STUDIES TOWARD THE TOTAL SYNTHESIS OF BIELSCHOWSKYSIN

By

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To LaToya,

My Mom and Uncle Stacye,

My brother and sisters.

Education is the passport to the future,

for tomorrow belongs to those who prepare for it today.

Malcolm X

ACKNOWLEDGEMENTS

I am deeply grateful to my advisor, Prof. Gary Sulikowski, for the education he provided me. I am thankful for his perpetual faith in the process, especially when I was close to losing faith myself! Above all, he has been unwavering in his support of me during my graduate career and there is no doubt any success I find in the future will be a result of the opportunities Gary has given me. I can only hope to emulate his exceptional scholarship in my future pursuits.

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This work was supported by predoctoral fellowships from the UNCF, Merck, and Pfizer. The educational achievement gap in the United States is atrocious. Whether this is a consequence of deficient mentorship or poor K-12 preparation is debatable. What is not, is the fact that one of the most segregated places in the US is the science lab. Blacks and Latinos account for less than 2% of graduate students in the physical sciences and hold 3% of PhDs in this area. I appreciate the efforts of the UNCF, Merck, and Pfizer to curb this trend by offering research experience, mentorship, and funding to underrepresented students.

I reserve my greatest gratitude for my family. I thank my mother for her love, concern, and support. She placed a high emphasis on education, discipline, and responsibility. The struggles we encountered have given me the ability to triumph over

any problem. I appreciate my grandmother for her sacrifices and for spending her life ensuring our survival. I'd like to thank my uncles for the immeasurable amount of support they've provided me. To my brother and sisters, always remember, "success is to be measured not so much by the position that one has reached in life as by the obstacles which he has had to overcome while trying to succeed."

To conclude, I want to thank my wife LaToya for helping to make this experience worthwhile. She is truly a great friend. Her love and support is immeasurable and essential. She has always devoted herself to helping me achieve my dreams and I doubt I would have made it through graduate school without her; at the very least I wouldn't have wanted to. I am thankful for all of her love, sacrifice, and patience.

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LIST OF ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
aq.	aqueous
$BF_3{\cdot}OEt_2$	boron trifluoride diethyl etherate
Bn	benzyl
Bz	benzoyl
^oC	degrees Celsius
cat.	catalytic
CCl_4	carbon tetrachloride
$CDCl_3$	chloroform-*d*
$CHCl_3$	chloroform
CH_3CN	acetonitrile
$(COBr)_2$	oxalyl bromide
$(COCl)_2$	oxalyl chloride
conc	concentrated
CSA	10-camphorsulfonic acid
δ	chemical shift in ppm
d	doublet
DABCO	1,4-diazobicyclo[2.2.2]octane
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DCC	*N,N*'-dicyclohexylcarbodiimide
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DME	ethylene glycol dimethyl ether
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dt	doublet of triplets
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
eq.	equivalent
Et	ethyl
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
g	gram
H_2O	water

h	hour
HCl	hydrochloric acid
HMPA	hexamethylphosphoramide
HRMS	high-resolution mass spectrum
IBX	*o*-iodoxybenzoic acid
imH	imidazole
J	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
L	liter(s)
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
LRMS	low resolution mass spectrum
μ	micro
m	milli, medium (FTIR), multiplet (NMR)
M	moles per liter
mCPBA	meta-chloroperoxybenzoic acid
Me	methyl
MeOH	methanol
$MgSO_4$	magnesium sulfate
MHz	megahertz
min	minute(s)
mol	mole(s)
mp	melting point
NaOH	sodium hydroxide
$NaHCO_3$	sodium carbonate
$Na_2S_2O_3$	sodium thiosulfate
NBS	*N*-bromosuccinimide
NH_4Cl	ammonium chloride
NIS	*N*-iodosuccinimide
NMO	4-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
OAc	acetoxy
OTf	trifluoromethanesulfonate
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Piv	pivaloyl
PMB	p-methoxybenzyl
PPh_3	triphenylphosphine
ppm	parts per million
PPTS	pyridinium 4-toluenesulfonate
p-tsa	p-toluenesulfonic acid
pyr	pyridine
q	quartet
s	singlet

TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBS	*tert*-butyldimethylsilyl
TBPDS	*tert*-butyldiphenylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TPAP	tetra-*n*-propylammoniumperruthenate
Ts	4-toluenesulfonyl
2,2-DMP	2,2-dimethoxypropane

CHAPTER I

BACKGROUND AND SIGNIFICANCE

Introduction

With over 200 documented species, gorgonian corals represent an inexhaustible source of diterpenes possessing interesting biological activity and unparalleled molecular architecture.[1-3] Specifically, the furanocembranes and pseudopteranes are large families of diterpenes isolated solely from octocorals. Together, these natural products reveal how nature generates complex carbon skeletons through oxidation of well-established terpene frameworks.

Structure

The furanocembranes and pseudopteranes are cembrane-derived diterpenes featuring fourteen and twelve membered macrocycles, respectively. Additionally, these molecules incorporate butenoloide and furan heterocycles (Fig. 1.1). The furanocembranes are loosely organized into two classes, regular and complex, based on the presence of bridged and fused ring systems. Apart from this, a multitude of oxidative patterns have been observed: The electron rich furan ring is a site for epoxidation, dihydroxylation, and oxidative cleavage. C2 is often hydroxylated or

acetylated. C18 can attain the oxidation state of an alcohol, aldehyde, carboxylic acid, or ester. Oxidation of the $\Delta^{7,8}$ olefin and the electron deficient $\Delta^{11,12}$ olefin leads to 1,2-diols or epoxides, the latter of which can undergo further reaction to generate tertiary alcohols at C8 or C12. C13 is regularly acetylated. Lastly, the configuration of the $\Delta^{7,8}$ olefin can be both *(E)* and *(Z)*.[4]

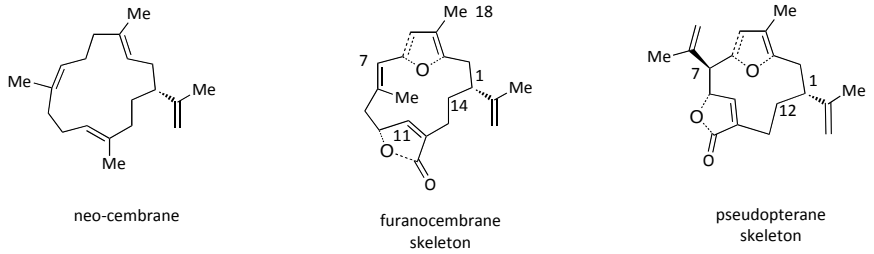


Figure 1.1. Neo-cembrane, furanocembrane, and pseudopterane skeletons.

Isolation and Pharmacology

The furanocembranes and pseudopteranes have been isolated entirely from gorgonian corals. In 1975 pukalide (**1.1**) became the first furanocembrane reported in the literature after it's isolation from the soft coral *Sinularia abrupta* by the Scheuer lab (Figure 1.2).[5] Pukalide's (**1.1**) ability to induce vomiting in fish implicates its importance as a defense mechanism against marine predators.[6, 7] Pukalide (**1.1**) has since been isolated from *Leptogorgia alba*, *Leptogorgia setacea,* and *Sinularia polydactyla* alongside 13-acetoxy-11,12-epoxypukalide (**1.2**), 13-acetoxypukalide (**1.3**), pukalide aldehyde (**1.4**), and 11,12-epoxypukalide (**1.5**).[8, 9]

Isolated from corals of the species *Lophogorgia,* Fenical reported the structure of lophotoxin (**1.6**) in 1981.[10, 11] Due to its role as an irreversible inhibitor of the nicotinic acetylcholine receptor, lophotoxin (**1.6**) is the most studied furanocembrane.[12-15] Structurally, it is believed the lactone heterocycle is a necessary component for enzyme recognition. Moreover, tyrosine residues in the α-subunit of the nicotinic acetylcholine receptor bind covalently with the epoxide of lophotoxin (**1.6**) at C7.[16-19]

The related compounds lophodiol A (**1.7**), lophodiol B (**1.8**), deoxylophotoxin (**1.9**), and 17-acetoxylophotoxin (**1.10**) were isolated from *Lophogorgia peruana*.[20] Of particular interest is the diol functionality of lophodiol B (**1.8**). Usually, C7-C8 epoxides result from oxidation of the (*E*) configured $\Delta^{7,8}$ olefin. The configuration of the diol of lophodiol B (**1.8**) results from an unusual oxidation of the (*Z*) configured $\Delta^{7,8}$ olefin.

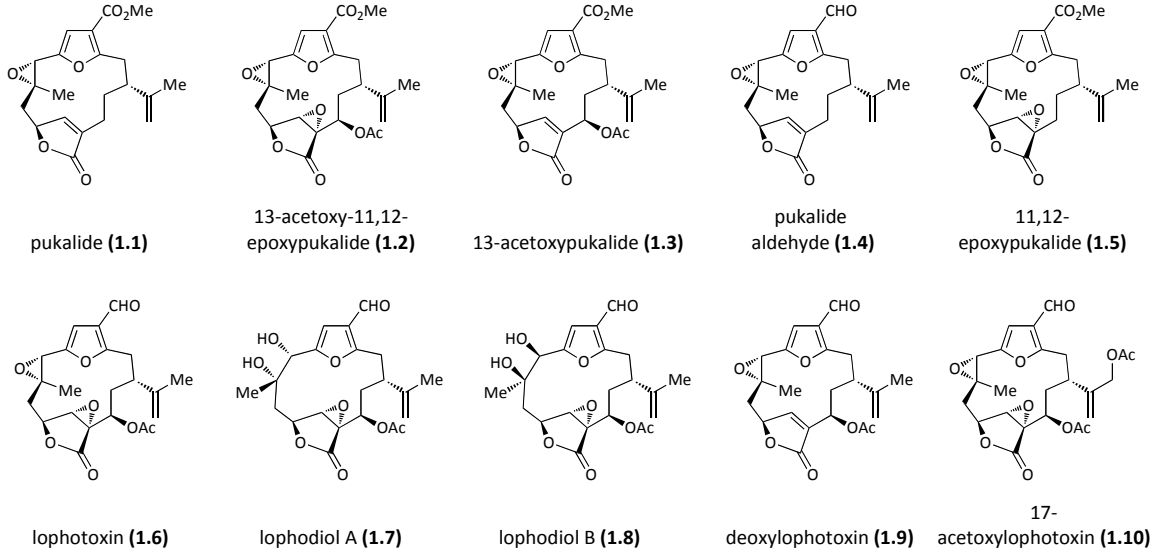


Figure 1.2. The regular furanocembranes.

Bipinnatins A-Q (**1.11**)-(**1.27**) were isolated from *Pseudopterogorgia bipinnata* (Fig. 1.3).[21-24] Bipinnatins A (**1.11**), B (**1.12**), C (**1.13**), and D (**1.14**) displayed *in vitro* activity against the P388 murine tumor cell line with IC_{50} values of 0.9 μg, 3.2 μg, 46.6 μg and 1.5 μg.[25-28] The isolation of the bipinnatins has unearthed key information regarding the biosynthesis of the complex furanocembranes. It has been hypothesized the bipinnatins are precursors to the more intricate family members, *vide infra*. Furthermore, the bipinnatins showcase the power of oxidative enzymes involved in their biosynthesis. For example, bipinnatin L (**1.22**) incorporates nearly every oxidative pattern observed in the family. Its furan has been completely digested and instead of the standard heterocycle the ring contains an epoxide and two alcohols. The isoprene unit contains a methyl ester and the carbon chain features C2 and C7 acetates. Similarly, enzymatic oxidative command is on display when the structures of bipinnatins N (**1.24**), O (**1.25**), P (**1.26**), and Q (**1.27**) are examined.

Acerosolide (**1.28**) was isolated from *Pseudopterogorgia acerosa* and was the first furanocembrane to succumb to total synthesis.[29-31] Of interest is the atypical ketone oxidation state of C14. The representative furanocembrane, rubifolide (**1.29**), was isolated from *Gersemia rubiformis* and *Tochuina tetraquetra.*[32]

The coralloidolides (**1.30**) - (**1.35**) are a group of natural products isolated from the Mediterranean coral *Alcyonium coralloidolides* by Pietra.[33-35] The first furanocembranes isolated from a non-Caribbean source, the coralloidolides serve as a bridge between the regular and complex furanocembranes. For example, coralloidolides B (**1.31**) and D (**1.33**) feature transannular bond formation within their carbon network.

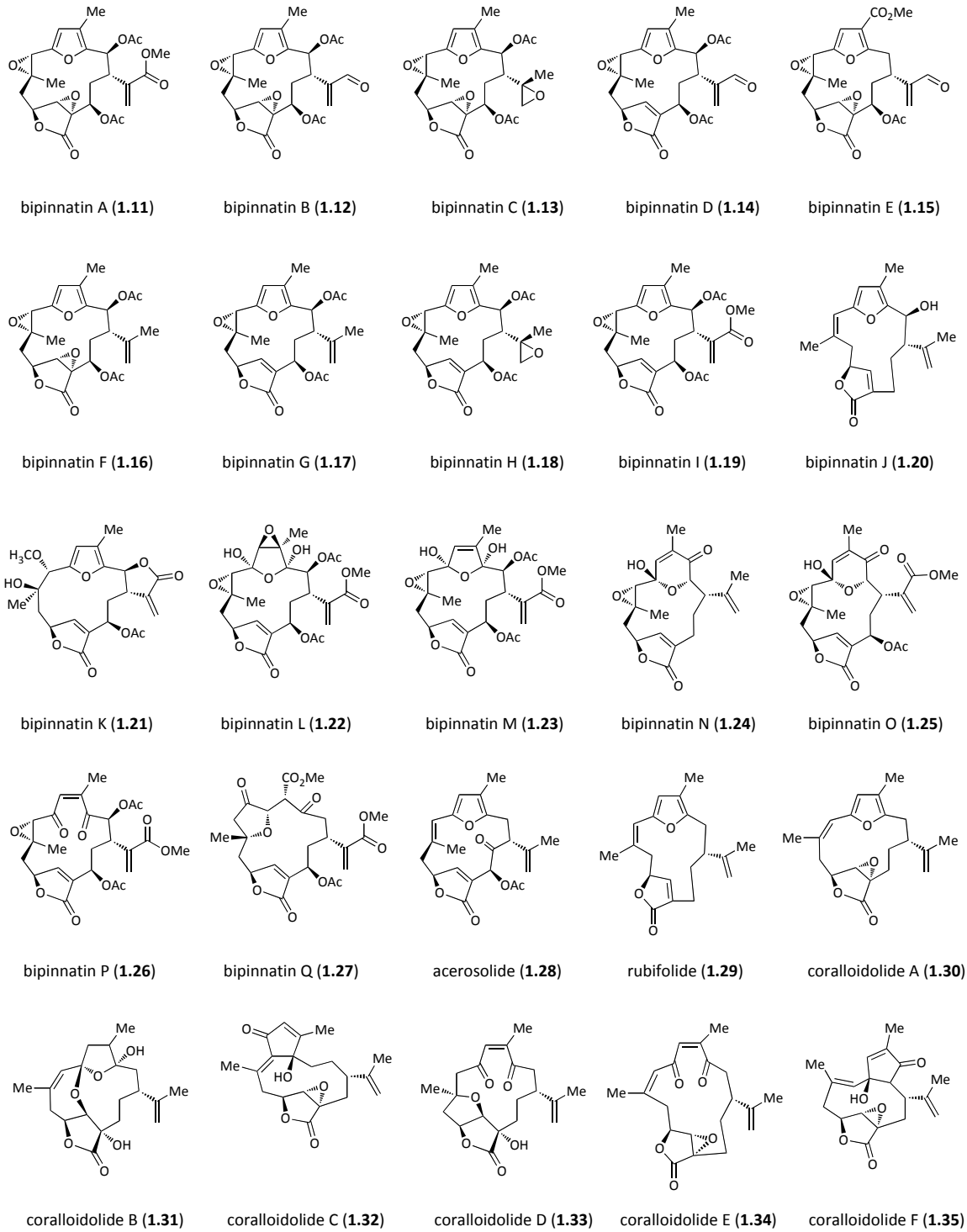


Figure 1.3. The regular furanocembranes con't.

Bielschowskysin (**1.36**) was isolated in 2004 from *Pseudopterogorgia kallos* (Figure 1.4).[36] The highly oxygenated, hexacyclic diterpene features an unique tricyclo[9.3.0.0^{2,10}]tetradecane ring system and was shown to demonstrate antiplasmodial activity against *Plasmodium falciparum* (IC_{50} = 10 μg). Additionally, bielschowskysin (**1.36**) displayed strong and specific *in vitro* cytotoxicity against EKVX nonsmall cell lung cancer (GI_{50} < 0.01 μM) and CAKI-1 renal cancer (GI_{50} < 0.51 μM) using the NCI's *in vitro* antitumor screen.

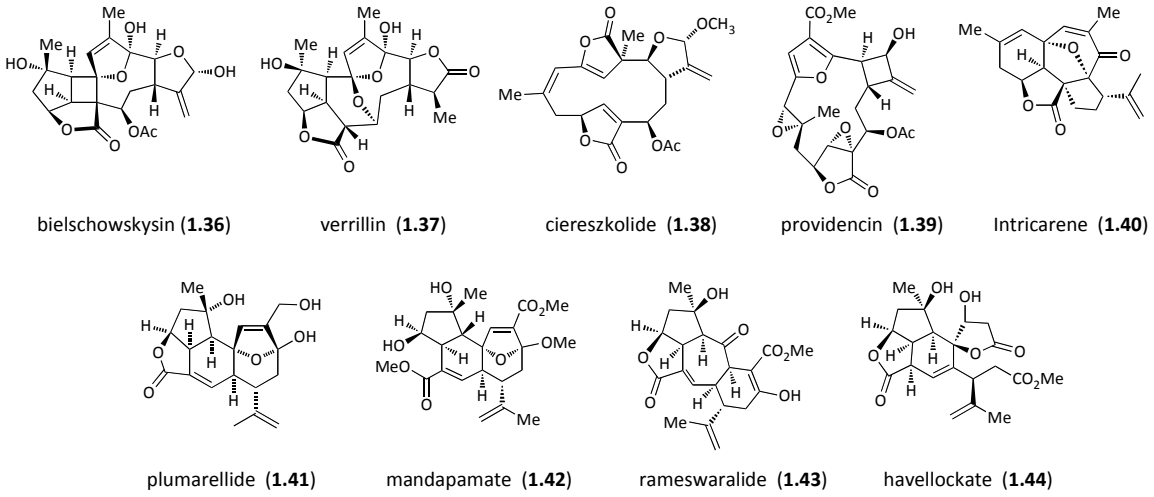


Figure 1.4. The complex furanocembranes.

Verrillin (**1.37**) was isolated from *Pseudopterogorgia bipinnata* in 2000.[37] The molecule features a cis-bicyclo[9.3.0]tetradecane nucleus. Verillin's (**1.37**) carbon skeleton is vastly different from other compounds isolated from *Pseudopterogorgia bipinnata*, namely bipinnatins A-Q. Since the same coral produces both the bipinnatins and verrillin (**1.37**), it is possible the latter arises through a different biosynthetic

pathway. Antituberculosis screening against *Mycobacterium tuberculosis* H37Rv (6.25 μg/mL) showed 0% inhibition. Scarcity of material has hindered further testing.

Ciereszkolide (**1.38**) was isolated from *Pseudopterogorgia kallos* in 2004.[38] The structure incorporates two butenolides and a lactol across an uncommon 13-membered macrocycle. As such, one can surmise a biogenesis beginning with a furanocembrane precursor involving ring contraction (migration of the C2-C3 σ bond to C4) to arrive at the ciereszkolide skeleton (Scheme 1.7). *In vitro,* antituberculosis screening against *Mycobacterium tuberculosis* H37Rv and *in vivo* cytotoxicity in the brine shrimp lethality bioassay (BSLT) caused 0% inhibition.

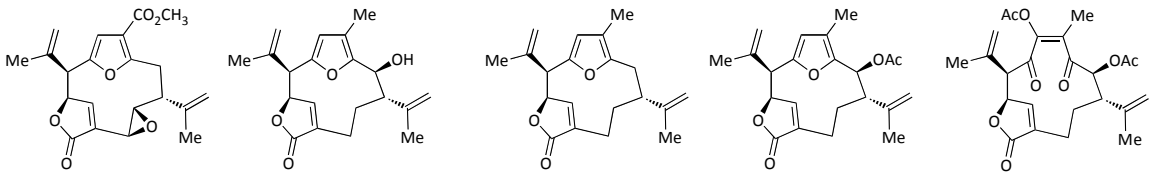
In 2003 providencin (**1.39**) was isolated from *Pseudopterogorgia kallos*.[39] This metabolite was the first of two compounds isolated from *P. kallos* that incorporates a cyclobutane in its framework (see bielschowskysin (**1.36**)). Additionally, the structure is based on a bicyclo[12.2.0]hexadecane ring system. Providencin (**1.39**) displayed *in vitro* cytotoxicity against MCF7 breast cancer (57% growth inhibition), NCI-H46- nonsmall cell lung cancer (39% growth inhibition), and SF-268 CNS cancer (94% growth inhibition).

Intricarene (**1.40**) was isolated in 2005 from *Pseudopterogorgia kallos*.[40] The molecule contains a unique trispiropentacyclic ring system. The biogenesis of intricarene (**1.40**) is storied and will be discussed in the subsequent section. Lastly, the compound was tested for inhibitory activity against *Mycobacterium tuberculosis* H37Rv (ATCC 27294) in the microplate Alamar Blue assay, and resulted in 15% inhibition at 128 μg/mL concentration of intricarene (**1.40**).

Four advanced furanocembranes have been isolated from Indian Ocean corals (**1.41**-**1.44**). Plumarellide (**1.41**) was isolated from *Plumarella sp.* in 2002.[41] The compound was isolated alongside its ethyl ester, the latter, likely an artifact resulting from ethanol extraction of the crude broth. Plumarellide (**1.41**) displayed moderate hemolytic activity (50% hemolysis of mice blood at 140 and 250 μM).

Mandapamate (**1.42**) and rameswarallide (**1.43**) were isolated from the soft coral *Sinularia dissecta.*[42, 43] While the authors speculate their cyclohexene cores are assembled through transannular Diels-Alder cyclization, Fenical has suggested mandapamate (**1.42**) is an artifact resulting from methanolysis during isolation of rameswarallide (**1.43**).[44] Lastly, havellockate (**1.44**) was isolated from *Sinularia granosa* and to date displays no biological activity.[45]

Similar to the furanocembranes, the pseudopteranes have been isolated from gorgonian corals (Figure 1.5). Pseudopterolide (**1.45**) was isolated in 1982 from *Pseudopterogorgia acerosa*.[46] At concentrations of 1-10 μM the molecule was shown to inhibit cytokinesis in fertilized urchin eggs without interfering with cell division.[47] Kallolide A (**1.46**), kallolide A acetate (**1.47**), kallolide B (**1.48**), and kallolide C (**1.49**) were isolated from *Pseudopterogorgia kallos* and *Pseudopterogorgia bipinnata* in 1985.[48] Of these, kallolide A (**1.46**) exhibits strong anti-inflammatory activity equivalent to indometacin for the inhibition of phorbol ester induced inflammation.[48]



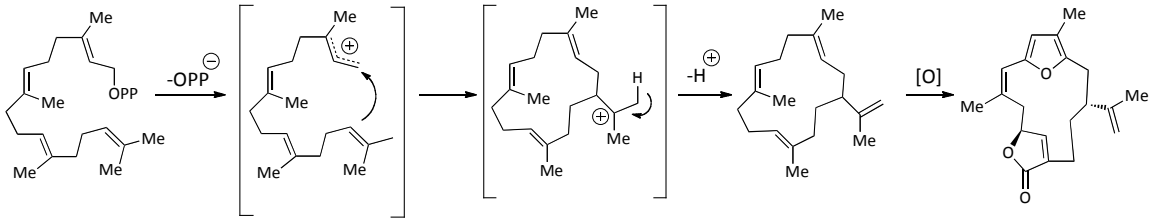
pseudopteroide (**1.45**) kallolide A (**1.46**) kallolide B (**1.47**) kallolide A acetate (**1.48**) kallolide C (**1.49**)

Figure 1.5. The pseudopteranes.

Biosynthetic Speculations

The preceding sections have presented the structural diversity of the furanocembranes and pseudopteranes. While a number of these features are a consequence of enzyme promoted transformations, others are the result of isolation methods. Whatever the case may be, their intricate architectures have inspired theories about furanocembrane and pseudopterane biogenesis.

The biosynthesis of *neo*-cembrane is well established (Scheme 1.1).[49] Cyclization of geranylgeranyl diphosphate (GGPP) (**1.50**) generates a 14-membered macrocycle by way of carbocation **1.52**. Loss of a proton delivers neo-cembrane (**1.53**). Enzymatic oxidation and isomerization of the $\Delta^{7,8}$ olefin provides rubifolide (**1.29**).

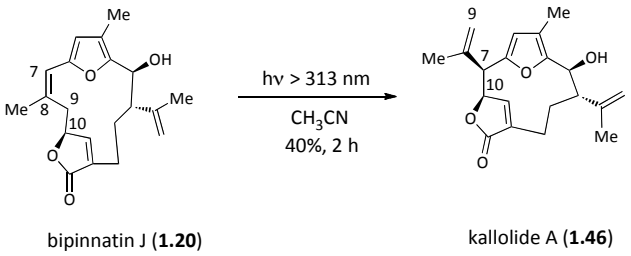


GGPP (**1.50**) **1.51** **1.52** *neo*-cembrane (**1.53**) rubifolide (**1.29**)

Scheme 1.1. Cyclization of GGPP (**1.50**) and its conversion to rubifolide (**1.29**).

In his original report on the isolation of pseudopterolide (**1.45**) Clardy observed the pseudopterane skeleton could be dissected symmetrically, revealing two geranyl units, *vide supra*.[50] This would suggest a biosynthesis involving dimerization of the two subunits. Conversely, the occurrence of 14-membered cembranoids in soft corals producing 12-membered pseudopteranes suggests an alternative pathway. In fact, Rodriguez has established the pseudopterane skeleton can arise from ring contraction of a cembranoid precursor.[51, 52]

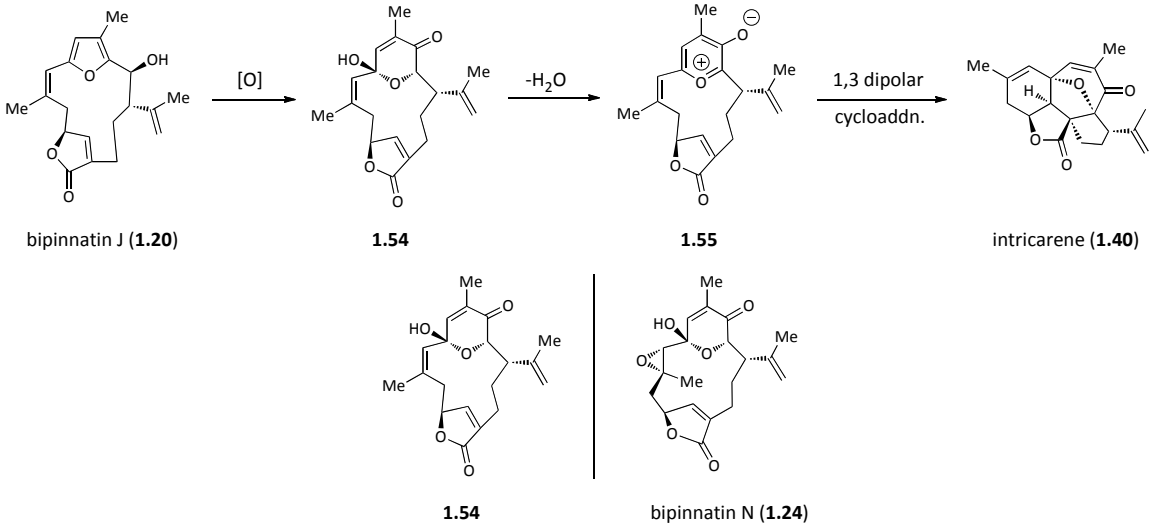
Irradiation of an CH_3CN solution of bipinnatin J (**1.20**) provided kallolide A (**1.46**) in 40% yield (Scheme 1.2). This observation provides evidence that the biosynthesis of kallolide A (**1.46**) involves a photochemically allowed [1,3]-allyl shift. Upon irradiation, the C9-C10 σ bond of bipinnatin J (**1.20**) migrates suprafacially to C7 with concomitant reorganization of the π system and retention of configuration of the migrating butenolide. Expectantly, the results of this study have fueled biosynthetic speculations regarding the origins of the pseudopteranes and the biogenesis of the complex furanocembranes.



bipinnatin J (**1.20**) kallolide A (**1.46**)

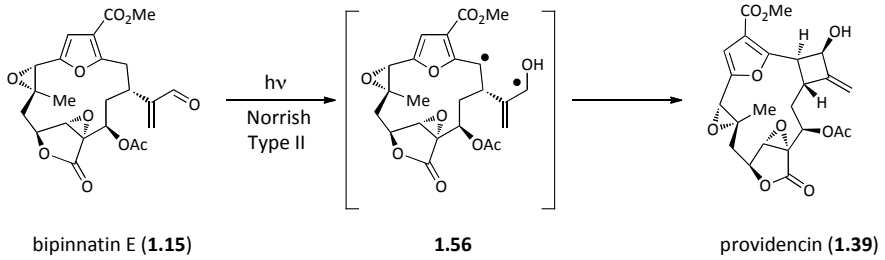
Scheme 1.2. Photocycloisomerization of bipinnatin J (**1.20**) to kallolide A (**1.46**).

A proposed biosynthesis of intricarene (**1.40**) is shown in Scheme 1.3. Oxidation of bipinnatin J (**1.20**) provides hydroxy pyranone **1.54**. Elimination of water gives dipole **1.55**, which can undergo a 1,3-dipolar cycloaddition to provide intricarene (**1.40**). This hypothesis is supported by Trauner and Pattenden's syntheses of intricarene (**1.40**); and the isolation of bipinnatin N (**1.24**), a compound structurally similar to intermediate **1.54**.[53-55] Tantillo has calculated a 20 kcal/mol energy barrier for the intricarene (**1.40**) forming cycloaddition, demonstrating the need for enzymatic intervention in this step.[56]



Scheme 1.3. Speculative biosynthesis of intricarene (**1.40**).

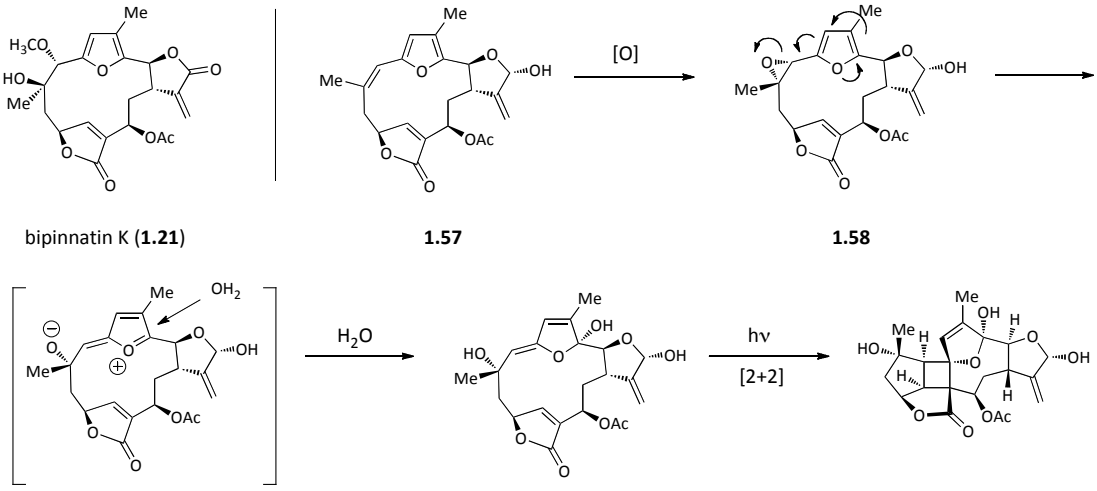
Cyclobutanols are formed from excited carbonyls by intramolecular γ-hydrogen abstraction and recombination of the 1,4-diradical.[57, 58] In theory, providencin (**1.39**) may be the Norrish type II product from photolysis of bipinnatin E (**1.15**) (Scheme 1.4).



bipinnatin E (**1.15**) **1.56** providencin (**1.39**)

Scheme 1.4. Speculative biosynthesis of providencin (**1.39**).

[2+2] Photocycloaddition may form the cyclobutane of bielschowskysin (**1.36**) (Scheme 1.5). Oxidation of the $\Delta^{7,8}$ olefin of **1.57**, which is similar to bipinnatin K (**1.21**), yields epoxide **1.58**. Intramolecular opening gives intermediate **1.59**. Addition of water affords an alkylidene dihydrofuran **1.60**, which is photolyzed to bielschowskysin (**1.36**).



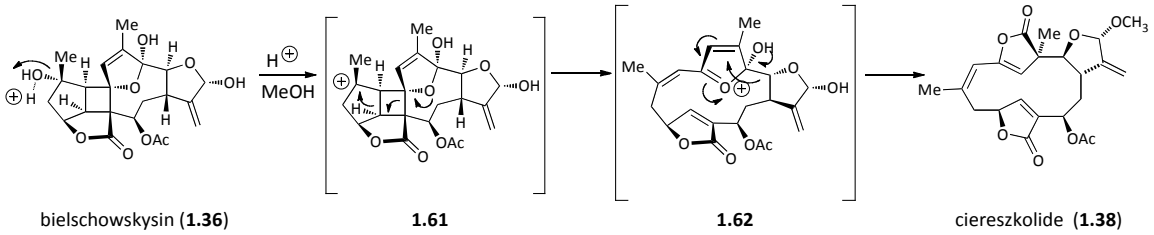
bipinnatin K (**1.21**) **1.57** **1.58**

1.59 **1.60** bielschowskysin (**1.36**)

Scheme 1.5 Speculative biosynthesis of bielschowskysin (**1.36**).

We speculate ciereszkolide (**1.38**) is formed through a Pinacol rearrangement (Scheme 1.6). Due to bielschowskysin (**1.36**) and ciereszkolides (**1.38**) isolation from *P. kallos*, the possibility exists that ciereszkolide (**1.38**) is an artifact resulting from $CHCl_3$

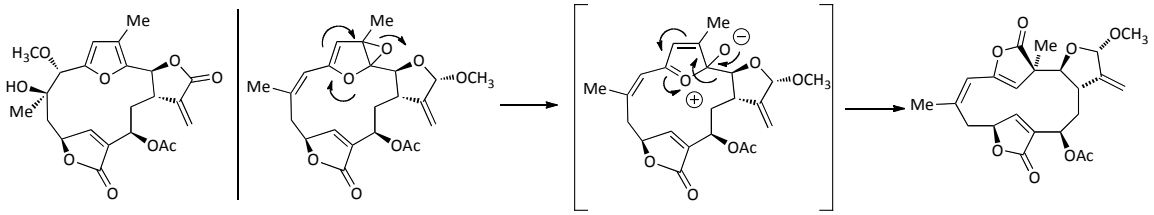
and MeOH extraction. Treating bielschowskysin (**1.36**) with acidic methanol generates tertiary carbocation **1.61**. Ring fragmentation provides oxonium intermediate **1.62**. Pinacol rearrangement of **1.62** and methyl acetal formation affords ciereszkolide (**1.38**).



bielschowskysin (**1.36**) **1.61** **1.62** ciereszkolide (**1.38**)

Scheme 1.6. Conversion of bielschowskysin (**1.36**) to ciereszkolide (**1.38**).

There exists another possibility for the formation of ciereszkolide (**1.38**) (Scheme 1.7). Since the furan is susceptible to oxidation, spiro epoxide **1.63** could be generated from a molecule similar to bipinnatin K (**1.21**). Ring opening of the epoxide would provide intermediate **1.64**, suitable for Pinacol rearrangement to ciereszkolide (**1.38**).

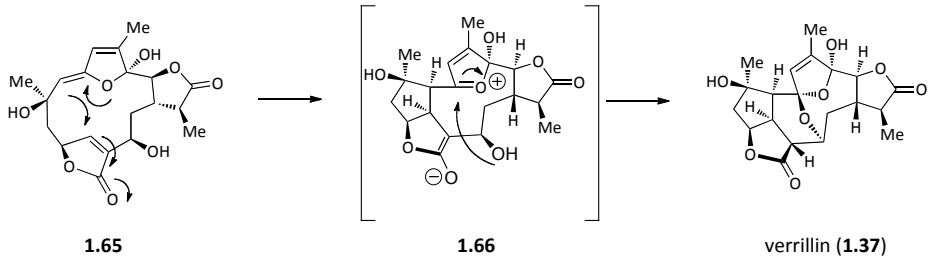


bipinnatin K (**1.21**) **1.63** **1.64** ciereszkolide (**1.38**)

Scheme 1.7. Conversion of **1.63** to ciereszkolide (**1.38**).

Analogous to our proposed biosynthesis of bielschowskysin (**1.36**), we propose verrillin (**1.37**) and plumarellide (**1.41**) are formed by reaction of an alkylidene

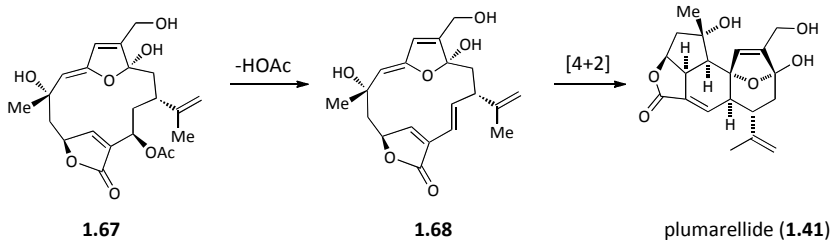
dihydrofuran (Scheme 1.8 and Scheme 1.9). Concerning verrillin (**1.37**), intramolecular Michael addition of enol ether **1.65**, generates intermediate **1.66**. Trapping of the furan oxocarbenium ion with the alcohol would yield verrillin (**1.37**).



Scheme 1.8. Speculative biosynthesis of verrillin (**1.37**).

Similarly, elimination of acetic acid from **1.67** generates diene **1.68**. Inverse electron demand Diels-Alder cycloaddition would provide plumarellide (**1.41**).

It is important to mention the biosynthetic pathways proposed in this section are speculative. While it is with ease that we as synthetic chemists associate certain structural motifs with photochemical reactions, cycloadditions, or sigmatropic rearrangements; the exact enzymatic method for synthesizing these functionalities remains unknown.



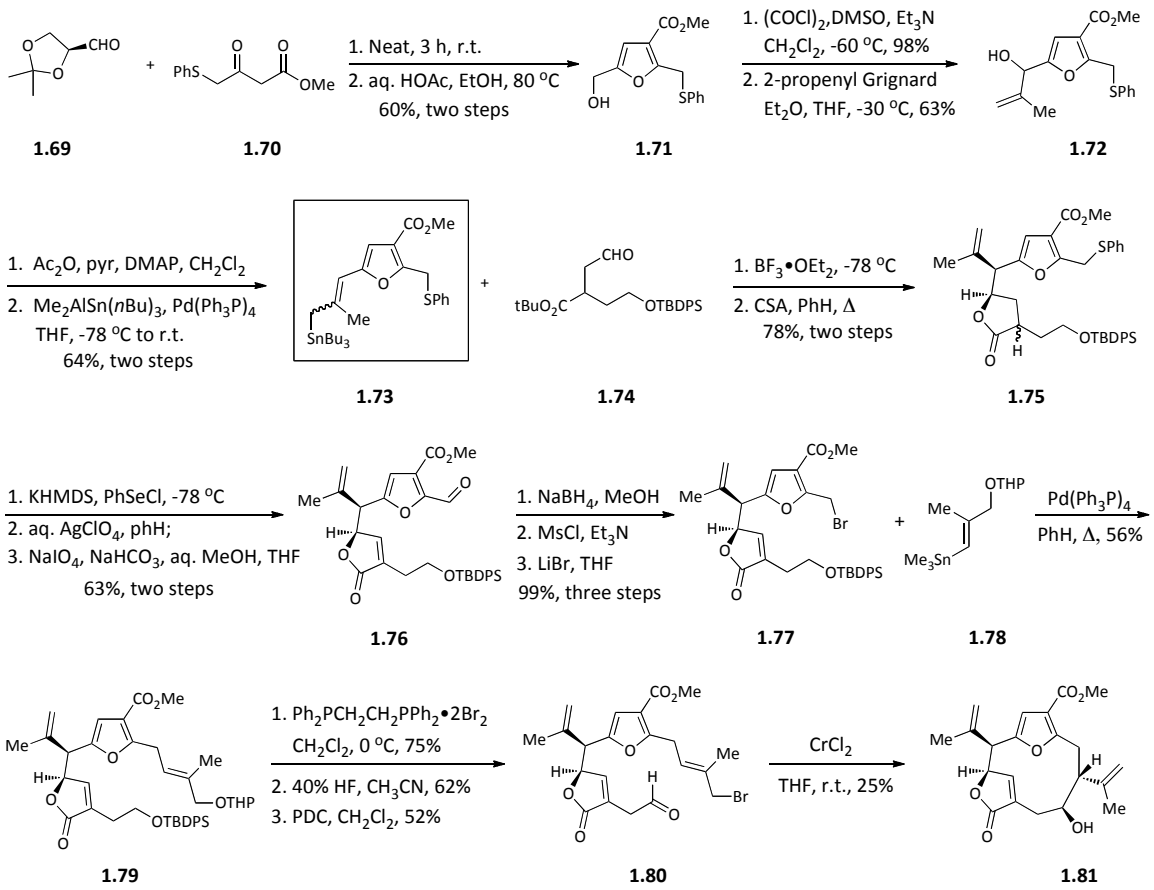
Scheme 1.9. Speculative biosynthesis of plumarellide (**1.41**).

Synthetic Methodology

For absolute structural audacity and chemical complexity, few classes of natural products rival the furanocembranes and pseudopteranes. Their highly oxidized carbon skeletons and intricate ring systems present menacing obstacles for synthetic chemists, and as a result only a small body of work has been reported. There are central issues to be considered when planning a furanocembrane or pseudopterane program: 1) Construction of the substituted furan; 2) Synthesis of the α-substituted butenolide; 3) Macrocyclization of the 12 or 14-membered furanocycle; and 4) Installation of correct oxidation states. This section will examine contributions to these central problems.

In 1990, Paquette reported the synthesis of dihydropseudopterolide (**1.81**) (Scheme 1.10).[59, 60] The Paquette synthesis was the first successful approach to the pseudopterane skeleton and laid the foundation for the groups pioneering total syntheses of acerosolide (**1.28**) and other cembrane derivatives.[30, 31, 60, 61]

Recognizing the difficulty in synthesizing functionalized furans, the Paquette synthesis commenced with condensation of D-glyceraldehyde acetonide **1.69** and methyl (phenylthio) acetoacetate **1.70** followed by heating in aqueous acetic acid to give furan alcohol **1.71** in 60% yield. Swern oxidation occurred in high yield to generate an aldehyde that was reacted with 2-propenyl Grignard to afford an epimeric mixture of allylic alcohol **1.72**. Acetylation was followed by palladium-catalyzed stannylation to give stannane **1.73**. This compound serves as the key intermediate for the other Paquette cembrane syntheses.



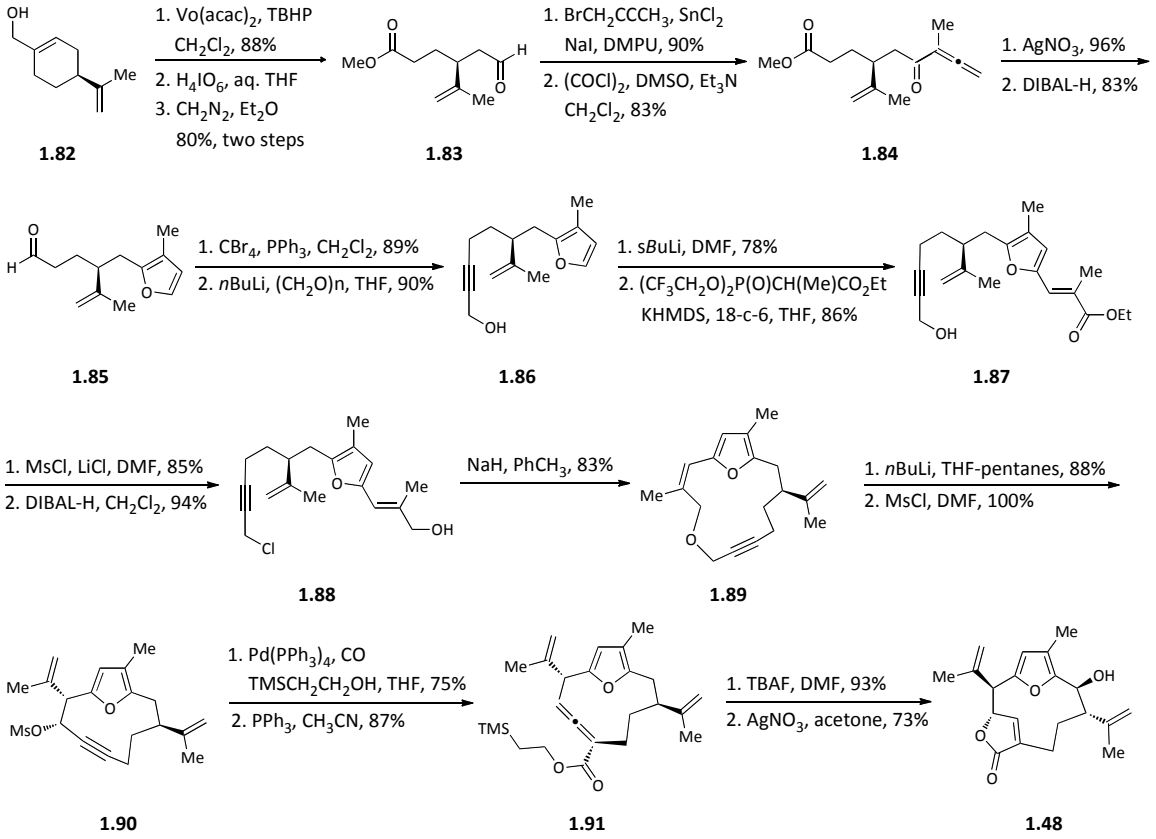
Scheme 1.10. Paquette's synthesis of dihydropseudopterolide (**1.81**).

Treatment of **1.73** and **1.74** with BF_3•OEt_2 gave, after heating with CSA, an inconsequential diastereomeric mixture of lactone **1.75**. Bisphenylselenation was accomplished by treatment of the KHMDS generated dianion with excess PhSeCl. Hydrolysis of the mixed (selenide-sulfide) acetal with aqueous $AgClO_4$ liberated the aldehyde, while $NaIO_4$ effected selenide oxidation to the selenoxide and elimination to give butenolide **1.76** in 63% yield. After conversion of the aldehyde to the bromide, palladium catalyzed vinylstannylation with **1.78** proceeded in high yield to provide the remainder of the carbon framework. To complete the synthesis the THP substituent

was directly exchanged for a bromide using 1,2-bis-(diphenylphosphino)ethane tetrabromide. The silyl ether was cleaved by treatment with HF in CH_3CN and the resultant primary alcohol oxidized with PCC to provide the highly anticipated aldehyde **1.80**. Lastly, Nozaki-Hiyama-Kishi macrocyclization using $CrCl_2$ formed the 12-membered ring and provided dihydropseudopterolide (**1.81**).

Similar to the Paquette program, Marshall focused on novel methodology to synthesize the substituted furan moiety. In addition, while pursuing kallolide B (**1.48**), Marshall developed methodology to access the α-substituted butenolide and address the 12-membered macrocycle.[62-64] Starting with (-)-perillyl alcohol **1.82**, hydroxyl directed epoxidation provided a diastereomeric mixture of epoxides that were subjected to oxidative cleavage by sodium periodate (Scheme 1.11). Esterification of the resultant carboxylic acid afforded methyl ester **1.83**. Addition of the stannane derived from 2-bromo-2-butyne and $SnCl_2$ worked in excellent yield (90%) to provide an allenol that was oxidized to the allenone **1.84** under Swern conditions. $AgNO_3$ promoted cyclization generated the furan in near quantitative yield and was followed by temperature-controlled reduction of the ester with DIBAL-H to give aldehyde **1.85**.

With the synthesis of the furan complete the authors moved forward with constructing the remainder of the carbon skeleton. Extension using the Corey-Fuchs procedure, subsequent generation of the organolithium species, and reaction with para-formaldehyde provided propargyl alcohol **1.86**.



Scheme 1.11. Marshall's synthesis of kallolide B (**1.48**).

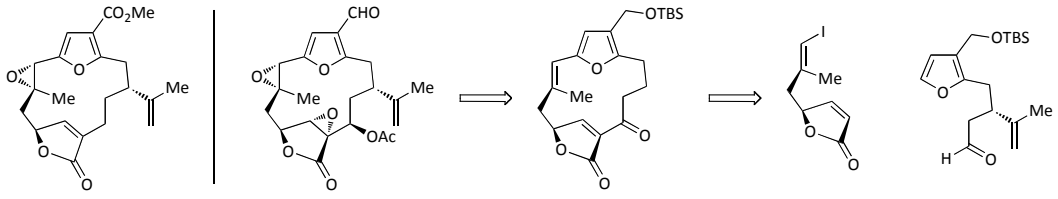
Formylation of the furan and homologation under Horner-Emmons conditions gave α, β-unsaturated ester **1.87**. The alcohol was converted to the propargylic chloride and successive reduction of the ester to the allylic alcohol using DIBAL-H provided chloro alcohol **1.88**. Generation of the sodium alkoxide of **1.88** induced macrocyclization to provide ether **1.89**.

To complete the synthesis, a perilous, diastereoselective [2,3] Wittig ring contraction of cyclic ether **1.89** was employed. Treatment with *n*BuLi in THF-pentanes provided the *syn* product in 88% yield. After mesylation, a single isomer of allenoate **1.91** was produced in 75% yield. To achieve the desired configuration of the butenolide

the authors isomerized the allenoate using PPh_3 in benzene. Cleavage of the TMS ethyl ester with TBAF afforded an allylic acid that was converted to the butenolide using $AgNO_3$, providing kallolide B **1.48** in 73% yield. This methodology was used to complete the total synthesis of kallolide A (**1.46**).[65]

Even though there has been major biomedical interest in pukalide (**1.1**) and lophotoxin (**1.6**), there have been no total syntheses of either molecule to date. There have been several important reports regarding synthetic progress made in this area.[66-68] Of note are accounts by the Paterson and Wipf groups.[69-72]

The Paterson approach to pukalide (**1.1**) and lophotoxin (**1.6**) relies on installing sensitive functionality during the final stages of the program.[70] As such, the authors proposed a common synthetic intermediate would arise from: 1) removal of the epoxides at C7-C8 and C11-C12; 2) installation of the C13 acetoxy group by diastereoselective reduction of a ketone; and 3) conjugate addition of the isoprene unit at C1. This macrocycle, **1.92**, would arise from fragments **1.93** and **1.94** (Scheme 1.12).



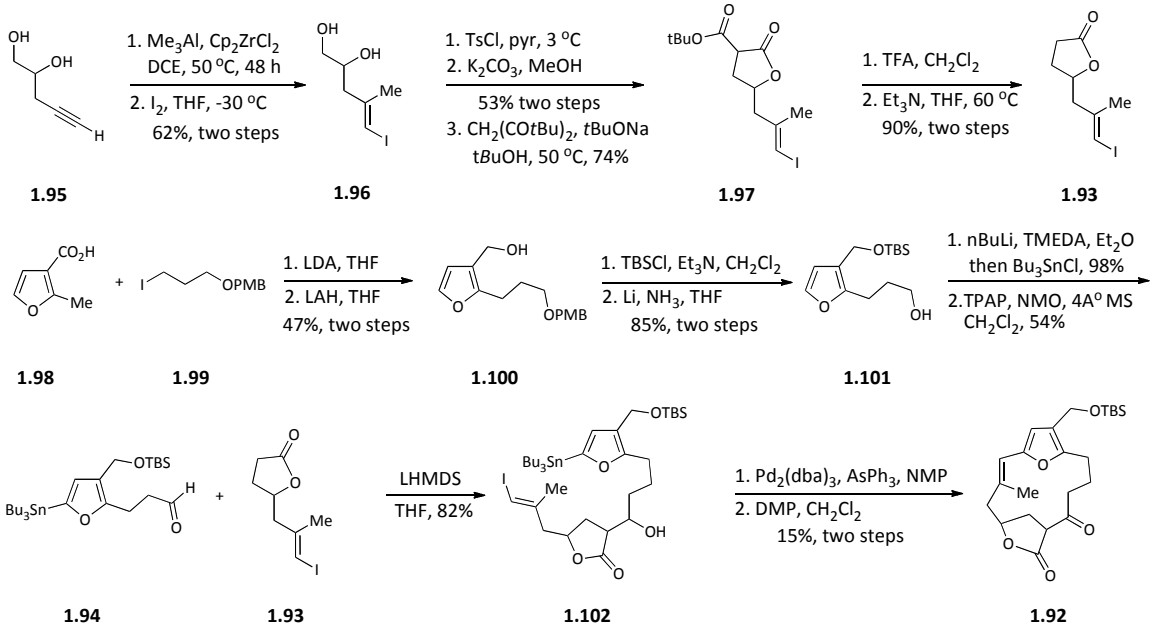
pukalide (**1.1**) lophotoxin (**1.6**) **1.92** **1.93** **1.94**

Scheme 1.12. Paterson's retrosynthetic analysis of pukalide (**1.1**) and lophotoxin (**1.6**).

Starting from the adduct of lithium acetylide and glycidol, carbometallation of the alkyne and iodination gave iodide **1.95** in 62% yield (Scheme 1.13).[69] The diol was

converted to an epoxide that was opened with the sodium enolate of di-*t*-butyl malonate to provide, after transesterification, lactone **1.97** in 74% yield. Ester hydrolysis of **1.97** using TFA gave an acid that was decarboxylated under basic conditions to give iodide **1.93** in 90% yield.

To synthesize the coupling partner, the dianion of furoic acid **1.98** was generated using LDA and alkylated at C2 with iodide **1.99**. Reduction of the acid with LAH, silyl protection, and oxidative cleavage of the PMB ether afforded alcohol **1.101**. Once more, dianion generation using *n*BuLi was followed by reaction with Bu_3SnCl to afford the furyl stannane in 98% yield. TPAP oxidation of the alcohol provided the acid sensitive aldehyde **1.94** in modest yield.

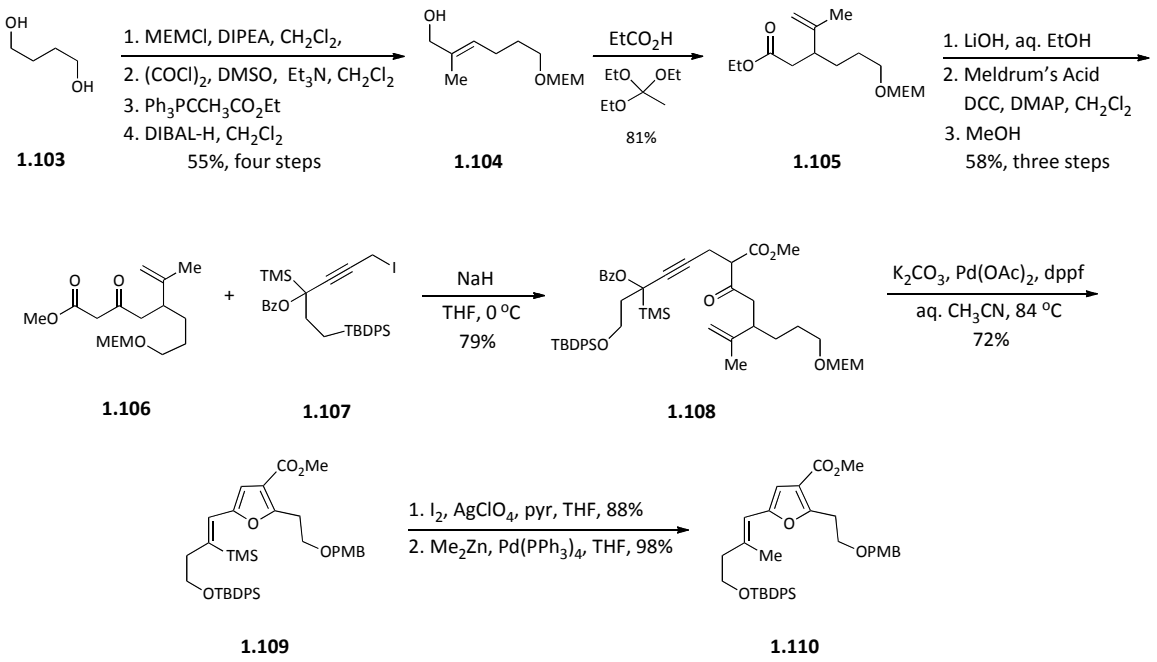


Scheme 1.13. Patterson's synthesis of the macrocycle common to pukalide (**1.1**) and lophotoxin (**1.6**).

Completion of the synthesis required aldol union of the two units without compromising the furyl stannane. Using LHMDS as a base, aldol coupling of units **1.93** and **1.94** gave alcohol **1.102** in 82% yield as a mixture of diastereomers, without corrosion of the stannane. Stille coupling was accomplished using $Pd_2(dba)_3$ and PPh_3. The crude residue was oxidized using Dess-Martin periodinane to give a 1:1 diastereomeric mixture of macrocycle **1.92**.

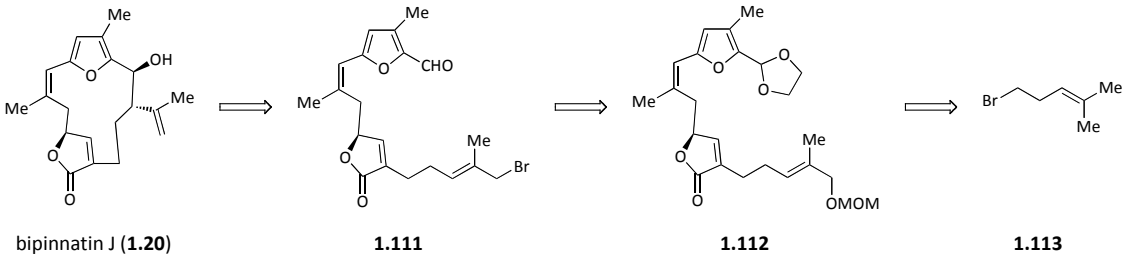
The Wipf lab presented a stylish approach for the cyclization of α-propargyl-β-ketoesters to 2-alkenylfurans (Scheme 1.14). Following monoprotection of 1,4-butanediol **1.103**, combination Swern-Wittig reaction provided an α,β-unsaturated ester. DIBAL-H reduction afforded alcohol **1.104**, which was subjected to a Johnson-Claisen rearrangement to give ester **1.105** in 81% yield. Saponification, using aqueous LiOH, provided an acid that was immediately converted to β-keto ester **1.106**. Alkylation of the sodium enolate of **1.106** with iodide **1.107** gave alkyne **1.108**, which was cyclized to siloxy furan **1.109**.

Mechanistically, this reaction likely proceeds through an intermediate allene that isomerizes to the desired substituted furan. To close the synthesis silane-iodide exchange afforded a vinyl iodide, which was reacted with dimethylzinc under palladium(0) catalysis to provide the C1-C18 segment of pukalide (**1.110**). During a parallel synthesis the C1-C18 segment of lophotoxin was prepared using this methodology.[72]



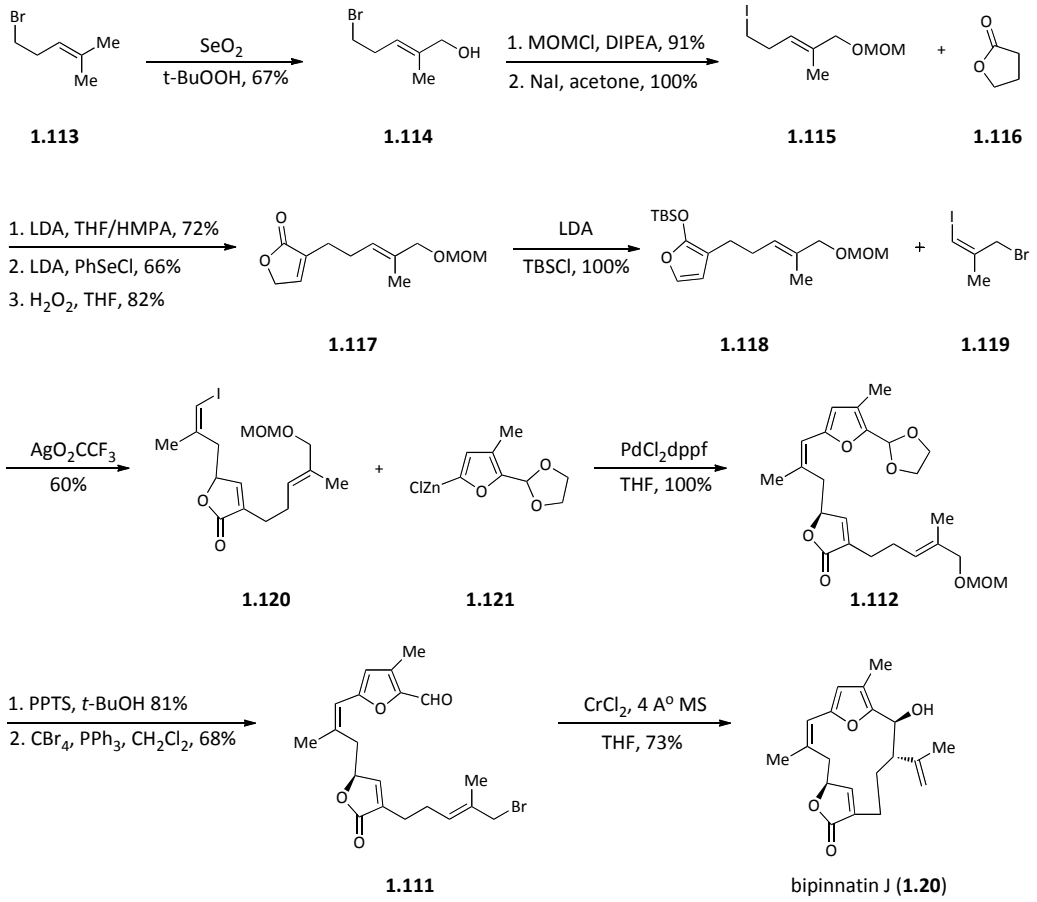
Scheme 1.14. Wipf cyclization method.

Two highly convergent approaches to bipinnatin J (**1.20**) have been reported. Racemic bipinnatin J (**1.20**) was reported in a well-designed synthesis by the Rawal lab.[73] Their analysis hinged on the use of an S_N1 alkylation of a siloxyfuran and macrocyclization using an NHK reaction, a precedent set during the Paquette furanocembrane program (Scheme 1.15).



Scheme 1.15. Rawal's retrosynthetic analysis of bipinnatin J (**1.20**).

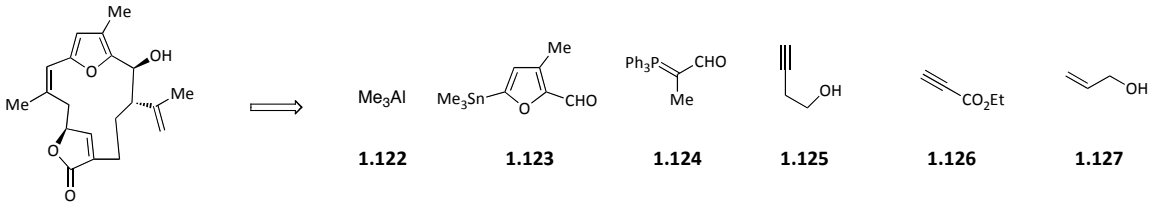
Starting from commercially available 5-bromo-2-methylpent-2-ene **1.113**, allylic oxidation with SeO_2-TBHP proceeds regioselectively to provide allylic alcohol **1.114** in 67% yield (Scheme 1.16). After MOM protection of the alcohol, bromide-iodide exchange under Finkelstein conditions gave iodide **1.115**. α-Alkylation of the lithium enolate of γ-butyrolactone **1.116** with iodide **1.115** generated the substituted lactone in 72% yield. The butenolide was introduced through a two-step, phenylselenation/selenoxide elimination cycle. Generation of the siloxy furan proceeded smoothly to furnish **1.118** in near quantitative yield.



Scheme 1.16. Rawal's synthesis of bipinnatin J (**1.20**).

Treatment of **1.119** with $Ag(O_2CCF_3)_2$ followed by reaction with siloxy furan **1.118** provided iodide **1.120** in 60% yield. Negishi cross-coupling of **1.120** with organozinc reagent **1.121**, occurred in the presence of $PdCl_2$dppf to provide the coupled product. Treatment with PPTS in *t*-BuOH simultaneously liberated the aldehyde and cleaved the MOM ether to advance the material in 81% yield. The alcohol was converted to the bromide in moderate yield, using PPh_3 and CBr_4. Lastly, NHK macrocyclization provided bipinnatin J (**1.20**) in 73% yield.

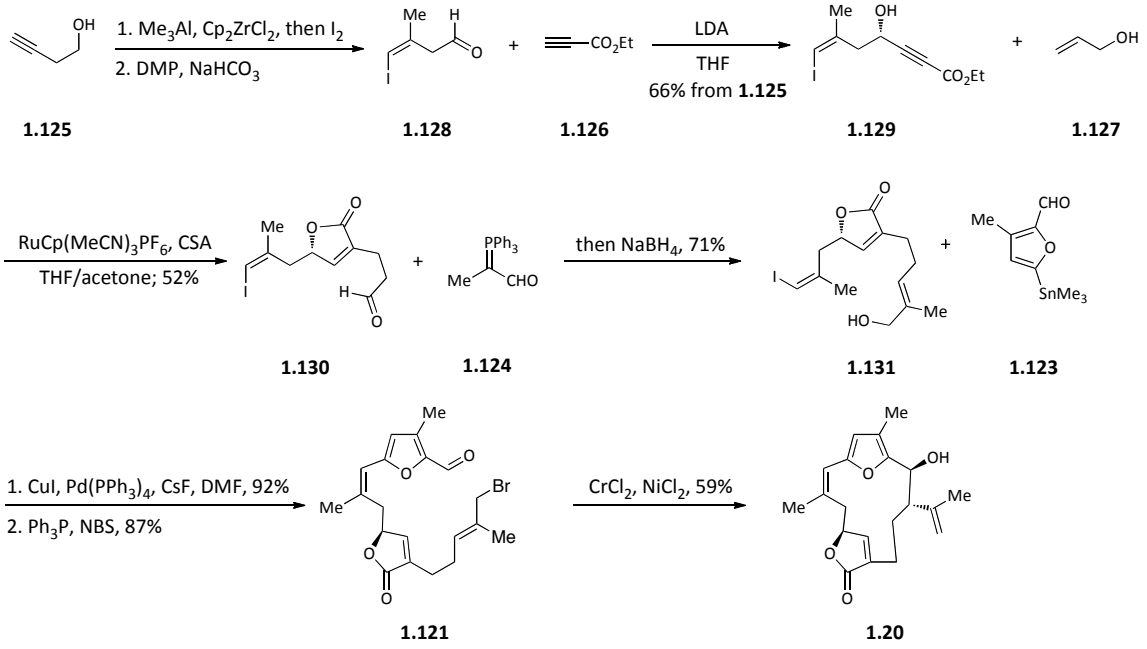
In contrast to others, the Trauner furanocembrane program has a core goal of elucidating the biosynthetic relationship between the regular and complex members of the class. Although their syntheses feature the use of strong bases, oxidants, and excessive temperatures to mimic "enzyme" mediated alterations, it is exciting to speculate what machinery nature has assembled to promote the necessary chemoselective transformations to generate the complex furanocembranes. The center of the Trauner program begins with racemic and asymmetric syntheses of bipinnatin J (**1.20**).[74] Their analysis of the molecule revealed six fragments that could be united in a nine-step sequence (Scheme 1.17).



bipinnatin J (**1.20**)

Scheme 1.17. Trauner's analysis of bipinnatin J (**1.20**).

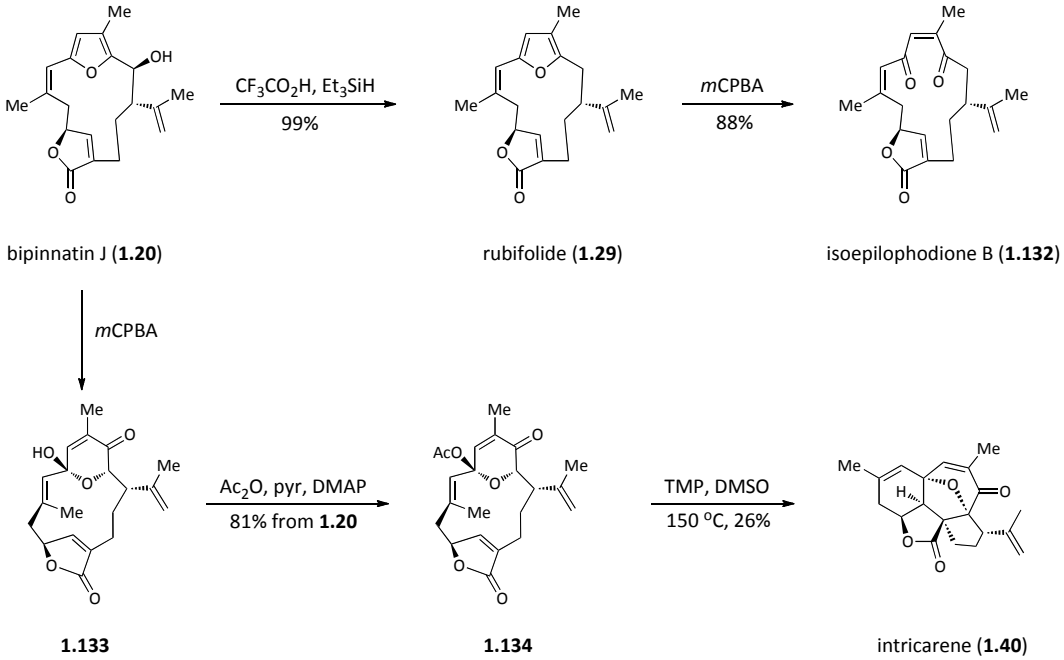
Zirconium mediated carboalumination of commercially available 3-butynol **1.125** was followed by isomerization, iodination, and Dess-Martin oxidation of the alcohol to give iodo-aldehyde **1.128** (Scheme 1.18). Nucleophilic addition of lithium ethyl propiolate afforded racemic propargylic alcohol **1.129**. Ru(II)-catalyzed Trost enyne reaction of **1.129** with allyl alcohol **1.127** was accompanied by tautomerization and transesterification to give butenolide **1.130**. Homologation with stabilized Wittig reagent **1.124** and chemoselective reduction of the resultant aldehyde with $NaBH_4$ gave allylic alcohol **1.131** in 99% yield. Stille coupling of **1.131** and **1.123** gave **1.121** in excellent yield. The alcohol was converted to the allylic bromide using PPh_3 and NBS, and identical to the Rawal protocol, NHK macrocyclization provided bipinnatin J (**1.20**) in 59% yield.



Scheme 1.18. Trauner's synthesis of bipinnatin J (**1.20**).

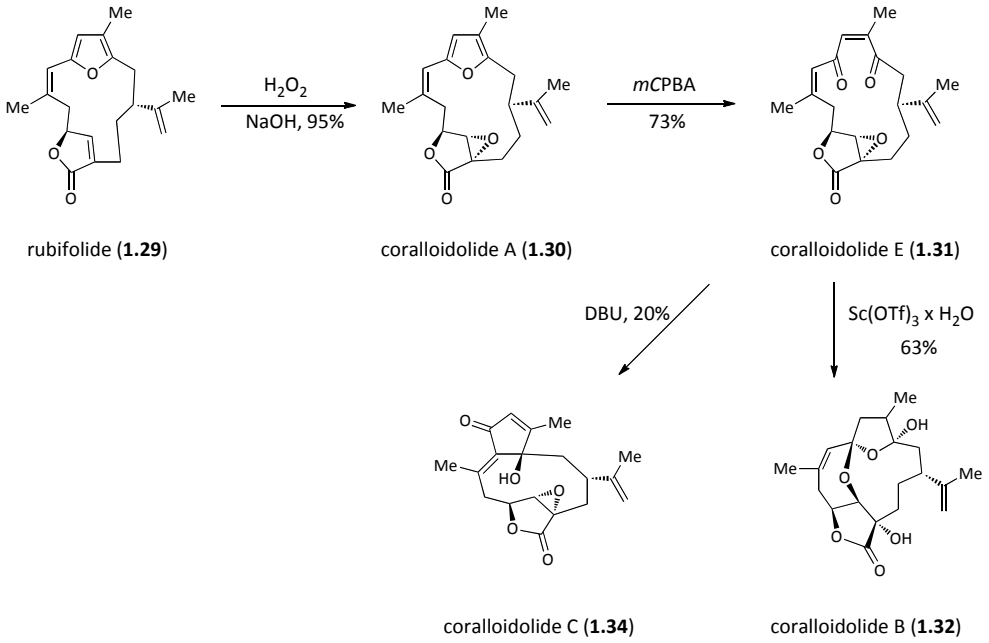
In a later publication, an asymmetric synthesis of bipinnatin J (**1.20**) was accomplished along with the biomemetic synthesis of intricarene (**1.40**), rubifolide (**1.29**), and isoepilophodione (**1.132**) (Scheme 1.19).[53] Synthetic rubifolide (**1.29**) was obtained in near quantitative yield through S_N1-deoxygenation of (-)-bipinnatin J (**1.20**) using TFA and Et_3SiH. Chemoselective oxidation by *m*CPBA, cleaved the furan to provide (+)-isoepilophodione B (**1.132**) in 88% yield. In this case the authors noted addition of singlet oxygen to the furan of rubifolide also provided (+)-isoepilophodione B (**1.132**), a hint to the possible biosynthesis of this metabolite.

Extending this study, bipinnatin J (**1.20**) was treated with *m*CPBA to provide hydroxypyranone **1.133**. After generation of acetate **1.134**, elimination of acetic acid was followed by 1,3-dipolar cycloaddition to provide (+)-intricarene (**1.40**) in 26% yield.



Scheme 1.19. Trauner's biomimetic syntheses.

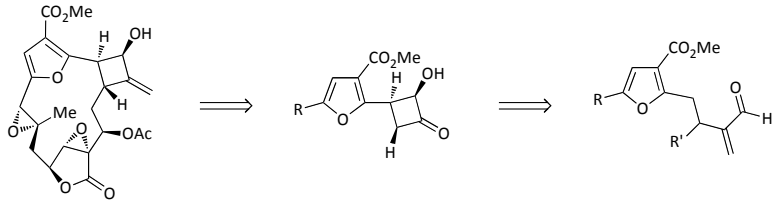
Expanding their program, the Trauner lab completed biomimetic syntheses of coralloidolides A (**1.30**), B (**1.31**), C (**1.32**), and E (**1.34**) (Scheme 1.20).[75] Starting with rubifolide (**1.29**) chemoselective nucleophilic epoxidation of the electron deficient butenolide gave coralloidolide A (**1.30**) as a single diastereomer, in 95% yield. Oxidative cleavage of the furan heterocycle with mCPBA provided coralloidolide E (**1.34**) in 88% yield. Hydration of this compound was accomplished, after treatment with the hydrate of scandium triflate in dioxane, to provide coralloidolide B (**1.31**) in 63% yield. Additionally, coralloidolide E (**1.34**) was advanced to coralloidolide C (**1.32**) via DBU promoted transannular aldol reaction. Interestingly, DBU was the only base capable of promoting this transformation.



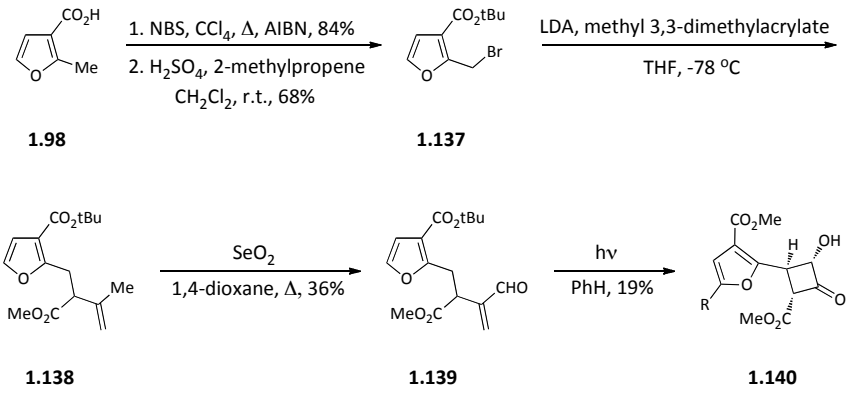
Scheme 1.20. Trauner's synthesis of the coralloidolides.

Methods to construct the carbon framework of rameswaralide (**1.43**) and havellockate (**1.44**) have been reported.[76-80] The ever-increasing interest in bielschowskysin (**1.37**) and providencin (**1.39**) is noteworthy. Following Sulikowski and Doroh's initial reporting of an unprecedented butenolide-alkylidene butenolide [2+2] photocycloaddition to synthesize the tetracyclic core of bielschowskysin (**1.37**) (Chapter II), the Lear lab reported a butenolide-allene [2+2] photocycloaddition following a similar synthetic route.[81, 82] Ongoing interest from added groups keeps bielschowskysin (**1.37**) at the forefront of furanocembrane targets.[83, 84]

In 2006, Pattenden and co-workers addressed the unique cyclobutanol substituted furan of providencin (**1.39**) using a model system.[85] Their analysis was based on a photochemically mediated, intramolecular C-H insertion of aldehyde precursor **1.136** (Scheme 1.21). Commercially available 2-methyl-3-furoic acid **1.98** was converted to the t-butyl ester and subjected to allylic bromination, to provide bromide **1.137** (Scheme 1.22).



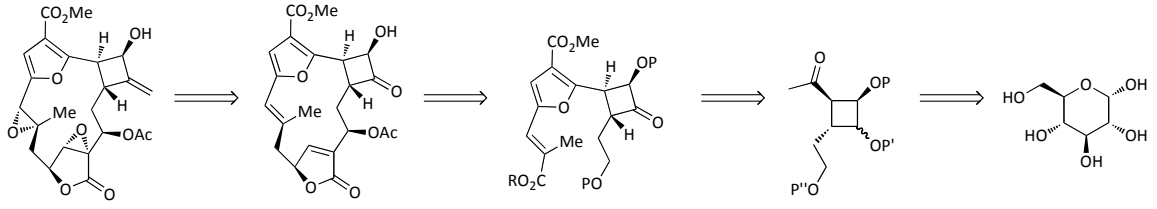
Scheme 1.21. Pattenden's analysis of providencin (**1.39**).



Scheme 1.22. Pattenden's approach to providencin (**1.39**).

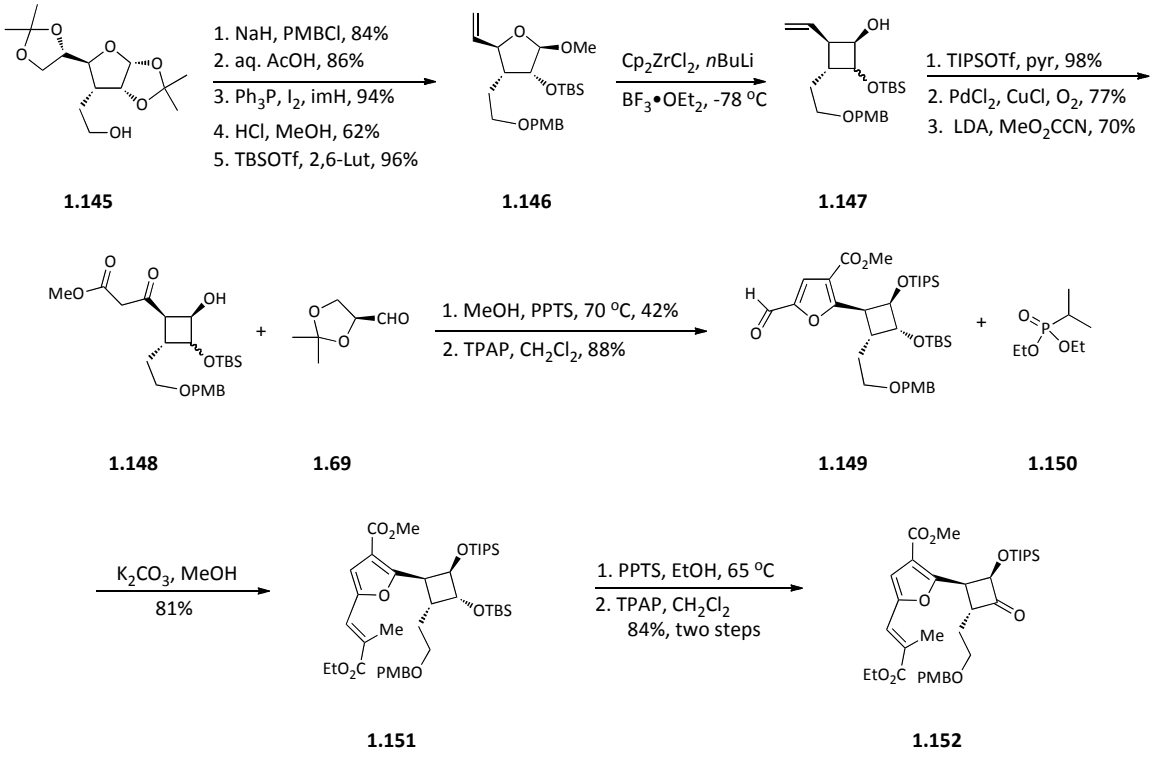
Lithiation of methyl 3,3-dimethylacrylate with LDA, followed by reaction with bromide **1.137** provided ester **1.138**. Allylic oxidation using SeO_2 gave aldehyde **1.139**, albeit in low yield. Lastly, photolysis of the aldehyde using a 400 W medium pressure Hg lamp led to a single photocycloadduct **1.140** in 19% yield. Although the reaction generated the cyclobutanol, it was of undesired configuration. The authors speculate the conformational bias imposed by performing the photochemistry on a congener with a complete macrocycle will deliver the correct stereochemistry.

The White approach to providencin (**1.39**) features a zirconium mediated deoxygenative ring contraction to synthesize the cyclobutane (Scheme 1.23).[86]



Scheme 1.23. White's analysis of providencin (**1.39**).

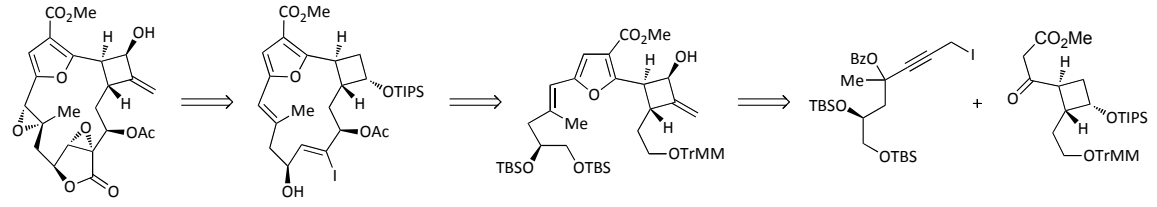
Alcohol **1.145** was prepared in six steps from α-D-glucose **1.144** and protected as its PMB ether (Scheme 1.24). Selective hydrolysis of the exocyclic acetonide provided a diol. Treatment of the latter with I_2, PPh_3, and imidazole gave a vinyl tetrahydrofuran in excellent yield. Methanolysis furnished an alcohol that was protected as its TBS ether. To affect the oxygen abstraction, dicyclopentadienylzirconium(0) was generated by treatment of dicyclopentadienylzirconium dichloride with *n*BuLi in $PhCH_3$. Tetrahydrofuran **1.146** was added and the reaction proceeded in the presence of BF_3•OEt_2 to provide cyclobutanol **1.147** with full transcription of all stereocenters from the furan. Following generation of the TIPS ether, Wacker oxidation yielded a methyl ketone. Reaction of the kinetic enolate with Mander's reagent gave β-keto ester **1.148**.



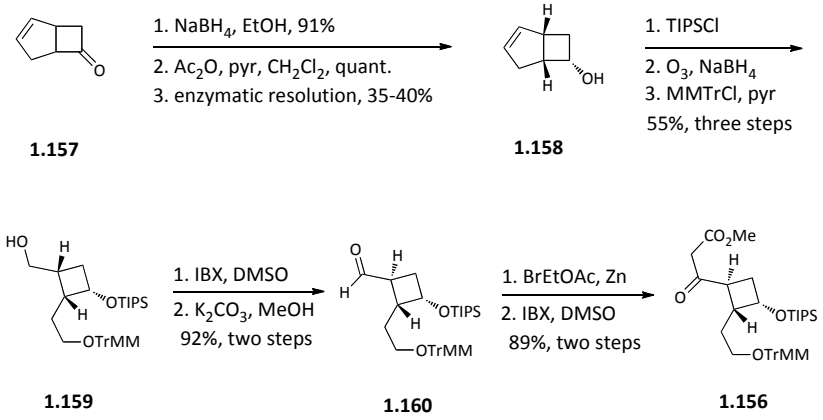
Scheme 1.24. White's approach to providencin (**1.39**).

Acid promoted Knoevenagel condensation with D-glyceraldehyde acetonide **1.69** gave an intermediate lactone. TPAP oxidation provided aldehyde **1.149** in 88% yield. Horner Wadsworth Emmons olefination with ethyl 2-(diethoxyphosphono) propionate **1.150** affords α, β-unsaturated ester **1.151** in 81% yield. Lastly, selective cleavage of the TBS ether, followed by TPAP oxidation gave ketone **1.152**, the precursor to exo-methylene installation.

The Mulzer group has made significant progress toward providencin.[87, 88] Their strategy hinged on furan cyclization utilizing the Wipf protocol (Scheme 1.25).[71] Known cyclobutanone **1.157** was reduced with sodium borohydride, acetylated, and resolved enzymatically to provide enantiomerically pure **1.158** (Scheme 1.26). Conversion to the TIPS ether and reductive ozonolysis gave a diol. The less hindered of the primary alcohols was protected as its monomethoxytrityl ether to give **1.159**. The other alcohol was oxidized to the aldehyde and epimerized to afford **1.160**. Reformatsky reaction of **1.160** and oxidation gave β-keto ester **1.156**.

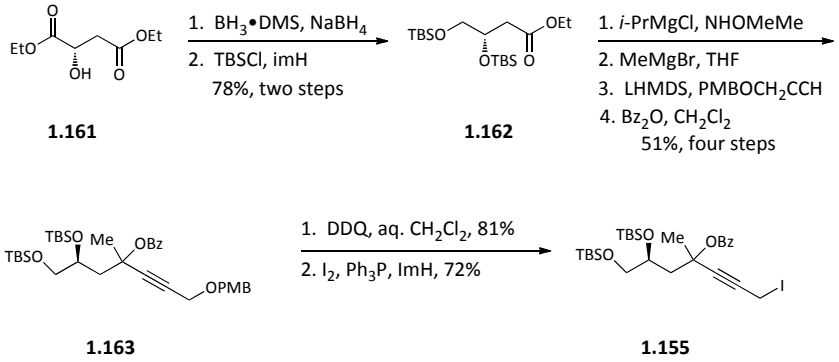


Scheme 1.25. Mulzer's first-generation retrosynthetic analysis of providencin (**1.39**).



