PROGRESS TOWARD THE TOTAL SYNTHESIS OF AMMOCIDIN D

By

STEPHEN THOMAS CHAU

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Approved By:

Dr. Gary A. Sulikowski

Dr. Jeffrey N. Johnston

Dr. Brian O. Bachmann

Dr. Michael P. Stone

To my parents

Richard and Johanna Chau

My momma always said,

"Life was like a box of chocolates.

You never know what you're gonna get."

Forrest Gump

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LIST OF ABBREVIATIONS

Ac = Acetyl

AcO = Acetate

Ac_2O = Acetic anhydride

Ar = Aryl

Aq. = aqueous

9-BBN = 9-Borabicyclononane

BH_3·THF = Borane-tetrahydrofuran complex

BF_3·OEt_2 = boron trifluoride diethyletherate

Bn = Benzyl

BOP = Bis(2-oxo-3-oxazolidinyl)phosphine

Bu or *n*-Bu = n-Butyl

s-Bu or sBu = sec-Butyl

t-Bu or *t*Bu = tert-Butyl

Bz = Benzoyl

Bzl = Benzyl

Cat. = catalytic

Cod = Cyclooctadiene

18-crown-6 = 1,4,7,10,13,16-Hexaoxacyclooctadecane

CSA = Camphorsulphonic acid

°C = degrees Celcius

d = doublet

dd = doublet of doublets

ddd = doublet of doublets of doublets

DABCO = 1,4-Diazabicyclo[2.2.2]octane

DAST = Diethylaminosulphur trifluoride

dba = Dibenzylideneacetone

DBU = 1,8-Diazabyciclo[5.4.0]undec-7-ene

DCC = 1,3-Dicyclohexylcarbodiimide

DCM = Dichloromethane

DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

DIBAL = Diisobutylaluminium hydride

DIBAL-H = Diisobutylaluminium hydride

DIPEA = Diisopropylethylamine

DMAP = 4-Dimethylaminopyridine

DMDO = 2,2-dimethyldioxirane

DME = 1,2-Dimethoxyethane

DMF = N,N-Dimethylformamide

DMP = Dess-Martin periodinaneDMPM = 3,4-Dimethoxybenzyl

DMS = Dimethylsulphide

DMSO = Dimethylsulphoxide

DPA = Diisopropylamine

Eq. = equivalents

EDC = 1-Ethyl-3-(3-dimethylaminopropy)carbodiimide

EDCI = 1-Ethyl-3-(3-dimethylaminopropy)carbodiimide hydrochloride

Et_2O = Diethyl ether

h = hour

g= grams

HMDS = Hexamethyldisilazane

HMPA = Hexamethylphosphoramide

HOBt = 1-Hydroxybenzotriazole

IPA = Isopropyl alcohol

Im = Imidazole

Ipc = Isopinocampheyl

KDA = Potassium diisopropylamide

KHMDS = Potassium bis(trimethylsilyl)amide

LAH = Lithium aluminium hydride

LC/MS = Liquid chromatography/ mass spectrometry

LDA = Lithium diisopropylamide

LHMDS = Lithium bis(trimethylsilyl)amide

*m*CPBA = meta-chloroperoxybenzoic acid

Me = Methyl

MPM = p-Methoxybenzyl

MS = Molecular sieves

Ms = Methanesulphonyl

NaHMDS = Sodium bis(trimethylsilyl)amide

NBS = N-Bromosuccinimide

NCS = N-Chlorosuccinimide

NIS = N-Iodosuccinimide

NMM = N-Methylmorpholine

NMO = N-Methylmorpholine-N-oxide

NMP = N-Methylpyrrolidone

PDC = Pyridinium dichlorochromate

PCC = Pyridinium chlorochromate

Ph = Phenyl

PPh_3 = triphenylphosphine

Piv = Pivaloyl, 2,2-dimethylacetyl

PMB = p-Methoxybenzyl

PPTS = Pyridinium p-toluensulphonate

n-Pr = n-Propyl

Pr = Propyl

i-Pr or iPr = iso-propyl

PTSA = p-Toluenesulphonic acid

Pv = Pivaloyl, 2,2-dimethylacetyl

Py = Pyridine

t = triplet

TBAF = Tetrabutylammonium fluoride

TBDMS = tert-Butyldimethylsilyl

TBDPS = tert-Butyldiphenylsilyl

TBHP = tert-Butylhydroperoxide

TBS = tert-Butyldimethylsilyl

TEA = Triethylamine

TES = Triethylsilyl

TESH = Triethylsilane

Tf = Trifluoromethanesulfonyl

TfO = Trifluoromethanesulfonate

Tf_2O = Trifluoromethanesulfonyl anhydride

TfOH = Trifluoromethanesulfonic acid

TFA = Trifluoroacetic acid

TFAA = Trifluoroacetic anhydride

THF = Tetrahydrofuran

TIPS = Triisopropylsilyl

TMEDA = N,N,N',N'-Tetramethylethylendiamine

TMS = Trimethylsilyl

Tol = toluene

TPAP = Tetra-n-propylammonium perruthenate

TPS = Tripropylsilyl

Tr = Trityl, triphenylmethyl

Trt = Trityl, triphenylmethyl

Ts = p-Toluenesulphonyl

p-TsOH = p-Toluenesulphonic acid

CHAPTER I

AMMOCIDINS AND RELATED CYTOTOXIC MACROLIDES

Introduction

In the course of screening extracts for apoptosis inducers in Ras-dependent Ba/F3-V12 cells, Hayakawa[1] and co-workers isolated the macrolide ammocidin A **1.1** from a culture broth of *Saccharothrix sp.* AJ9571 in 2001. Ammocidin A was isolated as a colorless powder comprised of a molecular formula of $C_{59}H_{96}O_{22}$ as determined by high resolution FAB-MS. Extensive nuclear magnetic resonance spectroscopy analysis (^{1}H, ^{13}C, COSY, HMBC, HMQC) elucidated the two dimensional molecular structure of ammocidin A, and acidic methanolysis of ammocidin A established the absolute stereochemistry for the sugar moieties (Figure 1.1). In 2009, Hayakawa[2] reported on the isolation and biological properties of three new ammocidins, B **1.2**, C **1.3**, and D **1.4**. The molecular formulae of ammocidins B-D were determined by high resolution electrospray ionization mass spectra to be $C_{60}H_{98}O_{22}$, $C_{53}H_{98}O_{22}$, and $C_{46}H_{74}O_{16}$, respectively.

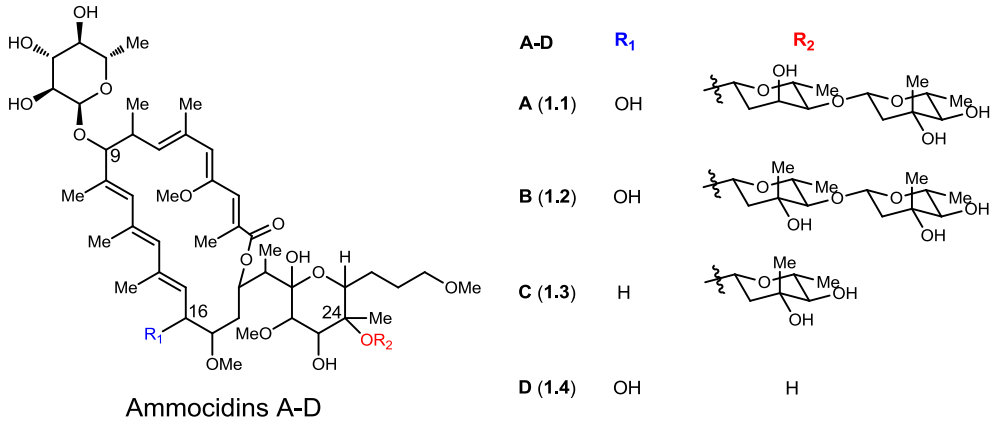


Figure 1.1 Assigned structures of ammocidins A-D

Structurally, ammocidins A-D share a common 20 membered macrolactone encompassing two unsaturated triene moieties of *E*,*E*,*E* (C10-C15) and *E*,*Z*,*E* (C1-C7) configuration. Additional common structures include a 28-carbon seco-acid incorporating a C21-C25 cyclic acetal and 6-deoxy glucose located at C9. The ammocidins differ primarily in glycosylation pattern at C24. Specifically, ammocidin A possesses a β-D-olivomycose-β-D-digitoxose, ammocidin B contains two β-D-olivomycose residues, ammocidin C possesses a terminal olivomycose residue, whereas ammocidin D is completely devoid of sugars at C24. Finally, ammocidin C was reported to be a 16-deoxy metabolite.

Hayakawa determined the cytotoxic activities of the ammocidins on human A549 lung carcinoma cells, MCF-7 human breast carcinoma cells, and HCT116 human colon carcinoma cells. The cell proliferation assay showed potent cytotoxic activities of ammocidin A and B with IC_{50} values ranging from 0.06-0.4 μM, whereas ammocidin C and D exhibited IC_{50} values ranging from 1.8 to 23 μM. It was concluded by Hayakawa that although all the ammocidins contain cytotoxic activities, ammocidins A and B were more potent than C and D. Therefore, the deoxysugar moieties located at C24 play an important role in anti-proliferative activities of

ammocidins. This observation is in accord to the findings on structurally related apoptolidins within our research group.[3]

Communication with Hayakawa[4] provided unpublished 2-D NMR data revealing the following NOE correlations and coupling constants (Figure 1.2, 1.3). The absolute configuration of C9 was tentatively assigned a 9*S* configuration determined by the observed NOE between the C1' methine of the 6-deoxy-L-glucose sugar. The relative configuration of H22 and Me24 was tentatively assigned as a *cis* configuration due to the observed NOE. The relative configuration of H23 and H25 was tentatively assigned as a *cis* configuration due to the observed NOE (Figure 1.2). Finally, the C20 methyl is tentatively assigned as *syn* relative to the C19 hydroxyl based on NOE and coupling constants.

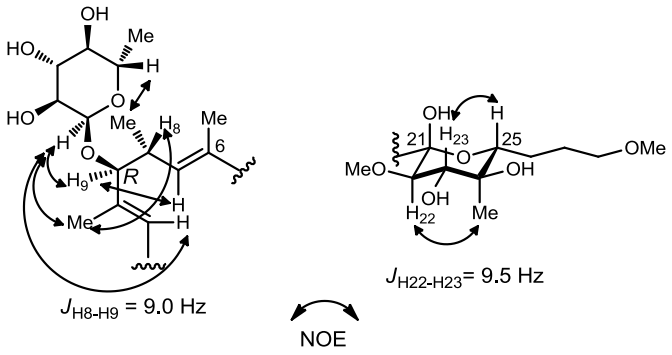


Figure 1.2 C6-C11, C21-28 NOE correlations and coupling constants.

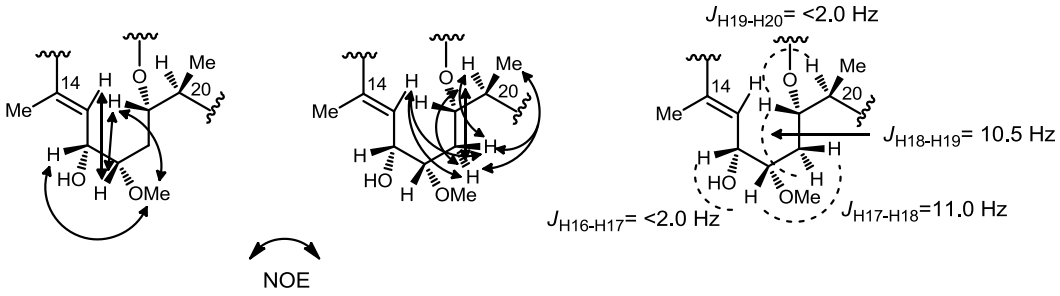


Figure 1.3 C14-C20 NOE correlations and coupling constants.

Given only the two dimensional structure of the common aglycone (ammocidinone) was assigned by NMR analysis with the relative stereochemistry between the C8-C9, C16-C20, C21-C25 regions relying on NOE data, Hayakawa has noted that the structure of the ammocidins bears a resemblance to apoptolidin A, a macrolide of fully assigned stereochemistry that has succumbed to several total syntheses[5]. The ammocidins and the apoptolidins likely share evolutionarily related biosynthetic pathways where their respective configurations at C8, C9, C17 and C19 are assumed to be identical.

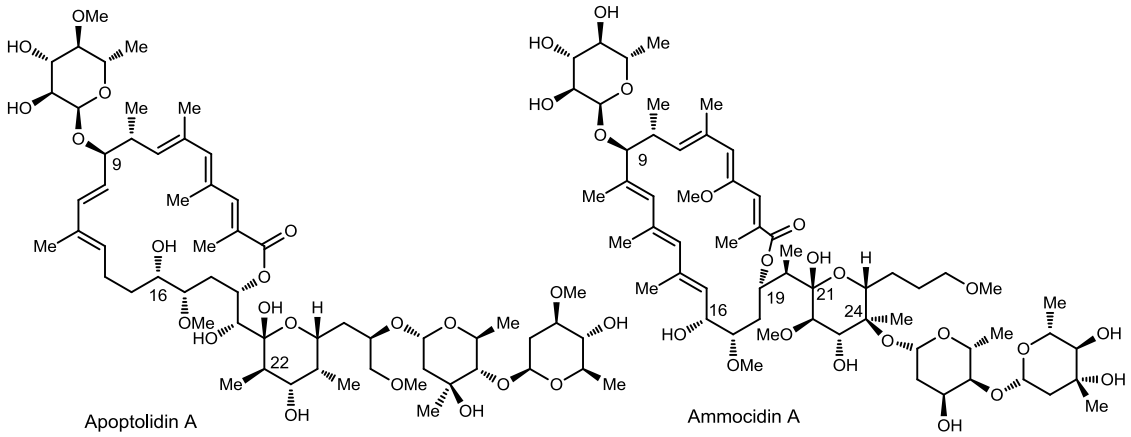


Figure 1.4 Apoptolidin A and tentative assignment of ammocidin A.

Structural comparison between apoptolidin A[6] and ammocidin A indicated that these molecules have similarities in stereochemistry (Figure 1.4). The relative stereochemistry of C17-C19 and C21-C25 were tentatively determined to be identical. Both the C22 methoxy in ammocidin and C22 methyl in apoptolidin occupy an equatorial position and both C24 methyl groups hold an axial orientation (congruent with the NOE data). However, the relative stereochemistry between C16-C17 in apoptolidin, have a *syn* relationship, while in ammocidin, C16-C17 is tentatively assigned as *anti*. While the absolute and relative configuration remains unclear, based on NOE correlations and the known stereochemistry of apoptolidin, ammocidin A has been tentatively assigned as Figure 1.4.

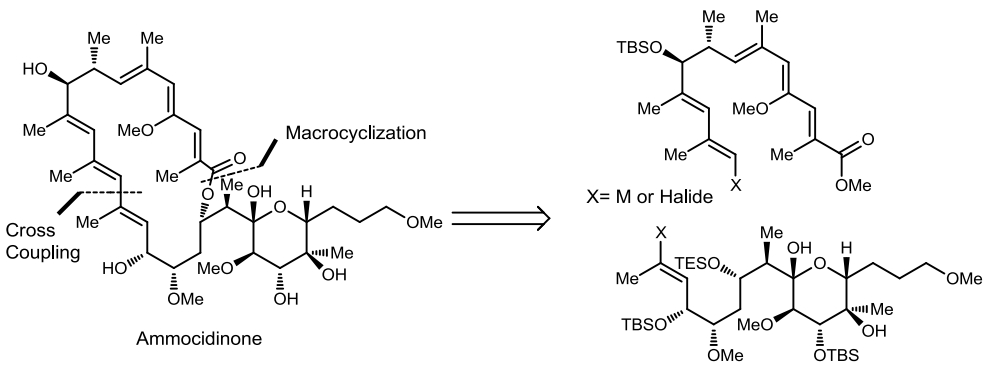


Figure 1.5 Structurally common aglycone ammocidinone from the ammocidins.

The structure of ammocidinone is depicted in Figure 1.5 containing a structurally common 20-membered macrocycle and the highly substituted pyranoside.

Syntheses of Apoptolidin A

Due to the structural similarities of apoptolidins and ammocidins, we reviewed literature precedence that may aid in our synthetic design of ammocidin D. In 2003, Nicolaou[7] and co-workers assembled apoptolidin A in a convergent manner incorporating an intermolecular Stille[8] coupling followed by a Yamaguchi[9] macrocyclization. The sugar moieties were incorporated late in the course of the total synthesis (Figure 1.6).

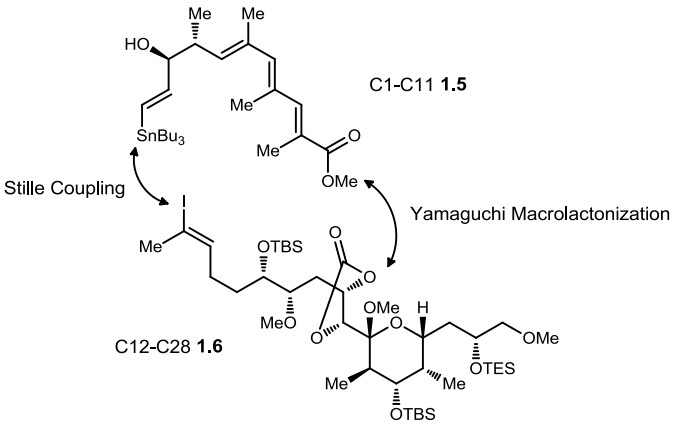
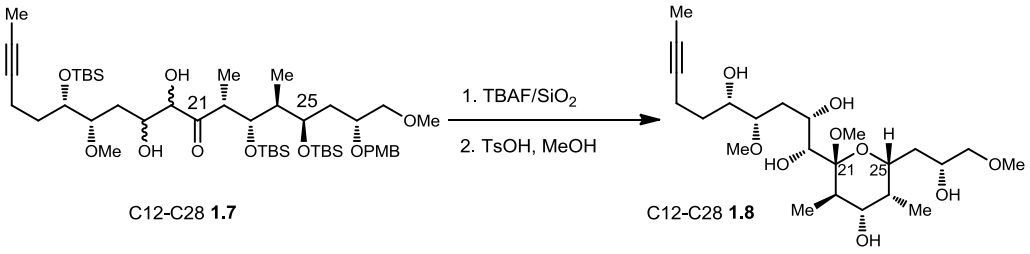


Figure 1.6 Nicolaou's synthesis of apoptolidin A.

Nicolaou and coworkers synthesized the C12-C28 fragment (**1.6**) that incorporates the C21-C25 pyran ketal moiety with the deprotection of C25 (**1.7**). Treating **1.6** in the presence of TBAF resulted in the rapid formation of the hemiacetal and concomitantly protected as the methyl acetal (**1.8**) (Scheme 1.1).



Scheme 1.1 Nicolaou's synthesis of the C12-C28 region of apoptolidin A.

In 2004, Koert[10] and coworkers published the highly convergent synthesis of apoptolidin A following a similar reaction sequence as Nicolaou's group.

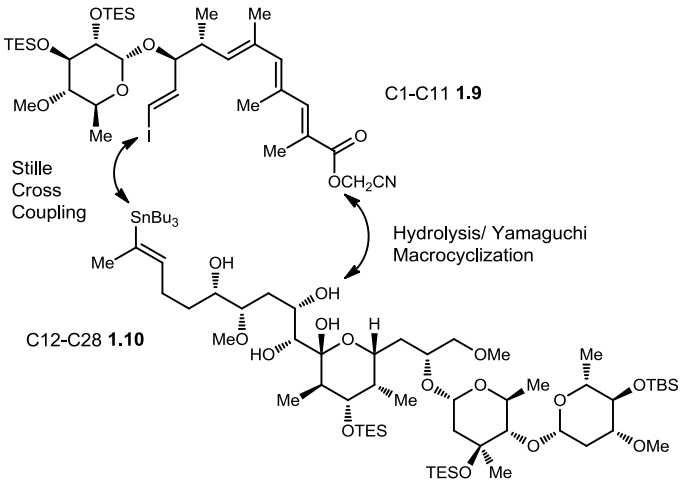
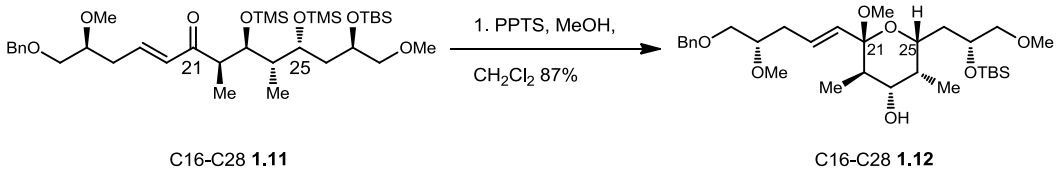


Figure 1.7 Koert's synthesis of apoptolidin A.

Koert and coworkers completed the synthesis of apoptolidin A through an intermolecular Stille coupling with C1-C11 (**1.9**) and C12-C28 (**1.10**) in the presence of copper(I) thiophenecarboxylate[11]. Koert subsequently performed a hydrolysis, Yamaguchi macrocyclization and a global deprotection providing the apoptolidin A (Figure 1.7).



Scheme 1.2 Koert's synthesis of the pyran system of apoptolidin A.

Koert and co-workers synthesized the C16-C28 acetal moiety (**1.12**) in apoptolidin with the deprotection of C25 in the presence of PPTS in methanol. Upon treatment of the C16-C28

region with acid, resulted in the rapid formation of the hemiacetal and concomitantly protected as the methyl acetal (Scheme 1.2).

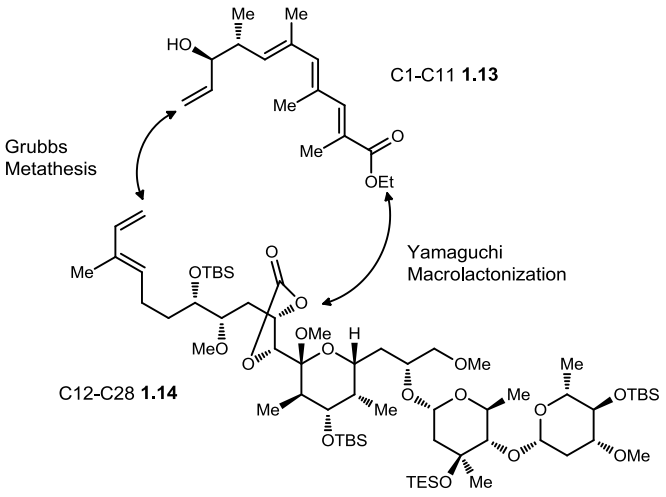
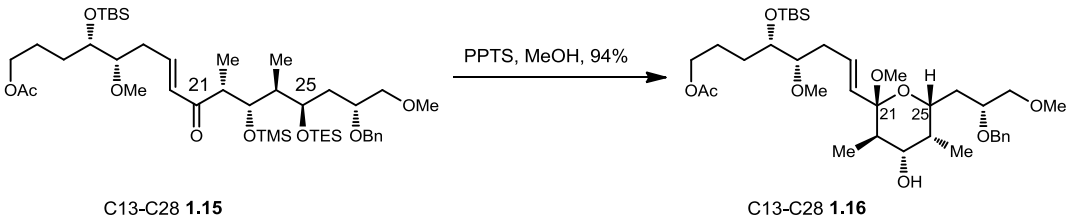


Figure 1.8 Crimmins' synthesis of apoptolidin A.

In 2009, Crimmins and co-workers[12] completed the synthesis of apoptolidin A with an olefin metathesis reaction with a Grubbs[13] heterocyclic carbene catalyst between **1.13** and **1.14** in high yield and olefin metathesis stereoselectivity. Crimmins continued the synthesis with a glycosylation at C9 and hydrolysis of the ethyl ester and Yamaguchi cyclization completed the carbon framework (Figure 1.8).

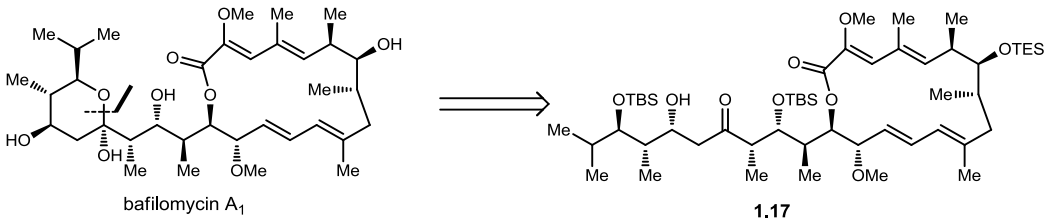


Scheme 1.3 Crimmins' synthesis of the C13-C28 (**1.16**) Fragment.

Crimmins' and co-workers synthesized the C13-C28 (**1.16**) acetal moiety of apoptolidin with the deprotection of C25 in the presence of PPTS in methanol which resulted in the formation of the hemiacetal and concomitantly protected as the methyl acetal. Crimmins' strategy towards the C13-C28 fragment represents a similar strategy compared to that of Koert and Nicolaou (Scheme 1.3).

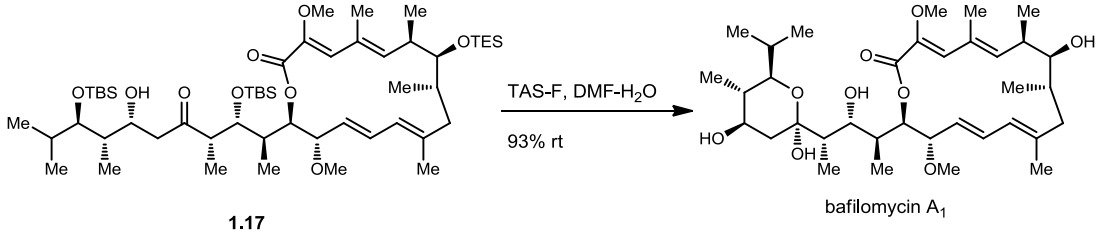
Synthesis of bafilomycins

A different but structurally related macrolide, bafilomycin A_1, a member of the plecomacrolide family of antibiotics, attracted the attention of the synthetic community with its potent antibacterial and antifungal activity.



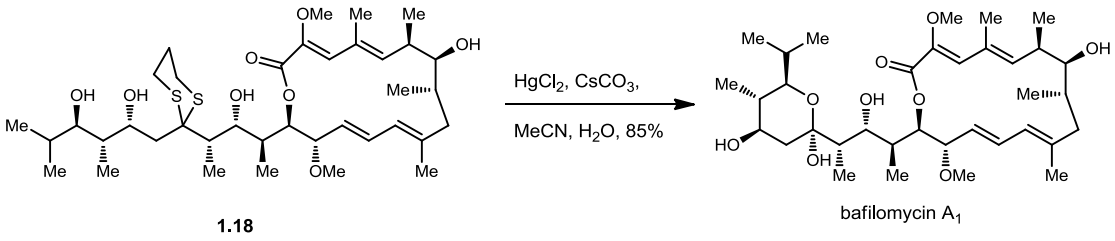
Scheme 1.4 Roush's retrosynthesis of bafilomycin A_1.

In 2002, Roush's[14] synthesis of bafilomycin A_1 contained an acid and base sensitive hemi acetal moiety that was disconnected giving rise to the ketone functionality in **1.17** (Scheme 1.4). This strategy is important and similar to the ammocidins and apoptolidins in the formation of hemiketals.



Scheme 1.5 Roush's formation of bafilomycin A_1.

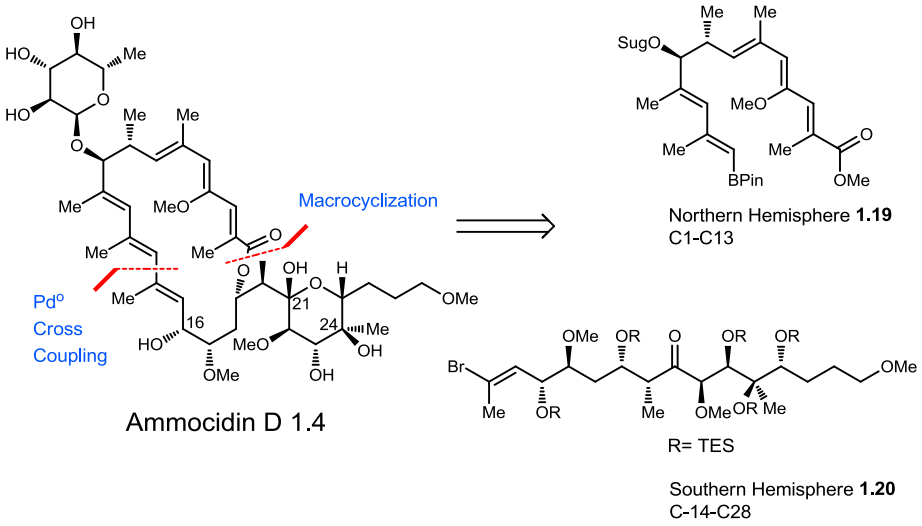
Roush completed the synthesis of bafilomycin A_1 with the careful moderation of basicity of the tris-(dimethylamino)sulfonium difluorosilicate (TAS-F) reagent with aqueous DMF affording the hemiacetal in bafilomycin A_1 (Scheme 1.5).



Scheme 1.6 Hanessian's formation of bafilomycin A.

Hanessian's[15] synthesis of bafilomycin A_1 was completed by treatment of the thioacetal (**1.18**) with mercuric chloride and calcium carbonate in aqueous acetonitrile effecting smooth dethioacetalization to afford bafilomycin A_1 (Scheme 1.6).

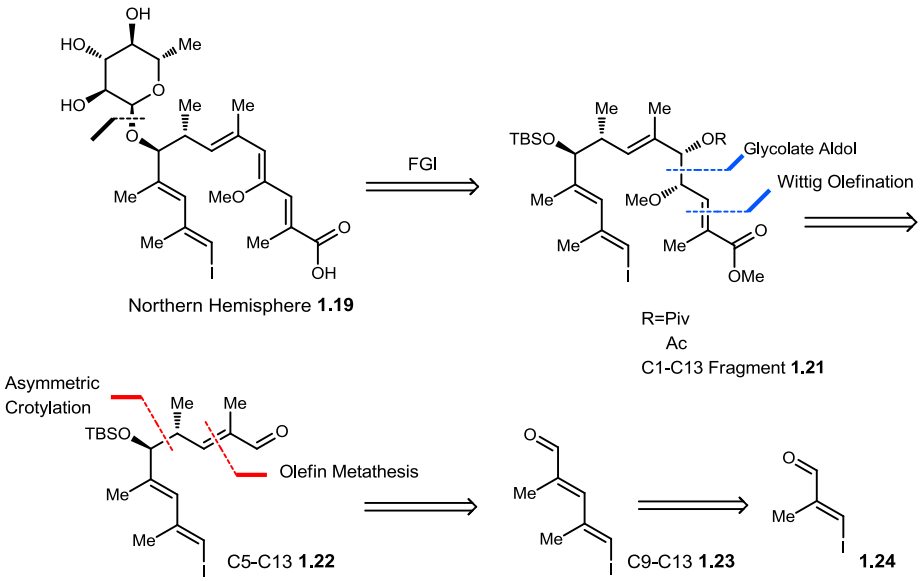
Sulikowski's 1st Generation Retrosynthesis of Ammocidin D (1.4)



Scheme 1.7 Retrosynthetic analysis of ammocidin D.

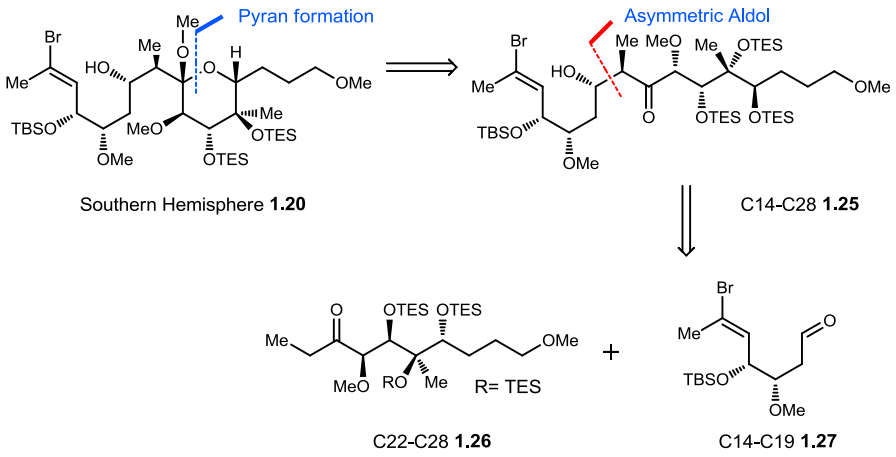
Sulikowski's first generation approach towards the synthesis of the southern fragment of ammocidin D shares a similar strategy to that of Nicolaou, Koert and Crimmins. The early plan for the synthesis of ammocidinone began by using the logical precedent to form the pyranose ring system in the presence of methanol and pTSA in the well established method of constructing ketals. The main over arching goal is the total synthesis of ammocidin D which will determine the absolute and relative stereochemistry of the natural product.

Sulikowski and Liu envisioned the synthesis of ammocidinone and ammocidin D (**1.4**) through a macrocyclization and metal catalyzed cross coupling reaction providing two hemispheres (C1-C13, C14-C28). The chosen bond disconnections assemble the macrolide in an efficient and highly convergent manner in the forward sense.



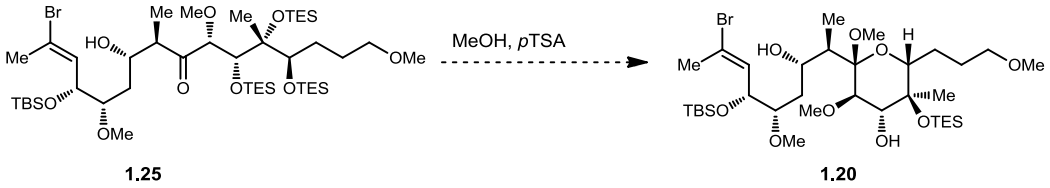
Scheme 1.8 1st Generation Sulikowski retrosynthesis of the northern hemisphere **1.19**.

Sulikowski's retrosynthetic analysis of the northern hemisphere (**1.19**) leads to disconnections to provide the sugarless methyl ester fragment C1-13 (**1.21**). The complete C1-C13 carbon framework can be further disconnected with a Wittig olefination and a glycolate aldol reaction in the forward sense providing advanced unsaturated aldehyde C5-C13 (**1.22**). The unsaturated aldehyde **1.22** can be envisioned from an olefin methathesis[16] and an asymmetric crotylation[17] providing fragment C9-C13 (**1.23**).



Scheme 1.9 1st Generation Sulikowski retrosynthesis of the southern hemisphere.

Sulikowski's retrosynthetic analysis of the southern hemisphere leads to a disconnection that provides an asymmetric aldol adduct (C14-C28 **1.25**). The aldol adduct can be obtained from the ethyl ketone (C22-C28 **1.27**) and aldehyde (C14-19 **1.27**).



Scheme 1.10 Envisioned cyclization to form ammocidin D pyran acetal **1.20**.

Conclusion

Chapter 1 discusses the physical attributes of ammocidin A-D isolated by Hayakawa and co-workers, its stereochemical challenges and relative similiarity to that of apoptolidin. The key synthetic steps were examined in the total syntheses' of apoptolidin, primarily the construction of the pyran acetal and the formation of the macrocycle. Related macrolides that are structurally relevant to ammocidins revealed similar strategies in forming hemi ketals.

Notes and References

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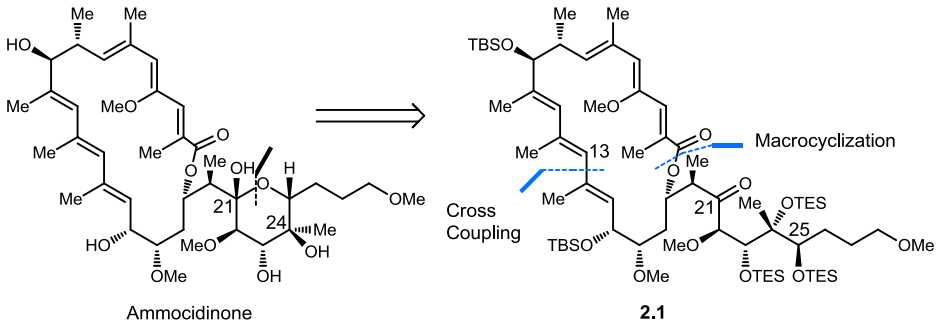
CHAPTER II

EARLY APPROACHES TOWARDS THE PYRAN ACETAL OF AMMOCIDINONE

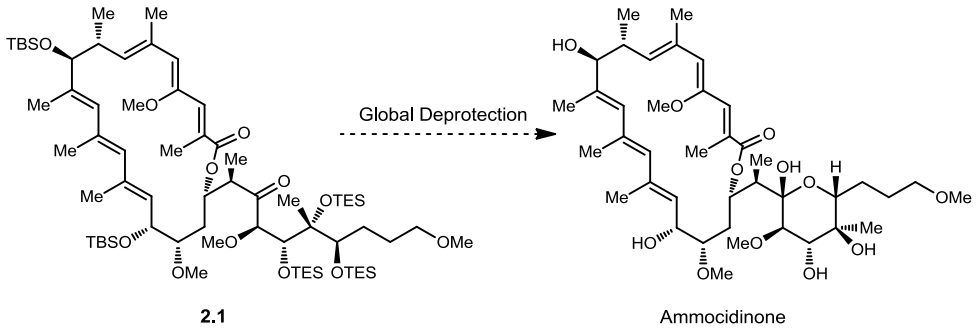
Retrosynthetic Analysis

Our retrosynthetic analysis of ammocidinone started with a disconnection at the hemiacetal bond suggesting ketone **2.1** as a penultimate intermediate. This strategy discussed in chapter 1 exhibited strong precedence in the synthesis of apoptolidin[1] and bafilomycin[2]. Unique to the synthesis of the ammocidins is the incorporation of a tertiary hydroxyl group located at C24 which is absent in the apoptolidin natural products (Scheme 2.1).



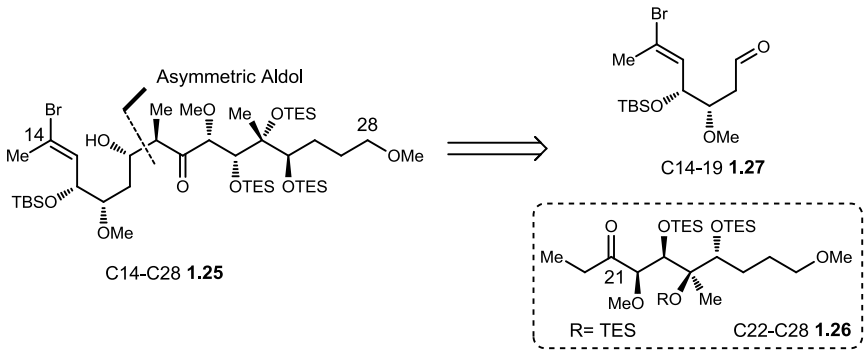
Scheme 2.1 1st Generation retrosynthesis of ammocidinone.

We disconnected three bonds, first at the hemiacetal functionality, second at the ester functionality and third between the C13-14 sp^2-sp^2 carbon bonds. It was envisioned in the forward sense that these bonds would be formed via a cross coupling reaction followed by a macrocyclization reaction. Finally, the hemiacetal functionality would be formed in a late stage following global deprotection of ketone **2.1** (Scheme 2.2).



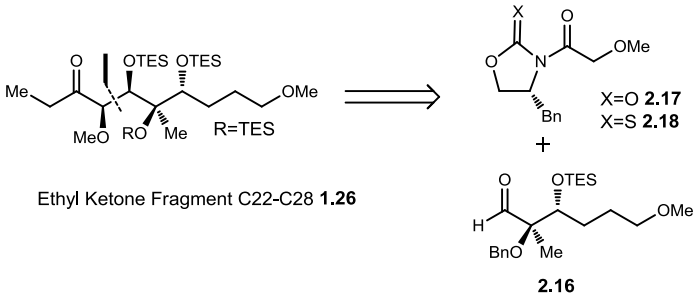
Scheme 2.2 Anticipated global deprotection providing ammocidinone.

Examination of the southern hemisphere C14-C28 fragment **1.25** revealed a highly functionalized array of oxygenated stereocenters. The synthesis of the desired isomer would require the application of asymmetric aldol reactions reactions enabling each stereocenter to be formed in sequential succession (Scheme 2.3).



Scheme 2.3 1st Generation retrosynthesis for fragment C14-C28 **1.25**.

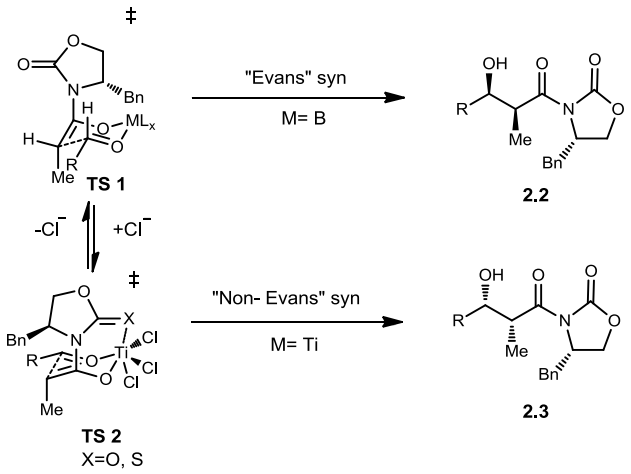
Further disconnection of the C14-C28 fragment provided C14-C19 aldehyde **1.27** and C22-C28 ethyl ketone **1.26**. Synthetic efforts toward the ethyl ketone fragment **1.26** focused on three strategies including an intermolecular auxiliary based aldol reactions, intermolecular and intramolecular Mukaiyama[3] based aldol approaches (Scheme 2.4).



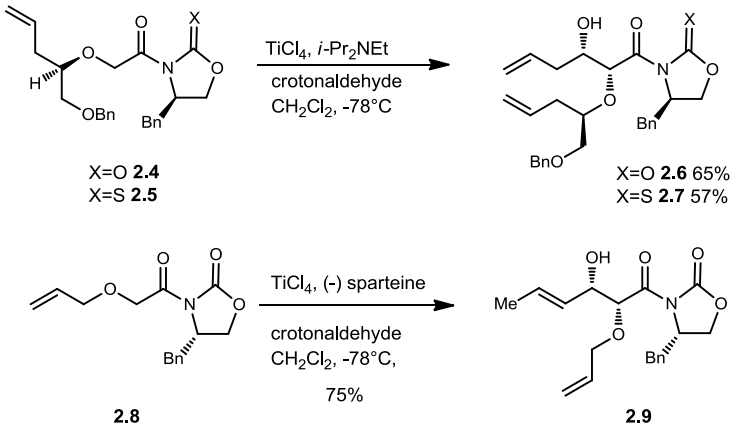
Scheme 2.4 1st Retrosynthesis of fragment C22-C28.

The first synthetic approach to ketone **1.26** was developed by Qingsong Liu and relied on an auxiliary based glycolate aldol reaction developed by Evans[4] and Crimmins[5]. Methods for

producing *syn* diastereomers include the Evans boron enolate aldol addition using *N*-glycolyloxazolidinones and Crimmins' titanium enolates of *N*-glycolyloxazolidinones and *N*-glycolyloxazolidinethiones. Crimmins has proposed that transition state 1 (**TS 1**) for the boron enolate and the titanium enolate gives the "Evans" syn aldol adduct. If chloride ion is sequestered by excess $TiCl_4$, the titanium enolate can also proceed through transition state 2 (**TS 2**) in which both the aldehyde and the auxiliary are coordinated to titanium[6]. These aldol additions are very sensitive to the amount of Lewis acid employed and to the nature of the amine base utilized in the reaction. Therefore, the preparation of either the Evans *syn* or non-Evans *syn* can be achieved by simply changing the stoichoimetry of the Lewis acid and the amine base as illustrated in Scheme 2.5.

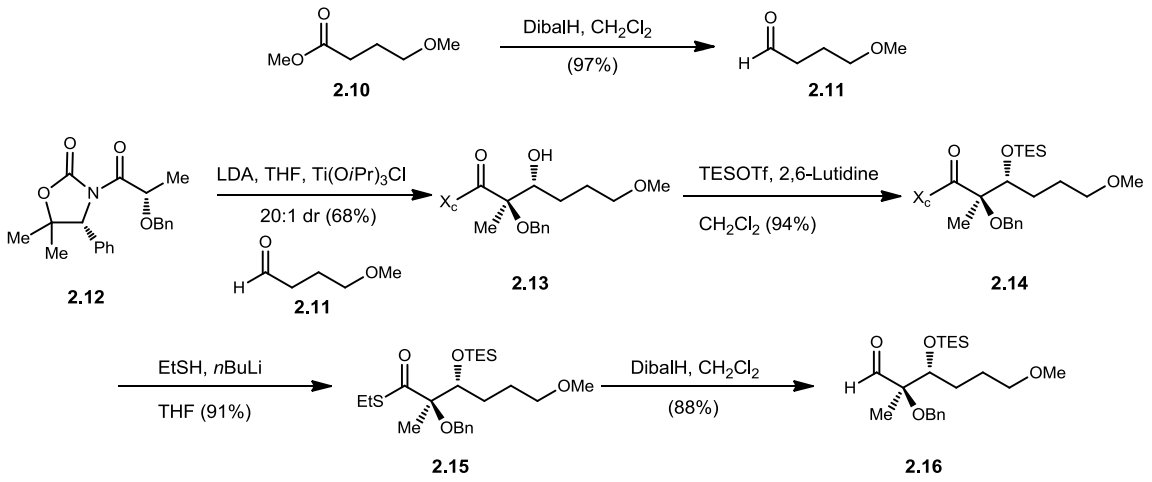


Scheme 2.5 Transition state model for Evans and non Evans *syn* aldols.



Scheme 2.6 Application of Crimmins' *syn* aldol.

In the synthesis of (+)-prelaureatin and (+)-laurallene, Crimmins[7] applied the asymmetric aldol reaction between 3-butenal and the chlorotitanium enolate of the acyl oxazolidinethione to afford aldol adduct **2.7** in high *syn* stereoselectivity (Scheme 2.6). Interestingly, Crimmins successfully demonstrated the flexibility in applying the titanium enolate by using 1.1 equivalents of $TiCl_4$ and 2.5 equivalents of (-) sparteine providing the Evans *syn* adduct **2.6**/**2.7**. Conversely, application of 2.1 equivalents of $TiCl_4$ and 1.1 equivalents of (-) sparteine provided the non-Evans *syn* aldol adduct **2.9**. With this established precedent, we were confident that an auxiliary approach using Crimmins' acyl oxazolidinethione or oxazolidinone would provide the desired *syn* diastereomer for **1.26**.



Scheme 2.7 Formation of aldehyde **2.16**.

The synthesis began with formation of the requisite aldehyde **2.16.** Commercially available methyl 4-methoxy butanoate **2.10** was treated with DibalH producing aldehyde **2.11** in high yield. Applying the Kobayashi[8] methodology towards aldehyde **2.11** provided the *anti* aldol adduct **2.13** in high diastereoselectivity. Protection of aldol adduct **2.13** as the TES ether (94%) and displacement of the auxiliary with ethanethiol (91%) provided thioester **2.15**. Finally, reduction of thioester (88%) **2.15** provided key aldehyde **2.16** (Scheme 2.7).

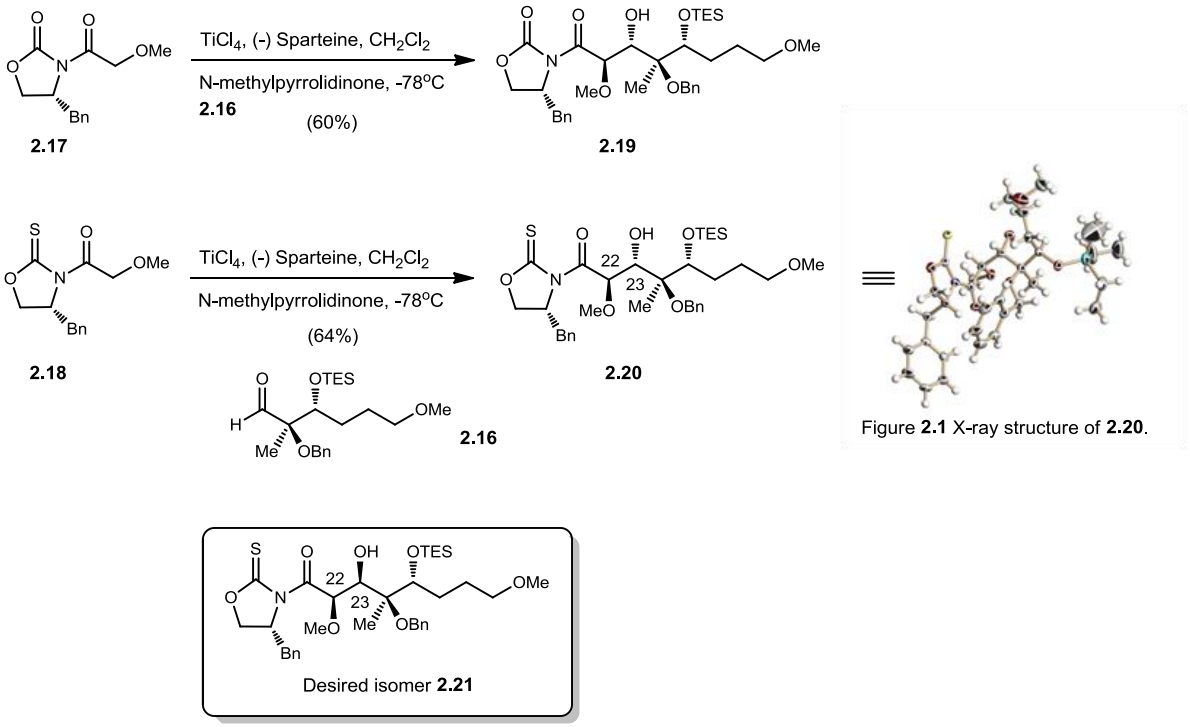
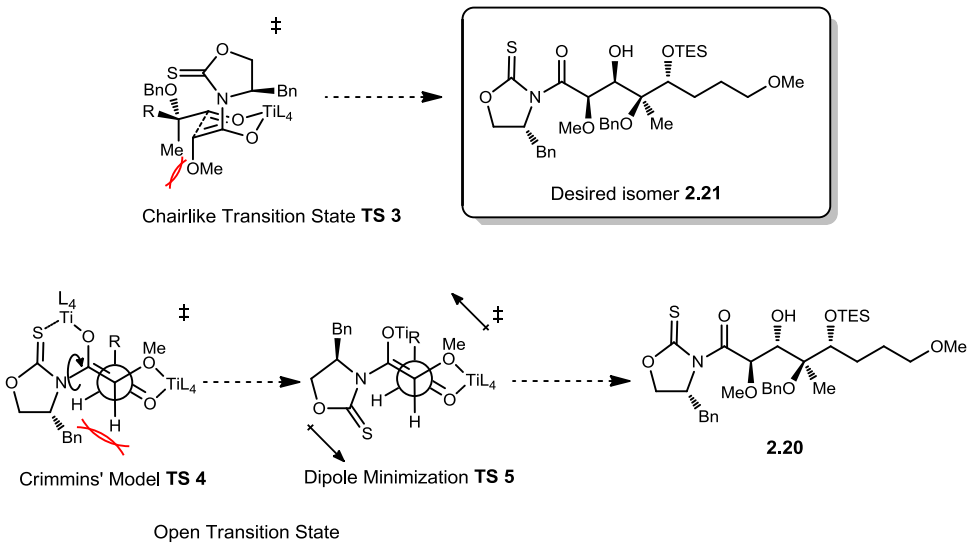


Figure **2.1** X-ray structure of **2.20**.

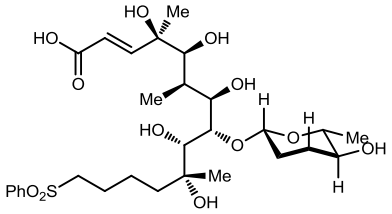
Scheme 2.8 Auxiliary approach towards ethyl ketone C22-C28 **1.26**.

Application of the Evans oxazolidinone **2.17** and Crimmins oxazolidinethione **2.18** surprisingly provided the undesired *anti* C22-C23 stereoisomer; **2.19** and **2.20** in 60% and 64% yield respectively. The unexpected relative stereochemistry was assigned by X-ray crystallography[9] for **2.20** (Figure 2.20 inset Scheme 2.8). Further exploration utilizing the Evans[10] protocol using dibutyl boron triflate with oxazolidinone **2.17** and aldehyde **2.16** again failed to provide any aldol product (Scheme 2.8).

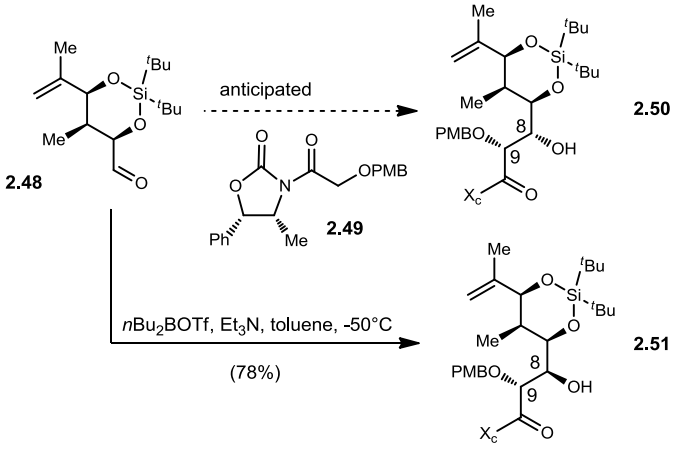


Scheme 2.9 Open transition state rationale for **2.20**.

The proposed Zimmerman Traxler[11] chairlike transition state (**TS 3**) would accurately predict the desired *syn* isomer. However, the quaternary alpha stereocenter from the aldehyde presents a destabilizing *syn* pentane interaction preventing the chair transition state from occuring in the reaction pathway. Crimmins has stated that the addition to the titanium enolate can occur via an open transition state, also supported by Heathcock[12], to explain propionate *anti* aldol additions using *N*-acyloxazolidinones. In addition, the glycolate oxygen may coordinate to the $TiCl_4$ serving to activate the aldehyde. Upon close examination of the open transition state model, direct application of Crimmins' model would have the aldehyde approaching from the more sterically hindered alpha face. Because aldol product **2.20** was unambiguously determined by X-ray crystallography, Crimmins' model would not accurately portray the addition event. Therefore, it is postulated that a bond rotation may occur in an effort to reduce the dipole moment in the transition state, providing rationale for the obtained product (TS **4** vs. TS **5** Scheme 2.9).



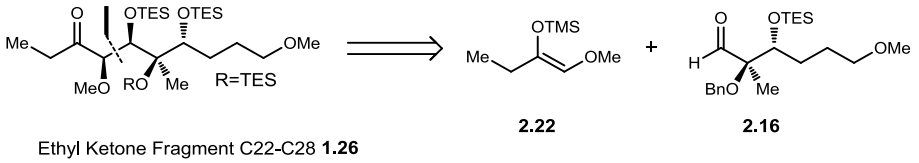
Polyol Glycoside Subunit of Cytovaricin



Scheme 2.10 Evans' unexpected product via auxiliary approach towards cytovaricin B.

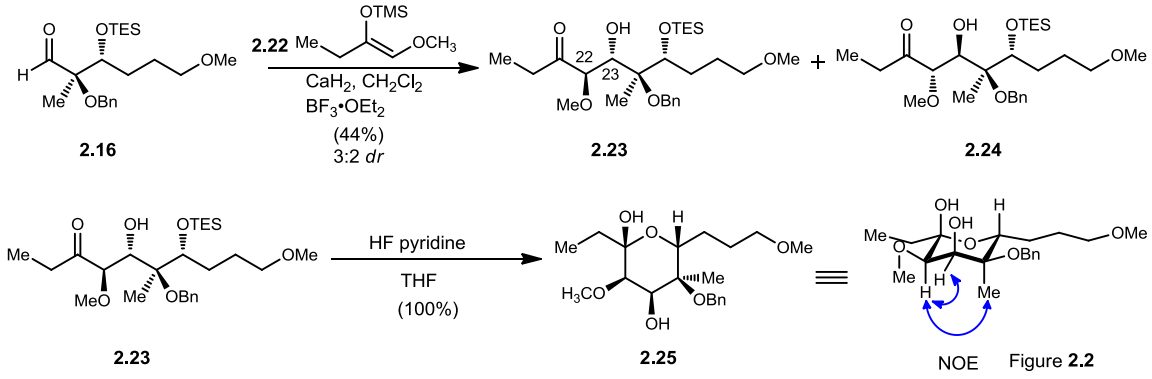
Evans' synthesis of the antibiotic cytovaricin[13] also revealed unexpected stereoselectivity of a glycolate aldol. Evans explanation was the Felkin-Ahn diastereofacial bias in aldehyde **2.48** is sufficiently large to override the inherent β-selectivity of the aldol addition reaction. The chirality in the enolate defines the C9 stereocenter whereas the C8 center is controlled by the chirality of the aldehyde reaction partner. Further attempts by Evans to obtain the desired *syn* aldol adduct was met with failure. This finding by Evans is in accord with our studies using an asymmetric aldol reaction aided by an auxiliary. Ultimately, the auxiliary approach towards our desired stereochemistry proved unsuccessful (Scheme 2.10).

Upon joining the laboratory, I sought to continue our synthetic efforts towards the ethyl ketone fragment **1.26** via the open transition state with the intermolecular Mukaiyama[14] aldol reaction.



Scheme 2.11 2nd Retrosynthesis of fragment C22-C28.

The second route towards the C22-C28 fragment **1.26** involved an intermolecular Mukaiyama variant that required silyl enol **2.22** and key aldehyde **2.16**. If successful, the intermolecular Mukaiyama aldol reaction would produce fragment C22-C28 in a more convergent manner compared to that of the auxiliary based approach (Scheme 2.11).



Scheme 2.12 Mukaiyama aldol based approach towards C22-C28.

Treating the sterically demanding aldehyde **2.16** with silyl enol ether **2.22** and $BF_3{\cdot}OEt_2$ afforded undesired ethyl ketone **2.23** and **2.24** in combined yield of 44% (3:2 dr). Unfortunately, upon deprotection of the TES silyl ether and concomitant formation of the pyranose ring system furnishing **2.25**, NOE correlations (Figure 2.2 inset Scheme 2.12) provided evidence for the *anti* Mukaiyama glycolate aldol adduct **2.23** (Scheme 2.12). The *anti* Mukiayama product between the C22-C23 fragment **2.23** would be epimeric at C23 required for the ammocidins.

The *anti* Mukaiyama glycolate aldol adduct **2.23** can be reasoned through a Felkin-Ahn[15] model (Figure 2.3) where the diastereofacial selection is achieved when the nucleophile approaches the aldehyde opposite the benzyl ether substituent. The major isomer minimizes the unfavorable gauche interaction between the methoxy substituent and the sterically bulky Lewis acid (Figure 2.3). This observation supports the report by Evans[13] where the inherent β selectivity (C23) is dictated by the sterically encumbered aldehyde.

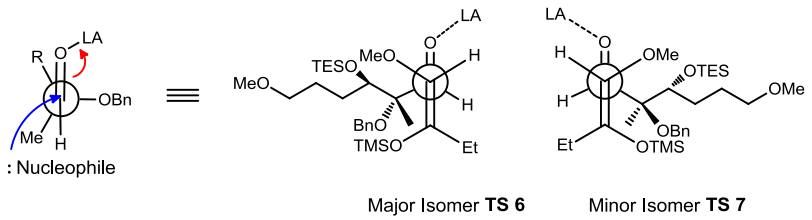


Figure 2.3 Felkin Ahn approach to aldehyde 2.16.

While experimental data supports the Felkin-Ahn approach, application of the chelation control model proposed by Mukaiyama[16] (Figure 2.4) predicts the desired *syn* stereochemistry. 1,2-Asymmetric induction may control the diastereofacial preference that involves chelation of

the bidentate Lewis acid to the α benzyl ether and the aldehyde oxygen. Upon chelation, the approach of the silyl enol ether would be towards the sterically less demanding methyl substituent. Furthermore, the methoxy substituent should avoid unfavorable gauche interactions with the Lewis acid, thereby providing the desired *syn* stereochemistry.

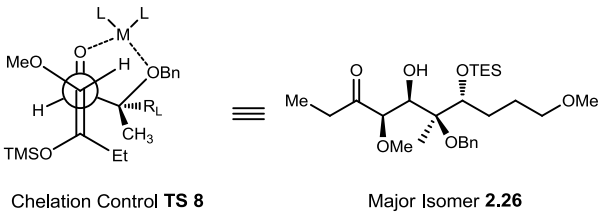
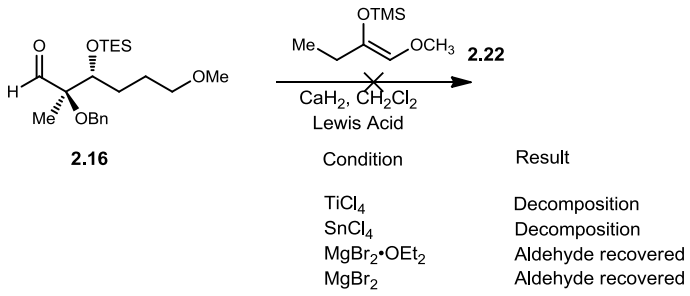


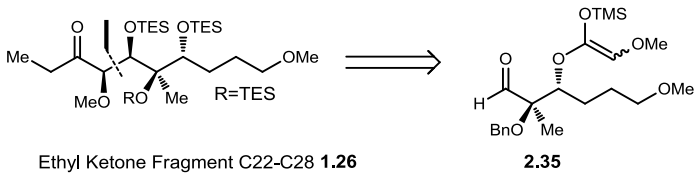
Figure 2.4 Chelation control providing the desired isomer.



Scheme 2.13 Attempted chelation control between silyl enol **2.22** and aldehyde **2.16**.

Upon application of this hypothesis, a survey of bidentate Lewis acids was examined. Reactions involving titanium tetrachloride and stannic chloride resulted in decomposition of starting material. Magnesium bromide and magnesium bromide diethyl etherate resulted in poor reactivity even under elevated temperatures. With minimal success with the

intermolecular Mukaiyama aldol strategy, a new approach towards ethyl ketone C22-C28 **1.26** was necessary (Scheme 2.13).



Scheme 2.14 3rd Retrosynthesis of fragment C22-C28.

Alternatively, fragment **1.26** can be disconnected via an intramolecular Mukaiyama aldol reaction to provide the silyl ketene acetal **2.35**. The third retrosynthesis of fragment C22-C28 was devised through an intramolecular variant requiring silyl ketene acetal **2.35**. We further expected the quaternary carbon at C24 to increase the rate of lactone formation due to the Thorpe Ingold[17] effect (Figure 2.5).

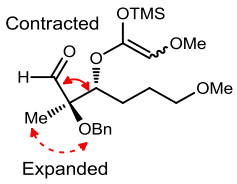
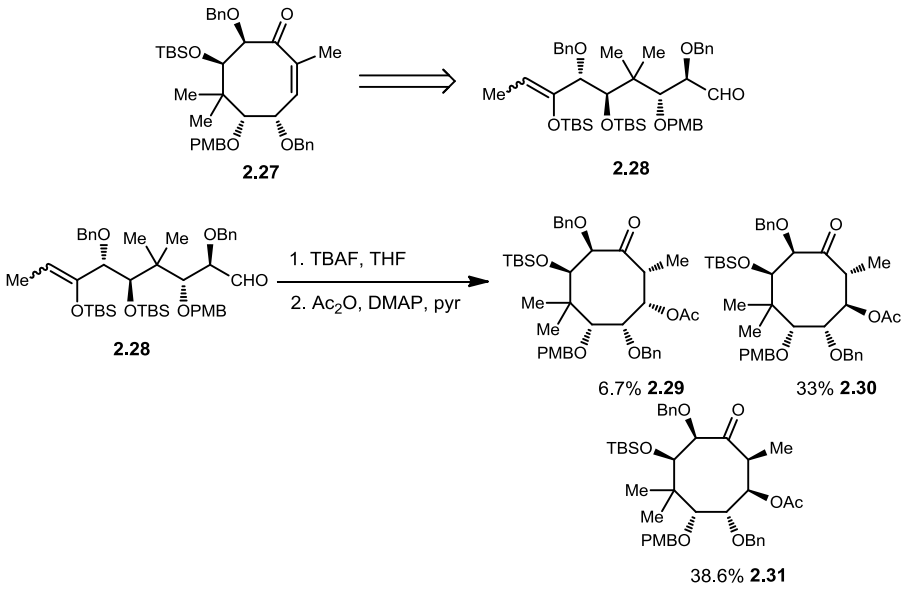
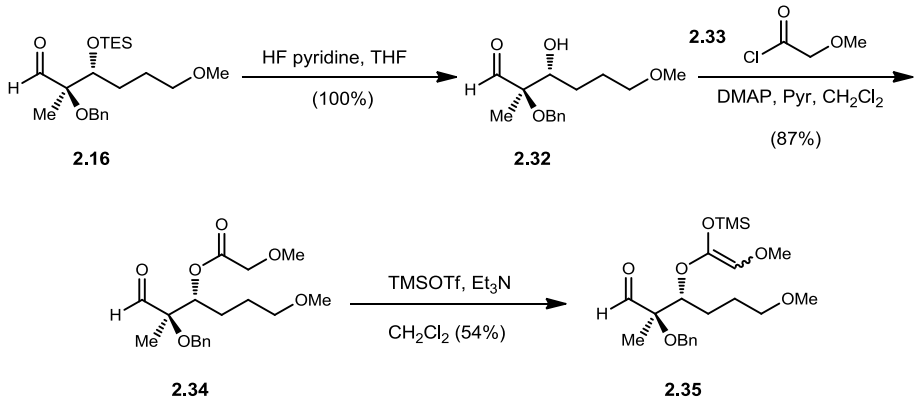


Figure 2.5 Thorpe Ingold effect.



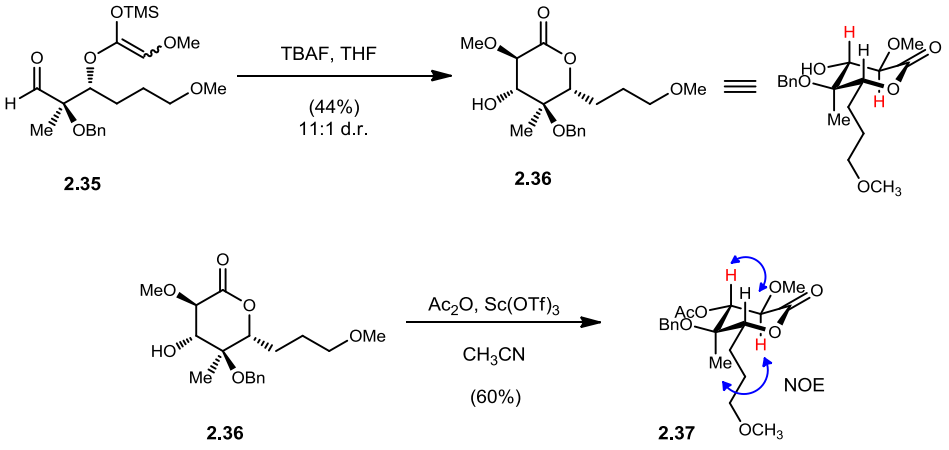
Scheme 2.15 Mukaiyama's fluoride mediated aldol addition.

A similar intramolecular Mukaiyama aldol approach was successfully employed by Mukaiyama [18]and co-workers in order to develop an alternative method for the polyoxy 8-membered ring compound **2.27** corresponding to the B ring of Taxol. In this precedent, tetrabutyl ammonium fluoride mediated intramolecular aldol reaction with **2.28** provided an inseparable mixture that was further acetylated to provide **2.29**, **2.30**, and **2.31** in 6.7%, 33%, and 38.6% yields respectively (Scheme 2.15).



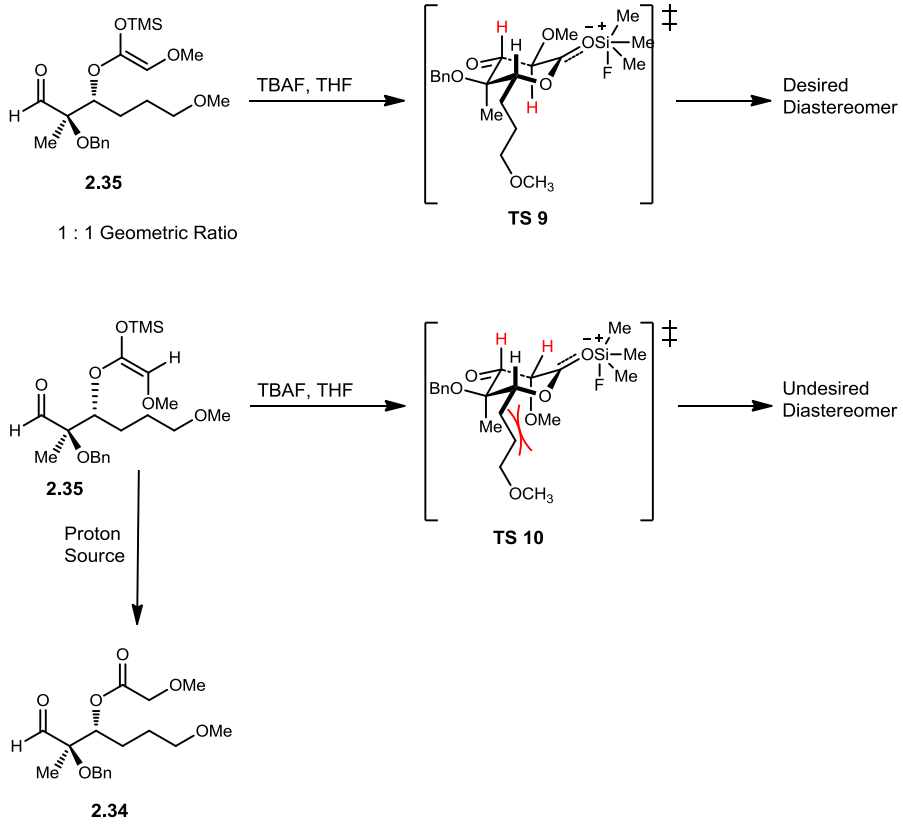
Scheme 2.16 Synthesis of the intramolecular Mukaiyama precursor.

Synthesis of the necessary intramolecular aldol precursor of **2.35** commenced with HF ·pyridine treatment of aldehyde **2.16** to provide the β-hydroxy aldehyde **2.32**. Subsequently, **2.32** was treated with methoxy acetyl chloride and pyridine (**2.33**) to furnish ester **2.34**. Ester **2.34** was then converted to the silyl ketene acetal **2.35** in the presence of TMSOTf and triethylamine furnishing an inseparable 1:1 mixture of geometrical isomers (Scheme 2.16).



Scheme 2.17 Fluoride ion mediated intramolecular Mukaiyama addition.

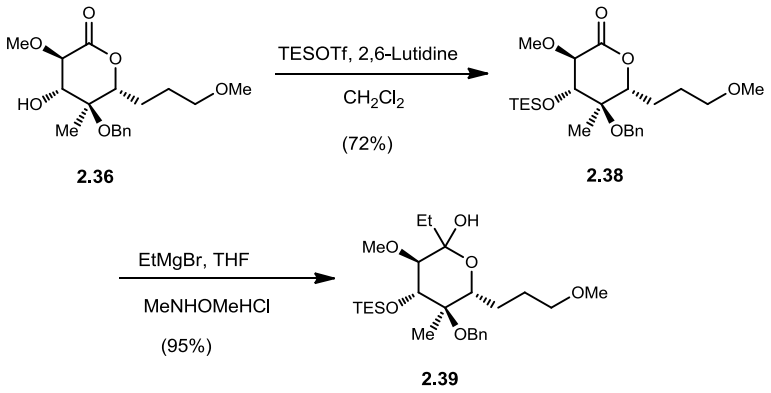
Much to our delight silyl ketene acetal **2.35** was treated with TBAF providing lactone **2.36** in 44% yield (11:1 dr). Gratifyingly, lactone **2.36** was acylated in the presence of scandium triflate[19] confirming the desired stereochemistry relative to the ammocidins. The H_{22}-H_{23} coupling constants at 7.8 Hz and NOE correlations provided evidence for the two axial oriented protons (Scheme 2.17).



Scheme 2.18 Rationalization for the desired diasteromer.

The transitions state models (Scheme 2.18) provide a detailed rationale of the diastereoselectivity. Upon addition of nucleophilic fluoride, the *Z*-geometric isomer provides the

desired chair transition state (**TS 9** Scheme 2.18). The *E*-geometric isomer which experiences an undesirable *syn* pentane interaction in the chair conformer (**TS 10** Scheme 2.18) is instead protonated by water leading to **2.34**. Anhydrous tetrabutyl ammonium triphenyl difluoro silicate (TBAT) demonstrated a diastereomeric ratio of 1 : 1. Furthermore, TBAF dried under molecular sieves provided a distereomeric ratio of 2 : 1. Overall, the transition state model illustrates the importance of the *Z*-geometrical isomer which ultimately provides the desired stereoisomer (Scheme 2.18).

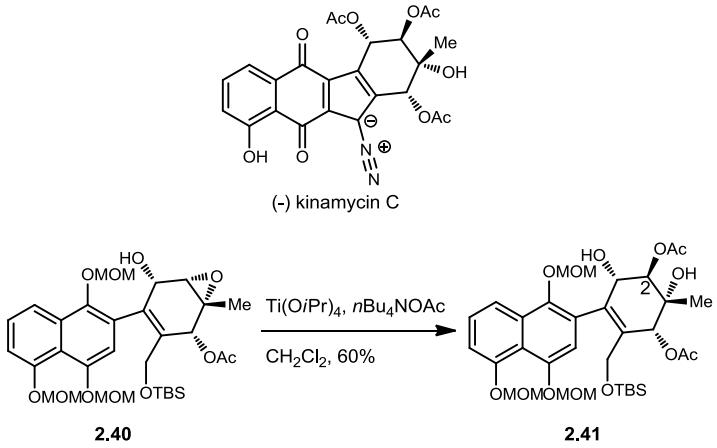


2.36 **2.38** **2.39**

Scheme 2.19 Synthesis of lactol **2.39**.

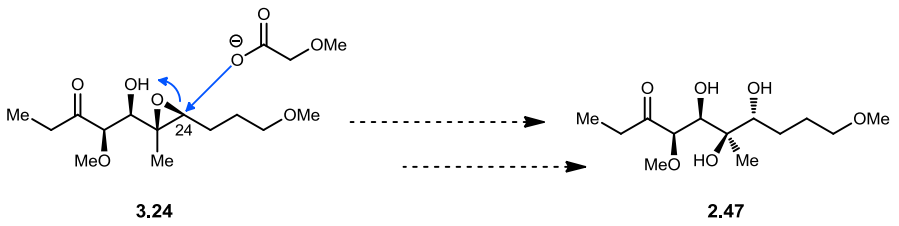
With the desired stereochemistry established for lactone **2.36**, it was necessary to access the ethyl ketone functionality to further advance the synthesis. Protection of lactone **2.36** as the TES ether provided **2.38** in 72% yield. Treatment with ethyl magnesium bromide and the Weinreb[20] hydrochloride salt provided lactol **2.39** in high yield. Our efforts to form the Weinreb amide or equilibrate to the ethyl ketone with TESCl and either sodium hydride or imidazole were unsuccessful. This result was detrimental towards this route since we were

unable to furnish the ethyl ketone functionality required for progress in the synthesis (Scheme 2.19). Therefore, we began to modify the synthesis to avert this problem following the seminal work by Porco in a key step in the synthesis of the kinamycins.

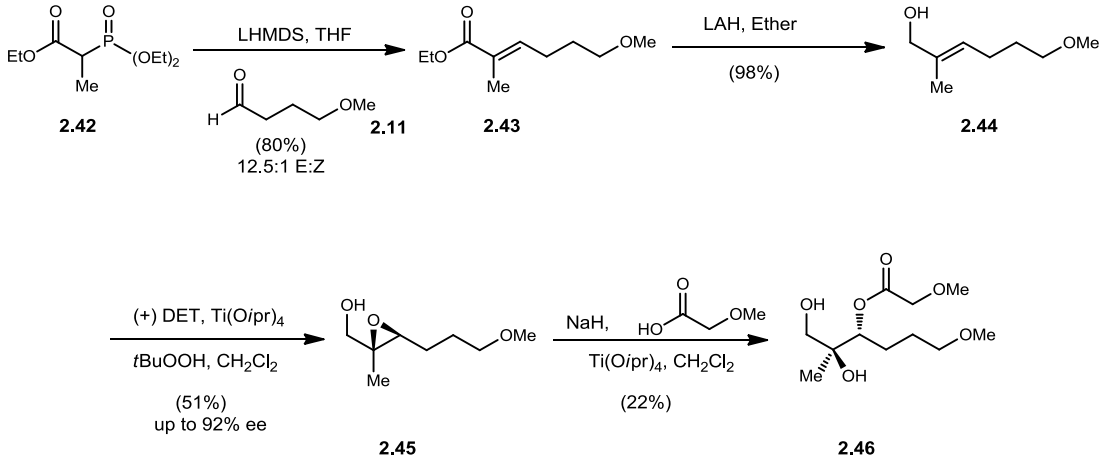


Scheme 2.20 Porco's synthesis of kinamycin C.

In Porco's synthesis of kinamycin C[21] which contained a highly oxygenated cyclohexene ring with an epoxide opening reaction mediated by $Ti(^{i}Pr\ O)_4$. *Syn* epoxy alcohol **2.40** was subjected to tetrabutyl ammonium acetate in the presence of titanium isopropoxide giving rise to diol **2.41** with inversion of stereochemistry at C2. This work provided the initial notion of an epoxide opening reaction with acetic acid at C24 could establish the desired stereochemistry for ethyl ketone **1.26** (Scheme 2.21).



Scheme 2.21 Revised synthetic strategy towards ethyl ketone fragment **2.47**.



Scheme 2.22 Expedited synthesis of the Mukaiyama precursor.

A new route was devised to in order to implement an improvement in the epoxide opening and second, to remove the benzyl protecting group of lactone **2.36**. Commercially available ethyl 2-(diethoxyphosphoryl)propanoate reagent **2.42** was condensed with aldehyde **2.11** in the presence of LHMDS to provide conjugated ester **2.43** in a 12.5:1 *E*:*Z* ratio. Reduction of ester **2.43** gave allylic alcohol **2.44** in high yield and treatment of the allylic alcohol towards the Sharpless epoxidation[22] protocol provided epoxy alcohol **2.45** in low to moderate yield. Unfortunately, addition of α-methoxy acetic acid in the presence of titanium Lewis acid

furnished **2.46** in only 22% yield (Scheme 2.22). The reaction suffered greatly from acyl migration after the epoxide opening event, and consequently the synthetic route needed to be redesigned. In order to alleviate the problematic acyl migration it was decided the ethyl ketone moiety would be installed prior to the epoxide opening. This methodology generated a successful avenue towards the pyran acetal discussed in Chapter 3.

Conclusion

In this chapter we explored various aldol disconnections in an effort to establish the desired stereochemistry for the pyranose ring required in the ammocidins. The intermolecular Mukaiyama provided the undesired stereoisomer whereas the intramolecular variant provided the desired stereoisomer. Unfortunately we were unable to establish the ethyl ketone moiety required to proceed with the synthesis in the intramolecular pathway. However, the new epoxide chemistry provided the first seeds which matured into a new and productive methodology described in chapter 3.

Experimental Methods

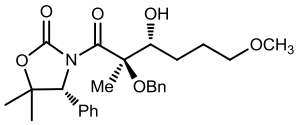
General Procedure: All non-aqueous reactions were performed in flame-dried or oven dried round-bottomed flasks under an atmosphere of argon. Stainless steel syringes or cannula were used to transfer air- and moisture-sensitive liquids. Reaction temperatures were controlled using a thermocouple thermometer and analog hotplate stirrer. Reactions were conducted at room temperature (rt, approximately 23 °C) unless otherwise noted. Flash column chromatography was conducted as described by Still et. al. using silica gel 230-400 mesh[1]. Where necessary, silica gel was neutralized by treatment of the silica gel prior to chromatography with the eluent containing 1% triethylamine. Analytical thin-layer chromatography (TLC) was performed on E. Merck silica gel 60 F254 plates and visualized using UV, and potassium permanganate stain. Yields were reported as isolated, spectroscopically pure compounds.

Materials: Solvents were obtained from either a MBraun MB-SPS solvent system or freshly distilled (tetrahydrofuran was distilled from sodium-benzophenone; toluene was distilled from calcium hydride and used immediately; dimethyl sulfoxide was distilled from calcium hydride and stored over 4 Å molecular sieves). Commercial reagents were used as received. The molarity of *n*-butyllithium solutions was determined by titration using diphenylacetic acid as an indicator (average of three determinations).

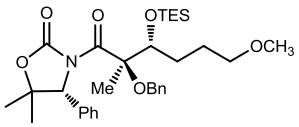
Instrumentation: Infrared spectra were obtained as thin films on NaCl plates using a Thermo Electron IR100 series instrument and are reported in terms of frequency of absorption (cm^{-1}). ^{1}H NMR spectra were recorded on Bruker 300, 400, 500, or 600 MHz spectrometers and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad, app = apparent), coupling constants (Hz), and integration. Deuterated chloroform was standardized to 7.26 ppm. ^{13}C NMR spectra were recorded on Bruker 75, 100, 125, or 150 MHz spectrometers and are reported relative to deuterated solvent signals. LC/MS was conducted and recorded on an Agilent Technologies 6130 Quadrupole instrument. High-resolution mass spectra were obtained from the Department of Chemistry and Biochemistry, University of Notre Dame using either a JEOL AX505HA or JEOL LMS-GCmate mass spectrometer. Optical rotations were obtained using a Perkin Elmer 341 polarimeter.

[1] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

Preparative Procedures

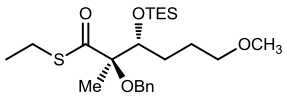


(R)-3-((2R,3R)-2-(benzyloxy)-3-hydroxy-6-methoxy-2-methylhexanoyl)-5,5-dimethyl-4-phenyloxazolidin-2-one (2.13). *n*Butyl lithium (1.92 mL, 1.80 M) was added to a solution of diisopropylamine (.51 mL, 3.69 mmol) in THF (10 mL) at 0°C. After 20 min, chiral auxiliary (**2.12**) (.77 g, 2.30 mmol) in THF (7 mL) was added at -78°C. Titanium chlorotriisopropoxide (2.40 g, 9.23 mmol) in THF (7 mL) was added to the reaction mixture and stirred for 30 min before warming to -40°C. After 1h, the reaction was cooled to -78°C before the dropwise addition of aldehyde (35) (.47 g, 4.61 mmol) in THF (7 mL). The reaction was warmed to -40°C for a final 2h. The reaction was washed with saturated ammonium chloride solution, stirred with celite for 30 min and extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried and concentrated *in vacuo* furnishing a yellow oil. The residue was purified by flash chromatography (5:1, hexane: ethyl acetate) to afford .71 g (68%) of the aldol adduct **2.13**. $[\alpha]_D^{25}$ -56.7 (*c* 1.0, $CHCl_3$); IR (neat) 2932, 1779, 1455, 1102 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ 7.43 (d, *J* =7.6 Hz, 2 H), 7.23-6.96 (m, 8H), 4.94 (s, 1H), 4.82 (t,6.8 Hz, 1 H), 4.58 (d, *J* = 11.2 Hz, 1H), 4.53 (d, *J* = 11.2 Hz, 1 H), 3.25-3.10 (m, 2H), 3.05 (s, 3H), 1.90-1.57 (m, 4H), 1.81 (s, 3H),1.07 (s, 3H), 0.58 (s, 3 H); ^{13}C NMR (100 MHz, C_6D_6): δ 174.21, 152.02, 139.11, 137.19, 86.36, 81.60, 73.50, 72.31, 69.12, 66.96, 58.17,29.41, 28.11, 26.76,23.40, 17.00; HRMS calcd for $C_{26}H_{33}$ $LiNO_6$ 462.2468 [M+Li] found 462.2471.

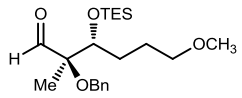


(R)-3-((2R,3R)-2-(benzyloxy)-6-methoxy-2-methyl-3-(triethylsilyloxy)hexanoyl)-5,5-dimethyl-4-phenyloxazolidin-2-one (2.14). TESOTf (.78 mL, 3.4 mmol) was added to a solution of 2, 6-lutidine (.60 mL, 5.19 mmol) and aldol adduct **2.13** (.77 g, 1.73 mmol) in dichloromethane (2.0 mL) at 0°C. After 1h, the reaction was washed with water and extracted dichloromethane (3 x 10 mL). The combined organic layers were dried and concentrated *in vacuo* producing a yellow oil. The residue was purified by flash chromatography (10 : 1, hexane: ethyl acetate) to afford .91 g (93%) of silyl protected aldol adduct **2.14**. : $[\alpha]_D^{25}$ +9.7 (*c* 1.0, $CHCl_3$); IR(neat) 1954, 1456, 1118 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.40-7.26 (m, 8H), 7.16 (m, 2H), 5.13 (s, 1H), 4.78 (d, *J* = 12 Hz,

1H), 4.69 (t, *J* = 4 Hz, 1H), 4.53 (d, *J* = 12 Hz, 1H), 3.27 (s, 3H), 3.26-3.23 (m, 2H), 1.76-1.68 (m, 1H), 1.58 (s, 3H), 1.56-1.47 (m, 3H), 1.43 (s, 3H), 0.95-0.88 (m, 12H), 0.52 (q, J = 8Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): δ; 175.8, 151.8, 138.7, 136.5, 128.6, 128.5, 128.2, 127.2, 127.1, 85.6, 81.7, 76.3, 72.8, 69.2, 67.0, 58.3, 29.8, 28.4, 26.5, 23.8, 16.4, 7.0, 5.4; HRMS calcd for $C_{32}H_{47}NO_6SiLi$ [M+Li] 576.3333 found 576.3339.

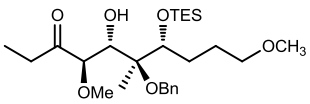


(2R,3R)-S-ethyl-2-(benzyloxy)-6-methoxy-2-methyl-3-(triethylsilyloxy)hexanethioate (2.15). *n*Butyl lithium (1.39 mL, 1.8 M) was added to a solution of ethanethiol (.15 mL, 2.09 mmol) in THF (2 mL) at -78°C. After 10 min, silyl protected aldol aduct **2.14** in THF (.25 mL) was added. For 10 min at -78°C the solution was warmed to rt for 30 min. The mixture was washed with 1 M NaOH solution (pH 7) and extracted with diethyl ether (3 x 5 mL). The combined organic layers were dried and concentrated *in vacuo* furnishing a yellow oil. The residue was purified by flash chromatography (20 : 1, hexane: ethyl acetate) to afford 280 mg (91%) of thioester **2.15**. $[\alpha]_D^{25}$ +29.0 (*c* 1.2, $CHCl_3$); IR (neat) 2954, 1875, 1454, 1120 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.28 (m, 5H), 4.69 (d, *J* = 12 Hz, 1H), 4.61 (d, *J* = 12 Hz, 1H), 4.02 (t, *J* = 4 Hz, 1H), 3.35-3.32 (m, 2H), 3.30 (s, 3H), 2.84 (m, 2H), 1.72-1.68 (m, 2H), 1.61-1.53 (m, 2H), 1.47 (s, 3H), 1.26 (t, *J* = 4 Hz, 3H), 0.97 (t, *J* = 8 Hz, 9H), 0.62 (q, *J* = 8 Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 205.0, 138.7, 128.2, 127.2, 87.9, 77.7, 72.9, 66.6, 58.4, 29.7, 26.7, 22.7, 16.7, 14.4, 7.0, 5.4; HRMS calcd for $C_{23}H_{40}O_4LiSSi$ [M+Li] 447.2577 found 447.2583.

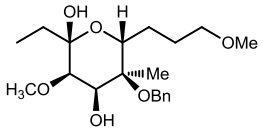


(2R,3R)-2-(benzyloxy)-6-methoxy-2-methyl-3-(triethylsilyloxy)hexanal (2.16). Dibal-H (.12 mL, .69 mmol) was added to a solution of thioester **2.15** (.10 g, .23 mmol) (2.15) in dichloromethane at -78°C. After for 1h, MeOH (3 mL) was added dropwise. The reaction was washed with saturated NaK tartrate Rochelle salts (100 mL) and stirred vigorously until two phases were apparent. The reaction mixture was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried and concentrated *in vacuo* furnishing a clear oil. The residue was purified by flash chromatography (25 : 1, hexane: ethyl acetate) to afford .79 g (88%) of aldehyde **2.16**. $[\alpha]_D^{25}$ +58.5 (*c* 0.5, $CHCl_3$); IR (neat) 2954, 1737, 1453, 1116 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.63 (s, 1H), 7.37-7.28 (m,

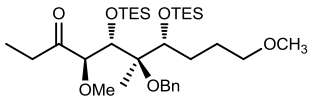
5H), 4.58 (d, *J* = 12 Hz, 1H), 4.38 (d, *J* = 12 Hz, 1H), 3.97 (dd, *J* = 8, 4 Hz, 1H), 3.37 (t, J = 4Hz, 2H), 3.32 9(s, 3H), 1.78-1.69 (m, 2H), 1.62-1.54 (m, 2H), 1.33 (s, 3H), 0.93 (t, *J* = 8Hz, 9H), 0.60 (q, *J* = 8Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 204.0, 138.3, 128.3, 127.6, 127.5, 84.7, 75.7, 72.7, 66.5, 58.5, 29.3, 26.5, 12.8, 6.9, 5.3; HRMS calcd for $C_{21}H_{36}O_4$ LiSi [M+Li] 387.2543 found 387.2584.



