Total Synthesis of Irciniastatin A

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Abstract

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(Under the direction of Professor Michael T. Crimmins)

The total synthesis of (+)-irciniastatin A (psymberin) is reported in 19 steps and 6% overall yield. Key reactions include a highly convergent enolsilane-oxocarbenium ion union to generate the C8-C25 fragment and a late-stage coupling of a hemiaminal and acid chloride to complete the synthesis. In addition, efforts toward a second generation formal synthesis are described.

For the Stevens Family

Acknowledgements

When I started graduate school at Carolina I couldn't have imagined how much I would possibly learn and accomplish in 5 short years. Therefore, I feel that it is important to recognize those who have provided me with guidance and support on this extraordinary journey. I would first like to acknowledge my advisor Professor Michael T. Crimmins for his continued support throughout my time at UNC. I am grateful that Mike has provided me with the opportunity to develop independently as a scientist and that he always expected the best from me. I know that I am a better from having been able to explore my ideas while also learning from my mistakes. Mike's door was always open when I needed advice on either my project or career, and I am grateful for his dedication to my education and success.

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I am greatly indebted to Gregory Schaaf for providing such a solid foundation to the irciniastatin project. If not for Greg's work developing a scalable procedure for the the Diels-Alder aromatization reaction, preparing 12 g of the Kiyooka adduct, and demonstrating the effectiveness of the oxocarbenium ion coupling, this work may not have been possible. I am sincerely grateful for his role in this project.

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Ac	Acetyl
Ac_2O	Acetic anhydride
APT	Attached proton test
AZADO	2-Azaadamantane-N-oxyl
BAIB	bis-Acetoxyiodobenzene
Bn	Benzyl
BOM	Benzyloxymethyl
Bz	Benzoyl
CAN	Ceric ammonium nitrate
CBS	Corey-Bakshi-Shibata
COSY	Correlation spectroscopy
CSA	Camphorsulfonic acid
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
DET	Diethyltartrate
DEPT	Distortionless Enhanced Polarization Transfer
DHP	Dihydropyran
DIAD	Diisopropylazadicarboxylate
DIPCl	Diisopinocampheolchloroborane
DIPT	Diisopropyltartrate
DMAP	*N,N*-Dimethylaminopyridine
DMDO	Dimethyldioxirane
DMF	Dimethylformamide

DMSO	Dimethylsulfoxide
HMQC	Heteronuclear multiple quantum coherence
Ipc	Isopinocampheol
MOM	Methoxymethyl
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine oxide
NMP	*N*-methylpyrrolidinone
nOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
Ph	Phenyl
Piv	Pivalate
PKS	Polyketide synthase
PMB	*para*-methoxybenzyl
PMBTCA	*para*-methoxybenzyltrichloroacetimidate
PPTS	Pyridinium *para*-toluenesulfonic acid
PVP	Polyvinylpyridine
Red-Al	Sodium bis(2-methoxyethoxy)aluminum hydride
ROESY	Rotational nuclear Overhauser effect spectroscopy
SEM	Trimethylsilylethoxymethyl
TASF	tris(Dimethylamino)sulfoniumdifluorotrimethylsilicate
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TEMPO	2,2,6,6-Tetramethylpiperidyl-1-oxyl

Teoc	Trimethylsilylethoxycarbamate
TES	Triethylsilyl
Tf	Triflyl
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
TOCSY	Total correlation spectroscopy
Ts	Tosyl
TsA	Toluenesulfonic acid

Chapter 1: Isolation, Bioactivity, and Biosynthesis of Irciniastatin A

1.1 The Isolation of Irciniastatin A and B by Pettit

In 2003 Pettit first reported the isolation of two powerful (GI_{50} from 0.001 to < 0.0001 μg/mL) murine and cancer cell growth inhibitors harvested from the Indo-Pacific marine sponge *Ircinia ramosa* off the coast of Samporna Borneo, which were named irciniastatins A and B.[1] The initial extraction of ~ 1 kg of wet sponge provided 34.7 mg of irciniastatin A in 3.51 10^{-3} % yield and 2.2 mg of irciniastatin B in 2.23 x 10^{-4} % yield.

The initial activity screens of both of these compounds showed significant cancer cell growth inhibition against murine P388 leukemia cell line and six human cancer cell lines with GI_{50} values of 10^{-3}-10^{-4} μg/mL. These cell lines included BXPC-3 pancreas, MCF-7 breast, SF268 CNS, NCI-H460 lung, KM20L2 colon and DU-145 prostate cancers as well as P388 leukemia. What was particularly intriguing is that although irciniastatin A and B only differ in the oxidation state at C11, irciniastatin B proved to be 10 times stronger than irciniastatin A against BXPC-3, MCF-7, and SF268 cell lines whereas irciniastatin A was at least 10 times more active than irciniastatin B against NCI-H460. In addition irciniastatin A was shown to exhibit powerful antivascular activity against human umbilical vein endothelial cells

(HUVEC) and also displayed marginal antifungal and antimicrobial activities, with minimum inhibitory concentrations of 16 μg/mL and 64 μg/mL against *Cryptococcus neoformans* and *Neisseria gonorrhoeae*, respectively.

The initial structural assignment of the irciniastatins by Pettit was elucidated by high resolution mass spectrometry and extensive 500 MHz 2D-NMR experiments, including APT, ^{1}H-^{1}H-COSY, TOCSY, HMQC, ROESY and NOESY in chloroform-d_3. Pettit observed that irciniastatins A and B both contained a structurally unusual dihydroisocoumarin moiety and only differed by one degree of unsaturation, which was determined to be the oxidation state at C11 (Figure 1.1.1). While the absolute stereochemical assignments of the 6 stereocenters embedded within the dihydroisocoumarin and tetrahydropyran fragments could be definitively assigned, the absolute stereochemical assignment of the 3 stereocenters of the acyclic hemiaminal side chain could not be assigned with certainty. Pettit postulated that the

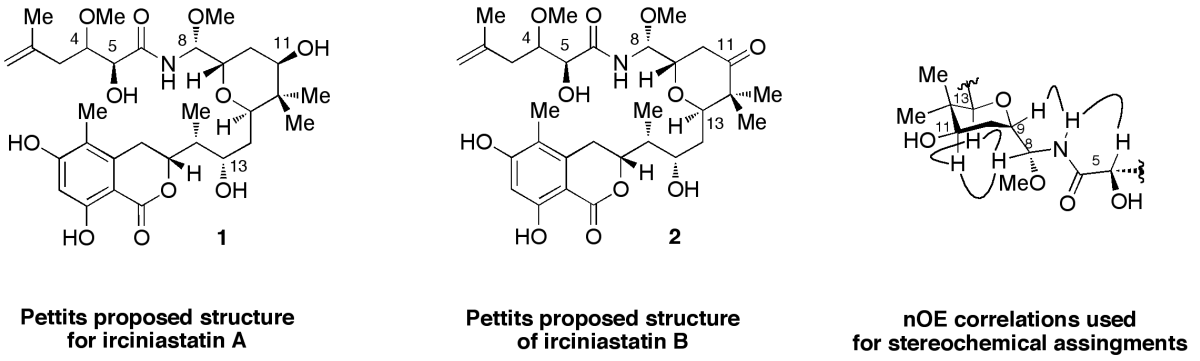


Figure 1.1.1 Pettits Proposed Structure for Irciniastatins A and B

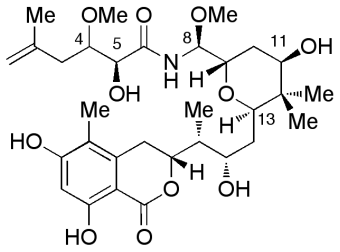
network of nOE correlations between the protons on each side of the hemiaminal linkage provided for an absolute assignment as 5*S*, 8*R*, and 9*S* while insufficient data precluded the absolute determination of the C4 stereochemistry.

1.2 The Isolation of Psymberin (Irciniastatin A) by Crews

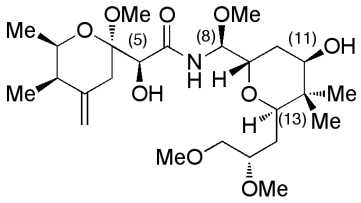
Less than one year following the report by Pettit, an independent report by Crews in 2004 disclosed the isolation of a nearly identical molecule.[2] The compound, named psymberin, was isolated from an undescribed inconspicuous sponge *Psammocinia* sp. from the waters of Papua New Guinea. From an initial 18.6 kg of wet sponge a total of 17 mg of psymberin was isolated in a 9.1 x 10^{-5} % yield. Like irciniastatin A, psymberin was also found to be a potent cancer cell growth inhibitor against a selection of NCI cell lines including SK-MEL-5 melanoma, MDA-MB-435 breast cancer, and HCT-116 colon cancer. Remarkably, psymberin showed > 10^4 fold activity differential against similar colon cancer cell lines. This astounding cell line specific activity proved especially exciting as it may possibly indicate that psymberin binds to a distinct cellular target.

The structural assignment of psymberin was elucidated by high resolution mass spectrometry and extensive 500 MHz 2D-NMR experiments, including ^{1}H-^{1}H-COSY, DEPT, HMBC, HSQMBC and NOESY in methanol-d_4. The absolute stereochemistry of the 6 stereocenters of embedded in the dihydroisocoumarin and tetrahydropyran fragments could be determined by nOE enhancements and evaluation of coupling constants. However, as with irciniastatin A, the absolute assignment of the C1-C8 side chain could not be definitively assigned (Figure 1.2.1). Crews noted that psymberin shares very similar structural architecture to both the pederin and the mycalamide family of natural products. Examination of the coupling constant data from these molecules against the data for psymberin lead to the assignment of 5*S*, 8*S*, and 9*S*, while C4 could not be definitively assigned. This

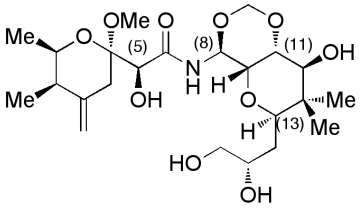
assignment contradicted the C8 assignment proposed for irciniastatins A and B and at the time it was unclear whether the two molecules shared the same absolute stereochemistry, although Crews postulated that the two molecules were identical.



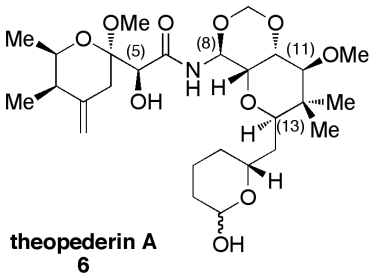
Crews proposed structure of psymberin
3



pederin
4



mycalamide A
5



theopederin A
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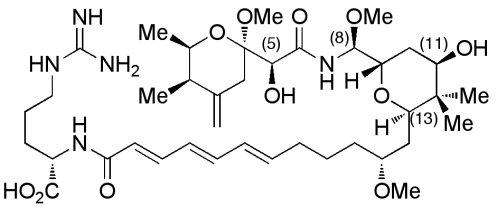

onnamide A
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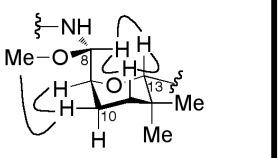
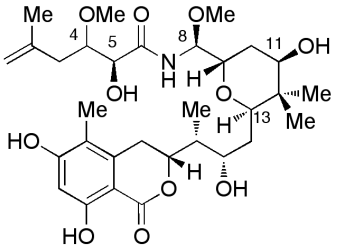


nOE enhancements used for stereochemical assingments



Actual structure of irciniastatin A (psymberin) determined by total synthesis
8

Figure 1.2.1. Crews Proposed Structure for Psymberin (Irciniastatin A)

The following year Crews proposed structure was proven to be correct and the identity of the C4 stereocenter was first established as the (*S*)-configuration through Williams substructure NMR shift correlation[3] then by Floreancig's natural product degradation analysis,[4] and ultimately the first total synthesis by DeBrabander.[5]

1.3 Biosynthesis of Irciniastatin A

A total of thirty four pederin-like molecules have been reported in the literature. Of them, the irciniastatins are the only molecule lacking the pendant oxane ring or 1,3-dioxane and the only structures that feature a dihydroisocoumarin fragment. In the initial report, Crews suggested that the biosynthesis of pederin and irciniastatin A are similar and that irciniastatin A is likely produced from a sponge microsymbiont as opposed to the *Paederus* blister beetle symbiont responsible for the biosynthesis of pederin. In 2009, five years after their initial report, Crews reported the isolation of biosynthetic gene clusters from *Psammocinia* aff. *bulbosa* that are responsible for the biosynthesis of irciniastatin A, which also showed compelling evidence that they were bacterial in origin.[6] Several domains of the polyketide synthase domain architecture were nearly identical to counterparts of onnamide and pederin PKS domain architecture while others shared little similarity. These correlations provided that the onnamides, pederins, mycalamides and irciniastatins are synthesized through similar biosynthetic machinery,[7] and allowed for Crews to propose a biosynthesis for irciniastatin A that also explained the lack of the pendant oxane and the incorporation of the dihydroisocoumarin moiety (Figure 1.3.1). Crews proposed that irciniastatin A is assembled in a linear fashion starting at C1 and building toward C25 through a series of predominantly acyl transferase and keto reductase operations. While the biosynthesis appears straightforward there are several interesting aspects and may hold implications for future synthetic efforts. The first is that the synthesis of the tetrahydropyran is formed through an oxy-Michael addition. While a number of 6-*exo*-dig cyclizations have been used to form the

tetrahydropyran in the synthetic campaigns that will be described, none have used this biomimetic approach to form that carbon oxygen bond. The other interesting aspect is that the biosynthesis of the dihydroisocoumarin occurs through tricarbonyl

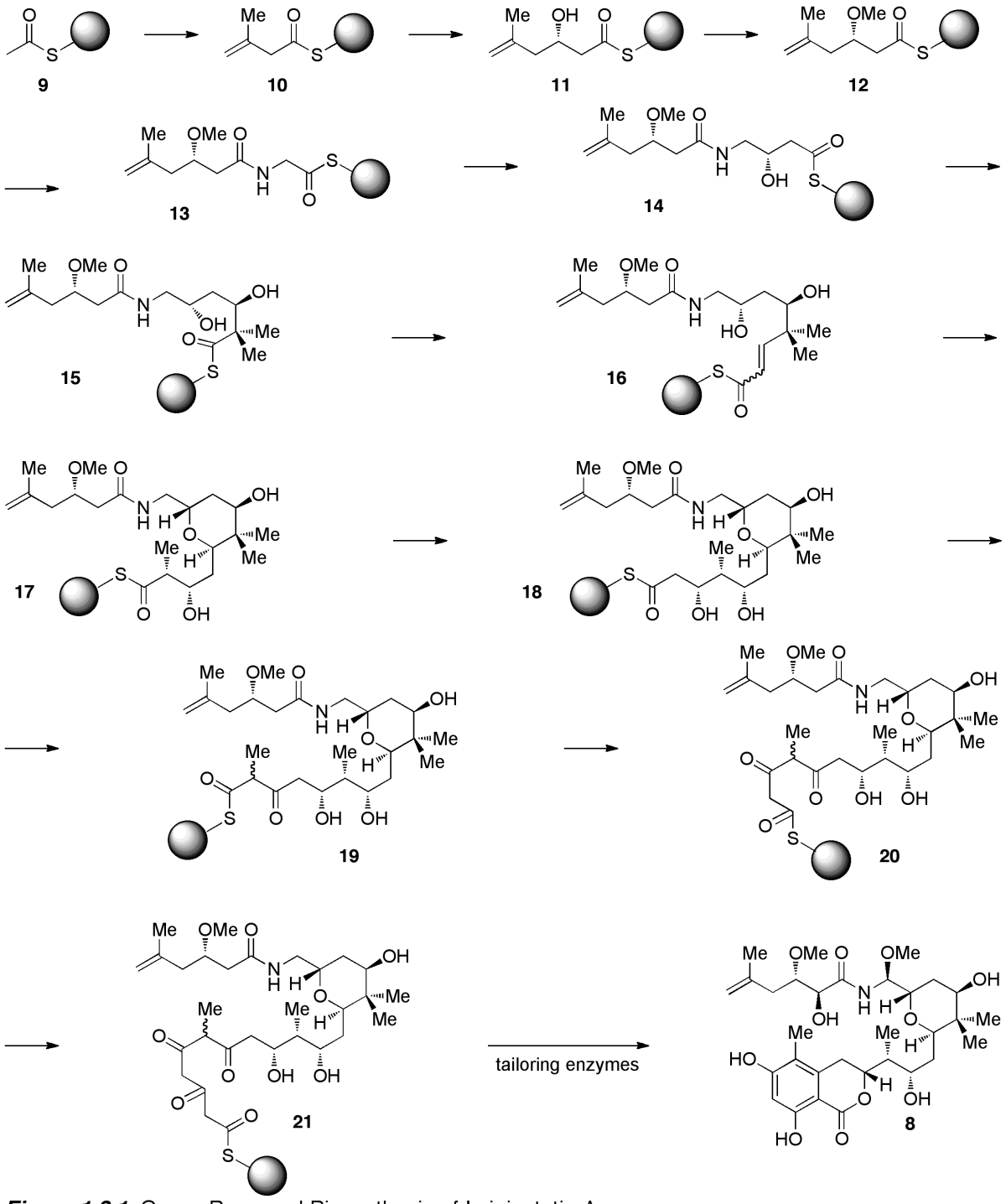


Figure 1.3.1. Crews Proposed Biosynthesis of Irciniastatin A

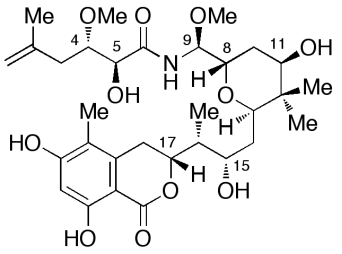
condensation, which also has not been explored as a synthetic avenue for the construction of this fragment

1.4 Biological Activity of Irciniastatin A and Irciniastatin Analogs

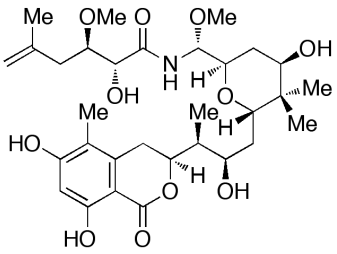
The identity of the cellular target and the specific mode of action for irciniastatin bioactivity remain unknown as of 2010. While the pederin family of natural products are uniformly potent protein synthesis inhibitors,[8] the unique structure of irciniastatin A and cell line specific cytotoxicity that is not observed for pederin natural products suggest a unique mode of action. Support for this was garnered through the preparation of an analog of irciniastatin A, psympederin **23** (Figure 1.4.1).[9] This analog contained the side chain and tetrahydropyran functions but the dihydroisocoumarin moeity was substituted for the 1,2-dimethoxy terminus common to pederin natural products. This analog showed a 1000 fold reduced activity compared to natural irciniastatin thereby revealing its important role in bioactivity of irciniastatin A (Table 1.4.1). Similarly, psympederin, which was also a pederin/mycalamide analog, revealed that the acyclic side chain results in a 300 fold reduction in antiproliferative activity when compared with mycalamide A that contains the cyclic pederate side chain. These data suggest a unique mode of action for irciniastatin A while also underscoring the need for reliable synthetic avenues to access additional material for biological evaluation.

To further probe the structural factors responsible for the cell line specific cytotoxicity of irciniastatin A, a number of analogs have been prepared by the groups of DeBrabander,[9] Schering-Plough,[10] and Watanabe [11] (Figure 1.4.2). It was determined by Watanabe that irciniastatin is not a chemical reagent and that an

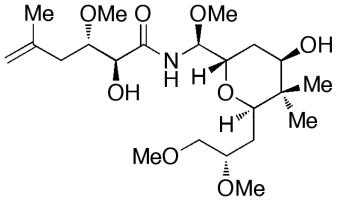
enantio-differential recognition event occurs at the cellular binding site, as (-)-irciniastatin A (**22**) showed no cytotoxicity against HeLa cells, whereas (+)-irciniastatin A was highly active (Table 1.4.1). As stated previously it is also known that completely removing the dihydroisocoumarin shows a 1000 fold reduction in



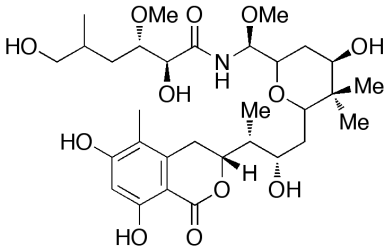
8: (+)-irciniastatin A



22: (-)-irciniastatin A



23: psympederin



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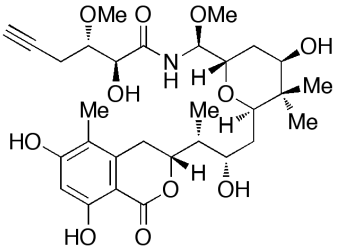
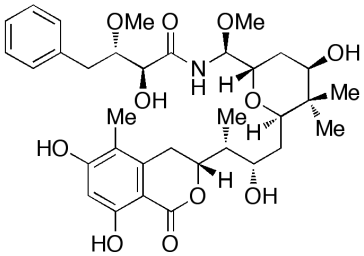


25: alkymberin



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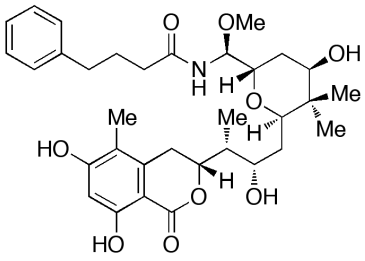

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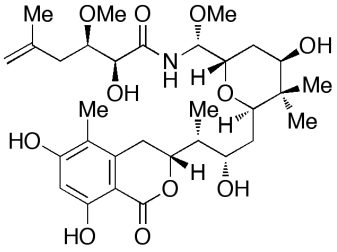
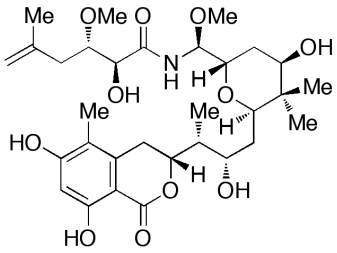
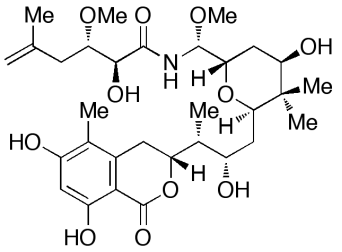


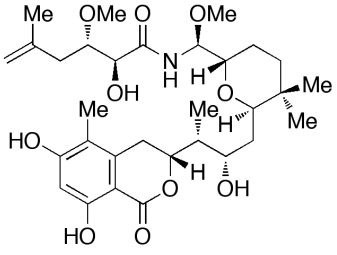
28: 4-epi-irciniastatin A



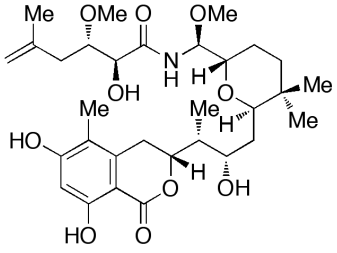
29: 8-epi-irciniastatin A



30: 8,9-epi-irciniastatin A



31: 8-epi-11-deoxy-irciniastatin A



32: 11-deoxy-irciniastatin A

Figure 1.4.1. Irciniastatin A Analogs

activity. However, aside from that one example there haven't been any further studies to investigate the role of that subunit more thoroughly. Most of the analogs currently known have focused on probing the side chain function. What has been discovered about the role of the side chain is that loss of unsaturation at C1 produces a marked drop in cytotoxicity as observed for **24**, however, if the alkene is substituted for either an alkyne **25**, or arene **26**, the activity is diminished but not quite as drastically. It has also been demonstrated that both the C4 and

Cell Line	KM12	PC3	SKMQ-5	T98G	HOP62	ACHN	MB231	SW620	HeLa
8	0.45	0.98	2.29	1.37	0.42	0.76	0.27	0.82	0.20
22									>1000
23	710.00	821.00	>1000	>1000					
24					200.00		>1000		
25									1.20
26					32.00		615.00		
27					>1000		>1000		
28	126.00	347.00	763.00		187.00				
29	37.10	200.00	352.00						
30	3100.00				4600.00	6800.00	4200.00		
31		2.90			3.00	8.70	5.30	6.10	
32		0.07			0.06	0.27	0.14	0.16	

Table 1.4.1. Comparison of Ircinastatin A and Irciniastatin A Analogs

C5 stereocenters are required for cytotoxicity. The analog **27** that lacks substitution at these positions showed a 100 fold reduction in cytotoxicity when compared with **26**, and the 4-epi-irciniastatin A analog **28** showed significant reduction in activity

compared to irciniastatin A. Similarly, the C8-aminal epimer **29** was also less active while the corresponding 8,9-epi-irciniastatin A **30** showed the highest overall reduction in cytotoxicity among tested analogs. Lastly, it was found that the C11 stereochemistry does not play a key role in the bioactivity of irciniastatin A. The analogs 8-epi-11-deoxy-irciniastatin A **31** retained most of the potency of irciniastatin A, however, the analog 11-deoxy-irciniastatin A **32** was actually more potent than the natural product.

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[11] Watanabe, T.; Imaizumi, T.; Chinen, T.; Nagumo, Y.; Shibuya, M.; Usui, T.; Kanoh, N.; Iwabuchi, Y. *Org. Lett.* **2010**, *12*, 1040.

Chapter 2: Previous Syntheses and Structural Determination of Irciniastatin A

After the two initial independent isolation reports it still remained unclear if irciniastatin A and psymberin were stereochemically identical. This stereochemical uncertainty as well as challenge of designing a strategy to gain access to a new and unexplored molecular framework was certainly enough to pique the interest of the synthetic community. If not reason enough already to initiate a synthetic campaign toward this novel structure, the unprecedented potency and selectivity of these cytotoxins prompted over a dozen publications related to stereochemical identification,[1,2] total[3,4,5,6,7] and formal[8] synthesis, fragment synthesis[9,10,11,12] and several analog syntheses[13,14,15] from 2005 to 2010.

Two independent syntheses of the psymberate side chain were disclosed in 2005[1-2] to address the unresolved side chain stereochemistry of the natural product although these studies did not address the C8 stereochemical uncertainty. The first total synthesis was reported by DeBrabander[3] shortly thereafter in 2005, which proved that irciniastatin A and psymberin were in fact identical compounds, and that the structure proposed by Crews was indeed correct. Shortly thereafter in 2005 Floreancig[9] reported the synthesis of the N7-C25 fragment of irciniastatin A, and after a quiet year, Williams[8] reported a formal total synthesis in 2007 and the second

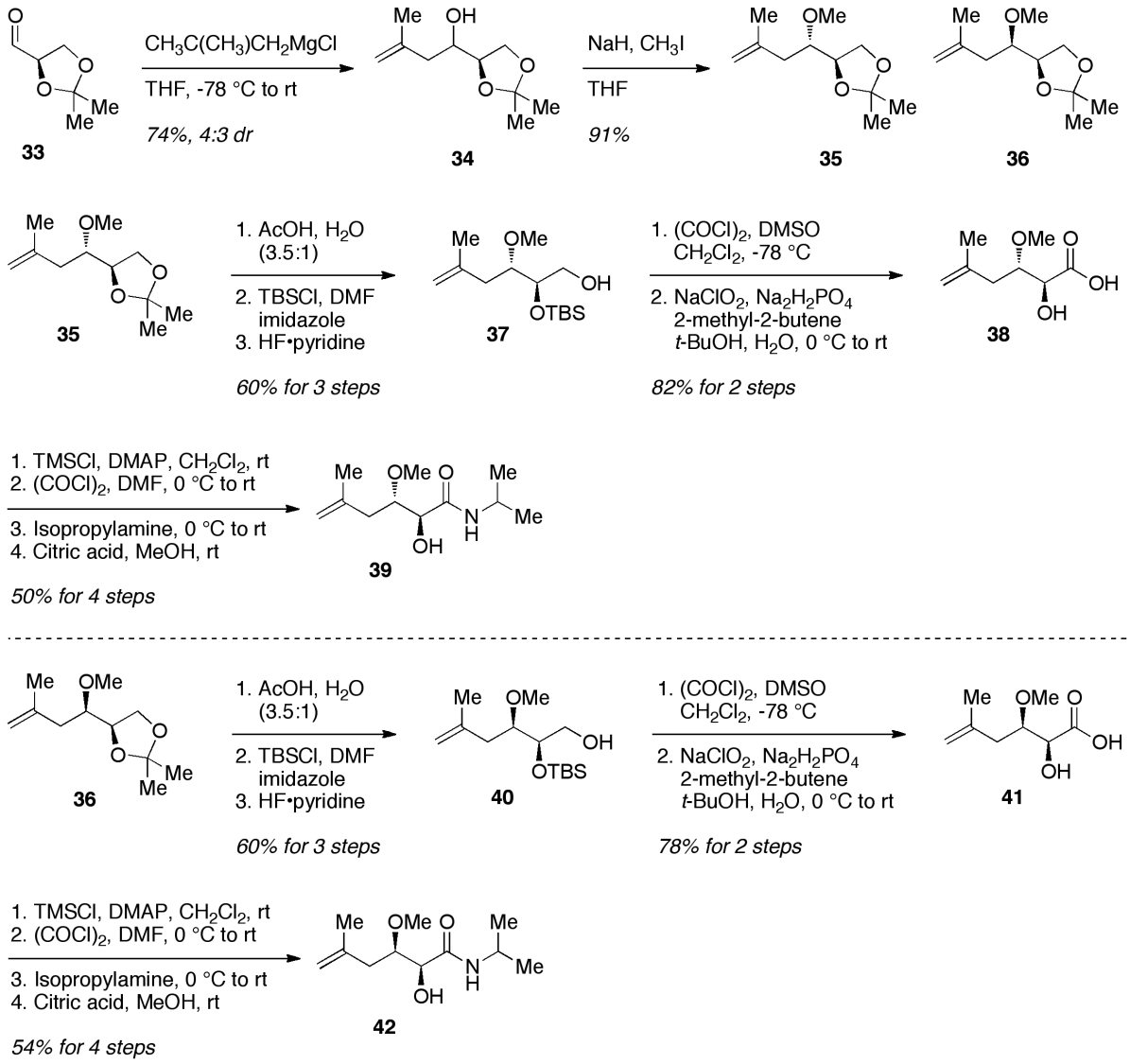
total synthesis was reported by Schering Plough.[4] In 2008 Smith[5] disclosed the third total synthesis followed nine months later by our[6] efforts in 2009 and the most recent total synthesis by Watanabe[7] in 2010. In addition to the mentioned fragment and total syntheses, several other reports concerning small fragment syntheses[10-12] and analog syntheses[13-15] have appeared in the literature and will not be discussed in this chapter. This section of the chapter will cover all of the total syntheses to date and only fragment and formal syntheses that are relevant to this work and to those seeking to initiate future synthetic studies toward the ircinastatins or related molecules.

2.1 Williams Synthesis of the Psymberate Side Chain

The potent and selective nature of the irciniastatins as well as their intriguing structure prompted efforts to determine the absolute stereochemistry of the acyclic side chain. In 2005 Williams[1] reported the synthesis of both *syn* and *anti* isomers of the irciniastatin amide side chain (Scheme 2.1.1).[16] Their approach compared the NMR spectral data for the irciniastatin side chain with the spectral data of the *syn* and *anti* isomers of a structurally similar model compound. This method is based on the hypothesis that the ^{1}H and ^{13}C NMR signatures of stereoclusters are inherent to the specific arrangement of the stereogenic carbons and are virtually context independent.[17,18,19,20,21] Toward this end the mannitol derived aldehyde **33** was subjected to a stereodivergent methallylation, wherein methylation of the resultant carbinols **34** afforded methyl ether diastereomers **35** and **36** that were then separated. The *anti* (4*S*, 5*S*) isomer was subjected to acidic dioxolane deprotection, followed by reprotection of the diol as the bis-TBS ethers and then selective

deprotection of the primary TBS ether to give carbinol **37**. A two step oxidation protocol gave glycolic acid **38** that was carried forward over four steps to glycolamide **39**. The *syn* (4*R*, 5*S*) glycolamide diasteromer was then prepared using

Scheme 2.1.1. Williams synthesis of the psymberate side chain



33 **34** **35** **36** **37** **38** **39** **40** **41** **42**

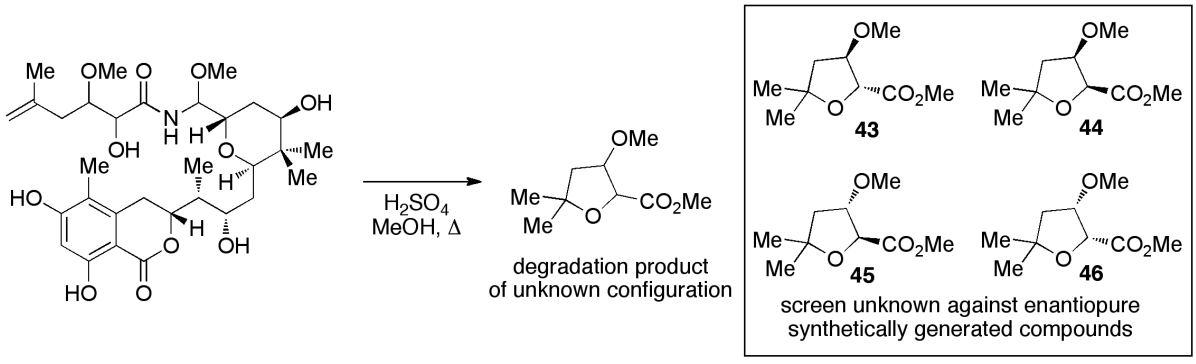
an analogous sequence. The criteria for structural assignment based on comparison of spectral data with simple models is that the difference between the ^{1}H chemical shift difference is < 0.05 for ^{1}H and < 0.50 for ^{13}C. The correlation of the

anti (4*S*, 5*S*) isomer **39** with irciniastatin A showed that the chemical shift differences for the ^{1}H is < 0.05 ppm and < 0.5 ppm for the ^{13}C spectrum, indicating good correlation. Conversely the correlation of the *syn* (4*R*, 5*S*) isomer **42** with irciniastatin A showed > 0.25 ppm for the ^{1}H signals and > 1.0 ppm for the ^{13}C signals on average, indicating significant a deviation from the unknown system. Based on the chemical shift correlation as well as the correlation between the observed coupling constants between the model *anti* (4*S*, 5*S*) isomer **39** and the psymberate side chain, Williams proposed the side chain of irciniastatin A was *anti* (4*S*, 5*S*). While this provided clarity on the nature of the C4 and C5 stereocenters the absolute configuration of the C8 stereocenter remained unresolved.

2.2 Floreancig Synthesis of the Psymberate Side Chain.

Within 3 months of the report by Williams, Floreancig reported a supporting analysis of the configuration of the C4 and C5 stereocenters on the psymberate side chain through degradation studies.[2] Floreancig hypothesized that the acidic methanolysis of the hemiaminal of irciniastatin A would produce a tetrahydrofuran product. It would then be possible to generate a chromatographic signature for this

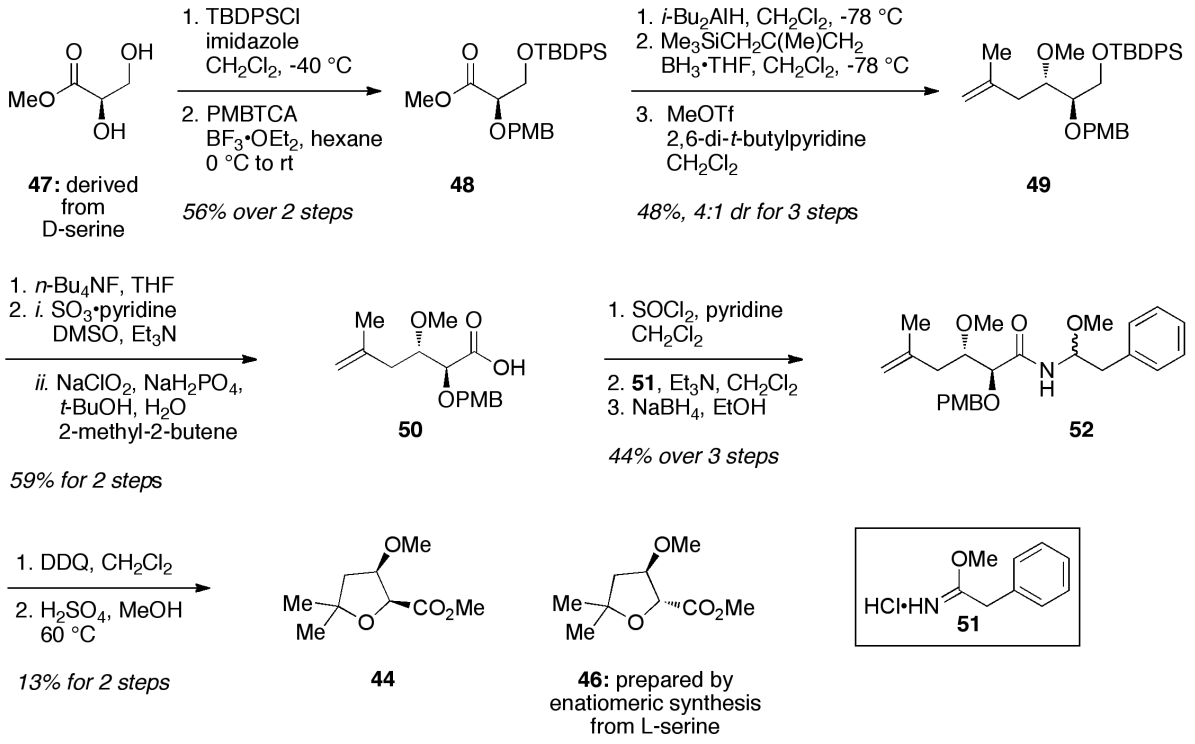
Scheme 2.2.1. Floreancigs Strategy for Determination of the Side Chain Stereochemistry



degradation product and make a comparison against all 4 possible stereoisomers of the degradation product of known configuration (Scheme 2.2.1).

The synthesis of the 4 tetrahydrofuran diastereomers began from diol **47**, prepared from D-serine.[22] The primary alcohol was selectively protected as the TBDPS ether and the vacant secondary alcohol was protected as the PMB ether **48**.

Scheme 2.2.2. Floreancig Synthesis of the *syn*-Tetrahydrofurans

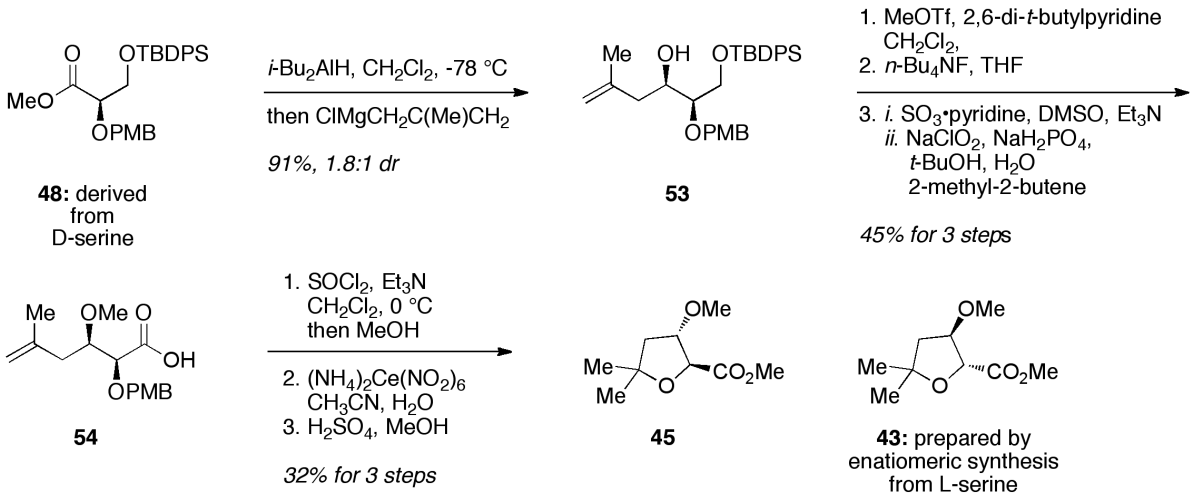


Reduction of methyl ester **48** to the aldehyde allowed for a Felkin-Anh stereocontrolled addition of methallyl trimethylsilane with 4:1 dr to give the resultant alcohol,[23][24] which was then alkylated to give methyl ether **49**. The acid **50** was then obtained through silyl ether deprotection followed by a two step oxidation sequence. Acid **50** was converted to the acid chloride and subjected to a methyl imidate coupling followed by imine reduction to give hemiaminal **52**. Removal of the PMB ether and acidic methanolysis then provided tetrahydrofuran **44**, while also

demonstrating the feasibility of acidic degradation of the hemiaminal irciniastatin A without epimerization. Tetrahydrofuran **46** was prepared through an enantiomeric synthesis starting from L-serine.

To access the *syn* tetrahydrofuran isomers, ester **48** was reduced to the resultant aldehyde and subjected to chelation controlled methallylmagnesium chloride addition to give *syn* isomer **53** with only modest stereocontrol.[25] Methylation of alcohol **54** was followed by silyl ether deprotection and a two step oxidation protocol that afforded acid **54**. A more straightforward synthesis of *syn* tetrahydrofuran **45** was carried out through methyl esterification of acid **54**, PMB deprotection and acidic methanolysis, also without any observed epimerization. Tetrahydrofuran **43** was prepared through and enantiomeric synthesis starting from L-serine.