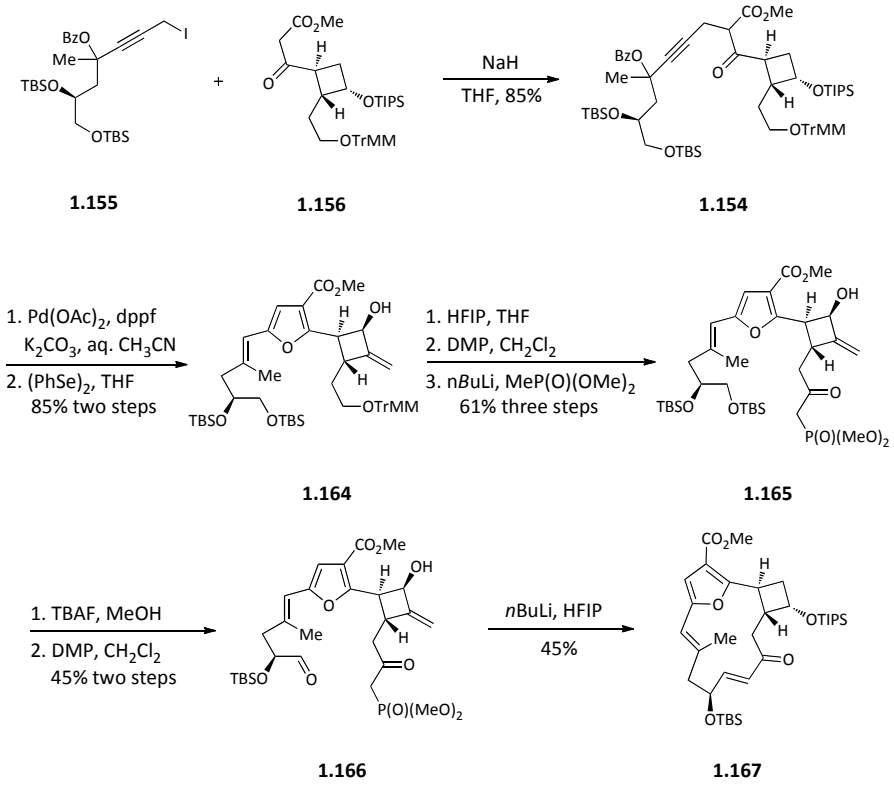
Scheme 1.26. Mulzer's synthesis of β-keto ester **1.156**.

In a parallel synthesis, (-)-diethyl malate **1.162** was converted to the bis silyl ether **1.163** (Scheme 1.27). Following conversion of the ester to a methyl ketone, addition of the organolithium reagent derived from PMB protected propargyl alcohol provided an inconsequential mixture of tertiary alcohols that were subsequently converted to the benzoyl esters **1.164**. Oxidative cleavage of the PMB ether and iodination gave fragment **1.155** in good yield.



Scheme 1.27. Mulzer's synthesis of propargyl iodide **1.155**.

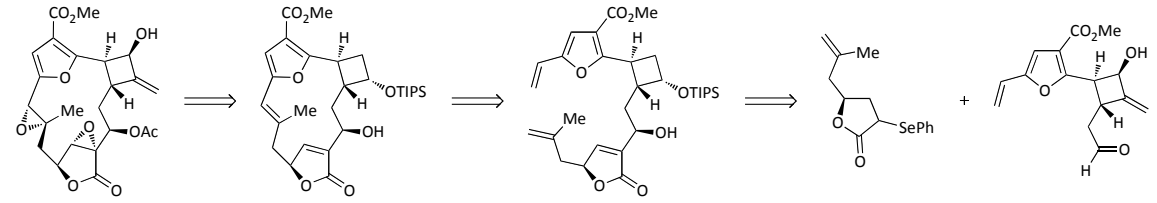
Alkylation of β-keto ester **1.156** with propargyl iodide **1.155** proceeded smoothly to furnish alkyne **1.154** (Scheme 1.28). Wipf cyclization occurred to give a mixture of *E*- and *Z*-olefins in quantitative yield. The mixture was equilibrated to the *E*-isomer **1.164** by reversible addition/elimination of a phenylselenyl radical. Deprotection and oxidation of the primary alcohol gave the corresponding aldehyde, which was converted into keto phosphonate **1.165**. The alcohol was liberated and oxidized to aldehyde **1.166** using Dess-Martin periodinane. Horner-Emmons cyclization gave macrocycle **1.167**.



Scheme 1.28. Mulzer's HWE macrocyclization method.

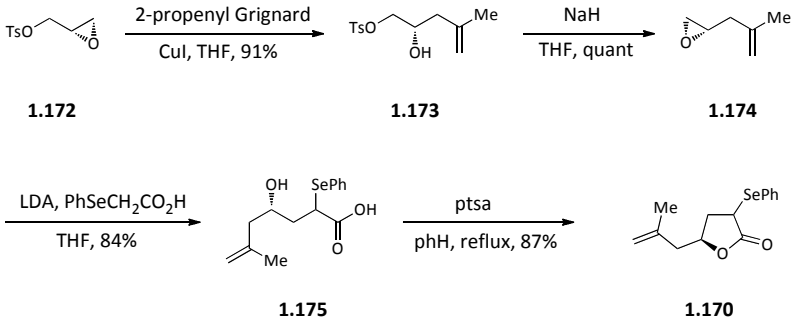
The inability to further macrocycle **1.167** to iodide **1.153** forced the authors to abandon this route. In a second-generation approach, Mulzer envisioned a ring closing

metathesis strategy to construct the macrocycle (Scheme 1.29). This approach would hinge on the ability to generate the desired olefin geometry in the metathesis event.



Scheme 1.29. Mulzer's second-generation analysis of providencin (**1.39**).

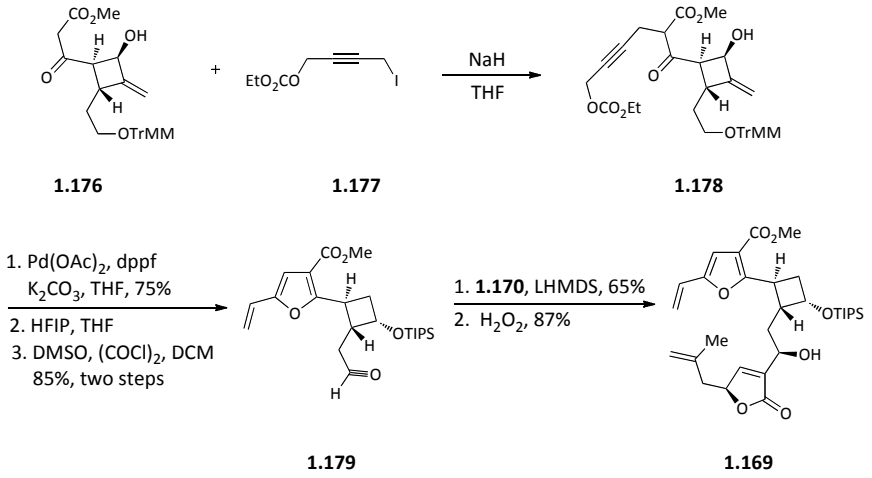
Cuprate addition to tosylate **1.172** provided homoallylic alcohol **1.173**, which was converted back to epoxide **1.174** under basic conditions (Scheme 1.30). Dianion addition of (phenylseleno)acetic acid gave hydroxy acid **1.175**, with subsequent acid mediated lactonization providing selenolactone **1.170**.



Scheme 1.30. Mulzer's synthesis of lactone **1.170**.

Alkylation of the previously prepared β-keto ester **1.176** with propargyl iodide **1.177** provided alkyne **1.178** (Scheme 1.31). Removal of the protecting group and

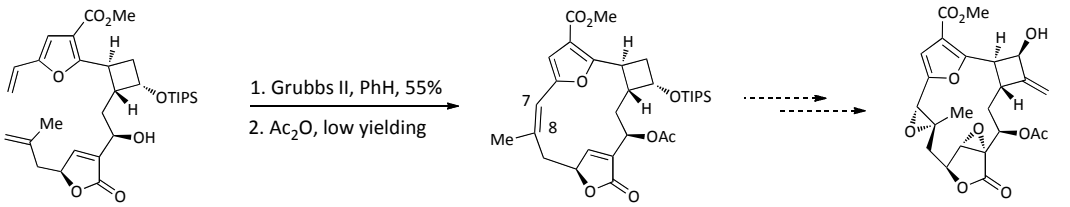
oxidation of the alcohol generated an aldehyde that was reacted with the lithium derivative of selenide **1.170**. Oxidative elimination led to butenolide **1.169**.



1.176 **1.177** **1.178** **1.179** **1.169**

Scheme 1.31. Mulzer's synthesis of metathesis precursor.

While ring-closing metathesis proceeded in moderate yield to provide olefin **1.180**, the group was unable to reliably advance the material to providencin (**1.39**) (Scheme 1.32). Installation of the C7-C8 epoxide proved to be especially problematic.



1.169 **1.180** providencin (**1.39**)

Scheme 1.32. Mulzer's RCM macrocyclization method.

Conclusion

Investigations into the natural products chemistry of gorgonian corals have revealed fascinating metabolites with interesting biological activity. Results from biomimetic synthetic programs suggest members of the furanocembranes and pseudopteranes are linked through oxidative alterations and non-enzymatic rearrangements. With the isolation of more complex members of the families, synthetic activity will only increase in the future.

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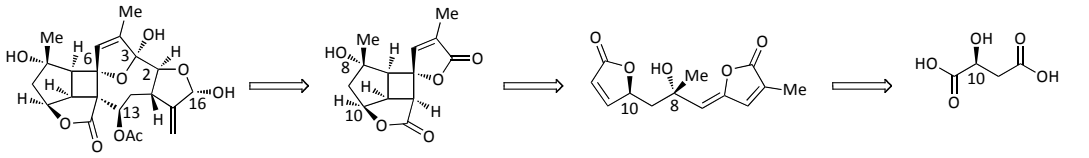
CHAPTER II

SYNTHETIC ANALYSIS AND DEMONSTRATION OF [2+2] PHOTOCYCLOADDITION

Synthetic Analysis

From a chemical perspective, bielschowskysin (**1.36**) illustrates nature's aptitude for manufacturing intricate metabolites with interesting biological activity. Assessment of the medicinal properties of this compound along with the heuristic challenges posed by its structure prompted our interest in a total synthesis program. Dr. Brandon Doroh designed the work described herein.

Taking into account reasonable disconnections for bielschowskysin (**1.36**), our initial focus was its most audacious feature: a strained cyclobutane that incorporates a spirocyclic center at C6 and a quaternary center at C12. Although a cationic cyclization is likely responsible for its presence, it is possible the system is assembled through transannular [2+2] photocycloaddition of the appropriate macrocyclic alkylidene dihydrofuran (Scheme 1.5). As illustrated in Scheme 2.1, we opted to introduce the eastern ring late stage in order to examine the stereochemical outcome of the intramolecular [2+2] photocycloaddition on an austere model system. Of importance would be the diastereoselectivity of the reaction, particularly at C6, and its dependence on the geometry of the alkylidene butenolide **2.2**.[1]



Bielschowskysin: (**1.36**) **2.1** **2.2** (-) - malic acid (**2.3**)

Scheme 2.1. Model system retrosynthetic analysis.

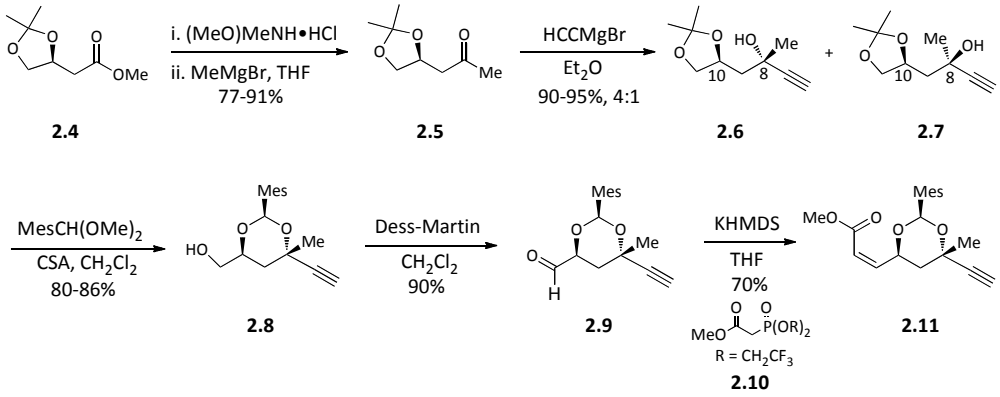
This strategy would allow us to take advantage of macrocyclic stereocontrol later in the synthesis as the rigidity and conformation of the western tetracycle could be used to direct installation of the stereocenters at C2 and C3. Without specifying how this endgame requirement will be accomplished, until chapter IV, the general strategy adumbrated above forecasts the tetracycle **2.1** should result from photolysis of bisbutenolide **2.2**. The 8,10-anti relationship of the two stereocenters would be established from (-)-malic acid (**2.3**).[2]

Demonstration of [2+2] Photocycloaddition

The three-step protocol for preparation of ester **2.4** from (-)-malic acid (**2.3**) was previously reported and serves as the starting point for the synthesis (Scheme 2.2).[2, 3] Ester **2.4** was converted directly to methyl ketone **2.5** by in situ generation of the Weinreb amide followed by reaction with methyl magnesium bromide.[4] Compound **2.5** was subjected to the action of ethynylmagnesium bromide, under chelation control, to provide a 4:1 mixture of tertiary alcohols **2.6** and **2.7** in good yield.[5, 6] This result allowed us to take advantage of stereodivergence as the major 8,10-anti diastereomer **2.6**

provides the required stereochemistry for bielschowskysin (**1.36**), while the 8,10-syn diastereomer **2.7** can be advanced to other furanocembranes (Scheme 1.4).

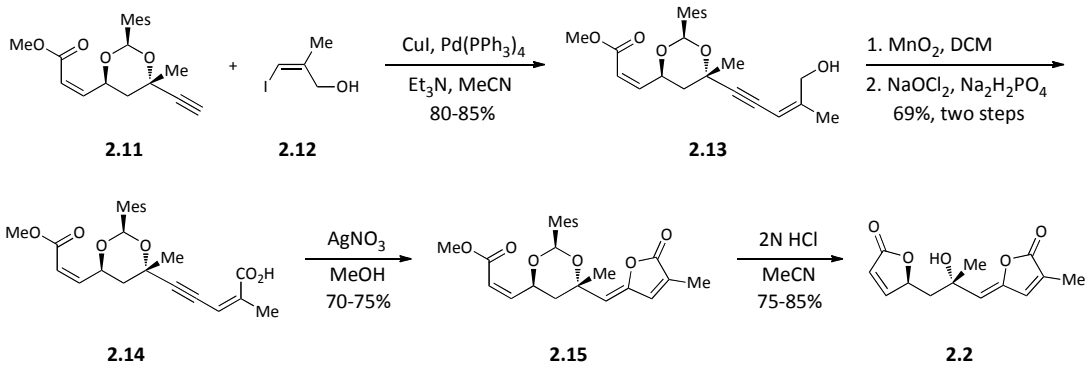
Tertiary alcohol **2.6** was taken forward and the 1,2- acetonide exchanged for a 1,3-dioxane, liberating the primary alcohol in 80-86% yield.[7] $NaHCO_3$ buffered oxidation with Dess-Martin periodinane gave aldehyde **2.9** in 90% yield.[8] Olefination following the Still-Gennari modification of the Horner-Wadsworth-Emmons reaction provided the Z-enoate **2.11** in 70% yield.[9-11]



Scheme 2.2. Synthesis of Z-enoate **2.11**.

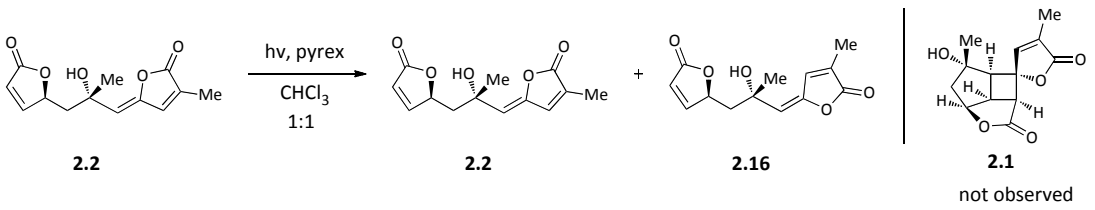
The (Z)-enoate **2.11** was advanced through Sonogashira coupling with known iodide **2.12** to afford allylic alcohol **2.13** in 80-85% yield (Scheme 2.3).[12, 13] Deoxygenation of the CH_3CN using the "freeze-pump-thaw" protocol is vital as aerated CH_3CN promotes formation of the homo-coupled acetylene. Additionally, large-scale Sonogashira coupling between **2.11** and **2.12** is far more expeditious when using excess of Et_3N (3-5 eq). Oxidation of allylic alcohol **2.13** with freshly prepared MnO_2 provided an aldehyde that was prone to decomposition within 1 h.[14, 15] As such, the crude

aldehyde was subjected directly to Pinnick oxidation to give carboxylic acid **2.14** in moderate yield.[16] Silver catalyzed cycloisomerization with $AgNO_3$ in MeOH provided alkylidene butenolide **2.15** as a single geometric isomer.[17, 18] Lastly, hydrolysis of the mesitylidene acetal with 2N HCl in CH_3CN and concomitant translactionization generated bis-butenolide **2.2**.



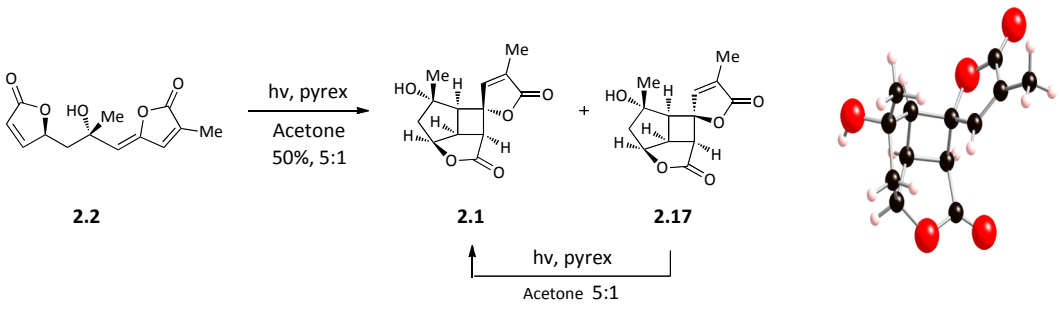
Scheme 2.3. Synthesis of bisbutenolide **2.2**.

With bis-butenolide **2.2** in hand, we turned our attention to the [2+2] photocycloaddition (Scheme 2.4). Irradiation of a chloroform solution of **2.2** with a 275 W sun lamp in a Pyrex test tube for 2 h led to a 3.6:1 ratio of geometric isomers **2.2** and **2.16** as determined by ^{1}H NMR. Further irradiation of the chloroform solution resulted in consumption of both geometric isomers and production of a complex mixture of unidentifiable compounds. Similarly, prolonged irradiation in CH_2Cl_2, THF, EtOAc, hexanes, and pentanes generated a mixture of geometric isomers followed by unproductive consumption of the starting material.



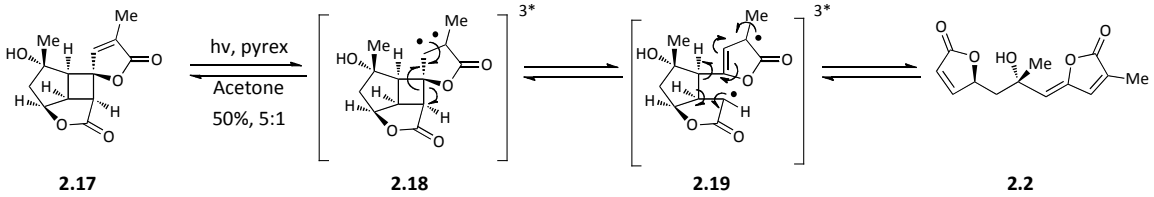
Scheme 2.4. Initial attempt at [2+2] photocycloaddition.

It is well established that [2+2] photocycloadditions involving α,β-unsaturated ketones occur with simple light absoprtion.[19-21] Conversely, α,β-unsaturated esters undergo [2+2] photocycloaddition in the presence of a sensitizer.[22-25] This precedent, in addition to our observations, indicated the reaction would need to be sensitized to achieve cyclobutane formation.[19, 26, 27] Indeed, the system behaved quite differently when acetone was used as both solvent and sensitizer (Scheme 2.5). Irradiation of an acetone solution of **2.2** with a 450 W Hanovia mercury lamp in a Pyrex test tube for 2 h led to a 1:1 mixture of geometric isomers **2.2** and **2.16**. Further exposure for 8 h led to a 5:1 ratio of photoadducts **2.1** and **2.17** in 50% yield. The structure of **2.1** was unambiguously determined by single-crystal X-ray analysis.



Scheme 2.5. Intramolecular [2+2] photocycloaddition.

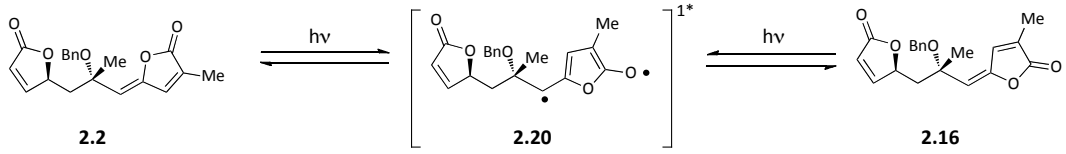
Of importance, is our ability to photolytically convert the minor C6 epimer **2.17** to the major isomer **2.1** through regeneration of the starting alkylidene butenolide **2.2** (Scheme 2.6). Excitation of the **2.17** generates a triplet diradical, shown as resonance contributor **2.18**. Fragmentation of the cyclobutane ring provides diradical intermediate **2.19**. After fragmentation of the cyclopentane ring, butenolide **2.2** is restored and undergoes photolysis to provide a mixture of **2.1** and **2.17** (Scheme 2.5).



2.17 **2.18** **2.19** **2.2**

Scheme 2.6. Conversion of **2.17** to **2.2**.

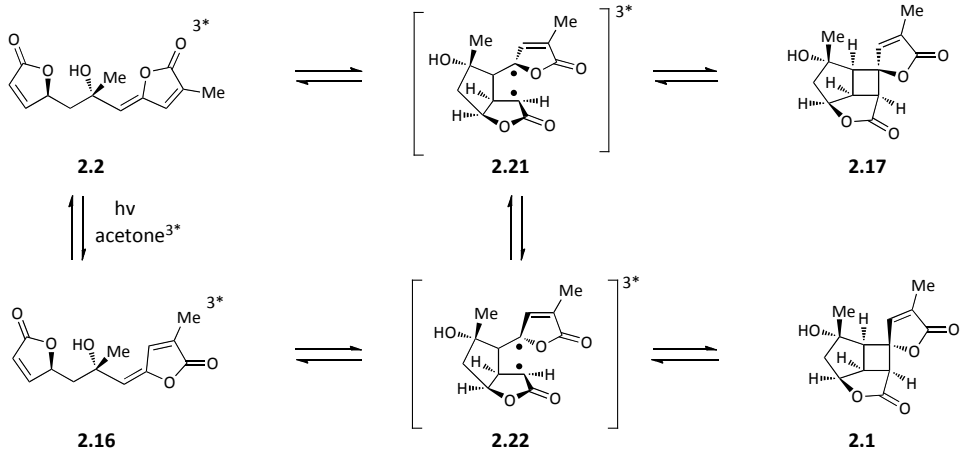
Although the [2+2] photocycloaddition of enones and butenolides with alkenes, alkynes, and allenes has been reported in the literature, the butenolide-alkylidene photocycloaddition is unprecedented.[19, 26-29] Mechanistically, the initial excitation of the alkylidene butenolide in $CHCl_3$ is probably $^1\pi\pi^*$ (Scheme 2.7).[26] Given that single bond rotation is uninhibited, cis-trans isomerization competes with intersystem crossing (ISC) and the successive photocycloaddition.



2.2 **2.20** **2.16**

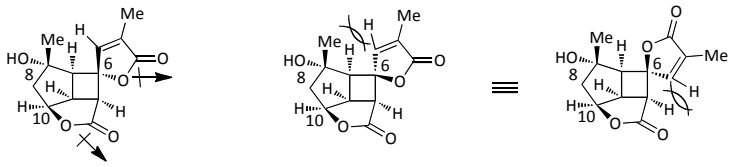
Scheme 2.7. Singlet state reaction.

Applying a study by Bartlett to our system suggests that upon irradiation, triplet acetone should transfer its energy to **2.2** and **2.16** through a collision type process (Scheme 2.8).[30] Excited **2.2** and **2.16** ($^3n\pi^*$) react following the "rule of five" to form the cyclopentane and 1,4-diradicals **2.21** and **2.22**.[31-33] Reversion of the 1,4-diradicals to ground state **2.2** and **2.16** competes with spin inversion and subsequent ring closure to provide cyclobutane photoadducts **2.1** and **2.17**.[33, 34]



Scheme 2.8. Triplet state reaction.

As revealed previously (Scheme 2.5), irradiation of **2.2** leads to a 5:1 diastereomeric mixture of **2.1** and **2.17** at C6. The favored production of **2.1** could involve an unfavorable steric interaction between the vinyl proton at C5 and the methine protons at C7 and C12 of the minor diastereomer (Figure 2.1). Additionally, unfavorable dipole or electrostatic interactions developed during the diradical closure could promote the formation of one isomer as was reported by the Crimmins group during their ginkgolide program.[35]



major **2.1** minor **2.17** minor **2.17**

Figure 2.1. Photoadduct comparison.

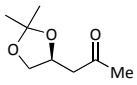
Conclusion

Presented in this chapter is the concise assembly of tetracycle (**2.1**). [2+2] photocycloaddition of this model system was significant, as it demonstrated the ability to introduce the spirocyclic center at C6 with the required stereochemistry to continue pursuit of bielschowskysin (**1.36**). In fact, this study provided precedence for the other reported work toward bielschowskysin. In 2009 the Lear lab reported a butenolide-allene [2+2] photocycloaddition to synthesize the cyclobutane ring system.[36]

Experimental Methods

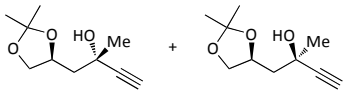
General. All non-aqueous reactions were performed under an argon atmosphere in oven-dried glassware. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Diethyl ether (Et_2O), acetonitrile (CH_3CN), dichloromethane (CH_2Cl_2), and dimethylformamide (DMF) were obtained by passing commercially available formulations through activated alumina columns (MBraun MB-SPS solvent system). Tetrahydrofuran (THF) was obtained by distillation from benzophenone-sodium. Triethylamine (Et_3N) and diisopropylamine were distilled from calcium hydride and stored over sodium hydroxide. Reactions were monitored by thin-layer chromatography (TLC) using E. Merck precoated silica gel 60 F254 plates. Visualization was accomplished with UV light and aqueous stain followed by charring on a hot plate. Flash chromatography was conducted using the indicated solvents and silica gel (230-400 mesh). Yields refer to chromatographically and spectroscopically homogeneous materials. Infrared spectra were obtained as thin films on NaCl plates using a Thermo Electron IR100 series instrument and are reported in terms of frequency of absorption (cm-1). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 300, 400, 500, or 600 MHz spectrometers and are reported relative to deuterated solvent signals (7.27 and 77.2). High-resolution mass spectra (ESI) were obtained at the Department of Chemistry and Biochemistry, University of Notre Dame. Dr. Joseph Reibenspies solved x-crystal structures at the X-ray diffraction facility of Department of Chemistry, Texas A&M University.

Preparative Procedures



2.5

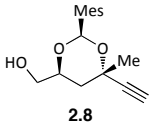
To a slurry of methyl ester **2.4** (1.0 eq, 65 g, 0.37 mol) and $MeNHOCH_3$•HCl (1.3 eq, 48 g, 0.49 mol) in THF (500 mL) at -10 ^oC was added MeMgBr (3.0 M in Et_2O, 5.0 eq, 620 mL, 1.9 mol) over 6 h. The reaction was warmed to ambient temperature and stirred 12 h. Saturated aqueous ammonium chloride was added and the layers separated. The organics were washed with water (1 x 500 mL), brine (1 x 500 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by distillation (0.1 mm Hg, 60-66 ^oC) to provide ketone **2.5** (32 g, 0.24 mol, 64%) as a colorless oil. Spectral data consistent with reported values.[37]



2.6 **2.7**

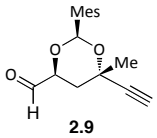
To a solution of ketone **2.5** (1.0 eq, 4.6 g, 29 mmol) in Et_2O (300 mL) at -78 ^oC was added HCCMgBr (0.5 M in THF, 2.5 eq, 150 mL, 73 mmol). The reaction was stirred 3 h, warmed to ambient temperature, and washed with saturated aqueous ammonium chloride (3x 100 mL), water (1 x 100 mL), brine (1 x 100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (4:1 hexanes/EtOAc) to provide tertiary alcohols **2.6** (3.9 g, 21 mmol, 72%) and **2.7** (800 mg, 4.3 mmol, 15%) as pale yellow oils: **2.6**: $[\alpha]^{23}_D$ +4.2^o (*c* 1.11, CH_2Cl_2); R_f 0.31 (3:1 hexanes/EtOAc); IR (thin film, cm^{-1}): 3439, 2984, 1371, 1246, 1216, 1156, 1052; ^1H NMR (400 MHz, $CDCl_3$) δ 4.70 (1H, dddd, *J* = 7.2, 6.8, 6.4, 6.4 Hz), 4.20 (1H, s), 4.15 (dd, *J* = 7.6, 6.8 Hz, 1H), 3.61 (dd, *J* = 7.6, 7.2 Hz, 1H), 2.50 (s, 1H), 1.87 (d, *J* = 3.2 Hz, 1H), 1.85 (s, 1H), 1.53 (s, 3H), 1.45 (s, 3H),

1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 110.2, 87.3, 74.6, 72.2, 69.9, 67.8, 45.9, 30.9, 27.3, 26.1; HRMS (ESI) calcd for $C_{10}H_{16}O_3Li$ $[M+Li]^+$ 191.1259 found 191.1260. **2.7**: $[\alpha]^{24}_D$ +27.6^o (*c* 1.11, CH_2Cl_2); R_f 0.25 (3:1 hexanes/EtOAc); IR (neat, cm^{-1}): 3430, 2934, 1372, 1246, 1217, 1163, 1052; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40 (dddd, *J* = 8.0, 6.8, 6.0 5.6 Hz, 1H), 4.14 (*J* = dd, 8.0, 5.6 Hz, 1H), 3.65 (*J* = dd, 8.0, 8.0 Hz, 1H), 2.47 (s, 1H), 2.11 (dd, *J* = 14.0, 6.8 Hz, 1H), 1.91 (dd, *J* = 14.0, 6.0 Hz, 1H), 1.57 (s, 3H), 1.41 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 108.7, 87.2, 73.3, 71.6, 70.0, 66.7, 45.8, 30.3, 26.8, 25.8; HRMS (ESI) calcd for $C_{10}H_{16}O_3Li$ $[M+Li]^+$ 191.1259 found 191.1260.



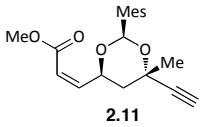
2.8

To a solution of alcohol **2.6** (1.0 eq, 4.3 g, 23 mmol) in CH_2Cl_2 (250 mL) at 0 ^{o}C was added mesitaldehyde dimethylacetal (1.8 eq, 7.8 g, 42 mmol) and CSA (0.2 eq, 700 mg, 0.46 mmol). The reaction was stirred 3 h and warmed to ambient temperature. The organics were washed with saturated aqueous sodium bicarbonate (1 X 50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (4:1 hexanes/EtOAc) to provide mesitylidene acetal **2.8** (5.5 g, 20 mmol, 85 %) as a red gel: $[\alpha]_D^{23}$ +4.2° (*c* 2.26, CH_2Cl_2); R_f 0.2 (3:1 hexanes/EtOAc); IR (thin film, cm^{-1}): 3513, 3273, 2928, 1138, 1065, 987; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.84 (s, 2H), 6.42 (s, 1H), 4.26 (dddd, *J* = 11.6, 8.8, 6.1, 2.7 Hz, 1H), 3.73 (dd, *J* = 11.8, 4.0 Hz, 1H), 3.62 (dd, *J* = 11.8, 6.2 Hz, 1H), 2.63 (s, 1H), 2.46 (s, 6H), 2.25 (s, 3H), 1.83 (dd, *J* = 12.9, 11.8 Hz, 1H), 1.69 (dd, *J* = 12.9, 8.7 Hz, 1H), 1.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 136.7, 130.2, 129.6, 95.6, 83.6, 74.4, 69.9, 65.2, 60.1, 37.9, 29.4, 20.8, 20.6; HRMS (ESI) calcd for $C_{17}H_{22}O_3Li$ $[M+Li]^+$ 281.1729 found 281.1742.



2.9

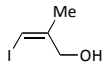
To a solution of alcohol **2.8** (1.0 eq, 2.5 g, 9.1 mmol) in CH_2Cl_2 (100 mL) at ambient temperature was added $NaHCO_3$ (3.0 eq, 27 mmol, 2.3 g) and Dess-Martin periodinane (1.2 eq, 11.0 mmol, 4.6 g). The reaction was stirred 2 h and diluted with Et_2O (100 mL). The solution was washed with saturated aqueous sodium bicarbonate (1 X 100 mL), saturated aqueous sodium thiosulfate (1 x 100 mL), brine (2 x 50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2:1 hexanes/EtOAc) to provide aldehyde **2.9** (2.2 g, 8.2 mmol, 90 %) as a colorless oil: $[\alpha]_D^{23}$ -20.9° (*c* 1.20, CH_2Cl_2); R_f 0.3 (2:1 hexanes/EtOAc); IR (thin film, cm^{-1}): 2931, 1739, 1613, 1453, 1374, 1254; ^1H NMR (300 MHz, $CDCl_3$): δ 9.74 (s, 1H), 6.85 (s, 2H), 6.47 (s, 1H), 4.61 (dd, *J* = 12.0, 2.7 Hz, 1H), 2.70 (s, 1H), 2.47 (s, 6H), 2.26 (s, 3H), 2.04 (dd, *J* = 13.1, 2.7 Hz, 1H), 1.81 (dd, *J* = 13.0, 11.9 Hz, 1H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.6, 138.5, 136.8, 129.6, 95.7, 82.5, 77.9, 75.4, 70.1, 36.8, 29.4, 20.6, 20.1; HRMS (ESI) calcd for $C_{17}H_{20}O_3Li$ $[M+Li]^+$ 279.1572 found 279.1561.



2.11

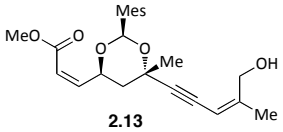
To a solution of bis(2,2,2-trifluoroethyl) methylphosphonate (1.1 eq, 1.3 g, 4.1 mmol) in THF (40 mL) at -78 °C was added KHMDS (0.5 M in $PhCH_3$, 1.1 eq, 8.2 mL, 4.5 mmol). After stirring 10 min, aldehyde **2.9** (1.0 eq, 1.0 g, 3.7 mmol) was added as a solution in THF (5 mL). The reaction was stirred 1 h at -78 °C and warmed to ambient temperature. The reaction was diluted with EtOAc (20 mL), washed with water (1 x 20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (4:1 hexanes/EtOAc) to provide

ester **2.11** (820 mg, 2.6 mmol, 71 %) as a colorless oil: $[\alpha]_D^{23}$ +98.8° (*c* = 0.24, CH_2Cl_2); R_f 0.5 (4:1 hexanes/EtOAc); IR (thin film, cm^{-1}): 3271, 2926, 1722, 1437, 1204, 1126, 985, 822; ^1H NMR (300 MHz, $CDCl_3$): δ 6.82 (s, 2H), 6.46 (s, 1H), 6.31 (dd, *J* = 11.8, 6.9 Hz, 1H), 5.81 (dd, *J* = 11.8, 1.5 Hz, 1H), 5.68 (ddd, *J* = 12.2, 6.2, 3.0 Hz, 1H), 3.77 (s, 3H), 2.73 (s, 1H), 2.47 (s, 6H), 2.23 (s, 3H), 2.05 (dd, *J* = 12.9, 2.4 Hz, 1H), 1.72 (dd, *J* = 12.8, 11.3 Hz, 1H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 147.5, 137.0, 135.7, 129.2, 128.5, 117.8, 94.3, 82.3, 73.5, 71.1, 69.0, 50.2, 39.1, 28.3, 19.6, 19.0; HRMS (ESI) calcd for $C_{24}H_{24}O_4Li$ $[M+Li]^+$ 335.1835 found 335.1888.



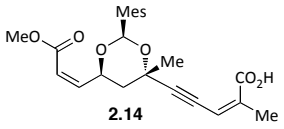
2.12

To a slurry of CuI (1.0 eq, 26 g, 0.14 mol) in Et_2O (300 mL) at -10 °C was added MeMgBr (3.0 M in Et_2O, 2.3 eq, 110 mL, 0.32 mol) and the reaction was stirred 10 min. Propargyl alcohol (1.0 eq, 8.0 mL, 0.14 mol) was added dropwise and the reaction stirred 2 h. After warming to ambient temperature, ICl (1.0 M in CH_2Cl_2, 1.0 eq, 300 mL, 0.14 mol) was added over 1 h. After stirring 18 h, saturated aqueous ammonium chloride was added and the reaction layers separated. The organics were washed with brine (3 x 100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (4:1 hexanes/EtOAc) to provide alcohol **2.12** (11 g, 60 mmol, 40%) as a colorless oil. Spectral data consistent with reported values.[13]



2.13

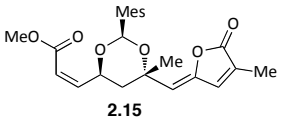
To a degassed solution of ester **2.11** (1.0 eq, 580 mg, 1.8 mmol) and iodide **2.12** (1.0 eq, 360 mg, 1.8 mmol) in CH_3CN (20 mL) at ambient temperature was added $Pd(PPh_3)_4$ (0.1 eq, 41 mg, 0.04 mmol), CuI (0.1 eq, 7 mg, 0.04 mmol), and Et_3N (2.0 eq, 500 μL, 3.6 mmol). The reaction was stirred 16 h, treated with celite (5 g) and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (4:1 hexanes/EtOAc) to provide allylic alcohol **2.13** (595 mg, 1.5 mmol, 83%) as a colorless oil: $[\alpha]_D^{23}$ +86.6° (*c* = 0.38, CH_2Cl_2); R_f 0.2 (4:1 hexanes/EtOAc); IR (thin film, cm^{-1}): 3453, 2919, 1721, 1438, 1264; ^1H NMR (300 MHz, $CDCl_3$): δ 6.81 (s, 2H), 6.44 (s, 1H), 6.36 (dd, *J* = 11.5, 7.3 Hz, 1H), 5.85-5.77 (m, 1H), 5.52 (d, *J* = 1.5 Hz, 1H), 4.47 (d, *J* = 12.3 Hz, 1H), 4.38 (d, *J* = 12.3 Hz, 1H), 3.74 (s, 3H), 2.47 (s, 6H), 2.23 (s, 3H), 2.11-2.04 (m, 1H), 1.98 (d, *J* = 1.6 Hz, 3H), 1.78 (dd, *J* = 12.8, 11.3 Hz, 1H), 1.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 147.5, 137.0, 135.7, 129.2, 128.5, 117.8, 94.3, 82.3, 73.5, 71.1, 69.0, 50.2, 39.1, 28.3, 19.6, 19.0; HRMS (ESI) calcd for $C_{24}H_{24}O_4Li$ $[M+Li]^+$ 335.1835 found 335.1888.



2.14

To a solution of allylic alcohol **2.13** (1.0 eq, 300 mg, 0.88 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added freshly prepared MnO_2 (10 eq, 750 mg, 8.8 mmol) and the reaction was stirred 2 h. The reaction mixture was filtered through a plug of celite and the filtrate concentrated *in vacuo*. To a solution of crude aldehyde (1.0 eq, 290 mg, 0.74 mmol) in t-BuOH (10 mL) was added 2-methyl-2-butene (1 mL) and $NaOCl_2$ (7.5 eq, 510 mg, 5.5 mmol) and $Na_2H_2PO_4$ (7.6 eq, 780 mg, 5.6 mmol) as a solution in water (5 mL). After 30 min the reaction was diluted with EtOAc

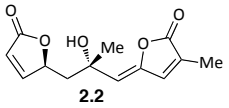
(15 mL). The aqueous layer was extracted with EtOAc (15 mL) and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2:1 hexanes/EtOAc) to provide acid **2.14** (250 mg, 6.2 mmol, 70 %) as a colorless oil: $[\alpha]_D^{23}$ +58.3° (*c* = 0.46, CH_2Cl_2); R_f 0.2 (1:1 hexanes/EtOAc); IR (thin film, cm^{-1}): 3453, 2919, 1721, 1694, 1438, 1264; ^1H NMR (300 MHz, $CDCl_3$): δ 6.80 (s, 2H), 6.44 (s, 1H), 6.26 (dd, *J* = 11.8, 7.6 Hz, 1H), 6.09 (d, *J* = 1.6 Hz, 1H), 5.85 (dd, *J* = 11.8, 1.2 Hz, 1H), 5.73-5.67 (m, 1H), 2.45 (s, 6H), 2.23 (s, 3H), 2.08 (d, *J* = 1.6 Hz, 3H), 2.03 (dd, *J* = 12.9, 2.6 Hz, 1H), 1.76 (dd, *J* = 12.9, 11.5 Hz, 1H), 1.60 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7, 165.8, 148.5, 138.7, 137.9, 136.7, 130.4, 129.5, 119.0, 117.8, 98.0, 95.4, 83.1, 71.7, 70.7, 51.4, 40.3, 29.1, 20.6, 20.1, 19.5; HRMS (ESI) calcd for $C_{24}H_{27}O_6Li$ [M-H] 411.1808 found 411.1010.



2.15

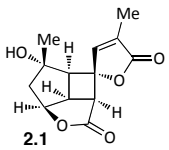
To a solution of acid **2.14** (1.0 eq, 410 mg, 0.87 mmol) in MeOH (87 mL) at ambient temperature was added $AgNO_3$ (0.1 eq, 15 mg, 0.09 mmol) in water (1 mL). The reaction was stirred 1 h, treated with celite (1g) and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (4:1 hexanes/EtOAc) to provide alkylidene butenolide **2.15** (307 mg, 0.65 mmol, 75%) as a colorless oil: $[\alpha]_D^{23}$ +76.2° (*c* = 0.53, CH_2Cl_2); R_f 0.3 (4:1 hexanes/EtOAc); IR (thin film, cm^{-1}): 2956, 1777, 1720, 1437, 1203, 1181; ^1H NMR (300 MHz, $CDCl_3$): δ 7.14 (d, *J* = 1.5 Hz, 1H), 6.82 (s, 2H), 6.30 (dd, *J* = 11.7, 7.0 Hz, 1H), 6.17 (s, 1H), 5.78 (dd, *J* = 11.7, 1.4 Hz, 1H), 5.51-5.45 (m, 2H), 3.66 (s, 3H), 2.57 (dd, *J* = 13.3, 2.2 Hz, 1H), 2.46 (s, 6H), 2.23 (s, 3H), 2.06 (s, 3H), 1.80 (dd, *J* = 13.3, 12.2 Hz, 1H), 1.54 (s,

3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 165.9, 149.6, 148.9, 138.3, 138.1, 137.3, 132.3, 130.3, 129.5, 119.1, 115.7, 96.3, 75.7, 73.0, 51.2, 40.5, 29.5, 21.2, 20.9, 10.4; HRMS (ESI) calcd for $C_{24}H_{28}O_6Li$ $[M+Li]^+$ 419.2046 found 419.2036.



2.2

To a solution of alkylidene butenolide **2.15** (1.0 eq, 19 mg, 0.05 mmol) in CH_3CN (5 mL) at ambient temperature was added 2N HCl (1 mL). The reaction was stirred 6 h and diluted with EtOAc (5 mL). The reaction mixture was washed with saturated sodium bicarbonate (1 x 5 mL), brine (1 x 5 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (4:1 hexanes/EtOAc) to provide bisbutenolide **2.2** (10 mg, 0.04 mmol, 85%) as a colorless oil: $[\alpha]_D^{23}$ +12.8° (*c* = 0.36, CH_2Cl_2); R_f 0.3 (1:1 hexanes/EtOAc); IR (thin film, cm^{-1}): 3449, 2924, 1751, 1713, 1380, 1239, 1169; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (dd, *J* = 5.7, 1.6 Hz, 1H), 7.02 (dt, *J* = 1.5, 1.4 Hz, 1H), 6.12 (dd, *J* = 5.7, 2.1 Hz, 1H), 5.37 (s, 1H), 5.24 (dddd, *J* = 9.2, 3.6, 2.1, 1.6 Hz, 1H), 2.46 (dd, J = 14.8, 3.6 Hz, 1H), 2.02 (s, 3H), 1.93 (dd, *J* = 14.8, 9.2, 1H), 1.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.9, 170.4, 157.4, 146.4, 138.9, 130.0, 121.4, 119.3, 81.3, 72.4, 45.2, 29.4, 11.0; HRMS (ESI) calcd for $C_{13}H_{14}O_5Li$ $[M+Li]^+$ 257.1001 found 257.1026.



2.1

A 450 W Hanovia medium pressure mercy vapor lamp was lowered inside a water-cooled Pyrex immersion well. A solution of bisbutenolide **2.2** (1.0 eq, 12 mg, 0.05 mmol) in acetone (5 mL) was irradiated for 8 h and concentrated *in vacuo*. The crude residue was purified by flash column

chromatography (4:1 hexanes/EtOAc) to provide photoadduct **2.1** (5 mg, 0.02mmol, 43%) as a crystalline solid: mp 252-255 ^{o}C; $[\alpha]_D^{23}$ +21.7° (*c* = 0.12, CH_2Cl_2); R_f 0.3 (2:1 hexanes/EtOAc); IR (CH_2Cl_2, cm^{-1}): 3412, 2963, 1772, 1736, 1655, 1561; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01 (q, *J* = 1.6 Hz, 1H), 5.42 (ddd, *J* = 8.1, 8.1, 4.5 Hz, 1H), 3.67 (ddd, *J* = 8.1, 8.0, 7.4 Hz, 1H), 3.50 (dd, J = 8.1, 1.7Hz, 1H), 3.21 (dt, *J* = 7.2, 1.8 Hz, 1H), 2.68 (ddd, *J* = 15.4, 8.04, 2.04 Hz, 1H), 2.04 (dd, *J* = 15.6, 4.5, 1H), 1.97 (d, *J* = 1.6 Hz, 3H), 1.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.6, 171.1, 143.3, 133.0, 85.5, 85.0, 60.8, 49.4, 46.8, 39.0, 23.7, 10.9; HRMS (ESI) calcd for $C_{13}H_{14}O_5Li$ $[M+Li]^+$ 257.1001 found 257.0096.

Notes and References

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Appendix A1:

Spectra Relevant to Chapter II.

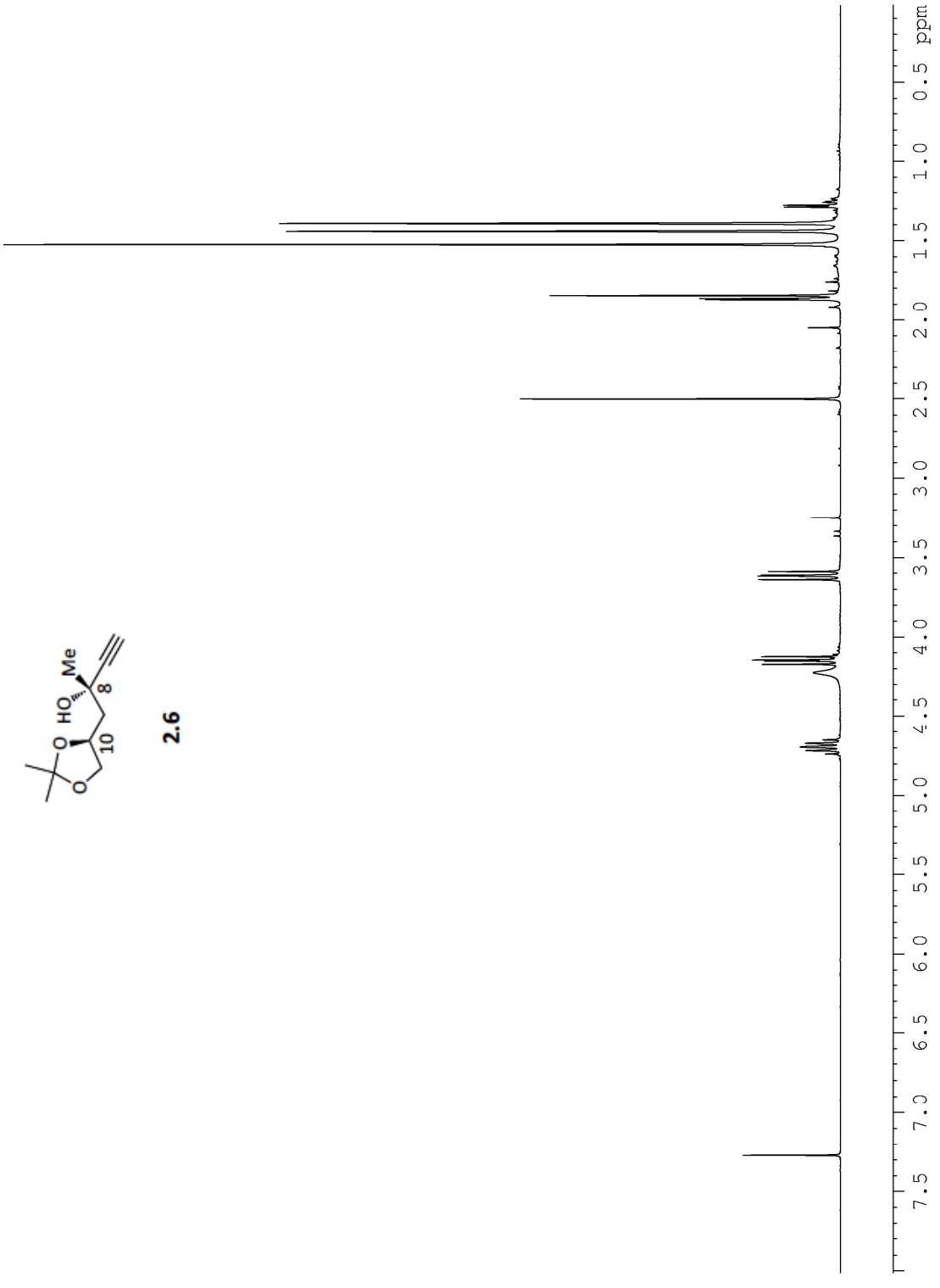


Figure A1.1. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **2.6**.

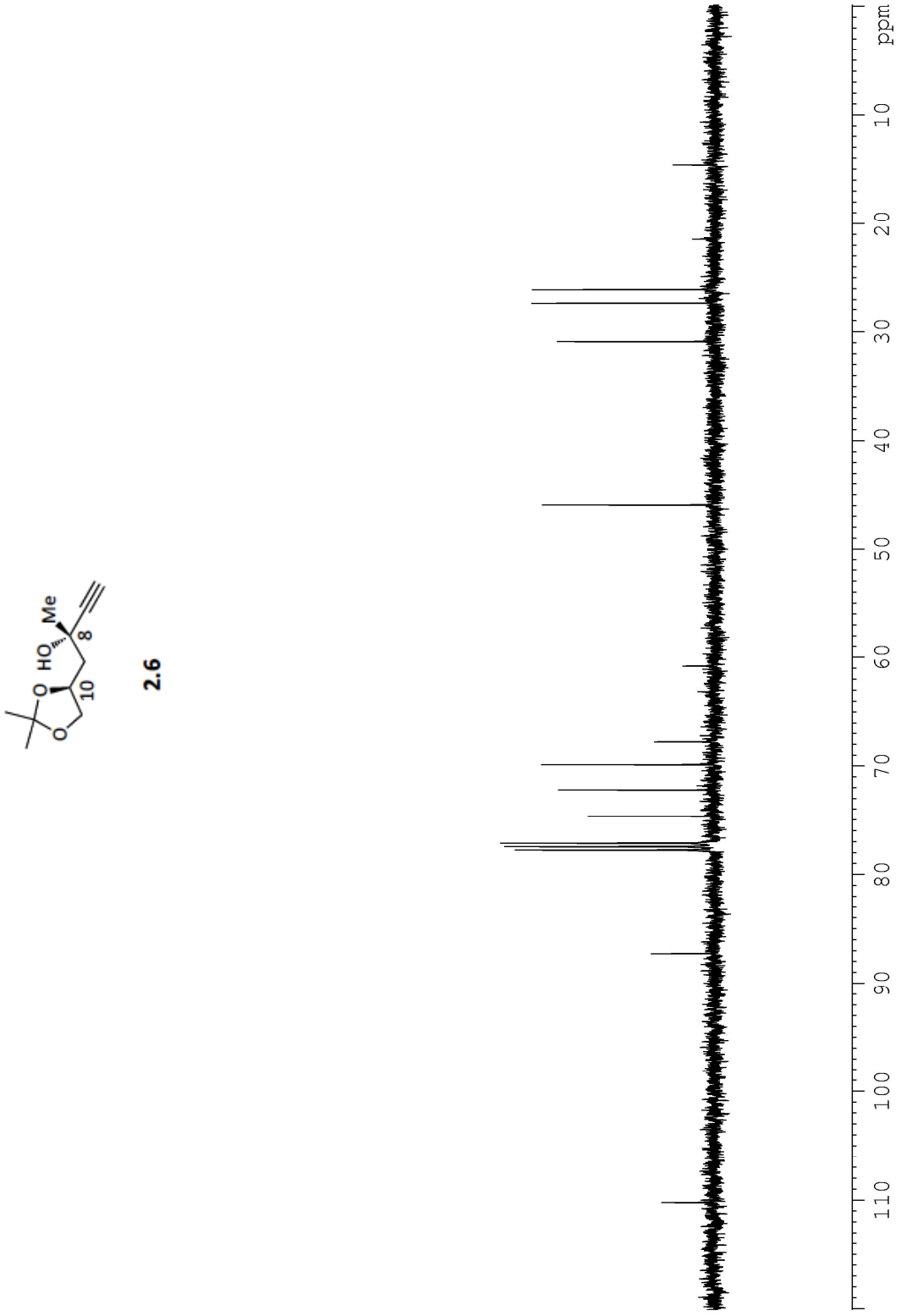


Figure A1.2. ^{13}C NMR spectra (100 MHz, C_6D_6) of compund **2.6.**

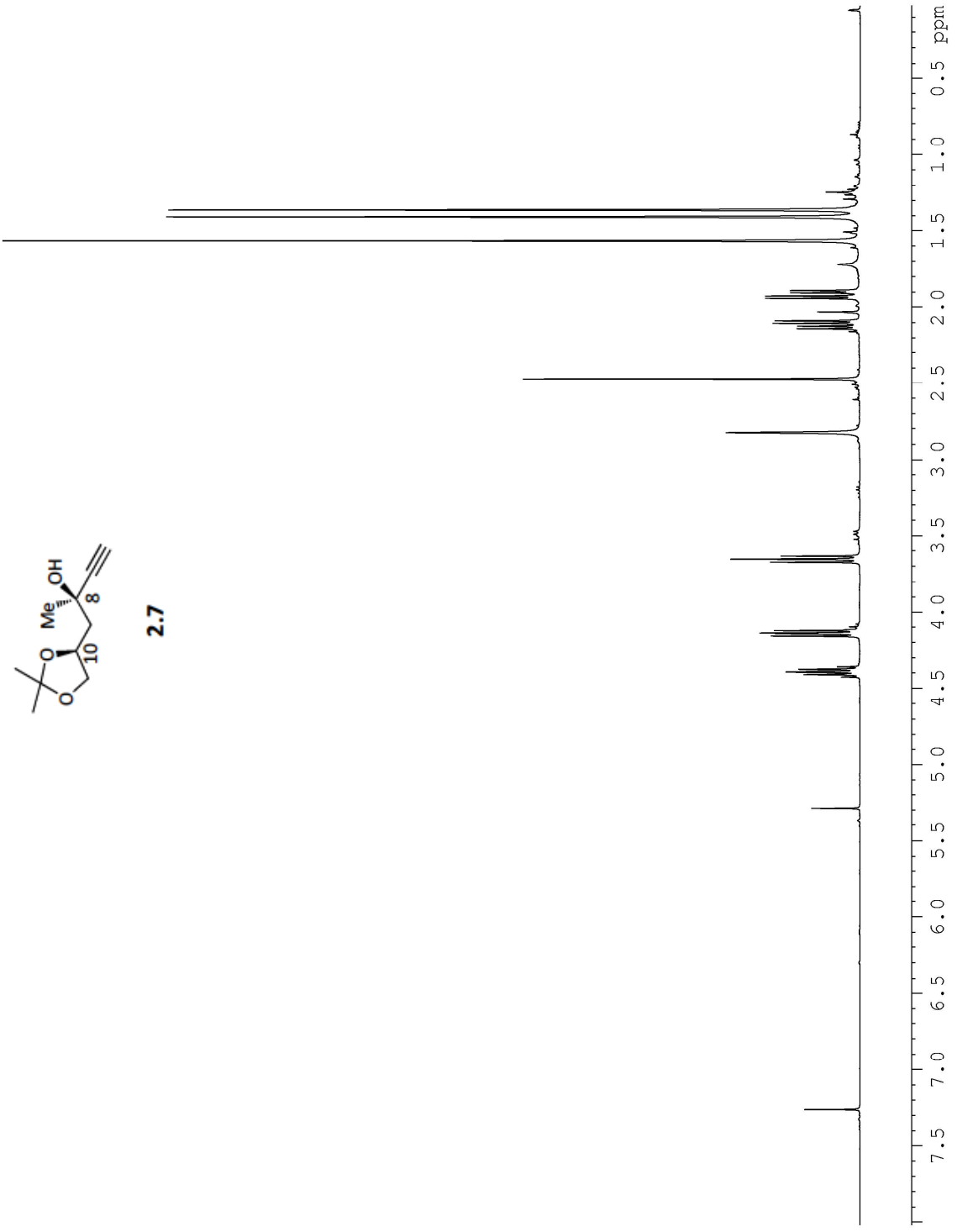


Figure A1.3. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **2.7**.

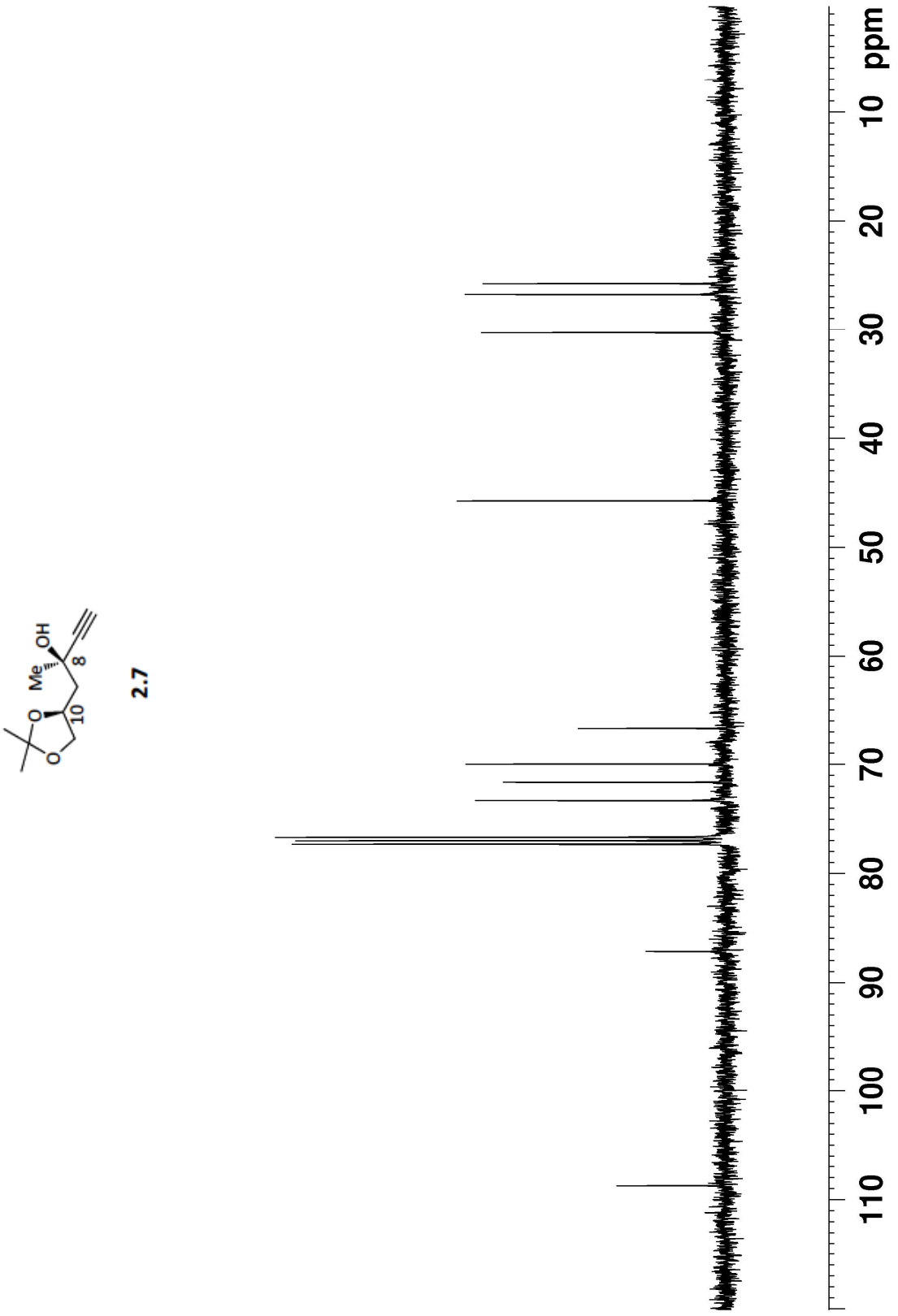


Figure A1.4. ^{13}C NMR spectra (100 MHz, $CDCl_3$) of compund **2.7.**

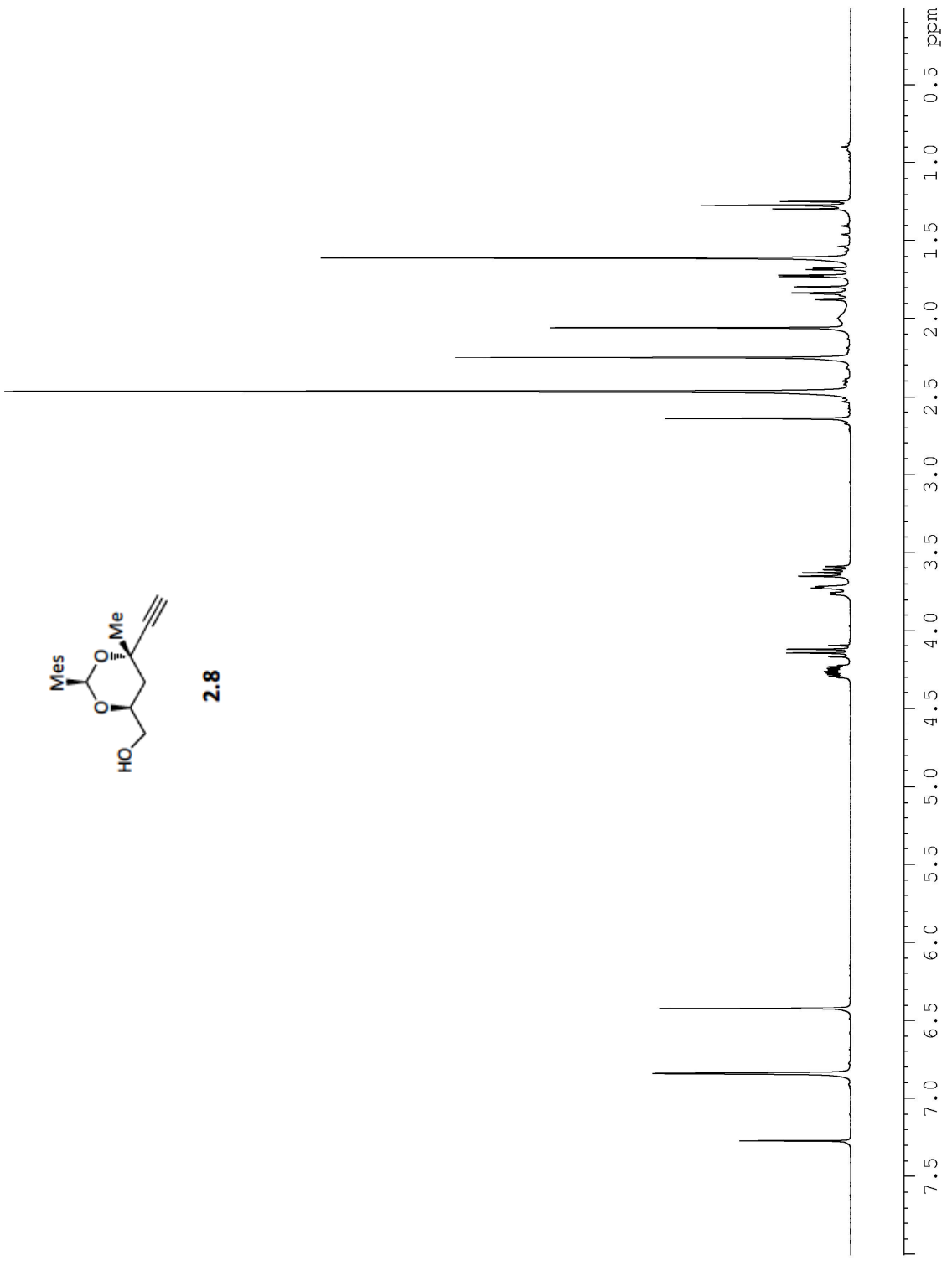


Figure A1.5. ^{1}H NMR spectra (300 MHz, $CDCl_3$) of compound **2.8**.

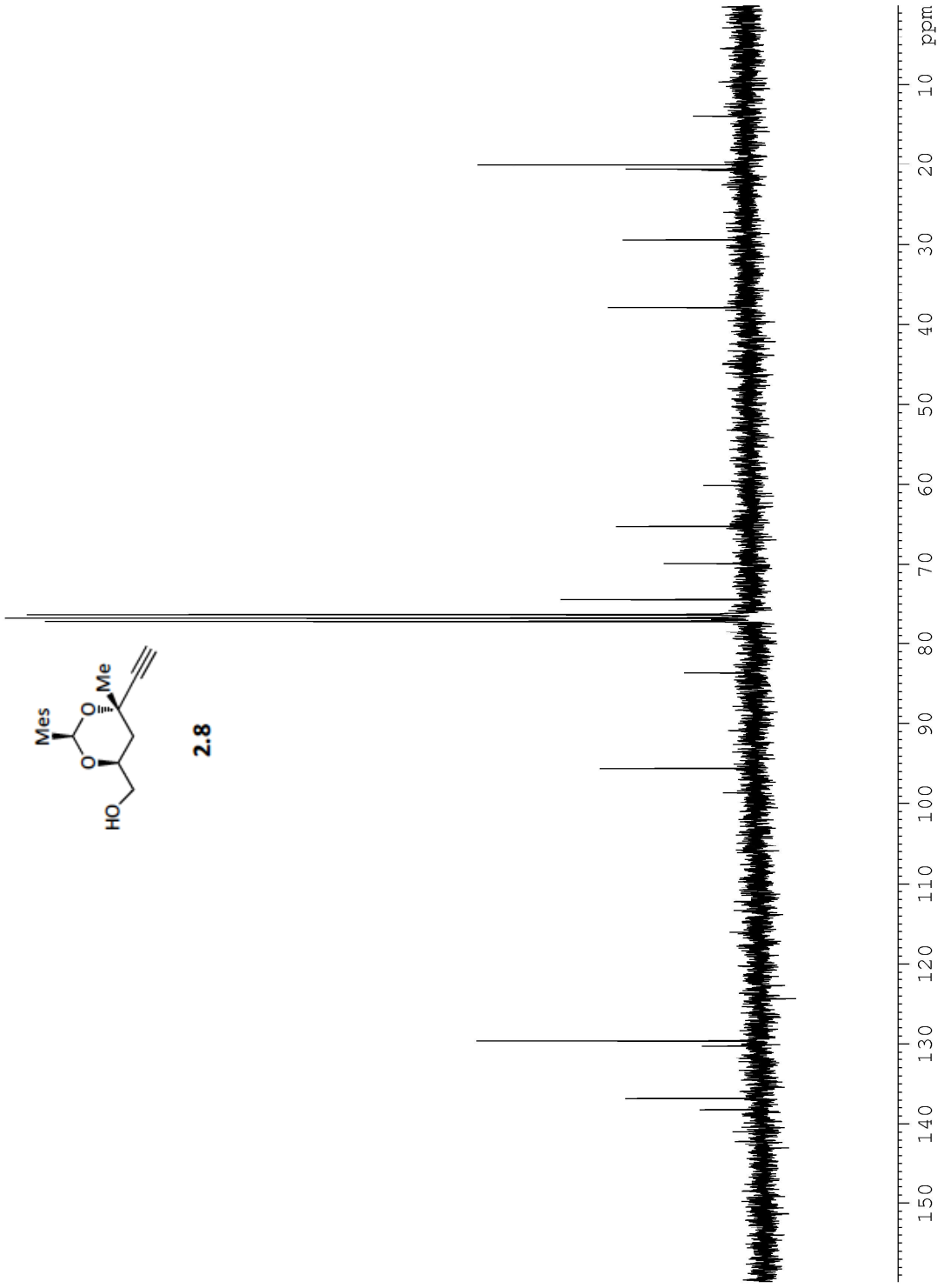


Figure A1.6. ^{13}C NMR spectra (100 MHz, $CDCl_3$) of compund **2.8.**

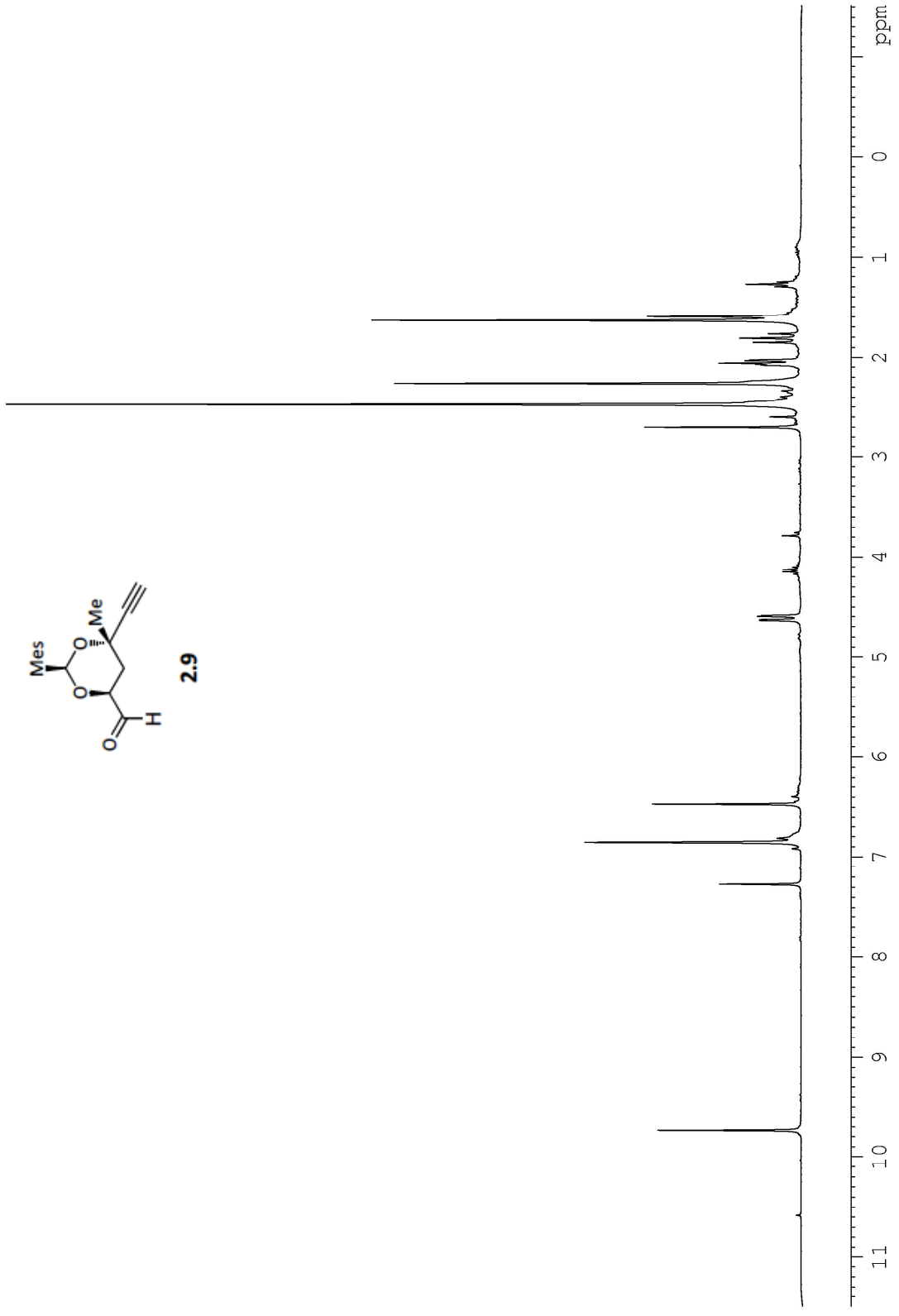


Figure A1.7. ^{1}H NMR spectra (300 MHz, $CDCl_3$) of compound **2.9**.

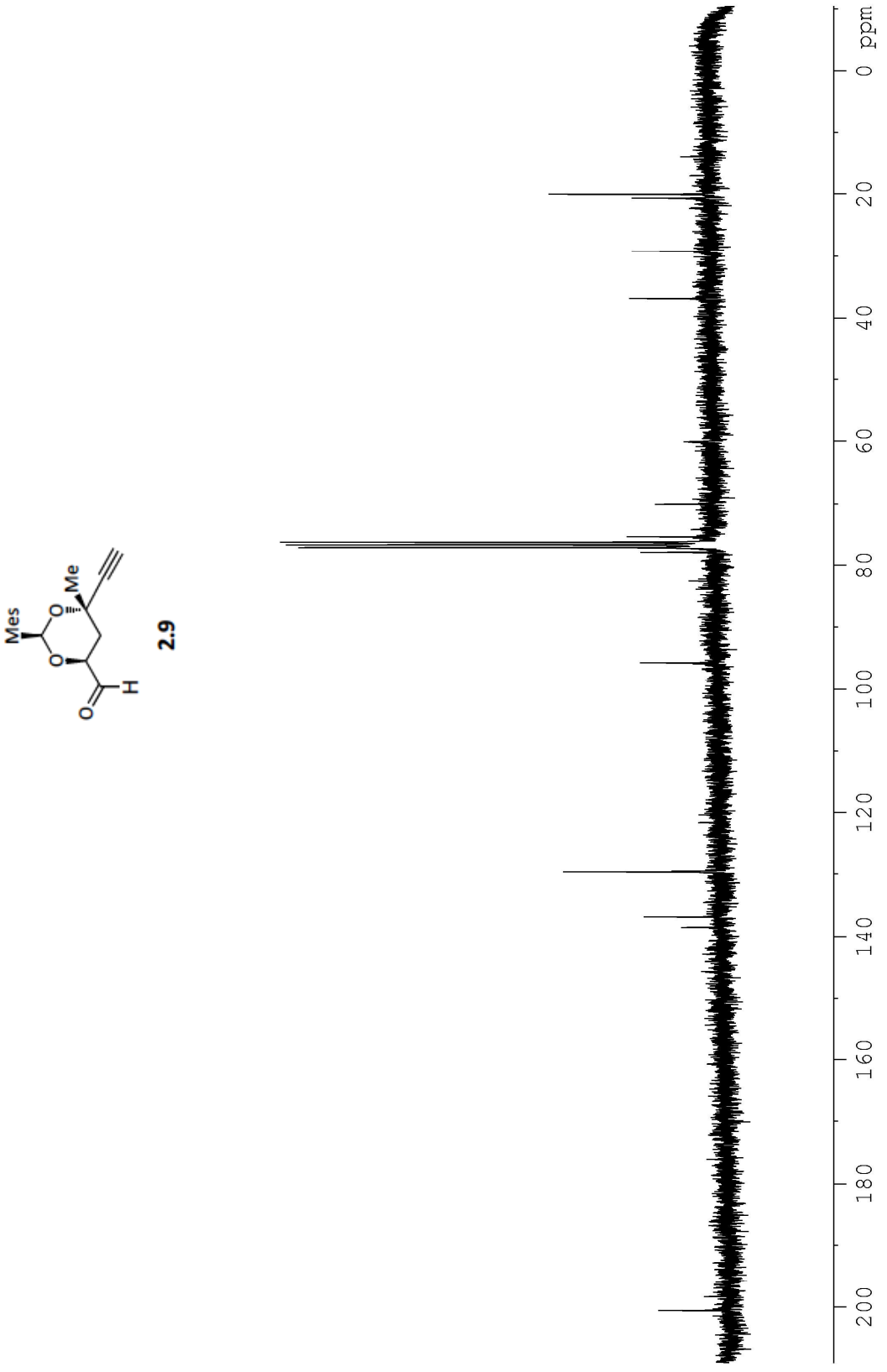


Figure A1.8. ^{13}C NMR spectra (100 MHz, $CDCl_3$) of compund **2.9.**

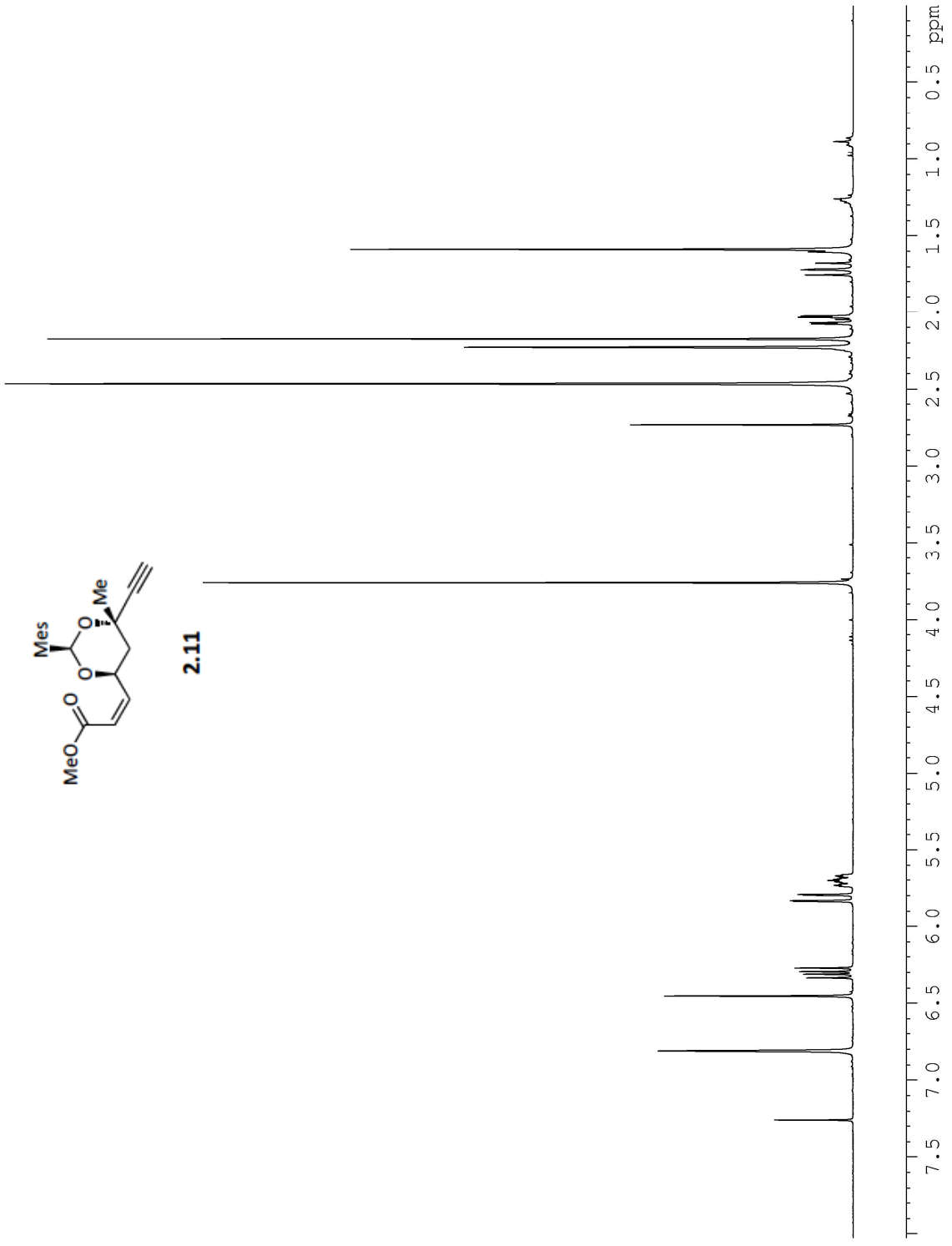


Figure A1.9. ^{1}H NMR spectra (300 MHz, $CDCl_3$) of compound **2.11**.

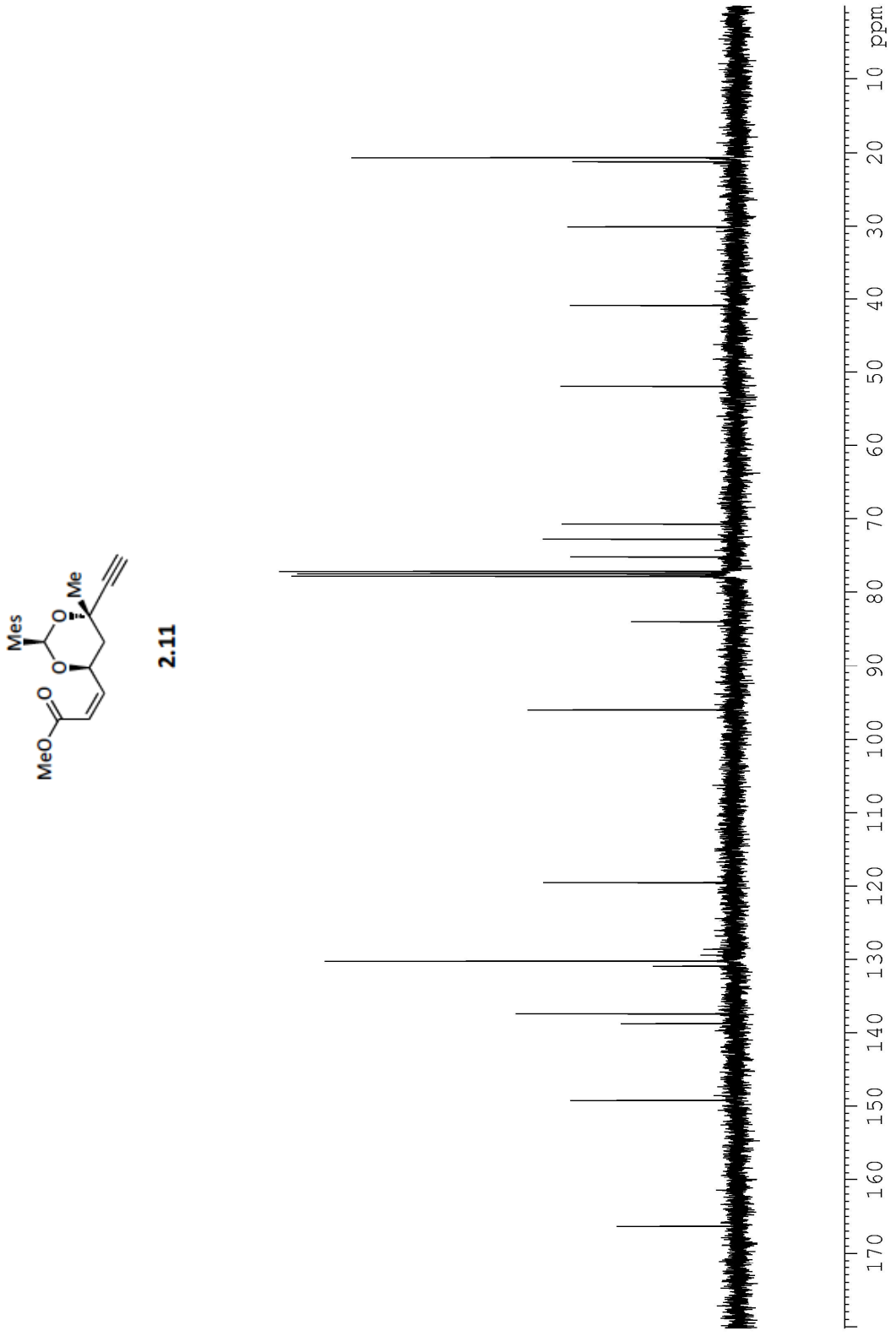


Figure A1.10. ^{13}C NMR spectra (100 MHz, $CDCl_3$) of compund **2.11.**

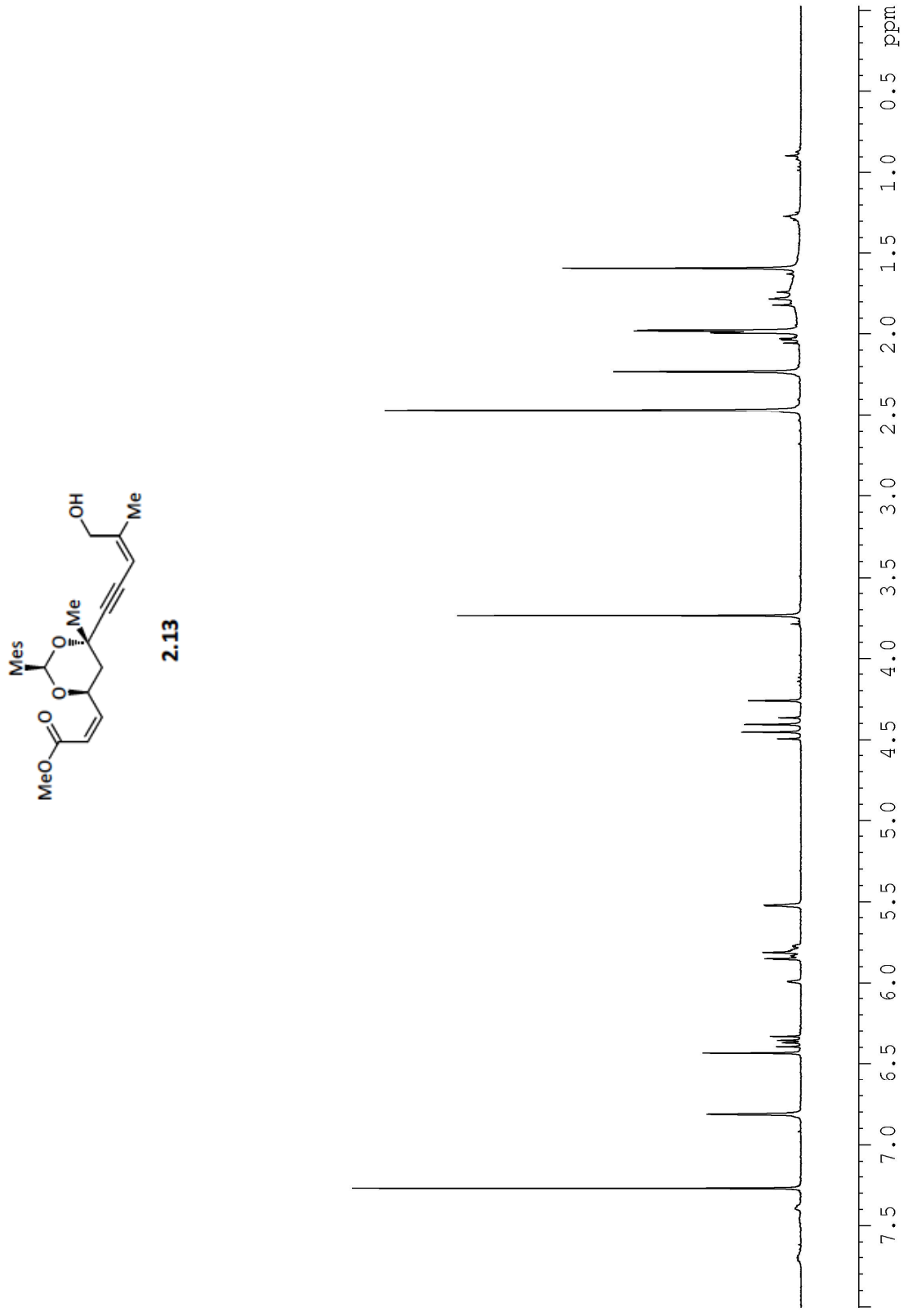


Figure A1.11. ^{1}H NMR spectra (300 MHz, $CDCl_3$) of compound **2.13**.

