg, 77%) as a yellow oil.



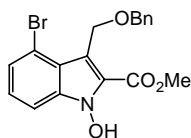
**2.9a:**  $R_f=0.10$  (silica gel, EtOAc/hexanes, 1:1); IR (film)  $\nu_{\max}$  3406, 2917, 1629, 1527, 1352, 1095, 1038, 718  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz, CD<sub>3</sub>OD)  $\delta$  8.03–7.99 (m, 2H), 7.51–7.48 (m, 1H), 6.89 (s, 1H), 6.22 (s, 1H);  $^{13}\text{C}$  NMR (150 MHz, CD<sub>3</sub>OD)  $\delta$  194.6, 171.0, 152.0, 144.3, 138.9, 135.4, 134.7, 131.8, 127.2, 124.8; HRMS (ESI-TOF) calcd for C<sub>10</sub>H<sub>6</sub>BrNO<sub>5</sub>H<sup>+</sup> [M+H<sup>+</sup>] 297.9357, found 297.9354.

**General procedure for the synthesis of *N*-hydroxyindoles (method A):** A stirred suspension of Zn dust (4.9 equiv) and dibromoethane (0.33 equiv) in THF (0.20 M) was heated to reflux (70 °C) for approximately 5 min and then allowed to cool to 25 °C. The refluxing/cooling process was repeated three times. TMSCl (0.2 equiv) was then added and the resulting gray suspension was stirred at 25 °C for 10 min. A separate stirred solution containing a mixture of aqueous 1 N NH<sub>4</sub>Cl (2.2 equiv) and nitro ketoester (0.01–0.06 mmol, 1.0 equiv) in THF (0.10 M) was added via cannula to the activated Zn suspension and stirring was continued for 15–30 min in the absence of light at 25 °C. The crude reaction mixture was purified directly by PTLC to afford tertiary alcohol **2.11**, which was added to a stirred solution of *p*TsOH (3.0 equiv), nucleophile (5.0 equiv) and 4 Å molecular sieves (20 wt%) in DME (0.05–0.10 M) at 25 °C. After 10 min, the reaction mixture was warmed to 40 °C, stirred for 1–3 h,

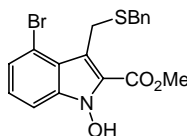
cooled to room temperature, and purified directly by PTLC to afford the targeted *N*-hydroxyindoles.



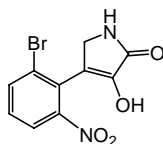
**2.11:**  $R_f=0.53$  (silica gel, EtOAc/hexanes, 6:4); IR (film)  $\nu_{\max}$  3389, 2954, 2849, 1737, 1596, 1566, 1460, 1431, 1290, 1255, 1231, 1184, 1155, 1096, 1026, 885, 802, 749  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  7.64 (s, 1H), 7.14 (t,  $J=7.9$  Hz, 1H), 7.11 (dd,  $J=7.9, 1.3$  Hz, 1H), 6.85 (dd,  $J=7.9, 1.3$  Hz, 1H), 6.32 (s, 1H), 5.40 (s, 1H), 5.08 (br s, 1H), 3.61 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  170.3, 154.8, 144.3, 132.1, 127.3, 123.4, 117.9, 111.8, 111.7, 98.9, 53.6; HRMS (ESI-TOF) calcd for  $\text{C}_{11}\text{H}_{10}\text{BrNO}_4\text{Na}^+$  [ $\text{M}+\text{Na}^+$ ] 321.9685, found 321.9684.



**2.13:** *Method A and B:*  $R_f=0.58$  (silica gel, EtOAc/hexanes, 6:4); IR (film)  $\nu_{\max}$  3194, 2952, 2848, 1710, 1525, 1433, 1353, 1312, 1255, 1226, 1185, 1122, 1047, 1024, 909, 874, 771, 730, 690  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.49 (br s, 1H), 7.45 (d,  $J=8.1$  Hz, 1H), 7.39–7.23 (m, 6H), 7.18 (t,  $J=8.1$  Hz, 1H), 5.10 (s, 2H), 4.61 (s, 2H), 3.88 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  162.2, 139.9, 137.2, 129.2 (2C), 128.9 (2C), 128.3, 127.1, 126.9, 126.8, 121.0, 116.0, 115.9, 110.2, 72.7, 61.8, 52.9; HRMS (ESI-TOF) calcd for  $\text{C}_{18}\text{H}_{16}\text{BrNO}_4\text{Na}^+$  [ $\text{M}+\text{Na}^+$ ] 412.0155, found 412.0155.



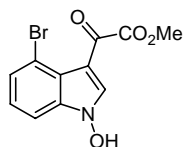
**2.14:** *Method A and B:*  $R_f=0.57$  (silica gel, EtOAc/hexanes, 6:4); IR (film)  $\nu_{\max}$  3354 (br), 2955, 2908, 2837, 1708, 1672, 1608, 1514, 1484, 1442, 1390, 1255, 1232, 1185, 1120, 738, 692  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.30 (br s, 1H), 7.45 (dd,  $J=8.2$ , 0.7 Hz, 1H), 7.33–7.23 (m, 5H), 7.22–7.16 (m, 2H), 4.45 (s, 2H), 3.83 (s, 3H), 3.79 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  162.4, 139.9, 137.8, 129.8 (2C), 129.3 (2C), 127.7, 127.4, 126.7, 125.6, 120.1, 117.8, 116.1, 110.4, 52.8, 37.2, 26.7; HRMS (ESI-TOF) calcd for  $\text{C}_{18}\text{H}_{16}\text{BrNO}_3\text{SNa}^+ [\text{M}+\text{Na}^+]$  427.9926, found 427.9924.



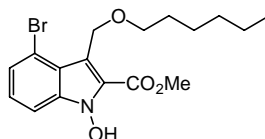
**2.16:**  $R_f=0.20$  (silica gel, EtOAc/hexanes, 6:4); IR (film)  $\nu_{\max}$  3271 (br), 2955, 2919, 1684, 1525, 1455, 1414, 1349, 1220, 1108, 1037, 903, 803, 780  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.99 (d,  $J=8.3$  Hz, 1H), 7.95 (d,  $J=8.3$  Hz, 1H), 7.49 (t,  $J=8.3$  Hz, 1H), 6.85 (br s, 1H), 4.05 (br s, 2H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  168.5, 154.2, 151.8, 145.1, 138.2, 131.8, 129.1, 126.7, 124.6, 45.1; HRMS (ESI-TOF) calcd for  $\text{C}_{10}\text{H}_7\text{BrNO}_3^- [\text{M}-\text{H}^-]$  279.9607, found 279.9615.

**General procedure for the synthesis of *N*-hydroxyindoles (method B):** To a stirred solution of  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  (2.2–2.5 equiv) and 4 Å molecular sieves (20 wt%) in DME (0.12–0.16 M) were added nucleophile (5.0 equiv) and nitro ketoester (0.03–

0.10 mmol, 1.0 equiv) at 25 °C. The reaction mixture was warmed to 40–45 °C and stirring was continued for 1–72 h in the absence of light. Direct purification of the crude reaction mixture by PTLC afforded the desired *N*-hydroxyindoles.

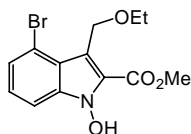


**2.18:**  $R_f=0.18$  (silica gel, EtOAc/hexanes, 4:6); IR (film)  $\nu_{\max}$  3149, 2914, 2855, 1722, 1634, 1553, 1370, 1311, 1258, 1199, 1164, 1123, 1070, 976, 841, 753, 729  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.54 (br s, 1H), 7.54 (d,  $J=8.2$  Hz, 1H), 7.52 (d,  $J=7.9$  Hz, 1H), 7.25 (dd,  $J=8.2, 7.9$  Hz, 1H), 3.88 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  178.7, 165.7, 137.4, 137.0, 129.3, 126.1, 122.9, 114.9, 110.1, 109.0, 53.5; HRMS (ESI-TOF) calcd for  $\text{C}_{11}\text{H}_8\text{BrNO}_4^+ [\text{M}+\text{H}^+]$  297.9709, found 297.9709.

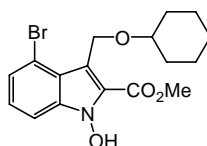


**2.19:**  $R_f=0.60$  (silica gel, EtOAc/hexanes, 6:4); IR (film)  $\nu_{\max}$  3178 (br), 2955, 2920, 2849, 1714, 1531, 1437, 1396, 1355, 1314, 1255, 1226, 1185, 1149, 1120, 1073, 879, 773, 732  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.48 (br s, 1H), 7.41 (dd,  $J=8.2, 0.7$  Hz, 1H), 7.32 (dd,  $J=7.5, 0.7$  Hz, 1H), 7.15 (dd,  $J=8.2, 7.5$  Hz, 1H), 5.00 (s, 2H), 3.91 (s, 3H), 3.53 (t,  $J=6.4$  Hz, 2H), 1.57–1.50 (m, 2H), 1.35–1.21 (m, 6H), 0.86–0.82 (m, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  162.2, 137.3, 126.9, 126.8, 126.7, 121.0, 116.3, 116.0, 110.2, 70.7, 61.9, 52.9, 32.4, 30.5, 26.7, 23.4, 14.3; HRMS (ESI-TOF) calcd for  $\text{C}_{17}\text{H}_{22}\text{BrNO}_4\text{Na}^+ [\text{M}+\text{Na}^+]$  406.0624, found 406.0618.

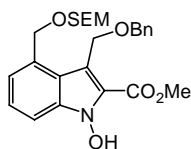




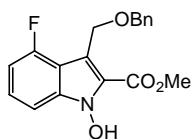
**2.20:**  $R_f=0.53$  (silica gel, EtOAc/hexanes, 6:4); IR (film)  $\nu_{\max}$  3166 (br), 2978, 2861, 1713, 1531, 1355, 1249, 1226, 1185, 1126, 1073, 991, 732  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.36 (br s, 1H), 7.40 (d,  $J=8.3$  Hz, 1H), 7.32 (d,  $J=7.5$  Hz, 1H), 7.15 (dd,  $J=8.3, 7.5$  Hz, 1H), 5.02 (s, 2H), 3.92 (s, 3H), 3.60 (q,  $J=7.0$  Hz, 2H), 1.17 (t,  $J=7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  162.8, 137.8, 127.7, 127.4, 121.5, 118.9, 116.9, 116.6, 110.7, 66.7, 62.4, 53.5, 16.2; HRMS (ESI-TOF) calcd for  $\text{C}_{13}\text{H}_{14}\text{BrNO}_4\text{Na}^+$  [ $\text{M}+\text{Na}^+$ ] 349.9998, found 349.9996.



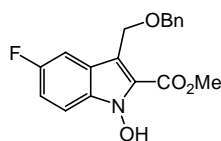
**2.21:**  $R_f=0.58$  (silica gel, MeOH/ $\text{CH}_2\text{Cl}_2$ , 5:95); IR (film)  $\nu_{\max}$  3173 (br), 2922, 2853, 1713, 1530, 1433, 1348, 1256, 1228, 1188, 1148, 1125, 1057, 948, 771, 736  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.33 (s, 1H), 7.40 (d,  $J=8.3$  Hz, 1H), 7.32 (d,  $J=7.5$  Hz, 1H), 7.14 (t,  $J=7.9$  Hz, 1H), 5.05 (s, 2H), 3.91 (s, 3H), 3.52–3.49 (m, 1H), 1.97–1.93 (m, 1H), 1.73–1.69 (m, 2H), 1.55–1.50 (m, 1H), 1.34–1.21 (m, 6H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  162.2, 137.1, 127.1, 127.0, 126.7, 120.8, 116.6, 115.9, 110.1, 78.0, 59.3, 52.8, 33.0 (2C), 26.6 (2C), 25.8; HRMS (ESI-TOF) calcd for  $\text{C}_{17}\text{H}_{20}\text{BrNO}_4\text{Na}^+$  [ $\text{M}+\text{Na}^+$ ] 404.0468, found 404.0469.



**2.22:**  $R_f=0.69$  (silica gel, EtOAc/hexanes, 4:6); IR (film)  $\nu_{\max}$  2950, 1718, 1439, 1248, 1057, 835  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.24 (s, 1H), 7.46 (d,  $J=8.0$  Hz, 1H), 7.36–7.26 (m, 6H), 7.46 (d,  $J=7.0$  Hz, 1H), 5.05 (s, 2H), 5.02 (s, 2H), 4.71 (s, 2H), 4.56 (s, 2H), 3.88 (s, 3H), 3.61 (t,  $J=8.5$  Hz, 2H), 0.88 (t,  $J=8.5$  Hz, 2H),  $-0.01$  (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  162.7, 139.9, 136.7, 133.6, 130.9, 130.4, 129.2 (2C), 128.6 (2C), 128.3, 126.3, 125.7, 122.9, 110.3, 94.9, 72.1, 68.2, 65.8, 63.2, 52.7, 18.6,  $-1.4$  (3C); HRMS (ESI-TOF) calcd for  $\text{C}_{25}\text{H}_{33}\text{NO}_6\text{SiNa}^+$  [ $\text{M}+\text{Na}^+$ ] 494.1969, found 494.1969.

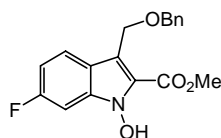


**2.23:**  $R_f=0.76$  (silica gel, MeOH/ $\text{CH}_2\text{Cl}_2$ , 5:95); IR (film)  $\nu_{\max}$  3194, 2939, 2862, 1711, 1628, 1523, 1434, 1362, 1318, 1263, 1229, 1135, 1097, 1044, 1025, 991, 936, 775, 731, 692  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.30 (br s, 1H), 7.34–7.24 (m, 7H), 6.84 (dd,  $J=11.4, 7.5$  Hz, 1H), 4.97 (s, 2H), 4.55 (s, 2H), 3.88 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  162.2, 159.2 (d,  $J=249.1$  Hz), 140.6, 138.2 (d,  $J=10.3$  Hz), 129.8 (2C), 129.3 (2C), 128.9, 127.9 (d,  $J=8.4$  Hz), 126.2, 115.2 (d,  $J=4.0$  Hz), 112.3 (d,  $J=20.6$  Hz), 107.5 (d,  $J=4.0$  Hz), 107.4 (d,  $J=19.3$  Hz), 73.7, 64.1, 53.4; HRMS (ESI-TOF) calcd for  $\text{C}_{18}\text{H}_{16}\text{FNO}_4\text{Na}^+$  [ $\text{M}+\text{Na}^+$ ] 352.0955, found 352.0952.

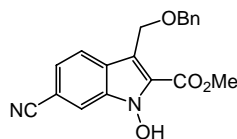


**2.24:**  $R_f=0.78$  (silica gel, EtOAc/hexanes, 1:1); IR (film)  $\nu_{\max}$  3315 (br), 2954, 1708, 1528, 1444, 1259, 1192, 1105  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.22 (s, 1H),

7.49–7.45 (m, 2H), 7.36–7.30 (m, 5H), 7.21–7.15 (m, 1H), 4.96 (s, 2H), 4.54 (s, 2H), 3.88 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  162.3, 159.0 (d,  $J=234.0$  Hz), 139.8, 133.1, 129.2 (2C), 128.7 (2C), 128.4, 126.0, 123.2 (d,  $J=16.4$  Hz), 116.8 (d,  $J=2.3$  Hz), 115.6 (d,  $J=27.3$  Hz), 112.0 (d,  $J=9.8$  Hz), 106.4 (d,  $J=24.2$  Hz), 72.6, 63.6, 52.6; HRMS (ESI-TOF) calcd for  $\text{C}_{18}\text{H}_{15}\text{FNO}_4^-$  [ $\text{M}-\text{H}^-$ ] 328.0991, found 328.0995.

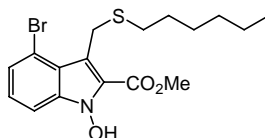


**2.25:**  $R_f=0.63$  (silica gel, EtOAc/hexanes, 4:6); IR (film)  $\nu_{\text{max}}$  3205 (br), 3032, 2951, 2860, 1714, 1628, 1529, 1438, 1355, 1177, 1054, 917, 832, 755  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.19 (s, 1H), 7.81 (dd,  $J=8.4, 4.8$  Hz, 1H), 7.36–7.23 (m, 5H), 7.19 (dd,  $J=9.0, 1.8$  Hz, 1H), 6.96 (dt,  $J=9.3, 2.4$  Hz, 1H), 4.98 (s, 2H), 4.54 (s, 2H), 3.88 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  162.9 (d,  $J=240.3$  Hz), 162.3, 139.7, 136.5 (d,  $J=13.1$  Hz), 129.2 (2C), 129.1, 128.7 (2C), 128.4, 127.6, 124.2 (d,  $J=10.4$  Hz), 119.7, 111.1 (d,  $J=25.7$  Hz), 96.3 (d,  $J=27.2$  Hz), 72.7, 63.6, 52.5; HRMS (ESI-TOF) calcd for  $\text{C}_{18}\text{H}_{16}\text{FNO}_4\text{Na}^+$  [ $\text{M}+\text{Na}^+$ ] 352.0955, found 352.0949.

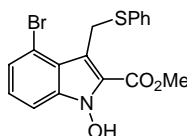


**2.26:**  $R_f=0.71$  (silica gel, EtOAc/hexanes, 1:1); IR (film)  $\nu_{\text{max}}$  2925, 1854, 2225, 1717, 1660, 1573, 1527, 1438, 1416, 1364, 1258, 1144, 1084, 1018, 867, 735, 698  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.38 (br s, 1H), 7.94 (d,  $J=8.5$  Hz, 1H), 7.93–7.91 (m, 1H), 7.39 (dd,  $J=8.0, 1.5$  Hz, 1H), 7.35–7.30 (m, 5H), 4.99 (s, 2H), 4.55 (s, 2H), 3.91 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  162.4, 139.6, 129.2 (2C), 128.7 (2C), 128.5,

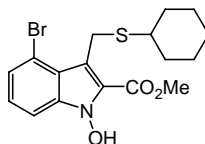
127.7, 125.5, 123.9, 123.5, 120.8, 120.4, 117.0, 115.9, 108.8, 72.8, 63.4, 52.9; HRMS (ESI-TOF) calcd for  $C_{19}H_{15}N_2O_4^-$   $[M-H^-]$  335.1037, found 335.1049.



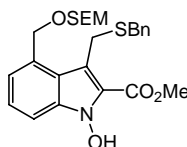
**2.27:**  $R_f=0.63$  (silica gel, EtOAc/hexanes, 6:4); IR (film)  $\nu_{max}$  3349 (br), 2956, 2912, 2847, 1703, 1681, 1517, 1440, 1397, 1342, 1304, 1255, 1195, 1146, 1118, 982, 872, 774, 741  $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $CD_3CN$ )  $\delta$  9.18 (s, 1H), 7.46 (d,  $J=8.5$  Hz, 1H), 7.34 (d,  $J=7.5$  Hz, 1H), 7.22 (dd,  $J=8.5, 7.5$  Hz, 1H), 4.44 (s, 2H), 3.93 (s, 3H), 2.48 (t,  $J=7.3$  Hz, 2H), 1.52–1.46 (m, 2H), 1.33–1.19 (m, 6H), 0.84 (t,  $J=6.6$  Hz, 3H);  $^{13}C$  NMR (125 MHz,  $CD_3CN$ )  $\delta$  162.5, 137.9, 127.4, 126.7, 125.6, 120.0, 118.9, 116.2, 110.4, 52.8, 32.2, 32.1, 30.5, 29.3, 25.9, 23.2, 14.3; HRMS (ESI-TOF) calcd for  $C_{17}H_{21}BrNO_3S^-$   $[M-H^-]$  398.0431, found 398.0420.



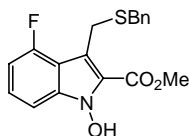
**2.28:**  $R_f=0.60$  (silica gel, EtOAc/hexanes, 6:4); IR (film)  $\nu_{max}$  3342 (br), 2943, 1684, 1514, 1437, 1396, 1343, 1308, 1255, 1191, 1144, 1120, 1020, 979, 873, 773, 738, 691  $cm^{-1}$ ;  $^1H$  NMR (600 MHz,  $CD_3CN$ )  $\delta$  9.18 (br s, 1H), 7.46 (d,  $J=8.3$  Hz, 1H), 7.35 (d,  $J=7.4$  Hz, 1H), 7.28–7.19 (m, 6H), 4.83 (s, 2H), 3.69 (s, 3H);  $^{13}C$  NMR (100 MHz,  $CD_3CN$ )  $\delta$  162.0, 137.6, 136.4, 132.8 (2C), 129.8 (2C), 128.1, 127.3, 126.7, 125.8, 119.8, 116.6, 116.1, 110.4, 52.6, 30.1; HRMS (ESI-TOF) calcd for  $C_{17}H_{14}BrNO_3SNa^+$   $[M+Na^+]$  413.9770, found 413.9761.



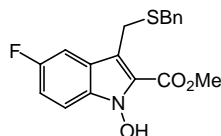
**2.29:**  $R_f=0.65$  (silica gel, EtOAc/hexanes, 6:4); IR (film)  $\nu_{\max}$  3349 (br), 2956, 2912, 2847, 1703, 1681, 1517, 1440, 1397, 1342, 1304, 1255, 1195, 1146, 1118, 982, 872, 774, 741  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.17 (s, 1H), 7.45 (d,  $J=9.7$  Hz, 1H), 7.33 (d,  $J=9.0$  Hz, 1H), 7.20 (dd,  $J=9.7, 9.0$  Hz, 1H), 4.47 (s, 2H), 3.94 (s, 3H), 2.72–2.64 (m, 1H), 1.95–1.88 (m, 1H), 1.75–1.67 (m, 2H), 1.59–1.54 (m, 1H), 1.33–1.21 (m, 6H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  162.5, 137.9, 127.3, 126.6, 125.5, 120.0, 119.2, 116.1, 110.3, 52.8, 44.1, 34.7 (2C), 26.9 (2C), 26.5, 24.5; HRMS (ESI-TOF) calcd for  $\text{C}_{17}\text{H}_{21}\text{BrNO}_3\text{S}^+$   $[\text{M}+\text{H}^+]$  420.0239, found 420.0236.



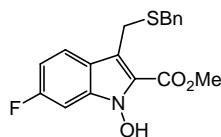
**2.30:**  $R_f=0.65$  (silica gel, EtOAc/hexanes, 4:6); IR (film)  $\nu_{\max}$  2950, 1709, 1527, 1440, 1248, 1027, 859, 835, 753  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.20 (s, 1H), 7.44 (dd,  $J=8.4, 1.2$  Hz, 1H), 7.34–7.22 (m, 6H), 7.13 (d,  $J=6.8$  Hz, 1H), 4.95 (s, 2H), 4.64 (s, 2H), 4.38 (s, 2H), 3.83 (s, 3H), 3.80 (s, 2H), 3.83 (t,  $J=7.6$  Hz, 2H), 0.87 (t,  $J=7.6$  Hz, 2H),  $-0.02$  (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  162.8, 139.7, 137.1, 133.3, 129.6 (2C), 129.3 (2C), 127.7, 126.5, 124.6, 123.3, 120.6, 117.3, 110.7, 94.8, 68.7, 65.9, 52.5, 37.2, 27.6, 18.6,  $-1.4$  (3C); HRMS (ESI-TOF) calcd for  $\text{C}_{25}\text{H}_{33}\text{NO}_5\text{SSiNa}^+$   $[\text{M}+\text{Na}^+]$  510.1741, found 510.1731.



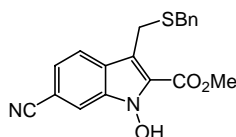
**2.31:**  $R_f=0.65$  (silica gel, EtOAc/hexanes, 4:6); IR (film)  $\nu_{\max}$  3356, 2950, 1700, 1630, 1532, 1451, 1355, 1321, 1262, 1236, 1137, 948, 924  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.22 (s, 1H), 7.33–7.20 (m, 7H), 6.81 (dd,  $J=10.5$ , 6.5 Hz, 1H), 4.25 (s, 2H), 3.85 (s, 3H), 3.77 (s, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  162.3, 158.4 (d,  $J=248.5$  Hz), 139.7, 138.5 (d,  $J=10.3$  Hz), 129.6 (2C), 129.2 (2C), 127.7, 127.5 (d,  $J=8.0$  Hz), 125.2, 116.5 (d,  $J=4.0$  Hz), 111.6 (d,  $J=20.0$  Hz), 106.9 (d,  $J=4.3$  Hz), 106.5 (d,  $J=19.3$  Hz), 52.6, 37.0, 27.9; HRMS (ESI-TOF) calcd for  $\text{C}_{18}\text{H}_{15}\text{FNO}_3\text{S}^-$  [ $\text{M}-\text{H}^-$ ] 344.0762, found 344.0765.



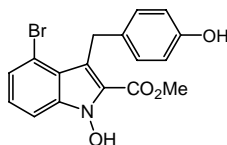
**2.32:**  $R_f=0.52$  (silica gel, EtOAc/hexanes, 1:1); IR (film)  $\nu_{\max}$  2956, 1718, 1522, 1442, 1262, 1180  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.13 (br s, 1H), 7.45 (dd,  $J=8.5$ , 4.0 Hz, 1H), 7.34–7.22 (m, 6H), 7.17 (dt,  $J=9.5$ , 2.5 Hz, 1H), 4.15 (s, 2H), 3.84 (s, 3H), 3.72 (s, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  162.3, 158.8 (d,  $J=233.8$  Hz), 139.7, 133.4, 129.6 (2C), 129.3 (2C), 127.7, 125.8, 122.9 (d,  $J=9.9$  Hz), 117.5, 115.7 (d,  $J=27.4$  Hz), 112.2 (d,  $J=9.5$  Hz), 106.0 (d,  $J=24.0$  Hz), 52.5, 37.0, 26.3; HRMS (ESI-TOF) calcd for  $\text{C}_{18}\text{H}_{15}\text{FNO}_3\text{S}^-$  [ $\text{M}-\text{H}^-$ ] 344.0762, found 344.0769.



**2.33:**  $R_f=0.53$  (silica gel, EtOAc/hexanes, 3:7); IR (film)  $\nu_{\max}$  3315 (br), 2955, 1720, 1530, 1532, 1445, 1399, 1351, 1291, 1266, 1178, 1123  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.19 (br s, 1H), 7.65 (dd,  $J=8.8, 5.2$  Hz, 1H), 7.34–7.23 (m, 5H), 7.16 (dd,  $J=9.2, 2.4$  Hz, 1H), 6.95–6.90 (m, 1H), 4.17 (s, 2H), 3.82 (s, 3H), 3.72 (s, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  163.0 (d,  $J=240.4$  Hz), 162.3, 139.7, 136.8 (d,  $J=13.3$  Hz), 129.7 (2C), 129.4, 128.3 (2C), 128.0, 127.7, 123.8 (d,  $J=10.4$  Hz), 119.5, 110.8 (d,  $J=25.6$  Hz), 96.4 (d,  $J=27.0$  Hz), 52.4, 37.0, 26.3; HRMS (ESI-TOF) calcd for  $\text{C}_{18}\text{H}_{15}\text{FNO}_3\text{S}^-$   $[\text{M}-\text{H}^-]$  344.0762, found 344.0769.

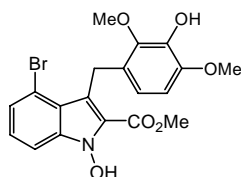


**2.34:**  $R_f=0.59$  (silica gel, EtOAc/hexanes, 1:1); IR (film)  $\nu_{\max}$  2924, 2360, 2224, 1715, 1523, 1444, 1264, 1116  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.31 (s, 1H), 7.89 (s, 1H), 7.77 (d,  $J=8.5$  Hz, 1H), 7.36 (d,  $J=8.5$  Hz, 1H), 7.28–7.22 (m, 5H), 4.18 (s, 2H), 3.86 (s, 3H), 3.72 (s, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  161.9, 139.5, 134.9, 132.2, 129.6 (2C), 129.3 (2C), 127.7, 125.1, 123.6, 123.0, 120.4, 117.7, 115.9, 109.0, 52.8, 37.0, 26.0; HRMS (ESI-TOF) calcd for  $\text{C}_{19}\text{H}_{15}\text{N}_2\text{O}_3\text{S}^-$   $[\text{M}-\text{H}^-]$  351.0809, found 351.0813.

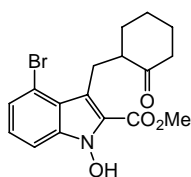


**2.35:**  $R_f=0.41$  (silica gel, EtOAc/hexanes, 6:4); IR (film)  $\nu_{\max}$  3342 (br), 2943, 1690, 1614, 1508, 1443, 1343, 1249, 1173, 1120, 873, 756, 732  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.16 (br s, 1H), 7.49 (d,  $J=8.3$  Hz, 1H), 7.30 (d,  $J=7.4$  Hz, 1H), 7.19 (dd,

$J=8.3, 7.4$  Hz, 1H), 6.92 (d,  $J=8.5$  Hz, 2H), 6.65 (d,  $J=8.5$  Hz, 2H), 4.62 (s, 2H), 3.86 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  162.5, 155.6, 137.8, 133.5, 129.9 (2C), 127.2, 126.4, 126.0, 120.6, 120.3, 116.0, 115.6 (2C), 110.3, 52.5, 29.3; HRMS (ESI-TOF) calcd for  $\text{C}_{17}\text{H}_{14}\text{BrNO}_4\text{Na}^+$  [ $\text{M}+\text{Na}^+$ ] 397.9998, found 397.9987.



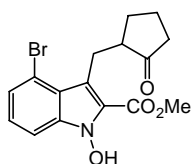
**2.36:**  $R_f=0.42$  (silica gel, EtOAc/hexanes, 6:4); IR (film)  $\nu_{\text{max}}$  3414, 2934, 2835, 1708, 1675, 1615, 1489, 1440, 1396, 1347, 1287, 1249, 1085, 1030, 894, 746  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.21 (s, 1H), 7.51 (d,  $J=7.9$  Hz, 1H), 7.28 (d,  $J=7.9$  Hz, 1H), 7.21 (t,  $J=7.9$  Hz, 1H), 6.46 (d,  $J=8.6$  Hz, 1H), 6.38 (s, 1H), 5.92 (d,  $J=8.6$  Hz, 1H), 4.62 (s, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 3.74 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  162.5, 147.5, 146.0, 139.7, 138.0, 128.6, 127.3, 126.5, 126.4, 121.2, 119.2, 118.6, 116.3, 110.4, 107.5, 60.4, 56.7, 52.6, 24.7; HRMS (ESI-TOF) calcd for  $\text{C}_{19}\text{H}_{18}\text{BrNO}_6\text{Na}^+$  [ $\text{M}+\text{Na}^+$ ] 458.0210, found 458.0200.



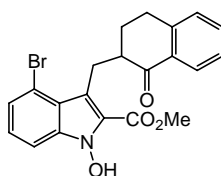
**2.37:**  $R_f=0.38$  (silica gel, EtOAc/hexanes, 4:6); IR (film)  $\nu_{\text{max}}$  3319, 2928, 2855, 1705, 1515, 1436, 1399, 1341, 1304, 1251, 1230, 1120, 882, 756, 729  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.14 (br s, 1H), 7.45 (d,  $J=8.0$  Hz, 1H), 7.30 (d,  $J=8.0$  Hz, 1H), 7.17 (t,  $J=8.0$  Hz, 1H), 3.90 (s, 3H), 3.73 (dd,  $J=14.2, 4.4$  Hz, 1H), 3.18 (dd,  $J=14.2, 9.2$  Hz, 1H), 2.83–2.75 (m, 1H), 2.37–2.26 (m, 2H), 2.02–1.96 (m, 1H), 1.90–1.84 (m,



1H), 1.78–1.71 (m, 1H), 1.68–1.58 (m, 1H), 1.57–1.42 (m, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  212.7, 162.9, 138.1, 127.1, 126.7, 126.5, 120.8, 120.0, 116.2, 110.4, 53.6, 52.6, 42.7, 33.6, 28.8, 25.8, 24.5; HRMS (ESI-TOF) calcd for  $\text{C}_{17}\text{H}_{18}\text{BrNO}_4\text{Na}^+$   $[\text{M}+\text{Na}^+]$  402.0311, found 402.0299.

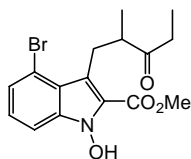


**2.38:**  $R_f=0.32$  (silica gel, EtOAc/hexanes, 4:6); IR (film)  $\nu_{\text{max}}$  3318, 2954, 2872, 1713, 1689, 1531, 1437, 1396, 1349, 1307, 1243, 1184, 1143, 1119, 1078, 978, 884, 773, 737  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.29 (br s, 1H), 7.45 (d,  $J=7.9$  Hz, 1H), 7.29 (d,  $J=7.9$  Hz, 1H), 7.17 (t,  $J=7.9$  Hz, 1H), 3.89 (s, 3H), 3.68 (dd,  $J=13.8, 6.2$  Hz, 1H), 3.25 (dd,  $J=13.8, 9.2$  Hz, 1H), 2.63–2.54 (m, 1H), 2.20–2.09 (m, 1H), 1.97–1.91 (m, 2H), 1.90–1.83 (m, 1H), 1.74–1.65 (m, 2H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  200.0, 162.7, 137.9, 127.1, 126.3, 125.8, 120.4, 120.2, 116.1, 110.3, 52.5, 51.6, 38.5, 29.6, 24.7, 21.0; HRMS (ESI-TOF) calcd for  $\text{C}_{16}\text{H}_{16}\text{BrNO}_4\text{Na}^+$   $[\text{M}+\text{Na}^+]$  388.0155, found 388.0148.

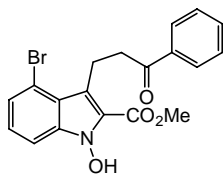


**2.39:**  $R_f=0.35$  (silica gel, EtOAc/hexanes, 4:6); IR (film)  $\nu_{\text{max}}$  3310, 2944, 2850, 1708, 1676, 1598, 1519, 1451, 1399, 1352, 1300, 1242, 1221, 1116, 1022, 980, 881, 776, 734  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.27 (br s, 1H), 7.92 (d,  $J=7.7$  Hz, 1H), 7.51–7.43 (m, 2H), 7.31 (t,  $J=7.7$  Hz, 2H), 7.26 (d,  $J=7.7$  Hz, 1H), 7.18 (t,  $J=7.7$  Hz,

1H), 4.06 (br s, 1H), 3.74 (s, 3H), 3.39 (br s, 1H), 3.02–2.92 (m, 2H), 2.91–2.80 (m, 1H), 2.07–1.97 (m, 1H), 1.95 (s, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  199.7, 162.8, 145.4, 138.0, 134.1, 133.4, 129.9, 127.7, 127.4, 127.2, 126.5, 126.2, 120.8, 119.8, 116.2, 110.4, 52.5, 50.6, 29.0, 28.7, 24.9; HRMS (ESI-TOF) calcd for  $\text{C}_{21}\text{H}_{18}\text{BrNO}_4\text{Na}^+$   $[\text{M}+\text{Na}^+]$  450.0311, found 450.0297.

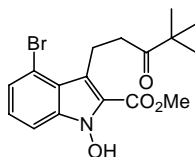


**2.40:**  $R_f=0.37$  (silica gel, EtOAc/hexanes, 4:6); IR (film)  $\nu_{\text{max}}$  3300, 2965, 2923, 1708, 1680, 1514, 1441, 1341, 1247, 1184, 1148, 1116, 1090, 1033, 975, 881, 771, 734  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.22 (br s, 1H), 7.45 (d,  $J=7.9$  Hz, 1H), 7.32 (d,  $J=7.9$  Hz, 1H), 7.19 (t,  $J=7.9$  Hz, 1H), 3.91 (s, 3H), 3.49 (br s, 1H), 3.35 (br s, 1H), 3.03–2.97 (m, 1H), 2.51–2.43 (m, 1H), 2.34–2.26 (m, 1H), 0.99 (d,  $J=7.0$  Hz, 3H), 0.89 (d,  $J=7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  215.2, 162.6, 138.0, 127.2, 126.6, 126.3, 120.6, 119.4, 116.1, 110.4, 52.6, 48.9, 35.3, 27.7, 15.9, 7.9; HRMS (ESI-TOF) calcd for  $\text{C}_{16}\text{H}_{18}\text{BrNO}_4\text{Na}^+$   $[\text{M}+\text{Na}^+]$  390.0311, found 390.0307.

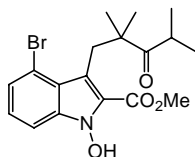


**2.41:**  $R_f=0.35$  (silica gel, EtOAc/hexanes, 4:6); IR (film)  $\nu_{\text{max}}$  3357, 2914, 1708, 1674, 1594, 1520, 1441, 1395, 1310, 1242, 1146, 1117, 771, 737, 686  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.29 (br s, 1H), 7.99–7.94 (m, 2H), 7.60–7.55 (m, 1H), 7.49–7.43 (m, 3H), 7.30 (br s, 1H), 7.18 (t,  $J=7.7$  Hz, 1H), 3.85 (s, 3H), 3.63 (br s, 2H), 3.35

(t,  $J=7.7$  Hz, 2H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  200.1, 162.5, 137.8, 133.9, 129.5, 128.7, 128.6, 127.1, 126.2, 125.5, 121.0, 120.4, 116.0, 110.3, 52.5, 41.7, 20.2 (3C); HRMS (ESI-TOF) calcd for  $\text{C}_{19}\text{H}_{16}\text{BrNO}_4\text{Na}^+$   $[\text{M}+\text{Na}^+]$  424.0155, found 424.0154.

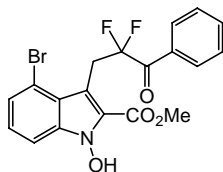


**2.42:**  $R_f=0.46$  (silica gel, EtOAc/hexanes, 4:6); IR (film)  $\nu_{\text{max}}$  3283, 2942, 2872, 1725, 1707, 1519, 1437, 1396, 1349, 1243, 1178, 1149, 1119, 984, 884, 779, 737  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.34 (br s, 1H), 7.44 (br s, 1H), 7.29 (br s, 1H), 7.17 (t,  $J=7.4$  Hz, 1H), 3.90 (s, 3H), 3.40 (br s, 2H), 2.87 (t,  $J=7.9$  Hz, 2H), 1.09 (s, 9H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  215.7, 162.6, 138.6, 127.2, 126.3, 124.8, 121.5, 120.5, 116.1, 110.3, 52.7, 44.6, 39.7, 26.6, 20.1 (3C); HRMS (ESI-TOF) calcd for  $\text{C}_{17}\text{H}_{20}\text{BrNO}_4\text{Na}^+$   $[\text{M}+\text{Na}^+]$  404.0468, found 404.0456.

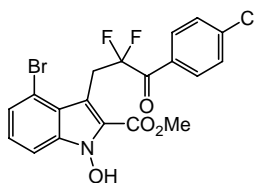


**2.43:**  $R_f=0.45$  (silica gel, EtOAc/hexanes, 4:6); IR (film)  $\nu_{\text{max}}$  3309, 2972, 2868, 1712, 1689, 1515, 1464, 1440, 1379, 1346, 1271, 1234, 1182, 1140, 1117, 1042, 1000, 878, 798, 775, 742  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.49 (br s, 1H), 7.49 (br s, 1H), 7.33 (br s, 1H), 7.18 (t,  $J=7.2$  Hz, 1H), 3.90 (s, 3H), 3.67 (br s, 2H), 3.30 (hept,  $J=6.6$  Hz, 1H), 1.04 (d,  $J=6.6$  Hz, 6H), 0.97 (s, 6H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  220.1, 162.9, 137.6, 128.1, 127.2, 126.6, 121.8, 116.1, 115.6, 110.4, 52.6, 50.6, 35.0,

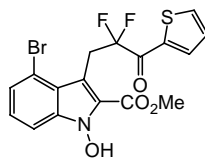
29.5, 23.0 (2C), 20.4 (2C); HRMS (ESI-TOF) calcd for  $C_{18}H_{22}BrNO_4Na^+$  [ $M+Na^+$ ] 418.0624, found 418.0620.



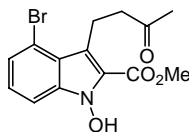
**2.44:**  $R_f=0.47$  (silica gel, EtOAc/hexanes, 4:6); IR (film)  $\nu_{max}$  3360, 2955, 2919, 1698, 1520, 1449, 1311, 1264, 1184, 1127, 914, 764, 716  $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $CD_3CN$ )  $\delta$  9.24 (br s, 1H), 8.04–8.02 (m, 2H), 7.68 (t,  $J=7.3$  Hz, 1H), 7.53–7.50 (m, 3H), 7.38–7.36 (m, 1H), 7.24–7.21 (m, 1H), 4.46 (t,  $J=17.7$  Hz, 2H), 3.80 (s, 3H);  $^{13}C$  NMR (125 MHz,  $CD_3CN$ )  $\delta$  190.5, 162.1, 137.2, 135.4, 133.0, 130.7 (t,  $J=3.4$  Hz, 2C), 129.7 (2C), 127.4, 127.2, 127.1, 121.1, 119.1, 115.9, 110.4, 108.9, 52.7, 29.7 (t,  $J=23.8$  Hz); HRMS (ESI-TOF) calcd for  $C_{19}H_{15}BrF_2NO_4^+$  [ $M+H^+$ ] 438.0147, found 438.0145.



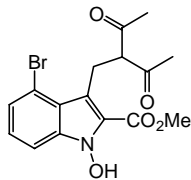
**2.45:**  $R_f=0.31$  (silica gel, EtOAc/hexanes, 2:8); IR (film)  $\nu_{max}$  1702, 1588, 1448, 1401, 1265, 1091, 762  $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $CD_3CN$ )  $\delta$  9.24 (br s, 1H), 7.96 (d,  $J=8.8$  Hz, 2H), 7.53–7.50 (m, 3H), 7.37 (d,  $J=7.5$  Hz, 1H), 7.23 (t,  $J=8.8$  Hz, 1H), 4.45 (t,  $J=17.5$  Hz, 2H), 3.82 (s, 3H);  $^{13}C$  NMR (125 MHz,  $CD_3CN$ )  $\delta$  189.0, 161.6, 140.8, 136.8, 132.0 (t,  $J=3.6$  Hz, 2C), 131.2, 129.5 (2C), 129.4, 128.5, 126.8, 126.7, 120.6, 115.4, 110.0, 108.3, 52.2, 29.3 (t,  $J=23.8$  Hz); HRMS (ESI-TOF) calcd for  $C_{19}H_{14}BrClF_2NO_4^+$  [ $M+H^+$ ] 471.9757, found 471.9752.



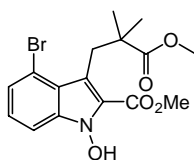
**2.46:**  $R_f=0.25$  (silica gel, EtOAc/hexanes, 4:6); IR (film)  $\nu_{\max}$  3335 (br), 3105, 2954, 1714, 1679, 1614, 1517, 1447, 1411, 1345, 1311, 1266, 1186, 1148, 1127, 1058, 932, 879, 839, 761, 733  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.36 (br s, 1H), 7.95 (dd,  $J=4.5, 1.3$  Hz, 1H), 7.86–7.84 (m, 1H), 7.51 (d,  $J=8.5$  Hz, 1H), 7.38 (d,  $J=7.0$  Hz, 1H), 7.26–7.18 (m, 2H), 4.44 (t,  $J=17.0$  Hz, 2H), 3.84 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  183.8, 162.1, 139.3, 138.3, 137.2, 137.1 (t,  $J=5.4$  Hz), 130.1, 127.5, 127.3, 127.1, 121.1, 118.9, 115.9, 110.5, 108.8, 52.7, 30.0 (t,  $J=23.8$  Hz); HRMS (ESI-TOF) calcd for  $\text{C}_{17}\text{H}_{13}\text{BrF}_2\text{NO}_4\text{S}^+$   $[\text{M}+\text{H}^+]$  443.9711, found 443.9711.



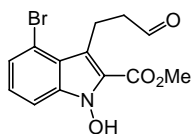
**2.47:**  $R_f=0.37$  (silica gel, EtOAc/hexanes, 1:1); IR (film)  $\nu_{\max}$  3342, 2942, 1707, 1519, 1437, 1396, 1354, 1243, 1184, 1119, 879, 773, 737  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.36 (br s, 1H), 7.45 (d,  $J=8.2$  Hz, 1H), 7.30 (d,  $J=8.2$  Hz, 1H), 7.18 (t,  $J=8.2$  Hz, 1H), 3.91 (s, 3H), 3.44 (t,  $J=8.0$  Hz, 2H), 2.78 (t,  $J=8.0$  Hz, 2H), 2.11 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  208.7, 162.5, 137.9, 127.2, 126.3, 125.6, 121.1, 120.4, 116.0, 110.4, 52.7, 46.3, 29.9, 19.8; HRMS (ESI-TOF) calcd for  $\text{C}_{14}\text{H}_{14}\text{BrNO}_4\text{Na}^+$   $[\text{M}+\text{Na}^+]$  361.9998, found 361.9990.



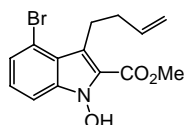
**2.48:**  $R_f=0.23$  (silica gel, EtOAc/hexanes, 4:6); IR (film)  $\nu_{\max}$  3392, 2956, 1710, 1697, 1617, 1519, 1433, 1353, 1243, 1180, 1140, 1117, 870, 773, 733  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.11 (br s, 1H), 7.47 (d,  $J=7.0$  Hz, 1H), 7.35 (d,  $J=7.0$  Hz, 1H), 7.21 (t,  $J=7.0$  Hz, 1H), 4.26 (t,  $J=6.0$  Hz, 1H), 3.90 (s, 3H), 3.71 (d,  $J=6.0$  Hz, 2H), 2.04 (s, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  205.1 (2C), 162.3, 137.9, 127.3, 126.7, 126.6, 120.4, 117.4, 115.8, 110.5, 69.6, 52.7, 30.7, 23.7 (2C); HRMS (ESI-TOF) calcd for  $\text{C}_{16}\text{H}_{16}\text{BrNO}_5\text{Na}^+$   $[\text{M}+\text{Na}^+]$  404.0104, found 404.0100.



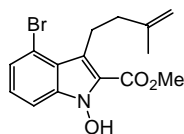
**2.49:**  $R_f=0.36$  (silica gel, EtOAc/hexanes, 4:6); IR (film)  $\nu_{\max}$  3323, 2944, 1714, 1513, 1433, 1393, 1347, 1249, 1180, 1134, 1025, 985, 865, 773, 733  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.12 (br s, 1H), 7.48 (d,  $J=7.5$  Hz, 1H), 7.33 (d,  $J=7.5$  Hz, 1H), 7.18 (t,  $J=7.5$  Hz, 1H), 3.89 (s, 3H), 3.72 (s, 2H), 3.51 (s, 3H), 1.11 (s, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  178.3, 162.8, 137.7, 127.8, 127.2, 126.7, 121.8, 116.6, 116.3, 110.5, 52.7, 52.3, 44.7, 32.7, 25.1 (2C); HRMS (ESI-TOF) calcd for  $\text{C}_{16}\text{H}_{18}\text{BrNO}_5\text{Na}^+$   $[\text{M}+\text{Na}^+]$  406.0260, found 406.0243.



**2.50:**  $R_f=0.20$  (silica gel, EtOAc/hexanes, 4:6); IR (film)  $\nu_{\max}$  3471, 1701, 1695, 1537, 1437, 1384, 1237, 1190, 1172, 1149, 1119, 920, 873, 773, 737  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.77 (s, 1H), 9.31 (br s, 1H), 7.46 (d,  $J=7.9$  Hz, 1H), 7.32 (d,  $J=7.9$  Hz, 1H), 7.20 (t,  $J=7.9$  Hz, 1H), 3.91 (s, 3H), 3.56 (t,  $J=7.7$  Hz, 2H), 2.80 (t,  $J=7.7$  Hz, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  203.0, 162.4, 137.9, 127.3, 126.3, 125.5, 120.6, 120.4, 115.9, 110.4, 52.7, 46.7, 18.2; HRMS (ESI-TOF) calcd for  $\text{C}_{13}\text{H}_{11}\text{BrNO}_4^-$  [ $\text{M}-\text{H}^-$ ] 323.9877, found 323.9863.

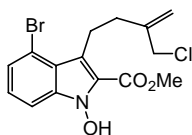


**2.51:**  $R_f=0.67$  (silica gel, MeOH/ $\text{CH}_2\text{Cl}_2$ , 3:97); IR (film)  $\nu_{\max}$  3360, 2953, 1679, 1638, 1615, 1516, 1440, 1341, 1312, 1254, 1143, 1120, 911, 876, 771, 736  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.23 (br s, 1H), 7.44 (d,  $J=7.9$  Hz, 1H), 7.30 (d,  $J=7.9$  Hz, 1H), 7.18 (t,  $J=7.9$  Hz, 1H), 6.00–5.89 (m, 1H), 5.03 (dd,  $J=17.2, 1.9$  Hz, 1H), 4.95 (d,  $J=10.2$  Hz, 1H), 3.91 (s, 3H), 3.39–3.33 (m, 2H), 2.38 (q,  $J=7.5$  Hz, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  162.8, 139.2, 137.9, 127.2, 126.4, 125.4, 122.2, 120.5, 116.2, 115.3, 110.3, 52.6, 37.3, 24.7; HRMS (ESI-TOF) calcd for  $\text{C}_{14}\text{H}_{15}\text{BrNO}_3^+$  [ $\text{M}+\text{H}^+$ ] 324.0230, found 324.0234.

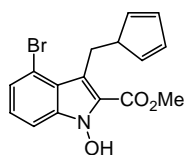


**2.52:**  $R_f=0.69$  (silica gel, MeOH/ $\text{CH}_2\text{Cl}_2$ , 1:99); IR (film)  $\nu_{\max}$  3346, 2960, 2925, 1679, 1511, 1440, 1398, 1342, 1271, 1257, 1239, 1117, 986, 882, 775, 737  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.19 (br s, 1H), 7.44 (d,  $J=7.9$  Hz, 1H), 7.30 (d,  $J=7.9$  Hz, 1H),

7.17 (t,  $J=7.9$  Hz, 1H), 4.75 (s, 2H), 3.92 (s, 3H), 3.41–3.35 (m, 2H), 2.35–2.30 (m, 2H), 1.81 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  162.7, 146.8, 137.7, 127.1, 126.2, 125.0, 122.4, 120.3, 116.1, 110.6, 110.2, 52.5, 41.2, 24.2, 22.5; HRMS (ESI-TOF) calcd for  $\text{C}_{15}\text{H}_{15}\text{BrNO}_3^-$  [ $\text{M}-\text{H}^-$ ] 336.0241, found 336.0238.



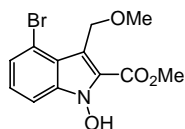
**2.53:**  $R_f=0.70$  (silica gel,  $\text{MeOH}/\text{CH}_2\text{Cl}_2$ , 1:99); IR (film)  $\nu_{\text{max}}$  3377, 2954, 2907, 1678, 1513, 1443, 1396, 1343, 1313, 1255, 1119, 908, 879, 787, 732  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.20 (s, 1H), 7.45 (d,  $J=8.0$  Hz, 1H), 7.32 (d,  $J=8.0$  Hz, 1H), 7.19 (t,  $J=8.0$  Hz, 1H), 5.20 (s, 1H), 5.05 (s, 1H), 4.19 (s, 2H), 3.93 (s, 3H), 3.42 (t,  $J=8.4$  Hz, 2H), 2.49 (t,  $J=8.4$  Hz, 2H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  162.7, 146.5, 137.8, 127.2, 126.3, 125.2, 121.7, 120.3, 116.1, 115.4, 110.3, 52.7, 49.0, 36.0, 24.2; HRMS (ESI-TOF) calcd for  $\text{C}_{15}\text{H}_{14}\text{BrClNO}_3^-$  [ $\text{M}-\text{H}^-$ ] 369.9851, found 369.9852.



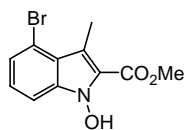
**2.54:**  $R_f=0.75$  (silica gel,  $\text{MeOH}/\text{CH}_2\text{Cl}_2$ , 1:99); IR (film)  $\nu_{\text{max}}$  3356, 2943, 1675, 1614, 1515, 1445, 1398, 1342, 1304, 1257, 1121, 986, 878, 775, 737  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.38 (br s, 1H), 7.47 (d,  $J=7.9$  Hz, 1H), 7.28 (d,  $J=7.9$  Hz, 1H), 7.18 (t,  $J=7.9$  Hz, 1H), 6.34–6.29 (m, 1H), 6.24–6.19 (m, 1H), 5.83 (br s, 1H), 4.43 (br s, 2H), 3.89 (s, 3H), 2.93 (s, 2H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  162.6, 150.3, 138.0,



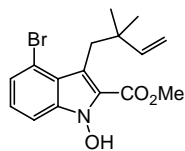
133.2, 131.7, 127.7, 127.2, 126.4, 125.7, 120.5, 120.4, 116.3, 110.4, 52.6, 44.1, 26.4;  
HRMS (ESI-TOF) calcd for  $C_{16}H_{13}BrNO_3^-$   $[M-H^-]$  346.0084, found 346.0072.



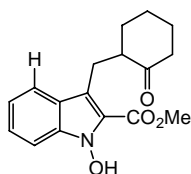
**2.55:**  $R_f=0.32$  (silica gel, EtOAc/hexanes, 4:6); IR (film)  $\nu_{max}$  3175, 2937, 2887, 1709, 1525, 1436, 1404, 1346, 1311, 1257, 1227, 1187, 1123, 1073, 934, 879, 775, 736, 666  $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CD_3CN$ )  $\delta$  9.38 (br s, 1H), 7.44 (dd,  $J=8.3, 0.7$  Hz, 1H), 7.34 (dd,  $J=7.6, 0.7$  Hz, 1H), 7.18 (dd,  $J=8.3, 7.6$  Hz, 1H), 4.97 (s, 2H), 3.93 (s, 3H), 3.35 (s, 3H);  $^{13}C$  NMR (125 MHz,  $CD_3CN$ )  $\delta$  162.3, 137.3, 127.1, 127.0, 126.8, 121.0, 116.0, 115.9, 110.2, 63.4, 57.7, 52.9; HRMS (ESI-TOF) calcd for  $C_{12}H_{12}BrNO_4Na^+$   $[M+Na^+]$  335.9842, found 335.9834.



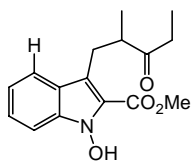
**2.56:**  $R_f=0.58$  (silica gel, MeOH/ $CH_2Cl_2$ , 1:99); IR (film)  $\nu_{max}$  3436, 2919, 1672, 1613, 1519, 1443, 1272, 1184, 1119, 978, 873, 761, 726, 679, 608, 561  $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CD_3CN$ )  $\delta$  9.09 (s, 1H), 7.43 (d,  $J=7.9$  Hz, 1H), 7.29 (d,  $J=7.9$  Hz, 1H), 7.17 (t,  $J=7.9$  Hz, 1H), 3.92 (s, 3H), 2.78 (s, 3H);  $^{13}C$  NMR (125 MHz,  $CD_3CN$ )  $\delta$  162.9, 138.2, 127.3, 126.1, 125.7, 121.4, 118.5, 116.7, 110.3, 52.6, 12.0; HRMS (ESI-TOF) calcd for  $C_{11}H_9BrNO_3^-$   $[M-H^-]$  281.9771, found 281.9770.



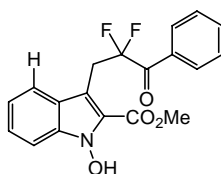
**2.57:**  $R_f=0.53$  (silica gel, EtOAc/hexanes, 4:6); IR (film)  $\nu_{\max}$  3366, 2951, 2917, 1686, 1519, 1439, 1387, 1306, 1254, 1122, 1018, 903, 868, 793, 770, 742, 684  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.08 (s, 1H), 7.46 (s, 1H), 7.31 (s, 1H), 7.16 (t,  $J=7.2$  Hz, 1H), 5.87 (dd,  $J=17.4, 10.8$  Hz, 1H), 4.77 (d,  $J=10.8$  Hz, 1H), 4.69 (d,  $J=17.4$  Hz, 1H), 3.88 (s, 3H), 3.49 (br s, 2H), 0.97 (s, 6H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  163.2, 149.0, 137.7, 128.0, 127.2, 126.6, 121.8, 117.2, 116.4, 110.9, 110.3, 52.5, 40.1, 34.8, 26.5 (2C); HRMS (ESI-TOF) calcd for  $\text{C}_{16}\text{H}_{17}\text{BrNO}_3^-$  [ $\text{M}-\text{H}^-$ ] 350.0397, found 350.0396.



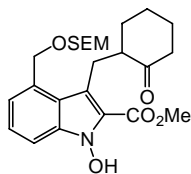
**2.61:**  $R_f=0.26$  (silica gel, EtOAc/hexanes, 2:8); IR (film)  $\nu_{\max}$  3020, 1742, 1702, 1528, 1447, 1214  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.03 (br s, 1H), 7.68 (d,  $J=9.6$  Hz, 1H), 7.44 (d,  $J=9.6$  Hz, 1H), 7.36 (t,  $J=9.0$  Hz, 1H), 7.12 (t,  $J=9.0$  Hz, 1H), 3.91 (s, 3H), 3.45 (dd,  $J=16.5, 5.7$  Hz, 1H), 2.89 (dd,  $J=11.1, 5.7$  Hz, 1H), 2.75–2.70 (m, 1H), 2.37–2.33 (m, 2H), 2.03–1.97 (m, 1H), 1.86–1.83 (m, 1H), 1.77–1.73 (m, 1H), 1.67–1.63 (m, 1H), 1.54 (ddt,  $J=30.0, 14.4, 4.2$  Hz, 1H), 1.47–1.39 (ddd,  $J=30.0, 14.4, 4.2$  Hz, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  212.7, 163.1, 136.8, 126.8, 124.5, 123.7, 121.9, 121.4, 121.3, 110.5, 52.4, 52.3, 42.5, 34.3, 28.7, 25.5, 25.1; HRMS (ESI-TOF) calcd for  $\text{C}_{17}\text{H}_{20}\text{NO}_4^+$  [ $\text{M}+\text{H}^+$ ] 302.1387, found 302.1387.



**2.62:**  $R_f=0.63$  (silica gel, EtOAc/hexanes, 4:6); IR (film)  $\nu_{\max}$  2929, 1700, 1540, 1507, 1457, 1259, 119  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.06 (br s, 1H), 7.66 (d,  $J=8.5$  Hz, 1H), 7.44 (d,  $J=8.5$  Hz, 1H), 7.38–7.35 (m, 1H), 7.15–7.12 (m, 1H), 3.93 (s, 3H), 3.30–3.26 (m, 1H), 3.01–2.94 (m, 2H), 2.50–2.42 (m, 1H), 2.34–2.26 (m, 1H), 1.01 (d,  $J=7.0$  Hz, 3H), 0.86 (t,  $J=7.5$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  215.2, 162.3, 126.9, 124.2, 123.4, 122.3, 121.8, 121.5, 120.6, 110.5, 52.3, 47.8, 35.4, 28.8, 16.7, 7.9; HRMS (ESI-TOF) calcd for  $\text{C}_{16}\text{H}_{19}\text{NO}_4\text{Na}^+$   $[\text{M}+\text{Na}^+]$  312.1206, found 312.1199.

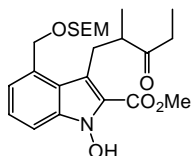


**2.63:**  $R_f=0.52$  (silica gel, EtOAc/hexanes, 2:8); IR (film)  $\nu_{\max}$  3375, 1697, 1598, 1535, 1448, 1264, 1122  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.12 (br s, 1H), 8.04–7.99 (m, 2H), 7.72–7.68 (m, 2H), 7.55–7.51 (m, 3H), 7.4 (t,  $J=3.0$  Hz, 1H), 7.2 (t,  $J=3.0$  Hz, 1H), 4.1 (t,  $J=21.3$  Hz, 2H), 3.8 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  190.5 (t,  $J=28.5$  Hz), 162.4, 136.2, 135.4, 135.1, 130.7 (t,  $J=3.2$  Hz), 130.6 (t,  $J=3.2$  Hz), 129.8, 129.7, 126.9, 125.8, 123.8, 122.1, 121.9, 110.5, 52.4, 31.1 (t,  $J=24.4$  Hz); HRMS (ESI-TOF) calcd for  $\text{C}_{19}\text{H}_{16}\text{F}_2\text{NO}_4^+$   $[\text{M}+\text{H}^+]$  360.1042, found 360.1039.

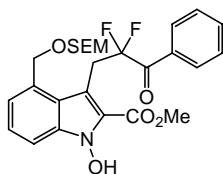


**2.64:**  $R_f=0.25$  (silica gel, EtOAc/hexanes, 2:8); IR (film)  $\nu_{\max}$  3240 (br), 2936, 2860, 1709, 1438, 1396, 1235, 1125, 1037  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.11 (br s,

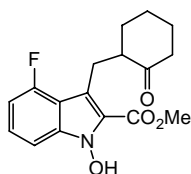
1H), 7.43 (d,  $J=7.0$  Hz, 1H), 7.31–7.30 (m, 1H), 7.11 (d,  $J=6.5$  Hz, 1H), 4.85 (br s, 2H), 4.67 (s, 2H), 3.90 (s, 3H), 3.65–3.56 (m, 3H), 3.12–3.05 (m, 1H), 2.65–2.63 (m, 1H), 2.35–2.30 (m, 2H), 2.05–1.97 (m, 1H), 1.88–1.84 (m, 1H), 1.80–1.73 (m, 1H), 1.65–1.61 (m, 1H), 1.53–1.42 (m, 2H), 0.88 (dd,  $J=9.0, 8.0$  Hz, 2H),  $-0.01$  (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  212.7, 163.3, 137.5, 133.5, 129.6, 126.2, 125.5, 123.2, 120.7, 110.7, 94.7, 68.3, 65.8, 53.3, 52.3, 42.5, 33.7, 28.6, 25.7, 18.6,  $-1.4$  (3C); HRMS (ESI-TOF) calcd for  $\text{C}_{23}\text{H}_{36}\text{NO}_6\text{Si}^+$  [ $\text{M}+\text{H}^+$ ] 462.2306, found 462.2304.



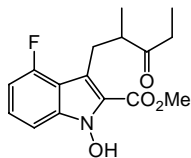
**2.65:**  $R_f=0.50$  (silica gel, EtOAc/hexanes, 4:6); IR (film)  $\nu_{\text{max}}$  3240 (br), 2950, 1714, 1520, 1456, 1398, 1248, 1128, 1102, 1028, 859, 836  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.14 (br s, 1H), 7.44 (d,  $J=8.0$  Hz, 1H), 7.32–7.29 (m, 1H), 7.13 (d,  $J=6.5$  Hz, 1H), 4.94 (d,  $J=12.0$  Hz, 1H), 4.90 (d,  $J=12.0$  Hz, 1H), 4.70 (s, 2H), 3.92 (s, 3H), 3.59 (dd,  $J=9.0, 8.0$  Hz, 2H), 3.42 (dd,  $J=14.0, 6.0$  Hz, 1H), 3.19 (dd,  $J=14.0, 7.0$  Hz, 1H), 2.93 (dd,  $J=14.0, 7.0$  Hz, 1H), 2.47–2.37 (m, 1H), 2.25–2.18 (m, 1H), 1.01 (d,  $J=7.0$  Hz, 3H), 0.90–0.83 (m, 5H),  $-0.01$  (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  215.2, 163.1, 133.4, 126.2, 125.0, 124.5, 123.3, 120.9, 120.0, 110.7, 94.7, 68.4, 65.9, 52.4, 48.6, 35.6, 29.3, 18.6, 16.3, 7.8,  $-1.4$  (3C); HRMS (ESI-TOF) calcd for  $\text{C}_{23}\text{H}_{35}\text{NO}_6\text{SiNa}^+$  [ $\text{M}+\text{Na}^+$ ] 472.2126, found 472.2126.



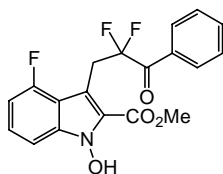
**2.66:**  $R_f=0.36$  (silica gel, EtOAc/hexanes, 1:5); IR (film)  $\nu_{\max}$  2951, 1700, 1449, 1251, 1096, 1028  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.21 (br s, 1H), 8.07–8.03 (m, 2H), 7.71–7.68 (m, 1H), 7.55–7.49 (m, 3H), 7.36–7.33 (m, 1H), 7.16 (d,  $J=6.5$  Hz, 1H), 4.95 (d,  $J=16.0$  Hz, 2H), 4.66 (s, 2H), 4.32 (t,  $J=18.0$  Hz, 2H), 3.79 (s, 3H), 3.54 (t,  $J=8.0$  Hz, 2H), 0.81 (t,  $J=8.0$  Hz, 2H),  $-0.04$  (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  196.2, 159.9, 136.2, 136.1, 133.6, 131.5 (t,  $J=3.0$  Hz, 2C), 130.6, 130.5 (2C), 130.4, 126.9, 126.5, 124.5, 120.7, 114.4, 100.6, 95.3, 69.2, 66.6, 53.2, 32.1, 19.2,  $-0.8$  (3C); HRMS (ESI-TOF) calcd for  $\text{C}_{26}\text{H}_{31}\text{F}_2\text{NO}_6\text{SiNa}^+$  [ $\text{M}+\text{Na}^+$ ] 542.1781, found 542.1767.



**2.67:**  $R_f=0.47$  (silica gel, EtOAc/hexanes, 4:6); IR (film)  $\nu_{\max}$  3295 (br), 2931, 2849, 1702, 1631, 1566, 1531, 1443, 1401, 1361, 1314, 1255, 1231, 1131, 937, 785, 732  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.19 (br s, 1H), 7.29–7.23 (m, 2H), 6.77 (dd,  $J=11.4, 7.4$  Hz, 1H), 3.92 (s, 3H), 3.50 (dd,  $J=14.0, 4.8$  Hz, 1H), 2.99 (dd,  $J=14.0, 5.7$  Hz, 1H), 2.72–2.66 (m, 1H), 2.35–2.27 (m, 2H), 2.00–1.93 (m, 1H), 1.87–1.85 (m, 1H), 1.75–1.72 (m, 1H), 1.67–1.59 (m, 1H), 1.56–1.49 (m, 1H), 1.46–1.39 (m, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  212.8, 162.7, 158.8 (d,  $J=248.4$  Hz), 138.8 (d,  $J=10.3$  Hz), 127.3 (d,  $J=8.0$  Hz), 125.0, 118.8 (d,  $J=3.4$  Hz), 112.4 (d,  $J=19.5$  Hz), 106.9 (d,  $J=3.4$  Hz), 106.2 (d,  $J=20.6$  Hz), 52.7, 52.5, 42.5, 33.7, 28.6, 26.3, 25.5; HRMS (ESI-TOF) calcd for  $\text{C}_{17}\text{H}_{18}\text{FNO}_4\text{Na}^+$  [ $\text{M}+\text{Na}^+$ ] 342.1112, found 342.1102.

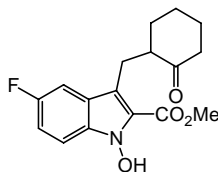


**2.68:**  $R_f=0.46$  (silica gel, EtOAc/hexanes, 4:6); IR (film)  $\nu_{\max}$  3299 (br), 2970, 1714, 1633, 1538, 1455, 1404, 1361, 1318, 1235, 1137  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.18 (br s, 1H), 7.31–7.26 (m, 2H), 6.80 (dd,  $J=12.0, 7.5$  Hz, 1H), 3.97 (s, 3H), 3.35 (dd,  $J=13.5, 5.5$  Hz, 1H), 3.09 (dd,  $J=13.5, 9.0$  Hz, 1H), 2.97–2.91 (m, 1H), 2.53–2.43 (m, 1H), 2.41–2.35 (m, 1H), 0.99 (d,  $J=7.0$  Hz, 3H), 0.92 (t,  $J=7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  214.9, 162.6, 158.6 (d,  $J=248.0$  Hz), 138.6, 132.1, 127.3 (d,  $J=8.3$  Hz), 124.8, 112.6, 106.9 (d,  $J=3.9$  Hz), 106.2 (d,  $J=19.8$  Hz), 52.5, 48.1, 34.9, 29.6, 15.8, 7.9; HRMS (ESI-TOF) calcd for  $\text{C}_{16}\text{H}_{18}\text{FNO}_4\text{Na}^+$   $[\text{M}+\text{Na}^+]$  330.1112, found 330.1109.

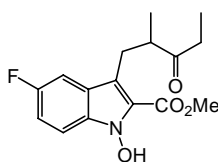


**2.69:**  $R_f=0.52$  (silica gel, EtOAc/hexanes, 4:6); IR (film)  $\nu_{\max}$  3364 (br), 2956, 2926, 2848, 1700, 1636, 1540, 1450, 1323, 1269, 1240, 1142, 1091, 946, 764, 716  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.21 (br s, 1H), 8.02 (d,  $J=7.8$  Hz, 2H), 7.69–7.66 (m, 1H), 7.52 (dd,  $J=8.0, 7.3$  Hz, 2H), 7.33–7.28 (m, 2H), 6.85–6.81 (m, 1H), 4.12 (t,  $J=17.3$  Hz, 2H), 3.97 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  190.4, 161.8, 137.3, 136.4, 135.4, 132.9, 130.6 (t,  $J=3.8$  Hz, 2C), 129.6 (2C), 127.2 (d,  $J=8.6$  Hz), 126.1, 117.3, 113.0, 107.1, 106.8 (d,  $J=3.8$  Hz), 106.6 (d,  $J=20.0$  Hz), 52.4, 32.8 (t,

$J=26.7$  Hz); HRMS (ESI-TOF) calcd for  $C_{19}H_{15}F_3NO_4^+$   $[M+H^+]$  378.0948, found 378.0943.

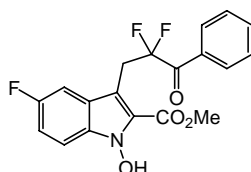


**2.70:**  $R_f=0.65$  (silica gel, EtOAc/hexanes, 1:1); IR (film)  $\nu_{max}$  3311 (br), 2937, 2855, 1707, 1577, 1532, 1447, 1403, 1342, 1251, 1192, 1169, 849, 799, 757  $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $CD_3CN$ )  $\delta$  9.04 (s, 1H), 7.43 (dd,  $J=9.0$ , 4.5 Hz, 1H), 7.40 (dd,  $J=9.5$ , 2.5 Hz, 1H), 7.15 (dt,  $J=9.5$ , 2.5 Hz, 1H), 3.89 (s, 3H), 3.39 (dd,  $J=14.0$ , 5.0 Hz, 1H), 2.85 (dd,  $J=14.0$ , 8.5 Hz, 1H), 2.73–2.68 (m, 1H), 2.39–2.27 (m, 2H), 2.04–1.98 (m, 1H), 1.89–1.83 (m, 1H), 1.77–1.73 (m, 1H), 1.68–1.50 (m, 2H), 1.44–1.40 (m, 1H);  $^{13}C$  NMR (125 MHz,  $CD_3CN$ )  $\delta$  212.8, 162.7, 158.8 (d,  $J=233.1$  Hz), 133.6, 126.1, 123.8 (d,  $J=9.5$  Hz), 120.8 (d,  $J=5.4$  Hz), 115.6 (d,  $J=26.9$  Hz), 112.0 (d,  $J=9.4$  Hz), 106.3 (d,  $J=24.0$  Hz), 52.4, 52.3, 42.5, 34.4, 28.7, 25.6, 25.2; HRMS (ESI-TOF) calcd for  $C_{17}H_{19}FNO_4^+$   $[M+H^+]$  320.1293, found 320.1289.

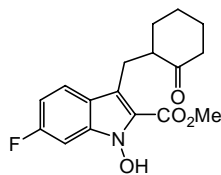


**2.71:**  $R_f=0.58$  (silica gel, EtOAc/hexanes, 1:1); IR (film)  $\nu_{max}$  3300 (br), 2934, 1699, 1540, 1522, 1456, 1250, 1178, 1110  $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $CD_3CN$ )  $\delta$  9.08 (br s, 1H), 7.44 (dd,  $J=9.0$ , 4.5 Hz, 1H), 7.36 (dd,  $J=9.5$ , 2.5 Hz, 1H), 7.18–7.14 (m, 1H), 3.93 (s, 3H), 3.26–3.21 (m, 1H), 2.97–2.92 (m, 2H), 2.54–2.43 (m, 1H), 2.32–2.26 (m, 1H), 1.02 (d,  $J=7.5$  Hz, 3H), 0.86 (t,  $J=7.5$  Hz, 3H);  $^{13}C$  NMR (125 MHz,  $CD_3CN$ )  $\delta$

215.2, 162.6, 158.9 (d,  $J=233.3$  Hz), 133.4, 125.8, 123.5 (d,  $J=9.6$  Hz), 120.1 (d,  $J=5.1$  Hz), 115.6 (d,  $J=27.5$  Hz), 112.1 (d,  $J=9.5$  Hz), 106.2 (d,  $J=23.8$  Hz), 52.4, 47.7, 35.3, 28.7, 16.7, 7.8; HRMS (ESI-TOF) calcd for  $C_{16}H_{19}FNO_4^+$   $[M+H^+]$  330.1112, found 330.1104.



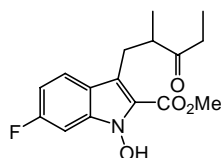
**2.72:**  $R_f=0.50$  (silica gel, EtOAc/hexanes, 4:6); IR (film)  $\nu_{max}$  3383 (br), 2922, 2851, 1700, 1598, 1580, 1528, 1438, 1402, 1379, 1337, 1304, 1251, 1190, 1169, 1108, 1079, 1015, 970, 952, 936, 913, 850, 794, 785, 762, 732, 707, 682  $cm^{-1}$ ;  $^1H$  NMR (600 MHz,  $CD_3CN$ )  $\delta$  9.11 (s, 1H), 8.00 (d,  $J=7.8$  Hz, 2H), 7.70 (t,  $J=7.2$  Hz, 1H), 7.53 (t,  $J=7.82$  Hz, 2H), 7.48 (dd,  $J=9.0, 4.2$  Hz, 1H), 7.40 (d,  $J=9.6$  Hz, 1H), 7.20 (dt,  $J=9.6, 2.4$  Hz, 1H), 4.04 (t,  $J=17.4$  Hz, 2H), 3.76 (s, 3H);  $^{13}C$  NMR (150 MHz,  $CD_3CN$ )  $\delta$  191.1, 162.7, 158.9 (d,  $J=233.9$  Hz), 136.2, 133.7, 131.4 (t,  $J=3.3$  Hz, 2C), 131.2, 130.5 (2C), 127.9, 124.7 (d,  $J=10.4$  Hz), 120.4, 120.2, 116.5 (d,  $J=27.3$  Hz), 112.8 (d,  $J=9.6$  Hz), 106.8 (d,  $J=24.3$  Hz), 53.2, 31.8 (t,  $J=24.5$  Hz); HRMS (ESI-TOF) calcd for  $C_{19}H_{15}F_3NO_4^+$   $[M+H^+]$  378.0948, found 378.0943.



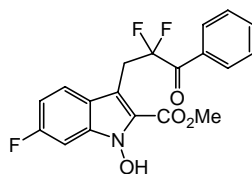
**2.73:**  $R_f=0.44$  (silica gel, EtOAc/hexanes, 3:7, eluted two times); IR (film)  $\nu_{max}$  3286 (br), 2924, 2854, 1706, 1629, 1537, 1446, 1402, 1352, 1264, 1219, 1177, 1110, 1034, 924, 834, 809  $cm^{-1}$ ;  $^1H$  NMR (600 MHz,  $CD_3CN$ )  $\delta$  9.06 (s, 1H), 7.68 (dd,  $J=8.8,$



4.8 Hz, 1H), 7.13 (dd,  $J=9.6, 2.2$  Hz, 1H), 7.91 (dt,  $J=9.6, 2.5$  Hz, 1H), 3.87 (s, 3H), 3.42 (dd,  $J=14.0, 4.8$  Hz, 1H), 2.86 (dd,  $J=14.0, 9.2$  Hz, 1H), 2.72–2.67 (m, 1H), 2.37–2.23 (m, 2H), 2.01–1.98 (m, 1H), 1.86–1.84 (m, 1H), 1.76–1.72 (m, 1H), 1.65–1.58 (m, 1H), 1.56–1.49 (m, 1H), 1.44–1.37 (m, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  213.0, 163.2 (d,  $J=239.5$  Hz), 163.0, 135.6, 125.3, 124.2 (d,  $J=11.4$  Hz), 122.0, 120.7, 110.8 (d,  $J=25.1$  Hz), 96.5 (d,  $J=27.4$  Hz), 52.7, 52.6, 42.8, 34.7, 29.0, 25.9, 25.4; HRMS (ESI-TOF) calcd for  $\text{C}_{17}\text{H}_{19}\text{FNO}_4^+$  [ $\text{M}+\text{H}^+$ ] 320.1293, found 320.1282.

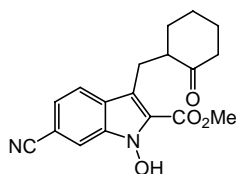


**2.74:**  $R_f=0.56$  (silica gel, EtOAc/hexanes, 1:1); IR (film)  $\nu_{\text{max}}$  3313, 2924, 2877, 1698, 1539, 1456, 1396, 1260, 1223, 1175, 1110  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.10 (br s, 1H), 7.68–7.65 (m, 1H), 7.15 (dd,  $J=9.5, 2.5$  Hz, 1H), 6.95–6.91 (m, 1H), 3.92 (s, 3H), 3.30–3.24 (m, 1H), 3.00–2.93 (m, 2H), 2.51–2.43 (m, 1H), 2.33–2.25 (m, 1H), 1.02 (d,  $J=6.5$  Hz, 3H), 0.86 (t,  $J=7.5$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  215.2, 163.0 (d,  $J=239.8$  Hz), 162.6, 132.9, 124.9, 123.8 (d,  $J=10.5$  Hz), 121.0, 120.2, 110.7 (d,  $J=25.6$  Hz), 96.3 (d,  $J=27.1$  Hz), 52.4, 47.8, 35.4, 28.7, 16.7, 7.9; HRMS (ESI-TOF) calcd for  $\text{C}_{16}\text{H}_{18}\text{FNO}_4\text{Na}^+$  [ $\text{M}+\text{Na}^+$ ] 330.1112, found 330.1110.

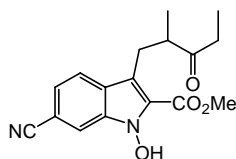


**2.75:**  $R_f=0.52$  (silica gel, EtOAc/hexanes, 3:7, eluted two times); IR (film)  $\nu_{\text{max}}$  3362, 2962, 2923, 2853, 1699, 1632, 1598, 1537, 1449, 1401, 1355, 1264, 1223, 1177, 1112,

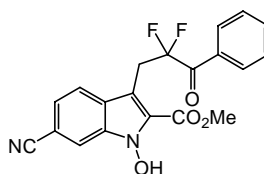
1063, 924, 907, 880, 834, 812  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.12 (br s, 1H), 7.99 (d,  $J=7.9$  Hz, 2H), 7.71–7.67 (m, 2H), 7.51 (t,  $J=7.9$  Hz, 2H), 7.18 (dd,  $J=9.1$ , 1.7 Hz, 1H), 6.98 (dt,  $J=9.1$ , 1.7 Hz, 1H), 4.06 (t,  $J=17.5$  Hz, 2H), 3.74 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  191.0, 163.3 (d,  $J=240.6$  Hz), 162.5, 136.8 (d,  $J=14.7$  Hz), 135.9, 133.5, 131.1 (t,  $J=3.4$  Hz, 2C), 130.3, 130.2 (2C), 126.9 (d,  $J=3.4$  Hz), 124.4 (d,  $J=10.3$  Hz), 121.0, 120.1, 111.9 (d,  $J=26.2$  Hz), 96.7 (d,  $J=27.4$  Hz), 52.8, 31.5 (t,  $J=23.9$  Hz); HRMS (ESI-TOF) calcd for  $\text{C}_{19}\text{H}_{15}\text{F}_3\text{NO}_4^+$   $[\text{M}+\text{H}^+]$  378.0948, found 378.0941.



**2.76:**  $R_f=0.42$  (silica gel, EtOAc/hexanes, 6:4); IR (film)  $\nu_{\text{max}}$  3300 (br), 2930, 2856, 2359, 2221, 1711, 1519, 1446, 1263, 1117  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.22 (br s, 1H), 7.88 (s, 1H), 7.85 (d,  $J=8.5$  Hz, 1H), 7.36 (dd,  $J=8.5$ , 1.0 Hz, 1H), 3.92 (s, 3H), 3.45 (dd,  $J=14.0$ , 5.0 Hz, 1H), 2.88 (dd,  $J=14.0$ , 9.0 Hz, 1H), 2.72–2.68 (m, 1H), 2.38–2.26 (m, 2H), 2.03–1.99 (m, 1H), 1.89–1.84 (m, 1H), 1.77–1.73 (m, 1H), 1.67–1.50 (m, 2H), 1.46–1.38 (m, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  212.6, 162.3, 135.0, 127.5, 126.0, 123.3, 123.2, 120.7, 120.5, 115.8, 108.8, 52.7, 52.4, 42.5, 34.5, 28.7, 25.6, 25.0; HRMS (ESI-TOF) calcd for  $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_4\text{Na}^+$   $[\text{M}+\text{Na}^+]$  349.1159, found 349.1149.



**2.77:**  $R_f=0.55$  (silica gel, EtOAc/hexanes, 6:4); IR (film)  $\nu_{\max}$  3242 (br), 2969, 2357, 2224, 1712, 1537, 1445, 1259, 1233, 1117  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.31 (br s, 1H), 7.87 (s, 1H), 7.81 (d,  $J=8.5$  Hz, 1H), 7.36 (dd,  $J=8.5, 1.5$  Hz, 1H), 3.95 (s, 3H), 3.28 (m, 1H), 3.00–2.93 (m, 2H), 2.51–2.43 (m, 1H), 2.32–2.24 (m, 1H), 0.86 (d,  $J=7.0$  Hz, 3H), 1.01 (t,  $J=7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  215.1, 162.2, 134.8, 127.3, 125.7, 123.4, 123.1, 120.4, 120.0, 115.8, 108.8, 52.7, 47.7, 35.4, 28.4, 16.8, 7.9; HRMS (ESI-TOF) calcd for  $\text{C}_{17}\text{H}_{19}\text{N}_2\text{O}_4^+$   $[\text{M}+\text{H}^+]$  315.1339, found 315.1331.