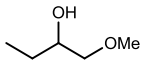
(4R,5S,6S,7R)-6-(benzyloxy)-5-hydroxy-4,10-dimethoxy-6-methyl-7-(triethylsilyloxy)decan-3-one (2.23). Calcium hydride (15 mg) was added to a solution of silyl enol ether **2.22** (160 mg, .92 mmol) and aldehyde **2.16** (70 mg, .18 mmol) in CH_2Cl_2 (.18 mL). After 1h, $BF_3{\cdot}OEt_2$ (.20 mL, .5M in CH_2Cl_2) at -78°C was added slowly. For 1h at -78°C, the reaction was warmed to 0°C. After 1h, the mixture was washed with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried and concentrated *in vacuo* producing a yellow oil. The residue was purified by flash chromatography (5 : 1, hexane: ethyl acetate) to afford 39 mg (44%) of Mukaiyama aldol adduct **2.23**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (m, 5H), 4.54 (dd, *J* = 11.1 Hz, 2H), 4.01 (dd, *J* = 5.1 Hz, 1H), 3.89 (d, *J* = 5.1 Hz, 2H), 3.36 (t, *J* = 2.1 Hz, 2H), 3.29 (s,3H), 3.28 (s,3H), 3.06 (d, *J* = 6.9 Hz, 1H), 2.46-2.29 (m, 2H), 1.78 (broad d, *J* = 3.6 Hz, 2H), 1.34 (s, 3H), 0.93 (t, *J* = 8.1 Hz, 9H), 0.77 (t, *J* = 9 Hz, 3H), 0.63 (q, *J* = 9 Hz, 6H).



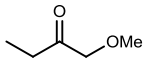
(2S,3R,4S,5S,6R)-5-(benzyloxy)-2-ethyl-3-methoxy-6-(3-methoxypropyl)-5-methyltetrahydro-2H-pyran-2,4-diol (2.25). HF pyridine (.5 mL) was added to a solution of aldol adduct **2.23** (3.20 mg, 6.63 µmol) in THF (.1 mL) at 0°C for 1h. The reaction was washed with saturated $NaHCO_3$ and extracted with diethyl ether (3 x 10 mL). The combined organic layers were dried and concentrated *in vacuo* furnishing a clear oil. The residue was purified by flash chromatography (1 : 1, hexane: ethyl acetate) to afford 2.7 mg (100%) of pyranose **2.25**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.30 (m,5H), 5.13 (s, 1H), 4.53 (dd, *J* = 11.4 Hz, 2H), 4.37 (broad s, 1H), 3.84 (d, *J* = 9.9 Hz, 1H), 3.50 (s, 3H), 3.43 (t, *J*= 5.1 Hz, 2H), 3.32 (s, 3H), 3.08 (broad s, 1H), 3.04 (d, *J* = 2.4 Hz, 1H), 1.3 (s, 3H), 0.88 (t, *J* = 7.5 Hz, 3H).



(4R,5S,6R,7R)-6-(benzyloxy)-4,10-dimethoxy-6-methyl-5,7-bis(triethylsilyloxy)decan-3-one (S1). TES-Cl (1.30 µL, 19 µmol) was added to a solution of imidazole (6.75 µg, 9.94 µmol) and aldol adduct **2.23** (2.40 mg, 4.97 µmol) in CH_2Cl_2 (.5 mL) at 0°C. After 1h, the solution was washed with water and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried and concentrated *in vacuo* furnishing a yellow oil ketone (**S1**). The residue was purified by flash chromatography (10: 1, hexane: ethyl acetate) to afford 2.7 mg (90%) of silyl protected aldol adduct **S1**. $[\alpha]_D^{25}$ +14.6 (*c* 0.6, $CHCl_3$); IR (neat) 2955, 1711, 1456, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.31-7.21 (m, 5H), 4.75 (d, *J* = 12 Hz, 1H), 4.57 (d, *J* = 12 Hz, 1H), 4.26 (narrow d, 1H), 3.84 (dd, *J* = 8, 4 Hz, 1H), 3.79 (narrow d, 1H), 3.40-3.35 (m, 2H), 3.37 (s, 3H), 3.33 (s, 3H), 2.45-2.35 (m, 1H), 2.30-2.20 (m, 1H), 1.85-1.76 (m,1H), 1.73-1.69 (m, 1H), 1.46 (s, 3H), 1.03-0.96 (m, 18), 0.71-0.59 (m, 15H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 210.2, 139.3, 128.0, 127.54, 126.86, 89.4, 82.4, 77.5, 77.2, 73.2, 66.6, 58.9, 58.5, 32.7, 28.9, 27.5, 14.2, 7.1, 7.0, 6.7, 5.8, 5.6; HRMS calcd for $C_{32}H_{60}O_6$ $LiSi_2$ [M+Li] 603.4089 found 603.4084.

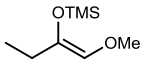


1-methoxybutan-2-ol (S2). 1,2- Epoxybutane (5.00 g, 69.33 mmol) was added to a solution of sodium methoxide (7.49 g, 138.67 mmol) in methanol (70 mL) at rt. After 24 h at 50°C, the solution was washed with saturated ammonium chloride solution and extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried and concentrated *in vacuo* furnishing a clear oil. Without further purification the reaction afforded 4.32g (61%) of alcohol **S2**. ^1H NMR (300 MHz, $CDCl_3$): δ 3.69 (broad, 1H), 3.43 (dd, *J* =9.3, 3 Hz 1H), 3.36 (s, 3H), 3.24 (dd, *J* = 8.1 Hz, 1H), 2.25 (broad, 1H), 1.47 (dq, J = 6.6 Hz, 1H), .967 (t, *J* = 7.5 Hz, 3H).

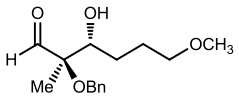


1-methoxybutan-2-one (S3). Oxalyl chloride (13.41 mL, 153.72 mmol) was added to a solution of dichloromethane (270 mL). Dimethyl sulfoxide (23.78 mL, 307.45 mmol) was added in dichloromethane (15 mL) at -78°C over 15 min. After 15 min, 1-methoxybutan-2-ol **S2** (10.00g, 96.07 mmol) was added over 10 min. After an additional 15 min, triethylamine (66.95 mL, 480.4 mmol) was added over 20 min. The reaction was stirred for 20 min and washed with water, extracted with CH_2Cl_2 (3x 50mL). The organic layers were washed

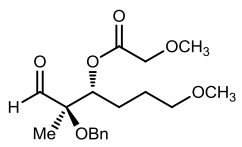
with 1M HCl solution, followed by $NaHCO_3$ saturated solution. The combined organic layers were dried and concentrated at 0°C *in vacuo*. The resulting mixture was distilled at 73-77°C at 118 mmHg, furnishing 4.83 g (47%) of ketone **S3**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.02 (s, 2H), 3.42 (s, 3H), 2.47 (q, *J* = 7.2 Hz, 2H), 1.08 (t, *J* = 7.2, 3H).



(Z)-(1-methoxybut-1-en-2-yloxy)trimethylsilane (2.22). ^{n}Butyl lithium (1.82 mL, 1.7 M) was added dropwise to a solution of diisopropylamine (.43 mL, 3.08 mmol) in THF (2.25 mL) at 0°C. After 20 min, 1-methoxybutan-2-one **S3** (.30g, 2.80 mmol) in THF (.25 mL) was added at -78°C. The resulting solution was stirred for 1 h before the addition of TMSOTf (.65 mL, 3.64 mmol). After 30 min, the reaction was washed with saturated $NaHCO_3$, extracted with diethyl ether (3 x 10 mL). The combined organic layers were dried, and concentrated *in vacuo* furnishing a yellow oil. The residue was purified by flash chromatography (50:1, hexanes: ethyl acetate) to afford .263g (54%) of silyl enol ether **2.22**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.38 (s, 1H), 3.49 (s, 1H), 1.90 (q, *J* = 7.2 Hz, 2H), .96 (t, *J* = 7.5 Hz, 3H), 0.17 (s, 9H).

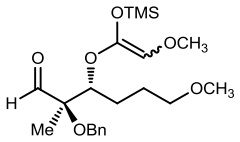


(2R,3R)-2-(benzyloxy)-3-hydroxy-6-methoxy-2-methylhexanal (2.32). Hydrogen fluoride (60%) in pyridine (.5mL) was added dropwise to a solution of aldehyde **2.16** (100 mg, .29 mmol) in THF (12 mL) at 0°C. The reaction was stirred for 1h and washed with $NaHCO_3$ (15 mL), extracted with diethyl ether (3 x 10mL). The combined organic layers were dried, and concentrated *in vacuo* furnishing a clear oil in quantitative yield. Alcohol 2.32 was immediately carried through without further purification.

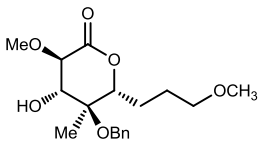


(2R,3R)-2-(benzyloxy)-6-methoxy-2-methyl-1-oxohexan-3-yl 2-methoxyacetate (2.34). 4-Dimethylaminopyridine (5.0 mg, .05 mmol) was added to a solution of alcohol **2.23** (.267 g, .95 mmol) in CH_2Cl_2 (1 mL) at 0°C. After 5 min, pyridine (.76 mL, 9.53 mmol) is added dropwise followed by the dropwise addition of 2-methoxyacetyl chloride (.43 mL, 4.76 mmol). The resulting solution was stirred for 24h at rt and washed with $NaHCO_3$, extracted with CH_2Cl_2 (3 x 10mL). The combined organic layers were dried, and concentrated *in vacuo* furnishing a clear oil. The residue was

purified by flash chromatography (4:1, hexanes: ethyl acetate) to afford 280 mg (87%) of **2.34**. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.61 (s, 1H), 7.28-7.189 (m, 5H), 5.38 (d, *J* = 2.4, 1H), 4.52 (d, *J* =10.8, 1H), 4.34 (d, *J* =10.8, 1H), 3.97 (d, *J* = 16.8, 1H), 3.91 (d, *J* =16.8, 1H). 3.31 (s, 3H), 3.28 (t, 2H), 3.22 (s, 3H), 1.76-1.63 (m, 1H), 1.62-1.60 (m, 1H), 1.59-1.48 (m, 2H), 1.30 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 202.7, 169.8, 137.6, 128.3, 127.7, 127.3, 83.4, 74.5, 71.7, 69.4, 66.3, 59.2, 58.5, 25.9, 25.5, 13.8.

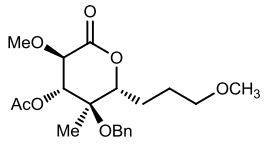


(2R,3R)-2-(benzyloxy)-6-methoxy-3-(2-methoxy-1-(trimethylsilyloxy)vinyloxy)-2-methylhexanal (2.35). Triethylamine (.88 mL, 6.36 mmol) was added dropwise to a solution of **2.34** (215 mg, .636 mmol) in CH_2Cl_2 (.60 mL) at 0°C. After 5 min, trimethylsilyl trifluromethane sulfonate (.57 mL, 3.18 mmol) was added dropwise to the solution and stirred for 1h. The reaction was washed with $NaHCO_3$, extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried, and concentrated *in vacuo* furnishing a clear oil. The residue was purified by flash chromatography (6:1, hexanes: ethyl acetate) to afford 140 mg (59% BRMS) of silyl ketene acetal **2.35**. ^{1}H NMR (600 MHz, $CDCl_3$): δ9.55 (s, 1H), 9.54 (s, 1H), 5.33 (d, *J* = 10.2, 1H), 5.30 (d, *J* = 9.6, 1H), 4.52 (d, *J* = 7.2, 1H), 4.50 (d, *J* = 7.2, 1H), 4.34, (d, 10.8, 1H), 4.32 (d, J =10.8, 1H), 3.51 (s, 1H), 3.49 (s, 1H), 3.32-δ3.30 (m, 4H), 3.27 (s, 3H), 3.24 (s, 3H), δ3.23 (s, 3H), 3.22 (s, 3H), 1.8-1.7 (m, 2H), 1.59-1.53 (m, 6H), 1.29 (s, 3H), 1.28 (s, 3H), 0.03 (s, 9H), 0.01 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$): 202.7, 202.6, 173.01, 172.8, 137.7, 137.6, 128.4, 128.3, 127.7, 127.7, 127.5, 127.4, 83.4, 83.2, 77.6, 73.9, 73.8, 71.9, 71.7, 66.3, 66.1, 61.3, 61.2, 58.5, 58.4, 26.1, 26.1, 25.8, 25.8, 13.8, 13.6, -3.2, -3.4.

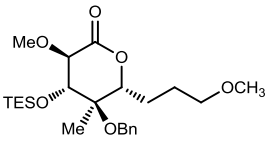


(3R,4R,5S,6R)-5-(benzyloxy)-4-hydroxy-3-methoxy-6-(3-methoxypropyl)-5-methyltetrahydro-2H-pyran-2-one (2.36). Tetrabutyl ammonium fluoride (.28 mL, .28 mmol, 1M in THF) was added dropwise to a solution of silyl ketene acetal **2.35** (59 mg, .14 mmol) in THF (.5 mL) at -40°C. After 15 min, the reaction was washed with saturated NH_4Cl solution, extracted with diethyl ether (3 x 10mL). The combined organic layers were dried, and concentrated *in vacuo* furnishing a clear oil. The residue was purified by flash chromatography (2:1, hexanes: ethyl acetate) to afford 21 mg (44%) of lactone **2.36**. ^{1}H NMR (600 MHz, $CDCl_3$):

δ7.29-7.21 (m, 5H), 4.63 (d, *J* = 11.4, 1H), 4.57 (d, *J* = 11.4, 1H), 4.17 (d, *J* =10.2, 1H), 4.00 (d, *J* = 8.8, 1H), 3.64 (s, 3H), 3.62 (d, *J* = 8.8, 1H), 3.40-3.37 (m, 2H), 3.26 (s, 3H), 3.07 (broad s, 1H), 1.94-1.82 (m, 2H), 1.67-1.56 (m, 2H), 1.27 (s, 3H).[13]C NMR (150 MHz, $CDCl_3$): δ169.66, 138.27, 128.31, 127.49, 127.28, 81.42, 81.00, 76.52, 75.67, 71.86, 65.24, 60.34, 58.36, 26.04, 25.32, 12.25.

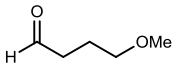


(2R,3R,4R,5R)-3-(benzyloxy)-5-methoxy-2-(3-methoxypropyl)-3-methyl-6-oxotetrahydro-2H-pyran-4-yl acetate (2.37). Scandium triflate (1% mmol) was added to a solution of lactone **2.36** (5mg, .014 mmol) in acetonitrile (.40 mL) at 0°C. After 10 min, acetic anhydride (13.97 µL, .14 mmol) is added dropwise and the resulting solution was stirred for 20 min. The reaction was washed with $NaHCO_3$, extracted with diethyl ether (3 x 10mL). The combined organic layers were dried, and concentrated *in vacuo* furnishing a clear oil. The residue was purified by flash chromatography (4:1, hexanes: ethyl acetate) to afford 3.35 mg (60%) of lactone **2.37**. [1]H NMR (600 MHz, C_6D_6): δ 7.26 – 7.017 (m, 5H), 5.69 (d, *J* = 7.8, 1H), 4.43 (d, *J* = 10.8, 1H), 4.13 (d, *J* = 10.8, 1H), 4.02 (d, *J* = 12.0, 1H), 3.67 (d, *J* = 7.8, 1H), 3.46 (s, 3H), 3.31 (t, 2H), 3.08 (s, 3H), 1.80 (m, 2H), 1.58 (s, 3H), 1.00 (s, 3H).[13]C NMR (150 MHz, $CDCl_3$): δ 169.5, 168.5, 137.5, 128.4, 127.7, 127.5, 80.7, 79.4, 74.0, 71.7, 64.7, 59.2, 58.5, 29.6, 26.0, 25.4, 20.9, 14.0.

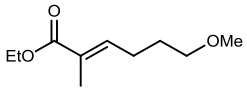


(3R,4R,5R,6R)-5-(benzyloxy)-3-methoxy-6-(3-methoxypropyl)-5-methyl-4-(triethylsilyloxy)tetrahydro-2H-pyran-2-one (2.38). 2,6-Lutidine (19.6 µL, .16 mmol) was added to a solution of lactone **2.36** (19 mg, 56.2 µmol) in CH_2Cl_2 (1 mL) at 0°C. After 5 min, triethylsilyl trifluoromethane sulfonate (25.3 µL, .11 mmol) was added dropwise to the resulting solution. The reaction was warmed to rt and stirred for 1h, washed with $NaHCO_3$, extracted with CH_2Cl_2 (5 mL). The combined organic layers were dried, and concentrated *in vacuo* furnishing a clear oil. The residue was purified by flash chromatography (6:1, hexanes: ethyl acetate) to afford 13.60 mg (54%) of lactone **2.38**. [1]H NMR (600 MHz, $CDCl_3$): δ7.33-7.24 (m, 5H), 4.57 (d, *J* = 10.8, 1H), 4.50 (d, *J* = 10.8, 1H), 4.40 (d, *J* = 10.8, 1H), 3.90 (d, *J* = 5.4, 1H), 3.71 (d, *J* = 5.4, 1H), 3.62 (s, 3H), δ3.47-3.41 (m, 2H). 3.34 (s, 3H), 1.97-1.84 (m, 3H), 1.69-1.66 (m, 1H), 1.33 (s, 3H), 1.00 (t, 9H) 0.67 (q, 6H).[13]C NMR (150

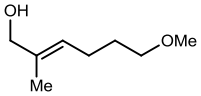
MHz, $CDCl_3$): δ170.0, 138.0, 128.25, 127.4, 82.7, 81.5, 78.4, 71.8, 64.36, 59.4, 58.8, 26.5, 25.9, 14.5, 6.7, 4.8.



4-methoxybutanal (2.11). Diisobutyl aluminum hydride (4.89 mL, 27.52 mmol) was added dropwise to a solution of ester **3.27** (3.0 mL, 22.02 mmol) in CH_2Cl_2 (22 mL) at -78°C. The resulting solution was stirred for 1h and methanol (5 mL) was added dropwise. The slurry was stirred vigorously in NaK tartrate Rochelle salt solution (400mL) for 1h, extracted with dichloromethane (3 x 150 mL). The combined organic layers were dried, and carefully concentrated at 760mmHg to furnish a clear oil. The residue was further distilled under vacuum at 118 mmHg at 81-82°C furnishing 1.26 g (55%) of aldehyde **2.11**. ^{1}H NMR (300 MHz, $CDCl_3$): δ9.78 (s, 1H), 3.40 (t, *J* = 6.3, 2H), 3.32 (s, 1H), 2.54 (t, *J* = 7.2, 2H), 1.93-1.88 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.1, 71.50, 58.5, 40.8, 22.3.

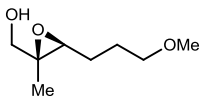


(*E*)-ethyl 6-methoxy-2-methylhex-2-enoate (2.43). Lithium hexamethyldisilazide (146 mL, 146 mmol, 1.0 M in toluene) was added dropwise to a solution of triethylphosphopropionate (34.8 g, 146 mmol) in THF at 0 °C. After 15 min, neat 4-methoxybutanal **2.11** (13.0 g, 127mmol) was added dropwise and stirred for 1 h. The reaction was washed with water (15 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography (10:1, hexanes: ethyl acetate) to afford 14.7g (88%) of ester **2.43** (E/Z 12:1) as a clear oil: R_f 0.5 (9:1, H:EA); IR (neat) 2981, 2931, 2828, 1712, 1651 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.75 (t, *J* = 7.2 Hz, 1H), 4.19 (q, *J* = 3.6 Hz, 4H), 3.38 (t, *J* = 6.6 Hz, 2H), 3.37 (s, 3H), 2.45 (q, *J* = 15 Hz, 2H), 1.83 (s, 3H), 1.71 (m, 2H), 1.29 (t, *J* = 3.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 167.8, 141.0, 128.0, 71.5, 60.1, 58.2, 28.3, 25.0, 14.0, 11.9. HRMS calcd for $C_{10}H_{18}NaO_3$ $[M+Na]^+$ 209.1148, found 209.1155.

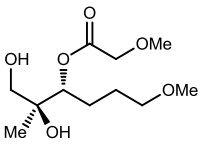


(*E*)-6-methoxy-2-methylhex-2-en-1-ol (2.44). To a solution of (*E*)-ethyl 6-methoxy-2-methylhex-2-enoate **2.43** (7.26 g , 39.0 mmol) in CH_2Cl_2 (39.0 mL, 1.0 M) was added DibalH (15.3 mL, 85.0 mmol) and stirred for 2 h at -78°C. To the solution was

carefully added MeOH (10 mL) followed by a solution of saturated Rochelle salt solution (200 mL) and stirring continued for 1 h. The solution was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (4:1, hexanes: ethyl acetate) to afford 5.43 g (97 %) of alcohol **2.44** as a clear oil: R_f 0.25 (4:1, H:EA); IR (neat) 3390, 2923, 2866 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.27 (t, *J* = 7.2 Hz, 1H), 3.83 (s, 2H), 3.27 (dd, *J* = 1.6 Hz, 2H), 3.24 (s, 3H), 1.98 (q, *J* = 7.2 Hz, 2H), 1.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.1, 124.5, 71.9, 68.0, 58.1, 29.0, 23.8, 12.23 ; HRMS calcd for $C_8H_{16}NaO_2$ $[M+Na]^+$ 167.1043, found 167.1046.



((2S,3S)-3-(3-methoxypropyl)-2-methyloxiran-2-yl)methanol (2.45). (+) Diethyl tartrate (1.44 mL, 8.44 mmol) was added to a solution of allylic alcohol **2.44** (814 mg, 5.63 mmol) in dichloromethane (5 mL) at -40°C. After 30 min, titanium isopropoxide (2.47 mL, 8.44 mmol) was added dropwise and stirred 1h. Tertbutyl hydroxyl peroxide (11 mL, 56.3 mmol, 5-6M in decane) was added dropwise and the resulting solution was stirred for 5 days at -35°C. The reaction was stirred with 1N NaOH solution for 1h. The solution was extracted with diethyl ether (3 x 10mL). The combined organic layers were dried, and concentrated *in vacuo* furnishing a clear oil. The residue was purified by flash chromatography (2:1, hexanes: ethyl acetate) to afford 500 mg (71% BRSM, up to 92% ee) of oxirane **2.45**. ^1H NMR (400 MHz, $CDCl_3$): δ3.68 (d, *J* =4.4 Hz, 1H), 3.65 (d, *J* =4.4 Hz, 1H), 3.44 (q, 2H), 3.33 (s, 3H), 3.05 (t, *J* =6 Hz, 1H), 2.39 (broad s, 1H) 1.78-1.63 (m, 4H), 1.29 (s, 3H).^{13}C NMR (150 MHz, $CDCl_3$): 72.0, 65.5, 60.9, 59.9, 58.4, 26.4, 24.9, 14.0.



(2S,3R)-1,2-dihydroxy-6-methoxy-2-methylhexan-3-yl 2-methoxyacetate (2.46). Titanium isopropoxide (.18 mL, .62 mmol) was added dropwise to a solution oxirane **2.45** (50 mg, .31 mmol) in CH_2Cl_2 (.3 mL). The resulting solution was allowed to stir for 1h at rt. To a separate flask, methoxy ethanoic acid (.23 mL, 1.25 mmol) was added dropwise to a solution of NaH in dichloromethane at 0°C. After 15 min, the solution was warmed to rt and added to oxirane (71) via cannula. The reaction was stirred for 24h at rt, washed with water and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried, and concentrated *in vacuo* furnishing a clear oil. The

residue was purified by flash chromatography (1:1, hexanes: ethyl acetate) to afford 17mg (22%) of diol **2.46**. ^{1}H NMR (500 MHz, $CDCl_3$): δ4.93 (d, *J* = 10, 1H), 4.07 (s, 2H), 3.45 (broad s, 5H), 3.39 (t, 2H), 3.32 (s, 3H), 2.80 (broad s, 1H), 2.67 (broad s, 1H), 1.94-1.92 (m, 1H), 1.70-1.77 (m, 2H), δ1.08 (s, 3H).^{13}C NMR (150 MHz, $CDCl_3$): Major Isomer: 171.1, 76.3, 73.2, 72.0, 69.5, 66.6, 59.2, 58.4, 26.3, 25.1, 18.4. Minor Isomer: 170.4, 75.8, 73.4, 72.7, 69.6, 68.6, 59.2, 58.4, 28.4, 27.0, 20.0.

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Appendix A1

Spectra Relevant to Chapter II

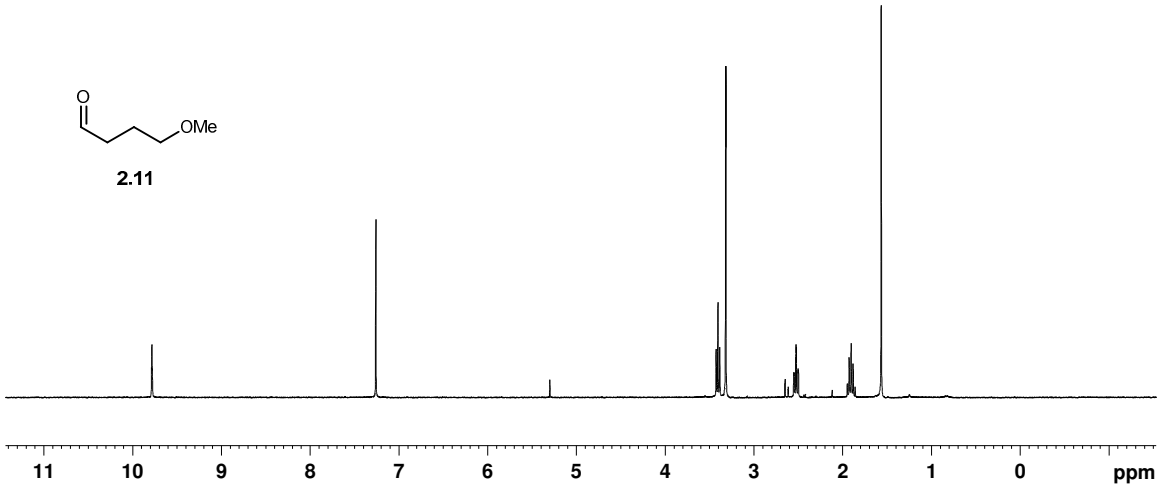


Figure A1.1 300 MHz ^{1}H- NMR spectrum of **2.11** in $CDCl_3$

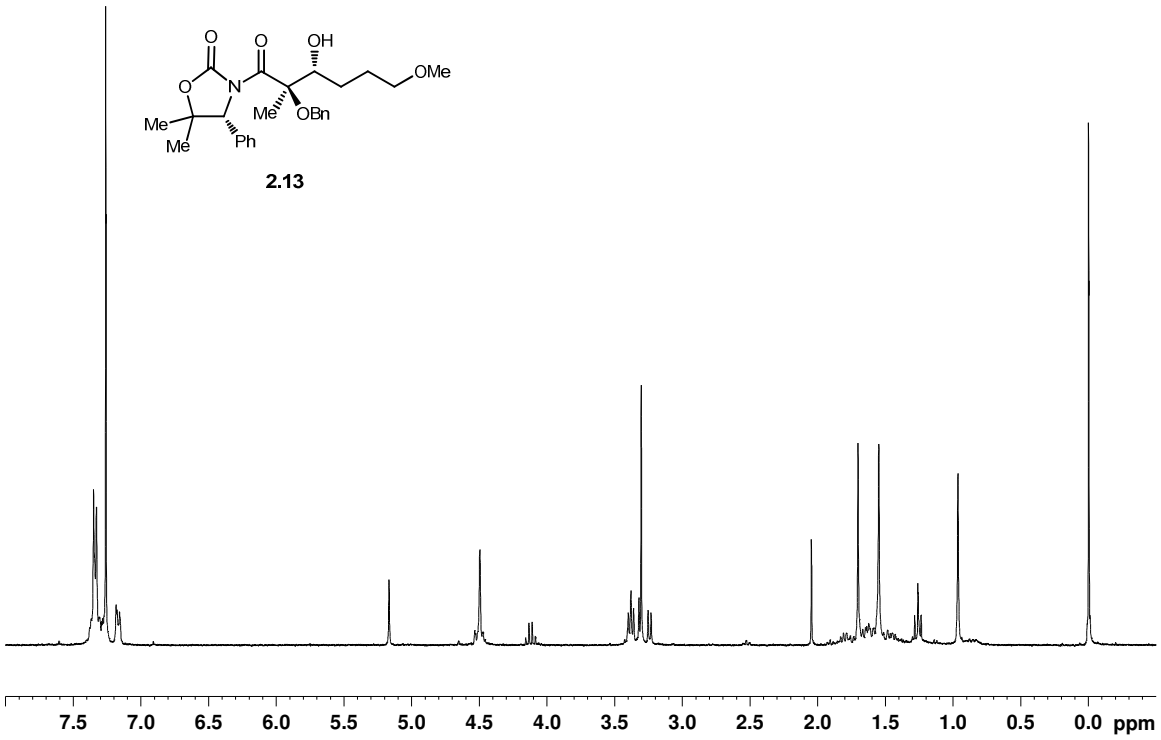


Figure A1.2 300 MHz ^{1}H- NMR spectrum of **2.13** in $CDCl_3$

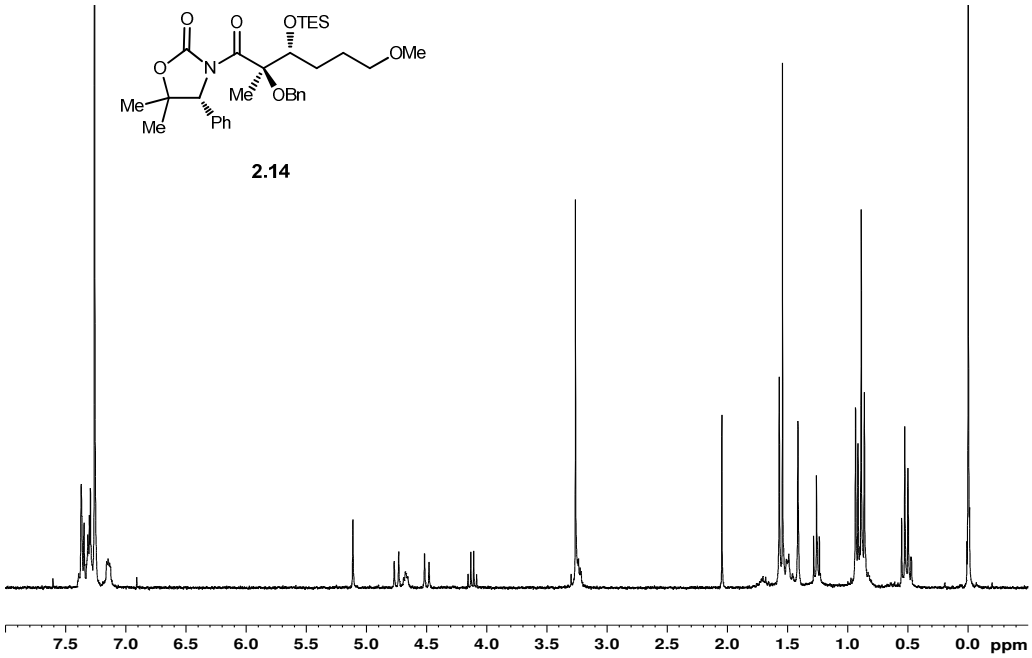


Figure A1.3 300 MHz ^{1}H- NMR spectrum of **2.14** in $CDCl_3$

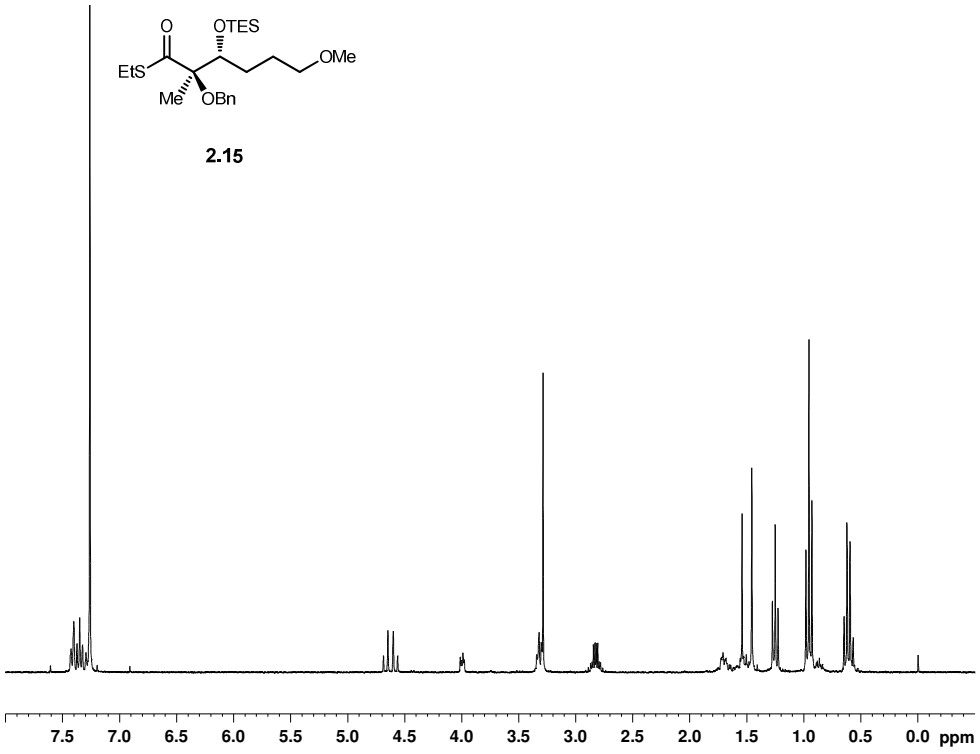


Figure A1.4 300 MHz ^{1}H- NMR spectrum of **2.15** in $CDCl_3$

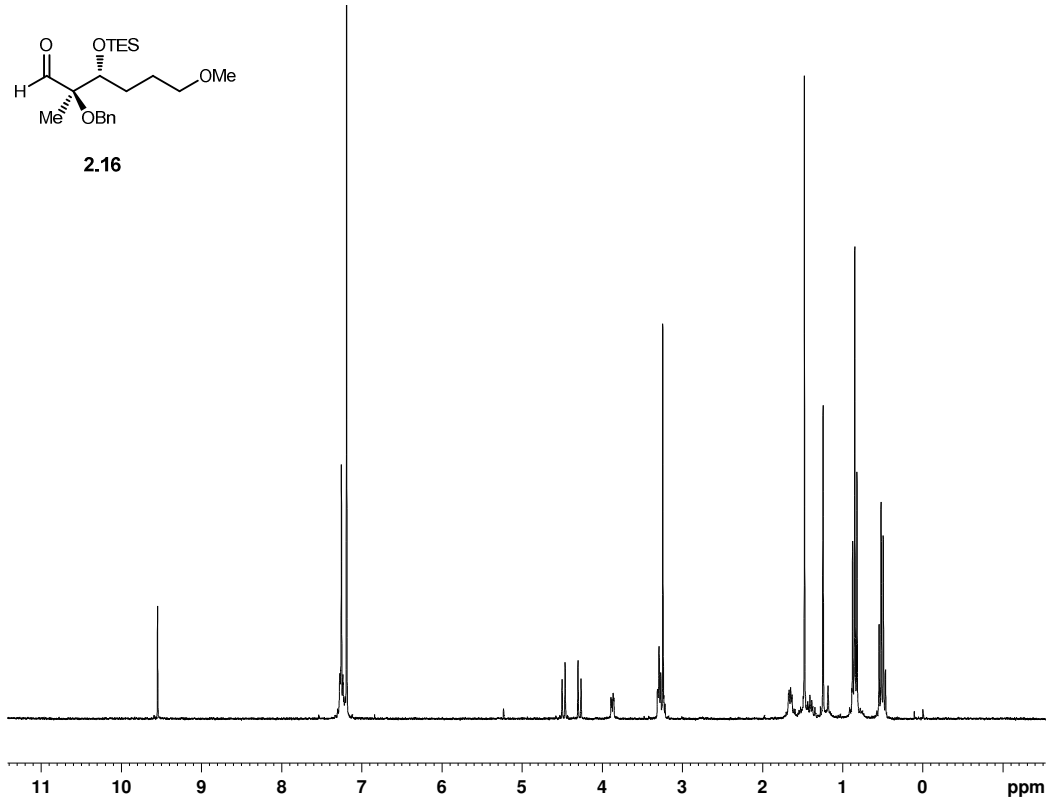


Figure A1.5 300 MHz ^{1}H- NMR spectrum of **2.16** in $CDCl_3$

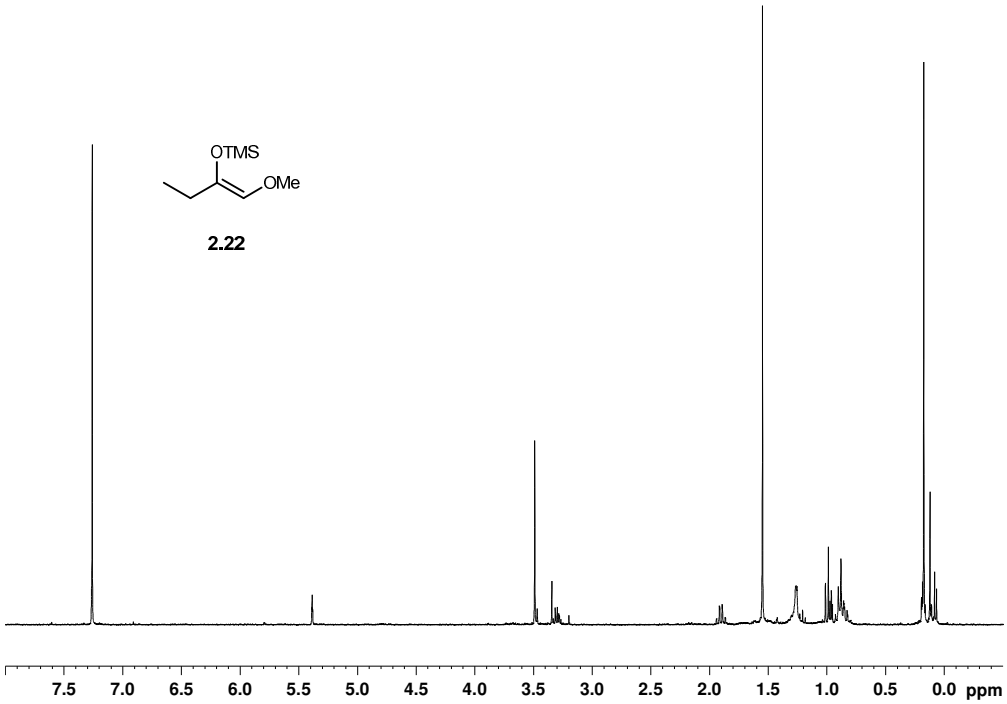


Figure A1.6 300 MHz ^{1}H- NMR spectrum of **2.22** in $CDCl_3$

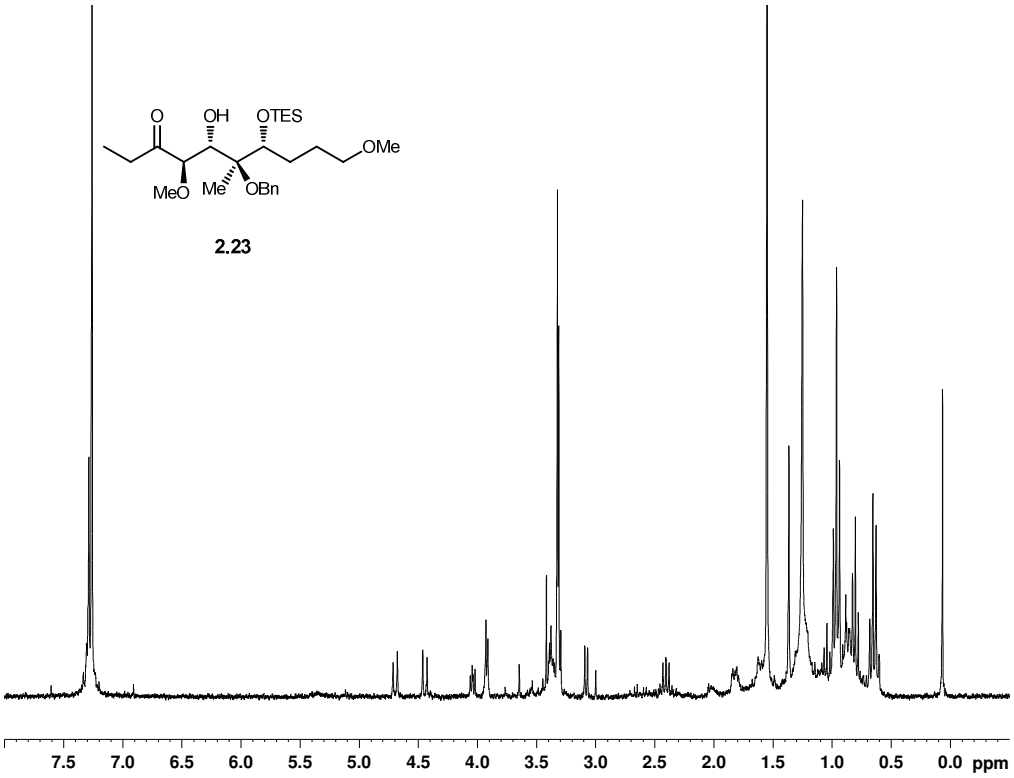


Figure A1.7 300 MHz ^{1}H- NMR spectrum of **2.23** in $CDCl_3$

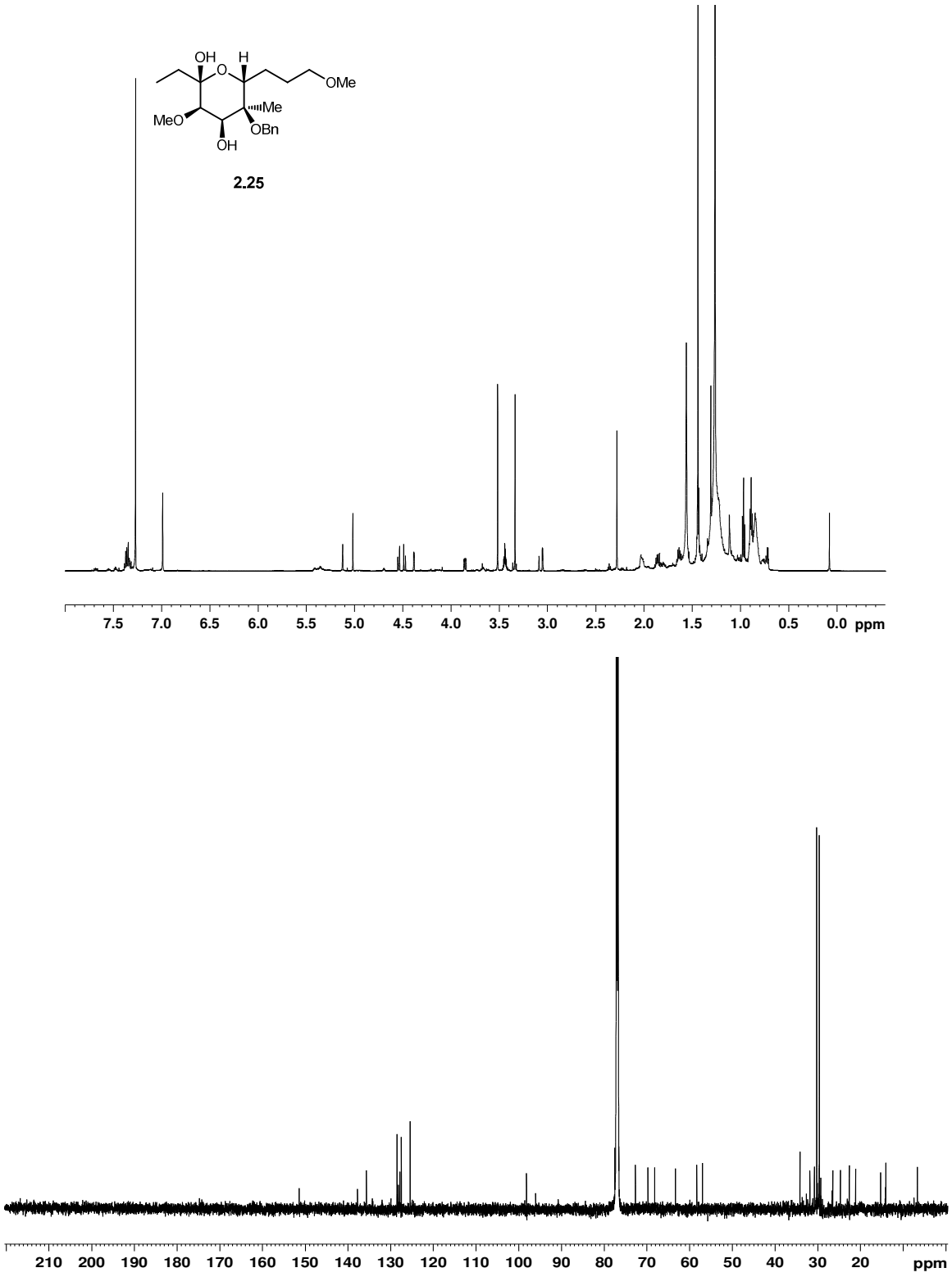


Figure A1.8 600 MHz ^{1}H- NMR and 150 MHz ^{13}C-NMR spectrum of **2.25** in $CDCl_3$

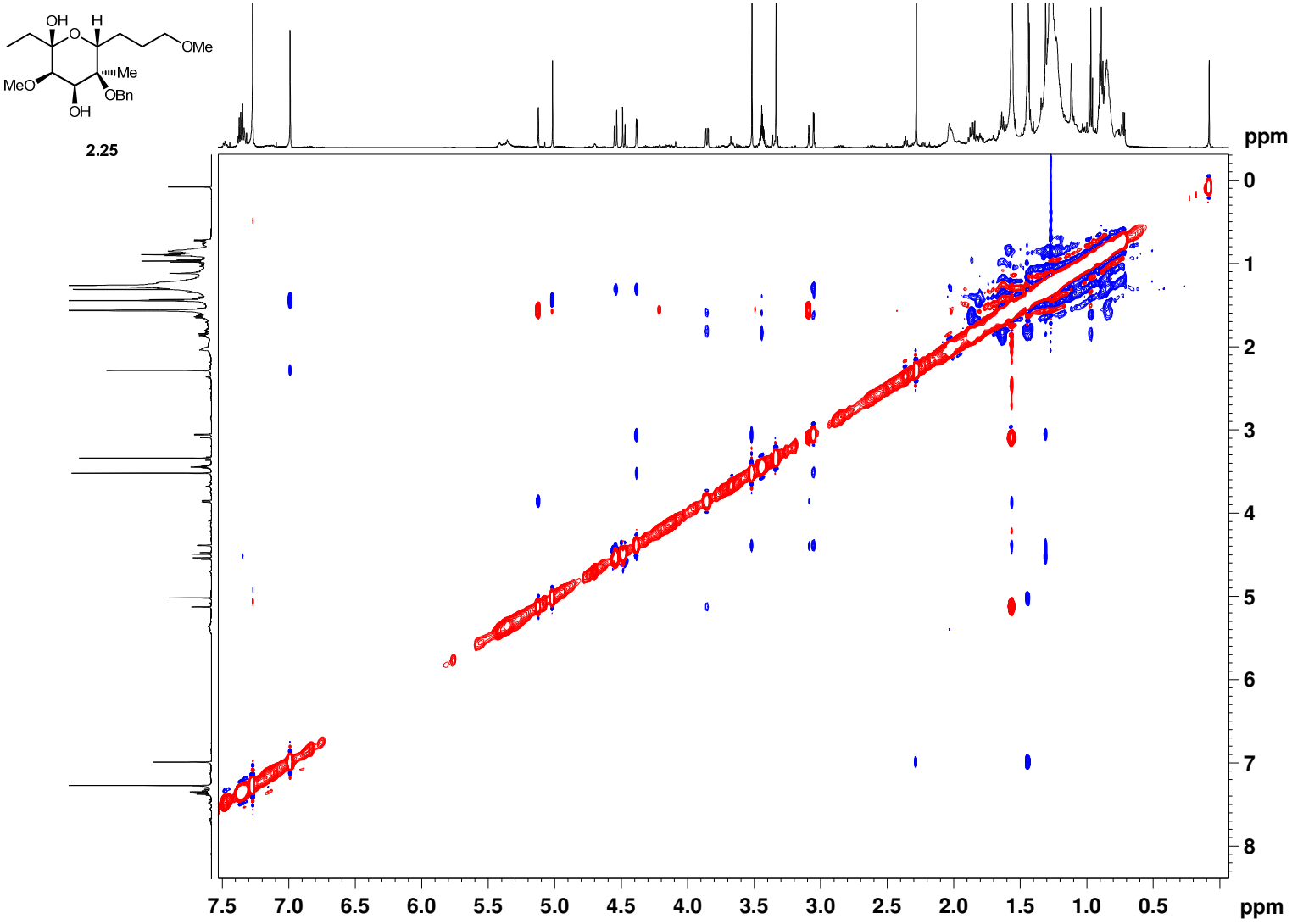


Figure A1.9 600 MHz NOESY NMR spectrum of **2.25** in $CDCl_3$

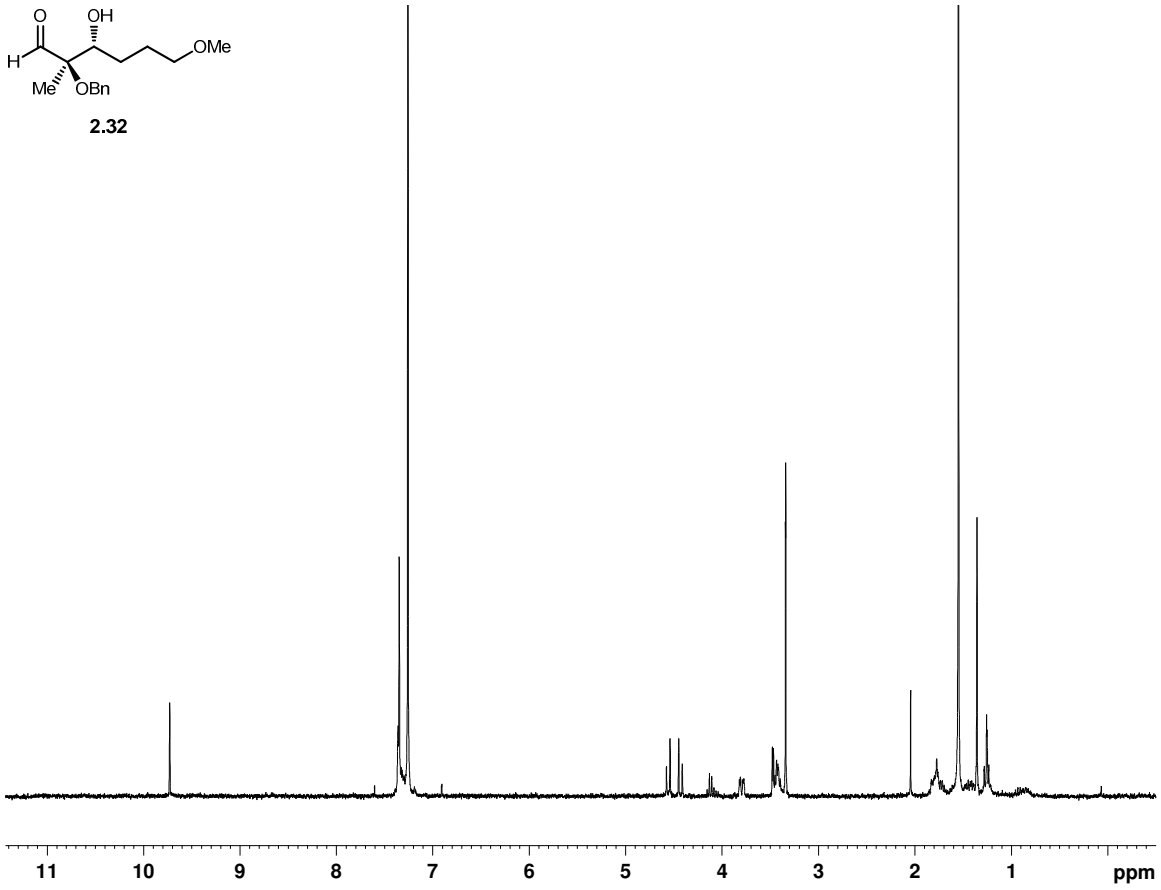


Figure A1.10 300 MHz ^{1}H- NMR spectrum of **2.32** in $CDCl_3$

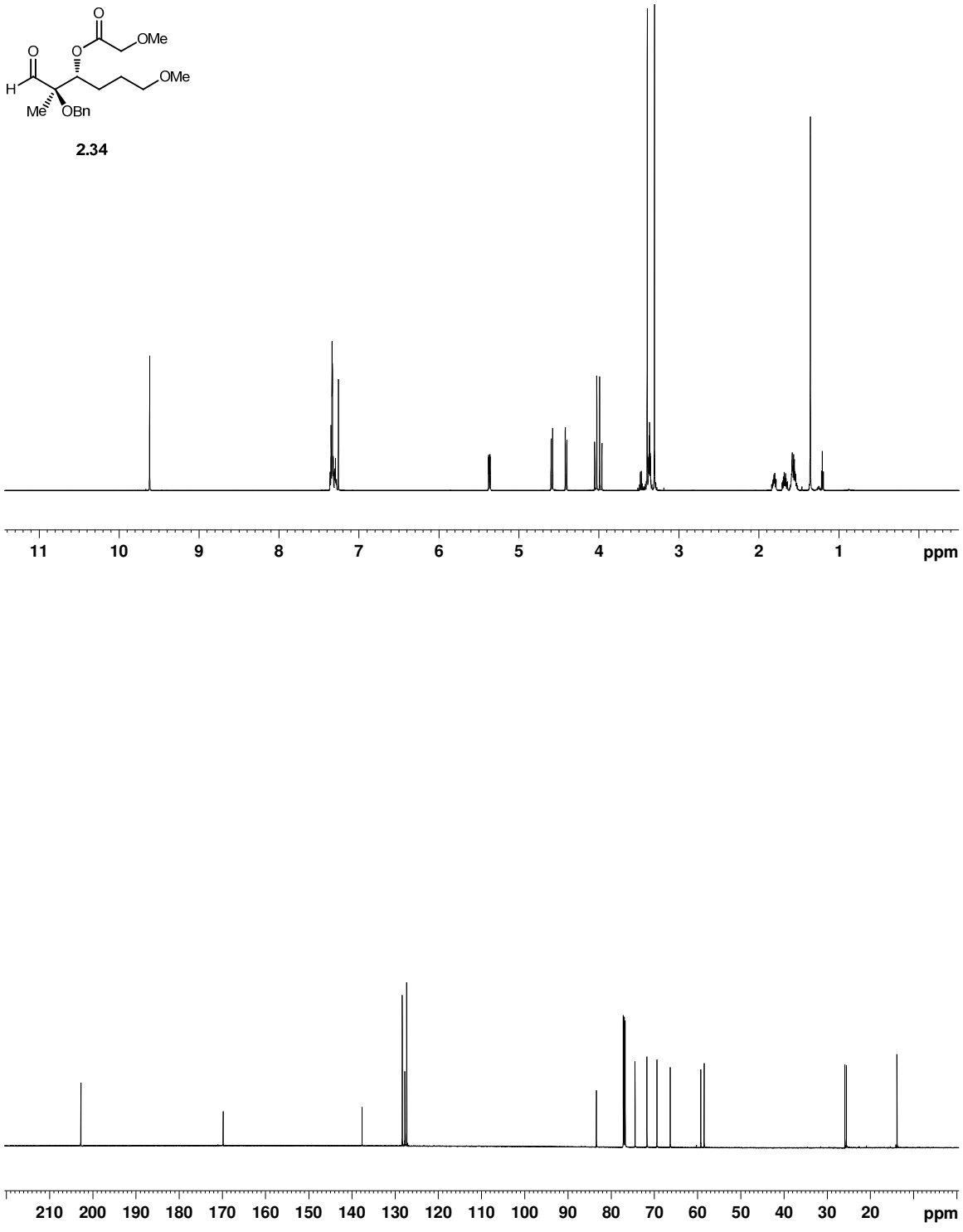


Figure A1.11 600 MHz ^{1}H- NMR and 150 MHz ^{13}C-NMR spectrum of **2.34** in $CDCl_3$

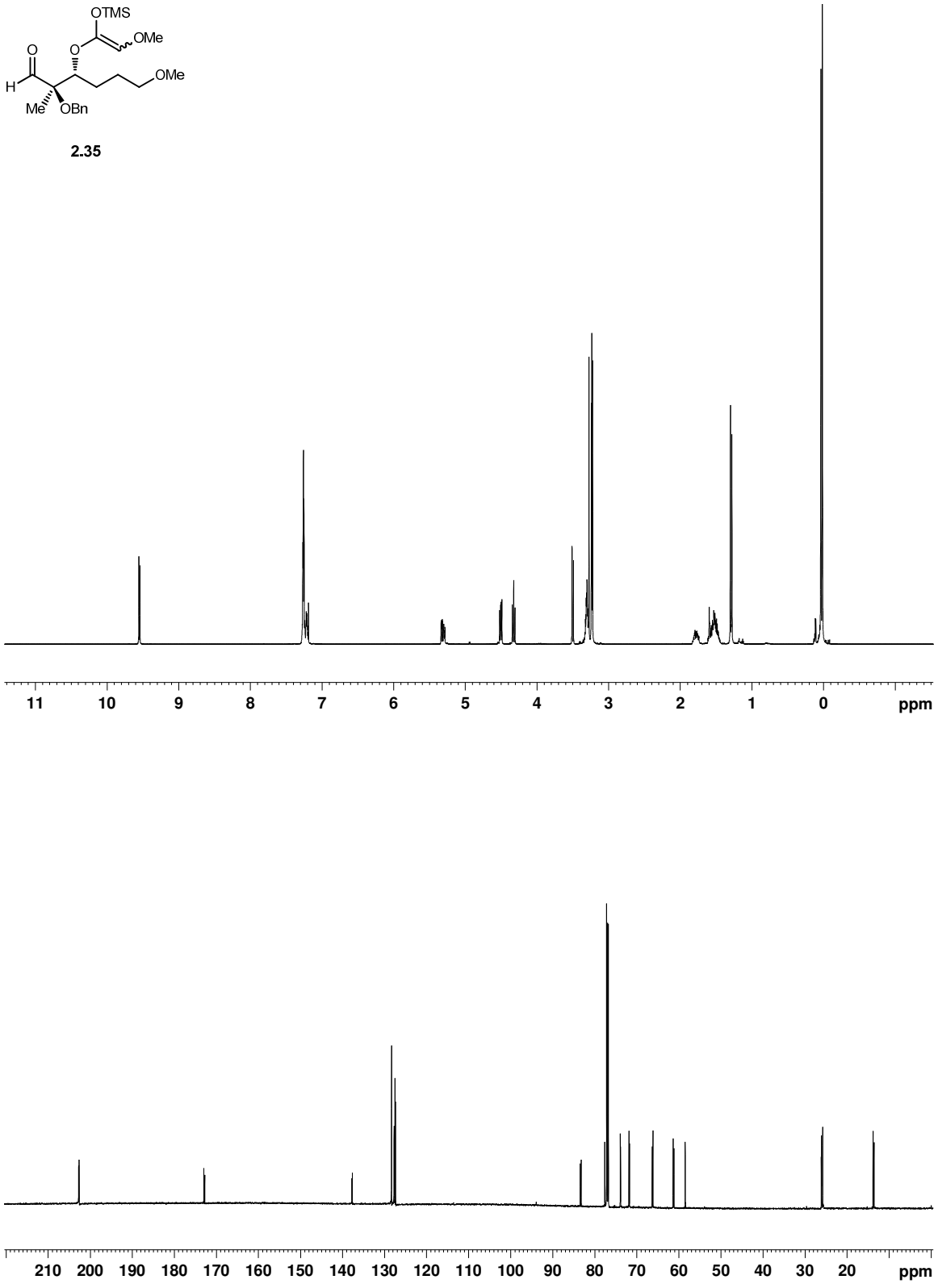


Figure A1.12 600 MHz ^{1}H- NMR and 150 MHz ^{13}C-NMR spectrum of **2.35** in $CDCl_3$

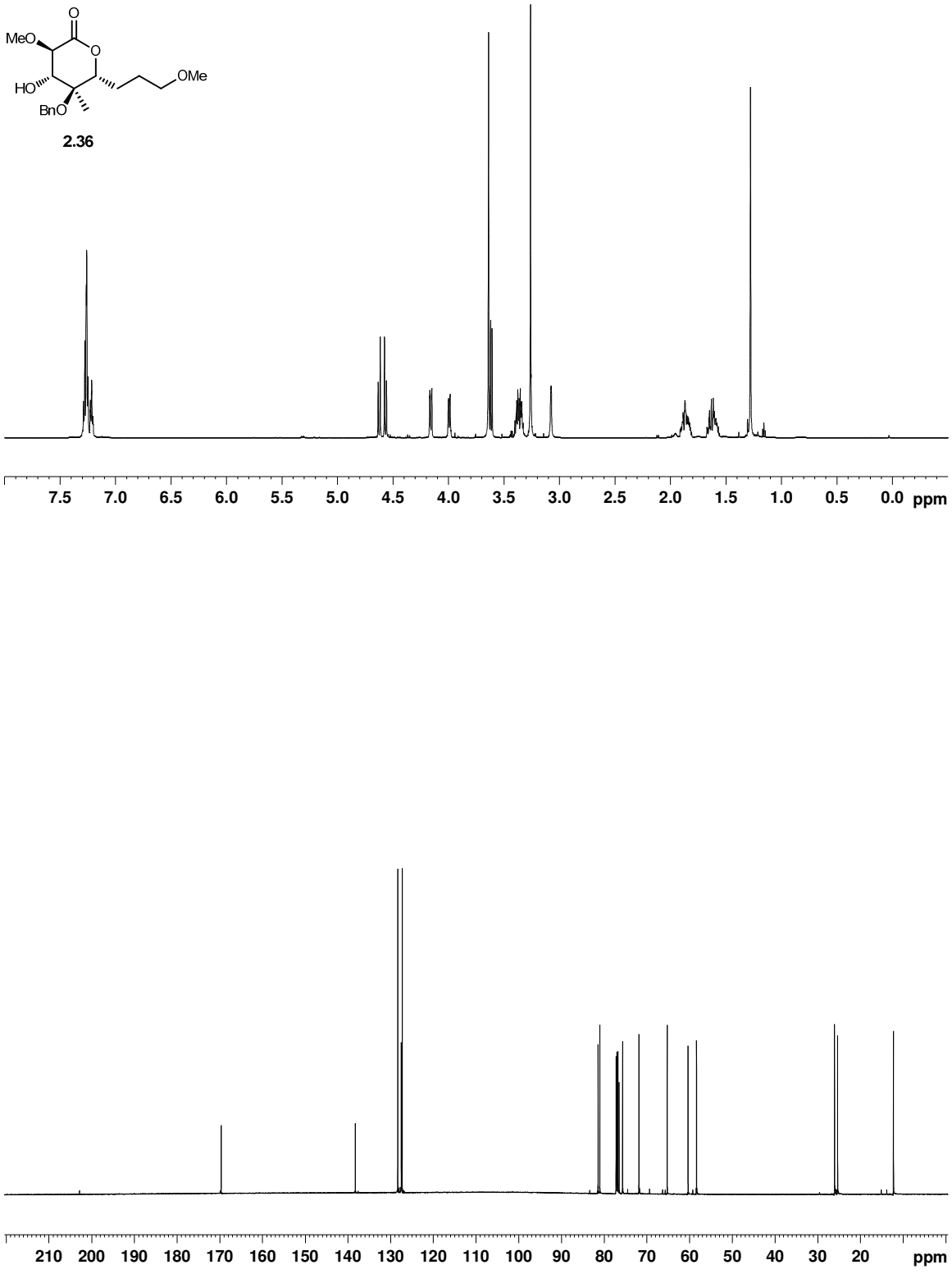


Figure A1.13 600 MHz ^{1}H- NMR and 150 MHz ^{13}C-NMR spectrum of **2.36** in $CDCl_3$

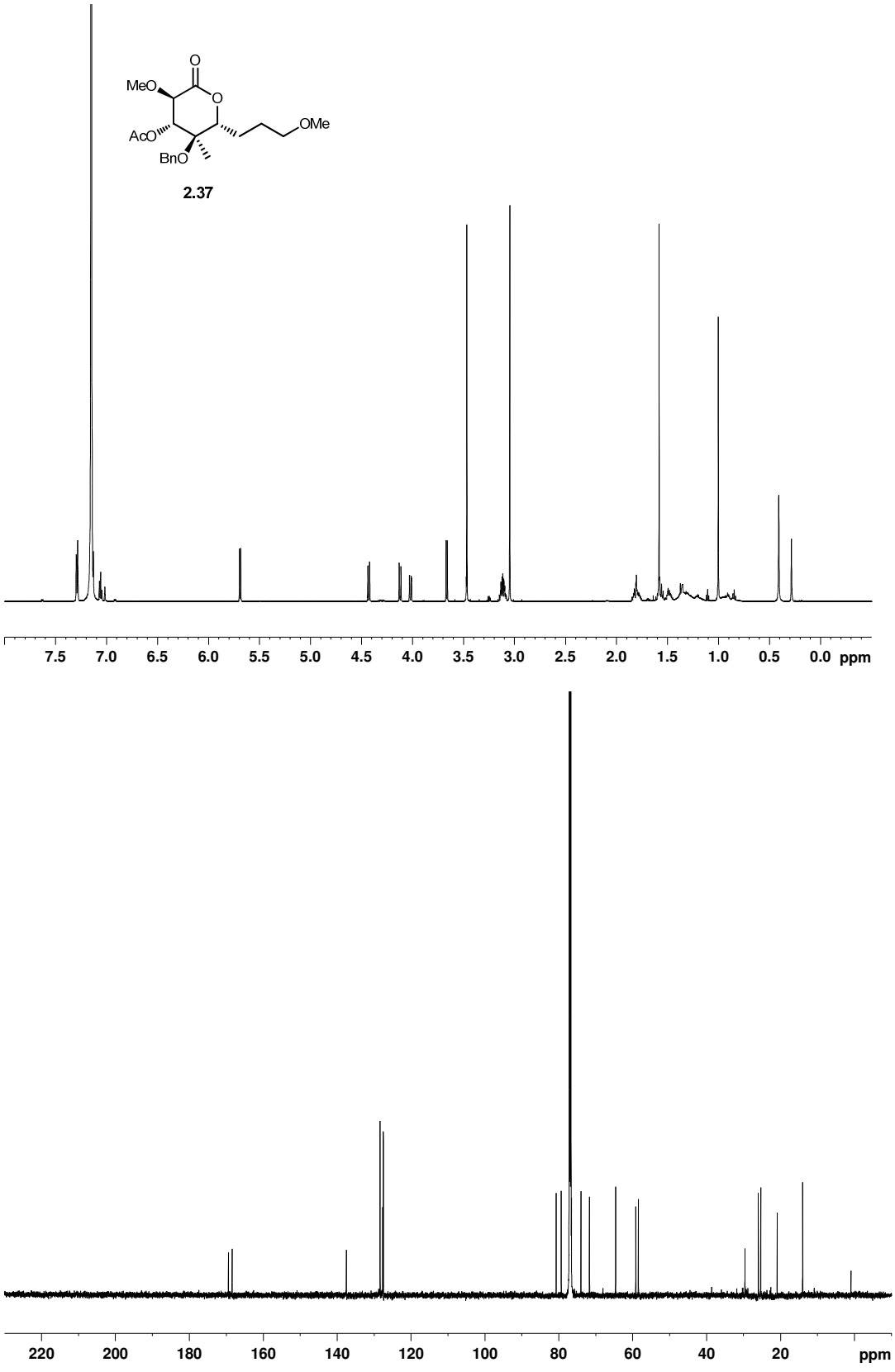


Figure A1.14 600 MHz ^{1}H- NMR and 150 MHz ^{13}C-NMR spectrum of **2.37** in $CDCl_3$

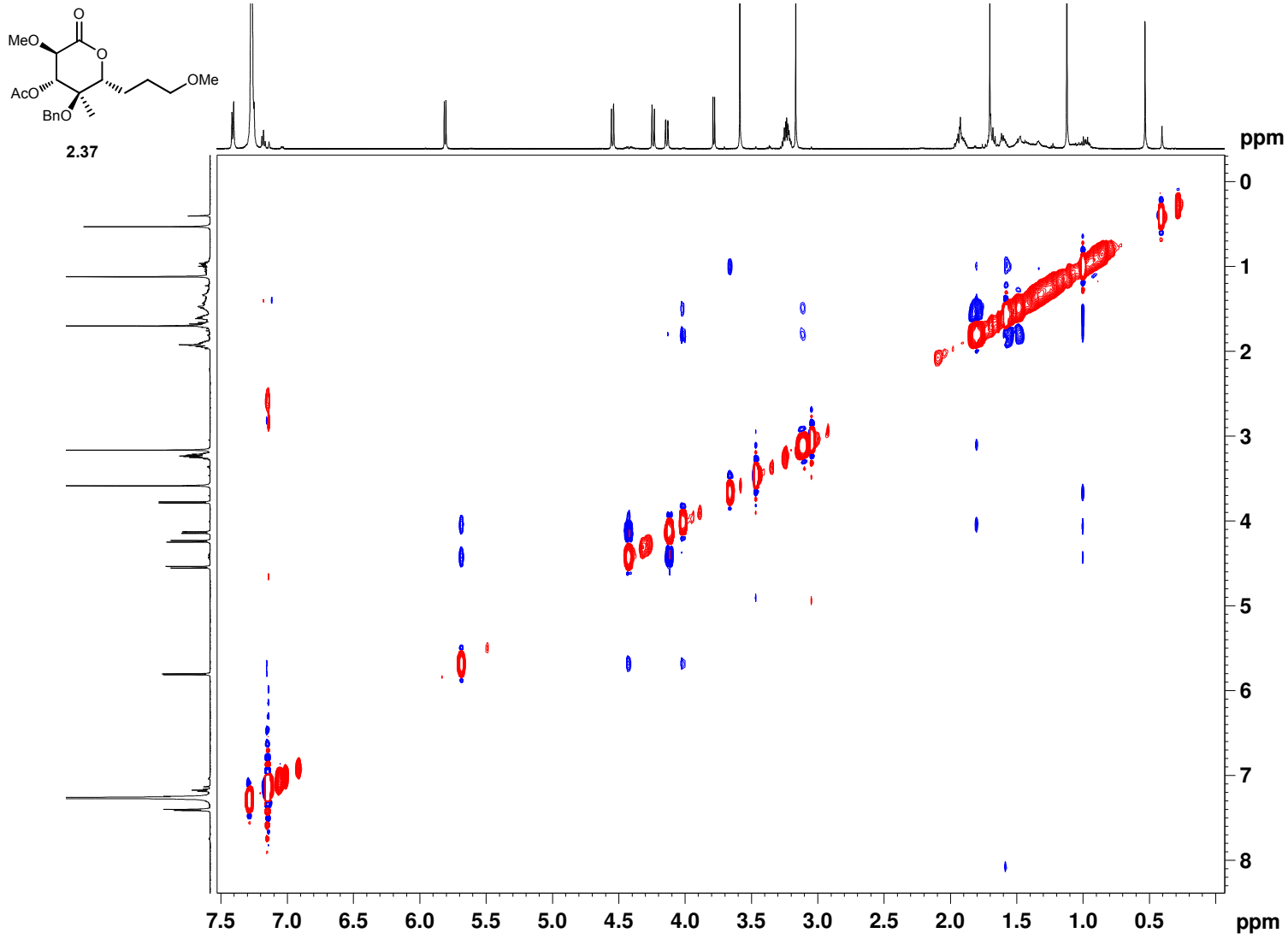


Figure A1.15 600 MHz NOESY NMR spectrum of **2.37** in $CDCl_3$

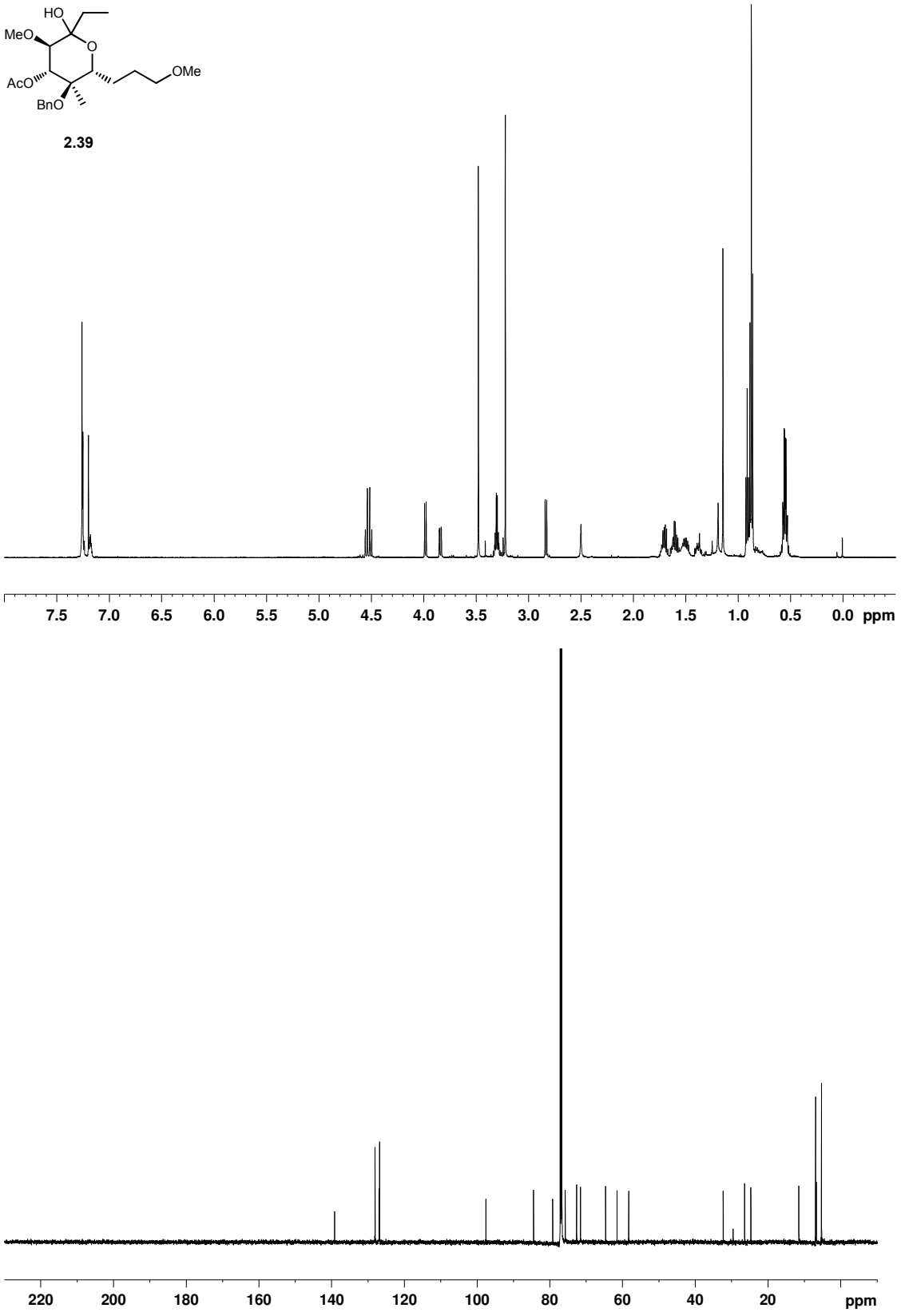


Figure A1.16 600 MHz ^{1}H- NMR and 150 MHz ^{13}C-NMR spectrum of **2.39** in $CDCl_3$

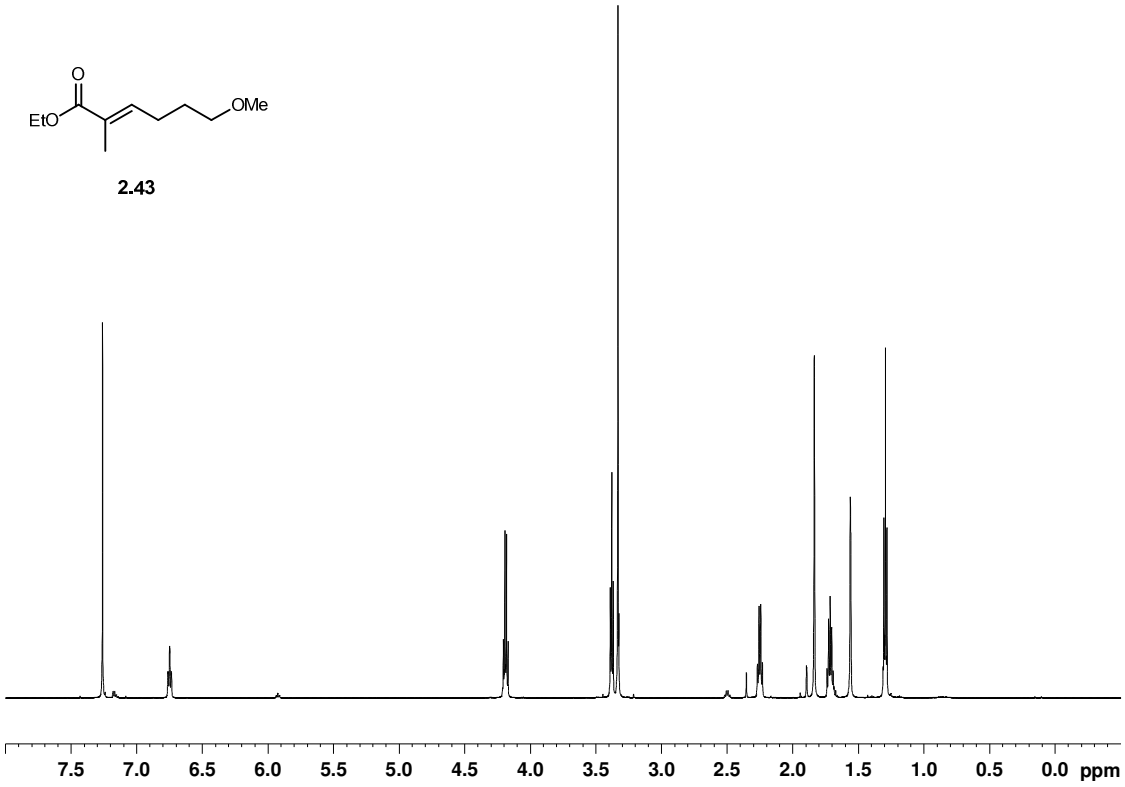


Figure A1.17 600 MHz ^{1}H- NMR spectrum of **2.43** in $CDCl_3$

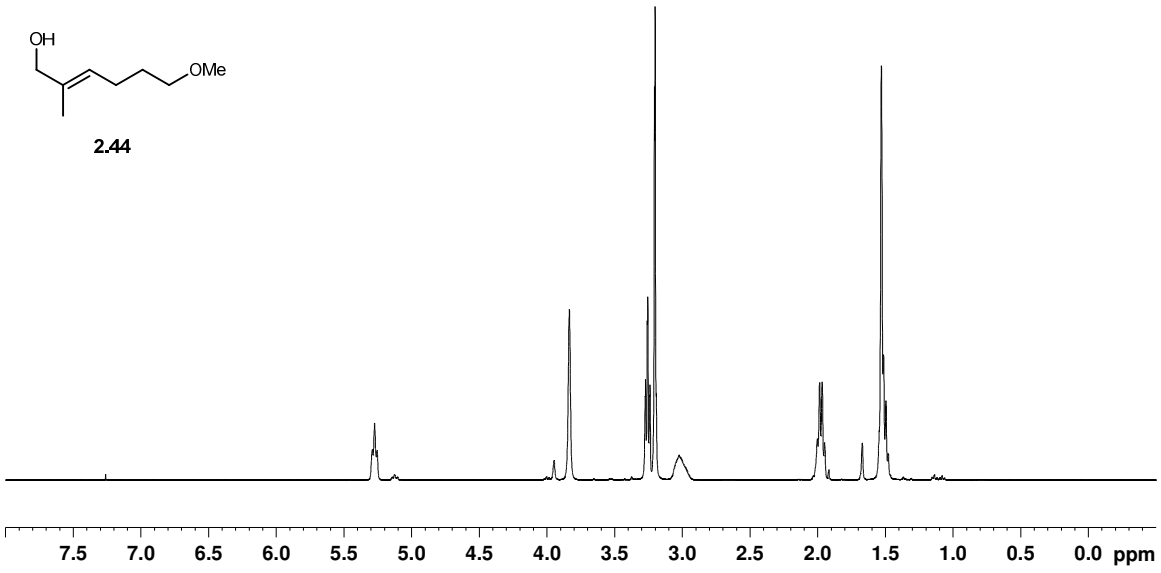
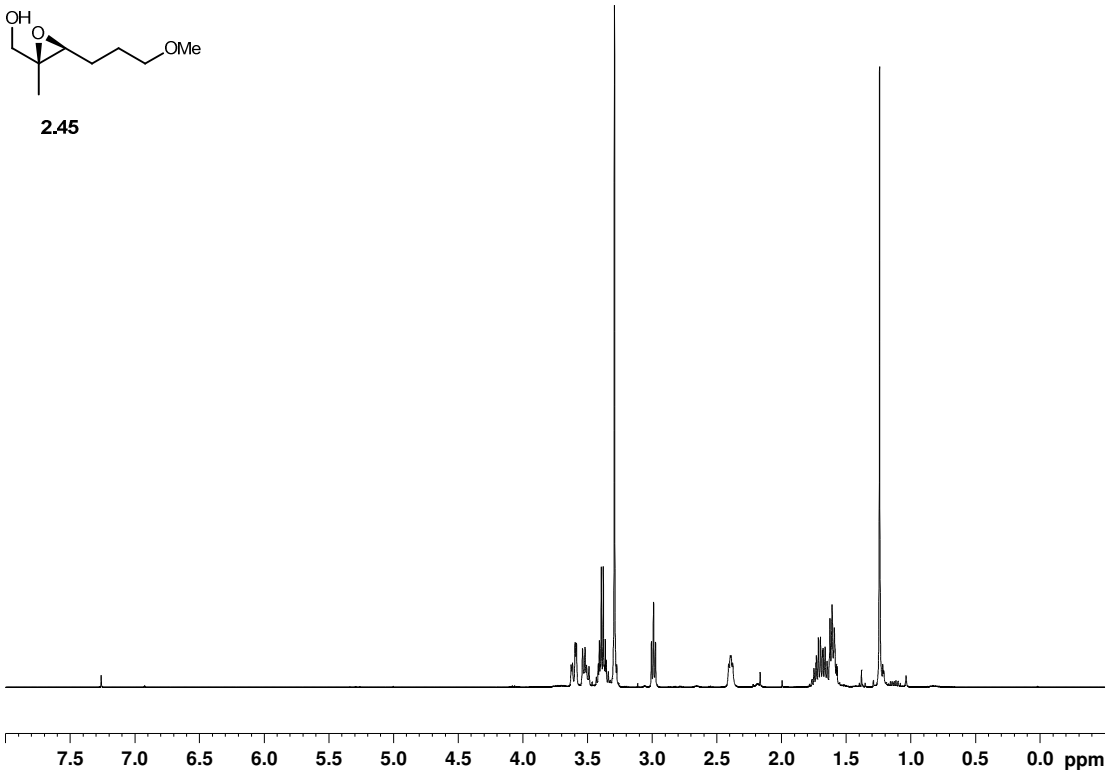


Figure A1.18 400 MHz ^{1}H- NMR spectrum of **2.44** in $CDCl_3$



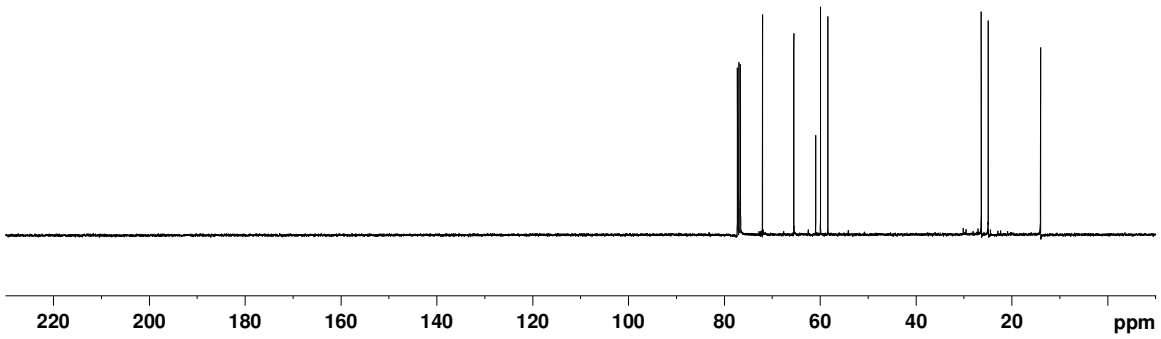


Figure A1.19 400 MHz ^{1}H- NMR and 100 MHz ^{13}C-NMR spectrum of **2.45** in $CDCl_3$

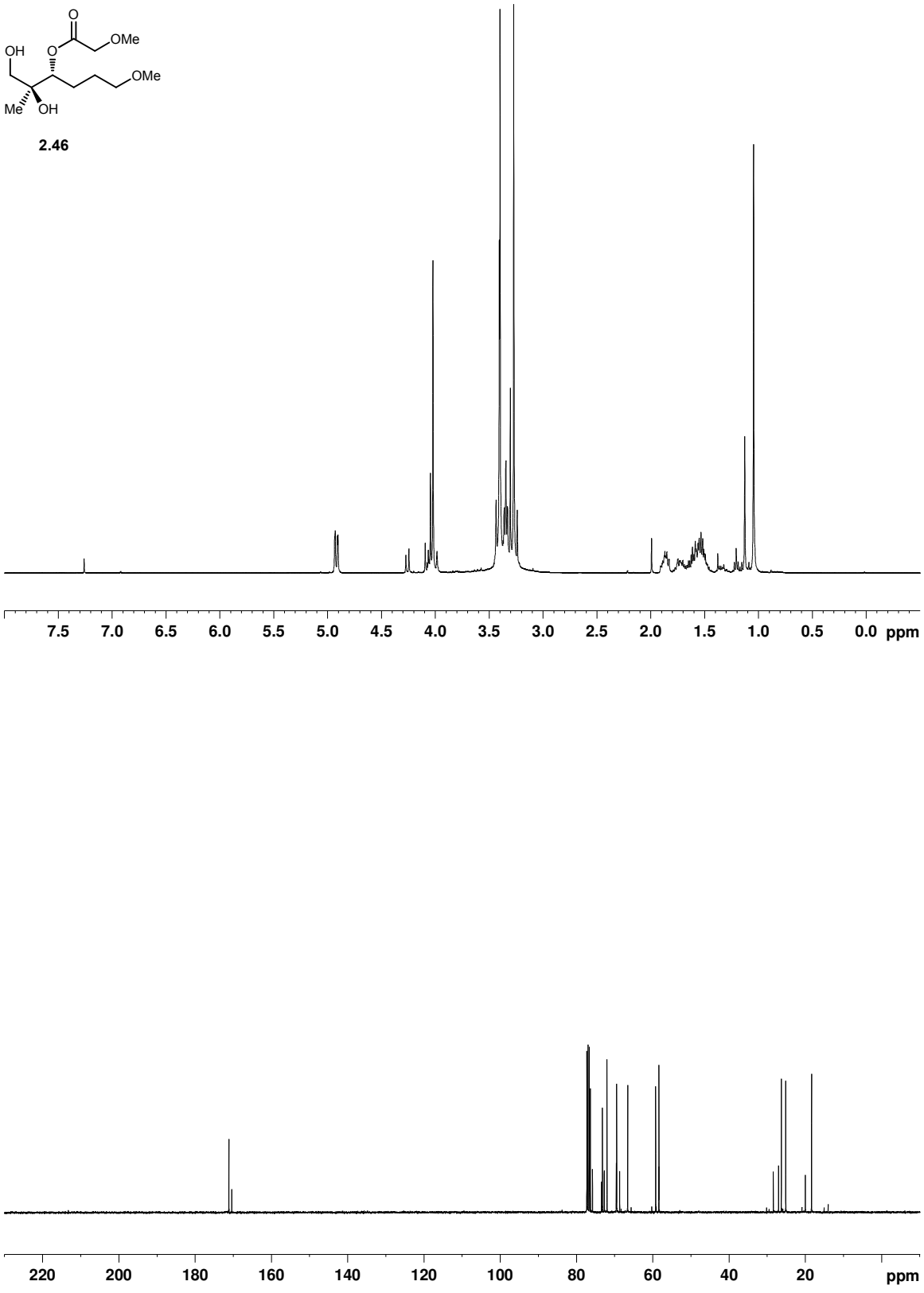


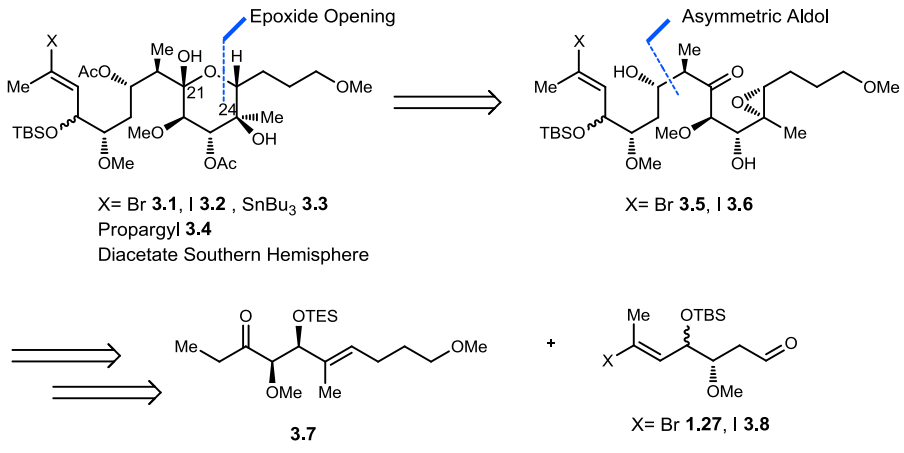
Figure A1.20 400 MHz ^{1}H- NMR and 100 MHz ^{13}C-NMR spectrum of **2.46** in $CDCl_3$

CHAPTER III

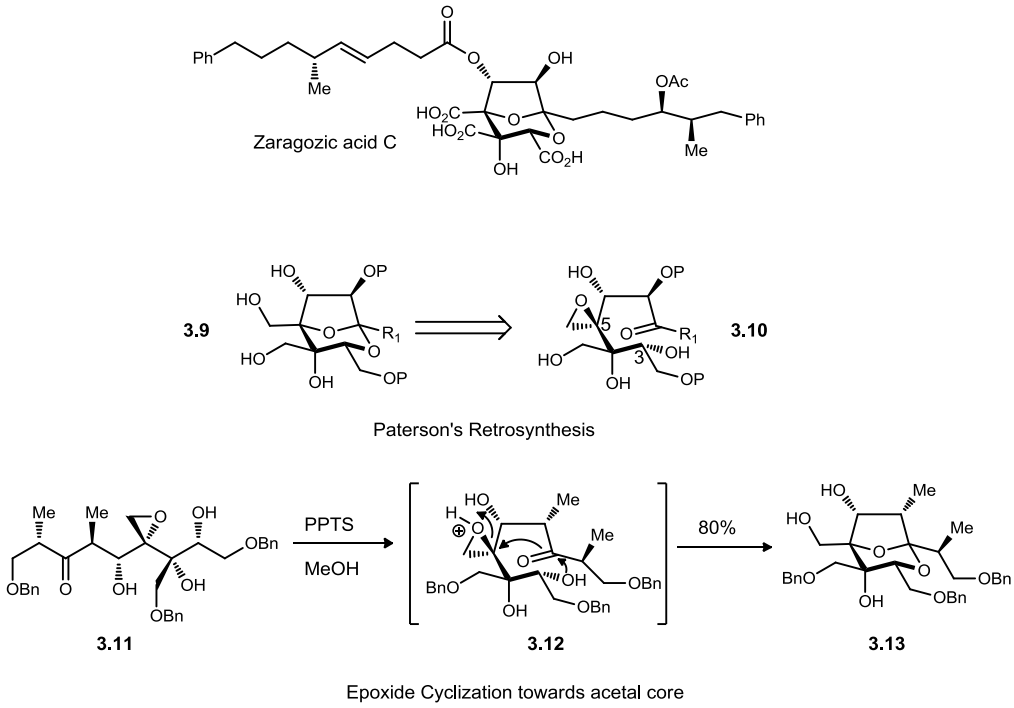
MECHANISTIC STUDIES AND SYNTHESIS OF THE SOUTHERN HEMISPHERE

Retrosynthetic Analysis of the Southern Hemisphere

During our reassessment in constructing the structurally complex and functionalized pyranose ring system, we determined the *anti* relationship between C24 and C25 oxygens in the southern hemisphere could arrive from epoxide opening from either epoxyketone **3.5/3.6**. Epoxyketone **3.5/3.6** could be further disconnected providing ethyl ketone **3.7** and aldehyde **1.27/3.8**. This strategy would provide an efficient and convergent route towards the southern half of ammocidinone or ammocidin D (Scheme 3.1).