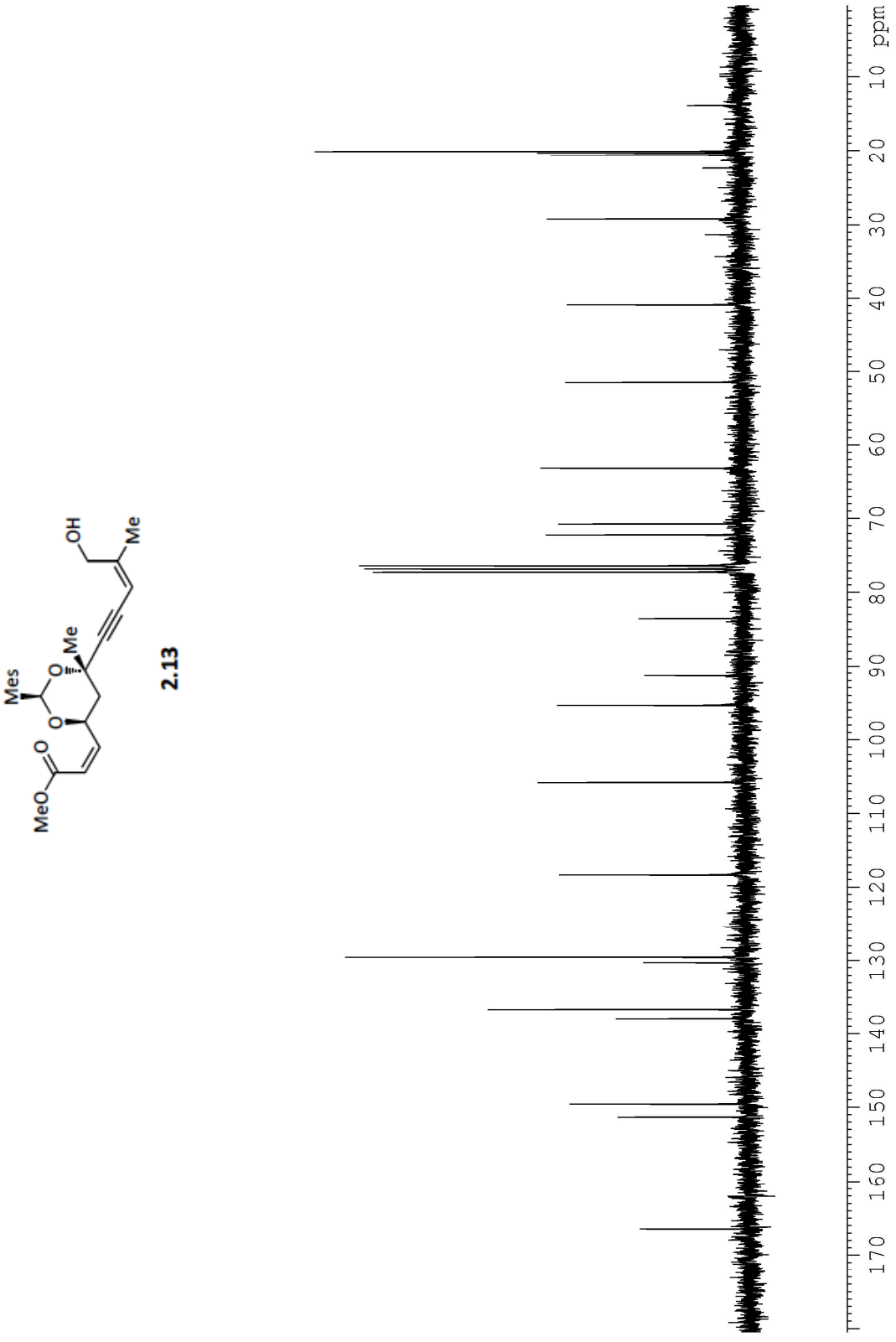


Figure A1.12. ^{13}C NMR spectra (100 MHz, $CDCl_3$) of compund **2.13.**

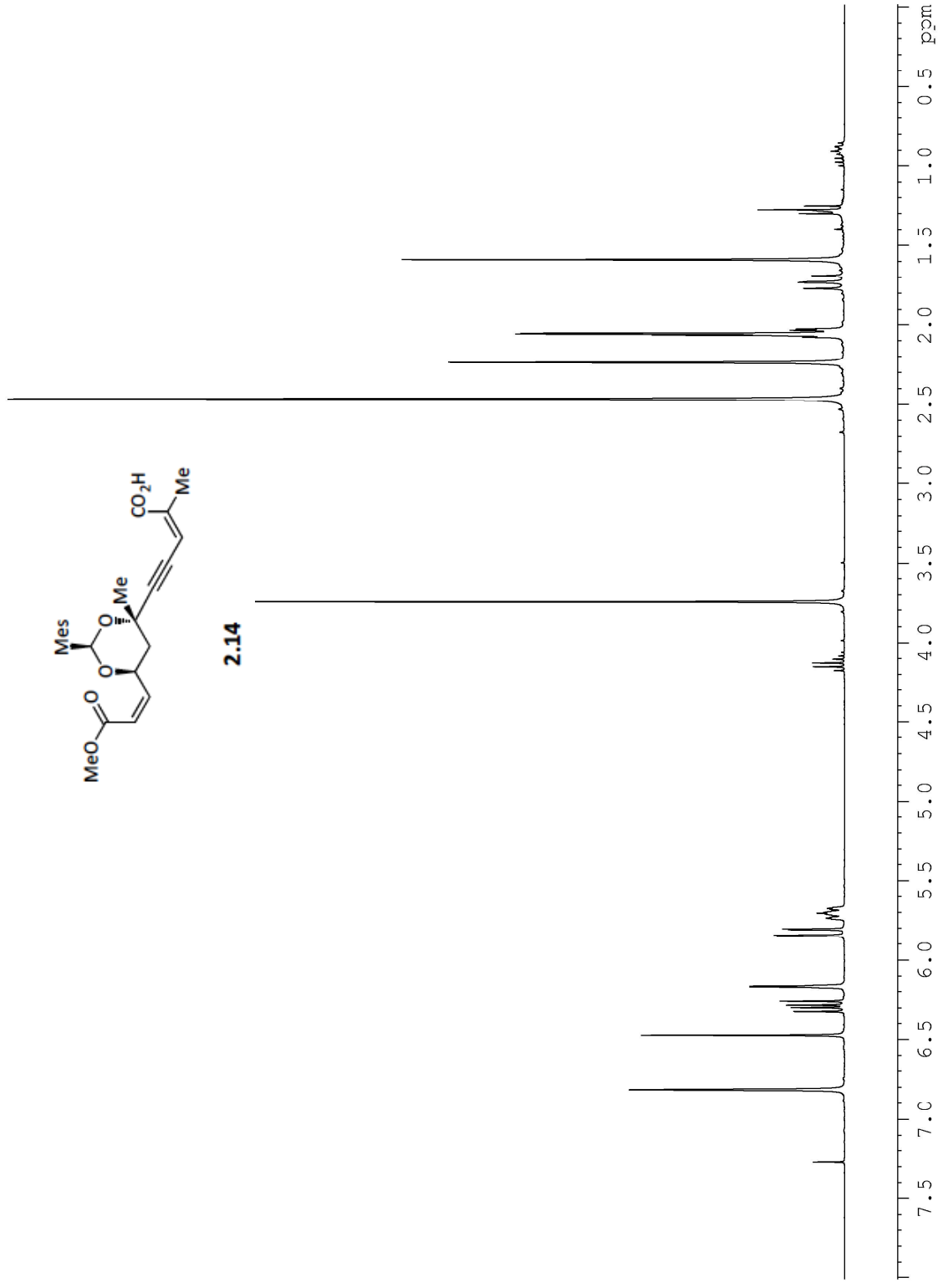


Figure A1.13. ^{1}H NMR spectra (300 MHz, $CDCl_3$) of compound **2.14**.

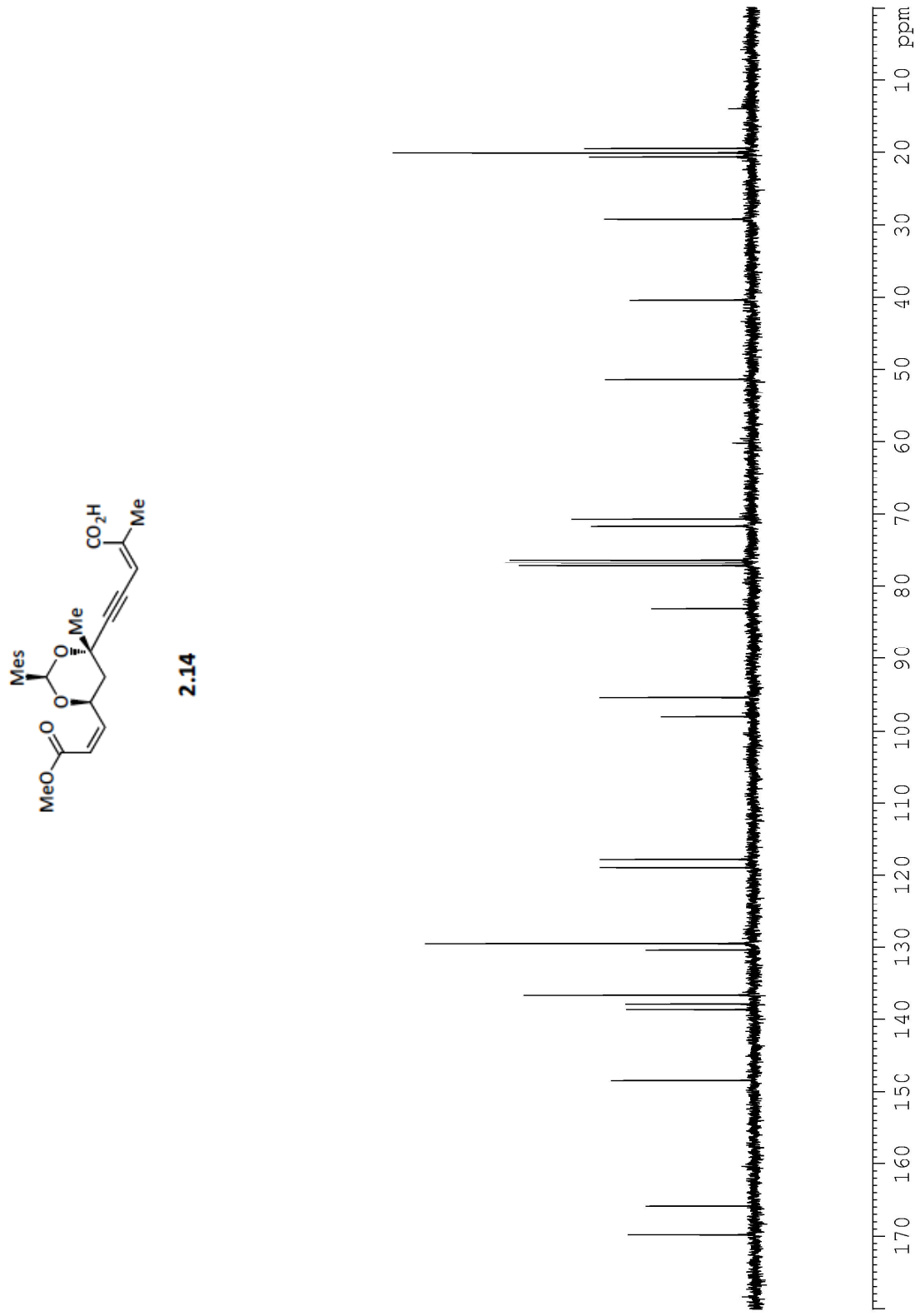


Figure A1.14. ^{13}C NMR spectra (125 MHz, $CDCl_3$) of compund **2.14.**

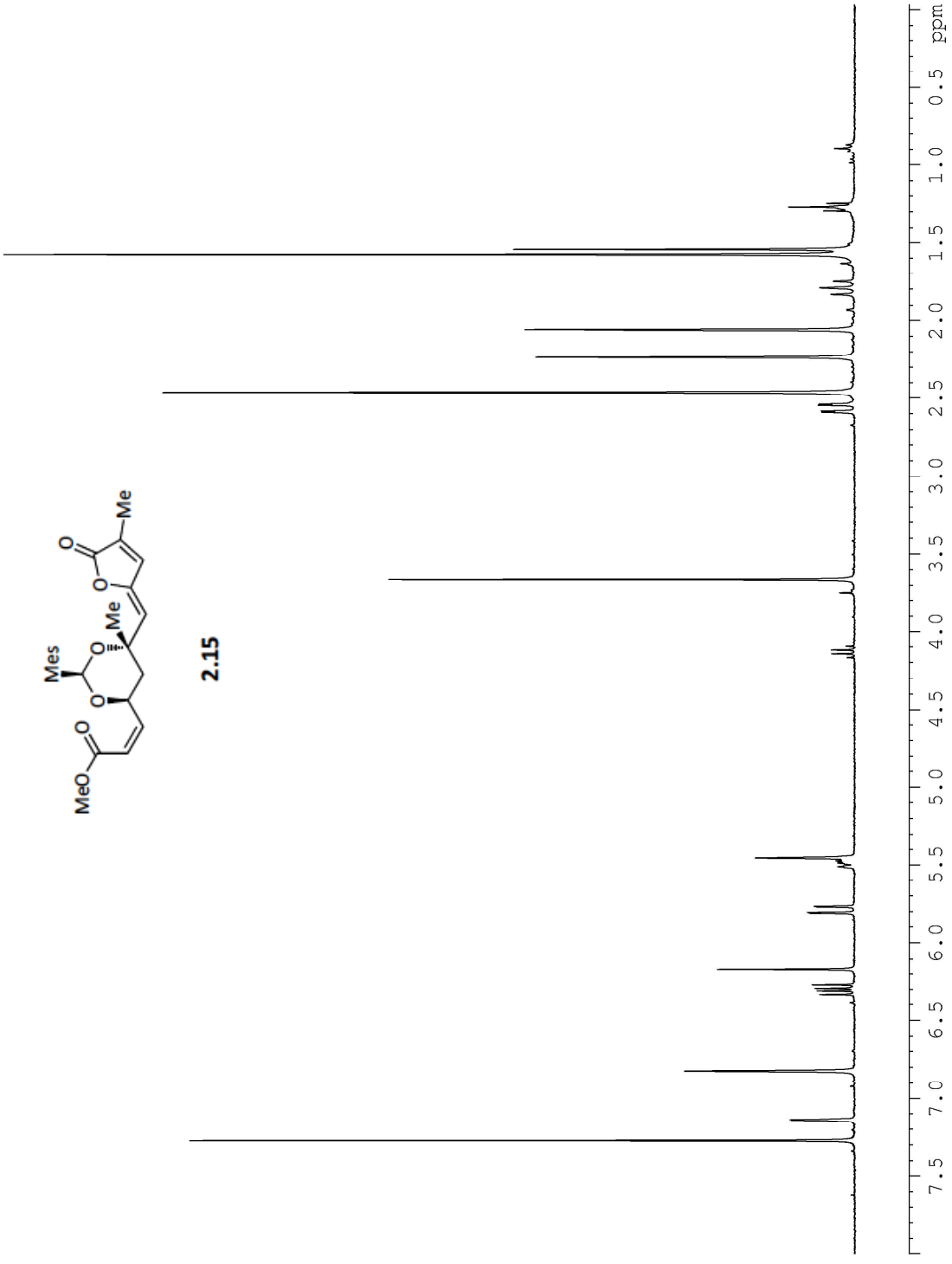


Figure A1.15. ^{1}H NMR spectra (300 MHz, $CDCl_3$) of compound **2.15**.

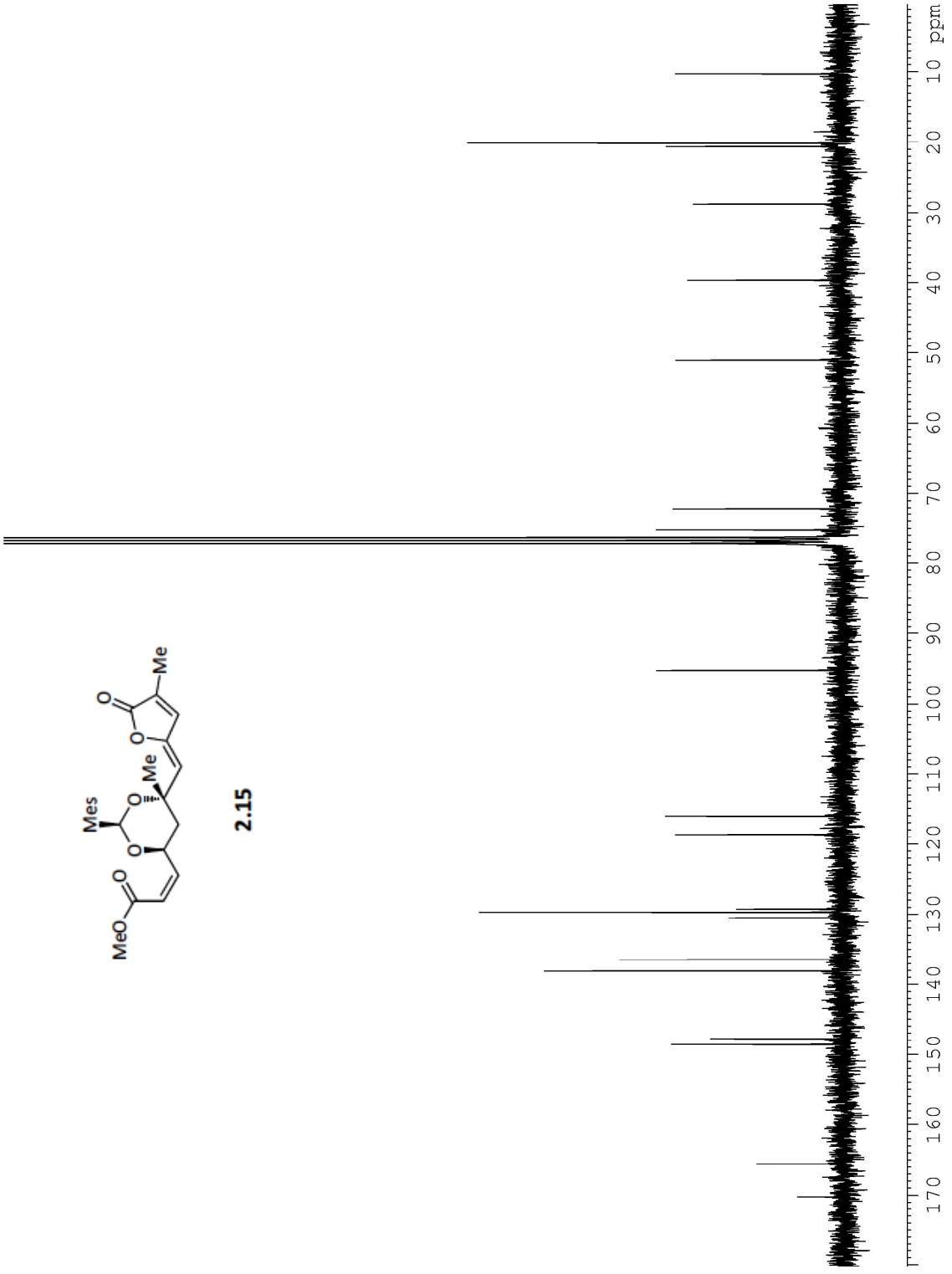


Figure A1.16. ^{13}C NMR spectra (125 MHz, $CDCl_3$) of compund **2.15.**

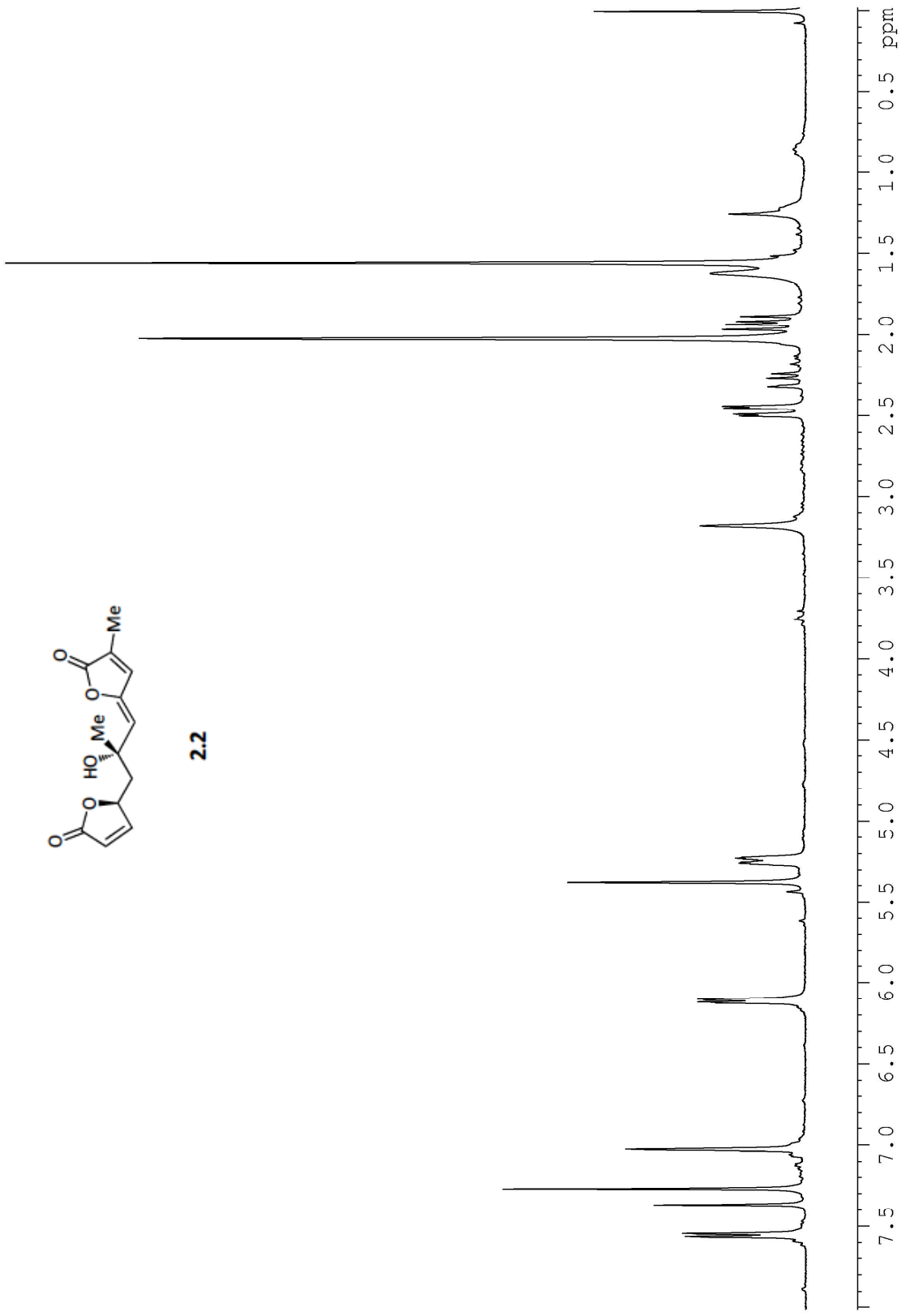


Figure A1.17. ^{1}H NMR spectra (300 MHz, $CDCl_3$) of compound **2.2**.

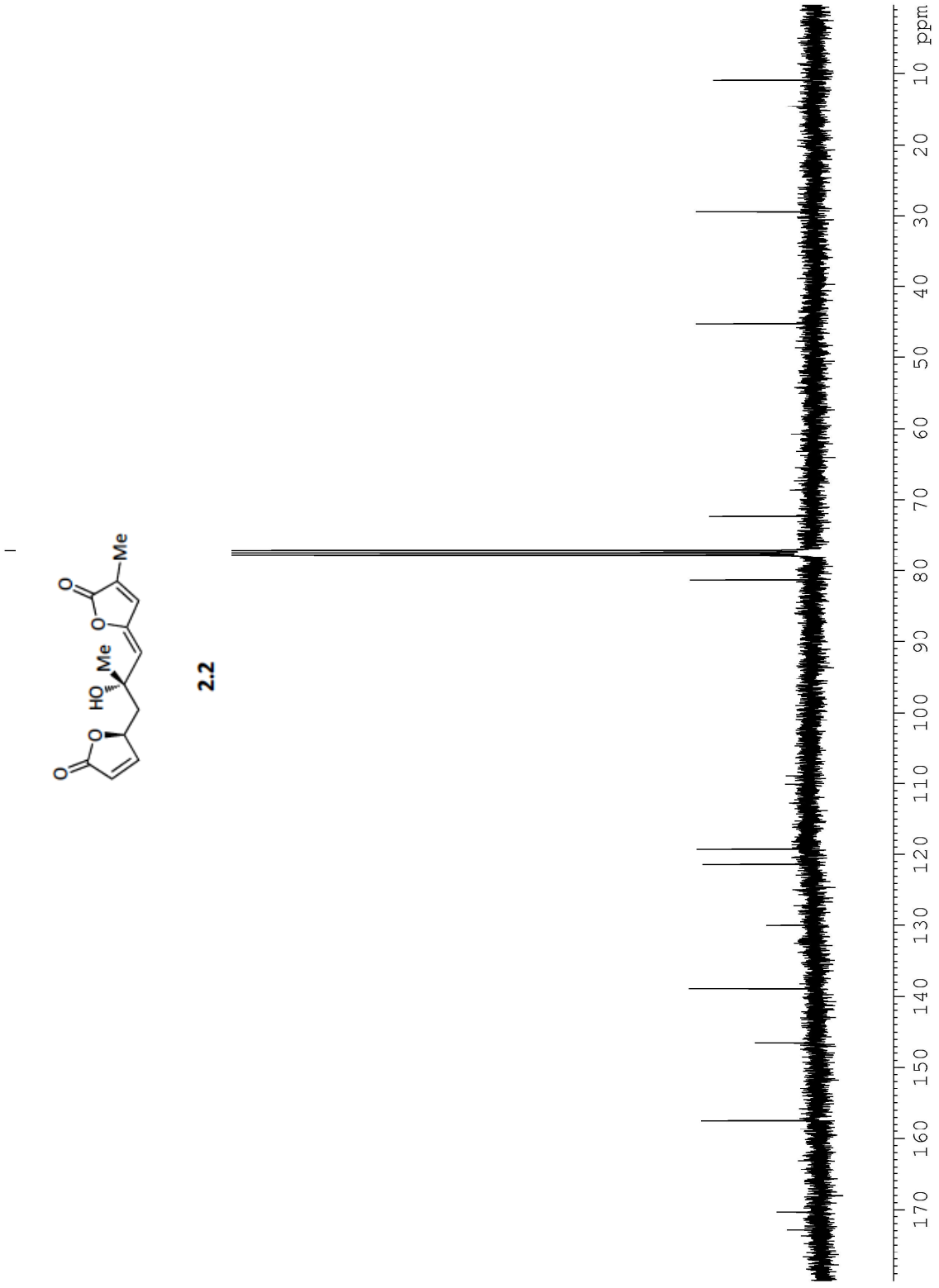


Figure A1.18. ^{13}C NMR spectra (125 MHz, $CDCl_3$) of compund **2.2.**

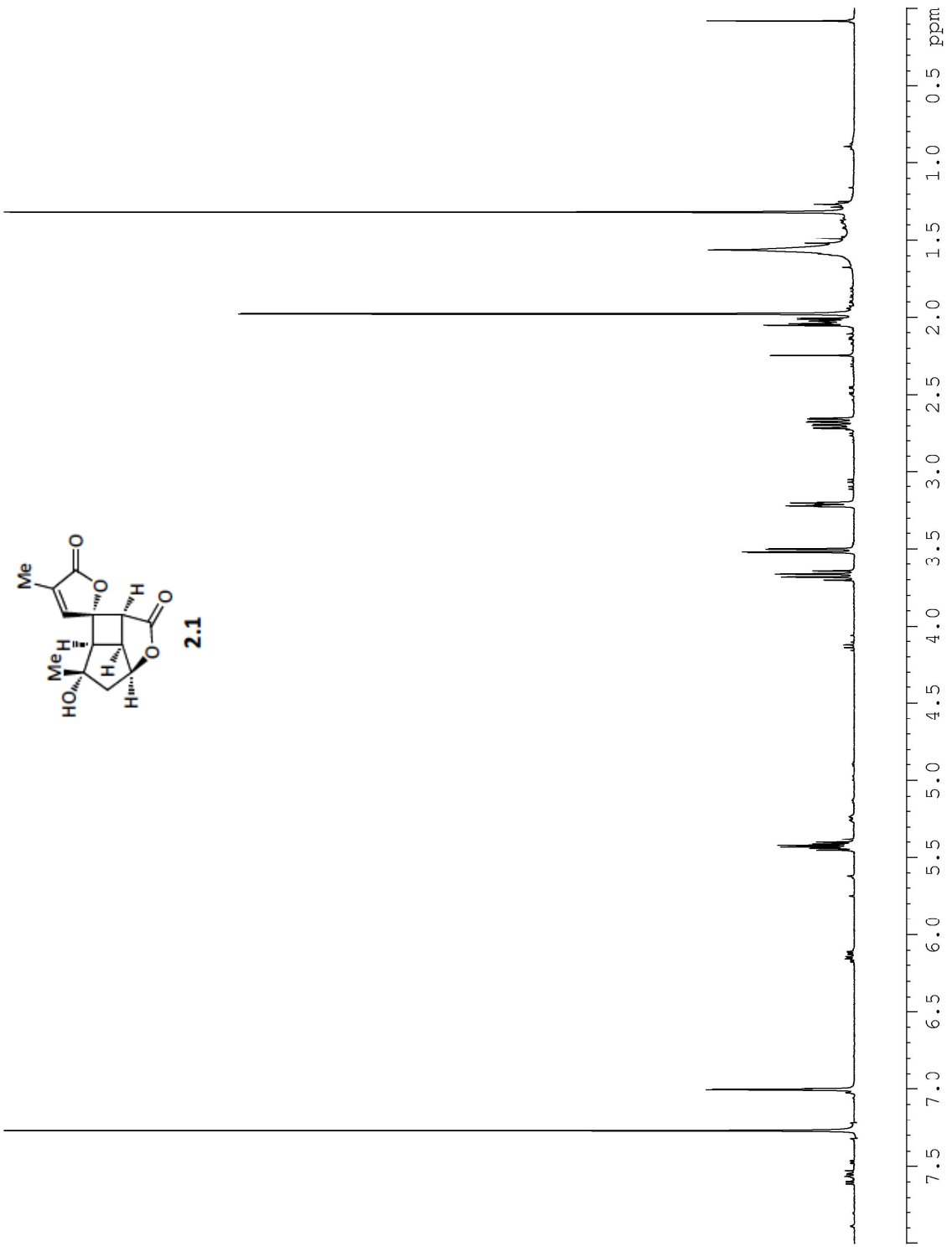


Figure A1.19. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **2.1**.

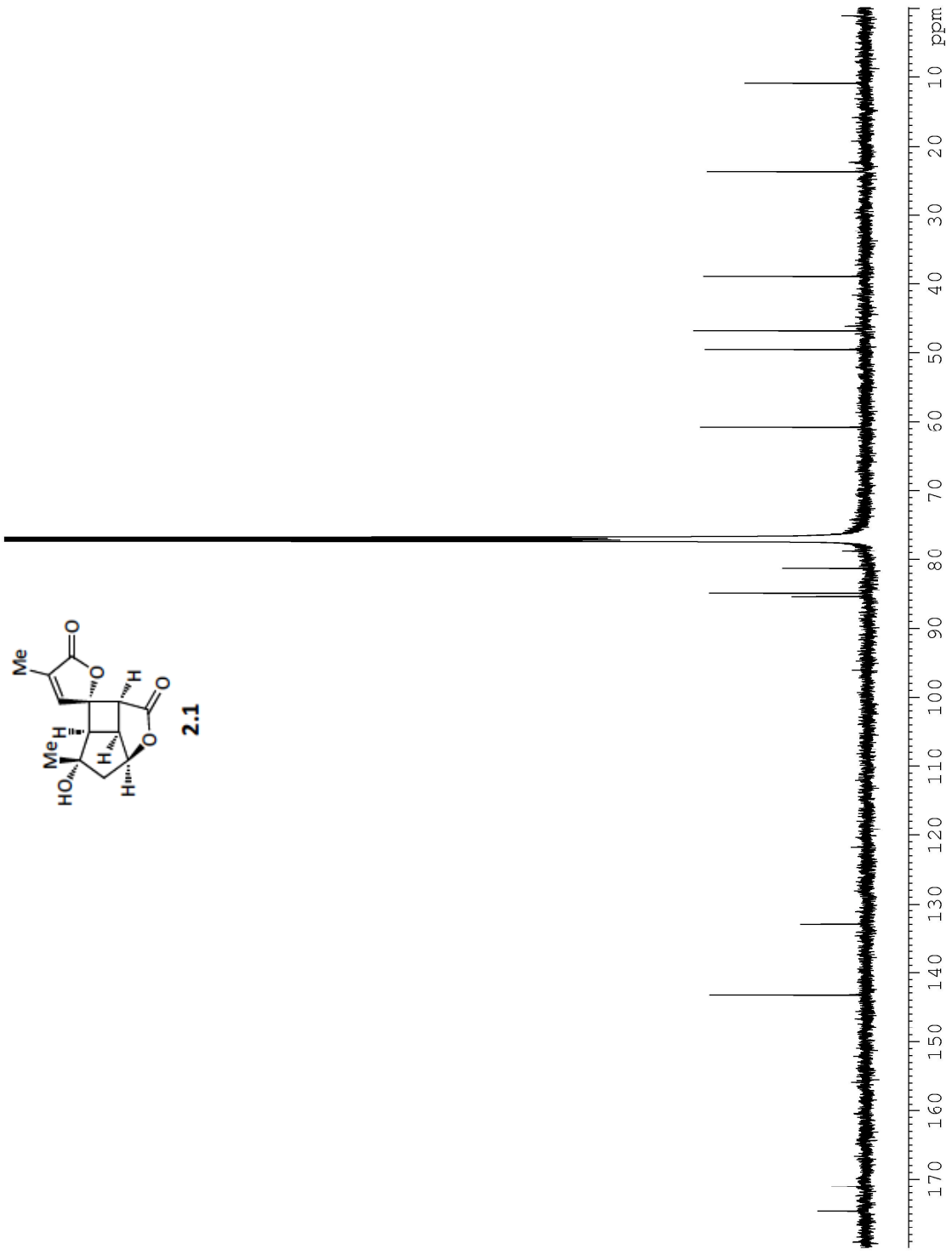


Figure A1.20. ^{13}C NMR spectra (125 MHz, $CDCl_3$) of compund **2.1.**

Appendix A2:

Crystallographic Information File (CIF) for 2.1.

DATA COLLECTION

A Leica MZ7 polarizing microscope was used to identify a suitable specimen from a representative sampling of materials. The microscope was then fixed to a nylon loop, which in turn was fashioned to a copper-mounting pin. The mounted powder was then placed in a cold nitrogen stream (Oxford) maintained at 110K.

A BRUKER D8 GADDS general-purpose three-circle X-ray diffractometer was employed for sample screening and data collection. The goniometer was controlled using the GADDS software suite (Microsoft Win 2000 operating system). The sample was optically centered with the aid of a video camera such that no translations were observed as the crystal was rotated through all positions. The detector was set at 5.0cm from the crystal sample (MWPC Hi-Star Detector, 512x512 pixel). The X-ray radiation employed was generated from a Cu sealed X-ray tube (K_α = 1.54184Å with a potential of 40 kV and a current of 40 mA) and filtered with a graphite monochromator in the parallel mode (175 mm collimator with 0.5 mm pinholes).

A rotation exposure was taken to determine crystal quality and the X-ray beam intersection with the detector. The beam intersection coordinates were compared to the configured coordinates and changes were made accordingly. The rotation exposure indicated acceptable crystal quality and the unit cell determination was undertaken. Sixty data frames were taken at widths of 0.5° with an exposure time of 10 seconds. Over 200 reflections were centered and their positions were determined. These reflections were used in the auto-indexing procedure to determine the unit cell. A suitable cell was found and refined by nonlinear least squares and Bravais lattice procedures and reported here in Table 1. The unit cell was verified by examination of the hkl overlays on several frames of data,

including zone photographs. No super-cell or erroneous reflections were observed.

After careful examination of the unit cell, a standard data collection procedure was initiated. This procedure consists of collection of one hemisphere of data collected using omega scans, involving the collection 2520 0.5° frames at fixed angles for ϕ, 2θ, and Χ (2θ = -28°, Χ = 54.73°, 2θ = -90°, Χ = 54.73°), while varying omega. Addition data frames were collected to complete the data set. Each frame was exposed for 10 sec. The total data collection was performed for duration of approximately 24 hours at 110 K. No significant intensity fluctuations of equivalent reflections were observed.

After data collection, the crystal was measured carefully for size, morphology and color.These measurements are reported in Table 1.

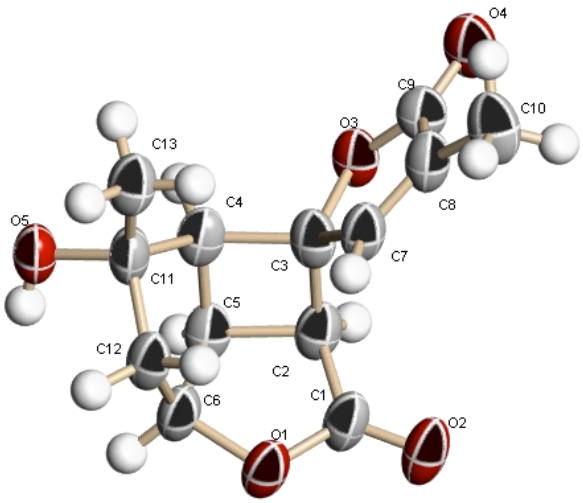


Table 1. Crystal data and structure refinement for XX.

Identification code	gs62	
Empirical formula	C13 H14 O5	
Formula weight	250.24	
Temperature	110(2) K	
Wavelength	1.54178 Å Monoclinic	
Crystal system	C2	
Space group		
Unit cell dimensions	a = 13.784(2) Å	α= 90°.
	b = 6.0900(10) Å	β= 104.151(9)°.
	c = 15.200(3) Å	γ = 90°.
Volume	1237.2(4) $Å^3$	
Z	4	
Density (calculated)	1.343 Mg/m^3	
Absorption coefficient	0.872 mm^{-1}	
F(000)	528	
Crystal size	0.20 x 0.10 x 0.01 mm^3	
Theta range for data collection	3.00 to 59.26°.	
Index ranges	-15<=h<=15, -6<=k<=5, -16<=l<=16	
Reflections collected	5183	
Independent reflections	1597 [R(int) = 0.0835]	
Completeness to theta = 59.26°	98.2 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9913 and 0.8449	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1597 / 1 / 169	
Goodness-of-fit on F^2	1.002	
Final R indices [I>2sigma(I)]	R1 = 0.0604, wR2 = 0.1378	
R indices (all data)	R1 = 0.0842, wR2 = 0.1515	
Absolute structure parameter	-0.7(5)	
Largest diff. peak and hole	0.261 and -0.272 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for XX. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	7910(2)	6375(6)	751(2)	55(1)
O(2)	6694(2)	5305(6)	1405(3)	64(1)
O(3)	8894(2)	750(5)	2817(2)	49(1)
O(4)	8709(3)	-597(7)	4146(3)	66(1)
O(5)	11094(3)	4682(6)	1387(3)	52(1)
C(1)	7477(4)	4907(9)	1215(4)	54(2)
C(2)	8121(4)	2879(9)	1447(4)	49(1)
C(3)	8873(4)	2911(9)	2386(4)	50(1)
C(4)	9759(4)	3069(9)	1911(3)	49(1)
C(5)	8993(3)	3188(8)	986(3)	46(1)
C(6)	8910(3)	5680(9)	715(4)	51(1)
C(7)	8735(3)	4422(10)	3122(4)	50(1)
C(8)	8655(4)	3365(9)	3872(4)	53(2)
C(9)	8760(3)	970(9)	3659(3)	47(1)
C(10)	8500(5)	4111(11)	4748(4)	68(2)
C(11)	10429(3)	5150(9)	1965(4)	50(1)
C(12)	9694(3)	6884(9)	1454(4)	48(1)
C(13)	11032(4)	5792(10)	2891(3)	55(1)

Table 3. Bond lengths [Å] and angles [°] for XX.

O(1)-C(1)	1.363(6)
O(1)-C(6)	1.456(5)
O(2)-C(1)	1.207(6)
O(3)-C(9)	1.342(5)
O(3)-C(3)	1.468(6)
O(4)-C(9)	1.221(6)
O(5)-C(11)	1.445(6)
C(1)-C(2)	1.512(8)
C(2)-C(5)	1.543(6)
C(2)-C(3)	1.545(8)
C(3)-C(7)	1.497(8)
C(3)-C(4)	1.566(6)
C(4)-C(5)	1.539(7)
C(4)-C(11)	1.558(7)
C(5)-C(6)	1.569(7)
C(6)-C(12)	1.541(7)
C(7)-C(8)	1.337(7)
C(8)-C(10)	1.470(8)
C(8)-C(9)	1.509(8)
C(11)-C(13)	1.500(7)
C(11)-C(12)	1.536(7)

C(1)-O(1)-C(6)	111.5(4)
C(9)-O(3)-C(3)	110.1(4)
O(2)-C(1)-O(1)	121.4(5)
O(2)-C(1)-C(2)	128.1(5)
O(1)-C(1)-C(2)	110.5(4)
C(1)-C(2)-C(5)	105.8(4)
C(1)-C(2)-C(3)	115.3(4)
C(5)-C(2)-C(3)	89.8(4)
O(3)-C(3)-C(7)	102.1(4)
O(3)-C(3)-C(2)	109.7(4)
C(7)-C(3)-C(2)	121.3(4)
O(3)-C(3)-C(4)	109.2(4)

C(7)-C(3)-C(4)	124.3(4)
C(2)-C(3)-C(4)	89.9(4)
C(5)-C(4)-C(11)	106.0(4)
C(5)-C(4)-C(3)	89.2(4)
C(11)-C(4)-C(3)	123.0(4)
C(4)-C(5)-C(2)	90.9(4)
C(4)-C(5)-C(6)	106.0(4)
C(2)-C(5)-C(6)	102.9(4)
O(1)-C(6)-C(12)	109.6(4)
O(1)-C(6)-C(5)	106.2(4)
C(12)-C(6)-C(5)	106.0(4)
C(8)-C(7)-C(3)	113.2(5)
C(7)-C(8)-C(10)	133.1(6)
C(7)-C(8)-C(9)	104.4(5)
C(10)-C(8)-C(9)	122.4(5)
O(4)-C(9)-O(3)	122.8(5)
O(4)-C(9)-C(8)	127.1(5)
O(3)-C(9)-C(8)	110.1(4)
O(5)-C(11)-C(13)	109.4(4)
O(5)-C(11)-C(12)	105.4(4)
C(13)-C(11)-C(12)	116.1(4)
O(5)-C(11)-C(4)	105.3(4)
C(13)-C(11)-C(4)	116.6(4)
C(12)-C(11)-C(4)	102.9(4)
C(11)-C(12)-C(6)	107.4(4)

Symmetry transformations used to generate equivalent atoms:

Table 3. Bond lengths [Å] and angles [°] for XX.

O(1)-C(1)	1.363(6)
O(1)-C(6)	1.456(5)
O(2)-C(1)	1.207(6)
O(3)-C(9)	1.342(5)
O(3)-C(3)	1.468(6)
O(4)-C(9)	1.221(6)
O(5)-C(11)	1.445(6)
C(1)-C(2)	1.512(8)
C(2)-C(5)	1.543(6)
C(2)-C(3)	1.545(8)
C(3)-C(7)	1.497(8)
C(3)-C(4)	1.566(6)
C(4)-C(5)	1.539(7)
C(4)-C(11)	1.558(7)
C(5)-C(6)	1.569(7)
C(6)-C(12)	1.541(7)
C(7)-C(8)	1.337(7)
C(8)-C(10)	1.470(8)
C(8)-C(9)	1.509(8)
C(11)-C(13)	1.500(7)
C(11)-C(12)	1.536(7)

C(1)-O(1)-C(6)	111.5(4)
C(9)-O(3)-C(3)	110.1(4)
O(2)-C(1)-O(1)	121.4(5)
O(2)-C(1)-C(2)	128.1(5)
O(1)-C(1)-C(2)	110.5(4)
C(1)-C(2)-C(5)	105.8(4)
C(1)-C(2)-C(3)	115.3(4)
C(5)-C(2)-C(3)	89.8(4)
O(3)-C(3)-C(7)	102.1(4)
O(3)-C(3)-C(2)	109.7(4)
C(7)-C(3)-C(2)	121.3(4)
O(3)-C(3)-C(4)	109.2(4)

C(7)-C(3)-C(4)	124.3(4)
C(2)-C(3)-C(4)	89.9(4)
C(5)-C(4)-C(11)	106.0(4)
C(5)-C(4)-C(3)	89.2(4)
C(11)-C(4)-C(3)	123.0(4)
C(4)-C(5)-C(2)	90.9(4)
C(4)-C(5)-C(6)	106.0(4)
C(2)-C(5)-C(6)	102.9(4)
O(1)-C(6)-C(12)	109.6(4)
O(1)-C(6)-C(5)	106.2(4)
C(12)-C(6)-C(5)	106.0(4)
C(8)-C(7)-C(3)	113.2(5)
C(7)-C(8)-C(10)	133.1(6)
C(7)-C(8)-C(9)	104.4(5)
C(10)-C(8)-C(9)	122.4(5)
O(4)-C(9)-O(3)	122.8(5)
O(4)-C(9)-C(8)	127.1(5)
O(3)-C(9)-C(8)	110.1(4)
O(5)-C(11)-C(13)	109.4(4)
O(5)-C(11)-C(12)	105.4(4)
C(13)-C(11)-C(12)	116.1(4)
O(5)-C(11)-C(4)	105.3(4)
C(13)-C(11)-C(4)	116.6(4)
C(12)-C(11)-C(4)	102.9(4)
C(11)-C(12)-C(6)	107.4(4)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 1.

The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	43(2)	42(2)	88(3)	5(	27(2)	7(2)
O(2)	47(2)	39(3)	116(3)	0(	40(2)	3(2)
O(3)	53(2)	25(2)	75(2)	1(	32(2)	-2(2)
O(4)	72(3)	40(3)	96(3)	10(2)	42(2)	1(2)
O(5)	49(2)	49(2)	68(3)	2(	31(2)	-3(2)
C(1)	40(3)	36(3)	91(4)	3(	27(3)	0(2)
C(2)	44(3)	36(3)	73(4)	-3(2)	25(3)	2(2)
C(3)	53(3)	34(3)	70(4)	0(	30(3)	-5(2)
C(4)	48(3)	29(3)	77(4)	-4(3)	27(3)	-1(3)
C(5)	48(3)	28(3)	70(4)	-5(3)	27(3)	-2(2)
C(6)	40(3)	45(4)	76(3)	4(	28(2)	7(3)
C(7)	47(3)	38(3)	75(4)	-1(3)	31(3)	4(2)
C(8)	51(3)	37(3)	82(4)	-1(3)	36(3)	-1(3)
C(9)	50(3)	35(3)	59(3)	-2(3)	18(2)	-2(2)
C(10)	83(4)	46(4)	87(4)	-8(3)	45(3)	-16(3)
C(11)	44(3)	42(4)	74(4)	5(	33(3)	0(3)
C(12)	43(3)	29(3)	78(4)	2(	27(3)	-4(2)
C(13)	50(3)	45(4)	77(4)	-5(3)	27(3)	-5(3)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 1.

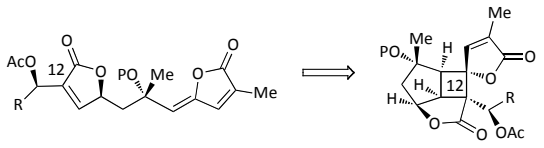
	x	y	z	U(eq)
H(5)	10830(40)	4780(100)	780(40)	57(18)
H(2)	7750	1463	1296	59
H(4)	10161	1685	1980	59
H(5A)	9058	2100	511	56
H(6)	9029	5917	99	61
H(7)	8707	5975	3063	60
H(10A)	8583	5709	4795	101
H(10B)	8991	3405	5243	101
H(10C)	7823	3718	4789	101
H(12A)	10054	7986	1175	58
H(12B)	9364	7648	1877	58
H(13A)	11489	4594	3147	83
H(13B)	10582	6084	3286	83
H(13C)	11419	7117	2843	83

CHAPTER III

THE C12 FUNCTIONALIZATION PROBLEM: EARLY APPROACHES

Construction of α-substituted Butenolides

Following the initial report of the [2+2] photocycloaddition, we encountered the deceptive problem of functionalizing the C12 position (Scheme 3.1). It was in this spirit the program developed into a study of the synthesis of α-substituted butenolides in order to form the C12-C13 bond prior to the [2+2] photocycloaddition. Of importance, would be our ability to install the correct configuration at C13.

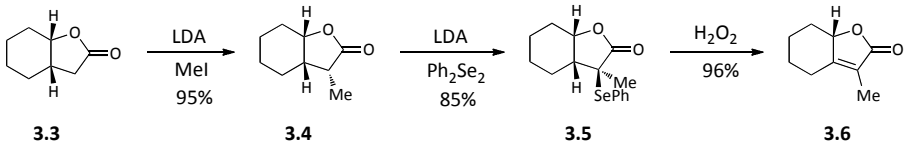


3.1 **3.2**

Scheme 3.1. C12 Functionalization.

Classically, the butenolide synthon has inspired the development of novel synthetic methodology. A review of methods for the preparation of substituted butenolides serves as the starting point for our discussion of the C12 functionalization problem. In 1974, Grieco reported a general method for the conversion of lactones to α-substituted butenolides, employing elimination of a phenylselenoxide (Scheme 3.2).[1]

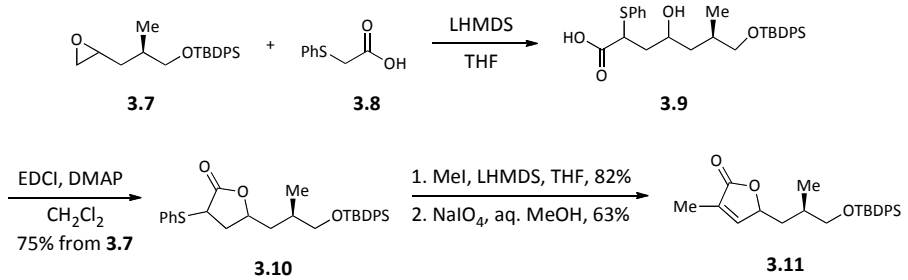
This methodology was an extension of the original work by Sharpless who demonstrated acyclic, α-β unsaturated esters could be synthesized according to this protocol.[2, 3] For example, the lithium enolate of lactone **3.3** was alkylated with methyl iodide, followed by generation of phenylselenide **3.5** (Scheme 3.2). Oxidation and elimination of the resultant selenoxide occurred at ambient temperature to provide butenolide **3.6**.



3.3 **3.4** **3.5** **3.6**

Scheme 3.2. α-substituted butenolides by selenoxide elimination.

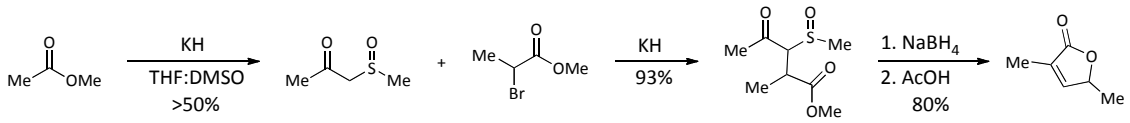
A related approach involves elimination of a phenylsulfoxide (Scheme 3.3). The dianion of (phenylthio)acetic acid (PTAA) **3.8** reacts with terminal epoxide **3.7** to provide 4-hydroxy-2-(phenylthio)alkanoic acid **3.9**.[4, 5] Lactonization occurs thermally to give **3.10**. Subsequent alkylation is followed by oxidation and elimination of the sulfoxide to provide the α-substituted butenolide **3.11**. Hannessian and Reich have established a facile version of this reaction using the dianion of (phenylseleno)acetic acid (PSAA).[6, 7]



3.7 **3.8** **3.9** **3.10** **3.11**

Scheme 3.3. α-substituted butenolides by sulfoxide elimination.

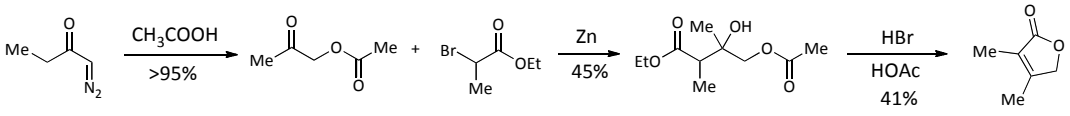
Bartlett reported a method to synthesize α-substituted butenolides from β-keto sulfoxides (Scheme 3.4).[8] Addition of dimsyl anion to methyl acetate **3.12** gives keto sulfoxide **3.13**. Alkylation with methyl-2-bromopropionate **3.14** followed by reduction with $NaBH_4$ and acid promoted cyclization provides methyl butenolide **3.16** in 80% yield.



3.12 **3.13** **3.14** **3.15** **3.16**

Scheme 3.4. α-substituted butenolides from β-keto sulfoxides.

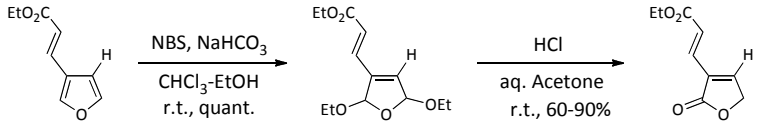
The Reformatsky reaction has been used to synthesize butenolides (Scheme 3.5).[9] Treatment of diazoketone **3.17** with acetic acid provides acetoxyacetone **3.18**. Reformatsky reaction with ethyl 2-bromopropionate **3.19** in the presence of Zn affords adduct **3.20**. Acid catalyzed lactonization gives butenolide **3.21** in 41% yield.



3.17 **3.18** **3.19** **3.20** **3.21**

Scheme 3.5. α, β-disubstituted butenolides using the Reformatsky reaction.

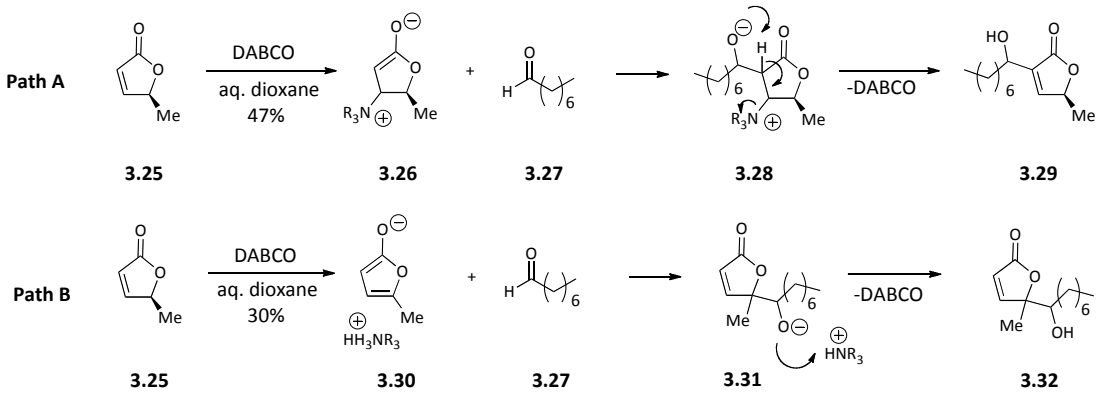
3-Substituted furans are converted, oxidatively, to α-substituted butenolides (Scheme 3.6).[10] Treatment of furan **3.22** with NBS in buffered $CHCl_3$/EtOH afforded the corresponding diethoxy dihydrofuran **3.23** in nearly quantitative yield. Subsequent acid hydrolysis of the latter provides the α-substituted butenolide **3.24** in varying yield.



3.22 **3.23** **3.24**

Scheme 3.6. α-substituted butenolides from 3-substituted furans.

Although Morita-Baylis-Hillman (MBH) reactions with acrylates and acrylonitriles are common, reactions with butenolides are rare due to the acidity of the γ-hydrogen ($pK_a \approx 23$) (Scheme 3.7).[11, 12] However, when the γ position of the butenolide is substituted, low yielding MBH reactions are possible.[13] Following Path A, Michael addition of DABCO to butenolide **3.25** generates enolate **3.26**. Reaction with **3.27** and subsequent elimination of DABCO provides the MBH adduct **3.29** in 47% yield. Unfortunately, Path B is competitive. Deprotonation of **3.25** followed by aldol reaction with **3.27** gives aldol adduct **3.32** in 30% yield.

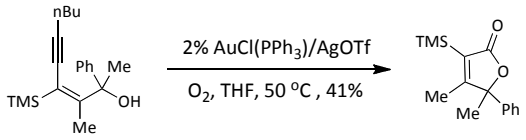


3.25 **3.26** **3.27** **3.28** **3.29**

3.25 **3.30** **3.27** **3.31** **3.32**

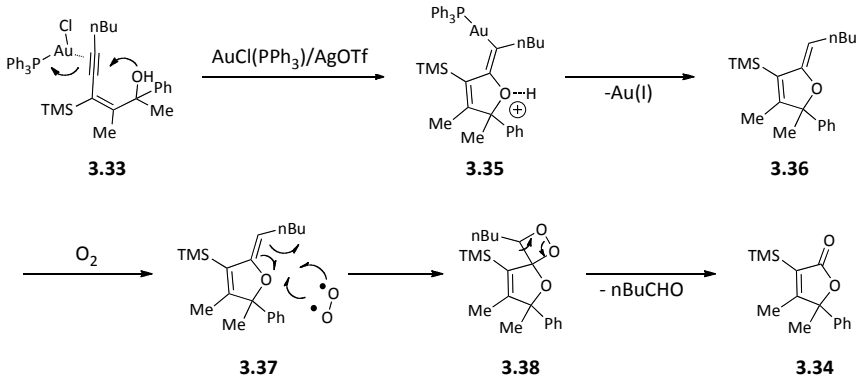
Scheme 3.7. α-substituted butenolides using the Morita-Baylis-Hillman reaction.

Over the past few decades, metal catalyzed cyclizations have allowed for the efficient synthesis of substituted butenolides (Scheme 3.8). In particular, the Liu group reported an interesting Au-catalyzed cascade cyclization/oxidative cleavage sequence to produce α,β,-disubstituted butenolides.[14] Mechanistically, this reaction is quite interesting (Scheme 3.9). Oxidative cleavage of an olefin to a carbonyl is a common functional group transformation and is typically achieved by ozonolysis or stoichiometric oxidation.[15, 16] This reaction appears to involve a surprising gold-catalyzed cleavage of an enol ether. Working to elucidate the reaction mechanism the authors noted no reaction was observed in the absence of Au(I). Additionally, the reaction was completely suppressed in the presence of radical scavengers, implying the involvement of triplet oxygen. Lastly, while enol ethers are reactive under the reaction conditions "standard" olefins are inert. Together, these results reveal Au(I) likely catalyzes both the cyclization to the dihydrofuran and the oxidative cleavage of the enol ether to the butenolide. It is noteworthy that while the α-trimethylsilyl compound was obtained in 41% yield, α-aliphatic compounds were isolated in excess of 90% yield.



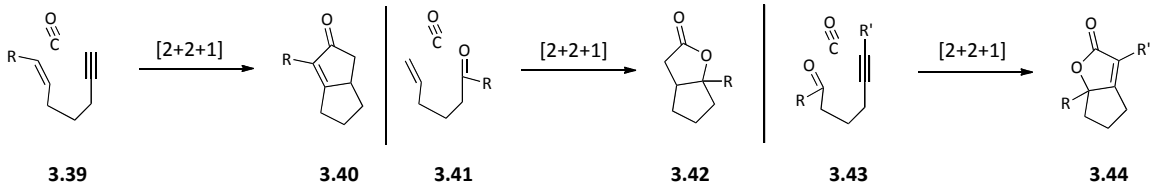
3.33 **3.34**

Scheme 3.8. α-β disubstituted butenolides by cascade/oxidative cleavage of an enynol.



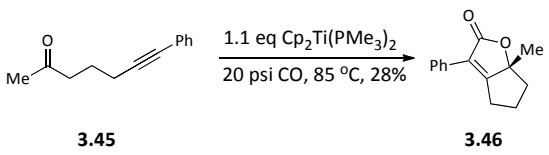
Scheme 3.9. Mechanism of the Au(I)-catalyzed cascade/oxidative cleavage of an enynol.

The Pauson-Khand cyclization is one of the most convergent methods known for the synthesis of cyclopentenones (Scheme 3.10).[17, 18] The reaction has been modified for the diastereoselective production of lactones and α-substituted butenolides.[19, 20]



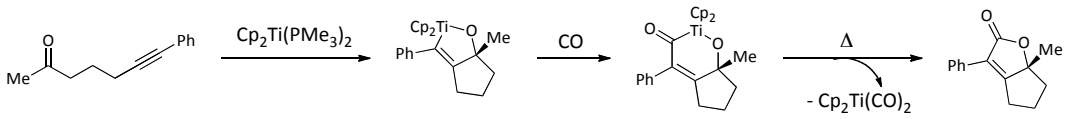
Scheme 3.10. Synthesis of carbocycles using the Pauson Khand reaction.

One variant by the Buchwald lab involves a $Cp_2Ti(PMe_3)_2$ mediated reaction in which the olefin is replaced with a carbonyl (Scheme 3.11).[19]



Scheme 3.11. Buchwald's $Cp_2Ti(PMe_3)_2$ mediated Pauson Khand reaction.

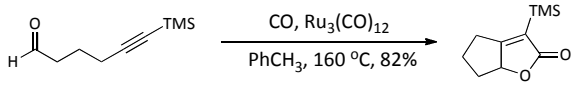
In this reaction, treatment of **3.45** with $Cp_2Ti(PMe_3)_2$ generates oxatitanacycle **3.46** (Scheme 3.12). Insertion of CO into the hindered Ti-C(sp^2) bond forms carbonylated metallacycle **3.47**, the structure of which was confirmed by X-ray crystallography. Reductive elimination is induced thermally resulting in formation of butenolide **3.48**. The authors speculate the low yield is a consequence of poor CO insertion.



3.45 **3.46** **3.47** **3.48**

Scheme 3.12. Mechanism of the $CP_2Ti(PMe_3)_2$ mediated Pauson Khand reaction.

Similarly, Murai reported a variation of this reaction in which $Ru_3(CO)_{12}$ is used as the catalyst (Scheme 3.13).[20] Treatment of yne-aldehyde **3.49** with CO and $Ru_3(CO)_{12}$ provides butenolide **3.50** in 82% yield.

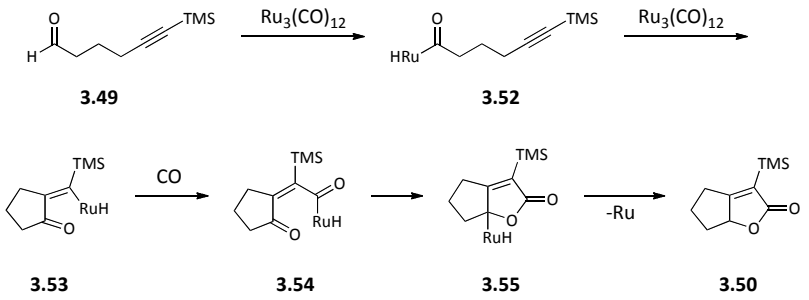


3.49 **3.50**

Scheme 3.13. Murai's $Ru_3(CO)_{12}$ mediated Pauson Khand reaction.

While the possibility exists that the reaction follows the same pathway as the Buchwald system, the authors suggest an alternative pathway (Scheme 3.14). Oxidative insertion of Ru(0) into the aldehyde C-H bond generates ruthenium ester **3.52**. Migratory insertion to **3.52** forms the congested vinyl complex **3.53**. Subsequent CO

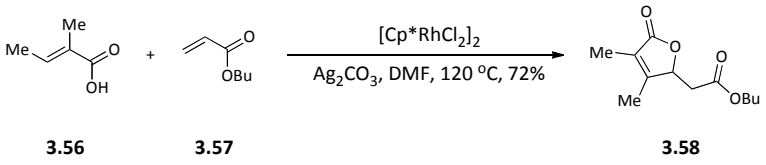
insertion is rapid due to the release of steric congestion around the Ru center to give **3.54**. Lactonization and reductive elimination then provides butenolide **3.50**.



Scheme 3.14. Mechanism of the $Ru_3(CO)_{12}$ mediated Pauson Khand reaction.

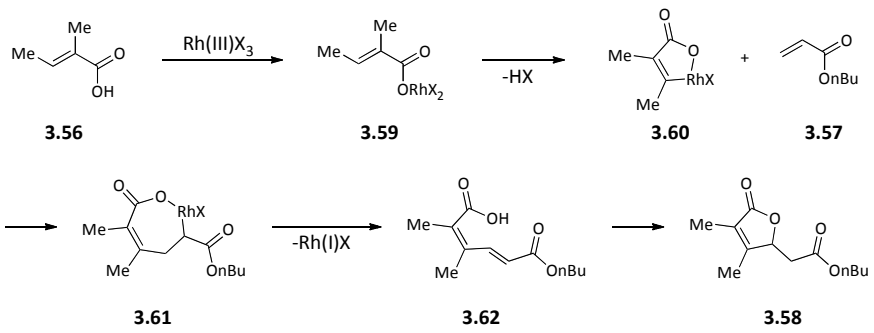
While the previous reactions are conducted under a CO atmosphere, the ability to run this reaction in a CO gas-free environment using $Mo(CO)_3(DMF)_3$ as a catalyst has been demonstrated.[21]

α,β-Disubstituted butenolides are also prepared by Rh-catalyzed oxidative coupling of substituted acrylic acids with acrylates (Scheme 3.15).[22]



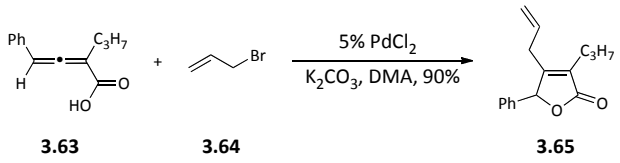
Scheme 3.15. α,β-Disubstituted butenolides by Rh-catalyzed coupling.

Generation of the rhodium ester **3.59** and directed cyclorhodination provides rhodacycle **3.60** (Scheme 3.16). Olefin insertion generates the seven-membered rhodacycle **3.61**. β-hydrogen elimination and cyclization gives butenolide **3.58**.



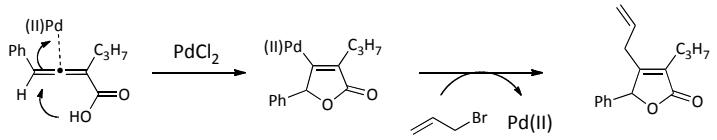
Scheme 3.16. Mechanism of the $[Cp^*RhCl_2]_2$ mediated cyclization.

It is important to close with a review of the contributions made by Shengming Ma to butenolide synthesis. Over the past decade his lab has reported transition metal-catalyzed methodology involving cyclization of allenoic acids with a multitude of coupling partners, including alkynes, allenols, and allenes.[23-26] In addition, the Pd(II)-catalyzed coupling cyclization of 2,3-allenoic acids with allylic halides works efficiently to install α or β substitution (Scheme 3.17).[27] Reaction of acid **3.63** with allyl bromide **3.64** in the presence of $PdCl_2$ and K_2CO_3 provides butenolide **3.65** in 90% yield.



Scheme 3.17. α,β-disubstituted butenolides by coupling of allenoic acids and allyl halides.

Mechanistically, the allylation likely proceeds according to the pathway illustrated in Scheme 3.18.[28] Electrophilic Pd(II) coordinates to **3.63**. 5-Endo cyclization provides furyl palladium species **3.66**. Coupling with allyl bromide affords butenolide **3.65**.



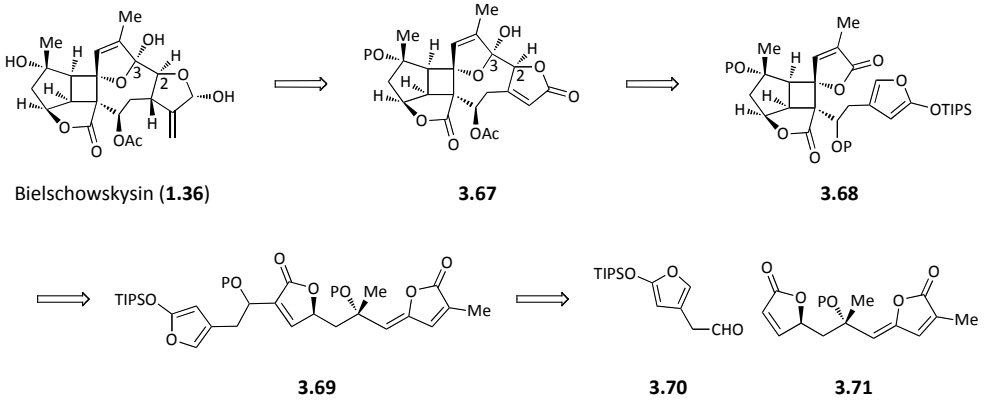
3.63 **3.66** **3.64** **3.65**

Scheme 3.18. Mechanism of the Pd(II) mediated cyclization/coupling.

First Generation Analysis
Morita-Baylis-Hillman (MBH)

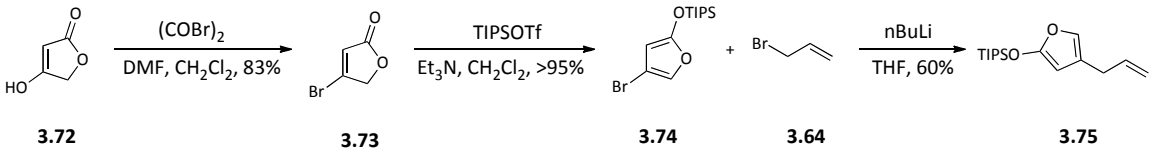
As was illustrated above, there are many methods to synthesize α-substituted butenolides. We were especially concerned with methods amenable to our established route to the tetracyclic core of bielschowskysin (**1.37**) (Chapter II). As fate would have it, these initial strategies proved to be more obstructive than helpful. While the didactic value of the unproductive routes cannot be understated, our obstinacy blinded us to a straightforward solution to the C12 functionalization problem. Scheme 3.19 outlines our first approach to an α-substituted butenolide that would serve as a substrate for the [2+2] photocycloaddition.

Reducing the synthesis of bielschowskysin to precursor **3.67** reveals several exploitable features. In particular, examination of the C2-C3 bond reveals a 1,5 α,β-unsaturated hydroxy ester, a synthon for a vinylogous aldol reaction.[29] We anticipated forming this bond through an intramolecular Mukaiyama aldol reaction of the appropriate siloxy furan precursor **3.68**.[30] Photo substrate **3.69** was envisioned to result from MBH reaction between furyl aldehyde **3.70** and butenolide **3.71**.



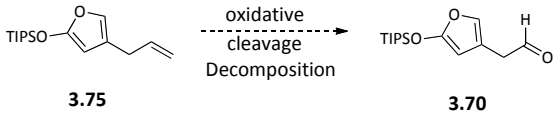
Scheme 3.19. First-generation analysis.

We initiated our investigation by probing the synthesis of aldehyde **3.70** (Scheme 3.20). Starting from commercially available tetronic acid **3.72**, bromination using $(COBr)_2$ in a DMF/CH_2Cl_2 solvent system provided bromo butenolide **3.73** in 83% yield.[31] Generation of the siloxy furan occurs in excellent yield to provide siloxy furan **3.74**. Lithium halogen exchange and reaction with allyl bromide gave **3.75** in 60% yield.



Scheme 3.20. Synthesis of allyl furan **3.75**.

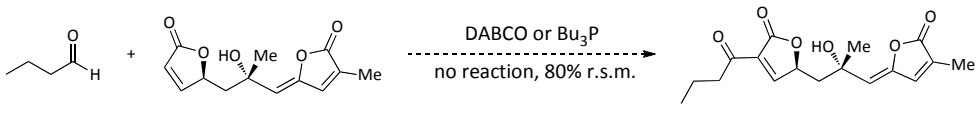
With the necessary compound in hand, we began examination of the oxidative cleavage of **3.75** (Scheme 3.21). Unfortunately, subjection of **3.75** to osmylation or one pot cleavage under Lemieux Johnson conditions proved unsuccessful. In hindsight, the siloxy furan is too electron rich to survive an oxidative environment.



3.75 **3.70**

Scheme 3.21. Failed oxidative cleavage of **3.75**.

Though we were unable to synthesize the desired coupling partner, we were still intrigued with the possibility of using the MBH reaction to generate an α-substituted butenolide. To prove whether or not this strategy was feasible **3.77** was exposed to freshly distilled butyraldehyde **3.76** and DABCO. These conditions failed to provide the desired adduct **3.78** (Scheme 3.22). Interestingly, starting material was recovered from this reaction mixture in high yield. In contrast to the MBH reactions discussed in the previous sections, we believe the greatest issue with this reaction was poor catalyst turnover due to the extra Michael acceptors located on the molecule. It is important to note that protection of the tertiary alcohol, an increase in reaction temperature, prolonged reaction times, a screening of known MBH bases, and the addition of stoichiometric base all failed to provide **3.78**.

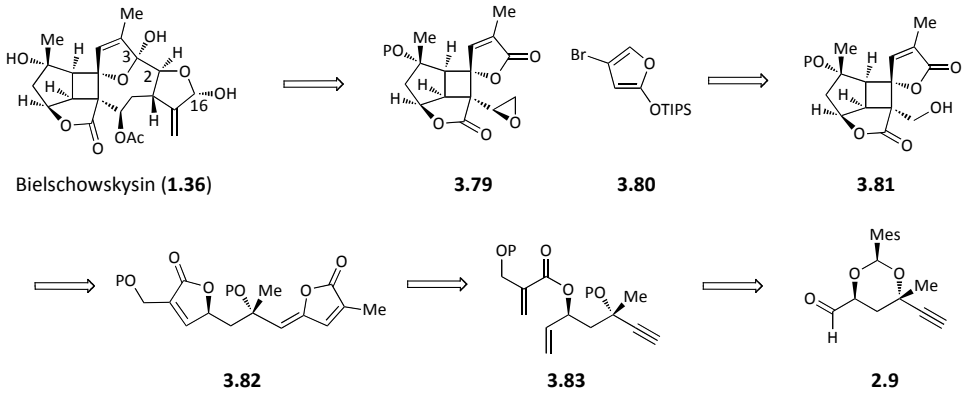


3.76 **3.77** **3.78**

Scheme 3.22. Failed Morita-Baylis-Hillman reaction.

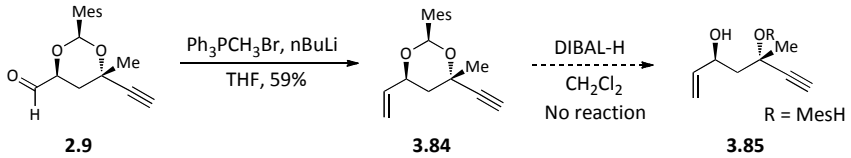
Second-Generation Analysis
Ring Closing Metathesis

On the basis of these results we found it advantageous to reevaluate our analysis (Scheme 3.23). Expecting to form the C2-C3 bond in the manner previously described, we were interested in obtaining epoxide **3.79**. In this context, ring opening of the epoxide with the cuprate derived from **3.80** would form the C14-C1 bond. It was envisioned this epoxide would arise from alcohol **3.81** by one of two methods. The first called for oxidation to the aldehyde and reaction with a sulfur ylide. The second possibility was oxidation to the aldehyde, Wittig olefination, and epoxidation. With both routes the chief concern would be the configuration of the epoxide at C13. Since the molecule is unlikely to assert any bias, this stereocenter would need to be installed through reagent control. To deliver the precursor to the [2+2] photocycloaddition, the α-substituted butenolide was expected to arise from ring-closing metathesis of diene **3.83**. This diene could be prepared from the previously synthesized aldehyde **2.9**.



Scheme 3.23. Second-generation analysis.

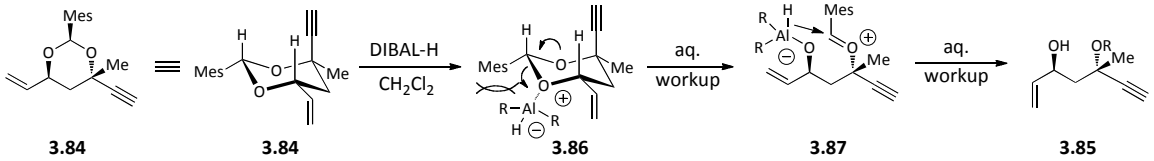
Aldehyde **2.9** was subjected to Wittig olefination to provide olefin **3.84** in 59% yield (Scheme 3.24). Due to the protecting group pattern we found it beneficial to take advantage of the chelating power of DIBAL-H to reductively cleave the mesitylidene acetal.[32, 33] In theory, this would allow us to liberate the secondary alcohol while leaving the tertiary alcohol protected as an alkyl ether. Unfortunately, this transformation was unsuccessful.



2.9 **3.84** **3.85**

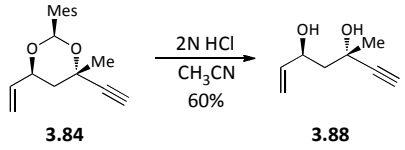
Scheme 3.24. Failed reductive cleavage.

Conformationally, mesitylidene acetal **3.84** exists in the chair shown in Scheme 3.25. Due to steric constraints, it was expected DIBAL-H would coordinate to the secondary alcohol. With this oxygen now possessing a partial positive charge, generation of the oxocarbenium ion would be followed by intramolecular hydride delivery to provide, after aqueous work-up, allylic alcohol **3.85**. While the reductive cleavage of benzylidene acetals is well established, reactions with the corresponding mesitylidene acetals are unknown. It is likely the steric bulk of the mesitylidene acetal prevents formation of the aluminum complex. It is important to note that similar reactions with less sterically cumbersome reducing systems such as $NaCNBH_3$/HCl and Et_3Si/TFA failed to produce the desired product.[34]



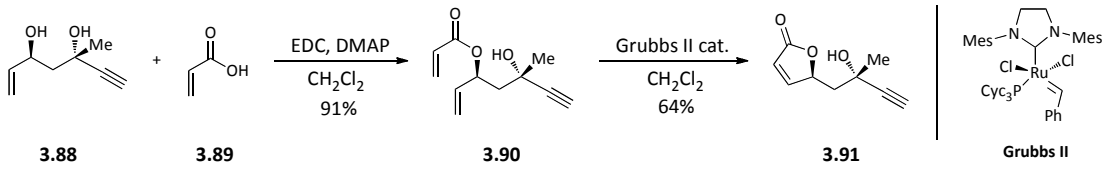
Scheme 3.25. Rationale for the failed reductive cleavage of **3.84**.

Unwilling to invest additional time in this reaction, we opted to hydrolyze the mesitylidene acetal with 2N HCl in CH_3CN, which occurred to provide diol **3.88** in 60% yield (Scheme 3.26). If necessary, the tertiary alcohol could be protected later.



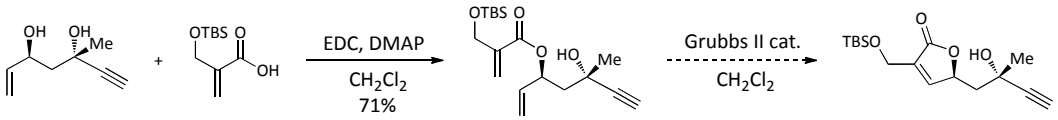
Scheme 3.26. Synthesis of diol **3.88**.

Before attempting the metathesis on the real system, we felt it advantageous to conduct a model study (Scheme 3.27).[35, 36] Esterification of **3.88** with acrylic acid, using EDC, provided diene **3.90** in 91% yield. Pleasantly, treatment of **3.90** with Grubbs second-generation catalyst in refluxing CH_2Cl_2 for 18 h provided a 64% yield of butenolide **3.91**.



Scheme 3.27. Synthesis of butenolide **3.91** by ring closing metathesis.

Encouraged by these results, we moved to duplicate this success on the actual system (Scheme 3.28). To this end, esterification of diol **3.88** with known acid **3.92** provided diene **3.93** in 71% yield.[37] Regrettably, the ring closing metathesis reaction failed to occur under the established conditions. Additionally, the Grubbs first generation catalyst and Hoveyda-Grubbs catalyst failed to promote the reaction.



3.88 **3.92** **3.93** **3.94**

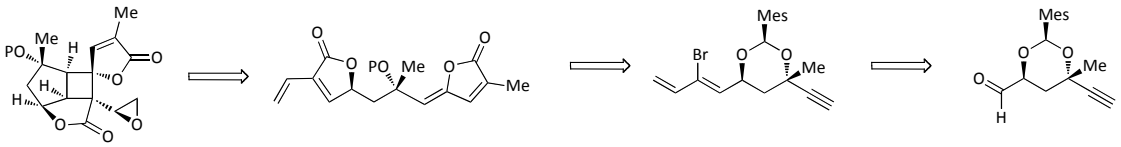
Scheme 3.28. Failed ring-closing metathesis.

Our model studies were conducted in the presence of a free tertiary alcohol; therefore, we were certain the alcohol was not disrupting the reaction by inhibiting catalyst turnover. Moreover, it has been suggested unprotected alcohols on metathesis substrates aid in promoting the metathesis process.[38] The culprit was likely the allylic silyl ether, which could have asserted a negative steric interaction with the ruthenium catalyst. This unanticipated issue led us to reexamine our route to epoxide **3.79**.

Third-Generation Analysis
Pd(0)-Catalyzed Carbonylation

The goal of our second-generation approach was to obtain an α-substituted butenolide that would allow us to install an olefin after the [2+2] photocycloaddition.

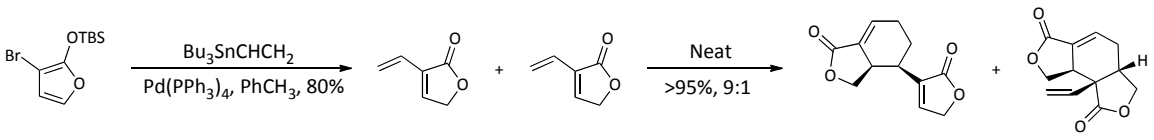
Rather than installing the olefin post photocycloaddition, we soon realized an interesting compound to carry into the photolysis would be vinyl butenolide **3.95** (Scheme 3.29). Photocycloaddition of this compound would allow convergence with our previous analysis. Compound **3.95** would arrive through Pd-catalyzed carbonylation of **3.96**, which itself would arise from the previously synthesized alcohol **2.8**.



3.79 **3.95** **3.96** **2.9**

Scheme 3.29. Third-generation synthetic analysis.

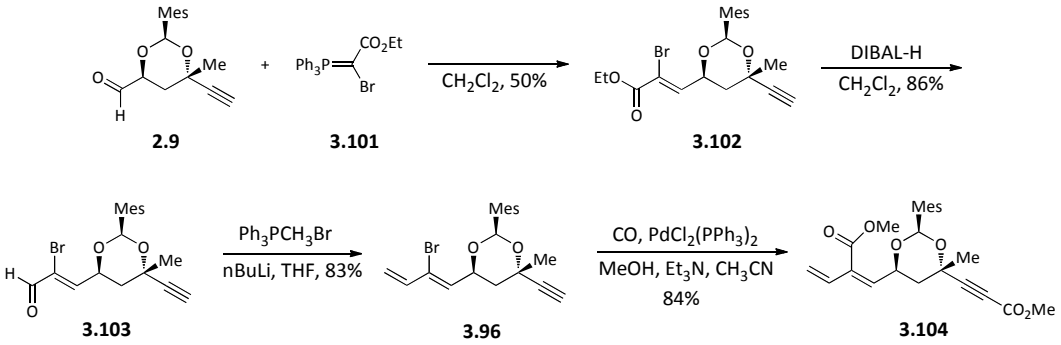
As an aside, the preparation of a 2-vinyl butenolide has only been reported twice in the literature (Scheme 3.30).[39, 40] Hoye noted these compounds are rapidly prone to spontaneous dimerization when stored neat at room temperature. This instability is similar to the unsteadiness of 2-cyanobutadiene, which is also prone to dimerization at ambient temperature.[41]



3.97 **3.98** **3.98** **3.99** **3.100**

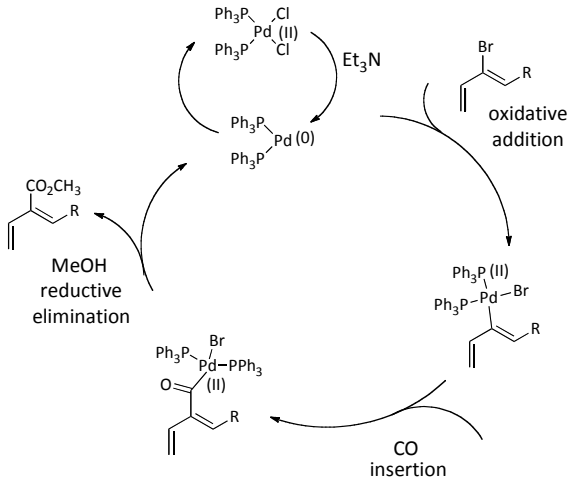
Scheme 3.30. Hoye's preparation of 2-vinylbutenolide.

Inspired by the elusiveness of this target compound, we moved forward with this route (Scheme 3.31). Aldehyde **2.9** was converted to ester **3.102** by the action of known stabilized ylide **3.101**.[42] At low temperature, slow addition of DIBAL-H to **3.102** provided aldehyde **3.103** in good yield.[43] Following an uneventful Wittig olefination, carbonylation occurred to provide diester **3.104** in 84% yield.[44-46]



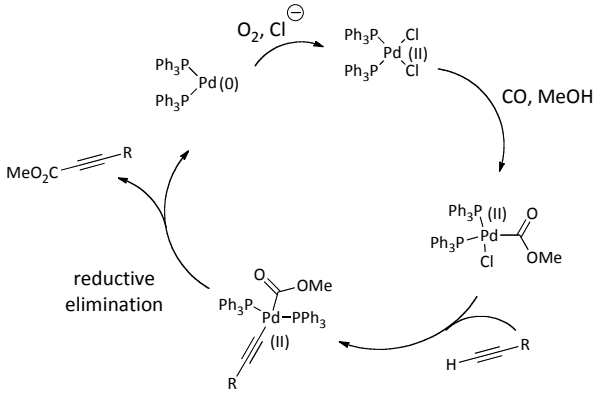
Scheme 3.31. Alkyne carbonylation.

The carbonylation of the vinyl bromide likely proceeds through the pathway illustrated in Scheme 3.32. Following reduction of palladium(II) to palladium(0), oxidative addition to the carbon-bromine bond generates the palladium(II) complex. Insertion of CO leads to an acyl palladium(II) intermediate. Following methanolysis, reductive elimination regenerates palladium(0) and delivers the desired product.