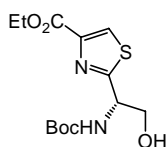


**2.78:**  $R_f=0.47$  (silica gel, EtOAc/hexanes, 1:1); IR (film)  $\nu_{\max}$  2930, 2846, 2358, 2222, 1711, 1560, 1437, 1260, 1117  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.38 (br s, 1H), 8.00 (d,  $J=8.0$  Hz, 2H), 7.92 (s, 1H), 7.85 (d,  $J=8.5$  Hz, 1H), 7.71–7.68 (m, 1H), 7.54–7.51 (m, 2H), 7.41 (dd,  $J=8.5, 1.0$  Hz, 1H), 4.08 (t,  $J=17.5$  Hz, 2H), 3.79 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  203.1, 170.7, 135.6, 135.3, 133.7, 133.6, 130.8 (t,  $J=3.1$  Hz, 2C), 129.8, 129.7 (2C), 126.0, 123.8, 123.4, 120.8, 114.6, 105.9, 105.6, 54.3, 31.4; HRMS (ESI-TOF) calcd for  $\text{C}_{20}\text{H}_{13}\text{F}_2\text{N}_2\text{O}_4^-$   $[\text{M}-\text{H}^-]$  383.0849, found 383.0850.

### Synthesis of nocathiacin model systems **2.81** and **2.88a–c**

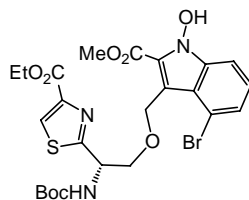
**2.80:** Thiazole ethyl ester **2.79**<sup>8</sup> (150 mg, 0.42 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (2.8 mL) and MeOH (1.4 mL) and cooled to 0 °C. Trifluoroacetic acid (4.2 mL) was

added dropwise over 5 min to the reaction mixture, and after stirring at 0 °C for 2.5 h, toluene (5 mL) was added and the reaction mixture was concentrated. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and washed with saturated aqueous NaHCO<sub>3</sub> solution (5 mL), brine (5 mL), and dried over Na<sub>2</sub>SO<sub>4</sub>. The solution was then concentrated and the residue was subjected to flash column chromatography (silica gel, EtOAc/hexanes, 1:1→80:20) to afford primary alcohol **2.80** (91 mg, 68%) as a yellow foam.



**2.80**:  $R_f=0.40$  (silica gel, MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 5:95); IR (film)  $\nu_{\max}$  3354 (br), 2978, 2919, 1707, 1502, 1484, 1390, 1361, 1337, 1231, 1167, 1091, 1055, 1020, 856, 756 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN)  $\delta$  8.17 (s, 1H), 6.04 (s, 1H), 4.93 (s, 1H), 4.31 (ddd,  $J=7.8, 3.1, 0.9$  Hz, 2H), 3.88 (t,  $J=6.1$  Hz, 2H), 3.22 (t,  $J=5.7$  Hz, 1H), 1.42 (br s, 9H), 1.33 (t,  $J=6.1$  Hz, 3H); <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>CN)  $\delta$  173.9, 162.0, 156.4, 147.8, 129.0, 80.4, 64.5, 62.0, 56.0, 28.5, 14.5 (3C); HRMS (ESI-TOF) calcd for C<sub>13</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>SN<sup>+</sup> [M+Na<sup>+</sup>] 339.0985, found 339.0985.

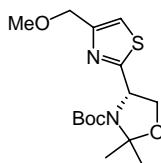
**2.81**: Primary alcohol **2.80** (16.9 mg, 0.05 mmol) was dissolved in DME (350  $\mu$ L) and to this solution were added 4 Å molecular sieves (20 wt%), *p*TsOH (7.6 mg, 0.04 mmol), and tertiary alcohol **2.11** (4.0 mg, 0.013 mmol) at 25 °C. After stirring for 10 min, the reaction mixture was heated to 40 °C for 2 h after which the crude reaction mixture was allowed to cool to room temperature and purified directly by PTLC (silica gel, EtOAc/hexanes, 7:3) to afford model system **2.81** (3.5 mg, 44%) as a yellow oil.



**2.81:**  $R_f=0.43$  (silica gel, EtOAc/hexanes, 7:3);  $[\alpha]_D^{32} -3.0$  ( $c$  0.50,  $\text{CHCl}_3$ ); IR (film)  $\nu_{\text{max}}$  3354, 2978, 2919, 1707, 1490, 1460, 1437, 1390, 1360, 1255, 1231, 1161, 1119, 1090, 1025, 879, 773, 743  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ , 66 °C)  $\delta$  9.22 (s, 1H), 8.06 (s, 1H), 7.50 (d,  $J=7.7$  Hz, 1H), 7.36 (d,  $J=7.7$  Hz, 1H), 7.22 (t,  $J=7.7$  Hz, 1H), 5.81 (br s, 1H), 5.17 ( $^1/2\text{ABq}$ ,  $J=11.4$  Hz, 1H), 5.14 ( $^1/2\text{ABq}$ ,  $J=11.4$  Hz, 1H), 5.04 (dt,  $J=7.4$ , 4.8 Hz, 1H), 4.33 (q,  $J=7.0$  Hz, 2H), 3.97 (s, 3H), 3.96 (dd,  $J=10.0$ , 4.8 Hz, 1H), 3.93 (dd,  $J=10.0$ , 4.8 Hz, 1H), 1.39 (s, 9H), 1.35 (t,  $J=7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  174.0, 162.2, 162.0, 156.2, 147.7, 137.2, 128.9, 127.2, 127.0, 126.9, 120.9, 115.9, 115.2, 110.2, 80.4, 71.2, 62.1, 61.9, 54.2, 53.1, 28.4 (3C), 14.5; HRMS (ESI-TOF) calcd for  $\text{C}_{24}\text{H}_{28}\text{BrN}_3\text{O}_8\text{SNa}^+$   $[\text{M}+\text{Na}^+]$  620.0673, found 620.0674.

**2.82:** Thiazole ethyl ester **2.79**<sup>8</sup> (530 mg, 1.49 mmol) was dissolved in toluene (6.0 mL) and cooled to 0 °C. DIBAL-H (2.0 mL, 3.0 mmol, 1.5 M in toluene) was then added dropwise and the reaction mixture stirred for 2.5 h after which the reaction was slowly quenched at 0 °C with MeOH (2 mL) and the resulting mixture was warmed to 25 °C and stirred for 12 h with saturated aqueous sodium potassium tartrate solution (5 mL). The mixture was extracted with EtOAc (3×20 mL) and the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and the resulting solution was concentrated. The residue was taken up in THF (6.0 mL) and cooled to 0 °C, and to this solution

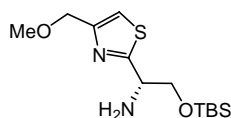
were added NaH (150 mg, 3.7 mmol, 60% dispersion in mineral oil) and MeI (649  $\mu\text{L}$ , 10.43 mmol). The reaction mixture was allowed to warm to 25  $^{\circ}\text{C}$  over 12 h at which time the reaction mixture was poured over ice water (10 mL), extracted with EtOAc (20 mL), washed with brine (10 mL), and dried ( $\text{Na}_2\text{SO}_4$ ). The solution was then concentrated and the residue was subjected to flash column chromatography (silica gel, EtOAc/hexanes, 60:40 $\rightarrow$ 80:20) to afford methyl ether **2.82** (360 mg, 74% over two steps) as a yellow oil.



**2.82:**  $R_f=0.52$  (silica gel, EtOAc/hexanes, 7:3);  $[\alpha]_D^{33} -24.1$  ( $c$  0.60,  $\text{CHCl}_3$ ); IR (film)  $\nu_{\text{max}}$  3383 (br), 2971, 1874, 1698, 1455, 1371, 1255, 1164, 1092, 1049  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ , 66  $^{\circ}\text{C}$ )  $\delta$  7.22 (s, 1H), 5.19 (dd,  $J=6.2, 1.9$  Hz, 1H), 4.47 (d,  $J=0.7$  Hz, 2H), 4.29 (dd,  $J=9.2, 6.2$  Hz, 1H), 4.07 (dd,  $J=9.2, 1.9$  Hz, 1H), 3.37 (s, 3H), 1.69 (s, 3H), 1.52 (s, 3H), 1.38 (br s, 9H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ , 66  $^{\circ}\text{C}$ )  $\delta$  174.6, 155.2, 147.8, 117.2, 95.3, 81.2, 71.2 (2C), 70.1, 60.7, 58.8 (2C), 28.9 (3C); HRMS (ESI-TOF) calcd for  $\text{C}_{15}\text{H}_{25}\text{N}_2\text{O}_4\text{S}^+$   $[\text{M}+\text{H}^+]$  329.1529, found 329.1518.

**2.83:** Methyl ether **2.82** (50 mg, 0.152 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (761  $\mu\text{L}$ ) and cooled to 0  $^{\circ}\text{C}$ . TFA (761  $\mu\text{L}$ ) was then added dropwise and the reaction mixture stirred for 10 min at 0  $^{\circ}\text{C}$  and then 1 h at 25  $^{\circ}\text{C}$  at which time the reaction mixture was diluted with toluene (2 mL) and concentrated (3 $\times$ ). After drying under high vacuum for 30 min, the crude amino alcohol was dissolved in  $\text{CH}_2\text{Cl}_2$  (317  $\mu\text{L}$ ) and cooled to

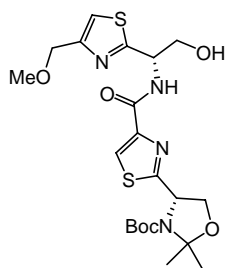
0 °C. Et<sub>3</sub>N (70 μL, 0.50 mmol) and TBSCl (50 mg, 0.33 mmol) were then added and the reaction mixture was warmed to 25 °C. After 3 h, the mixture was washed with saturated aqueous NaHCO<sub>3</sub> solution (1 mL), brine (1 mL), and then dried over Na<sub>2</sub>SO<sub>4</sub>. The resulting solution was concentrated and the residue was subjected to flash column chromatography (silica gel, EtOAc/hexanes, 80:20→100:0) to afford primary amine **2.83** (39.0 mg, 85% over two steps) as a yellow oil.



**2.83**:  $R_f=0.57$  (silica gel, MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 5:95);  $[\alpha]_D^{31} -7.6$  ( $c$  1.23, CH<sub>2</sub>Cl<sub>2</sub>); IR (film)  $\nu_{\max}$  3378 (br), 2931, 2848, 1461, 1255, 1091, 838, 764, 602 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN)  $\delta$  7.19 (s, 1H), 4.44 (s, 2H), 4.19 (dd,  $J=6.1, 4.3$  Hz, 1H), 3.88 (dd,  $J=9.9, 4.3$  Hz, 1H), 3.78 (dd,  $J=9.9, 6.1$  Hz, 1H), 3.33 (s, 3H), 0.85 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>CN)  $\delta$  177.1, 154.9, 117.5, 71.2, 69.1, 58.8, 56.9, 26.3 (3C), 19.0, -4.87, -4.94; HRMS (ESI-TOF) calcd for C<sub>13</sub>H<sub>27</sub>N<sub>2</sub>O<sub>2</sub>SSi<sup>+</sup> [M+H<sup>+</sup>] 303.1484, found 303.1487.

**2.85**: Amine **2.83** (846 mg, 2.80 mmol) was dissolved in DMF (7 mL), cooled to 0 °C, and then *i*Pr<sub>2</sub>NEt (974 μL, 5.59 mmol) was added followed by cannula addition of thiazole acid **2.84**<sup>8</sup> (918 mg, 2.80 mmol) dissolved in DMF (7 mL). HATU (1.17 g, 3.08 mmol) and HOAt (419 mg, 3.08 mmol) were then added and the reaction mixture stirred for 1 h at 0 °C and 2 h at 25 °C after which EtOAc (25 mL) was added and the reaction mixture was washed with aqueous 5% HCl solution (10 mL), H<sub>2</sub>O (10 mL),

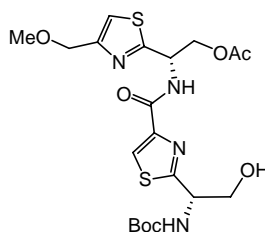
saturated aqueous NaHCO<sub>3</sub> solution (10 mL), brine (10 mL), and dried over Na<sub>2</sub>SO<sub>4</sub>. The resulting solution was concentrated and the residue was taken up in THF (75 mL) and cooled to 0 °C. TBAF (3.36 mL, 1.0 M in THF) was added dropwise and after 30 min, the reaction mixture was quenched with saturated aqueous NH<sub>4</sub>Cl solution (20 mL), extracted with EtOAc (2×25 mL), washed with brine (20 mL), and dried over Na<sub>2</sub>SO<sub>4</sub>. The resulting solution was concentrated and the residue was subjected to flash column chromatography (silica gel, EtOAc/hexanes, 20:80→90:10) affording complex alcohol **2.85** (1.21 g, 87% over two steps) as a light yellow foam.



**2.85**:  $R_f=0.42$  (silica gel, MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 5:95);  $[\alpha]_D^{32} -10.9$  ( $c$  0.80, CH<sub>2</sub>Cl<sub>2</sub>); IR (film)  $\nu_{\max}$  3389 (br), 2966, 2731, 2872, 1696, 1467, 1531, 1472, 1373, 1249, 1167, 1091, 1049, 761 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>CN, 66 °C)  $\delta$  8.13 (d,  $J=5.5$  Hz, 1H), 8.07 (d,  $J=1.0$  Hz, 1H), 7.26 (d,  $J=1.0$  Hz, 1H), 5.41–5.37 (m, 1H), 5.24 (d,  $J=6.6$  Hz, 1H), 4.51 (s, 2H), 4.34–4.31 (m, 1H), 4.16–4.13 (m, 1H), 4.10–4.04 (m, 2H), 3.97 (dd,  $J=11.4, 4.8$  Hz, 1H), 3.39 (s, 3H), 1.72 (s, 3H), 1.57 (s, 3H), 1.39 (br s, 9H); <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>CN, 66 °C)  $\delta$  175.9, 171.9, 162.3, 155.9, 155.8, 151.0, 125.6, 118.3, 71.6, 70.3, 65.8, 65.7, 61.1, 61.0, 59.4, 55.0 (2C), 29.3 (3C); HRMS (ESI-TOF) calcd for C<sub>21</sub>H<sub>31</sub>N<sub>4</sub>O<sub>6</sub>S<sub>2</sub><sup>+</sup> [M+H<sup>+</sup>] 499.1679, found 499.1670.



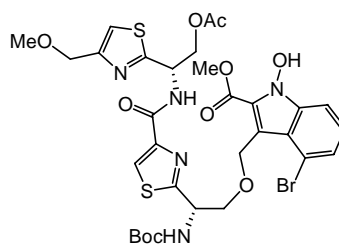
**2.86:** A solution of complex alcohol **2.85** (95 mg, 0.19 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) was cooled to 0 °C and Et<sub>3</sub>N (80 μL, 0.57 mmol) and 4-DMAP (2.3 mg, 0.02 mmol) were added followed by Ac<sub>2</sub>O (90 μL, 0.95 mmol). After 10 min at 0 °C, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (3 mL) and washed with aqueous 5% HCl solution (3 mL), saturated aqueous NaHCO<sub>3</sub> solution (3 mL), brine (3 mL), and dried over Na<sub>2</sub>SO<sub>4</sub>. The resulting solution was concentrated and the residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (1.26 mL) and MeOH (630 μL) and cooled to 0 °C. TFA (1.88 mL) was then added dropwise and after 30 min the reaction mixture was diluted with toluene (5 mL) and concentrated (3×). The residue was subjected to flash column chromatography (silica gel, EtOAc/hexanes, 1:1→100:0) affording hydroxy acetate **2.86** (78 mg, 82% over two steps) as a yellow oil.



**2.86:**  $R_f=0.17$  (silica gel, EtOAc/hexanes, 8:2);  $[\alpha]_D^{31} -6.8$  ( $c$  0.50, CHCl<sub>3</sub>); IR (film)  $\nu_{\max}$  3309 (br), 2930, 1712, 1661, 1533, 1460, 1382, 1248, 1165, 1059, 797, 679, 590 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN, 66 °C)  $\delta$  8.16 (d,  $J=4.8$  Hz, 1H), 8.10 (s, 1H), 7.30 (s, 1H), 5.41–5.37 (m, 1H), 5.92 (br s, 1H), 5.62–5.64 (m, 1H), 4.99–4.96 (m, 1H), 4.62 (ddd,  $J=11.8, 4.8, 1.3$  Hz, 1H), 4.57 (ddd,  $J=11.8, 6.5, 0.8$  Hz, 1H), 4.51 (s, 2H), 3.97–3.95 (m, 2H), 3.39 (s, 3H), 2.00 (s, 3H), 1.45 (s, 9H); <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>CN)  $\delta$  173.7, 171.4, 169.4, 161.6, 156.4, 154.8, 149.8, 125.4, 118.1, 80.3, 70.5,

65.5, 64.4, 58.4, 55.9, 51.3, 28.4 (3C), 20.8; HRMS (ESI-TOF) calcd for  $C_{20}H_{29}N_4O_7S_2^+$   $[M+H^+]$  501.1472, found 501.1459.

**2.87**: *Method A*: To a stirred solution of *p*TsOH (13.3 mg, 0.07 mmol) and 4 Å molecular sieves (20 wt%) in DME (470  $\mu$ L) were added hydroxy acetate **2.86** (23 mg, 0.046 mmol) and tertiary alcohol **2.11** (7 mg, 0.023 mmol) at 25 °C. After 10 min, the reaction mixture was warmed to 40 °C, stirred for 3 h, allowed to cool to room temperature and purified directly by PTLC (silica gel, EtOAc/hexanes, 80:20) to afford *N*-hydroxyindole **2.87** (10 mg, 56%) as a yellow oil; *Method B*: To a stirred solution of  $SnCl_2 \cdot 2H_2O$  (10.4 mg, 0.046 mmol) and 4 Å molecular sieves (20 wt%) in DME (110  $\mu$ L) were added hydroxy acetate **2.86** (41 mg, 0.082 mmol) in DME (100  $\mu$ L) and ketoester **2.8a** (6.6 mg, 0.021 mmol) at 25 °C. The reaction mixture was warmed immediately to 40 °C and stirring was continued for 6 h in the absence of light at which time the reaction mixture was allowed to cool to 25 °C and purified directly by PTLC (silica gel, MeOH/Et<sub>2</sub>O, 2:98) to afford *N*-hydroxyindole **2.87** (6.6 mg, 40%) as a yellow oil.

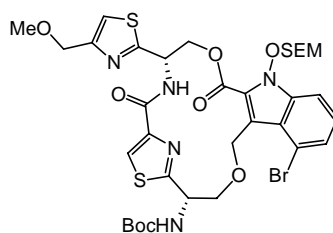


**2.87**:  $R_f=0.26$  (silica gel, EtOAc/hexanes, 7:3);  $[\alpha]_D^{31} +1.7$  ( $c$  0.20,  $CH_2Cl_2$ ); IR (film)  $\nu_{max}$  3331 (br), 2919, 2849, 1725, 1708, 1400, 1531, 1449, 1431, 1378, 1249, 1061, 761  $cm^{-1}$ ;  $^1H$  NMR (600 MHz,  $CD_3CN$ , 66 °C)  $\delta$  9.30 (br s, 1H), 8.09–8.05 (m, 1H),

7.97 (d,  $J=9.6$  Hz, 1H), 7.48 (d,  $J=8.3$  Hz, 1H), 7.34 (d,  $J=7.8$  Hz, 1H), 7.31 (d,  $J=6.1$  Hz, 1H), 7.20 (t,  $J=7.7$  Hz, 1H), 5.84 (br s, 1H), 5.66–5.63 (m, 1H), 5.19–5.14 (m, 2H), 5.07–5.03 (m, 1H), 4.61–4.55 (m, 2H), 4.52 (s, 2H), 4.01 (dd,  $J=10.1, 5.2$  Hz, 1H), 3.97–3.94 (m, 4H), 3.39 (s, 3H), 1.99 (s, 3H), 1.40 (s, 9H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  173.8, 171.4, 169.3, 162.0 (2C), 161.5, 156.2, 154.8, 149.7, 137.3, 127.0, 126.8, 126.2, 125.2, 120.7, 115.8, 115.1, 110.1, 80.4, 71.3, 70.4, 65.5, 64.7, 58.4, 54.1, 52.9, 51.3, 28.4 (3C), 20.8; HRMS (ESI-TOF) calcd for  $\text{C}_{31}\text{H}_{36}\text{BrN}_5\text{O}_{10}\text{S}_2\text{Na}^+$   $[\text{M}+\text{Na}^+]$  804.0979, found 804.0979.

**2.88a:** *N*-Hydroxyindole **2.87** (34 mg, 0.043 mmol) was dissolved in DMF (1.5 mL) and cooled to 0 °C at which time *i*Pr<sub>2</sub>NEt (23  $\mu\text{L}$ , 0.130 mmol), SEMCl (15  $\mu\text{L}$ , 0.087 mmol), and TBAI (1.6 mg, 0.004 mmol) were added and the reaction mixture was warmed to 25 °C. After 10 min, the reaction mixture was diluted with EtOAc (5 mL), washed with aqueous 5% HCl solution (3 mL), and dried over  $\text{Na}_2\text{SO}_4$ . The resulting solution was concentrated and the residue was taken up in THF (2.58 mL), MeOH (860  $\mu\text{L}$ ), and  $\text{H}_2\text{O}$  (860  $\mu\text{L}$ ) and then cooled to 0 °C. LiOH (3 mg, 0.129 mmol) was added and, after warming to 25 °C over 4 h, the reaction mixture was diluted with EtOAc (5 mL), cooled to 0 °C, quenched with aqueous 5% HCl solution (5 mL), separated, and the organic layer was dried ( $\text{Na}_2\text{SO}_4$ ). After azeotroping with toluene (3 $\times$ 5 mL), the residue was dissolved in toluene (4.3 mL), and Et<sub>3</sub>N (240  $\mu\text{L}$ , 1.72 mmol) and 2,4,6-trichlorobenzoyl chloride (202  $\mu\text{L}$ , 1.29 mmol) were added. After stirring for 12 h at 25 °C, the reaction mixture was added dropwise

over the course of 12 h (syringe pump) to a solution of 4-DMAP (158 mg, 1.29 mmol) in toluene (80 mL). After addition was complete, the resulting mixture was stirred at 25 °C for a further 12 h, then cooled to 0 °C and acidified to pH~3 with an aqueous 10 mg/mL solution of KHSO<sub>4</sub>. The layers were separated and the aqueous layer was re-extracted with EtOAc (2×40 mL). The combined organic layers were then washed with a 1:1 solution of saturated aqueous NaHCO<sub>3</sub>/brine (40 mL) and the aqueous layer was re-extracted with EtOAc (2×40 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The residue was purified by PTLC (silica gel, EtOAc/hexanes, 60:40) to give macrocycle **2.88a** (14 mg, 38% over three steps) as a yellow oil.

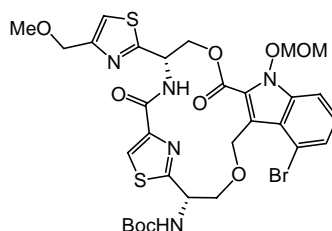


**2.88a**:  $R_f=0.37$  (silica gel, EtOAc/hexanes, 8:2);  $[\alpha]_D^{33} -12.3$  ( $c$  0.72, CH<sub>2</sub>Cl<sub>2</sub>); IR (film)  $\nu_{\max}$  3353 (br), 2924, 2854, 2086, 1712, 1536, 1494, 1366, 1214, 1170, 1105, 859, 836, 777 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN)  $\delta$  8.44 (d,  $J=7.5$  Hz, 1H), 8.04 (s, 1H), 7.51 (dd,  $J=8.3, 0.9$  Hz, 1H), 7.41 (dd,  $J=7.4, 0.9$  Hz, 1H), 7.30 (s, 1H), 7.24 (t,  $J=7.9$  Hz, 1H), 6.00 (d,  $J=7.9$  Hz, 1H), 5.66–5.62 (m, 1H), 5.34 (d,  $J=3.9$  Hz, 1H), 5.21 (d,  $J=10.1$  Hz, 1H), 5.18 (dd,  $J=11.4, 3.9$  Hz, 1H), 5.14–5.12 (m, 2H), 5.08 (d,  $J=7.5$  Hz, 1H), 5.04 (dd,  $J=11.4, 5.7$  Hz, 1H), 4.48 (s, 2H), 4.17–4.14 (m, 1H), 3.94 (dd,  $J=9.6, 2.6$  Hz, 1H), 3.80–3.70 (m, 2H), 3.36 (s, 3H), 1.40 (br s, 9H), 0.86 (t,  $J=7.0$  Hz, 2H),  $-0.02$  (s, 9H); <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>CN)  $\delta$  170.9, 170.1, 163.0,

162.0, 161.7, 155.3, 149.4, 138.1, 128.0, 127.8, 127.5, 126.7, 122.1, 119.2, 116.3, 113.2, 111.5, 103.3, 72.2, 70.8, 69.6, 65.6, 65.2, 62.7, 58.8, 52.7, 52.6, 28.6 (3C), 18.9, -1.3 (3C); HRMS (ESI-TOF) calcd for  $C_{34}H_{45}BrN_5O_9S_2Si^+$   $[M+H^+]$  838.1606, found 838.1604.

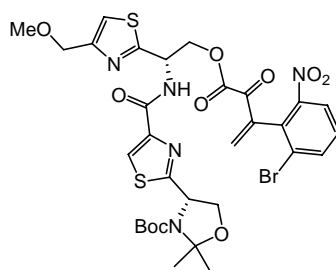
**2.88b:** *N*-Hydroxyindole **2.87** (30 mg, 0.038 mmol) was dissolved in DMF (1.9 mL) and cooled to 0 °C at which time *i*Pr<sub>2</sub>NEt (20 μL, 0.114 mmol), MOMCl (6 μL, 0.076 mmol), and TBAI (1.4 mg, 0.004 mmol) were added and the reaction mixture was warmed to 25 °C. After 10 min, the reaction mixture was diluted with EtOAc (5 mL), washed with aqueous 5% HCl solution (3 mL), and dried over Na<sub>2</sub>SO<sub>4</sub>. The resulting solution was concentrated and the residue was taken up in THF (2.28 mL), MeOH (760 μL), and H<sub>2</sub>O (760 μL) and then cooled to 0 °C. LiOH (2.7 mg, 0.114 mmol) was added and after warming to 25 °C over 4 h, the reaction mixture was diluted with EtOAc (5 mL), cooled to 0 °C, quenched with aqueous 5% HCl solution (5 mL), separated, and the organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>). After azeotroping with toluene (3×5 mL), the residue was dissolved in toluene (4.0 mL), and Et<sub>3</sub>N (212 μL, 1.52 mmol) and 2,4,6-trichlorobenzoyl chloride (178 μL, 1.14 mmol) were added. After stirring for 12 h at 25 °C, the reaction mixture was added dropwise over the course of 12 h (syringe pump) to a solution of 4-DMAP (139 mg, 1.14 mmol) in toluene (71 mL). After addition was complete, the resulting mixture was stirred at 25 °C for a further 12 h, then cooled to 0 °C and acidified to pH~3 with an aqueous 10 mg/mL solution of KHSO<sub>4</sub>. The layers were separated and the aqueous layer was

re-extracted with EtOAc (2×40 mL). The combined organic layers were then washed with a 1:1 solution of saturated aqueous NaHCO<sub>3</sub>/brine (40 mL) and the aqueous layer was re-extracted with EtOAc (2×40 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The residue was purified by PTLC (silica gel, EtOAc/hexanes, 80:20) to give macrocycle **2.88b** (12.7 mg, 44% over three steps) as a yellow oil.



**2.88b**:  $R_f=0.36$  (silica gel, EtOAc/hexanes, 8:2);  $[\alpha]_D^{32} -10.5$  ( $c$  0.68, CH<sub>2</sub>Cl<sub>2</sub>); IR (film)  $\nu_{\max}$  3330 (br), 2919, 2849, 1725, 1713, 1608, 1531, 1449, 1384, 1260, 1067, 803 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN)  $\delta$  8.45 (d,  $J=7.9$  Hz, 1H), 8.04 (s, 1H), 7.52 (dd,  $J=8.3, 0.9$  Hz, 1H), 7.42 (dd,  $J=7.5, 0.9$  Hz, 1H), 7.30 (s, 1H), 7.26 (dd,  $J=8.3, 7.5$  Hz, 1H), 6.00 (d,  $J=8.3$  Hz, 1H), 5.66–5.62 (m, 1H), 5.36–5.33 (m, 1H), 5.22–5.18 (m, 2H), 5.13 (d,  $J=10.1$  Hz, 1H), 5.09 (d,  $J=7.5$  Hz, 1H), 5.05 (d,  $J=7.5$  Hz, 1H), 5.02 (dd,  $J=11.4, 5.2$  Hz, 1H), 4.48 (s, 2H), 4.18–4.14 (m, 1H), 3.95 (dd,  $J=10.1, 3.1$  Hz, 1H), 3.52 (s, 3H), 3.36 (s, 3H), 1.40 (br s, 9H); <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>CN, 66 °C)  $\delta$  171.0, 170.1, 163.0, 162.0, 161.7, 155.3, 149.4, 138.2, 128.2, 127.9, 127.7, 126.8, 122.2, 119.3, 116.3, 113.2, 111.5, 105.3, 80.7, 72.2, 70.8, 65.2, 62.8, 59.0, 58.8, 52.7, 52.6, 28.7 (3C); HRMS (ESI-TOF) calcd for C<sub>30</sub>H<sub>34</sub>BrN<sub>5</sub>O<sub>9</sub>S<sub>2</sub>Na<sup>+</sup> [M+Na<sup>+</sup>] 774.0873, found 774.0869.

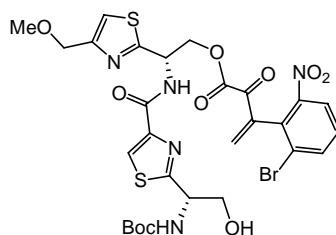
**2.89:** Acid **2.9a** (18 mg, 0.06 mmol) was dissolved in THF (80  $\mu$ L), cooled to 0  $^{\circ}$ C, and oxalyl chloride (3.5  $\mu$ L, 0.04 mmol) was added followed by DMF (one drop). After 45 min at 0  $^{\circ}$ C, Et<sub>3</sub>N (11  $\mu$ L, 0.08 mmol) and complex alcohol **2.85** (10 mg, 0.02 mmol) in THF (80  $\mu$ L) were added and the reaction mixture was allowed to warm to 25  $^{\circ}$ C over 2 h. THF was concentrated in vacuo and the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 mL), washed with ice H<sub>2</sub>O (5 mL), and dried (Na<sub>2</sub>SO<sub>4</sub>). The resulting solution was concentrated and the residue was purified by PTLC (silica gel, EtOAc/hexanes, 80:20) to afford  $\alpha$ -ketoester **2.89** (12 mg, 77%) as a yellow oil.



**2.89:**  $R_f=0.71$  (silica gel, EtOAc/hexanes, 8:2);  $[\alpha]_D^{32} -3.5$  ( $c$  0.34, CHCl<sub>3</sub>); IR (film)  $\nu_{\max}$  3377 (br), 3119, 2978, 2919, 1754, 1689, 1666, 1531, 1443, 1372, 1255, 1149, 1091, 1049, 961, 908, 808, 755  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz, CD<sub>3</sub>CN, 70  $^{\circ}$ C)  $\delta$  8.17 (d,  $J=8.8$  Hz, 1H), 8.10 (d,  $J=1.7$  Hz, 1H), 8.00 (dd,  $J=8.3, 1.3$  Hz, 1H), 7.97 (dd,  $J=7.8, 0.8$  Hz, 1H), 7.50 (t,  $J=8.3$  Hz, 1H), 7.32 (d,  $J=0.9$  Hz, 1H), 6.61 (s, 1H), 6.25 (dd,  $J=10.1, 0.9$  Hz, 1H), 5.84–5.80 (m, 1H), 5.24–5.21 (m, 1H), 4.95–4.87 (m, 2H), 4.50 (s, 2H), 4.32–4.29 (m, 1H), 4.16 (dd,  $J=9.1, 1.7$  Hz, 1H), 3.38 (s, 3H), 1.69 (s, 3H), 1.56 (s, 3H), 1.28 (br s, 9H);  $^{13}\text{C}$  NMR (150 MHz, CD<sub>3</sub>CN, 66  $^{\circ}$ C)  $\delta$  175.9, 169.2, 163.7, 162.2, 156.1, 150.3, 143.1, 139.1, 137.1, 133.0, 132.5, 126.9, 125.9, 125.2

(2C), 119.0, 96.4, 81.5, 71.3 (2C), 68.1, 60.60, 60.59, 59.2, 51.8 (2C), 29.1 (3C); HRMS (ESI-TOF) calcd for  $C_{31}H_{35}BrN_5O_{10}S_2^+$   $[M+H^+]$  780.1003, found 780.1001.

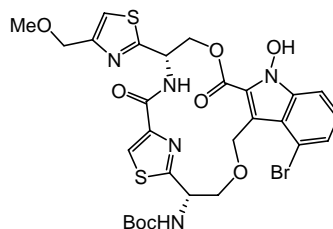
**2.90**:  $\alpha$ -Ketoester **2.89** (10 mg, 0.013 mmol) was dissolved in  $CH_2Cl_2$  (330  $\mu$ L) and MeOH (170  $\mu$ L) and cooled to 0  $^\circ$ C. TFA (500  $\mu$ L) was added dropwise and, after stirring for 1 h at 0  $^\circ$ C, the reaction mixture was diluted with toluene (3 mL) and concentrated (2 $\times$ ). The residue was purified by PTLC (silica gel, EtOAc/hexanes, 80:20) to afford *N*-Boc amino alcohol **2.90** (6.8 mg, 72%) as a yellow oil.



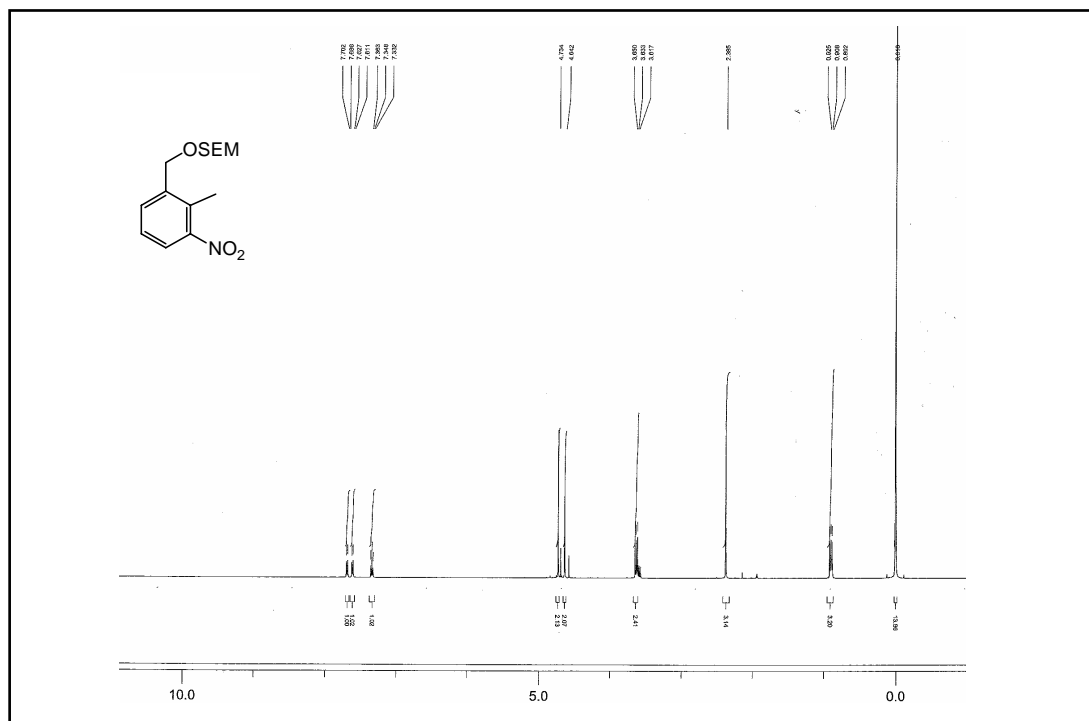
**2.90**:  $R_f=0.29$  (silica gel, EtOAc/hexanes, 8:2);  $[\alpha]_D^{33} -0.4$  ( $c$  0.78,  $CH_2Cl_2$ ); IR (film)  $\nu_{max}$  3383 (br), 3109, 2971, 2923, 2850, 1746, 1698, 1686, 1649, 1528, 1346, 1243, 1158, 1031, 740, 595  $cm^{-1}$ ;  $^1H$  NMR (600 MHz,  $CD_3CN$ )  $\delta$  8.19 (d,  $J=7.0$  Hz, 1H), 8.09 (s, 1H), 8.01–7.98 (m, 1H), 7.98–7.96 (m, 1H), 7.52–7.48 (m, 1H), 7.32 (s, 1H), 6.62 (dd,  $J=2.2, 0.9$  Hz, 1H), 6.25 (dd,  $J=6.1, 1.3$  Hz, 1H), 5.87–5.80 (m, 2H), 4.98–4.90 (m, 3H), 4.51 (s, 2H), 4.95–4.85 (m, 2H), 3.39 (s, 3H), 1.43 (br s, 9H);  $^{13}C$  NMR (150 MHz,  $CD_3CN$ )  $\delta$  185.3, 174.0, 171.8, 168.9, 163.4, 161.9, 155.5, 151.2, 150.1, 142.6, 138.8, 136.9, 132.5, 132.1, 126.5, 125.8, 124.9, 120.5, 118.6, 80.8, 70.9, 67.6, 64.8, 58.8, 51.3, 28.8 (3C); HRMS (ESI-TOF) calcd for  $C_{28}H_{31}BrN_5O_{10}S_2^+$   $[M+H^+]$  740.0690, found 740.0687.



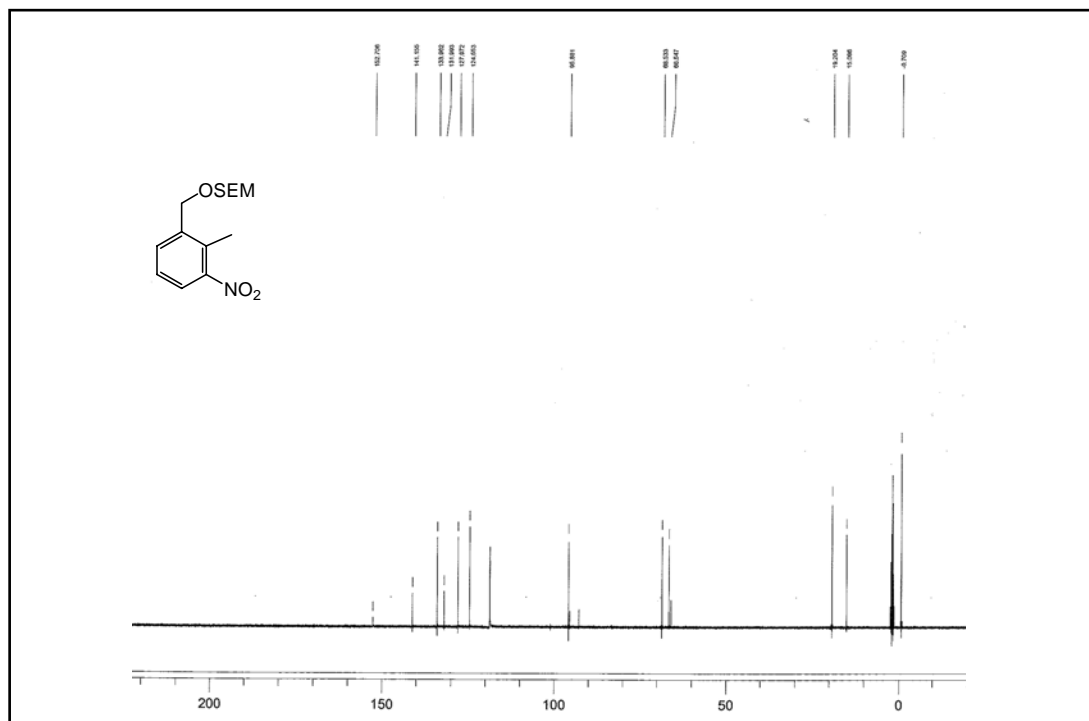
**2.88c:** *Method A:* A stirred suspension of Zn dust (5.0 mg, 0.078 mmol) and dibromoethane (0.46  $\mu$ L, 0.005 mmol) in THF (79  $\mu$ L) was heated to reflux (70  $^{\circ}$ C) for approximately 5 min and then allowed to cool to 25  $^{\circ}$ C. The refluxing/cooling process was repeated three times. TMSCl (0.41  $\mu$ L, 0.003 mmol) was then added and the resulting gray suspension was stirred at 25  $^{\circ}$ C for 10 min. A separate stirred solution containing a mixture of aqueous 1 N  $\text{NH}_4\text{Cl}$  (36  $\mu$ L, 0.036 mmol) and *N*-Boc amino alcohol **2.90** (12 mg, 0.016 mmol) in THF (153  $\mu$ L) was added via cannula to the activated Zn suspension and stirring was continued for 15 min at 25  $^{\circ}$ C. The crude reaction mixture was diluted with EtOAc (5 mL) and washed with saturated aqueous  $\text{NaHCO}_3$  solution (1 mL) filtered through celite and dried ( $\text{Na}_2\text{SO}_4$ ). The resulting solution was concentrated and the residue was dissolved in DME (16 mL). Molecular sieves (20 wt%, 4  $\text{\AA}$ ) and *p*TsOH (9 mg, 0.048 mmol) were added and, after 10 min at 25  $^{\circ}$ C and 12 h at 40  $^{\circ}$ C, the reaction mixture was cooled to 25  $^{\circ}$ C and purified by PTLC (silica gel, MeOH/Et<sub>2</sub>O, 5:95) to give *N*-hydroxyindole macrocycle **2.88c** (4.6 mg, 40%) as a yellow oil; *Method B:* To a stirred solution of  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  (5.2 mg, 0.022 mmol) and 4  $\text{\AA}$  molecular sieves (20 wt%) in DME (50  $\mu$ L) was added *N*-Boc amino alcohol **2.90** (5.3 mg, 0.007 mmol) in DME (50  $\mu$ L) at 25  $^{\circ}$ C. The reaction mixture was warmed immediately to 45  $^{\circ}$ C and stirring was continued for 3 h in the absence of light at which time the reaction mixture was allowed to cool to room temperature and purified directly by PTLC (silica gel, MeOH/Et<sub>2</sub>O, 7:93) to afford *N*-hydroxyindole macrocycle **2.88c** (0.51 mg, 10%) as a yellow oil.



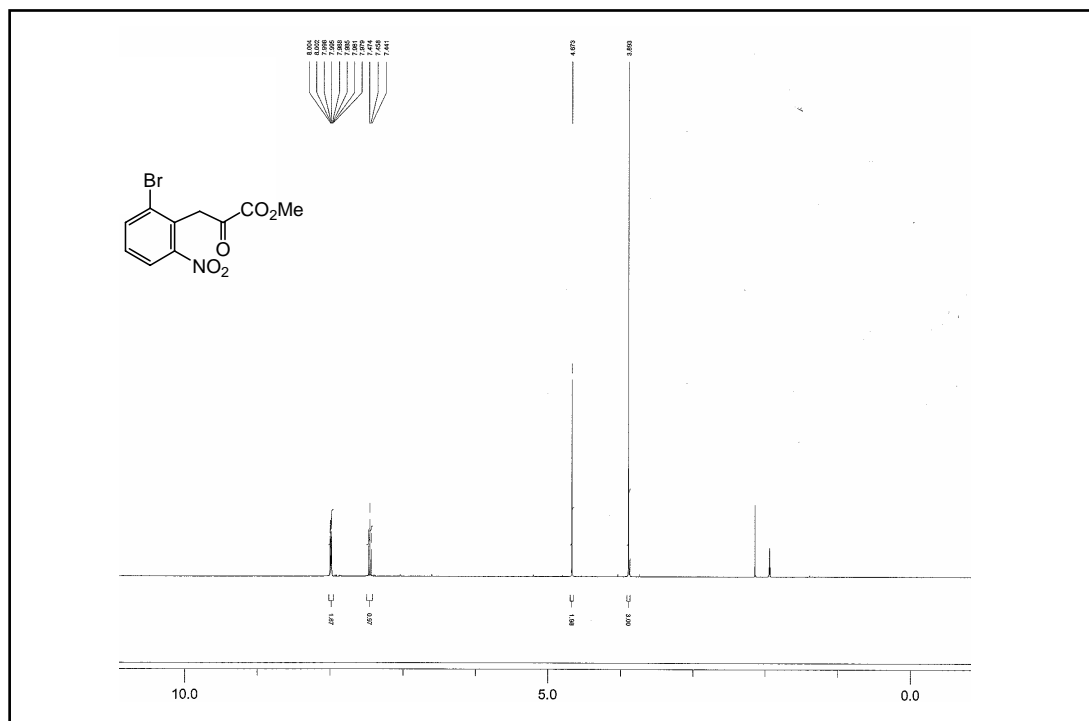
**2.88c (+2.88c')** [ca. 1:1 mixture of *N*-Boc rotamers ( $^1\text{H}$  NMR)]:  $R_f=0.63$  (silica gel, MeOH/Et<sub>2</sub>O, 5:95);  $[\alpha]_D^{33} +1.0$  (*c* 0.23, CH<sub>2</sub>Cl<sub>2</sub>); IR (film)  $\nu_{\text{max}}$  3346, 2924, 2850, 1709, 1668, 1534, 1494, 1458, 1365, 1251, 1223, 1185, 1163, 1122, 1100, 778, 743 cm<sup>-1</sup>;  $^1\text{H}$  NMR (600 MHz, CD<sub>3</sub>CN, 67 °C)  $\delta$  9.05 (s, 1H), 8.97 (s, 1H), 8.47 (d,  $J=8.3$  Hz, 1H), 8.47 (d,  $J=6.1$  Hz, 1H), 8.01 (s, 1H), 7.97 (s, 1H), 7.48 (dd,  $J=8.3, 2.6$  Hz, 1+1H), 7.39 (dd,  $J=7.8, 2.1$  Hz, 1+1H), 7.34 (s, 1H), 7.32 (s, 1H), 7.23 (dd,  $J=8.3, 7.8$  Hz, 1+1H), 5.85 (br s, 1+1H), 5.68–5.63 (m, 1+1H), 5.43 (d,  $J=10.5$  Hz, 1H), 5.37–5.35 (m, 1+1H), 5.33–5.31 (m, 1+1H), 5.26 (d,  $J=10.1$  Hz, 1H), 5.23 (d,  $J=10.1$  Hz, 1H), 5.18–5.14 (m, 1H), 5.08–5.04 (m, 1H), 5.01 (dd,  $J=11.8, 4.3$  Hz, 1H), 5.01 (dd,  $J=11.8, 4.9$  Hz, 1H), 4.54 (d,  $J=0.8$  Hz, 2H), 4.53 (d,  $J=0.8$  Hz, 2H), 4.37 (dd,  $J=10.1, 3.5$  Hz, 1H), 4.37 (dd,  $J=10.1, 3.5$  Hz, 1H), 4.02 (dd,  $J=9.6, 3.0$  Hz, 1H), 3.41 (s, 3H), 3.40 (s, 3H), 1.46 (s, 9H), 1.44 (s, 9H);  $^{13}\text{C}$  NMR (150 MHz, CD<sub>3</sub>CN)  $\delta$  169.6, 167.6, 162.4, 162.3, 156.3, 149.1, 137.7, 130.9, 127.8, 127.7, 127.2, 125.9, 121.4, 121.3, 116.2, 111.7, 110.6, 70.7, 64.4, 62.6, 62.0, 48.7, 53.1, 52.8, 52.6, 28.6 (3C); HRMS (ESI-TOF) calcd for C<sub>28</sub>H<sub>31</sub>BrN<sub>5</sub>O<sub>8</sub>S<sub>2</sub><sup>+</sup> [M+H<sup>+</sup>] 708.0792, found 708.0786.



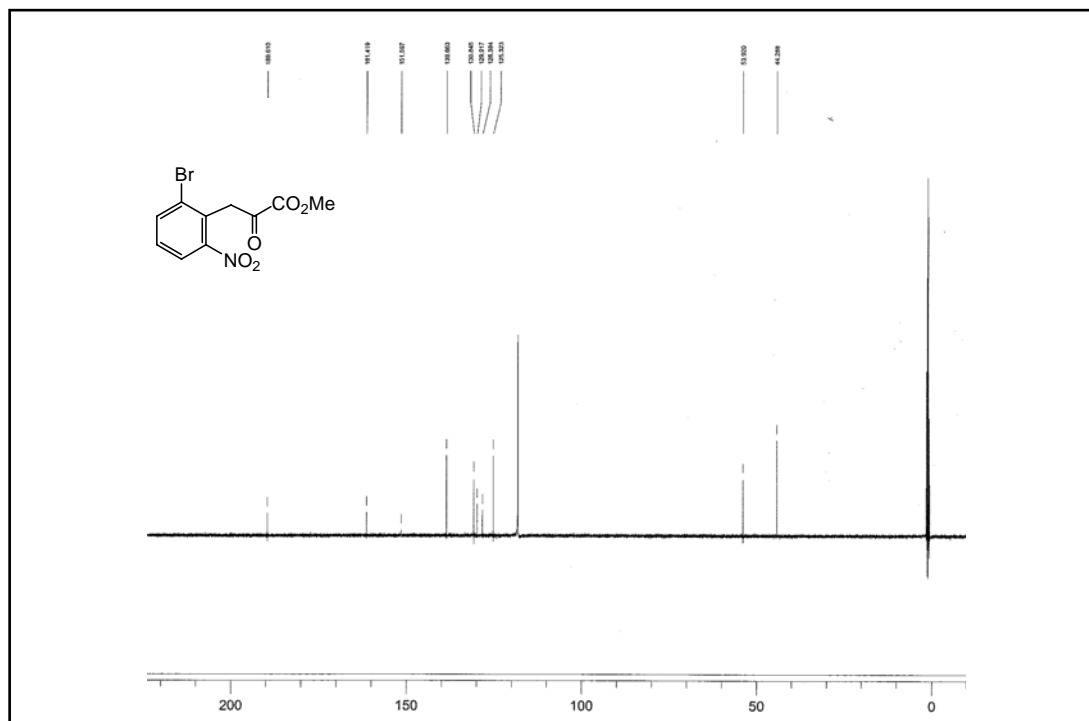
**Spectrum 2.1**  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.6c**.



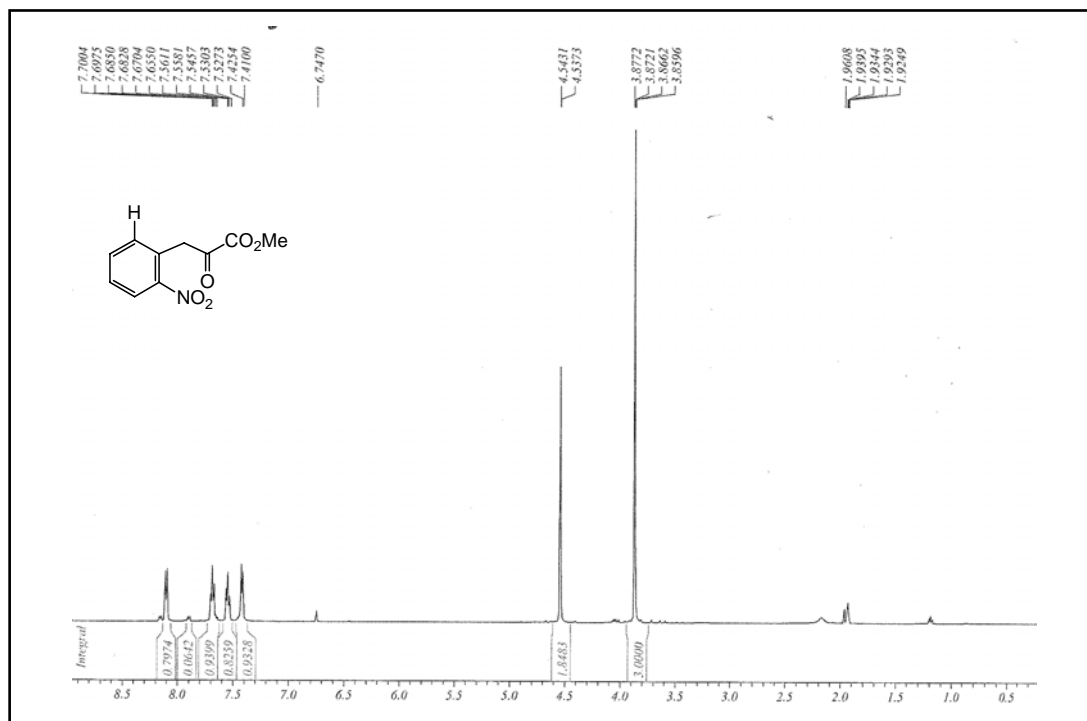
**Spectrum 2.2**  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.6c**.



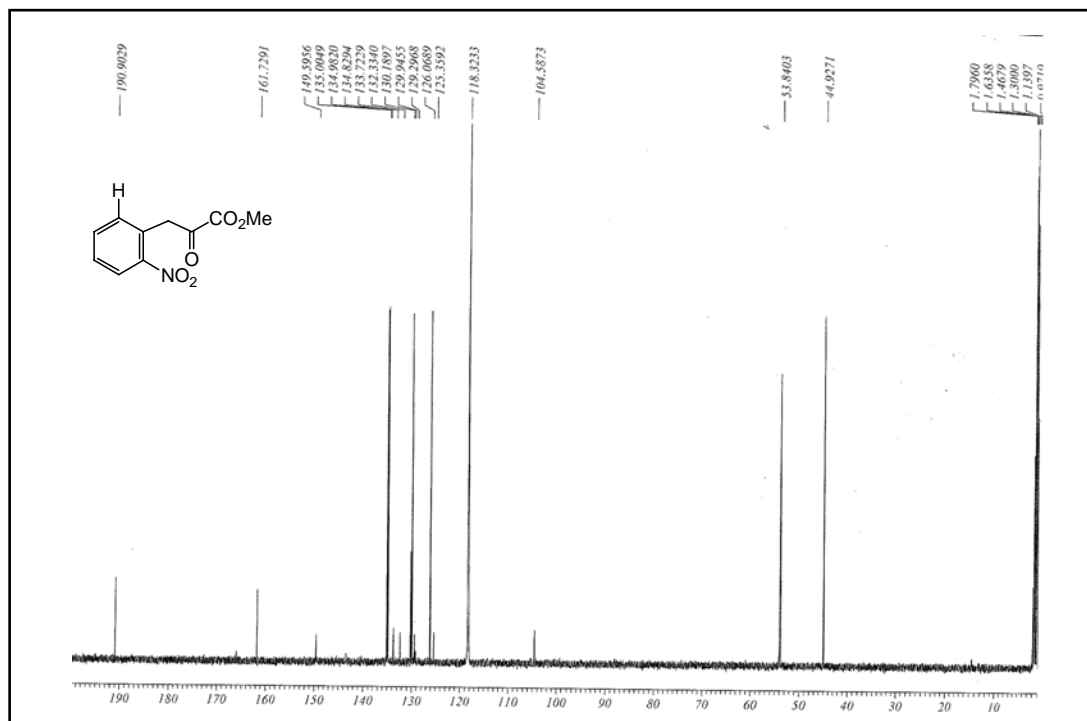
**Spectrum 2.3**  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.7a**.



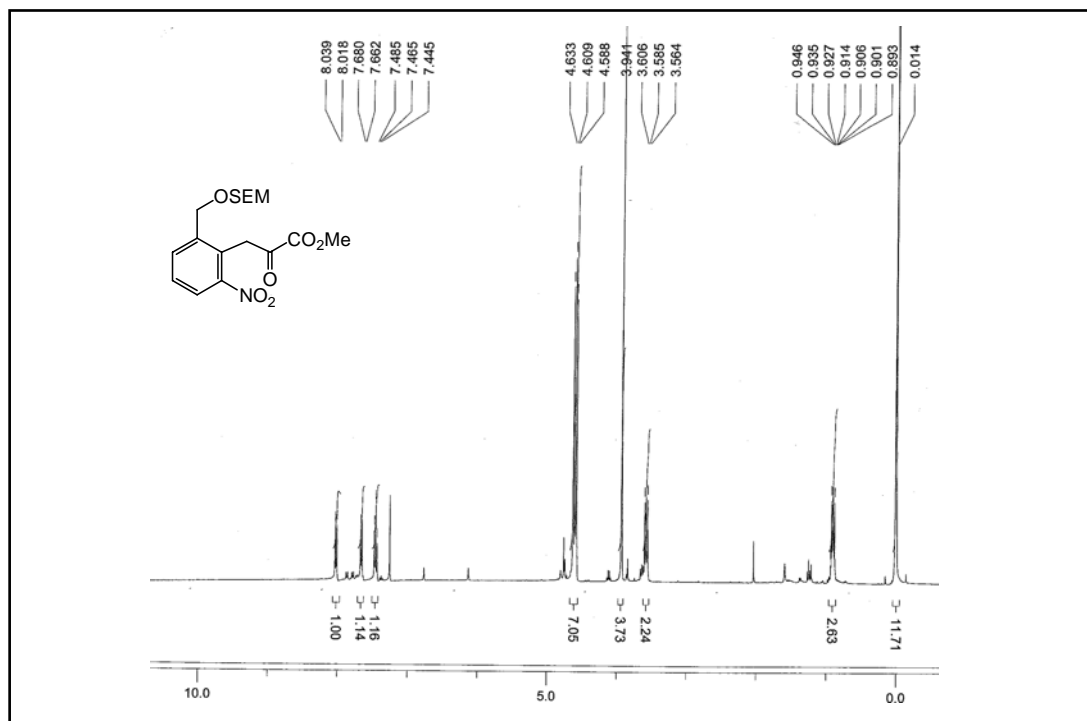
**Spectrum 2.4**  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.7a**.



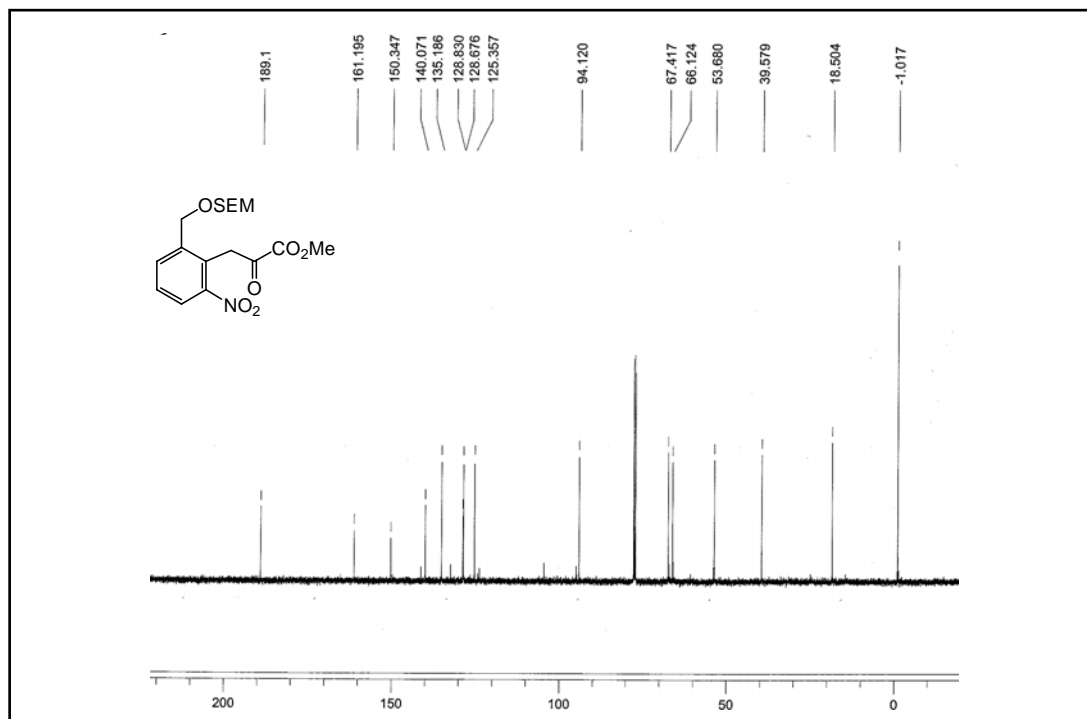
**Spectrum 2.5**  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.7b**.



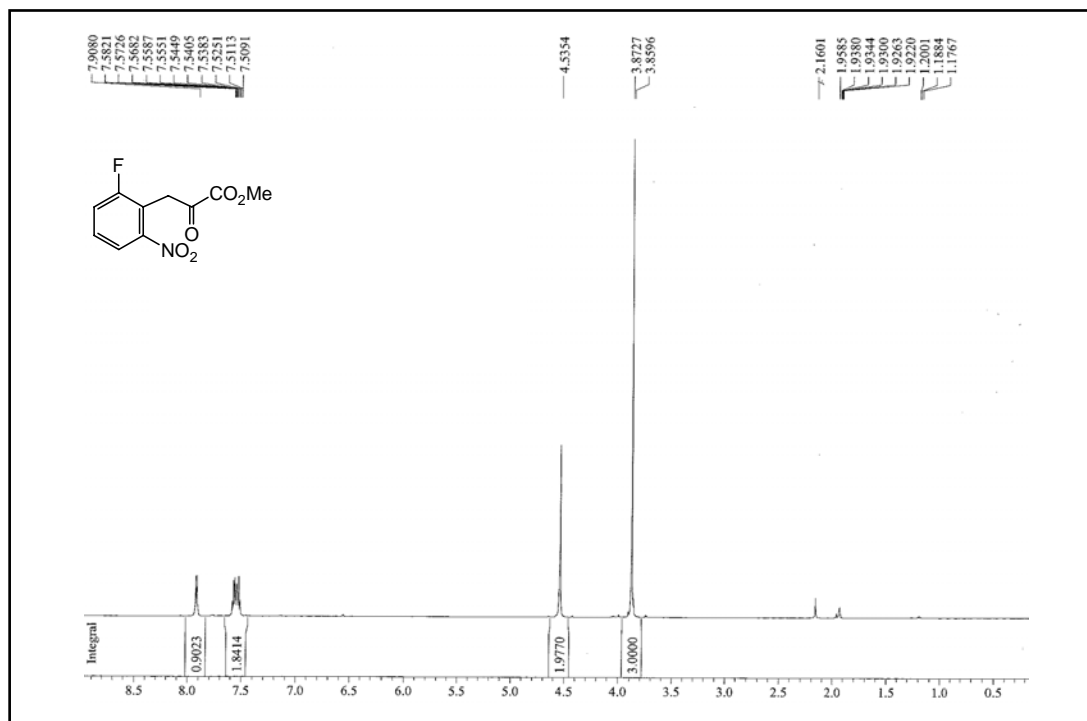
**Spectrum 2.6**  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.7b**.



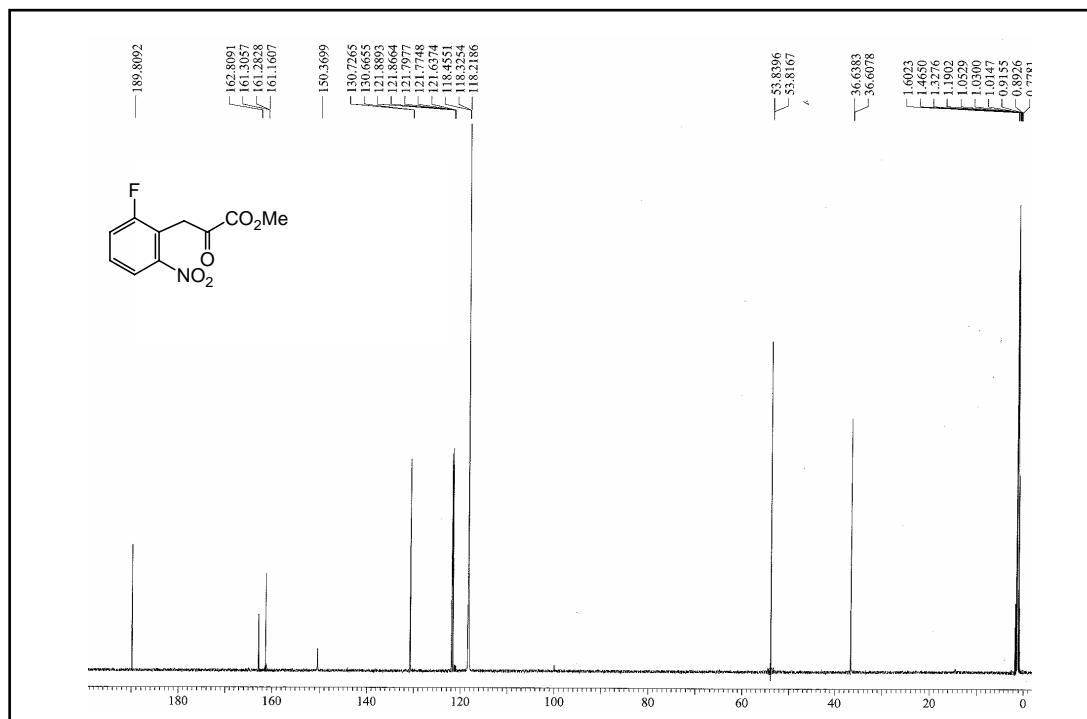
**Spectrum 2.7**  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.7c**.



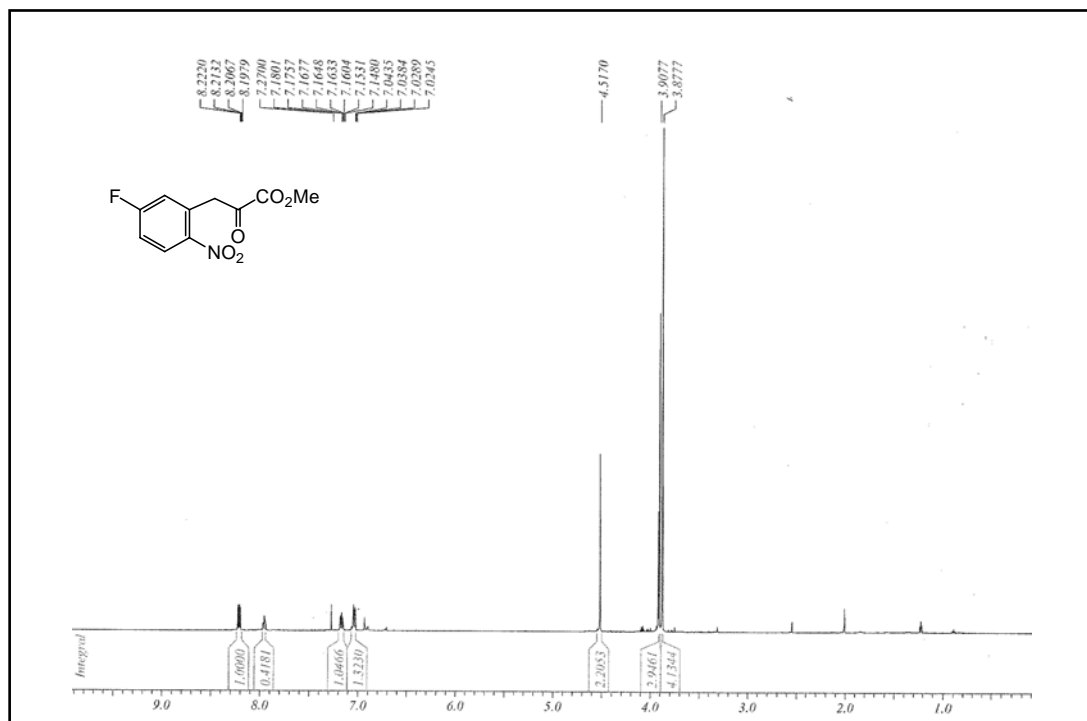
**Spectrum 2.8**  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.7c**.



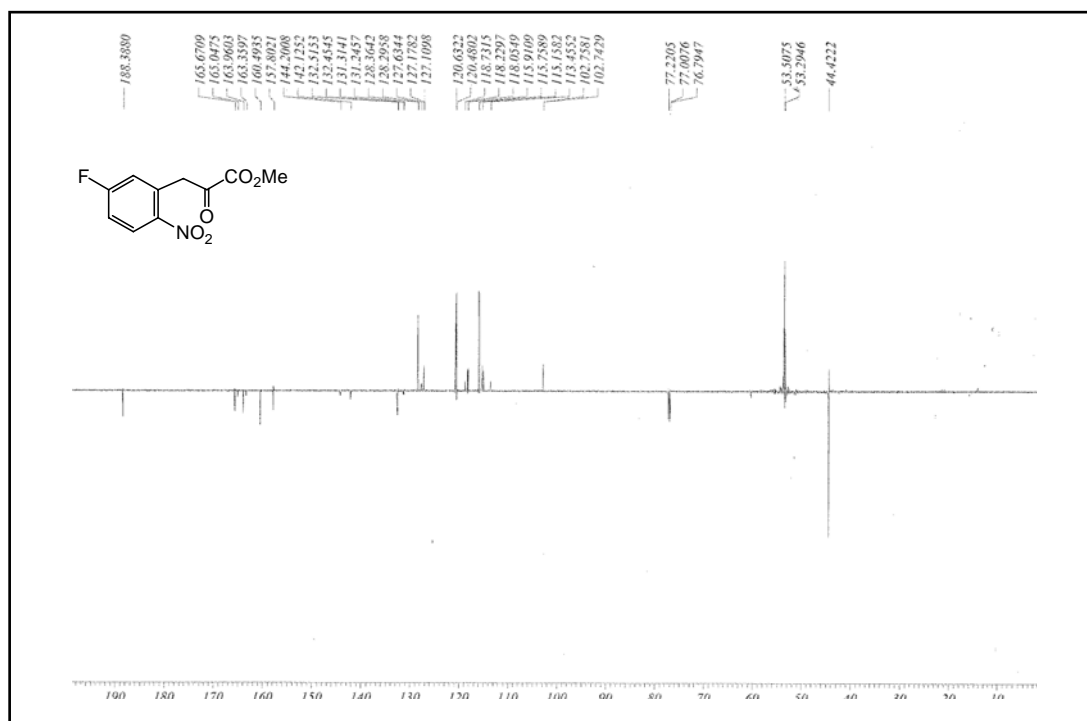
**Spectrum 2.9** <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN) spectrum of compound 2.7d.



**Spectrum 2.10** <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>CN) spectrum of compound 2.7d.



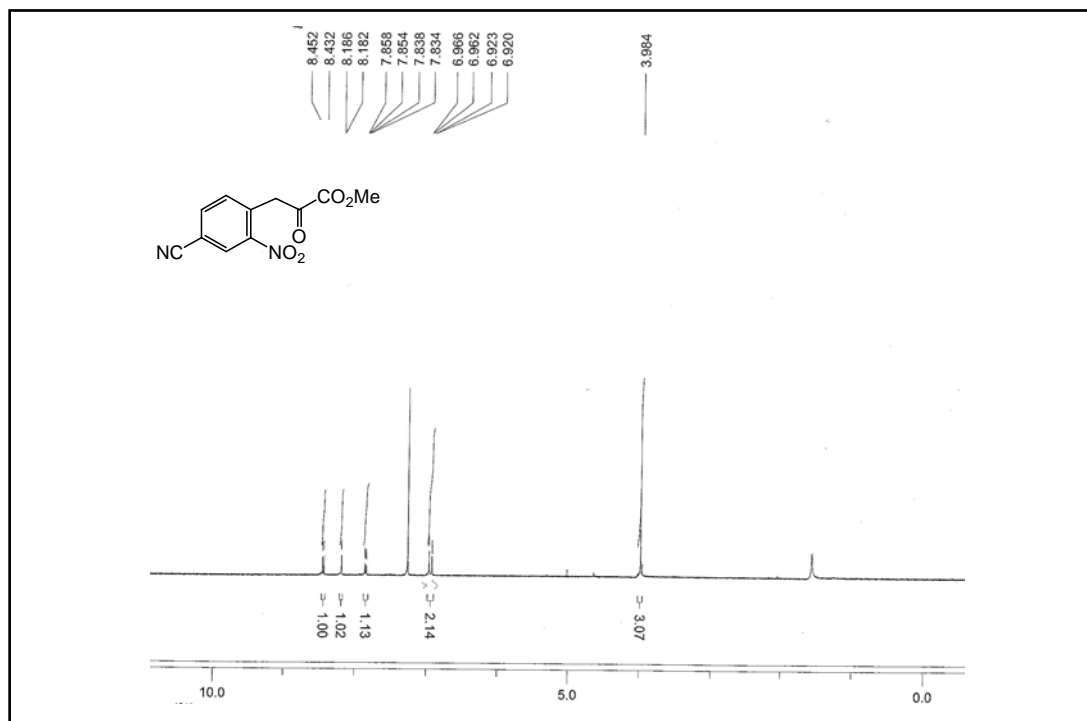
Spectrum 2.11  $^1\text{H NMR}$  (600 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.7e.



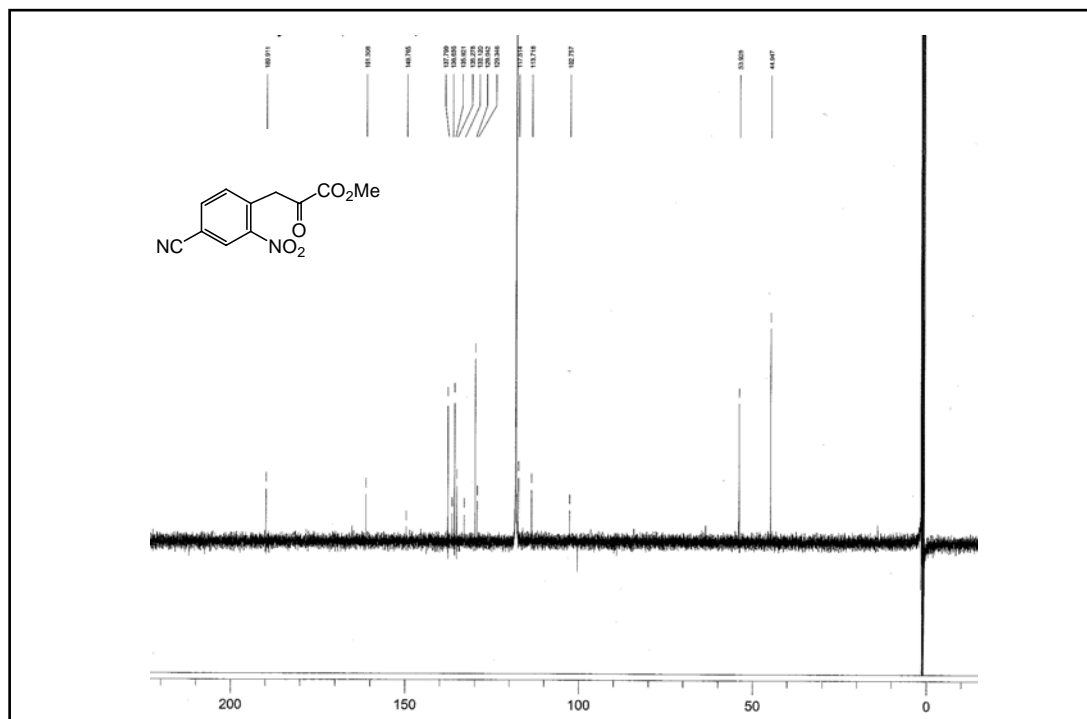
Spectrum 2.12  $^{13}\text{C NMR}$  (150 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.7e.

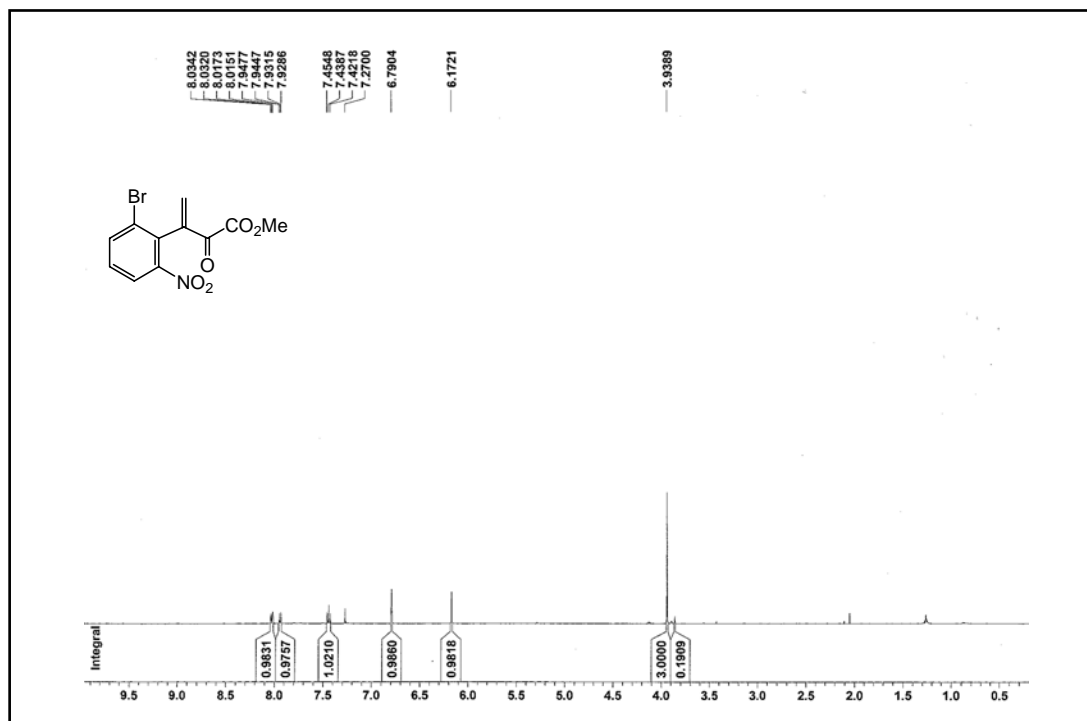




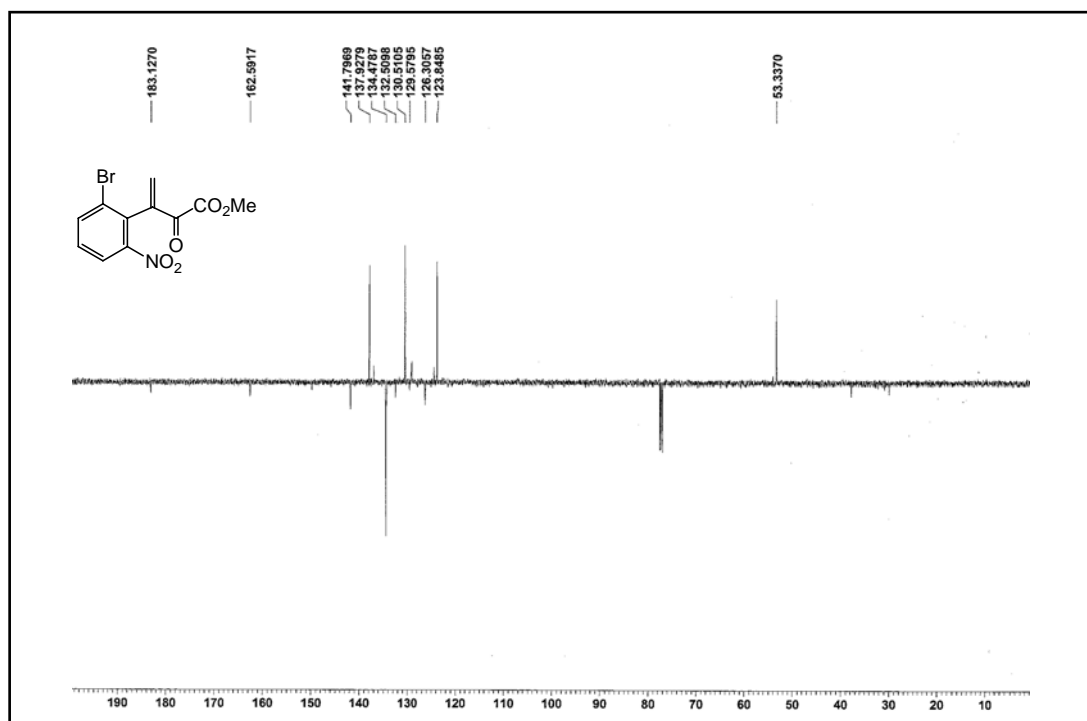


**Spectrum 2.15**  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.7g**.

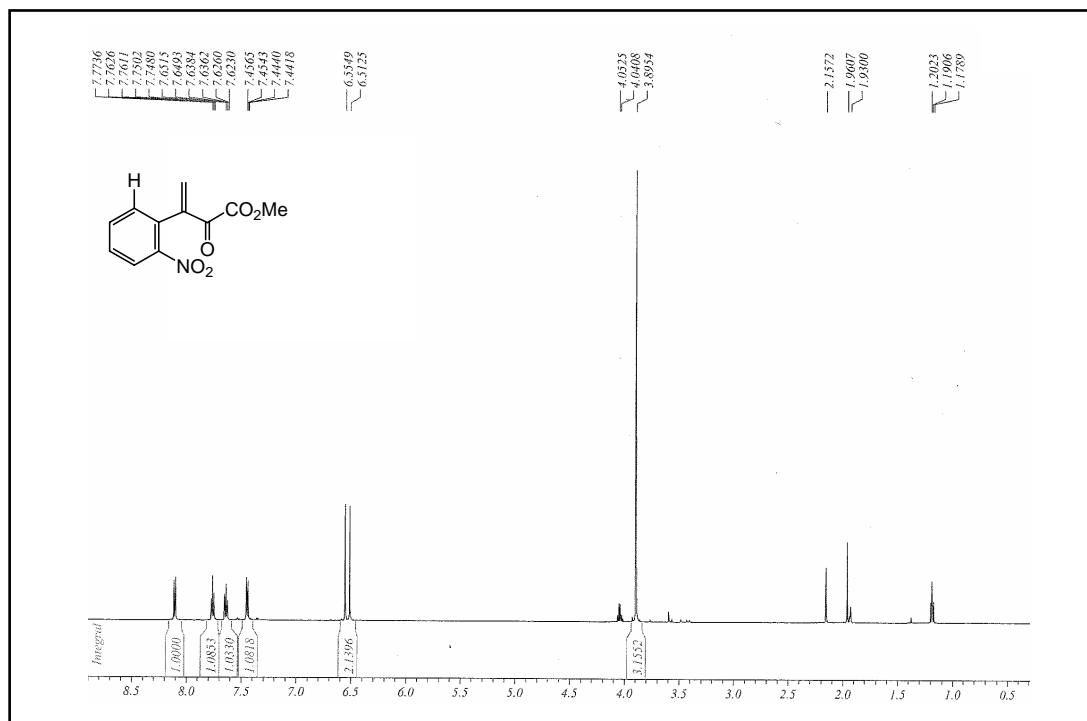




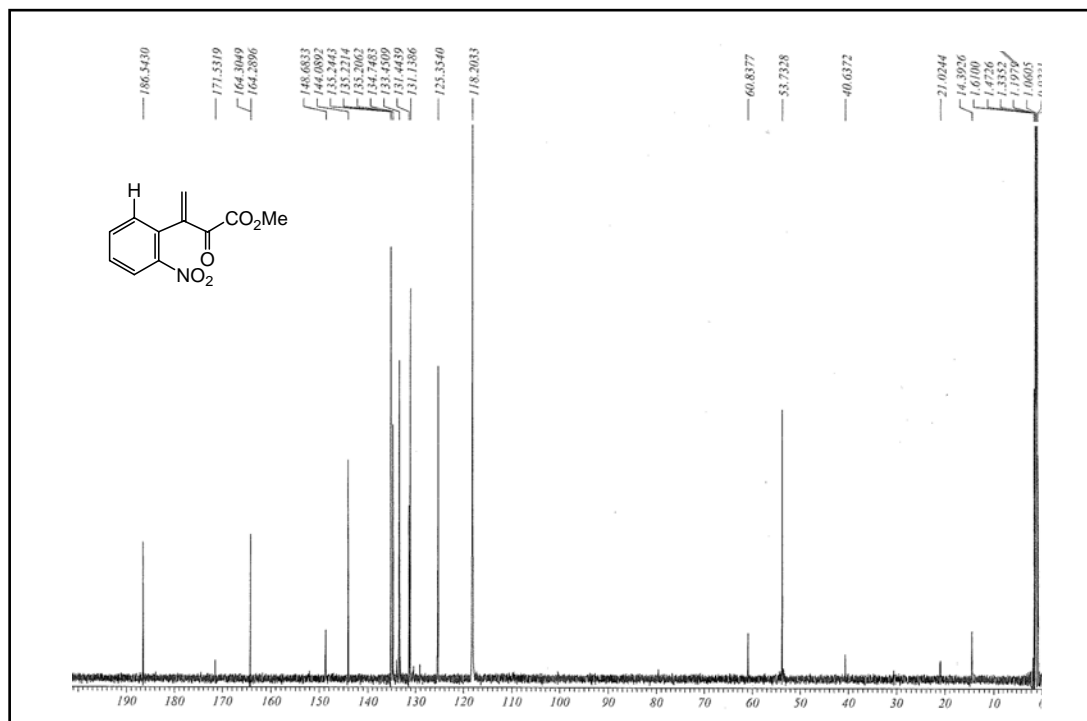
**Spectrum 2.17**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) spectrum of compound **2.8a**.