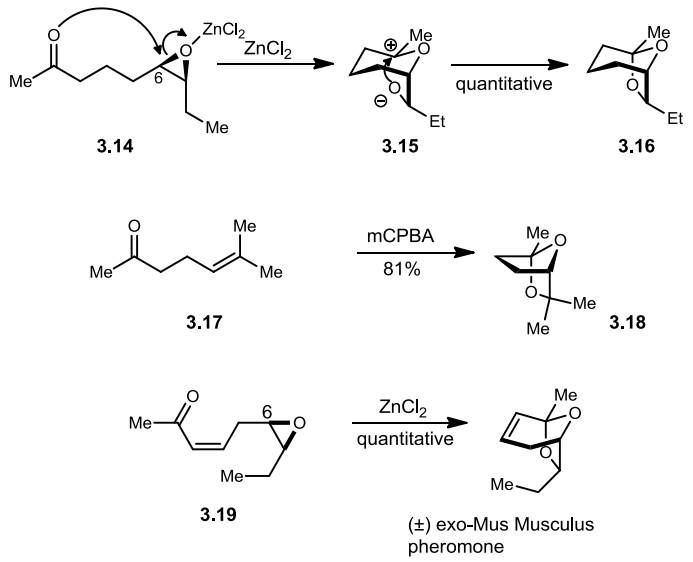


Scheme 3.1 2nd generation retrosynthetic analysis of the southern hemisphere.



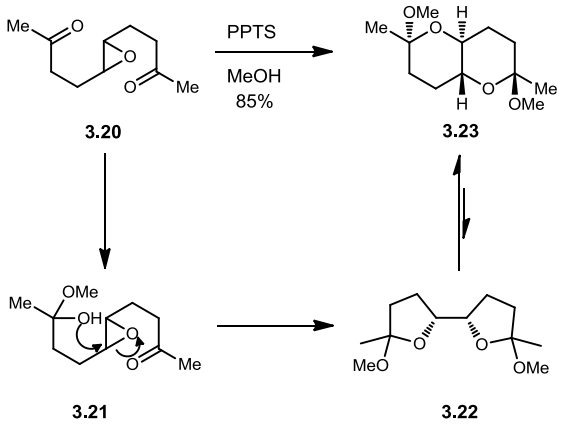
Scheme 3.2 Paterson's approach towards zaragozic acid C.

Literature precedent reveals that others have used ketoepoxide openings to form furan and pyran acetals ring systems. Paterson's[1] approach towards constructing a reduced version of the bicyclic acetal core **3.9** of zaragozic acid C is centered on the epoxide cyclization. Paterson envisaged that the protonated epoxide in **3.12** should allow stereospecific opening at C5 via a 5-exo opening by the ketone with concomitant attack by the C3 hydroxy to generate the required bicyclic acetal. If successful, this process would serve to convert the open chain system into the highly functionalized [3.2.1] bicyclooctane core. Paterson accomplished this cyclization event starting from ketone **3.11**, upon treatment of with PPTS in anhydrous methanol to provide the required bicyclic acetal in 80% yield. The stereochemistry of the reduced core was established with NOE correlations (Scheme 3.2).



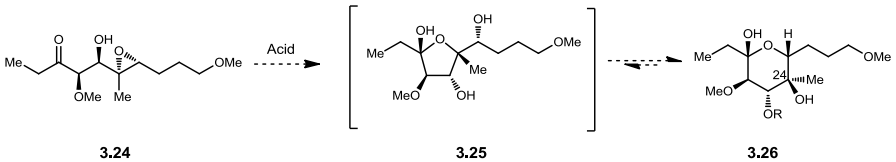
Scheme 3.3 Wasserman's studies on γ,δ-epoxy, δ,ε-epoxy ketone openings.

Studies of intramolecular ring opening of γ,δ-epoxy, δ,ε-epoxy ketones catalyzed by Brønsted or Lewis acids to form dioxabicyclo skeletons have been reported by Wasserman[2]. In the presence of zinc chloride the δ,ε-epoxy ketone **3.14** underwent a 5-exo epoxide opening followed by the trapping of the oxocarbenium ion by the intermediate alkoxide **3.15** in quantitative yield. Furthermore, treatment of γ,δ-epoxy ketone **3.17** with *m*CPBA directly furnished the cyclization adduct **3.18**. Importantly, Wasserman's carbonyl epoxide opening reaction in the synthesis of mus musculus pheromone occurs with remarkable stereospecificity with inversion of configuration at C6 in **3.19** (Scheme 3.3).



Scheme 3.4 Nelson's synthesis of intermediate **3.23** towards hemibrevetoxin B.

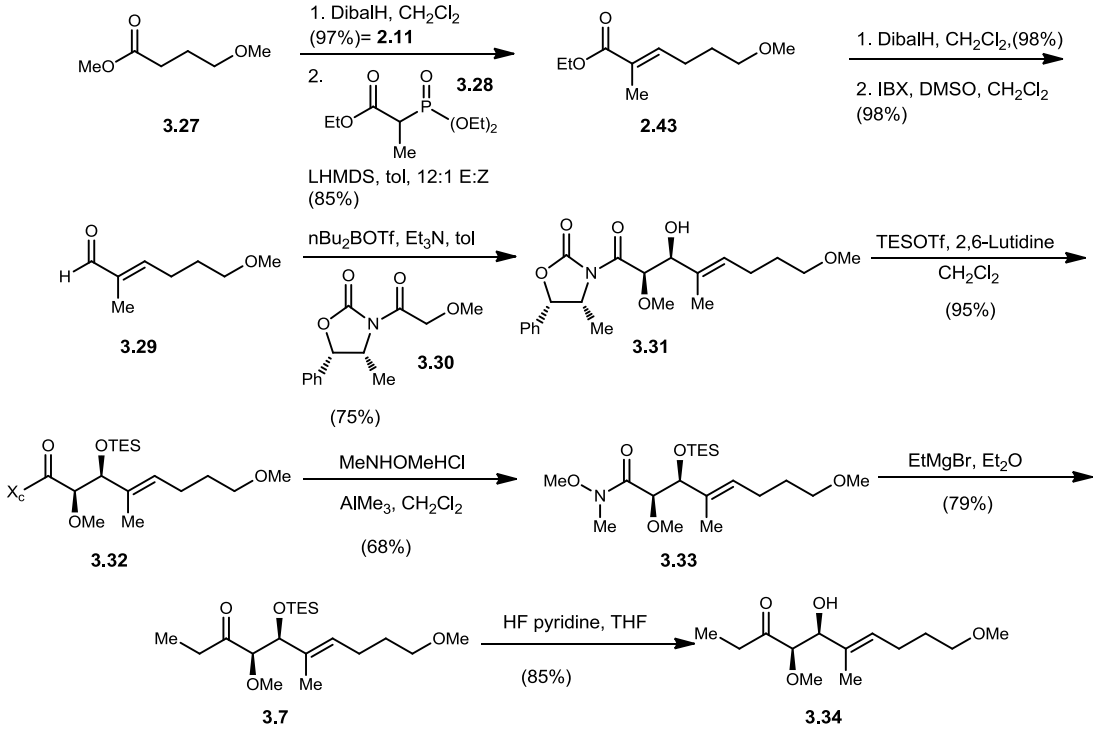
Studies by Nelson[3] towards hemibrevetoxin B was particularly attractive to our synthesis of the C14-C28 fragment of ammocidinone. Nelson exhibited that cyclization of epoxy diketone **3.20** with PPTS in methanol provided furan acetal **3.22** which equilibrated to provide the thermodynamically favored six member pyran acetal **3.23** (Scheme 3.4). The examples by Paterson, Wasserman and Nelson provided the necessary precedence to begin our synthesis of the pyran acetal moiety in ammocidinone. Our initial goal was to develop a model study to demonstrate the keto epoxide ring opening reaction starting from **3.24**. We anticipated a 5-exo closure to **3.25** followed by the concomitant isomerization to the desired pyranose ring system **3.26** (Scheme 3.5).



Scheme 3.5 Ketoepoxide ring opening with isomerization of the furan acetal to the pyran acetal.

Model studies towards the pyranose ring system

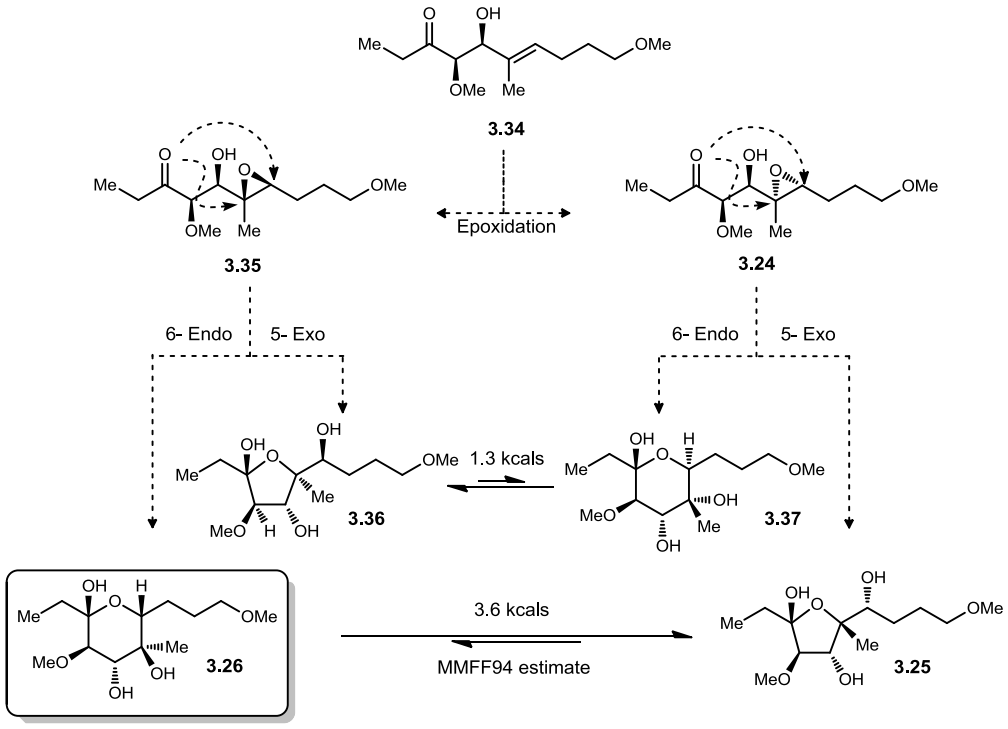
The synthesis of ethyl ketone fragment **3.34** was required for the ketoepoxide/ isomerization model study to commence. Commercially available methyl-4-methoxy butanoate **3.27** was reduced to form aldehyde **2.11** in 97% yield. Use of the Horner Wadsworth Emmons[4] protocol with known ethyl 2-(diethoxyphosphoryl)propanoate **3.28** provided **2.43** in a 12:1 E:Z ratio in 85% yield. A reduction-oxidation sequence was followed by an Evans asymmetric glycolate aldol[5] with the aid of the norephedrine based auxiliary **3.30** to produce aldol adduct **3.31** in high diastereomeric ratio (20:1 dr). Silyl protection and formation of the Weinreb[6] amide provided **3.33**. Ethylation and deprotection of the TES ether provided the key δ,γ-unsaturated β-hydroxy ethyl ketone **3.34** (Scheme 3.6).



Scheme 3.6 Synthesis of Ketone Fragment **3.34**.

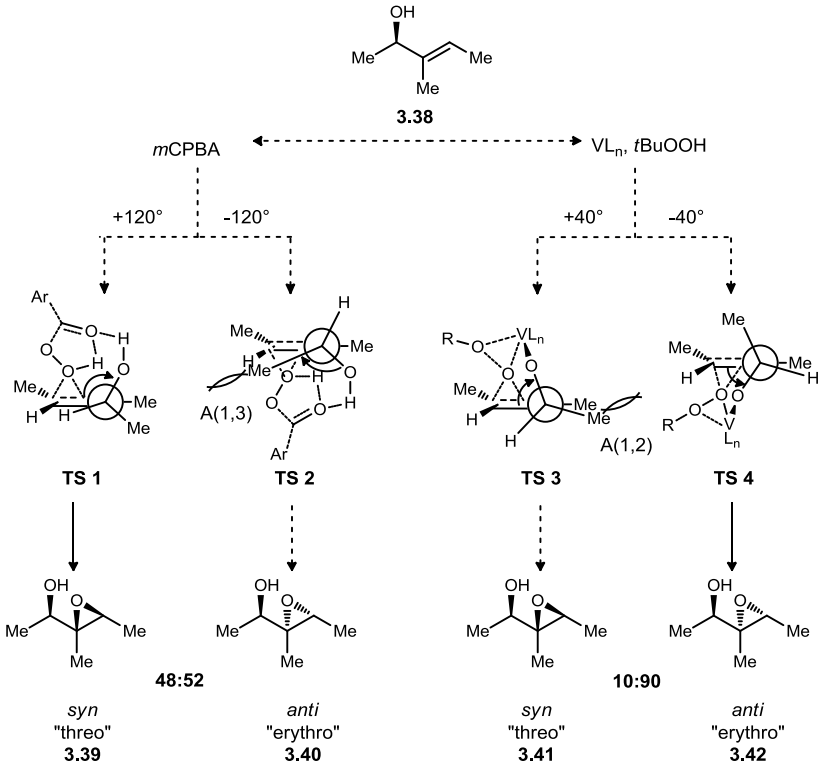
Mechanistic rationale toward desired pyranose system

With **3.34** in hand, we began efforts towards demonstrating the key cyclization reaction based on literature precedent suggesting **3.34** can provide δ,γ-epoxy ketones **3.35** and **3.24** from peracid and metal catalyzed epoxidations, respectively[7]. Epoxyketones **3.35** and **3.24** can lead to pyran acetal **3.26** by two possible pathways, 5-exo and 6-endo. *Syn* epoxyketone **3.35** can achieve the desired product directly through a 6-endo opening. In addition, *anti* epoxy ketone **3.24** can achieve the desired product through a 5-exo pathway followed by an isomerization to the desired pyranose ring system. However, Merck Molecular Force Field calculations (MMFF94) surprisingly predicted furan acetal **3.25** is 3.6 kcals/mol more stable than the desired pyran acetal **3.26** system (Scheme 3.7).



Scheme 3.7 Mechanistic rationale towards **3.26**.

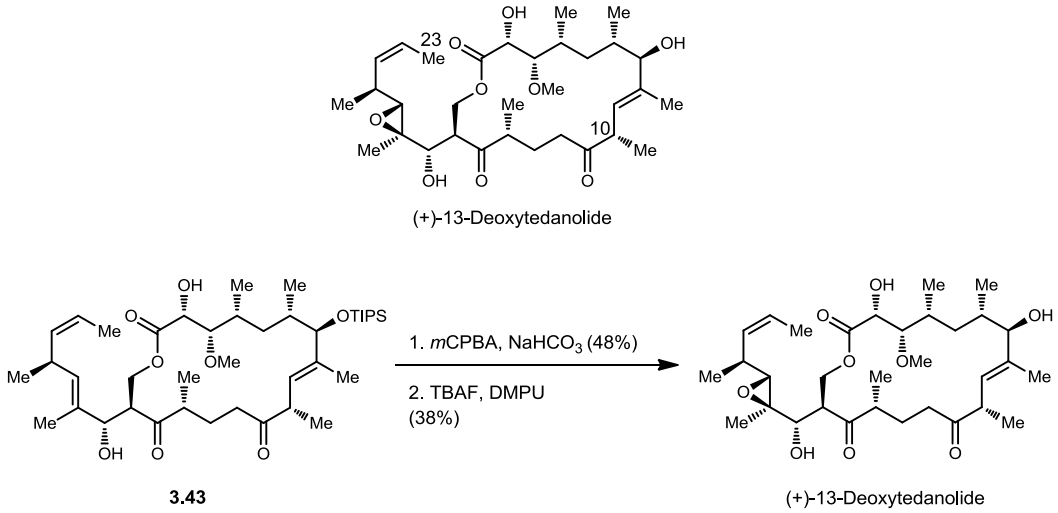
As illustrated in Scheme 3.7 the undesired pyran **3.37** and furan **3.36** acetals isomers are also possible products. *Syn* epoxyketone **3.35** can also undergo a 5-exo pathway leading to the undesired furan acetal **3.36**. Furthermore, *anti* ketoepoxide **3.24** can undergo a 6-endo opening to arrive at **3.37**. According the MMFF94 calculations, pyran acetal **3.37** could rearrange to the more stable furan acetal **3.36** due to the sterically encumbering axial subsituents (Scheme 3.7).



Scheme 3.8 Transition state models for peracid and metal catalyzed epoxidations.

Henbest[8] proposed the synergistic interplay between conformational control and substrate/reagent interaction through hydrogen bonding in the highly diastereoselective peracid epoxidation allylic alcohols. The epoxidation of **3.38** by *m*CPBA affords epoxy alcohol

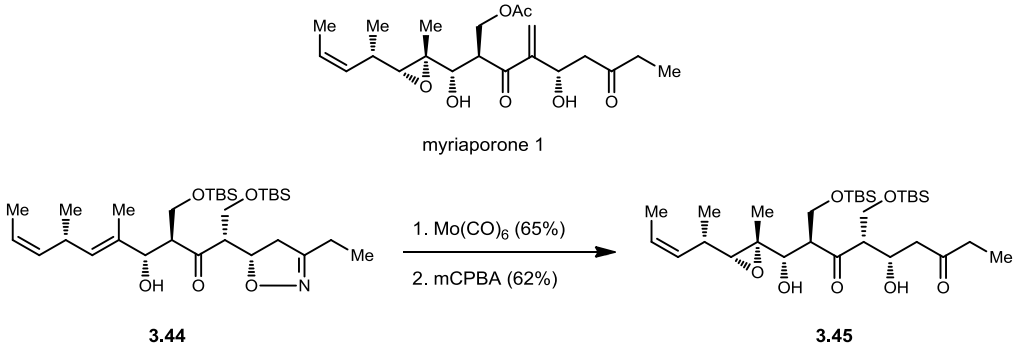
3.39 and **3.40** in a 1:1 ratio. For the peracid oxidant[9], the allylic alcohol associates by hydrogen bonding with an estimated dihedral angle of ±120°. Of the two conformations, minimization of A(1,3) strain in found **TS 1** dictates the energetically favored *syn* transition state geometry. In contrast, for the vanadium oxidant, metal alcohol binding between the allylic oxygen atom and the metal center favors a dihedral angle of ±40° for effective oxygen transfer, and the preferred *anti* or *erythro* diastereoselectivity is governed by A(1,2) strain found in **TS 3**. These two mechanistically distinctive epoxidations, *m*CPBA (hydrogen bonding) versus $VO(acac)_2$ (metal alcohol binding) would theoretically provide flexibility in our route towards the pyranose ring system **3.26** (Scheme 3.8).



Scheme 3.9 Smith's synthesis of (+)-13-Deoxytedanolide.

Literature precedence of 2,3-syn epoxidations with peracids was examined by Smith[10] and co-workers. Smith envisioned the construction of (+)-13-deoxytedanolide from a late state epoxidation of **3.43**. In the event, treatment of the allylic alcohol **3.43** with *m*CPBA in the

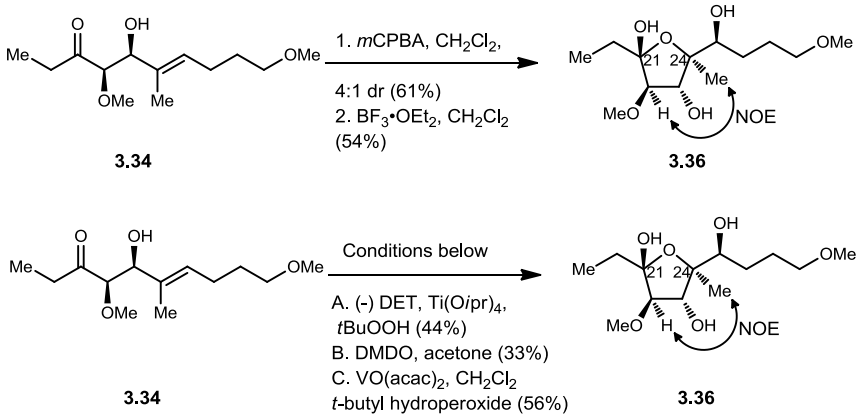
presence of $NaHCO_3$ afforded the desired *syn*-2,3 epoxide with excellent stereoselectivity (15:1) in 48% yield. Taylor[11] and co-workers also examined peracid epoxidations in the synthesis of myriaporone 1 a related class of natural products to the tedanolides. The myriaporones are nearly identical structurally to the C10-C23 section of tedanolide and 13-deoxytedanolides (Scheme 3.9). A late stage reduction of isoxazoline **3.44** with $Mo(CO)_6$ successfully unmasked the β-hydroxy ketone and set the stage for the key epoxidation. Under the optimized conditions of less than one equivalent of *m*CPBA at -50°C, the desired *syn*-2,3 epoxide **3.45** as a single diastereomer and unreacted starting material was obtained (Scheme 3.10).



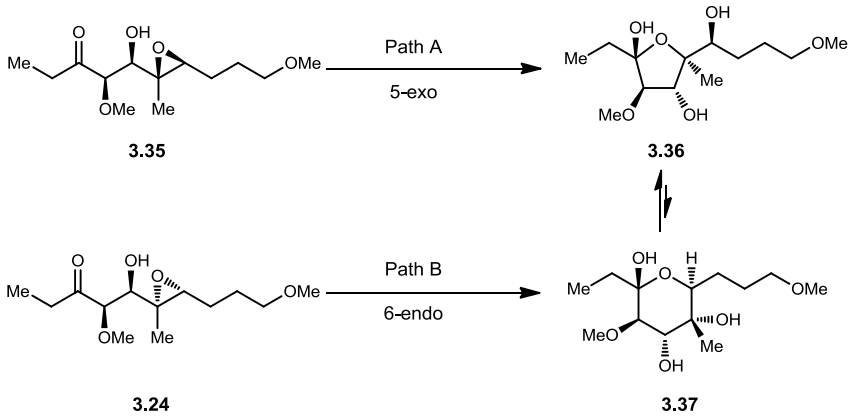
Scheme 3.10 Taylor's synthesis of myriaporone via late stage peracid epoxidation.

With the literature precedent and the epoxidation models in hand, peracid epoxidation of ethyl ketone **3.34** provided an isolable epoxyketone of undetermined stereochemistry at this point (Scheme 3.11). However, further treatment with boron trifluoride diethyl etherate produced furan **3.36**. Experimental data[12 13] of **3.36** indicated the coupling constants between H_{22} and H_{23} was 2.4 Hz compared with that of ammocidin D (9.9 Hz). Furthermore, the acetal carbon at C21 resonated at 110 ppm approximated 10 ppm further downfield compared to

ammocidin D (100 ppm). Further evidence for furan **3.36** was provided by two dimensional NMR analysis whereby an NOE crosspeak between H_{22} and Me_{24} was observed and a HMBC cross peak between C_{21} and H_{25} was absent. Therefore, furan **3.36** not only possessed the undesired ring tautomer but also the inverted stereochemistry at C24 and C25 relative to that required for the ammocidins. Interestingly, metal catalyzed epoxidations (mechanistically distinct from the peracid) with $VO(acac)_2$ and Sharpless epoxidations[14] also provided furan **3.36** directly. In light of the two distinct epoxidation mechanisms, this outcome was unique and unexpected (Scheme 3.11).

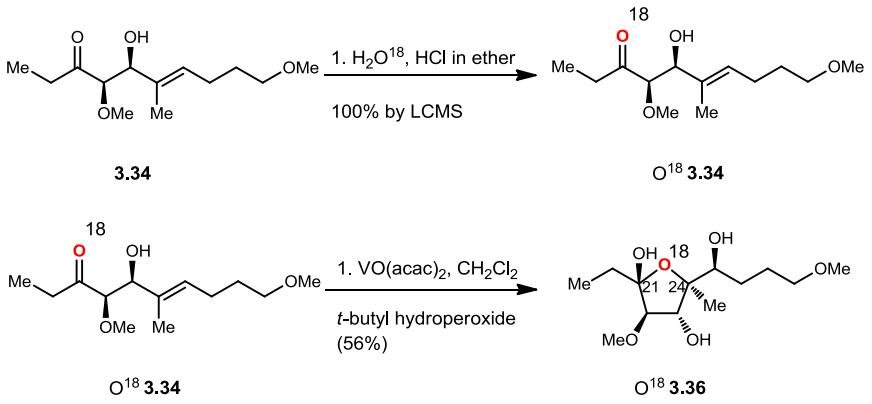


Scheme 3.11 Peracid and metal catalyzed epoxidation of **3.34**.



Scheme 3.12 Possible routes leading to furan **3.36**.

With the determined stereochemistry and ring size, two possible reaction pathways could account for the unexpected production of furan **3.36**. Based on literature precedent, we assumed furan **3.36** arrived from *syn* epoxyketone **3.35** via a 5-exo opening (Path A). However, as stated by Sharpless[15], direct assignment of *syn/anti* relative stereochemistry of 2,3-epoxy alcohols by NMR analysis is historically difficult. In order to provide evidence for path A, **3.34** was isotopically labeled with H_2O^{18} in the presence of acid to provide O^{18} **3.34**. The cyclization of O^{18} **3.34** would allow path A and path B to be distinguished by the assignment of the O^{18} induced shift relative to the abundant O^{16} carbon signal in the ^{13}C NMR spectrum[16] (Scheme 3.12).



Scheme 3.13 O^{18} Assisted analysis of epoxidation-cyclization.

The labeled O^{18} **3.34** was treated to the same $VO(acac)_2$ protocol and led to the isolation of O^{18} **3.36.** Examination of the ^{13}C NMR spectrum indicated resonances corresponding to C21 and C24 were accompanied by O^{18} induced carbon shifts at 110 and 84 ppm respectively (Figure 3.1, Scheme 3.13).

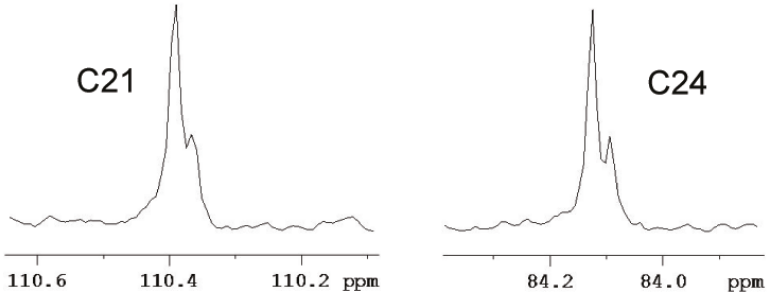


Figure 3.1 NMR analysis assisted by mixing O^{16} and O^{18} labeled **3.36**.

The <u>combination</u> of the assigned stereochemistry and isotope position in furan acetal O^{18} **3.36** revealed *syn*-2,3 epoxyketone **3.35** underwent a 5-exo opening to form **3.36** in support

of path A. A tentative model used to rationalize the observed selectivity in the epoxidation of **3.34** begins with the preorganization of an intramolecular hydrogen bond (Figure 3.2).

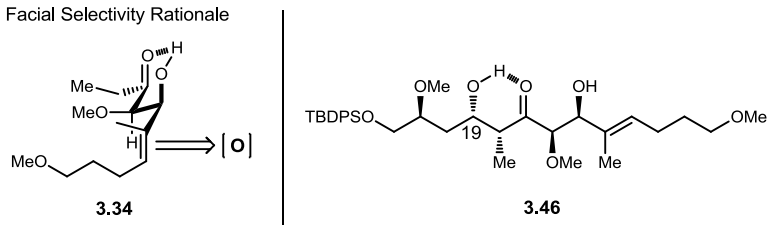
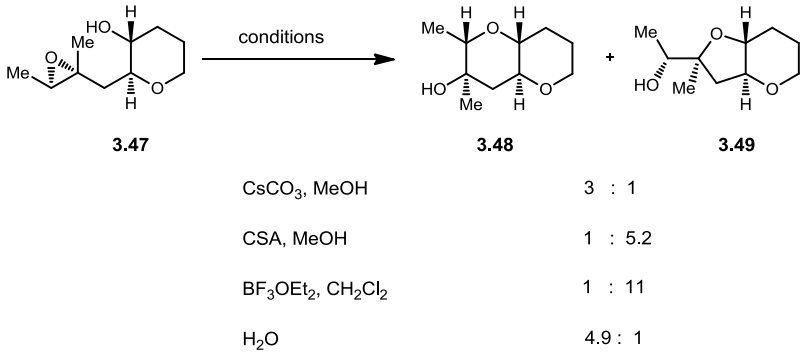


Figure 3.2 Assumed hydrogen bonding of **3.34** and **3.46**.

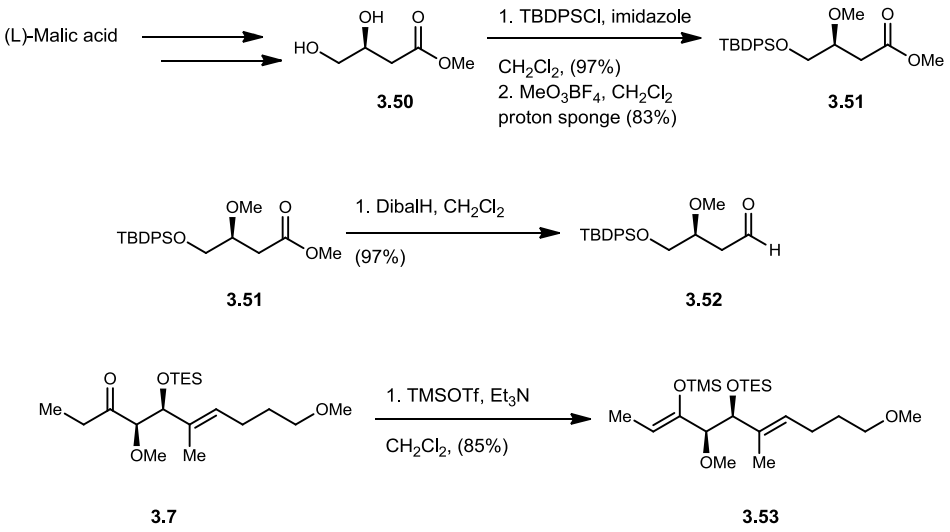
We speculated the incorporation of a second hydrogen bond by way of the C19 hydroxyl group in **3.46** may alter the stereoselectivity to favor the *anti* epoxy ketone or allow isolation of the *syn* epoxy ketone by slowing the rate of keto-epoxide cyclization. In the latter case, we would examine a 6-endo closure of the *syn* epoxy ketone promoted by aqueous solvent to afford the ammocidin acetal pyran based on the work of Jamison. Alternatively, hydrogen bonding could provide access to the anti epoxy alcohol. In short, we hoped to change the reaction course favoring 6-endo.



Scheme 3.14 Jamison's work on water epoxide opening cascades.

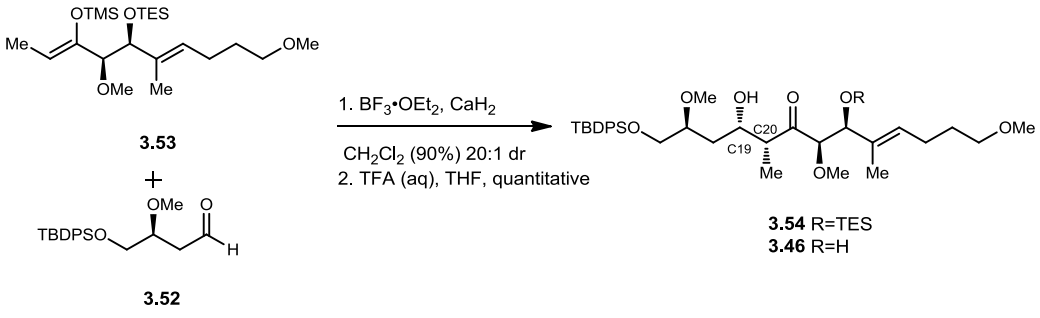
Jamison[17] reported on a simple and general method for regioselective epoxide openings that involve trisubstituted epoxides. Jamison stated the crux of the problem is that the methyl group in **3.47** is generally a strong director of epoxide opening regioselectivity, particularly under acid catalysis. Unsurprisingly, both Bronsted and Lewis acids were highly exo-selective affording **3.49**. Conversely and strikingly, water effected endo cyclization with nearly 5:1 selectivity for **3.48** over **3.49** and improved to 6:1 endo/exo with potassium phosphate buffer at pH 8-10. This methodology provided a possible interesting solution from a mechanistic point of view favoring endo selectivity over exo (Scheme 3.14).

Preparation of **3.46** required for our new model study with incorporation a new hydrogen bond by way of C19 required aldehyde **3.52** and silyl enol ether **3.53**. Aldehyde **3.52** can be readily prepared from (L)-malic acid[18] via **3.50**. The primary hydroxyl in **3.50** was protected as a TBDPS silyl ether and subjected to methylation using Meerwein salt[19] in the presence of proton sponge[20] to furnish **3.51**. Facile reduction of **3.51** afforded aldehyde **3.52** in 97% yield. Silyl enol **3.53** was formed from ethyl ketone **3.7** following treatment with TMSOTf and triethylamine in high yield and geometric fidelity (Scheme 3.15).



Scheme 3.15 Required fragments for the assembly of **3.46**.

The double diastereoselective Mukaiyama aldol reaction[21] between aldehyde **3.52** and silyl enol **3.53** provided *syn* aldol adduct **3.54** in 76% yield and 13% of alcohol **3.46**. The exquisite diastereocontrol of >20:1 dr can be attributed to the matching Felkin addition to aldehyde **3.52** described by Evans[22]. *Syn* aldol adduct **3.54** was treated with TFA (aq.) to furnish allylic alcohol **3.46** in quantitative yield (Scheme 3.16).



Scheme 3.16 Assembly of 3.23 C16- C28 fragment.

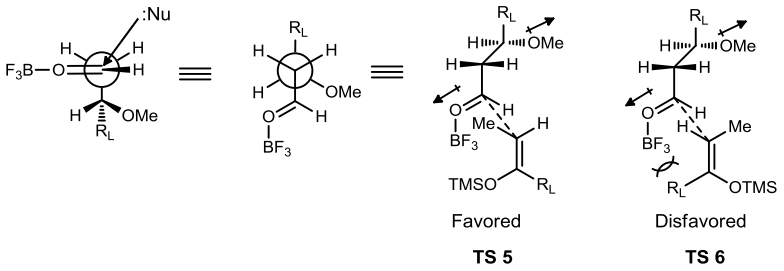
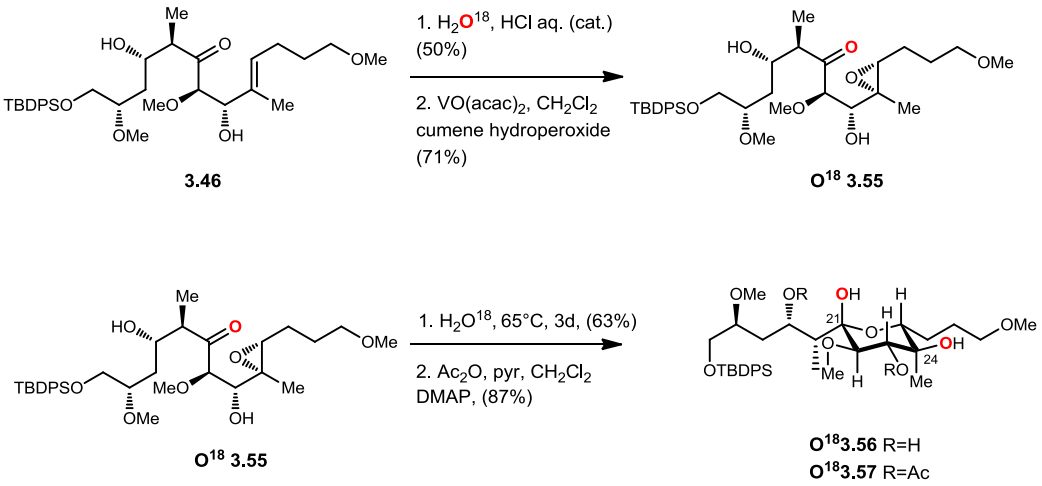


Figure 3.3 1,3-Asymmetric induction polar model.

Examining the 1,3 asymmetric induction Felkin-Ahn polar model we speculate that the aldehyde facial selectivity is governed by steric and electrostatic dipole repulsions. The model proposes that the β-methoxy substituent reduces the dipole interaction with the aldehyde affording the preferred transition state **TS 5** (Figure 3.3) leading to the favored 1,3-*anti* diastereomer. Steric interaction between the aldehyde and the sterically demanding β-alkyl substituent (R_L) are expected to be minimized when they are oriented anti periplanar to the C_α-C=O bond. The approach of the enolsilane is expected to be in a staggered conformation where the sterically demanding Lewis acid and the R_L of the enolsilane are minimized[22] (Figure 3.3).

Applying the earlier strategy, incorporation of H_2O^{18} at the ketocarbonyl of **3.46** proceeded with 50% conversion as determined by LC/MS. Epoxidation of O^{18} **3.46** under the $VO(acac)_2$ protocol afforded the single 2,3-epoxy ketone O^{18} **3.55** isolable by flash chromatography, implying that hydrogen bonding of the C19 hydroxyl group retarded the rate of cyclization as previously hypothesized. In fact, if the C19 hydroxyl group of aldol adduct **3.46** were acetylated, rapid ketoepoxide cyclization occurs during the reaction, and upon aqueous workup produces undesired acetylated furan **3.59** (Scheme 3.17/ 3.18).



3.46

O^{18} 3.55

O^{18} 3.55

O^{18}3.56 R=H
O^{18}3.57 R=Ac

Scheme 3.17 Cyclization to pyran acetal **3.56**.

Delightfully, upon heating ketoepoxide **O^{18} 3.55** in H_2O^{18} for 3 days provided **O^{18} 3.56** in 63% yield. Following acetylation of **O^{18}3.56**, ^{13}C NMR analysis of diacetate **O^{18}3.57** indicated incorporation of O^{18} at C21 (99 ppm) and C24 (74 ppm) (Figure 3.4). The C13 signal for C21 at 99 ppm and the H_{22}-H_{23} coupling constant at 9.6 Hz were both congruent relative to that of ammocidin D at 100 ppm and 10 Hz respectively. Two dimensional analysis of the NOE and HMBC spectrums confirmed the desired stereochemistry relative to the ammocidins (Figure 3.5). It is interesting to note that the O^{18} marker was lost if the cyclization was run under H_2O^{16}, suggesting that carbonyl hydration was faster than the ketoepoxide cyclization event. Furthermore, it was discovered that the rate of acetylation is remarkably different. The nucleophilicity of the hydroxyl at C23 is higher, thus, it is more rapidly acetylated compared to that of the hydroxyl at C18, for monoacetylation of **3.56** can be easily achieved (Scheme 3.17).

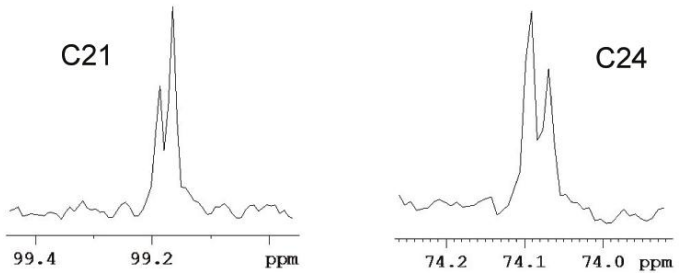


Figure 3.4 C^{13} signals of O^{18} Incorporation at C21 and C24.

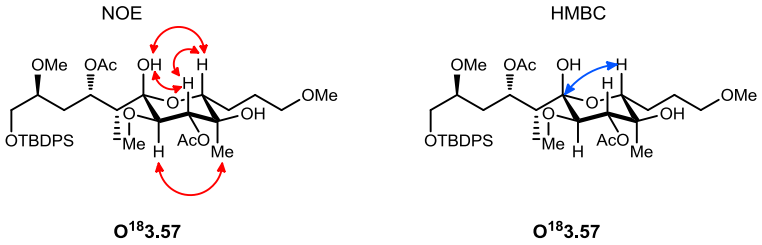
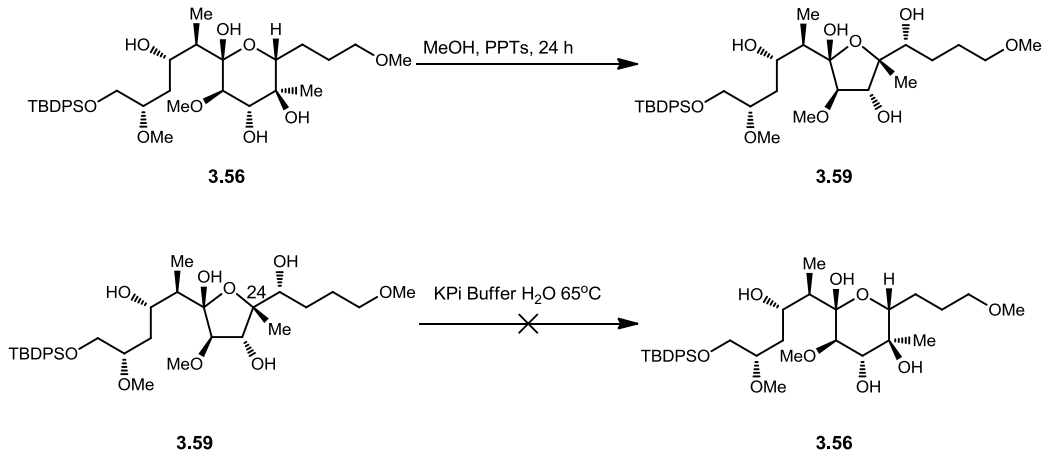


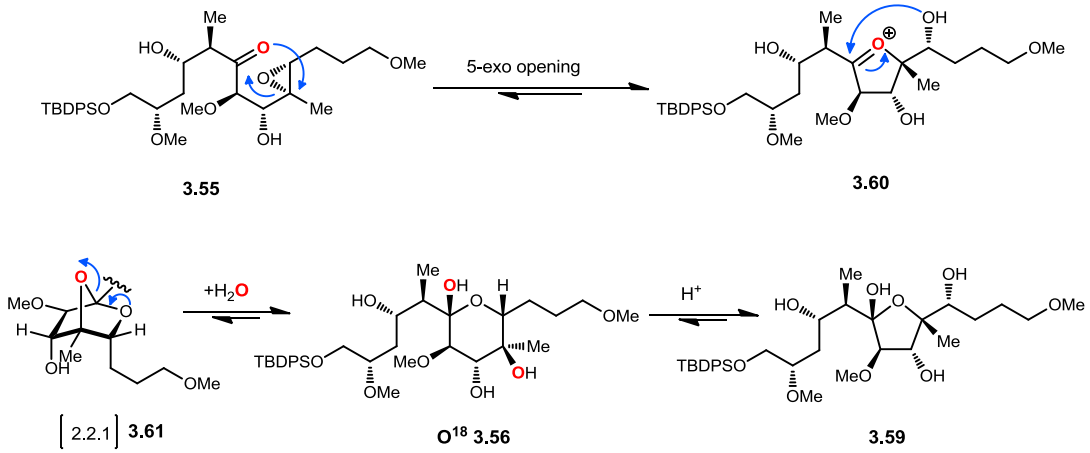
Figure 3.5 NOE and HMBC crosspeaks for the desired pyran rings system.

The combination of both the stereochemistry in **3.57** and the O^{18} labeling study provided evidence for the generation of *anti* ketoepoxide **3.55** that upon heating in water yielded pyran acetal **3.56** via a 5-exo opening. Furthermore, our results are in direct contrast to the work of Jamison where water did not overcome the methyl group directing effect in epoxide opening cascades. It is noteworthy that this epoxide formation with $VO(acac)_2$ provided the opposite stereoisomer compared to that of *syn* keto epoxide **3.35** (Scheme 3.11). Therefore, we deduced from the preceding experiments that it is essential for the C19 hydroxyl group to hydrogen bond with the C21 ketone in order for the desired keto epoxide cyclization to afford the apropos pyranose ring system found in the family of ammocidins.



Scheme 3.18 Isomerization of pyran acetal **3.55** to furan acetal **3.59**.

Surprisingly, in an attempt to protect hemiacetal **3.55** as the methyl acetal, we unexpectedly observed complete isomerization to furan acetal **3.59** (Scheme 3.18). This finding exemplifies that the thermodynamic equilibrium favors the undesired furanose ring system which is in agreement with our computational models (MMFF94). Of paramount importance, we discovered that in contrast to the established work from the apoptolidin series, the pyranose ring system of ammocidin would be not formed during a late stage global deprotection but instead the furan acetal due to the unique hydroxyl group located at C24!

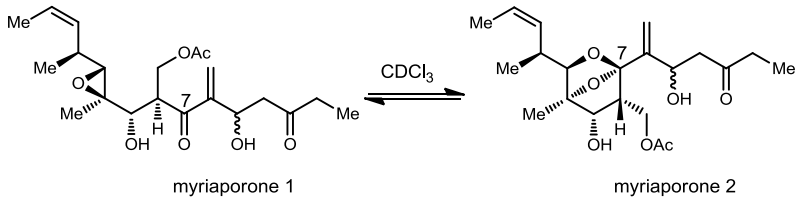


Scheme 3.19 Revised Mechanism for the formation of pyran acetal **3.56**.

Based on the results of the O^{18} model study, we revised our mechanistic rationale whereby ketoepoxide **3.55** underwent a 5-exo opening to form the oxocarbenium intermediate **3.60**. This intermediate is intercepted by the newly revealed alcohol at C24 forming a [2.2.1.] bicyclic system. After opening of the [2.2.1] bicyclic system and trapping of the oxocarbenium ion with water, the [2.2.1] system furnishes the kinetically favored desired pyranose system **3.56**. The Lewis and Bronsted acid sensitive pyranose system can then isomerize to the thermodynamically favored furan acetal **3.59** (Scheme 3.19).

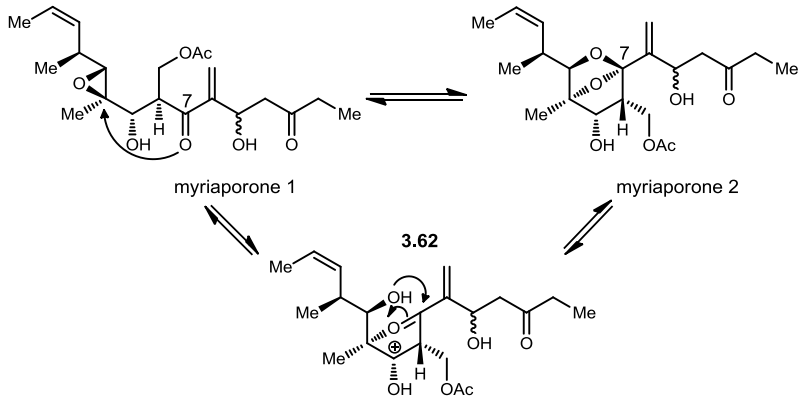
Sulikowski's approach toward the synthesis of the southern fragment of ammocidin D differs from the classic formation of ketals used by Nicolaou, Koert and Crimmins. Instead our approach in synthesizing the more complex pyran acetal of ammocidin resembles the isomerization of myriaporone 1 to myriaporone 2 (Scheme 3.20).

Myriaporone isomerization



Scheme 3.20 Isomerization of myriaporone 1 to myriaporone 2.

Cheng[23] and coworkers' isolated myriaporones 1-4 from the Mediterranean bryozoans *Myriaproa truncate* a polyketide metabolite. It was determined that myriaporone 1 was isomeric to that of myriaporone 2. It was determined that the ^{1}H NMR spectrum of 2 was different from that of 1 in coupling constants and chemical shifts, however, the carbon framework was identified to be the same as that of 1. Of interest was that the carbonyl shift at δ202.9 observed in 1 (C-7) was replaced by a ketal resonance at δ109.5 for 2 (C-7). In addition, the isomerization of myriaporone 1 to 2 was detected in the ^{1}H NMR spectrum of pure compound 1 in $CDCl_3$ (Scheme 3.20).



Scheme 3.21 Plausible mechanism from myriaporone 1 to 2.

Therefore, a plausible stereospecific mechanism from myriaporone 1 to 2 includes a 5-exo opening of the epoxide from the carbonyl functionality. The formation of the oxocarbenium ion **3.62** is intercepted by the newly revealed alcohol forming the [2.2.1] ketal moiety (Scheme 3.21). Applying the myriaporone isomerization precedent, we concluded our synthesis of the southern hemisphere occured through a stereocontrolled ketoepoxide opening rearrangement strategy.

Synthesis of the Southern Hemisphere C14-C28

After successfully synthesizing the pyran acetal system, we turned our attention to a series of C14-C28 southern fragments that would allow metal coupling reactions with the C1-C13 northern fragment. These fragments variants included an alkyne, vinyl bromide, vinyl iodide and a vinyl stannane.

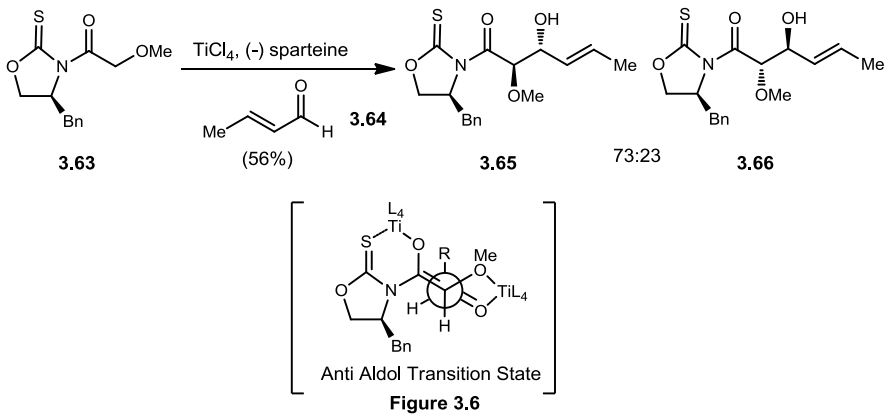


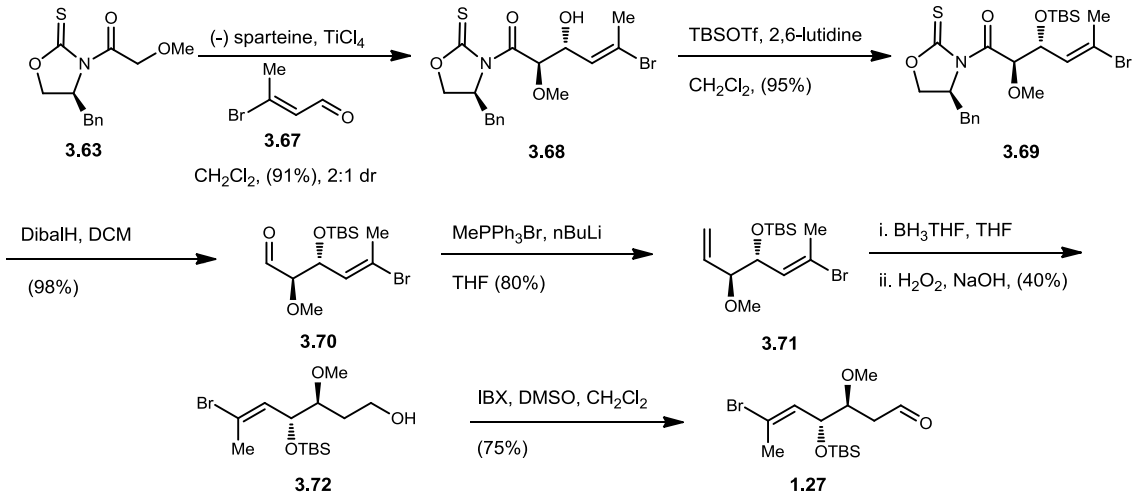
Figure 3.6

Scheme 3.22 Crimmin's *anti* selective aldol reactions with titanium enolates.

Crimmins[24] reported on the highly diastereoselective *anti* aldol addition utilizing *N*-glycolyloxazolidinethiones. Enolization of **3.63** with $TiCl_4$ and (-) sparteine followed by addition of an aldehyde activated with additional $TiCl_4$ resulted in highly anti-selective aldol additions. Crimmins stated the degree of *anti* selection was highly dependent on the amount of $TiCl_4$ used to activate the aldehyde. α-β Unsaturated crotonaldehyde provided 73:23:4 ratio of **3.65**: **3.66**: *syn* isomer, respectively. The open transition state was proposed based on the observation that pre-complexing the aldehyde with a Lewis acid leads to the *anti* isomer. In addition, the glycolate oxygen may coordinate to the $TiCl_4$ that serves to activate the aldehyde as shown in Figure 3.6. Finally, positioning the aldehyde substituent away from the auxiliary leads to the observed *anti* product (Scheme 3.22).

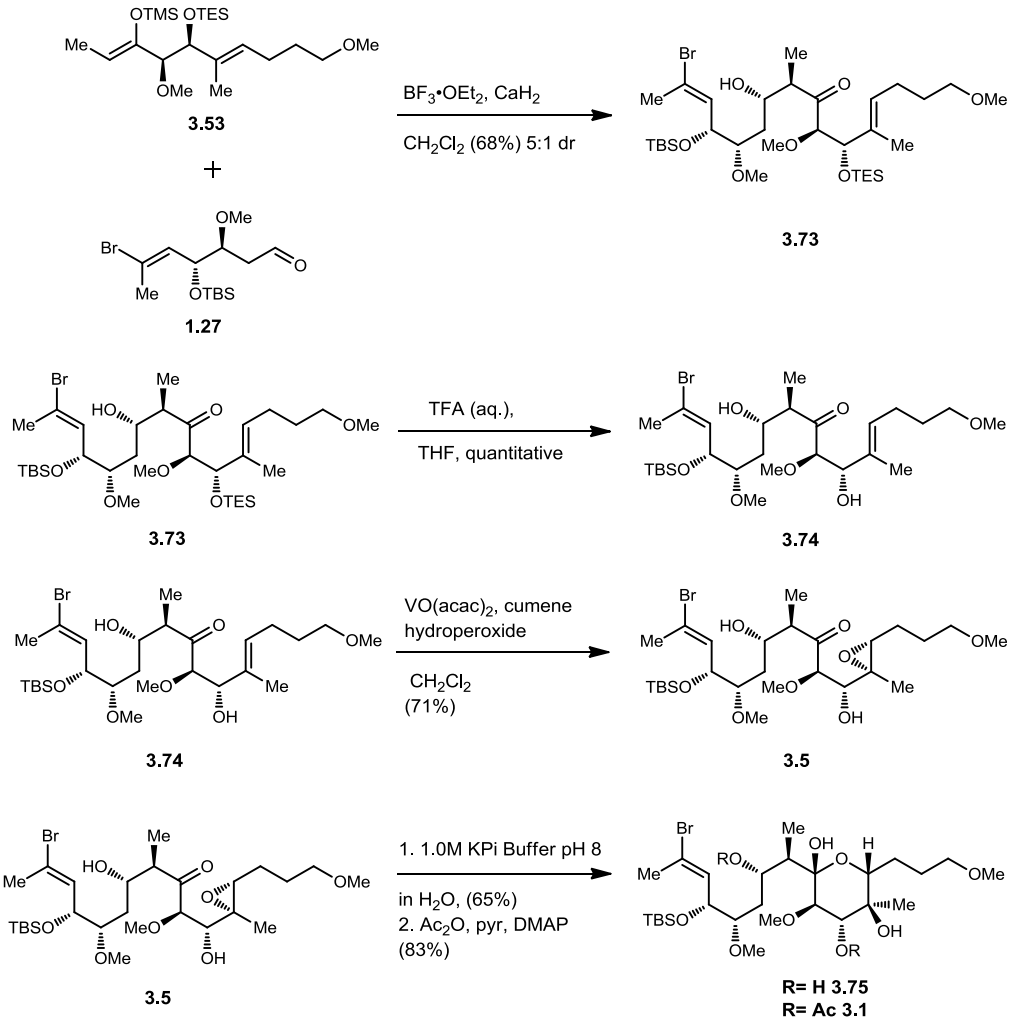
Beginning with a Crimmins titanium mediated glycolate aldol reaction with aldehyde **3.67** and known auxiliary **3.63** in the presence of (-) sparteine provided *anti* aldol adduct in 91% yield, (2:1 dr). Aldol adduct **3.68** was protected as the TBS silyl ether and jettison of the auxiliary provided aldehyde **3.70**. Wittig olefination and hydroboration/oxidation sequence provided

primary alcohol **3.72**. Finally, IBX oxidation of alcohol **3.72** provided aldehyde **1.27** in 75% yield (Scheme 3.23).



Scheme 3.23 Synthesis vinyl bromide **1.27** via Crimmins *anti* aldol reaction.

With aldehyde **1.27** in hand, we carried out the required Mukaiyama aldol reaction providing **3.73** (5:1 d.r) in 68% yield. Treatment of the aldol adduct with TFA (aq.) provided allylic alcohol **3.74** which was subsequently epoxidized in the presence of $VO(acac)_2$ furnishing *anti* ketoepoxide **3.5** in 71% yield. The *anti* ketoepoxide **3.5** was heated in 1.0 M KPi buffer at 65°C for three days providing pyran acetal 3.75 which was treated with acetic anhydride providing the diacetate vinyl bromide **3.1**, the vinyl bromide C14-C28 southern hemisphere of ammocidin D (Scheme 3.24).



Scheme 3.24 Vinyl bromide C14-C28 southern hemisphere.

Analyses of the NOE and HMBC experiments were in accord with our previous model and those required for the ammocidins. The ^{13}C signal for the lactol carbon resonated at 99 ppm and the H_{22}-H_{23} observed a coupling constant of 9.6 Hz, both in agreement with experimental data relative to the ammocidins (Figure 7).

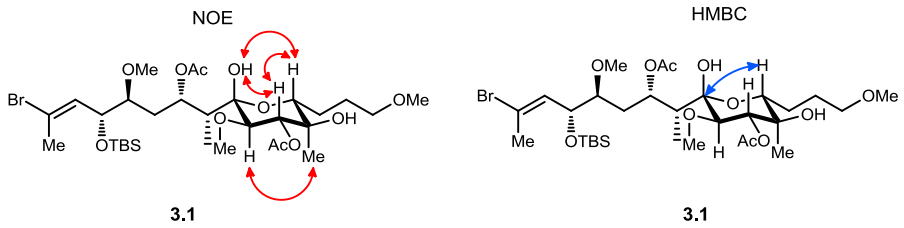
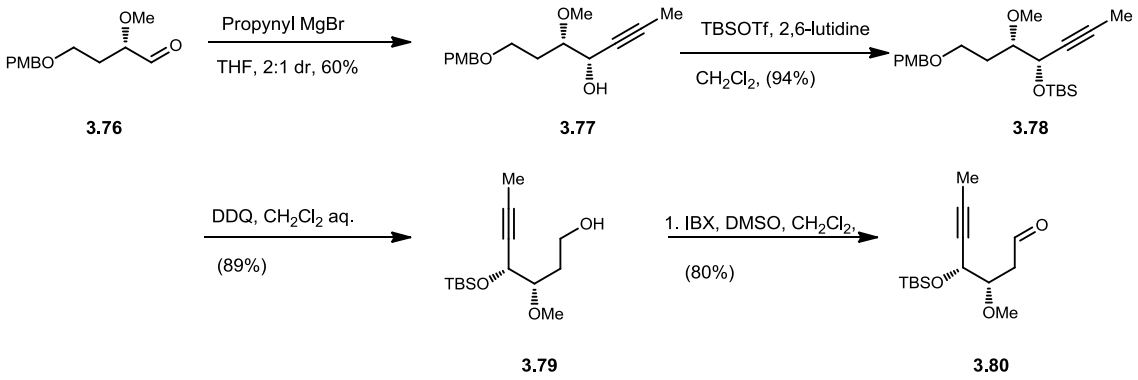


Figure 3.7 NOE and HMBC crosspeaks of the vinyl bromide C14-C28 southern semisphere **3.1**.

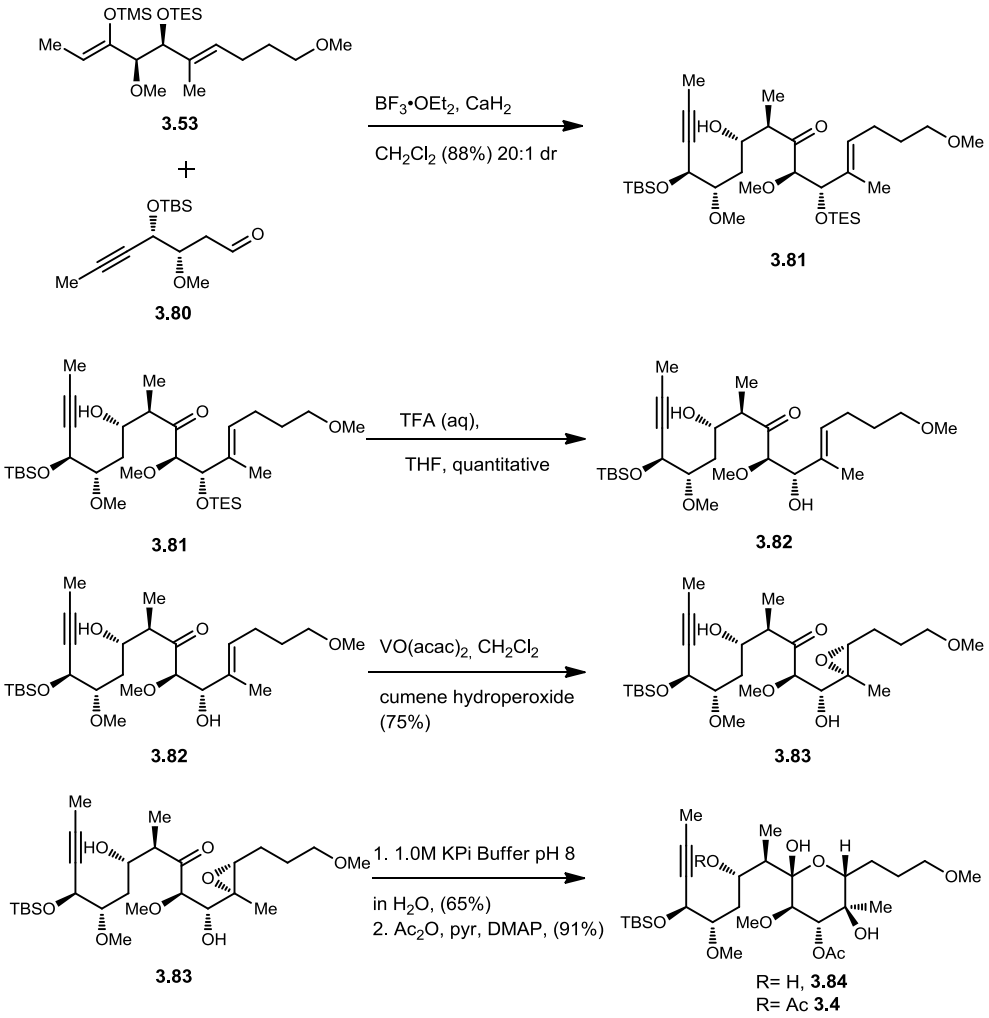
In order to examine multiple substrates required in the unification of the northern and southern fragments, we developed three new variants of the southern hemisphere. These variants included alkyne **3.4**, vinyl stannane **3.3**, and vinyl iodide **3.2** were applied towards the unification discussed in Chapter 4.

Beginning with known aldehyde[25] **3.76**, Grignard addition provided the *syn* propargylic alcohol in 2:1 dr with 60% yield for the desired diastereomer. We presumed the Grignard addition would proceed via the chelate model[26] which may provide the epimer required at C16 for the ammocidin family. Protection of secondary alcohol as the TBS ether in 94% yield and removal of the PMB ether with DDQ provided primary alcohol **3.79** in 89 % yield. Oxidation with IBX provided unstable aldehyde **3.80** which was used immediately in the forthcoming reaction (Scheme 3.25).

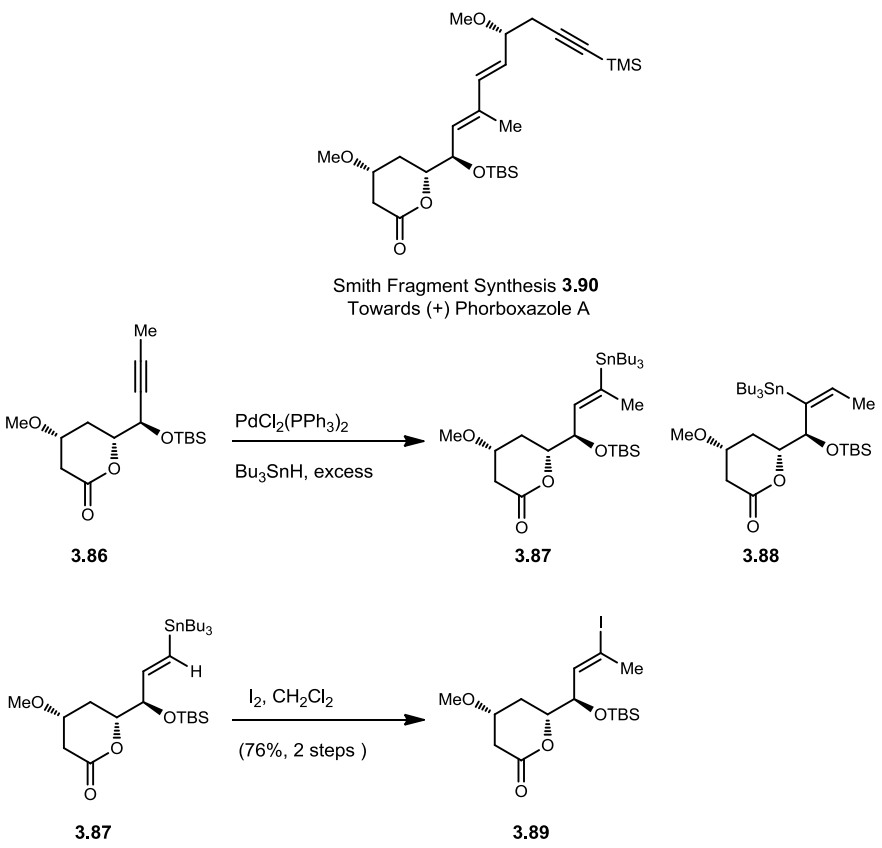


Scheme 3.25 Synthesis of propargylic aldehyde **3.80**.

The synthesis of alkyne **3.4** began with aldehyde **3.80** , we carried out the required Mukaiyama aldol reaction with silyl enol **3.53** and aldehyde **3.80** to furnish the product in high diastereoselectivity (20:1 d.r.). Both the silylated and TES deprotected products were formed in a combined yield of 88%. Treatment of the aldol adduct with TFA (aq.) provided allylic alcohol **3.82** which was subsequently epoxidized in the presence of $VO(acac)_2$ to furnish *anti* keto epoxide **3.83** in 71% yield as a single isomer. Ketoepoxide **3.83** was heated in 1.0 M KPi buffer at 65°C for three days. Diol **3.84** was treated with acetic anhydride providing the diacetate **3.4**, the propargylic C14-C28 southern hemisphere of ammocidin (Scheme 3.26).

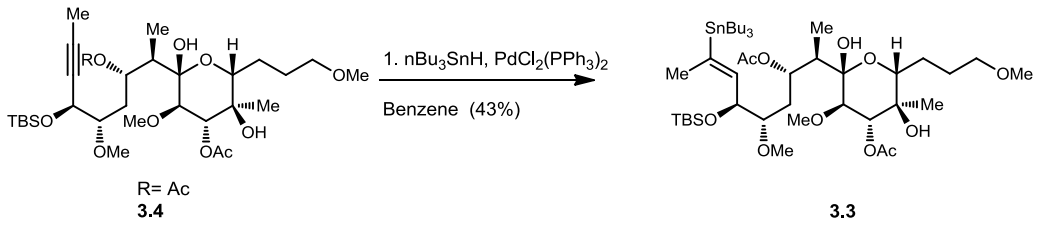


Scheme 3.26 Propargylic C14-C28 southern hemisphere **3.4**.



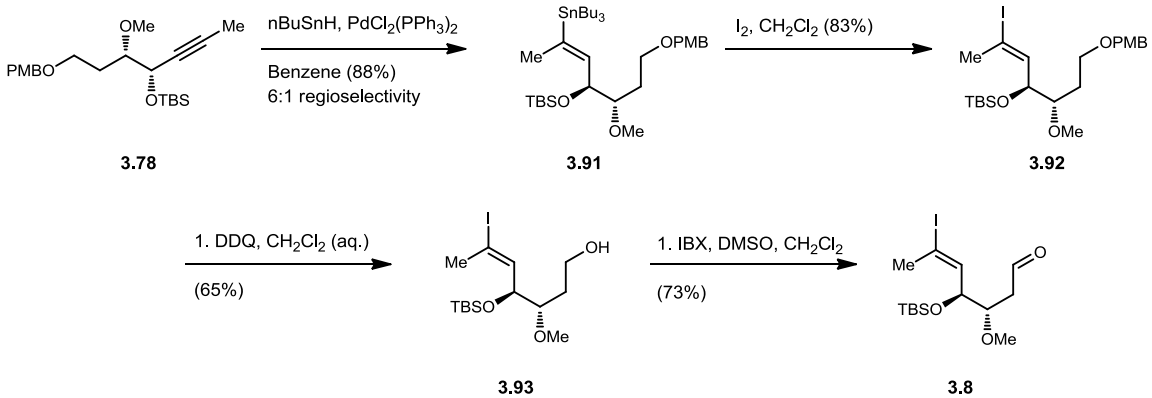
Scheme 3.27 Smith's synthesis of fragment **3.90** towards (+) phorboxazole A.

Our route towards the vinyl stannane was realized with the literature precedent from Smith and coworkers. In Smith's synthesis of fragment **3.90** towards the potent antiproliferative agent (+)-phorboxazole[27] (not depicted) involved the two step palladium mediated reaction sequence whereby slow addition of excess Bu_3SnH to alkyne **3.86** in the presence of catalytic $PdCl_2(PPH_3)_2$ yielded a regioselective mixture (5:1) favoring vinyl stannane **3.87**. Subsequent exposure of the mixture to iodine provided the desired *E*-vinyl iodide **3.89** (Scheme 3.27). Following the approach from Smith, propargylic fragment **3.4** can be further elaborated into vinyl stannane **3.3** in the presence of Bu_3SnH and $PdCl_2(PPH_3)_2$ in 6:1 distal/proximal regioselectivity (Scheme 3.28).

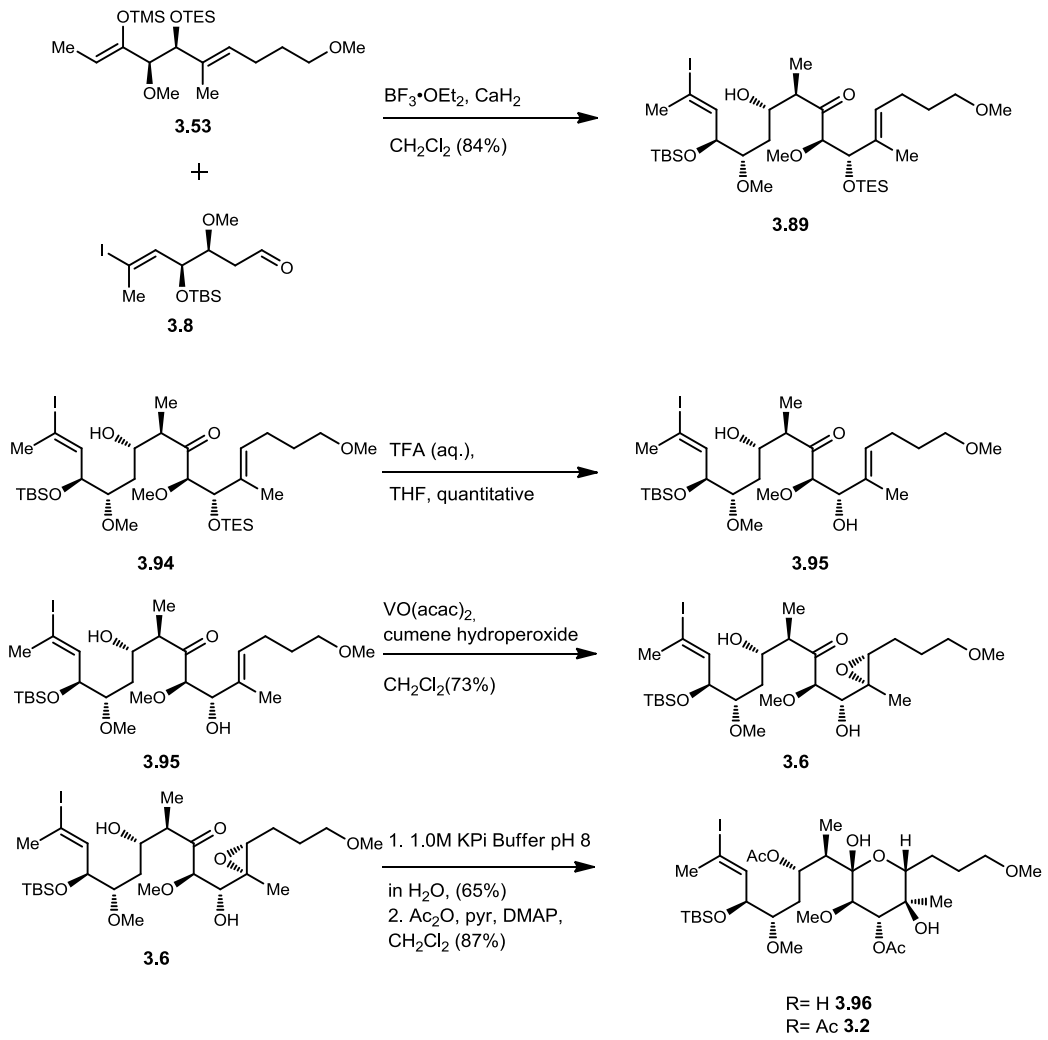


Scheme 3.28 Vinyl stannane C14-C28 southern hemisphere.

Preparation of vinyl iodide fragment **3.2** began with previously synthesized TBS protected propargylic ether **3.78**. Treatment of **3.78** with Bu_3SnH in the presence of $PdCl_2(PPH_3)_2$ provided vinyl stannane fragment **3.91** in high yield. Addition of iodine to vinyl stannane **3.91** provided vinyl iodide **3.92** in 83% yield, and treatment with DDQ[28] promoted the removal of the PMB protecting group. Oxidation of the newly liberated primary alcohol furnished aldehyde **3.93** (Scheme 3.29). Aldehyde **3.8** was taken through the same reaction sequence as aldehyde **3.80** to provide pyran acetal **3.96**. (Scheme 3.30).



Scheme 3.29 Vinyl iodide aldehyde synthesis.



Scheme 3.30 Vinyl iodide C14-C28 southern hemisphere.

Conclusion

The stereocontrolled synthesis of the highly substituted pyran acetal ring system found in the ammocidin family of natural products was accomplished. The key transformations included a stereospecific 5-exo opening of an *anti* ketoepoxide rearrangement pathway that

provided the key subunit. This pathway was carefully examined via a labeling study of the carbonyl carbon with O^{18} which can be examined by ^{13}C NMR. After developing a robust route to the pyran system, we turned our attention unification of to the northern and southern subunits.

Experimental Methods

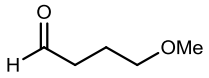
General Procedure: All non-aqueous reactions were performed in flame-dried or oven dried round-bottomed flasks under an atmosphere of argon. Stainless steel syringes or cannula were used to transfer air- and moisture-sensitive liquids. Reaction temperatures were controlled using a thermocouple thermometer and analog hotplate stirrer. Reactions were conducted at room temperature (rt, approximately 23 °C) unless otherwise noted. Flash column chromatography was conducted as described by Still et. al. using silica gel 230-400 mesh[1]. Where necessary, silica gel was neutralized by treatment of the silica gel prior to chromatography with the eluent containing 1% triethylamine. Analytical thin-layer chromatography (TLC) was performed on E. Merck silica gel 60 F254 plates and visualized using UV, and potassium permanganate stain. Yields were reported as isolated, spectroscopically pure compounds.

Materials: Solvents were obtained from either a MBraun MB-SPS solvent system or freshly distilled (tetrahydrofuran was distilled from sodium-benzophenone; toluene was distilled from calcium hydride and used immediately; dimethyl sulfoxide was distilled from calcium hydride and stored over 4 Å molecular sieves). Commercial reagents were used as received. The molarity of *n*-butyllithium solutions was determined by titration using diphenylacetic acid as an indicator (average of three determinations).

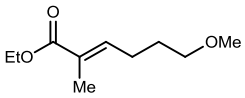
Instrumentation: Infrared spectra were obtained as thin films on NaCl plates using a Thermo Electron IR100 series instrument and are reported in terms of frequency of absorption (cm^{-1}). ^{1}H NMR spectra were recorded on Bruker 300, 400, 500, or 600 MHz spectrometers and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad, app = apparent), coupling constants (Hz), and integration. Deuterated chloroform was standardized to 7.26 ppm. ^{13}C NMR spectra were recorded on Bruker 75, 100, 125, or 150 MHz spectrometers and are reported relative to deuterated solvent signals. LC/MS was conducted and recorded on an Agilent Technologies 6130 Quadrupole instrument. High-resolution mass spectra were obtained from the Department of Chemistry and Biochemistry, University of Notre Dame using either a JEOL AX505HA or JEOL LMS-GCmate mass spectrometer. Optical rotations were obtained using a Perkin Elmer 341 polarimeter.

[1] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

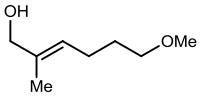
Preparative Procedures



4-methoxybutanal (2.11). To a solution of methyl 4-methoxybutanoate (3.50 mL, 25.7 mmol) in CH_2Cl_2 (26 mL, 1.0 M) at -78 °C. DibalH (5.72 mL, 32.1 mmol) was added dropwise and stirred for 30 min. To the solution was carefully added MeOH (10 mL) followed by a solution of saturated Rochelle salt solution (200 mL) and stirring continued for 1 h. The reaction solution was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were dried ($MgSO_4$), filtered and dichloromethane removed by distillation at 1 atm. The resulting solution was further distilled under vacuum at 118 mmHg at 81-82 °C furnishing 4.68 g (90%) of aldehyde **2.11** as a clear oil. Identical in all respects to published data.[2]



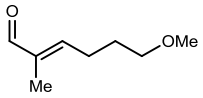
(*E*)-ethyl 6-methoxy-2-methylhex-2-enoate (2.43). Lithium hexamethyldisilazide (146 mL, 146 mmol, 1.0 M in toluene) was added dropwise to a solution of triethylphosphopropionate (34.8 g, 146 mmol) in THF at 0 °C. After 15 min, neat 4-methoxybutanal (13.0 g, 127mmol) was added dropwise and stirred for 1 h. The reaction was washed with water (15 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography (10:1, hexanes: ethyl acetate) to afford 14.7g (88%) of ester **2.43** (E/Z 12:1) as a clear oil. R_f 0.5 (9:1, H:EA); IR (neat) 2981, 2931, 2828, 1712, 1651 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 6.75 (t, *J* = 7.2 Hz, 1H), 4.19 (q, *J* = 3.6 Hz, 4H), 3.38 (t, *J* = 6.6 Hz, 2H), 3.37 (s, 3H), 2.45 (q, *J* = 15 Hz, 2H), 1.83 (s, 3H), 1.71 (m, 2H), 1.29 (t, *J* = 3.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 167.8, 141.0, 128.0, 71.5, 60.1, 58.2, 28.3, 25.0, 14.0, 11.9. HRMS calcd for $C_{10}H_{18}NaO_3$ $[M+Na]^+$ 209.1148, found 209.1155.



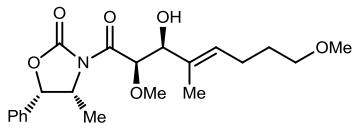
(*E*)-6-methoxy-2-methylhex-2-en-1-ol (2.44). To a solution of (*E*)-ethyl 6-methoxy-2-methylhex-2-enoate (7.26 g , 39.0 mmol) in CH_2Cl_2 (39.0 mL, 1.0 M) was added DibalH (15.3 mL, 85.0 mmol) and stirred for 2 h at -78 °C. To the solution was carefully added MeOH (10 mL) followed by a solution of saturated Rochelle salt solution (200 mL) and stirring continued for 1 h. The solution was extracted with CH_2Cl_2 (3 x 50 mL) and the

[2] K. E. Borbas, C. Ruzle, J. S. Lindsey *Org. Lett*. **2008**, *10*, 1931-1934.

combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (4:1, hexanes: ethyl acetate) to afford 5.43 g (97 %) of alcohol **2.44** as a clear oil. R_f 0.25 (4:1, H:EA); IR (neat) 3390, 2923, 2866 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.27 (t, *J* = 7.2 Hz, 1H), 3.83 (s, 2H), 3.27 (dd, *J* = 1.6 Hz, 2H), 3.24 (s, 3H), 1.98 (q, *J* = 7.2 Hz, 2H), 1.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.1, 124.5, 71.9, 68.0, 58.1, 29.0, 23.8, 12.23 ; HRMS calcd for $C_8H_{16}NaO_2$ $[M+Na]^+$ 167.1043, found 167.1046.

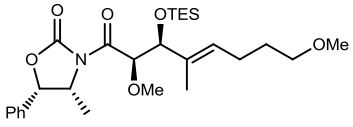


(*E*)-6-methoxy-2-methylhex-2-enal (3.29). To allylic alcohol **2.44** (8.00 g, 55.5 mmol) in a 1:1 mixture of CH_2Cl_2 and DMSO (55 mL, 1.0 M) was added IBX (23.0 g, 83.3 mmol) at 0 °C. The solution was warmed to rt and stirred for an additional 2 h. Upon consumption of the alcohol judged by TLC, the solution was filtered washed with water (50 mL). The filtrate was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (10:1, hexanes: ethyl acetate) to afford 6.79 g (88%) of **3.29** as a clear oil. R_f 0.8 (4:1, H:EA); IR (neat) 2926, 2761, 1688, 1644 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.28 (s, 1H), 6.39 (t, *J* = 7.6 Hz, 1H), 3.29 (t, *J* = 5.6 Hz, 2H), 3.27 (s, 3H), 2.33 (q, *J* = 14.8 Hz, 2H), 1.65 (m, 2H), 1.62 (s, 3H);.^{13}C NMR (100 MHz, $CDCl_3$): δ 194.4, 153.6, 139.3, 71.3, 58.2, 28.0, 25.4, 8.7 ; HRMS calcd for $C_8H_{15}O_2$ $[M+H]^+$ 143.1067, found 143.1086.

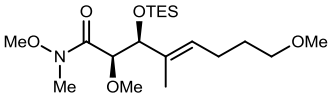


(4*R*,5*S*)-3-((2*R*,3*S*,*E*)-3-hydroxy-2,8-dimethoxy-4-methyloct-4-enoyl)-4-methyl-5-phenyloxazolidin-2-one (3.31). To a solution of methyl glycolate oxazolidinone **3.30** (12.7 g, 47.8 mmol) in toluene (48 mL , 1.0 M) at -40 °C was added Et_3N (7.98 mL, 57.3 mmol) then (nBu)$_2$BOTf (45.4 mL, 45.4 mmol, 1.0 M in CH_2Cl_2). The resulting solution was stirred for 1 h, aldehyde **3.29** added dropwise (neat) and stirring continued for 2 h at -40 °C. Upon consumption of the aldehyde as judged by TLC, the reaction mixture was quenched with pH 7 buffer (15 mL) and 30% aqueous H_2O_2 solution (50 mL). The mixture was stirred vigorously for 2 h, extracted with CH_2Cl_2 (3 x 50 mL), the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (3:1, hexanes: ethyl acetate) to afford 14.2 g (80%) of **3.31** as a yellow oil. $[\alpha]_D^{26}$ +34.5 (*c* 0.45, $CHCl_3$); R_f 0.25 (2:1, H:EA); IR (neat) 3406, 2931, 1779 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.22 (m, 5H), 5.64 (d, *J* = 7.20 Hz, 1H), 5.43 (t, *J* = 7.3 Hz, 1H), 5.13 (d, *J* = 4.3 Hz, 1H), 4.67 (t, *J* = 6.6 Hz, 1H), 4.27 (broad d, *J* = 3.5 Hz, 1H), 3.38 (s, 3H), 3.35 (t,

J = 4.0 Hz, 2H), 3.29 (s, 3H), 2.06 (q, *J* = 7.3 Hz, 2H), 1.65 (s, 3H), 1.57 (p, *J* = 13.8, 6.9Hz, 2H), 0.88 (d, *J* = 4.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 152.6, 133.5, 132.6, 128.4, 128.3, 126.1, 125.3, 125.2, 80.9, 79.3, 76.1, 71.6, 58.3, 58.0, 55.1, 28.9, 23.7, 14.1, 12.3 ; HRMS calcd for $C_{21}H_{29}NNaO_6$ $[M+Na]^+$ 414.1887, found 414.1895.

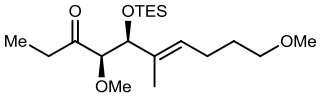


(4*R*,5*S*)-3-((2*R*,3*S*,*E*)-2,8-dimethoxy-4-methyl-3-((triethylsilyl)oxy)oct-4-enoyl)-4-methyl-5-phenyloxazolidin-2-one (3.32). To aldol **3.31** (14.1 g, 36.1 mmol) in CH_2Cl_2 (36 mL, 1.0 M) was added 2,6-lutidine (12.6 mL, 108.2 mmol) at 0 °C followed by TESOTf (12.2 mL, 54.1 mmol). The reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched with aqueous 1N HCl, extracted with CH_2Cl_2 (3 x 15 mL) and the combined extracts were washed with aqueous $NaHCO_3$ (10 mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (10:1, hexanes: ethyl acetate) to afford 16.0 g (91%) of **3.32** as a dark yellow oil. $[\alpha]_D^{26}$ +9.3 (*c* 0.21, $CHCl_3$); R_f 0.25 (9:1, H:EA); IR (neat) 2952, 1789, 1711, 1496 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.23 (m, 5H), 5.54 (d, *J* = 6.9 Hz, 1H), 5.39 (t, *J* = 7.2 Hz, 1H), 5.13 (d, *J* = 6.0 Hz, 1H), 4.59-4.53 (p, *J* = 6.5 Hz, 1H), 4.35 (d, *J* = 6.0 Hz, 1H), 3.38 (s, 3H), 3.47-3.32 (m, 2H), 3.26 (s, 3H), 2.09-2.00 (m, 2H), 1.63 (s, 3H), 1.60-1.55 (t, *J* = 6.5, 2H), 0.90 (t, *J* = 4.5 Hz, 9H), 0.56 (q, *J* = 8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 152.5, 134.5, 132.7, 132.6, 128.5, 128.4, 127.1, 125.3, 82.1, 79.2, 78.5, 76.7, 71.8, 58.8, 58.1, 55.4, 29.0, 23.4, 14.1, 12.1, 6.5, 4.5 ; HRMS calcd for $C_{27}H_{43}NNaO_6Si$ $[M+Na]^+$ 528.2752, found 528.2744.

