UNIVERSITY OF CALIFORNIA, SAN DIEGO

Synthetic Explorations of Structurally Complex Bioactive Cembrenolides

A dissertation submitted in partial satisfaction of the
requirements for the degree
Doctor of Philosophy

in

Chemistry

by

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2013

The dissertation of Alec Saitman is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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EPIGRAPH

Satisfaction of one's curiosity is one of the greatest sources of happiness in life.

— Dr. Linus Pauling

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF SCHEMES

LIST OF SPECTRA

LIST OF ABBREVIATIONS

Ac..... acetyl

ACN..... acetic acid

Bu..... butyl

t-Bu..... tert-butyl

°C..... degrees Celcius

calcd..... calculated

CAN..... ceric ammonium nitrate

CCDC..... Cambridge Crystallographic Data Center

$CDCl_3$..... deuterated chloroform

$CHCl_3$..... chloroform

CH_2Cl_2..... dichloromethane

CH_3OH..... methanol

CSA..... camphorsulfonic acid

DBU..... 1,8-diazabicyclo[5.4.0]undec-7-ene

DCM ..... dichloromethane

DMAP..... N,N-dimethylaminopyridine

DMF..... N,N-dimethylformamide

DMP..... Dess-Martin periodinane

ED_{50}..... effective mean dose

eq..... equivalents

Et..... ethyl

EtOAc..... ethyl acetate

EtOH..... ethanol

Et_3N..... triethyl amine

g..... gram

h..... hours

hν..... irradiation with light

HMDS..... hexamethyldisiloxane

HRMS..... high-resolution mass spectrometry

IBX..... o-iodoxybenzoic acid

IC_{50} ..... mean inhibitory concentration

LDA..... lithium diisopropylamide

LiHMDS..... lithium bis(trimethylsilyl)amide

M..... molar

Me..... methyl

MeOH..... methanol

MOM..... methoxymethyl

MHz..... megahertz

mL..... milliliter

μL..... microliter

μmol..... micromole

mmol..... millimole

NaHMDS..... sodium bis(trimethylsilyl)amide

NBS..... N-Bromosuccinimide

NHK..... Nozaki-Hiyama-Kishi

NMO..... N-methylmorpholine N-oxide

NMR ..... nuclear magnetic resonance

[O]..... oxidation

OsO_4..... osmium tetroxide

P..... phosphate

PP..... diphosphate (pyrophosphate)

$Pd(dba)_2$..... bis(dibenzylideneacetone)palladium(0)

$Pd(PPh_3)_4$..... tetrakis(triphenylphosphine)palladium(0)

Ph..... phenyl

PhH..... benzene

PhMe..... toluene

PPh_3..... triphenylphosphine

ppm..... parts per million

PPTS..... pyridinium p-toluenesulfonate

Rf..... retention factor

SAR..... structure activity relationship

TBAF..... tetrabutylammonium fluoride

TBS..... t-butyldimethyl silyl

TES..... triethyl silyl

TFA..... trifluoroacetic acid

THF..... tetrahydrofuran

TLC..... thin layer chromatography

TPP..... triphenylphosphine

UV..... ultraviolet

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Chapter 2, in part is a reprint of material as it appears in A strategy toward the synthesis of C_{13}-oxidized cembrenolides in Tetrahedron Letters, 2013. Saitman, A.; Sullivan, S. D. E.; Theodorakis, E. A., 2013. The dissertation author was the primary author of this paper.

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A., 2013. The dissertation author was the primary author of this paper.

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Saitman, A.; Rulliere, P.; Sullivan, S. D. E.; Theodorakis, E. A. "Total Synthesis of Norcembrenolide B and Scabrolide D", *Org. Lett.*, **2011**, *13*, 5854-5857.

Saitman, A.; Sullivan, S. D. E.; Theodorakis, E. A. "A Strategy Toward the Synthesis of C_{13}-Oxidized Cembrenolides", *Tetrahedron. Lett.*, **2013**, *54*, 1612-1615.

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ABSTRACT OF THE DISSERTATION

Synthetic Explorations of Structurally Complex Bioactive Cembrenolides

by

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The work described herein is a culmination of synthetic studies in the area of cembrenolide natural products, compounds that are synthetically intriguing not only for their highly intricate structures, but also for their array of bioactivities. The synthetic studies toward this family of natural products is divided into 4 chapters: (1) an overview of the first generation of the synthesis with discussion of the total synthesis of norcembrenolide B and scabrolide D; (2) a discussion of the second generation of the synthesis of the family of cembrenolides, specifically, the introduction of the C_{13} hydroxy functionality and its oxidative rearrangement patterns; (3) an overview of the third generation which involves further carbon skeletal rearrangements toward the synthesis of highly complex cembrenolides such as verrillin; (4) concluding remarks which describe

the evolution of each generation and highlight each generation's strengths. Discussions of synthetic strategies and design are also discussed in great detail.

Chapter 1

The Total Synthesis of Norcembrenolide B and Scabrolide D

1.1 Introduction

1.1.1 Soft Corals and Octocorals.

Figure 1.1: Selected *Sinularia* Species

Soft corals and Octocorals, which inhabit the warm shallow waters of tropical seas near the equator, make up a diverse array of structural morphologies and abundances. The Indo-Pacific genus *Sinularia* in particular demonstrates a highly variable growth form, which can range from small individual polyps to colonies that can span many square meters of reef surfaces.[1] As their name suggests, soft corals contain a

meek or often times absent hard calcium carbonate skeleton[2] which renders them prone to attack by predators. In an evolutionary response, soft corals often produce secondary metabolites, which are proposed to be biologically beneficial to the producing organisms as a means of chemical defense against this predation[3,4,5]

1.1.2 Selected Norcembrenolides and Bioactivities

A class of bioactive secondary metabolites which are frequently produced by these soft corals are a family of diterpenes called cembranes which are typified by a 14-membered carbon framework.[6,7,8,9] A subclass of these cembranes called furanocembrenolides contain an embedded furan moiety at the C_3-C_6 juncture along with other modifications. Rubifolide (**1**), bipinnatin J (**4**) and coralloidolide A (**7**) isolated from soft corals *Gersemia rubiformis*[10], *Pseudopterogorgia bipinnata*[11] and *Alcyonium coralloides*[12] respectively, represent a series of this subclass. Another highly oxygenated subclass of cembranes called norcembrenolides contain a signature tetrahydrofuranone moiety at the C_5-C_8 juncture along with a flanking β-ketone at C_3 carbon. This subclass of highly oxygenated norcembrenolides demonstrates a notable display of cytotoxicities and bioactivities. Scabrolide D (**3**) isolated from *Sinularia inelegans*[13] and more recently, *Sinularia scabra*[14] has been to shown to inhibit LPS-induced iNOS production up to 47% at 10 μM.[15] Norcembrenolide B (**2**) isolated from *Sinularia numerosa*[13] which is absent of the epoxide at C_{11}-C_{12} present in scabrolide D (**3**) and has not been shown to exhibit any cytotoxicity.[13] Norcembrenolide B's C_{10} diastereomer, gyrosanolide E (**9**) and the C_8 opened alcohol gyrosanolide D (**8**) both isolated from *Sinularia gyrosa*[15] have not been fully analyzed for their biological potential. On the other hand, the C_5 epimers 5-episinuleptolide (**5**) and sinuleptolide (**6**) isolated from *Sinularia leptoclados*[16] and isolated from *Sinularia querciformis*[13] have both been shown to inhibit LPS-induced TNF-α production in a dose-dependent manner at 20 μg/ml.[17] More recently, (**5**) and (**6**) were also found to cause cell cycle arrest during the G_2/M phase in squamous cell carcinoma (SCC25 cell line) at a concentration of 11.2 μM and 14.4 μM respectively, leading to apoptosis.[18]

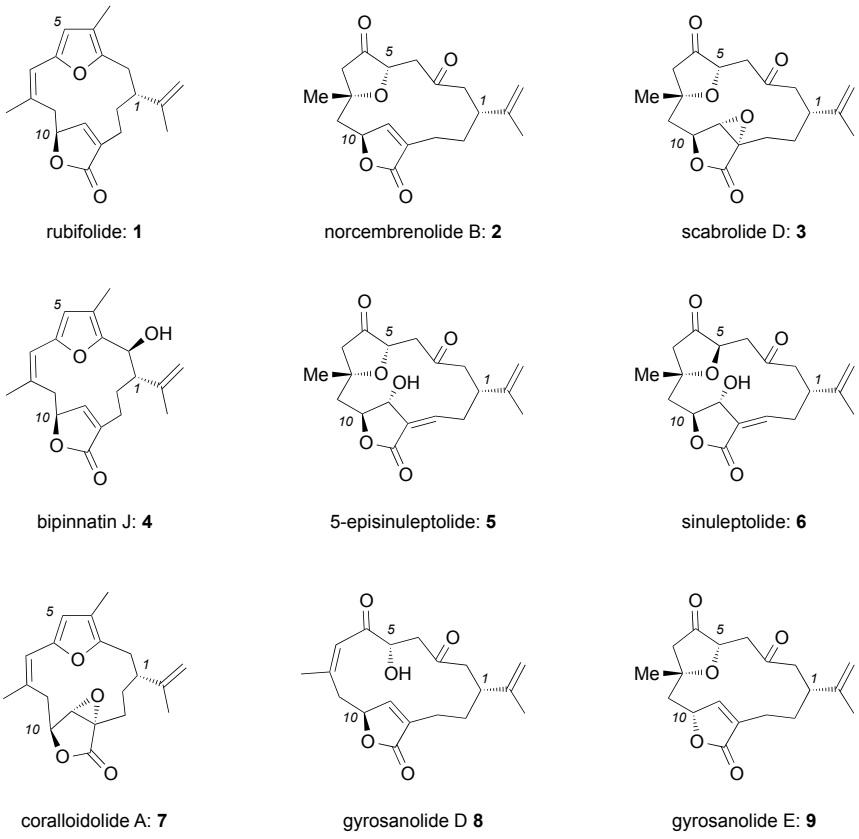


Figure 1.2: Selected Norcembrenolides

1.1.3 Cembrenolide Biosynthesis

The biosynthesis for the production of cembranes by the parent organism is proposed to go through the mevalonate pathway.[19] Two molecules of acetyl-CoA (**10**) go through a Claisen condensation forming acetoacetyl-CoA (**11**).[19] An aldol condensation of an additional enzyme linked acetyl-CoA followed by hydrolysis creates the carboxylic acid HMG-CoA (**12**). Reduction with NADPH creates the unstable mevalic acid hemithioacetyl (**13**), which collapses to the aldehyde, mevaldic acid (**14**). Further reduc-

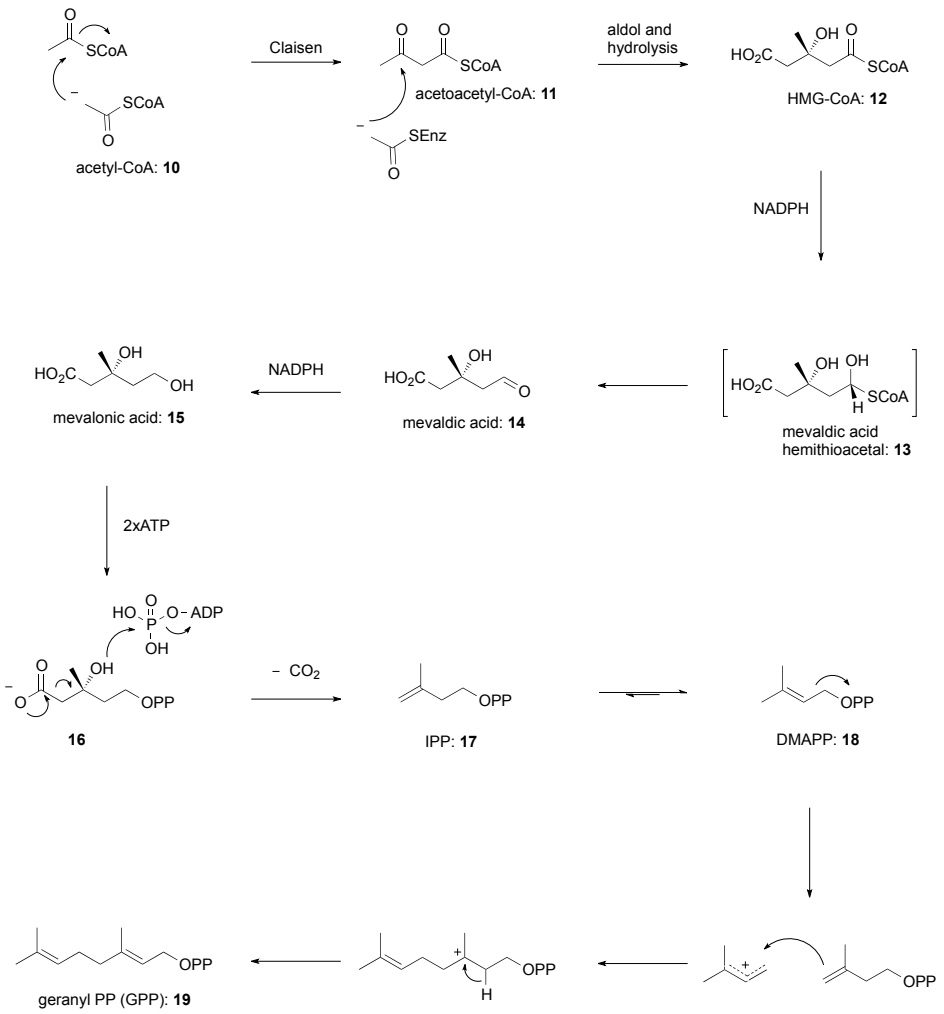


Figure 1.3: Diterpene Biosynthesis

tion with NADPH furnishes the alcohol mevalonic acid which diphosphates with two molecules of ATP at each alcohol center (**16**). Subsequent decarboxylation and elimination of the tertiary diphosphate ester creates the isoprene unit isopentenyl diphosphate (IPP) (**17**). Under enzymatic catalysis (IPP) can be interconverted to the more stable dimethylallyl diphosphate (DMAPP) (**18**).[19] Terpene synthesis then commences with the diphosphate ester of DMAPP leaving in an Sn^1 fashion. The electron rich alkene of an IPP unit then creates the C-C linkage followed by a proton extraction and elimination to form geranyl diphosphate (GPP) (**19**). Additions of two more IPP units in an iterative manner form geranylgeranyl diphosphate (GGPP) (**20**) consisting of the linear

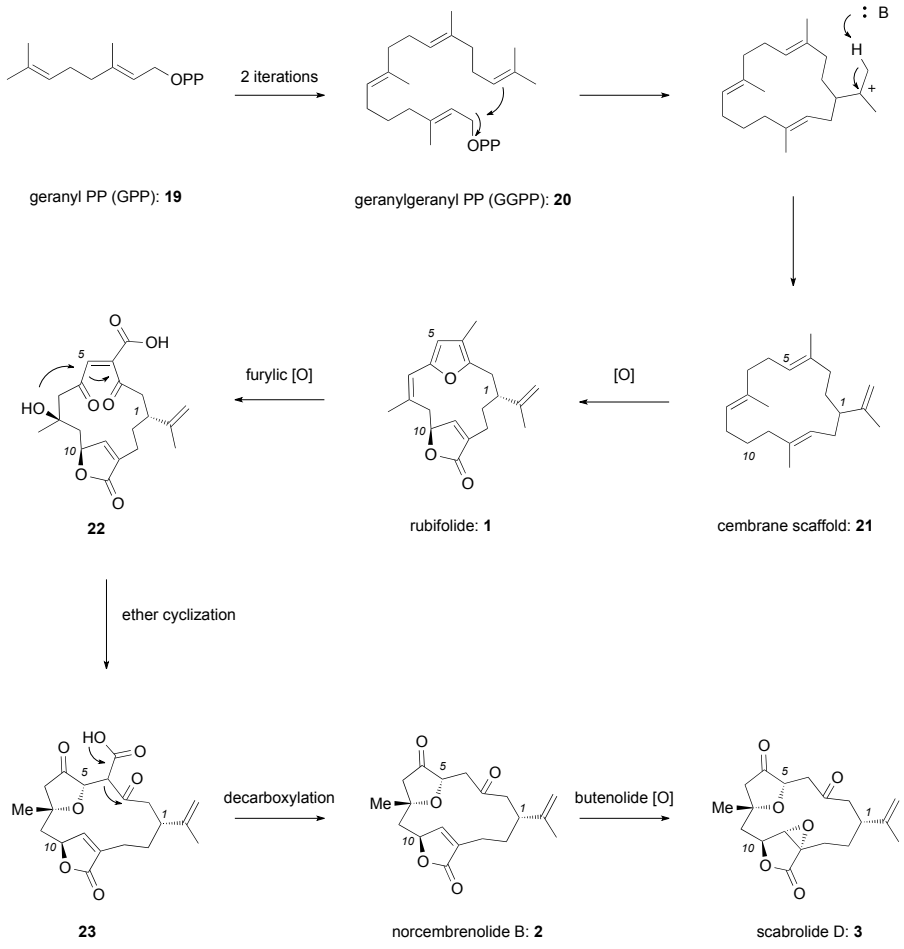


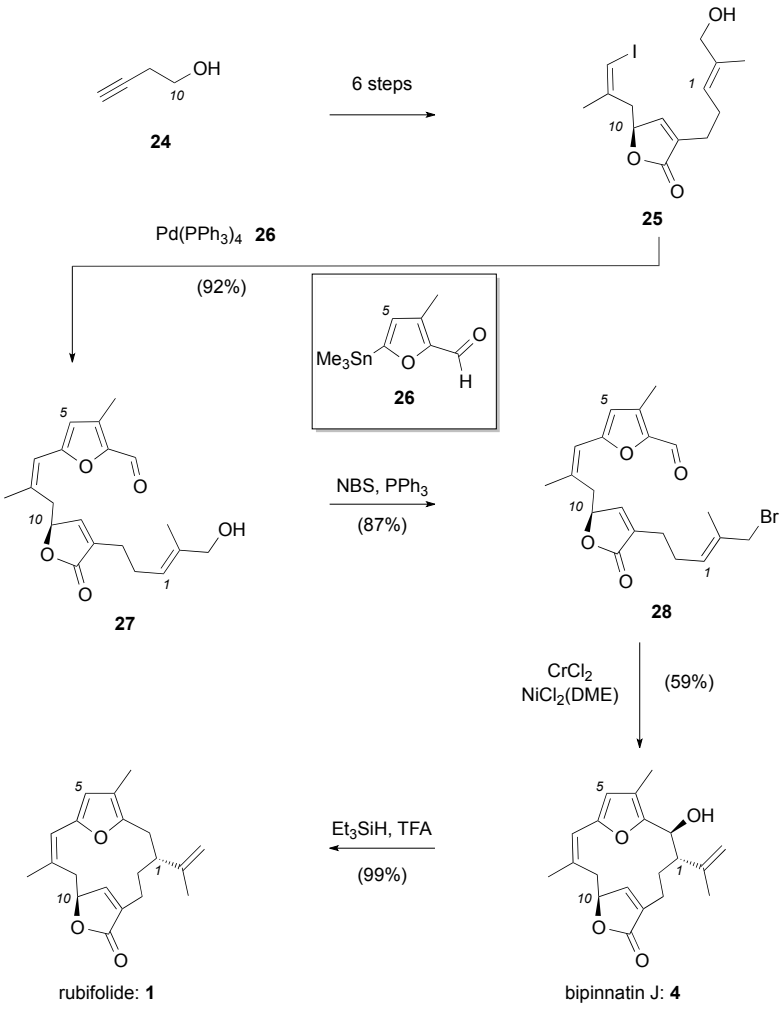
Figure 1.4: Norcembrenolide Biosynthesis

20-carbon diterpene unit. Sn^1 leaving of the single diphosphate unit in (GGPP) forms a primary allyl carbocation which is then quenched intramolecularly with the terminous alkene of the same (GGPP) unit. Deprotonation and subsequent quenching of the resultant tertiary carbocation forms the 14 membered carbon skeleton of cembrane scaffolds (**21**). Oxidation of the C_3-C_6 carbons and the C_{10}-C_{12} carbons form the embedded furan and butenolide moieties present in the simplest of furanocembrenolides, rubifolide (**1**).[8,9] Oxidation of the furylic methyl group to a carboxylic acid and oxidation of the furan moiety would produce the very reactive ene-dione unit (**22**).[8,9] This proposed reactive intermediate can undergo nucleophilic hydration at the C_8 center followed by and ethereal closure of the resulting pendant alcohol with the C_5 carbon, forming the signature β-keto tetrahydrofuranone functionality (**23**). Decarboxylation of the C_6 carboxylic acid would then form norcembrenolide B (**2**)[8,9] and subsequent epoxidation of the C_{11}-C_{12} unit could form scabrolide D (**3**).[8,9]

1.1.4 Trauner's Synthesis of Bipinnatin J

A number of research groups have designed synthetic routes towards furanocembrenolides such as rubifolide (**1**),[20] bipinnatin J (**4**)[21,22] and coralloidolide A (**7**).[20]

Trauner's synthesis of racemic rubifolide (**1**),[20,21] in particular, presents a facile method for the production of this simple cembrane scaffold capable of producing gram quantities in ten linear steps. Commercially available 3-butyne-1-ol **24** was transformed into the advanced vinyl iodo intermediate **25** in six steps. Stille coupling with methyl furfural stannane **26** under Pd(0) catalysis created the furan derivative **27**. This intermediate was brominated using NBS and TPP forming **28** and then subjected to Negishi-Hiyama-Kishi (NHK) conditions involving Ni(II) salts to form bipinnatin J (**4**). Finally, the C_2 alcohol was reduced to the methylene using TFA and TESH to produce rubifolide (**7**).[20]



Scheme 1.1: Trauner's Synthesis

1.2 Retrosynthetic Plan

Inspired by Trauner's work[21] toward the total synthesis of bipinnatin J and by the combination of interesting chemical motifs and unexplored bioactivities, we sought to develop a divergent synthesis toward this family of norcembrenolide compounds. The

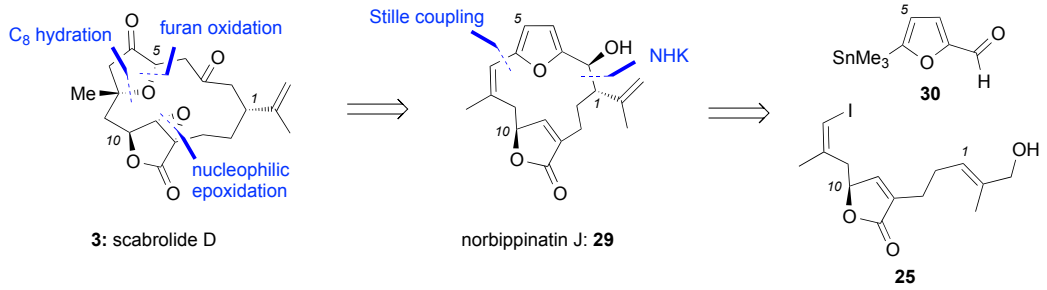
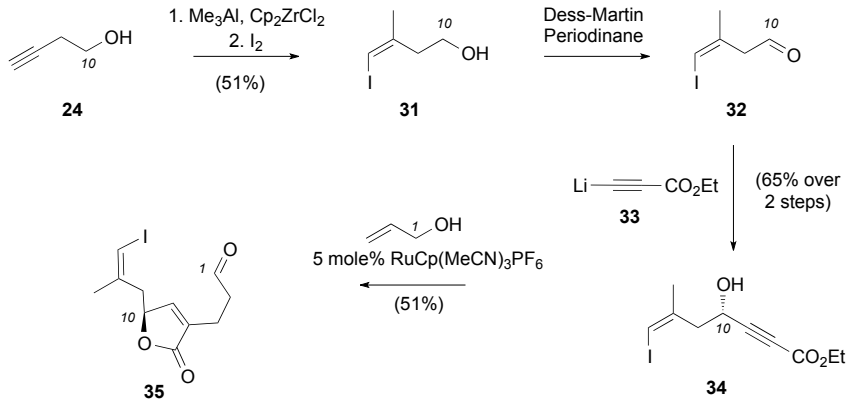


Figure 1.5: Retrosynthesis

key features of the approach are applied to the synthesis of scabrolide D (**3**). A series of synthetic steps involving the deoxygenation at the C_2 center followed by a selective dihydroxylation, selective deoxygenation at the C_7 center and finally furan oxidation/cyclization would furnish **3** from norbipinnatin J (**29**). As per previous synthetic approaches, the main cembrane scaffold could be assembled from nor methylated furfuryl aldehyde **30** and butenolide **25** using established Stille and NHK coupling protocol.[21,22]

1.3 Synthesis of Norcembrenolide B and Scabrolide D

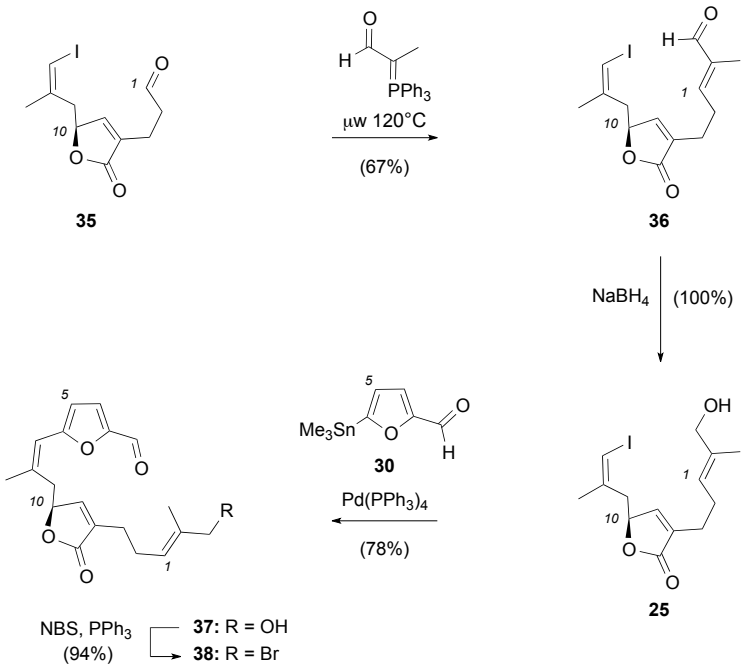
The synthesis toward norcembrenolide B (**2**) and scabrolide D (**3**) began with commercially available 3-butyne-1-ol (**24**), containing the C_7-C_{10} cembrane fragment. Conversion of **24** using neat trimethyl aluminum and zirconocene dichloride and refluxing this solution for 72 hours followed by quenching the reaction mixture with molecular iodine[21,23] selectively afforded the Z-vinyl iodo-alcohol **31** in 63% yield. Initially, a 1.6M solution of trimethyl aluminum in hexanes was used, however, the lower reflux temperature unfortunately led to a mixture of the desired Z-conformer and but also the E-conformer (4:1), even when refluxed for prolonged periods of time. We then decided to use neat trimethyl aluminum instead which allowed for an increase of the reflux tem-



Scheme 1.2: Construction of Butenolide Fragment

perature. The increased temperature of reflux by removal of hexanes (85 °C to 105 °C) allowed for the desired shift in equilibrium, which completely converted the product to the Z-conformer in good yield (51%). Oxidation of the resultant primary alcohol using Dess-Martin periodinane[24] provided the sensitive aldehyde **32** that upon addition of lithiated ethyl propiolate[21] (**33**), produced secondary alcohol **34** in 65% combined yield over two steps. It should be noted that in our initial efforts to lithiate **33**, we utilized freshly prepared LDA as our deprotonating base. Under these conditions, however, we produced significant amounts of a side product arising from the nucleophilic addition of LDA to **33**. Use of freshly prepared LiHMDS[25,26] however corrected this problem and afforded the desired product **34** cleanly and in high yield (72%). Using allyl alcohol as a 3-carbon source, the framework of **34** was extended under Trost ruthenium alderene[27]chemistry to create, after in-situ lactonization with CSA[28], butenolide **35** in 47% yield.

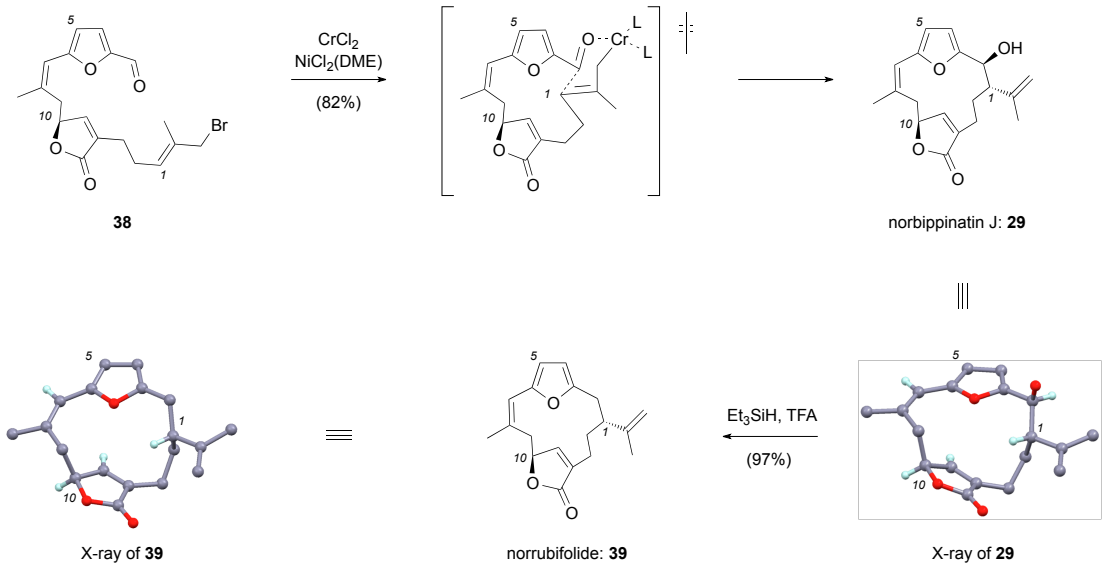
Continued elongation of the carbon framework of **35** was accomplished via Wittig olefination[21] affording the corresponding α,β-unsaturated aldehyde **36** in 67% yield. We found that this conversion, which normally requires twelve hours under conventional heating, could be accelerated considerably without foregoing yield under microwave conditions[25] (120 °C for 40 min). The reduction of aldehyde **36** using $NaBH_4$ afforded alcohol **25** in quantitative yield. Stille coupling[21,25] of alcohol **25** with stannane **30** produced aldehyde **37** in 78% yield. In preparation for the NHK coupling, **37** was subjected to Appel[29] conditions creating allyl bromide **38** in 85% yield.



Scheme 1.3: Elongation of the Carbon Framework

Treatment of **38** with $CrCl_2/NiCl_2$[21,22,30,31] gave rise to norbipinnatin J (**29**), in a substrate-controlled fashion with a diastereoselectivity of 9:1 (82% yield). This diastereoselectivity is based on a suspected lowest energy transition state involving a stable six membered chair structure intermediate[21], which forms during the macrocyclization event. The relative stereochemistry of norbipinnatin J (**29**) was unambiguously determined by single-crystal X-ray diffraction analysis.[32] Deoxygenation of the C_2 hydroxyl group was accomplished using TFA/TESH[20,25,33] affording norrubifolide (**39**) in 97% yield.

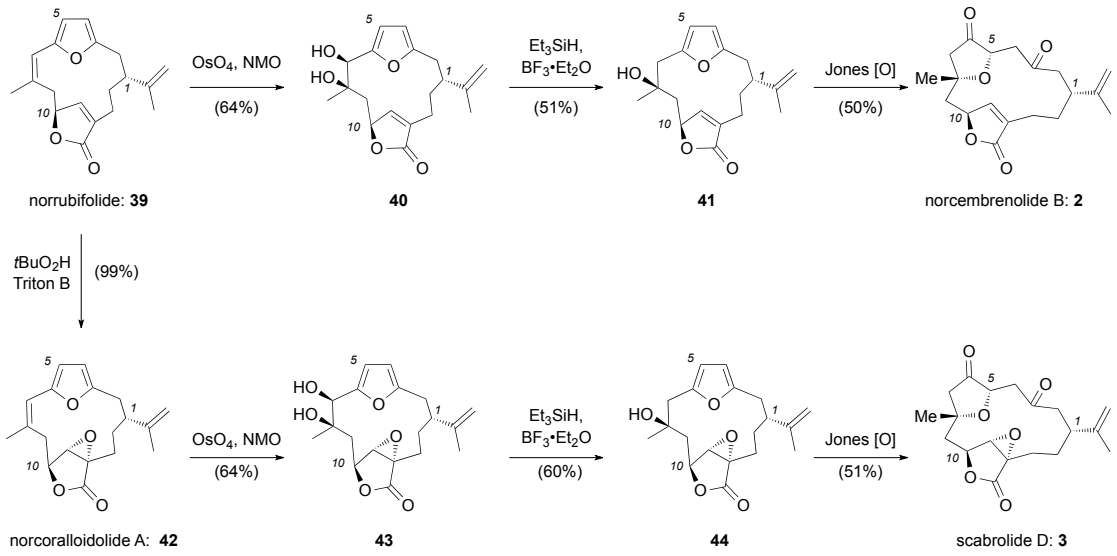
Norrubifolide (**39**) represents a crucial branching point of our strategy. The crystallographic data[32] pertaining to norrubifolide's structure shows a rigid scaffold, which is amenable to regio and stereoselective manipulations at both the C_7-C_8 and C_{11}-C_{12} double bonds. This versatility allows for a divergent synthesis towards norcembrenolide B (**2**) and scabrolide D (**3**). The selective oxygenation at C_8 center was best achieved using a two step process which involved dihydroxylation of the C_7-C_8 alkene affording diol **40**, followed by regioselective deoxygenation of the C_7 hydroxyl group affording hydroxyl compound **41**.



Scheme 1.4: Macrocyclization and Formation of Norrubifolide

The dihydroxylation reaction was best accomplished under Upjohn[34] conditions (OsO_4, NMO) and gave diol **40** as a single isomer in 64% yield. As predicted, the hydroxyl groups were introduced from the sterically more accessible β-face of the cembrane ring. Deoxygenation of the extraneous C_7 hydroxyl group was initially attempted using TFA/TESH[33] conditions, which was successful for the deoxygenation of norbippinnatin J (**29**) toward norrubifolide (**39**). We unfortunately, however recovered only the starting diol. We equate this lack of conversion to the strong hydrogen bonding of the diol moiety preventing the required activation of the C_7 hydroxy group by the acid source from TFA. Use of the stronger $BF_3 \bullet Et_2O$/TESH[35] system did cleanly produce compound **41** in 51% yield. Oxidation of the β-hydroxy-furan to the β-keto-tetrahydrofuranone was accomplished with the use of Jones reagent.[36]

It is believed that the transformation begins with an initial oxidation of the furan in compound **41** to form the Z-ene-dione intermediate that is quickly attacked by the C_7 tertiary alcohol, under the acidic conditions of Jones reagent. This attack then cyclizes in a 5-exo-trig[25] manner, producing norcembrenolide B (**2**) in 50% yield. The relative stereochemistry of **2** was confirmed via single crystal X-ray diffraction.[32] Our strategy diverges toward the synthesis of scabrolide D (**3**) with a regioselective epoxidation of **39** using anhydrous $tBuO_2H$[37] and catalytic Triton B furnishing norcoralloidolide A (**42**) in



Scheme 1.5: Divergent Approach to Norcembrenolide B and Scabrolide D

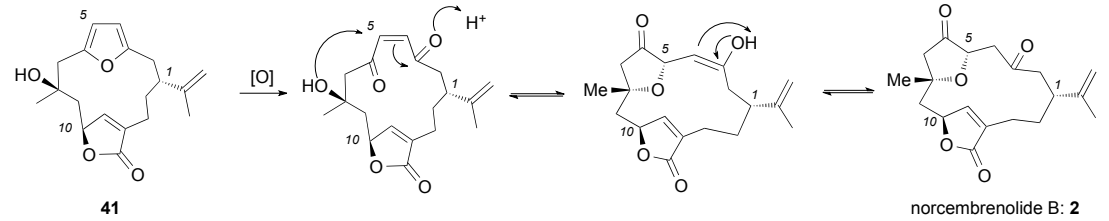


Figure 1.6: Oxidative Cyclization Mechanism

quantitative yield. This epoxidation event proceeded selectively from the α-face of the butenolide motif as expected.[20] The structure of **42** was also unambiguously confirmed via a single crystal X-ray analysis.[32] Further manipulation of norcoralloidolide A (**42**) using analogous conditions described for the synthesis of norcembrenolide B (**2**) gave rise to scabrolide D (**3**) in three steps in a 17% combined yield.[25]

1.3.1 Revisions of Scabrolide D's Stereochemistry

Interestingly, the suggested structure of scabrolide D, as reported by Sheu *et al*[38] showed relative stereochemistry of compound **45** in which the epoxide extends from the β-face which is the same face as the C_{10} lactone oxygen. Spectroscopic (^{1}H and ^{13}C NMR) evaluation of synthetic **3** recorded in $CDCl_3$ with the data reported for

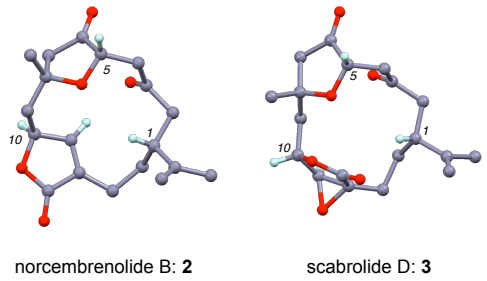


Figure 1.7: X-ray Structures of Norcembrenolide B and Scabrolide D

scabrolide D (**3**) reveals that the structures are identical. Moreover, X-ray crystallographic analysis[32] of synthetic scabrolide D (**3**) confirmed the structural makeup leading to the revision of the relative stereochemistry at the C_{11} and C_{12} centers, with the

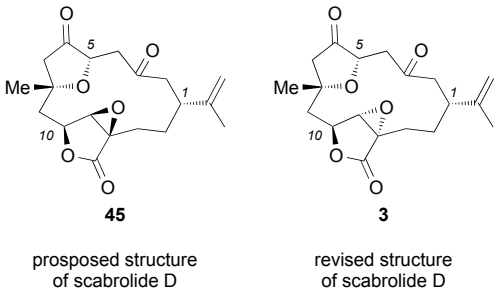
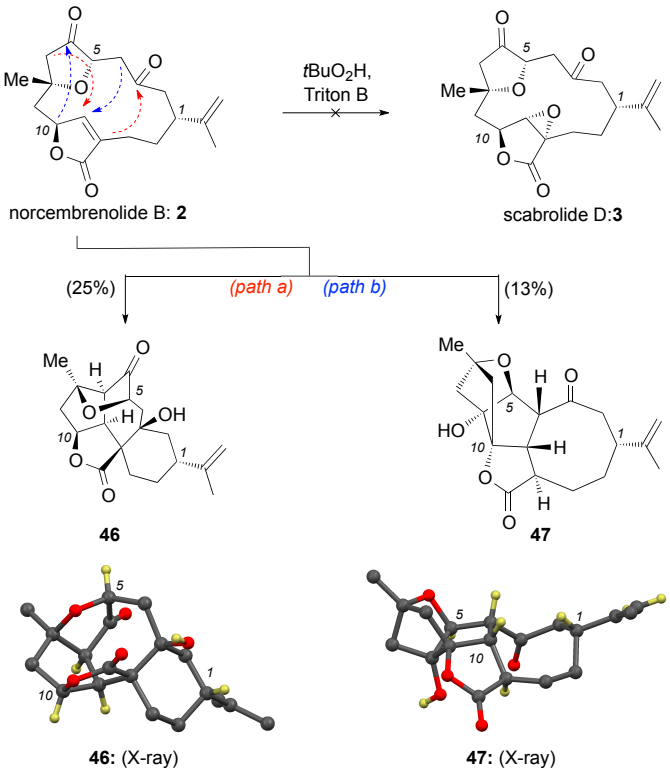


Figure 1.8: Revision of Scabrolide D's Relative Stereochemistry

epoxide occurring on the α-face, opposite in regard to the C_{10} lactone oxygen. It was previously unrealized, but in fact, scabrolide D (**3**) is identical to the compound norcembrenolide C which was analyzed in benzene-d_6 and first reported by the Fenical group[13] nineteen years earlier.

1.4 Interesting Intramolecular Cyclizations

In principle, a stereoselective epoxidation of the C_{11}-C_{12} alkene of norcembrenolide B (**2**) would produce scabrolide D (**3**). With this in mind, we attempted the epoxidation of norcembrenolide B (**2**) under the same nucleophilic conditions ($tBuO_2H$ and Triton B)[37] that produced norcoralloidolide A. To our surprise, we found that this reaction

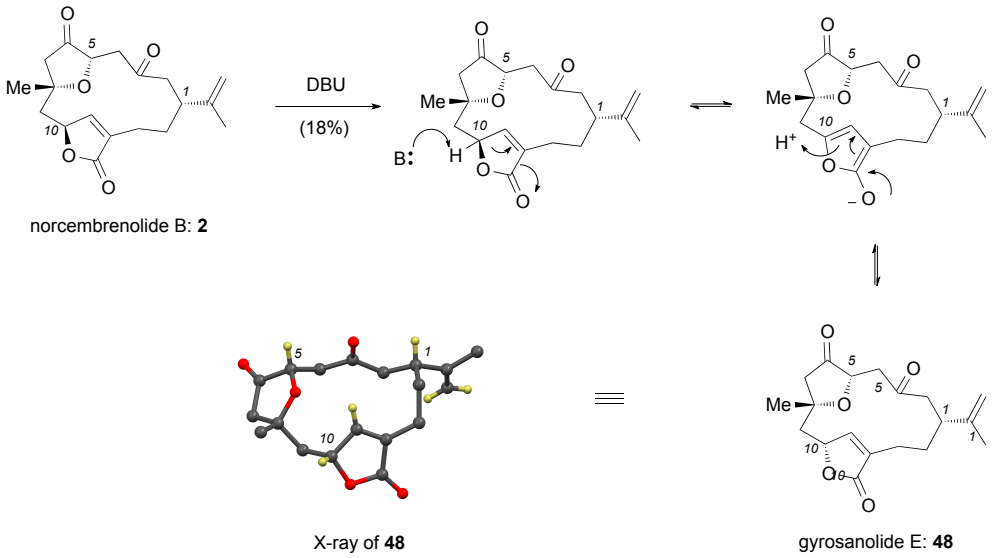


Scheme 1.6: Mechanistic Evaluation of Polycyclic Products

did not produce scabrolide D (**3**) but instead, produced two complex polycyclic products **46** and **47**, the structures of which were determined via X-ray crystallography.[32] Mechanistically, **46** is likely formed via an intramolecular Michael addition of the C_7 enolate at the C_{11} butenolide of **2** and subsequent nucleophilic attack of the resulting C_{12} enolate at the proximal C_3 carbonyl group (path a) in 25% yield. On the other hand, compound **47** is presumably formed via abstraction of the acidic C_{10} hydrogen and cyclization of the resulting extended enolate at the C_6 carbonyl group (path b). Subsequent cyclization across the C_4-C_{11} centers forms the pentacyclic motif of **47** in 13% yield.

1.5 The Synthesis of Gyrosanolide E

With the reactivity observed in the formation of **47**, we envisioned that a set of milder conditions would isomerize the acidic C_{10} lactone center to yield the natural product gyrosanolide E (**48**).[15] Thus the treatment of norcembrenolide B (**2**) with DBU

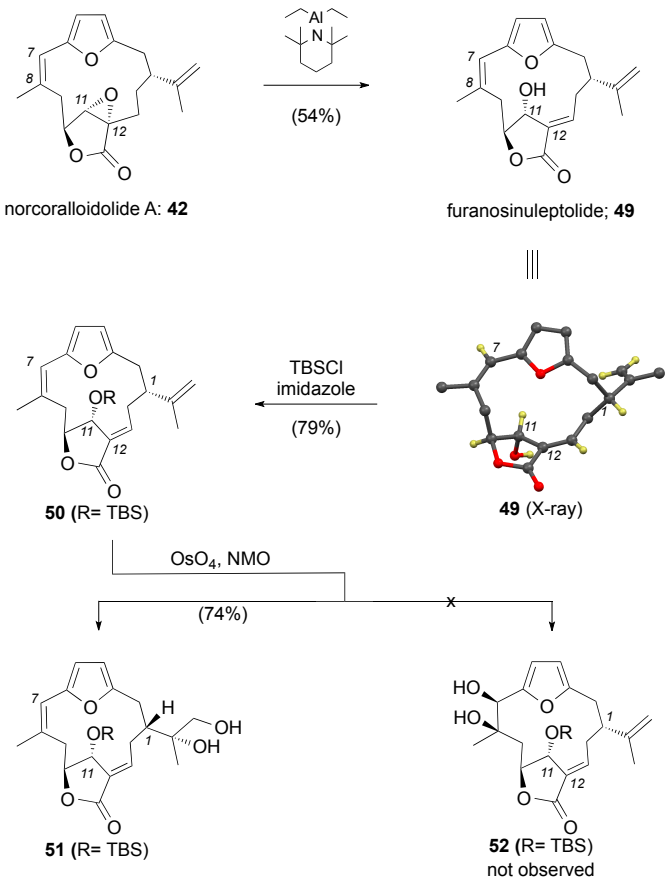


Scheme 1.7: Synthesis and Proposed Mechanistic Process of Gyrosanolide E

allowed epimerization of the proton at C_{10} leading to the structure of gyrosanolide E (**48**) in 18% yield. Under these conditions compounds **2** and **48** were in a 1:1 ratio after one hour determined by crude H^1 NMR analysis. The structure of **48** was also confirmed by X-ray crystallography.[32]

1.6 The Synthesis of Norfurano-sinsuleptolide and Progress Toward 5-episinuleptolide

After structural analysis of the natural product 5-episinuleptolide (**5**),[16] we envisioned a nucleophilic opening of the C_{11}-C_{12} epoxide found in previously synthesized norcoralloidolide A (**42**) could furnish the allylic alcohol moiety present in (**5**). Protection of this resulting alcohol followed by manipulations analogous in the total synthesis of previously described norcembrenolide B (**2**) and scabrolide D (**3**)[25] would produce 5-episinuleptolide (**5**). We began this strategy starting again from norcoralloidolide A (**42**). We sought to find conditions to selectively convert the C_{11}-C_{12} epoxide to the desired allylic alcohol unit. To this end, we were happy to find that diethylaluminum tetramethylpiperidine (DATMP)[39] cleanly produced desired nor-



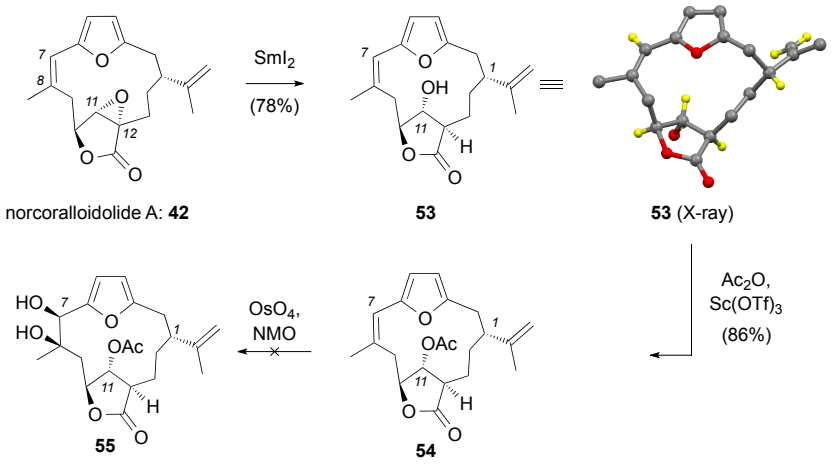
Scheme 1.8: Synthesis of Norfurano-sinsuleptolide and Further Manipulations

furanosinsuleptolide (**49**) in 54% yield whose structure was confirmed by X-ray crystallography.[32] Use of other known epoxide isomerization conditions either yielded recovered starting material or lead to complete degradation producing intractable mixtures. Direct isomerization of scabrolide D (**3**) that would theoretically produce 5-episinuleptolide (**5**) using DATMP also resulted in an intractable mixture that was anticipated due to the previously observed sensitivity of scabrolide D (**3**).

1.6.1 Attempts Toward 5-episinuleptolide from Allyl Alcohol (49).

With the synthesis of 5-episinuleptolide (**5**) still in mind, we then converted allylic alcohol **49** to its corresponding silyl ether[40] **50** (79% yield). Surprisingly, under the Upjohn dihydroxylation conditions we did not observe the anticipated formation of **52**

but instead, isolated compound **51** in which the isopropenyl group had undergone selective dihydroxylation as the sole product (74% yield) rather than across the C_7-C_8 alkene as observed in previous systems. After comparison of crystallographic data[32] between both pre-dihydroxylated substrates norrubifolide (**39**) norfurano-sinuleptolide (**49**), we postulate that the inability to dihydroxylate the C_7-C_8 alkene of **49** is due to a conformational change resulting from the installation of the allyl alcohol unit (C_{11}-C_{13} bonds) causing a shift in oxidative reactivity. Intrigued to whether this conformational change

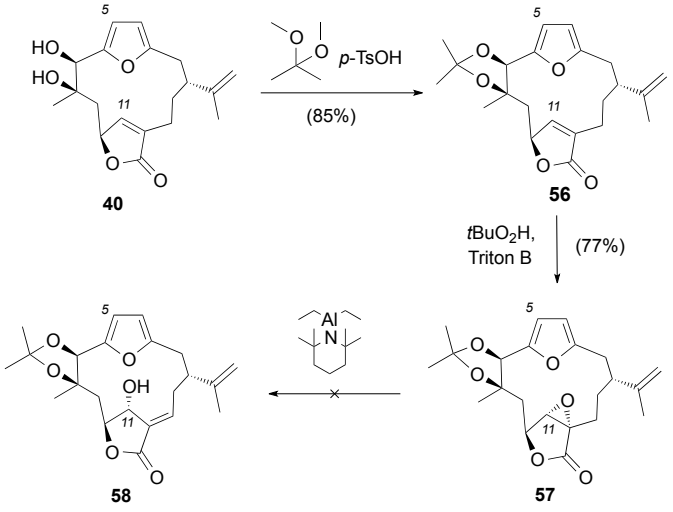


Scheme 1.9: Investigations in Oxidative Regio-control

preventing the desired dihydroxylation was due primarily to the alcohol functionality or to the alkene moiety, we instead reduced the epoxide in norcoralloidolide A (**42**) with samarium (II) iodide[41] to form the saturated secondary alcohol **53** in 78% yield. X-ray diffraction of crystalline[32] **53** showed strong similarities in the structural conformation to its unsaturated analogue **49**. We continued this study by converting the alcohol functionality to its acetate[42] **54** in 86% yield. Attempts at successful dihydroxylation of **54**[34] across the C_7-C_8 alkene, creating compound **55**, again were unsuccessful as expected.

1.6.2 Attempts at 5-episinuleptolide (5) from Diol (40).

To address the conformational issues previously faced, we decided to perform the C_7-C_8 dihydroxylation prior to the epoxide isomerization thus avoiding the issue of oxidative regioselectivity entirely. The synthetic study toward **5** was resumed from

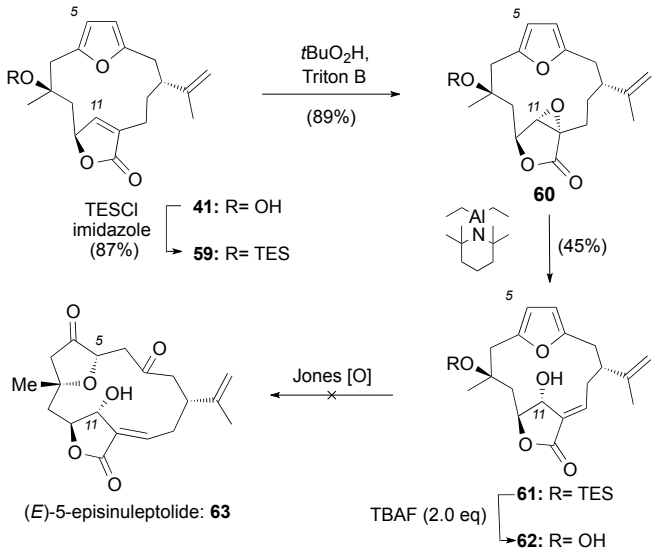


Scheme 1.10: Protection of Diol and Rearrangement Attempts

diol **40**,which was protected with 2,2-dimethoxypropane[43] as a solvent and catalytic *p*-TsOH, forming protected substrate **56** in 85% yield. Nucleophilic epoxidation[37] at the C_{11}-C_{12} alkene of **56** was easily achieved, forming epoxide **57** in 77% yield. Unfortunately, the opening of the epoxide **57** forming the desired allyl alcohol **58** using previously successful conditions (DATMP)[39] failed to produce compound **58** in any appreciable yield.

1.6.3 Attempts at 5-episinuleptolide (5) from Tertiary Alcohol (41).

To determine whether the hindrance of the epoxide opening was due to the strain added from the protection of the C_7-C_8 diol, we decided to investigate the C_8 hydroxyl derivative **41** as a potential precursor to 5-episinuleptolide (**5**). On these grounds, we protected alcohol **41** as the silyl ether[40] **59** in 87% yield. Epoxidation[37]of **59** cleanly afforded epoxide **60** with complete diastereoselectivity in 89% yield. We were excited to find that opening of the newly formed epoxide **60** with DATMP[39] gave desired allyl alcohol **61** in 45% yield as an inseparable mixture with an uncharacterized side product (ca 5:1). TBAF[44] deprotection yielded a mixture of the same two products now desilylated (**62**). Jones oxidation[36] of this mixture was conducted, however, did not afford the expected cyclization product **63** but instead, lead to complete decomposition of the



Scheme 1.11: Protection of Tertiary Alcohol and Rearrangement Attempts

substrate. We postulate that undesired oxidations of the allyl alcohol moiety competed with our desired oxidative cyclization of the C_8 hydroxy group onto the furan.

1.7 Conclusion

In conclusion, a divergent strategy for the synthesis of norcembrenolide B (**2**) and scabrolide D (**3**),[25] two members of a family of structurally complex and biologically interesting marine natural products was developed. This methodology utilizes highly substrate-controlled manipulations, which allows for an efficient, stereoselective and protecting group free access to this series of scaffolds. Our synthesis also establishes that norcembrenolide C[13] is structurally identical to scabrolide D (**3**)[38] based on crystallographic X-ray diffraction[32] and H^1 NMR comparative analysis. With the total synthesis of norcembrenolide B (**2**) and scabrolide D (**3**) also came synthetic manipulations mimicking proposed biosynthetic pathways producing two new intricate polycyclic structures **46** and **47**. A series of synthetic modifications toward the synthesis of the natural product 5-episinuleptolide (**5**) were also developed. These manipulations draw their inspiration from proposed biological transformations responsible for the diverse range of cyclization patterns and oxidation states found in these cembrane families. A se-

quence of various transformations, such as dihydroxylation (C_7-C_8 alkene),[25,34] epoxidation (C_{11}-C_{12} enone),[25,37] epoxide opening (hydroxylation at C_{11}),[25,39] have been developed in order to access several natural product analogues of this family. We have also demonstrated that tuning of the cembrane core's macrocyclic structure has strong impact on its regioselectivity toward oxidative manipulation.

1.8 Experimental Section

1.8.1 General Techniques

All reagents were commercially obtained (Aldrich, Acros, Strem) at highest commercial quality and used without further purification except where noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 40 °C at approximately 15 mmHg. All non-aqueous reactions were carried out under anhydrous conditions using flame-dried glassware within an argon atmosphere in dry, freshly distilled solvents, unless otherwise noted. Tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), toluene ($PhCH_3$) and benzene (PhH) were purified by passage through a bed of activated alumina. Dimethylformamide (DMF) were distilled from calcium hydride under reduced pressure (20 mmHg) and stored over 4 angstrom molecular sieves until needed. Yields refer to chromatographically and spectroscopically (^{1}H NMR, ^{13}C NMR) homogeneous materials, 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 the visualizing agent and 10% ethanolic phosphomolybdic acid (PMA) or Potassium Permanganate solution ($KMnO_4$) in water and heat as developing agents. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography. Preparative thin-layer chromatography separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Varian Mercury 400 and/or Jeol Unity 500 MHz instruments and calibrated using the residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad, dd = doublet of doublet, dt = doublet of triplet.

High resolution mass spectra (HRMS) were recorded on a VG 7070 HS or on a VG ZAB-ZSE mass spectrometers. X-ray data were recorded on a Bruker SMART APEX 3kW Sealed Tube X-ray diffraction system.

1.8.2 Experimental Procedures and Data

Vinyl-iodo alcohol (31): To a solution of $ZrCp_2Cl_2$ (5.00 g, 17.12 mmol) in 1,2-dichloroethane (140 mL) at 0 °C was added a solution of trimethylaluminum (6.8 mL) in hexanes dropwise. A solution of but-3-yn-1-ol (6.49 mL, 86 mmol) in 1,2-dichloroethane (20 mL) was then added dropwise. The solution was stirred at 25 °C for 24 h. The solution was then warmed to 86 °C and gently refluxed for 4 days. The reaction was then cooled to -40 °C and a solution of iodine (43.5 g, 171 mmol, 2 eq) in 100 mL of dry THF was added via cannula. The solution turned black and was stirred for 30 minutes. The reaction was warmed up to 0 °C and 60 ml of saturated K_2CO_3 was added very slowly (the solution frothed and bubbled) until eventually turning yellow with aluminum gel precipitate. Ether (250 mL) was added and the solution was filtered through fritted funnel. The gel was extracted with a large amount of ether to remove all organics. 200 mL of water was added to the organic layer which was separated. The aqueous layer was then extracted 3x with 100 mL of ether. The combined organic layers were washed once with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (up to 20% EtOAc in hexanes) of the crude mixture gave alcohol **31** (9.3 g, 43.9 mmol, 51% yield) as a light brown oil. R_f= 0.30 (20% EtOAc in Hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.01 (d, 1H, *J*= 1.4 Hz), 3.78 (t, 2H, *J*= 6.7 Hz), 2.53 (t, 2H, *J*= 6.7 Hz), 1.94 (d, 3H, *J*= 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.3, 76.3, 60.1, 41.6, 23.8.

Alkyne (34): To an oven-dried flask was added dry HMDS (bis(trimethylsilyl)-amine) (19.93 mL, 94 mmol) and THF (95 mL). The solution was cooled to -78 °C and n-BuLi (1.6M in hexanes, 56.7 mL, 91 mmol) was added dropwise. The solution turned yellow and was then warmed up to 0 °C and stirred for 20 minutes. The reaction was cooled back down to -78 °C and a solution of ethyl propiolate (9.51 mL, 94 mmol) in THF (60 mL) was added dropwise over 30 minutes. The solution remained pale yellow.

The reaction was stirred at -78 °C for 1 hour. During this time, to a solution of the alcohol **31** (6.63 g, 31.3 mmol) in CH_2Cl_2 (156 mL) at 25 °C was added $NaHCO_3$ (15.76 g, 188 mmol) followed by Dess-Martin periodinane (17.24 g, 40.7 mmol) in one portion. After 15 minutes, the reaction was completed. A 1:1:1 mixture of saturated $Na_2S_2O_3$, saturated $NaHCO_3$ and water (160 mL) was added slowly to the CH_2Cl_2 solution and was stirred vigorously for 20 minutes. Layers were separated and the aqueous layer was extracted 3x with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure at 25 °C to yield aldehyde **32** which was used without further purification. The aldehyde **32** was then taken up in dry THF (50 mL) and was cooled to -78 °C in a separate cooling bath. The cold aldehyde solution was added via cannula quickly to the solution of the lithiated alkyne **33** at -78 °C. The solution turned dark red and was stirred for 30 minutes at -78 °C. The reaction was then quenched with saturated NH_4Cl solution (100 mL). The organic layer was separated, and the aqueous layer was extracted 3x with 100 mL of ether. The combined organic layers were washed once with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (up to 18% EtOAc in hexanes) of the crude mixture gave alkyne **34** (5.54 g, 17.98 mmol, 65% yield over 2 steps) as a light red oil. R_f= 0.34 (silica, 20% EtOAc in Hexanes),^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.13 (d, 1H, *J*= 1.4 Hz), 4.72 (td, 1H, *J*= 6.1 Hz, *J*= 8.3 Hz), 4.25 (q, 2H, *J*= 7.1 Hz), 2.80 (dd, 1H, *J*= 8.3 Hz, *J*= 13.6Hz), 2.65 (dd, 1H, *J*= 6.0 Hz, *J*= 13.6 Hz), 2.00 (d, 3H, *J*= 1.4 Hz), 1.32 (t, 3H, *J*= 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.3, 142.4, 86.9, 78.4, 76.7, 62.2, 60.1, 45.3, 24.6, 13.9; HRMS calcd. for $[M+Na]^+$ 330.9802, found 330.9803.

Aldehyde (35): To a solution of the alkyne **34** (0.592 g, 1.921 mmol) in dry DMF (3.84 mL) was added allyl alcohol (0.261 mL, 3.84 mmol), CSA (0.112 g, 0.480 mmol) under an argon atmosphere. The reaction mixture was sparged with argon for 15 minutes before adding Tris(acetonitrile)cyclopentadienylruthenium (II) hexafluorophosphate (0.042 g, 0.096 mmol). The reaction was heated to 50 °C for 1.5 hrs. The reaction mixture was then quenched with 10 mL of saturated $NaHCO_3$ solution and extracted 4x with 10 mL of ether. Organics were combined dried and concentrated. Flash chromatography (up to 40% EtOAc in hexanes) of the crude mixture gave aldehyde **35** (0.314 g, 0.98 mmol, 51% yield) as a dark orange oil, R_f= 0.32 (silica, 40% EtOAc

in Hexanes),^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.73 (s, 1H), 7.11 (q, 1H, *J*= 1.4 Hz), 6.06 (d, 1H, *J*= 1.4 Hz), 5.01 (qdd, 1H, *J*= 1.6 Hz, *J*= 6.1 Hz, *J*= 7.7 Hz), 2.73 (t, 2H, *J*= 7.0 Hz), 2.57 (m, 3H), 2.49 (dd, 1H, *J*= 7.5 Hz, *J*= 13.6 Hz), 1.92 (d, 3H, *J*= 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 200.3, 172.7, 148.6, 142.0, 132.4,79.3, 78.6, 42.2, 40.9, 24.6, 17.8; HRMS calcd. for $[M+H]^+$ 320.9982, found 320.9884.

Alpha-Beta Unsaturated Aldehyde (36): To a solution of aldehyde **35** (0.680 g, 2.124 mmol) in dry benzene (14.16 mL) was added 2-(triphenylphosphoranylidene) propanal (1.352 g, 4.25 mmol) in a microwave tube. The reaction mixture was sparged with argon for 10 minutes. The reaction was then microwaved for 40 minutes at 120 °C. The reaction was quenched with sat. NH_4Cl solution (10 mL), the organic layer was separated and the aqueous layer was extracted 3x with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (up to 30% EtOAc in hexanes) of the crude mixture gave aldehyde **36** (0.513 g, 1.423 mmol, 67% yield) as a yellow oil. R_f= 0.52 (silica, 50% EtOAc in Hexanes),^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.36 (s, 1H), 7.14 (d, 1H, *J*= 1.3 Hz), 6.42 (dt, 1H, *J*= 1.2 Hz, *J*= 7.1 Hz), 6.08 (d, 1H, *J*= 1.4 Hz), 5.05 (dt, 1H, *J*= 1.6 Hz, *J*= 7.1 Hz), 2.57 (m, 6H), 1.94 (d, 3H, *J*= 1.3 Hz), 1.71 (d, 3H, *J*= 0.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.8, 172.8, 151.7, 148.2, 142.1, 140.2, 132.9, 79.4, 78.7, 42.2, 26.5, 24.7, 24.0, 9.3; HRMS calcd. for $[M+Na]^+$ 383.0112, found 383.0115.

Allyl Alcohol (25): To a solution of aldehyde **36** (1.58 g, 4.39 mmol) in MeOH (88 mL) at -20 °C was added sodium borohydride (0.183 g, 4.83 mmol) in one portion. The solution went from orange-red to yellow. The reaction was stirred at -20 °C for 15 minutes. The reaction was quenched with 60 mL of saturated NH_4Cl solution (50 mL), the organic layer was separated and the aqueous layer was extracted 3x with 50 mL of EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (up to 55% EtOAc in hexanes) of the crude mixture gave alcohol **25** (1.589 g, 4.39 mmol, 100% yield), as a pale yellow oil, R_f= 0.30 (silica, 50% EtOAc in Hexanes),^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.08 (d, 1H, *J*= 1.4 Hz), 6.07 (d, 1H, *J*= 1.4 Hz), 5.35 (m, 1H), 5.02 (ddd, 1H, *J*= 1.5 Hz, *J*= 6.1 Hz, *J*=

7.5 Hz), 3.94 (s, 2H), 2.61 (dd, 1H, *J*= 6.0 Hz, *J*= 13.6 Hz), 2.50 (dd, 1H, *J*= 7.5 Hz, *J*= 13.6 Hz), 2.29 (m, 4H), 2.12 (s, 1H), 1.94 (d, 3H, *J*= 1.4 Hz), 1.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ:173.7, 148.2, 142.6, 136.5, 134.1, 123.9, 79.7, 78.8, 68.5, 42.6, 25.6, 25.3, 25.0, 14.0; HRMS calcd. for $[M+Na]^+$ 385.0271, found 385.0273.

Furfural Stannane (30): To a suspension of N,O-dimethylhydroxylammonium chloride (3.62 g, 37.1 mmol) in THF (190 mL) was added the first amount of butylithium (46.3 mL, 74.1 mmol) at -40 °C over 15 minutes. After 30 minutes stirring, furan-2-carbaldehyde (2.36 mL, 28.5 mmol) was added dropwise over 10 minutes. The reaction was stirred at -40 °C for 45 minutes. The second amount of butylithium (26.7 mL, 42.8 mmol) was added dropwise over 10 minutes. The reaction was stirred at -40 °C for 1 hour. Then a solution of the chlorotrimethylstannane (6.82 g, 34.2 mmol) in 20 mL of dry THF was added over 5 minutes. The reaction was stirred for 30 minutes then was quenched with saturated NH_4Cl solution (150 mL), the organic layer was separated and the aqueous layer was extracted 3x with 20 mL of ether. The combined organic layers were washed once with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (up to 10% EtOAc in hexanes) of the crude oil. It yielded stannane **30** (5.32 g, 20.53 mmol, 72% yield) as a pale yellow oil, R_f= 0.33 (silica, 10% EtOAc in Hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.64 (s, 1H), 7.22 (d, 1H, *J*= 3.5 Hz), 6.71 (d, 1H, *J*= 3.4 Hz), 0.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.3, 171.3 157.5, 123.1, 121.4, -9.1; HRMS calcd. for $[M+H]^+$ 252.9958, found 252.9961.

Carbaldehyde (37): To a solution of alcohol **25** (1.59 g, 4.39 mmol) in DMF (29.3 mL) was added stannane **30** (1.364g, 5.27 mmol). The solution was sparged with argon for 15 minutes. To this solution was added $Pd(PPh_3)_4$ (0.203 g, 0.176 mmol), copper iodide (0.067 g, 0.351 mmol) and cesium fluoride (1.334 g, 8.78 mmol) in one portion at 25 °C. The solution went from yellow to brownish-grey and became heterogeneous. After 10 minutes of stirring, the reaction was quenched with saturated NH_4Cl solution (10 mL), the organic layer was separated and the aqueous layer was extracted 3x with 10 mL of ether. The combined organic layers were washed once with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (up to 70% EtOAc in hexanes) of the crude mixture gave carbaldehyde **37** (1.13 g, 3.42

mmol, 78% yield) as a yellow oil, R_f= 0.23 (silica, 60% EtOAc in Hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.48 (s, 1H), 7.32 (d, 1H, *J*= 1.4 Hz), 7.22 (d, 1H, *J*= 3.7 Hz), 6.35 (d, 1H, *J*= 3.7 Hz), 6.23 (s, 1H), 5.39 (ddd, 1H, *J*= 1.3 Hz, *J*= 5.5 Hz, *J*= 7.9 Hz), 5.13 (qdd, 1H, *J*= 1.6 Hz, *J*= 3.5 Hz, *J*= 8.6 Hz), 3.98 (s, 2H), 3.24 (dd, 1H, *J*= 3.5 Hz, *J*= 13.8 Hz), 2.44 (dd, 1H, *J*= 8.6 Hz, *J*= 13.8 Hz), 2.33 (m, 4H), 2.06 (d, 3H, *J*= 1.4 Hz), 1.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.4, 173.8, 157.9, 151.2, 148.9, 141.8, 136.4, 133.4, 124.4, 123.6, 115.4, 111.2, 81.4, 68.3, 38.2, 26.6, 25.2, 24.8, 13.6; HRMS calcd. for $[M+Na]^+$ 353.1359, found 353.1356.

Allyl Bromide (38): To a solution of carbaldehyde **37** (1.13 g, 3.42 mmol) in dry CH_2Cl_2 (86 mL) at -20 °C was added triphenylphosphine (0.987 g, 3.76 mmol), the reaction mixture was stirred until it dissolved. N-bromosuccinimide (0.670 g, 3.76 mmol) was then added. After 15 minutes the reaction was complete. The reaction was diluted with water (50 mL), the organic layer was separated and the aqueous layer was extracted 3x with 10mL of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (up to 30% EtOAc in hexanes) of the crude mixture gave allyl bromide **38** (1.26 g, 3.22 mmol, 94% yield) as a pale yellow oil, R_f= 0.49 (silica, 40% EtOAc in Hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.52 (s, 1H), 7.26 (s, 1H), 7.20 (d, 1H, *J*= 3.7 Hz), 6.35 (d, 1H, *J*= 3.7 Hz), 6.24 (s, 1H), 5.54 (t, 1H, *J*= 6.8 Hz), 5.13 (ddd, 1H, *J*= 1.7 Hz, *J*= 3.9 Hz, *J*= 8.3 Hz), 3.93 (s, 2H), 3.19 (dd, 1H, *J*= 4.0 Hz, *J*= 13.8 Hz), 2.53 (dd, 1H, *J*= 8.4 Hz, *J*= 13.8 Hz), 2.36 (m, 2H), 2.28 (m, 2H), 2.05 (d, 3H, *J*= 1.3 Hz), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.3, 173.5, 157.8, 151.4, 148.9, 141.3, 133.5, 133.2, 129.3, 123.9, 123.8, 115.6, 111.2, 81.2, 41.2, 38.2, 26.7, 25.9, 24.6, 14.7; HRMS calcd. for $[M+Na]^+$ 415.0515, found 415.0516.

Norbipinnatin J (29): Under an argon atmosphere, to dry THF (399 mL) were added powdered molecular sieves (11 g), $CrCl_2$ (3.24 g, 26.4 mmol) and $Ni(DME)_2Cl_2$ (1.448 g, 6.59 mmol). The reaction was stirred vigorously and sparged with argon for 10 minutes. The amount of allyl bromide **38** (0.864 g, 2.197 mmol) was taken up in dry THF (50 mL) and added to the stirring mixture via syringe pump over 1.5 Hrs at 25 °C. The reaction was left to stir at 25 °C overnight. 100 mL of water was then added and the solution and was diluted in 300 mL of ether. The organic layer was separated and the

aqueous layer was extracted 3x with 100mL ether. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (up to 25% EtOAc in hexanes) of the crude mixture gave norbipinnatin J **29** (0.566 g, 1.80 mmol, 82% yield) as a white solid, R_f= 0.21 (silica, 30% EtOAc in Hexanes) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.82 (t, 1H, *J*= 1.6 Hz), 6.36 (d, 1H, *J*= 3.2 Hz), 6.16 (s, 1H), 6.14 (d, 1H, *J*= 3.2 Hz), 5.15 (m, 1H), 5.05 (s, 1H), 4.99 (m, 1H), 4.46 (dd, 1H, *J*= 2.3 Hz, *J*= 11.0 Hz), 3.22 (t, 1H, *J*= 11.9 Hz), 2.74 (dd, 1H, *J*= 4.4 Hz, *J*= 11.8Hz), 2.40 (dt, 1H, *J*= 3.1 Hz, *J*= 14.5 Hz), 2.35 (t, 1H, *J*= 10.9 Hz), 2.09 (m, 1H), 2.00 (d, 3H, *J*= 1.2 Hz), 1.97 (d, 1H, *J*= 2.6 Hz), 1.77 (d, 3H, *J*= 0.6 Hz), 1.67 (tdd, 1H, *J*= 3.4 Hz, *J*= 10.9 Hz, *J*= 13.9 Hz), 0.88 (dt, 1H, *J*= 3.6 Hz, *J*= 13.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.3, 153.8, 152.3, 152.1, 141.9, 132.6, 129.2, 118.7, 117.4, 112.0, 111.0, 78.6, 67.4, 51.2, 39.6, 30.0, 25.9, 19.6, 17.4; HRMS calcd. for $[M+Na]^+$ 337.1410, found 337.1414.

Norrubifolide (39): To a solution of norbipinnatin J **29** (0.456 g, 1.450 mmol) in dry CH_2Cl_2 (58.0 mL) at 0 °C was first added triethylsilane (1.019 mL, 6.38 mmol), then trifluoroacetic acid (0.246 mL, 3.19 mmol) dropwise. After 15 minutes, the reaction was quenched with saturated $NaHCO_3$ solution (25 mL), the organic layer was separated and the aqueous layer was extracted 3x with 10mL of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (up to 15% EtOAc in hexanes) of the crude mixture gave rubifolide **39** (0.407 g, 1.41 mmol, 97% yield) as a white solid, R_f= 0.70 (silica, 30% EtOAc in Hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.88 (s, 1H), 6.11 (s, 1H), 6.09 (d, 1H, *J*= 3.2 Hz), 6.03 (dd, 1H, *J*= 1.4 Hz, *J*= 3.1 Hz), 4.97 (tdd, 1H, *J*= 1.8 Hz, *J*= 4.0 Hz, *J*= 11.8 Hz), 4.90 (m, 1H), 4.88 (s, 1H), 3.25 (t, 1H, *J*= 11.8 Hz), 2.69 (m, 2H), 2.58 (dd, 1H, *J*= 12.5 Hz, *J*= 15.3 Hz), 2.39 (m, 2H), 2.09 (m, 1H), 1.99 (s, 3H), 1.72 (s, 3H), 1.65 (tdd, 1H, *J*= 3.4 Hz, *J*= 10.8 Hz, *J*= 14.0 Hz), 1.18 (ddt, 1H, *J*= 0.9 Hz, *J*= 3.5 Hz, *J*= 13.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ; 174.5, 154.1, 152.0, 151.2, 145.2, 132.9, 127.3, 117.5, 113.2, 111.1, 108.7, 78.7, 43.4, 39.6, 32.9, 31.1, 25.8, 20.0, 19.1; HRMS calcd. for $[M+Na]^+$ 321.1461, found 321.1460.

Diol (40): To a solution of norrubifolide **39** (0.064 g, 0.214 mmol) in a 1:1:1 ratio of water (0.298 mL), THF (0.298 mL) and acetone (0.298 mL) was added NMO (0.030

g, 0.257 mmol). The mixture was cooled to 0 °C and treated with osmium tetroxide 4% solution in water (0.136 mL, 0.021 mmol) added dropwise. The reaction went from light yellow to brown and then turned dark green. It was stirred at 0 °C for 1.5 h and then warmed up to 25 °C and stirred for an additional 1.5 h. The solution was quenched with 5 mL of saturated Na_2SO_3 solution, the organic layer was separated and the aqueous layer was extracted 3x with 10 mL of EtOAc. The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure. Flash chromatography (up to 80% EtOAc in hexanes) of the crude mixture gave diol **40** (0.046 g, 0.137 mmol, 64% yield) as a white solid, R_f= 0.20 (silica, 50% Ethyl acetate in Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.24 (d, 1H, *J*= 3.0 Hz), 6.12 (d, 1H, *J*= 3.0 Hz), 5.74 (s, 1H), 4.94 (d, 1H, *J*= 11.4 Hz), 4.81 (s, 1H), 4.77 (s, 1H), 4.55 (s, 1H), 2.70 (d, 1H, *J*= 13.3 Hz), 2.51 (dd, 1H, *J*= 12.3 Hz, *J*= 14.3 Hz), 2.34 (m, 2H), 2.24 (dd, 1H, *J*= 11.5 Hz, *J*= 14.4 Hz), 2.11 (m, 2H), 1.73 (s, 3H), 1.70 (m, 2H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.7, 154.4, 149.8, 148.7, 146.3, 133.3, 112.4, 109.4, 108.7, 79.2, 75.7, 73.3, 43.9, 40.0, 33.1, 27.8, 23.4, 21.6, 18.9; HRMS calcd. for $[M+Na]^+$ 355.1516, found 355.1518.

Tertiary Alcohol (41): To a solution of diol **40** (0.0496 g, 0.149 mmol) in CH_2Cl_2 (9.95 mL) at -40 °C was added boron trifluoride diethyl etherate (0.057 mL, 0.448 mmol) and triethylsilane (0.143 mL, 0.895 mmol). After 10 minutes, the reaction was quenched with saturated $NaHCO_3$ solution (3 mL), the organic layer was separated and the aqueous layer was extracted 3x with 5 mL of CH_2Cl_2. The combined organic layers were washed once with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (up to 60% EtOAc in hexanes) of the crude mixture gave tertiary alcohol **41** (0.024 g, 0.075 mmol, 51% yield) as clear crystals, R_f= 0.29 (silica, 50% EtOAc in Hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.08 (m, 2H), 6.02 (d, 1H, *J*= 3.0 Hz), 4.88 (d, 1H, *J*= 11.3 Hz), 4.79 (m, 1H), 4.77 (s, 1H), 2.88 (q, 2H, *J*= 14.7 Hz), 2.65 (dd, 1H, *J*= 1.5 Hz, *J*= 14.7 Hz), 2.49 (dd, 1H, *J*= 11.6 Hz, *J*= 14.7 Hz), 2.42 (dd, 1H, *J*= 4.0 Hz, *J*= 14.0 Hz), 2.33 (ddd, 1H, *J*= 4.2 Hz, *J*= 11.5 Hz, *J*= 15.9 Hz), 2.13 (m, 2H), 1.93 (bs, 1H), 1.85 (dd, 1H, *J*= 11.4 Hz, *J*= 14.0 Hz), 1.77 (m, 2H), 1.72 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.7, 153.9, 149.7, 149.3, 146.5, 133.0, 112.2, 108.9, 108.2, 79.1, 71.2, 45.6, 44.3, 43.2, 33.0, 28.4, 26.6, 21.6, 18.8; HRMS calcd. for $[M+Na]^+$ 339.1567, found 339.1565.

Norcembrenolide B (2): To a solution of alcohol **41** (0.124 g, 0.392 mmol) in acetone (1.3 mL) at 0 °C was added Jones reagent (0.161 mL, 0.431 mmol) dropwise. After 20 minutes, the reaction was quenched with sat. $NaHCO_3$ solution (100 mL), the organic layer was separated and the aqueous layer was extracted 3x with 1mL of ethyl acetate. The combined organic layers were washed once with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (up to 6% Acetone in CH_2Cl_2) of the crude mixture gave Norcembrenolide B **2** (0.0646 g, 0.194 mmol, 50% yield) as a white solid, R_f= 0.30 (silica, 5% Acetone in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.21 (s, 1H), 5.13 (bs, 1H), 4.80 (s, 1H), 4.68 (s, 1H), 4.15 (dd, 1H, *J*= 3.5 Hz, *J*= 8.3 Hz), 2.97 (dd, 1H, *J*= 3.4 Hz, *J*= 15.3 Hz), 2.59 (dd, 1H, *J*= 6.8 Hz, *J*= 16.9 Hz), 2.53 (dd, 1H, *J*= 10.7 Hz, *J*= 24.6 Hz), 2.50 (m, 1H) 2.44 (d, 1H, *J*= 18.1 Hz), 2.39 (m, 2H), 2.35 (dd, 1H, *J*= 5.9 Hz, *J*= 12.8 Hz), 2.22 (m, 3H), 1.94 (ddd, 1H, *J*= 2.4 Hz, *J*= 4.7 Hz, *J*= 14.6 Hz), 1.76 (m, 1H), 1.66 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ: 211.6, 206.5, 173.4, 150.3, 146.1, 127.6, 112.9, 78.2, 77.8, 74.6, 47.8, 46.1, 45.6, 42.7, 40.8, 27.8, 24.6, 21.1, 18.0; HRMS calcd. for $[M+Na]^+$ 355.1516, found 355.1514.

Norcoralloidolide (42): To a solution of Norrubifolide **39** (0.288 g, 0.965 mmol) in dry THF (3.11 mL) at 0 °C was added tBuOOH (0.241 mL, 1.448 mmol) dropwise. The reaction was stirred for 5 minutes at 0 °C. triton B (4.39 μl, 9.65 μmol) was then immediately added dropwise. The reaction was then stirred at 0 °C and monitored by TLC. The reaction completed within 10 minutes. The reaction was quenched by adding 100 mg of solid Na_2SO_3 and stirred for 30 minutes. The reaction was then diluted with dry ether and filtered over celite. The reaction was concentrated under reduced pressure and yielded norcoralloidolide **42** (0.300 g, 0.956 mmol, 99% yield) as a white solid which was used without further purification. R_f= 0.55 (silica, 20% EtOAc in Hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.18 (s, 1H), 6.11 (d, 1H, *J*= 3.1 Hz), 6.04 (dd, 1H, *J*= 1.5 Hz, *J*= 3.1 Hz), 4.96 (m, 1H), 4.87 (s, 1H), 4.56 (dd, 1H, *J*= 4.3 Hz, *J*= 12.7 Hz), 3.76 (s, 1H), 3.68 (t, 1H, *J*= 12.7 Hz), 2.78 (d, 1H, *J*= 14.8 Hz), 2.60 (m, 1H), 2.55 (m, 3H), 1.98 (s, 3H), 1.73 (s, 3H), 1.55 (m, 2H), 1.03 (dd, 1H, *J*= 12.3 Hz, *J*= 14.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.3, 152.9, 150.7, 144.5, 127.0, 117.9, 113.4, 110.8, 108.4, 77.1, 61.3, 60.7, 44.1, 36.1, 32.9, 27.6, 25.0, 21.5, 19.1; HRMS calcd. for

$[M+Na]^+$ 337.1410, found 337.1408.

Diol (43): Norcoralloidolide **42** (0.059 g, .188 mmol) was subjected to identical conditions found for diol **40**. Flash chromatography (up to 80% EtOAc in hexanes) of the crude mixture gave diol **43** (0.027 g, 0.076 mmol, 42% yield) as a white solid, R_f= 0.20 (silica, 50% EtOAc in Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.24 (d, 1H, *J*= 3.1 Hz), 6.04 (dd, 1H, *J*= 1.1 Hz, *J*= 3.1 Hz), 4.92 (s, 2H), 4.67 (dd, 1H, *J*= 6.9 Hz, *J*= 8.9 Hz), 4.53 (s, 1H), 3.54 (s, 1H), 2.77 (d, 1H, *J*= 13.7 Hz), 2.62 (m, 2H), 2.40 (m, 1H), 2.00 (dd, 1H, *J*= 9.0 Hz, *J*= 15.1 Hz), 1.81 (dd, 1H, *J*= 6.9 Hz, *J*= 15.1 Hz), 1.74 (s, 3H), 1.55 (m, 2H), 1.38 (s, 3H), 1.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.5, 153.8, 150.4, 145.3, 112.8, 109.6, 107.9, 75.4, 75.3, 73.1, 62.6, 60.5, 43.2, 39.8, 32.0, 27.2, 25.9, 21.3, 19.3; HRMS calcd. for $[M+Na]^+$ 371.1465, found 371.1463.

Tertiary Alcohol (44): diol **43** (0.0245 g, 0.070 mmol) was subjected to identical conditions found for tertiary alcohol **41** to afford tertiary Alcohol **44** (0.014g, 0.042mmol, 60% yield) as clear crystals, R_f= 0.32 (silica, 50% EtOAc in Hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.06 (d, 1H, *J*= 3.0 Hz), 5.96 (d, 1H, *J*= 2.9 Hz), 4.99 (s, 1H), 4.90 (m, 1H), 4.71 (t, 1H, *J*= 8.1 Hz), 3.83 (s, 1H), 3.20 (d, 1H, *J*= 14.7 Hz), 2.93 (m, 1H), 2.81 (d, 1H, *J*= 14.7 Hz), 2.72 (dd, 1H, *J*= 2.1 Hz, *J*= 15.7 Hz), 2.59 (dd, 1H, *J*= 11.8 Hz, *J*= 15.8 Hz), 2.44 (m, 1H), 1.73 (s, 3H), 1.66 (dd, 2H, *J*= 5.1 Hz, *J*= 8.1 Hz), 1.62 (dd, 1H, *J*= 3.9 Hz, *J*= 8.1 Hz), 1.45 (m, 3H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.8, 152.9, 149.8, 145.7, 112.7, 108.9, 107.4, 75.3, 71.6, 62.7, 60.9, 42.1, 41.9, 41.0, 31.7, 29.1, 27.7, 22.0, 19.1; HRMS calcd. for $[M+Na]^+$ 355.1516, found 355.1511.

Scabrolide D (Norcembrenolide C) 3: Tertiary alcohol **44** (0.0363 g, 0.109 mmol) was subjected to identical conditions as norcembrenolide A **2**. Flash chromatography (up to 4% Acetone in CH_2Cl_2) of the crude mixture gave scabrolide D **3** (0.019 g, 0.055 mmol, 51% yield) as a white solid, R_f= 0.45 (silica, 5% Acetone in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.93 (s, 1H), 4.86 (s, 1H), 4.74 (t, 1H, *J*= 6.6 Hz), 4.20 (dd, 1H, *J*= 4.0 Hz, *J*= 5.7 Hz), 3.95 (s, 1H), 3.09 (dd, 1H, *J*= 4.0 Hz, *J*= 16.4 Hz), 2.73 (dd, 1H, *J*= 5.8 Hz, *J*= 16.4 Hz), 2.63 (d, 1H, *J*= 18.2 Hz), 2.61 (m, 1H), 2.52 (dd, 1H, *J*= 2.4 Hz, *J*= 12.0 Hz), 2.49 (d, 1H, *J*= 18.2 Hz), 2.31 (dd, 1H, *J*= 7.0 Hz, *J*= 14.9 Hz),

2.20 (m, 2H), 2.11 (dd, 1H, *J*= 6.2 Hz, *J*= 14.9 Hz), 1.75 (m, 1H), 1.68 (s, 3H), 1.65 (dd, 1H, *J*= 3.5 Hz, *J*= 8.2 Hz), 1.47 (s, 3H), 1.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 213.8, 207.6, 172.3, 145.7, 112.7, 79.1, 75.8, 75.0, 62.7, 60.7, 49.7, 48.3, 44.7, 42.4, 40.7, 26.9, 25.6, 21.3, 18.7; HRMS calcd. for $[M+Na]^+$ 371.1465, found 371.1466.

Polycyclic cembrenolides (46) and (47): To a solution of norcembrenolide B **2** (4.0 mg, 0.012 mmol) in dry THF at 0 °C was added was added tBuOOH (0.024 ml, 0.014 mmol,) dropwise followed by a 40 wt.% Triton B solution in methanol (0.001 ml, 0.002 mmol) dropwise. The reaction was stirred at 0 °C for 10 minutes, and then quenched with 100 mg of solid Na_2SO_3 and allowed to stir for 30 minutes. The reaction was diluted in ether, filtered over celite, and concentrated under reduced pressure. Flash chromatography (up to 3% Acetone in CH_2Cl_2) of the crude mixture gave polycyclic cembrenolide **47** (0.5 mg, 1.5 μmol, 13% yield) as a white solid, R_f= 0.34 (40% EtOAc in hexanes), and polycyclic cembrenolide **46** (1.0 mg, 3.0 μmol, 25% yield) as a white solid, R_f= 0.19 (40% EtOAc in hexanes); **47**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: (400 MHz) 4.74 (s, 1H) 4.72 (s, 1H) 4.29 (s, 1H) 3.67 (d, 1H, *J*= 9.8 Hz) 3.02 (dd, 1H, *J*= 10.2 Hz, *J*= 11.3 Hz) 2.64 (dd, 1H, *J*= 1.6 Hz, *J*= 12.7 Hz) 2.53 (m, 1H) 2.41 (m, 3H) 2.30 (t, 1H, *J*= 11.3 Hz) 2.09 (s, 1H) 1.98 (dd, 2H, *J*= 2.7 Hz, *J*= 10.3 Hz) 1.73 (m, 3H) 1.38 (s, 3H); HRMS calcd. For 355.1516, observed 355.1517; **46**: ^{1}H-NMR (400 MHz) 5.18 (s, 1H) 4.72 (s, 1H) 4.66 (s, 1H) 4.12 (dd, 1H, *J*= 2.5 Hz, *J*= 4.7 Hz) 3.33 (m, 1H) 2.64 (d, 1H, *J*= 9.2 Hz) 2.58 (d, 1H, *J*= 15.4 Hz) 2.46 (dt, 1H, *J*= 3.7 Hz, *J*= 13.2 Hz) 2.17 (s, 1H) 1.97 (dd, 1H, *J*= 4.6 Hz, *J*= 15.4 Hz) 1.43 (s, 3H) 1.24 (s, 3H); HRMS calcd. For $[M+Na]^+$ 355.1516, observed 355.1517.

Gyrosanolide E (**48**): To a solution of norcembrenolide B (**2**) (2.5 mg, 0.0075 mmol) in dry benzene (0.19 ml) at 0 °C was added DBU (0.0028 ml, 0.019 mmol) dropwise. The solution immediately became bright yellow was then quenched with 2 ml of 0.5 molar HCl and diluted with ether. The organic layer was separated and the aqueous layer was extracted 3x with 1 ml of ether. The combined organic layers were washed once with 2 mL of brine, dried over $MgSO_4$ and concentrated under reduced pressure. gave gyrosanolide E **48** (0.46mg, 0.014 mmol, 18% yield) as a white solid in a 1:1 ratio with norcembrenolide B, R_f= 0.53 (silica, 60% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ:7.44 (bd, 1H), 5.08 (m, 1H), 4.86 (s, 1H), 4.69 (s, 1H), 4.54

(dd, 1H, *J*= 3.3 Hz, *J*= 9.9 Hz), 1.74 (s, 3H), 1.51 (s, 3H); HRMS calcd. For $[M+Na]^+$ 355.1516, observed 355.1518.

Furanosinuleptolide (49): To a solution of 2,2,6,6-tetramethylpiperidine (0.15 ml, 0.88 mmol) in dry toluene (0.290 ml) at 0 °C was added butylithium (0.55 ml, 0.88 mmol) dropwise. The solution was warmed to 25 °C and stirred for 30 minutes. The solution was then cooled to 0 °C and diethylaluminum chloride (0.98 ml, 0.88 mmol) added dropwise and stirred for 40 minutes. In a separate container, norcoralloidolide (**42**) (0.023 g, 0.073 mmol) was dissolved in dry toluene (0.60 ml) and cooled to 0 °C. The first solution was transferred via cannula into the solution containing norcoralloidolide (**42**) and stirred at 0 °C. Reaction was completed in 5 minutes and quenched with 5 ml of saturated NH_4Cl. The organic layer was dilute with 5ml of EtOAc, separated, and the aqueous layer was extracted 3x with 5 ml of EtOAc. The combined organic layers were washed once with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (up to 35% EtOAc in hexanes) of the crude mixture gave allyl alcohol **49** (0.011 g, 0.035 mmol, 54% yield) as a white solid, R_f= 0.36 (20% EtOAc in hexanes) and recollection of starting material; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.00 (dd, 1H, *J*= 2.5 Hz, *J*= 12.3 Hz) 6.11 (s, 1H) 6.07 (d, 1H, *J*= 3.2 Hz) 5.90 (d, 1H, *J*= 3.1 Hz) 4.89 (s, 1H) 4.72 (s, 1H) 4.61 (dd, 1H, *J*= 3.8 Hz, *J*= 12.6 Hz) 4.49 (s, 1H) 3.18 (t, 1H, *J*= 12.6 Hz) 2.82 (d, 1H, *J*= 14.8 Hz) 2.71 (dd, 1H, *J*= 5.1 Hz, *J*= 14.9 Hz) 2.60 (m, 1H) 2.40 (d, 1H, *J*= 15.0 Hz) 2.29 (dd, 1H, *J*= 3.6 Hz, *J*= 12.8 Hz) 2.19 (td, 1H, *J*= 12.3 Hz, *J*= 15.1 Hz) 1.96 (s, 3H) 1.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.0, 151.2, 145.4, 145.1, 131.4, 128.7, 118.0, 111.8, 111.0, 109.7, 84.0, 69.5, 44.1, 37.4, 31.9, 29.9, 29.1, 25.2, 22.9; HRMS calcd. For $[M+Na]^+$ 315.1591, observed 315.1589.

Protected allyl alcohol (50): To a solution of allyl alcohol **49** (0.066 g, 0.210 mmol) in DMF (0.525 mL) at 0 °C was added first imidazole (0.036 g, 0.525 mmol) followed by TBS-Cl (0.038 g, 0.252 mmol). The solution was allowed to warm to 25 °C and stirred for 4 hours. Methanol (0.1 mL) was added to quench the remaining TBS-Cl, and the solution was added to 5 ml of saturated NH_4Cl. The organic layer was diluted with ether, separated, and the aqueous layer was extracted 3x with 5 ml of ether. The combined organic layers were washed once with 15 mL of brine, dried over $MgSO_4$

and concentrated under reduced pressure. Flash chromatography (up to 15% EtOAc in hexanes) of the crude mixture gave protected allyl alcohol **50** (0.076 g, 0.178 mmol, 85% yield) as a white solid, R_f= 0.63 (silica, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.88 (dd, 1H, *J*= 2.7 Hz, *J*= 12.1 Hz) 6.12 (s, 1H) 6.09 (d, 1H, *J*= 3.2 Hz) 5.90 (d, 1H, *J*= 3.2 Hz) 4.89 (s, 1H) 4.66 (s, 1H) 4.46 (dd, 1H, *J*= 3.8 Hz, *J*= 12.7 Hz) 4.42 (s, 1H) 3.19 (t, 1H, *J*= 12.7 Hz) 2.80 (d, 1H, *J*= 13.6 Hz) 2.73 (dd, 1H, *J*= 5.0 Hz, *J*= 14.9 Hz) 2.57 (m, 1H) 2.31 (d, 1H, *J*= 14.9 Hz) 2.24 (dd, 1H, *J*= 3.7 Hz, *J*= 12.6 Hz) 2.07 (td, 1H, *J*= 12.2 Hz, *J*= 14.8 Hz) 1.96 (s, 3H) 1.83 (s, 3H) 0.81 (s, 9H) -0.02 (s, 3H) -0.08 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 170.6, 151.3, 151.1, 145.7, 143.1, 131.7, 129.0, 117.9, 111.5, 111.1, 109.6, 84.7, 69.8, 44.0, 37.3, 32.4, 29.2, 25.8, 25.7, 25.3, 22.9, 18.0, -4.3, -4.5; HRMS calcd. For $[M+H]^+$ 429.2383, observed 429.2386.

Diol (51): Protected allyl alcohol **50** (0.037 g, 0.086 mmol) was subjected to identical conditions found for diol **40**. Flash chromatography (up to 80% EtOAc in hexanes) of the crude mixture gave diol **51** (0.030 g, 0.064 mmol, 74% yield) as a white solid, R_f= 0.16 (silica, 50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.91 (d, 1H, *J*= 8.8 Hz) 6.17 (d, 1H, *J*= 3.1 Hz) 6.15 (s, 1H) 6.10 (d, 1H, *J*= 3.1 Hz) 4.84 (s, 1H) 4.50 (dd, 1H, *J*= 3.7 Hz, *J*= 12.7 Hz) 3.54 (dd, 2H, *J*= 10.9 Hz, *J*= 43.5 Hz) 3.23 (d, 1H, *J*= 15.8 Hz) 3.01 (t, 1H, *J*= 12.7 Hz) 2.57 (dd, 1H, *J*= 4.1 Hz, *J*= 15.4 Hz) 2.42 (d, 1H, *J*= 9.7 Hz) 2.25 (m, 3H) 1.95 (s, 3H) 1.12 (s, 3H) 0.82 (s, 9H) 0.00 (s, 1H) -0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.5, 153.2, 151.1, 143.7, 131.3, 129.8, 117.8, 110.5, 110.2, 84.3, 74.5, 69.9, 68.5, 43.7, 37.4, 29.8, 26.0, 25.5, 24.7, 21.9, 17.8, -4.5, -4.6; HRMS calcd. For $[M+H]^+$ 463.2438, observed 463.2436.

Secondary alcohol (53): To a solution of norcoralloidolide (**42**) (0.026 g, 0.070 mmol) in 5.6 ml of dry THF and 1.4 ml of dry MeOH at -78 °C was added SmI_2 (0.01 molar) (2.09 ml, 0.209 mmol) dropwise. The reaction was then stirred for 10 minutes. The reaction was then quenched with 5 ml of saturated $NaHCO_3$. The reaction was extracted 3X with 5ml of ether. The organics were combined, dried and concentrated to yield a pale yellow oil. Flash chromatography (up to 55% EtOAc in hexanes) of the crude mixture gave secondary alcohol **53** (0.017 g, 0.054 mmol, 78% yield) as a white solid, R_f= 0.13 (30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: ppm 6.11

(s, 1H), 6.06 (d, 1H, *J*= 3.1Hz), 5.93 (d, 1H, *J*= 3.1Hz), 4.79 (s, 1H), 4.56 (dd, 1H, *J*= 3.6Hz, *J*= 12.9Hz), 4.49 (s, 1H), 4.22 (s, 1H), 3.59 (t, 1H, *J*= 12.8Hz), 2.98 (dd, 1H, *J*= 6.3Hz, *J*= 15.2Hz), 2.70 (d, 1H, *J*= 15.0Hz), 2.46 (dd, 1H, *J*= 4.0Hz, *J*= 13.7Hz), 2.38 (dd, 1H, *J*= 3.4Hz, *J*= 12.6Hz), 2.31 (m, 1H), 2.22 (ddd, 1H, *J*= 2.8Hz, *J*= 13.4Hz, *J*= 26.7Hz), 1.96 (s, 3H), 1.92 (m, 1H), 1.77 (s, 3H), 1.51 (m, 1H), 1.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.0, 152.2, 147.3, 142.9, 127.8, 117.8, 110.8, 110.4, 109.4, 86.4, 71.9, 51.2, 43.2, 37.5, 29.4, 28.6, 27.6, 24.7, 22.7; HRMS calcd. For $[M+H]^+$ 339.1561, observed 339.1563.

Acetate (54): To a solution of **53** (3.0 mg, 9.48 μmol) in MeCN (0.190 ml) at 0 °C was added acetic anhydride (2.0 μl, 0.019 mmol) followed by scandium triflate (0.5 mg, 0.95 μmol). The reaction was then stirred for 10 minutes at 0 °C. 1 ml of saturated $NaHCO_3$ was then added and the reaction was then stirred for an additional ten minutes. The reaction was then extracted 3X with 2 ml of ether. The organics were then combined dried and concentrated to leave a clear oil. Flash chromatography (up to 55% EtOAc in hexanes) of the crude mixture gave acetate **54** (2.9 mg, 0.08 mmol, 86% yield) as a white solid, R_f= 0.23 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.12 (s, 1H), 6.07 (d, 1H, *J*= 3.2Hz), 5.94 (d, 1H, *J*= 3.2Hz), 5.03 (s, 1H), 4.79 (s, 1H), 4.67 (dd, 1H, *J*= 3.8Hz, *J*= 12.9Hz), 4.54 (s, 1H), 3.69 (t, 1H, *J*= 12.9Hz), 2.98 (dd, 1H, *J*= 6.3Hz, *J*= 15.1Hz), 2.71 (dd, 1H, *J*= 1.9Hz, *J*= 15.2Hz), 2.54 (dd, 1H, *J*= 4.1Hz, *J*= 13.8Hz), 2.42 (dd, 1H, *J*= 1.6Hz, *J*= 12.7Hz), 2.31 (m, 3H), 2.03 (s, 3H), 1.98 (m, 1H), 1.93 (s, 3H), 1.77 (s, 3H), 1.48 (dt, 1H, *J*= 5.9Hz, *J*= 10.8Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 178.1, 169.8, 152.1, 151.0, 147.2, 127.2, 117.9, 110.8, 110.6, 109.5, 83.0, 74.5, 48.2, 43.4, 37.4, 29.4, 28.6, 27.8, 24.6, 22.6, 21.1; HRMS calcd. For $[M+Na]^+$ 381.1672, observed 381.1675.

Protected diol (56): To a solution of **40** (0.055 g, 0.17 mmol) in 2,2-dimethoxypropane (0.20 ml, 1.7 mmol) at 25 °C was added *p*-TsOH (3.2 mg, 0.017 mmol) in one portion. The reaction was then stirred for 20 minutes at which time, a few drops of triethyl amine to bring the pH up to 8. The reaction was then diluted in 1 ml of ether and 1 ml of water and extracted 3X with 1 ml of ether. The combined extracts were dried, concentrated to yield a clear oil. Flash chromatography (up to 35% EtOAc in hexanes) of the crude mixture **56** (0.053 mg, 0.14 mmol, 86% yield) as a white solid, R_f= 0.65

(60% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.38 (d, 1H, *J*= 3.1Hz), 6.13 (d, 1H, *J*= 2.9Hz), 5.41 (s, 1H), 4.82 (m, 1H), 4.79 (s, 1H), 4.75 (s, 1H), 4.68 (s, 1H), 2.81 (d, 1H, *J*= 13.3Hz), 2.51 (dd, 1H, *J*= 12.2Hz, *J*= 14.4Hz), 2.43 (dd, 1H, *J*= 11.3Hz, *J*= 14.1Hz), 2.34 (m, 2H), 2.13 (m, 2H), 1.82 (m, 1H), 1.74 (s, 3H), 1.62 (tdd, 1H, *J*= 3.6Hz, *J*= 11.1Hz, *J*= 14.6Hz), 1.56 (s, 2H, *J*= 13.8Hz), 1.44 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.4, 156.7, 148.5, 147.1, 145.9, 132.7, 112.5, 111.7, 108.6, 107.3, 80.7, 80.1, 79.0, 43.0, 41.4, 33.3, 28.2, 28.1, 26.6, 23.0, 21.9, 19.5; HRMS calcd. For $[M+Na]^+$ 395.1823, observed 395.1825.

Epoxide (57): To a solution of **56** (0.053 g, 0.14 mmol) in THF (0.47 ml) at 0 °C was added tBuOOH (0.069 ml, 0.71 mmol) dropwise. The reaction was stirred for 5 minutes at 0 °C. Triton B (0.019 ml, 0.043 mmol) was then added dropwise The reaction was then stirred for 10 minutes at which time 100 mg of solid sodium sulfite was added and stirred for an additional 10 minutes. The reaction was filtered over a small pad of celite and washed 3 X times with 3 ml of ether. Flash chromatography (up to 25% EtOAc in hexanes) of the crude mixture **57** (0.043 mg, 0.11 mmol, 77% yield) as a white solid, R_f= 0.65 (50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.39 (d, 1H, *J*= 3.1Hz), 6.09 (dd, 1H, *J*= 1.2Hz, *J*= 3.1Hz), 4.85 (s, 1H), 4.80 (s, 1H), 4.74 (s, 1H), 4.42 (dd, 1H, *J*= 3.1Hz, *J*= 12.5Hz), 2.89 (d, 1H, *J*= 14.6Hz), 2.73 (dd, 1H, *J*= 12.5Hz, *J*= 14.9Hz), 2.51 (dd, 1H, *J*= 11.4Hz, *J*= 14.6Hz), 2.25 (m, 2H), 2.13 (dd, 1H, *J*= 2.3Hz, *J*= 15.0Hz), 2.04(s, 1H), 1.79 (dd, 1H, *J*= 5.4Hz, *J*= 7.8Hz), 1.75 (s, 3H), 1.71 (m, 1H), 1.56 (s, 3H), 1.46 (s, 3H), 1.42 (s, 3H), 1.19 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.3, 156.0, 146.4, 146.0, 112.5, 112.2, 108.2, 107.7, 80.8, 80.2, 77.5, 61.9, 60.2, 44.5, 38.7, 33.1, 28.2, 26.5, 26.1, 23.6, 21.8, 19.2; HRMS calcd. For $[M+Na]^+$ 411.1778, observed 411.1780.

Protected tertiary alcohol (59): To a solution of tertiary alcohol **41** (0.094 g, 0.30 mmol) in CH_2Cl_2 (3.0 ml) at 0 °C was added imidazole (0.20 g, 3.0 mmol) followed by TES-Cl (0.25 g, 1.5 mmol) dropwise and then DMAP (3.6 mg, 0.030 mmol). The solution was allowed to warm to 25 °C and stirred overnight. A few drops of methanol were added to quench the remaining TES-Cl, and the solution was added to 6 ml of saturated NH_4Cl. The organic layer was diluted with 5 mL of ether, separated, and the aqueous layer was extracted 3x with 10 ml of ether. The combined organic layers were

washed once with 5 mL of brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was run through a plug of silica (10% EtOAc in hexanes) giving protected tertiary alcohol **59** (0.11 g, 0.26 mmol, 87% yield) as a white solid, R_f= 0.45 (10% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.03 (m, 2H) 5.69 (s, 1H) 4.82 (d, 1H, *J*= 11.9 Hz) 4.77 (d, 2H, *J*= 7.8 Hz) 2.86 (dd, 2H, *J*= 14.5 Hz, *J*= 43.5 Hz) 2.63 (dd, 1H, *J*= 2.3 Hz, *J*= 14.4 Hz) 2.49 (dd, 1H, *J*= 3.8 Hz, *J*= 14.2 Hz) 2.44 (dd, 1H, *J*= 12.1 Hz, *J*= 14.4 Hz) 2.29 (m, 1H) 2.08 (ddd, 2H, *J*= 2.6 Hz, *J*= 5.7 Hz, *J*= 7.4 Hz) 1.95 (dd, 1H, *J*= 11.9 Hz, *J*= 14.1 Hz) 1.71 (s, 3H) 1.69 (d, 1H, *J*= 5.4 Hz) 1.40 (s, 3H) 0.96 (t, 9H, *J*= 7.9 Hz) 0.61 (q, 6H, *J*= 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.6, 153.1, 150.4, 149.0, 146.6, 132.6, 111.9, 108.9, 108.6, 79.3, 77.3, 77.0, 76.6, 73.7, 46.5, 44.6, 44.2, 33.1, 27.4, 26.5, 21.7, 18.8, 7.0, 6.7; HRMS calcd. For $[M+Na]^+$ 453.2432, observed 453.2435.

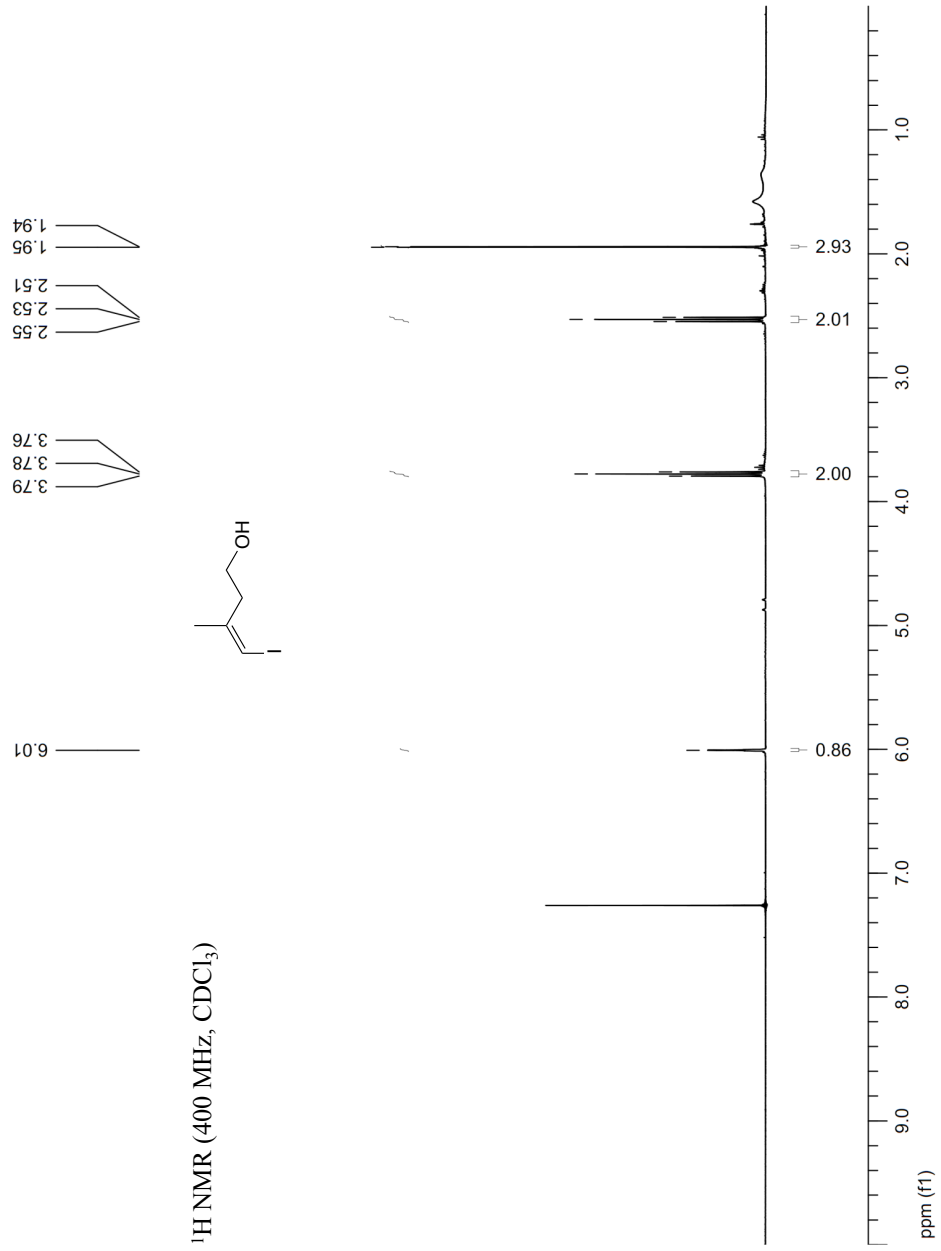
Epoxide (60): Protected tertiary alcohol **59** (0.11 g, 0.26 mmol) was subjected to identical conditions found for norcoralloidolide **42**. Flash chromatography (up to 7% EtOAc in hexanes) of the crude mixture gave epoxide **60** (0.098 g, 0.22 mmol, 85% yield) as a white solid, R_f= 0.46 (10% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.98 (d, 1H, *J*= 3.0 Hz) 5.92 (d, 1H, *J*= 2.6 Hz) 5.04 (s, 1H) 4.91 (s, 1H) 4.71 (dd, 1H, *J*= 6.2 Hz, *J*= 9.9 Hz) 3.62 (s, 1H) 3.39 (d, 1H, *J*= 14.3 Hz) 3.09 (t, 1H, *J*= 11.4 Hz) 2.72 (m, 2H) 2.56 (dd, 1H, *J*= 12.1 Hz, *J*= 16.0 Hz) 2.44 (m, 1H) 1.73 (s, 3H) 1.65 (dd, 2H, *J*= 6.0 Hz, *J*= 14.5 Hz) 1.52 (dd, 2H, *J*= 10.0 Hz, *J*= 14.4 Hz) 1.41 (m, 1H) 1.36 (s, 3H) 0.98 (t, 9H, *J*= 7.9 Hz) 0.64 (dd, 6H, *J*= 7.7 Hz, *J*= 15.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.3, 152.3, 150.9, 145.9, 112.7, 108.7, 107.2, 75.2, 74.0, 63.0, 61.1, 42.1, 41.9, 41.3, 31.9, 30.0, 27.6, 22.3, 18.9, 7.0, 6.7; HRMS calcd. For $[M+Na]^+$ 469.2381, observed 469.2379.

Allyl alcohol (61): Epoxide **60** (0.020 g, 0.045 mmol) was subjected to identical conditions found for furanosinuleptolide **49**. Flash chromatography (up to 35% EtOAc in hexanes) of the crude mixture gave allyl alcohol **61** (9.0 mg, 0.020 mmol, 45% yield) as a white solid, R_f= 0.25 (30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.96 (dd, 1H, *J*= 3.2 Hz, *J*= 12.4 Hz) 5.98 (d, 1H, *J*= 3.0 Hz) 5.91 (d,1H, *J*= 3.0 Hz) 4.95 (s, 1H) 4.84 (s, 1H) 4.68 (s, 1H) 4.55 (dd, 1H, *J*= 3.1 Hz, *J*= 12.7 Hz) 0.85 (t, 9H,

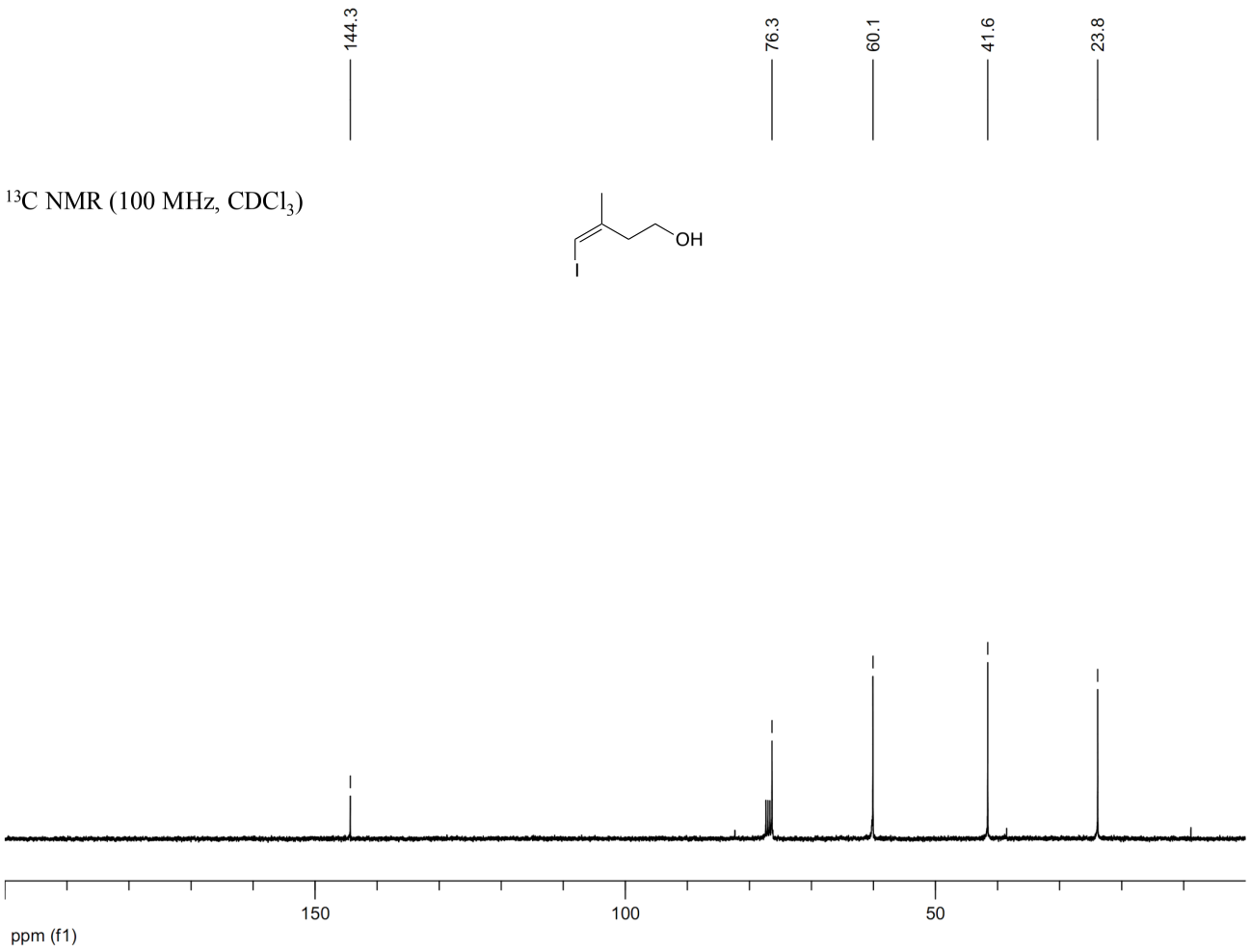
J= 7.9 Hz) 0.50 (q, 6H, *J*= 7.8 Hz); HRMS calcd. For $[M+H]^+$ 447.2631, observed 447.2563.

Deprotected Allyl alcohol (62): To a solution of allyl alcohol **61** (0.018 g, 0.040 mmol) in THF (0.4 ml) at 0 °C was added TBAF (0.081 ml, 0.040 mmol) dropwise. The solution was stirred at 0 °C for 2 hours and quenched with 1 ml of saturated $NaHCO_3$. The organic layer was diluted with 1ml of EtOAc, separated, and the aqueous layer was extracted 3x 1 ml of EtOAc. The combined organic layers were washed once with 1 mL of brine, dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (up to 90% EtOAc in hexanes) of the crude mixture gave allyl alcohol **62** (12.0 mg, 0.040 mmol, 90% yield) as a pale yellow solid, R_f= 0.14 (60% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.98 (dd, 1H, *J*= 2.7 Hz, *J*= 12.4 Hz) 6.10 (d, 1H, *J*= 3.0 Hz) 5.93 (d, 1H, *J*= 3.0 Hz) 5.22 (s, 1H) 4.82 (s, 1H) 4.67 (s, 1H) 4.60 (m, 1H) 1.76 (s, 3H) 1.45 (s, 3H); HRMS calcd. For $[M+Na]^+$ 355.1516, observed 355.1518.