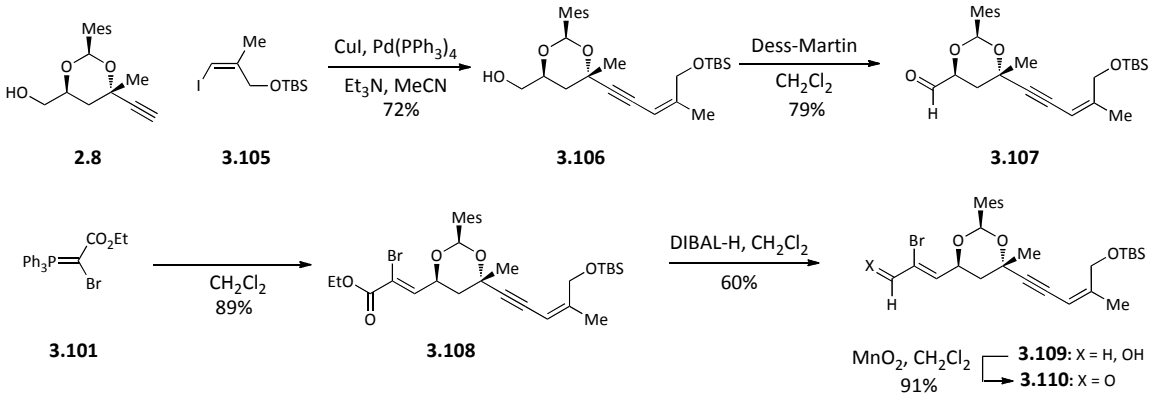
Scheme 3.32. Carbonylation of a vinyl halide.

A suggested mechanism for the carbonylation of the alkyne is presented in Scheme 3.33.[47] Formation of the methoxycarbonyl palladium species from Pd(II) is the first step in the sequence. Reaction with the alkyne followed by reductive elimination generates the alkynoate and Pd(0). Pd(0) is oxidized by air to Pd(II) to drive the catalytic cycle.



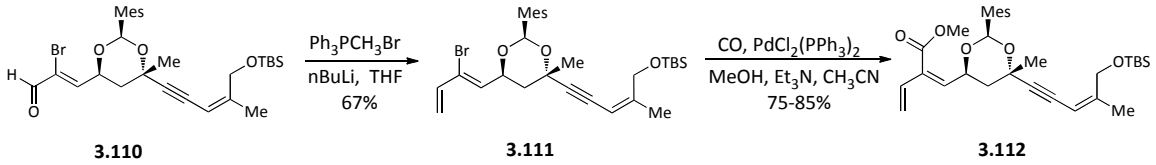
Scheme 3.33. Carbonylation of an alkyne.

After isolating this undesired product, we realized protection of the alkyne was instrumental to continuing the desired route (Scheme 3.34). Thus, alcohol **2.8** was advanced through Sonogashira coupling with known iodide **3.105** in 72% yield.[48, 49] Oxidation with Dess-Martin periodinane proceeded smoothly to deliver aldehyde **3.107**. Again, employing stabilized ylide **3.101**, homologation occurred in excellent yield to provide ester **3.108**.[42] In this case we were unable to control the DIBAL-H reduction, and as such, the allylic alcohol **3.109** was isolated. Oxidation to the aldehyde, using excess MnO_2, gave aldehyde **3.110** in 91% yield.



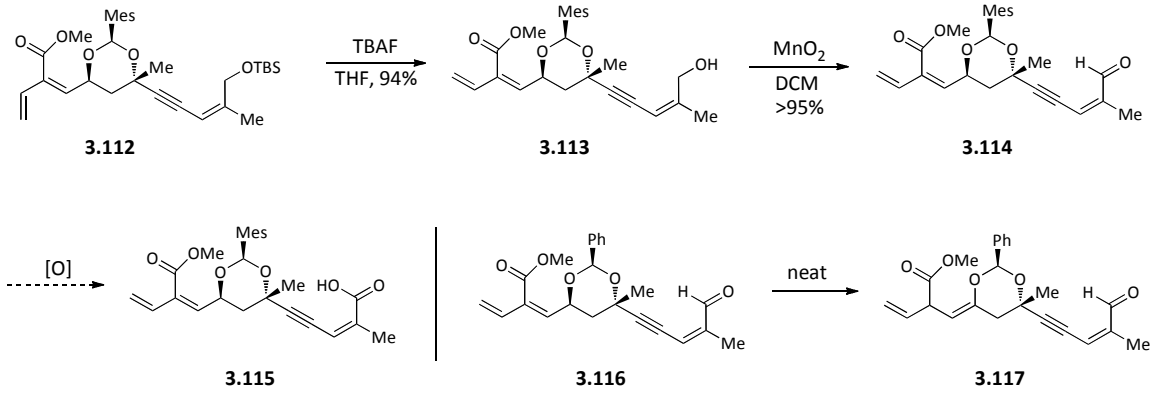
Scheme 3.34. Synthesis of aldehyde **3.110**.

Olefination occurred in good yield to give vinyl bromide **3.111** (Scheme 3.35). To our delight, carbonylation using $PdCl_2(PPh_3)_3$, Et_3N, and MeOH provided methyl ester **3.112** in 75-85% yield. Additionally, this reaction occurred under rather mild conditions (atmospheric pressure, 60 ^oC).



Scheme 3.35. Successful Pd(0) catalyzed carbonylation.

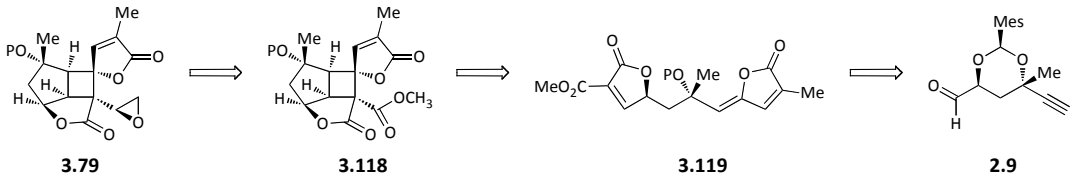
After successful installation of the methyl ester, our attention turned to the alkylidene butenolide (Scheme 3.36). Cleavage of the silyl ether gave allylic alcohol **3.113**. Oxidation with MnO_2 provided aldehyde **3.114** in excellent yield. Disappointingly, oxidation to the carboxylic acid was problematic. Moreover, attempts to oxidize allylic alcohol **3.113** to the acid in one step using TEMPO and the Jones protocol led to unidentifiable compounds. During the development of this methodology, we exchanged the mesitylidene acetal for a benzyl acetal. Interestingly, aldehyde **3.116**, which is analogous to aldehyde **3.115**, was shown to be unstable. Storing the compound neat at -20 ^{o}C led to an interesting olefin migration (see Appendix A3).



Scheme 3.36. Failed synthesis of acid **3.115**.

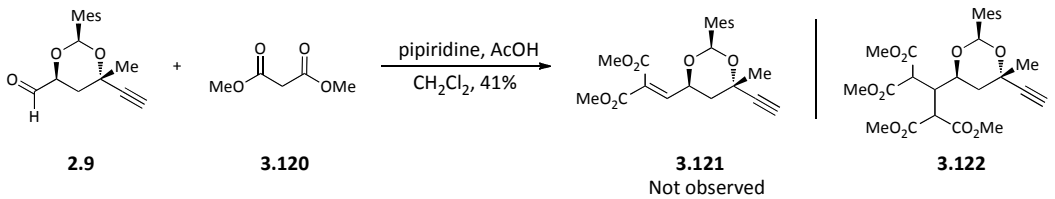
Fourth-Generation Analysis
Knoevenagel Condensation

Absorbed with the idea of synthesizing epoxide **3.79**, a fourth generation approach was designed to overcome the difficulties encountered in the previous pathways (Scheme 3.37). Expecting to readily convert ester **3.118** to epoxide **3.79**, we were intrigued with the photolysis of ester butenolide **3.119**. Starting from the previously synthesized aldehyde **2.9**, Knoevenagel condensation to the diester followed by lactonization would provide the desired butenolide.



Scheme 3.37. Fourth-generation analysis.

Interestingly, while Knoevenagel condensation with dimethyl malonate **3.120** worked well, we were unable to isolate adduct **3.121** (Scheme 3.36).[50] Instead, we consistently isolated tetraester **3.122** in 41% yield. Our attempts to eliminate the additional malonate unit were unsuccessful and this route was terminated.



Scheme 3.38. Knoevenagel condensation.

Conclusion

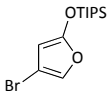
Our goal in this chapter was to provide the reader with a brief overview of known protocols to synthesize α-substituted butenolides and disclose our initial efforts to exploit a few of these methods. While our ability to conduct the idealized retrosynthetic steps in the forward sense were ineffective, we were exposed to the ultimate testing ground for development of furanocembrane synthetic methodology. At this juncture we found it paramount to remain inspired by our previous setbacks and frustrations; and to focus on restructuring our synthetic plan in a manner that would overpower the complex features of bielschowskysin (**1.36**).

Experimental Methods

General. All non-aqueous reactions were performed under an argon atmosphere in oven-dried glassware. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Diethyl ether (Et_2O), acetonitrile (CH_3CN), dichloromethane (CH_2Cl_2), and dimethylformamide (DMF) were obtained by passing commercially available formulations through activated alumina columns (MBraun MB-SPS solvent system). Tetrahydrofuran (THF) was obtained by distillation from benzophenone-sodium. Triethylamine (Et_3N) and diisopropylamine were distilled from calcium hydride and stored over sodium hydroxide. Reactions were monitored by thin-layer chromatography (TLC) using E. Merck precoated silica gel 60 F254 plates. Visualization was accomplished with UV light and aqueous stain followed by charring on a hot plate. Flash chromatography was conducted using the indicated solvents and silica gel (230-400 mesh). Yields refer to chromatographically and spectroscopically homogeneous materials. Infrared spectra were obtained as thin films on NaCl plates using a Thermo Electron IR100 series instrument and are reported in terms of frequency of absorption (cm-1). ^{1}H NMR spectra were recorded on Bruker 300, 400, 500, or 600 MHz spectrometers and are reported relative to deuterated solvent signals (7.27).

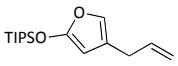
3.73

To a suspension of tetronic acid **3.72** (1.0 eq, 9.0 g, 90 mmol) in CH_2Cl_2 (200 mL) at 0 ^oC was added DMF (1.3 eq, 9.0 mL, 117 mmol). $(COBr)_2$ (1.2 eq, 10 mL, 108 mmol) was added dropwise over 30 min. After stirring 1 h, water (100 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with saturated sodium bicarbonate (3 x 100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was recrystallized (Et_2O/hexanes) to provide bromide **3.73** (12.1 g, 75 mmol, 83%) as a white crystalline solid: Spectral data was consistent with reported values.[31]



3.74

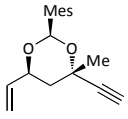
To a solution of **3.73** (1.0 eq, 1.0 g, 6.1 mmol) and Et_3N (1.3 eq, 1.1 mL, 8.0 mmol) in CH_2Cl_2 (50 mL) at 0 ^oC was added TIPSOTf (1.2 eq, 2.0 mL, 7.4 mmol). After 15 min, the reaction was diluted with pentanes (50 mL) and the reaction mixture washed with water (3 x 50 mL), brine (1 x 50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo.* The crude residue was purified by flash column chromatography (4:1 hexanes/EtOAc) to provide siloxy furan **3.74** (1.9 g, 5.9 mmol, 96%) as colorless oil: Spectral data was consistent with reported values.[31]



3.75

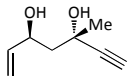
3.74 (1.0 eq, 250 mg, 0.78 mmol) was co-evaporated with PhH (3 x 10 mL). THF (10 mL) was added and the reaction cooled to -78 ^oC. nBuLi (2.5 M in THF, 1.0 eq, 310 μL, 0.78 mmol) was added and the reaction stirred 15 min.

Allyl bromide (1.2 eq, 10μL, 0.94 mmol) was added and the reaction was stirred 1h. The reaction mixture was diluted with EtOAc (10 mL) and the organics were washed with water (1 x 10 mL), brine (1 x 10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (20:1 hexanes/EtOAc) to provide allyl furan **3.75** (130 mg, 0.46 mmol, 60%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 (s, 1H), 6.71-6.70 (m, 2H), 6.12-6.10 (m, 2H), 5.03 (d, *J* = 3.2, 0.8 Hz, 2H), 1.21-1.16 (m, 3H), 1.00 (d, *J* = 8.0 Hz, 18H).



3.84

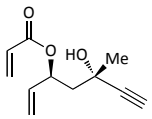
To a suspension of methyltriphenylphosphonium bromide (1.5 eq, 6.8 g, 19 mmol) in THF (125 mL) at 0 ^{o}C was added nBuLi (1.8 M, 1.5 eq, 11 mL, 19 mmol). After stirring 30 min, a solution of aldehyde **2.9** (1.0 eq, 3.5 g, 13 mmol) in THF (10 mL) was added and the reaction stirred for 3 h. MeOH (50 mL) was added, the mixture was filtered through a plug of celite, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (4:1 hexanes/EtOAc) to provide olefin **3.84** (2.1 g, 7.7 mmol, 59%) as a pale yellow gel: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.80 (s, 2H), 6.40 (s, 1H), 5.90 (ddd, *J* = 17.2, 10.8, 2.6 Hz, 1H), 5.36 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.31 (dd, *J* = 9.6, 1.2 Hz, 1H), 4.63-4.59 (m, 1H), 2.62 (s, 1H), 2.46 (s, 6H), 2.23 (s, 3H) 1.85 (dd, *J* = 13.2, 2.4 Hz, 1H), 1.74 (dd, *J* = 13.0, 11.6 Hz, 1H), 1.58 (s, 3H).



3.88

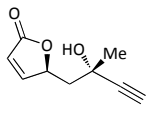
To a suspension of **3.84** (1.0 eq, 2.0 g, 7.3 mmol) in CH_3CN (75 mL) at 0 ^{o}C was added 2N HCl (75 mL). The reaction was stirred 12 h and diluted with EtOAc (100 mL). The organics were washed with saturated sodium bicarbonate (1 x 100

mL), water (1 x 100 mL), brine (1 x 100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:1 hexanes/EtOAc) to provide diol **3.88** (610 mg, 4.4 mmol, 60%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.91 (ddd, *J* = 17.4, 11.4, 4.8 Hz, 1H), 5.30 (d, *J* = 17.1, 1H), 4.88-4.81 (m, 1H), 2.52 (s, 1H), 2.10 (bs, 1H), 1.84-1.78 (m, 2H), 1.54 (s, 3H).



3.90

To a solution of diol **3.88** (1.0 eq, 550 mg, 3.9 mmol) and acrylic acid **3.89** (1.5 eq, 401 μL, 5.9 mmol) in CH_2Cl_2 (40 mL) at 0 ^{o}C was added EDCI (1.5 eq, 1.1 g, 5.9 mmol). DMAP (1 crystal) was added and the reaction was warmed to 80 ^{o}C. After 12 h the reaction mixture was cooled to ambient temperature, washed with water (3 x 50 mL), brine (1 x 50mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2:1 hexanes/EtOAc) to provide ester **3.90** (690 mg, 3.5 mmol, 91%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.48 (dd, *J* = 17.5, 1.0 Hz, 1H), 6.17 (dd, *J* = 10.5, 6.5 Hz, 1H), 5.97 – 5.87 (m, 2H), 5.33 (dd, *J* = 17.4, 4.4, 1H), 5.23 (d, *J* = 10.5, 1H), 2.92 (s, 1H), 2.19 (ddd, *J* = 15.0, 9.5, 3.0 Hz, 1H), 2.05 (dd, *J* = 15.0, 3.5, 1H), 1.59 (s, 3H).



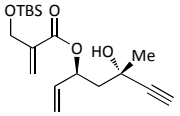
3.91

To a degassed solution of acrylic ester **3.90** (1.0 eq, 300 mg, 1.5 mmol) in CH_2Cl_2 (30 mL) at ambient temperature was added Grubbs second generation catalyst (0.1 eq, 128 mg, 0.15 mmol) and the reaction was warmed to reflux. After stirring 18 h, activated charcoal (1 g) was added and a stream of air was passed through the reaction mixture for 3 h. The reaction mixture was filtered

and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2:1 hexanes/EtOAc) to provide butenolide **3.91** (64%, 160 mg, 0.96 mmol) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (dd, *J* = 5.6, 1.6 Hz, 1H), 6.17 (dd, *J* = 5.6, 2.0 Hz, 1H), 5.55 (ddd, *J* = 8.9, 4.1, 1.8 1H), 2.54 (s, 1H), 2.09 (dd, *J* = 14.4, 4.3, 1H), 1.61 (s, 3H), 1.96 (dd, *J* = 14.2, 9.0 Hz, 1H).

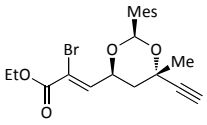
3.92

To a stirred solution of paraformaldehyde (1.0 eq, 10.8 g, 360 mmol) and methyl acrylate (1.5 eq, 50 mL, 560 mmol) at ambient temperature was added DABCO (0.1 eq, 4.3 g, 36mmol). After 72 h, the mixture was diluted Et_2O (180 mL) and washed with water (3 x 50 mL). The organics were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by distillation (1 mm Hg, 60-63 ^oC) to provide the alcohol (10.1 g, 86 mmol, 24%) as a colorless oil. To a stirred solution of the alcohol (1.0 eq, 19.1 g, 165 mmol) in CH_2Cl_2 (400 mL) at ambient temperature was added Et_3N (1.2 eq, 27.8 mL, 198 mmol) and TBSCl (1.1 eq, 27.4 g, 182 mmol). After stirring 15 h the reaction was washed with saturated aqueous ammonium chloride (250 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Bulb to bulb distillation (1 mm Hg, 100 ^oC) provided the silyl ether (35 g, 330 mmol, 91%) as a colorless oil. The oil (1.0 eq, 35 g, 330 mmol) was dissolved in THF (500 mL) and treated with 2M LiOH (250 mL). After stirring 48 h, the reaction mixture was extracted with EtOAc (3 x 100 mL) and the organics dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Bulb to bulb distillation (1 mm Hg, 130 ^oC) provided acid **3.92** (31 g, 325 mmol, >95%) as a colorless oil: Spectral data consistent with reported values.[37]



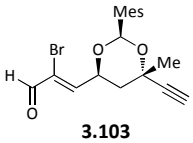
3.93

To a solution of diol **3.88** (1.0 eq, 421 mg, 3.0 mmol) and acid **3.92** (2.0 eq, 1.3 g, 6.0 mmol) in CH_2Cl_2 (30 mL) at 0 ^oC was added EDCI (2.0eq, 1.1 g, 6.0 mmol). DMAP (1 crystal) was added and the reaction was warmed to 80 ^oC. After 12 h the reaction mixture was washed with water (3 x 50 mL), brine (1 x 50mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (4:1 hexanes/EtOAc) to provide acrylic ester **3.93** (710 mg, 2.1 mmol, 71%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$): δ 6.28 (d, *J* = 1.5 Hz, 1H), 5.93 – 5.77 (m, 3H), 5.30 (d, *J* = 17.1, 1H), 5.20 (d, *J* = 10.2, 1H), 4.39 (dd, *J* = 15.0, 13.2 Hz, 2H), 3.15 (s, 1H), 2.49 (s, 1H), 2.17 (dd, *J* = 14.9, 9.3 Hz, 1H), 2.02 (dd, *J* = 14.7, 3.3, 1H), 1.53 (s, 3H), 0.92 (s, 9H), 0.10 (s, 6H).



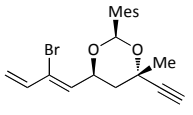
3.102

To a solution of aldehyde **2.9** (1.0 eq, 1.7g, 6.2 mmol) in CH_2Cl_2 (60 mL) at ambient temperature was added ylide **3.101** (1.1 eq, 2.9 g, 6.9 mmol). After stirring 12 h, celite (5 g) was added and the reaction mixture concentrated *in vacuo*. The crude residue was purified by flash column chromatography (4:1 hexanes/EtOAc) to provide ester **3.102** (710 mg, 2.1 mmol, 71%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$): δ 7.34 (d, *J* = 7.0 Hz, 1H), 6.83 (s, 2H), 6.43 (s, 1H), 5.14 (ddd, *J* = 11.5, 6.5, 2.5 Hz, 1H), 4.31 (q, *J* = 6.5 Hz, 2H), 2.71 (s, 1H), 2.48 (s, 6H), 2.25 (s, 3H), 2.06 (dd, *J* = 13.0, 2.5 Hz, 1H), 1.79 (dd, *J* = 12.5, 12.5 Hz, 1H), 1.57 (s, 3H), 1.32 (t, *J* = 7.0 Hz, 3H).



3.103

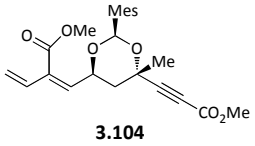
To a solution of ester **3.102** (1.0 eq, 420 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) at -78 ^oC was added DIBAL-H (1.0 M in hexanes, 1.0 eq, 420 μL, 1.0 mmol) dropwise over 1 h. The reaction was allowed to stir an additional 1 h at -78 ^oC. Saturated sodium tartrate (5 mL) was added and the mixture was stirred 3 h. The reaction mixture was diluted with EtOAc (10 mL), washed with brine (10 mL), and the organics dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (3:1 hexanes/EtOAc) to provide aldehyde **3.103** (320 mg, 0.86 mmol, 86%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$): δ 9.23 (s, 1H), 7.20 (d, *J* = 6.5 Hz, 1H), 6.85 (s, 2H), 6.48 (s, 1H), 5.33 (ddd, *J* = 12.0, 6.5, 2.5 Hz), 2.76 (s, 1H), 2.50 (s, 6H), 2.25 (s, 3H), 2.13 (dd, *J* = 13.5, 2.5 Hz, 1H), 1.84 (dd, *J* = 13.0, 12.0 Hz, 1H), 1.60 (s, 3H).



3.96

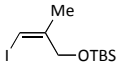
To a suspension of methyltriphenylphosphonium bromide (2.5 eq, 430 mg, 2.5 mmol) in THF (25 mL) at 0 ^oC was added nBuLi (1.8 M in THF, 2.5 eq, 1.4 mL, 2.5 mmol). After stirring 30 min, a solution of aldehyde **3.103** (1.0 eq, 380 mg, 1.0 mmol) in THF (10 mL) was added dropwise and the reaction stirred for 2 h. After the addition of MeOH (10 mL), the mixture was filtered through a plug of celite and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (10:1 hexanes/EtOAc) to provide vinyl bromide **3.96** (310 mg, 0.83 mmol, 83%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$): δ 6.92 (s, 2H), 6.43 (s, 1H), 6.30 (dd, *J* = 16.2, 10.2 Hz, 1H), 6.09 (d, *J* = 6.9 Hz, 1H), 5.64 (d, *J* = 16.2 Hz, 1H), 5.29 (d, *J* =

10.2 Hz, 1H), 5.17 (ddd, *J* = 11.1, 6.9, 2.4 Hz, 1H), 2.70 (s, 1H), 2.47 (s, 6H), 2.23 (s, 3H), 2.00 (dd, *J* = 13.1, 2.4 Hz, 1H), 1.75 (dd, *J* = 12.9, 11.7 Hz, 1H), 1.57 (s, 3H).



3.104

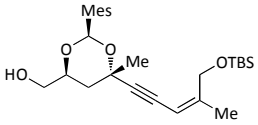
Carbon monoxide gas was bubbled through a solution of vinyl bromide **3.96** (1.0 eq, 375 mg, 1.0 mmol) in CH_3CN (10 mL) at ambient temperature. After 10 min, Et_3N (5.0 eq, 700 μL, 5.0 mmol), MeOH (5 mL) and $PdCl_2(PPh_3)_2$ (0.1 eq, 74 mg, 0.1 mmol) were added and carbon monoxide gas was bubbled through the reaction mixture for 10 additional min. After placing the reaction under an atmosphere of carbon monoxide, the temperature was raised to 60 ^oC and the reaction stirred for 8 h. After cooling to ambient temperature, celite (5 g) was added and the mixture was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (4:1 hexanes/EtOAc) to provide methyl ester **3.104** (350 mg, 0.84 mmol, 84%) as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$): δ 6.82 (s, 2H), 6.64 (d, *J* = 8.0 Hz, 1H), 6.47 (dd, *J* = 17.6, 11.6, 1H), 6.36 (s, 1H), 5.64 (d, *J* = 17.2 Hz, 1H), 5.50 (d, *J* = 11.6 Hz, 1H), 5.07 (ddd, *J* = 10.8, 8.0, 3.2 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 1H), 2.47 (s, 6H), 2.24 (s, 3H), 1.97-1.87 (m, 2H), 1.63 (s, 3H).



3.105

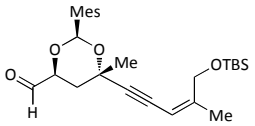
To a solution of alcohol **2.12** (1.0 eq, 5.0 g, 25 mmol) in DMF (10 mL) at ambient temperature was added imH (1.0 eq, 3.4 g, 50 mmol), TBSCl (1.0 eq, 4.2 g, 25 mmol) and DMAP (1 crystal). After stirring 3 h, the reaction mixture was diluted with EtOAc (100 mL), washed with water (3 x 50 mL), brine (1 x 50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was filtered through a plug of

celite to provide silyl ether **3.105** (7.5 g, 24 mmol, >95%) as a colorless oil: Spectral data was consistent with reported values.[49]



3.106

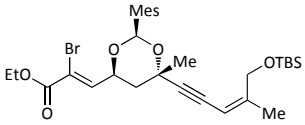
To a degassed solution of alcohol **2.8** (1.0 eq, 2.7 g, 10 mmol) and iodide **3.105** (1.3 eq, 3.9 g, 130 mmol) in CH_3CN (100 mL) at ambient temperature was added $Pd(PPh_3)_4$ (0.1 eq, 600 mg, 0.5 mmol), CuI (0.1 eq, 100 mg, 0.5 mmol), and Et_3N (2.0 eq, 3 mL, 20 mmol). The reaction was stirred 16 h, treated with celite (5 g) and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (4:1 hexanes/EtOAc) to provide alcohol **3.106** (3.3 g, 7.2 mmol, 72%) as a red oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.83 (s, 2H), 6.39 (s, 1H), 5.41 (s, 1H), 4.42 (s, 2H), 4.26-4.22 (m, 1H), 3.76-3.70 (m, 1H), 3.65-3.58 (m, 1H), 2.46 (s, 6H), 2.25 (s, 3H), 2.06-2.00 (m, 1H), 1.90 (s, 3H), 1.82 (s, 3H), 1.45-1.39 (m, 1H), 0.92 (s, 9H), 0.09 (s, 6H).



3.107

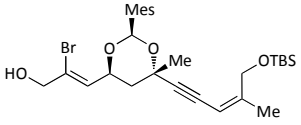
To a solution of alcohol **3.106** (1.0 eq, 460 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) at ambient temperature was added Dess-Martin periodinane (1.5 eq, 640 mg, 1.5 mmol). After stirring 2 h, the solution was diluted with Et_2O (25 mL) and washed with saturated sodium thiosulfate (2 x 25 mL), and saturated sodium bicarbonate (2 x 25 mL). The organics were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (3:1 hexanes/EtOAc) to provide aldehyde **3.107** (380 mg, 0.79 mmol, 79%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (s, 1H), 6.84 (s, 2H), 6.43 (s, 1H),

5.41 (s, 1H), 4.57 (dd, *J* = 9.6, 2.4 Hz, 1H), 4.40 (s, 2H), 2.45 (s, 6H), 2.24 (s, 3H), 2.10-2.05 (m, 1H), 1.90 (s, 3H), 1.86-1.80 (m, 1H), 0.91 (s, 9H), 0.08 (s, 6H).



3.108

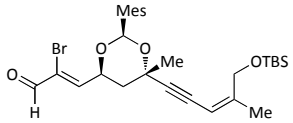
To a solution of aldehyde **3.107** (1.0 eq, 230 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) at ambient temperature was added ylide **3.101** (1.5 eq, 320 mg, 0.8 mmol). The reaction was stirred 16 h, treated with celite (1 g), and concentrated *in vacuo*. The crude residue was purified by flash chromatography (20:1 hexanes/EtOAc) to provide ester **3.108** (270 mg, 0.45 mmol, 89%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 (d, *J* = 6.6 Hz, 1H), 6.91 (s, 2H), 6.42 (s, 1H), 5.45 (s, 1H), 5.09 (ddd, *J* = 9.6, 6.9, 2.4 Hz, 1H), 4.50 (s, 2H), 4.28 (d, *J* = 7.0 Hz, 2H), 2.47 (s, 6H), 2.24 (s, 3H), 2.06 (s, 3H), 1.90 (s, 3H), 1.60 (dd, *J* = 14.6, 7.2 Hz, 1H), 1.34 (dd, *J* = 14.4, 2.4 Hz, 1H), 1.26 (s, 3H), 0.91 (s, 9H), 0.09 (s, 6H).



3.109

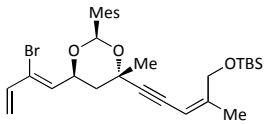
To a solution of ester **3.108** (1.0 eq, 600 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) at -20 ^{o}C was added DIBAL-H (3.0 eq, 530 μL, 3.0 mmol) and the reaction stirred 1 h while warming to 0 ^{o}C. Saturated sodium tartrate (10 mL) was added and the mixture was stirred an additional 3 h. The reaction mixture was diluted with EtOAc (25 mL), washed with brine (25 mL) and the organics dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (2:1 hexanes/EtOAc) to provide alcohol **3.109** (500 mg, 0.90 mmol, 90%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.81 (s, 2H), 6.41 (s, 1H), 6.19 (d, *J* = 6.8 Hz, 1H), 5.45 (s, 1H), 5.03 (ddd, *J* = 10.8, 7.6, 2.0 Hz, 1H), 4.46

(s, 2H), 4.24 (d, *J* = 6.4 Hz, 2H), 2.46 (s, 6H), 2.23 (s, 3H), 1.98-1.94 (m, 1H), 1.81-1.75 (m, 1H), 1.62 (s, 3H), 0.92 (s, 9H), 0.10 (s, 6H).



3.110

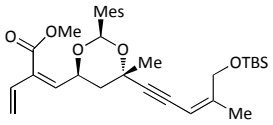
To a solution of alcohol **3.109** (1.0 eq, 500 mg, 0.9 mmol) in CH_2Cl_2 (10 mL) at ambient temperature was added freshly prepared MnO_2 (50.0 eq, 3.9 g, 45 mmol). After 10 min the reaction was filtered through a short plug of celite, dried ($MgSO_4$), and concentrated *in vacuo* to provide aldehyde **3.110** (460 mg, 91%, 0.82 mmol) without further purification as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.20 (s, 1H), 7.23 (d, *J* = 6.0 Hz, 1H), 6.83 (s, 2H), 6.45 (s, 1H), 5.45 (s, 1H), 5.31-5.30 (m, 1H), 4.58 (d, *J* = 5.0 Hz, 2H), 2.59 (s, 6H), 2.23 (s, 3H), 2.11-2.05 (m, 1H), 1.90 (s, 3H), 1.86-1.81 (m, 1H), 1.63 (s, 3H), 0.91 (s, 9H), 0.09 (s, 6H).



3.111

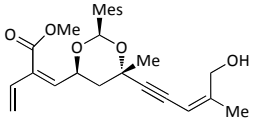
To a suspension of methyltriphenylphosphonium bromide (2.5 eq, 640 mg, 1.8 mmol) in THF (20 mL) at 0 ^{o}C was added nBuLi (1.8 M in THF, 2.5 eq, 990 μL, 1.8 mmol). After stirring 30 min, a solution of aldehyde **3.110** (1.0 eq, 400 mg, 0.71 mmol) in THF (10 mL) was added dropwise and the reaction stirred for an additional 2 h. After the addition of MeOH (10 mL), the mixture was filtered through a plug of celite and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (20:1 hexanes/EtOAc) to provide vinyl bromide **3.111** (270 mg, 5.1 mmol, 67%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.81 (s, 2H), 6.42 (s, 1H), 6.30 (ddd, *J* = 16.2, 10.5, 5.7 Hz, 1H), 6.11 (d, *J* = 7.2 Hz, 1H),

5.63 (d, *J* = 16.5 Hz, 1H), 5.46 (s, 1H), 5.28 (d, *J* = 10.2 Hz, 1H), 5.14 (ddd, *J* = 16.2, 9.0, 7.2 Hz, 1H), 4.47 (s, 2H), 2.47 (s, 6H), 2.29 (s, 3H), 2.06-1.99 (m, 1H), 1.90 (s, 3H), 1.81-1.73 (m, 1H), 1.61 (s, 3H).



3.112

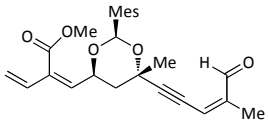
Carbon monoxide gas was bubbled through a solution of vinyl bromide **3.111** (1.0 eq, 560 mg, 1.0 mmol) in CH_3CN (25 mL) at ambient temperature. After 10 min, Et_3N (5.0 eq, 700 μL, 5.0 mmol), MeOH (5 mL) and $PdCl_2(PPh_3)_2$ (0.1 eq, 74 mg, 0.1 mmol) were added and carbon monoxide gas was bubbled through the reaction mixture for 10 additional min. After placing the reaction under an atmosphere of carbon monoxide, the temperature was raised to 60 ^oC and the reaction stirred for 8 h. After cooling to ambient temperature, celite (5 g) was added and the mixture was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (4:1 hexanes/EtOAc) to provide methyl ester **3.112** (436 mg, 0.81 mmol, 81%) as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$): δ 6.81 (s, 2H), 6.69 (d, *J* = 8.0 Hz, 1H), 6.48 (ddd, *J* = 17.5, 11.5, 6.5, 1H), 6.39 (s, 1H), 5.67 (d, *J* = 17.5 Hz, 1H), 5.48-5.44 (m, 2H), 5.12 (ddd, *J* = 10.5, 8.5, 2.0 Hz, 1H), 4.44-4.40 (m, 2H), 3.78 (s, 3H), 2.47 (s, 6H), 2.23 (s, 3H), 1.91 (s, 3H), 1.84-1.83 (m, 1H), 1.61 (s, 3H), 1.60-1.58 (m, 1H), 0.94 (s, 9H), 0.09 (s, 6H).



3.113

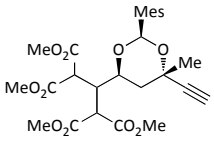
To a solution of ester **3.112** (1.0 eq, 470 mg, 1.0 mmol) in THF (10 mL) at ambient temperature was added TBAF (1.0 M, 1.0 eq, 1 mL). After stirring 2 h, the reaction was diluted with EtOAc (10

mL) and washed with saturated ammonium chloride (3 x 10 mL). The organics were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2:1 hexanes/EtOAc) to provide allylic alcohol **3.113** (400 mg, 0.94 mmol, 94%) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.81 (s, 2H), 6.69 (d, *J* = 7.9 Hz, 1H), 6.51 (ddd, *J* = 17.6, 11.5, 6.1 Hz), 6.39 (s, 1H), 5.63 (d, *J* = 17.5, 1H), 5.50-5.46 (m, 2H), 5.14-5.08 (m, 1H), 4.41 (s, 2H), 3.73 (s, 3H), 2.47 (s, 6H), 2.23 (s, 3H), 1.94 (s, 3H), 1.88-1.79 (m, 2H), 1.63 (s, 3H).



3.114

To a solution of allylic alcohol **3.113** (1.0 eq, 400 mg, 0.94 mmol) in CH_2Cl_2 (10 mL) at ambient temperature was added MnO_2 (50 eq, 4.0 g, 50 mmol). After 1 h the reaction was filtered through a short plug of celite, dried ($MgSO_4$), and concentrated *in vacuo* to provide aldehyde **3.114** (280 mg, 71%, 0.67mmol) without further purification as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.38 (s, 1H), 6.82 (s, 2H), 6.70-6.65 (m, 2H), 6.46 (ddd, *J* = 17.7, 11.4, 6.3 Hz, 1H), 6.36 (s, 1H), 5.63 (dd, *J* = 17.7, 1.5 Hz, 1H), 5.49 (d, *J* = 11.4 Hz, 1H), 5.06 (ddd, *J* = 16.5, 9.9, 2.7 Hz, 1H), 3.77 (s, 3H), 2.46 (s, 6H), 2.24 (s, 3H), 2.01-1.97 (m, 1H), 1.93 (s, 3H), 1.84-1.83 (m, 1H), 1.64 (s, 3H).



3.119

To a solution of aldehyde **2.9** (1.0 eq, 500 mg, 1.8 mmol) and dimethyl malonate (1.1 eq, 231 μL, 2.0 mmol) in CH_2Cl_2 (20 mL) at ambient temperature was added 4 A^o molecular sieves (1 g). Freshly prepared piperidinium acetate (0.1 eq, 26 mg, 0.2 mmol) was added and the reaction mixture was

stirred. After 18 h the reaction mixture was washed with water (1 x 25 mL), brine (1 x 25 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (3:1 hexanes/EtOAc) to provide tetra ester **3.119** (382 mg, 0.74 mmol, 41%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.78 (s, 2H), 6.24 (s, 1H), 4.57 (ddd, *J* = 11.3, 9.2, 1.9 Hz, 1H), 3.97 (d, *J* = 6.2 Hz, 1H), 3.89 (d, *J* = 4.0 Hz, 1H), 3.76 (s, 3H), 3.65 (s, 3H), 3.56 (s, 3H), 3.52 (s, 3H), 3.23 (ddd, *J* = 10.4, 6.6, 4.0 Hz, 1H), 2.63 (s, 1H), 2.41 (s, 6H), 2.22 (s, 3H), 2.10 (s, 1H), 1.86 (dd, *J* = 12.6, 1.9 Hz, 1H), 1.66 (dd, *J* = 12.8, 11.6 Hz), 1.56 (s, 3H).

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Appendix A3:

Spectra Relevant to Chapter III.

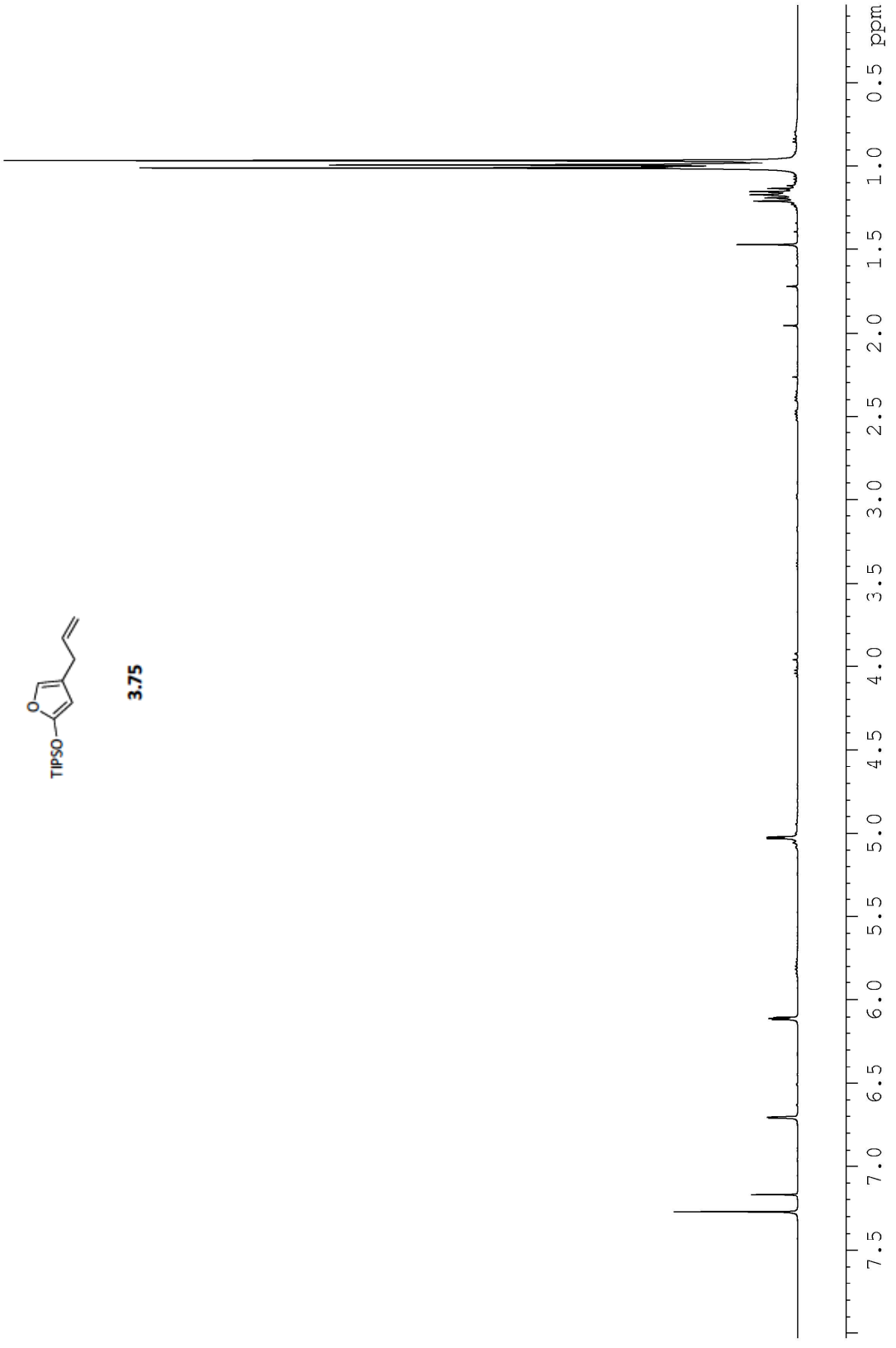


Figure A3.1. ^{1}H NMR spectra (300 MHz, $CDCl_3$) of compound **3.75**.

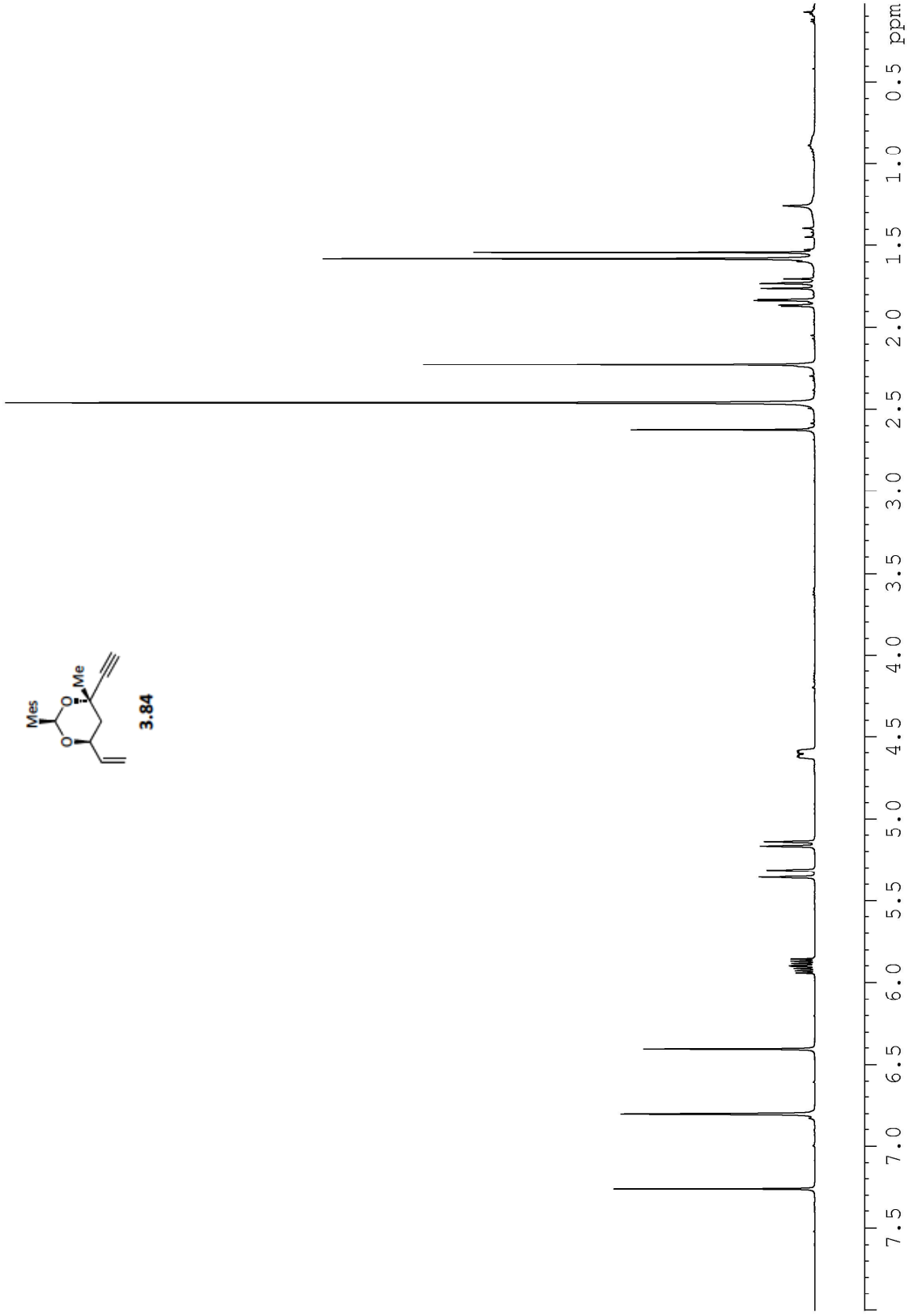


Figure A3.2. ^{1}H NMR spectra (300 MHz, $CDCl_3$) of compound **3.84**.

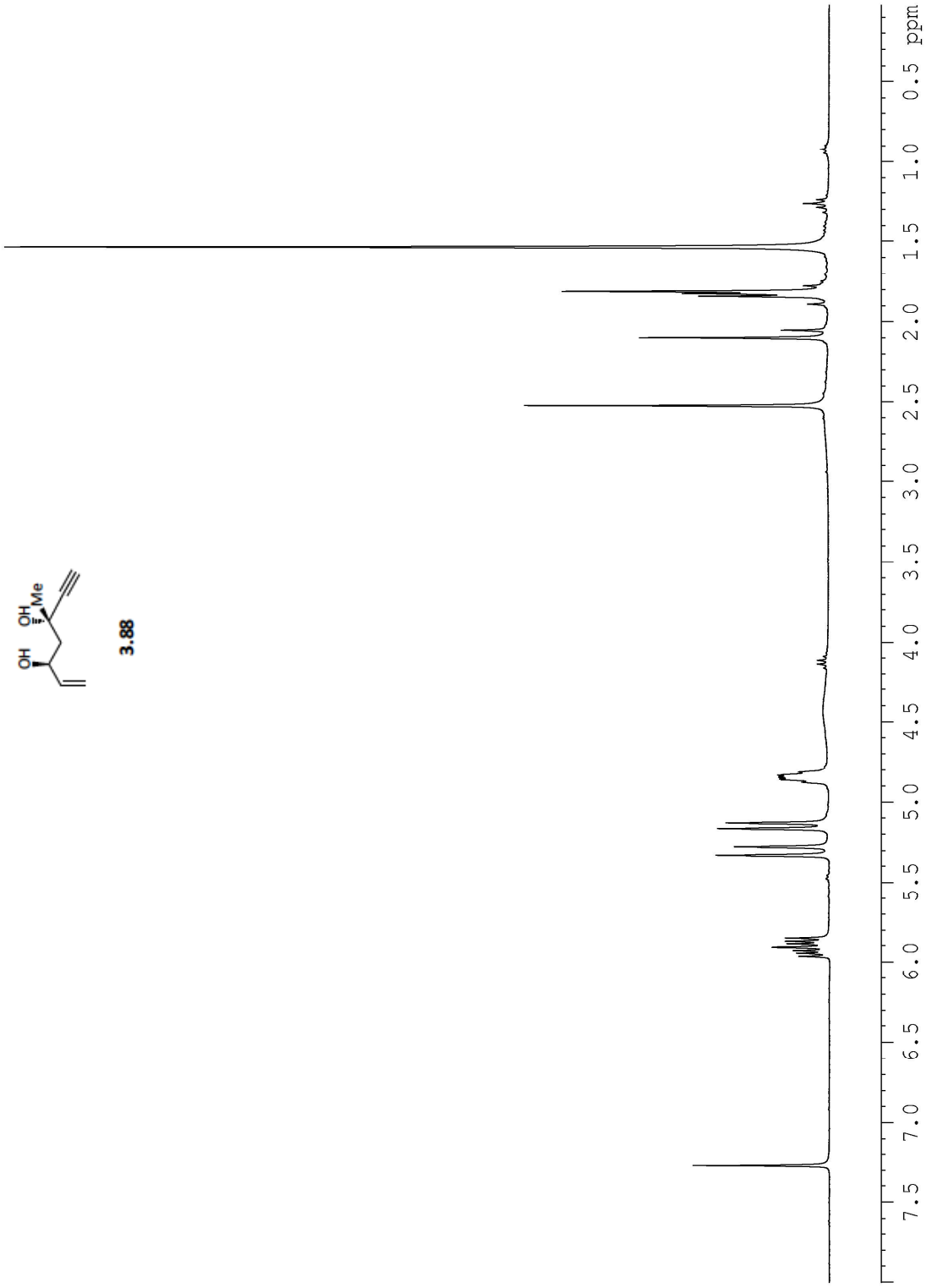


Figure A3.3. ^{1}H NMR spectra (300 MHz, $CDCl_3$) of compound **3.88**.

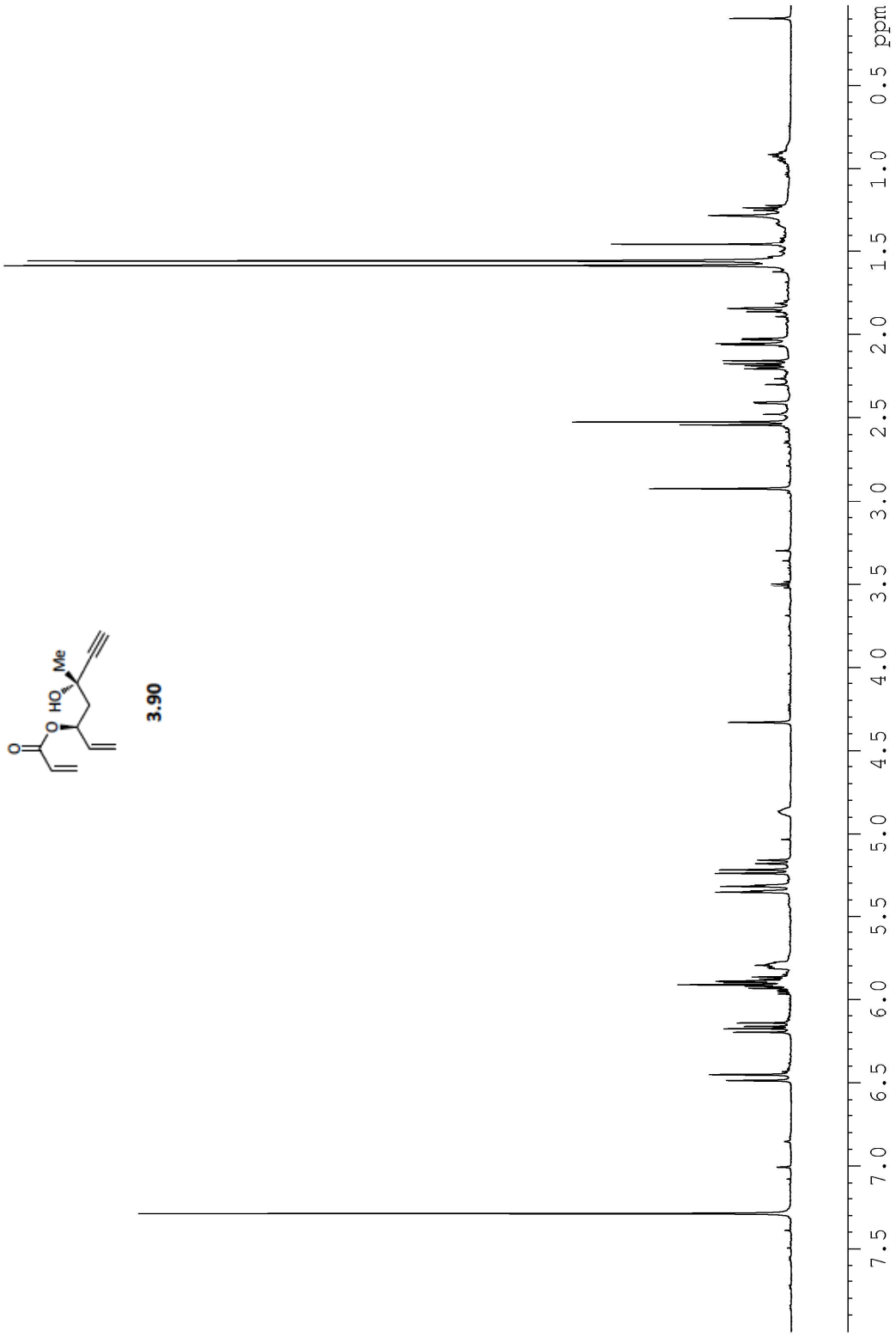


Figure A3.4. ^{1}H NMR spectra (500 MHz, $CDCl_3$) of compound **3.90**.

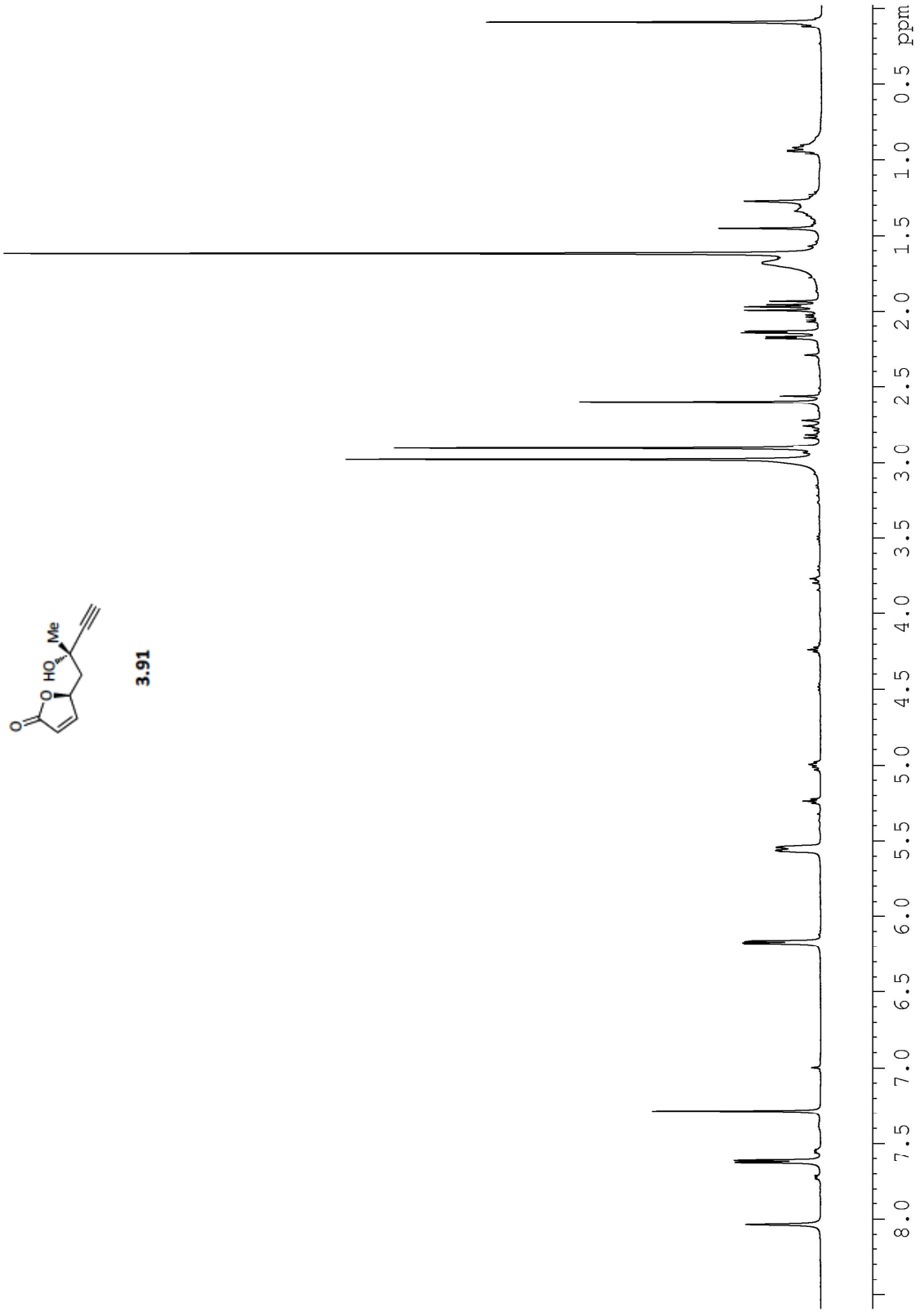


Figure A3.5. ^{1}H NMR spectra (500 MHz, $CDCl_3$) of compound **3.91**.

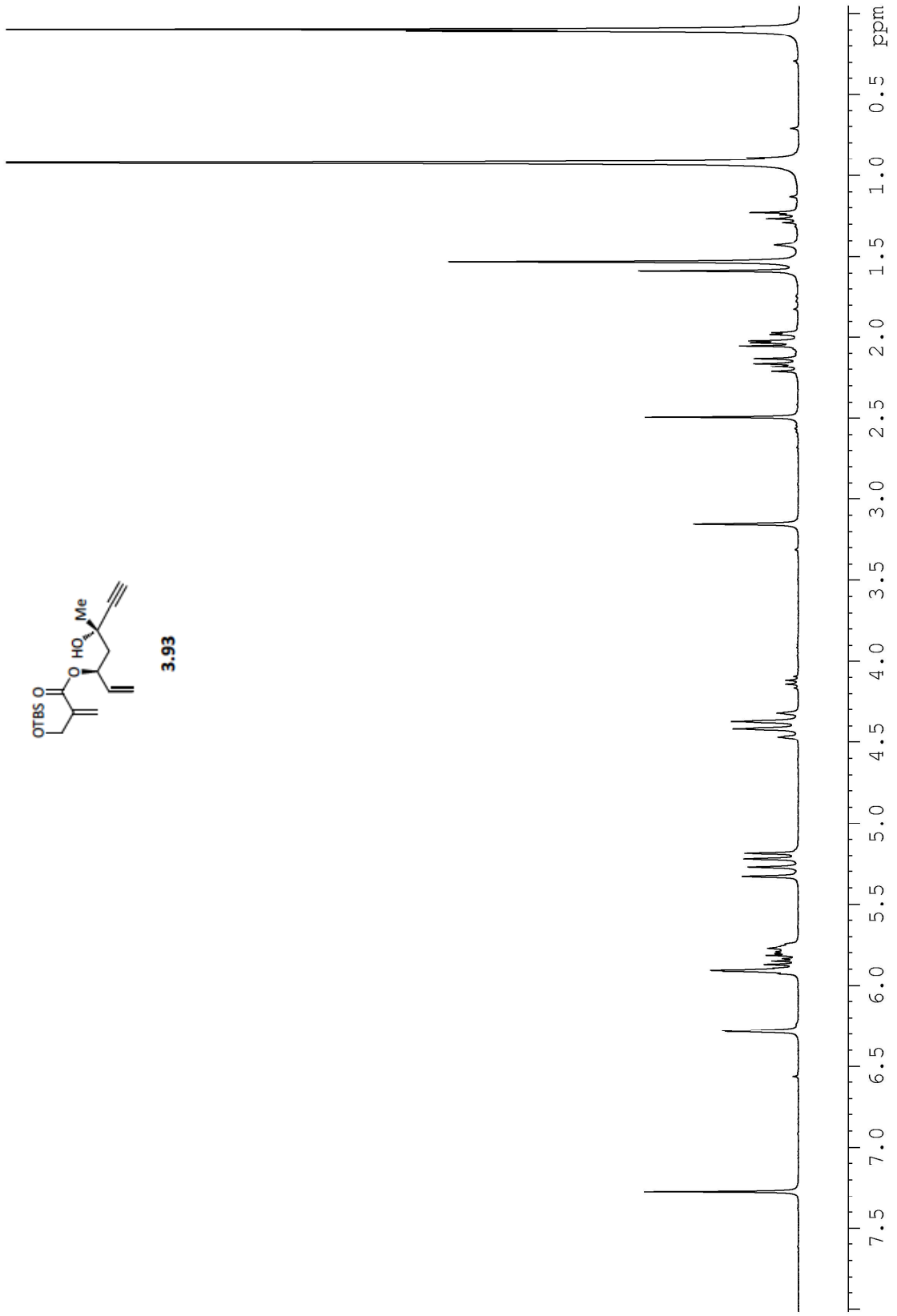


Figure A3.6. ^{1}H NMR spectra (300 MHz, $CDCl_3$) of compound **3.93**.

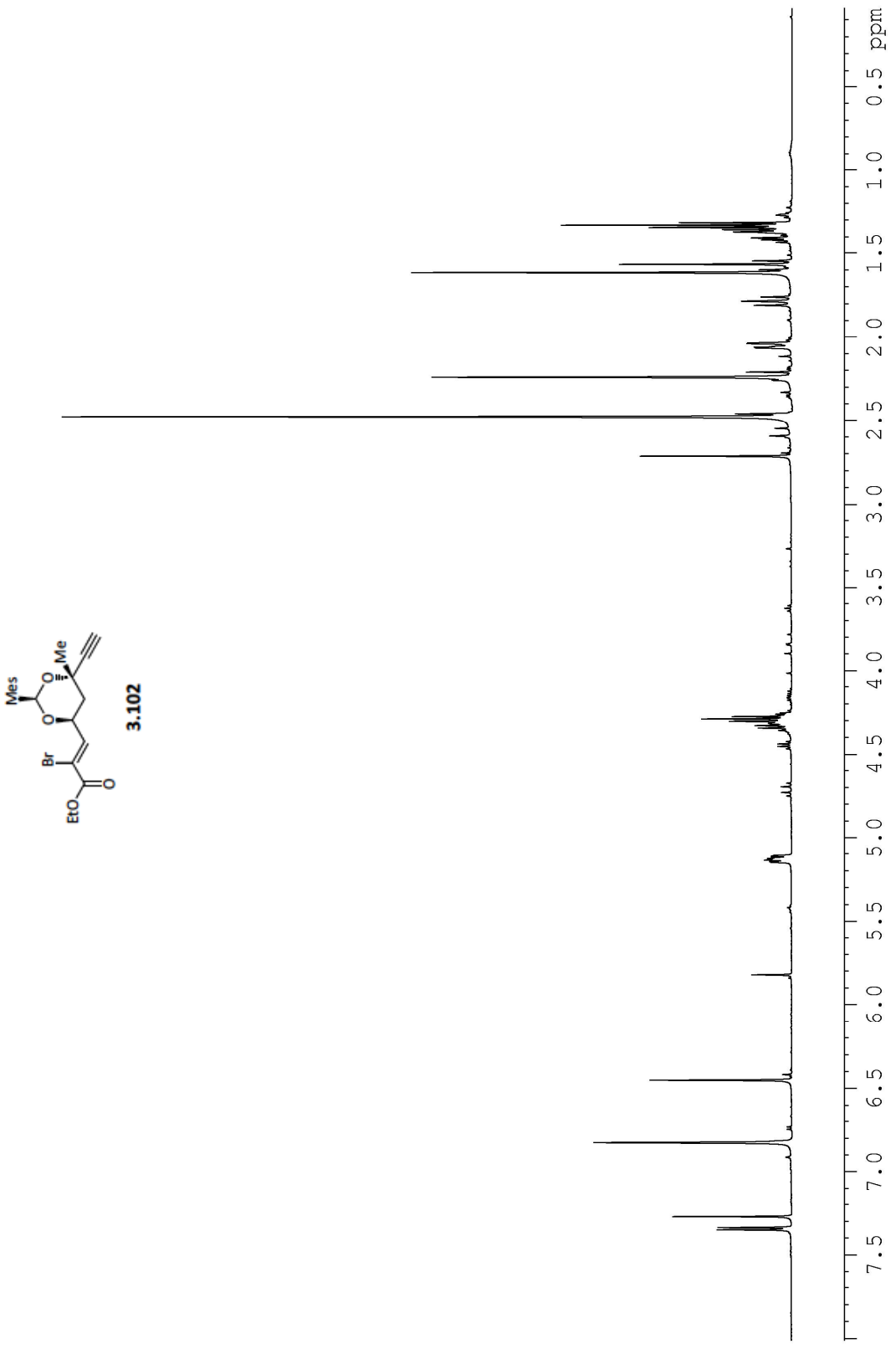


Figure A3.7. ^{1}H NMR spectra (300 MHz, $CDCl_3$) of compound **3.102**.

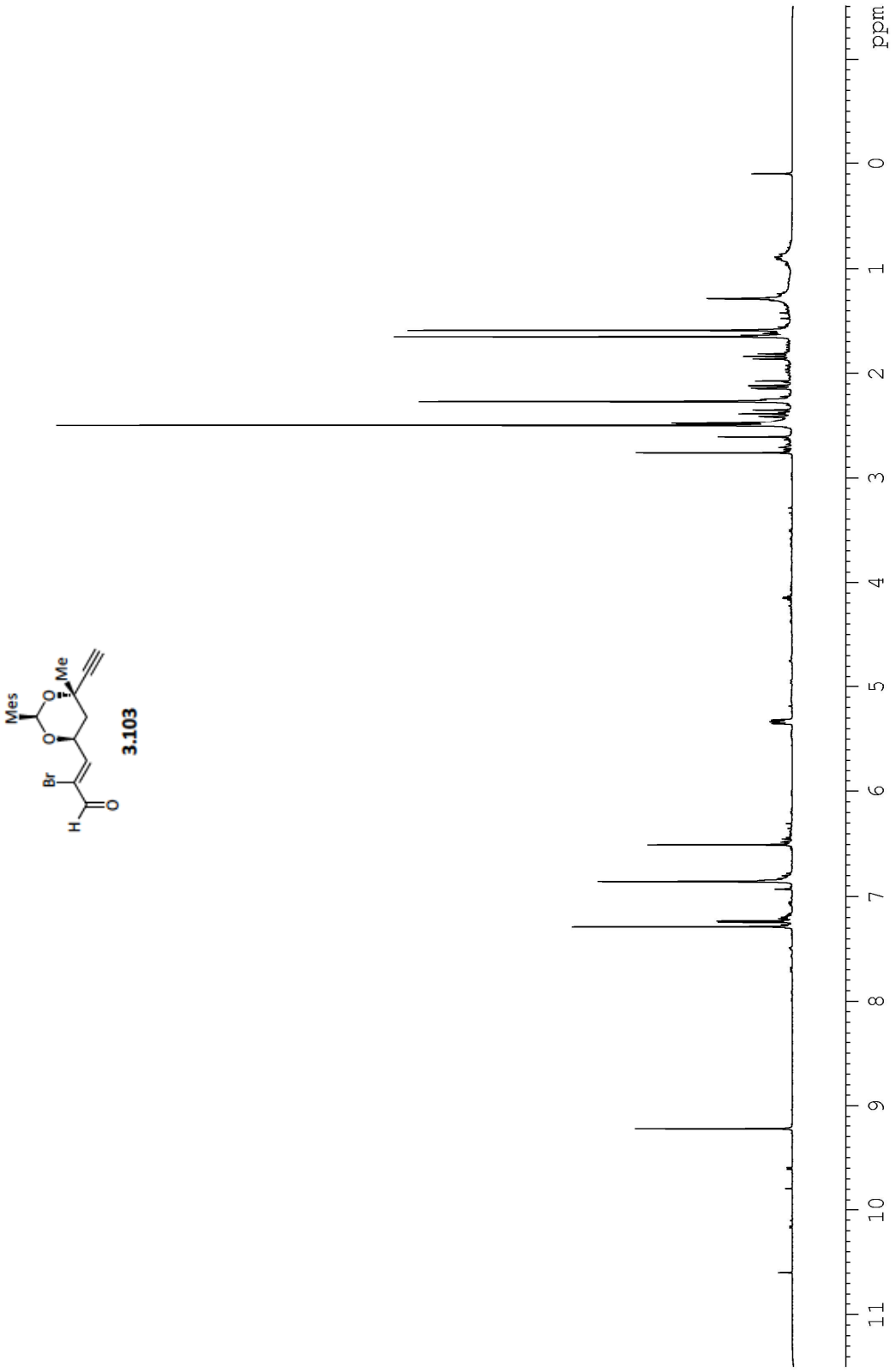


Figure A3.8. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **3.103**.

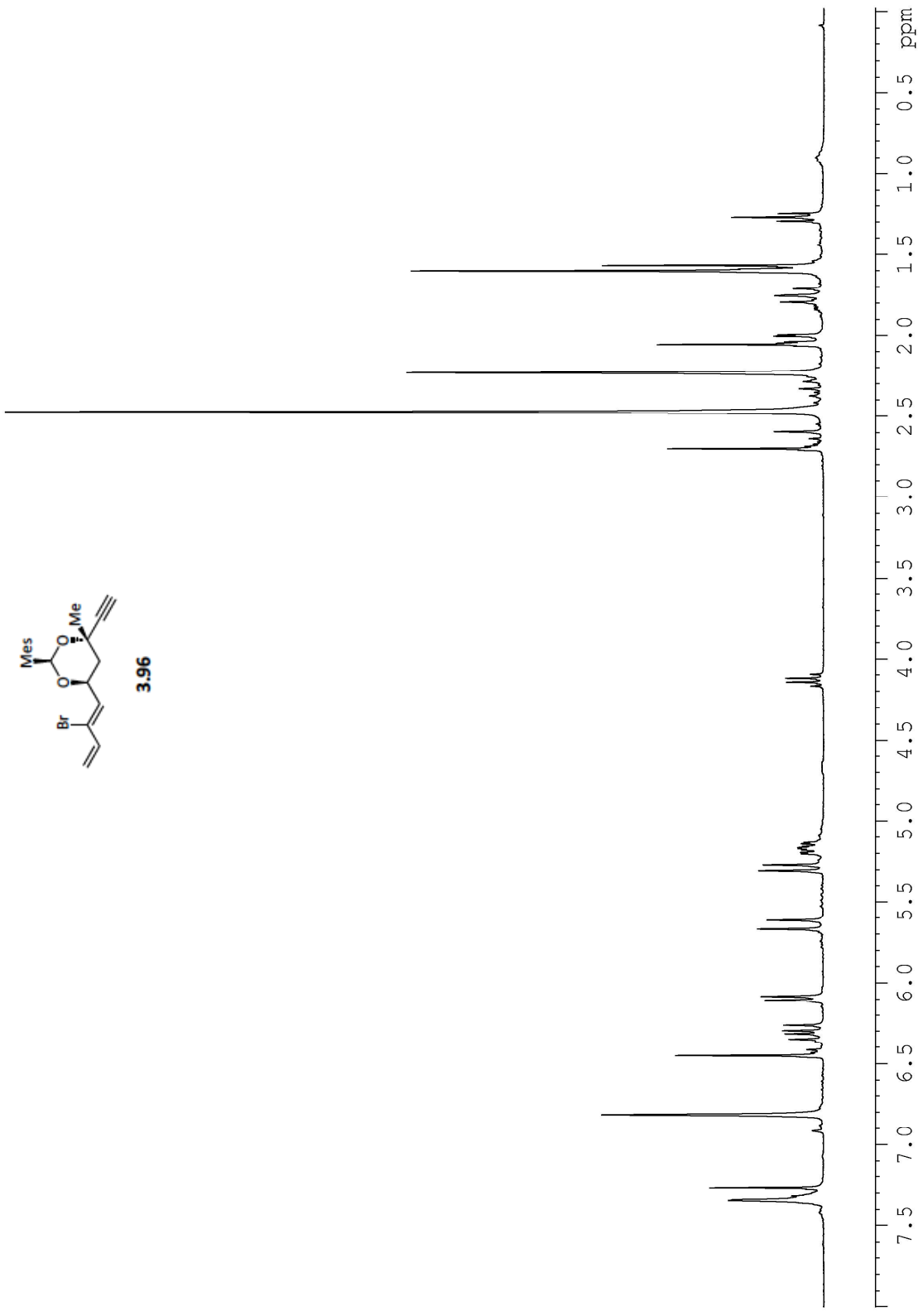


Figure A3.9. ^{1}H NMR spectra (300 MHz, $CDCl_3$) of compound **3.96**.

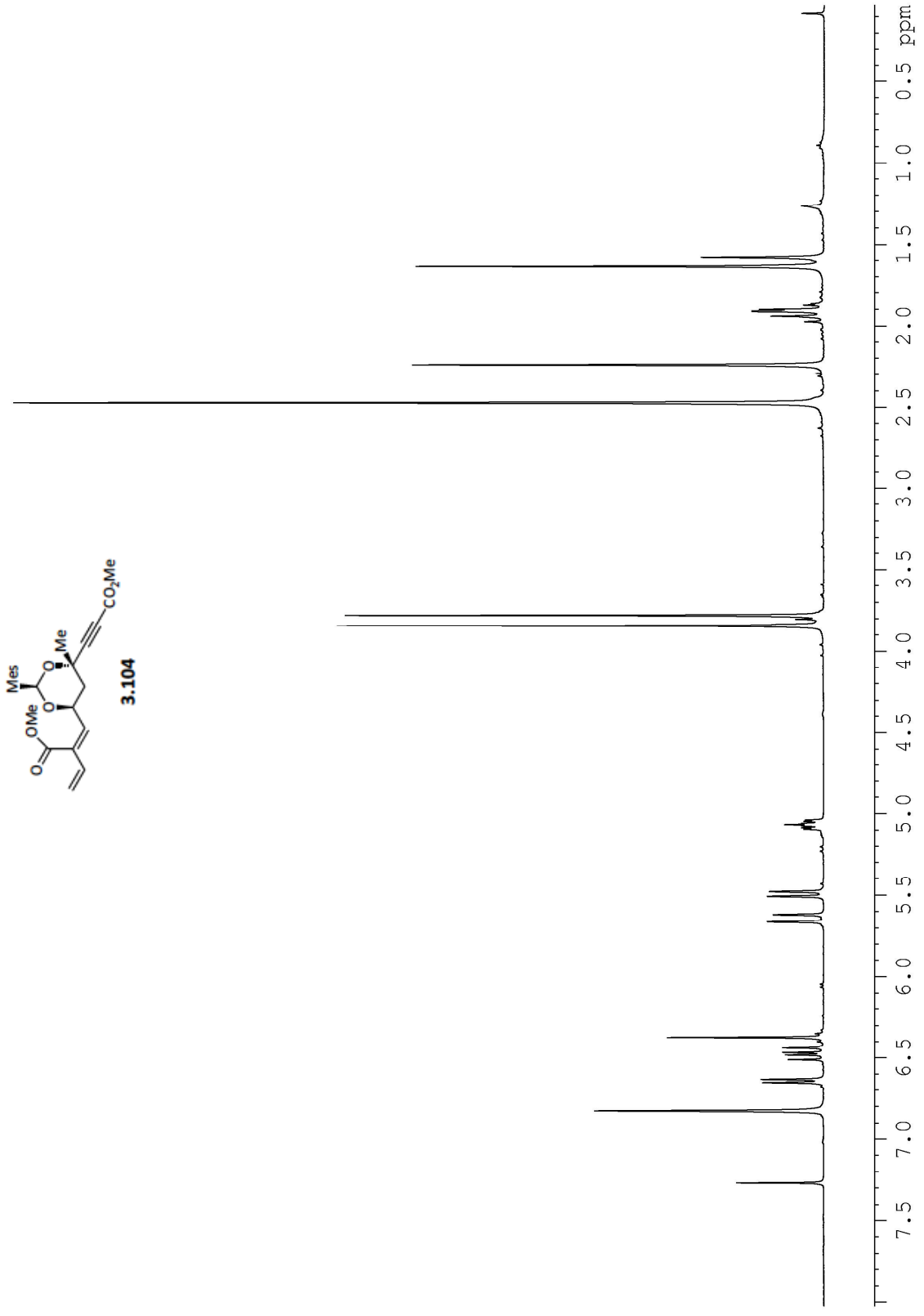


Figure A3.10. ^{1}H NMR spectra (500 MHz, $CDCl_3$) of compound **3.104**.

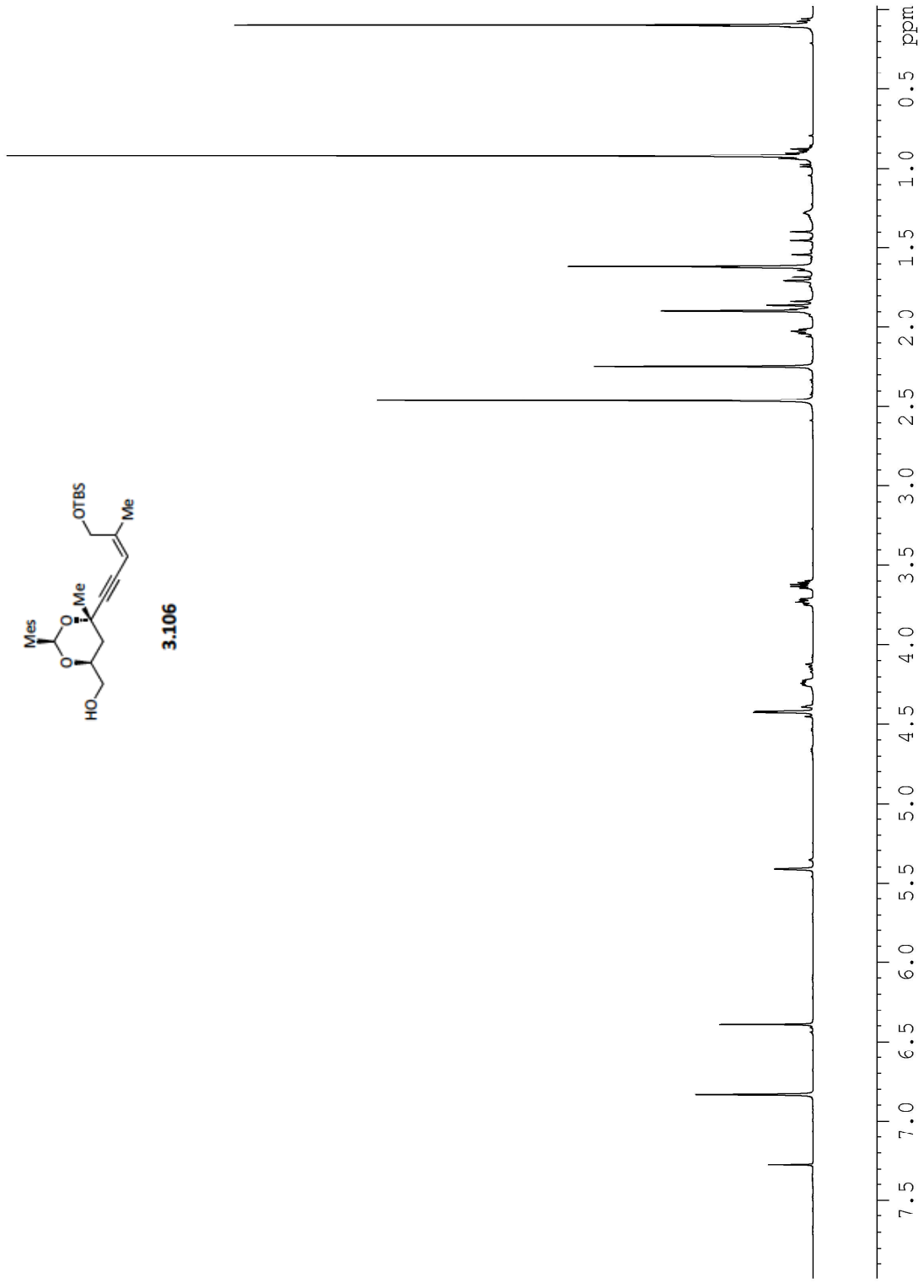


Figure A3.11. ^{1}H NMR spectra (300 MHz, $CDCl_3$) of compound **3.106**.

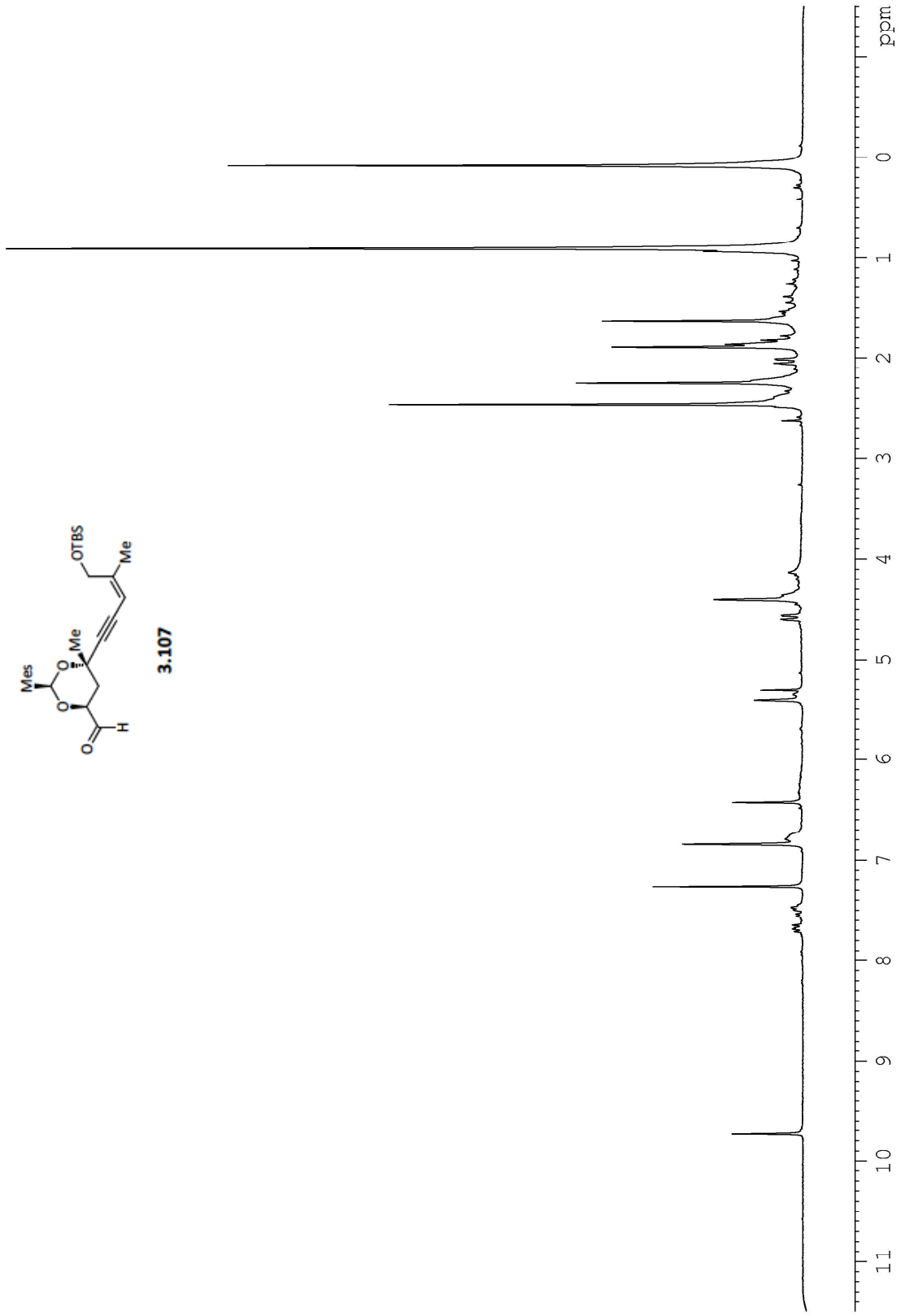


Figure A3.12. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **3.107**.

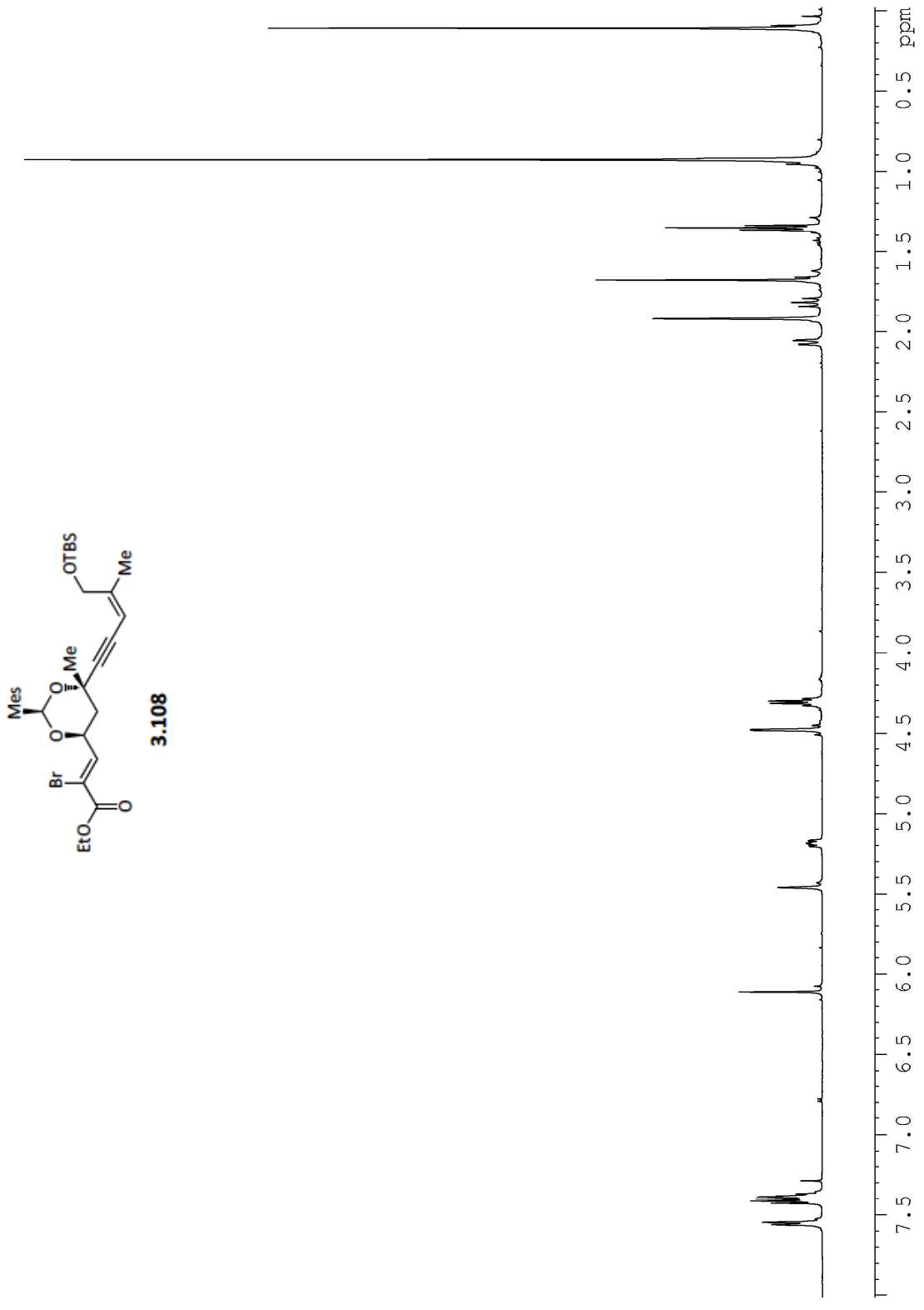


Figure A3.13. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **3.108**.