Scheme 2.2.3. Floreancig Synthesis of the *anti*-Tetrahydrofurans



With all four tetrahydrofuran diastereomers in hand, a chromatographic analysis method was developed using chiral gas chromatography that clearly resolved each isomer. A sample of natural irciniastatin A was provided by Professor

Crews and was subjected to acidic methanolysis and the degradation product corresponding to **45** was observed by GC and exhibited and identical fragmentation pattern by GC-MS. Thus the *anti* (4*S*, 5*S*) configuration of the psymberate side chain was assigned based on the degradation studies and supported the NMR correlation study conducted by Williams.

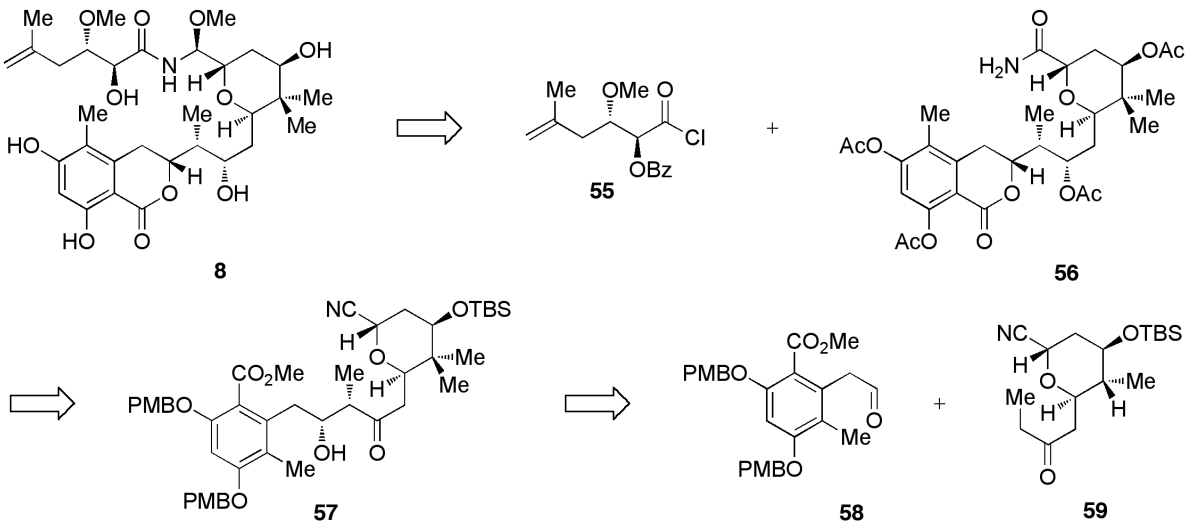
After two separate isolations and two separate reports of structural determination studies the C8 stereochemistry remained an unresolved issue. The structural determination studies confirmed the side chain stereochemistry matched the known stereochemistry of the structurally related pederin and mycalamide natural products. This information lead to a consensus that the C8 stereochemistry was likely that of the *S* configuration. However, there was no definitive spectroscopic data to confirm this assumption and it still had yet to be determined whether irciniastatin A and psymberin shared the same absolute configuration. At this stage, it seemed that total synthesis was the only way to solve this current ambiguity.

2.3 DeBrabander Total Synthesis

With a clear need for total synthesis to resolve conflicting stereochemical assignments DeBrabander reported the first total synthesis of Irciniastatin A in 2005.[3] Importantly, DeBrabander devised a stereodivergent endgame strategy that would provide access to both C8 stereoisomers. This strategy provided for installation of the psymberate side chain at a late stage through a non-selective coupling of the methoxyimidate derived from amide **56** with acid chloride **55**. This tactic, although non-selective, would provide for the isolation of both C8 isomers for comparison to both natural products and settle the conflicting reports for the

configuration at this carbon. Additionally, this would allow for installation of both the *syn* and *anti* side chain isomers that would then absolutely resolve the identity of the side chain stereochemistry at C4. Amide **56** would be prepared from nitrile **57**, the product of a boron mediated aldol reaction between aldehyde **58** and ketone **59**, a

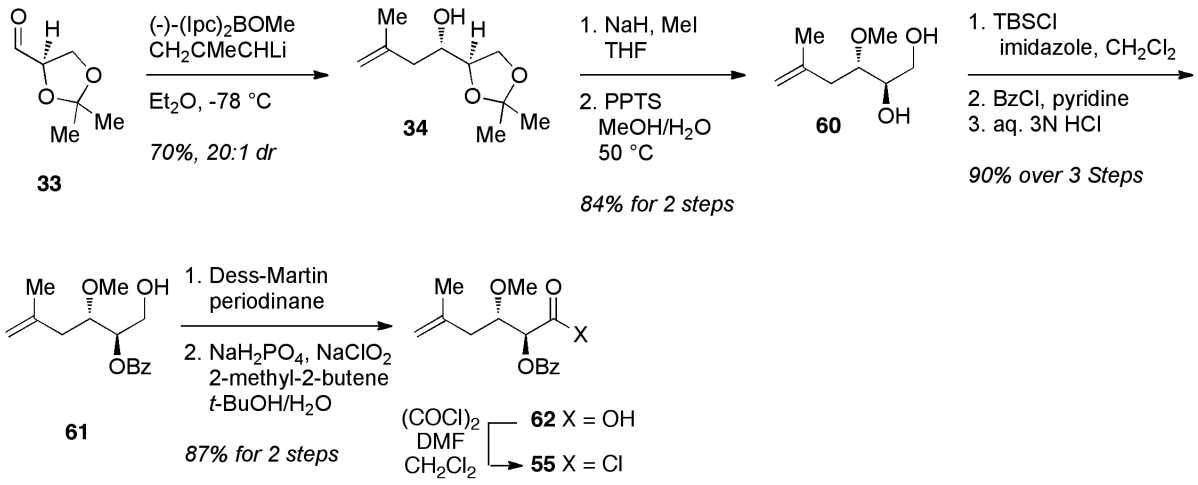
Scheme 2.3.1. DeBrabander Retrosynthetic Analysis



reaction that will be utilized in several subsequent syntheses. The aldol coupling strategy would prove to be a convergent means for the union of the dihydroisocoumarin and tetrahydropyran fragments, however the increased convergence would come at the expense of diastereoselectivity and modularity of the synthesis.

DeBrabanders synthesis of the psymberate side chain was very similar to the previous report by Williams, starting from the chiral pool (4*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (**33**), available from Aldrich for $100 per gram. A diastereoselective methallylation afforded alcohol **34** in 20:1 dr, a significant improvement to the previously reported 4:3 dr by Williams.[26] Methylation of alcohol

Scheme 2.3.2. DeBrabander Psymberate Side Chain Synthesis



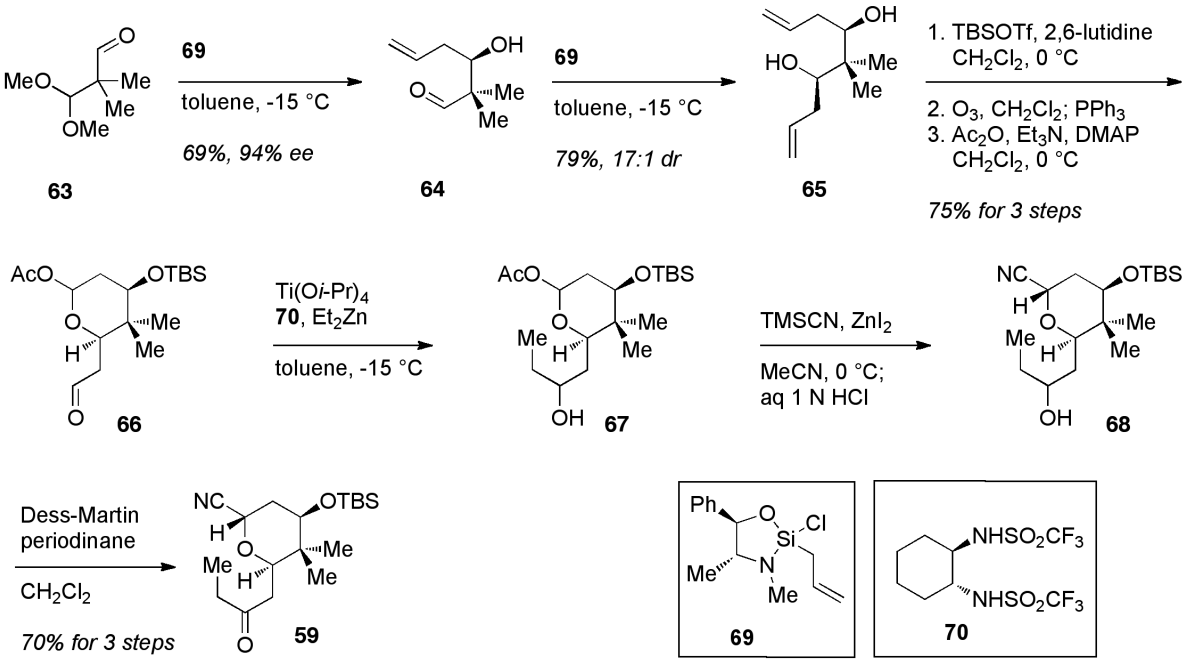
34 followed by deprotection of the 1,2-diol acetonide afforded 1,2-diol **60**. The protection strategy was then adjusted over a three step sequence to give the free primary carbinol **61** with the secondary carbinol protected as the benzyl ester. A two step oxidation protocol revealed carboxylic acid **62** (8 steps, 46% yield), which is readily converted to the acid chloride coupling partner **55**.

While the chiral pool approach served well for the synthesis of the acid chloride fragment, DeBrabander chose to construct the tetrahydropyran fragment utilizing a series of enantio- and diasteroselective allylation reactions. Starting from aldehyde **63** prepared over 3 steps in 68% yield from isobutyraldehyde, an enantioselective Leighton allylation provided homoallylic alcohol **64** in 69% yield and 94% ee while also unmasking the protected aldehyde.[27] A second Leighton allylation gave the C2-symmetric 1,3-diol **65** in 17:1 dr. Desymmetrization of diol **65** through a mono-TBS protection was followed by ozonolysis of both the terminal alkenes with concomitant cyclization to give the lactol, which was then protected to deliver lactol-acetate **66**. A Kobayashi diethylzinc addition[28] gave secondary alcohol **67**, which

was oxidized to ketone **59** after displacement of the acetate with TMSCN, completing the synthesis of the tetrahydropyran core (11 steps, 19% overall yield).

The dihydroisocoumarin functionality of irciniastatin A is a structurally distinct subunit that has not been observed in other natural products. Therefore, the

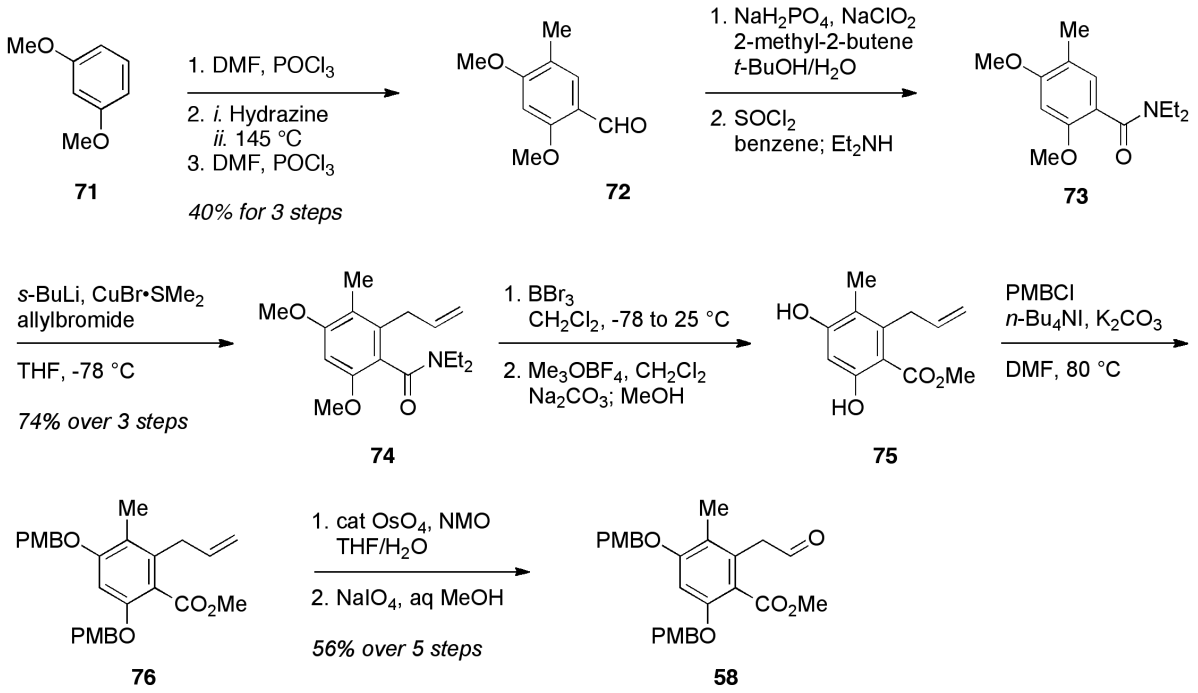
Scheme 2.3.3. DeBrabander Tetrahydropyran Synthesis



preparation of this fragment provided an opportunity to utilize the wealth of reactions available for constructing and functionalizing aromatic rings. DeBrabander chose a directed metallation approach for the preparation of the aryl portion of the dihydroisocoumarin. Starting from 1,3-dimethoxyresorcinol (**71**), a known three step protocol was followed to deliver aldehyde **72** in 40% yield.[29] The aldehyde was then converted to the diethyl amide directing group over two steps to give amide **73**. A directed ortho-metallation/allylation gave terminal alkene **74**, representing the carbon nucleus of the dihydroisocoumarin.[30,31] Removal of the methyl ether protecting

groups and conversion of the diethylamide to the methyl ester gave catechol **75**, which was reprotected to give the bis-PMB protected catechol **76**. The target aldehyde **58** was then accessed through a dihydroxylation-oxidative cleavage

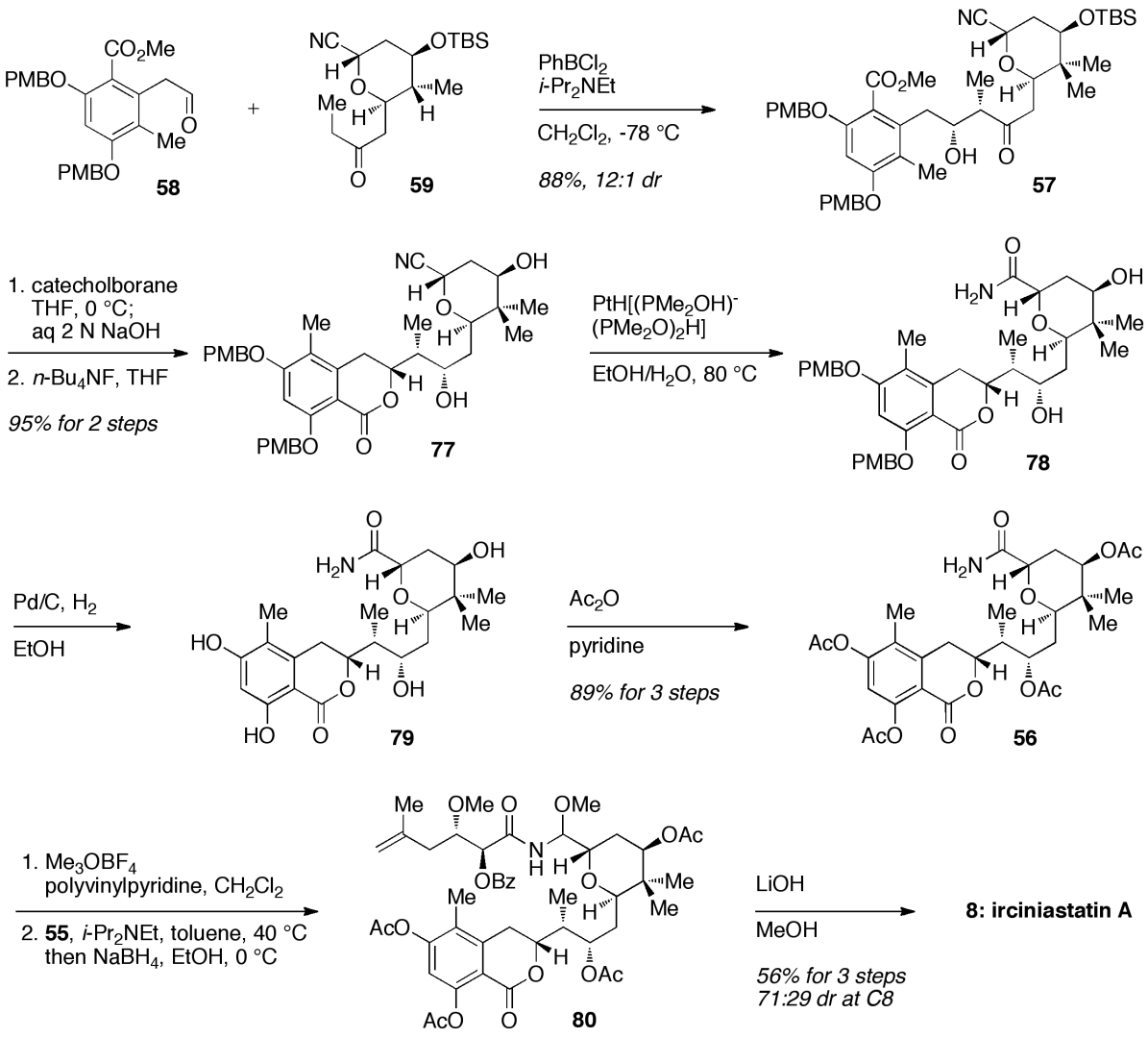
Scheme 2.3.4. DeBrabander Dihydroisocoumarin Synthesis



sequence to completing the fragment synthesis (10 steps, 17% yield).

Having accessed their three fragments, the union of the tetrahydropyran and the dihydroisocoumarin was investigated. Treatment of the (Z)-chlorophenylboryl enolate derived from ketone **59** with aldehyde **58** yielded the major *syn*-aldol product in 12:1 dr, as predicted from enolate facial bias imposed by the β-alkoxy substituent.[32] The C15 stereochemistry was then set through a catecholborane mediated chelation controlled reduction[33] and basic work-up to generate the lactone, which upon treatment with TBAF then gave diol **77**. The amide function was revealed through hydrogenation of the nitrile with the platinum(II) catalyst of Ghaffar

Scheme 2.3.5. DeBrabander Total Synthesis of Irciniastatin A



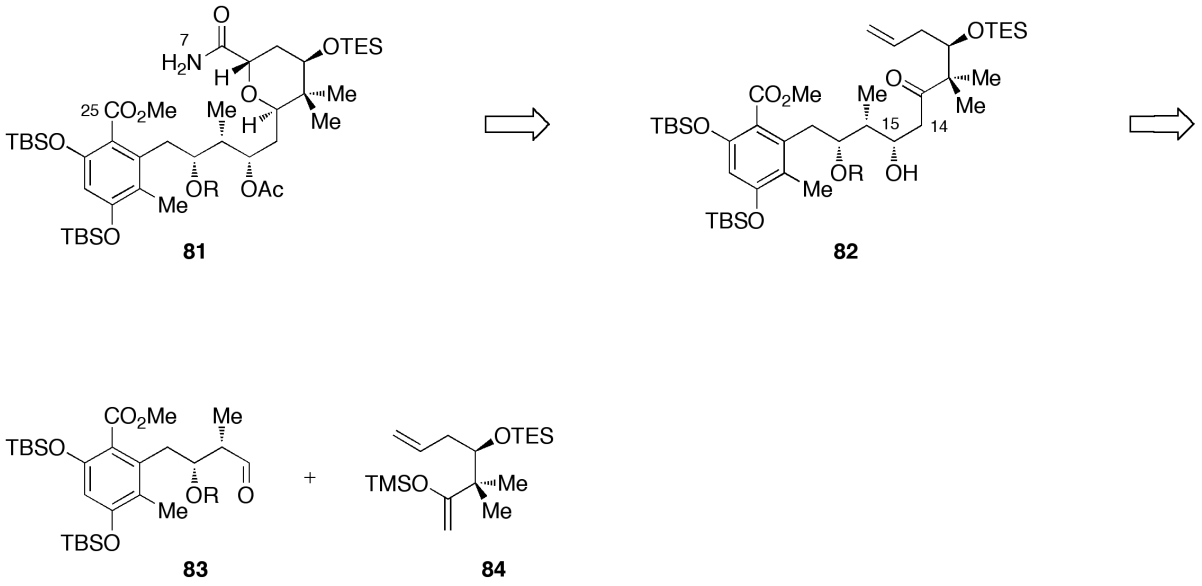
and Parkins to yield amide **78**.[34] Hydrogenolysis of the PMB ethers gave the fully deprotected N7-C25 fragement **79** that was subjected to global reprotection to give tetraacetate **56**. The second key coupling, a strategy successfully employed in the synthesis of pederin,[35] was executed by first preparing the methoxyimidate using Me_3OBF_4 and immobilized pyridine and then adding a solution of acid chloride **55** and Hünigs base. The coupled product was then treated with an ethanolic solution of

$NaBH_4$, wherein after work-up the crude products were saponified to afford a 71:29 ratio of irciniastatin A (21 steps, 6% overall) to 8-*epi*-irciniastatin A. The synthetic material of known (4*S*, 5*S*, 8*S*) configuration exactly matched the ^1H and ^{13}C NMR spectral data previously reported for both irciniastatin A ($CDCl_3$) and psymberin (MeOD). Additionally, the optical rotation of synthetic irciniastatin A ($[\alpha]_D$ = +25.2, *c* = 0.11, MeOH) agreed with those reported for natural irciniastatin A ($[\alpha]_D$ = +24.4, *c* = 0.55, MeOH) and natural psymberin ($[\alpha]_D$ = +29, *c* = 0.02, MeOH).

2.4 Floreancig Advanced Fragment Synthesis

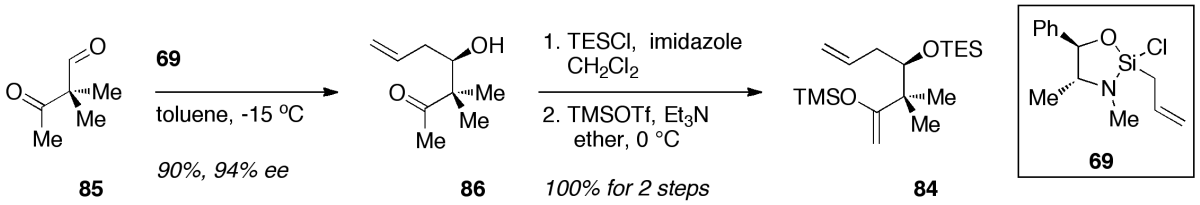
The report following the first total synthesis by DeBrabander was from Floreancig in 2005.[9] Floreancig's strategy was distinct from the strategy executed by DeBrabander although the target N7-C25 fragment **81** closely resembled Debrabander's late stage amide **56** (Scheme 2.4.1). The target amide would be prepared from terminal alkene **82** that would arise from a Mukaiyama aldol reaction between enolsilane **84** and aldehyde **83**.

Scheme 2.4.1. Floreancig Retrosynthetic Analysis



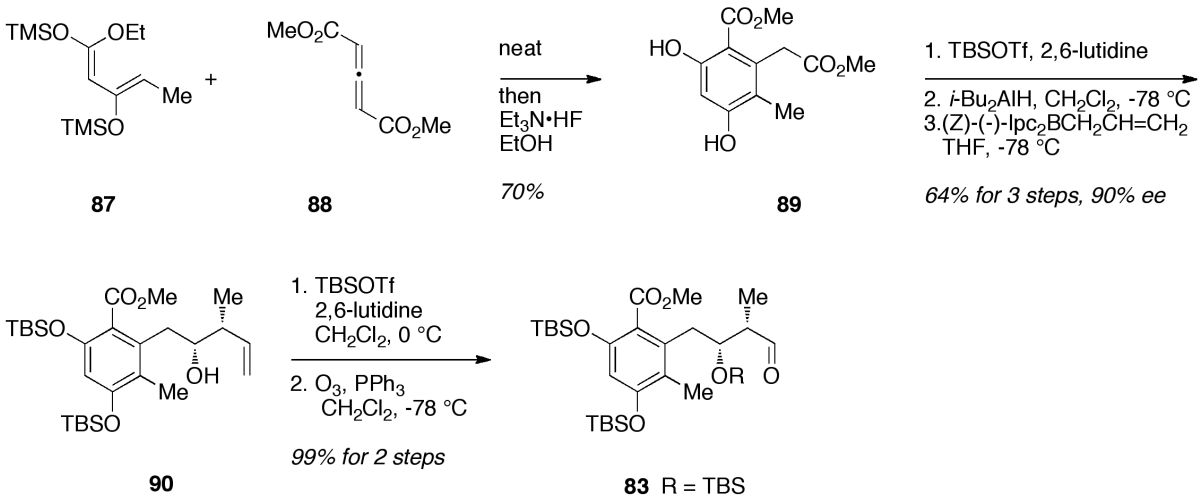
Floreancig's approach toward the precursor to the C9-C14 fragment utilized an enantioselective Leighton allylation[36] of aldehyde **85**, in the presence of a ketone (Scheme 2.4.2). The homoallylic alcohol **86** was then protected as the TES ether and the ketone was subsequently converted to enolsilane **84** to complete the fragment synthesis.

Scheme 2.4.2. Floreancig Synthesis of the Tetrahydropyran Framework



To synthesize the aromatic portion of irciniastatin A, Floreancig chose to use methodology developed by Langer,[37] utilizing the cycloaddition of allene **88**[38] and diene **87** (Scheme 2.4.3).[39] This strategy provided the fully decorated aromatic ring **89** in three steps from commercially available material. Most importantly the chemistry was run on 12 g scale, providing rapid access to multi gram quantities of

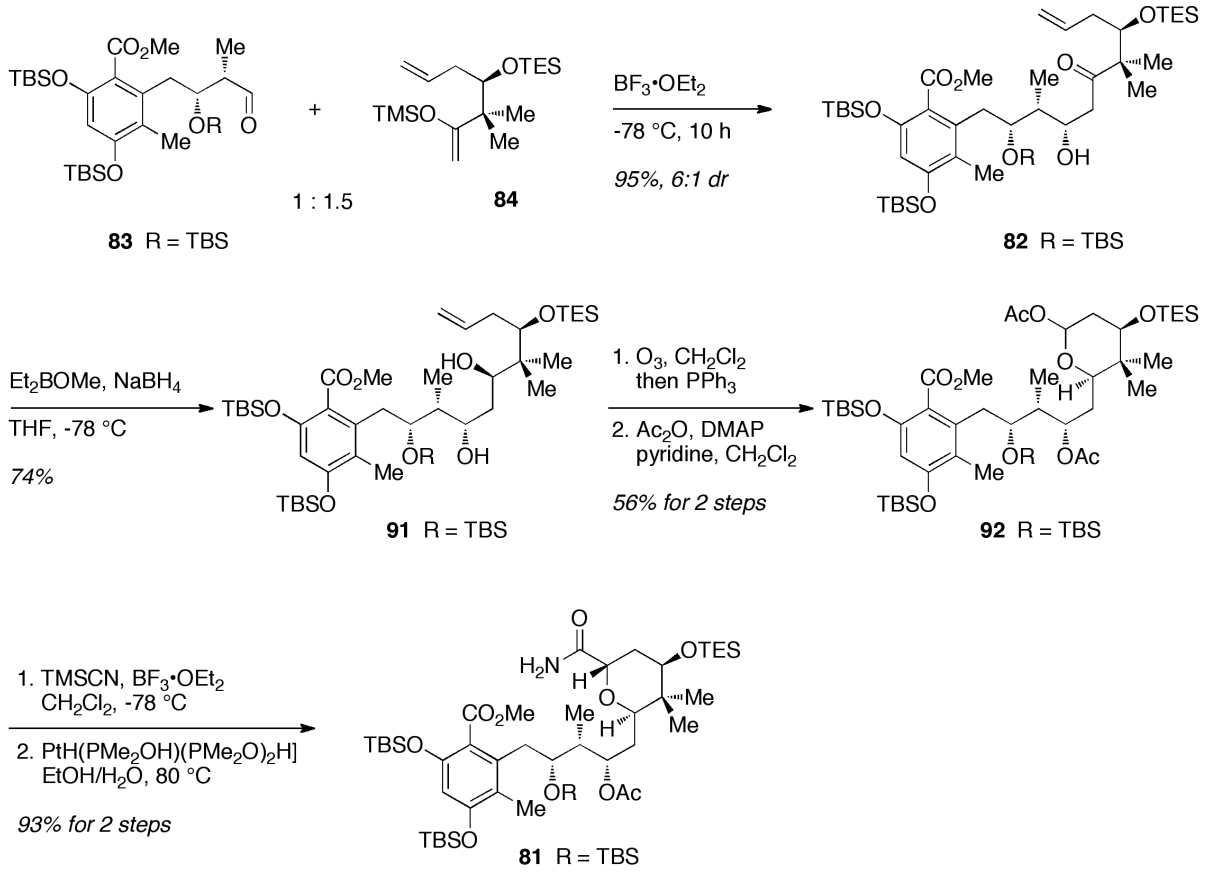
Scheme 2.4.3. Floreancig Dihydroisocoumarin Synthesis



this valuable synthetic intermediate. Protection of catechol **89** followed by a chemoselective reduction of the benzylic ester to the corresponding aldehyde that was subjected to an enantioselective Brown crotylation gave homoallylic alcohol **90** in 64% over 3 steps and 90% ee.[40] Protection of the hydroxyl and ozonolysis of the terminal alkene afforded aldehyde **83** to finish the synthesis of the dihydroisocoumarin fragment (5 steps, 44% overall from catechol **89**)

The Mukaiyama aldol coupling of enolsilane **84** with aldehyde **83** (Scheme 2.4.4) employed by Floreancig could occur with either α- or β-stereodirection from the substituents at C16 and C17. The α-directed Felkin-Anh[41,42,43] approach of the nucleophile would provide the desired *syn,syn*-product, whereas β-direction from the β-silyloxy group would yield the *anti,syn*-product. Consistent with Evans[44] observations that α-direction prevails when bulky nucleophiles are employed, the Mukaiyama aldol between **84** and **83** provided the aldol product **82** with modest selectivity for the *syn,syn*-product through a Felkin-Anh approach. This strategy provided an excellent method for the union of the dihydroisocoumarin and tetrahydropyran frameworks, although it requires that the tetrahydropyran must be formed at a late-stage. A chelation controlled reduction using the alcohol handle proceeded to give the single *syn*-isomer in 74% yield.[45] The tetrahydropyran was then formed by ozonolysis of the terminal alkene with concomitant ring closure to give the lactol, which was followed by diacetylation to give lactol acetate **92**. The synthesis of the advanced fragment was then completed by substitution of the acetate using TMSCN and hydrolysis of the resultant nitrile to give amide **81** (11 steps, 14% overall yield from catechol **89**). It was particularly curious that the total

Scheme 2.4.4. Floreancig Synthesis of the N7-C25 Fragment of Irciniastatin A

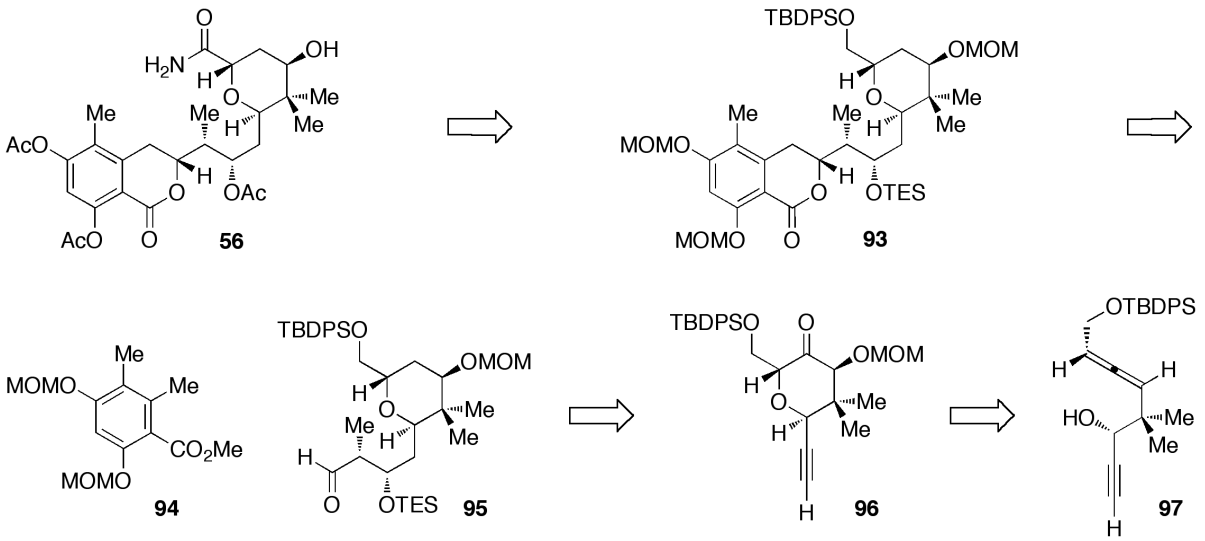


synthesis was not completed as the late-stage intermediate was so similar to DeBrabander's amide **59**, and that this work would represent a significant improvement over DeBrabander's synthesis. The notable differences are that the lactone of the dihydroisocoumarin had yet to be installed and that aryl ether protection strategy was different. Both of differences would prove to be critical issues in subsequent synthetic campaigns.

2.5 Williams Formal Synthesis of Irciniastatin A

After a year without any publications concerning the synthesis of ircinastatin A or any of its fragments, one of the most interesting and unique syntheses was disclosed. In 2006 Williams[8] reported the formal synthesis of irciniastatin A that

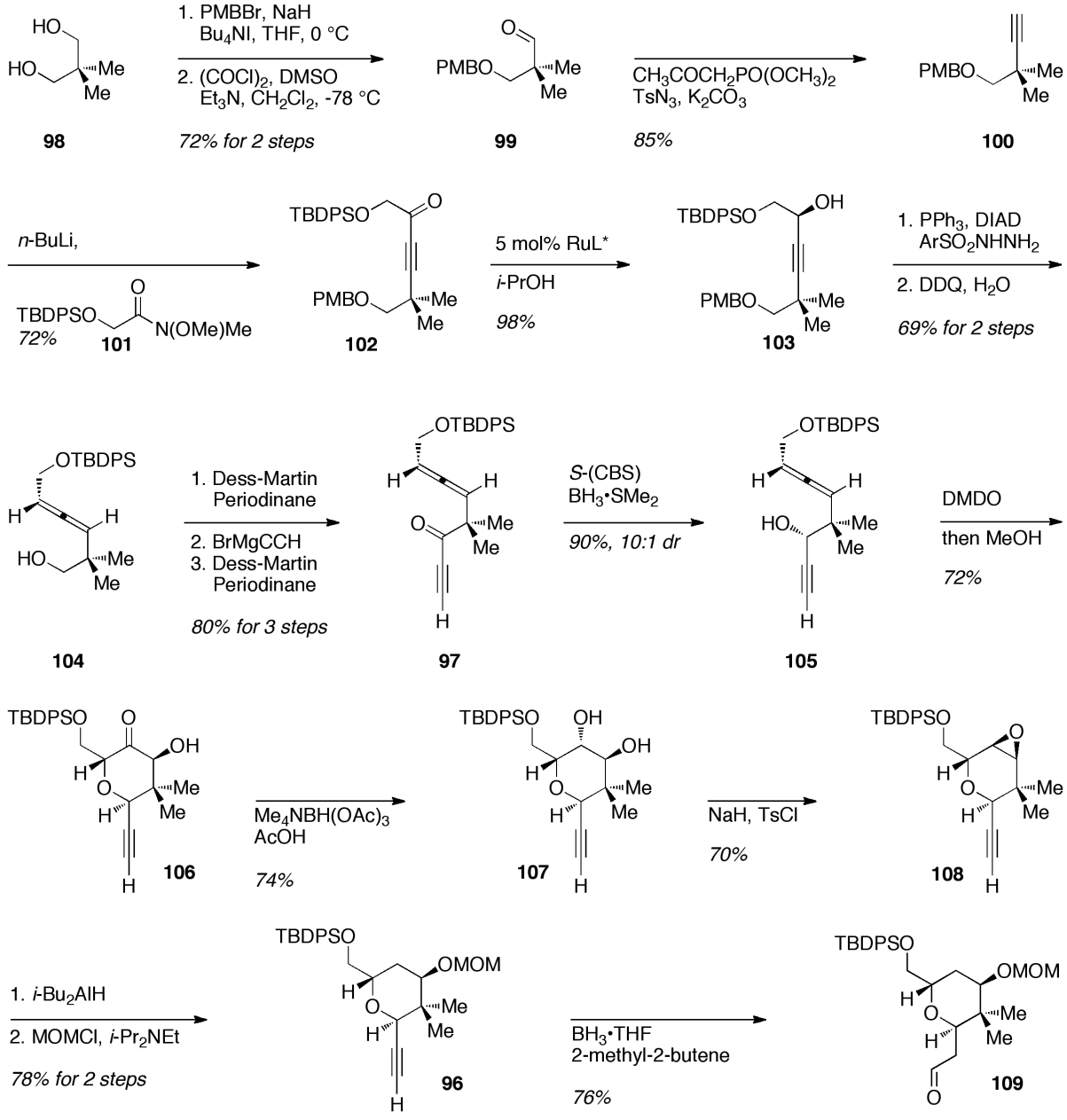
Scheme 2.5.1. Williams Retrosynthetic Analysis



accessed DeBrabander's late stage amide **56**[3] (Scheme 2.5.1). In this synthetic effort, Williams sought to access the target amide **56** through protected carbinol **93**, which was derived from the nucleophilic addition of the aryl homoenolate from **94** to the advanced aldehyde **95**. Aldehyde **95** would arise from the alkyne **96** that is generated from a spirodiepoxide opening. This strategy was particularly interesting as it still stands as the only synthetic effort that couples the tetrahydropyran and the dihydroisocoumarin in this fashion. Furthermore, this synthesis highlights the utility of spirodiepoxide opening reactions toward the synthesis of complex tetrahydropyrans.

Williams synthesis of tetrahydropyran **96** started with 2,2-dimethyl-1,3-propane diol (**98**) that was monoprotected and oxidized to aldehyde **99**, which was then subjected to an Ohira-Bestmann[46] reaction to give alkyne **100** (Scheme 2.5.2). After acylation of the acetylide derived from **100** with amide **101**, the resulting alkynone **102** was reduced under Noyori[47] conditions to give the enantioenriched

Scheme 2.5.2. Williams Tetrahydropyran Synthesis

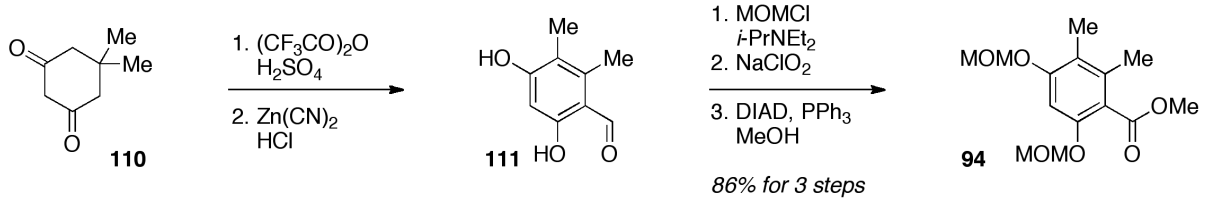


propargylic alcohol **103**. The chiral allene **104** was accessed through Myers[48] procedure and deprotection of PMB ether. Alcohol **104** was converted to ynone **105**, which served well as a substrate for the diasteroselective CBS reduction to access the spirodiepoxide precursor **97** with 10:1 dr.[49,50] Subjecting allene **97** to DMDO provided the desired spirodiepoxide opened product **106** as a single isomer in 72%

yield. What was especially remarkable about this transformation was the variety of function groups present on the product. Tetrahydropyranone **106** featured fully differentiable alcohol, ketone, terminal alkyne, and protected alcohol functional groups, which demonstrated the utility of this chemistry for building complex molecules outward from a core tetrahydropyran structure. The power of accessing these complex structures with differentiable protecting groups was exemplified as Williams performed a reduction of the α-hydroxy ketone to provide the *anti*-1,3-diol[51] that was subsequently converted to the epoxide **108**. The selective opening of epoxide **108**[52] and protection of the resultant carbinol provided MOM ether **96**. Lastly, the terminal alkyne that remained idle throughout these manipulations, was reduced with borane in the presence of 2-methyl-2-butene to reveal the advanced aldehyde **109**.