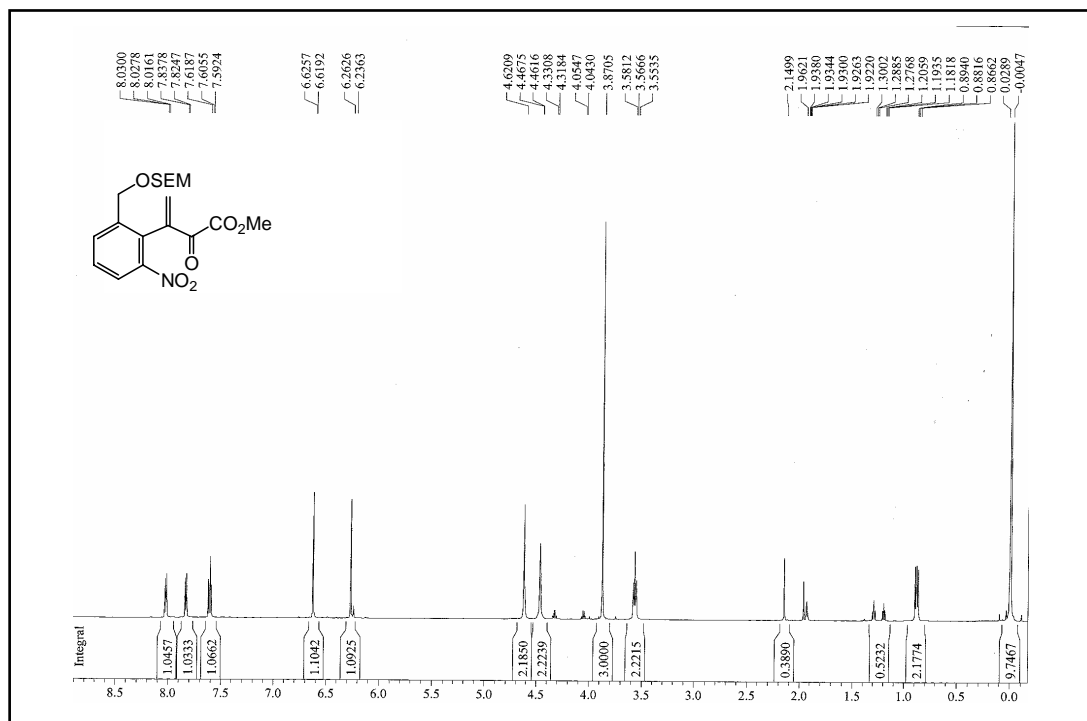
**Spectrum 2.18**  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) spectrum of compound **2.8a**.



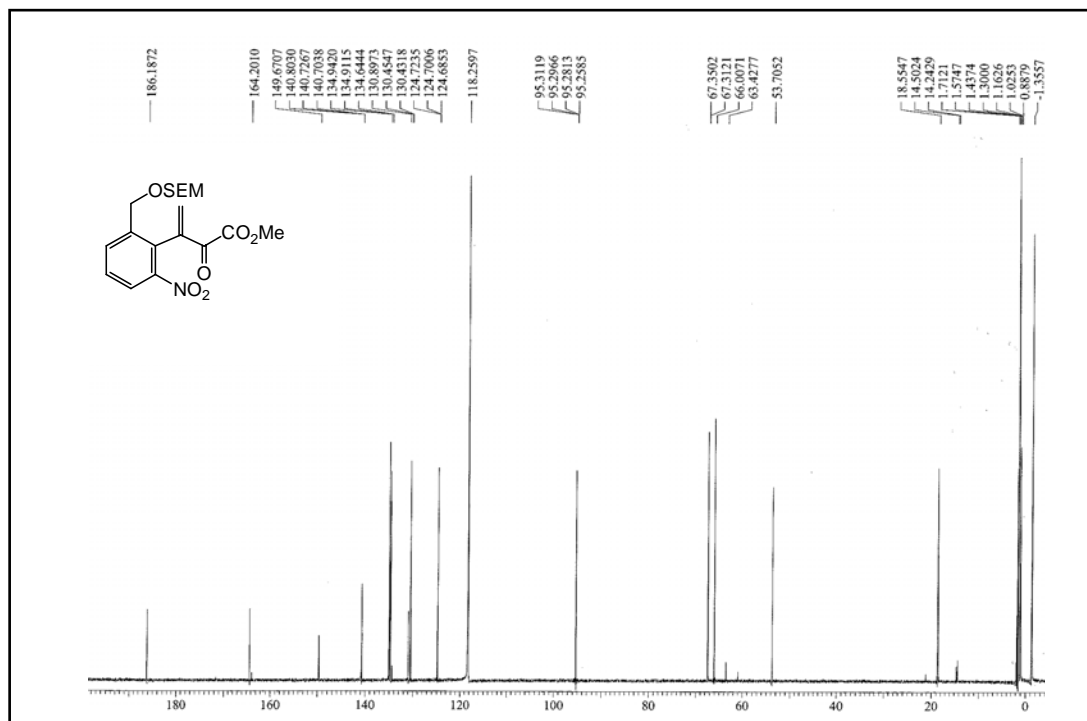
Spectrum 2.19  $^1\text{H NMR}$  (600 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.8b.



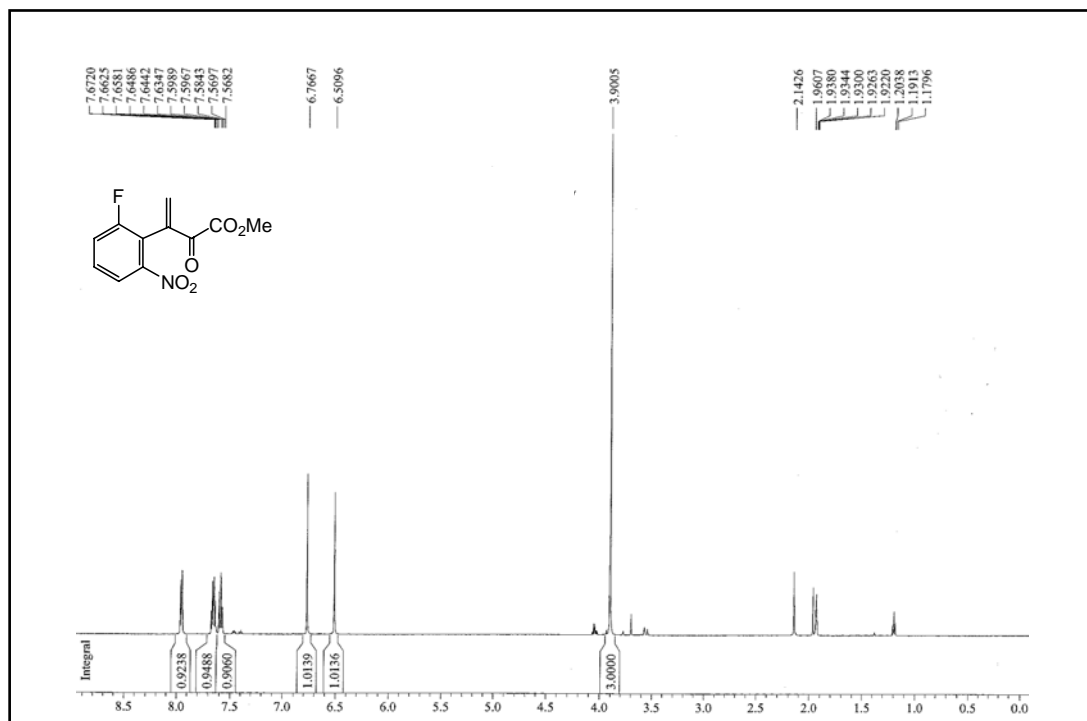
Spectrum 2.20  $^{13}\text{C NMR}$  (150 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.8b.



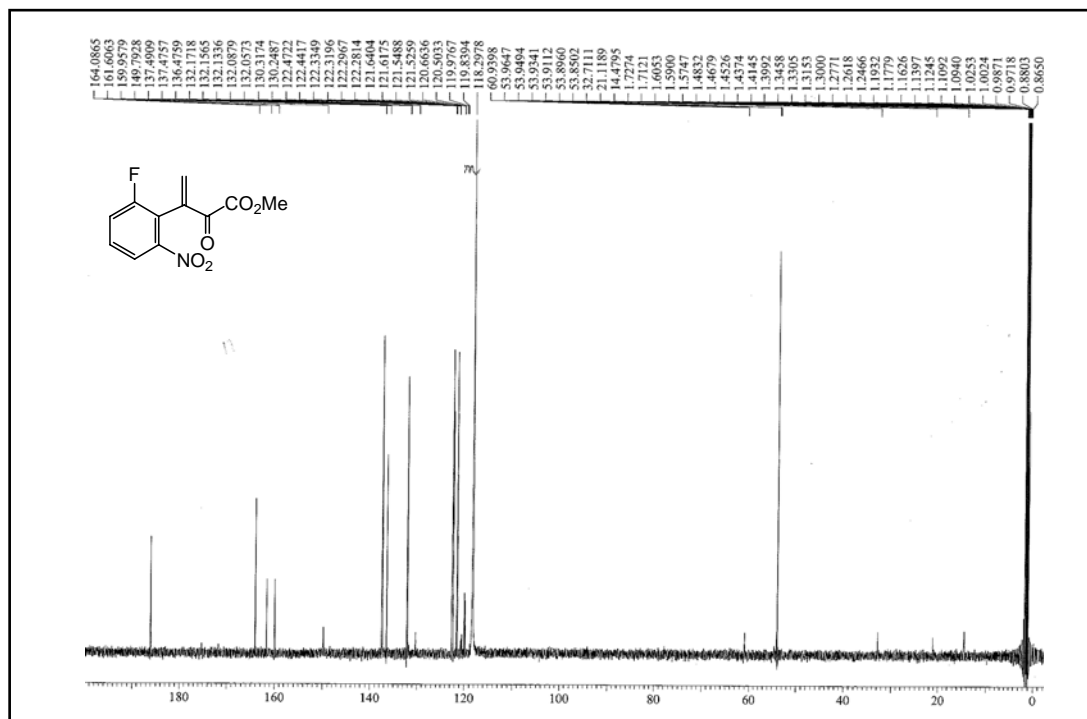
Spectrum 2.21 <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN) spectrum of compound 2.8c.



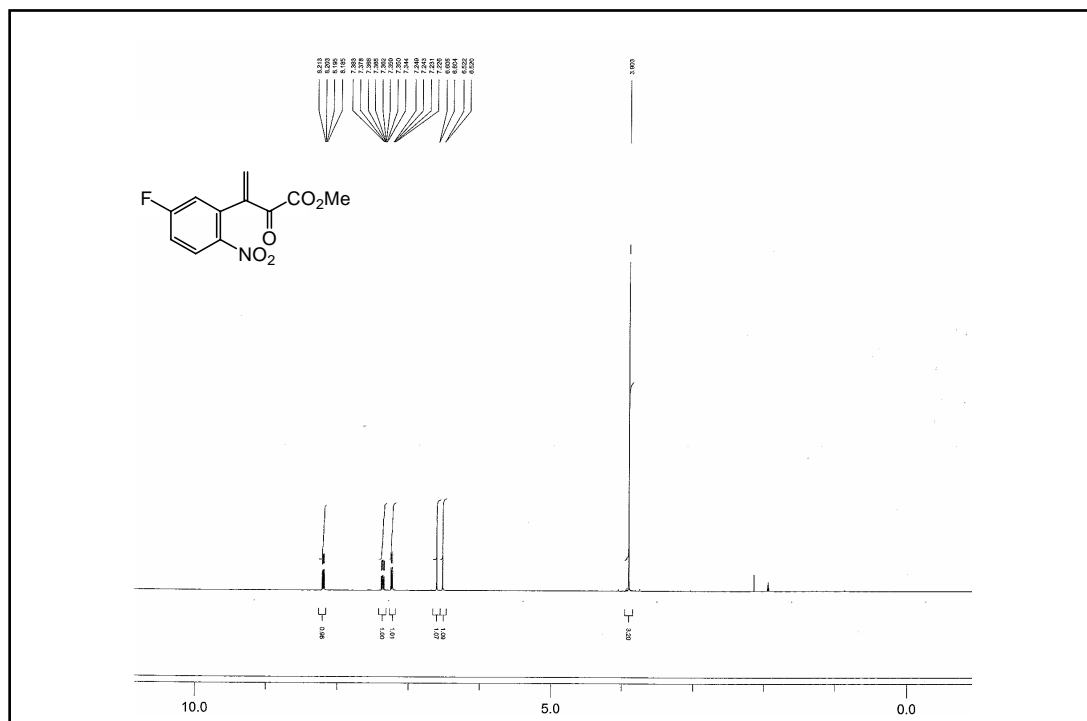
Spectrum 2.22 <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>CN) spectrum of compound 2.8c.



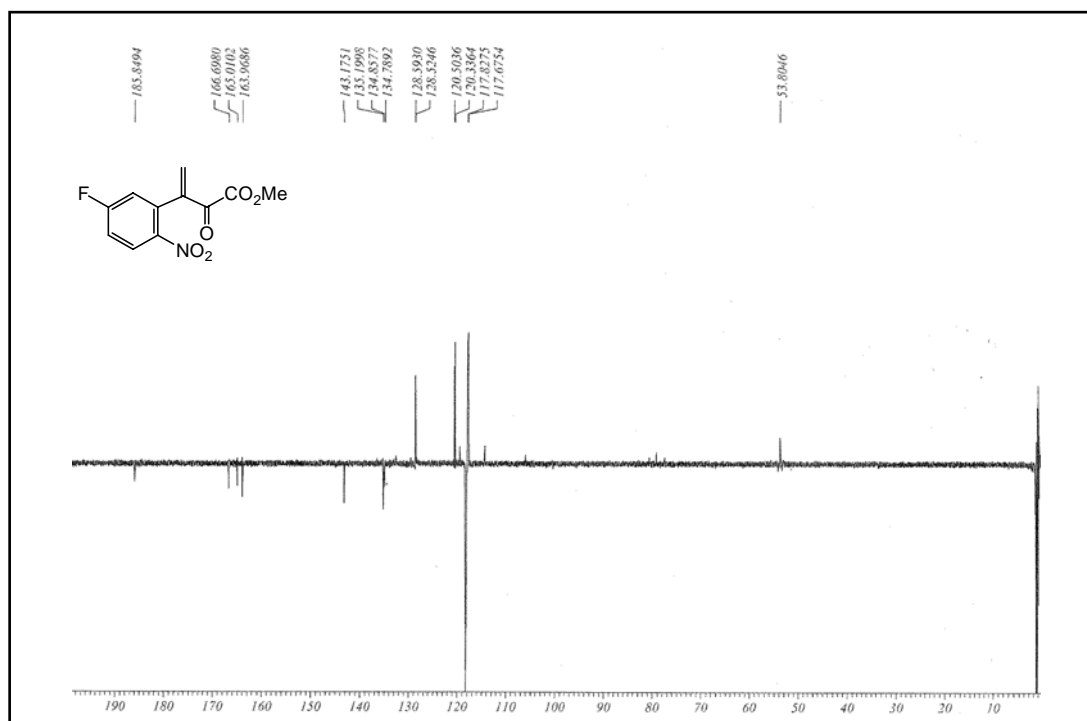
Spectrum 2.23 <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>CN) spectrum of compound 2.8d.



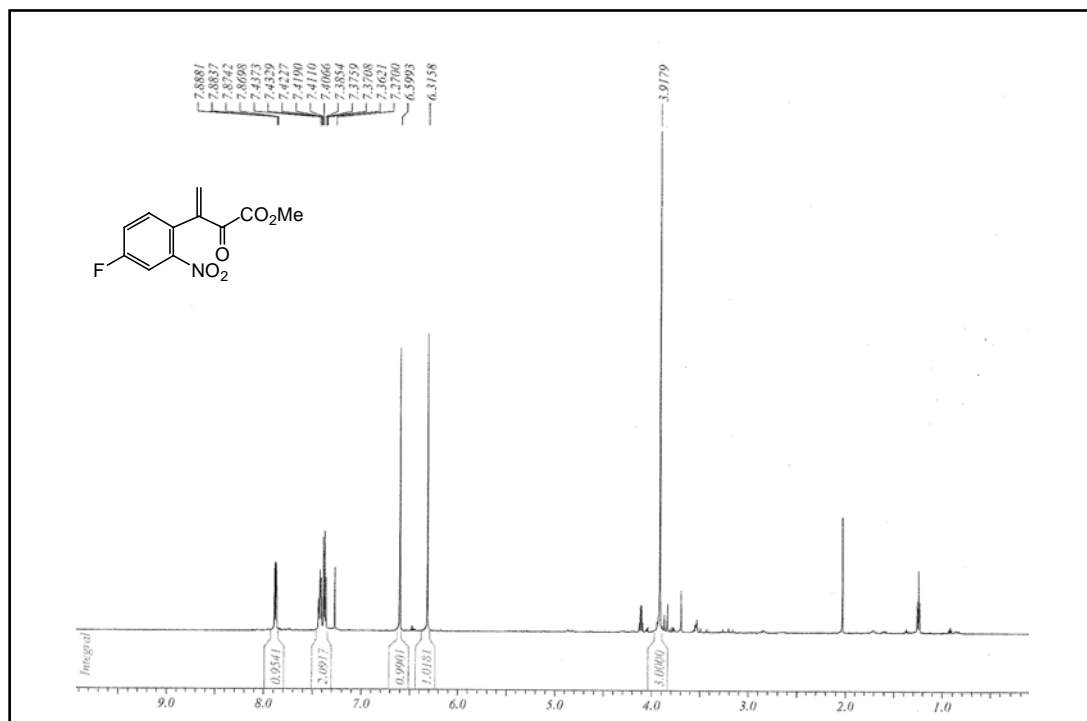
Spectrum 2.24 <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>CN) spectrum of compound 2.8d.



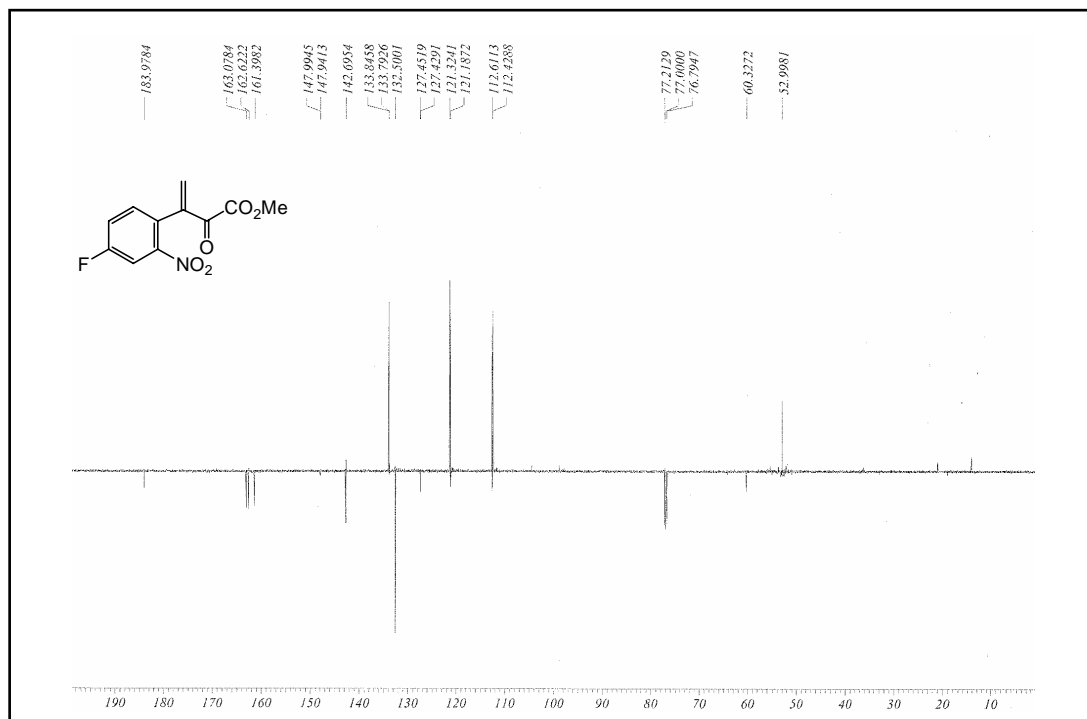
**Spectrum 2.25**  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ) spectrum of compound **2.8e**.



**Spectrum 2.26**  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ) spectrum of compound **2.8e**.

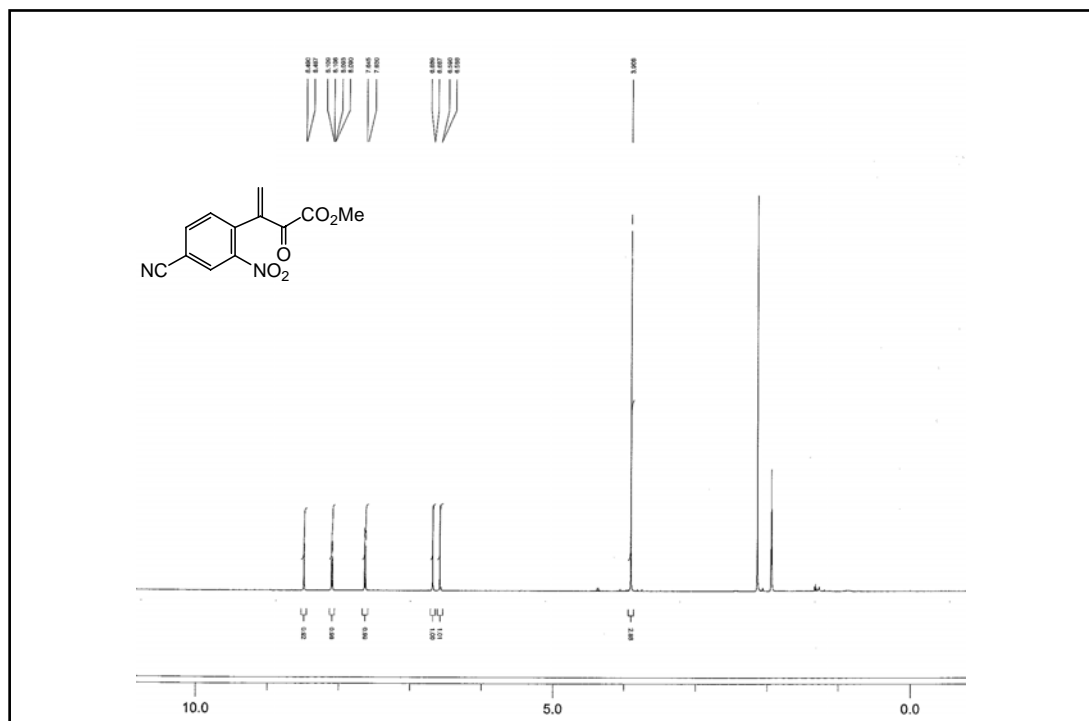


**Spectrum 2.27**  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ) spectrum of compound **2.8f**.

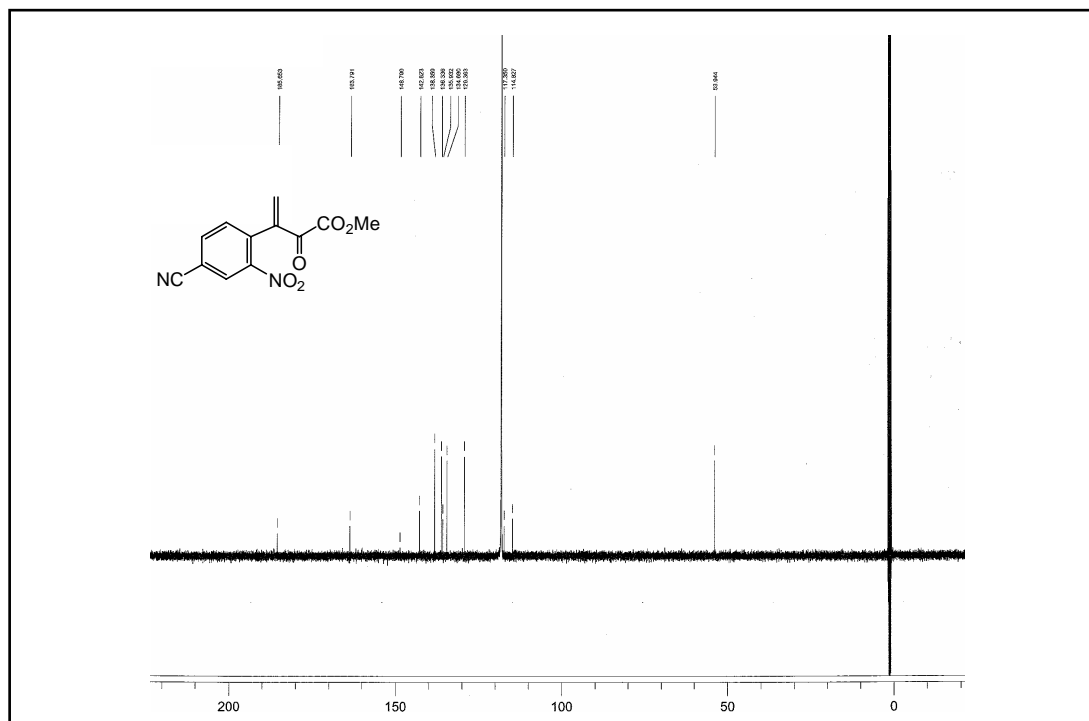


**Spectrum 2.28**  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ) spectrum of compound **2.8f**.

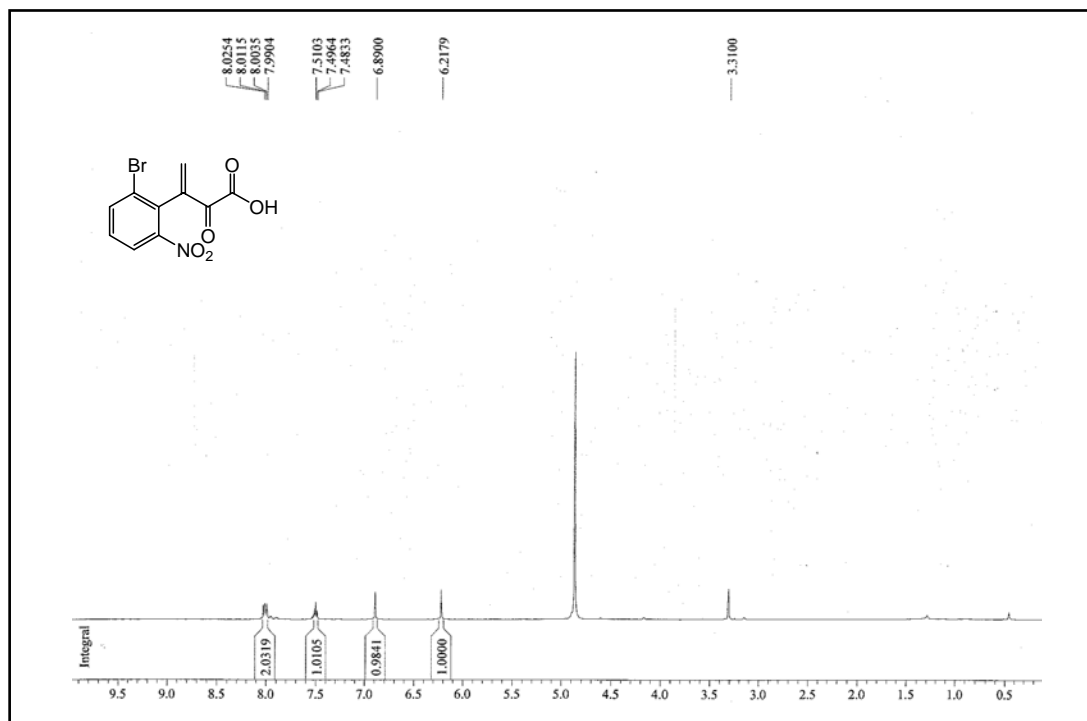




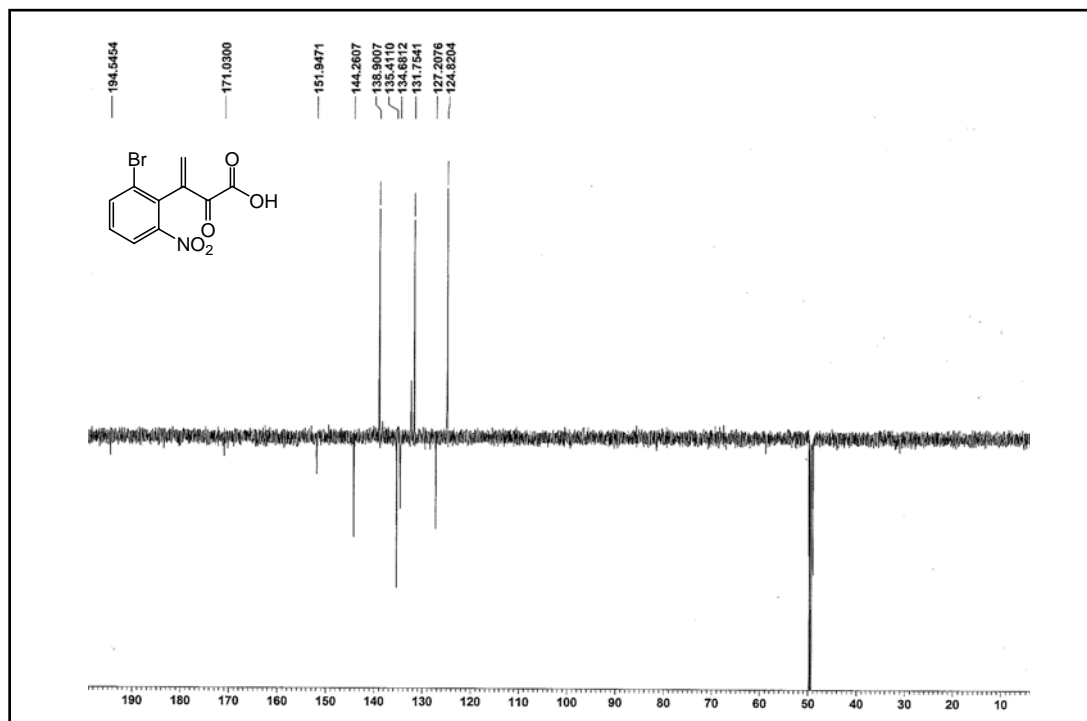
**Spectrum 2.29**  $^1\text{H}$  NMR (400 MHz, CDCl<sub>3</sub>) spectrum of compound **2.8g**.



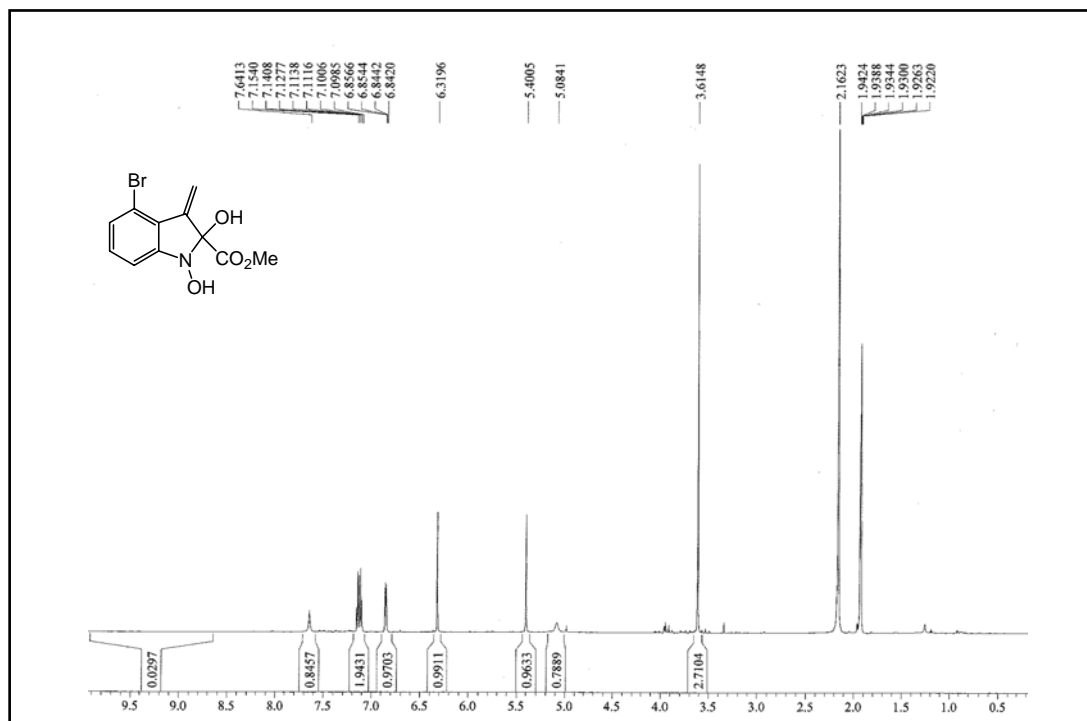
**Spectrum 2.30**  $^{13}\text{C}$  NMR (125 MHz, CD<sub>3</sub>CN) spectrum of compound **2.8g**.



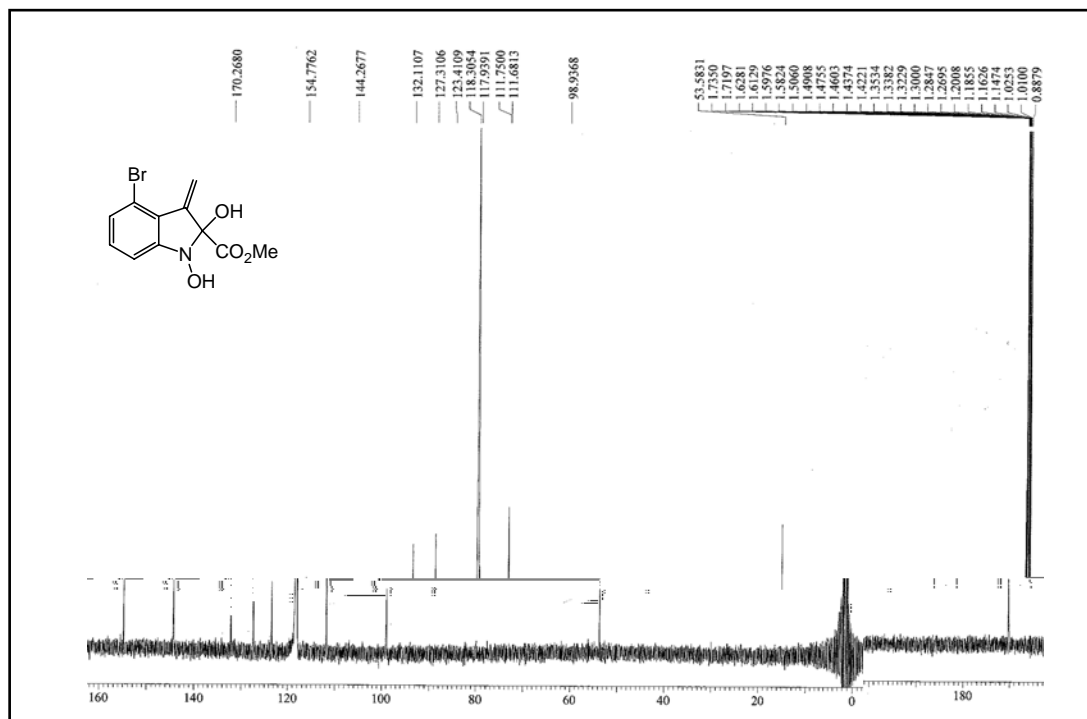
**Spectrum 2.31**  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{OD}$ ) spectrum of compound **2.9a**.



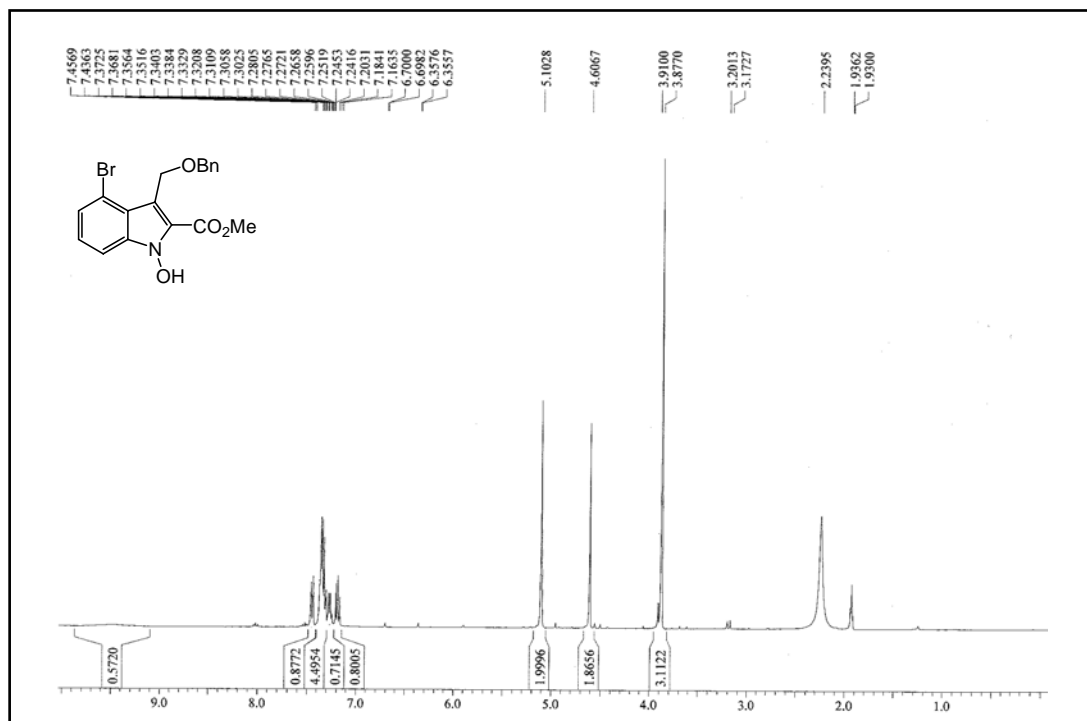
**Spectrum 2.32**  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{OD}$ ) spectrum of compound **2.9a**.



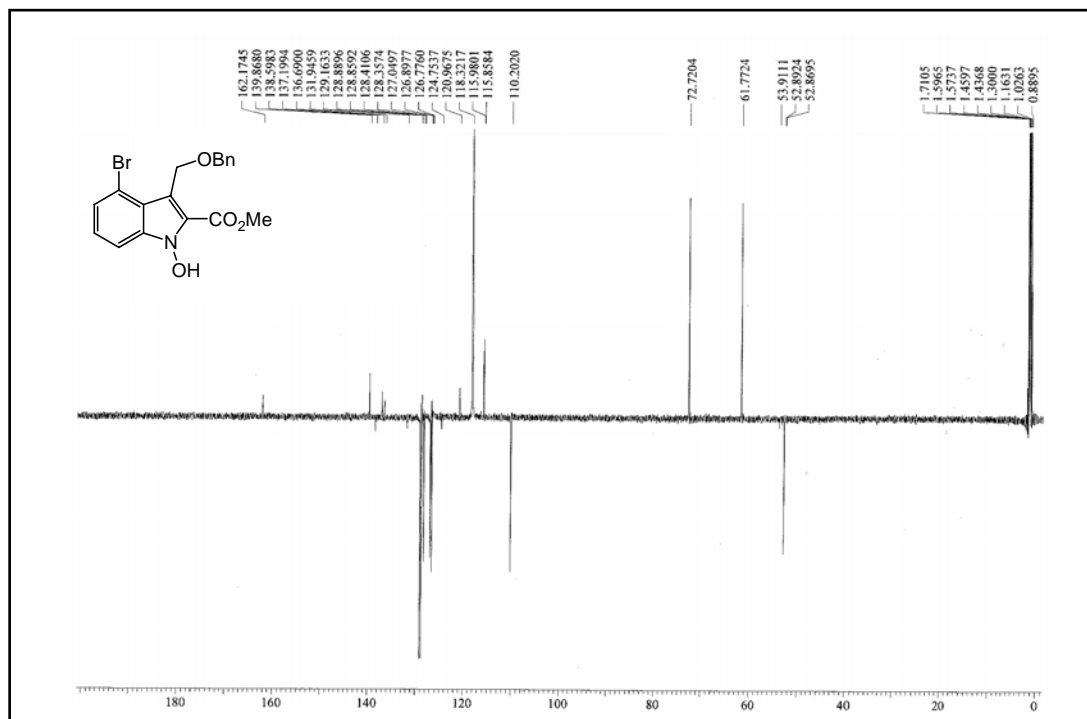
**Spectrum 2.33**  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.11**.



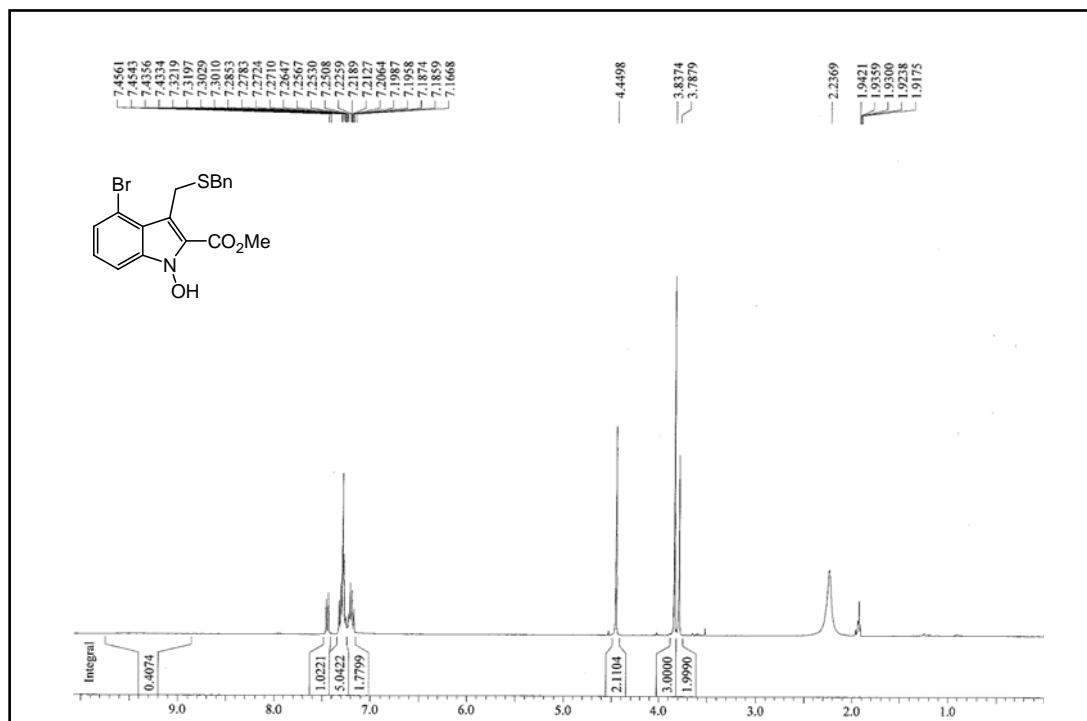
**Spectrum 2.34**  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.11**.



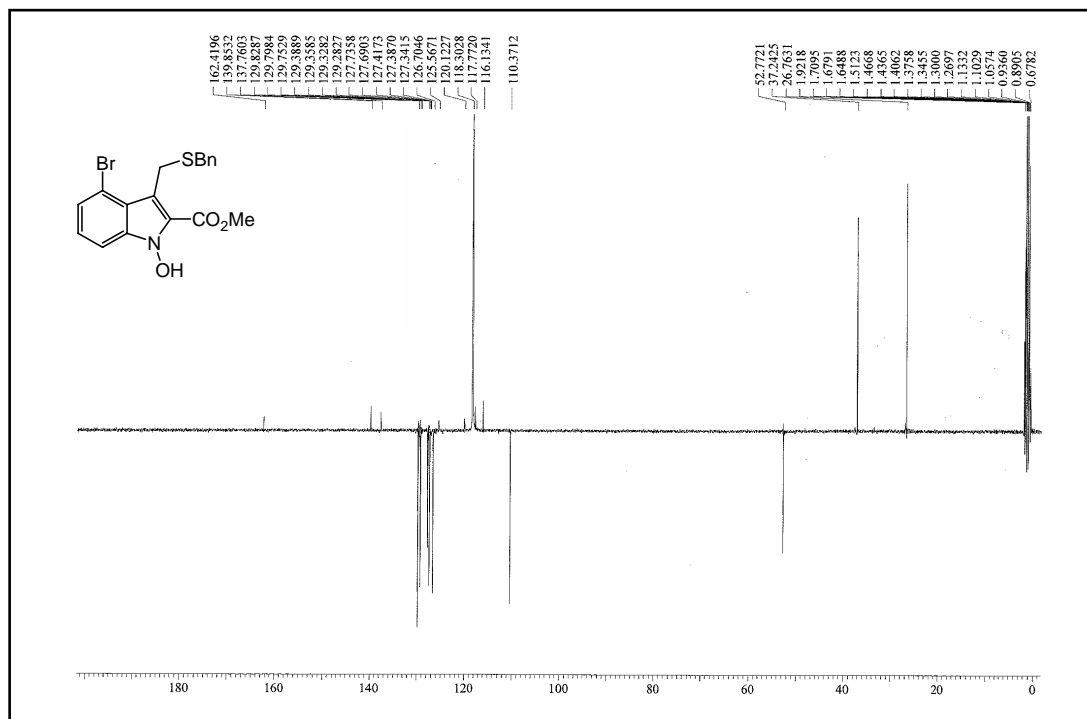
Spectrum 2.35  $^1\text{H NMR}$  (400 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.13.



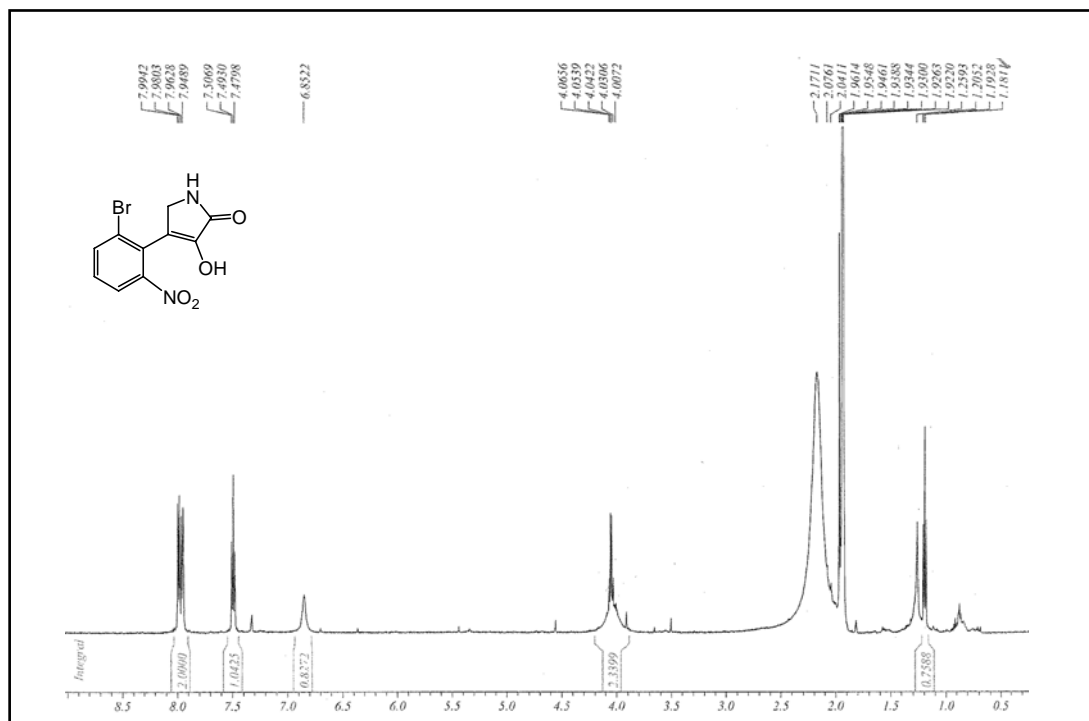
Spectrum 2.36  $^{13}\text{C NMR}$  (150 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.13.



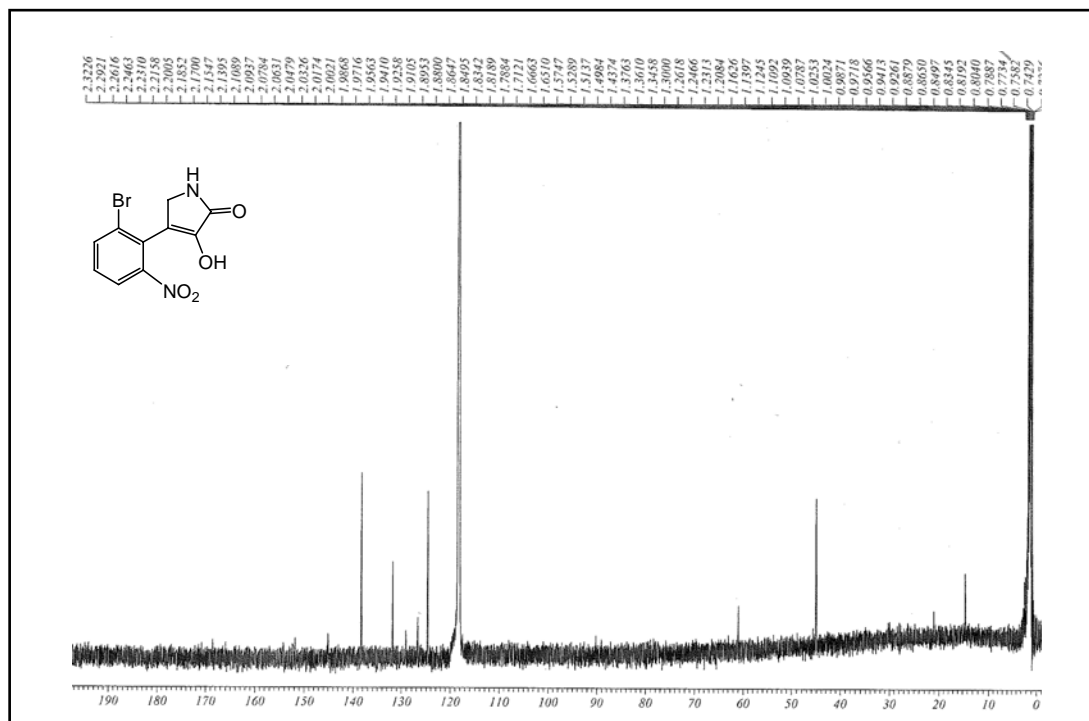
Spectrum 2.37 <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN) spectrum of compound 2.14.

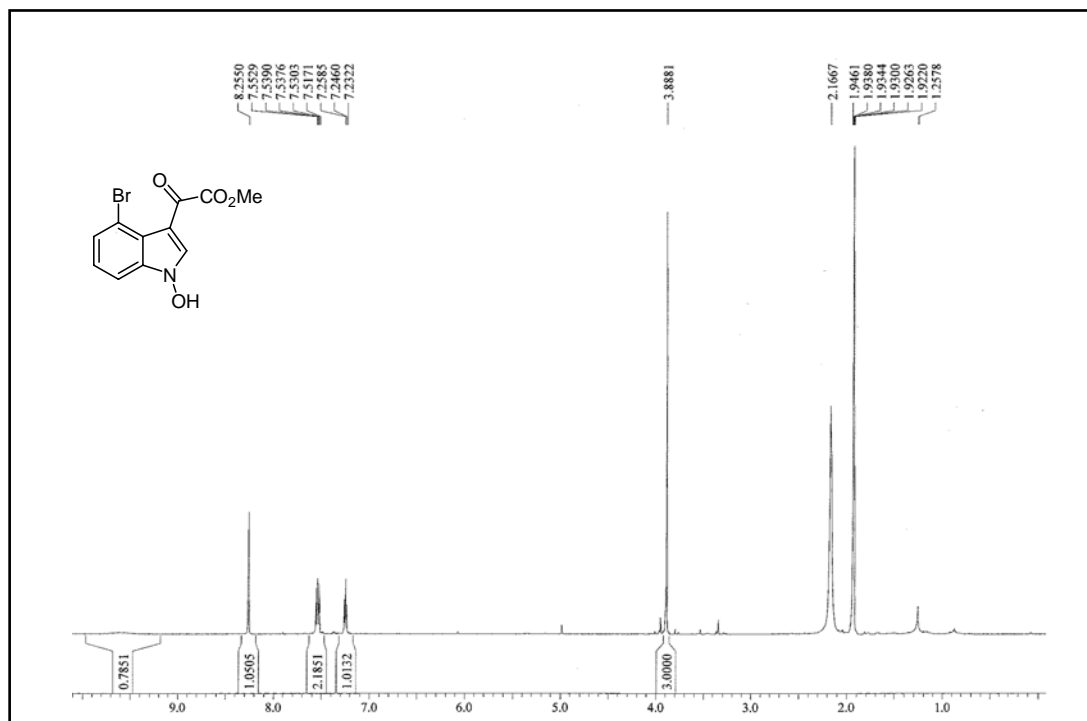


Spectrum 2.38 <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>CN) spectrum of compound 2.14.

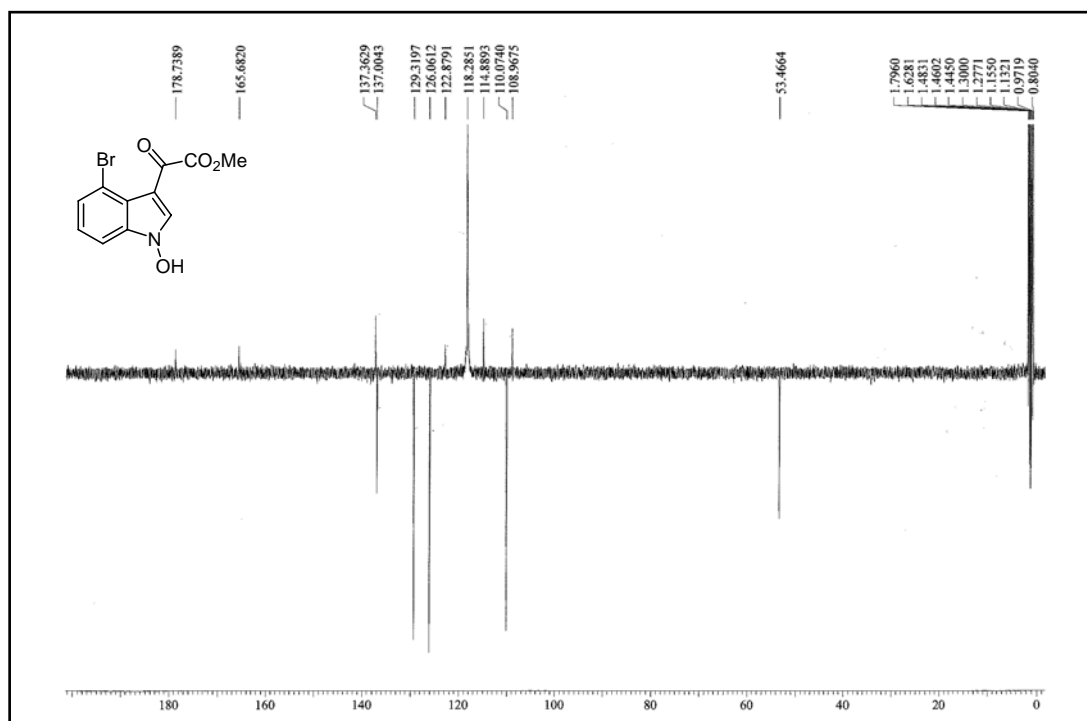


Spectrum 2.39  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ) spectrum of compound 2.16.

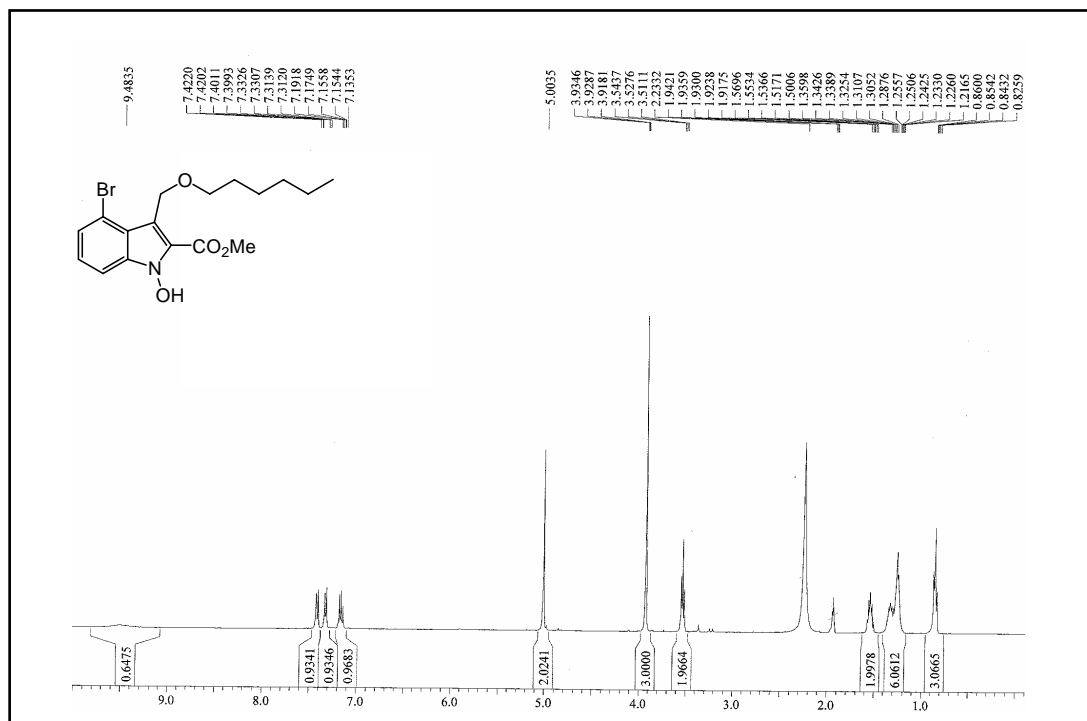




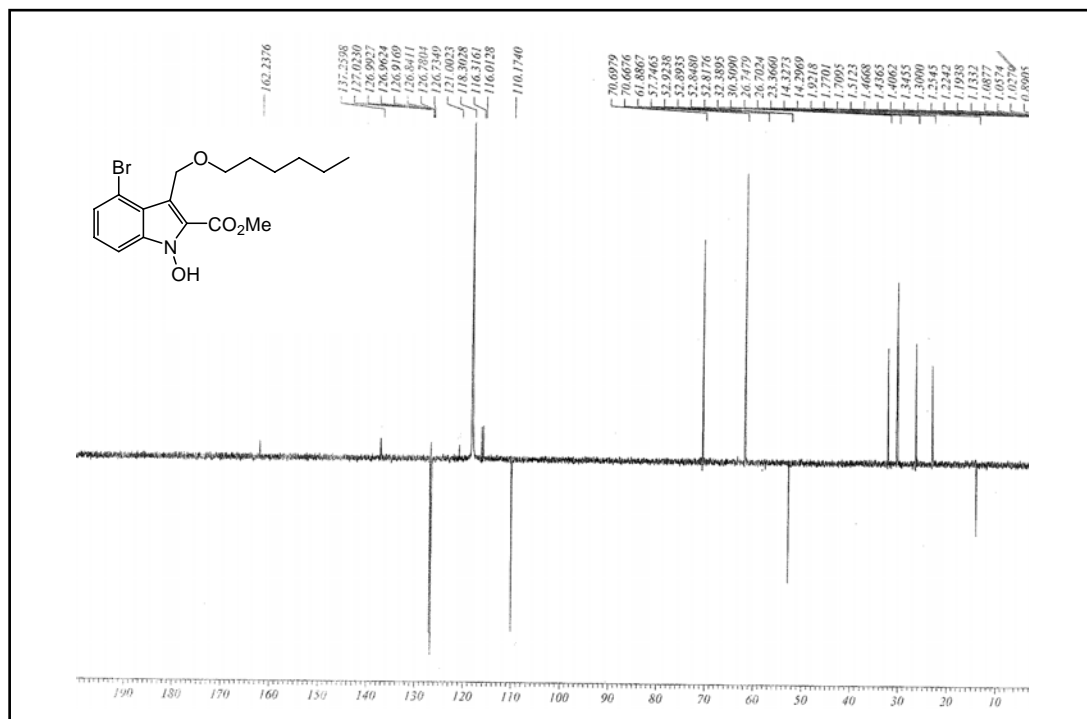
Spectrum 2.41  $^1\text{H NMR}$  (600 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.18.



Spectrum 2.42  $^{13}\text{C NMR}$  (125 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.18.

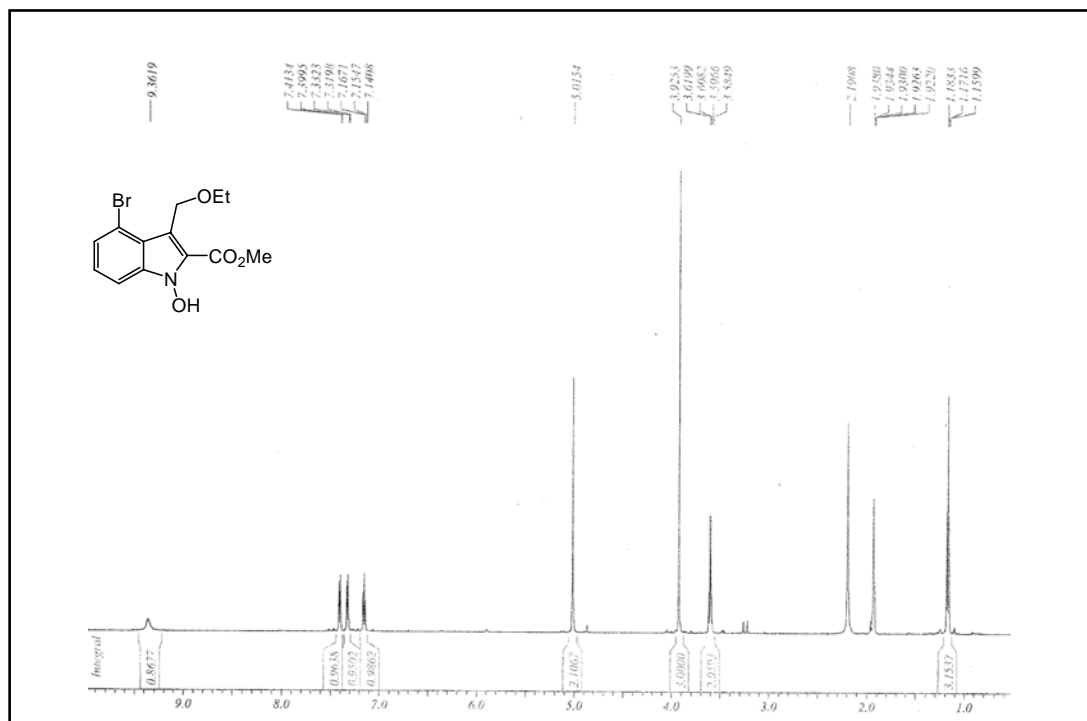


Spectrum 2.43  $^1\text{H NMR}$  (400 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.19.

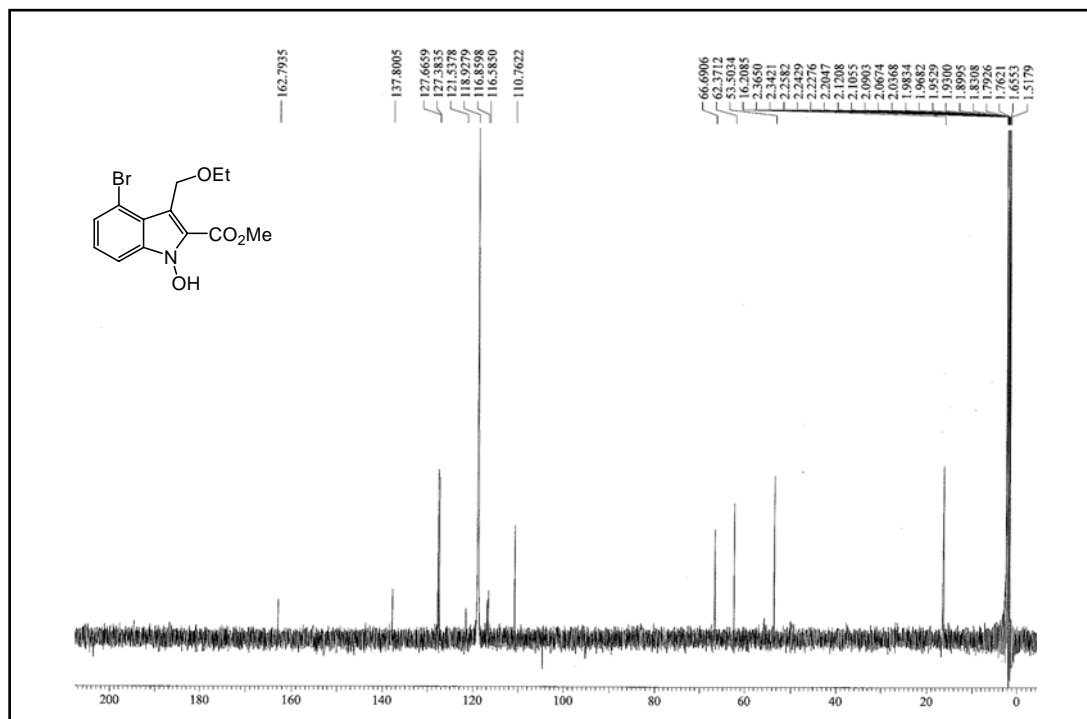


Spectrum 2.44  $^{13}\text{C NMR}$  (100 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.19.

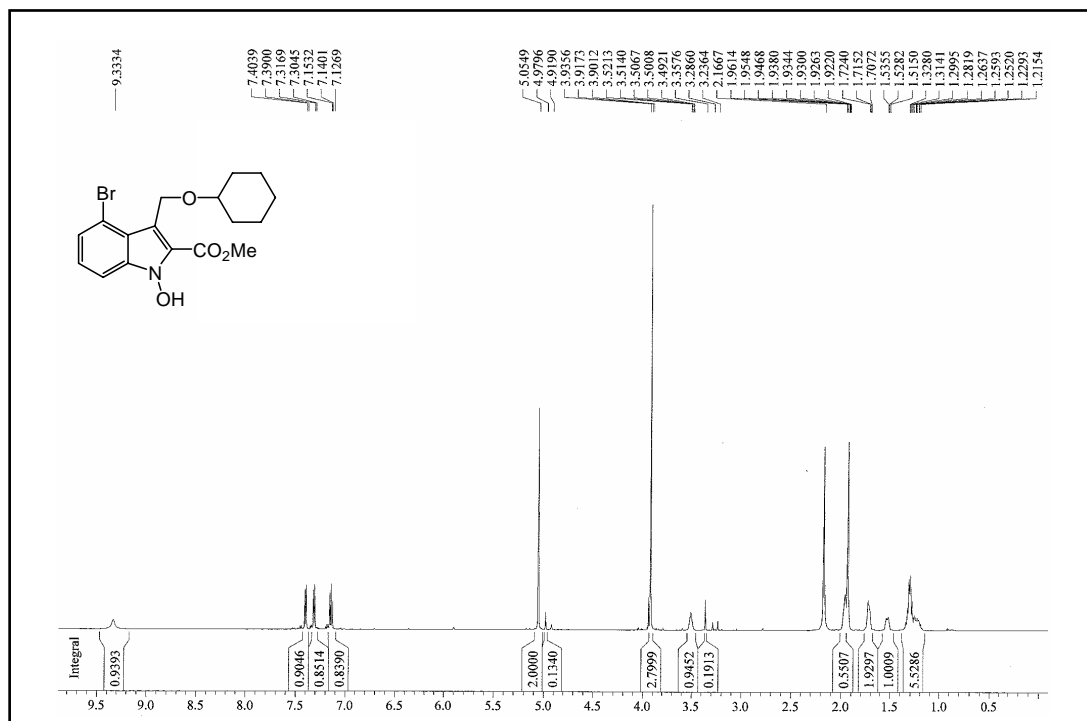




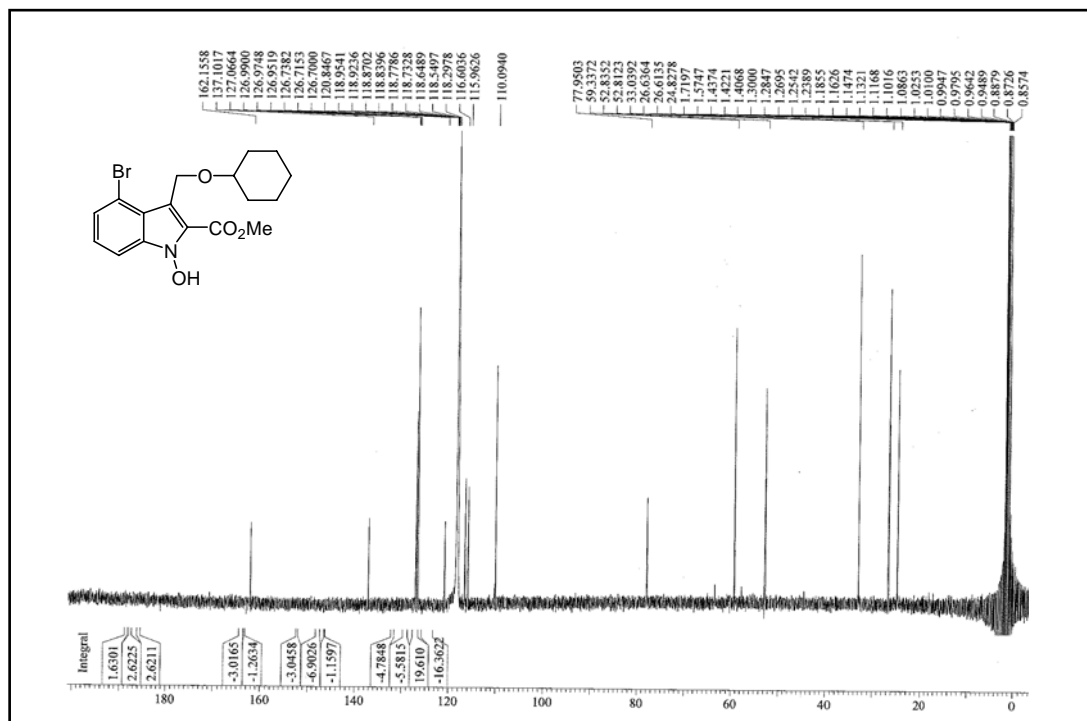
**Spectrum 2.45**  $^1\text{H NMR}$  (600 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.20.



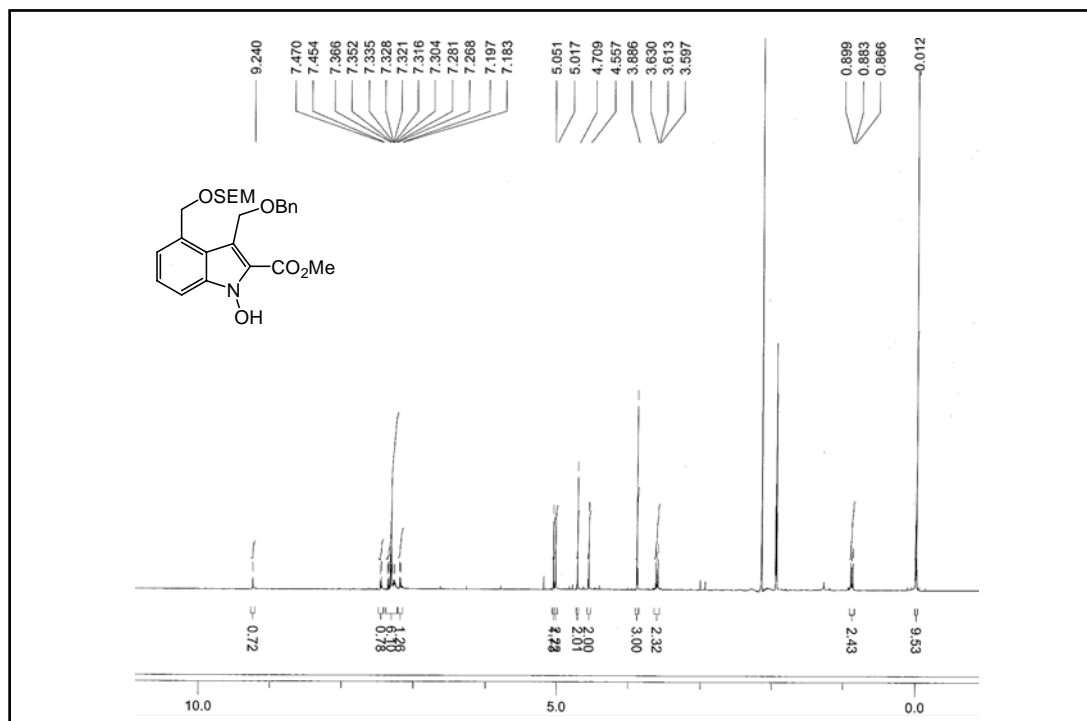
**Spectrum 2.46**  $^{13}\text{C NMR}$  (150 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.20.



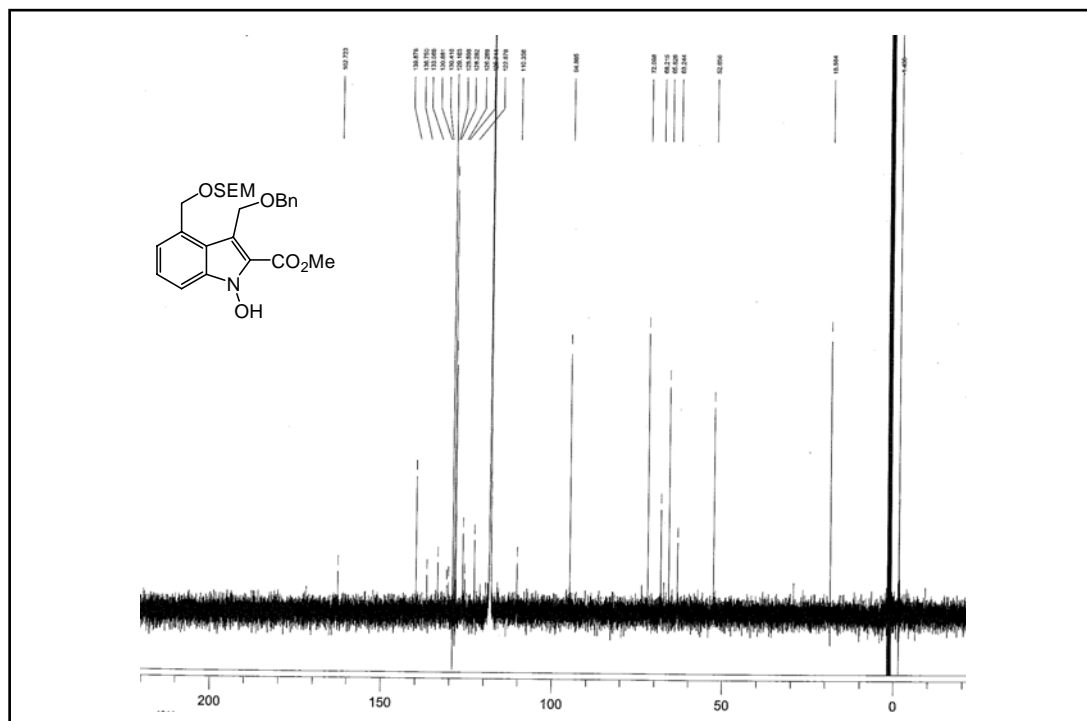
Spectrum 2.47 <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN) spectrum of compound 2.21.



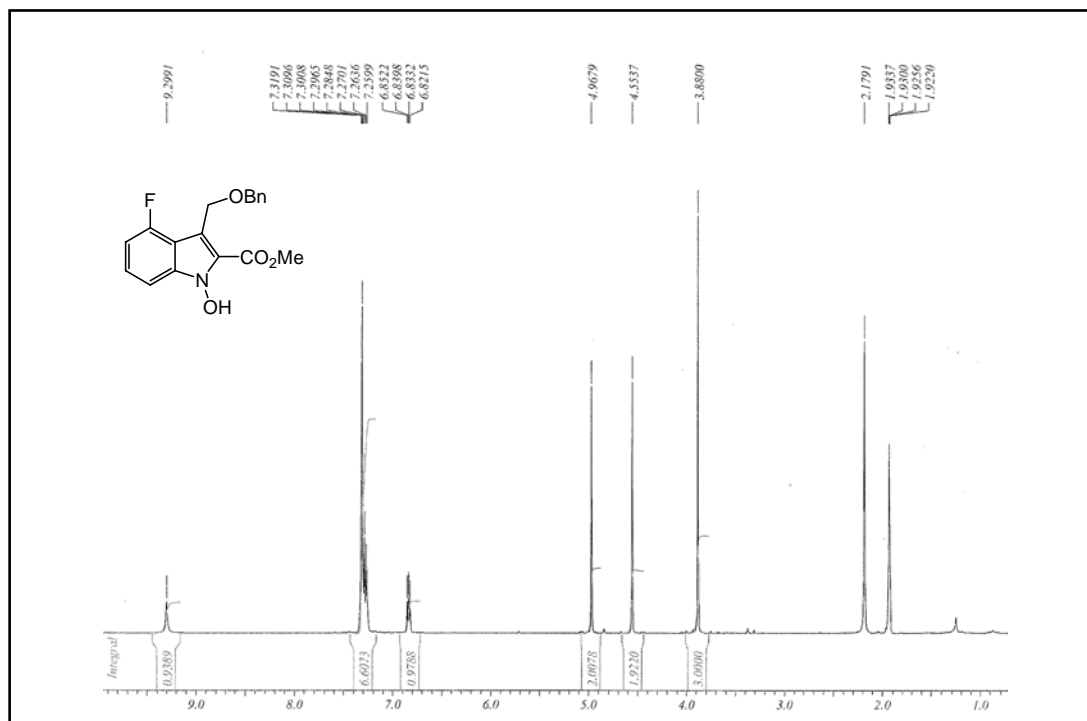
Spectrum 2.48 <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>CN) spectrum of compound 2.21.