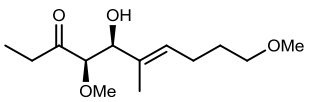


(2*R*,3*S*,*E*)-N,2,8-trimethoxy-N,4-dimethyl-3-((triethylsilyl)oxy)oct-4-enamide (3.33). To a suspension of Weinreb amide salt (115 mg, 1.18 mmol) in CH_2Cl_2 (600 µL, 0.66 M) was added trimethylaluminum (594 µL, 2.0 M in CH_2Cl_2) at 0 °C. The solution was warmed to rt, stirred for 1 h and a solution of **3.32** (200 mg, 0.39 mmol) added dropwise. The reaction mixture was stirred for 2 h at rt (gas evolution). The reaction mixture was carefully added aqueous $NaHCO_3$ (10 mL), extracted with CH_2Cl_2 (3 x 15 mL), the combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (3:1, 2:1 hexanes: ethyl acetate) to afford 135 mg (88%) of **3.33** as a yellow oil. $[\alpha]_D^{26}$ +26.3 (*c* 1.2, $CHCl_3$); R_f 0.25 (4:1 H:EA); IR (neat) 2936, 2876, 1670, 1654 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.33 (t, *J* = 7.2 Hz,

1H), 4.35 (d, *J* = 7.6 Hz, 1H), 4.10 (d, *J* = 8.0 Hz, 1H), 3.68 (s, 3H), 3.40 (s, 3H), 3.33 (t, *J* = 6.4 Hz, 2H), 3.31 (s, 3H), 3.10 (s, 3H), 2.08-2.00 (m, 2H), 1.74 (s, 3H), 1.59 (t, *J* = 7.0 Hz, 3H), 0.95 (t, *J* = 7.7 Hz , 9H), 0.58 (q, *J* = 8.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 134.8, 127.4, 86.2, 83.0, 79.0, 72.5, 61.3, 58.5, 58.4, 32.2, 29.2, 24.0, 12.8, 11.8, 6.7, 4.7 ; HRMS calcd for $C_{19}H_{39}NNaO_5Si$ $[M+Na]^+$ 412.2490, found 412.2482.

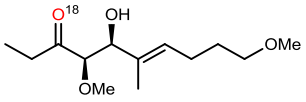


(4*R*,5*S*,*E*)-4,10-dimethoxy-6-methyl-5-((triethylsilyl)oxy)dec-6-en-3-one (3.7). To Weinreb amide **3.33** (7.60 g, 19.5 mmol) in diethyl ether (20 mL) was added ethyl magnesium bromide (19.5 mL, 58.6 mmol, 3.0 M in diethyl ether) at 0 °C. Upon consumption of **3.33** as judged by TLC, the reaction was quenched with saturated ammonium chloride (20 mL), extracted with CH_2Cl_2 (3 x 15 mL) and the combined extracts dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (20:1, hexanes: ethyl acetate) to afford 6.60 g (83%) of **3.7** as a yellow oil. $[\alpha]_D^{26}$ +75.8 (*c* 0.40, $CHCl_3$); R_f 0.35 (9:1, H:EA); IR (neat) 2877, 2826, 1716 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.33 (t, *J* = 7.6 Hz, 1H), 4.16 (d, *J* = 5.2 Hz, 1H), 3.53 (d, *J* = 5.2 Hz, 1H), 3.23 (s, 3H), 3.13 (m, 2H), 3.29 (s, 3H), 2.58-2.41 (m, 2H), 2.03 (m, 2H), 1.57 (s, 3H), 0.09 (t, *J* = .72 Hz, 3H), 0.08 (t, *J* = 2.8 Hz, 9H), 0.05 (q, *J* = 2.8 Hz, 6H);.^{13}C NMR (100 MHz, $CDCl_3$): δ 212.4, 134.7, 127.2, 91.0, 79.2, 72.1, 59.5, 58.4, 32.6, 29.2, 23.9, 12.2, 6.8, 6.7, 4.6 ; HRMS calcd for $C_{19}H_{38}NaO_4Si$ $[M+Na]^+$ 381.2432, found 381.2431.

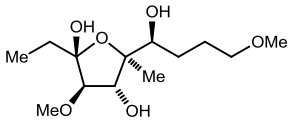


(4R,5S,E)-5-hydroxy-4,10-dimethoxy-6-methyldec-6-en-3-one (3.34). To a solution of TES ether **3.33** (103 mg, 0.28 mmol) in THF (3 mL) at rt was added HF pyridine 70% (21.6 µL, 0.86 mmol) dropwise. The resulting solution was stirred for 45 min, quenched with saturated $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (2:1, hexanes: ethyl acetate) to afford 66.5 mg (95%) of **3.34** as a clear oil. $[\alpha]_D^{26}$ +80.9 (*c* 0.87, $CHCl_3$); R_f .25 (4:1, H:EA); IR (neat) 3444, 2937, 2828, 1715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.39 (t, *J* = 7.2, 1H), 4.11 (t, *J* = 10.4 Hz, 1H), 3.66 (d, *J* = 6.1 Hz, 1H), 3.38 (s, 3H), 3.32 (t, *J* = 6.4 Hz, 2H), 3.30 (s, 3H), 4.48 (d, *J* = 4.5 Hz, 1H), 2.57-2.42 (m, 2H), 2.07 (q, *J* = 7.4 Hz, 2H), 1.65 (s, 3H), 1.58 (p, *J* = 6.7 Hz, 2H), 1.01 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.7, 133.3, 128,5, 89.0, 77.5, 72.0,

59.1, 58.6, 32.4, 29.11, 24.1, 12.1, 7.0 ; HRMS calcd for $C_{13}H_{24}NaO_4$ $[M+Na]^+$ 267.1567, found 267.1581.

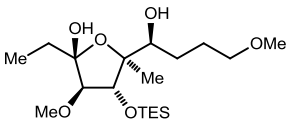


(4R,5S,E)-5-hydroxy-4,10-dimethoxy-6-methyldec-6-en-3-one (^{18}O-**3.34).** To a solution of ketone **3.34** (75 mg, 0.307 mmol) in THF (300 µL, 1 M) was added 97% H_2O^{18} (18.4 µL, 0.92 mmol) followed by HCl (15.5 µL, 0.031 mmol, 2.0 M in ether) in diethyl ether (2.0 M). The solution was stirred for 2 h, washed with aqueous $NaHCO_3$ (10 mL), and extracted with diethyl ether (3 x 15 mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was used without further purification to afford 75 mg (100% by LCMS) of ^{18}O-**3.34** as a clear oil. $[\alpha]_D^{26}$ +80.9 (*c* 0.87, $CHCl_3$); R_f .25 (4:1, H:EA); IR (neat) 3444, 2937, 2828, 1715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.39 (t, *J* = 7.2, 1H), 4.11 (t, *J* = 10.4 Hz, 1H), 3.66 (d, *J* = 6.1 Hz, 1H), 3.38 (s, 3H), 3.32 (t, *J* = 6.4 Hz, 2H), 3.30 (s, 3H), 4.48 (d, *J* = 4.5 Hz, 1H), 2.57-2.42 (m, 2H), 2.07 (q, *J* = 7.4 Hz, 2H), 1.65 (s, 3H), 1.58 (p, *J* = 6.7 Hz, 2H), 1.01 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.6, 133.3, 128,5, 89.0, 77.5, 72.0, 59.1, 58.6, 32.4, 29.11, 24.1, 12.1, 7.0 ; HRMS calcd for $C_{13}H_{24}Na^{18}OO_3$ $[M+Na]^+$ 269.1609, found 269.1643.

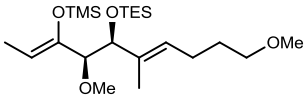


(2*S*,3*R*,4*R*,5*S*)-2-ethyl-5-((*S*)-1-hydroxy-4-methoxybutyl)-3-methoxy-5-methyltetrahydrofuran-2,4-diol (3.36 and ^{18}O-**3.36).** To allylic alcohol **3.34** (30 mg, 0.122 mmol) in CH_2Cl_2 (120 µL) was added $VO(acac)_2$ (4 mg, 0.018 mmol) and the mixture cooled to -78 °C. A solution of *t*-butyl hydroperoxide (0.244 mmol, 44.3 µL, 5.5 M in decane) was added dropwise and stirring continued for 30 min at 0 °C. The resulting solution was washed with water, extracted with CH_2Cl_2 (3 x 15 mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (3:2, hexanes: ethyl acetate) to afford 19 mg (56 %) of **3.36** as a yellow oil. $[\alpha]_D^{26}$ -74.3 (*c* 0.14, $CHCl_3$); R_f .25 (1:1, H:EA); IR (neat) 3422, 2933, 2828, 1452 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.84 (s, 1H), 3.58 (dd, *J* = 8.1, 1.5 Hz, 1H), 3.45 (d, *J* = 2.88 Hz, 1H), 3.42-3.38 (m, 2H), 3.40 (s, 3H), 3.33 (s, 3H), 2.10 (broad s, 1H), 1.96-1.91 (m, 1H), 1.85 (q, *J* = 7.5 Hz, 2H), 1.81-175 (m, 2H), 1.62 (broad s, 2H), 1.45 (s, 3H), 1.00 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.5 (110.4, O^{18}), 89.1, 85.5, 84.8, 84.18 (84.15, O^{18}),

72.6, 58.6, 56.8, 28.0, 27.1, 22.3, 15.7, 7.1 ; HRMS calcd for $C_{13}H_{26}O_6$ $[M+Na]^+$ 301.1622, found 301.1592, HRMS calcd for $C_{13}H_{26}{}^{18}OO_5$ $[M+Na]^+$ 303.1664, found 303.1668.

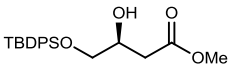


(2*S*,3*R*,4*R*,5*S*)-2-ethyl-5-((*S*)-1-hydroxy-4-methoxybutyl)-3-methoxy-5-methyl-4-((triethylsilyl)oxy)tetrahydrofuran-2-ol (S1). To a solution of alcohol **3.34** (18 mg, 0.065 mmol) in CH_2Cl_2 (128 µL,) was added imidazole (13 mg, 0.19 mmol) and TESCl (32 µL, 0.19 mmol). The resulting solution was stirred for 24 h, washed with saturated $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (10:1, hexanes: ethyl acetate) to afford 10 mg (40 %) of **S1** as a yellow oil. $[\alpha]_D{}^{26}$ +21.5 (*c* 0.47, $CHCl_3$); R_f 0.8 (4:1, H:EA); IR (neat) 2954, 2827, 2358, 1455 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.79 (dd, *J* = 2.6, 1.7, 1H), 3.53 (dd, *J* = 3.1, 1.5 Hz, 1H), 3.44 (s, 3H), 3.42-3.34 (m, 2H), 3.32 (s, 3H), 3.30 (d, *J* = 2.7 Hz, 1H), 2.01-195 (m, H), 1.92-1.78 (m, 2H), 1.76-1.71 (m, 1H), 1.60-1.55 (m, 1H), 1.38 (s, 3H), 1.02 (t, *J* = 7.5 Hz, 3H), 0.97 (t, *J* = 15.9 Hz, 9H), 0.62 (q, *J* = 7.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.6, 90.4, 85.8, 84.9, 83.8, 72.7, 59.0, 58.5, 28.0, 27.1, 22.2, 15.7, 7.0, 6.6, 4.6 ; HRMS calcd for $C_{19}H_{39}O_5Si$ $[M-OH]^+$ 375.2561, found 375.2577.

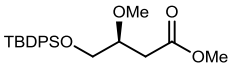


(5*R*,6*S*)-8,8-diethyl-4-ethylidene-5-methoxy-6-((*E*)-6-methoxyhex-2-en-2-yl)-2,2-dimethyl-3,7-dioxa-2,8-disiladecane (3.53). To a solution of ketone **3.7** (300 mg, 0.84 mmol) in CH_2Cl_2 (0.8 mL, 1M) at 0 °C was added Et_3N (0.70 mL, 5.02 mmol) followed by TMSOTf (0.45 mL, 2.51 mmol). The resulting solution was stirred for 30 min, washed with aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (40:1, 30:1 hexanes: ethyl acetate) to afford 301 mg (84%) of silyl enol ether **3.53** as a pale yellow oil. $[\alpha]_D{}^{26}$ +49.3 (*c* 0.36, $CHCl_3$); R_f 0.8 (9:1, H:EA); IR (neat) 2954, 2876, 2822, 1673 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.27 (t, *J* = 7.2 Hz, 1H), 4.63 (q, *J* = 6.4 Hz, 1H), 4.04 (d, *J* = 7.6 Hz, 1H), 3.32 (m, 2H), 3.31 (s, 3H), 3.27 (s, 3H), 3.22 (d, *J* = 7.6 Hz, 1H), 2.08-2.95 (m, 2H), 1.45 (s, 3H), 1.45 (d, *J* = 6.8 Hz, 3H), 0.93 (t, *J* = 8 Hz, 9H), 0.56 (q, *J* = 0.76 Hz, 6H), 0.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.3, 135.2, 126.7, 105.9, 87.7,79.4, 72.0, 58.5, 57.4,

29.3, 23.8, 11.3, 10.5, 6.8, 4.8, 0.7 ; HRMS calcd for $C_{22}H_{46}NaO_4Si_2$ $[M+Na]^+$ 453.2827, found 453.2806.

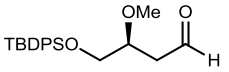


(*S*)-methyl 4-((*tert*-butyldiphenylsilyl)oxy)-3-hydroxybutanoate (S2). To a solution of methyl 3,4-dihydroxybutanoate[3] (1.00 g, 7.46 in CH_2Cl_2 (7.5 mL) was added imidazole (1.52 g, 8.20 mmol), DMAP (91.0 mg, 0.74 mmol) and TBDPSCl (2.12 mL, 8.20 mmol). The resulting solution was stirred for 24 h, washed with aqueous 1M HCl and extracted with CH_2Cl_2 (3 x 15 mL). The combined extracts were washed with aqueous $NaHCO_3$ (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (8:1, hexanes: ethyl acetate) to afford 2.0 g (72%) of **S2** as a yellow oil. $[\alpha]_D^{26}$ -8.1 (*c* 0.55, $CHCl_3$); R_f 0.5 (4:1, H:EA); IR (neat) 3482, 2954, 2858, 1738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (dd, *J* = 2.4 Hz, 4H), 7.44-7.37 (m, 6H), 4.20-4.12 (m, 1H), 3.69 (s, 3H), 3.67 (t, *J* = 12.0 2H), 2.86 (d, *J* = 4.8 Hz, 1H), 2.55 (dd, *J* = 4.9, 2.4 Hz, 2H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 135.5, 133.0, 132.9, 129.8, 129.7, 127.8, 127.7, 68.6, 66.8, 51.7, 37.8, 26.8, 19.2 ; HRMS calcd for $C_{21}H_{28}NaO_4Si$ $[M+Na]^+$ 395.1649, found 395.1646.

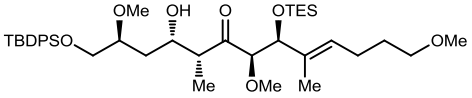


(*S*)-methyl 4-((*tert*-butyldiphenylsilyl)oxy)-3-methoxybutanoate (3.51). To a suspension of Meerwein salt (1.16 g, 6.45 mmol) in CH_2Cl_2 (2.15 mL, 1.0 M) at 0 °C was added proton sponge (2.76 g, 12.9 mmol) followed by alcohol **S2** (800 mg, 2.15 mmol). The reaction mixture was stirred at rt for 2 h, quenched with aqueous $NaHCO_3$ (10 mL), and extracted with CH_2Cl_2 (3 x 15 mL). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (7:1, hexanes: ethyl acetate) to afford 794 mg (95%) of **3.51** as a yellow oil. $[\alpha]_D^{26}$ -18.0 (*c* 0.42, $CHCl_3$); R_f 0.4 (8:1, H:EA); IR (neat) 3071, 1931, 1738, 1589 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.68 (m, 4H), 7.39 (m, 6H), 3.79-3.73 (m, 2H), 3.73 (s, 3H), 3.64 (dd, *J* = 5.2 Hz, 1H), 3.35 (s, 3H), 2.65 (dd, *J* = 4.4, 4.3 Hz, 1H), 2.55 (dd, *J* = 8.0, 8.1 Hz, 1H), 1.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ172.1, 135.6, 135.55, 135.51, 133.3, 133.2, 129.7, 127.7, 127.6, 78.3, 64.5, 58.0, 51.6, 37.1, 26.8, 26.7, 19.2 ; HRMS calcd for $C_{22}H_{30}NaO_4Si$ $[M+Na]^+$ 409.1806, found 409.1810.

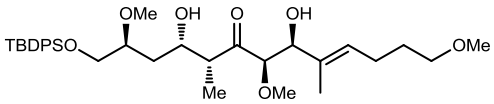
[3] S. Saito, T. Ishikawa, A. Kuroda, K. Koga, T. Moriwake *Tetrahedron* **1992**, *48*, 4067-4086



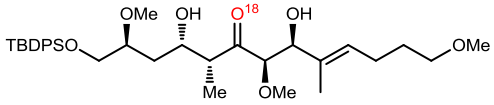
(*S*)-4-((*tert*-butyldiphenylsilyl)oxy)-3-methoxybutanal (3.52). To ester **3.51** (119 mg, 0.305 mmol) in CH_2Cl_2 (0.90 mL, 0.3 M) at -78 °C was added DibalH (59.9 µL, 0.34 mmol) dropwise. The resulting solution was stirred for 1 h and carefully added MeOH (5 mL) and stirred vigorously with saturated Rochelle salt solution (100 mL) for 1 h. The solution was extracted with CH_2Cl_2 (3 x 50 mL), the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (10:1, hexanes: ethyl acetate) to afford 94 mg (86%) of **3.52** as a clear oil. $[a]_D^{26}$ -20.5 (*c* 0.08, $CHCl_3$); R_f 0.3 (8:1, H:EA); IR (neat) 3439, 3071, 2724, 1728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.83 (t, *J* = 2.0, 1H), 7.72-7.67 (m, 5H), 7.49-7.40 (m, 7H), 3.84-3.67 (m, 3H), 3.36 (s, 3H), 2.71 (dd, *J* = 2.0, 0.64 Hz, 2H), 1.07 (s, 9Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.1, 135.6, 135.55, 135.52, 133.1, 133.0, 129.8, 129.7, 127.72, 127.71, 127.7 ; HRMS calcd for $C_{21}H_{28}NaO_3Si$ $[M+Na]^+$ 379.1700, found 379.1681.



(5*S*,6*R*,8*R*,9*S*,11*S*)-3,3-diethyl-9-hydroxy-6,11-dimethoxy-5-((*E*)-6-methoxyhex-2-en-2-yl)-8,15,15-trimethyl-14,14-diphenyl-4,13-dioxa-3,14-disilahexadecan-7-one (3.54). A solution of silyl enol **3.53** (94.0 mg, 0.220 mmol) and aldehyde **3.52** (94.0 mg, 0.264 mmol) in CH_2Cl_2 (0.73 mL) over CaH_2 (15 mg) was stirred for 30 min. The reaction mixture was then cooled to -78 °C and $BF_3 \bullet OEt_2$ (30.4 µL, 0.242 mmol) added. The solution was stirred for 20 min, washed with aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (3:1, 2:1 hexanes: ethyl acetate) to afford 119 mg (75 %) of **3.54** as a clear oil, accompanied by 22 mg (16 %) of alcohol **3.46**. $[\alpha]_D^{26}$ +5.45 (*c* 0.16, $CHCl_3$); R_f 0.5 (3:1, H:EA); IR (neat) 3503, 2932, 1713, 1460 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 6.7, 4H), 7.41-7.36 (m, 7H), 5.38 (t, *J* = 7.0 Hz, 1H), 4.25 (d, *J* = 6.0 Hz, 1H), 4.1 (d, *J* = 9.2 Hz, 1H), 3.82 (d, *J* = 6.0 Hz, 1H), 3.68 (broad s, 2H), 3.55 (d, *J* = 6.0 Hz, 1H), 3.41 (s, 3H), 3.37 (s, 3H), 3.34 (t, *J* = 12.9 Hz, 2H), 3.31 (s, 3H), 3.13 (s, 1H), 2.91 (dq, *J* = 18.6, 7.0, 1.8 Hz, 1H), 2.07 (m, 2H), 1.64 (s, 3H), 1.63-1.59 (m, 2H), 1.48-1.42 (m, 1H), 1.21-1.18 (m, 1H), 1.06 (s, 9H), 0.94 (t, *J* = 7.9, 9H), 0.60 (q, *J* = 7.8 Hz, 6H),; ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.6, 135.5, 134.5, 133.4, 129.6, 127.9, 127.6, 90.2, 79.2, 78.3, 72.1, 67.7, 65.6, 59.9, 58.4, 58.2, 47.5, 35.8, 29.0, 26.7, 24.0, 19.1, 12.3, 9.4, 6.7, 4.7; HRMS calcd for $C_{40}H_{66}NaO_7Si_2$ $[M+Na]^+$ 737.4239, found 737.4240.

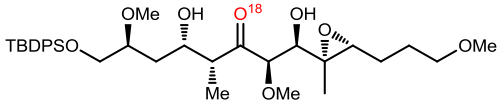


(2*S*,4*S*,5*R*,7*R*,8*S*,*E*)-1-((*tert*-butyldiphenylsilyl)oxy)-4,8-dihydroxy-2,7,13-trimethoxy-5,9-dimethyltridec-9-en-6-one (3.46). To a solution of aldol **3.54** (119 mg, 0.166 mmol) in a THF: H_2O (3:1, 0.322 mL) was added TFA until pH 2 was reached. The reaction mixture was stirred 45 min, quenched with aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (3:1, hexanes: ethyl acetate) to afford 90 mg (90%) of **3.46** as a yellow oil. $[\alpha]_D^{26}$ -7.39 (*c* 0.14, $CHCl_3$); R_f 0.25 (2:1, H:EA); IR (neat) 3442, 3071, 2858, 1711 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 6.5, 4H), 7.44-7.36 (m, 6H), 5.47 (t, *J* = 7.2 Hz, 1H), 4.19 (t, *J* = 4.9 Hz, 1H), 4.14 (dd, *J* = 7.3, 2.8 Hz, 1H), 3.91 (d, *J* = 4.7 Hz, 1H), 3.68 (dd, *J* = 5.4, 5.4 Hz, 2H), 3.54 (dd *J* = 7.4, 3.5 Hz, 1H), 3.42 (s, 3H),3.35 (app t, *J* = 12.8 Hz, 2H), 3.35 (s, 3H), 3.31 (s, 3H), 3.25 (d, *J* = 2.3 Hz, 1H), 3.00 (dq, *J* = 3.6 Hz, 1H), 2.77 (d, *J* = 5.4 Hz, 1H), 2.16-2.07 (m, 2H), 1.70 (s, 3H), 1.67-1.56 (m, 3H), 1.05 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.93, 135.6, 133.5, 133.3, 133.25, 129.7, 127.7, 88.1, 79.4, 72.1, 68.6, 65.1, 59.6, 58.5, 58.2, 47.1, 34.8, 29.2, 26.8, 24.2, 19.1, 12.7, 10.2; HRMS calcd for $C_{34}H_{52}NaO_7Si$ $[M+Na]^+$ 623.3375, found 623.3383.

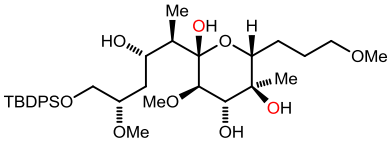


(2*S*,4*S*,5*R*,7*R*,8*S*,*E*)-1-((*tert*-butyldiphenylsilyl)oxy)-4,8-dihydroxy-2,7,13-trimethoxy-5,9-dimethyltridec-9-en-6-one (^{18}O-3.46**).** To a solution of ketone **3.46** (75 mg, 0.124 mmol) in THF (0.5 mL, .25 M) was added 97% H_2O^{18} (24.8 µL, 1.24 mmol) followed by HCl (6.20 µL, 12.4 µmol, 2.0 M in ether). The solution was stirred for 2 h, washed with aqueous $NaHCO_3$ (10 mL), and extracted with diethyl ether (3 x 15 mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 75 mg (~50% incorporation of O^{18} by ^{13}C) of ^{18}O-**3.46** as a yellow oil. $[\alpha]_D^{26}$ -7.39 (*c* 0.14, $CHCl_3$); R_f .25 (2:1, H:EA); IR (neat) 3442, 2931, 2858, 1711, 1461 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ7.67 (d, *J* = 6.5, 4H), 7.44-7.36 (m, 6H), 5.47 (t, *J* = 7.2 Hz, 1H), 4.19 (t, *J* = 4.9 Hz, 1H), 4.14 (dd, *J* = 7.3, 2.8 Hz, 1H), 3.91 (d, *J* = 4.7 Hz, 1H), 3.68 (dd, *J* = 5.4, 5.4 Hz, 2H), 3.54 (dd *J* = 7.4, 3.5 Hz, 1H), 3.42 (s, 3H), 3.35 (app t, *J* = 12.8 Hz, 2H), 3.35 (s, 3H), 3.31 (s, 3H), 3.25 (d, *J* = 2.3 Hz, 1H), 3.00 (dq, *J* = 3.6 Hz, 1H), 2.77 (d, *J* = 5.4 Hz,

1H), 2.16-2.07 (m, 2H), 1.70 (s, 3H), 1.67-1.56 (m, 3H), 1.05 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.98, 135.6, 133.5, 133.3, 133.25, 129.7, 127.7, 88.1, 79.4, 72.1, 68.6, 65.1, 59.6, 58.5, 58.2, 47.1, 34.8, 29.2, 26.8, 24.2, 19.1, 12.7, 10.2; HRMS calcd for $C_{34}H_{52}Na^{18}OO_6Si$ $[M+Na]^+$ 625.3440, found 625.3411.

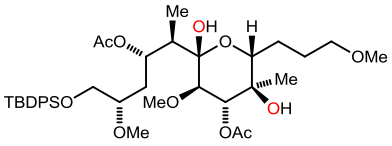


(1*R*,2*R*,4*R*,5*S*,7*S*)-8-((*tert*-butyldiphenylsilyl)oxy)-1,5-dihydroxy-2,7-dimethoxy-1-((2*R*,3*R*)-3-(3-methoxypropyl)-2-methyloxiran-2-yl)-4-methyloctan-3-one (^{18}O-**3.55).** To a solution of allylic alcohol ^{18}O-**3.46** (150 mg, 0.250 mmol) in CH_2Cl_2 (0.50 mL, 0.50 M) cooled to -78 °C was added $VO(acac)_2$ (66.0 mg, 0.250 mmol) followed by cumene hydroperoxide (1.25 mL, 0.184 mmol). The green solution was warmed to 0 °C upon which the solution turns dark red. The reaction mixture was monitored by TLC and stirred at 0 °C for approximately 12-15 min. The reaction mixture was directly absorbed on a silica gel column buffered with 1% Et_3N (1:1, hexanes: ethyl acetate) to afford 108 mg (70%) of epoxide **^{18}O-3.55** as a pale yellow oil. The use of TBHP did not alter the outcome of the stereoisomer. $[\alpha]_D^{26}$ -8.40 (*c* 0.22, $CHCl_3$); R_f .25 (1:1, H:EA); IR (neat) 3455, 2931, 2360, 2246, 1714 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68-7.66 (dd, *J* = 7.7, 1.4, 4H), 7.43-7.36 (m, 6H), 4.19 (dd, *J* = 3.5, 2.7 Hz, 1H), 4.00 (, *J* = 2.7 Hz, 1H), 3.91 (d, *J* = 5.1 Hz, 1H), 3.73-3.66 (m, 2H), 3.55 (dd, *J* = 3.9, 3.5 Hz, 1H), 3.42 (app t, *J* = 14.8 Hz, 2H), 3.43 (s, 3H), 3.36 (s, 3H), 3.33 (s, 3H), 3.11 (dd, *J* = 6.9, 6.3 Hz, 2H), 2.57 (d, *J* = 2.5 Hz, 1H), 1.72-1.59 (m, 7H), 1.36 (s, 3H), 1.08 (d, *J* = 7.0 Hz 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ213.5, (2.13.4 O^{18}), 135.6, 133.29, 133.23, 129.7, 127.6, 86.7, 79.4, 77.2, 74.0, 72.0, 68.7, 65.1, 60.6, 60.5, 59.4, 58.5, 58.2, 46.7, 34.6, 26.7, 26.3, 24.8, 21.0, 19.1, 14.1, 13.9, 10.5; HRMS calcd for $C_{34}H_{52}NaO_8Si$ $[M+Na]^+$ 639.3324, found 639.3327.

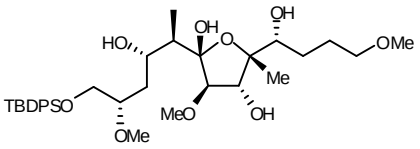


(2*S*,3*R*,4*R*,5*S*,6*R*)-2-((2*R*,3*S*,5*S*)-6-((*tert*-butyldiphenylsilyl)oxy)-3-hydroxy-5-methoxyhexan-2-yl)-3-methoxy-6-(3-methoxypropyl)-5-methyltetrahydro-2H-pyran-2,4,5-triol (^{18}O-**3.56).** To epoxide ^{18}O-**3.55** (108 mg, 0.175 mmol) was added 97% H_2O^{18} (0.175 mL) in a teflon sealed glass vial and the mixture stirred for 3 days at 65 °C. The resulting solution was extracted with CH_2Cl_2 (3 x 15 mL) and the combined exxtracts were dried ($MgSO_4$),

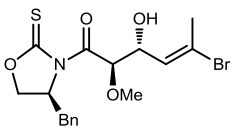
filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (1:6, hexanes: ethyl acetate) to afford 85 mg (63%) of ^{18}O-**3.56** as a clear oil. $[\alpha]_D^{26}$ +9.25 (*c* 0.32, $CHCl_3$); R_f .25 (1:6, H:EA); IR (neat) 3400, 2931, 2858, 1471 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (dd, *J* = 6.4, 1.3, 4H), 7.44-7.35 (m, 6H), 4.43 (d, *J* = 10.1 Hz, 1H), 4.31 (s, 1H), 3.80 (dd, *J* = 12.3, 9.7 Hz, 2H), 3.68 (d, *J* = 5.8 Hz, 2H), 3.59 (s, 3H), 3.57 (d, *J* = 5.2 Hz, 1H), 3.42 (s, 3H), 3.44-3.31 (m, 3H), 3.11 (d, *J* = 9.4 Hz, 1H), 2.97 (broad s, 1H), 2.64 (broad s, 1H), 1.95-1.50 (m, 8H), 1.27-1.16 (m, 4H), 1.10 (s, 3H), 1.05 (s, 9H), 0.97 (d, *J* = 7.1 Hz, 3H), x; ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.6, 133.5, 133.4, 129.6, 127.7, 100.1, 80.9, 79.5, 77.4, 77.2, 74.0, 73.8, 68.1, 65.8, 61.1, 58.5, 58.4, 42.5, 36.3, 26.7, 26.6, 24.5, 19.2, 13.9, 8.9; HRMS calcd for $C_{34}H_{54}NaO_9Si$ $[M+Na]^+$ 657.3429, found 657.3452 mass given for ^{16}O isotope.



(2*R*,3*S*,5*S*)-2-((2*S*,3*R*,4*R*,5*R*,6*R*)-4-acetoxy-2,5-dihydroxy-3-methoxy-6-(3-methoxypropyl)-5-methyltetrahydro-2H-pyran-2-yl)-6-((*tert*-butyldiphenylsilyl)oxy)-5-methoxyhexan-3-yl acetate (^{18}O-3.57). To a solution of pyran acetal ^{18}O-**3.56** (18 mg, 0.037 mmol) in CH_2Cl_2 (40.0 µL, 0.1 M) was added pyridine (15.2 µL, 0.189 mmol) and acetic anhydride (35.0 µL, 0.378 mmol). The resulting solution was stirred for 1 h, washed with aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (3:2, 1:1 hexanes: ethyl acetate) to afford 23 mg (84%) of ^{18}O-**3.57** as a clear oil. $[\alpha]_D^{26}$ +5.74 (*c* 0.18, $CHCl_3$); R_f 0.3 (1:1, H:EA); IR (neat) 3418, 2929, 2857, 1734 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.67 (dd, *J* = 6.7, 1.0, 4 H), 7.44-7.37 (m, 6H), 5.50 (d, *J* = 9.6 Hz, 1H), 5.20 (d, *J* = 9.7 Hz, 1H), 4.77 (s, 1H), 3.72 (dd, *J* = 9.2, 2.8 Hz, 1H), 3.68 (dd, *J* = 10.6, 5.3 Hz, 1H), 3.56 (dd, *J* = 10.7, 5.1 Hz, 1H), 3.47 (s, 3H), 3.35-3.32 (m, 3H), 3.29 (s, 3H), 3.27 (s, 3H), 3.17 (d, *J* = 9.4 Hz, 1H), 3.12-3.09 (m, 1H), 2.62 (s, 1H), 2.16 (s, 3H), 2.04 (s, 3H), 2.01-1.95 (m, 2H), 1.72-1.62 (m, 2H), 1.54-1.49 (m, 2H), 1.06 (s, 12H), 1.04 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.5, 172.4, 135.6, 133.5, 133.4, 129.7, 129.6, 127.7, 99.2 (99.1 O^{18}), 80.0, 78.8, 78.6, 74.2, 74.04 (74.02 O^{18}), 72.6, 70.2, 65.6, 61.0, 58.5, 41.8, 36.3, 30.3, 26.8, 26.6, 24.5, 21.5, 21.2, 19.2, 14.4, 8.9, ; HRMS calcd for $C_{38}H_{58}NaO_{11}Si$ $[M+Na]^+$ 741.3641, found 741.3634, HRMS calcd for $C_{38}H_{58}Na^{18}O_2O_9Si$ $[M+Na]^+$ 745.3721, found 745.3714.

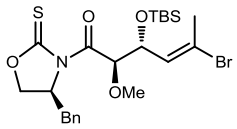


(2S,3R,4R,5R)-2-((2R,3S,5S)-6-((tert-butyldiphenylsilyl)oxy)-3-hydroxy-5-methoxyhexan-2-yl)-5-((R)-1-hydroxy-4-methoxybutyl)-3-methoxy-5-methyltetrahydrofuran-2,4-diol (3.59). To pyranose (3.58) (20 mg, 0.0315 mmol) in MeOH: CH_2Cl_2 1:1 mixture (0.3 mL: 0.3 mL, .05 M) at 0°C was added catalytic PPTS (.1 eq.) and slowly warmed to rt. The reaction was monitored by TLC and was complete after 24h at rt. The resulting solution was washed with $NaHCO_3$ (5mL), extracted with CH_2Cl_2 (10 mL x 3). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* furnishing a clear oil. The residue was purified by flash chromatography (1.5:1, hexanes: ethyl acetate) to afford 17 mg (85%) of (S11). $[\alpha]_D^{26}$ -41.2 (*c* .84, $CHCl_3$); R_f .8 (1:6, H:EA); IR (neat) 3413, 2930, 2858, 1462 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 7.1 Hz, 4H), 7.43-7.35 (m, 6H), 4.37 (d, *J* = 9.6 Hz, 1H), 3.87 (s, 1H), 3.71-3.63 (m, 2H), 3.60 (d, *J* = 8.4 Hz, 1H), 3.55-3.51 (m, 1H), 3.48 (d, *J* = 2.6 Hz, 1H), 3.40 (s, 3H), 3.42- 3.39 (m,1H), 3.38 (s, 3H), 3.32 (s, 3H), 2.25 (s, 1H), 2.11 (q, *J* = 7.2 Hz, 1H), 2.02-1.94 (m, 1H), 1.8-1.65 (m, 4H), 1.48 (s, 3H), 1.04 (s, 9H), 1.03 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.6, 133.7, 129.5, 127.6, 112.6, 87.9, 85.0, 84.5, 78.7, 72.5, 66.9, 66.2, 58.6, 58.2, 56.0, 36.7, 36.3, 28.0, 26.9, 26.8, 19.2, 15.7, 7.4; HRMS calcd for $C_{34}H_{54}O_9Si$ [M+Na] 657.3452 , found 657.3429.

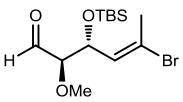


(2*R*,3*R*,*E*)-1-((*S*)-4-benzyl-2-thioxooxazolidin-3-yl)-5-bromo-3-hydroxy-2-methoxyhex-4-en-1-one (3.68). To the thioauxiliary **3.63** (3.46 g, 13.0 mmol) in CH_2Cl_2 (52 mL, .25M) at -78°C was added $TiCl_4$ (1.43 mL, 13.1 mmol), stirred for 5 min, then added (-) sparteine (3.59 mL, 15.6 mmol) in CH_2Cl_2 (5 mL) dropwise. The deep purple solution was stirred for 20 min allowing enolate formation. The resulting solution was treated with additional $TiCl_4$ (4.29 mL, 39.2 mmol) and immediately added aldehyde (**3.67**) (2.71 g, 18.3 mmol). The solution was stirred for 45 min, carefully washed with saturated ammonium chloride solution and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried and concentrated *in vacuo* furnishing a dark yellow oil. The residue was purified by flash chromatography (3:1, hexanes: ethyl acetate) to afford 5.20 g (91%, 3:1 dr) of **3.68** as a mixture of inseparable diastereomers. $[\alpha]_D^{26}$ +188.9 (*c* 2.17, $CHCl_3$); R_f 0.3 (2:1, H:EA); IR (neat) 3456, 2927, 1703, 1651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ7.35-7.22 (m, 5H), 6.13

(d, *J* = .8 Hz, 1H), 6.11 (d, *J* = .8 Hz, 1H), 5.01-5.00 (m, 1H), 4.70 (dd, *J* = 16.3, 9.2 Hz, 1H), 4.39 (m, 2H), 3.41 (s, 3H), 3.28 (dd, *J* = 13.6 Hz, 1H), 3.06 (d, *J* = 10 Hz, 1H), 2.72 (dd, *J* = 7.8 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.0, 171.5, 134.8, 131.0, 129.3, 129.0, 127.5, 126.7, 81.2, 71.2, 70.1, 60.3, 58.7, 37.4, 24.3 ; HRMS calcd for $C_{17}H_{20}BrNNaO_4S$ $[M+Na]^+$ 436.0189, found 436.0179.

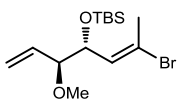


(2*R*,3*R*,*E*)-1-((*S*)-4-benzyl-2-thioxooxazolidin-3-yl)-5-bromo-3-((*tert*-butyldimethylsilyl)oxy)-2-methoxyhex-4-en-1-one (3.69). To aldol adduct **3.68** (6.05 g, 14.6 mmol) in CH_2Cl_2 (14.6 mL, 1.0 M) at 0°C was added 2,6-lutidine (5.09 mL, 43.9 mmol), then added TBSOTf (5.04 mL, 21.9 mmol) dropwise. The resulting solution was then added aqueous 1N HCl until pH 2, extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers were washed with aqueous $NaHCO_3$ (3 x 15). The layers were separated, dried and concentrated *in vacuo* furnishing a dark yellow oil. The residue was purified by flash chromatography (10:1, 8:1, hexanes: ethyl acetate) to afford 5.18 g (67%) of the desired isomer **3.69**. $[\alpha]_D^{26}$ +49.6 (*c* 0.38, $CHCl_3$); R_f 0.7 (3:1, H:EA); IR (neat) 2954, 2929, 2865, 1703 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ7.33-7.215 (m, 5H), 6.09 (d, *J* = 6.5 Hz, 1H), 6.06 (d, *J* = 9.5 Hz, 1H), 4.94-4.89 (m, 1H), 4.78 (dd, *J* = 9.3, 6.5 Hz, 1H), 4.30 (m, 2H), 3.42 (s, 3H), 3.35 (dd, *J* = 13.1, 2.9 Hz, 1H), 2.60 (dd, *J* = 12.9, 11.1 Hz, 1H), 2.30 (s, 3H), 0.85 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.9, 171.8, 135.3, 132.0, 129.2, 127.4, 124.0, 80.5, 71.1, 70.5, 60.4, 59.4, 37.6, 25.7, 24.4, 17.9, -4.3,-.4.7 ; HRMS calcd for $C_{23}H_{34}NBrNaO_4SSi$ $[M+Na]^+$ 550.1053, found 550.1079.

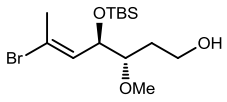


(2*R*,3*R*,*E*)-5-bromo-3-((*tert*-butyldimethylsilyl)oxy)-2-methoxyhex-4-enal (3.70). To the silyl aldol adduct **3.69** (1.88 g, 3.57 mmol) in CH_2Cl_2 (3.5 mL, 1.0 M) at -78°C was DibalH (1.59 mL, 8.93 mmol) dropwise. The resulting solution was stirred for 2 h and carefully added MeOH (5 mL) and stirred vigorously with saturated Rochelle salt solution (200 mL) for 1 h. The solution was extracted with CH_2Cl_2 (3 x 50 mL), the combined organic layers were dried and concentrated *in vacuo* furnishing a clear oil. The residue was purified by flash chromatography (15:1, hexanes: ethyl acetate) to afford 1.16 g (97%) of (3.70). $[\alpha]_D^{26}$ -5.07 (*c* 0.35, $CHCl_3$); R_f 0.3 (9:1, H:EA); IR (neat) 2955, 2858, 1737 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ9.06 (d, *J* = 2 Hz, 1H), 5.91 (dd, *J* = 1.6 Hz, 1H), 4.52 (dd, *J* = 9.2, 5.4 Hz, 1H), 3.49 (dd, *J* = 5.4, 2.0 Hz, 1H), 3.44 (s, 3H), 2.46 (d, *J* = 1.2 Hz, 3H), 0.84 (s, 9H), 0.03 (s, 6H); ^{13}C

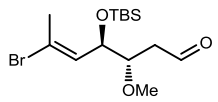
NMR (100 MHz, $CDCl_3$): δ 201.8, 131.4, 123.4, 88.3, 70.6, 59.2, 25.5, 24.2, 17.9, -4.5, -5.1 ; HRMS calcd for $C_{13}H_{25}BrNaO_3Si$ $[M+Na]^+$ 359.0649, found 359.0656.



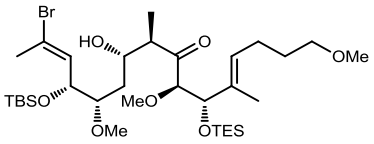
(((3*S*,4*R*,*E*)-6- bromo-3- methoxy hepta-1,5-dien-4-yl) oxy) (*tert*-butyl) dimethylsilane (3.71). Methylphosphonium bromide (9.66 g, 27.1 mmol) in THF (18 mL, 0.5 M) at was added *n*BuLi (12.0 mL, 1.9 M in THF) and stirred 30 min. The orange red solution cooled to 0°C, then added aldehyde **3.70** (3.04 g, 9.02 mmol) and stirred at rt for 2 h. The resulting solution was added saturated ammonium chloride solution and extracted with diethyl ether (3 x 50 mL). The combined organic layers were dried and concentrated *in vacuo* furnishing a yellow oil. The residue was purified by flash chromatography (30:1, hexanes: ethyl acetate) to afford 2.13 g (70%) of **3.71**. $[\alpha]_D^{26}$ -8.0 (*c* 0.37, $CHCl_3$); R_f 0.85 (9:1, H:EA); IR (neat) 2955, 2929, 2823, 1655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.86 (dd, *J* = 9.0, 1.3 Hz, 1H), 5.70 (ddd, *J* = 7.5, 7.4, 6.6 Hz, 1H), 5.28 (dd, *J* = 8.0, 0.8 Hz, 1H), 5.24 (dd, *J* = 13.39, 1.7 Hz, 1H), 4.20 (dd, *J* = 9.0, 5.3 Hz, 1H), 3.42 (dd, *J* = 5.3, 1.0 Hz, 1H), 3.28 (s, 3H), 2.26 (d, *J* = 1.3 Hz, 3H), 0.86 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ135.5, 133.0, 121.9, 118.8, 86.3, 72.6, 57.0, 25.7, 24.3, 18.2, -4.5, -4.8 ; HRMS calcd for $C_{14}H_{27}BrNaO_2Si$ $[M+Na]^+$ 357.0856, found 357.0831.



(3*S*,4*R*,*E*)-6-bromo-4-((*tert*-butyldimethylsilyl)oxy)-3-methoxyhept-5-en-1-ol (3.72). To alkene **3.71** (2.38 g, 7.15 mmol) in THF (7.1 mL, 1 M) at 0°C was added BH_3•THF (21.45 mL, 1.0 M in THF) and stirred 3 h. The reaction was then carefully added 3 M NaOH (30 mL) and 30% H_2O_2 (30 mL) and stirred an additional 3 h at 0 °C. The solution was extracted with diethyl ether (3 x 50 mL) and the combined organic layers were dried and concentrated *in vacuo* furnishing a clear oil. The residue was purified by flash chromatography (6:1, hexanes: ethyl acetate) to afford 1.20 g (47%) of **3.72**. $[\alpha]_D^{26}$ -34.8 (*c* 0.76, $CHCl_3$); R_f 0.3 (6:1, H:EA); IR (neat) 3402, 2955, 2857, 1652 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.89 (dd, *J* = 9.0, 1.2 Hz, 1H), 4.29 (dd, *J* = 9.0, 4.5 Hz, 1H), 3.77 (dd, *J* = 15.4, 5.0 Hz, 1H), 3.46 (s, 3H), δ3.32 (dt, *J* = 8.3, 8.0 1H), 2.45 (t, *J* = 4.4 Hz, 1H), 2.27 (d, *J* = 1.2 Hz, 3H), 1.78-1.68 (m, 2H), 0.87 (s, 9H), 0.06 (d, *J* = 3.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.8, 121.7, 84.2, 72.0, 60.4, 59.0, 32.8, 25.7, 24.1, 18.0, -4.5, -5.0 ; HRMS calcd for $C_{14}H_{29}BrNaO_3Si$ $[M+Na]^+$ 375.0962, found 375.0948.

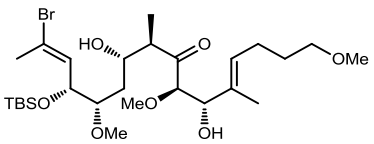


(3*S*,4*R*,*E*)-6-bromo-4-((*tert*-butyldimethylsilyl)oxy)-3-methoxyhept-5-enal (1.27). To alcohol **3.72** (375 mg, 1.06 mmol) in a 1:1 mixture of CH_2Cl_2: DMSO (1 mL, 1 M) at 0 °C was added IBX (1.49 g, 5.32 mmol). The resulting solution was slowly warmed to rt and stirred for 6 h. The milky slurry was filtered through a fritted funnel, and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried and concentrated *in vacuo* furnishing a yellow oil. The residue was purified by flash chromatography (10:1, hexanes: ethyl acetate) to afford 275 mg (73%) of **1.27**. $[\alpha]_D^{26}$ -40.4 (*c* 0.28, $CHCl_3$); R_f 0.25 (9:1, H:EA); IR (neat) 2955, 2930, 1727, 1653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.79 (t, *J* = 1.6, 1H), 5.83 (dd, *J* = 8.9, 1.3 Hz, 1H), 4.29 (dd, *J* = 8.9, 5.0 Hz, 1H), 3.59 (dd, *J* = 6.8, 5.0 Hz, 1H), 3.41 (s, 3H), 2.60-2.57 (m, 2H), 2.27 (d, *J* = 1.2 Hz, 3H), .087 (s, 9H), 0.05 (d, *J* = 4.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.1, 132.6, 122.4, 80.2, 71.6, 58.7, 45.1, 25.7, 24.2, 18.0, -4.5, -5.0.

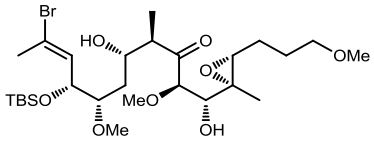


(5*S*,6*R*,8*R*,9*S*,11*S*,12*R*)-12-((*E*)-2-bromoprop-1-en-1-yl)-3,3-diethyl-9-hydroxy-6,11-dimethoxy-5-((*E*)-6-methoxyhex-2-en-2-yl)-8,14,14,15,15-pentamethyl-4,13-dioxa-3,14-disilahexadecan-7-one (3.73). To the silyl enol **3.53** (1.08 g, 2.51 mmol) and aldehyde **1.27** (802 mg, 2.29 mmol) was stirred with CaH_2 (50 mg) in CH_2Cl_2 (7.63 mL, 0.3 M) at rt for 30 min. The solution was then cooled to -78 °C and added $BF_3 \bullet OEt_2$ (0.316 mL, 2.51 mmol). The resulting solution was stirred for 30 min, washed with aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried and concentrated *in vacuo* furnishing a yellow oil. The residue was purified by flash chromatography (8:1, hexanes: ethyl acetate) to afford 959 mg (60 %, 5:1 dr) of **3.73**. Concomitant TES deprotection furnished 178 mg (13 %) of **3.74**. $[\alpha]_D^{26}$ -2.65 (*c* 1.59, $CHCl_3$); R_f .25 (9:1, H:EA); IR (neat) 3472, 2954, 2877, 1711,1653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.89 (dd, *J* = 9.1, 1.2, 1H), 5.37 (t, *J* = 7.2 Hz, 1H), 4.24 (dd, *J* = 13.3, 5.9 Hz, 2H), 4.07 (d, *J* = 10.4 Hz, 1H), 3.73 (d, *J* = 5.8 Hz, 1H), 3.44 (s, 3H), 3.41 (s, 3H), 3.39-3.37 (m, 2H), 3.34 (t, *J* = 6.5 Hz, 2H), 3.31 (s, 3H), 3.04 (broad s, 1H), 2.88 (dq, *J* = 7.0, 1.6 Hz, 1H), 2.26 (d, *J* = 1.0 Hz, 3H), 2.04 (m, 2H), 1.63 (s, 3H), 1.61-1.56 (m, 2H), 1.26-1.21 (m, 2H), 1.04 (d, *J* = 7.1 Hz, 3H), 0.92 (t, *J* = 7.9 Hz, 9H), 0.87 (s, 9H), 0.58 (q, *J* = 7.9 Hz, 6H), 0.03 (d, *J* = 3.9 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 216.6, 134.6, 132.8, 128.0, 121.6, 90.2, 81.7, 79.2, 72.7, 72.2, 67.2, 60.2, 59.7,

58.5, 47.1, 35.3, 29.1, 25.7, 24.1, 18.0, 12.4, 9.2, 6.8, 4.7, -4.5, -5.0 ; HRMS calcd for $C_{33}H_{65}BrNaO_7Si_2$ $[M+Na]^+$ 731.3344, found 731.3316.

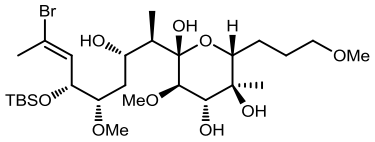


(4*E*,6*S*,7*R*,9*R*,10*S*,12*S*,13*R*,14*E*)-15-bromo-13-((*tert*-butyldimethylsilyl)oxy)-6,10-dihydroxy-1,7,12-trimethoxy-5,9-dimethylhexadeca-4,14-dien-8-one (3.74). To the aldol adduct **3.73** (155 mg, 0.218 mmol) in a 3:1 mixture of THF: H_2O (1 mL, .3 mL, 0.17 M) was added TFA until pH is 2 at rt. Upon consumption of **3.73**, the solution was washed with aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried and concentrated *in vacuo* furnishing a yellow oil. The residue was purified by flash chromatography (2:1, hexanes: ethyl acetate) to afford 126 mg (97 %) of **3.74**. $[\alpha]_D^{26}$ -16.0 (*c* 0.13, $CHCl_3$); R_f .25 (2:1, H:EA); IR (neat) 3445, 2928, 2359, 1713, 1651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.91 (dd, *J* = 9.1, 1.2, 1H), 5.50 (t, *J* = 7.3 Hz, 1H), 4.27 (dd, *J* = 9.0, 4.8 Hz, 1H), 4.24 (t, *J* = 5.1 Hz, 1H), 4.18 (dd, *J* = 10.4, 2.6 Hz, 1H), 3.87 (d, *J* = 4.6 Hz, 1H), 3.47 (s, 3H), 3.46 (s, 3H), 3.39 (t, *J* = 6.4 Hz, 2H), 3.34 (s, 3H), 3.00 (dq, *J* = 7.0, 3.0 Hz, 1H), 2.67 (d, *J* = 5.6 Hz, 1H), 2.29 (s, 3H), 2.1 (p, *J* = 6.9 Hz, 2H), 1.72 (s, 3H), 1.71-1.64 (m, 2H), 1.58 (s, 3H), 1.45-1.40 (m, 1H), 1.08 (d, *J* = 7.0 Hz, 3H), 0.90 (s, 9H), 0.05 (d, *J* = 3.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.6, 133.5, 132.8, 127.5, 121.8, 88.2, 82.0, 76.7, 72.3, 72.0, 67.8, 65.7, 59.7, 59.5, 58.5, 46.9, 34.5, 29.1, 26.7, 24.1, 24.0, 18.3, 17.9, 15.2, 12.7, 9.8, -4.5, -5.0 ; HRMS calcd for $C_{27}H_{51}BrNaO_7Si$ $[M+Na]^+$ 617.2480, found 617.2461.

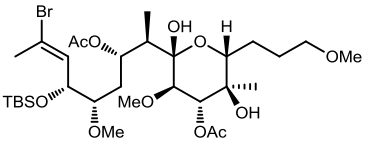


(1*R*,2*R*,4*R*,5*S*,7*S*,8*R*,E)-10-bromo-8-((*tert*-butyldimethylsilyl)oxy)-1,5-dihydroxy-2,7-dimethoxy-1-((2*R*,3*R*)-3-(3-methoxypropyl)-2-methyloxiran-2-yl)-4-methylundec-9-en-3-one (3.5). To the allylic alcohol **3.74** (30 mg, 0.050 mmol) in CH_2Cl_2 (0.50 mL, 0.1 M) was cooled to -78 °C, added $VO(acac)_2$ (38 mg, 0.050 mmol) and then added cumene hydroperoxide (37.0 µL, 0.252 mmol). The green solution was warmed to 0°C upon which the solution turns dark red. The solution was monitored closely by TLC and stirred at 0°C for approximately 12-15 min. The resulting solution was immediately purified by a silica gel column buffered with 1% Et_3N (1:1, hexanes: ethyl acetate) to afford 22 mg (73 %) of **3.5**. $[\alpha]_D^{26}$ -18.6 (*c* 1.45, $CHCl_3$); R_f .25 (1:1, H:EA); IR (neat) 3445, 2928, 2856, 1732, 1651 cm^{-1}; ^1H NMR (600 MHz,

$CDCl_3$): δ 5.88 (dd, *J* = 9.1, 1.2 Hz, 1H), 4.24 (dd, *J* = 9.1, 4.8 Hz, 1H), 4.21 (d, *J* = 2.6 Hz, 1H), 3.91 (d, *J* = 7.2 Hz, 1H), 3.9 (d, *J* = 7.0 Hz, 1H), 3.44 (s, 6H), 3.42-3.37 (m, 2H), 3.33 (s, 3H), 3.18 (d, *J* = 3.1 Hz, 1H), 3.10 (t, *J* = 6.1 Hz, 1H), 3.05 (dq, *J* = 7.0, 6.9 Hz, 1H), 2.57 (d, *J* = 2.3 Hz, 1H), 2.26 (s, 3H), 1.77-1.65 (m, 6H), 1.36 (s, 3H), 1.08 (d, *J* = 7.0 Hz, 1H), 0.87 (s, 9H), 0.04 (d, *J* = 3.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.4, 132.9, 121.2, 86.8, 82.2, 74.3, 72.5, 72.1, 67.9, 60.7, 60.5, 59.7, 59.6, 58.6, 46.9, 34.5, 26.4, 25.7, 24.9, 24.2, 18.0, 13.9, 10.0, -4.4, -5.0 ; HRMS calcd for $C_{27}H_{51}BrNaO_8Si$ $[M+Na]^+$ 633.2429, found 633.2418.

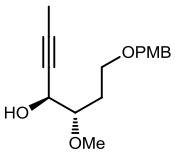


(2*S*,3*R*,4*R*,5*S*,6*R*)-2-((2*R*,3*S*,5*S*,6*R*,*E*)-8-bromo-6-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-5-methoxynon-7-en-2-yl)-3-methoxy-6-(3-methoxypropyl)-5-methyltetrahydro-2H-pyran-2,4,5-triol (3.75). To oxirane **3.5** (12.4 mg, 20.3 μmol) was added pH 8 KPi buffer (3 mL) and stirred in a teflon sealed glass vial for 3 d at 65°C. The resulting solution was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers were dried and concentrated *in vacuo* furnishing a clear oil. The residue was purified by flash chromatography (1:4, 0:1, hexanes: ethyl acetate) to afford 10.2 mg (80%) of **3.75** as a yellow foam. $[\alpha]_D^{26}$ -6.50 (*c* .615, $CHCl_3$); R_f .25 (1:4, H:EA); IR (neat) 3416, 2928, 2857, 1651 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.92 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.49 (d, *J* = 10.3 Hz, 1H), 4.26 (dd, *J* = 9.2, 4.3 Hz, 1H), 3.80 (d, *J* = 9.2 Hz, 1H), 3.79 (d, *J* = 10.3 Hz, 1H), 3.61 (s, 3H), 3.50 (s, 3H), 3.43-3.39 (m, 3H), 3.31 (s, 3H), 3.16 (d, *J* = 9.4 Hz, 1H), 3.06 (broad s, 1H), 2.36 (broad s, 1H), 2.27 (s, 3H), 2.09 (broad s, 1H), 1.82-1.70 (m, 4H), 1.62-1.59 (m, 1H), 1.31-1.25 (m, 2H), 1.29 (s, 3H), 0.99 (d, *J* = 7.1 Hz, 3H), 0.88 (s, 9H), 0.05 (d, *J* = 4.9 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 132.8, 121.6, 100.5, 82.4, 80.6, 77.7, 74.1, 73.7, 72.8, 72.5, 66.9, 61.1, 59.8, 58.4, 43.2, 36.1, 30.3, 29.7, 26.6, 25.7, 24.6, 24.1, 18.0, 14.0, 8.3, -4.5, -5.0 ; HRMS calcd for $C_{27}H_{53}BrNaO_9Si$ $[M+Na]^+$ 651.2534, found 651.2551.

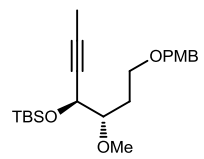


(2*R*,3*S*,5*S*,6*R*,*E*)-2-((2*S*,3*R*,4*R*,5*R*,6*R*)-4-acetoxy-2,5-dihydroxy-3-methoxy-6-(3-methoxypropyl)-5-methyltetrahydro-2H-pyran-2-yl)-8-bromo-6-((*tert*-butyldimethylsilyl)oxy)-5-methoxynon-7-en-3-yl acetate (3.1). To pyranose **3.75** (30 mg, 47.7 μmol) in CH_2Cl_2 (0.47 mL, 0.1 M) at rt was added pyridine (19.2 μL, 0.24 mmol), DMAP (0.58 μg, 4.77 μmol) and acetic anhydride (22.5 μL, 0.24 mmol). The resulting solution was stirred for 1 h, washed with aqueous

$NaHCO_3$ and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried and concentrated *in vacuo* furnishing a clear oil. The residue was purified by flash chromatography (1:1, hexanes: ethyl acetate) to afford 20 mg (59%) of **3.1**. $[\alpha]_D^{26}$ +3.84 (*c* 0.01, $CHCl_3$); R_f .25 (1:1, H:EA); IR (neat) 3448, 2934, 1735, 1719, 1654 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.88 (dd, *J* = 9.0, 1.2, 1H), 5.49 (d, *J* = 9.6 Hz, 1H), 5.20 (d, *J* = 9.7 Hz, 1H), 4.77 (s, 1H), 4.20 (dd, *J* = 9.0, 4.7 Hz, 1H), 3.71 (dd, *J* = 9.0, 2.8 Hz, 1H), 3.48 (s, 3H), 3.71-3.34 (m, 2H), 3.35 (s, 3H), 3.31 (s, 3H), 3.18 (dd *J* = 9.7, 0.9 Hz, 1H), 2.94 (ddd, *J* = 10.1, 4.6, 1.8 Hz, 1H), 2.63 (s, 1H), 2.27 (d, *J* = 1.0 Hz, 3H), 2.16 (s, 3H), 2.07 (s, 3H), 2.06-2.02 (m, 1H), 1.93 (ddd, *J* = 14.4, 10.0, 1.9 Hz, 1H), 1.74-1.61 (m, 2H), 1.46-1.43 (m, 2H), 1.34-1.28 (m, 2H), 1.02 (d, *J* = 7.1 Hz, 3H), 0.88 (s, 9H), 0.04 (d, *J* = 9.0 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.7, 172.4, 132.8, 121.9, 99.1, 81.9, 80.0, 78.8, 74.3, 74.1, 72.7, 72.2, 69.9, 61.1, 59.6, 58.6, 42.0, 35.6, 26.7, 25.7, 24.6, 24.2, 21.6, 21.2, 18.1, 14.5, 8.7, -4.4, -5.0 ; HRMS calcd for $C_{31}H_{57}BrNaO_{11}Si$ $[M+Na]^+$ 735.2746, found 735.2771.

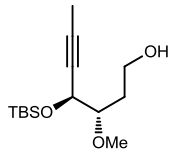


(4S,5S)-5-methoxy-7-((4-methoxybenzyl)oxy)hept-2-yn-4-ol (3.77). To the freshly prepared aldehyde **3.76** (2.6g, 11.1 mmol) in THF (11 mL) at 0°C was added propynyl Grignard (44.7 mL, .5M in THF) and stirred for 1 h. The resulting solution was washed with saturated NH_4Cl (15mL), extracted with ether (10 mL x 3). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* furnishing a yellow oil. The residue was purified by flash chromatography (7:3, hexanes: ethyl acetate) to afford 1.5 g, 3:1 d.r. (50%) of **3.77**. $[\alpha]_D^{26}$ -13.5 (*c* 0.24, $CHCl_3$); R_f .25 (7:3, H:EA); IR (neat) 3412, 2923, 422 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, *J* = 8.5, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 4.45 (dd, *J* = 10.4, 11.2 Hz, 2H), 4.29 (m, 1H), 3.79 (s, 3H), 3.57 (dd, *J* =1.5 ,8.0, Hz, 2H), 3.46 (s, 3H), 3.4 (m, 1H), 2.94 (d, *J* = 6.1 Hz, 1H), 2.02 (m, 1H), 1.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 130.2, 129.3, 113.7, 82.2, 81.7, 77.8, 72.6, 66.3, 64.6, 58.9, 55.2, 30.9, 3.6 ; HRMS calcd for $C_{16}H_{22}NaO_4$ [M+Na] 301.1410, found 301.1417.

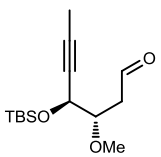


tert-butyl(((4S,5S)-5-methoxy-7-((4-methoxybenzyl)oxy)hept-2-yn-4-yl)oxy)dimethylsilane (3.78). To the alcohol (1.51 g, 5.46 mmol) in CH_2Cl_2 (5 mL) was added 2,6-lutidine (1.89 mL, 16.3 mmol) then TBSOTf (2.50 mL, 10.9 mmol) at 0°C, warmed to rt and stirred for 45 min. The resulting solution was

washed with 1N HCl (5mL), extracted with CH_2Cl_2 (10 mL x 3). The organic layers were washed with $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* furnishing a clear oil. The residue was purified by flash chromatography (20:1, 10:1 hexanes: ethyl acetate) to afford 2.06 g (96%) of **3.78**. $[\alpha]_D^{26}$ -2.72 (*c* 0.11, $CHCl_3$); R_f .25 (20:1, H:EA); IR (neat) 2930, 2857, 1513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.6, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 4.47 (dd, *J* = 11.6, 11.4 Hz, 2H), 3.81 (s, 3H), 3.59 (m, 2H), 3.46 (s, 3H), 3.33 (m, 1H), 2.1 (m, 1H), 1.84 (d, *J* = 2.1 Hz, 3H), 1.75 (m, 1H), 0.93 (s, 9H), 0.16 (d, *J* = 9.80 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.9, 130.6, 129.2, 129.1, 113.6, 81.8, 81.3, 78.1, 72.2, 66.5, 65.7, 59.3, 55.1, 30.8, 25.7, 18.2, 3.5, -4.7, -5.1 ; HRMS calcd for $C_{22}H_{36}O_4SiNa$ [M+Na] 415.2275, found 415.2286.

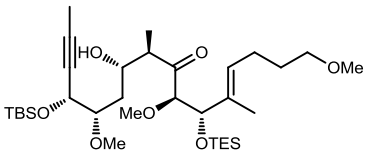


(3S,4S)-4-((tert-butyldimethylsilyl)oxy)-3-methoxyhept-5-yn-1-ol (3.79). To the PMB protected alcohol **3.78** (1.17 g, 2.98 mmol) in CH_2Cl_2: H_2O (1:1, 3 mL: 3 mL) was added DDQ (846 mg, 3.73 mmol) at 0°C then warmed to rt and stirred for 1 h. The dark red reaction solution was filtered through celite and washed excessively with H_2O (2000 mL) until the organic layer becomes clear. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* furnishing a dark yellow oil. The residue was purified by flash chromatography (4:1, 2:1 hexanes: ethyl acetate) to afford 686 mg (85%) of **3.79**. $[\alpha]_D^{26}$ -10.72 (*c* 0.23, $CHCl_3$); R_f .25 (4:1, H:EA); IR (neat) 3419, 2930, 2361, 1253 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.50 (m, 1H), 3.81 (m, 1H), 3.50 (s, 3H), 3.36 (m, 1H), 2.48 (t, *J* = 5.54 Hz, 1H), 2.0 (m, 1H), 1.86 (s, 3H), 1.90-1.82 (m, 1H), 0.93 (s, 9H), 0.16 (d, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 83.8, 65.2, 60.8, 58.8, 32.8, 25.8, 18.2, 3.7, -4.7, -5.1 ; HRMS calcd for $C_{14}H_{28}O_3SiNa$ [M+Na] 295.1700, found 295.1728.

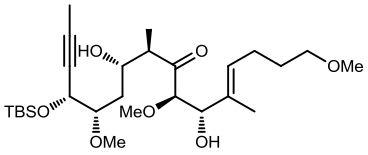


(3S,4S)-4-((tert-butyldimethylsilyl)oxy)-3-methoxyhept-5-ynal (3.80). To the alcohol **3.79** (320 mg, 1.17 mmol) in CH_2Cl_2:DMSO (1 mL: 1 mL) was added IBX (2.63 g, 9.4 mmol) and stirred at rt for 5 h. Reaction solution was filtered through celite and washed with $NaHCO_3$ (5mL), extracted with CH_2Cl_2 (10 mL x 3). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* furnishing a clear oil. The residue was purified by flash chromatography (12:1, hexanes: ethyl acetate) to

afford 308 mg (80%) of **3.79**. The aldehyde was used immediately in the proceeding reaction due to its instability. R_f .25 (10:1, H:EA); IR (neat) 2931, 2858, 1727, 1467 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.82 (t, *J* = 1.9, 1H), 4.51 (m, 1H), 3.71 (m, 1H), 3.46 (s, 3H), 2.0 (ddd, *J* = 4.6, 1.8 Hz, xH), 2.67 (ddd, *J* = 7.6, 2.1 Hz, 1H), 1.83 (s, 3H), 0.89 (s, 9H), 0.11 (d, *J* = 8.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ200.8, 79.4, 64.5, 58.7, 44.8, 25.7, 18.2, 3.6, -4.6, -5.1 ; HRMS Not calculated due to its instability.

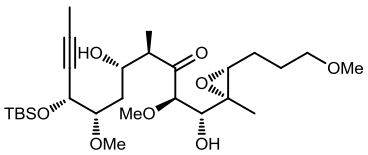


(5S,6R,8R,9S,11S,12R)-3,3-diethyl-9-hydroxy-6,11-dimethoxy-5-((E)-6-methoxyhex-2-en-2-yl)-8,14,14,15,15-pentamethyl-12-(prop-1-yn-1-yl)-4,13-dioxa-3,14-disilahexadecan-7-one (3.81). To the silyl enol **3.53** (1.39 g, 3.25 mmol) and aldehyde **3.80** (968 mg, 3.58 mmol) was stirred with CaH_2 (50 mg) in CH_2Cl_2 (14.3 mL, 0.25 M) at rt for 30 min. The solution was then cooled to -78°C and added BF_3•OEt_2 (0.449 mL, 3.58 mmol). The resulting solution was stirred for 15 min, washed with aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried and concentrated *in vacuo* furnishing a yellow oil. The residue was purified by flash chromatography (9:1,8:1, hexanes: ethyl acetate) to afford 1.3 g (63%) of **3.81**. Concomitant TES deprotection furnished 178 mg (13 %) of **3.82**. $[\alpha]_D^{26}$ -10.3 (*c* 0.8, $CHCl_3$); R_f .25 (9:1, H:EA); IR (neat) 3514, 2932, 1710, 1461 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.35 (t, *J* = 7.2, 1H), 4.45 (dd, *J* = 5.5, 2.2 Hz, 1H), 4.22 (d, *J* = 6.1 Hz, 1H), 4.08 (dd, *J* = 10.5, 2.0 Hz, 1H), 3.86 (d, *J* = 6.1 Hz, 1H), 3.46 (s, 3H), 3.40 (s, 3H), 3.34 (t, *J* = 13.1, 2H), 3.31 (s, 3H), 3.10 (d, *J* = 1.4 Hz, 1H), 2.93-2.87 (m, 1H), 2.11-1.99 (m, 2H), 1.82 (d, *J* = 2.1 Hz, 3H), 1.63 (s, 3H), 1.60 (s, 3H), 1.53-1.47 (dd, *J* = 8.76, 4.4 Hz, 1H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.92 (t, *J* = 7.9 Hz, 9H), 0.90 (s, 9H), 0.58 (q, *J* = 8.0 Hz, 6H), 0.12 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.3, 134.6, 127.9, 89.9, 81.7, 79.2, 72.2, 67.9, 65.3, 59.8, 59.3, 58.5, 47.9, 34.6, 29.1, 25.8, 24.1, 18.3, 12.4, 9.5, 6.8, 4.8, 3.7, -4.7, -5.1 ; HRMS calcd for $C_{33}H_{65}O_7Si_2$ [M+] 629.4263, found 629.4248.

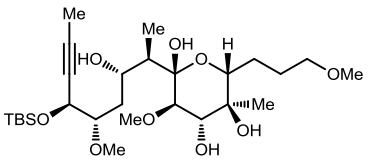


(6S,7R,9R,10S,12S,13R,E)-13-((tert-butyldimethylsilyl)oxy)-6,10-dihydroxy-1,7,12-trimethoxy-5,9-dimethylhexadec-4-en-14-yn-8-one (3.82). To the aldol adduct **3.81** (155 mg, 0.218

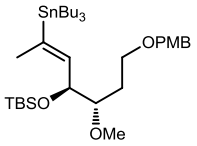
mmol) in a 3:1 mixture of THF: H_2O (1 mL, .3 mL, 0.17 M) was added TFA until pH is 2 at rt. Upon consumption of **3.81**, the solution was washed with aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried and concentrated *in vacuo* furnishing a yellow oil. The residue was purified by flash chromatography (2:1, hexanes: ethyl acetate) to afford 126 mg (97 %) of 3.82. $[\alpha]_D^{26}$ -12.44 (*c* 0.9, $CHCl_3$); R_f .25 (2:1, H:EA); IR (neat) 3452, 2930, 2858, 1710, 1460 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.46 (t, *J* = 7.2, 1H), 4.49 (dd, *J* = 5.7, 2.2 Hz, 1H), 4.17 (dd, *J* = 4.9 Hz, 1H), 4.12 (dd, *J* = 8.1, 2.4 Hz, 1H), 3.97 (d, *J* = 4.9 Hz, 1H), 3.45 (s, 3H), 3.42 (s, 3H), 3.41-3.38 (m, 2H), 3.35 (t, *J* = 2.6 Hz, 2H), 3.31 (s, 3H), 3.28 (d, *J* = 2.2 Hz, 1H), 2.99-2.95 (m, 1H), 2.77 (d, *J* = 5.1 Hz, 1H), 2.10 (m, 2H), 1.82 (s, 3H), 1.70 (s, 3H), 1.68-1.60 (m, 3H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.5, 133.5, 127.8, 88.0, 82.2, 77.6, 76.8, 72.1, 68.9, 65.2, 59.4, 59.1, 58.5, 47.5, 34.0, 29.1, 25.8, 24.2, 18.2, 12.6, 10.2, 3.6, -4.7, -5.1 ; HRMS calcd for $C_{33}H_{64}O_7Si_2$ [M+] 515.3399, found 515.3417.



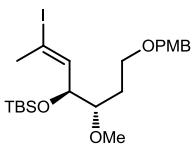
(1R,2R,4R,5S,7S,8R)-8-((tert-butyldimethylsilyl)oxy)-1,5-dihydroxy-2,7-dimethoxy-1-((2R,3R)-3-(3-methoxypropyl)-2-methyloxiran-2-yl)-4-methylundec-9-yn-3-one (3.83). To the allylic alcohol **3.82** (85 mg, 0.165 mmol) in CH_2Cl_2 (0.50 mL) was cooled to 0°C, added $VO(acac)_2$ (43 mg, 0.165 mmol) and then added cumene hydroperoxide (73.3 µL, 0.495 mmol). The solution was monitored closely by TLC and stirred at 0°C for approximately 12-15 min. The resulting red solution was immediately purified by a silica gel column buffered with 1% Et_3N (2:1, 1:1, hexanes: ethyl acetate) to afford 69 mg (79 %) of **3.83**. R_f .25 (1:1, H:EA); IR (neat) 3458, 2930, 1714, 1492 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.47 (dd, *J* = 2.1, 1.9, 1H), 4.16 (dd, *J* = 10.6, 2.4 Hz, 1H), 4.07 (d, *J* = 2.8 Hz, 1H), 3.92 (t, *J* = 2.8 Hz, 1H), 3.46 (s, 3H), 3.43 (s, 3H), 3.41-4.37 (m, 2H), 3.33 (s, 3H), 3.10 (t, *J* = 6.3 Hz, 1H), 3.08 (dd, *J* = 6.9, 3.5 Hz, 1H), 2.55 (d, *J* = 2.7 Hz, 1H), 1.81 (d, *J* = 2.1 Hz, 3H), 1.86-1.61 (m, 9H), 1.36 (s, 3H), 1.10 (d, *J* = 6.9 Hz, 3H), 0.91 (s, 9H), 0.14 (d, *J* = 10.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.9, 86.5, 82.6, 82.3, 77.6, 73.9, 72.1, 69.1, 65.3, 60.7, 59.2, 59.1, 58.5, 47.1, 33.8, 26.3, 24.9, 18.2, 13.9, 10.5, 3.6, -4.7, -5.1 ; HRMS calcd for $C_{27}H_{50}O_8Na$ [M+Na] 553.3167, found 553.3180.



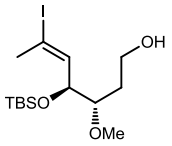
(2S,3R,4R,5S,6R)-2-((2R,3S,5S,6S)-6-((tert-butyldimethylsilyl)oxy)-3-hydroxy-5-methoxynon-7-yn-2-yl)-3-methoxy-6-(3-methoxypropyl)-5-methyltetrahydro-2H-pyran-2,4,5-triol (3.84). To oxirane **3.83** (60 mg, 113.2 μmol) was added pH 8 KPi buffer (3 mL) and stirred in a teflon sealed glass vial for 3 d at 65 °C. The resulting solution was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers were dried and concentrated *in vacuo* furnishing a clear oil. The residue was purified by flash chromatography (1:4, 0:1, hexanes: ethyl acetate) to afford 43 mg (70%) of **3.84** as a white foam. $[\alpha]_D^{26}$ +8.46 (*c* 2.6, $CHCl_3$); R_f .25 (1:6, H:EA); IR (neat) 3412, 2931, 2858, 1462 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.45 (dd, *J* = 1.88 Hz, 1H), 4.42 (d, *J* = 11 Hz, 1H), 4.34 (s, 1H), 3.79 (m, 2H), 3.59 (s, 3H), 3.49 (s, 3H), 3.4-3.39 (m, 3H), 3.30 (s, 3H), 3.12 (d, *J* = 9.5 Hz, 1H), 2.91 (d, *J* = 2.5 Hz, 1H), 2.58 (s, 1H), 2.08-2.01 (m, 1H), 1.96 (m, 2H), 1.82 (s, 3H), 1.77-1.39(m, 5H), 1.10 (s, 3H), 1.00 (d, *J* = 7.1 Hz, 3H), 0.90 (s, 9H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 100.6, 82.2, 80.9, 78.0, 73.9, 73.8, 72.5, 68.3, 65.4, 61.0, 59.4, 58.4, 42.5, 34.9, 26.6, 25.8, 24.5, 18.3, 13.8, 9.0, 3.7, -4.7, -5.0 ; HRMS calcd for $C_{27}H_{52}NaO_9Si$ [M+] 571.3273, found 571.3275.



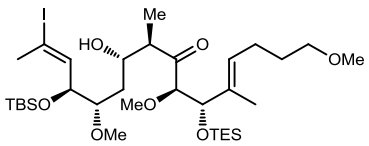
tert-butyl(((4S,5S,E)-5-methoxy-7-((4-methoxybenzyl)oxy)-2-(tributylstannyl)hept-2-en-4-yl)oxy)dimethylsilane (3.91). To the alkyne **3.78** (918 mg, 2.34 mmol) in benzene (2 mL) was added cat. $PdCl_2(PPh_3)_2$ followed by the dropwise addition of Bu_3SnH (4.17 mL, 17.55 mmol) and heated to 80°C overnight. The reaction solution was concentrated and placed straight on a silica gel column. The residue was purified by flash chromatography (40:1, 20:1 hexanes: ethyl acetate) to afford 1.45 g (88%) of **3.91** as a clear oil. R_f .25 (10:1, H:EA); ^1H NMR (400 MHz, $CDCl_3$): δ 7.26-7.19 (dd, *J* = 8.6, 2H), 6.82-6.80 (dd, *J* = 8.6 Hz, 2H), 5.46 (dd, *J* = 8.4, 1.8 Hz, 1H), 4.44 (dd, *J* = 8.4, 6.0 Hz, 1H), 4.37 (d, *J* = 4.6 Hz, 2H), 3.74 (s, 3H), 3.52-3.41 (m, 3H), 3.38 (s, 3H), 3.19-3.14 (m, 1H), 1.8 (d, *J* = 1.7 Hz, 3H), 1.48 (s, 9H), 1.44-1.48 (m, 8H), 1.27-1.15 (m, 10H), 0.82 (bs, 34H), -0.024 (d, *J* = 9.5 Hz, 6H).



tert-butyl(((4S,5S,E)-2-iodo-5-methoxy-7-((4-methoxybenzyl)oxy)hept-2-en-4-yl)oxy)dimethylsilane (3.92). To a solution of the stannane **3.91** (1.1 g, .877 mmol) in CH_2Cl_2 (1 mL) at 0°C was added a saturated solution of I_2 until a light purple color persisted. The reaction solution was washed with $Na_2S_2O_3$ (2 mL) then extracted with CH_2Cl_2 (3 X 5 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* furnishing a clear oil. The residue was purified by flash chromatography (40:1, 20:1, 10:1 hexanes: ethyl acetate) to afford 911 mg (83%) of **3.92** as a clear oil. R_f .25 (10:1, H:EA); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (dd, *J* = 8.6, 2H), 6.87 (dd, *J* = 8.6 Hz, 2H), 6.13 (dd, *J* = 9.0, 1.4 Hz, 1H), 4.43 (d, *J* = 4.5 Hz, 2H), 4.30 (dd, *J* = 9.0, 5.7 Hz, 1H), 3.80 (s, 3H), 3.56-3.52 (m, 2H), 3.41 (s, 3H), 3.23 (m, 1H), 2.41 (d, *J* = 1.4 Hz, 3H), 1.89-1.80 (m, 1H), 1.60-1.50 (m, 1H), 0.88 (s, 9H), 0.04 (d, *J* = 4.8 Hz, 6H).

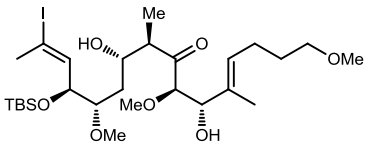


(3S,4S,E)-4-((tert-butyldimethylsilyl)oxy)-6-iodo-3-methoxyhept-5-en-1-ol (3.93). To the PMB ether **3.92** (911 mg, 1.73 mmol) in CH_2Cl_2 and H_2O (10:1, 2 mL: .2mL) was added DDQ (588 mg, 2.59 mmol) at 0°C. The reaction was slowly warmed to rt and stirred for an additional hr. The reaction solution was filtered through celite and washed excessively with water (2000 mL) then the combined organic layer (CH_2Cl_2) was dried ($MgSO_4$) and concentrated *in vacuo* furnishing a yellow oil. The residue was purified by flash chromatography (4:1, hexanes: ethyl acetate) to afford 571 mg (82%) of 3.93 as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.14 (dd, *J* = 9.0, 1.4, 1H), 4.40 (dd, *J* = 9.0, 5.5 Hz, 1H), 3.77-3.69 (m, 3H), 3.48 (s, 3H), 3.30 (m, 1H), 2.44 (d, *J* = 1.3 Hz, 3H), 1.79-1.55 (m, 2H), 0.89 (s, 9H), 0.06 (d, *J* = 5.7 Hz, 6H).

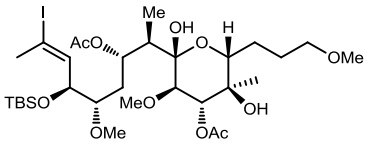


(5S,6R,8R,9S,11S,12S)-3,3-diethyl-9-hydroxy-12-((E)-2-iodoprop-1-en-1-yl)-6,11-dimethoxy-5-((E)-6-methoxyhex-2-en-2-yl)-8,14,14,15,15-pentamethyl-4,13-dioxa-3,14-disilahexadecan-7-one (3.89). To the silyl enol **3.53** (350 mg, .813 mmol) and aldehyde **3.8** (374 mg, .939 mmol) was stirred with CaH_2 (50 mg) in CH_2Cl_2 (3 mL, 0.25 M) at rt for 30 min. The solution was then cooled to -78°C and added BF_3•OEt_2 (.127 mL, 1.03 mmol). The resulting solution was stirred for 15 min, washed with aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 15

mL). The combined organic layers were dried and concentrated *in vacuo* furnishing a yellow oil. The residue was purified by flash chromatography (10:1,8:1, 1:1 hexanes: ethyl acetate). Concomitant TES deprotection product was collected and the yield was compiled over two steps.

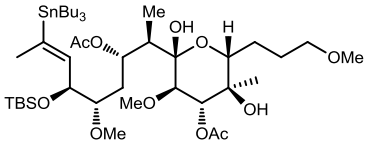


(4E,6S,7R,9R,10S,12S,13S,14E)-13-((tert-butyldimethylsilyl)oxy)-6,10-dihydroxy-15-iodo-1,7,12-trimethoxy-5,9-dimethylhexadeca-4,14-dien-8-one (3.95). To the aldol adduct **3.89** (155 mg, 0.218 mmol) in a 3:1 mixture of THF: H_2O (1 mL, .3 mL, 0.17 M) was added TFA until pH is 2 at rt. Upon consumption of **3.89**, the solution was washed with aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried and concentrated *in vacuo* furnishing a yellow oil. The residue was purified by flash chromatography (2:1, 1:1, hexanes: ethyl acetate) to afford 546 mg (90 %) over two steps of **3.95**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.12 (dd, *J* = 9.0, 1.1, 1H), 5.48 (t, *J* = 7.1 Hz, 1H), 4.39 (dd, *J* = 9.0, 5.5 Hz, 1H), 4.21 (t, *J* = 4.88 Hz, 1H), 4.06 (dd, *J* = 10.4, 2.4 Hz, 1H), 3.89 (d, *J* = 4.6 Hz, 1H), 3.68 (d, *J* = 6.0 Hz, 1H), 3.45 (s, 3H), 3.44 (s, 3H), 3.38-3.34 (m, 2H), 3.32 (s, 3H), 3.23 (d, 1H), 2.97 (m, 1H), 2.66 (d, *J* = 5.4, 1H), 2.44 (d, *J* = 1.00 Hz, 3H), 2.12 (m, 3H), 1.7 (s, 3H), 1.67-1.58 (m, 5H), 1.54 (s, 6H), 0.88 (s, 9H), 0.07 (d, 6H).



(2R,3S,5S,6S,E)-2-((2S,3R,4R,5R,6R)-4-acetoxy-2,5-dihydroxy-3-methoxy-6-(3-methoxypropyl)-5-methyltetrahydro-2H-pyran-2-yl)-6-((tert-butyldimethylsilyl)oxy)-8-iodo-5-methoxynon-7-en-3-yl acetate (3.2). To pyranose **3.96** (84 mg, .124 mmol) in CH_2Cl_2 (0.5 mL, 0.25 M) at rt was added pyridine (.1 mL, 1.24 mmol), DMAP (cat.) and acetic anhydride (93 µL, 0.996 mmol). The resulting solution was stirred for 3 h, washed with aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried and concentrated *in vacuo* furnishing a clear oil. The residue was purified by flash chromatography (1:1, hexanes: ethyl acetate) to afford 40 mg (42%) over 3 steps **3.2**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.02 (dd, *J* = 8.9, 1.4, 1H), 5.41 (d, *J* = 9.8 Hz, 1H), 5.14 (d, *J* = 9.7 Hz, 1H), 4.33 (dd, *J* = 8.88, 5.24 Hz, 1H), 3.42 (s, 3H), 3.38-3.32 (m, 2H), 3.31 (s, 3H), 3.25 (s, 3H),

3.13 (d, *J* = 9.8 Hz, 1H), 2.90 (m, 1H), 2.37 (d, *J* = 1.2 Hz, 1H), 2.09 (s, 3H), 2.00 (s, 3H), 1.97 (s, 3H), 0.97 (s, *J* = 7.44 Hz, 3H), 0.82 (s, 9H), 0.0008 (d, *J* = 2.9 Hz, 6H).



(2R,3S,5S,6S,E)-2-((2S,3R,4R,5R,6R)-4-acetoxy-2,5-dihydroxy-3-methoxy-6-(3-methoxypropyl)-5-methyltetrahydro-2H-pyran-2-yl)-6-((tert-butyldimethylsilyl)oxy)-5-methoxy-8-(tributylstannyl)non-7-en-3-yl acetate (3.3). To the alkyne **3.4** (60 mg, 2.34 mmol) in benzene (2 mL) was added cat. $PdCl_2(PPh_3)_2$ followed by the dropwise addition of Bu_3SnH (.191 mL, .711 mmol) and heated to 80°C overnight. The reaction solution was concentrated and placed straight on a silica gel column. The residue was purified by flash chromatography (2:1, 1:1, 0:1 hexanes: ethyl acetate) to afford 22 mg (25%) of **3.3** as a clear oil. R_f .25 (10:1, H:EA); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.40 (d, *J* = 17.4, 1H), 5.15 (d, *J* = 9.7 Hz, 1H), 4.84 (s, 1H), 4.46 (dd, *J* = 8.4, 6.2 Hz, 1H), 3.65 (dd, *J* =8.0, 6.3 Hz, 1H), 3.39 (s, 3H), 3.35 (s, 3H), 3.32-3.26 (m, 3H), 3.24 (s, 3H), 3.11 (d, *J* = 8.8 Hz, 1H), 2.91 (m, 1H), 2.58 (s, 1H), 2.09 (s, 3H), 2.00 (s, 3H), 1.88-1.84 (m, 2H), 1.81 (d, *J* = 1.6, 2H), 1.67-1.55 (m, 3H), 1.48-1.38 (m, 5H), 1.30-1.16 (m, 11H), 0.88-0.74 (m, 25 H), 0.00-0.05 (d, *J* = 9.5, 6H).