Williams synthesis of the arene subunit of irciniastatin A proved to be one of the most concise (Scheme 2.5.3). The commercially available dimedone **110** was aromatized[53] under acidic conditions and subsequently formylated with $Zn(CN)_2$/ HCl[54] to provide arene **111**, which was carried forward to aryl ester **94** through

Scheme 2.5.3. Williams Synthesis of the Arene Subunit of Irciniastatin A

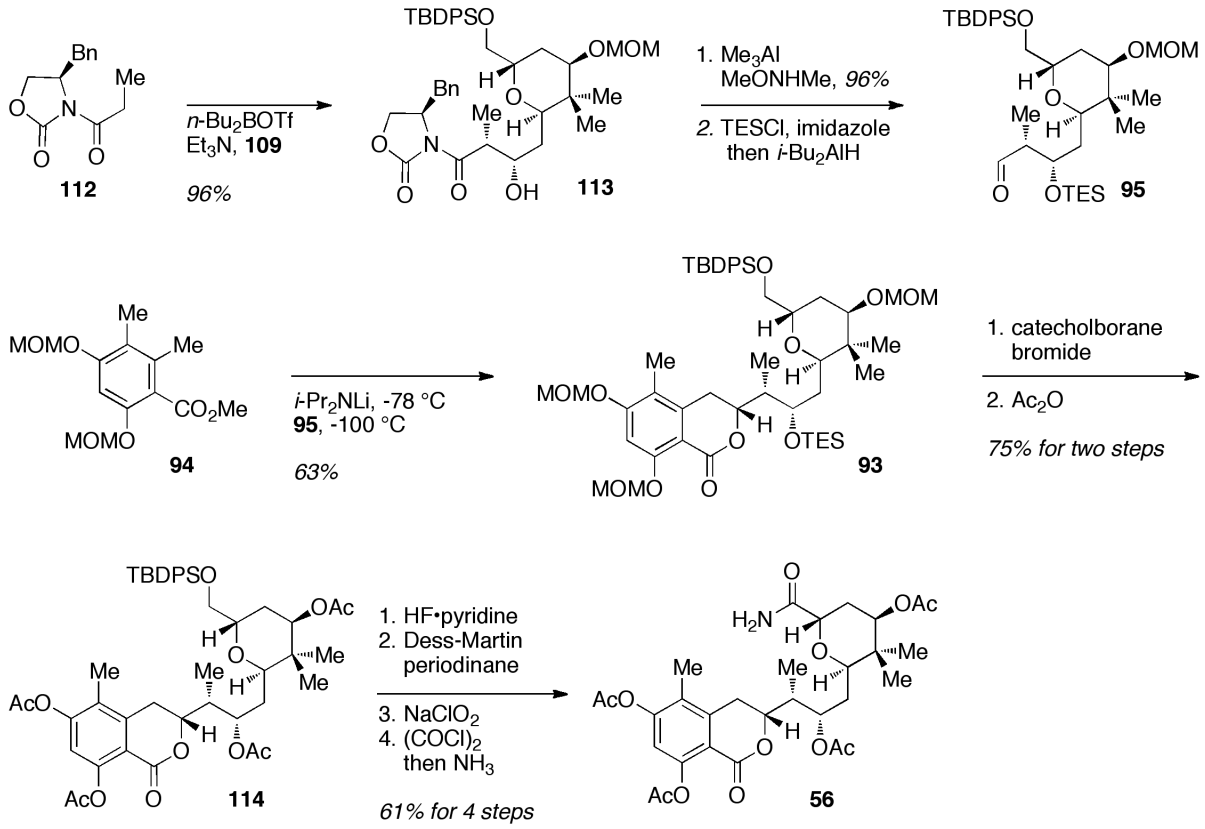


standard protecting group and oxidation state manipulations.

With the two core fragments available, aldehyde **109** was converted to the desired coupling partner **95** through and Evans *syn*-aldol with subsequent removal

of the chiral auxiliary (Scheme 2.5.4). The two fragments were then united upon exposure of the homoenolate of **94** to aldehyde **95** to produce the coupled product

Scheme 2.5.4. Williams Formal Synthesis of Irciniastatin A

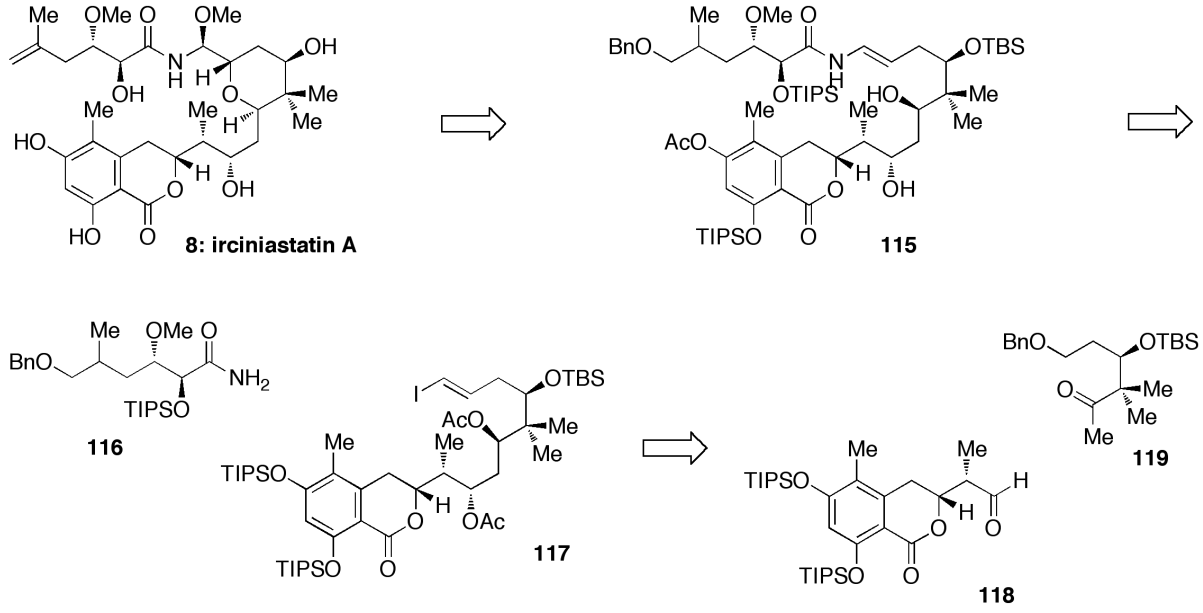


93 in 63% yield with 3:1 dr. Although the yield and diastereoselectivity were modest, the utility of the coupling can be taken from the ease with which the dihydroisocoumarin was generated at a late stage that could provide quick access to a variety of dihydroisocoumarin modified irciniastatin analogs. To access the target amide **56**, the MOM and TES protecting groups were replaced with the requisite acetate protecting groups of DeBrabander's intermediate. Finally, the TBDPS ether of peracetylated **114** was converted over 4 steps to amide **56** (27 steps overall).

2.6 Schering Plough Total Synthesis

In 2007, a group from Schering Plough reported the second total synthesis of irciniastatin A.[4] Their synthetic approach differed significantly from the earlier work by DeBrabander. The Schering group sought to install the hemiaminal functionality while closing the tetrahydropyran ring from N-acyl enamine **115** using their BAIB mediated oxidative cyclization (Scheme 2.6.1). While this novel method for generating N-acyl hemiaminals from enamides was both unique and substantially different from the DeBrabander methoxyimidate-acid chloride coupling, it was not clear whether this method would provide improved stereoselective entry to the C8-aminal over the methoxyimidate method. Enamide **115** would be generated from Buchwald coupling of amide **116** and vinyl iodide **117** to couple the psymberate side chain and tetrahydropyran subunits. The union of the dihydroisocoumarin and the tetrahydropyran carbon framework would arise from a substrate controlled

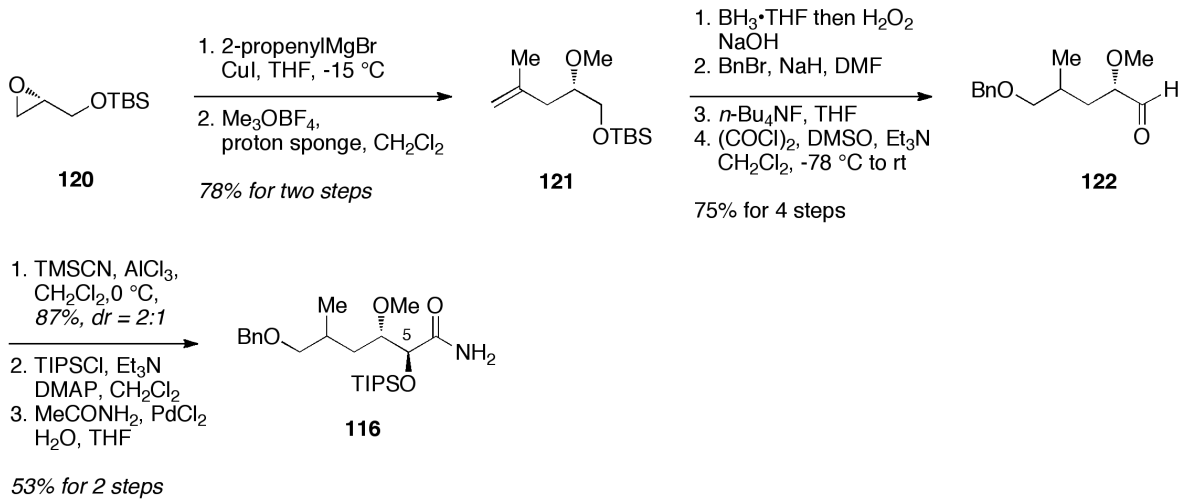
Scheme 2.6.1. Schering Plough Retrosynthetic Analysis



Mukaiyama aldol reaction to connect C14-C15 that was similar to Floreancig's strategy.

As with all the previous reports for the synthesis of the psymberate side chain, the Schering group utilized a chiral pool strategy (Scheme 2.6.2). Starting from TBS protected (*R*)-glycidol **120**, regioselective epoxide opening with isopropenylmagnesium bromide gave a secondary alcohol that was protected as the methyl ether **121**. As the terminal alkene would not be tolerated for their late stage oxidative cyclization to form the hemiaminal, it was masked at this stage by hydroboration and protection the resultant alcohol as the benzyl ether. Deprotection of the TBS group followed by Swern oxidation provided aldehyde **122**. A unique method to install the C5 carbinol stereochemistry was used through

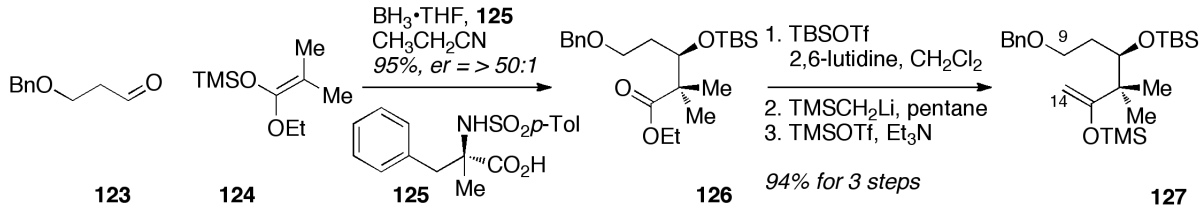
Scheme 2.6.2. Schering Plough Synthesis of the Psymberate Side Chain



diastereoselective cyanohydrin formation using TMSCN and $AlCl_3$, although only poor selectivity was observed, giving a 2:1 ratio of alcohol diastereomers. The desired carbinol isomer was protected as the TIPS ether and the nitrile was hydrolyzed[55] to give amide **116** (9 steps, 27% overall yield).

The late stage formation of the tetrahydropyran as outlined by Schering, set two of the three stereocenters of the tetrahydropyran core after the carbon framework of this fragment was to be coupled to the dihydroisocoumarin unit. As a result, the synthesis of the C9-C13 fragment was concise (Scheme 2.6.3). An enantioselective Masamune aldol reaction of silylenol ether **124** with aldehyde **123** set the single stereocenter of this fragment with > 50:1 er.[56] Protection of the resultant alcohol as the TBS ether was followed by ketone formation directly from the ester with trimethylsilylmethyl lithium[57] and then conversion to enolsilane **127** (4 steps, 89% overall).

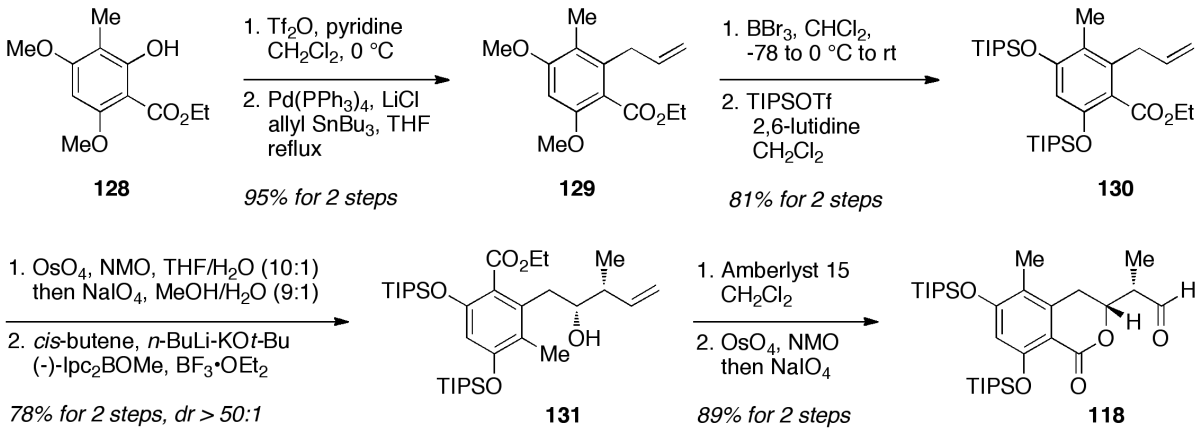
Scheme 2.6.3. Schering Plough Synthesis of the Tetrahydropyran Framework



123 **124** **125** **126** **127**

Similar to the strategy employed by DeBrabander, the Schering group sought to access the dihydroisocoumarin subunit by elaborating a commercially available aromatic ring as opposed to *de novo* synthesis (Scheme 2.6.4). Starting from phenol **128**, available over 2 steps in 46% yield from commercially available 2,4,6-trimethoxytoluene,[58] conversion to the aryl triflate was followed by a Stille coupling to give alkene **129**. Removal of the methyl ether protecting groups and reprotection as TIPS ethers gave bis-TIPS protected catechol **130**. The terminal alkene was converted over two steps to the corresponding aldehyde, which was then subjected to an enantioselective Brown crotylation reaction to provide *syn*-**131** with excellent

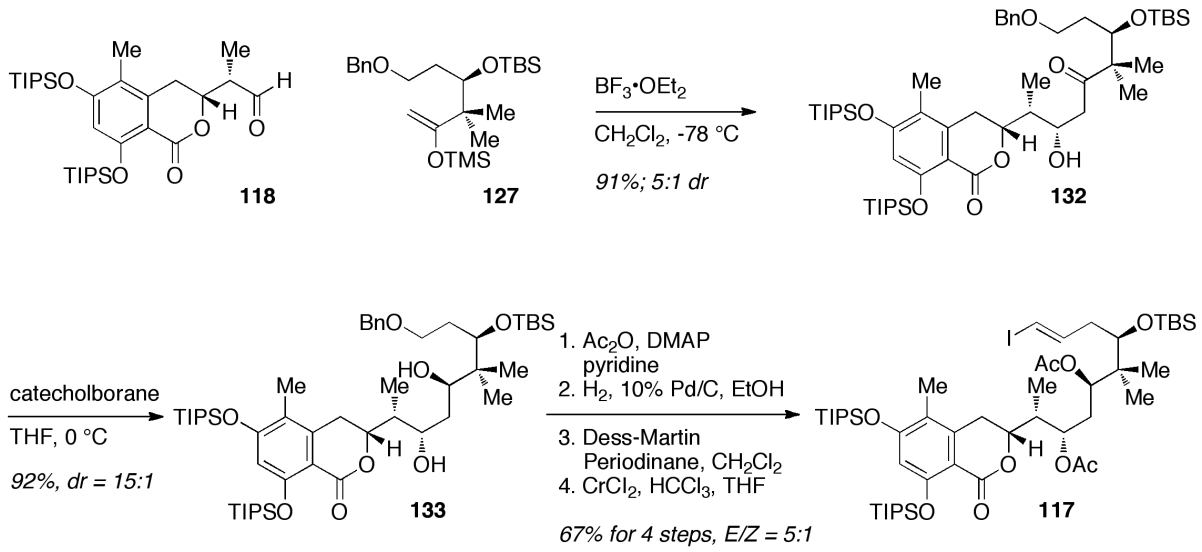
Scheme 2.6.4. Schering Plough Synthesis of the Dihydroisocoumarin



diastereoselectivity (> 50:1) and enantioselectivity (90% ee).[40] At this stage the lactone was closed under acidic conditions and the terminal alkene was converted to the corresponding aldehyde **118** (10 steps, 24% overall).

With all three fragments available, the union of enolsilane **127** and aldehyde **118** was realized through a substrate controlled aldol reaction to give ketone **132** in 76% yield as the desired isomer (Scheme 2.6.5).[59] This reaction demonstrates the

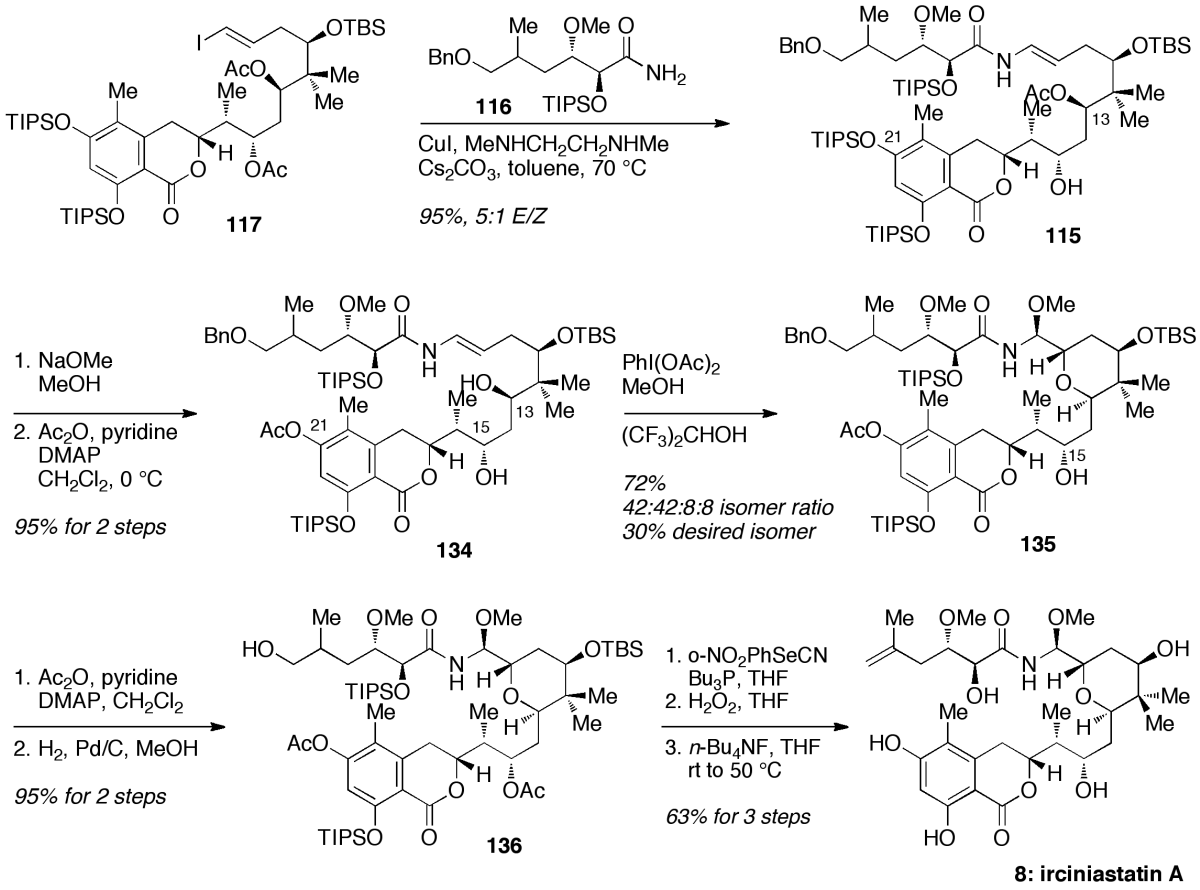
Scheme 2.6.5. Schering Plough Union of the Dihydroisocoumarin with the Tetrahydropyran Precursor



power of the Mukaiyama aldol reaction for coupling complex fragments in a diastereoselective fashion. It is also noteworthy that this represents the only union of the dihydroisocoumarin and the tetrahydropyran framework with a preformed lactone of the dihydroisocoumarin. A chelation controlled reduction utilizing catecholborane to set the C13 stereocenter gave carbinol **133** with 15:1 dr.[33] The *syn*-1,3-diol was protected as the diacetate and the primary benzyl ether was deprotected to allow for a Dess-Martin oxidation to the aldehyde that was subjected to a Takai olefination[60] to give vinyl iodide **117** (*E*/*Z* = 5:1).

With the successful union of the dihydroisocoumarin and the tetrahydropyran framework and elaboration to vinyl iodide **117**, the novel endgame strategy of Buchwald amidation and oxidative cyclization to form the tetrahydropyran and N-acyl hemiaminal could be investigated (Scheme 2.6.6). The coupling of vinyl iodide **117** and amide **116** was realized using CuI to give the protected N-acyl enamine **115** in excellent yield.[61] At this stage the C13 carbinol required deprotection so the carbinol could participate in the oxidative cyclization event. Deprotection of the acetate protecting groups was accompanied by removal the O21 TIPS protecting group, which was subsequently reacetylated. The $PhI(OAc)_2$ mediated oxidative cyclization[62] reaction occurred to give a mixture of all four possible isomers in a 42:42:8:8 ratio, giving a 30% yield of the desired isomer **135**. Although this represented a new method for the construction of hemiaminals, a severely under explored functionality, the lack of compatibility with the terminal alkene of the psymberate side chain and the lack of stereocontrol severely weakened the effectiveness of this strategy. With the carbon skeleton of the natural product in

Scheme 2.6.6. Schering Plough Total Synthesis of Irciniastatin A



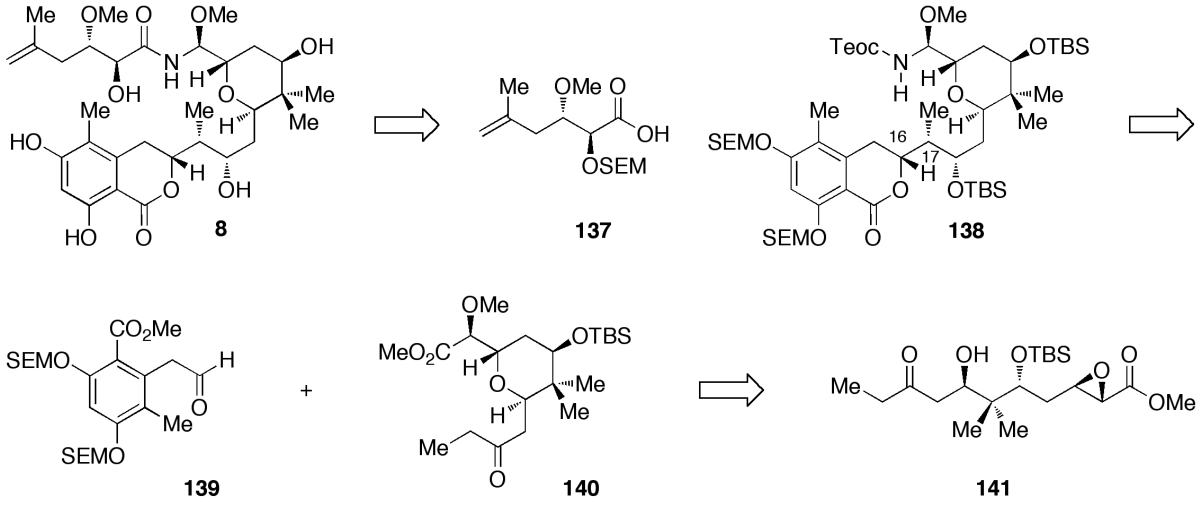
place, the alkene of the psymberate side chain would need to be revealed. The C15 alcohol was protected as the acetate and the primary benzyl ether was deprotected to give alcohol **136**. A two step selenium mediated dehydration was followed by global deprotection to provide synthetic irciniastatin A (**8**) (21 steps longest linear, 8% overall).

2.7 Smith Total Synthesis

The third total synthesis of irciniastatin A came from the Smith group in 2008.[5] Their approach carried some similar elements to the syntheses from DeBrabander and Floreancig, while offering a new and unique approach to the tetrahydropyran

and the only stereospecific installation of the N-acyl hemiaminal. According to their retrosynthetic analysis, irciniastatin A would arise from a late stage installation of the side chain and N-acyl hemiaminal, an approach that was common to both earlier reports (Scheme 2.7.1). The N-acyl hemiaminal **138** would arise from the Curtius rearrangement of the corresponding carboxylic acid. This strategy represents a significant improvement over previous endgame approaches as it would be the first to gain stereospecific entry to the C8 hemiaminal. In similarity to DeBrabander's

Scheme 2.7.1. Smith Retrosynthetic Analysis

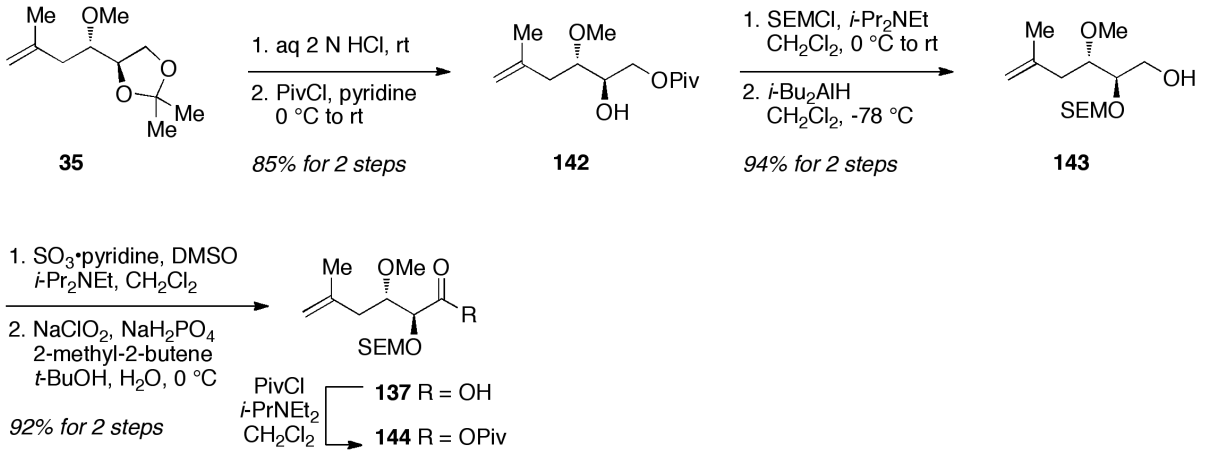


approach, a Paterson boron mediated aldol between aldehyde **139** and ketone **140** would install the C16 and C17 stereocenters. Aldehyde **140** would be prepared using Floreancig's strategy, while a series of catalytic reagent controlled reactions would be employed to generate the tetrahydropyran precursor **141**. The advantage of this tactic would be rapid access to a wide variety of stereochemically diverse congeners, simply by changing the enantiomer of the catalyst, thereby avoiding significant strategy redesign to access analogs.

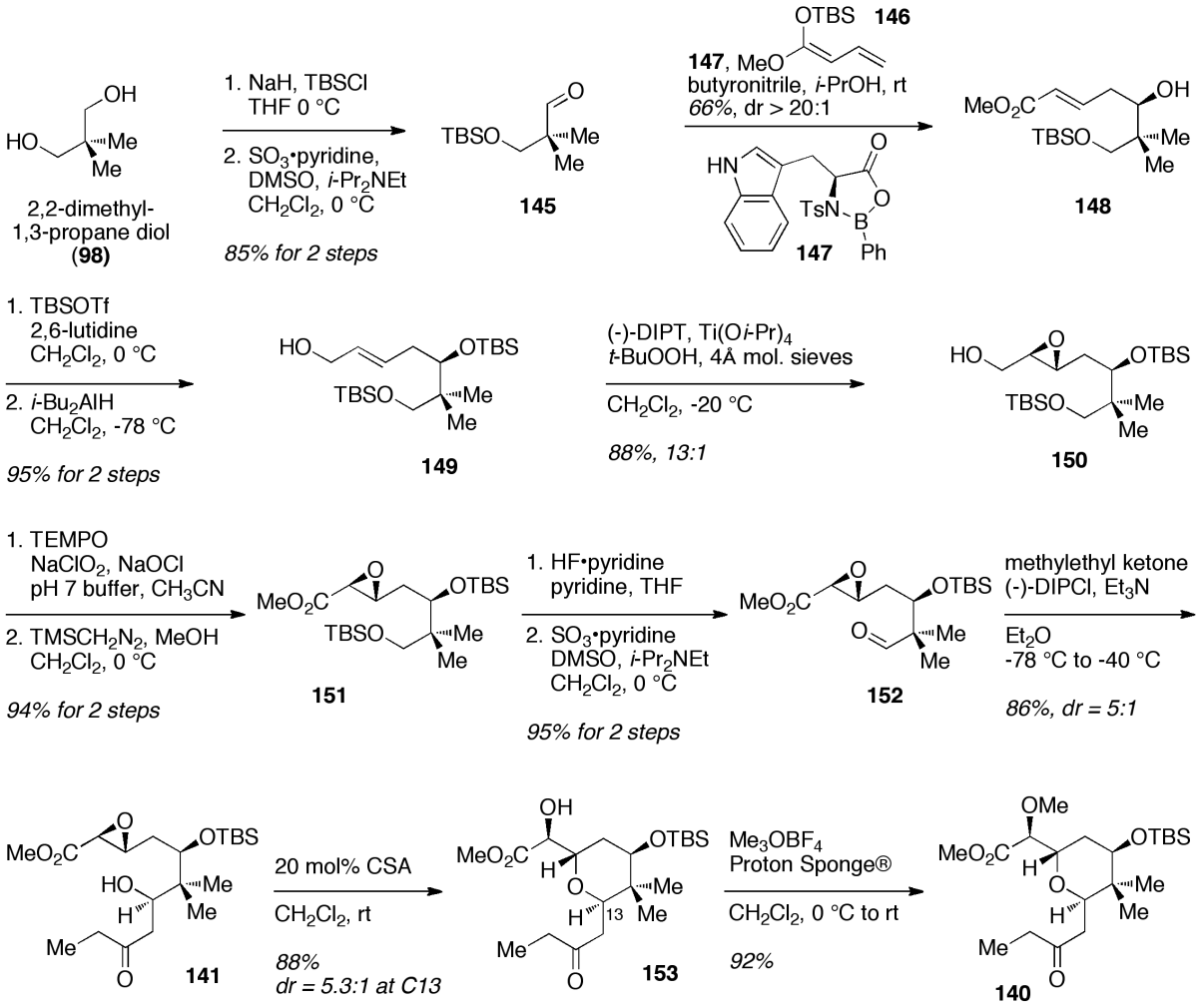
Smith's synthesis of the psymberic acid side chain followed a chiral pool approach that was nearly identical to DeBrabander's and William's strategy (Scheme 2.7.2). The 1,2-diol acetonide **35**, known from DeBrabander's work, was deprotected to give the resultant diol that was selectively protected at the primary alcohol to give pivalate ester **142**. Protection of the secondary alcohol as the SEM ether and removal of the temporary pivalate ester gave alcohol **143**. A two-step oxidation sequence afforded carboxylic acid **137** that could be converted to the mixed pivalate anhydride **144** required for the late stage side chain installation.

The synthesis of the tetrahydropyran fragment began with commercially available 2,2-dimethyl-1,3-propane diol (**98**) that was mono-TBS protected and oxidized to give aldehyde **145**. A vinylogous Mukaiyama aldol reaction[63] with silyl ketene acetal **146** using the oxazaborolidinone **147** promoter gave carbinol **148** as a single enantiomer in 66% yield. The resultant alcohol was protected as the TBS ether and the allylic alcohol **149** was revealed through *i*-Bu_2AlH reduction of the

Scheme 2.7.2. Smith Synthesis of the Psymberate Side Chain



Scheme 2.7.3. Smith Synthesis of the Tetrahydropyran

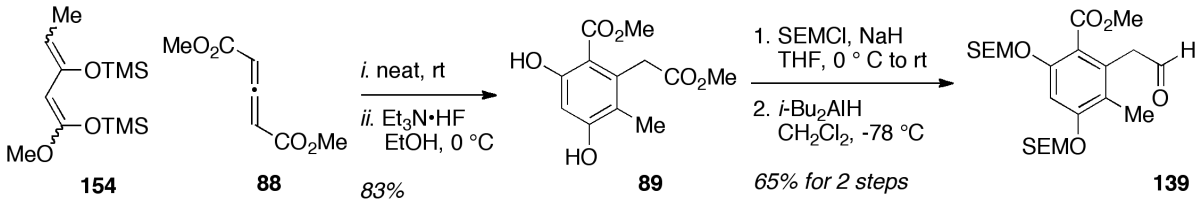


corresponding methyl ester. A Sharpless asymmetric epoxidation[64] gave the epoxide **150** in 88% with a 13:1 dr, which was followed by TEMPO oxidation to furnish the carboxylic acid that was methylated using $TMSCH_2N_2$ to give methyl ester **151**. Selective removal of the primary TBS ether with subsequent Parikh-Doering oxidation of the resultant alcohol completed the construction of aldehyde **152**. The final elaboration toward alcohol **141**, the requisite tetrahydropyran precursor, entailed treatment of 2-butanone with (-)-DIPCl and Et_3N according to the Paterson method,[65,66] followed by addition of the aldehyde **151** to give the aldol adduct **141** in

86% yield in 5:1 dr. Treatment of **141** with catalytic CSA in CH_2Cl_2 gave the desired tetrahydropyran in 74% yield, which after methylation of the free hydroxyl completed the synthesis tetrahydropyran fragment **140** (13 steps, 23% overall).

The last of the three fragments employed a slight derivation of the Langer method previously employed by Floreancig (Scheme 2.7.4). Using the 1,3-bis (trimethylsiloxy)-1,3-diene **154**[67] derived from methylpropionyl acetate rather than ethylpropionyl acetate, the Diels-Alder reaction occurred in an improved 83% yield over the previously reported 70% yield, although the authors did not provide an explanation or procedure to shed light on these improvements. Aldehyde **139** was

Scheme 2.7.4. Smith Synthesis of the Dihydroisocoumarin



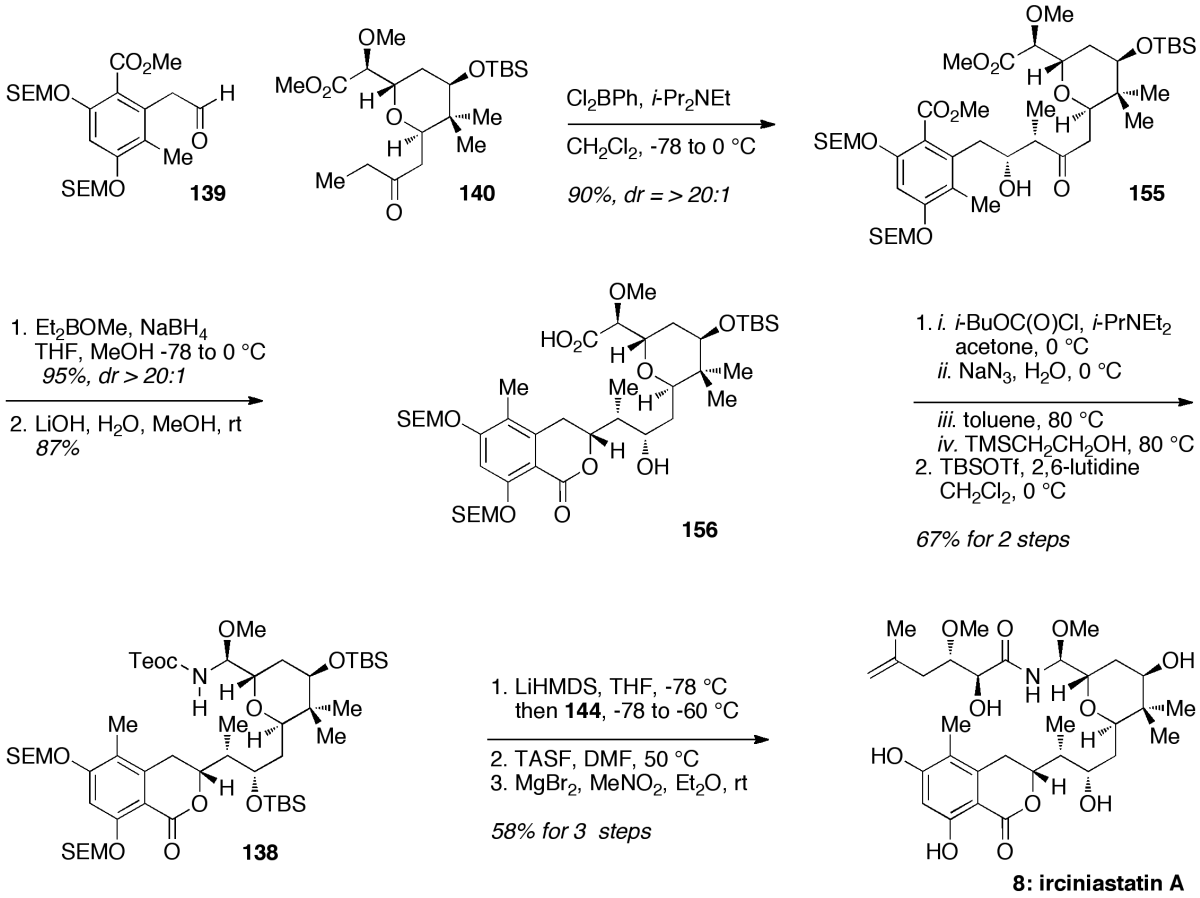
154 **88** **89** **139**

then accessed over two steps in 65% yield to complete the last remaining fragment.

With all three fragments in hand, Smith investigated the union of the tetrahydropyran and dihydroisocoumarin fragments (Scheme 2.7.5). Similar to the DeBrabander coupling, the (Z)-chlorophenylboryl enolate derived from ketone **140** with aldehyde **139** yielded the major *syn*-aldol product in 20:1 dr, invoking substrate control to explain observed stereodirection.[32] Again in similar fashion, a 1,3-chelation controlled reduction[45] was employed to generate the 1,3-*syn*-diol, which upon exposure to lithium hydroxide effected hydrolysis of the methyl ester and concomitant lactonization to provide dihydroisocoumarin **156**. Employing a Curtius

degradation strategy that had been successful in their total syntheses of (+)-zampanolide and (+)-dactylolide,[68] the Teoc-protected hemiaminal **138** was isolated after TBS protection of the free hydroxyl. To finish the total synthesis all that remained was to form the N7-C6 bond. Smith explicitly stated the difficulty they

Scheme 2.7.5. Smith Total Synthesis of Irciniastatin A



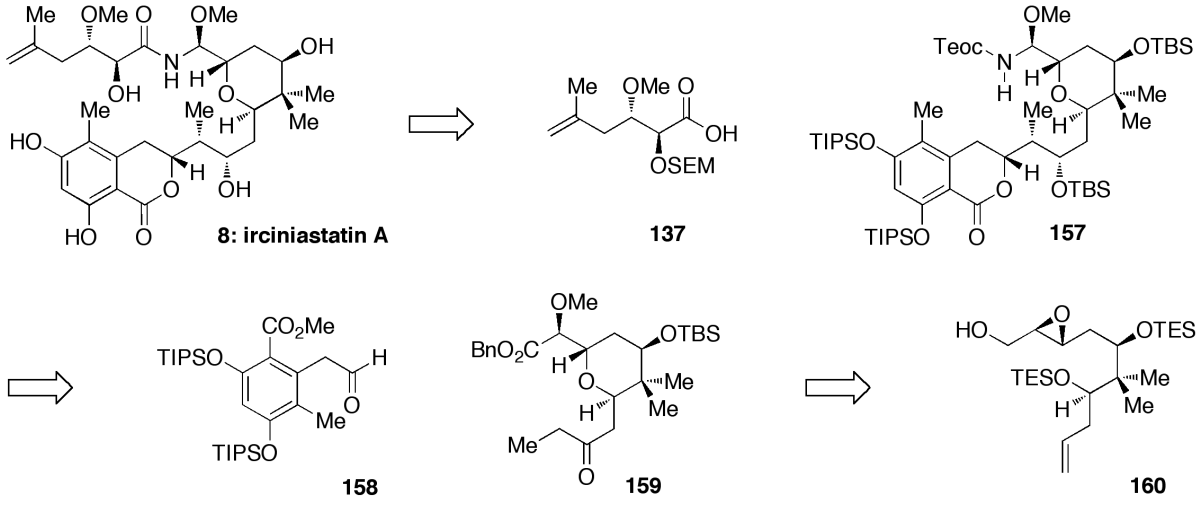
encountered while exploring this union, however a detailed account of these difficulties was not provided. Nevertheless, they were able to execute the coupling using LiHMDS as the base and the mixed pivalate anhydride **144** as the coupling

partner, which after a two-stage deprotection afforded synthetic irciniastatin A (**8**) (21 steps, 6% overall).