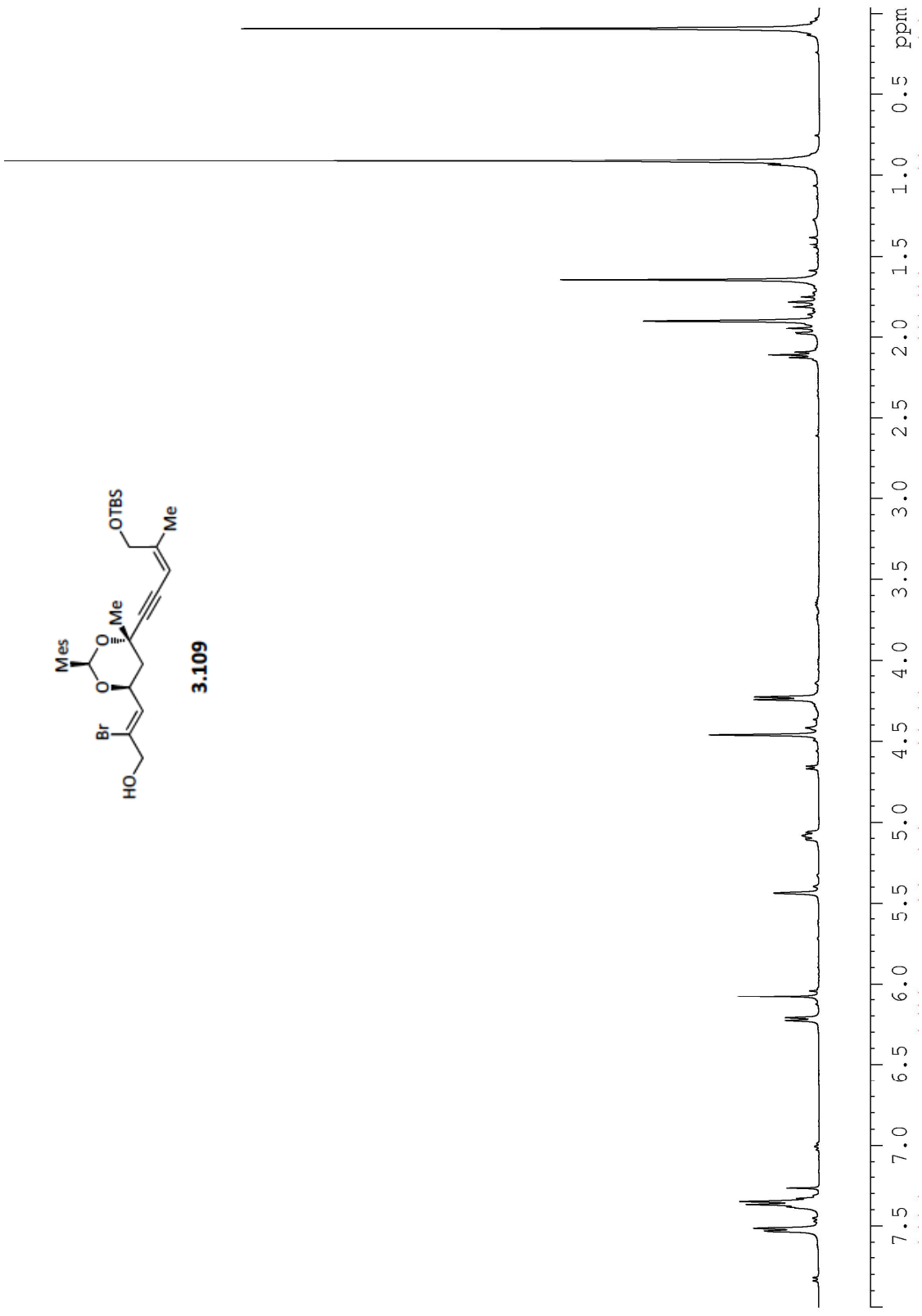


Figure A3.14. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **3.109**.

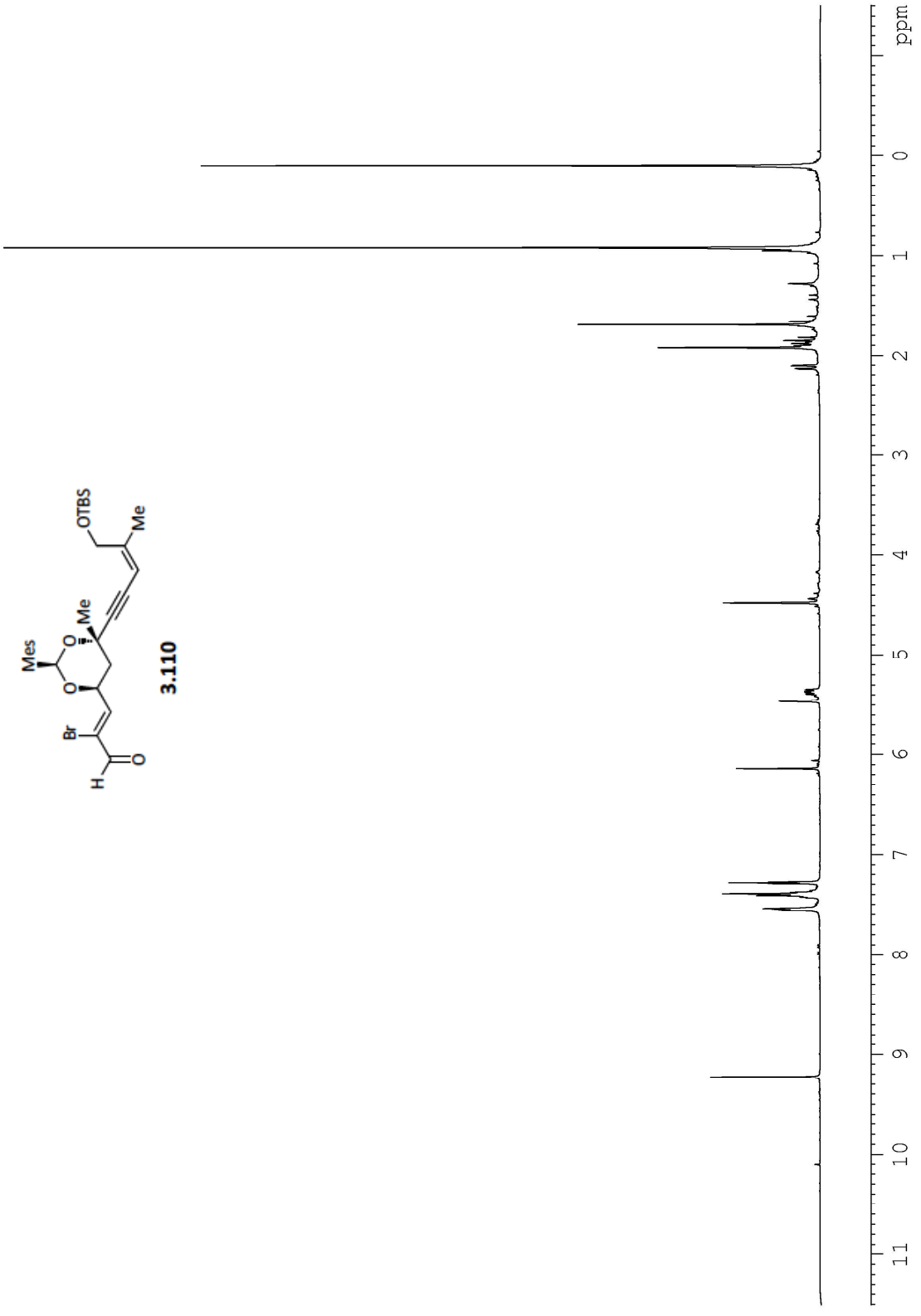


Figure A3.15. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **3.110**.

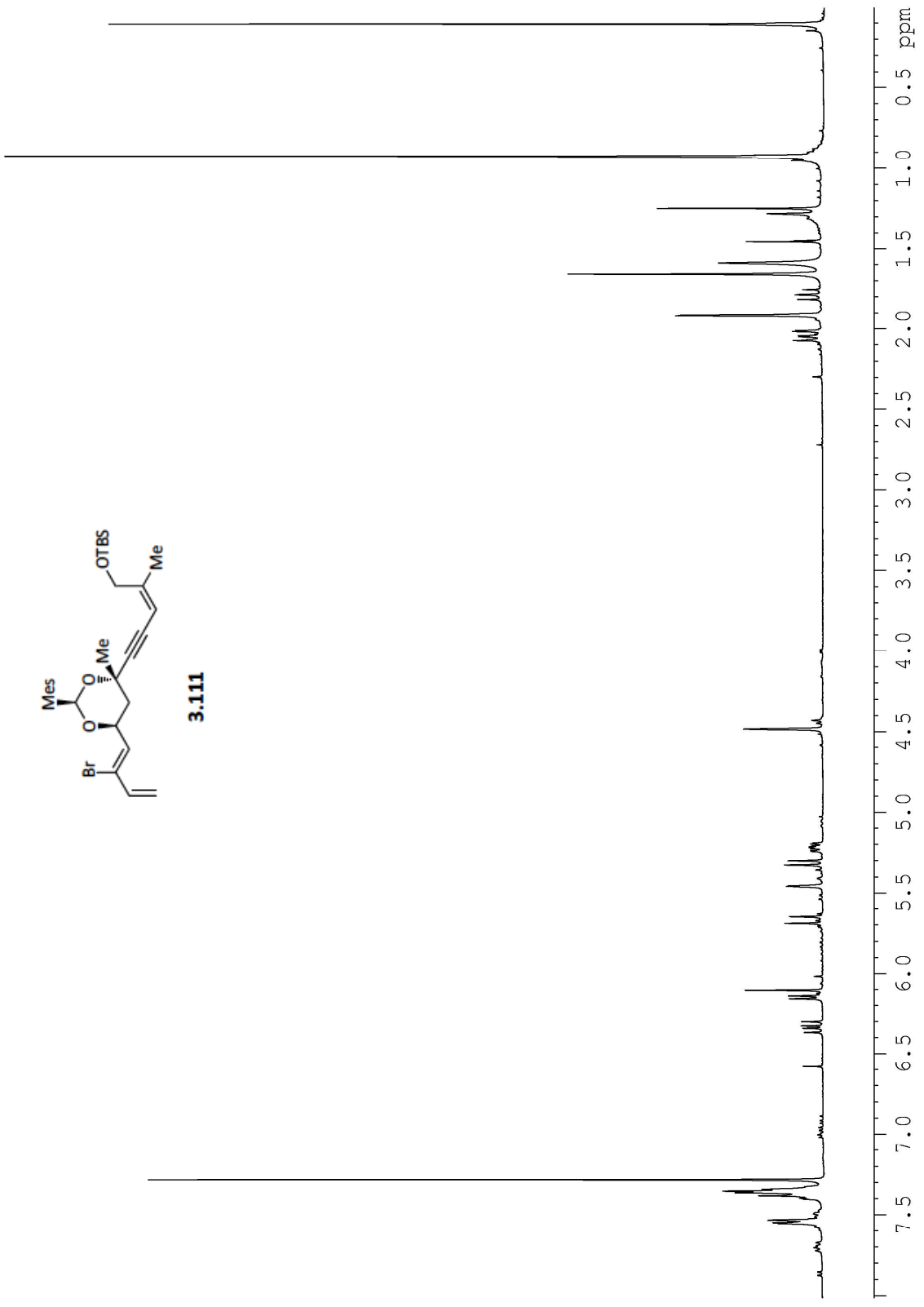


Figure A3.16. ^{1}H NMR spectra (300 MHz, $CDCl_3$) of compound **3.111**.

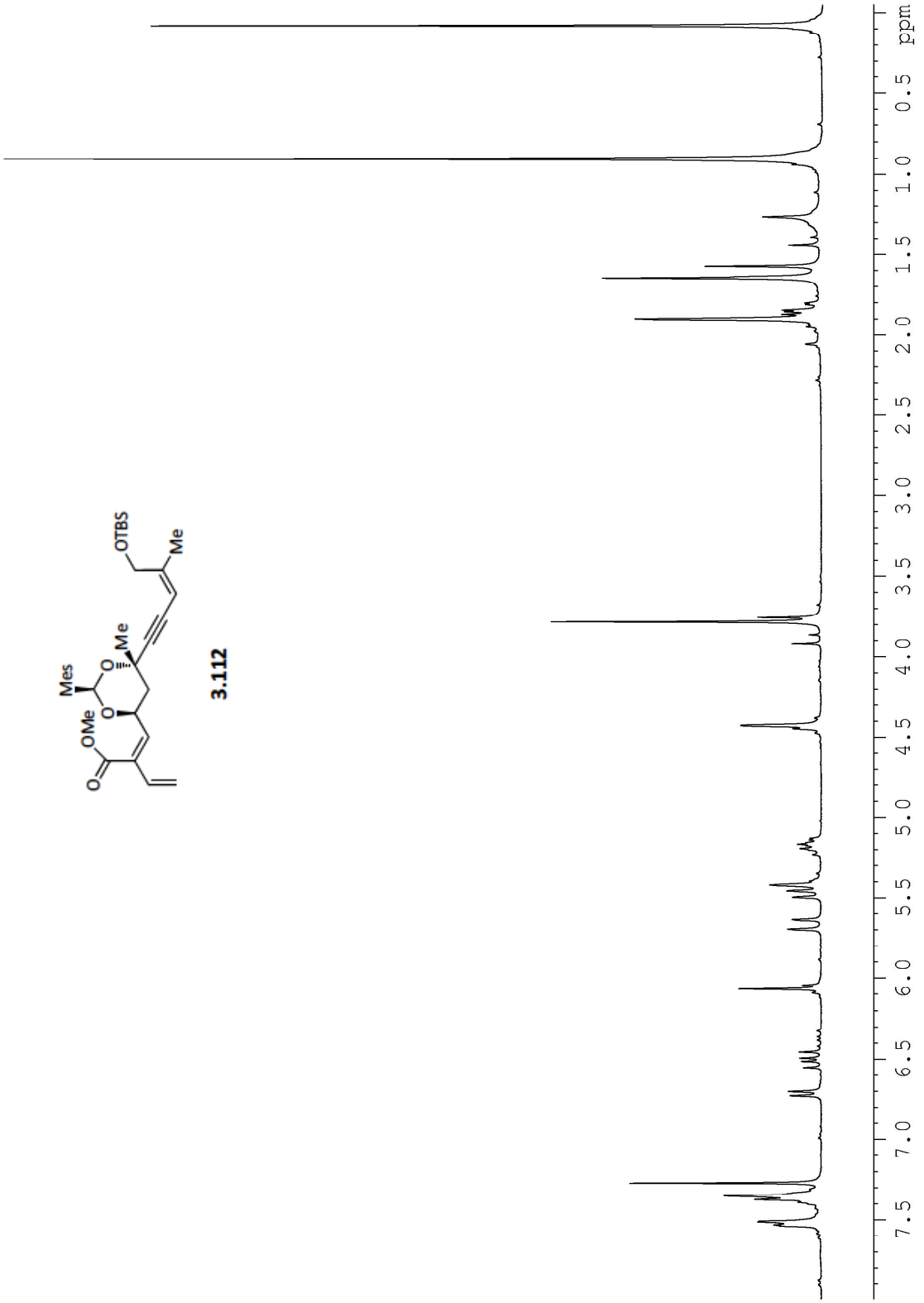


Figure A3.17. ^{1}H NMR spectra (500 MHz, $CDCl_3$) of compound **3.112**.

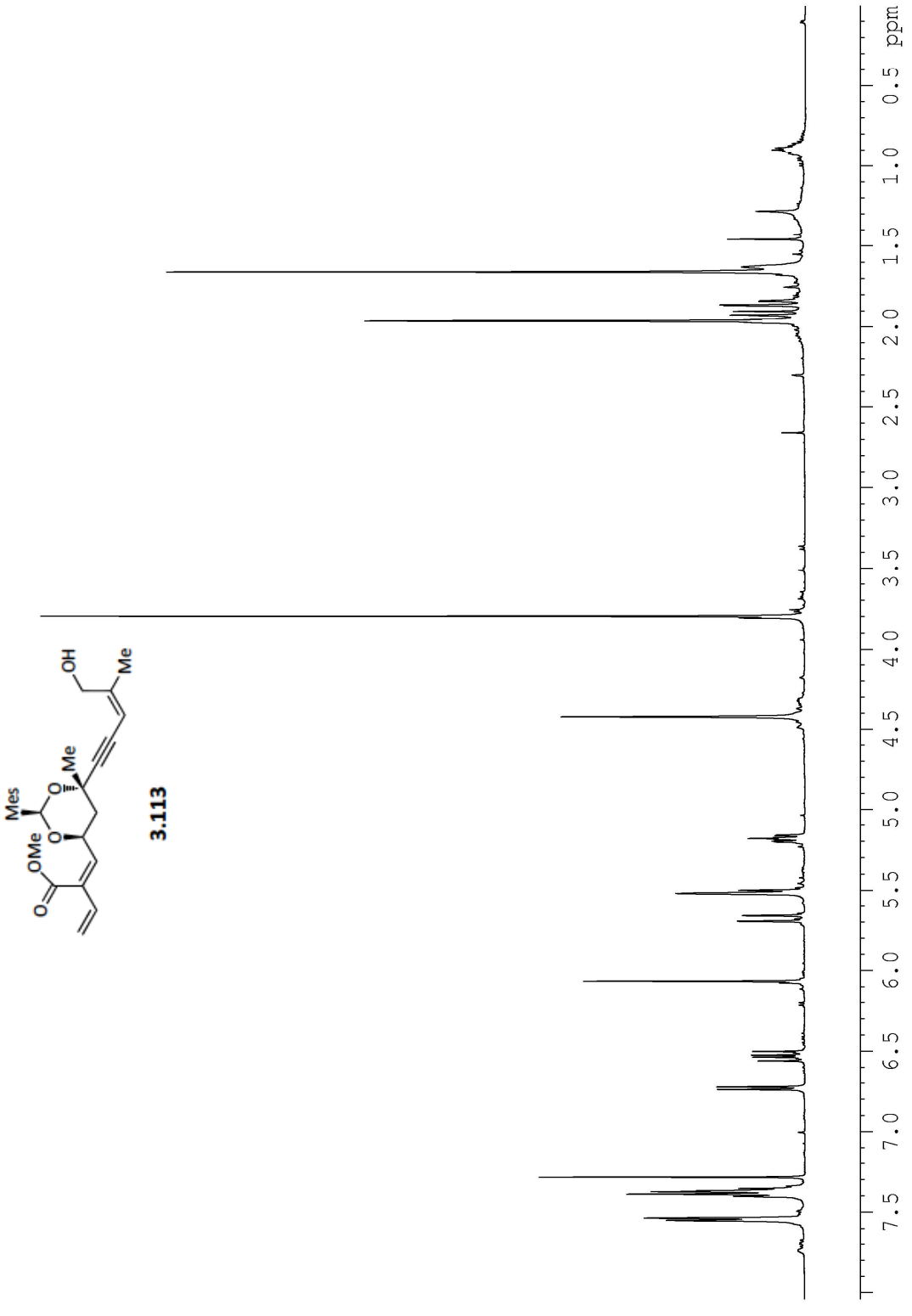


Figure A3.18. ^{1}H NMR spectra (300 MHz, $CDCl_3$) of compound **3.113**.

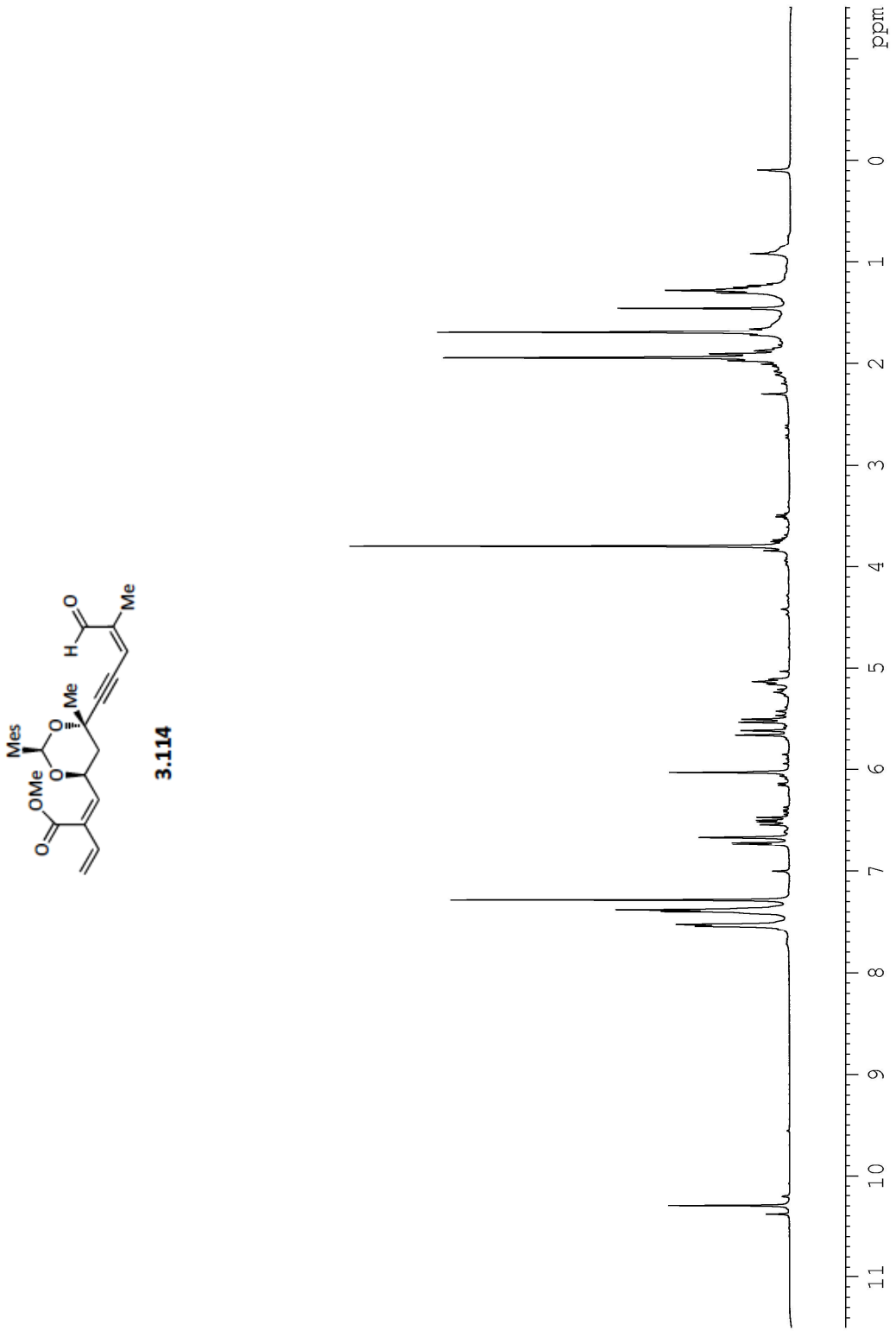


Figure A3.19. ^{1}H NMR spectra (300 MHz, $CDCl_3$) of compound **3.114**.

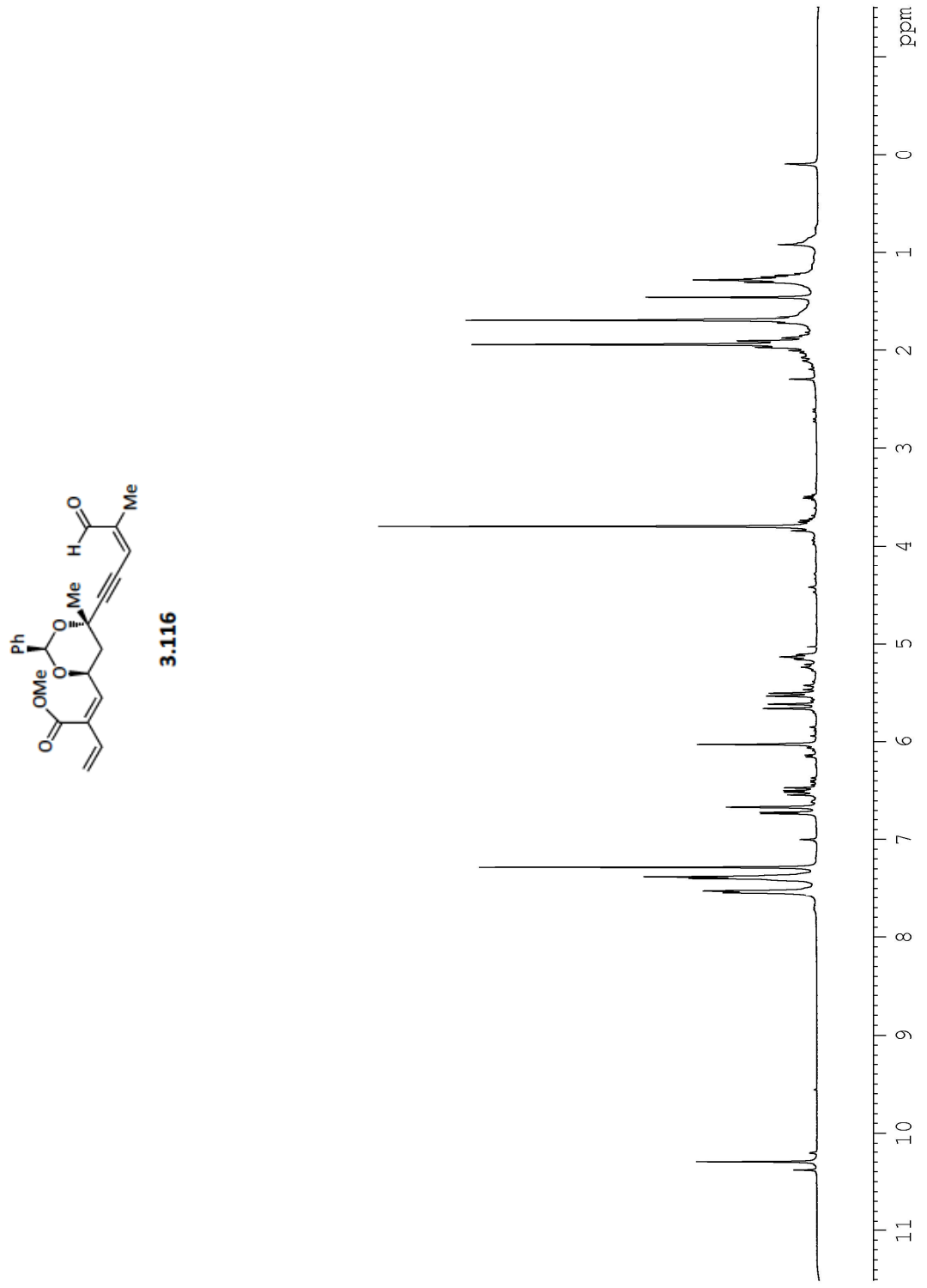


Figure A3.20. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **3.116**.

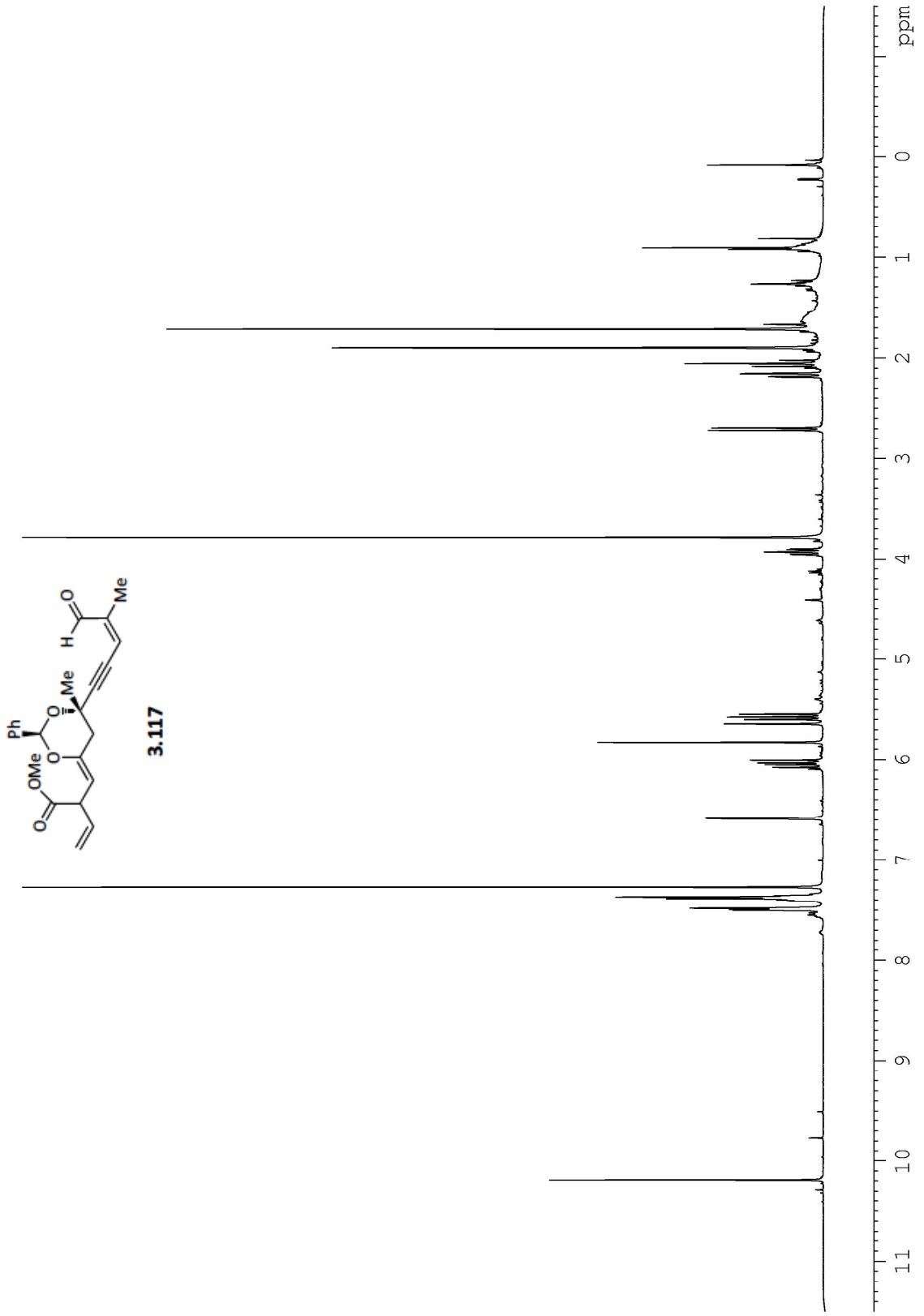


Figure A3.21. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **3.117**.

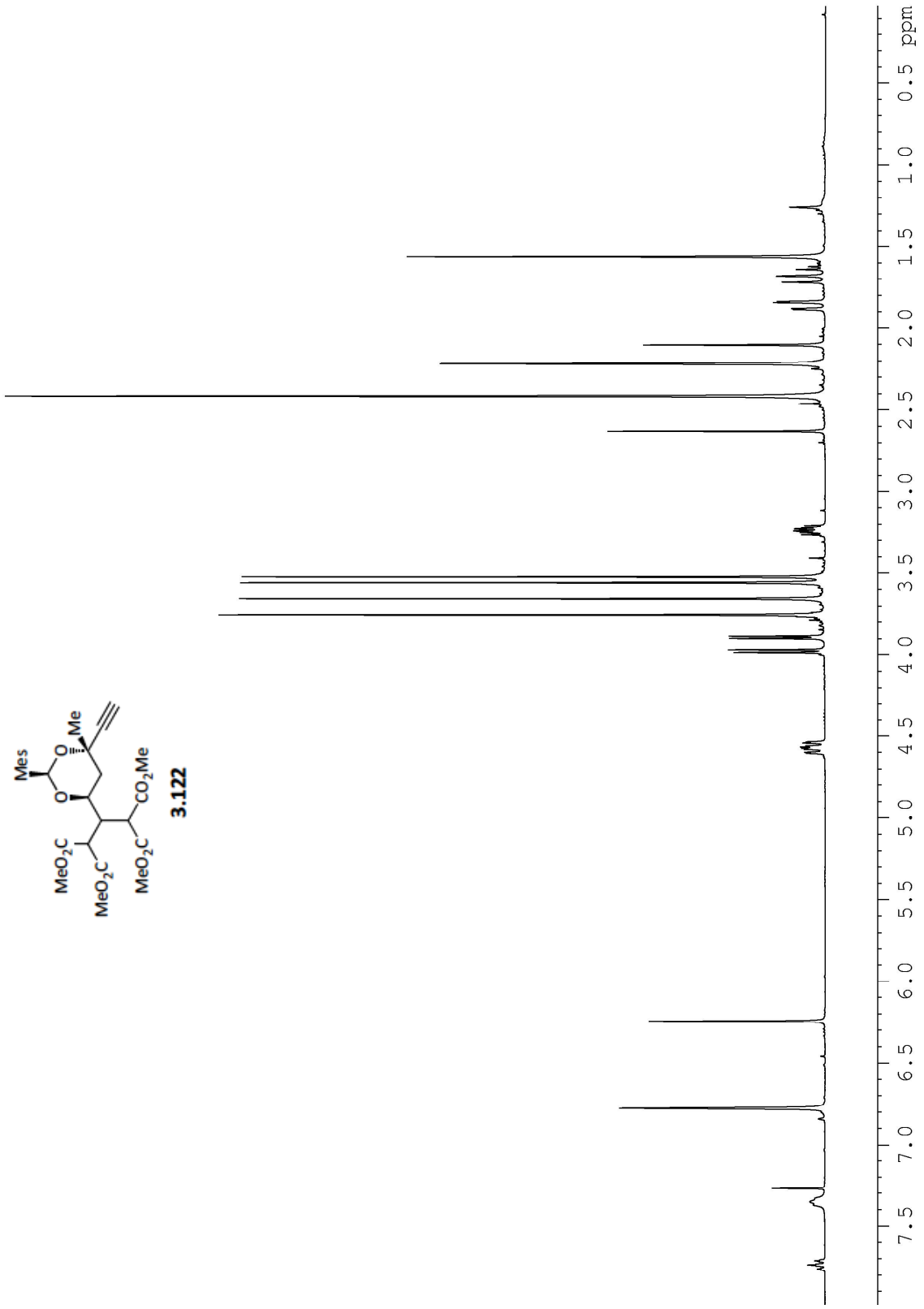


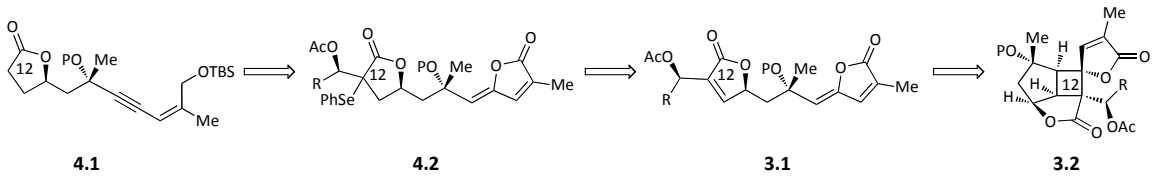
Figure A3.22. ^{1}H NMR spectra (300 MHz, $CDCl_3$) of compound **3.122**.

CHAPTER IV

A DIRECT METHOD FOR THE ASSEMBLY OF α-SUBSTITUTED BUTENOLIDES

Introduction

In our earlier approaches we encountered difficulties with synthesizing a suitable α-substituted butenolide to undergo [2+2] photocycloaddition. We thus approached our last analysis realizing the Grieco method in which α-substituted butenolides are synthesized from phenylselenolactones, was a facile method to synthesize an α-substituted butenolide.[1] In this context, we could install the desired C12 substitution and correct the oxidation state at a moment of our choosing (Scheme 4.1). Our first task, however, was to synthesize a γ-lactone.

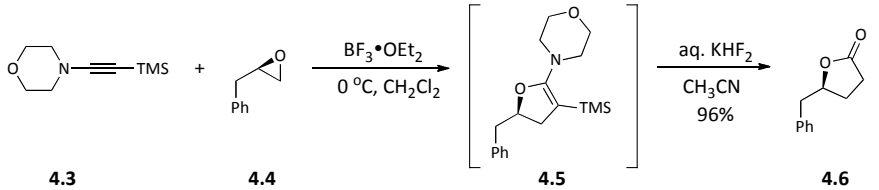


Scheme 4.1. C12 Functionalization.

Conversion of Epoxides to Lactones

Classically, synthetic chemists have been intrigued with accessing substituted lactones by ring opening epoxides with acetate enolates or their equivalent.[2] It is well established, however, that group one enolates of esters and ketones do not react directly with epoxides. The erratic nature of this type of transformation has resulted in a void of general synthetic methodology.[3-6]

One approach, reported by Jacobsen and Movassaghi, allows for the efficient conversion of terminal epoxides to lactones (Scheme 4.2).[7] For example, in this reaction the Lewis acid coordinates to phenylglycidol **4.4**, which undergoes reaction with ynamine **4.3** to provide the cyclic keteneaminal **4.5**. Monitoring the reaction by React-IR, the authors observed immediate loss of the ynamine absorption band at 2149 cm^{-1} with concomitant appearance of the keteneaminal band at 1618 cm^{-1}. This provides unmistakable evidence for the formation of intermediate **4.5**. Protodesilylation and hydrolysis affords lactone **4.6** in 96% yield. Overall, the net transformation is equivalent to an acetate enolate opening of the epoxide.



4.3 **4.4** **4.5** **4.6**

Scheme 4.2. Direct conversion of an epoxide to a lactone.

In order to familiarize the reader with the capabilities of the ynamine, a brief introduction follows. Unlike the revolutionary use of enamines to catalyze asymmetric transformations, the widespread use of the ynamine as a synthetic tool has remained limited, with the exception of work completed by Professor Richard Hsung.[8] This is due, in part, to the difficulty in their preparation, their sensitivity toward hydrolysis, and their incredible reactivity.[9, 10]

As illustrated in Figure 4.1, the ynamine holds the oxidation state of an acid and its reactivity towards electrophiles provides a particularly reactive ketene-immonium ion. As one might expect, nucleophilic attack and electrophilic addition to the triple bond occur regioselectively and is predictable based on the well-known electronic nature of ynamines.[11]

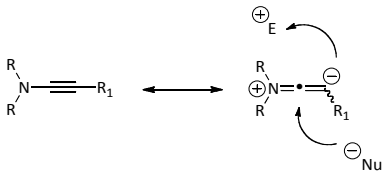


Figure 4.1. Electronics of ynamines.

The nucleophilicity of an ynamine is a function of the substitution of the nitrogen and the alkyne terminus. In both cases electron-donating groups are associated with an increase in reactivity and a decrease in stability, while electron-withdrawing groups drive the opposite effect. If the nitrogen is substituted with aryl groups, the ynamine only reacts with strong electrophiles.[12, 13] Interestingly, the use of trifluoromethyl substituents has such a profound effect that it renders the ynamine unreactive to most electrophiles.[14] To balance reactivity and stability, some advances have been made in

synthesizing so called “push-pull” ynamines that contain alkyl or aryl groups on nitrogen and sterically cumbersome groups on the alkyne terminus. A qualitative order of decreasing reactivity of a series of substituted ynamines is shown in Figure 4.2.[15-17]

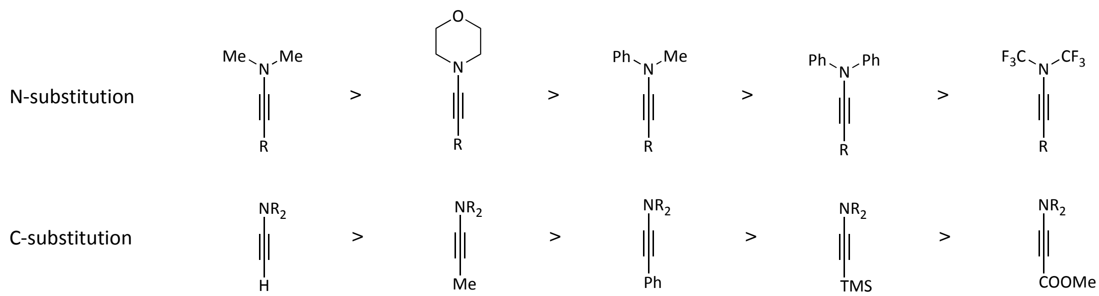
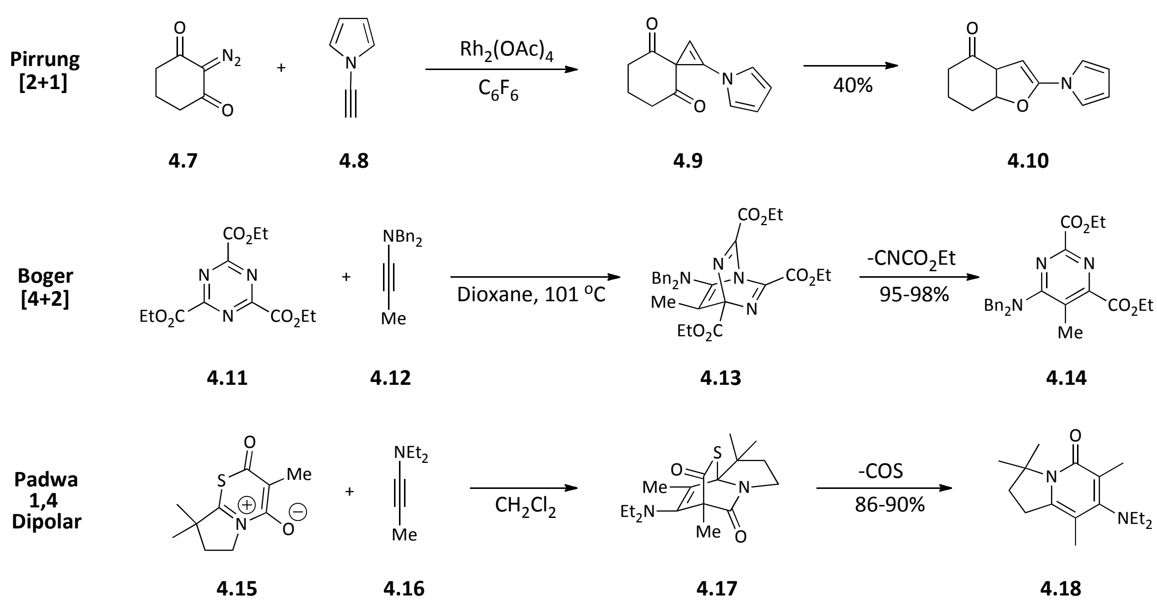


Figure 4.2. Reactivity of ynamines.

To close, a list of noteworthy reactions using ynamines to synthesize heterocycles is shown below (Scheme 4.3).[18-21]

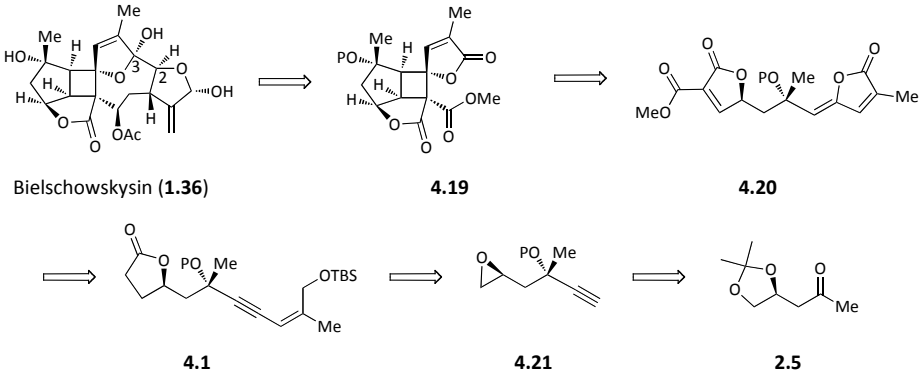


Scheme 4.3. Examples of ynamine utility.

The C12 Functionalization Solution

Scheme 4.4 illustrates the key strategic bond disconnections used to plan our synthetic strategy toward bielschowskysin (**1.36**), in which Jacobsen's ynamine is used en-route to an α-substituted butenolide.

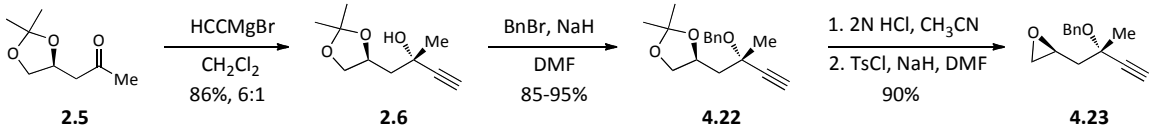
We believe bielschowskysin (**1.36**) will result from manipulation of photoadduct **4.19**. The precursor to the [2+2] photocycloaddition, **4.20**, would then arrive from functionalization of lactone **4.1** by way of epoxide **4.21**.



Scheme 4.4. Revised analysis of bielschowskysin (**1.36**).

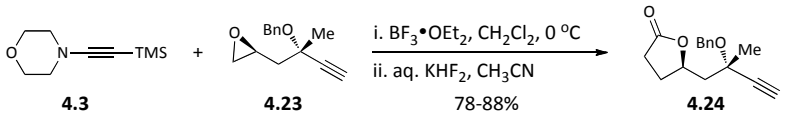
Methyl ketone **2.5** was subjected to the action of ethynyl Grignard to afford the 8,10-anti (bielschowskysin numbering) stereoisomer as the major product (ca. 6:1 anti/syn) (Scheme 4.5). Using CH_2Cl_2 as a solvent, we were able to increase the diastereoselectivity of the reaction from the previously reported 4:1 value in our original report.[22] An uneventful benzylation of the tertiary alcohol occurred to provide benzyl ether **4.22**.[23] Following hydrolysis of the acetonide, the resultant 1,2-diol was treated

with 2.5 eq of NaH and a slight molar excess of TsCl to provide epoxide **4.23** in 90% yield for the two-step sequence.[24, 25]



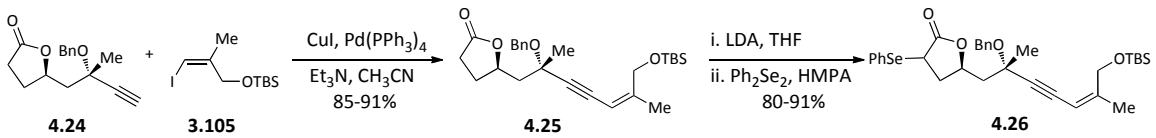
Scheme 4.5. Synthesis of epoxide **4.23**.

The much-anticipated Lewis acid promoted reaction of epoxide **4.23** with the Jacobsen-Movassaghi ynamine **4.3** afforded, after work-up, lactone **4.24** in 78-88% yield (Scheme 4.6).[7] In addition to using freshly prepared ynamine, it is important to maintain an internal temperature of 0 ^{o}C throughout the first step of the reaction. Warming of the reaction mixture was accompanied by a dramatic decrease in reaction yield.



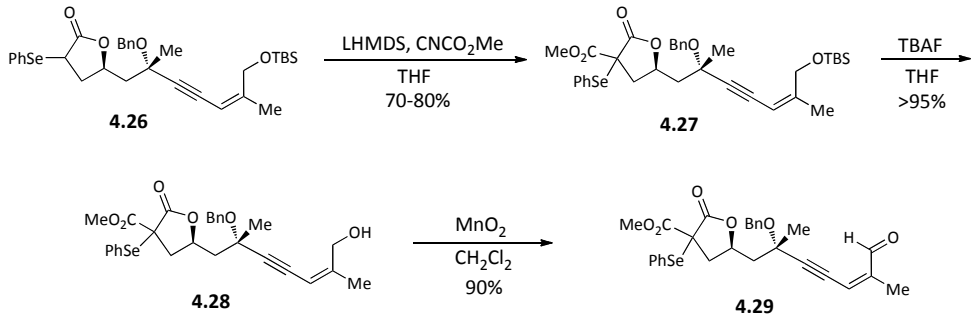
Scheme 4.6. Synthesis of lactone **4.24**.

Lactone **4.24** was advanced to **4.25** through Sonogashira coupling with iodide **3.105** (Scheme 4.7).[26, 27] Following the Grieco protocol, the lithium enolate of **4.25** was generated by the action of LDA and reacted with Ph_2Se_2 to afford phenylselenolactone **4.26** in yields ranging from 80-91%.[1]



Scheme 4.7. Synthesis of phenylselenolactone **4.26**.

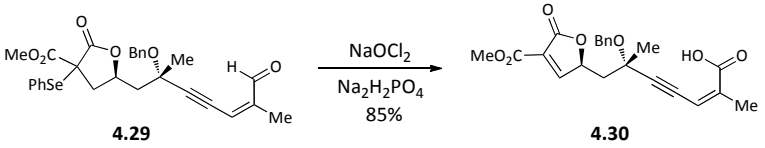
The lithium enolate of **4.26** was reacted with Mander's reagent to provide methyl ester **4.27** as an inconsequential mixture of diastereomers (Scheme 4.8).[28] Removal of the silyl ether occurred under the action of TBAF to provide allylic alcohol **4.28** in excellent yield.[29] Oxidation using MnO_2 occurred rapidly to provide the sensitive aldehyde **4.29** in 90% yield.



Scheme 4.8. Synthesis of aldehyde **4.29**.

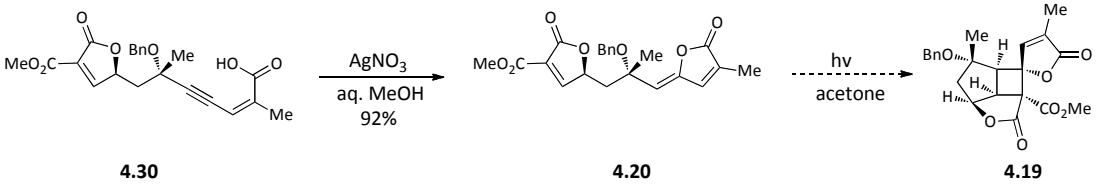
At this stage, we were concerned about the timing of the selenide oxidation and elimination sequence. Typically, this elimination occurs in the presence of H_2O_2 or $NaIO_4$.[30-33] To our delight, Pinnick oxidation of the unsaturated aldehyde **4.29** was accompanied by selenide oxidation and elimination of the selenoxide to provide butenolide **4.30** in 85% yield (Scheme 4.9). A thorough literature search has revealed no

precedence for a $NaOCl_2$ mediated oxidation of a selenide and subsequent elimination of the selenoxide, although reasonable.



Scheme 4.9. $NaOCl_2$ oxidation of **4.30**.

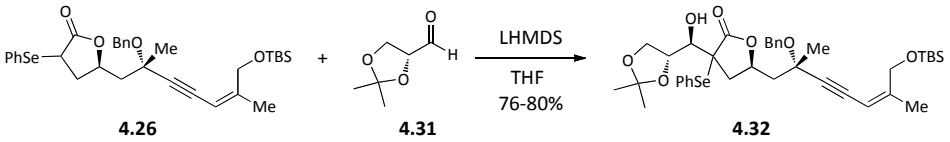
At this stage, acid **4.30** was exposed to $AgNO_3$ in aq. MeOH to arrive at bis-butenolide **4.20** in 92% yield (Scheme 4.10).[34, 35] Unfortunately, photolysis of this substrate failed to provide the desired photo-isomer **4.19**.



Scheme 4.10 Failed photolysis of **4.33**.

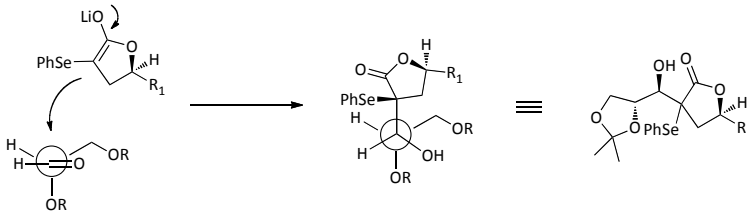
Realizing the bridgehead ester may have lowered the stability of the resultant cyclobutane; we felt it advantageous to install this side chain at a lower oxidation state. In this context, functionalization using a chiral aldehyde as the coupling partner would permit formation of the C12-C13 bond with correct configuration at C13. Glyceraldehyde acetonide was selected as the coupling partner because it is readily prepared from D-mannitol or L-gulonic acid, and after minor functional group

manipulations provides a handle to access the eastern heterocycle.[36, 37] The lithium enolate of **4.26** was generated using LHMDS and subjected to Aldol reaction with freshly distilled D-glyceraldehyde acetonide **4.31** (prepared from D-mannitol) to afford alcohol **4.32** as a single diastereomer (Scheme 4.11).



Scheme 4.11. Aldol reaction with glyceraldehyde acetonide.

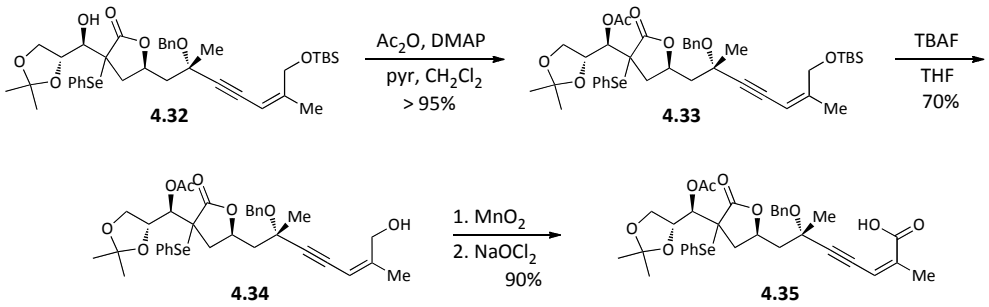
The initial configuration was assigned according to literature precedent and the mechanistic rationale depicted in Scheme 4.12.[38-42] It is known that glyceraldehyde acetonide **4.31** possesses a moderate *re* facial preference for the addition of nucleophiles affording 'anti' products. In accord, the enolate approaches the aldehyde syn to the γ hydrogen, avoiding the alkyl chain.



Scheme 4.12. Newman projection of the double diastereoselective aldol reaction.

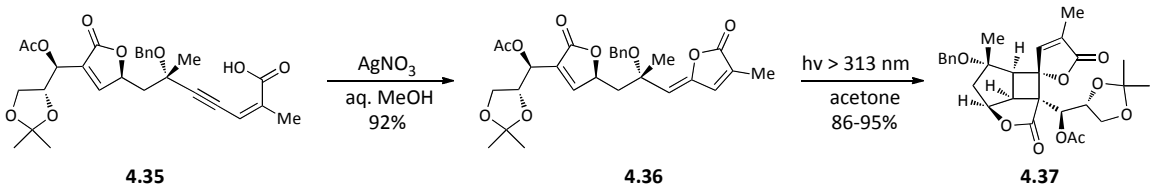
While the configuration of C12 was inconsequential, the configuration of C13 needed to unambiguously agree with the structure of bielschowskysin. Working under

the assumption that our model was correct, we decided to continue forward with the synthesis and solve the C13 stereochemistry at a later time. In the interim, alcohol **4.32** was converted to acetate **4.33** under standard conditions (Scheme 4.13).[43, 44] Following the chemistry established in Schemes 4.8 and 4.9, silyl ether **4.33** was converted to carboxylic acid **4.35**.



Scheme 4.13. Synthesis of acid **4.35**.

Acid **4.35** was exposed to $AgNO_3$ in aq. MeOH to arrive at bis-butenolide **4.36** in 92% yield (Scheme 4.14).[34, 35] In the photochemical event, irradiation of an acetone solution of **4.36** with a 450 W Hanovia mercury lamp provided photoadduct **4.37** as a single isomer in 90 min.



Scheme 4.14. [2+2] photocycloaddition.

Interestingly, irradiation of **4.36** differed significantly from the photolysis of model compound **2.2**.[22] Earlier, we rationalized the favored production of isomer **2.2** was due to the unfavorable steric interaction between the C5 vinyl proton and the methine protons at C7 and C12 (Figure 2.1). Taking these considerations into account, substitution of the hydrogen at C12 for an alkyl group provides an increase in the unfavorable steric interaction and higher selectivity for the desired isomer **4.37** (Figure 4.3). Additionally, the stereochemical assignment of **4.37** rested on an observed nOe between the C5 vinyl proton and the endo-oriented methyl group at C8.

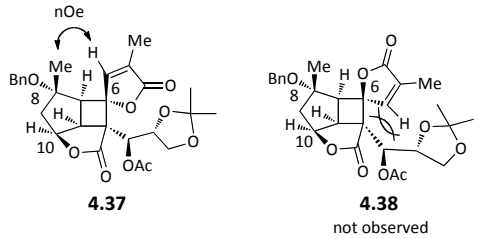
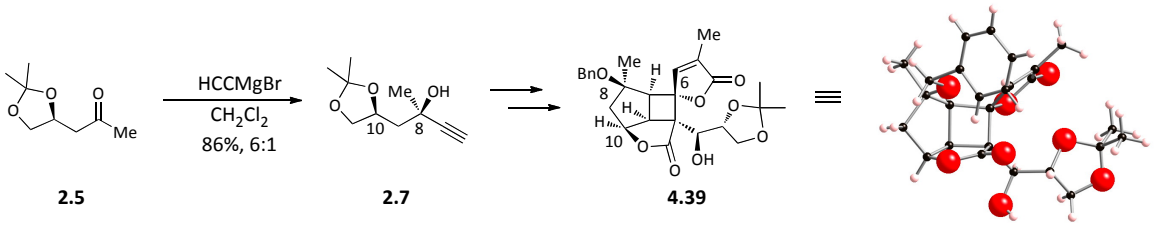


Figure 4.3. Comparison of photoadduct **4.37** and unobserved adduct **4.38**.

With this compound in hand, we turned our attention to elucidating the configuration of C13. However, we were quite discouraged by our inability to recrystallize the material to a state that was satisfactory for single-crystal x-ray analysis. Luckily, data from a related compound was obtained and correlated to our system.

Earlier, we demonstrated chelation controlled addition of ethynyl Grignard to methyl ketone **2.5** provided tertiary alcohols **2.6** and **2.7** (Scheme 4.15). In pursuit of verrillin (**1.37**), Dr. Hiroki Tanimoto advanced the minor 8,10-syn diastereomer to tetracycle **4.39** using the chemistry described in this section. Fortunately, **4.39** was

isolated as a crystalline solid. Single-crystal X-ray analysis revealed the configuration of C13 was in agreement with C13 of verrillin (**1.37**).



Scheme 4.15. Synthesis of tetracycle 4.39.

Tetracycle **4.39** is a diastereomer of tetracycle **4.37** from the bielschowskysin (**1.36**) series, as they differ in configuration only at C8. For both tetracycles, the configuration of C13 is a result of the previously described aldol reaction of which C8 likely bears no consequence. We therefore conclude the configuration of C13 for tetracycle **4.37** is identical to tetracycle **4.39**.

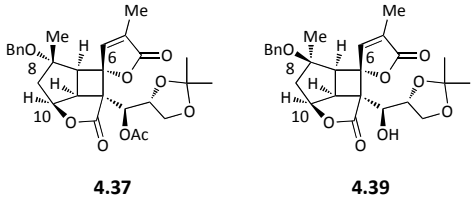
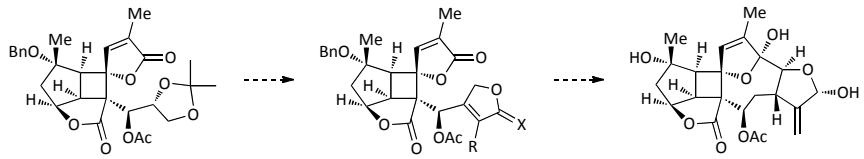


Figure 4.4. Comparison of tetracycles **4.37** and **4.39**.

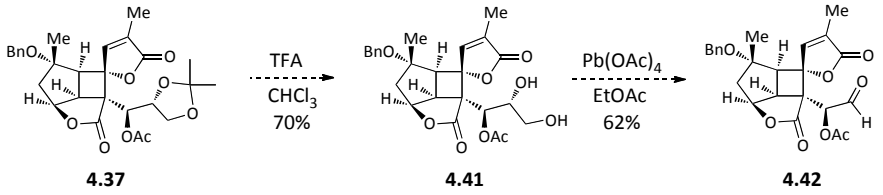
Future Directions

With the key subunit in hand, the stage is set for conversion of the material to bielschowskysin (**1.36**). This section discusses our early efforts to advance acetonide **4.37** to an oxygenated heterocycle (Scheme 4.16).



Scheme 4.16. End-game approach.

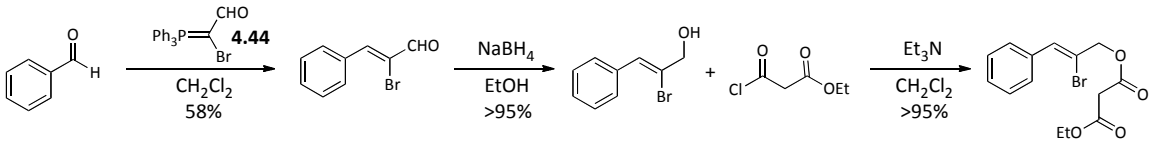
It was determined that treatment of acetonide **4.37** with TFA resulted in removal of the acetonide, providing the 1,2-diol **4.41** (Scheme 4.17). Oxidative cleavage using $Pb(OAc)_4$ gave the sensitive aldehyde **4.42** in 45% yield for the two step sequence.[45]



Scheme 4.17. Synthesis of aldehyde **4.42**.

With the ability to synthesize aldehyde **4.42**, we moved forward with designing two approaches to convert an aldehyde to an oxygenated heterocycle similar to **4.40**. Our model studies are presented below.

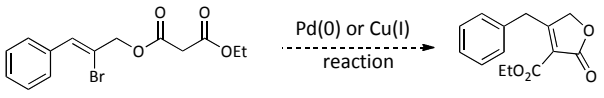
Starting with commercially available benzaldehyde **4.43**, Wittig olefination using known stabilized ylide **4.44** occurred in reasonable yield to provide α-bromocinnamaldehyde **4.45** (Scheme 4.18).[46, 47] $NaBH_4$ reduction worked in excellent yield to provide allylic alcohol **4.46**.[48] Esterification with malonyl chloride **4.47**, to provide mixed malonate ester **4.48**, occurred in greater than 95% yield.



4.43 **4.45** **4.46** **4.47** **4.48**

Scheme 4.18. Synthesis of mixed malonate ester **4.48**.

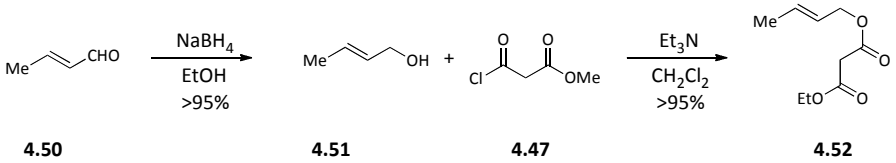
We examined Pd(0) and Cu(I) intramolecular cross coupling of **4.48**.[49, 50] To our disappointment both metals were unable to catalyze the coupling reaction to provide butenolide **4.49** (Scheme 4.19).



4.48 **4.49**

Scheme 4.19. Failed Pd(0) and Cu(I) catalyzed cyclizations.

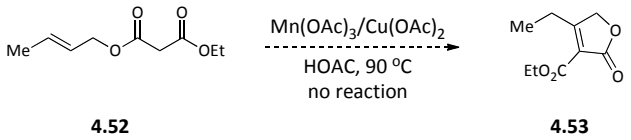
Intrigued by this cyclization, an analogous model compound was prepared (Scheme 4.20). Reduction of crotonaldehyde **4.50** with $NaBH_4$ provided crotyl alcohol **4.51**. Esterification with malonyl chloride **4.47** gave allyl malonate **4.52** in high yield.



4.50 **4.51** **4.47** **4.52**

Scheme 4.20. Synthesis of allyl malonate **4.52**.

At this point, we were hopeful that subjection to one of two sets of conditions would provide the desired heterocycle. In theory, treatment of **4.52** with $Mn(OAc)_3/Cu(OAc)_2$ would promote oxidative cyclization, followed by migration of the olefin into conjugation to provide butenolide **4.53**. Although this reaction has been demonstrated with β-keto esters as substrates, the analogous cyclization using a 1,3 diester is unprecedented.[51-53] Unfortunately, subjection to a $Mn(OAc)_3/Cu(OAc)_2$ catalyst system failed to provide (Scheme 4.21).

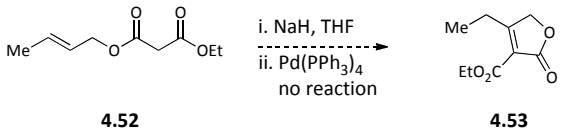


4.52 **4.53**

Scheme 4.21. Failed oxidative cyclization.

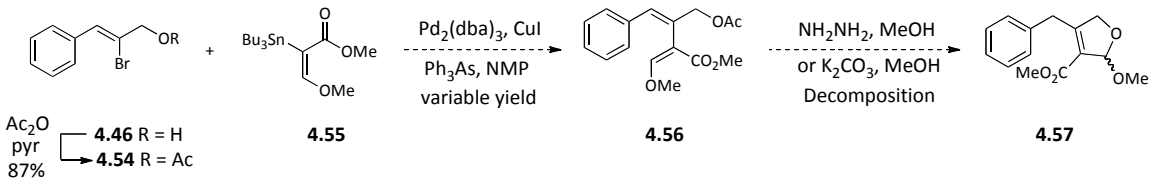
An alternative approach for this family of compounds was to examine an enolate coupling to the unactivated olefin.[54, 55] Similar to the previously discussed reactions, this

sequence too was unsuccessful, as subjection to the reaction conditions described in Scheme 4.22 failed to promote cyclization.



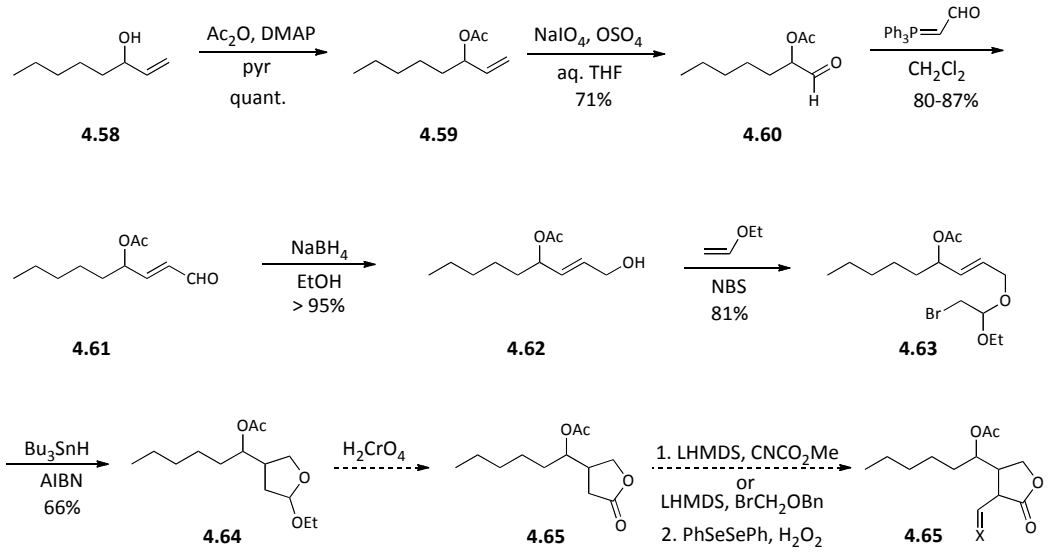
Scheme 4.22. Failed Heck cyclization.

We envisioned an alternative approach to access the eastern heterocycle. This strategy involves initial coupling to the vinyl bromide followed by formation of the ring system. To this end, alcohol **4.46** was converted to allylic acetate **4.54** under standard conditions. Stille coupling with known stannane **4.55** was unreliable and provided the unstable diene **4.56** in varying yield.[56, 57] We anticipated liberation of the alcohol would be accompanied by cyclization to provide **4.57**. Unfortunately, acetate cleavage led to rapid decomposition of starting material (Scheme 4.23).



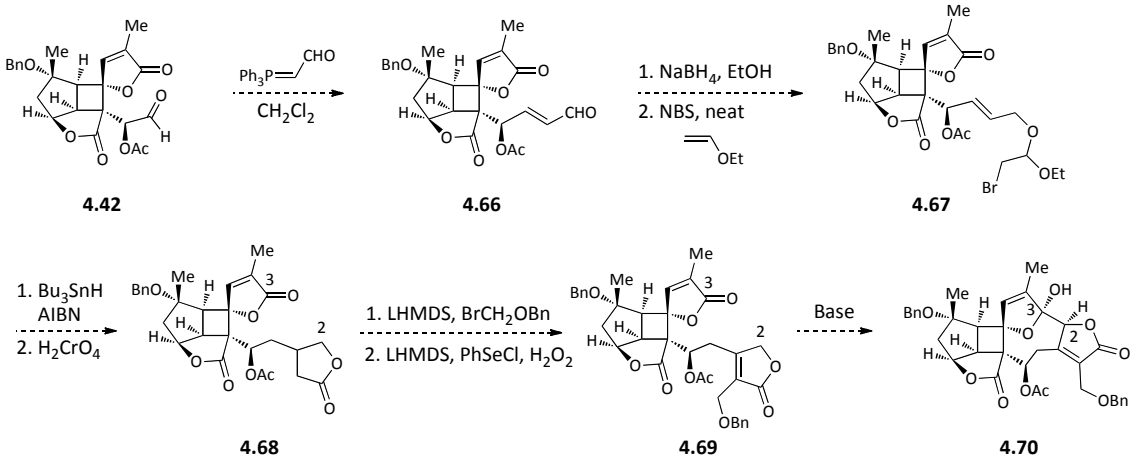
Scheme 4.23. Failed cyclization via stannane **4.57**.

The difficulties in synthesizing the eastern heterocycle of bielschowskysin (**1.36**) parallels those described in Chapter III. After realizing the synthesis of the eastern butenolide was more complex than anticipated, we designed a new sequence to achieve the desired functionality (Scheme 4.24). Starting with commercially available 3-octen-1-ol, acetylation proceeded in near quantitative yield to provide allyl acetate **4.59**. The olefin was converted to an aldehyde under Lemieux-Johnson conditions to give aceto-aldehyde **4.60** in reasonable yield.[58] Homologation of the aldehyde using the known, stabilized ylide gave unsaturated aldehyde **4.61** in 80-87% yield.[59, 60] Reduction with $NaBH_4$ was followed by transacetylation with ethyl vinyl ether in the presence of NBS to provide bromoacetal **4.63** in excellent yield.[61] Radical cyclization occurred in the presence of Bu_3SnH and AIBN to give cyclic acetal **4.64** in 66% yield.[62] From this point, we anticipate subjection of **4.64** to Jones oxidative conditions will provide lactone **4.65**. Installation of the α-substituent will provide the necessary oxygenated heterocycle.



Scheme 4.24. Synthesis of an α, β-disubstituted butenolide.

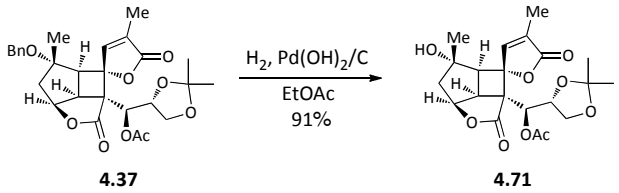
After applying this model work to our actual system, our attention will turn to formation of the C2-C3 bond and production of the hexacyclic core of bielschowskysin (**1.36**) (Scheme 4.25). Treatment of **4.69** with base under kinetic conditions (LHDMS, DMF) will lead to hexacycle **4.70** via the corresponding di-enolate. Molecular modeling indicates the ring closure should occur on the desired face of the C3 carbonyl, due to the structural constraints imposed by the western tetracycle. This topology would also lead to the correct configuration of C2.



Scheme 4.25. C2-C3 bond formation.

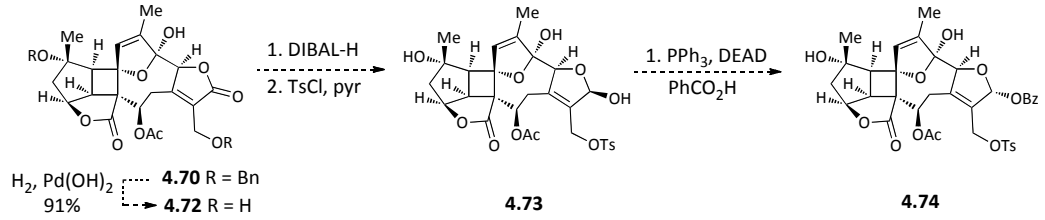
The final stages of the synthesis would involve some rather risky transformations, including diastereoselective reduction of the C16 lactone, functionalization of the heterocycle, and hydrogenolysis of the benzyl ethers. The latter of these transformations has been demonstrated in our lab. Based on the congestion of tetracycle **4.37** and the exo orientation of the benzyl ether, exposure to H_2 in the presence of Pearlman's catalyst cleanly removed the benzyl ether in five minutes

(Scheme 4.26). Interestingly, a cell viability assay with HCT 116 cells revealed only ~15% inhibition of HCT 116 cell growth at 80 μM concentration.



Scheme 4.26. Hydrogenolysis of the benzyl ether.

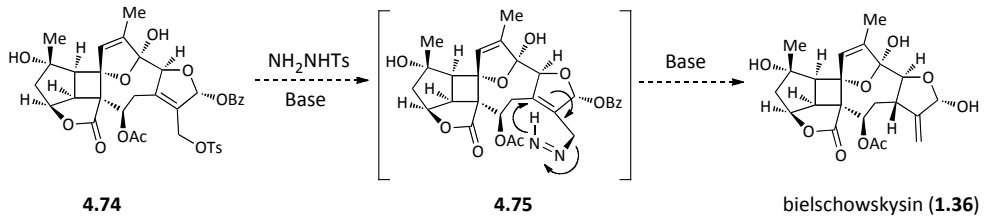
Applying this result to our future sequence, we anticipate cleaving the benzyl ether to provide alcohol **4.72** (Scheme 4.27). Exposure to TsCl should react selectively, converting the primary alcohol to a primary tosylate. Reduction of the C16 lactone should occur from the less hindered face to give the undesired epimer. While one can imagine equilibration of this center using acid and water, we envision using a Mitsunobu reaction to invert the configuration and provide benzoate **4.74**.



Scheme 4.27. Functionalization of the hexacyclic core.

After direct displacement of the tosylate with tosylhydrazide, the stage would be set to employ a very attractive sigmatrophic rearrangement of the allylic diazene (Scheme 4.28).[63] While it is expected hydride delivery will occur opposite the benzoate,

we are aware that this transformation would need to occur on the *endo* face of the caged structure. Therefore, the selectivity in the reaction may be poor.

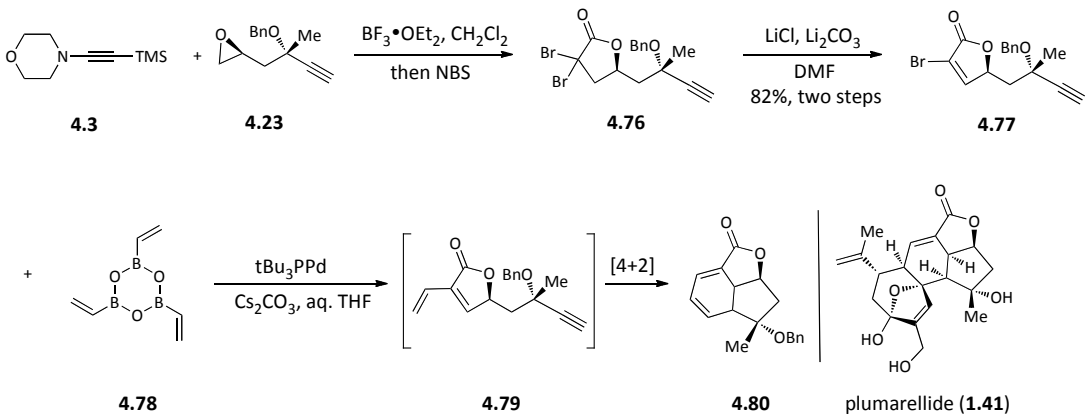


4.74 **4.75**

Scheme 4.28. Diazene rearrangement en route to bielschowskysin (**1.36**).

The Vinyl Butenolide

While working toward the synthesis of an α-substituted butenolide, we initially examined a rather interesting reaction using ynamine **4.3**. Reaction with epoxide **4.23** under the established conditions provides a keteneaminal. This intermediate can be intercepted by electrophiles to generate functionalized lactones.[7] With this reaction available to us, the keteneaminal was intercepted with excess NBS to provide dibromo lactone **4.76**. The crude dibromide was subjected to dehydrohalogenation using LiCl and Li_2CO_3 in DMF to provide vinyl bromide **4.77** in 82% yield (Scheme 4.29). Suzuki cross-coupling between **4.77** and vinylboronic acid trimer **4.78** led to isolation of tricycle **4.80** in yields varying from 61%-76%.[64]



Scheme 4.29. The vinyl butenolide.

Mechanistically, this reaction features an initial Suzuki coupling to provide vinyl butenolide **4.77**. As demonstrated by the Hoye lab, this functionality is unstable and in our hands undergoes [4+2] cycloaddition followed by double bond isomerization to give tetracycle **4.80**. Coincidentally, this corresponds to the eastern tricycle of plumarellide (**1.41**) and has triggered our interest in developing a program geared toward the synthesis of this compound.

Conclusion

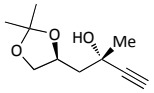
Whereas Chapter I serves as an introduction to the furanocembrane and pseudopterane family of natural products, Chapters II-IV are meant to disclose the progress our lab has made toward the synthesis of bielschowskysin (**1.36**). Additionally, it is our aim to impress upon the reader a few key points. The first is that recent advances in synthetic methodology have made the synthesis of complex molecules attainable if one makes the correct bond disconnections and modifies the target to an exploitable motif. While we eventually recognized the necessary pattern to access our desired functionality, the progression of our synthesis suffered in its infancy due to the initial success in synthesizing the model system. Though this is counterintuitive, it draws upon our second point. Early in my graduate career, Prof. Sulikowski taught me that the method in which a synthetic chemist draws a molecule influences their holistic approach to its synthesis. In this context, it is easy to see that rather than viewing bielschowskysin (**1.36**) in its totality, we attempted to engineer every pathway in a manner that intercepted our previously established chemistry. The value of maintaining a holistic viewpoint during a total synthesis program cannot be understated.

Lastly, working toward bielschowskysin (**1.36**) provided the opportunity to work on a metabolite with previously unknown molecular architecture. Obviously, congested and complex structures are fascinating because they provide an opportunity to uncover new chemistry and reactivity, even when the target isn't reached. With a clear end-game strategy, we hope to report the synthesis of bielschowskysin (**1.36**) in due time.

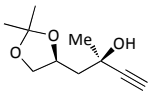
Experimental Methods

General. All non-aqueous reactions were performed under an argon atmosphere in oven-dried glassware. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Diethyl ether (Et_2O), acetonitrile (CH_3CN), dichloromethane (CH_2Cl_2), and dimethylformamide (DMF) were obtained by passing commercially available formulations through activated alumina columns (MBraun MB-SPS solvent system). Tetrahydrofuran (THF) was obtained by distillation from benzophenone-sodium. Triethylamine (Et_3N) and diisopropylamine were distilled from calcium hydride and stored over sodium hydroxide. Reactions were monitored by thin-layer chromatography (TLC) using E. Merck precoated silica gel 60 F254 plates. Visualization was accomplished with UV light and aqueous stain followed by charring on a hot plate. Flash chromatography was conducted using the indicated solvents and silica gel (230-400 mesh). Yields refer to chromatographically and spectroscopically homogeneous materials. Infrared spectra were obtained as thin films on NaCl plates using a Thermo Electron IR100 series instrument and are reported in terms of frequency of absorption (cm-1). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 300, 400, 500, or 600 MHz spectrometers and are reported relative to deuterated solvent signals (7.27 and 77.2). High-resolution mass spectra (ESI) were obtained at the Department of Chemistry and Biochemistry, University of Notre Dame. Dr. Joseph Reibenspies solved x-crystal structures at the X-ray diffraction facility of Department of Chemistry, Texas A&M University.

Preparative Procedures

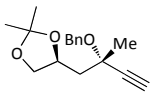


2.6



2.7

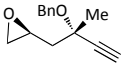
To a solution of ketone **2.5** (1.0 eq, 7.9 g, 50 mmol) in CH_2Cl_2 (500 mL) at 0 ^oC was added ethynylmagnesium bromide (0.5 M in THF, 2.0 eq, 100 mmol, 200 mL) and the reaction was stirred 3 h. Saturated aqueous ammonium chloride (100 mL) was added and the layers separated. The organics were washed with water (3 x 100 mL), brine (3 x 100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (4:1, Hexanes/EtOAc) to provide tertiary alcohols **2.6** (6.8 g, 37 mmol, 74%) and **2.7** (1.1 g, 6 mmol, 12%) as pale yellow oils: Spectral data was consistent with values reported in chapter II.



4.22

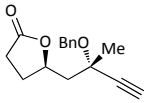
To a slurry of NaH (1.5 eq, 360 mg, 15 mmol) in DMF (150 mL) at ambient temperature was added BnBr (1.5 eq, 1.8 mL, 15 mmol) and the slurry was stirred. Tertiary alcohol **2.7** (1.0 eq, 1.8 g, 10 mmol) was added dropwise and the reaction stirred 18 h. The reaction was diluted with EtOAc (100 mL), washed with water (3 x 100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (4:1 hexanes/EtOAc) to provide benzyl ether **4.22** (2.0 g, 8.6 mmol, 86%) as a colorless oil: $[\alpha]_D^{23}$ +11.2^o (*c* 0.5, $CHCl_3$); R_f 0.8 (4:1 hexanes/EtOAc); IR (thin film, cm^{-1}): 3200, 3030, 2985, 2934, 2869, 1496, 1454, 1378; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38-7.34 (m, 5H), 4.69 (d, *J* = 11.2 Hz, 1H), 4.60 (d, *J* = 11.2 Hz, 1H), 4.40 (d, *J* = 8.0, 7.6, 5.6, 4.8 Hz, 1H), 4.15 (dd, *J* = 8.0, 5.6 Hz, 1H), 3.64 (dd, *J* = 8.0, 8.0 Hz, 1H), 2.54 (s, 1H), 2.27 (dd, *J* = 14.4, 4.8 Hz, 1H), 2.08 (dd, *J* = 14.0, 7.2 Hz, 1H),

1.58 (s, 3H), 1.41 (s, 3H), 1.37 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 138.7, 128.2, 127.4, 127.3, 108.0, 84.9, 73.9, 72.3, 71.5, 70.2, 66.2, 45.6, 26.9, 26.4, 25.9; HRMS calcd for $C_{17}H_{23}O_3$ $[M+H]^+$ 275.1647 found 275.1642; HRMS calcd for $C_{17}H_{22}NaO_3$ $[M+Na]^+$ 297.1467 found 297.1469.



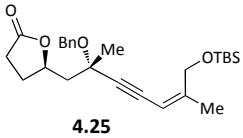
4.23

To a solution of benzyl ether **4.22** (1.0 eq, 2.7 g, 10 mmol) in CH_3CN (100 mL) at ambient temperature was added 2N HCl (50 mL). After stirring 1 h the reaction was diluted with EtOAc (100 mL), washed with saturated sodium bicarbonate (1 x 50 mL), water (1 x 50 mL), brine (1 x 50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude diol (1.0 eq, 2.0 g, 8.6 mmol) was added to a slurry of NaH (2.5 eq, 520 mg, 22 mmol) and TsCl (1.1 eq, 1.8 g, 10 mmol) in DMF (200 mL) at ambient temperature. The reaction was stirred 1 h, diluted with EtOAc (100 mL), and washed with water (3 x 50 mL) and brine (3 x 50 mL). The organics were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (4:1 Hexanes/EtOAc) to provide epoxide **4.23** (1.7 g, 7.7 mmol, 90%) as a colorless oil: $[\alpha]_D^{23}$ +3.8° (*c* 0.9, $CHCl_3$); R_f 0.5 (4:1 hexanes/EtOAc); IR (thin film, cm^{-1}): 3285, 3033, 2990, 2925, 2868, 1454, 1372, 1263; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.28 (m, 5H), 4.75 (d, *J* = 10.8 Hz, 1H), 4.67 (d, *J* = 10.8 Hz, 1H), 3.27 (dddd, *J* = 6.0, 5.6, 4.4, 2.8 Hz), 2.84 (dd, *J* = 4.8, 4.4 Hz, 1H), 2.63 (m, 2H), 2.10 (dd, *J* = 14.0, 6.0 Hz, 1H), 2.00 (dd, *J* = 14.4, 5.6 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 138.6, 128.2, 127.4, 127.3, 84.5, 74.0, 72.1, 66.2, 48.5, 46.5, 44.6, 26.4; HRMS calcd for $C_{14}H_{17}O_2$ $[M+H]^+$ 217.1229 found 217.1223; HRMS calcd for $C_{14}H_{16}NaO_2$ $[M+Na]^+$ 239.1048 found 239.1043.



4.24

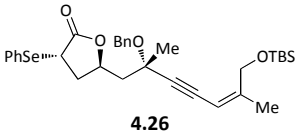
To a solution of ynamine **4.3** (3.0 eq, 5.5 g, 30 mmol) in CH_2Cl_2 (100 mL) at 0 ^oC was added $BF_3 \bullet OEt_2$ (3.0 eq, 3.7 mL, 30 mmol). Epoxide **4.23** (1.0 eq, 2.2 g, 10 mmol) is added to the yellow solution and the reaction is stirred 30 min. The red reaction mixture was diluted with CH_3CN (25 mL) and KHF_2 (5.0 eq, 3.9 g, 50 mmol) was added as an aqueous solution (10 mL). After stirring 30 min, 2N HCl (50 mL) was added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic extracts washed with water (1 x 50 mL) and brine (1 x 50 mL). The organics were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (4:1 Hexanes/EtOAc) to provide lactone **4.24** (2.3 g, 8.8 mmol, 88%) as a red oil: $[\alpha]_D^{23}$ +16.4^o (*c* 0.9, $CHCl_3$); R_f 0.3 (4:1 hexanes/EtOAc); IR (thin film, cm^{-1}): 3280, 3032, 2963, 2859, 1788, 1454, 1380, 1260; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36-7.28 (m, 5H), 4.84 (dddd, *J* = 12.0, 8.8, 6.0, 5.6 Hz, 1H), 4.71 (d, *J* =11.2 Hz, 1H), 4.68 (d, *J* = 11.2 Hz, 1H), 2.58 (s, 1H), 2.50 (dd, *J* = 9.6, 6.0 Hz, 2H), 2.41 (dd, *J* = 12.4, 6.0 Hz, 1H), 2.30 (dd, *J* = 14.4, 6.4 Hz, 1H), 2.16 (dd, *J* = 14.8, 5.2 Hz, 1H), 2.00 (td, *J* = 12.4, 3.2, 9.2 Hz, 1H), 1.61 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 176.9, 138.5, 128.2, 127.7, 127.4, 84.6, 74.2, 71.3, 70.5, 66.3, 47.1, 29.6, 28.8, 26.5; HRMS calcd for $C_{16}H_{19}O_3$ $[M+H]^+$ 259.1334 found 259.1329; HRMS calcd for $C_{16}H_{18}NaO_3$ $[M+Na]^+$ 281.1154 found 281.1148.



4.25

To a degassed solution of lactone **4.24** (1.0 eq, 880 mg, 3.4 mmol) and iodide **3.105** (1.2 eq, 1.3 g, 4.1 mmol) in CH_3CN (35 mL) at ambient temperature was added $Pd(PPh_3)_4$ (0.1 eq, 390 mg, 0.34 mmol), CuI (0.1 eq, 65

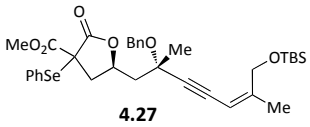
mg, 0.34 mmol), and Et_3N (2.5 eq, 1.2 mL, 8.5 mmol). The reaction was stirred 16 h, treated with celite (5 g) and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (4:1 hexanes/EtOAc) to provide lactone **4.25** (1.2 g, 2.7 mmol, 80%) as a colorless oil: $[\alpha]_D^{23}$ +10.3° (*c* 0.5, $CHCl_3$); R_f 0.6 (4:1 hexanes/EtOAc); IR (thin film, cm^{-1}): 2929, 2856, 1775, 1461, 1380, 1252, 1175; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.28 (m, 5H), 5.38 (s, 1H), 4.85 (dddd, *J* = 9.2, 6.4, 5.6, 5.2 Hz, 1H), 4.71 (d, *J* =11.2 Hz, 1H), 4.68 (d, *J* = 11.2 Hz, 1H), 4.39 (s, 2H), 2.51 (dd, *J* = 9.6, 6.4 Hz, 2H), 2.40 (dd, *J* = 12.4, 6.4 Hz, 1H), 2.32 (d, *J* = 14.4, 5.2 Hz, 1H), 2.16 (dd, *J* = 14.8, 5.2 Hz, 1H), 2.01-1.96 (m, 1H), 1.87 (s, 3H), 1.62 (s, 3H), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 177.0 151.7, 138.7, 128.3, 127.5, 127.4, 104.3, 93.4, 82.8, 74.5, 72.0, 66.2, 63.9, 47.4, 29.4, 28.9, 26.7, 25.8, 19.8, 18.3, -5.3; HRMS calcd for $C_{26}H_{39}O_4Si$ $[M+H]^+$ 443.2618 found 443.2612; HRMS calcd for $C_{26}H_{38}NaO_4Si$ $[M+Na]^+$ 465.2437 found 465.2432.