Notes and References

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Appendix A2:

Spectra Relevant to Chapter III

Figure A.2A Key NOE assignments for C15-C28 fragment of ammocidin A

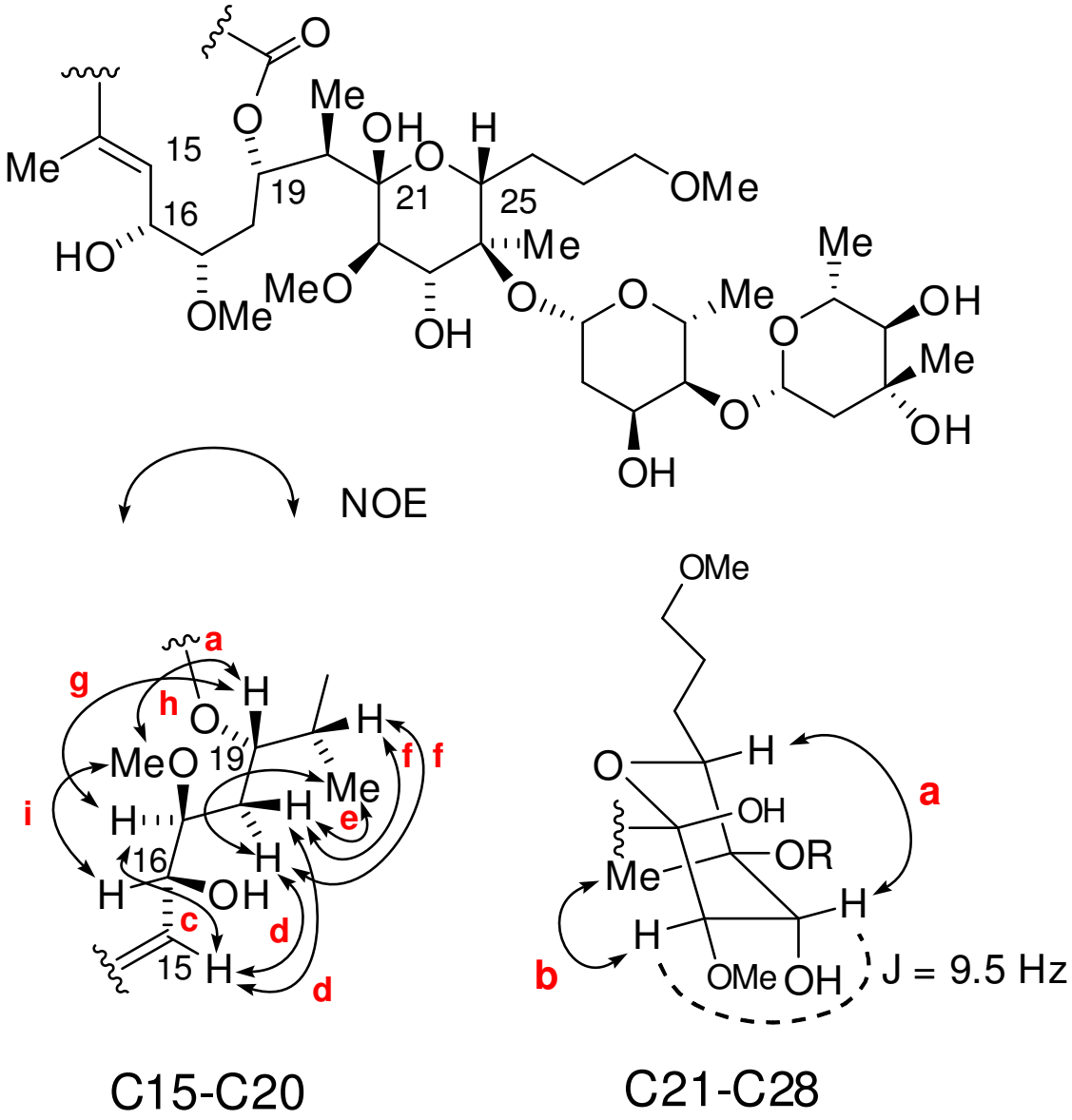


Figure A.2B NOE spectral data of ammocidin A

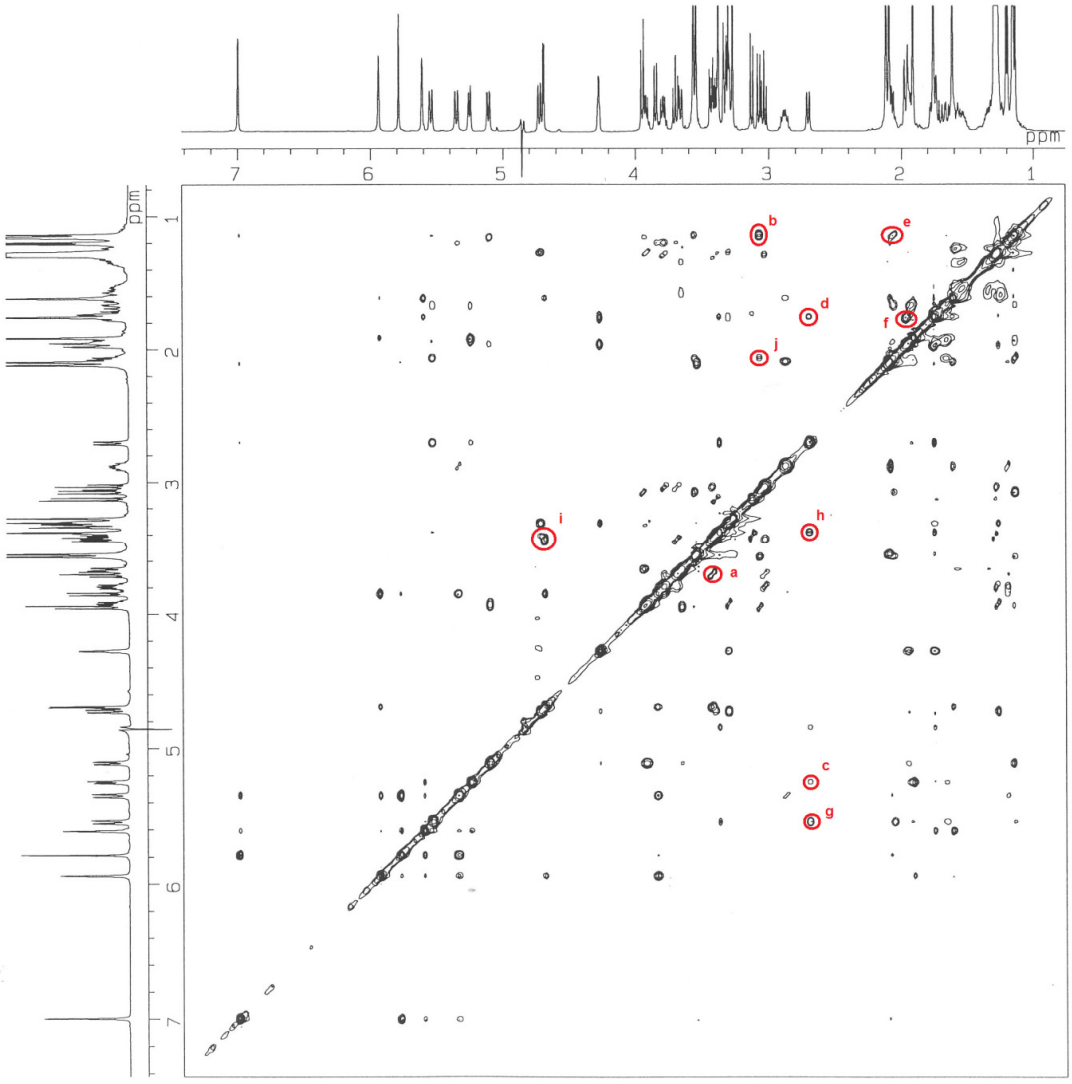
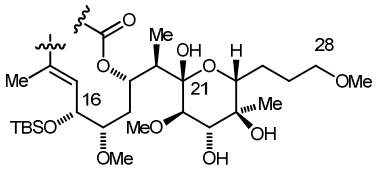
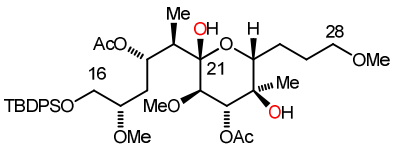


Figure A.2C Comparison of NMR data for 13 to ammocidins D.



C-16-C28 Fragment of Ammocidin D



MeOD	Observed Value ^{13}C NMR	Literature Value[1] ^{13}C NMR	Observed Value ^{1}H NMR	Literature Value[2] ^{1}H NMR
C25	75.1	75.5	3.72 (dd, *J* = 9.2, 2.8 Hz, 1H)	3.54 (t, *J* = 9.0 Hz, 1H)
C24	74.4	75.0	-	-
C24 Me	14.5	13.8	1.10 (s, 3H)	1.03 (s, 3H)
C23	80.9	78.3	5.20 (d, *J* = 9.7 Hz, 1H)	3.78 (d, *J* = 9.5 Hz, 1H)
C22	80.0	82.3	3.18 (d, *J* = 9.4 Hz, 1H)	3.01 (d, *J* = 9.5 Hz, 1H)
C22 OMe	60.9	61.6	3.45 (s, 3H)	3.54 (s, 3H)
C21	99.2	100.3	-	-
C20	45.2	44.8	2.04 (m, 1H)	2.03 (m , 1H)
C20 Me	9.5	9.2	1.04 (d, *J* =7.1 Hz 3H)	1.10 (d, 3H)
C19	71.4	72.3	5.50 (d, *J* =9.6 Hz, 1H)	5.50 (m, 1H)
C18	37.8	35.8	1.54-1.49 (m, 2H)	1.90-1.62 (m, 2H)
C17	79.8	82.9	3.12-3.09 (m, 1H)	2.67 (m, 1H)
C17 OMe	58.7 or 58.4	57.6	3.29 (s, 3H)	3.34 (s, 3H)
C16	66.2	67.8	3.72 (dd, *J* = 9.2, 2.8 Hz, 2H)	4.82 (dd, 1H)

[1] R. Murakami, J. Shinozaki, T. Kajiura, I. Kozone, M. Takagi, K. Shin-Ya, H. Seto, Y. Hayakawa, *J. Antibiot.* **2009**, *62*, 123-127

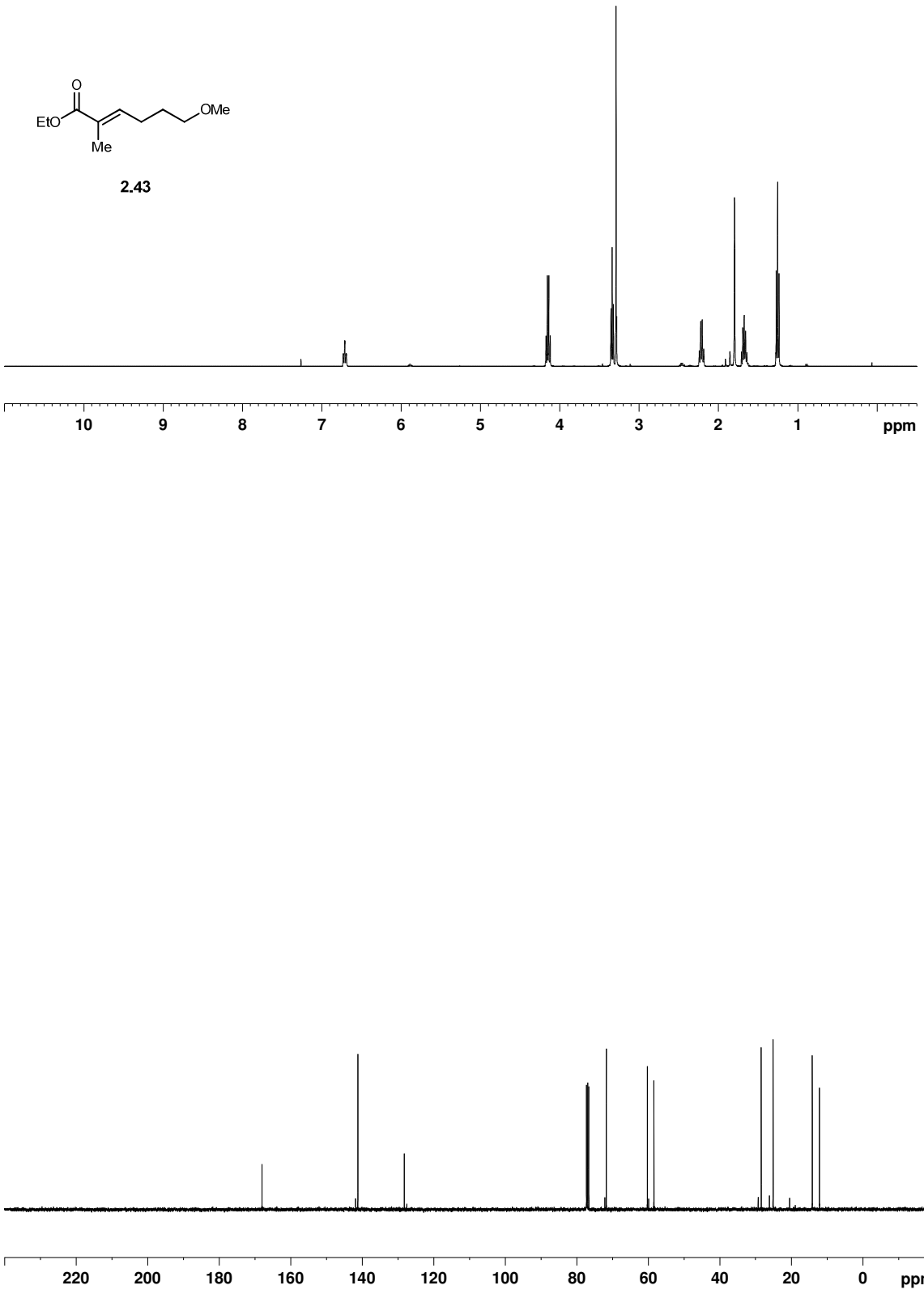


Figure A2.1 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **2.43** in $CDCl_3$

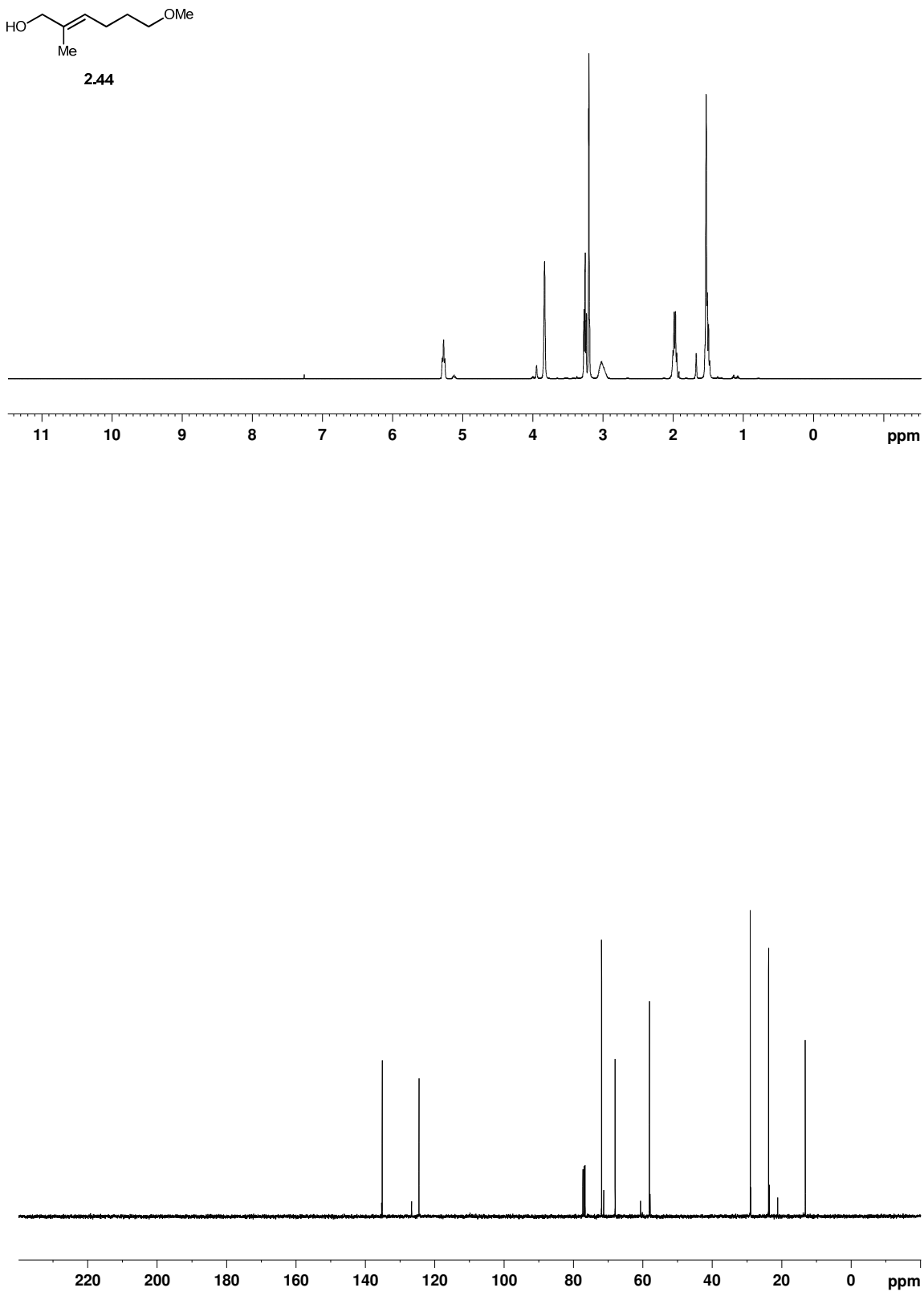


Figure A2.2 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **2.44** in $CDCl_3$

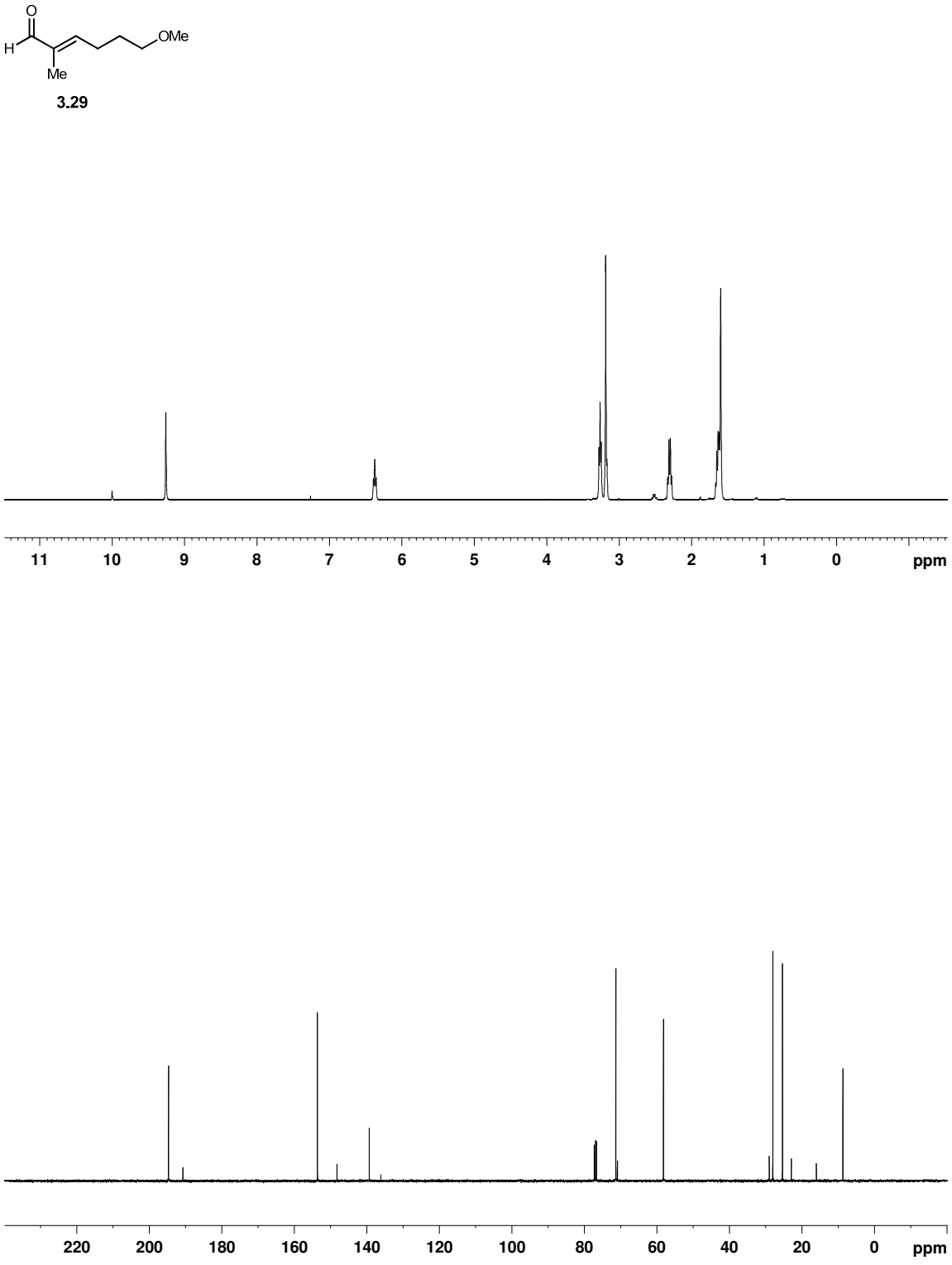
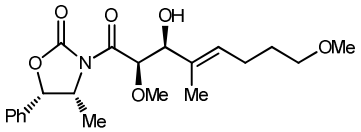


Figure A2.3 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **3.29** in $CDCl_3$



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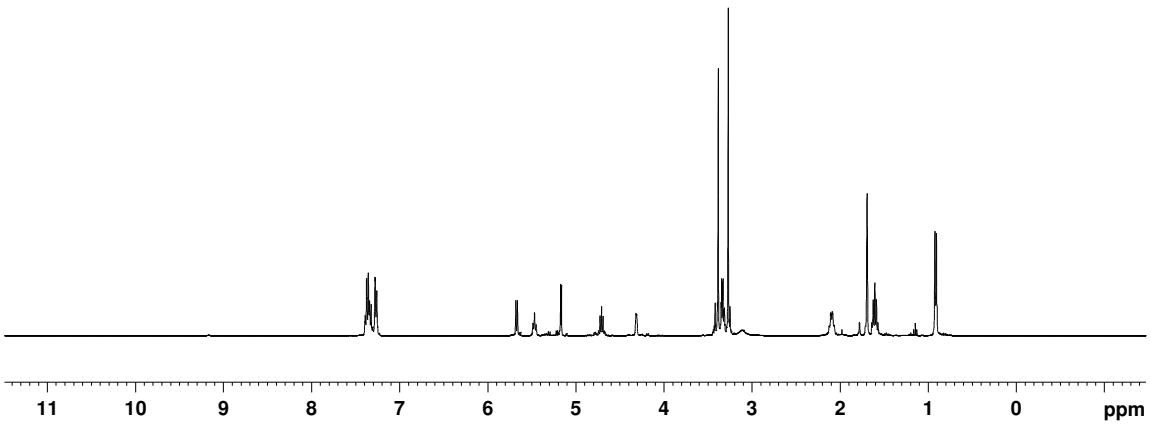


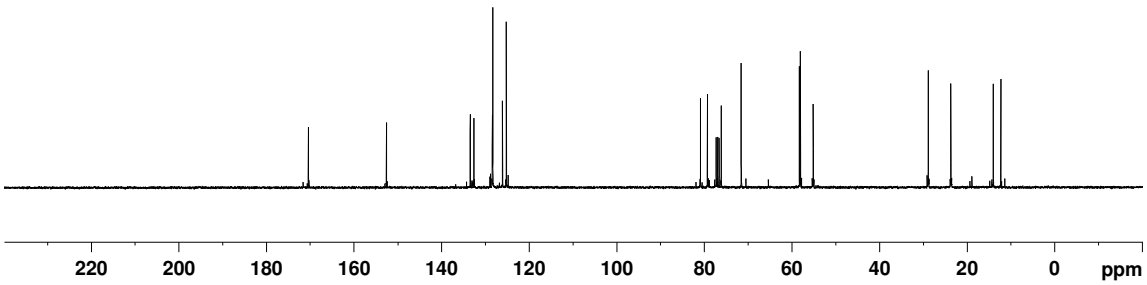
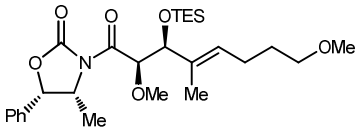
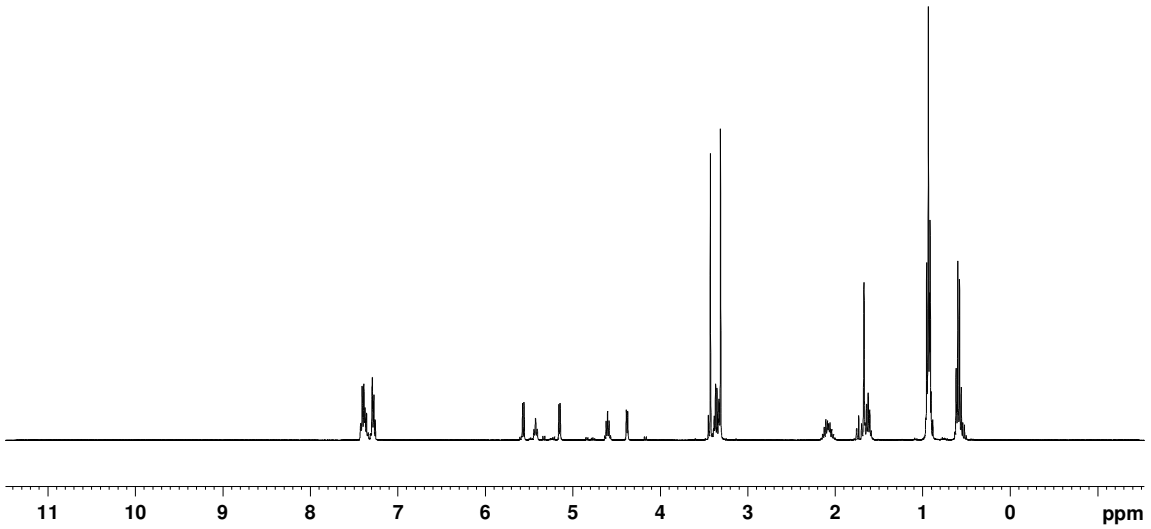


Figure A2.4 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **3.31** in $CDCl_3$



3.32



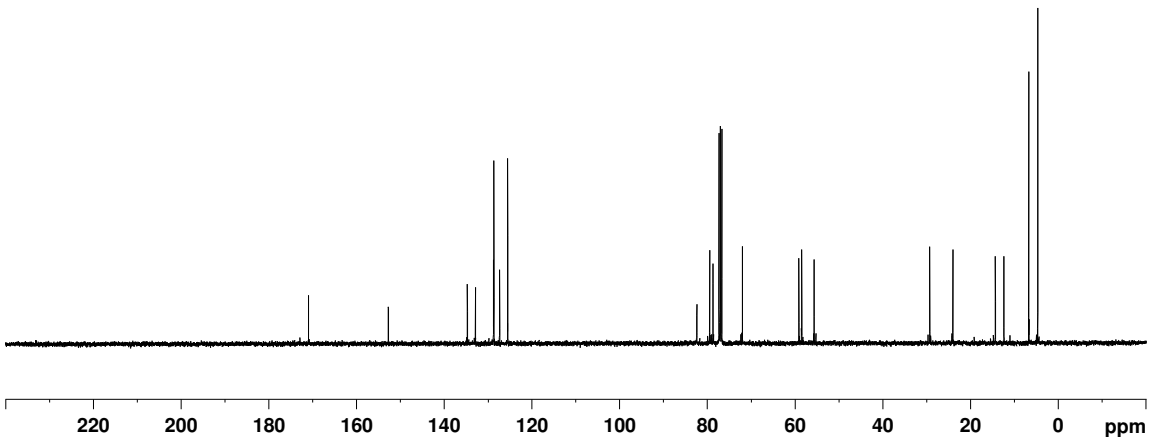
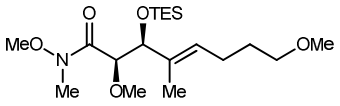
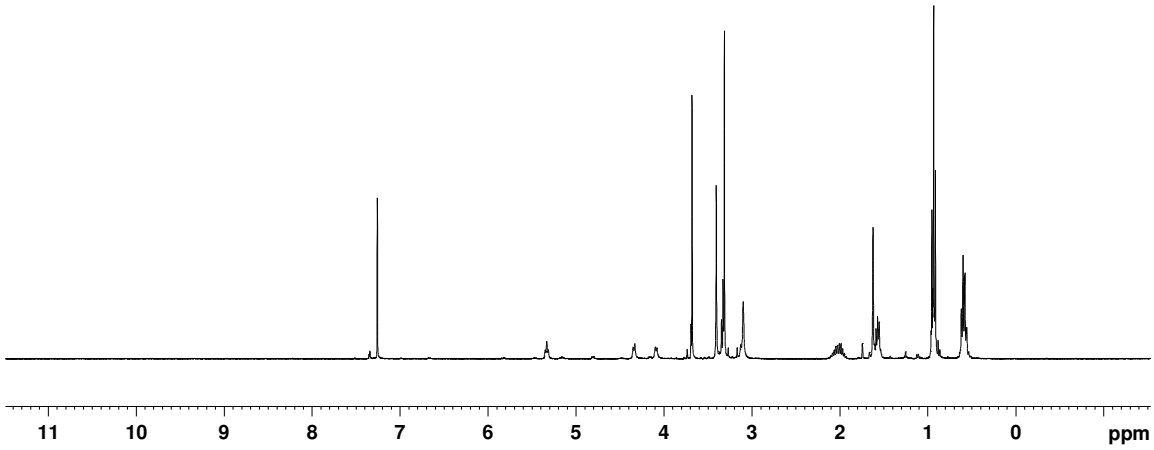


Figure A2.5 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **3.32** in $CDCl_3$



3.33



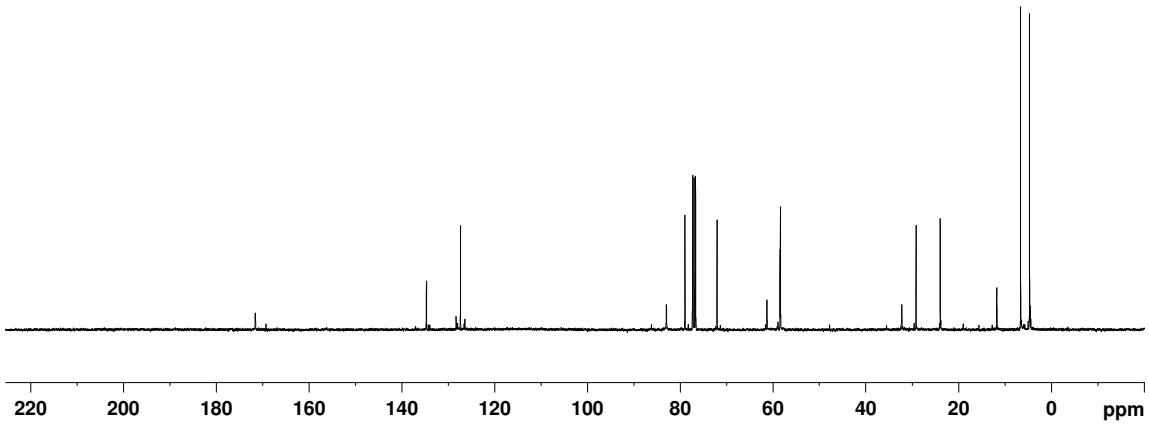
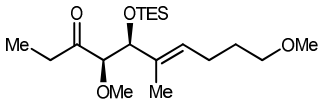
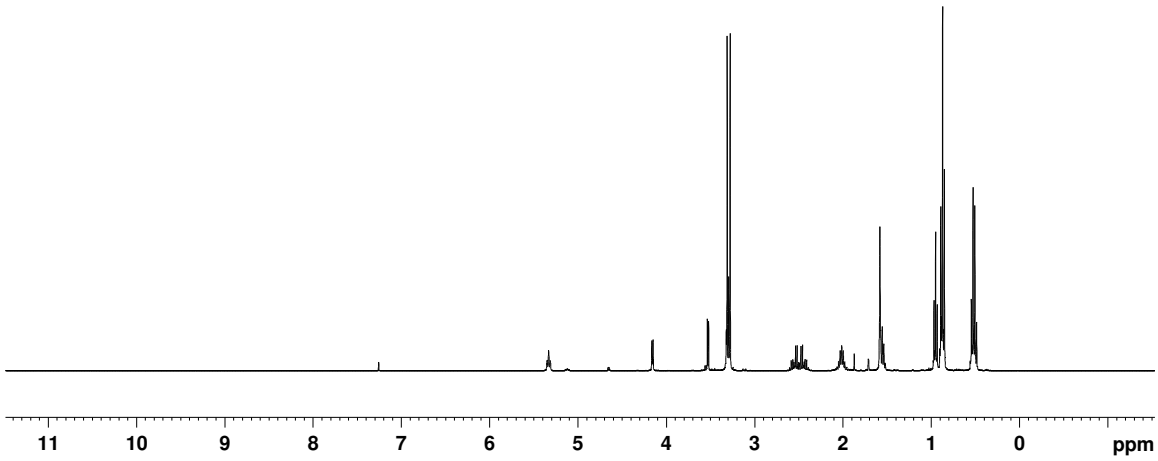


Figure A2.6 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **3.33** in $CDCl_3$



3.7



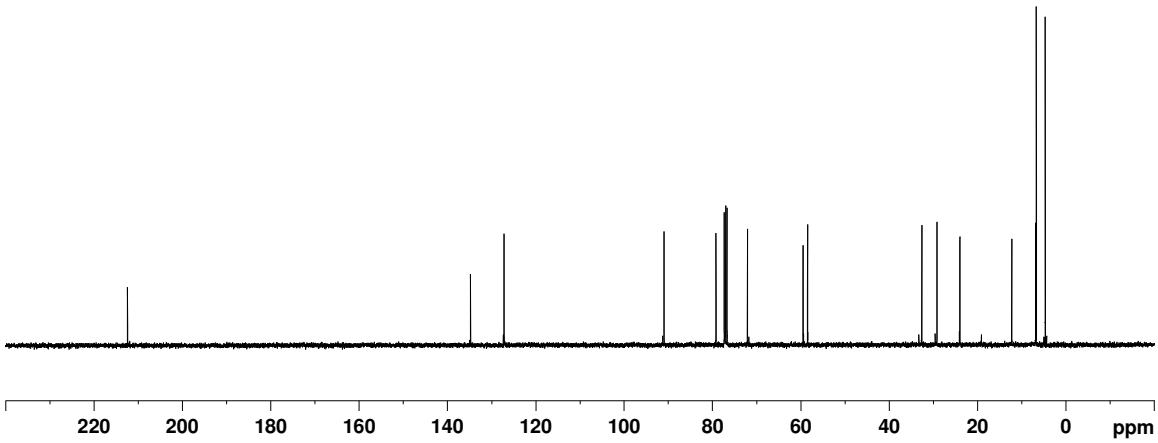
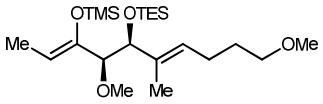


Figure A2.7 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **3.7** in $CDCl_3$



3.53

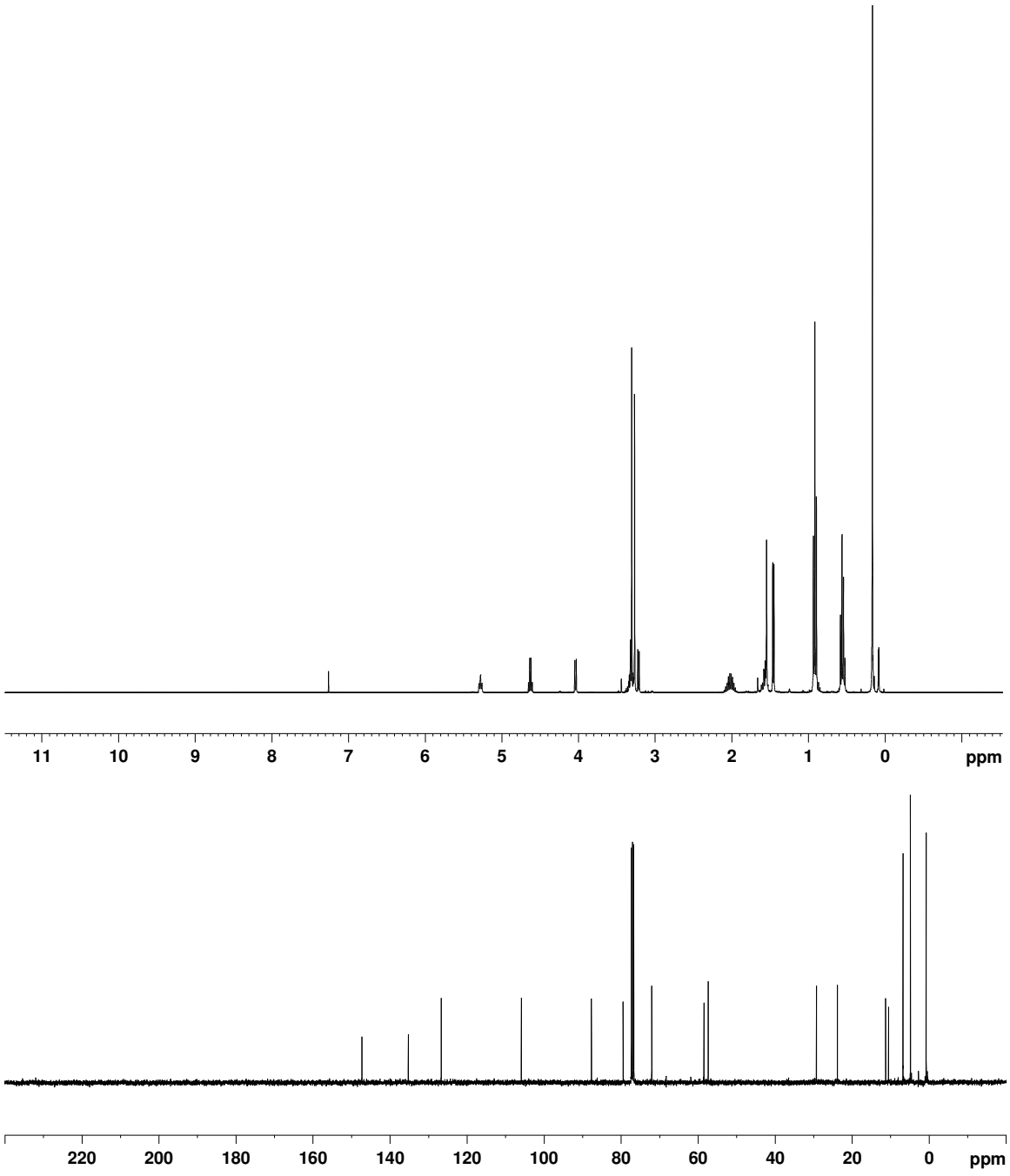
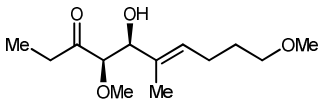
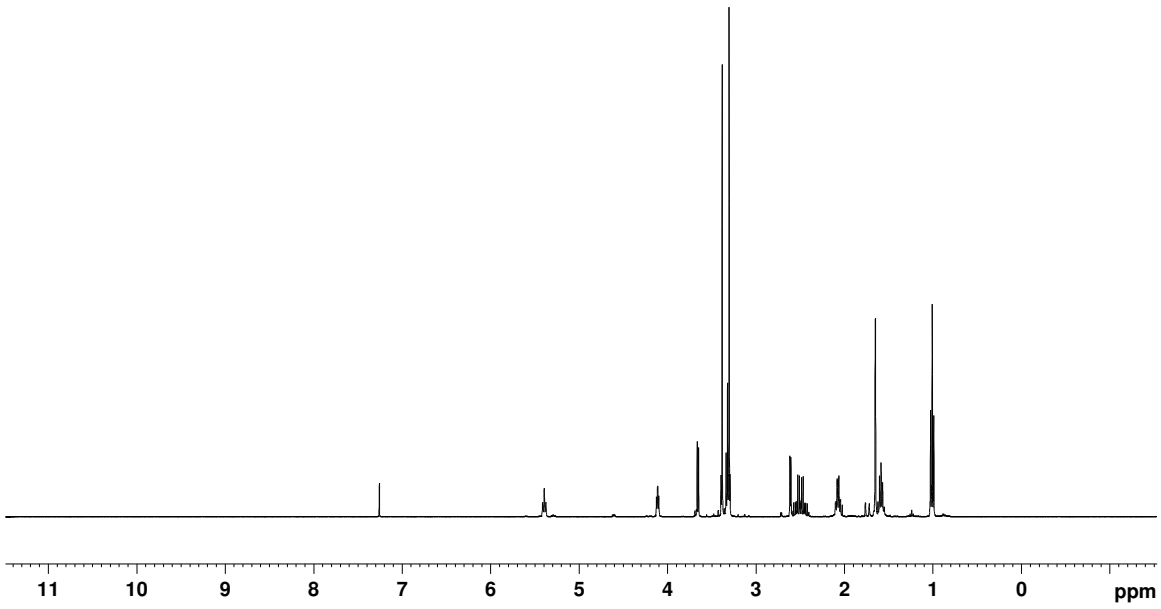


Figure A2.8 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **3.53** in $CDCl_3$



3.34



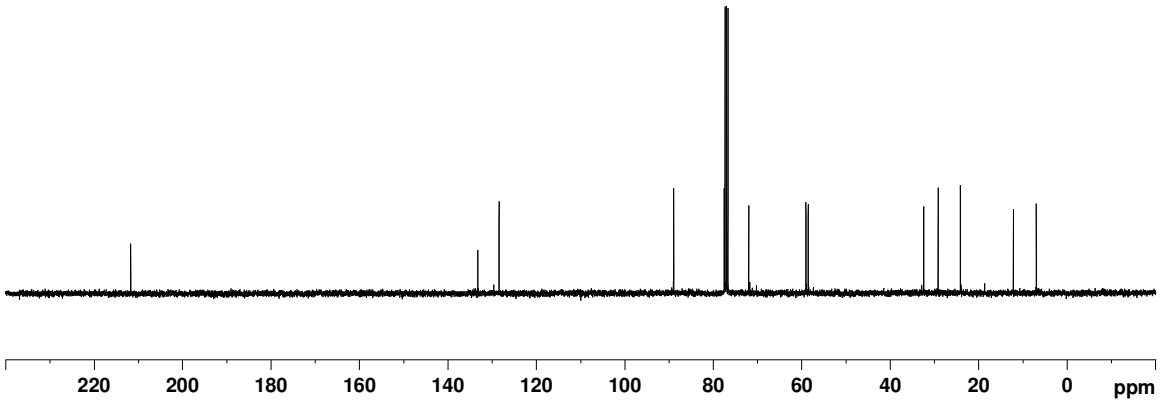


Figure A2.9 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **3.34** in $CDCl_3$

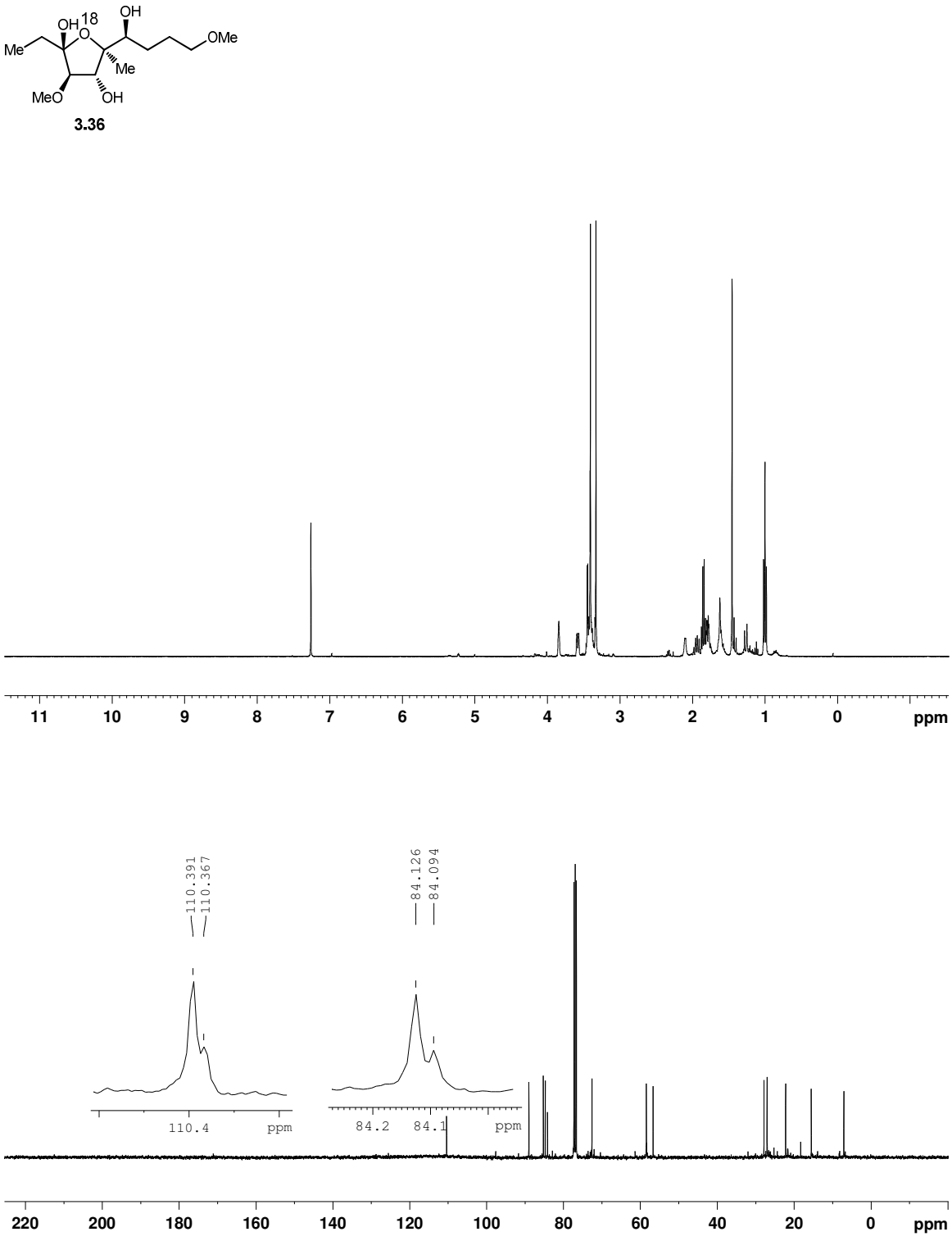


Figure A2.10 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of ^{18}O **3.36** in $CDCl_3$

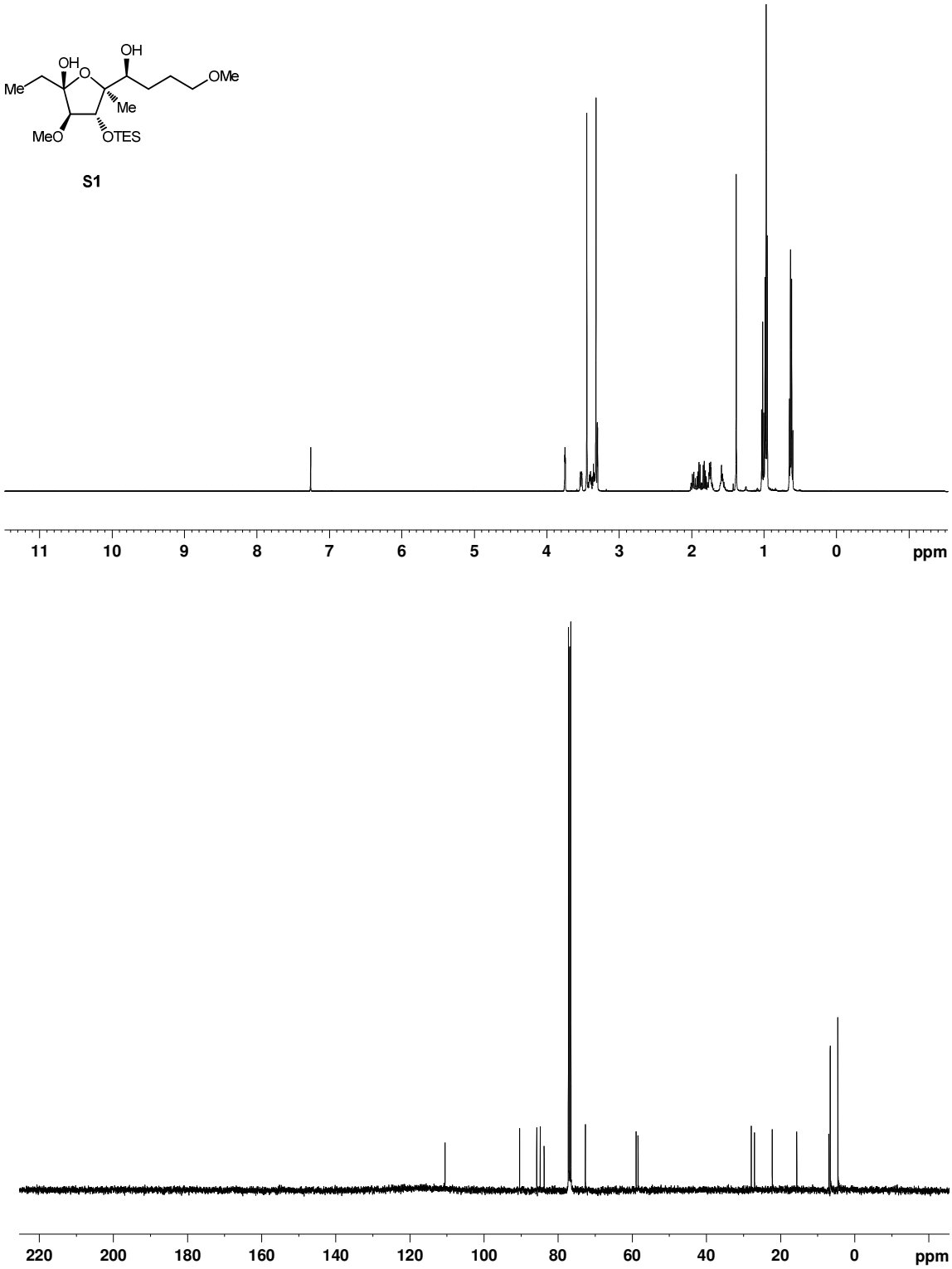


Figure A2.11 500 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **S1** in $CDCl_3$

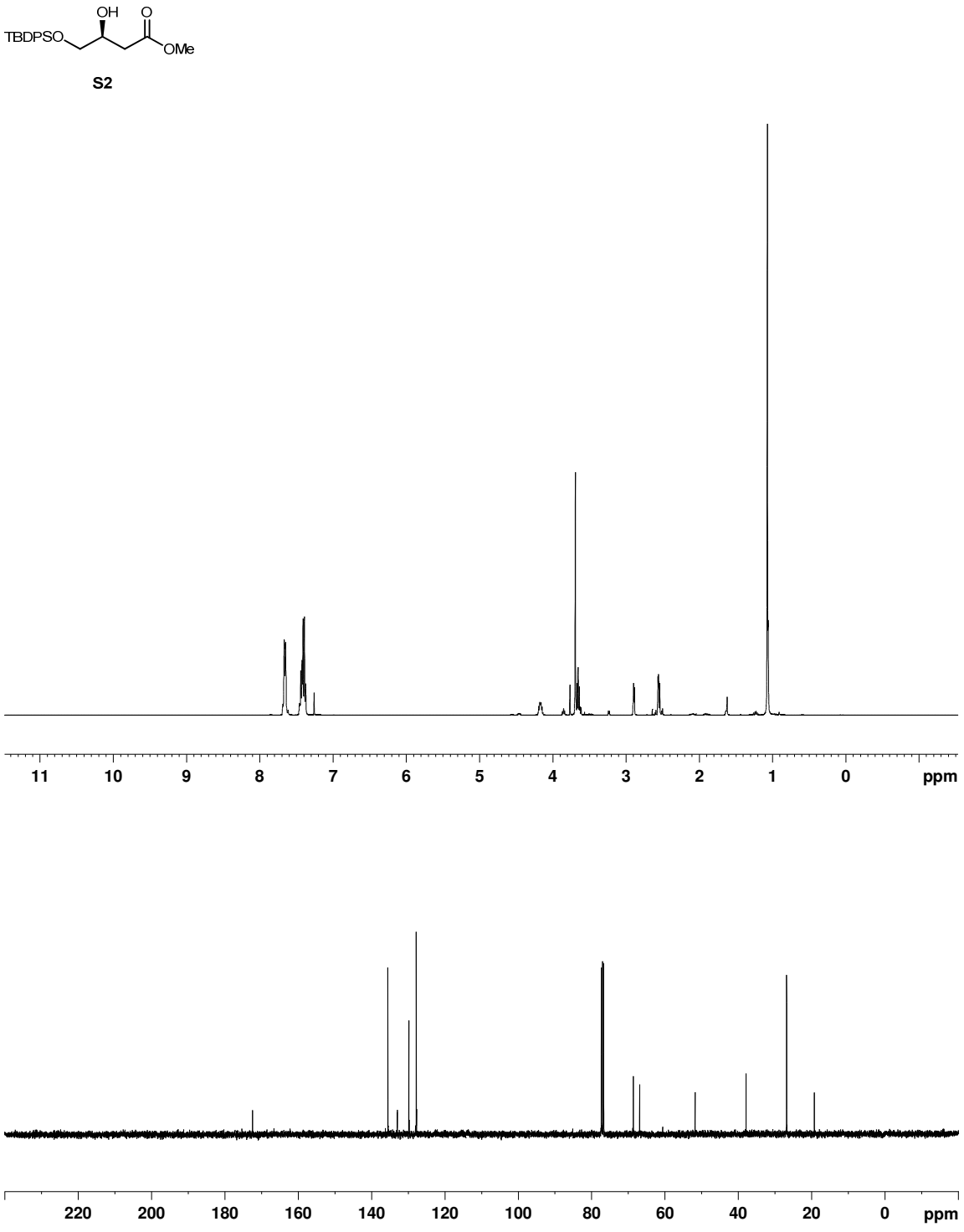
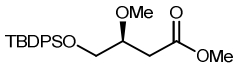


Figure A2.12 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **S2** in $CDCl_3$



3.51

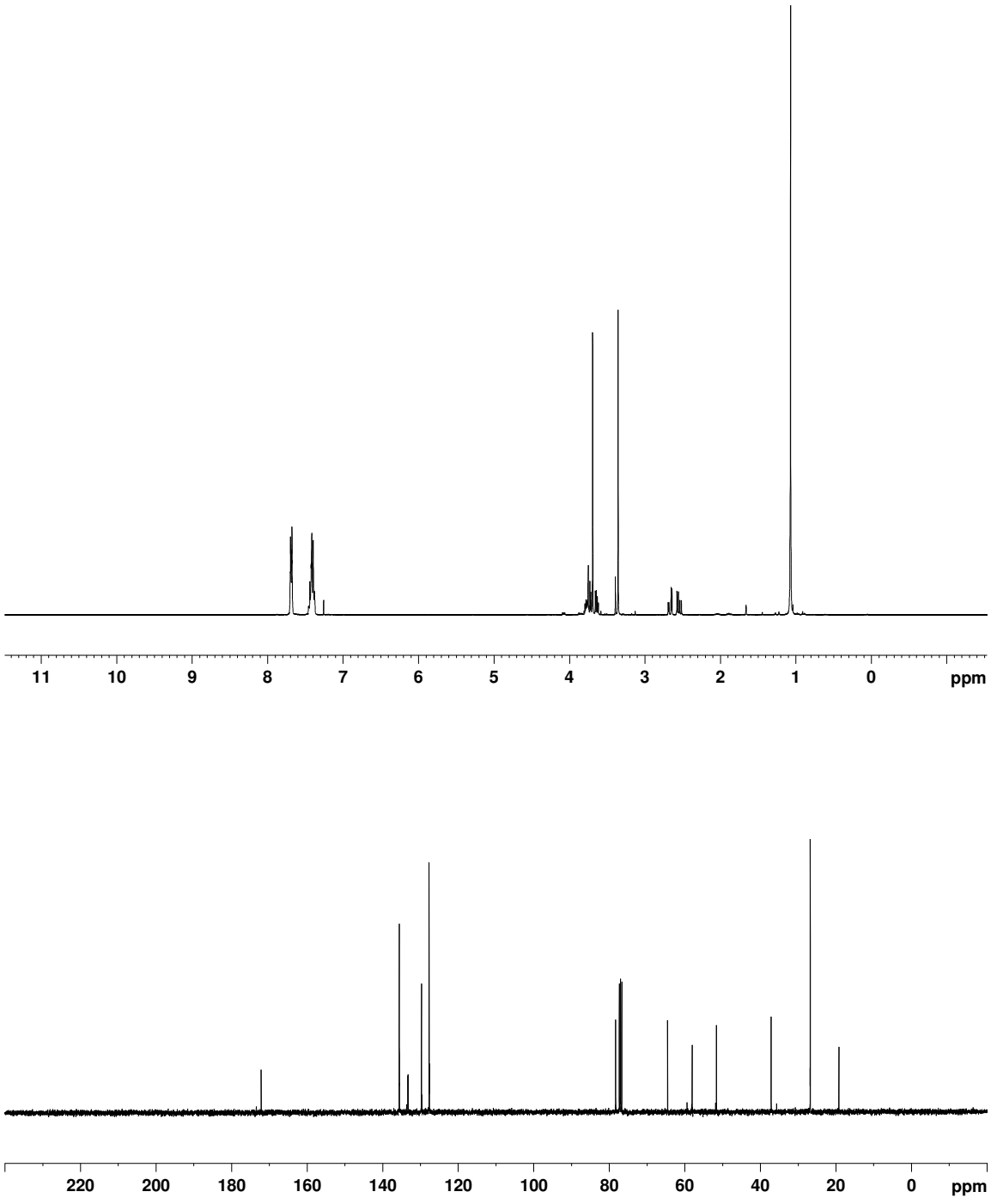


Figure A2.13 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **3.51** in $CDCl_3$

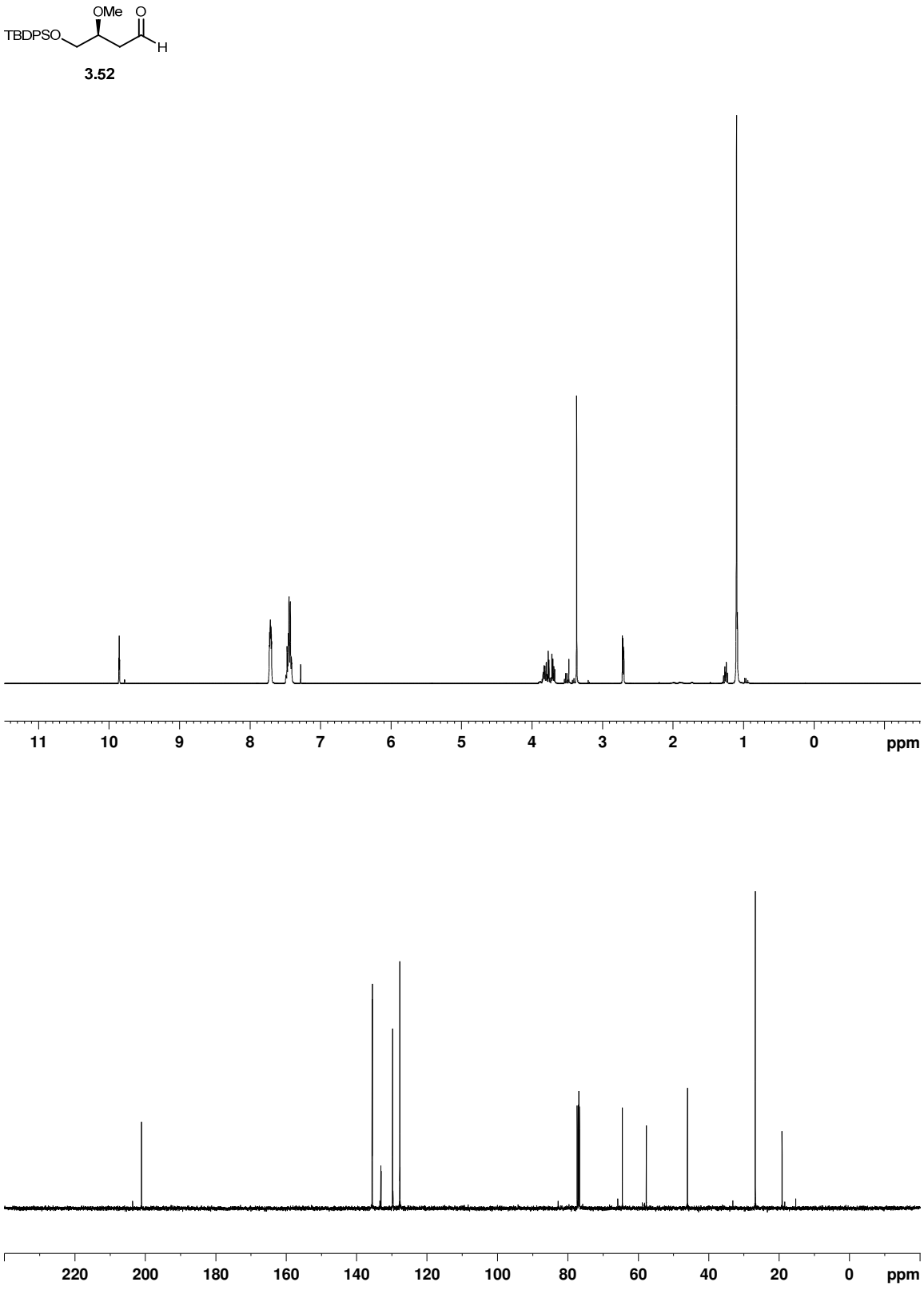


Figure A2.14 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **3.52** in $CDCl_3$

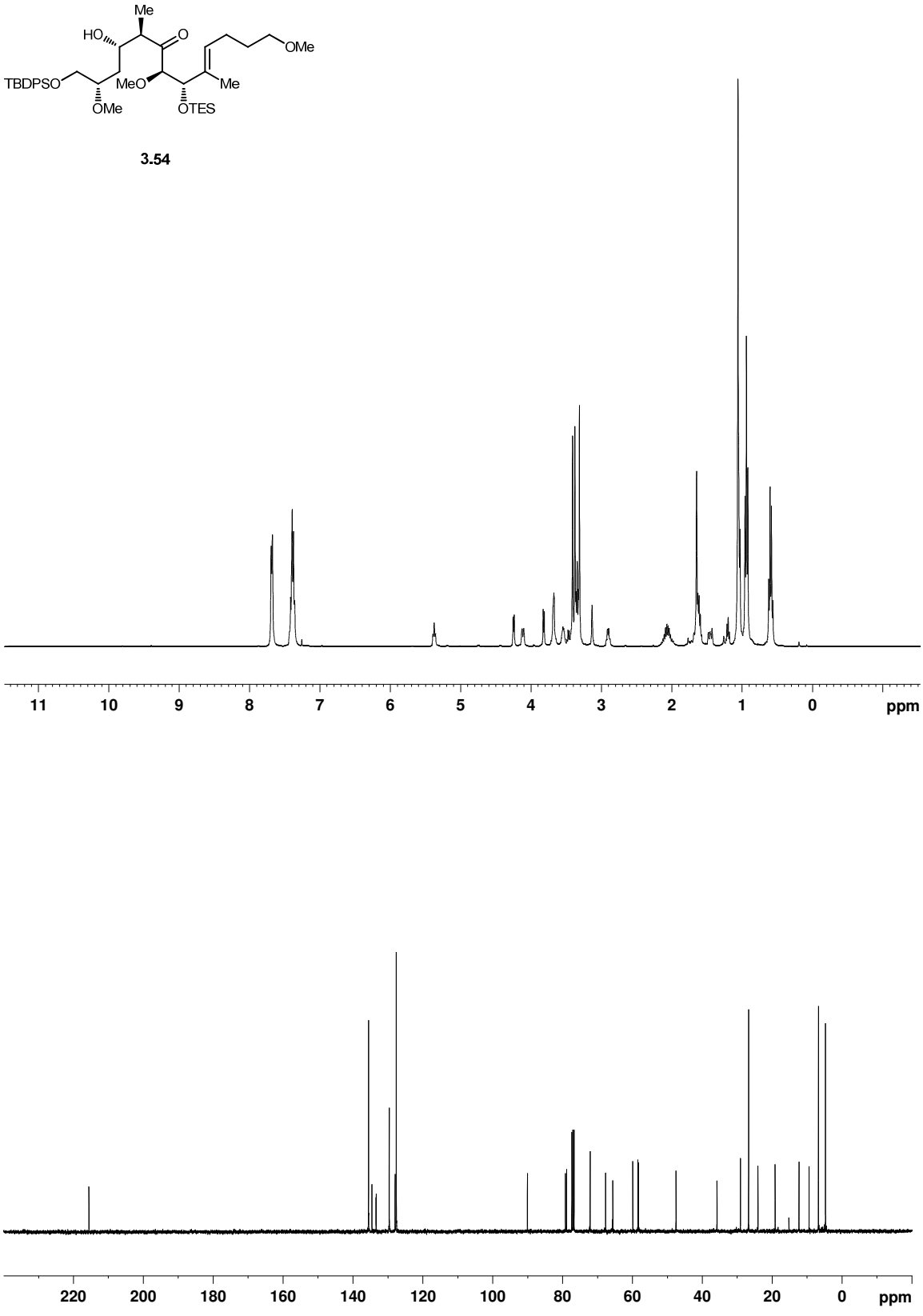


Figure A2.15 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **3.54** in $CDCl_3$

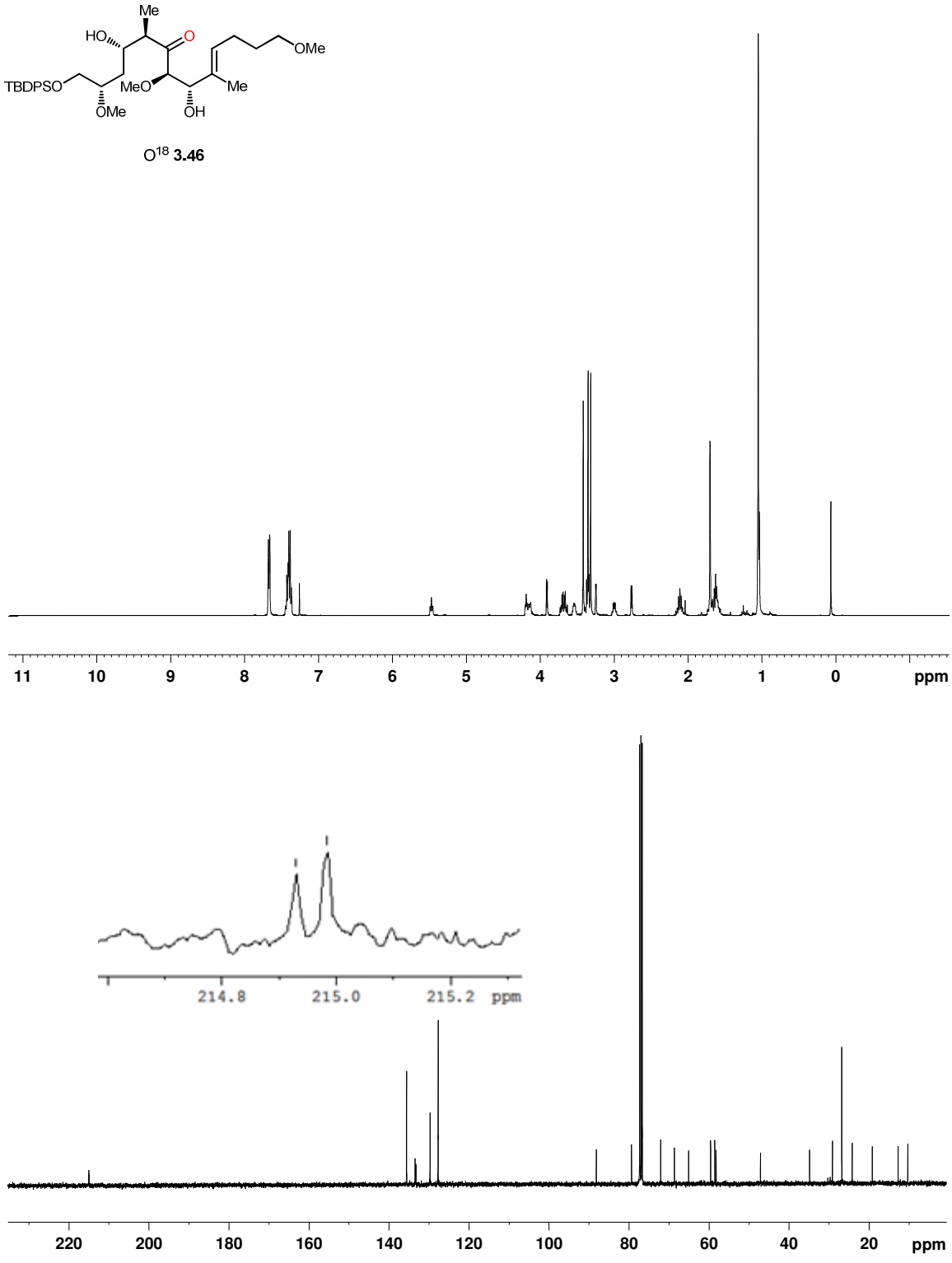


Figure A2.16 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of ^{18}O-**3.46** in $CDCl_3$

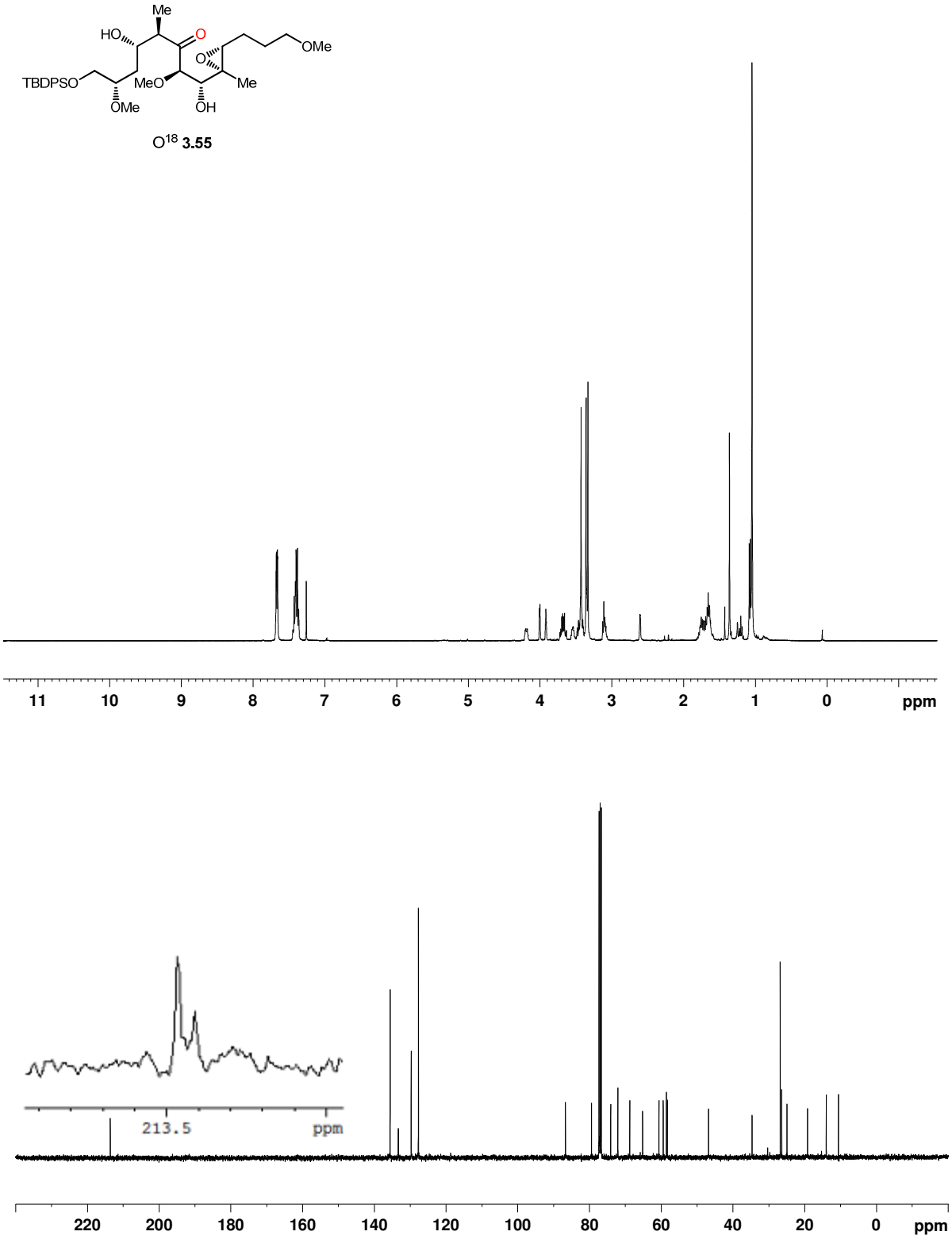
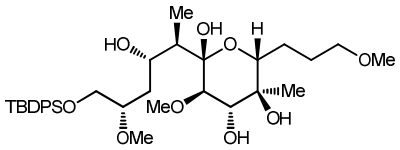


Figure A2.17 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of ^{18}O-**3.55** in $CDCl_3$



3.56

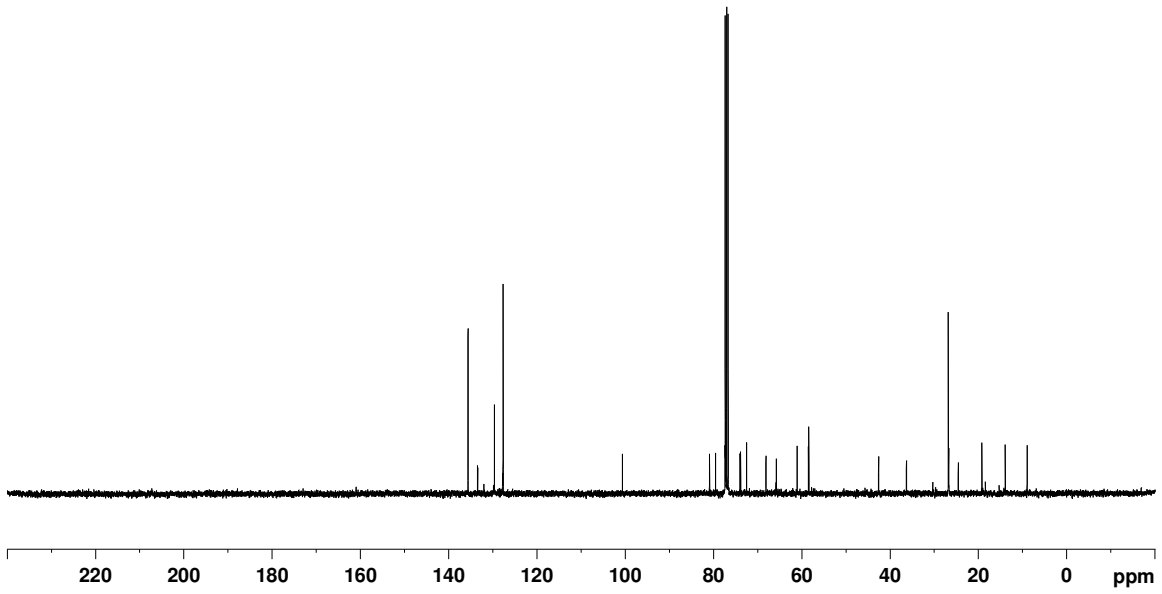


Figure A2.18 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **3.56** in $CDCl_3$

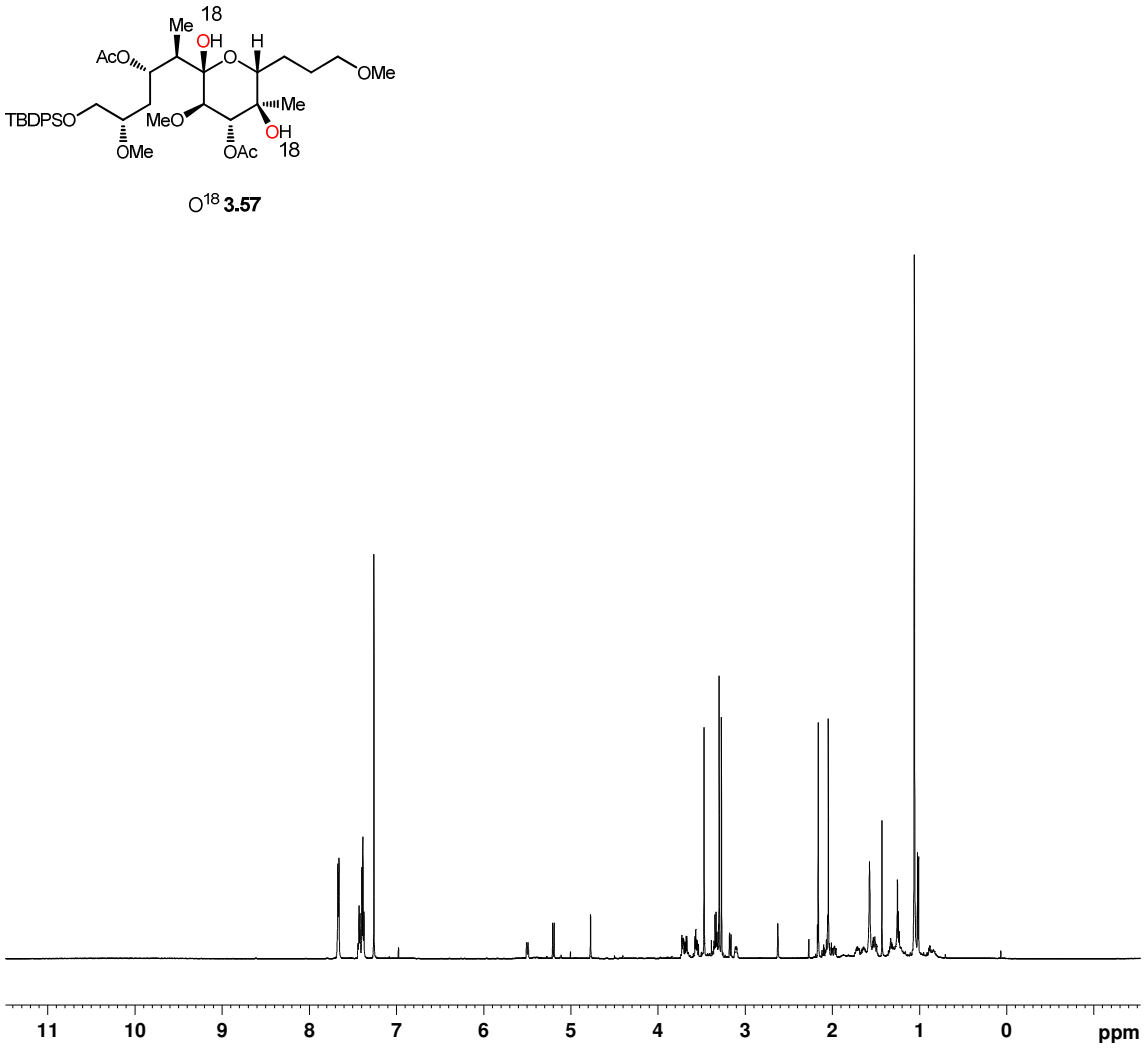


Figure A2.19600 MHz ^{1}H-NMR spectrum of ^{18}O-**3.57**in $CDCl_3$

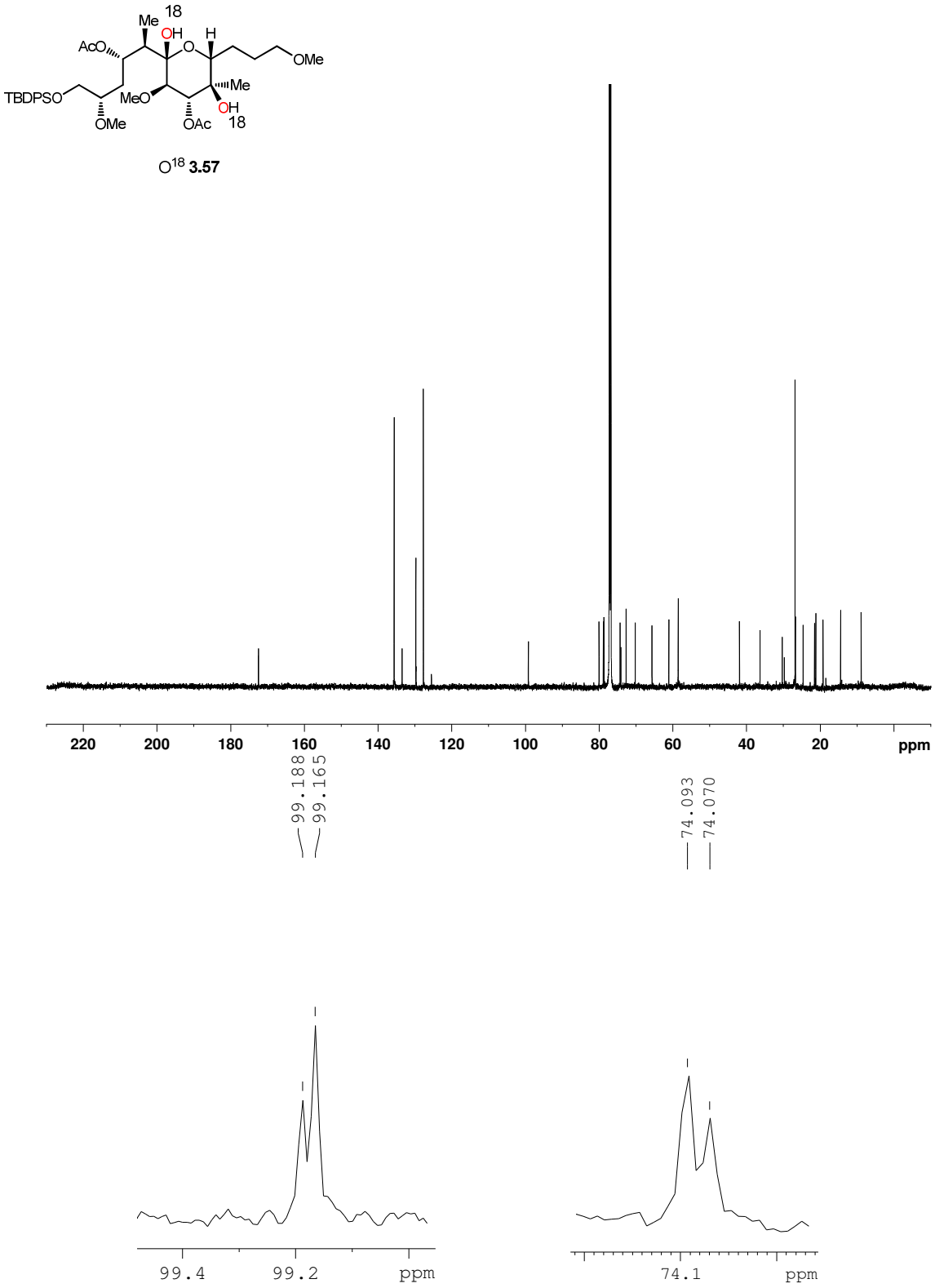


Figure A2.20 150 MHz ^{13}C-NMR spectrum of ^{18}O-**3.57** in $CDCl_3$

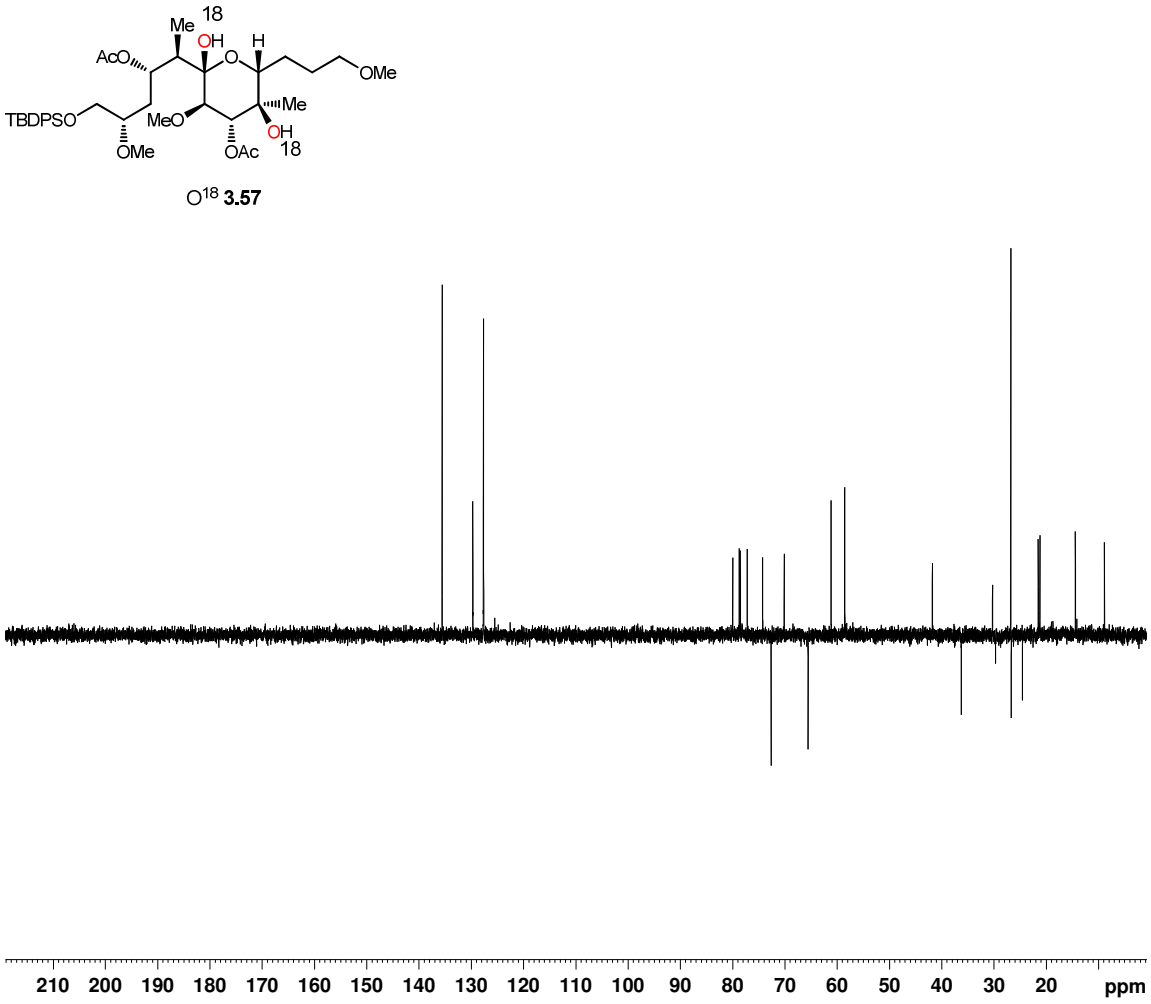
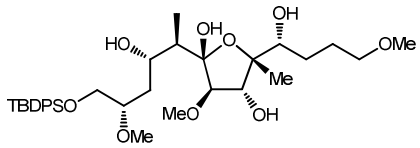
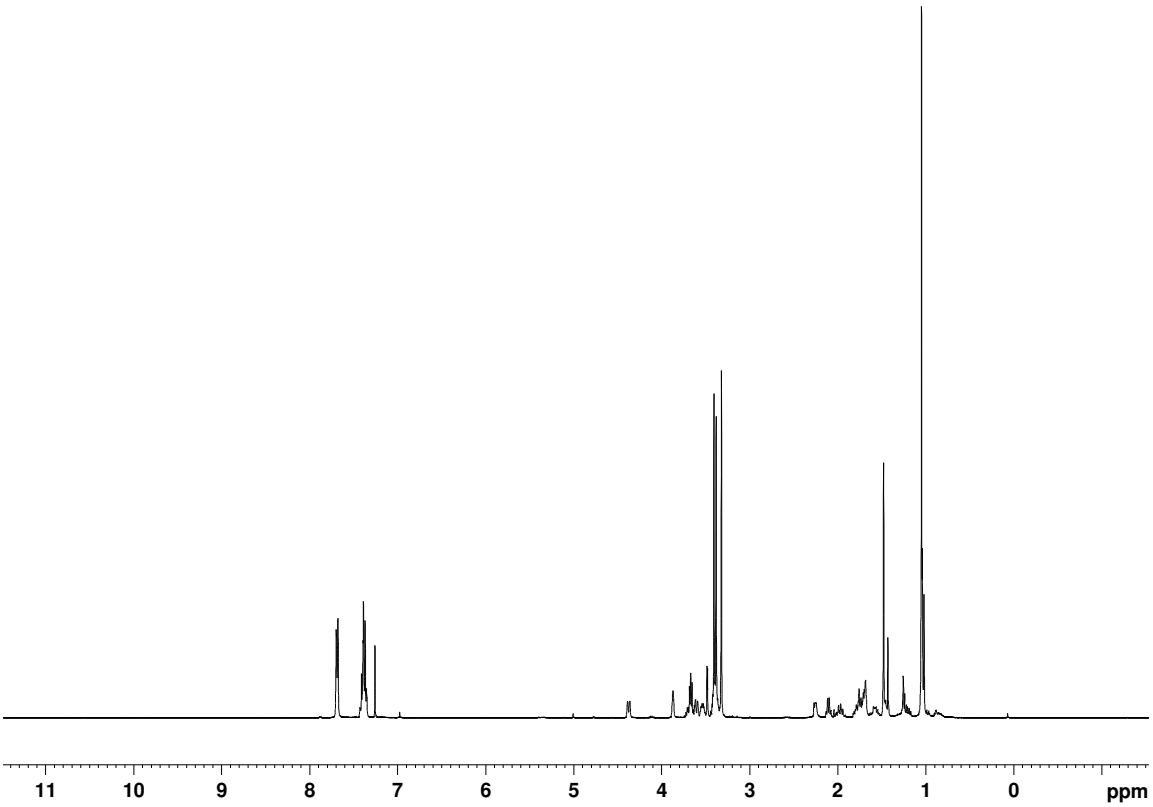