2.8 Watanabe Total Synthesis

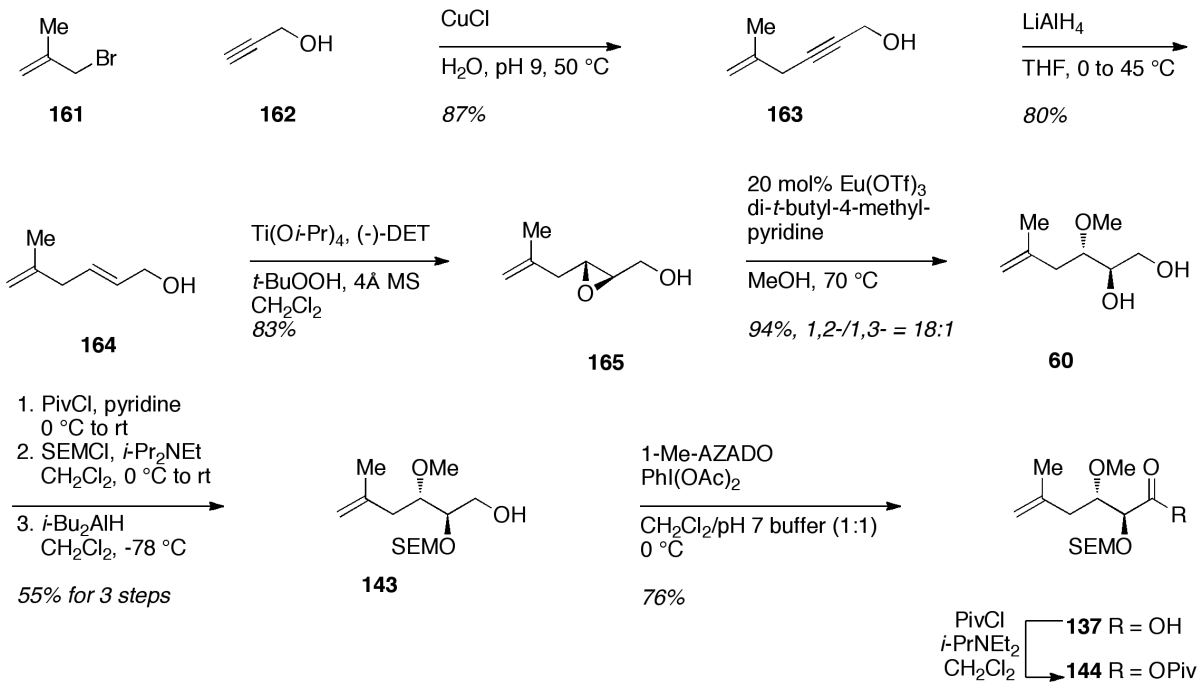
In 2010 Watanabe reported the fifth total synthesis of (+)-irciniastatin A, which also included the separate enantioselective synthesis of (-)-irciniastatin A and the synthesis of a single analog.[7] Their overall disconnection strategy closely resembled Smith's strategy although they provided a novel approach to the psymberate side chain (Scheme 2.8.1). Comparable to the Crimmins and Smith strategies, Watanabe sought to access irciniastatin A (**8**) through a late-stage installation of the side chain and hemiaminal through a Curtius rearrangement followed by a hemiaminal acylation sequence. Hemiaminal **157** would be derived from the product of a boron enolate aldol reaction of known aldehyde **158** and ketone **159**, which was nearly identical to strategy reported by Smith. The ketone coupling partner **159** would arise from the manipulation of epoxide **160**.

Scheme 2.8.1. Watanabe Retrosynthesis



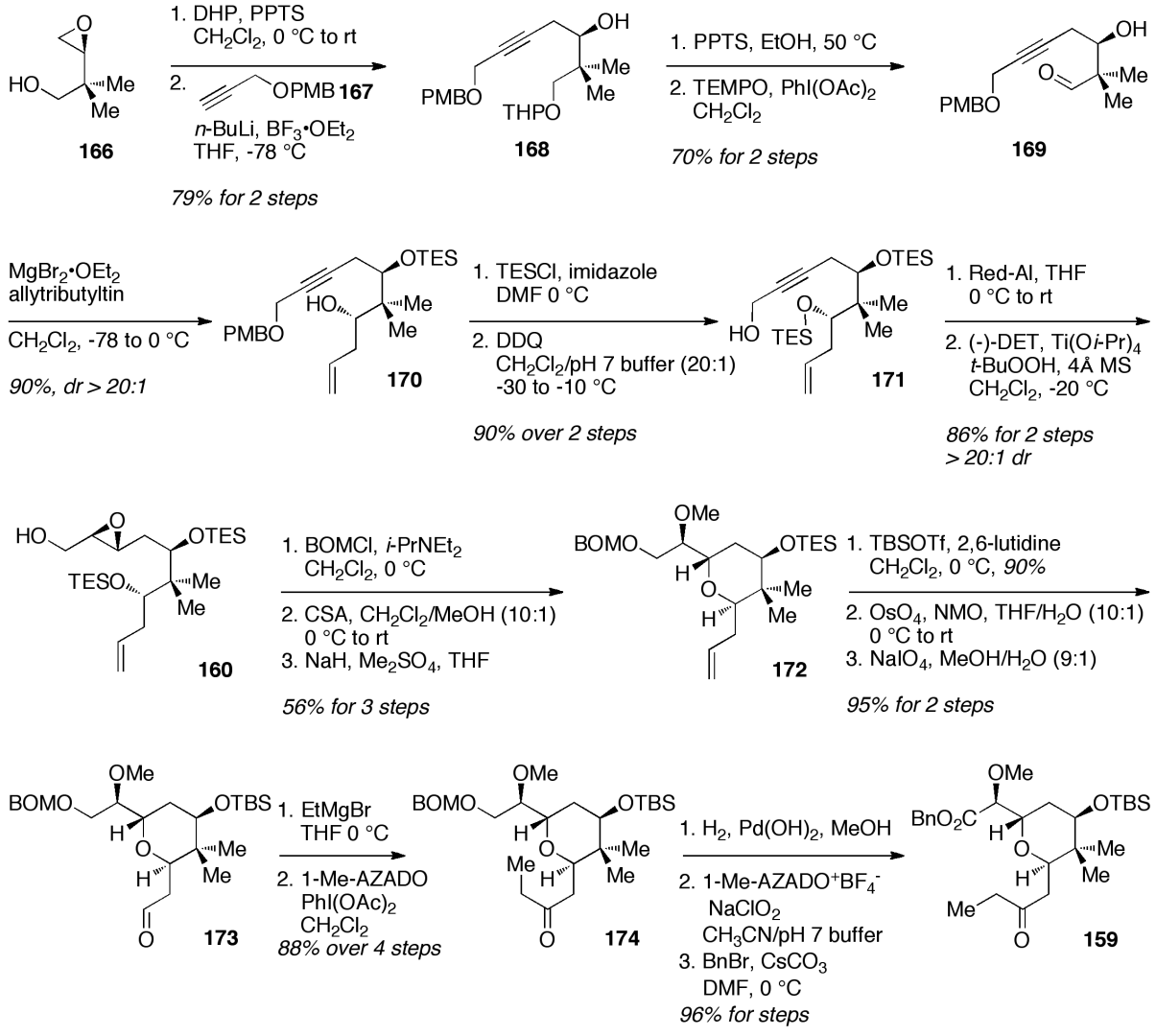
The hallmark of the synthesis reported by Watanabe was their concise and scalable approach toward the psymberate side chain (Scheme 2.8.2). Starting with the copper(I) chloride promoted coupling of methallybromide **161** and propargyl alcohol **162**,the internal alkyne product **163** was then converted to the allylic alcohol that was enantioselectively epoxidized under Sharpless conditions to give epoxide **165**. A regioselective epoxide opening of under Lewis acidic conditions with methanol provided diol **60** in 94% yield with 18:1 regioselectivity.[69] A series of protecting group manipulations provided primary alcohol **143** that was oxidized directly to the carboxylic acid[70] to complete the enantioselective synthesis of the psymberate side chain (8 steps, 22% overall), which could then be converted to Smith's pivalate anhydride **144** required for coupling.

Scheme 2.8.2. Watanabe Synthesis of the Psymberate Side Chain



While Watanabe's synthesis of the psymberate side chain offered a concise and unique approach to that fragment, their synthesis of the tetrahydropyran was quite the opposite (Scheme 2.8.3). The synthesis of this piece was longer than all current total syntheses of the natural product and utilized an epoxide opening to form the tetrahydropyran that was very similar to that of Smith. Starting from known epoxide **166**[71] the protection of the free alcohol and subsequent acetylide addition into the epoxide[72] to give alcohol **168** was followed by deprotection and oxidation to

Scheme 2.8.3. Watanabe Synthesis of the Tetrahydropyran

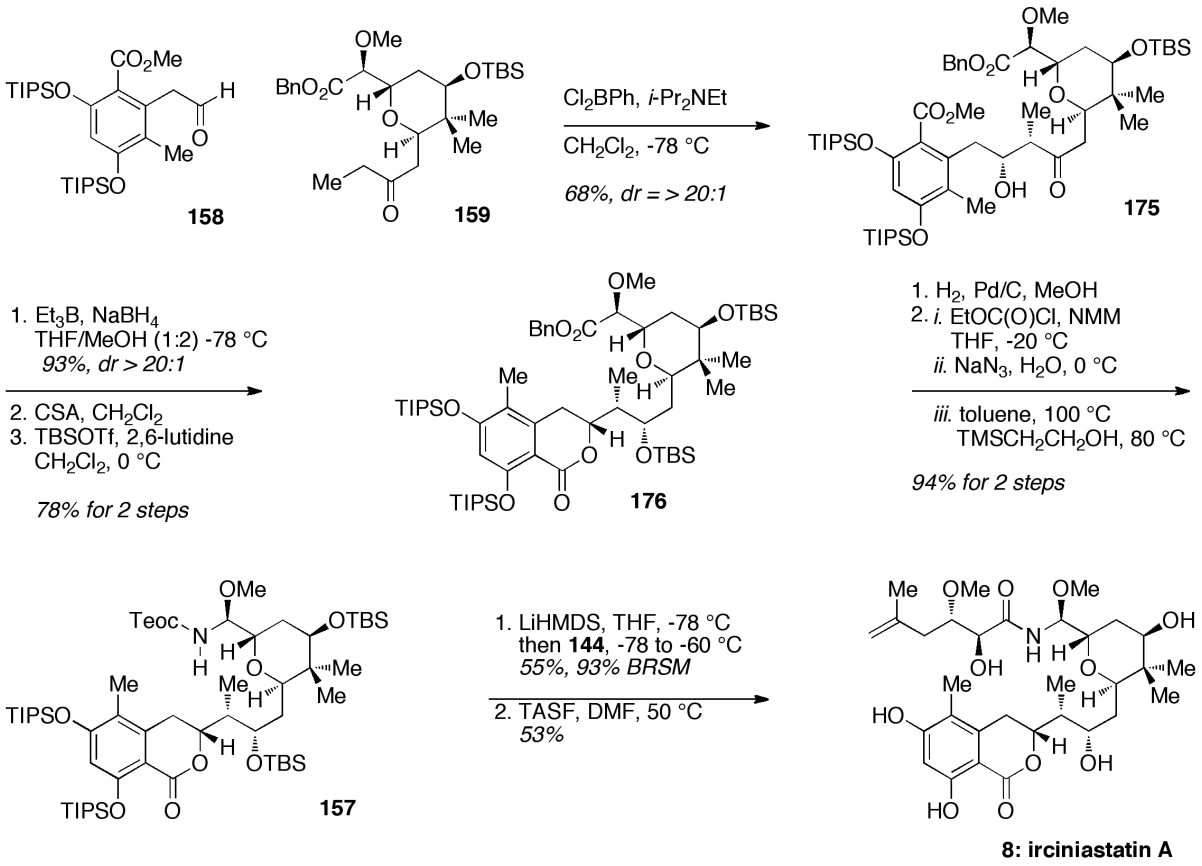


aldehyde **169**. The C13 stereocenter was then set through a diastereoselective allylation[73] that was followed by several protecting group manipulations to provide propargyl alcohol **170**. Reduction of the alkyne to the allylic alcohol using Red-Al allowed for a Sharpless epoxidation of the resultant alkene to give epoxide **160**. Epoxide **160** was then subjected to a sequence of protection, deprotection-cylclization and methyl etherification to give tetrahydropyran **172** in a manner very similar to Smith's. Having constructed the key tetrahydropyran their sights were set on converting the terminal alkene to the requisite ethyl ketone. This effort began with reprotection of the silyl ether that was lost during the cyclization step and oxidative cleavage of the terminal alkene to reveal aldehyde **173**. The ethyl ketone was then installed through Grignard addition to the aldehyde and an ensuing oxidation to ketone **174**. To complete the synthesis of the desired coupling partner **159** the primary BOM ether was converted to it's corresponding benzyl ester over three steps (20 steps, 16% overall from **166**).

Having devised synthetic routes to both the psymberic acid and tetrahydropyran fragments, Watanabe utilized DeBrabander's method for the synthesis of Crimmins aldehyde **158**,[6] and the endgame strategy commenced (Scheme 2.8.4). The union of aldehyde **158** and the boron enolate of **159** was again utilized in this work giving a 68% yield and > 20:1 dr of alcohol **175**, further demonstrating the power of the Paterson aldol in complex molecule synthesis.[32] The aldol adduct was then subjected to chelation controlled β-hydroxy carbonyl reduction to give the 1,3-*syn* diol[74] that was lactonized and TBS protected to give silyl ether **176**. The hemiaminal **157** was then revealed through hydrogenolysis of the benzyl

ester and Curtius degradation[75] of the resultant carboxylic acid. In accord with the two previous syntheses that featured a late stage hemiaminal acylation, Watanabe described significant difficulty achieving this transformation. The union was achieved using the conditions reported by Smith albeit in 24% lower yield even though the

Scheme 2.8.4. Watanabe Total Synthesis of Irciniastatin A



only difference between the two separate reports were the TIPS protecting groups on the aromatic ring as opposed to the SEM ethers used by Smith. Lastly, global deprotection using TASF in DMF gave irciniastatin A (28 steps, 2% overall from **166**)

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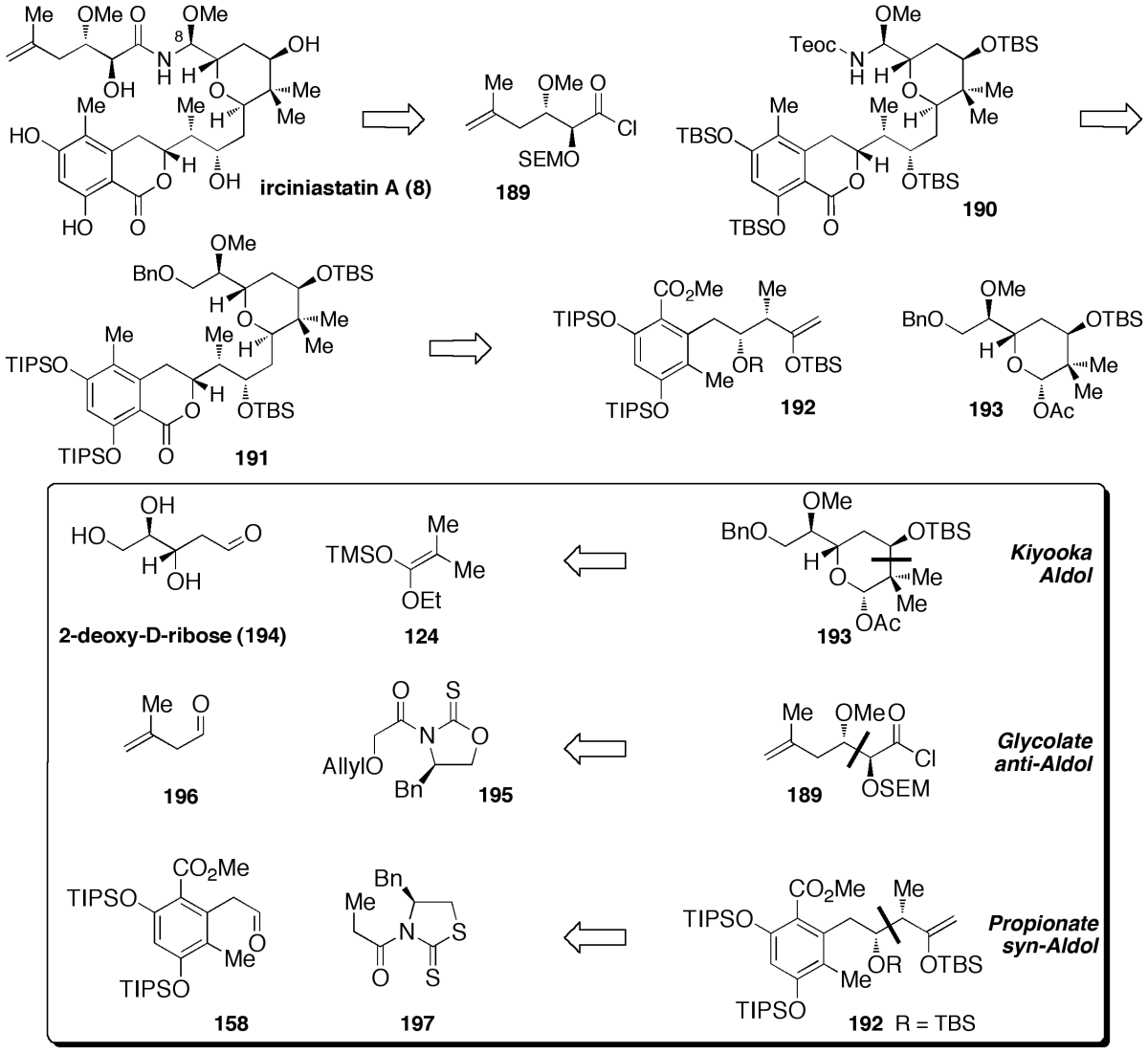
Chapter 3: Total Synthesis of Irciniastatin A

Irciniastatin A, a unique member of the pederin family of natural products, caught our attention through its challenging molecular structure and its remarkable anti-proliferative activity. The array of potential aldol disconnections observed in the natural product would provide an opportunity to extend the breadth of the Crimmins aldol reactions to a new class of natural products that have yet to be explored in our laboratory, the pederins and mycalamides. Our goal was to develop a modular and highly convergent synthetic strategy toward irciniastatin A that would also be suitable for analog preparation. Ultimately, our efforts culminated in the most step efficient, modular, and highly convergent synthesis of irciniastatin A, which will be discussed in this chapter.[1]

3.1 Retrosynthetic Analysis

Retrosynthetically, (+)-irciniastatin A (**8**) was envisioned to arise from two key disconnections (Scheme 3.1.1). A late-stage attachment of the psymberic acid chain would be accomplished by coupling of acid chloride **189** with hemiaminal **190**, the product of a Curtius rearrangement of the carboxylic acid derived from the corresponding benzyl ether of **191**. This tactic would allow for a highly stereocontrolled entry to the C8 hemiaminal and efficient incorporation of the side chain. Tetrahydropyran **191** would arise from the stereoselective addition of enolsilane **192** to the oxocarbenium ion derived from acetate **193**. These two key

Scheme 3.1.1. Crimmins Retrosynthetic Analysis



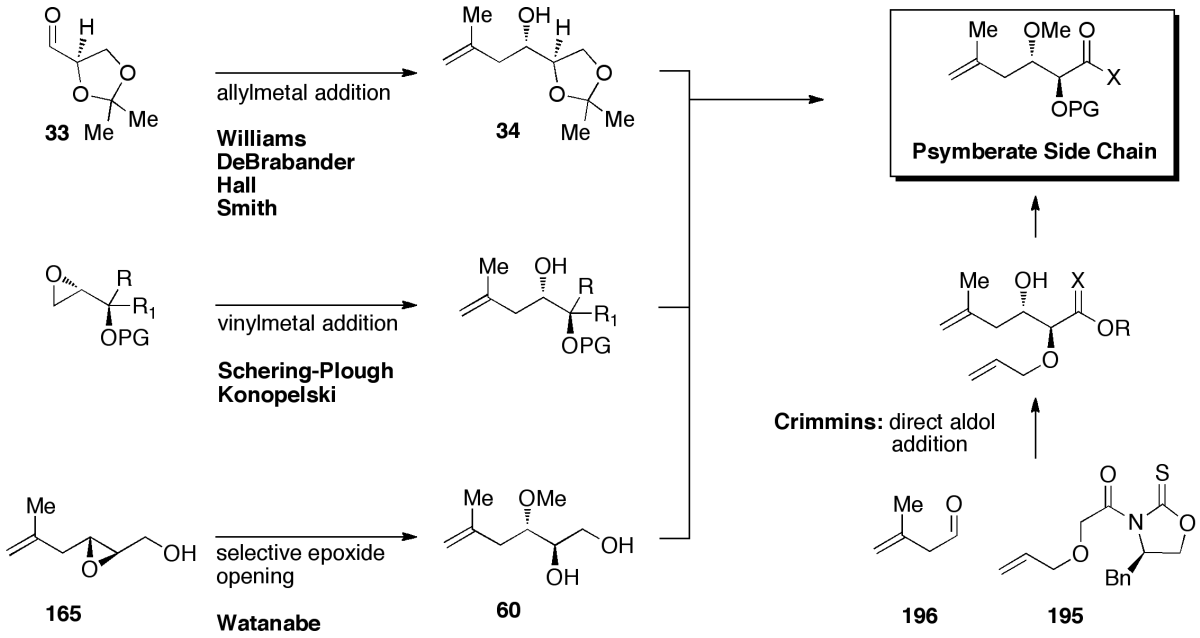
disconnections segregate the three major subunits of irciniastatin A (**8**), each of similar size and complexity and accessible in a highly stereocontrolled fashion from standard aldol synthons.

3.2 Synthesis of the Psymberic Acid Side Chain of Irciniastatin A

Until recently,[2,3] all reported syntheses of the psymberate side chain have relied on functionalizing commercially available chiral pools[4,5,6,7,8,9] or enzymatic

resolutions[10,11] (Scheme 3.2.1). In addition, analogue studies[2,12,13,14] have shown the side chain to be required for high activity. Therefore, an enantioselective and highly tunable synthesis of the side chain would be ideal for further investigation of side chain function. We reasoned that an oxazolidinethione asymmetric glycolate aldol

Scheme 3.2.1. Current Strategies for the Synthesis of the Psymberate Side Chain

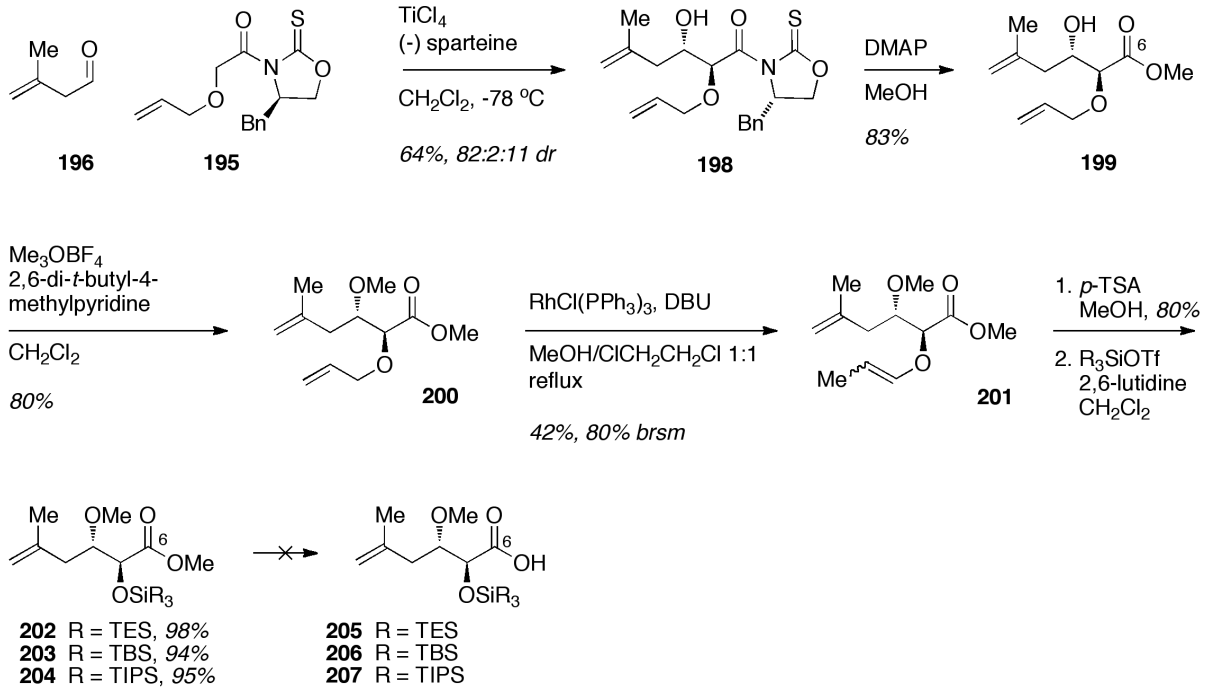


reaction[15,16] would allow for enantioselective entry to the psymberate side chain as well as provide sufficient opportunities for derivatization and congener synthesis.

The synthesis of acid chloride **189** (Scheme 3.2.2) began with the known[17] *anti*-aldol reaction of glycolate **195** and 3-methyl-but-3-enal (**196**) to give aldol adduct **198** in 64% and 87:2:11 dr. The auxiliary was subsequently removed by methanol substitution to give β-hydroxy methyl ester **199**. Methylation of alcohol **199** required the use of the Meerwein reagent to avoid β-elimination side products to furnish methyl ether **200** in 80% yield. While the allyl substituted glycolyloxazolidinethione has been shown to deliver the highest selectivity and yield for the *anti*-aldol reaction,

the subsequent removal of the allyl protecting group can often be cumbersome.[18] It was found that Wilkinson's catalyst could isomerize the allyl group to the 1:1 mixture of *E/Z*-enol ethers **201** in the presence of the disubstituted alkene giving a 42% yield and 38% recovered starting material when the reaction was stopped at 50% conversion. The 1:1 mixture of *E* and *Z*- enol isomers were subjected to acidic methanolysis to afford the alcohol that was reprotected to give silyl ethers **202-204**. Unfortunately, at the last step of our synthetic route it was found that both the TES and TBS ethers **202** and **203** did not survive the hydrolysis conditions, particularly

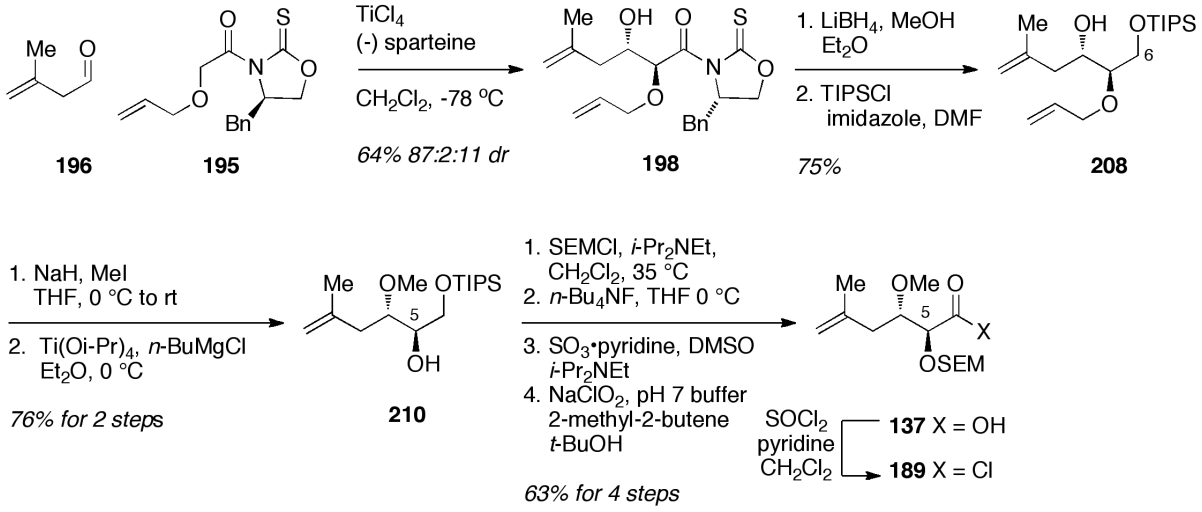
Scheme 3.2.2. Crimmins Initial Attempt Toward the Synthesis of the Psymberate Side Chain



the mildly acidic work-up, and the ester with the α-TIPS ether **204** was exceedingly resistant to hydrolysis. The inability to access the desired acids **205-207** from the methyl ester and the inefficient allyl deprotection prompted the investigation of an alternative strategy to access the protected psymberic acid side chain.

The previous route toward the psymberic acid side chain demonstrated that the *anti*-aldol strategy was effective for gaining enantioselective entry to the carbon skeleton of psymberic acid skeleton. However, attempting to maintain the ester oxidation state at C6 throughout the synthetic sequence limited the methods available for the allyl ether deprotection and the required hydrolysis of the ester limited the tolerance for silicon protecting groups at C5. It was reasoned that having C6 at the alcohol oxidation state in the form of a protected alcohol would allow more latitude for the allyl deprotection step and would also allow entry to the desired acid through an alcohol deprotection-oxidation sequence. Additionally, the previous effort demonstrated that TES, TBS and TIPS ethers were not suitable protecting groups at

Scheme 3.2.3. Crimmins Modified Synthesis of the Psymberate Side Chain



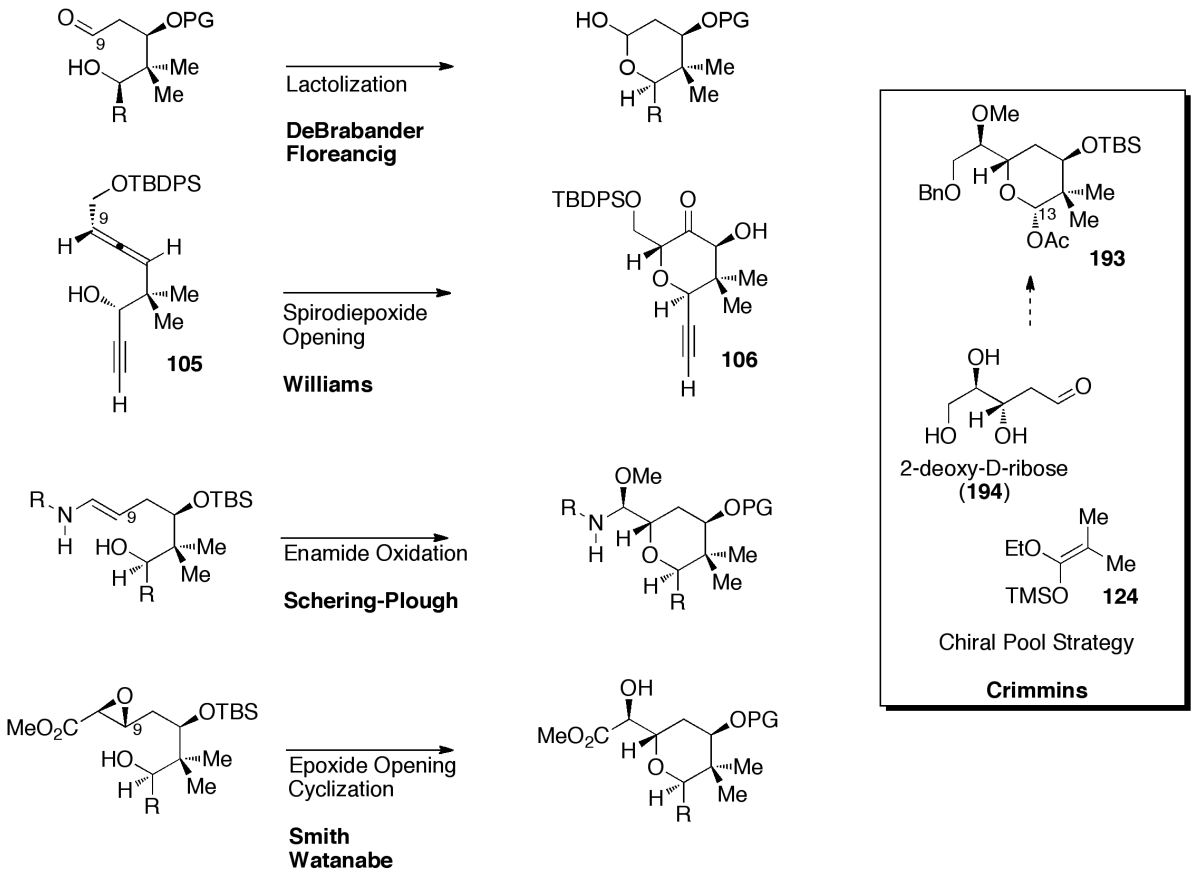
the glycolyl oxygen and that a less acid labile SEM ether could serve as a suitable replacement. Toward these ends, the *anti*-aldol adduct **198** was carried forward to the primary TIPS ether **208** using known procedures from our laboratory (Scheme 3.2.3).[17] Methylation of the alcohol was followed by removal of the allyl protecting

group under Kulinkovich conditions[19] to give alcohol **210** in much improved yield over the previous sequence. Protection of alcohol **210** as the SEM ether was followed by selective removal of the primary TIPS ether and oxidation of the primary alcohol to the carboxylic acid **137** over two steps. At this stage it was demonstrated that the acid **137** (9 steps, 28% overall) could be converted to acid chloride **189** for the final coupling.

3.3 Synthesis of the Tetrahydropyran Precursor of Irciniastatin A

As the tetrahydropyran represents the core of irciniastatin A, both the dihydroisocoumarin and psymberic acid fragments will need to be coupled to this core fragment, thereby highlighting the need for an efficient and tunable synthesis to

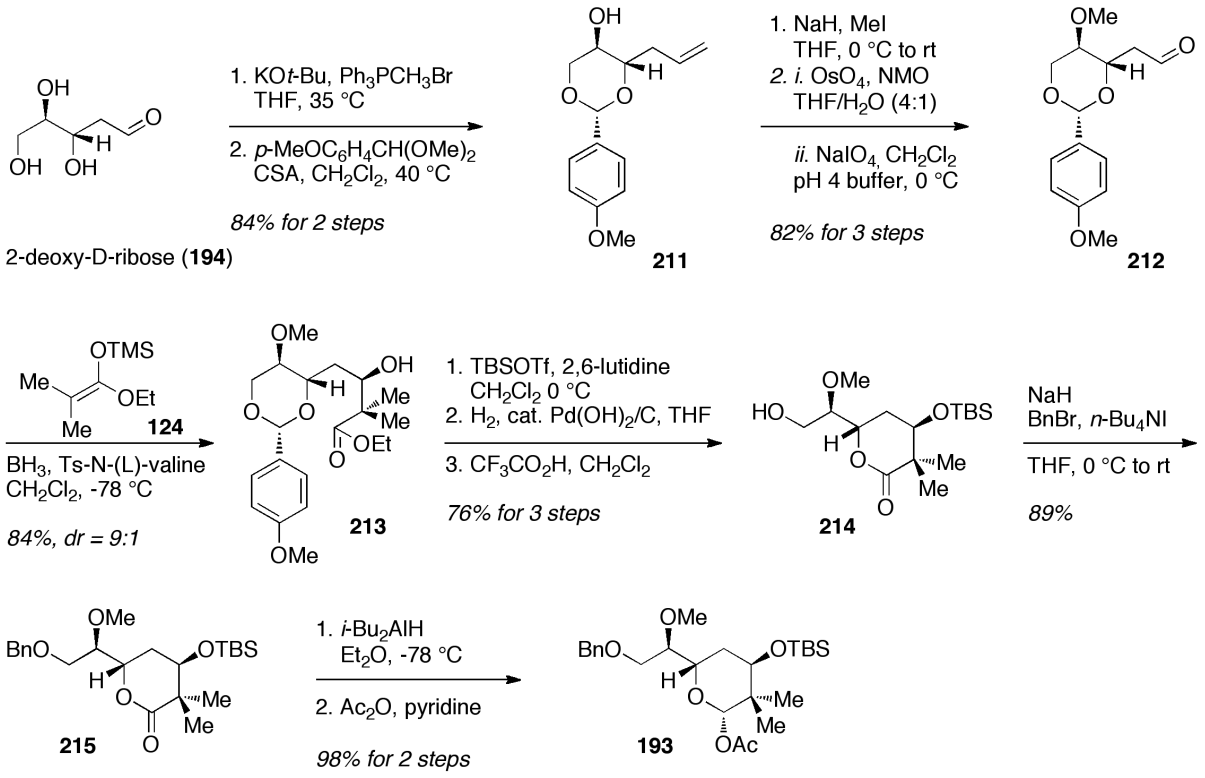
Scheme 3.3.1. Current Strategies for the Synthesis of the Tetrahydropyran of Irciniastatin A



accommodate two separate coupling strategies. A survey of all the strategies employed in total synthesis or advanced fragment synthesis have formed the tetrahydropyran through a cyclization of the C13 alcohol onto C9 in various fashions (Scheme 3.3.1).[3-7,9] Our approach sought to construct the tetrahydropyran framework in the opposite direction by cyclizing a C9 alcohol onto C13 through a straightforward lactonization. The chiral pool 2-deoxy-D-ribose contains a significant portion of the highly oxygenated carbon skeleton of the target lactol-acetate **193** including 2 of the 3 stereocenters, and would provide an ideal starting point toward the synthesis of this fragment. Although the chiral pool approach would lack modularity for subsequent analog synthesis, the structural homology between 2-deoxy-D-ribose with our desired fragment would provide rapid and scalable access to acetate **193** that would meet our immediate goal toward the synthesis of irciniastatin A.

The synthesis of lactol acetate **193** (Scheme 3.2.2) began from known *p*-methoxybenzylidine acetal **211**[20,21] available from 2-deoxy-D-ribose (**194**) in two steps. Methylation of alcohol **211** was followed by a dihydroxylation-oxidative cleavage sequence to reveal aldehyde **212**. A catalyst-controlled Kiyooka[22] aldol reaction of aldehyde **212** and enolsilane **124**[23] provided carbinol **213** in 84% yield and 9:1 dr. Protection of alcohol **213** to give TBS ether was followed by hydrogenolysis of the *p*-methoxybenzylidine acetal and acid promoted lactonization to afford lactone **214** over 3 steps. Protection of the primary alcohol as the benzyl ether and reduction of the lactone with diisobutylaluminum hydride allowed for protection of the resultant lactol, giving lactol-acetate **193** over 3 steps. While the

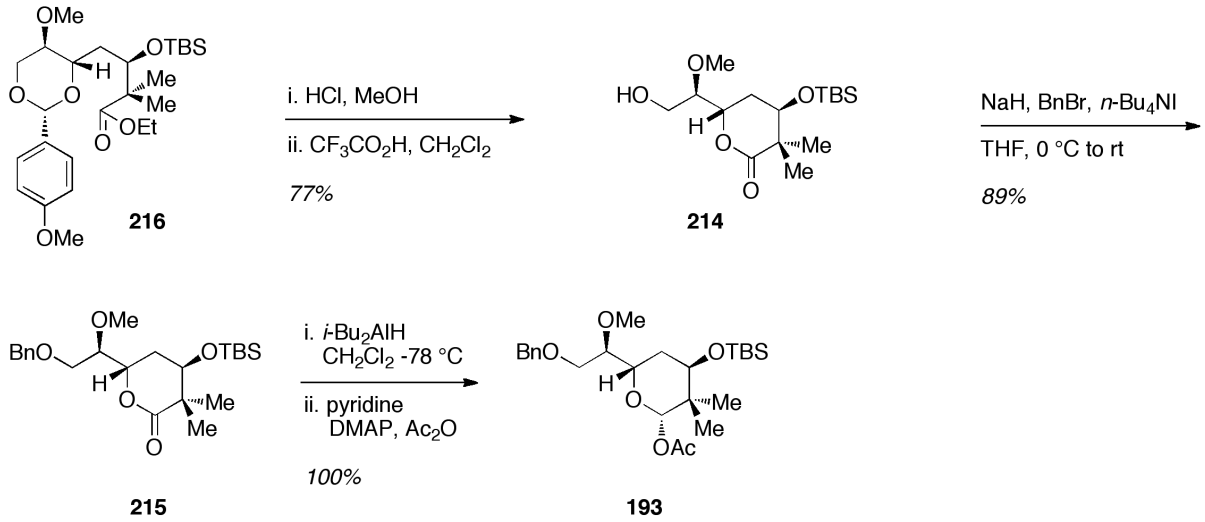
Scheme 3.3.2. Crimmins Synthesis of the Tetrahydropyran Precursor



yield of every step of this sequence exceeded 80%, we felt the total of 11 synthetic steps from commercially available material could be optimized to provide an even shorter and more efficient sequence.