4.26

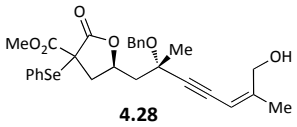
To a freshly prepared solution of LDA (1.1 eq, 3.3 mmol) in THF (50 mL) at -78 °C was added lactone **4.25** (1.0 eq, 1.3 g, 3.0 mmol) as a THF solution (10 mL). The reaction was stirred 1 h at -78 °C and Ph_2Se_2 (1.5 eq, 1.4 g, 4.5 mmol) was added as a solution in HMPA (10 mL). After stirring 2 h at -78 °C, saturated aqueous ammonium chloride (10 mL) was added and the reaction allowed to warm to ambient temperature. The reaction mixture was diluted with EtOAc (50 mL) and the layers separated. The organics were washed with water (3 x 10 mL), brine (3 x 10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (10:1 Hexanes/EtOAc) to provide selenide

4.26 (1.5 g, 2.6 mmol, 85%) as an orange oil: $[\alpha]_D^{23}$ +2.8^o (*c* 0.1, $CHCl_3$); R_f 0.8 (4:1 hexanes/EtOAc); IR (thin film, cm^{-1}): 2929, 2856, 1773, 1439, 1253, 1177, 1090; ^1H NMR (400 MHz, $CDCl_3$): δ 7.67-7.65 (m, 2H), 7.37-7.28 (m, 8H), 5.39 (s, 1H), 4.70 (dddd, *J* = 7.2 ,7.2, 6.8, 5.2 Hz, 1H), 4.66 (d, *J* = 10.8 Hz, 1H), 4.52 (d, *J* = 10.8 Hz, 1H), 4.41 (s, 2H), 3.90 (dd, *J* = 6.4, 4.0 Hz, 1H), 2.45-2.41 (m, 2H), 2.25 (dd, *J* = 14.0, 5.2 Hz, 1H), 2.04 (dd, *J* = 14.0, 6.8 Hz, 1H), 1.91 (s, 3H), 1.56 (s, 3H), 0.92 (s, 9H), 0.09 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 175.5, 152.0, 138.5, 135.8 129.3, 104.2, 92.1, 83.6, 77.3, 72.8, 66.3, 63.9, 47.4, 38.3, 37.0, 27.1, 25.8, 19.8, 18.3, -5.3; HRMS calcd for $C_{32}H_{43}O_4SeSi$ $[M+H]^+$ 599.2096 found 599.2092; HRMS calcd for $C_{32}H_{42}NaO_4SeSi$ $[M+Na]^+$ 621.1915 found 621.1912.



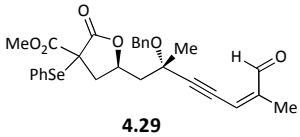
4.27

To a solution of selenide **4.26** (1.0 eq, 600 g, 1mmol) in THF (10 mL) at -78 ^{o}C was added KHMDS (1.25 eq, 230 mg, 1.25 mmol) and the reaction was stirred 1 h. Methylcyanoformate (1.25eq, 180 μL, 2.5 mmol) was added and the reaction stirred 1 h at -78 ^{o}C. Saturated aqueous ammonium chloride (1 mL) was added and the reaction warmed to ambient temperature. The reaction mixture was diluted with EtOAc (25 mL) and washed with water (3 x 10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2:1 Hexanes/EtOAc) to provide methylester **4.27** (490mg, 0.75 mmol, 75%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 6.8 Hz, 2H), 7.45-7.28 (m, 8H), 5.37 (s, 1H), 4.78-4.59 (m, 3H), 4.38 (s, 2H), 3.87 (s, 3H), 2.71 (dd, *J* = 9.2, 4.8 Hz, 1H), 2.52 (dd, *J* = 10.4, 8.8 Hz, 1H), 2.28 (dd, *J* = 14.8, 6.4 Hz, 1H), 2.11 (dd, *J* = 14.4, 5.6 Hz, 1H), 1.88 (s, 3H), 1.56 (s, 3H), 0.92 (s, 9H), 0.10 (s, 6H).



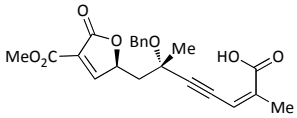
4.28

To a solution of silyl ether **4.27** (1.0 eq, 40 mg, 0.62 mmol) in THF (1 mL) at 0 ^{o}C was added TBAF (1.0 M in THF, 2.0 eq, 250 μL 1.2 mmol). After stirring 6 h, the reaction mixture was diluted with EtOAc (5mL) and saturated aqueous ammonium chloride (5 mL) was added. The layers were separated and the organics were washed with water (1x 10 mL), brine (1 x 10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2:1 Hexanes/EtOAc) to provide allylic alcohol **4.28** (34 mg, 0.0.61 mmol, 96%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 6.8 Hz, 2H), 7.45-7.28 (m, 8H), 5.37 (s, 1H), 4.78-4.59 (m, 3H), 4.38 (s, 2H), 3.87 (s, 3H), 2.71 (dd, *J* = 9.2, 4.8 Hz, 1H), 2.52 (dd, *J* = 10.4, 8.8 Hz, 1H), 2.28 (dd, *J* = 14.8, 6.4 Hz, 1H), 2.11 (dd, *J* = 14.4, 5.6 Hz, 1H), 1.88 (s, 3H), 1.56 (s, 3H).



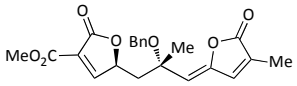
4.29

To a slurry of MnO_2 (10 eq, 320 mg, 3.8 mmol) in CH_2Cl_2 (1 mL) at ambient temperature was added allylic alcohol **4.28** (1.0 eq, 20mg, 0.38 mmol). After 12 h, $MgSO_4$ (100 mg) was added and the reaction mixture was filtered through a plug of celite. The organics were concentrated *in vacuo* to provide aldehyde **4.29** (19 mg, 0.36 mmol, 95%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.2 (s, 1H), 7.65 (d, *J* = 7.2 Hz, 2H), 7.46-7.29 (m, 8H), 6.56 (s, 1H), 4.67-4.52 (m, 3H), 3.82 (s, 3H), 2.71 (dd, *J* = 9.2, 4.8 Hz, 1H), 2.52 (dd, *J* = 10.4, 8.8 Hz, 1H), 2.28 (dd, *J* = 14.8, 6.4 Hz, 1H), 2.11 (dd, *J* = 14.4, 5.6 Hz, 1H), 1.88 (s, 3H), 1.56 (s, 3H).



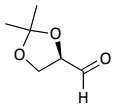
4.30

To a solution of aldehyde **4.29** (1.0 eq, 0.37 mmol, 200 mg) in t-BuOH (10 mL) was added 2-methyl-2-butene (10 eq, 400 μL, 3.7 mmol). $NaOCl_2$ (7.5 eq, 260 mg, 2.8 mmol) and $Na_2H_2PO_4$ (7.6 eq, 390 mg, 2.8 mmol) were dissolved in water (5 ml) and added to the reaction mixture dropwise. After stirring 1 h, the green reaction mixture was diluted with EtOAc (10 mL) and washed with 1N HCl (1 x 10 mL) and water (1 x 10 mL). The organics were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:1 Hexanes/EtOAc) to provide acid **4.30** (180 mg, 3.2 mmol, 90%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.28 (s, 5H), 6.10 (s, 1H), 4.92-4.80 (m, 1H), 4.72 (s, 1H) 4.74 (d, *J* = 11.2 Hz, 1H), 4.62 (d, *J* = 11.2 Hz, 1H), 3.78 (s, 3H), 2.30 (d, *J* = 5.6 Hz, 1H), 2.05 (s, 3H), 1.64 (s, 3H).



4.20

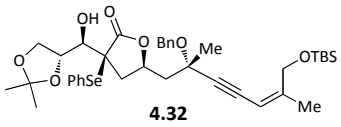
To a solution of acid **4.30** (1.0 eq, 90 mg, 0.2 mmol) in MeOH (10 mL) at 0 ^{o}C was added $AgNO_3$ (0.1 eq, 2 mg, 0.02 mmol) as a solution in water (100 μL). The reaction was stirred 1 h and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2:1 Hexanes/EtOAc) to provide alkylidene butenolide **4.20** (80 mg, 0.18 mmol, 92%) as a colorless gel: ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38-7.29 (m, 5H), 7.02 (s, 1H), 5.28 (s, 1H), 5.21 (t, *J* = 5.6, 5.2 Hz, 1H), 4.56-4.40 (m, 3H), 3.79 (s, 3H), 2.38 (dd, *J* = 14.8, 4.8 Hz, 1H), 2.18 (dd, *J* = 14.8, 7.6 Hz, 1H), 2.04 (s, 3H), 1.77 (s, 3H).



4.31

A 1-L, three-necked flask equipped with overhead stirrer, heating mantle, and condenser with drying tube was charged with D-mannitol (1.0 eq, 100 g, 0.55 mol), 2,2-dimethoxypropane (2.4 eq, 160 mL, 1.3 mol) and 1,2-dimethoxyethane (240 mL). Stirring was begun and $SnCl_2$ (100 mg) was added. The remaining neck was capped with a septum and the stirred slurry heated to reflux until the mixture reached clarity (30–50 min). After 30 min, the heating mantle was removed and the solution cooled to ambient temperature. Pyr (200 µL) was added through the septum via syringe and the contents transferred to a tared, 1-L, one-necked flask. The contents were concentrated *in vacuo* to give the crude diacetonide (80 g, 0.3 mol, 56% yield). A large, magnetic stir bar was added to the flask and the solid dissolved in CH_2Cl_2 (800 mL). The flask was equipped with a condenser and the slurry stirred vigorously at reflux until the solids were digested to an even consistency. The slurry was cooled to ambient temperature treated with celite (10 g). The contents were vacuum-filtered through a pad of celite on a glass frit filter into a three-necked, 2-L vessel. The flask was rinsed with CH_2Cl_2 (50 mL) and the rinse filtered through the funnel. The 2-L vessel as equipped with an overhead stirrer, thermometer, and water bath, and stirring begun at 300–350 rpm. A solution of saturated aqueous sodium bicarbonate (45 mL) was added with stirring and $NaIO_4$ (2.0 eq, 140 g, 0.6 mol) was added over 2–3 min. After stirring 2 hr, $MgSO_4$ (50 g) was added and stirring is continued for 20 min. The slurry was vacuum-filtered through a glass frit filter into a 2-L flask and concentrated *in vacuo*. The crude oil was purified by distillation (30 mm Hg, 65 °C) to provide D-glyceraldehyde

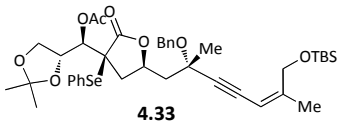
acetonide **4.31** (68 g, 0.26 mol, 85%) as a colorless oil: Spectral data consistent with reported values.[23]



4.32

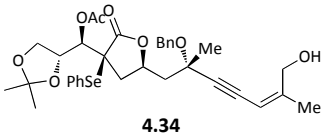
To a solution of selenide **4.26** (1.0 eq, 1.1 g, 1.8 mmol) in THF (25 mL) at -78 ^{o}C was added LHMDS (1.0 M in $PhCh_3$, 1.1 eq, 2 mL, 2 mmol) and the reaction was stirred 1 h. Freshly distilled glyceraldehyde acetonide **4.31** (1.1 eq, 260 mg, 2.0 mmol) was added as a solution in THF (1 mL) and the reaction stirred 1 h at -78 ^{o}C. Saturated aqueous ammonium chloride (1 mL) was added and the reaction warmed to ambient temperature. The reaction mixture was diluted with EtOAc (25 mL) and the layers separated. The organics were washed with water (3 x 10 mL), brine (1 x 10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2:1 Hexanes/EtOAc) to provide alcohol **4.32** (940 mg, 1.3 mmol, 70%) as a colorless oil: $[\alpha]_D^{23}$ +22.5^{o} (*c* 0.1, $CHCl_3$); R_f 0.3 (4:1 hexanes/EtOAc); IR (thin film, cm^{-1}): 3246, 2930, 2857, 1760, 1455, 1380, 1254, 1185, 1071; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68-7.66 (d, *J* = 6.8 Hz, 2H), 7.41-7.29 (m, 8H), 5.35 (s, 1H), 4.91 (dddd, *J* = 8.0, 6.4, 6.0, 5.2 Hz, 1H), 4.65 (d, *J* = 11.2 Hz, 1H), 4.53 (d, *J* = 11.2 Hz, 1H), 4.40-4.35 (m, 3H), 4.19 (dd, *J* = 8.8, 6.4 Hz, 1H), 3.98 (dd, *J* = 14.0, 5.6 Hz, 1H), 3.74 (d, *J* = 7.2 Hz, 1H), 2.91 (dd, *J* = 15.2, 8.8 Hz, 1H), 2.19 (td, *J* = 7.6, 5.6 Hz, 2H), 2.05 (dd, *J* = 14.0, 6.8 Hz, 1H), 1.86 (s, 3H), 1.54 (s, 3H), 1.41-1.38 (m, 1H), 1.32 (d, *J* = 4.4 Hz, 6H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 176.7, 151.9, 138.7, 137.9, 129.8, 129.2, 128.3, 127.5, 127.4, 126.4, 109.8, 104.3, 92.4, 83.4, 76.2, 75.9, 75.2, 73.1, 67.6, 66.2, 63.9, 54.1, 47.7, 37.3, 27.2, 26.1, 25.8, 25.1, 19.8, 18.3, -5.3;

HRMS calcd for $C_{38}H_{53}O_7SeSi$ $[M+H]^+$ 729.2726 found 729.2723; HRMS calcd for $C_{38}H_{52}NaO_7SeSi$ $[M+Na]^+$ 751.2545 found 751.2543.



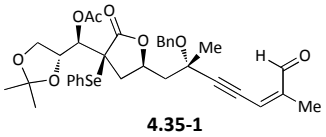
4.33

To a solution of alcohol **4.32** (1.0 eq, 730 mg, 1.0 mmol) in CH_2Cl_2 (10mL) at 0 ^oC was added pyr (10.0 eq, 810 μL, 10 mmol), Ac_2O (5.0 eq, 472 μL, 5 mmol) and DMAP (1 crystal). After 3 h, the reaction was diluted with CH_2Cl_2 (10 mL) and washed with 1N HCl (2 x 25 mL), saturated aqueous sodium bicarbonate (1 x 25 mL), and brine (1 x 15 mL). The organics were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (6:1 Hexanes/EtOAc) to provide acetate **4.33** (760 mg, 9.9 mmol, 99%) as a red oil: $[\alpha]_D^{23}$ +12.8^o (*c* 0.3, $CHCl_3$); R_f 0.7 (6:1 hexanes/EtOAc); IR (thin film, cm^{-1}): 3061, 2984, 2931, 2857, 2252, 1760, 1721, 1578, 1497; ^1H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 6.8 Hz, 2H), 7.47-7.28 (m, 8H), 5.58 (d, *J* = 4.4 Hz, 1H), 5.35 (s, 1H), 4.86 (dddd, *J* = 8.0, 6.0, 6.0, 5.6 Hz, 1H), 4.69-4.56 (m, 3H), 4.39 (s, 2H), 4.06 (dd, *J* = 8.0, 6.4 Hz, 1H), 3.93 (dd, *J* = 8.0, 7.6 Hz, 1H), 2.81 (dd, *J* = 14.4, 8.4 Hz, 1H), 2.24 (dd, *J* = 14.4, 5.6 Hz, 1H), 2.14 (dd, *J* = 14.4, 6.0 Hz, 1H), 2.05 (s, 3H), 1.95 (dd, *J* = 14.4, 6.0 Hz, 1H), 1.90 (s, 3H), 1.55 (s, 3H), 1.38 (s, 6H), 0.90 (s, 9H), 0.09 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 174.8, 169.6, 151.8, 138.6, 137.9, 129.9, 129.3, 129.2, 128.2, 127.4, 127.3, 127.2, 126.2, 109.8, 104.2, 93.4, 82.8, 75.6, 75.4, 74.5, 71.7, 66.8, 66.1, 63.9, 51.9, 47.4, 38.5, 27.1, 26.7, 25.8, 25.6, 25.2, 20.6, 20.5, 19.8, 18.2, 0.9, -5.3; HRMS calcd for $C_{40}H_{55}O_8SeSi$ $[M+H]^+$ 771.2831 found 771.2790; HRMS calcd for $C_{40}H_{54}NaO_8SeSi$ $[M+Na]^+$ 793.2651 found 793.2649.



4.34

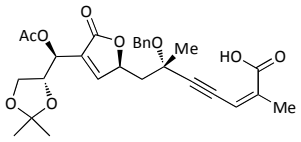
To a solution of silyl ether **4.33** (1.0 eq, 770 mg, 1.0 mmol) in THF (10 mL) at 0 ^{o}C was added TBAF (1.0 M in THF, 1.1 eq, 1.1 mL, 1.1 mmol). After stirring 6 h, the reaction mixture was diluted with EtOAc (10 mL) and saturated aqueous ammonium chloride (10 mL) was added. The layers were separated and the organics were washed with water (1x 10 mL), brine (1 x 10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2:1 Hexanes/EtOAc) to provide allylic alcohol **4.34** (465 mg, 0.72 mmol, 70%) as a colorless oil: $[\alpha]_D^{23}$ +20.0^{o} (*c* 0.1, $CHCl_3$); R_f 0.3 (4:1 hexanes/EtOAc); IR (thin film, cm^{-1}): 3484, 3030, 2985, 2936, 1760, 1639, 1477, 1372, 1220; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 6.8 Hz, 2H), 7.44-7.29 (m, 8H), 5.39-5.38 (m, 2H), 4.74 (dd, *J* = 6.8, 6.0 Hz, 1H), 4.61-4.52 (m, 3H), 4.30 (d, *J* = 5.2 Hz, 2H), 4.09 (dd, *J* = 8.8, 6.4 Hz, 1H), 3.86 (dd, *J* = 8.8, 6.4 Hz, 1H), 2.83 (dd, *J* = 14.8, 7.6 Hz, 1H), 2.24 (dd, *J* = 15.2, 7.6 Hz, 1H), 2.10-2.07 (m, 1H), 2.03 (s, 3H), 1.93 (s, 3H), 1.73 (dd, *J* = 14.0, 5.6 Hz, 1H), 1.52 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 175.1, 169.9, 151.4, 138.7, 137.9, 129.9, 129.3, 128.3, 127.4, 126.2, 109.8, 105.4, 93.1, 82.9, 75.8, 75.4, 74.7, 71.7, 66.8, 66.1, 63.5, 51.9, 47.5, 38.7, 26.6, 25.7, 25.2, 20.6, 20.1, 14.1; HRMS calcd for $C_{34}H_{40}O_8Se$ $[M-H]^-$ 655.1810 found 655.1807; HRMS calcd for $C_{34}H_{40}NaO_8Se$ $[M+Na]^+$ 679.1786 found 679.1783.



4.35-1

To a slurry of MnO_2 (10 eq, 520 mg, 6.1 mmol) in CH_2Cl_2 (10 mL) at ambient temperature was added allylic alcohol **4.34** (1.0 eq, 400 mg, 0.61 mmol). After 12 h, $MgSO_4$ (1 g) was added and the reaction

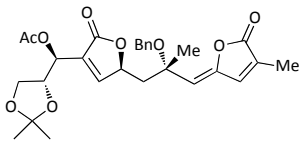
mixture was filtered through a plug of celite. The organics were concentrated *in vacuo* to provide aldehyde **4.35-1** (323 mg, 0.47 mmol, 95%) as a colorless oil: $[\alpha]_D^{23}$ +15.0° (*c* 0.3, $CHCl_3$); R_f 0.5 (4:1 hexanes/EtOAc); IR (thin film, cm^{-1}): 3030, 2986, 2935, 2252, 1760, 1686, 1604, 1578, 1372; ^1H NMR (400 MHz, $CDCl_3$): δ 10.2 (s, 1H), 7.65 (d, *J* = 7.2 Hz, 2H), 7.46-7.29 (m, 8H), 6.56 (s, 1H), 5.38 (d, *J* = 6.0 Hz, 2H), 4.76 (ddd, *J* = 7.2, 6.8, 6.4, 6.4 Hz, 1H), 4.65-4.58 (m, 2H), 4.47 (dd, *J* = 12.4, 6.0 Hz, 1H), 4.10 (dd, *J* = 8.4, 6.8 Hz, 1H), 3.86 (dd, *J* = 8.4, 6.4 Hz, 1H), 2.84 (dd, *J* = 14.8, 8.0 Hz, 1H), 2.19 (dd, *J* = 14.8, 7.2 Hz, 1H), 2.04 (s, 3H), 2.03-1.96 (m, 2H), 1.91 (s, 3H), 1.57 (s, 3H), 1.35 (s, 3H), 1.31 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 191.1, 174.8, 169.6, 146.6, 138.1, 137.8, 129.3, 129.2, 128.3, 128.2, 127.5, 127.2, 124.3, 109.9, 100.1, 80.4, 75.5, 75.1 ,73.8, 71.8, 66.4, 51.9, 47.0, 38.1, 26.1, 25.5, 25.1, 20.5, 15.1; HRMS calcd for $C_{34}H_{38}NaO_8Se$ $[M+Na]^+$ 677.1630 found 677.1625; HRMS calcd for $C_{34}H_{38}KO_8Se$ $[M+K]^+$ 693.1369 found 693.1367.



4.35

To a solution of aldehyde **4.35-1**(1.0 eq, 0.47 mmol, 323 mg) in t-BuOH (10 mL) was added 2-methyl-2-butene (10 eq, 500 μL, 4.7 mmol). $NaOCl_2$ (7.5 eq, 320 mg, 3.5 mmol) and $Na_2H_2PO_4$ (7.6 eq, 490 mg, 3.6 mg) were dissolved in water (5 ml) and added to the reaction mixture dropwise. After stirring 1 h, the green reaction mixture was diluted with EtOAc (10 mL) and washed with 1N HCl (1 x 10 mL) and water (1 x 10 mL). The organics were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:1 Hexanes/EtOAc) to provide acid **4.35** (200 mg, 0.39mmol, 85%) as a colorless oil: $[\alpha]_D^{23}$ +72.1° (*c* 0.3, $CHCl_3$); R_f 0.2 (2:1

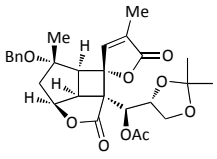
hexanes/EtOAc); IR (thin film, cm^{-1}): 3490, 2986, 2935, 2575, 2253, 1760, 1720, 1617, 1497, 1454, 1373, 1225; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 4.4 Hz, 5H), 6.22 (dt, *J* = 7.6, 2.4 Hz, 1H), 6.10 (d, *J* = 1.6 Hz, 1H), 5.74 (dd, *J* = 6.8, 6.8 Hz, 1H), 4.92 (ddd, *J* = 7.2, 6.8, 6.0 Hz, 1H), 4.74 (d, *J* = 11.2 Hz, 1H), 4.62 (d, *J* = 11.2, 1H), 4.31 (dd, *J* = 8.0, 6.8 Hz, 2H), 3.60 (dd, *J* = 8.0, 6.4 Hz, 1H), 2.37 (dd, *J* = 14.4, 6.0 Hz, 1H), 2.15 (dd, *J* = 14.4, 6.8 Hz, 1H), 2.06 (s, 3H), 1.64 (s, 3H), 1.48 (s, 3H), 1.46 (s, 3H), 1.42 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 171.0, 169.7, 154.3, 138.5, 138.4, 129.2, 128.3, 127.9, 127.5, 127.4, 118.2, 110.1, 98.7, 83.9, 78.5, 77.3, 77.0, 76.7, 74.9, 71.7, 68.0, 66.5, 65.3, 44.8, 26.5, 26.3, 24.9, 20.7, 19.8; HRMS calcd for $C_{28}H_{32}NaO_9$ $[M+Na]^+$ 535.1939 found 535.1939.



4.36

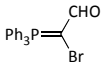
To a solution of acid **4.35** (1.0 eq, 125 mg, 0.5 mmol) in MeOH (10 mL) at 0 °C was added $AgNO_3$ (0.1 eq, 16 mg, 0.1 mmol) as a solution in water (100 μL). The reaction was stirred 1 h and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2:1 Hexanes/EtOAc) to provide alkylidene butenolide **4.36** (115 mg, 0.48 mmol, 92%) as a white amorphous powder: mp 253-255 °C; $[\alpha]_D^{23}$ +9.6° (*c* 0.2, $CHCl_3$); R_f 0.3 (4:1 hexanes/EtOAc); IR (thin film, cm^{-1}): 2986, 2934, 1758, 1667, 1626, 1497, 1372, 1225, 1153; ^1H NMR (600 MHz, $CDCl_3$): δ 7.43 (s, 1H), 7.38-7.29 (m, 5H), 7.01 (d, *J* = 1.2 Hz, 1H), 5.62 (d, *J* = 5.2 Hz, 1H), 5.29 (dd, *J* = 7.4, 5.0 Hz, 1H), 5.21 (s, 1H), 4.61-4.51 (m, 2H), 4.45 (d, *J* = 13.2 Hz, 1H), 4.02 (dd, *J* = 8.8, 6.8 Hz, 1H), 3.88 (dd, *J* = 8.4, 5.2 Hz, 1H), 2.38 (dd, *J* = 14.8, 4.8 Hz, 1H), 2.18 (dd, *J* = 14.8, 7.6 Hz, 1H), 2.04 (d, *J* = 4.4 Hz, 6H), 1.76 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H); ^{13}C (150 MHz, $CDCl_3$) δ 170.9, 170.3, 169.5, 154.0, 148.0,

138.5, 138.4, 129.9, 129.6, 128.4, 127.5, 127.3, 116.3, 110.0, 78.5, 76.2, 74.9, 68.0, 65.4, 43.5, 30.2, 26.3, 24.9, 23.9, 20.7, 10.4; HRMS calcd for $C_{28}H_{32}NaO_9$ $[M+Na]^+$ 535.1939 found 535.1939.



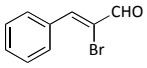
4.37

A 450 W Hanovia medium pressure mercy vapor lamp was lowered inside a water-cooled Pyrex immersion well. A solution of bisbutenolide **4.36** (1.0 eq, 51 mg, 0.1 mmol) in acetone (10 mL) was irradiated for 2 h and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (4:1 hexanes/EtOAc) to provide photoadduct **4.37** (48 mg, 0.1 mmol, >95%) as a white amorphous solid: mp 274-277 ^oC; $[\alpha]_D^{23}$ +4.1^o (*c* 0.2, $CHCl_3$); R_f 0.4 (4:1 hexanes/EtOAc); IR (thin film, cm^{-1}): 2985, 2932, 1773, 1680, 1454, 1373, 1219, 1159, 1048; ^1H NMR (600 MHz, $CDCl_3$): δ 7.39-7.31 (m, 5H), 7.04 (d, *J* = 1.6 Hz, 1H), 5.55 (d, *J* = 5.2 Hz, 1H), 5.24 (ddd, *J* = 9.2, 8.0, 7.6 Hz, 1H), 4.39 (d, *J* = 11.6 Hz, 1H), 4.34 (d, *J* = 11.6 Hz, 1H), 4.29 (ddd, 7.6, 6.8, 5.2 Hz, 1H), 4.05 (dd, *J* = 8.4, 6.8 Hz, 1H), 3.84 (dd, *J* = 8.4, 7.6 Hz, 1H), 3.61 (dd *J* = 8.0, 8.0 Hz, 1H), 3.51 (d, *J* = 8.0 Hz, 1H), 2.82 (qd, 8.0, 8.0, 1.6 Hz, 1H), 2.16 (s, 3H), 2.10-2.04 (m, 1H), 1.98 (d, *J* = 1.2 Hz, 3H), 1.45 (s, 3H), 1.36 (d, *J* = 7.6 Hz, 6H) ^{13}C (150 MHz, $CDCl_3$) δ 174.1, 170.8, 169.8, 144.4, 138.1, 132.3, 128.5, 127.7, 127.6, 127.2, 127.1, 125.5, 109.9, 86.3, 85.9, 83.4, 70.4, 67.1, 65.8, 64.7, 56.6, 56.4, 48.3, 42.4, 30.3, 25.5, 25.3, 20.9, 19.4, 15.3, 10.9, 1.0; HRMS calcd for $C_{28}H_{33}O_9$ $[M+H]^+$ 513.2112 found 513.2119; HRMS calcd for $C_{28}H_{32}NaO_9$ $[M+Na]^+$ 535.1932 found 535.1939.



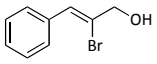
4.44

To a solution of (triphenylphosphoranylidene)acetaldehyde (1.0 eq, 3.0 g, 10 mmol) and NaOAc (1.25 eq, 1.0 g, 12.5 mmol) in AcOH (25 mL) at 0 ^{o}C was added Br_2 (1.0 eq, 512μL, 10 mmol) as a solution in AcOH (5 mL). After 5 min, conc. HCl (5 mL) was added and the residue concentrated *in vacuo*. The residue was crystallized from 1N NaOH (5 mL) to provide ylide **4.44** (2.0 g, 5.2 mmol, 52%) as a brown solid: Spectral data was consistent with reported values.[45, 46]



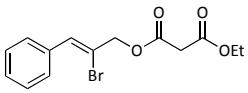
4.45

To a solution of PhCHO (1.0 eq, 106 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) was added ylide **4.44** (1.0 eq, 383 mg, 1.0 mmol) and the reaction was warmed to 40 ^{o}C. After 18 h, the mixture was cooled to ambient temperature and concentrated *in vacuo*. The crude residue was recrystallized (acetone/hexanes) to provide α-bromo cinnamaldehyde **4.45** (127 mg, 0.6 mmol, 60%) as a white crystalline solid: Spectral data was consistent with a commercial sample.



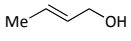
4.46

To a solution of α-bromo cinnamaldehyde **4.45** (1.0 eq, 211 mg, 1.0 mmol) in EtOH (10 mL) at ambient temperature was added $NaBH_4$ (1.0 eq, 38 mg, 1.0 mmol) and the reaction was stirred 1 h. The reaction mixture was concentrated *in vacuo* and the crude residue dissolved in EtOAc (10 mL). The organics were washed with water (1 x 10 mL), brine (1 x 10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to provide alcohol **4.46** (149 mg, 0.72 mmol, 72%) as a colorless oil: Spectral data was consistent with reported values.[65]



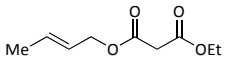
4.48

To a solution of alcohol **4.46** (1.0 eq, 1 g, 5 mmol) in CH_2Cl_2 (50 mL) at ambient temperature was added Et_3N (2.0 eq, 1.3 mL, 9.4 mmol), DMAP (1 crystal), and ethyl chloromalonate **4.46** (1.0 eq, 591 μL, 5 mmol). After 1h, the organics were washed with water (1 x 25 mL), brine (1 x 25 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (4:1 hexanes/EtOAc) to provide malonate **4.48** (1.3 g, 4.0 mmol, 86%) as a colorless oil: R_f 0.7 (4:1 hexanes/EtOAc); IR (thin film, cm^{-1}): 3057, 283, 1735, 1651, 1492, 1264, 1145; ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 7.2 Hz, 2H), 7.39-7.31 (m, 3H), 7.11 (s, 1H), 5.01 (s, 2H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.64 (s, 2H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 166.1, 165.8, 134.5, 131.5, 129.0, 128.5, 128.4, 128.3, 128.2, 118.1, 70.5, 61.6, 41.4, 14.0; LRMS calcd for $C_{14}H_{15}BrNaO_4$ $[M+Na]^+$ 349.0 found 350.1.



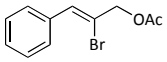
4.51

To a solution of crotonaldehyde **4.50** (1.0 eq, 700 mg, 10 mmol) in EtOH (10 mL) at ambient temperature was added $NaBH_4$ (1.0 eq, 380 mg, 10 mmol) and the reaction was stirred 1 h. The reaction mixture was concentrated *in vacuo* and the crude residue dissolved in EtOAc (10 mL). The organics were washed with water (1 x 10 mL), brine (1 x 10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to provide crotyl alcohol **4.51** (700 mg, 9.5 mmol, 95%) as a colorless oil: Spectral data was consistent with a commercial sample.



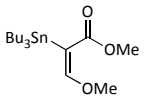
4.52

To a solution of crotyl alcohol **4.51** (1.0 eq, 720 mg, 10 mmol) in CH_2Cl_2 (100 mL) at ambient temperature was added Et_3N (2.0 eq, 2.7 mL, 20 mmol), DMAP (1 crystal), and ethyl chloromalonate **4.47** (1.0 eq, 1.2 mL, 10 mmol). After 1h, the organics were washed with water (1 x 50 mL), brine (1 x 50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (4:1 hexanes/EtOAc) to provide malonate **4.52** (1.3 g, 4.0 mmol, 86%) as a colorless oil: R_f 0.6 (4:1 hexanes/EtOAc); IR (thin film, cm^{-1}): 2983, 1732, 1677, 1448, 1269, 1150; ^1H NMR (400 MHz, $CDCl_3$): δ 5.80 (dt, *J* = 14.0, 6.4 Hz, 1H), 5.56 (qd, *J* = 13.6, 6.8 Hz, 1H), 4.56 (d, *J* = 6.4 Hz, 2H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.36 (s, 2H), 1.71 (d, *J* = 6.8 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 166.4, 166.3, 131.9, 124.4, 66.0, 61.4, 41.5, 17.6, 13.9; LRMS calcd for $C_9H_{14}NaO_4$ $[M+Na]^+$ 209.1 found 210.1.



4.54

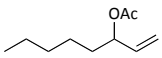
To a solution of alcohol **4.46** (1.0 eq, 210 mg, 1 mmol) in CH_2Cl_2 (10 mL) at ambient temperature was added pyr (5 mL), Ac_2O (2.5 mL), and DMAP (1 crystal). The reaction was stirred 1 h, washed with 1N HCl (3 x 10 mL), brine (1 x 25 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (10:1 hexanes/EtOAc) to provide acetate **4.54** (250 mg, 1 mmol, 99%) as a colorless oil: Spectral data was consistent with reported values.[66]



4.55

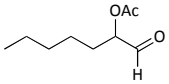
To a solution of methyl trans-3-methoxyacrylate (1.0 eq, 5.4 mL, 50 mmol) in $CHCl_3$ (50 mL) was added AcOH (2.0 eq, 5 mL, 100 mmol) and NIS (1.3 eq,

7.3 g, 65 mmol). After stirring 12 h, the reaction was washed with saturated sodium bicarbonate (2 x 25 mL), water (1 x 25 mL), brine (1 x 25 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude oil was dissolved in CH_2Cl_2 (50 mL), treated with Et_3N (2.0 eq, 14 mL, 100 mmol), and warmed to reflux. After 3 h, the reaction mixture was washed with water (1 x 50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was recrystallized (acetone/hexanes) to provide the vinyl iodide (4.8 g, 34 mmol, 77%) as a crystalline solid. The iodide (1.0 eq, 1.2 g, 5.0 mmol) was dissolved in $PhCH_3$ (50 mL). $(Bu_3)_2Sn_2$ (1.2 eq, 3.6 g, 6.2 mmol) and $Pd(PPh_3)_4$ (0.1 eq, 600 mg, 0.5 mmol) was added and the reaction warmed to reflux. After stirring 48 h, the reaction was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (10:1 hexanes/EtOAc) to provide stannane **4.55** (1.1 g, 2.7 mmol, 54%) as a colorless oil: Spectral data was consistent with reported values.[56, 57]



4.59

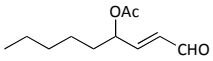
To a solution of alcohol **4.58** (1.0 eq, 9.5 g, 74.2 mmol) in CH_2Cl_2 (120 mL) at ambient temperature was added pyr (10 mL), Ac_2O (5 mL), and DMAP (1 crystal). The reaction was stirred 1 h, washed with 1N HCl (3 x 50 mL), brine (1 x 50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by distillation (72-74 ^oC) to provide acetate **4.59** (12.6 g, 74.0 mmol, 99%) as a colorless oil: Spectral data was consistent with reported values.[67]



4.60

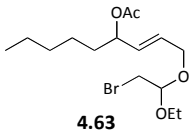
To a solution of acetate **4.59** (1.0 eq, 1.7 g, 10 mmol) in THF (200 mL) at ambient temperature was added OsO_4 (1 crystal). $NaIO_4$ (5 eq, 10.6 g, 50

mmol) was added as a slurry in water (100 mL). The reaction was stirred 4 h, diluted with Et_2O (200 mL) and washed saturated sodium bicarbonate (3 x 50 mL), brine (1 x 50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to provide aldehyde **4.60** (1.2 g, 0.7 mmol, 71%) as a colorless oil: Spectral data was consistent with reported values.[67]



4.61

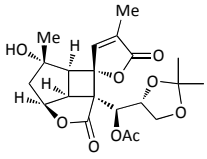
To a solution of aldehyde **4.60** (1.0 eq, 172 mg, 1 mmol) in CH_2Cl_2 (10 mL) at ambient temperature was added (formylmethylene) triphenylphosphorane (1.0 eq, 304 mg, 1 mmol). After warming to reflux, the reaction was stirred 3 h. Celite (1 g) was added and the reaction was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (4:1 hexanes/EtOAc) to provide aldehyde **4.61** (162 mg, 0.82 mmol, 82%) as a pale yellow oil: R_f 0.6 (2:1 hexanes/EtOAc); IR (thin film, cm^{-1}): 2932, 2861, 1745, 1694, 1644, 1467, 1373; ^1H NMR (400 MHz, $CDCl_3$): δ 9.7 (d, *J* = 7.6 Hz, 1H), 6.75 (dd, *J* = 15.6, 4.8 Hz, 1H), 6.21 (dd, *J* = 15.6, 7.6 Hz, 1H), 5.52 (dd, *J* = 6.8, 5.2, 1H), 2.13 (s, 3H), 1.75-1.69 (m, 2H), 1.44-1.27 (m, 6 H), 0.93-0.89 (m, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 192.9, 170.0, 153.9, 131.4, 72.2, 33.5, 31.3, 24.6, 22.3, 20.9, 13.9; LRMS calcd for $C_{11}H_{18}NaO_3$ $[M+Na]^+$ 221.2 found 222.2.



4.63

To a solution of aldehyde **4.61** (1.0 eq, 198 mg, 1 mmol) in EtOH (10 mL) at ambient temperature was added $NaBH_4$ (1.0 eq, 380 mg, 10 mmol) and the reaction was stirred 1 h. The reaction mixture was concentrated *in vacuo* and the crude residue dissolved in EtOAc (10 mL). The organics

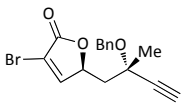
were washed with water (1 x 10 mL), brine (1 x 10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude alcohol was lowered to -20 ^oC and stirred vigorously. Ethyl vinyl ether (10 eq, 740 mg, 10 mmol) was added and the reaction allowed to stir 5 min. NBS (1.0 eq, 178 mg, 1 mmol) was added while maintaining an internal temperature below 0 ^oC. After 30 min, hexanes (10 mL) was added and the reaction filtered through a plug of celite. The organics were washed with 1N HCl (3 x 10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (6:1 hexanes/EtOAc) to provide acetal **4.63** (284 mg, 0.81 mmol, 81%) as a colorless oil: R_f 0.5 (4:1 hexanes/EtOAc); IR (thin film, cm^{-1}): 2790, 1745, 1650, 1500, 1188, 1080; ^1H NMR (400 MHz, $CDCl_3$): δ 5.83-5.68 (m, 2H), 5.27 (dd, *J* = 6.8, 6.4 Hz, 1H), 4.71 (t, *J* = 5.6 Hz, 1H), 4.19-4.07 (m, 2H), 3.74-3.56 (m, 2H), 3.38 (d, *J* = 5.6 Hz, 1H), 2.06 (s, 3H), 1.66-1.54 (m, 2H), 1.30-1.21 (m, 6 H), 0.91-0.88 (m, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 170.3, 131.4, 131.3, 128.3, 100.9, 73.9, 66.3, 62.4, 34.2, 31.6, 31.4, 24.7, 22.4, 21.2, 15.1, 13.9; LRMS calcd for $C_{15}H_{27}NaO_4$ $[M+Na]^+$ 373.1 found 373.3.



4.71

H_2 gas was bubbled through a solution of $Pd(OH)_2/C$ (5 mg) in EtOAc (1 mL) for 5 min. Tetracycle **4.37** (1.0 eq, 0.04 mmol, 20 mg) was added and H_2 gas was bubbled through the reaction mixture for an additional 5 min. N_2 gas was bubbled through the reaction mixture, celite (250 mg) was added and the reaction mixture concentrated *in vacuo*. The crude residue was purified by flash column chromatography (4:1 hexanes/EtOAc) to provide alcohol **4.71** (14 mg, 0.03 mmol, 84%) as a white powder: mp 260-263 ^oC; $[\alpha]_D^{23}$ +114.6^o (*c* 0.2, $CHCl_3$); R_f 0.2 (4:1

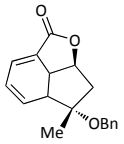
hexanes/EtOAc); IR (thin film, cm^{-1}): 3450, 2980, 2932, 1770, 1677, 1454, 1373, 1219, 1159; ^1H NMR (400 MHz, $CDCl_3$): δ 6.98 d, *J* = 1.2 Hz, 1H), 5.55 (d, *J* = 4.8 Hz, 1H), 5.31 (ddd, *J* = 8.0, 7.6, 3.6 Hz, 1H), 4.26 (ddd, *J* = 6.8, 6.8, 4.8 Hz, 1H), 4.04 (dd, *J* = 6.8, 6.8 Hz, 1H), 3.83 (dd, *J* = 8.0, 7.6 Hz, 1H), 3.68 (dd, *J* = 8.0, 8.0 Hz, 1H), 3.22 (dd, *J* = 8.0, 1.2 Hz, 1H), 2.62 (ddd, *J* = 16.0, 7.6, 1.6 Hz, 1H), 2.15 (s, 3H), 2.06 (dd, *J* = 16.8, 3.6 Hz, 1H), 1.96 (s, 3H), 1.36 (s, 3H), 1.32 (s, 3H), 1.27 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 173.9, 170.7, 169.8, 144.1, 132.3, 128.3, 109.8, 85.8, 83.4, 81.0, 75.5, 70.2, 66.9, 59.9, 56.2, 49.8, 42.3, 25.5, 25.1, 24.1, 20.9, 10.8, 0.9; LRMS calcd for $C_{21}H_{25}NaO_9$ $[M+Na]^+$ 444.1 found 445.1.



4.77

To a solution of ynamine **4.3** (1.4 eq, 130 g, 0.7 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added BF_3•OEt_2 (1.4, 86 μL, 0.7 mmol). Epoxide **4.23** (1.0 eq, 130 mg, 0.5 mmol) was added to the yellow solution and the reaction was stirred 30 min. NBS (3.0 eq, 270 mg, 1.5 mmol) was added and the red reaction mixture was stirred 30 min. The reaction was diluted with CH_2Cl_2 (5 mL) and 2N HCl (10 mL) was added. After separation of the layers the organics were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was dissolved in DMF (5 mL) and treated with LiCl (5.0 eq, 320 mg, 7.5 mmol) and Li_2CO_3 (1.0 eq, 37 mg, 0.5 mmol). After warming to 80 °C, the reaction was warmed to ambient temperature. The reaction mixture was diluted with EtOAc (10 mL), extracted with water (3 x 10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (4:1 hexanes/EtOAc) to provide the very sensitive vinyl bromide **4.77** (132 mg, 0.41 mmol, 81%) as a colorless oil: $[\alpha]_D^{23}$ +10.2° (*c* 0.05, $CHCl_3$); R_f 0.5 (4:1

hexanes/EtOAc); IR (thin film, cm^{-1}): 3287, 2983, 2931, 2863, 1770, 1665, 1454; ^1H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, *J* = 1.2 Hz, 1H), 7.41-7.32 (m, 5H), 5.32 (ddd, *J* = 6.6, 5.4, 1.8 Hz, 1H), 4.72 (d, *J* = 10.8 Hz, 1H), 4.60 (d, *J* = 10.8 Hz, 1H), 2.67 (s, 2H), 2.34 (dd, *J* = 14.4, 5.4 Hz, 1H), 2.23 (dd, *J* = 14.4, 6.6 Hz, 1H), 1.65 (s, 3H), ^{13}C (100 MHz, $CDCl_3$) δ 162.3, 153.4, 138.0, 128.2, 128.1, 127.5, 66.3, 66.2, 65.9, 65.8, 65.2, 46.7, 43.2, 36.2, 31.1; HRMS calcd for $C_{16}H_{16}BrO_3$ $[M+H]^+$ 334.0205 found 334.0212.



4.80

To a solution of bromide **4.77** (1.0 eq, 35 mg, 0.1 mmol) and **4.78** (1.0 eq, 12 mg, 0.08 mmol) in THF (2 mL) at ambient temperature was added Cs_2CO_3 (1.5 eq, 50 mg, 0.15 mmol), tBu_3PPd (0.1 eq, 5 mg, 0.01 mmol) and water (1 mL). The reaction was warmed to 40 ^oC and stirred for 8 h, after which the reaction was treated with celite (500 mg) and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (4:1 hexanes/EtOAc) to provide tricycle **4.80** (16 mg, 0.06 mmol, 60%) as a colorless oil: $[\alpha]_D^{23}$ +74.2^o (*c* 0.05, $CHCl_3$); R_f 0.3 (4:1 hexanes/EtOAc); IR (thin film, cm^{-1}): 3063, 2962, 2870, 1765, 1454, 1261; ^1H NMR (400 MHz, $CDCl_3$): δ 7.48-7.38 (m, 5H), 6.17 (dd, *J* = 5.2, 4.0 Hz, 1H), 6.05 (dd, *J* = 5.2, 2.4 Hz, 1H), 5.93 (dd, *J* = 4.0, 2.0 Hz, 1H), 5.14 (ddd, *J* = 7.2, 6.8, 2.4 Hz, 1H), 4.35 (d, *J* = 11.6 Hz, 1H), 4.15 (d, *J* = 11.6 Hz, 1H), 3.72 (dd, *J* = 7.2, 6.8 Hz, 1H), 3.44 (ddd, *J* = 6.8, 5.6, 1.2 Hz, 1H), 2.74 dd, *J* = 15.2, 6.8 Hz, 1H), 1.98 (dd, *J* = 15.2, 2.4 Hz, 1H), 1.51 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 168.0, 153.4, 138.6, 128.4, 127.4, 124.9, 112.4, 83.8, 79.4, 76.2, 70.8, 66.6, 42.1, 26.6; HRMS calcd for $C_{18}H_{18}NaO_3$ $[M+H]^+$ 305.1154 found 305.1162.

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Appendix A4:

Spectra Relevant to Chapter IV.

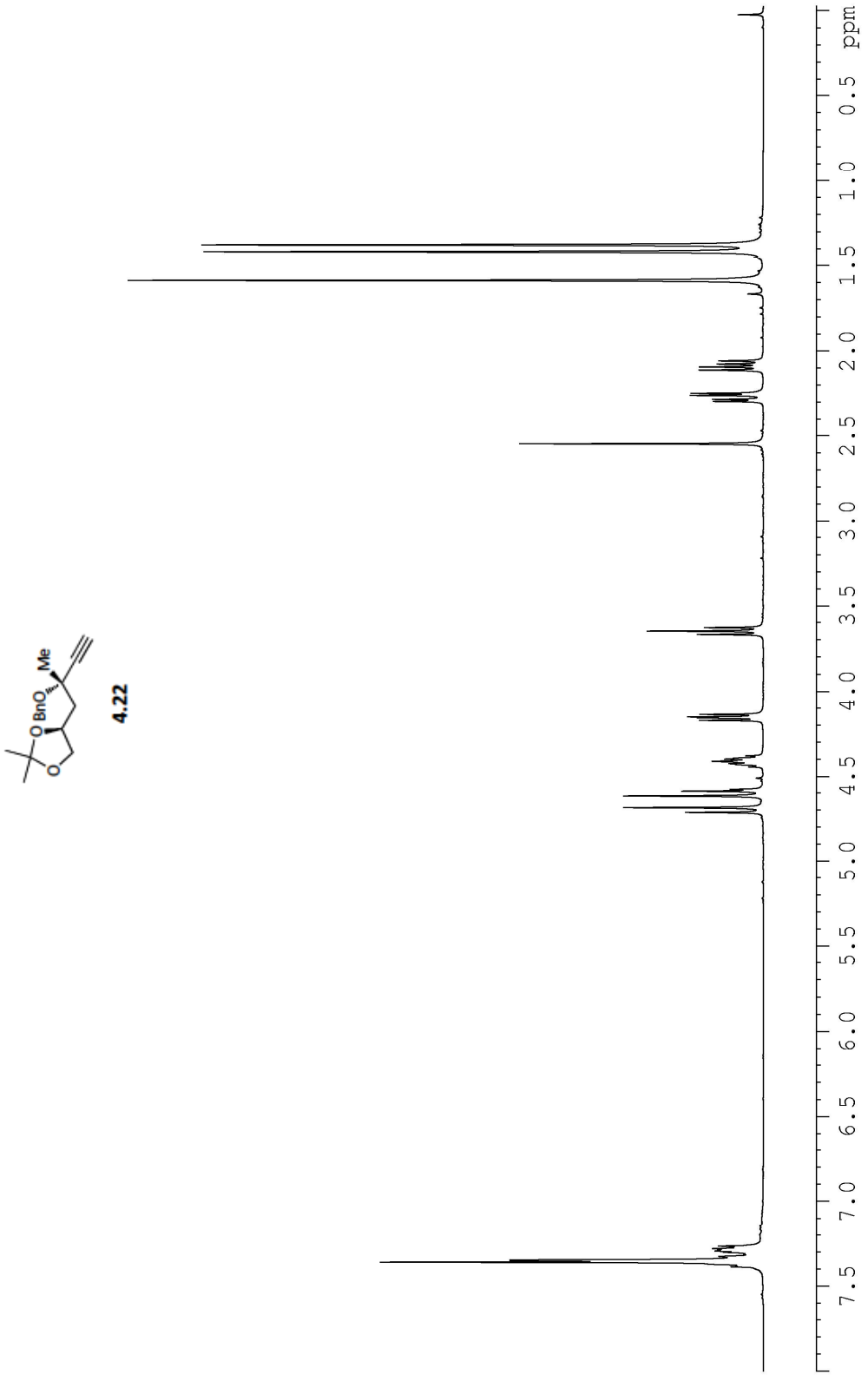


Figure A4.1. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **4.22**.

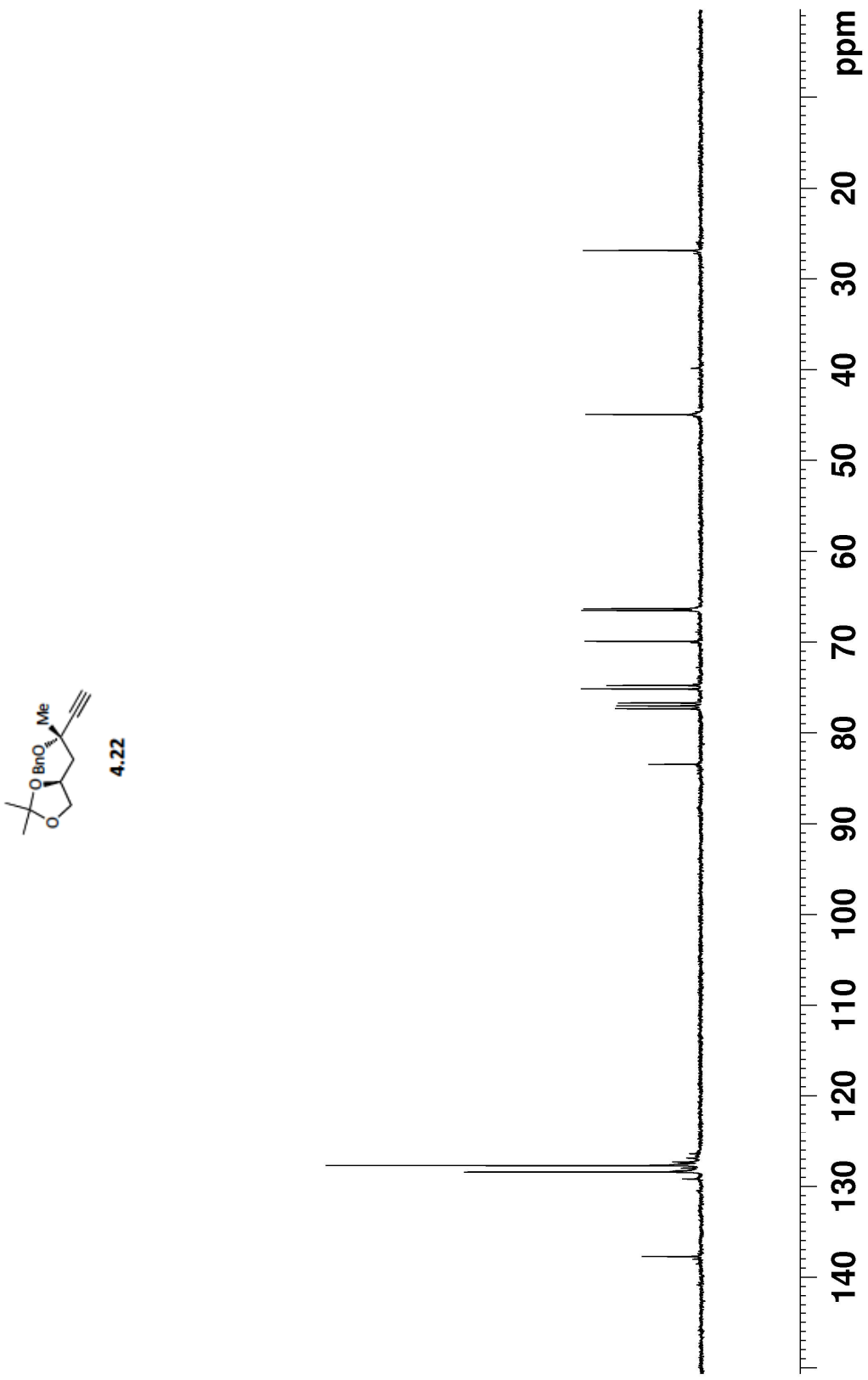


Figure A4.2. ^{13}C NMR spectra (100 MHz, $CDCl_3$) of compound **4.22.**

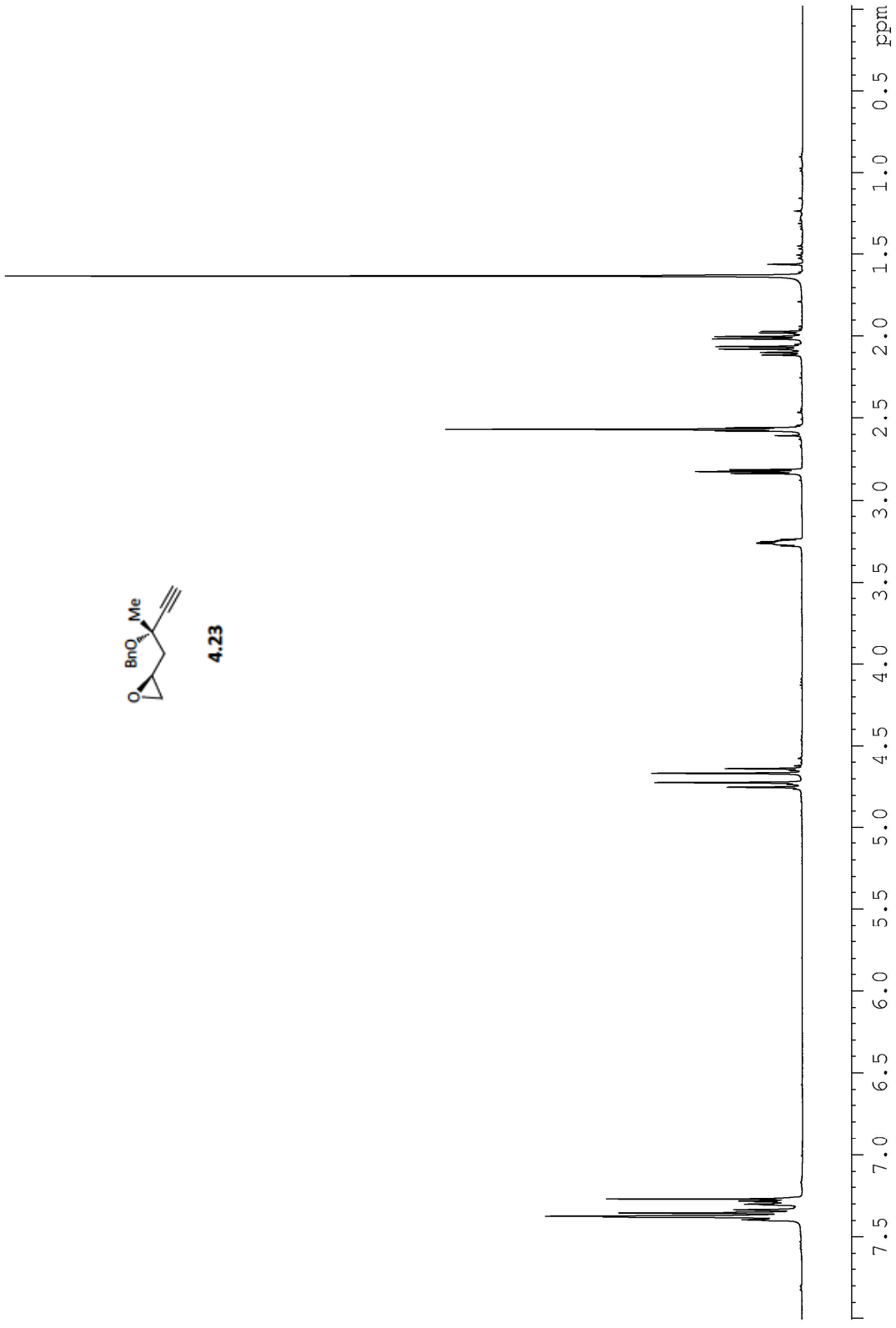


Figure A4.3. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **4.23**.

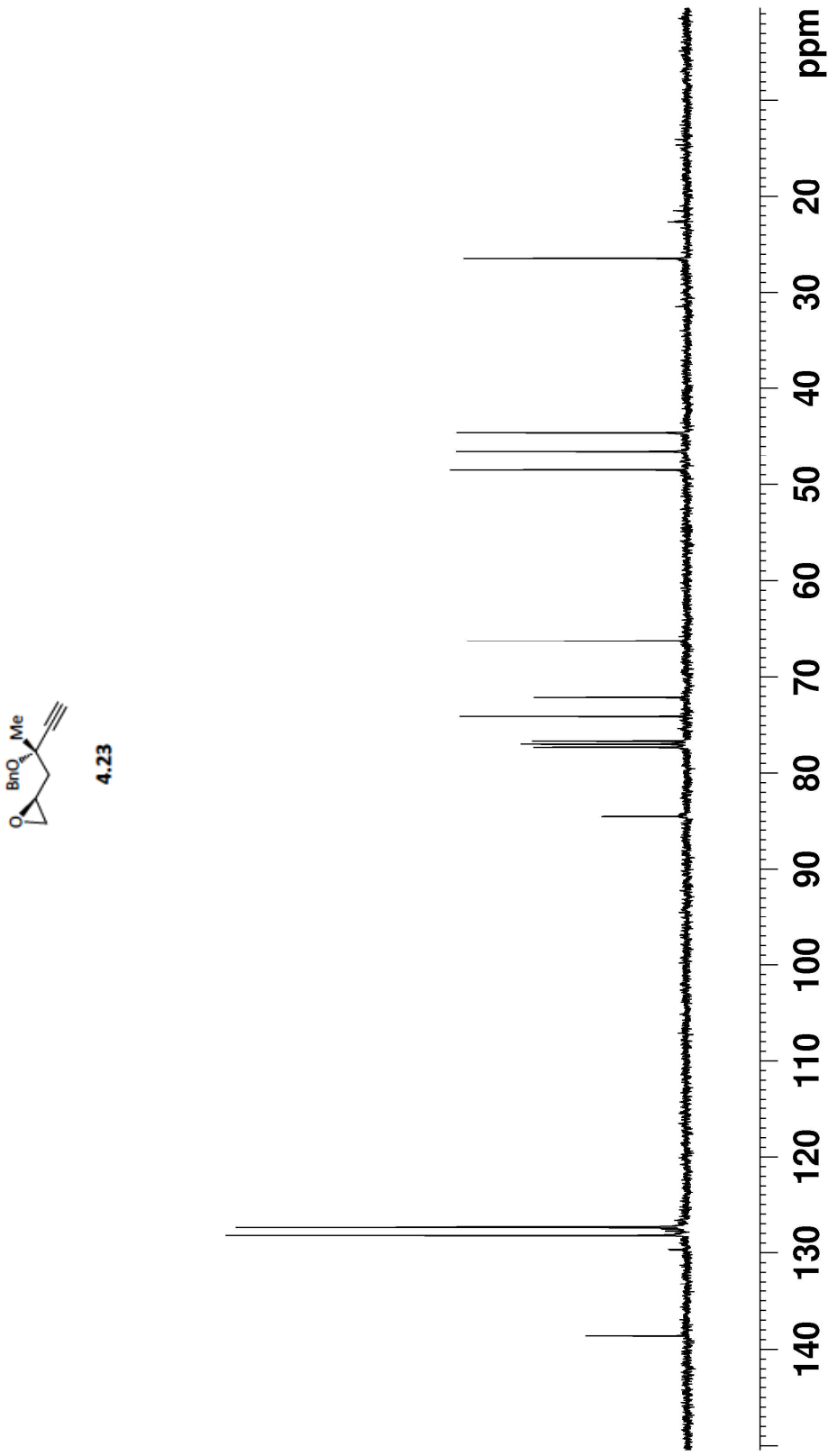


Figure A4.4. ^{13}C NMR spectra (100 MHz, $CDCl_3$) of compound **4.23.**

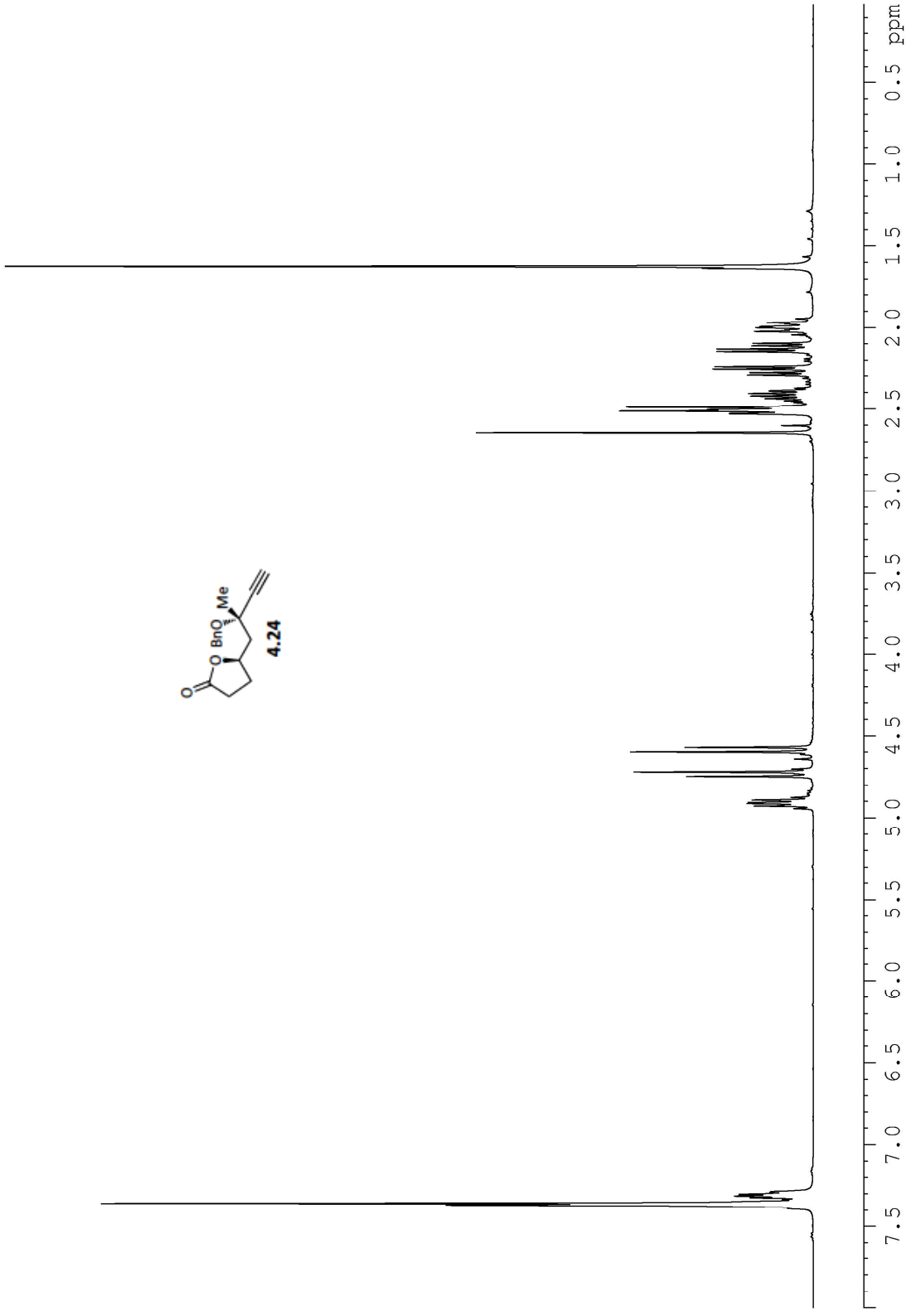


Figure A4.5. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **4.24**.

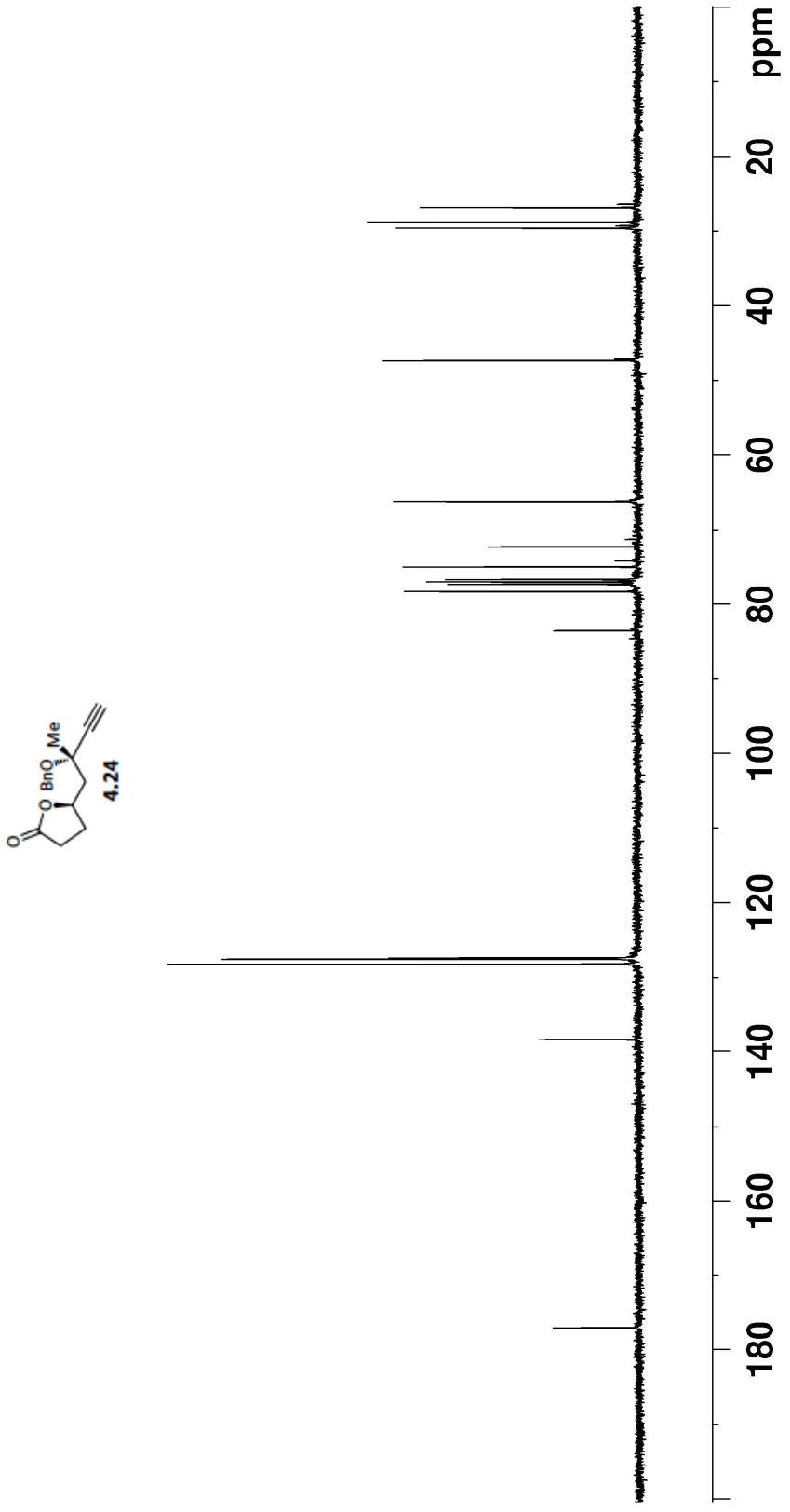


Figure A4.6. ^{13}C NMR spectra (100 MHz, $CDCl_3$) of compound **4.24.**

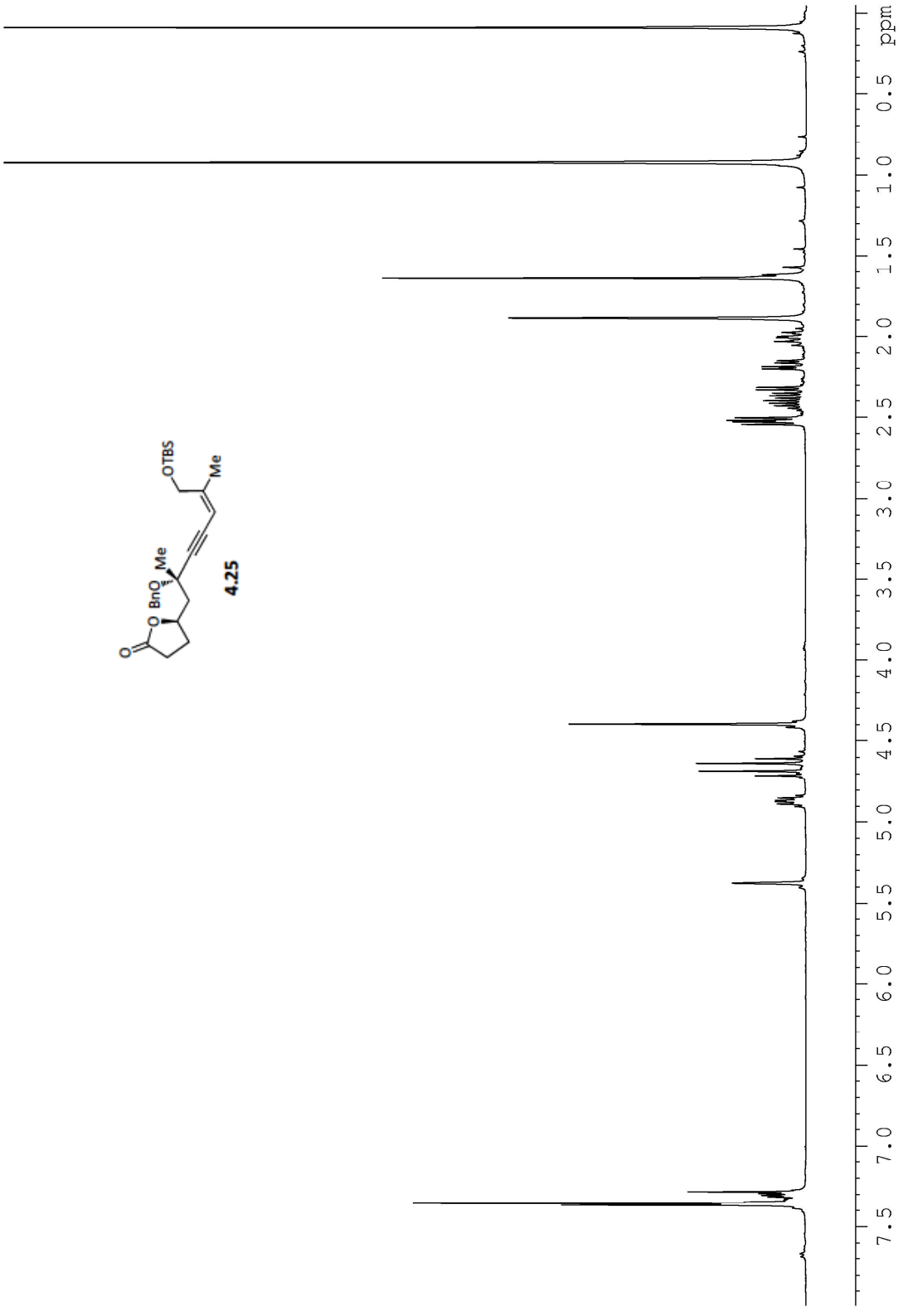


Figure A4.7. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **4.25**.

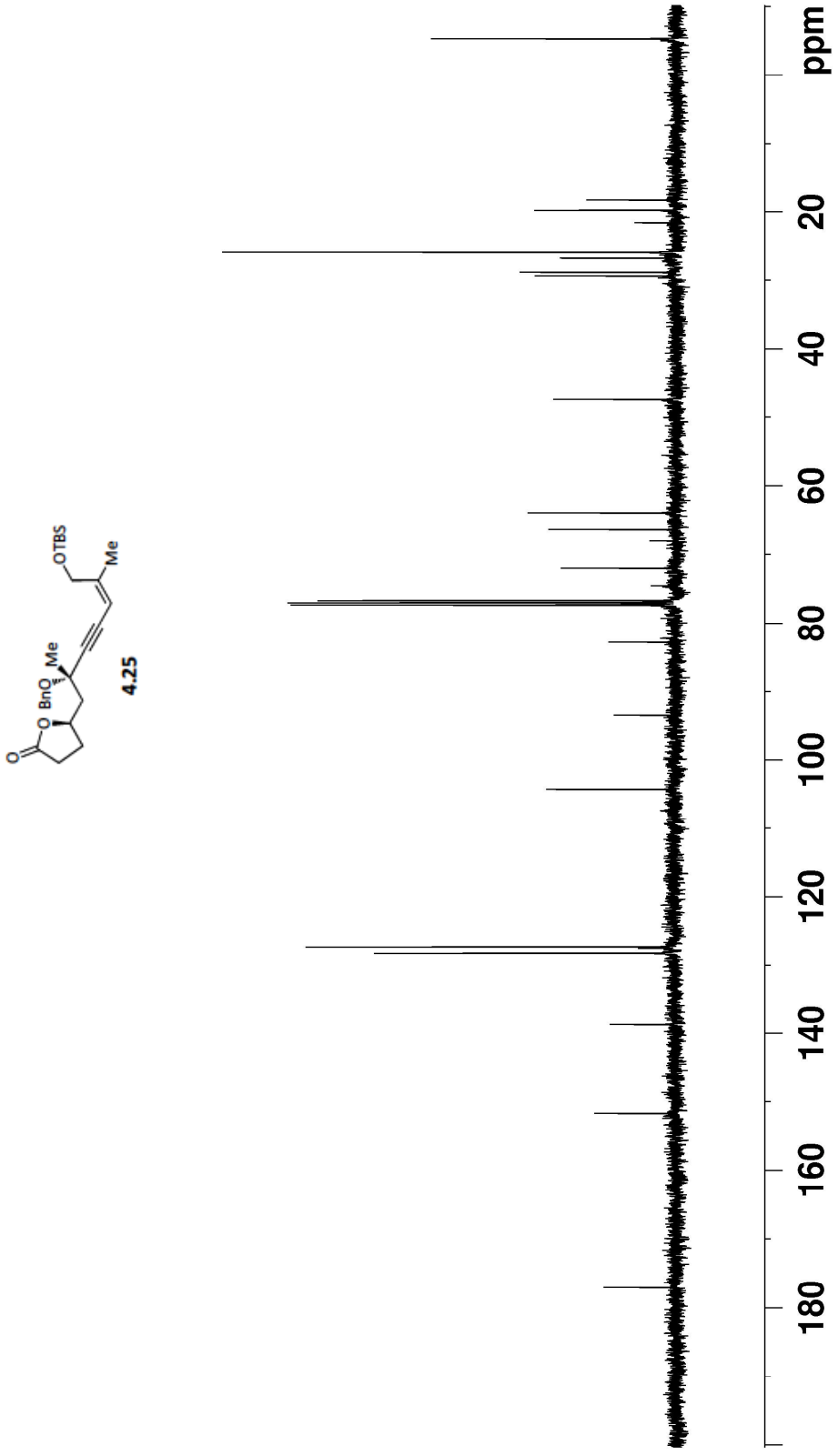


Figure A4.8. ^{13}C NMR spectra (100 MHz, $CDCl_3$) of compound **4.25.**

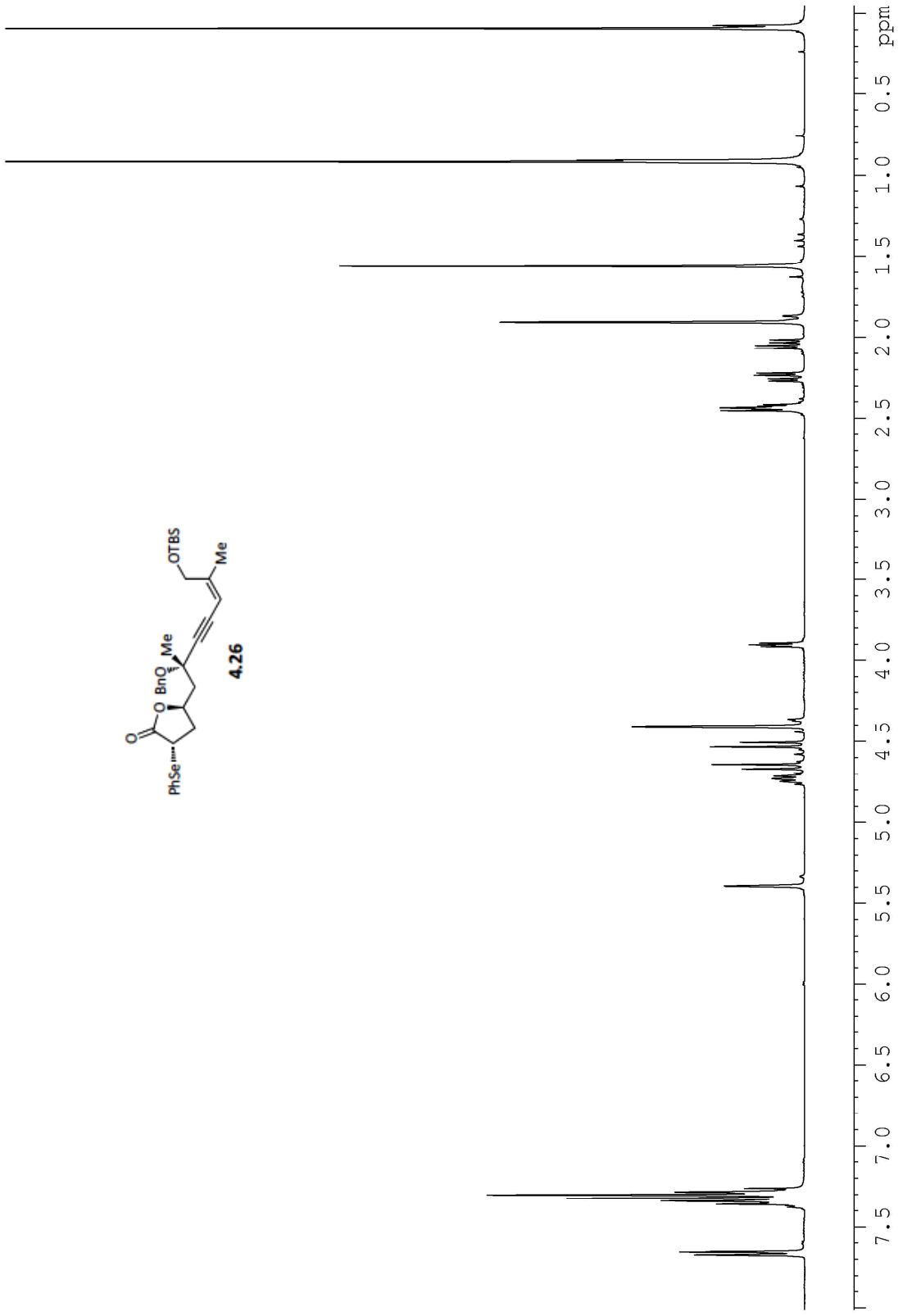


Figure A4.9. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **4.26**.

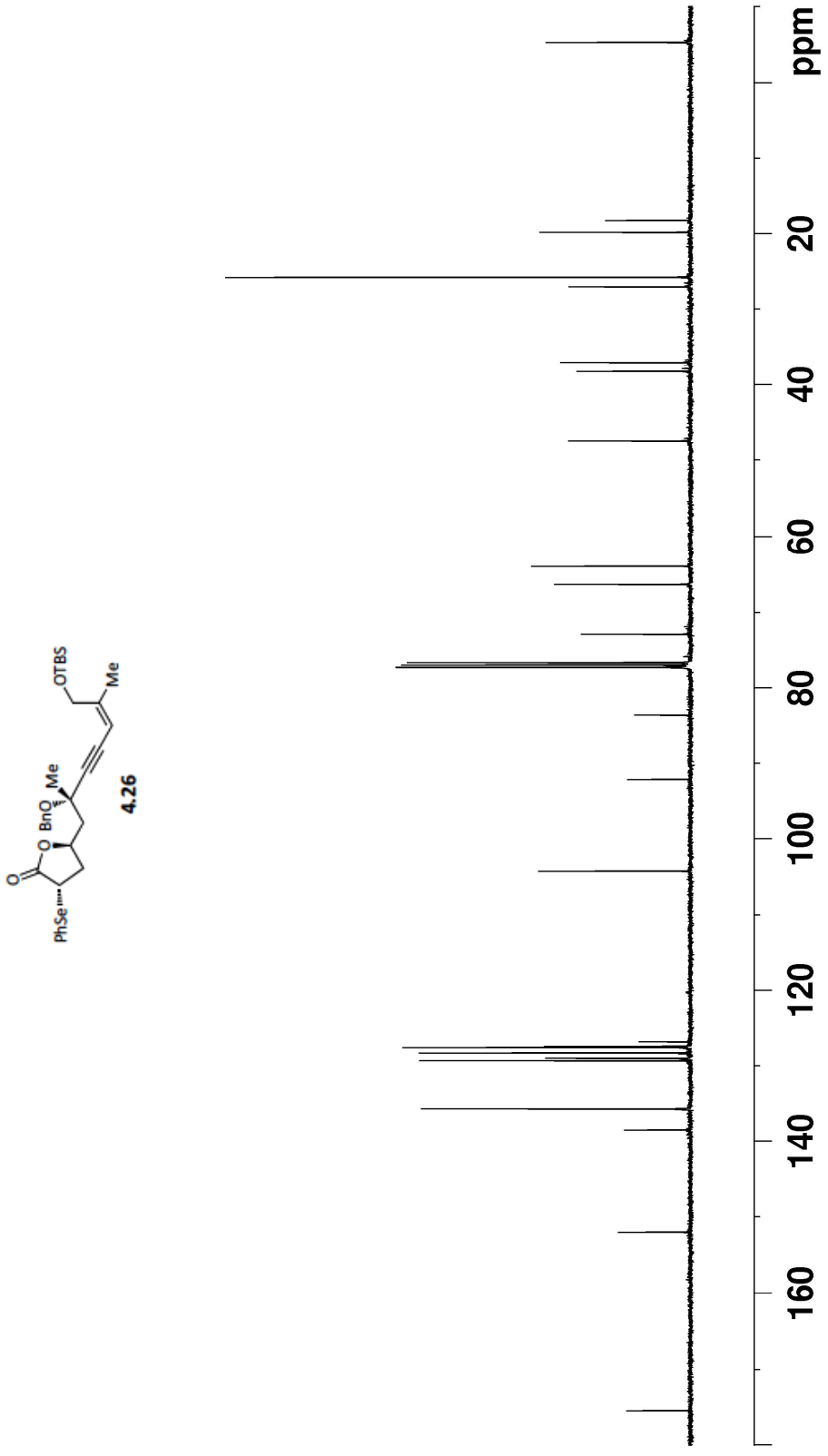


Figure A4.10. ^{13}C NMR spectra (100 MHz, $CDCl_3$) of compound **4.26.**

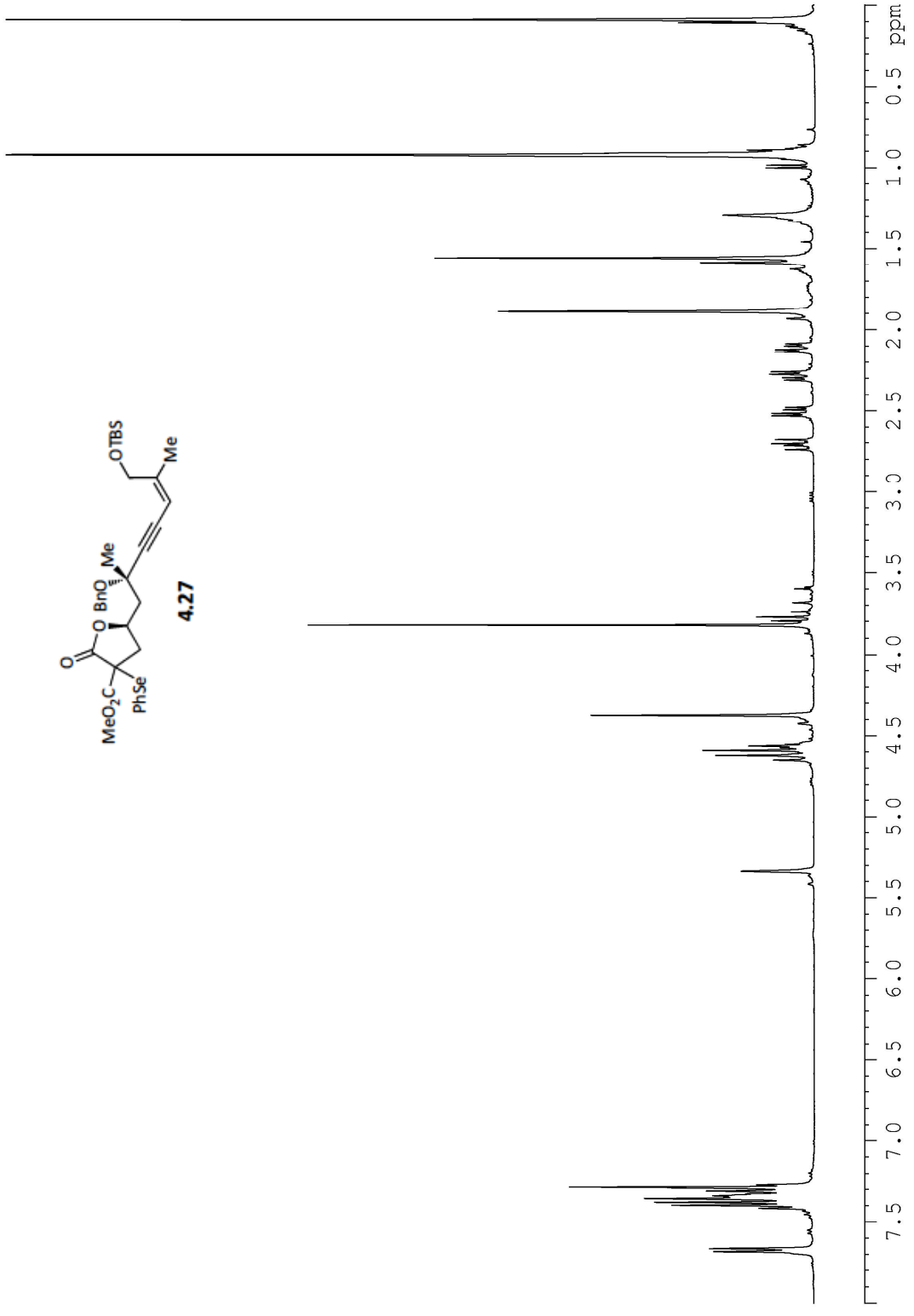


Figure A4.11. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **4.27**.