Figure A2.21 150 MHz ^{13}C-135 NMR spectrum of ^{18}O-**3.57** in $CDCl_3$



3.59



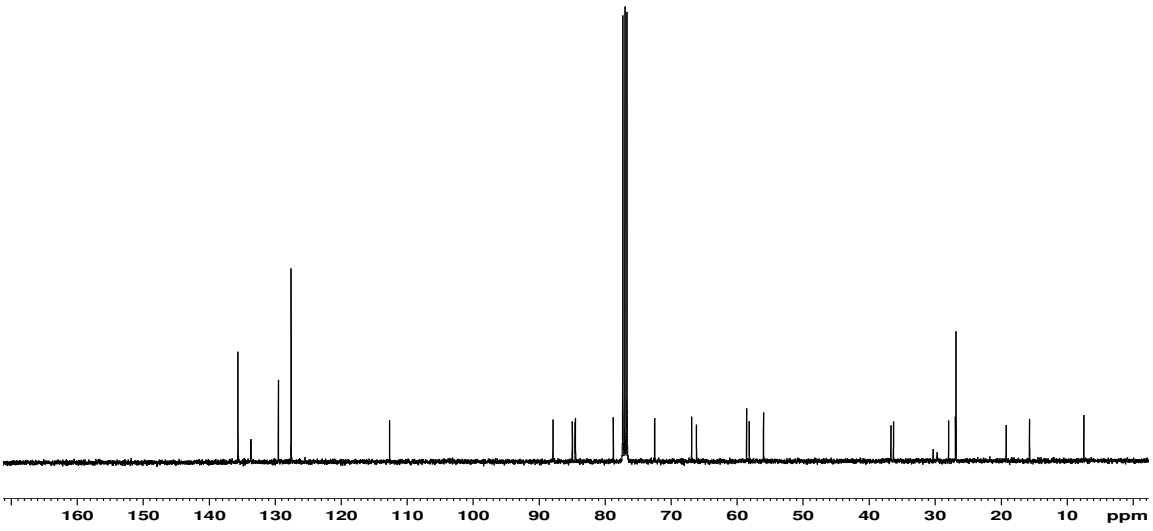


Figure A2.22 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **3.59** in $CDCl_3$

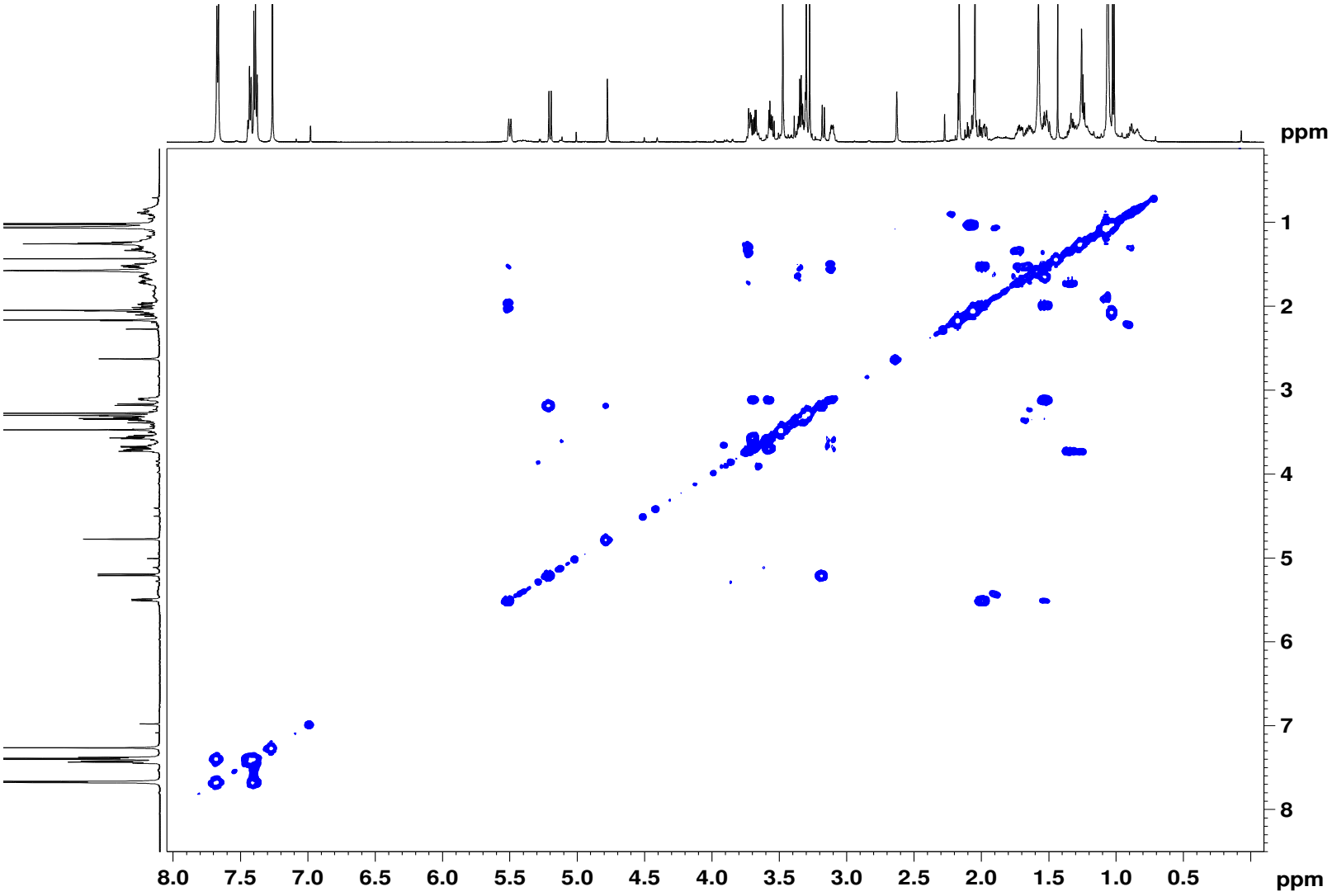


Figure A2.23 COSY Spectrum 600 MHz NMR of ^{18}**O-3.57** in $CDCl_3$

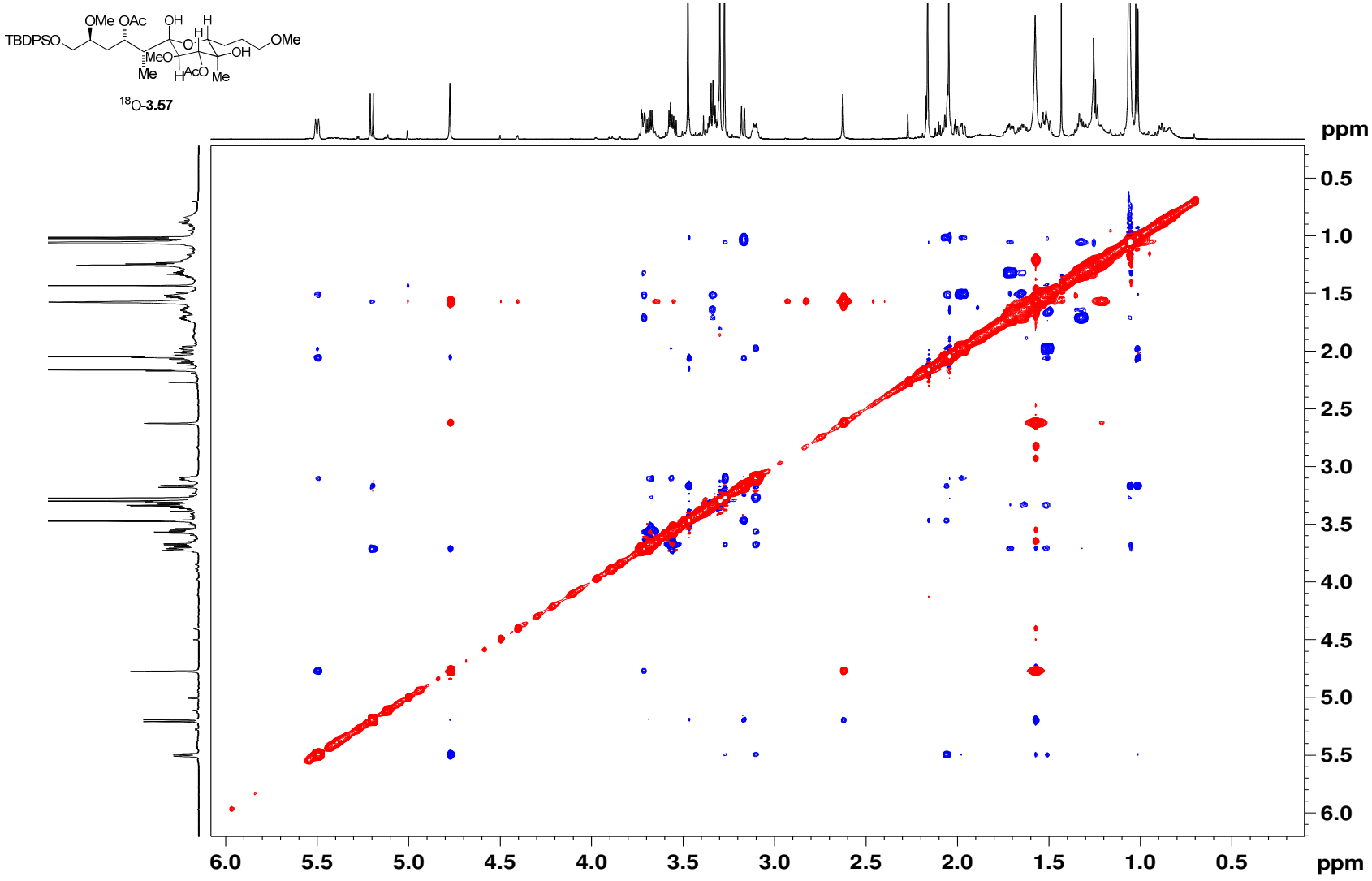


Figure A2.24 NOESY Spectrum 600 MHz NMR of ^{18}O-**3.57** in $CDCl_3$

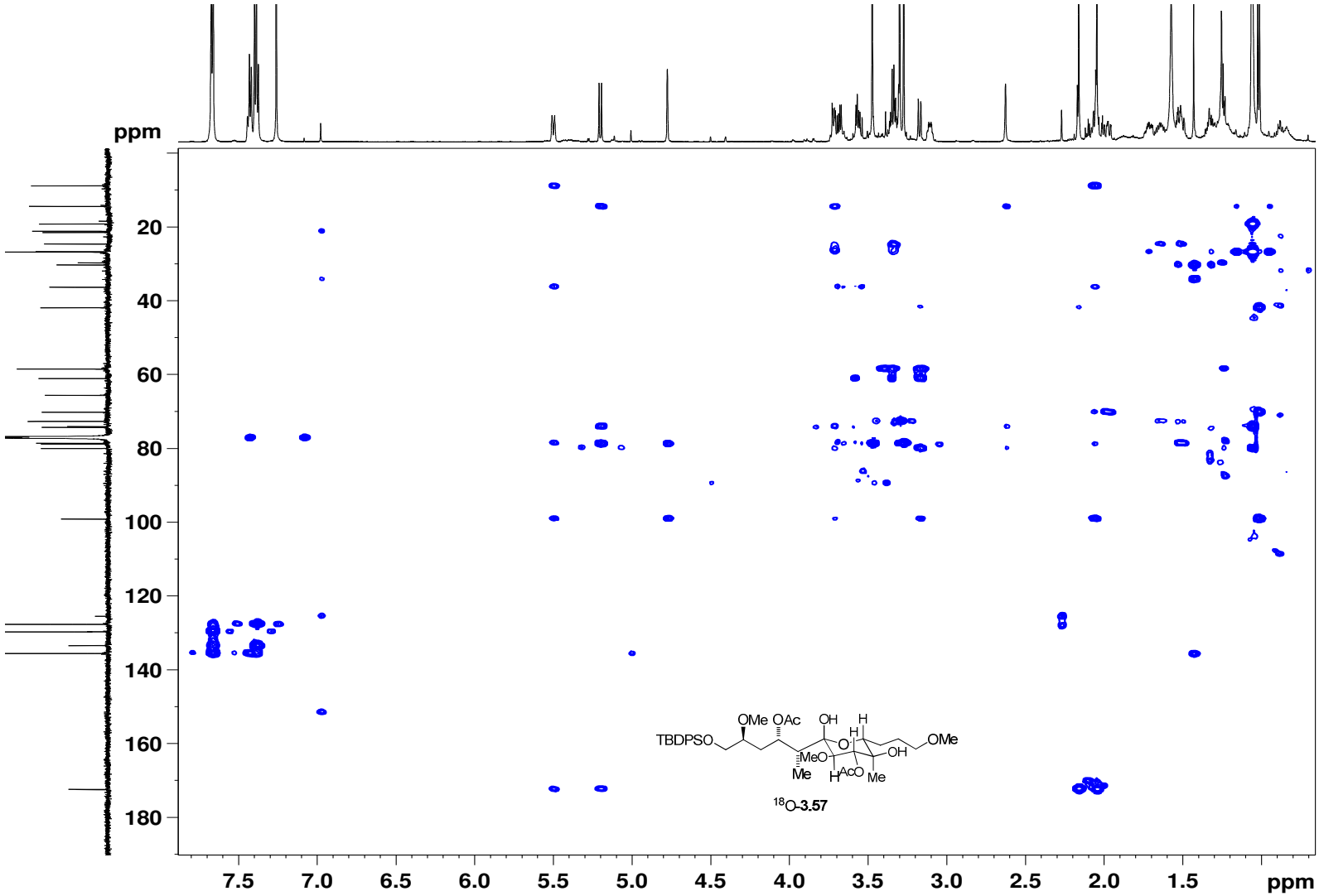


Figure A2.25 HMBC Spectrum 600 MHz NMR of **^{18}O-3.57** in $CDCl_3$

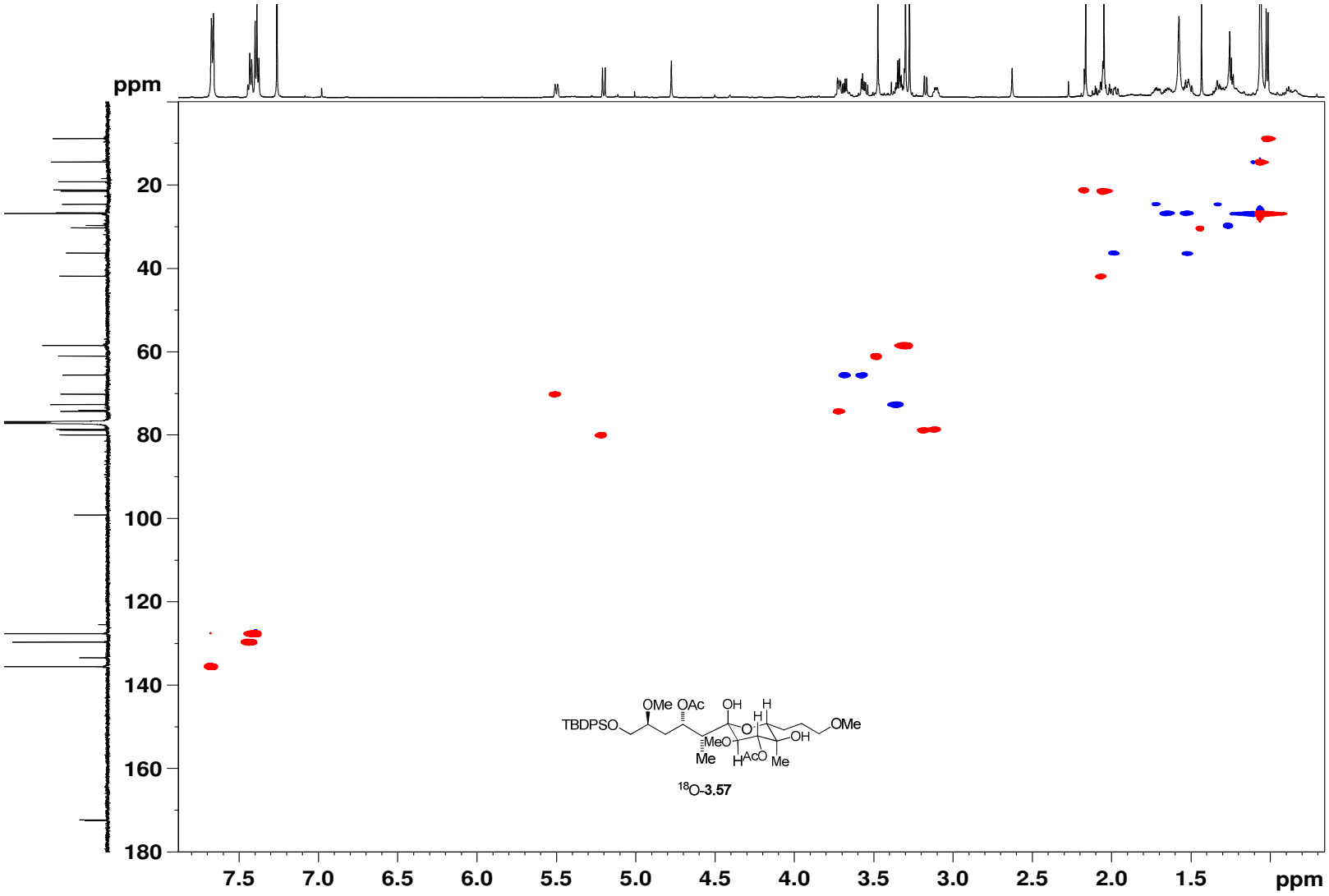


Figure A2.26 HSQC Spectrum 600 MHz NMR of **^{18}O-3.57** in $CDCl_3$

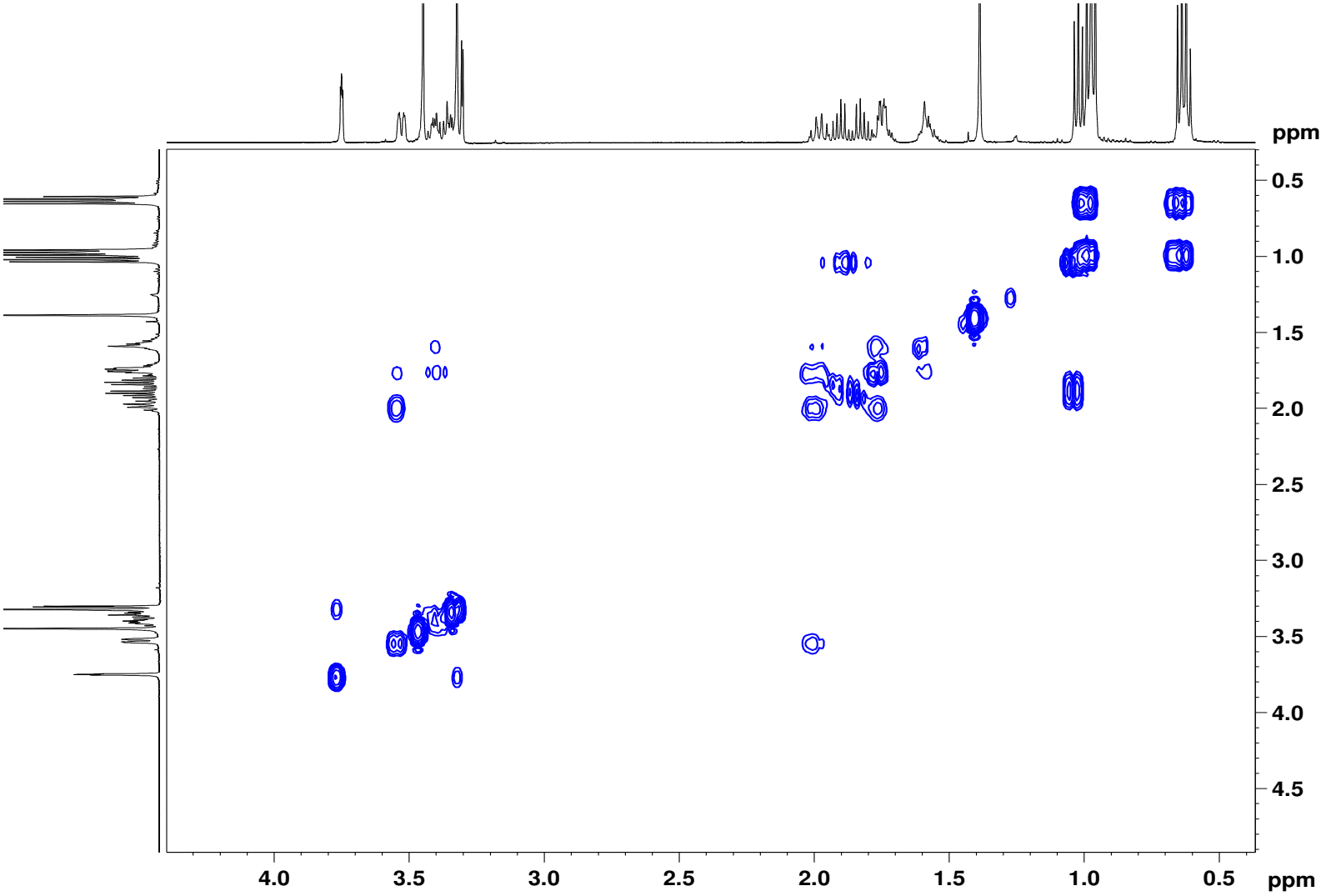


Figure A2.27 COSY Spectrum 500 MHz NMR of **S1** in $CDCl_3$

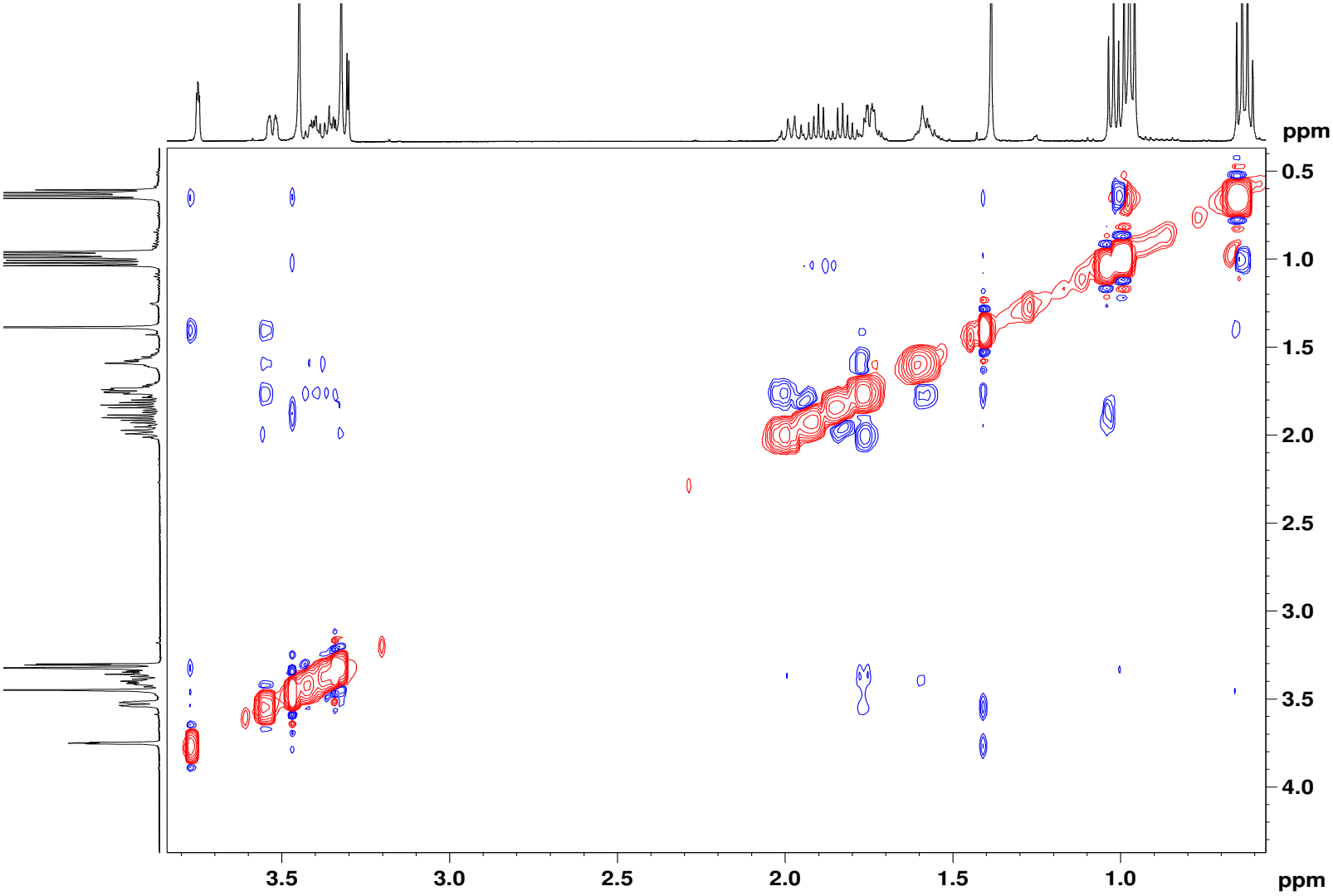


Figure A2.28 NOSY Spectrum 500 MHz NMR of **S1** in $CDCl_3$

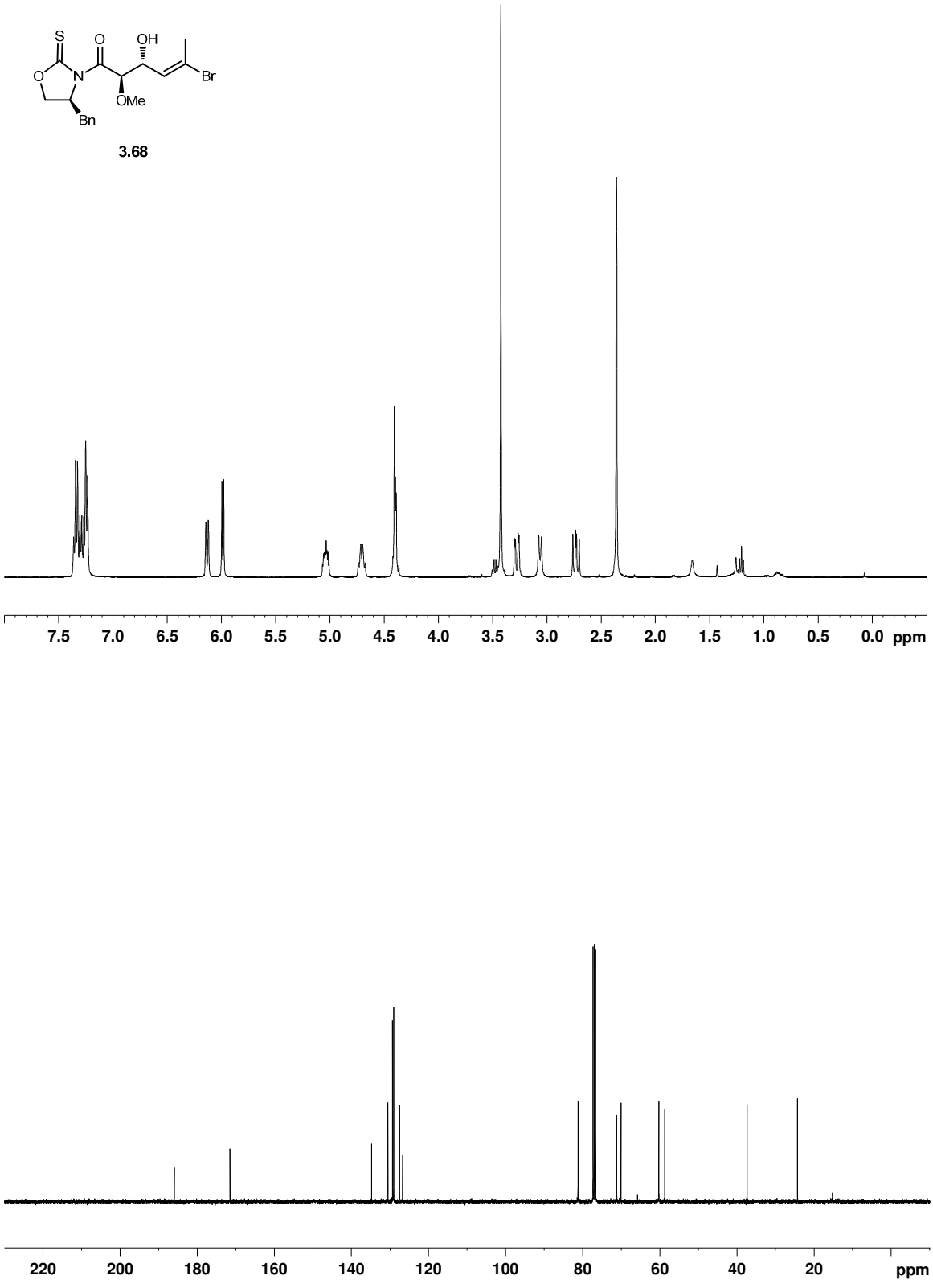


Figure A2.29 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **3.68** in $CDCl_3$

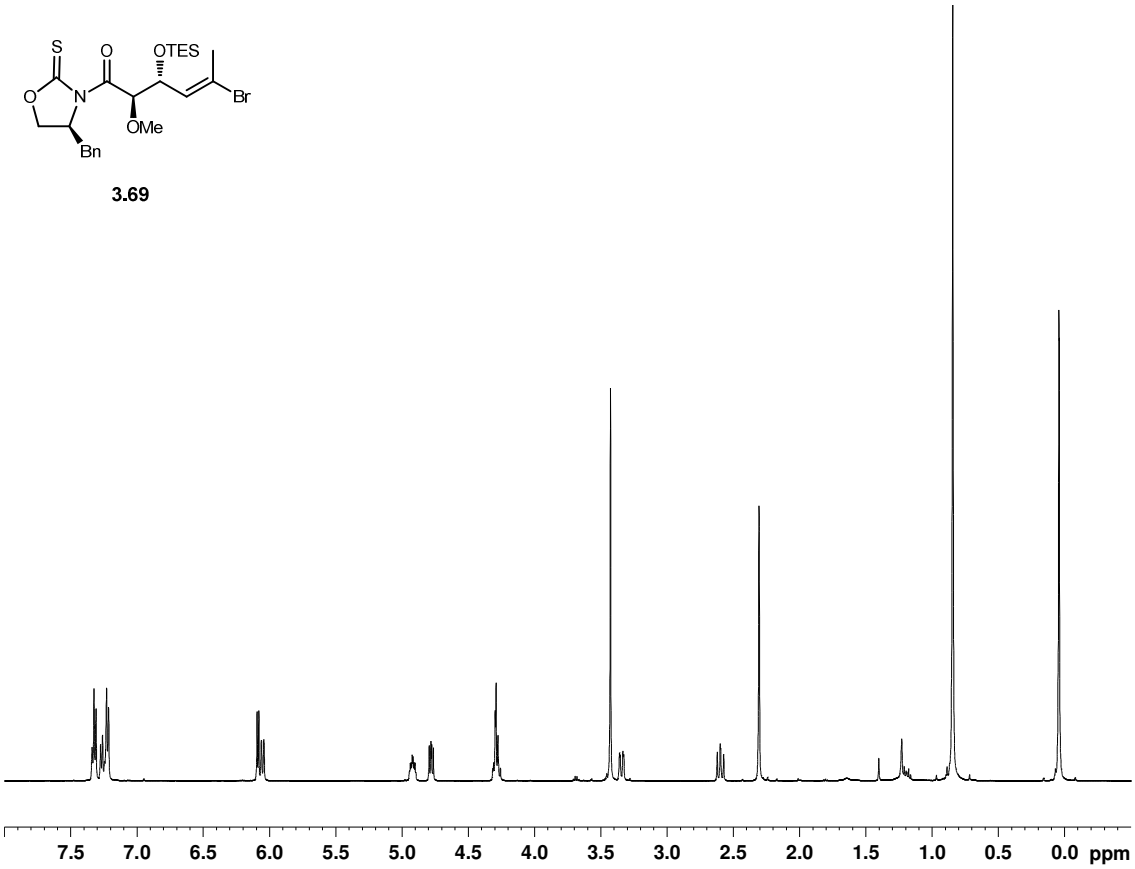


Figure A2.30 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **3.69** in $CDCl_3$

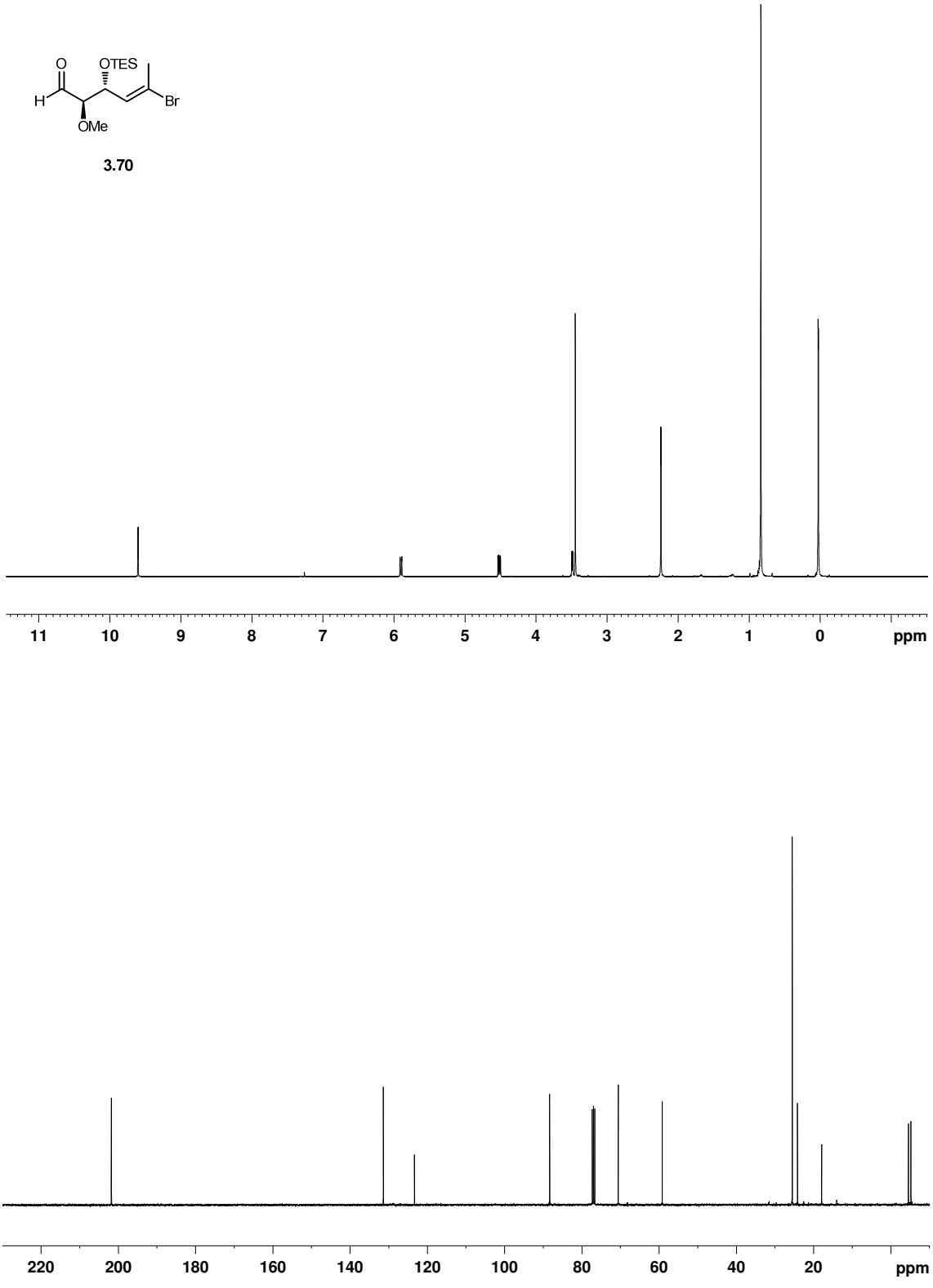


Figure A2.31 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **3.70** in $CDCl_3$

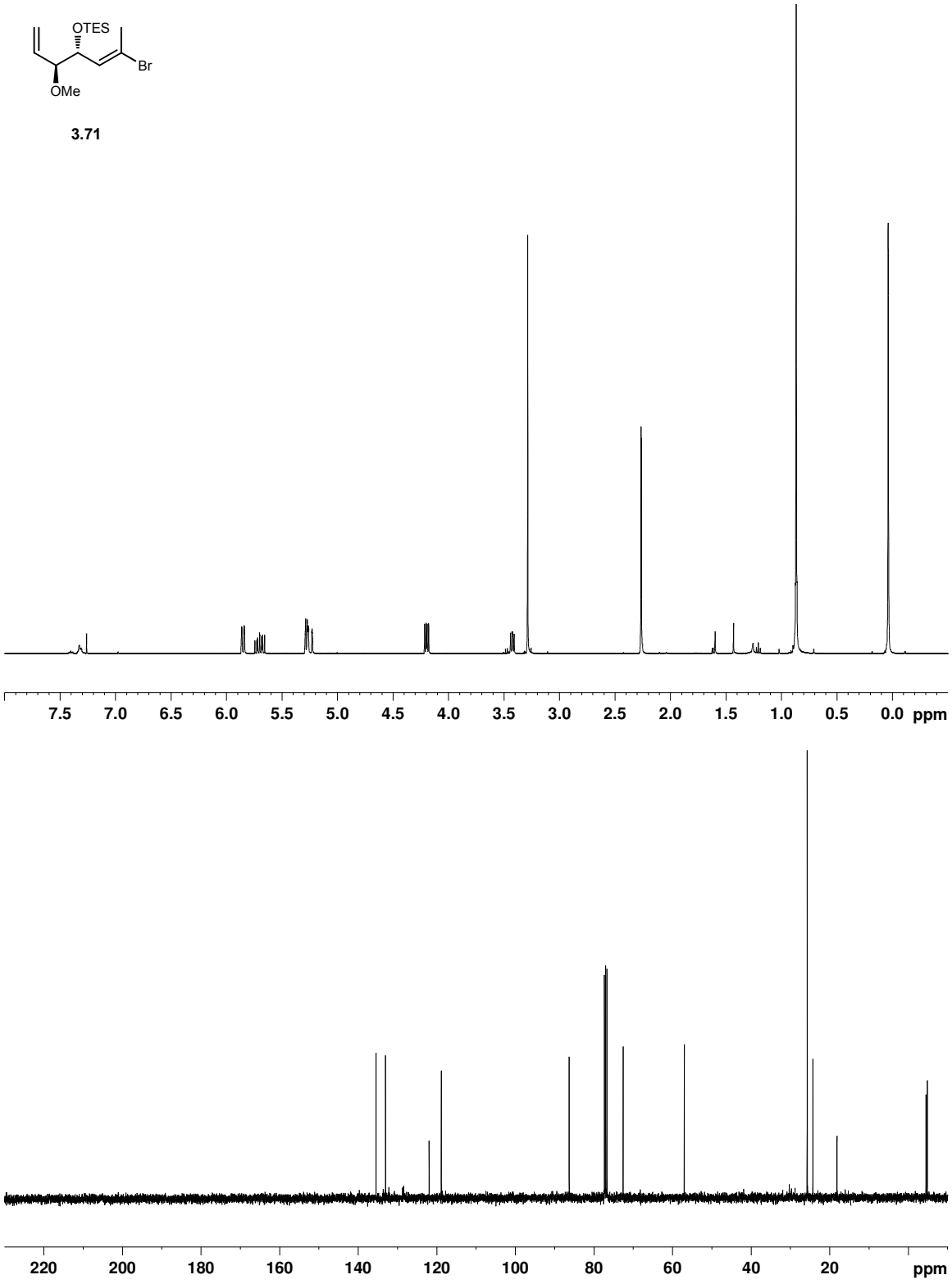


Figure A2.32 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **3.71** in $CDCl_3$

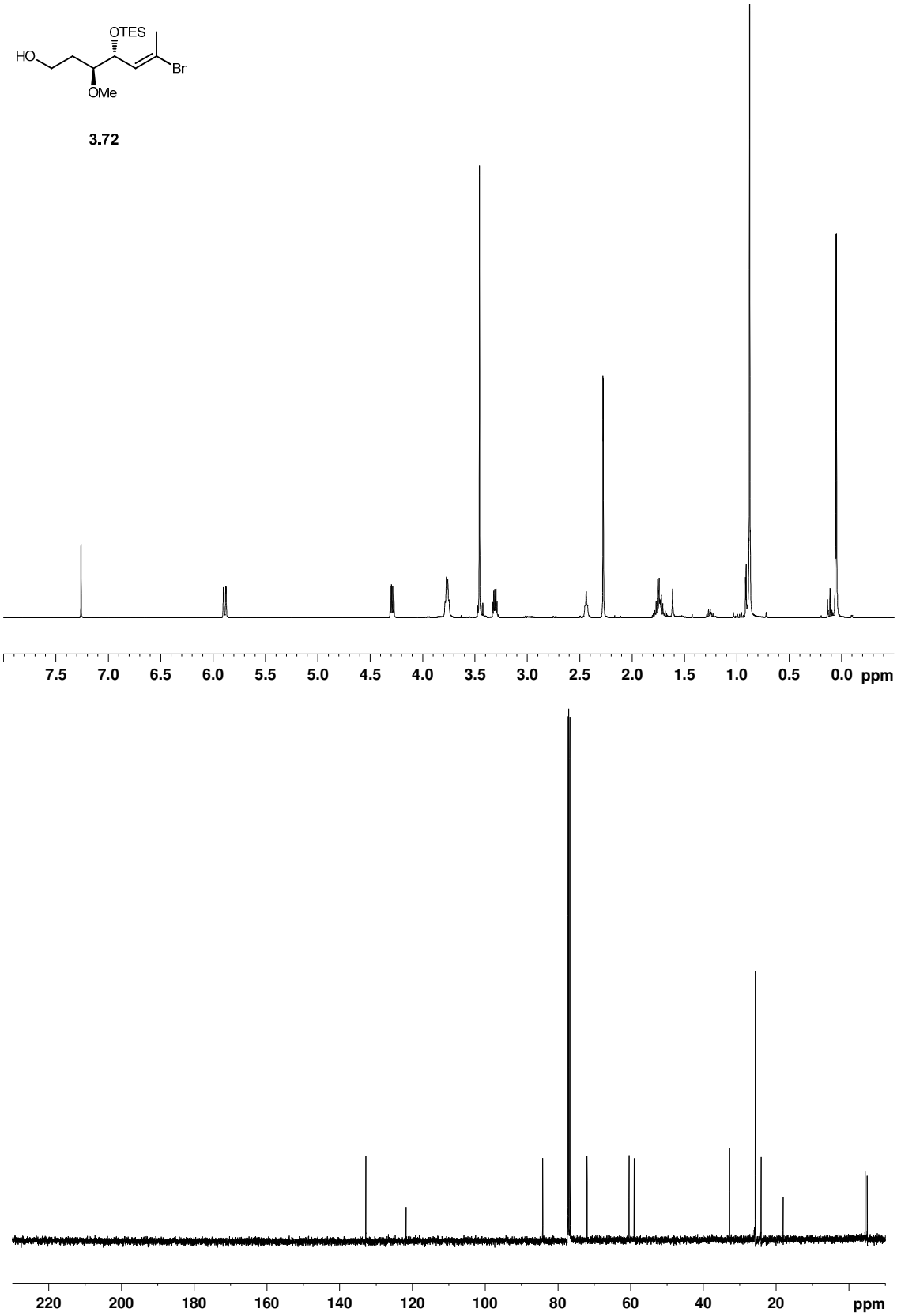


Figure A2.33 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **3.72** in $CDCl_3$

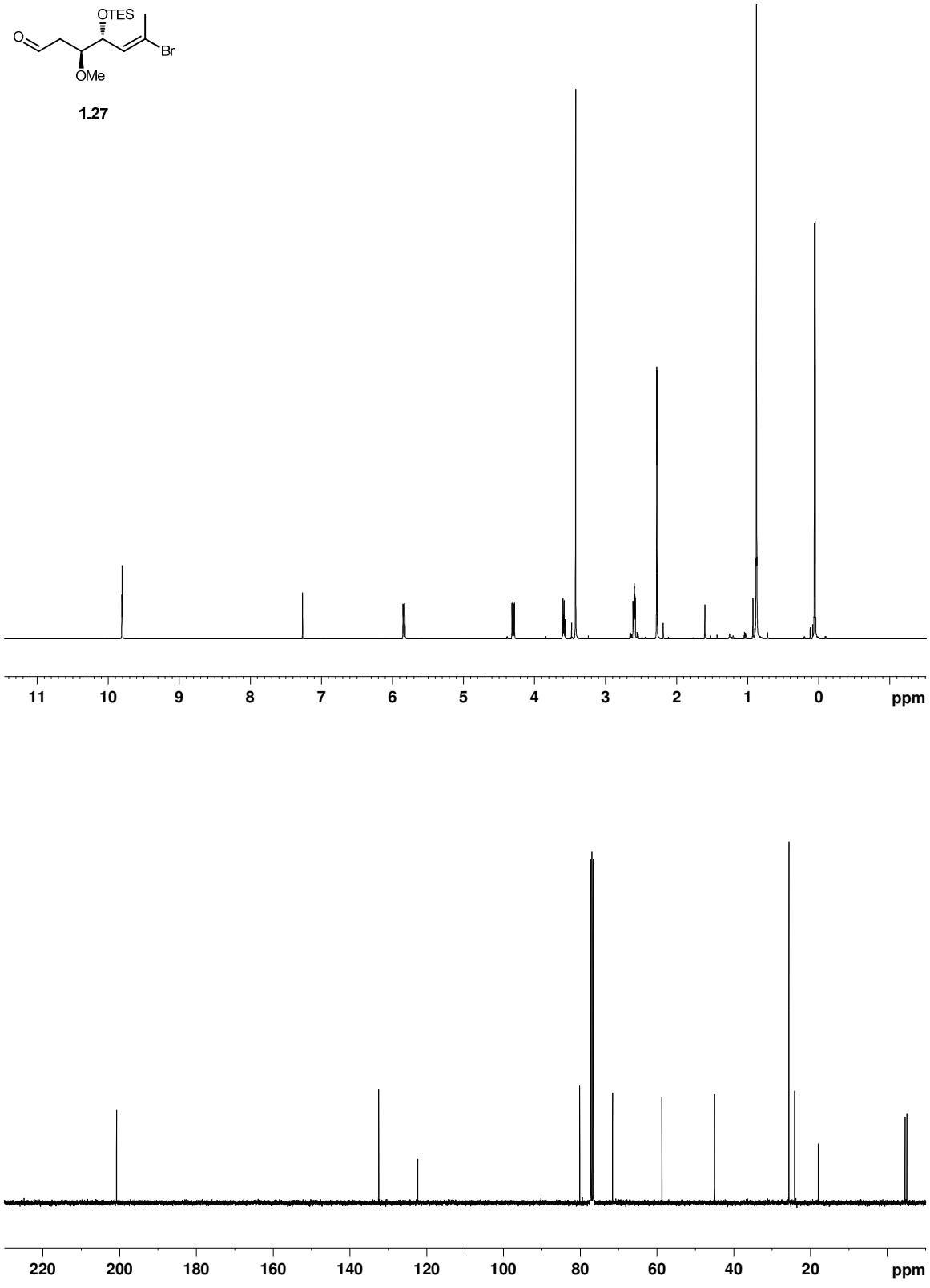


Figure A2.34 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **1.27** in $CDCl_3$

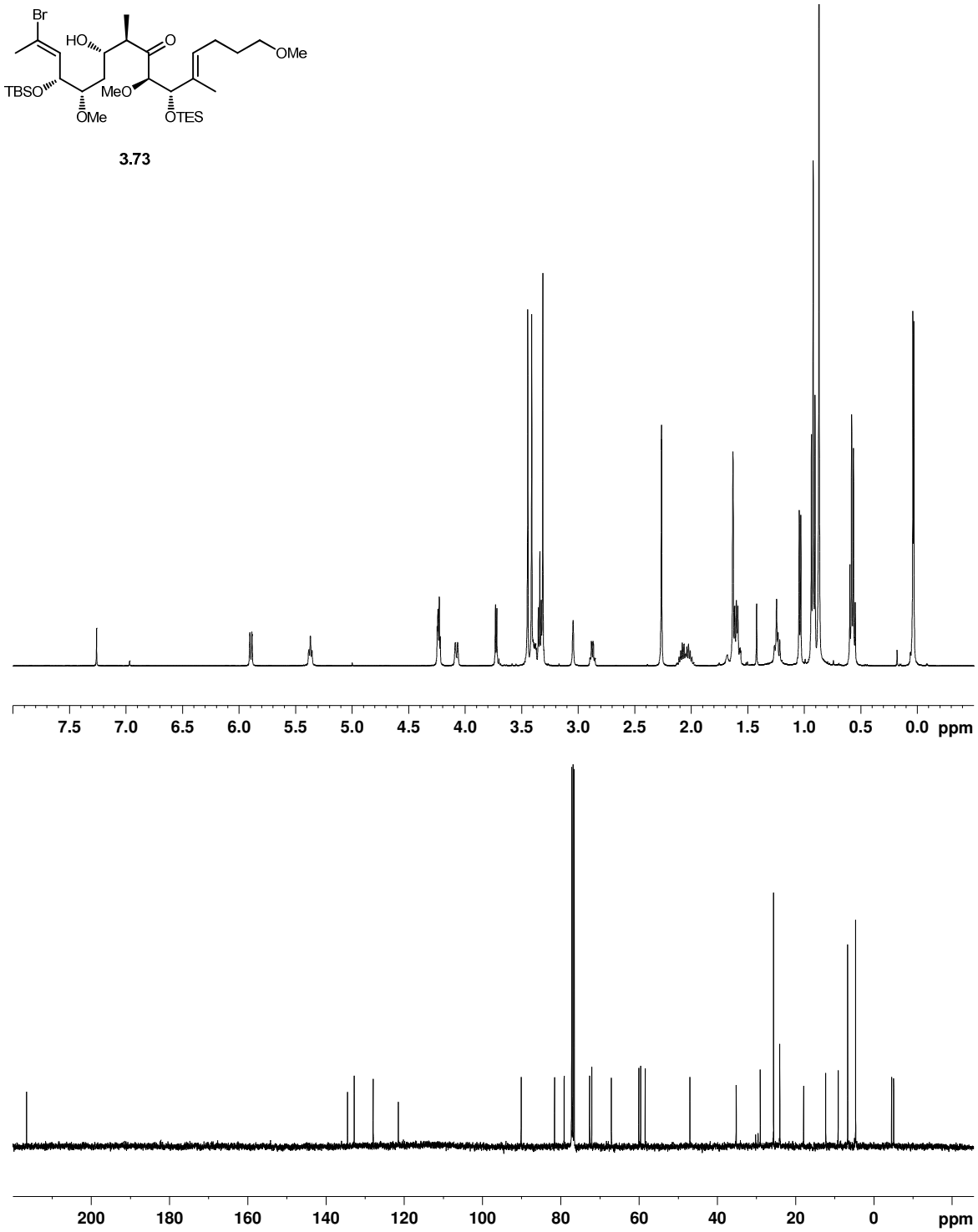


Figure A2.35 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **3.73** in $CDCl_3$

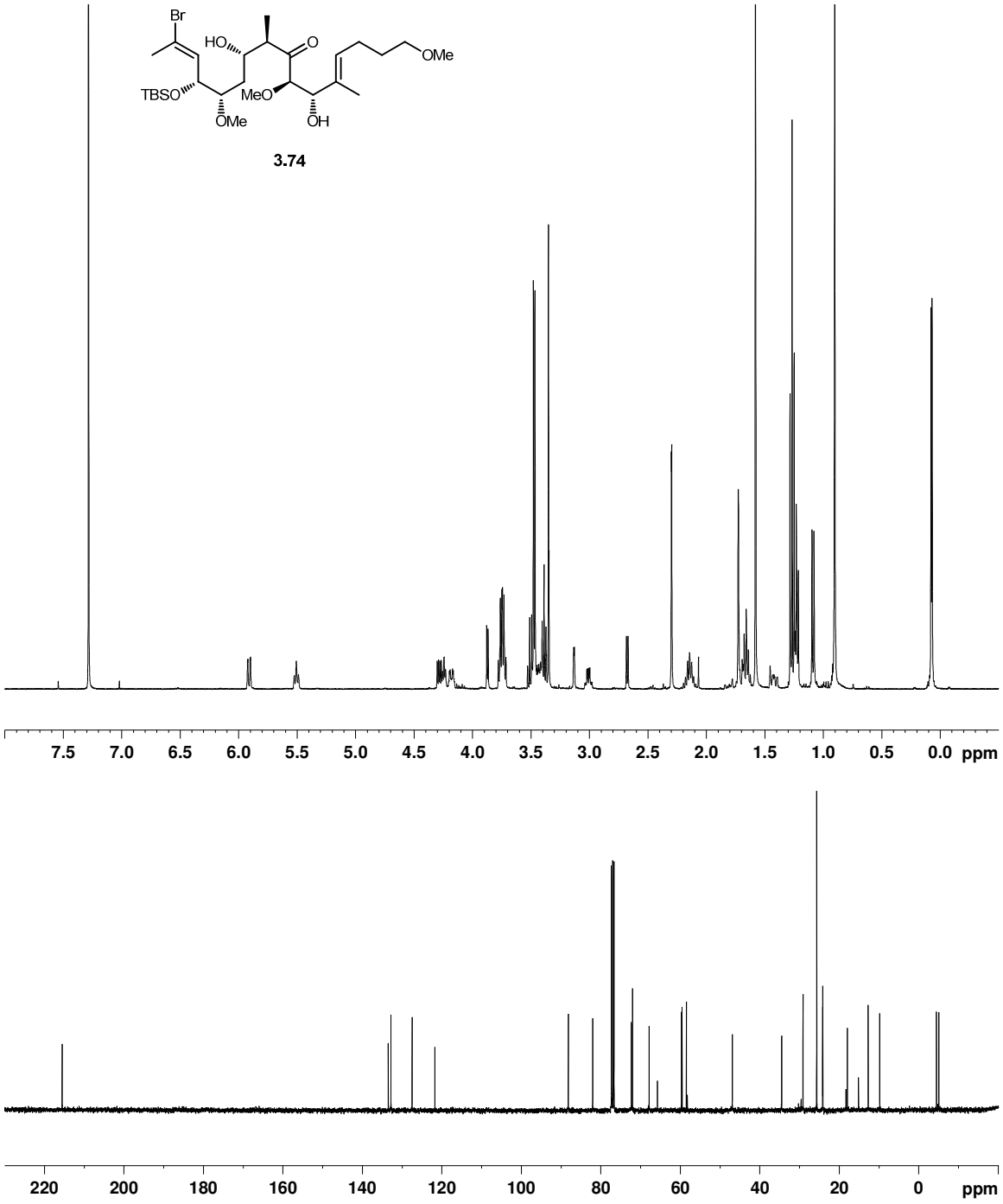


Figure A2.36 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **3.74** in $CDCl_3$

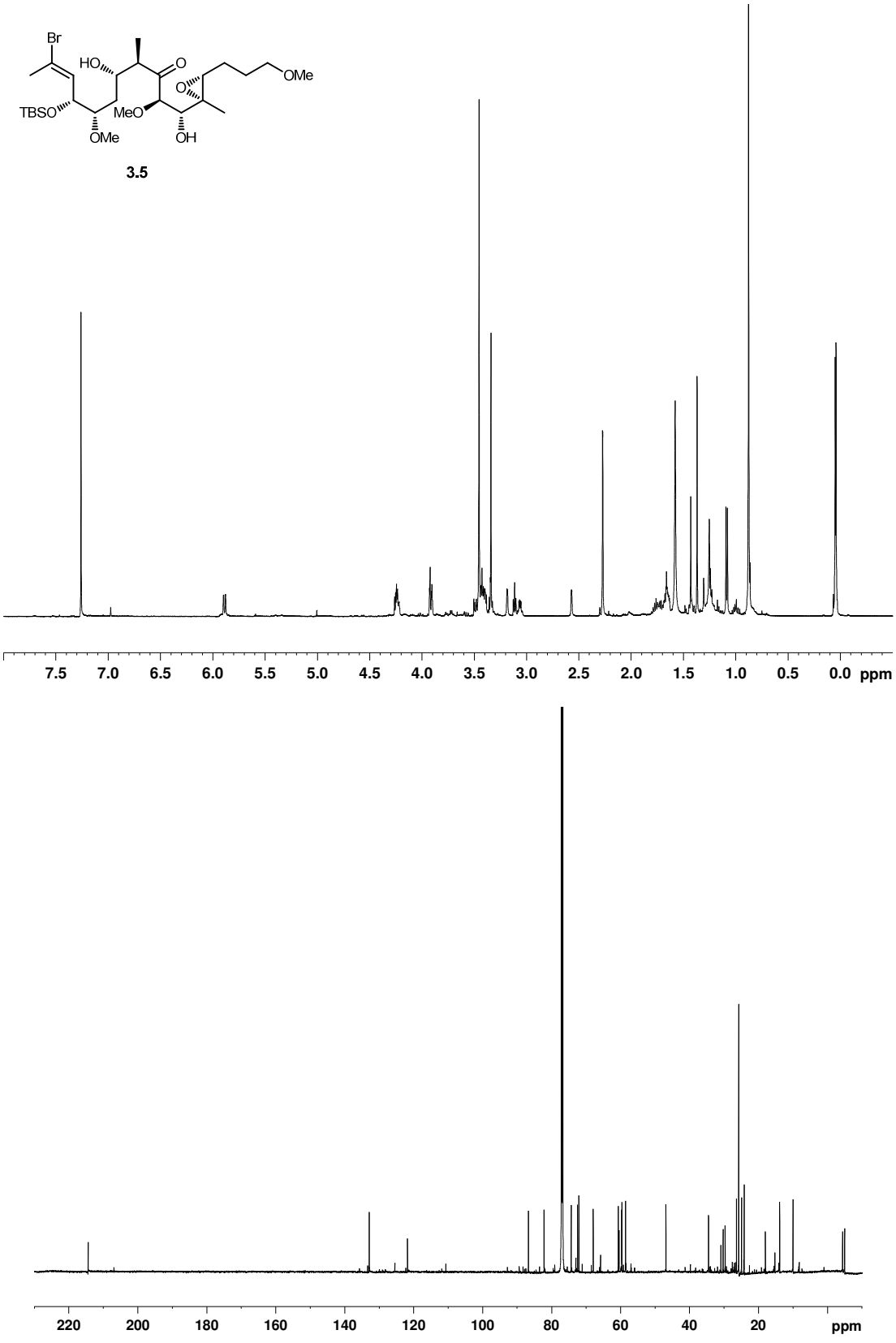


Figure A2.37 500 MHz ^{1}H-NMR and 150 MHz ^{13}C-NMR spectrum of **3.5** in $CDCl_3$

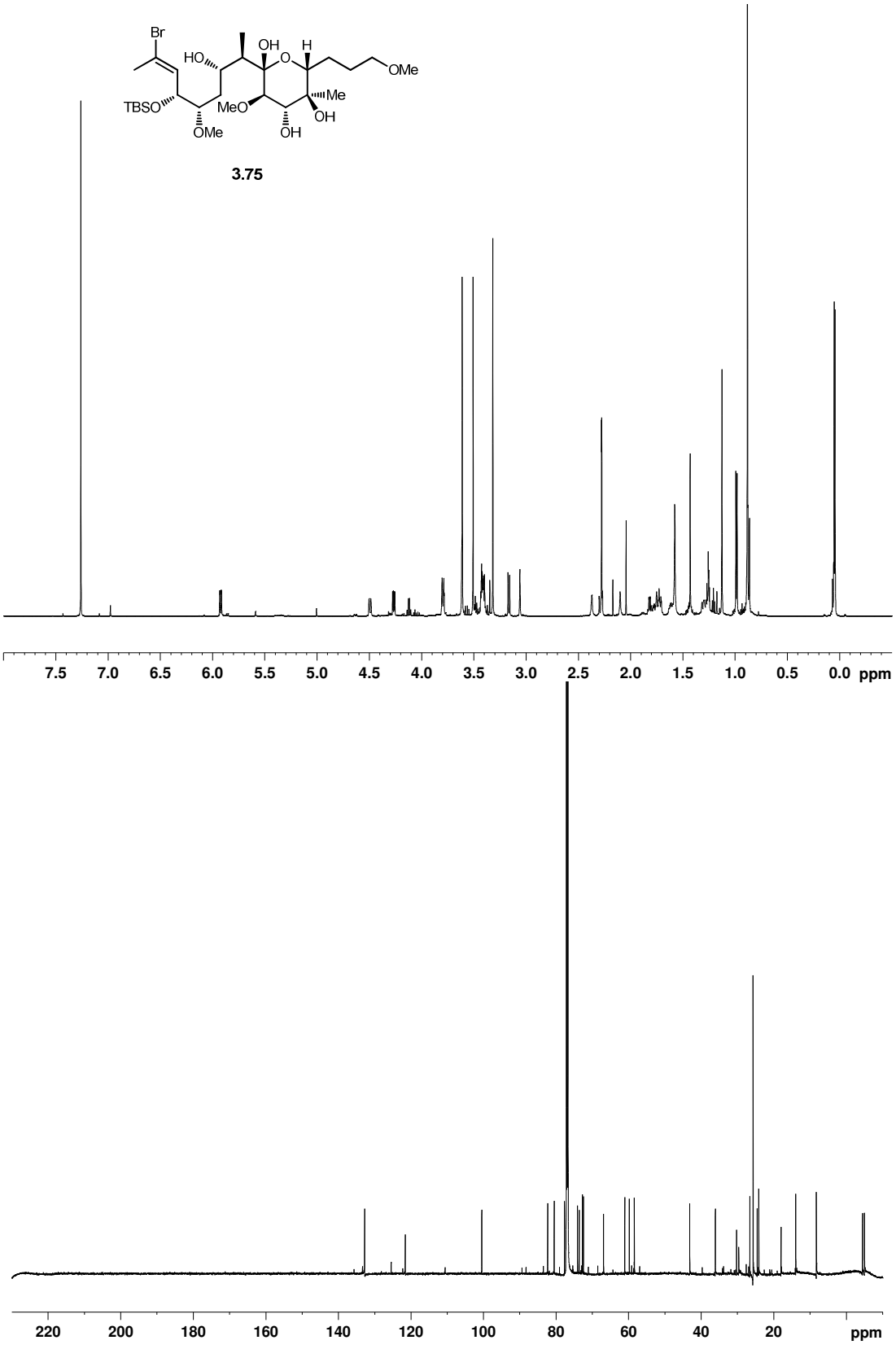


Figure A2.38 600 MHz ^{1}H-NMR and 150 MHz ^{13}C-NMR spectrum of **3.75** in $CDCl_3$

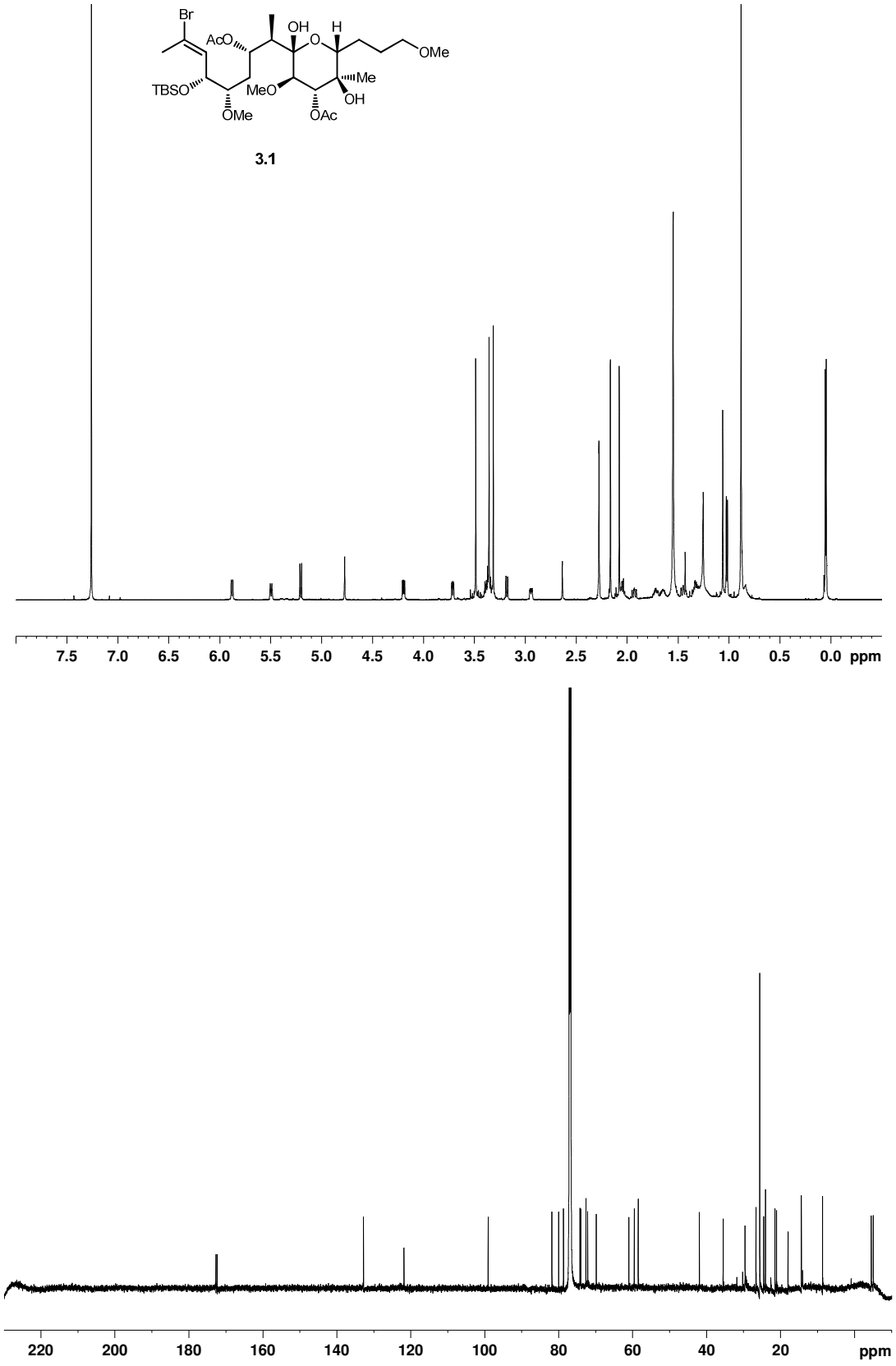


Figure A2.39 600 MHz ^{1}H-NMR and 150 MHz ^{13}C-NMR spectrum of **3.1** in $CDCl_3$

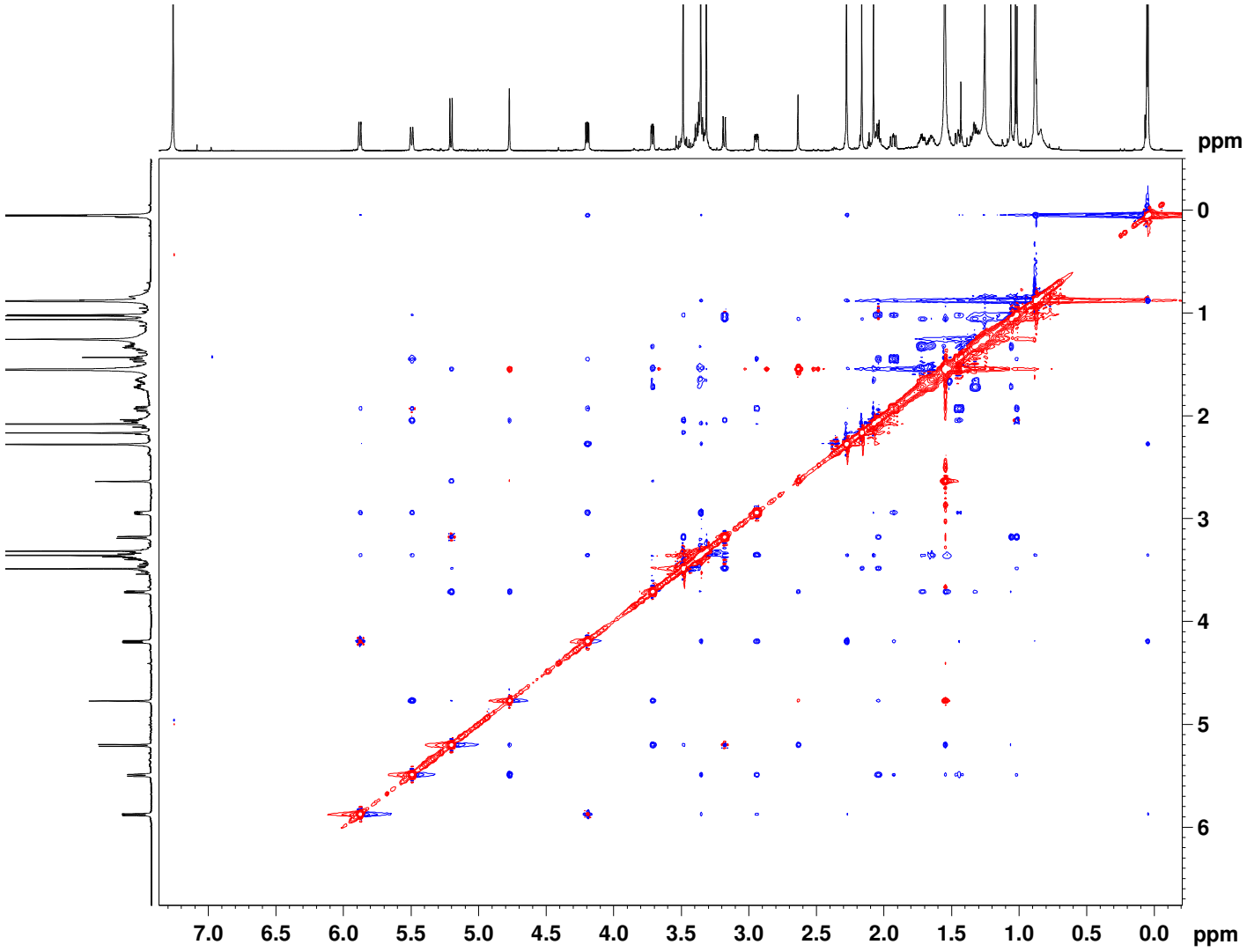


Figure A2.40 600 MHz NOESY NMR spectrum of **3.1** in $CDCl_3$

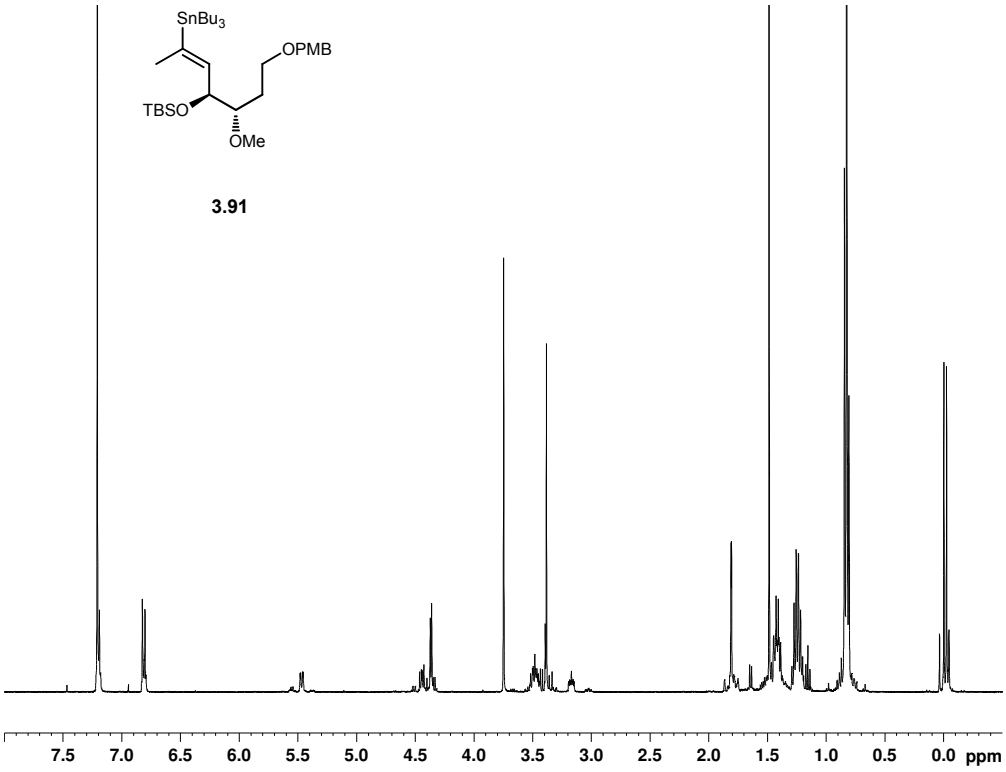


Figure A2.41 400 MHz ^{1}H-NMR of **3.91** in $CDCl_3$

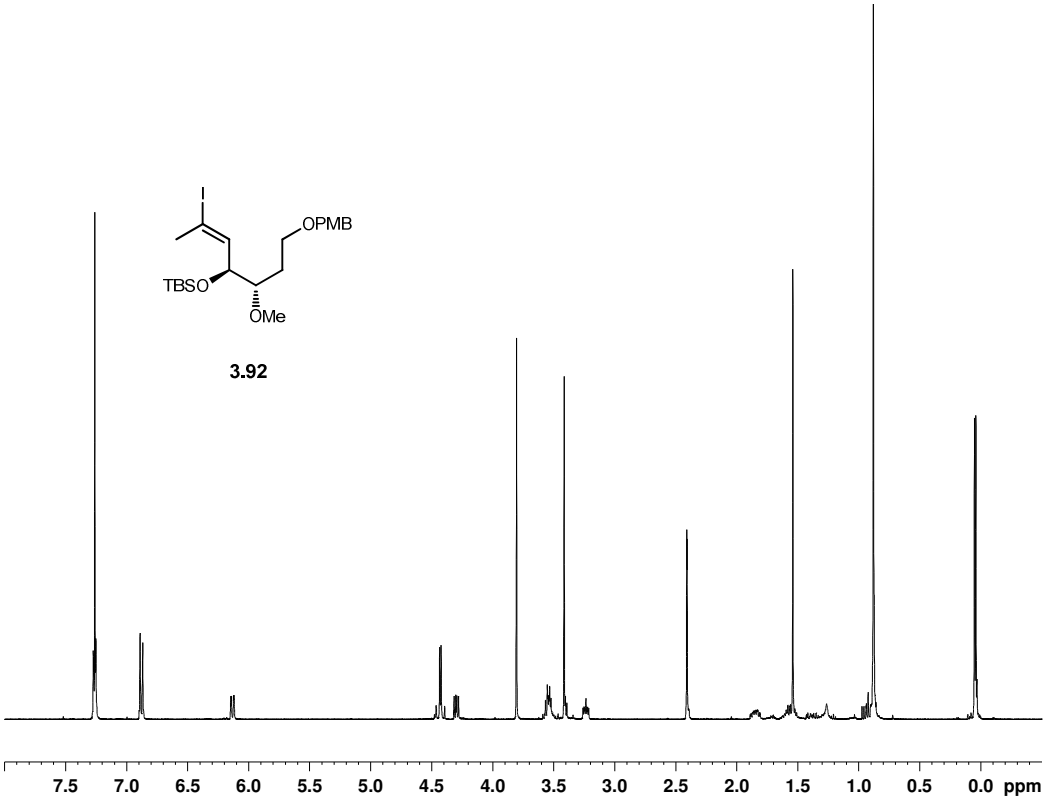


Figure A2.42 400 MHz ^{1}H-NMR of **3.92** in $CDCl_3$

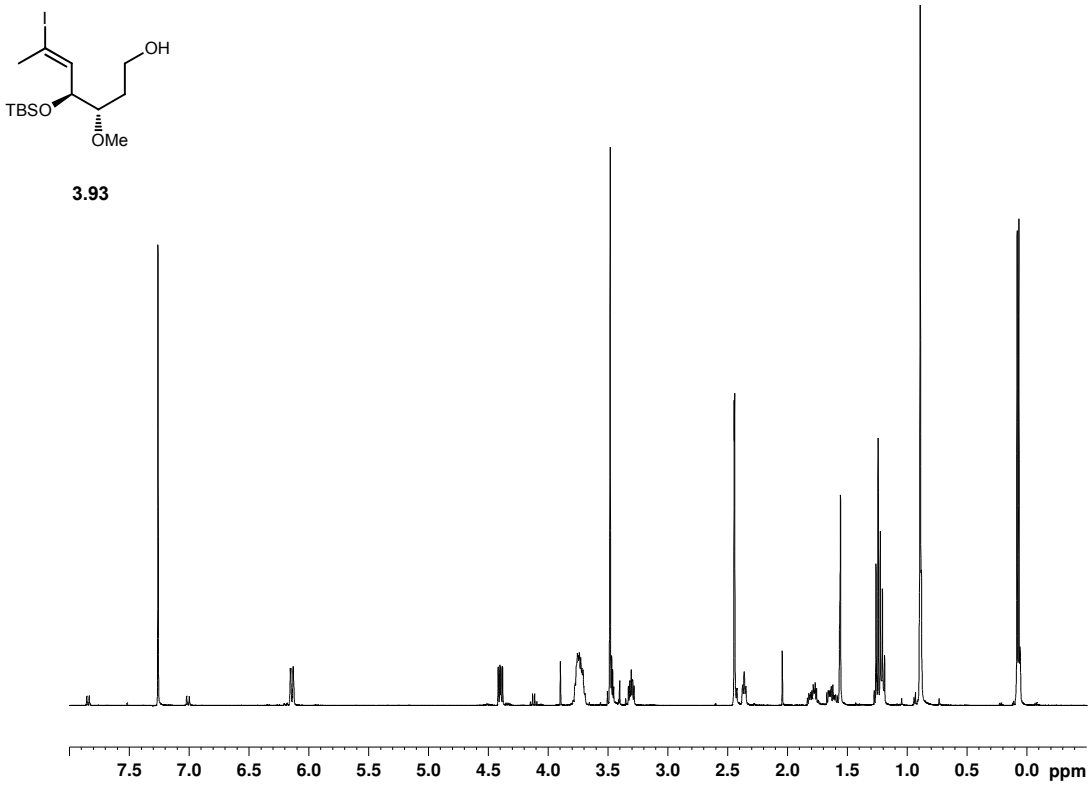


Figure A2.43 400 MHz ^{1}H-NMR of **3.93** in $CDCl_3$

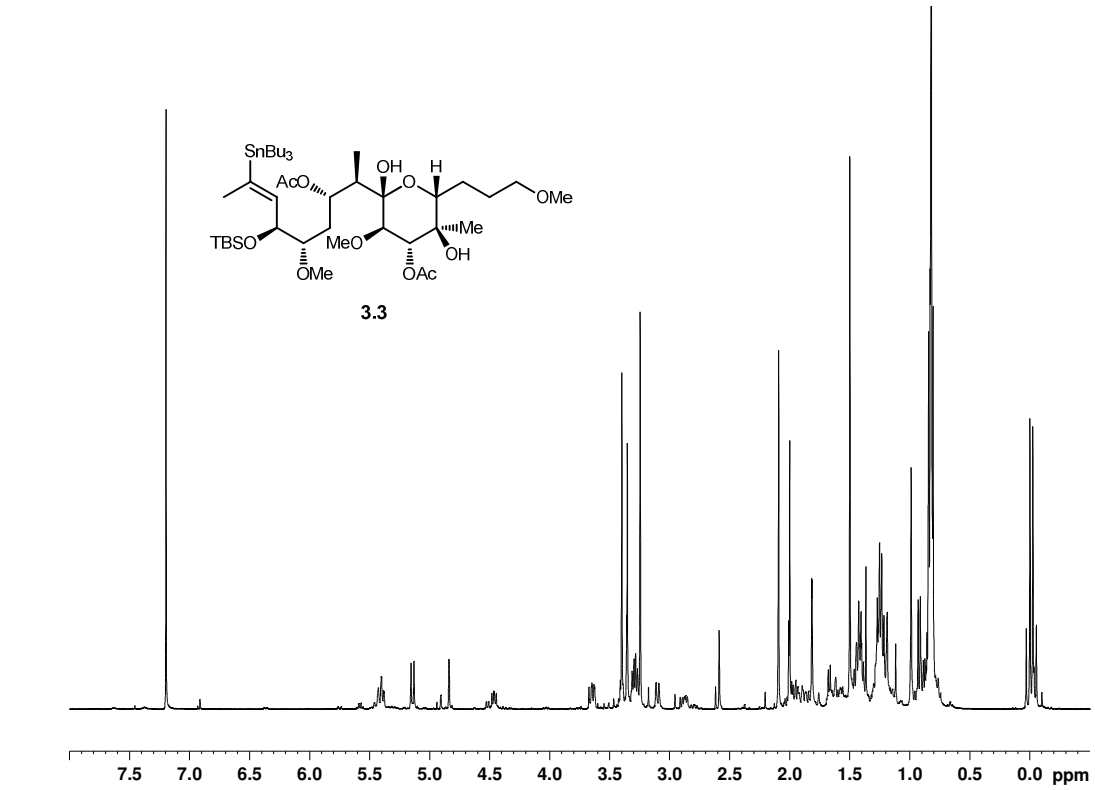


Figure A2.44 400 MHz ^{1}H-NMR of **3.3** in $CDCl_3$

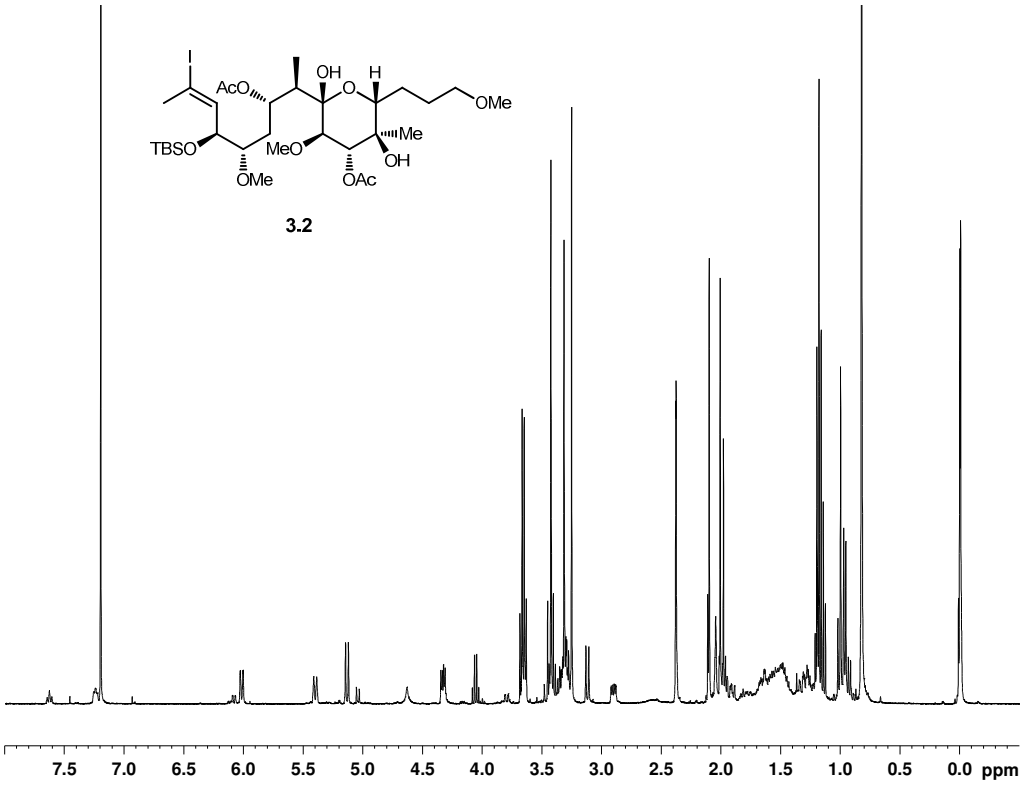


Figure A2.45 400 MHz ^{1}H-NMR of **3.2** in $CDCl_3$

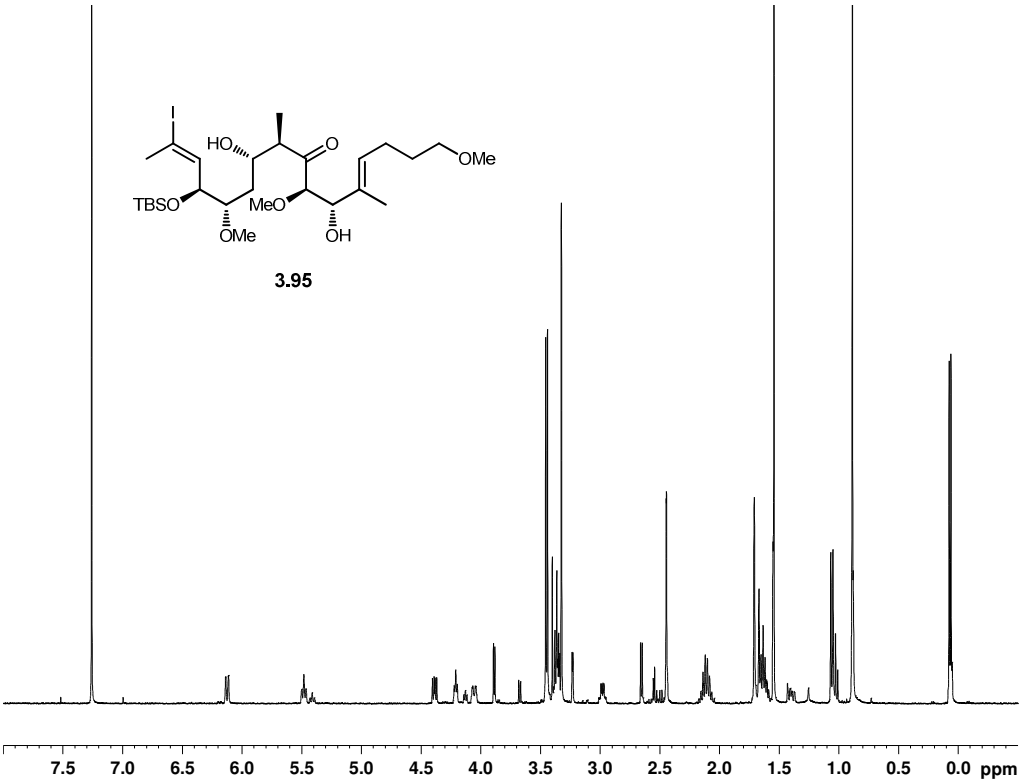


Figure A2.46 400 MHz ^{1}H-NMR of **3.95** in $CDCl_3$

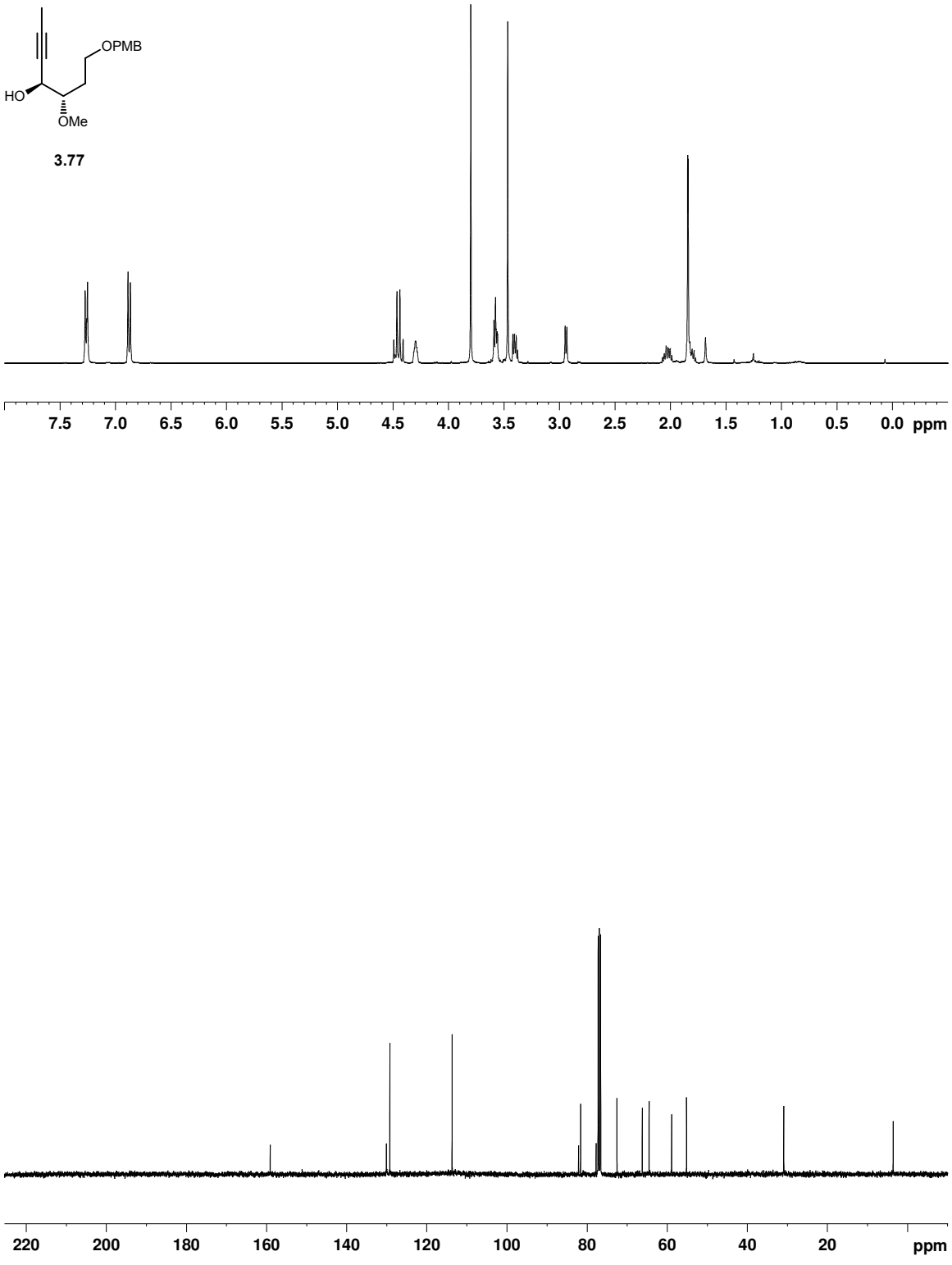


Figure A2.47 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **3.77** in $CDCl_3$