To improve the step economy, several one-pot procedures were investigated (Scheme 3.3.3). The deprotection of the *p*-methoxybenzylidine acetal with concomitant lactonization was realized in a one-pot fashion by simply using dilute HCl in methanol to give a 10:1 mixture of lactone **214** and the corresponding diol, which was completely converted to lactone **214** by exposure to trifluoroacetic acid. Protection of the primary alcohol gave benzyl ether **215** and subsequent one-pot reductive acetylation[24,25] afforded acetate **193** in quantitative yield. These

Scheme 3.3.3. Crimmins Improved Synthesis of the Tetrahydropyran Precursor

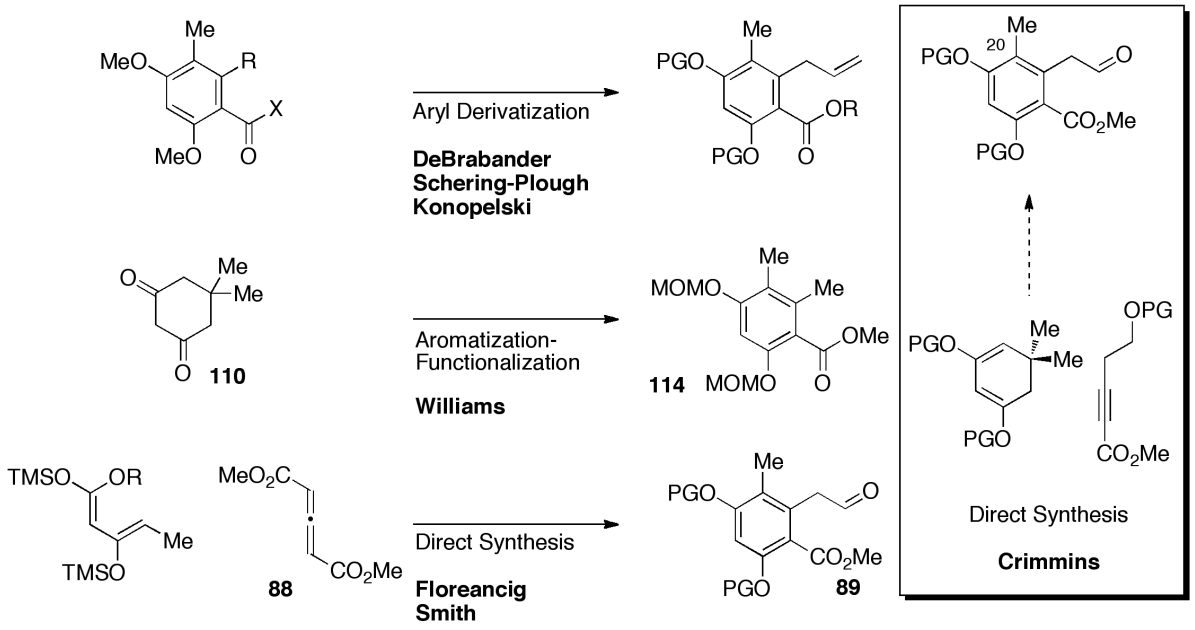


improvements shortened our route by two steps and have provided access to multi gram quantities of acetate **193** (9 steps, 34% overall from 2-deoxy-D-ribose).

3.4 Synthesis of the Dihydroisocoumarin of Irciniastatin A

The dihydroisocoumarin subunit of irciniastatin A was a previously unknown structural element of natural products and therefore its efficient preparation would need to be addressed during the course of a synthetic campaign. Previous efforts have chosen to either functionalize an aromatic system,[6,8] generate an aromatic system from its respective aliphatic skeleton,[26] or to directly construct[9,27] the desired aromatic ring (Scheme 3.4.1). In seeking to incorporate as much versatility as possible into our synthesis for the benefit of potentially straightforward analog syntheses down the road, we chose to construct the aryl portion of irciniastatin A using a Diels-Alder aromatization/aryl methylation strategy. This tactic would allow for efficient construction of the aromatic ring with the ability to selectively install a variety of functionality at the C20 position.

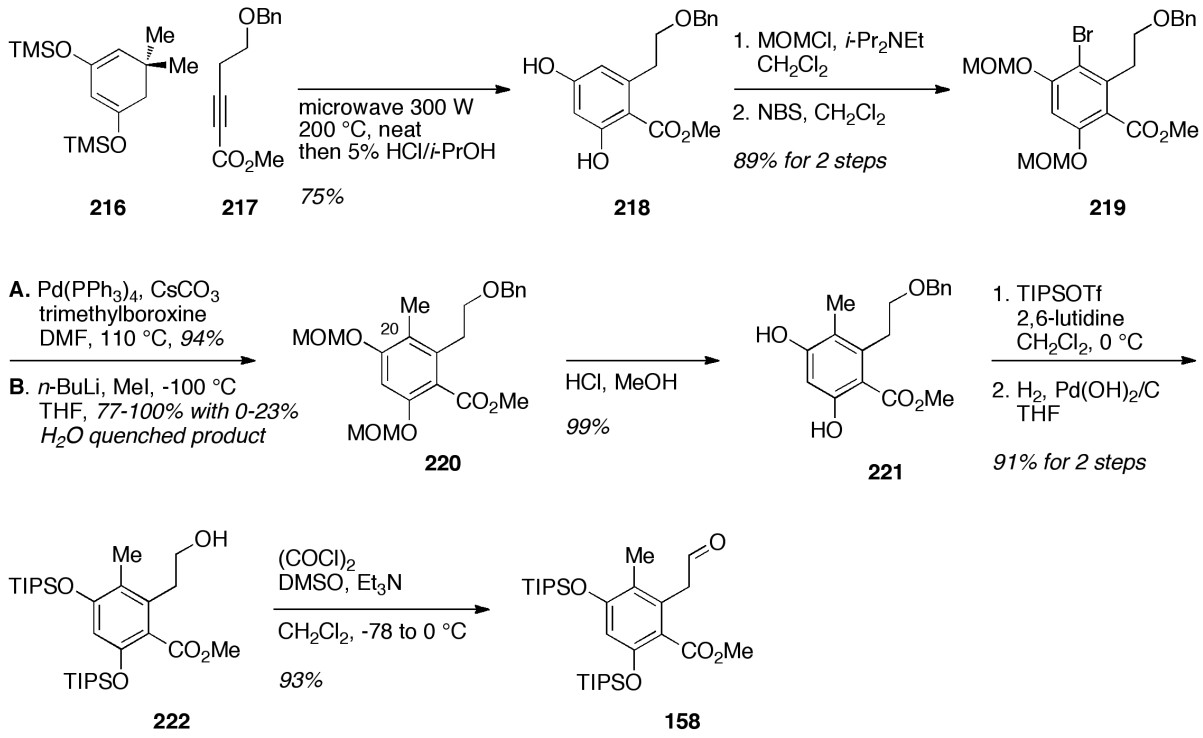
Scheme 3.4.1. Current Strategies for the Synthesis of the Aromatic Subunit of Irciniastatin A



The synthesis of the aromatic ring of the dihydroisocoumarin fragment began with a Diels–Alder aromatization reaction of diene **216**[28] and alkynoate **217**[29] through the extrusion of 2-methylpropene (Scheme 3.4.2). This method for directly constructing the aromatic ring was quite efficient and reliable, requiring only 30 min in the microwave while giving less than 3% variation in yield over 10 runs. However, the major drawback of this strategy is that the maximum capacity for the microwave reactor is only 2 g, which severely limited the scalability of the synthesis, although a total of 8 g of **218** have been prepared using this method. The Diels–Alder product **218** was protected as the bis-MOM ether and selectively brominated with *N*-bromosuccinimide to give aryl bromide **219**. Extensive investigation revealed that the MOM ethers were required for a successful Suzuki reaction. If TBS or TIPS ethers were employed the reaction simply turned black and only gave decomposition products. It is thought that the bulky nature of the TBS and TIPS groups hinders the

critical oxidative addition step while the less sterically encumbering MOM ethers are less intrusive. Thus the C20 methyl substituent of arene **220** was installed through the an sp^2-sp^3 Suzuki coupling[30] of aryl bromide **219** with trimethylboroxine. As an alternative to the Suzuki coupling, a lithium-halogen exchange[31] could also be employed to prepare arene **220** by generating the corresponding aryl anion of aryl bromide **219**, which could undergo alkylation with MeI. While this offered a both cheaper and more abundant metal and alkyl source, the need for extreme cryogenic temperatures and the variable amounts of the inseparable reduced starting material weakened the utility of this method. Following the Suzuki reaction, acidic removal of both MOM ethers was followed by TIPS protection of the intermediate catechol **221**, and hydrogenation of the benzyl ether furnished alcohol **222**. A Swern oxidation of the resultant alcohol then provided the target aldehyde **158**. While the synthesis of

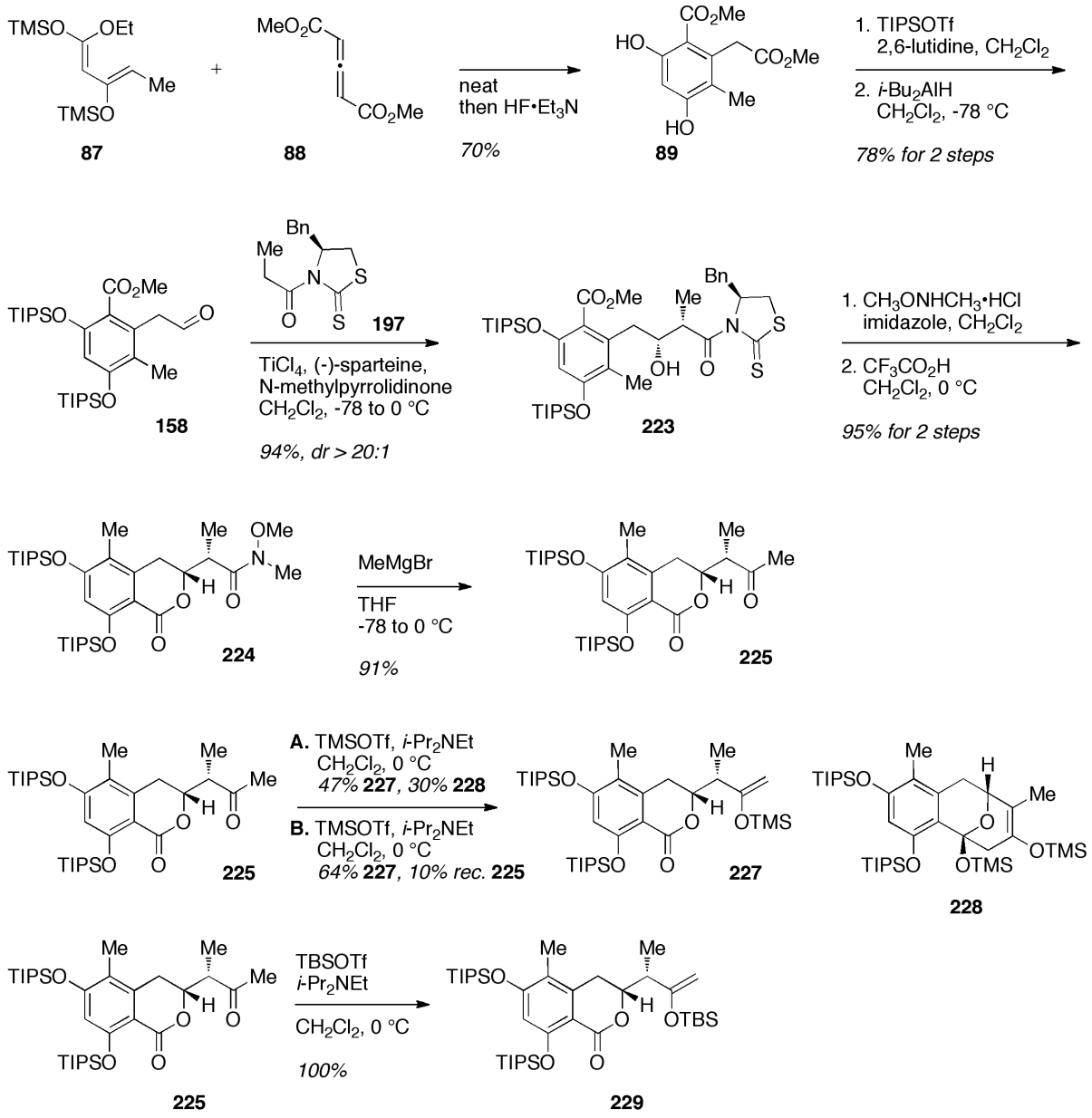
Scheme 3.4.2. Crimmins Synthesis of the Aryl Portion of Irciniastatin A



aldehyde **158** over the 8 steps proceeded with excellent yields, specifically all yields after the cycloaddition exceeding 90%, Floreancig's report of the synthesis of a nearly identical aldehyde was only a mere 3 steps, and had been run on 12 g scale (Scheme 2.4.3).[27] Although our synthesis offered greater opportunity for derivatization through the use of the Suzuki reaction, the brevity of Floreancig's synthesis would best serve our immediate goal of synthesizing irciniastatin A.

The revised synthesis of aldehyde **158** and subsequently enolsilane **192** began from known catechol **89**[32] that was prepared by the cycloaddition of allene **88**[33,34] and diene **87** (Scheme 3.4.3).[35] Protection of catechol **89** as the bis- TIPS ether was followed by selective ester reduction to give aldehyde **158** in 78% yield over 2 steps. An asymmetric propionate aldol[36,37,38] reaction of aldehyde **158** and propionyl thiazolidinethione **197** afforded the Evans-*syn*-aldol adduct **223** in 94% yield and >20:1 dr. A direct displacement of the chiral auxiliary with Weinreb's amine was followed by acid promoted lactonization to give the dihydroisocoumarin **224** that was converted to methyl ketone **225** (6 steps; 63% overall from catechol **89**). An initial attempt to convert the methyl ketone to the TMS enolsilane **227** surprisingly formed significant amounts of trimethylsilyl protected acetal **228** in addition to the desired enolsilane **227**. This unfortunate intramolecular attack was likely due to a combination factors. The first was that the excess TMSOTf Lewis acid required for the soft enolization was likely activating the lactone toward nucleophilic attack. The second possible factor was the conformational rigidity imposed by the dihydroisocoumarin, which positions the ketone directly underneath the lactone, inviting intramolecular attack by the enolsilane. The solution to this problem proved

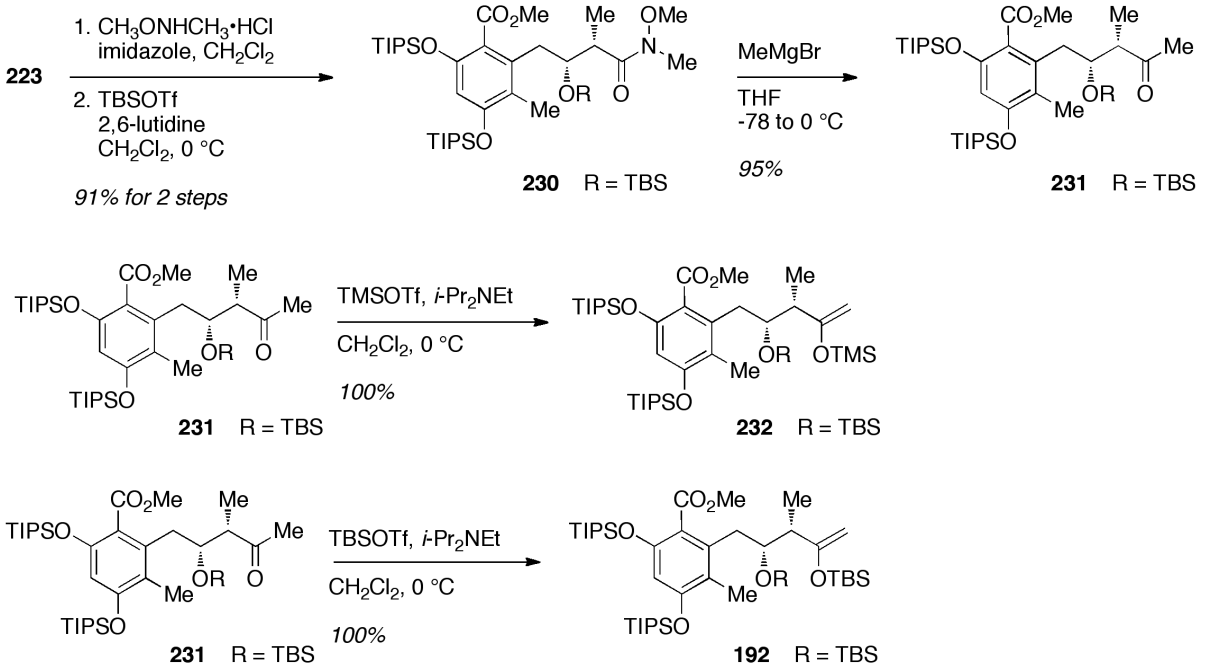
Scheme 3.4.3. Crimmins Synthesis of the Dihydroisocoumarin



to be stopping the reaction at ~60% conversion, which allowed for isolation of clean product before significant quantities of the byproduct formed. Alternatively, the corresponding TBS enolsilane **229** prepared with the less Lewis acidic and bulkier TBSOTf could be prepared without any observed side products in excellent yield.

In addition to enolsilanes **227** and **229**, their non-lactonized counterparts could be accessed through an analogous sequence (Scheme 3.4.4). A direct displacement of the chiral auxiliary with Weinreb's amine was followed by protection of the

Scheme 3.4.4. Crimmins Synthesis of the Non-Lactonized Dihydroisocoumarins Subunit

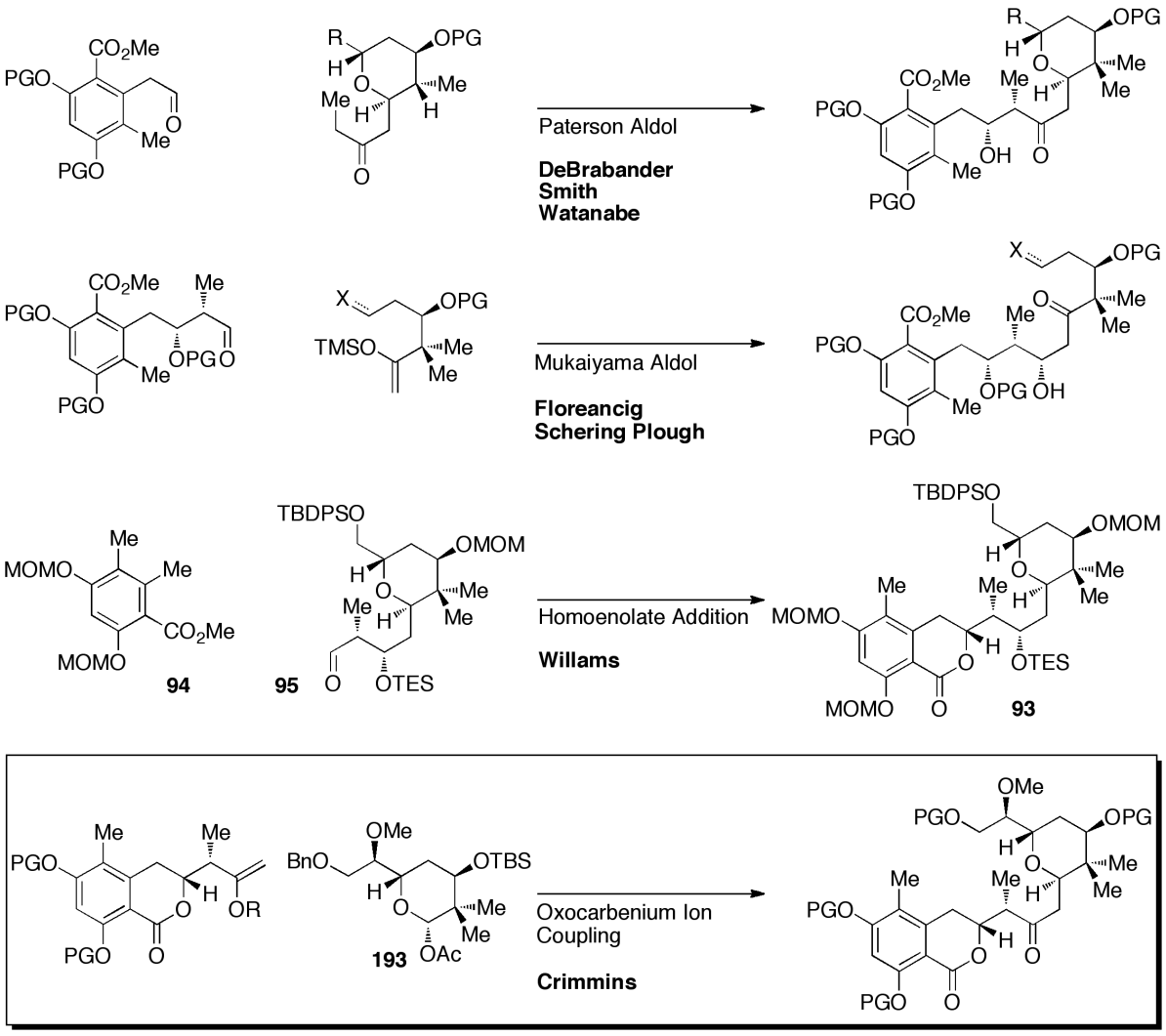


secondary alcohol as a TBS ether to deliver silyl ether **230**, which was subsequently converted to methyl ketone **231** (6 steps; 66% overall from catechol **89**). In stark contrast to ketone **226** featuring the dihydroisocoumarin moiety, the conversion of ketone **231** to the TMS enolsilane **232** did not occur with any side products. This is likely due to a combination of the increased conformational flexibility of the non-lactonized substrate and the overall lower electrophilicity of esters compared with lactones. In addition, ketone **231** could also be converted to enolsilane **192** in excellent yield.

3.5 Diastereoselective Coupling of the Enolsilane and Lactol-Acetate Fragments

The union of the tetrahydropyran and the dihydroisocoumarin subunits have been critical to the successful synthesis of irciniastatin A. This has been a challenging endeavor due to the dense array of chiral centers at the juncture of these two fragments. All synthetic approaches to this union have utilized aldol chemistry, specifically the Mukaiyama aldol[39,7,27] and the Paterson aldol,[3,6,9,40,41] to

Scheme 3.5.1. Current Strategies for the Union of the Dihydroisocoumarin and Tetrahydropyran

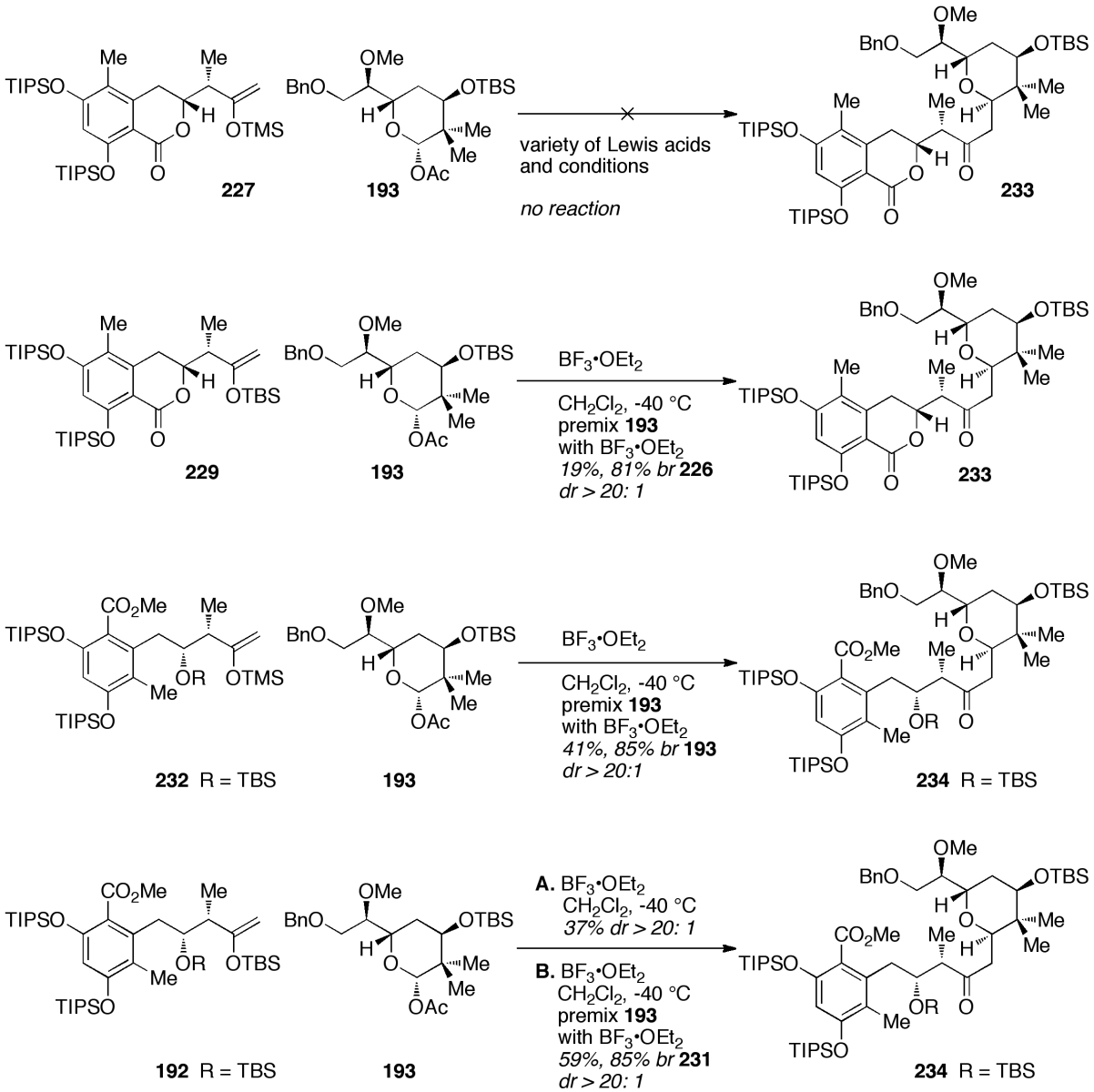


address this problem (Scheme 3.5.1). While these methods took advantage of stereodirection from the dihydroisocoumarin fragment, we sought to develop a more direct coupling that would capitalize on tetrahydropyran controlled stereodirection. We felt the observed substitution pattern about the tetrahydropyran would allow for a highly diastereoselective union of these two densely functionalized subunits.

Having devised highly stereocontrolled routes to all three key fragments, the union of acetate **193** and the enolsilanes **227**,**229**,**232** and **192** were investigated (Scheme 3.5.2). Rigorous experimentation revealed that $BF_3 \cdot OEt_2$ was the optimum Lewis acid and that the TBS enolsilanes **229** and **192** performed better than their corresponding TMS enolsilanes **227** and **232** for the formation of the tetrahydropyran products. It was also observed that the yields employing the open-chain enolsilanes **232** and **192** were consistently higher than those observed for enolsilanes **227** and **229** with the lactone appendage. Most intriguing, however, was that addition of a solution of enolsilane **192** to a premixed solution of **193** and $BF_3 \cdot OEt_2$ at -40 °C was required for efficient coupling, yet this did not improve the efficiency of the coupling of enolsilane **232** and acetate **193**. In all cases, the union proceeded with high diastereoselectivity, giving tetrahydropyrans **233** and **234** as the only detectable diastereomer in each case, which represents the most highly selective coupling of the tetrahydropyran and dihydroisocoumarin subunits.

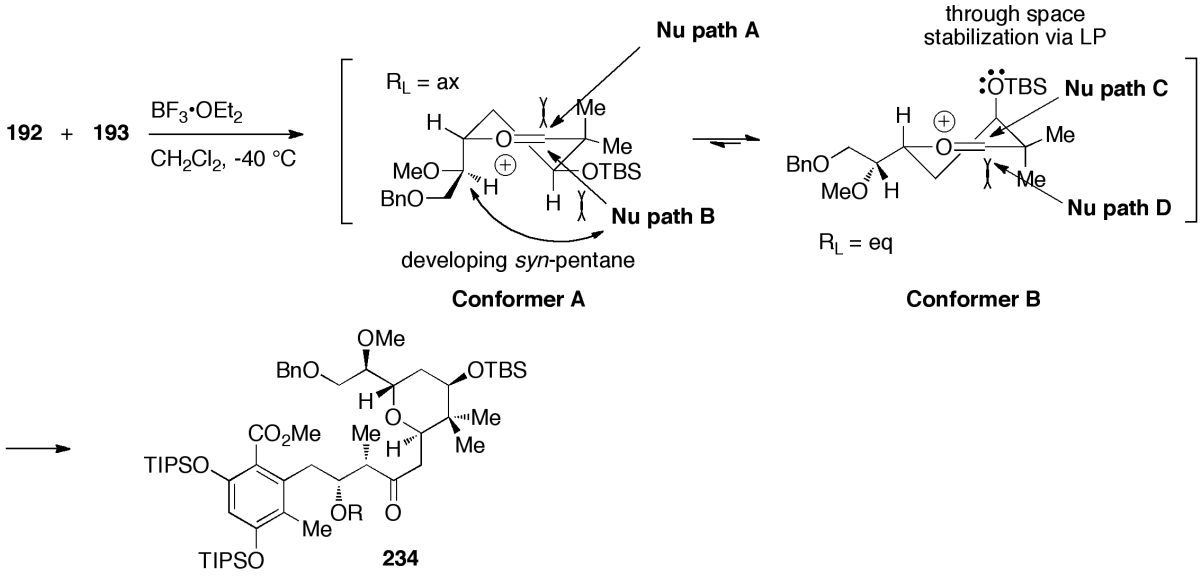
The high diastereoselectivity can be rationalized by well precedented pseudoaxial addition of the nucleophile along path C to the highest populated oxocarbenium conformer **B**, proceeding through a favorable chair like conformation as opposed to the disfavored path D that would proceed through a high energy twist-

Scheme 3.5.2. The Diastereoselective Union of the Dihydroisocoumarin and Tetrahydropyran



boat. (Scheme 3.5.3).[42] Conformer **B** would also be expected to be favored as a result of through-space stereoelectronic stabilization of the oxocarbenium ion by the axially positioned C11 ether, whereas no such stabilization is present in conformer **A**. While nucleophile path A would be disfavored as a result of proceeding through a high energy twist-boat, path B that proceeds through a chair like conformation would

Scheme 3.5.3. Model for the Diastereoselectivity Observed for the Union of **192** and **193**

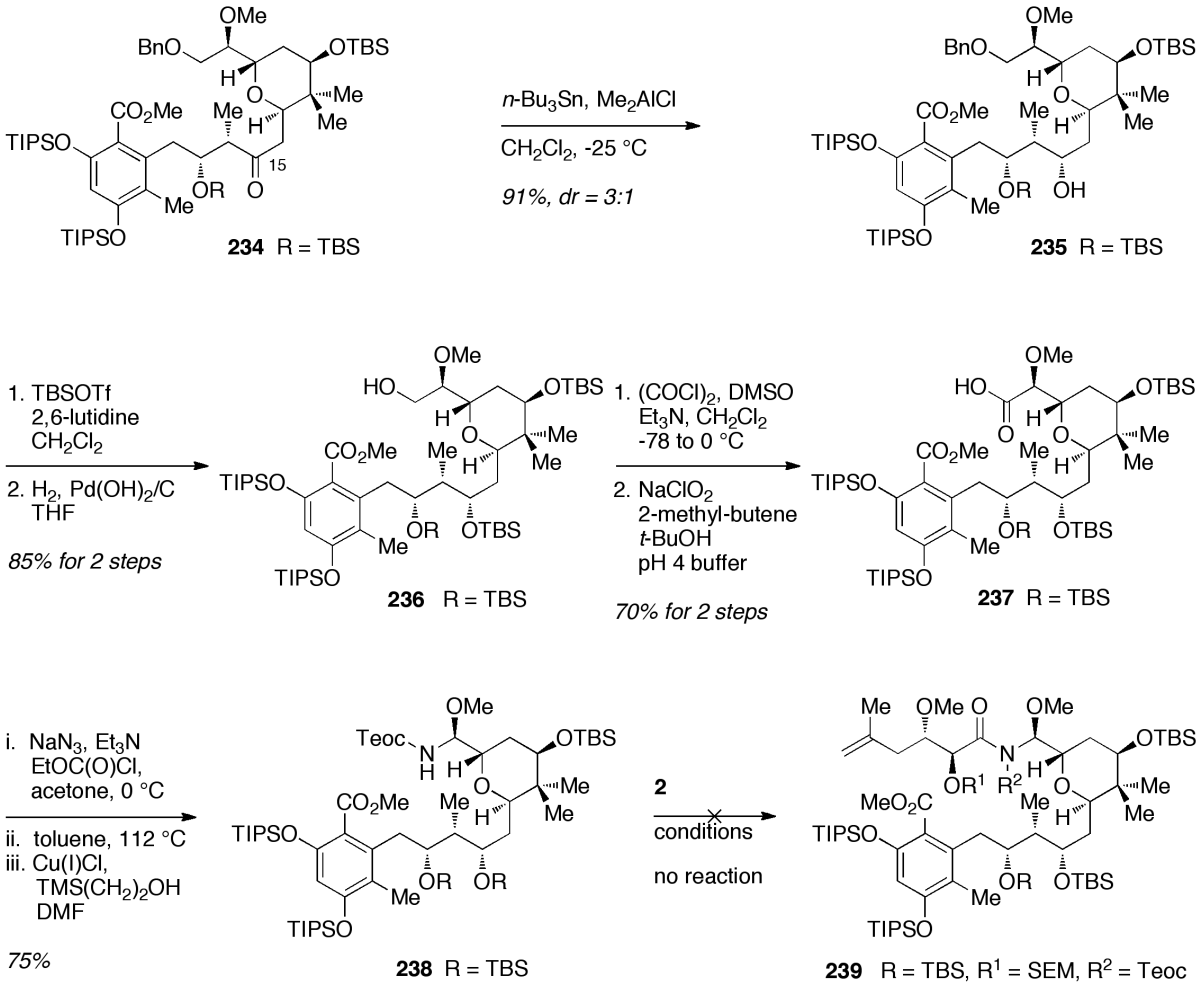


also be disfavored due to the developing high energy *syn*-pentane interaction in the product

3.6 Completing the Total Synthesis of Irciniastatin A

Having coupled the dihydroisocoumarin with the tetrahydropyran, conditions to set the C15 stereocenter were investigated (Scheme 3.6.1). Standard achiral reducing agents proved to be nonselective or were completely selective for the undesired diastereomer in the case of *i*-Bu_2AlH. At initial glance it would seem as though there weren't any synthetic handles available to direct the reduction. However, Evans has reported the use of TBS ethers to direct 1,3-carbonyl reductions, which was exactly what was present in our system.[43] It was found that by slightly modifying the reported conditions, a modest 3:1 selectivity could be obtained with 91% overall yield to give alcohol **235** in 70% isolated yield. The major isomer was carried forward to the 1,3-diol acetonide **240** whose ^{13}C spectrum showed the

Scheme 3.6.1. Initial Endgame Investigations

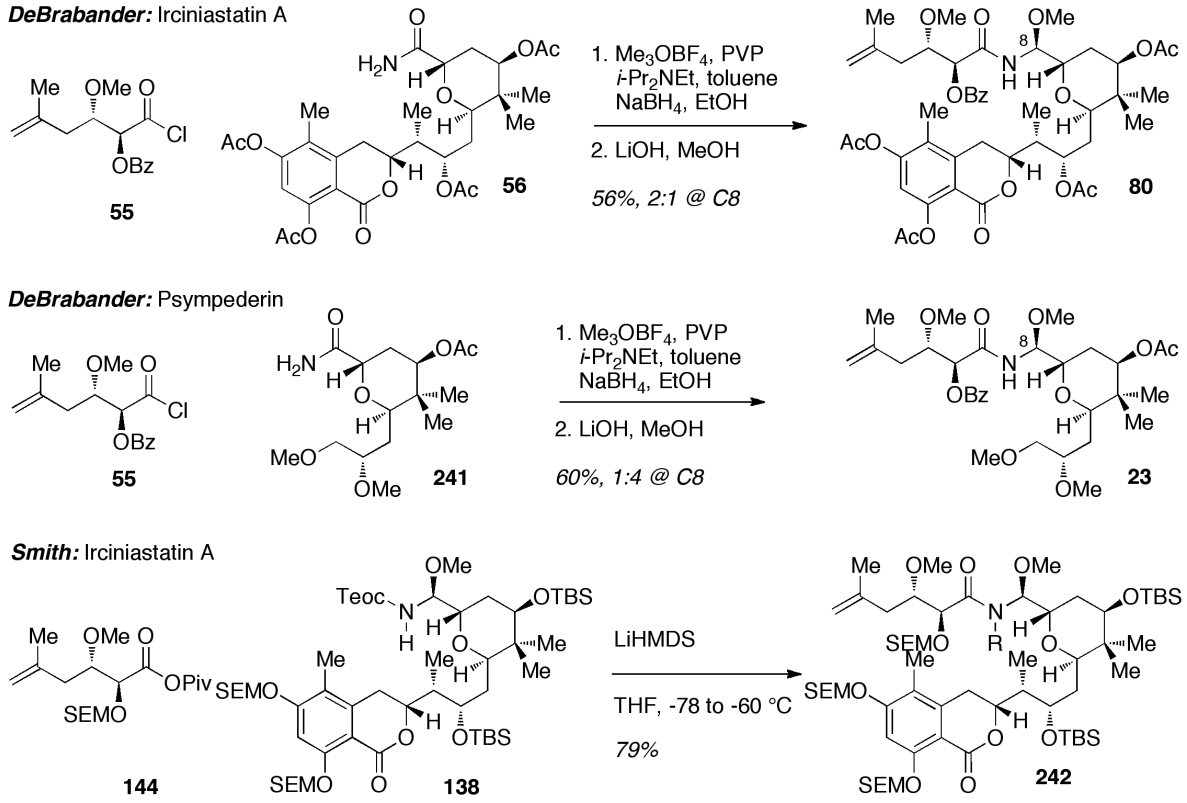


characteristic acetonide chemical shifts indicating the desired *syn*-1,3 relationship.[44] After protection of the secondary alcohol as its TBS ether and cleavage of the benzyl ether, carbinol **236** was oxidized over 2 steps to carboxylic acid **237**. Initial studies

into a one pot Curtius reaction with (*O*,*O*)-diphenylphosphoryl azide[45] were found to be ineffective, providing significant quantities of inseparable carbamoyl azide impurity.[46,47,48] Therefore, Weinstock's procedure[49,50] was employed to generate the intermediate isocyanate, which under mild conditions using copper(I) chloride afforded Teoc-protected hemiaminal **238**.[51,52] Much to our dismay, a screen of reported conditions for acylation of structurally related intermediates never yielded *N*-acyl hemiaminal **239**.[9,53,54,55,56]

A survey of all of the previous syntheses of irciniastatin A at the time revealed that all feature a late stage aminal and side chain incorporation with a preformed lactone of the dihydroisocoumarin (Scheme 3.6.2). In addition, DeBrabander had observed a close spatial relationship between these two regions of the molecule in

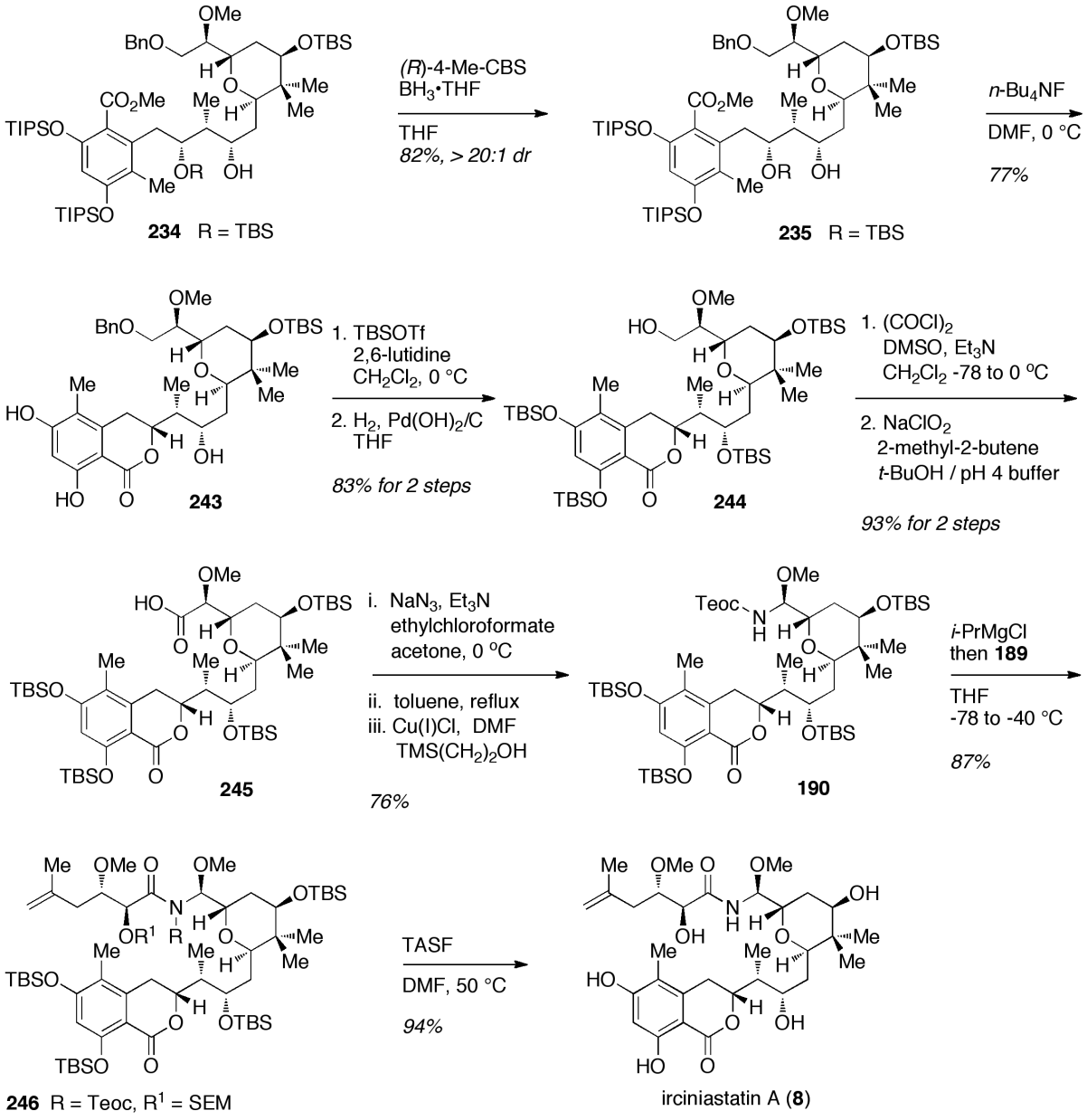
Scheme 3.6.2. Current Strategies for the Late Stage Installation of the Psymberate Side Chain



his synthesis of the analog psympederin **23**.[12] To lend further support that the dihydroisocoumarin was spatially close to the hemiaminal, the selectivity of the methoxyimidate coupling was completely reversed when comparing irciniastatin A (**8**) with the dihydroisocoumarin intact, and psympederin (**23**) that lacks the dihydroisocoumarin. Albeit unlikely that such remote functionality should have any effect on the hemiaminal coupling, the limited number of available options warranted pursuit of this lead.