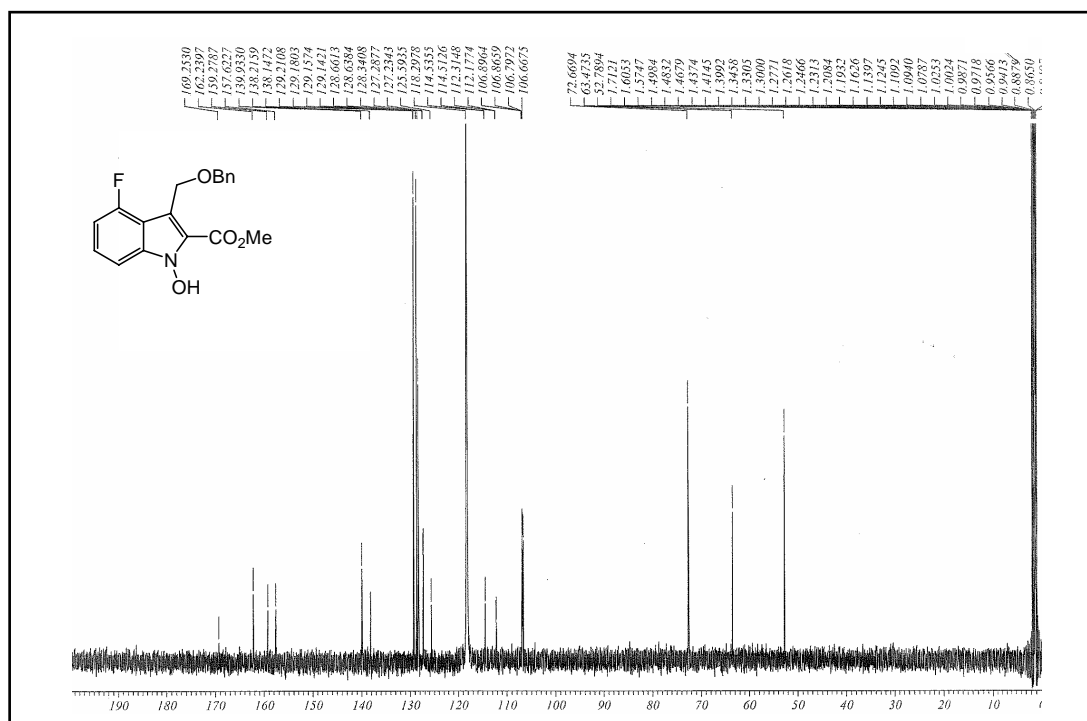
**Spectrum 2.49**  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.22**.



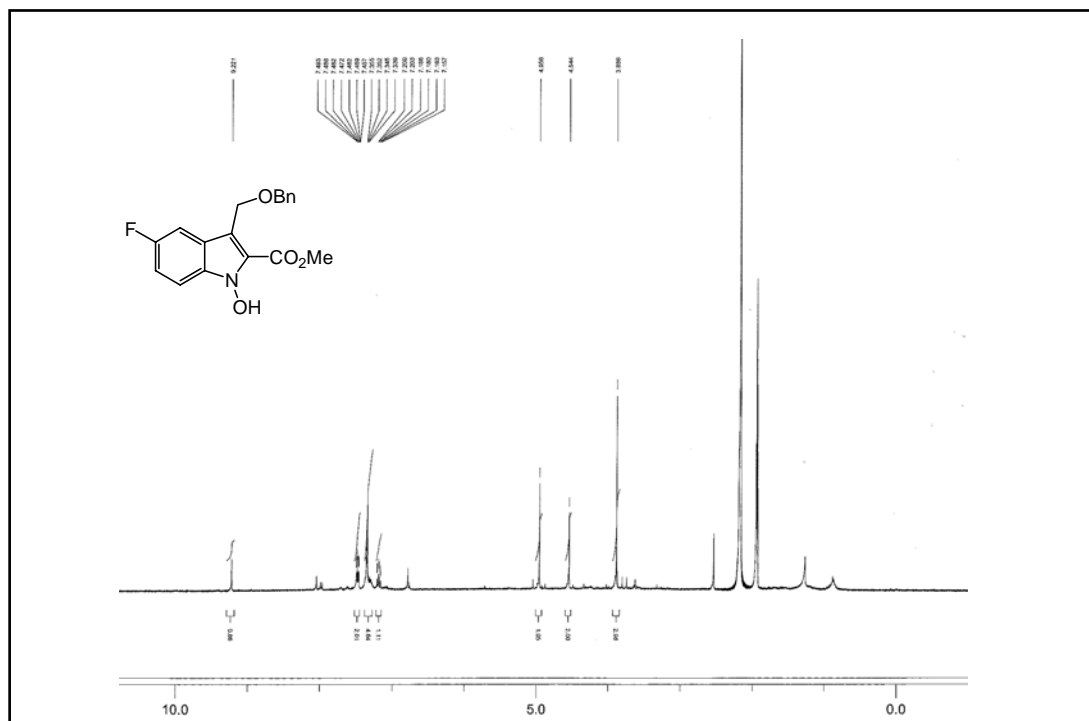
**Spectrum 2.50**  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.22**.



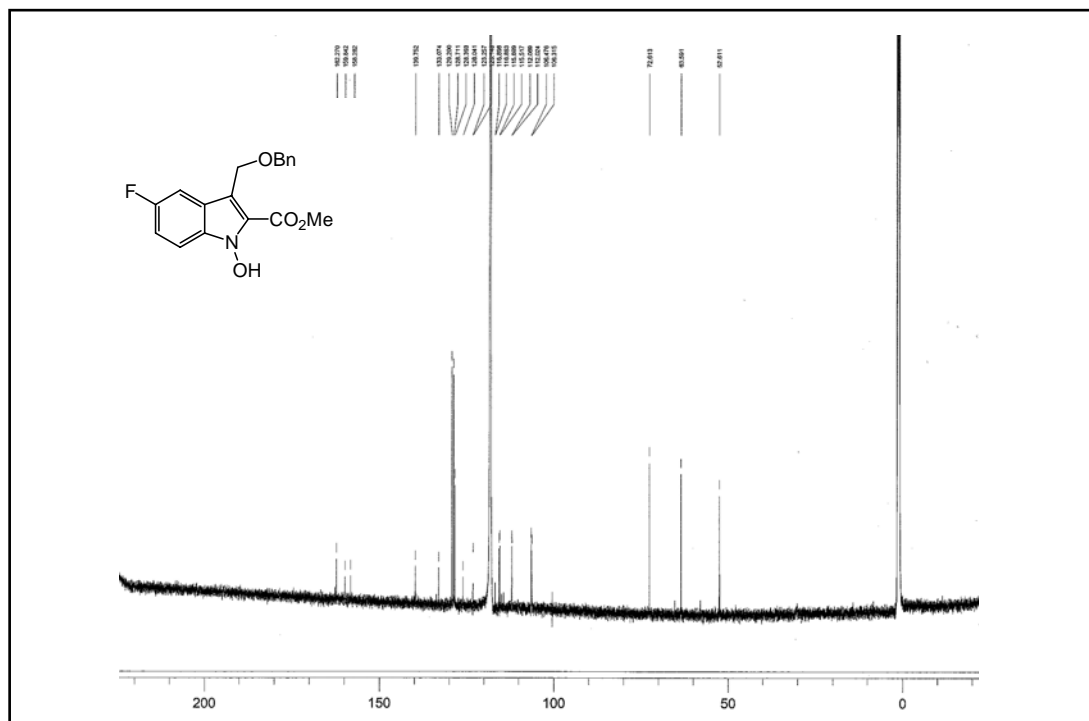
Spectrum 2.51 <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN) spectrum of compound 2.23.



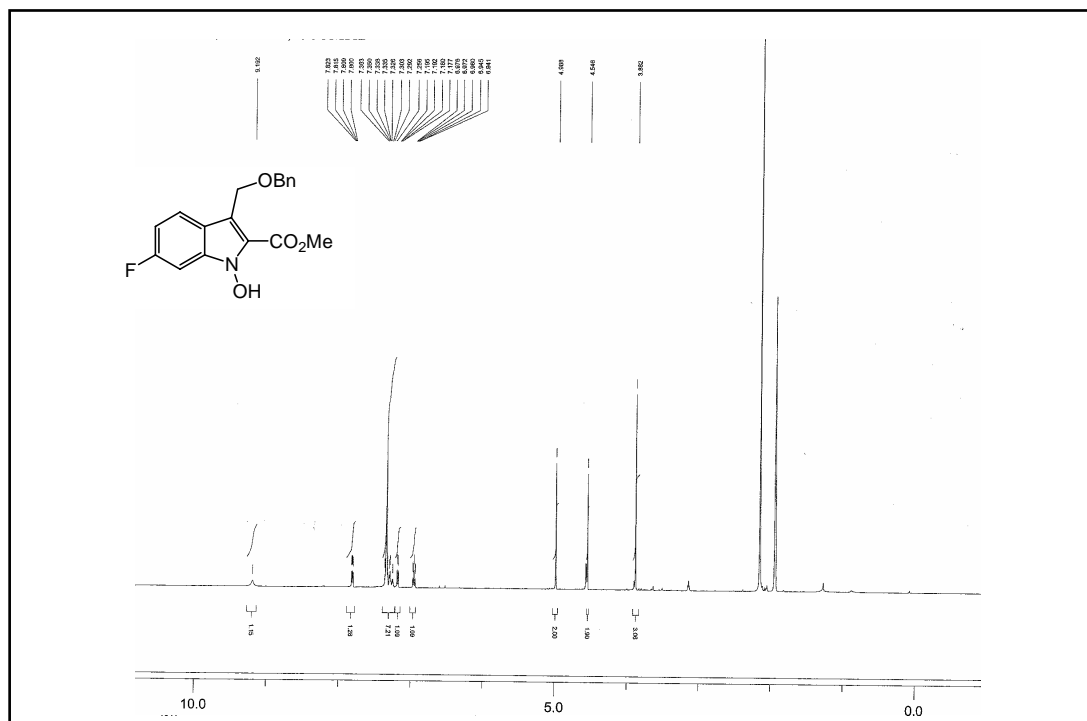
Spectrum 2.52 <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>CN) spectrum of compound 2.23.



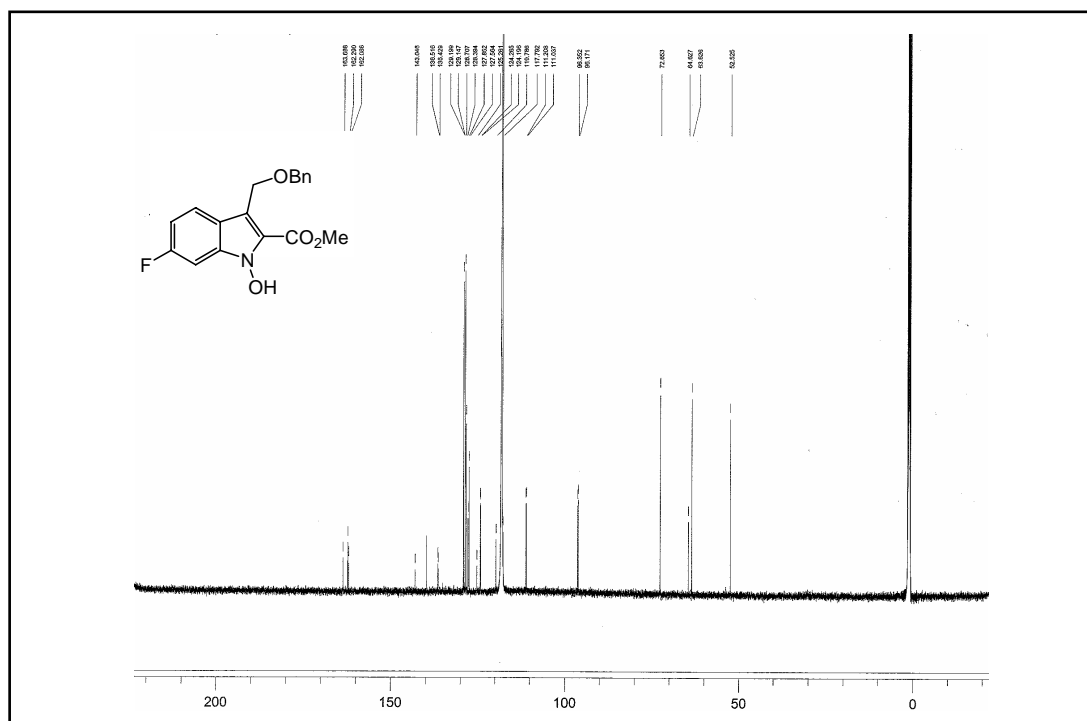
**Spectrum 2.53**  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.24.



**Spectrum 2.54**  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.24.

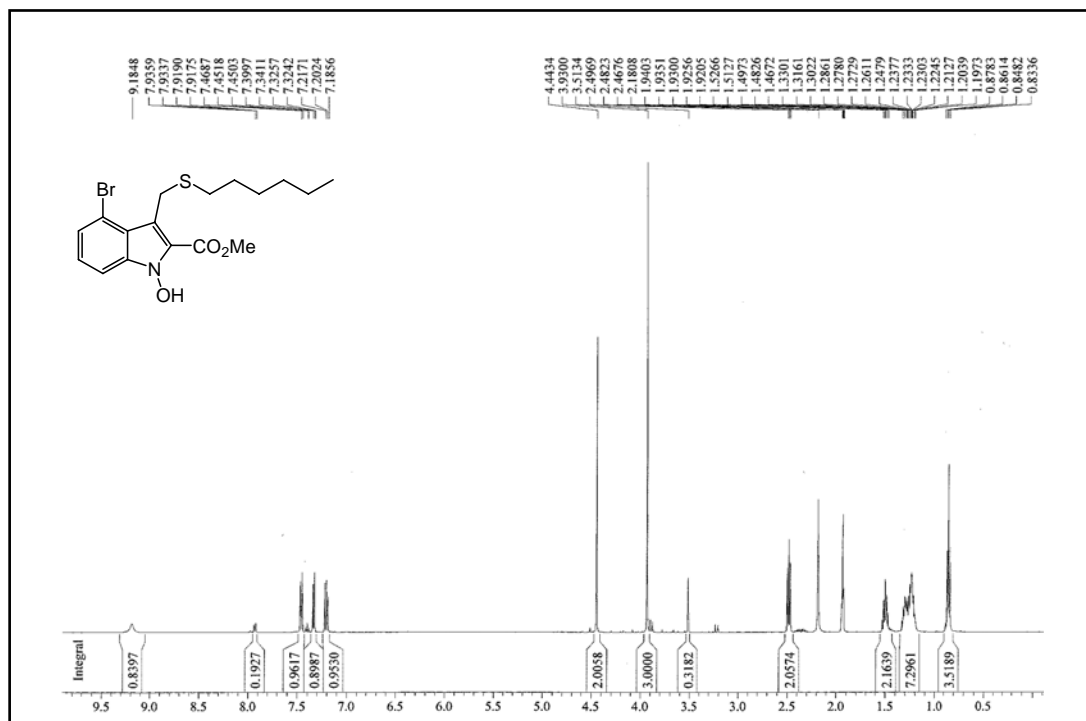


**Spectrum 2.55**  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.25.

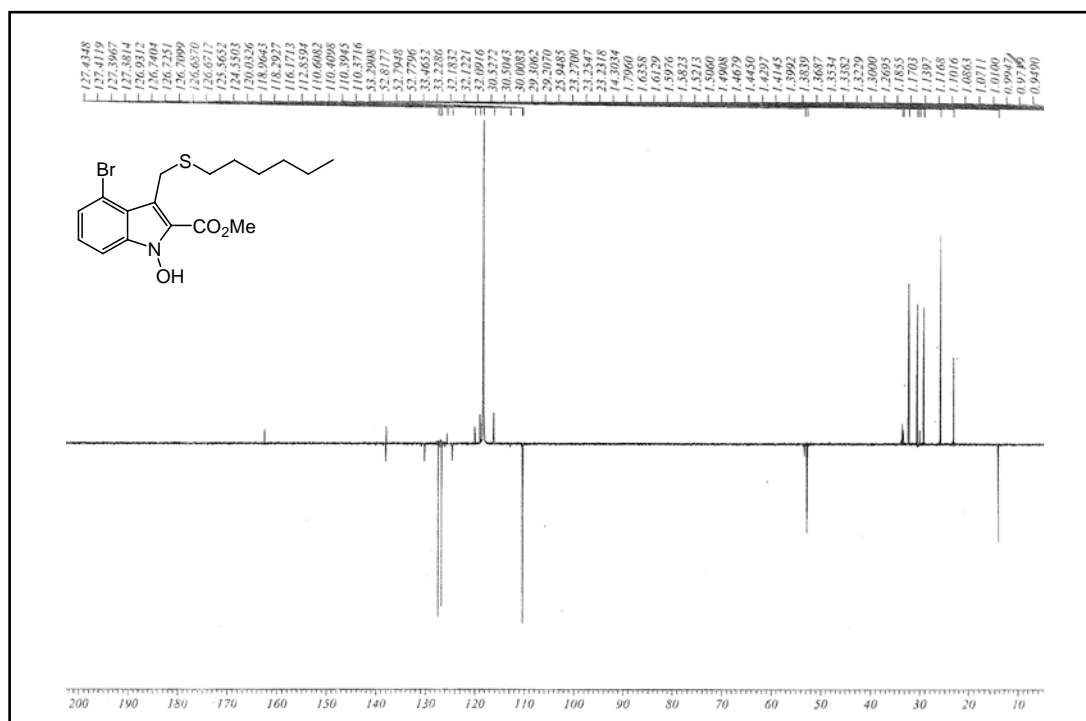


**Spectrum 2.56**  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.25.



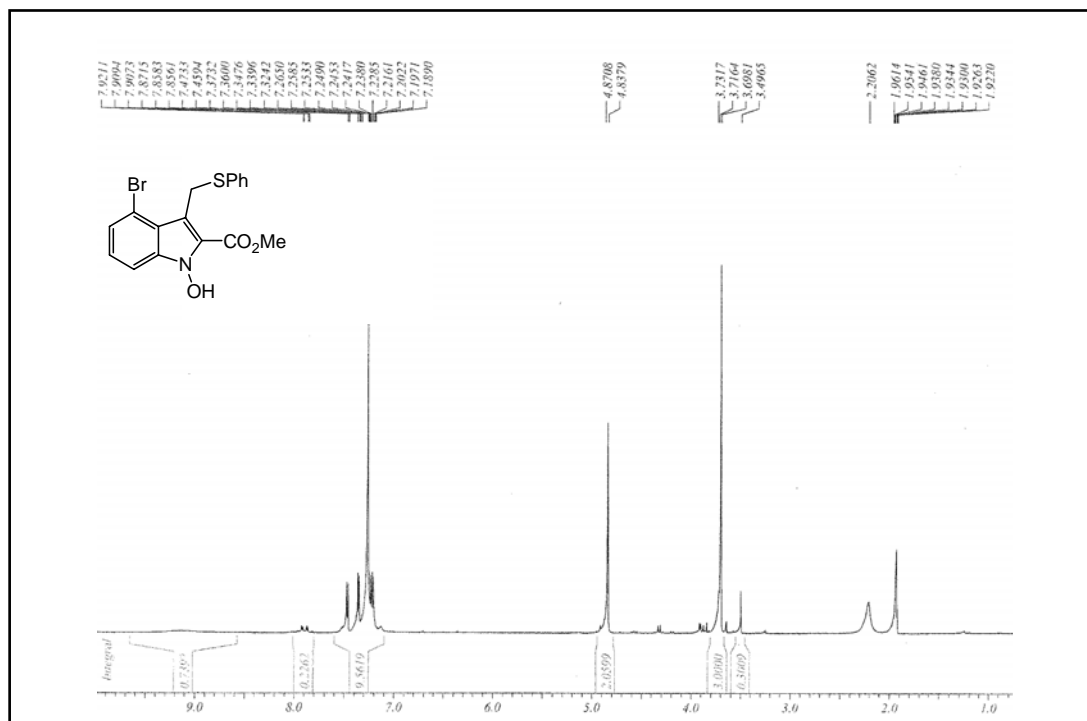


Spectrum 2.59 <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>CN) spectrum of compound 2.27.

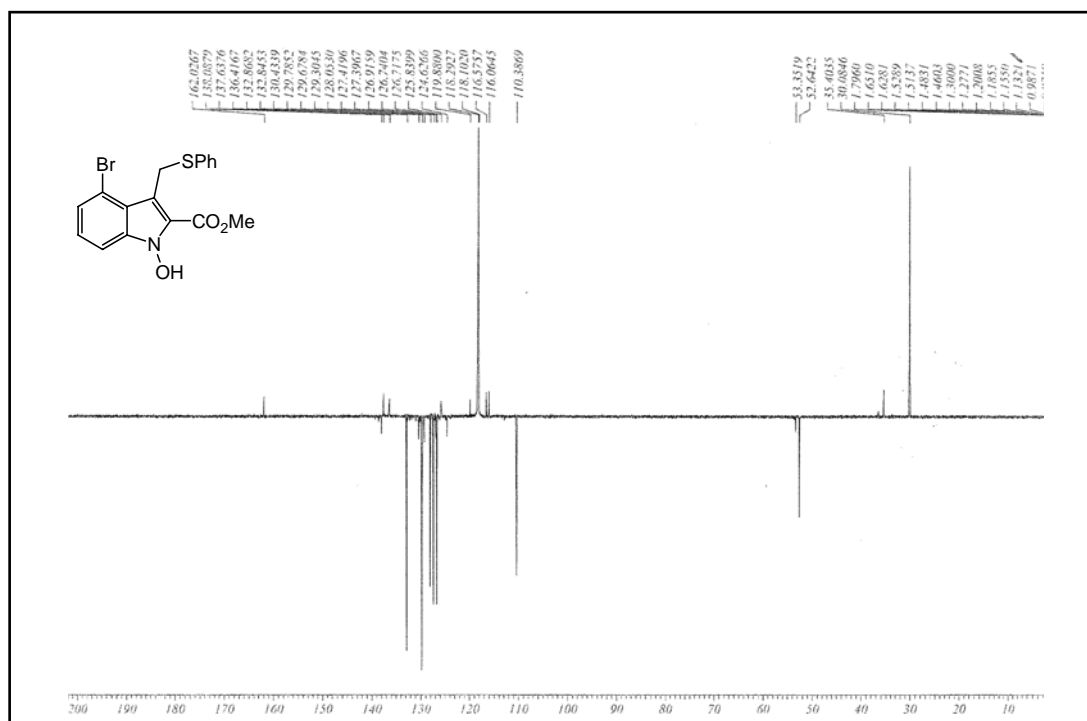


Spectrum 2.60 <sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>CN) spectrum of compound 2.27.

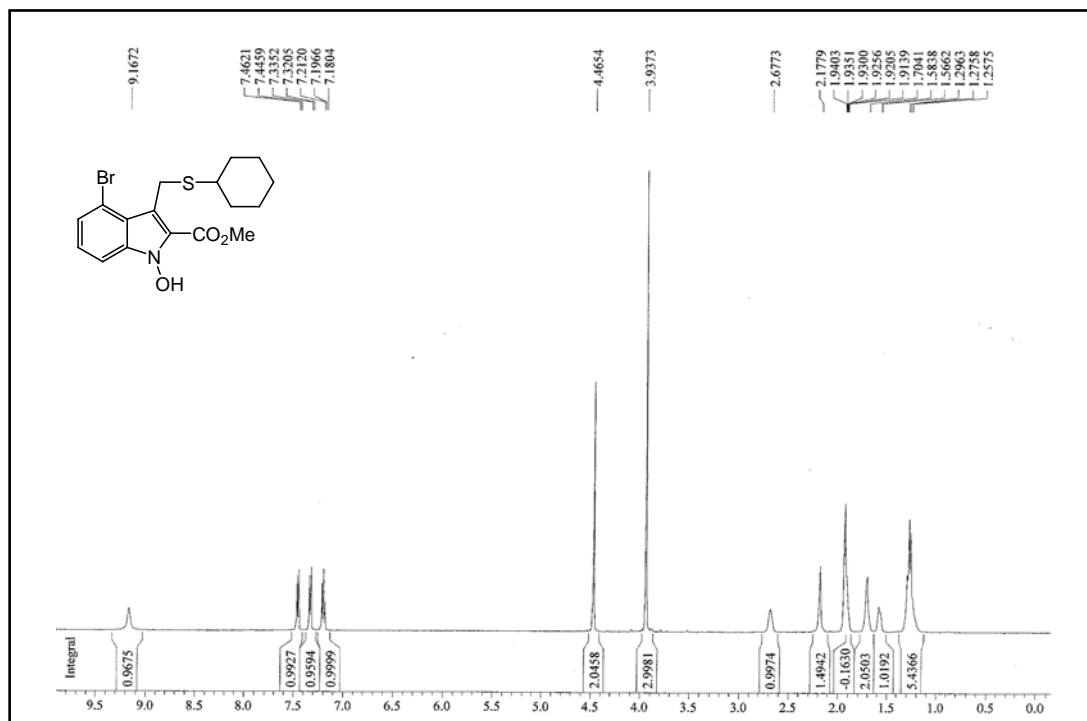




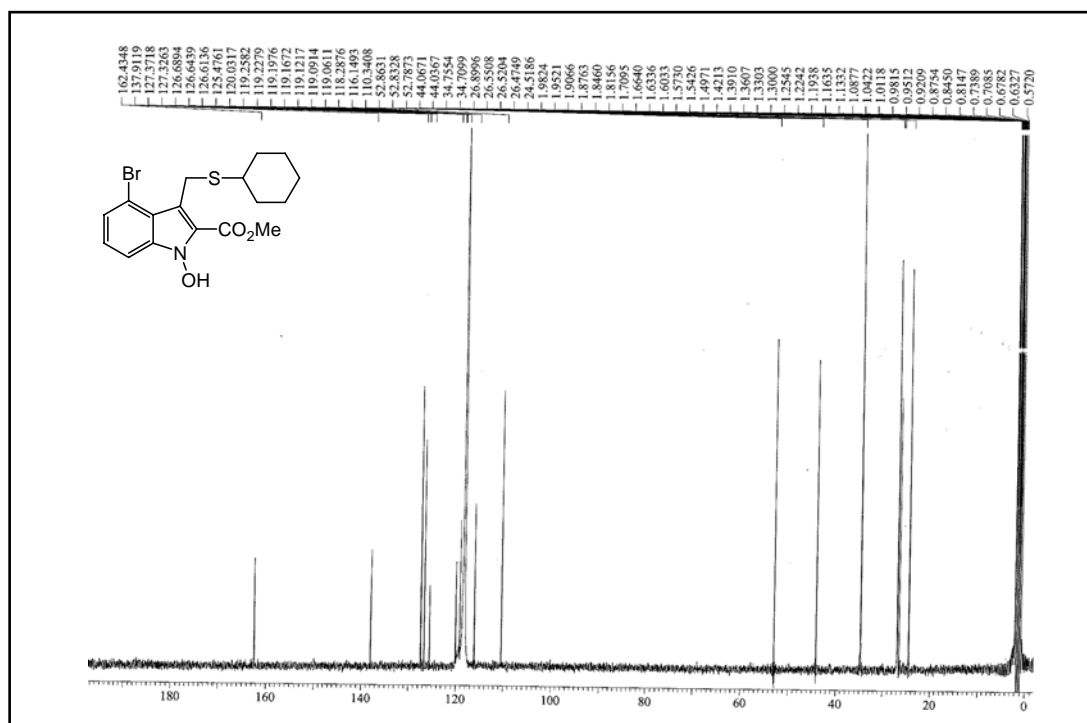
**Spectrum 2.61**  $^1\text{H NMR}$  (600 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.28.



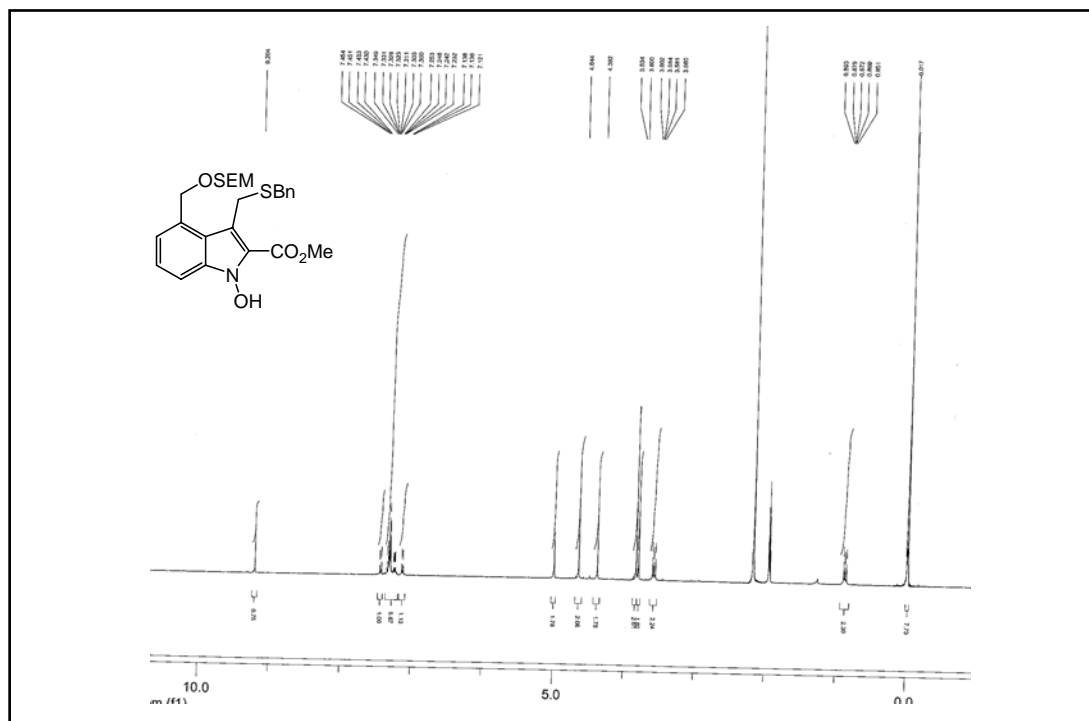
**Spectrum 2.62**  $^{13}\text{C NMR}$  (100 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.28.



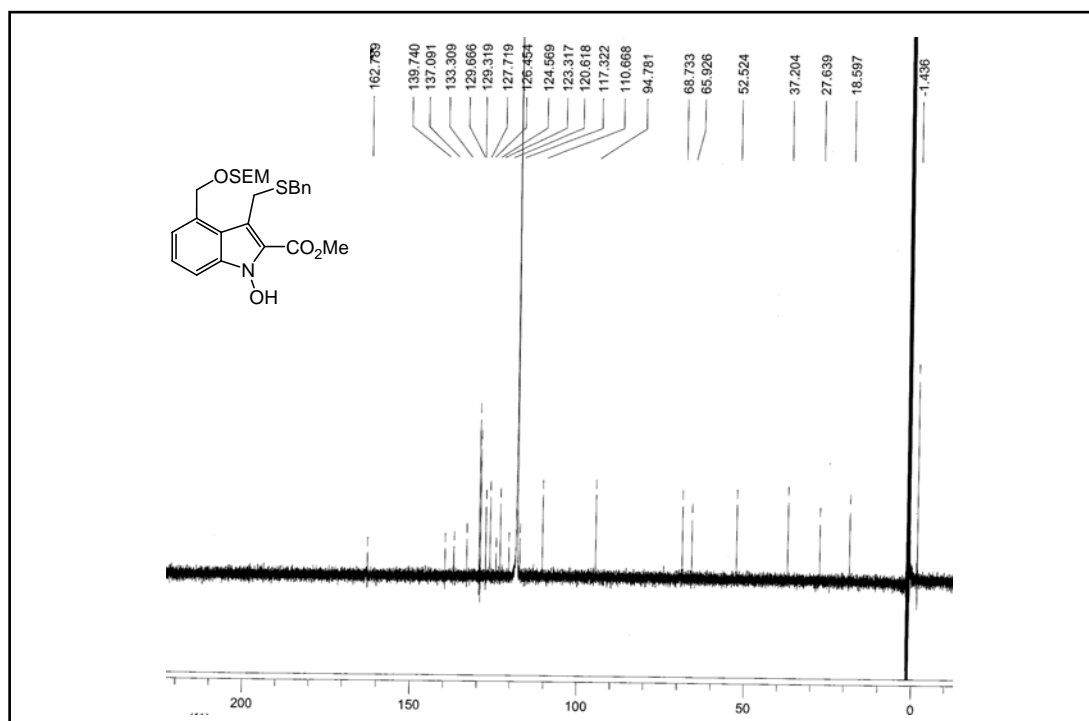
Spectrum 2.63 <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN) spectrum of compound 2.29.



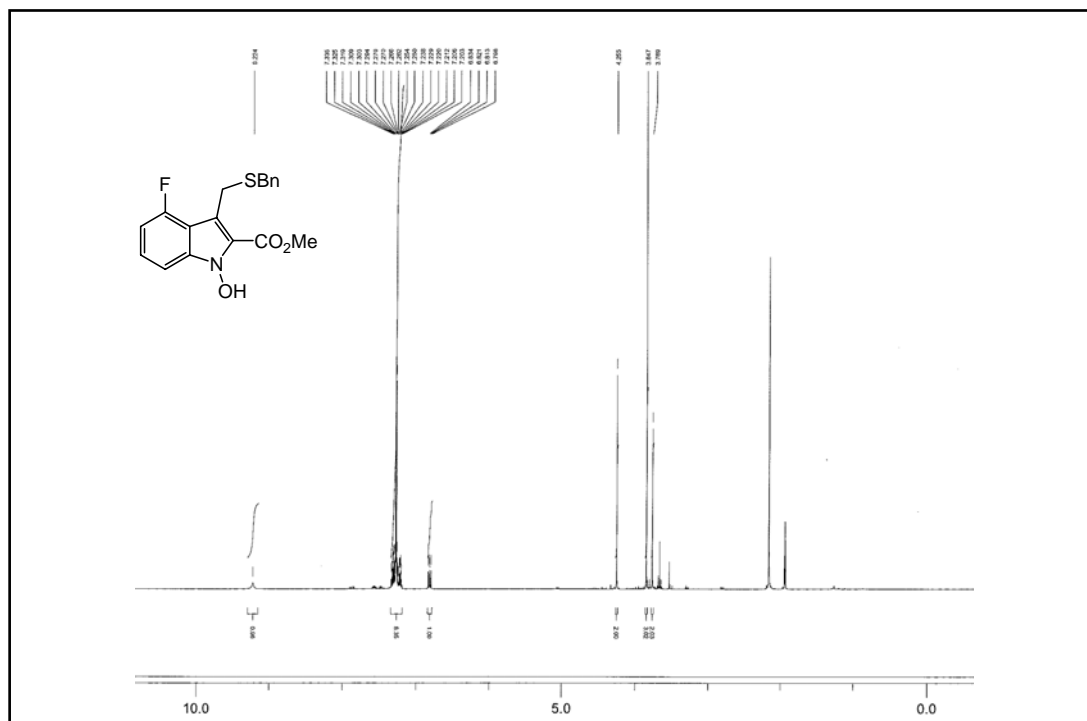
Spectrum 2.64 <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>CN) spectrum of compound 2.29.



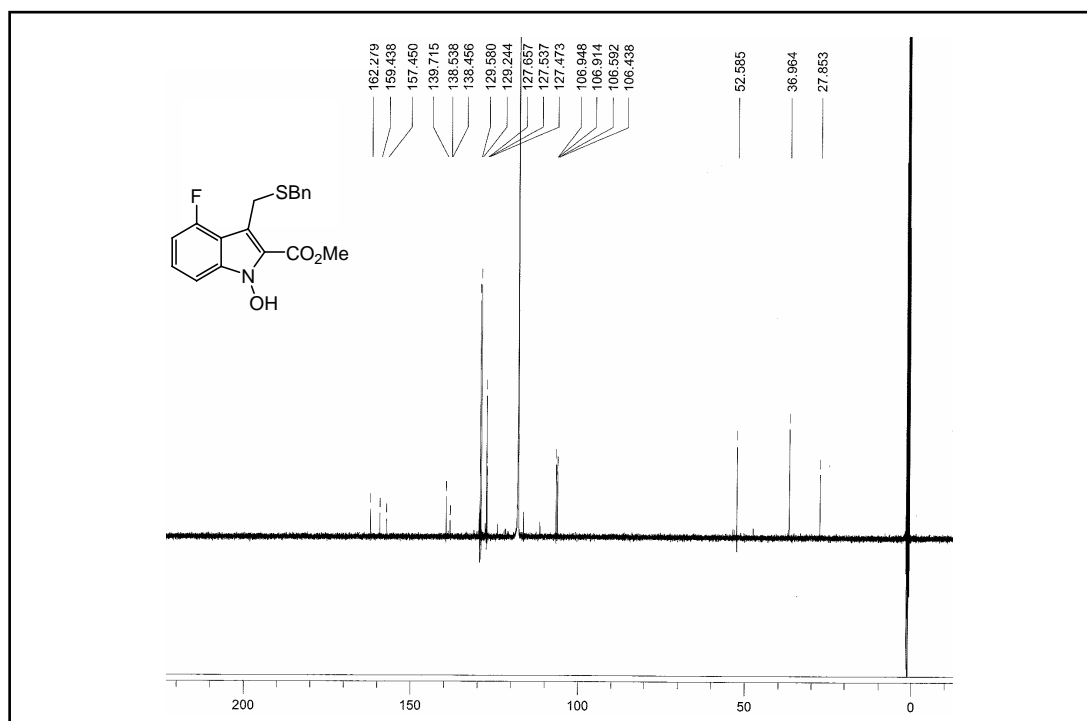
Spectrum 2.65 <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN) spectrum of compound 2.30.



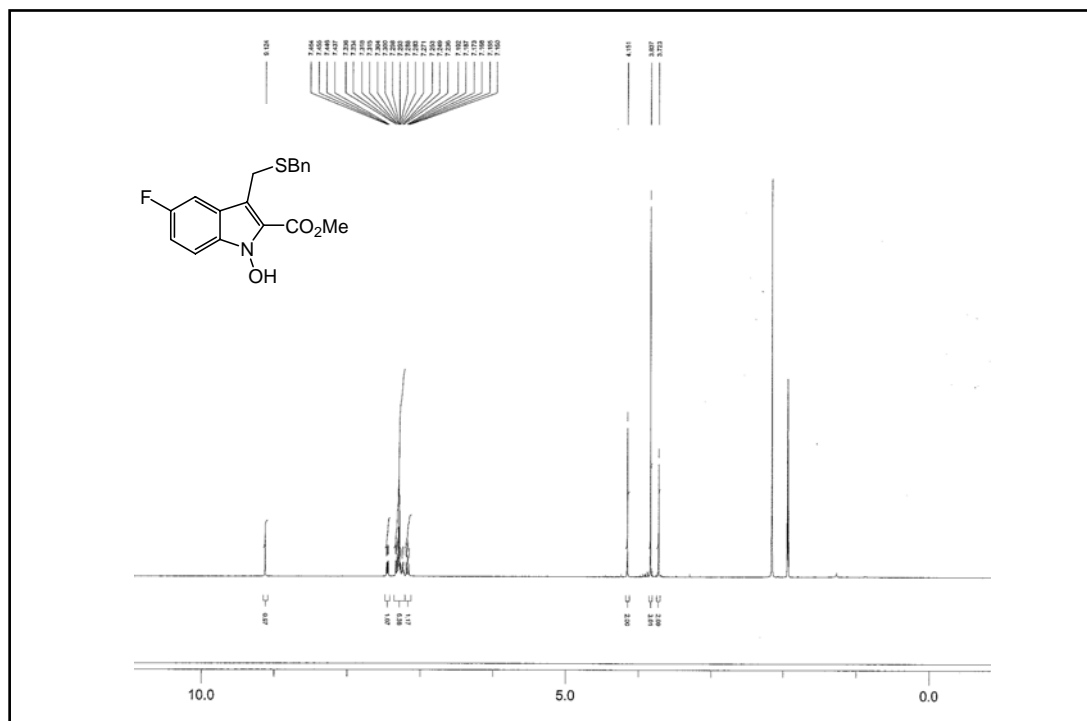
Spectrum 2.66 <sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>CN) spectrum of compound 2.30.



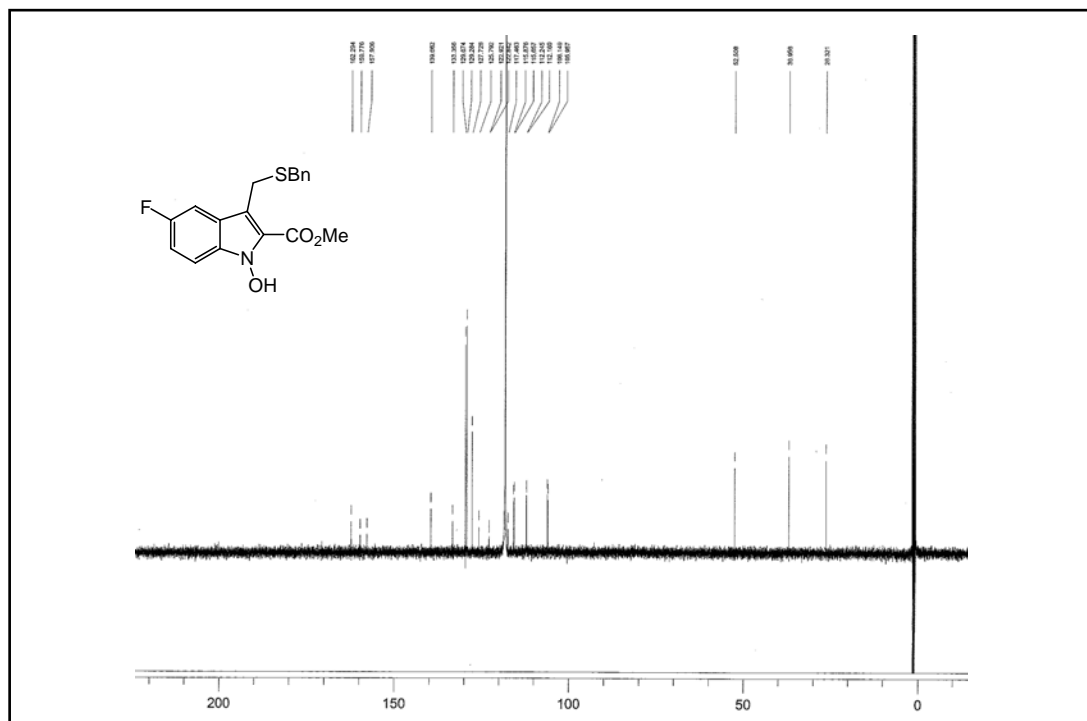
**Spectrum 2.67**  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.31**.



**Spectrum 2.68**  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.31**.

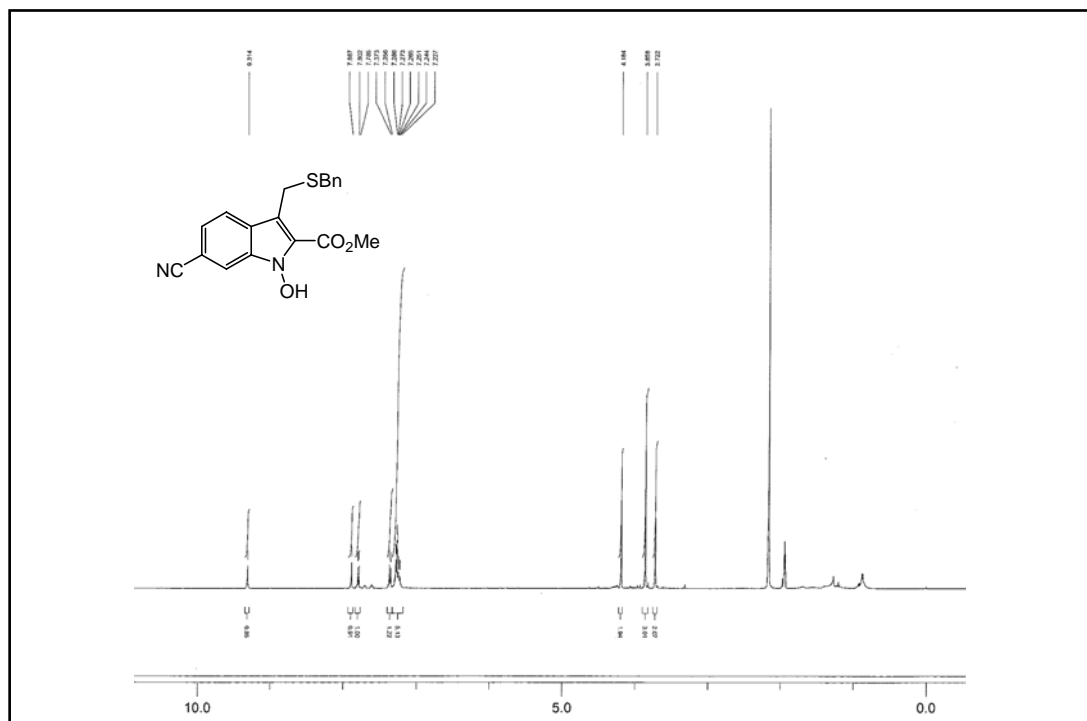


**Spectrum 2.69**  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.32.

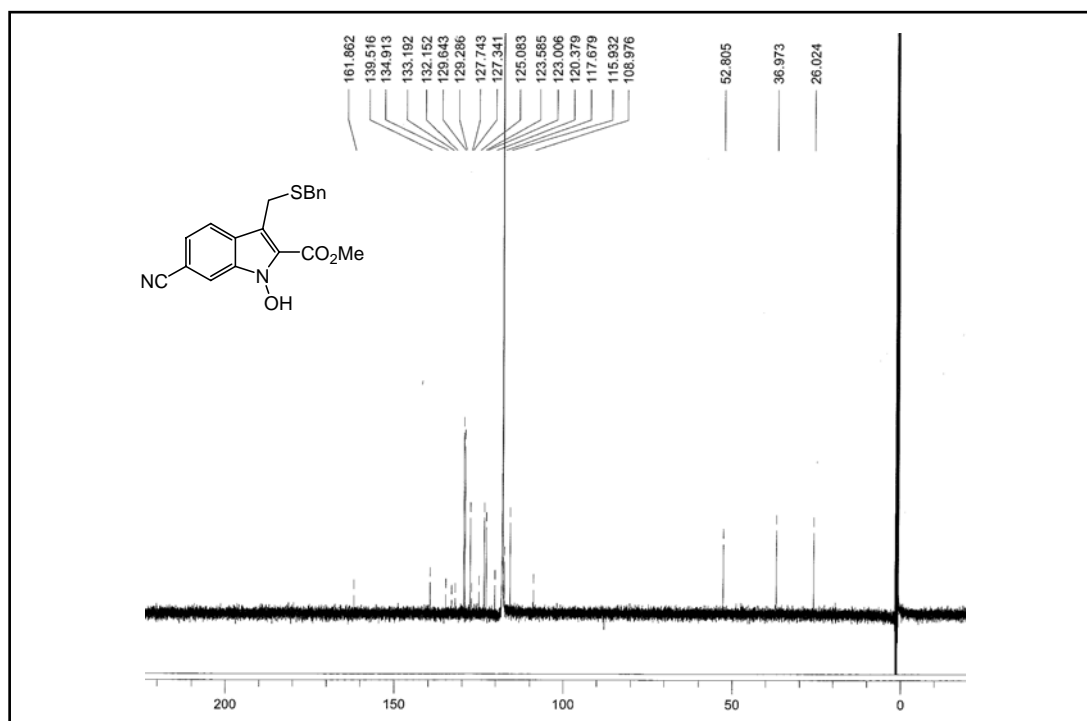


**Spectrum 2.70**  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.32.

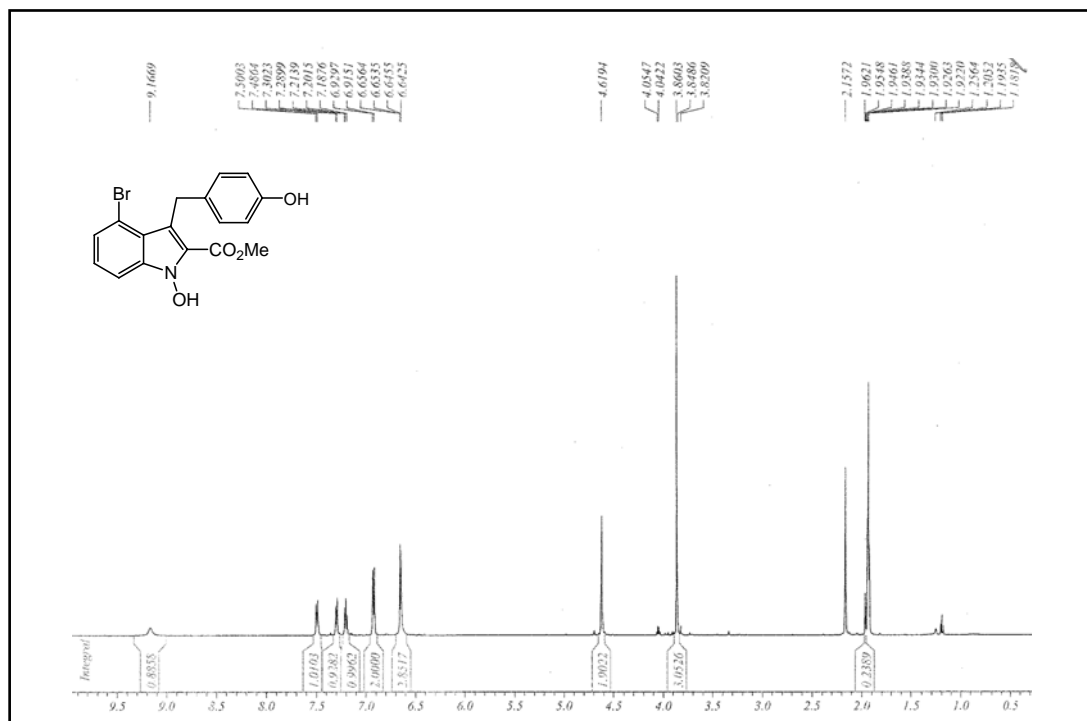




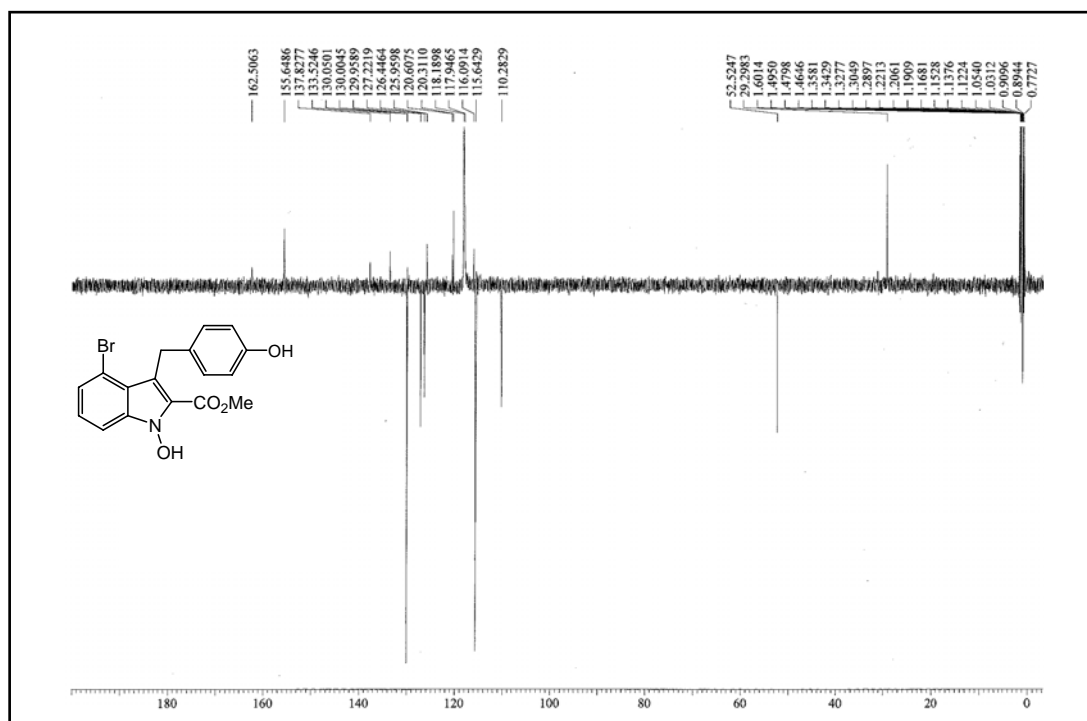
**Spectrum 2.73**  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.34**.



**Spectrum 2.74**  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.34**.

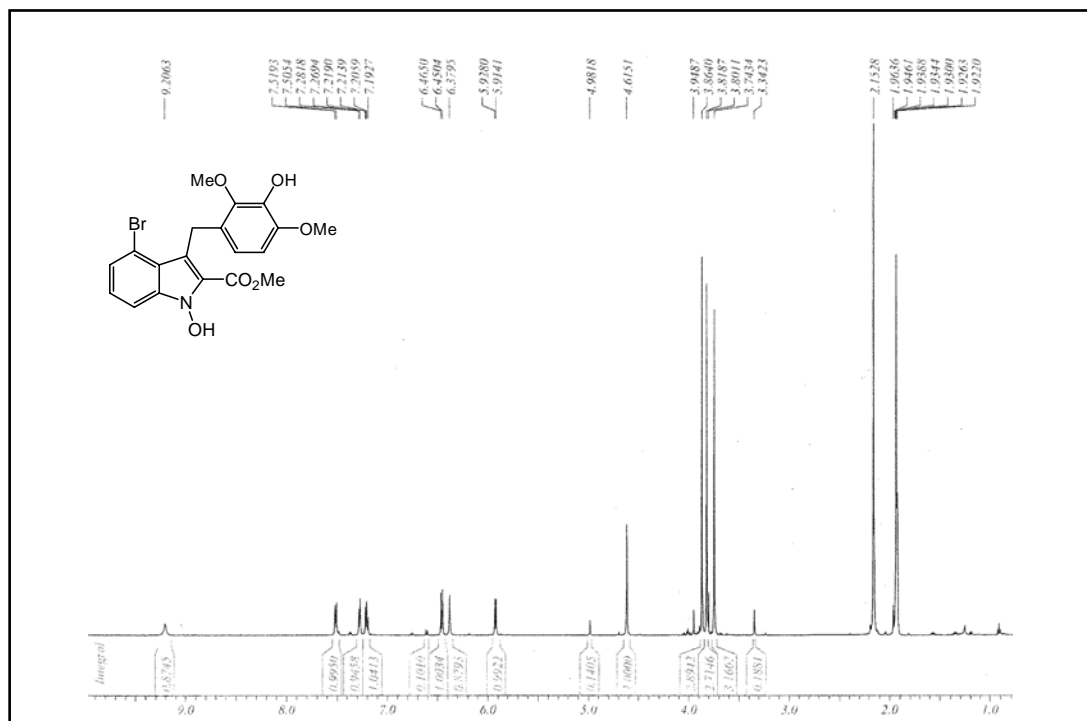


Spectrum 2.75 <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN) spectrum of compound 2.35.

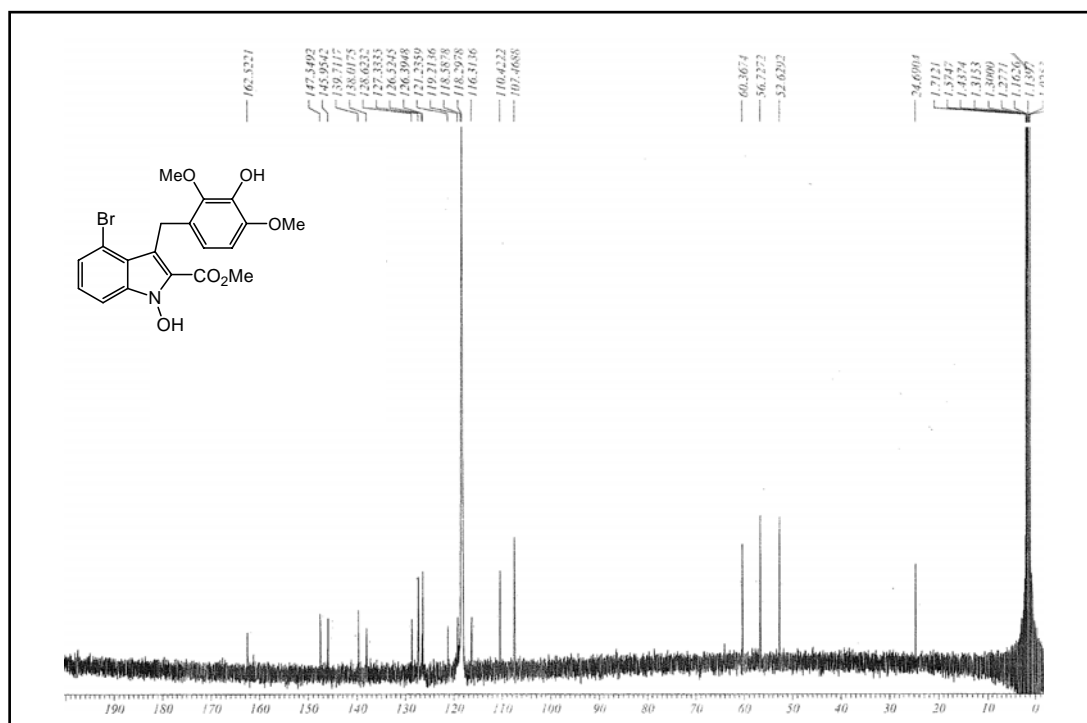


Spectrum 2.76 <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>CN) spectrum of compound 2.35.

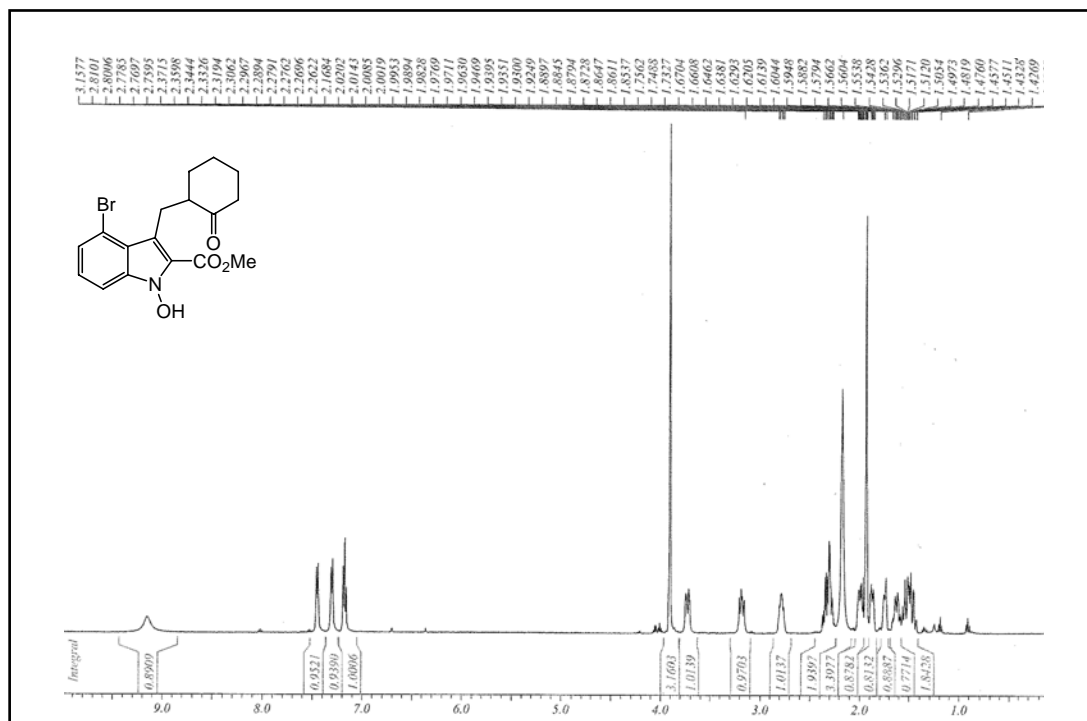


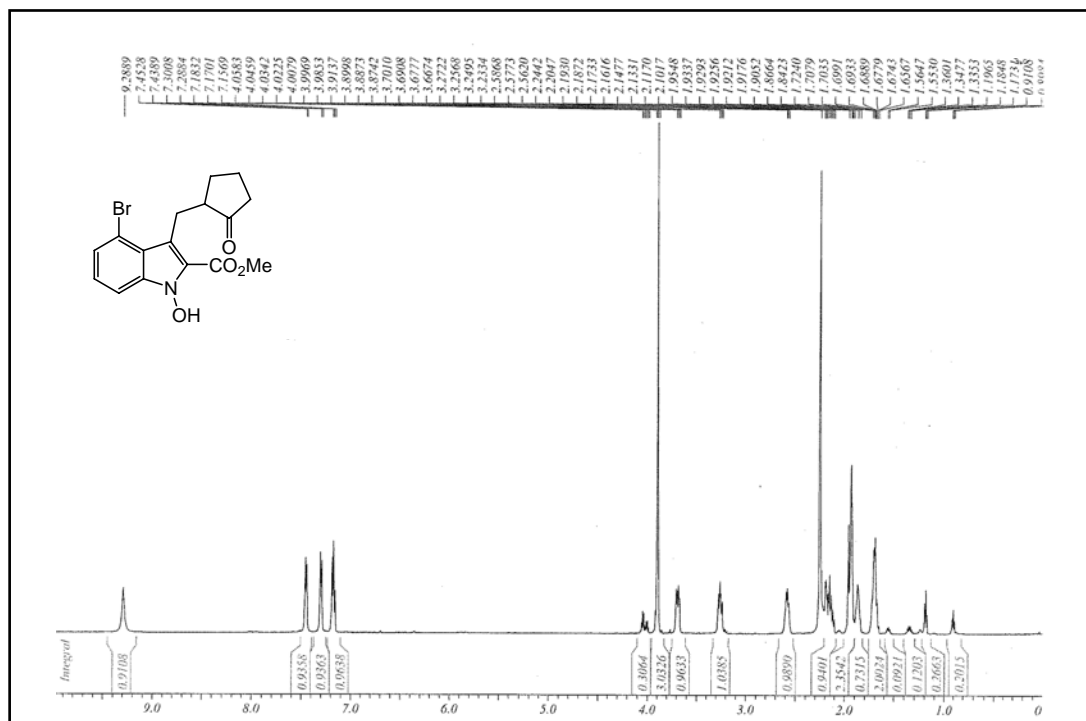


Spectrum 2.77  $^1\text{H NMR}$  (600 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.36.

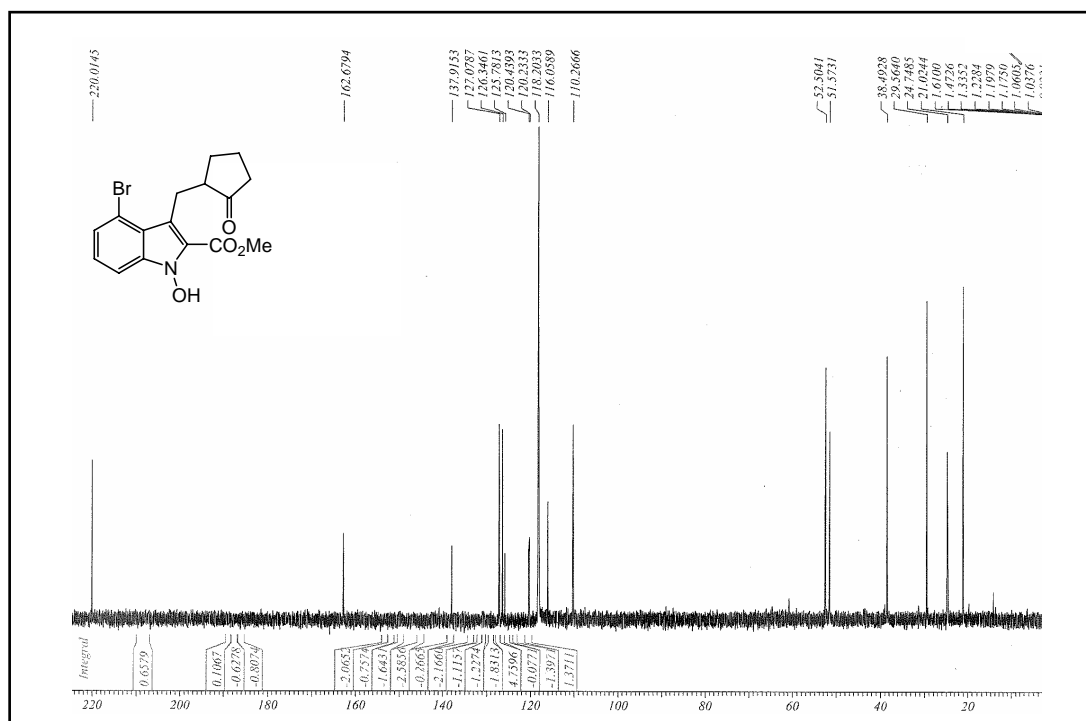


Spectrum 2.78  $^{13}\text{C NMR}$  (150 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.36.

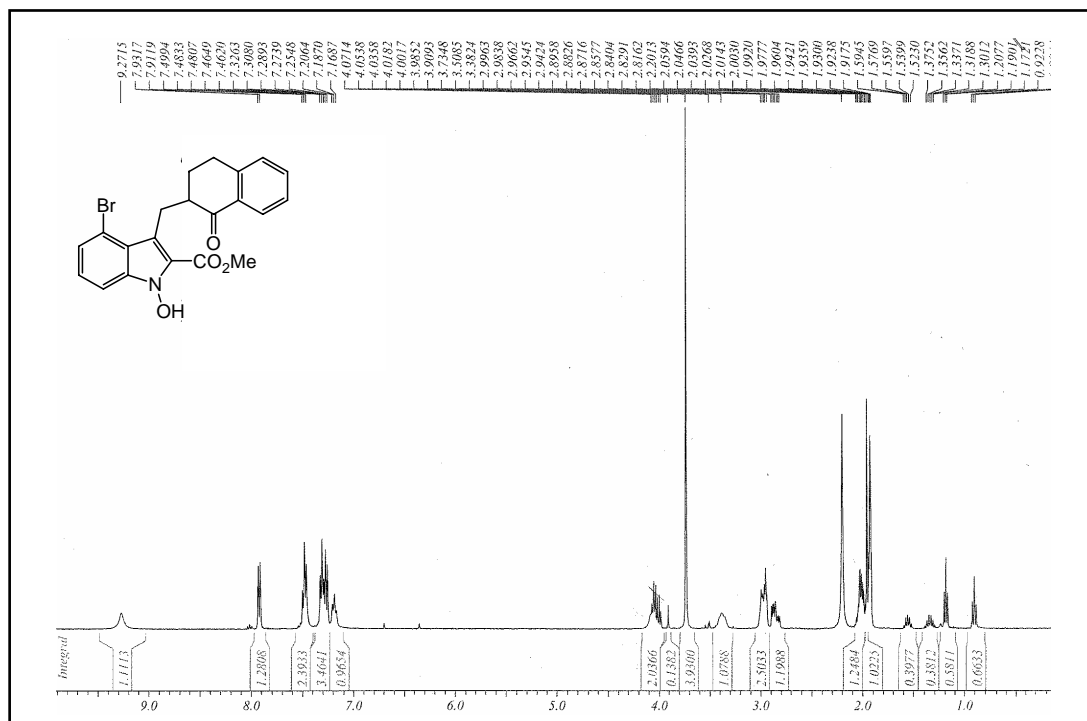




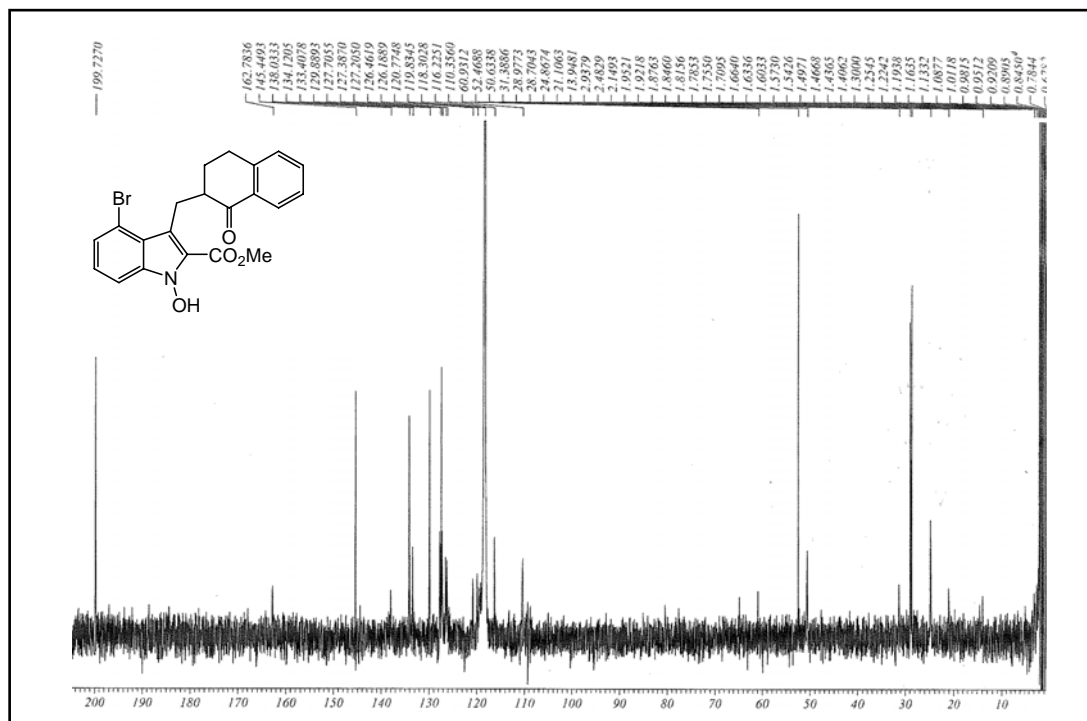
Spectrum 2.81 <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN) spectrum of compound 2.38.



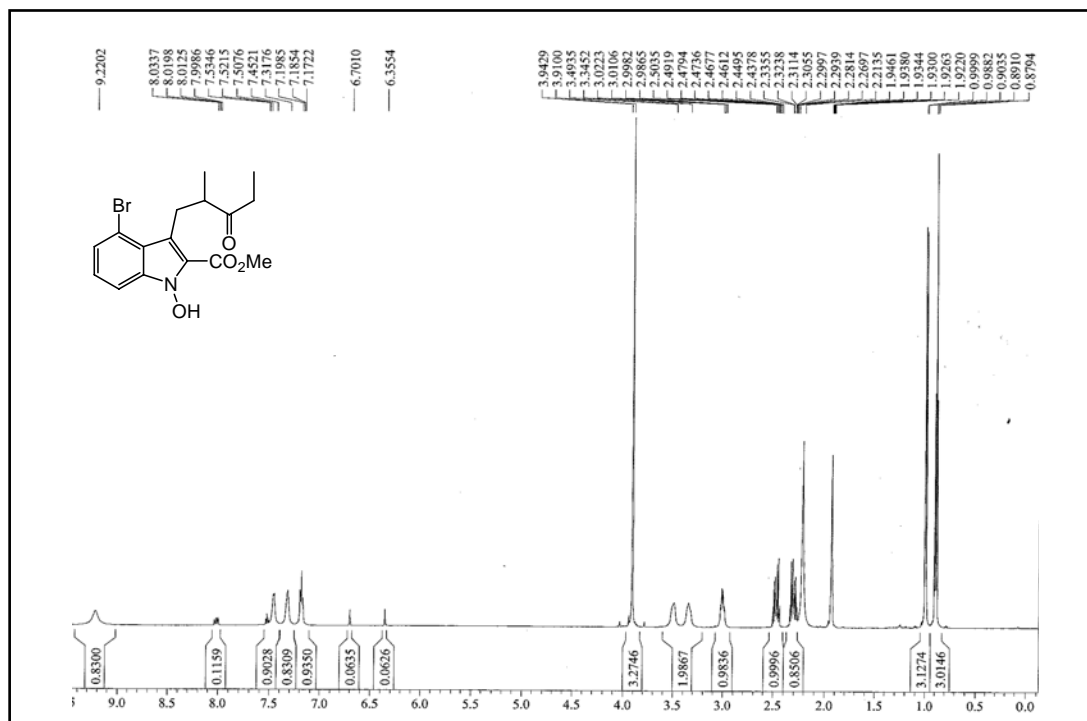
Spectrum 2.82 <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>CN) spectrum of compound 2.38.



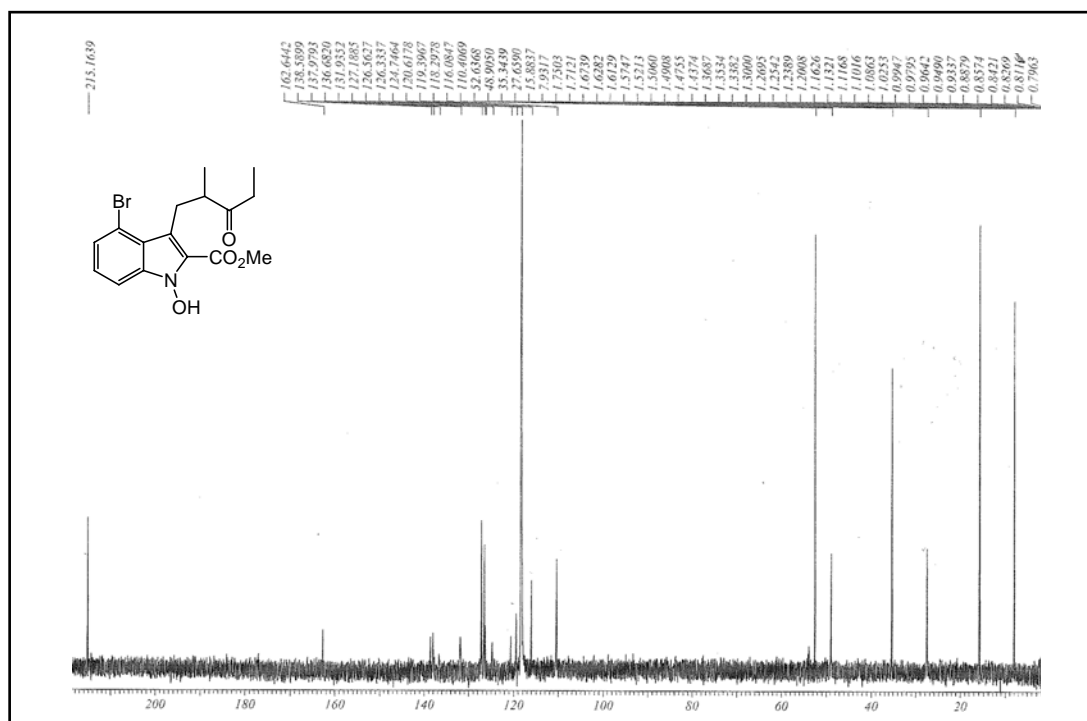
**Spectrum 2.83**  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.39**.



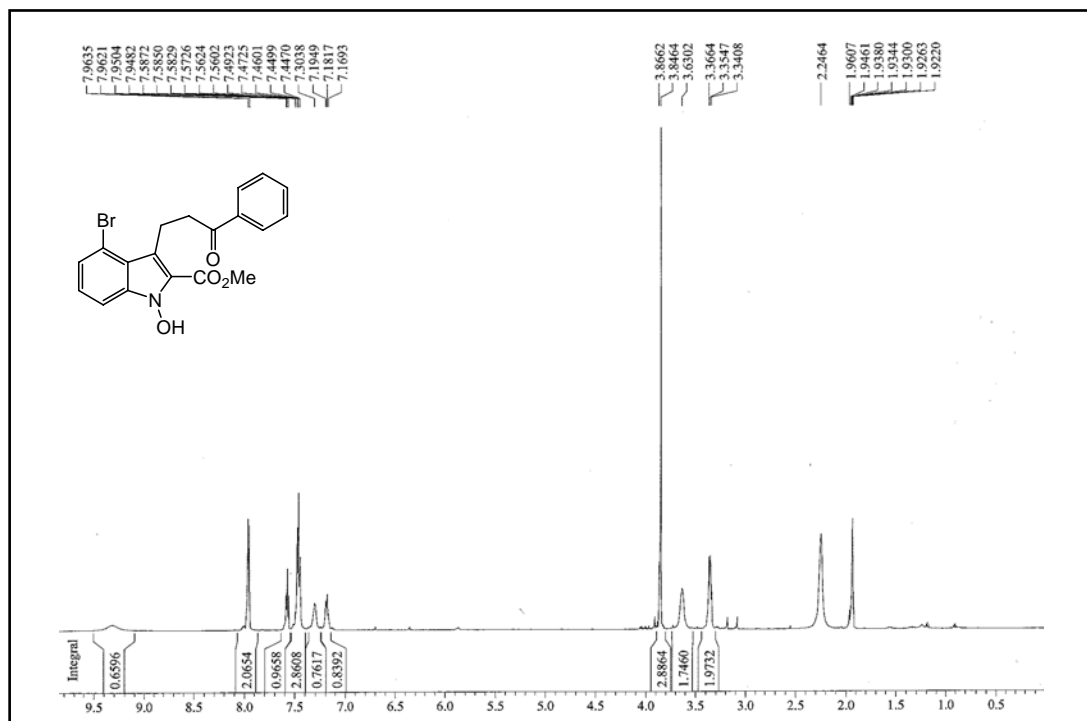
**Spectrum 2.84**  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.39**.



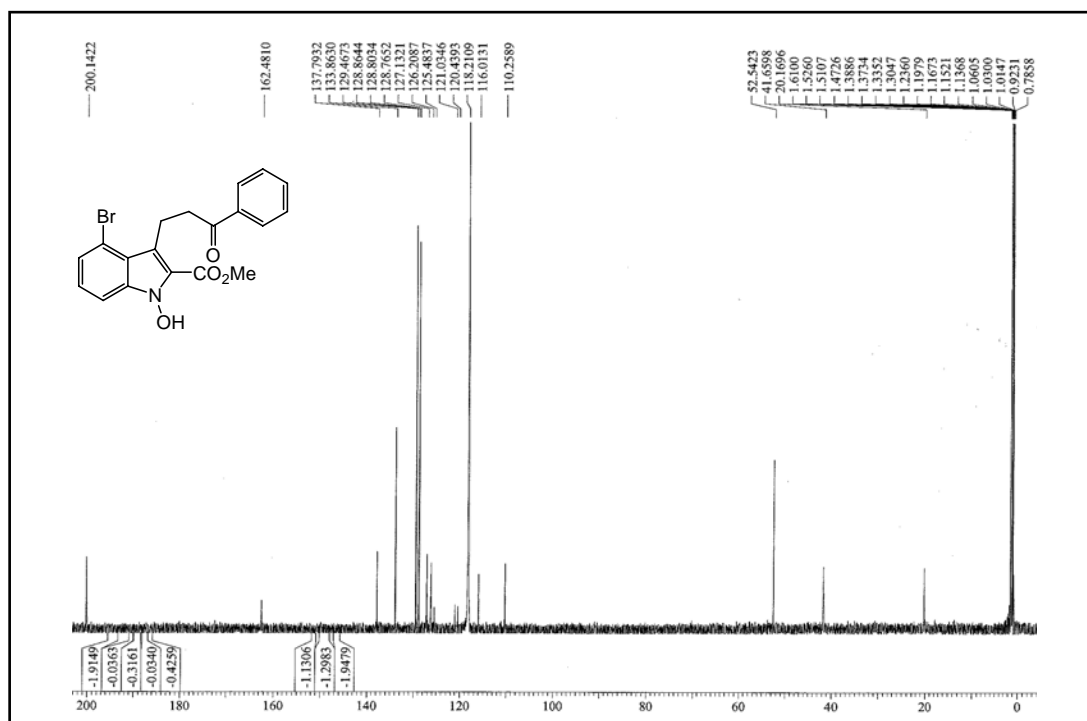
Spectrum 2.85 <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN) spectrum of compound 2.40.



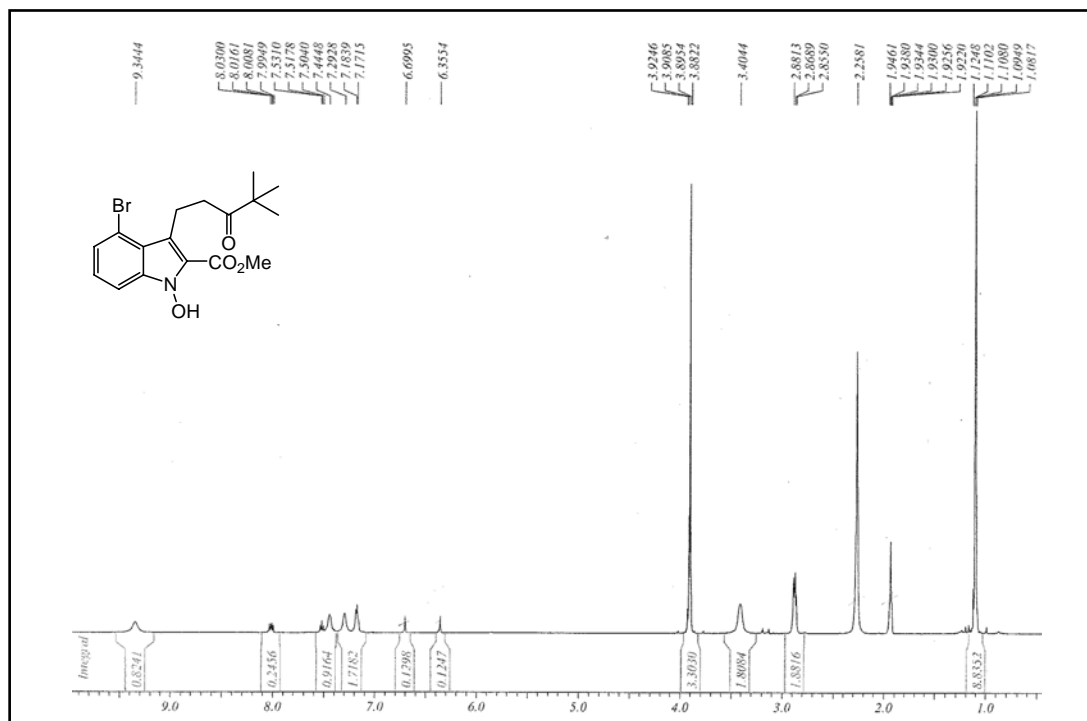
Spectrum 2.86 <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>CN) spectrum of compound 2.40.