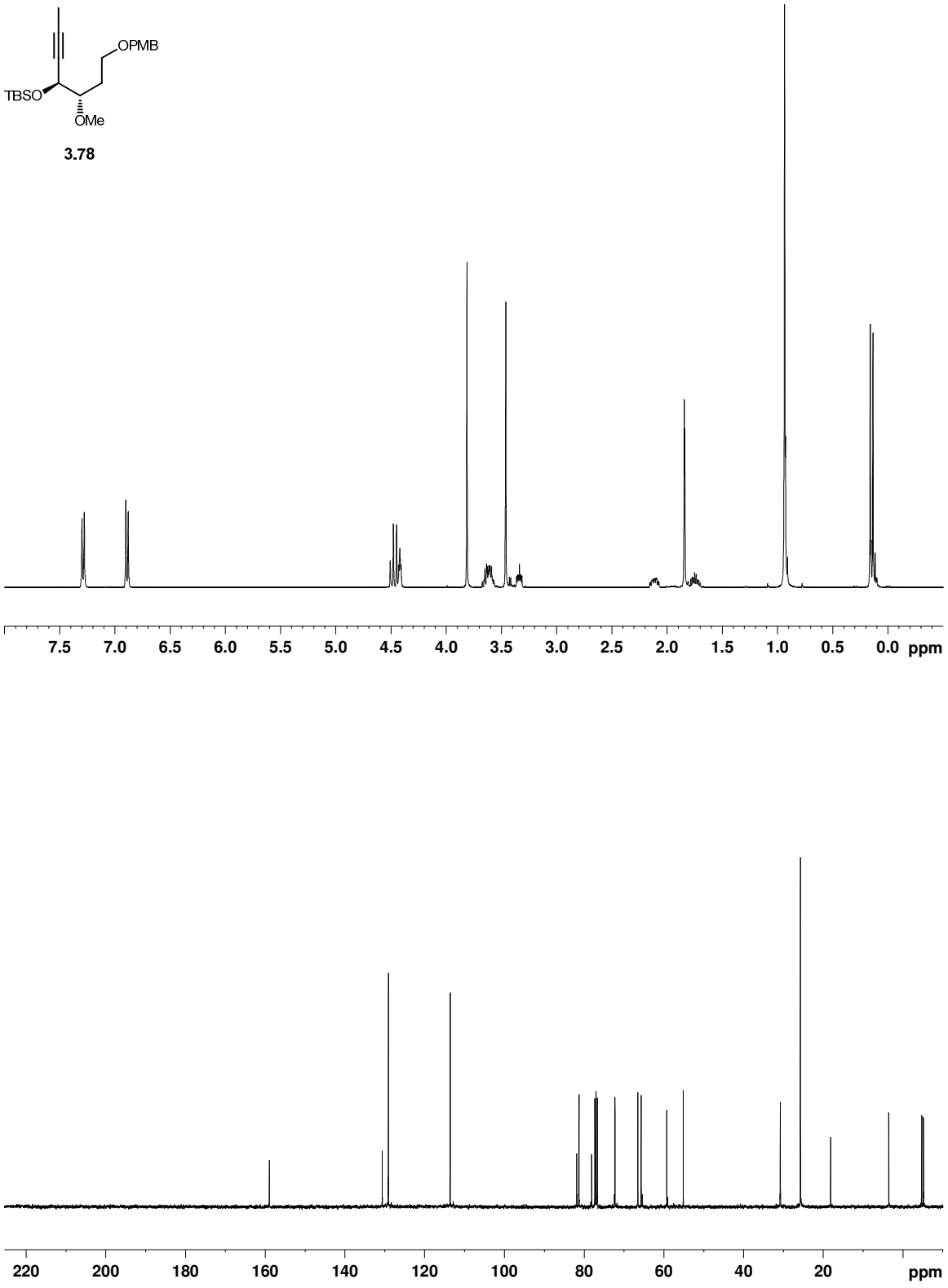


Figure A2.48 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **3.78** in $CDCl_3$

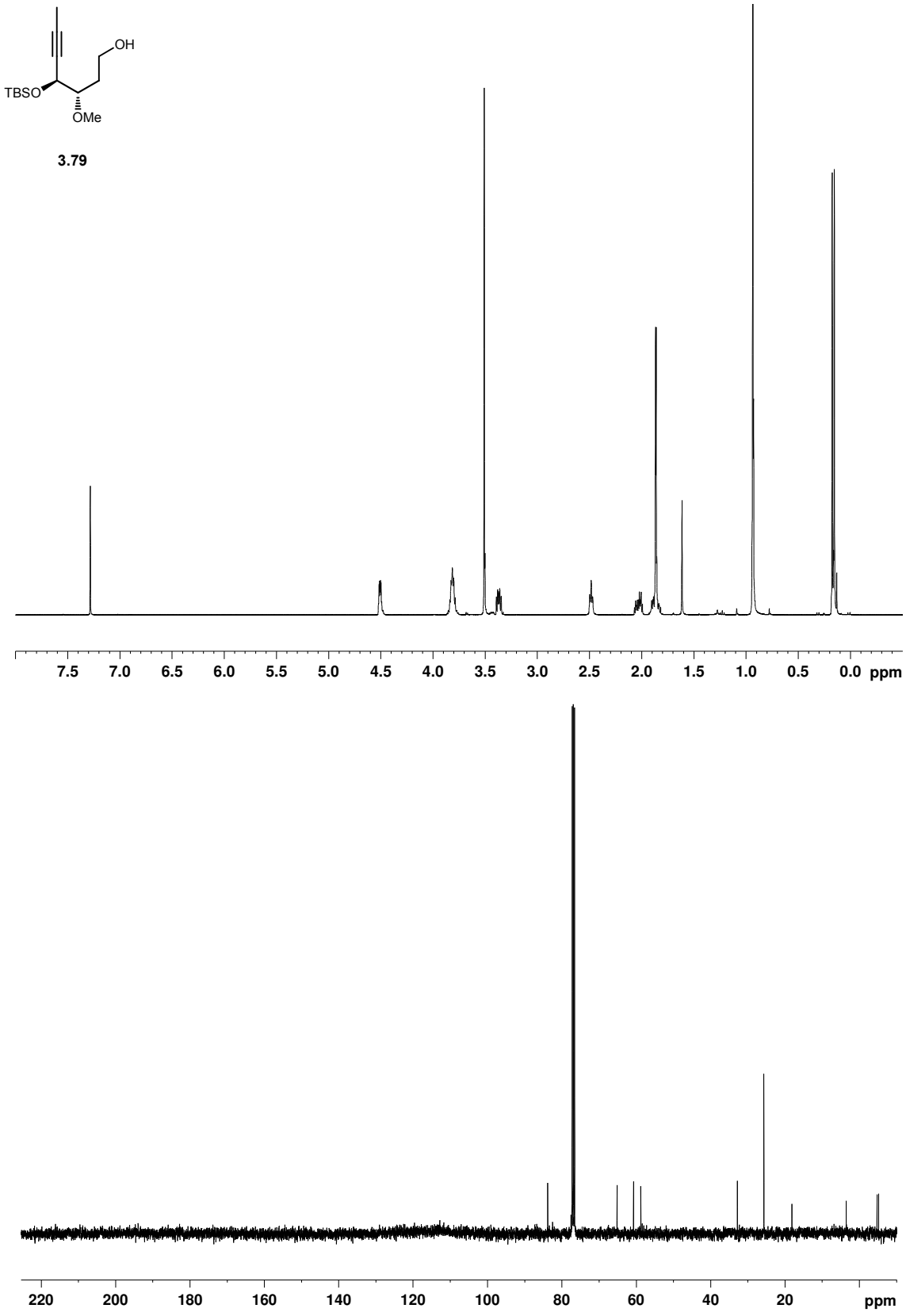


Figure A2.49 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **3.79** in $CDCl_3$

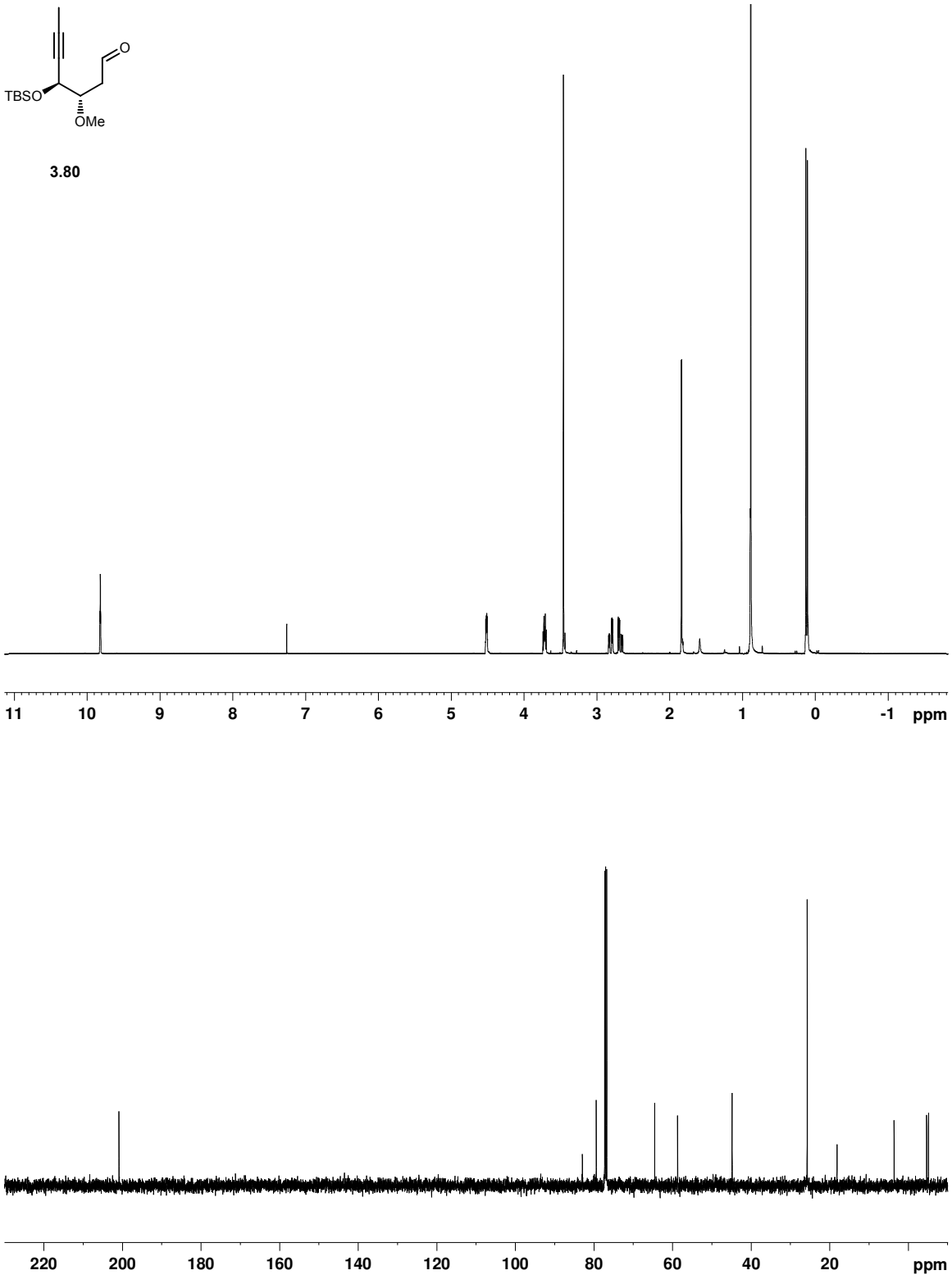


Figure A2.50 400 MHz ^{1}H-NMR and 125 MHz ^{13}C-NMR spectrum of **3.80** in $CDCl_3$

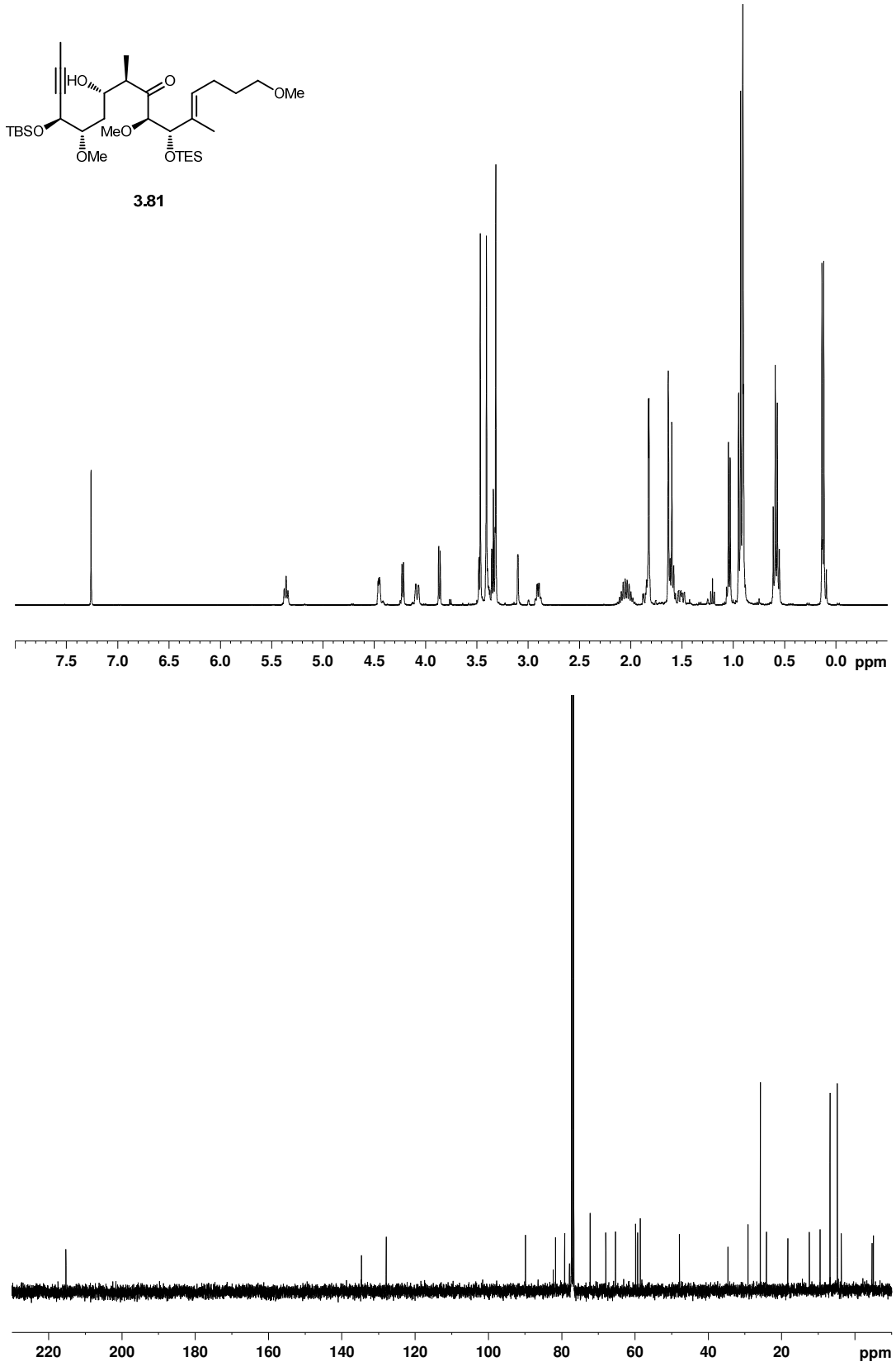


Figure A2.51 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **3.81** in $CDCl_3$

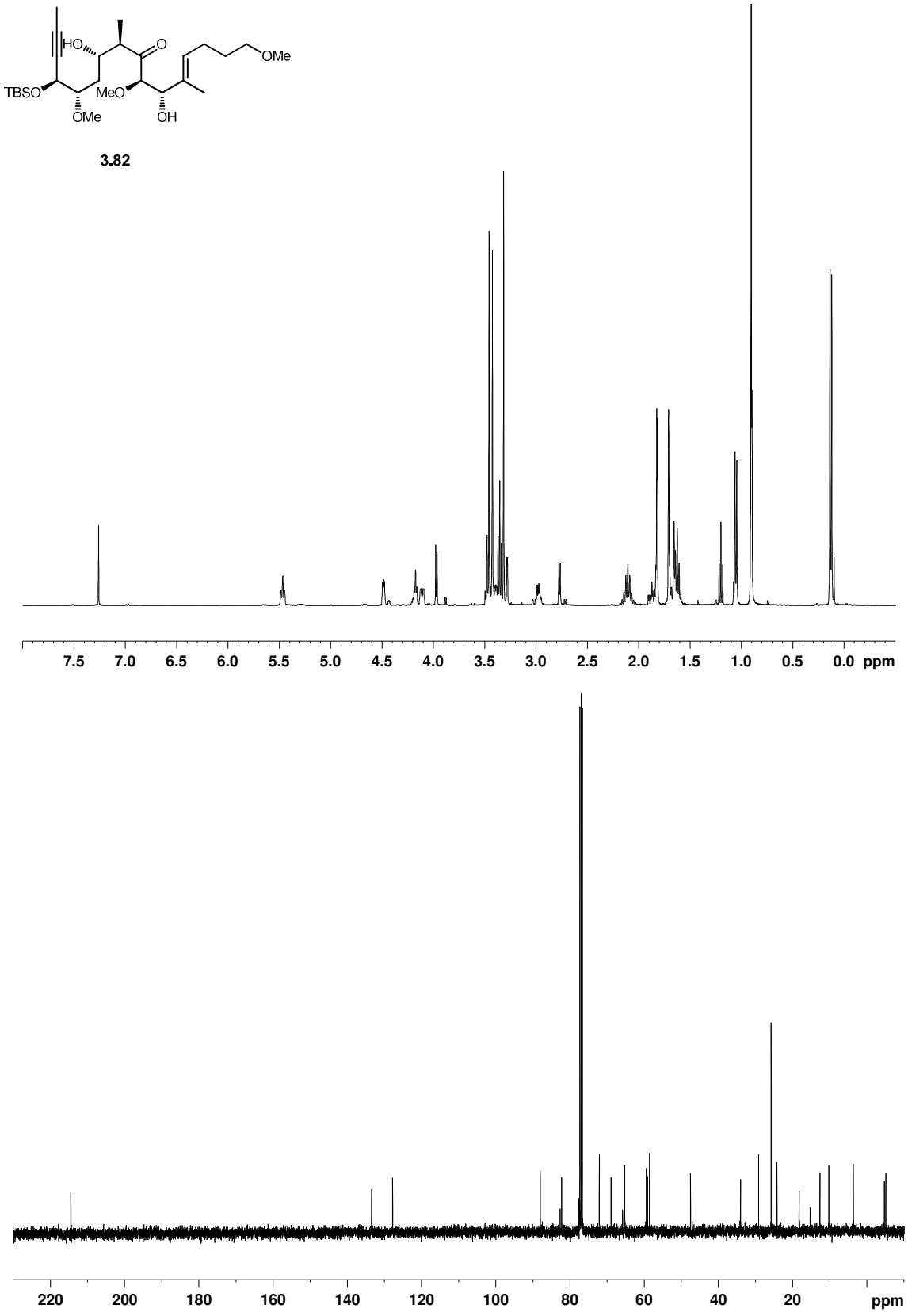


Figure A2.52 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **3.82** in $CDCl_3$

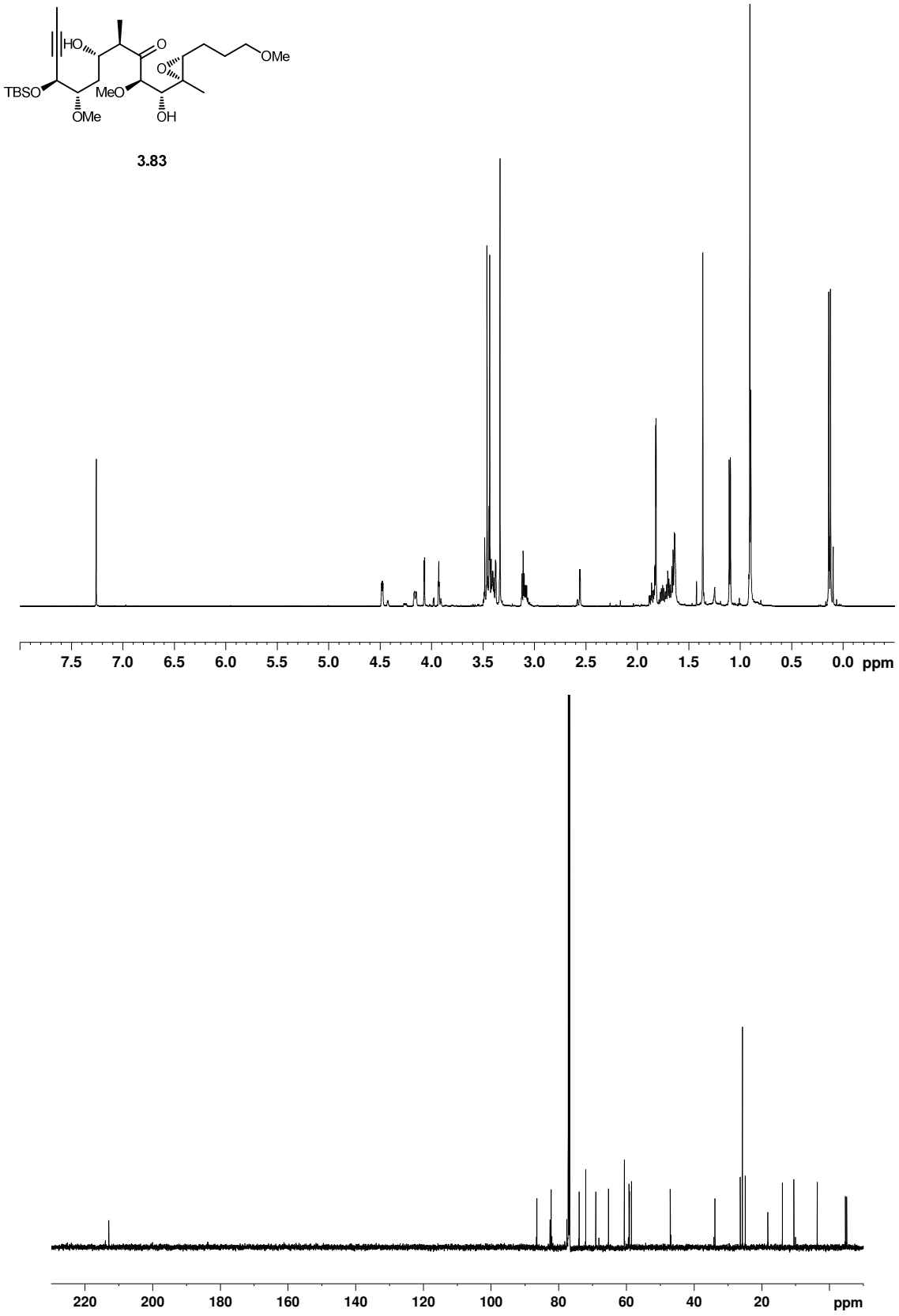


Figure A2.53 600 MHz ^{1}H-NMR and 150 MHz ^{13}C-NMR spectrum of **3.83** in $CDCl_3$

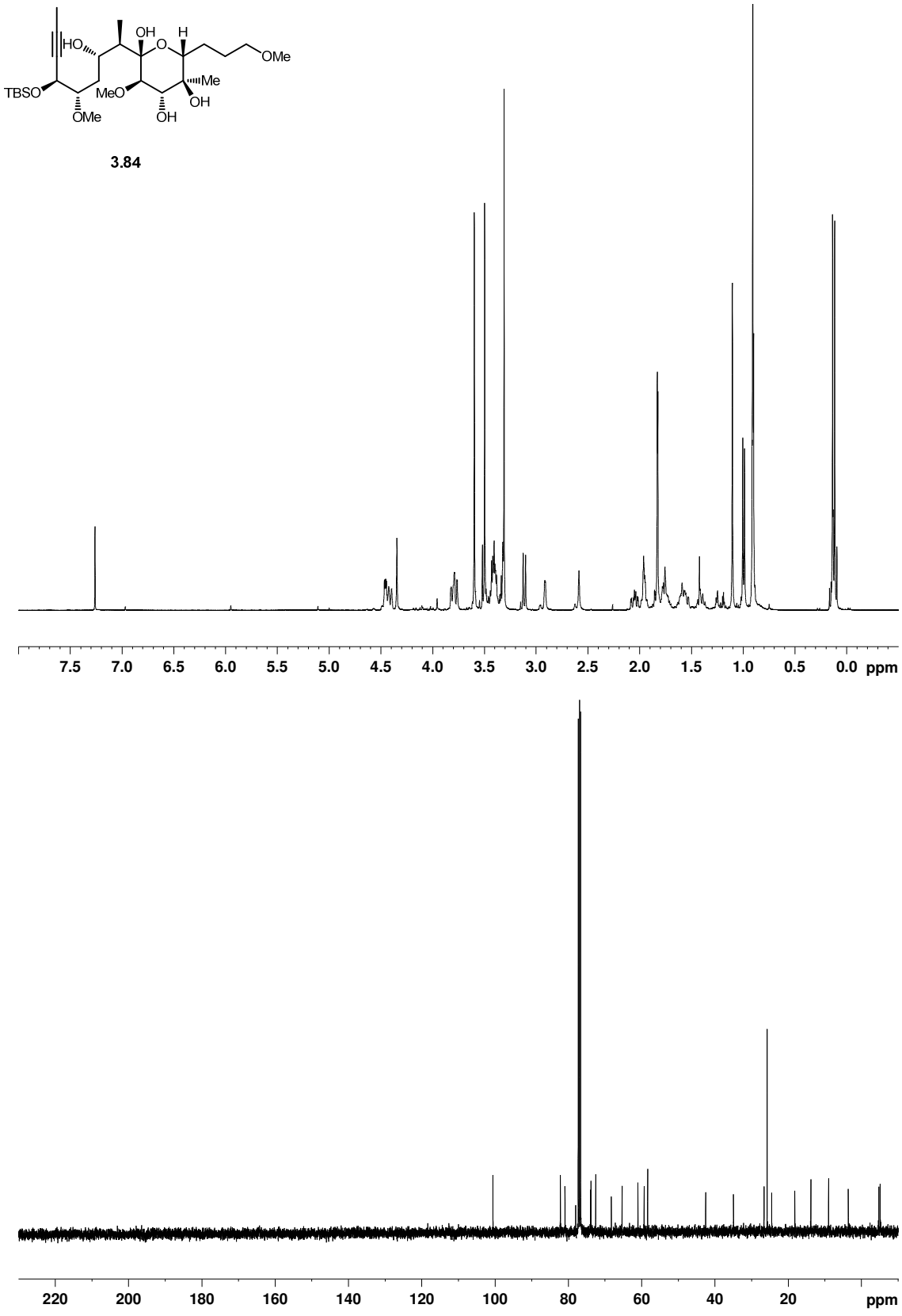


Figure A2.54 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **3.84** in $CDCl_3$

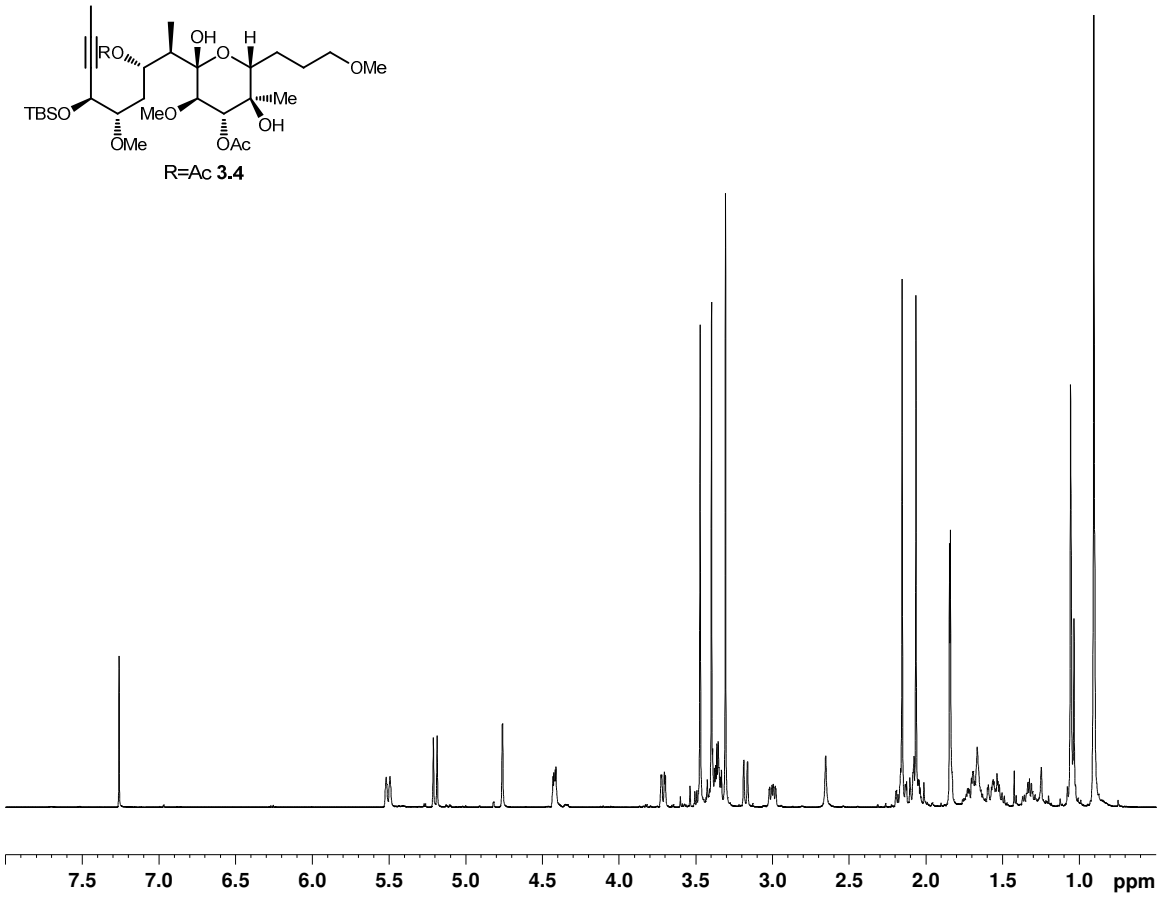


Figure A2.55 400 MHz ^{1}H-NMR spectrum of **3.84** in $CDCl_3$

CHAPTER IV

APPROACHES TOWARDS THE SYNTHESIS OF AMMOCIDINONE

After the successful synthetic endeavor toward the southern hemisphere, we turned our efforts to the unification of the northern and southern hemispheres with the ultimate goal of synthesizing ammocidinone and ammocidin D. Our initial efforts towards the synthesis of the aglycone commenced with Pd(0) cross coupling reactions between the northern and southern fragments similar in strategy to the apoptolidin series discussed in Chapter 1. After the successful formation of the key carbon carbon bond, saponification, macrocyclization, elimination and global deprotection steps would be necessary in forming ammocidinone.

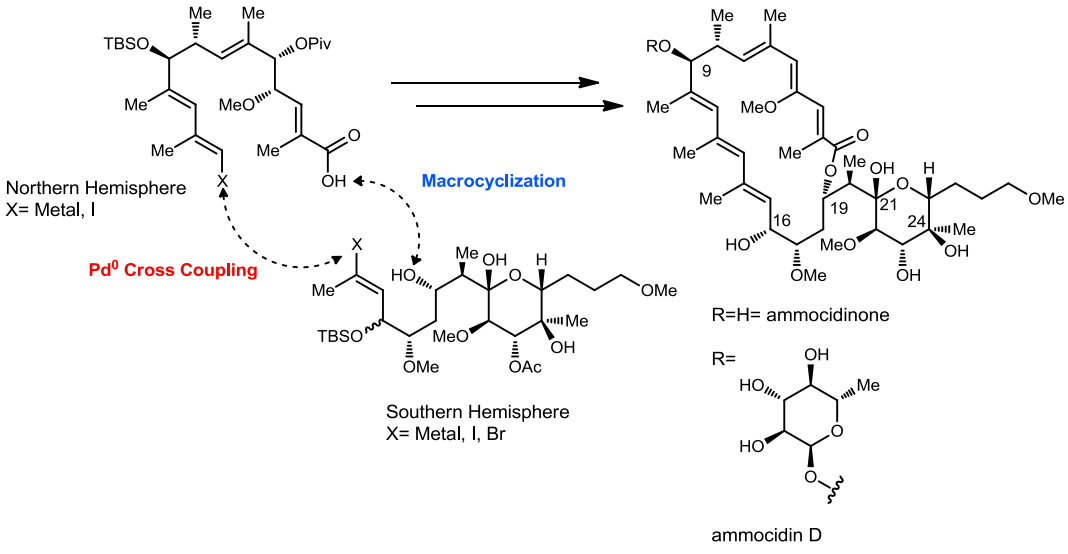
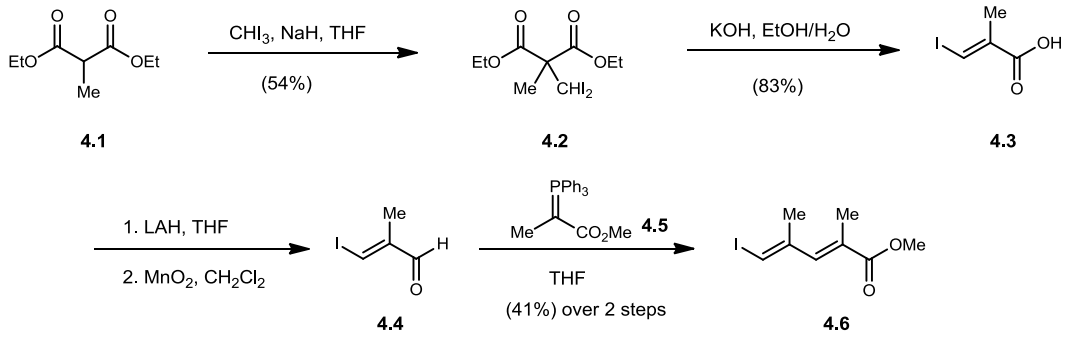


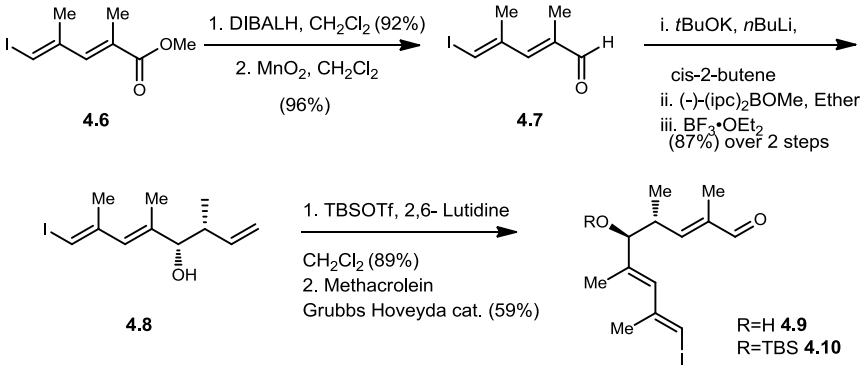
Figure 4.1 Intended unification of the two hemispheres.

Synthesis of the Northern Hemisphere



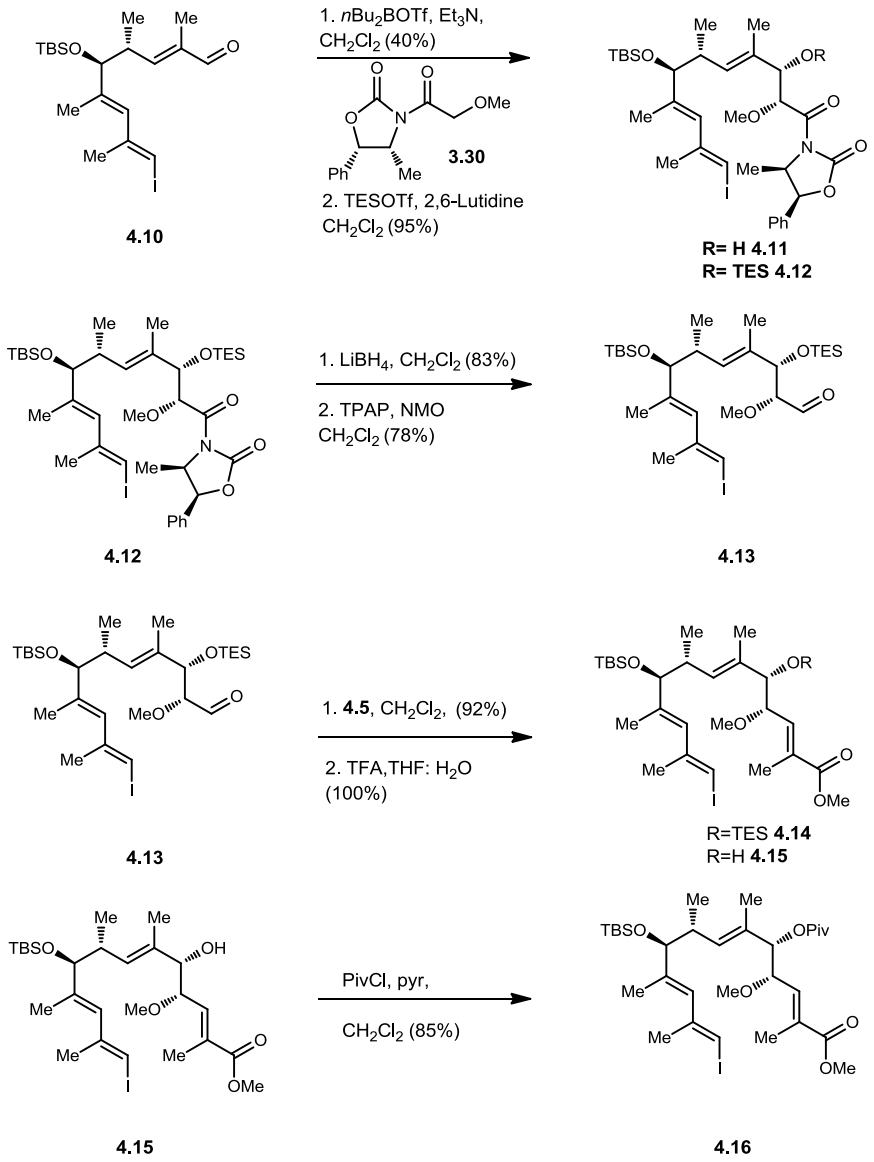
Scheme 4.1 Synthesis of the C9-C13 fragment.

Synthesis of the northern hemisphere commenced under the direction of a postdoctoral associate Dr. Jesse Teske with alkylation of diethyl 2-methylmalonate followed by a decarboxylation elimination sequence in the presence of base providing acid **4.3**. Acid **4.3** is subjected to a reduction oxidation series providing vinyl iodide aldehyde **4.4**, followed by a stabilized Wittig olefination reaction to afford methyl ester **4.6** (Scheme 4.1).



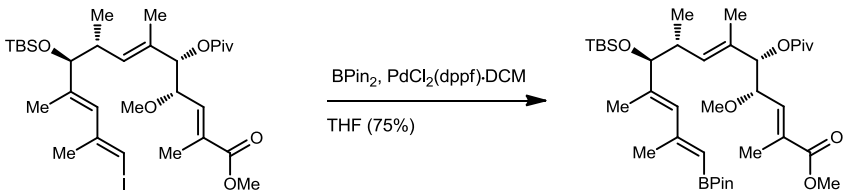
Scheme 4.2 Synthesis of the C5-C13 fragment

Methyl ester **4.6** is subsequently reduced to aldehyde **4.7** and subjected to an asymmetric Brown crotylation[1] to provide alcohol **4.8** in 87% yield over 2 steps. Protection of alcohol **4.8** as the TBS ether **4.9** (89%) was then followed by a Grubbs[2] cross metathesis under microwave conditions providing advanced aldehyde **4.10** in 59% yield (Scheme 4.2).



Scheme 4.3 Synthesis of the C1-C13 fragment.

The unstable aldehyde **4.10** was then immediately subjected to the stereoelectronically important Evans[3] *syn*-aldol protocol required in our late stage elimination afforded the silyl aldol adduct **4.11** in 40% yield. Silyl protected adduct **4.12** was subjected to a reduction/oxidation and stabilized Wittig olefination sequence to provide ester **4.14** with complete (*E*)-geometric selectivity. Facile silyl deprotection with TFA (aq.) and pivalation afforded triene precursor **4.16** in 59% over five steps.

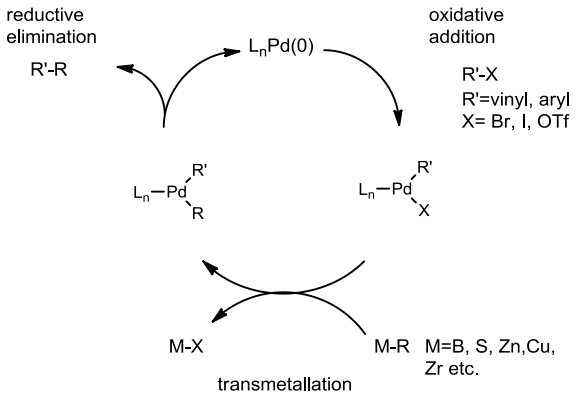


4.16 **4.17**

Scheme 4.4 Installation of the pinacol ester **4.17**.

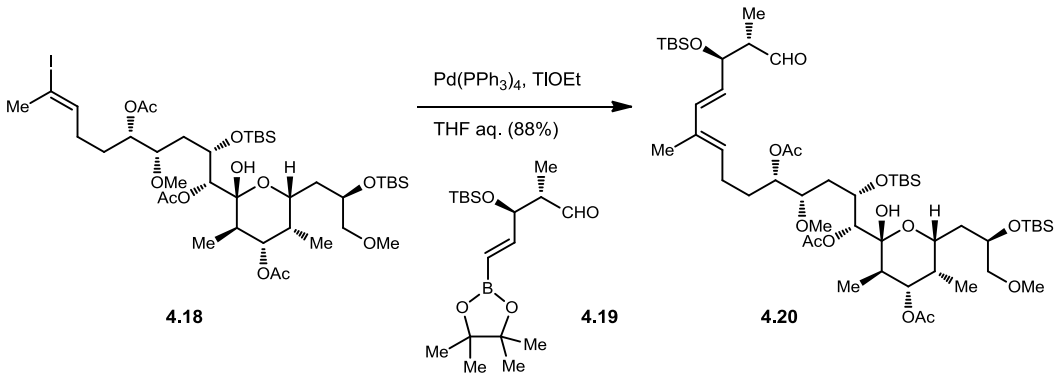
Finally, boronic ester **4.17** can be furnished from vinyl iodide **4.16** with the treatment of bispinacolatodiboron[4] in the presence of a Pd (II) source in 75% yield. With our desired northern and southern fragments, we turned our attention to the coupling of the two fragments that would provide the advanced intermediate towards the aglycone via a cross coupling reaction.

Metal Cross Couplings



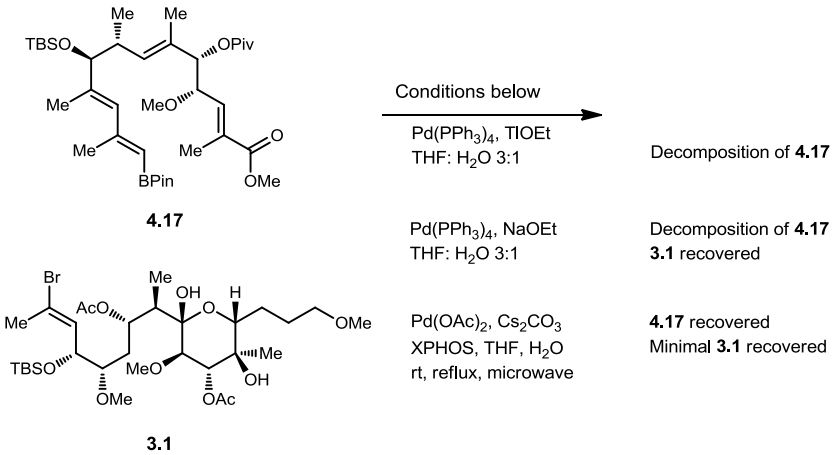
Scheme 4.5 Palladium cross coupling cycle.

Metal cross coupling reactions[5] are one of the most prevalent and important carbon carbon bond forming reactions found in organometallic and organic chemistry. The Suzuki-Miyaura[6] and Stille[7] coupling reactions begin mechanistically with the oxidative addition of palladium(0) providing the electrophilic palladium(II) species. Transmetalation with the boronic acid (Suzuki coupling) or the organostannane (Stille coupling) forms a new palladium(II) species, which produces the desired product after a reductive elimination and regeneration of the palladium(0) species. Finally, an important key aspect of the cross coupling reaction is the formation of a product that retains the stereochemical configuration of the respective reactants (Scheme 4.5).



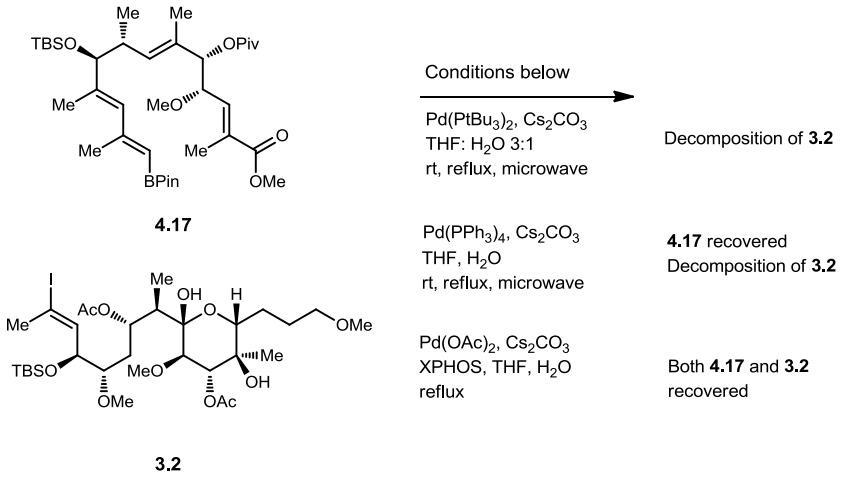
Scheme 4.6 Sulikowski's Suzuki approach towards apoptolidin A.

Sulikowski[8] and co-workers performed a successful Suzuki-Miyaura cross coupling reaction between boronate **4.19** and vinyl iodide **4.18** in the presence of $Pd(PPh_3)_4$ and TlOEt providing the C12-C28 fragment of apoptolidin **4.20** in 88% yield. We began our synthetic efforts based on this Suzuki Miyaura Csp^2-Csp^2 bond forming precedent (Scheme 4.6).



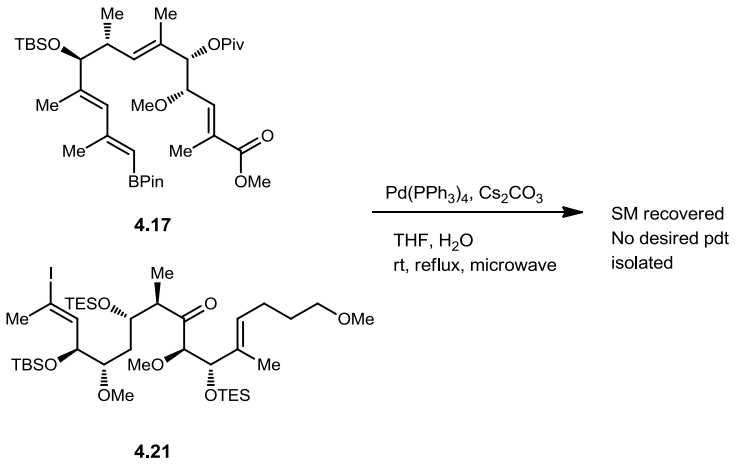
Scheme 4.7 Attempted Suzuki couplings with vinyl bromide **3.1** and boronate **4.17**.

Pinacol boronate **4.17** and vinyl bromide **3.1** were treated with $Pd(PPh_3)_4$, and $Pd(OAc)_2$ with a variety of bases and temperatures. Unfortunately, decomposition of the northern and southern hemisphere occurred when subjected towards the applied conditions. We hypothesized that the trisubstituted vinyl bromide may have been sluggish towards oxidative addition. Thus we proceeded with the vinyl iodide, as vinyl iodides traditionally undergo faster oxidation with metals relative to vinyl bromides due to the bond strength and length (Scheme 4.7).



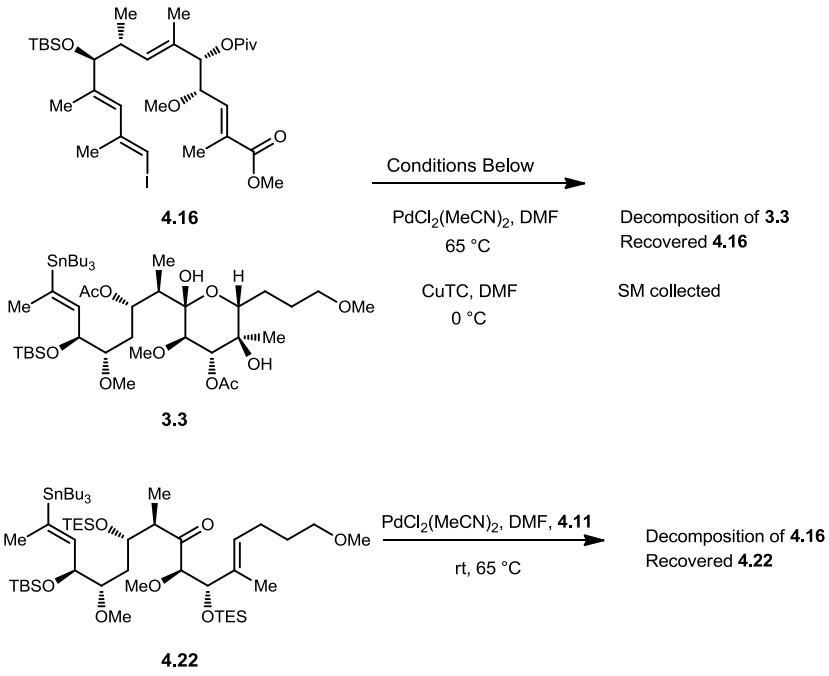
Scheme 4.8 Attempted Suzuki Couplings with vinyl iodide **3.2** and boronate **4.17**.

Unfortunately, conditions applied to the vinyl iodide **3.2** and pinacol **4.17** including Fu's[9] catalyst or $Pd(PPh_3)_4$ in the presence of Cs_2CO_3 and a varying array of temperatures provided only decomposition of the southern hemisphere. We surmised that since the change between the vinyl bromide and vinyl iodide did not achieve our desired coupling that the ketal functionality may be problematic and incompatible (Scheme 4.8).



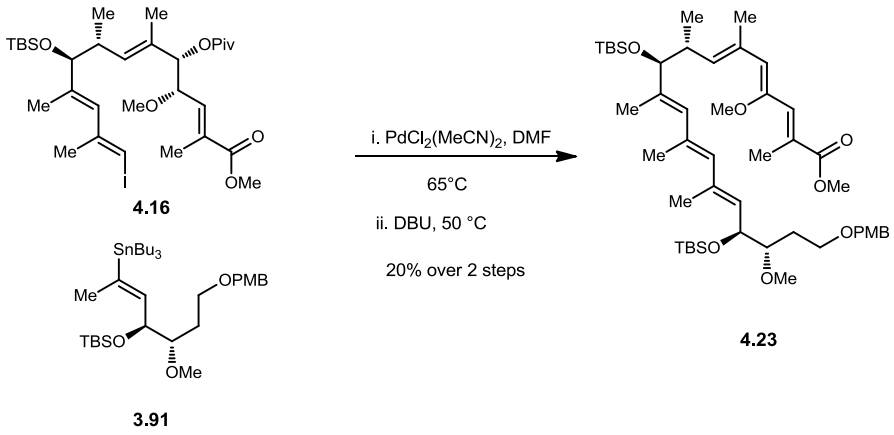
Scheme 4.9 Attempted Suzuki coupling with keto vinyl iodide **4.21**.

In order to alleviate any functional group incompatibility, we attempted a Suzuki coupling with keto vinyl iodide **4.21**. Unfortunately, Suzuki coupling in the presence of $Pd(PPh_3)_4$, Cs_2CO_3 and varying temperatures failed to provide any desired coupling product. We hypothesized that the two sterically encumbering methyl groups located on both coupling partners may be preventing proper bond formation. We subsequently abandoned the Suzuki coupling in favor of the Stille coupling in an effort to change metal species that may improve reactivity between the two coupling partners (Scheme 4.9).



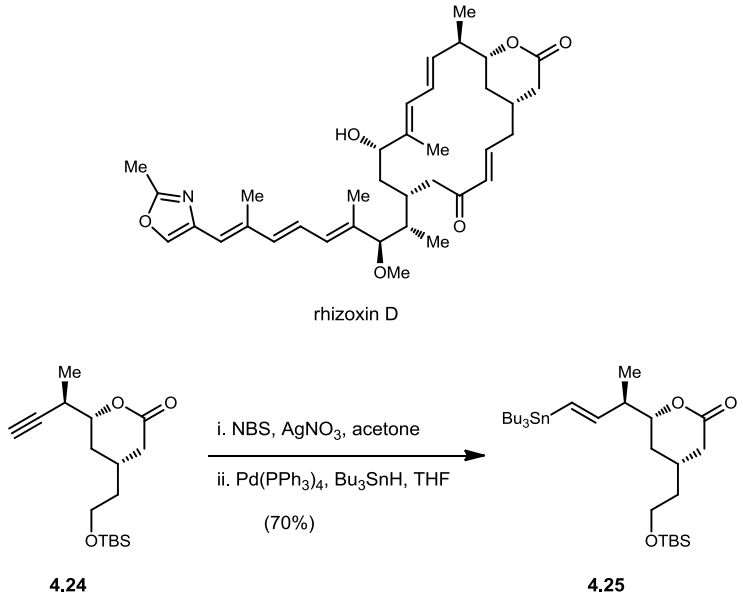
Scheme 4.10 Attempted Stille couplings with vinyl stannane **3.3**/**4.22**.

Vinyl stannane **3.3** and vinyl iodide **4.16** were subjected to $PdCl_2(MeCN)_2$[10] or copper thiophene carboxylate[11], and both reaction conditions failed to provide the desired coupling adduct. An attempted Stille coupling with keto vinyl stannane **4.22** with vinyl iodide **4.16** also failed to provide any desired product. Unfortunately, we concluded that both the Suzuki and Stille intermolecular variants suffered from steric repulsion from the two vicinal methyl groups that hindered bond formation (Scheme 4.10).



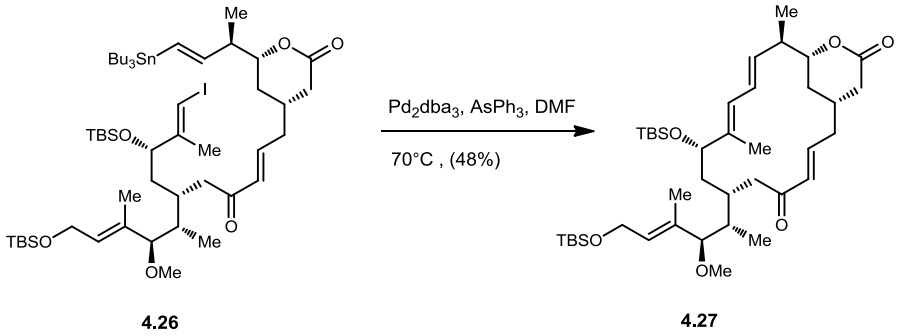
Scheme 4.11 Stille Coupling with vinyl stannane **3.91** and vinyl iodide **4.16**.

Our first successful coupling product occurred between vinyl iodide **4.16** and vinyl stannane **3.91** in the presence of $PdCl_2(MeCN)_2$. The product was subsequently subjected to an elimination with DBU to provide methyl ester **4.23** in 20% yield over two steps. Unfortunately, the coupling sequence suffered from a lack of reproducibility and overall poor yield, thus it was concluded that an intramolecular variant may improve the overall yield (Scheme 4.11).



Scheme 4.12 Pattenden's stepwise approach towards the Stille coupling.

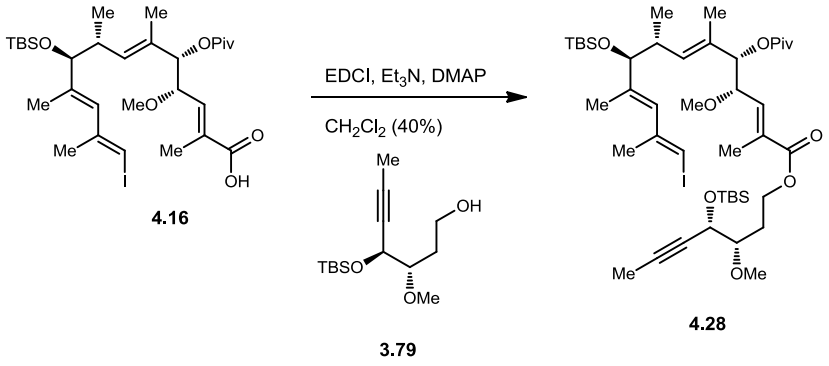
An investigation of intramolecular Stille couplings began with Pattenden's[12] synthesis of rhizoxin D a potent antitumor and antifungal polyketide. Pattenden's synthesis revealed a facile intramolecular Stille coupling as a key step. The terminal acetylene in **4.24** was converted into the *E*-vinyl stannane in a two step process in the presence of NBS, $AgNO_3$ leading to the bromoalkyne. The bromoalkyne was immediately subjected to $Pd(PPH_3)_4$ and $n Bu_3SnH$ resulting in vinyl stannane **4.25**. The two main fragments were joined via a Horner Wadsworth Emmons[13] reaction thereby setting the stage for the key macrocyclization via the Stille protocol (Scheme 4.12).



4.26 **4.27**

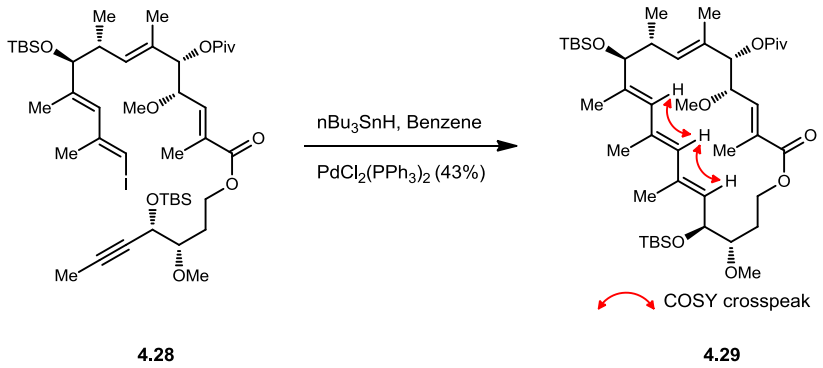
Scheme 4.13 Pattenden's formation of the Csp^2-Csp^2 bond in rhizoxin D.

When vinyl stannane-vinyl iodide **4.26** was treated with $AsPH_3$, Pd(0) dibenzylideneacetone in degassed DMF at 70°C for 5 hours provided smooth intramolecular Csp^2-Csp^2 coupling occurred to provide **4.27**. The reaction proceeded with preservation of the double bond geometries leading to the 16-membered macrocyclic lactone core in rhizoxin in an acceptable yield of 48%. This synthesis provided precedent for the intramolecular route towards the western triene of ammocidinone (Scheme 4.13).



4.16 **3.79** **4.28**

Scheme 4.14 In situ Hydrostannylation/Stille coupling model study

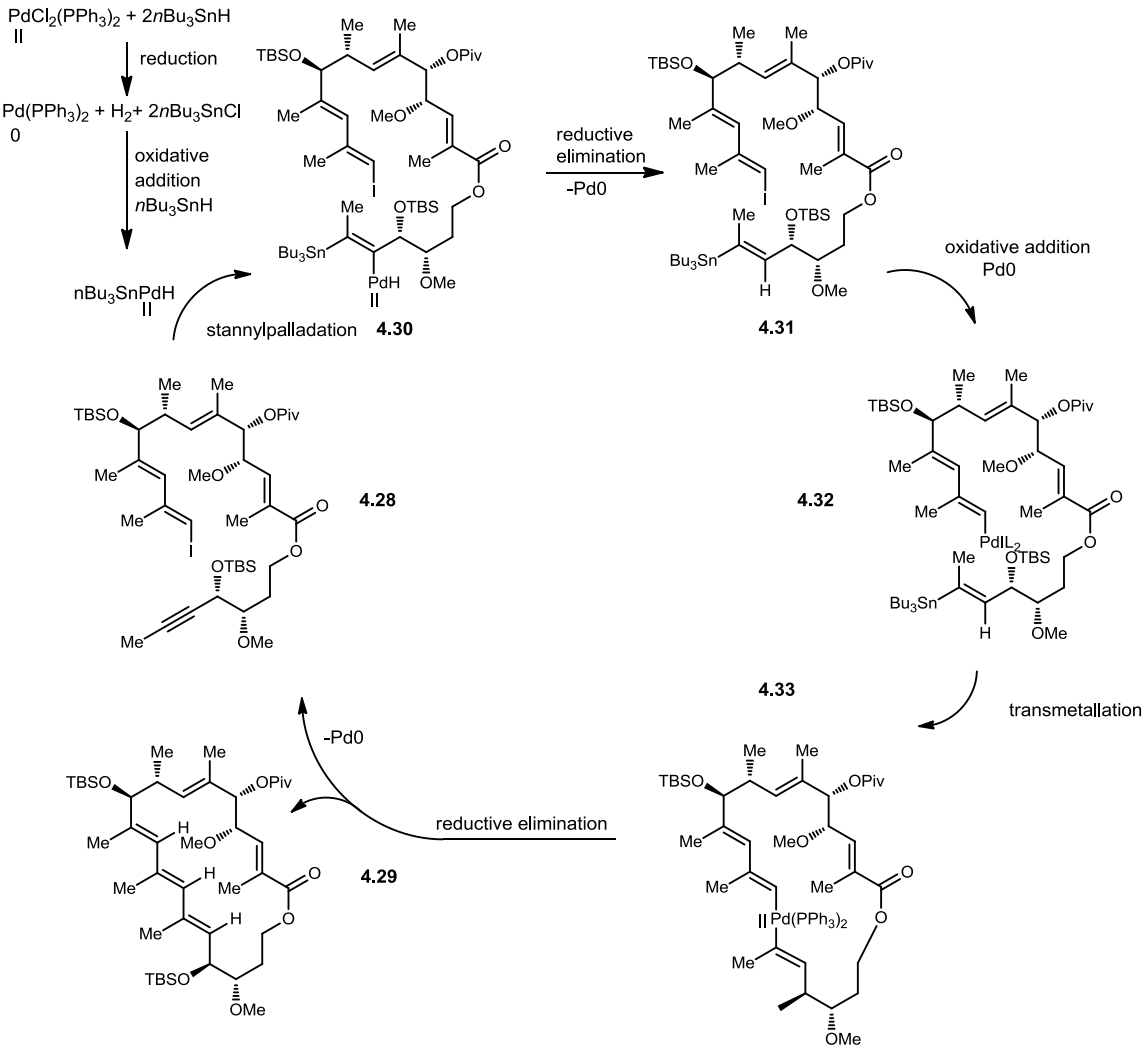


4.28 **4.29**

Scheme 4.14 In situ Hydrostannylation/Stille coupling model study continued.

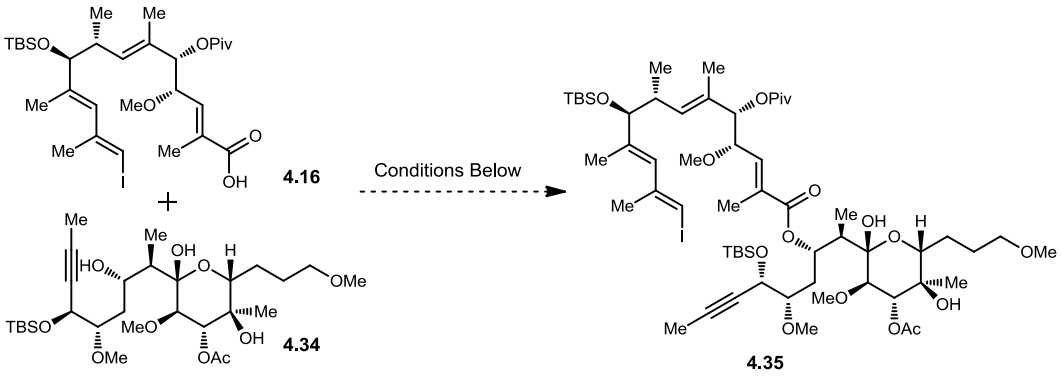
Our second successful formation of the western triene system was achieved with an esterification between acid **4.16** and alcohol **3.79** providing ester **4.28**. Advanced ester **4.28** was subjected to an in situ formation of the vinyl stannane followed by an intramolecular Stille cross coupling reaction providing macrocycle **4.29** with complete double bond fidelity. COSY NMR crosspeaks indicated the key correlations required of the triene moiety. This successful sp^2-sp^2 carbon bond forming step is a novel and ambitious step due to its brevity and convergent execution (Scheme 4.14).

The proposed mechanism[14] of the triene formation can be summarized in a catalytic cycle. First, $PdCl_2(PPh_3)_2$ is reduced in situ to provide hydrogen gas, tributyl tin chloride and $Pd(PPh_3)_2$ followed by an oxidative addition with additional *n*Bu_3SnH. With the generation of an electrophilic reagent, regioselective stannylpalladation occurs across alkyne **4.28** providing **4.30**. Next, reductive elimination forms vinyl stannane **4.31** with generation of palladium (0) which then undergoes an intramolecular Stille cross coupling. Oxidative addition with the newly generated vinyl stannane provides **4.32** and transmetalation with the vinyl stannane affords **4.33**. Finally, reductive elimination of **4.33** provides the triene **4.29** (Scheme 4.15).



Scheme 4.15 Proposed mechanism of the transformation between **4.28** and **4.29**.

With the gratifying stannylpalladation/Stille model study sequence, we quickly revised our synthetic strategy towards the full aglycone. Our current route involves an esterification between the northern hemisphere and the C19 alcohol of the southern hemisphere followed by the stannylation/Stille Csp^2-Csp^2 coupling which was previously examined.

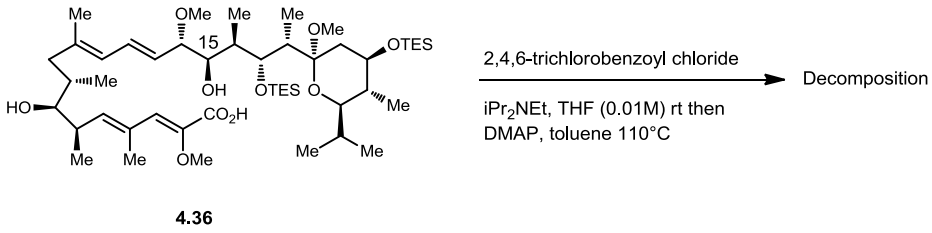


entry	conditions	result
1	EDCI, DMAP, Et_3N, CH_2Cl_2, rt	Anhydride isolated
2	2,4,6-trichlorobenzoyl chloride, DMAP, Et_3N, CH_2Cl_2, rt	Anhydride isolated
3	$Sc(OTf)_3$, MeCN, *p*-nitrobenzoic anhydride, rt	Isomerization to furanose
4	Pyr-S-S-Pyr, PPh_3, Benzene, reflux	Thioester formation
5	BOPCl, Et_3N, DMAP, CH_2Cl_2	SM recovered
6	Ghosez's reagent, DMAP, Et_3N, CH_2Cl_2, 0°C	Decomposition of S. Hemisphere

Table 4.1 Attempted intermolecular esterification of **4.16** and **4.34**.

Our attempts at the intermolecular esterification are summarized in Table **4.1**, however each failed to provide any desired coupling adduct. Treatment of the acid **4.16** with EDCI and Yamaguchi[15] conditions provided the stable symmetrical anhydride. Under Yamamoto[16] conditions with scandium triflate, rapid isomerization of the pyranose ring system to the furanose system was observed, further confirming the use of Lewis acids as detrimental to the southern hemisphere. Usage of the Corey-Nicolaou macrolactonization[17] strategy with dipyridyl disulfide produced the stable and isolable thioester. Finally, application of BOPCl provided

recovery of the starting material and Ghosez's[18] reagent 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine resulted in decomposition of the southern hemisphere.



4.36

Scheme 4.16 Marshall's attempted intramolecular Yamaguchi cyclization.

To our astonishment, Marshall[19] and co-workers also experienced difficulty in their intramolecular esterification under the Yamaguchi protocol towards bafilomycin C. In the presence of acid **4.36**, 2,4,6- trichlorobenzoyl chloride, diisopropyl ethyl amine, and DMAP refluxing in toluene resulted in decomposition of the starting material judged by TLC and NMR analysis of the crude product. Marshall concluded that the mixed anhydride was formed but that the lactonization was the problematic step, possibly due to the unreactive C15 alcohol. Our own unsuccessful attempts at a difficult esterification revealed that the substitution pattern between bafilomycin C and the southern hemisphere was similar. It was our hypothesis that a hydrogen bonding network between the C21 and C19 alcohols and C17 the methoxy group reduced the nucleophilicity of the C19 alcohol and in turn retarded the rate of esterification at C19. This observation was supported by the fact that the C19 alcohol is acetylated at a slower rate than the C23 alcohol (Figure 4.2).

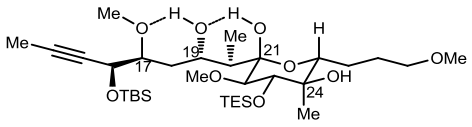
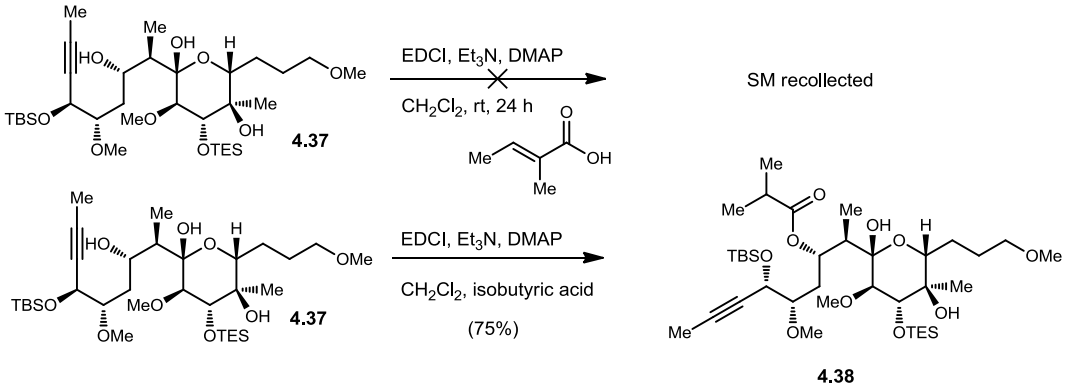
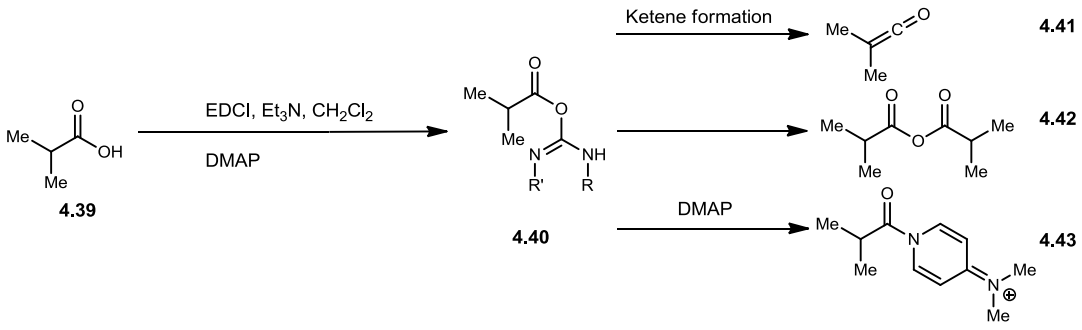


Figure 4.2 Hypothesized hydrogen bonding network in the C14-C28 fragment.



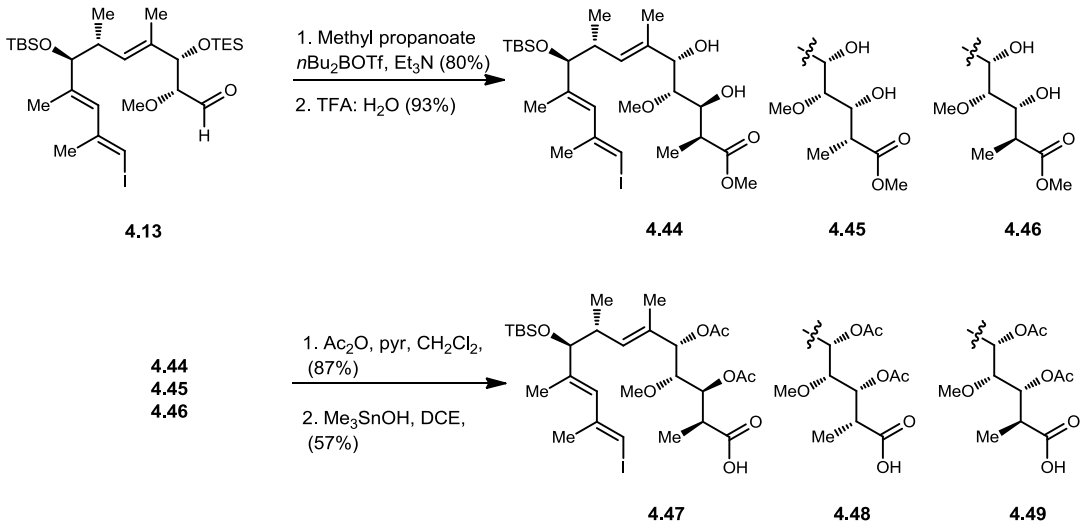
Scheme 4.17 Model study esterifications with tiglic acid and isobutyric acid.

Dismayed by these results, we attempted couplings of the southern hemisphere with model acids. It was our hypothesis that the α,β-unsaturation in **4.16** was incompatible with the attempted coupling conditions. Treatment of **4.37** with EDCI, tiglic acid or isobutyric acid produced interesting results. A simple unsaturated acid, tiglic acid, failed to provide any coupling adduct even in 10 equimolar amounts relative to the southern fragment. Interestingly, saturated acid, isobutyric acid furnished the ester bond to **4.38** in 75% yield in only one hour. In addition, it should be noted at this juncture the southern hemisphere was converted to a triethylsilyl group at C23 for facile deprotection in the later stages (Scheme 4.17).



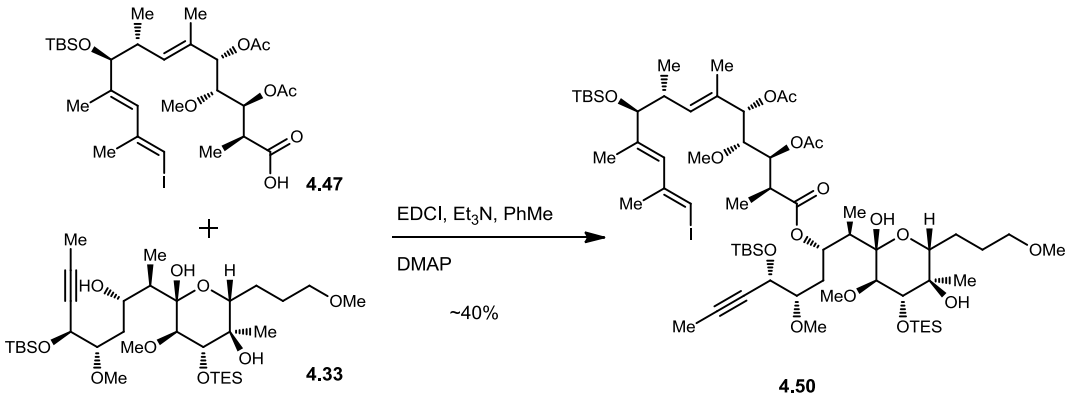
Scheme 4.18 Possible reactive intermediates in the esterifcation reaction.

We surmised that the structure had great influence on the mechanism of the reaction. The acid is activated with EDCI resulting in the formation of acyl isourea **4.40** which can be the active species responsible for the ester coupling event. However, the saturated acids may undergo formation of ketene[20] **4.41** which is a different reactive intermediate that is not accessible with the unsaturated acid. Other reactive intermediates that could be formed in the reaction pot include the symmetrical anhydride **4.42** or the activated *N*-acylpyridinium **4.43**. Therefore, we concluded from this model study that it was possible the ketene intermediate was pivotal in the formation of the key ester bond. Thus, this prompted the modification of the northern hemisphere by installing the saturated functionality (Scheme 4.18).



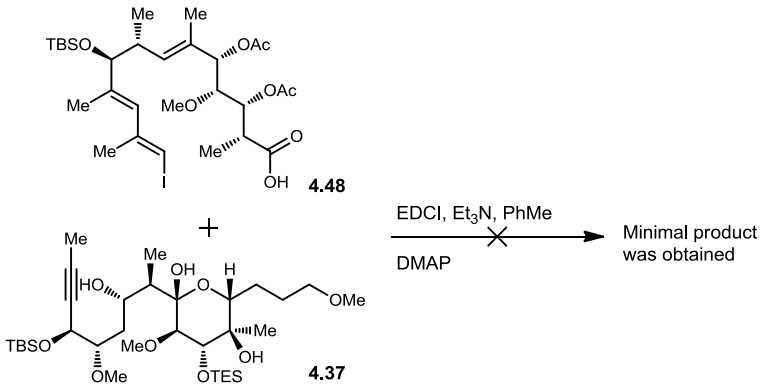
Scheme 4.19 Formation of saturated acid **4.47-4.49**.

Advanced aldehyde **4.13** was subjected to a boron mediated aldol with methyl propionate providing a mixture of three diastereomers **4.44, 4.45, 4.46** (1:0.8:0.3 ratio) in a combined yield of 80% after deprotection with TFA (aq.). We anticipated that the mixture of diastereomers (**4.44, 4.45, 4.46**) from the aldol reaction with methyl propionate to be inconsequential due to expected dual elimination to reestablish the eastern triene moiety. The relative stereochemistries of **4.44, 4.45, 4.46** were determined from the 2D NOE correlations of the lactone between the C1 and C3 alcohol. The mixture of diastereomers was expected due to the lack of facial discrimination from the aldehyde in the aldol reaction. Acetylation of the diols **4.44, 4.45, 4.46** provided the bis-acetate and saponification of the methyl ester in the presence of Me_3SnOH[21] gave saturated acids **4.47, 4.48, 4.49** (Scheme 4.19).

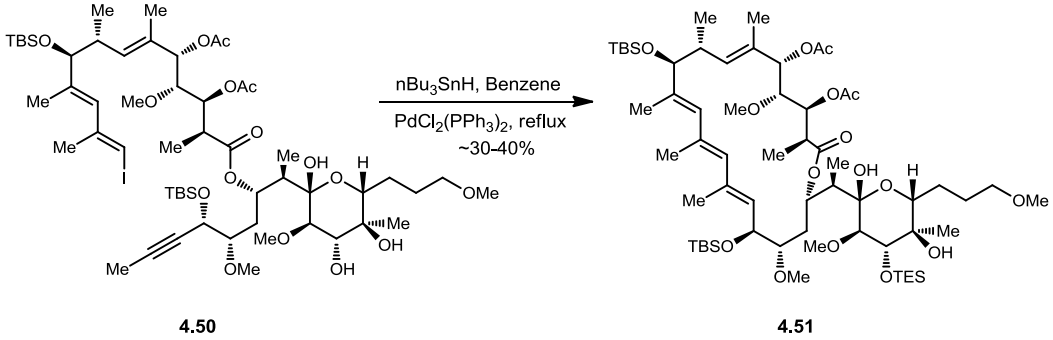


Scheme 4.20 Esterification of the saturated acid with the southern hemisphere.

To our delight, saturated acid **4.47** provided the coupling adduct **4.50** in 40% yield as a single diastereomer with EDCI, Et_3N, DMAP, in toluene. This key reaction represents the first occasion the complete northern and southern sections have been unified in the synthesis towards the aglycone. Interestingly, if the reactive intermediate were the ketene moiety, racemization would potentially have occurred at the C2 position resulting in a mixture of diastereomers; however such was not observed. It could be possible that the addition of a proton at the C2 position could be stereoselective thereby providing the single product. In addition, it should be noted that surprisingly, only one diastereomer provided the desired coupling adduct. This observation leads us to conclude that the reactive species is dictated by the orientation of the C3 acetate (Scheme 4.21).



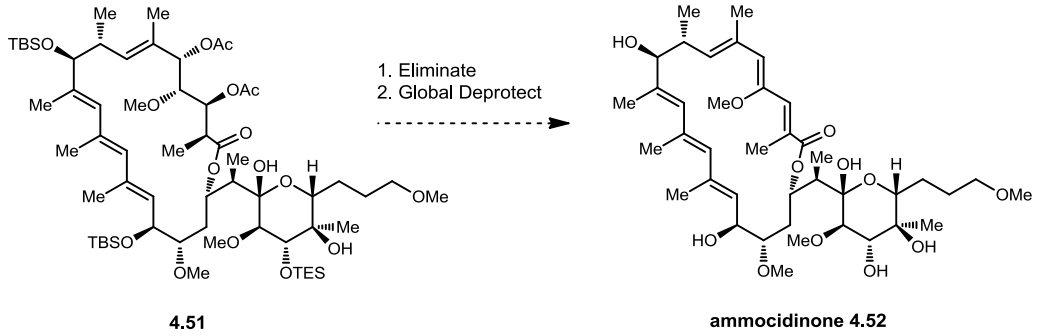
Scheme 4.21 Attempted esterification with the saturated acid isomer **4.48** and the southern hemisphere **4.37**.



Scheme 4.22 Stannylation/ Stille coupling and formation of the macrocycle.

The next task was the formation of the western triene resulting in the closure of the macrocycle. Gratifyingly, subjecting ester adduct **4.50** to *n*Bu_3SnH and $PdCl_2(PPh_3)_2$ in benzene [22]at reflux for 24 h provided the 20-membered ring system **4.51** in 30-40% yield. Importantly, the previous model study accurately depicted the stannylation/Stille event. This reaction represents a novel one pot hydrostannylation/Stille cross coupling with an alkyne and a vinyl

iodide arriving at a Csp^2-Csp^2 bond (Scheme 4.22). The wider utility of this reaction can be applied toward the rapid construction of Csp^2-Csp^2 bonds.



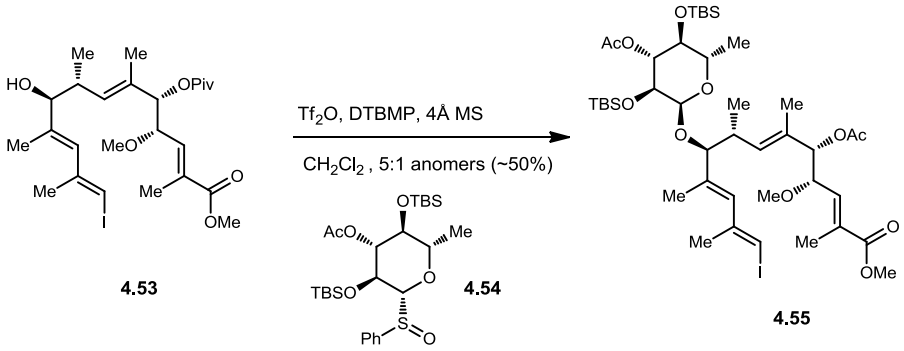
Scheme 4.23 Expected completion of ammocidinone **4.52**.

The anticipated completion of ammocidinone involves an elimination of the bisacetates in **4.51** followed by the removal of all silyl protecting groups. Upon completion of an isomer of ammocidinone, a careful examination of spectral data will determine if the relative stereochemistry is accurate.

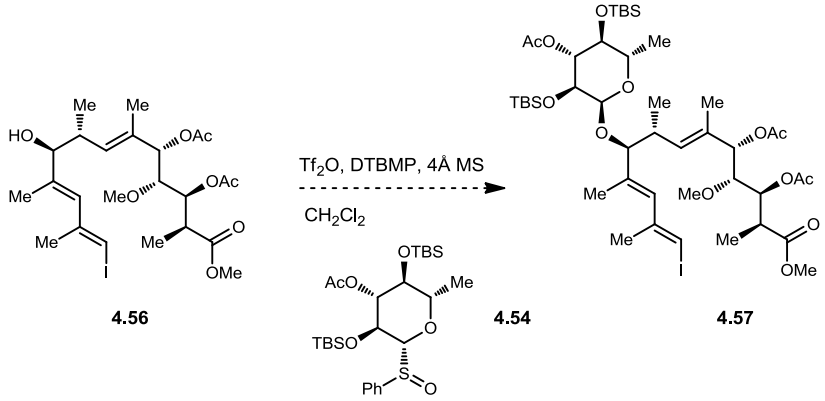
Future Goals

Synthetic efforts towards the completion of ammocidin D includes the stereoselective glycosylation of 6-deoxyglucose of C9 for the northern hemisphere. With the glycosylated precursor **4.53** in hand, the same reaction sequence used to assemble ammocidinone will be employed towards the synthesis of ammocidin D. With the completion of synthetic ammocidin

D, a careful comparison of spectral data with natural ammocidin D will determine of the relative stereochemistry is accurate more so than ammocidinone.



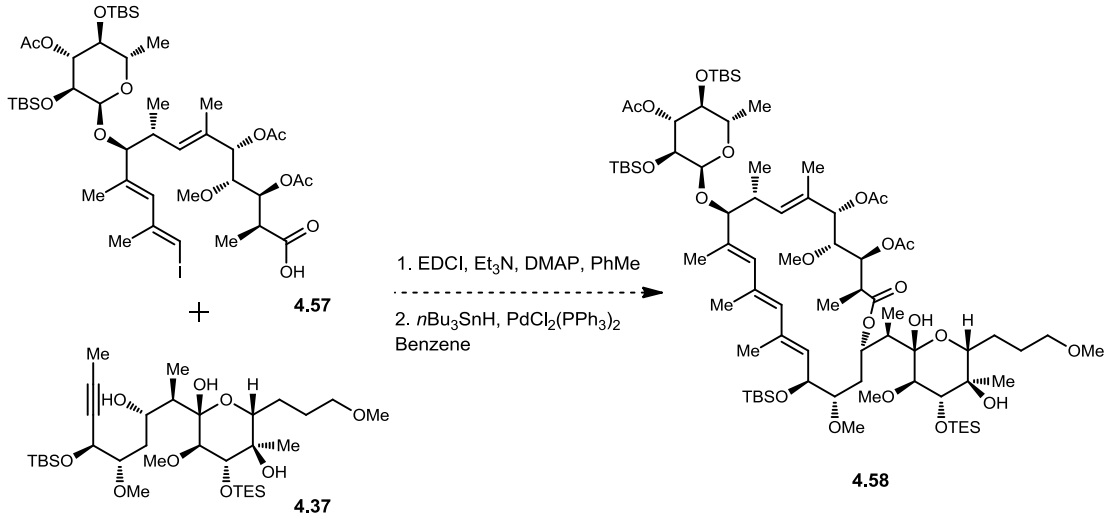
Scheme 4.24 Glycosylation of the unsaturated northern hemisphere **4.53**.



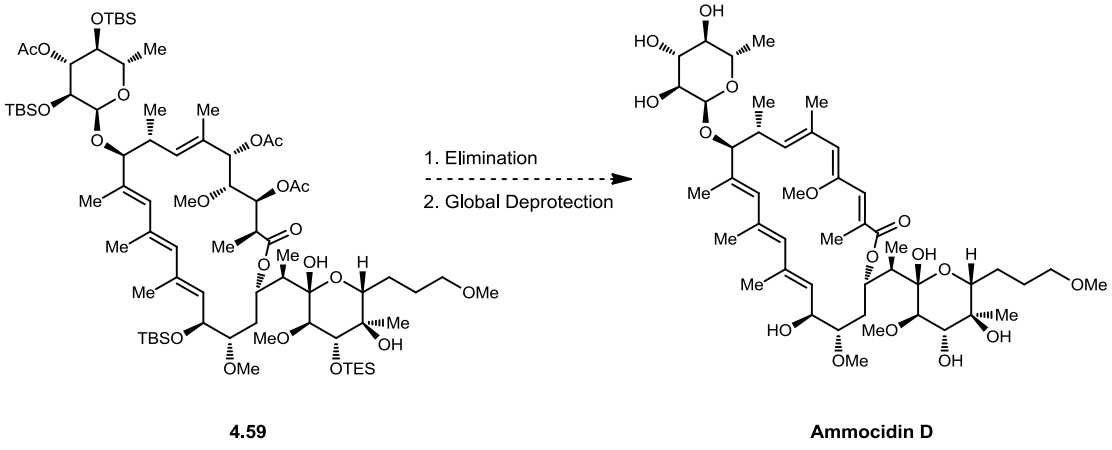
Scheme 4.25 Glycosylation of the northern hemisphere.

Glycosylation model studies located at C9 were performed under the direction of Dr. Jesse Teske. Utilizing unsaturated acid **4.53** and phenyl sulfoxide **4.54** were treated with triflic anhydride, 2,6-di-*tert*butyl-4-methyl pyridine and 4Å MS to provide the glycosylated[23] northern

hemisphere **4.55** in a 5:1 mixture of anomers in approximately 50% yield (Scheme 4.24). The glycoslylation of the saturated acid **4.56** is expected to proceed in a similar fashion (Scheme 4.25).



Scheme 4.26 Projected esterification/ ring closing towards ammocidin D.



Scheme 4.27 Projected elimination/ global protection completing ammocidin D.

Esterification with the southern hemisphere and formation of the macrocycle is anticipated to occur in a similar fashion to the formation of ammocidinone. Finally, the elimination and global deprotection would provide an isomer of ammocidin D. A careful examination of spectral data will determine if the relative stereochemistry is accurate.

Conclusion

The synthetic efforts towards ammocidinone and ammocidin D were examined. Our first attempts at an intermolecular C-C bond coupling failed but provided us insight in regards to an intramolecular variant. Next, we focused our attention on the successful esterification bringing together the two units. Using carefully applied models studies, intramolecular hydrostannylation/ Stille coupling provided the key macrocycle. Finally, the anticipated completion of ammocidinone and ammocidin D was outlined. With the completion of synthetic ammocidin D, a careful comparison of spectral data with natural ammocidin D will determine if the relative stereochemistry is accurate. Such a comparison is more reliable than the comparison of ammocidinone to natural ammocidin D.