Having been presented with the necessity to modify our current endgame strategy, it proved to be an ideal time to reinvestigate the C15 reduction (Scheme 3.6.3). It was found that the (*R*)-CBS agent[57,58] was completely selective for desired isomer **235** while also providing high and consistent yields. Strategically, after the ketone reduction, the lactone was formed concomitantly with removal of the TBS ether to give **243**, adding only one synthetic step over the original plan. An analogous sequence of TBS protection of the C15 carbinol and hydrogenolysis of the benzyl ether gave carbinol **244**, which was elaborated over two steps to acid **245**. Acid **245** was subjected to the previously established Curtius conditions to give hemiaminal **190**. With hemiaminal **190** featuring the lactonized dihydroisocoumarin, it was found that *i*-PrMgCl, a base not previously used for this transformation, successfully effected reaction with acid chloride **189** in a remarkable 87% yield. While this doesn't conclude that having the preformed lactone of the dihydroisocoumarin is requisite for a coupling of this type, it certainly lends strong support that that portion of the molecule does have a considerable influence. What was particularly interesting was that our advanced hemiaminal **190**, which only

Scheme 3.6.3. Crimmins Total Synthesis of Irciniastatin A



differs from Smith's hemiaminal **138** in the aryl ether protection (Crimmins TBS vs Smith SEM), was a completely ineffective coupling partner under Smitha's reported conditions using his pivalate anhydride **144**. The role of the seemingly remote aryl protecting groups in the late-stage hemiaminal acylation was highlighted further in

the subsequent synthesis by Watanabe (TIPS aryl ethers), which was 25% less efficient than Smith (SEM aryl ethers). These discrepancies clearly highlight a need to gain further insight on the structures of these advanced intermediates while also underscoring the pressing need to develop new technology for installing N-acyl hemiaminal functionality in complex structures. Finally, to complete the total synthesis, a global deprotection with TASF in DMF at 50 °C provided (+)-irciniastatin A (**8**) in 94% yield.

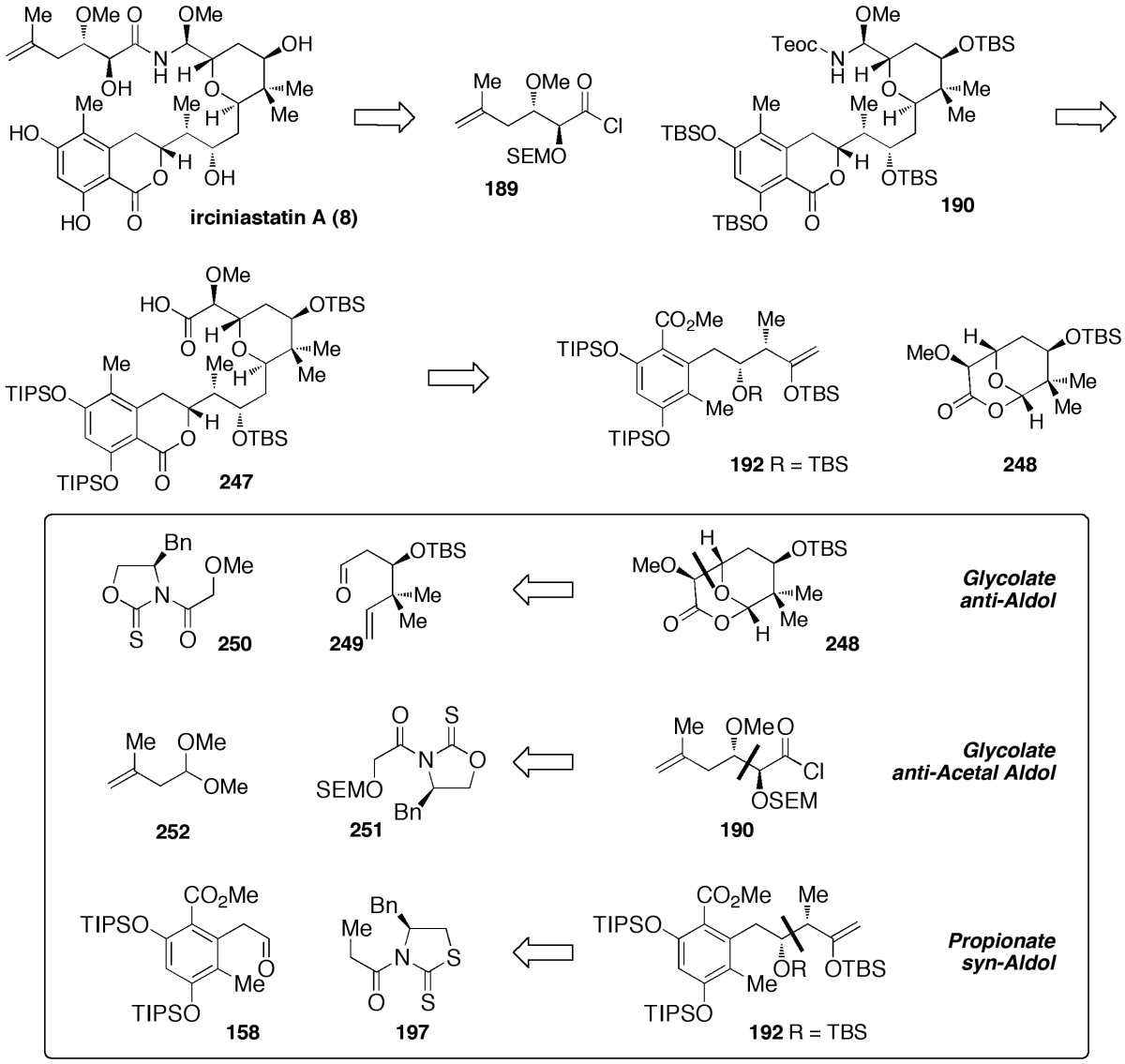
In summary, the total synthesis of (+)-irciniastatin A (**8**) was completed in 19 steps with a 6% overall yield from 2-deoxy-D-ribose. The successful application of this strategy allowed for rapid assembly of the three key fragments with high diastereocontrol. The 5 mg of synthetic irciniastatin A procured through these synthetic efforts has allowed for collaboration with the Lineberger Comprehensive Cancer Center to further evaluate the anti-tumor activity of irciniastatin A.

3.7 Second Generation Retrosynthetic Analysis

After the completion of the most step efficient and convergent synthesis of irciniastatin A, our attention turned to streamlining our previous synthesis to add increased scalability and modularity. By strengthening these aspects of our synthesis it would be possible to rapidly assemble the parent natural product as well a library of analogues without significant changes to the synthetic route. Furthermore, a synthetic route with increased scalability would provide additional irciniastatin A for screening against additional cell lines and provide an opportunity to install an affinity probe to identify the cellular target.

Retrosynthetically, the psymberate side chain would be installed at a late stage as it was for our previous synthesis through the coupling of acid chloride **189** with hemiaminal **190** (Scheme 3.7.1). The hemiaminal would arise from the Curtius degradation of carboxylic acid **247**, which would arise from the coupling between enolsilane **192** and acyl dioxanone **248**. This strategy would eliminate the need for late stage protecting group and oxidation state manipulations. Acyl dioxanone **248**

Scheme 3.7.1. Crimmins Second Generation Retrosynthesis

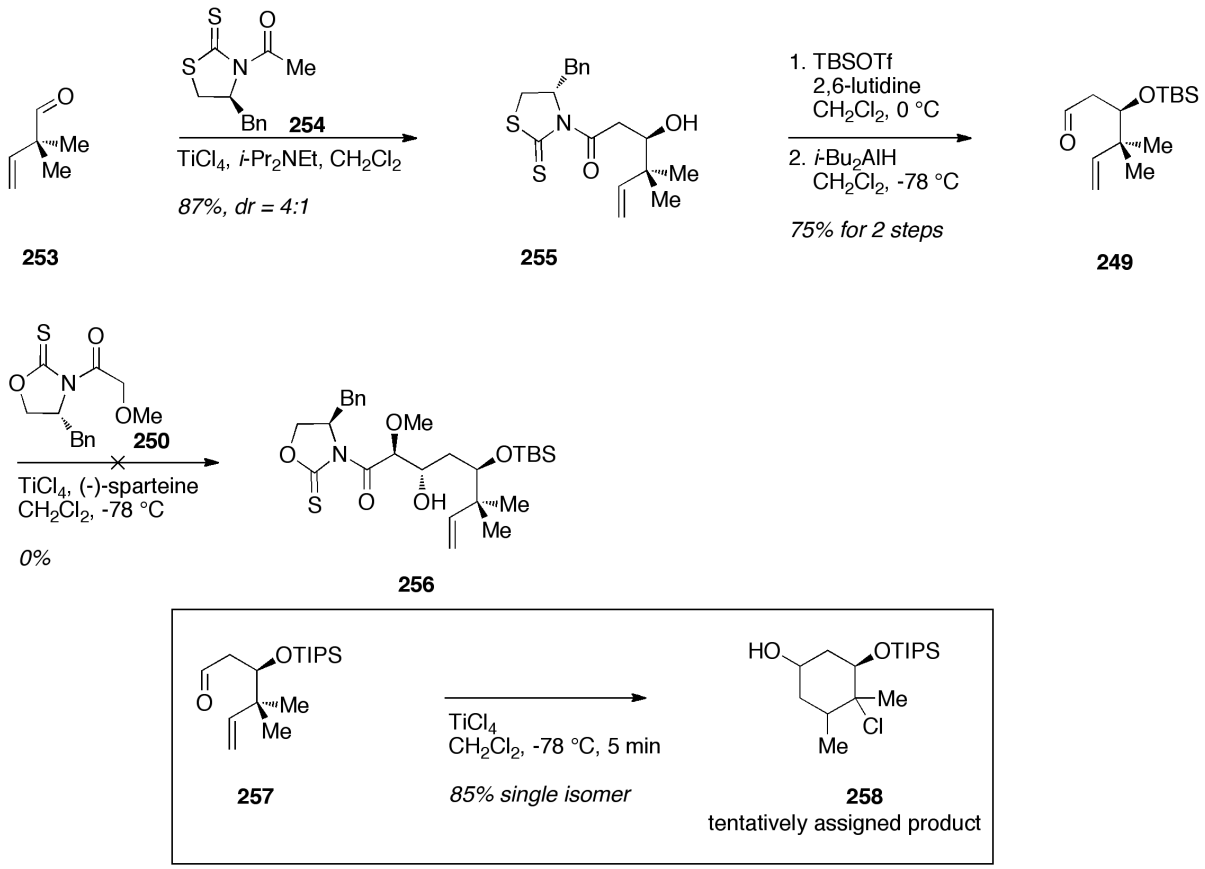


would be prepared through a combination of Crimmins acetate aldol[59] and glycolate *anti*-aldol reactions.[15] By switching from a chiral pool approach to an iterative aldol approach toward the tetrahydropyran fragment, the preparation of analogs of this fragment could be prepared by varying either the aldehyde or enolate component in these reactions. The fully protected carbon skeleton of the psymberate side chain was envisioned to arise through a direct *anti*-acetal aldol reaction, that would drastically streamline the synthesis of this fragment by eliminating redundant oxidation state and protecting group manipulations. Lastly, enolsilane coupling partner **192** would be prepared as it was previously through a diene-allene cycloaddition, although our previously developed enoate-diene cycloaddition would allow entry to C20 analogs should the need arise.

3.8 Efforts Toward the Second Generation Synthesis Toward Irciniastatin A

The second generation synthesis of the tetrahydropyran core of irciniastatin A began through the acetate aldol reaction of known aldehyde **253**[60,61] and acetylthiazolidinethione **254**, giving the aldol adduct **255** in 87% yield and a modest 4:1 dr (Scheme 3.8.1). While it was anticipated that using Crimmins mesityl thiazolidinethione chiral auxiliary would provide superior selectivity, the ease of preparation of the benzyl thiazolidinethione **254** auxiliary and the facile separation of the product diastereomers provided that this avenue would be ideal for initial investigations. The alcohol **255** was protected as the TBS ether and reductive removal of the chiral auxiliary provided aldehyde **249**. With aldehyde **249** in hand, the Crimmins *anti*-aldol reaction was then investigated. Much to our surprise, the major product of the *anti*-aldol appeared to be a mixture of products resulting from a

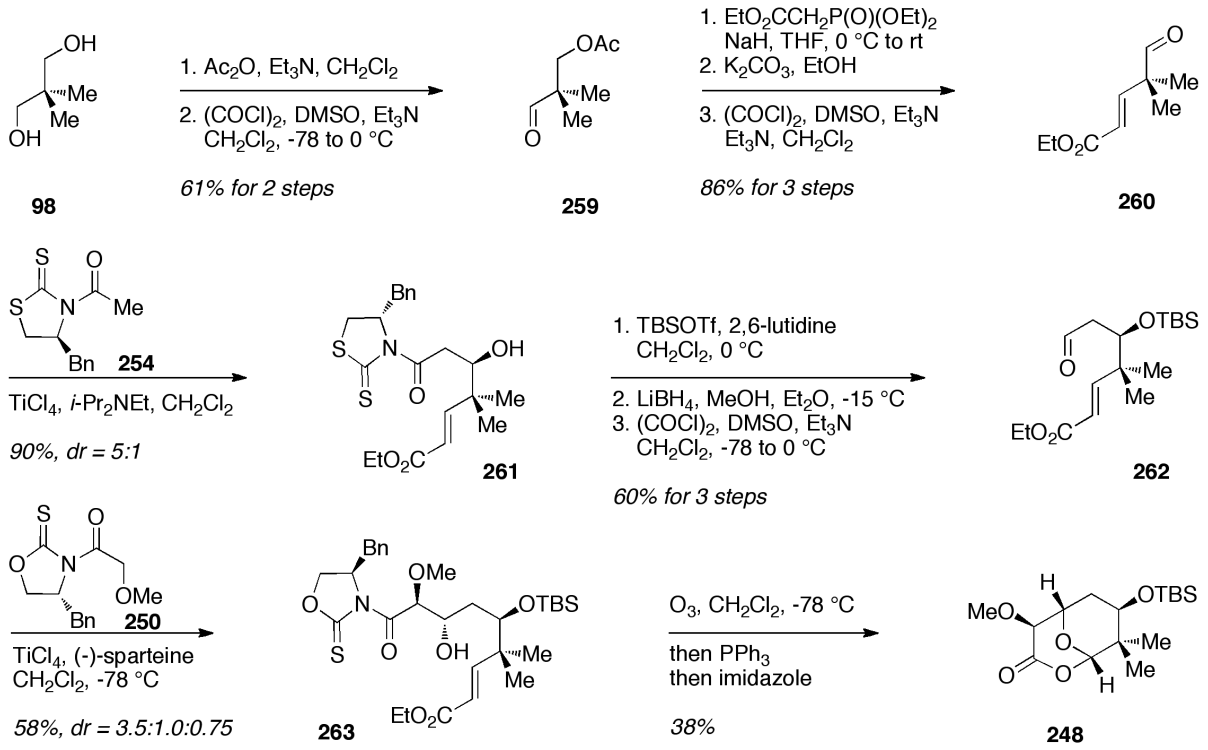
Scheme 3.8.1. Crimmins Synthesis of the Tetrahydropyran Precursor



Prins-type cyclization as indicated by the presence of new CH_2 protons, carbinol and alcohol protons, and lack of terminal alkene protons in the ^1H NMR. In fact, the TIPS protected β-hydroxy aldehyde **257** provided the impurity in 87% yield as a single isomer upon exposure to 2 equivalents $TiCl_4$ at -78 °C over 10 min. The required use of at least 2 equivalents of the $TiCl_4$ Lewis acid for the *anti*-aldol and that the *gem*-dimethyl groups likely create a significant Thorpe-Ingold effect, the rearrangement was perhaps not that surprising. The molecular weight and incorporation of a chlorine atom were confirmed by mass spectrometry. Based on the known molecular formula and the ^1H NMR data, alcohol **258** is likely the rearranged product, however more data would be needed for a definitive structural assignment.

Having discovered an unfortunate, although interesting, Prins-cyclization, our efforts turned to shutting down the byproduct reaction pathway. The $TiCl_4$ Lewis acid responsible for activating the addition of the alkene to the aldehyde is required for the Crimmins *anti*-aldol and efforts to address this aspect of the problem were likely to be unfruitful. Similarly, installing the *gem*-dimethyl group after the *anti*-aldol would likely require significant changes to our synthetic route. Instead, our attention focused on modifying the olefin component of our substrate that was responsible for undesired intramolecular nucleophilic addition to the aldehyde. The most straightforward modification that would require only small alterations to our current route would be to exchange the nucleophilic terminal alkene for an enoate, which would render the Prins cyclization electronically unfavorable. Toward this end aldehyde **260**[62] is a known compound prepared over 3 steps from isobutyraldehyde (Scheme 3.8.2). While the known route is quite concise, it wasn't clear if it would meet our scalability needs. Therefore, a new route employing simple chemistry that used cheap and abundant starting materials was devised. Starting from 2,2-dimethyl-1,3-propane diol (**98**), a mono-acetate protection and oxidation sequence provided aldehyde **259**, which was subjected to a Horner-Wadsworth-Emmons reaction, ethanolysis and oxidation to arrive at the desired aldehyde **260**. The scalability of this route was exemplified by the ability to prepare 100 mmol of the alcohol precursor to aldehyde **260**. An acetate aldol reaction of aldehyde **260** with the titanium enolate of acetylthiazolidinethione **254** provided a slightly improved 5:1 dr and 90% yield over the previous sequence, which was also displayed scalability as it was run on 35 mmol scale. The protection of the β-hydroxy alcohol was

Scheme 3.8.2. Crimmins Revised Synthesis of the Tetrahydropyran Precursor

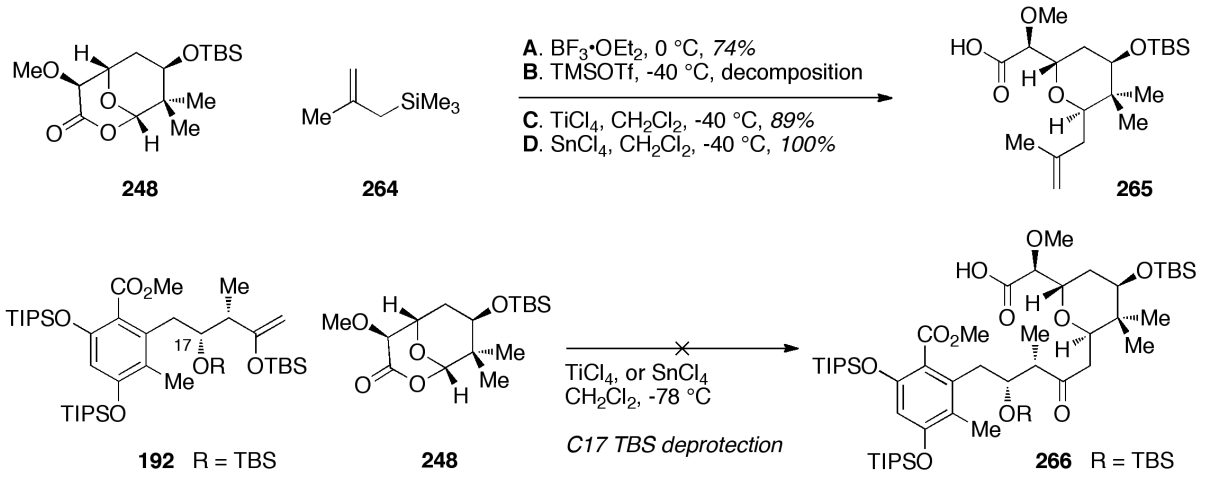


followed by a two-step reduction and oxidation sequence as the direct reduction of the auxiliary to the aldehyde was not possible in the presence of the enoate ester. The modified aldol substrate **262** was subjected to the Crimmins *anti*-aldol reaction and found to produce the desired product **263** with a mediocre 3.5:1:0.75 dr although with a 58% yield of the desired isomer. Indeed, the installation of an enoate moiety had electronically disabled the undesired Prins reaction, although it's subsequent removal proved exceedingly difficult. A survey of transition metal catalyzed oxidative cleavage reactions resulted in either oxidation of the sulfur atom of the chiral auxiliary, or no reaction, as was observed for OsO_4. Similar problems were also encountered with ozonolysis reactions as oxidation of the oxazolidinethione to the oxazolidinone competed with enoate oxidation. Efforts to

completely oxidize the both oxazolidinethione and the enoate were only moderately successful but experienced further setbacks as the removal of the oxazolidinone was exceedingly difficult. The best results were obtained by adding a substoichiometric amount of ozone followed by a triphenylphosphine quench and imidazole promoted cyclization to give acyl dioxanone **248** in a one-pot fashion in 38% yield.

Having accessed the elusive acyl dioxanone **248**, it's ability to participate in as an electrophilic coupling partner was explored (Scheme 3.8.3). It was initially found that the reaction of methallyltrimethylsilane **264** with acyl dioxanone **248** was unproductive using $BF_3{\cdot}OEt_2$ or TMSOTf as the Lewis acid at temperatures below -25 °C. In fact, the desired coupling product was only isolated when $BF_3{\cdot}OEt_2$ was used as the Lewis acid at 0 °C, a temperature that would definitely be too high to be compatible with our Lewis acid sensitive enolsilane coupling partner. The silver lining was that although the conditions were unfavorable at this stage, the oxocarbenium ion was forming and dioxanone **248** was participating in a productive coupling

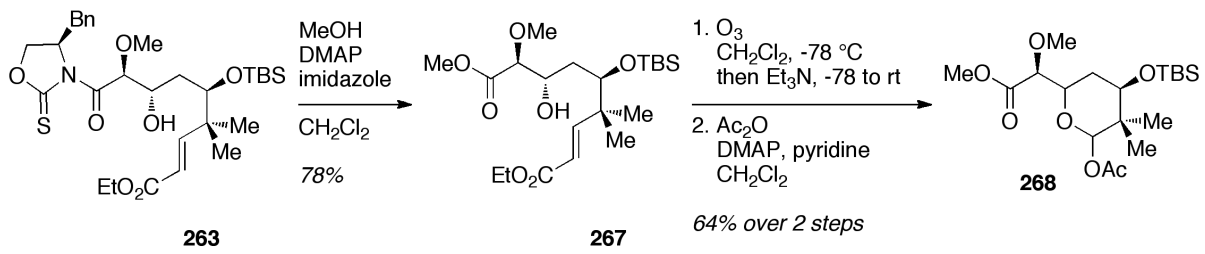
Scheme 3.8.3. Diastereoselective Union of the Tetrahydropyran and the Dihydroisocoumarin



reaction. It was thought that the coupling with dioxanone **248** was reluctant compared with our previous lactol-acetate **193** due to the loss in entropic driving force for the reaction as the leaving group was now tethered to our substrate. A potential solution for this problem was to employ a Lewis acid that could accommodate two ligands to give bidentate chelation of Lewis acid between the carboxyl and α-methoxy groups, which might provide a longer lifetime for the oxocarbenium ion. Also, a Lewis acid of this type, when doubly ligated would also lose a counter anion that could also stabilize the oxocarbenium ion. This hypothesis was supported by our experiments that showed a much improved reaction at lower temperatures by using $SnCl_4$ or $TiCl_4$. While the initial results for our model coupling were exciting, it was found that when these conditions were extended to our desired coupling reaction with enolsilane **192**, the major product was deprotection of the C17 TBS ether of the enolsilane in both cases. At this stage it was felt that the difficulty in accessing dioxanone **248** and its reluctance to participate in even simple coupling reactions warranted exploring other options.

One of the significant drawbacks to installing the enoate in our previous fragment was that its oxidation to the aldehyde/lactol was particularly challenging. The main problem with the ozonolysis was that the oxazolidinethione was

Scheme 3.8.4. Crimmins Synthesis of the Second Generation Lactol Acetate

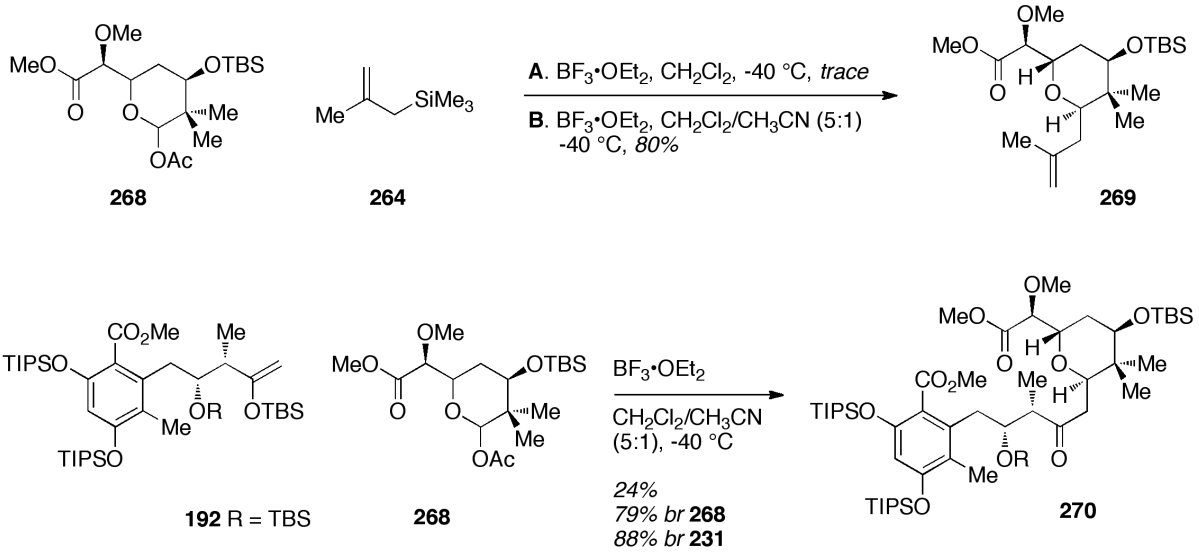


263 **267** **268**

undergoing competitive oxidation to the oxazolidinone, which was incredibly difficult to remove and cyclize to form the dioxanone **248**. This problem could be alleviated by removing the auxiliary prior to the ozonolysis via esterification. Thus our sites were set on the synthesis of a more familiar lactol-acetate with a C7 ester instead of the dioxanone. Toward this end the aldol adduct **263** was directly esterified to give methyl ester **267** that was subjected to a much improved ozonolysis and then acetylated to give lactol-acetate **268** (Scheme 3.8.4).

With our modified coupling partner **268** in hand, its ability to function as an electrophilic coupling partner in our desired reaction was investigated (Scheme 3.8.5). It was initially found that while lactol-acetate **268** showed improved reactivity at lower temperatures with $BF_3{\cdot}OEt_2$ than dioxanone **248**, the reactivity at lower temperatures was drastically increased by adding acetonitrile to the reaction. One possibility for the improved reactivity could be that the polar acetonitrile solvent is stabilizing the oxocarbenium ion, which might otherwise be anchimerically stabilized

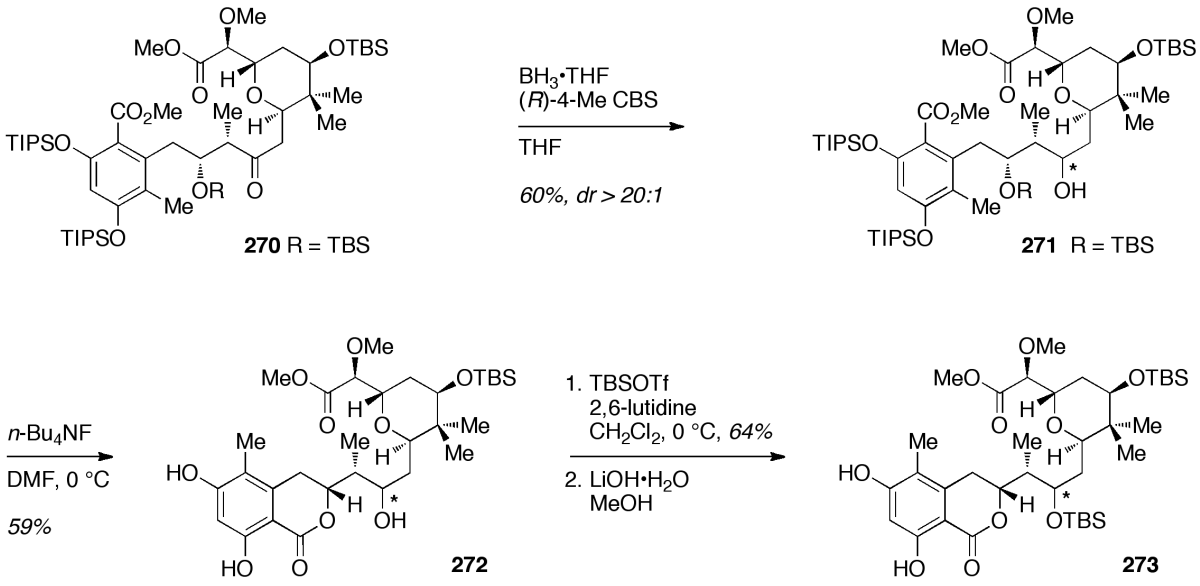
Scheme 3.8.5. Diastereoselective Coupling with the Modified Lacol-Acetate



by the carbonyl of the methyl ester resulting in lower reactivity. The conditions were applied to our desired coupling of enolsilane **192** and acetate **268** giving a 24% yield of the tetrahydropyran **270**, and recovery of most of the starting materials. While the coupling still required optimization, it was exciting that this was the first time we had achieved a productive coupling with C7 in the correct oxidation state. What was particularly interesting in this case was that our optimized conditions for our original coupling that required premixing that lactol acetate and $BF_3{\cdot}OEt_2$ prior to enolsilane addition actually led to a decreased yield of 12% in the present case.

Before extensive optimization of our coupling reaction, the remaining chemistry of the endgame sequence was explored (Scheme 3.8.6). In accord with our previous endgame the (*R*)-CBS agent provided a single carbinol diastereomer, whose identity would be confirmed upon completing the formal synthesis. A deprotection-lactonization reaction then afforded dihydroisocoumarin **272**. A global reprotection as TBS ethers was then followed by an attempted hydrolysis of the

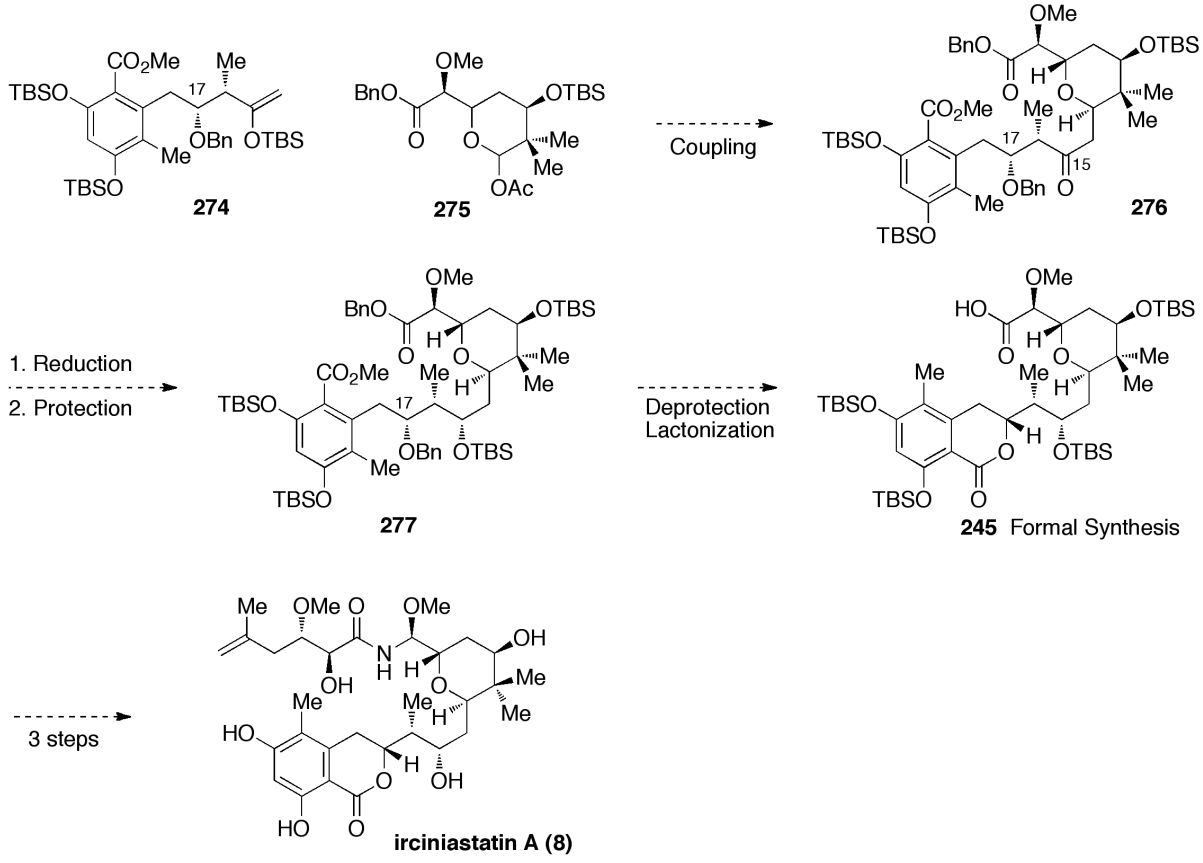
Scheme 3.8.6. Initial Endgame Investigations



methyl ester, which unfortunately resulted in deprotection of the aryl TBS ethers to give **278** with the methyl ester still in tact.

Although our previous endgame had failed at the last step we believed the general template for our endgame strategy had a solid foundation from which to improve. The most pressing issue aside from the low-yielding coupling, was certainly the hydrolysis of the methyl ester, which could be alleviated by employing a benzyl ester that could be removed under more compatible hydrogenolysis conditions. This would then lead to the revised lactol acetate fragment **275** that would be prepared in an analogous fashion to the previous methyl ester **268** (Scheme 3.8.7). In addition, our previous endgame approaches suffered from a low yielding deprotection-

Scheme 3.8.7. Second Generation Prospective Endgame

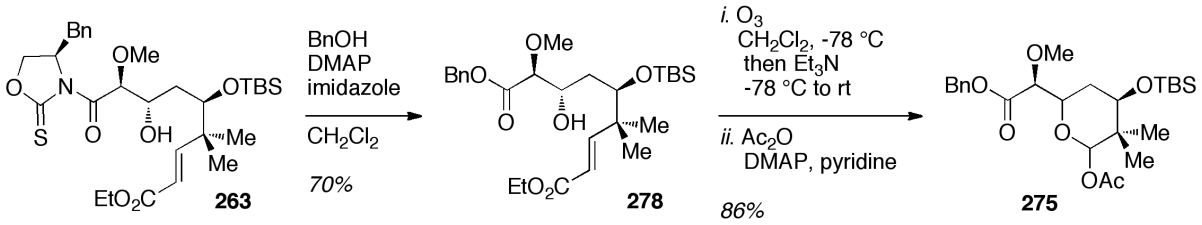


lactonization reaction, which was followed by a redundant reprotection. By employing a modified enolsilane coupling partner featuring a benzyl protected ether at the C17 position it would then be possible after the coupling, and C15 carbonyl reduction-protection sequence, to hydrogenolyze both the benzyl ester and benzyl ether while forming the desired lactone. The successful implementation of this strategy would solve the current problem of ester hydrolysis and improve our original endgame sequence by 3 steps.

With a revised strategy in place our efforts began with the synthesis of lactol-acetate **275** starting with esterification of aldol adduct **263** to provide benzyl ester **278** (Scheme 3.8.8). In an improvement over the previous protocol, a one-pot ozonolysis-lactolization-acetate protection sequence was carried out to give the desired lactol acetate **275** in a remarkable 86% yield

Future work on this project will focus on the development of an efficient coupling reaction between acetate **275** and enolsilane **274** as well as the subsequent endgame chemistry. Our revised synthesis of the tetrahydropyran

Scheme 3.8.8. Crimmins Revised Synthesis of the Second Generation Lactol-Acetate



precursor will allow for the synthesis tetrahydropyran analogs to be screened for biological activity alongside the additional synthetic irciniastatin A prepared through our research efforts.

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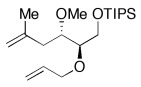
Chapter 4: Experimental Procedures and NMR Spectra

4.1 Materials and Methods

Infrared (IR) spectra were obtained using a Jasco 460 Plus Fourier transform infrared spectrometer. Nuclear magnetic resonance (^{1}H, ^{13}C, COSY, NOESY) spectra were recorded on Bruker model Avance 400 (^{1}H at 400 MHz; ^{13}C at 100 MHz) and Bruker model Avance 500 (^{1}H at 500 MHz; ^{13}C at 125 MHz) instruments. Chemical shifts are reported relative to chloroform (δ 7.26), benzene (δ 7.15) or methanol (δ 4.78) for ^{1}H NMR spectra and chloroform (δ 77.23), benzene or (δ 128.0) methanol (δ 49.3), for ^{13}C spectra. ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. Optical rotations were determined using a Jasco P1010 polarimeter. Mass spectra were obtained using a Bruker BioTOF II mass spectrometer with electrospray ionization (ESI). Thin layer chromatography (TLC) was conducted on silica gel F254 TLC plates purchased from EMD Chemicals Inc. Visualization was accomplished with UV light and/or aqueous ceric ammonium molybdate solution followed by heating unless otherwise noted. Flash column chromatography was carried out using Ultra Pure Silica Gel Silia-P (40 to 63 μm) purchased from SiliCycle Inc. Dichloromethane (CH_2Cl_2), diethyl ether

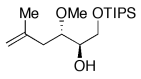
(Et_2O), tetrahydrofuran (THF), and toluene ($PhCH_3$) were dried by passage through a column of neutral alumina under argon immediately prior to use. All alkylamines, 2,6-lutidine, benzene, pyridine, and chlorotrimethylsilane (TMSCl) were distilled from calcium hydride immediately prior to use. Boron trifluoride-diethyl etherate was distilled from calcium hydroxide immediately prior to use. Iodomethane was distilled prior to use. Anhydrous N,N-dimethylformamide (DMF) was purchased from Aldrich chemical company in 1L Sure/SealTM bottles. Dess-Martin periodinane was prepared according to literature procedures and stored at -20 ºC. Procedures calling for pH = 4 buffer employed Fisher Scientific Buffer Solution pH 4.00 (0.05 M potassium biphthalate buffer). Sodium hydride, 60% oil dispersion, was washed with pentanes under positive argon pressure prior to use. All other reagents and solvents were used as received from the manufacturer. All air and water sensitive reactions were performed in flasks flame dried under positive flow of argon and conducted under an argon atmosphere. Yield refers to isolated yield of analytically pure material unless otherwise noted.

4.2 Experimental Procedures



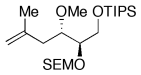
(-)-Methyl Ether To a 0 °C slurry of 60% NaH oil dispersion (128 mg, 3.19 mmol) in THF (10 mL) was added a solution of alcohol (910 mg, 2.66 mmol) in THF (3.5 mL) over 2 min followed by a THF rinse (3.5 mL). The reaction was stirred at 0 °C for 20 min and was then treated with iodomethane (0.25 mL, 3.98 mmol), stirred at 0 °C for

5 min, then the white slurry was warmed to room temperature. After 1 h the transparent reaction was quenched with saturated aqueous NH_4Cl (12 mL), the layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (5% EtOAc/Hexanes) gave (-)-methyl ether (905 mg, 2.53 mmol) as a clear oil in 96% yield. $[\alpha]^{23}_D$ = -4.94 (c = 0.26, CH_2Cl_2); IR (film) 3076, 2942, 2866, 1647, 1382, 1327, 1246, 1107, 1012, 996, 919, 883, 796, 682, 659; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (m, 21 H), 1.79 (s, 3H), 2.30 (m, 2H), 3.40 (s, 3H), 3.55 (m, 2H), 3.79 (m, 2H), 4.17 (m, 2H), 4.80 (m, 2H), 5.14 (dd, *J* = 1.6, 10.2 Hz, 1H), 5.26 (dd, *J* = 1.6, 17.2 Hz, 1H), 5.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 18.0, 22.8, 38.5, 57.9, 63.2, 72.0, 80.1, 80.7, 112.24, 116.3, 135.5, 143.2; MS (ESI+) for $C_{20}H_{40}O_3Si$ [M+Na] calc 379.2644 found 379.2639.