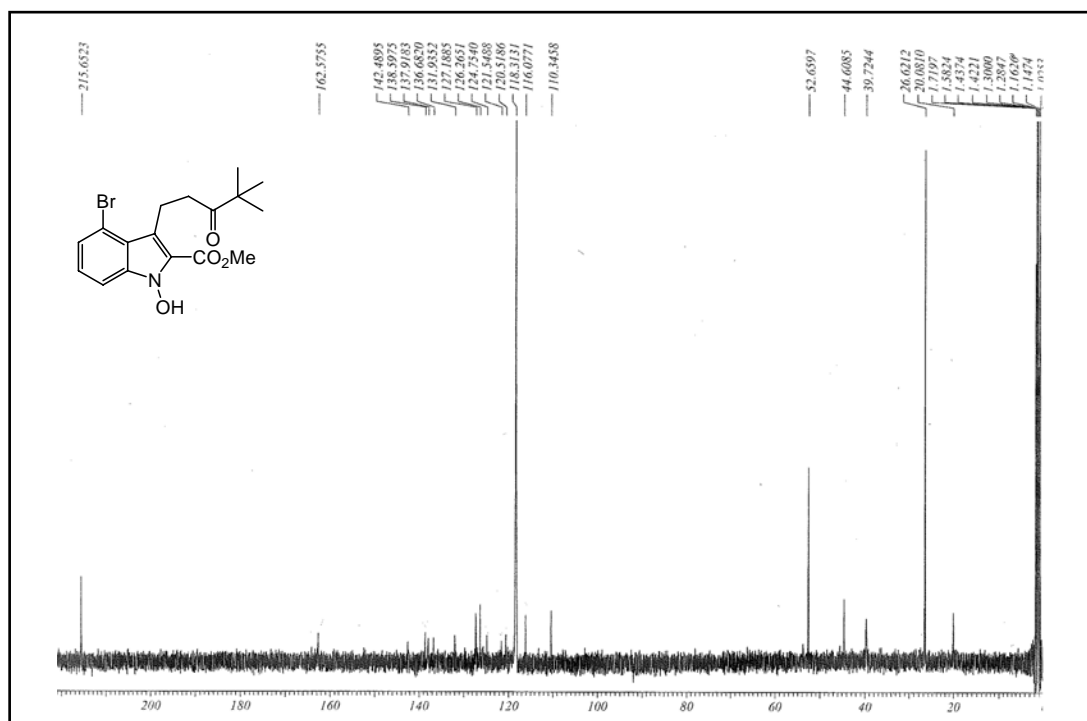
Spectrum 2.87 <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN) spectrum of compound 2.41.



Spectrum 2.88 <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>CN) spectrum of compound 2.41.



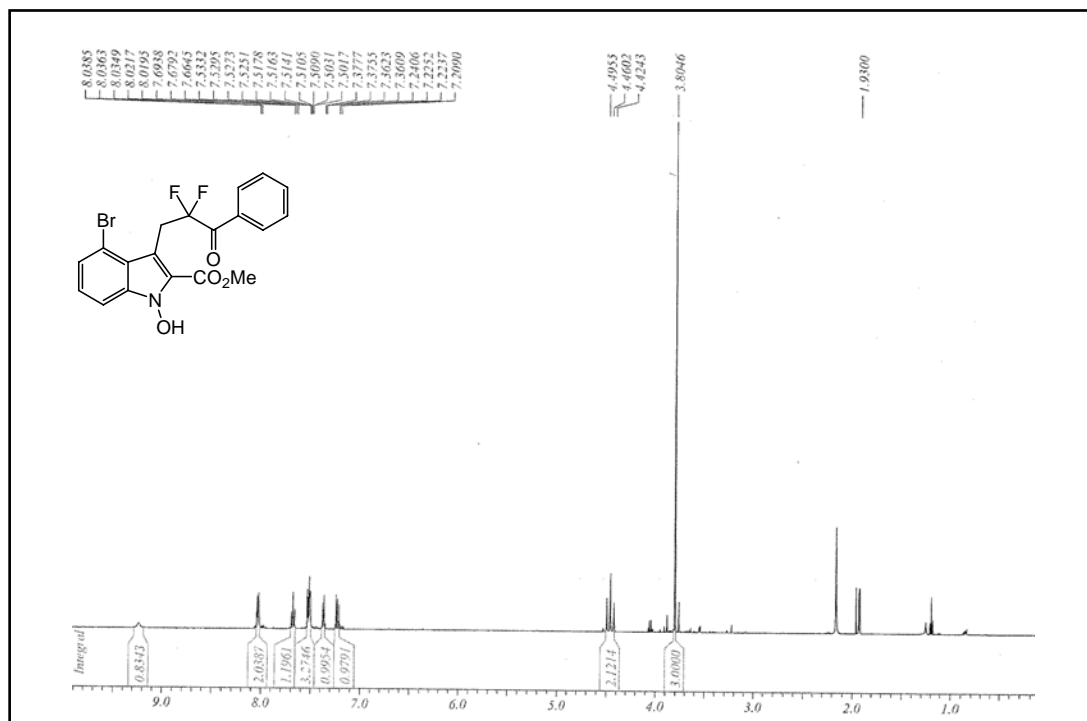
**Spectrum 2.89**  $^1\text{H NMR}$  (600 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.42.



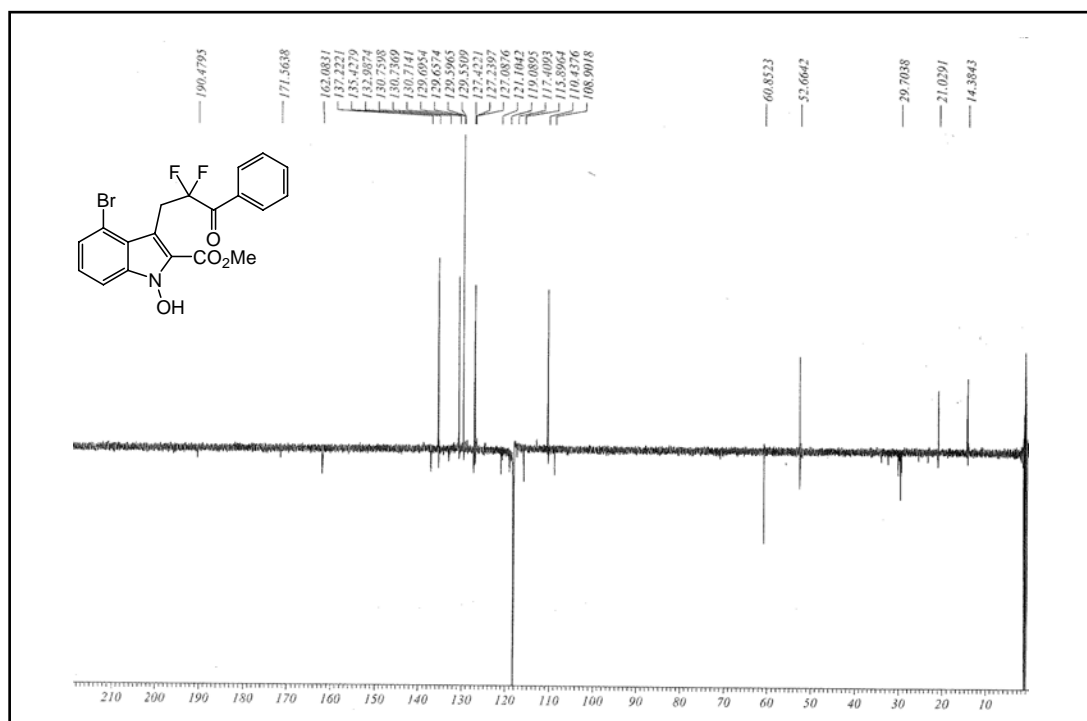
**Spectrum 2.90**  $^{13}\text{C NMR}$  (150 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.42.



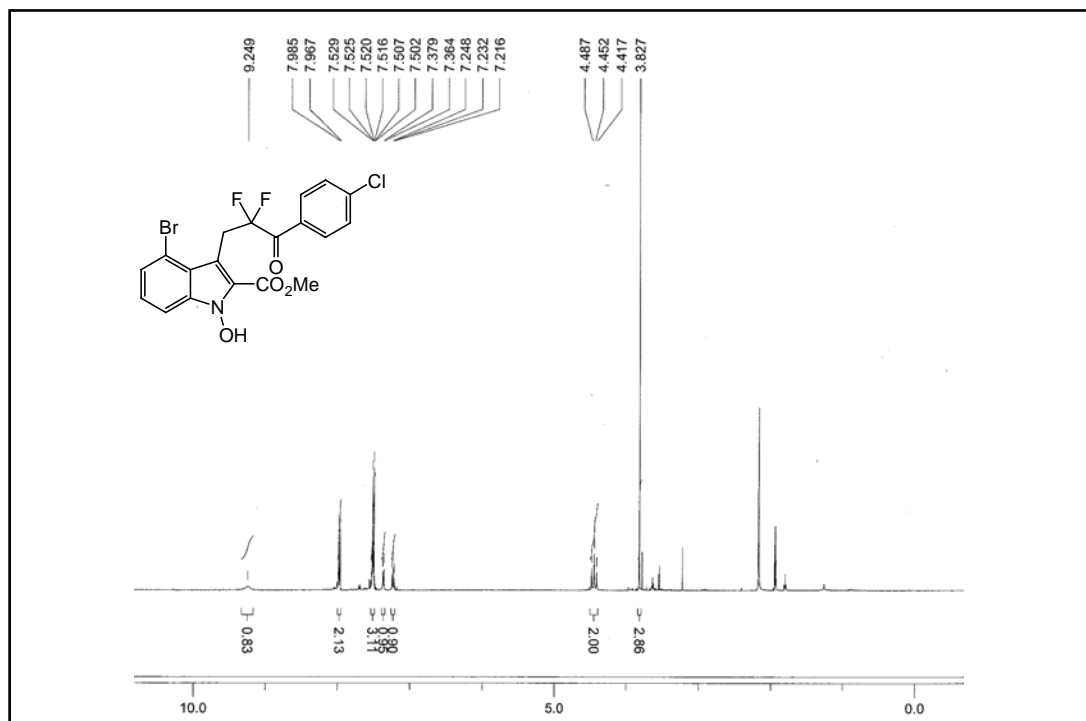




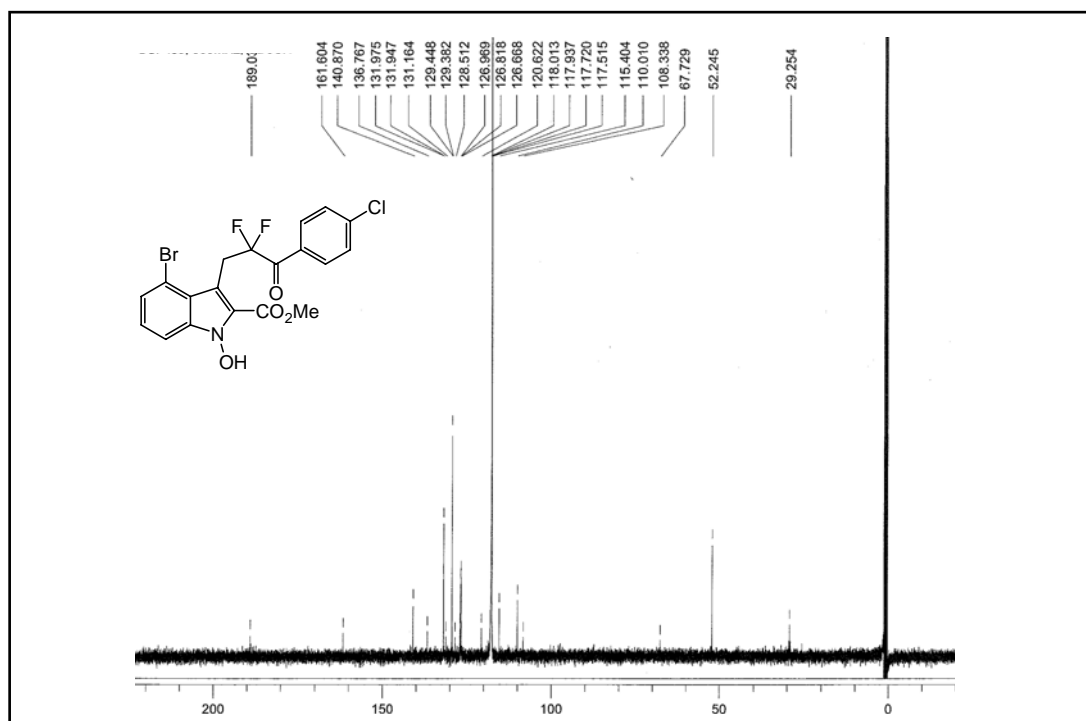
**Spectrum 2.93**  $^1\text{H NMR}$  (500 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.44.



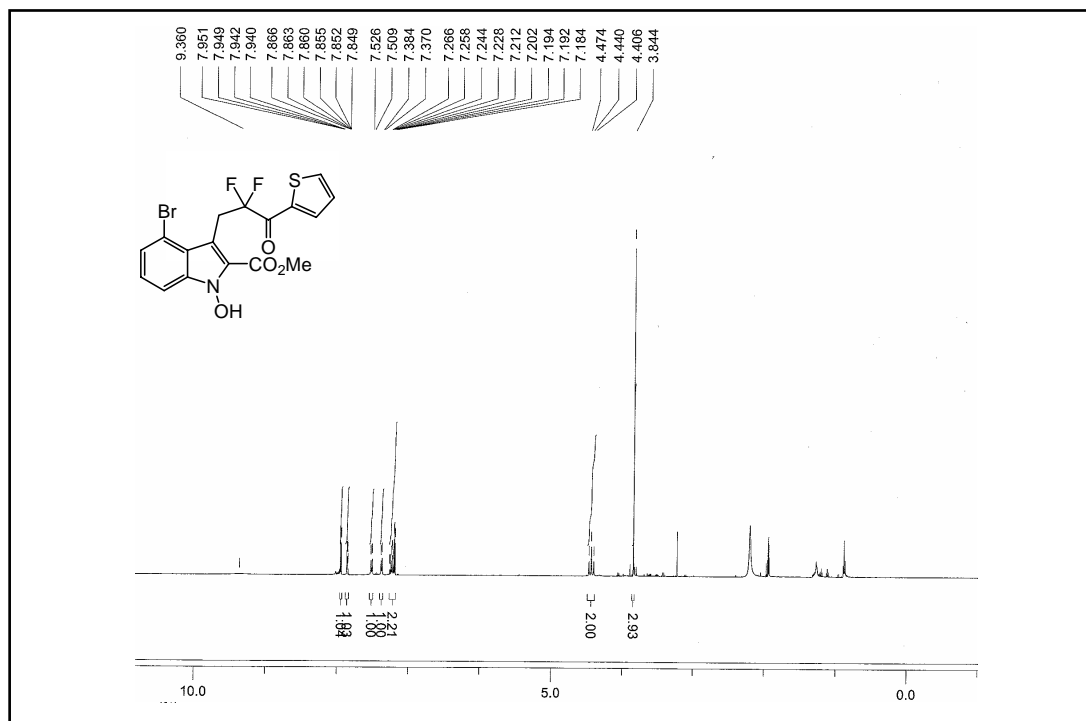
**Spectrum 2.94**  $^{13}\text{C NMR}$  (125 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.44.



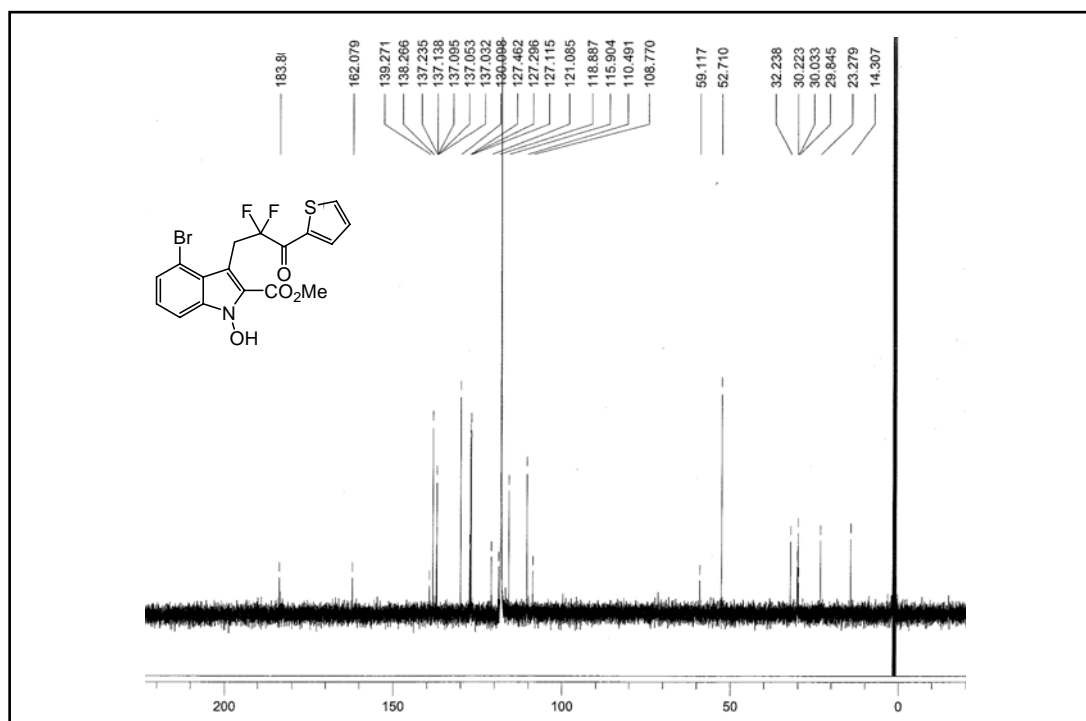
**Spectrum 2.95**  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.45**.



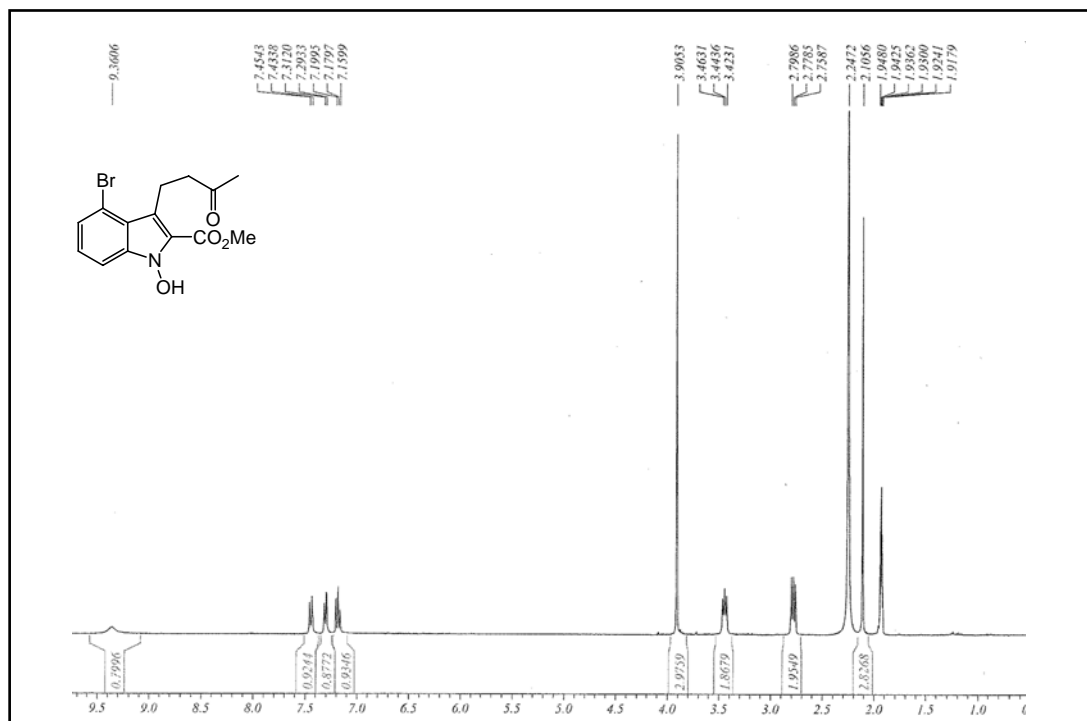
**Spectrum 2.96**  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.45**.



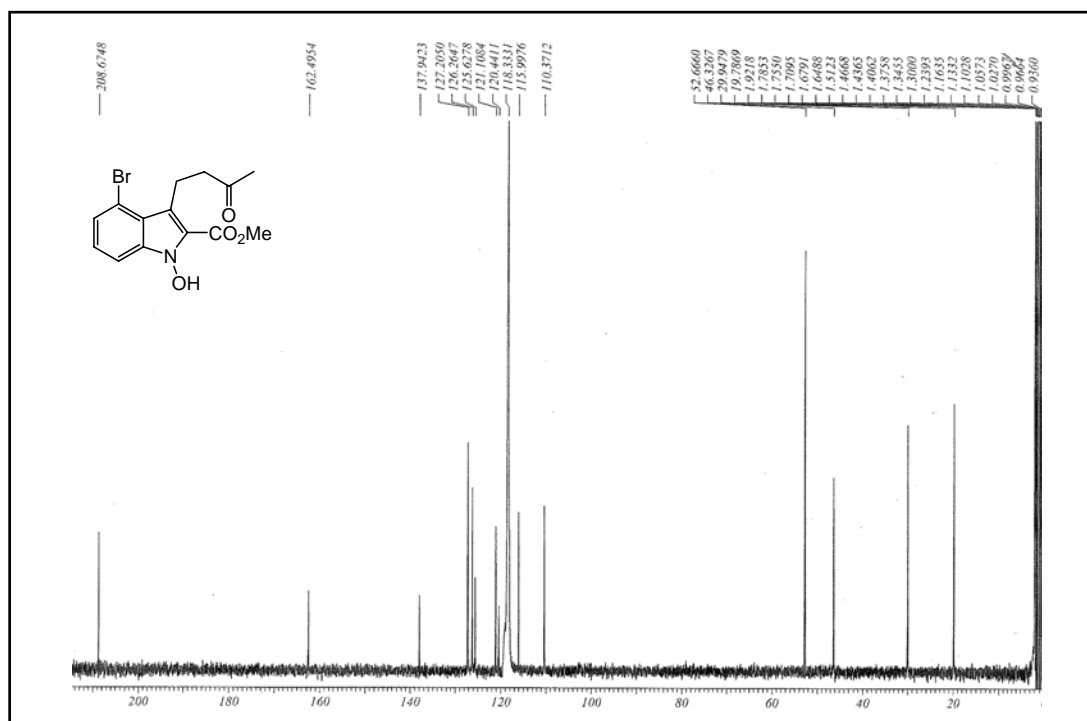
Spectrum 2.97  $^1\text{H NMR}$  (500 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.46.



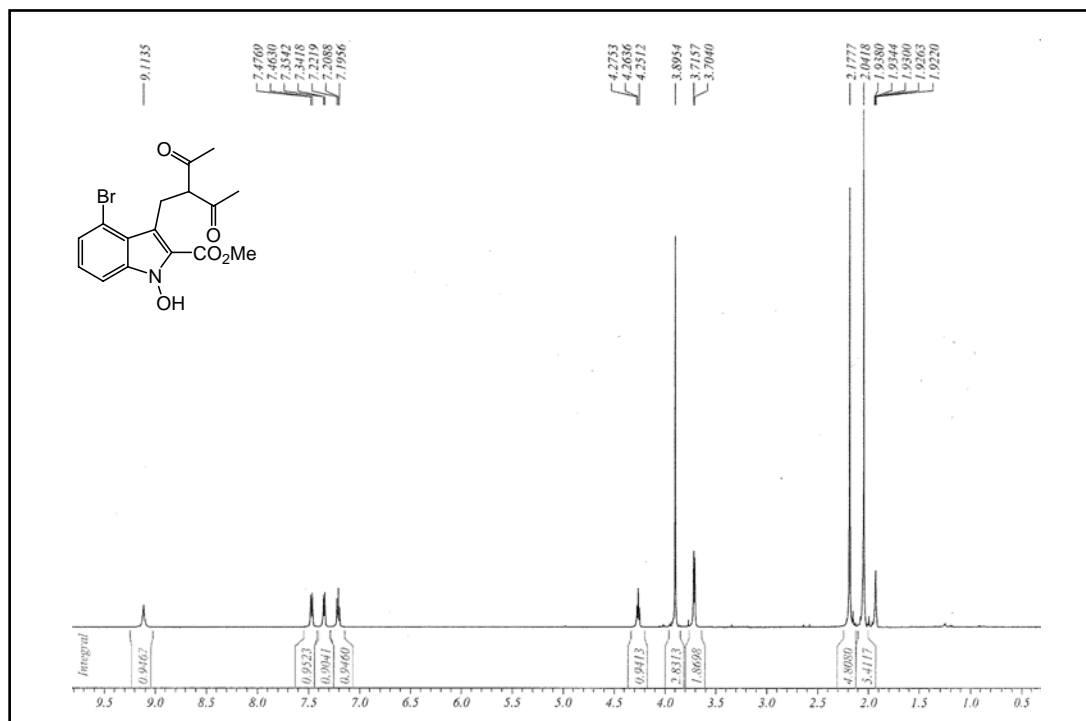
Spectrum 2.98  $^{13}\text{C NMR}$  (125 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.46.



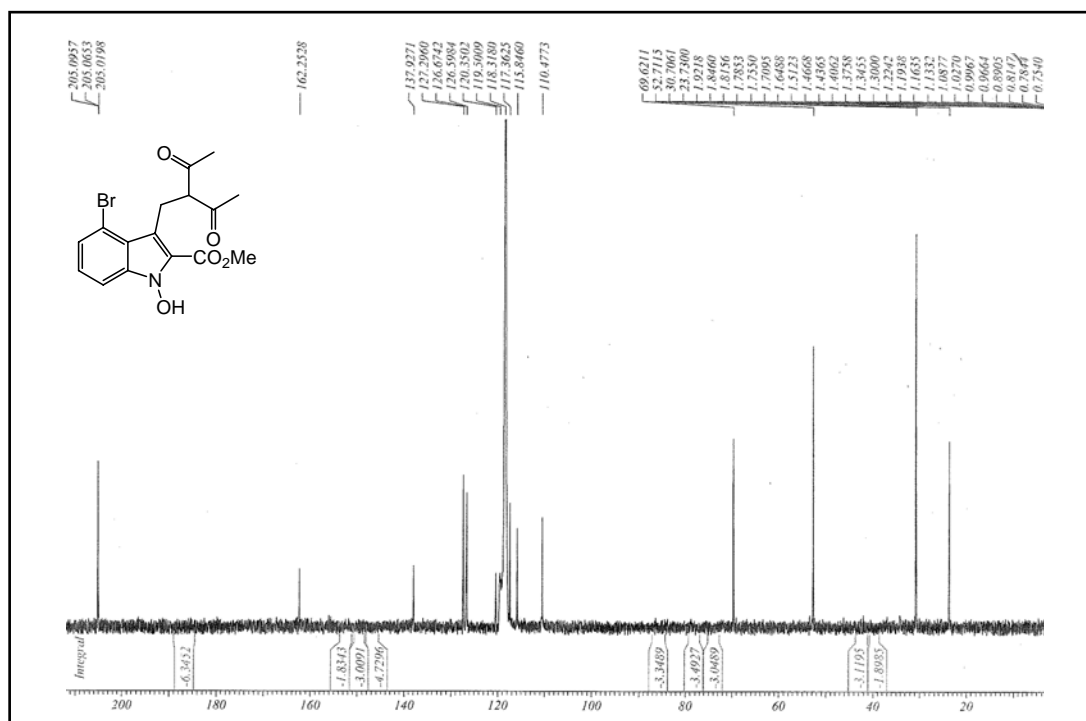
Spectrum 2.99  $^1\text{H NMR}$  (400 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.47.



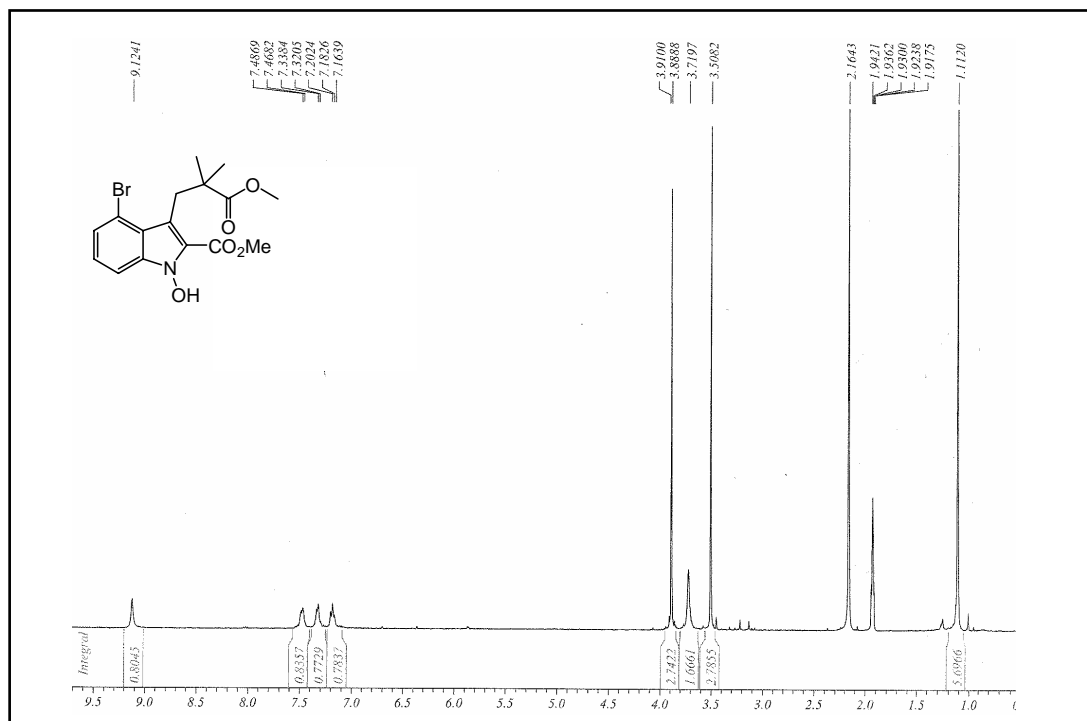
Spectrum 2.100  $^{13}\text{C NMR}$  (125 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.47.



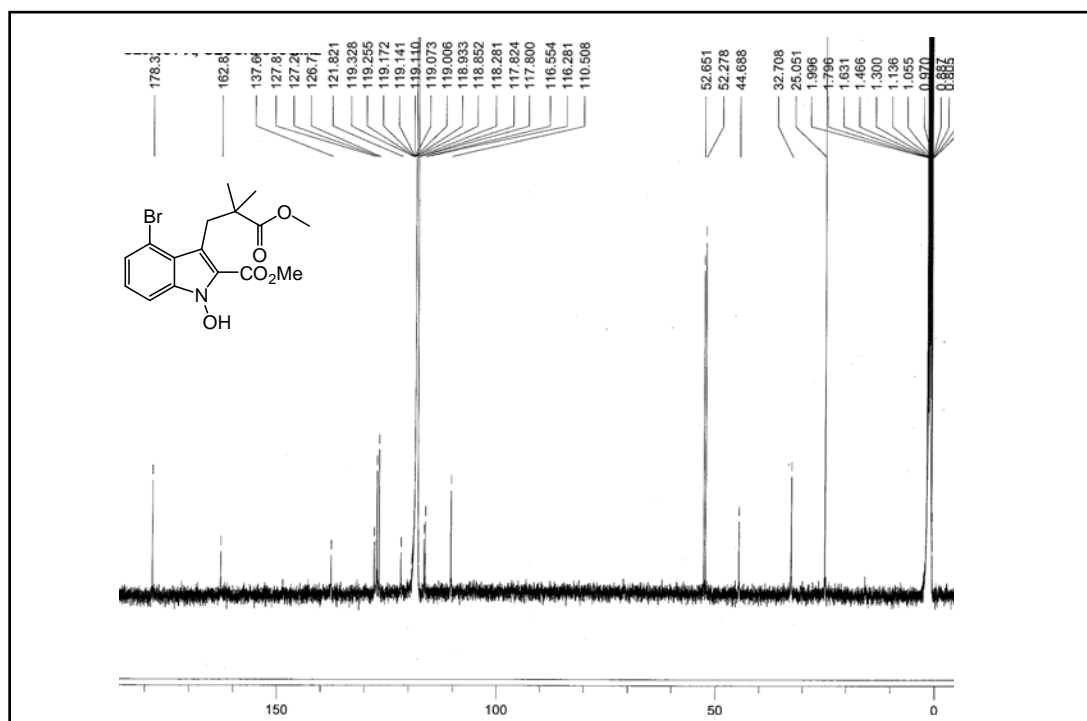
**Spectrum 2.101** <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>CN) spectrum of compound 2.48.



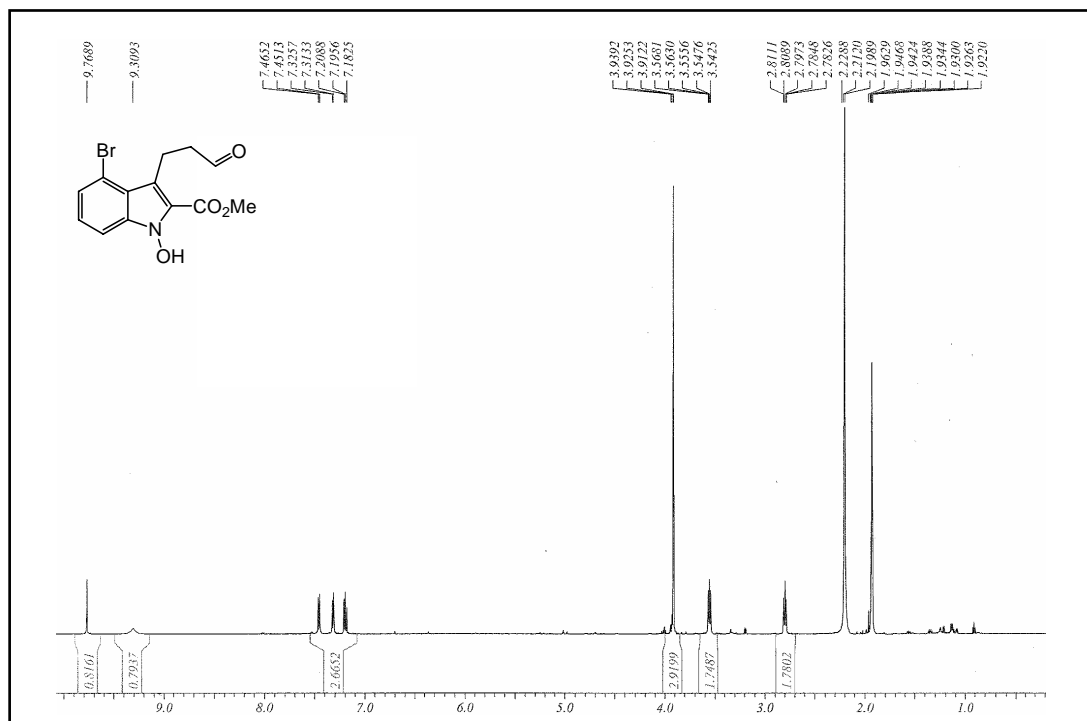
**Spectrum 2.102** <sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>CN) spectrum of compound 2.48.



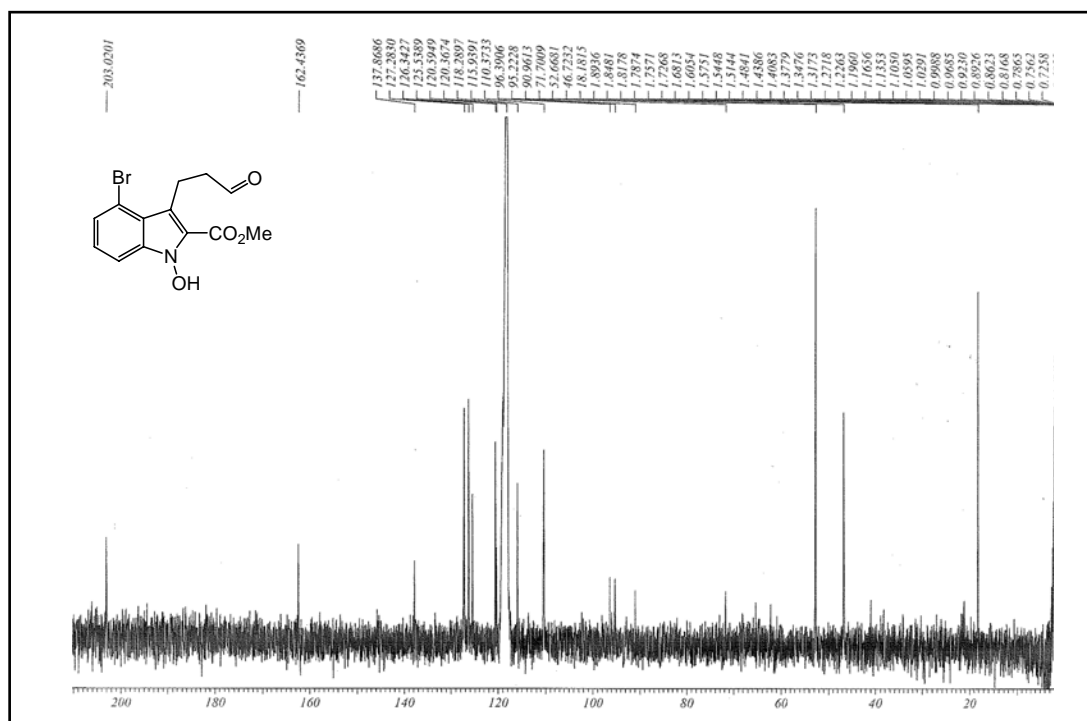
**Spectrum 2.103** <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN) spectrum of compound 2.49.



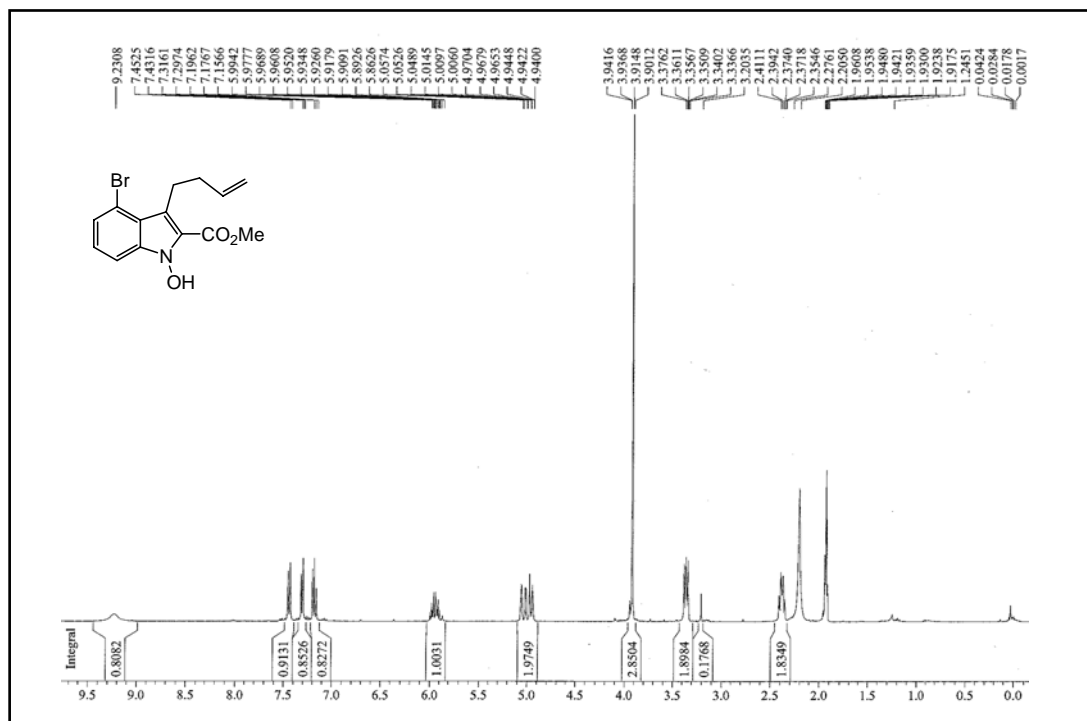
**Spectrum 2.104** <sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>CN) spectrum of compound 2.49.



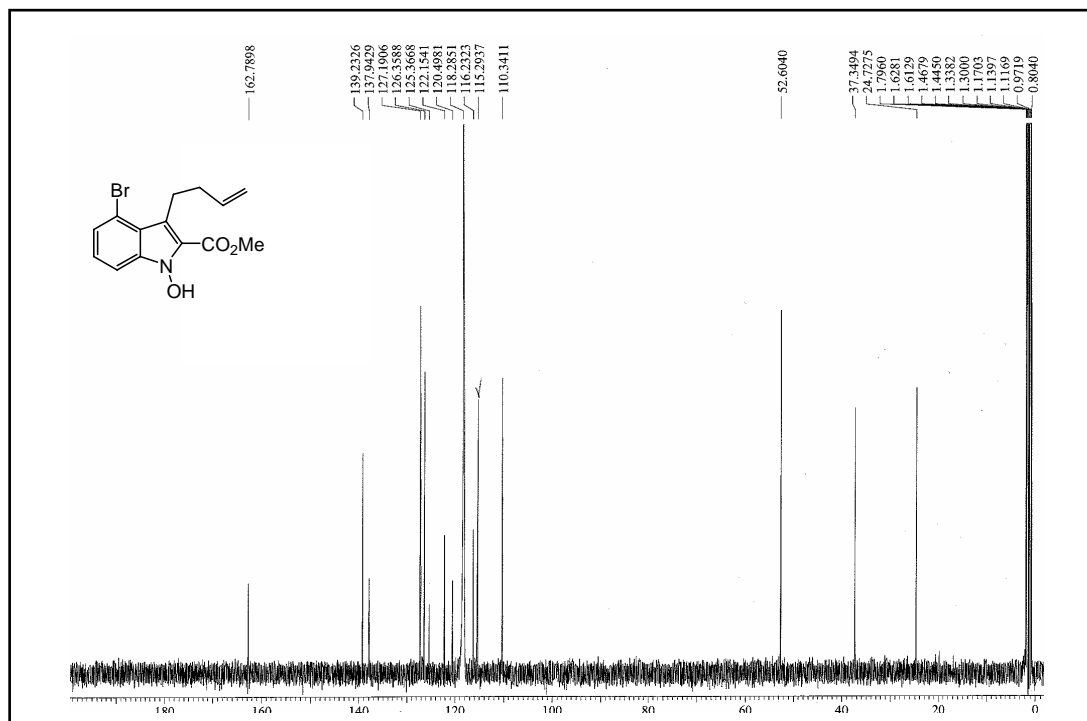
**Spectrum 2.105** <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN) spectrum of compound **2.50**.



**Spectrum 2.106** <sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>CN) spectrum of compound **2.50**.

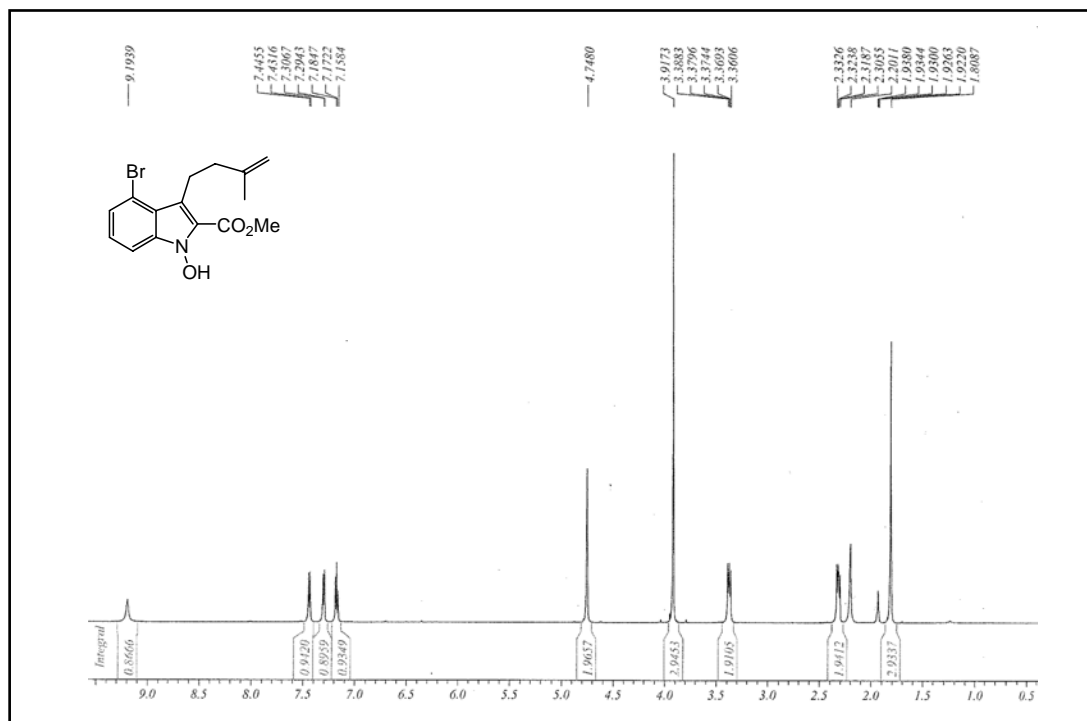


**Spectrum 2.107** <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN) spectrum of compound **2.51**.

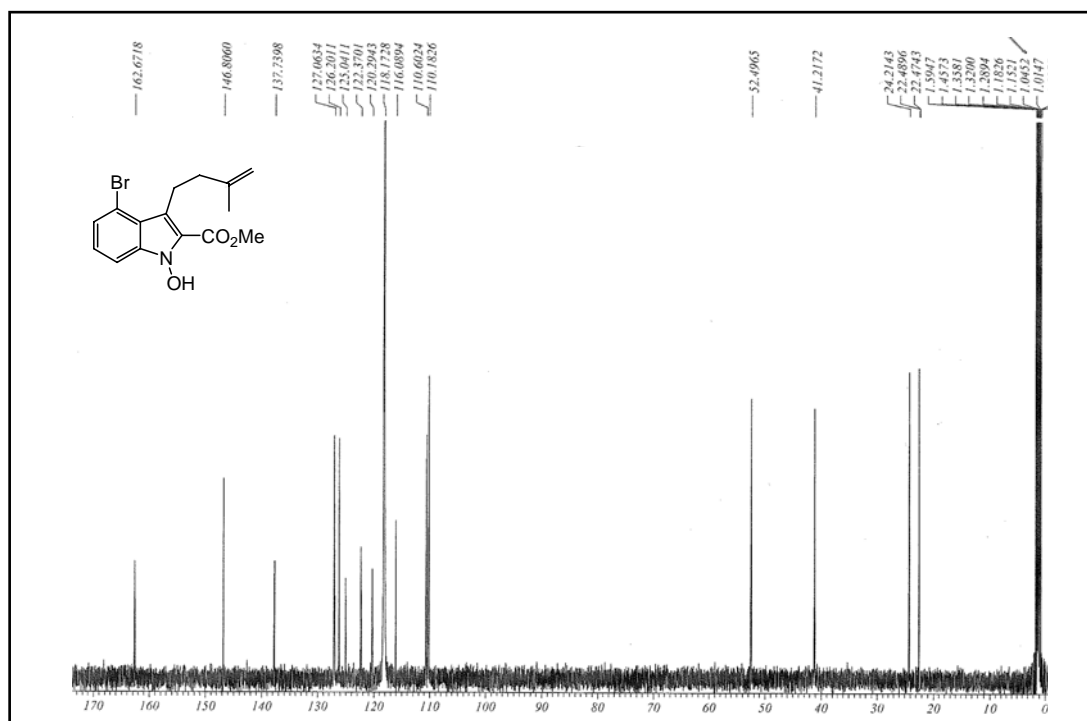


**Spectrum 2.108** <sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>CN) spectrum of compound **2.51**.

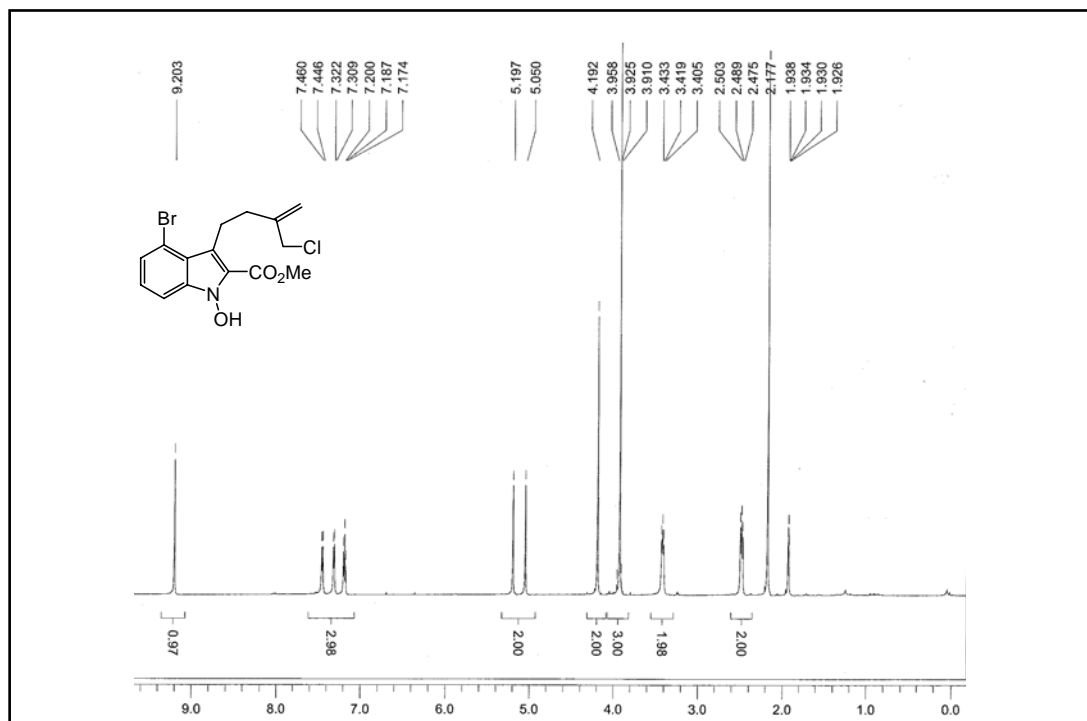




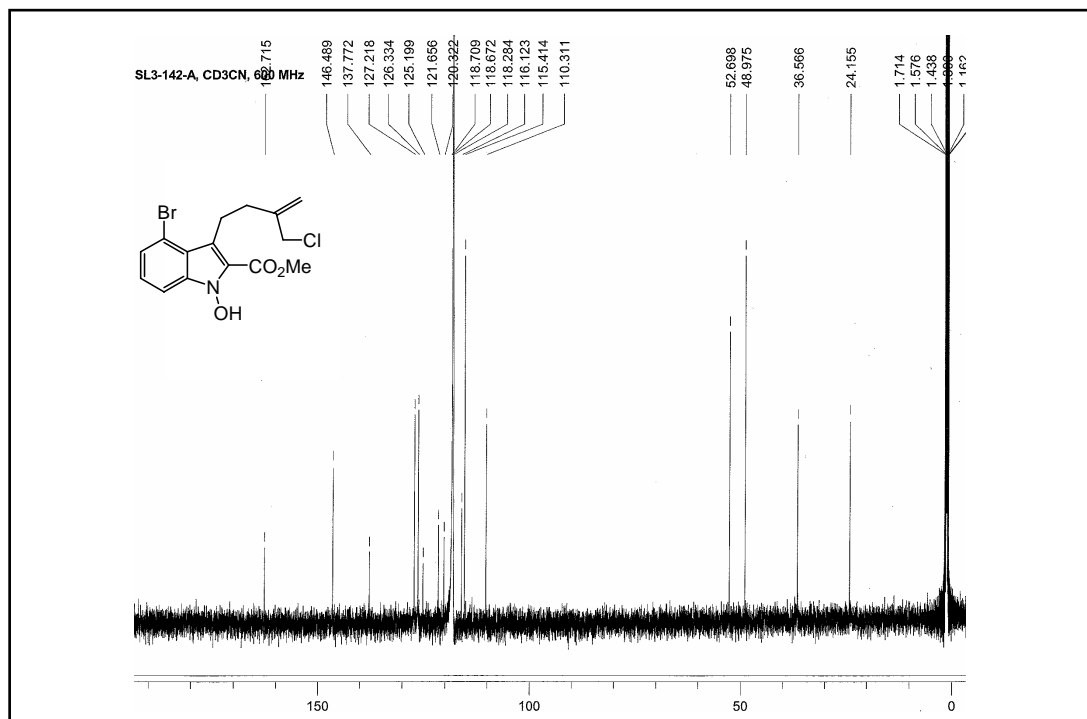
**Spectrum 2.109** <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN) spectrum of compound 2.52.



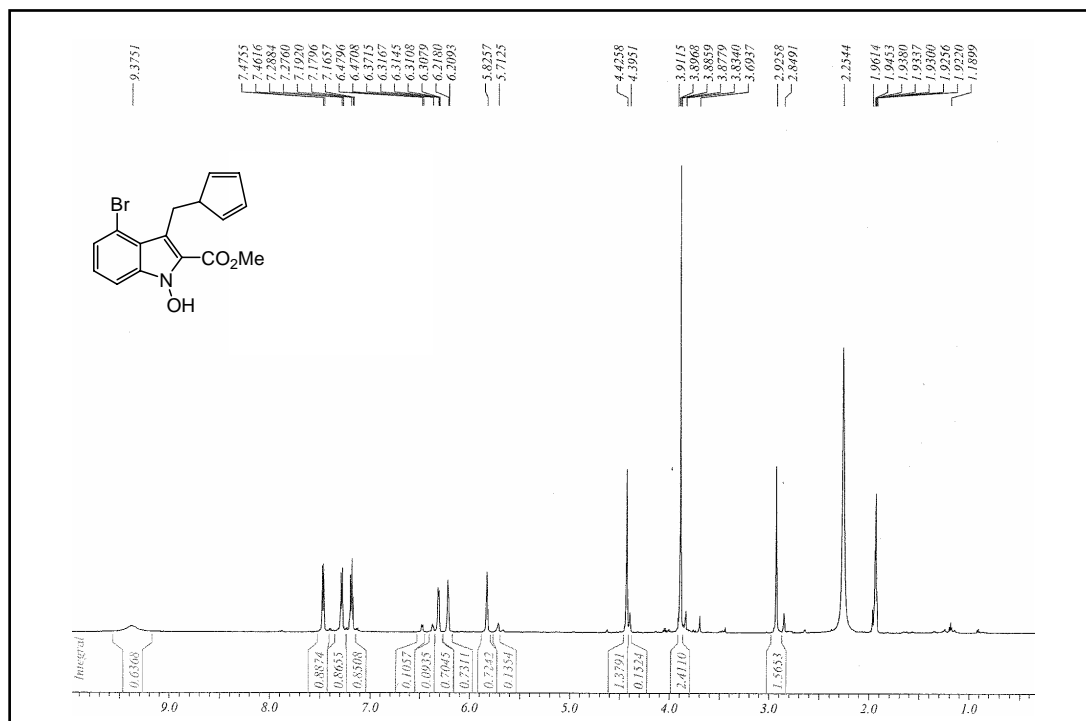
**Spectrum 2.110** <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>CN) spectrum of compound 2.52.



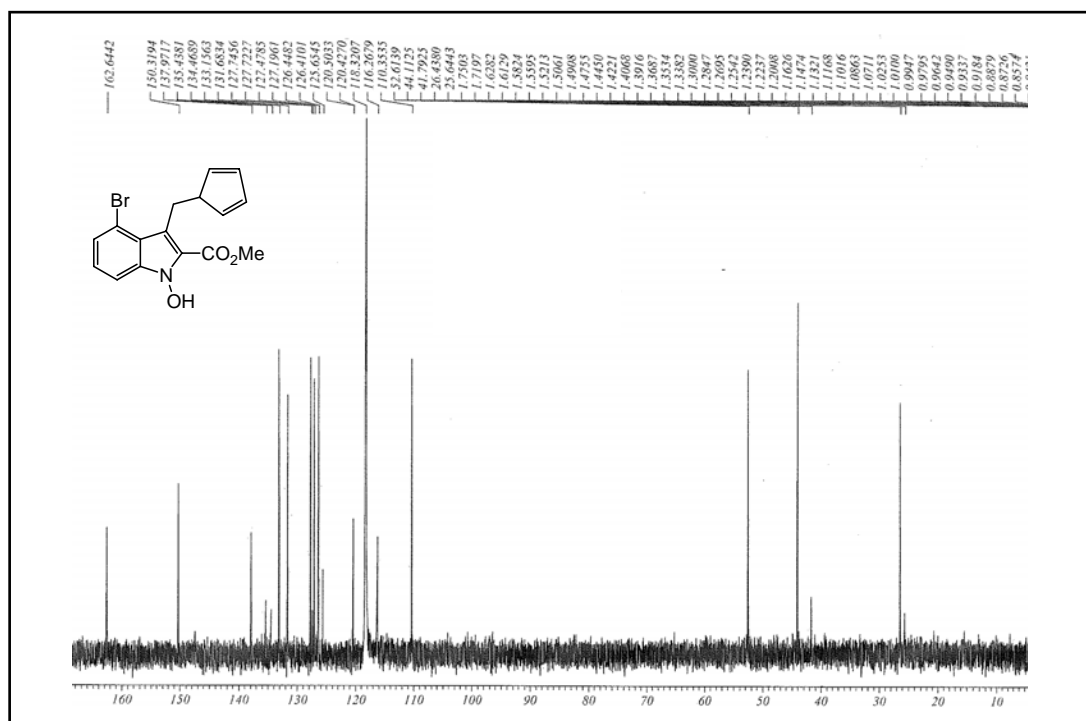
Spectrum 2.111  $^1\text{H NMR}$  (600 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.53.



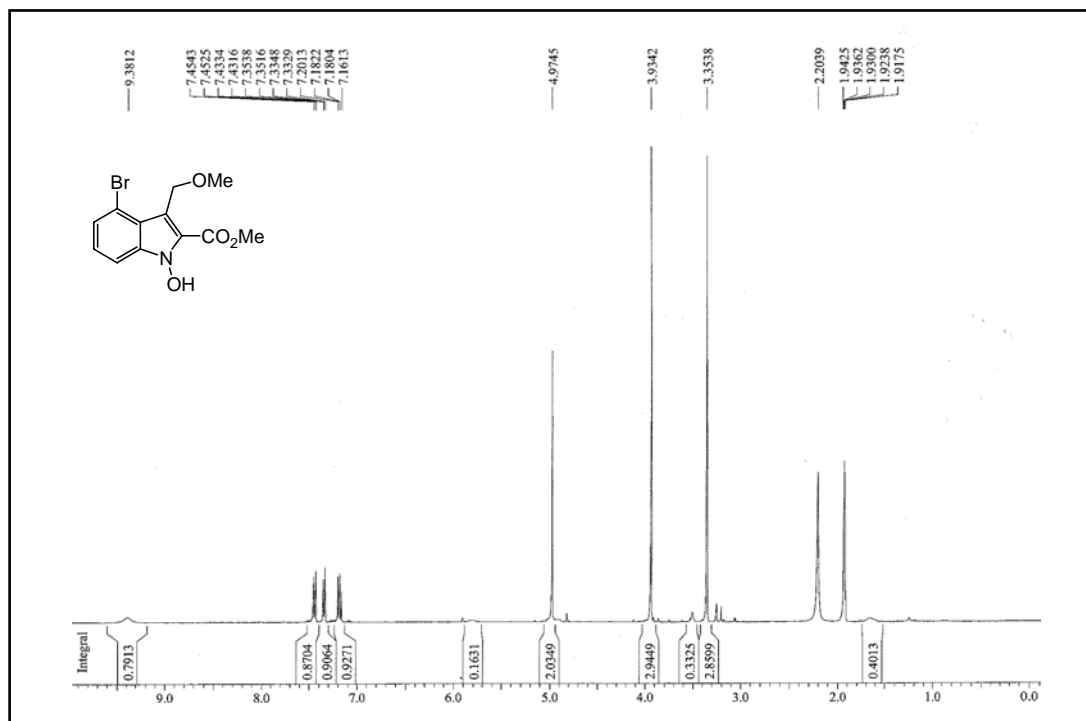
Spectrum 2.112  $^{13}\text{C NMR}$  (150 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.53.



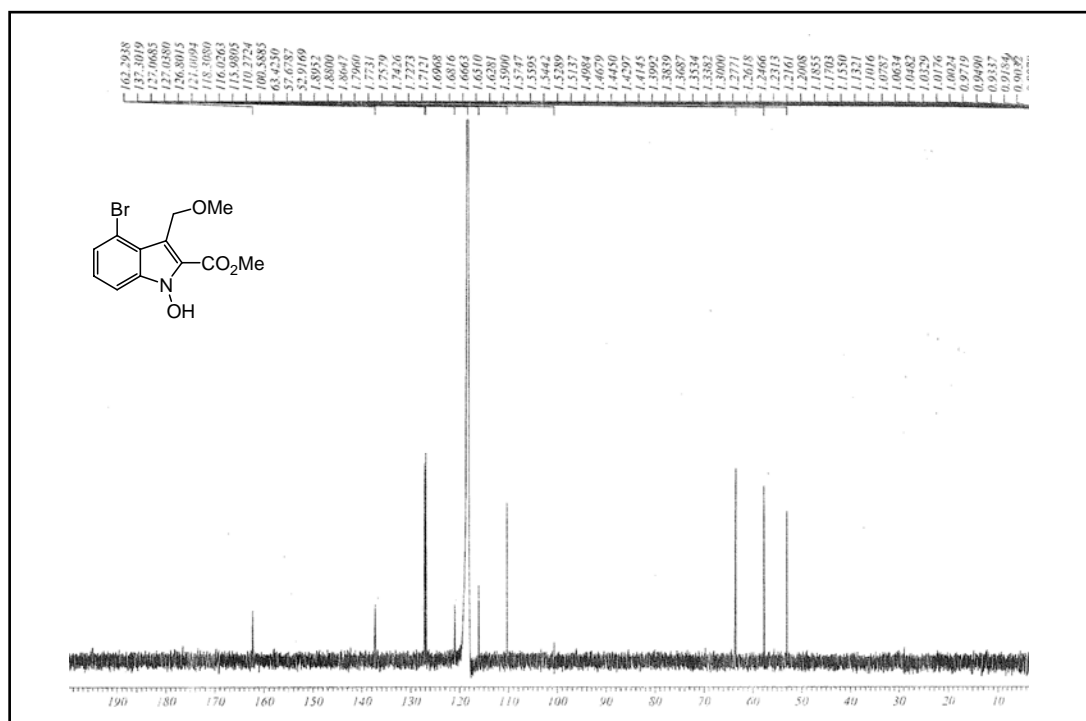
Spectrum 2.113  $^1\text{H NMR}$  (600 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.54.



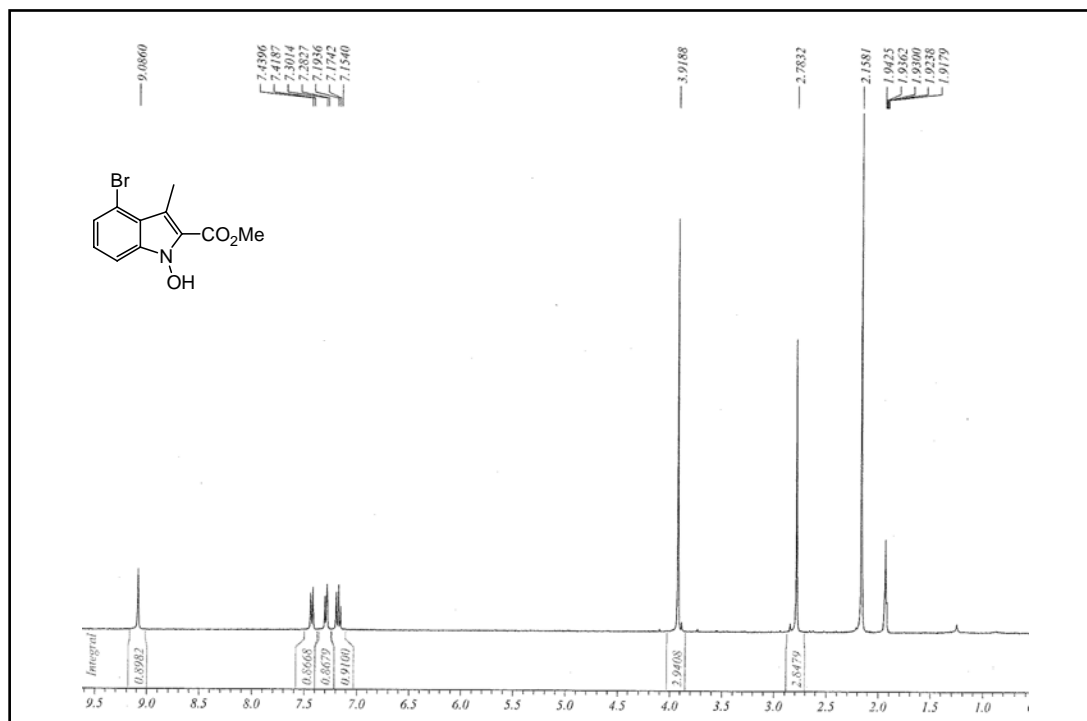
Spectrum 2.114  $^{13}\text{C NMR}$  (150 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.54.



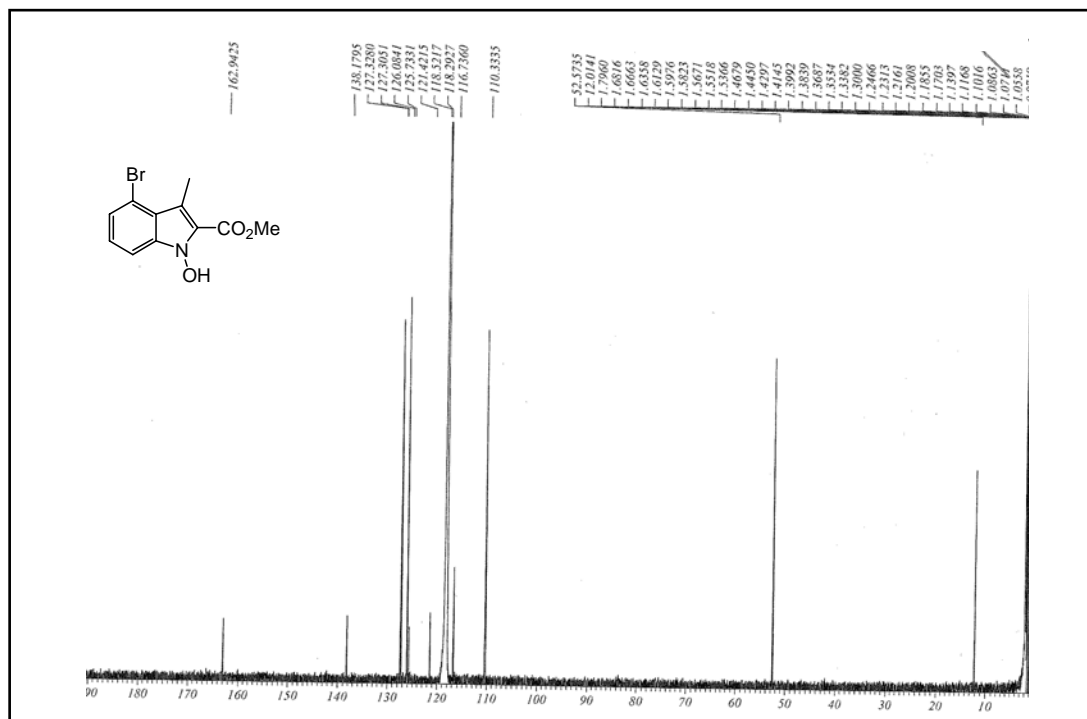
Spectrum 2.115 <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN) spectrum of compound 2.55.



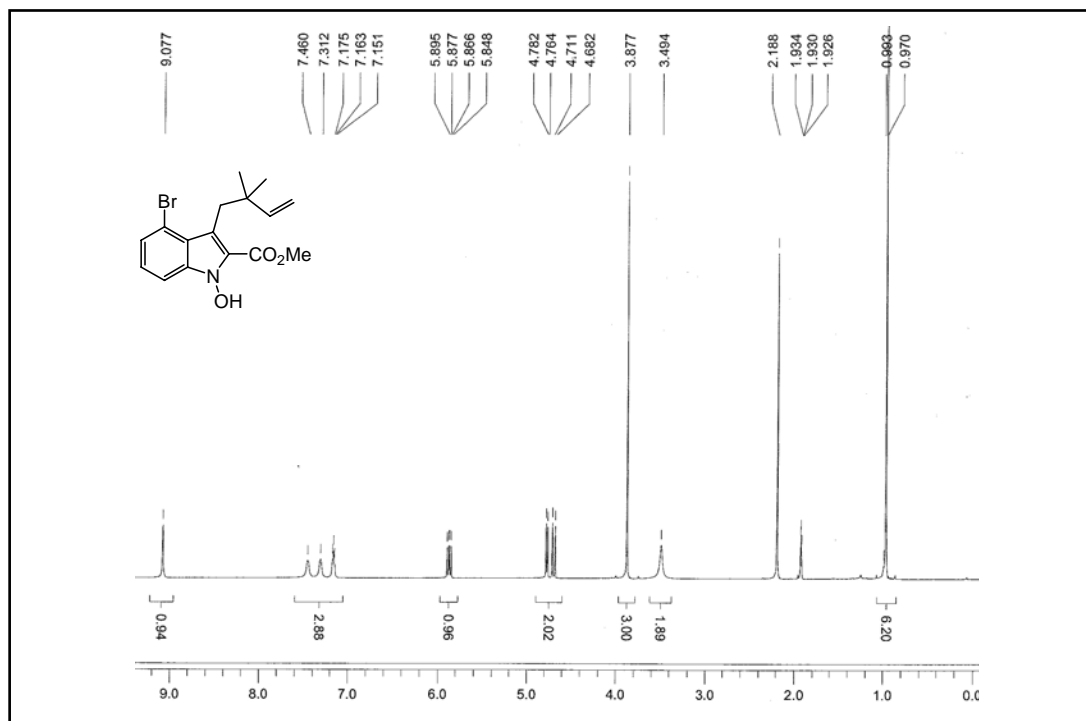
Spectrum 2.116 <sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>CN) spectrum of compound 2.55.



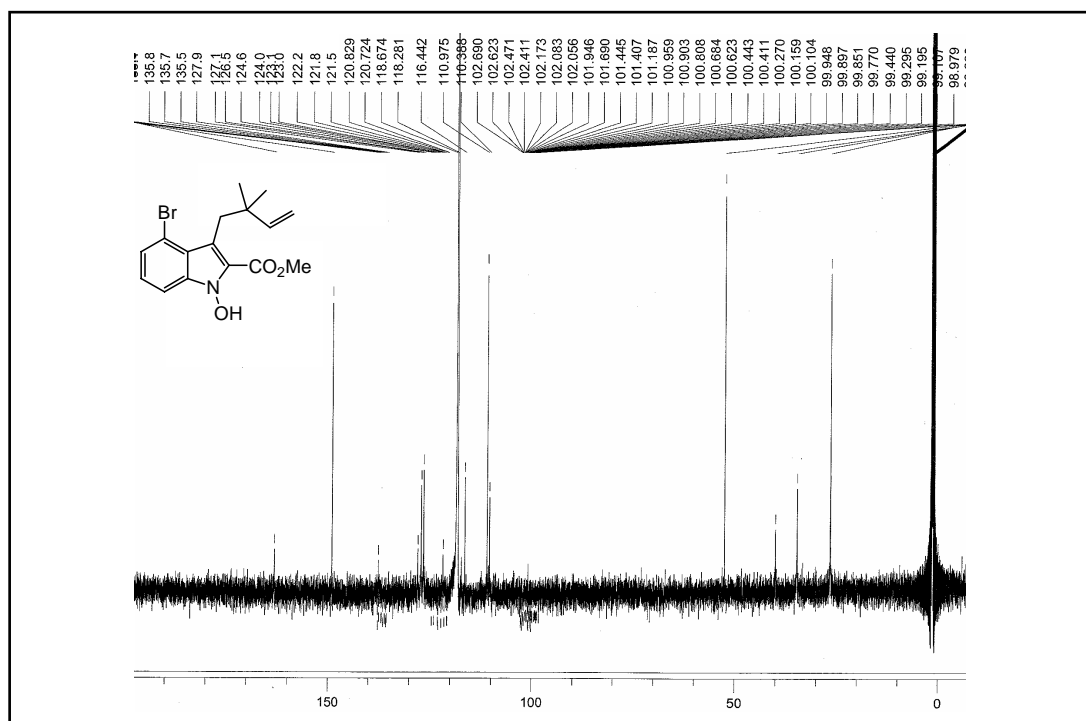
**Spectrum 2.117** <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN) spectrum of compound **2.56**.



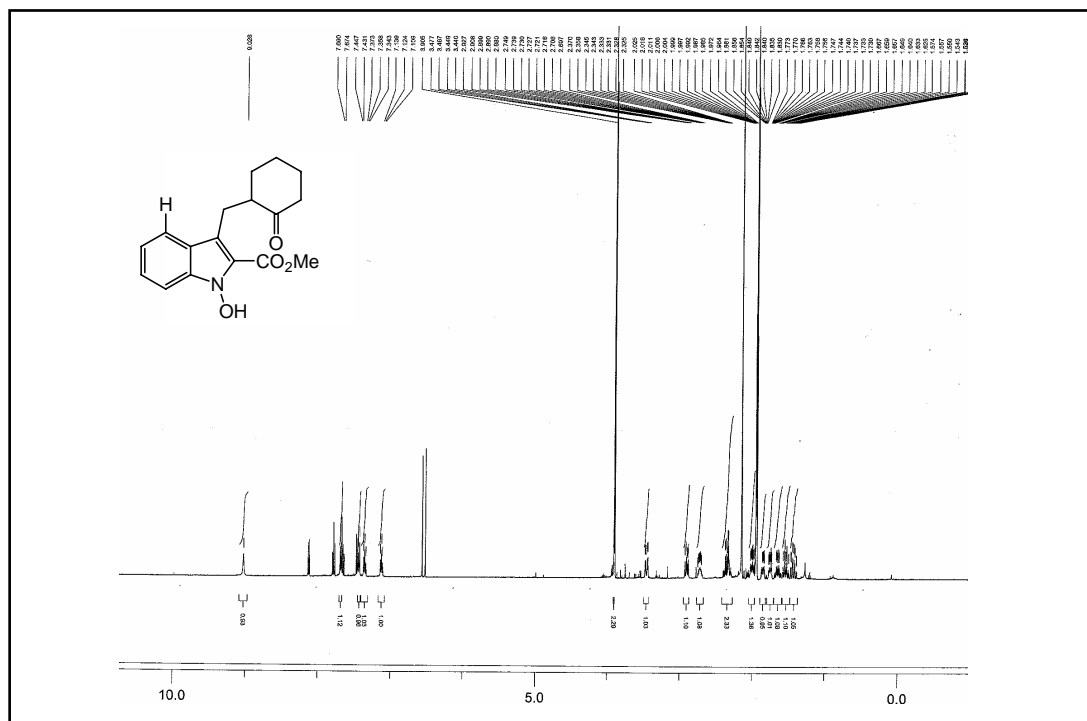
**Spectrum 2.118** <sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>CN) spectrum of compound **2.56**.



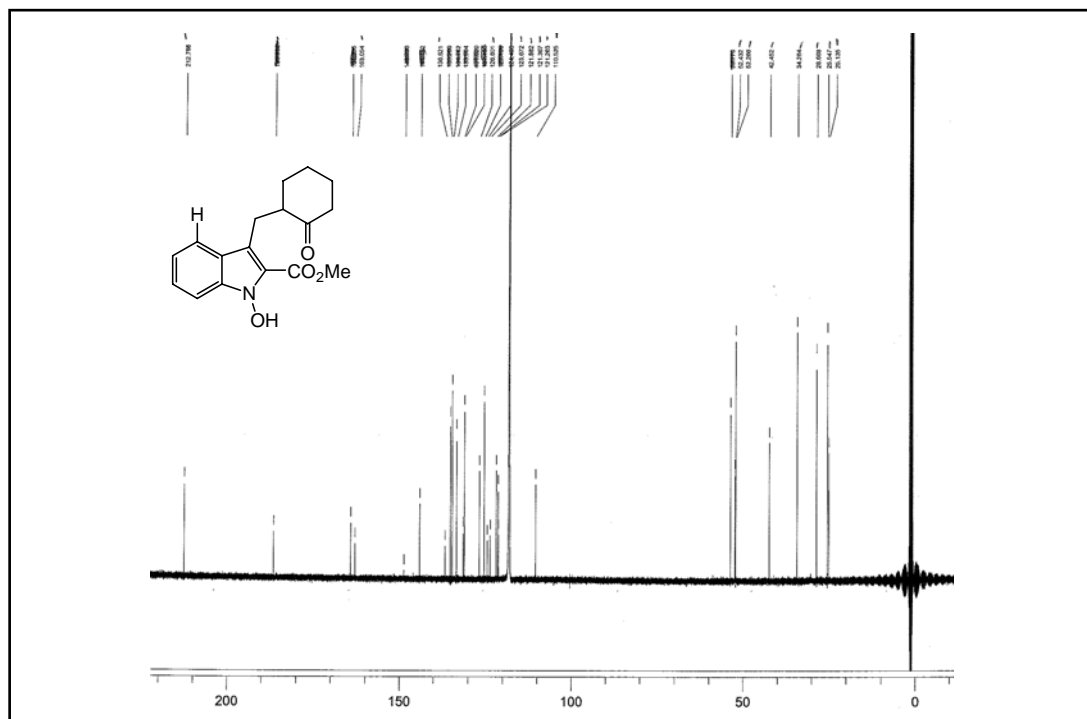
Spectrum 2.119  $^1\text{H NMR}$  (600 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.57.



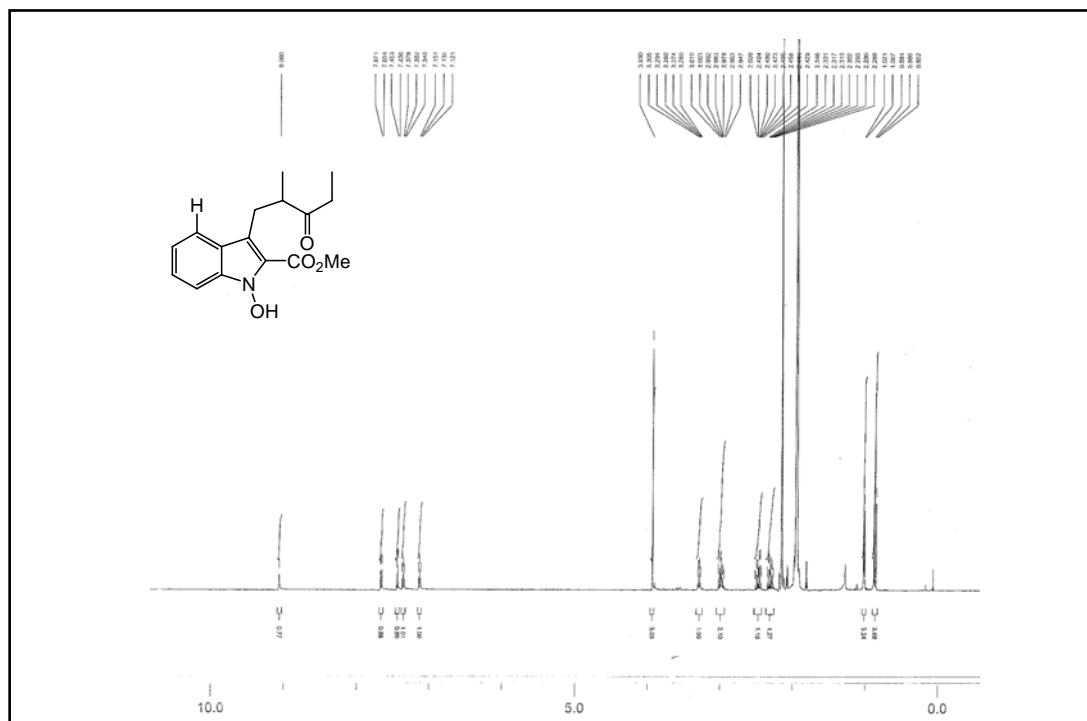
Spectrum 2.120  $^{13}\text{C NMR}$  (150 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.57.



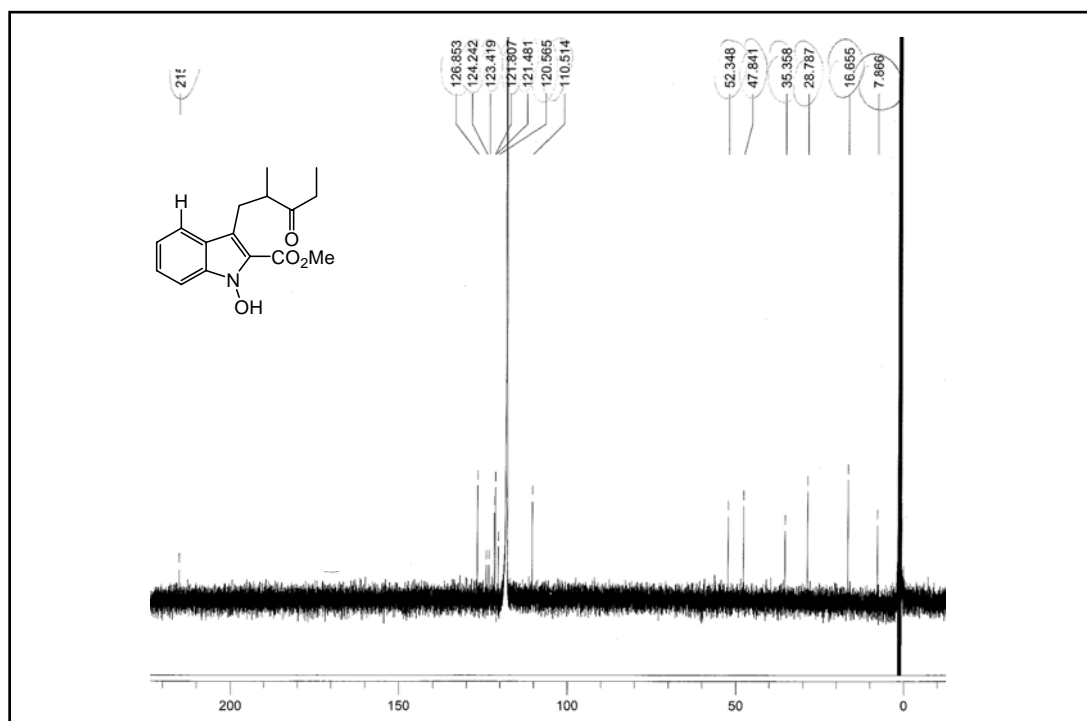
**Spectrum 2.121** <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN) spectrum of compound **2.61**.