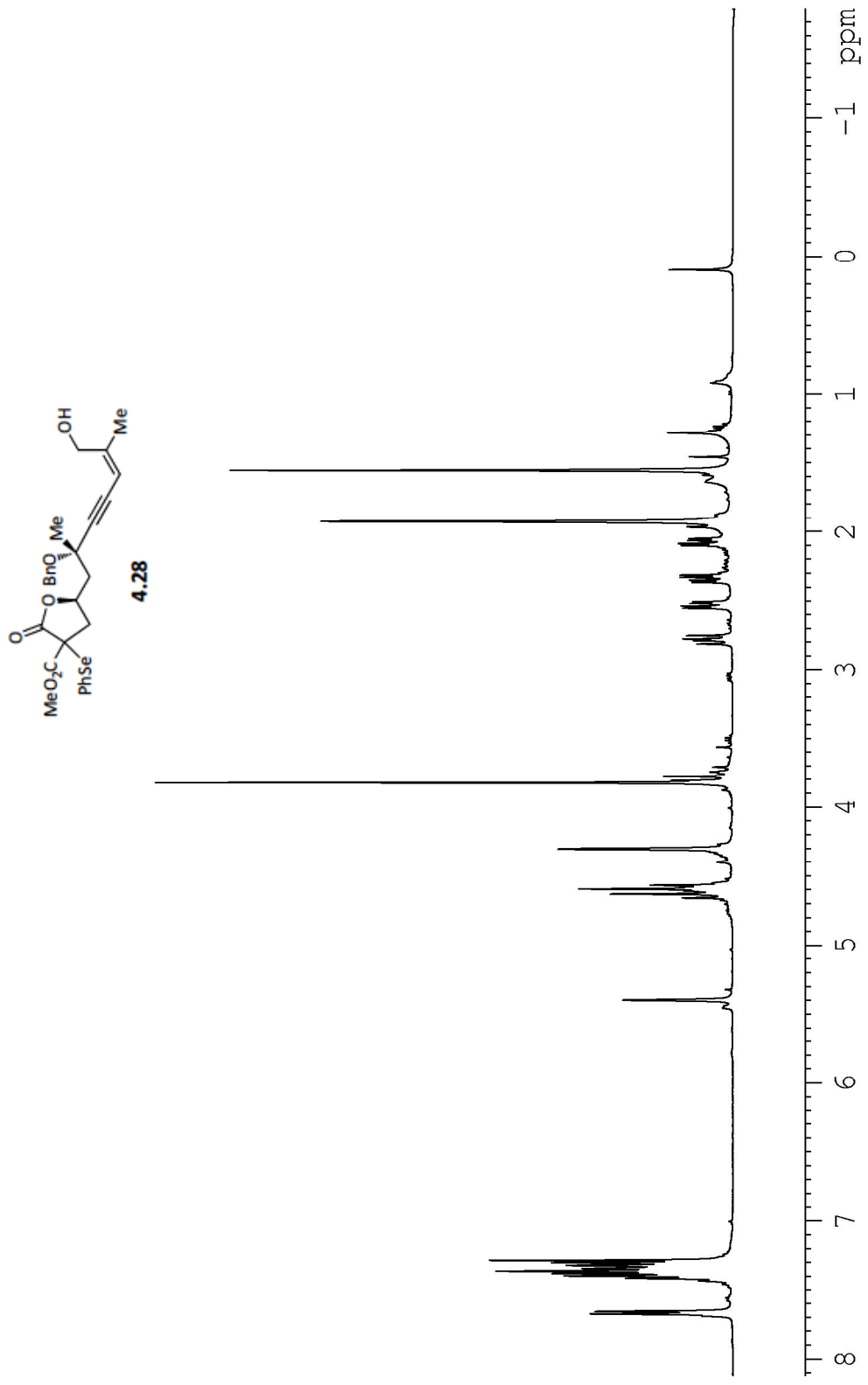


Figure A4.12. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **4.28**.

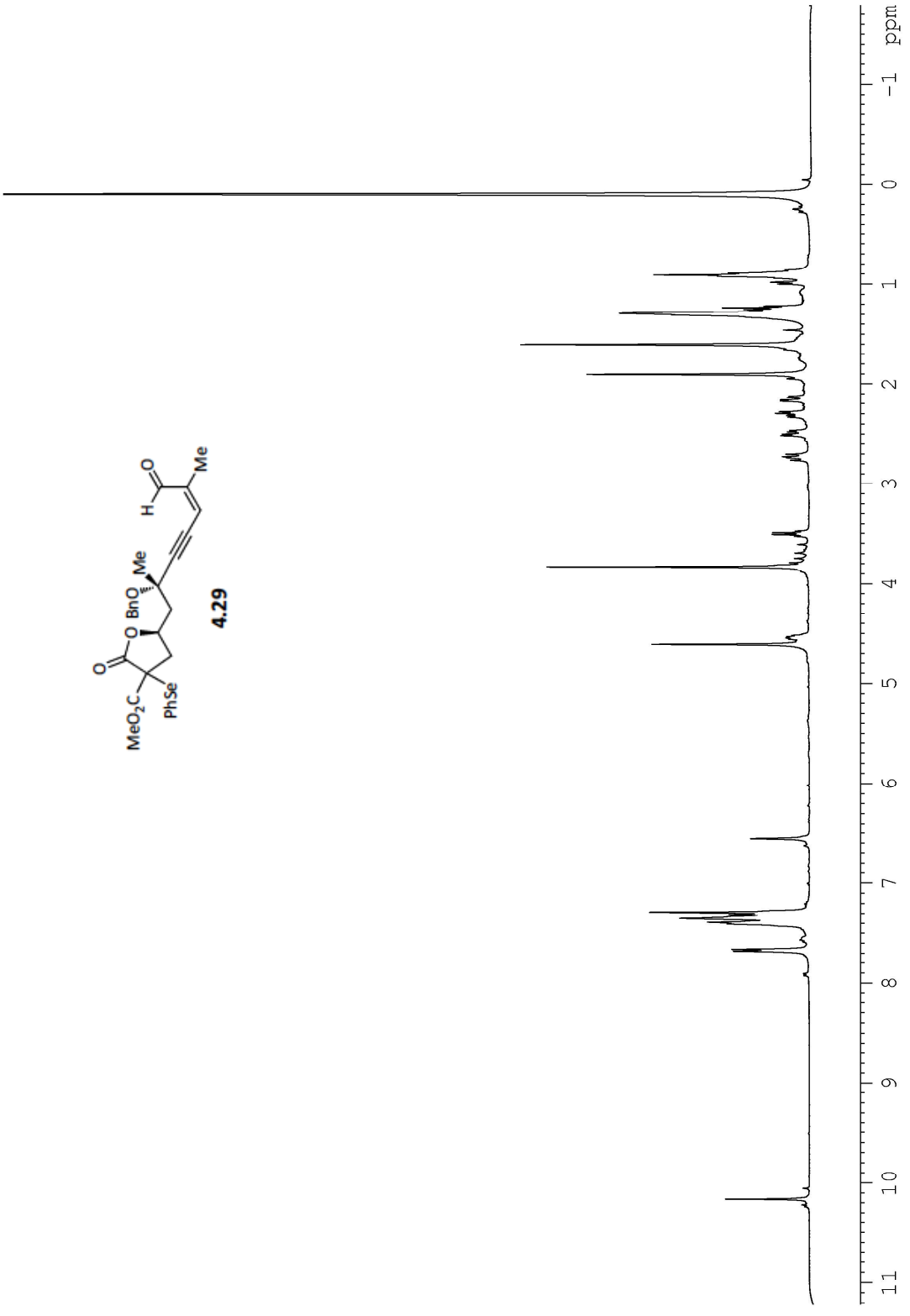


Figure A4.13. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **4.29**.

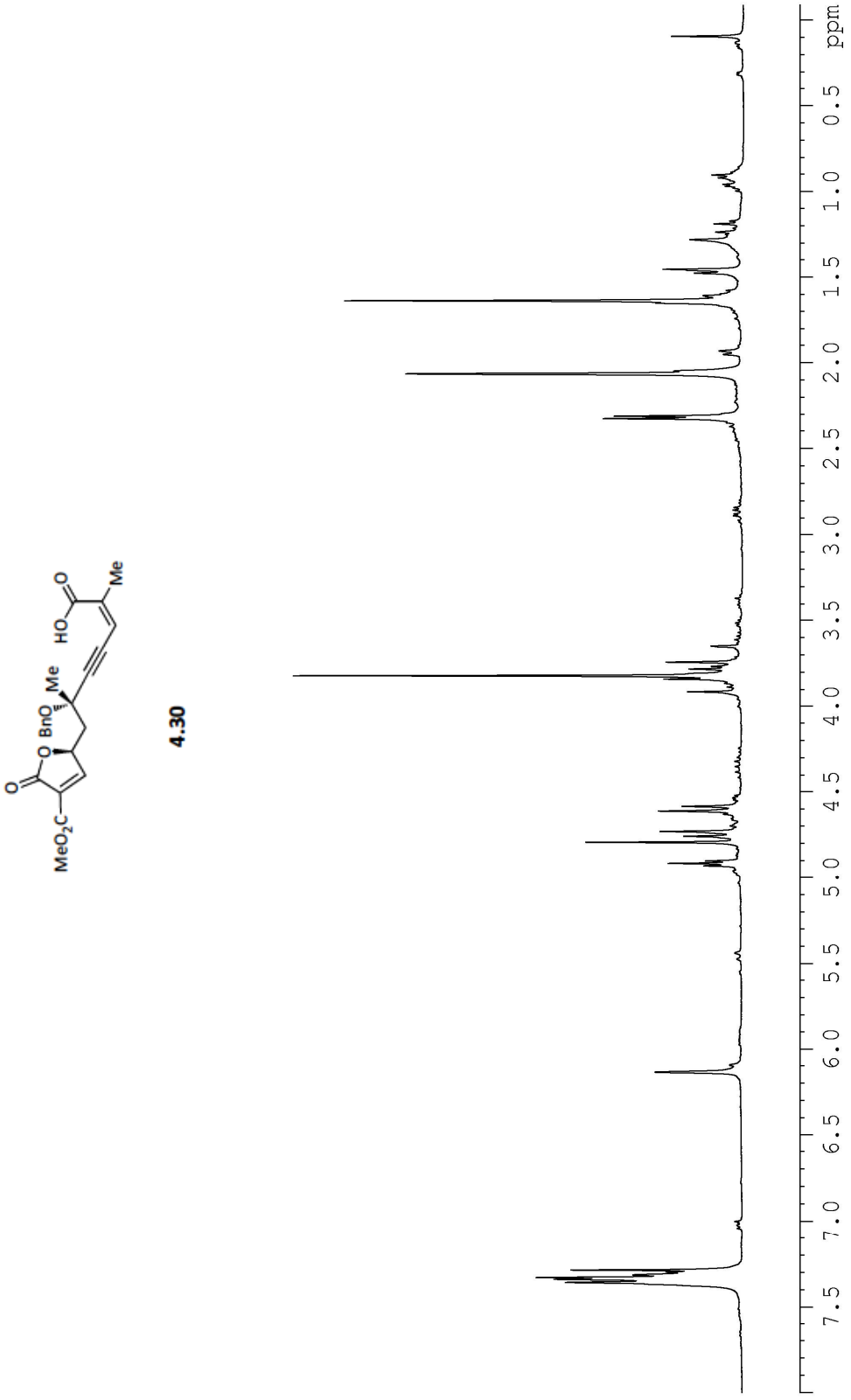


Figure A4.14. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **4.30**.

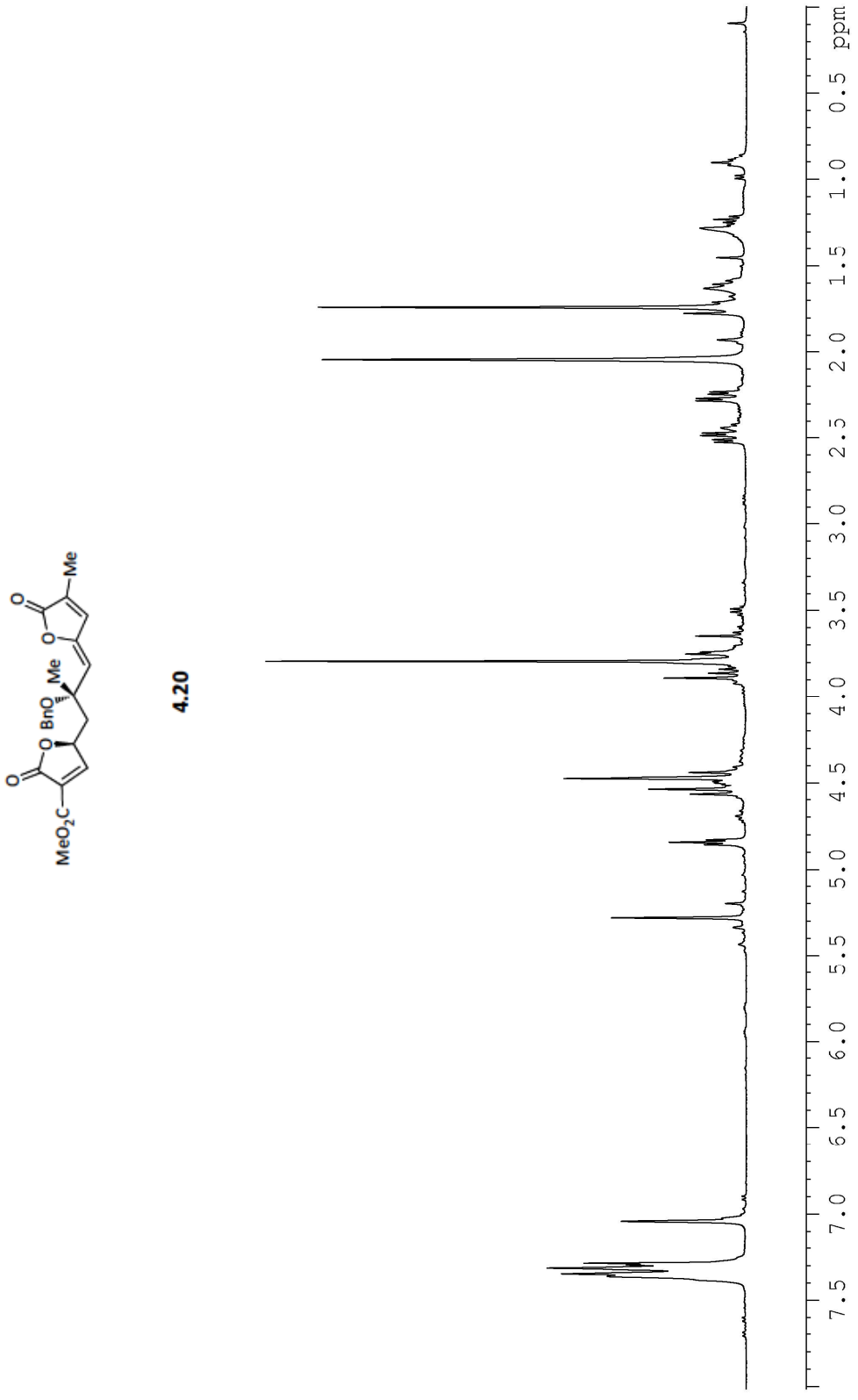


Figure A4.15. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **4.20**.

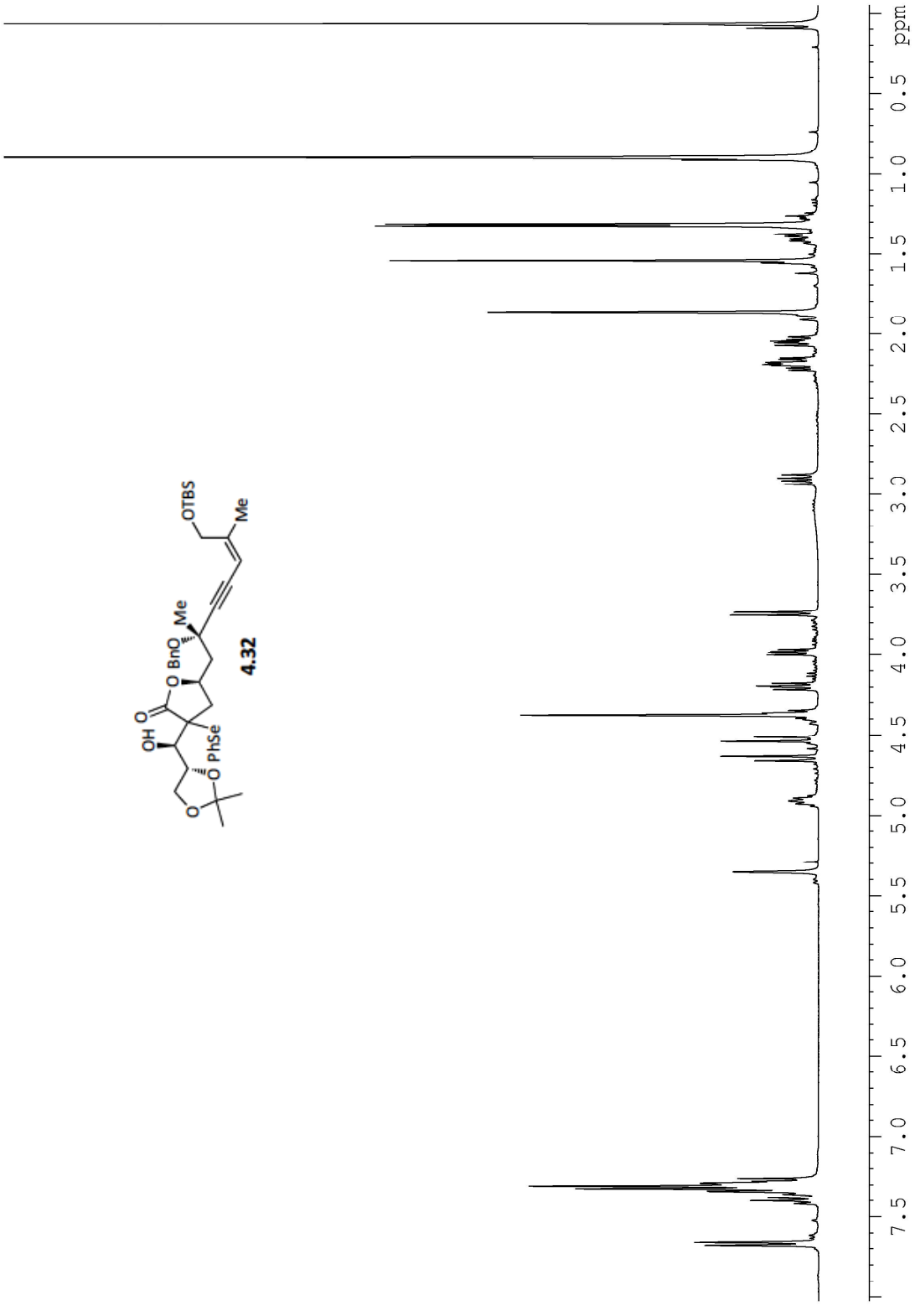


Figure A4.16. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **4.32**.

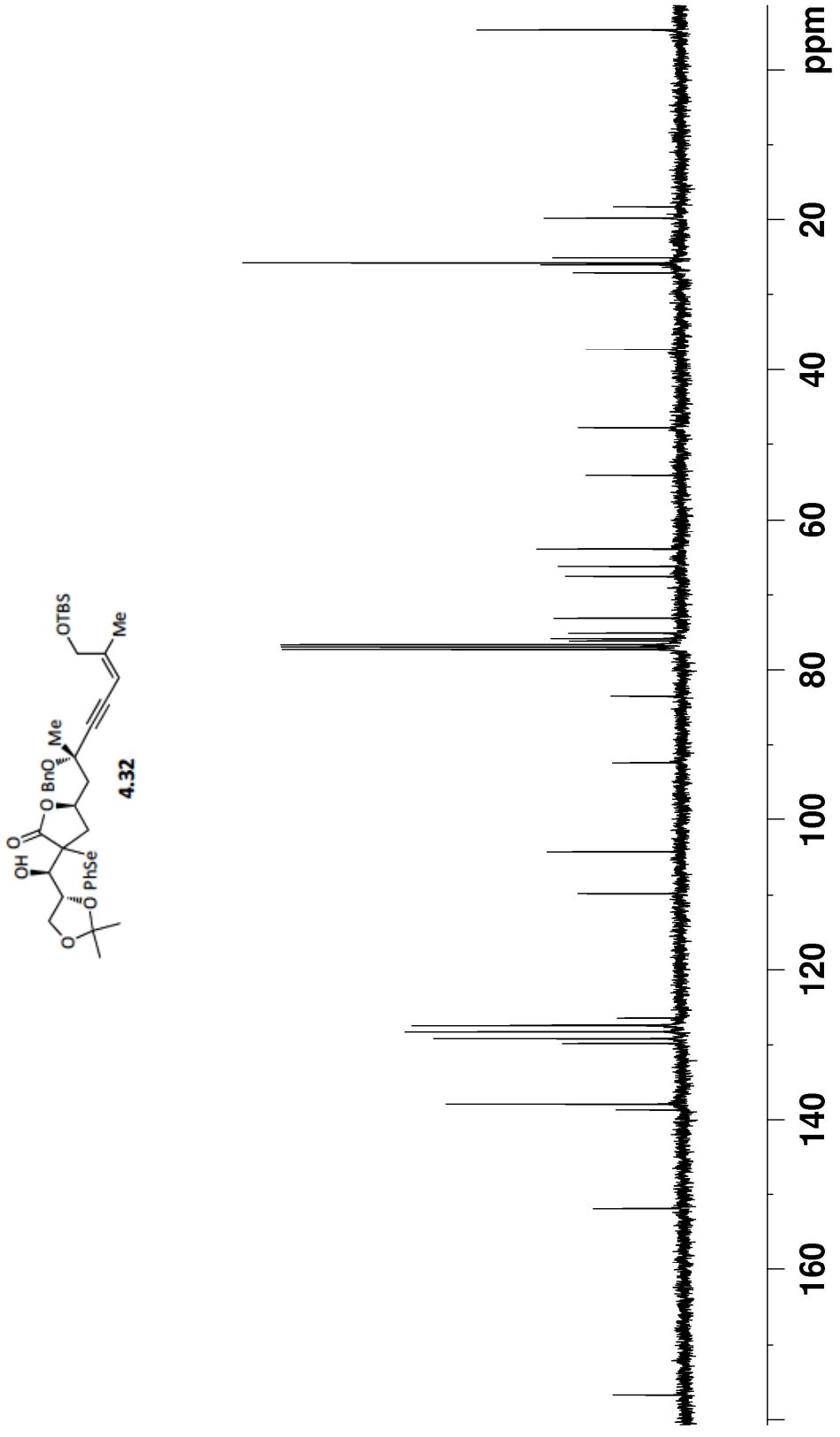


Figure A4.17. ^{13}C NMR spectra (100 MHz, $CDCl_3$) of compound **4.32.**

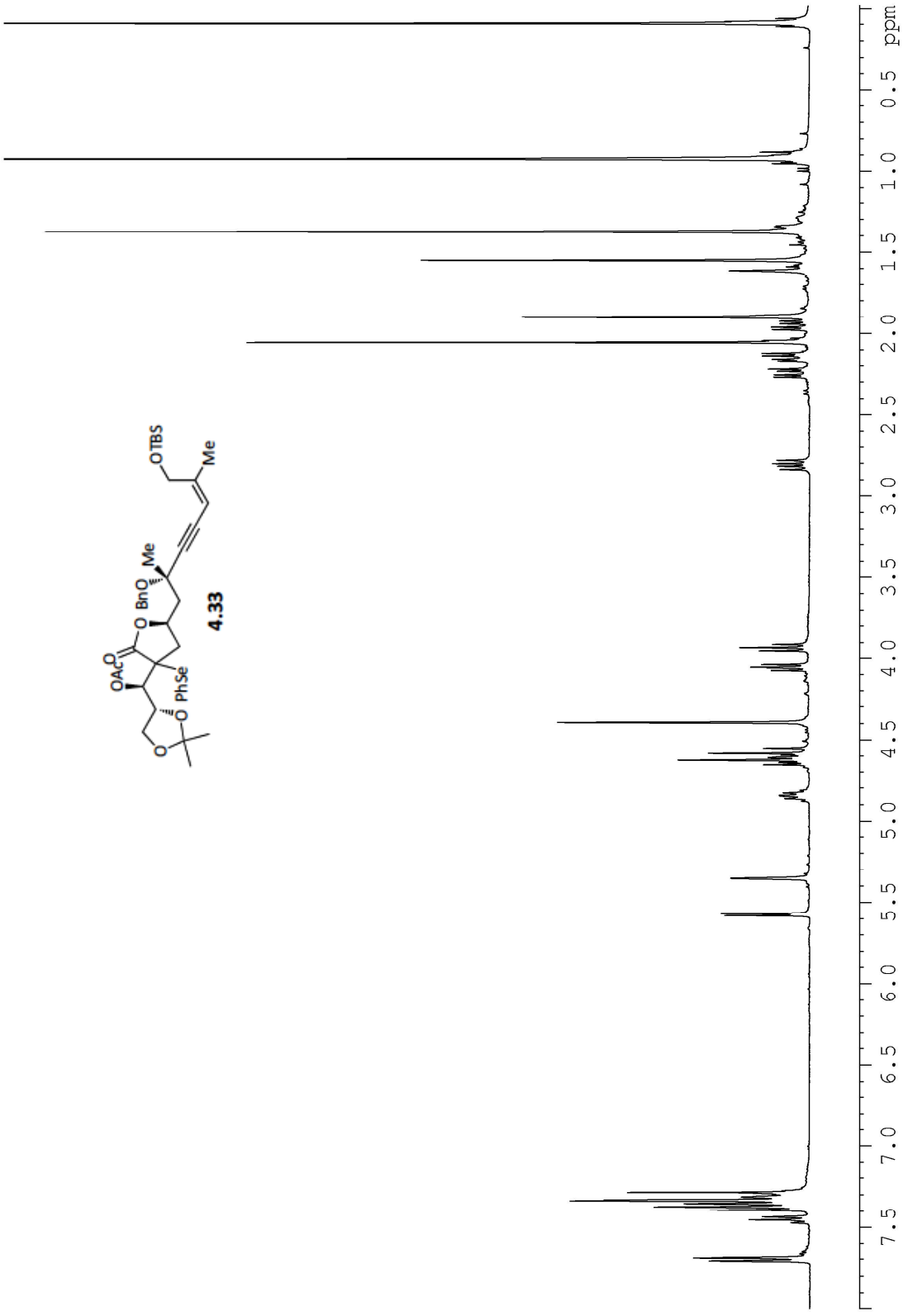


Figure A4.18. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **4.33**.

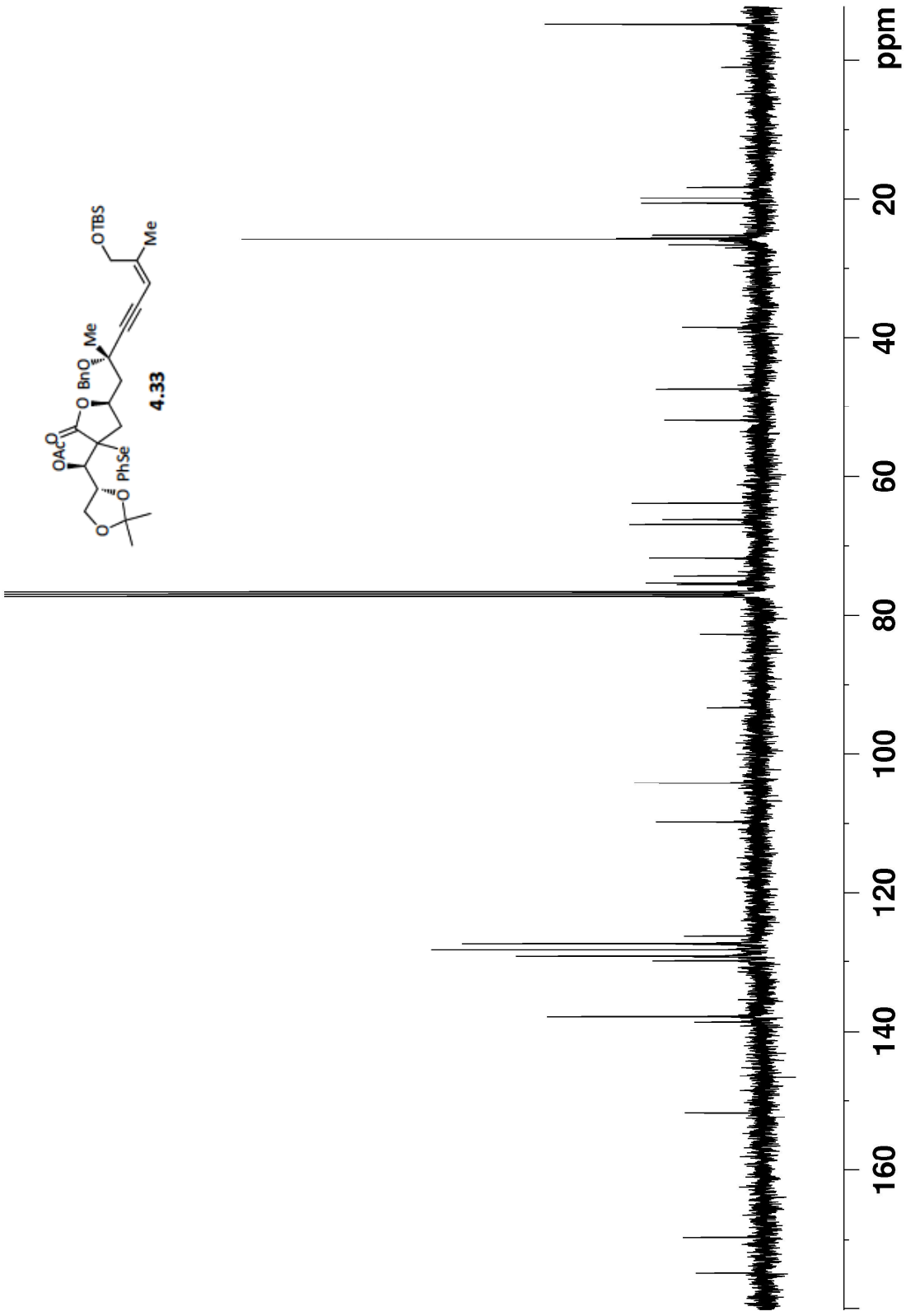


Figure A4.19. ^{13}C NMR spectra (100 MHz, $CDCl_3$) of compound **4.33.**

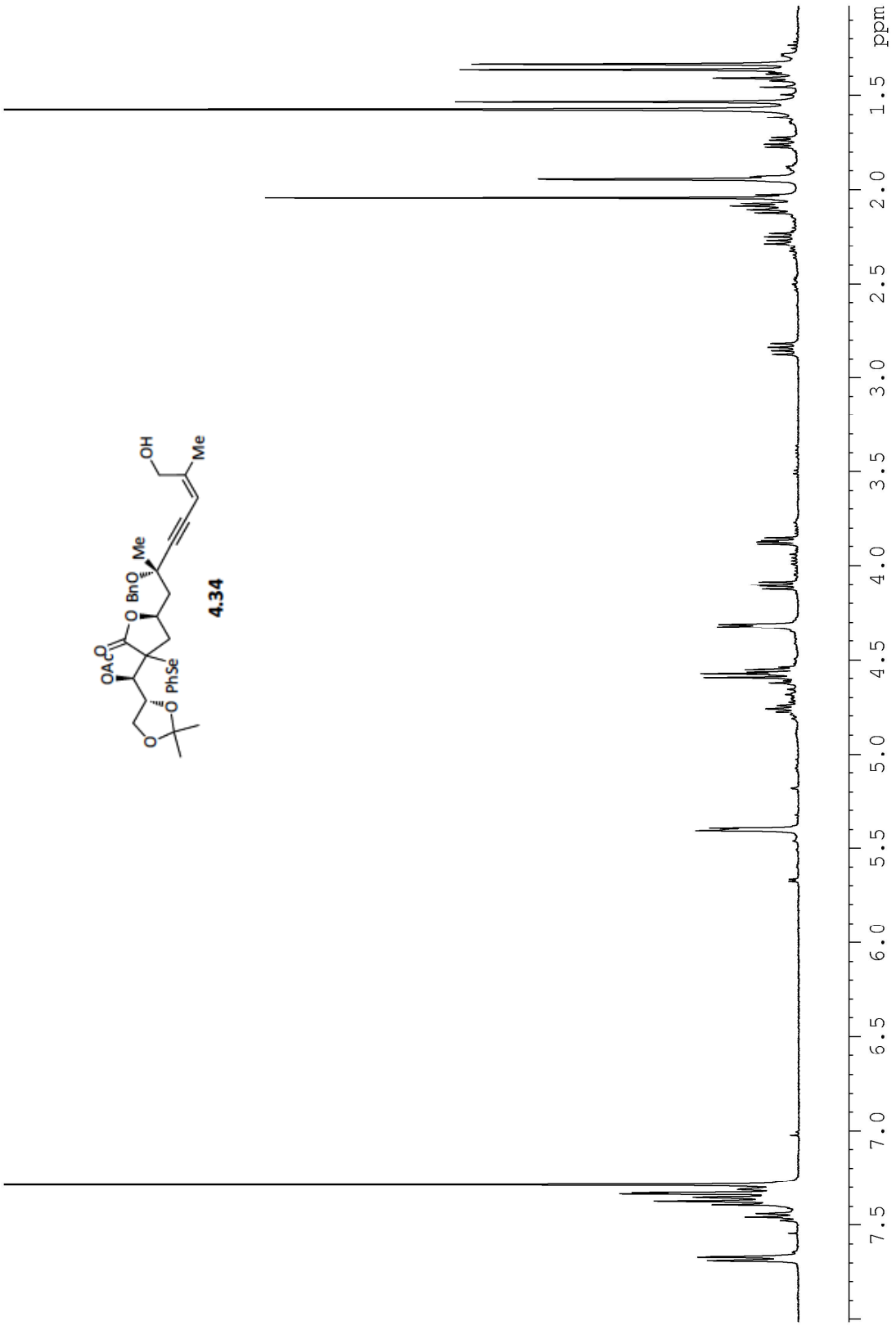


Figure A4.20. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **4.34**.

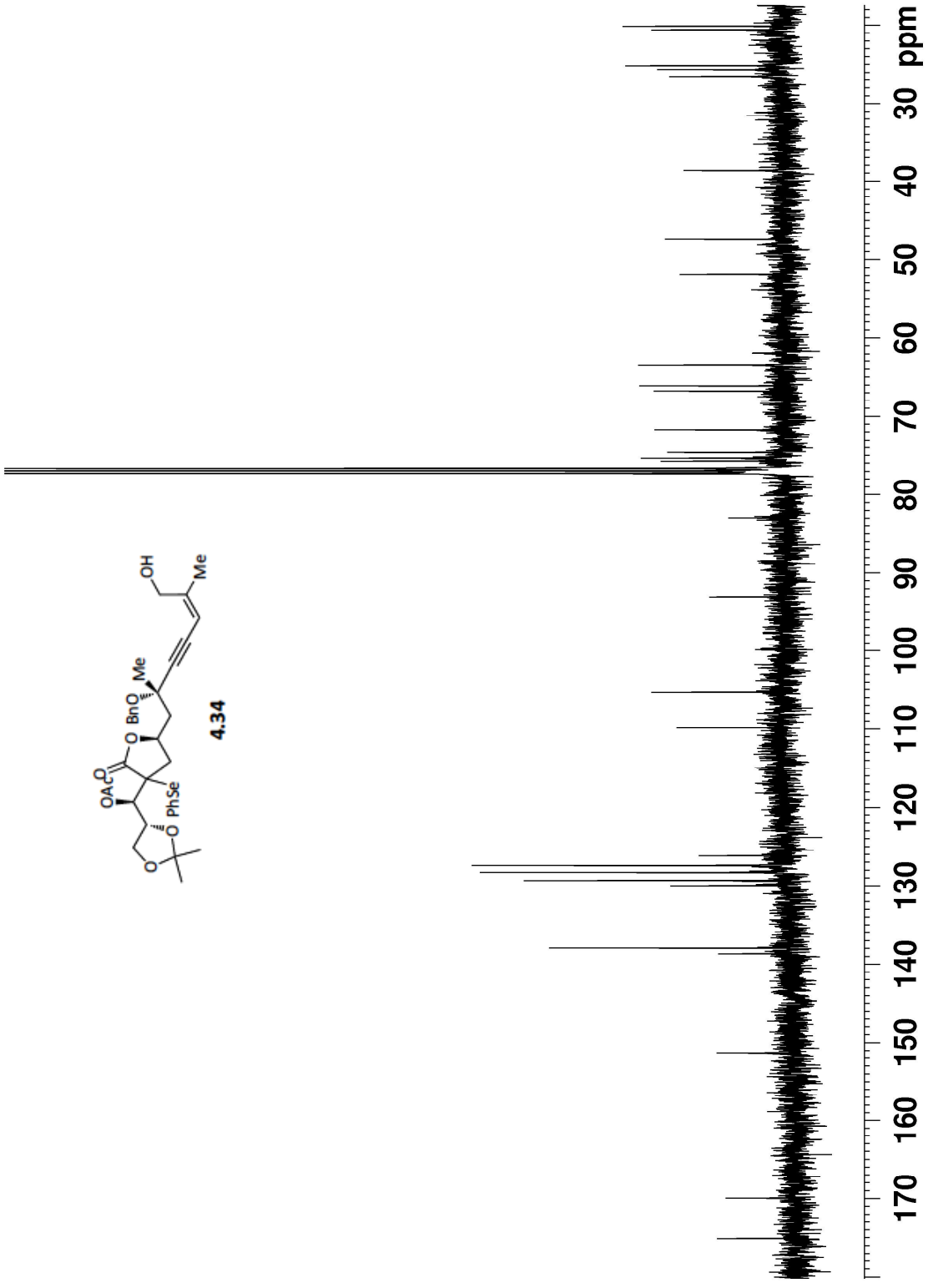


Figure A4.21. ^{13}C NMR spectra (100 MHz, $CDCl_3$) of compound **4.34.**

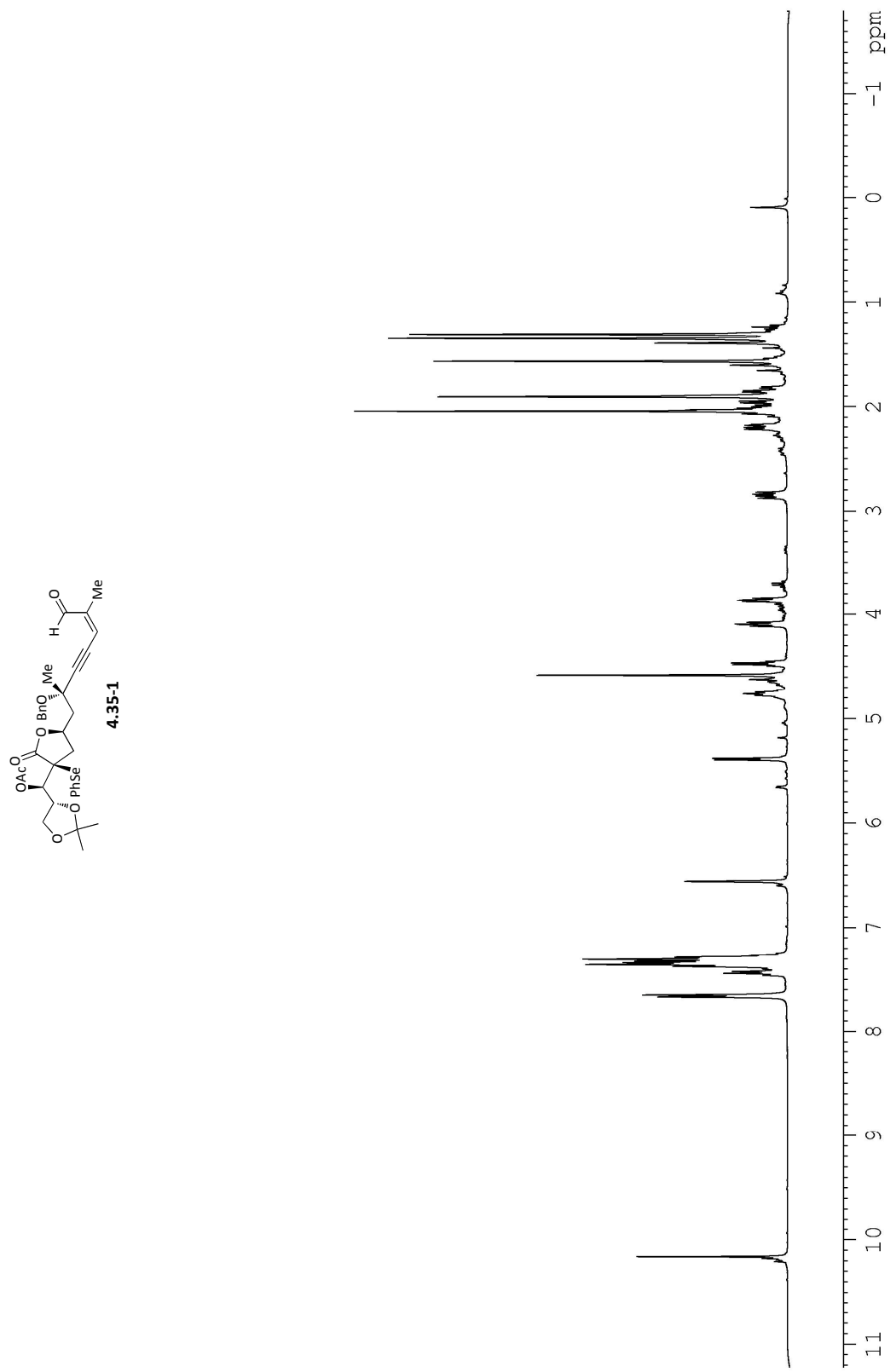


Figure A4.22. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **4.35-1**.

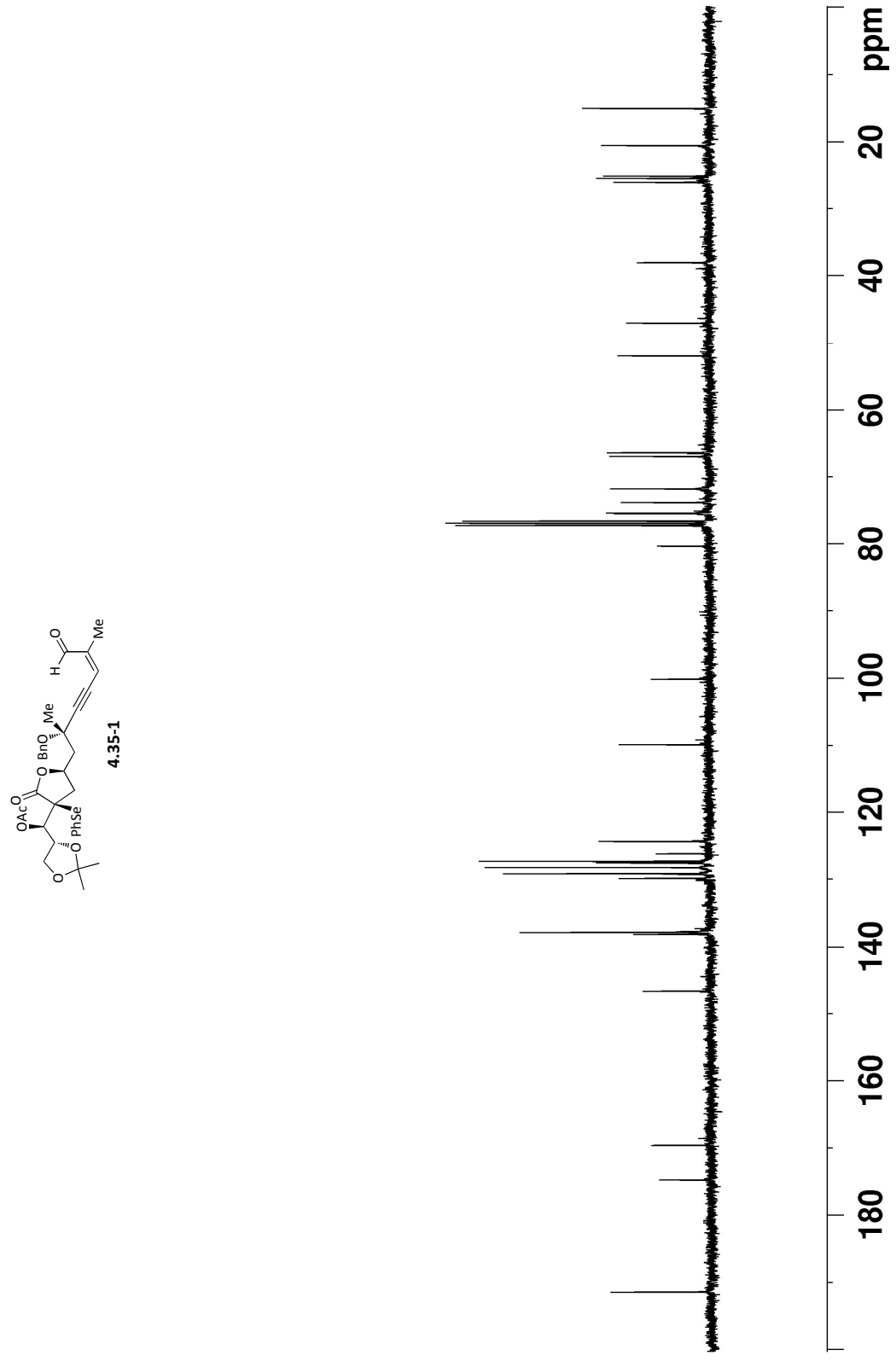


Figure A4.23 ^{13}C NMR spectra (100 MHz, $CDCl_3$) of compound **4.35-1.**

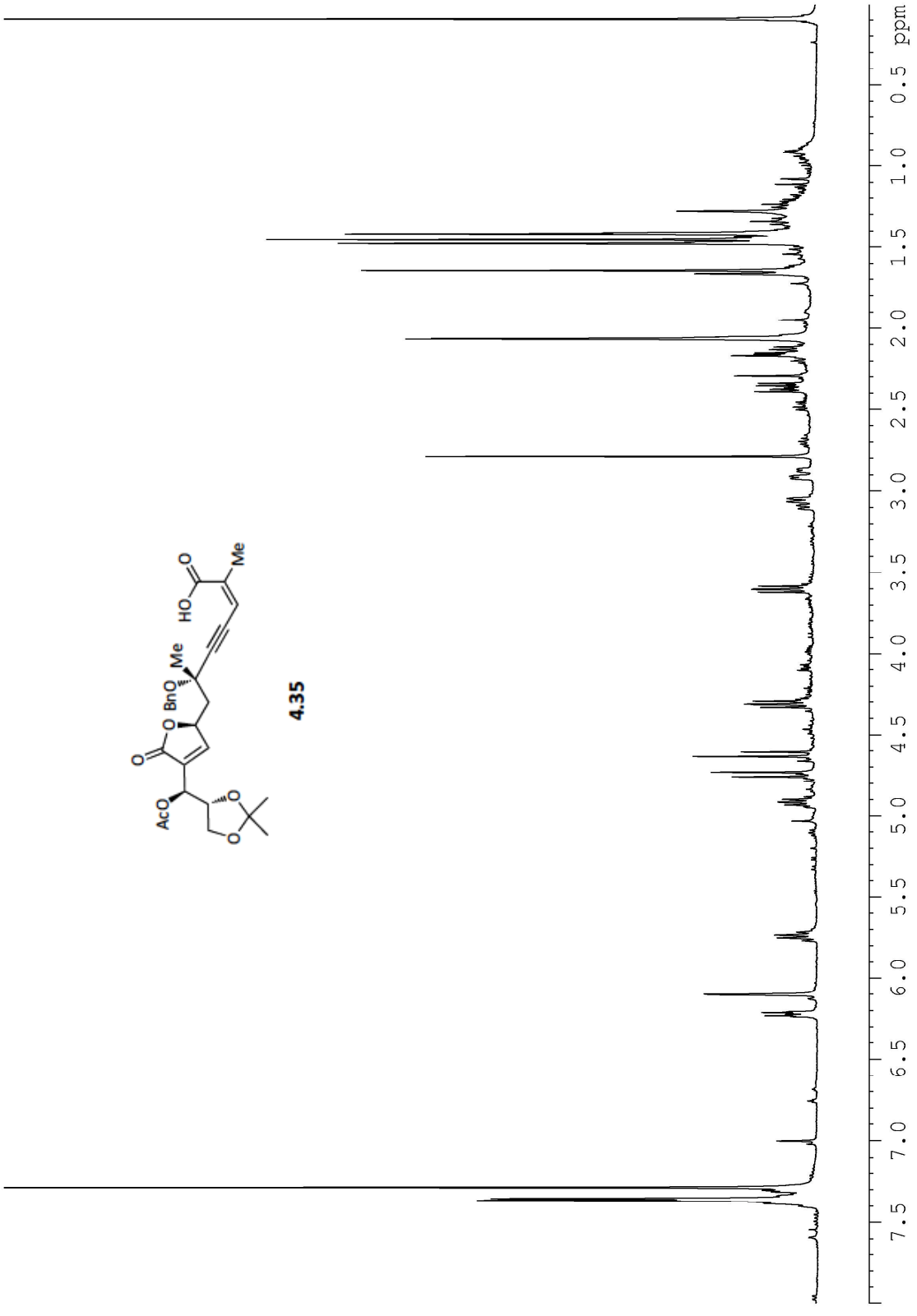


Figure A4.24. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **4.35**.

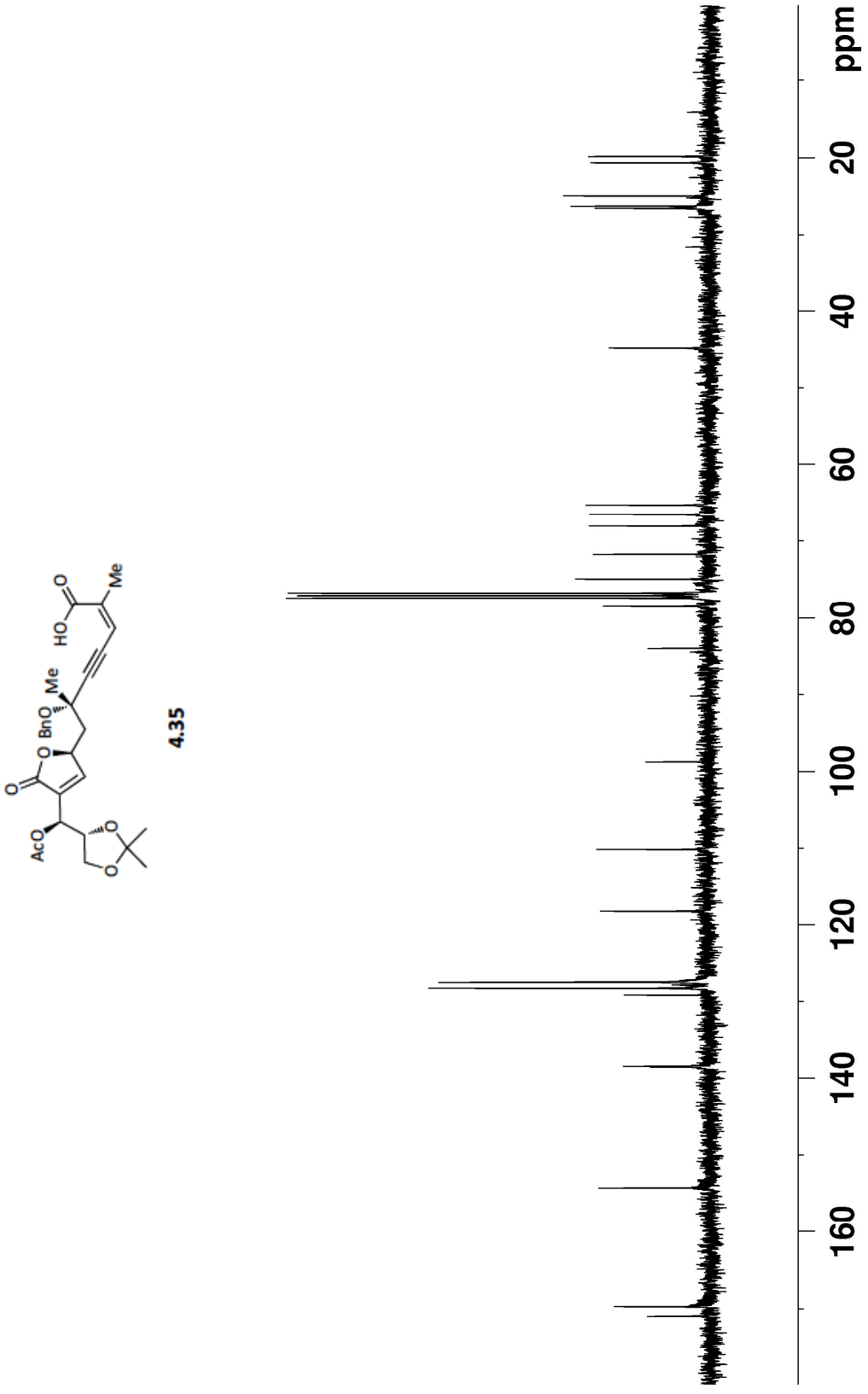


Figure A4.25. ^{13}C NMR spectra (100 MHz, $CDCl_3$) of compound **4.35.**

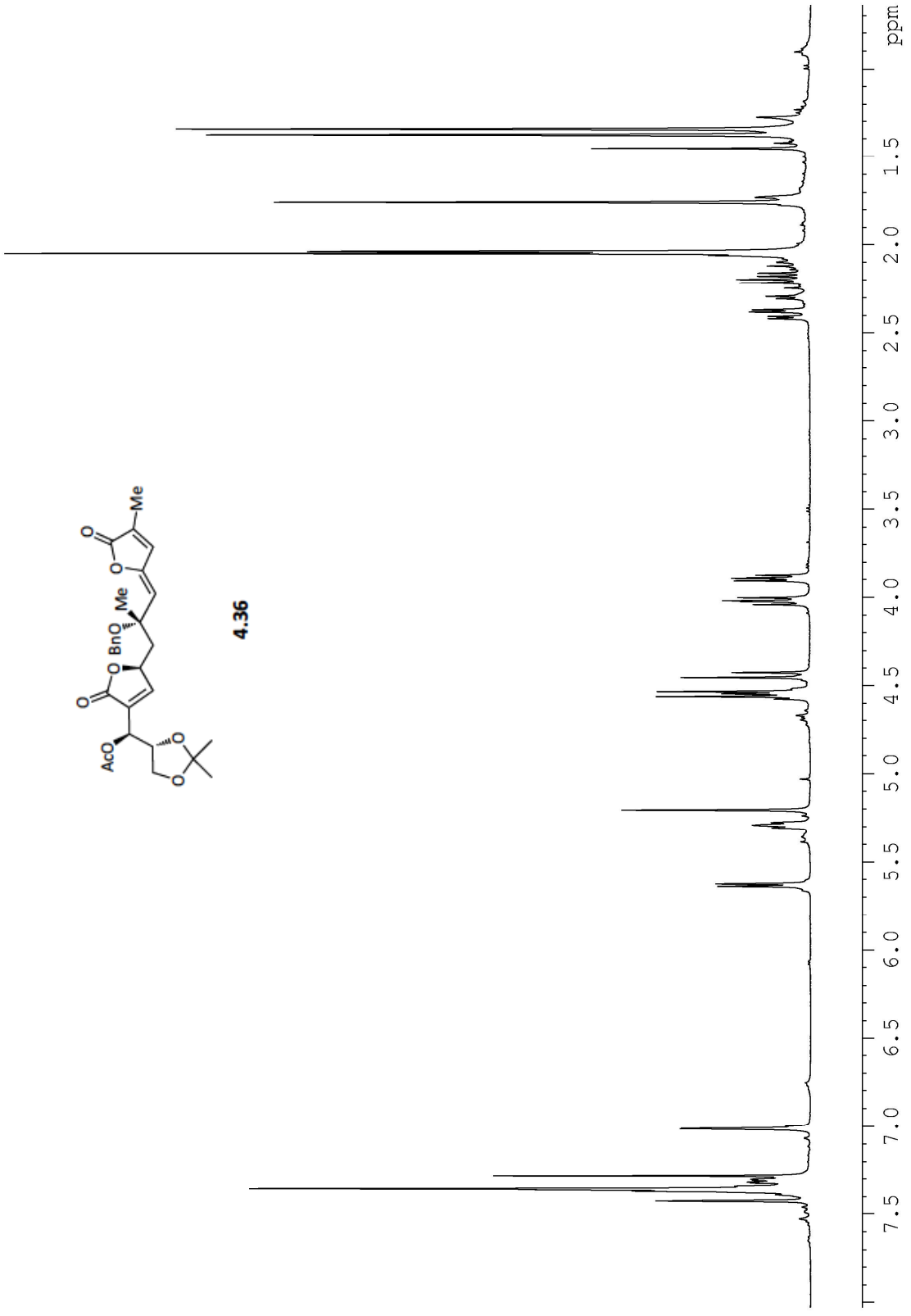


Figure A4.26. ^{1}H NMR spectra (600 MHz, $CDCl_3$) of compound **4.36**.

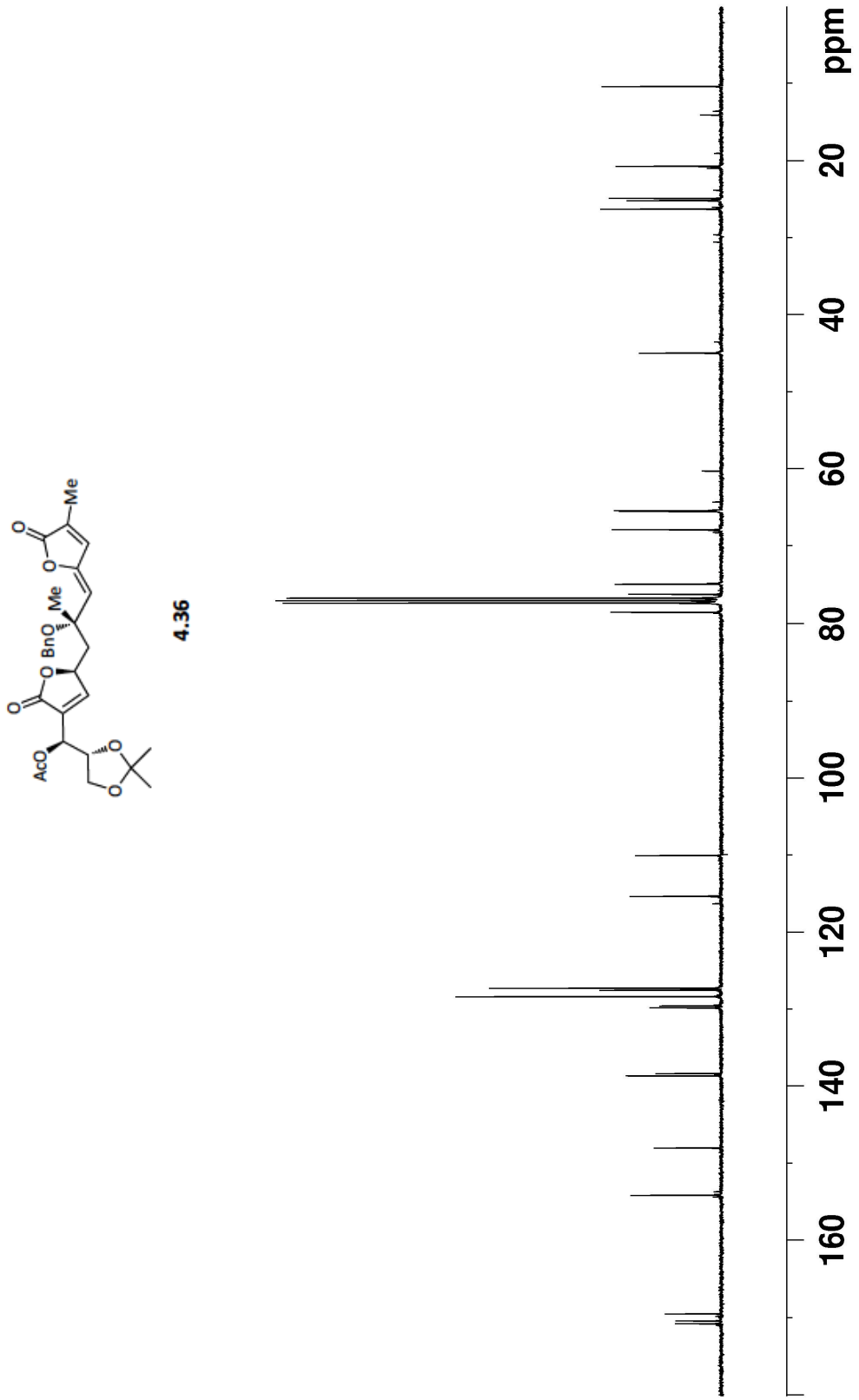


Figure A4.27. ^{13}C NMR spectra (150 MHz, $CDCl_3$) of compound **4.36.**

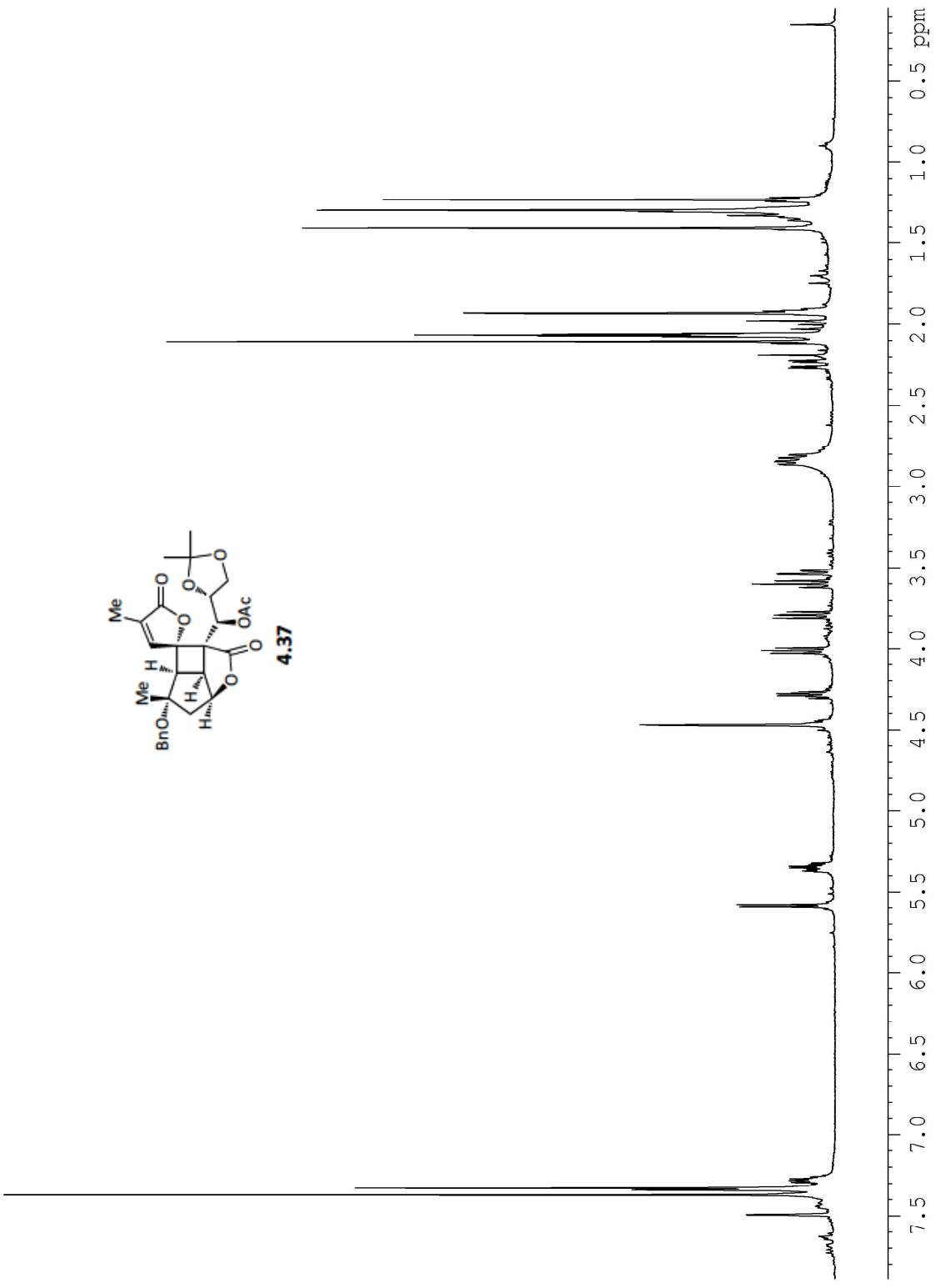


Figure A4.28. ^{1}H NMR spectra (600 MHz, $CDCl_3$) of compound **4.37**.

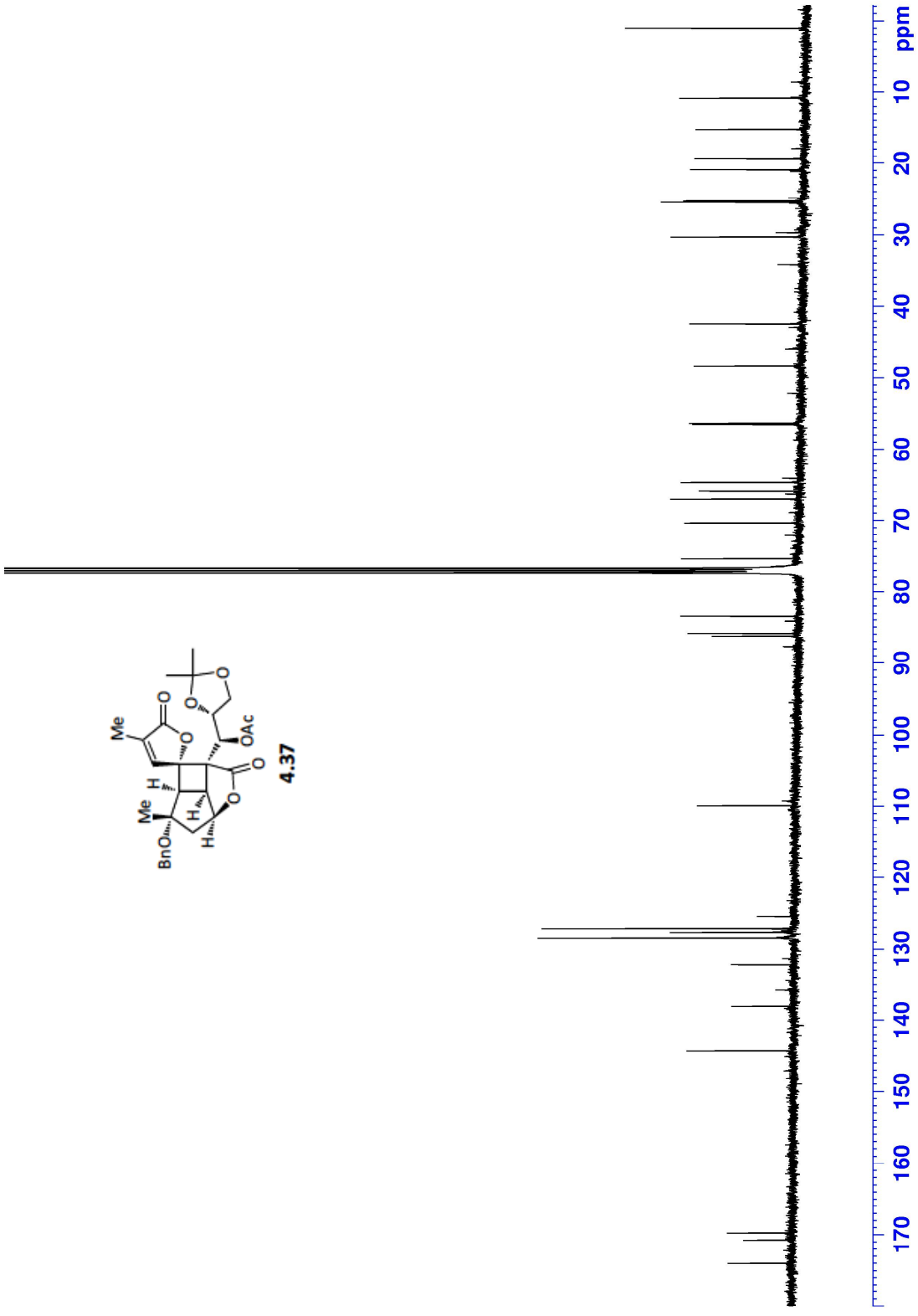


Figure A4.29. ^{13}C NMR spectra (150 MHz, $CDCl_3$) of compound **4.37.**

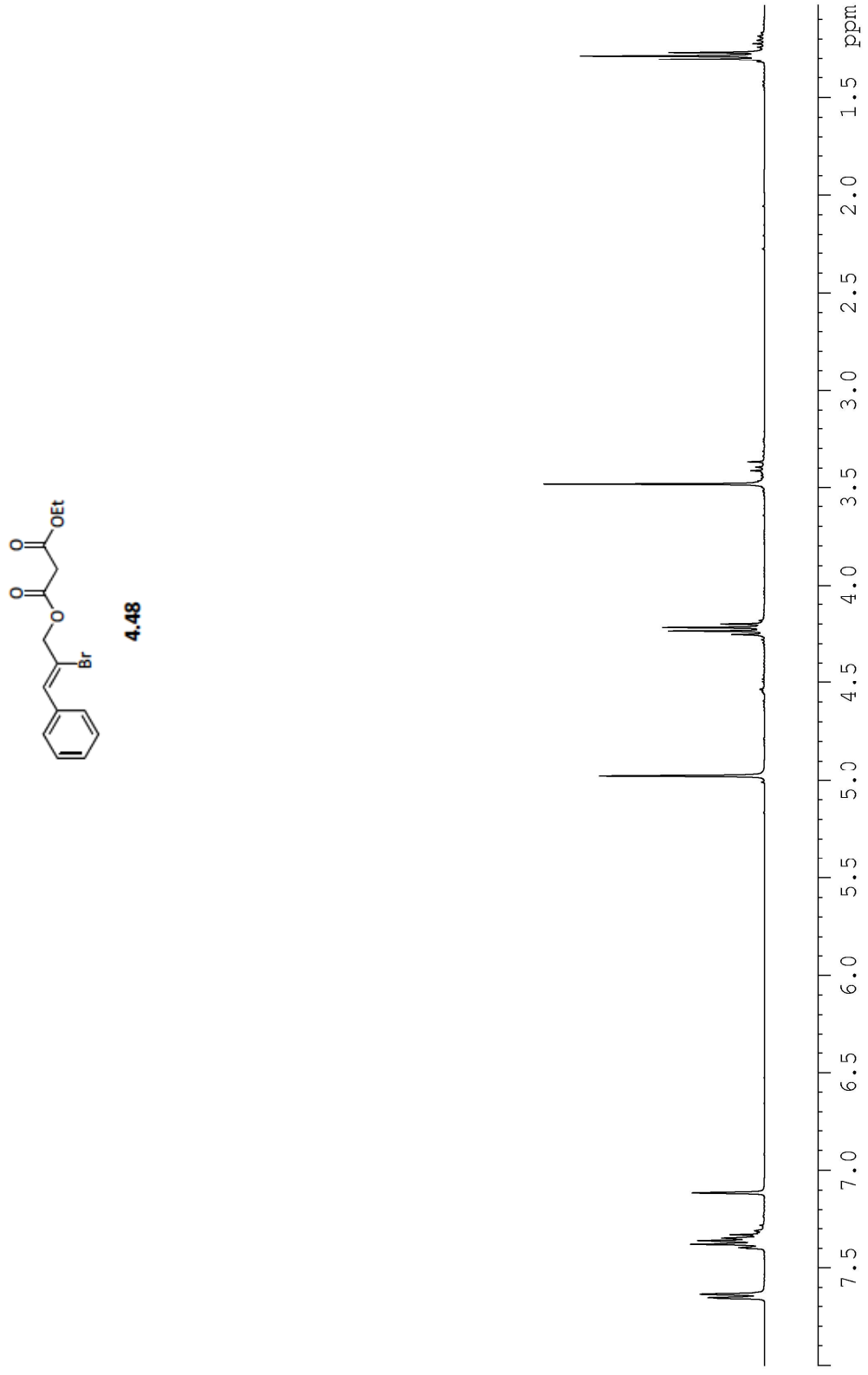


Figure A4.30. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **4.48**.

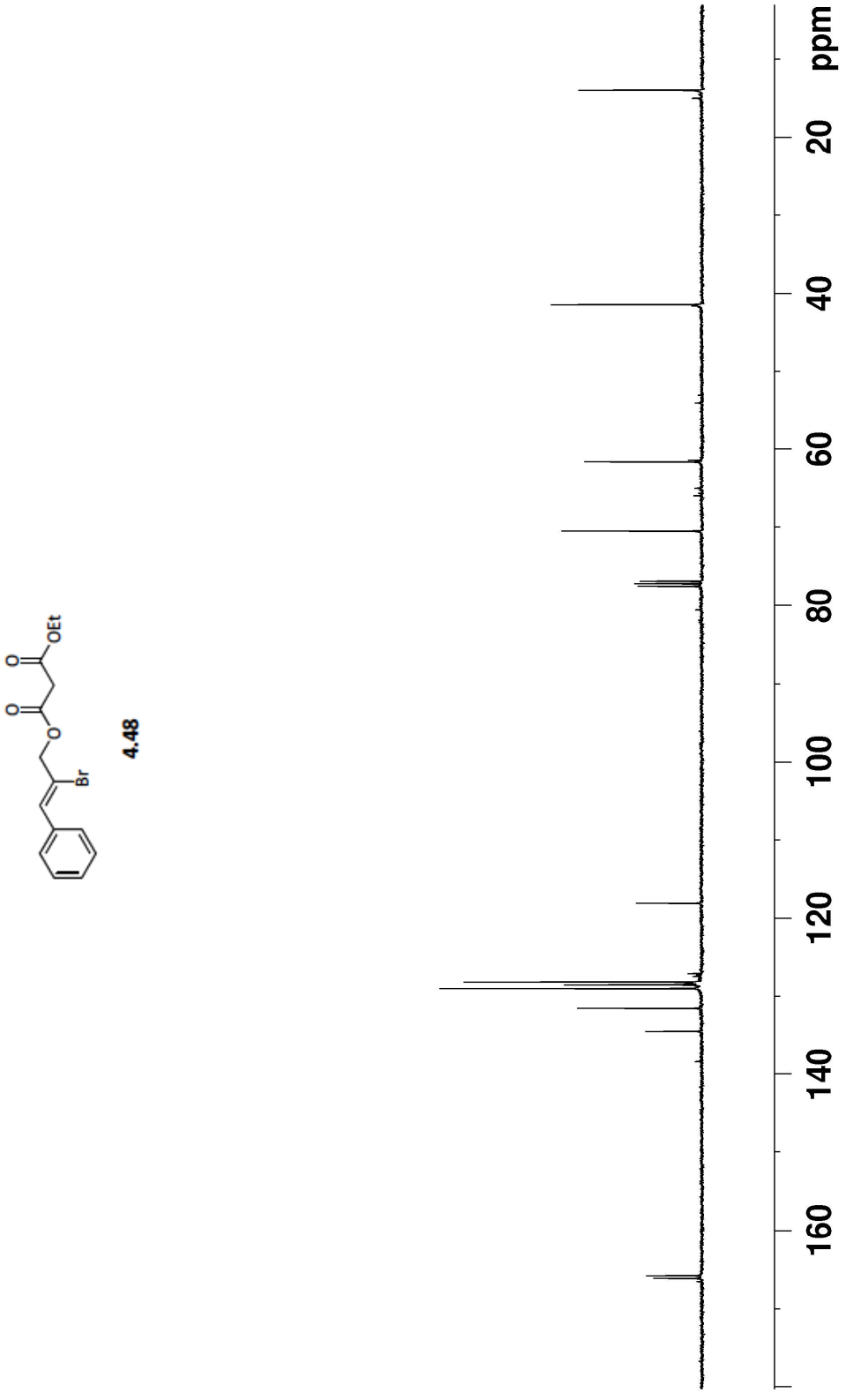


Figure A4.31. ^{13}C NMR spectra (100 MHz, $CDCl_3$) of compound **4.48.**

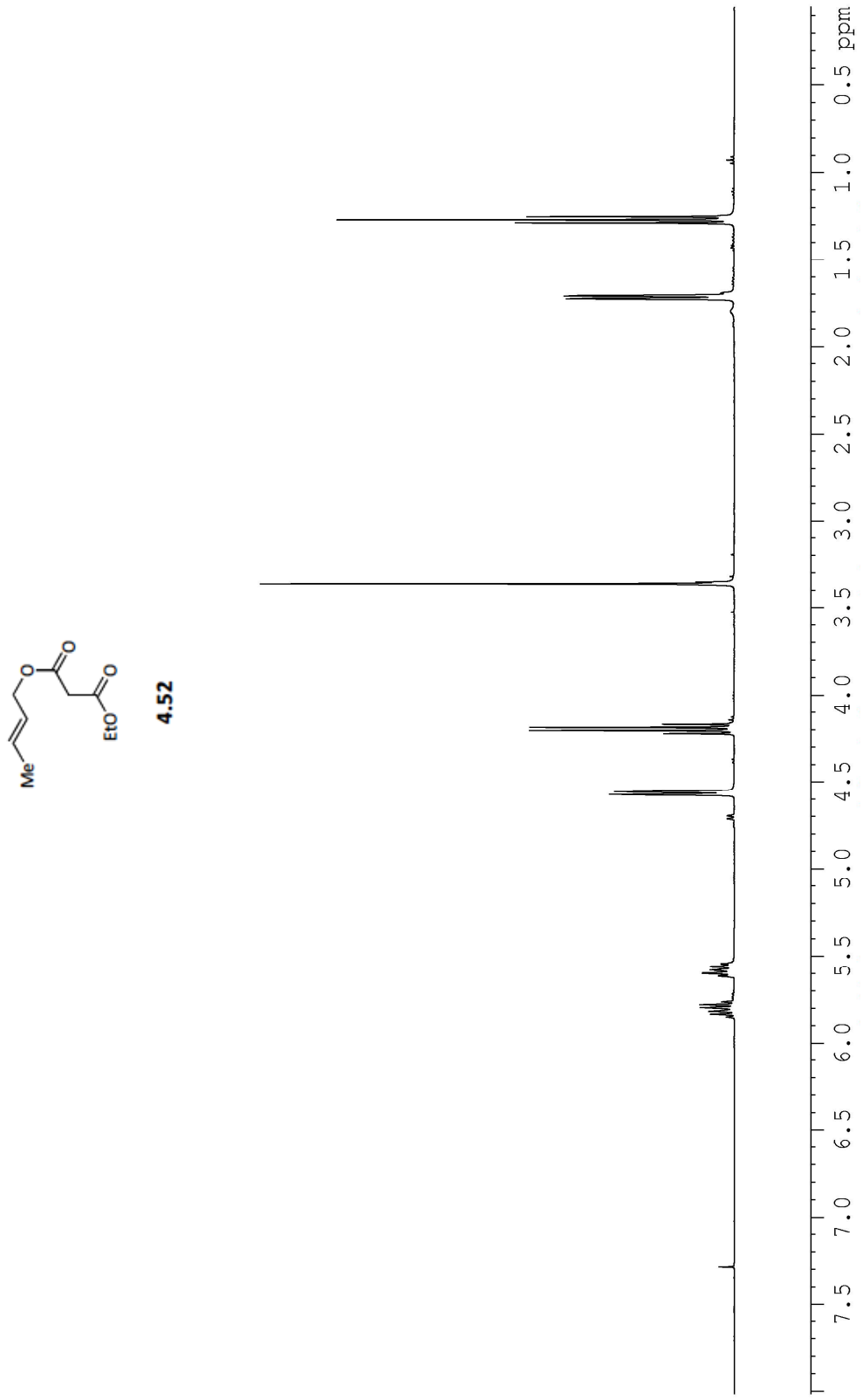


Figure A4.32. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **4.52**.