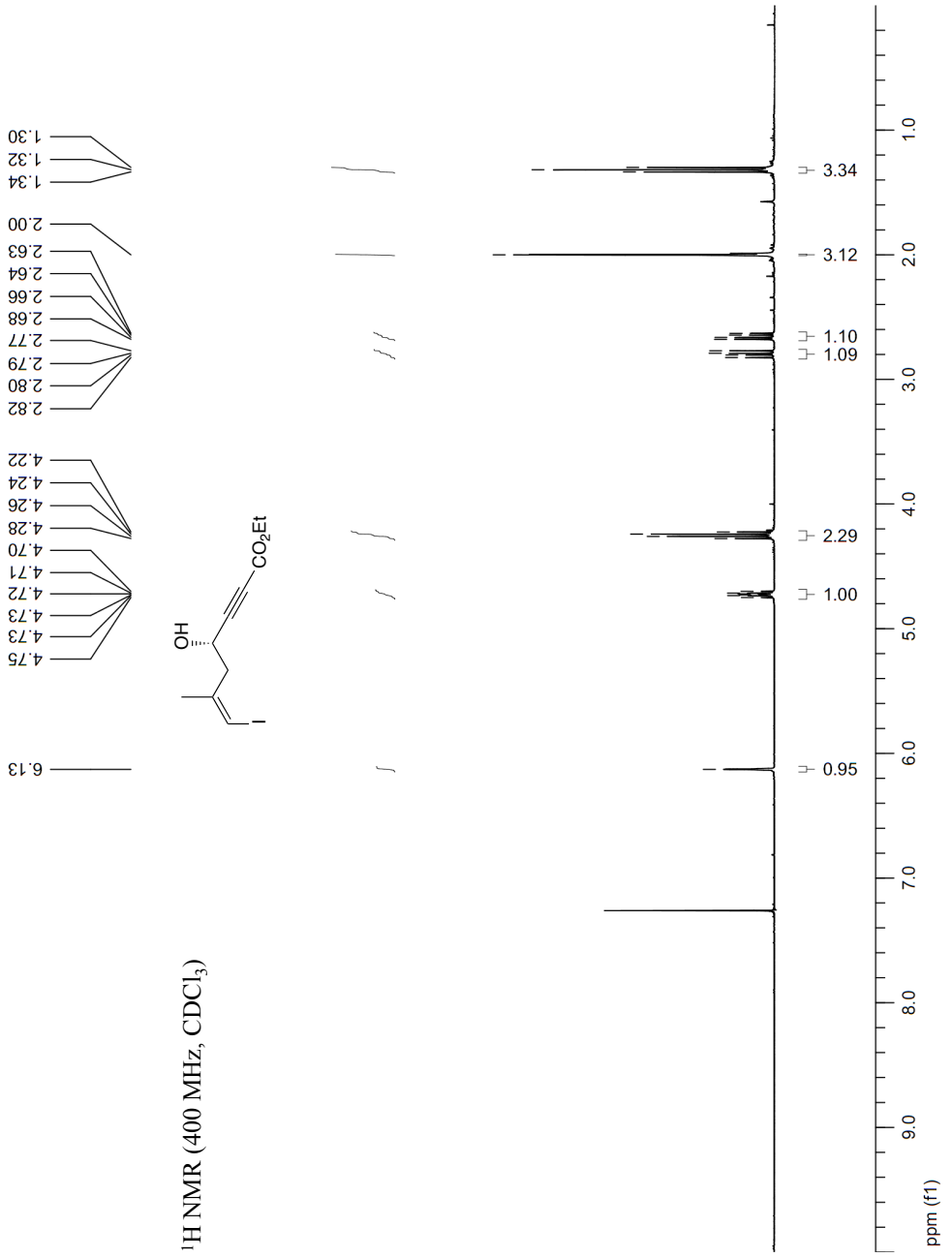
1.8.3 ^{1}H and ^{13}C NMR Spectra



Spectrum 1.1: Compound 31: ^{1}H NMR

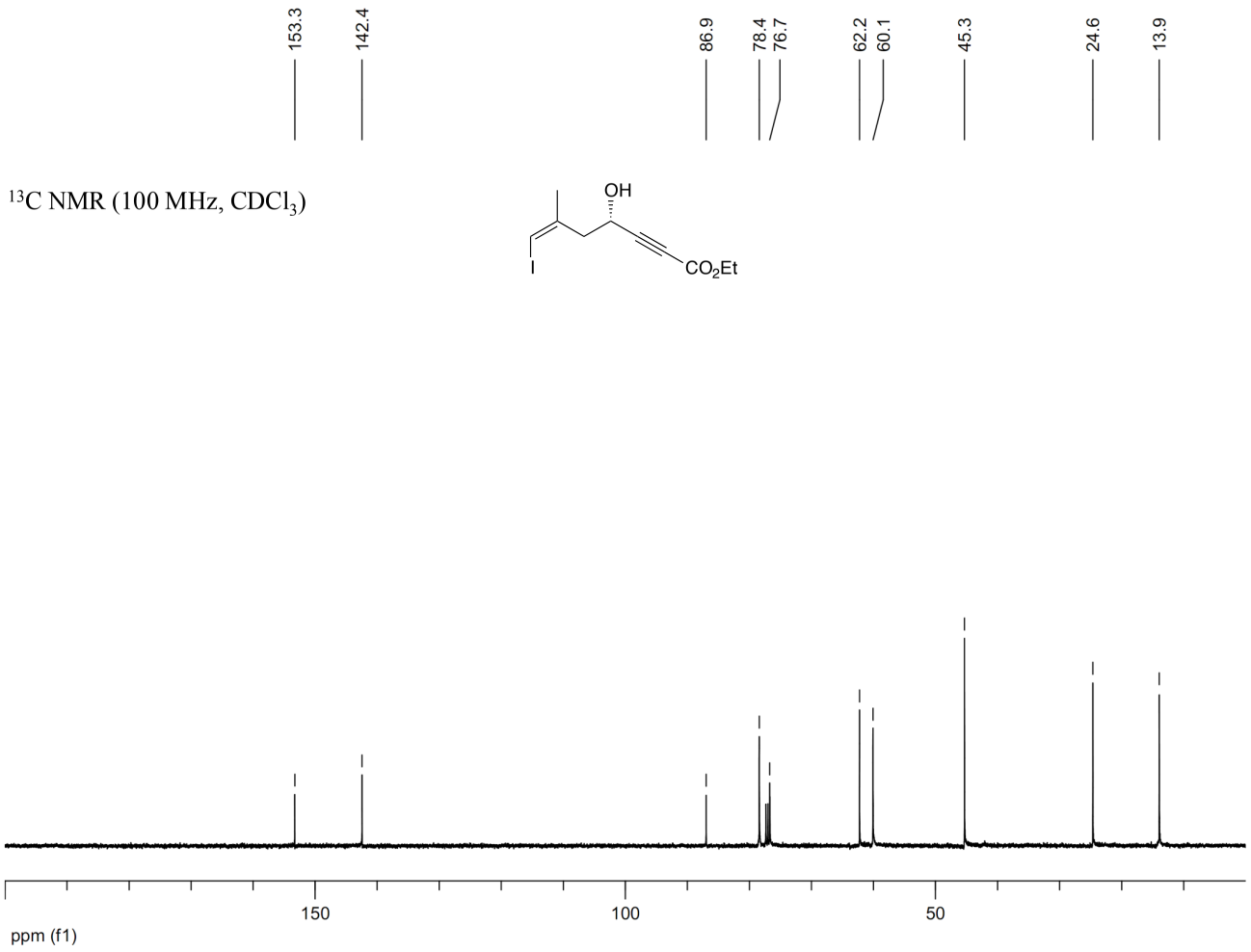


Spectrum 1.2: Compound 31: ^{13}C NMR

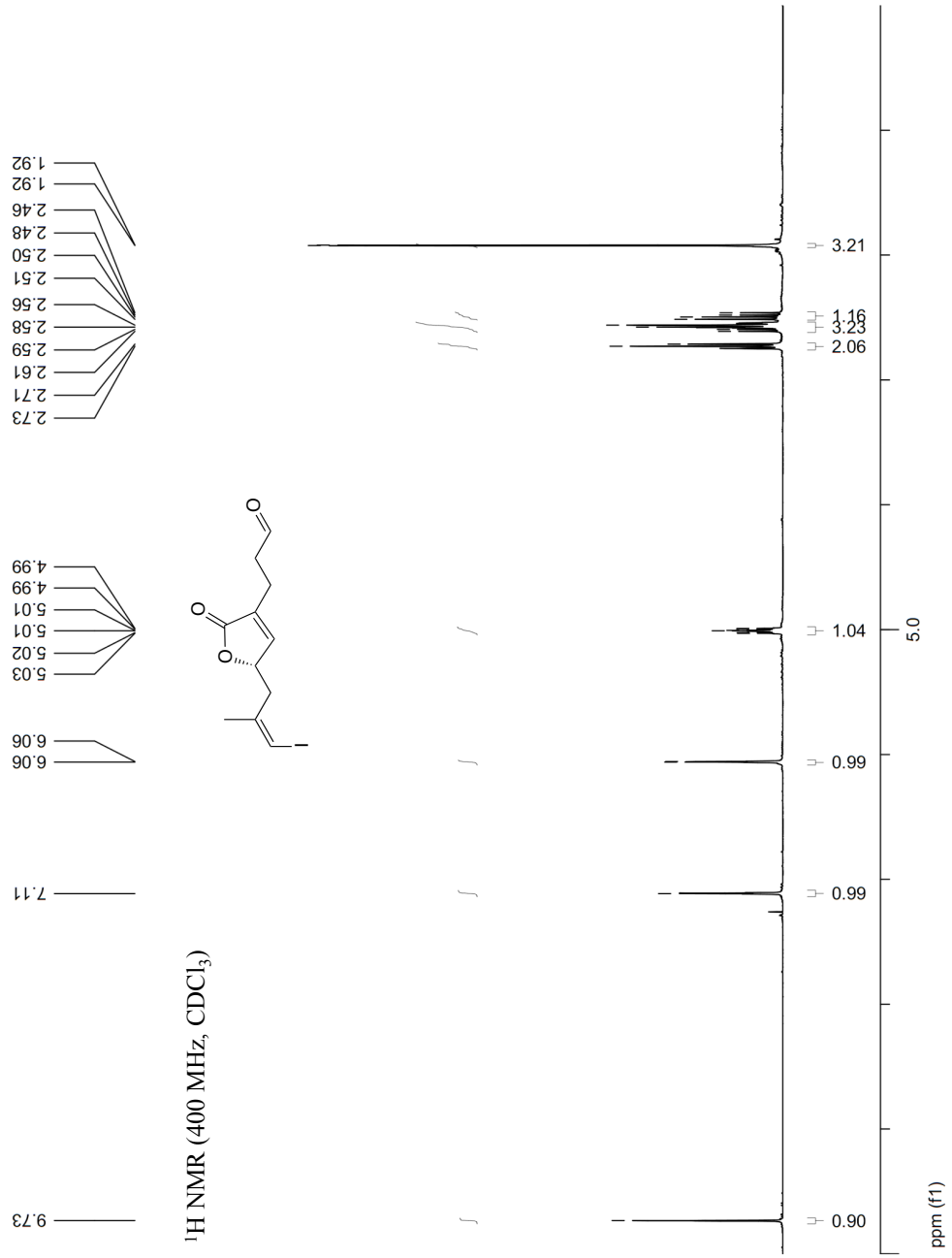


^{1}H NMR (400 MHz, $CDCl_3$)

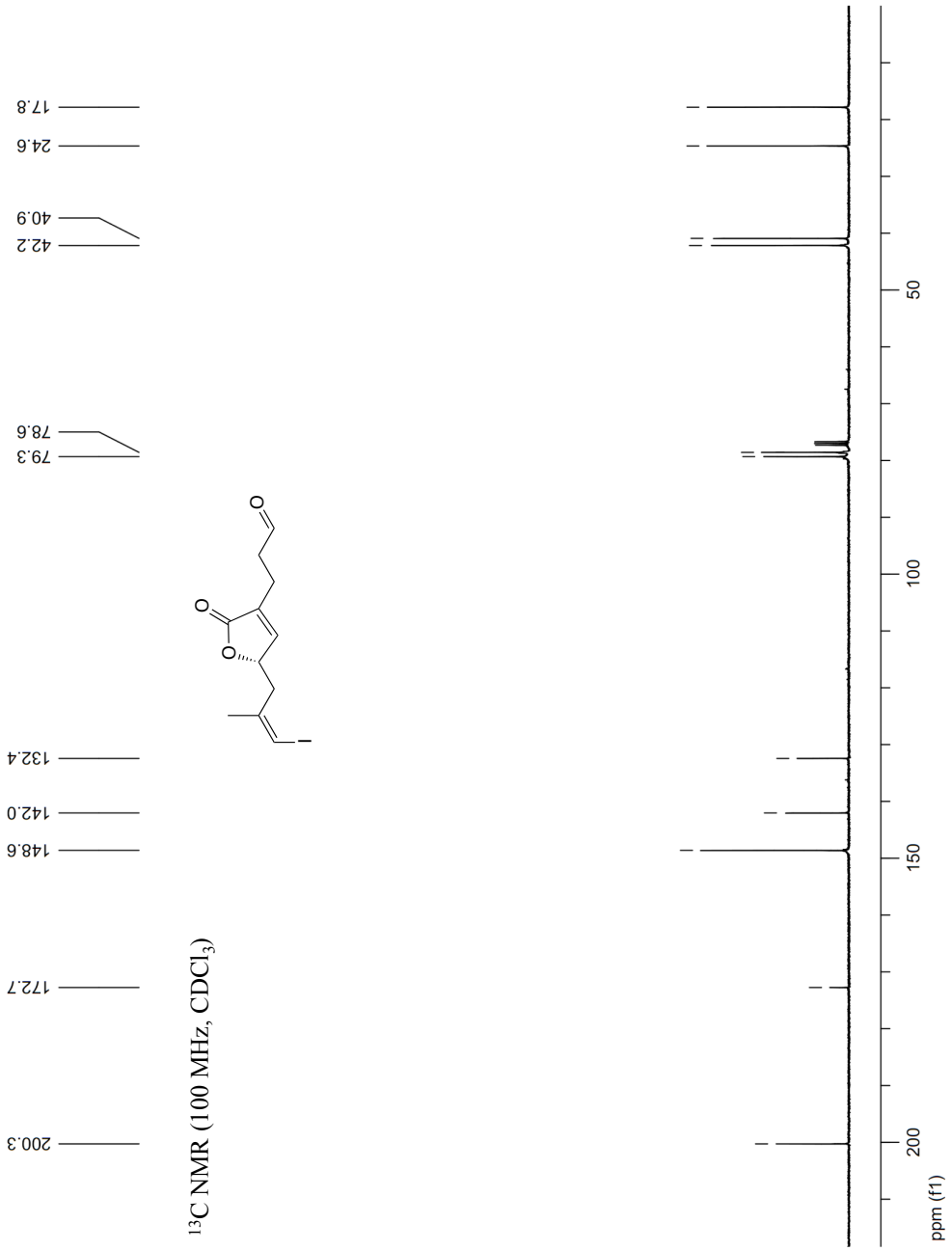
Spectrum 1.3: Compound 34: ^{1}H NMR



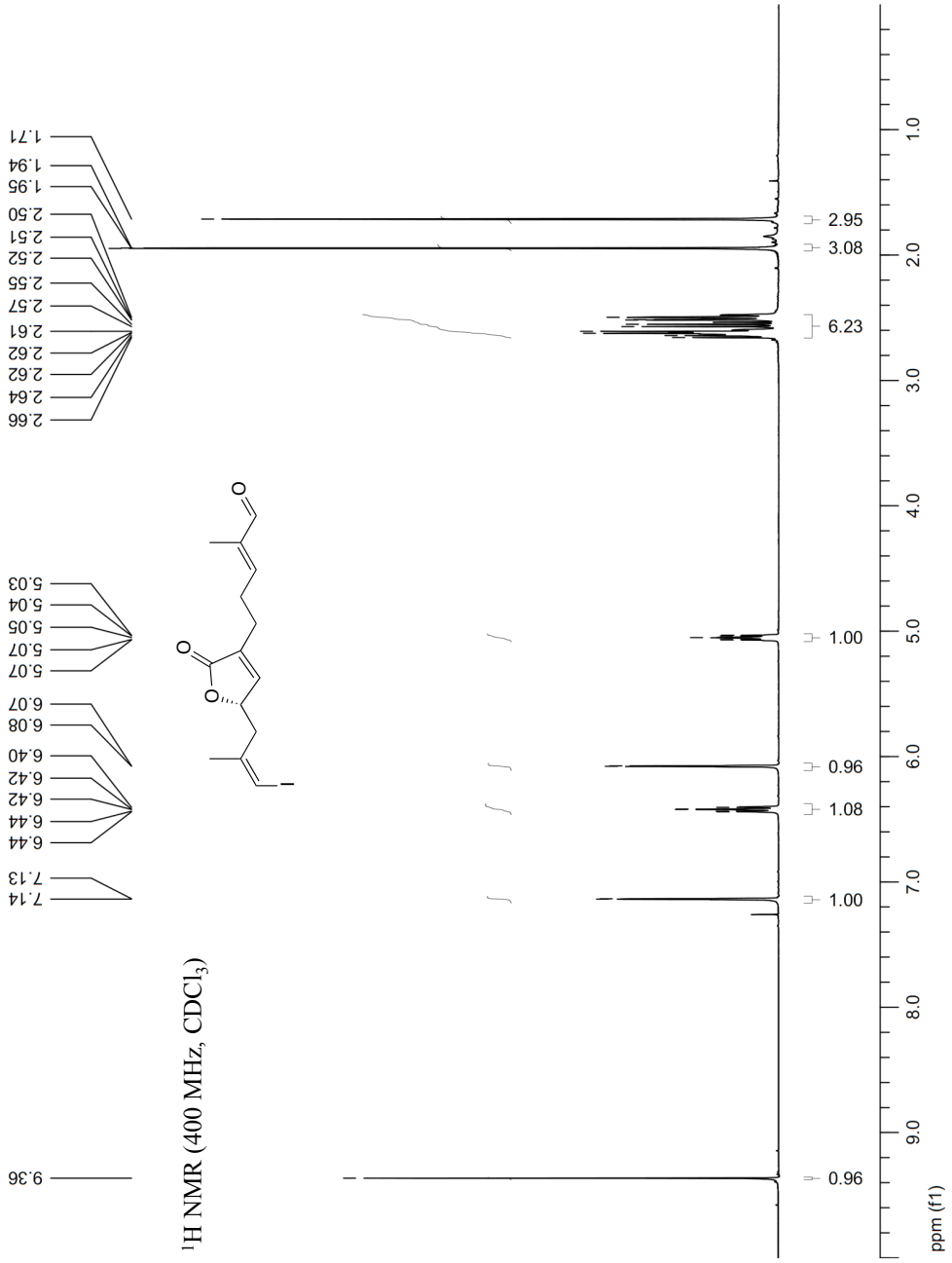
Spectrum 1.4: Compound 34: ^{13}C NMR



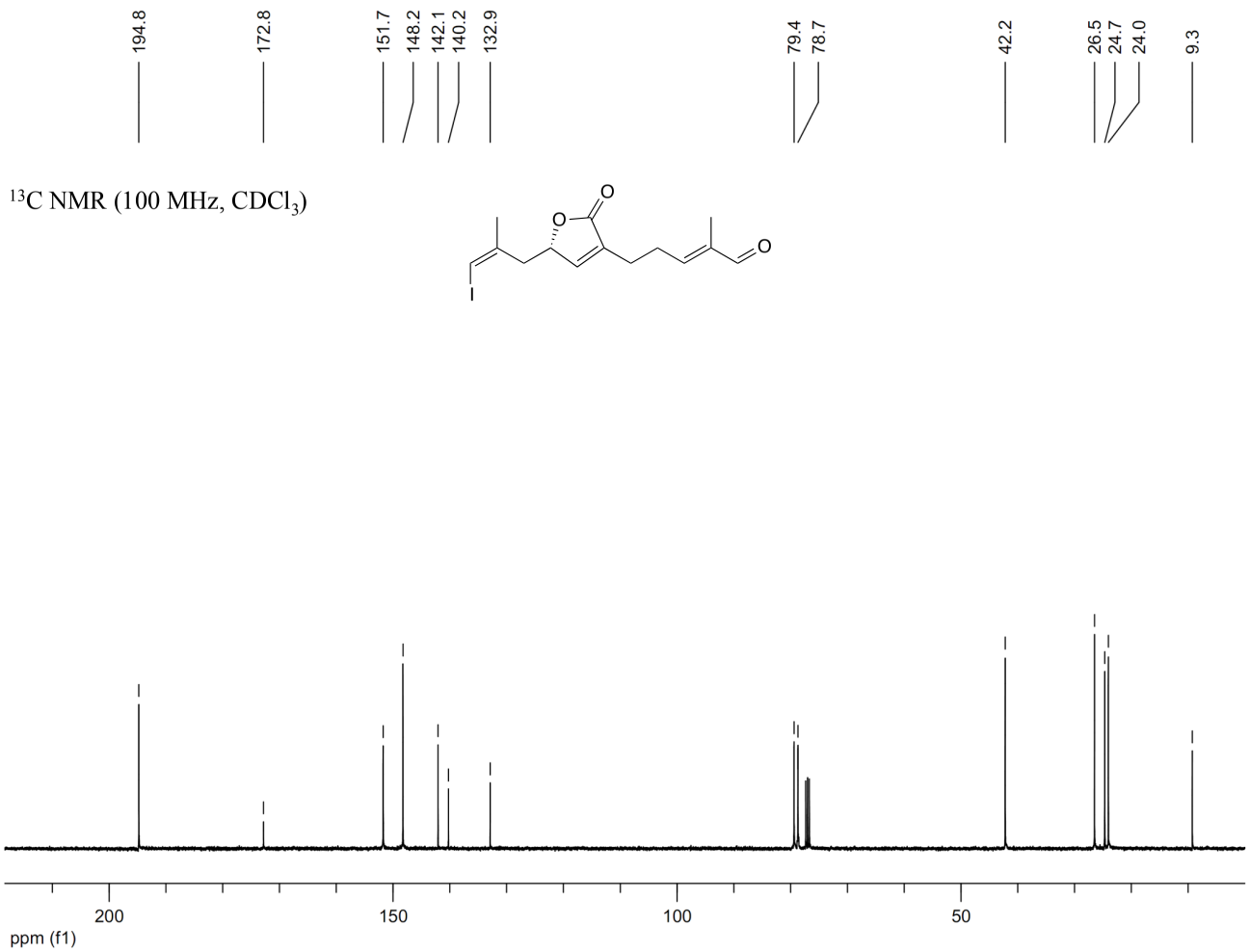
Spectrum 1.5: Compound 35: ^{1}H NMR



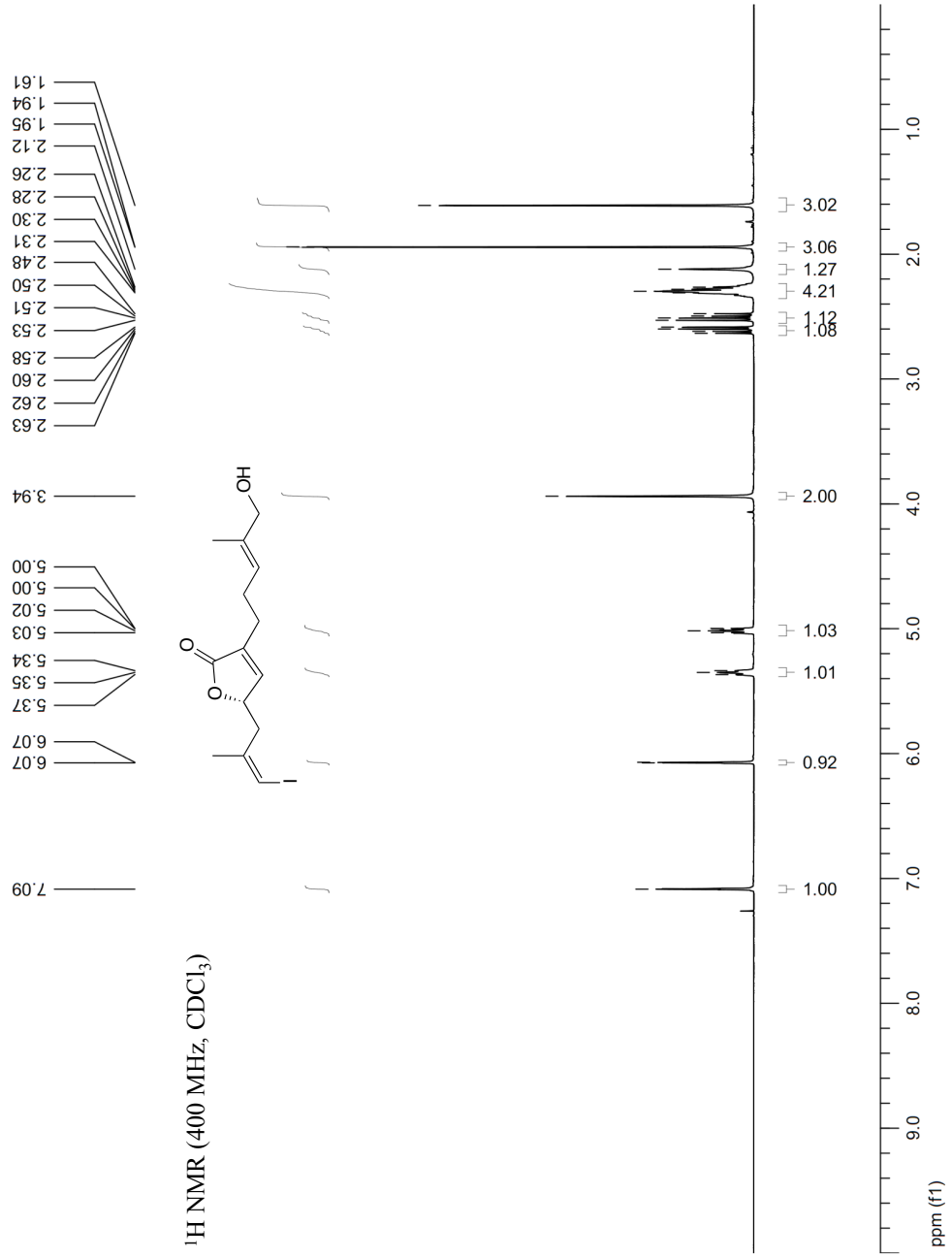
Spectrum 1.6: Compound 35: ^{13}C NMR



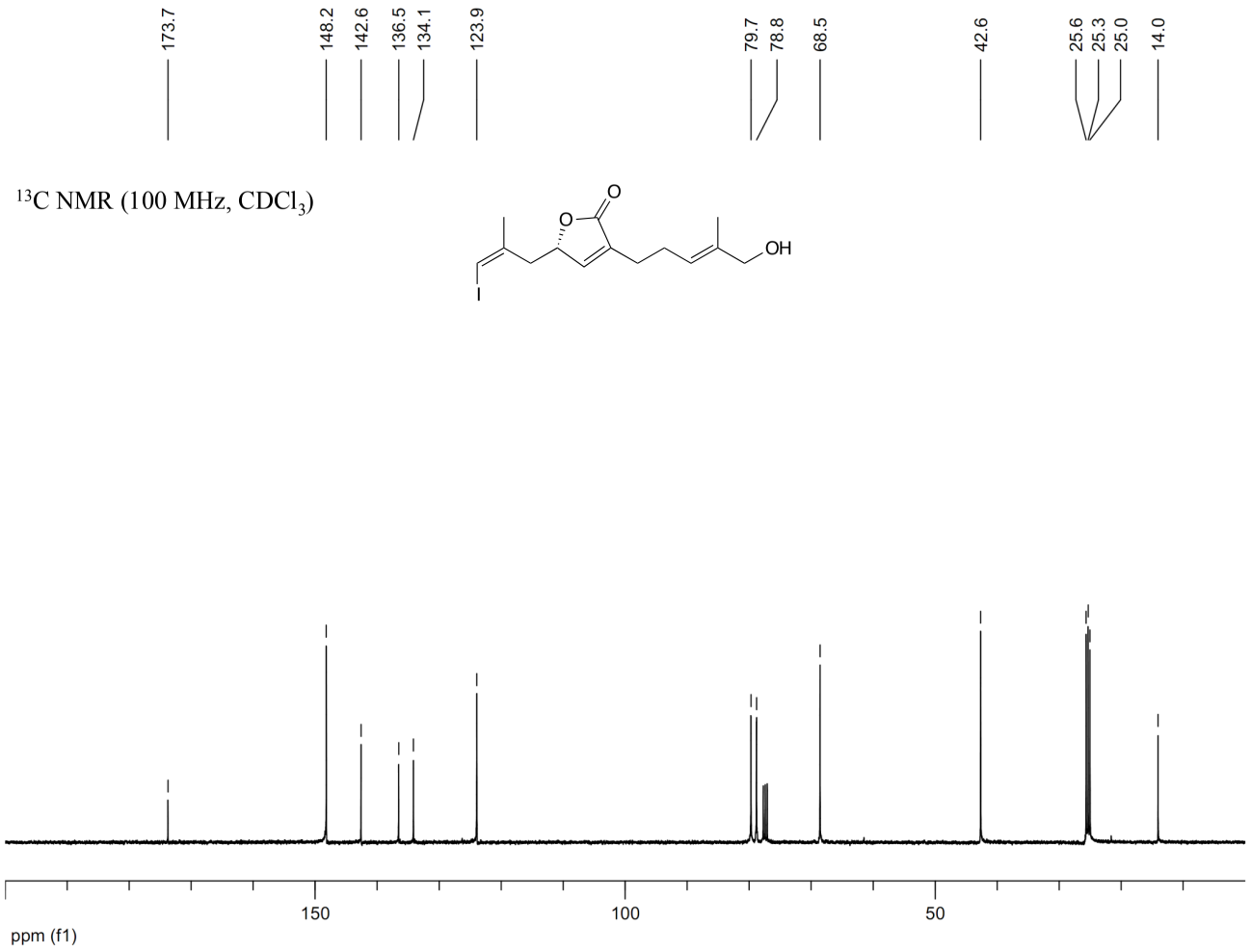
Spectrum 1.7: Compound 36: ^{1}H NMR



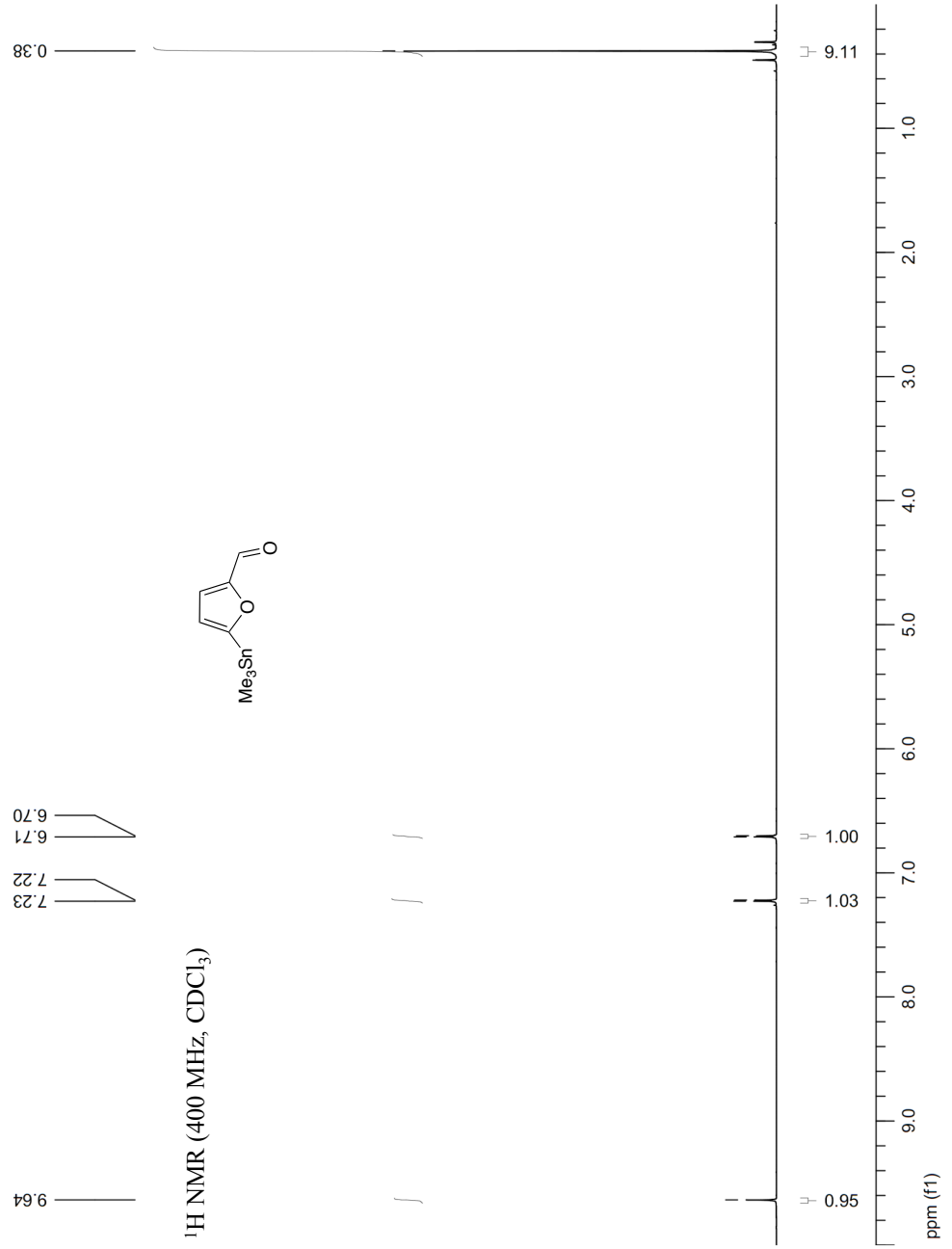
Spectrum 1.8: Compound 36: ^{13}C NMR



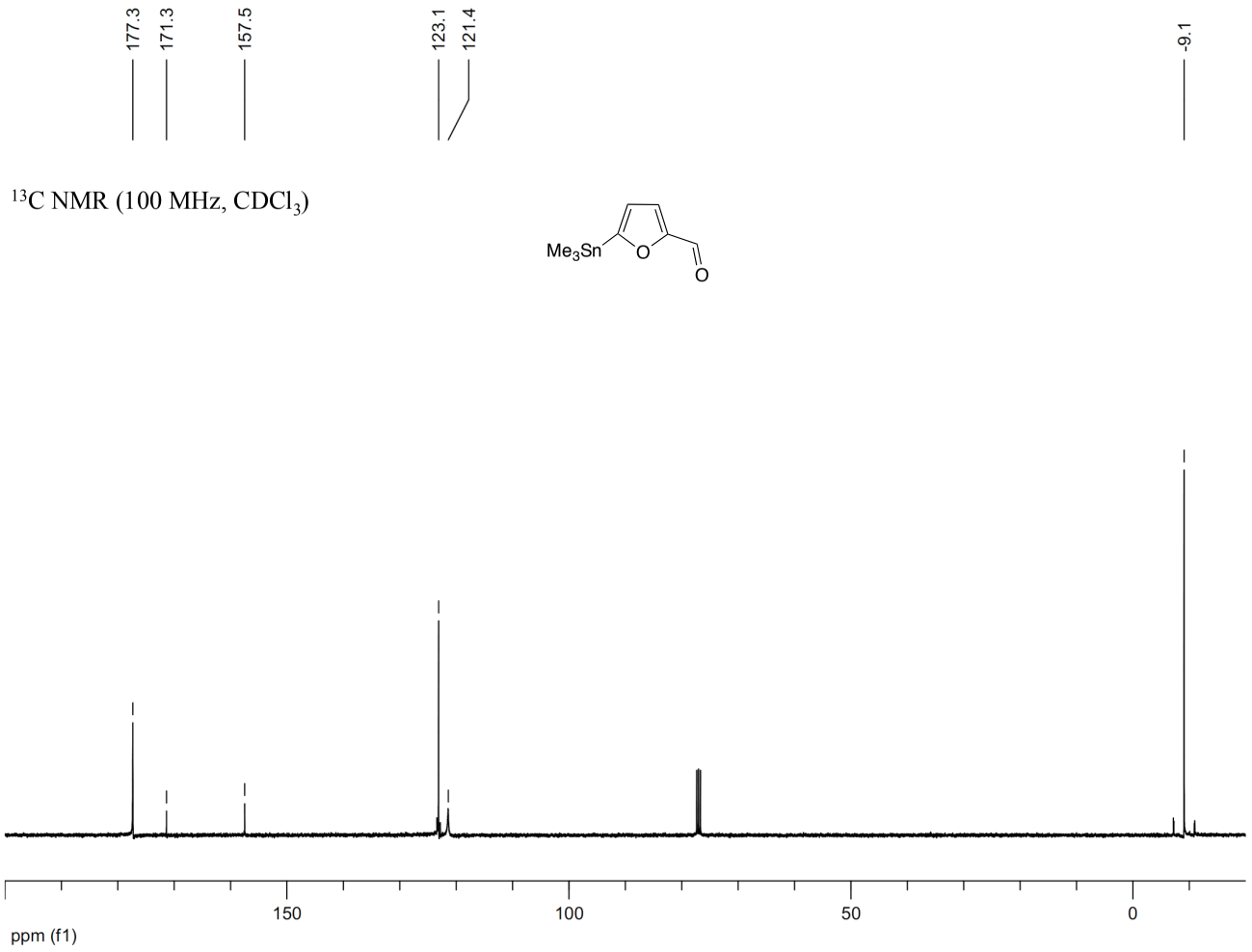
Spectrum 1.9: Compound 25: ^{1}H NMR



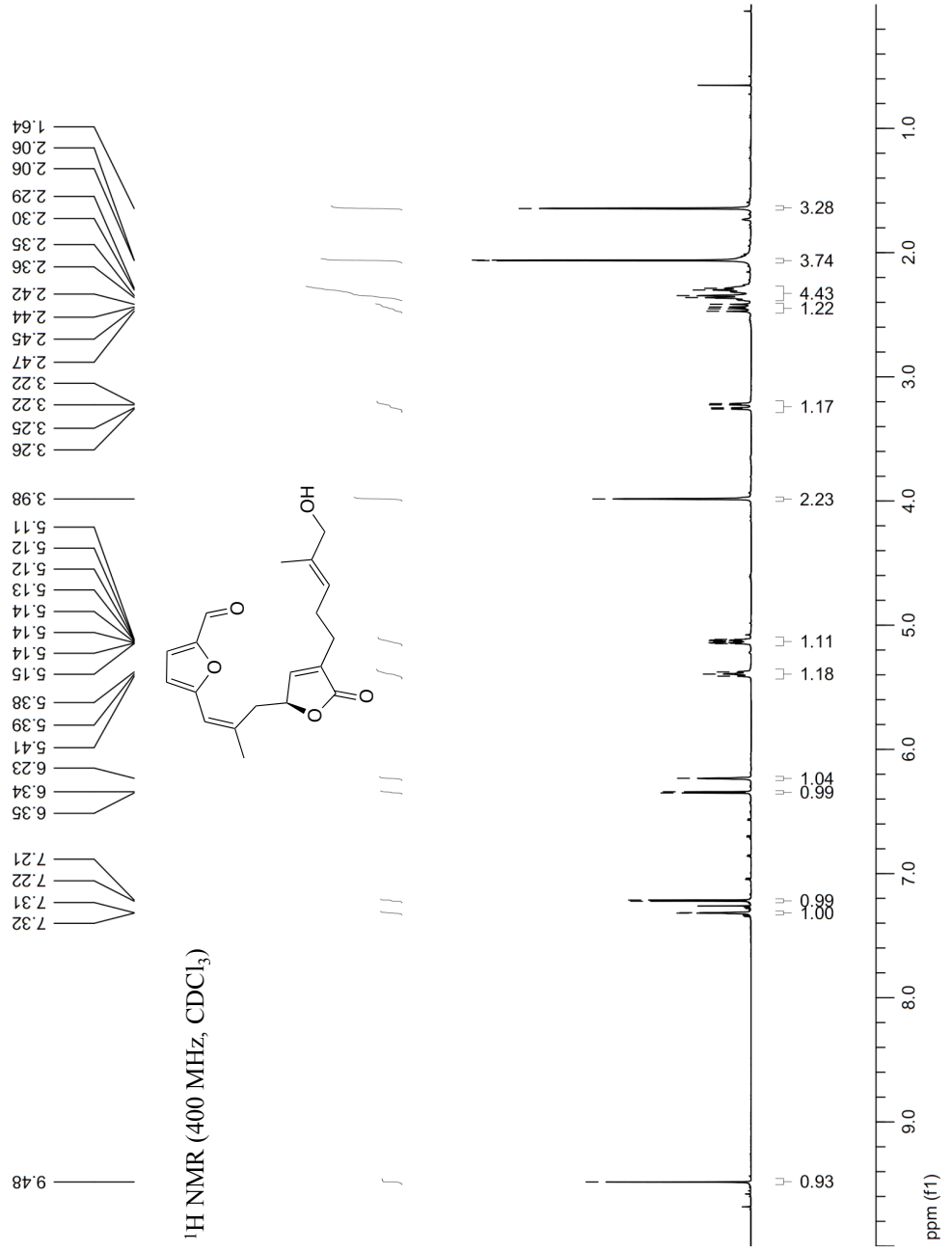
Spectrum 1.10: Compound 25: ^{13}C NMR



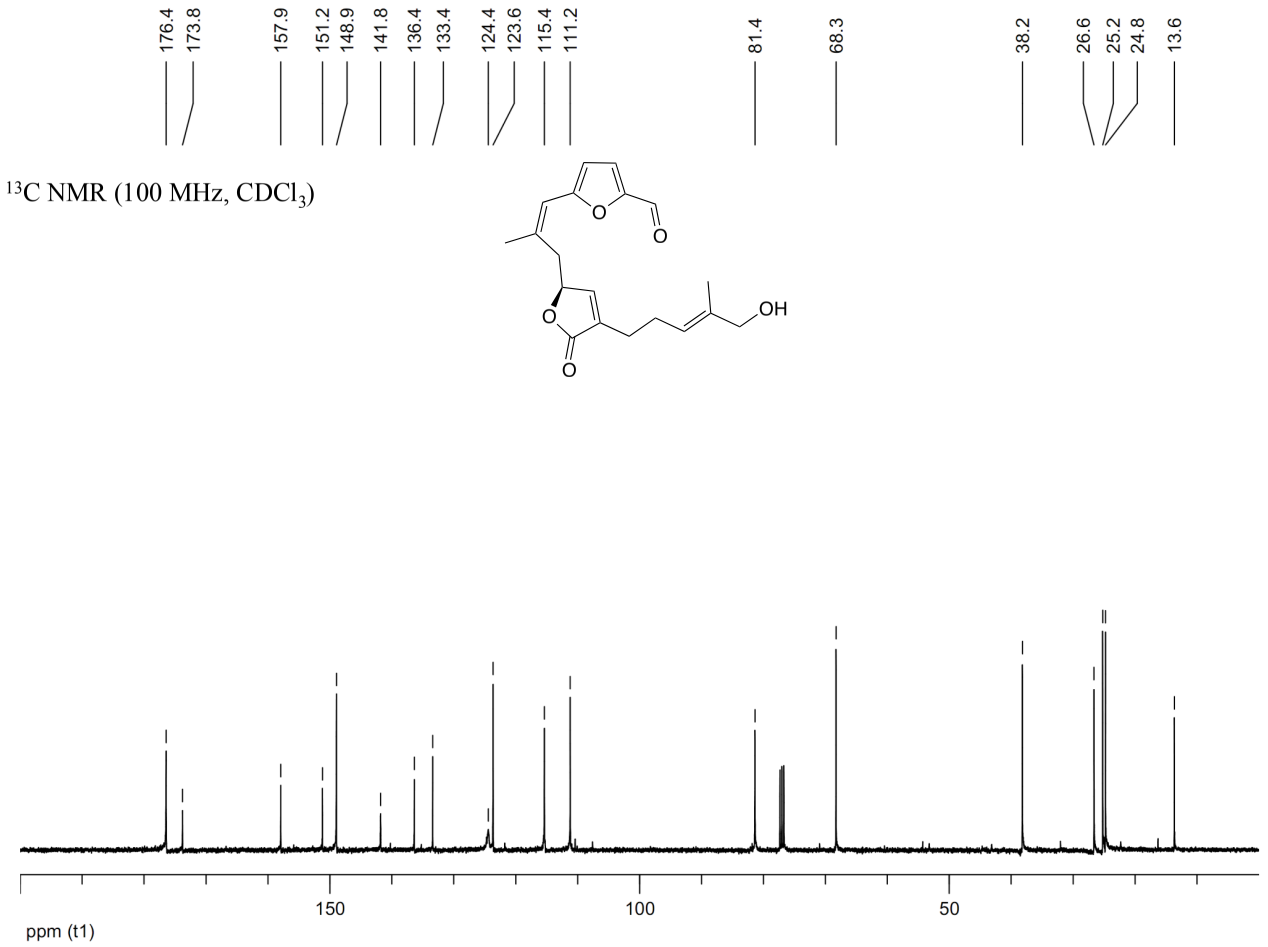
Spectrum 1.11: Compound 30: ^{1}H NMR



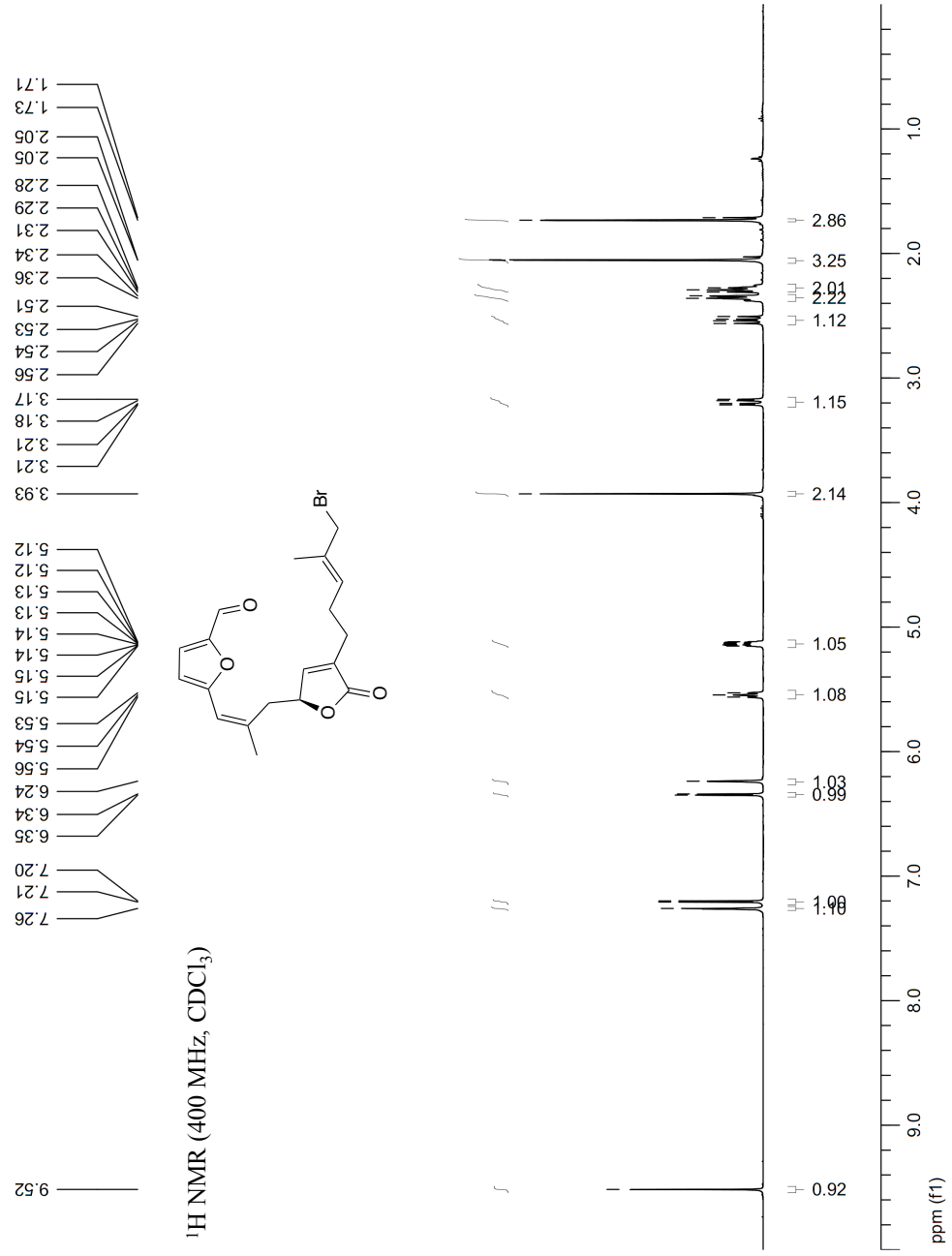
Spectrum 1.12: Compound 30: ^{13}C NMR



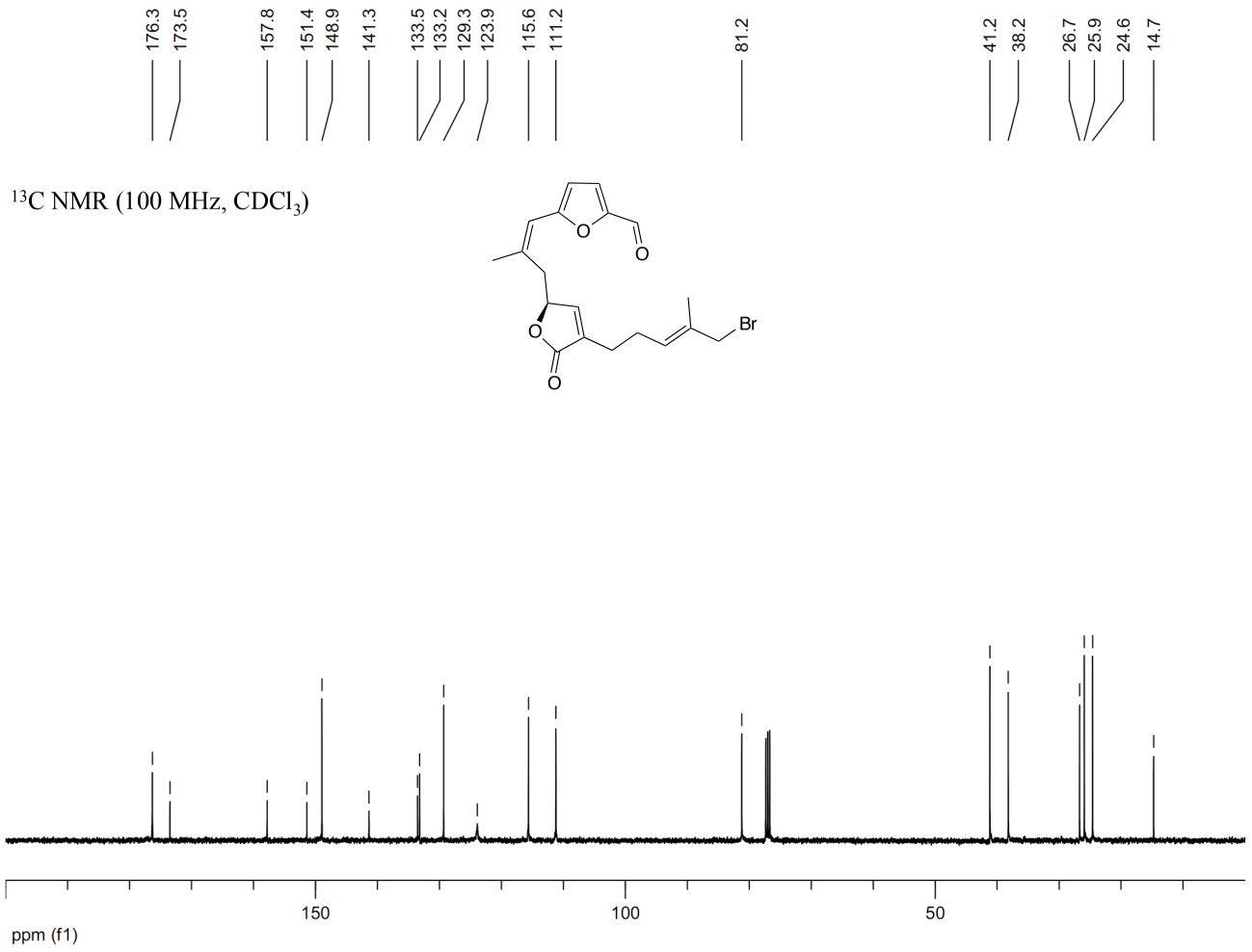
Spectrum 1.13: Compound 37: ^{1}H NMR



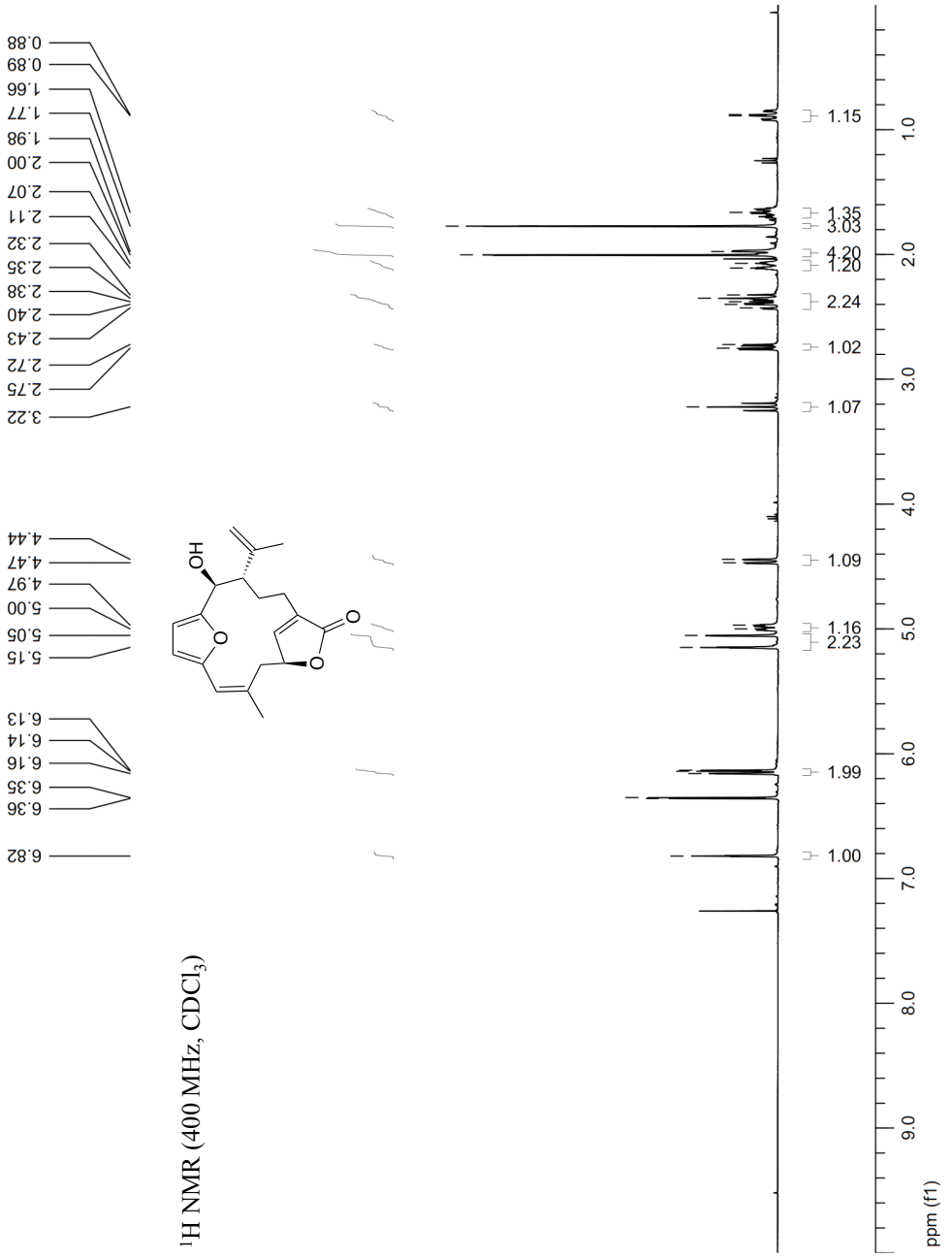
Spectrum 1.14: Compound 37: ^{13}C NMR



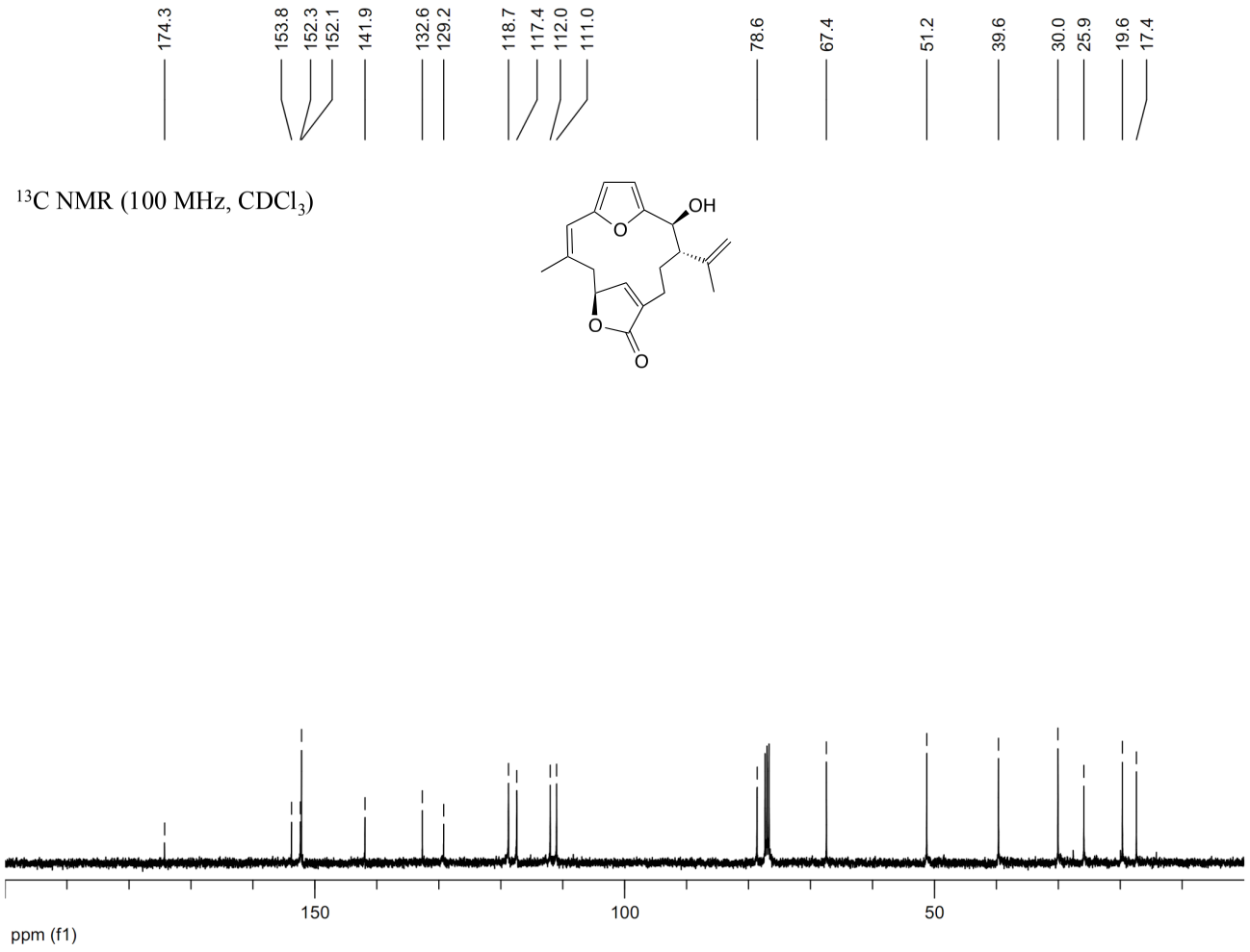
Spectrum 1.15: Compound 38: ^{1}H NMR



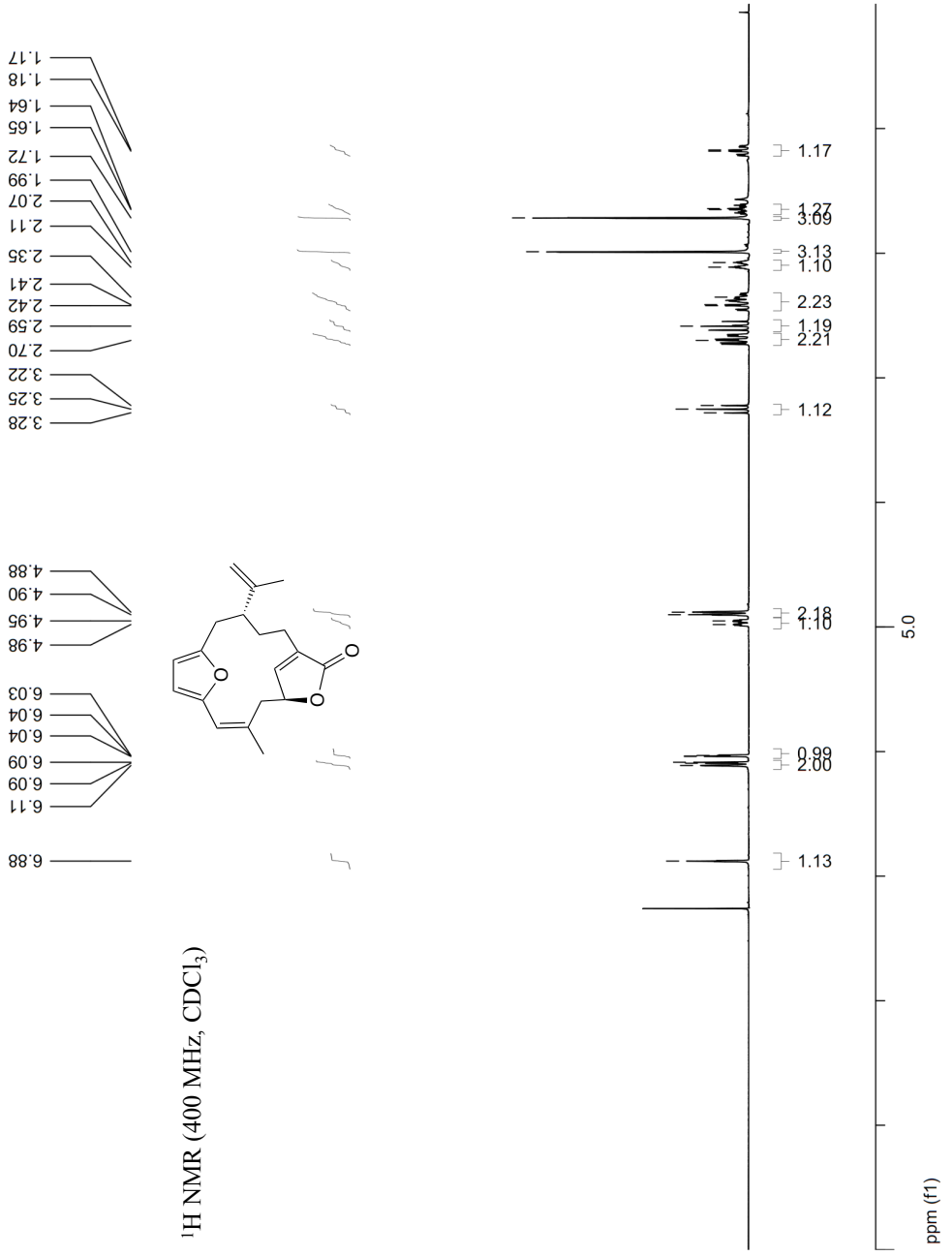
Spectrum 1.16: Compound 38: ^{13}C NMR



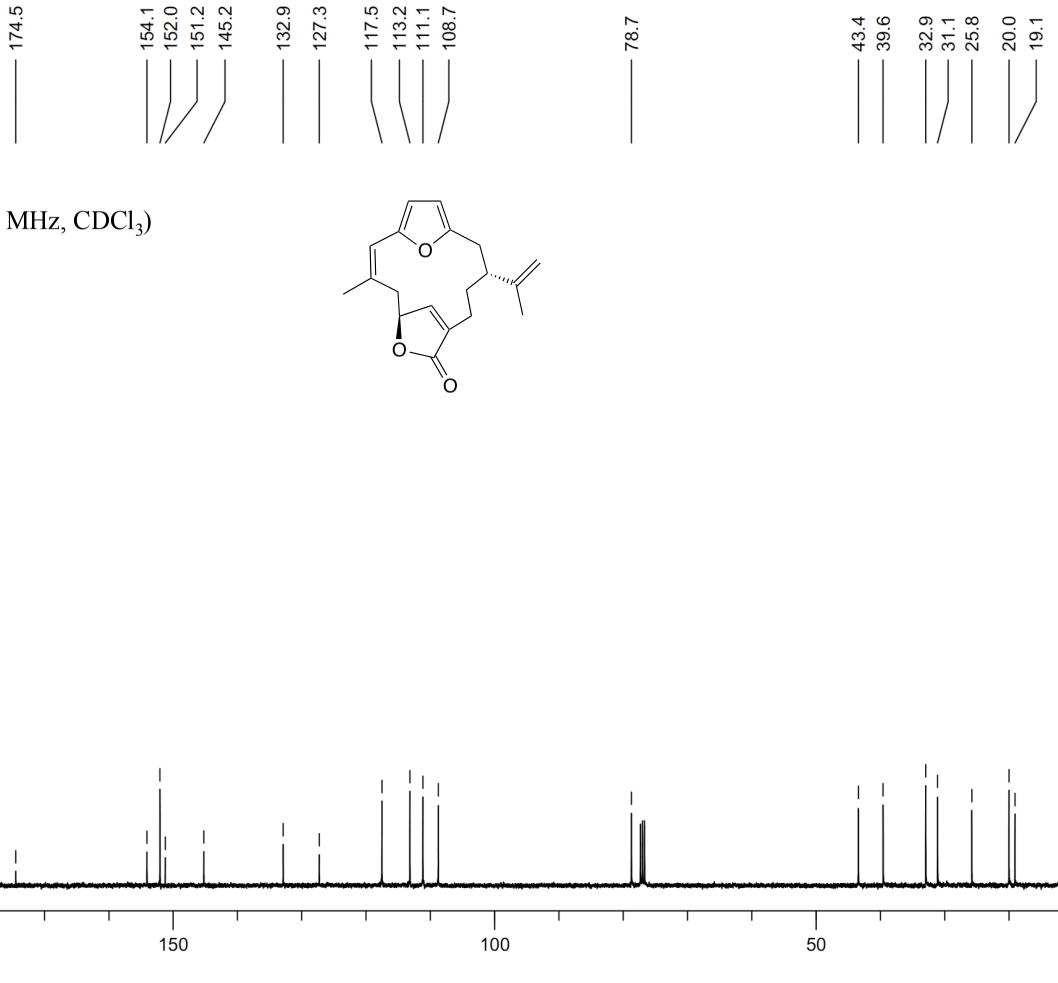
Spectrum 1.17: Compound 29: ^{1}H NMR



Spectrum 1.18: Compound 29: ^{13}C NMR

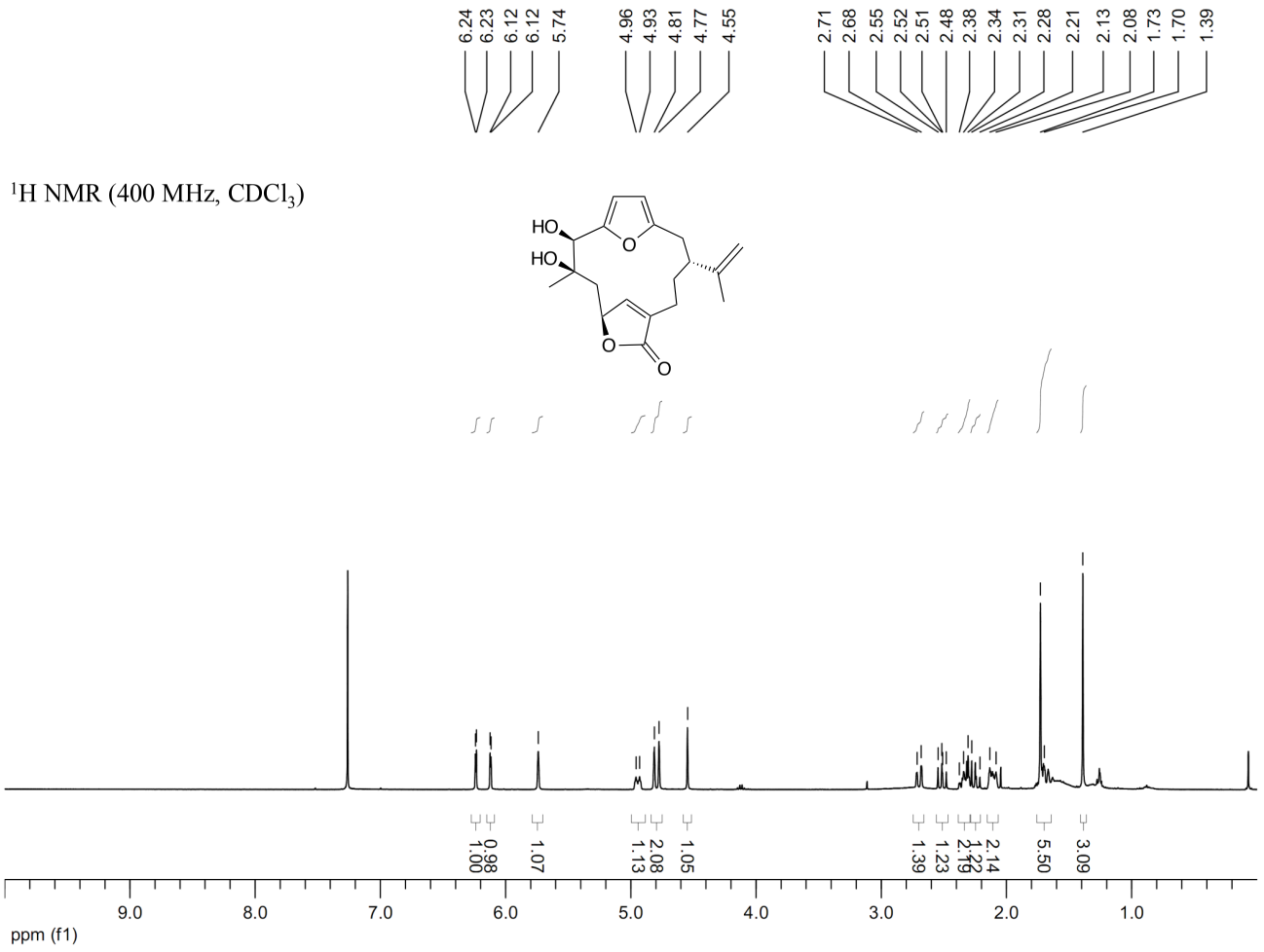


Spectrum 1.19: Compound 39: ^{1}H NMR

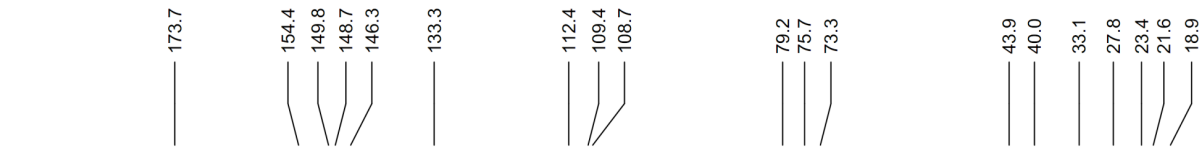


Spectrum 1.20: Compound 39: ^{13}C NMR

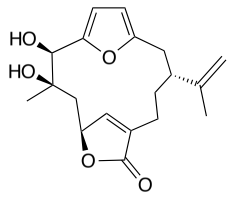
^{1}H NMR (400 MHz, $CDCl_3$)

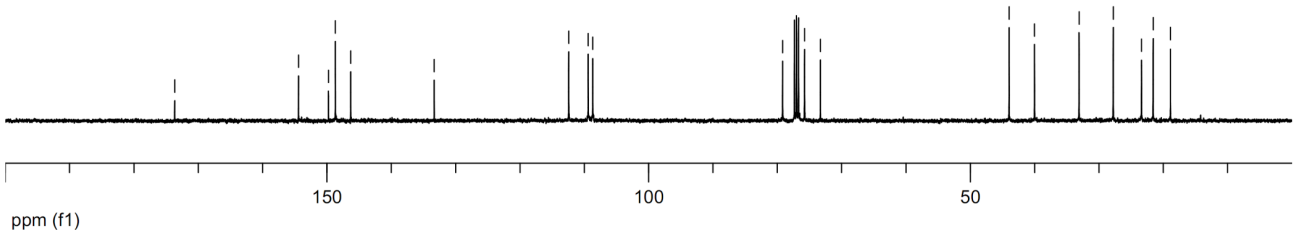


Spectrum 1.21: Compound 40: ^{1}H NMR

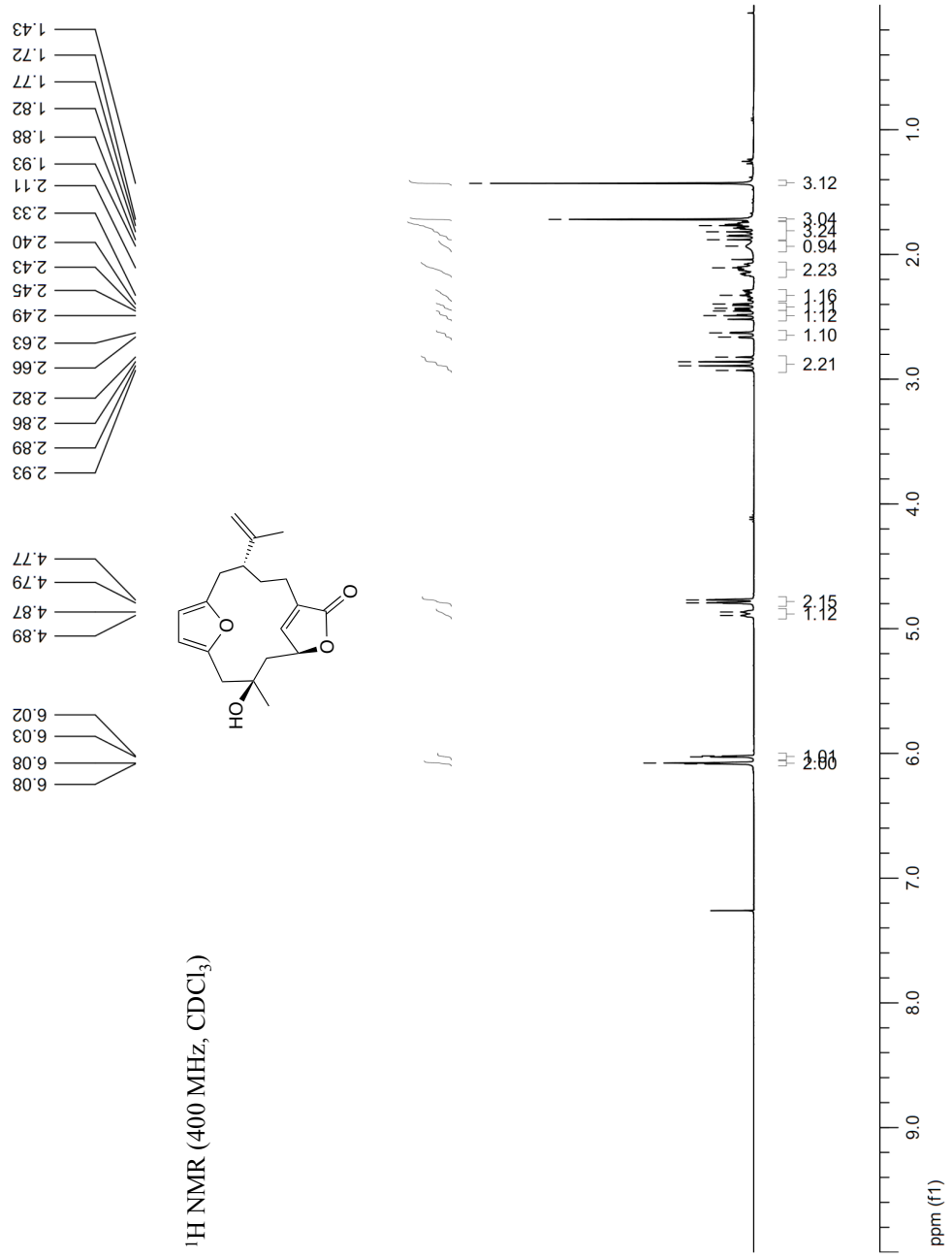


^{13}C NMR (100 MHz, $CDCl_3$)

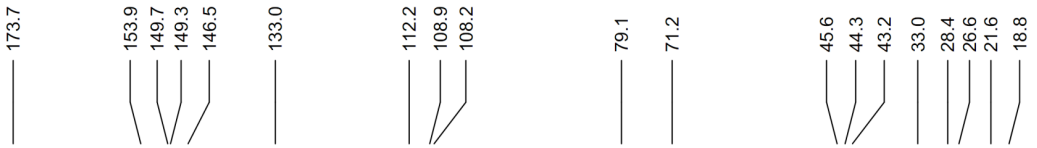




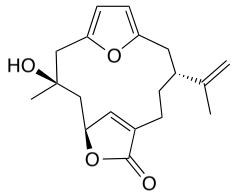
Spectrum 1.22: Compound 40: ^{13}C NMR

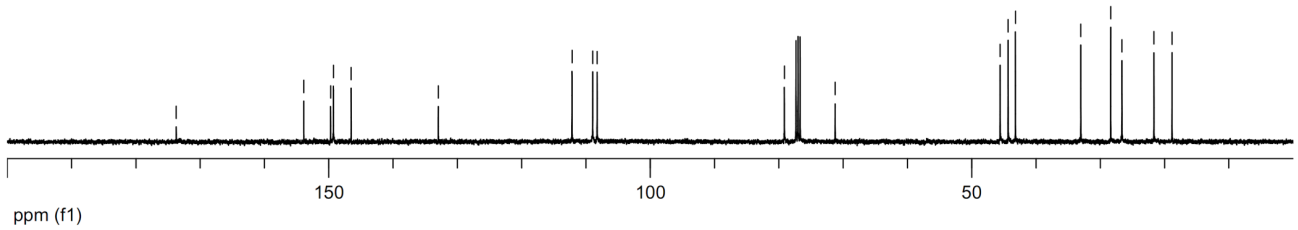


Spectrum 1.23: Compound 41: ^{1}H NMR

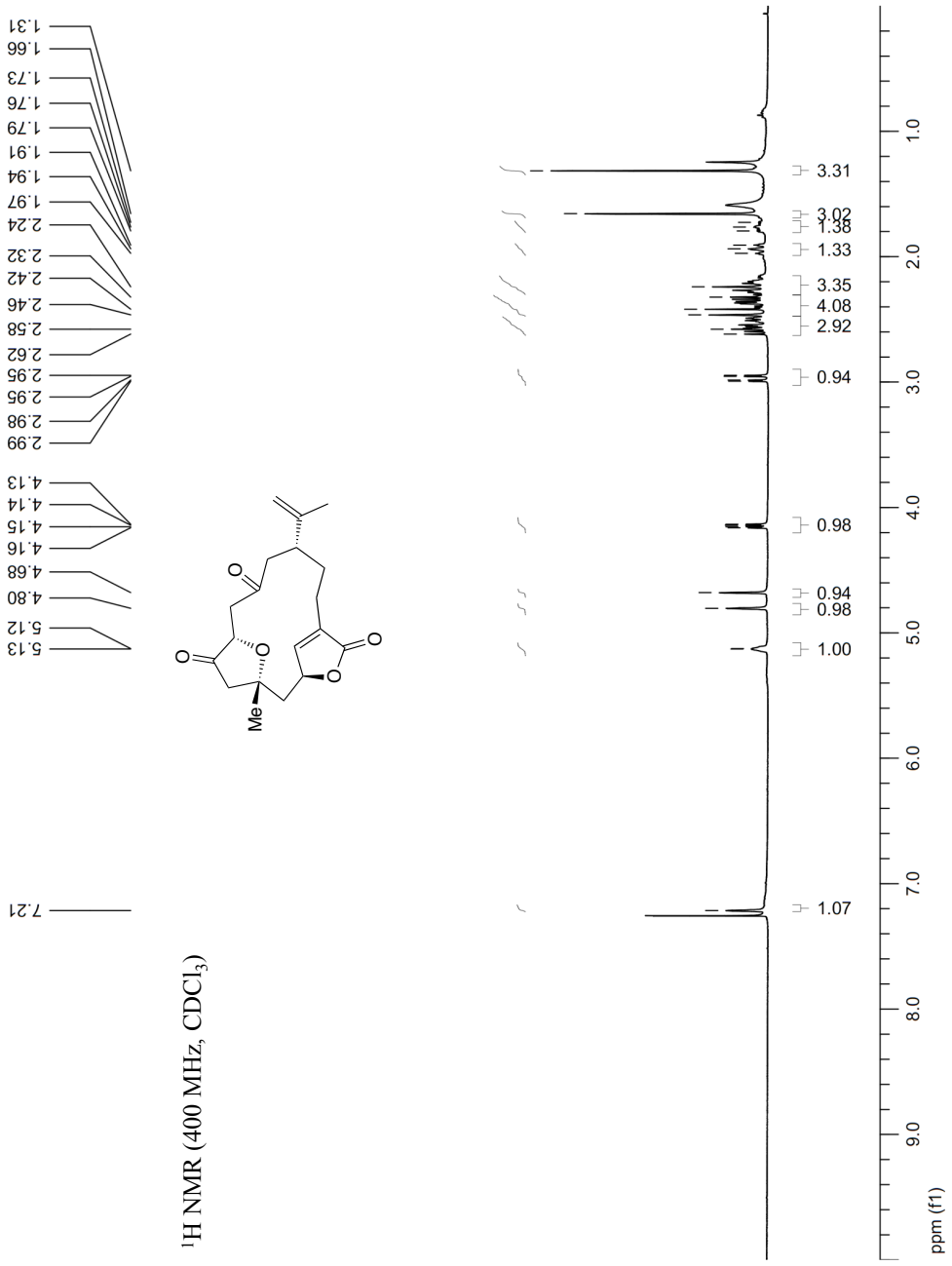


^{13}C NMR (100 MHz, $CDCl_3$)

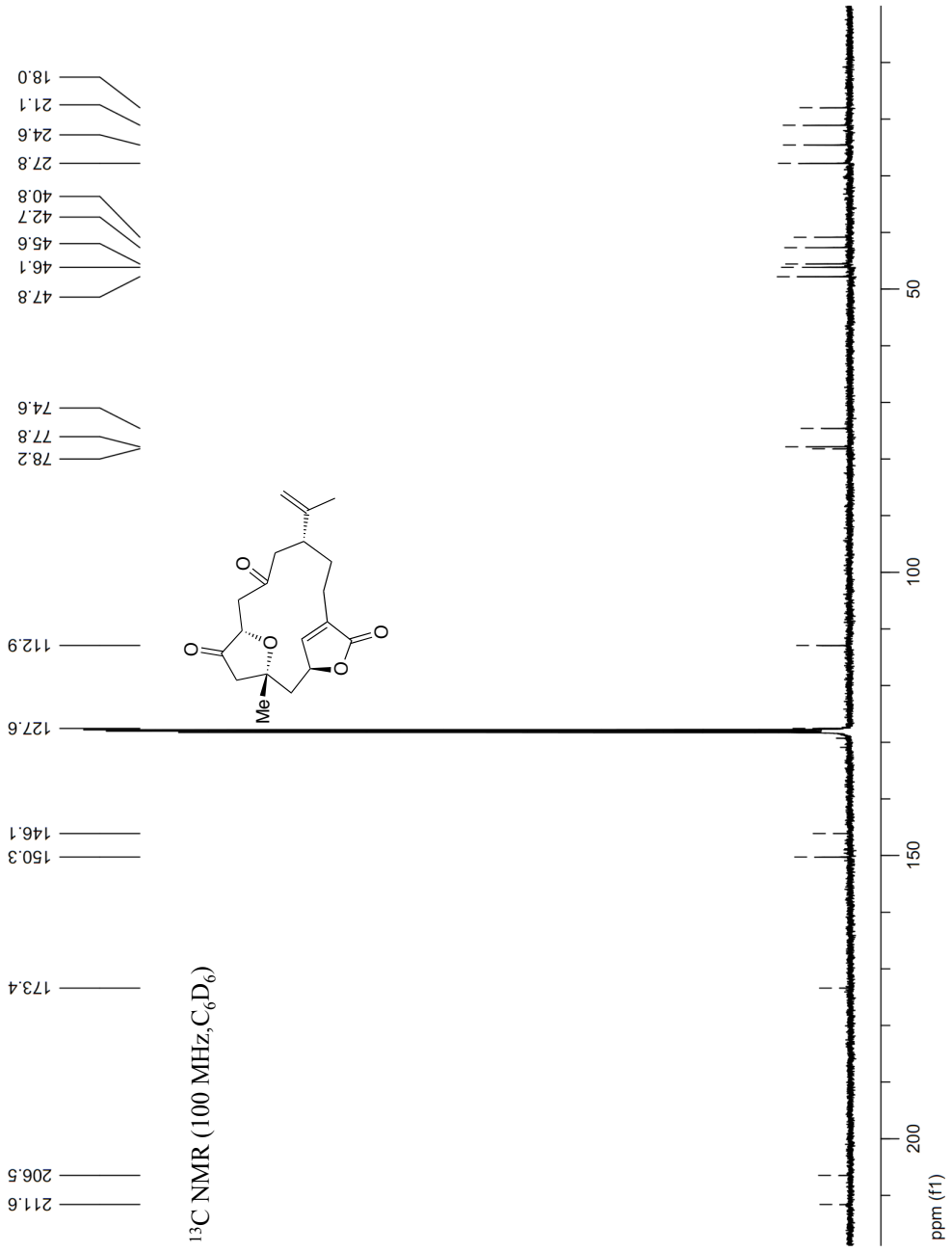




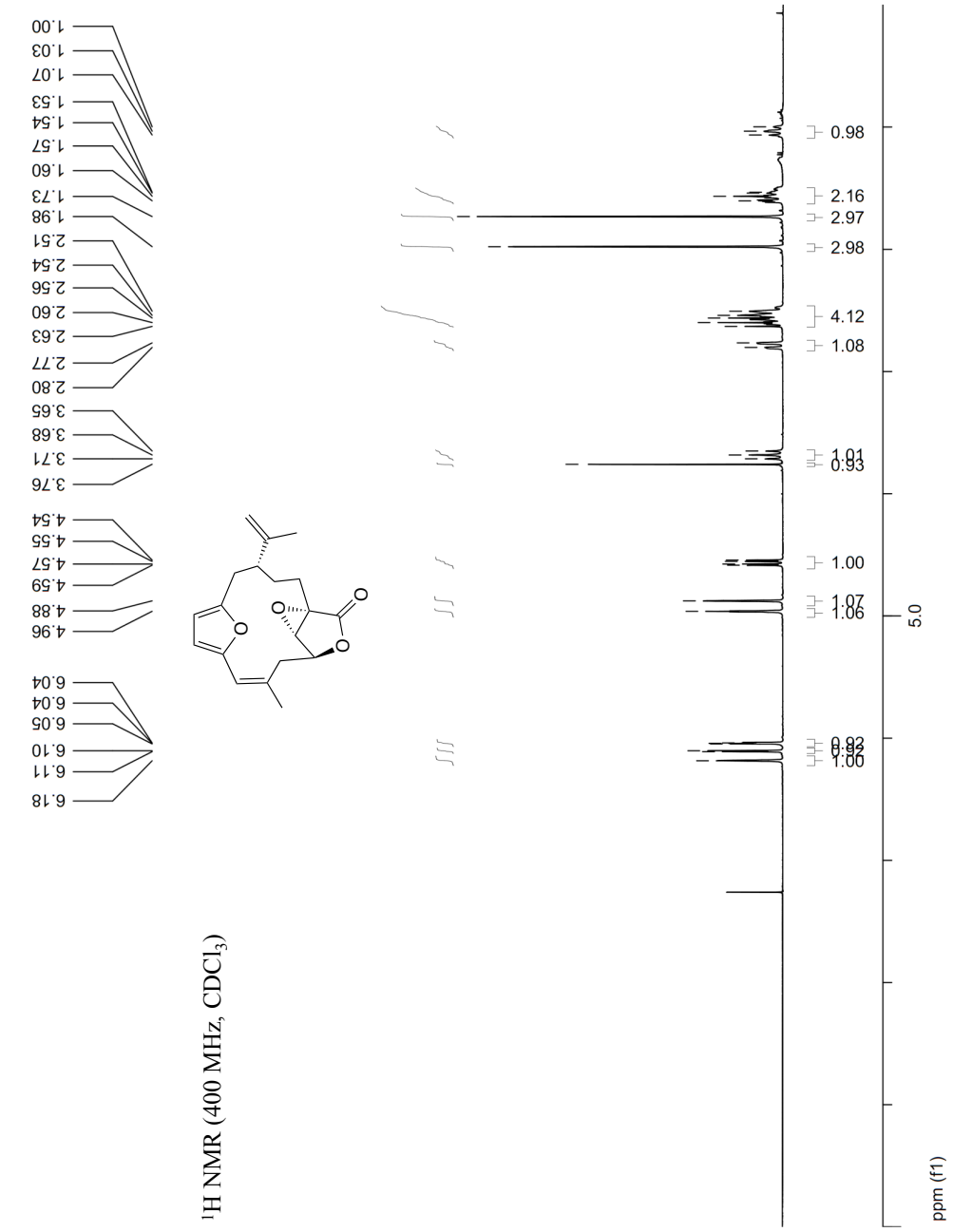
Spectrum 1.24: Compound 41: ^{13}C NMR



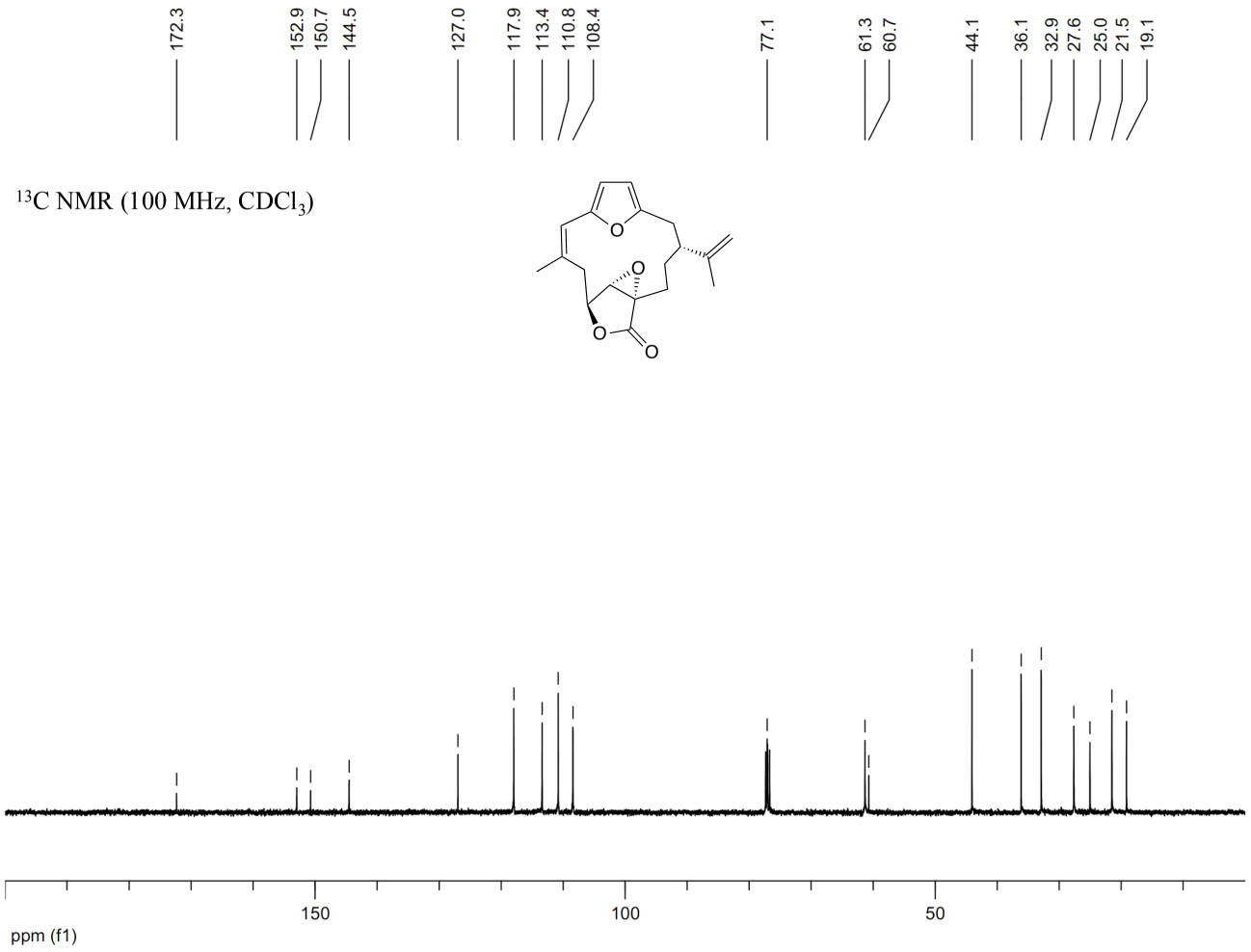
Spectrum 1.25: Compound 2: ^{1}H NMR



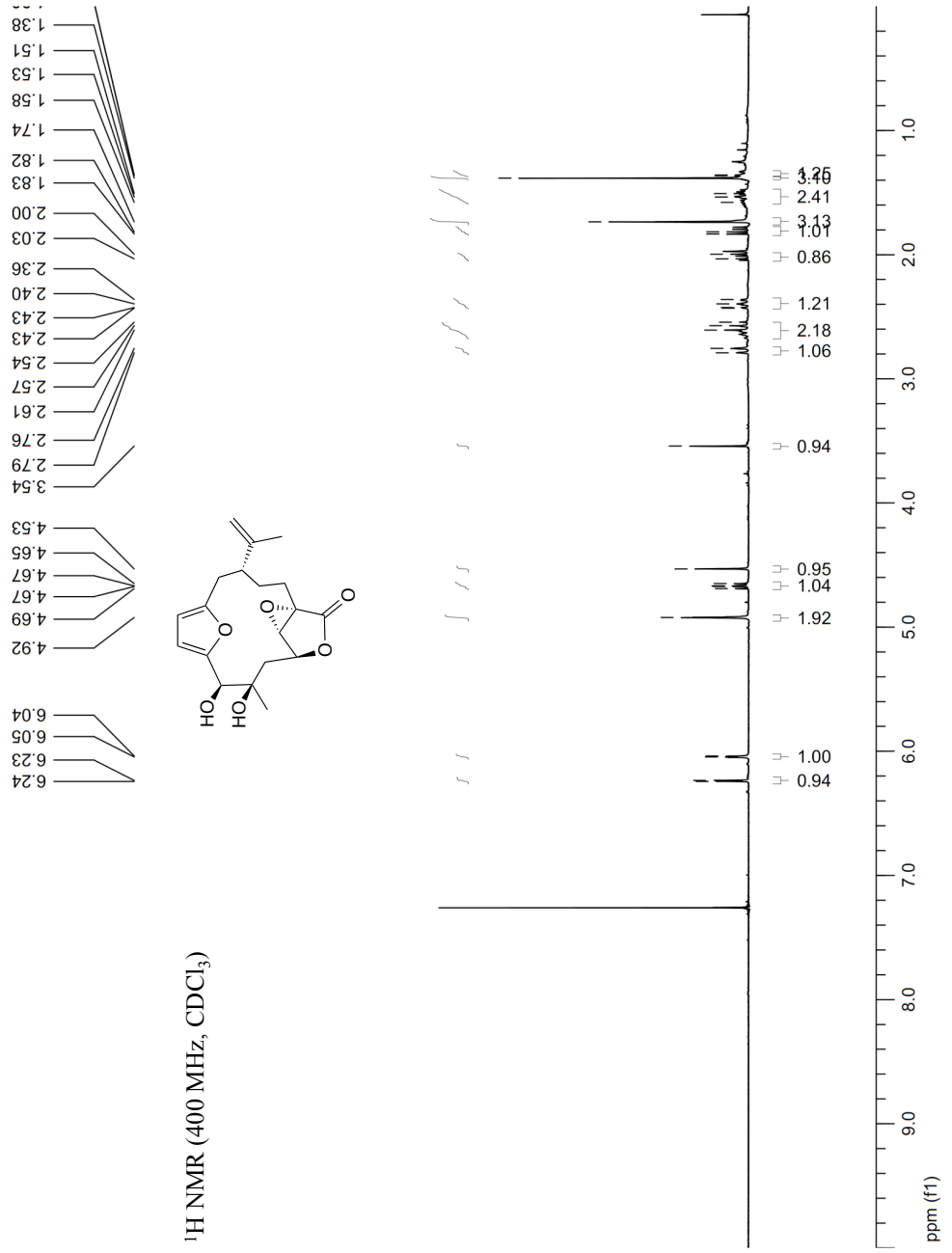
Spectrum 1.26: Compound 2: ^{13}C NMR



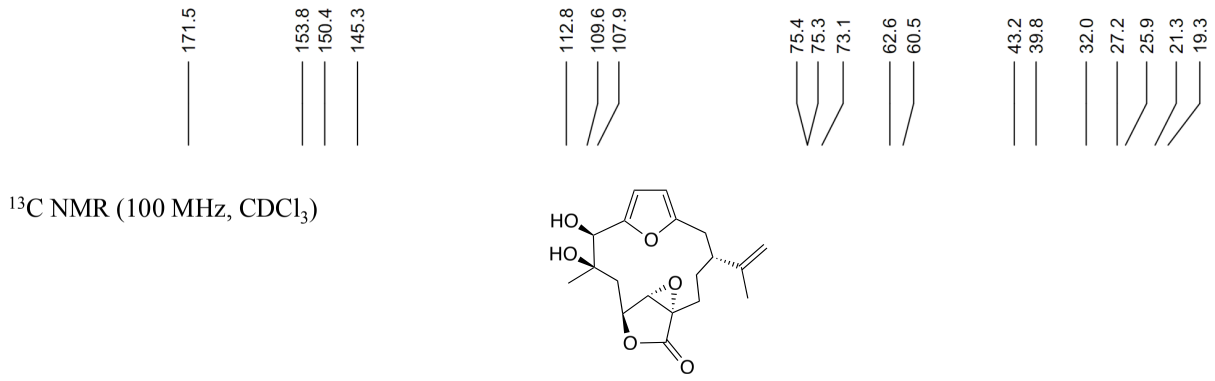
Spectrum 1.27: Compound 42: ^{1}H NMR



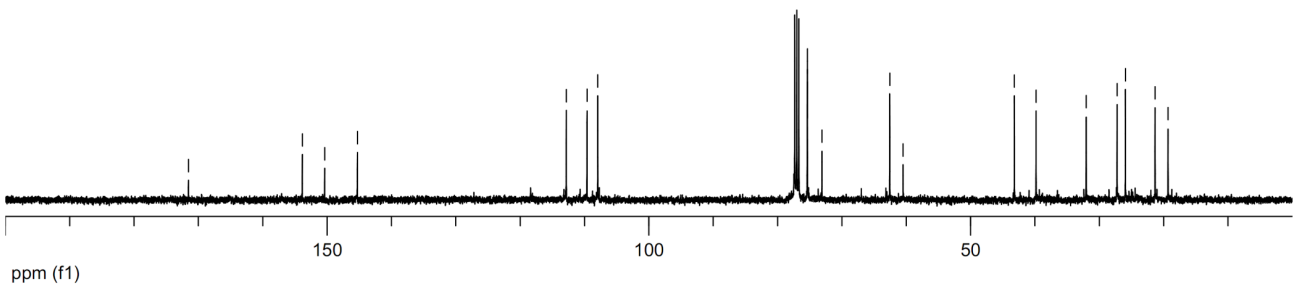
Spectrum 1.28: Compound 42: ^{13}C NMR



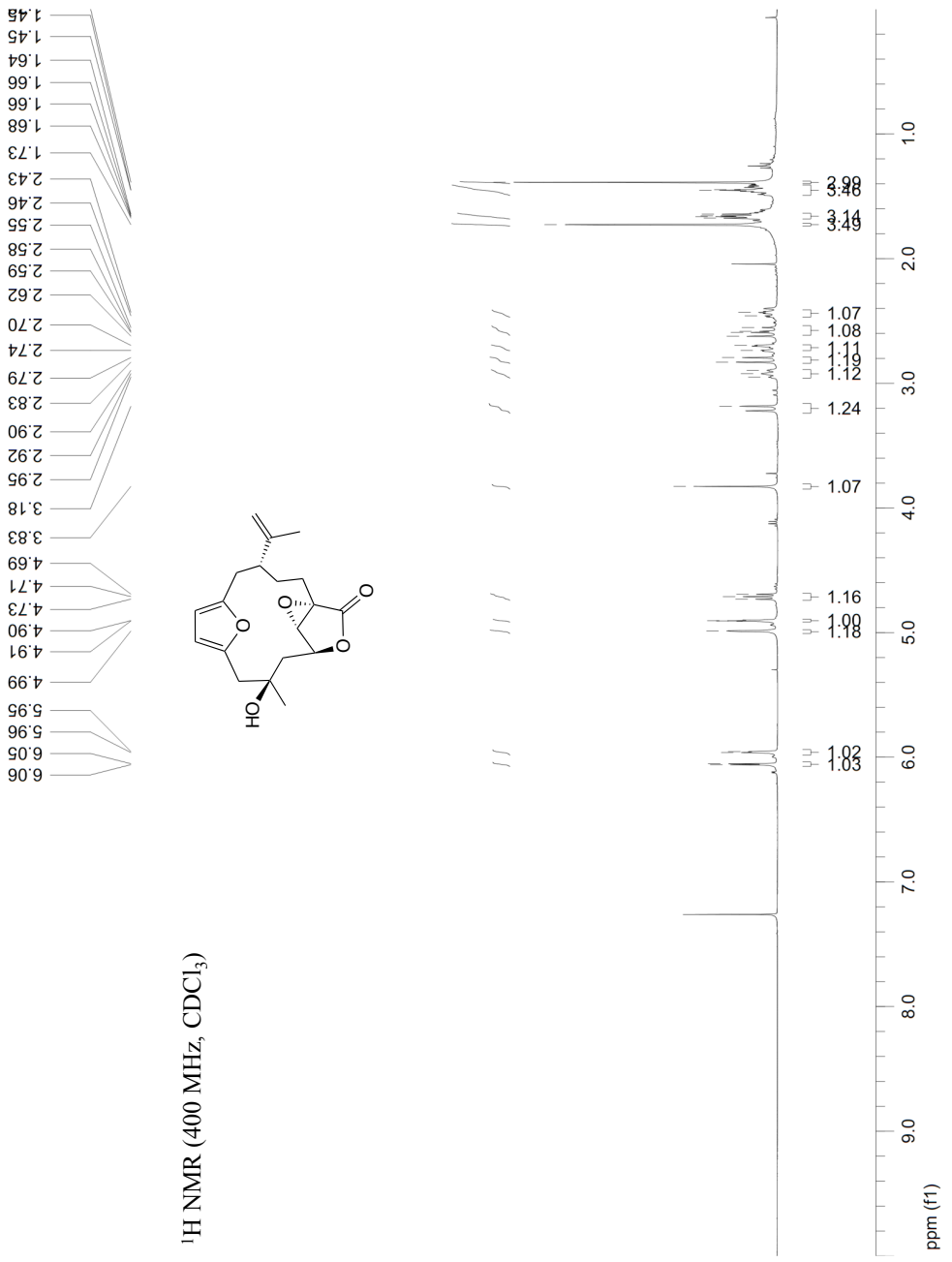
Spectrum 1.29: Compound 43: ^{1}H NMR



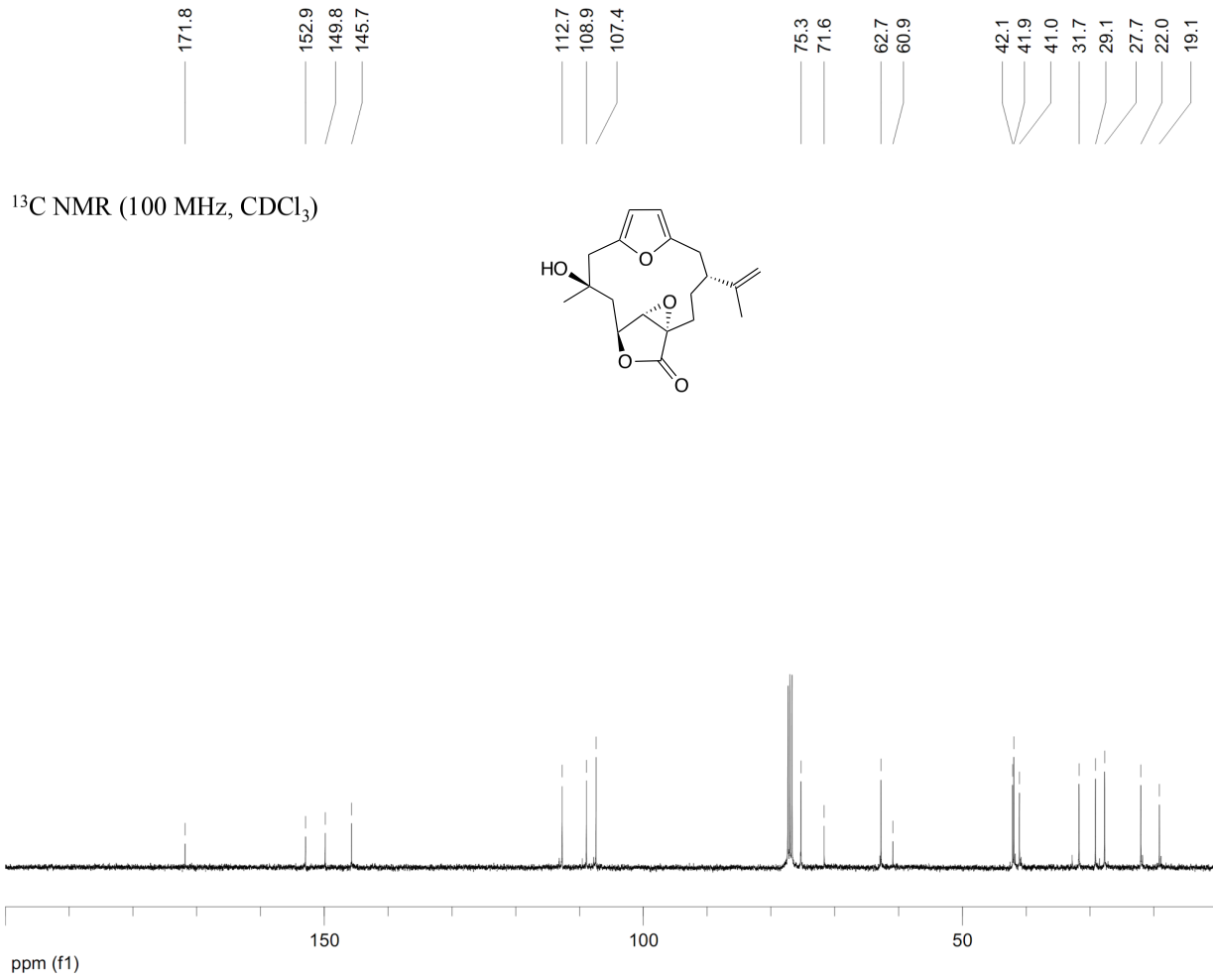
^{13}C NMR (100 MHz, $CDCl_3$)