**Spectrum 2.122** <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>CN) spectrum of compound **2.61**.

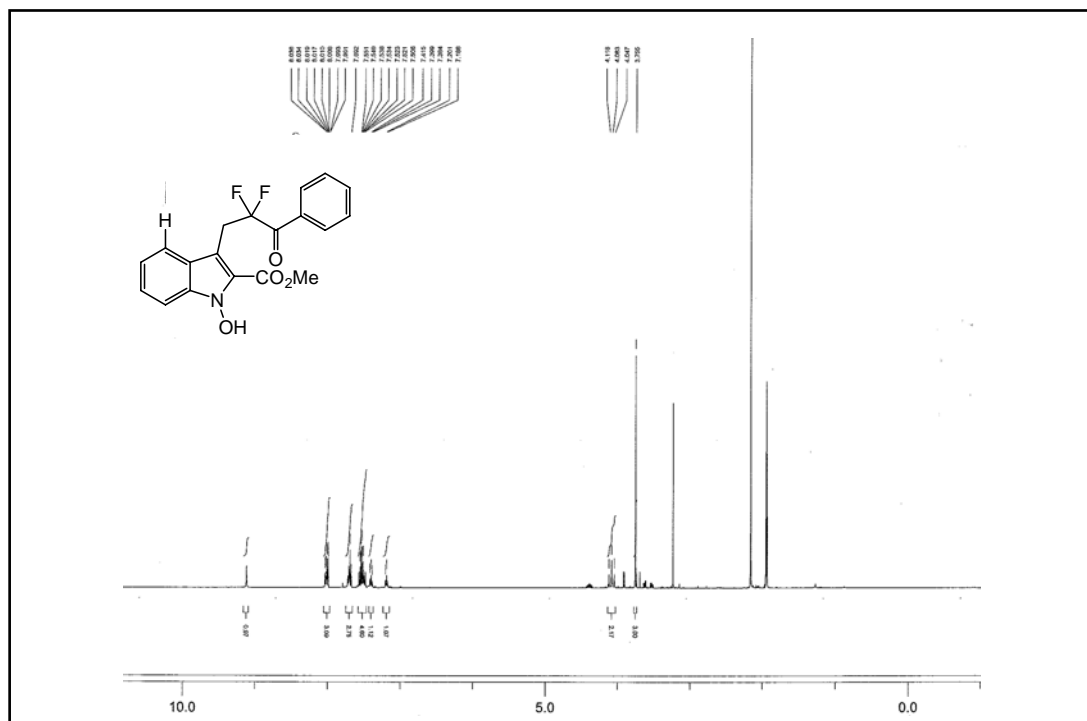


**Spectrum 2.123**  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.62**.

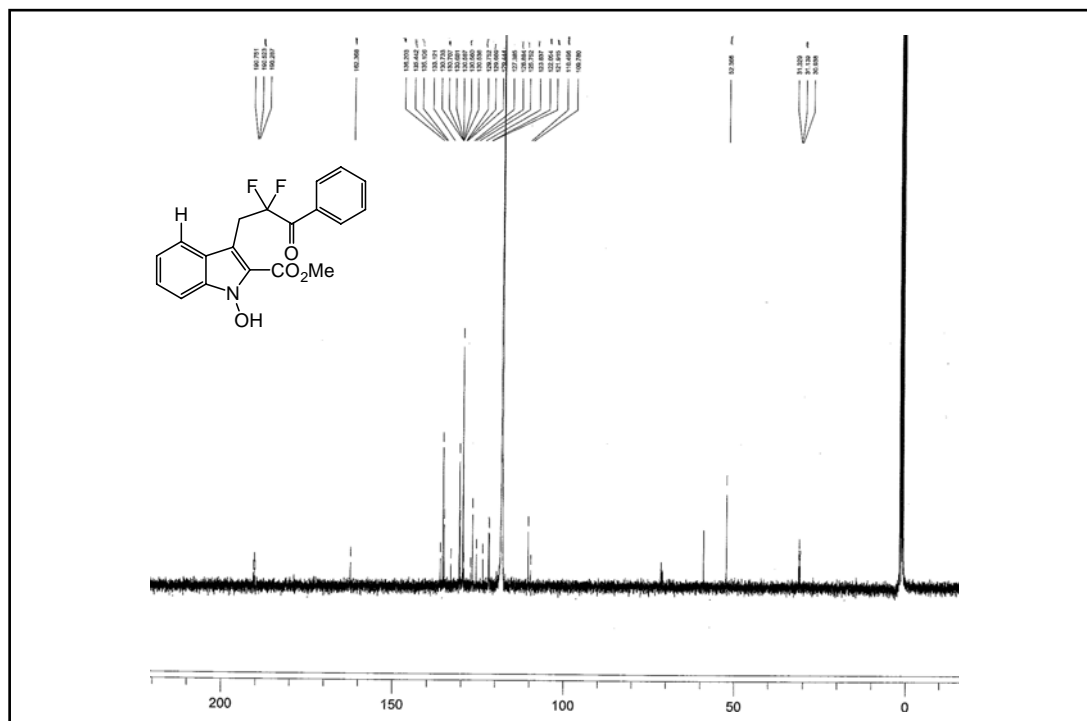


**Spectrum 2.124**  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.62**.

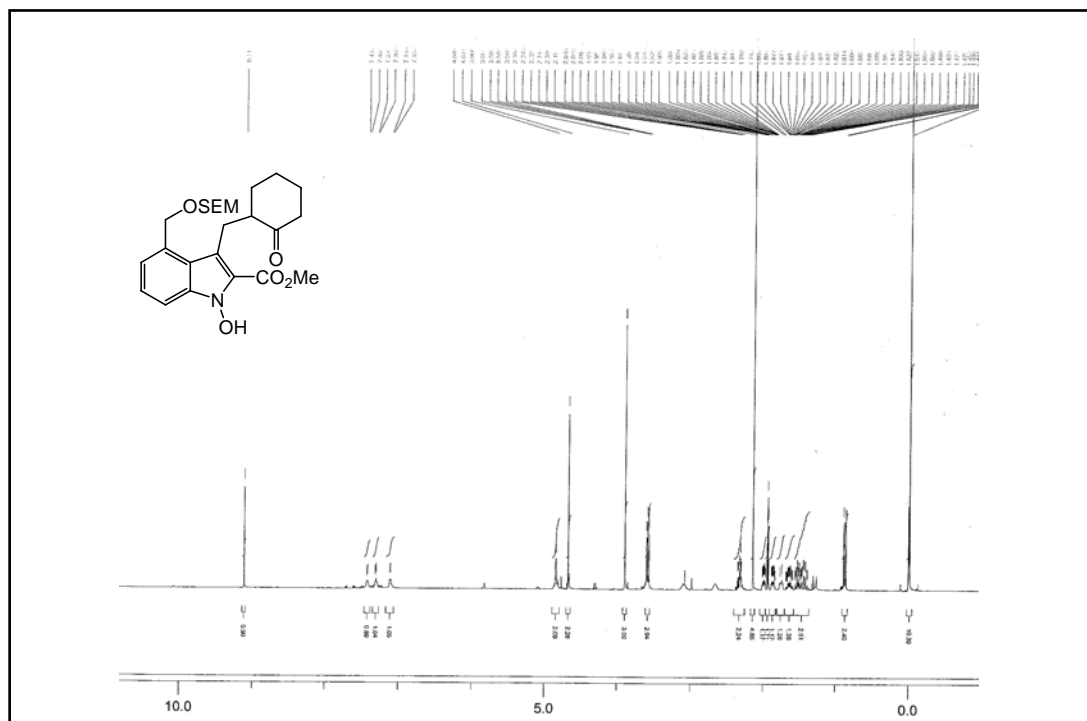




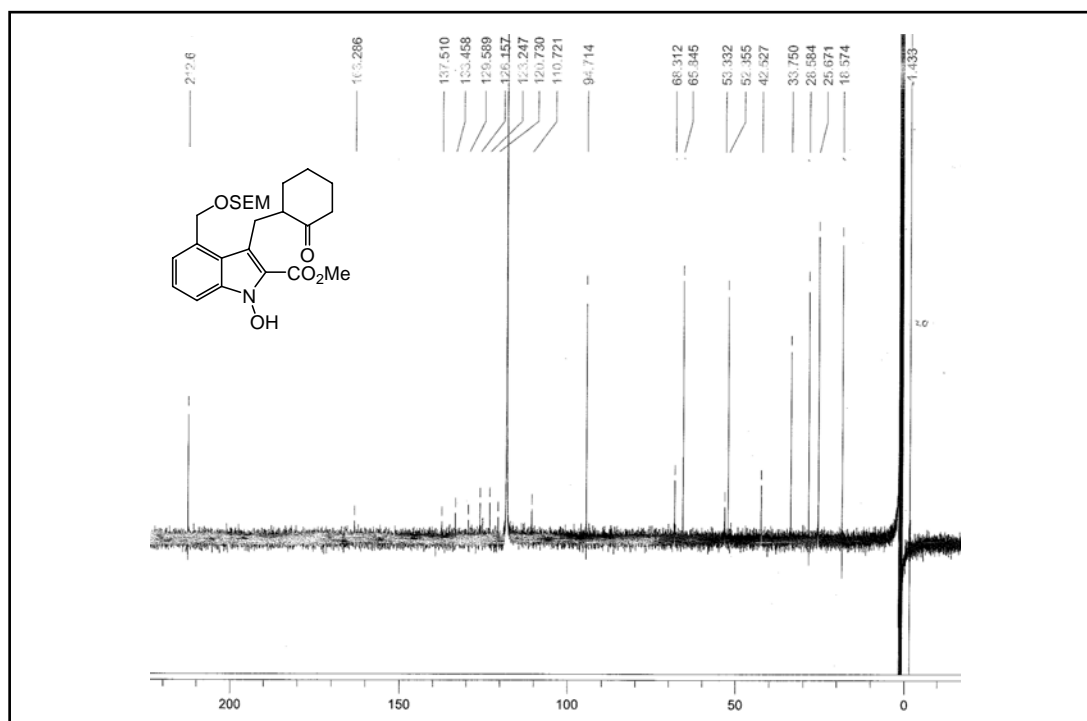
**Spectrum 2.125**  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.63.



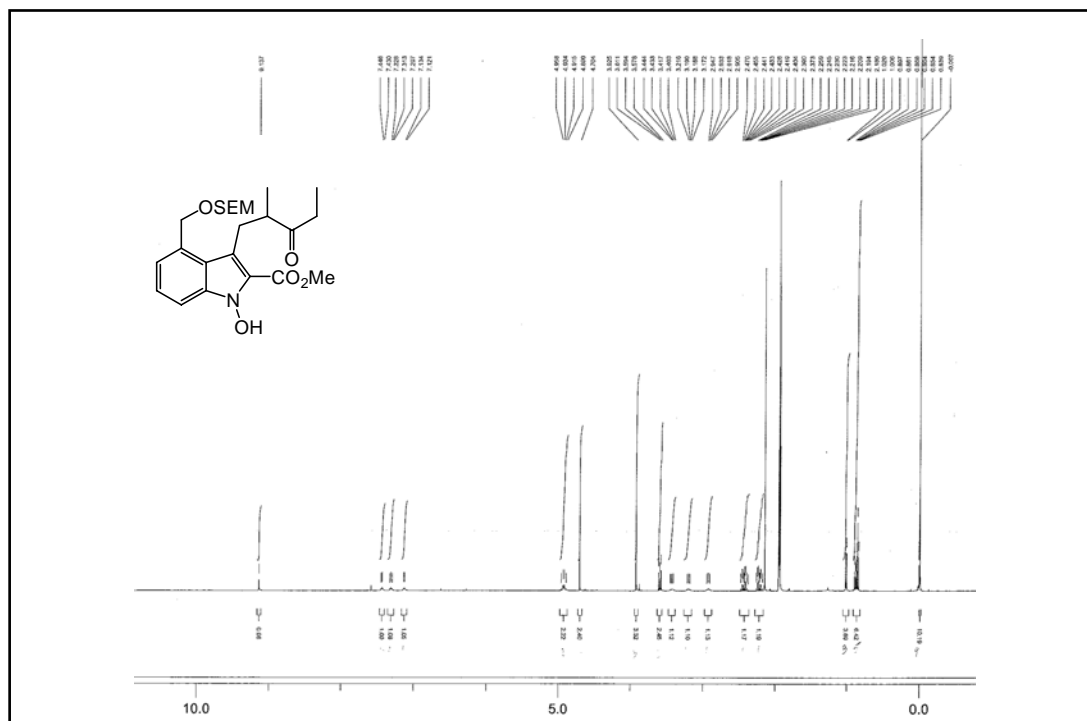
**Spectrum 2.126**  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.63.



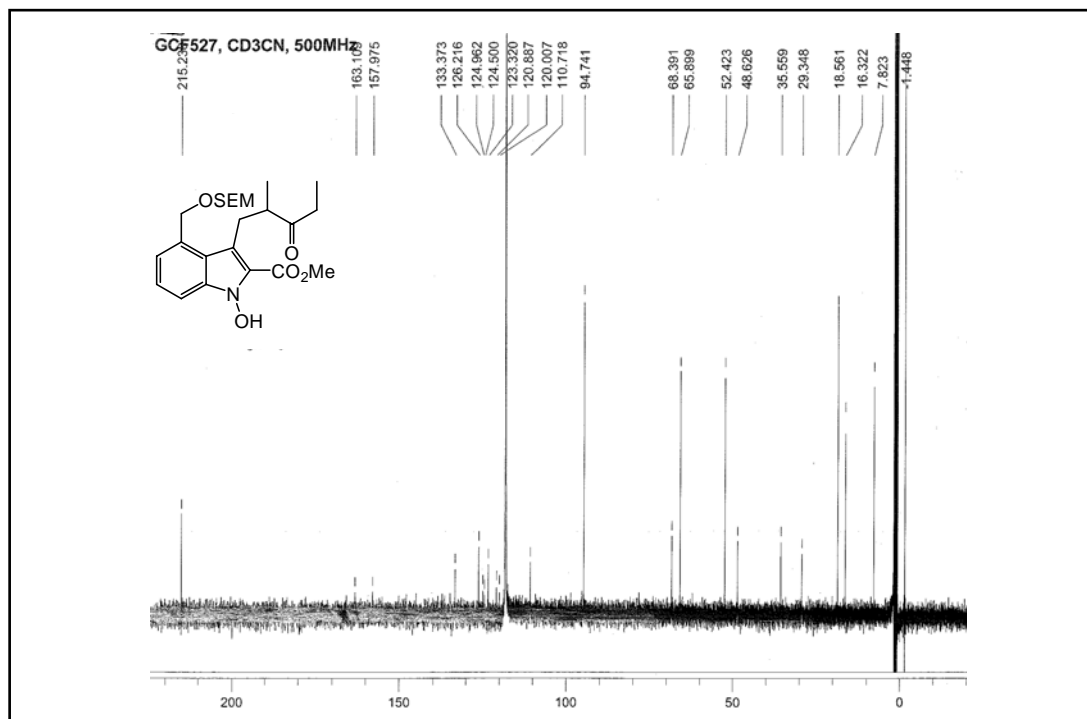
**Spectrum 2.127**  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.64**.



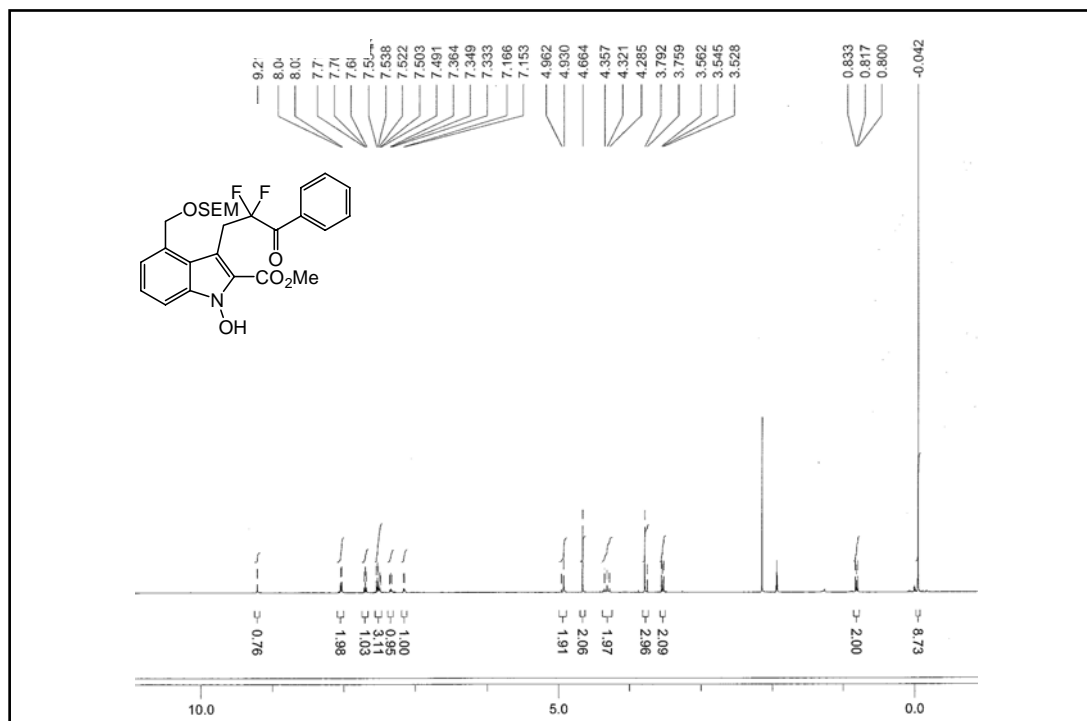
**Spectrum 2.128**  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.64**.



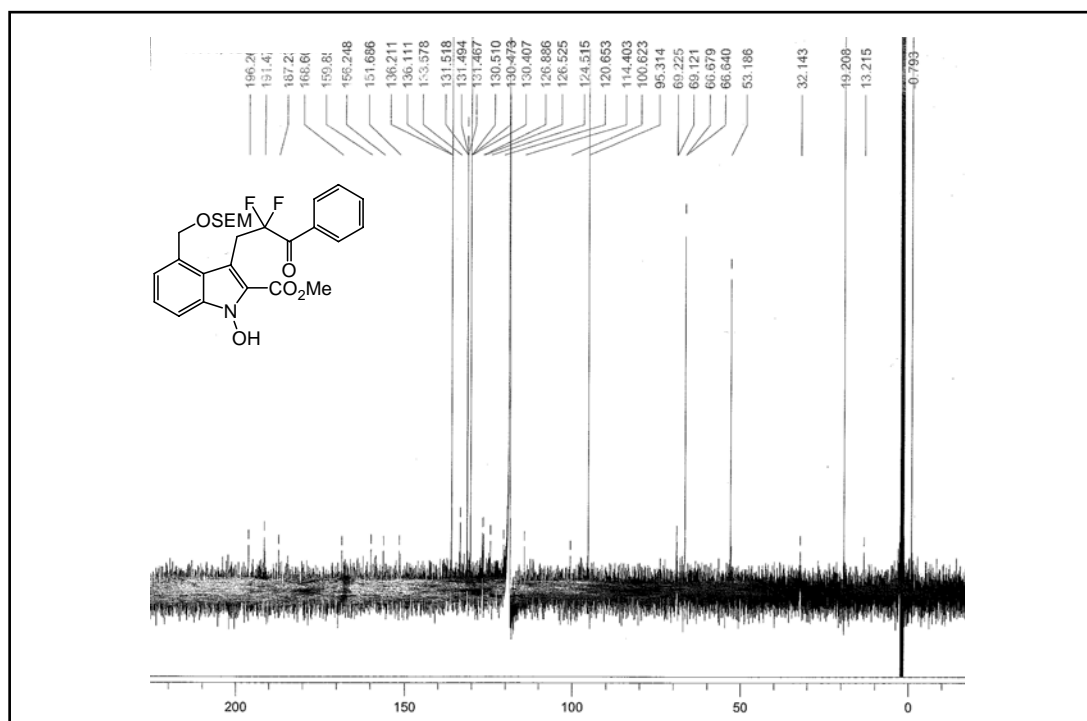
**Spectrum 2.129**  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.65**.



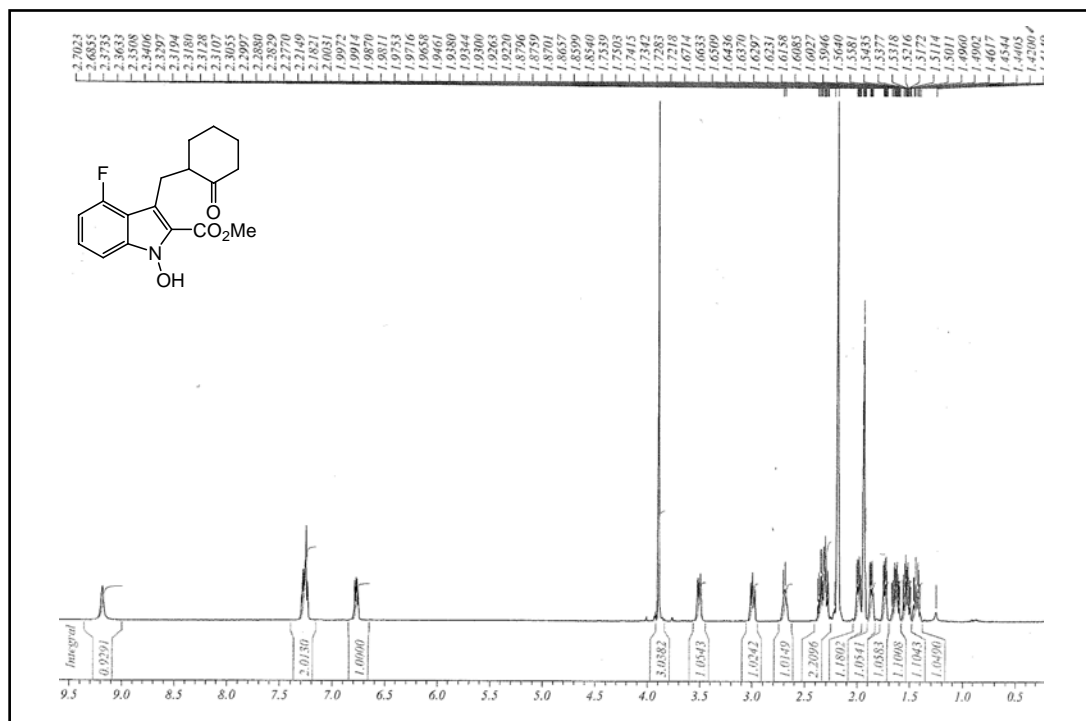
**Spectrum 2.130**  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.65**.



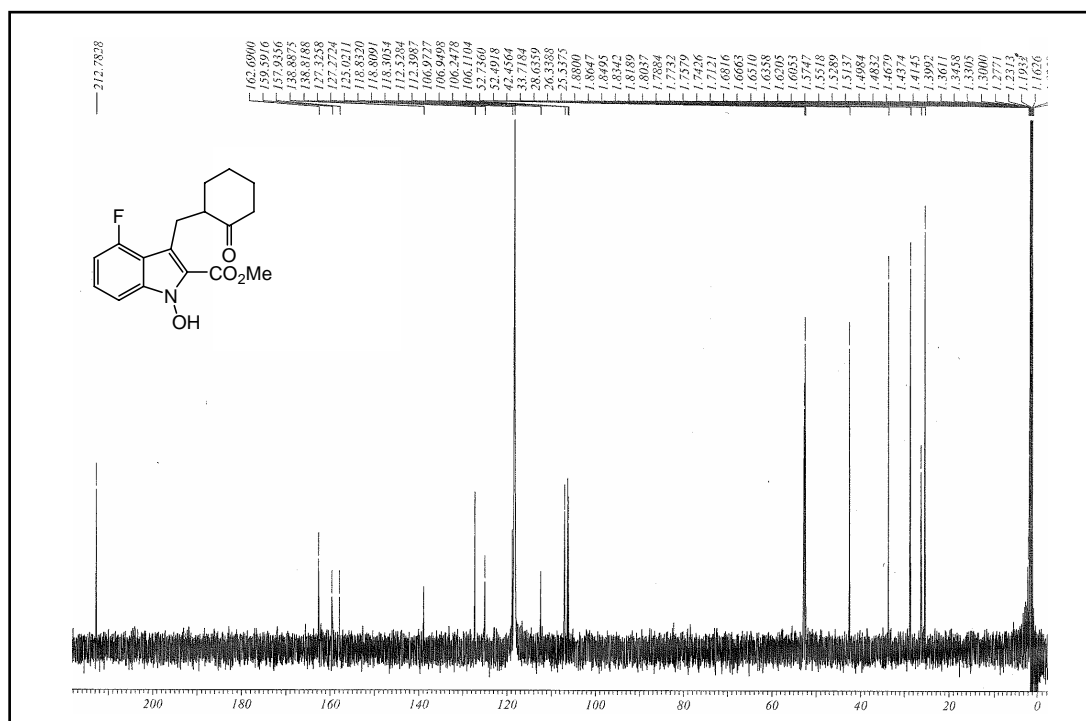
**Spectrum 2.131**  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.66**.



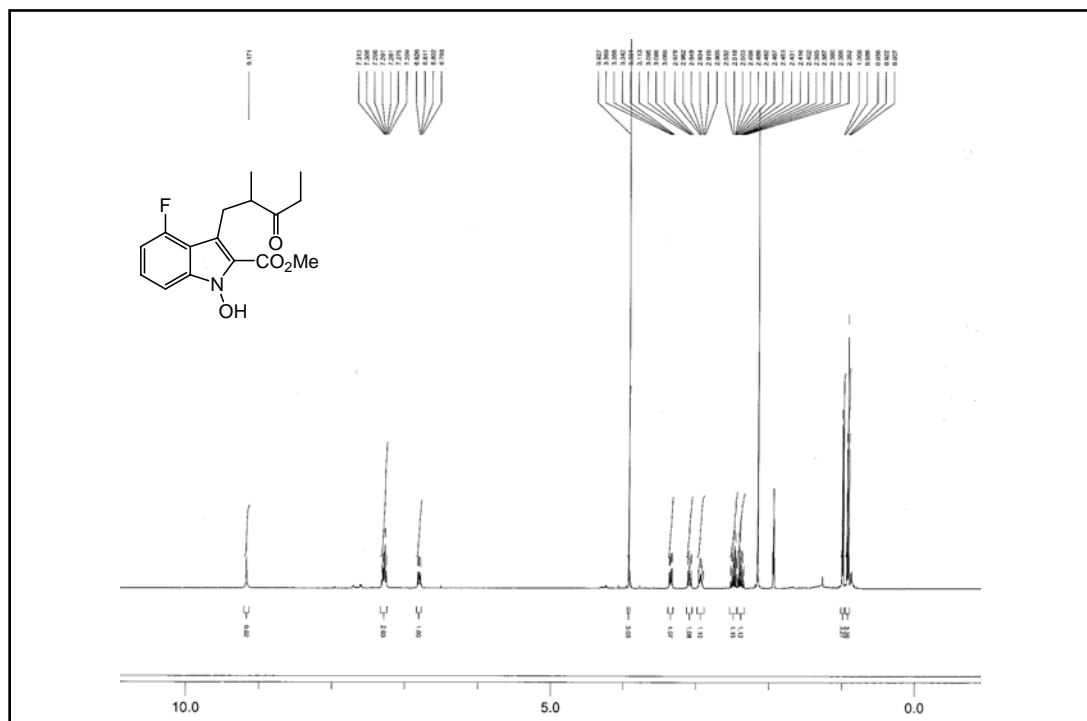
**Spectrum 2.132**  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.66**.



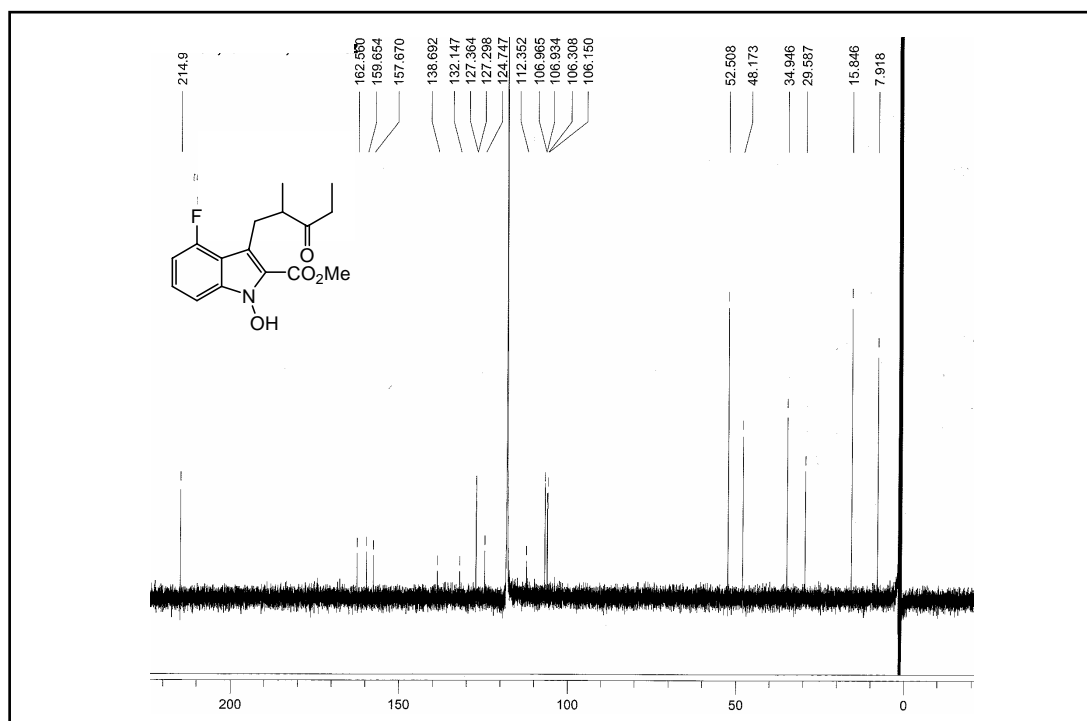
Spectrum 2.133 <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN) spectrum of compound 2.67.



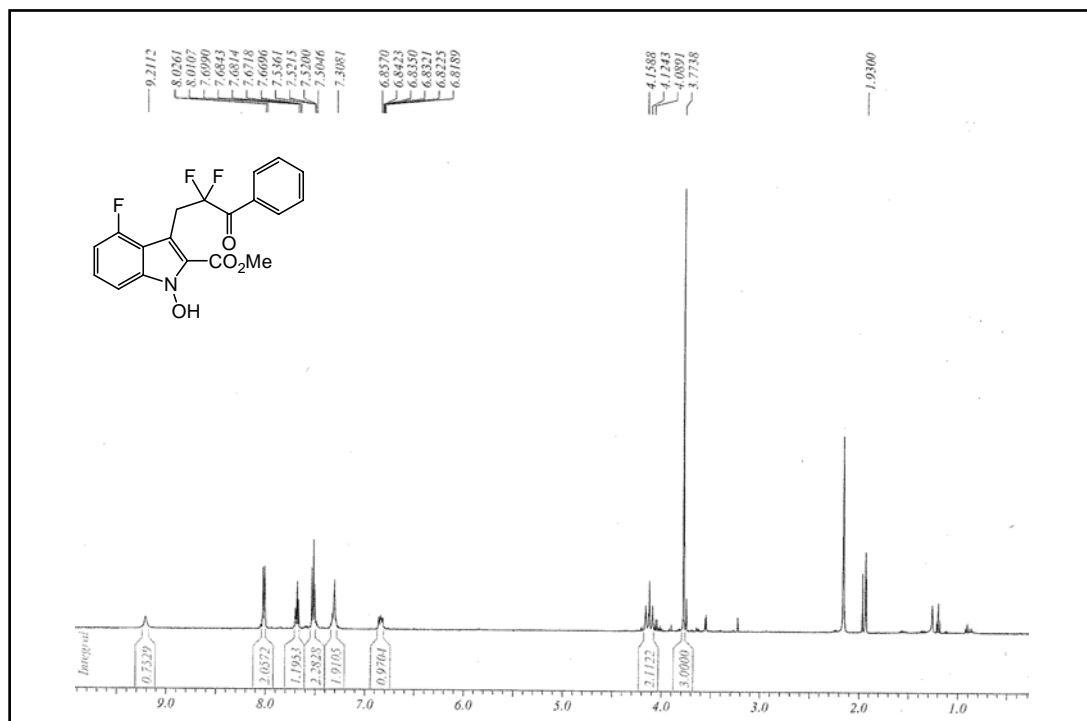
Spectrum 2.134 <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>CN) spectrum of compound 2.67.



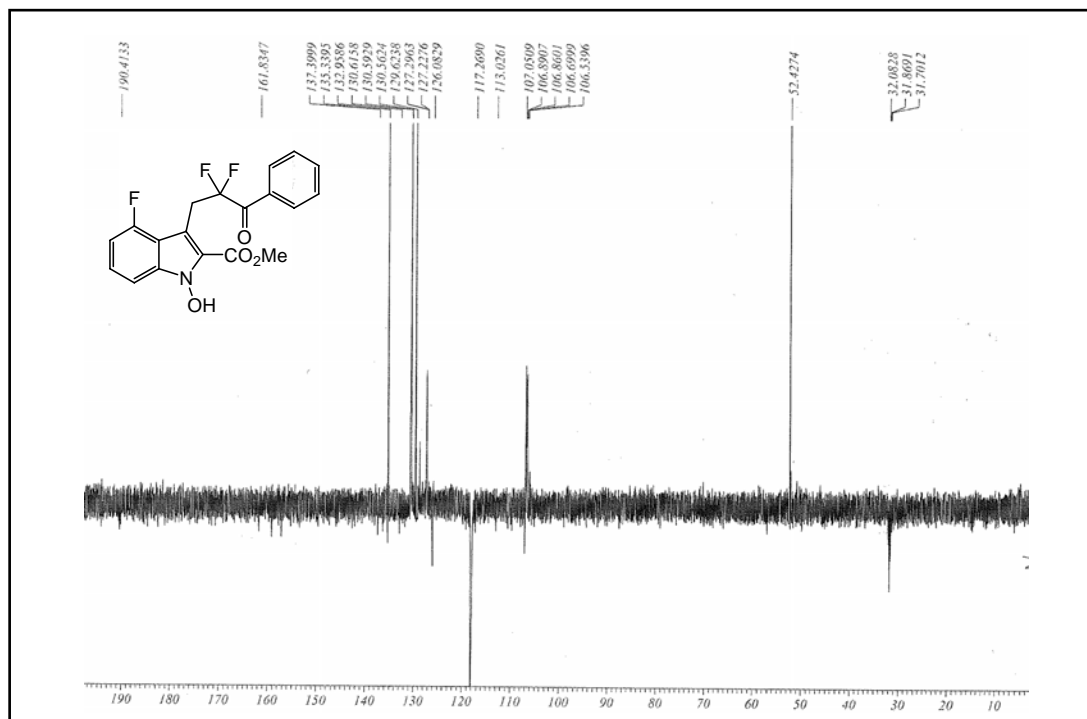
**Spectrum 2.135**  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.68**.



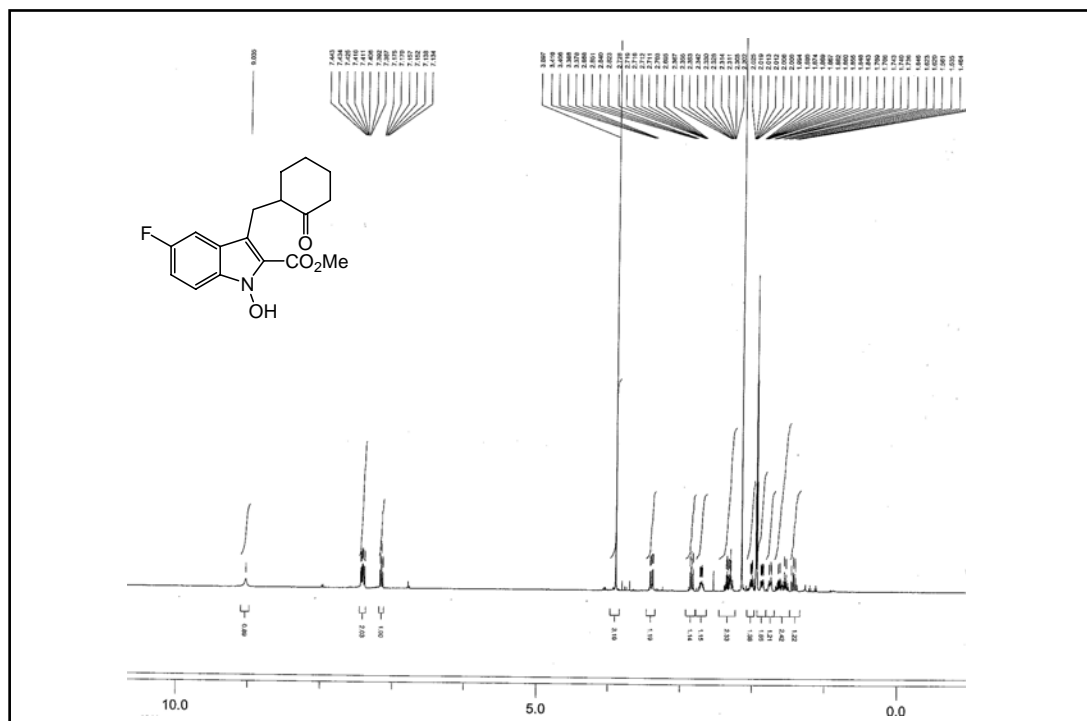
**Spectrum 2.136**  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.68**.



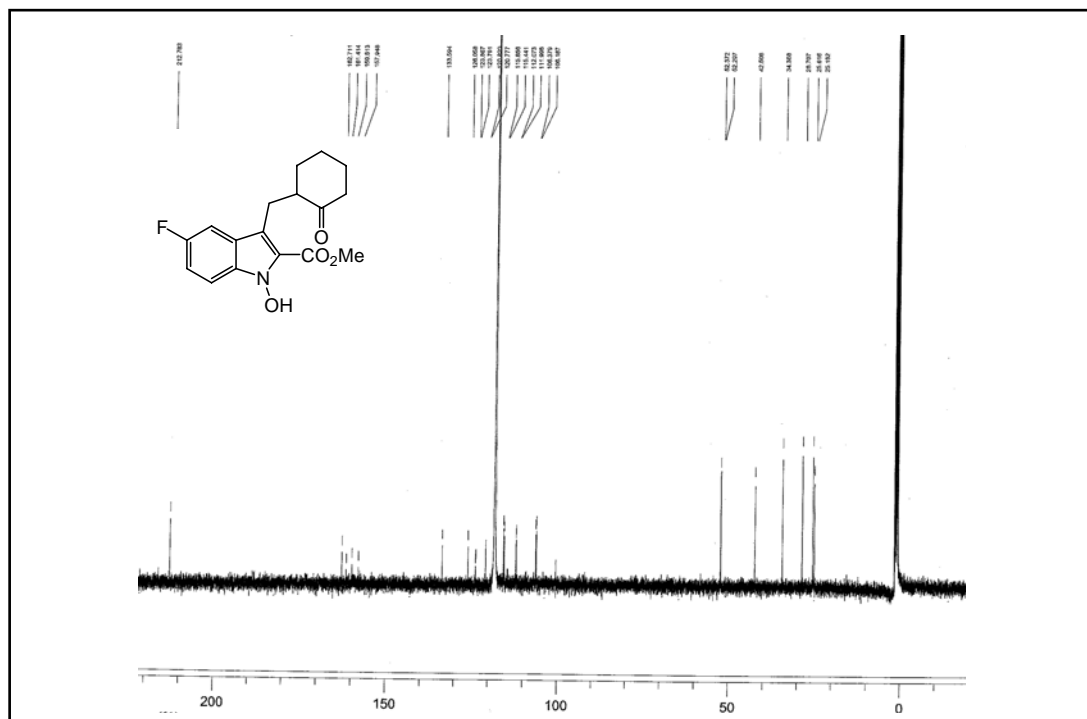
**Spectrum 2.137**  $^1\text{H NMR}$  (500 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.69.



**Spectrum 2.138**  $^{13}\text{C NMR}$  (125 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.69.



**Spectrum 2.139**  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.70**.

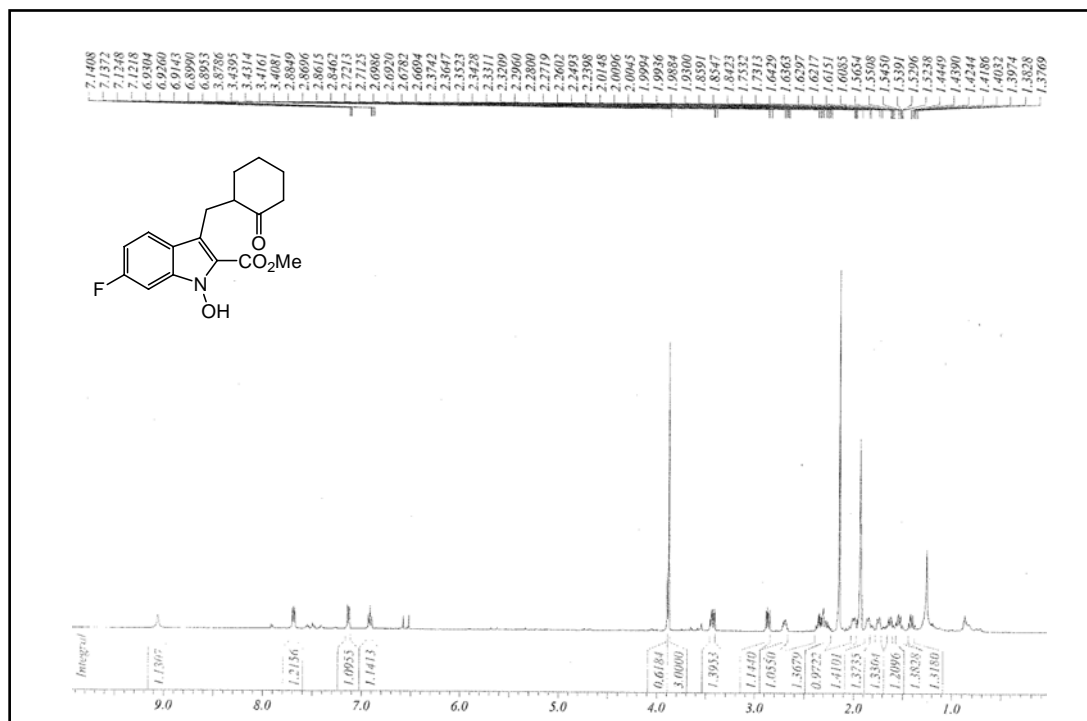


**Spectrum 2.140**  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound **2.70**.

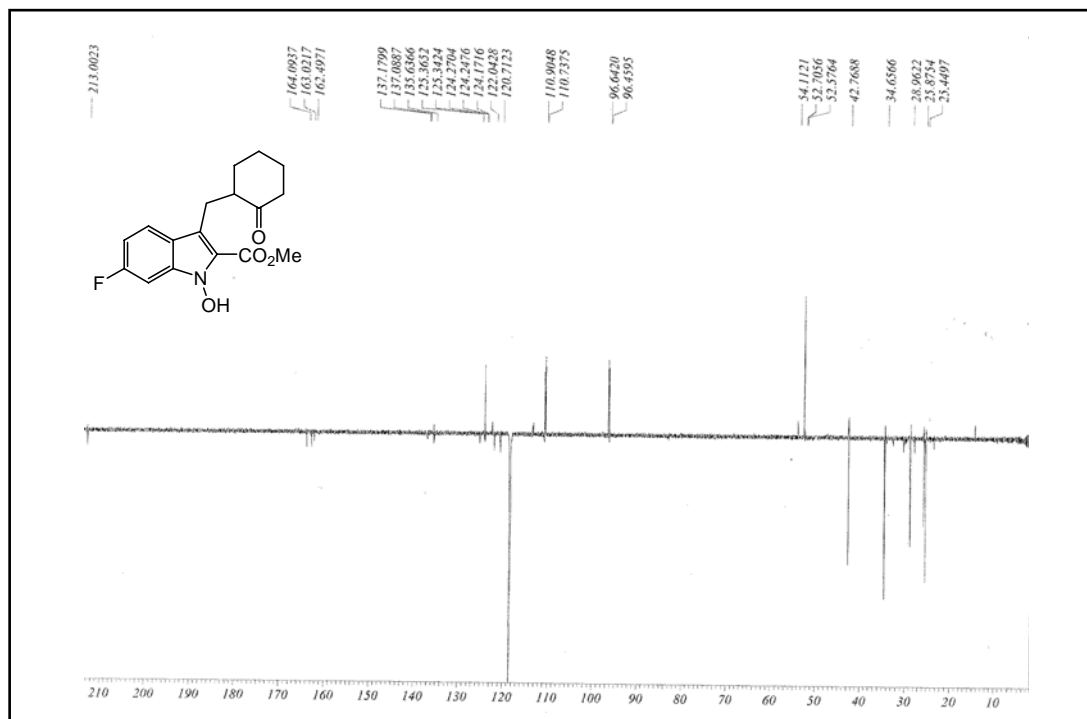




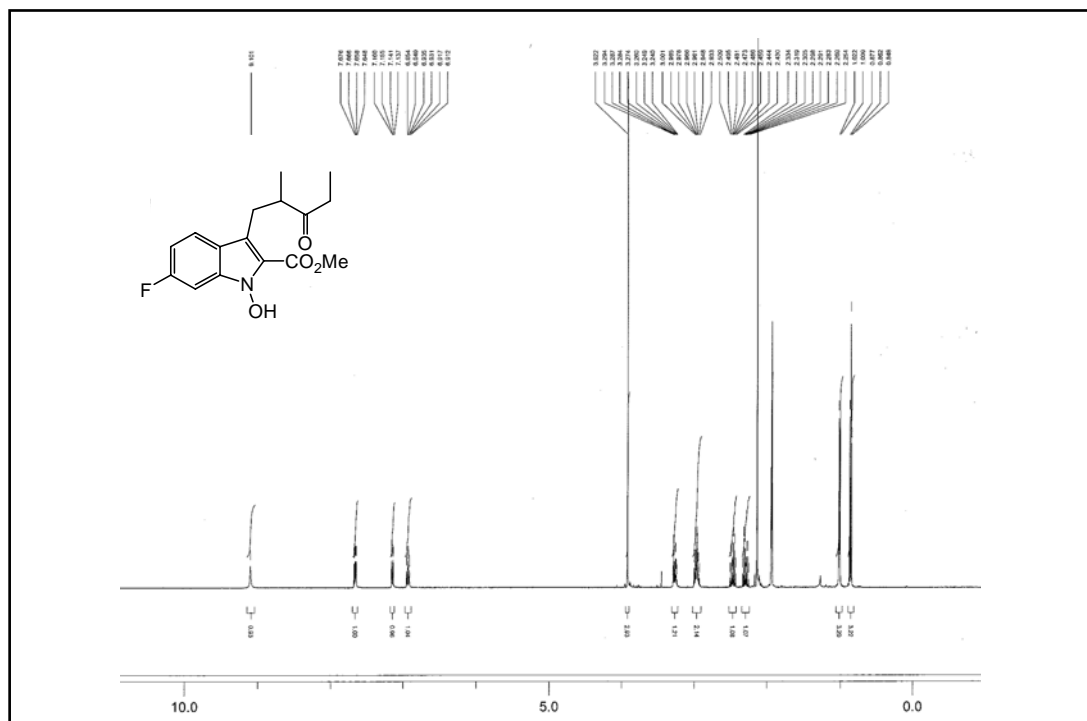




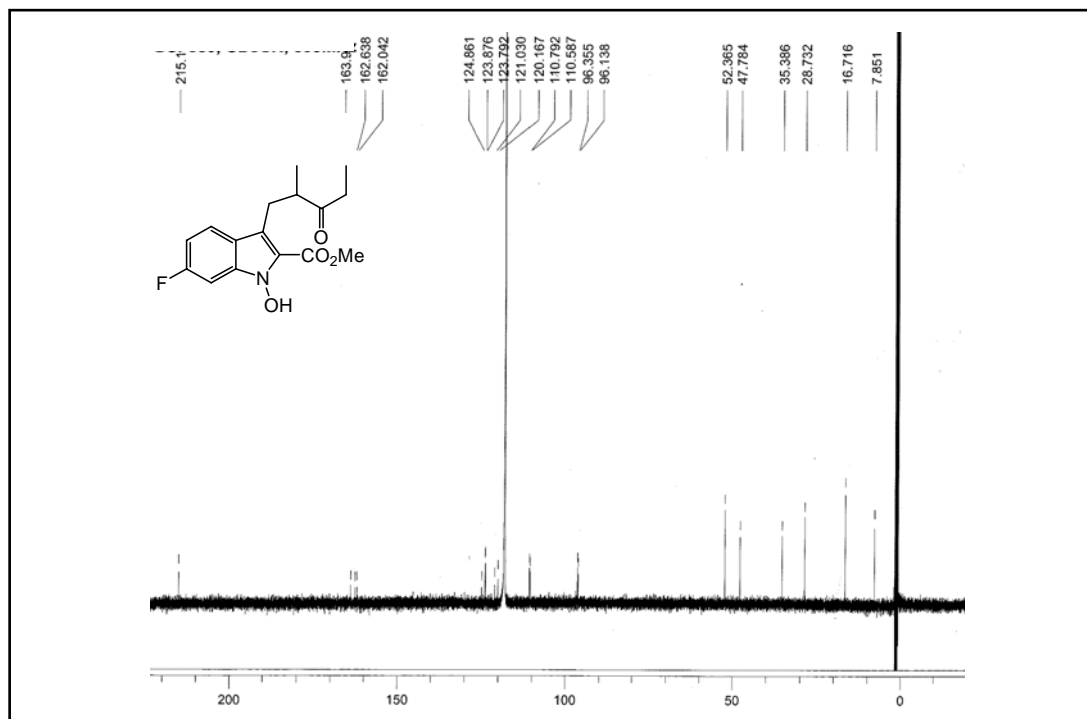
Spectrum 2.145 <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN) spectrum of compound 2.73.



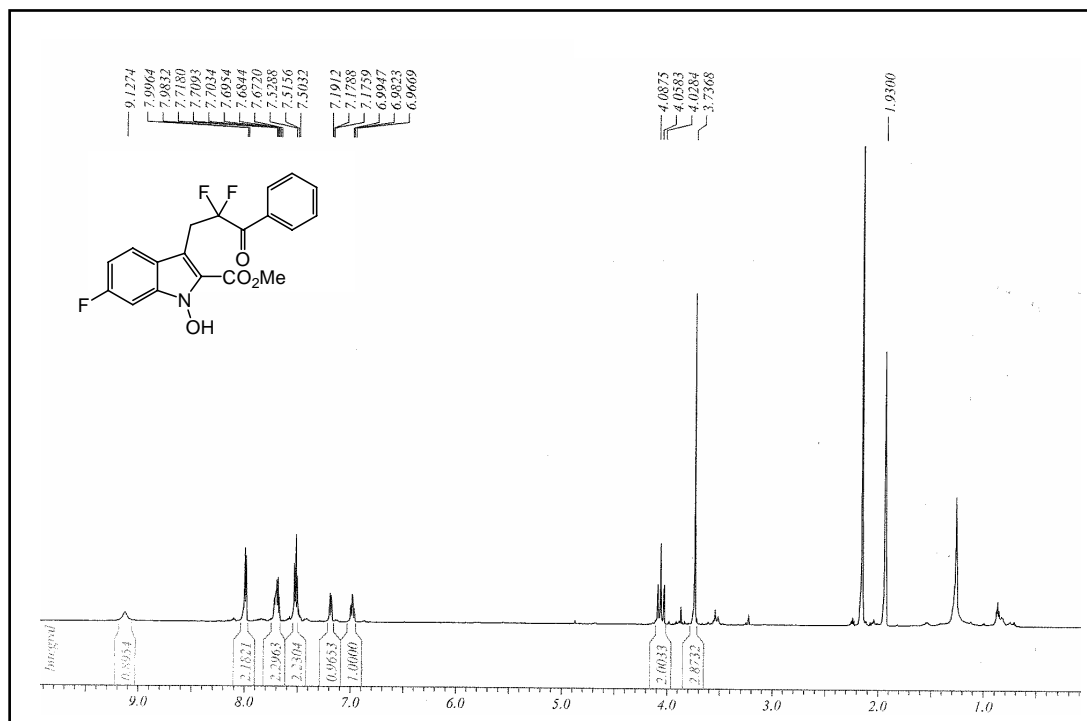
Spectrum 2.146 <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>CN) spectrum of compound 2.73.



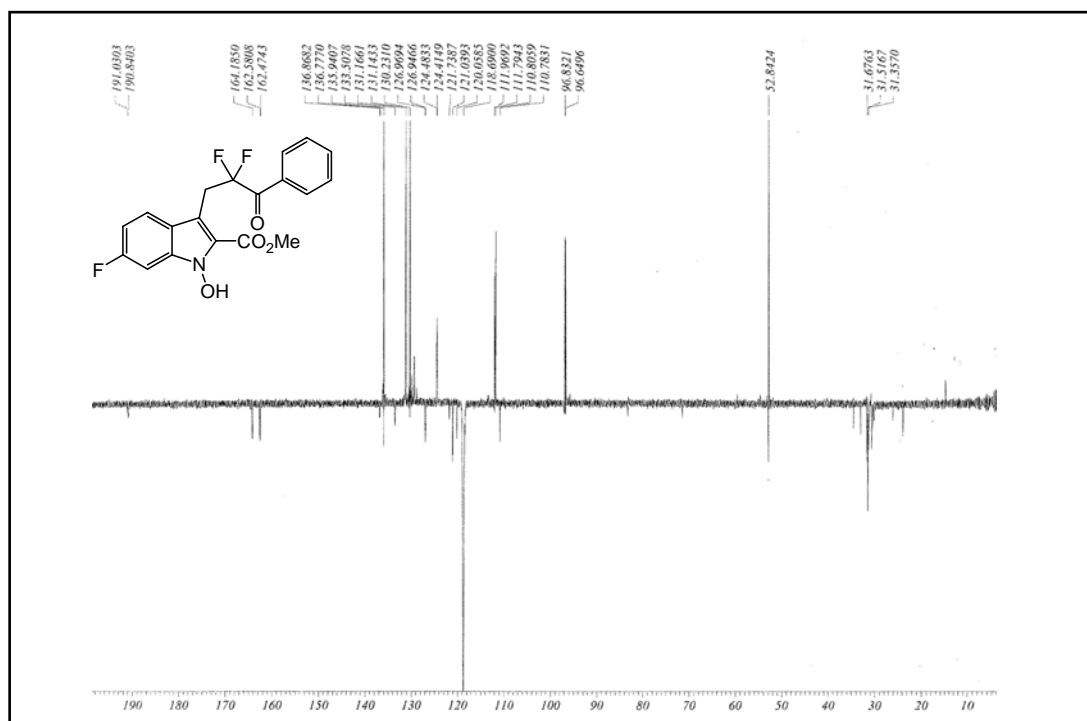
**Spectrum 2.147** <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>CN) spectrum of compound **2.74**.



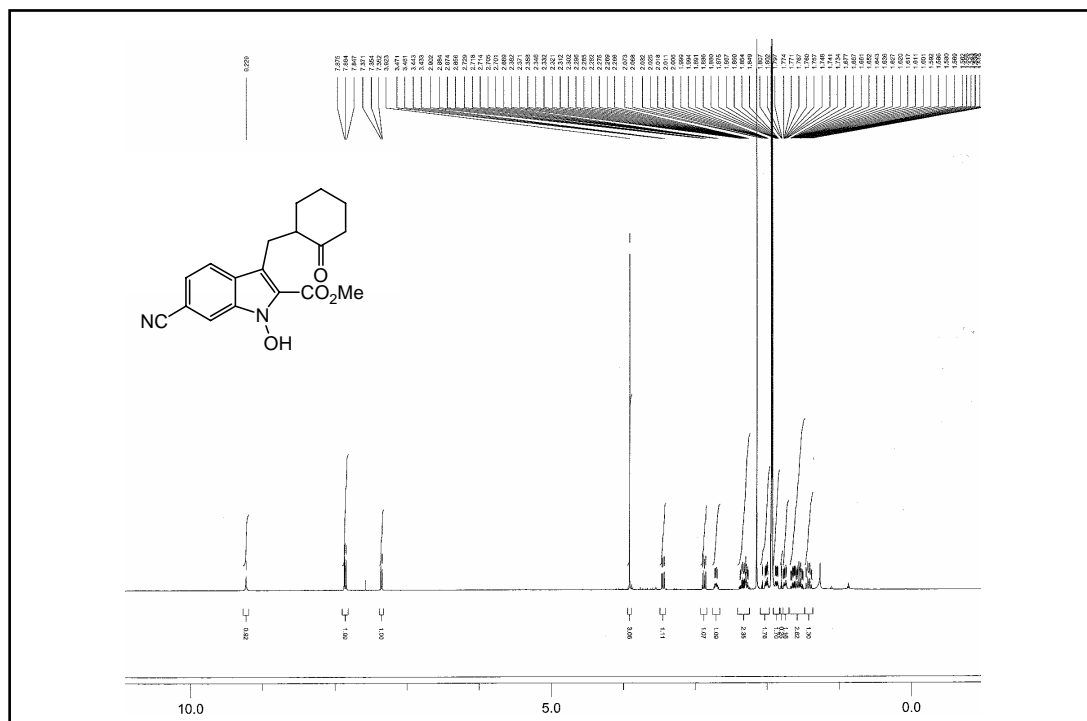
**Spectrum 2.148** <sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>CN) spectrum of compound **2.74**.



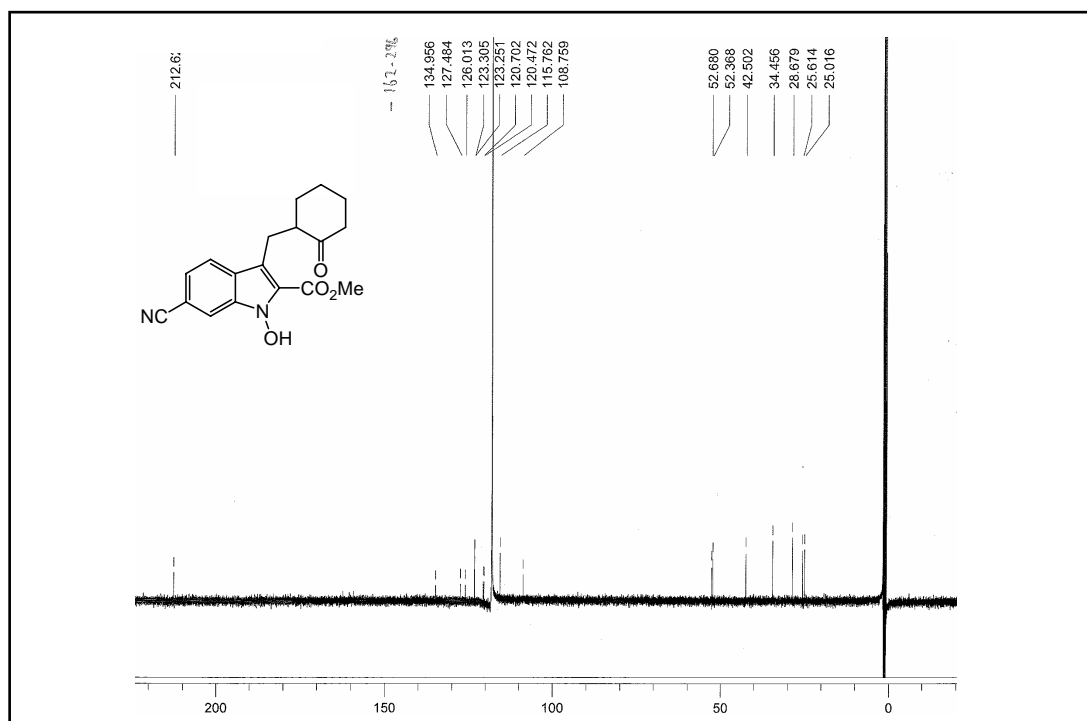
**Spectrum 2.149**  $^1\text{H NMR}$  (600 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.75.



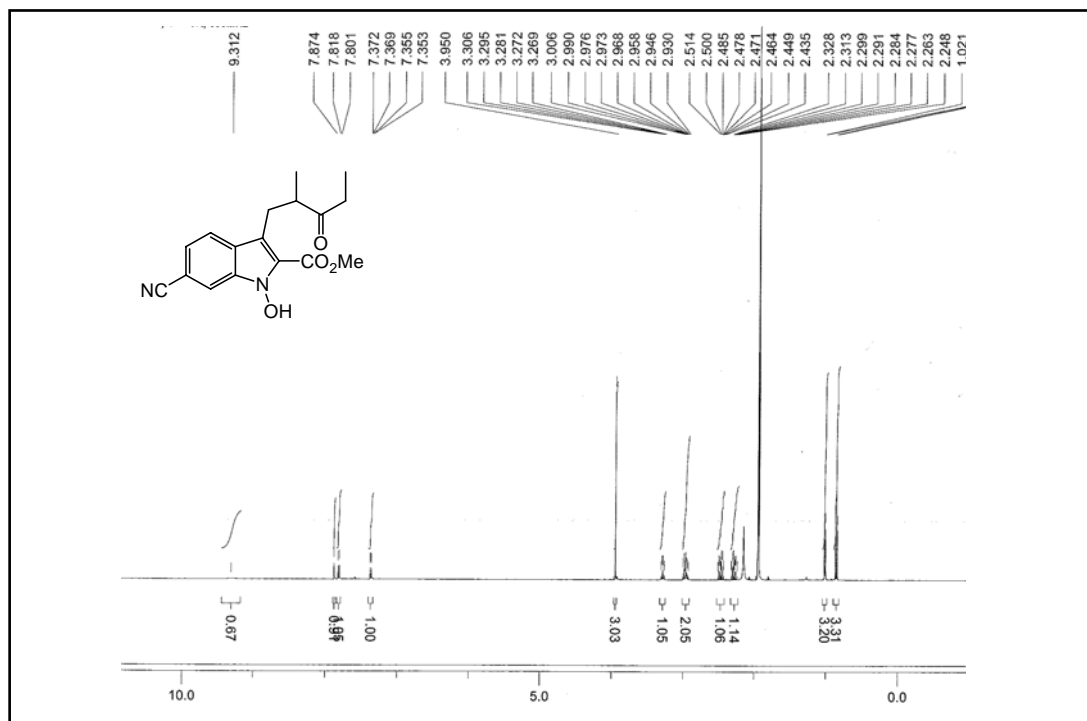
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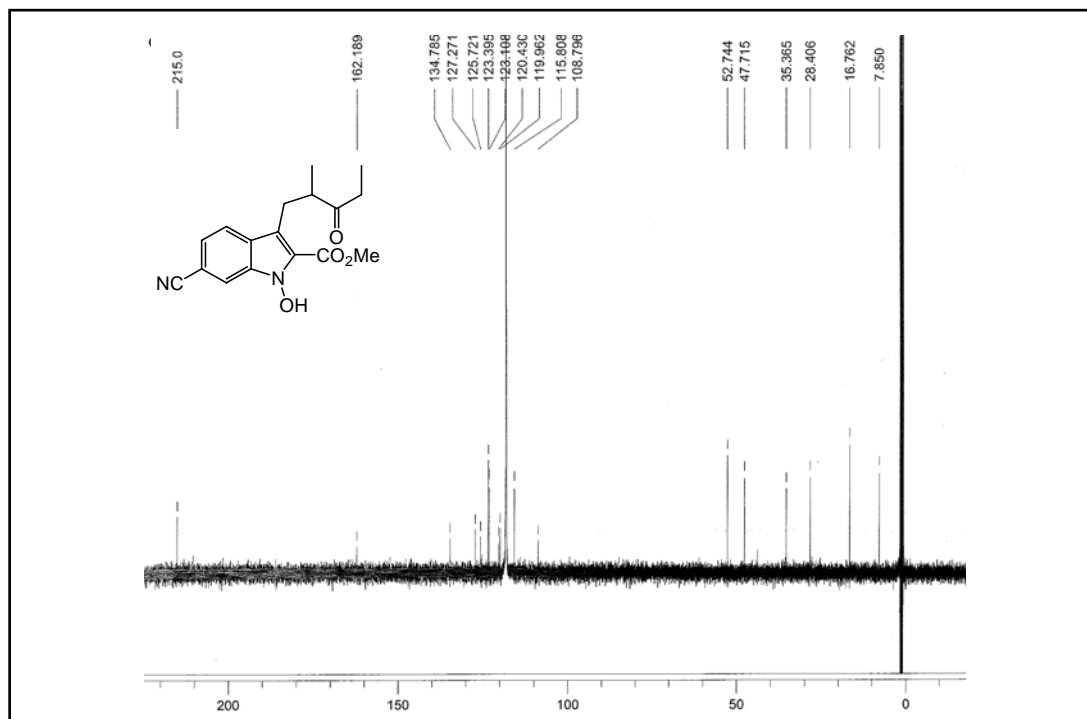
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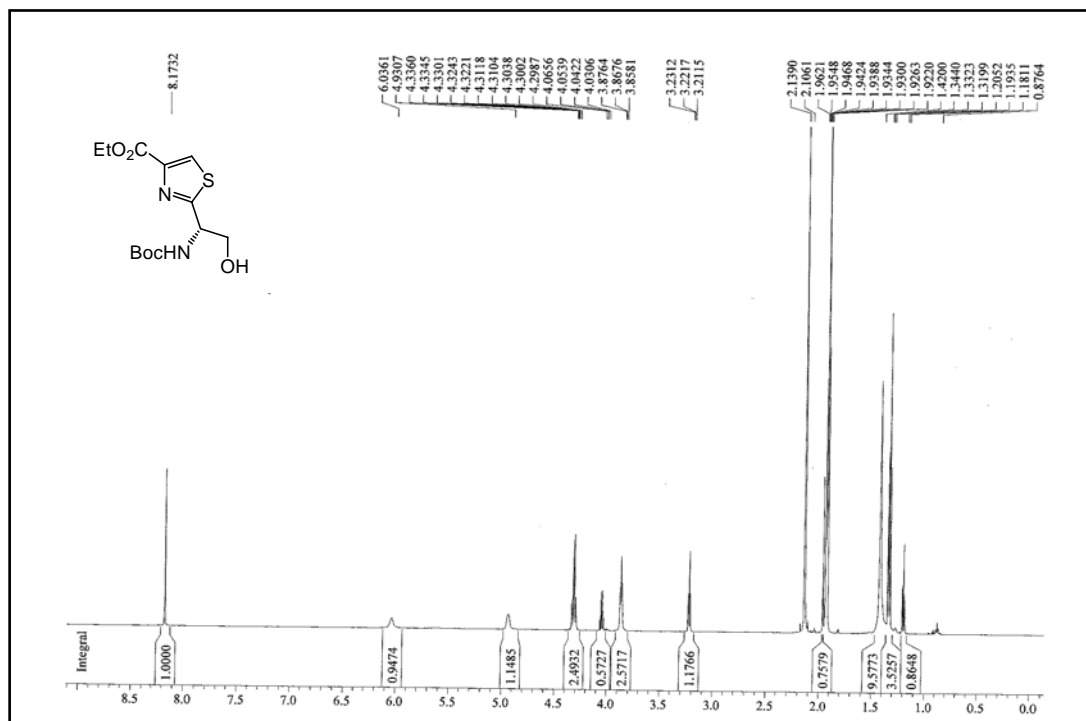
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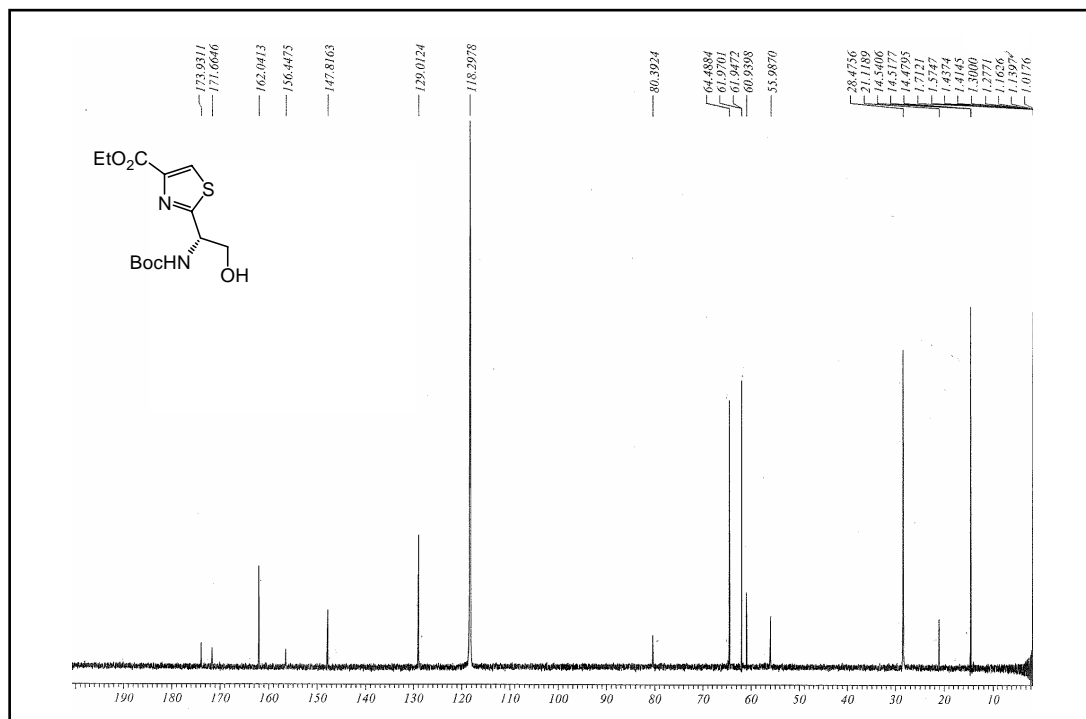
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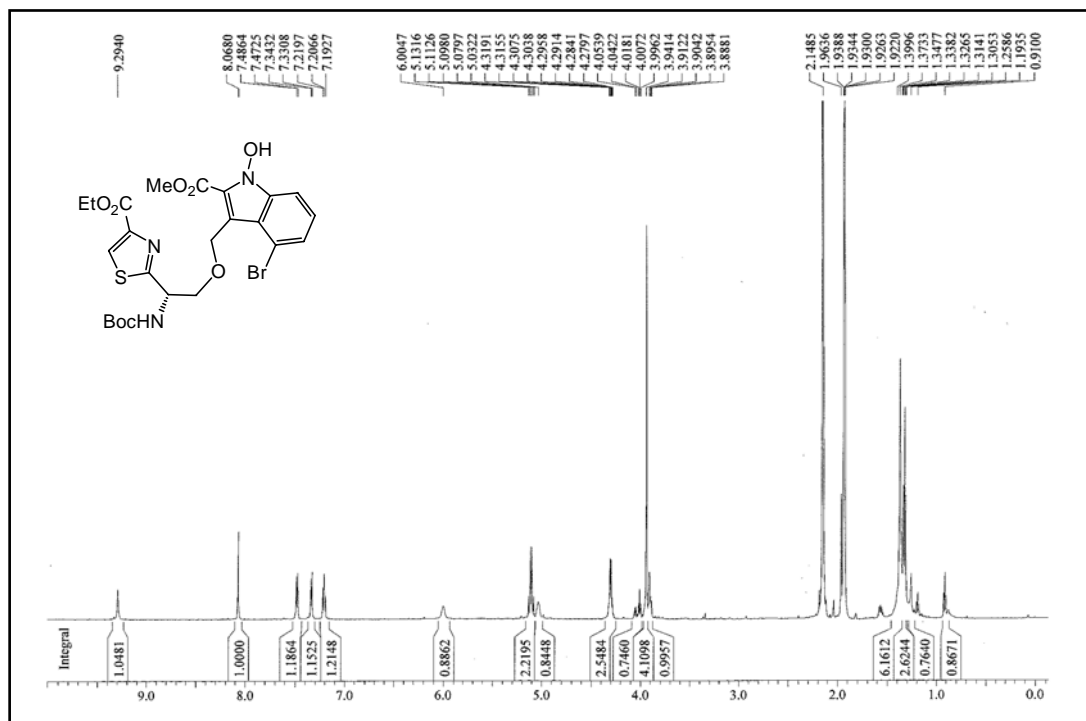




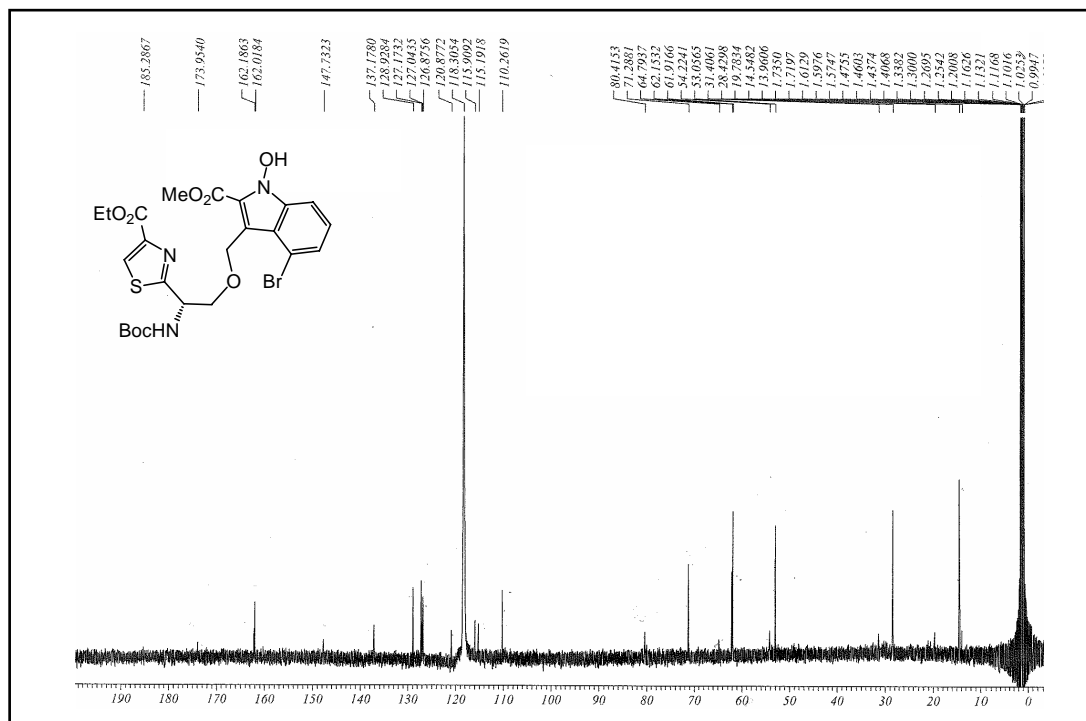
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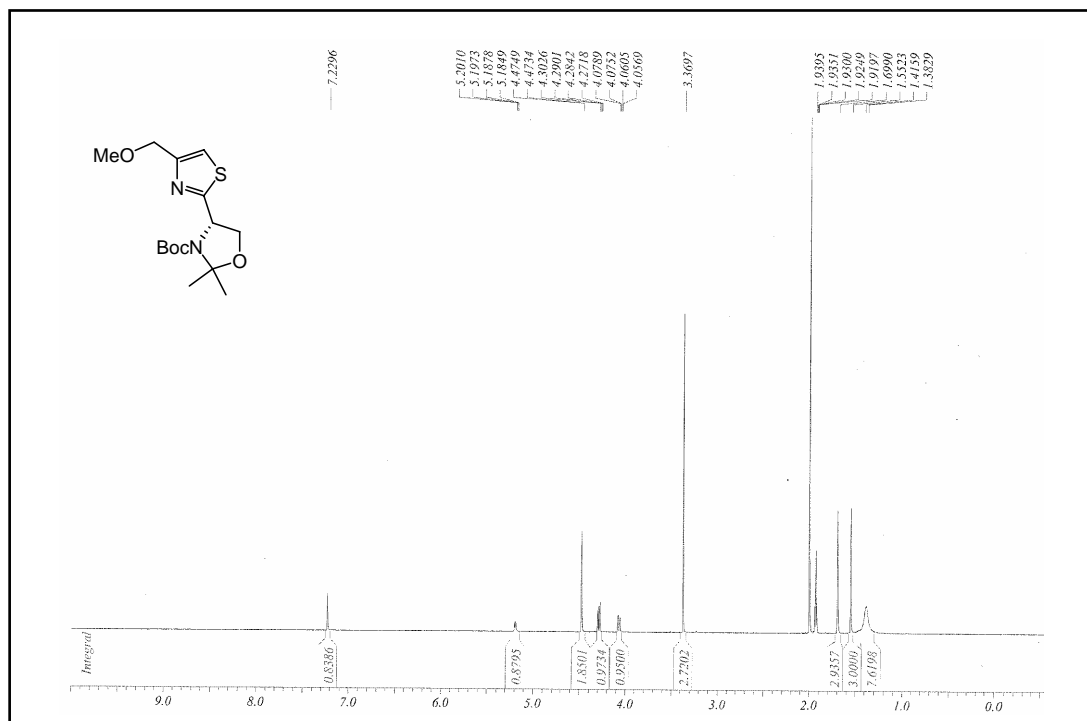
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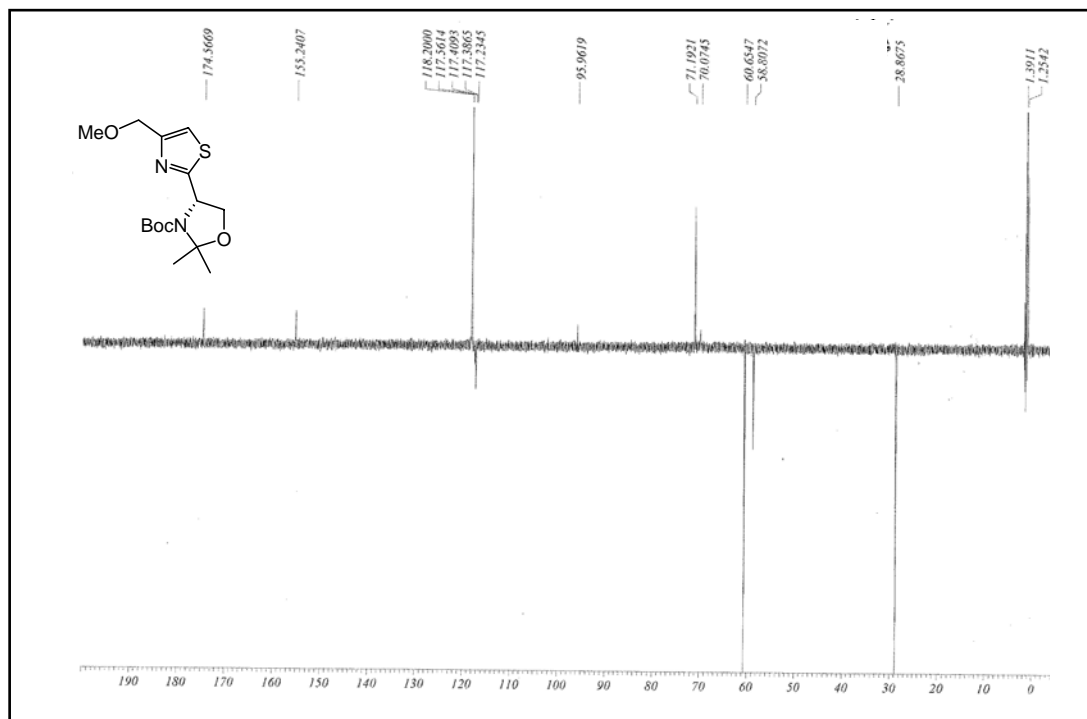
**Spectrum 2.159** <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN, 66 °C) spectrum of compound 2.81.



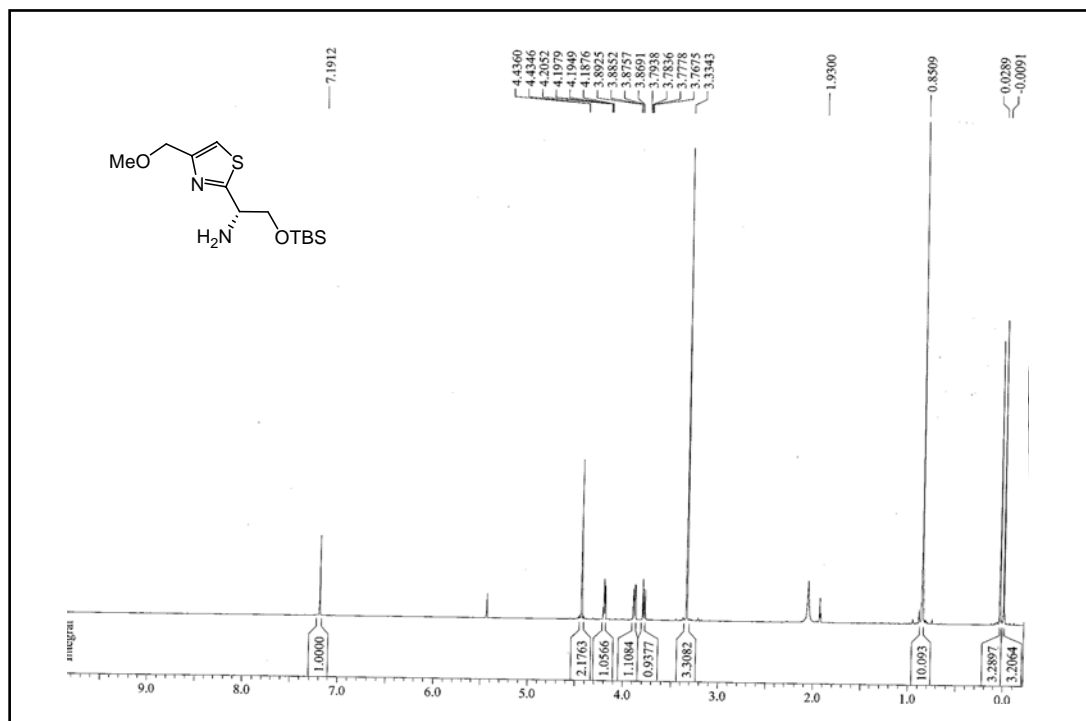
**Spectrum 2.160** <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>CN) spectrum of compound 2.81.