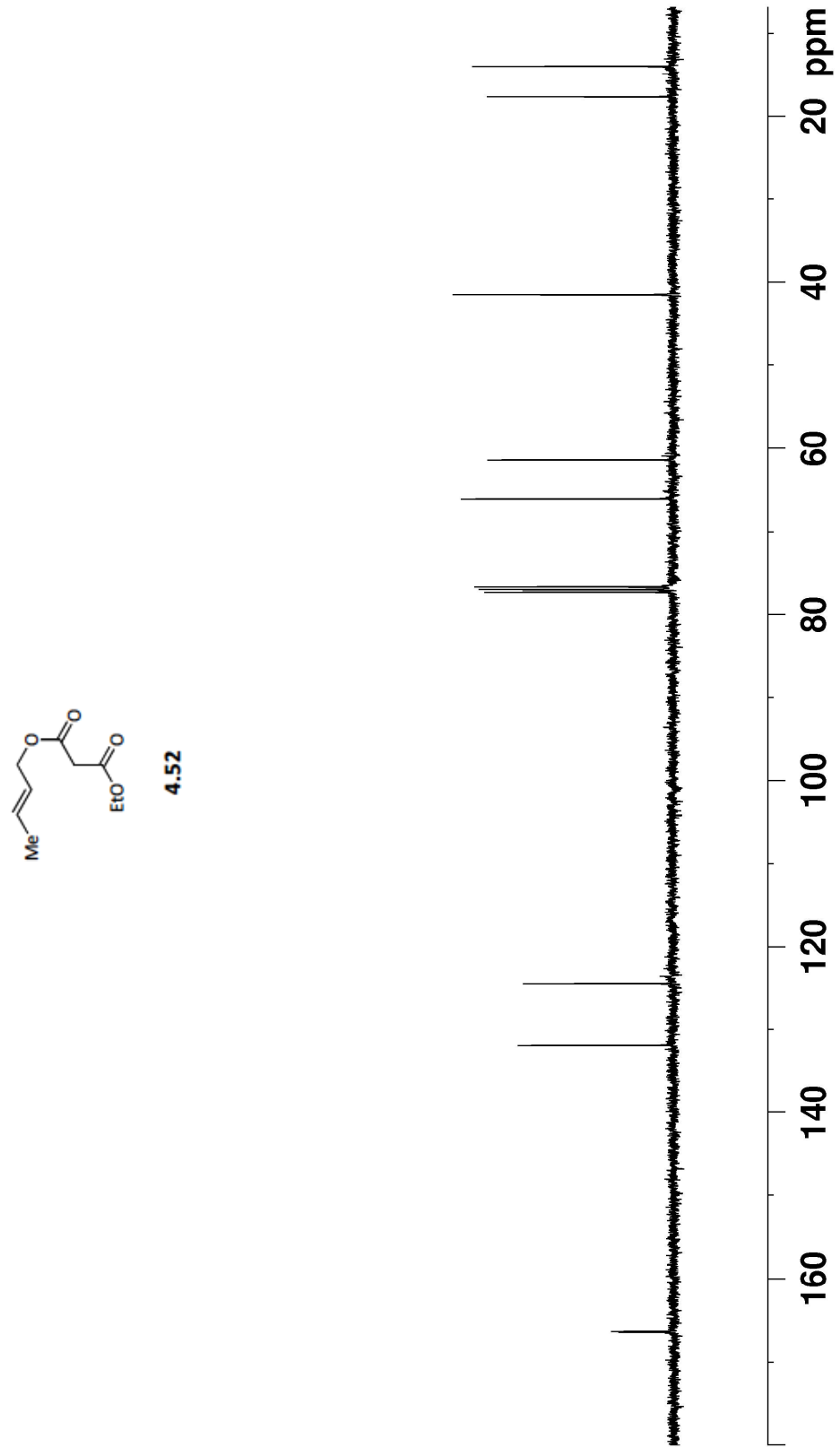


Figure A4.33. ^{13}C NMR spectra (100 MHz, $CDCl_3$) of compound **4.52.**

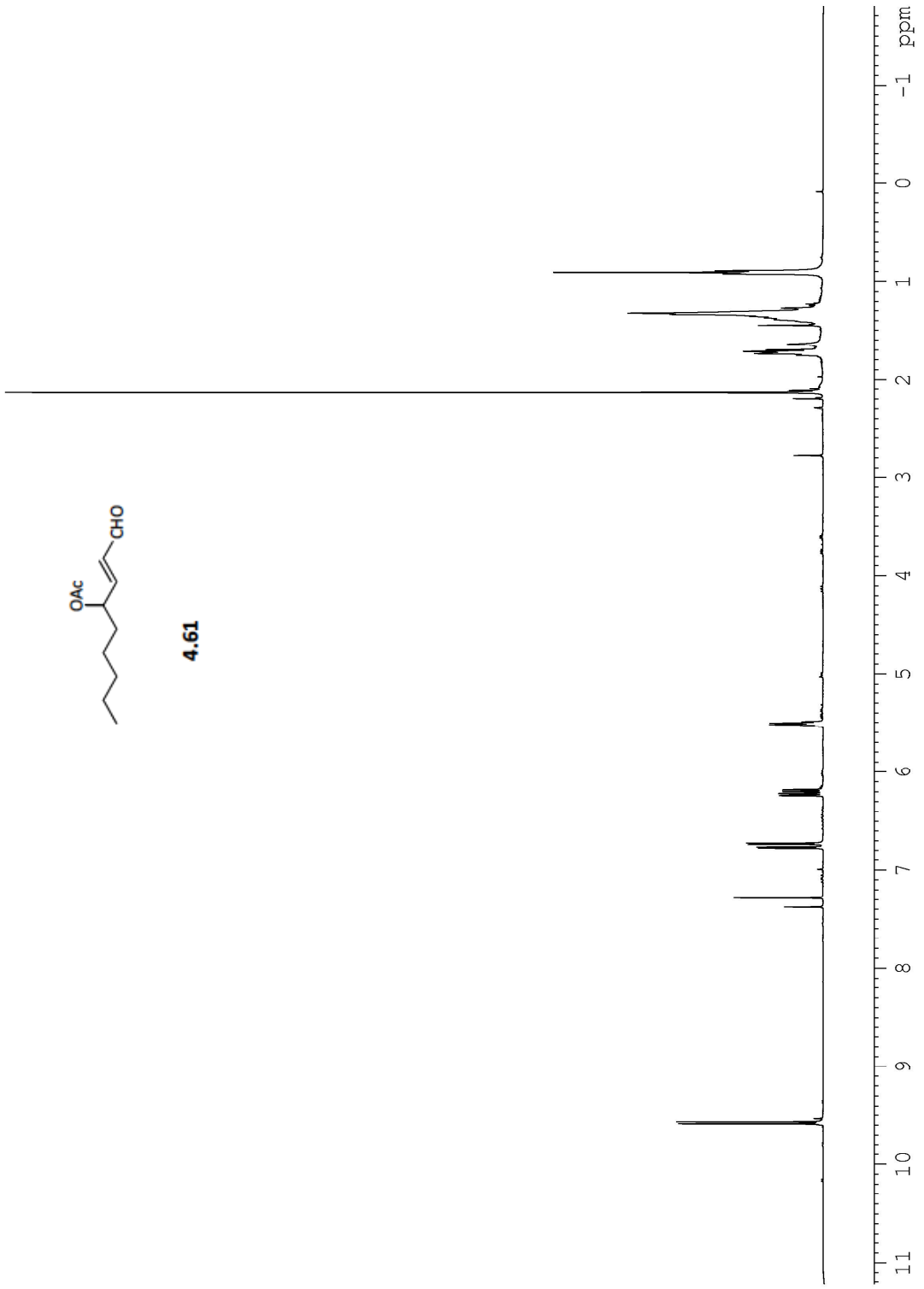


Figure A4.34. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **4.61.**

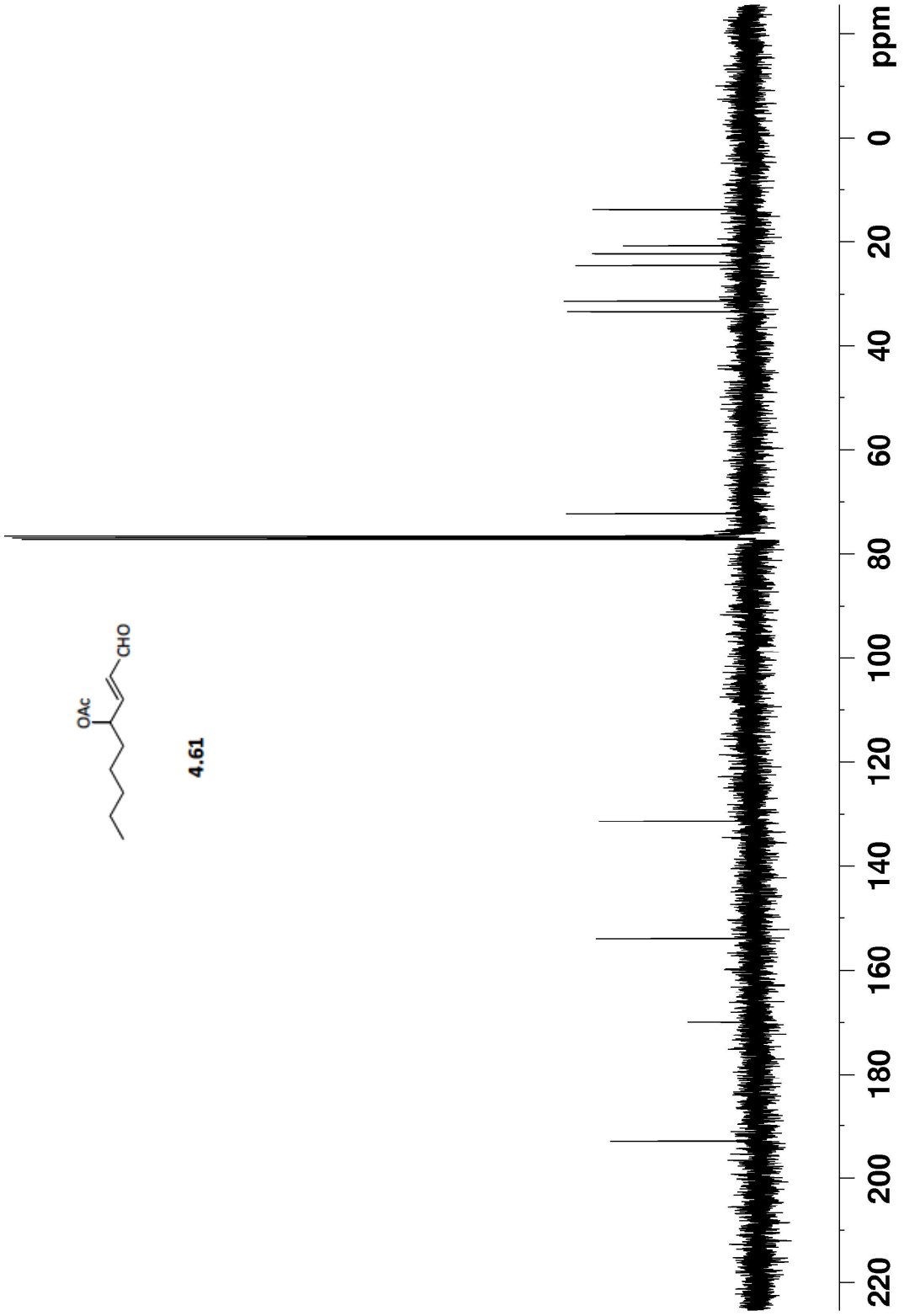


Figure A4.35. ^{13}C NMR spectra (100 MHz, $CDCl_3$) of compound **4.61.**

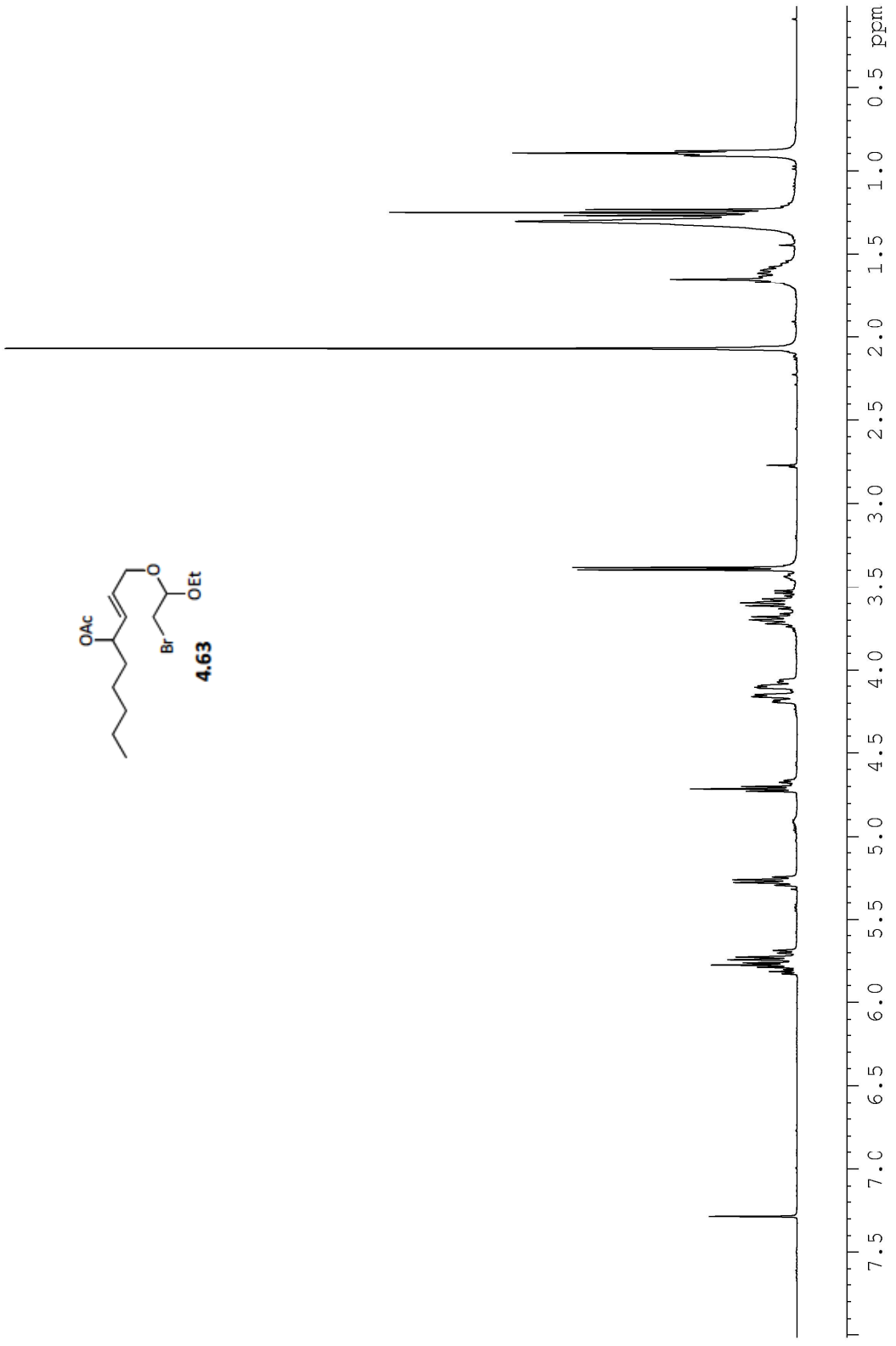


Figure A4.36. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **4.63.**

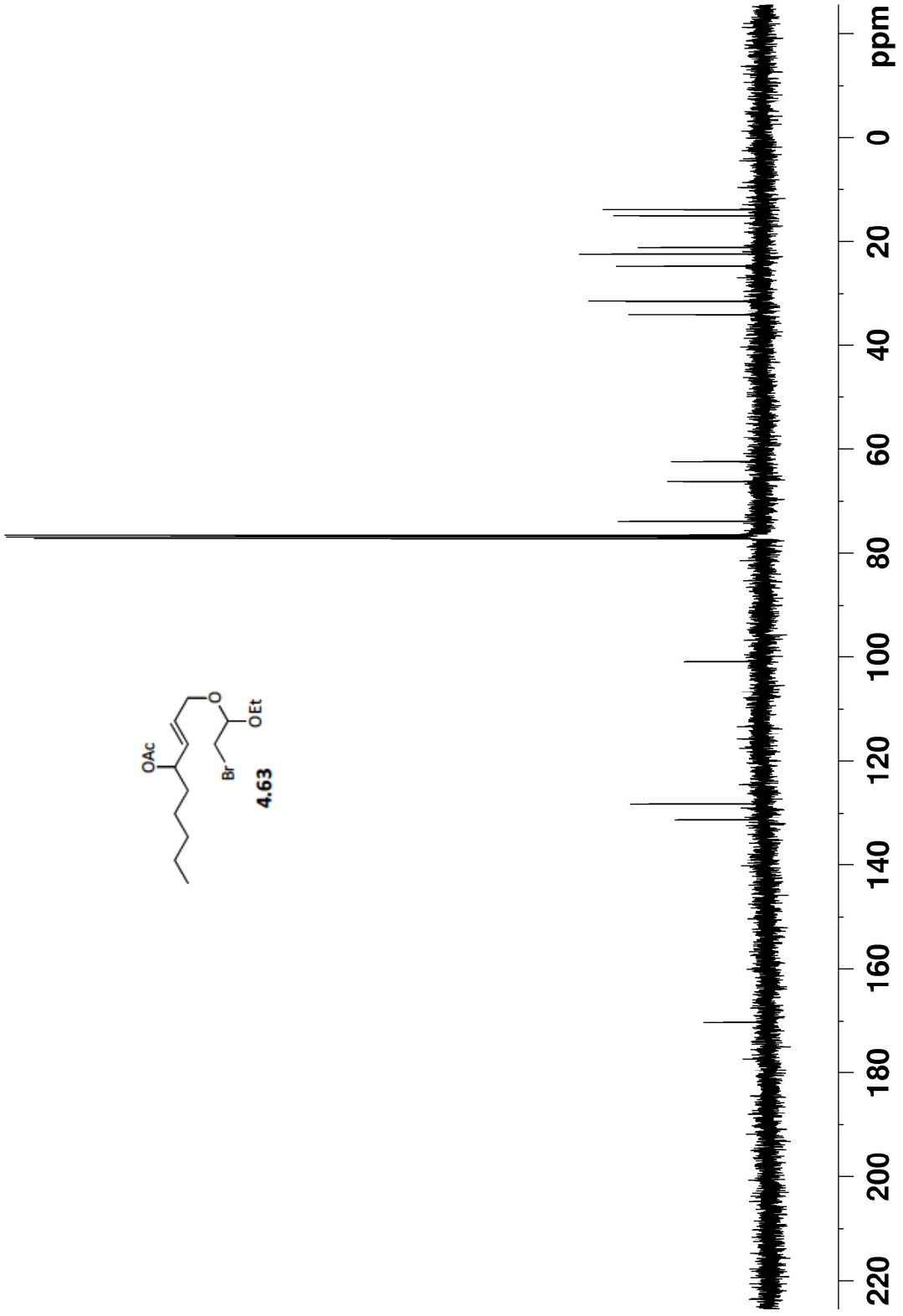


Figure A4.37. ^{13}C NMR spectra (100 MHz, $CDCl_3$) of compound **4.63.**

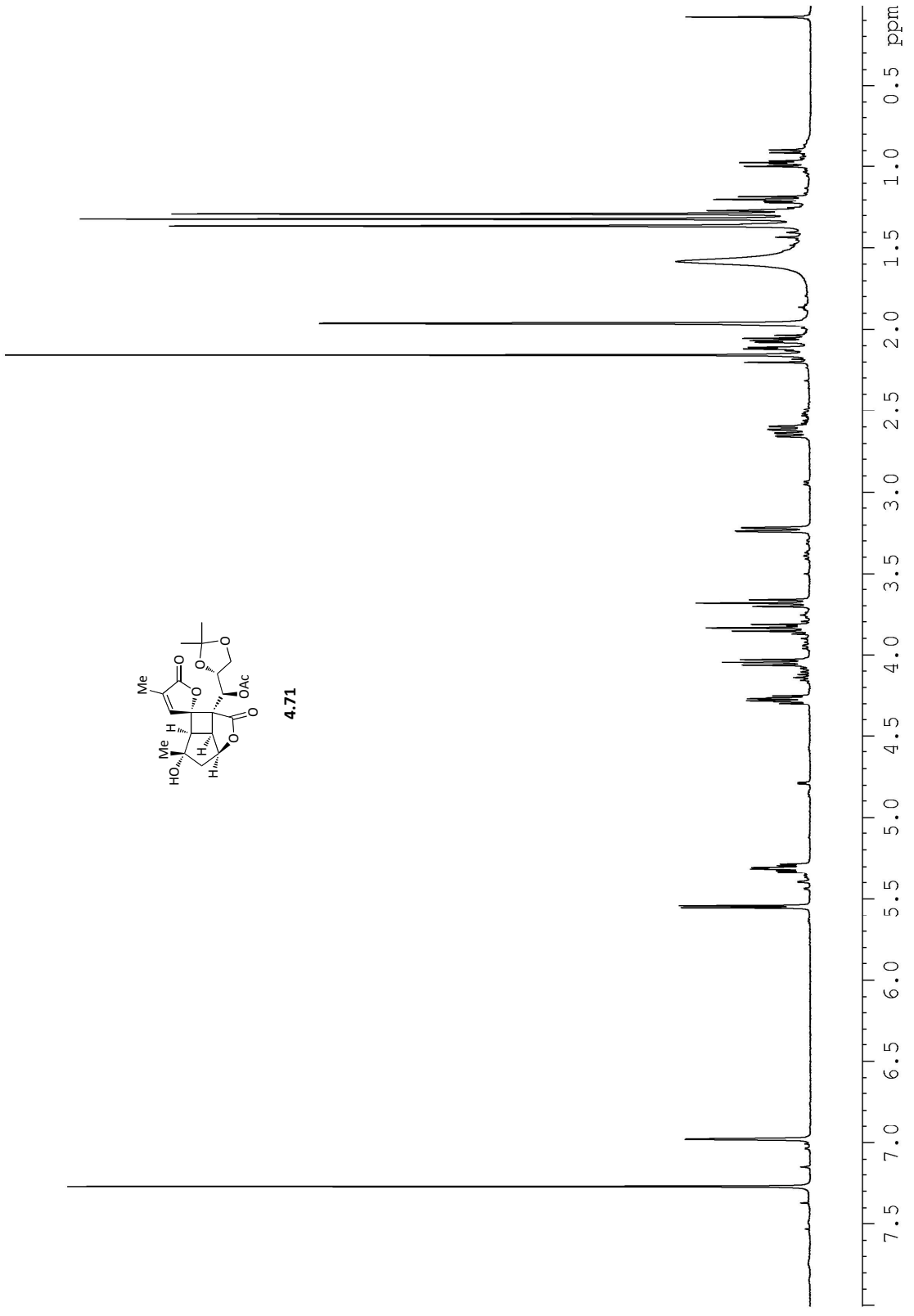


Figure A4.38. ^{1}H NMR spectra (600 MHz, $CDCl_3$) of compound **4.71**.

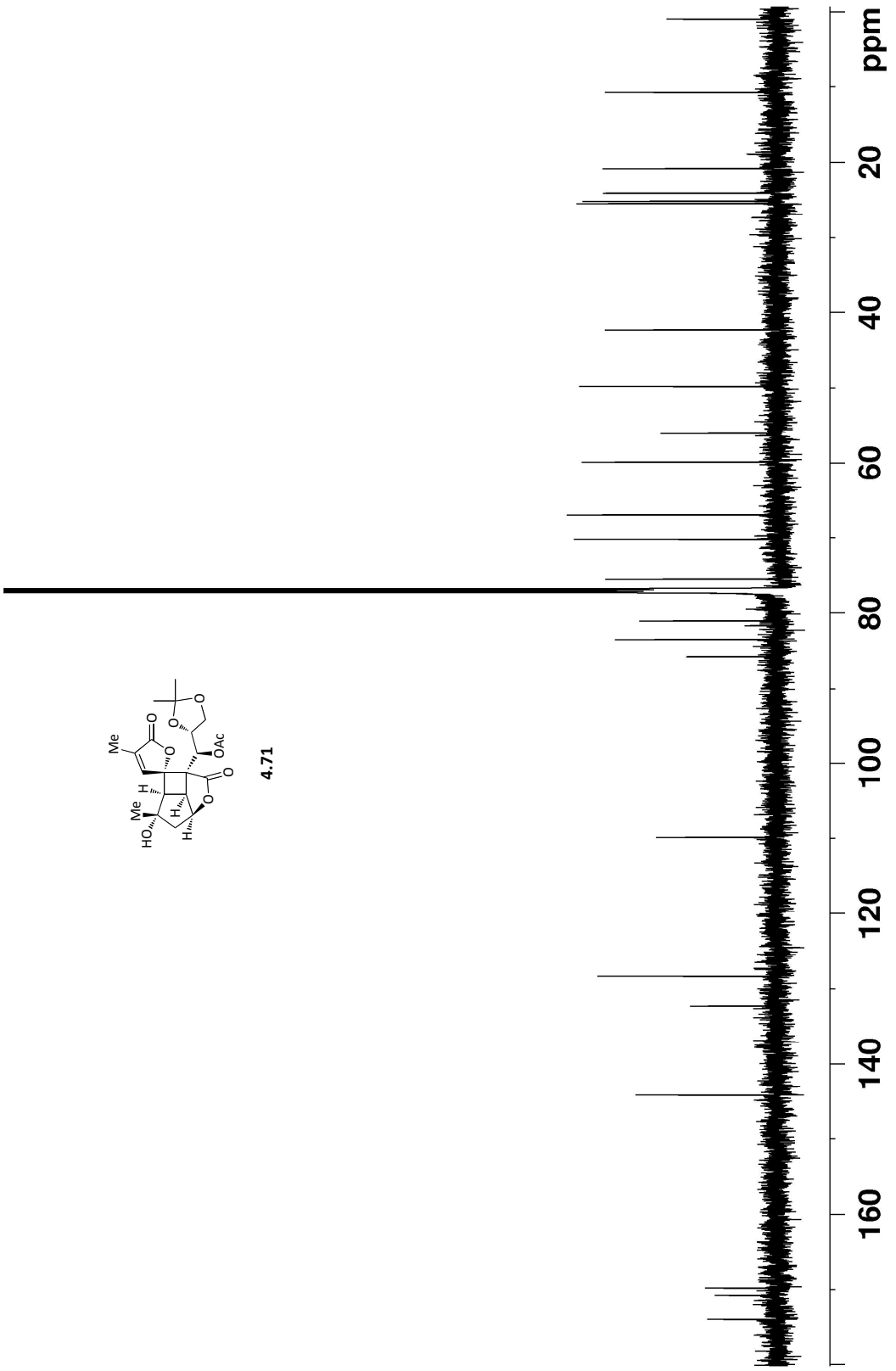


Figure A4.39. ^{13}C NMR spectra (150 MHz, $CDCl_3$) of compound **4.71.**

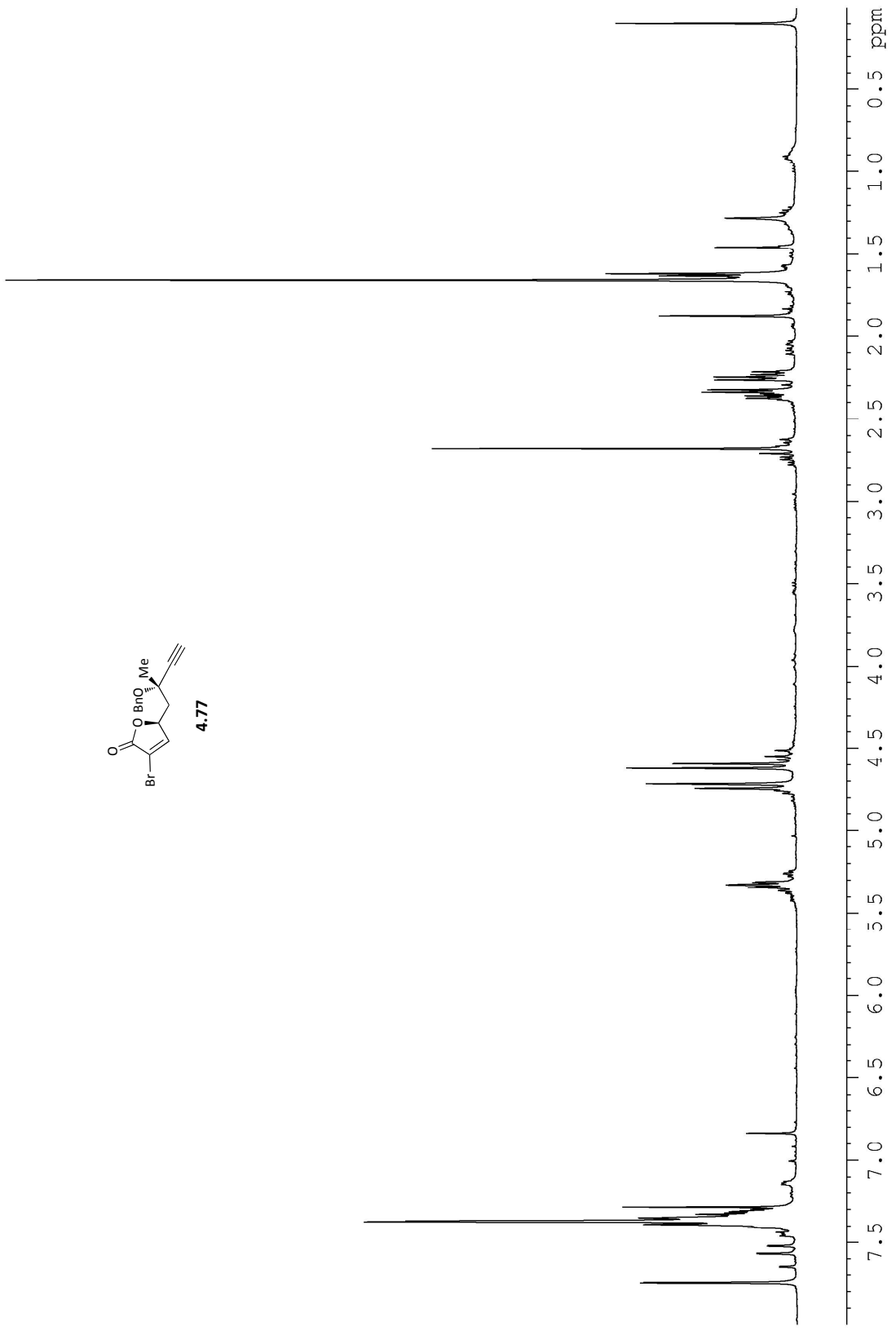


Figure A4.40. ^{1}H NMR spectra (600 MHz, $CDCl_3$) of compound **4.77**.

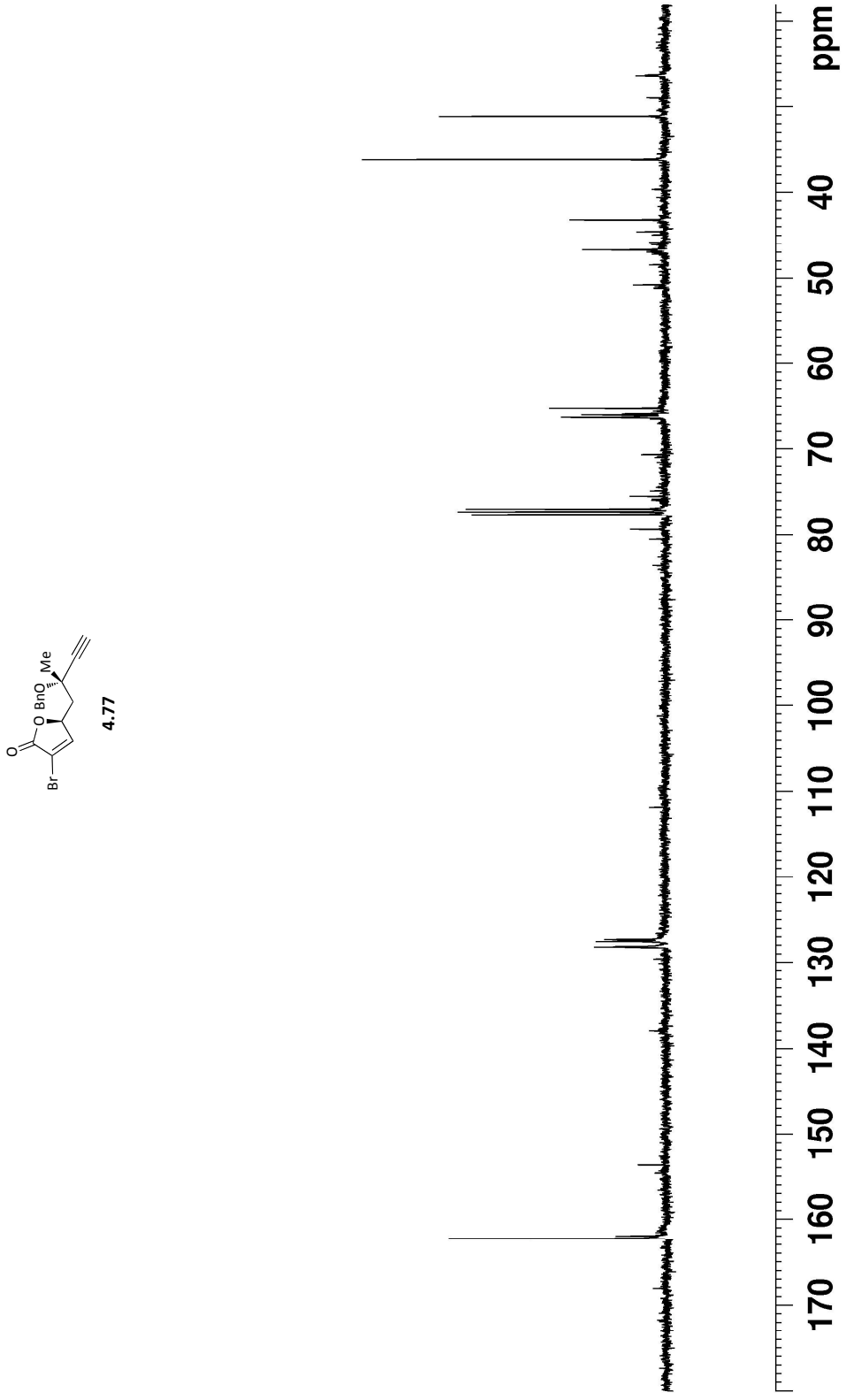


Figure A4.41. ^{13}C NMR spectra (150 MHz, $CDCl_3$) of compound **4.77.**

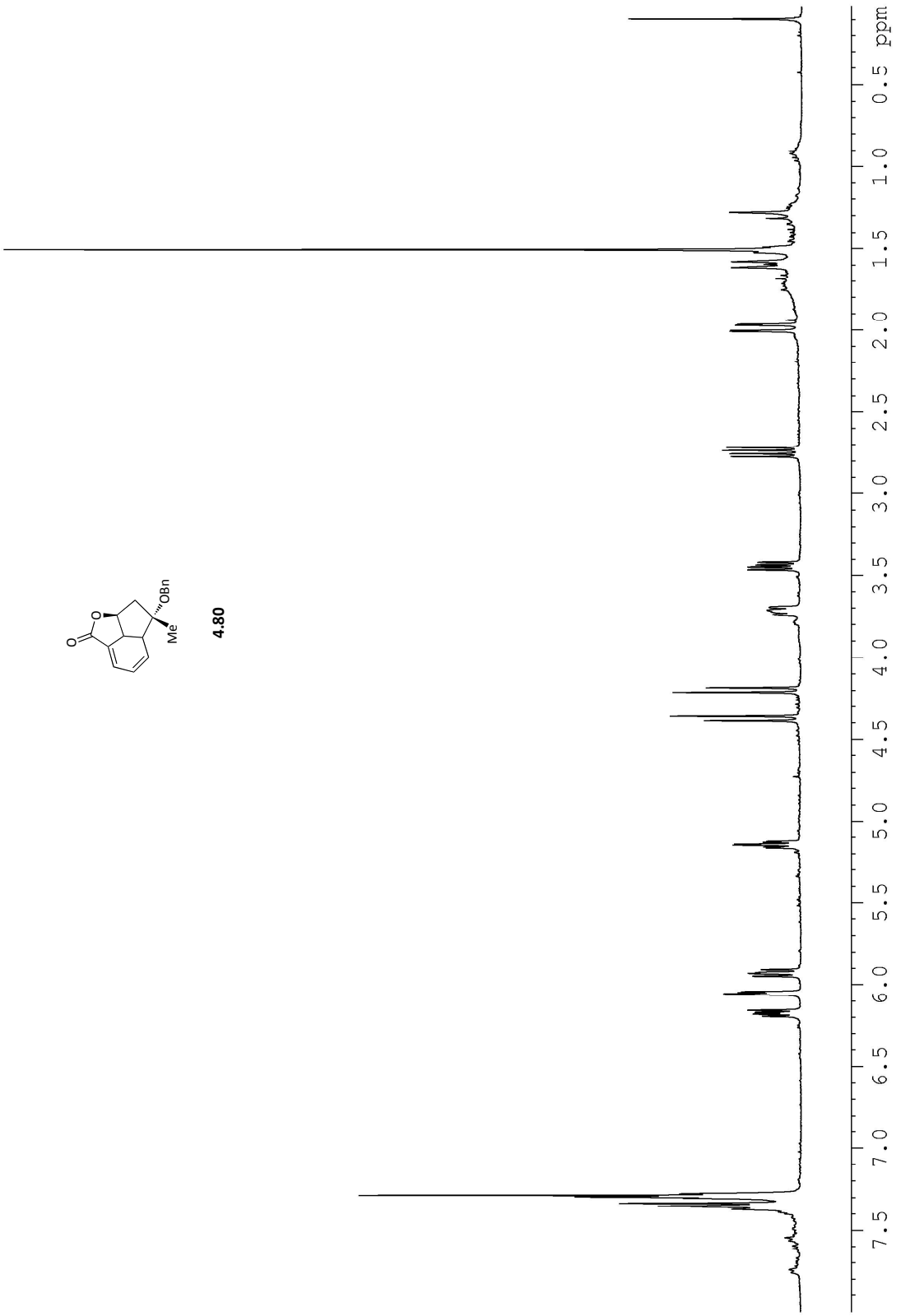


Figure A4.42. ^{1}H NMR spectra (600 MHz, $CDCl_3$) of compound **4.80**.

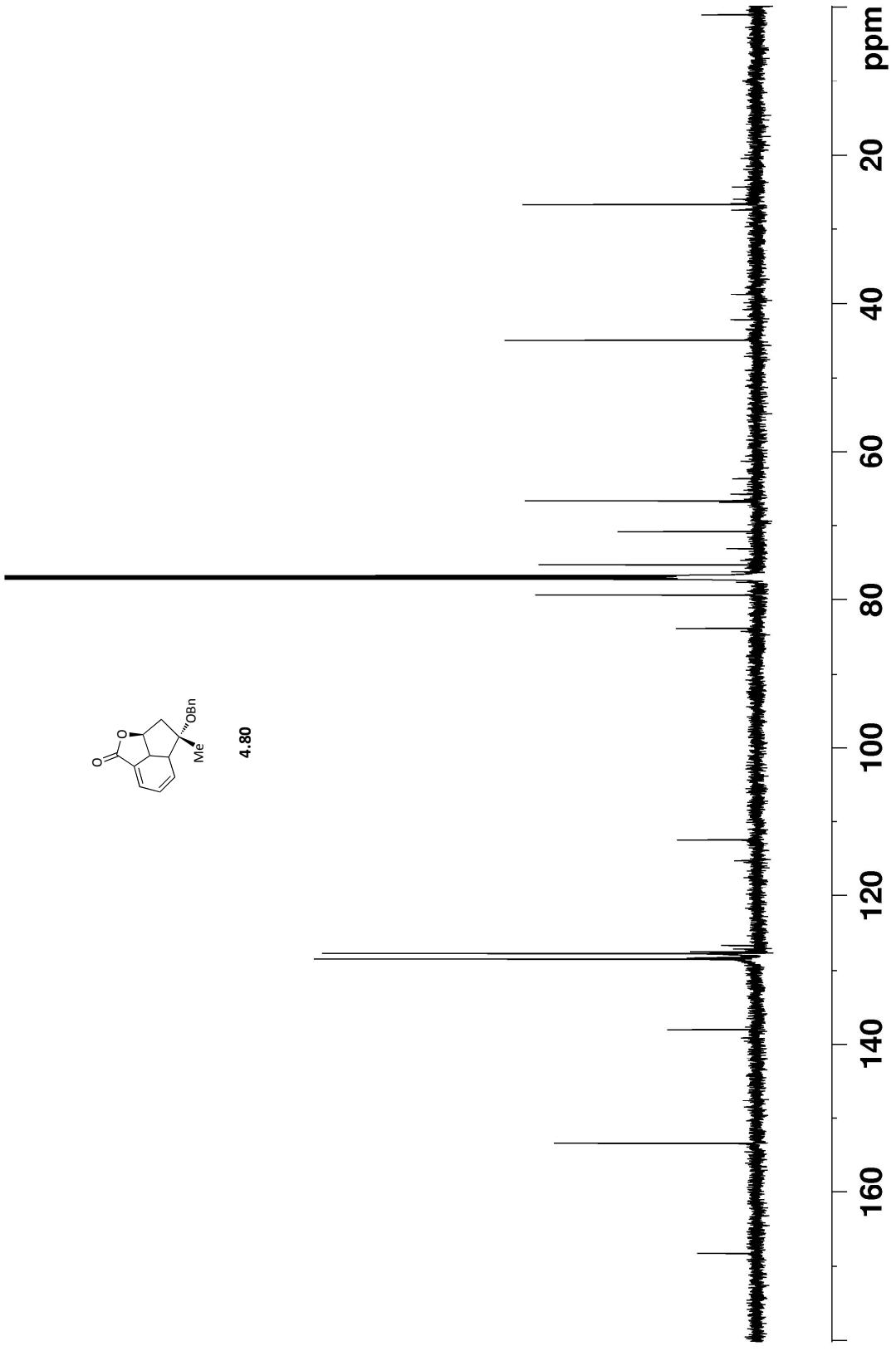


Figure A4.43. ^{13}C NMR spectra (150 MHz, $CDCl_3$) of compound **4.80.**

Appendix A5:

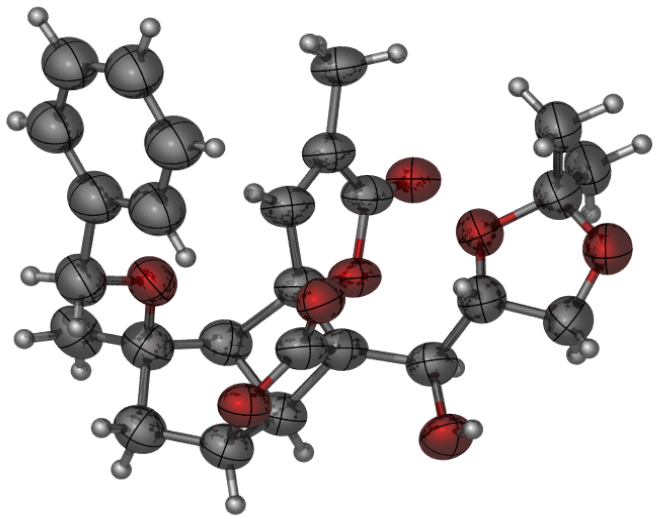
Crystallographic Information File (CIF) for 4.39.

Notes :

The crystals of the compound were small and twinned. A very small crystal was chosen for data collection and the structure was solved and refined. To maintain a chemically reasonable structure similarity restraints were applied to all atoms.

Chirality of unknown centers was determined by comparison to centers of known chirality.

The Model has Chirality at C1 (Verify) S
The Model has Chirality at C2 (Verify) S
The Model has Chirality at C3 (Verify) S
The Model has Chirality at C4 (Verify) R
The Model has Chirality at C5 (Verify) R
The Model has Chirality at C7 (Verify) S
The Model has Chirality at C13 (Verify) S
The Model has Chirality at C14 (Verify) R



Crystal Selection, Unit Cell Determination and Data Collection

A Leica MZ 75 microscope was used to identify a suitable colorless multi-faceted crystal with very well defined faces with dimensions (max, intermediate, and min) 0.1 mm x 0.005 mm x 0.005mm from a representative sample of crystals of the same habit. The crystal mounted on a nylon loop was then placed in a cold nitrogen stream (Oxford) maintained at 110K.

A GADDS BRUKER X-ray (three-circle) diffractometer was employed for crystal screening, unit cell determination, and data collection. The goniometer was controlled using the FRAMBO software suite[1]. The sample was optically centered with the aid of a video camera such that no translations were observed as the crystal was rotated through all positions. The detector was set at 5.0 cm from the crystal sample. The X-ray radiation employed was generated from a Cu sealed X-ray tube (K_α = 1.54178Å with a potential of 50 kV and a current of 40 mA) fitted with a graphite monochromator in the parallel mode (175 mm collimator with 0.5 mm monocapillary).

One hundred and sixty data frames were taken at widths of 0.5° with an exposure time of 10 seconds. These reflections were used in the auto-indexing procedure to determine the unit cell. A suitable cell was found and refined by nonlinear least squares and Bravais lattice procedures. The unit cell was verified by examination of the *h k l* overlays on several frames of data. No super-cell or erroneous reflections were observed.

After careful examination of the unit cell, a standard data collection procedure was initiated using omega scans. Each frame was exposed for 10 sec. The total data collection was performed for duration of approximately 24 hours at 110 K. No significant intensity fluctuations of equivalent reflections were observed. After data collection, the crystal was measured carefully for size, morphology and color.

Data Reduction, Structure Solution, and Refinement

Integrated intensity information for each reflection was obtained by reduction of the data frames with the program SAINT.[2] The integration method employed a three dimensional profiling algorithm and all data were corrected for Lorentz and polarization factors, as well as for crystal decay effects. Finally the data was merged and scaled to produce a suitable data set. The absorption correction program SADABS[3] was employed to correct the data for absorption effects.

Systematic reflection conditions and statistical tests for the data suggested the space group $P2_1$. A solution was obtained readily using SHELXTL (SHELXS).[4] All non-hydrogen atoms were refined with anisotropic thermal parameters. The Hydrogen atoms bound to carbon were placed in idealized positions [C–H = 0.96 Å, $U_{ISO}(H) = 1.2 \times U_{ISO}(C)$]. The structure was refined (weighted least squares refinement on F^2) to convergence.[5] X-seed was employed for the final data presentation and structure plots.[4]

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[1] SMART "Program for Data Collection on Area Detectors" BRUKER AXS Inc., 5465 East Cheryl Parkway, Madison, WI 53711-5373 USA

[2] SAINT "Program for Data Reduction for SMART 1000 X-ray Diffractometers" BRUKER AXS Inc., 5465 East Cheryl Parkway, Madison, WI 53711-5373 USA

[3] SADABS, Sheldrick, G.M. "Program for Absorption Correction of Area Detector Frames", BRUKER AXS Inc., 5465 East Cheryl Parkway, Madison, WI 53711-5373 USA

[4] SHELXTL, Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122

[5] Barbour, L.J.,(2001) "X-Seed - A software tool for supramolecular crystallography" *J. Supramol. Chem.* **2001**, *1,* 189-191.

Table 1. Crystal data and structure refinement for gs78a.

Identification code	gs78a	
Empirical formula	C26 H30 O8	
Formula weight	470.50	
Temperature	110(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 10.066(4) Å	α= 90°.
	b = 8.291(4) Å	β= 105.171(16)°.
	c = 14.543(6) Å	γ = 90°.
Volume	1171.6(9) $Å^3$	
Z	2	
Density (calculated)	1.334 Mg/m^3	
Absorption coefficient	0.818 mm^{-1}	
F(000)	500	
Crystal size	0.10 x 0.01 x 0.01 mm^3	
Theta range for data collection	5.33 to 59.97°.	
Index ranges	-11<=h<=11, -9<=k<=8, -16<=l<=16	
Reflections collected	6675	
Independent reflections	2463 [R(int) = 0.2589]	
Completeness to theta = 59.97°	84.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9919 and 0.9227	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2463 / 339 / 298	
Goodness-of-fit on F^2	1.001	
Final R indices [I>2sigma(I)]	R1 = 0.0855, wR2 = 0.1741	
R indices (all data)	R1 = 0.2398, wR2 = 0.2626	
Absolute structure parameter	0.3(8)	
Largest diff. peak and hole	0.162 and -0.233 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for gs78a. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	10419(9)	3123(9)	1561(7)	72(2)
O(2)	8933(8)	5468(9)	4008(6)	67(2)
O(3)	7418(8)	6191(11)	4768(7)	76(2)
O(4)	10498(9)	962(10)	3614(6)	79(2)
O(7)	8251(8)	2281(10)	1510(6)	72(2)
O(8)	9034(8)	6281(11)	1294(6)	78(2)
C(1)	8957(13)	5197(16)	3025(11)	69(1)
C(2)	10227(13)	6135(17)	2805(10)	74(2)
C(3)	11074(13)	4454(17)	3076(10)	72(2)
C(4)	9611(13)	3536(15)	3026(10)	69(1)
C(5)	10384(15)	6698(15)	1940(10)	76(2)
C(6)	11608(14)	5689(16)	1730(10)	76(2)
C(7)	11484(14)	4064(16)	2172(10)	75(2)
C(8)	9341(14)	2917(14)	1965(10)	69(2)
C(9)	7535(12)	5514(15)	2475(10)	69(2)
C(10)	6712(12)	5934(16)	3043(10)	68(2)
C(11)	7574(12)	6014(17)	3992(10)	66(2)
C(12)	5258(12)	6380(16)	2909(10)	71(3)
C(13)	9526(13)	2148(17)	3653(11)	74(2)
C(14)	8086(13)	1311(18)	3467(11)	83(2)
C(15)	8189(15)	120(19)	4243(12)	87(2)
O(5)	6920(10)	220(13)	4445(8)	96(2)
O(6)	7244(9)	2514(12)	3785(7)	84(2)
C(16)	6335(15)	1594(19)	4197(11)	89(2)
C(17)	4932(14)	1220(20)	3488(10)	91(3)
C(18)	6145(15)	2502(19)	5069(12)	92(3)
C(19)	10674(15)	8550(17)	1899(11)	87(3)
C(20)	9036(14)	6587(18)	333(10)	84(2)
C(21)	7387(8)	6210(12)	-223(7)	90(2)
C(22)	7069(9)	4576(11)	-263(7)	93(2)
C(23)	5748(10)	4062(10)	-723(7)	95(3)
C(24)	4745(8)	5182(13)	-1143(7)	96(3)
C(25)	5064(9)	6816(12)	-1103(7)	94(3)
C(26)	6385(10)	7330(10)	-643(7)	93(2)

Table 3. Bond lengths [Å] and angles [°] for gs78a.

O(1)-C(8)	1.374(15)
O(1)-C(7)	1.432(15)
O(2)-C(11)	1.436(14)
O(2)-C(1)	1.454(17)
O(3)-C(11)	1.189(13)
O(4)-C(13)	1.399(14)
O(7)-C(8)	1.241(14)
O(8)-C(20)	1.422(16)
O(8)-C(5)	1.477(17)
C(1)-C(9)	1.470(19)
C(1)-C(4)	1.526(18)
C(1)-C(2)	1.598(19)
C(2)-C(5)	1.390(18)
C(2)-C(3)	1.63(2)
C(2)-H(2A)	1.0000
C(3)-C(7)	1.513(18)
C(3)-C(4)	1.642(19)
C(3)-H(3A)	1.0000
C(4)-C(13)	1.484(19)
C(4)-C(8)	1.58(2)
C(5)-C(19)	1.57(2)
C(5)-C(6)	1.583(18)
C(6)-C(7)	1.512(19)
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-H(7A)	1.0000
C(9)-C(10)	1.359(15)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(11)	1.426(18)
C(10)-C(12)	1.473(16)
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800
C(13)-C(14)	1.565(18)
C(13)-H(13A)	1.0000
C(14)-O(6)	1.461(17)
C(14)-C(15)	1.48(2)
C(14)-H(14A)	1.0000
C(15)-O(5)	1.387(17)
C(15)-H(15A)	0.9900
C(15)-H(15B)	0.9900
O(5)-C(16)	1.290(17)
O(6)-C(16)	1.436(15)
C(16)-C(18)	1.53(2)
C(16)-C(17)	1.55(2)
C(17)-H(17A)	0.9800
C(17)-H(17B)	0.9800
C(17)-H(17C)	0.9800
C(18)-H(18A)	0.9800
C(18)-H(18B)	0.9800

C(18)-H(18C)	0.9800
C(19)-H(19A)	0.9800
C(19)-H(19B)	0.9800
C(19)-H(19C)	0.9800
C(20)-C(21)	1.675(15)
C(20)-H(20A)	0.9900
C(20)-H(20B)	0.9900
C(21)-C(22)	1.3900
C(21)-C(26)	1.3900
C(22)-C(23)	1.3900
C(22)-H(22A)	0.9500
C(23)-C(24)	1.3900
C(23)-H(23A)	0.9500
C(24)-C(25)	1.3900
C(24)-H(24A)	0.9500
C(25)-C(26)	1.3900
C(25)-H(25A)	0.9500
C(26)-H(26A)	0.9500

C(8)-O(1)-C(7)	110.4(10)
C(11)-O(2)-C(1)	107.1(9)
C(20)-O(8)-C(5)	110.2(9)
C(9)-C(1)-O(2)	104.1(10)
C(9)-C(1)-C(4)	121.3(12)
O(2)-C(1)-C(4)	104.9(10)
C(9)-C(1)-C(2)	121.4(12)
O(2)-C(1)-C(2)	110.0(11)
C(4)-C(1)-C(2)	94.1(10)
C(5)-C(2)-C(1)	129.1(12)
C(5)-C(2)-C(3)	109.3(11)
C(1)-C(2)-C(3)	86.0(9)
C(5)-C(2)-H(2A)	109.7
C(1)-C(2)-H(2A)	109.7
C(3)-C(2)-H(2A)	109.7
C(7)-C(3)-C(2)	102.5(11)
C(7)-C(3)-C(4)	107.9(11)
C(2)-C(3)-C(4)	88.8(9)
C(7)-C(3)-H(3A)	117.7
C(2)-C(3)-H(3A)	117.7
C(4)-C(3)-H(3A)	117.7
C(13)-C(4)-C(1)	127.4(11)
C(13)-C(4)-C(8)	108.9(11)
C(1)-C(4)-C(8)	109.2(11)
C(13)-C(4)-C(3)	121.8(11)
C(1)-C(4)-C(3)	87.9(9)
C(8)-C(4)-C(3)	96.7(10)
C(2)-C(5)-O(8)	101.1(10)
C(2)-C(5)-C(19)	115.5(12)
O(8)-C(5)-C(19)	110.8(11)
C(2)-C(5)-C(6)	106.0(11)
O(8)-C(5)-C(6)	112.8(10)
C(19)-C(5)-C(6)	110.4(11)
C(7)-C(6)-C(5)	103.5(9)

C(7)-C(6)-H(6A)	111.1
C(5)-C(6)-H(6A)	111.1
C(7)-C(6)-H(6B)	111.1
C(5)-C(6)-H(6B)	111.1
H(6A)-C(6)-H(6B)	109.0
O(1)-C(7)-C(6)	110.7(11)
O(1)-C(7)-C(3)	109.1(10)
C(6)-C(7)-C(3)	104.6(10)
O(1)-C(7)-H(7A)	110.8
C(6)-C(7)-H(7A)	110.8
C(3)-C(7)-H(7A)	110.8
O(7)-C(8)-O(1)	120.7(13)
O(7)-C(8)-C(4)	124.1(12)
O(1)-C(8)-C(4)	115.1(11)
C(10)-C(9)-C(1)	112.1(12)
C(10)-C(9)-H(9A)	109.2
C(1)-C(9)-H(9A)	109.2
C(10)-C(9)-H(9B)	109.2
C(1)-C(9)-H(9B)	109.2
H(9A)-C(9)-H(9B)	107.9
C(9)-C(10)-C(11)	106.7(10)
C(9)-C(10)-C(12)	136.6(12)
C(11)-C(10)-C(12)	116.6(11)
O(3)-C(11)-C(10)	136.6(11)
O(3)-C(11)-O(2)	112.6(11)
C(10)-C(11)-O(2)	109.7(11)
C(10)-C(12)-H(12A)	109.5
C(10)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
C(10)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
O(4)-C(13)-C(4)	111.5(10)
O(4)-C(13)-C(14)	107.9(11)
C(4)-C(13)-C(14)	115.9(12)
O(4)-C(13)-H(13A)	107.0
C(4)-C(13)-H(13A)	107.0
C(14)-C(13)-H(13A)	107.0
O(6)-C(14)-C(15)	98.3(11)
O(6)-C(14)-C(13)	103.3(11)
C(15)-C(14)-C(13)	106.7(12)
O(6)-C(14)-H(14A)	115.5
C(15)-C(14)-H(14A)	115.5
C(13)-C(14)-H(14A)	115.5
O(5)-C(15)-C(14)	103.7(12)
O(5)-C(15)-H(15A)	111.0
C(14)-C(15)-H(15A)	111.0
O(5)-C(15)-H(15B)	111.0
C(14)-C(15)-H(15B)	111.0
H(15A)-C(15)-H(15B)	109.0
C(16)-O(5)-C(15)	111.8(11)
C(16)-O(6)-C(14)	104.8(10)
O(5)-C(16)-O(6)	107.0(12)

O(5)-C(16)-C(18)	110.4(13)
O(6)-C(16)-C(18)	108.4(12)
O(5)-C(16)-C(17)	106.3(12)
O(6)-C(16)-C(17)	113.5(12)
C(18)-C(16)-C(17)	111.1(12)
C(16)-C(17)-H(17A)	109.5
C(16)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5
C(16)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5
C(16)-C(18)-H(18A)	109.5
C(16)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
C(16)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5
C(5)-C(19)-H(19A)	109.5
C(5)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
C(5)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5
O(8)-C(20)-C(21)	100.6(9)
O(8)-C(20)-H(20A)	111.6
C(21)-C(20)-H(20A)	111.6
O(8)-C(20)-H(20B)	111.6
C(21)-C(20)-H(20B)	111.6
H(20A)-C(20)-H(20B)	109.4
C(22)-C(21)-C(26)	120.0
C(22)-C(21)-C(20)	113.0(8)
C(26)-C(21)-C(20)	127.0(8)
C(21)-C(22)-C(23)	120.0
C(21)-C(22)-H(22A)	120.0
C(23)-C(22)-H(22A)	120.0
C(24)-C(23)-C(22)	120.0
C(24)-C(23)-H(23A)	120.0
C(22)-C(23)-H(23A)	120.0
C(25)-C(24)-C(23)	120.0
C(25)-C(24)-H(24A)	120.0
C(23)-C(24)-H(24A)	120.0
C(26)-C(25)-C(24)	120.0
C(26)-C(25)-H(25A)	120.0
C(24)-C(25)-H(25A)	120.0
C(25)-C(26)-C(21)	120.0
C(25)-C(26)-H(26A)	120.0
C(21)-C(26)-H(26A)	120.0

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for gs78a. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

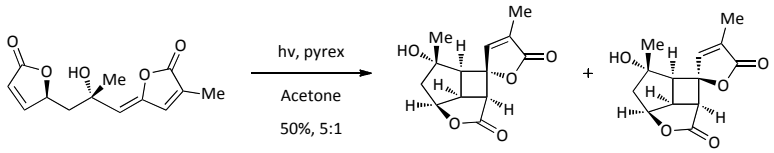
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	60(3)	74(3)	78(3)	-4(3)	12(3)	1(3)
O(2)	53(3)	65(3)	80(3)	-6(3)	12(2)	6(3)
O(3)	66(4)	81(5)	82(4)	-6(5)	18(4)	7(4)
O(4)	78(4)	76(5)	86(5)	6(4)	27(4)	27(4)
O(7)	62(4)	73(5)	77(5)	8(4)	9(4)	1(4)
O(8)	71(3)	89(4)	76(3)	4(4)	22(3)	-3(3)
C(1)	58(2)	70(3)	79(3)	-3(3)	15(2)	6(3)
C(2)	63(3)	76(3)	79(3)	-6(3)	15(2)	-3(3)
C(3)	59(3)	78(3)	79(3)	-7(3)	16(3)	1(3)
C(4)	57(3)	70(3)	80(3)	-2(3)	16(2)	7(2)
C(5)	70(3)	82(3)	79(3)	-4(3)	21(3)	-3(3)
C(6)	67(3)	83(4)	78(4)	-6(3)	18(3)	-5(3)
C(7)	62(3)	82(3)	79(3)	-7(3)	16(3)	-3(3)
C(8)	58(3)	69(4)	78(3)	-2(3)	13(3)	8(3)
C(9)	58(3)	65(4)	80(4)	-4(4)	13(3)	8(3)
C(10)	55(3)	66(4)	80(4)	-3(4)	12(3)	6(3)
C(11)	51(3)	65(4)	80(4)	-5(4)	12(3)	3(3)
C(12)	55(4)	76(7)	78(6)	-6(6)	9(4)	10(5)
C(13)	64(3)	74(3)	84(3)	5(3)	20(3)	11(3)
C(14)	70(3)	88(4)	90(4)	18(3)	21(3)	3(3)
C(15)	73(4)	93(4)	94(5)	22(4)	18(4)	3(3)
O(5)	77(4)	104(4)	104(4)	30(4)	20(3)	-1(3)
O(6)	69(3)	93(4)	92(4)	23(3)	25(3)	4(3)
C(16)	72(4)	99(4)	97(4)	24(4)	25(3)	0(3)
C(17)	78(5)	104(8)	90(7)	27(6)	20(5)	-6(5)
C(18)	78(7)	113(7)	86(6)	23(5)	25(5)	-13(6)
C(19)	84(7)	85(4)	97(7)	-4(5)	35(6)	-10(4)
C(20)	76(4)	100(4)	78(3)	8(4)	22(3)	-6(4)
C(21)	78(4)	108(5)	81(4)	3(4)	14(3)	-5(4)
C(22)	80(5)	110(5)	83(5)	0(5)	12(4)	-7(4)
C(23)	82(5)	111(5)	85(5)	-2(5)	9(4)	-7(4)
C(24)	82(5)	115(6)	86(5)	1(5)	10(4)	-6(4)
C(25)	78(5)	115(5)	85(5)	4(5)	12(4)	-4(4)
C(26)	79(4)	112(5)	83(5)	2(5)	13(4)	-4(4)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for gs78a.

	x	y	z	U(eq)
H(2A)	10588	6954	3314	88
H(3A)	11806	4410	3692	87
H(6A)	11501	5588	1036	92
H(6B)	12507	6196	2029	92
H(7A)	12382	3476	2320	89
H(9A)	7533	6394	2015	82
H(9B)	7158	4536	2108	82
H(12A)	4773	6306	2232	107
H(12B)	5201	7488	3130	107
H(12C)	4831	5645	3275	107
H(13A)	9760	2564	4321	89
H(14A)	7700	889	2807	99
H(15A)	8353	-979	4030	105
H(15B)	8943	406	4808	105
H(17A)	5077	574	2960	137
H(17B)	4477	2238	3239	137
H(17C)	4351	626	3816	137
H(18A)	7042	2647	5528	137
H(18B)	5539	1880	5365	137
H(18C)	5732	3559	4872	137
H(19A)	9882	9159	1987	130
H(19B)	10828	8819	1279	130
H(19C)	11495	8831	2405	130
H(20A)	9667	5850	117	101
H(20B)	9289	7718	241	101
H(22A)	7754	3810	25	111
H(23A)	5530	2945	-750	114
H(24A)	3842	4830	-1458	115
H(25A)	4378	7581	-1391	113
H(26A)	6602	8447	-616	111

Appendix A6:

^{1}H NMR (400 mHz, $CDCl_3$) Monitoring of [2+2] Photocycloaddition.



2.2 **2.1** **2.17**

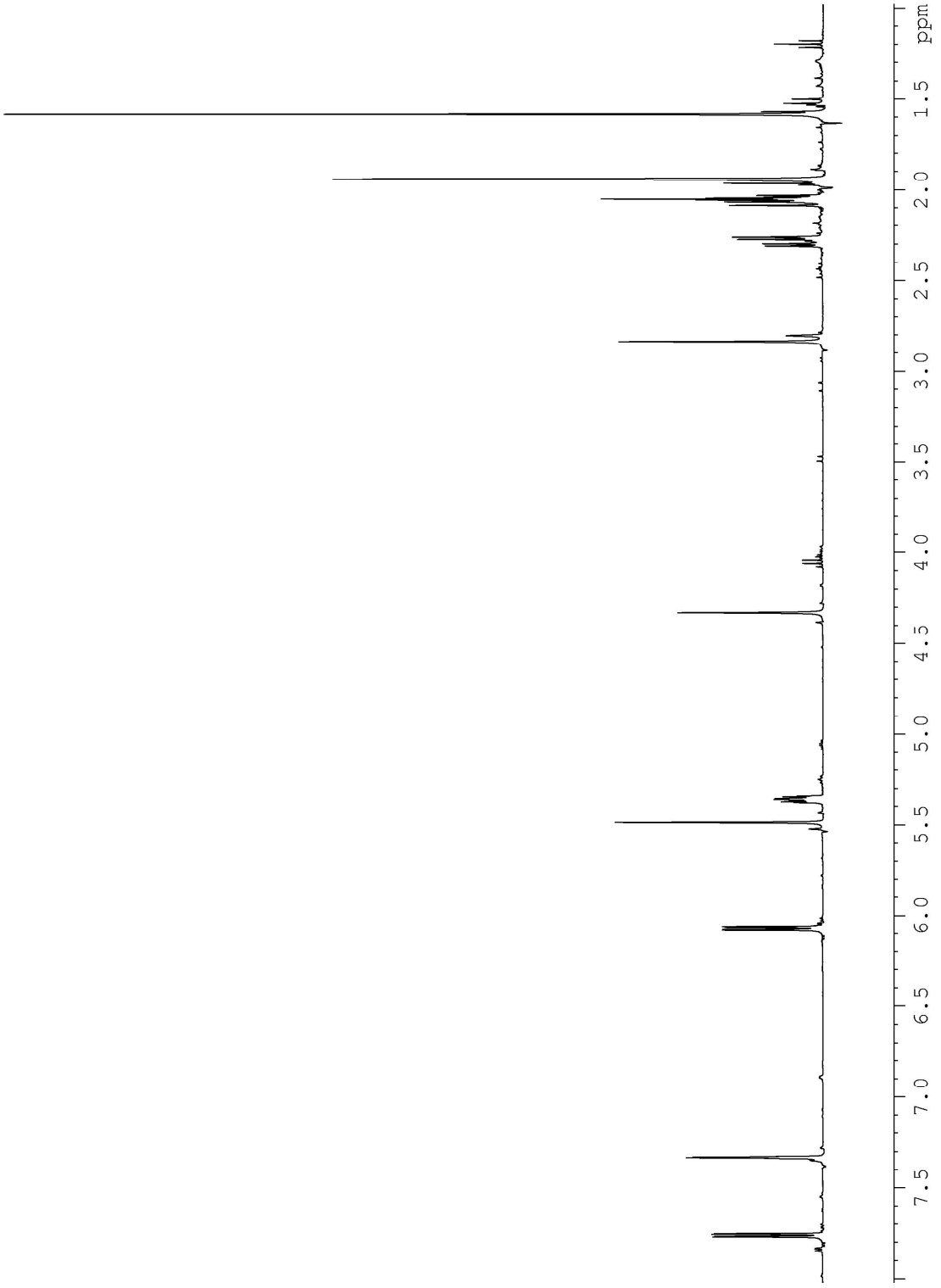


Figure A6.1. Irradiation of compound **2.2** at t = 0 h.

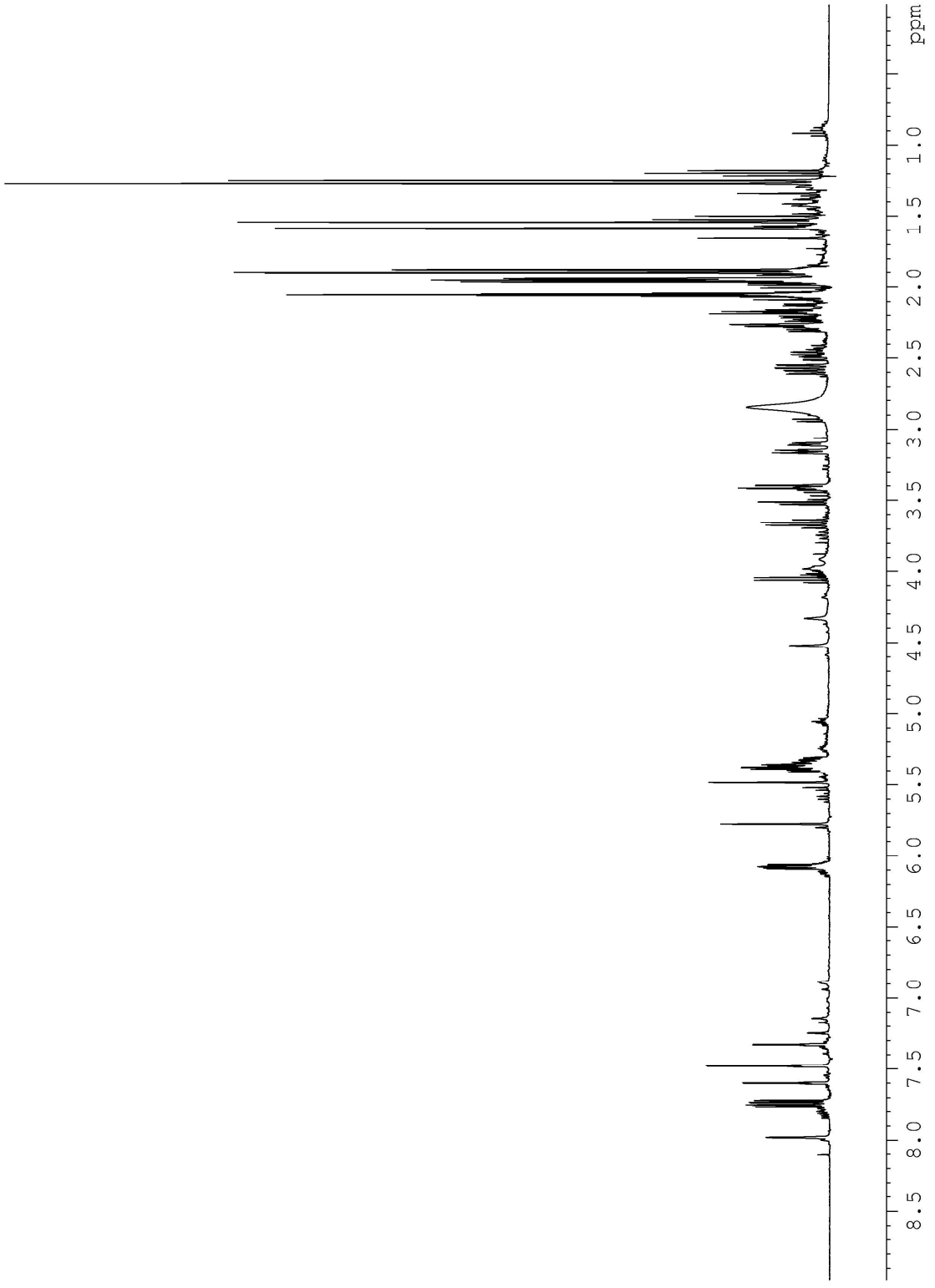


Figure A6.2. Irradiation of compound **2.2** at t = 4 h.

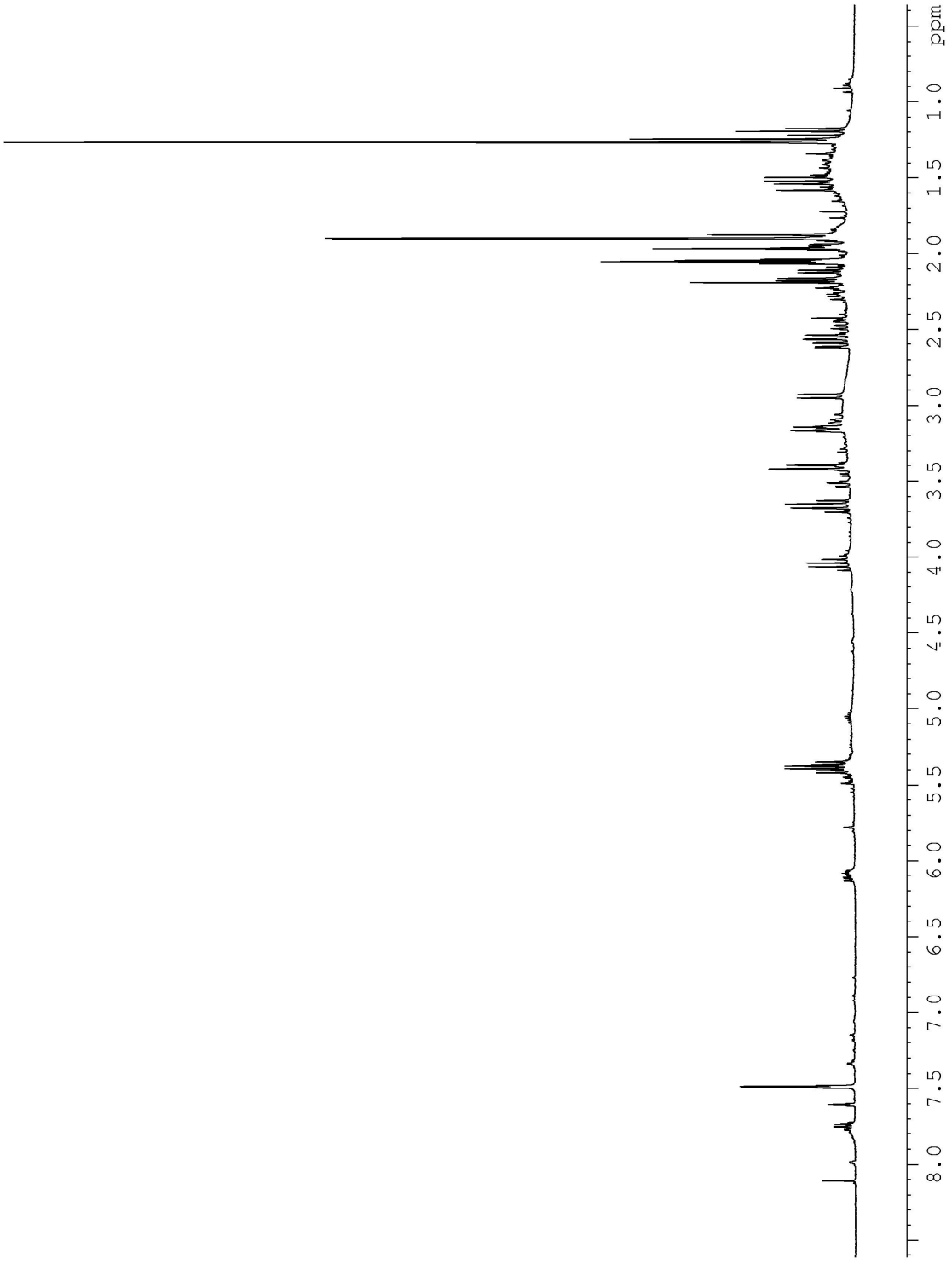
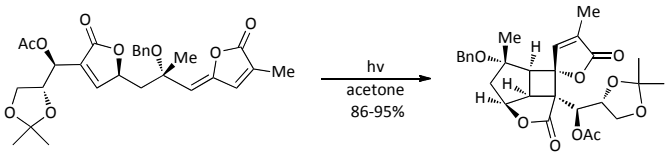


Figure A6.3. Irradiation of compound **2.2** at t = 8 h.



4.36 **4.37**

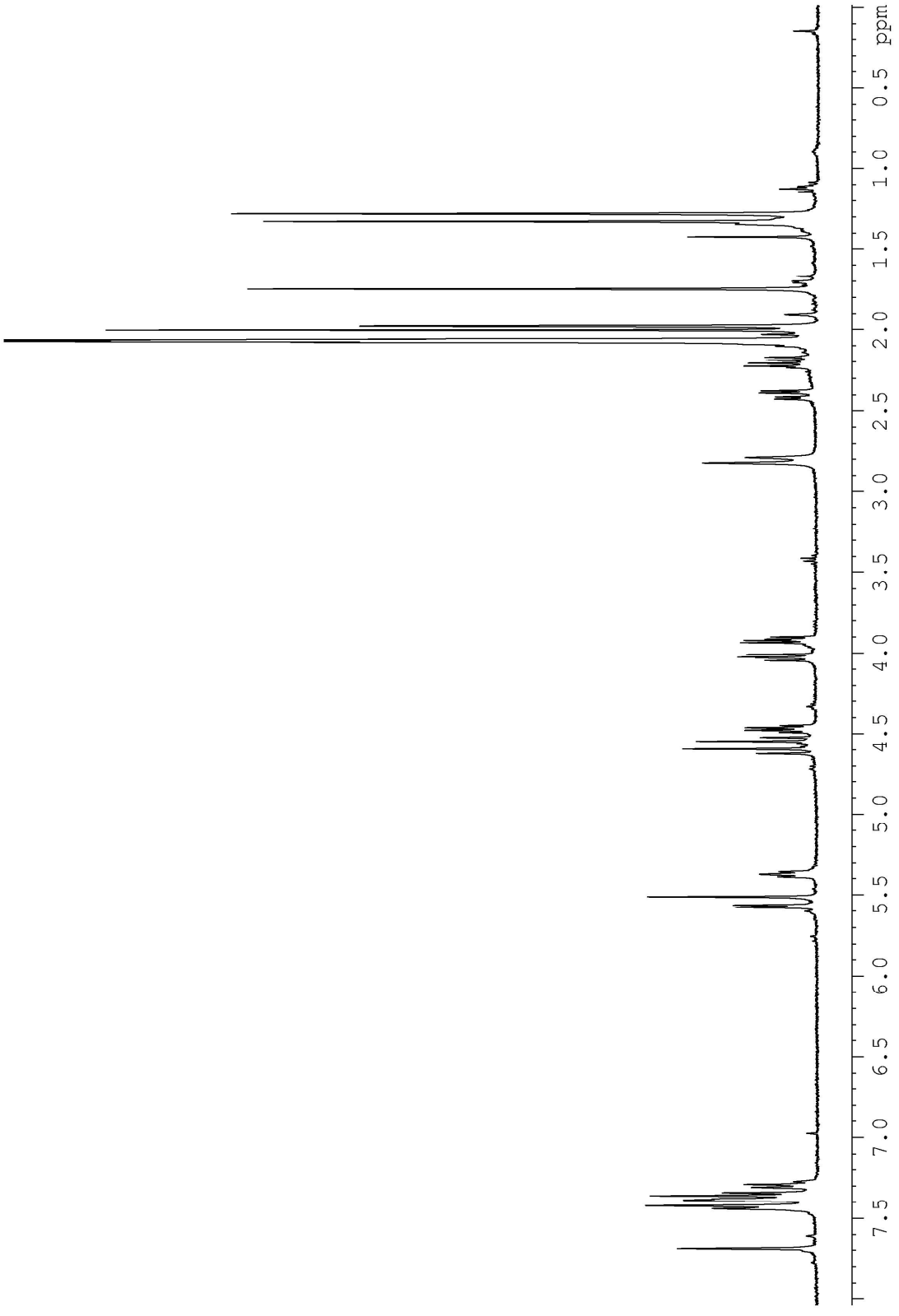


Figure A6.4. Irradiation of compound **4.36** at t = 0 min.

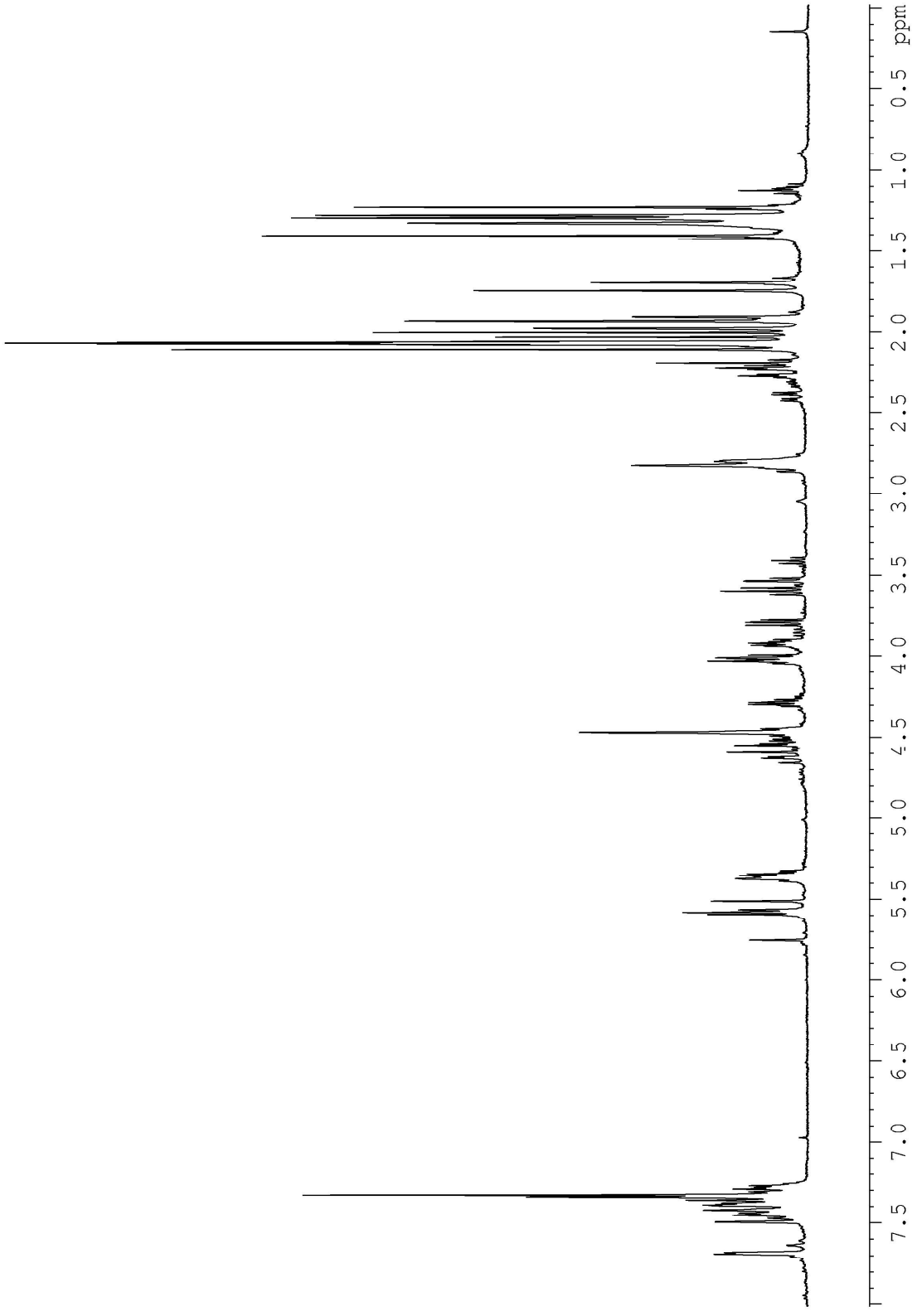


Figure A6.5. Irradiation of compound **4.36** at t = 30 min.

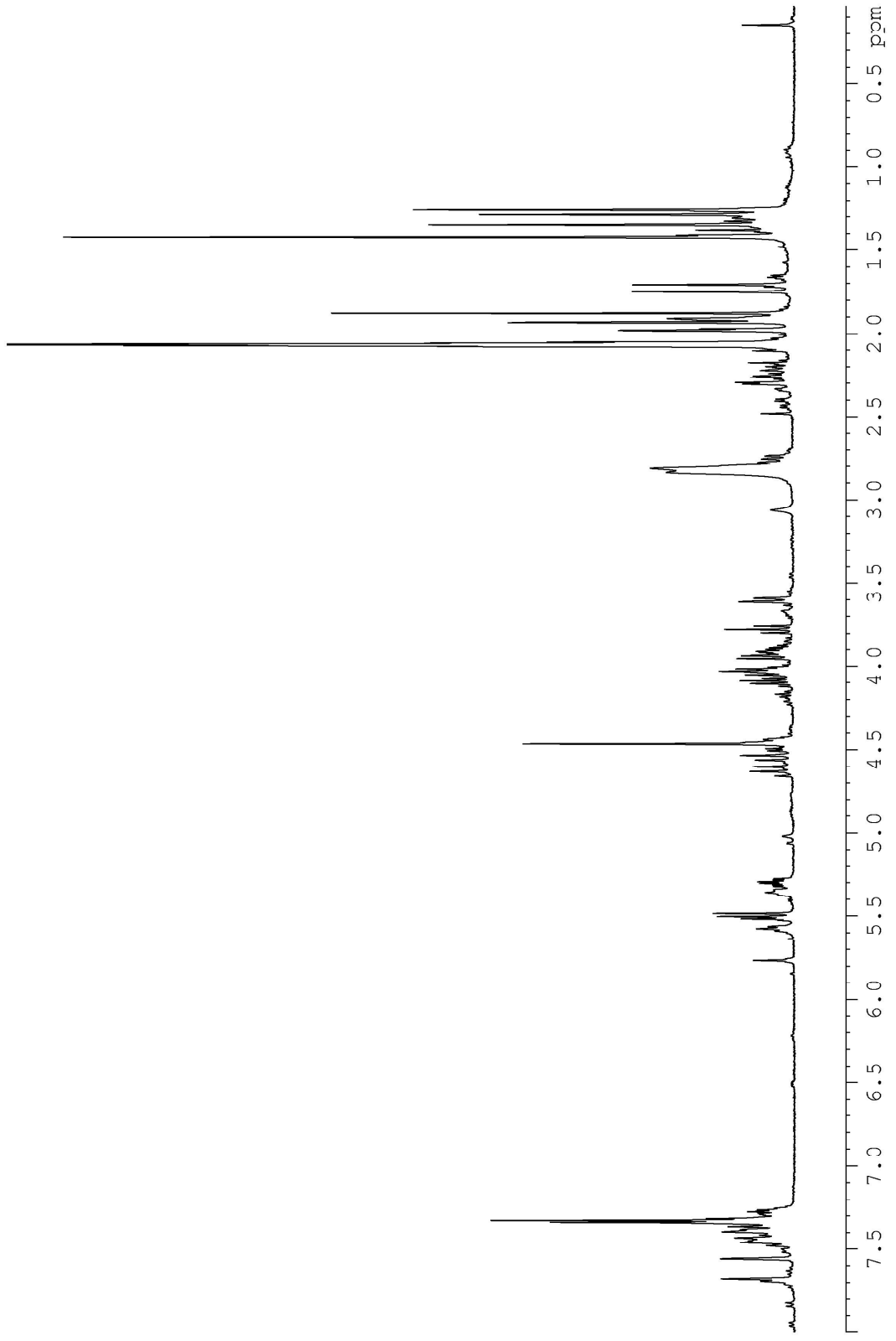


Figure A6.6. Irradiation of compound **4.36** at t = 60 min.

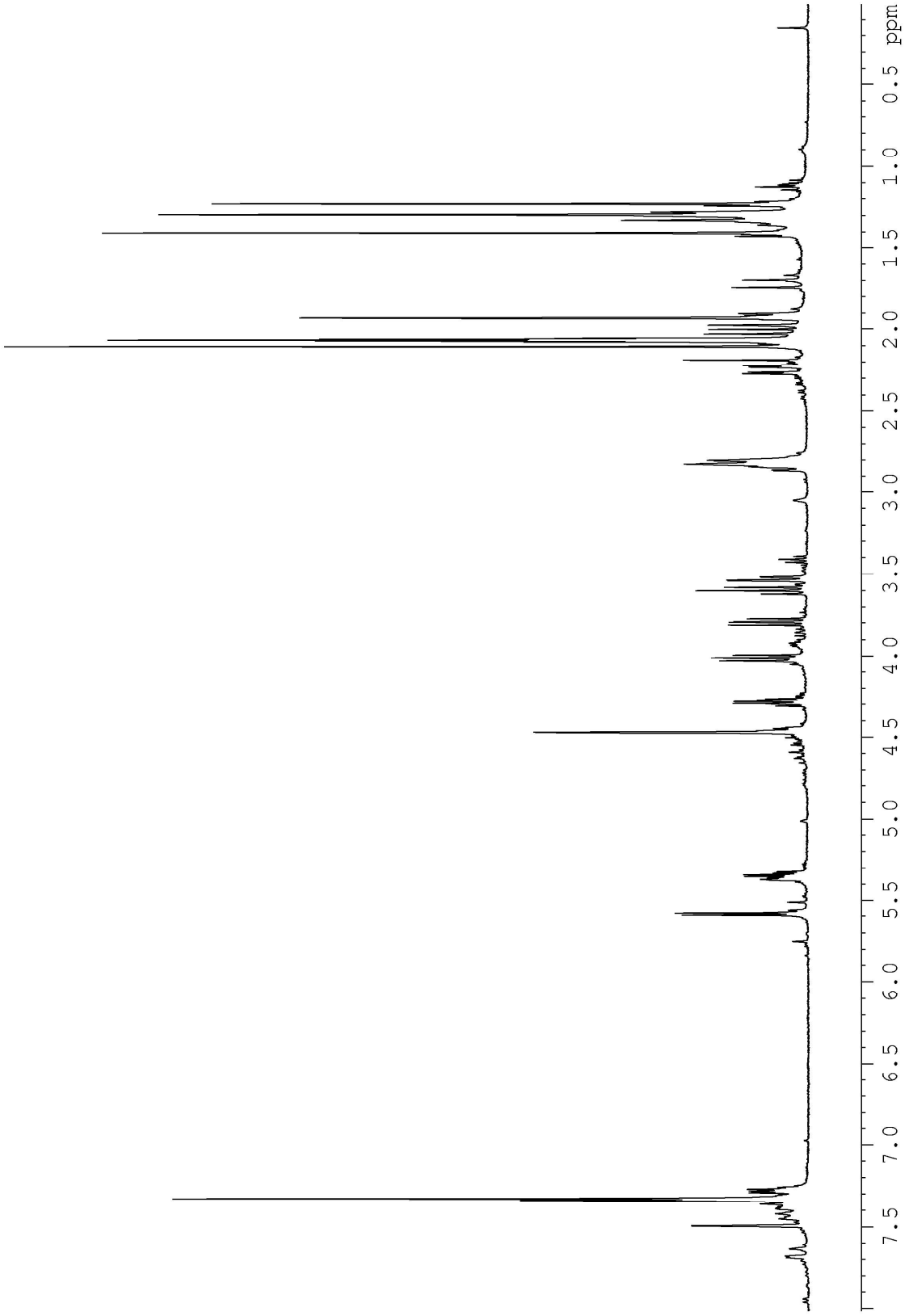


Figure A6.7. Irradiation of compound **4.36** at t = 90 min

About the Author

"I know I got it made while the masses of black people are catchin' hell,

but as long as they ain't free, I ain't free."

Muhammad Ali

I was born March 3rd 1983 in Detroit, Michigan to Frankie Townsend. The oldest of five children, I was later joined by Chauncey (1986), Linnea (1990), Bria (1993), and Danielle (1998). With the exception of three years that were spent in Columbus, Ohio (1993-1996), I was raised solely on the eastside of Detroit. A naturally observant person, my early worldviews were heavily influenced by the "crack epidemic" of the late 1980's. The great toll drug abuse had on families and communities forced me to watch, as mothers were lost to the streets, fathers were sent to jail, and children were left to raise themselves in a cycle of despair. It goes without saying that I have witnessed and experienced things some people only see on television! In the midst of this environment my family steered me toward education and encouraged honest work.

In the 4th grade I entered the annual "What I want to be when I grow up" oratorical contest. At the time my Uncle Stacye was a student at Michigan State and I famously told the audience: "I want to grow up to be a scientist like Louis Pasteur and go to college at Harvard, Yale, or Michigan State!" I took third place because the judges believed my Mom wrote the essay. Other than writing a 10th grade term paper on an element from the periodic table (I can't remember whether it was manganese or

molybdenum) I did not have any real interest in science. I was much more interested in history, literature, and sports.

When I was 14 I assumed my first job at a car wash on the "white" side of 8-mile road (Warren, Mi). Interestingly, this place was a converted garage and only had one entrance. This meant customers had to drive into the shop and back out once their car had been serviced. The shop could only fit two cars at a time. Needless to say, business was horrible. After my boss took an unexpected vacation, I decided to go and work at the more successful car wash across the street on the "black" side of 8-mile road (Detroit, Mi). Although I made more money at this establishment, I realized the place was a cover for a small drug business. Additionally, most of the customers were involved with prostitution. Although I never told my Mom, I knew this was unacceptable.

As soon as I turned 15 I went to work at Joe Louis arena and Tiger stadium. During my junior and senior years I also worked as a student intern in the Department's of Anesthesia and Gastroenterology at Henry Ford hospital, an experience that triggered an interest in human health and wellness. Although hockey and baseball fans are fanatical, the craziest thing I witnessed during this period was the dreaded colonoscopy!

After graduating from the Math, Science, and Applied Technology program at M.L. King High School in 2001, I matriculated to Oakland University in Rochester, MI. Initially a biochemistry major intent on attending medical school, I realized I lacked a sufficient interest in (and understanding of) biology and decided to drop the "bio" and pursue chemistry full-time. I came to this realization when I failed to stay awake during

the first semester of biochemistry. This would not be the last time I failed to stay awake during a lecture or seminar.

While at Oakland I spent three years with the freshman orientation team and two years as a resident assistant for the basketball and baseball teams. There were times when I wondered which team featured the greatest number of idiot's? Was it the team that tossed mattresses out of their bedroom windows and stole the couch from the community area or the team that gradually formed a mountain of beer cans outside of their bedroom windows? It was definitely a draw. These experiences taught me how to interact with (and lead) large groups of people. I also witnessed first hand, the fragile nature of the human condition as I was forced to deal with a gauntlet of issues.

From an academic prospective I was fortunate to receive several awards, two of which were the Keeper of the Dream award (for contributions to interracial understanding and good will) and the Alfred G. Wilson founder's medal (top graduating senior). Graduate school was the next logical step and I still don't remember how that decision was made! I do remember narrowing my selection down to Ohio State, Case Western, Syracuse, and Notre Dame. I was prepared to attend Case Western when a very aggressive professor from Ohio State called me (four times over a seven day period) to convince me that Case had nothing to offer and I would be better off going elsewhere. Eventually, I felt he was right and on the last day possible I decided to attend Vanderbilt. There was no magical reason. Honestly, the department left me with a horrible impression. There were only two black graduate students in the department and that the faculty was composed primarily of white men. I quickly

realized this was not just a Vanderbilt issue. This was the face of science and to an extent higher education in the United States. Quite frankly, there are too many people who believe such social issues are not their concern. Pathetic.

After an interesting set of first year courses I joined the Sulikowski lab because I believed Gary would help me develop into an independent thinker. I also experienced my fair share of personal tragedies; events that helped clarify my professional and civic goals. Lastly, I got married shortly after my candidacy exam and it was without question the best decision I've made to date.

After 5 ½ years I defended my Ph.D. and will head off to Memorial Sloan Kettering Institute to begin the next phase of my career. Although I entered graduate school with the intention of becoming a professor, observing the interactions between faculty members at Vanderbilt has deteriorated much of that passion. I now have an open mind and will consider a career in industry as well. Without question, I believe that I must spend a significant amount of time working to erase the educational achievement gap that exists in this country. My penultimate goal is to develop a science academy where I can attack inner-city education first hand.