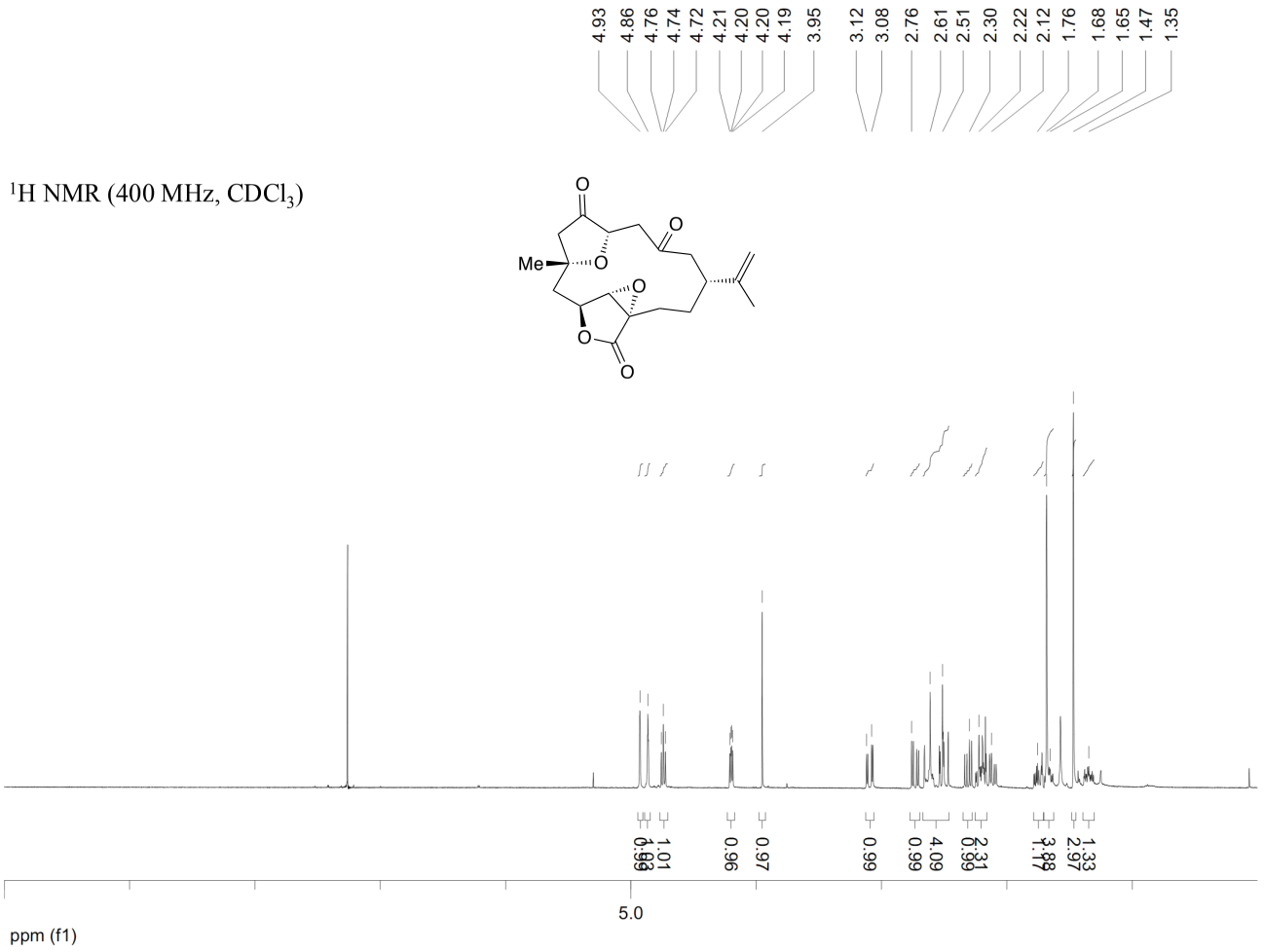
Spectrum 1.30: Compound 43: ^{13}C NMR



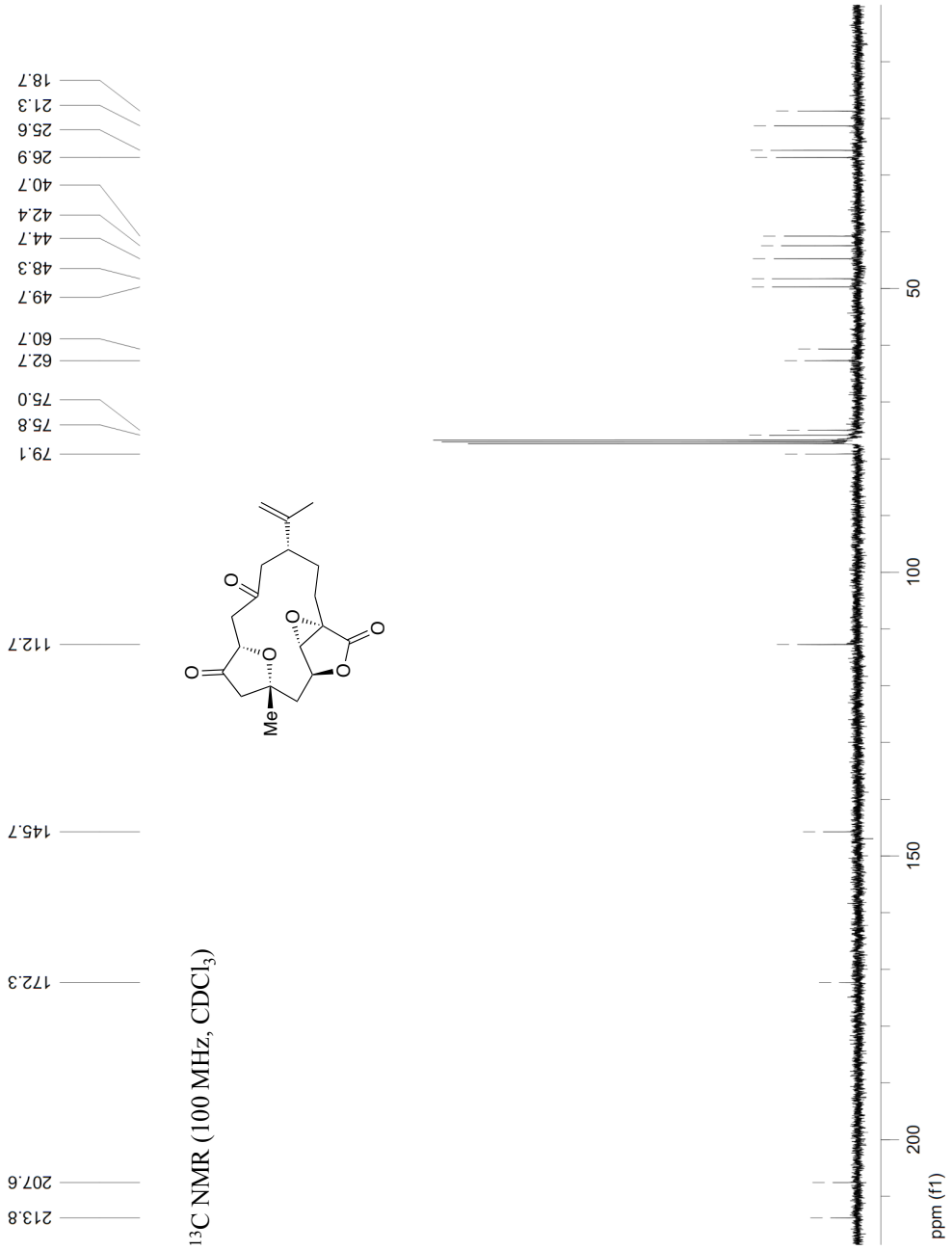
Spectrum 1.31: Compound 44: ^{1}H NMR



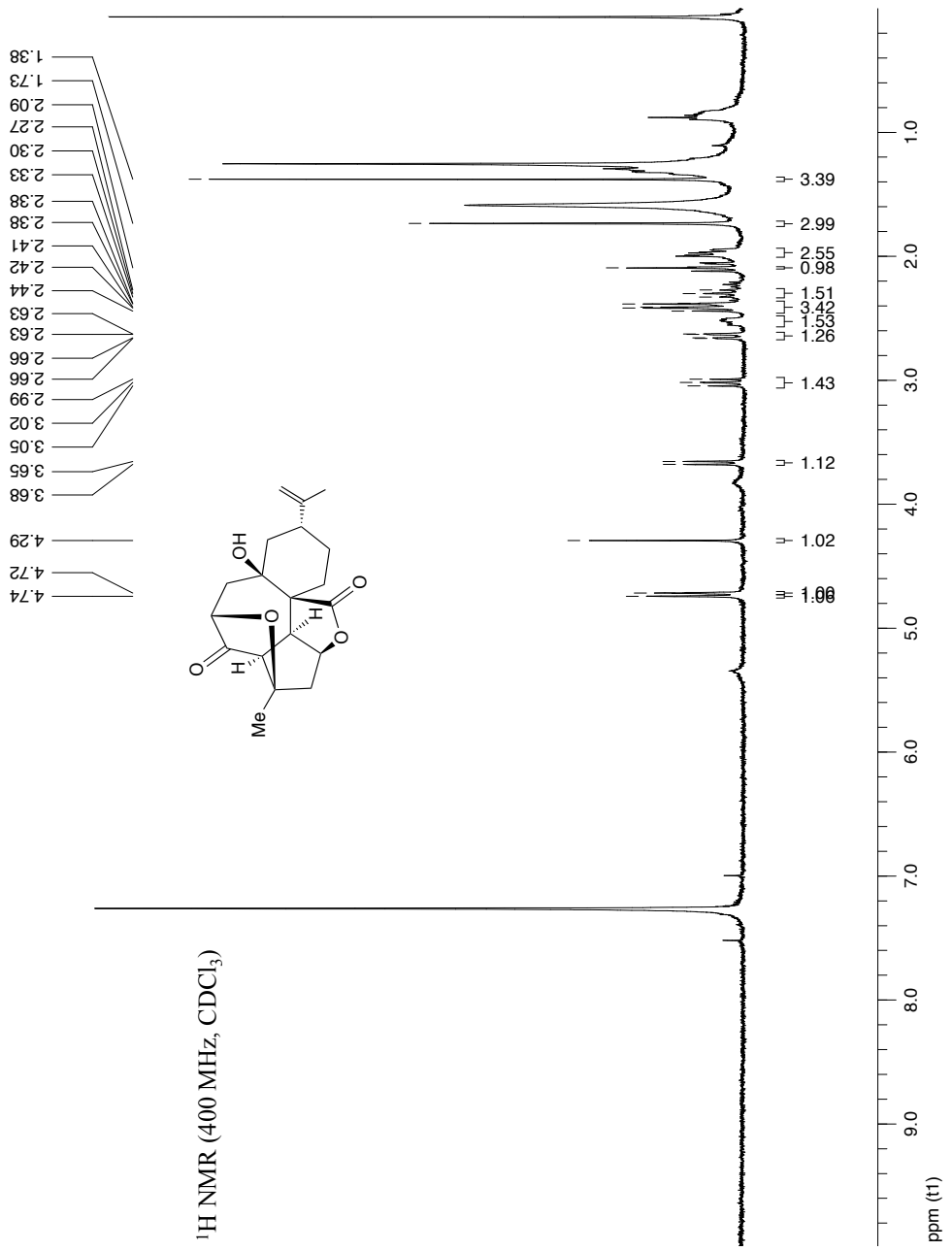
Spectrum 1.32: Compound 44: ^{13}C NMR



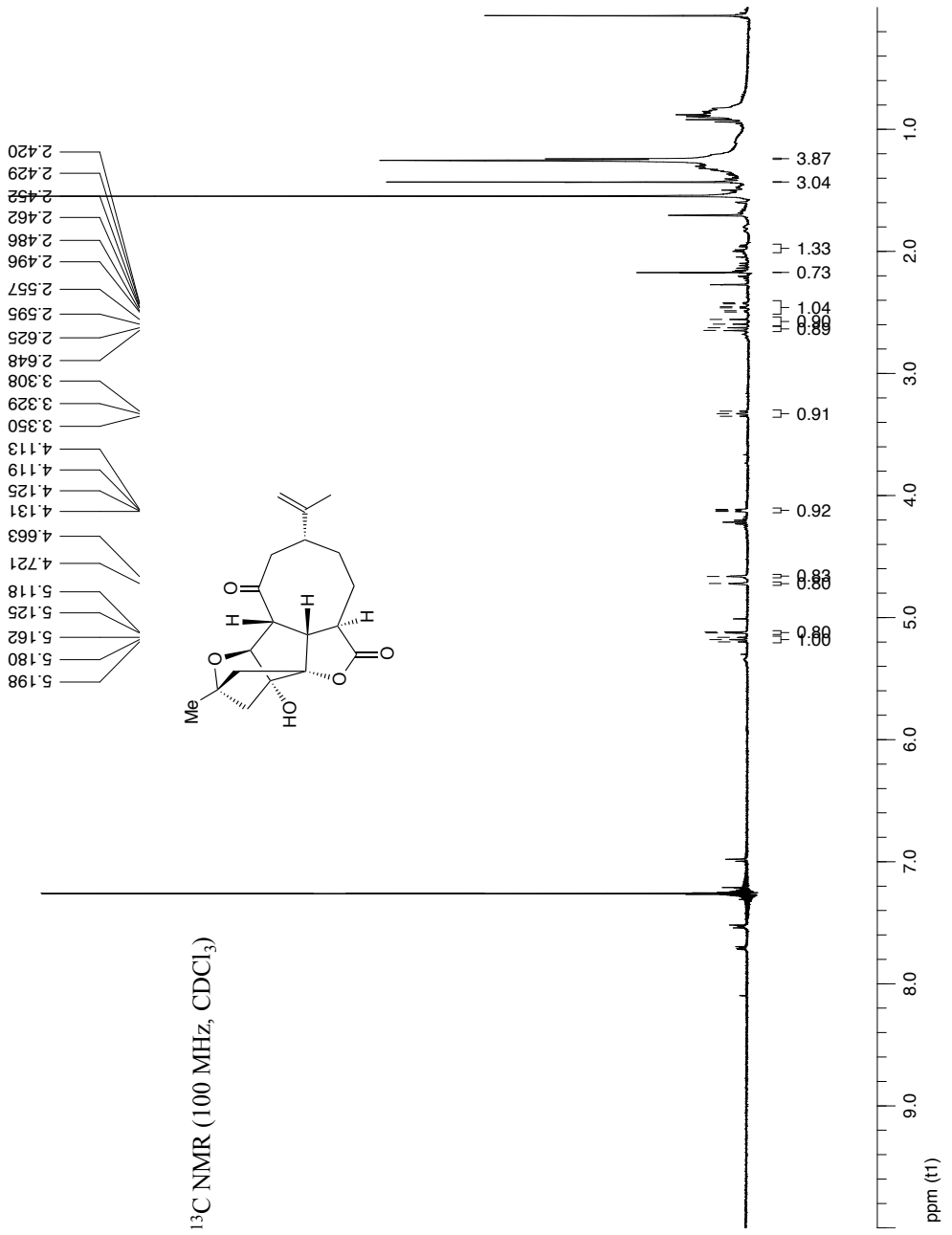
Spectrum 1.33: Compound 3: ^{1}H NMR



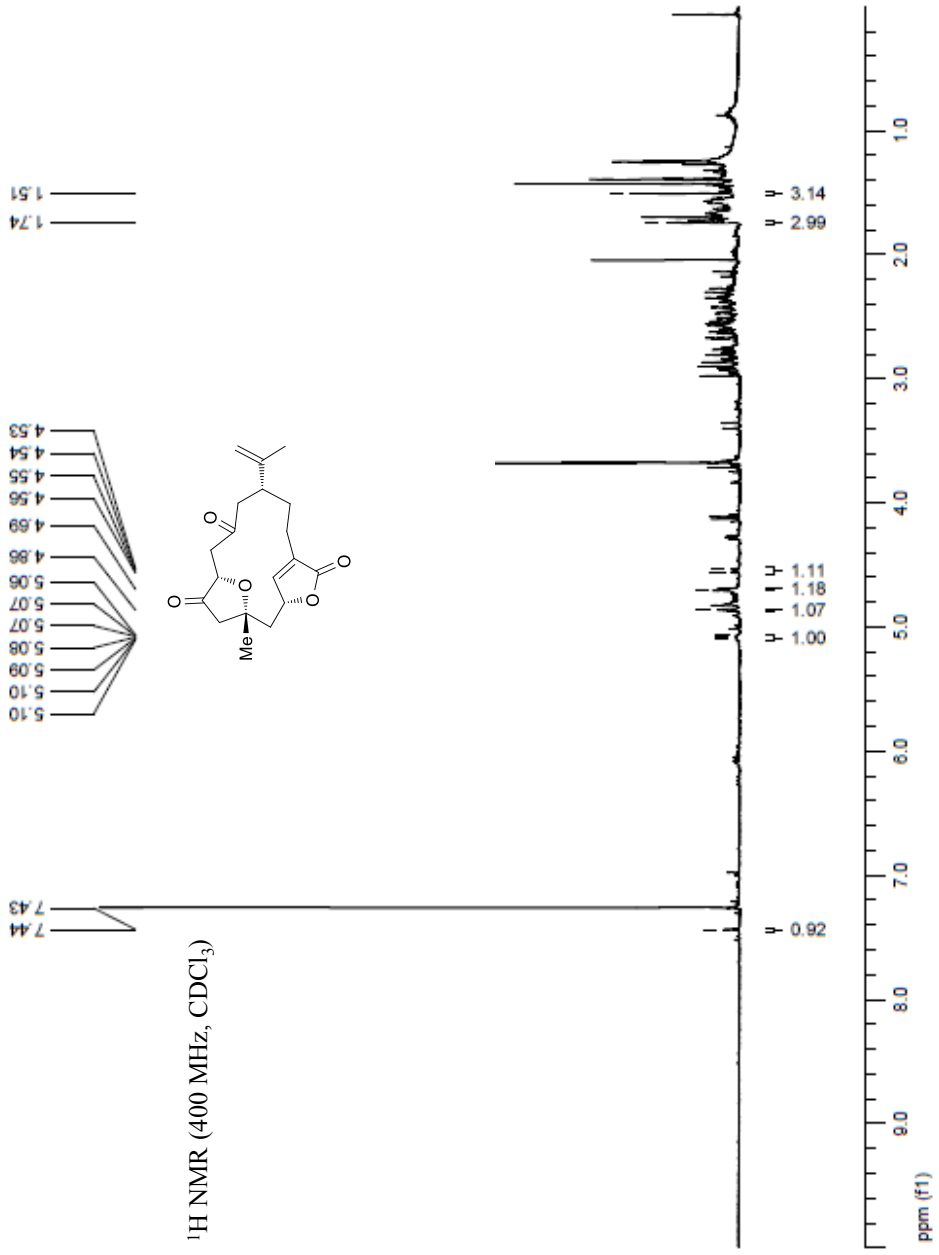
Spectrum 1.34: Compound 3: ^{13}C NMR



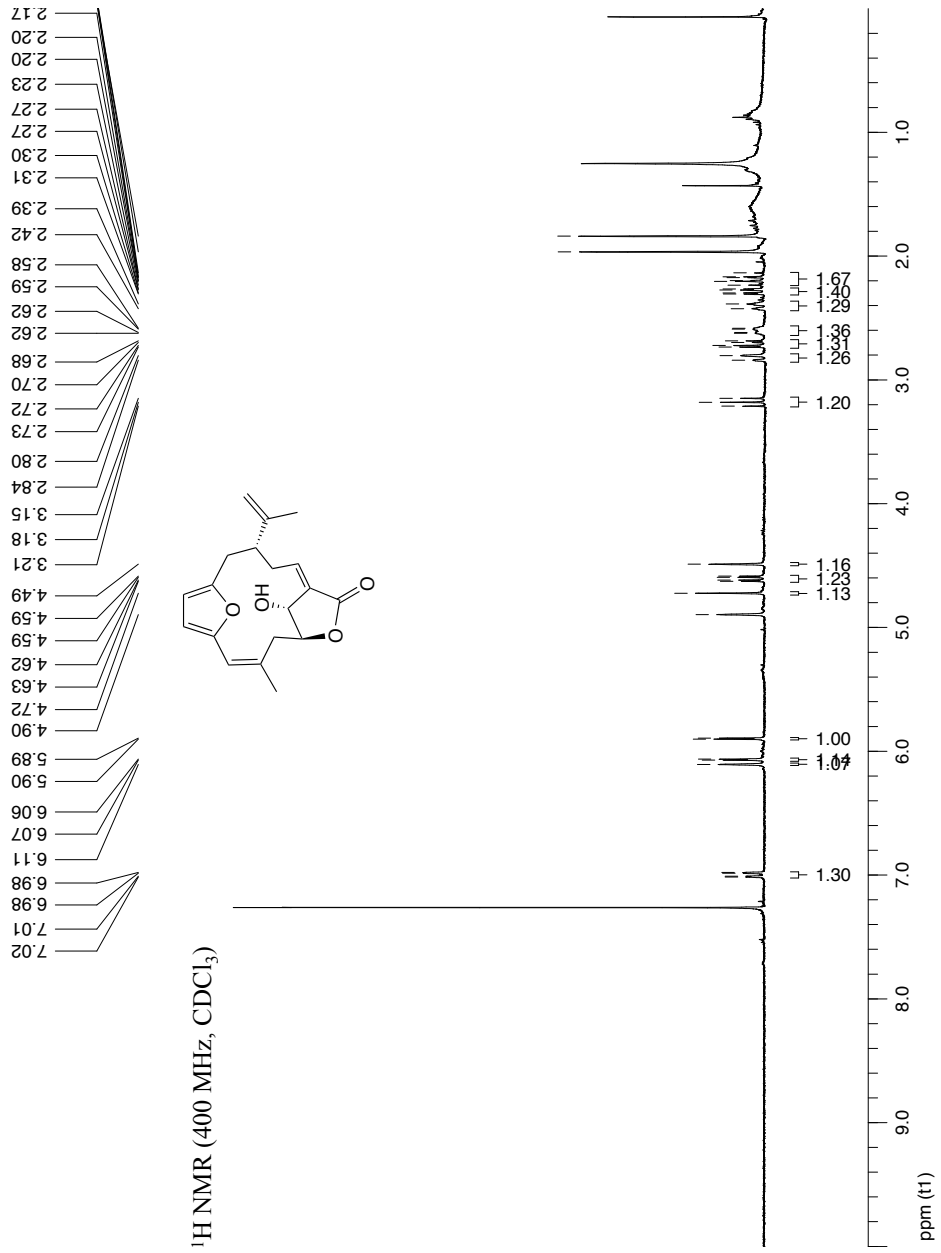
Spectrum 1.35: Compound 46: ^{1}H NMR



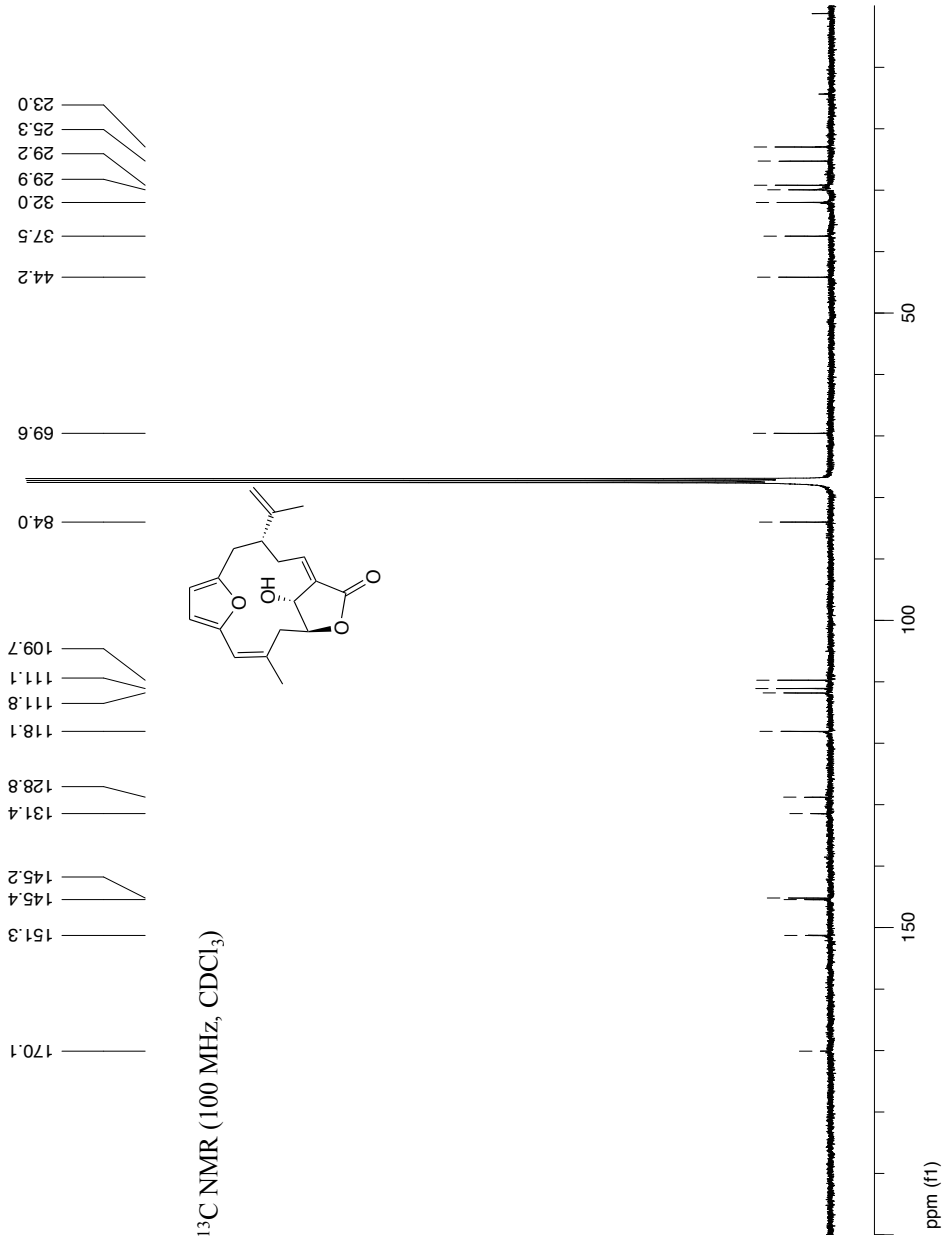
Spectrum 1.36: Compound 47: ^{13}H NMR



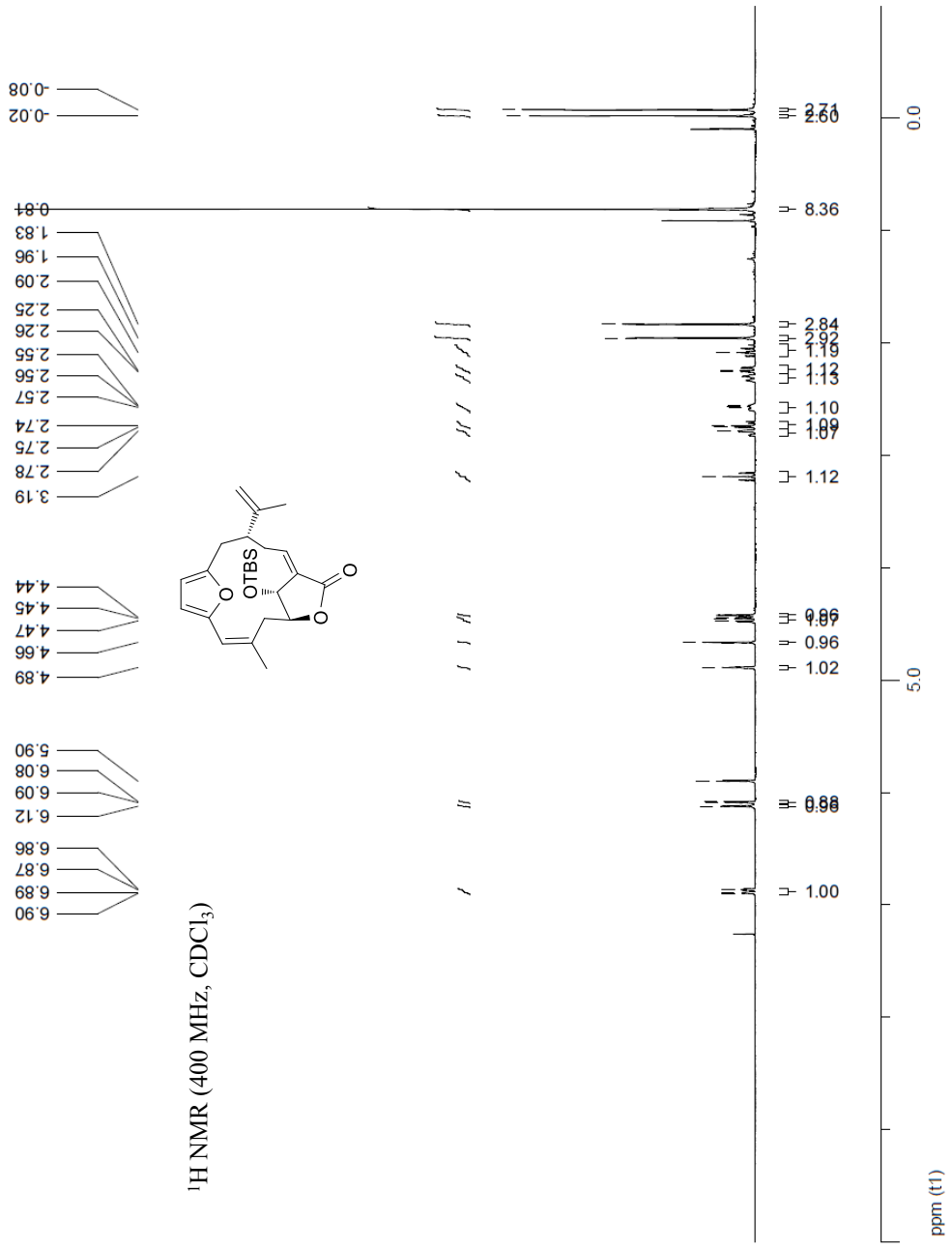
Spectrum 1.37: Compound 48: ^{1}H NMR



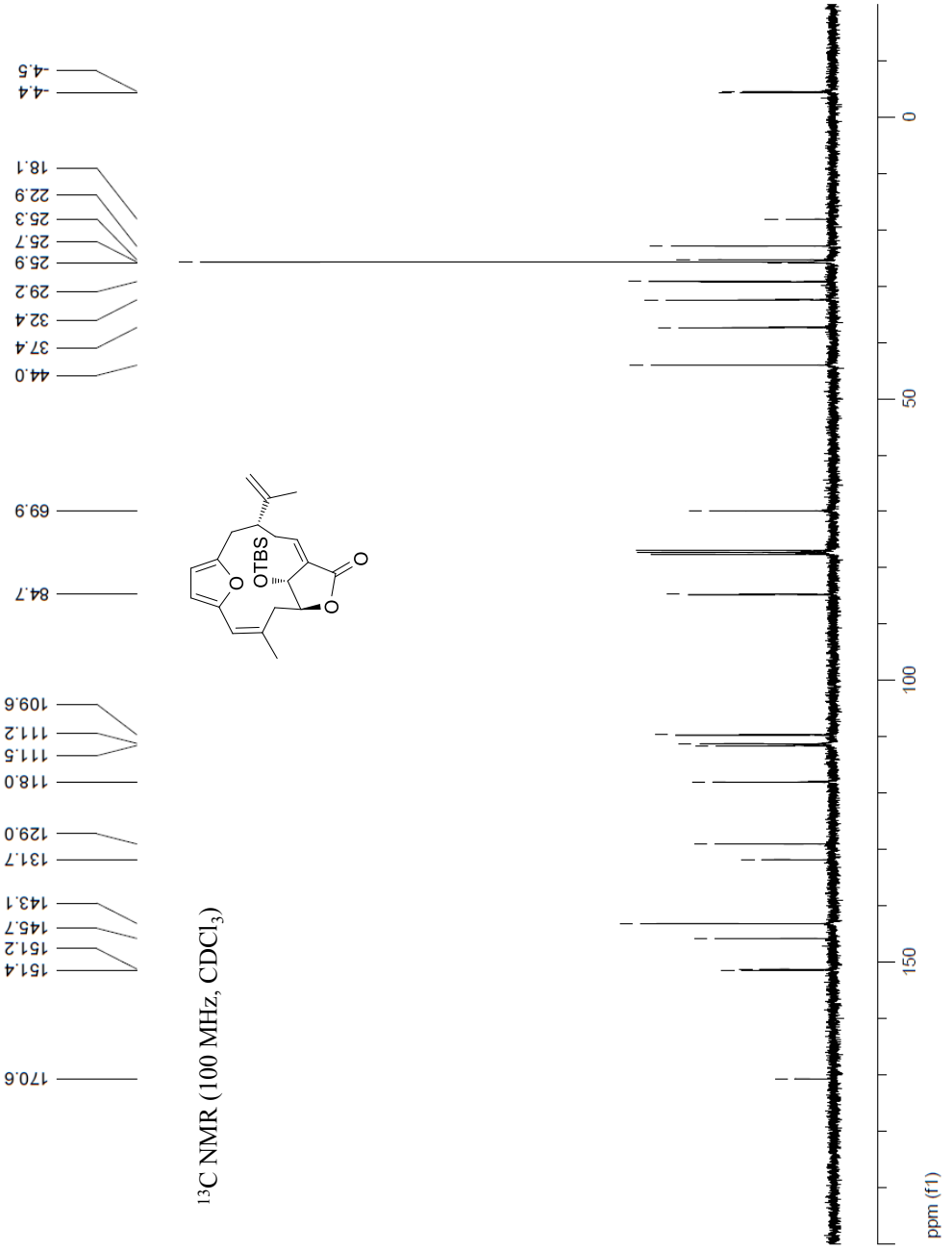
Spectrum 1.38: Compound 49: ^{13}H NMR



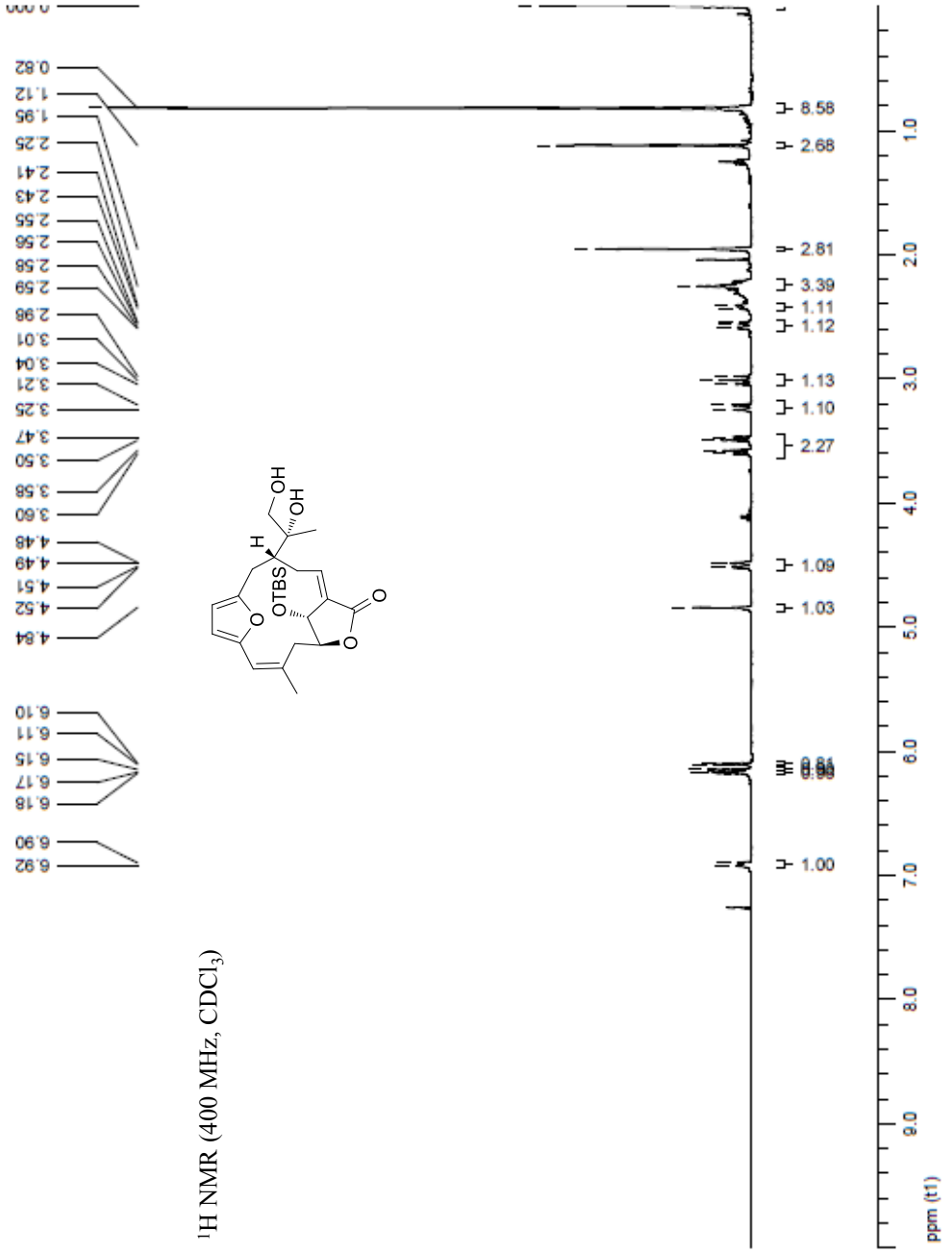
Spectrum 1.39: Compound 49: ^{1}C NMR



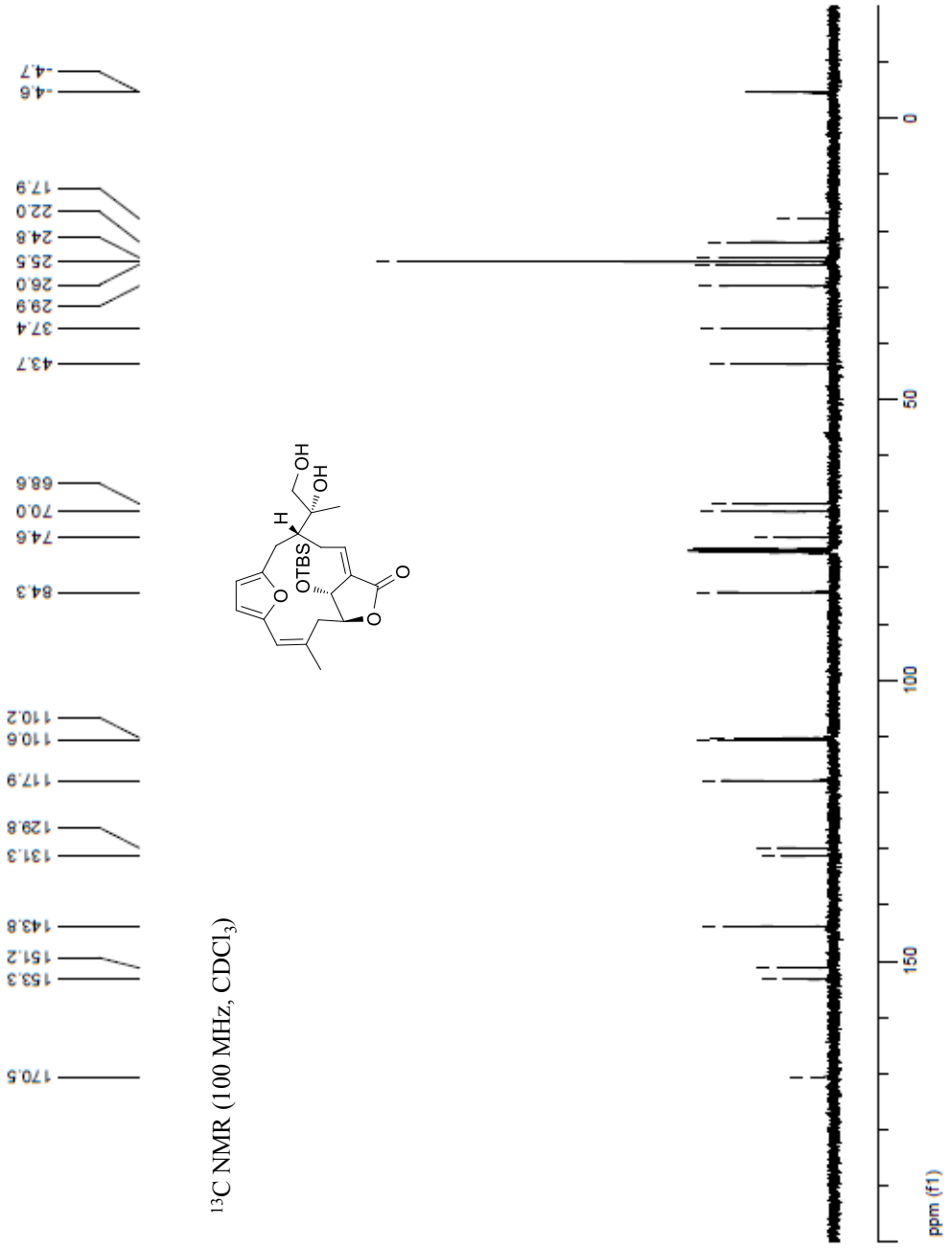
Spectrum 1.40: Compound 50: ^{13}H NMR



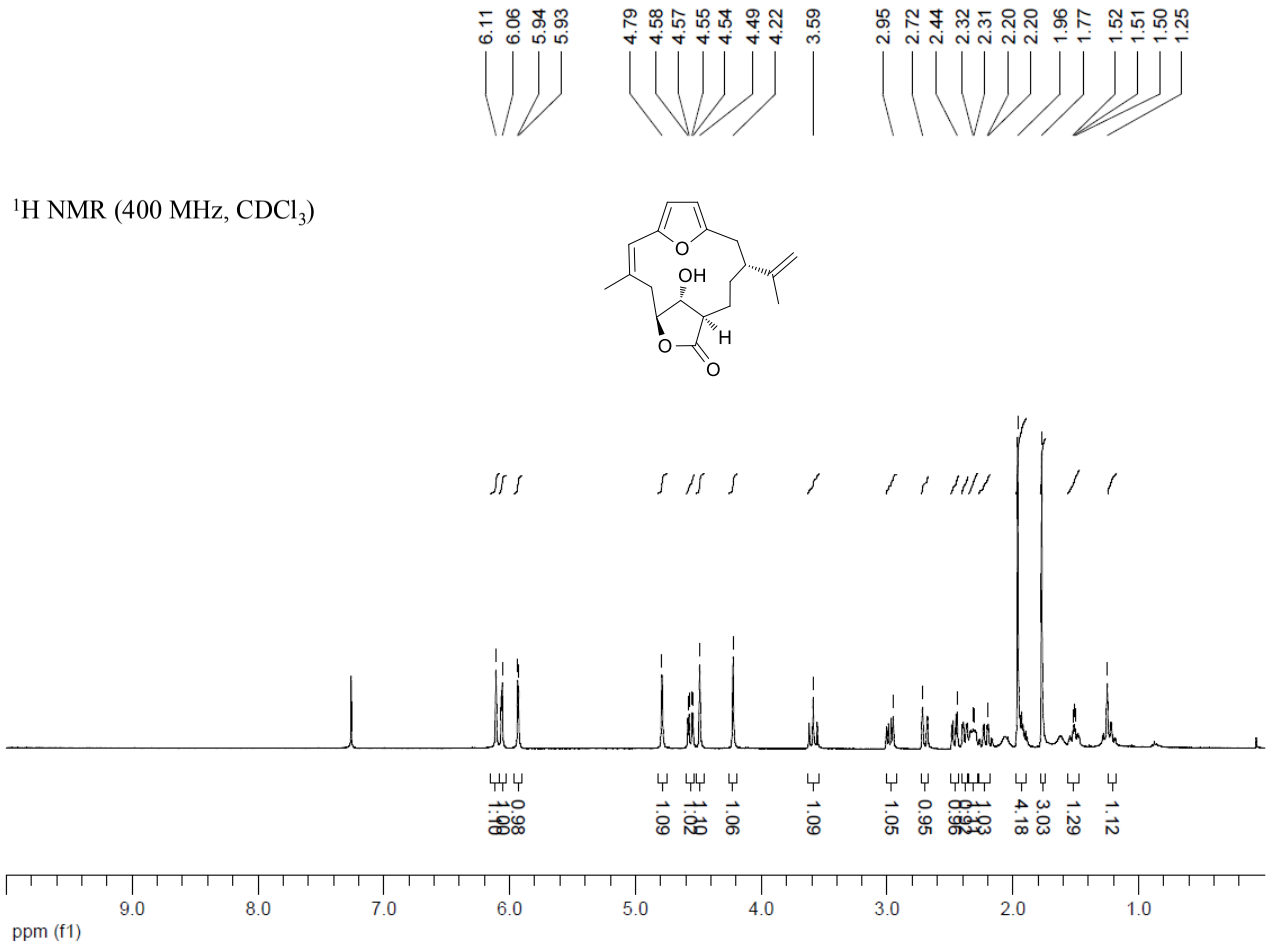
Spectrum 1.41: Compound 50: ^{1}C NMR



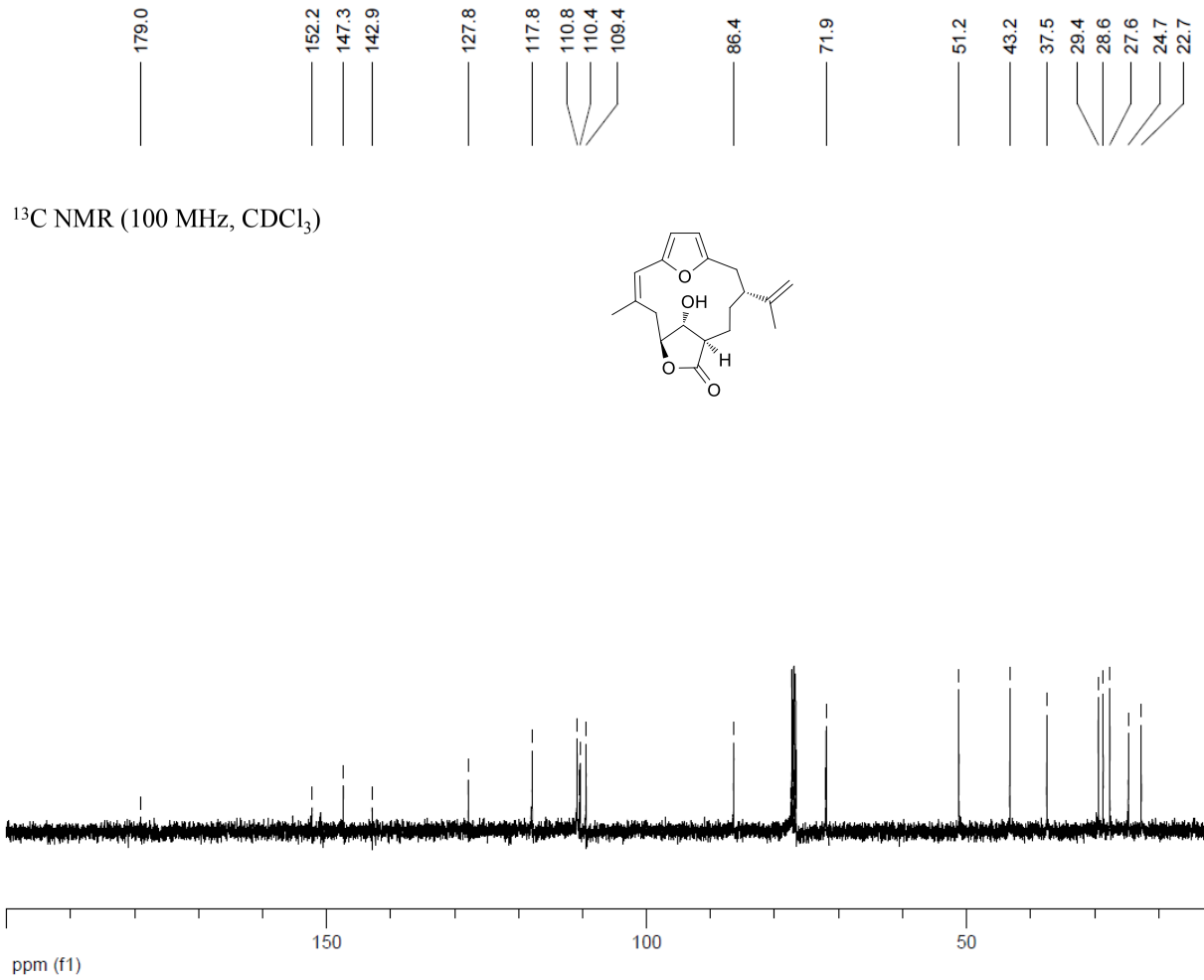
Spectrum 1.42: Compound 51: ^{13}H NMR



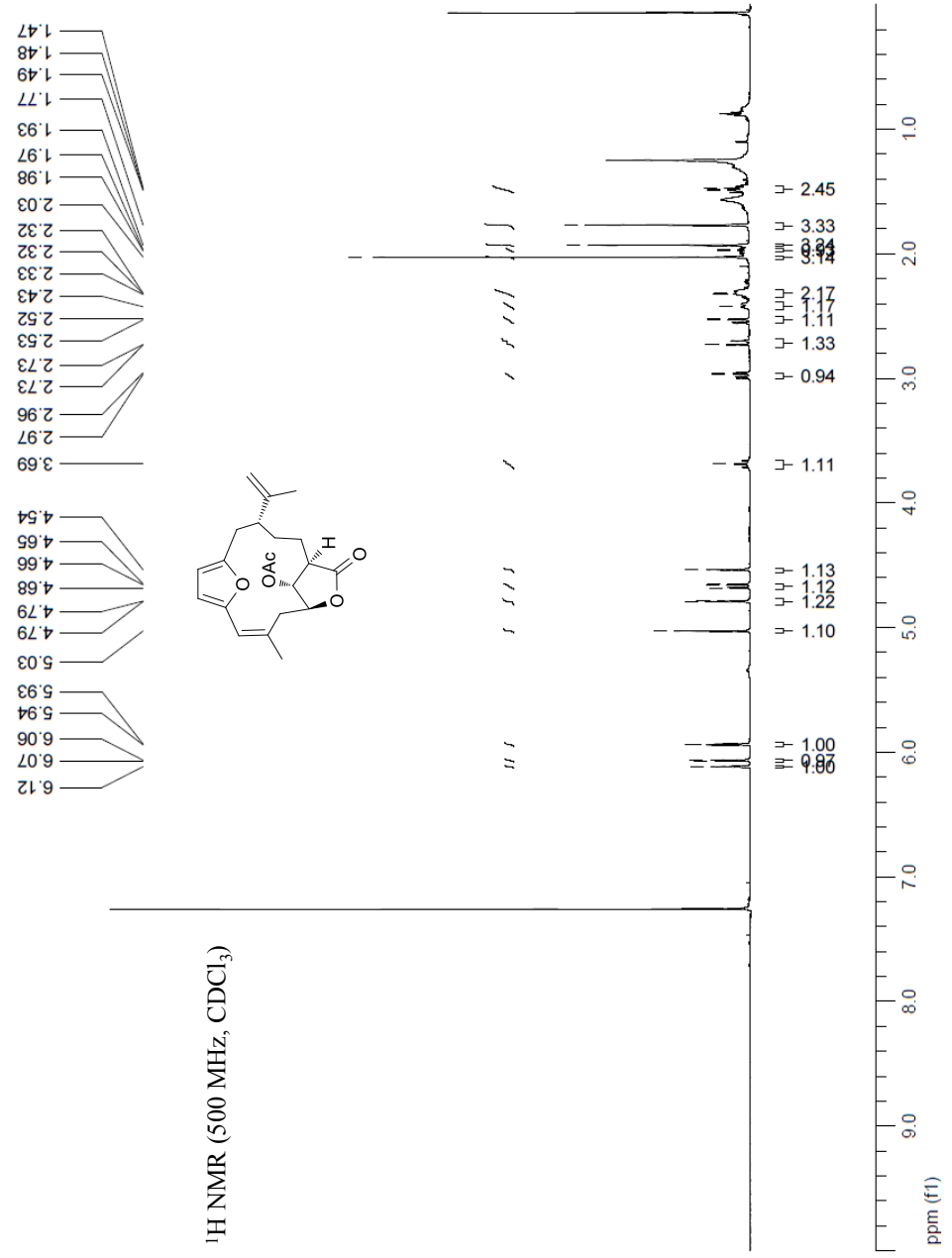
Spectrum 1.43: Compound 51: ^{1}C NMR



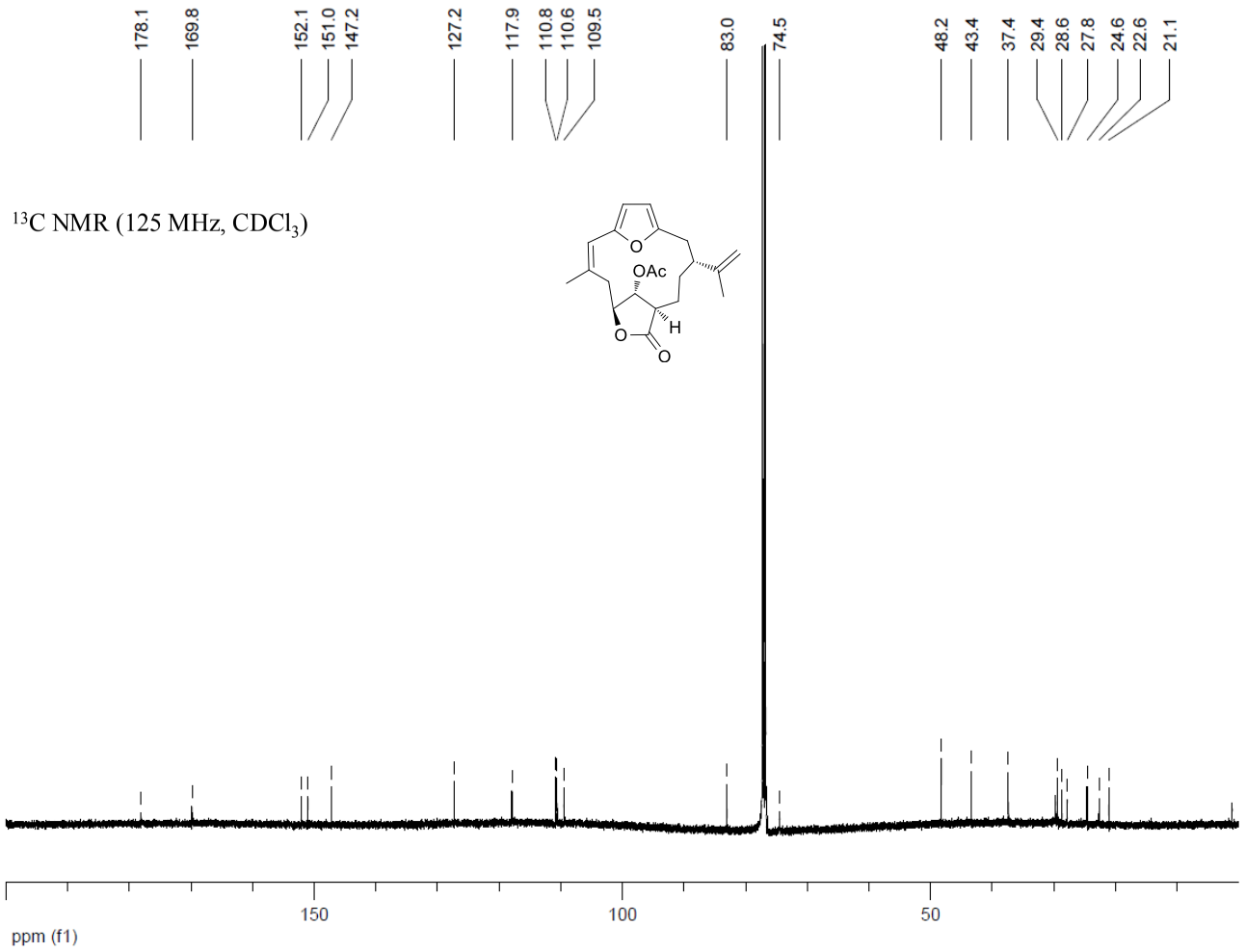
Spectrum 1.44: Compound 53: ^{13}H NMR



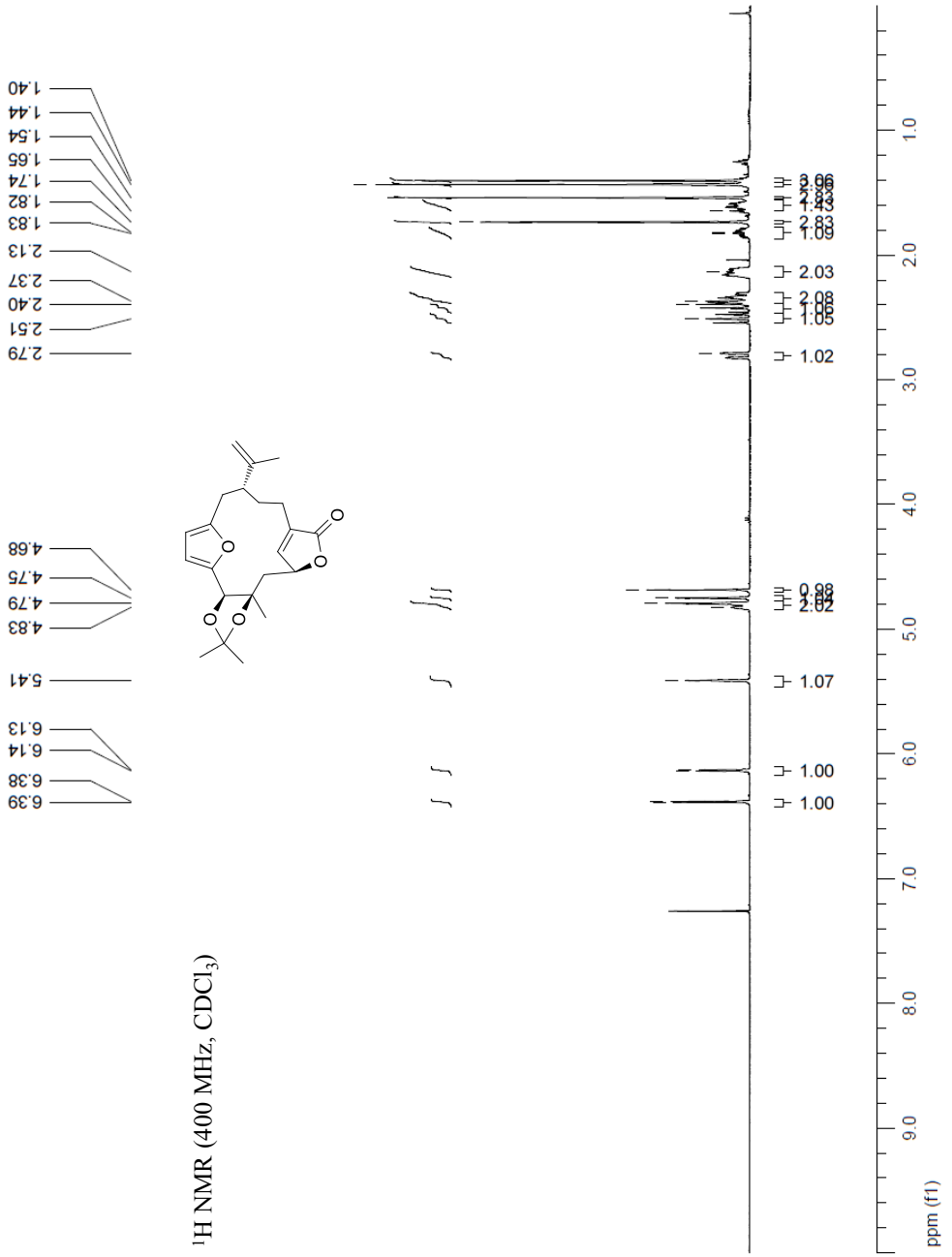
Spectrum 1.45: Compound 53: ^{1}C NMR



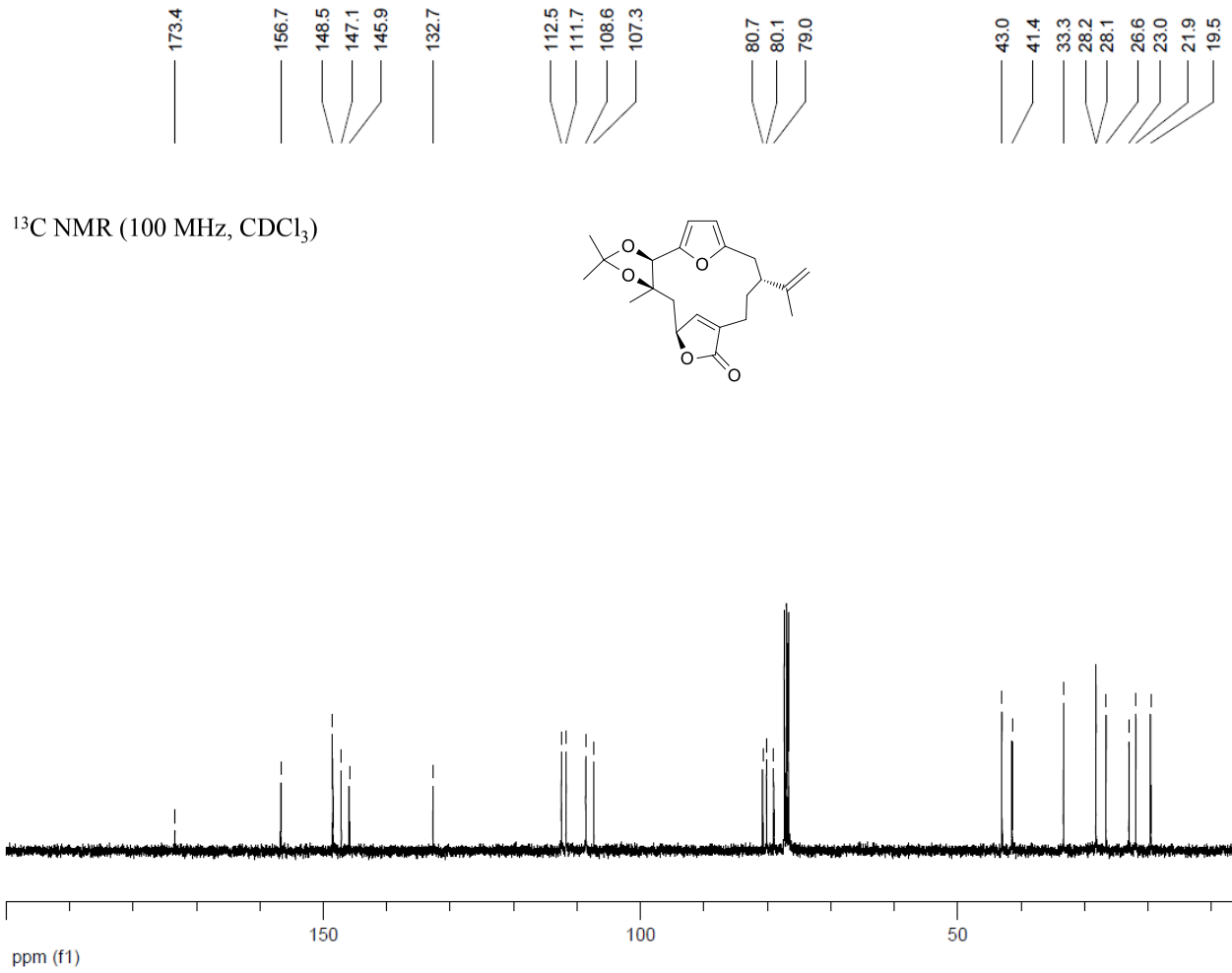
Spectrum 1.46: Compound 54: ^{13}H NMR



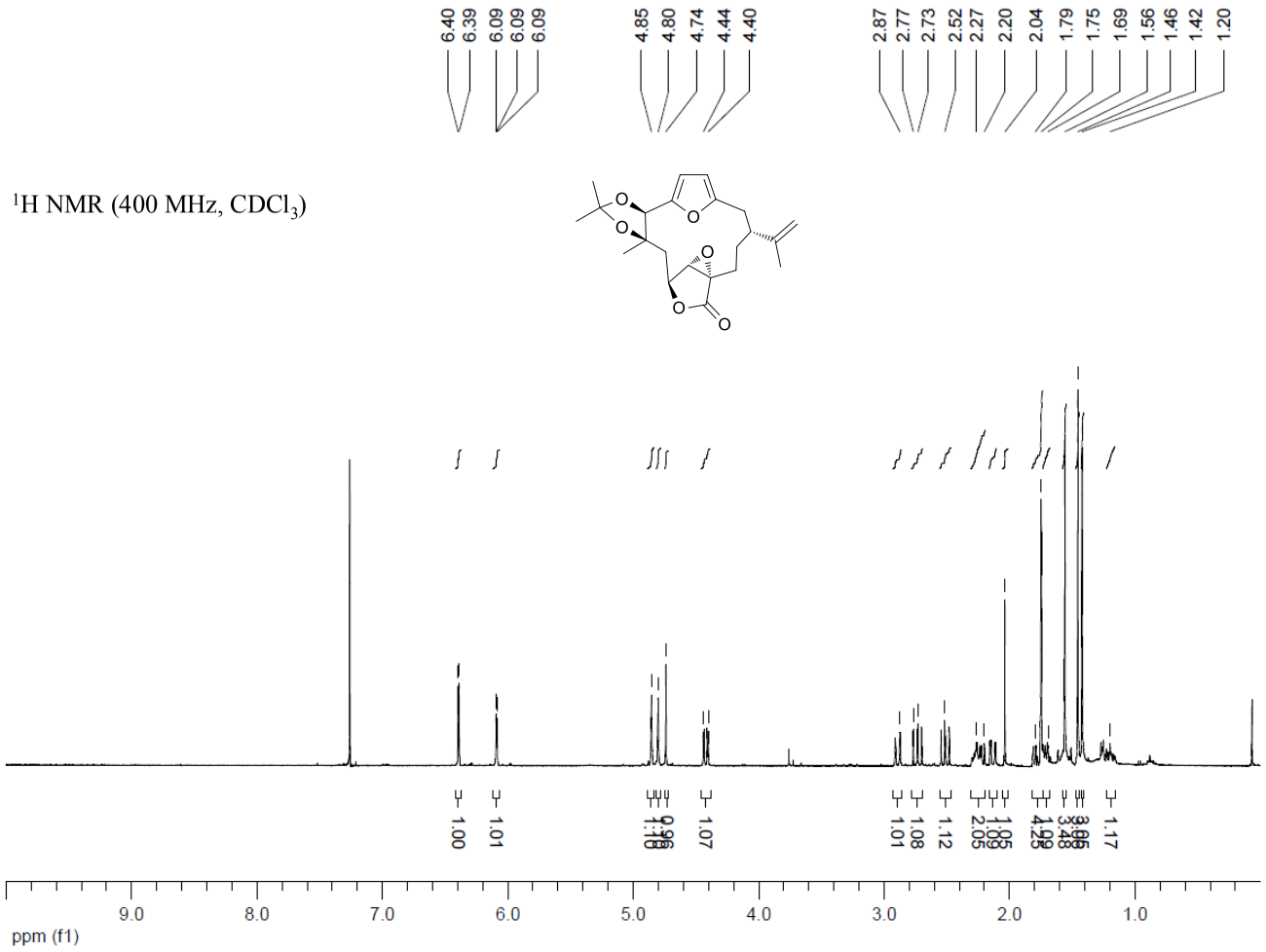
Spectrum 1.47: Compound 54: ^{1}C NMR



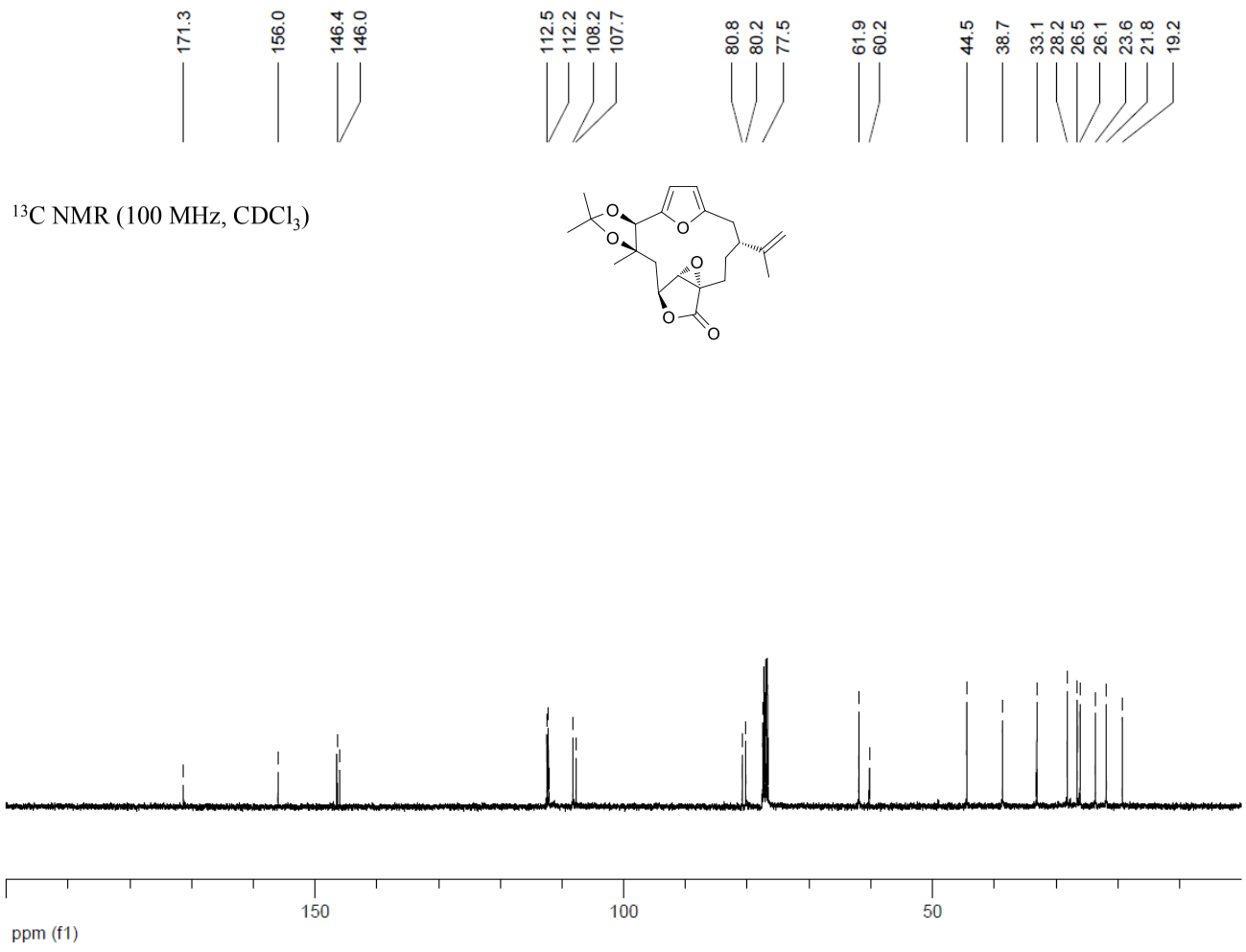
Spectrum 1.48: Compound 56: ^{13}H NMR



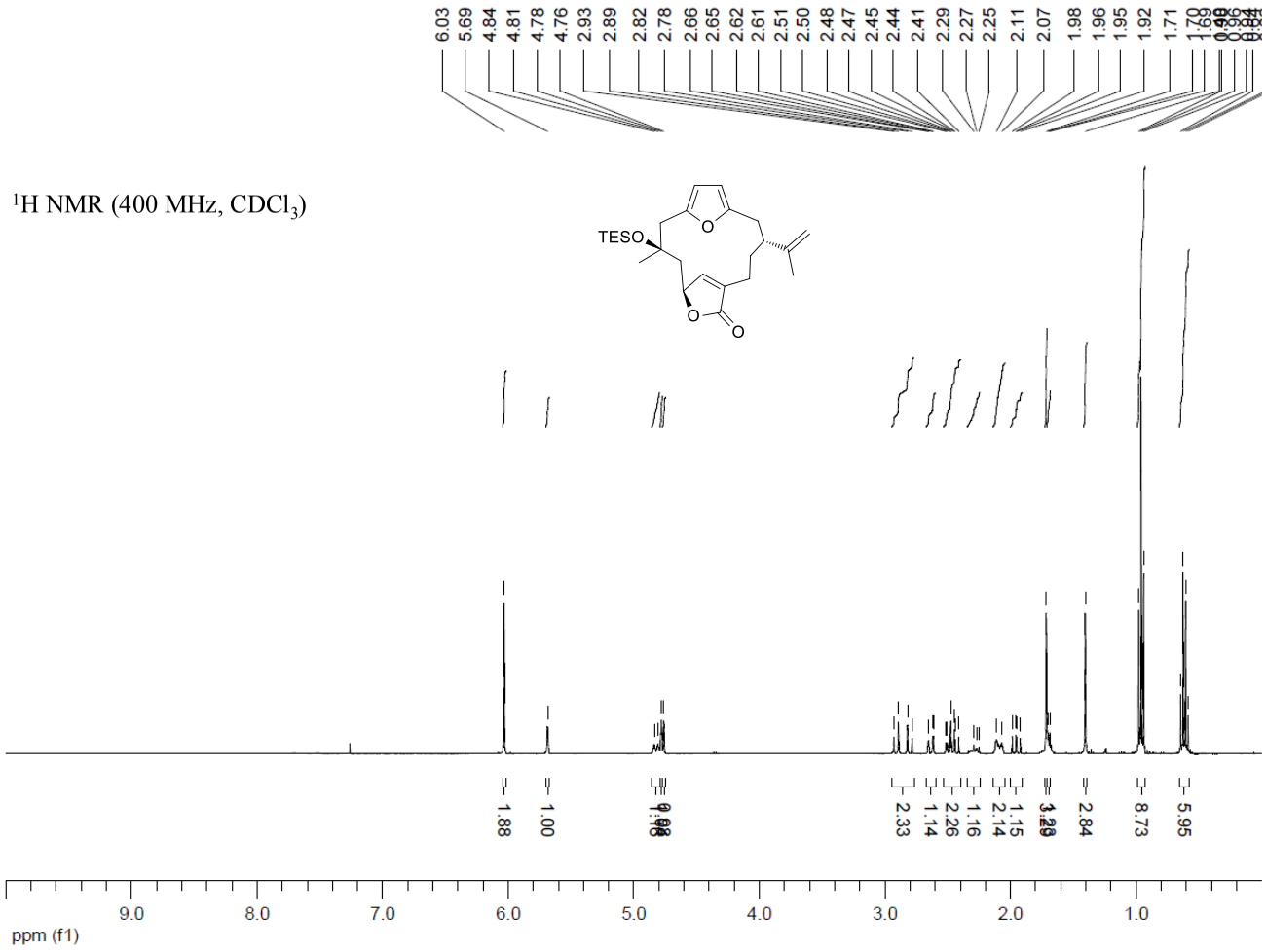
Spectrum 1.49: Compound 56: ^{1}C NMR



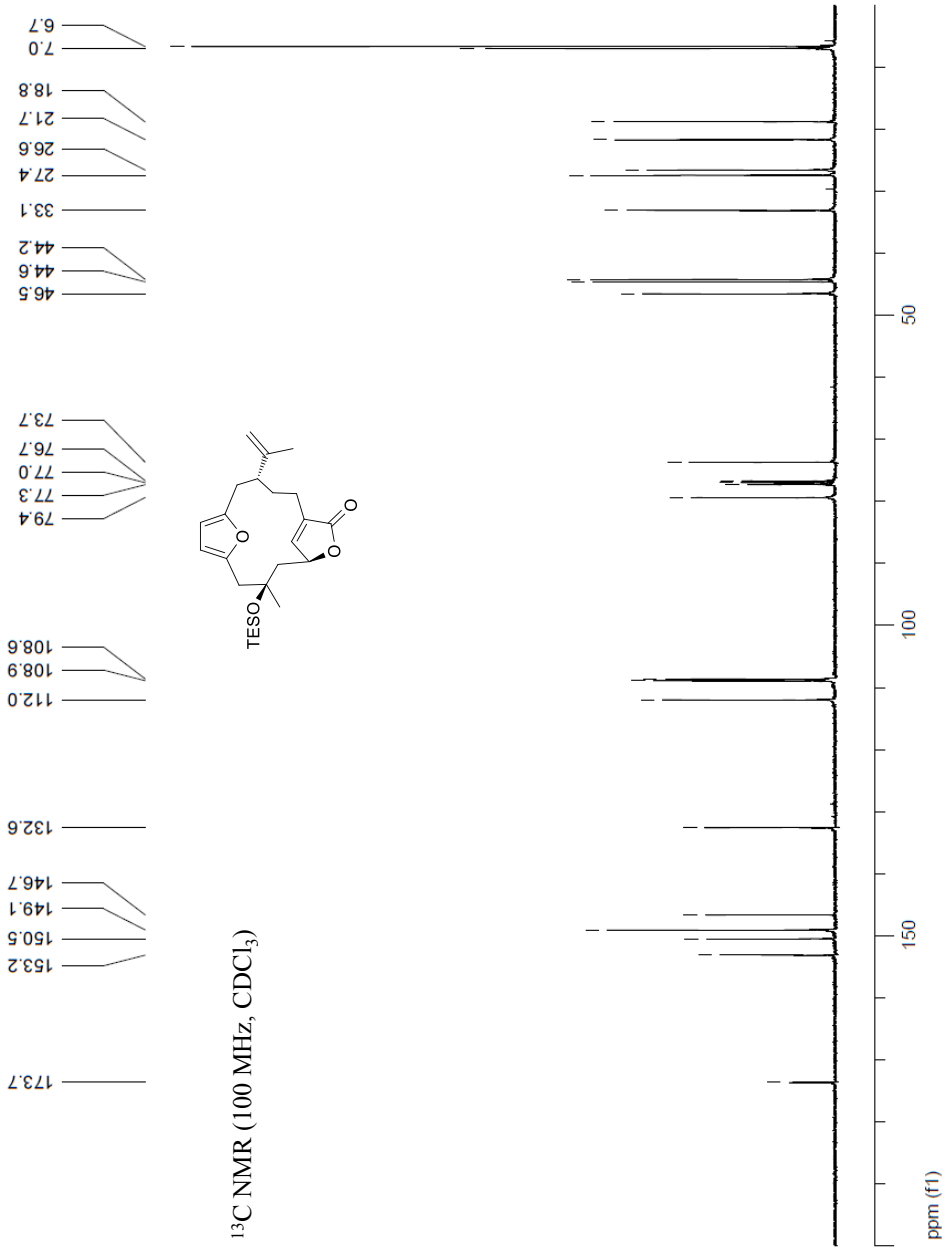
Spectrum 1.50: Compound 57: ^{13}H NMR



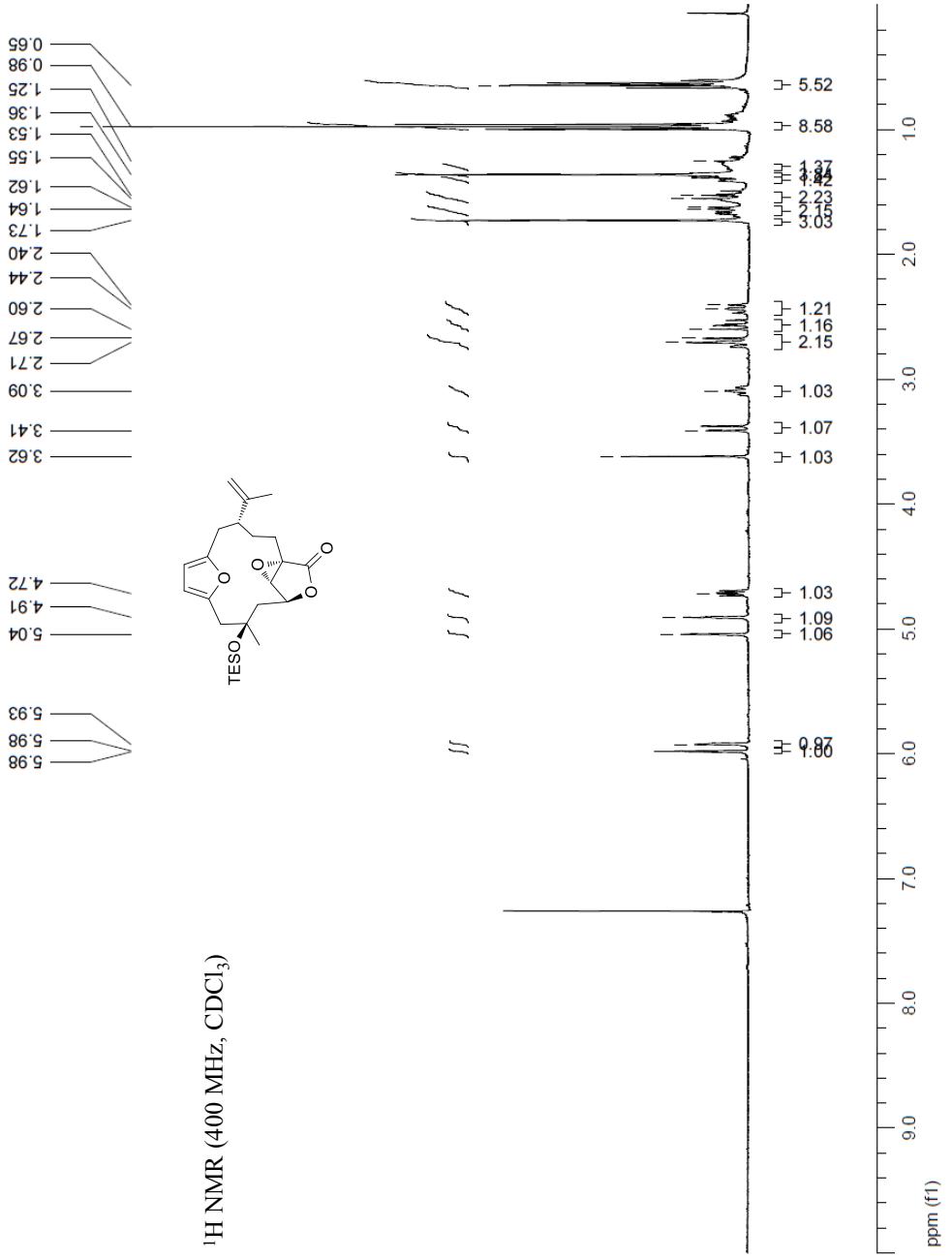
Spectrum 1.51: Compound 57: ^{1}C NMR



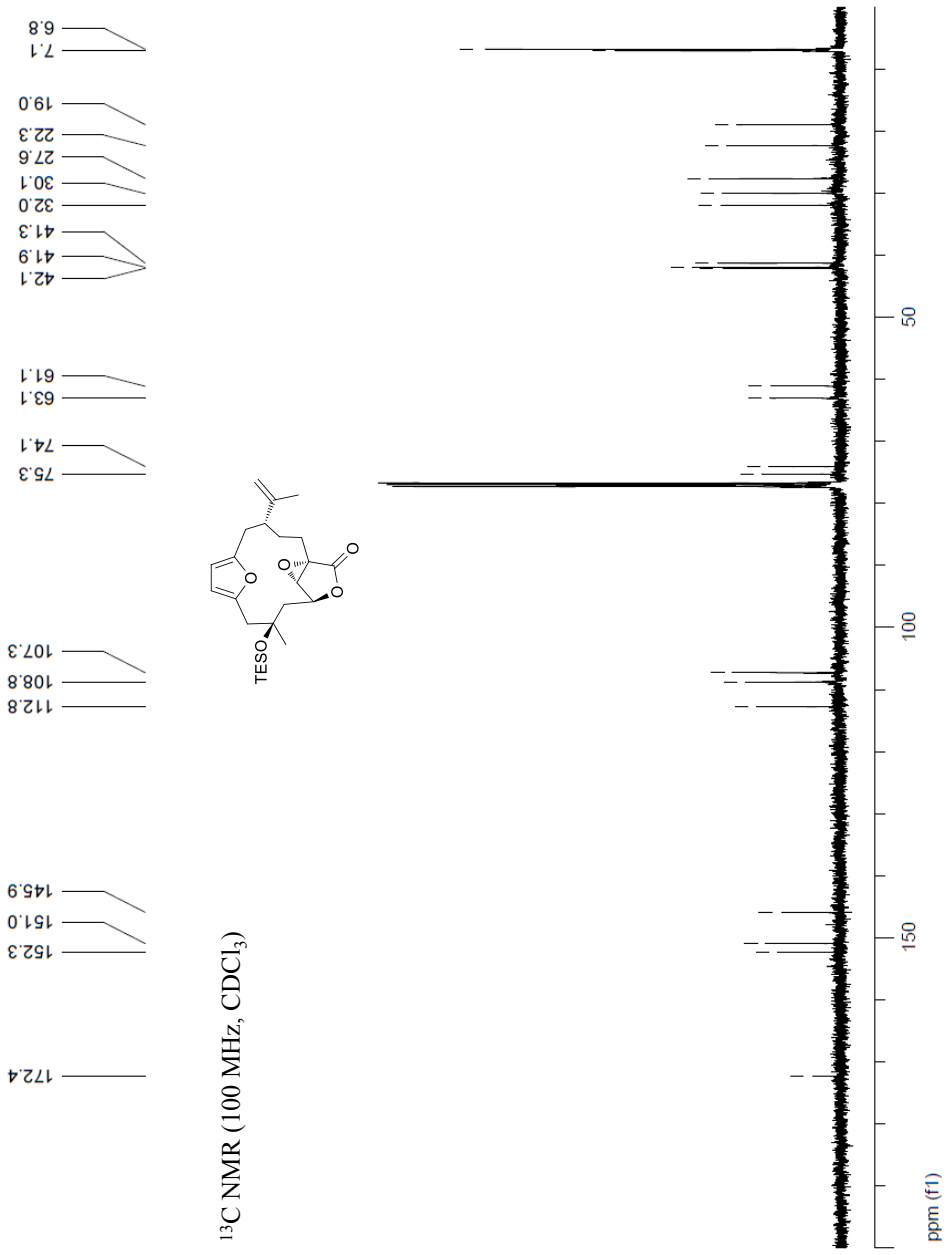
Spectrum 1.52: Compound 59: ^{13}H NMR



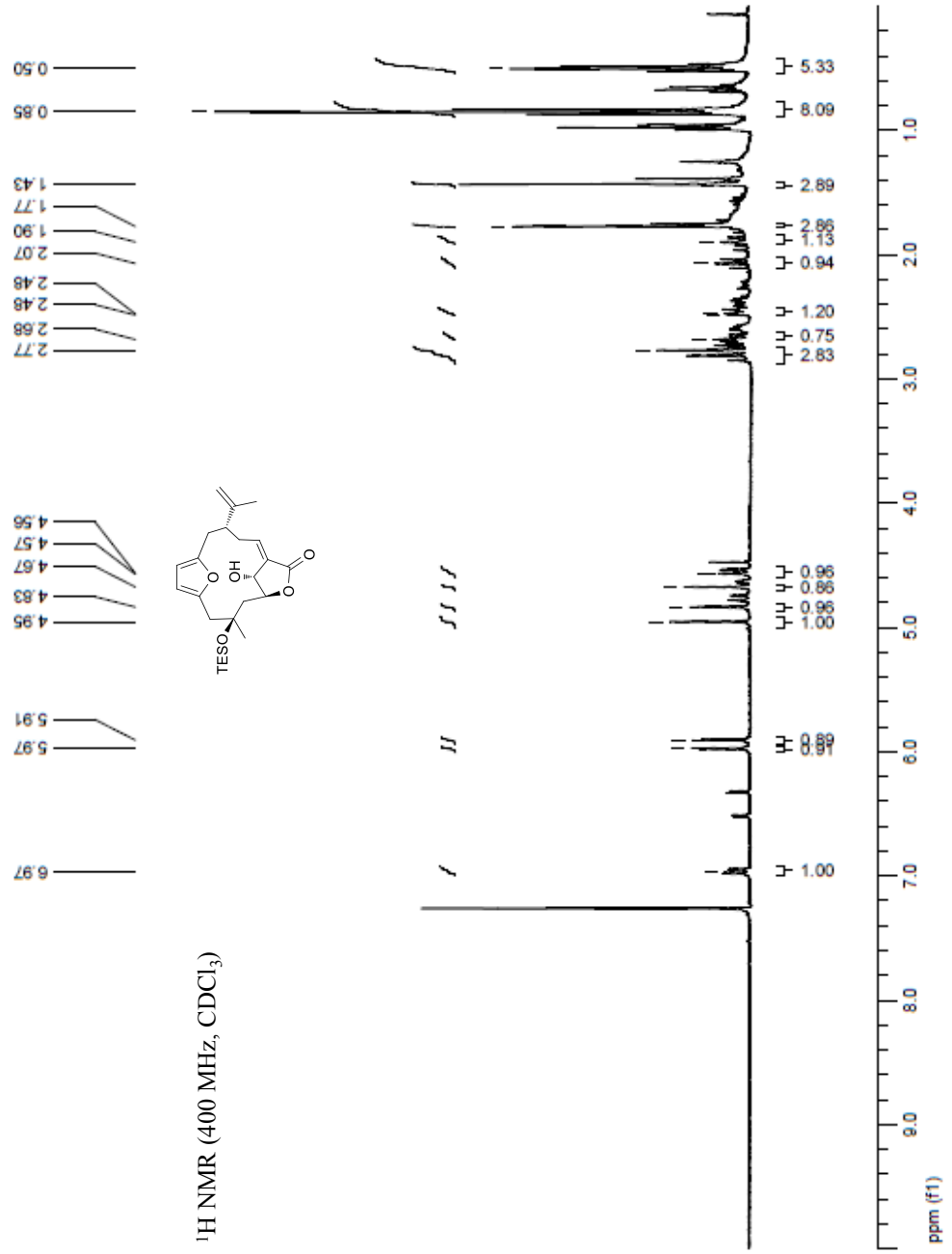
Spectrum 1.53: Compound 59: ^{1}C NMR



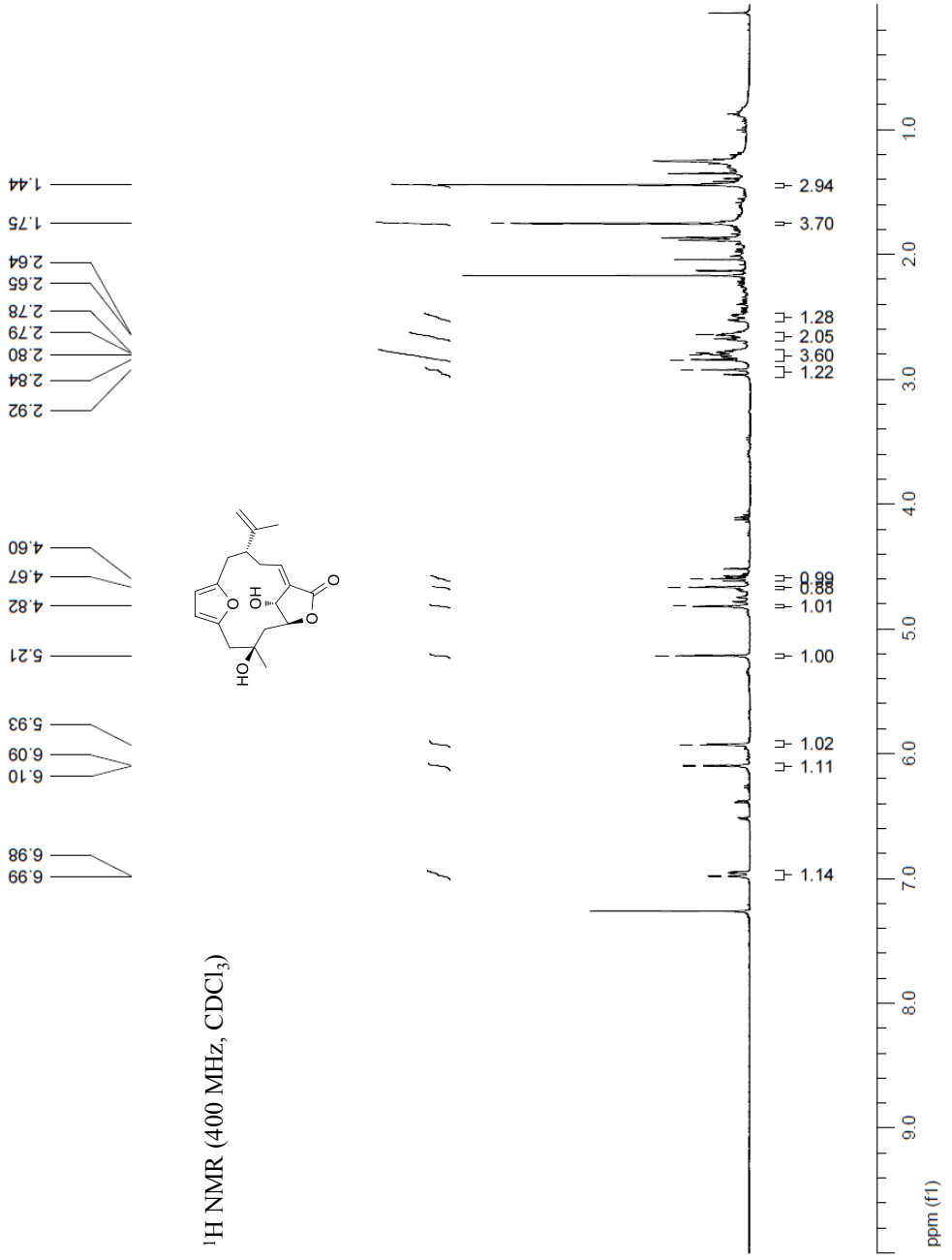
Spectrum 1.54: Compound 60: ^{13}H NMR



Spectrum 1.55: Compound 60: ^{13}C NMR



Spectrum 1.56: Compound 61: ^{1}H NMR



Spectrum 1.57: Compound 62: ^{1}H NMR

This chapter, in part, has been submitted for publication. Saitman, A.; Rulliere, P.; Sullivan, S. D. E.; Theodorakis, E. A. Total synthesis of norcembrenolide B and scabrolide D. *Org. Lett.* **2011**, *13*, 5854-5857. The dissertation author was the primary author and investigator of this material.

Chapter 2

The Synthesis of C_{13} Oxygenated Cembrenolides.

2.1 Introduction

2.1.1 Selected C_{13} Oxygenated Norcembrenolides and Bioactivities

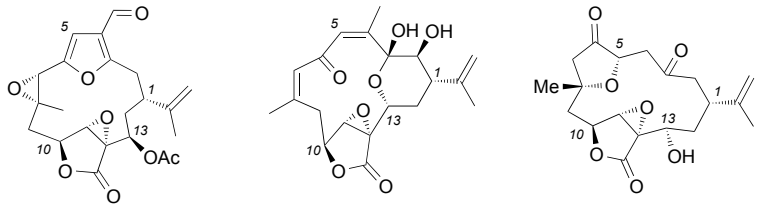


Figure 2.1: Selected C_{13} Oxygenated Norcembrenolides

A second class of bioactive cembrenolides which have been extensively studied contain additional oxidation at the C_{13} carbon[6,8,9] adjacent to the butenolide functionality. This oxidation pattern sets the stage for further oxidative skeletal rearrangements ultimately producing a wide array of polycyclic metabolites. These compounds have not only been pursued synthetically for their unusual structural motifs but also for their biological and pharmacological potential as well. For instance, lophotoxin (**64**) isolated from the Pacific sea whip genus *Lophogorgia*[45] was found to be a potent nicotinic acetyl-

choline receptor inhibitor with an LD_{50} of 8 mg/kg in mice[4] and, since its isolation, it has become a synthetic conundrum. On the other hand, the bioactivities of bipinnatolide F (**65**) isolated from *Pseudopterogorgia bipinnata*[46] and scabrolide G (**66**) isolated from *Sinularia scabra*[14] have yet to be fully explored.

2.1.2 C_{13} Oxidized Cembrenolide Biosynthesis

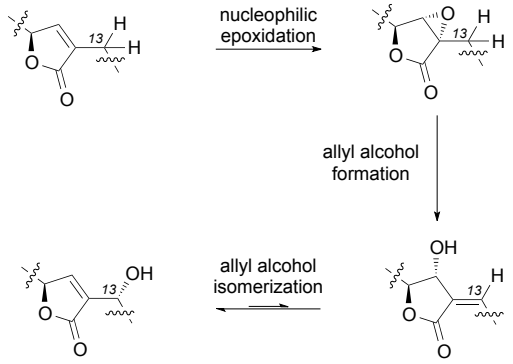
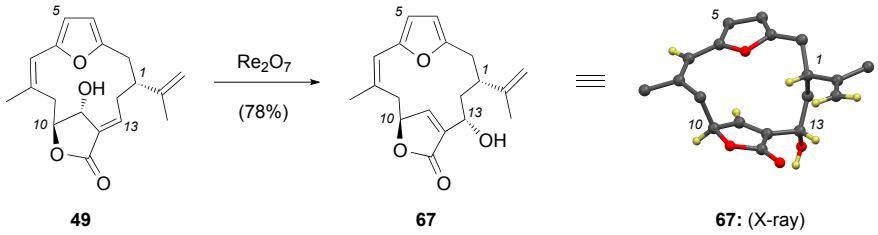


Figure 2.2: Biosynthesis of C_{13} Oxygenated Unit

The oxidative pathways that provide this C_{13} oxidation are proposed to go through an initial epoxidation of the C_{11}-C_{12} butenolide alkene.[8,9] This is supported through the isolation of many cembrenolides containing epoxidized butenolide moieties such as scabrolide D (**3**)[13] and coralloidolide A (**42**).[12] Enzymatic opening of this epoxide could be responsible for the C_{11} allylic alcohol functionality present in natural cembrenolides such as 5-episinuleptolide (**5**)[16] and sinuleptolide (**6**).[16] Further enzymatic isomerization[8,9] would create the discussed C_{13} allylic alcohol moiety present in lophotoxin (**64**), bipinnatolide F (**65**) and scabrolide G (**66**). This isomerization occurs readily, presumably due to the enhanced stability achieved through the reintroduction of the C_{11}-C_{12} butenolide alkene. Lophotoxin's C_{13} alcohol is further modified to an acetate[47] functionality whereas bipinnatolide F undergoes furan oxidation in which its C_{13} alcohol forms a 6 membered stable hemi-acetal group. Scabrolide G, on the other hand, undergoes oxidative rearrangements similar to that of norcembrenolide B (**2**) and scabrolide D (**3**) but retains its C_{13} functionality as a free hydroxyl group.

2.2 Retrosynthetic Plan



Scheme 2.1: Synthesis of C_{13} Alcohol with Rhenium (vii) Salts

Irrespective of the final biosynthetic outcome, all three of these cembrenolides originate from a C_{13} free hydroxyl group and therefore we set out to install this functionality in order to gain access to this family of compounds. We envisioned a synthetic pathway toward a C_{13} oxidized bipinnatin J derivative (**67**) could be constructed from our norfurano-sinsuleptolide (**49**) analogue. After extensive literature searching, we found protocol using Re (VII) salts[48] to catalyze the isomerization of allyl alcohols. We were delighted to find that treatment of norfurano-sinsuleptolide (**49**) with catalytic rhenium (VII) oxide[49] completely isomerized to the C_{13}-hydroxylated bipinnatin J (**67**) derivative in 78% yield with complete diastereoselectivity. The structure of **67** that confirmed our stereochemical assignments was determined by single crystal X-ray diffraction.[32] This procedure allows us to gain access to the C_{13} hydroxy functionality and also helps to support our proposed enzymatic assisted biosynthetic pathway[8,9] toward these C_{13} oxidized derivatives however, it was found that the synthesis as a whole was not amenable to scale up attempts. We then sought a more concise pathway, which could bring us gram quantities of an advanced C_{13} oxidized derivative **68** and also improve pathway scalability. Our new strategy entails construction of the C_{13}-hydroxyl group prior to the NHK macrocyclization event.[30,31] From a synthetic standpoint, C_{13} oxidized derivative **68** could derive from the union of three components: **69**, a C_7-C_{12} fragment containing a masked butenolide; **70** a C_{13}-C_1 aldehyde motif; and the previously used **30** the C_2-C_6 framework containing a furan ring.

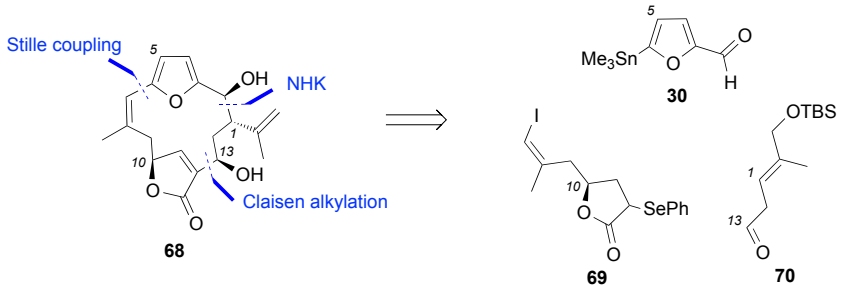
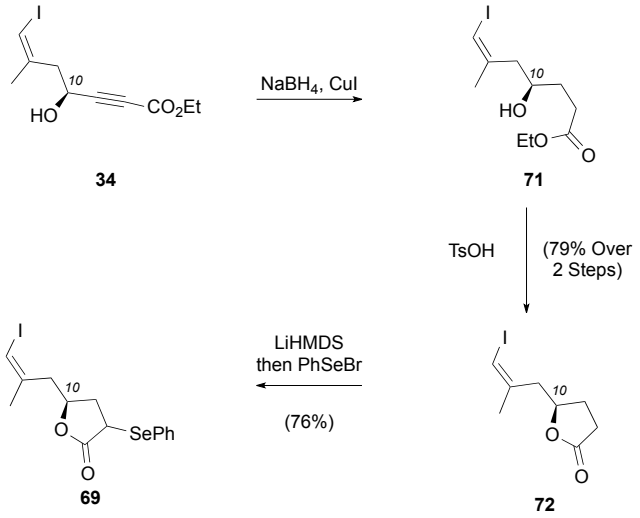


Figure 2.3: Retrosynthetic Plan for C_{13} Oxygenated Cembrenolides

2.3 The Synthesis of C_{13} Oxygenated Substrates

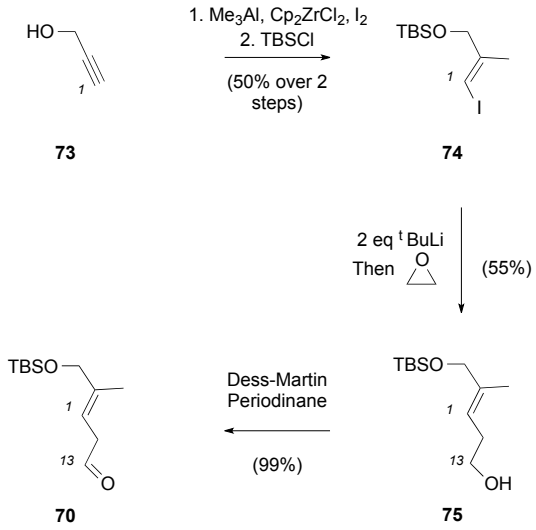
The synthesis of **68** began with construction of the C_7-C_{12} fragment **69**, in which the butenolide ring is introduced as an α-selenolactone.[49] To this end, propargyl ester **34**, available from commercial but-3-yn-1-ol in 3 steps,[21,25] was reduced to saturated ester **71** using excess $NaBH_4$ and CuI.[50,51] The crude material was then treated with cat. *p*-TsOH in benzene to form lactone **72** in a 79% yield over two steps. It is worth noting that this approach represents a significant improvement over the previously reported synthesis of compound **69**.[52] Treatment of **72** with LiHMDS/PhSeBr[52,53] then afforded **69** in a 76% yield.



Scheme 2.2: Construction of the Lactone Fragment

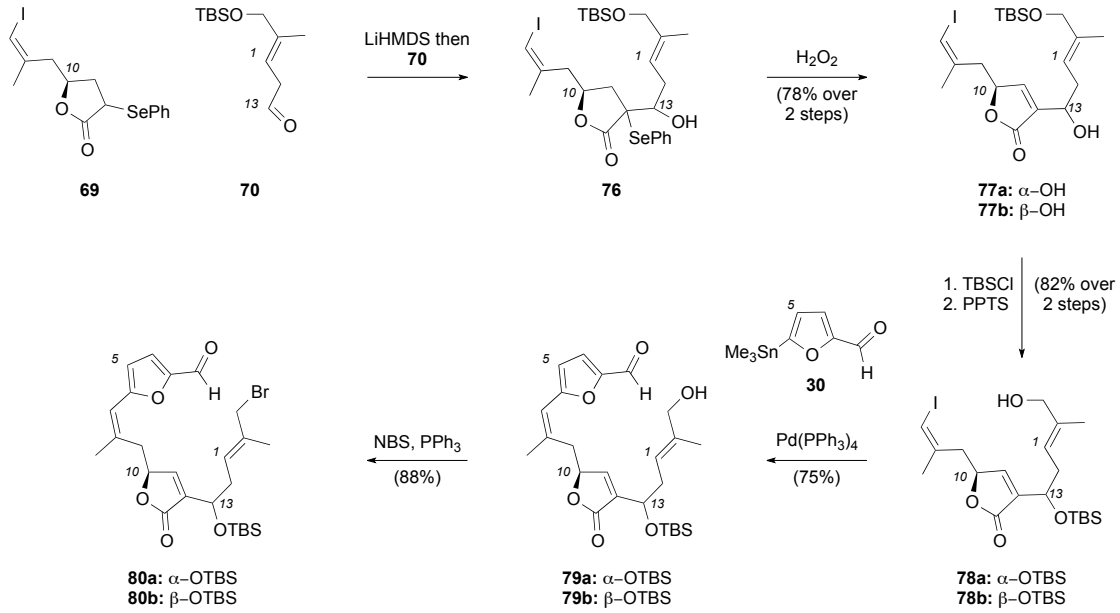
Aldehyde **70**, representing the C_{13}-C_1 component, was prepared beginning from

propargyl alcohol **73**. Zr-assisted carboalumination/iodination[23,54] of **73** followed by protection of the pendant allylic alcohol as a TBS silyl ether[40] afforded **74** in 50% combined yield. Lithiation of the resulting vinyl iodide[55] and quenching of the reac-



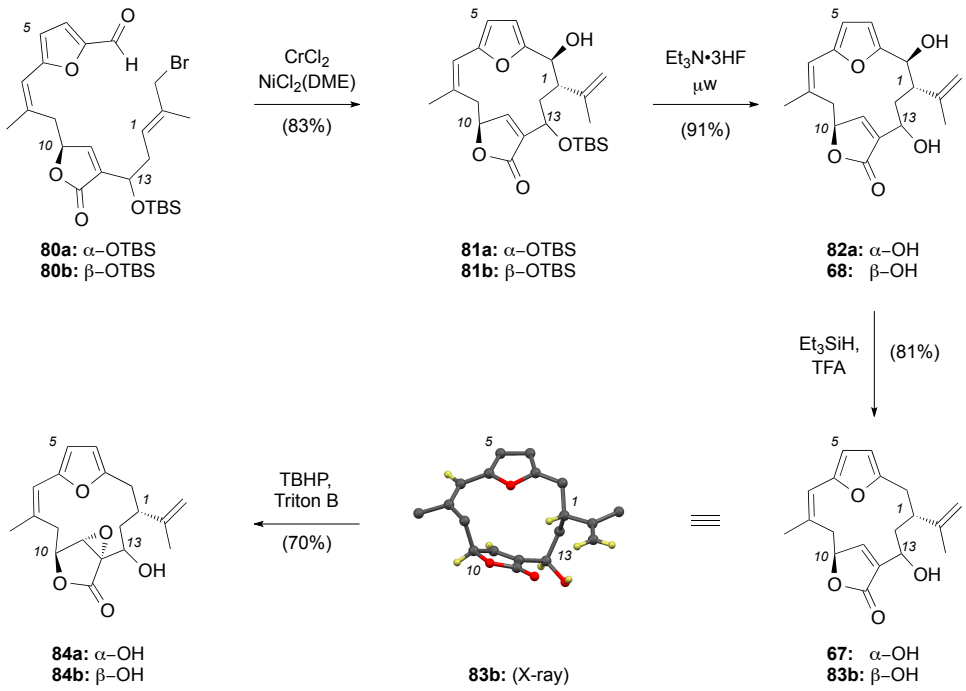
Scheme 2.3: Construction of the Aldehyde Fragment

tion with excess oxirane[55] yielded **75** in 55% yield. Oxidation of **75** with Dess-Martin periodinane[24] cleanly afforded β,γ-unsaturated aldehyde **70**[56] that was used without further purification. Coupling of compounds **69** and **70** was accomplished by lithiation at the C_{12} center (LiHMDS, -78 °C)of compound **69** and addition of aldehyde **70** to produce the Claisen-alkylation[56] products as a mixture of 4 diastereomers. The crude mixture was oxidatively deselenated[49,57] to afford butenolide **77** as a 1:1 mixture of C_{13} diastereomers **77a** and **77b** that were easily separated by column chromatography (78% combined yield). The stereochemistry of the C_{13} hydroxyl group was determined after macrocyclization. Protection of **77a** and **77b** with TBSCl[40] produced the di-silylated compounds that, after selective deprotection of the primary TBS group using PPTS in ethanol,[58] produced primary alcohols **78a** and **78b** (ca. 82% yield over 2 steps). Coupling of compounds **78a** and **78b** with previously synthesized stannylated furfural **30** was performed via a modified Stille[21,25,56] reaction to afford **79a** and **79b**. This modification of the original protocol removed the stoichiometric additive cesium fluoride, which was found to de-constructively cleave the secondary TBS group. Although we ob-



Scheme 2.4: Coupling of the Fragments

served slower reaction times (ca. 4 hours) we were delighted to obtain compounds **79a** and **79b** in 75% average yield. Bromination of the allylic alcohol using Appel[29,21,25,56] conditions produced allylic bromides **80a** and **80b** in 88% yield. We were concerned that the presence of the new C_{13} stereocenter, containing a sterically encumbering TBS ether on a linear uncyclized motif, might disrupt the high diastereoselectivity of the macrocylization that has been observed in previous systems.[21,22,25,30,31] However, to our satisfaction, this macrocylization proceeded smoothly using previously established $CrCl_2$/$NiCl_2$(DME) and formed compound **81a** and **81b** in 83% average yield. As was previously observed, the diastereoselectivity of this reaction is controlled by the configuration of the C_{10} center in the butenolide motif.[25] We found that acidic removal of the no-longer-needed TBS group using acids like *p*-TsOH created a large number of uncharacterized side products and basic fluoride sources such as TBAF[44] severely decomposed the starting material. Fortunately, removal of the extraneous silyl group was achieved using the TEA-buffered HF[59] reagent under microwave irradiation[56] conditions (80 °C for 20 min). This treatment cleanly afforded diols **82a** and **68** in 91% average yield. Reduction of the furylic C_2 alcohol of **82a** and **68** with TFA and TESH[33] gave rise to **67** and **83b** respectively, the stereochemistry of **67** that was already determined previously

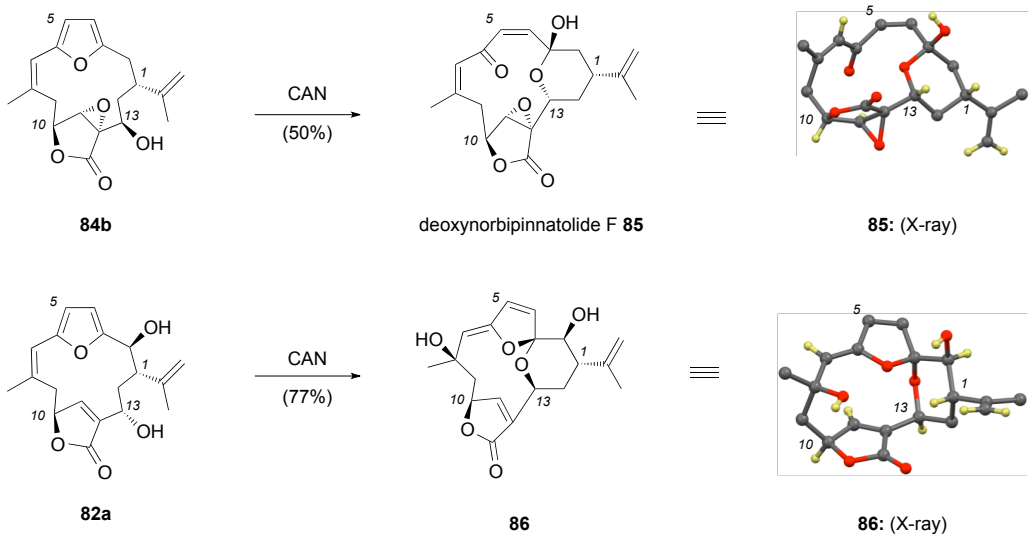


Scheme 2.5: Macrocyclization of C_{13} Oxygenated Cembrenolides

and the **83b** of which was determined via a single crystal X-ray analysis.[32] Selective epoxidation under TBHP/Triton B[37] conditions created, irrespective of the orientation of the adjacent C_{13} alcohol, α-epoxides **84a** and **84b** in a 70% average yield.

2.4 Oxidative Cyclizations

We then explored the effect of the C_{13} hydroxyl functionality during oxidative cyclizations of furanocembrenolides.[60,61] With an eye toward the scaffold of bipinnatolide F (**65**), we treated **68** under oxidative conditions mediated by CAN[56,62,63] (benzene/water: 20/1 at 10 °C). Unfortunately, only a complex mixture of products was observed. Interestingly, CAN-mediated oxidation of (**84b**) (benzene/water: 20/1 at 10 °C) led to isolation of compound **85** in which an intermediate ene-dione, produced upon furan oxidation, underwent hemi-ketalizationat the C_3 center by the pendant C_{13} β-hydroxyl group. Hemi-ketal **85** is stabilized by the diaxial orientation[64,65] of the oxygen substituents (anomeric effect)[64,65] and by the equatorial orientation of the C_1 and C_{13}



Scheme 2.6: Oxidation Patterns of Alcohol Epimers

side-chains. As projected, the structure of **85** is reminiscent to that of bipinnatolide F (**65**).[46] On the other hand, when identical oxidative conditions were applied to **82a**, containing the C_{13}-hydroxyl group on the α-face of the cembrenolide scaffold, we observed the formation of 5,6-spiro ketal **86**. This spiroketal motif is presumably stabilized by the diaxial orientation[64,65] of the ketal oxygens (anomeric effect), despite the axial orientation of the C_{13} butenolide side chain.

2.5 Conclusion

In conclusion, an efficient strategy toward C_{13}- oxidized cembrenolide scaffolds that pave the way for the synthesis of a collection of higher-complexity cembrenolides.[14,45,46] The developed approach allows construction of such scaffolds in thirteen steps from readily available starting materials. Our studies suggest that the stereochemistry of the C_{13} hydroxyl group affects the mode of cyclization upon oxidation of the furan-containing starting materials creating compounds **85** and **86**.[56] The resulting polycyclic motifs bear structural similarities to more intricate natural products. These studies could set the stage for a divergent, biomimetic synthesis of various bioactive natural products of the cembrenolide family.

2.6 Experimental Section

2.6.1 General Techniques

All reagents were commercially obtained (Aldrich, Acros, Strem) at highest commercial quality and used without further purification except where noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 40 °C at approximately 15 mmHg. All non-aqueous reactions were carried out under anhydrous conditions using flame-dried glassware within an argon atmosphere in dry, freshly distilled solvents, unless otherwise noted. Tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), toluene ($PhCH_3$) and benzene (PhH) were purified by passage through a bed of activated alumina. Dimethylformamide (DMF) were distilled from calcium hydride under reduced pressure (20 mmHg) and stored over 4 angstrom molecular sieves until needed. Yields refer to chromatographically and spectroscopically (^{1}H NMR, ^{13}C NMR) homogeneous materials, 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 the visualizing agent and 10% ethanolic phosphomolybdic acid (PMA) or Potassium Permanganate solution ($KMnO_4$) in water and heat as developing agents. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography. Preparative thin-layer chromatography separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Varian Mercury 400 and/or Jeol Unity 500 MHz instruments and calibrated using the residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad, dd = doublet of doublet, dt = doublet of triplet. High resolution mass spectra (HRMS) were recorded on a VG 7070 HS or on a VG ZAB-ZSE mass spectrometers. X-ray data were recorded on a Bruker SMART APEX 3kW Sealed Tube X-ray diffraction system.

2.6.2 Experimental Procedures and Data

Alcohol (67): To a solution of furanosinuleptolide **49** (0.02 g, 0.064 mmol) in dry, degassed chloroform (0.64 ml) and 4 angstrom activated molecular sieves (300 mg) at 25 °C was added rhenium (VII) oxide (3.0 mg, 0.006 mmol). The reaction was stirred overnight and quenched with 0.5 ml of saturated $NaHCO_3$. The organic layer was diluted with 1.0 ml of CH_2Cl_2, separated, and the aqueous layer was extracted 3x with 1.0 ml of CH_2Cl_2. The combined organic layers were washed once with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (up to 40% EtOAc in hexanes) of the crude mixture gave alcohol **67** (16.0 mg, 0.050 mmol, 78% yield) as a white solid, R_f= 0.22 (40% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.17 (d, 1H, *J*= 1.3 Hz) 6.13 (s, 1H) 6.11 (d, 1H, *J*= 3.2 Hz) 6.07 (dd, 1H, *J*= 1.1 Hz, *J*= 3.1 Hz) 5.04 (ddd, 1H, *J*= 1.3 Hz, *J*= 4.5 Hz, *J*= 11.8 Hz) 4.89 (s, 2H) 4.57 (dd, 1H, *J*= 4.0 Hz, *J*= 11.8 Hz) 3.21 (t, 1H, *J*= 11.8 Hz) 2.75 (dd, 1H, *J*= 4.6 Hz, *J*= 11.9 Hz) 2.61 (m, 2H) 2.17 (dt, 1H, *J*= 5.0 Hz, *J*= 11.6 Hz) 2.00 (s, 3H) 1.94 (m, 1H) 1.75 (s, 3H) 1.30 (t, 1H, *J*= 12.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.0, 153.9, 153.6, 151.1, 145.3, 135.9, 126.9, 117.6, 113.0, 111.4, 109.2, 79.1, 62.7, 42.2, 39.7, 39.3, 32.8, 25.7, 19.2; HRMS calcd. For $[M+Na]^+$ 337.1410, observed 337.1407.

Vinyl-iodo alcohol (71): To a solution of **34** (0.54 g, 1.7 mmol) in MeOH (17.6 ml) at -78 °C was added copper (I) chloride (0.35 g, 3.5 mmol) followed by sodium borohydride (0.40 g, 10.6 mmol) portion-wise. The reaction was then stirred for 15 minutes at this temperature. The reaction was then quickly added to a vigorously stirred mixture of 50 ml of ether and 50 ml of 0.5M HCl . The solution was then extracted 3X with 25 ml of ether. The organic layers were combined, dried and concentrated to yield **71** as a yellow oil which was used without further purification. R_f= 0.55 (10% Ether in CH_2Cl_2), ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.01 (s, 1H), 4.14 (q, 2H, *J*= 7.1Hz), 3.86 (dq, 1H, *J*= 5.0Hz, *J*=8.6 Hz), 2.50 (t, 2H, *J*= 7.1Hz), 2.47 (dd, 1H, *J*=8.9 Hz, *J*=13.0 Hz), 2.36 (dd, 1H, *J*= 4.9Hz, *J*= 13.5Hz), 1.95 (d, 3H, *J*= 1.4Hz), 1.93 (d, 1H, *J*= 5.3Hz), 1.88 (ddd, 1H, *J*= 3.6Hz, *J*= 7.2Hz, *J*= 14.5Hz), 1.77 (tdd, 1H, *J*= 7.0Hz, *J*= 8.1Hz, *J*= 14.2Hz), 1.26 (t, 3H, *J*= 7.3Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.0, 144.7 69.6, 60.6, 46.2, 32.0, 30.7, 29.7, 24.4, 14.2; HRMS calcd. For $[M+Na]^+$ 335.0115, observed

335.0116.

Vinyl-iodo lactone (72): to a solution of **71** (0.55 g, 1.8 mmol) in benzene (17.6 ml) at 25 °C was added *p*-TsOH (0.035 g, 0.18 mmol). The solution was stirred for 30 minutes at rt. The reaction was then quenched with 15 ml of saturated $NaHCO_3$. The solution was extracted 3X with 25 ml of ether. The organic layers were combined, dried and concentrated. Flash chromatography (up to 50% EtOAc in Hexanes) of the crude material gave lactone **72** (0.37g, 1.4mmol, 79% yield over 2 steps) as an off-white waxy solid. R_f= 0.65 (10% ether in CH_2Cl_2), ^{1}H (400 MHz, $CDCl_3$) δ: 6.07 (s, 1H), 4.68 (m, 1H), 2.63 (dd, 1H, *J*= 5.8Hz, *J*= 13.9Hz), 2.57 (m, 3H), 2.34 (dddd, 1H, *J*= 5.5Hz, *J*= 6.5Hz, *J*= 8.9Hz, *J*= 12.3Hz), 1.97 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.8, 143.0, 78.9, 77.9, 43.8, 28.5, 27.5, 24.5; HRMS calcd. For $[M+Na]^+$ 288.9696, observed 288.9694.

Selenated lactone (69): To a solution of HMDS (0.42 ml, 2.0 mmol) in THF (3.14 ml) at 0 °C was added n-BuLi (1.19 ml, 1.9 mmol) dropwise under an argon atmosphere. The reaction was then allowed to stir for 30 minutes. The reaction was then lowered to -78 °C and to this solution was added **72** (0.46 g, 1.7 mmol) in a solution of THF (1.6 ml) dropwise. The reaction was allowed to then stir for 15 minutes. TMS-Cl (0.24 ml, 1.9 mmol) was then added dropwise and the solution was allowed to stir for an additional 30 minutes. Finally, a solution of phenyl hypobromoselenoite (0.45 g, 1.9 mmol) in THF (3.1 ml) was then added dropwise. The reaction was then allowed to stir for an additional 30 minutes and then gradually warmed to 25 °C over 30 minutes. The solution was then quenched with 25 ml of saturated NH_4Cl. The solution was then washed 3X with 25 ml of ether. The organic layers were combined, dried and concentrated. Flash chromatography (up to 20% EtOAc in Hexanes) of the crude material gave the selenated derivative **69** (0.55g, 1.3mmol, 76% yield). The product is a pale yellow oil as a mixture of separable diastereomers in a 2.25:1 ratio. **Diastereomer 1:** R_f= 0.60 (35% EtOAc in Hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66 (m, 2H), 7.34 (m, 3H), 6.03 (d, 1H, *J*= 1.4Hz), 4.42 (m, 1H), 3.96 (dd, 1H, *J*= 3.0Hz, *J*= 8.3Hz), 2.56 (dd, 1H, *J*= 5.7Hz, *J*= 13.9Hz), 2.50 (dd, 1H, *J*= 7.6Hz, *J*= 14.1Hz), 2.42 (t, 1H, *J*= 8.4Hz), 2.34 (ddd, 1H, *J*= 3.0Hz, *J*= 6.2Hz, *J*= 14.0Hz), 1.88 (d, 3H, *J*= 1.4Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.3, 142.6, 135.8, 129.4, 129.1, 126.4, 78.0, 77.4, 43.4, 36.6,

36.1, 24.4. **Diastereomer 2:** R_f= 0.56 (35% EtOAc in Hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66 (m, 2H), 7.34 (m, 3H), 5.99 (s, 1H), 4.57 (td, 1H, *J*= 6.7Hz, *J*= 7.9Hz), 4.01 (t, 1H, *J*= 9.6Hz), 2.74 (ddd, 1H, *J*= 6.4Hz, *J*= 9.3Hz, *J*= 13.6Hz), 2.51 (dd, 1H, *J*= 5.0Hz, *J*= 14.0Hz), 2.42 (dd, 1H, *J*= 7.7Hz, *J*= 14.0Hz), 2.04 (ddd, 1H, *J*= 8.8Hz, *J*= 11.8Hz, *J*= 16.7Hz), 1.86 (d, 3H, *J*= 1.4Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.3, 142.7, 135.9, 129.4, 128.9, 126.6, 78.0, 77.4, 43.6, 37.2, 35.4, 24.7; HRMS calcd. For $[M+H]^+$ 422.9355, observed 422.9352.

Vinyl iodide (74): To a solution of $ZrCp_2Cl_2$ (5.2 g, 17.8 mmol) in DCE (144 ml) at 0 °C was added 2M trimethylaluminum (111 ml, 223 mmol) in hexanes dropwise. Then propargyl alcohol (**73**) (5.19 ml, 89 mmol) diluted in 20 ml of DCE was added dropwise. The reaction was allowed to stir at 25 °C for 24 hours. The reaction was then cooled down to -40 °C and to it was added a solution of elemental iodine (45.3 g, 178 mmol) in dry THF (90 ml). The solution was allowed to warm up to 0 °C over 30 minutes at which point, 10 ml of saturated K_2CO_3 solution was added very slowly. The solution froths and bubbles eventually turning yellow with a large amount of aluminum gel. 250 ml of ether was added and the resulting slurry was filtered through a course fritted funnel. Excess ether was then used to rinse the solids. The resulting solution was concentrated to 100ml at which point was extracted with saturated brine. Organics were then separated, dried and concentrated. The resulting residue was then taken up in dry DCM (300ml) and lowered to 0 °C. To this solution was then added imidazole (18.2 g, 268 mmol) followed by DMAP (1.1 g, 8.92 mmol) followed by TBS-Cl (17.5 g, 116 mmol). The reaction was then warmed up to 25 °C and allowed to stir for 1 hour at which point, 1 ml of methanol was added to quench the remaining TBS-Cl. Excess saturated NH_4Cl was then added and the solution was extracted 3X with 100 ml of fresh DCM. Organics were then combined, dried and concentrated. Flash chromatography (up to 6% EtOAc in Hexanes) of the crude material gave vinyl iodide **74** (13.93g, 44.6mmol, 50% yield over two steps) as a clear oil. R_f= 0.35 (4% EtOAc in Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.20 (s, 1H), 4.10 (s, 2H), 1.77 (s, 3H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.7, 75.9, 67.0, 25.8, 21.1, 18.3, -5.4.