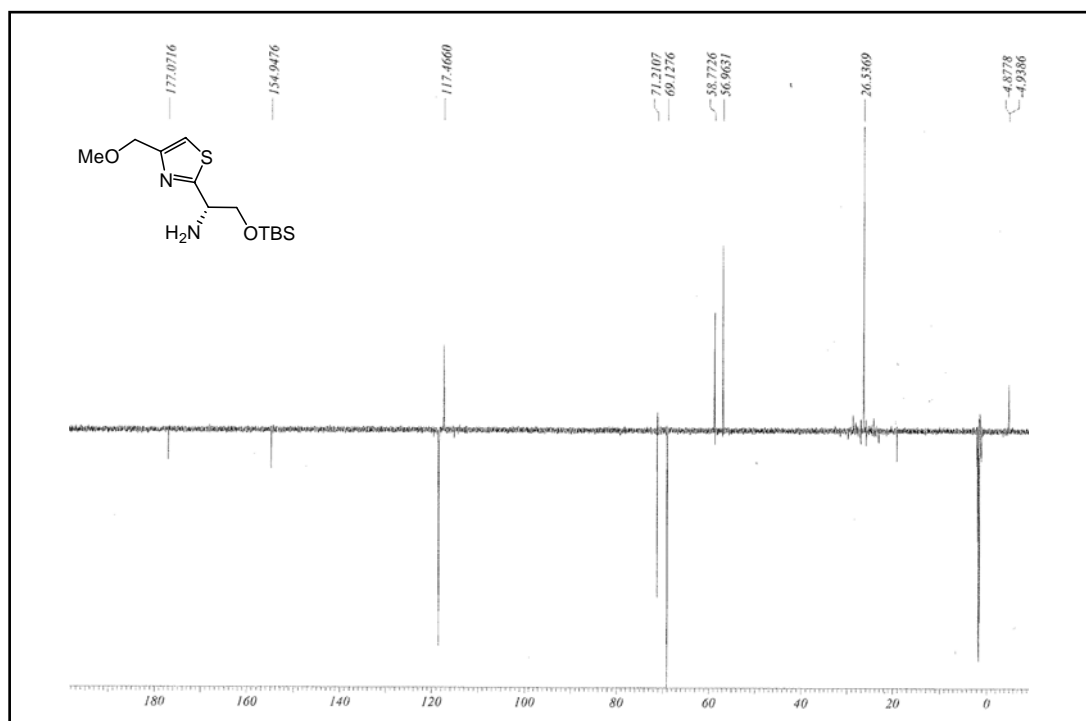
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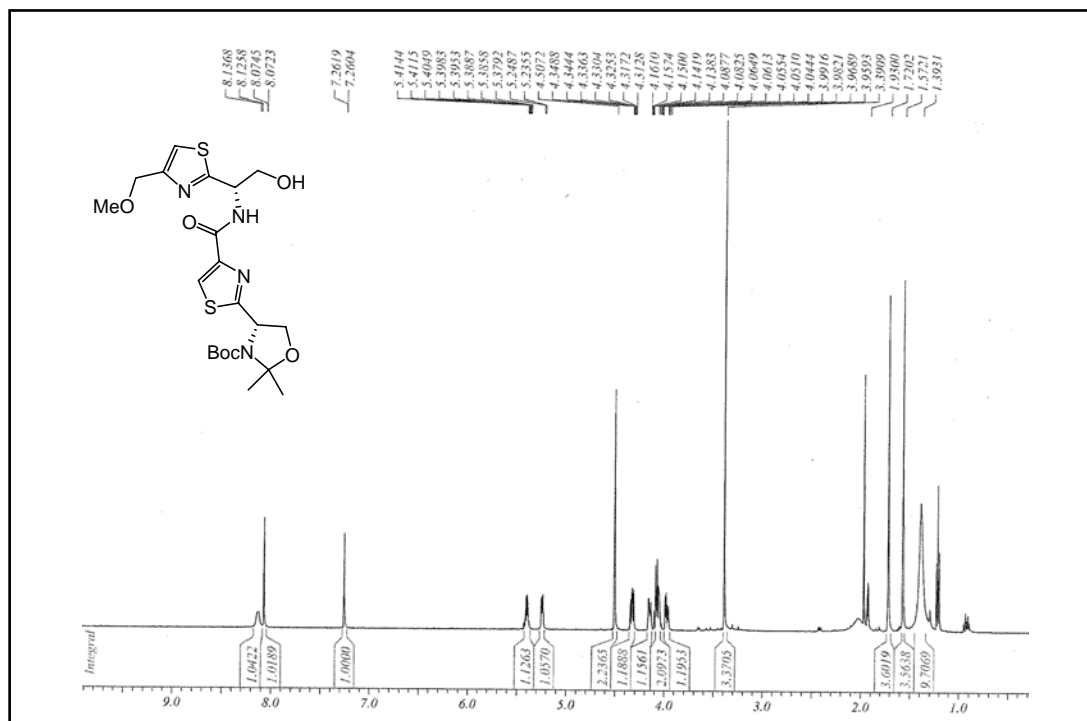
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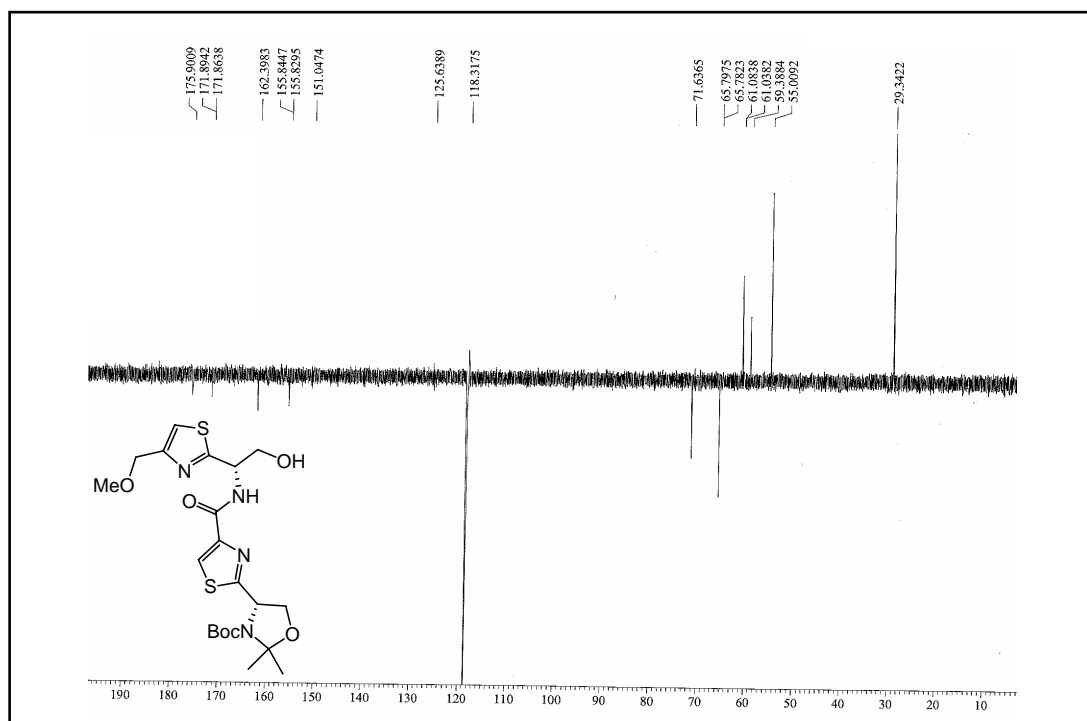
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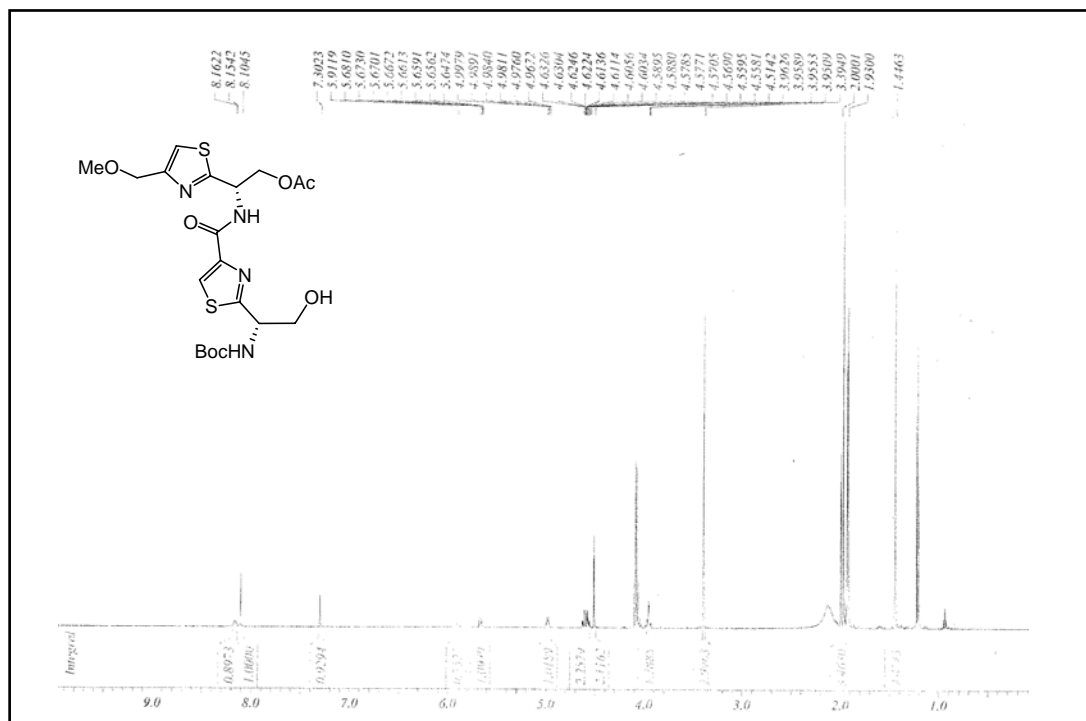
Spectrum 2.164 <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>CN) spectrum of compound 2.83.



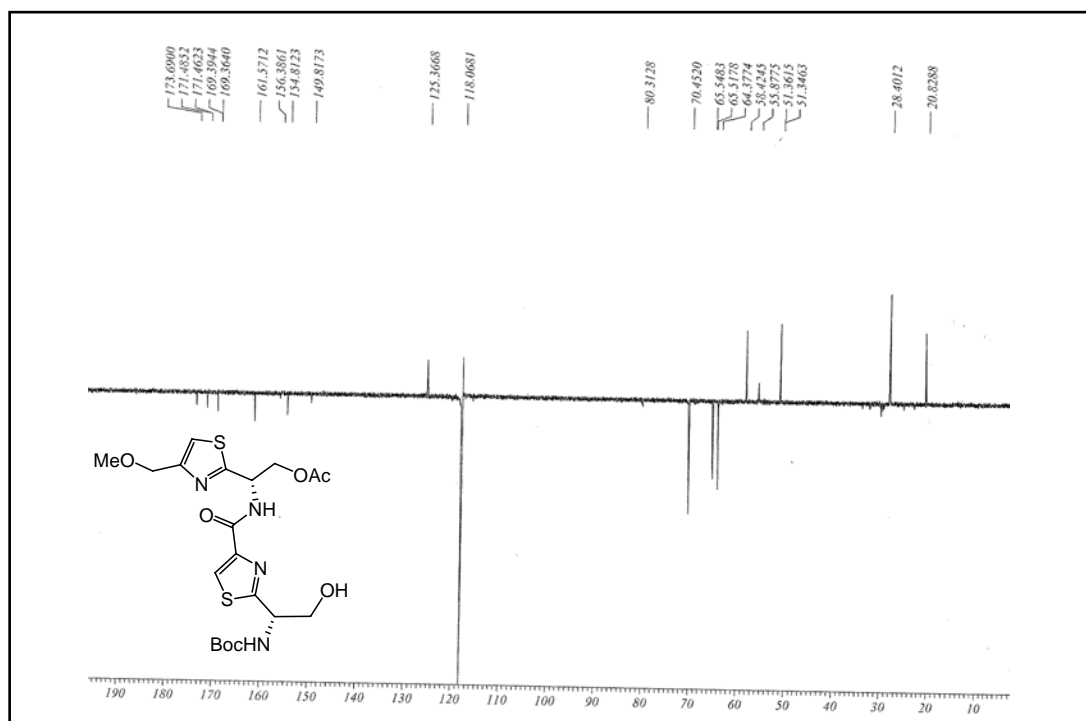
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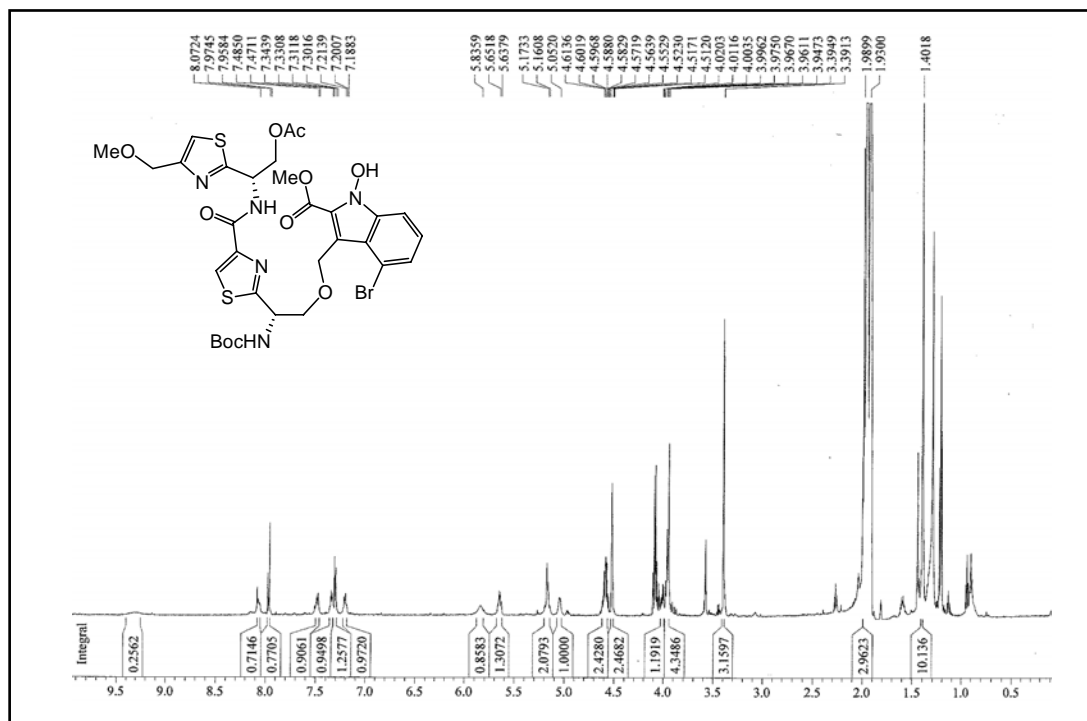
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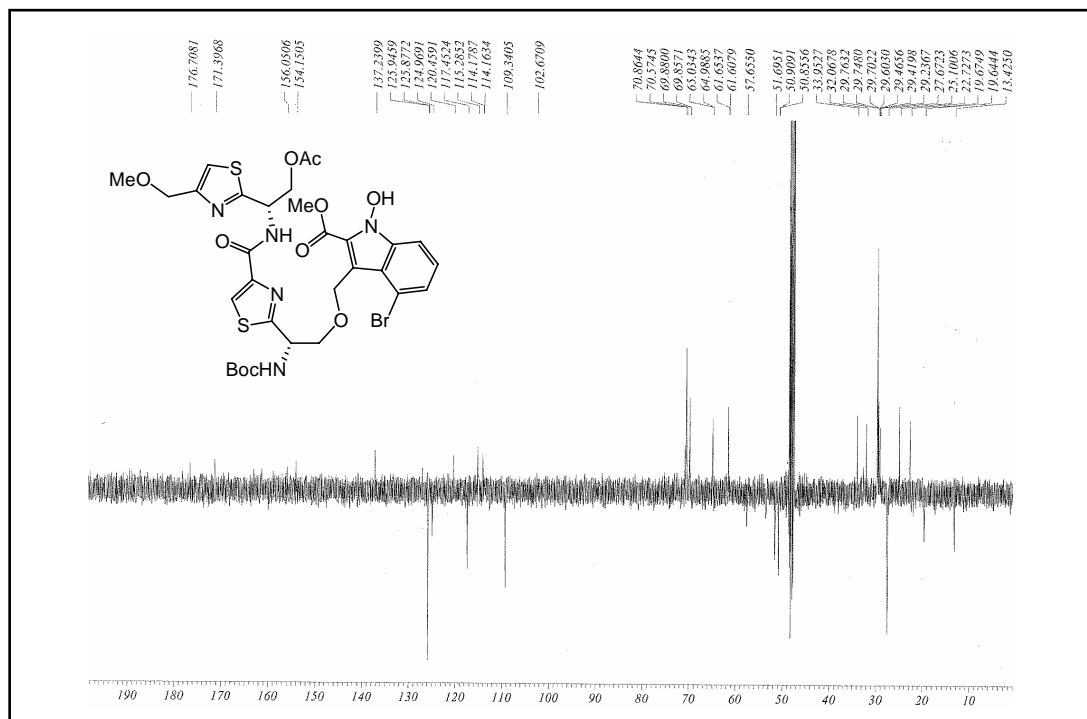
**Spectrum 2.167** <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN, 66 °C) spectrum of compound 2.86.



**Spectrum 2.168** <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>CN) spectrum of compound 2.86.



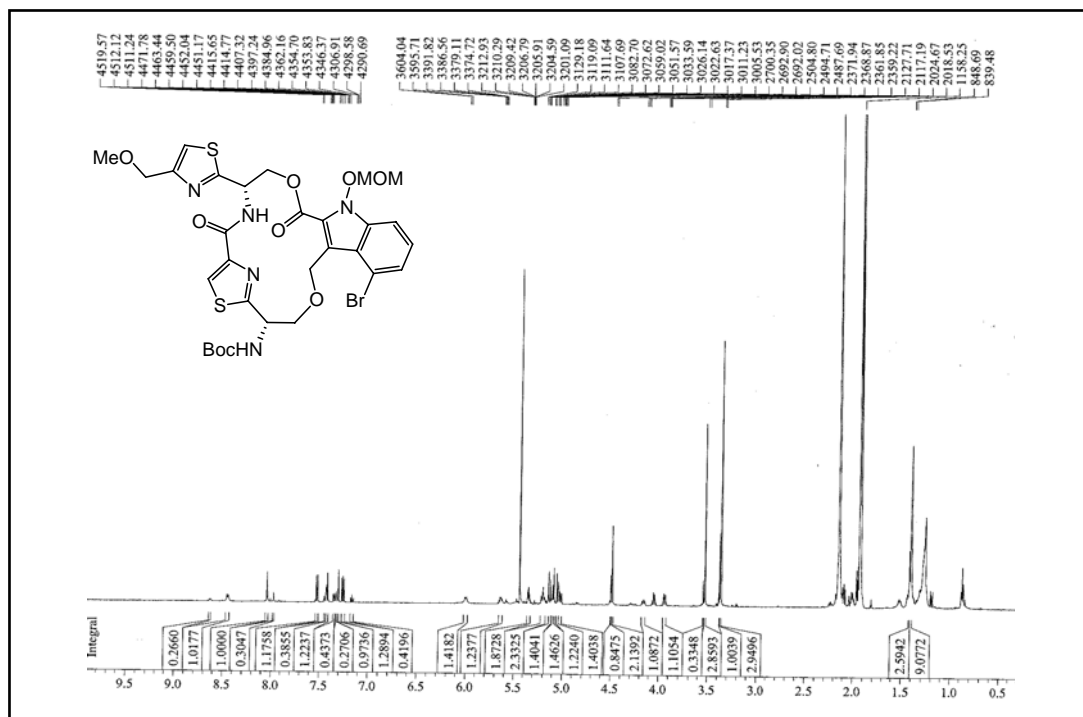
**Spectrum 2.169**  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ , 66 °C) spectrum of compound 2.87.



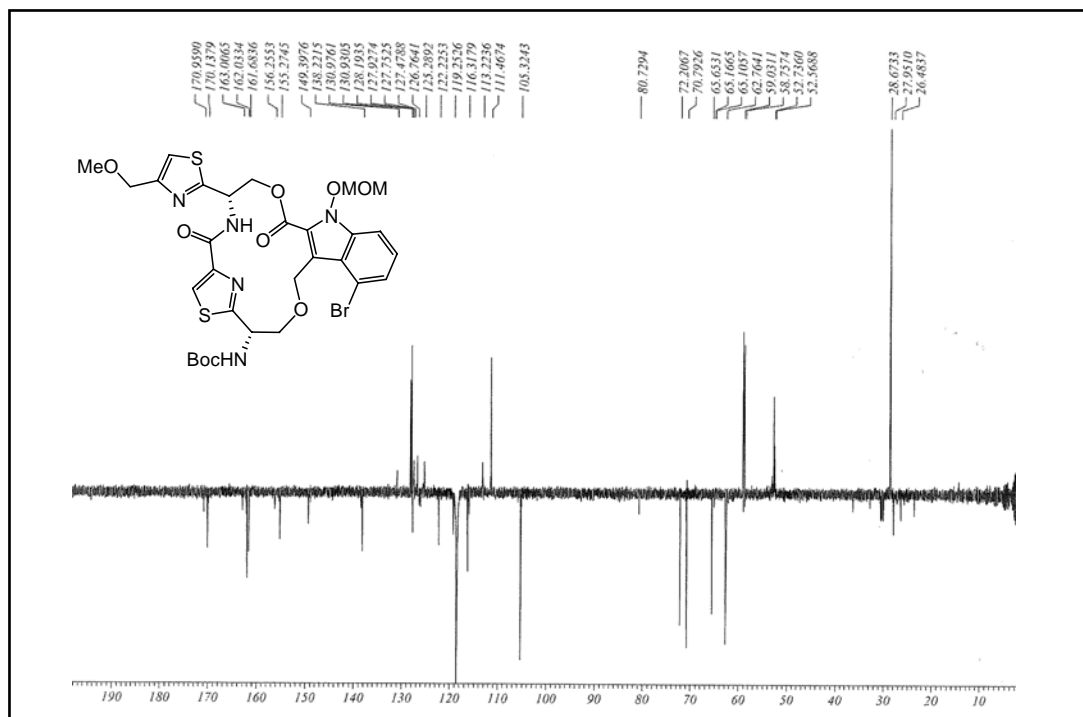
**Spectrum 2.170**  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ ) spectrum of compound 2.87.



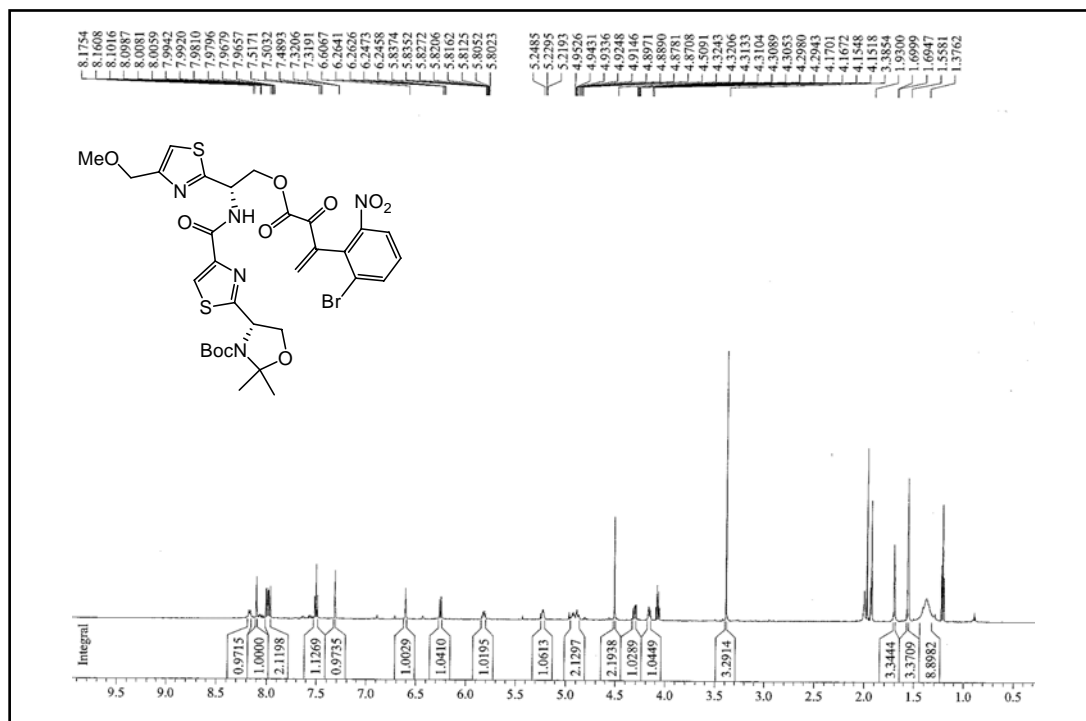




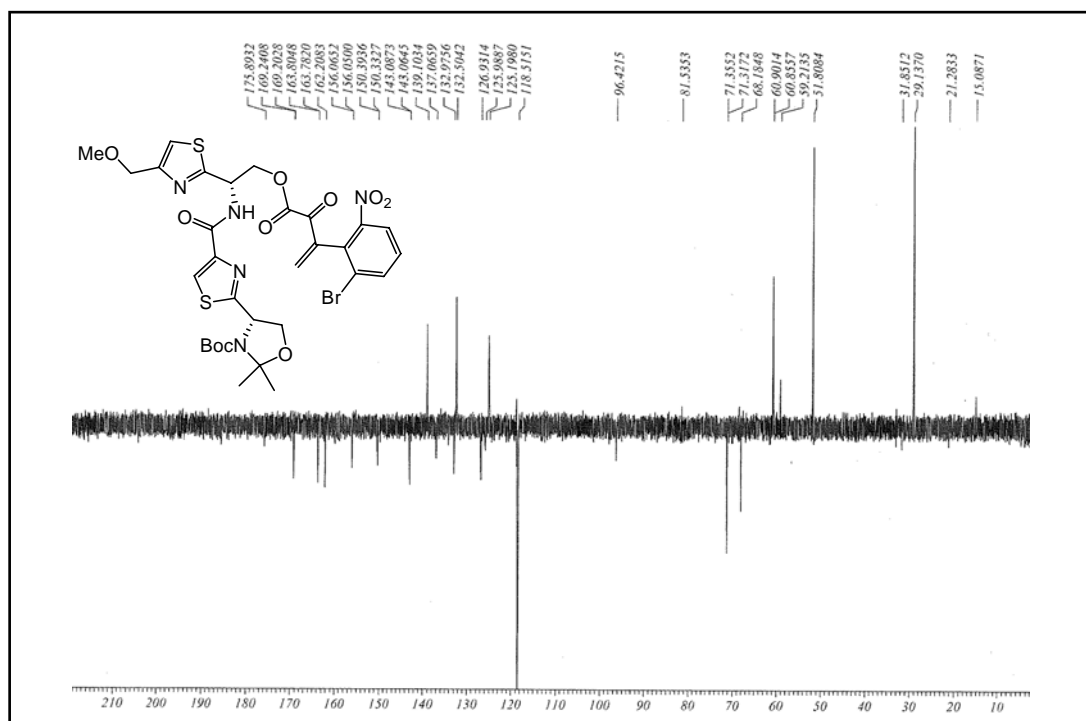
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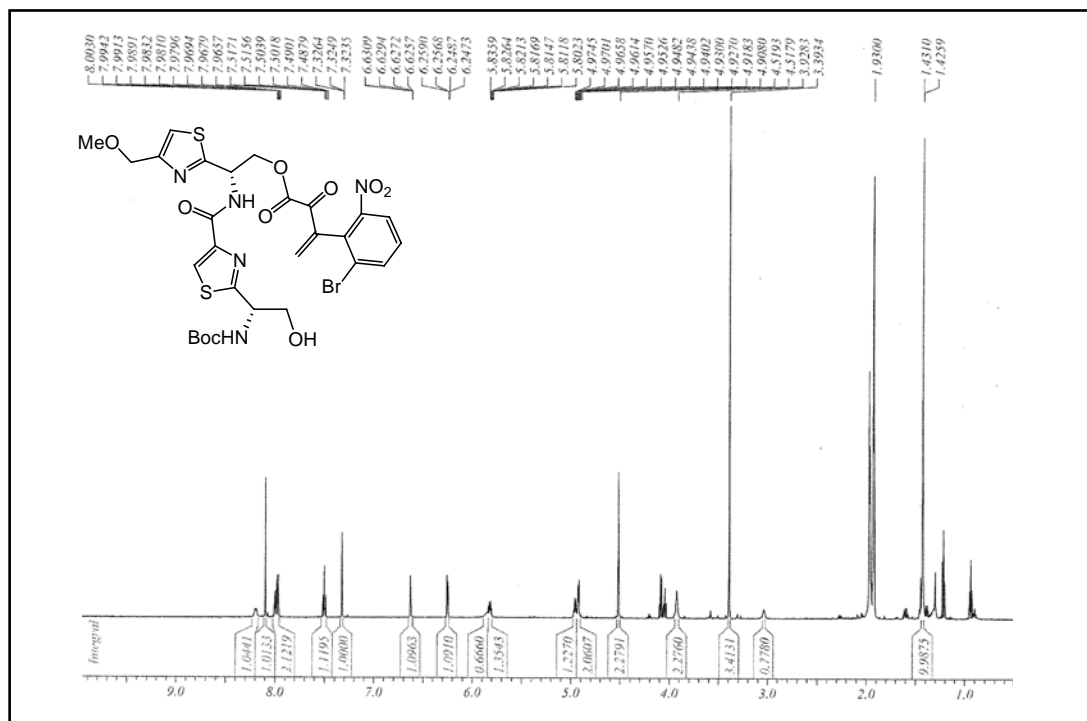
Spectrum 2.174  $^{13}\text{C NMR}$  (150 MHz,  $\text{CD}_3\text{CN}$ , 66 °C) spectrum of compound 2.88b.



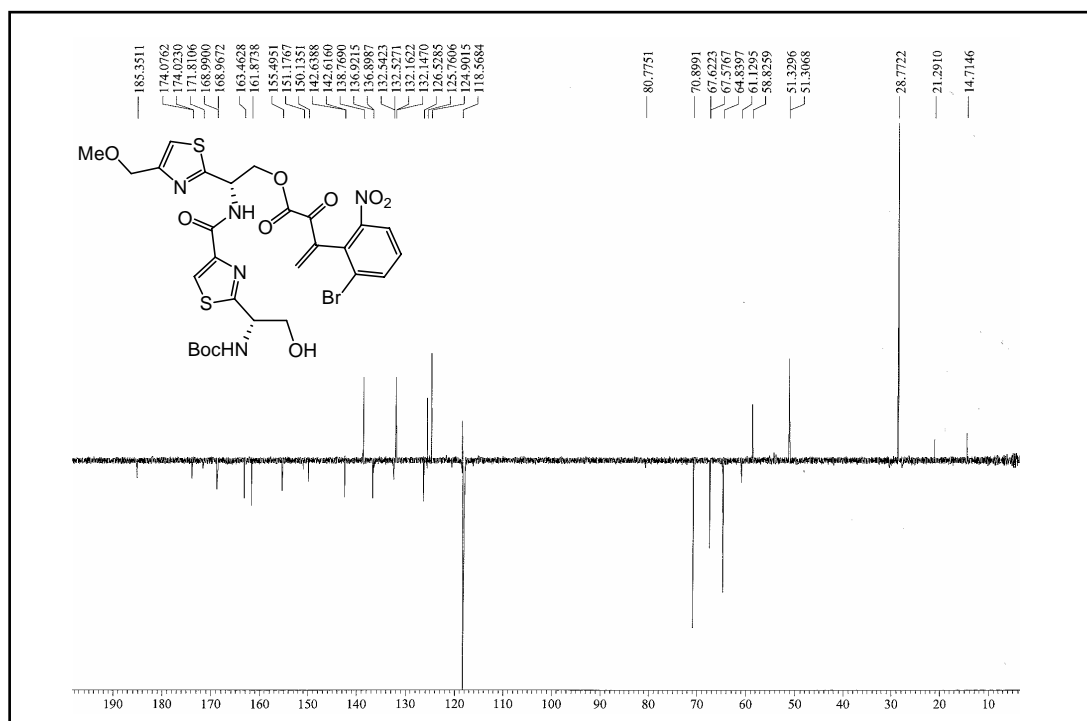
**Spectrum 2.175** <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN, 70 °C) spectrum of compound 2.89.



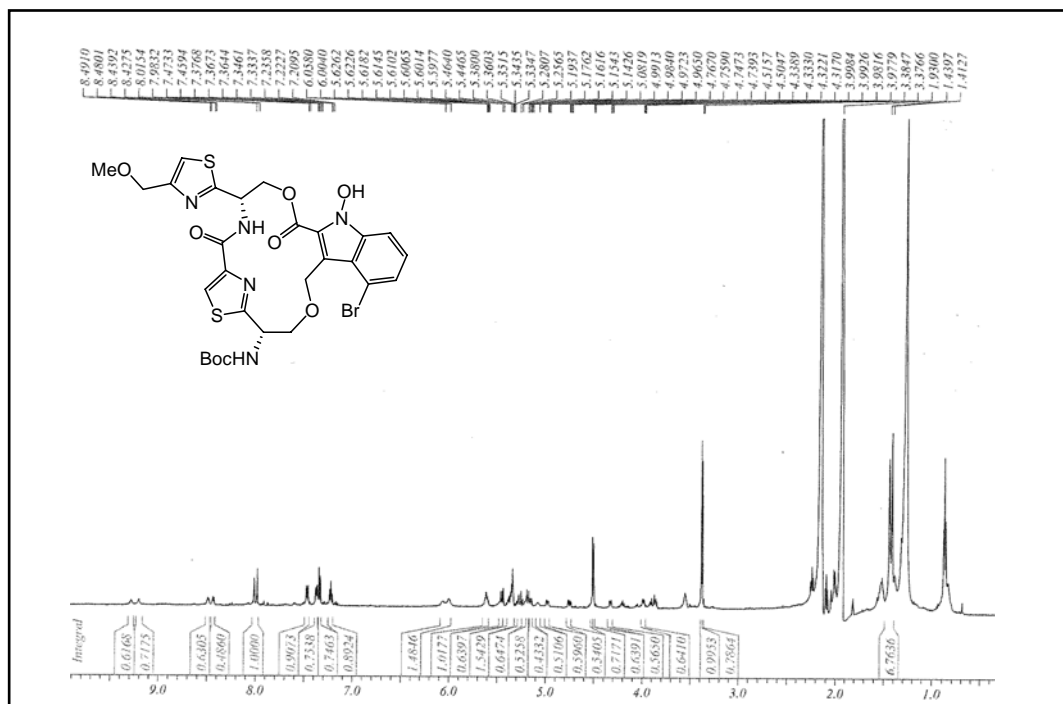
**Spectrum 2.176** <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>CN, 66 °C) spectrum of compound 2.89.



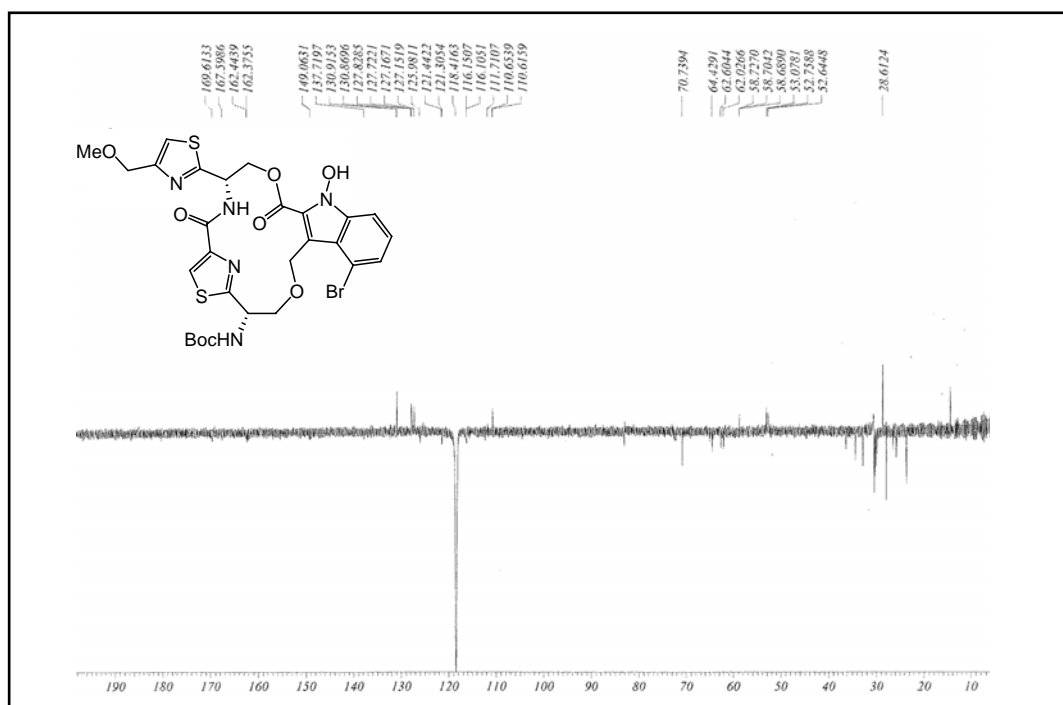
Spectrum 2.177 <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN) spectrum of compound 2.90.



Spectrum 2.178 <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>CN) spectrum of compound 2.90.



**Spectrum 2.179** <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN, 67 °C) spectrum of compound **2.88c** (+2.88c').



**Spectrum 2.180** <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>CN) spectrum of compound **2.88c** (+2.88c').

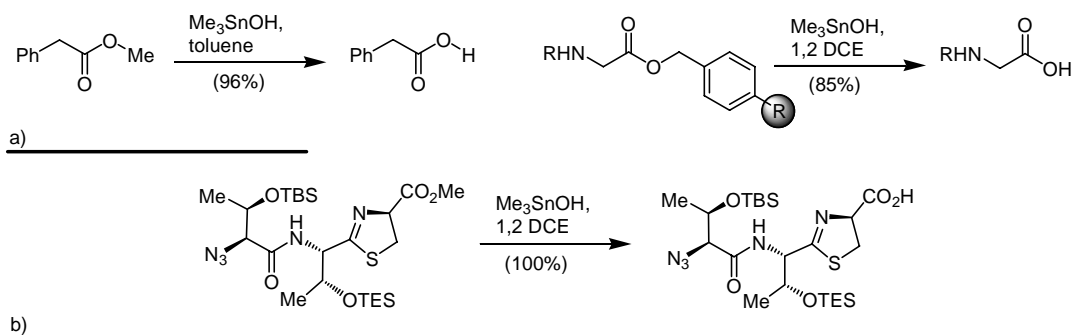
**Chapter 3: The Development of a Mild and Selective Method for the  
Hydrolysis of Esters with Trimethyltin Hydroxide**

## A. Introduction

The saponification of an ester functionality is one of the most commonly employed reactions in synthetic organic chemistry. However, despite the large collection of reagents that are used to accomplish this task, a mild and selective method for highly epimerization and elimination prone substrates remains absent. During our thioestrepton campaign we were faced with the challenge of carrying out ester hydrolyses on systems that proved too sensitive for virtually all of the existing methods in the literature. The lone exception proved to be the  $\text{Me}_3\text{SnOH}$  reagent.

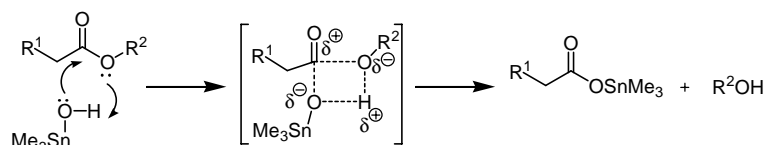
## B. Background and Mechanistic Rationale

$\text{Me}_3\text{SnOH}$  had been previously used by Mascaretti and co-workers<sup>1</sup> to cleave phenacyl ester anchored amino acids and peptides from a polystyrene resin and to hydrolyze methyl phenylacetate (Figure 3.1a). Utilizing this reagent on our highly epimerization sensitive system<sup>2</sup> (Figure 3.1b) remarkably resulted in quantitative conversion of the thiazoline methyl ester to the corresponding acid with negligible erosion of the stereochemical integrity.



**Figure 3.1** a) Literature precedent for  $\text{Me}_3\text{SnOH}$  hydrolysis of esters. b) Initial use of  $\text{Me}_3\text{SnOH}$  with thioestrepton fragment.

A probable mechanistic interpretation can be seen in Figure 3.2. Thus, the hydroxide moiety of the reagent engages the generic ester to create a polar tetra-coordinated transition state. This results in the formation of a tin ester intermediate (confirmed by  $^1\text{H}$ ,  $^{13}\text{C}$ , and  $^{119}\text{Sn}$  NMR spectroscopy)<sup>1b</sup> which is easily hydrolyzed upon aqueous workup to the desired acid. Additionally, the Sn atom most likely facilitates the reaction by participating as a weak Lewis acid and coordinating to the carbonyl oxygen of the ester starting material.

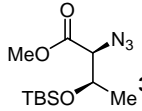
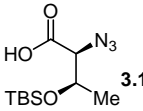
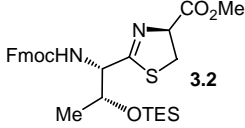
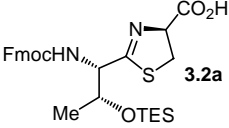
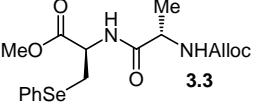
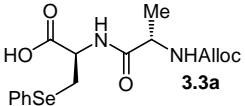
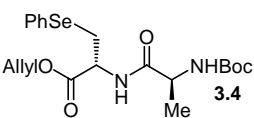
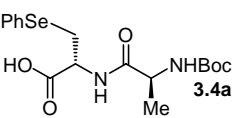
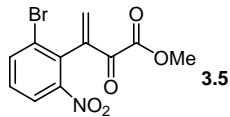
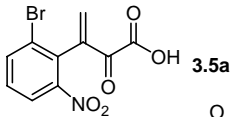
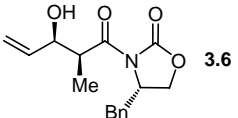
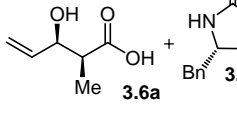
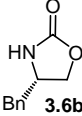
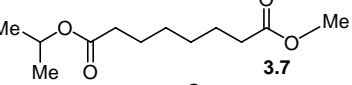
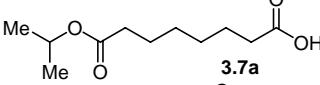
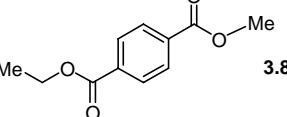
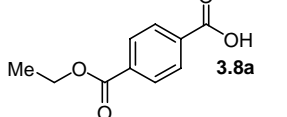
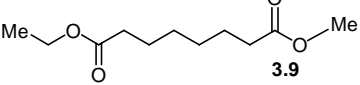
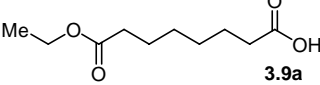
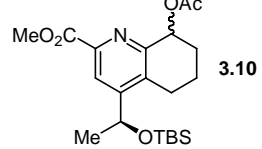
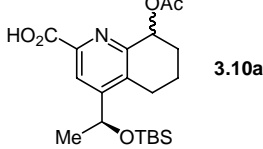
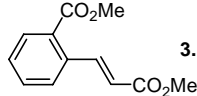
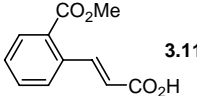


**Figure 3.2** Proposed mechanism of  $\text{Me}_3\text{SnOH}$  mediated hydrolysis of esters.

### C. Evaluation of the Trimethyltin Hydroxide Reagent

Upon completion of the total synthesis of thiostrepton, in which the utilization of  $\text{Me}_3\text{SnOH}$  played an extremely critical role in enabling us to synthesize the natural product,<sup>2</sup> the overall scope of the  $\text{Me}_3\text{SnOH}$  reagent was successfully examined.<sup>3</sup> The results of this investigation (Table 3.1) demonstrate the broad versatility of this reagent in cases where standard hydrolysis methods were unsatisfactory or unsuccessful. Thus, the large scale hydrolysis of ester **3.1** (entry 1), which undergoes epimerization at the azide-bearing stereocenter with  $\text{LiOH}$ , could be carried out in 98% yield to provide acid **3.1a** without any detectable racemization. The

**Table 3.1** Trimethyltin hydroxide mediated hydrolysis of esters and related compounds.

		$\text{RCO}_2\text{R}' \xrightarrow[1,2\text{-DCE, 25-80 } ^\circ\text{C}]{\text{Me}_3\text{SnOH (1-10 equiv)}} \text{RCO}_2\text{H}$			
Entry	Ester	Product(s)	%Yield	Selectivity for Methyl Ester	
1	 <b>3.1</b>	 <b>3.1a</b>	98	—	
2	 <b>3.2</b>	 <b>3.2a</b>	85	—	
3	 <b>3.3</b>	 <b>3.3a</b>	87	—	
4	 <b>3.4</b>	 <b>3.4a</b>	100	—	
5	 <b>3.5</b>	 <b>3.5a</b>	77	—	
6	 <b>3.6</b>	 <b>3.6a</b> +  <b>3.6b</b>	84	—	
7	 <b>3.7</b>	 <b>3.7a</b>	82	~10:1	
8	 <b>3.8</b>	 <b>3.8a</b>	70	~10:1	
9	 <b>3.9</b>	 <b>3.9a</b>	70	~3:1	
10	 <b>3.10</b>	 <b>3.10a</b>	67	—	
11	 <b>3.11</b>	 <b>3.11a</b>	70	~7:1	

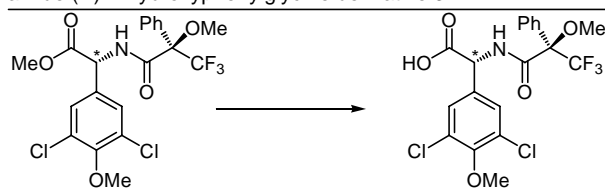


epimerization free hydrolysis of thiazoline methyl ester **3.2** (entry 2) generated acid **3.2a** in 85% yield without any cleavage of the Fmoc carbamate protecting group, a feat unachievable with other methods. The saponification of phenylselenium methyl (**3.3**, entry 3) and allyl (**3.4**, entry 4) esters did not generate any accompanying elimination by-products. The seemingly trivial hydrolysis of methyl ester **3.5** (entry 5) gave acid **3.5a** as the major product in 77% yield with a minor component resulting from intramolecular 1,4-addition of the resulting carboxylate onto the proximate Michael acceptor, which was the sole product with standard basic hydrolysis methods. Entry 6 reveals the additional ability of the  $\text{Me}_3\text{SnOH}$  reagent to cleave the Evans oxazolidinone chiral auxiliary<sup>4</sup> from aldol product **3.6** in 84% yield. Entries 7–10 illustrate the ability of the  $\text{Me}_3\text{SnOH}$  reagent to selectively hydrolyze methyl esters in the presence of isopropyl (entry 7, ~10:1), ethyl (entries 8 and 9, ~10:1 and ~3:1), and acetate (entry 10) esters.

Further complementing this new methodology is the ease with which the product carboxylic acids are isolated.  $\text{Me}_3\text{SnOH}$  is one of the few tin reagents that is water soluble and can therefore be extracted into the aqueous layer upon mild acidic workup. In most cases, the desired products were isolated virtually pure (typically < 2 mol % of  $\text{Me}_3\text{SnOH}$  by  $^1\text{H}$  NMR spectroscopy). In a final test to demonstrate the ultimate tolerance of epimerization-prone substrates to  $\text{Me}_3\text{SnOH}$ , (*R,R*)-dichlorinated phenyl glycine derivative **3.12**<sup>5</sup> (Table 3.2) was synthesized according to literature precedent<sup>6</sup> with a diastereomeric ratio (d.r.) of 96:4 (*R,R/S,R*) according to  $^1\text{H}$  NMR spectroscopic analysis. The attempted hydrolysis was then carried out under standard

LiOH and LiOOH conditions, and with Me<sub>3</sub>SnOH and KOSiMe<sub>3</sub>.<sup>7</sup> Thus, upon exposure of **3.12** to 1.1 equivalents of LiOH for 20 min at 0 °C, followed by warming to 25 °C for 20 min, a mixture of carboxylic acids was obtained in a ratio of 43:57 (*R,R/S,R*), while treatment with LiOOH caused decomposition. When the mixture of esters was treated with 1.5 equivalents of KOSiMe<sub>3</sub> for 4 h at 25 °C, a mixture of carboxylic acids (*R,R/S,R* 20:80) was isolated. However, when **3.12** was exposed to 3.0 equivalents of Me<sub>3</sub>SnOH in 1,2-dichloroethane at 80 °C for 20 min, the corresponding acid (**3.12a**) was isolated in 98% yield with negligible epimerization (*R,R/S,R* 94:6). Experimentation with the *R,S* diastereomer gave similar results.<sup>3</sup>

**Table 3.2** Methyl ester hydrolysis of chlorinated (*R*)-Mosher amide (*R*)-4-hydroxyphenylglycine derivative **3.12**.



Entry	Substrate	Conditions	Product [d.r.]
1	<b>3.12</b>	Me <sub>3</sub> SnOH (3.0 equiv), 1,2-DCE, 80 °C	[94:6]
2	<b>3.12</b>	LiOH (1.1 equiv), THF, MeOH, H <sub>2</sub> O, 0-25 °C	[43:57]
3	<b>3.12</b>	KOSiMe <sub>3</sub> (1.5 equiv) Et <sub>2</sub> O, 25 °C	[20:80]

## D. Conclusion

With these results standing as a testament to the mildness of this method, and with the implication of the  $\text{Me}_3\text{SnOH}$  reagent in a number of total syntheses<sup>8</sup> since the release of our publication into the scientific community, it is expected that the applicability and utility of this reagent in chemical synthesis will continue to be widespread.

## E. References

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## F. Experimental Section

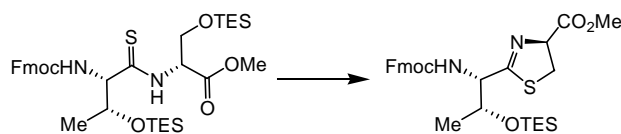
### 1. General Techniques

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, 1,2-dimethoxyethane (DME), and methylene chloride ( $\text{CH}_2\text{Cl}_2$ ) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically ( $^1\text{H}$  NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an ethanolic solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F<sub>254</sub>). Optical rotations were recorded on a Perkin–Elmer 343 polarimeter. NMR spectrum was recorded on Bruker DRX-600, DRX-500, AMX-500 or AMX-400 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s=singlet, d=doublet, t=triplet, q=quartet,  $\frac{1}{2}\text{ABq}=\frac{1}{2}\text{AB}$  quartet, m=multiplet, quin=quintuplet, sext=sextet, sep=septet, hept=heptet, br=broad. IR spectra were recorded on a Perkin–Elmer 1600 or Spectrum 100 series FTIR spectrometer.

Electrospray ionization (ESI) mass spectrometry (MS) experiments were performed on an API 100 Perkin–Elmer SCIEX single quadrupole mass spectrometer at 4000 V emitter voltage. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer using MALDI (matrix-assisted laser-desorption ionization) or ESI (electrospray ionization).

## 2. Preparation of Compounds

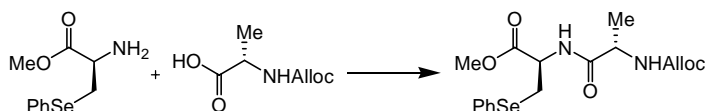
**3.2:** Thiazoline methyl ester **3.2** was prepared from the known thioamide<sup>2</sup> by stirring the thioamide (64 mg, 0.09 mmol) in a 10:3:1 mixture of THF:AcOH:H<sub>2</sub>O (1.61 mL) for 18 h at 25 °C. The reaction mixture was then cooled to 0 °C and solid NaHCO<sub>3</sub> (750 mg, 8.93 mmol) was added. After removing the THF in vacuo, H<sub>2</sub>O (5 mL) was added and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (5 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The resulting crude, labile primary alcohol was immediately dissolved in CH<sub>2</sub>Cl<sub>2</sub> (450 μL) and cooled to –78 °C. DAST (14 μL, 0.11 mmol) was added and the resulting mixture was stirred for 30 min at –78 °C, and then quenched with saturated aqueous NH<sub>4</sub>Cl solution (1 mL). The layers were separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2×5 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The crude residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 30:70) to give thiazoline methyl ester **3.2** (25 mg, 48% over two steps) as a pale yellow oil.



**3.2:**  $R_f=0.45$  (silica gel, EtOAc/hexanes, 3:7);  $[\alpha]_D^{33} -33.5$  ( $c$  0.53,  $\text{CH}_2\text{Cl}_2$ ); IR (film)  $\nu_{\text{max}}$  2923, 2872, 1733, 1496, 1449, 1209, 1079, 1014, 740  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.78 (br d,  $J=7.6$  Hz, 2H), 7.66–7.62 (m, 2H), 7.43–7.39 (m, 2H), 7.34–7.31 (m, 2H), 5.86 (br d,  $J=8.5$  Hz, 1H), 5.13 (t,  $J=10.0$  Hz, 1H), 4.53–4.47 (m, 2H), 4.45–4.42 (m, 1H), 4.39–4.35 (m, 1H), 4.31–4.27 (m, 1H), 3.81 (s, 3H), 3.60–3.55 (m, 1H), 3.51–3.46 (m, 1H), 1.26 (br s, 3H), 0.98 (br t,  $J=7.9$  Hz, 9H), 0.62 (br q,  $J=8.2$  Hz, 6H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  171.4, 156.7, 144.5 (2C), 144.1 (2C), 141.7, 128.1, 127.5, 125.7, 125.6, 120.4 (4C), 78.7, 70.0, 67.6, 60.0, 53.1, 47.7, 35.1, 7.2 (3C), 5.3 (3C); HRMS (ESI-TOF) calcd for  $\text{C}_{29}\text{H}_{39}\text{N}_2\text{O}_5\text{SSi}^+$   $[\text{M}+\text{H}^+]$  555.2343, found 555.2342.

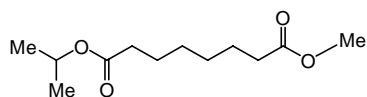
**3.3:** Phenylselenium methyl ester **3.3** was prepared from known derivatized amino acid building blocks.<sup>2</sup> Thus, amine (50 mg, 0.19 mmol) and *N*-Alloc-L-Ala-OH (34 mg, 0.19 mmol) were dissolved in DMF (970  $\mu\text{L}$ ). HOAt (29 mg, 0.21 mmol) and EDC (41 mg, 0.21 mmol) were successively added at 25 °C and the resulting mixture was allowed to stir for 2 h. The mixture was quenched with aqueous 5% HCl solution (500  $\mu\text{L}$ ) and then diluted with EtOAc (2 mL). After washing with saturated aqueous  $\text{NaHCO}_3$  solution (1 mL), brine (1 mL) and drying ( $\text{Na}_2\text{SO}_4$ ), the organic layer was concentrated and the residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 20:80) to afford dipeptide **3.3** (68 mg, 85%) as a colorless oil.





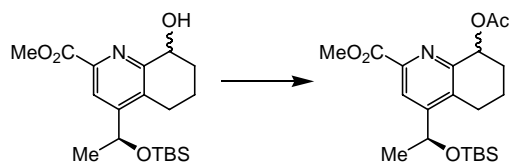
**3.3:**  $R_f=0.18$  (silica gel, EtOAc/hexanes, 3:7);  $[\alpha]_D^{33} +25.4$  ( $c$  1.74,  $\text{CH}_2\text{Cl}_2$ ); IR (film)  $\nu_{\text{max}}$  3317, 3060, 2978, 2952, 1719, 1669, 1520, 1439, 1217, 1070, 740  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.55–7.53 (m, 2H), 7.28–7.27 (m, 3H), 6.74 (br s, 1H), 5.97–5.90 (m, 1H), 5.32 (br d,  $J=17.1$  Hz, 1H), 5.23 (dd,  $J=10.6, 0.9$  Hz, 1H), 5.08 (br s, 1 H), 4.94–4.92 (m, 1 H), 4.6–4.58 (m, 2 H), 4.14 (br s, 1H), 3.54 (s, 3H), 3.41 (dd,  $J=13.1, 4.4$  Hz, 1H), 3.32 (dd,  $J=13.6, 4.9$  Hz, 1H), 1.30 (br d,  $J=6.5$  Hz, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  172.1, 170.8, 134.1, 132.9, 129.6, 129.1, 128.1, 118.3, 66.3, 52.8 (2C), 50.7, 30.0, 18.9; HRMS (ESI-TOF) calcd for  $\text{C}_{17}\text{H}_{23}\text{N}_2\text{O}_5\text{Se}^+$   $[\text{M}+\text{H}^+]$  415.0767, found 415.0756.

**3.7:** Suberic acid methyl ester (283 mg, 1.50 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (7.54 mL) and cooled to 0 °C. EDC (318 mg, 1.65 mmol), 4-DMAP (18 mg, 0.15 mmol) and *i*PrOH (1.15 mL, 15 mmol) were then added and the reaction mixture was stirred for 3 h at 25 °C. The mixture was quenched with aqueous 5% HCl solution (5 mL) and then diluted with  $\text{CH}_2\text{Cl}_2$  (10 mL). After washing with saturated aqueous  $\text{NaHCO}_3$  solution (5 mL), brine (5 mL) and drying ( $\text{Na}_2\text{SO}_4$ ), the organic layer was concentrated and the residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 30:70) to afford diester **3.7** (329 mg, 95%) as a yellow oil.



**3.7:**  $R_f=0.64$  (silica gel, EtOAc/hexanes, 3:7); IR (film)  $\nu_{\max}$  2980, 2937, 2860, 1736, 1437, 1374, 1178, 1110  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.96 (sep,  $J=6.2$  Hz, 1H), 3.63 (s, 3H), 2.28–2.20 (m, 4H), 1.61–1.57 (m, 4H), 1.31–1.28 (m, 4H), 1.18 (d,  $J=6.3$  Hz, 6H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  173.9, 173.0, 67.1, 51.2, 34.3, 33.7, 28.5, 28.4, 24.5, 24.5, 21.6; HRMS (ESI-TOF) calcd for  $\text{C}_{12}\text{H}_{22}\text{O}_4\text{Na}^+$   $[\text{M}+\text{Na}^+]$  253.1410, found 253.1407.

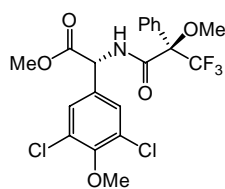
**3.10:** The known alcohol<sup>2</sup> (194 mg, 0.53 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (2.65 mL) and cooled to 0 °C.  $\text{Et}_3\text{N}$  (740  $\mu\text{L}$ , 5.3 mmol), 4-DMAP (32 mg, 0.27 mmol), and  $\text{Ac}_2\text{O}$  (250  $\mu\text{L}$ , 2.7 mmol) were then added and the reaction mixture stirred at 25 °C for 30 min. After removing the  $\text{CH}_2\text{Cl}_2$  in vacuo, the residue was diluted with EtOAc (10 mL), washed with aqueous 5% HCl solution (5 mL), saturated aqueous  $\text{NaHCO}_3$  solution (5 mL), brine (5 mL) and dried ( $\text{Na}_2\text{SO}_4$ ). The organic layer was then concentrated and the residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 30:70→50:50) to afford a ca. 1:1 mixture of diastereomeric acetates **3.10** (192 mg, 89%) as a yellow oil.



**3.10:** [ca. 1:1 mixture of inseparable diastereomers]  $R_f=0.80$  (silica gel, EtOAc/hexanes, 7:3);  $[\alpha]_D^{32}$   $-51.8$  ( $c$  5.26,  $\text{CH}_2\text{Cl}_2$ ); IR (film)  $\nu_{\max}$  2953, 2858, 1740, 1439, 1370, 1235, 1125, 833  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  8.28 (s, 1H), 8.26 (s, 1H), 6.00–5.97 (m, 1+1H), 5.05–4.97 (m, 1+1H), 3.96 (s, 3+3H), 2.92–2.79 (m,

1+1H), 2.75–2.58 (m, 1+1H), 2.26–2.20 (m, 1+1H), 2.12 (s, 3H), 2.11 (s, 3H), 2.00–1.93 (m, 2+2H), 1.90–1.88 (m, 1+1H), 1.37 (d,  $J=6.4$  Hz, 3H), 1.34 (d,  $J=6.4$  Hz, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H), –0.02 (s, 3H), –0.05 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  170.3, 166.0, 155.6, 153.5, 146.3, 132.7, 121.6, 71.7, 71.6, 66.3, 66.3, 28.2, 28.0, 25.8, 25.2, 25.0, 24.9, 24.8, 21.5, 18.2, 17.9, 17.8, –4.8, –4.9, –4.9; HRMS (ESI-TOF) calcd for  $\text{C}_{21}\text{H}_{34}\text{NO}_5\text{Si}^+$   $[\text{M}+\text{H}^+]$  408.2201, found 408.2207.

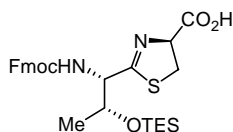
**3.12:** (*R,R*)-Dichlorinated phenyl glycine methyl ester derivative **3.12** was prepared according to a known literature procedure for the (*R,S*) diastereomer.<sup>6</sup>



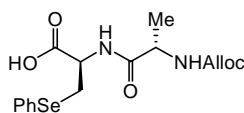
**3.12:**  $R_f=0.44$  (silica gel, EtOAc/hexanes, 2:8);  $[\alpha]_D^{32}$  –88.6 ( $c$  1.00,  $\text{CH}_2\text{Cl}_2$ ); IR (film)  $\nu_{\text{max}}$  3392, 2952, 2844, 1745, 1694, 1482, 1416, 1269, 1165, 1107  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.60–7.58 (m, 2H), 7.45–7.44 (m, 5H), 5.58 (br s, 1H), 3.87 (s, 3H), 3.73 (s, 3H), 3.41 (m, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  166.0, 152.6, 133.0, 131.5, 123.0, 129.7, 128.7, 127.9, 127.6, 124.8, 122.5, 60.7, 55.3, 54.9, 53.3, 29.7; HRMS (ESI-TOF) calcd for  $\text{C}_{20}\text{H}_{19}\text{Cl}_2\text{F}_3\text{NO}_5^+$   $[\text{M}+\text{H}^+]$  480.0587, found 480.0579.

**General procedure:** The carboxylic ester (0.01–0.15 mmol) was dissolved in 1,2-dichloroethane and after addition of trimethyltin hydroxide (1–10 equiv), the mixture

was heated at 60–80 °C until TLC analysis indicated a complete reaction. After completion of the reaction, the mixture was concentrated in vacuo, and the residue was taken up in EtOAc (5–15 mL). The organic layer was washed with aqueous KHSO<sub>4</sub> (0.01 M) or 5% HCl solution (3×5–15 mL). The organic layer was then washed with brine (5–15 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvent in vacuo afforded the carboxylic acid, often in > 98% purity (by <sup>1</sup>H NMR spectroscopy).

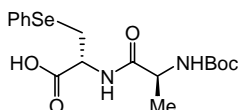


**3.2a:**  $R_f=0.45$  (silica gel, MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 1:9);  $[\alpha]_D^{33} -21.7$  ( $c$  0.20, CH<sub>2</sub>Cl<sub>2</sub>); IR (film)  $\nu_{\max}$  3284, 2955, 2924, 2861, 1718, 1654, 1508, 1449, 1251, 1106, 740 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.77 (br d,  $J=7.6$  Hz, 2H), 7.64–7.60 (m, 2H), 7.42–7.38 (m, 2H), 7.33–7.29 (m, 2H), 5.84 (br d,  $J=8.2$  Hz, 1H), 5.19 (br t,  $J=9.1$  Hz, 1H), 4.53–4.22 (m, 5H), 3.64–3.53 (m, 2H), 1.22 (br d,  $J=6.2$  Hz, 3H), 0.96 (br t,  $J=7.6$  Hz, 9H), 0.63–0.58 (m, 6H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$  174.5, 141.5 (2C), 140.2 (2C), 140.0, 132.3, 128.0, 127.3, 125.2, 120.2 (4C), 87.6, 74.9, 66.5, 49.8, 47.3, 32.1, 6.8 (3C), 6.0 (3C); HRMS (ESI-TOF) calcd for C<sub>22</sub>H<sub>21</sub>N<sub>2</sub>O<sub>4</sub>S<sup>+</sup> [M+H<sup>+</sup>] 409.1222, found 409.1214 (OTES antiperiplanar elimination occurred during ionization process).

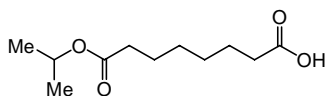


**3.3a:**  $R_f=0.20$  (silica gel, MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 1:9);  $[\alpha]_D^{33} -41.2$  ( $c$  2.73, MeOH); IR (film)  $\nu_{\max}$  3318, 3072, 2978, 2936, 1718, 1654, 1522, 1438, 1244, 1071, 738 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>OD)  $\delta$  7.56–7.54 (m, 2H), 7.27–7.26 (m, 3H), 5.97–5.92 (m, 1H), 5.32

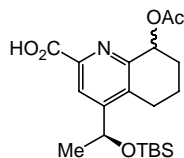
(br d,  $J=17.1$  Hz, 1H), 5.18 (br d,  $J=10.6$  Hz, 1H), 4.61–4.59 (m, 1 H), 4.56–4.55 (m, 2 H), 4.16–4.14 (m, 1H), 3.40 (dd,  $J=13.1, 5.3$  Hz, 1H), 3.21 (dd,  $J=12.7, 7.9$  Hz, 1H), 1.31 (d,  $J=6.7$  Hz, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  175.4, 173.5, 158.1, 134.5, 134.4, 130.8, 130.4, 128.6, 117.8, 66.7, 54.0, 51.9, 29.9, 18.5; HRMS (ESI-TOF) calcd for  $\text{C}_{16}\text{H}_{21}\text{N}_2\text{O}_5\text{Se}^+$  [ $\text{M}+\text{H}^+$ ] 401.0610, found 401.0619.



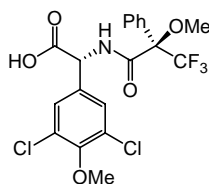
**3.4a:**  $R_f=0.12$  (silica gel, EtOAc/hexanes, 1:1);  $[\alpha]_D^{32} -32.5$  ( $c$  1.20,  $\text{CH}_2\text{Cl}_2$ ); IR (film)  $\nu_{\text{max}}$  3323, 3060, 2978, 2931, 1696, 1665, 1519, 1368, 1249, 1166, 1070, 737  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.56–7.54 (m, 2H), 7.26–7.25 (m, 3H), 7.09 (br d,  $J=7.4$  Hz, 1H), 4.89 (m, 2H), 3.48 (dd,  $J=13.1, 4.4$  Hz, 1H), 3.34 (m, 1H), 1.46 (br s, 9H), 1.25 (m, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  173.4, 172.9, 133.2, 129.4, 129.2, 127.4, 53.1, 50.0, 29.6, 29.2, 28.3, 18.1; HRMS (ESI-TOF) calcd for  $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_5\text{SeNa}^+$  [ $\text{M}+\text{Na}^+$ ] 439.0743, found 439.0743.



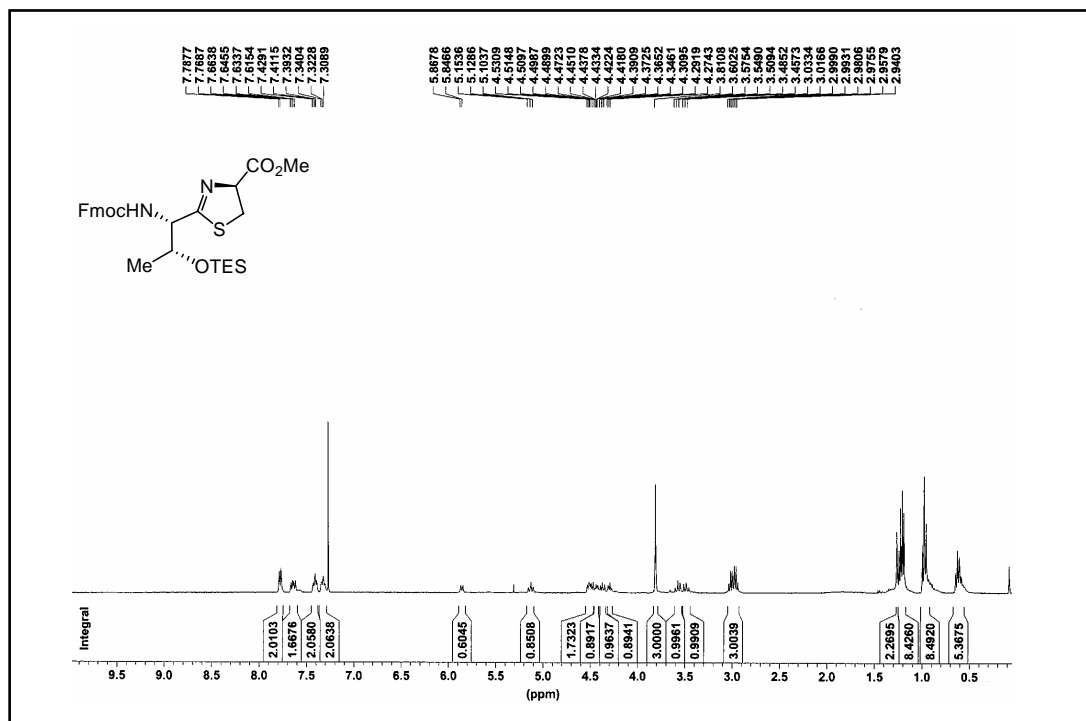
**3.7a:**  $R_f=0.30$  (silica gel, EtOAc/hexanes, 7:3); IR (film)  $\nu_{\text{max}}$  3460, 2980, 2934, 2859, 1731, 1714, 1467, 1374, 1181, 1109  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.00 (sep,  $J=6.2$  Hz, 1H), 2.37–2.24 (m, 4H), 1.65–1.60 (m, 4H), 1.36–1.33 (m, 4H), 1.22 (d,  $J=6.2$  Hz, 6H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  173.3, 67.4, 34.5, 28.6, 28.6, 24.7, 24.7, 24.6, 21.7; HRMS (ESI-TOF) calcd for  $\text{C}_{11}\text{H}_{20}\text{O}_4\text{Na}^+$  [ $\text{M}+\text{Na}^+$ ] 239.1254, found 239.1255.



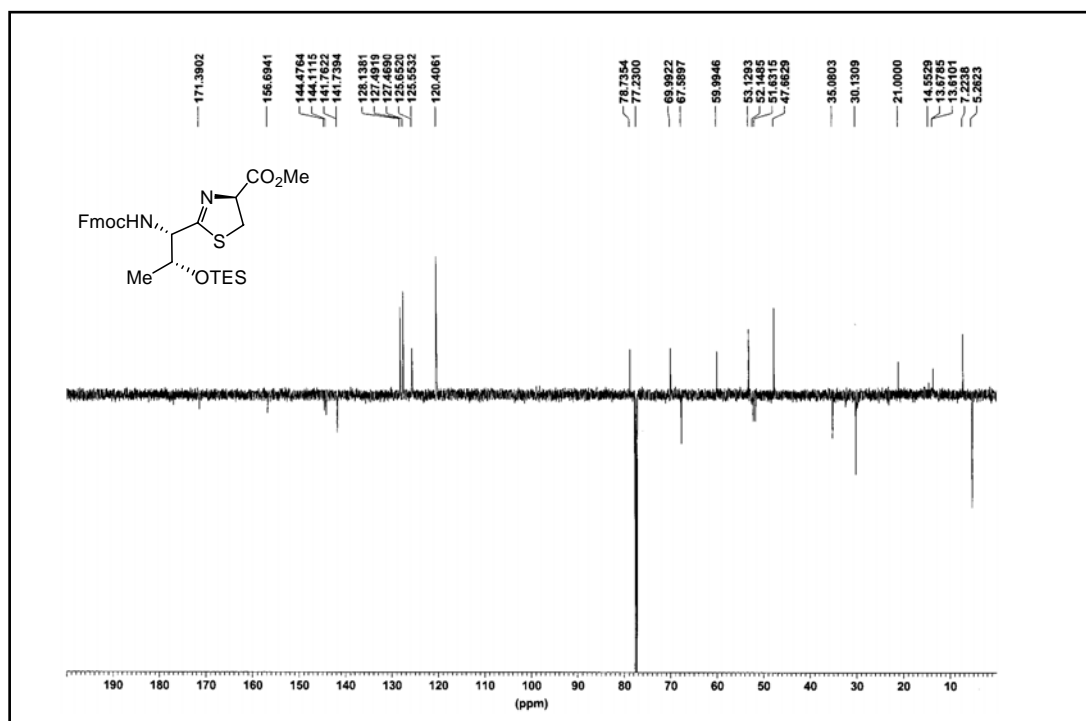
**3.10a:** [ca. 1:1 mixture of inseparable diastereomers]  $R_f=0.34$  (silica gel, EtOAc/hexanes, 7:3);  $[\alpha]_D^{32} -22.3$  ( $c$  0.60,  $\text{CH}_2\text{Cl}_2$ ); IR (film)  $\nu_{\text{max}}$  3380, 2925, 2854, 1737, 1719, 1460, 1375, 1252, 1094, 836  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  8.37 (s, 1+1H), 6.05 (m, 1+1H), 5.06–5.03 (m, 1+1H), 2.94–2.84 (m, 1+1H), 2.79–2.74 (m, 1+1H), 2.69–2.65 (m, 1+1H), 2.14 (s, 3+3H), 2.10–2.02 (m, 2+2H), 1.95 (m, 1+1H), 1.39 (d,  $J=6.12$  Hz, 3H), 1.36 (d,  $J=6.18$  Hz, 3H), 0.92 (s, 9H), 0.90 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H), 0.00 (s, 3H),  $-0.02$  (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  178.3, 170.6, 157.8, 152.4, 144.5, 134.0, 120.2, 70.3, 66.5, 66.4, 32.1, 29.9, 25.9, 25.9, 25.2, 25.0, 22.9, 21.5, 18.1,  $-4.6$ ,  $-4.6$ ,  $-4.7$ ; HRMS (ESI-TOF) calcd for  $\text{C}_{20}\text{H}_{32}\text{NO}_5\text{Si}^+$   $[\text{M}+\text{H}^+]$  394.2044, found 394.2049.



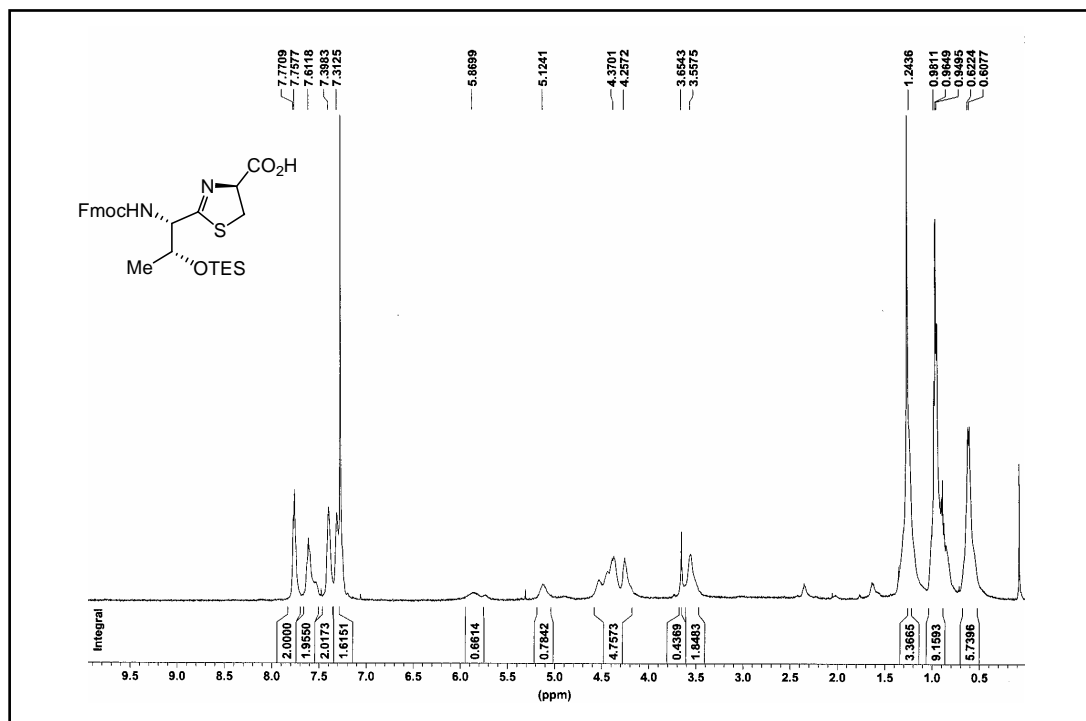
**3.12a:**  $R_f=0.34$  (silica gel, MeOH/ $\text{CH}_2\text{Cl}_2$ , 1:9);  $[\alpha]_D^{32} -62.6$  ( $c$  0.67, MeOH); IR (film)  $\nu_{\text{max}}$  3381, 2920, 2856, 1732, 1649, 1454, 1270, 1164, 1106  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.59–7.57 (m, 2H), 7.45–7.44 (m, 5H), 5.48 (br s, 1H), 3.88 (s, 3H), 3.40 (m, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  168.1, 153.4, 137.0, 133.7, 131.0, 130.5, 129.8, 129.5, 129.4, 126.5, 124.6, 61.3, 56.1, 55.7, 30.9; HRMS (ESI-TOF) calcd for  $\text{C}_{19}\text{H}_{17}\text{Cl}_2\text{F}_3\text{NO}_5^+$   $[\text{M}+\text{H}^+]$  466.0430, found 466.0429.



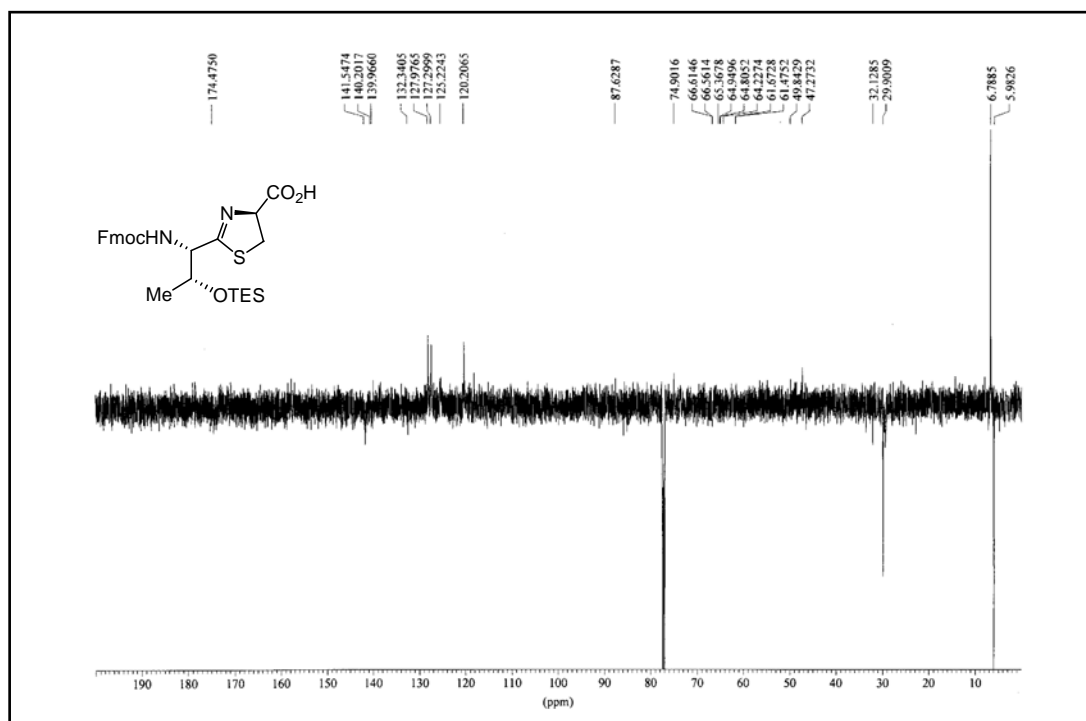
**Spectrum 3.1**  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ) spectrum of compound 3.2.