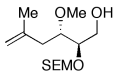
(+)-Alcohol 210 To a 0 °C solution of (-)-allyl ether (905 mg, 2.54 mmol) in ether (25 mL) was added titanium(IV) isopropoxide (0.75 mL, 2.53 mmol) to give a yellow solution, which was treated with 2.0 M *n*-BuMgCl in ether (3.17 mL, 6.344 mmol) over 1 h via syringe pump. Immediately following the addition the dark orange solution was quenched with water (3 mL), filtered through celite, and rinsed with EtOAc (50 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated

NH_4Cl, dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (5% EtOAc/Hexanes) afforded (+)-alcohol **210** (690 mg, 2.18 mmol) as yellow oil in 86% yield. $[\alpha]^{25}_D$ = +15.3 (c = 0.25, CH_2Cl_2); IR (film) 3459, 2942, 2867, 1462, 1104, 1066, 883, 800, 682, 660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.10 (m, 21H), 1.79 (s, 3H), 2.30 (m, 2H), 2.52 (d, *J* = 4.0 Hz, 1H), 3.40 (s, 3H), 3.45 (m, 1H), 3.67 (m, 1H), 3.80 (m, 2H), 4.81 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 17.9, 22.9, 38.4, 58.0, 63.8, 72.9, 80.1, 112.6, 142.9; MS (ESI+) for $C_{17}H_{36}O_3Si$ [M+Na] calc 339.2272 found 339.2096.

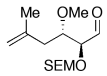


(-)-SEM Ether To a solution of alcohol (+)-**210** (220 mg, 0.690 mmol) in CH_2Cl_2 (2.22 mL) was added *i*-Pr_2NEt (0.97 mL, 5.55 mmol) followed by SEMCl (0.49 mL, 2.78 mmol). The reaction was heated to 30 ˚C and stirred for 1 h giving an orange solution. The reaction was poured into ice cold aqueous $NaHCO_3$, the layers were separated, and the aqueous extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (3% EtOAc/Hexanes) gave (-)-SEM ether (268 mg, 0.600 mmol) as clear oil in 86% yield. $[\alpha]^{23}_D$ = -14.1 (c = 0.28, CH_2Cl_2); IR (film) 2943, 2867, 1463, 1375, 1248, 1105, 1030, 883, 860, 835, 682 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.01 (s, 9H), 0.93 (t, *J* = 8.5 Hz, 2H), 1.06 (m, 21H), 1.78 (s, 3H), 2.23 (dd, *J* = 4.0, 14.5 Hz, 1H), 2.29 (dd, *J* = 9.5, 14.5 Hz, 1H), 3.39 (s, 3H), 3.60 (m, 2H), 3.66 (m, 1H), 3.73 (dd, *J* = 5.5, 9.5 Hz, 1H), 3.83 (m, 2H), 4.80 (m,

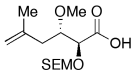
4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -1.4, 11.9, 18.0, 18.1, 22.7, 38.3, 57.9, 63.07, 65.1, 78.1, 79.9, 95.2, 112.3, 143.1; MS (ESI+) for $C_{23}H_{50}O_4Si_2$ [M+Cs] calc 579.2302 found 579.2332.



(+)-Alcohol To a 0 ˚C solution of (-)-TIPS ether (500 mg, 1.12 mmol) in THF (3.63 mL) was added 1.0 M TBAF in THF (2.23 mL, 2.23 mmol). The reaction stirred for 15 min at 0 °C and the reaction was poured into saturated aqueous NH_4Cl (3 mL), the layers were separated and the aqueous layer was extracted with EtOAc (3 x 3 mL). The combined organic layers were washed with water (2 mL) and brine (2 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (20% EtOAc/Hexanes) afforded (+)-alcohol (265 mg, 0.91 mmol) as clear oil in 82% yield. $[\alpha]^{20}_D$ = +38.7 (c = 0.25, CH_2Cl_2); IR (film) 3462, 2952, 1647, 1375, 1249, 1107, 1057, 1024, 860, 835, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 9H), 0.96 (t, *J* = 8.8 Hz, 2H), 1.77 (s, 3H), 2.20 (dd, *J* = 5.2, 14.0 Hz, 1H), 2.32 (dd, *J* = 8.0, 14.0 Hz, 1H), 3.25 (dd, 4.4, 8.0 Hz, 1H), 3.39 (s, 3H), 3.49 (m, 1H), 3.59 (m, 2H), 3.69 (m, 3H), 4.76 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -1.5, 18.1, 22.7, 39.3, 58.3, 62.3, 65.7, 80.8, 82.1, 95.3, 112.8, 142.4; MS (ESI+) for $C_{14}H_{30}O_4Si$ [M+Na] calc 313.1181 found 313.1806.

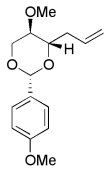


(-)-Aldehyde (-)-Aldehyde was prepared from (+)-alcohol according to literature procedures. Smith, A. B.; Jurica, J. A.; Walsh, S. P., *Org. Lett.* **2008**, *10*, 5625. $[\alpha]^{19}_{D}$ = -7.6 (c = 0.26, CH_2Cl_2); IR (film) 3078, 2953, 2891, 2826, 2724, 1732, 1644, 1377, 1249, 1109, 1059, 1027, 937, 860, 834 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ -0.09 (s, 9H), 0.81 (m, 2H), 1.61 (s, 3H), 2.20 (dd, *J* = 7.0, 14.0 Hz, 1H), 2.26 (dd, *J* = 6.5, 14.0 Hz, 1H), 3.31 (s, 3H), 2.42 (ddd, *J* = 7.0, 10, 10.0 Hz, 1H), 3.62 (m, 2H), 4.03 (s, 1H), 4.70 (m, 2H), 4.74 (s, 2H), 9.56 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -1.5, 18.0, 22.5, 38.7, 57.8, 65.8, 81.6, 82.3, 95.3, 114.1, 141.5, 202.0; MS (ESI+) for $C_{14}H_{28}O_4Si$ [M+Na] calc 311.1655 found 311.1622.



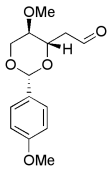
(-)-Acid 137. A solution of (-)-aldehyde (146 mg, 0.506 mmol) in *t*-BuOH (23 mL) and 2-methyl-2-butene (1.29 mL, 12.15 mmol) was treated with a solution of $NaClO_2$ (687 mg, 6.07 mmol) in 0.05 M potassium biphthalate pH 4 buffer (23 mL) in one portion. The yellow solution was stirred for 1 h, gradually turning clear. The reaction was then poured into brine (50 mL) and EtOAc (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (4 x 20 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by

column chromatography (25% EtOAc/Hexanes to 40% EtOAc/Hexanes) gave (-)-acid **137** (146 mg, 0.48 mmol) as a clear oil in 95% yield, that was stored frozen in benzene. $[\alpha]^{22}_{D}$ = -6.2 (c = 0.26, CH_2Cl_2); IR (film) 3076, 2953, 1725, 1443, 1376, 1249, 1190, 1158, 1111, 1061, 891, 860, 835, 758, 693 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ -0.02 (s, 9H), 0.93 (m, 2H), 1.70 (s, 3H), 2.50 (m, 2H), 3.21 (s, 3H), 3.65 (m, 2H), 3.84 (m, 1H), 4.45 (d, *J* = 3.2 Hz, 1H), 4.65 (q, *J* = 8.5, 19.5 Hz, 2H), 4.86 (s, 1H), 4.93 (s, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ -0.4, 19.1, 23.9, 40.2, 58.9, 67.0, 77.7, 82.3, 96.0, 114.5, 143.3, 177.5; MS (ESI+) for $C_{14}H_{28}O_5Si$ [M+Na] calc 327.1604 found 327.1586.



(-)-Methyl Ether To a 0 °C solution of alcohol (8.80 g, 35.16 mmol) and MeI (4.36 mL, 42.19 mmol) in THF (122 mL) and DMF (12.2 mL) was added NaH 60% oil dispersion (2.02 g, 84.38 mmol). The reaction mixture was stirred for 30 min at 0 °C and 1 h at room temperature then quenched with saturated aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted with EtOAc (5 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (Hexanes to 10% EtOAc/Hexanes) afforded (-)-methyl ether (8.50 g, 32.15 mmol) in 91% yield as clear oil. $[\alpha]^{22}_{D}$ = -44.03 (c = 0.55, CH_2Cl_2); IR (film) 3074, 2934, 2836, 1615, 1517, 1250, 1102, 1034, 827 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.42 (ddd, *J* = 7.5, 7.5, 14.5 Hz, 1H), 2.65 (m, 1H), 3.24 (ddd, *J* = 5.0, 9.5, 9.5, 1H), 3.43 (s, 3H), 3.56 (t, *J* = 11.0 Hz, 1H), 3.64 (m, 1H), 3.81

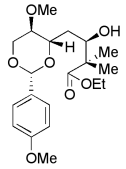
(s, 3H) 4.42 (dd, 5.0, 11.0 Hz, 1H), 5.12 (dd, *J* = 2.0, 10.0 Hz, 1H), 5.16 (dd, *J* = 2.0, 17.0 Hz, 1H), 5.43 (s, 1H), 5.99 (dddd, 7.5, 7.5, 10.0, 17.0 Hz, 1H), 6.89 (d, J = 9.0 Hz, 2H), 7.41 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.2, 55.3, 58.1, 69.0, 73.9, 80.1, 100.9, 113.6, 117.2, 127.4, 130.5, 134.4, 160.0; MS (ESI+) for $C_{15}H_{20}O_4$ [M+Cs] calc 397.0416 found 397.0423.



(-)-Aldehyde 212 To a solution of (-)-alkene (6.48 g, 24.5 mmol) in THF (48 mL) and water (48 mL) was added NMO (6.12 g, 52.24 mmol) followed by a 20 mg/1.0 mL solution of OsO_4 in water (0.64 mL, 0.05 mmol). The reaction mixture was stirred for 16 h and was quenched with solid $Na_2S_2O_3$ (3.2 g) and stirred for 1 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were concentrated and taken on to the next step without purification.

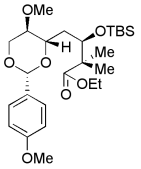
To a 0 °C biphasic solution of the crude diol (7.36 g, 24.5 mmol) in 0.05 potassium biphthalate pH 4 buffer (66 mL) and CH_2Cl_2 (66 mL), was added $NaIO_4$ (7.82 g, 36.56 mmol). The mixture stirred for 5 min at 0 °C and was then warmed to room temperature for 2 h. The reaction mixture was quenched with aqueous $Na_2S_2O_3$, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to crude oil. Purification by column chromatography (5% EtOAc/ Hexanes to 20% EtOAc/Hexanes) afforded (-)-aldehyde **212**. (6.3 g, 23.7 mmol) in

97% yield over 2 steps. $[\alpha]^{26}_{D}$ -41.2 (c 0.46, CH_2Cl_2); IR (film) 2935, 2837, 1725, 1615, 1518 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz); δ 2.71 (ddd, *J* = 2.4, 7.6, 16.4 Hz, 1H), 2.83 (ddd, *J* = 2.4, 4.8, 16.4 Hz, 1H), 3.21 (ddd, *J* = 5.2, 9.6, 19.2 Hz, 1H), 3.36 (s, 3H), 3.56 (dd, *J* = 10.4, 10.4 Hz, 1H), 3.76 (s, 3H), 4.12 (ddd, *J* = 4.4, 7.6, 9.2 Hz, 1H), 4.43 (dd, *J* = 5.2, 11.2 Hz, 1H), 5.48 (s, 1H); 6.86 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 9.78 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) ppm 46.3, 55.2, 57.7, 68.9, 74.0, 75.5, 101.0, 113.5, 127.3, 129.7, 199.8, 160.0; MS (ESI+) calc for $C_{14}H_{18}O_5$ (M +H) 267.12, found 267.2.



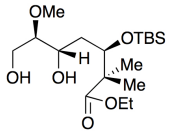
(-)-Alcohol 213 To a stirring solution of N-Ts-(L)-valine (2.89 g, 10.6 mmol) in CH_2Cl_2 (100 mL) at 0 ºC was added BH_3.THF (10.6 mL of a 1.0 M solution in THF, 10.6 mmol) in portions over 0.5 h. After the reaction mixture was cooled to -78 ºC neat silyl ketene acetal **124** (3.82 g, 20.2 mmol) was added and stirred for 5 min. (-)-Aldehyde **212** (2.7 g, 10.1 mmol) was added and stirred for 2 h. The reaction mixture was quenched by the addition of a 10% aqueous solution of $NaHCO_3$ (20 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (10% to 25% EtOAc/Hexanes) gave (-)-alcohol **213** (3.24 g, 8.47 mmol) in 84% yield as a 9:1 mixture of diastereomers. $[\alpha]^{18}_{D}$ -39.5 (c = 0.55, CH_2Cl_2); IR (film) 3535, 1726, 1615, 1519 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz); δ 1.17 (s, 3H), 1.14 (s, 3H), 1.22 (dd, *J* = 7.2, 7.2 Hz, 3H), 1.63 (m, 1H),

2.03 (m, 1H), 3.25 – 3.19 (m, 2H), 3.39 (s, 3H), 3.54 (dd, *J* = 10.4, 10.4 Hz, 1H), 3.76 (s, 3H), 3.81 (ddd, *J* = 9.2, 9.2, 2.4 Hz, 1H), 4.16 – 4.05 (m, 3H), 4.41 (dd, *J* = 10.8, 4.8 Hz, 1H), 5.44 (s, 1H), 6.83 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) ppm 14.1 20.4, 21.0, 33.8, 47.0, 55.2, 57.9, 60.5, 69.0, 74.5, 75.9, 81.5, 101.0, 113.6, 127.3, 129.6, 160.1, 177.8; MS (ESI+) calc for $C_{20}H_{30}O_7$ (M +H) 383.45, found 383.3.

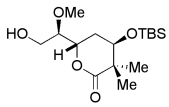


(-)-Silyl Ether To a solution of (-)-alcohol **213** (3.00 g, 7.83 mmol) in CH_2Cl_2, (50 mL) at 0 ºC was added 2,6-lutidine (2.28 mL, 19.7 mmol) followed by TBSOTf (2.72 g, 10.3 mmol).The reaction stirred for 1 h at 0 °C and warmed to room temperature and stirred for 1 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (10% EtOAc/Hexanes) gave (3.47 g, 7.00 mmol) of (-)-silyl ether in 89% yield as a clear oil. $[\alpha]^{26}_D$ -36.0 (c = 0.53, CH_2Cl_2); IR (film) 1730, 1616, 1518 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$); δ -0.06 (s, 3H), 0.05 (s, 3H), 0.83 (s, 9H), 1.11 (s, 3H), 1.17 (s, 3H), 1.23 (dd, *J* = 8.0, 8.0 Hz , 3H), 1.64 (ddd, *J* = 13.6, 8.0, 4.0 Hz, 1H), 2.19 (ddd, *J* = 14.8, 5.2, 5.2 Hz, 1H), 3.07 (ddd, *J* = 9.6, 9.6, 4.8 Hz, 1H), 3.55 – 3.46 (m, 2H), 3.39 (s, 3H), 4.05 (dd, *J* = 14.4, 7.2 Hz, 2H), 3.78 (s, 3H), 4.23 (dd, *J* = 4.8, 4.8 Hz, 1H), 4.37 (dd, *J* = 10.8, 4.8 Hz, 1H), 5.35 (s, 1H), 6.85 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.4

Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm -5.1, -3.9, 14.0, 18.1, 20.3, 21.2, 25.9, 38.2, 48.3, 55.2, 57.9, 60.3, 69.0, 73.2, 76.1, 78.6, 101.1, 113.4, 127.5, 130.3, 159.9, 177.0; MS (ESI+) calc for $C_{26}H_{44}O_7Si$ (M+H) 497.28, found 497.4.

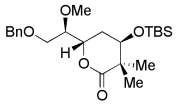


(-)-1,3-Diol. To a flask containing (-)-*p*-methoxybenzylidine acetal (533 mg, 1.072 mmol) added $Pd(OH)_2/C$ (275 mg) followed by THF (2 mL). The reaction was degassed under reduced pressure, charged with hydrogen, and stirred under a balloon of hydrogen for 5 h. The reaction was filtered through Celite®, washed with THF (75 mL), concentrated to clear oil and taken on crude to the next step. $[\alpha]^{18}_D$ = -9.8 (c = 0.27, CH_2Cl_2); IR (film) 3446, 2932, 2857, 1720, 1472, 1387, 1362, 1256, 1093, 836, 776 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.14 (s, 3H), 0.89 (s, 9H), 1.11 (s, 3H), 1.19 (s, 3H), 1.27 (t, *J* = 2.8 Hz, 3H), 1.60 (m, 1H), 1.82 (m, 1H), 2.29 (s, 1H), 2.41 (m, 1H), 2.81 (m, 1H), 3.07, (m 1H) 3.44 (s, 3H), 3.81 (m, 4H), 4.14 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.50, -3.91, 14.00, 18.12, 19.03, 23.24, 25.89, 38.05, 47.72, 57.66, 60.70, 69.76, 74.11, 83.36, 177.58; MS (ESI+) for $C_{18}H_{38}O_6Si$ [M+Cs] calc 511.1492 found 511.1479**.**



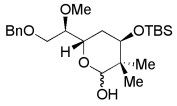
(-)-Lactone 214 Crude (-)-diol, dried azeotropically with toluene, was dissolved in CH_2Cl_2 (5 mL), cooled to 0 °C, then treated with TFA (40 µL, 0.536 mmol). The

reaction was stirred for 5 min at 0 °C then stirred at room temperature for 5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (1.5 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), dried over Na_2SO_4, filtered and concentrated to clear oil. Purification by column chromatography (25% EtOAc/ CH_2Cl_2) afforded pure (-)-lactone **214** (315 mg, 0.946 mmol) in 88% yield over 2 steps as clear oil. $[\alpha]^{18}_D$ = -36.6 (c = 0.22, CH_2Cl_2); IR (film) 3450, 2930, 1731, 1471, 1391, 1257, 1162, 1131, 1088, 835, 776 $^{cm-1}$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.86 (s, 9H), 1.24 (s, 3H), 1.25 (s, 3H), 1.80 (m, 1H), 2.11 (s, 1H), 2.22 (t, *J* = 12.3 Hz, 1H), 3.50 (s, 3H), 3.52 (m, 1H), 3.70 (m, 1H), 3.65 (m, 1H), 3.79 (s, 1H), 4.76 (dd, *J* = 3.3, 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.0, -4.6, 18.0, 22.9, 25.7, 26.1, 28.2, 44.2, 59.5, 60.9, 73.1, 76.7, 82.7, 176.8; MS (ESI+) for $C_{16}H_{32}O_5Si$ [M+Cs] calc 465.1073 found 465.1120.



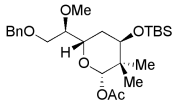
(-)-Benzyl Ether 215. To a flask containing sodium hydride 60% oil dispersion (220 mg, 5.73 mmol), washed with pentanes, was added THF (3.5 mL) and cooled to 0 °C. The resulting slurry was treated with a room temperature solution of alcohol (-)-lactone **214** (763 mg, 2.29 mmol), tetrabutylammonium iodide (170 mg, 0.45 mmol), and benzyl bromide (0.41 mL, 3.44 mmol) in THF (4.9 mL) over 10 min. The reaction mixture was stirred for 45 min at 0 °C and then warmed to room temperature and stirred for 5 h. The reaction was cooled to 0 °C and quenched with a saturated solution of aqueous NH_4Cl (7 mL) followed by dilution with ethyl acetate (7 mL) and

water (2 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (3 x 7 mL). The organics were combined and washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated to orange oil. Purification by column chromatography (5% EtOAc/Hexanes to 25% EtOAc/Hexanes) to afforded (-)-benzyl ether **215** (865 mg, 2.04) in 89% yield as clear oil. $[\alpha]^{21}_D$ = -27.3 (c = 0.27, CH_2Cl_2); IR (film) 2929, 2857, 1734, 1462, 1390, 1257, 1164, 1092, 1031, 1016, 835, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.05 (s, 3H), 0.85, (s, 9H) 1.23 (s, 3H), 1.25 (s, 3H); 1.75 (dt, *J* = 4.4, 4.4, 14.0 Hz, 1H), 2.26 (m, 1H), 3.46 (m, 4H), 3.54, (m, Hz, 1H); 3.78 (m, 1H), 3.78 (m, 1H), 4.50 (s, 2H), 4.82 (m, 1H), 7.30, (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.2, -4.7, 17.8, 22.8, 25.6, 25.7, 27.1, 44.0, 59.3, 68.6, 73.0, 73.4, 76.7, 81.0, 127.5, 127.6, 128.2, 137.7, 176.6; MS (ESI+) for $C_{23}H_{38}O_5Si$ [M+Cs] calc 555.1543 found 555.1550.

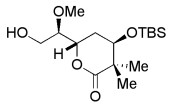


(-)-Lactol. To a -78 °C solution of (-)-lactone **215** (865 mg, 2.0 mmol) in ether (20 mL) added 1.0 M solution of diisobutylaluminum hydride in hexanes (3.58 mL, 3.58 mmol), dropwise, over 5 min. The reaction stirred for 2 h at -78 °C and was quenched with a saturated solution of Rochelle's salt (10 mL) at -78 °C. The mixture warmed to room temperature and stirred for 2.5 h. The aqueous phase was extracted with EtOAc (4 x 10 mL) and the combined organics were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated to clear oil. The oil was purified by column chromatography (10% EtOAc/Hexanes to 25% EtOAc/Hexanes)

to give (-)-lactol (844 mg, 1.99 mmol) as an inseparable 5:1 mixture of anomers that were carried forward to the anomerically stable lactol-acetate for characterization.

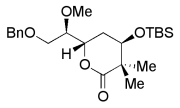


(-)-Lactol-Acetate 193 To a solution of (-)-lactol (561 mg, 1.321 mmol) in pyridine (1.6 mL) was added acetic anhydride (1.25 mL, 13.21 mmol) over 1 min and stirred for 16 h. The reaction mixture was diluted with CH_2Cl_2 (25 mL) and quenched with saturated aqueous sodium bicarbonate (2 mL). The layers were separated and the aqueous was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were washed with brine (5 mL), dried over Na_2SO_4, filtered, concentrated to yellow oil. Purification by flash column chromatography (10% EtOAc/Hexanes) gave (-)-lactol-acetate **193** (565 mg, 1.21 mmol) in quantitative yield as clear oil. $[\alpha]^{21}_D$ = -33.4 (c = 0.27, CH_2Cl_2); IR (film) 2929, 2857, 1753, 1473, 1457, 1391, 1364, 1226, 1058, 835, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.04 (s, 3H), 0.88 (s, 3 H), 0.09 (s, 9H), 0.098 (s, 3H), 1.54 (dt, *J* = 2.7, 2.7, 14.0 Hz, 1H), 1.92 (m, 1H), 2.09 (s, 3H), 3.48 (m, 5H), 3.61 (dd, *J* = 3.2, 9.8 Hz, 1H), 3.67, (t, *J* = 2.7 Hz, 1H), 4.10 (ddd , *J* = 2.7, 4.7, 11.7 Hz, 1H), 4.52 (s, 2H), 5.75 (s, 1H), 7.29 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.1, -4.6, 18.0, 18.6, 21.0, 21.6, 25.8, 30.6, 38.6, 58.8, 70.0, 72.1, 73.4, 75.0, 82.0, 96.1, 126.8, 127.4, 128.2, 128.6, 138.3, 169.6; MS (ESI+) for $C_{25}H_{42}O_6Si$ [M+Cs] calc 599.1805 found 599.1801.



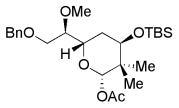
(-)-Lactone 214 To a solution of benzylidine acetal (1.00 g, 2.01 mmol) in methanol (5 mL) at 0 °C was added a 0 °C solution of 0.01 M HCl in methanol (10 mL, 0.10 mmol). The reaction was stirred for 1.25 h at 0 °C and was quenched with saturated aqueous $NaHCO_3$ (16 mL) the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered and concentrated to oil. Purification by column chromatography (25% EtOAc/CH_2Cl_2) afforded pure (-)-lactone **214** (470 mg, 1.40 mmol) in 70% yield as white solids, as well as diol (-)-1,3-diol (47 mg, 0.124 mmol) in 7% yield as clear oil. (-)-1,3-Diol (47 mg, 0.124 mmol) azeotroped with toluene, was dissolved in CH_2Cl_2 (5 mL), cooled to 0 °C, then treated with TFA (40 µL, 0.536 mmol). The reaction was stirred for 5 min at 0 °C then stirred at room temperature for 5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (1.5 mL) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated to white solids. Purification by column chromatography (25% EtOAc/CH_2Cl_2) afforded pure (-)-lactone **214** (41 mg, 0.124 mmol) in quantitative yield, for a combined 77% yield. $[\alpha]^{18}_D$ = -36.6 (c = 0.22, CH_2Cl_2); IR (film) 3450, 2930, 1731, 1471, 1391, 1257, 1162, 1131, 1088, 835, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.86 (s, 9H), 1.24 (s, 3H), 1.25 (s, 3H), 1.80 (m, 1H), 2.11 (s, 1H), 2.22 (t, *J* = 12.3 Hz, 1H), 3.50 (s, 3H),

3.52 (m, 1H), 3.70 (m, 1H), 3.65 (m, 1H), 3.79 (s, 1H), 4.76 (dd, *J* = 3.3, 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.0, -4.6, 18.0, 22.9, 25.7, 26.1, 28.2, 44.2, 59.5, 60.9, 73.1, 76.7, 82.7, 176.8; MS (ESI+) for $C_{16}H_{32}O_5Si$ [M+Cs] calc 465.1073 found 465.1120.



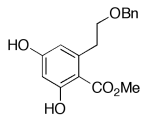
(-)-Benzyl Ether 215 To a flask containing sodium hydride 60% oil dispersion (220 mg, 5.73 mmol) was added THF (3.5 mL) and cooled to 0 °C. The resulting slurry was treated with an orange room temperature solution of (-)-alcohol **214** (763 mg, 2.29 mmol), tetrabutylammonium iodide (170 mg, 0.45 mmol), and benzyl bromide (0.41 mL, 3.44 mmol) in THF (4.9 mL) over 10 min. The reaction mixture was stirred for 45 min at 0 °C and then was warmed to room temperature and stirred 5 h. The reaction mixture was cooled to 0 °C and quenched with a saturated solution of aqueous NH_4Cl (7 mL) followed by dilution with ethyl acetate (7 mL) and water (2 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (3 x 7 mL). The organic layers were combined, washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated to orange oil. Purification by column chromatography (5% EtOAc/Hexanes to 25% EtOAc/Hexanes) afforded (-)-benzyl ether **215** (865 mg, 2.04) in 89% yield as clear oil. $[\alpha]^{21}_D$ = -27.3 (c = 0.27, CH_2Cl_2); IR (film) 2929, 2857, 1734, 1462, 1390, 1257, 1164, 1092, 1031, 1016, 835, 776 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.05 (s, 3H), 0.85, (s, 9H) 1.23 (s, 3H), 1.25 (s, 3H), 1.75 (dt, *J* = 4.4, 4.4, 14.0 Hz, 1H), 2.26 (m, 1H), 3.46 (m, 4H),

3.54, (m, 1H), 3.78 (m, 1H), 3.78 (m, 1H), 4.50 (s, 2H), 4.82 (m, 1H), 7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.2, -4.7, 17.8, 22.8, 25.6, 25.7, 27.1, 44.0, 59.3, 68.6, 73.0, 73.4, 76.7, 81.0, 127.5, 127.6, 128.2, 137.7, 176.6; MS (ESI+) for $C_{23}H_{38}O_5Si$ [M+Cs] calc 555.1543 found 555.1550.

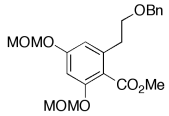


(-)-Lactol-Acetate 193 To a -78 °C solution of (-)-lactone **215** (546 mg, 1.29 mmol) in CH_2Cl_2 (8.3 mL) was added a 1.0 M solution of DIBAL in hexanes (3.2 mL, 3.23 mmol), dropwise, over 10 min. The solution stirred for 2 h at -78 °C and was treated with pyridine (0.39 mL, 4.85 mmol) over 5 min, a solution of DMAP (395 mg, 3.23 mmol) in CH_2Cl_2 (1.0 mL) over 5 min, and Ac_2O (1.0 mL, 10.34 mmol) over 5 min, respectively. The yellow solution stirred at -78 °C for 14 h and was warmed to 0 °C over 5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL) and stirred for 1 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (10% EtOAc/ Hexanes) afforded (-)-lactol-acetate **193** (600 mg, 1.29 mmol) in quantitative yield as pale yellow oil. $[\alpha]^{21}_D$ = -33.4 (c = 0.27, CH_2Cl_2); IR (film) 2929, 2857, 1753, 1473, 1457, 1391, 1364, 1226, 1058, 835, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.04 (s, 3H), 0.88 (s, 3 H), 0.09 (s, 9H), 0.098 (s, 3H), 1.54 (dt, *J* = 2.7, 2.7, 14.0 Hz, 1H), 1.92 (m, 1H), 2.09 (s, 3H), 3.48 (m, 5H), 3.61 (dd, *J* = 3.2, 9.8 Hz, 1H),

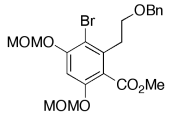
3.67 (t, *J* = 2.7 Hz, 1H), 4.10 (ddd , *J* = 2.7, 4.7, 11.7 Hz, 1H), 4.52 (s, 2H), 5.75 (s, 1H), 7.29 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.1, -4.6, 18.0, 18.6, 21.0, 21.6, 25.8, 30.6, 38.6, 58.8, 70.0, 72.1, 73.4, 75.0, 82.0, 96.1, 126.8, 127.4, 128.2, 128.6, 138.3, 169.6; MS (ESI+) for $C_{25}H_{42}O_6Si$ [M+Cs] calc 599.1805 found 599.1801.



Bis-phenol 218 To a microwave vial containing a stir bar was added with alkynoate **217** (1.0 g, 4.58 mmol) and bis-silylenol ether **216** (2.76 g, 9.42 mmol) and then microwaved at 300 W and 220 °C 30 min. The reaction mixture was cooled to room temperature, diluted with *i*-PrOH (6 mL) followed by 5% HCl (aq)/*i*-PrOH (2 mL) and stirred for 5 min. The biphasic solution was further diluted with water (5 mL) and ether (30 mL). The layers were separated and the aqueous layer was extracted with ether (3 × 10 mL).The combined organics were dried over $MgSO_4$, filtered and concentrated to orange oil. Purification by column chromatography (25% EtOAc/ Hexanes) afforded bis-phenol **218** (1.01 g, 3.34 mmol) as off-white solids in 73% yield. IR (film) 3266, 2952, 2865, 1653, 1619, 1436, 1321, 1260, 1194, 1169, 1108; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20 (t, *J* = 7.2 Hz, 2H), 3.64 (t, *J* = 7.2 Hz, 2H) 3.85 (s, 3H), 4.52 (s, 2H), 5.25 (s, 2H), 6.27 (d, *J* = 2.8 Hz, 1H), 6.31 (d, *J* = 2.8 Hz, 1H), 7.30 (m, 5H), 11.63 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.7, 51.9, 70.7, 72.9, 101.9, 104.7, 111.9, 127.8, 127.8, 128.3, 137.4, 143.4, 161.0, 165.0, 171.5; MS (ESI +) for $C_{17}H_{18}O_5$ [M+Na] calc 325.1052 found 325.1054**.**

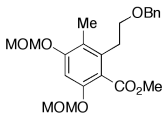


Bis-MOM ether To a 0 °C solution of bis-phenol **218** (2.079 g, 6.877 mmol) and diisopropylethylamine (12 mL, 68.77 mmol) in CH_2Cl_2 (22 mL) was added a 55% solution of chloromethyl methyl ether (4.75 mL, 34.38 mmol) over 5 min. The reaction stirred for 10 min at 0 °C then warmed to room temperature and stirred for 15 h. The red solution was quenched with saturated aqueous NH_4Cl (20 mL) and stirred for 10 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with 1N HCl (10 mL), saturated aqueous $NaHCO_3$ (20 mL), dried over $MgSO_4$, filtered and concentrated to red/orange oil (2.90 g). Purification by column (20% EtOAc/ Hexanes) gave bis-MOM ether (2.56 g, 6.57 mmol) as yellow oil in 95% yield. IR (film) 2952, 1729, 1605, 1271, 1147, 1018 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.84 (t, *J* = 7.2 Hz, 2H), 3.40 (s, 3H), 3.41 (s, 3H), 3.61 (t, *J* = 7.2 Hz, 2H), 3.78 (s, 3H), 4.45 (s, 2H), 5.08 (s, 2H), 5.09 (s, 2H), 6.58 (d, J = 1.6 Hz, 1H), 6.66 (d, *J* = 1.6 Hz, 1H), 7.22 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.2, 52.0, 56.1, 56.1, 70.5, 72.8, 94.3, 94.9, 102.0, 110.8, 118.8, 127.4, 127.5, 128.2, 138.4, 138.9, 155.4, 158.8, 168.2;



MS (ESI+) for $C_{21}H_{26}O_7$ [M+Na] calc 413.1576 found 413.1579**.**

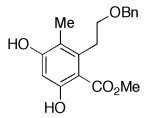
Aryl Bromide 219 To a 0 °C solution of bis-MOM ether (2.45 g, 6.27 mmol) in CH_2Cl_2 (30 mL) was added *N*-bromosuccinimide (1.12 g, 6.27 mmol) in one portion. The reaction mixture was stirred at 0 °C for 30 min then warmed to room temperature and stirred 6.5 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (15 mL), stirred 5 min, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated to yellow oil. Purification by column (20% EtOAc/Hexanes to 40% EtOAc/Hexanes) gave aryl bromide **219** (2.67 g, 5.71 mmol) as white solids in 91% yield. IR (film) 2952, 1731, 1589, 1321, 1261, 1222, 1154, 1095, 1066, 1043, 931 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.12 (t, *J* = 8.0 Hz, 2H), 3.46 (s, 3H), 3.50 (s, 3H), 3.67 (t, *J* = 8.0 Hz, 2H), 3.83 (s, 3H), 4.54 (s, 2H), 5.15 (s, 2H), 5.23 (s, 2H), 6.90 (s, 1H), 7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.6, 52.3, 56.3, 56.5, 68.7, 72.7, 94.9, 95.1, 101.7, 108.3, 120.7, 127.5, 127.6, 128.3, 136.8, 138.4, 1534.0, 155.2, 167.6; MS (ESI+) for $C_{21}H_{25}BrO_7$ [M+Na] calc 491.0681 found 491.0684.



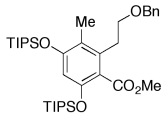
Arene 220. Method A: To a degassed mixture of aryl bromide **219** (1.73 g, 3.686 mmol) and Cs_2CO_3 (3.60 g, 11.059 mmol) in DMF (12 mL) was added $Pd(PPh_3)_4$ (426 mg, 0.369 mmol) and trimethylboroxine (0.510 mL, 3.686 mmol). The mixture was heated to 120 °C and stirred for 13 h. The reaction mixture was cooled to room temperature, filtered through Celite®, rinsed with EtOAc (50 mL) and concentrated

to black oil. The concentrate was dissolved in ether (50 mL), washed with water (1 × 20 mL) and the aqueous washes were back-extracted with ether (5 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated to black oil. Purification by column chromatography (30% EtOAc/Hexanes) gave arene **220** (1.36 g, 3.36 mmol) as white solids in 91% yield.

Method B: To a -100 °C solution of aryl bromide **219** (920 mg, 1.96 mmol) in THF (4.0 mL) was added 2.5 M *n*-BuLi in hexanes (0.87 mL, 2.16 mmol) dropwise and the resultant solution stirred for 10 min acquiring an orange/red color. The reaction was then treated with iodomethane (0.37 mL, 5.88 mmol) over 2 min and the red solution immediately turned clear. The reaction mixture stirred at -100 °C for 20 min and then was allowed to warm 0 °C and stirred for 20 min. The reaction mixture was quenched with a saturated solution of aqueous NH_4Cl (8 mL), the layers separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated to a crude orange oil (940 mg). The material was purified by column chromatography (2% to 10% ethyl acetate/hexanes) to afford the arene **220** (800 mg, 1.960 mmol) in quantitative yield. IR (film) 2951, 1729, 1594, 1476, 1315, 1267, 1152, 1094, 1058, 998, 923 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.15 (s, 3H), 2.92 (t, *J* = 7.5 Hz, 2H), 3.45 (s, 3H), 3.46 (s, 3H), 3.59 (t, *J* = 7.5 Hz, 2H), 3.83 (s, 3H), 4.51 (s, 2H), 5.13 (s, 2H), 5.17 (s, 2H), 6.82 (s, 1H), 7.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4, 31.6, 51.9, 56.0, 56.1, 69.6, 70.5, 94.7, 95.2, 100.7, 119.7, 120.2, 127.4, 127.5, 128.3, 135.5, 138.4, 152.6, 156.7, 168.8; MS (ESI+) for $C_{22}H_{28}O_7$ [M+Na] calc 427.1733 found 427.1736.

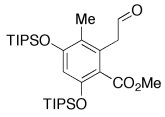


Bis-phenol 221 To a biphasic solution of arene **220** (1.86 g, 4.6 mmol) in methanol (9.3 mL) was added concentrated HCl (0.38 mL, 4.606 mmol) and the reaction mixture was heated to 40 °C for 17 h. The reaction mixture was cooled to room temperature and quenched with saturated aqueous $NaHCO_3$ (15 mL) and diluted with CH_2Cl_2 (50 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (4 × 20 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated to orange solids. Purification by column (20 % EtOAc/Hexanes) gave the bis-phenol **221** (1.411 g, 4.46 mmol) as white solids in 97% yield. IR (film) 3282, 2953, 1651, 1601, 1485, 1253, 1159 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.14 (s, 3H), 3.28 (t, *J* = 8.0 Hz, 2H), 3.58 (t, *J* = 8.0 Hz, 2H), 3.38 (s, 3H), 4.53 (s, 2H), 5.51 (s, 1H), 6.27 (s, 1H), 7.28 (m, 5H); ^{13}C NMR (100 MHz, MeOD) δ 11.3 32.7, 71.0, 73.8, 101.8, 108.1, 118.0, 128.7, 128.9, 129.4, 139.8, 140.4, 161.5, 161.6, 172.8; MS (ESI+) for $C_{18}H_{20}O_5$ [M+Na] calc 339.1208 found 339.1211.



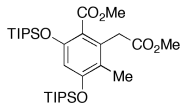
Bis-TIPS ether To a 0 °C slurry of bis-phenol **221** (1.38 g, 4.35 mmol) in CH_2Cl_2 (10 mL) was added 2,6-lutidine (2.41 mL, 20.68 mmol) that gave a transparent solution,

which was treated with TIPSOTf (2.75 mL, 10.23 mmol) dropwise over 10 min. The reaction mixture stirred for 60 min at 0 °C and was then warmed to room temperature for 14 h. The reaction was quenched with a saturated aqueous $NaHCO_3$ (15 mL) and diluted with additional CH_2Cl_2 (15 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (10 mL), dried with Na_2SO_4, filtered, concentrated. Purification by column chromatography (Hexanes to 10% EtOAc/Hexanes) gave bis-TIPS ether (2.74 g; 4.35 mmol) in quantitative yield. IR (film) 2945, 2866, 1730, 1590, 1470, 1345, 1261, 1166, 1068, 882, 686 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.08 (m, 36H), 1.23 (m, 6H), 2.13 (s, 3H), 2.89 (t, J = 8.0 Hz, 2H), 3.58 (t, J = 8.0 Hz, 2H), 3.78 (s, 3H), 4.51 (s, 2H), 6.23 (s, 1H), 7.27 (m, 2H), 7.30 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.9, 13.0, 13.2, 17.9, 18.0, 32.0, 51.9, 69.9, 72.9, 107.1, 120.2, 120.3, 127.5, 127.7, 128.4, 135.4, 138.5, 151.0, 155.4, 169.6; MS (ESI+) for $C_{36}H_{60}O_5Si_2$ [M+Cs] calc 761.3034 found 761.3053.