Alcohol (75): To a solution of *t*-BuLi in hexanes (47.3 ml, 80 mmol) at -78 °C was added **74** (12.56 g, 40.2 mmol) in a solution of dry toluene (67.0 ml) dropwise. The

reaction was allowed to stir at -78 °C for 30 minutes. Excess oxirane was then bubbled in the solution, which was then allowed to warm to 25 °C over 30 minutes. The solution was then quenched with 100 ml of saturated NH_4Cl. The solution was then extracted 3X with 50 ml of EtOAc. The organics were then combined, dried and concentrated. Flash chromatography (up to 40% EtOAc in Hexanes) of the crude material afforded **75** (5.10g, 22.1 mmol, 55% yield) as a clear oil. R_f= 0.20 (20% EtOAc in Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.39 (dt, 1H, *J*= 1.3Hz, *J*= 7.4Hz), 4.01 (s, 2H), 3.62 (t, 2H, *J*= 6.6Hz), 2.30 (q, 2H, *J*= 6.9Hz), 2.00 (bs, 1H), 1.62 (s, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.5, 119.9, 68.3, 62.2, 31.1, 25.9, 18.4, 13.6, -5.3; HRMS calcd. For $[M+Na]^+$ 253.1594, observed 253.1590.

Aldehyde (70): To a solution of **75** (0.95 g, 4.12 mmol) in CH_2Cl_2 (20.61 ml) at 25 °C was added solid $NaHCO_3$ (2.08 g, 24.7 mmol) followed by Dess-Martin Periodinane (2.27 g, 5.36 mmol). The solution was allowed to stir for 20 minutes at 25 °C then a 1:1:1 solution of saturated $Na_2S_2O_3$, $NaHCO_3$ and water (60 ml) was added. The mixture was allowed to stir vigorously for 20 minutes at which time was extracted 3X with 20 ml CH_2Cl_2. The organics were then combined dried and concentrated to yield **70** as a clear oil which was used in the next step without further purification. R_f= 0.45 (20% EtOAc in Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.60 (t, 1H, *J*= 2.0Hz), 5.58 (tdt, 1H, *J*= 1.4Hz, *J*= 2.9Hz, *J*= 7.3Hz), 4.03 (s, 2H), 3.13 (d, 2H, *J*= 7.3Hz), 1.58 (s, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 199.5, 140.0, 112.4, 67.6, 42.7, 25.8, 18.3, 13.7, -5.5; HRMS calcd. For $[M+Na]^+$ 251.1438, observed 251.1440.

Butenolide (77a) and (77b): To a solution of HMDS (0.79 ml, 3.8 mmol) in THF (9.50 ml) at 0 °C was added *n*-BuLi (2.16 ml, 3.5 mmol) dropwise. The reaction was then stirred for 30 minutes at 0 °C. The solution was then brought down to -78 °C and a solution of **69** (1.32 g, 3.13 mmol) was added dropwise. The reaction was then allowed to stir for 1 hr at -78 °C at which time a solution of **70** (0.93 g, 4.1 mmol) also at -78 °C was quickly added via cannula. The reaction was stirred at -78 °C for 20 minutes at which time, saturated NH_4Cl was added. The solution was then extracted 3X with 20 ml of ether. Organics were then combined dried and concentrated. The residue was then taken up in a 1:1 mixture of THF and EtOAc (30 ml). Solid $NaHCO_3$ (2.59 g, 30.8 mmol) was added at 25 °C followed by a dropwise addition of 30% H_2O_2 (0.94

ml, 9.2 mmol). The reaction was allowed to stir for 10 minutes at which time, 15 ml of a saturated solution of $Na_2S_2O_3$was added. The mixture was extracted 3X with 25 ml EtOAc. Organics were then combined, dried and concentrated. Flash chromatography (up to 35% EtOAc in Hexanes) of the crude material afforded **77a** and **77b** (2.10 g, 2.45 mmol, 78% yield over 2 steps) as a pale yellow oil in a 1:1 separable mixture of diastereomers. **77a** R_f= 0.40 (50% EtOAc in Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31 (s, 1H), 6.14 (s, 1H), 5.45 (t, 1H, *J*= 6.8Hz), 5.10 (m, 1H), 4.55 (m, 1H), 4.03 (s, 2H), 2.69 (dd, 1H, *J*= 6.0Hz, *J*= 13.7Hz), 2.63 (m, 1H), 2.56 (dd, 1H, *J*= 7.6Hz, *J*= 13.7Hz), 2.47 (m, 1H), 2.00 (d, 3H, *J*= 1.3Hz), 1.63 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.9, 148.1, 142.1, 139.1, 136.1, 118.0, 79.9, 78.9, 68.1, 66.9, 42.3, 33.8, 25.9, 24.8, 18.4, 13.8, -5.3; **77b** Pale yellow oil; R_f= 0.50 (50% EtOAc in Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30 (d, 1H, *J*= 1.2Hz), 6.14 (s, 1H), 5.44 (t, 1H, *J*= 6.9Hz), 5.11 (t, 1H, *J*= 6.7Hz), 4.56 (dd, 1H, *J*= 5.4Hz, *J*= 11.3Hz), 4.03 (s, 2H), 2.69 (dd, 1H, *J*= 5.9Hz, *J*= 13.4Hz), 2.63 (m, 1H), 2.55 (dd, 1H, *J*= 7.8Hz, *J*= 13.8Hz), 2.45 (m, 2H, 2.00 (s, 3H), 1.63 (s, 3H), 0.91 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.9, 148.2, 142.2, 138.9, 136.1, 117.9, 79.9, 78.6, 68.0, 66.9, 42.3, 33.6, 25.9, 24.8, 18.3, 13.7, -5.3; HRMS calcd. For $[M+Na]^+$ 515.1085, observed 515.1083.

Primary alcohol (78a) and (78b): To a solution of **77a** (0.94 g, 1.9 mmol) in DCM (3.8 ml) at 0 °C was added TBSCl (0.43 g, 2.9 mmol) and imidazole (0.52 g, 7.6 mmol). The reaction was then allowed to warm to 25 °C where it was stirred for 12 hours. The reaction was quenched with 1 ml of methanol followed by saturated NH_4Cl. The mixture was extracted 3X with 30 ml of ether. The organics were then combined, dried and concentrated. The residue was then taken up in ethanol (3.36 ml) and to this solution, was added PPTS (0.25 g, 0.99 mmol). The reaction was then allowed to stir at 25 °C for 12 hours at which time, a saturated solution of 30 ml $NaHCO_3$ was added. The mixture was then extracted 3X with 30 ml EtOAc. The organics were then combined, dried and concentrated. Flash chromatography (up to 50% EtOAc in Hexanes) of the crude material afforded **78a** (0.77g, 1.57mmol, 82% yield over 2 steps) as a clear oil. **78a** R_f= 0.35 (50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28 (t, 1H, *J*= 1.5Hz), 6.11 (d, 1H, *J*= 1.4Hz), 5.42 (t, 1H, *J*= 6.7Hz), 5.07 (m, 1H), 4.59 (ddd, 1H, *J*=

1.9Hz, *J*= 5.3Hz, *J*= 7.1Hz), 3.96 (s, 2H), 2.64 (dd, 1H, *J*= 5.7Hz, *J*= 13.8Hz), 2.51 (dd, 1H, *J*= 7.6Hz, *J*= 13.7Hz), 2.45 (m, 2H), 1.96 (d, 3H, *J*= 1.4Hz), 1.63 (s, 3H), 0.88 (s, 9H), 0.04 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.5, 148.7, 142.1, 137.9, 137.5, 120.3, 79.6, 78.6, 68.7, 67.3, 42.3, 34.6, 25.7, 24.7, 18.0, 13.9, -4.9, -5.0. The synthesis of **78b** was identical to that of **78a**. **78b:** (0.76 g, 1.55mmol, 81% yield; clear oil); R_f= 0.30 (50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28 (s, 1H), 6.11 (s, 1H), 5.43 (t, 1H, *J*= 6.9Hz), 5.09 (dd, 1H, *J*= 6.0Hz, *J*= 7.3Hz), 4.60 (t, 1H, *J*= 5.4Hz), 3.98 (s, 2H), 2.66 (dd, 1H, *J*= 5.9Hz, *J*= 13.8Hz), 2.59 (dd, 1H, *J*= 7.6Hz, *J*= 13.8Hz), 2.45 (dd, 2H, *J*= 7.4Hz, *J*= 14.2Hz), 1.98 (s, 3H), 1.63 (s, 3H), 0.90 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.6, 148.6, 142.2, 138.2, 137.5, 120.4, 79.8, 78.5, 68.7, 67.5, 42.2, 34.7, 25.8, 24.8, 18.1, 13.9, -4.7, -4.9; HRMS calcd. for $[M+Na]^+$ 515.1085, observed 515.1087.

Aldehyde (79a) and (79b): To a solution of **78a** (0.57 g, 1.16 mmol) and **30** (0.39 g, 1.51 mmol) in dry DMF (7.76 ml) was sparged with argon for 10 minutes. Copper (I) iodide (10 mg, 0.04 mmol) was added followed by $Pd(PPh_3)_4$ (50 mg, 0.05 mmol) and were added each in one portion at 25 °C. The reaction was allowed to stir for 2 hours. 50 ml of saturated NH_4Cl was then added and the aqueous was extracted 4X with 20 ml ether. The organics were then combined washed with brine and concentrated. Flash chromatography (up to 60% EtOAc in Hexanes) of the crude material afforded **79a** (0.40 g, 0.87 mmol, 75% yield) as a pale red oil**. 79a** R_f= 0.30 (50% EtOAc in Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.45 (s, 1H), 7.37 (s, 1H), 7.17 (d, 1H, *J*= 3.6Hz), 6.32 (d, 1H, *J*= 3.5Hz), 6.20 (s, 1H), 5.38 (t, 1H, *J*= 7.2Hz), 5.16 (m, 1H), 4.53 (s, 1H), 3.92 (d, 2H, *J*= 5.9Hz), 3.07 (dd, 1H, *J*= 3.7Hz, *J*= 13.9Hz), 2.62 (dd, 1H, *J*= 8.2Hz, *J*= 13.9Hz), 2.38 (m, 2H), 2.25 (t, 1H, *J*= 6.0Hz), 1.99 (s, 3H), 1.58 (s, 3H), 0.82 (s, 9H), -0.01 (s, 3H), -0.05 (s, 3H,); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.3, 171.8, 157.8, 151.4, 149.6, 140.8, 137.7, 137.5, 123.8, 120.5, 115.9, 111.3, 81.2, 68.7, 67.4, 38.0, 34.7, 26.5, 25.7, 18.0, 13.9, -4.9, -5.0; The synthesis of **79b** was identical to that of **79a**. **79b:** (0.42 g, 1.60mmol, 83% yield; clear oil); R_f= 0.25 (50% EtOAc in Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.48 (s, 1H), 7.42 (s, 1H), 7.18 (d, 1H, *J*= 3.7Hz), 6.32 (d, 1H, *J*= 3.6Hz), 6.20 (s, 1H), 5.40 (t, 1H, *J*= 7.3Hz), 5.18 (dd, 1H, *J*= 3.6Hz, *J*= 7.8Hz), 4.57 (t, 1H, *J*= 4.8Hz), 3.92 (s, 2H), 3.07 (dd, 1H, *J*= 3.8Hz, *J*=

13.9Hz), 2.63 (dd, 1H, *J*= 8.3Hz, *J*= 13.9Hz), 2.38 (m, 2H), 2.07 (s, 1H), 2.00 (s, 3H), 1.56 (s, 3H), 0.81 (s, 9H), 0.01 (s, 3H), -0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.4, 171.8, 157.6, 151.3, 149.7, 140.8, 137.6, 137.5, 123.7, 120.0, 115.8, 111.2, 81.3, 68.4, 67.2, 37.9, 34.4, 26.4, 25.5, 17.9, 13.7, -5.0, -5.1; HRMS calcd. For $[M+Na]^+$ 483.2173, observed 483.2171.

Primary bromide (80a) and (80b): To a solution of **79a** (0.27 g, 0.58 mmol) in CH_2Cl_2 (14.4 ml) at -20 °C was added PPh_3 (0.17 g, 0.64 mmol). Once dissolved, NBS (0.11 g, 0.64 mmol) was then added. The reaction was then stirred for 30 minutes at this temperature at which time, was quenched with water and then extracted with 20 ml of CH_2Cl_2 3X. The organic layers were then combined, dried and concentrated. Flash chromatography (up to 30% EtOAc in Hexanes) of the crude material afforded **80a** (0.27g, 0.51mmol, 88% yield) as a pale yellow oil. **80a** R_f= 0.70 (50% EtOAc in Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.53 (s, 1H), 7.42 (s, 1H), 7.20 (d, 1H, *J*= 3.7Hz), 6.36 (d, 1H, *J*= 3.6Hz), 6.25 (s, 1H), 5.61 (t, 1H, *J*= 7.2Hz), 5.22 (m, 1H), 4.60 (t, 1H, *J*= 4.8Hz), 3.94 (s, 2H), 3.17 (dd, 1H, *J*= 3.8Hz, *J*= 13.9Hz), 2.64 (dd, 1H, *J*= 8.3Hz, *J*= 13.9Hz), 2.43 (m, 1H), 2.05 (s, 3H), 1.74 (s, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.1, 171.5, 157.5, 151.3, 149.6, 140.6, 137.1, 134.3, 125.9, 123.5, 115.7, 111.1, 81.3, 67.0, 41.1, 37.9, 34.9, 26.6, 25.6, 17.9, 14.8, -5.0, -5.2; The synthesis of **80b** was identical to that of **80a**. **80b:** (0.25 g, 0.49 mmol, 81% yield; clear oil); R_f= 0.70 (50% EtOAc in Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.52 (s, 1H), 7.39 (t, 1H, *J*= 1.4Hz), 7.19 (d, 1H, *J*= 3.7Hz), 6.34 (d, 1H, *J*= 3.7Hz), 6.23 (s, 1H), 5.61 (t, 1H, *J*= 7.1Hz), 5.20 (tdd, 1H, *J*= 1.1Hz, *J*= 4.1Hz, *J*= 7.0Hz), 4.60 (s, 1H), 3.92 (s, 2H), 3.08 (dd, 1H, *J*= 4.3Hz, *J*= 13.9Hz), 2.72 (dd, 1H, *J*= 8.2Hz, *J*= 13.9Hz), 2.39 (m, 2H), 2.02 (d, 3H, *J*= 1.3Hz), 1.69 (s, 3H), 0.85 (s, 9H), 0.04 (s, 3H), -0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.4, 171.6, 157.5, 151.4, 149.6, 140.4, 137.4, 134.6, 126.0, 123.3, 116.0, 111.3, 81.2, 67.2, 41.2, 37.8, 34.9, 26.5, 25.6, 17.9, 14.8, -5.0, -5.1; HRMS calcd. For $[M+Na]^+$ 545.1329, observed 545.1326.

Norcembrenolide (81a) and (81b): To a vigorously stirred mixture of chromium (II) chloride (0.54 g, 4.4 mmol) and nickel (II) chloride DME complex (0.24 g, 1.09 mmol) in THF (66.0 ml) and activated powdered molecular sieves (1.8 g) was added **80a** (0.19 g, 0.36 mmol) in a solution of THF (6.6 ml) via syringe pump over 1.5 hours

at 25 °C. The reaction was then allowed to stir at 25 °C for 12 hours. The reaction was quenched by the addition of 50 ml of water and extracted 4X with 20 ml of fresh ether. The organic layers were then combined, washed with brine, dried and concentrated. Flash chromatography (up to 3% Acetonitrile in CH_2Cl_2) of the crude material afforded **81a** (0.13 g, 0.30 mmol, 83% yield) as a fluffy white powder. **81a** White powder mp 52-54 °C; R_f= 0.40 (2% Acetone in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.11 (s, 1H), 6.38 (d, 1H, *J*= 3.2Hz), 6.16 (m, 2H, *J*= 3.6Hz), 5.15 (s, 1H), 5.07 (m, 2H), 4.49 (d, 1H, *J*= 11.6Hz), 4.47 (m, 2H), 3.22 (t, 1H, *J*= 11.8Hz), 2.77 (dd, 1H, *J*= 4.7Hz, *J*= 11.9Hz), 2.19 (t, 1H, *J*= 11.1Hz), 2.01 (s, 3H), 1.94 (s, 1H),1.85 (m, 1H), 1.81 (s, 3H), 1.04 (t, 1H, *J*= 12.3Hz), 0.81 (s, 9H), 0.02 (s, 3H), -0.04 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.7, 153.7, 153.5, 152.3, 142.2, 136.3, 129.0, 118.5, 117.5, 112.3, 111.2, 78.9, 67.3, 63.0, 49.7, 39.8, 39.6, 29.7, 25.7, 18.0, 17.6, -4.8, -5.1; The synthesis of **81b** was identical to that of **81a**. **81b:** (0.13 g, 0.30mmol, 83% yield; white powder 50-52 °C; R_f= 0.35 (2% Acetone in DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.64 (s, 1H), 6.34 (d, 1H, *J*= 3.3Hz), 6.16 (s, 1H), 6.13 (d, 1H, *J*= 3.2Hz), 5.04 (s, 1H), 5.01 (s, 1H), 4.92 (dd, 1H, *J*= 5.1Hz, *J*= 11.6Hz), 4.61 (m, 1H), 4.42 (d, 1H, *J*= 10.3Hz), 3.22 (t, 1H, *J*= 11.8Hz), 2.75 (dd, 1H, *J*= 5.1Hz, *J*= 12.0Hz), 2.53 (m, 1H), 2.29 (s, 1H), 2.21 (m, 1H), 1.98 (s, 3H), 1.83 (s, 3H), 1.34 (td, 1H, *J*= 5.1Hz, *J*= 14.1Hz), 0.85 (s, 9H), -0.04 (s, 3H), -0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.1, 153.7, 152.6, 145.5, 133.0, 130.3, 117.4, 115.3, 111.5, 110.7, 77.5, 68.3, 37.4, 49.2, 40.0, 39.8, 26.0, 25.7, 19.8, 18.2, -5.1, -5.3; HRMS calcd. For $[M+Na]^+$ 467.2224, observed 467.2227.

Diol (82a) and (68): To a solution of **81a** (40 mg, 0.090 mmol) in MeCN (0.45 ml) was added triethylamine hydrogen fluoride complex (0.15 ml, 0.90 mmol). The reaction was then microwaved in a sealed tube at 80 °C for 20 minutes. The reaction was then quenched with 5 ml of saturated $NaHCO_3$. The mixture was then extracted 3X with 5 ml of EtOAc. The organic layers were then combined, dried, and concentrated. Flash chromatography (up to 55% EtOAc in Hexanes) of the crude material afforded **82a** (27mg, 0.08 mmol, 91% yield) as a white powder mp 170-174 °C; R_f= 0.30 (50% EtOAc in Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.15 (s, 1H), 6.39 (d, 1H, *J*= 3.2Hz), 6.18 (s, 1H), 6.16 (d, 1H, *J*= 3.3Hz), 5.14 (s, 1H), 5.07 (dd, 1H, *J*= 4.0Hz, *J*= 12.0Hz), 5.04 (s, 1H), 4.57 (dd, 1H, *J*= 4.0Hz, *J*= 11.9Hz), 4.50 (d, 1H, *J*= 10.8Hz),

3.23 (t, 1H, *J*= 11.9Hz), 2.79 (dd, 1H, *J*= 4.7Hz, *J*= 11.9Hz), 2.20 (t, 1H, *J*= 11.0Hz), 2.02 (s, 3H), 1.94 (m, 1H), 1.82 (s, 3H), 1.05 (t, 1H, *J*= 12.3Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.3, 154.2, 153.4, 150.7, 142.1, 135.8, 128.9, 118.5, 117.6, 112.4, 111.3, 79.1, 67.4, 62.5, 49.9, 39.5, 38.7, 25.8, 17.6; The synthesis of **68** was identical to that of **82a**. **68:** (25mg, 0.07mmol, 89% yield; white powder 182-185 °C; R_f= 0.35 (50% EtOAc in Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.76 (s, 1H), 6.37 (d, 1H, *J*= 3.3Hz), 6.16 (s, 1H), 6.13 (d, 1H, *J*= 3.2Hz), 5.14 (s, 2H), 5.10 (m, 1H), 4.90 (m, 1H), 4.64 (d, 1H, *J*= 8.7Hz), 4.38 (d, 1H, *J*= 10.6Hz), 3.32 (t, 1H, *J*= 11.9Hz), 2.81 (dd, 1H, *J*= 5.1Hz, *J*= 11.9Hz), 2.65 (t, 1H, *J*= 10.5Hz), 2.23 (m, 2H), 2.01 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.9, 153.3, 152.3, 150.9, 150.8, 145.1, 131.2, 128.9, 117.6, 112.5, 111.1, 79.3, 68.9, 66.9, 49.0, 39.5, 38.7, 25.6, 17.7; HRMS calcd. For $[M+Na]^+$ 353.1359, observed 353.1363.

C_{13}-alcohol (67) and (83b): To a solution of **82a** (21 mg, 0.064 mmol) in CH_2Cl_2 (1.27 ml) at -40 °C was added triethylsilane (0.041 ml, 0.25 mmol) followed by TFA (9.79 μl, 0.127 mmol). The reaction was stirred for 15 minutes at which time 10 ml of saturated $NaHCO_3$ solution was added. The solution was extracted 3X with 10 ml of fresh CH_2Cl_2. The organic layers were then combined, dried and concentrated. Flash chromatography (up to 30% EtOAc in Hexanes) of the crude material afforded **67** (16 mg, 0.05 mmol, 81% yield) as clear crystals who's spectral data is identical to its original synthetic procedure. **67**; clear crystals mp 162-164 °C; R_f= 0.25 (40% EtOAc in Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.17 (s, 1H), 6.13 (s, 1H), 6.11 (d, 1H, *J*= 3.2Hz), 6.07 (dd, 1H, *J*= 1.1Hz, *J*= 3.1Hz), 5.04 (ddd, 1H, *J*= 1.3Hz, *J*= 4.5Hz, *J*= 11.8Hz), 4.89 (s, 2H), 4.57 (dd, 1H, *J*= 4.0Hz, *J*= 11.8Hz), 3.21 (t, 1H, *J*= 11.8Hz), 2.75 (dd, 1H, *J*= 4.6Hz, *J*= 11.9Hz), 2.64 (m, 2H), 2.17 (dt, 1H, *J*= 5.1Hz, *J*= 11.4Hz), 2.00 (s, 3H), 1.93 (m, 1H), 1.81 (dd, 1H, *J*= 5.6Hz, *J*= 14.6Hz), 1.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.1, 154.0, 153.7, 151.2, 145.3, 135.9, 126.9, 117.7, 113.0, 111.5, 109.3, 79.2, 62.7, 42.3, 39.8, 39.4, 32.9, 25.7. 19.2; The synthesis of **83b** was identical to that of **67**. **83b:** (17 mg, 0.05mmol, 81% yield; clear crystals mp 168-169 °C; R_f= 0.25 (40% EtOAc in Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.79 (s, 1H), 6.11 (s, 1H), 6.08 (d, 1H, *J*= 3.2Hz), 6.03 (d, 1H, *J*= 2.8Hz), 5.06 (tdd, 1H, *J*= 1.4Hz, *J*= 4.8Hz, *J*= 11.7Hz), 4.97 (s, 1H), 4.85 (m, 2H), 4.25 (d, 1H, *J*= 8.7Hz), 3.30 (t, 1H, *J*= 11.8Hz),

2.77 (dd, 1H, *J*= 4.9Hz, *J*= 11.9Hz), 2.65 (m, 3H), 2.22 (ddd, 1H, *J*= 4.2Hz, *J*= 7.5Hz, *J*= 13.0Hz), 1.99 (s, 3H), 1.80 (s, 3H), 1.22 (dd, 1H, *J*= 2.2Hz, *J*= 4.0Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.0, 173.7, 153.8, 151.2, 148.4, 131.5, 127.4, 117.7, 112.1, 111.2, 108.9, 79.3, 69.0, 41.8, 39.8, 39.6, 34.0, 25.6, 19.1; HRMS calcd. For $[M+Na]^+$ 337.1410, observed 337.1407.

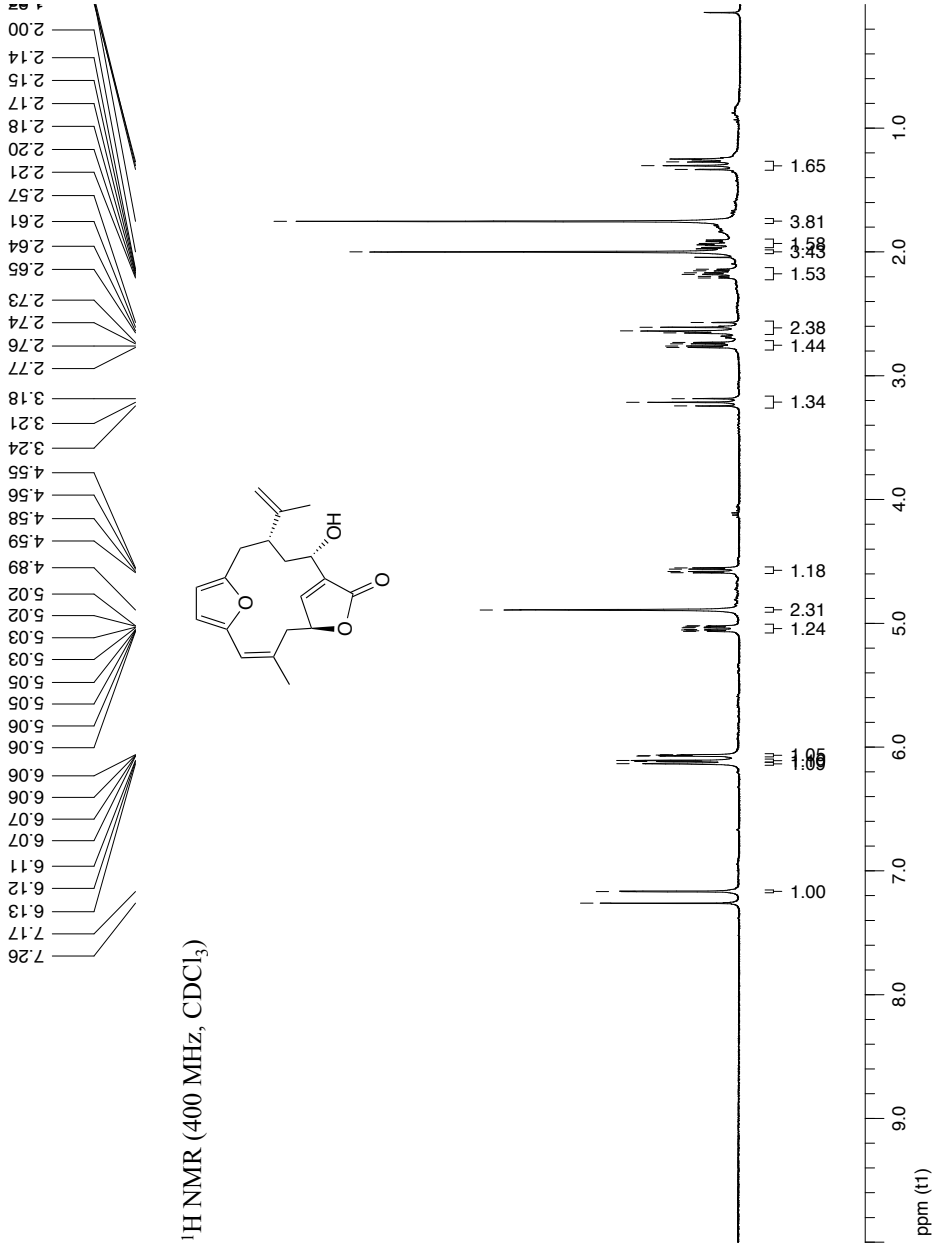
Epoxide (84a) and (84b): To a solution of **67** (20 mg, 0.064 mmol) in THF (1.2 ml) at 0 °C was added tBuOOH 5M in decane (0.02 ml, 0.1 mmol) followed by Triton B 40% in MeOH (2.9 μl, 6.36 μmol) The reaction was stirred for 10 minutes at which time was quenched with 5 ml of saturated $Na_2S_2O_3$ followed by saturated 5 ml of saturated NH_4Cl. The mixture was then extracted 3X with 5 ml of ethyl acetate. Organics were then dried and concentrated. Flash chromatography (up to 30% EtOAc in Hexanes) of the crude material afforded **84a** (15 mg, 0.045 mmol, 70% yield) as clear crystals**. 84a** clear crystals mp 150-155 °C; R_f= 0.40 (40% EtOAc in Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.19 (s, 1H), 6.11 (d, 1H, *J*= 3.0Hz), 6.05 (s, 1H), 4.96 (s, 1H), 4.91 (s, 1H), 4.67 (dd, 1H, *J*= 4.8Hz, *J*= 12.6Hz), 4.56 (dd, 1H, *J*= 3.2Hz, *J*= 11.2Hz), 3.90 (s, 1H), 3.70 (t, 1H, *J*= 12.7Hz), 2.82 (dd, 1H, *J*= 2.7Hz, *J*= 15.4Hz), 2.60 (dd, 1H, *J*= 12.1Hz, *J*= 15.3Hz), (dd, 1H, *J*= 5.1Hz, *J*= 12.4Hz), 2.46 (dt, 1H, *J*= 1.6Hz, *J*= 11.7Hz), 1.98 (s, 3H), 1.95 (m, 1H), 1.78 (s, 3H), 1.06 (t, 1H, *J*= 12.1Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.7, 152.7, 150.7, 144.7, 126.6, 118.2, 112.9, 111.1, 108.8, 77.1, 61.9, 61.3, 60.9, 40.9, 36.7, 36.0, 33.1, 25.0, 19.6; The synthesis of **84b** was identical to that of **84a**. **84b:** (14 mg, 0.045 mmol, 70% yield clear crystals mp 156-158 °C; R_f= 0.40 (40% EtOAc in Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.20 (s, 1H), 6.09 (d, 1H, *J*= 3.1Hz), 6.03 (d, 1H, *J*= 3.2Hz), 4.93 (s, 1H), 4.88 (s, 1H), 4.67 (dd, 1H, *J*= 5.1Hz, *J*= 12.6Hz), 3.89 (dd, 1H, *J*= 4.4Hz, *J*= 5.8Hz), 3.85 (s, 1H), 3.63 (t, 1H, *J*= 12.7Hz), 2.78 (m, 2H), 2.67 (m, 1H), 2.60 (dd, 1H, *J*= 5.4Hz, *J*= 13.1Hz), 2.23 (m, 1H),1.98 (s, 3H), 1.81 (s, 3H), 1.49 (td, 1H, *J*= 4.4Hz, *J*= 14.9Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.0, 152.9, 150.7, 147.5, 127.8, 118.3, 112.3, 110.6, 108.3, 77.0, 70.9, 62.4, 59.0, 41.8, 36.5, 36.4, 33.3, 24.8, 19.2; HRMS calcd. For $[M+Na]^+$ 353.1359, observed 353.1358.

Deoxynorbipinnatolide F (85): To a solution of **84b** (11 mg, 0.03 mmol) in PhH (0.4 ml) at 0 °C was added CAN (46 mg, 0.08 mmol) in one portion followed by two drops of water. The reaction was then stirred for 15 minutes. The solution was

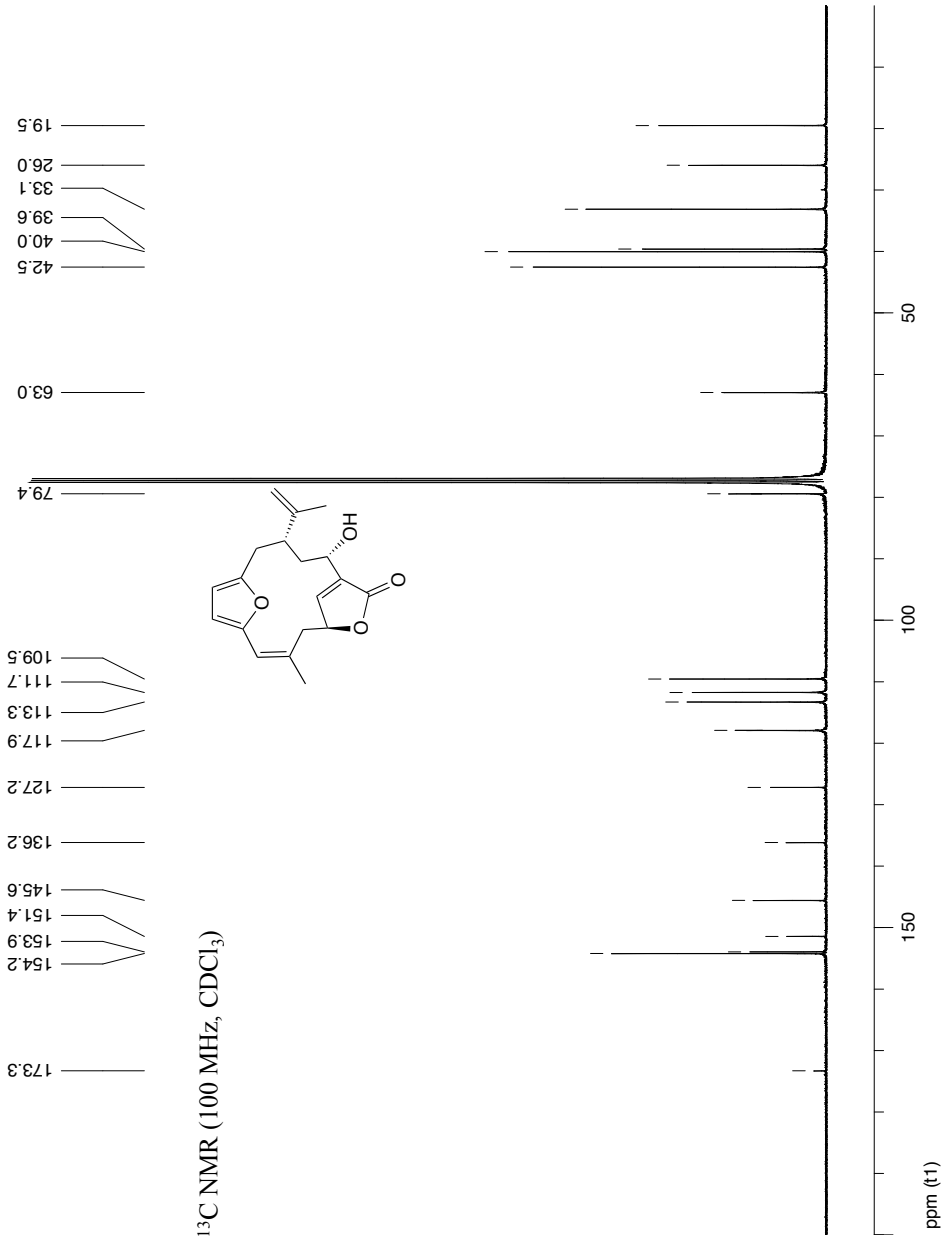
then quenched with 1 ml of saturated $NaHCO_3$ and extracted 3X with 1 ml of ether. The organic layers were combined, dried and concentrated. Flash chromatography (up to 40% EtOAc in Hexanes) of the crude material afforded **85** (5.7 mg, 0.017 mmol, 50% yield) as a white amorphous solid. **85** White solid mp 163-165 °C R_f= 0.35 (40% EtOAc in Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.25 (s, 1H), 5.92 (d, 1H, *J*= 12.3Hz), 5.63 (d, 1H, *J*= 12.3Hz), 4.92 (d, 1H, *J*= 8.3Hz), 4.88 (dd, 1H, *J*= 2.9Hz, *J*= 12.3Hz), 4.75 (s, 1H), 4.67 (s, 1H), 4.27 (s, 1H), 4.16 (d, 1H, *J*= 13.0Hz), 2.59 (dd, 1H, *J*= 8.2Hz, *J*= 12.9Hz), 2.58 (m, 1H), 2.35 (t, 1H, *J*= 7.5Hz), 1.98 (s, 3H), 1.95 (m, 1H), 1.70 (s, 3H), 1.63 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.6, 187.7, 153.8, 148.9, 134.1, 131.8, 127.9, 109.8, 95.8, 77.8, 77.2, 64.7, 59.1, 38.8, 35.5, 33.2, 30.1, 29.6, 20.8; HRMS calcd. For $[M+Na]^+$ 346.1457, observed 346.1453.

Spiro-ketal cembrenolide (86): To a solution of **82a** (10 mg, 0.03 mmol) in PhH (0.58 ml) at 0 °C was added CAN (41 mg, 0.08 mmol) followed by two drops of water. The reaction was allowed to stir for 20 minutes at which time, 1 ml of saturated. $NaHCO_3$ was added. The solution was then vigorously stirred for 10 minutes, and then extracted 3X times with 1 ml of EtOAc. The organic layers were then combined, dried and concentrated. Flash chromatography (up to 40% EtOAc in Hexanes) of the crude material afforded **86** (8.1 mg, 0.023 mmol, 77% yield) as a white solid. **86** clear crystals mp 138-139 °C R_f= 0.25 (80% EtOAc in Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46 (s, 1H), 6.35 (d, 1H, *J*= 5.7Hz), 6.24 (d, 1H, *J*= 5.8Hz), 5.11 (s, 1H), 4.94 (s, 2H), 4.79 (s, 1H), 4.75 (m, 1H), 3.87 (d, 1H, *J*= 10.8Hz), 3.06 (dd, 1H, *J*= 3.9Hz, *J*= 13.8Hz), 2.70 (m, 2H), 2.14 (dd, 1H, *J*= 4.2Hz, *J*= 15.5Hz), 1.97 (m, 1H), 1.81 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.9, 152.7, 151.7, 143.9, 132.9, 132.8, 129.9, 113.6, 110.8, 79.1, 72.6, 69.9, 66.8, 57.1, 47.0, 43.8, 32.8, 30.0, 19.3; HRMS calcd. For $[M+Na]^+$ 369.1309, observed 369.1308.

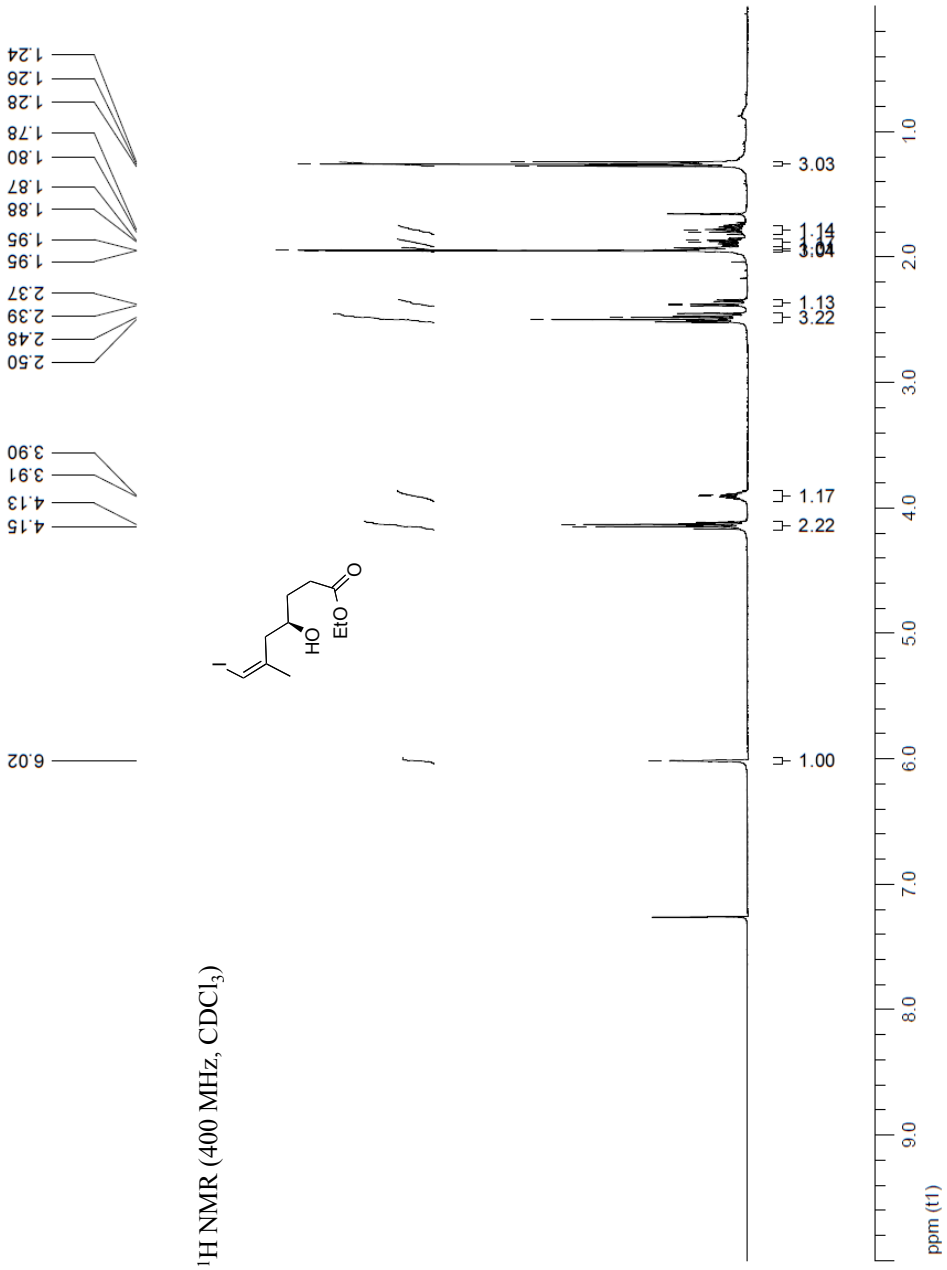
2.6.3 ^{1}H and ^{13}C NMR Spectra



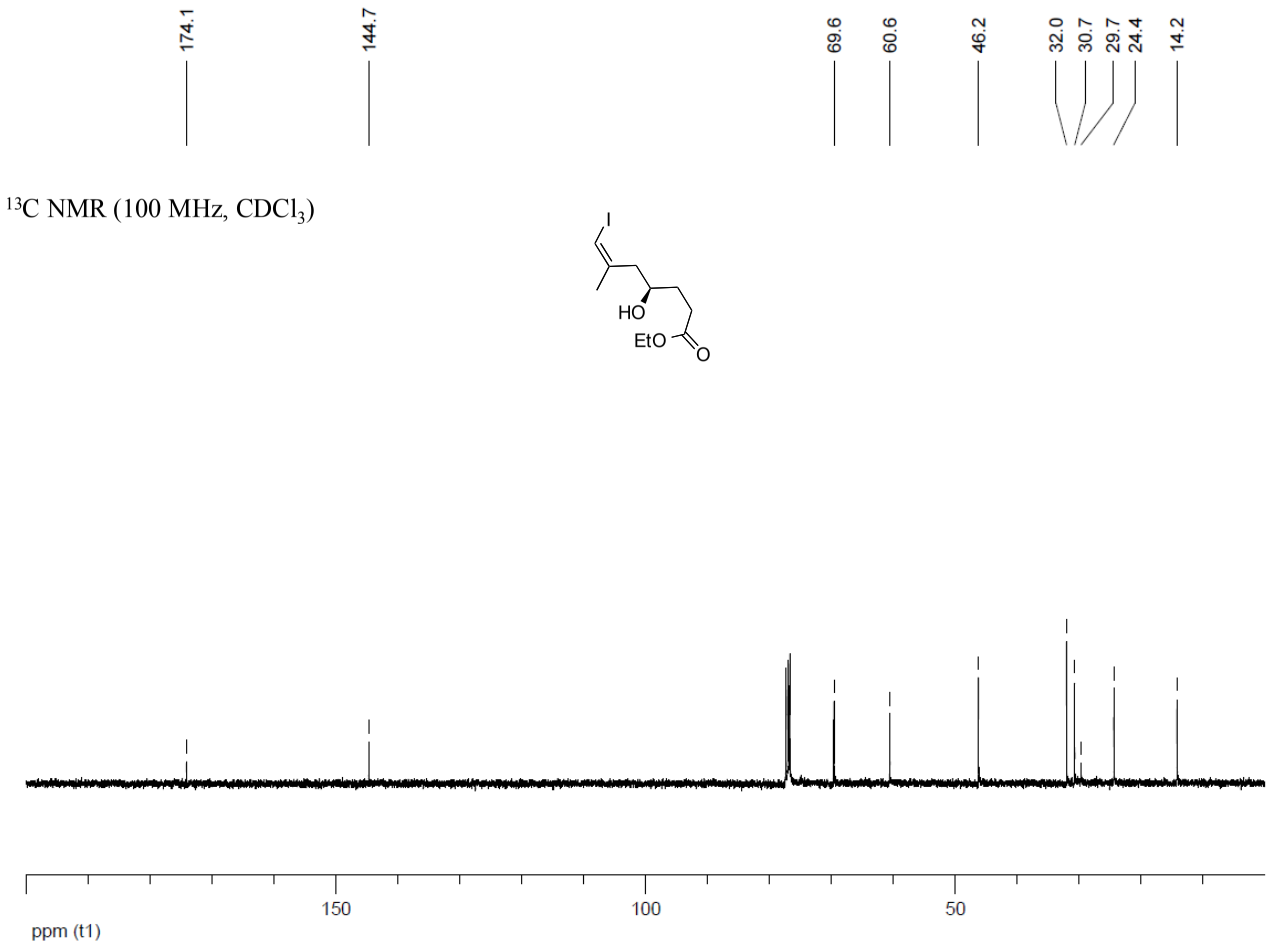
Spectrum 2.1: Compound *67*: ^{1}H NMR



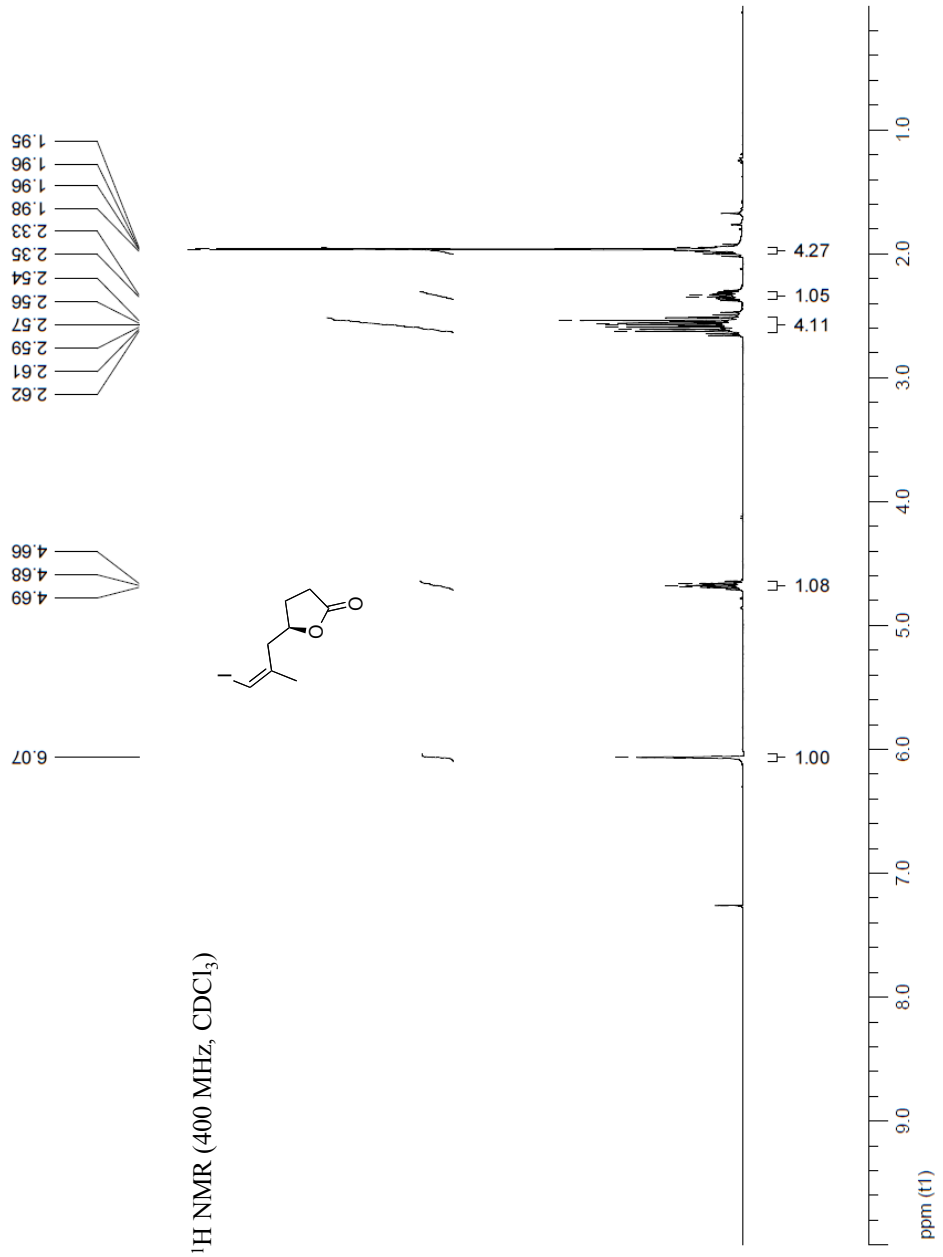
Spectrum 2.2: Compound 67: ^{13}C NMR



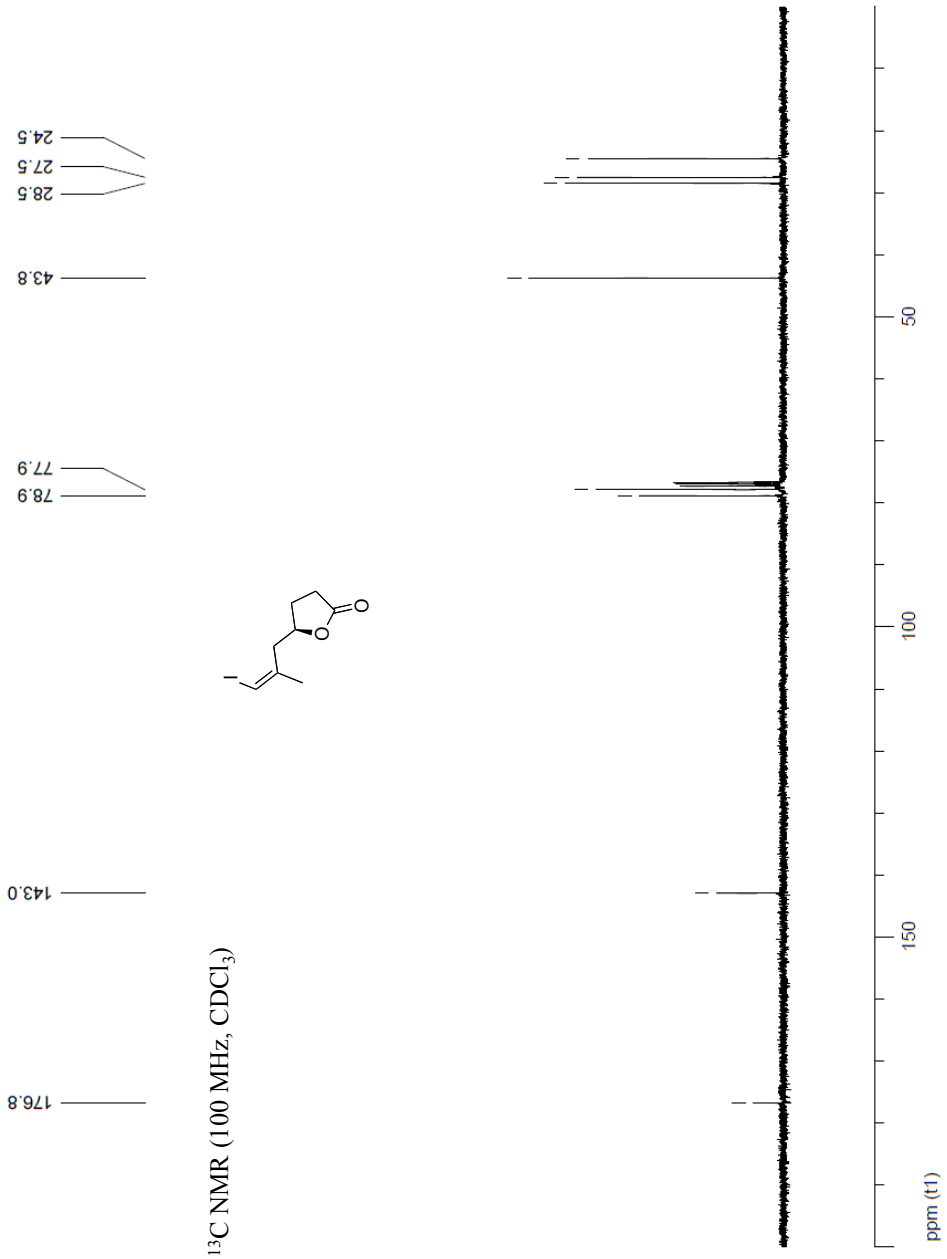
Spectrum 2.3: Compound 71: ^{1}H NMR



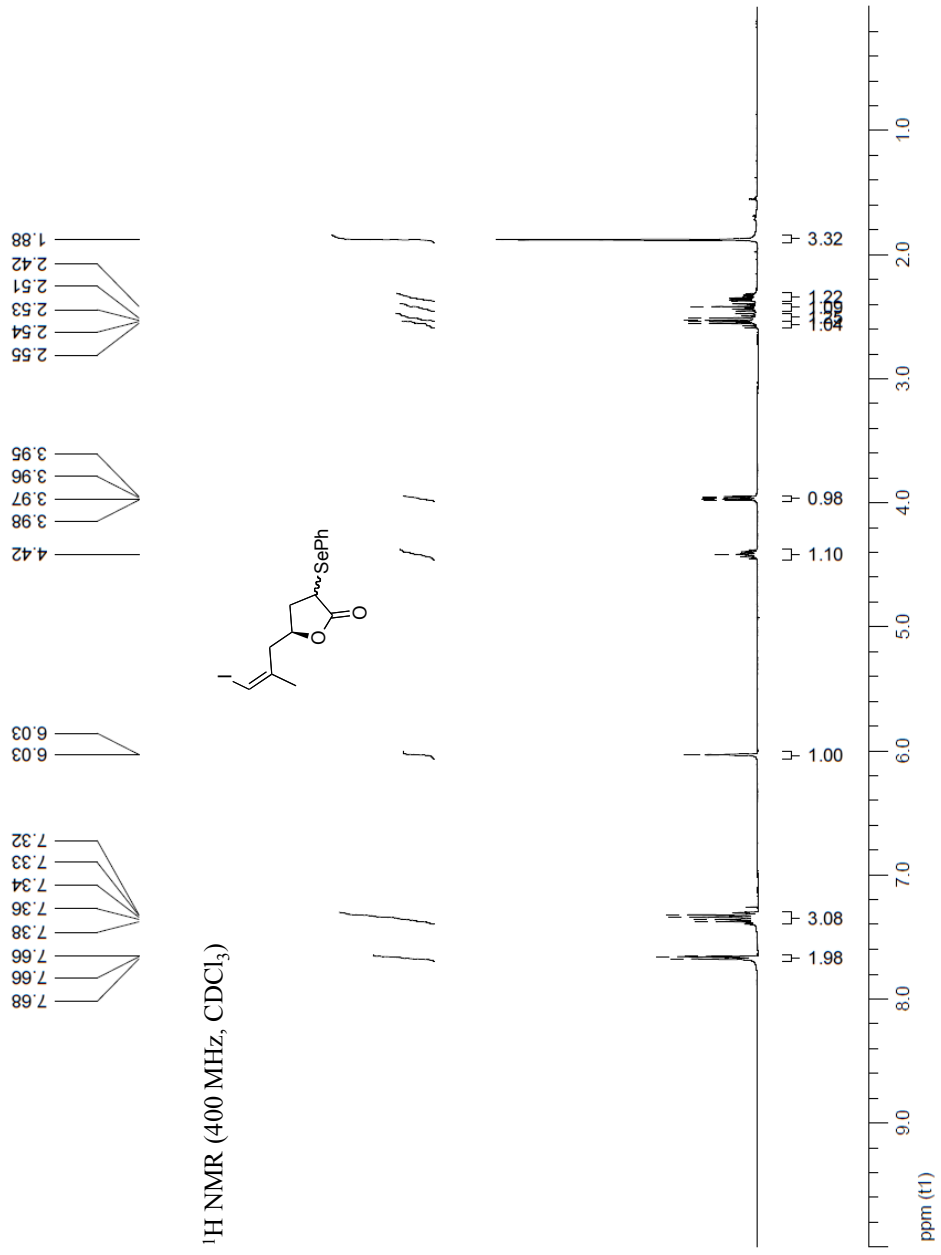
Spectrum 2.4: Compound 71: ^{13}C NMR



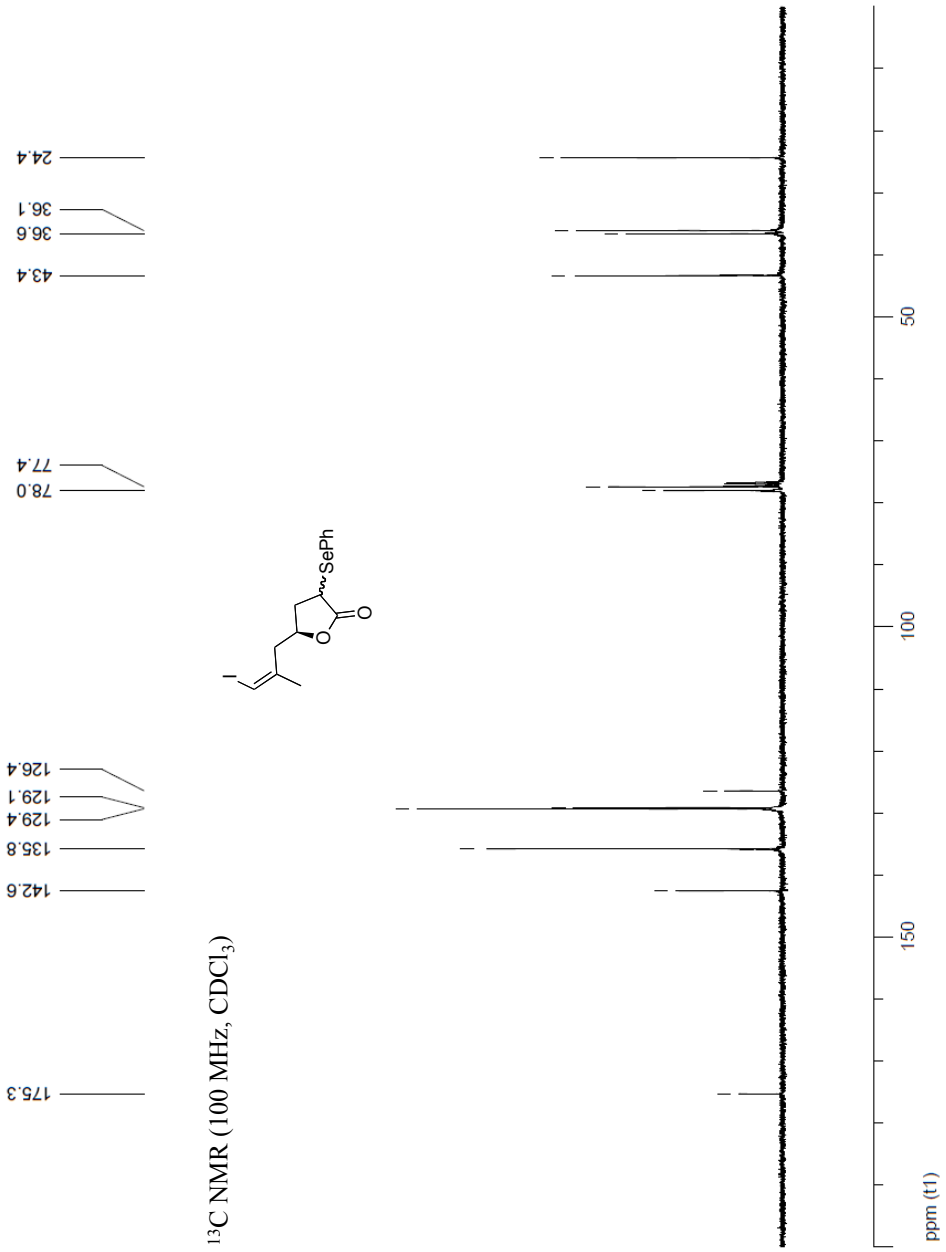
Spectrum 2.5: Compound 72: ^{1}H NMR



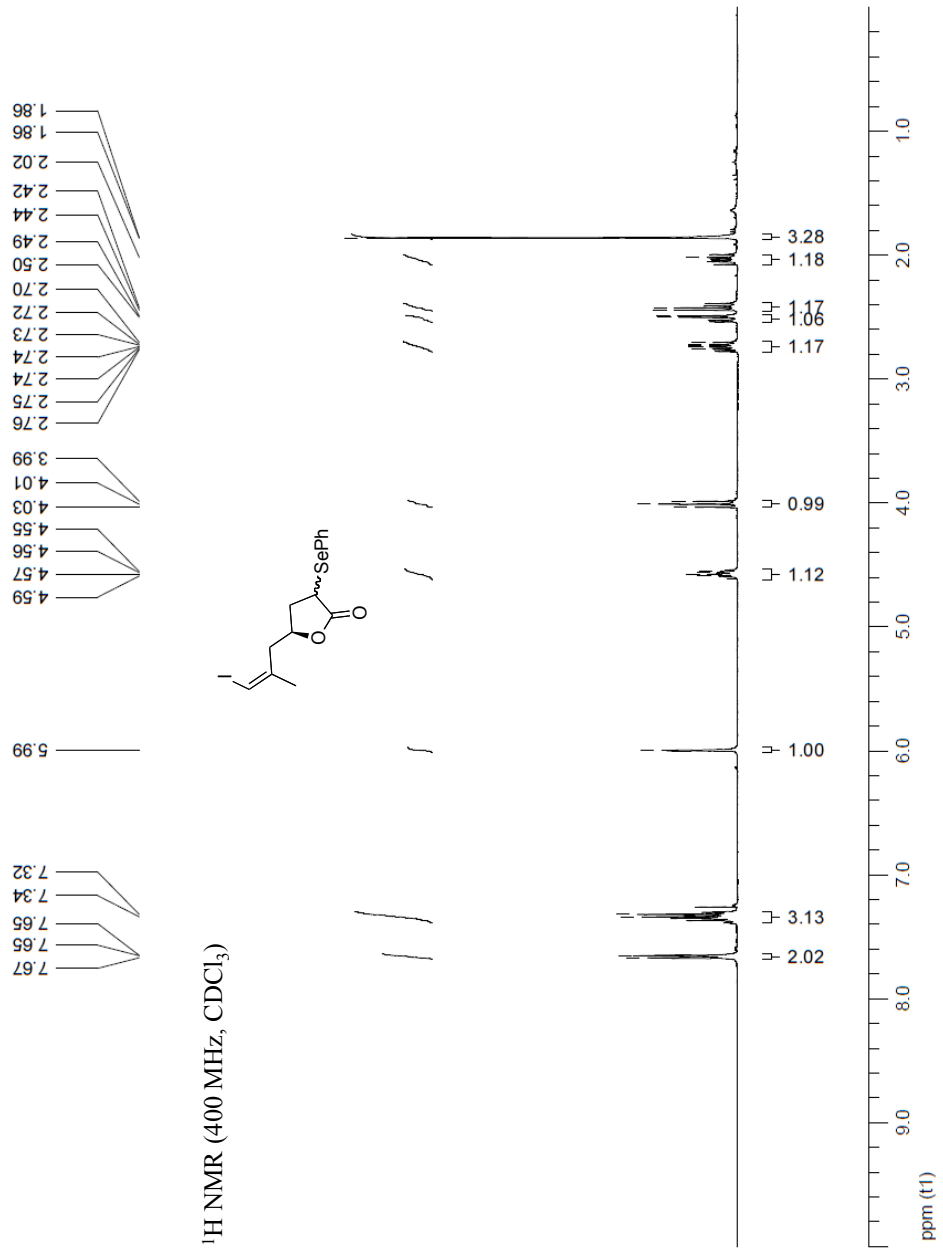
Spectrum 2.6: Compound 72: ^{13}C NMR



Spectrum 2.7: Compound 69i: ^{1}H NMR

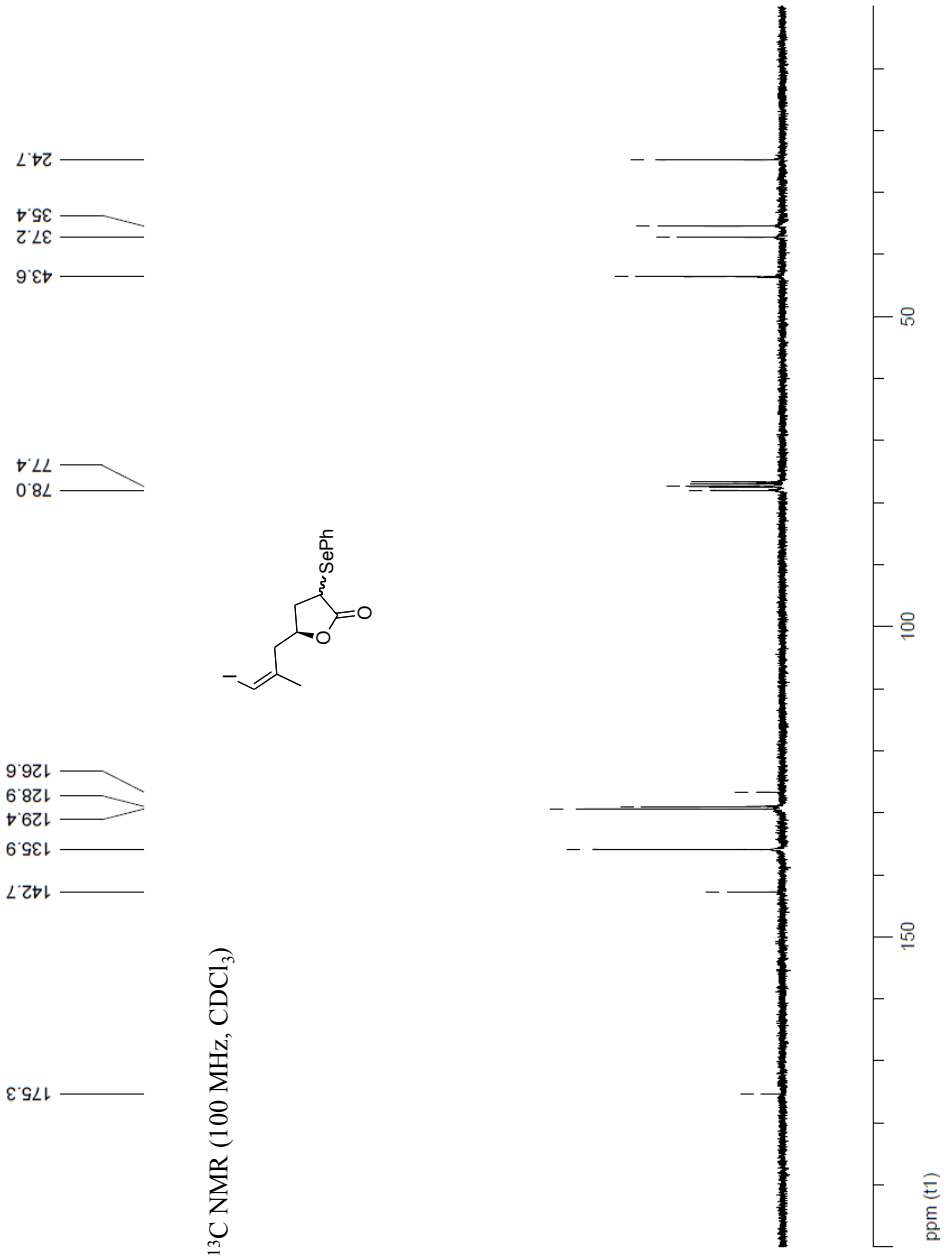


Spectrum 2.8: Compound 69i: ^{13}C NMR

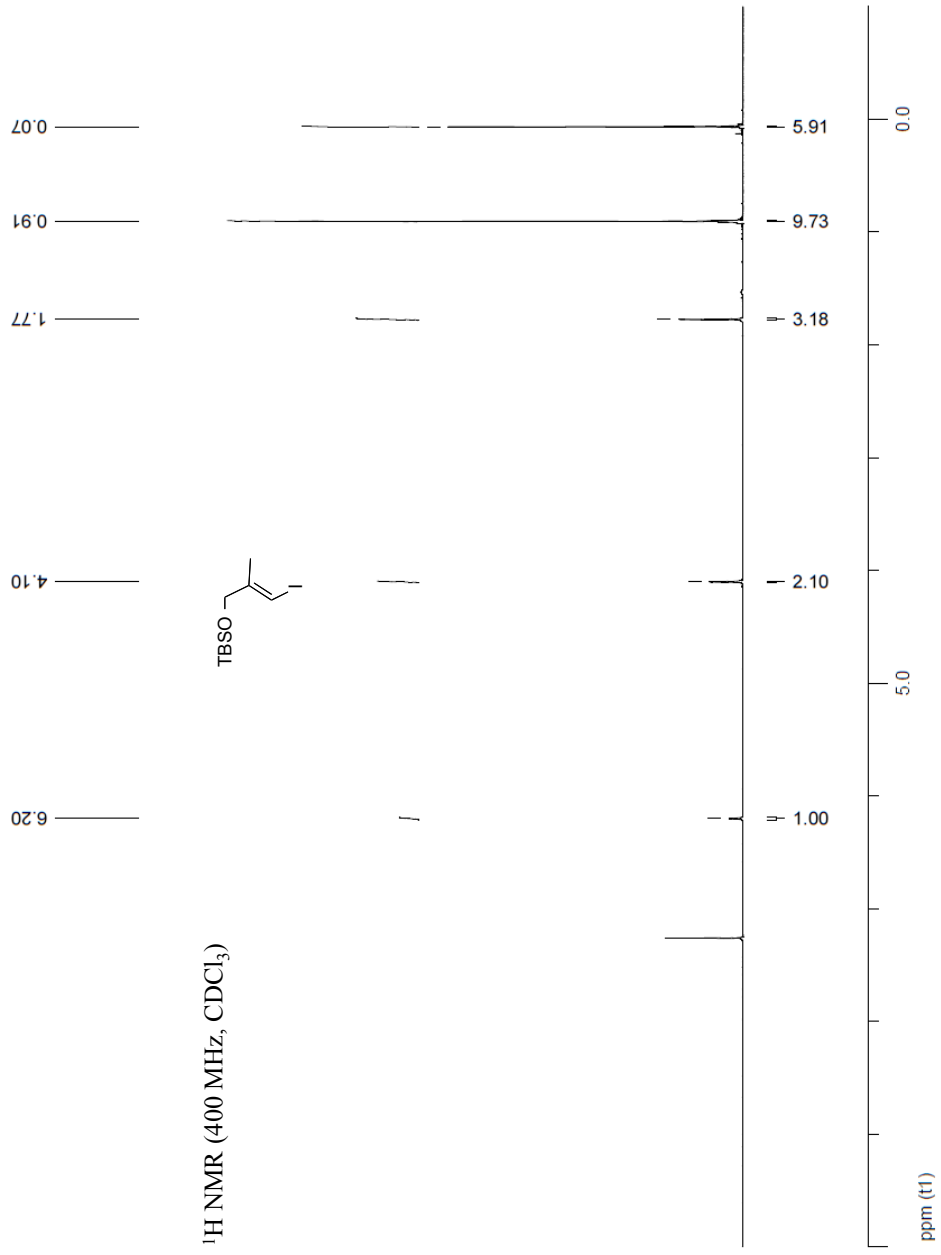


^{1}H NMR (400 MHz, $CDCl_3$)

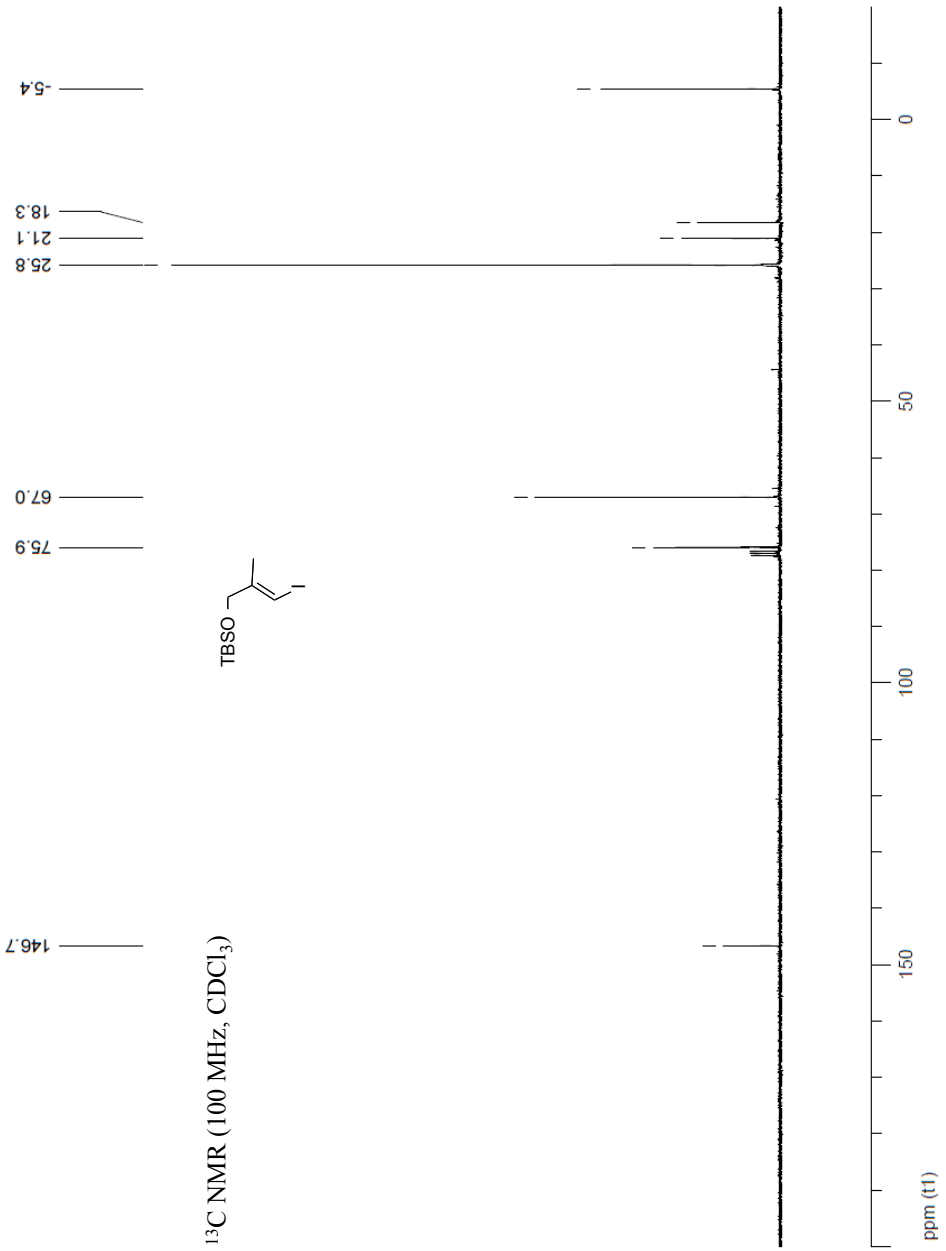
Spectrum 2.9: Compound 69ii: ^{1}H NMR



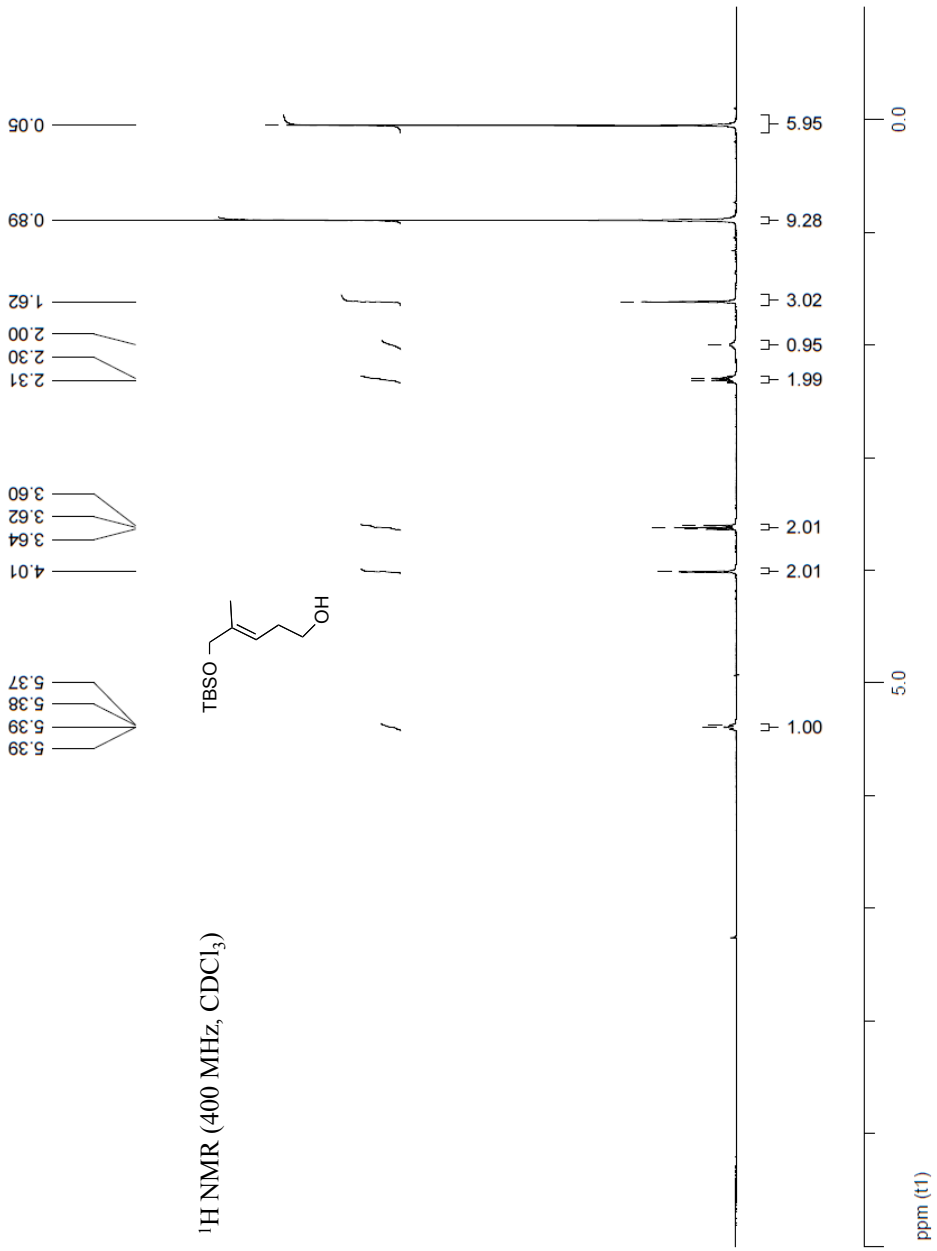
Spectrum 2.10: Compound 69ii: ^{13}C NMR



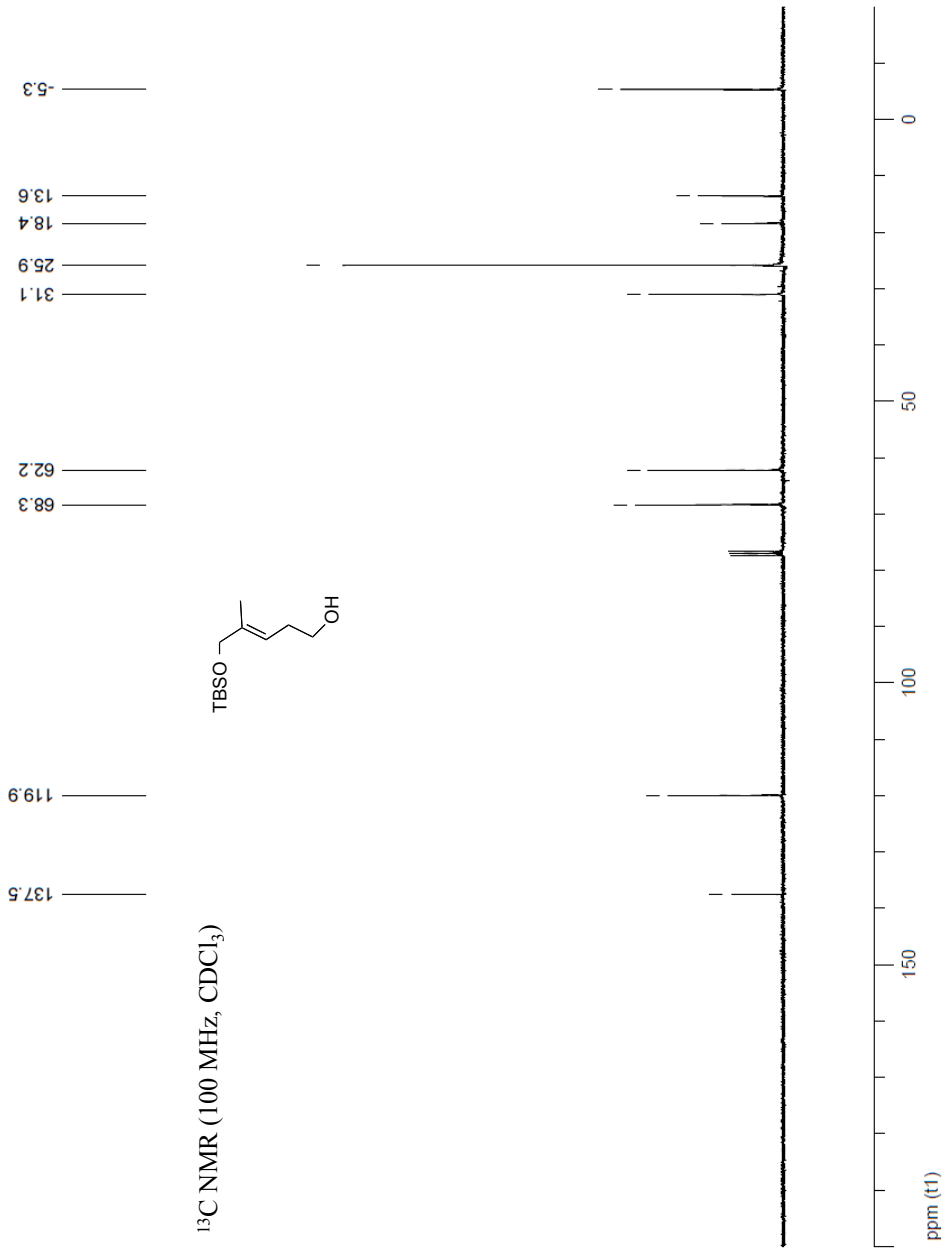
Spectrum 2.11: Compound 74: ^{1}H NMR



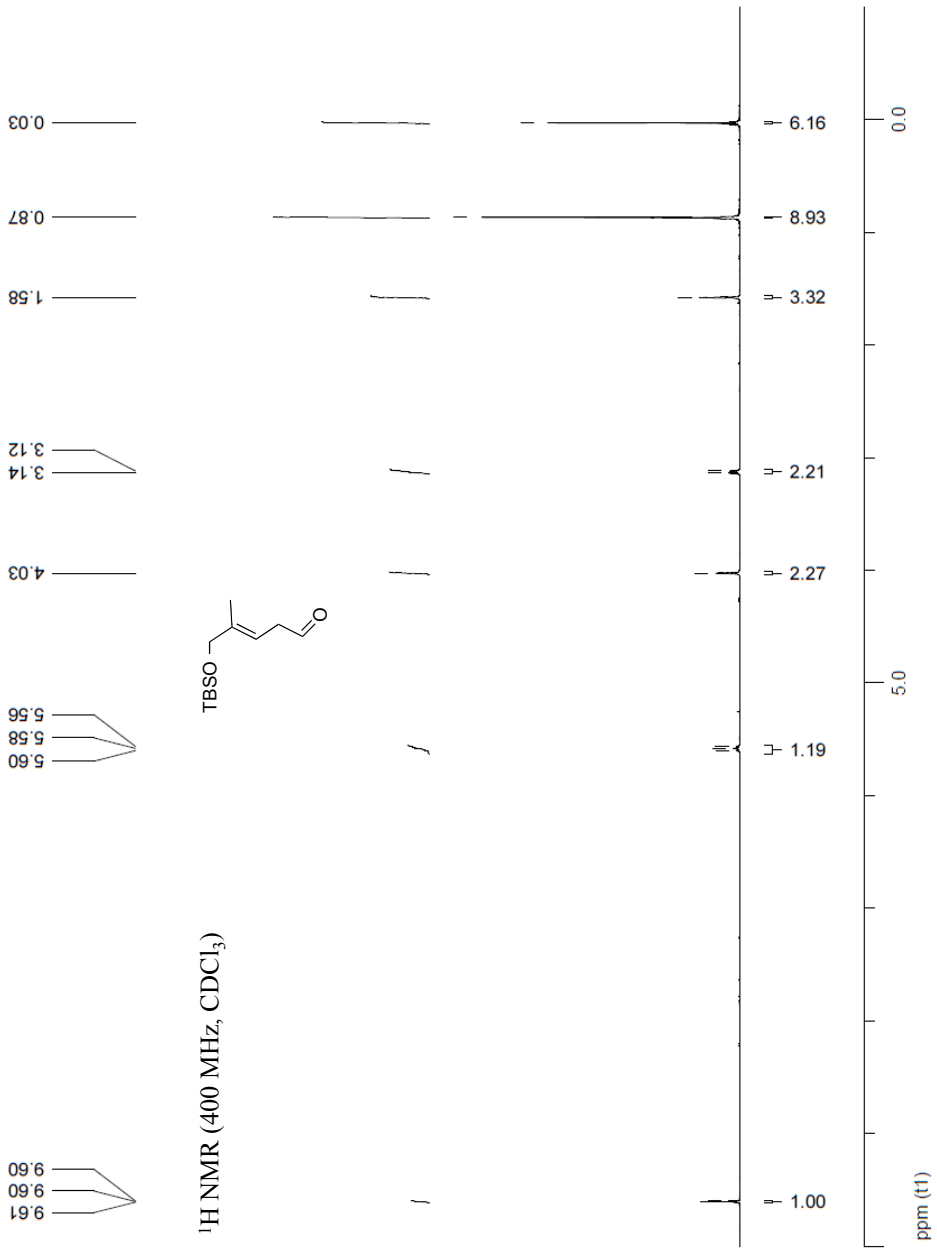
Spectrum 2.12: Compound 74: ^{13}C NMR



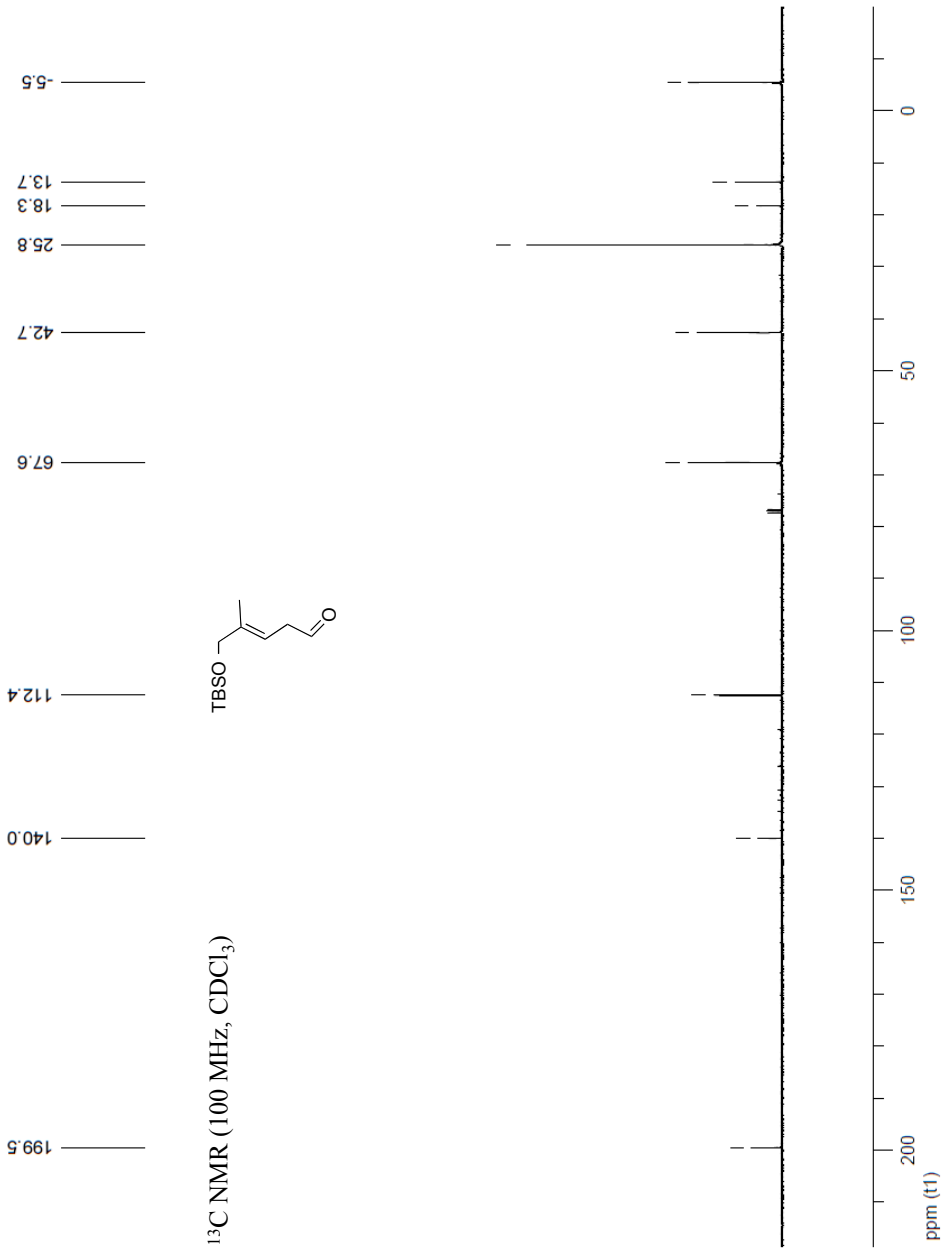
Spectrum 2.13: Compound 75: ^{1}H NMR



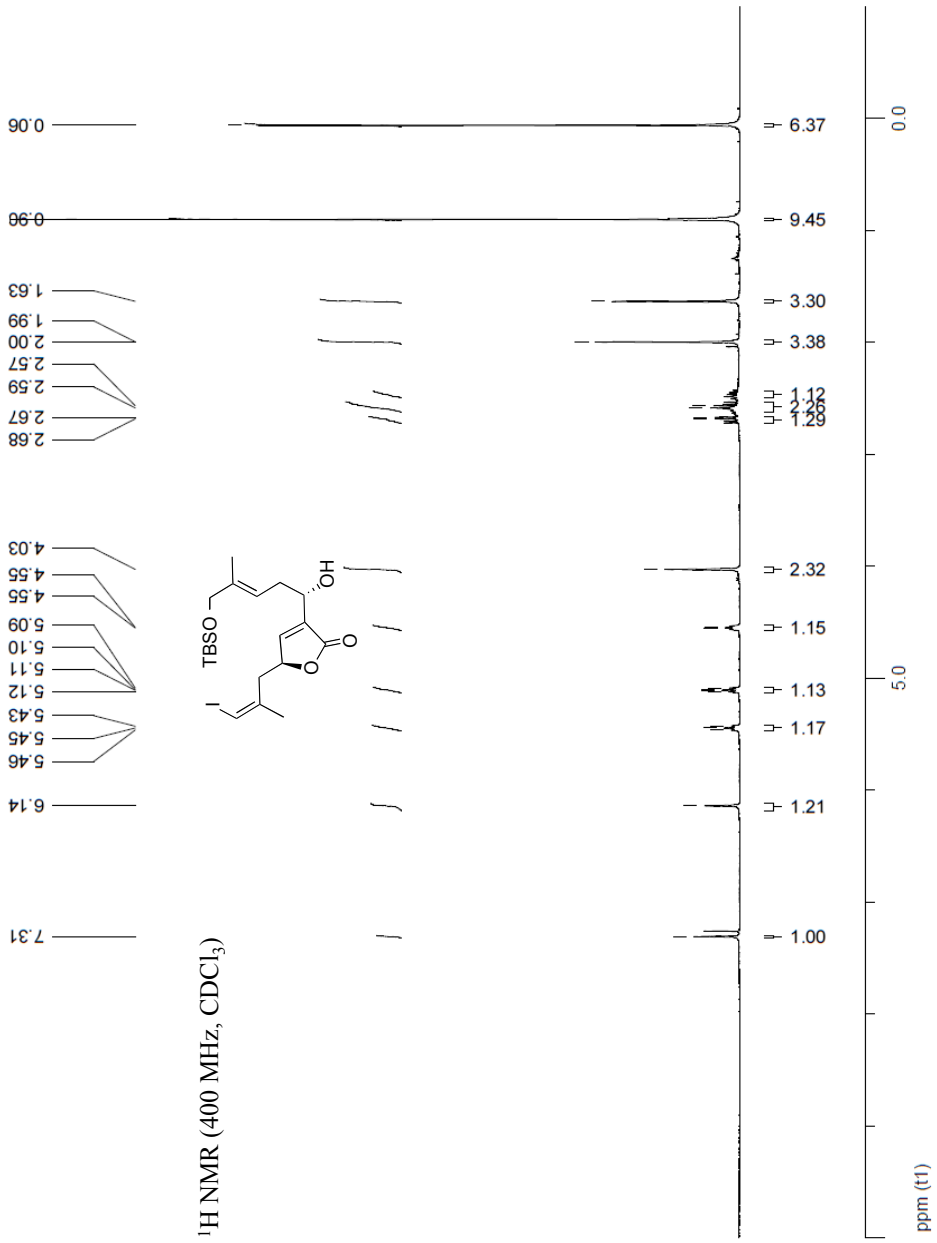
Spectrum 2.14: Compound 75: ^{13}C NMR



Spectrum 2.15: Compound 70: ^{1}H NMR

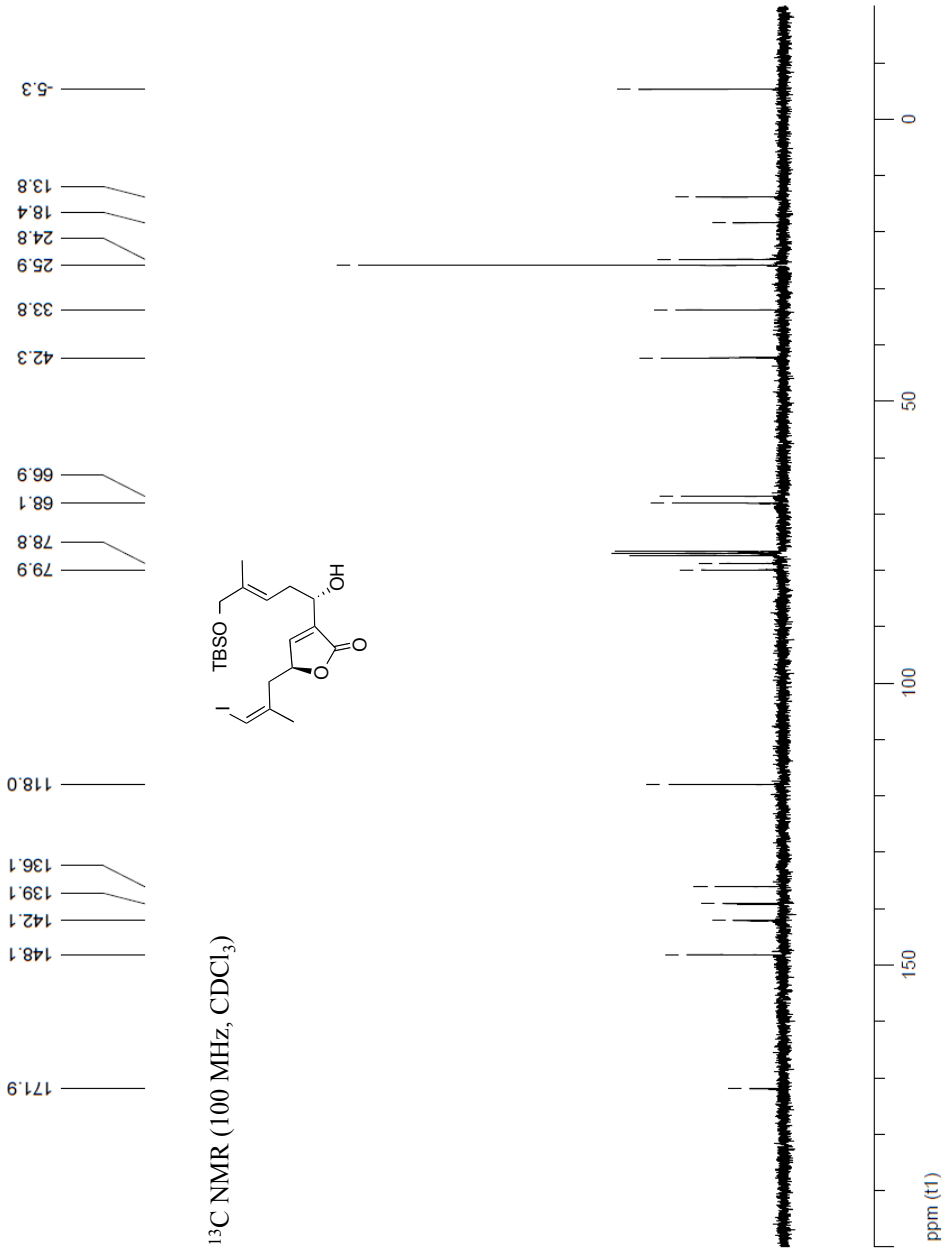


Spectrum 2.16: Compound 70: ^{13}C NMR

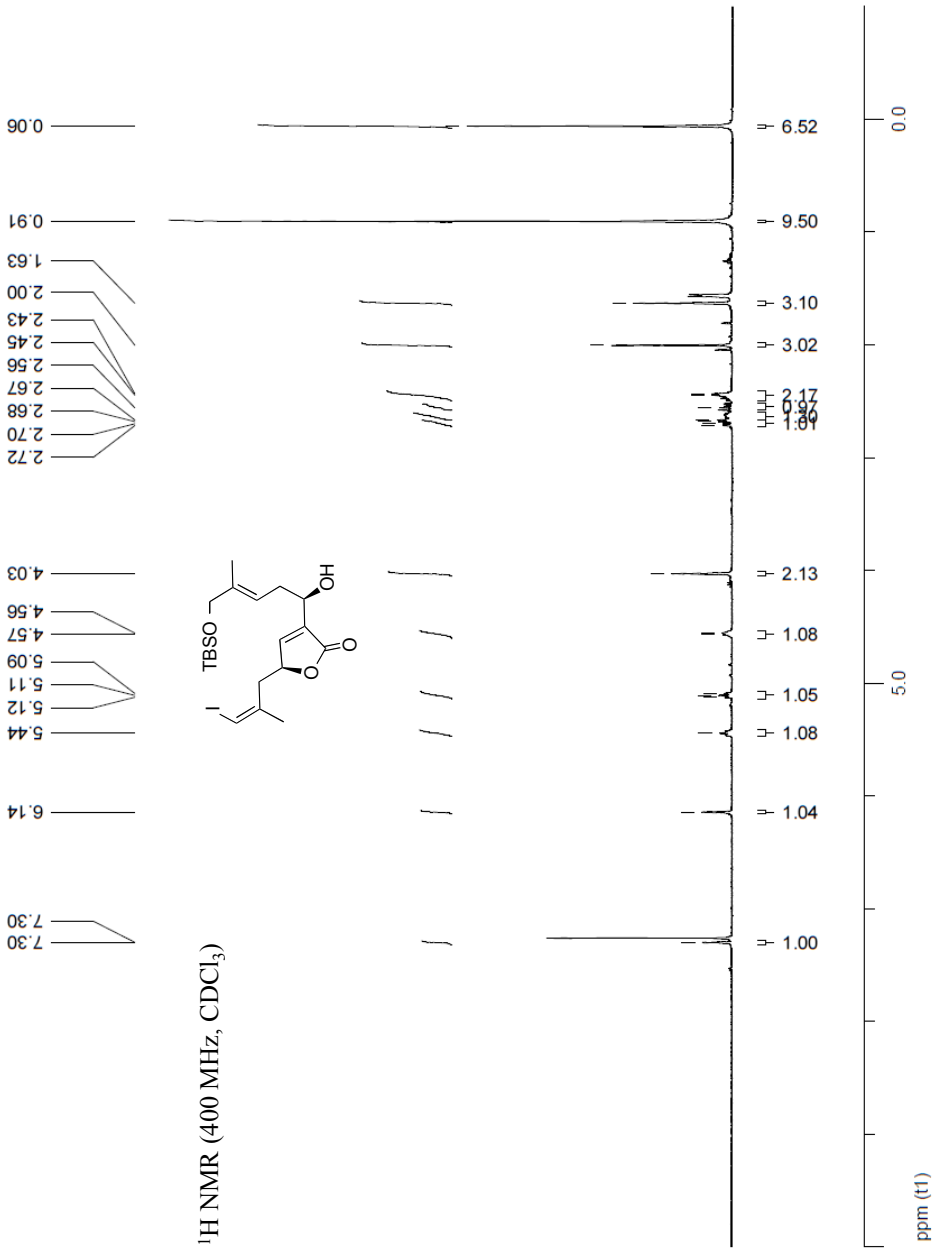


^{1}H NMR (400 MHz, $CDCl_3$)