Experimental Methods

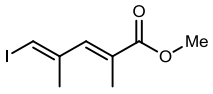
General Procedure: All non-aqueous reactions were performed in flame-dried or oven dried round-bottomed flasks under an atmosphere of argon. Stainless steel syringes or cannula were used to transfer air- and moisture-sensitive liquids. Reaction temperatures were controlled using a thermocouple thermometer and analog hotplate stirrer. Reactions were conducted at room temperature (rt, approximately 23 °C) unless otherwise noted. Flash column chromatography was conducted as described by Still et. al. using silica gel 230-400 mesh[1]. Where necessary, silica gel was neutralized by treatment of the silica gel prior to chromatography with the eluent containing 1% triethylamine. Analytical thin-layer chromatography (TLC) was performed on E. Merck silica gel 60 F254 plates and visualized using UV, and potassium permanganate stain. Yields were reported as isolated, spectroscopically pure compounds.

Materials: Solvents were obtained from either a MBraun MB-SPS solvent system or freshly distilled (tetrahydrofuran was distilled from sodium-benzophenone; toluene was distilled from calcium hydride and used immediately; dimethyl sulfoxide was distilled from calcium hydride and stored over 4 Å molecular sieves). Commercial reagents were used as received. The molarity of *n*-butyllithium solutions was determined by titration using diphenylacetic acid as an indicator (average of three determinations).

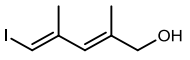
Instrumentation: Infrared spectra were obtained as thin films on NaCl plates using a Thermo Electron IR100 series instrument and are reported in terms of frequency of absorption (cm^{-1}). ^{1}H NMR spectra were recorded on Bruker 300, 400, 500, or 600 MHz spectrometers and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad, app = apparent), coupling constants (Hz), and integration. Deuterated chloroform was standardized to 7.26 ppm. ^{13}C NMR spectra were recorded on Bruker 75, 100, 125, or 150 MHz spectrometers and are reported relative to deuterated solvent signals. LC/MS was conducted and recorded on an Agilent Technologies 6130 Quadrupole instrument. High-resolution mass spectra were obtained from the Department of Chemistry and Biochemistry, University of Notre Dame using either a JEOL AX505HA or JEOL LMS-GCmate mass spectrometer. Optical rotations were obtained using a Perkin Elmer 341 polarimeter.

[1] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

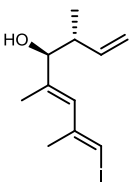
Preparation Procedures



(2*E*,4*E*)-methyl 5-iodo-2,4-dimethylpenta-2,4-dienoate (4.6). To a solution of **4.4** (2.02 g, 10.2 mmol) in DCM (72 mL) at 0 °C was added celite (4.6 g) and PCC (3.30 g, 15.3 mmol), and the mixture was allowed to stir for 3.5 h at 0 °C in the dark. After 3.5 h, the mixture was filtered over silica gel washing with ether and concentrated slowly to remove the ether. The resulting DCM solution was cooled to 0 °C, and methyl 2-(triphenylphosphoranylidene)propanoate (3.60 g, 10.3 mmol) was added. The reaction was stirred at rt for 1.5 h, concentrated, and filtered over silica washing with ether. The filtrate was concentrated, and the residue was purified by flash chromatography, eluting with hexanes/Et_2O (20:1) to give 1.91 g (70%) of **4.6** as a slightly yellow oil. Analytical data matches literature values.

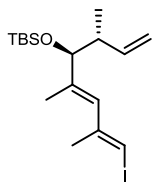


(2*E*,4*E*)-5-iodo-2,4-dimethylpenta-2,4-dien-1-ol (S1). To a solution of **4.6** (1.91 g, 7.18 mmol) in DCM (76 mL) at -78 °C was added DIBAL-H (3.2 mL, 17.9 mmol) dropwise over 20 min, and the reaction was stirred for 1 h. The reaction was quenched with MeOH (3 mL), warmed to rt, poured into a saturated solution of Rochelle's salt (75 mL) and stirred for 1 h. The mixture was extracted with DCM (3 × 50 mL), and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (6:1) to give 1.59 g (92%) of **S1** as a slightly yellow oil. IR: (neat) ν 3314, 2912, 1439, 1260 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.07 (s, 1 H), 5.91 (s, 1 H), 4.06 (d, *J* = 6.2 Hz, 2 H), 1.94 (s, 3 H), 1.76 (s, 3 H), 1.41 (t, *J* = 6.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 137.5, 125.4, 79.9, 68.2, 25.0, 15.4; HRMS (ESI) calcd for $[M + Na]^+$ $C_7H_{11}IO$ TBD



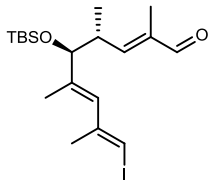
(3*R*,4*S*,5*E*,7*E*)-8-iodo-3,5,7-trimethylocta-1,5,7-trien-4-ol (4.8). To a solution of *t*-BuOK (dried overnight at 85 °C under high vacuum, 1.5 g, 13.4 mmol) in THF (34 mL) at -78 °C was added *cis*-2-butene (6.2 mL, 68.6 mmol). After 5 min, *n*-BuLi (2.5

M in hexanes, 5.3 mL, 13.4 mmol) was added dropwise to the solution. After 5 min, the reaction was warmed to -45 °C, stirred for 15 min, and recooled to -78 °C. A solution of (-)-(*i*pc)$_2$-BOMe (5.1 g, 16.1 mmol) in Et_2O (34 mL) was added via cannula, and the reaction was stirred for 30 min. Freshly distilled $BF_3{\cdot}Et_2O$ (2.6 mL, 18.0 mmol) was added dropwise, and the solution was stirred for 15 min. In the meantime, to a solution of **S1** (1.59 g, 6.68 mmol) in DCM (44 mL) at rt was added MnO_2 (11.1 g, 7 eq by wt), and the solution was stirred. After 1 h, the solution was filtered over celite washing with DCM and concentrated to 3-5 mL to provide a solution of aldehyde in DCM. This solution was added dropwise to the first solution 15 min after the addition of the $BF_3{\cdot}Et_2O$, and the reaction mixture was stirred at -78 °C overnight. In the morning, the reaction was quenched with NaOH (3 M, 23.7 mL) slowly and warmed to rt. H_2O_2 (30%, 9.1 mL) was added slowly and the mixture was heated at 60 °C for 2 h. After cooling to rt, the mixture was extracted with Et_2O (3 × 75 mL), and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (35:1) to give 1.70 g (87%) of **4.8** as a slightly yellow oil. $[\alpha]_D^{25}$ +8.1° (*c* 1.8, $CHCl_3$); IR (neat) ν 3410, 2973, 1451, 1296, 1008 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03 (s, 1 H), 5.87 (s, 1 H), 5.75 (ddd, *J* = 17.4, 10.5, and 7.3 Hz, 1 H), 5.11-5.02 (m, 2 H), 3.88 (dd, *J* = 6.2 and 3.5 Hz, 2 H), 2.50-2.39 (m, 1 H), 1.93 (s, 3 H), 1.71 (d, *J* = 1.2 Hz, 3 H), 1.57 (d, *J* = 3.5 Hz, 1 H), 1.02 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 140.7, 138.6, 127.0, 114.8, 78.0, 79.8, 41.1, 25.1, 14.3, 14.2; HRMS (ESI) calcd for $[M + Li]^+$ $C_{11}H_{17}ILiO$ 299.0484, found 299.0486. The enantiomeric excess of **4.8** was determined by ^{19}F NMR analysis after converting to the Mosher ester with (*R*)-(+)-α-(trifluoromethyl)phenylacetic acid (88% ee).

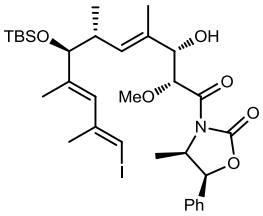


***tert*-Butyl(((3*R*,4*S*,5*E*,7*E*)-8-iodo-3,5,7-trimethylocta-1,5,7-trien-4-yl)oxy)dimethylsilane (S2).** To a solution of **4.8** (400 mg, 1.4 mmol) in DCM (9 mL) at - 78 °C was added 2,6-lutidine (480 µL, 4.1 mmol) followed by TBDMSOTf (630 µL, 2.7 mmol) dropwise, and the solution was stirred for 1 h. H_2O (10 mL) was added to the solution, and the mixture was allowed to warm to rt. The aqueous layer was extracted with DCM (3 × 10 mL), and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (250:1) to give 495 mg (89%) of **S2** as a slightly yellow oil. $[\alpha]_D^{20}$ +12.8 (*c* 0.69, $CHCl_3$); IR: (neat) ν 2956, 2857, 1471, 1254 cm^{-1}; ^{1}H NMR (400

MHz, $CDCl_3$) δ 5.96 (s, 1 H), 5.73 (s, 1 H), 5.63-5.54 (m, 1 H), 4.96 (d, *J* = 17.2 Hz, 1 H), 4.91 (d, *J* = 10.4 Hz, 1 H), 3.69 (d, *J* = 7.6 Hz, 1 H), 2.33-2.23 (m, 1 H), 1.90 (s, 3 H), 1.65 (s, 1 H), 1.00 (d, *J* = 6.4 Hz, 3 H), 0.89 (s, 9 H), 0.03 (s, 3 H), -0.03 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 141.3, 139.8, 127.0, 113.7, 82.1, 79.4, 42.6, 25.8, 25.0, 18.2, 15.8, 13.8, -4.9, -5.1; HRMS (ESI) calcd for $[M + Na]^+$ $C_{17}H_{31}INaOSi$ 429.1081, found 429.1063.

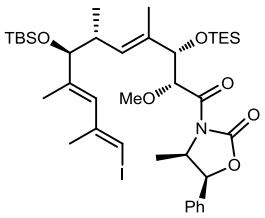


(2*E*,4*R*,5*S*,6*E*,8*E*)-5-((*tert*-butyldimethylsilyl)oxy)-9-iodo-2,4,6,8-tetramethylnona-2,6,8-trienal (4.9). Two 20 mL microwave vials were each charged with **S2** (400 mg, 0.98 mmol), methacrolein (810 µL, 9.8 mmol), Hoveyda-Grubbs second generation catalyst (92 mg, 0.15 mmol) and DCM (9.6 mL) and were irradiated in a Biotage Initiator microwave synthesizer at 100 °C for 1 h. After cooling, the mixtures were combined and concentrated, and the residue was purified by flash chromatography, eluting with hexanes/EtOAc (80:1) to give 520 mg (59%) of **4.9** as a slightly yellow oil. $[\alpha]_D^{20}$ -20.2 (*c* 0.64, $CHCl_3$); IR: (neat) ν 2956, 2857, 1691, 1255 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 1 H), 6.24 (d, *J* = 10.4 Hz, 1 H), 5.94 (s, 1 H), 5.79 (s, 1 H), 3.85 (d, *J* = 7.2 Hz, 1 H), 2.91-2.80 (m, 1 H), 1.87 (s, 3 H), 1.74 (d, *J* = 1.2 Hz, 3 H), 1.63 (d, *J* = 1.2 Hz, 3 H) 1.06 (d, *J* = 6.4 Hz, 3 H), 0.91 (s, 9 H), 0.04 (s, 3 H), -0.01 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.4, 156.7, 144.2, 139.0, 139.3, 127.6, 81.1, 80.0, 38.5, 25.9, 25.1, 18.3, 15.7, 14.0, 9.5, -4.3, -5.0; HRMS (ESI) calcd for $[M + Na]^+$ $C_{19}H_{33}INaO_2Si$ 471.1187, found 471.1180.

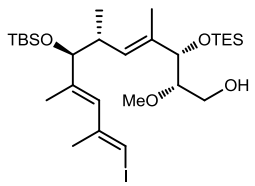


(4*R*,5*S*)-3-((2*R*,3*S*,4*E*,6*R*,7*S*,8*E*,10*E*)-7-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-11-iodo-2-methoxy-4,6,8,10-tetramethylundeca-4,8,10-trienoyl)-4-methyl-5-phenyloxazolidin-2-one (4.11). To a solution of (4*R*,5*S*)-3-(2-methoxyacetyl)-4-methyl-5-phenyloxazolidin-2-one (280 mg, 1.1 mmol) in $PhCH_3$ (2.2 mL) at -40 °C was added TEA (160 µL, 1.2 mmol) followed by *n*-Bu_2BOTf (1 M in DCM, 940 µL, 0.94 mmol) dropwise over 15 min, and the reaction mixture was allowed to stir for 1.5 h. A solution of **4.9** (134 mg, 0.30 mmol) in $PhCH_3$ (600 µL) was added dropwise to the reaction mixture, and the solution was stirred for 3 h. The reaction was quenched with MeOH (1 mL), diluted with pH 7 buffer (2 mL), treated with 30% H_2O_2 (2 mL), and allowed to stir for 1.5 at rt. The mixture was extracted with DCM (3 × 10 mL),

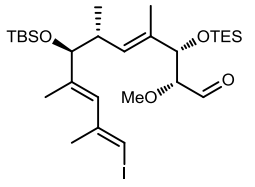
and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (7:1) to give 85 mg (40%) of **4.11** as a white solid. mp: 58-60 °C; $[\alpha]_D^{20}$ +45.3 (*c* 0.53, $CHCl_3$); IR: (thin film, $CHCl_3$) ν 3442, 2955, 2856, 1780, 1711, 1067 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52-7.36 (m, 3 H), 7.31-7.28 (m, 2 H), 5.97 (s, 1 H), 5.74 (s, 1 H), 5.68 (d, *J* = 6.9 Hz, 1 H), 5.24 (d, *J* = 10.0 Hz, 1 H), 5.19 (d, *J* = 3.8 Hz, 1 H), 4.75 (p, *J* = 6.9 Hz, 1 H), 4.26 (dd, *J* = 7.9 and 3.8 Hz), 3.73 (d, *J* = 7.4 Hz, 1 H), 3.40 (s, 3 H), 2.65-2.55 (m, 1 H), 2.44 (d, *J* = 7.9 Hz, 1 H), 1.90 (s, 3 H), 1.73 (s, 3 H), 1.63 (d, *J* = 1.2 Hz, 3 H), 0.99-0.95 (m, 6 H), 0.90 (s, 9 H), 0.05 (s, 3 H), -0.02 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 152.9, 144.4, 140.0, 132.8, 132.3, 129.9, 128.9, 128.8, 127.0, 125.5, 82.2, 80.8, 79.7, 79.5, 76.5, 58.6, 55.5, 37.2, 25.8, 25.0, 18.2, 17.0, 14.5, 13.7, 12.5, -4.5, -5.1; HRMS calcd for $[M + Na]^+$ $C_{32}H_{48}INNaO_6Si$ 720.2188, found 720.2207.



(4*R*,5*S*)-3-((2*R*,3*S*,4*E*,6*R*,7*S*,8*E*,10*E*)-7-((*tert*-butyldimethylsilyl)oxy)-3-((triethylsilyl)oxy)-11-iodo-2-methoxy-4,6,8,10-tetramethylundeca-4,8,10-trienoyl)-4-methyl-5-phenyloxazolidin-2-one (4.12). To a solution of **4.11** (540 mg, 0.78 mmol) in DCM (7.8 mL) at -78 °C was added 2,6-lutidine (270 μL, 2.3 mmol) followed by TESOTf (360 μL, 1.6 mmol) dropwise, and the solution was stirred for 25 min. H_2O (10 mL) was added to the solution, and the mixture was allowed to warm to rt. The aqueous layer was extracted with DCM (3 × 15 mL), and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (25:1) to give 598 mg (95%) of **4.12** as white solid. mp: 115-117 °C; $[\alpha]_D^{20}$ +5.6 (*c* 0.56, $CHCl_3$); IR: (thin film, $CHCl_3$) ν 2955, 2875, 1786, 1708, 1118 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.35 (m, 3 H), 7.30-7.28 (m, 2 H), 5.57 (d, *J*= 7.0 Hz, 1 H), 5.16-5.11 (m, 2 H), 4.66 (p, *J* = 6.7 Hz, 1 H), 4.36 (d, *J* = 6.4 Hz, 1 H), 3.69 (d, *J* = 8.0 Hz, 1 H), 3.42 (s, 3 H), 2.62-2.50 (m, 1 H), 1.91 (d, *J* = 0.6 Hz, 3 H), 1.68 (d, *J* = 1.0 Hz, 3 H), 1.64 (d, *J* = 1.1 Hz, 3 H), 0.97-0.91 (m, 15 H), 0.90 (s, 9 H), 0.61-0.53 (m, 6 H), 0.05 (s, 3 H), -0.02 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 152.7, 144.1, 139.8, 133.8, 132.9, 130.4, 128.9, 128.8, 127.4, 125.5, 82.7, 80.2, 79.2, 78.7, 59.1, 55.5, 37.1, 25.8, 25.1, 18.2, 17.3, 14.4, 13.5, 12.0, 6.9, 4.8, -4.4, -5.0; HRMS (ESI) calcd for $[M + Na]^+$ $C_{38}H_{62}INNaO_6Si_2$ 834.3053, found 834.3077.

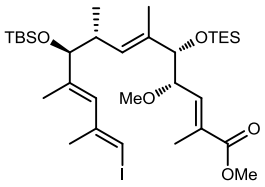


(2*S*,3*S*,4*E*,6*R*,7*S*,8*E*,10*E*)-7-((*tert*-butyldimethylsilyl)oxy)-11-iodo-2-methoxy-4,6,8,10-tetramethyl-3-((triethylsilyl)oxy)undeca-4,8,10-trien-1-ol (S3). To a solution of **4.12** (107 mg, 0.13 mmol) in THF (1.2 mL) at 0 °C was added $LiBH_4$ (2 M in THF, 150 µL, 0.30 mmol) dropwise, and the solution was stirred for 2 h as it warmed to rt. The mixture was diluted with saturated NH_4Cl (2 mL) slowly and Et_2O (5 mL) and allowed to stir 10 min. The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (9:1) to give 70 mg (83%) of **S3** as a colorless oil. $[\alpha]_D^{20}$ -22.8 (*c* 0.51, $CHCl_3$); IR: (neat) ν 3461, 2955, 2876, 1067 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.02 (s, 1 H), 5.76 (s, 1 H), 5.13 (d, *J* = 9.6 Hz, 1 H), 3.98 (d, *J* = 7.0 Hz, 1 H), 3.68 (d, *J* = 8.0 Hz, 1 H), 3.52 (s, 3 H), 3.48 (ddd, *J* = 11.6, 7.6, and 4.0 Hz, 1 H), 3.30 (ddd, *J* = 11.6, 6.8, and 5.0 Hz, 1 H), 3.20 (ddd, *J* = 7.0, 6.8, and 4.0 Hz, 1 H), 2.60-2.49 (m, 1 H), 2.01 (dd, *J* = 7.6 and 5.0 Hz, 1 H), 1.92 (d, *J* = 0.8 Hz, 3 H), 1.64 (d, *J* = 1.2 Hz, 3 H), 1.61 (d, *J* = 1.2 Hz, 3 H), 0.97-0.90 (m, 9 H), 0.89 (s, 9 H), 0.59-0.50 (m, 6 H), 0.04 (s, 3 H), -0.03 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1, 139.8, 134.4, 129.5, 127.4, 84.5, 83.0, 80.2, 78.9, 61.8, 59.9, 36.9, 25.8, 25.1, 18.2, 17.0, 13.4, 12.4, 6.8, 4.8, -4.4, -5.1; HRMS (ESI) calcd for $[M + Na]^+$ $C_{28}H_{55}INaO_4Si_2$ 661.2576, found 661.2597.

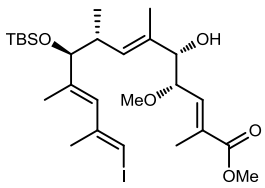


(2*R*,3*S*,4*E*,6*R*,7*S*,8*E*,10*E*)-7-((*tert*-butyldimethylsilyl)oxy)-11-iodo-2-methoxy-4,6,8,10-tetramethyl-3-((triethylsilyl)oxy)undeca-4,8,10-trienal (4.13). To a solution of oxalyl chloride (18.7 µL, 0.22 mmol) in DCM (200 µL) at -78 °C was added a solution of DMSO (26.4 µL, 0.37 mmol) in DCM (200 µL) dropwise, and the reaction was stirred for 30 min. To this solution was added a solution of **S3** (23.7 mg, 0.037 mmol) in DCM (400 µL) dropwise, and the reaction was stirred for 30 min. TEA (52 µL, 0.37 mmol) was then added, and the reaction was stirred for 30 min before warming to rt. H_2O (3 mL) was added, and the mixture was extracted with DCM (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (20:1) to give 23.6 mg (100%) of **4.13** as a colorless oil. $[\alpha]_D^{20}$ +23.7 (*c* 0.32, $CHCl_3$); IR: (neat) ν 2956,

2877, 1734, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.49 (d, *J* = 2.5 Hz, 1 H), 6.02 (s, 1 H), 5.74 (s, 1 H), 5.16 (d, *J* = 9.7 Hz, 1 H), 4.16 (d, *J* = 5.9 Hz, 1 H), 3.66 (d, *J* = 7.8 Hz, 1 H), 3.50 (dd, *J* = 5.9 and 2.5 Hz, 1 H), 3.40 (s, 3 H), 2.60-2.48 (m, 1 H), 1.90 (d, *J* = 0.7 Hz, 3 H), 1.62 (s, 6 H), 0.95-0.83 (m, 21 H), 0.59-0.49 (m, 6 H), 0.04 (s, 3 H), -0.03 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.8, 144.1, 139.9, 133.5, 130.2, 127.3, 89.4, 82.8, 80.2, 77.6, 59.1, 37.1, 25.8, 25.0, 18.2, 17.0, 13.5, 12.7, 6.8, 4.7, -4.4, -5.1; HRMS (ESI) calcd for $[M + Na]^+$ $C_{28}H_{53}INaO_4Si_2$ 659.2419, found 659.2391.

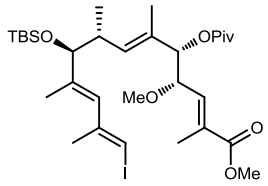


(2*E*,4*S*,5*S*,6*E*,8*R*,9*S*,10*E*,12*E*)-methyl-9-((*tert*-butyldimethylsilyl)oxy)-13-iodo-4-methoxy-2,6,8,10,12-pentamethyl-5-((triethylsilyl)oxy)trideca-2,6,10,12-tetraenoate (4.14). To a solution of **4.13** (51.6 mg, 0.081 mmol) in DCM (1.1 mL) at 0 °C was added methyl 2-(triphenylphosphoranylidene)propanoate (113 mg, 0.32 mmol), and the reaction was allowed to stir for 1 h before warming to rt. After 1 h, more phosphorane (85 mg, 0.24 mmol) was added and the reaction was stirred for 2 h before dilution with hexanes/EtOAc (10:1). The solution was filtered over silica washing with hexanes/EtOAc (10:1) and concentrated. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (25:1) to give 53.4 mg (93%) of **4.14** as a slight yellow oil. $[\alpha]_D^{20}$ +0.6 (*c* 0.25, $CHCl_3$); IR: (neat) ν 2955, 2876, 1721, 1112, 1075 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.36 (dq, *J* = 9.4 and 1.4 Hz, 1 H), 5.98 (s, 1 H), 5.75 (s, 1 H), 5.00 (d, *J* = 9.6 Hz, 1 H), 3.96-3.84 (m, 2 H), 3.72 (s, 3 H), 3.65 (d, *J* = 7.8 Hz, 1 H), 3.26 (s, 3 H), 2.51-2.40 (m, 1 H), 1.90 (d, *J* = 0.7 Hz, 3 H), 1.88 (d, *J* = 1.4 Hz, 3 H), 1.61 (d, *J* = 1.2 Hz, 3 H), 1.52 (d, *J* = 1.2 Hz, 3 H), 0.94-0.86 (m, 18 H), 0.79 (d, *J* = 6.7 Hz, 3 H), 0.59-0.49 (m, 6 H), 0.03 (s, 3 H), -0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 144.2, 139.9, 138.9, 134.1, 130.3, 130.2, 127.2, 82.8, 80.9, 80.8, 80.0, 57.2, 51.8, 37.0, 25.8, 25.1, 18.2, 16.8, 13.5, 13.1, 11.8, 6.8, 4.8, -4.4, -5.1; HRMS (ESI) calcd for $[M + Na]^+$ $C_{32}H_{59}INaO_5Si_2$ 729.2838, found 729.2841.

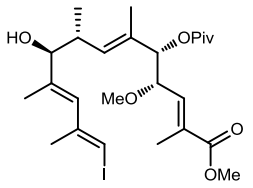


(2*E*,4*S*,5*S*,6*E*,8*R*,9*S*,10*E*,12*E*)-methyl 9-((*tert*-butyldimethylsilyl)oxy)-5-hydroxy-13-iodo-4-methoxy-2,6,8,10,12-pentamethyltrideca-2,6,10,12-tetraenoate (4.15). To a solution of **4.14** (320 mg, 0.45 mmol) in THF/H_2O (3:1, 14 mL) at rt was added TFA (140 μL) dropwise,

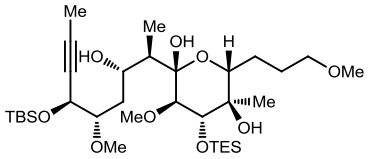
and the reaction was stirred for 40 min. Saturated $NaHCO_3$ (10 mL) was added, and the mixture was extracted with Et_2O (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (10:1) to give 250 mg (93%) of **4.15** as a colorless oil. mp: 68-70 °C $[\alpha]_D^{20}$ +10.9 (*c* 0.59, $CHCl_3$); IR: (neat) ν 3501, 2954, 2856, 1720, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.39 (dq, *J* = 9.3 and 1.4 Hz, 1 H), 5.95 (s, 1 H), 5.73 (s, 1H), 5.11 (d, *J* = 9.8 Hz, 1 H), 3.94-3.84 (m, 2 H), 3.74 (s, 3 H), 3.68 (d, *J* = 7.1 Hz, 1 H), 2.77 (d, *J* = 1.7 Hz, 1 H), 2.54-2.44 (m, 1 H), 1.88 (d, *J* = 0.5 Hz, 3 H), 1.86 (d, *J* = 1.4 Hz, 3 H), 1.60 (d, *J* =1.3 Hz, 3 H), 1.59 (d, *J* = 1.2 Hz, 3 H), 0.88 (s, 9 H), 0.80 (d, *J* = 6.7 Hz, 3 H). 0.02 (s, 3 H), -0.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 144.5, 139.8, 137.8, 132.8, 131.3, 126.8, 81.8, 79.5, 79.41, 79.38, 56.9, 52.0, 36.9, 25.8, 25.0, 18.2, 16.2, 13.8, 13.2, 11.7, -4.5, -5.1; HRMS (ESI) calcd for $[M + Na]^+$ $C_{26}H_{45}INaO_5Si$ 615.1973, found 615.1942.



(2*E*,4*S*,5*S*,6*E*,8*R*,9*S*,10*E*,12*E*)-methyl 9-((*tert*-butyldimethylsilyl)oxy)-13-iodo-4-methoxy-2,6,8,10,12-pentamethyl-5-(pivaloyloxy)trideca-2,6,10,12-tetraenoate (4.16). To a solution of **4.15** (247 mg, 0.42 mmol) in DCM (2.1 mL) at 0 °C was added DMAP (25 mg, 0.21 mmol), TEA (870 µL, 6.3 mmol), and PivCl (500 µL, 4.2 mmol), and the solution was allowed to stir at rt overnight. The reaction was quenched with sat. $NaHCO_3$ (5 mL) and extracted with DCM (3 × 10 mL). The combined organic extracts were washed with H_2O, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (15:1) to give 260 mg (91%) of **4.16** as slight yellow oil. $[\alpha]_D^{20}$ +22.8 (*c* 0.37, $CHCl_3$); IR: 2956, 2929, 2857, 1724, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.43 (dd, *J* = 9.6 and 1.4 Hz, 1 H), 5.97 (s, 1 H), 5.72 (s, 1 H), 5.20-5.13 (m, 2 H), 4.11 (dd, *J* = 9.6 and 7.7 Hz, 1 H), 3.74 (s, 3 H), 3.66 (d, *J* = 7.7 Hz, 1 H), 3.25 (s, 3 H), 2.52-2.40 (m, 1 H), 1.91 (d, *J* = 1.4 Hz, 3 H), 1.86 (s, 3 H), 1.58 (d, *J* = 1.2 Hz, 3 H), 1.56 (d, *J* = 1.0 Hz, 3 H), 1.20 (s, 9 H), 0.88 (s, 9 H), 0.84 (d, *J* = 6.6 Hz, 3 H), 0.03 (s, 3 H), -0.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 167.8, 144.3, 140.0, 137.4, 133.5, 131.5, 129.3, 127.1, 81.9, 79.7, 79.4, 78.0, 57.1, 52.0, 38.9, 37.5, 27.2, 25.8, 24.9, 18.2, 16.8, 13.6, 13.2, 12.5, -4.5, -5.1; HRMS (ESI) calcd for $[M + Na]^+$ $C_{31}H_{53}INaO_6Si$ 699.2548, found 699.2523.

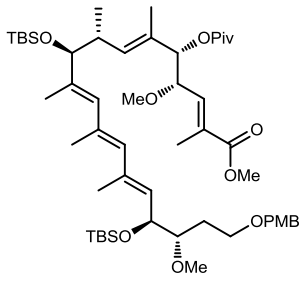


(2*E*,4*S*,5*S*,6*E*,8*R*,9*S*,10*E*,12*E*)-methyl 9-hydroxy-13-iodo-4-methoxy-2,6,8,10,12-pentamethyl-5-(pivaloyloxy)trideca-2,6,10,12-tetraenoate (4.56). To a solution of **4.16** (52 mg, 0.077 mmol) in THF (750 µL) at 0 °C was added HF·pyr (500 µL), and the solution was allowed to stir as it warmed to rt. After 30 min, the reaction was quenched with sat. $NaHCO_3$ (10 ml) and extracted with EtOAc (3 × 10 ml). The combined organic extracts were washed with sat. $NaHCO_3$, H_2O, brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (4:1) to give 31 mg (72%) of **4.56** as a yellow oil. $[\alpha]_D^{20}$ +23.0 (*c* 0.46, $CHCl_3$); IR: 3504, 2957, 2930, 2871, 1721, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.45 (dd, *J* = 9.6 and 1.4 Hz, 1 H), 6.05 (s, 1 H), 5.86 (s, 1 H), 5.28 (d, *J* = 9.6 Hz, 1 H), 5.15 (d, *J* = 7.0 Hz, 1 H), 4.14 (dd, *J* = 9.6 and 7.0 Hz, 1 H), 3.83 (dd, *J* = 6.8 and 4.0 Hz, 1 H), 3.75 (s, 3 H), 3.27 (s, 3 H), 2.62-2.50 (m, 1 H), 1.93 (d, *J* = 1.4 Hz, 3 H), 1.90 (s, 3 H), 1.71 (d, *J* = 4.0 Hz, 1 H), 1.64 (d, *J* = 1.2 Hz, 3 H), 1.61 (d, *J* = 0.8 Hz, 3 H), 1.21 (s, 9 H), 0.89 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 167.8, 144.2, 139.0, 137.4, 132.5, 131.6, 130.1, 127.3, 80.6, 80.1, 79.1, 77.9, 57.1, 52.0, 38.9, 36.3, 27.2, 25.1, 15.7, 14.1, 13.2, 13.1; HRMS (ESI) calcd for $[M + Na]^+$ $C_{25}H_{39}INaO_6$ 585.1684, found 585.1667.

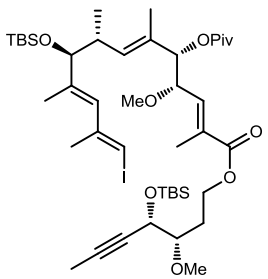


(2S,3R,4R,5R,6R)-2-((2R,3S,5S,6S)-6-((tert-butyldimethylsilyl)oxy)-3-hydroxy-5-methoxynon-7-yn-2-yl)-3-methoxy-6-(3-methoxypropyl)-5-methyl-4-((triethylsilyl)oxy)tetrahydro-2H-pyran-2,5-diol (4.37). To pyranose **3.84** (28 mg, 51 µmol) in CH_2Cl_2 (.5 mL) was added imidazole (9.5 mg, 63 µmol) then TESCl (0.127 mL, .5M solution) then stirred for 20 min at rt. Reaction solution was washed with $NaHCO_3$ (2 mL) then extracted with CH_2Cl_2 (3 X 5 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (1:1, hexanes: ethyl acetate) to afford 18 mg (53%) of **4.37** as clear oil. $[\alpha]_D^{26}$ +11.2 (*c* 2.6, $CHCl_3$); R_f .25 (1:1, H:EA); IR (neat) 3415, 2925, 2878 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.25 (s, 1H), 4.52 (dd, *J* = 5.6, 2.1 Hz, 1H), 4.06 (dd, *J* = 10.0, 3.3 Hz, 1H), 3.91 (dd, *J* = 9.8, 2.4 Hz, 1H), 3.79 (dd, *J* = 10.1, 2.1 Hz, 1H), 3.59 (s, 3H), 3.41 (s, 3H), 3.47-3.34 (m, 3H), 3.32 (s, 3H), 3.26 (dd, *J*

= 3.26 Hz, 1H), 2.93 (d, *J* = 9.8 Hz, 1H), 2.38 (qd, *J* = 7.2, 3.6 Hz, 1H), 2.29 (s, 1H), 2.14 (dd, *J* = 14.7, 10.3 Hz, 1H), 1.97-1.88 (m, 3H), 1.83 (s, 3H), 1.81-1.74 (m, 2H), 1.62 (s, 3H), 1.45-1.33 (m, 3H), 1.13 (s, 3H), 1.03 (t, *J* = 7.9 Hz, 9H), 0.95 (d, *J* = 7.2 Hz, 3H), 0.92 (s, 9H), 0.71 (m, 6H), 0.13 (d, *J* = 9.2 Hz, 6H), ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 100.8, 81.6, 81.59, 80.7, 77.9, 76.5, 75.0, 74.1, 73.2, 72.9, 64.2, 60.8, 58.3, 58.2, 40.8, 34.2, 26.9, 25.7, 25.7, 24.9, 18.2, 15.3, 14.0, 12.7, 6.7, 4.9, 4.8, 3.5, -4.7, -5.2 ; HRMS calcd for $C_{33}H_{66}O_9Si_2Na$ [M+Na] 685.4138, found 685.4159.

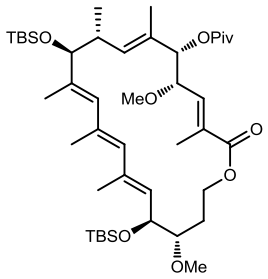


(2E,4S,5S,6E,8R,9S,10E,12E,14E,16S,17S)-methyl 9,16-bis((tert-butyldimethylsilyl)oxy)-4,17-dimethoxy-19-((4-methoxybenzyl)oxy)-2,6,8,10,12,14-hexamethyl-5-(pivaloyloxy)nonadeca-2,6,10,12,14-pentaenoate (4.23). To the methyl ester **4.16** (8 mg, 0.011 mmol) and the vinyl tin **3.91** (24 mg, .0355 mmol) in DMF (.25 mL) was degassed via freeze pump thaw (3 cycles). The reaction was added $PdCl_2(MeCN)_2$ and stirred at rt for 24h. After 24h at rt, considerable methyl ester was present by TLC thus reaction then heated to 65°C for 3 h. Reaction was then washed with water (10 mL) and extracted with CH_2Cl_2, dried ($MgSO_4$). The organic layers were concentrated and used immediately in the next reaction. The reaction content was added neat DBU (.200 mL) and was heated to 50°C overnight. The reaction contents was washed with H_2O and extracted with CH_2Cl_2 and dried over $MgSO_4$. The residue was purified by flash chromatography (15:1, hexanes: ethyl acetate) to afford 3 mg (20% over 2 steps) of **4.23** as clear oil. R_f .25 (15:1, H:EA); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96 (s, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.76 (s, 1H), 5.59 (s, 1H), 5.57 (s, 1H), 5.41 (d, *J* = 10.2 Hz, 1H), 5.27 (d, *J* = 9.12 Hz, 1H), 4.41 (dd, *J* = 6.2, 6.7 Hz, 2H), 3.79 (s, 3H), 3.75 (s, 3H), 3.58-3.52 (m, 2H), 3.47 (s, 3H), 3.34 (s, 3H), 3.25-3.23 (m, 1H), 2.65 (m, 1H), 2.09 (s, 3H), 1.95 (s, 3H), 1.83 (s, 3H), 1.70 (s, 3H), 1.67 (s, 3H), 1.25 (s, 15H), 0.97 (d, *J* = 6.5 Hz 3H), 0.89 (d, *J* = 11.0 Hz, 16H), 0.068,0.063 (s, 4H), 0.0377, 0.024 (s, 4H), -0.0114 (s, 2H).



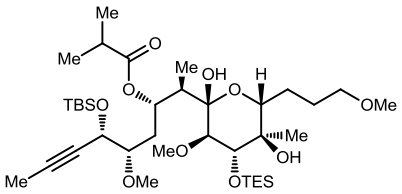
(2E,4S,5S,6E,8R,9S,10E,12E)-(3S,4S)-4-((tert-butyldimethylsilyl)oxy)-3-methoxyhept-5-yn-1-yl 9-((tert-butyldimethylsilyl)oxy)-13-iodo-4-

methoxy-2,6,8,10,12-pentamethyl-5-(pivaloyloxy)trideca-2,6,10,12-tetraenoate (4.28). To the acid **4.16** (15 mg, 22.65 µmol) was added CH_2Cl_2 (.5mL), Et_3N (9.4 µL, 67.97 µmol), EDCI (5.2 mg, 33.98 µmol), DMAP (cat.) and stirred at rt for 10 min. Consumption of the acid was observed by TLC and subsequently added alcohol **3.79** (12.3 mg, 45.31 µmol) and stirred for 24 h at rt. Reaction solution was washed with $NaHCO_3$ (2 mL) then extracted with CH_2Cl_2 (3 X 5 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (15:1, hexanes: ethyl acetate) to afford 9 mg (40%) of **4.28** as clear oil. $[\alpha]_D^{26}$ -1.5 (*c* 0.2, $CHCl_3$); R_f .25 (15:1, H:EA); IR (neat) 2929, 2858, 1721, 1255 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.45 (d, *J* = 9.5, 1H), 5.96 (s, 1H), 5.72 (s, 1H), 5.17 (d, *J* = 7.6 Hz, 2H), 4.43 (dd, *J* = 2.1, 5.5 Hz, 1H), 4.27 (m, 2H), 4.10 (dd, *J* = 7.6 Hz, 9.4, 1H), 3.65 (d, *J* = 3.65 Hz, 1H), 3.44 (s, 3H), 3.24 (s, 3H), 2.45 (sextet, *J* =9.6 Hz, 1H), 2.1 (m, 1H), 1.91 (s, 3H), 1.86 (s, 3H), 1.84 (s, *3*H), 1.57 (s, 3H), 1.20 (s, 9H), 0.91 (s 9H), 0.87 (s, 9H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.12 (d, *J* = 9.3 Hz, 6H), 0.02 (d, 26.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 167.2, 144.3, 139.7, 137.2, 133.5, 131.8, 129.2, 127.2, 82.3. 81.9, 81.2, 79.7, 79.5, 78.1, 77.7, 65.3, 62.0, 59.3, 57.1, 38.9, 37.5, 30.3, 29.8, 27.2, 25.8, 24.9, 18.2, 18.1, 16.9, 13.9, 13.2, 12.4, 3.6, -4.5, -4.6, -5.0 ; HRMS calcd for $C_{44}H_{77}O_8Si_2Na$ [M+Na] 939.4094, found 939.4086.

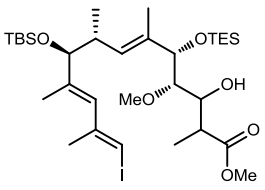


(3E,5S,6S,7E,9R,10S,11E,13E,15E,17S,18S)-10,17-bis((tert-butyldimethylsilyl)oxy)-5,18-dimethoxy-3,7,9,11,13,15-hexamethyl-2-oxooxacycloicosa-3,7,11,13,15-pentaen-6-yl pivalate (4.29). To the alkyne **4.28** (9 mg, 8.85 µmol) in benzene (.5 mL) was added nBu_3SnH (16.67 µL, 62.00 µmol), $PdCl_2(PPH_3)_2$ (cat.) and stirred overnight at 70°C. Gas evolution was observed upon addition of nBu_3SnH. The reaction solution was washed with $NaHCO_3$ (2 mL) then extracted with CH_2Cl_2 (3 X 5 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* furnishing a clear oil. The residue was purified by flash chromatography (20:1, hexanes: ethyl acetate) to afford 3 mg (43%) of **4.29** as a clear oil. R_f .25 (15:1, H:EA); IR (neat) 2956, 2858, 1720, 1253 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.46 (d, *J* = 7.2, 1H), 5.72 (s, 1H), 5.20 (d, *J* = 7.1 Hz, 2H), 4.92 (s, 1H), 4.71 (s, 1H), 4.43 (s, 1H), 4.28 (t, *J* = 7.3 Hz, 1H), 4.09 (t, *J* = 7.6 Hz, 1H), 3.67 (d, *J* = 7.2 Hz, 1H), 3.44 (s, 3H), 3.24 (s, 3H), 2.47 (q, 1H), 2.10 (m, 1H), 1.91 (s, 3H), 1.84 (d, 3H), 1.78 (s, 3H), 1.64 (s, 3H), 1.57 (s, 3H), 1.40 (m, 2H), 1.19 (s, 9H), 0.91 (s, 9H), 0.88 (s, 9H), 0.85 (d, *J* = 6.4 Hz, 3H), 0.13 (d, *J*

= 11.6 Hz, 6H), 0.01 (d, *J* = 18.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ176.8, 167.2, 152.6, 145.6, 141.6, 138.0, 137.2, 134.8, 133.9, 131.8, 130.9, 129.7, 129.1, 128.4, 127.7, 114.3, 82.5, 82.3, 81.2, 79.3, 78.2, 77.7, 65.3, 61.9, 59.3, 56.9, 38.8, 37.5, 31.6, 29.8, 27.1, 26.5, 25.8, 25.7, 23.5, 18.2, 16.8, 13.7, 13.7, 13.2, 12.6, 3.6, -4.5, -4.6, -5.0, -5.1 ; HRMS calcd for $C_{44}H_{78}O_8Si_2Na$ [M+Na] 813.5127, found 813.5165.

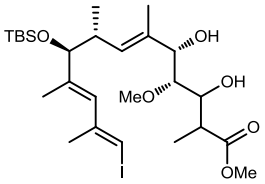


(2R,3S,5S,6S)-6-((tert-butyldimethylsilyl)oxy)-2-((2S,3R,4R,5R,6R)-2,5-dihydroxy-3-methoxy-6-(3-methoxypropyl)-5-methyl-4-((triethylsilyl)oxy)tetrahydro-2H-pyran-2-yl)-5-methoxynon-7-yn-3-yl isobutyrate (4.38). To the tiglic acid (3.2 mg, 36.4 µmol) in CH_2Cl_2 (.5 mL) was added Et_3N (10.1 µL, 72.2 µmol), DMAP (cat.) then EDCI (7 mg, 36.4 µmol) at rt. Reaction solution was stirred for 10 min then added southern hemisphere (5 mg, 7.2 µmol). The resulting solution was stirred at rt for 2h, washed with aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* furnishing a clear oil. The residue was purified by flash chromatography (4:1 hexanes: ethyl acetate) to afford 4 mg (75%) of **4.38**. R_f .25 (4:1, H:EA); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.25 (s, 1H), 5.15 (d, *J* = 9.8 Hz, 1H), 4.49 (s, 1H), 4.05 (d, *J* = 9.9 Hz, 1H), 3.85 (d, *J* = 9.2 Hz, 1H), 3.49 (s, 3H), 3.47 (s, 3H), 3.43-3.39 (m, 2H), 3.30 (s, 3H), 3.24 (dd, *J* = 10.1, 5.8 Hz, 1H), 3.12 (d, *J* = 9.8 Hz, 1H), 2.86 (s, 1H), 2.63 (p, 1H), 2.37 (dd, *J* = 7.0, 3.4 Hz, 1H), 2.11 (dd, *J* = 14.8, 10.5 Hz, 1H), 1.88 (m, 1H), 1.81 (s, 5H), 1.22 (t, *J* = 7.1 Hz, 9H), 2.58 (s, 3H), 1.00 (t, *J* = 7.9 Hz, 3H), 0.94 (d, *J* = 7.3 Hz, 3H), 0.90 (s, 9H), 0.74-0.63 (m, 6H), 0.12 (d, *J* = 9.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.8, 100.6, 80.7, 79.5, 79.4, 74.9, 74.3, 73.9, 72.9, 64.3, 60.5, 58.4, 58.2, 40.5, 34.4, 34.3, 27.0, 25.7, 24.7, 19.2, 18.8, 14.5, 12.6, 6.8, 4.8, 3.5, -4.7, -5.2.

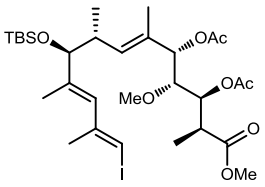


(4*S*,5*S*,6*E*,8*R*,9*S*,10*E*,12*E*)-methyl 9-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-13-iodo-4-methoxy-2,6,8,10,12-pentamethyl-5-((triethylsilyl)oxy)trideca-6,10,12-trienoate (S4). To a solution of methyl propionate (28 µL, 0.29 mmol) in DCM (700 µL) at -78 °C was added di-*n*-butylboron triflate (1 M in DCM, 250 µL, 0.25 mmol) followed by DIPEA (59 µL, 0.44

mmol) dropwise, and the reaction was stirred for 2 h. A solution of **4.13** (61 mg, 0.096 mmol) in DCM (600 µL) was added dropwise to the reaction mixture and was allowed to stir for 1 h. The reaction was quenched with MeOH (1 mL), pH 7 buffer (2 mL), and 30% H_2O_2 (1 mL) and allowed to stir at rt for 2 h. The mixture was extracted with DCM (3 × 8 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (25:1) to give 56 mg (80%) of **S4** as a mixture of three diastereomers. The mixture was brought forward, and each isomer was separated at a later point.

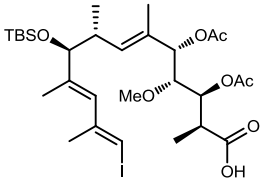


(4*S*,5*S*,6*E*,8*R*,9*S*,10*E*,12*E*)-methyl 9-((*tert*-butyldimethylsilyl)oxy)-3,5-dihydroxy-13-iodo-4-methoxy-2,6,8,10,12-pentamethyltrideca-6,10,12-trienoate (4.44-4.46). To a solution of **S4** (58 mg, 0.080 mmol) in THF/H_2O (3:1, 2.7 mL) at rt was added TFA (31 µL), and the reaction mixture was stirred until complete consumption of starting material. The reaction was quenched with aqueous $NaHCO_3$ (5 mL), extracted with Et_2O (3 × 5 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (4:1) to give 41 mg (84%) of **4.44** and **4.46** as a mixture of two diastereomers.

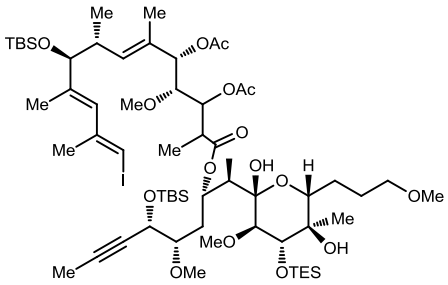


(2*S*,3*S*,4*S*,5*S*,6*E*,8*R*,9*S*,10*E*,12*E*)-9-((*tert*-butyldimethylsilyl)oxy)-13-iodo-1,4-dimethoxy-2,6,8,10,12-pentamethyl-1-oxotrideca-6,10,12-triene-3,5-diyl diacetate (S5). To a solution of **4.44** and **4.46** (40 mg, 0.066 mmol) and DMAP (cat.) in pyridine (540 µL) at 0 °C was added acetic anhydride (90 µL, 0.95 mmol), and the reaction mixture was stirred for 1 h. The reaction was quenched with aqueous $NaHCO_3$ (4 mL) and extracted with DCM (3 × 5 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (8:1) to give 35 mg (76%) of **S5** as a colorless oil. IR: 2953, 2857, 1743, 1237, 1067; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (s, 1 H), 5.71 (s, 1 H), 5.28-5.20 (m, 2 H), 5.14 (d, *J* = 5.0 Hz, 1 H), 3.68 (d, *J* = 7.6 Hz, 1 H), 3.65 (s, 3 H), 3.47 (dd, *J* = 6.4 and 5.2 Hz, 1 H), 3.38 (s, 3 H), 2.83 (dq, *J* = 7.1 and 4.2 Hz, 1 H), 2.55 (ddq, *J* = 10.0, 7.6, and 6.6 Hz, 1

H), 2.03 (s, 3 H), 2.01 (s, 3 H), 1.87 (s, 3 H), 1.66 (d, *J* = 1.0 Hz, 3 H), 1.62 (d, *J* = 1.2 Hz, 3 H), 1.19 (d, *J* = 7.1 Hz, 3 H), 0.92 (d, *J* = 6.6 Hz, 3 H), 0.88 (s, 9 H), 0.03 (s, 3 H), -0.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 169.7, 169.6, 144.4, 139.4, 132.7, 130.1, 127.1, 82.0, 81.8, 79.6, 77.1, 60.6, 51.9, 39.9, 37.3, 25.8, 24.9, 21.0, 20.7, 18.2, 16.6, 13.8, 12.8, 11.5, -4.5, -5.2; HRMS to be determined.

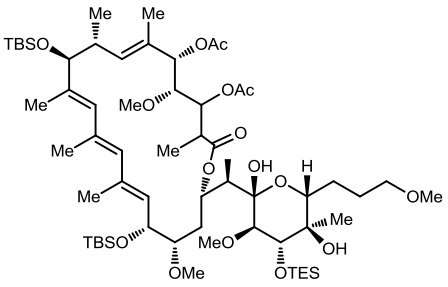


(2*S*,3*S*,4*S*,5*S*,6*E*,8*R*,9*S*,10*E*,12*E*)-3,5-diacetoxy-9-((*tert*-butyldimethylsilyl)oxy)-13-iodo-4-methoxy-2,6,8,10,12-pentamethyltrideca-6,10,12-trienoic acid (4.47). A suspension of **S5** (33 mg, 0.048 mmol) and Me_3SnOH (90 mg, 0.48 mmol) in DCE (1.1 mL) was irradiated in a Biotage Initiator microwave synthesizer at 135 °C for 2 h. After cooling, the mixture was purified directly by flash chromatography, eluting with DCM/MeOH (35:1) to give 18 mg (57%) of **4.47** as a colorless oil. IR: 2931, 2857, 1743, 1460 ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (s, 1 H), 5.71 (s, 1 H), 5.30-5.24 (m, 2 H), 5.15 (d, *J* = 5.3 Hz, 1 H), 3.68 (d, *J* = 7.6 Hz, 1 H) 3.51 (app t, *J* = 6.0 Hz, 1 H), 3.39 (s, 3 H), 2.83 (dq, *J* = 6.6 and 4.7 Hz, 1 H), 2.54 (ddq, *J* = 9.6, 7.1, and 6.8 Hz, 1 H), 2.04 (s, 3 H), 2.03 (s, 3 H), 1.87 (s, 3 H), 1.66 (s, 3 H), 1.61 (d, *J* = 0.9 Hz, 3 H), 1.23 (d, *J* = 7.1 Hz, 3 H), 0.92 (d, *J* = 6.6 Hz, 3 H), 0.88 (s, 9 H), 0.03 (s, 3 H), -0.04 (s, 3 H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 169.7, 144.3, 139.4, 133.0, 129.9, 127.1, 82.2, 81.8, 79.5, 71.6, 60.6, 40.1, 37.2, 25.8, 24.9, 21.0, 20.7, 18.1, 16.5, 13.8, 12.7, 11.8, -4.6, -5.2; HRMS to be determined.



(5R,6S,8S,13S,14S,17R,18S,E)-8-((R)-1-((2S,3R,4R,5R,6R)-2,5-dihydroxy-3-methoxy-6-(3-methoxypropyl)-5-methyl-4-((triethylsilyl)oxy)tetrahydro-2H-pyran-2-yl)ethyl)-18-((2E,4E)-5-iodo-4-methylpenta-2,4-dien-2-yl)-6,13-dimethoxy-2,2,3,3,11,15,17,20,20,21,21-undecamethyl-10-oxo-5-(prop-1-yn-1-yl)-4,9,19-trioxa-3,20-disiladocos-15-ene-12,14-diyl diacetate (4.50). To the acid **4.47** (10 mg, 14.7 µmol) in toluene (.3 mL) at rt was added Et_3N (10.22 µL, 73.5 µmol), DMAP (cat.), EDCI (3.37 mg, 17.6 µmol) and stirred 10 min. Upon

consumption of the acid (10 min) 4.33 (15 mg, 19 µmol) and heated to 70°C. The resulting solution was stirred for 6 h, washed with aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* furnishing a clear oil. The residue was purified by flash chromatography (5:1,4:1, 1:1 hexanes: ethyl acetate) to afford 14 mg (33%) of **4.50**. R_f .25 (4:1, H:EA); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.15 (s, 1H), 5.96 (s, 1H), 5.74 (s, 1H), 5.44 (t, *J* = 8.9, 1H), 5.28 (t, *J* = 10.4 Hz, 2H), 5.09 (d, *J* = 3.1 Hz, 1H), 4.49 (dd, *J* = 5.6, 2.1 Hz, 1H), 4.04 (dd, *J* = 3.1, 2.5 Hz, 1H), 3.88 (d, *J* = 8.8 Hz, 1H), 3.72 (d, *J* = 6.9 Hz, 1H), 3.47 (s, 3H), 3.42 (s, 3H), 3.41-3.38 (m, 2H), 3.33 (s, 3H), 3.29 (s, 3H), 3.25 (dd, *J* = 10.2, 6.0 Hz, 1H), 3.06 (d, *J* = 10.1 Hz, 1H), 2.72 (dq, *J* = 9.0, 7.1 Hz, 1H), 2.54 (dt, *J* = 9.5, 6.8 Hz, 1H), 2.34 (d, *J* = 3.4 Hz, 1H), 2.18 (d, *J* = 10.2 Hz, 1H), 2.04 (d, *J* = 2.8, 6H), 1.88 (s, 3H), 1.83-1.81 (d, *J* = 1.8 Hz, 5H), 1.63 (d, *J* = 5.2 Hz, 6H), 1.57 (s, 5H), 1.25 (s, 3H), 1.23 (d, *J* = 7.5 Hz, 3H), 1.17 (s, 3H), 0.99 (t, *J* = 7.9 Hz, 9H), 0.90 (d, *J* = 3.7 Hz, 18H), 0.75-0.62 (m, 6H), 0.12 (d, *J* = 9.66 Hz, 6H), 0.04 (d, *J* = 31 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 169.8, 169.7, 144.4, 139.3, 131.9, 130.1, 127.0, 100.7, 85.3, 81.6, 81.4, 80.8, 79.8, 79.6, 79.0, 77.8, 75.9, 74.8, 73.6, 73.1, 73.0, 71.2, 64.4, 61.5, 60.4, 58.3, 58.2, 44.0, 40.8, 37.2, 34.3, 30.3, 29.7, 27.0, 25.8, 25.7, 24.9, 20.8, 20.7, 18.2, 16.2, 15.7, 14.1, 14.0, 122.1, 12.6, 6.8, 4.8, 3.5, -4.4, -4.7, -5.1, -5.16 ; HRMS calcd for $C_{62}H_{113}IO_{16}Si_3Na$ [M+Na] 1347.6279, found 1347.8584.



(5S,6S,7E,9R,10S,11E,13E,15E,17R,18S,20S)-10,17-bis((tert-butyldimethylsilyl)oxy)-20-((R)-1-((2S,3R,4R,5R,6R)-2,5-dihydroxy-3-methoxy-6-(3-methoxypropyl)-5-methyl-4-((triethylsilyl)oxy)tetrahydro-2H-pyran-2-yl)ethyl)-5,18-dimethoxy-3,7,9,11,13,15-hexamethyl-2-oxooxacycloicosa-7,11,13,15-tetraene-4,6-diyl diacetate (4.51). To the ester **4.50** (14 mg, 10.5 µmol) in benzene (.5 mL) was added $PdCl_2(PPh_3)_2$ (cat.) then nBu_3SnH (19 µL, 74.0 µmol) at rt. Gas evolution is observed upon addition of nBu_3SnH. The resulting solution was stirred at 70°C for 24 h. Benzene was removed from the solution and added ether (5 mL) and stirred with saturated NaF solution for 1 h. Reaction solution was washed with aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* furnishing a dark oil. The residue was purified by flash chromatography

(10,8,5,4,3:1 hexanes: ethyl acetate) to afford 7 mg (~30-40%) of **4.51**. R_f .25 (4:1 H:EA); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.14 (s, 1H), 5.74 (s, 1H), 5.43 (t, *J* = 9.0 Hz, 1H), 5.28 (d, *J* = 10.0 Hz, 1H), 5.09 (d, *J* = 2.8 Hz, 1H), 4.94 (s, 1H), 4.73 (s, 1H), 4.48 (s, 1H), 4.04 (d, *J* = 9.9 Hz, 1H), 3.89 (d, *J* = 8.9 Hz, 1H), 3.70 (d, *J* = 7.00 Hz, 1H), 3.47 (s, 3H), 3.42 (s, 3H), 3.37-3.36 (m, 2H), 3.32 (s, 3H), 3.29 (s, 3H), 3.24 (dd, *J* = 10.1, 5.9 Hz, 1H), 3.06 (d, *J* = 9.9 Hz, 1H), 2.74-2.69 (m, 1H), 2.56-2.52 (m, 1H), 2.34 (dd, *J* = 3.5, 3.4 Hz, 1H) 2.16 (dq, *J* = 15.2, 10.0, 1H), 2.04 (s, 3H), 2.03 (s, 3H), 1.80 (m, 8H), 1.68 (s, H), 1.64 (s, 3H), 1.22 (d, *J* = 7.3 Hz, 3H), .99 (t, *J* = 7.7 Hz, 9H), .90 (s, 9H), .89 (s, 9H), .72-.64 (m, 7H), .12 (s, 3H), .10 (s, 3H), .06 (s, 3H), .04 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.6, 169.8, 169.6, 141.5, 137.8, 131.9, 129.7, 129.6; 128.5, 128.4, 114.4, 100.7, 85.0, 82.1, 81.6, 80.8, 79.7, 78.9, 77.8, 75.6, 74.8, 73.5, 73.1, 73.0. 71.2, 64.3, 61.5, 60.4, 58.3, 58.2, 44.1, 40.8, (unclear from this point onwards) 37.2, 34.3, 31.9, 31.5, 30.3, 29.3, 27.8, 27.0, 25.8, 25.7, 24.8, 23.5, 22.6, 20.8, 20.7, 18.24, 18.2, 16.3, 15.7, 14.1, 14.0, 13.2, 12.6, 6.8, 5.4, 4.8, 3.5, 1.0, -4.5, -4.7, -5.1, -5.16 HRMS to be determined.

Notes and References

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Appendix A3

Spectra Relevant to Chapter IV

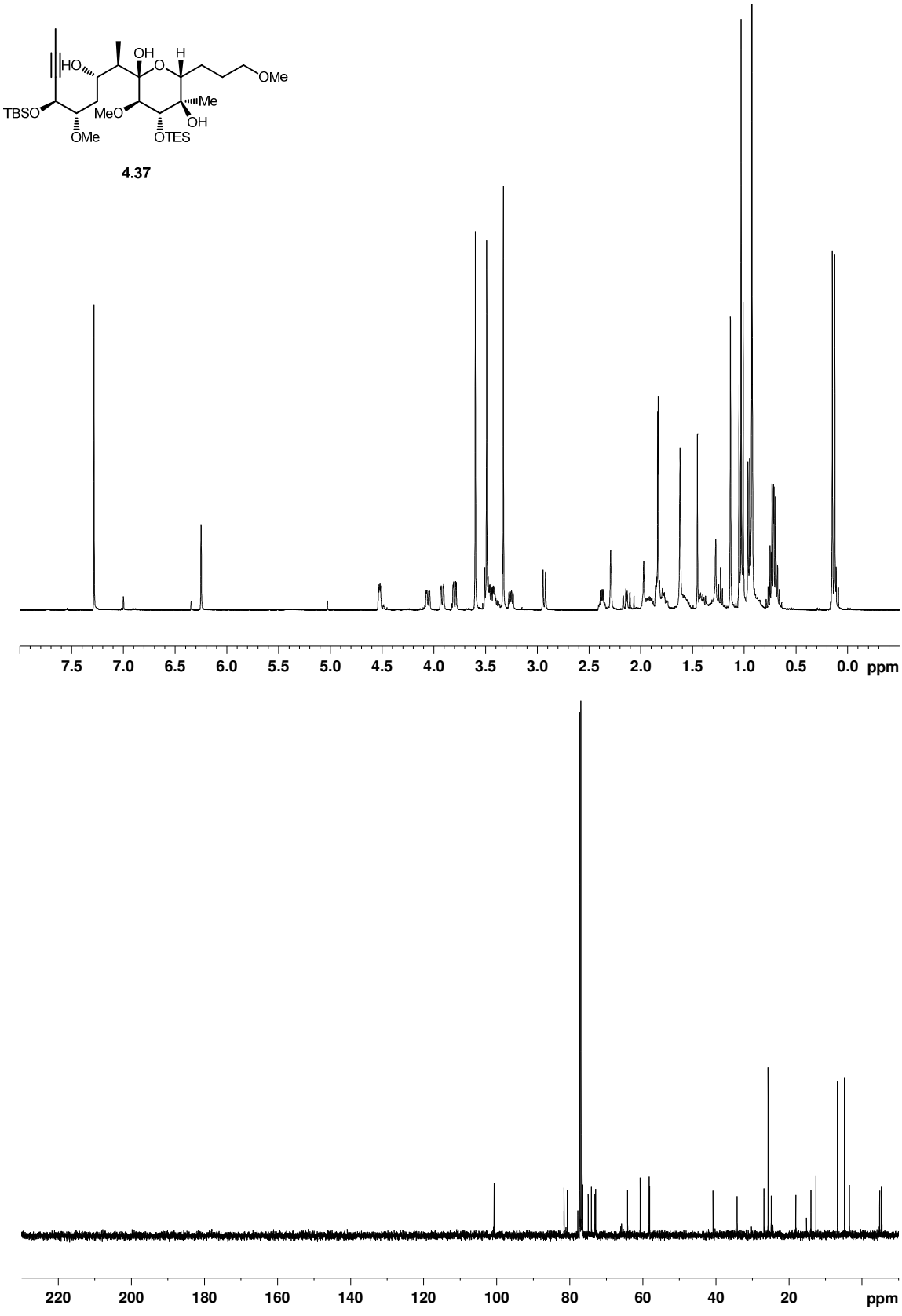


Figure A3.1 400 MHz ^{1}H- NMR and 100 MHz ^{13}C-NMR spectrum of **4.37** in $CDCl_3$

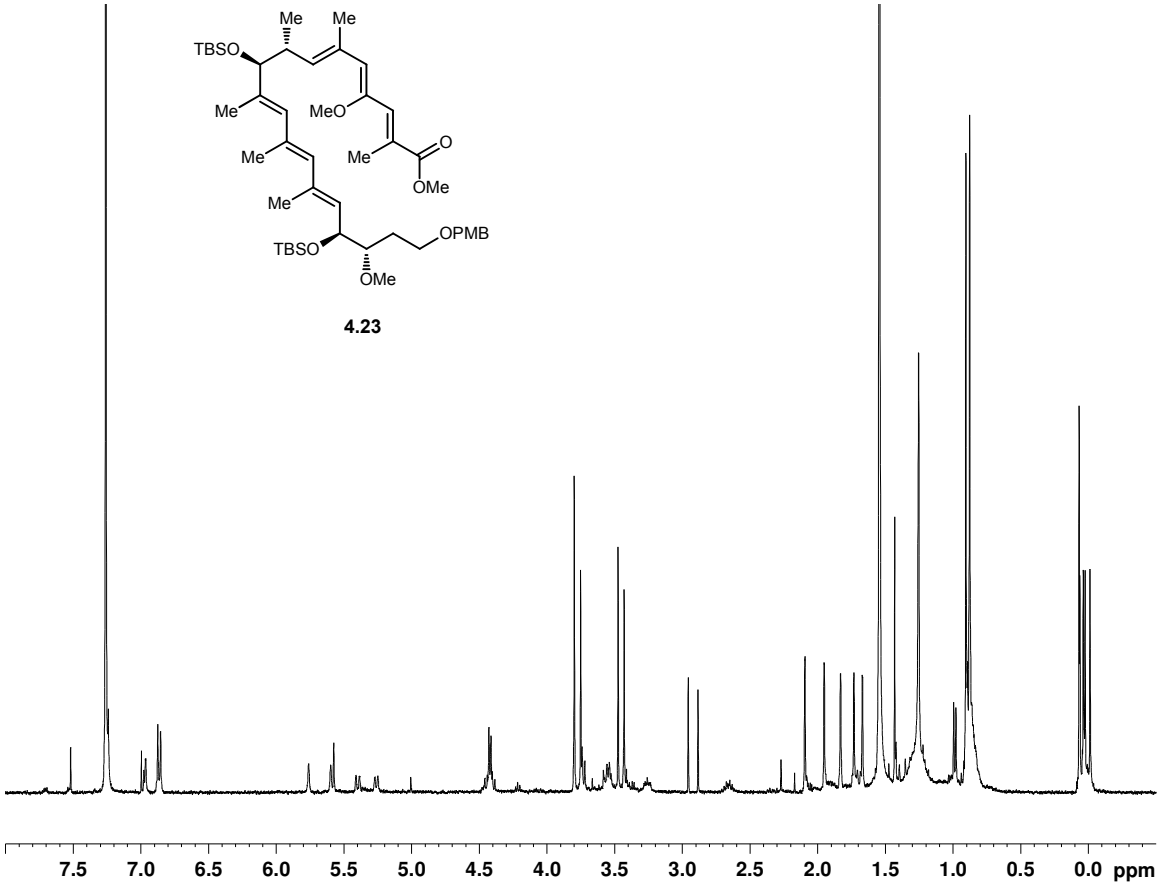


Figure A3.2 400 MHz ^{1}H- NMR and 100 MHz ^{13}C-NMR spectrum of **4.23** in $CDCl_3$

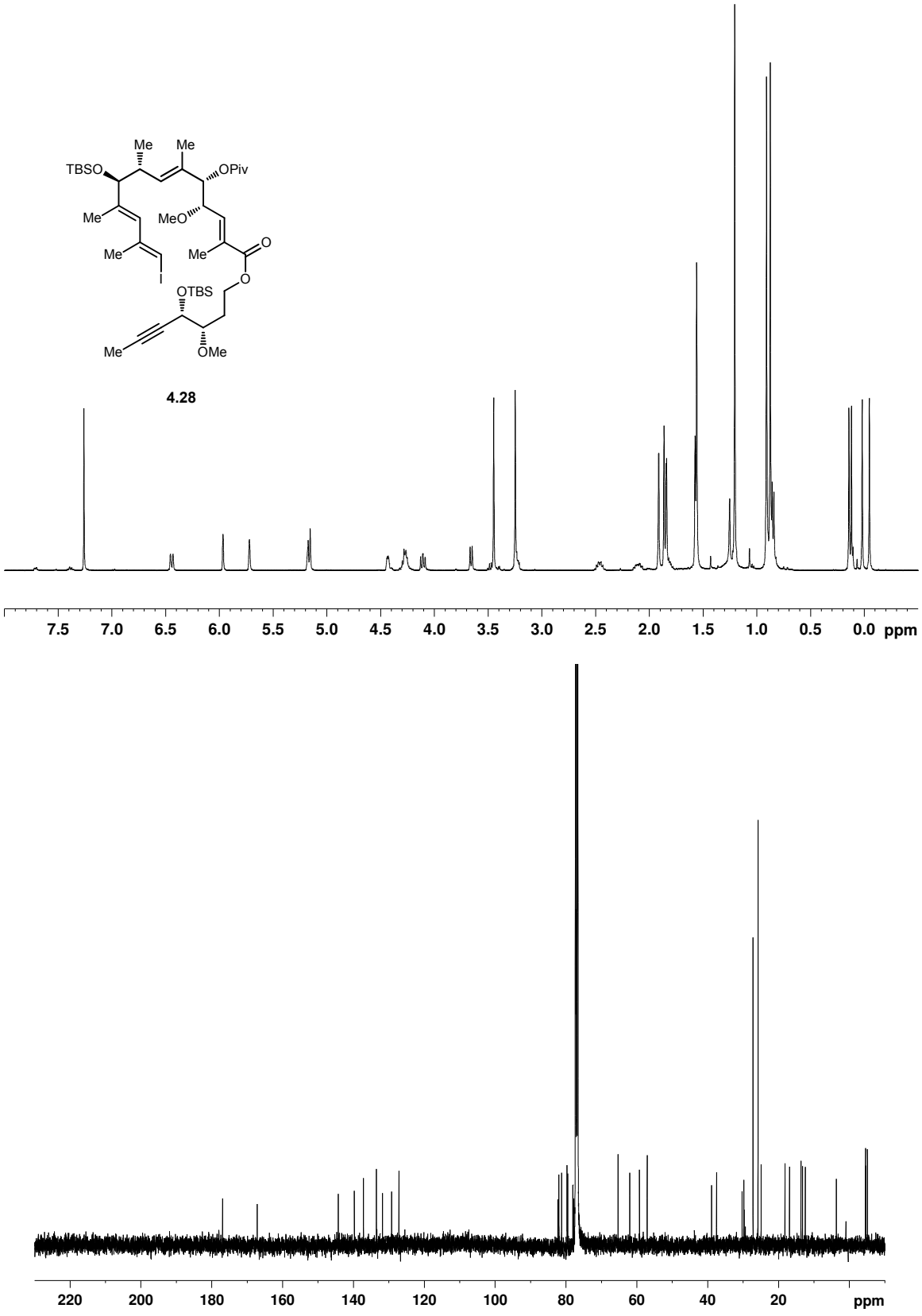


Figure A3.3 400 MHz ^{1}H- NMR and 100 MHz ^{13}C-NMR spectrum of **4.28** in $CDCl_3$

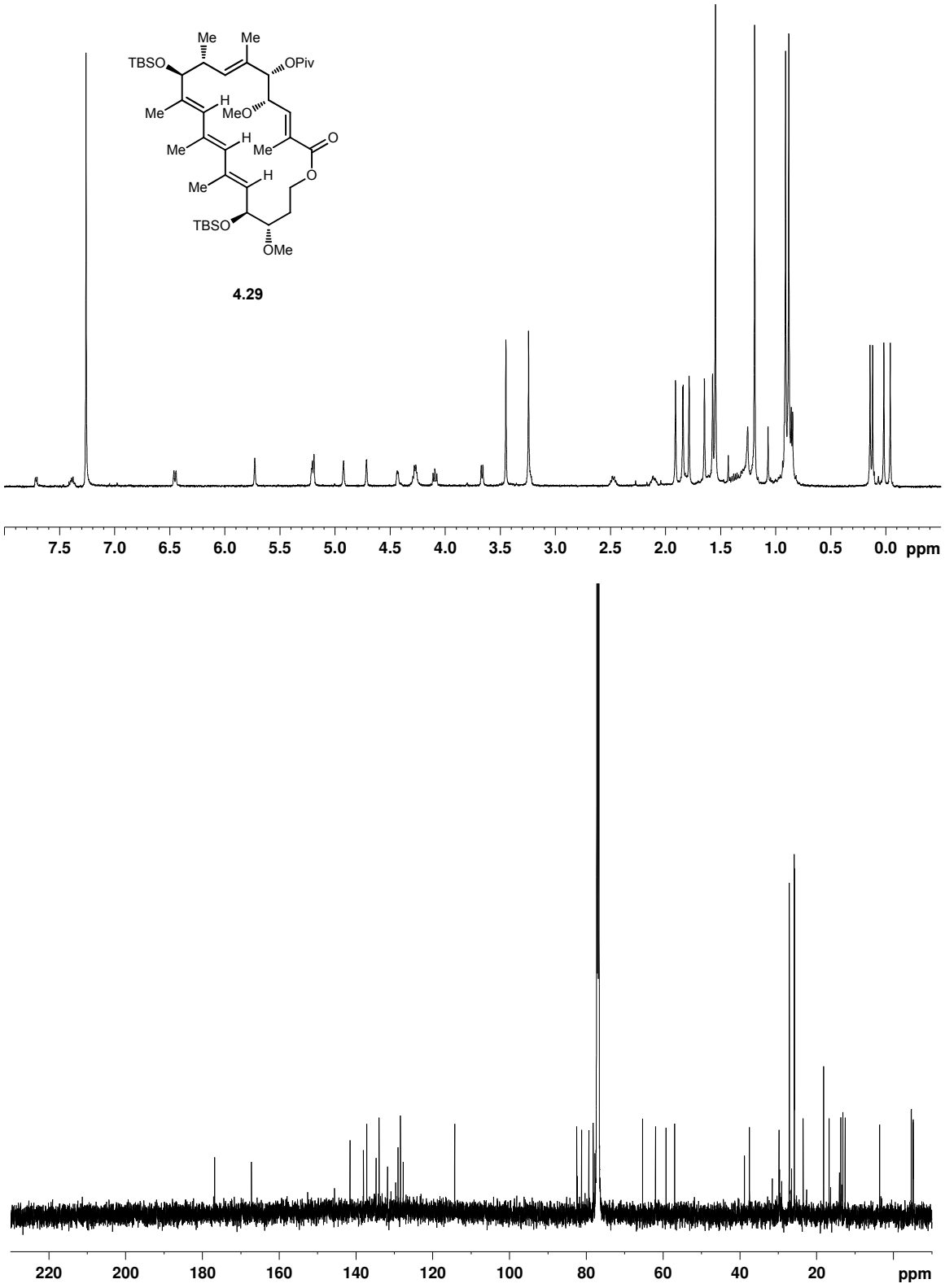


Figure A3.4 500 MHz ^{1}H- NMR and 125 MHz ^{13}C-NMR spectrum of **4.29** in $CDCl_3$

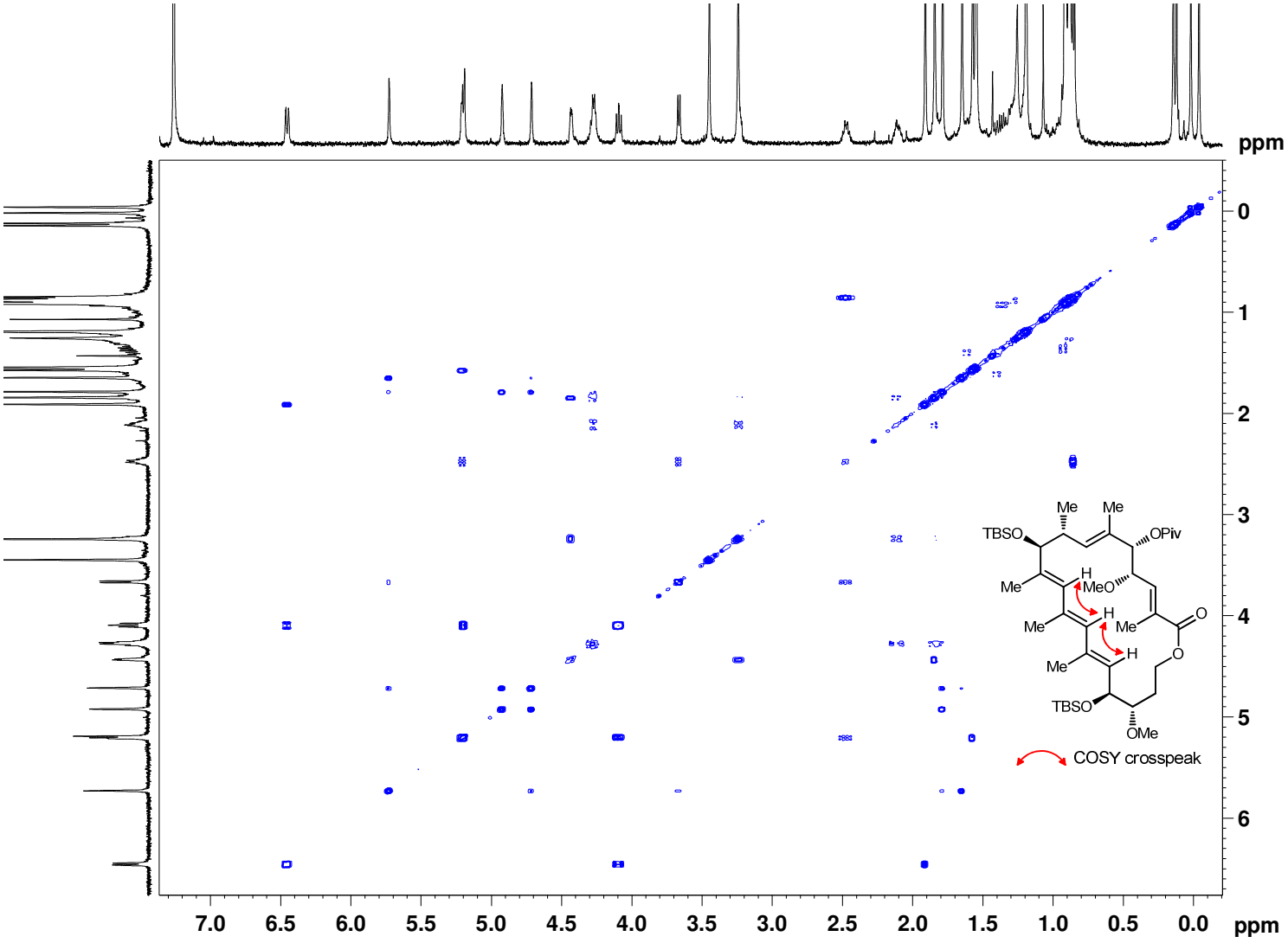
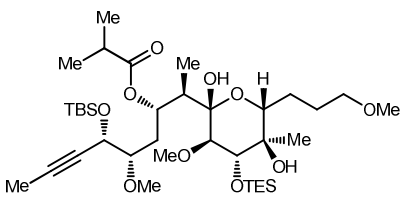


Figure A3.5 500 MHz COSY spectrum of **4.29** in $CDCl_3$



4.38

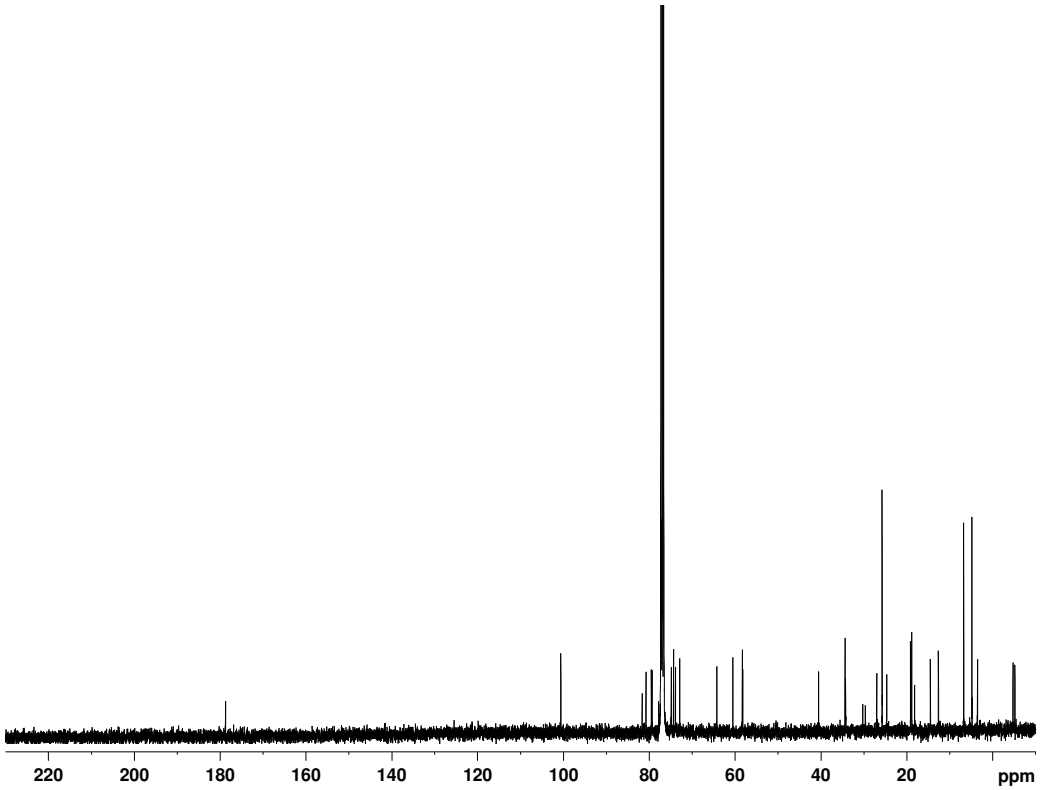


Figure A3.6 400 MHz ^{1}H- NMR and 100 MHz ^{13}C-NMR spectrum of **4.38** in $CDCl_3$

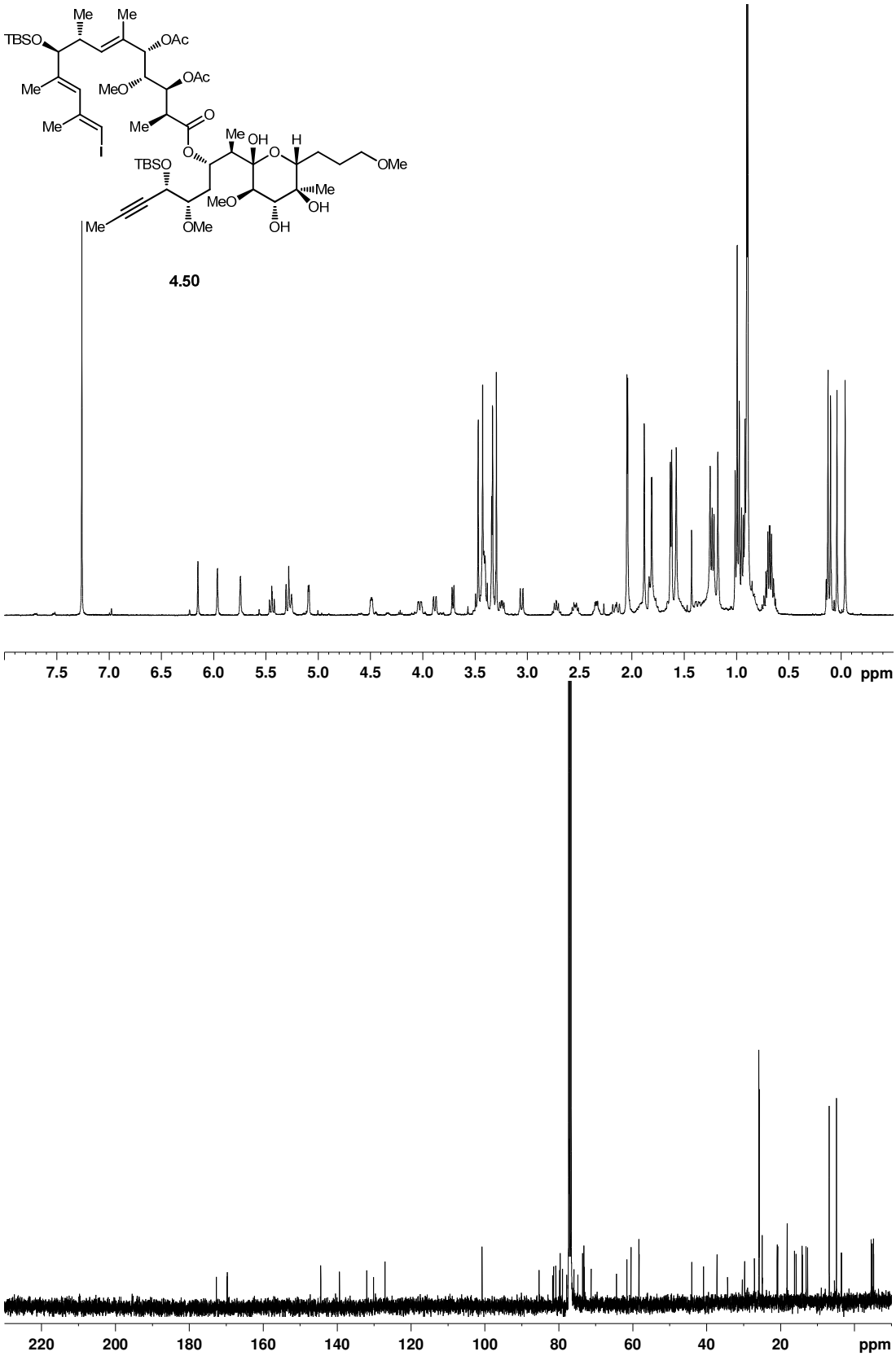


Figure A3.7 400 MHz ^{1}H- NMR and 100 MHz ^{13}C-NMR spectrum of **4.50** in $CDCl_3$

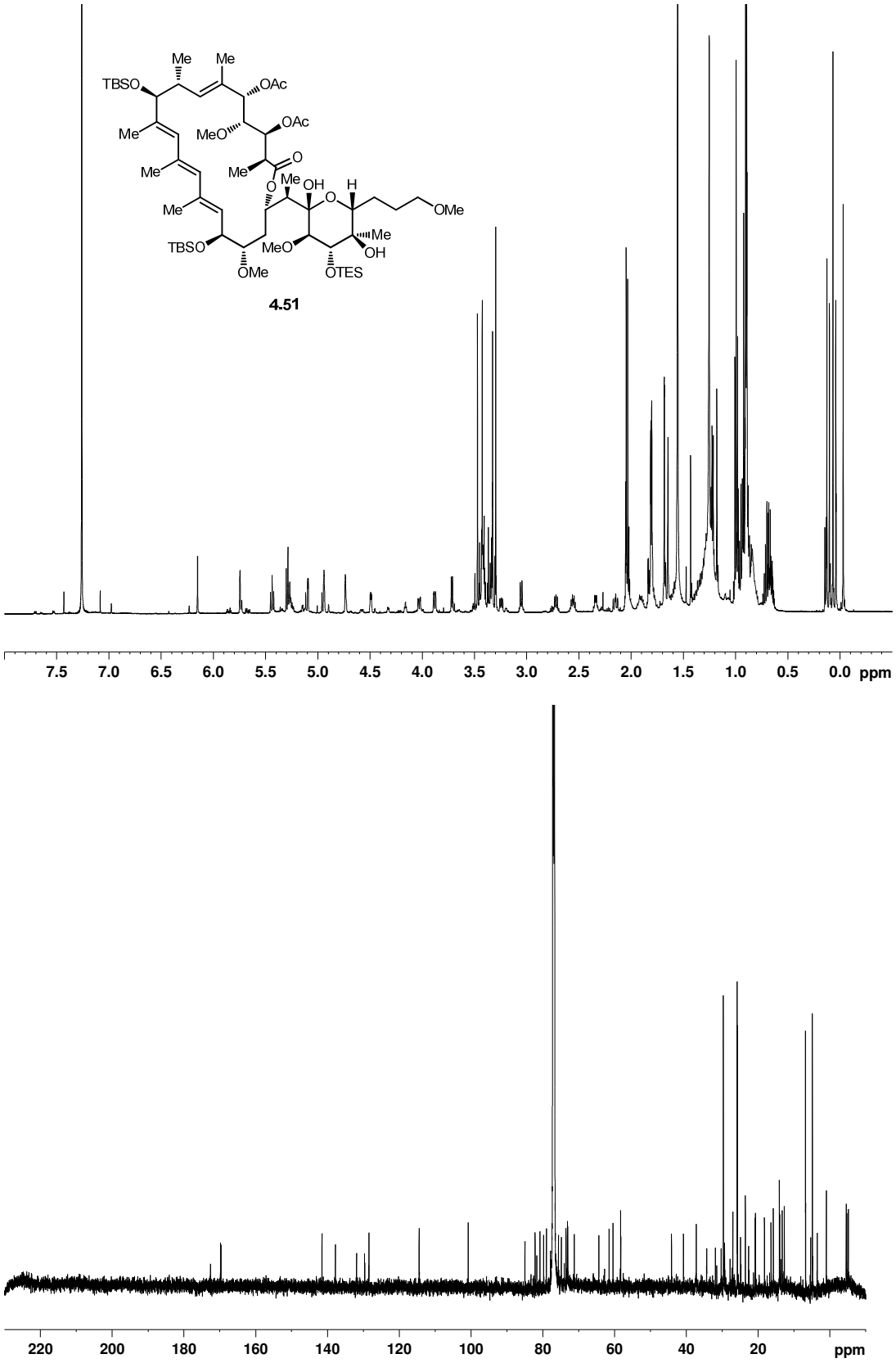


Figure A3.8 600 MHz ^{1}H- NMR and 150 MHz ^{13}C-NMR spectrum of **4.51** in $CDCl_3$

BIOGRAPHY

Stephen Thomas Chau was born February 7, 1984 in New York City, New York and is the only child to the parents of Richard and Johanna Chau. Stephen grew up in his hometown of Edison, New Jersey, where he attended John P. Stevens High School. After graduating high school in 2002, Stephen attended Rutgers, The State University of New Jersey where he majored in cell biology and neuroscience with a minor in chemistry. During his tenure at Rutgers he was drawn towards organic chemistry and gained his research experience in carbohydrate chemistry under the guidance of Dr. Spencer Knapp. Upon graduation in 2006, he began his graduate career at Vanderbilt University in chemistry and joined the laboratory of Dr. Gary A. Sulikowski. Under his tutelage, Stephen began his journey into complex natural product total synthesis. Stephen graduated from Vanderbilt University in 2011, and began his post doctoral studies at Princeton University in the laboratory of Dr. Abigail G. Doyle.