**Spectrum 3.2**  $^{13}\text{C NMR}$  (150 MHz,  $\text{CDCl}_3$ ) spectrum of compound 3.2.

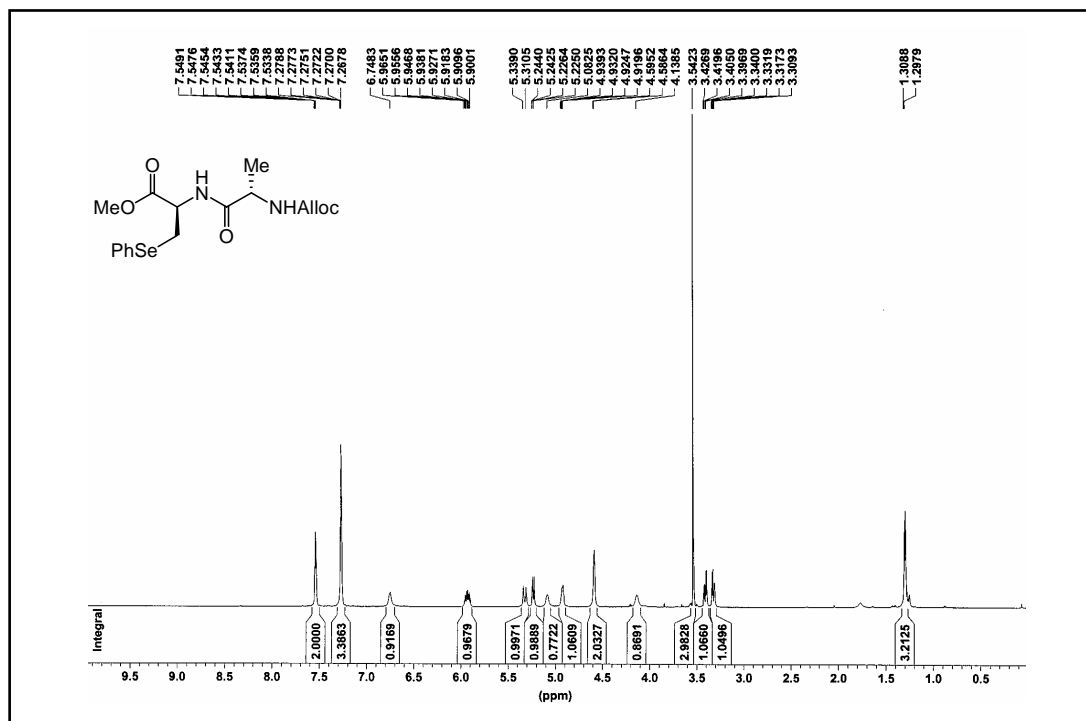


**Spectrum 3.3** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) spectrum of compound 3.2a.

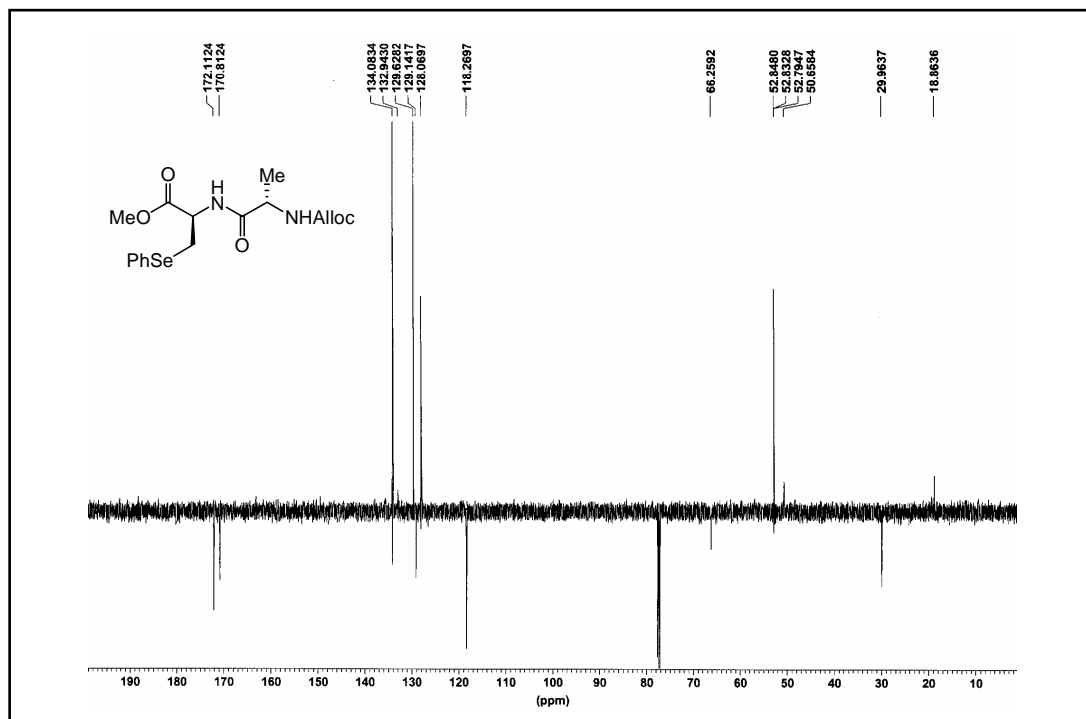


**Spectrum 3.4** <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) spectrum of compound 3.2a.

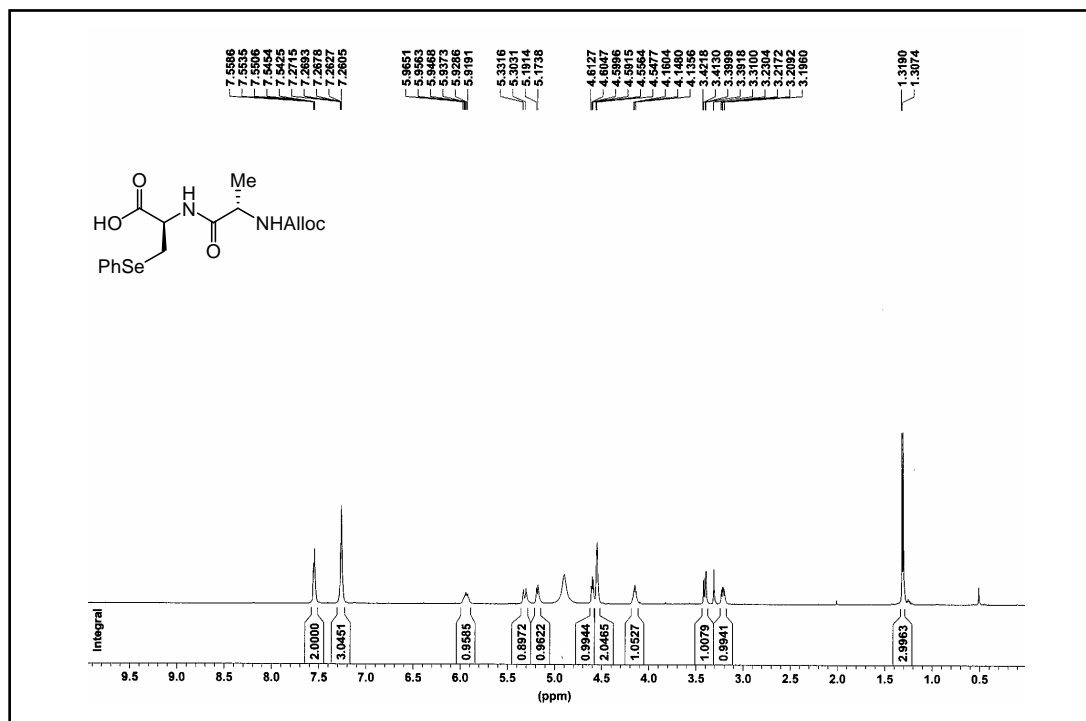




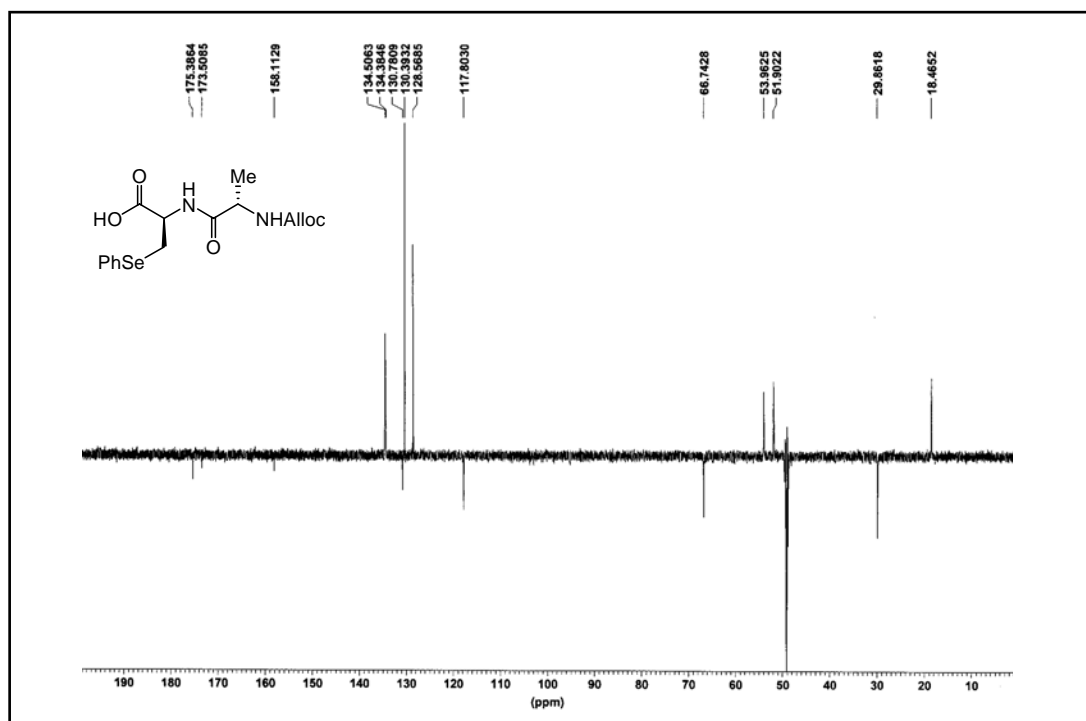
Spectrum 3.5 <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) spectrum of compound 3.3.



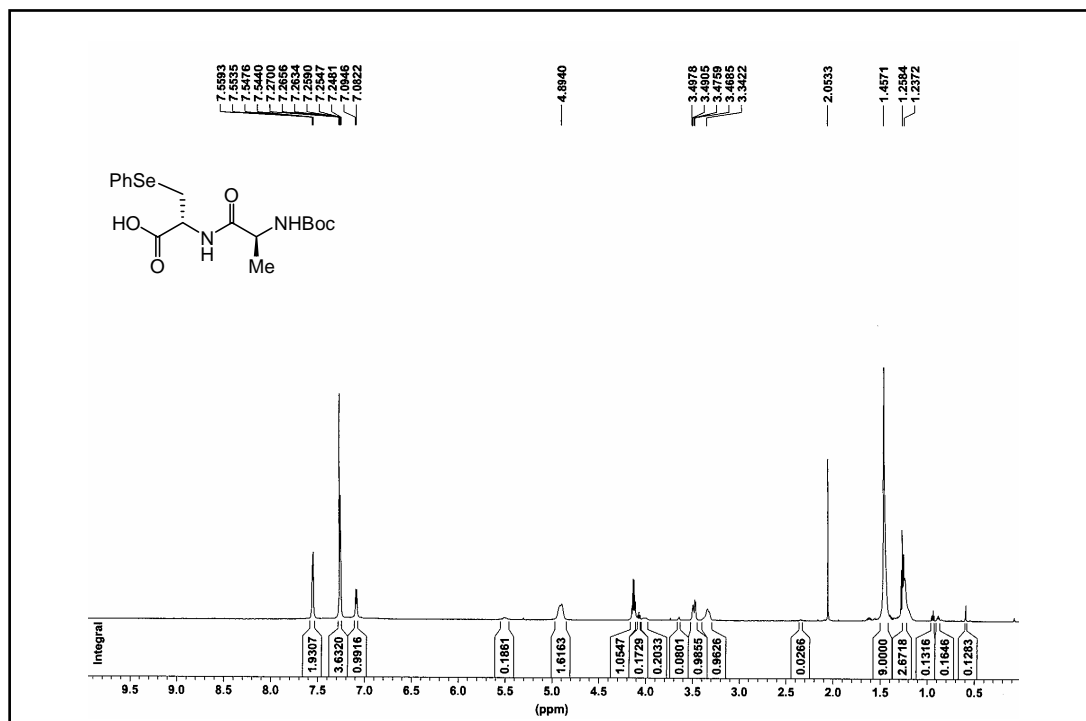
Spectrum 3.6 <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) spectrum of compound 3.3.



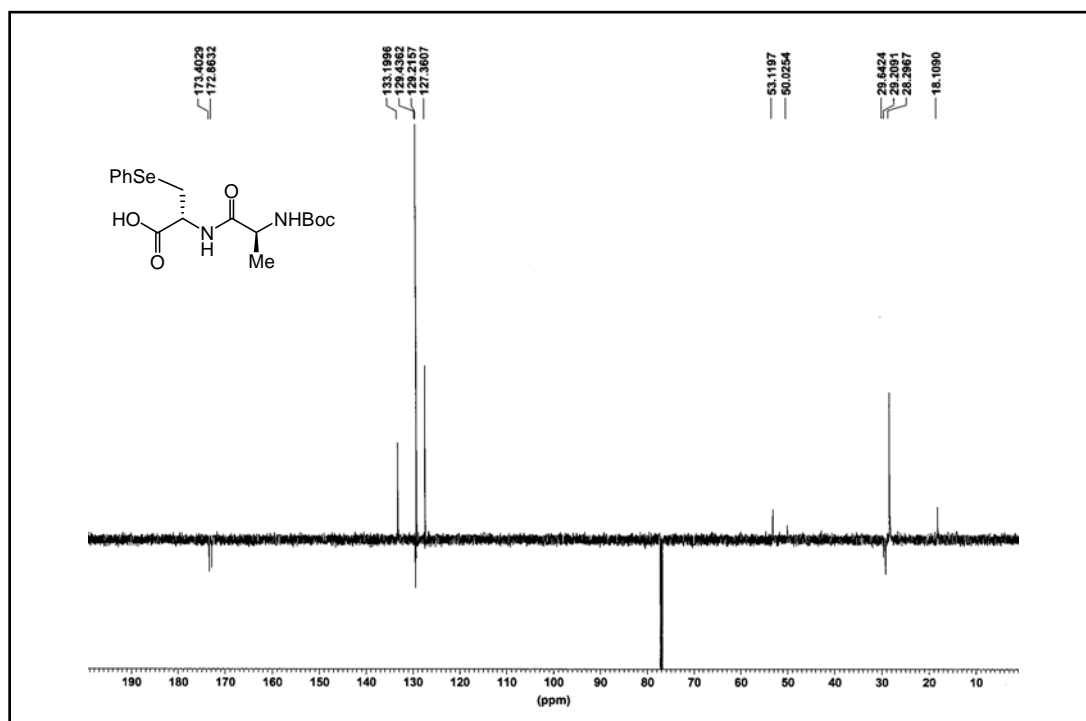
Spectrum 3.7 <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>OD) spectrum of compound 3.3a.



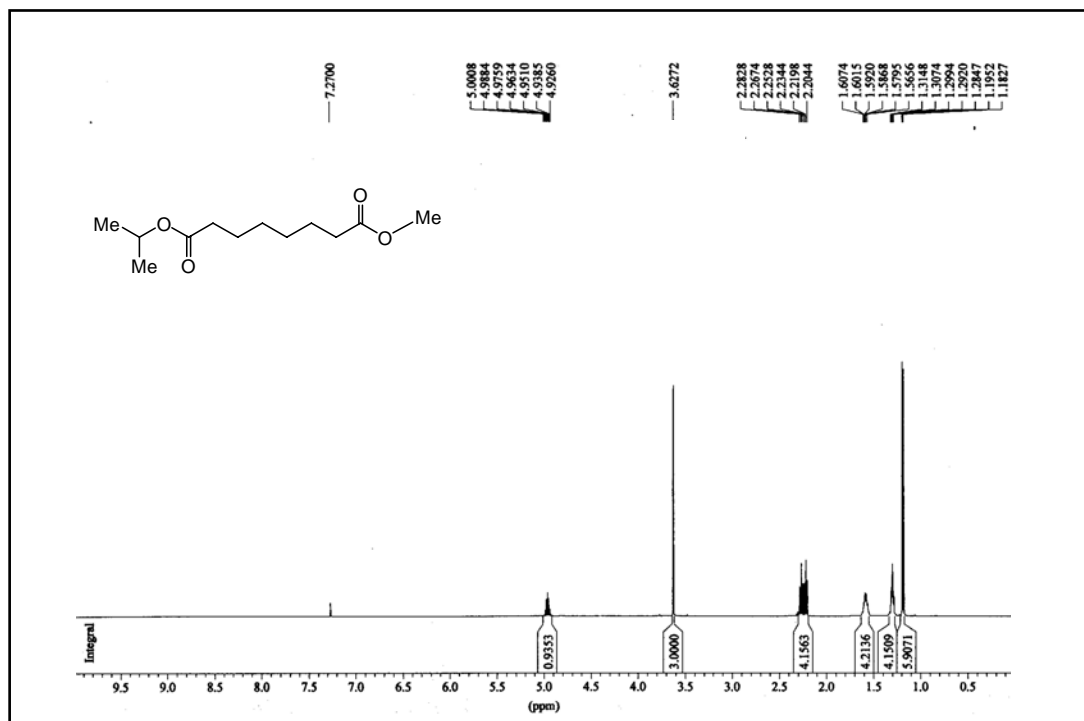
Spectrum 3.8 <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>OD) spectrum of compound 3.3a.



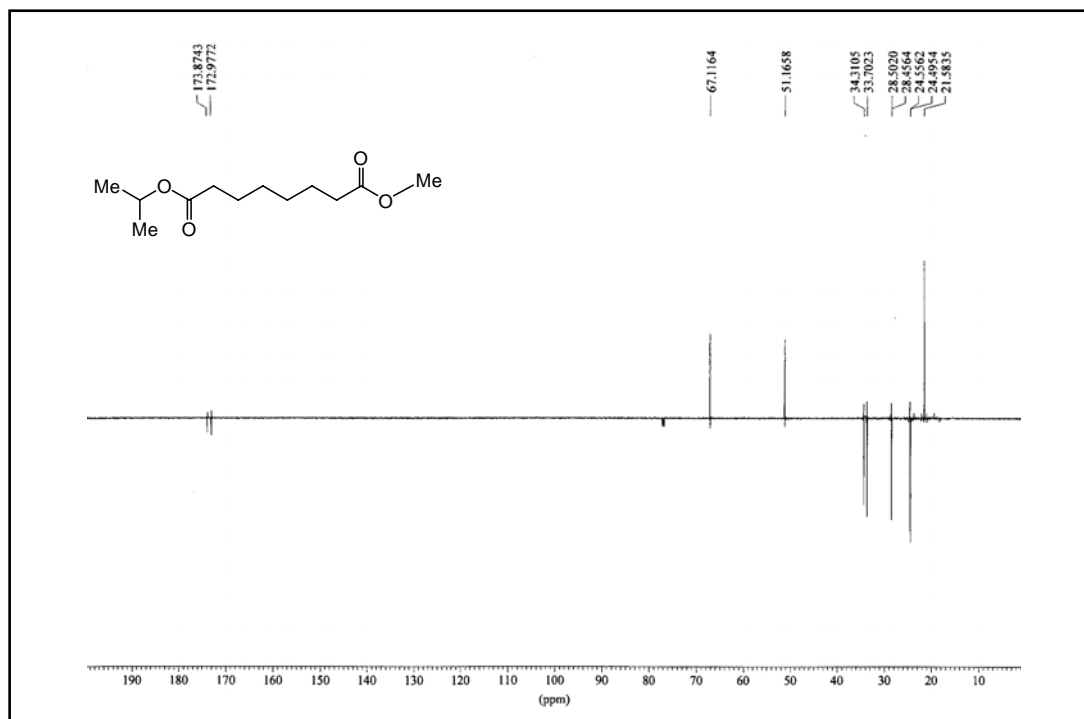
Spectrum 3.9  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ) spectrum of compound 3.4a.



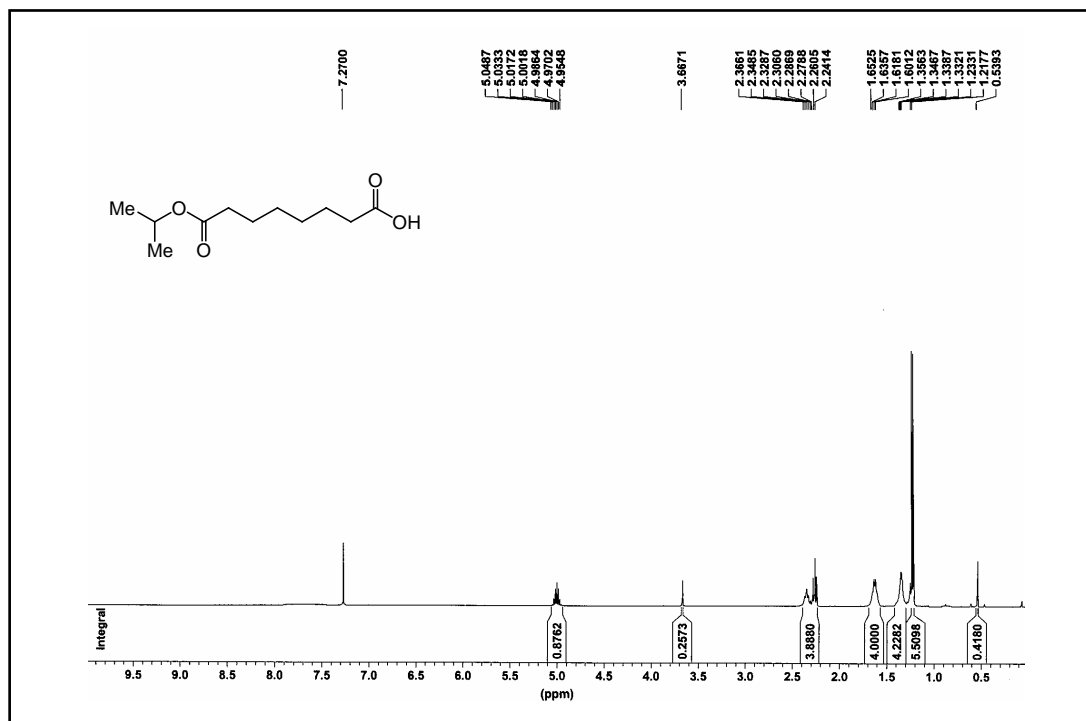
Spectrum 3.10  $^{13}\text{C NMR}$  (150 MHz,  $\text{CDCl}_3$ ) spectrum of compound 3.4a.



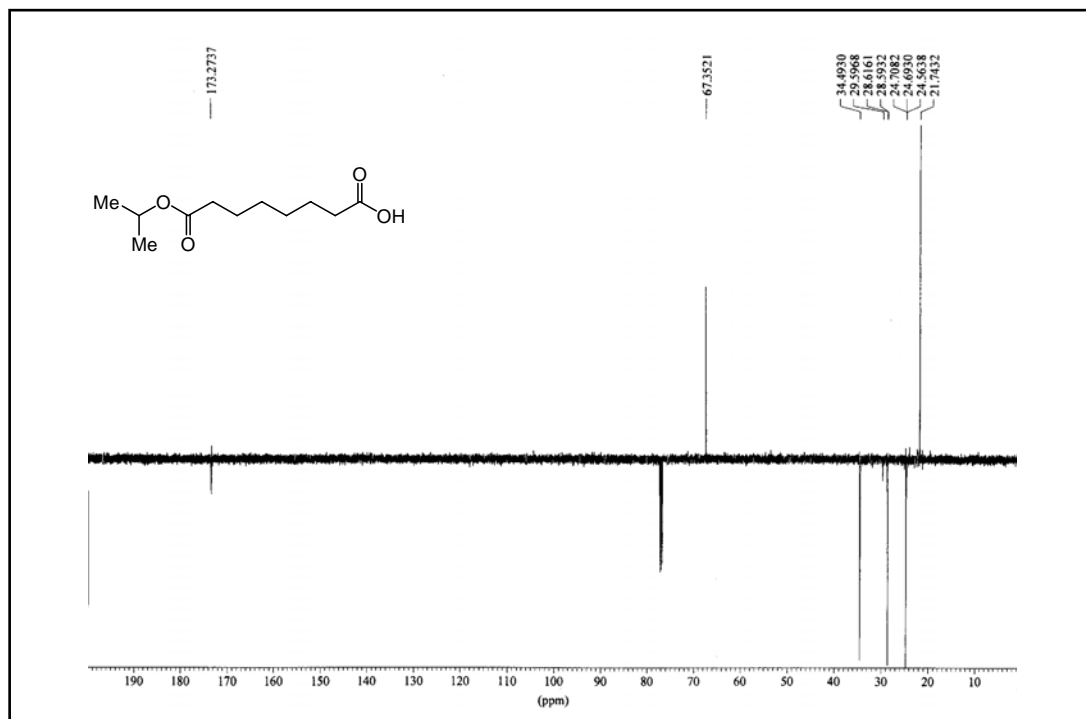
**Spectrum 3.11**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) spectrum of compound **3.7**.



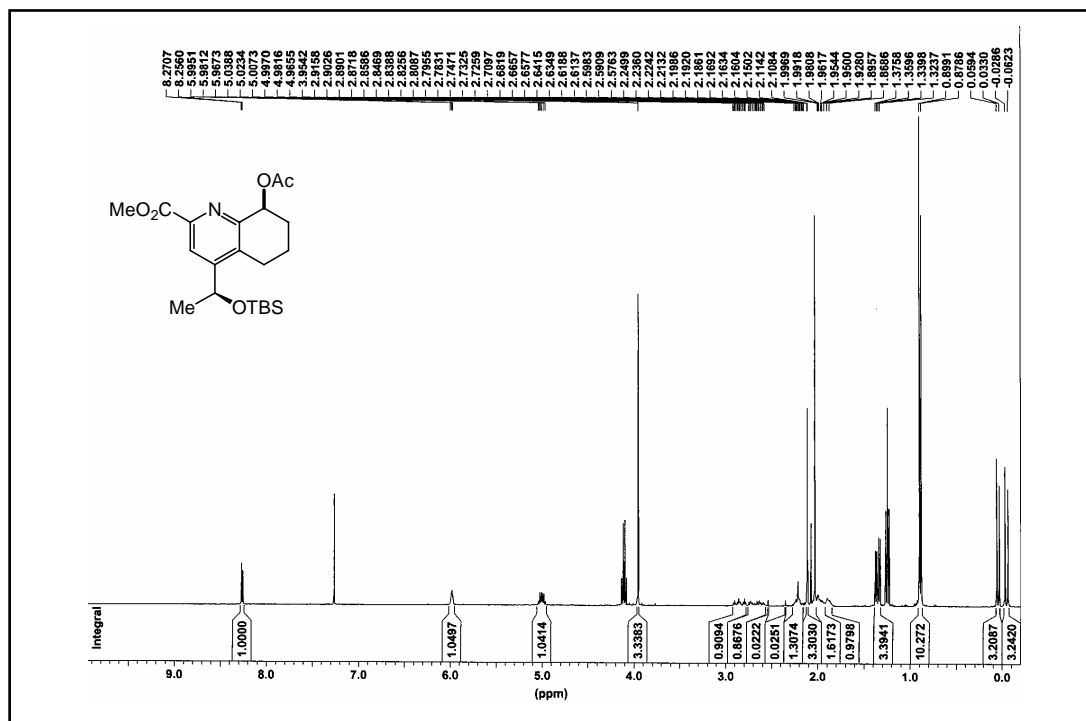
**Spectrum 3.12**  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ) spectrum of compound **3.7**.



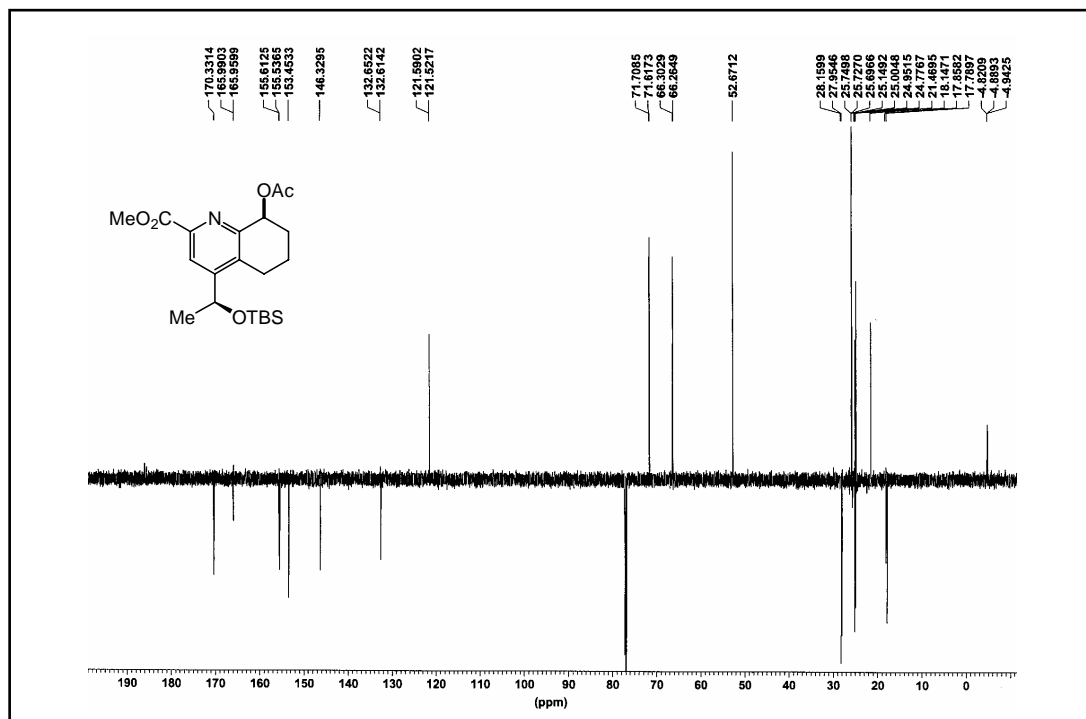
**Spectrum 3.13**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) spectrum of compound **3.7a**.



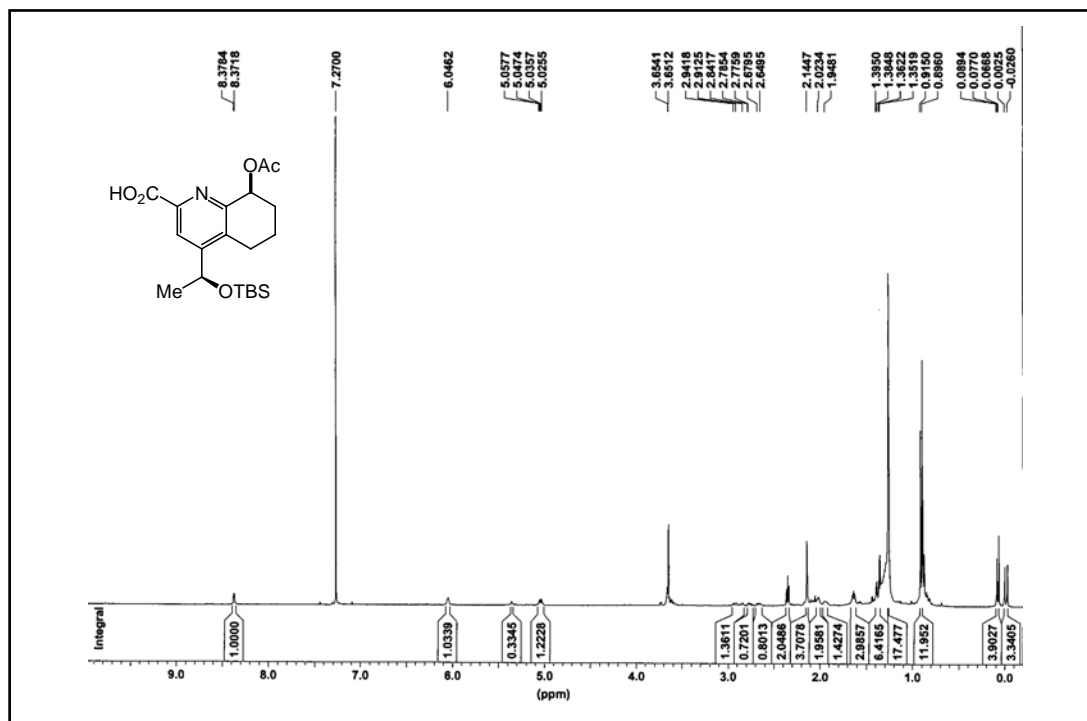
**Spectrum 3.14**  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ) spectrum of compound **3.7a**.



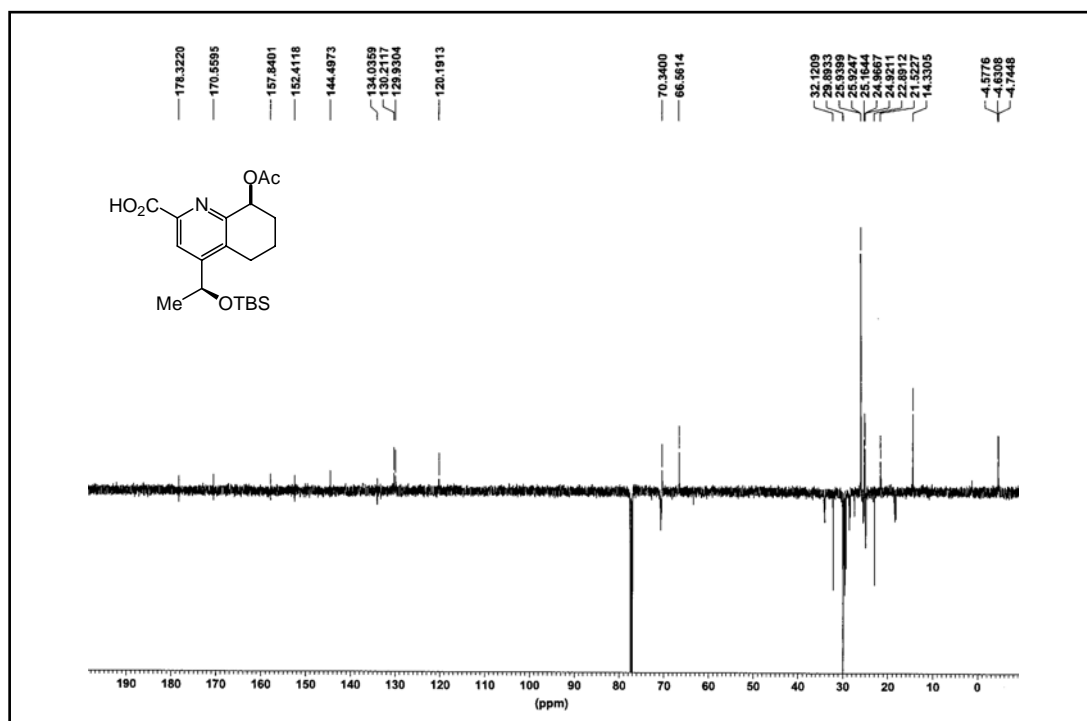
Spectrum 3.15  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ) spectrum of compound 3.10.



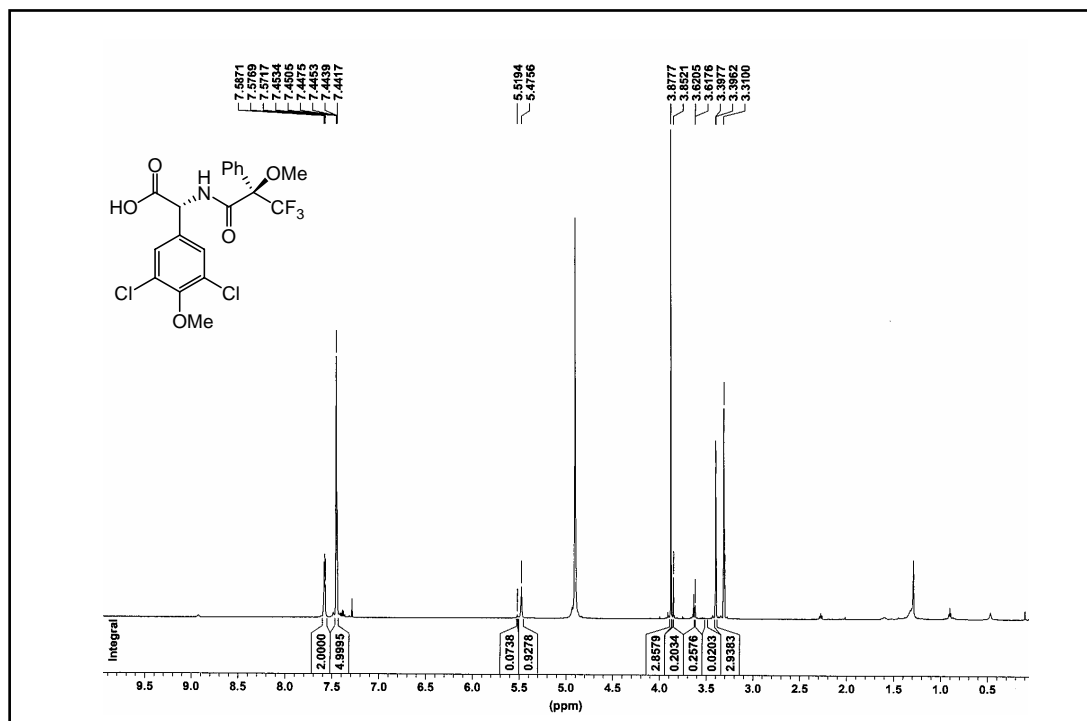
Spectrum 3.16  $^{13}\text{C NMR}$  (150 MHz,  $\text{CDCl}_3$ ) spectrum of compound 3.10.



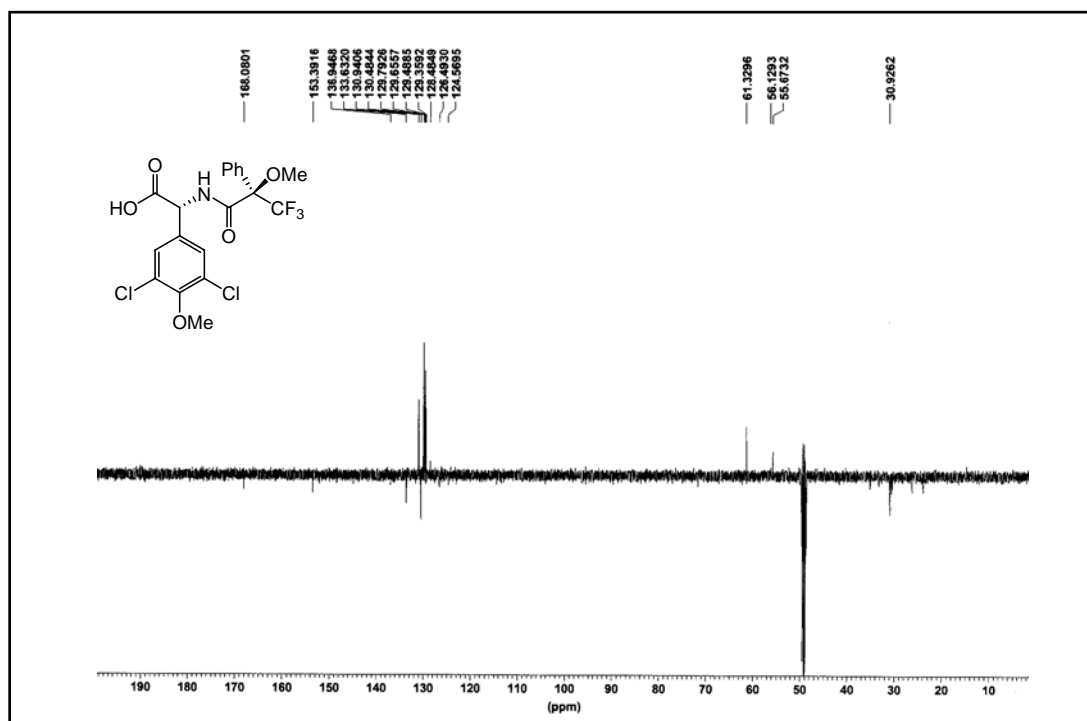
Spectrum 3.17 <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) spectrum of compound 3.10a.



Spectrum 3.18 <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) spectrum of compound 3.10a.



**Spectrum 3.19**  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{OD}$ ) spectrum of compound **3.12a**.



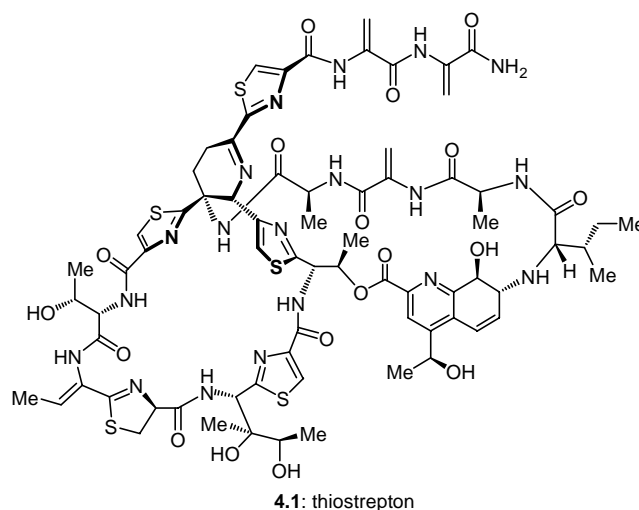
**Spectrum 3.20**  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{OD}$ ) spectrum of compound **3.12a**.



**Chapter 4: Contributions Towards the Total Synthesis of  
Thiostrepton**

## A. Introduction

Upon my arrival at Scripps in July of 2003, I was given the opportunity to join the thiostrepton team and provide assistance to a project already in progress. In May of 2004 we were able to complete the first total synthesis of thiostrepton<sup>1</sup> (**4.1**, Figure 4.1), a highly complex thiopeptide antibiotic, fifty years after its isolation.<sup>2</sup> While the majority of the work was completed by Dr. Brian Safina<sup>3</sup>, Dr. Mark Zak<sup>4</sup> and a number of post doctoral research associates, I was able to contribute to this accomplishment in a few significant areas.

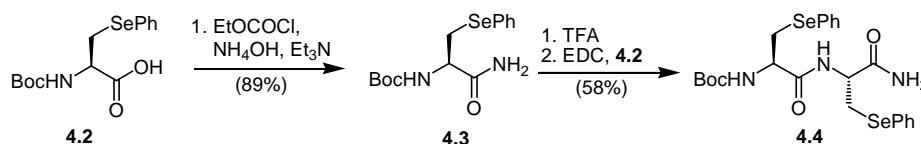


**Figure 4.1** Molecular structure of thiostrepton **4.1**.

## B. Construction of the Bis-dehydroalanine Tail Fragment

Dehydroalanine residues are common characteristics of the thiopeptide family of antibiotics. Thiostrepton (**4.1**) possesses a bis-dehydroalanine tail fragment, and the decision was made to mask the reactive olefins as phenylselenium progenitors, as

phenylselenium protecting groups could be mildly and efficiently removed with *t*BuOOH via a retro-hetero-ene reaction. Additionally, the van der Donk laboratory had already published the synthesis of acid **4.2** (Scheme 4.1), which can be accessed from Boc-L-Ser-OH.<sup>5</sup> Thus, amide formation (EtOCOCl, NH<sub>4</sub>OH, Et<sub>3</sub>N, 89%) produces primary amide **4.3**, which, after *N*-Boc deprotection (TFA), undergoes peptide coupling with acid **4.2** (EDC) to give the desired target **4.4** in 58% yield over two steps. This concise route allows for an expedient, multi-gram scale synthesis of the shelf stable bis-dehydroalanine tail fragment (**4.4**).

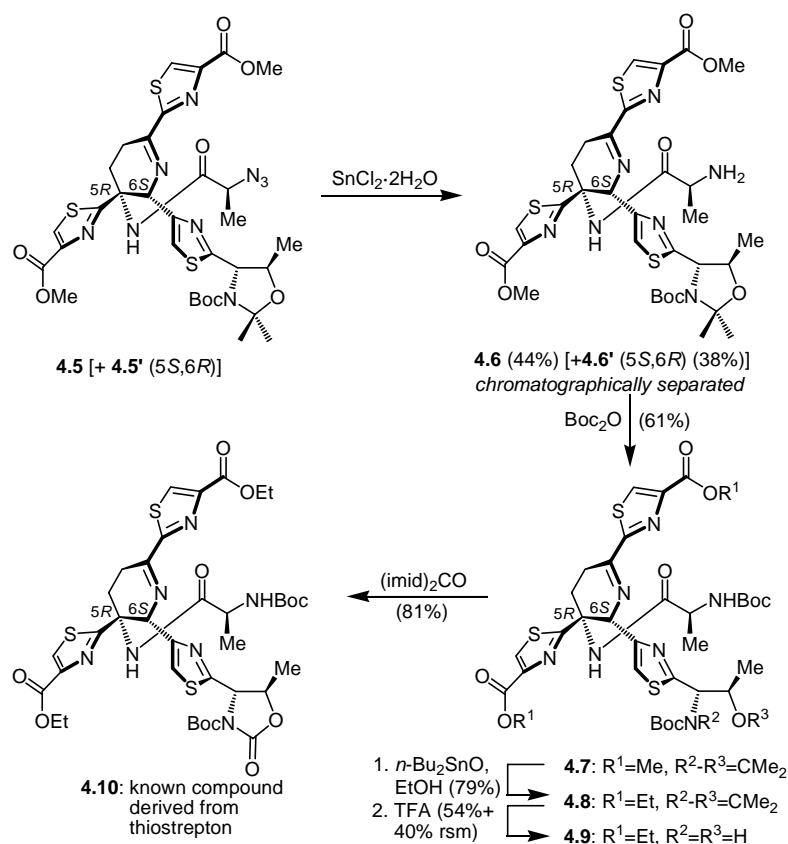


**Scheme 4.1** Construction of bis-dehydroalanine tail fragment **4.4**.

### C. Elucidation of the C5/C6 Dehydropiperidine Core Stereochemistry

The dehydropiperidine core of thiostrepton was constructed via a biosynthetically inspired aza-Diels–Alder dimerization.<sup>6</sup> Although this strategy allowed for the expedient synthesis of a highly complex core structure, there was no facial selectivity observed in the key reaction, which ultimately resulted in an inseparable mixture of *C5/C6* diastereomeric azides **4.5** and **4.5'** (Scheme 4.2). Fortunately, after reduction of this mixture [SnCl<sub>2</sub>·2H<sub>2</sub>O, **4.6** (*5R,6S* 44%), **4.6'** (*5S,6R* 38%)], chromatographic separation was achievable. The stereochemical assignment was then accomplished by taking the less polar diastereomer (**4.6**) and converting it to

a known compound (**4.10**) derived from thiostrepton.<sup>7</sup> Hence, *N*-Boc protection (Boc<sub>2</sub>O, 61%) of the primary amine, followed by Bu<sub>2</sub>SnO-mediated transesterification (79%) and selective isopropylidene acetal removal (TFA, MeOH, CH<sub>2</sub>Cl<sub>2</sub>, 54% + 40% rsm) afforded *N*-Boc amino alcohol **4.9**. Finally, cyclic carbamate formation with carbonyl diimidazole generated **4.10** (81%) whose <sup>1</sup>H and <sup>13</sup>C NMR spectra were in complete agreement with those reported for the naturally derived substance<sup>7</sup> confirming the correct 5*R*,6*S* stereochemistry of intermediate **4.6**.



**Scheme 4.2** Elucidation of C5/C6 stereochemistry of dehydropiperidine core of thiostrepton.

## D. Conclusion

The efficient multi-gram scale synthesis of bis-dehydroalanine tail **4.4** was accomplished in only three steps starting from van der Donk's phenylselenium acid **4.2**. Masking the dehydroalanine moiety proved critical to the stability of the fragment as several side reactions can occur with the exposed enamide moiety.<sup>1b</sup> Additionally, the elucidation of the *C5/C6* stereochemistry of the dehydropiperidine core simplified the total synthesis of thiostrepton by only having to elaborate upon more polar diastereomer **4.6** after chromatographic separation. This essentially reduced the workload by half, and provided further confirmation of our core structure by matching with a known degradation compound from the natural product.

## E. References

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7. S. Higashibayashi, K. Hashimoto, M. Nakata, *Tetrahedron Lett.* **2002**, *43*, 105–110.

## F. Experimental Section

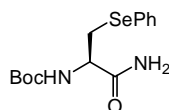
### 1. General Techniques

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, 1,2-dimethoxyethane (DME), and methylene chloride ( $\text{CH}_2\text{Cl}_2$ ) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically ( $^1\text{H}$  NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an ethanolic solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F<sub>254</sub>). Optical rotations were recorded on a Perkin–Elmer 343 polarimeter. NMR spectrum was recorded on Bruker DRX-600, DRX-500, AMX-500 or AMX-400 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s=singlet, d=doublet, t=triplet, q=quartet,  $\frac{1}{2}\text{ABq}=\frac{1}{2}\text{AB}$  quartet, m=multiplet, quin=quintuplet, sext=sextet, sep=septet, hept=heptet, br=broad. IR spectra were recorded on a Perkin–Elmer 1600 or Spectrum 100 series FTIR spectrometer.

Electrospray ionization (ESI) mass spectrometry (MS) experiments were performed on an API 100 Perkin–Elmer SCIEX single quadrupole mass spectrometer at 4000 V emitter voltage. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer using MALDI (matrix-assisted laser-desorption ionization) or ESI (electrospray ionization).

## 2. Preparation of Compounds

**4.3:** To a stirred solution of known carboxylic acid (**4.2**)<sup>5</sup> (6.78 g, 19.65 mmol) in anhydrous THF (98 mL) at 0 °C was added *i*Pr<sub>2</sub>NEt (3.6 mL, 20.6 mmol) and ethyl chloroformate (1.97 mL, 20.6 mmol). After 30 min at 0 °C and 1 h at 25 °C, NH<sub>4</sub>OH (3.8 mL) was added at 0 °C. After stirring for 1.5 h at 0 °C and 12 h at 25 °C, the reaction mixture was concentrated. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (100 mL), washed with H<sub>2</sub>O (100 mL), aqueous 5% HCl solution (100 mL), saturated aqueous NaHCO<sub>3</sub> solution (100 mL), brine (100 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. Purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes, 90:10) afforded *N*-Boc-protected amino selenoamide **4.3** (6.0 g, 89%) as a yellow oil.

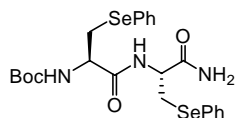


**4.3:** *R*<sub>f</sub>=0.20 (silica gel, EtOAc/hexanes, 1:1); [ $\alpha$ ]<sub>D</sub><sup>32</sup> -45.8 (*c* 0.17, CH<sub>2</sub>Cl<sub>2</sub>); IR (film)  $\nu_{\text{max}}$  3324, 2978, 1682, 1502, 1392, 1367, 1251, 1165, 1022, 738 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN, 66 °C)  $\delta$  7.56–7.54 (m, 2H), 7.30–7.29 (m, 3H), 6.33 (br s, 1H),



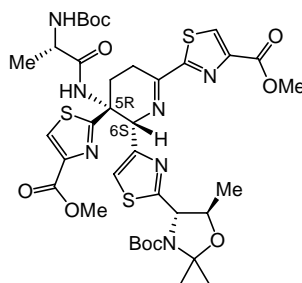
5.82 (br s, 1H), 5.53 (br s, 1H), 4.24–4.22 (m, 1H), 3.32 (dd,  $J=12.7, 5.2$  Hz, 1H), 3.16 (dd,  $J=13.1, 7.9$  Hz, 1H), 1.41 (br s, 9H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ , 66 °C)  $\delta$  174.4, 134.5, 131.7, 131.0, 128.9, 56.3, 31.5, 29.4; HRMS (ESI-TOF) calcd for  $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_3\text{SeNa}^+$  [ $\text{M}+\text{Na}^+$ ] 367.0531, found 367.0537.

**4.4:** To a stirred solution of amino selenoamide **4.3** (2.64 g, 7.69 mmol) in  $\text{CH}_2\text{Cl}_2$  (19 mL) at 0 °C was added TFA (19 mL) dropwise. After stirring for 5 min at 0 °C, the reaction mixture was warmed to 25 °C and stirred for 1 h. After diluting with toluene (25 mL) and concentrating (3 $\times$ ), the residue was dried under vacuum to give a clear oil. To the clear oil in anhydrous DMF (20 mL) at 0 °C was added *i*Pr<sub>2</sub>NEt (2.0 mL, 11.5 mmol), carboxylic acid **4.2** (3.18 g, 9.2 mmol; via cannula), EDC (1.62 g, 8.5 mmol), and HOAt (1.15 g, 8.5 mmol). After 20 min at 0 °C, the reaction mixture was warmed to 25 °C and stirred for an additional 5 h period. After dilution with  $\text{CH}_2\text{Cl}_2$  (50 mL),  $\text{H}_2\text{O}$  (50 mL) was added and the layers were separated. The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (2 $\times$ 25 mL) and the combined organic layers were washed with aqueous 5% HCl solution (50 mL), saturated aqueous  $\text{NaHCO}_3$  solution (50 mL), brine (50 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. Purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes, 90:10 $\rightarrow$  MeOH/ $\text{CH}_2\text{Cl}_2$ , 10:90) afforded bis(phenylseleno) peptide **4.4** (3.6 g, 82% over two steps) as a white foam.



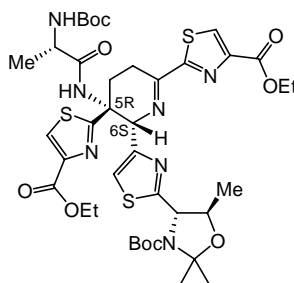
**4.4:**  $R_f=0.45$  (silica gel, EtOAc/hexanes, 9:1);  $[\alpha]_D^{32} -91.5$  ( $c$  0.17,  $\text{CHCl}_3$ ); IR (film)  $\nu_{\text{max}}$  3318, 2980, 1686, 1650, 1628, 1523, 1416, 1163, 733  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz, DMSO)  $\delta$  8.19 (d,  $J=7.9$  Hz, 1H), 7.50–7.45 (m, 4H), 7.31–7.20 (m, 6H), 4.43–4.39 (m, 1H), 4.15–4.12 (m, 1H), 3.29–3.26 (m, 1H), 3.24–3.21 (m, 1H), 3.16–3.12 (m, 1H), 3.07–3.03 (m, 1H), 1.39 (br s, 9H);  $^{13}\text{C}$  NMR (150 MHz, DMSO)  $\delta$  171.5, 170.4, 155.3, 131.7, 131.5, 130.4, 130.2, 129.3, 129.2, 126.8, 126.7, 78.6, 54.8, 52.6, 29.1, 29.0, 28.1; HRMS (ESI-TOF) calcd for  $\text{C}_{23}\text{H}_{30}\text{N}_3\text{O}_4\text{Se}_2^+$   $[\text{M}+\text{H}^+]$  572.0561, found 572.0569.

**4.7:** To a stirred solution of free amine **4.6**<sup>1a</sup> (64 mg, 0.09 mmol) in anhydrous THF (1.6 mL) was added *i*Pr<sub>2</sub>NEt (0.15 mL, 0.86 mmol), Boc<sub>2</sub>O (93 mg, 0.43 mmol) and 4-DMAP (1 mg, 0.01 mmol) at 25 °C. After stirring for 1 h, the reaction mixture was diluted with EtOAc (15 mL) and the layers were separated. The organic layer was then washed with aqueous 0.01 M KHSO<sub>4</sub> solution (5×5 mL), H<sub>2</sub>O (10 mL), saturated aqueous NaHCO<sub>3</sub> solution (10 mL), brine (10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. Purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes, 7:3) afforded *N*-Boc methyl ester **4.7** (44 mg, 61%) as a yellow oil.



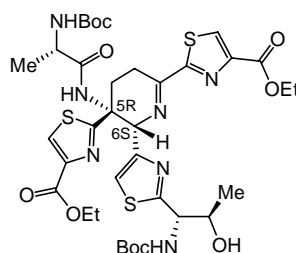
**4.7:**  $R_f=0.20$  (silica gel, EtOAc/hexanes, 7:3);  $[\alpha]_D^{32} +27.2$  ( $c$  0.18,  $\text{CHCl}_3$ ); IR (film)  $\nu_{\text{max}}$  3332, 2982, 2924, 1705, 1495, 1477, 1367, 1244, 1215, 1163, 755  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ , 66 °C)  $\delta$  8.43 (br s, 1H), 8.29 (s, 1H), 8.07 (s, 1H), 7.18 (s, 1H), 5.39 (br s, 1H), 5.29 (br s, 1H), 4.82 (d,  $J=7.0$  Hz, 1H), 4.35 (quin,  $J=6.6$  Hz, 1H), 4.01 (dd,  $J=7.3, 5.9$  Hz, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 3.50 (ddd,  $J=13.6, 6.2, 2.2$  Hz, 1H), 3.22–3.16 (m, 1H), 2.98–2.90 (m, 1H), 2.74–2.68 (m, 1H), 1.68 (s, 3H), 1.64 (s, 3H), 1.45 (d,  $J=5.9$  Hz, 3H), 1.38 (br s, 9H), 1.32 (d,  $J=7.3$  Hz, 3H), 1.30 (br s, 9H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ , 66 °C)  $\delta$  176.5, 174.2, 173.5, 170.3, 163.9, 162.3, 156.2, 152.9, 148.3, 147.4, 131.9, 129.1, 120.4, 96.1, 81.8, 80.7, 68.1, 67.2, 61.1, 53.1, 53.0, 52.8, 32.6, 29.0, 28.8, 28.4, 25.8, 19.2, 18.7, 18.6; HRMS (ESI-TOF) calcd for  $\text{C}_{37}\text{H}_{50}\text{N}_7\text{O}_{10}\text{S}_3^+$   $[\text{M}+\text{H}^+]$  848.2776, found 848.2793.

**4.8:** To a stirred solution of *N*-Boc methyl ester **3.7** (36 mg, 0.04 mmol) in EtOH (0.43 mL) was added  $n\text{Bu}_2\text{SnO}$  (53 mg, 0.21 mmol) and the reaction mixture was stirred for 5 h at 65 °C. After concentration, the residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 7:3) to afford *N*-Boc ethyl ester **4.8** (30 mg, 79%) as a yellow foam.



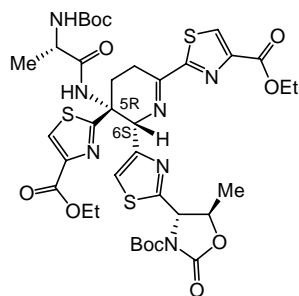
**4.8:**  $R_f=0.40$  (silica gel, EtOAc/hexanes, 6:4);  $[\alpha]_D^{32} +24.9$  ( $c$  1.00,  $\text{CHCl}_3$ ); IR (film)  $\nu_{\text{max}}$  3319, 2979, 2920, 1708, 1490, 1390, 1361, 1237, 1208, 1167, 750  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ , 66 °C)  $\delta$  8.42 (br s, 1H), 8.29 (s, 1H), 8.07 (s, 1H), 7.18 (s, 1H), 5.40 (br s, 1H), 5.29 (br s, 1H), 4.81 (d,  $J=7.0$  Hz, 1H), 4.42 (q,  $J=7.0$  Hz, 2H), 4.40–4.35 (m, 1H) 4.37 (q,  $J=6.6$  Hz, 2H), 4.01 (dq  $J=6.0$ , 1.5 Hz, 1H), 3.50 (ddd,  $J=13.6$ , 6.6, 2.6 Hz, 1H), 3.22–3.17 (m, 1H), 2.98–2.90 (m, 1H), 2.74–2.68 (m, 1H), 1.68 (s, 3H), 1.64 (s, 3H), 1.45 (d,  $J=6.3$  Hz, 3H), 1.42 (t,  $J=7.4$  Hz, 3H), 1.38 (t,  $J=7.0$  Hz, 3H), 1.37 (br s, 9H), 1.33 (d,  $J=7.3$  Hz, 3H), 1.31 (br s, 9H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ , 66 °C)  $\delta$  176.8, 174.6, 173.9, 170.6, 164.4, 162.2, 156.6, 153.4, 149.1, 148.2, 131.7, 128.9, 120.3, 96.1, 81.8, 80.7, 68.0, 67.1, 65.0, 62.3, 62.1, 61.1, 31.8, 28.9, 28.8, 28.4, 25.8, 20.0, 19.2, 18.7, 14.8; HRMS (ESI-TOF) calcd for  $\text{C}_{39}\text{H}_{53}\text{N}_7\text{O}_{10}\text{S}_3\text{Na}^+$   $[\text{M}+\text{Na}^+]$  898.2908, found 898.2917.

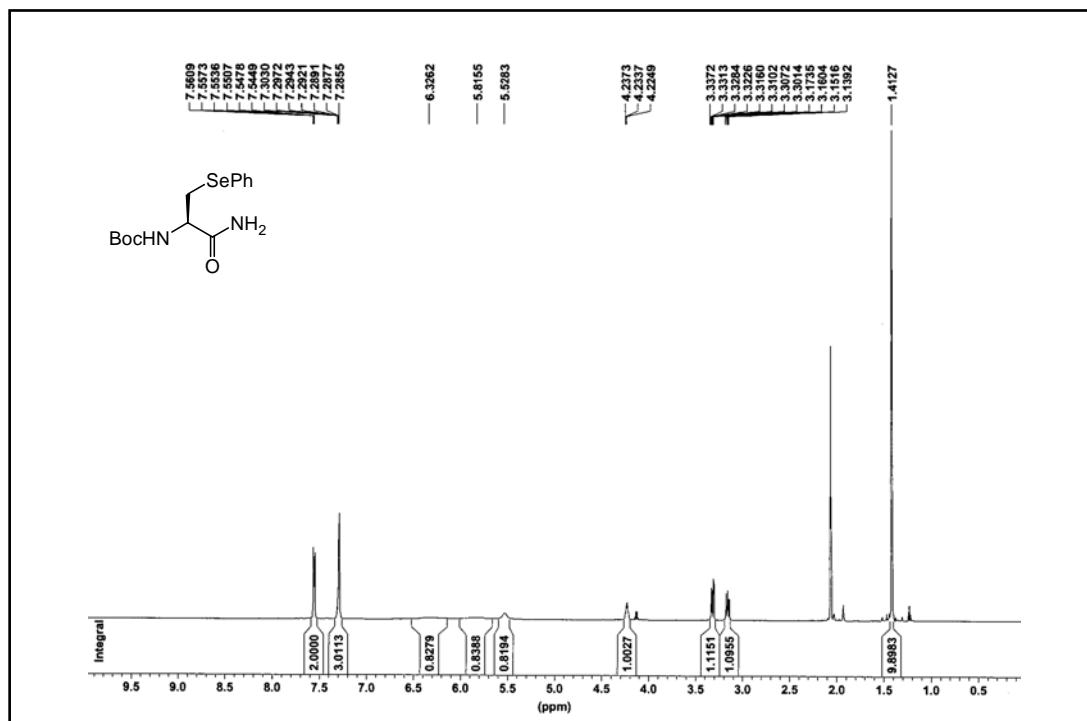
**4.9:** To a stirred solution of *N*-Boc ethyl ester **4.8** (28 mg, 0.03 mmol) in MeOH (400 L) was added TFA (400 L) dropwise at 0 °C. After stirring for 1 h, the reaction was diluted with toluene (1 mL) and concentrated (3 $\times$ ). Purification of the residue by preparative TLC (silica gel, EtOAc/hexanes, 7:3) afforded amino alcohol **4.9** (20 mg, 54% plus 40% recovered starting material) as a yellow foam.



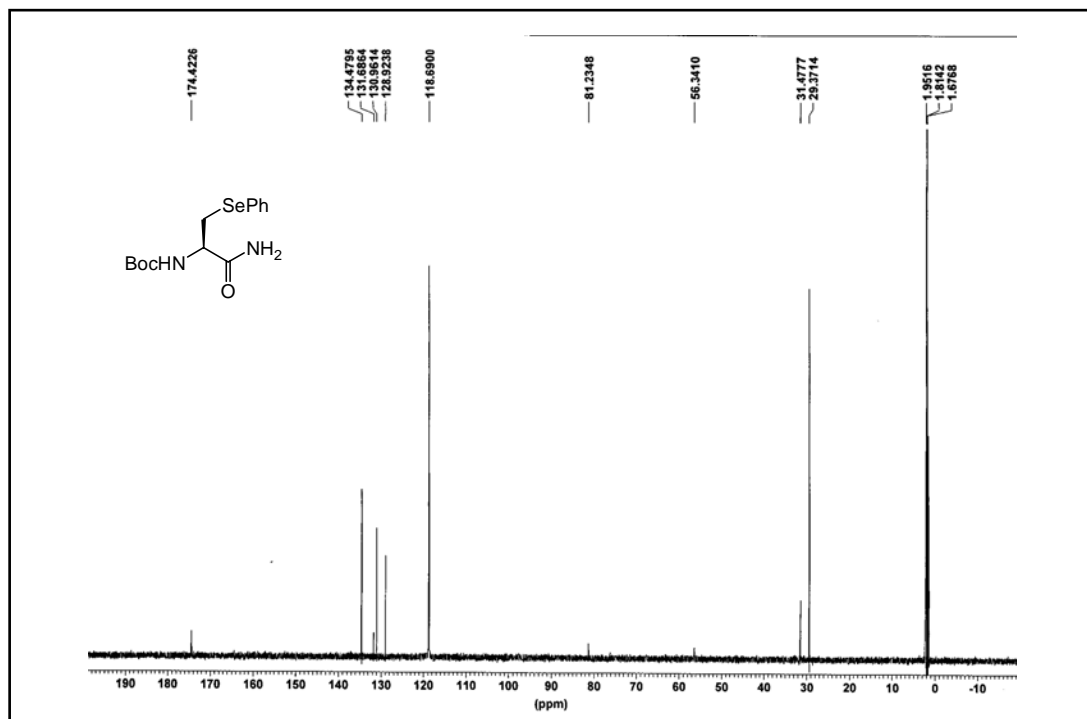
**4.9:**  $R_f=0.32$  (silica gel, EtOAc/hexanes, 7:3);  $[\alpha]_D^{32} +12.9$  ( $c$  0.23,  $\text{CH}_2\text{Cl}_2$ ); IR (film)  $\nu_{\text{max}}$  3313, 2923, 2849, 1718, 1508, 1465, 1370, 1241, 1216, 1165  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ , 66 °C)  $\delta$  8.50 (br s, 1H), 8.24 (s, 1H), 8.03 (s, 1H), 6.97 (s, 1H), 5.98 (br s, 1H), 5.29 (q,  $J=1.9$  Hz, 1H), 4.90 (dd,  $J=9.2, 3.3$  Hz, 1H), 4.39 (q,  $J=7.0$  Hz, 2H), 4.37–4.32 (m, 1H) 4.34 (q,  $J=7.0$  Hz, 2H), 3.93 (m, 1H), 3.48 (m, 1H), 3.31 (br s, 1H), 3.22–3.17 (m, 1H), 2.92–2.84 (m, 1H), 2.72–2.66 (m, 1H), 1.46 (br s, 9H), 1.38 (t,  $J=7.0$  Hz, 3H), 1.36 (t,  $J=7.0$  Hz, 3H), 1.29 (d,  $J=5.5$  Hz, 3H), 1.26 (d,  $J=7.3$  Hz, 3H), 1.22 (br s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{CN}$ , 66 °C)  $\delta$  177.5, 175.6, 174.6, 171.3, 164.7, 162.9, 162.8, 157.7, 157.5, 154.2, 149.8, 148.7, 132.3, 129.4, 120.5, 81.9, 81.5, 70.3, 68.8, 62.9, 62.7, 61.6, 60.3, 31.1, 29.5, 29.2, 28.8, 26.0, 20.8, 19.0, 15.4; HRMS (ESI-TOF) calcd for  $\text{C}_{36}\text{H}_{50}\text{N}_7\text{O}_{10}\text{S}_3^+$   $[\text{M}+\text{H}^+]$  836.2776, found 836.2768.

**4.10:** To a stirred solution of amino alcohol **4.9** (27 mg, 0.33 mmol) in anhydrous DMF (0.17 mL) was added 4-DMAP (15.8 mg, 0.13 mmol) and  $(\text{imid})_2\text{CO}$  (16 mg, 0.1 mmol) at 25 °C. After stirring for 48 h, the reaction mixture was diluted with EtOAc (15 mL), washed with aqueous 5% HCl solution (5 mL),  $\text{H}_2\text{O}$  (5 mL), saturated aqueous  $\text{NaHCO}_3$  solution (5 mL), brine (5 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. Purification of the residue by preparative TLC (silica gel, EtOAc:toluene, 1:1) afforded cyclic carbamate **4.10** (23 mg, 81%) as a yellow foam whose spectral data were in full agreement to those reported earlier for a derivative of a degradation product of thiostrepton.<sup>7</sup>





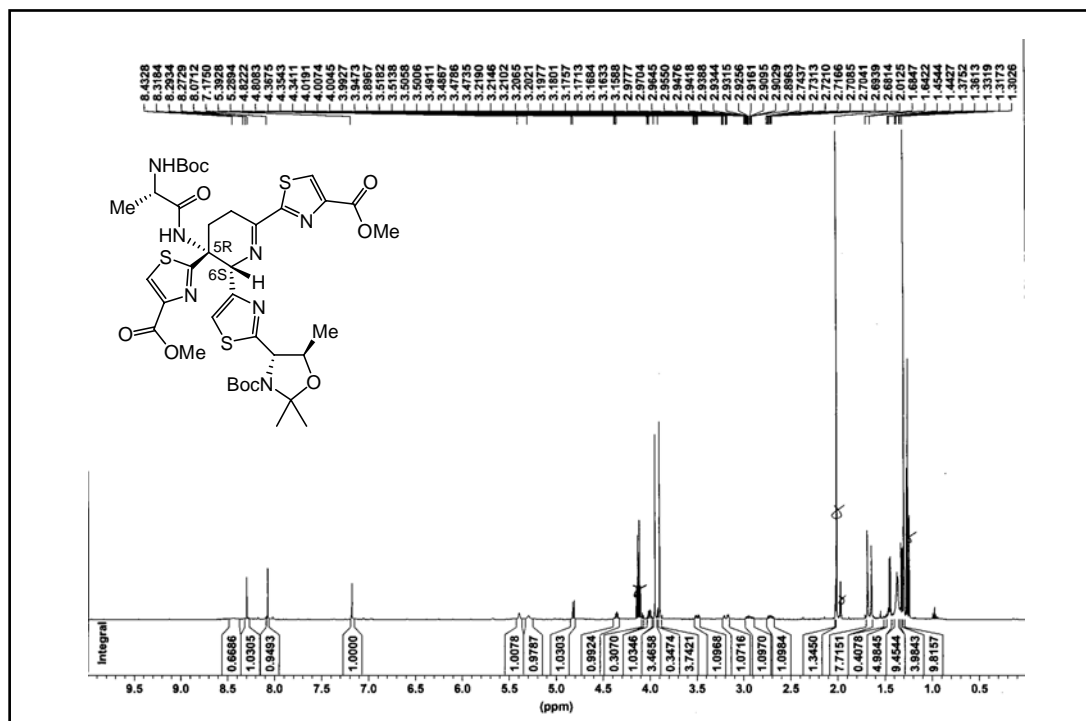
**Spectrum 4.1**  $^1\text{H NMR}$  (600 MHz,  $\text{CD}_3\text{CN}$ , 66 °C) spectrum of compound 4.3.



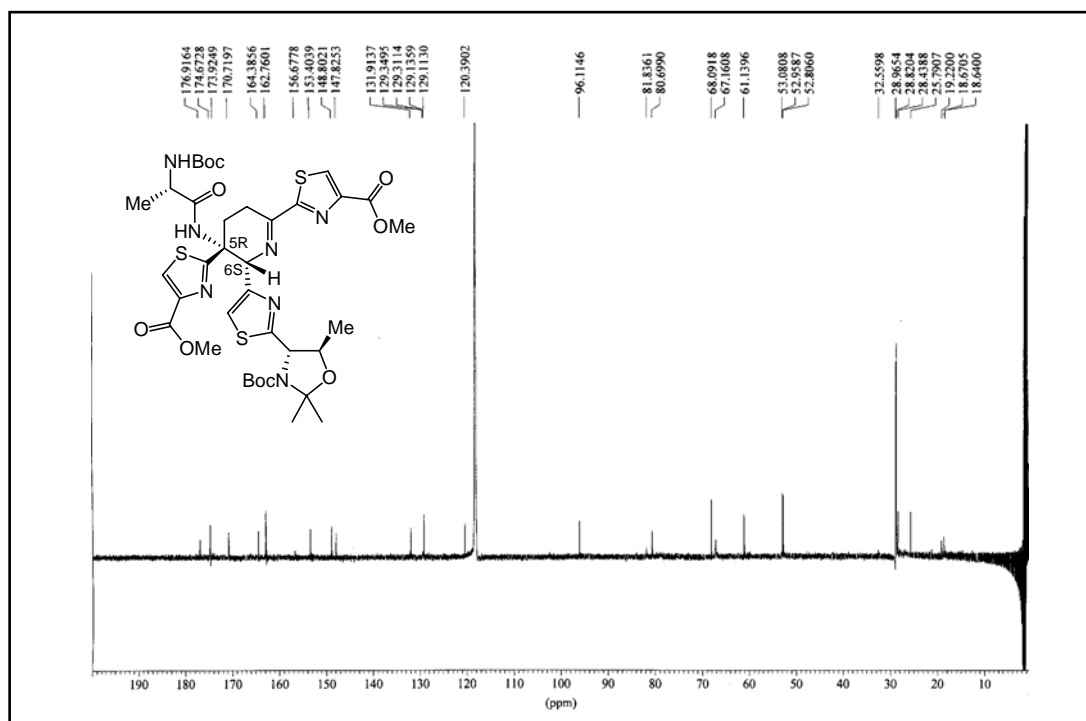
**Spectrum 4.2**  $^{13}\text{C NMR}$  (150 MHz,  $\text{CD}_3\text{CN}$ , 66 °C) spectrum of compound 4.3.



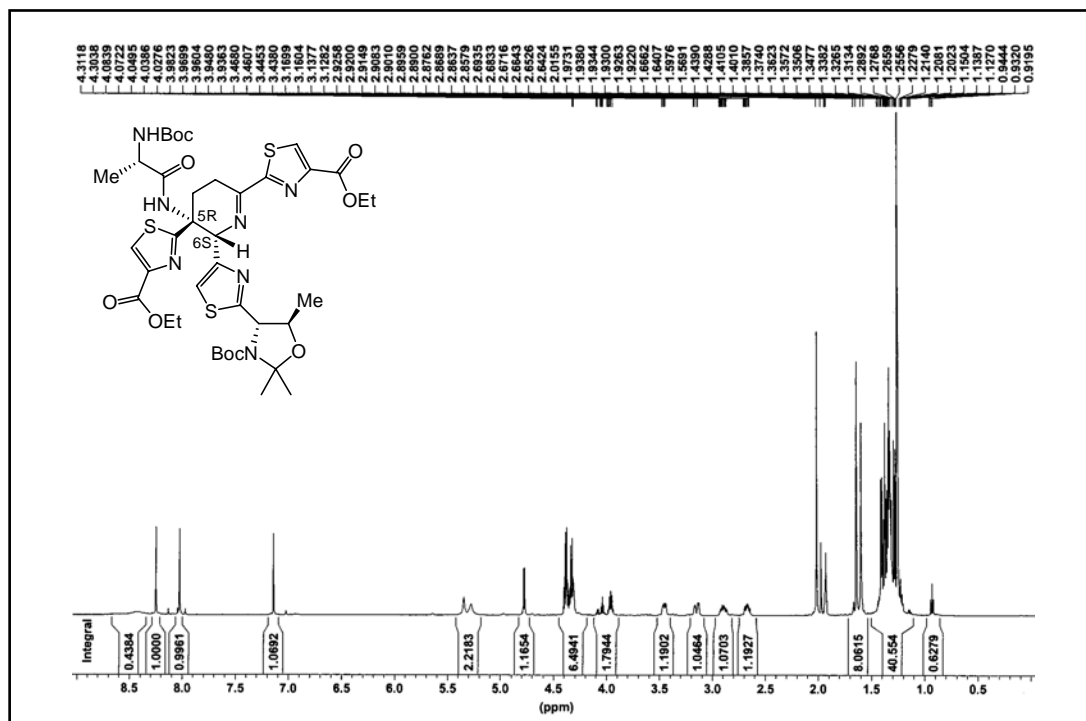




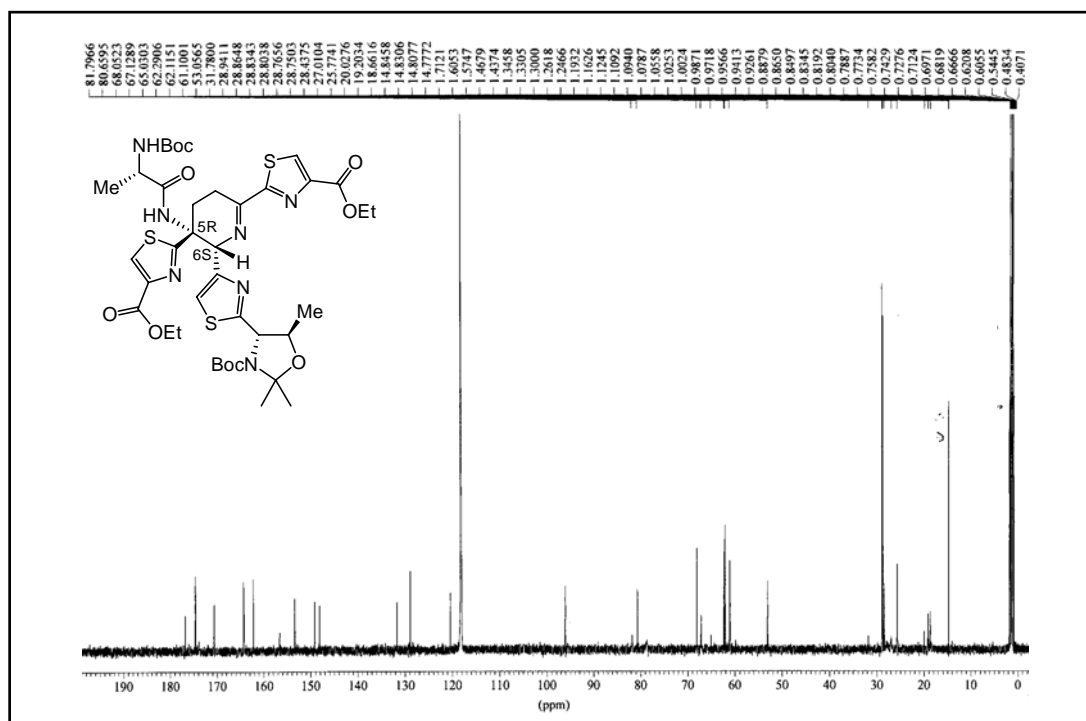
**Spectrum 4.5** <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>CN, 66 °C) spectrum of compound 4.7.



**Spectrum 4.6** <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>CN, 66 °C) spectrum of compound 4.7.

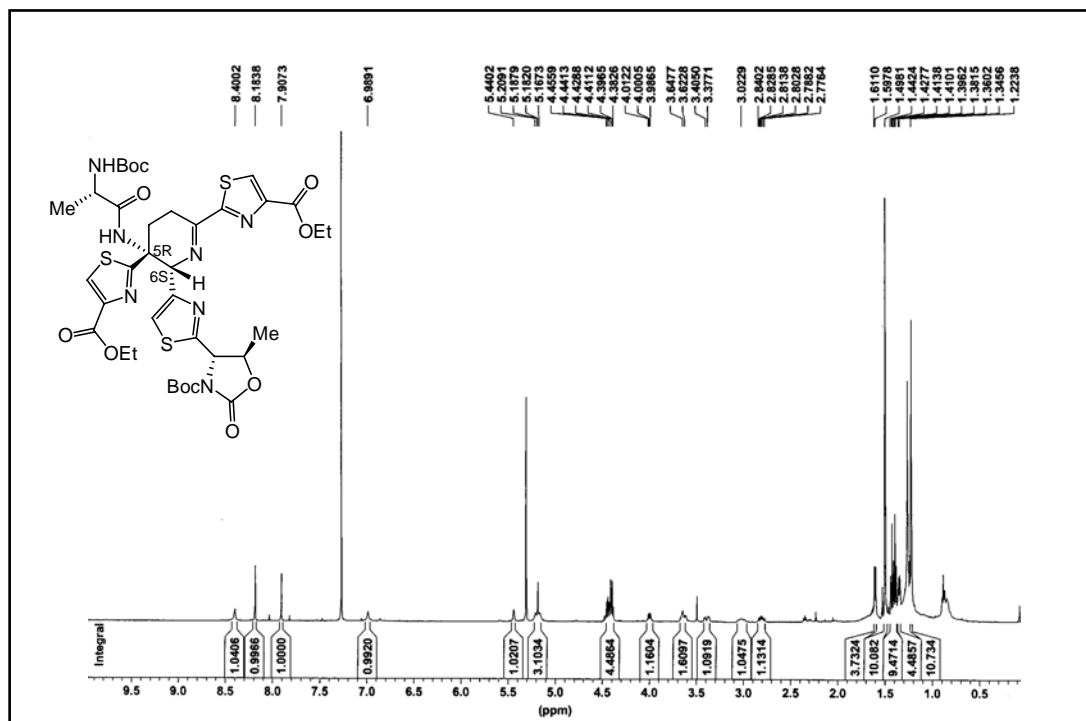


Spectrum 4.7  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ , 66 °C) spectrum of compound 4.8.

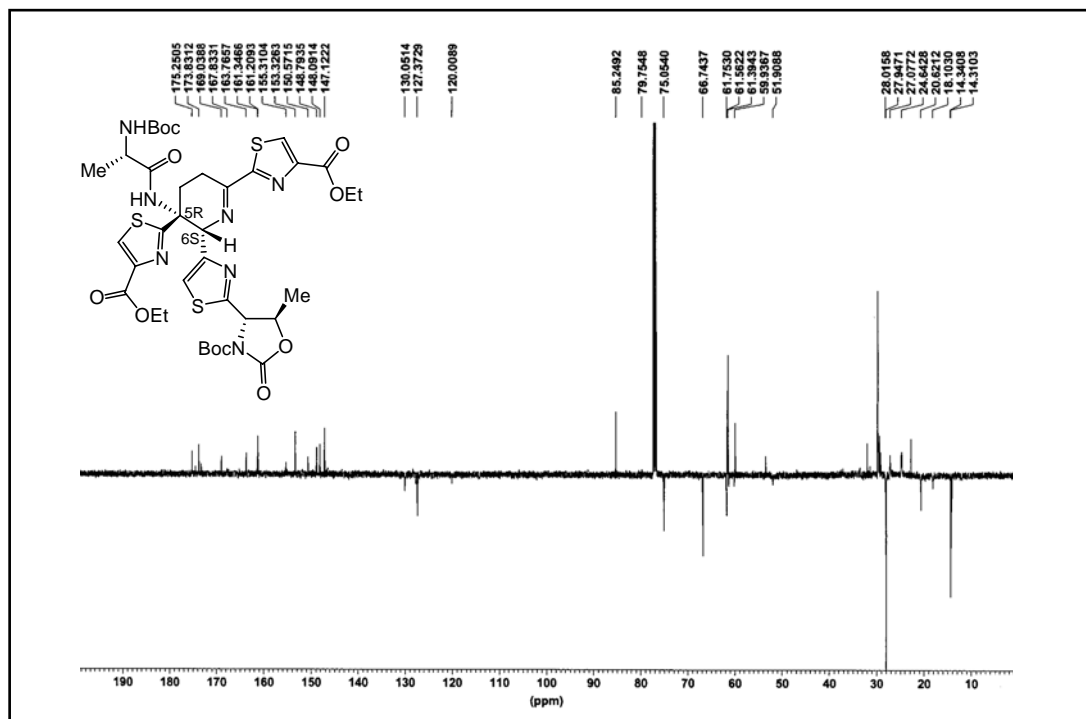


Spectrum 4.8  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ , 66 °C) spectrum of compound 4.8.





Spectrum 4.11  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) spectrum of compound 4.10.



Spectrum 4.12  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) spectrum of compound 4.10.