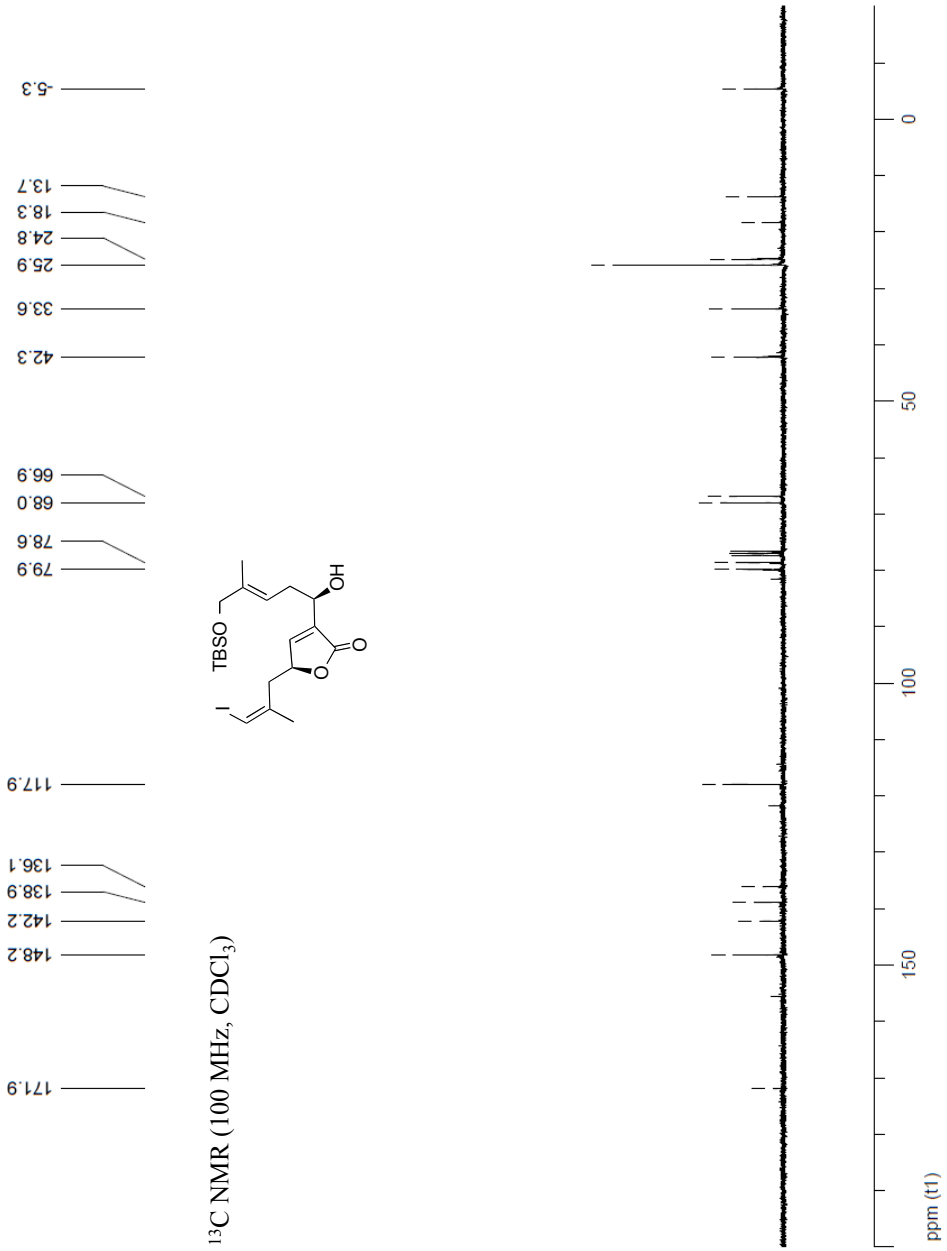
Spectrum 2.17: Compound 77a: ^{1}H NMR



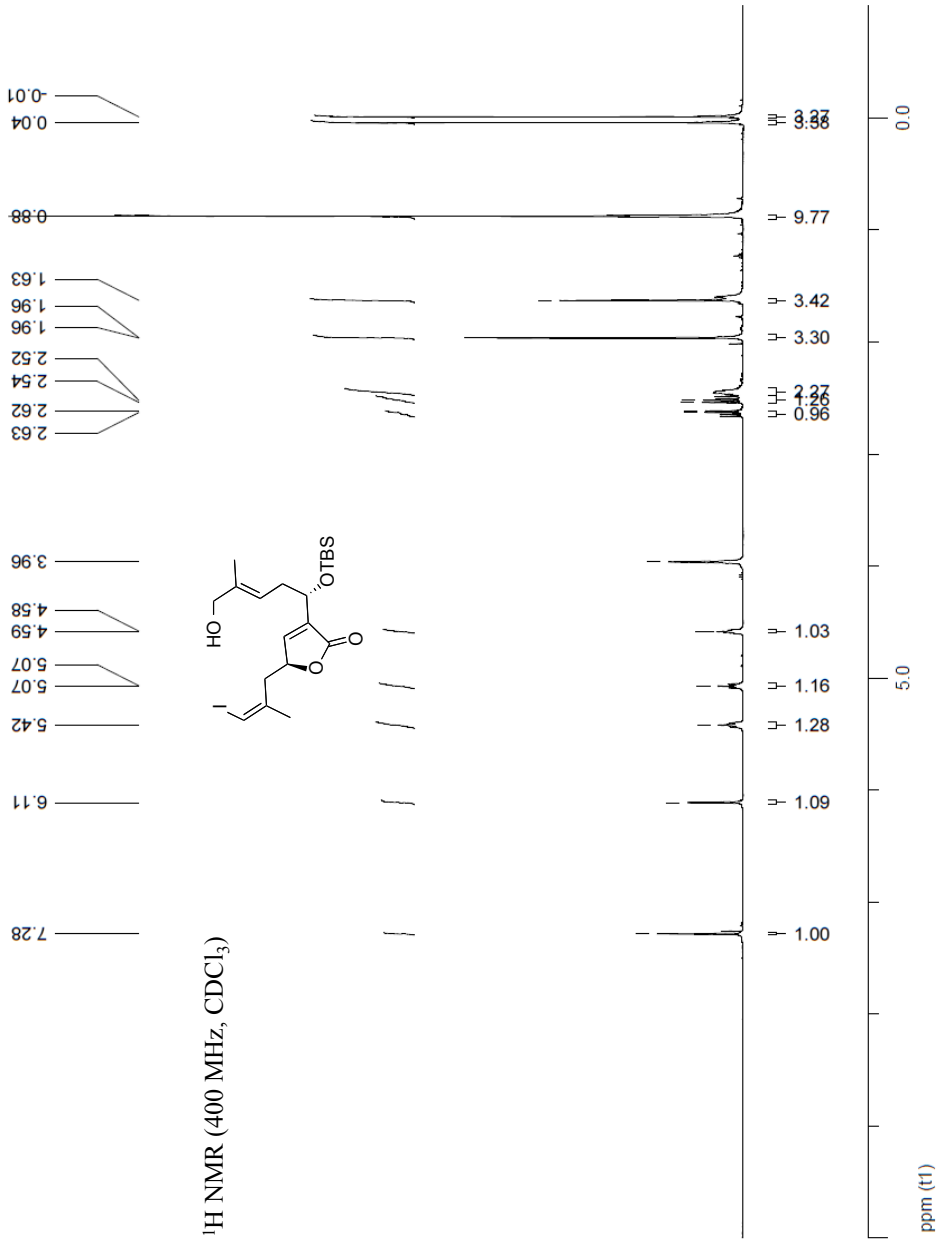
Spectrum 2.18: Compound 77a: ^{13}C NMR



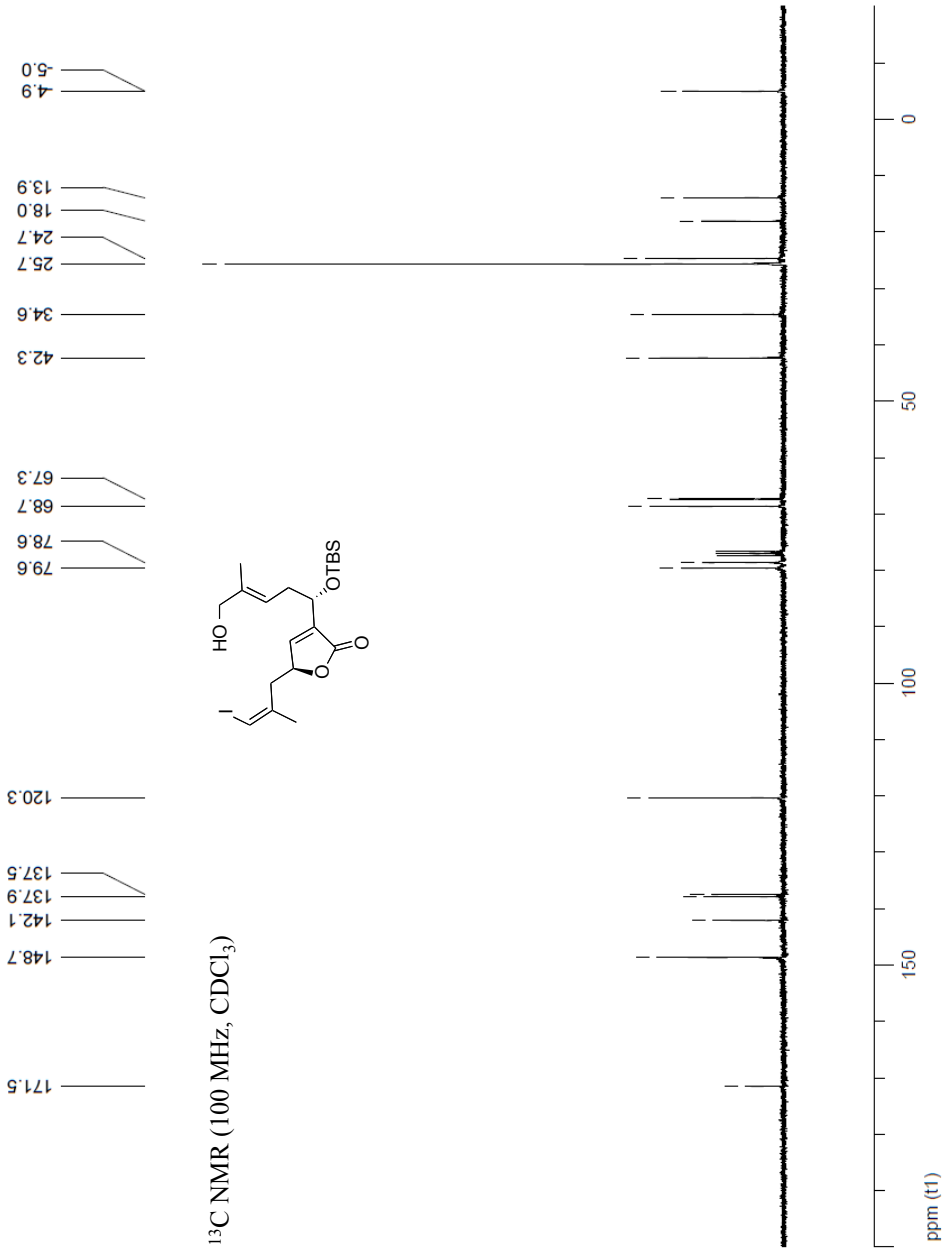
Spectrum 2.19: Compound 77b: ^{13}H NMR



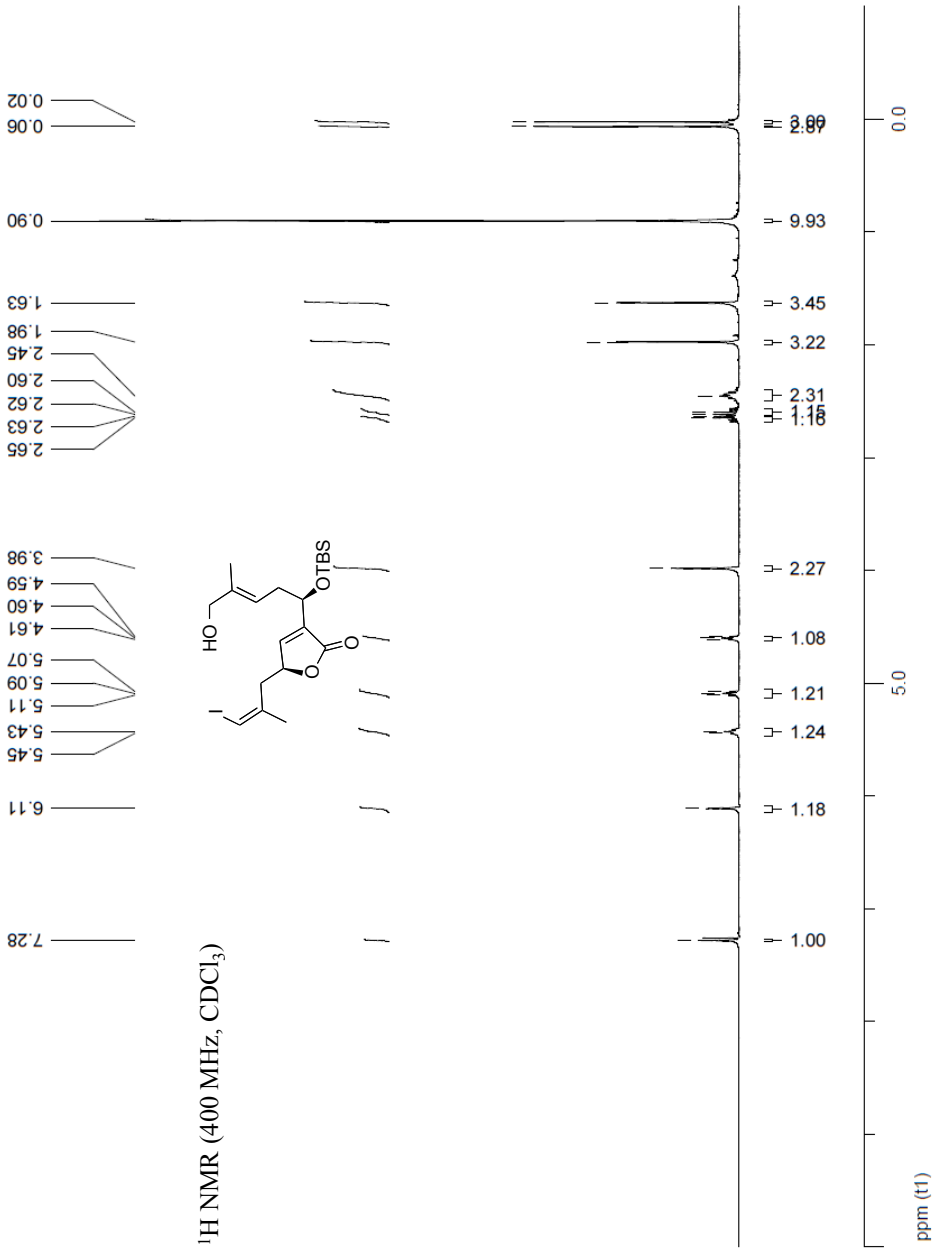
Spectrum 2.20: Compound 77b: ^{1}C NMR



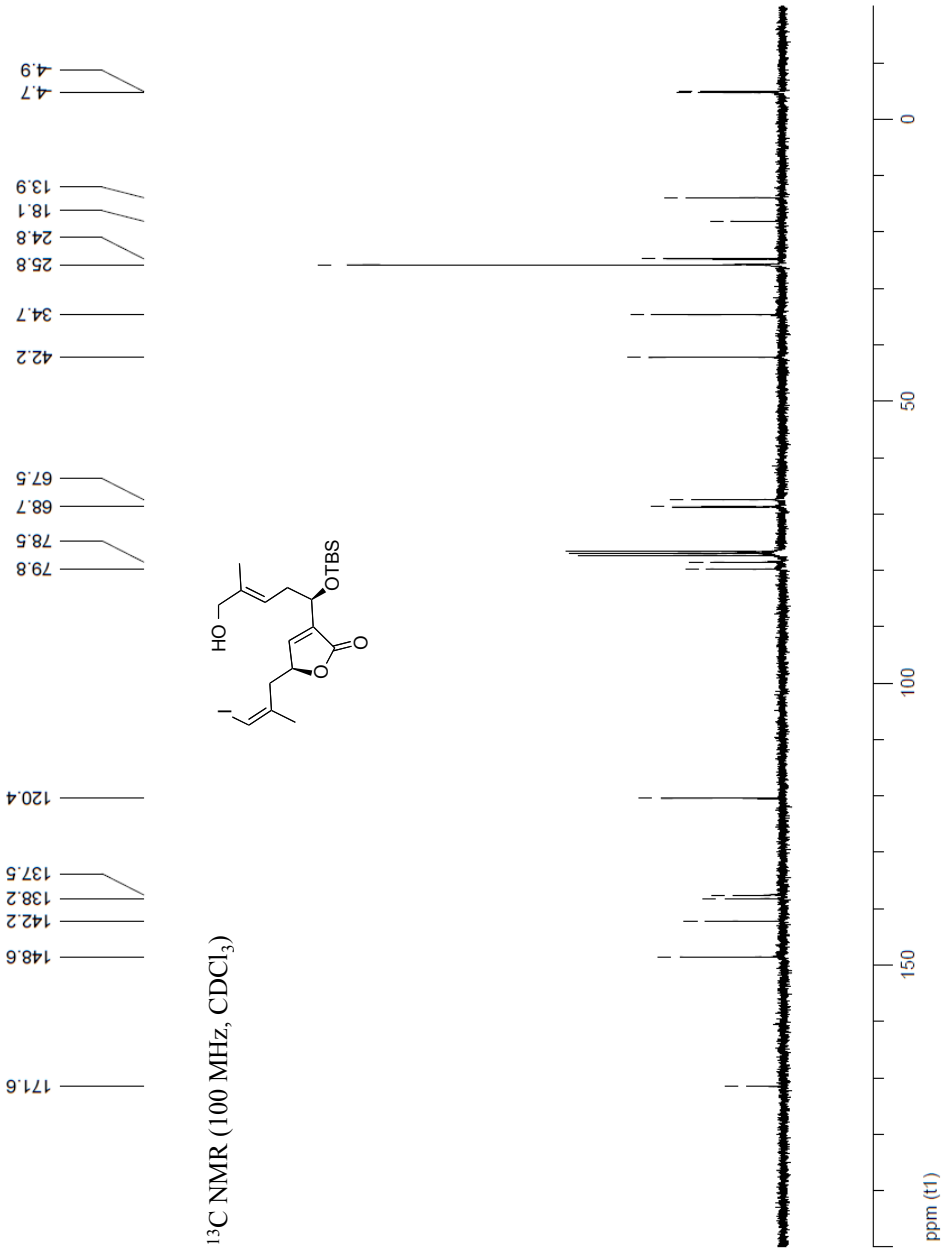
Spectrum 2.21: Compound 78a: ^{13}H NMR



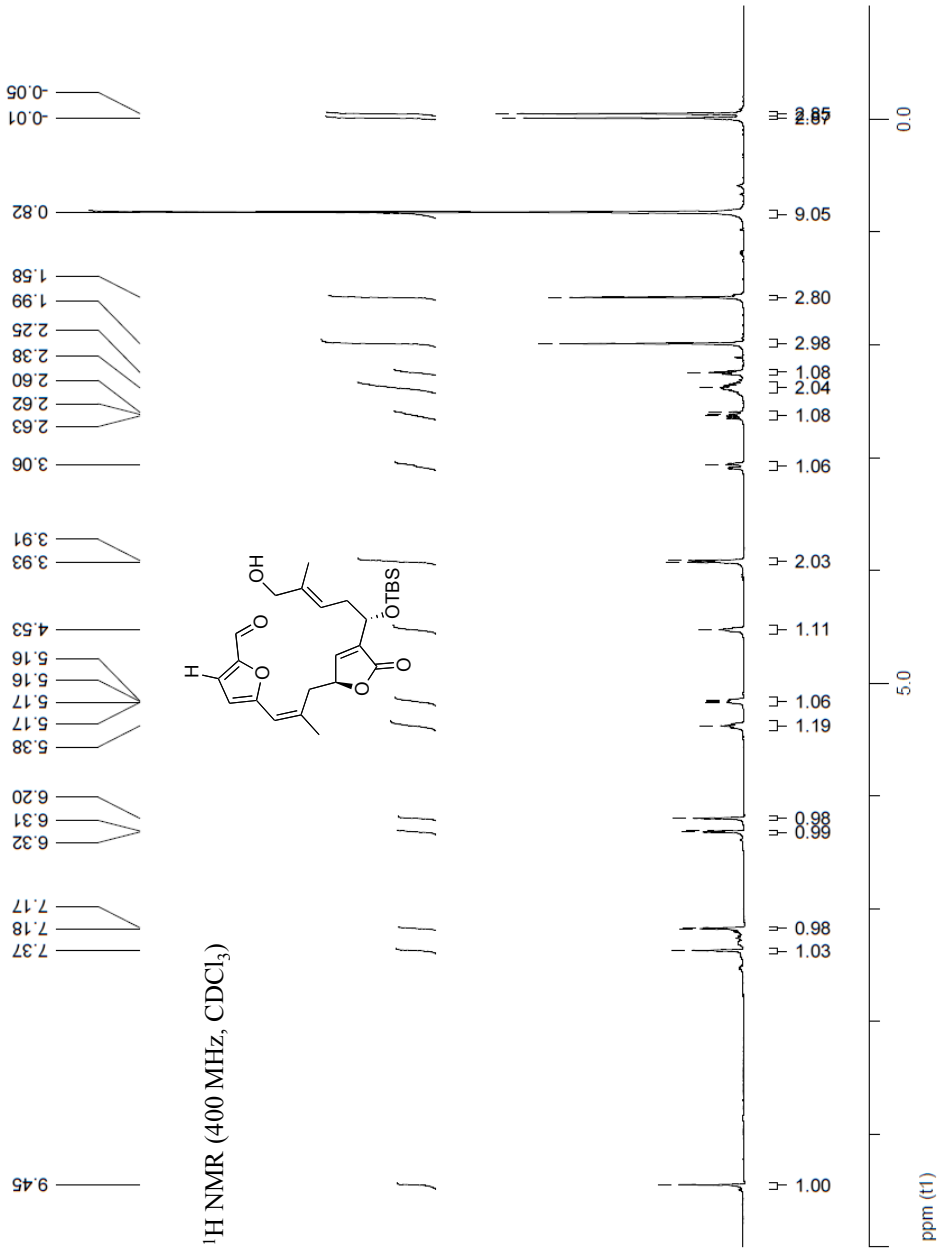
Spectrum 2.22: Compound 78a: ^{13}C NMR



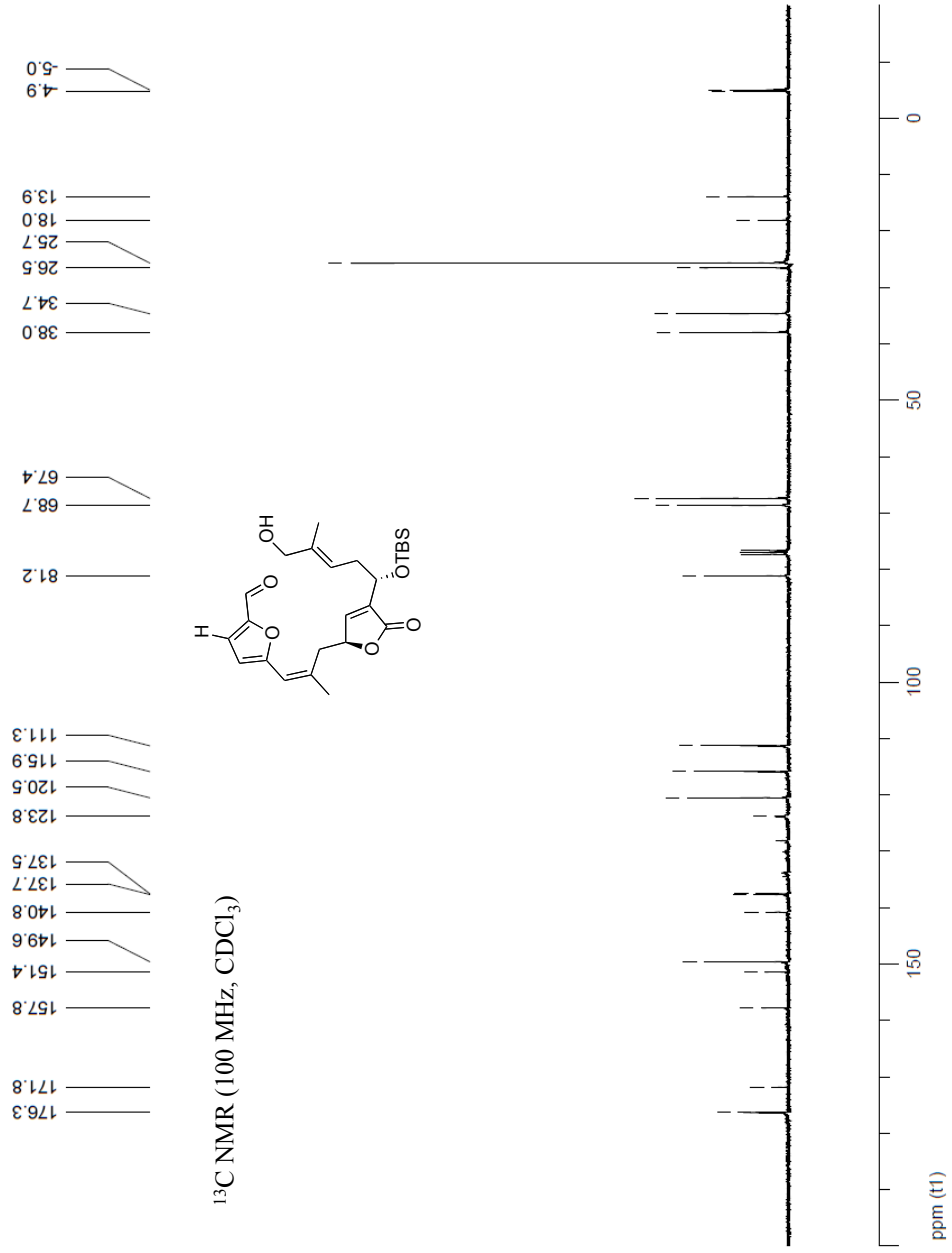
Spectrum 2.23: Compound 78b: ^{1}H NMR



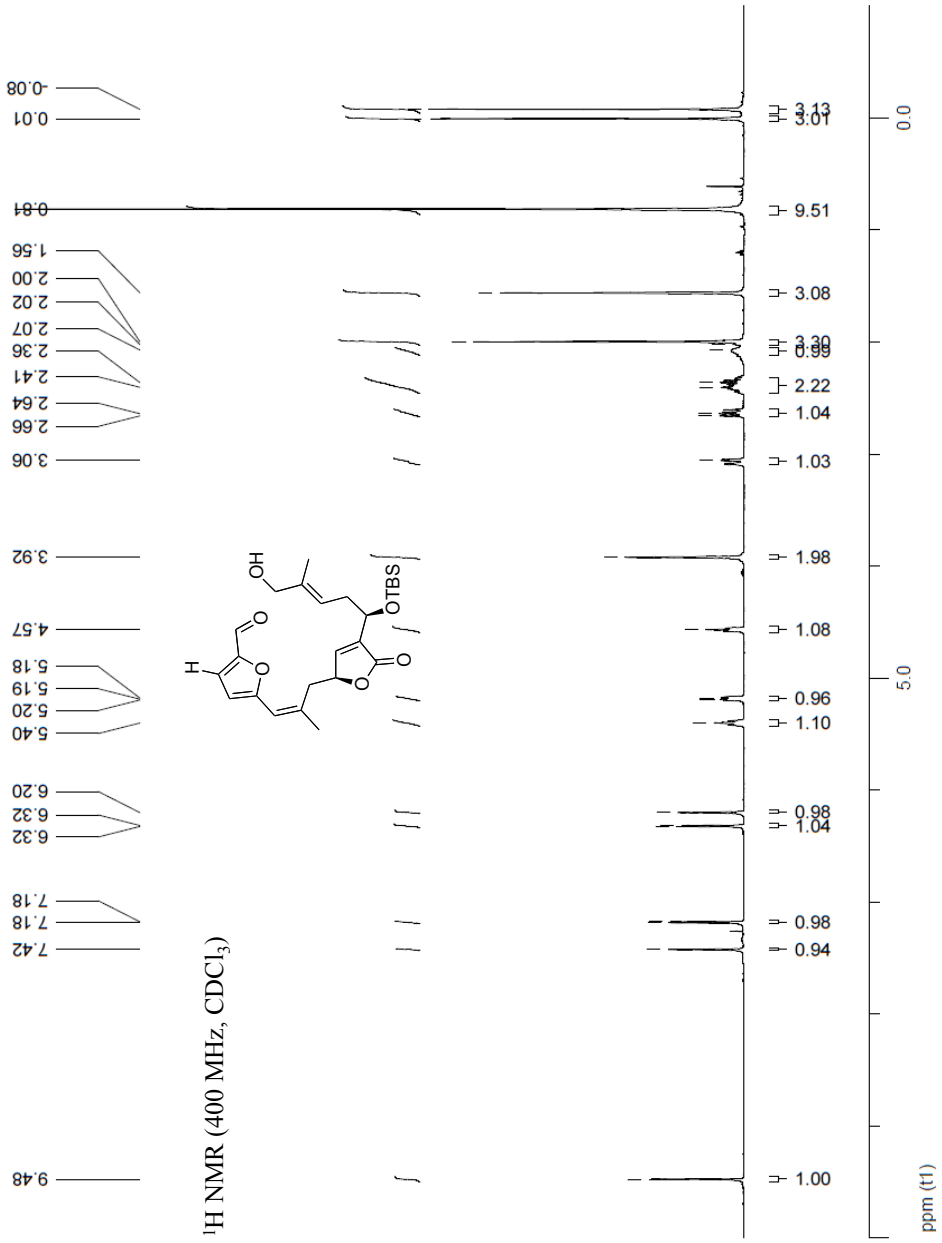
Spectrum 2.24: Compound 78b: ^{13}C NMR



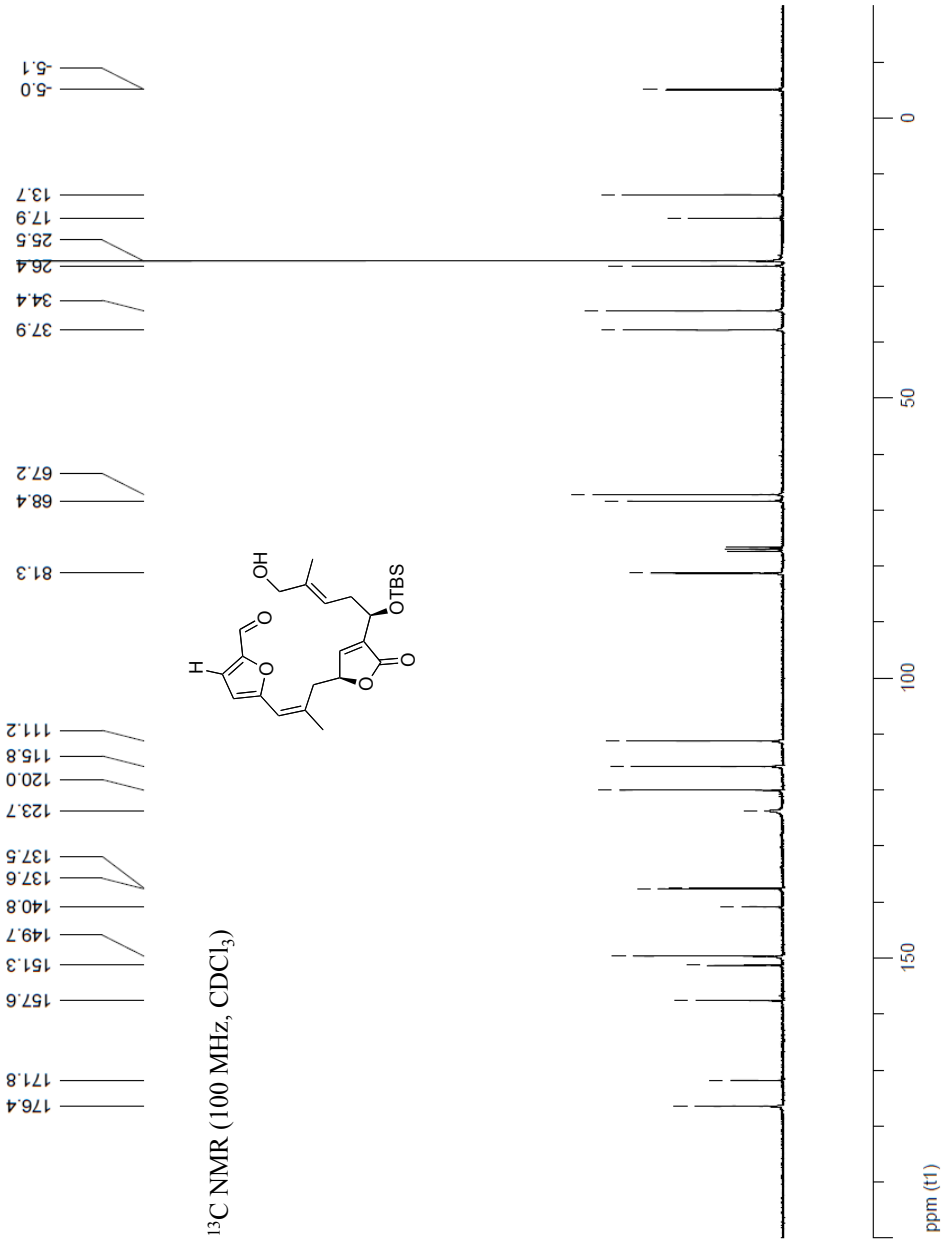
Spectrum 2.25: Compound 79a: ^{1}H NMR



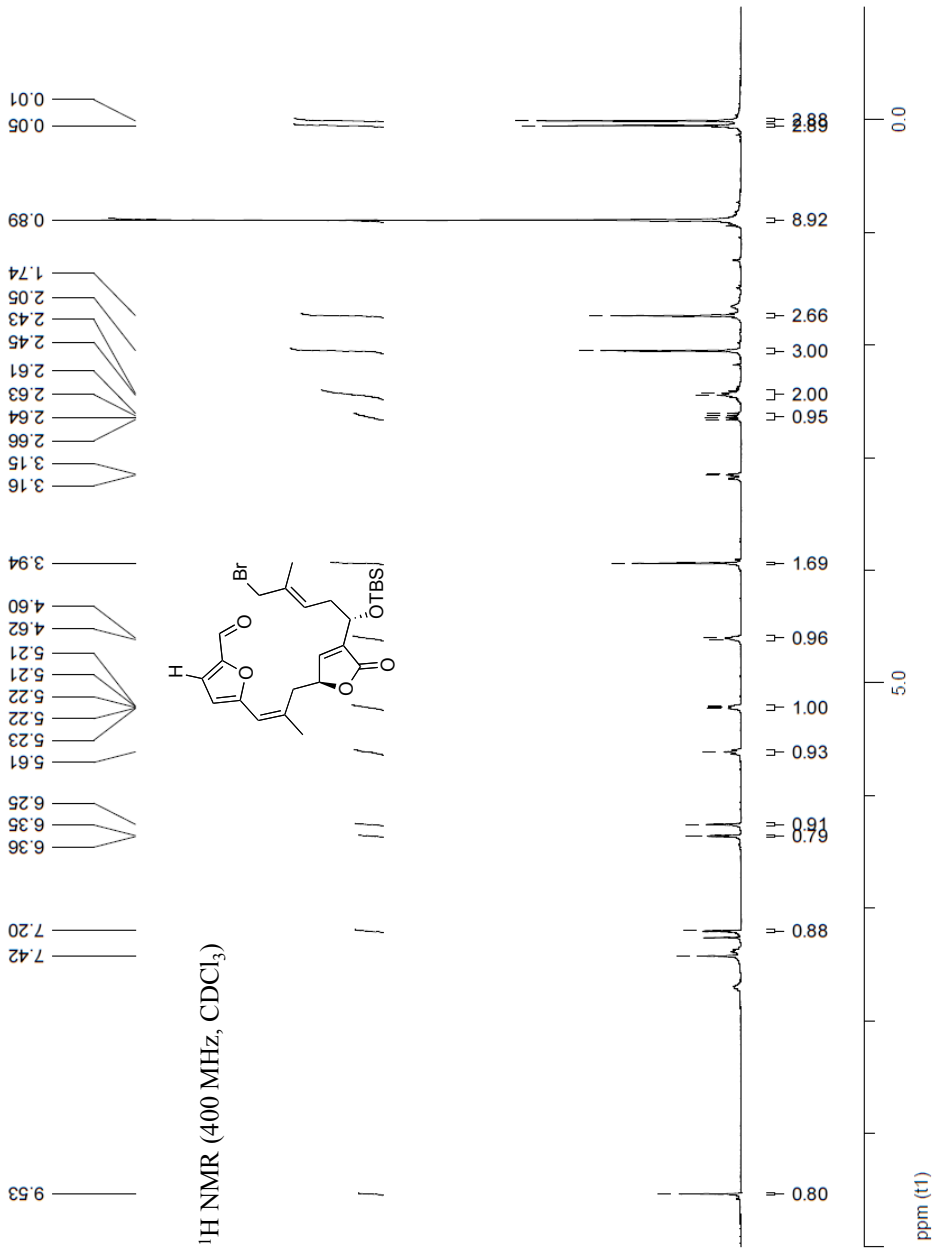
Spectrum 2.26: Compound 79a: ^{13}C NMR



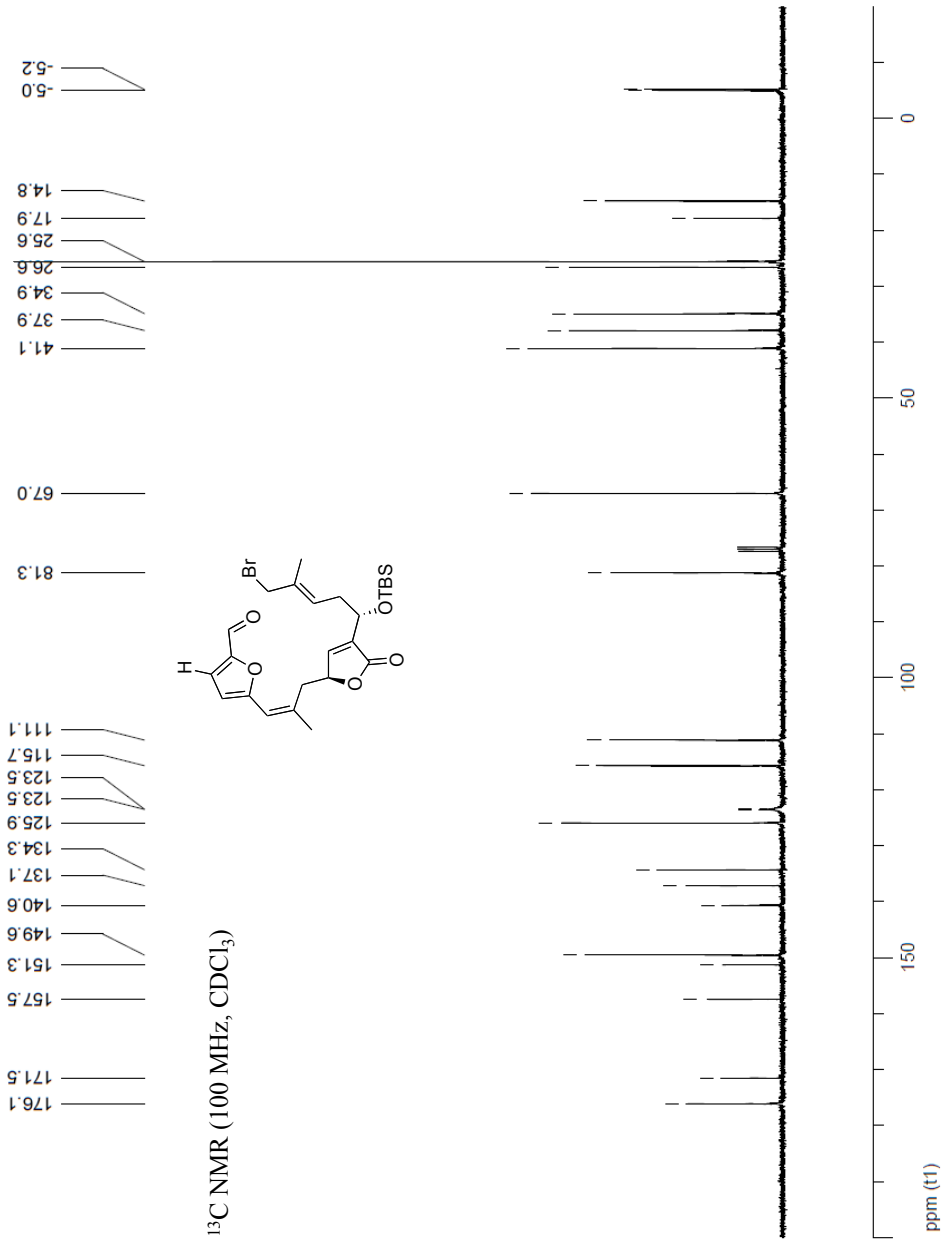
Spectrum 2.27: Compound 79b: ^{1}H NMR



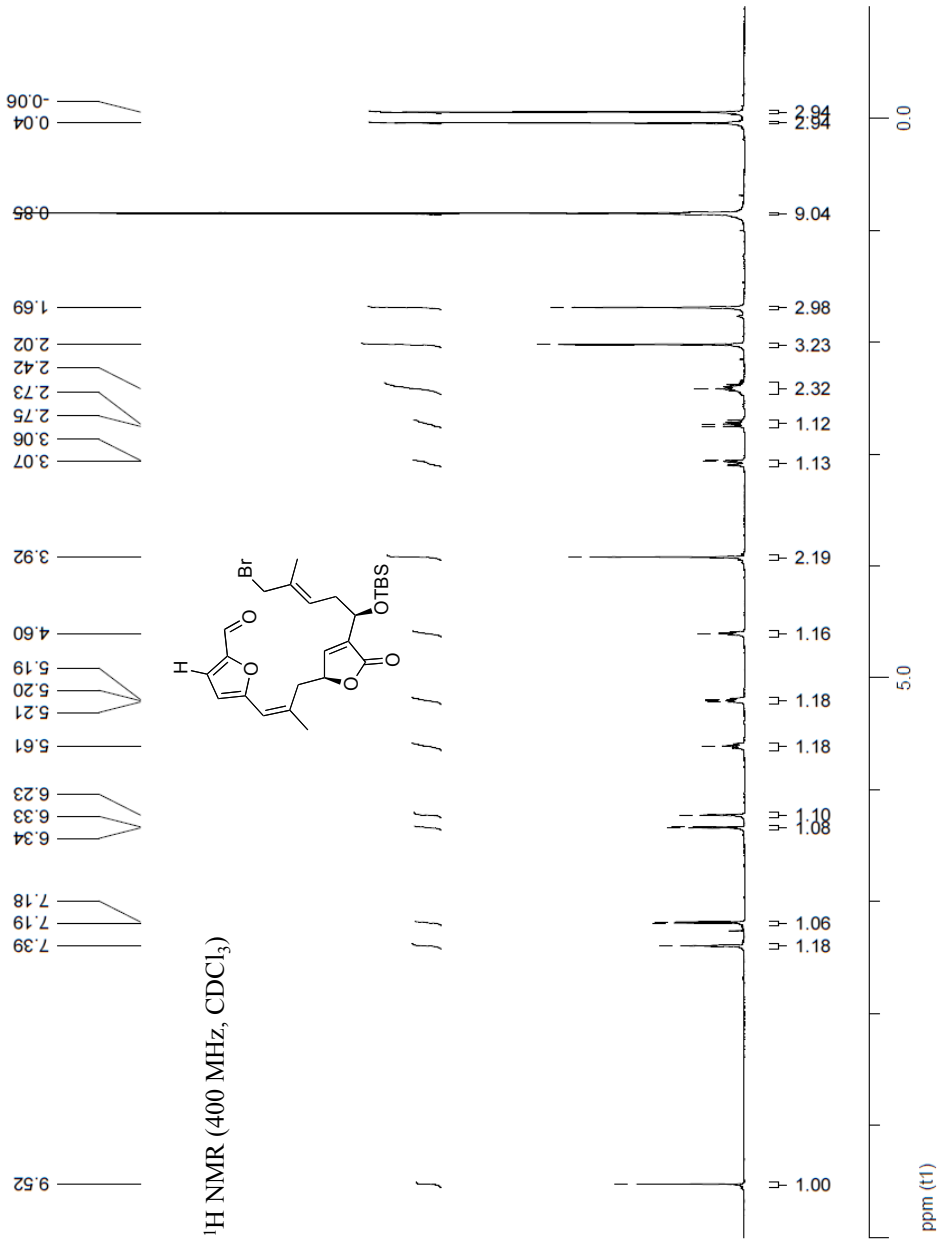
Spectrum 2.28: Compound 79b: ^{13}C NMR



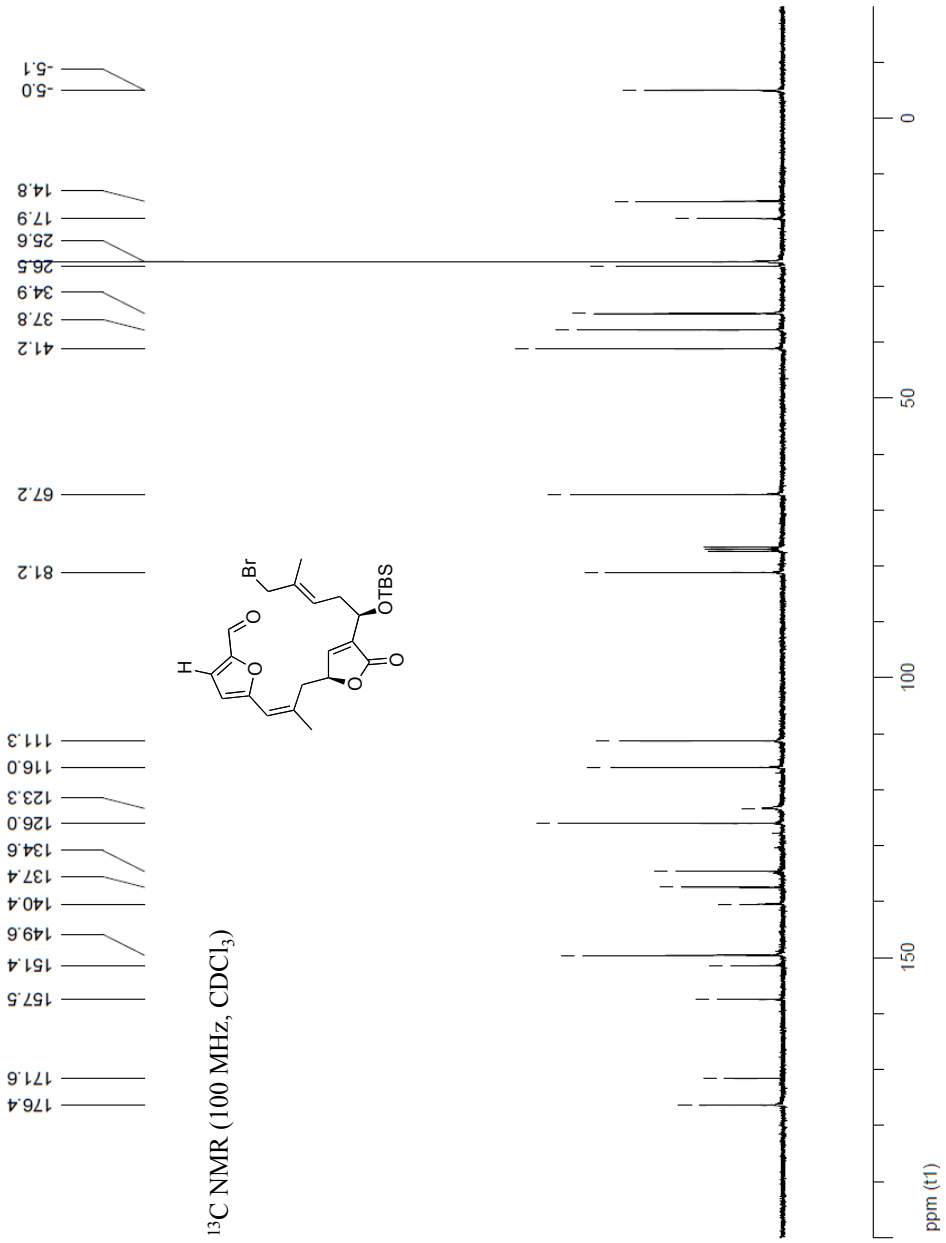
Spectrum 2.29: Compound 80a: ^{1}H NMR



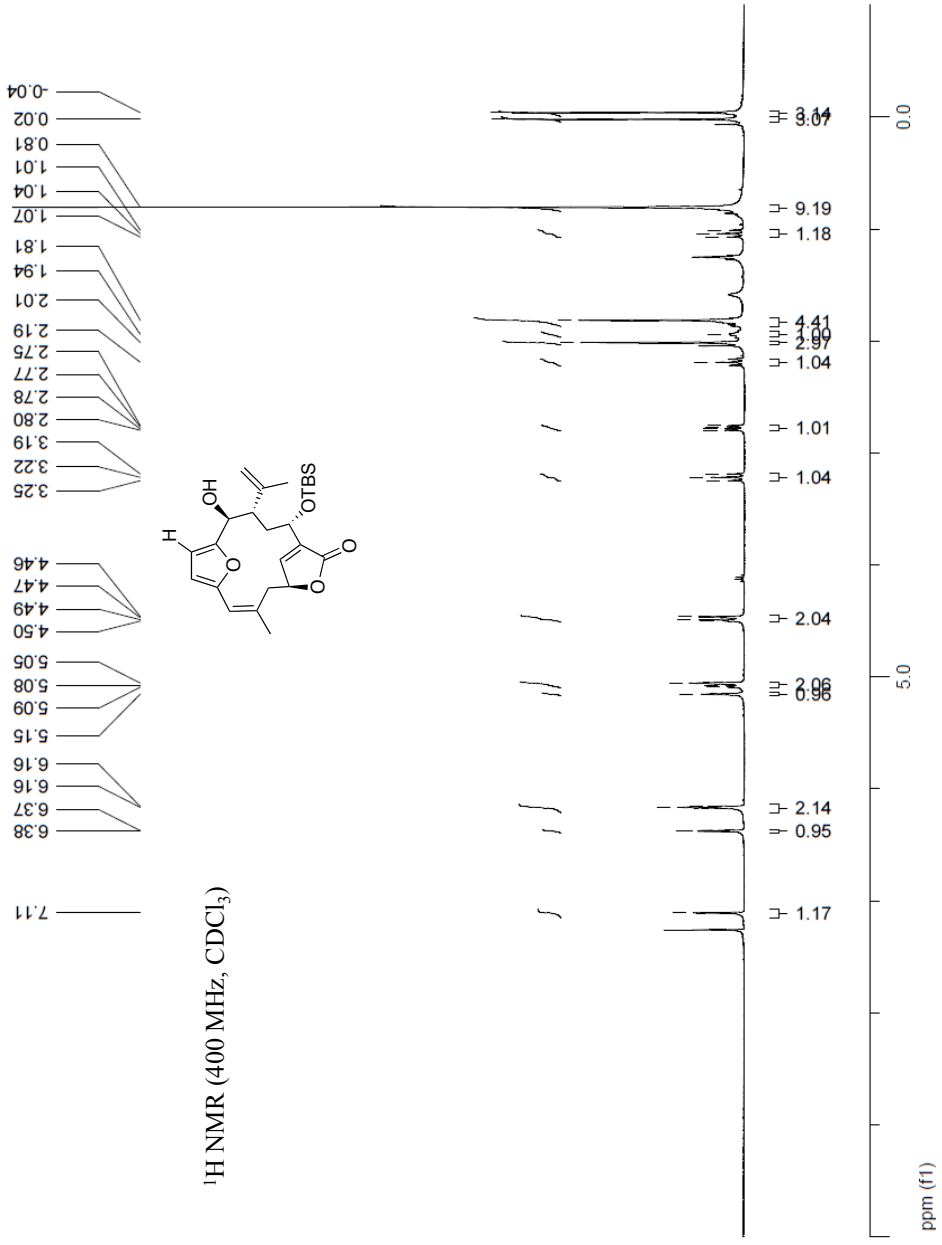
Spectrum 2.30: Compound 80a: ^{13}C NMR



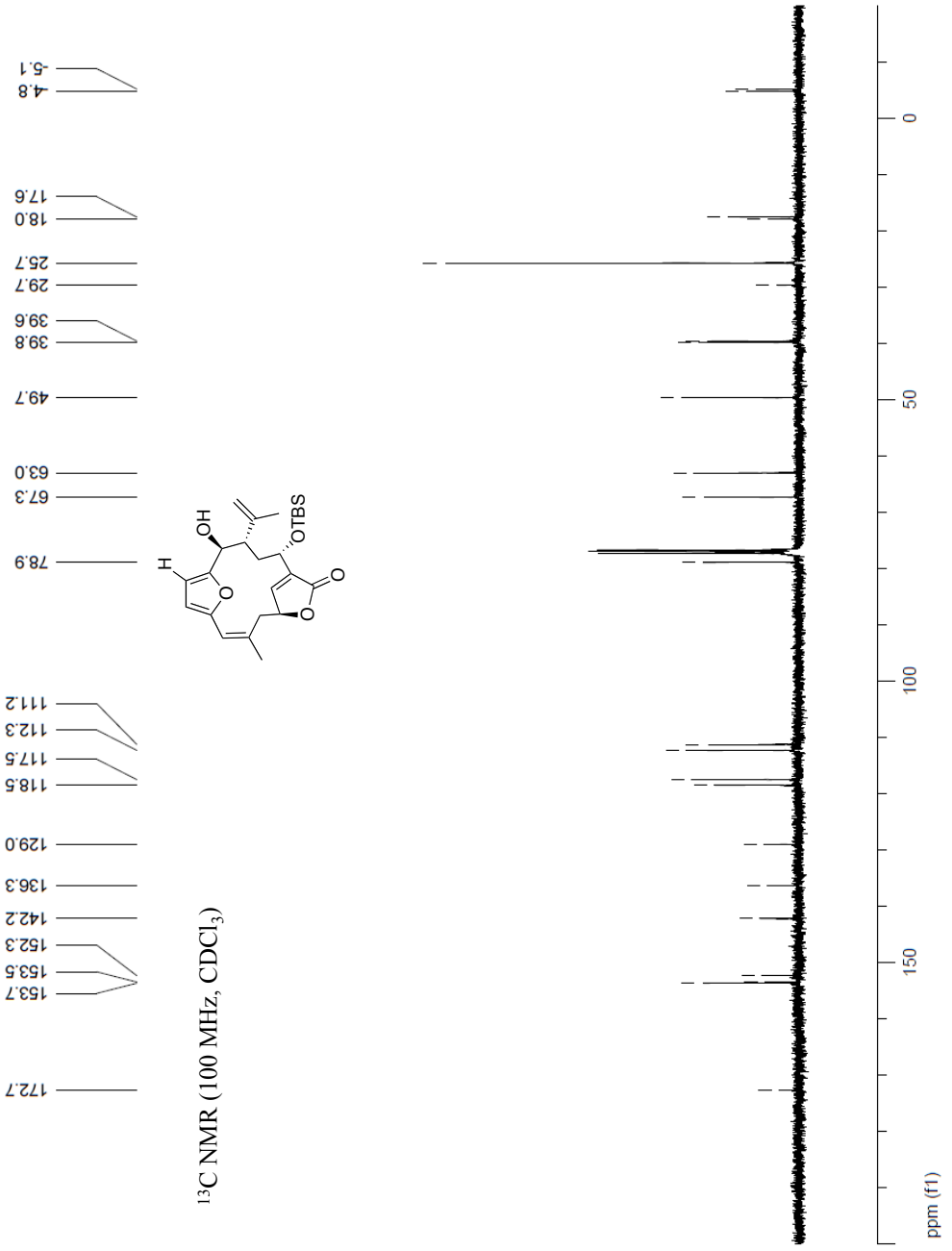
Spectrum 2.31: Compound 80b: ^{1}H NMR



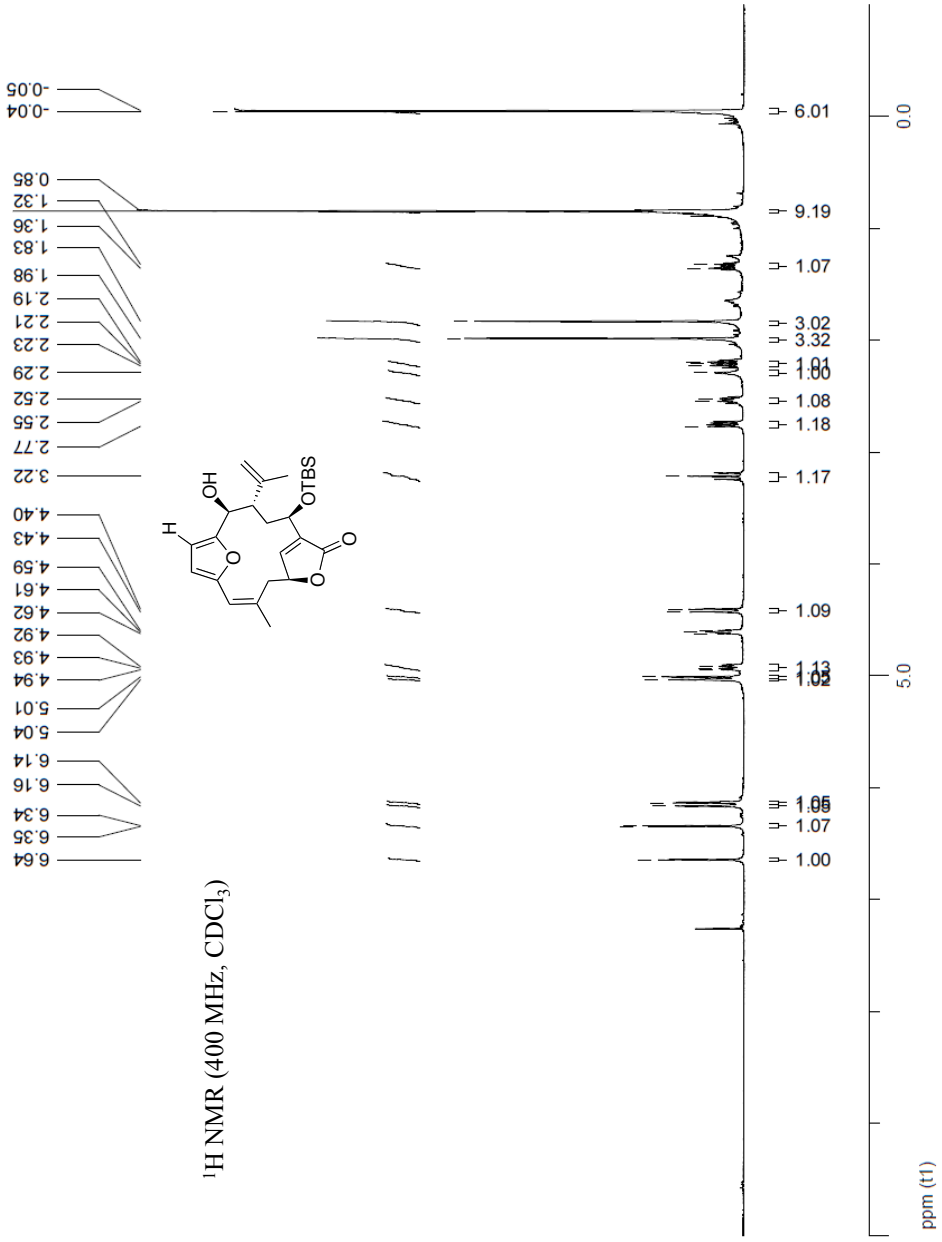
Spectrum 2.32: Compound 80b: ^{13}C NMR



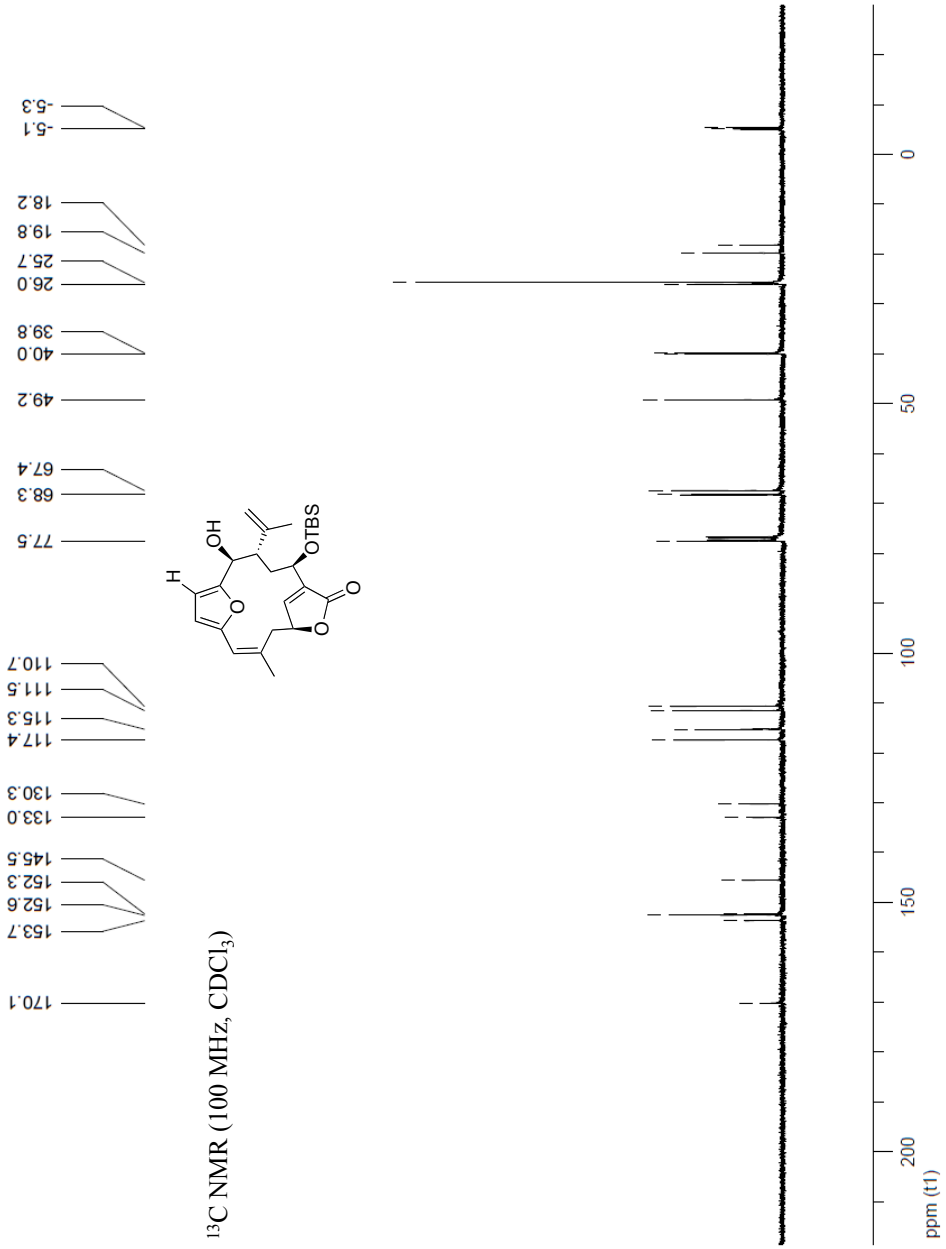
Spectrum 2.33: Compound 81a: ^{1}H NMR



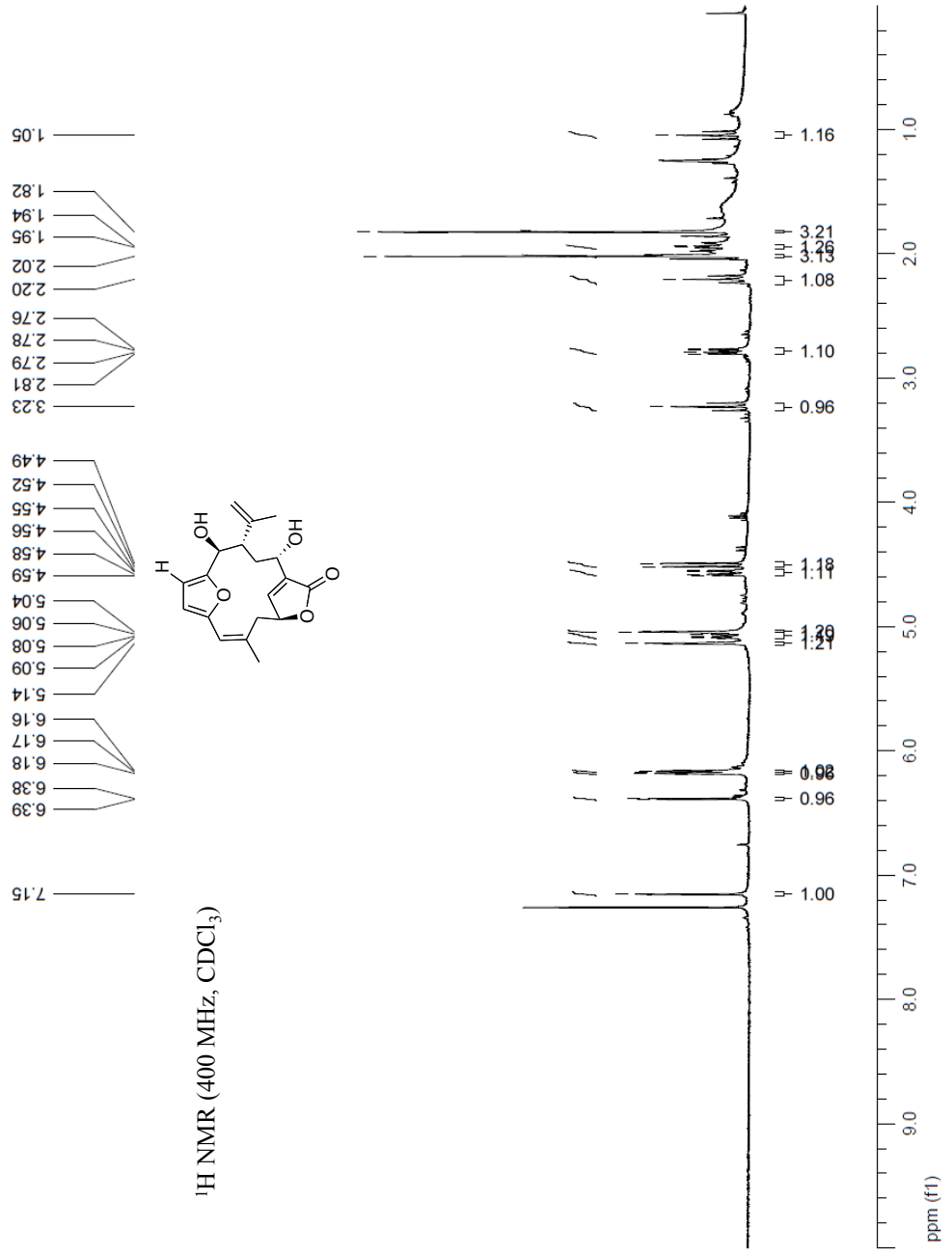
Spectrum 2.34: Compound 81a: ^{13}C NMR



Spectrum 2.35: Compound 81b: ^{1}H NMR

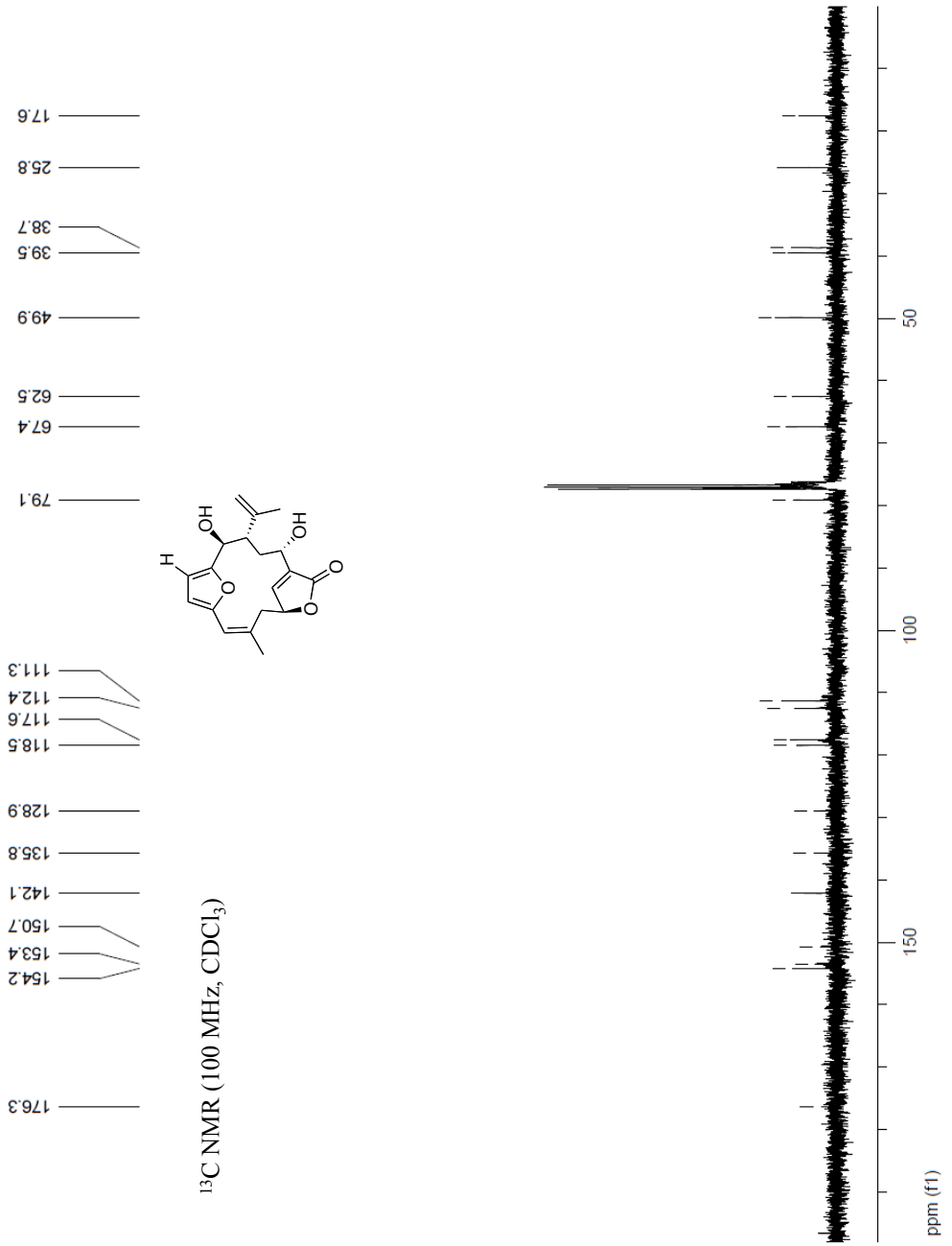


Spectrum 2.36: Compound 81b: ^{13}C NMR

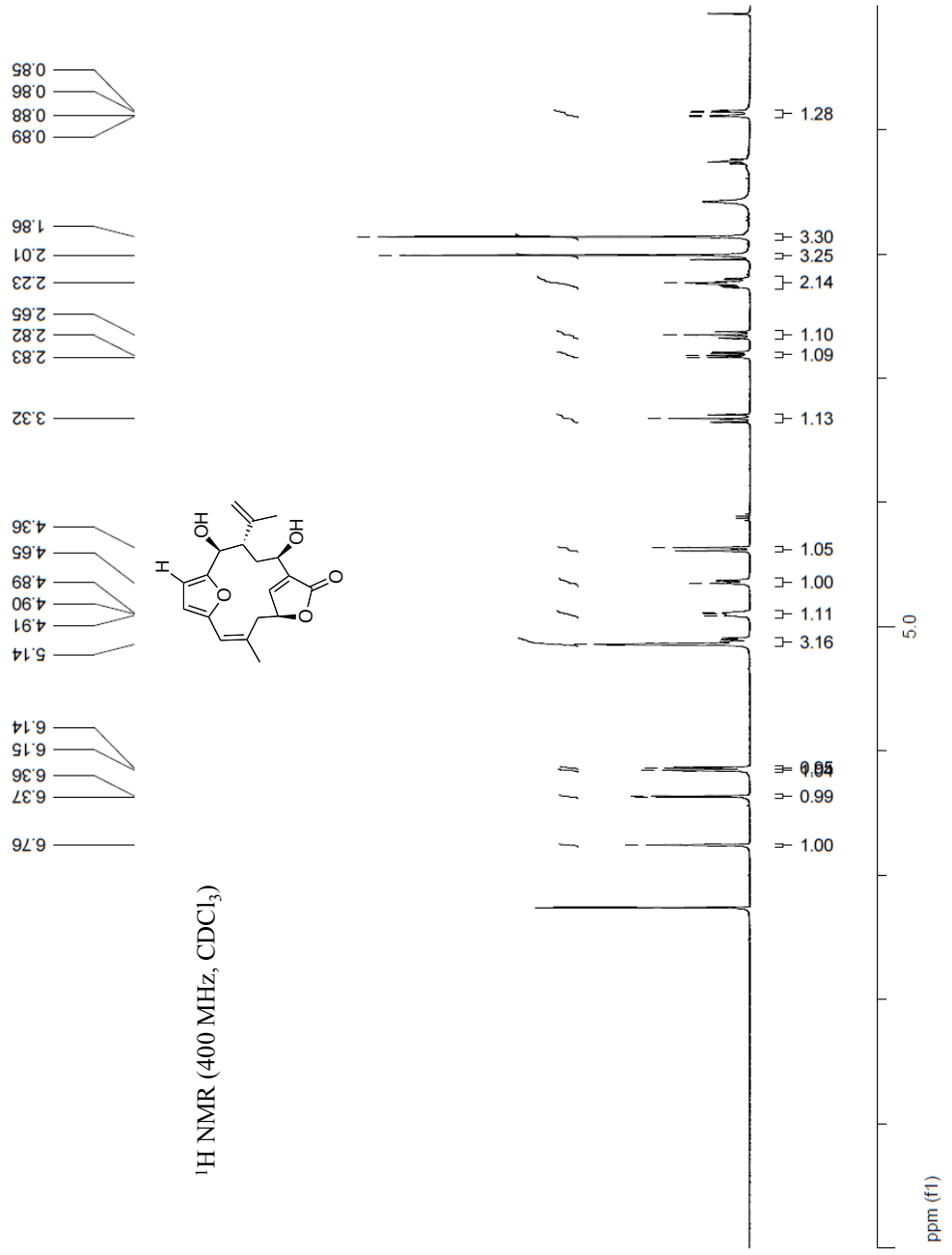


^{1}H NMR (400 MHz, $CDCl_3$)

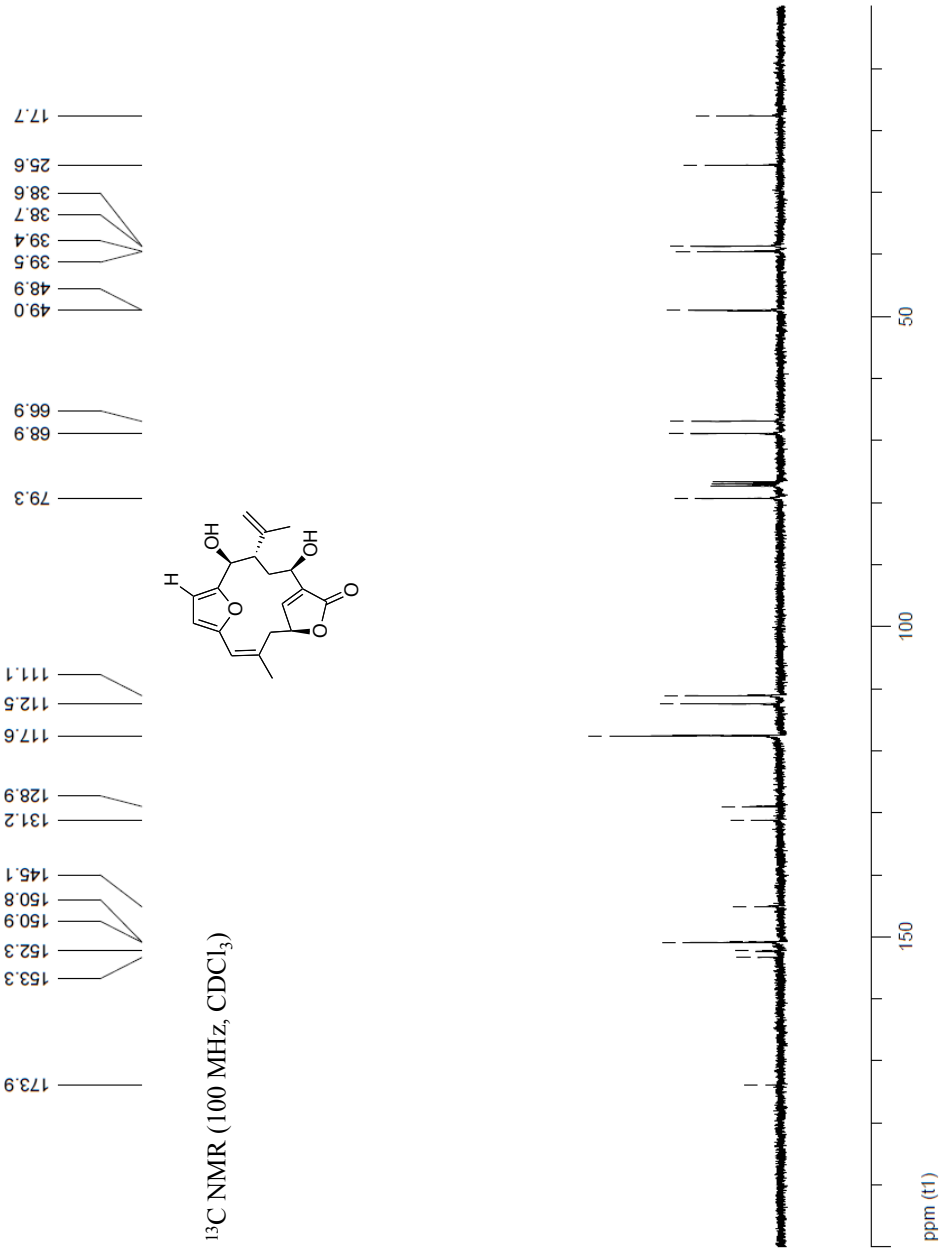
Spectrum 2.37: Compound 82a: ^{1}H NMR



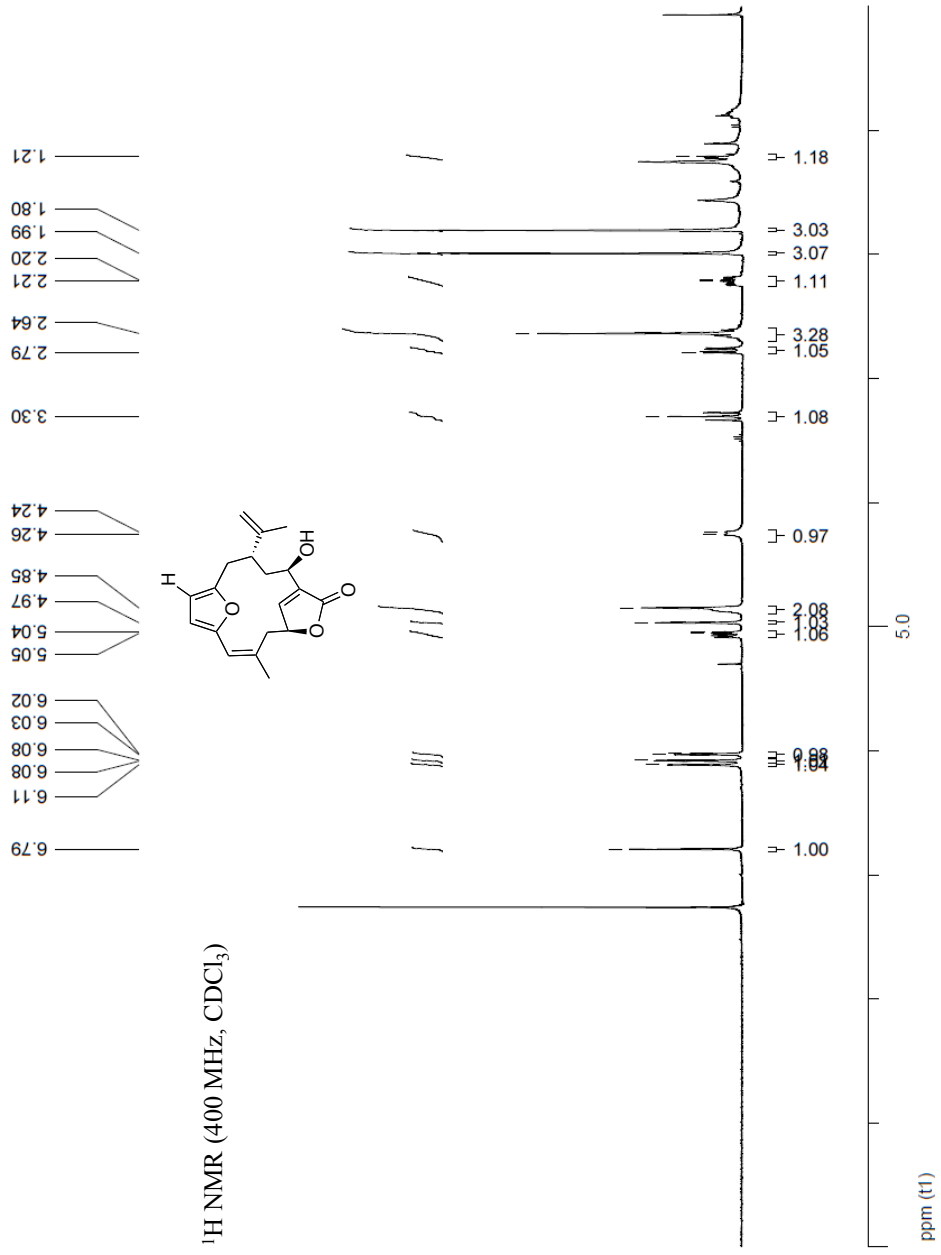
Spectrum 2.38: Compound 82a: ^{13}C NMR



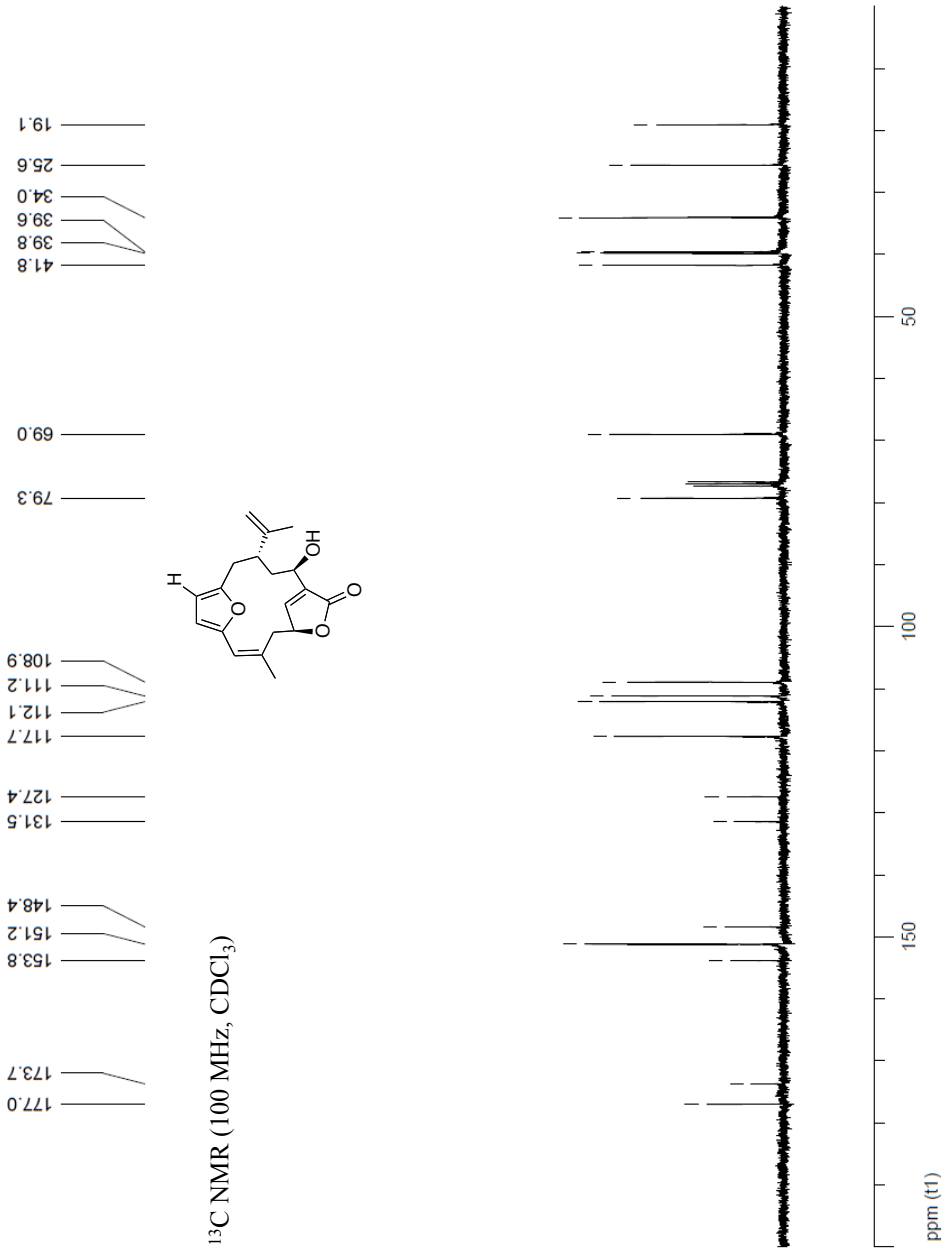
Spectrum 2.39: Compound 68: ^{1}H NMR



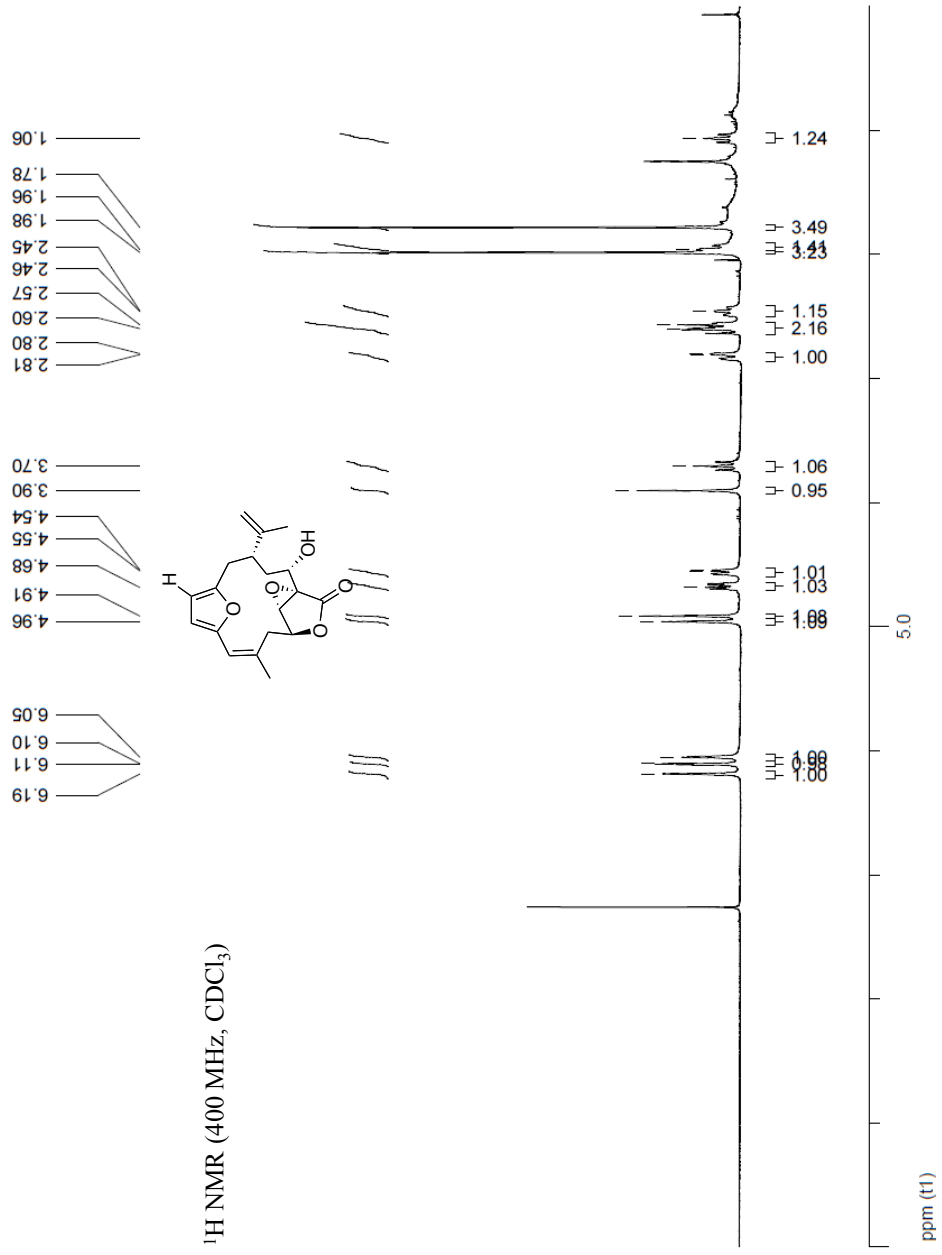
Spectrum 2.40: Compound 68: ^{1}C NMR



Spectrum 2.41: Compound 83b: ^{13}H NMR

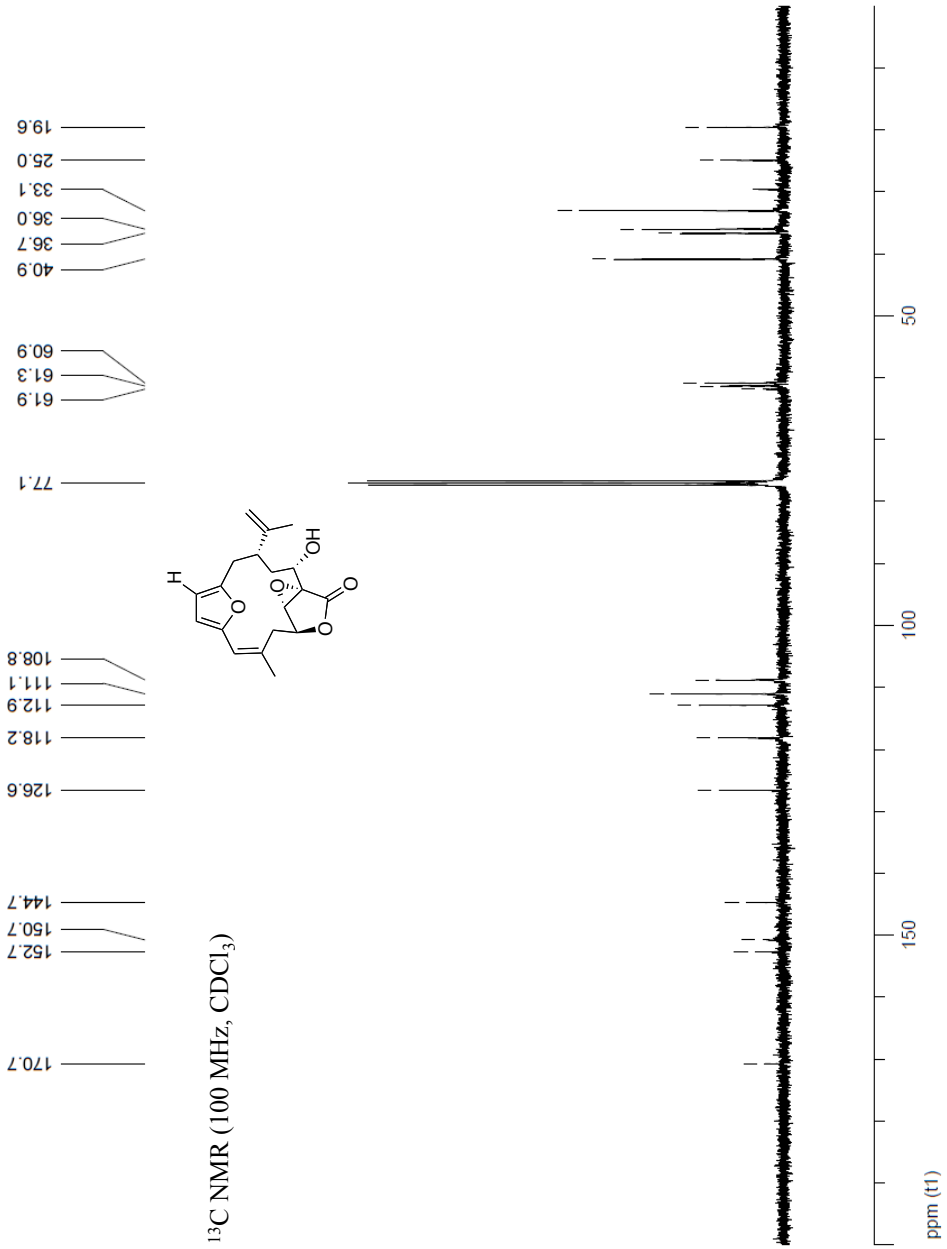


Spectrum 2.42: Compound 83b: ^{1}C NMR

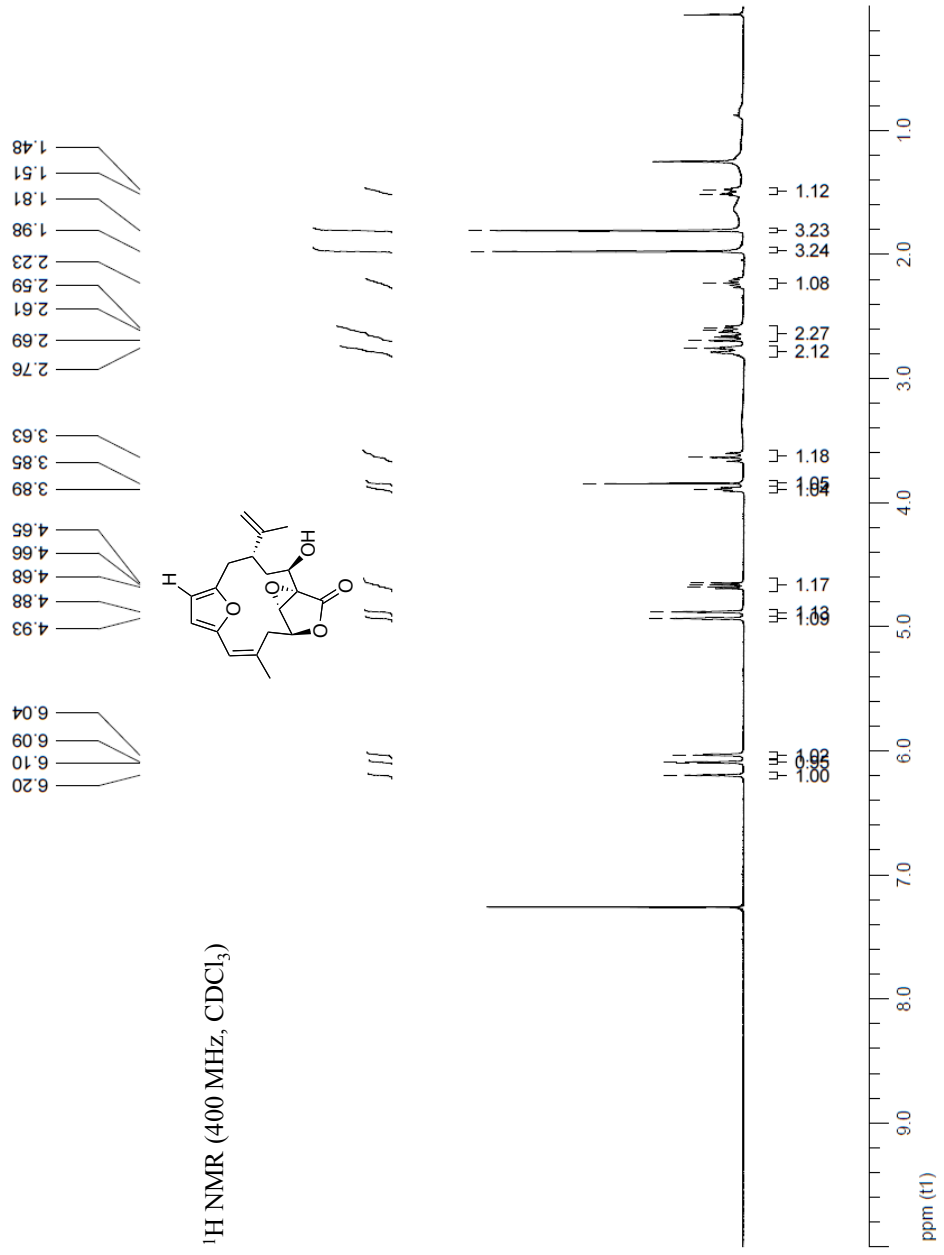


^{1}H NMR (400 MHz, $CDCl_3$)

Spectrum 2.43: Compound 84a: ^{13}H NMR

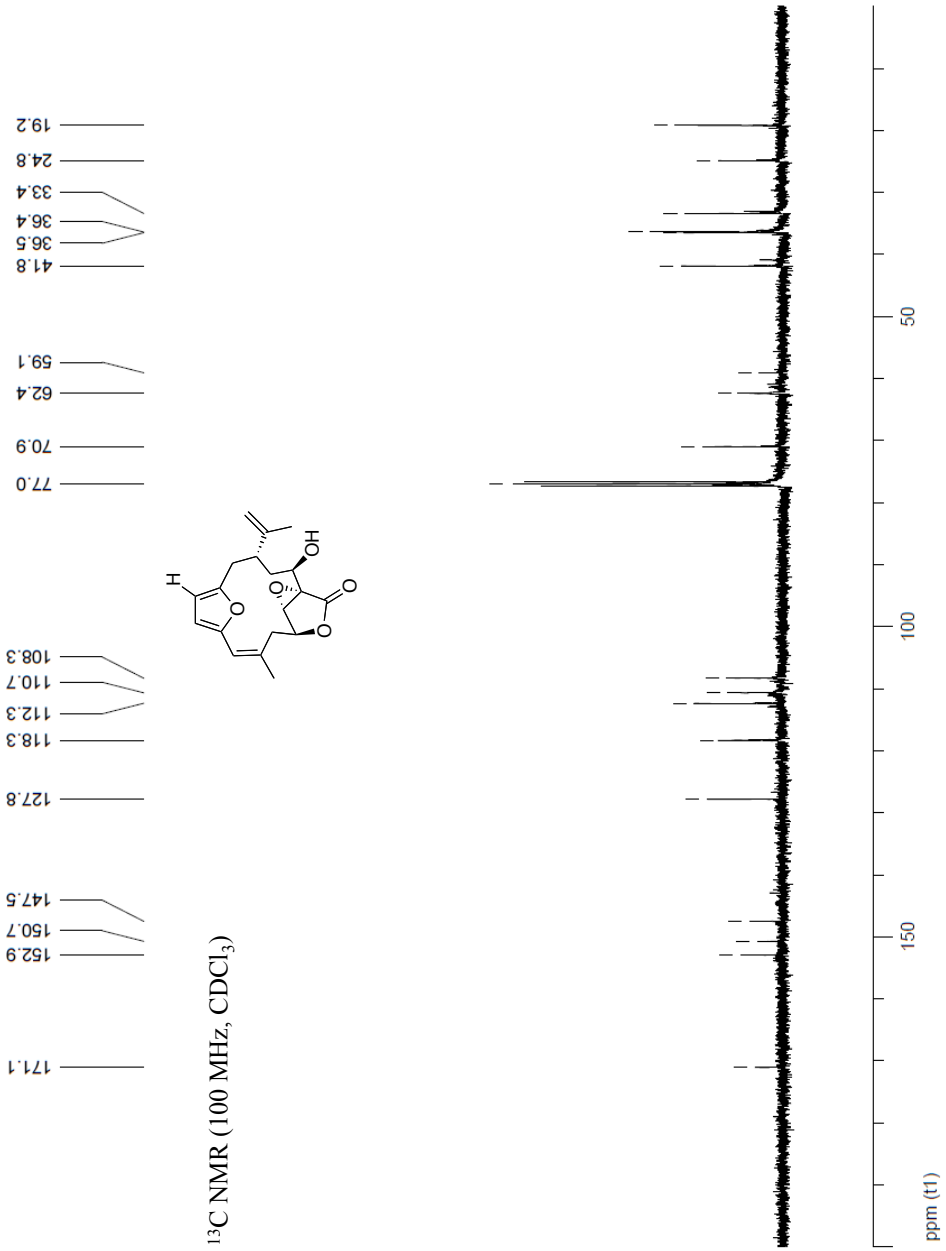


Spectrum 2.44: Compound 84a: ^{1}C NMR

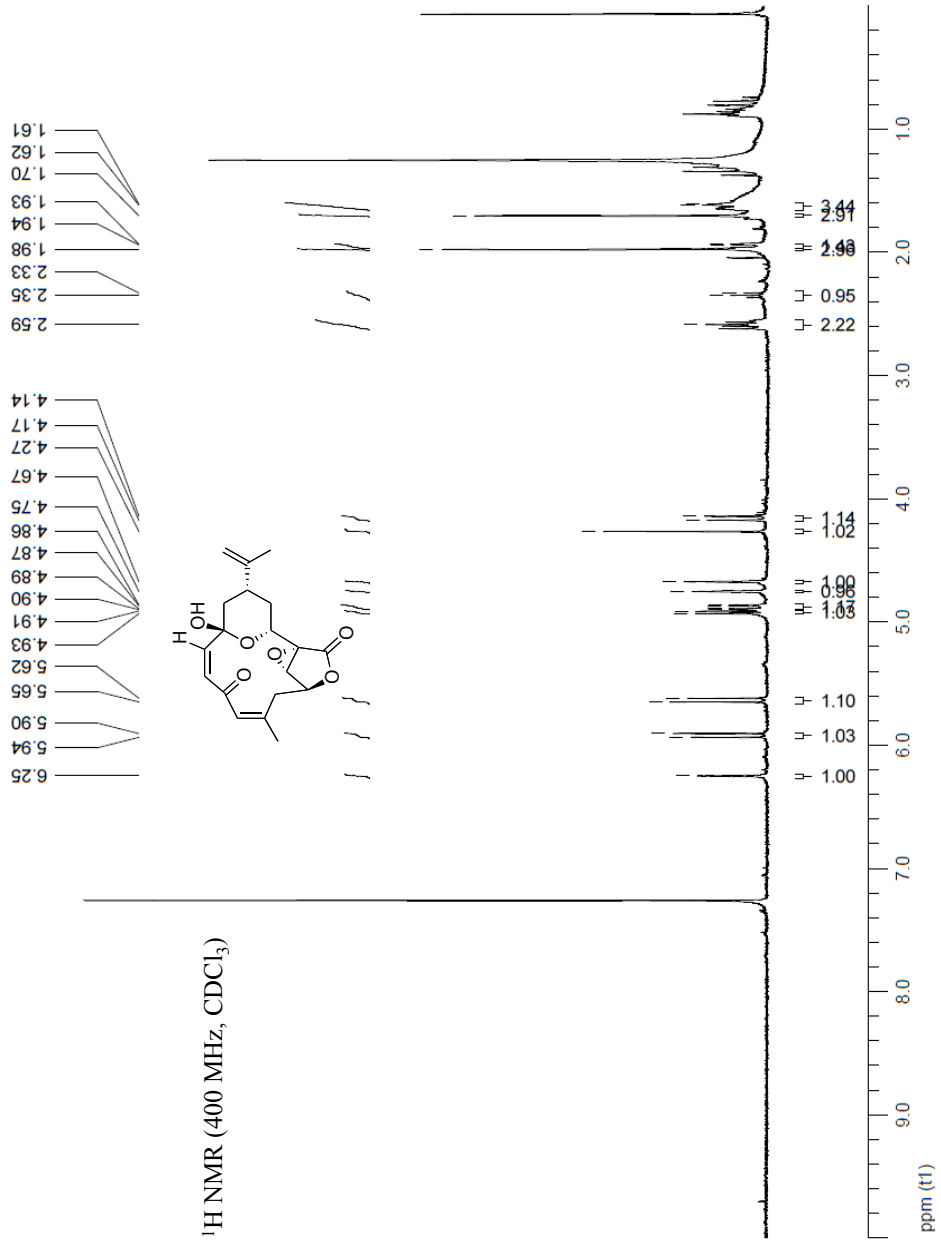


^{1}H NMR (400 MHz, $CDCl_3$)

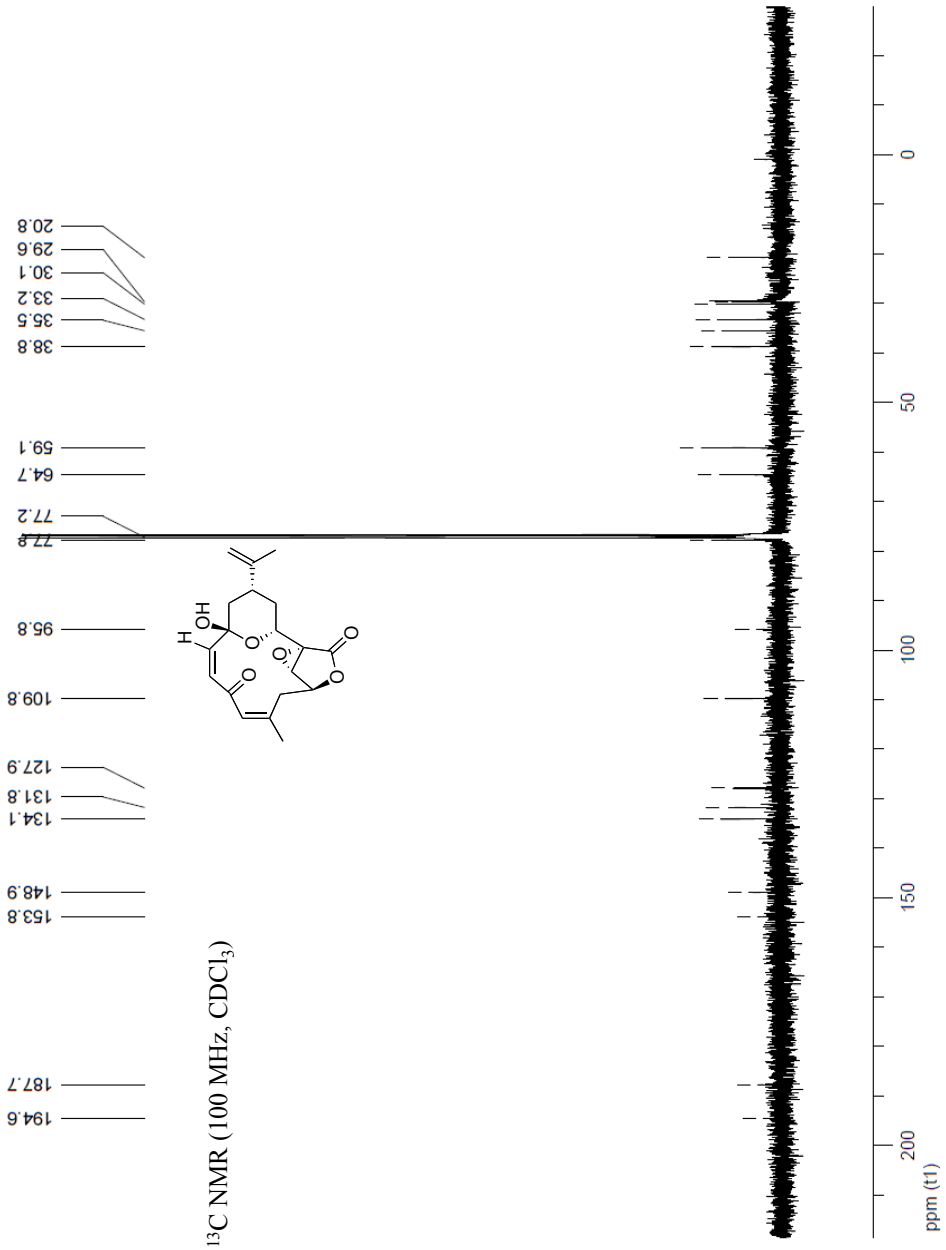
Spectrum 2.45: Compound 84b: ^{13}H NMR



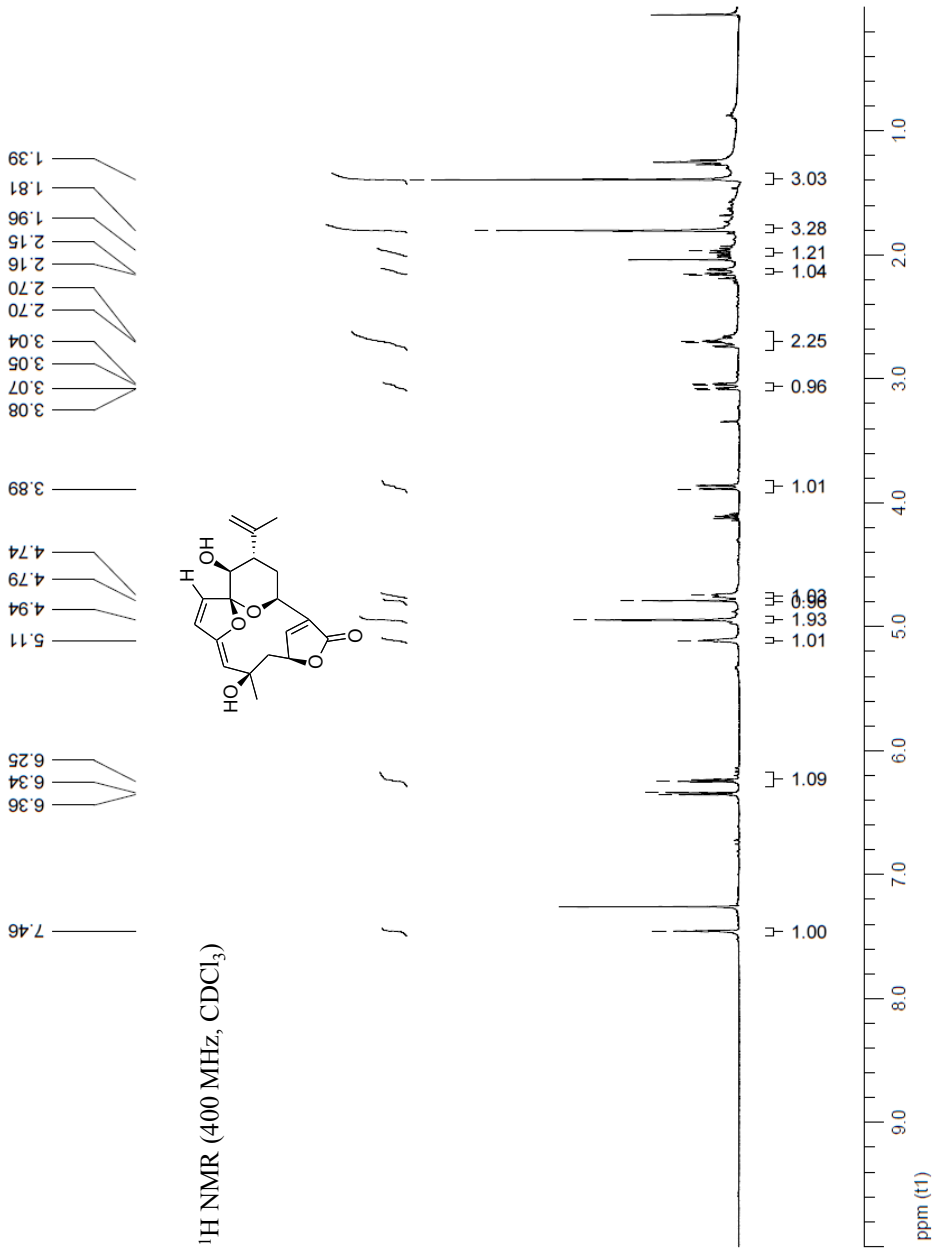
Spectrum 2.46: Compound 84b: ^{1}C NMR



Spectrum 2.47: Compound 85: ^{13}H NMR

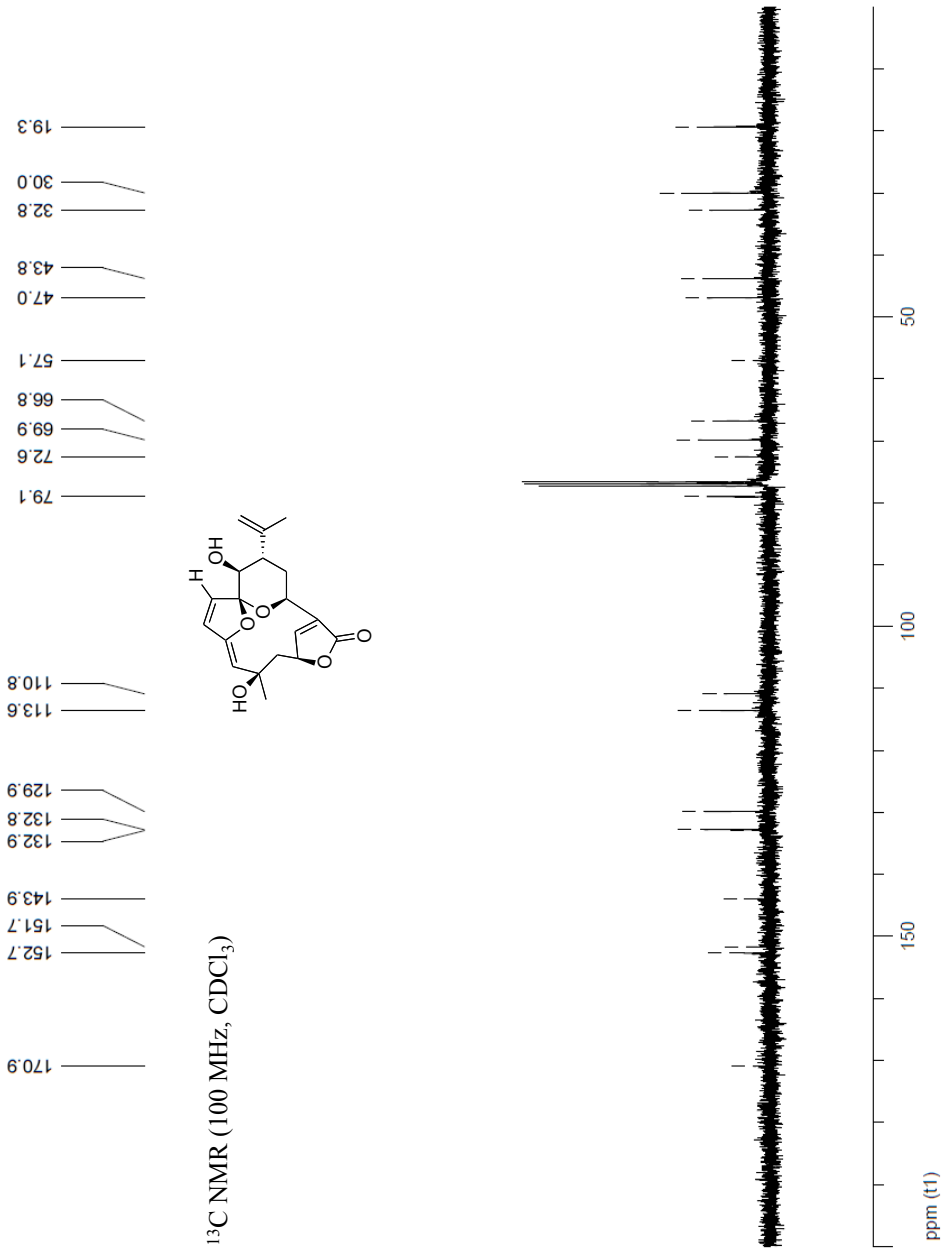


Spectrum 2.48: Compound 85: ^{1}C NMR



Spectrum 2.49: Compound 86: ^{13}H NMR

This chapter, in part, has been submitted for publication. Saitman, A.; Sullivan, S. D. E.; Theodorakis, E. A. A strategy toward the synthesis of C13-oxidised cembrenolides. *Tetrahedron Lett*. **2013**, *54*, 1612-1615. The dissertation author was the primary author and investigator of this material.



Spectrum 2.50: Compound 86: ^{13}C NMR

Chapter 3

The Synthesis Furanoverrillin and Derivatives.

3.1 Introduction

3.1.1 Selected Cyclopentane Containing Cembrenolides and Bioactivities

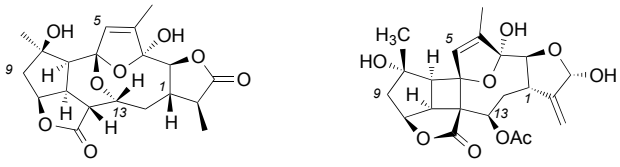


Figure 3.1: Selected Cyclopentane Containing Cembrenolides

The C_{13} oxidized modifications found in many of the more intricate and biolog-

ically active cembrenolides makes up the vast majority of the cembrenolide family.[8,9] An additional cyclization of the carbon framework, however, sets the stage for a new class of cembrenolides with higher intricacy and even higher bioactivity.[4] For example, bielschowskysin (**88**),[66] a multifarious hexacyclic cembrenolide isolated from the soft coral *Pseudopterogorgia kallos*,[66] was found to exhibit significant antimalarial activity against *Plasmodium falciparium* (IC_{50} ca. 10 μg/mL).[66] In addition, potent cytotoxicity data regarding **88** have been reported against nonsmall cell lung cancer (EKVX, GI_{50} ca. 0.01 μM) and renal cancer cells (CAKI-1, GI_{50} ca. 0.50 μM).[66] Along these lines, ineleganolide (**90**) isolated from *Sinularia inelegans*[67] displays strong cytoxicity against P-388 cancer cells (ED_{50} 3.82 μg/mL).[67] On the other hand, plumarellide (**89**) isolated from the soft coral genus *Plumarella*[68] exhibits moderate hemolytic activity in mice with 50% hemolysis of mouse blood erythrocytes at 140 μM[68] while the bioactivities of verrillin (**87**)[69] have not yet been studied.

3.1.2 Complex Cembrenolide Biosynthesis

Evaluation of the polycyclic motifs of verrillin (**87**) and bielschowskysin (**88**) suggests that both compounds can derive biosynthetically from the same precursor **91** (R_1 = Me)[8,9,56] whose cembrane macrocyclic core contains a furan in close proximity to a butenolide ring. Furan oxidation of **91** could produce intermediate **92** in which the electron rich enol[8,9,56] could react with the pendant butenolide to form intermediate **93**. Intermediate **93** contains the entire carbon backbone of verrillin (**87**). If the C_{13} β-alcohol is modified as an acetate group (R_2 = OAc), the resulting C_{12} carbanion could cyclize at the C_6 center creating the strained cyclobutane motif reminiscent to that found in bielschowskysin (**88**).

Both photochemical[62,70,71] and Lewis-acid[72,73,74] induced conditions could account for the formation of this ring. However, if the C_{13} β-alcohol is available (R_2 = H), it could cyclize at the C_6 center of **93**, forming a more energetically favorable six membered hemi-ketal ring encountered in the motif of verrillin (**87**). A proposed biosynthetic pathway towards plumarellide (**89**) involves the proposed intermediate (**94**) in which the C_{13} hydroxyl group is eliminated forming a diene moiety[9] which undergoes an immediate Diels-Alder cyclization. On the other hand, a different biosynthetic

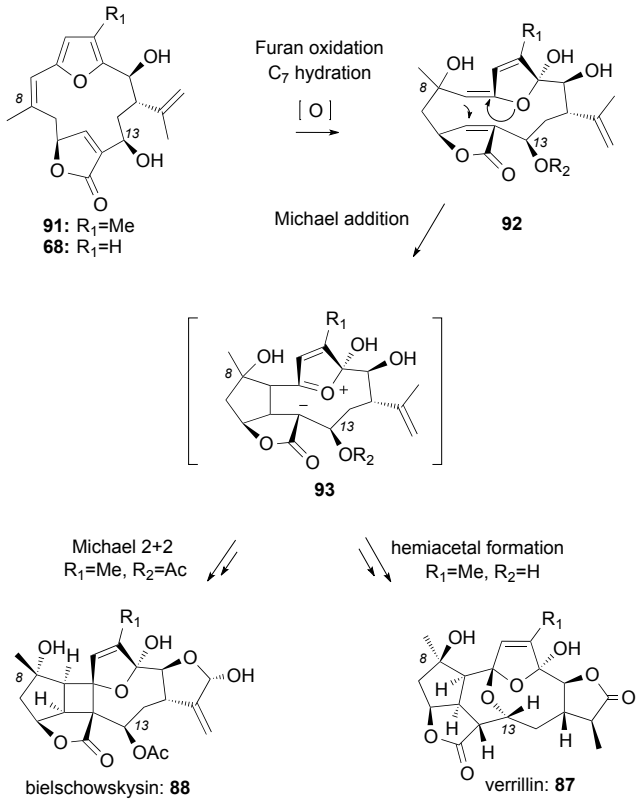


Figure 3.2: Proposed Biosynthesis of Verrillin and Bielschowskysin

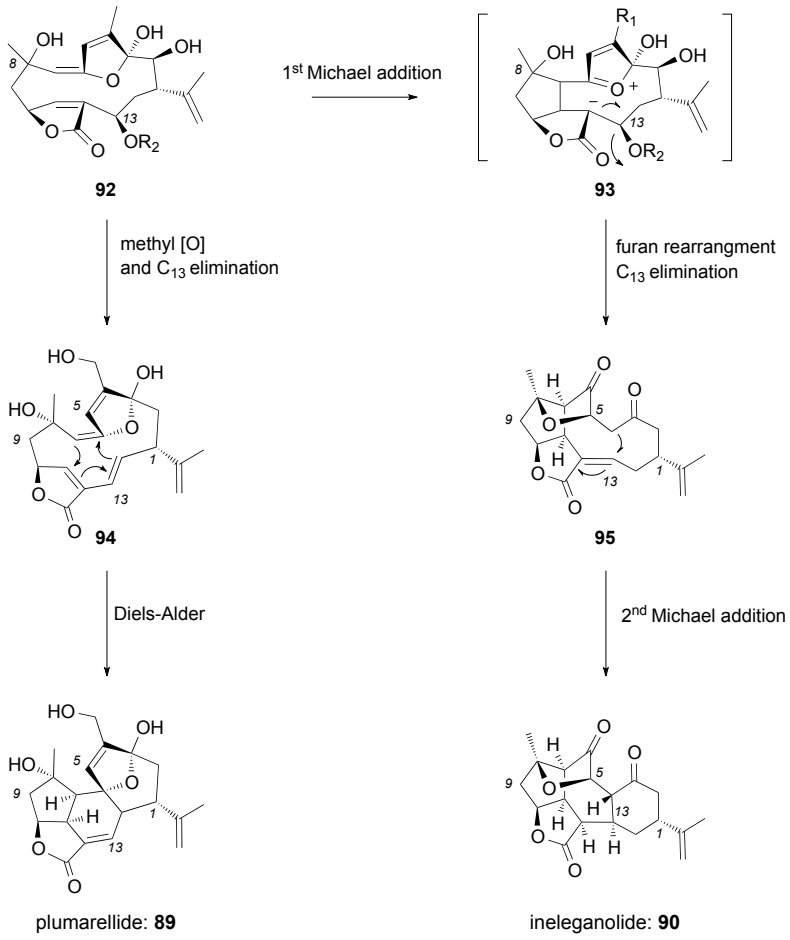


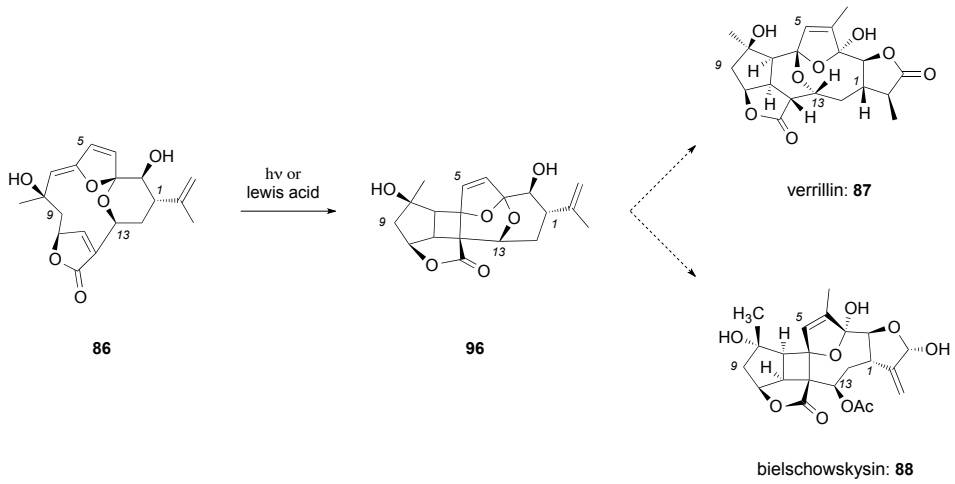
Figure 3.3: Proposed Biosynthesis of Plumarellide and Ineleganolide

pathway involving the subsequent opening of the oxidized furan moiety in intermediate (**95**) followed by ring contractions with the resulting enolates and the C_{13} center could furnish scaffolds like ineleganolide (**90**).[8,9]

3.2 Initial Photosynthetic Attempts

Compound **86**[56] in which the spiro ketal of the furan has allowed for a stabilized alkene terminously attached to the furan, represents an interesting and possibly synthetic intermediate towards the synthesis of verrillin and bielschowskysin scaffolds. Its resemblance to proposed biosynthetic intermediate **92** begged the question as to whether a photochemical[62,70,71] and/or Lewis acid[72,73,74] catalyzed ring contraction of the C_7-C_{11}

and C_{12}-C_6 cyclobutane fragments found in bielschowskysin (**88**) were possible. To



Scheme 3.1: Synthetic Attempts Toward Bielschowskysin Cores

this end, we subjected **86** in a solution of $CDCl_3$ to irradiation using a Rayonet®[62,71] irradiator with medium pressure mercury lamps. Unfortunately the anticipated **96** could not be obtained and prolonged exposure only degraded the starting material. We then sought to vary the light source, reaction time and solvent yet no combination of conditions was found to be successful. Reports also indicated that such cyclobutanes could also be synthetically derived from a Lewis acid catalyzed [2+2] cycloadditon of electron rich enolates and electron deficient alkenes. Use of previously successful Lewis acids such as TBS-(NTf_2),[72,73,74] $Yb(OTf)_3$[75] and $ZnBr_2$[76] on compound **86** in hopes of yielding **96** did not however yield any cyclobutane adducts but instead caused excessive decomposition of the starting material.

3.3 Cyclopentane Formation via Reductive Radical Cyclization.

Another approach in creating cembrenolide cores reminiscent to verrillin (**87**) and bielschowskysin (**88**) involved the reductive cyclization[77] with the present butenolide alkene forming the C_7-C_{11} cyclopentane ring. We envisioned an intermediate **97**

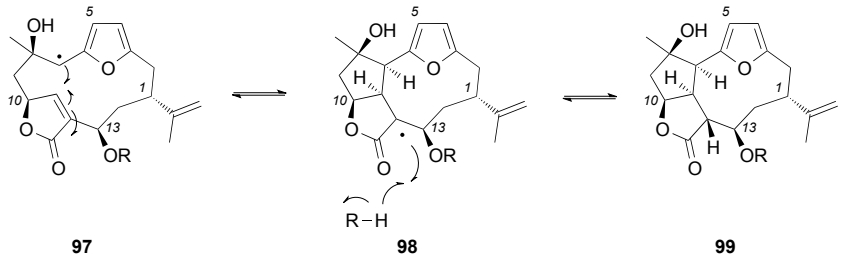
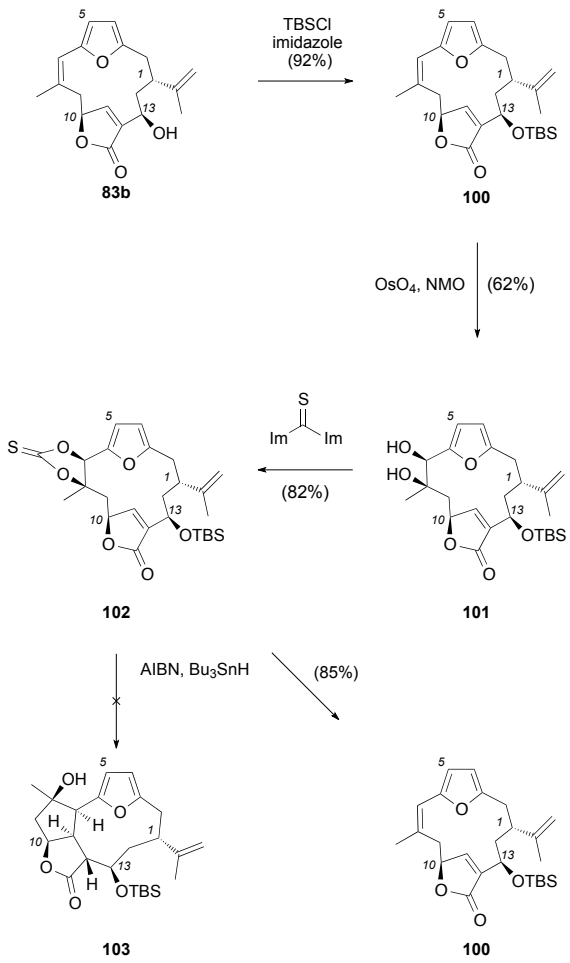


Figure 3.4: Proposed Radical Formation of Verrillin Cores

containing a furylic radical at C_7 would preferentially cyclize at the C_{11} carbon in a radical 5-exo-trig fashion. The resulting stabilized radical would then be localized at C_{12} creating intermediate **98** that upon reductive quench with a radical hydride source, could produce a verrillin derivative **99**. With this in mind, we protected β-alcohol derivative **83b** as the TBS ether **100** in 92% yield. Next, we dihydroxylated across the C_7-C_8 alkene using catalytic OsO_4 and NMO[34] as the stoichiometric oxidant which produced diol **101** in a 62% yield. We are confident of the regio and stereoselectivity of this dihydroxylation event by comparison of spectral data of **101** with its C_{13} deoxygenated analogue **40**.[25] In preparation for the reductive cyclization, we protected diol **101** to form its thiocarbonate[78] derivative **102** in 82% yield. Unfortunately, treatment of **102** with AIBN and tributyltin hydride[79] did not produce any expected **103** but instead reduced of the diol completely reforming compound **100** in 85% yield.

3.4 Retrosynthetic Plan

A commonality shared by these polycyclic cembrenolides is an oxidative ring contraction of the 14-membered cembrenolide ring across the C_7 and C_{11} carbons thereby producing the verrillane core (**104**).[8,9,66] Synthetically speaking, subsequent ring contractions across the C_6 and C_{12} or the C_6 and C_{14} centers would produce the bielschowskyane (**106**)[8,9,66] and the plumarane core (**108**)[9] respectively. On the other hand, oxidative demethylation followed by nucleophilic ring contraction at the C_4 and C_{13} centers could assemble the inelegane core. (**107**)[9] Although several strategies toward the synthesis of bielschowskysin (**88**)[62,70,71,80,81] and plumarellide (**89**)[82,83] have been



Scheme 3.2: Attempts at Reductive Radical Cyclizations

reported, none have generated the actual carbon scaffold with relevant carbon connections and oxidation patterns. Inspired by the challenge, we directed our efforts toward the synthesis of motif **105** that contains an appropriately functionalized verrillane core. Referred to herein as furano-verrillin, compound (**105**) represents a branching node toward the synthesis of verrillin (**87**) and its more intricate brethren. We envisioned that construction of the fused bicyclic lactone, present in our target, could be furnished via an Eschenmoser-Claisen rearrangement,[84,85] This disconnection reveals allylic alcohol **109** and commercially available amide acetal **110** as the coupling partners. Claisen alkylation[56] of this adduct with aldehyde **70** could then create the desired C_{12}-C_{13} connection as well as provide the important C_{13} oxidation present in this family of com-

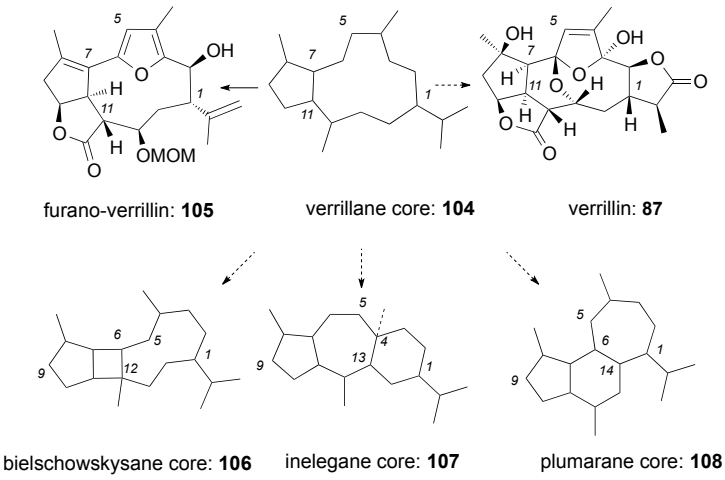


Figure 3.5: Cembrenolide Carbon Skeletons Originating from Verrillin

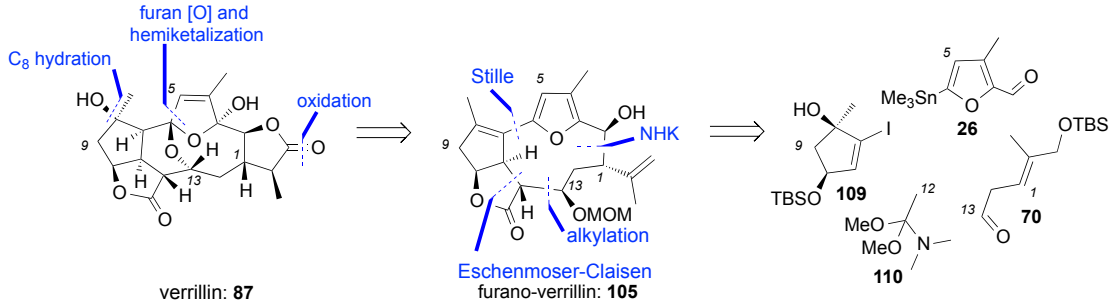
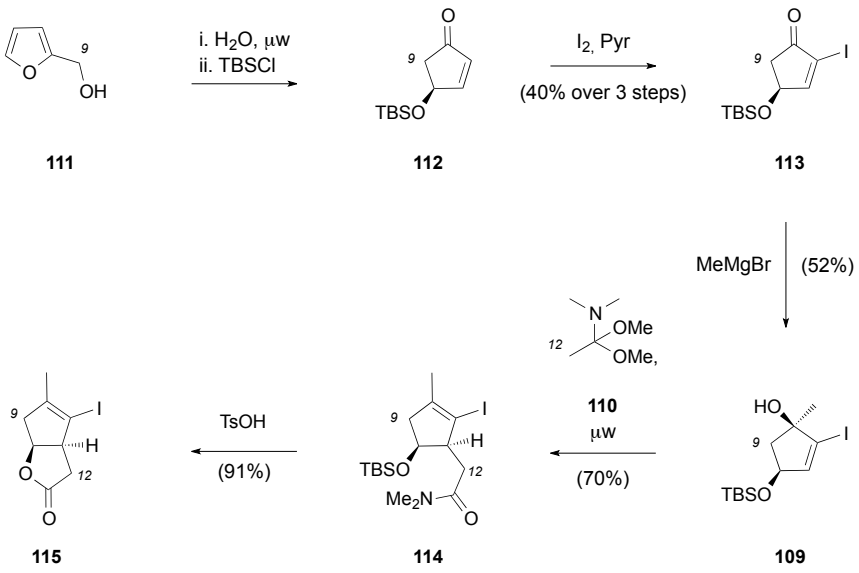


Figure 3.6: Retrosynthetic Plan Toward Furanoverrillin

pounds. Pd (0)-coupling[21,25,26] could then be used to join furan derivative **26** by creating the C_6-C_7 bond, while macrocylization under Nozaki-Hiyama-Kishi (NHK)[86,87,88] conditions could afford the final C_1-C_2 linkage.

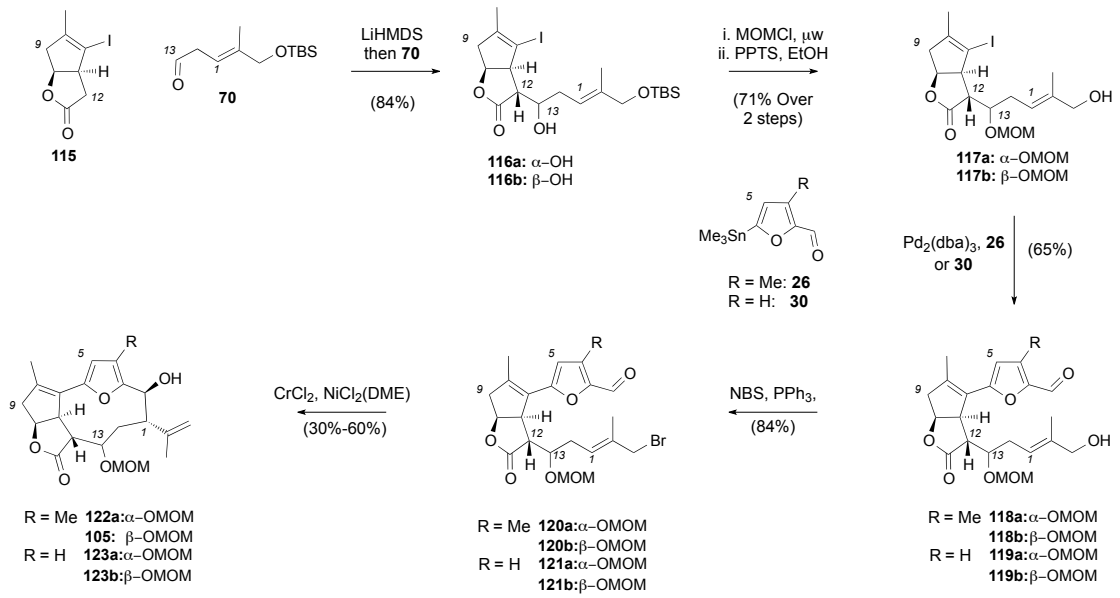
3.5 The Synthesis of Furanoverrillin

The synthesis of furano-verrillin (**105**) commenced with the formation of lactone **115**.[89] Furfuryl alcohol (**111**) was rearranged to a cyclopentenone derivative under microwave irradiation[90] that, after TBS protection and regioselective iodination,[91] gave rise to iodo-enone **113** (3 steps, 40% overall yield). Nucleophilic addition onto the carbonyl with methyl magnesium bromide[92] yielded tertiary alcohol **109** as a single



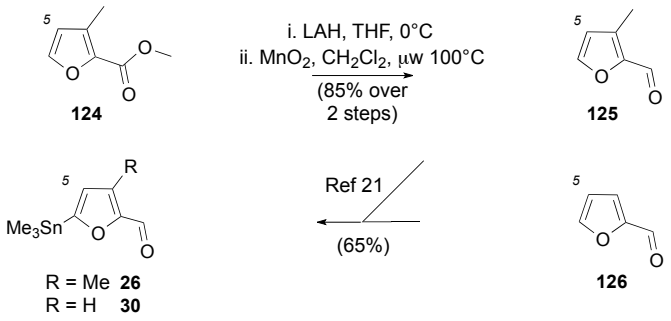
Scheme 3.3: Synthesis of Novel Bicyclic Vinyl-iodo Lactone

diastereomer in good yield (52%). To our satisfaction, the key Eschenmoser-Claisen rearrangement[93] of **109** with **110** proceeded smoothly and in a diastereoselective manner, to afford amide **114** (70% yield). Treatment of the crude amide **114** with excess acid led to rapid cleavage of the TBS group and cyclization of the resulting alcohol at the amide carbonyl center to produce lactone[89] **115** in 91% yield. Deprotonation of **115** with freshly prepared LiHMDS[25,56] followed by quick addition of the previously described aldehyde **70**[56] supplied Claisen alkylation[94,95] alcohol **116** as a 1:1.7 mixture of C_{13} diastereomers. These isomers, **116a** and **116b**, were separated by column chromatography and used separately in subsequent manipulations. TBS protection of the newly installed alcohol functionality was markedly slow and low yielding. Protection of the secondary alcohols **116a** and **116b** with MOMCl[96] was also slow at room temperature. Microwave irradiation conditions at 80 °C for 10 minutes[56] however, successfully yielded the desired MOM protected alcohols. Selective TBS deprotection of this crude material using PPTS in ethanol[58] afforded primary alcohols **117a** and **117b** (ca. 71% yield over 2 steps). The synthesis of methyl furfuryl stannane **26** was accomplished in which commercially available furan derivative **124** was reduced to the corresponding primary alcohol[97] that, after oxidation with manganese dioxide[98] under microwave irradiation[56,89] produced aldehyde **125** (2 steps, 85% yield). Stannylation of



Scheme 3.4: Coupling and Macrocyclization Producing Furanoverrillin

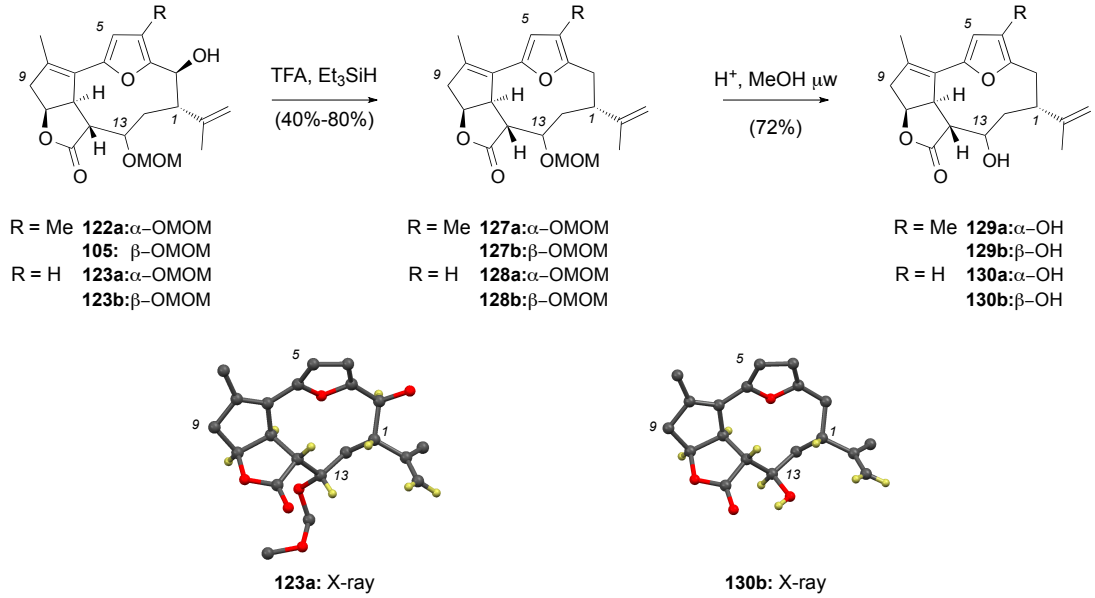
a transiently protected aldehyde **125** with trimethyltin chloride afforded stannane **26** in 65% yield. In a similar fashion, aldehyde **126** was converted to stannane **30**.[21] To our chagrin, coupling of stannane **26** with primary alcohols **117a** and **117b** under the previously established Stille conditions ($Pd(PPh_3)_4$/CuI)[21,25,56] was not successful. However, switching of reagents to catalytic $Pd_2(dba)_3$ and triphenylarsine[99,100,101] cleanly afforded alcohol **118a** and **118b** in 65% average yield. Appel bromination[29] conditions were employed to convert alcohols **118a** and **118b** to their corresponding bromides **120a** and **120b** (ca. 84% yield). The final macrocyclization event that would create the 10-membered macrocycle also proved to be more problematic than previously described leading to a complex mixture of products. Changing the solvent from THF to DMF[102] greatly improved the reaction outcome to afford furanoverrillin (**105**), containing the desired verrillin stereochemistry at C_{13}, together with its C_{13} R-isomer **122a** in 30% combined yield. The diastereoselectivity of the macrocyclization was 4/1 anti/syn with respect to the orientation of the C_2 alcohol and the C_1 isopropenyl group.[22,30,31] Compounds **122a** and **105** were subjected to standard C_2 deoxygenation conditions using TESH/TFA[33] conditions to produce deoxygenated products **127a** and **127b** in lower than expected yields (ca. 40% yield), Acid-induced MOM deprotection[103] under mi-



Scheme 3.5: Synthesis of Furfuryl Stannanes

crowave conditions afforded the corresponding alcohols **129a** and **129b** in an average yield of 72%.

3.6 The Synthesis of Norfuranoverrillin Derivatives



Scheme 3.6: Continued Functionalization of Verrillin Cores

During this study, we observed modest yields in converting **120a** and **120b** to **122a** and **105**, respectively. This may be due to the inherent tendency of these compounds to undergo carbocation rearrangements at the C_2 center, as previously reported

for certain C_2 hydroxy furanocembrenolides and pseudottedanolides.[104,105] An alternative explanation is to consider that, due to its high electronic density, the furan ring becomes sensitive to oxidative decomposition. To test this hypothesis we repeated the aforementioned sequence using the nonmethylated furfuraldehyde **126** instead of its methylated analogue **125**.[89] To this end, we coupled the previously synthesized[25,56] furfural stannane **30** with alcohols **117a** and **117b** to afford **119a** and **119b** in comparable yields (ca. 65% yield). Appel[29] conditions also smoothly afforded bromides **121a** and **121b** again, in nearly identical yields (ca. 84% yield). When optimized NHK conditions[86,87,88] were then applied using DMF[102] as a solvent, a clean conversion to the desired nor-furanoverrillin intermediates **123a** and **123b** was observed in good yields (ca. 60% yield). Deoxygenation at the C_2 center using TESH/TFA[33] conditions also cleanly produced deoxygenated intermediates **128a** and **128b** in noticeably increased yields. Finally, acidic removal of the MOM group[103] created alcohols **130a** and **130b** in similar yields (ca. 72% yield). Along with a striking improvement in reaction yields of the nor-furanoverrillin derivatives was the ability to then obtain X-ray structures[32] for compounds **123a** and **130b** which confirmed the proposed stereochemical assignments.

3.7 Conclusion

In conclusion, presented herein is a stereoselective synthesis of furanoverrillin (**105**), a branching node toward the synthesis of verrillin (**87**) and related polycyclic cembrenolides. Our approach relies on introduction of the C_7-C_{11} cyclopentene ring prior to the macrocyclization of the fully functionalized verrillin core.[89] We observed that the presence of a C_4 methyl group at the furan ring increases its susceptibility toward oxidative decomposition. In turn, this attests to the role of the C_4 methyl group in oxidative rearrangements that account for the plethora of polycyclic cembrenolides isolated thus far.[8,9] The described strategy produces, for the first time, the entire carbon framework of verrillin and allows for further functionalization toward verrillin (**87**) and structurally related natural products.

3.8 Experimental Section

3.8.1 General Techniques

All reagents were commercially obtained (Aldrich, Acros, Strem) at highest commercial quality and used without further purification except where noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 40 °C at approximately 15 mmHg. All non-aqueous reactions were carried out under anhydrous conditions using flame-dried glassware within an argon atmosphere in dry, freshly distilled solvents, unless otherwise noted. Tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), toluene ($PhCH_3$) and benzene (PhH) were purified by passage through a bed of activated alumina. Dimethylformamide (DMF) were distilled from calcium hydride under reduced pressure (20 mmHg) and stored over 4 angstrom molecular sieves until needed. Yields refer to chromatographically and spectroscopically (^{1}H NMR, ^{13}C NMR) homogeneous materials, 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 the visualizing agent and 10% ethanolic phosphomolybdic acid (PMA) or Potassium Permanganate solution ($KMnO_4$) in water and heat as developing agents. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography. Preparative thin-layer chromatography separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Varian Mercury 400 and/or Jeol Unity 500 MHz instruments and calibrated using the residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad, dd = doublet of doublet, dt = doublet of triplet. High resolution mass spectra (HRMS) were recorded on a VG 7070 HS or on a VG ZAB-ZSE mass spectrometers. X-ray data were recorded on a Bruker SMART APEX 3kW Sealed Tube X-ray diffraction system.

3.8.2 Experimental Procedures and Data

TBS protected C_{13} alcohol (100): To a solution of **83b** (0.21 g, 0.67 mmol) in 6.7 ml of CH_2Cl_2 at 0 °C was added imidazole (0.14 g, 2.00 mmol) followed by TBS-Cl (0.121 g, 0.80 mmol) and finally DMAP (8.0 mg, 0.07 mmol). The reaction was stirred at this temperature for 20 minutes. 20 ml of saturated NH_4Cl as added and the reaction was stirred for an additional 20 minutes. The reaction was then extracted 3X with 10 ml of CH_2Cl_2. Flash chromatography (up to 20% EtOAc in Hexanes) of the crude material yielded **100** (0.263 g, 0.61 mmol, 92 % yield) as a white powder. **100** clear crystals mp 101-104 °C R_f= 0.35 (15% EtOAc in Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.61 (s, 1H) 6.18 (s, 1H) 6.10 (d, 1H, *J*= 3.1Hz) 6.03 (d, 1H, *J*= 3.1Hz) 4.91 (ddd, 1H, *J*= 1.2Hz, *J*= 4.8Hz, *J*= 11.5Hz) 4.72 (s, 2H) 4.54 (dd, 1H, *J*= 5.4Hz, *J*= 10.1Hz) 3.01 (t, 1H, *J*= 11.7Hz) 2.73 (dd, 2H, *J*= 4.9Hz, *J*= 12.0Hz) 2.63 (dd, 1H, *J*= 9.5Hz, *J*= 15.5Hz) 2.51 (ddd, 1H, *J*= 3.0Hz, *J*= 10.2Hz, *J*= 13.4Hz) 2.20 (ddd, 1H, *J*= 3.2Hz, *J*= 6.3Hz, *J*= 13.0Hz) 1.98 (s, 3H) 1.77 (s, 3H) 1.70 (m, 1H) 0.83 (s, 9H) -0.02 (s, 3H) -0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.7, 154.5, 154.2, 150.5, 149.5, 132.2, 129.5, 117.8, 110.6, 109.6, 107.6, 78.1, 66.7, 42.4, 41.4, 40.4, 33.5, 26.1, 25.7, 21.0, 18.2, -4.7, -5.0; HRMS calcd. For $[M+Na]^+$ 451.2281, observed 451.2283.

Diol (101): To a solution of (0.263 g, 0.61 mmol) in 3.1 ml of THF and 3.1 ml of water at 0 °C was added NMO (0.072 g, 0.61 mmol) followed by a 4% solution of osmium tetroxide (0.48 ml, 0.061 mmol). The reaction was allowed to stir at this temperature for 3 hours. The reaction was then quenched by adding 10 ml of saturated sodium thiosulfate. The reaction was allowed to stir for an additional hour. The reaction was then extracted 3X with 10 ml of EtOAc. Flash chromatography (up to 60% EtOAc in Hexanes) of the crude material yielded **101** 0.176 g, 0.380 mmol, 62 % yield) as a white powder. **101** clear crystals mp 156-161 °C R_f= 0.25 (50% EtOAc in Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.26 (d, 1H, *J*=3.0Hz) 6.08 (m, 1H) 5.78 (s, 1H) 4.91 (dd, 1H, *J*= 5.8Hz, *J*= 11.5Hz) 4.75 (s, 1H) 4.73 (s, 1H) 4.63 (dd, 1H, *J* =5.4Hz, *J* =11.3Hz) 4.49 (d, 1H, *J* =4.2Hz) 3.16 (s, 1H) 2.84 (dd, 2H, *J*= 10.0Hz, *J*= 14.5Hz) 2.61 (m, 1H) 2.37 (dd, 1H, *J*= 5.9Hz, *J*=14.3 Hz) 2.21 (dd, 2H, *J*= 11.3Hz, *J*= 25.3Hz) 1.79 (s, 3H) 1.72 (dd, 1H, J= 5.4Hz, *J*= 13.1Hz) 1.40 (s, 3H) 0.83 (s, 9H) 0.00 (s, 3H) -0.06 (s, 3H); HRMS calcd. For $[M+Na]^+$ 485.2335, observed 485.2336.

Thiolcarbonate (102): To a solution of (0.18 g, 0.38 mmol) in 7.6 ml of THF was added di(1H-imidazol-1-yl)methanethione (0.136 g, 0.76 mmol) and DMAP (0.005 g, 0.038 mmol). The reaction was warmed to 40 °C and stirred for 3 hours. The reaction was then quenched with 20 ml of saturated NH_4Cl. The reaction was then extracted 3X with 10 ml of EtOAc. Flash chromatography (up to 60% EtOAc in Hexanes) of the crude material yielded **102** (0.157 g, 0.312 mmol, 82 % yield) as a white powder. **102** white powder mp 170-171 °C R_f= 0.30 (50% EtOAc in Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.61 (d, 1H, *J*= 3.2Hz) 6.19 (d, 1H, *J*= 3.2Hz) 5.68 (s, 1H) 5.42 (s, 1H) 4.85 (dd, 1H, *J*= 5.0Hz, *J*= 11.4Hz) 4.78 (d, 1H, *J*= 1.3Hz) 4.74 (s, 1H) 4.57 (dd, 1H, *J*= 5.9Hz, *J*= 11.1Hz) 2.89 (d, 1H, *J*= 14.9Hz) 2.66 (m, 3H) 2.48 (dd, 1H, *J*= 11.8Hz, *J*= 13.6Hz) 1.80 (s, 3H) 1.77 (s, 3H) 0.82 (s, 9H) -0.01 (s, 3H) -0.08 (s, 3H); For $[M+Na]^+$ 527.1900, observed 527.1898.

Attempt at 103: To a solution of **102** (0.157 g, 0.31 mmol) in 31.1 ml of PhH at 80 °C was added tributylstannane (0.33 ml, 1.24 mmol) followed by AIBN (0.026 g, 0.156 mmol). The reaction was stirred at this temperature for 20 minutes. The reaction was then cooled and evaporated to a residue. Flash chromatography (up to 20% EtOAc in Hexanes) of the crude material yielded **100** (0.113 g, 0.264 mmol, 85 % yield) as a white powder who's spectral data was identical to its previous synthesis.

Cyclopentenone (112): A solution of furfuryl alcohol (**111**) (5.0 ml, 57.4 mmol) and water (5.0 ml) were added to a 20 ml microwave tube and micro-waved at 170 °C for 10 minutes. Upon cooling, the top layer was decanted off and the residue is washed with an additional 5 ml of water 2X. The combined water mixtures were washed 2X with 50 ml PhMe. The water layer was then concentrated to yield cyclopentenone alcohol (**i**) as an orange to red oil and is used in the next step without further purification. R_f= 0.20 (80% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57 (dd, 1H, *J*= 2.3 Hz, *J*= 5.7 Hz), 6.24 (dd, 1H, *J*= 1.0 Hz, *J*= 5.7 Hz), 5.06 (ddd, 1H, *J*= 1.9 Hz, *J*= 3.4 Hz, *J*= 5.7 Hz), 2.79 (dd, 1H, *J*= 6.1 Hz, *J*= 18.5 Hz), 2.29 (dd, 1H, *J*= 2.1 Hz, *J*= 18.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.8, 163.3, 135.1, 70.4, 44.2; HRMS calcd. For $[M+H]^-$ 97.0295, observed 97.0297. To a solution of cyclopentenone alcohol (**i**) (0.62 g, 6.3 mmol) in CH_2Cl_2 (6.3 ml) at 0 °C was added imidazole (1.3 g, 18.8 mmol) followed TBS-Cl (1.0 g, 6.59 mmol) and DMAP (0.08 g, 0.63 mmol) The

reaction was monitored very closely until completion (20 minutes). The reaction was then immediately quenched with 10 ml of saturated NH_4Cl. The solution was extracted 3X with 10 ml of CH_2Cl_2. The organic layers were combined, dried and concentrated to yield a yellow oil. Flash chromatography (up to 10% EtOAc in hexanes) of the crude material gave TBS Ether **112** as a clear oil. R_f= 0.30 (10% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43 (dd, 1H, *J*= 2.3 Hz, *J*= 5.7 Hz), 6.15 (d, 1H, *J*= 6.0 Hz), 4.96 ddd, 1H, *J*= 1.9 Hz, *J*= 3.4 Hz, *J*= 5.7 Hz), 2.68 (dd, 1H, *J*= 6.0 Hz, *J*= 18.2 Hz), 2.22 (dd, 1H, *J*= 2.2 Hz, *J*= 18.2 Hz), 0.88 (s, 9H), 0.11 (s, 3), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.4, 163.8, 134.4, 70.8, 44.9, 25.7, 18.0, -4.8; HRMS calcd. For $[M+H]^+$ 213.1305, observed 213.1304.

Vinyl Iodide (113): To a solution of TBS Ether (**112**) (11.28 g, 53.1 mmol) in CH_2Cl_2 (22.1 ml) and pyridine (22.1 ml) at 0 °C was added a solution of iodine (23.26 g, 92 mmol) in DCM (44.2 ml) and pyridine (44.2 ml). The reaction was allowed to warm to room temperature over 20 minutes. The solution was then quenched with a saturated solution of sodium thiosulfate (100 ml). The reaction was then stirred vigorously for 30 minutes. The solution was extracted 3X with 50 ml of CH_2Cl_2. The organic layers were combined, dried and concentrated to yield a dark oil. Flash chromatography (up to 10% EtOAc in hexanes) of the crude material gave **113** as a clear oil which solidified upon standing. R_f= 0.35 (10% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.80 (d, 1H, *J*= 2.5 Hz), 4.95 (td, 1H, *J*= 2.3 Hz, *J*= 6.0 Hz), 2.86 (dd, 1H, *J*= 6.0 Hz, *J*= 18.2 Hz), 2.35 (dd, 1H, *J*= 2.1 Hz, *J*= 18.2 Hz), 0.91 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 200.2, 169.1, 104.9, 72.1, 42.3, 25.6, 18.0, -4.8.

Tertiary Alcohol (109): to a solution of **113** (1.7 g, 5.03 mmol) in THF (50.0 ml) at -30 °C was added methyl magnesium bromide 3.0M solution in diethyl ether (2.01 ml, 6.03 mmol) dropwise. The reaction was then monitored by TLC until completion (ca. 1hr). The reaction was then quenched with 50 ml of saturated NH_4Cl and extracted 3X with 50 ml of fresh Et_2O. The organic layers were combined, dried and concentrated to yield pale yellow oil. Flash chromatography (up to 15% EtOAc in hexanes) of the crude material gave **109** (0.93 g, 2.6 mmol, 52% yield) as a clear oil. R_f= 0.24 (10% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.17 (s, 1H), 4.61 (ddd, 1H, *J*= 1.7 Hz, *J*= 3.9 Hz, *J*= 6.5 Hz), 2.48 (ddd, 1H, *J*= 1.2 Hz, *J*= 6.8 Hz, *J*= 13.2 Hz), 2.03

(s, 1H), 1.91 (dd, 1H, *J*= 4.3 Hz, *J*= 13.2 Hz), 1.25 (s, 3H), 0.88 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.1, 113.6, 82.5, 75.4, 48.0, 27.2, 25.8, 18.1, -4.7; HRMS calcd. For $[M+Na]^+$ 377.0404, observed 377.0403.

Amide (114): To a solution of **109** (1.0 g, 2.82 mmol) in PhMe (1.4 ml) in a 5 ml microwave tube was added **110** (1.24 ml, 8.47 mmol) and was microwaved at 190 °C for 2.5 hours. The reaction was then concentrated to yield a dark oil. Flash chromatography (up to 25% EtOAc in hexanes) of the crude material gave **114** (0.84 g, 1.98 mmol, 70.3% yield) as a clear oil. R_f= 0.50 (30% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.56 (dt, 1H, *J*= 3.0 Hz, *J*= 6.6 Hz), 3.40 (m, 1H), 2.96 (s, 1H), 2.87 (s, 1H), 2.60 (dd, 1H, *J*= 10.6 Hz, *J*= 16.3 Hz), 2.50 (dd, 1H, *J*= 6.6 Hz, *J*= 16.1 Hz), 2.37 (dd, 1H, *J*= 3.3 Hz, *J*= 16.3 Hz), 2.22 (d, 1H, *J*= 17.4 Hz), 1.72 (s, 3H), 0.79 (s, 9H),-0.02 (s, 3H),-0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.1, 147.4, 102.5, 77.0, 58.9, 51.7, 42.7, 41.0, 37.7, 31.4, 25.2, 23.6, 0.9, 0.3; HRMS calcd. For $[M+H]^+$ 424.1163, observed 424.1165.

Lactone (115): To a solution of **114** (1.20 g, 2.82 mmol) in THF (25.7 ml) and Water (2.57 ml) was added *p*-TsOH (1.6 g, 8.47 mmol) in one portion. The reaction was then stirred at 25 °C for 4 hours. The reaction was then quenched with 50 ml of saturated $NaHCO_3$ and extracted 3X with 30 ml of fresh Et_2O. The organic layers were combined, dried and concentrated to yield a pale yellow oil. Flash chromatography (up to 35% EtOAc in hexanes) of the crude material gave **115** (0.68 g, 2.58 mmol, 91% yield) as an off-white solid. R_f= 0.30 (30% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.08 (dt, 1H, *J*= 1.9 Hz, *J*= 5.0 Hz), 3.62 (m, 1H), 2.68 (m, 4H), 1.81 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.4, 143.4, 94.2, 81.3, 53.6, 43.1, 33.4, 18.7; HRMS calcd. For $[M+Na]^+$ 286.9539, observed 286.9537.

Secondary Alcohol (116a) and (116b): To a solution of HMDS (0.83 ml, 3.98 mmol) in dry THF (10.6 ml) at 0 °C was added BuLi 1.6M in hexanes (2.39 ml, 3.82 mmol) dropwise. The reaction was then allowed to stir for 30 minutes at this temperature. **115** (0.84 g, 3.18 mmol) in a solution of dry THF (10.6 ml) was then lowered to -78 °C. The LiHMDS solution was then taken up in a syringe and added dropwise to the solution of **115** at -78 °C. The reaction was then allowed to stir for 30 minutes at which

time **70** (0.95 g, 4.14 mmol) in a solution of dry THF (10.6 ml) at -78 °C was added quickly via cannula to solution of **115**. The reaction was allowed to stir for 30 minutes at which time a 20 ml of saturated NH_4Cl was added and then extracted 3X with 30 ml of fresh Et_2O. The organic layers were combined, dried and concentrated to yield a pale yellow oil. Careful flash chromatography (up to 60% Et_2O in hexanes) of the crude material gave **116a** and **116b** (1.32 g, 2.68 mmol, 84 % yield) as a 1:1.7 mixture of diastereomers which were used separately for future manipulations. **116a**; R_f= 0.35 (50% Et_2O in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.52 (ddd, 1H, *J*= 1.3 Hz, *J*= 6.7 Hz, *J*= 8.1 Hz), 5.06 (dt, 1H, *J*= 1.7 Hz, *J*= 6.6 Hz), 4.20 (m, 1H), 4.04 (s, 1H), 3.71 (m, 1H), 2.69 (m, 3H), 2.45 (td, 1H, *J*= 8.8 Hz, *J*= 14.4 Hz), 2.33 (m, 1H), 2.23 (d, 1H, *J*= 3.0 Hz), 1.81 (s, 3H), 1.65 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.7, 143.2, 139.1, 118.2, 94.5, 81.7, 71.2, 68.0, 55.1, 51.2, 42.9, 33.7, 25.9, 18.9, 18.4, 13.9, -5.3; For $[M+Na]^+$ 515.1085, observed 515.1084; **116b**; R_f= 0.30 (50% Et_2O in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.47 (ddd, 1H, *J*= 1.3 Hz, *J*= 4.7 Hz, *J*= 8.2 Hz), 5.10 (dt, 1H, *J*= 1.9 Hz, *J*= 5.1 Hz), 4.04 (s, 1H), 3.91 (m, 1H), 3.54 (m, 1H), 2.67 (m, 4H), 2.44 (m, 1H), 2.13 (d, 1H, *J*= 2.2 Hz), 1.80 (s, 3H), 1.65 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.7, 143.2, 139.5, 118.4, 94.2, 81.2, 73.0, 68.0, 59.3, 50.3, 43.0, 33.0, 25.9, 18.7, 18.4, 13.9, -5.3, -5.3; For $[M+Na]^+$ 515.1085, observed 515.1084.

MOM Ether (116ai) and (116bi): To a solution of **116a** (0.65 g, 1.32 mmol) in CH_2Cl_2 (Volume: 1.32 ml) in a 2 ml microwave tube was added DIPEA (1.38 ml, 7.92 mmol) followed by MOM-Cl (0.30 ml, 3.96 mmol). The reaction was then microwaved at 80 °C for 10 minutes. The reaction was then quenched with 20 ml of saturated NH_4Cl and extracted 3X with 10 ml of fresh CH_2Cl_2. Organic combined dried and concentrated to yield **116ai** as a pale orange oil which was used without further purification. **116ai**; R_f= 0.35 (20% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.56 (dt, 1H, *J*= 1.3 Hz, *J*= 7.2 Hz), 5.04 (ddd, 1H, *J*= 2.3 Hz, *J*= 4.6 Hz, *J*= 6.5 Hz), 4.62 (dd, 2H, *J*= 6.8 Hz, *J*= 39.8 Hz), 4.13 (dt, 1H, *J*= 1.9 Hz, *J*= 8.0 Hz), 4.02 (s, 2H), 3.71 (m, 1H), 3.33 (s, 3H), 2.70 (m, 2H), 2.58 (m, 1H), 2.31 (m, 1H), 1.80 (s, 3H), 1.65 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.7, 143.4, 138.1, 118.1, 95.8, 94.5, 81.8, 77.3, 68.1, 55.8, 55.3, 49.9, 42.8, 30.8, 26.0, 18.9, 18.4, 14.0, -5.3; For

$[M+Na]^+$ 559.1347, observed 559.1346. The synthesis of **116bi** was identical to that of **116ai**. **116bi**; R_f= 0.35 (20% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.46 (ddd, 1H, *J*= 1.3 Hz, *J*= 6.7 Hz, *J*= 7.9 Hz), 5.03 (dt, 1H, *J*= 1.4 Hz, *J*= 5.7 Hz), 4.70 (dd, 2H, *J*= 7.0 Hz, *J*= 19.4 Hz), 4.01 (s, 1H), 3.89 (ddd, 1H, *J*= 2.8 Hz, *J*= 6.5 Hz, *J*= 7.8 Hz), 3.50 (m, 1H), 3.38 (s, 3H), 2.80 (t, 1H, *J*= 2.3 Hz), 2.69 (m, 2H), 2.58 (dd, 1H, *J*= 7.3 Hz, *J*= 14.8 Hz), 2.46 (dd, 1H, *J*= 6.8 Hz, *J*= 13.8 Hz), 1.78 (s, 3H), 1.66 (s, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.0, 142.9, 138.0, 118.4, 95.3, 94.3, 80.8, 78.3, 68.0, 58.6, 56.0, 48.0, 43.1, 29.6, 25.9, 18.6, 18.3, 13.7, -5.3, -5.3; For $[M+Na]^+$ 559.1347, observed 559.1346.

Primary Alcohol (117a) and (117b): To a solution of **116ai** (2.75 g, 5.13 mmol) in Ethanol (25.6 ml) at 25 °C was added PPTS (0.1 g, 0.51 mmol) in one portion. The reaction was then stirred for 12 hours at which point, 50 ml of saturated $NaHCO_3$ was added then extracted 3X with 50 ml of fresh Et_2O. The organic layers were combined, dried and concentrated to yield a yellow oil. Flash chromatography (up to 60% EtOAc in hexanes) of the crude material gave **117a** (1.54 g, 3.65 mmol, 71.2 % yield over 2 steps) as a clear oil. **117a**; R_f= 0.25 (40% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.57 (t, 1H, *J*= 7.1 Hz), 5.05 (dt, 1H, *J*= 2.0 Hz, *J*= 6.4 Hz), 4.62 (dd, 2H, *J*= 6.9 Hz, *J*= 38.9 Hz), 4.14 (ddd, 1H, *J*= 1.8 Hz, *J*= 7.9 Hz, *J*= 14.9 Hz), 4.03 (s, 1H), 3.70 (m, 1H), 3.33 (s, 3H), 2.71 (m, 2H), 2.59 (m, 1H), 2.32 (m, 1H), 1.80 (s, 3H), 1.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.6, 143.6, 138.4, 119.7, 95.8, 94.3, 81.9, 77.2, 68.5, 55.8, 55.2, 49.9, 42.8, 30.8, 18.9, 14.3; For $[M+Na]^+$ 445.0482, observed 445.0482; The synthesis of **117b** was identical to that of **117a**. **117b**; (1.56 g, 3.69 mmol, 72.1 % yield over 2 steps; clear oil); R_f= 0.30 (40% EtOAc in Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.48 (ddd, 1H, *J*= 1.3 Hz, *J*= 6.7 Hz, *J*= 8.0 Hz), 5.04 (td, 1H, *J*= 3.0 Hz, *J*= 5.6 Hz), 4.71 (dd, 2H, *J*= 7.0 Hz, *J*= 18.6 Hz), 4.02 (s, 2H), 3.90 (ddd, 1H, *J*= 2.8 Hz, *J*= 6.2 Hz, *J*= 14.7 Hz), 3.50 (m, 1H), 3.38 (s, 3H), 2.80 (t, 1H, *J*= 2.4 Hz), 2.70 (m, 2H), 2.60 (dd, 1H, *J*= 7.3 Hz, *J*= 15.2 Hz), 2.47 (m, 1H), 1.78 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.0, 143.0, 138.6, 120.3, 95.3, 94.3, 80.8, 78.2, 68.5, 58.6, 56.0, 47.9, 43.1, 29.7, 18.6, 14.0; For $[M+Na]^+$ 445.0482, observed 445.0482.

3-Methyl Furfural (27): To a solution of furfuryl methyl ester (**124**) (5.00 g,

35.7 mmol) in THF (119 ml) at 25 °C was added lithium aluminum hydride 1.0 M in THF (8.56 ml, 30.0 mmol) in a solution of THF (59.5 ml) via an addition funnel dropwise. The reaction was then allowed to stir at this temperature for 2 hours. The solution was then brought down to 0 °C and 5 ml of EtOAc was added dropwise to quench the remaining lithium aluminum hydride. 50 ml of water was then added slowly and the resulting slurry was filtered through a pad of celite and concentrated to a residue. The residue was then taken up in fresh CH_2Cl_2 and washed once with brine. Organics combined, dried and concentrated to leave a clear oil which was used without further purification. A solution of the crude alcohol in CH_2Cl_2 (Volume: 15.1 ml) in a 20 ml microwave tube was added manganese dioxide (26.3 g, 302 mmol). The mixture was microwaved at 100 °C for 2.5 hours. The mixture was then filtered through a pad of celite and washed thoroughly with fresh DCM (3X 40 ml). Organics were dried and concentrated to yield **125** (3.35 g, 30.4 mmol, 85 % yield) as a yellow oil which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.76 (s, 1H), 7.55 (s, 1H), 6.42 (s, 1H), 2.39 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.0, 148.7, 147.3, 147.2, 115.4, 10.4; $[M+H]^+$ 111.0441, observed 111.0444.

Methyl Furfuryl Stannane (26): To a suspension of N,O-dimethylhydroxyl ammonium chloride (2.43 g, 24.9 mmol) in dry THF (121 ml) at -40 °C was added BuLi 1.6M in hexanes (31.1 ml, 49.7 mmol) dropwise. The reaction was then allowed to stir for 30 min at -40 °C. A solution of **125** (2.19 g, 19.89 mmol) in THF (12.1 ml) was then added dropwise and allowed to stir for 45 minutes at -40 °C. A second amount of BuLi 1.6M in hexanes (18.7 ml, 29.8 mmol) was then added dropwise. The reaction was then allowed to stir for an additional hour before at -40 °C at which time, a solution of trimethyltin chloride (4.76 g, 23.9 mmol) was added dropwise. The reaction was then allowed to stir for 30 minutes while warming up to -10 °C. 100 ml of saturated NH_4Cl was then added and the solution was then extracted 3X with 50 ml of fresh Et_2O. The organic layers were combined, dried and concentrated to yield a pale yellow oil. Flash chromatography (up to 8% EtOAc in hexanes) of the crude material gave **26** (3.53 g, 12.9 mmol, 65.0 % yield) as a clear oil. R_f= 0.30 (5% EtOAc in Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.73 (s, 1H), 6.54 (s, 1H), 2.34 (s, 3H), 0.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.4, 170.1, 153.0, 133.7, 126.3, 10.1, -9.1; For $[M+H]^+$ 275.0090,

observed 275.0090.

Furano-alcohol (118a) and (118b): To a solution of **117a** (0.10 g, 0.24 mmol) and **26** (0.084 g, 0.31 mmol) in THF (Volume: 0.79 ml) at 50 °C was added $Pd_2(dba)_3$ (0.022 g, 0.024 mmol), triphenylarsine (7.3 mg, 0.024 mmol) and cesium fluoride (0.072 g, 0.474 mmol) in one portion. The reaction was then stirred at 50 °C for 2 hours at which time, 1 ml of saturated NH_4Cl was added and the reaction was washed 3X with 1 ml of EtOAc. Organics were combined, dried and concentrated to yield a dark oil. Flash chromatography (up to 90% EtOAc in hexanes) of the crude material gave **118a** (0.062 g, 0.153 mmol, 64.7 % yield) as a yellow oil. R_f= 0.35 (80% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.67 (s, 1H), 6.37 (s, 1H), 5.38 (t, 1H, *J*= 6.4 Hz), 5.15 (t, 1H, *J*= 5.7 Hz), 4.66 (dd, 2H, *J*= 6.7 Hz, *J*= 38.6 Hz), 4.07 (m, 2H), 3.97 (s, 2H), 3.36 (s, 3H), 2.93 (dd, 1H, *J*= 5.1 Hz, *J*= 18.5 Hz), 2.85 (d, 1H, *J*= 19.2 Hz), 2.72 (m, 2H), 2.49 (m, 1H), 2.39 (s, 3H), 2.03 (s, 3H), 1.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.1, 176.7, 154.6, 147.1, 142.0, 138.1, 135.3, 124.5, 119.6, 114.1, 95.9, 81.8, 77.9, 68.1, 55.8, 49.7, 49.1, 45.7, 30.9, 15.9, 13.8, 10.3; HRMS calcd. for $[M+Na]^+$ 427.1727, found 427.1735; The synthesis of **118b** was identical to that of **118a**. **118b**; (0.06 g, 0.148 mmol, 62.6 % yield, yellow oil) R_f= 0.35 (80% EtOAc in hexanes), 1H NMR (400 MHz, $CDCl_3$) δ: 9.58 (s, 1H), 6.29 (s, 1H), 5.38 (t, 1H, *J*= 7.3 Hz), 5.05 (t, 1H, *J*= 6.3 Hz), 4.68 (dd, 2H, *J*= 6.9 Hz, *J*= 43.7 Hz), 4.01 (m, 1H), 3.84 (2, 1H), 3.71 (m, 1H), 3.33 (s, 3H), 2.91 (dd, 1H, *J*= 5.9 Hz, *J*= 19.6 Hz), 2.77 (m, 2H), 2.64 (td, 1H, *J*= 8.9 Hz, *J*= 14.5 Hz), 2.51 (s, 1H), 2.43 (m, 1H), 2.31 (s, 3H), 2.00 (s, 3H), 1.63 (s, 3H); 13C NMR (100 MHz, $CDCl_3$) δ: 176.2, 175.8, 154.9, 146.9, 141.1, 138.4, 135.7, 124.1, 119.1, 113.3, 95.3, 80.5, 79.5, 67.7, 55.8, 53.3, 47.4, 46.2, 29.3, 15.8, 13.6, 10.1; HRMS calcd. for $[M+Na]^+$ 427.1727, found 427.1730.

Norfurano-alcohol (119a) and (119b): To a solution of **117a** (0.09 g, 0.21 mmol) and **30** (0.083 g, 0.32 mmol) in THF (1.06 ml) at 50 °C was added $Pd_2(dba)_3$ (0.020 g, 0.021 mmol), triphenylarsine (6.5 mg, 0.021 mmol) and cesium fluoride (0.065 g, 0.47 mmol) in one portion. The reaction was then stirred at 50 °C for 2 hours at which time, 1 ml of saturated NH_4Cl was added and the reaction was washed 3X with 1 ml of EtOAc. Organics were combined, dried and concentrated to yield a dark oil. Flash chromatography (up to 90% EtOAc in hexanes) of the crude material gave **119a** (0.054

g, 0.14 mmol, 64.9 % yield) as a yellow oil. R_f= 0.35 (80% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.55 (s, 1H), 7.28 (d, 1H, *J*= 3.7 Hz), 6.53 (d, 1H, *J*= 3.7 Hz), 5.38 (t, 1H, *J*= 7.1 Hz), 5.15 (t, 1H, *J*= 5.8 Hz), 4.66 (dd, 2H, *J*= 6.8 Hz, *J*= 39.7 Hz), 4.07 (m, 2H), 3.95 (s, 2H), 3.36 (s, 3H), 2.94 (dd, 1H, *J*= 4.7 Hz, *J*= 19.5 Hz), 2.86 (d, 1H, *J*= 19.3 Hz), 2.71 (m, 2H), 2.50 (m, 1H), 2.04 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.1, 176.9, 155.8, 151.2, 142.5, 138.2, 124.6, 123.3, 119.8, 111.2, 96.0, 81.8, 78.0, 68.3, 55.9, 49.8, 49.4, 45.8, 31.0, 16.1, 13.9; HRMS calcd. for $[M+Na]^+$ 413.1572, found 413.1572; The synthesis of **119b** was identical to that of **119a**. **119b**; (.055 g, 0.141 mmol, 66.1 % yield, yellow oil) R_f= 0.35 (80% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.52 (s, 1H), 7.26 (d, 1H, *J*= 3.8 Hz), 6.50 (d, 1H, *J*= 3.8 Hz), 5.44 (t, 1H, *J*= 7.4 Hz), 5.11 (t, 1H, *J*= 6.3 Hz), 4.73 (dd, 2H, *J*= 6.9 Hz, *J*= 45.1 Hz), 4.07 (ddd, 1H, *J*= 2.3 Hz, *J*= 5.1 Hz, *J*= 9.8 Hz), 3.89 (s, 2H), 3.79 (m, 1H), 3.39 (s, 3H), 2.96 (dd, 1H, *J*= 6.2 Hz, *J*= 19.5 Hz), 2.83 (m, 2H), 2.71 (td, 1H, *J*= 9.0 Hz, *J*= 14.2 Hz), 2.49 (m, 1H), 2.10 (s, 1H), 2.06 (s, 3H), 1.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.8, 175.8, 156.2, 150.9, 141.8, 138.5, 124.4, 123.9, 119.3, 110.6, 95.5, 80.6, 79.7, 68.0, 56.0, 53.6, 47.5, 46.4, 29.5, 16.0, 13.8; HRMS calcd. for $[M+Na]^+$ 413.1572, found 413.1573.

Bromide (120a) and (120b): To a solution of **118a** (0.094 g, 0.232 mmol) in CH_2Cl_2 (5.81 ml) at -20 °C was added triphenylphosphine (0.067 g, 0.26 mmol). Once dissolved, NBS (0.046 g, 0.26 mmol) was added in one portion. The reaction was stirred for 20 minutes at which time 10 ml of water was added. The solution was then stirred for 10 minutes at which time was extracted 3X with 5 ml of CH_2Cl_2. The organics were combined, dried and concentrate to yield a yellow oil. Flash chromatography (up to 50% EtOAc in hexanes) of the crude material gave **120a** (0.091 g, 0.20 mmol, 84 % yield) as a viscous yellow oil. R_f= 0.35 (50% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.68 (s, 1H), 6.36 (s, 1H), 5.59 (t, 1H, *J*= 7.0 Hz), 5.14 (t, 1H, *J*= 5.7 Hz), 4.65 (dd, 2H, *J*= 6.8 Hz, *J*= 25.3 Hz), 4.10 (dt, 1H, *J*= 2.7 Hz, *J*= 6.6 Hz), 4.05 (m, 1H), 3.93 (s, 3H), 3.36 (s, 1H), 2.94 (dd, 1H, *J*= 5.7 Hz, *J*= 19.3 Hz), 2.85 (d, 1H, *J*= 19.2 Hz), 2.71 (m, 2H), 2.49 (m, 1H), 2.40 (s, 1H), 2.03 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.8, 176.4, 154.4, 147.1, 141.9, 135.2, 135.0, 125.8, 124.6, 114.0, 96.2, 81.6, 77.4, 56.0, 50.1, 49.3, 45.8, 40.8, 32.1, 15.9, 15.0, 10.4; HRMS calcd.

for $[M+Na]^+$ 489.0883, found 489.0884; The synthesis of **120b** was identical to that of **120a**. **120b**; (0.09 g, 0.193 mmol, 83% yellow oil). R_f= 0.35 (50% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.69 (s, 1H), 6.33 (s, 1H), 5.65 (t, 1H, *J*= 7.3 Hz), 5.09 (t, 1H, *J*= 6.1 Hz), 4.73 (dd, 2H, *J*= 7.0 Hz, *J*= 33.9 Hz), 4.10 (ddd, 1H, *J*= 2.1 Hz, *J*= 5.4 Hz, *J*= 9.0 Hz), 3.86 (q, 2H, *J*= 9.4 Hz), 3.83 (m, 1H), 3.40 (s, 3H), 2.96 (dd, 1H, *J*= 6.2 Hz, *J*= 19.5 Hz), 2.83 (d, 1H, *J*= 19.5 Hz), 2.70 (m, 2H), 2.50 (m, 1H), 2.37 (s, 3H), 2.04 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.1, 175.7, 154.6, 147.0, 141.1, 135.7, 135.5, 125.9, 124.6, 113.3, 95.7, 80.5, 79.1, 56.0, 53.3, 47.7, 46.5, 41.0, 30.4, 15.9, 14.8, 10.3; HRMS calcd. for $[M+Na]^+$ 489.0883, found 489.0887.

Bromide (121a) and (121b): To a solution of **119a** (0.06 g, 0.154 mmol) in CH_2Cl_2 (1.54 ml) at -20 °C was added triphenylphosphine (0.044 g, 0.17 mmol). Once dissolved, NBS (0.030 g, 0.17 mmol) was added in one portion. The reaction was stirred for 20 minutes at which time 5 ml of water was added. The solution was then stirred for 10 minutes at which time was extracted 3X with 3 ml of CH_2Cl_2. The organics were combined, dried and concentrate to yield a yellow oil. Flash chromatography (up to 50% EtOAc in hexanes) of the crude material gave **121a** (0.06 g, 0.132 mmol, 86 % yield) as a viscous yellow oil. R_f= 0.33 (50% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.57 (s, 1H), 7.28 (d, 1H, *J*= 3.7 Hz), 6.52 (d, 1H, *J*= 3.7 Hz), 5.59 (t, 1H, *J*= 6.9 Hz), 5.15 (t, 1H, *J*= 5.8 Hz), 4.66 (dd, 2H, *J*= 6.8 Hz, *J*= 26.8 Hz), 4.11 (dt, 1H, *J*= 2.9 Hz, *J*= 6.6 Hz), 4.07 (m, 1H), 3.93 (s, 2H), 3.37 (s, 3H), 2.96 (dd, 1H, *J*= 5.6 Hz, *J*= 19.2 Hz), 2.87 (d, 1H, *J*= 19.1 Hz), 2.72 (m, 2H), 2.51 (m, 1H), 2.06 (s, 3H), 1.84 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.3, 176.6, 155.7, 151.2, 142.3, 135.2, 125.8, 124.5, 111.0, 111.0, 96.3, 81.7, 77.5, 56.1, 50.1, 49.4, 45.9, 40.8, 32.1, 16.1, 15.1; HRMS calcd. for $[M+Na]^+$ 475.0727, found 475.0726; The synthesis of **121b** was identical to that of **121a**. **121b**; (0.058 g, 0.128 mmol, 83% yellow oil). R_f= 0.33 (50% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.57 (s, 1H), 7.26 (d, 1H, *J*= 3.8 Hz), 6.48 (d, 1H, *J*= 3.7 Hz), 5.67 (t, 1H, *J*= 7.2 Hz), 5.11 (t, 1H, *J*= 6.2 Hz), 4.74 (dd, 2H, *J*= 7.0 Hz, *J*= 36.4 Hz), 4.11 (ddd, 1H, *J*= 2.1 Hz, *J*= 5.2 Hz, *J*= 9.2 Hz), 3.87 (q, 2H, *J*= 9.4 Hz), 3.82 (m, 1H), 3.40 (s, 3H), 2.98 (dd, 1H, *J*= 6.2 Hz, *J*= 19.5 Hz), 2.85 (d, 1H, *J*= 19.5 Hz), 2.72 (m, 2H), 2.51 (m, 3H), 2.07 (s, 1H), 1.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.5, 175.7, 155.8, 151.0, 141.4, 135.6,

125.8, 124.5, 123.7, 110.5, 95.7, 80.5, 79.2, 56.1, 53.4, 47.6, 46.5, 41.0, 30.4, 16.0, 14.8; HRMS calcd. for $[M+Na]^+$ 475.0727, found 475.0728.

Furano-verrillin (122a) and (105): To a solution of **120a** (0.071 g, 0.15 mmol) in dry and degassed DMF (27.6 ml) was added $CrCl_2$ (0.22 g, 1.82 mmol) and $NiCl_2$-(DME) (3.3 mg, 0.015 mmol) in one portion . The reaction was then allowed to stir for 2 hours at 25 °C. The reaction was then diluted in 60 ml of water and extracted 4X with 50 ml of Et_2O. The organics were then combined, dried and concentrated to yield a yellow oil. Flash chromatography (up to 50% EtOAc in hexanes) of the crude material gave **122a** (2 mg, 0.051 mmol, 33.9 % yield) as a white amorphous powder. R_f= 0.38 (50% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.15 (s, 1H), 5.03 (dt, 1H, *J*= 1.4 Hz, *J*= 7.6 Hz), 4.99 (s, 1H), 4.93 (s, 1H), 4.79 (d, 1H, *J*= 9.9 Hz), 4.59 (dd, 2H, *J*= 6.8 Hz, *J*= 19.2 Hz), 4.17 (m, 1H), 3.96 (m, 1H), 3.32 (s, 3H), 3.00 (dd, 1H, *J*= 7.1 Hz, *J*= 19.0 Hz), 2.77 (m, 2H), 2.21 (m, 2H), 2.13 (s, 3H), 1.94 (m, 1H), 1.88 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.2, 147.3, 146.4, 144.9, 130.8, 127.1, 118.8, 116.2, 111.1, 96.1, 79.8, 77.9, 68.8, 55.7, 52.6, 50.2, 46.1, 34.1, 29.7, 18.4, 14.8, 9.9; HRMS calcd. for $[M+Na]^+$ 411.1778, found 411.1778; The synthesis of **105** was identical to that of **122a**. **105**; (0.023 g, 0.059 mmol, 39.0 % yield, white powder); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.26 (s, 1H), 5.05 (d, 1H, *J*= 6.7 Hz), 4.99 (s, 1H), 4.96 (s, 1H), 4.53 (dd, 1H, *J*= 7.4 Hz, *J*= 73.9 Hz), 4.56 (s, 1H) 4.16 (dd, 1H, *J*= 5.1 Hz, *J*= 11.0 Hz), 3.80 (m, 1H), 3.33 (s, 3H), 3.02 (m, 2H), 2.77 (d, 1H, *J*= 19.5 Hz), 2.43 (m, 1H), 2.25 (m, 2H), 2.02 (s, 3H), 1.90 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.3, 150.4, 148.2, 148.0, 130.4, 127.4, 118.8, 111.5, 111.0, 94.8, 77.9, 74.7, 65.7, 56.0, 53.9, 47.5, 46.6, 46.5, 29.3, 23.4, 14.8, 9.5; HRMS calcd. for $[M+Na]^+$ 411.1778, found 411.1779.

Norfurano-verrillin (123a) and (123b): To a solution of **121a** (0.085 g, 0.19 mmol) in dry and degassed DMF (34.1 ml) was added $CrCl_2$ (0.28 g, 2.25 mmol) and $NiCl_2$(DME) (4.0 mg, 0.019 mmol) in one portion . The reaction was then allowed to stir for 2 hours at 25 °C. The reaction was then diluted in 60 ml of water and extracted 4X with 50 ml of Et_2O. The organics were then combined, dried and concentrated to yield a yellow oil. Flash chromatography (up to 50% EtOAc in hexanes) of the crude material gave **123a** (0.042 g, 0.112 mmol, 59.8 % yield) as a white solid. R_f= 0.36

(50% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.31 (d, 1H, *J*= 3.1 Hz), 6.25 (d, 1H, *J*= 3.1 Hz), 5.06 (t, 1H, *J*= 7.0 Hz), 4.96 (s, 1H), 4.91 (s, 1H), 4.75 (s, 1H), 4.63 (dd, 2H, *J*= 6.8 Hz, *J*= 35.2 Hz), 4.23 (m, 1H), 4.16 (d, 1H, *J*= 12.0 Hz), 3.35 (s, 3H), 3.02 (dt, 1H, *J*= 9.9 Hz, *J*= 20.0 Hz), 2.78 (d, 1H, *J*= 18.9 Hz), 2.23 (dd, 1H, *J*= 2.0 Hz, *J*= 3.0 Hz), 1.98 (m, 3H), 1.94 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.2, 153.1, 149.1, 147.7, 131.0, 127.7, 111.7, 108.7, 108.0, 95.8, 80.1, 78.1, 67.6, 55.7, 50.2, 50.0, 49.0, 46.2, 30.7, 22.2, 14.9; HRMS calcd. for $[M+Na]^+$ 397.1622, found 397.1620; The synthesis of **123b** was identical to that of **123a**. **123b**; (0.045 g, 0.120 mmol, 64.1 % yield white solid); R_f= 0.34 (50% EtOAc in hexanes), ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.30 (d, 1H, *J*= 3.1 Hz), 6.26 (d, 1H, *J*= 3.1 Hz), 5.06 (t, 1H, *J*= 6.8 Hz), 4.99 (s, 1H), 4.96 (s, 1H), 4.55 (s, 1H) 4.54 (dd, 2H, *J*= 7.4 Hz, *J*= 91.9 Hz), 4.18 (dd, 1H, *J*= 5.1 Hz, *J*= 11.1 Hz), 3.84 (m, 1H), 3.33 (s, 3H), 3.05 (m, 2H), 2.79 (d, 1H, *J*= 19.0 Hz), 2.49 (m, 1H), 2.29 (td, 1H, *J*= 5.1 Hz, *J*= 15.8 Hz), 2.18 (dd, 1H, *J*= 2.9 Hz, *J*= 11.2 Hz), 1.93 (s, 3H), 1.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.3, 152.7, 150.1, 148.9, 130.8, 127.2, 111.6, 108.7, 108.3, 94.7, 77.9, 74.6, 67.4, 56.1, 54.0, 47.4, 46.6, 46.5, 29.2, 23.4, 14.9; HRMS calcd. for $[M+Na]^+$ 397.1622, found 397.1620.

Deoxyfurano-verrillin (127a) and (127b): To a solution of **122a** (0.059 g, 0.152 mmol) in CH_2Cl_2 (3.10 ml) at 0 °C was added triethylsilane (0.24 ml, 1.52 mmol) followed by TFA (0.06 ml, 0.76 mmol) dropwise. The reaction was then stirred at this temperature for 30 minutes at which time quenched with 3 ml of saturated $NaHCO_3$. The reaction was then extracted 3X with 3 ml of fresh CH_2Cl_2. The organics were combined, dried and concentrated to yield a pale yellow oil. Flash chromatography (up to 20% EtOAc in hexanes) of the crude material gave **127a** (0.025 g, 0.067 mmol, 44.1 % yield) as a white powder; R_f= 0.30 (18% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.17 (s, 1H), 5.03 (t, 1H, *J*= 6.7 Hz), 4.74 (s, 1H), 4.69 (s, 1H), 4.61 (dd, 2H, *J*= 6.8 Hz, *J*= 32.7 Hz), 4.13 (m, 2H), 3.33 (s, 3H), 3.00 (dd, 1H, *J*= 6.6 Hz, *J*= 18.9 Hz), 2.73 (m, 2H), 2.57 (m, 2H), 2.28 (dd, 1H, *J*= 1.9 Hz, *J*= 3.4 Hz), 1.99 (ddd, 1H, *J*= 3.7 Hz, *J*= 5.5 Hz, *J*= 13.9 Hz), 1.94 (s, 3H), 1.89 (s, 3H), 1.86 (m, 1H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.5, 149.3, 148.8, 147.0, 128.6, 127.8, 110.9, 110.9, 109.8, 95.7, 80.2, 78.4, 55.7, 50.2, 50.1, 46.1, 44.6, 37.3, 30.5, 19.8, 14.8, 9.6; HRMS

calcd. for $[M+Na]^+$ 395.1829, found 395.1831; The synthesis of **127b** was identical to that of **127a**. **127b**; (0.022 g, 0.059mmol, 38.9 % yield, white powder); R_f= 0.29 (18% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.17 (s, 1H), 5.03 (t, 1H, *J*= 6.8 Hz), 4.83 (s, 1H), 4.70 (s, 1H), 4.61 (d, 1H, *J*= 7.4 Hz), 4.43 (d, 1H, *J*= 7.4 Hz), 4.12 (dd, 1H, *J*= 5.1 Hz, *J*= 10.7 Hz), 3.77 (m, 1H), 3.33 (s, 3H), 2.99 (dd, 1H, *J*= 6.4 Hz, *J*= 18.6 Hz), 2.75 (d, 1H, *J*= 18.9 Hz), 2.68 (dd, 1H, *J*= 11.7 Hz, *J*= 14.6 Hz), 2.55 (d, 1H, *J*= 15.5 Hz), 2.50 (dd, 1H, *J*= 1.6 Hz, *J*= 15.1 Hz), 2.45 (m, 1H), 2.28 (m, 1H), 2.19 (dd, 1H, *J*= 2.5 Hz, *J*= 10.7 Hz), 1.93 (s, 3H), 1.88 (s, 3H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.4, 150.1, 149.6, 146.8, 128.6, 127.5, 115.9, 111.5, 110.5, 94.7, 78.1, 75.0, 56.0, 54.3, 47.6, 46.5, 42.3, 34.1, 31.8, 19.7, 14.7, 9.5; HRMS calcd. for $[M+Na]^+$ 395.1829, found 395.1832.

Deoxynorfurano-verrillin (128a) and (128b): To a solution of **123a** (0.050 g, 0.134 mmol) in CH_2Cl_2 (3.00 ml) at 0 °C was added triethylsilane (0.22 ml, 1.34 mmol) followed by TFA (0.10 ml, 0.76 mmol) dropwise. The reaction was then stirred at this temperature for 30 minutes at which time quenched with 3 ml of saturated $NaHCO_3$. The reaction was then extracted 3X with 3 ml of fresh CH_2Cl_2. The organics were combined, dried and concentrated to yield a pale yellow oil. Flash chromatography (up to 20% EtOAc in hexanes) of the crude material gave **128a** (0.030 g, 0.084 mmol, 62.7 % yield) as a white powder; R_f= 0.28 (18% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.28 (d, 1H, *J*= 3.1 Hz), 6.00 (dd, 1H, *J*= 1.1 Hz, *J*= 3.0 Hz), 5.04 (t, 1H, *J*= 7.0 Hz), 4.73 (s, 1H), 4.69 (s, 1H), 4.61 (dd, 2H, *J*= 6.8 Hz, *J*= 33.0 Hz), 4.18 (m, 1H), 4.13 (m, 1H), 3.33 (s, 3H), 3.01 (dd, 1H, *J*= 6.5 Hz, *J*= 18.8 Hz), 2.84 (dd, 1H, *J*= 11.5 Hz, *J*= 14.7 Hz), 2.76 (d, 1H, *J*= 19.1 Hz), 2.60 (m, 2H), 2.25 (dd, 1H, *J*= 1.9 Hz, *J*= 3.3 Hz), 2.01 (m, 1H), 1.91 (s, 3H), 1.89 (m, 1H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.4, 153.4, 149.0, 147.9, 129.1, 127.7, 109.9, 108.4, 106.8, 95.7, 80.2, 78.3, 55.7, 50.3, 50.0, 46.1, 44.7, 37.4, 32.5, 19.8, 14.9; HRMS calcd. for $[M+Na]^+$ 381.1672, found 381.1671; The synthesis of **128b** was identical to that of **128a**. **128b**; (0.029 g, 0.081 mmol, 60.6 % yield, white solid); R_f= 0.26 (18% EtOAc in hexanes), ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.28 (d, 1H, *J*= 3.1 Hz), 6.00 (dd, 1H, *J*= 1.2 Hz, *J*= 3.0 Hz), 5.05 (t, 1H, *J*= 6.9 Hz), 4.83 (s, 1H), 4.70 (s, 1H), 4.52 (dd, 2H, *J*= 7.4 Hz, *J*= 91.9 Hz), 4.13 (dd, 1H, *J*= 4.5 Hz, *J*= 10.8 Hz), 3.81 (m, 1H), 3.33 (s, 3H), 3.00 (dd, 1H, *J*=

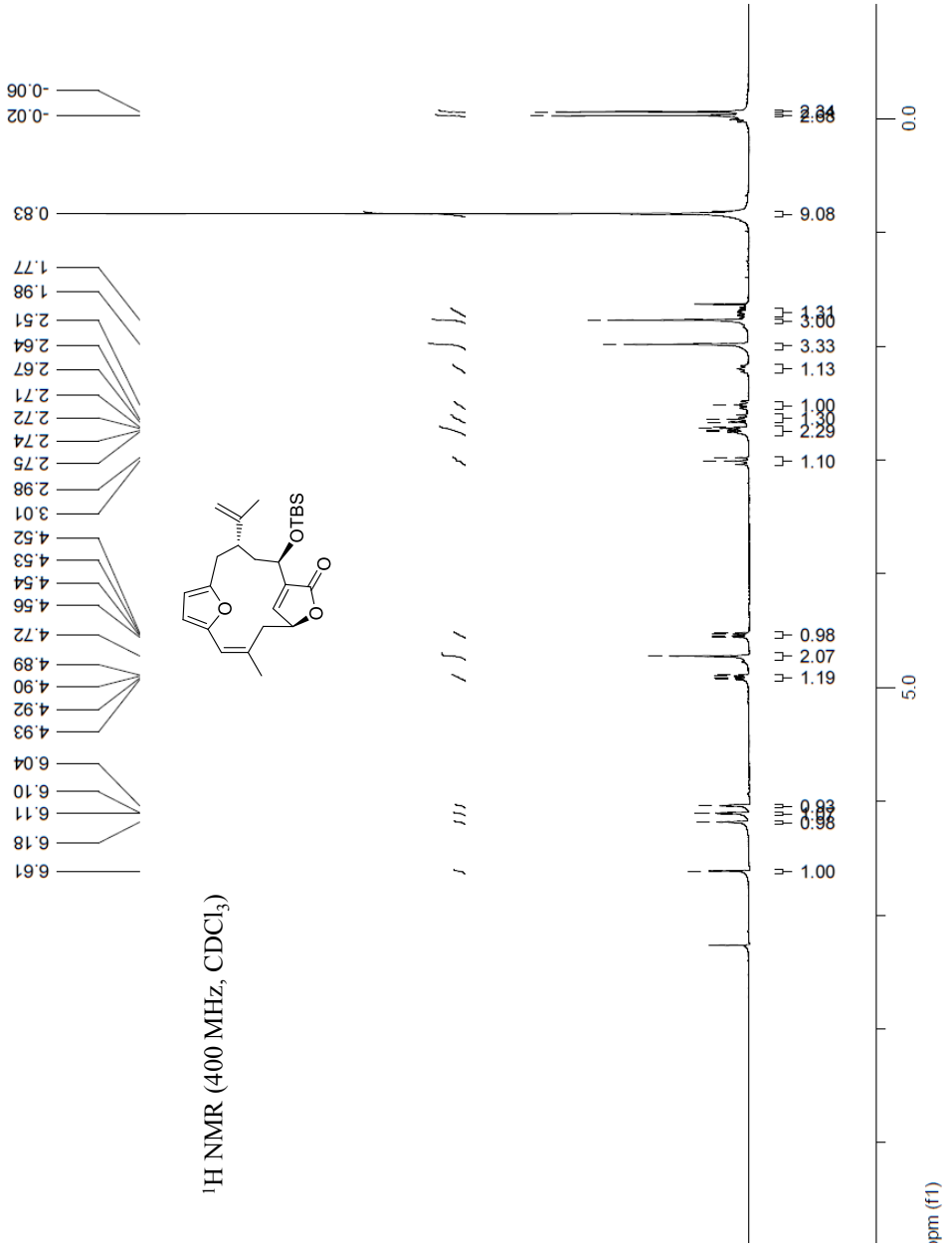
6.6 Hz, *J*= 18.9 Hz), 2.77 (m, 2H), 2.58 (ddd, 1H, *J*= 1.3 Hz, *J*= 2.7 Hz, *J*= 15.5 Hz), 2.51 (d, 1H, *J*= 13.5 Hz), 2.49 (m, 1H), 2.31 (m, 1H), 2.18 (dd, 1H, *J*= 2.8 Hz, *J*= 10.9 Hz), 1.91 (s, 3H), 1.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.3, 154.1, 149.9, 14.7, 129.1, 127.4, 110.7, 110.7, 108.8, 106.5, 94.6, 78.1, 74.9, 56.0, 54.3, 47.5, 46.6, 42.4, 34.1, 33.8, 19.6, 14.8; HRMS calcd. for $[M+Na]^+$ 381.1672, found 381.1677.

Furano-verrillin alcohol (129a) and (129b): To a solution of **127a** (0.020 g, 0.052 mmol) in methanol (1.75 ml) in a 5 ml microwave tube was added *p*-TsOH (10.0 mg, 0.052 mmol). The reaction was then microwaved at 80 °C for 15 minutes. The dark green solution was then quenched with 2 ml of saturated $NaHCO_3$. The reaction was then washed 3X with 3 ml of fresh Et_2O. Organics were then combined, dried and concentrated to yield a pale yellow solid. Flash chromatography (up to 40% EtOAc in hexanes) of the crude material gave **129a** (0.012 g, 0.037 mmol, 69.8 % yield) as white crystals.); R_f= 0.26 (35% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.17 (s, 1H), 5.02 (t, 1H, *J*= 6.7 Hz), 4.73 (s, 1H), 4.67 (s, 1H), 4.29 (d, 1H, *J*= 11.8 Hz), 4.12 (m, 1H), 3.01 (dd, 1H, *J*= 6.7 Hz, *J*= 18.9 Hz), 2.70 (m, 3H), 2.52 (dd, 1H, *J*= 1.7 Hz, *J*= 15.0 Hz), 2.28 (dd, 1H, *J*= 1.8 Hz, *J*= 3.5 Hz), 1.93 (s, 3H), 1.92 (m, 1H), 1.89 (s, 3H), 1.83 (m, 1H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.9, 149.3, 148.6, 146.9, 128.7, 127.7, 116.1, 110.7, 110.0, 80.2, 72.5, 50.6, 49.5, 46.1, 44.8, 41.3, 30.5, 19.3, 14.8, 9.5; HRMS calcd. for $[M+Na]^+$ 351.1567, found 351.1566; The synthesis of **129b** was identical to that of **129a**. **129b** (0.125 g, 0.038 mmol, 72.7 % yield, white crystals); R_f= 0.35 (35% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.19 (s, 1H), 5.08 (t, 1H, *J*= 7.1 Hz), 4.84 (s, 1H), 4.75 (s, 1H), 4.30 (s, 1H), 4.18 (dd, 1H, *J*= 5.1 Hz, *J*= 10.9 Hz), 3.78 (m, 1H), 3.02 (dd, 1H, *J*= 6.8 Hz, *J*= 19.0 Hz), 2.79 (d, 1H, *J*= 18.9 Hz), 2.71 (dd, 1H, *J*= 12.0 Hz, *J*= 14.7 Hz), 2.51 (m, 2H), 2.31 (m, 1H), 2.25 (dd, 1H, *J*= 3.4 Hz, *J*= 10.9 Hz), 1.96 (s, 3H), 1.90 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 181.0, 151.4, 149.3, 146.2, 128.4, 127.4, 115.7, 110.8, 110.1, 79.8, 71.7, 52.5, 48.5, 46.1, 37.7, 31.7, 20.1, 14.8, 9.5; HRMS calcd. for $[M+H]^+$ 329.1747, found 329.1747.

Norfurano-verrillin alcohol (130a) and (130b): To a solution of **128a** (0.024 g, 0.067 mmol) in methanol (2.23 ml) in a 5 ml microwave tube was added *p*-TsOH (13.0 mg, 0.067 mmol). The reaction was then microwaved at 80 °C for 15 minutes. The

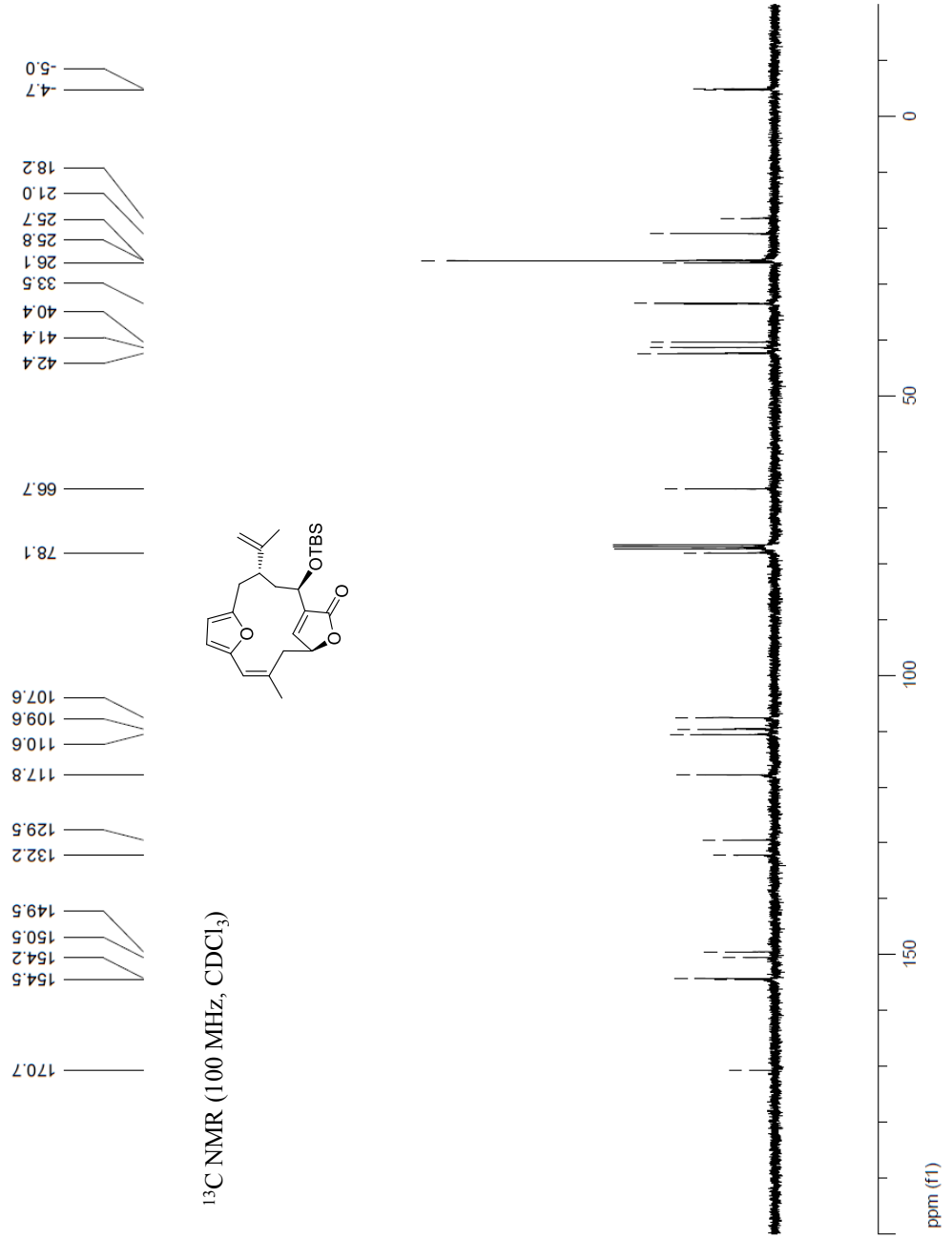
dark green solution was then quenched with 2 ml of saturated $NaHCO_3$. The reaction was then washed 3X with 3 ml of fresh Et_2O. Organics were then combined, dried and concentrated to yield a pale yellow solid. Flash chromatography (up to 40% EtOAc in hexanes) of the crude material gave **130a** (0.014 g, 0.045mmol, 66.5 % yield) as white crystals.); R_f= 0.25 (35% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.28 (d, 1H, *J*= 3.0 Hz), 6.01 (dd, 1H, *J*= 1.2 Hz, *J*= 3.0 Hz), 5.04 (t, 1H, *J*= 7.2 Hz), 4.73 (s, 1H), 4.67 (s, 1H), 4.31 (ddd, 1H, *J*= 1.7 Hz, *J*= 3.7 Hz, *J*= 11.9 Hz), 4.16 (m, 1H), 3.03 (dd, 1H, *J*= 6.7 Hz, *J*= 19.1 Hz), 2.85 (dd, 1H, *J*= 11.5 Hz, *J*= 14.7 Hz), 2.73 (m, 2H), 2.55 (dd, 1H, *J*= 1.6 Hz, *J*= 14.9 Hz), 2.25 (dd, 1H, *J*= 1.8 Hz, *J*= 3.5 Hz), 1.95 (m, 1H), 1.92 (s, 3H), 1.85 (ddd, 1H, *J*= 3.9 Hz, *J*= 5.4 Hz, *J*= 13.8 Hz), 1.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.9, 153.3, 149.1, 147.9, 129.2, 127.7, 110.2, 108.3, 106.8, 80.3, 72.6, 50.6, 49.7, 46.2 45.0, 41.4, 32.6, 19.4, 14.9; HRMS calcd. for $[M+Na]^+$ 337.1410, found 337.1411; The synthesis of **130b** was identical to that of **130a**. **130b** (.016 g, 0.051 mmol, 76.0 % yield, white crystals); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.30 (d, 1H, *J*= 2.2 Hz), 6.01 (s, 1H), 5.09 (t, 1H, *J*= 7.1 Hz), 4.83 (s, 1H), 4.75 (s, 1H), 4.29 (s, 1H), 4.19 (dd, 1H, *J*= 4.9 Hz, *J*= 10.9 Hz), 3.81 (m, 1H), 3.03 (dd, 1H, *J*= 6.5 Hz, *J*= 18.9 Hz), 2.80 (m, 2H), 2.55 (m, 3H), 2.33 (td, 1H, *J*= 4.7 Hz, *J*= 14.9 Hz), 2.22 (dd, 1H, *J*= 3.1 Hz, *J*= 10.7 Hz), 1.92 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 181.2, 154.1, 151.4, 147.4, 129.1, 127.5, 110.5, 108.5, 106.6, 80.0, 71.9, 52.8, 48.7, 46.3, 41.8, 37.9, 33.9, 20.3, 15.0; HRMS calcd. for $[M+Na]^+$ 337.1410, found 337.1409.

3.8.3 ^{1}H and ^{13}C NMR Spectra

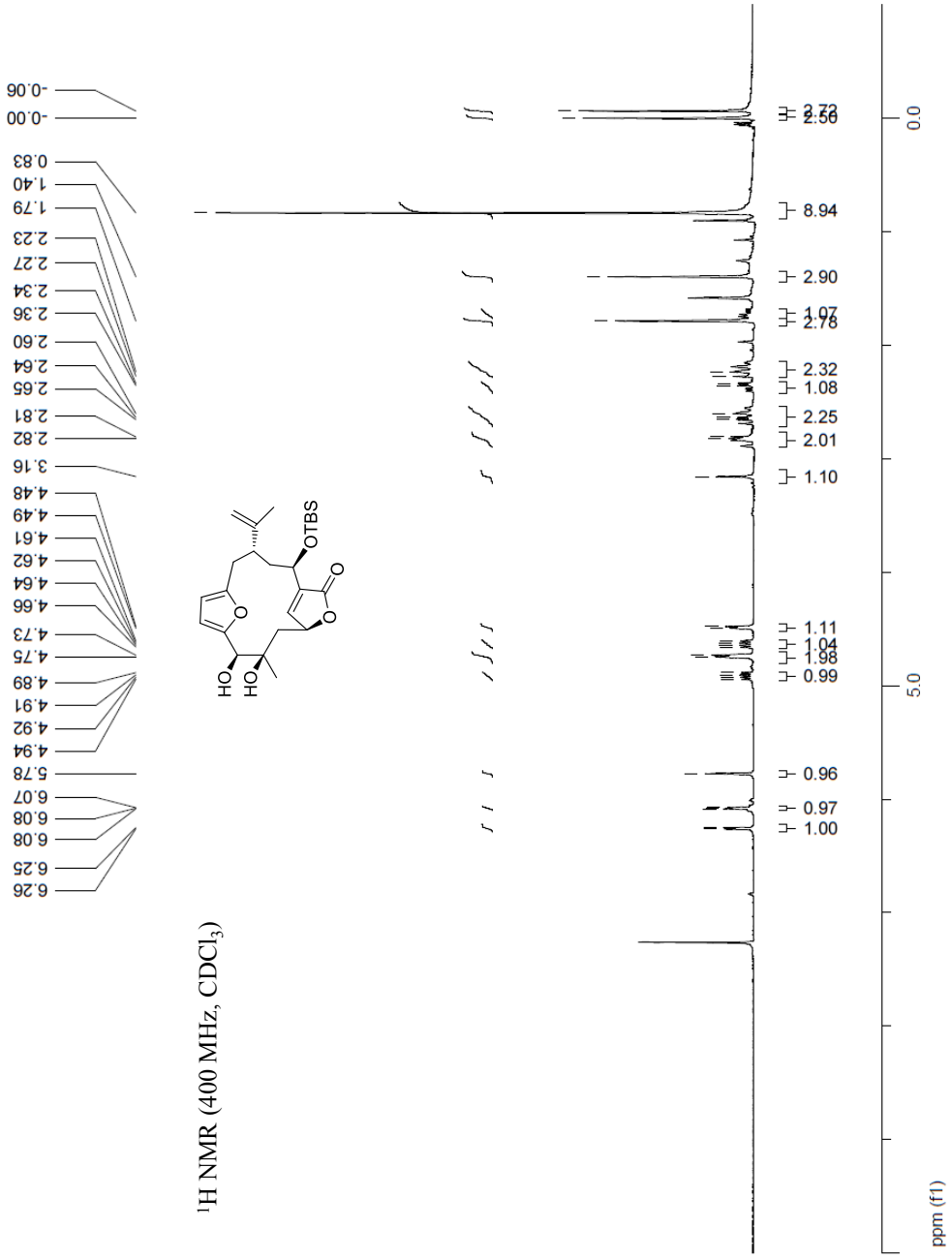


^{1}H NMR (400 MHz, $CDCl_3$)

Spectrum 3.1: Compound 100: ^{1}H NMR

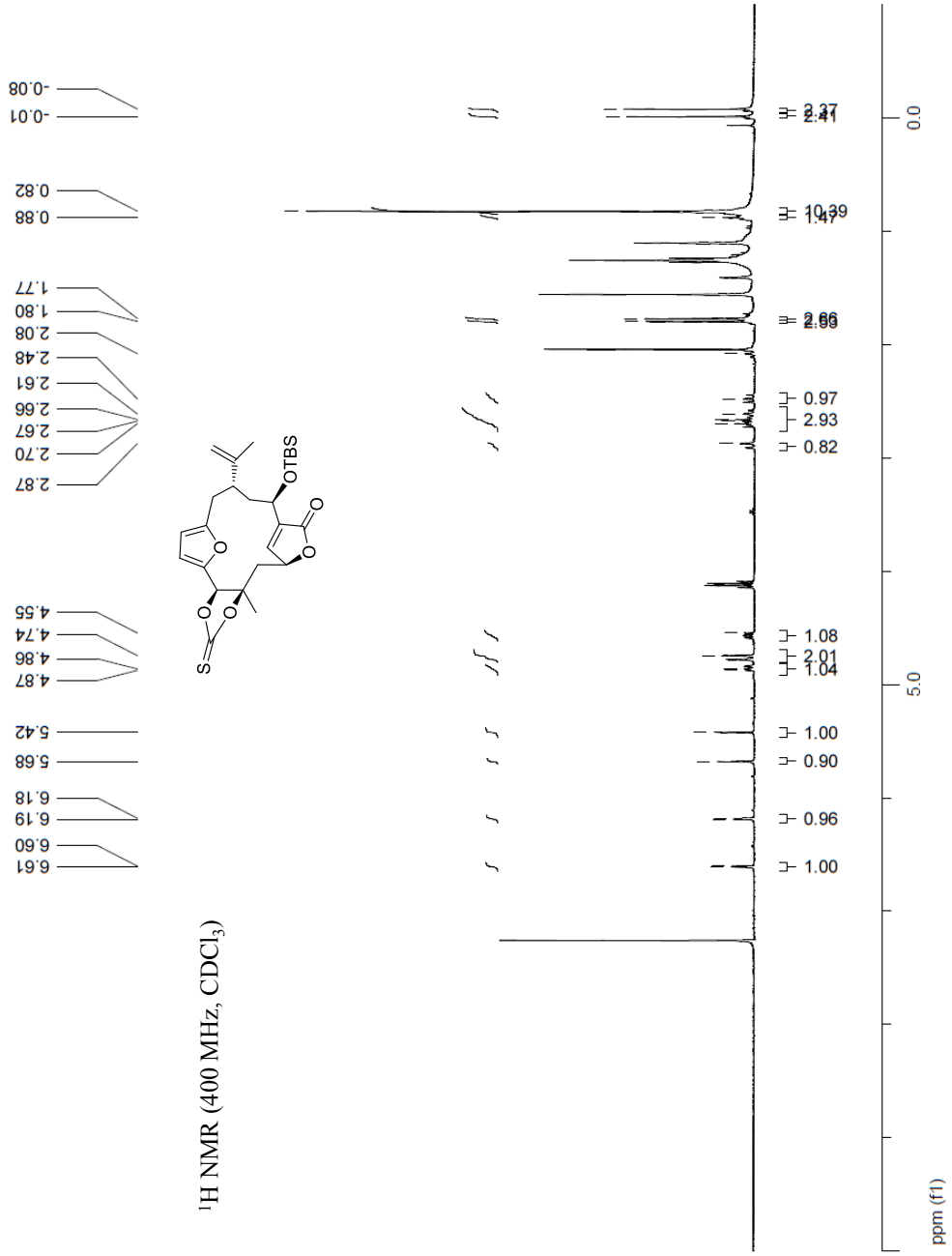


Spectrum 3.2: Compound 100: ^{13}C NMR



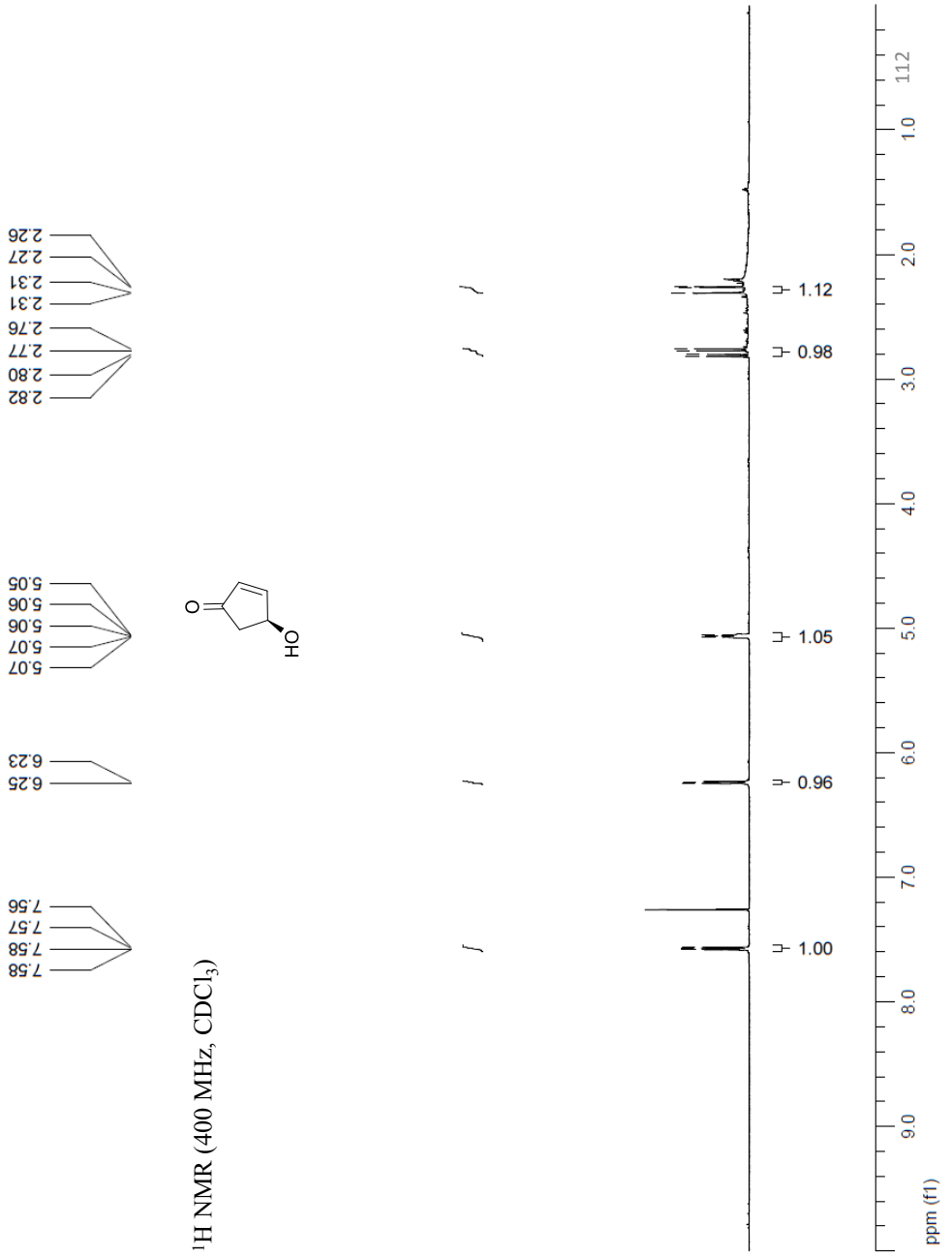
^{1}H NMR (400 MHz, $CDCl_3$)

Spectrum 3.3: Compound 101: ^{1}H NMR

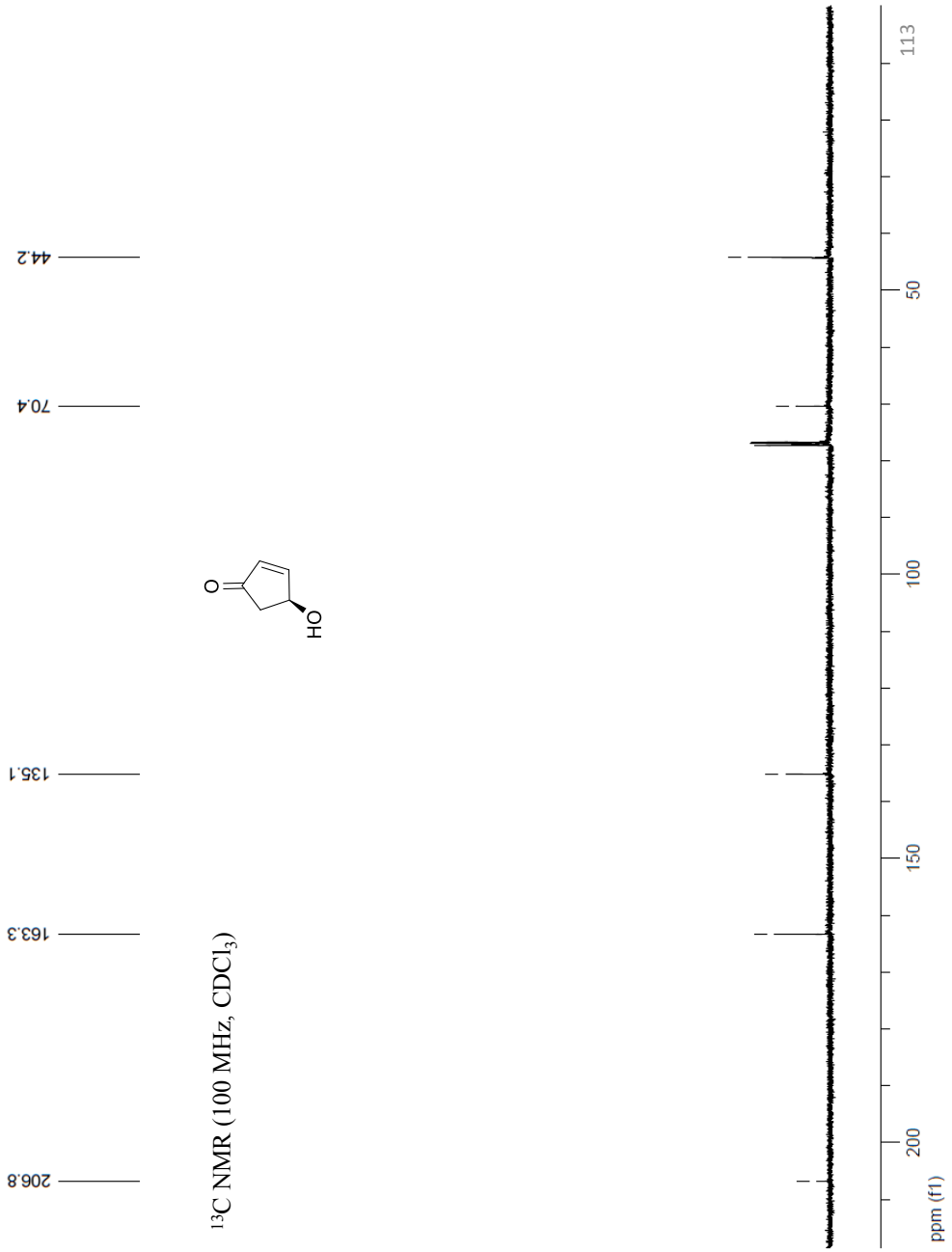


^{1}H NMR (400 MHz, $CDCl_3$)

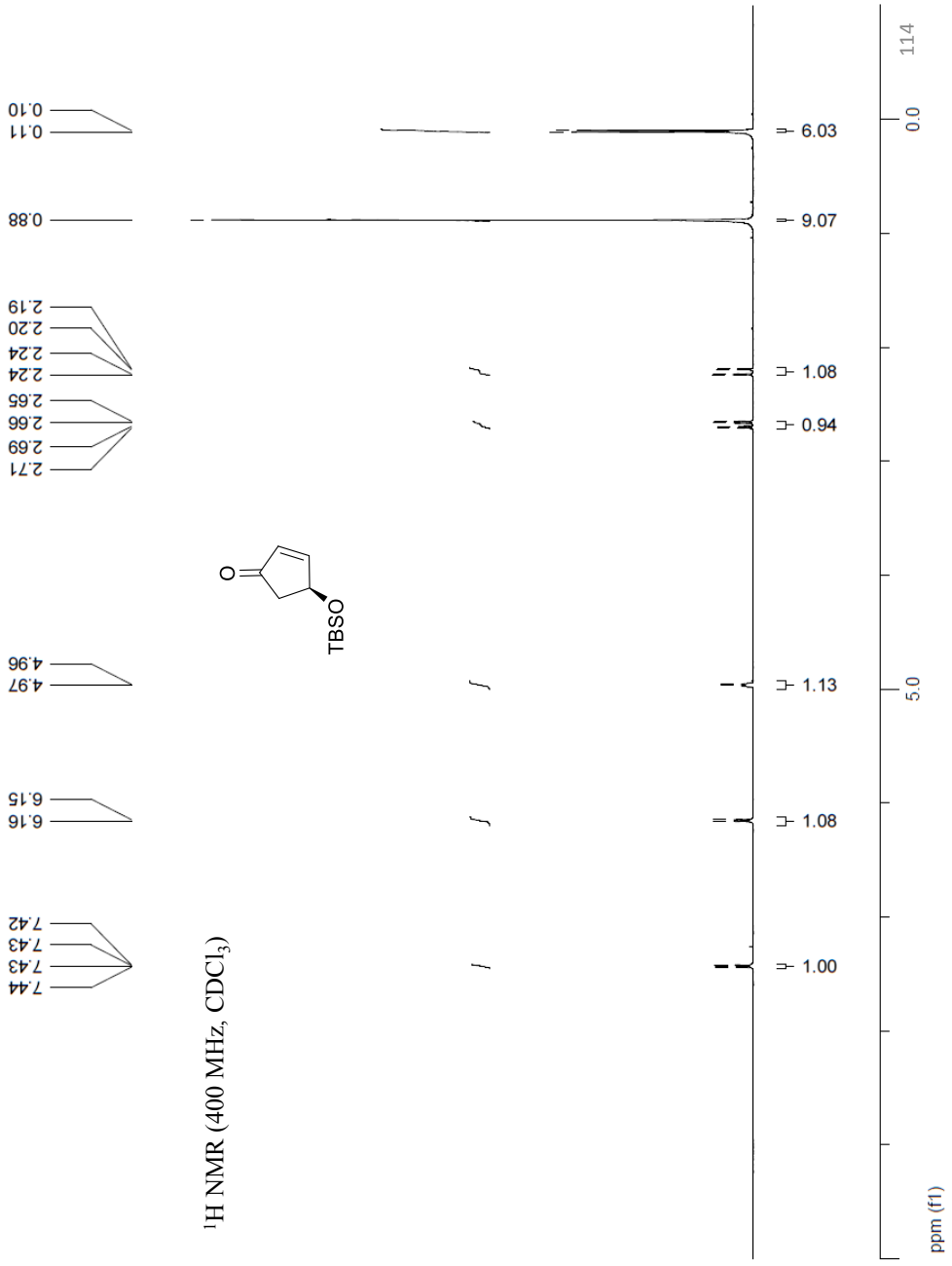
Spectrum 3.4: Compound 102: ^{13}H NMR



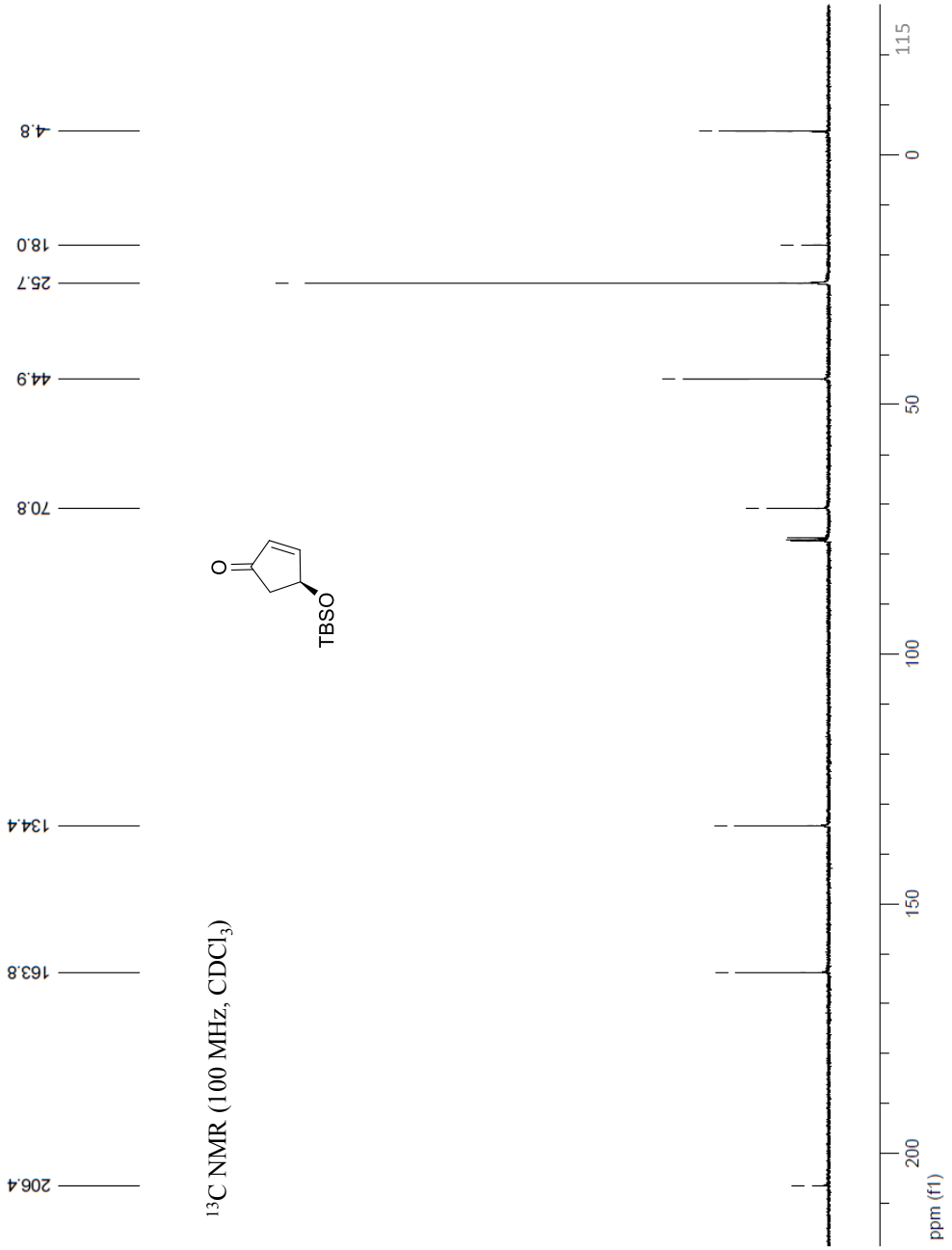
Spectrum 3.5: Compound 112i: ^{1}H NMR



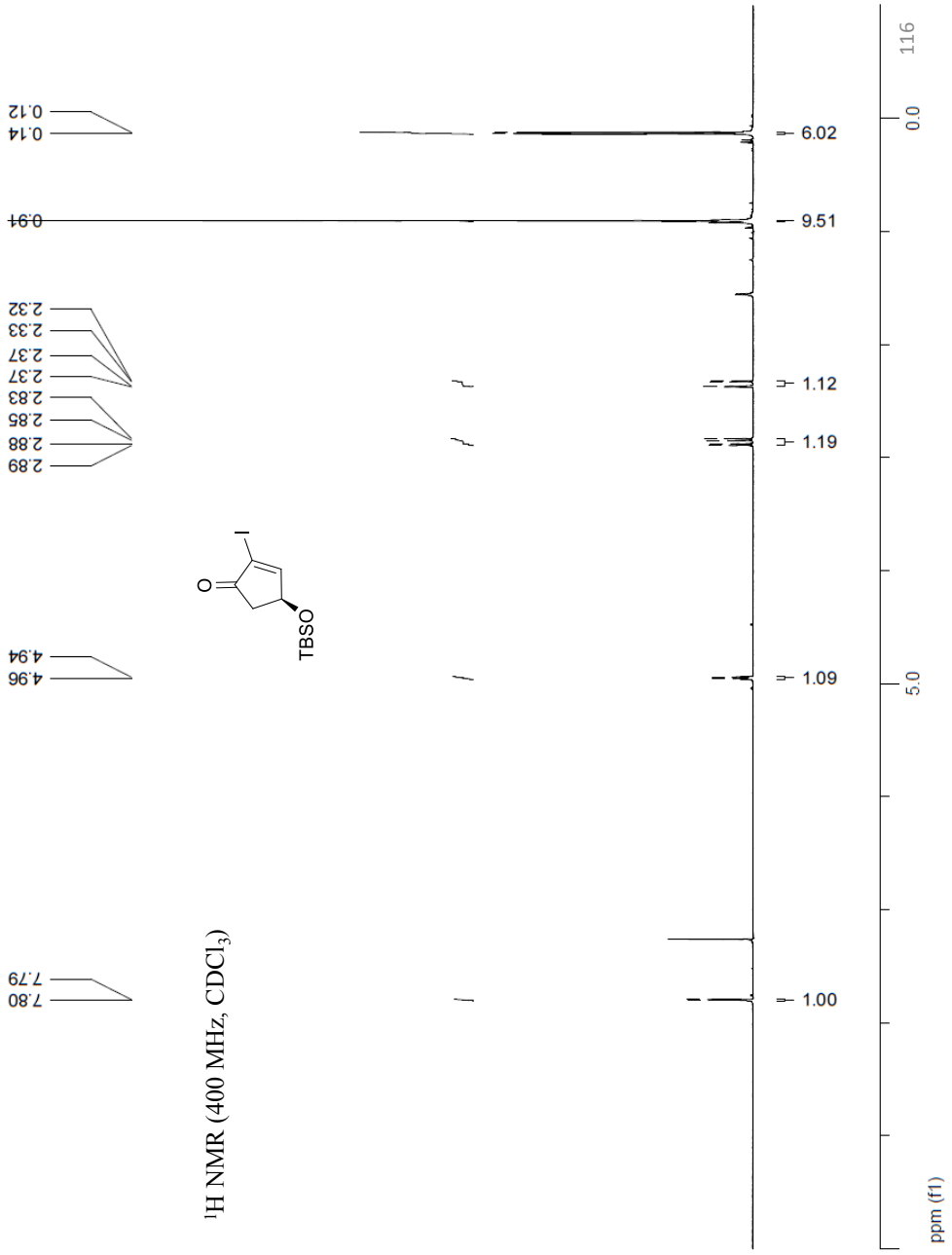
Spectrum 3.6: Compound 112i: ^{13}C NMR



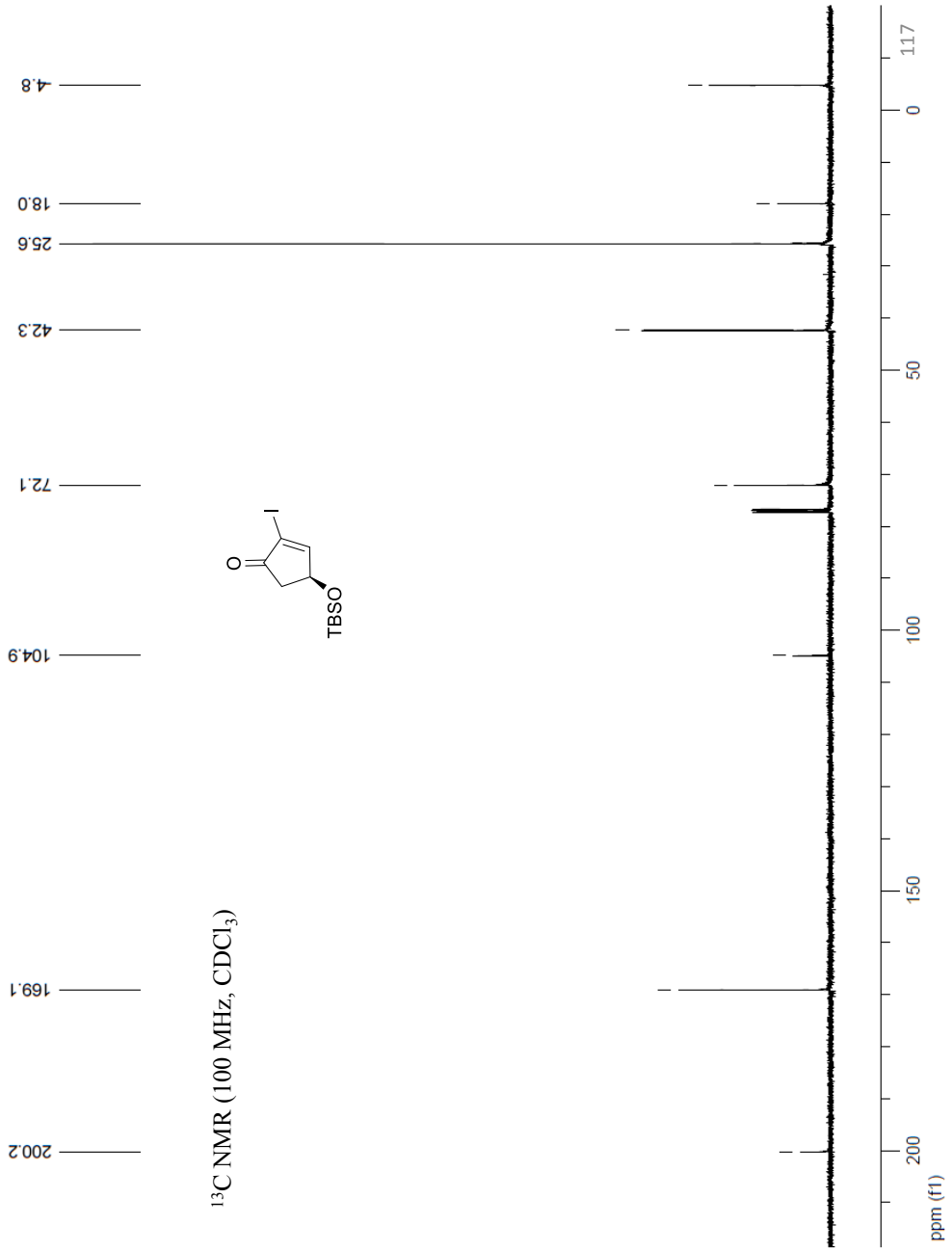
Spectrum 3.7: Compound 112: ^{1}H NMR



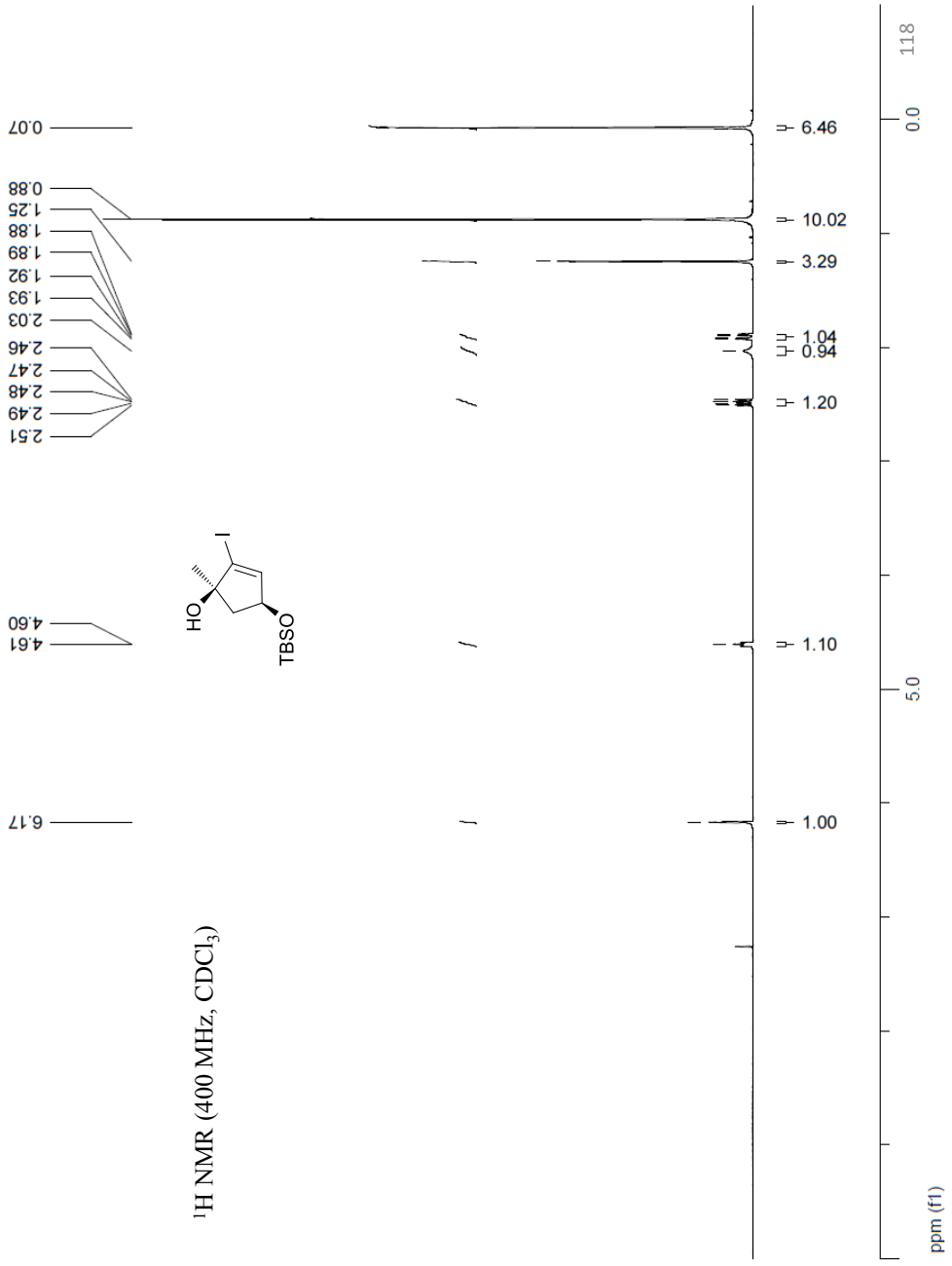
Spectrum 3.8: Compound 112: ^{13}C NMR



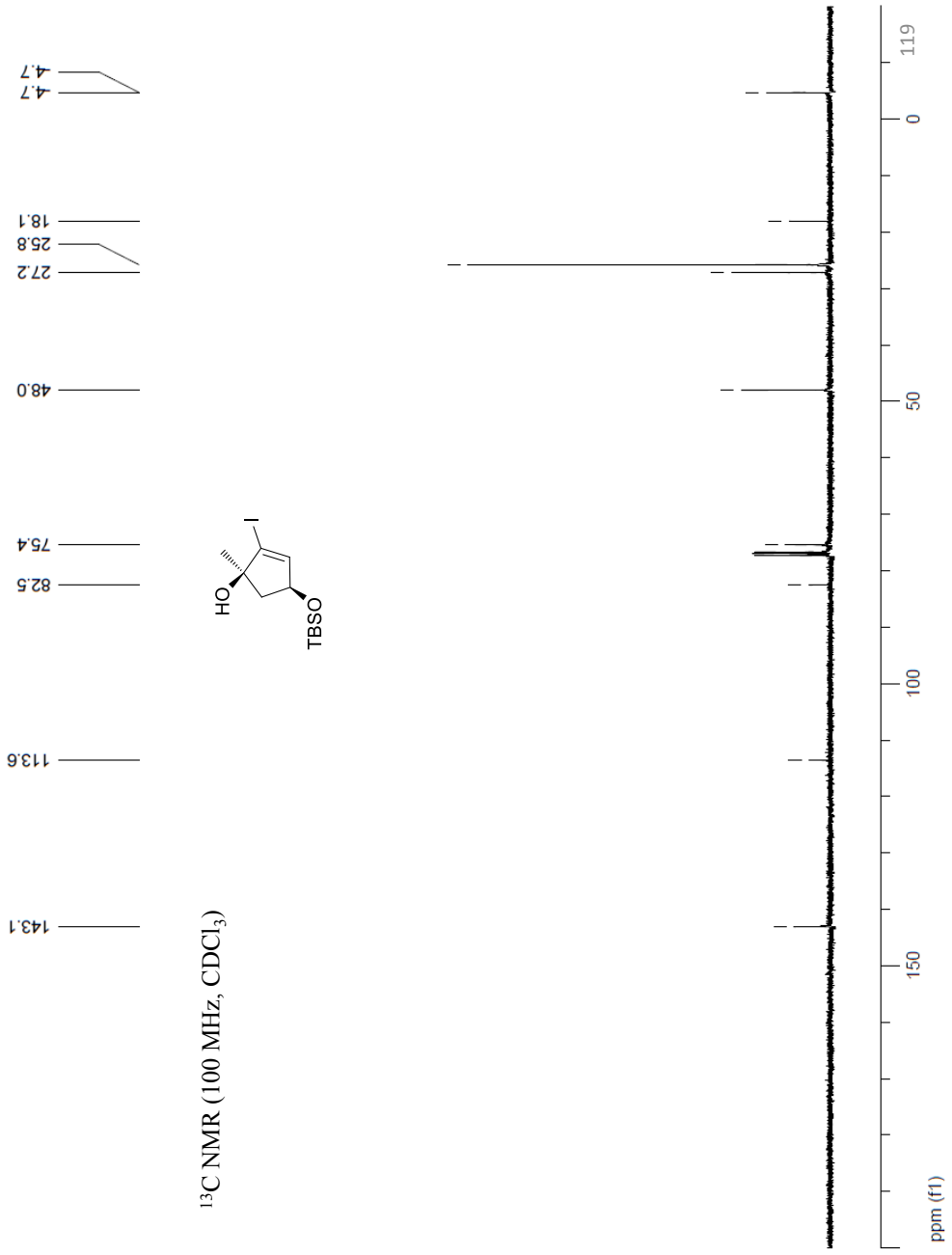
Spectrum 3.9: Compound 113: ^{1}H NMR



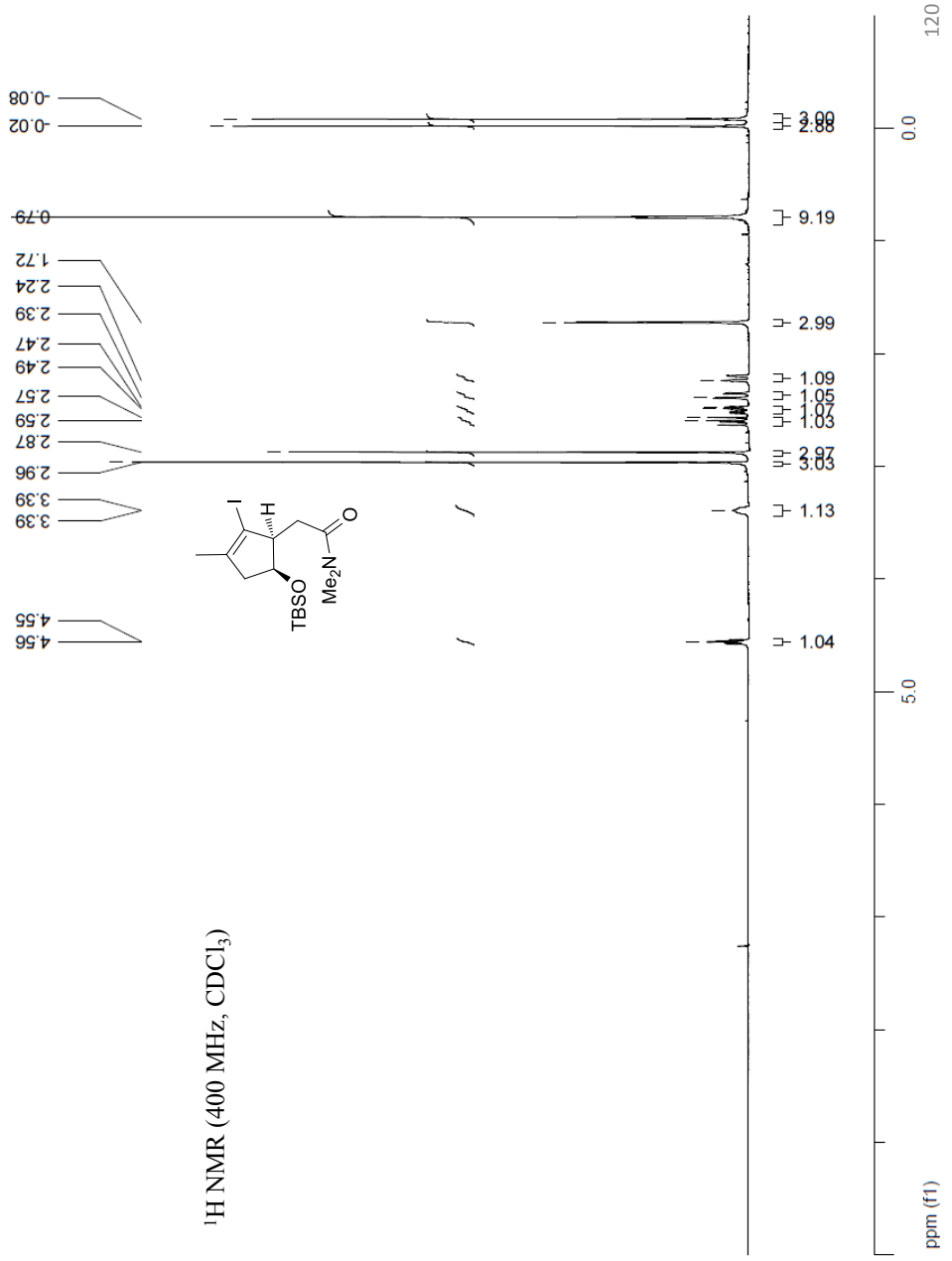
Spectrum 3.10: Compound 113: ^{13}C NMR



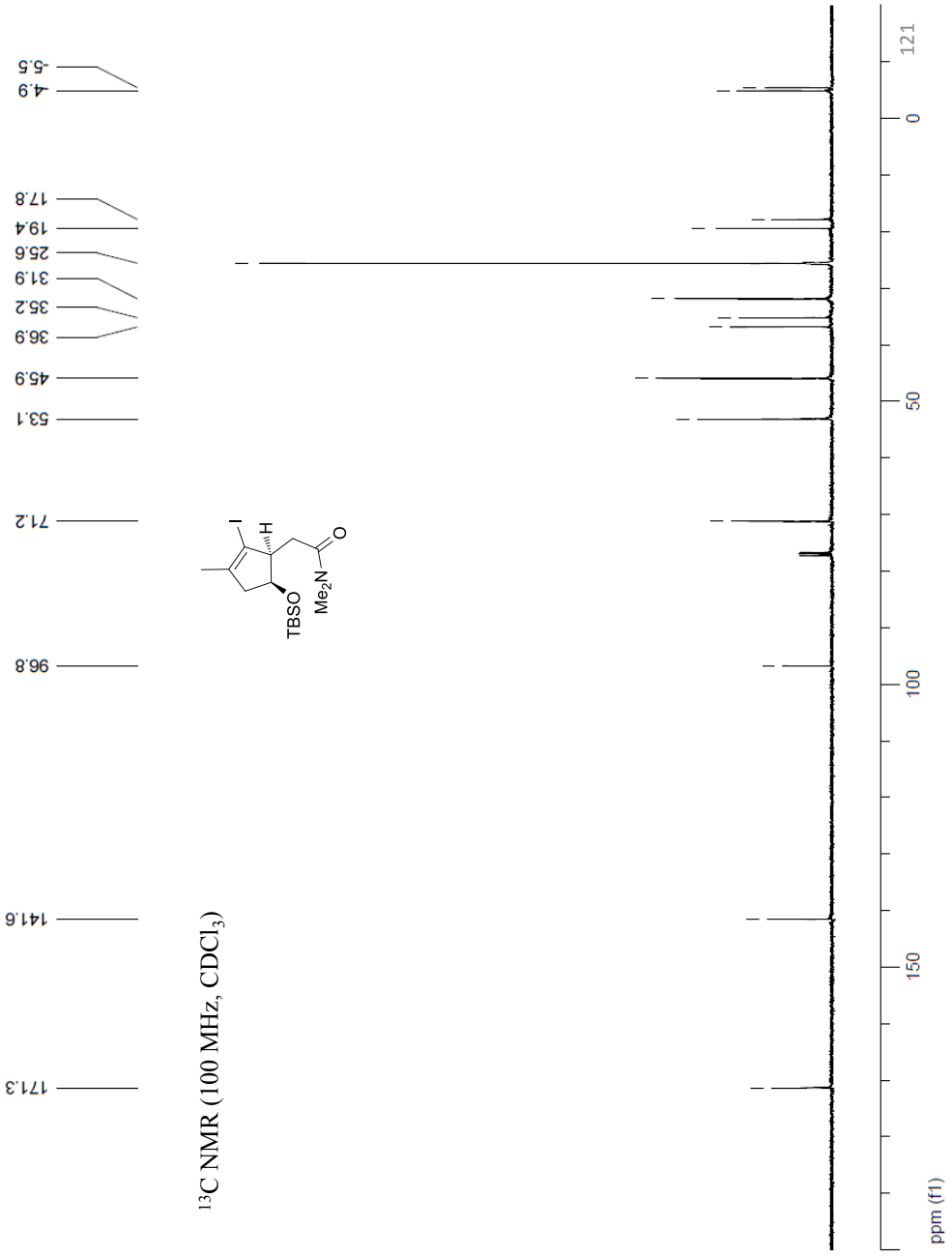
Spectrum 3.11: Compound 109: ^{1}H NMR



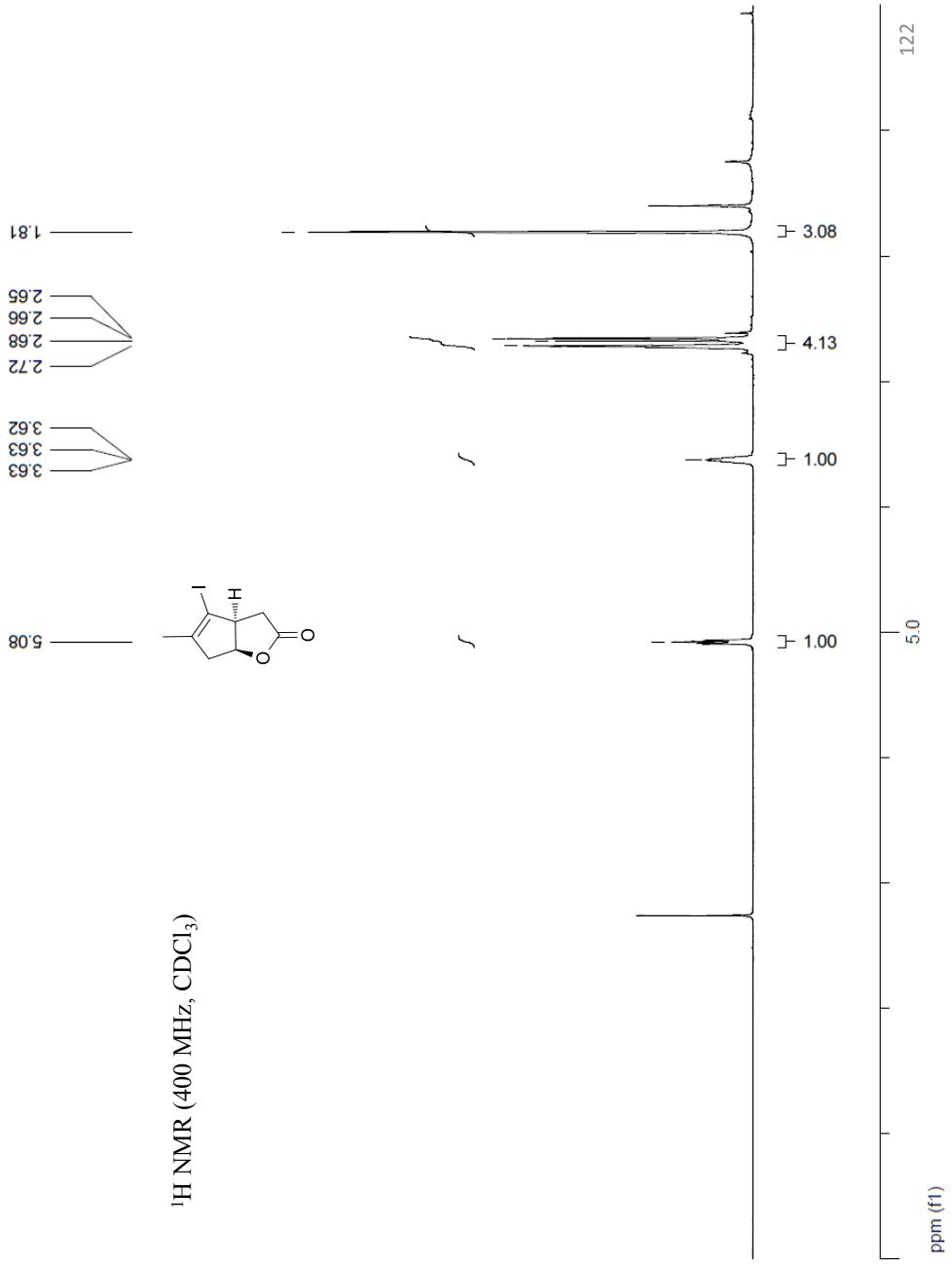
Spectrum 3.12: Compound 109: ^{13}C NMR



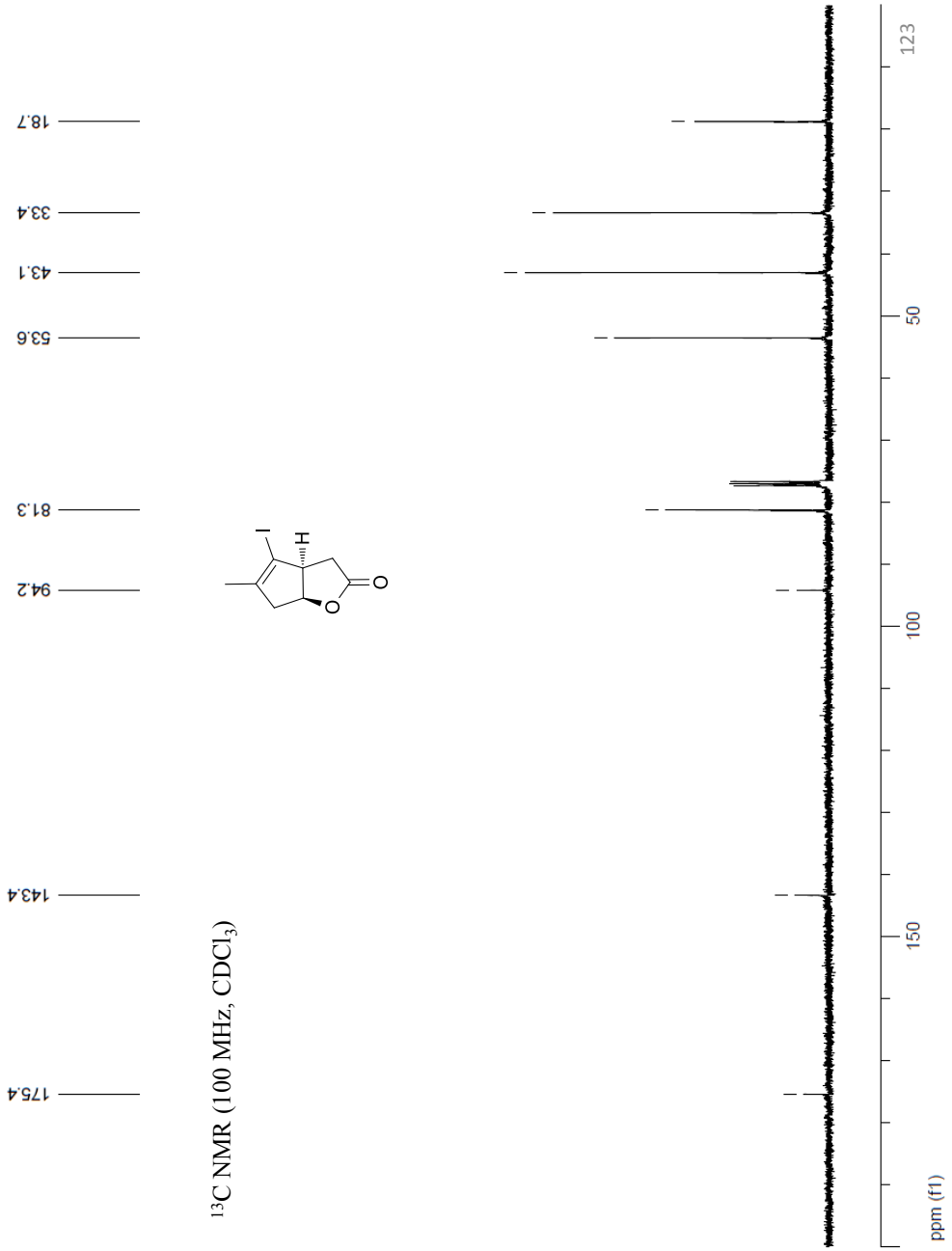
Spectrum 3.13: Compound 114: ^{1}H NMR



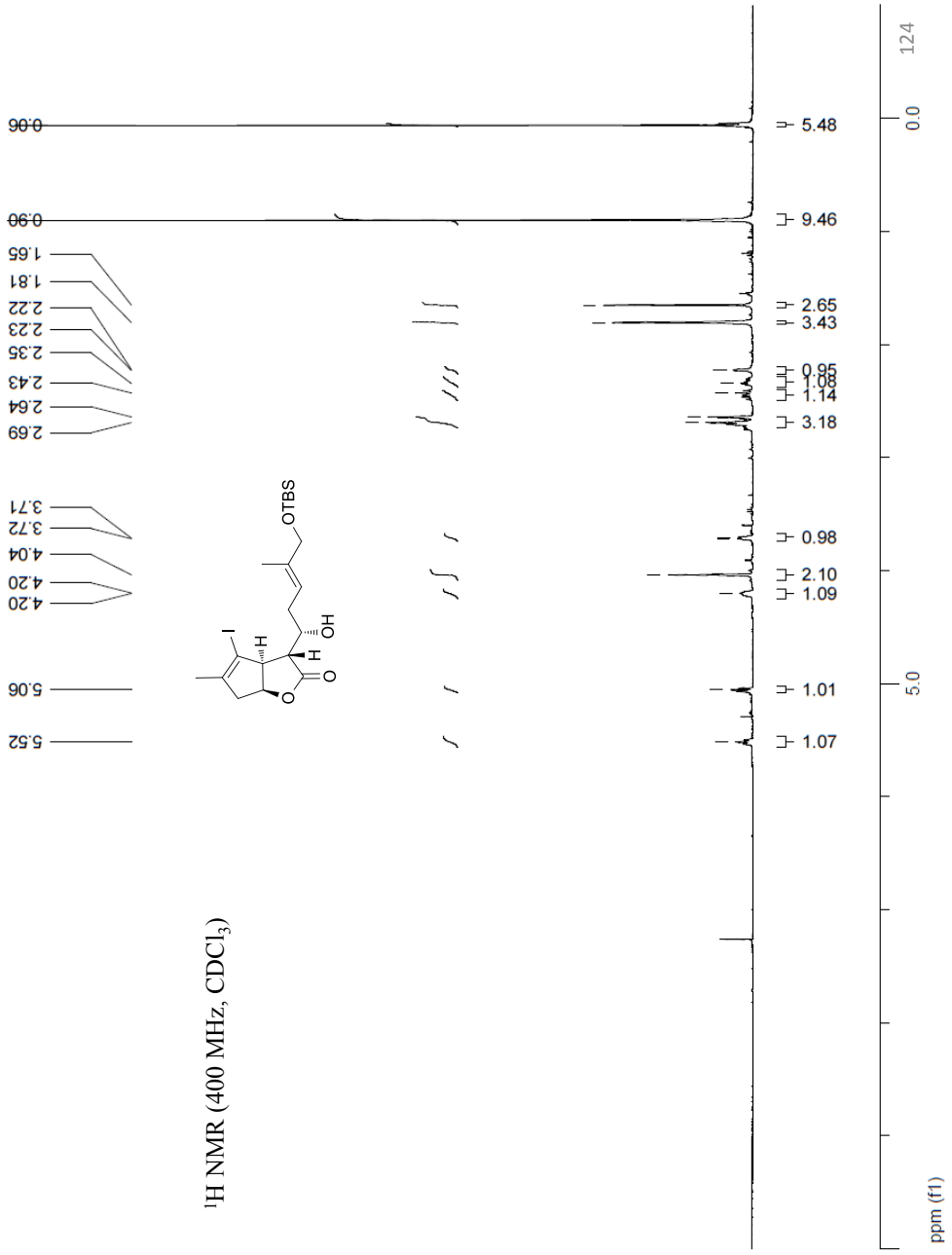
Spectrum 3.14: Compound 114: ^{13}C NMR



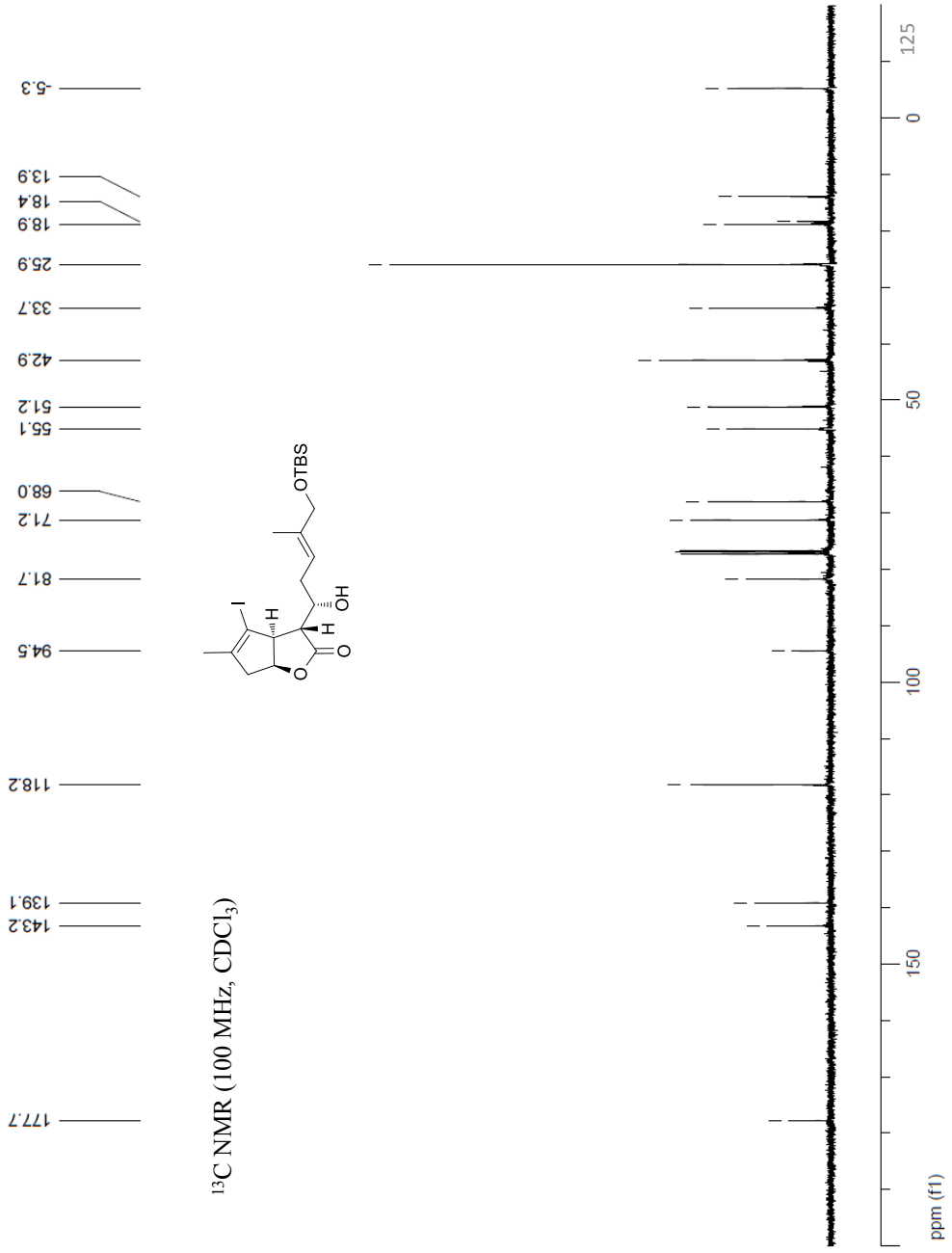
Spectrum 3.15: Compound 115: ^{1}H NMR



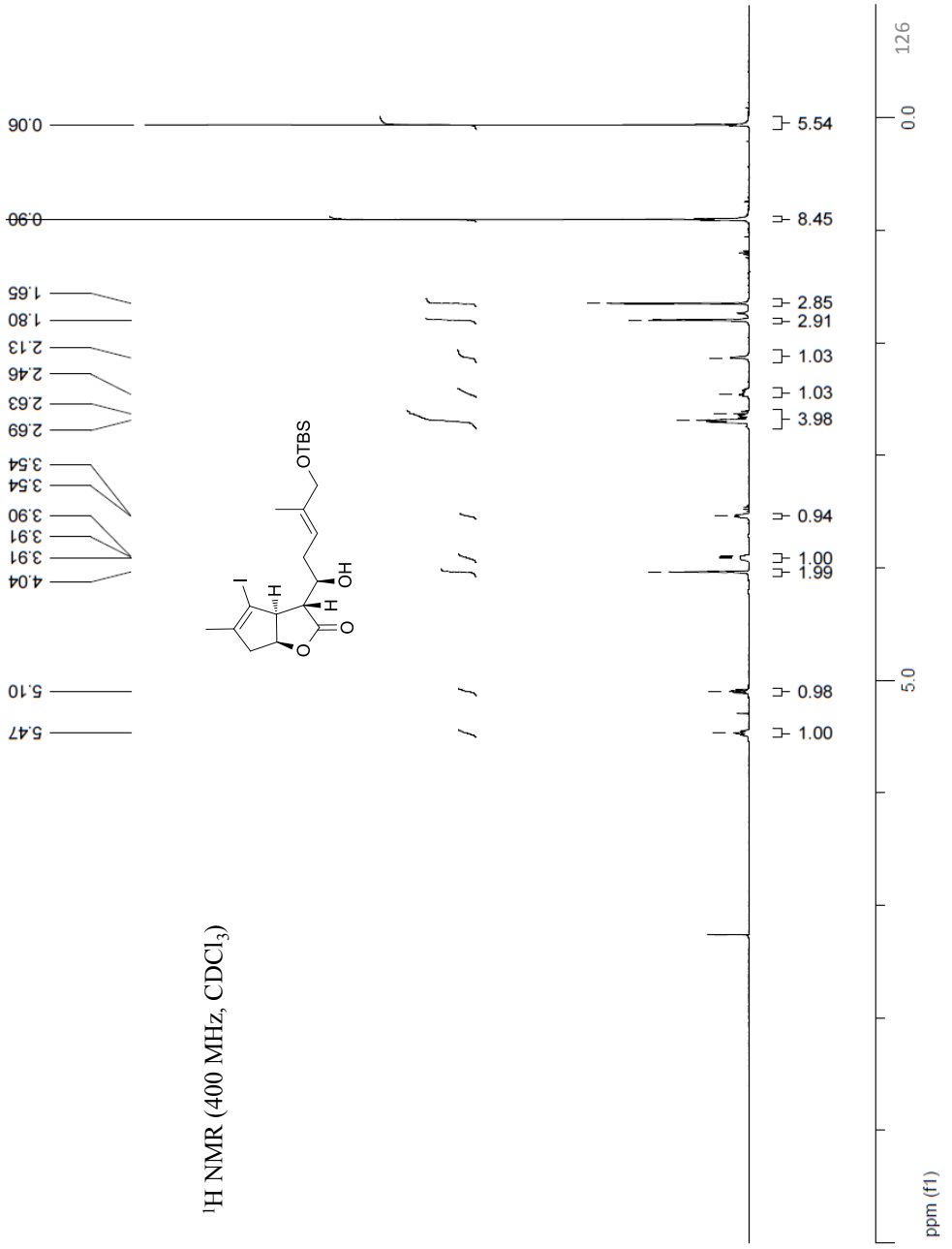
Spectrum 3.16: Compound 115: ^{13}C NMR



Spectrum 3.17: Compound 116a: ^{1}H NMR

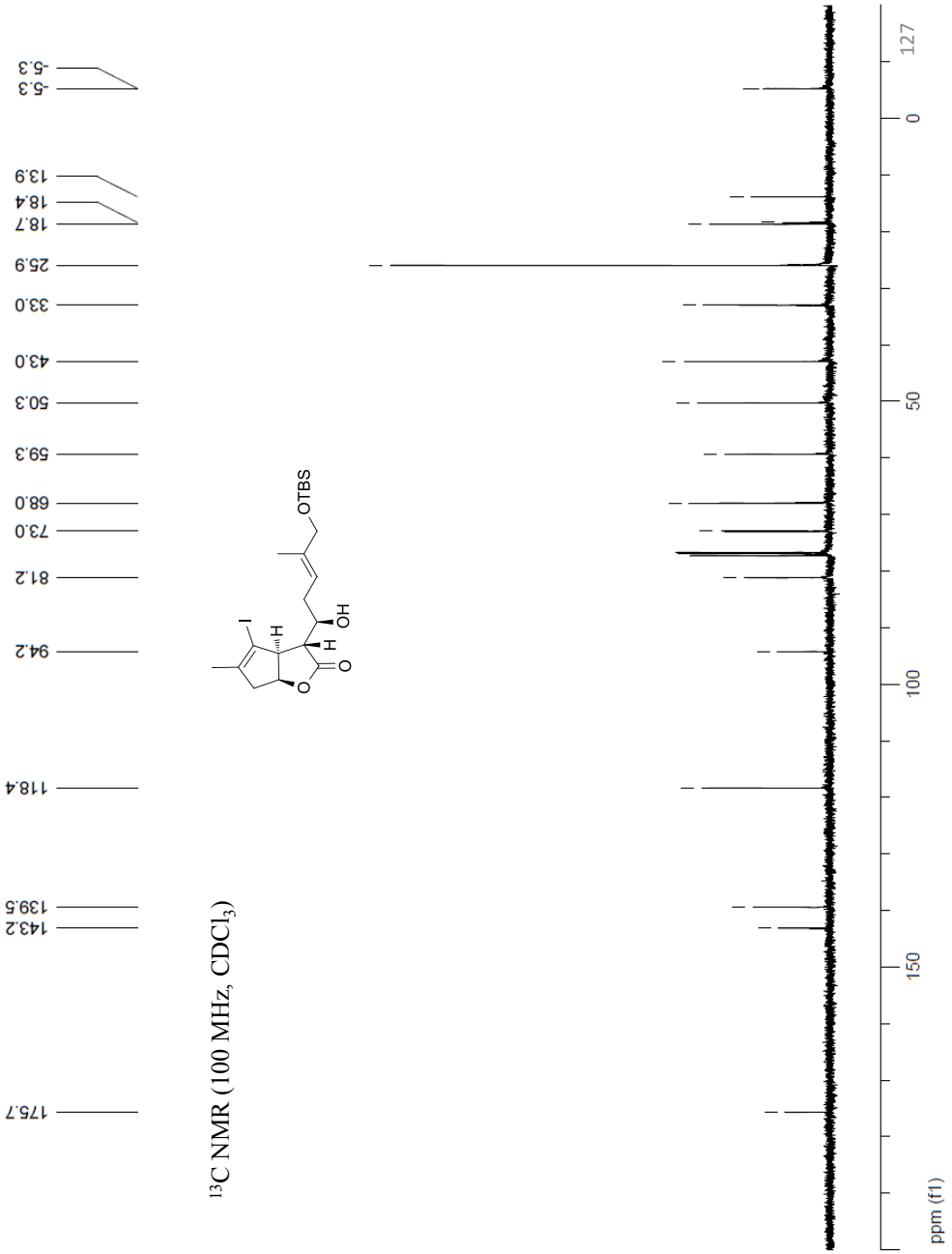


Spectrum 3.18: Compound 116a: ^{13}C NMR

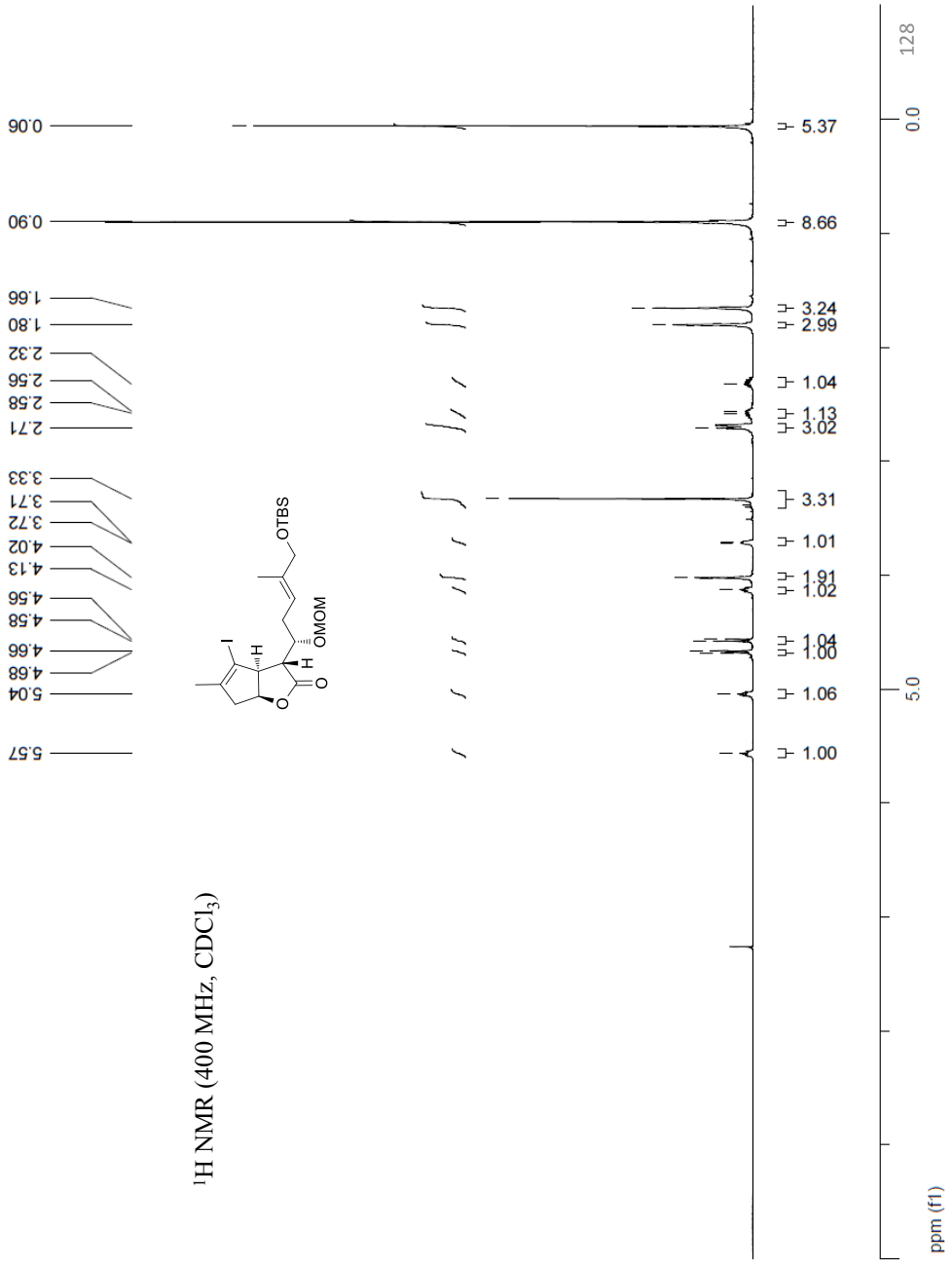


^{1}H NMR (400 MHz, $CDCl_3$)

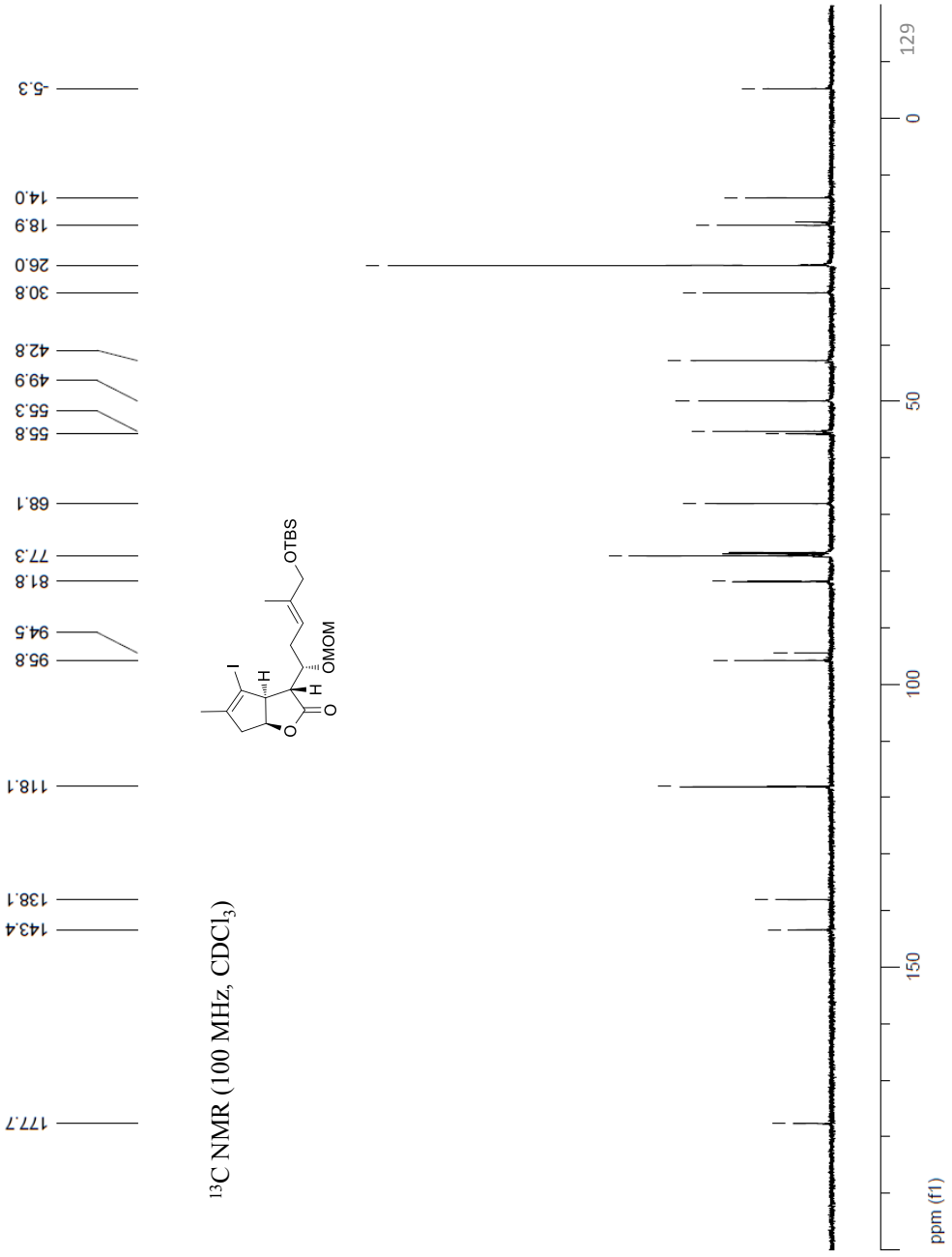
Spectrum 3.19: Compound 116b: ^{1}H NMR



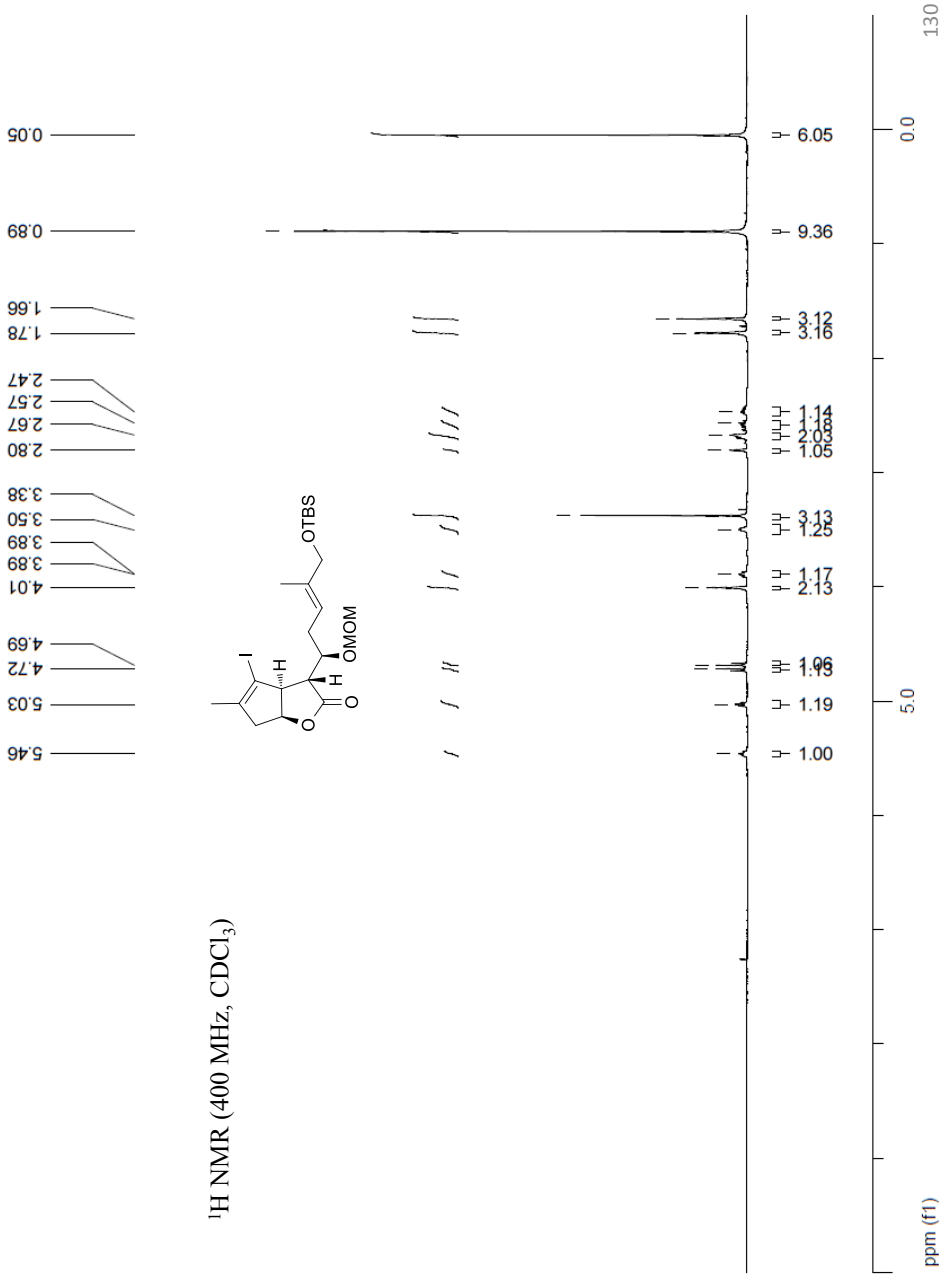
Spectrum 3.20: Compound 116b: ^{13}C NMR



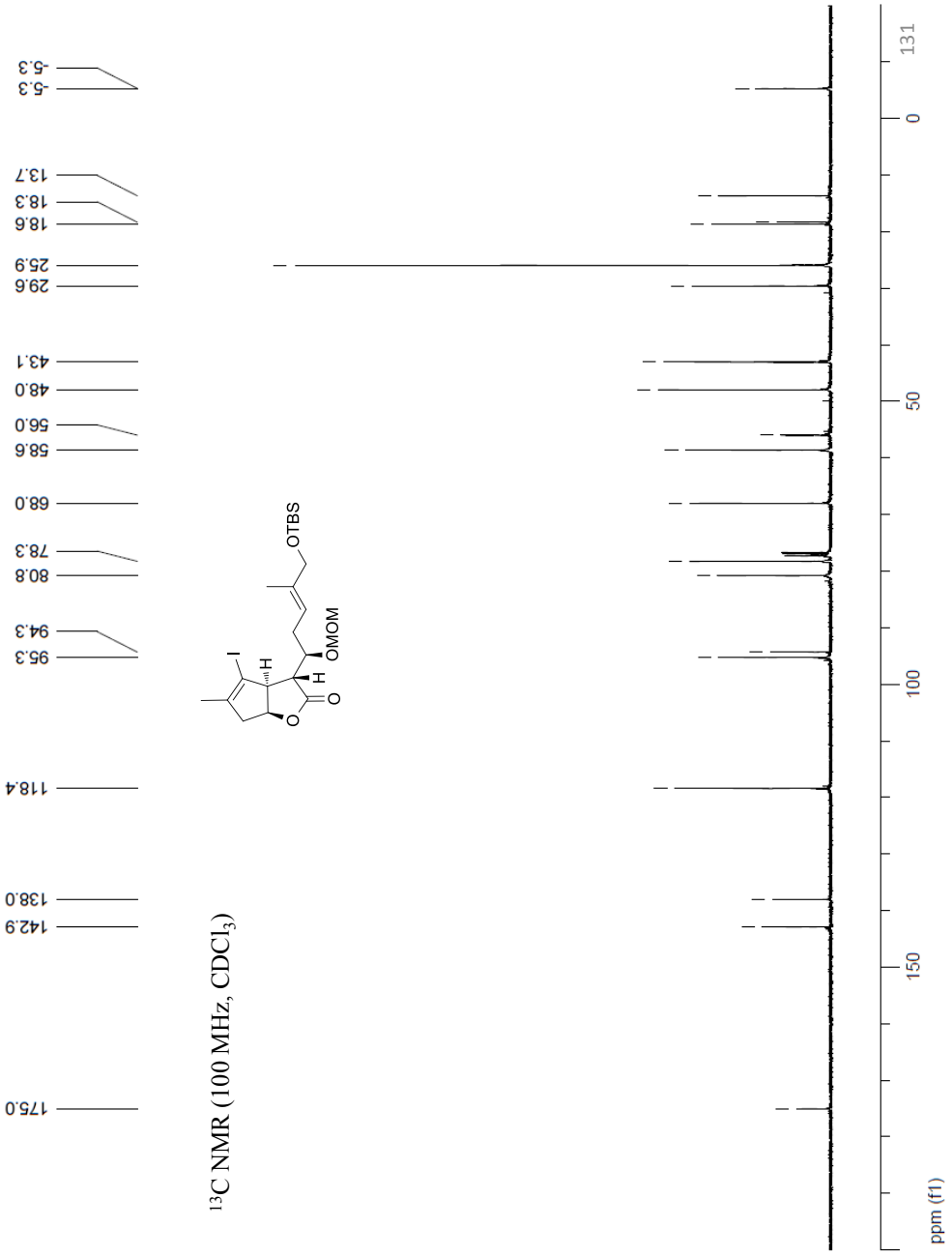
Spectrum 3.21: Compound 117ai: ^{1}H NMR



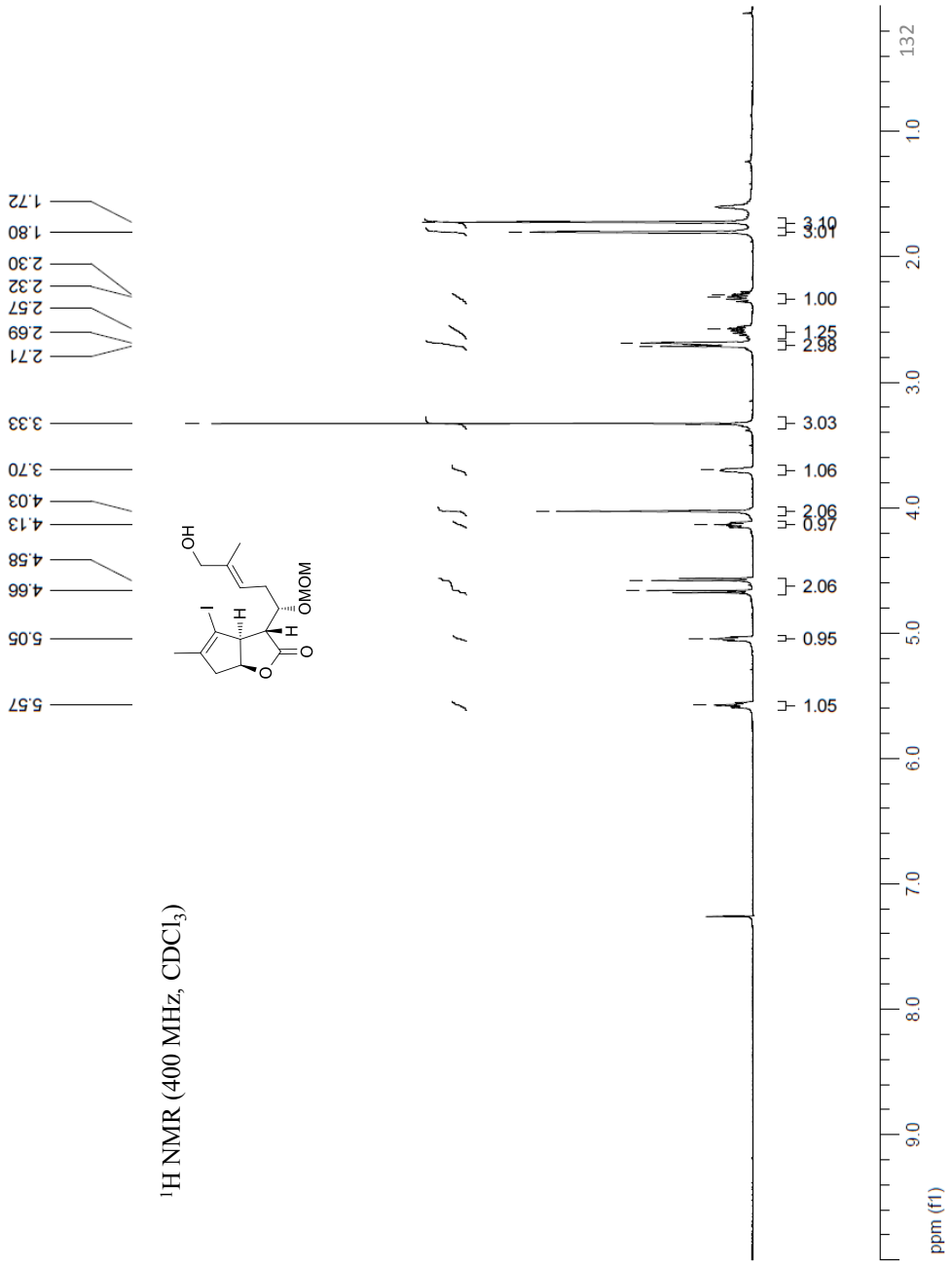
Spectrum 3.22: Compound 117ai: ^{13}C NMR



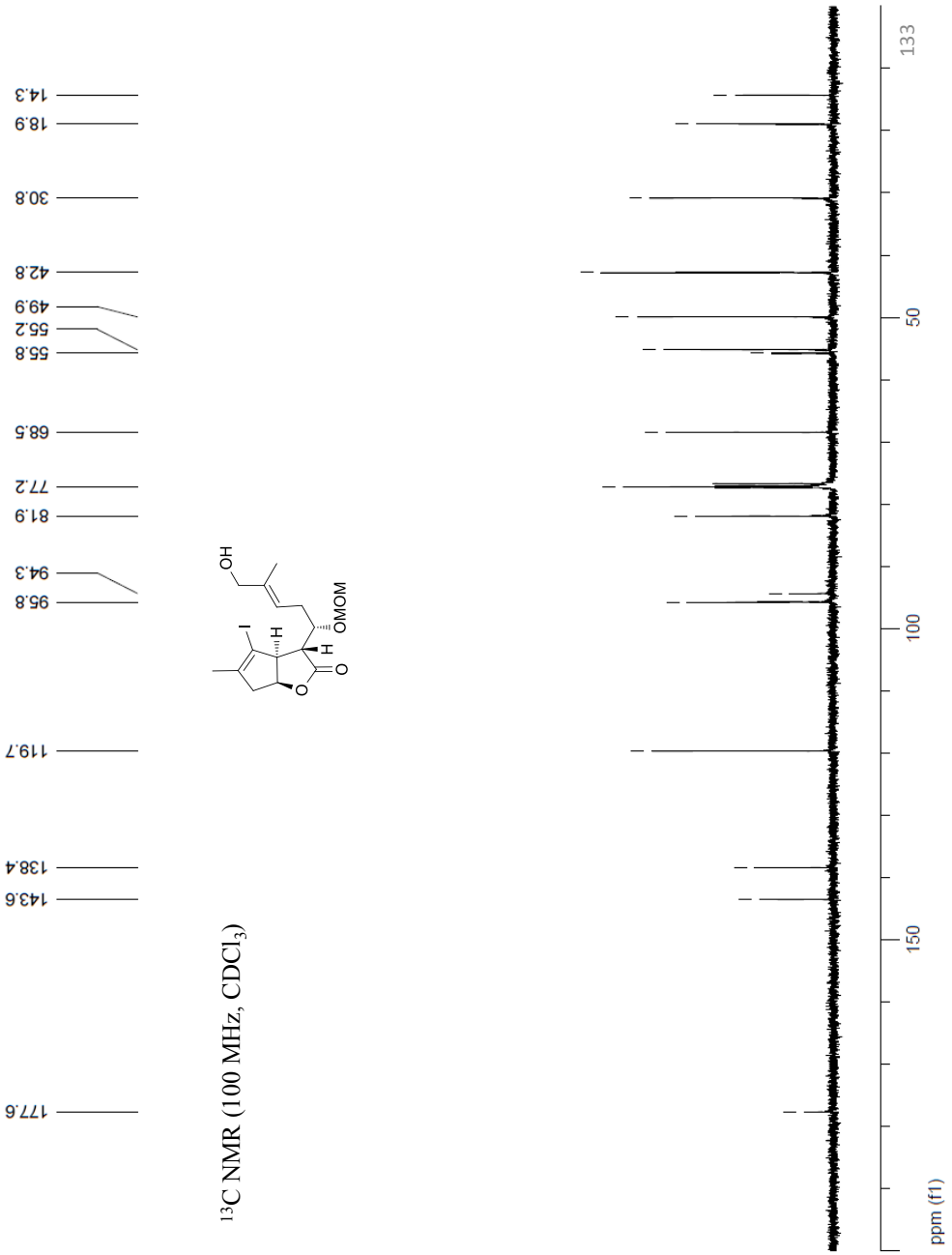
Spectrum 3.23: Compound 117bi: ^{1}H NMR



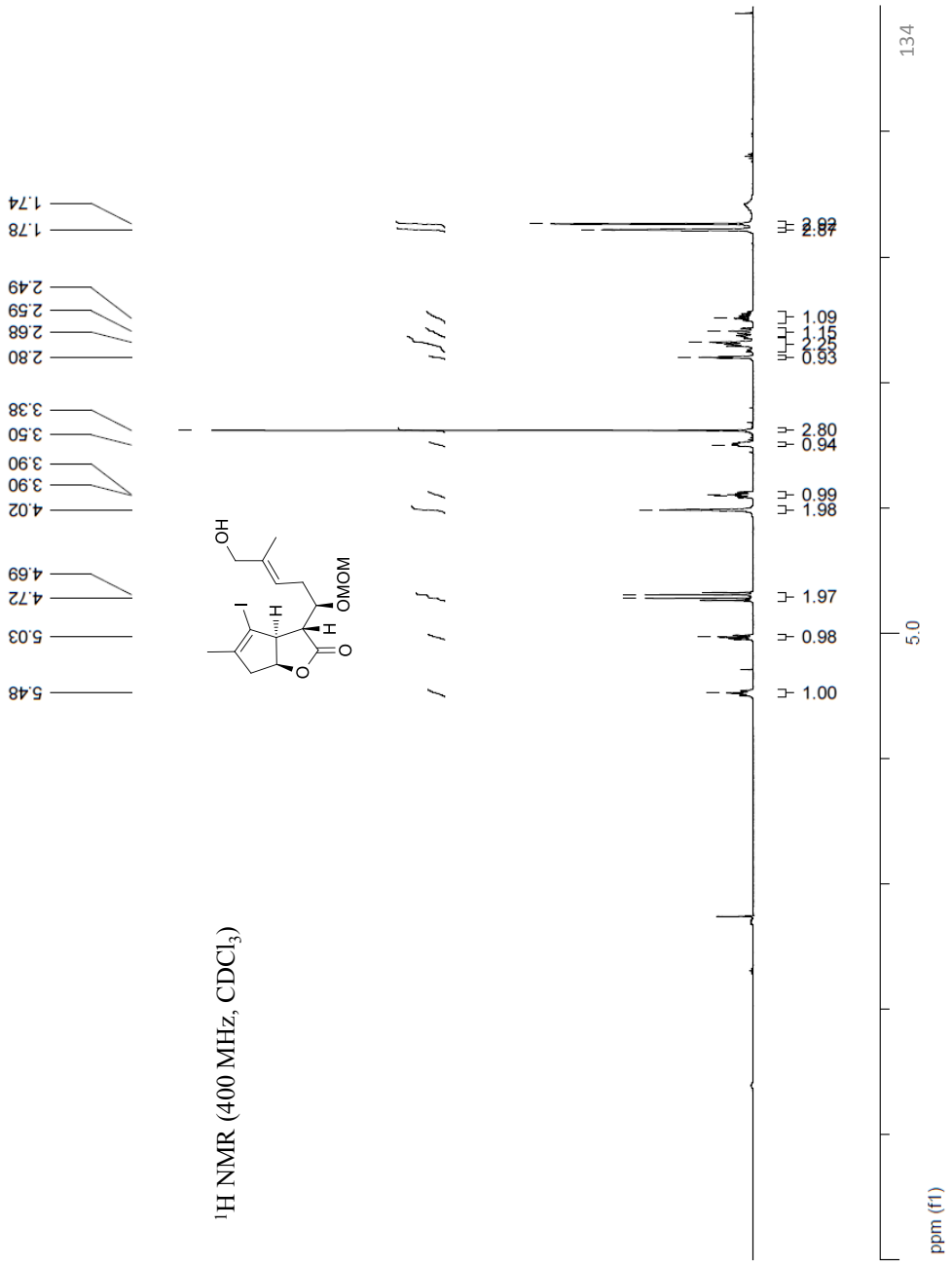
Spectrum 3.24: Compound 117bi: ^{13}C NMR



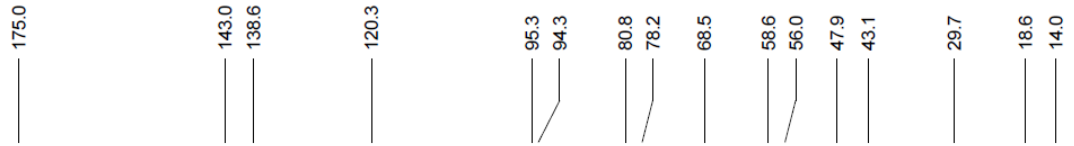
Spectrum 3.25: Compound 117a: ^{1}H NMR



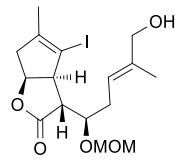
Spectrum 3.26: Compound 117a: ^{13}C NMR

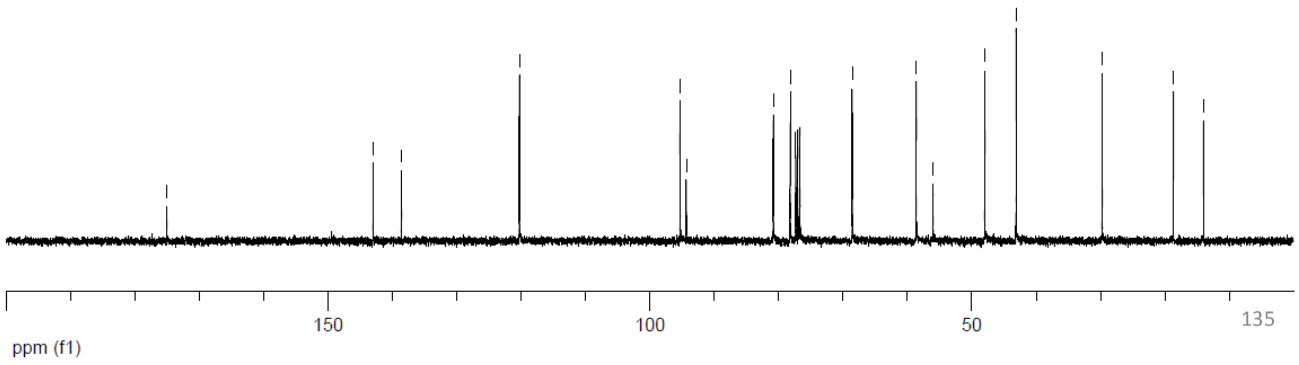


Spectrum 3.27: Compound 117b: ^{1}H NMR

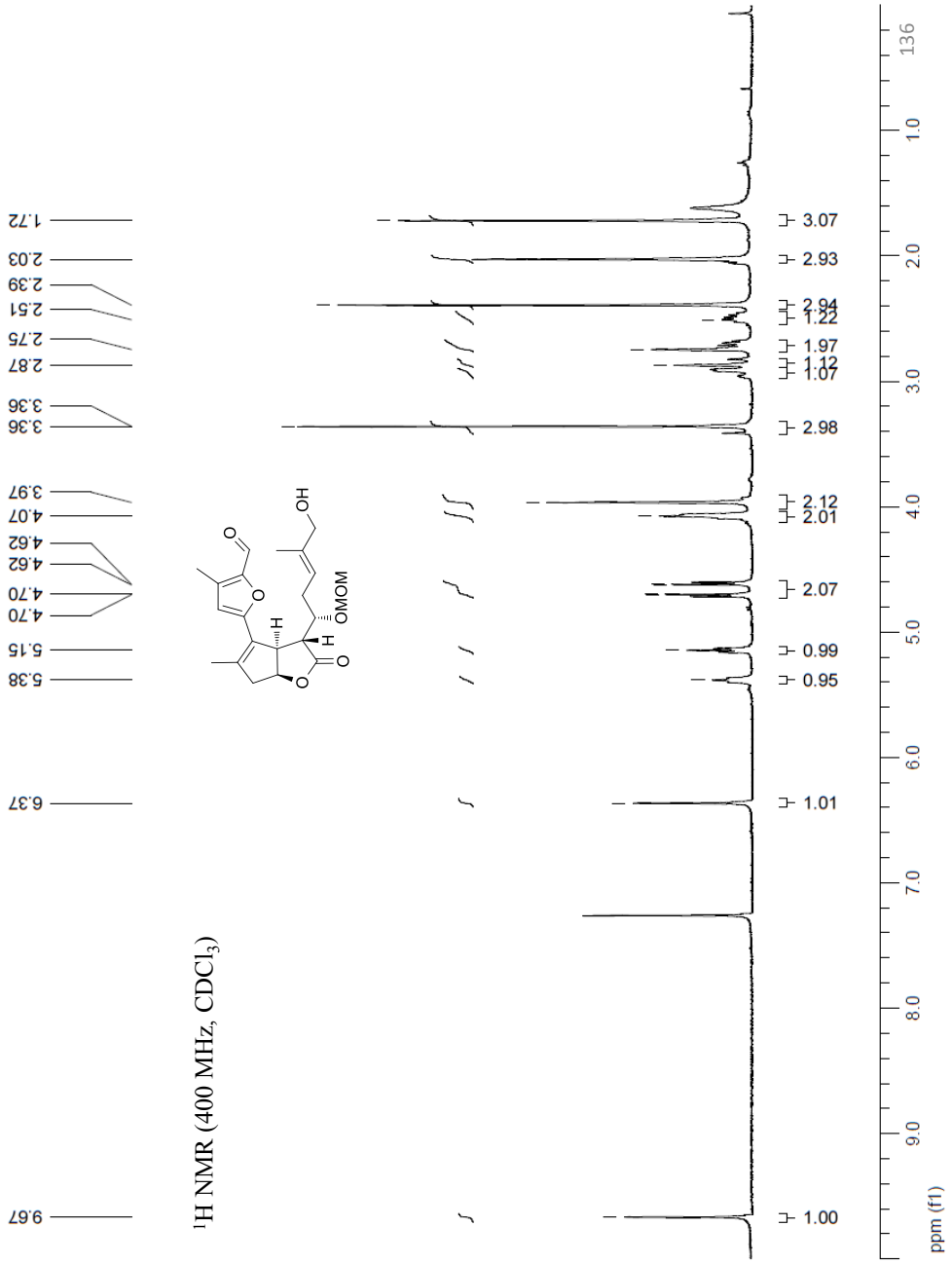


^{13}C NMR (100 MHz, $CDCl_3$)

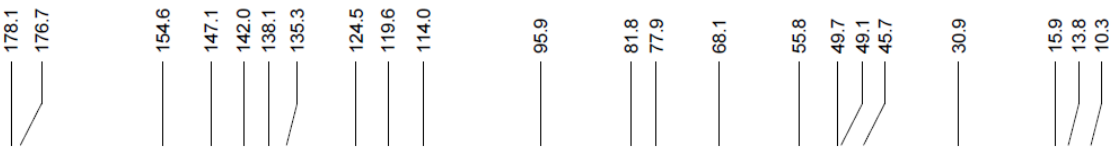




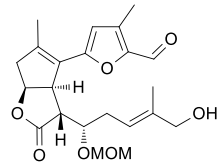
Spectrum 3.28: Compound 117b: ^{13}C NMR

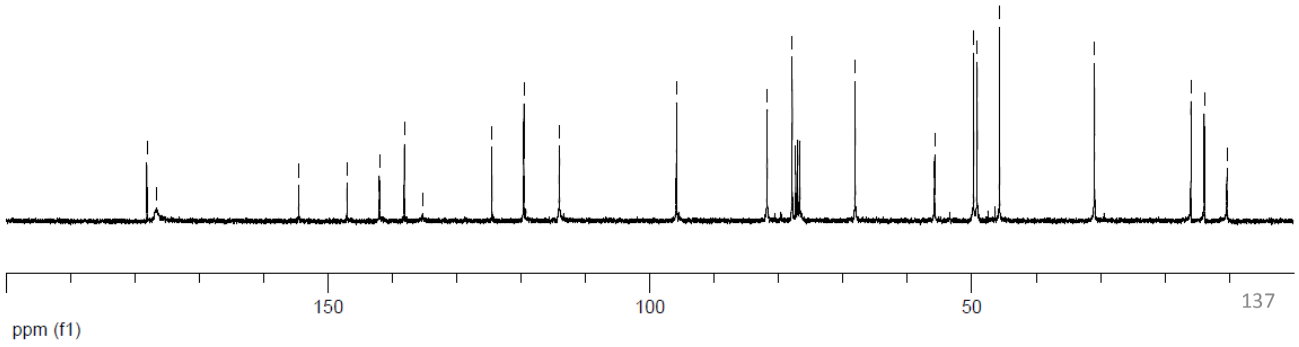


Spectrum 3.29: Compound 118a: ^{1}H NMR

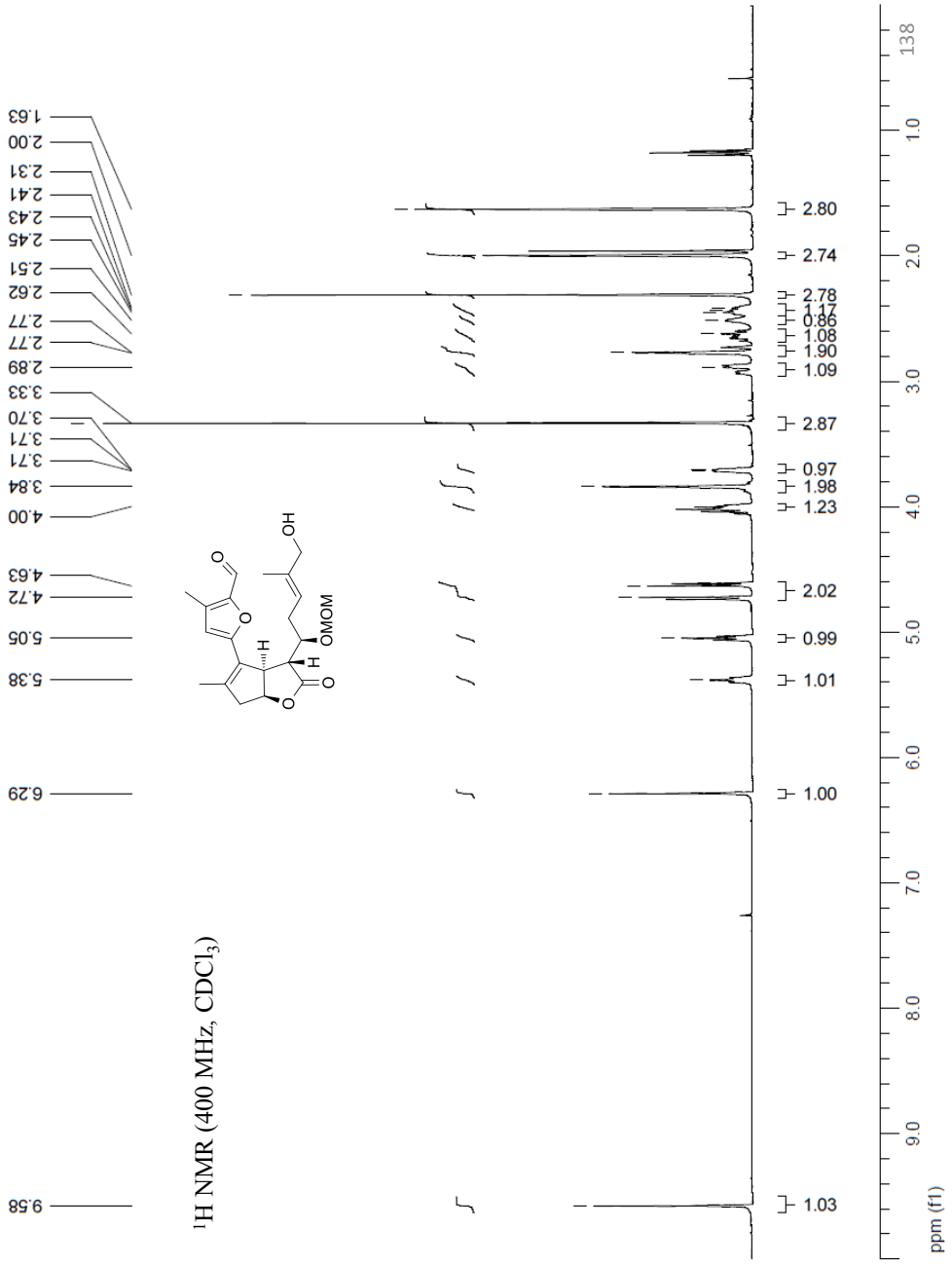


^{13}C NMR (100 MHz, $CDCl_3$)

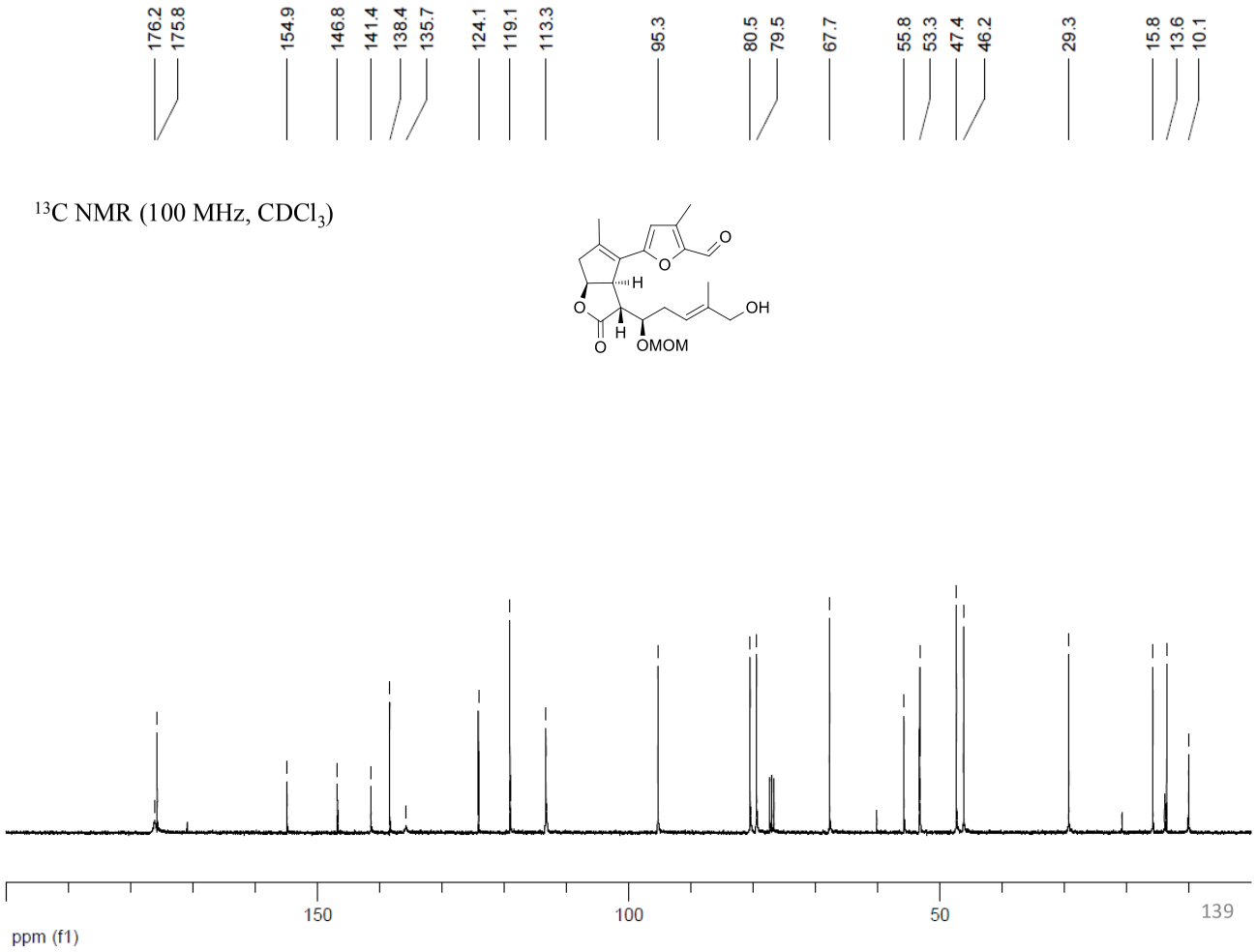




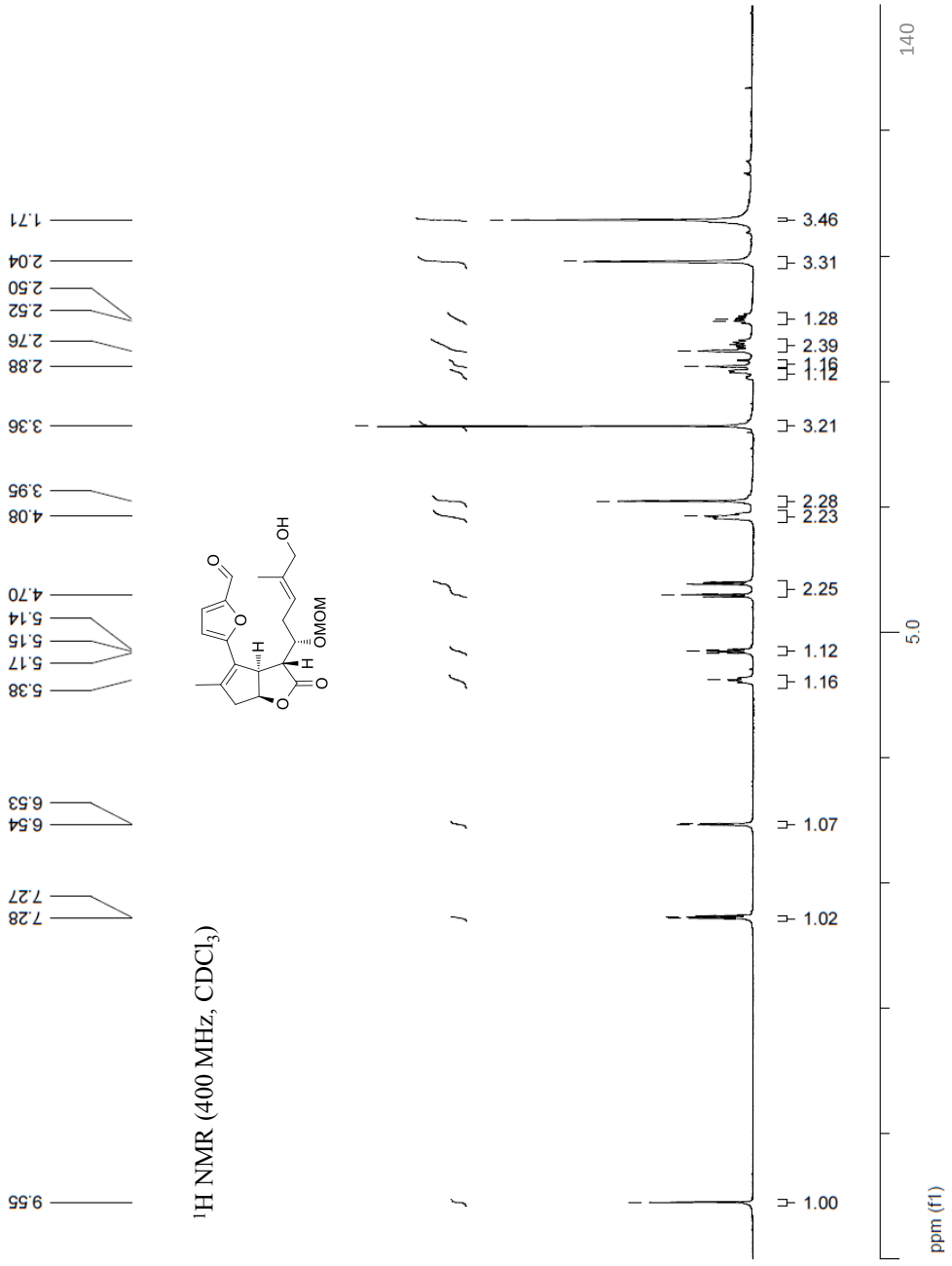
Spectrum 3.30: Compound 118a: ^{13}C NMR



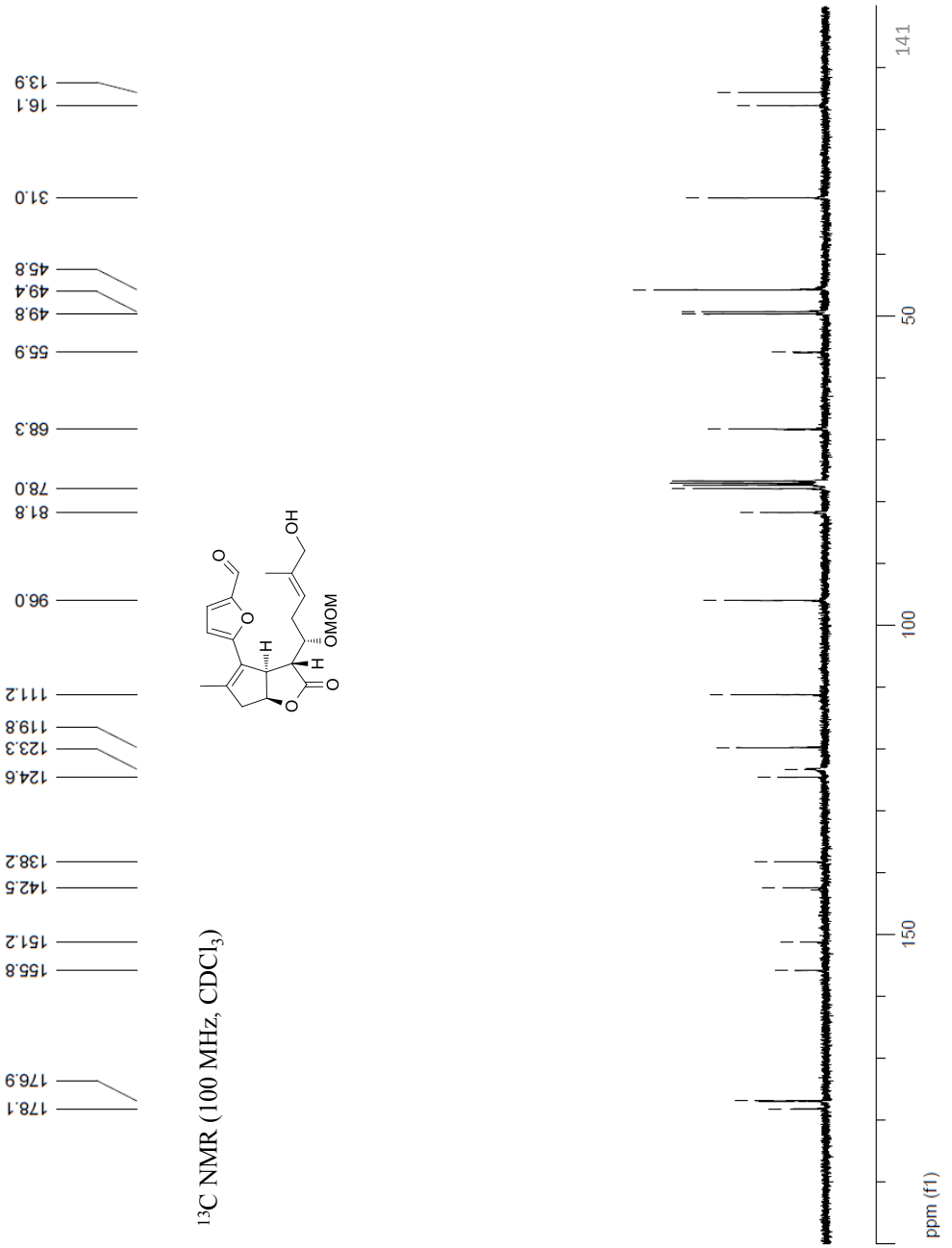
Spectrum 3.31: Compound 118b: ^{1}H NMR



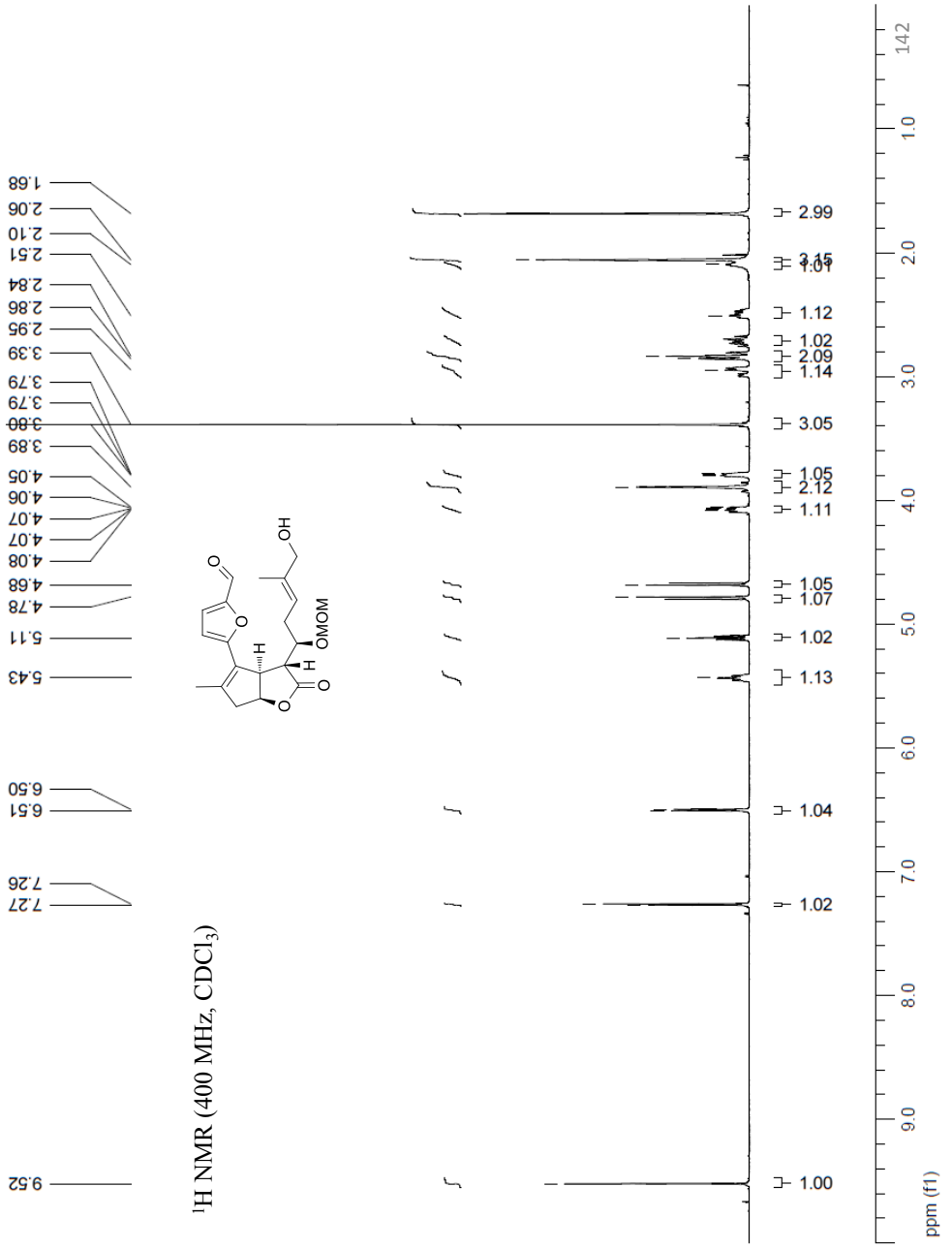
Spectrum 3.32: Compound 118b: ^{13}C NMR



Spectrum 3.33: Compound 119a: ^{1}H NMR

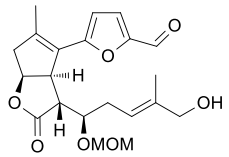


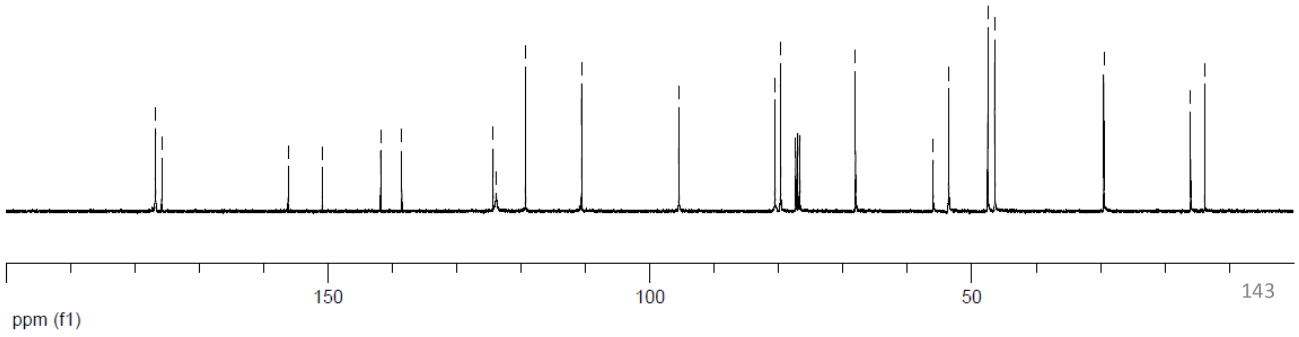
Spectrum 3.34: Compound 119a: ^{13}C NMR



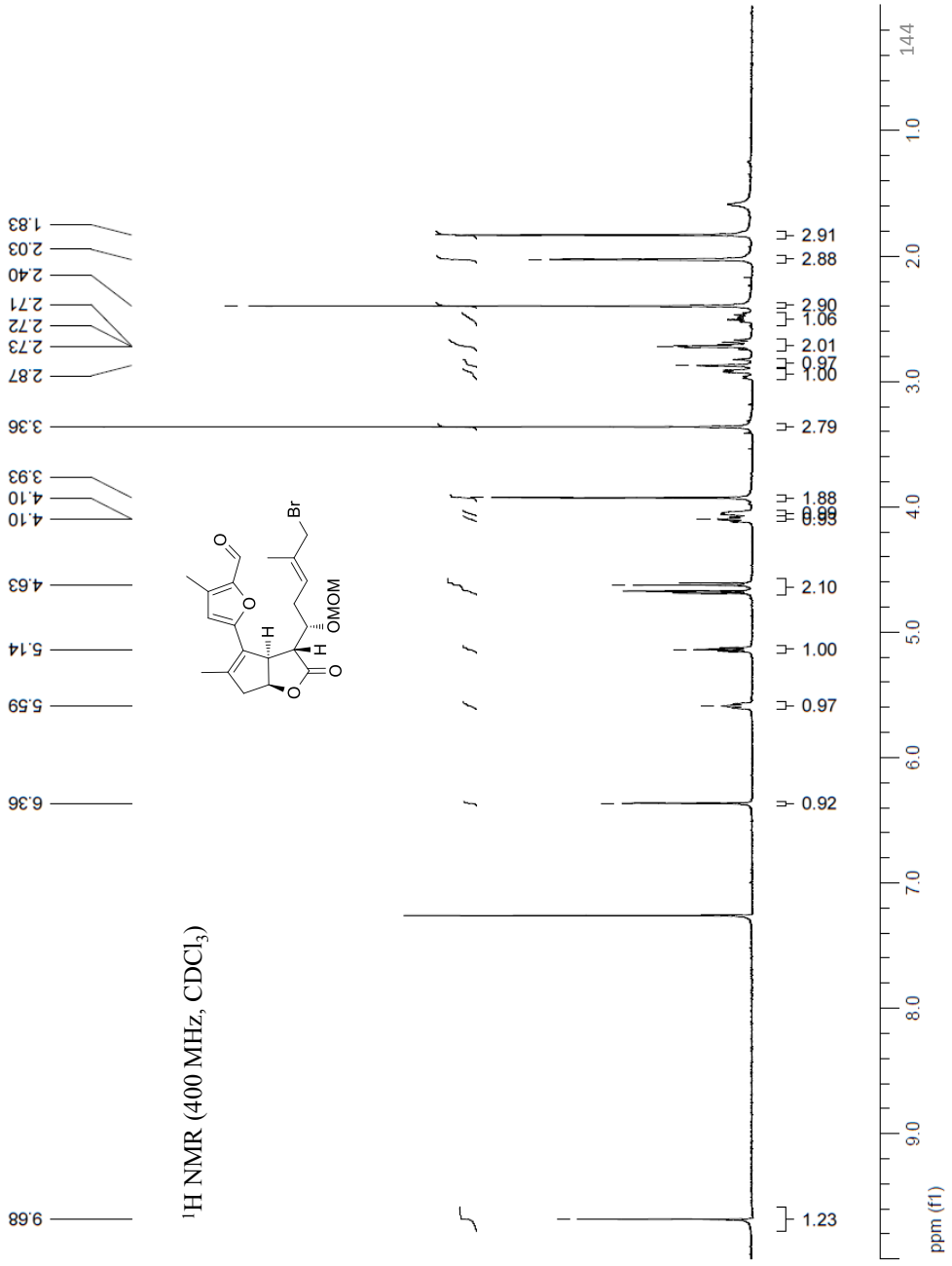
Spectrum 3.35: Compound 119b: ^{1}H NMR

^{13}C NMR (100 MHz, $CDCl_3$)

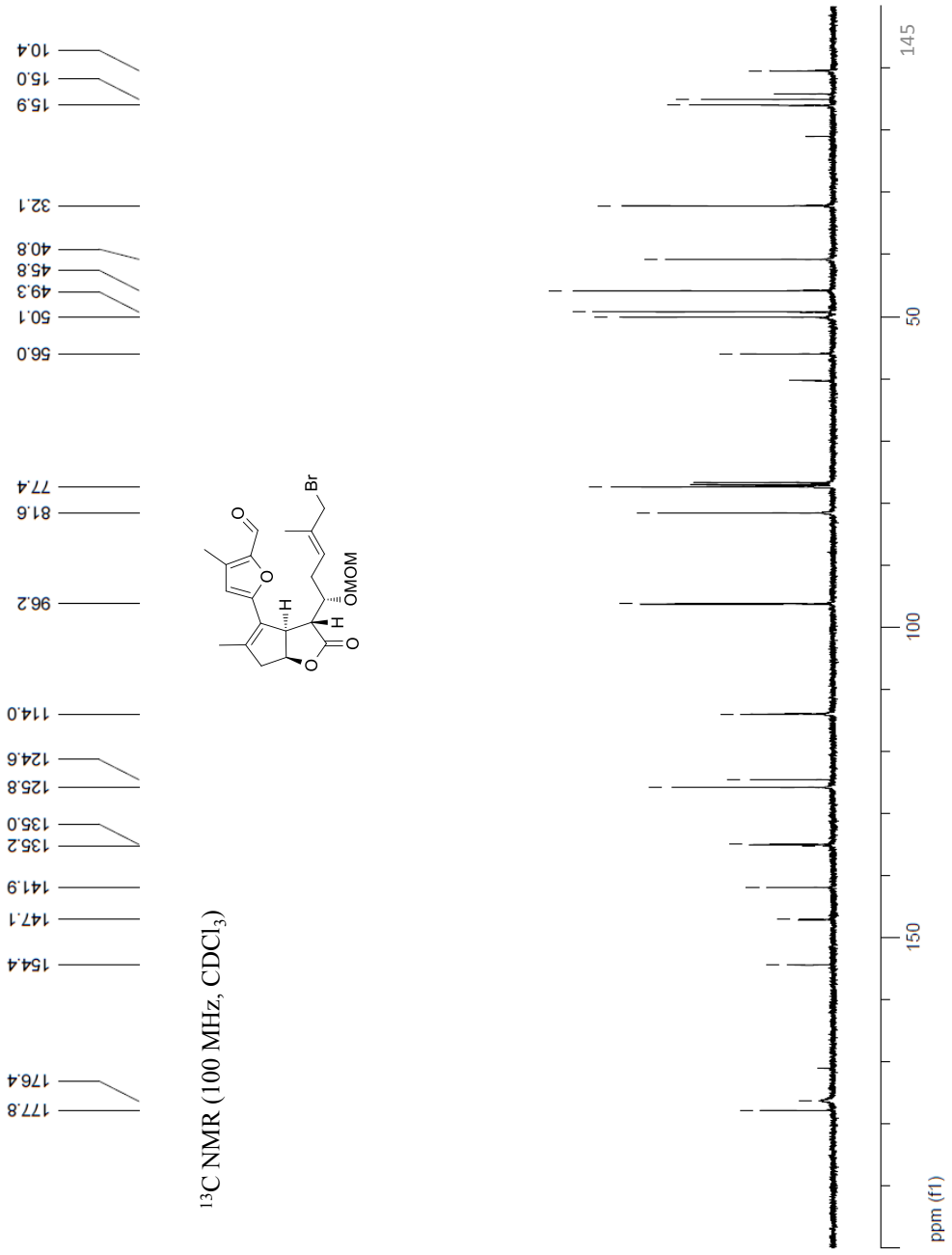




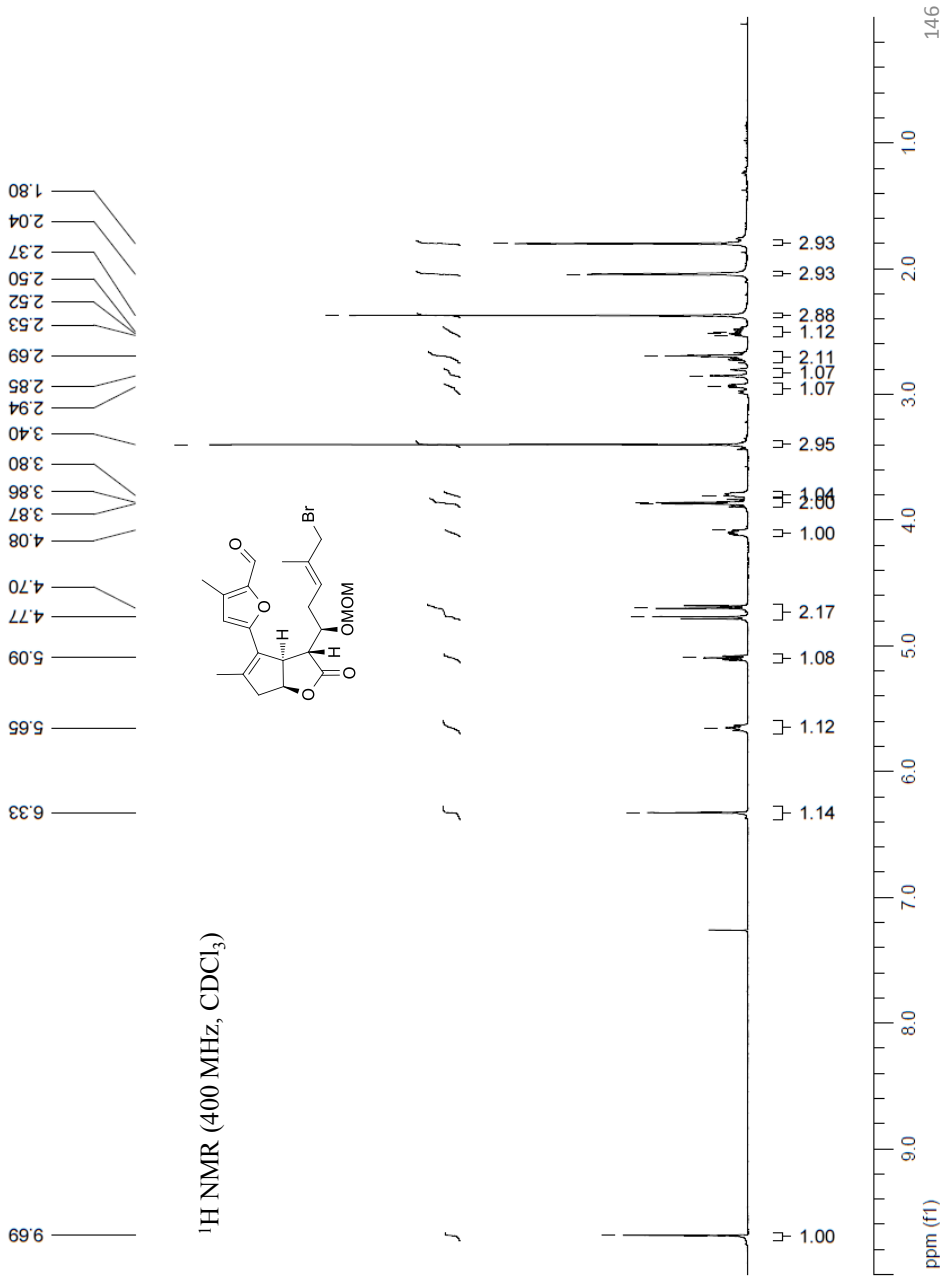
Spectrum 3.36: Compound 119b: ^{1}C NMR



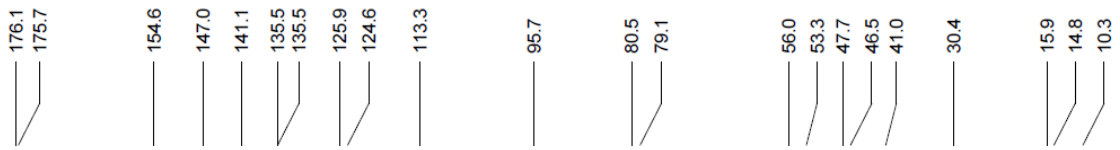
Spectrum 3.37: Compound 120a: ^{13}H NMR



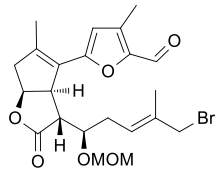
Spectrum 3.38: Compound 120a: ^{1}C NMR

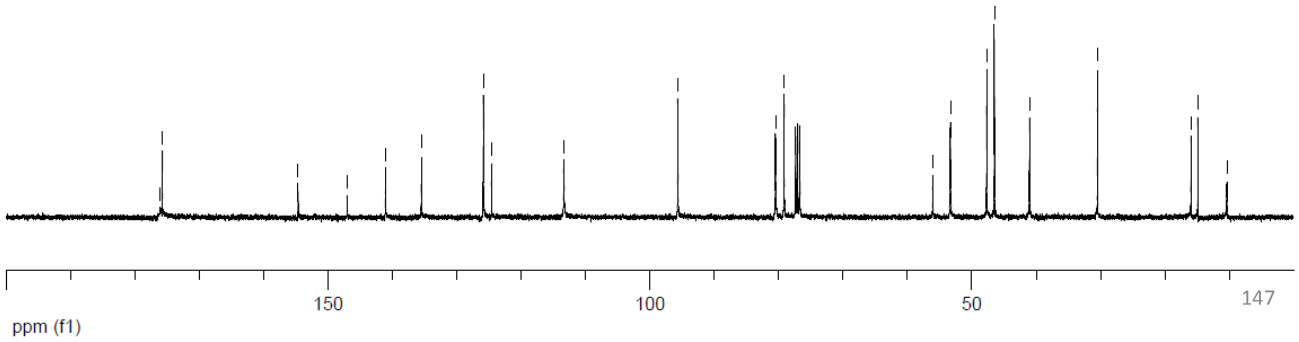


Spectrum 3.39: Compound 120b: ^{13}H NMR

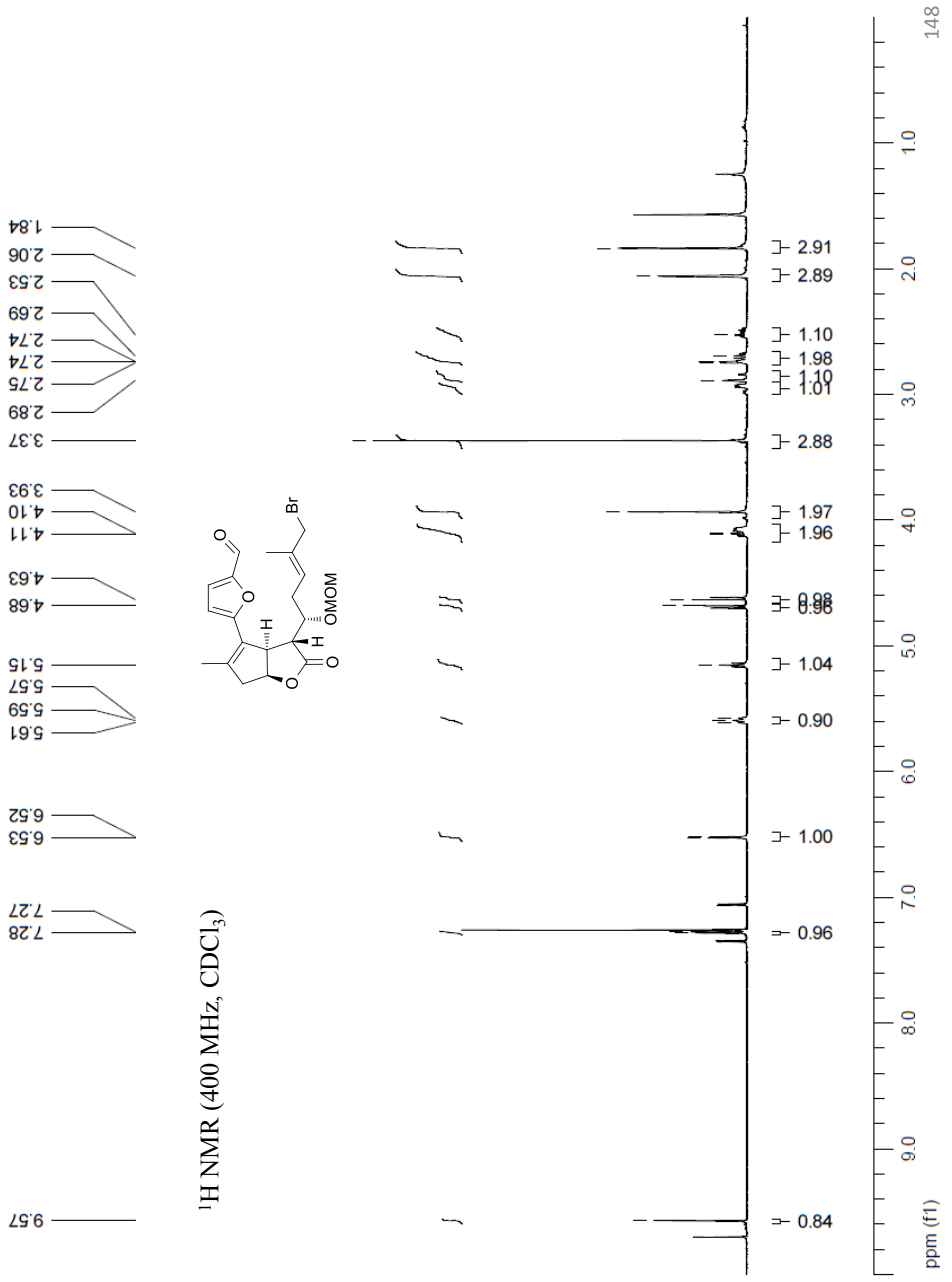


^{13}C NMR (100 MHz, $CDCl_3$)

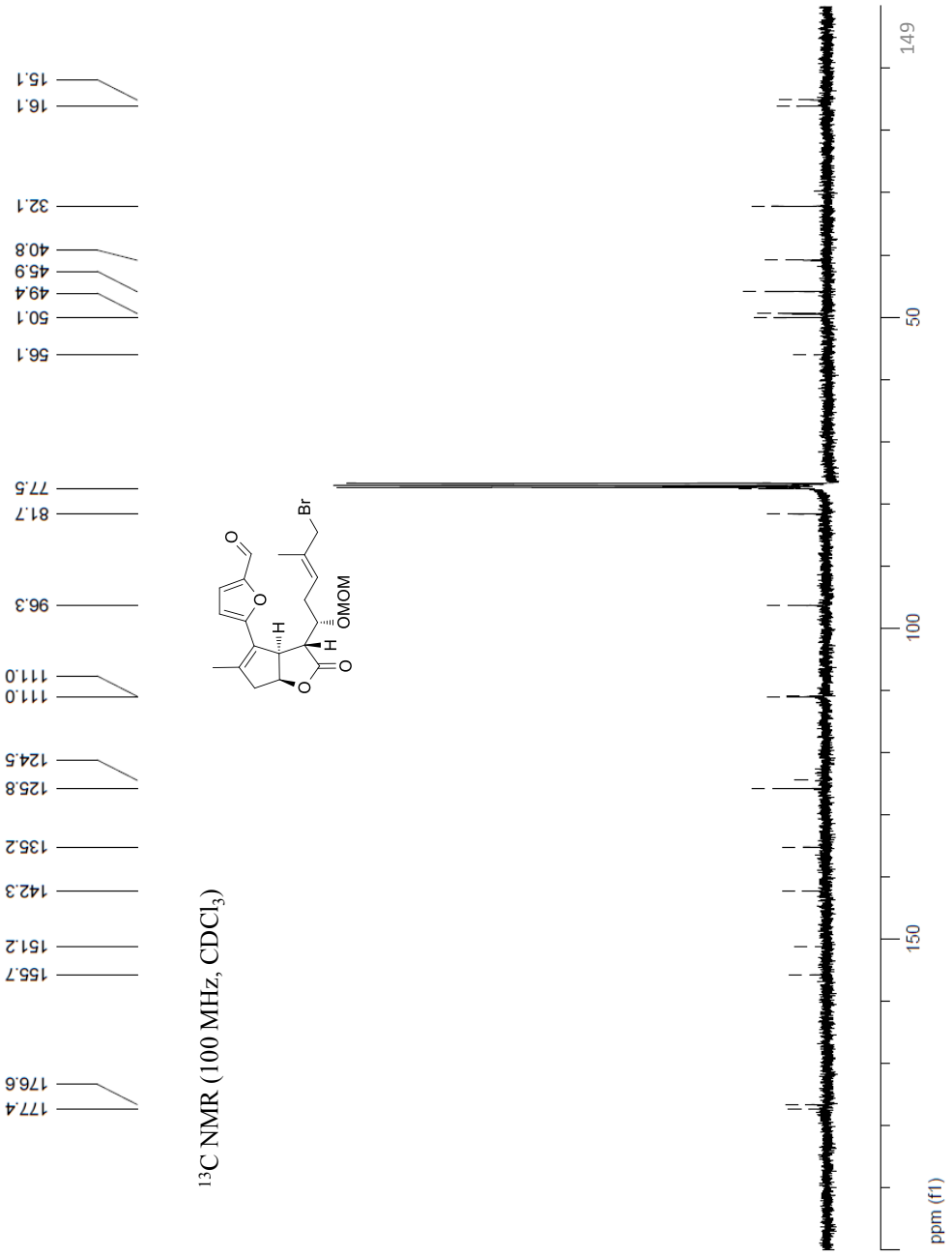




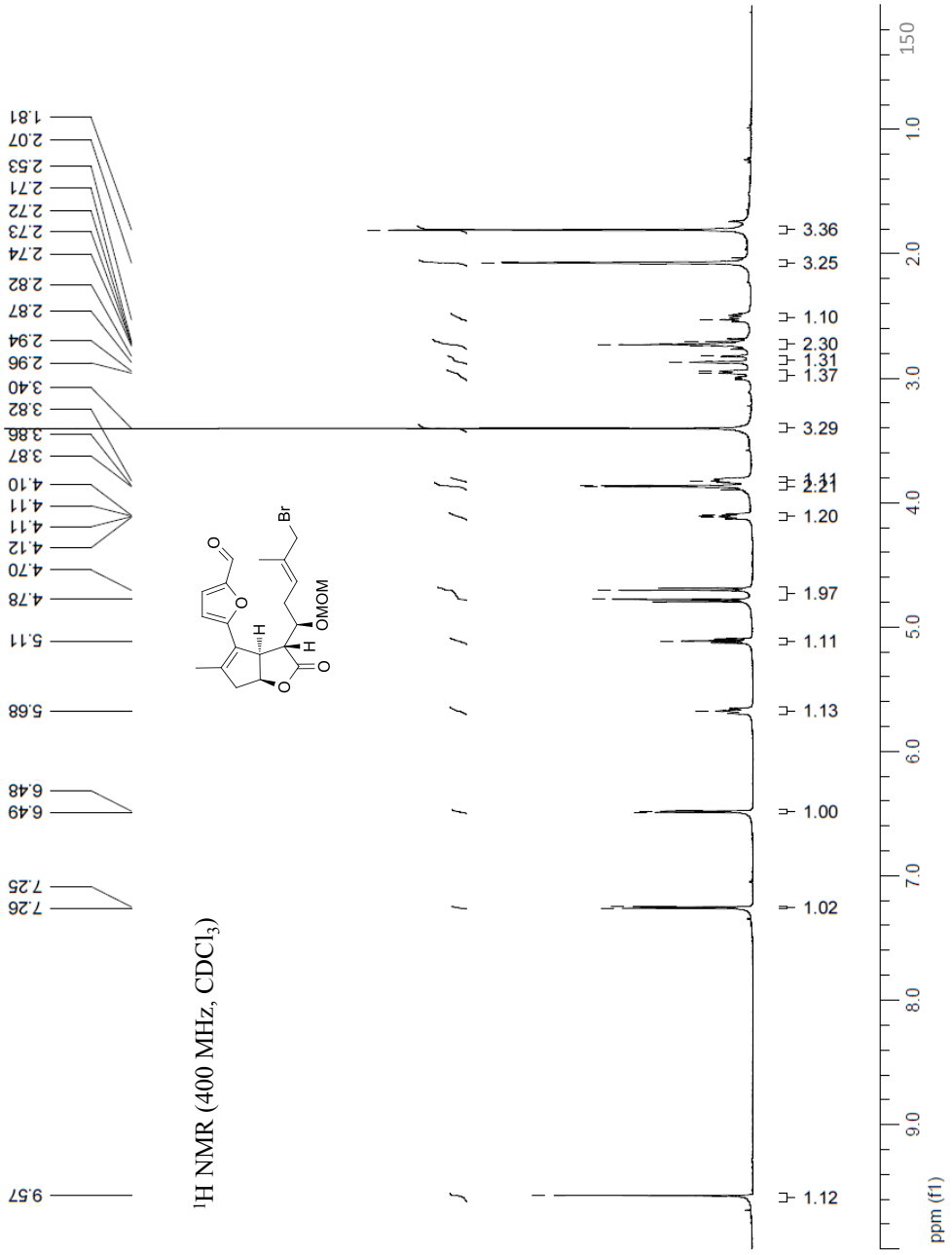
Spectrum 3.40: Compound 120b: ^{1}C NMR



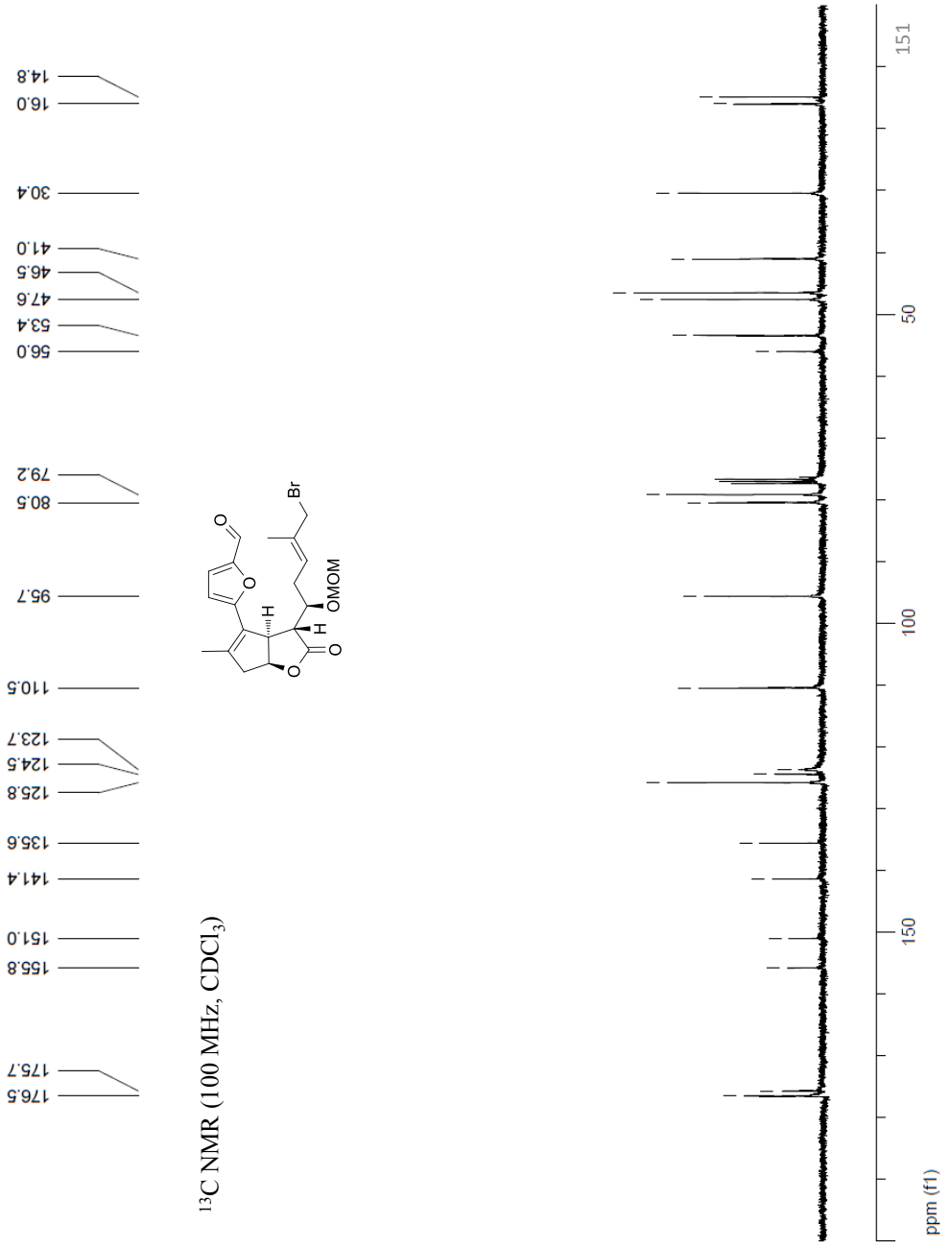
Spectrum 3.41: Compound 121a: ^{13}H NMR



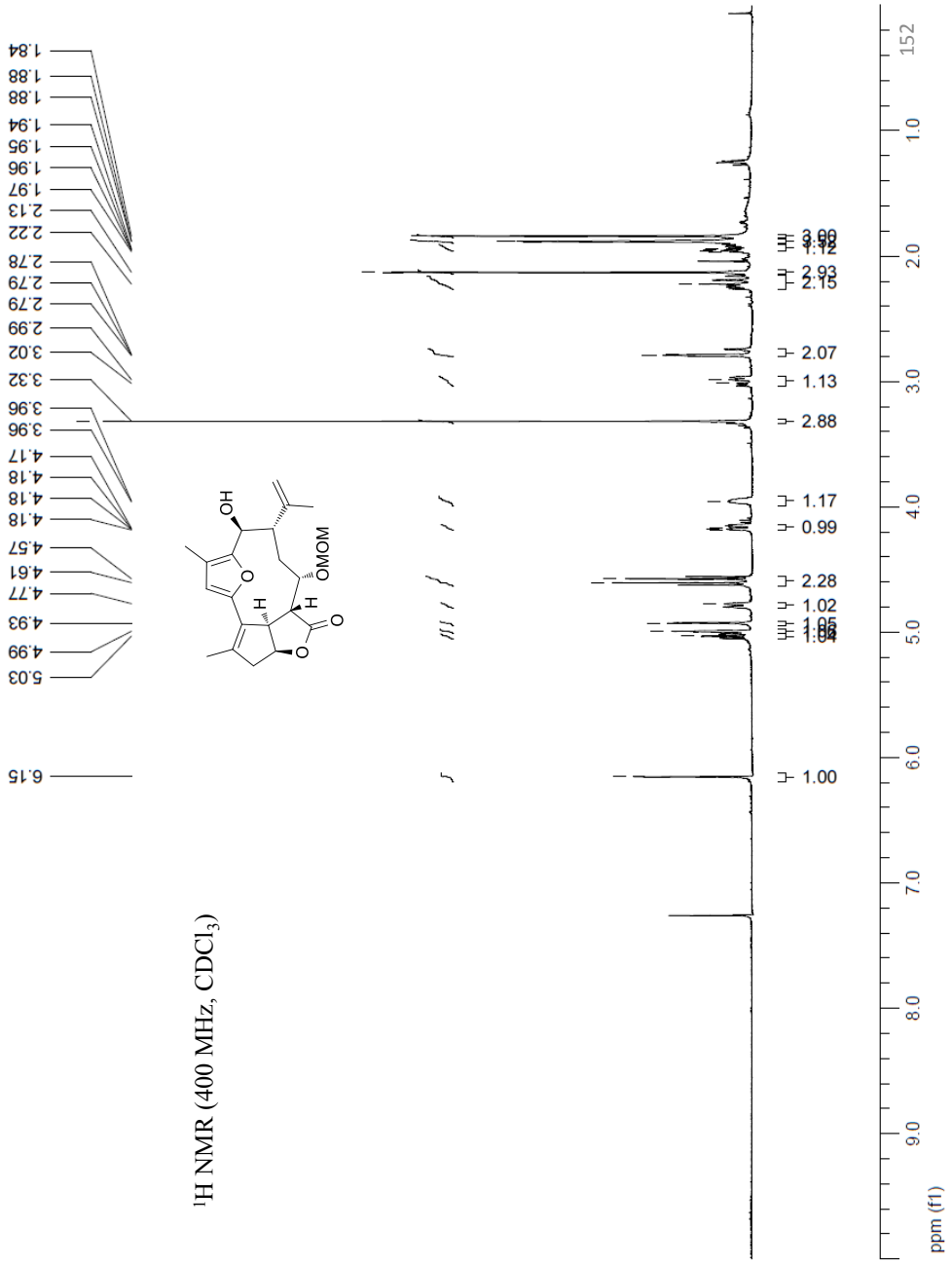
Spectrum 3.42: Compound 121a: ^{1}C NMR



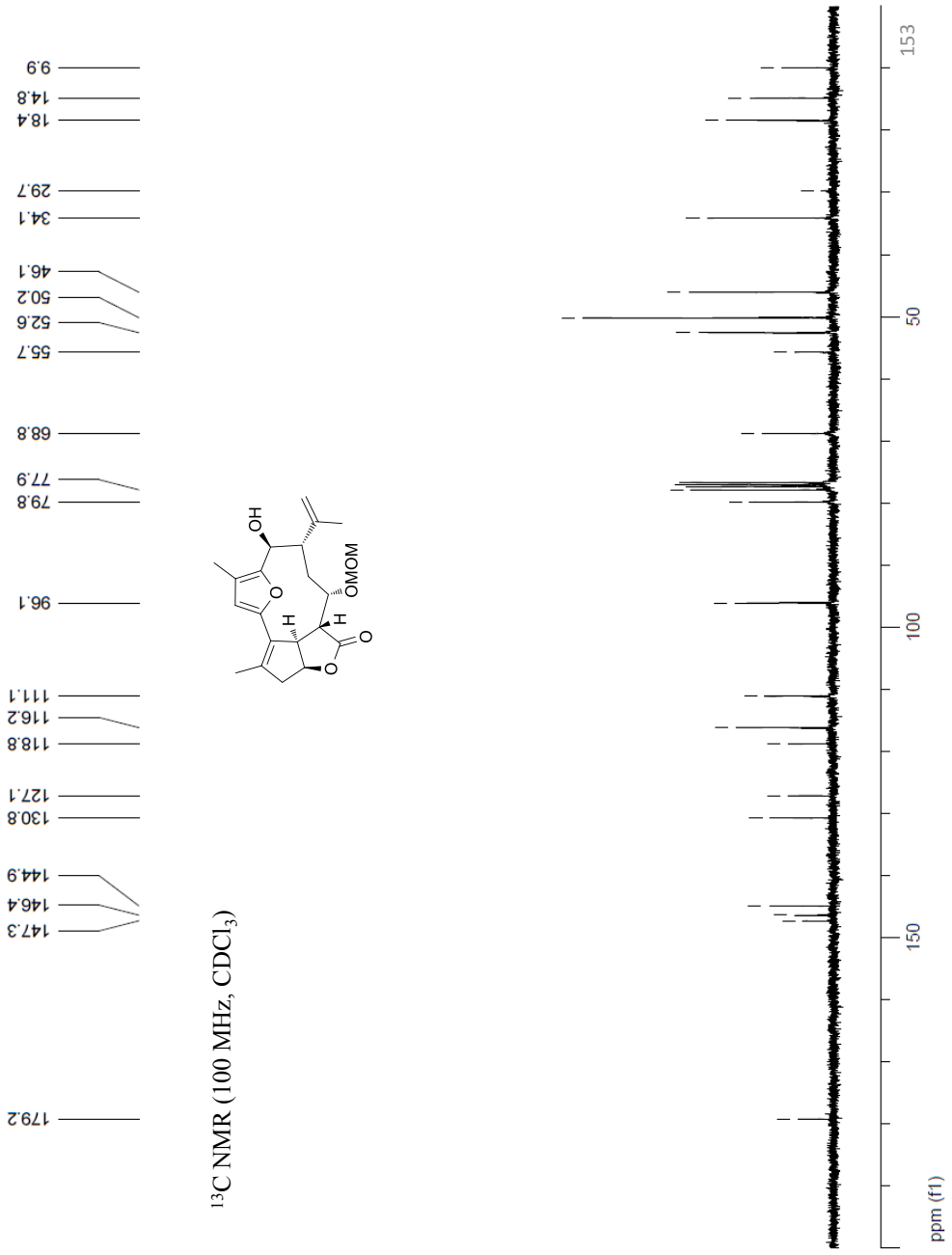
Spectrum 3.43: Compound 121b: ^{13}H NMR



Spectrum 3.44: Compound 121b: ^{1}C NMR

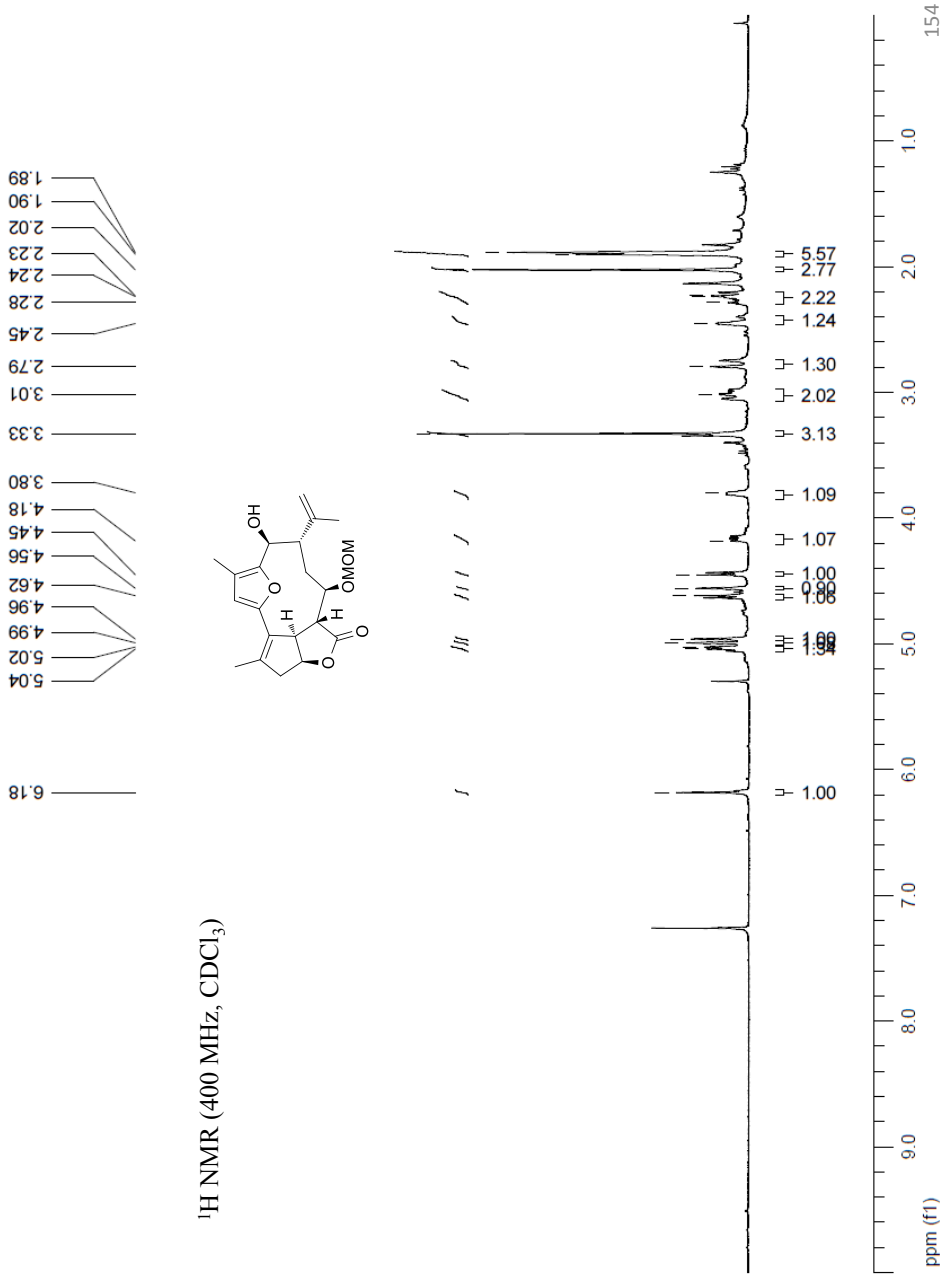


Spectrum 3.45: Compound 122a: ^{13}H NMR

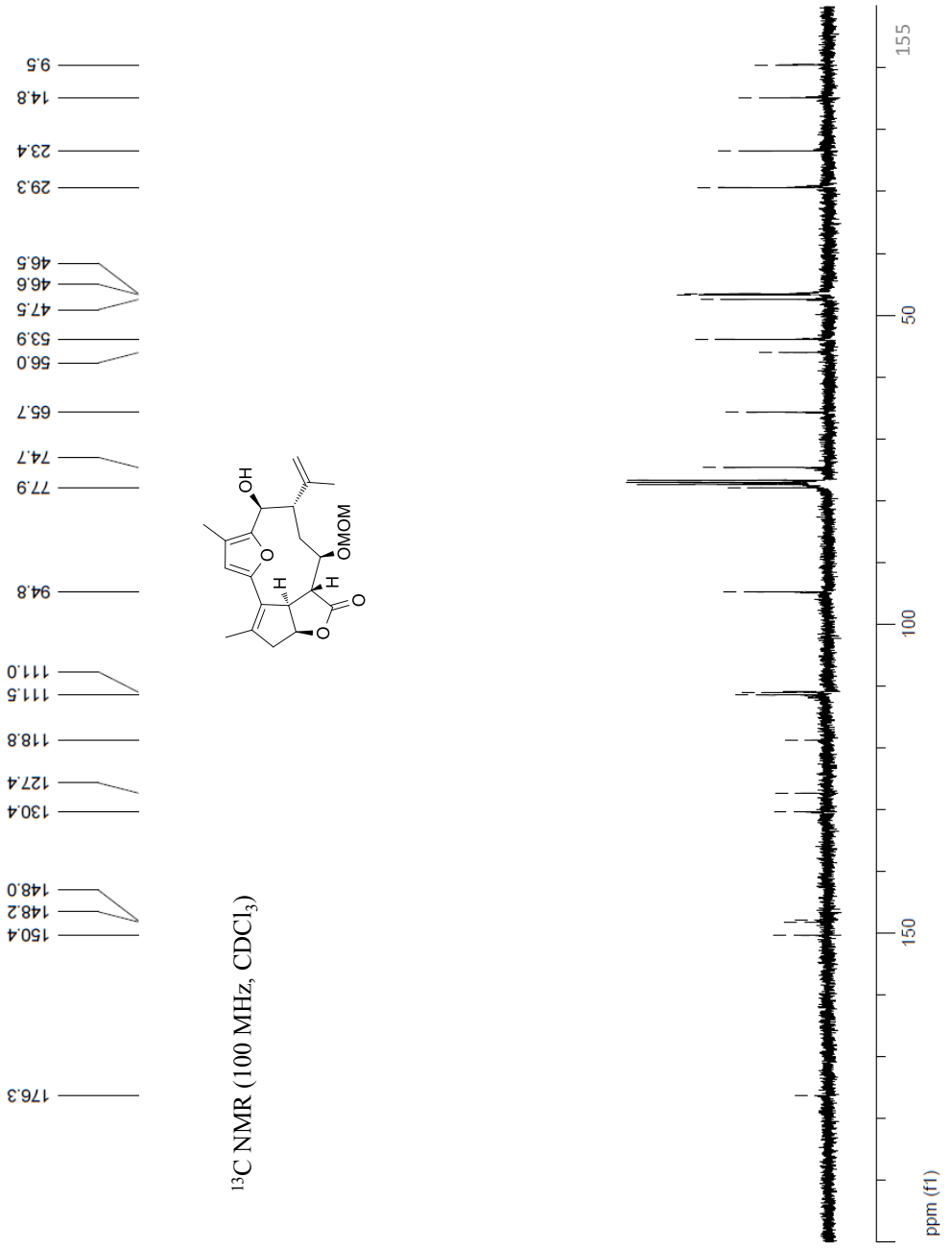


^{13}C NMR (100 MHz, $CDCl_3$)

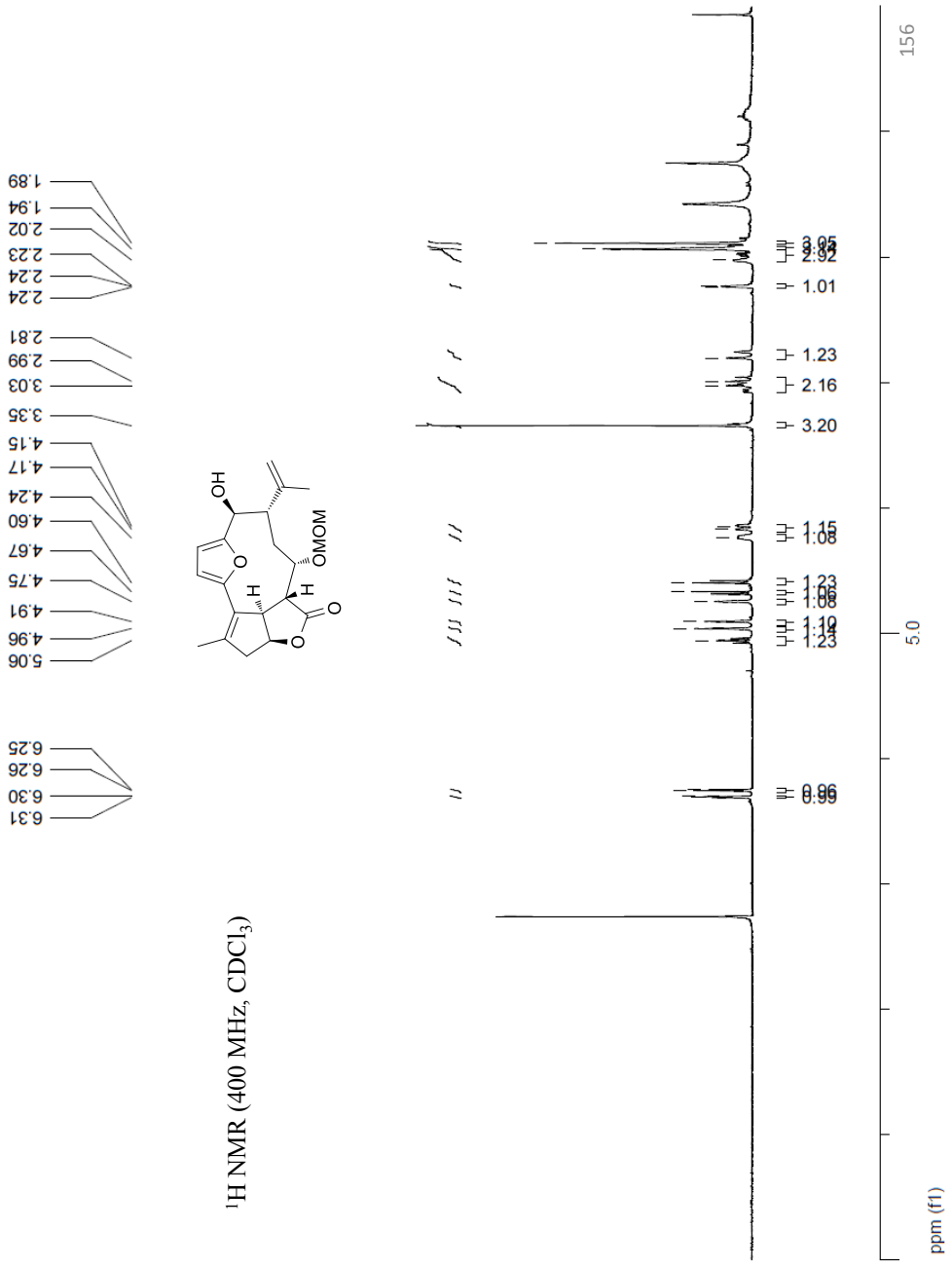
Spectrum 3.46: Compound 122a: ^{13}C NMR



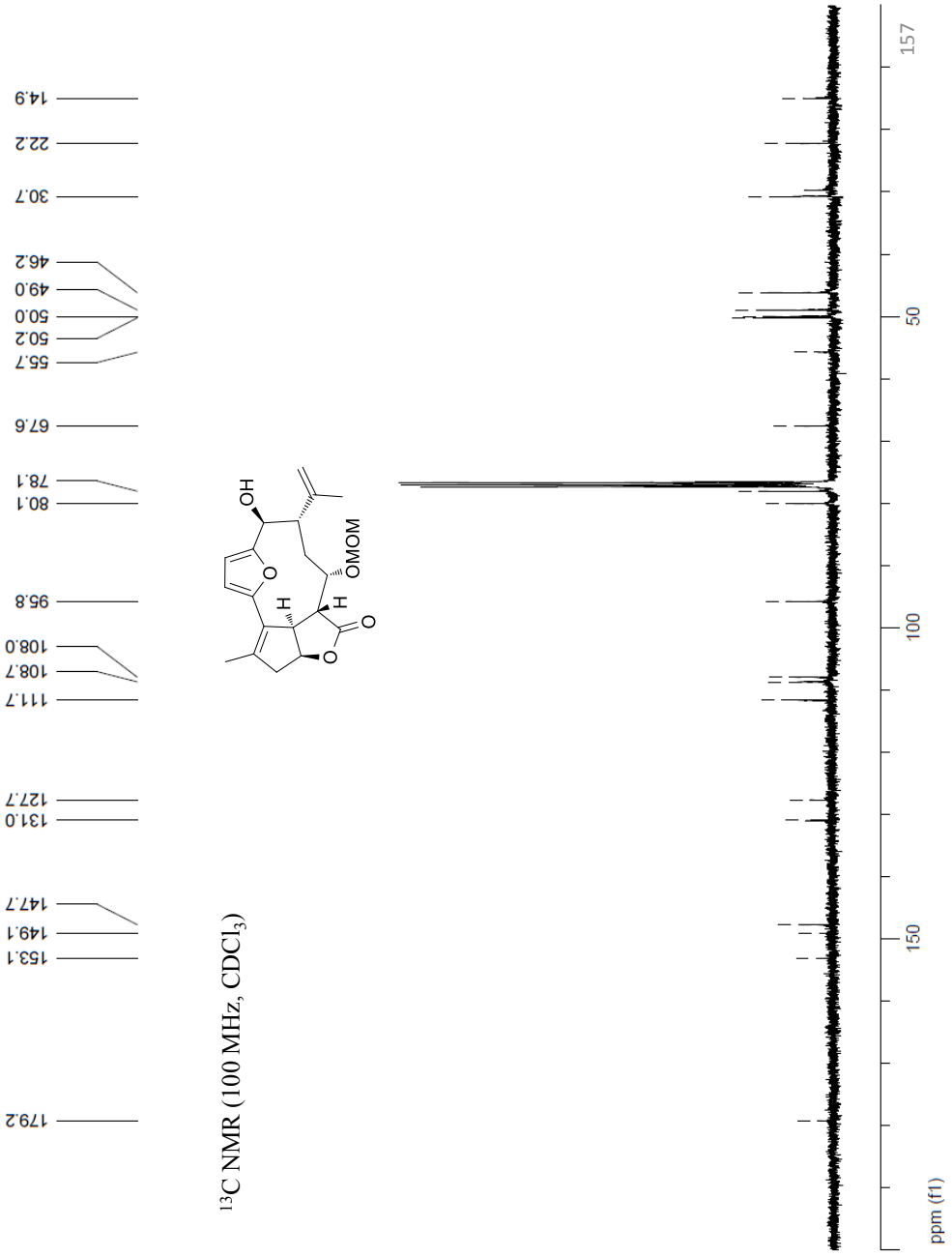
Spectrum 3.47: Compound 105: ^{1}H NMR



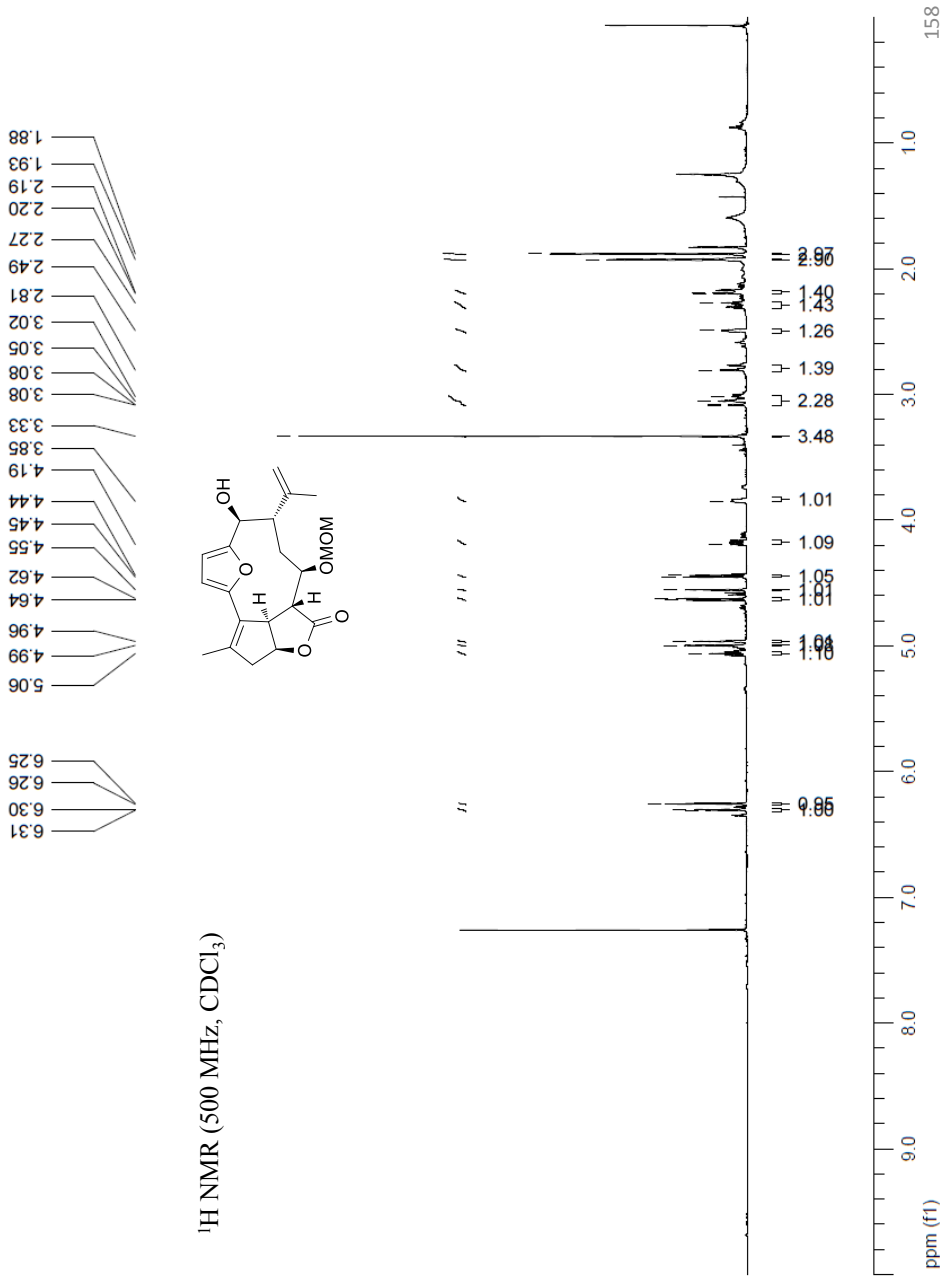
Spectrum 3.48: Compound 105: ^{13}C NMR



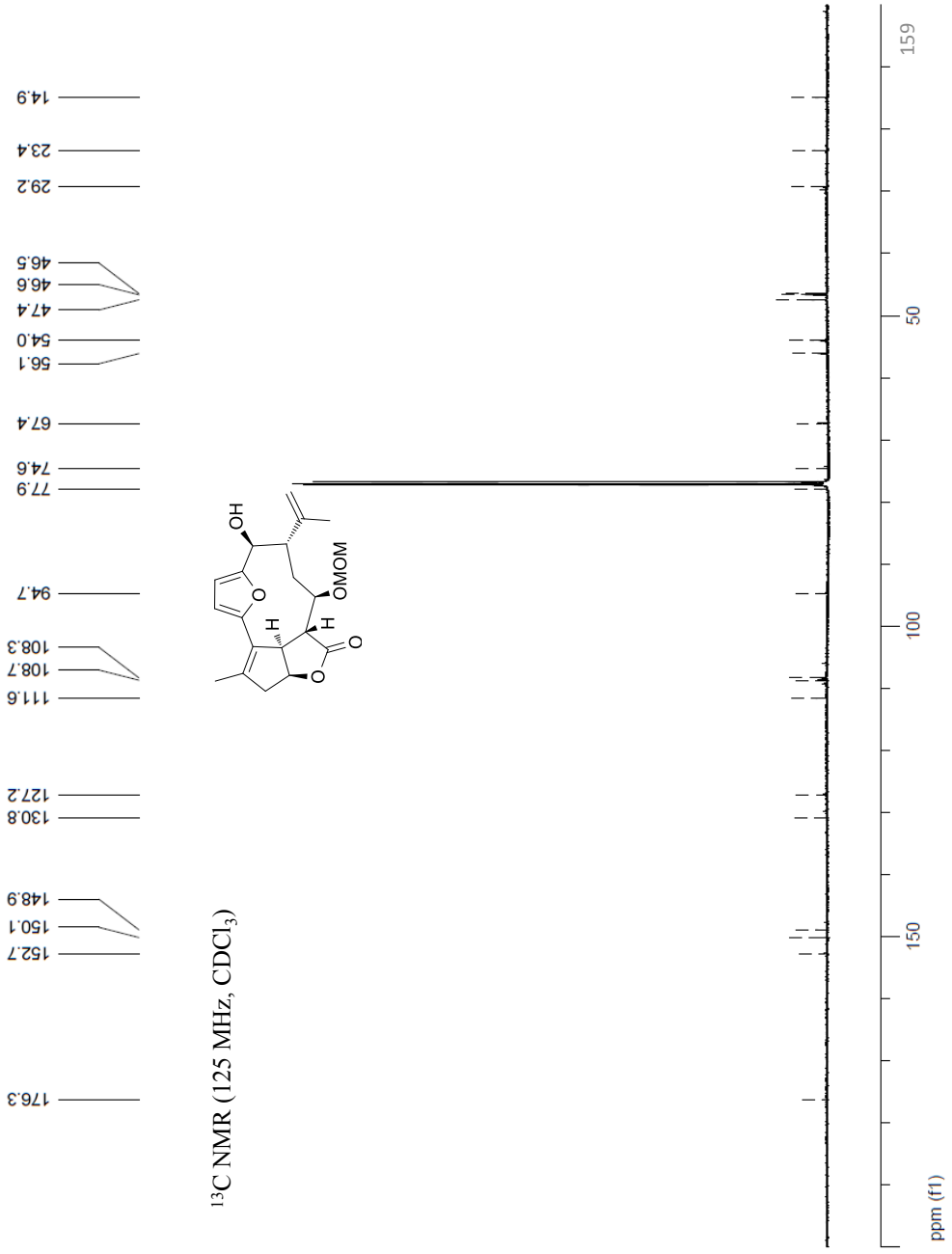
Spectrum 3.49: Compound 123a: ^{1}H NMR



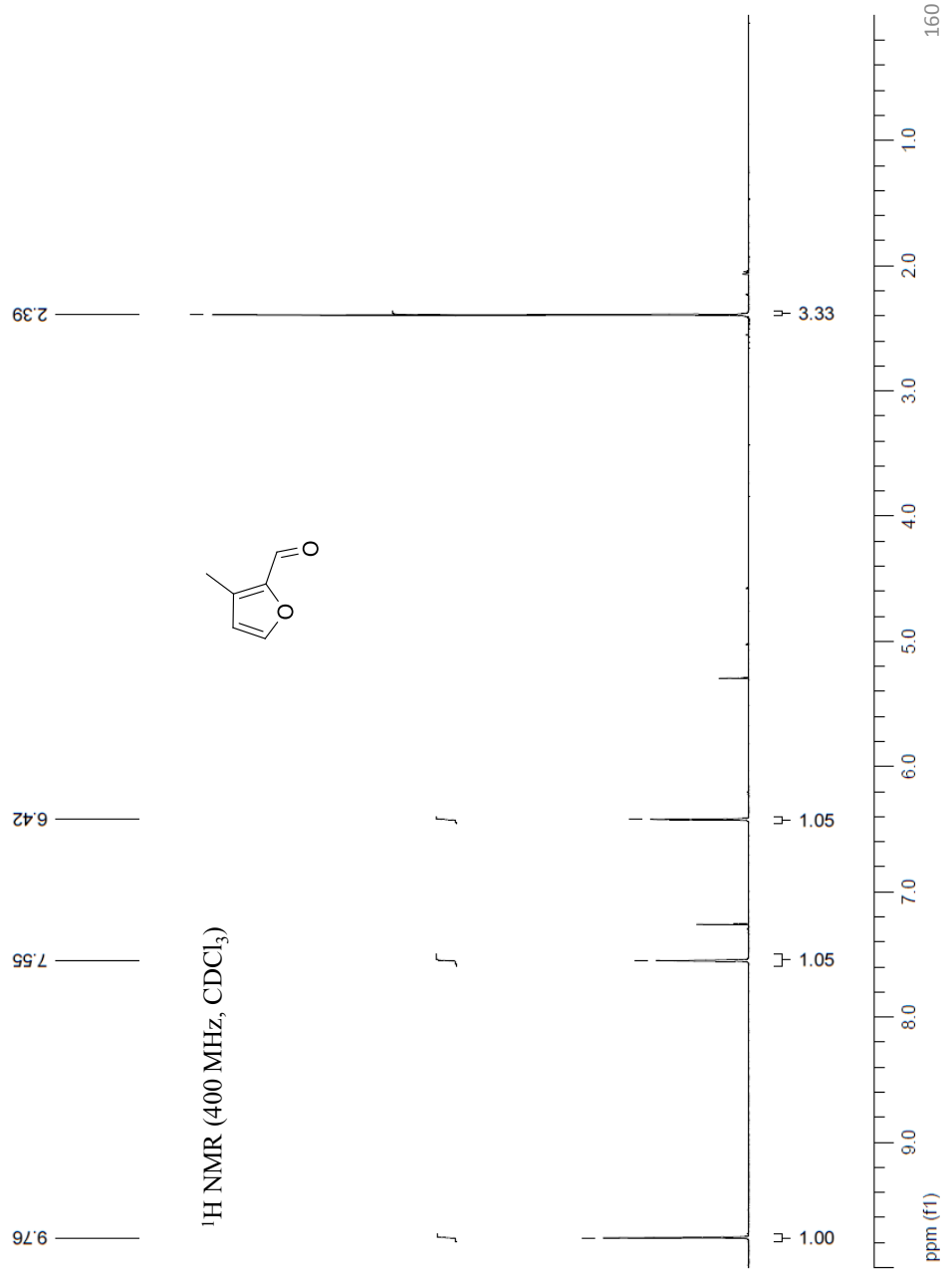
Spectrum 3.50: Compound 123a: ^{13}C NMR



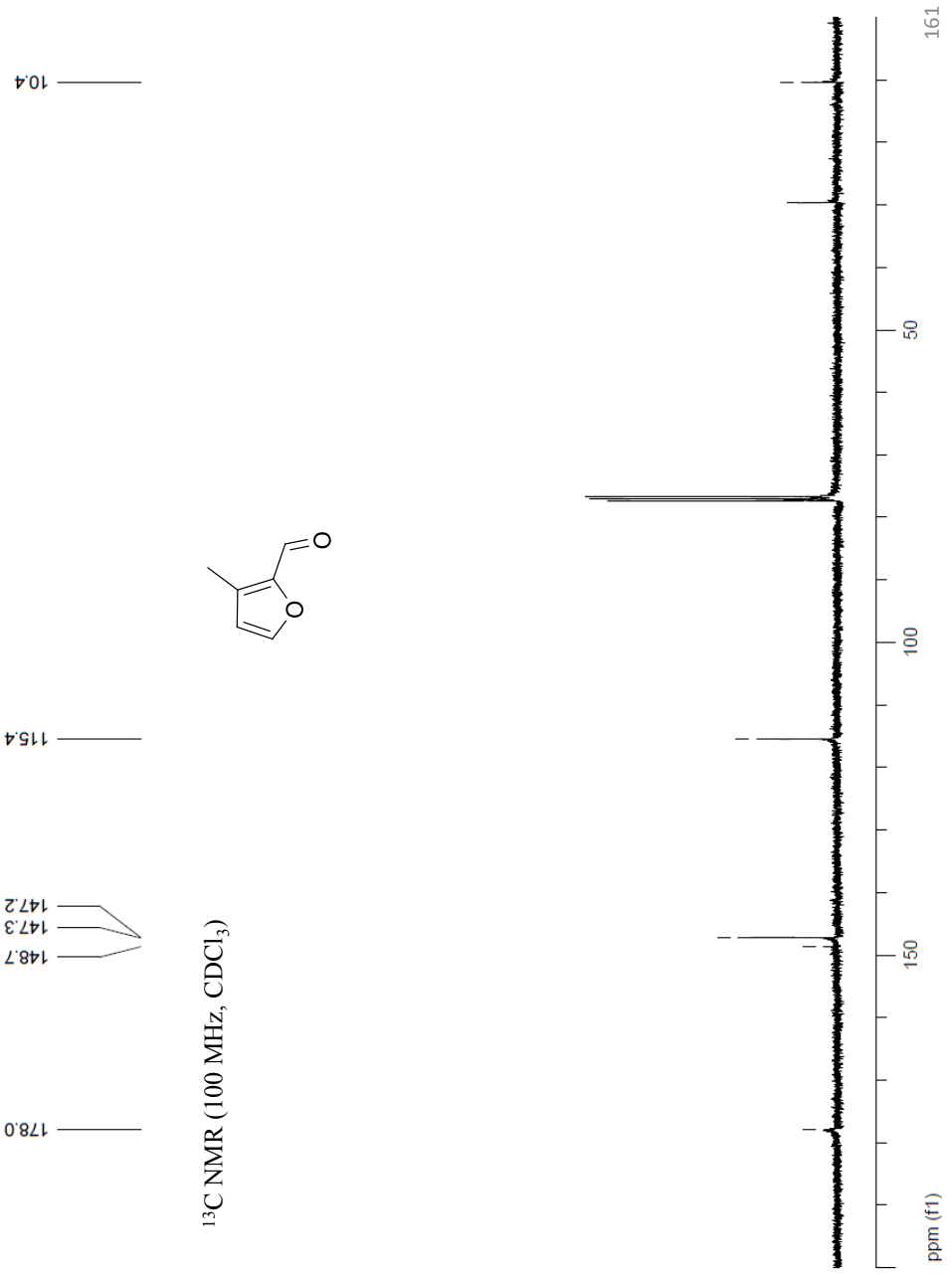
Spectrum 3.51: Compound 123b: ^{1}H NMR



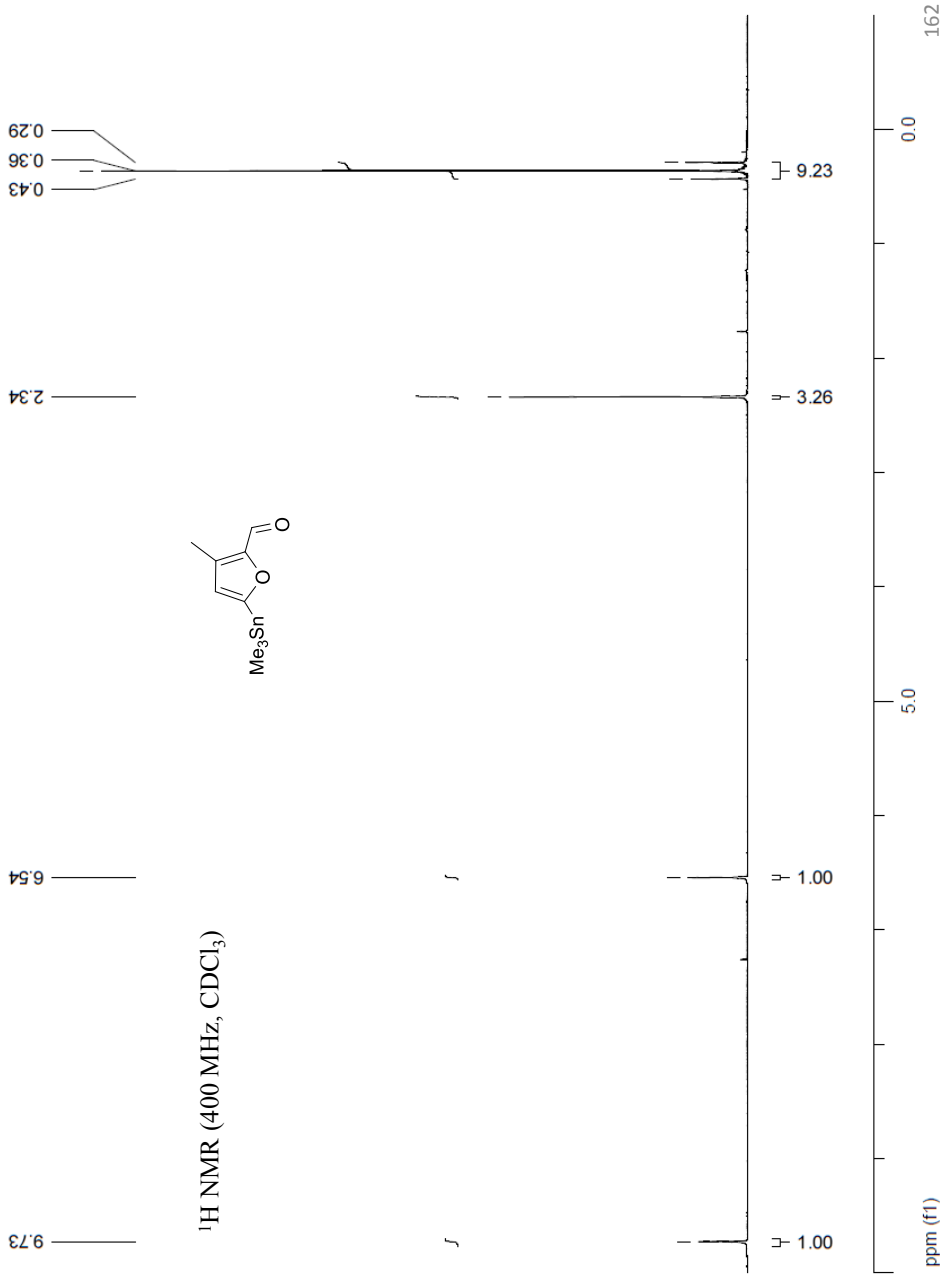
Spectrum 3.52: Compound 123b: ^{13}C NMR



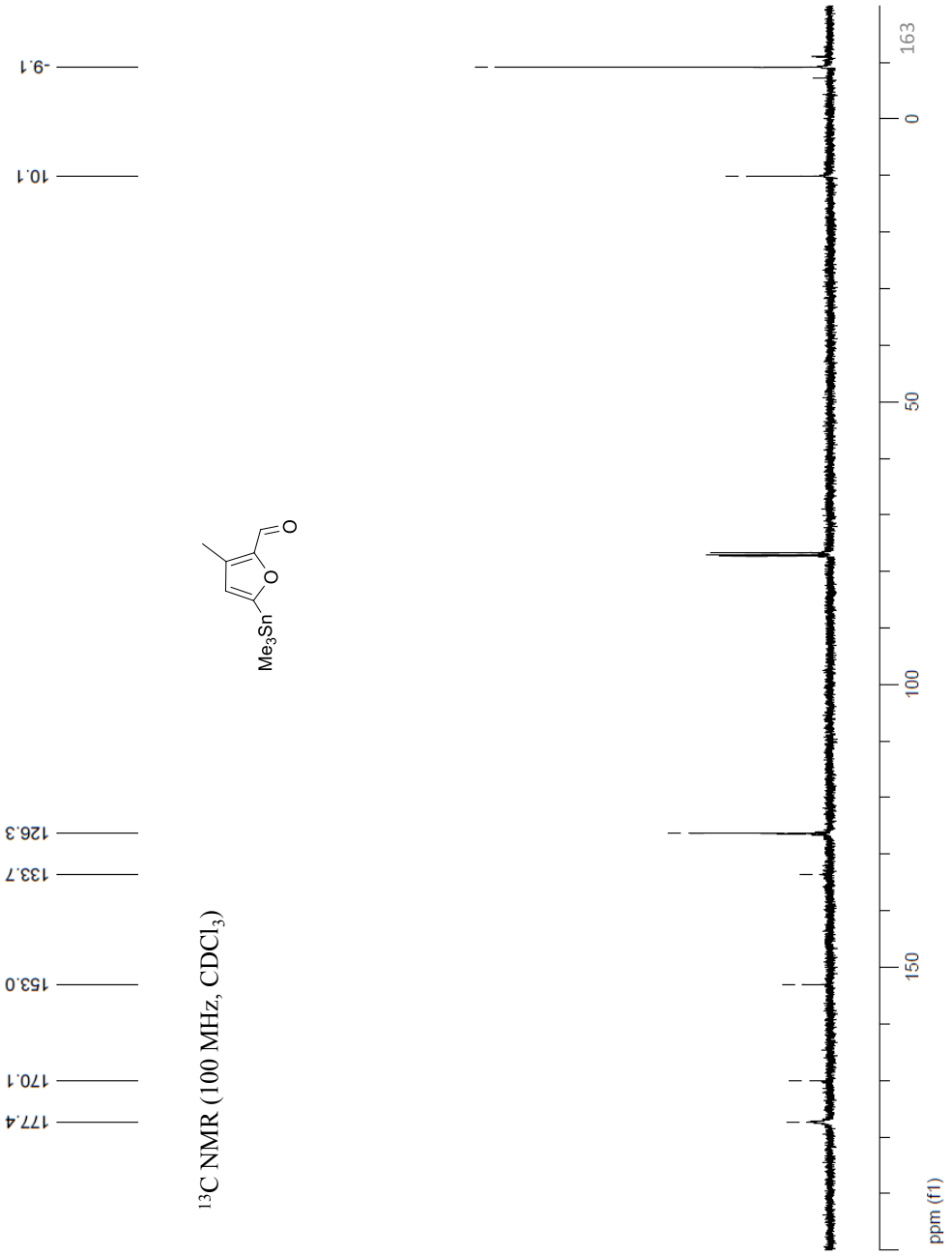
Spectrum 3.53: Compound 125: ^{1}H NMR



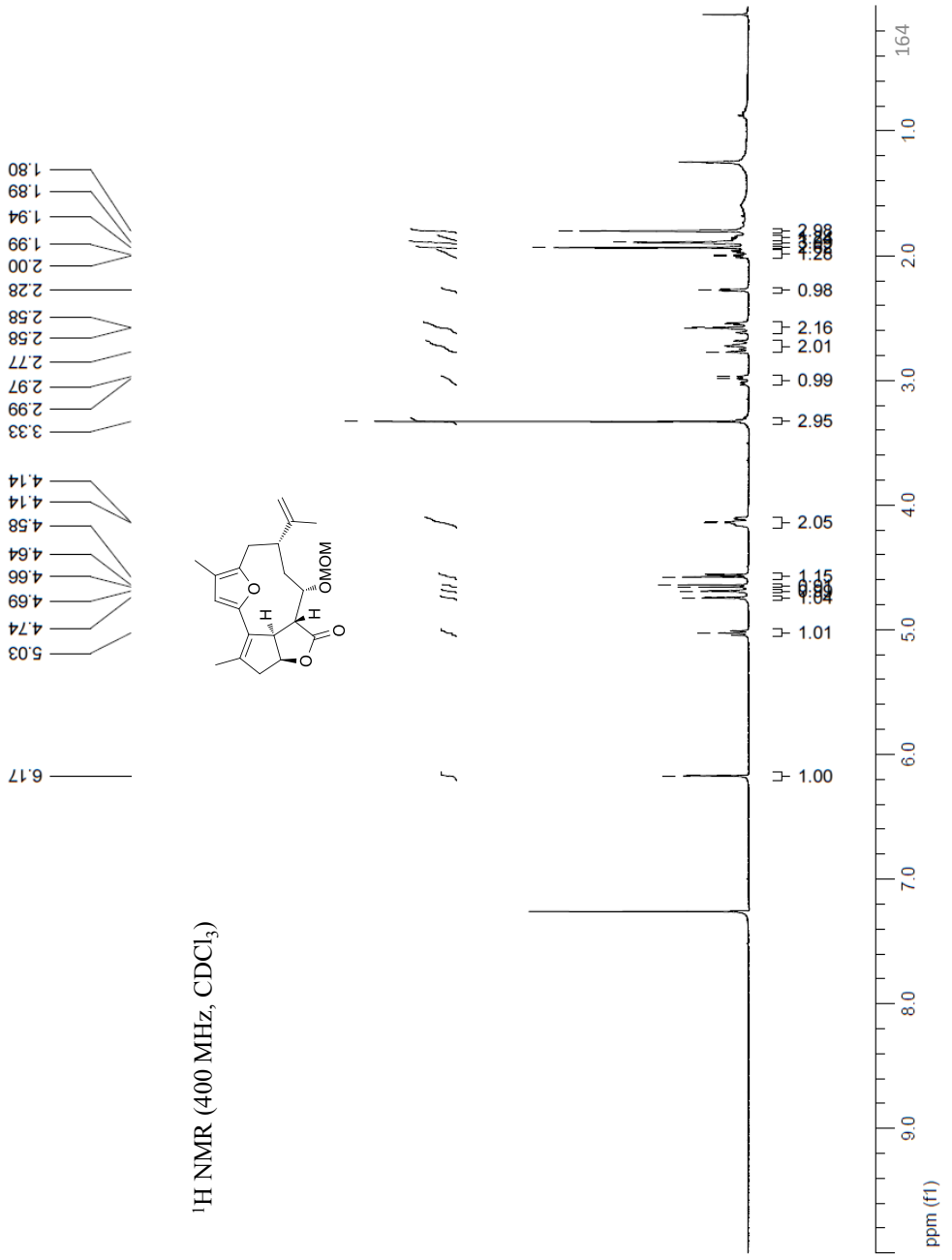
Spectrum 3.54: Compound 125: ^{13}C NMR



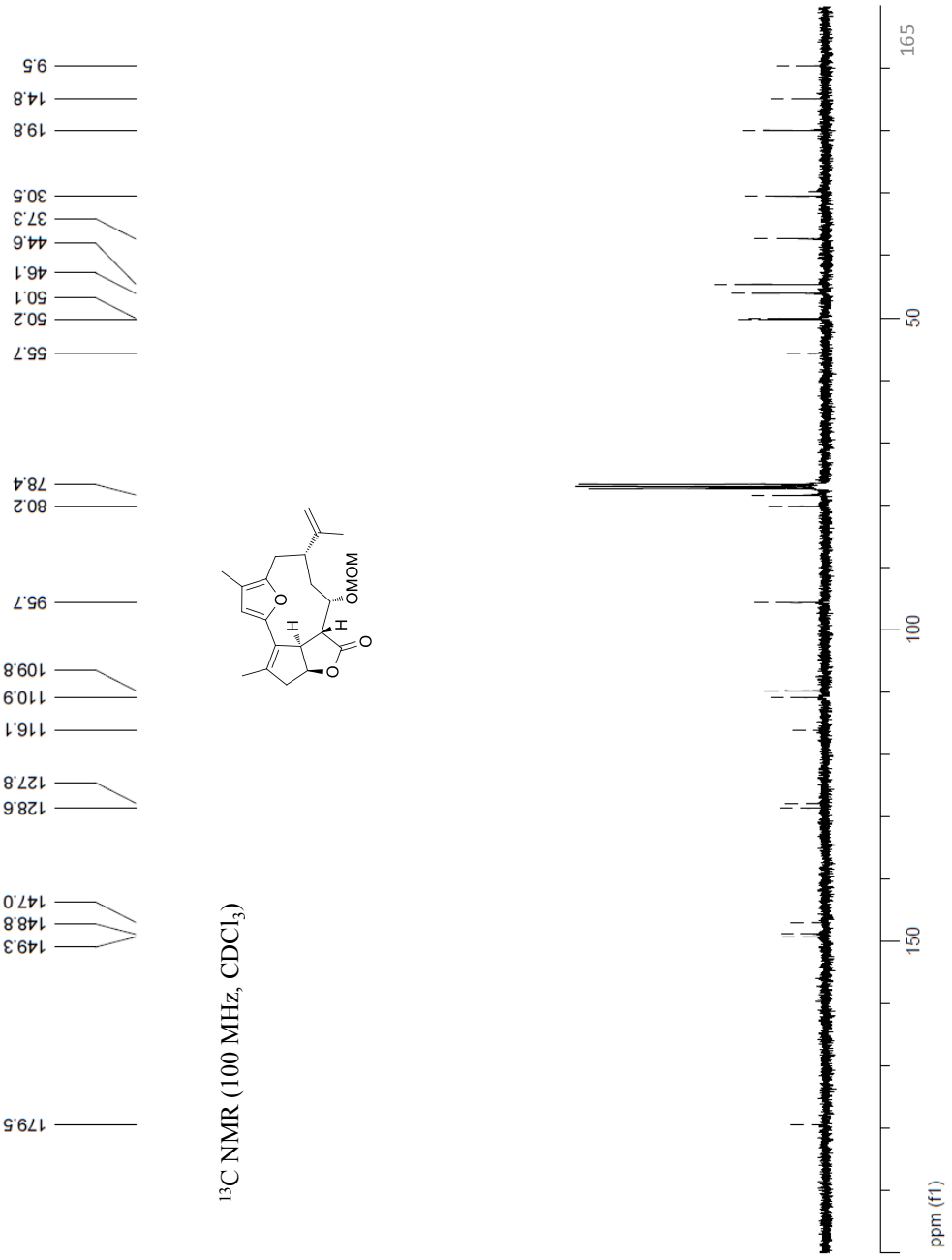
Spectrum 3.55: Compound 26: ^{1}H NMR



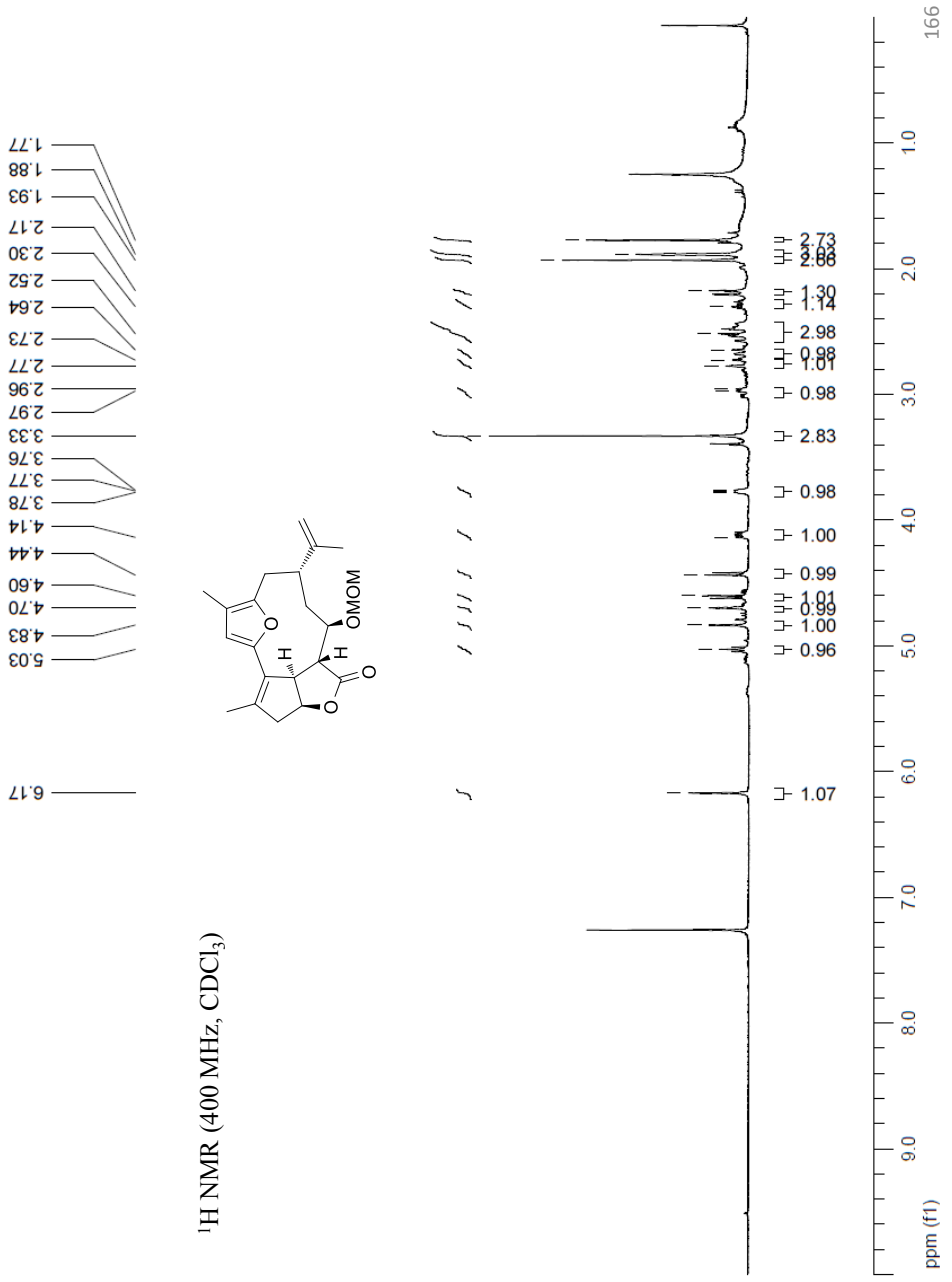
Spectrum 3.56: Compound 26: ^{13}C NMR



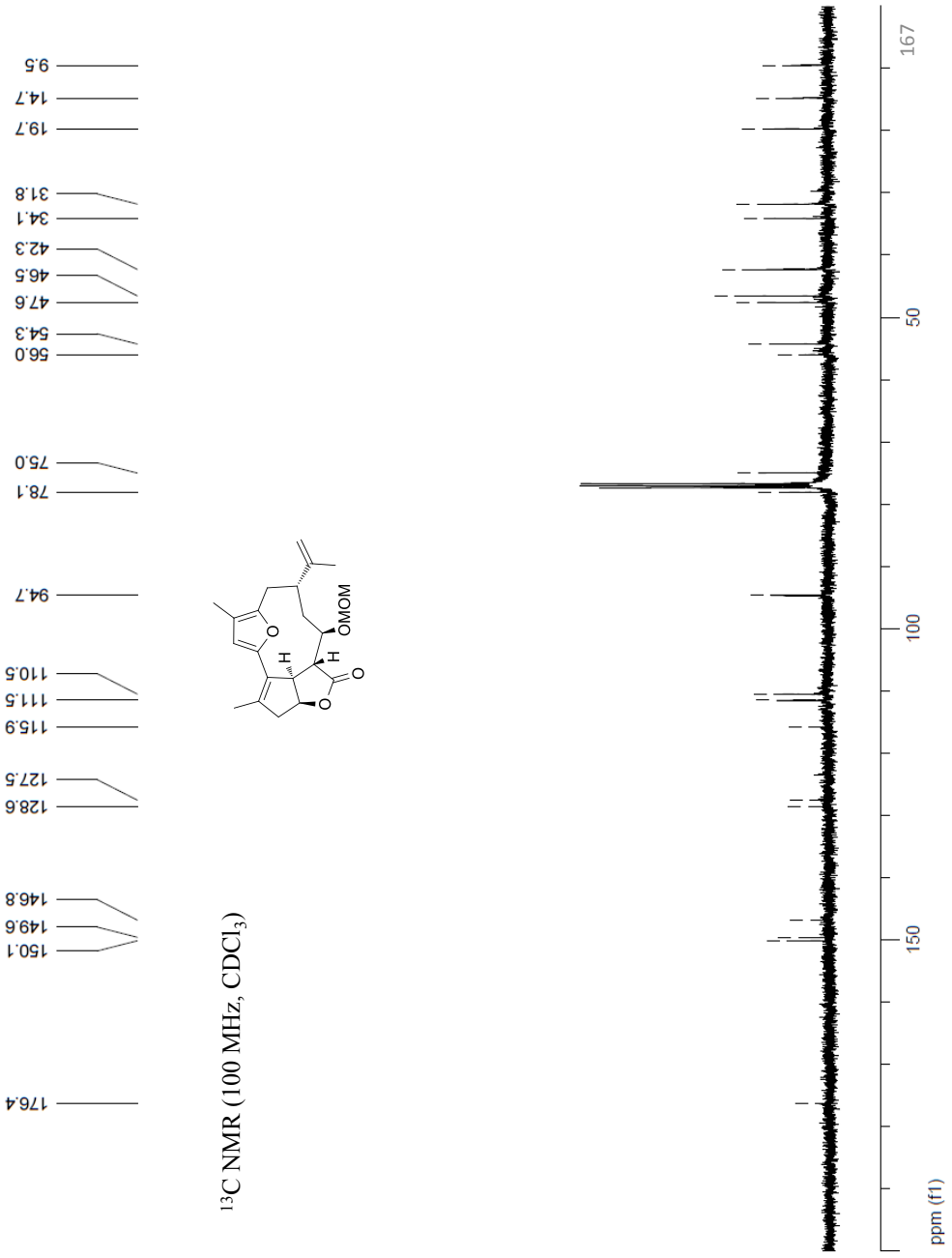
Spectrum 3.57: Compound 127a: ^{1}H NMR



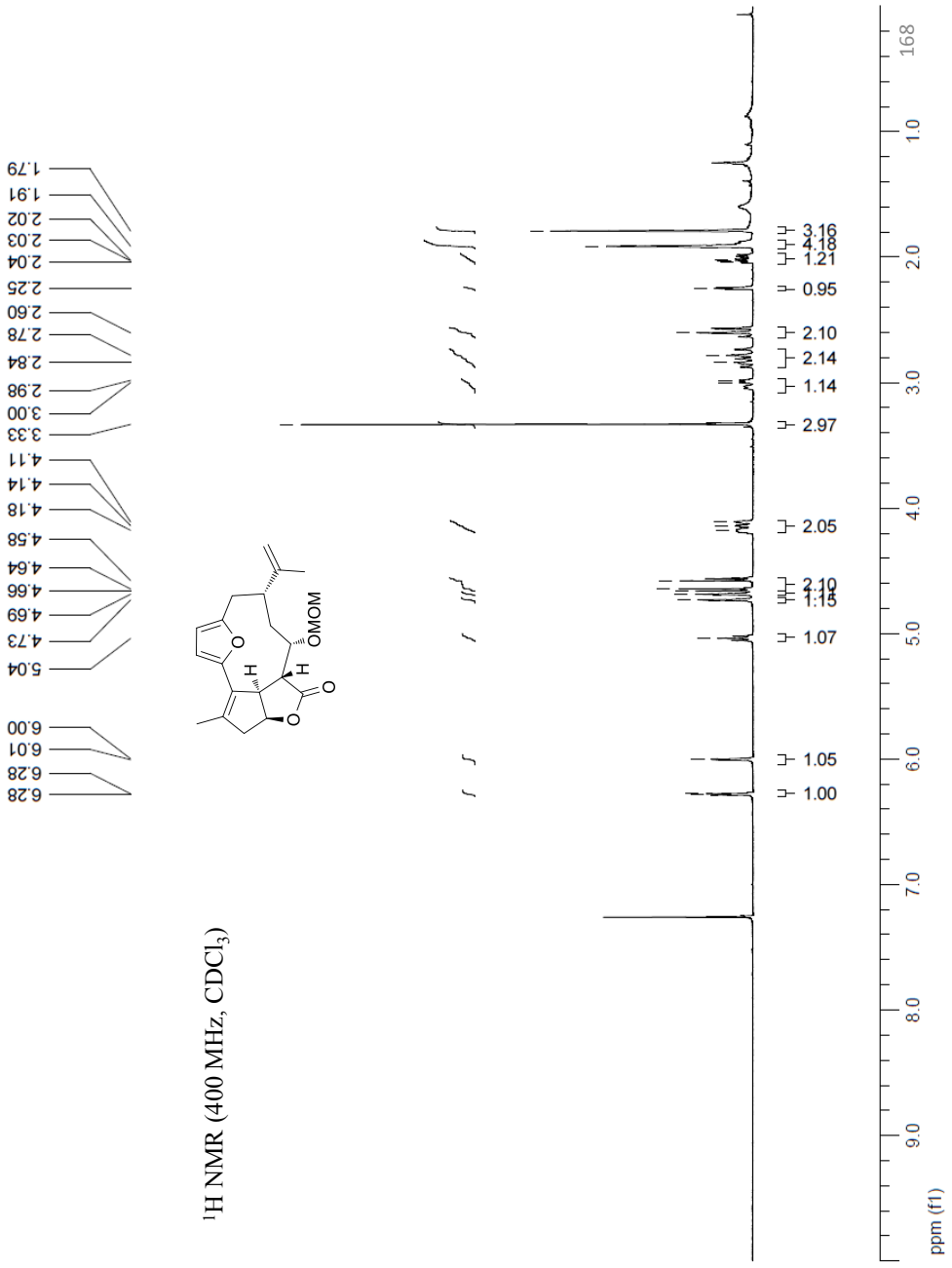
Spectrum 3.58: Compound 127a: ^{13}C NMR



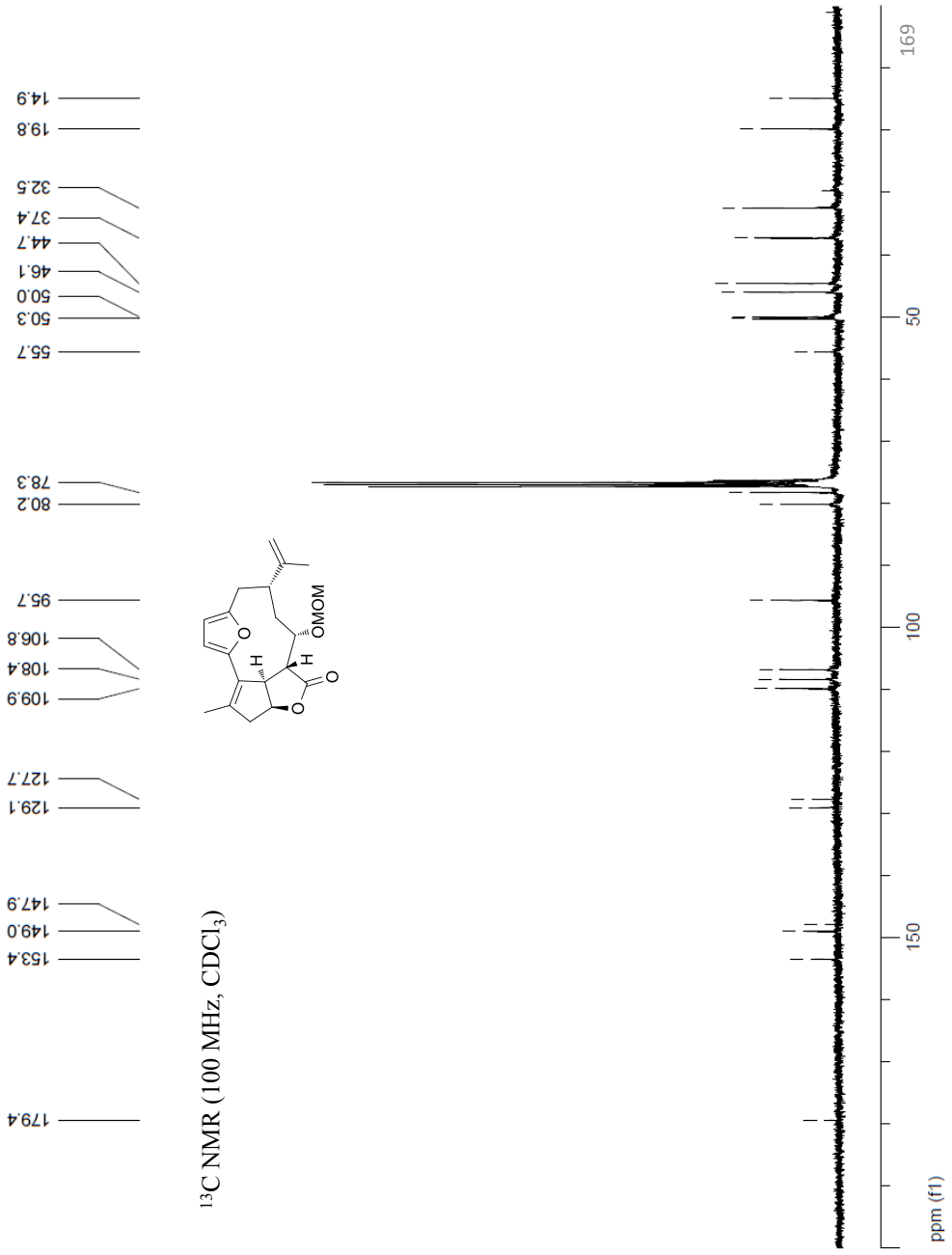
Spectrum 3.59: Compound 127b: ^{1}H NMR



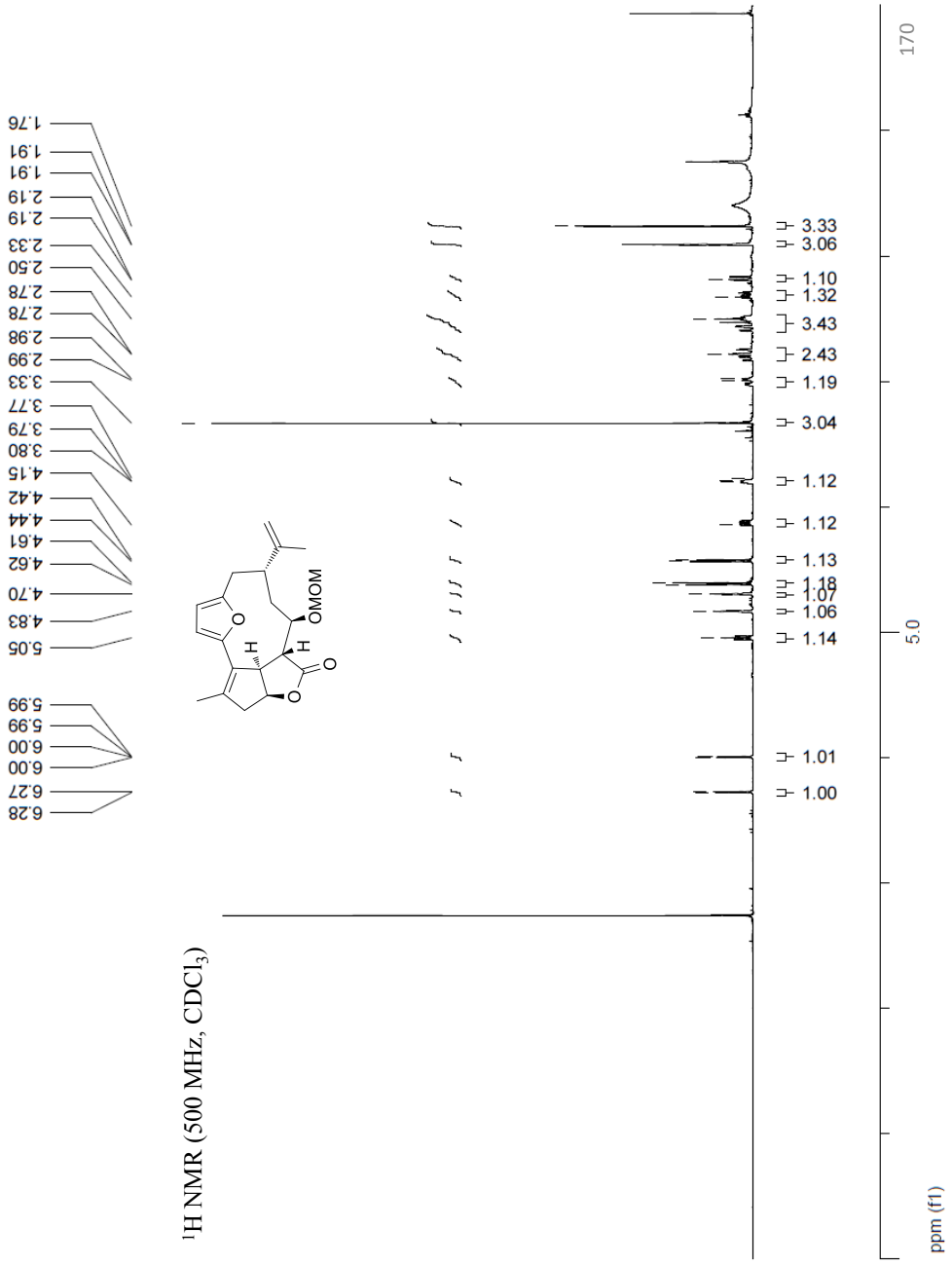
Spectrum 3.60: Compound 127b: ^{13}C NMR



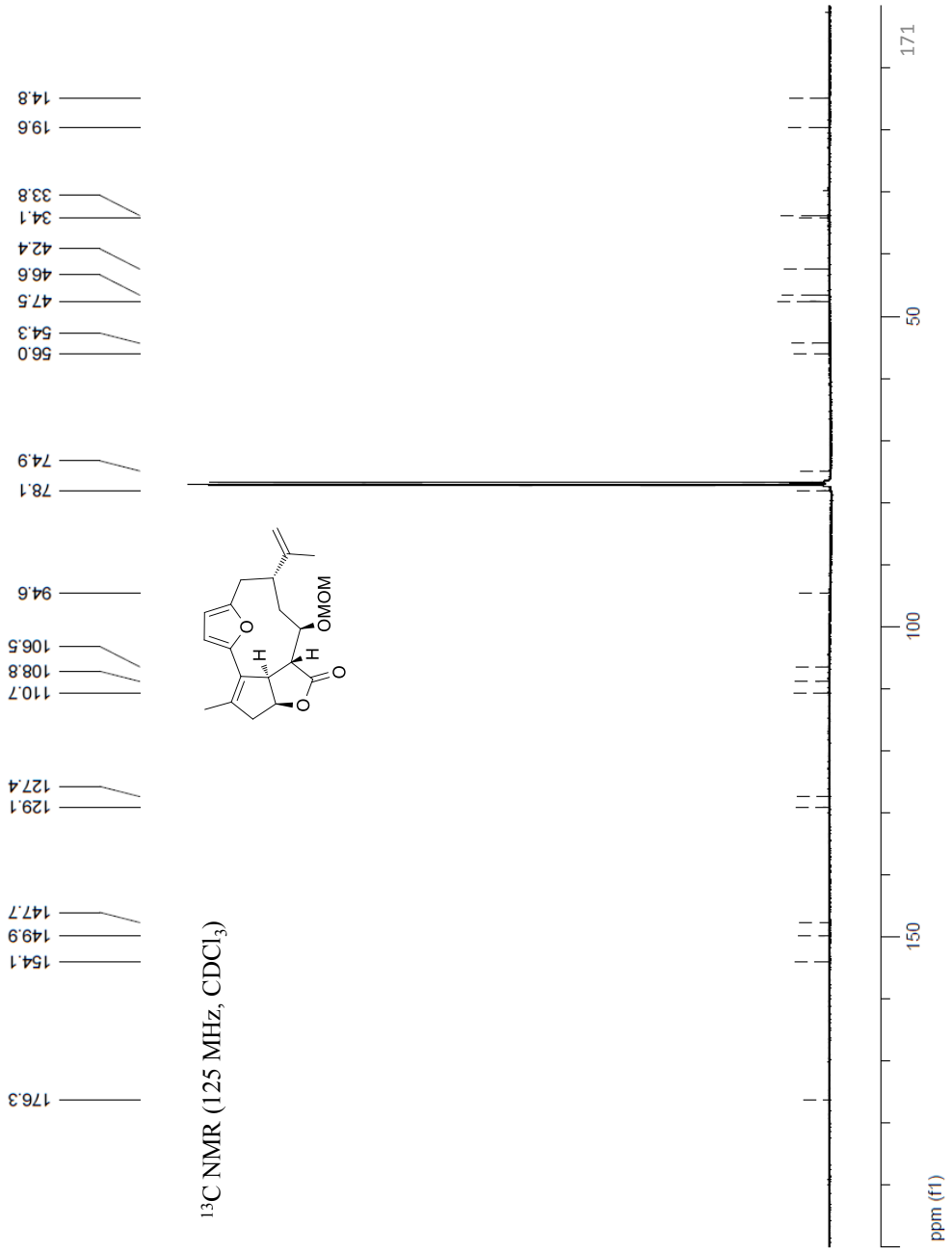
Spectrum 3.61: Compound 128a: ^{1}H NMR



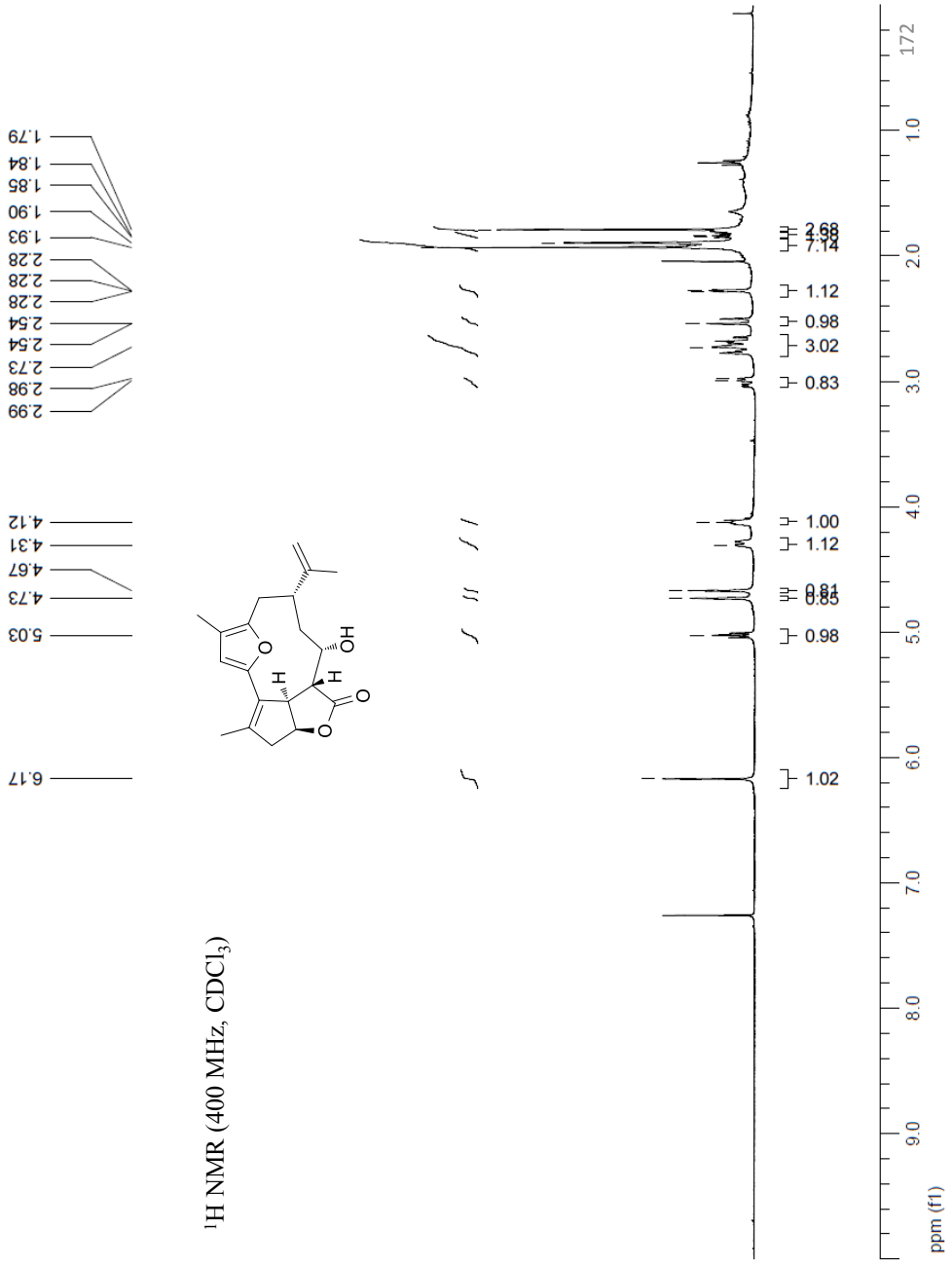
Spectrum 3.62: Compound 128a: ^{13}C NMR



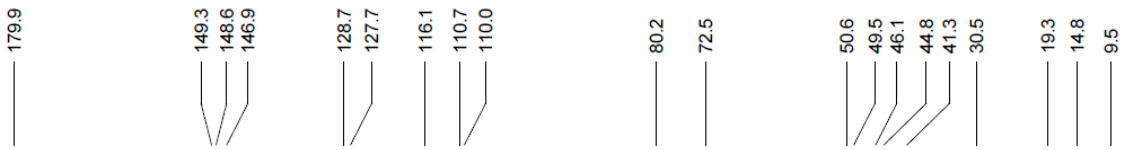
Spectrum 3.63: Compound 128b: ^{1}H NMR



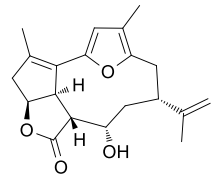
Spectrum 3.64: Compound 128b: ^{13}C NMR

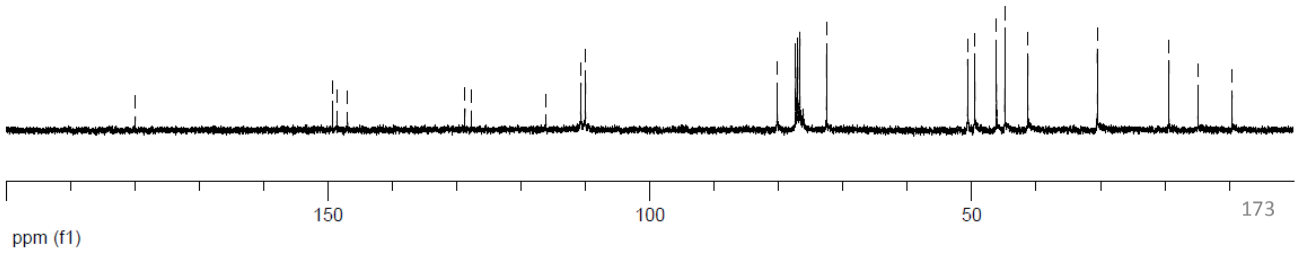


Spectrum 3.65: Compound 129a: ^{1}H NMR

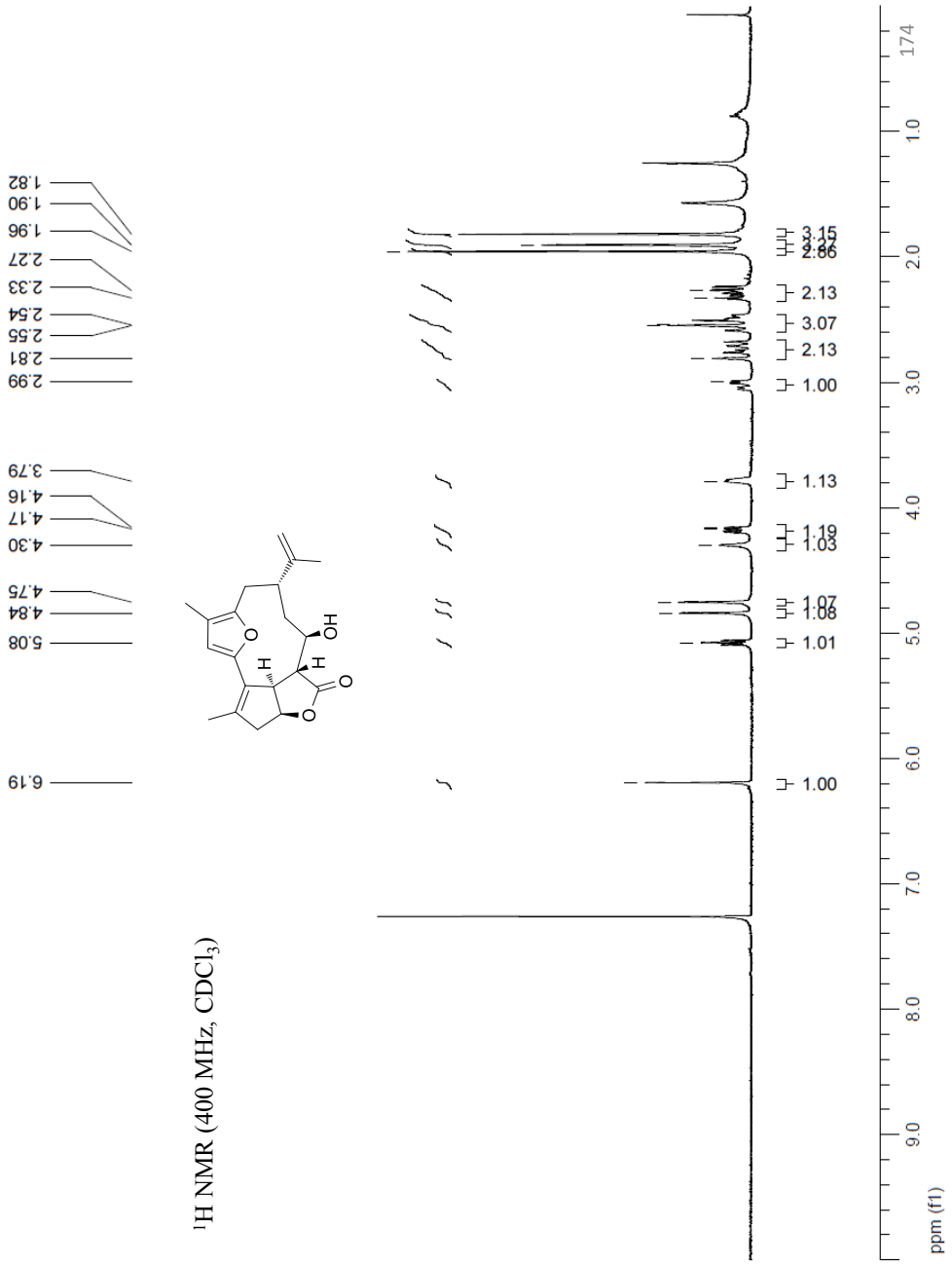


^{13}C NMR (100 MHz, $CDCl_3$)

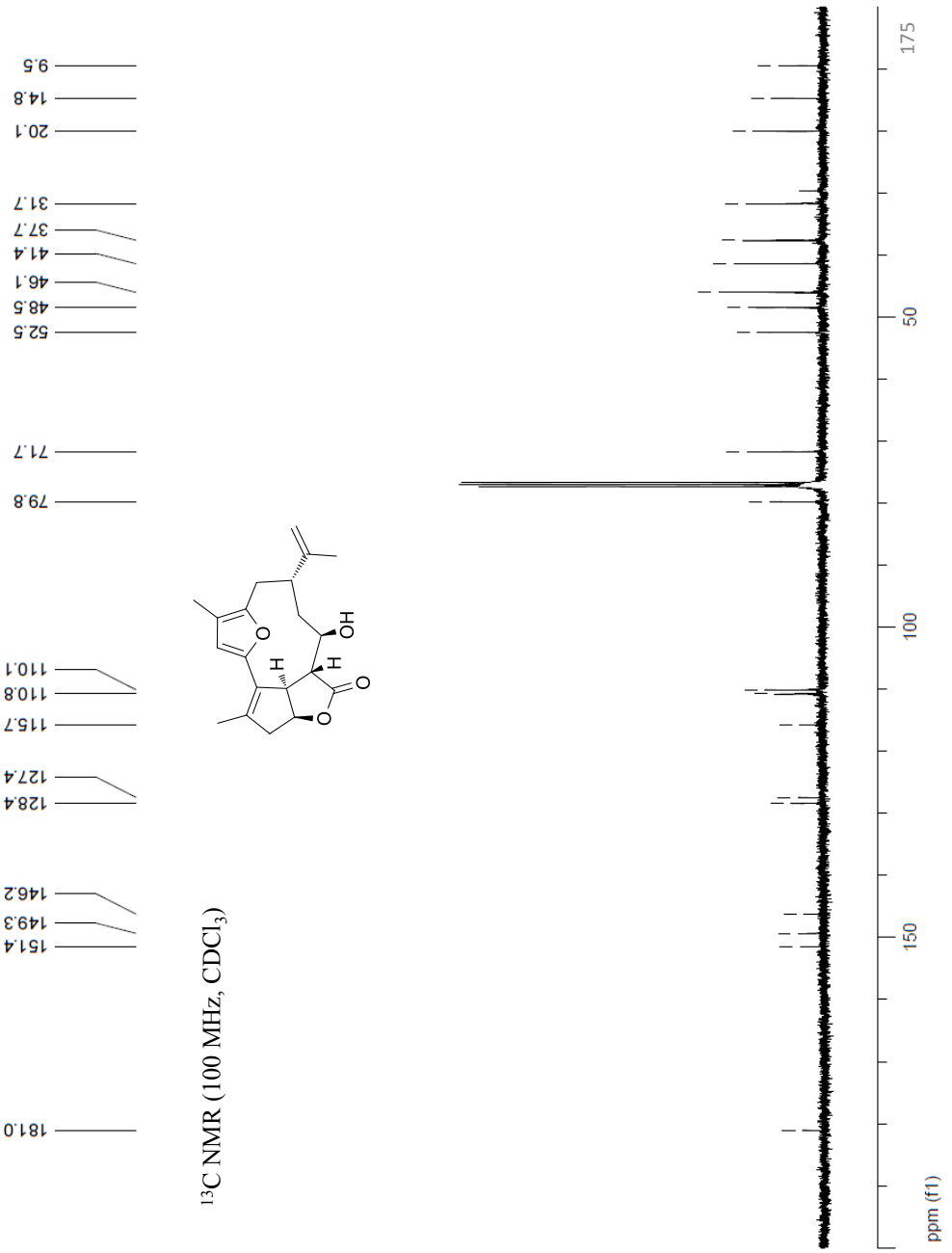




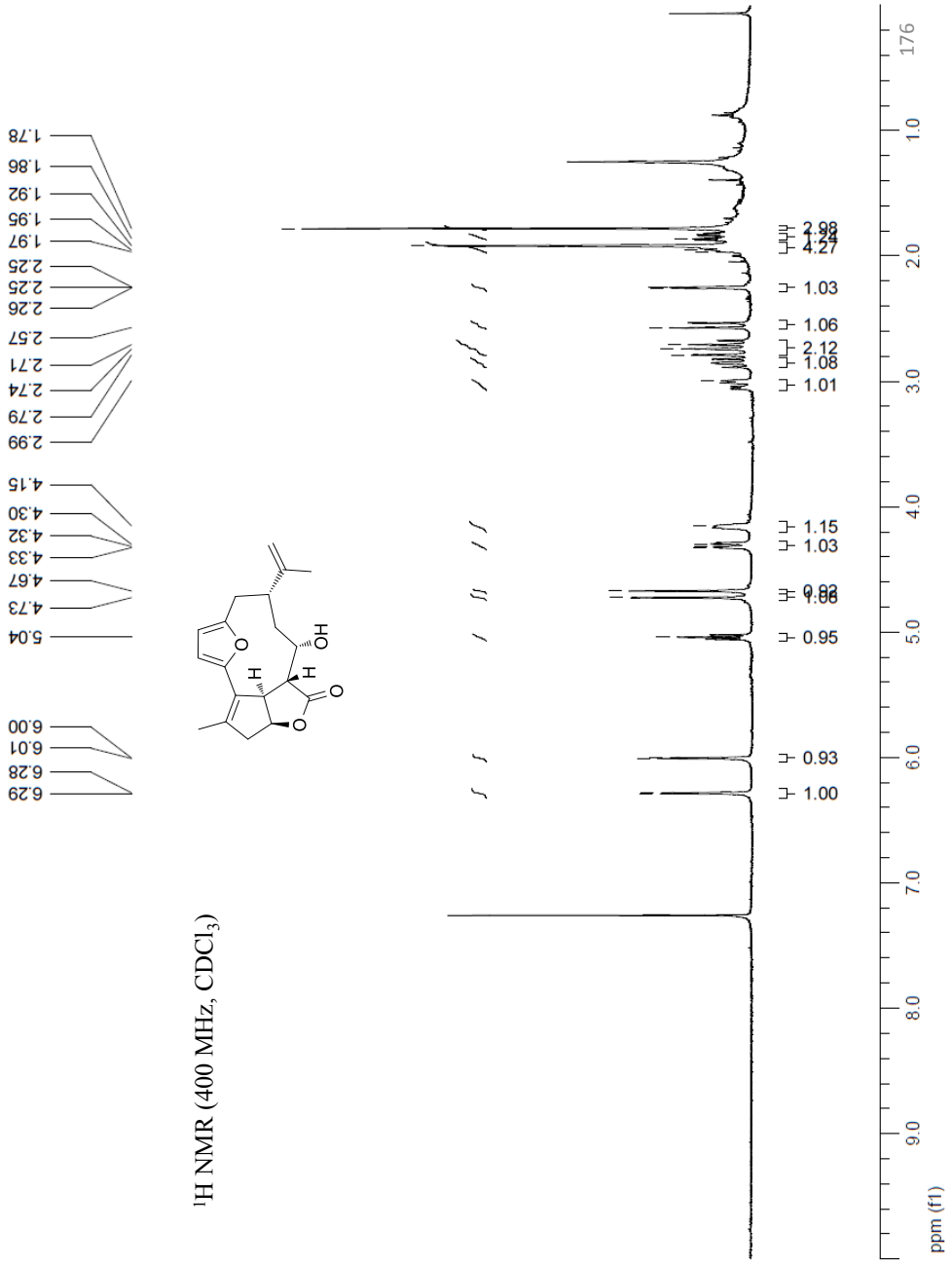
Spectrum 3.66: Compound 129a: ^{13}C NMR



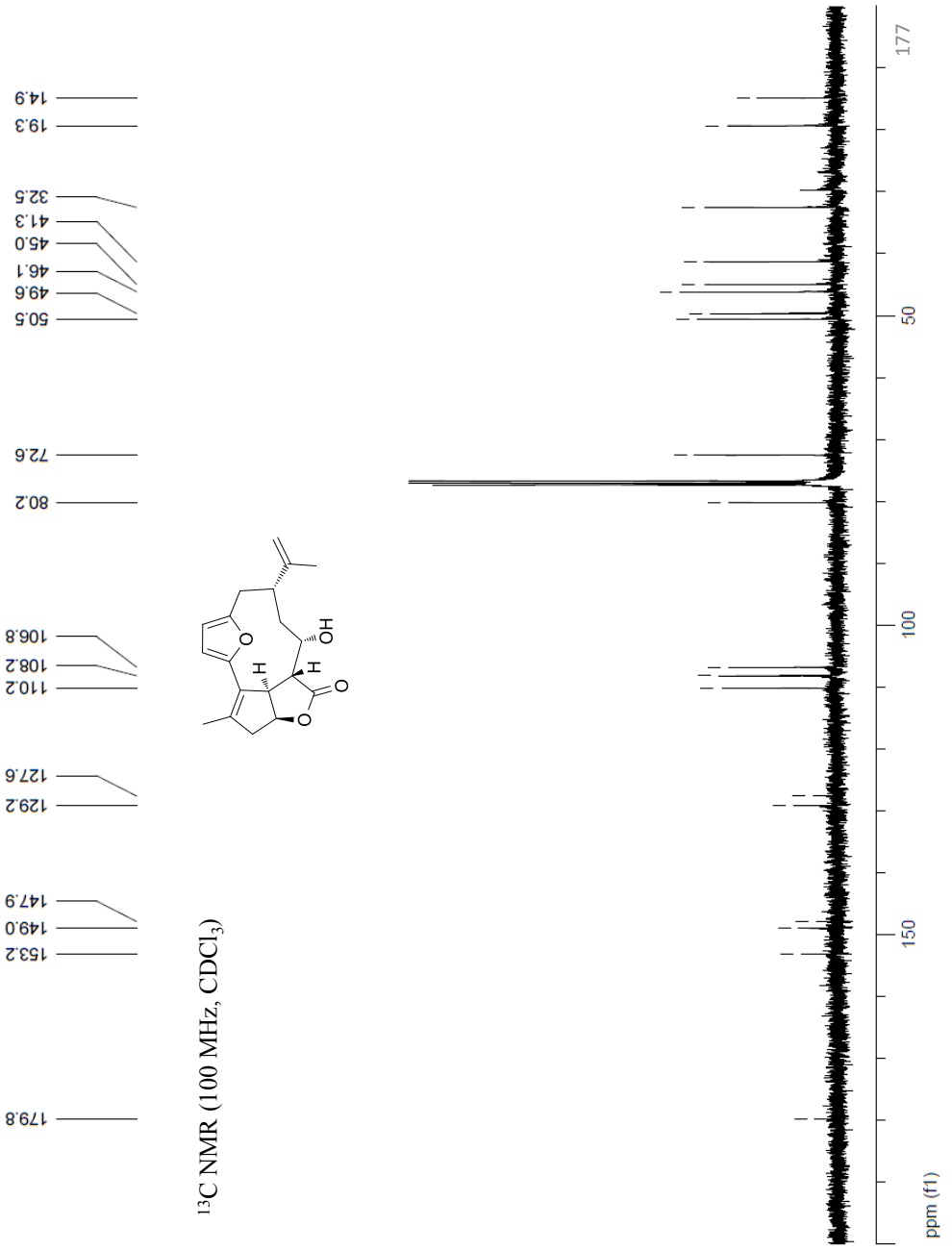
Spectrum 3.67: Compound 129b: ^{1}H NMR



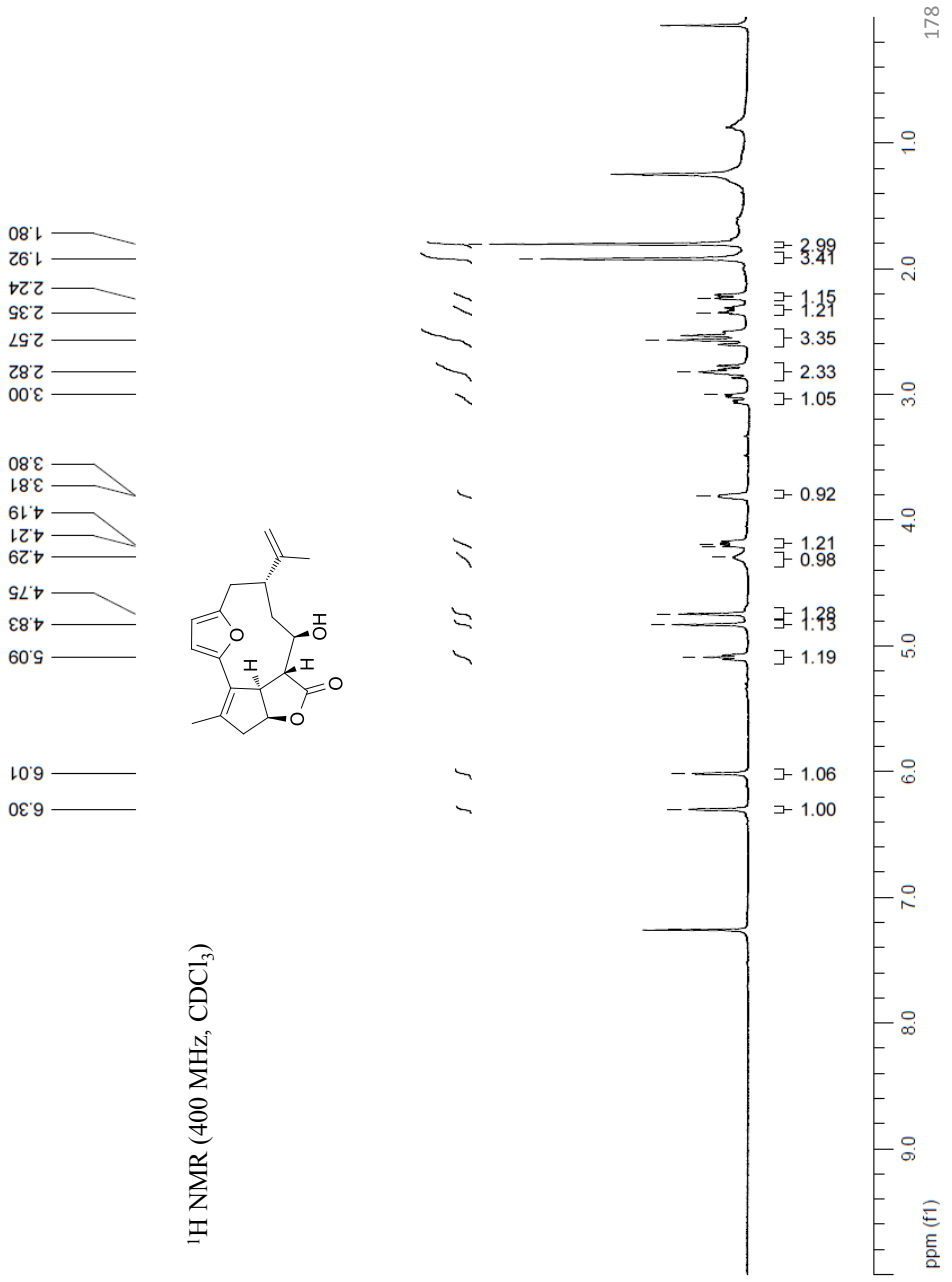
Spectrum 3.68: Compound 129b: ^{1}C NMR



Spectrum 3.69: Compound 130a: ^{13}H NMR

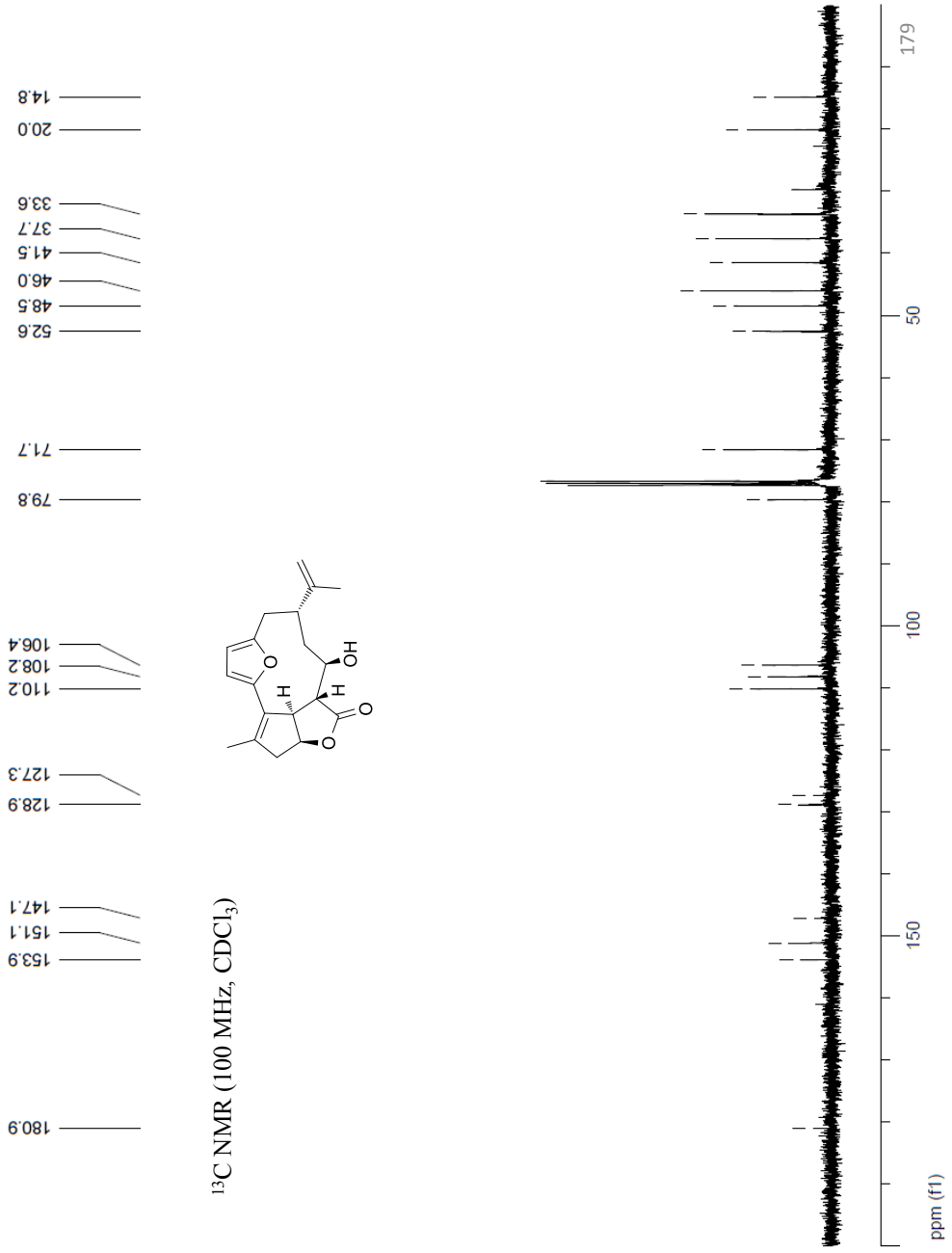


Spectrum 3.70: Compound 130a: ^{1}C NMR



Spectrum 3.71: Compound 130b: ^{13}H NMR

This chapter, in full, has been submitted for publication. Saitman, A.; Theodorakis, E. A. Synthesis of a highly functionalized core of verrillin. *Org Lett*. **2013**, *15*, 2410-2413. The dissertation author was the primary author and investigator of this material.



Spectrum 3.72: Compound 130b: ^{1}C NMR

Chapter 4

Conclusions

4.1 Conclusion

In conclusion, particular norcembrenolide and cembrenolide natural products of soft corals and octocorals have been targeted and synthesized systematically.[25,56,89] The first generational synthesis involved the total synthesis of the natural products norcembrenolide B (**2**) and scabrolide D (**3**).[25] This synthesis follows a biomimetic approach in which proposed oxidation patterns are synthetically adopted to produce the new scaffolds present in the aforementioned targets. A second generation synthesis of cembrenolides was developed involving the incorporation of additional C_{13} hydroxylation. This allows for the access to a class of more complex scaffolds such as lophotoxin (**64**)[45] and bipinnatolide F (**65**).[46] The successful synthesis of C_{13} hydroxylated analogues created two epimermic alcohols at the C_{13} center. Oxidation of the furan moieties of these of C_{13} hydroxylated analogues yielded two strikingly different cyclization products **85** and **86**,[56] product **85** of which exhibits high similarities to the natural product bipinnatolide F (**65**). We recognized that the structural intricacy of synthetically interesting unsynthesized cembrenolides not only contained a level of C_{13} oxidation, but also consisted of various ring contractions of the carbon framework. Our third generation capitalized on these structural motifs with the concept of constructing the framework of the verrillane core **104** prior to the macrocyclization event.[89] A number of furano-verrillin analogues were produced along with their nor-analogues the latter of which displayed a higher degree of stability. This difference in stability affected by a seemingly innocuous

methyl group,[89] further supports its importance in the enzymatic oxidation and cyclization, which occurs in many of these complex substrates.

Chapter 5

References

1. Van Ofwegen, L. P. *International Coral Reef Symposium.* **2000**, *1*, 167-171.

2. Jeng, M-S.; Huang, H-D.; Dai, C-F.; Hsiao, Y-C.; Benayahu, Y. *Coral Reefs*.**2011**,*30*, 925-933.

3. Kamel, H. N.; Slattery, M. *Pharmac. Biol.* **2005***, 43*, 253-269.

4. Abramson, S. N.; Fenical, W.; Taylor, P. *Drug. Dev. Res.* **1991***, 24,* 297-312.

5. Su, J-H.; Wen, Z-H. *Mar. Drugs*. **2011***, 9*, 944-951.

6. Roethle, P. A.; Trauner, D. *Nat. Prod. Rep.* **2008**, *25*, 298-317.

7. Lakshmi, V.; Kumar, R. *Nat. Prod. Res*. **2009**, *23*, 801-850.

8. Li, Y.; Pattenden, *G. Nat. Prod. Rep*. **2011**, *28*, 429-440.

9. Li, Y.; Pattenden, G. *Nat. Prod. Rep*. **2011**, *28*, 1269-1310.

10. Williams, D.; Andersen, R. J.; VanDuyne, G. D.; Clardy, J. *J. Org. Chem*. **1987**, *52*, 332-335.

11. Rodriguez, A. D.; Shi, J-G. *J. Org. Chem*. **1998**, *63*, 420-421.

12. D'Ambrosio, M.; Fabbri, D. A.; Pietra, F. *Helv. Chim. Acta*. **1987**, *70*, 63-70.

13. Sato, A.; Fenical, W.; Qi-tai, Z.; Clardy, J. *Tetrahedron* **1985**, *41*, 4303-4308.

14. Ahmed, A. F.; Su, J-H.; Kuo, Y-H.; Sheu, J-H. *J. Nat. Prod*. **2004**, *67*, 2079-2082.

15. Cheng, S-Y.; Chuang, C-T.; Wen, Z-H.; Wang, S-K.; Chiou, S-F.; Hsu, C-H.; Dai, C-F.; Duh, C-Y. *Bioorg. Med. Chem.* **2010**, *18*, 3379-3386.

16. Bowden, B. F.; Coll, J. C.; Mitchell, S. J.; Mulder, J.; Stokie, G. J. *Aust. J. Chem*. **1978**, *31*, 2049-2056.

17. Takaki, H.; Koganemaru, R.; Iwakawa, Y.; Higuchi, R.; Miyamoto, T. *Bio. Pharm. Bull.* **2003**, *26*, 380-382.

18. Liang, C-H.; Wang, G-H.; Chou, T-H.; Wang, S-H.; Lin, R-J.; Chan, L-P.; So, E. C.; Sheu, J-H. *Biochim. Biophys. Acta.* **2012**, *18*, 1149-1157.

19. Dewick, P. M. *Nat. Prod. Rep.* **2002**, *19*, 181-222.

20. Kimbrough, T. J.; Roethle, P. A.; Mayer, P.; Trauner, D. *Angew. Chem., Int. Ed*. **2010**, *49*, 2619-2621.

21. Roethle, P. A.; Trauner, D. *Org. Lett*. **2006**, *8*, 345-347.

22. Huang, Q.; Rawal, V. H. *Org. Lett*. **2006**, *8*, 543-545.

23. Ma, S.; Negishi, E. *J. Org. Chem.* **1997**, *62*, 784-785.

24. Dess, D. B.; Martin, J. C. *J. Org. Chem*. **1983**, *48*, 4155-4156.

25. Saitman, A.; Rulliere, P.; Sullivan, S. D. E.; Theodorakis, E. A. *Org. Lett*. **2011**, *13*, 5854-5857.

26. Johansson, M.; Kopcke, B.; Heidrun, A.; Sterner, O. *Tetrahedron*. **2002**, *58*, 2523-2528.

27. Trost, B. M.; Toste, F. D. *Tetrahedron Lett.* **1999**, *40*, 7739-7743.

28. Diwischek, F.; Morschhauser, J.; Holzgrabe, U. *Arch. Pharm. Chem. Life Sci.* **2009**, *342*, 150-164.

29. Appel, R. Angew. *Chem. Int. Ed*. **1975**, *14*, 801-811.

30. Paquette, L. A.; Astles, P. C. *J. Org. Chem*. **1993**, *58*, 165-169.

31. Rayner, C. M.; Astles, P. C.; Paquette, L. A. *J. Am. Chem. Soc*. **1992**, *114*, 3926-3936.

32. CCDC 831510 (**2**), 831515 (**3**), 831511 (**29**), 831516 (**39**), 831509 (**40**), 831512 (**42**), 831513 (**46**), 831514 (**47**), 888993 (**48**), 889637 (**49**), 931793 (**53**), 888992 (**67**), 888994 (**83b**), 905462 (**85**), 905463 (**86**), 929062 (**123a**) and 929063 (**130b**) contain the supplementary crystallographic data. This information can be obtained free of charge from the Cambridge Crystallographic Data Centre via www. ccdc.cam.ac.uk/products/-csd/request/. In the figures, some hydrogen atoms have been removed for clarity.

33. Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis*. **1974**, *9*, 633-651.

34. VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron*. **1976**, *17*, 1973-1976.

35. Nomura, S.; Sakamaki, S.; Hongu, M.; Kawanishi, E.; Koga, Y.; Sakamoto, T.; Yamamoto, Y.; Ueta, K.; Kimata, H.; Nakayama, K.; Tsuda-Tsukimoto, M. *J. Med. Chem*. **2010**, *53*, 6355-6360.

36. Hayes, S. J.; Knight, D. W.; Smith, A. W. T.; O'Halloran, M. J. *Tetrahedron Lett*. **2010**, *51*, 720-723.

37. Yoshimitsu, T; Nojima, S; Hashimoto, M; Tsukamoto, K; Tanaka, T *Synthesis.* **2009**, *17*, 2963-2969.

38. Sheu, J.-H.; Ahmed, A. F.; Shiue, R.-T.; Dai, C.-F.; Kuo, Y.-H. *J. Nat. Prod*. **2002**, *65*, 1904-1908.

39. Yamamoto, H.; Nozaki, H. *Angew. Chem. Int. Ed.* **1978**, *17*, 169-175.

40. Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190-6191.

41. Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28,* 4437-4440.

42. Lee, J-C.; Tai, C-A., H, S-C. *Tetrahedron Lett.* **2002**, *43,* 851-855.

43. Araki, T.; Ozawa, T.; Yokoe, H.; Kanematsu, Yoshida, M.; Shishido, K. *Org. Lett.* **2013**, *15*, 200-203.

44. Collington, E. W.; Finch, H.; Smith, I. J. *Tetrahedron Lett.* **1985**, *26*, 681-684.

45. Fenical, W.; Okuda, R. K.; Bandurraga, M. M.; Culver, P.; Jacobs, R. S. *Science.* **1981**, *212*, 1512-1514.

46. Rodriguez, A. D.; Shi, J. G.; Huang, S. D. *J. Nat. Prod*. **1999**, *62*, 1228-1237.

47. Sadoul, K.; Boyault, C.; Pabion, M.; Khochbin, S. *Biochimie.* **2008**, *90*, 306-312.

48. Herrmann, A. T.; Saito, T.; Stivala, C. E.; Tom, J.; Zakarian, A. *J. Am. Chem. Soc.* **2010**, *132*, 5962-5963.

49. Wipf, P.; Soth, M. J. *Org. Lett*. **2002**, *4*, 1787-1790.

50. Lin, L.; Zhao, Q. Y.; Li, A. N.; Ren, F. B.; Yang, F. Z.; Wang, R. *Org. Biomol. Chem*. **2009**, *7*, 3663-3665.

51. Jian, Y. J.; Wu, Y. K. *Org. Biomol. Chem*. **2010**, *8*, 811-821.

52. Tang, B.; Bray, C. D.; Pattenden, G. *Org. Biomol. Chem*. **2009**, *7*, 4448-4457.

53. Cases, M.; de Turiso, F. G. L.; Pattenden, G. *Synlett*. **2001**, *3*, 1869-1872.

54. Negishi, E.; Ma, S. M.; Sugihara, T.; Noda, Y. *J. Org. Chem*. **1997**, *62*, 1922-1923.

55. Andresen, G.; Eriksen, A. B.; Dalhus, B.; Gundersen, L. L.; Rise, F. J. *Chem. Soc., Perkin Trans*. *1* **2001**, 1662-1672.

56. Saitman, A.; Sullivan, S. D. E.; Theodorakis, E. A. *Tetrahedron Lett*. **2013**, *54*, 1612-1615.

57. Weinstabl, H.; Gaich, T.; Mulzer, J. *Org. Lett*. **2012**, *14*, 2834-2837.

58. Crouch, R. D. *Tetrahedron.* **2004**, *60*, 5833-5871.

59. Gaynor, J. W.; Brazier, J.; Cosstick, R. *Nucleosides Nucleotides Nucleic acids.* **2007**, *26*, 709-712.

60. Tofi, M.; Koltsida, K.; Vassilikogiannakis, G. *Org. Lett*. **2009**, *11*, 313-316.

61. Montagnon, T.; Tofi, M.; Vassilikogiannakis, G. *Acc. Chem. Res*. **2008**, *41*, 1001-1011.

62. Nicolaou, K. C.; Adsool, V. A.; Hale, C. R. H. *Angew. Chem., Int. Ed*. **2011**, *50*, 5149-5152.

63. Nicolaou, K. C.; Hale, C. R. H.; Ebner, C.; Nilewski, C.; Ahles, C.; Rhoades, D. *Angew. Chem. Int. Ed*. **2012**, *51*, 4726-4730.

64. Thatcher, G. R. J., Ed.; *ACS Symposium Series*. **1993**. Vol. 539.

65. Juaristi, E.; Cuevas, G. *Tetrahedron.* **1992**, *48*, 5019-5087.

66. Marrero, J.; Rodriguez, A. D.; Baran, P.; Raptis, R. G.; Sanchez, J. A.; Ortega-Barria, E.; Capson, T. L. *Org. Lett*. **2004**, *6*, 1661-1664.

67. Duh, C. Y.; Wang, S. K.; Chia, M. C.; Chiang, M. Y. *Tetrahedron Lett*. **1999**, *40*, 6033-6035.

68. Stonik, V. A.; Kapustina, I. I.; Kalinovsky, A. I.; Dmitrenok, P. S.; Grebnev, B. B. *Tetrahedron Lett*. **2002**, *43*, 315-317.

69. Rodriguez, A. D.; Shi, Y. P. J. *Org. Chem*. **2000**, *65*, 5839-5842.

70. Doroh, B.; Sulikowski, G. A. *Org. Lett*. **2006**, *8*, 903-906.

71. Miao, R.; Gramani, S. G.; Lear, M. J. *Tetrahedron Lett*. **2009**, *50*, 1731-1733.

72. Ihara, M.; Taniguchi, T.; Makita, K.; Takano, M.; Ohnishi, M.; Taniguchi, N.; Fukumoto, K.; Kabuto, C. *J. Am. Chem. Soc*. **1993**, *115*, 8107-8115.

73. Ihara, M.; Taniguchi, T.; Tokunaga, Y.; Fukumoto, K. J. *Org. Chem*. **1994**, *59*, 8092-8100.

74. Inanaga, K.; Takasu, K.; Ihara, M. *J. Am. Chem. Soc*. **2005**, *127*, 3668-3669.

75. Mahmoud, M.; Moustafa, A. R.; Pagenkopf, B. L. *Org. Lett.* **2010**, *12,* 4732-4735.

76. Baar, M. R.; Ballesteros, P.; Roberts, B. W. *Tetrahedron. Lett.* **1986**, *27*, 2083-2086.

77. Schollhorn, B.; Mulzer, J. *Chem-Eur. J.* **2012**, *18*, 10480-10486.

78. Marzi, M.; Misiti, D. *Tetrahedron. Lett.* **1989**, *30*, 6075-6076.

79. Nicolaou, K. C.; Sun, Y-P.; Korman, H.; Sarlah, D. *Angew. Chem. Int. Ed*. **2010**, *49*, 5875-5878.

80. Farcet, J.; Himmelbauer, M.; Mulzer, J. *Org. Lett*. **2012**, *14*, 2195-2197.

81. Jana, A.; Mondal, S.; Hossain, M. F.; Ghosh, S. *Tetrahedron Lett*. **2012**, *53*, 6830-6833.

82. Li, Y.; Pattenden, G. *Tetrahedron Lett*. **2011**, *52*, 2088-2092.

83. Palframan, M.; Pattenden, G. *Tetrahedron Lett*. **2013**, *54*, 324-328.

84. Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A. *Helv. Chim. Acta*. **1964**, *47*, 2425-2429.

85. Castro, A. M. M. *Chem. Rev*. **2004**, *104*, 2939-3002.

86. Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc*. **1979**, *99*, 3179-3181.

87. Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, T. *Tetrahedron Lett*. **1983**, *24*, 5281-5284.

88. Furster, A. *Chem. Rev*. **1999**, *99*, 991-1045.

89. Saitman, A.; Theodorakis, E. A. *Org. Lett.* **2013**, *15*, 2410-2414.

90. Kruger, G.; Harde, C.; Bohlmann, F. *Tetrahedron Lett*. **1985**, *49*, 6027-6030.

91. Otero, M. P.; Santin, E. P.; Rodriguez-Barrios, F.; Vaz, B.; De Lera, A. R. *Biorg. Med. Chem. Lett.* **2009**, *19*, 1883-1886.

92. Ramharter, J.; Mulzer, J. *Eur. J. Org. Chem*. **2012**, *2012*, 2041-2053.

93. Mulzer, J.; Giester, G.; Gilbert, M. *Helv. Chim. Acta*. **2005**, *88*, 1560-1579.

94. Lautens, M.; Paquin, J.-F. *Org. Lett*. **2003**, *5*, 3391-3394.

95. Bourcet, E.; Fache, F.; Piva, O. *Tetrahedron.* **2010**, *66*, 1319-1326.

96. Maegawa, T.; Otake, K.; Hirosawa, K.; Goto, A.; Fujioka, H. *Org. Lett*. **2012**, *14*, 4798-4801.

97. Aldington, R. M.; Baldwin, J. E.; Mayweg, A. V. W.; Pritchard, G. J. *Org. Lett*. **2002**, *4*, 3009-3011.

98. Hashami, A. S. K.; Haffner, T.; Yang, W.; Pankajakshan, S.; Schafer, S.; Schultes, L.; Rominger, F.; Frey, W. *Eur. J. Org. Chem*. **2012**, *18*, 10480-10486.

99. Farina, V.; Krishnan, B. *J. Am. Chem. Soc*. **1991**, *113*, 9585-9595.

100. Farina, V.; Kapadia, S.; Krishman, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem*. **1994**, *59*, 5905-5911.

101. Roth, G. P.; Farina, V. *Tetrahedron Lett*. **1995**, *36*, 2191-2194.

102. Maguire, R. J.; Mulzer, J.; Bats, J. W. *Tetrahedron Lett*. **1996**, *37*, 5487-5490.

103. Yadav, J. S.; Premalatha, K.; Harshavardhan, S. J.; Reddy, B. V. S. *Tetrahedron Lett*. **2008**, *49*, 6765-6767.

104. Hyde, E. G.; Thornhill, S. M.; Boyer, A. J.; Abramson, S. N. *J. Med. Chem*. **1995**, *38*, 4704-4709.

105. Rodriguez, A. D.; Shi, J.-G.; Shi, Y.-P. *J. Org. Chem.* **2000**, *65*, 3192-3199.