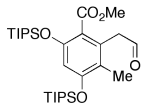
Alcohol 158. To a solution of benzyl ether (2.87 g, 4.56 mmol) in THF (37 mL) was added 20% $Pd(OH)_2/C$ (718 mg). The reaction mixture was degassed under vacuum then purged with H_2. The reaction stirred for 1 h under H_2 atmosphere (balloon) and was filtered through Celite®, rinsing the cake once with THF (100 mL). The filtrate was concentrated and taken on crude. To a flask containing CH_2Cl_2 (12 mL) and 2.0 M oxalyl chloride in CH_2Cl_2 (4.0 mL, 8.0 mmol) at -78 °C was added DMSO (1.13

mL, 16.02 mmol) dropwise over 10 min. The solution stirred for 25 min at -78 °C and was treated with a solution of alcohol **158** (2.15 g, 4.00 mmol) in CH_2Cl_2 (10 mL) over 5 min, followed CH_2Cl_2 rinses (2 × 5 mL). The turbid white mixture stirred for 1 h at -78 °C and was then treated with Et_3N (0.55 mL, 3.91 mmol) over 5 min. The reaction stirred for 10 min at -78 °C, warmed to 0 °C and stirred for 1 h, then warmed to room temperature and stirred for 20 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (8 mL), the layers separated and the aqueous layer was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to orange oil. Purification by column chromatography (5% EtOAc/Hexanes to 10% EtOAc/Hexanes) gave aldehyde **#** (2.00 g, 3.73 mmol) in 93% yield. IR (film) 2946, 2867, 2763, 2721, 1726, 1590, 1471, 1345, 1258, 1166, 882, 684 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (m, 36H), 1.26 (m, 6H), 2.07 (s, 3H), 3.60 (s, 2H), 3.82 (s, 3H), 6.33 (s, 1H), 9.59 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3, 13.0, 13.2, 17.8, 18.0, 46.1, 51.9, 108.4, 120.0, 121.2, 130.5, 151.9, 156.0, 169.1, 198.76; MS (ESI+) for $C_{29}H_{52}O_5Si_2$ [M+Cs] calc 669.2408 found 669.2411.



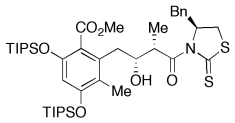
TiPS Protected Catechol. To a 0 °C solution of bis-phenol **89** (530 mg, 2.09 mmol) and 2,6-lutidine (1.21 mL, 10.42 mmol) in CH_2Cl_2 (20 mL) was added TIPSOTf (1.40 mL, 5.21 mmol), dropwise, over 2 min. The reaction was stirred for 15 min at 0 °C then warmed to room temperature and was stirred for 16 h. The reaction was

quenched with saturated aqueous $NaHCO_3$, the layers separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (Hexanes to 5% Ether/Hexanes) afforded bis-TIPS protected aryl ether (1.16 g, 2.04 mmol) in 98% yield as pale yellow oil. IR (film) 2946, 2867, 1738, 1592, 1471, 1324, 1262, 1165, 1068, 997, 882, 832, 793, 685 cm $^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (m, 36H), 1.24 (m, 6H), 2.11 (s, 3H), 3.64 (m, 5H), 3.80 (s, 3H), 6.29 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3, 13.0, 13.1, 17.9, 18.0, 36.3, 51.9, 51.9, 108.2, 119.8, 121.1, 132.4, 151.6, 155.7, 169.0, 171.1; MS (ESI+) for $C_{30}H_{54}O_6Si_2$ [M+Cs] calc 699.2513 found 699.2551.



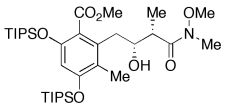
Aldehyde 158 To a -78 °C solution of methyl ester (1.15 g, 2.03 mmol) in CH_2Cl_2 (26 mL) was added 1.0 M DIBAL in hexanes (2.1 mL, 2.05 mmol) over 5 min. After 2 h at -78 °C the reaction was treated with additional 1.0 M DIBAL in hexanes (1.0 mL, 1.00 mmol) and stirred at -78 °C for 1 h. The reaction was quenched at -78 °C with saturated aqueous Rochelle's salt (10 mL) and warmed to room temperature and stirred for 3 hours. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with Na_2SO_4, filtered, and concentrated to yellow oil. Purification by column chromatography (7% EtOAc/Hexanes) afforded aldehyde **158** (847 mg, 1.58 mmol) in 78% yield as yellow oil. IR (film) 2946, 2867, 2763, 2721, 1726, 1590, 1471, 1345, 1258, 1166, 882, 684

cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (m, 36H), 1.26 (m, 6H), 2.07 (s, 3H), 3.60 (d, *J* = 2.0 Hz, 2H), 3.82 (s, 3H), 6.33 (s, 1H), 9.59 (t, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3, 13.0, 13.2, 17.8, 18.0, 46.1, 51.9, 108.4, 120.0, 121.2, 130.5, 151.9, 156.0, 169.1, 198.76; MS (ESI+) for $C_{29}H_{52}O_5Si_2$ [M+Cs] calc 669.2408 found 669.2411.



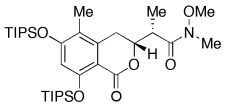
(+)-Alcohol 223 To a yellow 0 °C solution of *N*-acylpropionate thiazolidinethione **197** (703 mg, 2.65 mmol) in CH_2Cl_2 (20 mL) was added $TiCl_4$ (0.30 mL, 0.2.78 mmol), dropwise, over 2 min. The resulting orange slurry was stirred for 15 min at 0 °C and was treated with (-)-sparteine (0.67 mL, 2.65 mmol) over 3 min at 0 °C, giving a deep red solution. The reaction mixture stirred at 0 °C for 20 min then cooled to -78 °C and treated with 1-methyl-2-pyrrolidinone (0.085 mL, 0.85 mmol) over 2 min. The reaction mixture stirred at -78 °C for 10 min and was treated with a solution of aldehyde **158** (1.56 g, 2.91 mmol) in CH_2Cl_2 (5 mL) over 10 min followed by a CH_2Cl_2 rinse (5 mL). The reaction mixture stirred at -78 °C for 1 h then warmed to 0 °C and stirred for 1 h. The reaction mixture was quenched with half-saturated aqueous NH_4Cl (5 mL) and diluted with water (3 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), the organics combined, washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated to yellow oil. Purification by column chromatography (5% EtOAc/Hexanes to 10% EtOAc/ Hexanes gradient) afforded (+)-alcohol **223** (2.00 g, 2.50 mmol) in 94% yield as

bright yellow solids in > 20:1 dr as determined by ^{1}H NMR. $[\alpha]^{19}_D$ = +79.2 (c = 1.0, CH_2Cl_2); IR (film) 3429, 2946, 2868, 1696, 1589, 1469, 1342, 1266, 1166, 1065, 883, 687 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (m, 36H), 1.28 (m, 6H), 1.32 (d, *J* = 6.8 Hz, 3H), 2.16 (s, 3H), 2.63 (dd, *J* = 10.8, 14.0 Hz, 1H), 2.85 (d, *J* = 11.4 Hz, 1H), 2.87 (dd, *J* = 3.2, 14.0 Hz, 1H), 3.06 (dd, *J* = 10.8, 13.0 Hz, 1H), 3.31 (dd, *J* = 3.2, 13.0 Hz, 1H), 3.40 (dd, *J* = 7.2, 11.2 Hz, 1H), 3.87 (s, 3H), 3.90 (d, *J* = 6.8 Hz, 1H), 4.15 (m, 1H), 4.75 (m, 1H), 5.27 (m, 1H), 6.26 (s, 1H), 7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.9, 12.5, 13.1, 13.2, 17.9, 18.0, 32.2, 36.0, 36.7, 45.3, 69.7, 72.0, 107.6, 120.0, 120.7, 127.2, 128.9, 129.5, 136.3, 136.7**,** 151.6, 156.2, 171.4, 176.9, 201.6; MS (ESI+) for $C_{42}H_{67}NO_6S_2Si_2$ [M+K] calc 840.3585 found 840.3582.



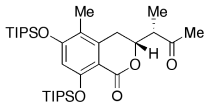
(+)-Weinreb Amide To a bright yellow solution of (+)-alcohol **223** (1.07 g, 1.33 mmol) in CH_2Cl_2 (12 mL) was added imidazole (364 mg, 5.34 mmol) and N,O-dimethylhydroxylamine•HCl (261 mg, 2.67 mmol) at room temperature. The reaction mixture was stirred for 16 h at room temperature and was quenched with saturated aqueous NH_4Cl (10 mL), stirred 5 min, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated to yellow oil. Purification by column chromatography (CH_2Cl_2 to 5% EtOAc/CH_2Cl_2 to 20% EtOAc/CH_2Cl_2) gave(+)-Weinreb amide (835 mg, 1.27 mmol) in 96% yield as clear oil. $[\alpha]^{22}_D$ = +21.1 (c = 0.25, CH_2Cl_2); IR (film) 3457, 2945, 2867, 172, 1589, 1467, 1342, 1266, 1191, 1166,

1066, 996, 882, 686 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.07 (m, 36H), 1.22 (m, 6H), 1.24 (d, *J* = 6.9 Hz, 3H), 2.17 (s, 3H), 2.64 (dd, *J* = 10.0, 14.0 Hz, 1H), 2.84 (dd, *J* = 5.0, 14.0 Hz, 1H), 2.96 (s, 1H), 3.17 (s, 3H), 3.62 (s, 3H), 3.66 (s, 1H), 3.89 (s, 3H), 3.92 (dq, 5.0, 5.0, 5.0, 10.0 Hz, 1H), 6.24 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 12.2, 13.0, 13.1, 13.2, 17.7, 17.9, 31.9, 35.8, 40.4, 51.9, 61.2, 72.3, 107.2, 120.0, 120.7, 128.2, 136.6, 151.2, 155.8, 170.4; MS (ESI+) for $C_{34}H_{63}NO_7Si_2$ [M+Na] calc 676.4041 found 676.4046.

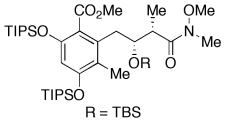


(+)-Lactone 224 To a solution of alcohol (515 mg, 0.787 mmol) in CH_2Cl_2 (25 mL) was treated with trifluoroacetic acid (72 µL, 0.95 mmol) over 2 min. and the solution stirred for at room temperature for 1.5 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and stirred for 5 min. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to yellow oil. Purification by column chromatography (5% to 15% EtOAc/CH_2Cl_2) gave pure (+)-lactone **224** (478 mg, 0.768 mmol) in 98% yield. $[\alpha]^{20}_D$ = +18.1 (c = 0.5,CH_2Cl_2); IR (film) 2944, 2867, 1727, 1661, 1591, 1566, 1472, 1243, 1172, 1076, 883, 733, 685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.11 (m, 36H), 1.28 (m, 6H), 1.33 (d, *J* = 6.8 Hz, 3H), 2.03 (s, 3H), 2.67 (dd, *J* = 10.4, 16.4 Hz, 1H), 2.94 (dd *J* = 2.6, 16.4 Hz, 1H) 3.20 (s, 3H), 3.29 (m, 1H), 3.66 (s, 3H), 4.40 (ddd, *J* = 2.6, 10.4, 10.4 Hz, 1H), 6.28 (s, 1H); ^{13}C NMR (100 MHz) δ 11.7, 13.1, 14.6, 17.9, 29.7, 39.8, 61.6,

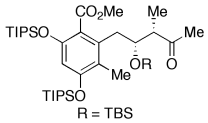
77.9, 109.9, 109.8, 118.3, 140.5, 157.6, 158.9, 162.3, 174.8; MS (ESI+) for $C_{33}H_{59}NO_6Si_2$



(+)-Ketone 225 To a -78 °C solution of (+)-amide **224** (474 mg, 0.762 mmol) in THF (6 mL) was added a 3.0 M solution of methylmagnesium bromide in THF (0.76 mL, 2.286 mmol) over 5 min. The reaction mixture was stirred at -78 °C for 20 min and was then warmed to 0 °C for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL), diluted with water (2 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (4 x 10 mL) and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated to yellow oil. Purification by column chromatography (10% EtOAc/ Hexanes) gave (+)-ketone **225** (401 mg, 0.695 mmol) in 91% yield. $[\alpha]^{20}_D$ +77.4 (c = 0.25, CH_2Cl_2); IR (film) 3854, 2945, 2892, 2867, 1726, 1591, 1566, 1473, 1354, 1243, 1202, 1172, 1069, 882, 852, 828, 685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.10 (m, 36 H), 1.29 (m, 9H), 2.05 (s, 3H), 2.26 (s, 3H), 2.60 (dd, *J* = 11.8, 16.1 Hz, 1H), 2.88 (dd, *J* = 2.6, 16.1 Hz, 1H), 2.94 (m, 1H), 4.44 (m, 1H), 6.29 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7, 12.8, 13.2, 13.3, 17.9, 18.0, 29.5, 30.2, 50.5, 109.5, 109.6, 118.1, 140.4, 157.7, 159.0, 162.2, 209.8; MS (ESI+) for $C_{32}H_{56}O_5Si_2$ [M+Na] calc 599.36 found 599.36.

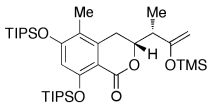


(+)-TBS ether 230 To a -78 °C solution of (+)-Weinreb amide (555 mg, 0.849 mmol) in CH_2Cl_2 (6 mL) was added 2,6-lutidine (0.26 mL, 3.39 mmol) followed by TBSOTf (0.39 mL, 1.70). The reaction was stirred for 60 min at -78 °C and then was quenched with a saturated aqueous solution of $NaHCO_3$ (2 mL), warmed to room temperature and diluted with CH_2Cl_2 (5 mL) and water (1 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (10% EtOAc/Hexanes) afforded (+)-TBS ether **230** (620 mg, 0.807 mmol) as a clear oil in 95% yield. $[\alpha]^{22}_D$ = +19.5 (c = 0.24, CH_2Cl_2); IR (film) 2947, 2868, 1731, 1667, 1589, 1470, 1341, 1257, 1166, 1066, 997, 882, 838, 777, 686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ -0.43 (s, 3H), -0.05 (s, 3H), 0.82 (s, 9H), 1.07 (m, 39H), 1.25 (m, 6H), 2.17 (s, 3H), 2.74 (dd, *J* = 5.2 Hz, 14.0 Hz, 1H), 2.89 (brs, 1H), 2.92 (dd, *J* = 8.4, 14.0 Hz, 1H), 3.14 (s, 3H), 3.48 (s, 3H), 3.84 (s, 3H), 4.20 (m, 1H), 6.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.9, 12.2, 12.9, 13.1, 13.2, 26.1, 36.7, 51.8, 60.9, 73.2, 106.3, 120.5, 121.4, 136.4, 151.0, 155.2,



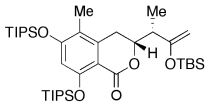
169.6; MS (ESI+) for $C_{40}H_{77}NO_7Si_3$ [M+Cs] calc 900.4062 found 900.4027.

(+)-Ketone 231 To a -78 °C solution of (+)-Weinreb amide **230** (600 mg, 0.781 mmol) in THF (6 mL) was added 3.0 M MeMgBr in Et_2O (0.78 mL, 2.34 mmol). The reaction mixture was stirred for 30 min at -78 °C and then warmed to 0 °C and was stirred for 45 min. The reaction mixture was quenched with saturated aqueous NH_4Cl (2 mL), warmed to room temperature, and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 4 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (5% EtOAc/Hexanes) provided (+)-ketone **231** (539 mg, 0.745 mmol) in 95% yield as clear oil. $[\alpha]^{20}_D$ = +53.6 (c = 0.26, CH_2Cl_2); IR (film) 2947, 2868, 1729, 1589, 1345, 1259, 1192, 1167, 1068, 839, 776, 685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ -0.35 (s, 3H), -0.08 (s, 3H), 0.82 (s, 9H), 1.07 (m, 39H), 1.23 (m, 6H), 2.14 (s, 3H), 2.20 (s, 3H), 2.62 (dd, *J* = 4.8, 14.4 Hz, 1H), 2.71 (m, 2H), 3.82 (s, 3H), 4.18 (m, 1H), 6.21 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.1, 11.8, 12.7, 13.1, 13.3, 17.9, 18.0, 26.0, 30.6, 34.7, 51.7, 52.7, 74.2, 106.7, 120.1, 121.3, 136.1, 151.1, 155.3, 169.5, 210.6; MS (ESI+) for $C_{39}H_{74}O_6Si_3$ [M+Cs] calc 855.3848 found 855.3774.



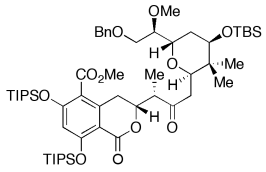
TMS Enolsilane 227. To a 0 °C solution of (+)-ketone **225** (45 mg, 0.078 mmol) in CH_2Cl_2 (0.62 mL) was added *i*-Pr_2NEt (82 µL, 0.47 mmol) followed by TBSOTf (53 µL, 0.234 mmol). The reaction stirred for 30 min a 0 °C and was quenched with saturated aqueous $NaHCO_3$ (0.6 mL) and warmed to room temperature. The

reaction was diluted with water (1 mL) and CH_2Cl_2 (3 mL), the layers separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to minimal volume and filtered through a silica gel plug (3% EtOAc/Hexanes with 1% Et_3N). The filtrate was concentrated to oil, azeotropically dried with toluene, and concentrated for 30 min under high vacuum. The formation of enolsilane **227** was confirmed by ^1H NMR analysis and was then used immediately in the next reaction without further analysis as it showed significant moisture sensitivity. ^1H NMR (400 MHz, C_6D_6) δ 0.20 (s, 9H), 1.08 (m, 36H), 1.28 (m, 9H), 2.07 (s, 3H), 2.40 (m, 1H), 2.66 (dd, *J* = 10.8, 16.4 Hz, 1H), 2.95 (dd, *J* = 2.8, 16.4 Hz, 1H), 4.07 (s, *J* = 14.4 Hz, 2H), 4.17 (m, 1H), 6.30 (s, 1H).



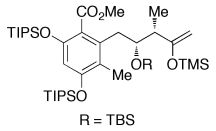
TBS Enolsilane 229 To a 0 °C solution of (+)-ketone **225** (45 mg, 0.078 mmol) in CH_2Cl_2 (0.62 mL) was added *i*-Pr_2NEt (82 µL, 0.47 mmol) followed by TBSOTf (53 µL, 0.234 mmol). The reaction stirred for 30 min a 0 °C and was quenched with saturated aqueous $NaHCO_3$ (0.6 mL) and warmed to room temperature. The reaction was diluted with water (1 mL) and CH_2Cl_2 (3 mL), the layers separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to minimal volume and filtered through a silica gel plug (3% EtOAc/Hexanes with 1% Et_3N). The filtrate was concentrated to oil, azeotropically dried with toluene, and concentrated for 30 min

under high vacuum. The formation of enolsilane **229** was confirmed by ^{1}H NMR analysis and was then used immediately in the next reaction without further analysis as it showed significant moisture sensitivity. ^{1}H NMR (400 MHz, C_6D_6) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.80 (s, 9H), 1.11 (m, 18H), 1.24 (m, 24H), 1.54 (m, 3H), 2.08 (s, 3H), 2.34 (m, 2H), 2.84 (dd, *J* = 2.4, 16.0 Hz, 1H), 3.96 (s, 2H), 4.16 (m, 1H), 6.60 (s, 1H).



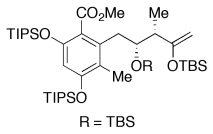
(+)-Tetrahydropyran 233: TBS Enolsilane Method: A -40 °C solution of lactol-acetate (30 mg, 0.049 mmol) in CH_2Cl_2 (0.22 mL) was treated with $BF_3{\cdot}OEt_2$ (12.5 µL, 0.099 mmol) and stirred at -40 °C for 3 min. The reaction was then treated with a solution of enolsilane (45 mg, 0.074 mmol) in CH_2Cl_2 (0.15 mL) dropwise over 3 min. The reaction stirred at -40 °C for 30 min and was then treated with additional $BF_3{\cdot}OEt_2$ (6.2 µL, 0.049 mmol) and stirred for 30 min at -40 °C. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (0.3 mL) and warmed to room temperature. The layers were separated and the aqueous was extracted with CH_2Cl_2 (3 x 1 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (10 to 25% Et_2O/Hexanes gradient) afforded the desired (+)-tetrahydropyran **233** (8.5 mg, 0.0095 mmol) in 19% yield as well as ketone **225** (22 mg, 0.038 mmol) for a 64% yield based on recovered ketone. $[\alpha]^{20}_D$ + 44.1 (c = 0.26, CH_2Cl_2); IR (film) 2946, 2866, 1729, 1591, 1566, 1471, 1412, 1358, 1245, 1172, 1070, 882, 835, 686 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ0.04 (s, 3H), 0.05 (s, 3H), 0.86 (s, 3H), 0.89 (s, 9H), 0.91 (s, 3H), 1.11 (m,

36 H), 1.25 (m, 9H), 1.65 (m, 1H), 1.94 (m, 1H), 2.03 (s, 3H), 2.54 (m, 2H), 2.91 (m, 3H)3.45 (m, 1H), 3.48 (s, 3H), 3.59 (m, 2H), 3.66 (m, 1H), 3.89 (m, 2H), 4.44 (m, 1H), 4.54 (s, 2H), 6.30 (s, 1H)7.32 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.0, -4.2, 11.8, 12.7, 13.1, 13.3, 18.0, 18.0, 18.0, 24.2, 25.8, 29.6, 29.8, 38.2, 42.6, 51.1, 58.6, 69.4, 72.8, 73.4, 75.2, 79.1, 109.5, 109.5, 118.1, 127.4, 127.6, 128.3, 138.6, 140.5, 157.7, 159.0, 162.4, 210.4; MS (ESI+) for $C_{55}H_{94}O_9Si_3$ [M+Cs] calc 1115.5260 found 1115.5308.

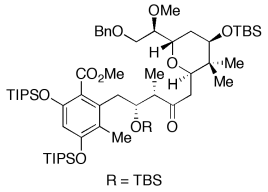


TMS Enolsilane 232. A 0 °C solution of ketone (54 mg, 0.075 mmol) in CH_2Cl_2 (0.6 mL) was treated with *i*-Pr_2NEt (0.8 mL, 0.45 mmol) followed by TMSOTf (41 µL, 0.224 mmol). After 60 min the reaction was then quenched with a saturated solution of aqueous $NaHCO_3$ (0.5 mL) and warmed to room temperature. The reaction was then diluted with saturated aqueous $NaHCO_3$ (1 mL) and CH_2Cl_2 (1 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL) and the combined organics were dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (1% Et_3N/Hexanes to 5% EtOAc/Hexanes with 1% Et_3N) gave (59 mg, 0.075 mmol) for a yield of 100%. The formation of enolsilane **232** was confirmed by ^{1}H NMR analysis and was then used immediately in the next reaction without further analysis as it showed significant moisture sensitivity. ^{1}H NMR (400 MHz C_6D_6) δ -0.17 (s, 3H), 0.13 (s, 3H), 0.18 (s, 9H), 1.01

(m, 9H), 1.16 (m, 36H), 1.27 (m, 9H), 2.32 (m, 1H), 2.44 (s, 3H), 3.12 (m, 2H), 3.70 (s, 3H), 4.21 (d, J = 18.0 Hz, 3H), 4.40 (m, 1H), 6.47 (s, 1H).



TBS Enolsilane 192 To a 0 °C solution of ketone **231** (231 mg, 0.319 mmol) in CH_2Cl_2 (2.5 mL) was added *i*-Pr_2NEt (0.33 mL, 1.92 mmol) followed by TBSOTf (0.22 mL, 0.958 mmol). The reaction stirred for 90 min a 0 °C and was quenched with saturated aqueous $NaHCO_3$ (2.5 mL) and warmed to room temperature. The reaction was diluted with water (1 mL) and CH_2Cl_2 (3 mL), the layers separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to minimal volume and filtered through a silica gel plug (3% EtOAc/Hexanes with 1% Et_3N). The filtrate was concentrated to oil, azeotropically dried with toluene, and concentrated for 30 min under high vacuum. The formation of enolsilane **192** was confirmed by ^1H NMR analysis and was then used immediately in the next reaction without further analysis as it showed significant moisture sensitivity. ^1H NMR (400 MHz C_6D_6) δ -0.32 (s, 3H), -0.05 (s, 3H), -0.08 (s, 3H), 0.14 (s, 3H), 0.84 (s, 9H), 0.88 (s, 9H), 1.01 (d, J = 7.2 Hz, 3H), 1.11 (m, 36H), 1.27 (m, 6H), 2.14 (m, 1H), 2.18 (s, 3H), 2.86 (m, 2H), 3.82 (s, 3H), 4.08 (m, 3H), 6.19 (s, 1H).



(+)-Tetrahydropyran 234

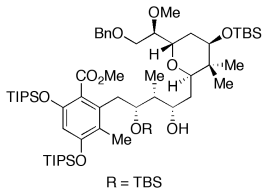
TMS Enolsilane Method: A -40 °C solution of (-)-acetate **193** (16.0 mg, 0.034 mmol) in CH_2Cl_2 (0.2 mL) was treated with $BF_3{\cdot}OEt_2$ (8.7 µL, 0.069 mmol), stirred for 4 min, then treated with a 5.0 M solution of enolsilane **192** in CH_2Cl_2 (137 µL, 0.069 mmol) and stirred 30 min at-40 °C. The reaction was quenched with sat'd aqueous NH_4Cl (0.1 mL) and warmed to room temperature. The reaction mixture was then diluted with CH_2Cl_2 (3 mL) and water (1 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude material was purified by column chromatography (5% to 10% EtOAc/Hex gradient) to afford (+)-tetrahydropyran **234** (15.5 mg, 0.014 mmol) and recovered (-)-acetate **193** (6.9 mg, 0.015 mmol).

TBS Enolsilane Method A: A mixture of acetate **193** (20.0 mg, 0.043 mmol) and enolsilane **192** (54 mg, 0.064 mmol) were azeotropically dried with toluene at 55 °C then dried further for 45 min under high vacuum. The mixture was then flushed with argon over 5 min, dissolved in CH_2Cl_2 (0.2 mL) and cooled to -40 °C. The clear solution was treated with $BF_3{\cdot}OEt_2$ (11 µL, 0.086 mmol) and stirred at -40 °C for 30 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (0.2 mL), warmed to room temperature and diluted with CH_2Cl_2 (3 mL) and water (1 mL). The layers were separated. and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL).

The combined organic layers were washed with brine (1 × 2 mL), dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (5% EtOAc/Hex to 10% EtOAc/Hex) gave the product **234** (18 mg, 0.016 mmol) in 37% yield.

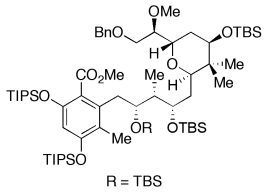
TBS Enolsilane Method B: A -40 °C solution of (-)-lactol-acetate **193** (103.0 mg, 0.221 mmol; azeotropically dried with toluene and dried further under high vacuum over 1 h immediately prior to use) in CH_2Cl_2 (1 mL) was treated with $BF_3{\cdot}OEt_2$ (56 µL, 0.44 mmol) and stirred at -40 °C for 2 min. The reaction was then treated with a 0.5 M solution of enolsilane **192** (0.54 mL, 0.27 mmol) in CH_2Cl_2 over 5 min followed by CH_2Cl_2 rinse (0.2 mL). The reaction stirred for 30 min at -40 °C and was then treated with a second portion of $BF_3{\cdot}OEt_2$ (28 µL, 0.22 mmol) and stirred for 30 min. The reaction was quenched with saturated aqueous NH_4Cl (1 mL), warmed to room temperature, then diluted with CH_2Cl_2 (3 mL) and water (1 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), the combined organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (5% EtOAc/Hexanes to 8% EtOAc/Hexanes) afforded (+)-tetrahydropyran **234** (144 mg, 0.13 mmol) in 59% yield as clear oil as well as recovered (+)-ketone **231** (103 mg, 0.14 mmol) for 85% yield based on recovered ketone. $[\alpha]^{20}_D$ = +49.1 (c = 0.25, CH_2Cl_2); IR (film) 2947, 2864, 1733, 1586, 1471, 1259, 1166, 882, 837 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ -0.19 (s, 3H), 0.04 (s, 3H), 0.08 (s, 3H), 0.10 (s, 3H), 0.97 (m, 21H), 1.14 (m, 39H), 1.26 (d, *J* = 6.9 Hz, 3H), 1.29 (m, 9H), 1.82 (ddd, *J* = 6.7, 11.7, 13.2 Hz, 1H), 2.14 (dd, *J* = 3.6, 13.2 Hz, 1H), 2.36 (s, 3H), 2.68 (d, *J* = 15.0 Hz, 1H) 2.87 (dd, *J* = 3.7, 6.9 Hz, 1H), 2.96 (m, 3H), 3.65 (m, 1H), 3.67 (s, 3H), 3.74 (dd, *J* = 5.8, 10.3 Hz, 1H), 3.79, (m, 1H), 3.96 (dd, *J* = 1.9, 10.3 Hz, 1H), 4.04 (t, *J* = 6.7 Hz,

1H), 4.09 (d, 9.5 Hz, 1H), 4.46 (m, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.70 (d, *J* = 12.0 Hz, 1H), 6.47 (s, 1H), 7.10 (t, 7.5, 7.5 Hz, 2H), 7.21 (t, *J* = 7.5, 7.5 Hz, 1H), 7.46 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ -4.7, -4.0, 12.5, 13.2, 13.5, 13.6, 13.8, 18.2, 18.2, 18.3, 23.7, 26.1, 26.4, 30.3, 35.4, 39.0, 44.5, 51.5, 54.2, 58.6, 71.2, 72.0, 73.3, 73.8, 75.1, 75.3, 79.0, 107.1, 121.4, 121.8, 127.5, 127.9, 128.2, 137.2, 139.7, 151.6, 155.5, 169.3, 210.4; MS (ESI+) for $C_{62}H_{112}O_{10}Si_4$ [M+Cs] calc 1261.6387 found 1261.638.



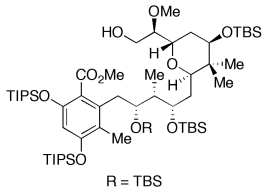
(+)-Alcohol 235 A vacuum dried, argon flushed vial containing ketone **234** (128 mg, 0.113 mmol) was charged with CH_2Cl_2 (0.55 mL) and cooled to -25 °C external temperature. The solution was then treated dropwise with a 1.0 M solution of Me_2AlCl (0.55 mL, 0.566 mmol) over 10 min and stirred for an additional 2 min. The reaction was then treated with *n*-Bu_3SnH (84 µL, 0.312 mmol; 2.75 eq) over 5 min at -25 °C. followed by treatment with additional *n*-Bu_3SnH (99 µL; 3.25 eq) dropwise over 2 h (3 µL, 0.1 equiv, every 4 min).The reaction gradually warmed to -10 °C for over 45 min and was then quenched with saturated aqueous $NaHCO_3$ (2 mL). he reaction was diluted with CH_2Cl_2 (10 mL) and water (5 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layers were then washed with brine (5 mL), dried with Na_2SO_4, filtered through a cotton plug, and concentrated. Purification by plug column chromatography (Hexanes to 5% EtOAc/Hex) afforded a mixture of isomers (117

mg, 0.103 mmol) in 91% yield as a 3:1 ratio of diastereomers by NMR. Purification by column chromatography (Hexanes to 5% EtOAc/Hex) afforded the desired isomer (89 mg, 0.079 mmol) for a 70% isolated yield of(+)-alcohol **235**. $[\alpha]^{21}_{D}$ = +30.6 (c = 0.26, CH_2Cl_2); IR (film) 3508, 2948, 2866, 1729, 1589, 1470, 1344, 1256, 1165, 1070, 881, 836, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ -0.43 (s, 3H), -0.11 (s, 3H), -0.08 (s, 6H), 0.81 (s, 9H), 0.88 (s, 3H), 0.91 (s, 3H), 0.92 (s, 9H), 0.99 (d, *J* = 6.5 Hz, 3H), 1.12 (m, 36H), 1.28 (m, 6H), 1.58 (m, 1H), 1.74 (m, 3H), 1.97 (m, 1H), 2.19 (s, 3H), 2.72 (m, 1H), 2.97 (dd, *J* = 10.5, 13.5 Hz, 1H), 3.50 (s, 3H), 3.53 (m, 1H), 3.61 (m, 3H), 3.81 (m, 4H), 3.92 (m, 1H), 3.98 (m, 1H), 4.05 (m, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 2H), 6.21 (s, 1H), 7.33 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.33, -5.09, -4.99, -4.22, 11.19, 12.95, 12.99, 13.17, 17.87, 17.88, 17.98, 18.01, 23.84, 25.75, 25.93, 29.71, 33.00, 34.88, 39.03, 45.73, 51.63, 58.42, 69.13, 70.69, 71.77, 72.32, 73.36, 77.25, 78.90, 81.92, 106.04, 119.85, 121.43, 127.43, 127.53, 127.58, 128.20, 128.23, 137.80, 138.21, 150.79, 154.95, 169.66; MS (ESI+) for $C_{62}H_{114}O_{10}Si_4$ [M+Cs] calc 1263.654 found 1263.652.



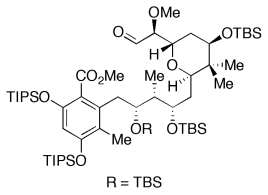
(+)-TBS ether To a 0 °C solution of (+)-alcohol **235** (154 mg, 0.136 mmol) in CH_2Cl_2 (0.7 mL) was added 2,6-lutidine (40 µL, 0.544 mmol) followed by TBSOTf (63 µL, 0.272 mmol). The reaction stirred for 15 min and was warmed to room temperature over 1 h, stirred 15 h at room temperature, and was quenched with $NaHCO_3$ (0.5 mL) and CH_2Cl_2 (0.5 mL). The layers were separated and the aqueous phase was

extracted with CH_2Cl_2 (4 x 3 mL), the organics combined, dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (Hexanes to 3% EtOAc/ Hexanes) gave (+)-TBS ether (144 mg, 0.116 mmol) in 85% yield as clear oil. $[\alpha]^{25}_D$ = +25.3 (c = 0.25, CH_2Cl_2); IR (film) 2949, 2866, 1729, 1588, 1256, 1165, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ -0.42 (s, 3H), -0.15 (s, 3H), 0.06 (m, 12H), 0.87 (m, 33H), 1.09 (m, 39H), 1.28 (m, 6H), 1.59 (m, 2H), 1.75 (m, 2H), 1.89 (m, 1H), 2.20, (s, 3H), 2.73 (m, 1H), 2.80 (m 1H), 3.35 (d, *J* = 8.4 Hz, 1H), 3.46 (s, 3H), 3.52 (m, 3H), 3.72 (d, *J* = 8.8 Hz, 2H) 3.81 (s, 3H), 3.98 (brs, 2H), 4.54 (m, 2H), 6.18 (s, 1H), 7.28 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.0, -4.7, -4.7, -4.2, -3.2, -1.0, 10.6, 13.1, 13.2, 17,9, 18.0, 18.0, 18.1, 18.1, 18.1, 24.6, 25.9, 26.1, 26.3, 29.7, 29.9, 33.9, 35.2, 38.6, 43.2, 51.5, 58.7, 69.5, 71.0, 73.2, 73.4, 79.3, 106.1, 120.5, 121.3, 127.8, 127.4, 128.1, 137.5, 138.8, 150.9, 155.0, 169.5; MS (ESI+) for $C_{68}H_{128}O_{10}Si_5$ [M+Cs] calc 1377.741 found 1377.744



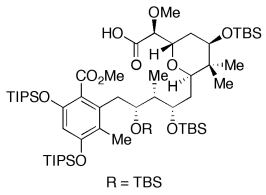
(+)-Alcohol 236. A degassed solution of (+)-benzyl ether (106 mg, 0.085 mmol) in THF (0.57 mL) was purged with H_2 and treated with $Pd(OH)_2/C$ (24 mg). The reaction mixture was stirred under H_2 atmosphere for 5 h and was filtered through Celite®, washed with EtOAc (15 mL), and concentrated to clear oil. Purification by plug column chromatography (5% EtOAc/Hexanes) gave (+)-alcohol **236** (99 mg, 0.085 mmol) in quantitative yield as waxy white solids. $[\alpha]^{22}_D$ = +22.0 (c = 0.25 CH_2Cl_2); IR (film) 3507, 2949, 2866, 1729, 1589, 1471, 1255, 1165, 835, 773 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ -0.31 (s, 3H), -0.12 (s, 3H), 0.32 (s, 6H), 0.07 (m, 6H), 0.80 (s, 3H), 0.82 (s, 9H), 0.88 (s, 3H), 0.88 (m, 21H), 1.09 (m, 36H), 1.21 (m, 6H), 1.56 (m, 2H), 1.72 (m, 1H), 1.80 (m, 2H), 2.19 (s, 3H), 2.45 (brs 1H), 2.77 (m, 2H), 3.31 (m, 2H), 3.41 (s, 3H), 3.46 (m, 1H), 3.67 (m, 2H), 3.72 (s, 1H), 3.81 (s, 3H), 3.97 (m, 2H), 6.17 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.0, -4.8, -4.4, -4.2, -3.3, 1.0, 10.6, 12.9, 13.3, 13.5, 17.9, 18.0, 18.1, 18.1, 18.2, 24.5, 25.8, 26.0, 26.2, 29.7 30.4, 33.5, 35.7, 38.6, 51.7 58.1 61.5 69.9 73.0, 75.6, 80.54, 106.2, 120.4, 121.2 137.2 150.9 155.1 169.8; MS (ESI+) for $C_{61}H_{122}O_{10}Si_5$ [M+Cs] calc 1287.694 found 1287.694



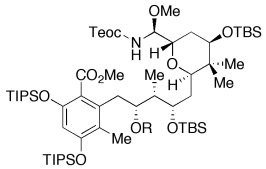
(+)-Aldehyde To a solution of 2.0 M oxalyl chloride in CH_2Cl_2 (85 µL, 0.170 mmol) in CH_2Cl_2 (0.27 mL) at -78 °C was added a solution of DMSO (24 µL, 0.339 mmol) diluted with CH_2Cl_2 (24 µL). The resultant solution stirred at -78 °C for 25 min and was then treated dropwise with a solution of (+)-alcohol **236** (98 mg, 0.085 mmol) in CH_2Cl_2 (0.3 mL) at -78 °C, followed by CH_2Cl_2 rinse (2 x 0.1 mL). The resulting cloudy white mixture was stirred at -78 °C for 1 h and was treated with triethylamine (50.0 µL, 0.339 mmol) and stirred for 30 min at -78 °C. The reaction mixture was warmed to 0 °C for 1 h and quenched with saturated $NaHCO_3$. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 4 mL), the combined organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by plug column (Hexanes to 4% Ethyl Acetate/Hexanes) afforded (+)-

aldehyde (75.5 mg, 0.065 mmol) in 79% yield. $[\alpha]^{25}_{D}$ = +26.0 (c = 0.25, CH_2Cl_2); IR (film) 2949, 2866, 2732, 2713, 1731, 1589, 1471, 1256, 1165, 836, 773 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ -0.39 (s, 3H), -0.12 (s, 3H), 0.03 (s, 6H), 0.08 (m, 6H), 0.80 (s, 3H), 0.82 (m, 6H), 0.88 (m, 27H), 1.09 (m, 36H), 1.22 (m, 6H), 1.52 (m, 1H), 1.63 (m, 1H), 1.75 (m, 3H), 2.19 (s, 3H), 2.77 (m, 2H), 3.42 (s, 3H), 3.50 (m, 3H), 3.72 (m, 1H), 3.81 (s, 3H), 3.94 (m, 2H), 6.17 (s, 1H), 9.66 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.2, -5.0, -4.7, -4.6, -4.4, -3.2, -3.1, 1.0, 10.2, 10.4, 12.9, 13.1, 13.2, 17.9, 18.0, 18.1, 18.1, 22.2, 24.7, 25.9, 26.1, 26.2, 26.3, 29.6, 29.7, 30.2, 33.8, 34.4, 38.4, 43.8, 51.6, 58.8, 59.2, 69.1, 72.9, 84.3, 85.7, 106.0, 120.4, 121.4, 137.5, 150.8, 155.0, 169.7, 202.1; MS (ESI+) for $C_{61}H_{120}O_{10}Si_5$ [M+Cs] calc 1285.768 found 1285.675.



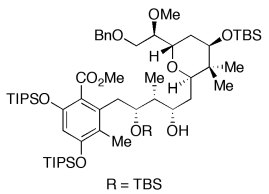
(+)-Acid 237 To a solution of (+)-aldehyde (75 mg, 0.065 mmol) in *t*-BuOH (3 mL) was added 2-methyl-2-butene (0.17 mL, 1.156 mmol) followed by dropwise addition of a pre-made solution of $NaClO_2$ (71 mg, 0.780 mmol) in 0.05 M potassium biphthalate pH 4 buffer (3 mL). The yellow solution stirred for 1 h, gradually becoming clear and colorless. The reaction was then diluted with brine (10 mL) and EtOAc (10 mL) and stirred for 5 min. The layers were separated and the aqueous was extracted with EtOAc (4 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and absorbed on silica gel. Purification by column chromatography (5% EtOAc/Hexanes) afforded (+)-acid **237** (67 mg, 0.057 mmol) in

88% yield over two steps. $[\alpha]^{22}_D$ = +25.7 (c = 0.25, CH_2Cl_2); IR (film) 3168, 2949, 2866, 1721, 1589, 1471, 1255, 1166, 1069, 882, 836, 774 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ -0.48 (s, 3H), -0.15, (s, 3H), 0.03 (s, 3H), 0.04 (s, 3H), 0.10 (s, 3H), 0.11 (s, 3H), 0.80 (m, 15H), 0.90 (m, 21H), 1.10 (m, 36H), 1.21 (m, 6H), 1.50 (m, 1H), 1.66 (m, 1H), 1.74 (m, 1H), 1.87 (m, 1H), 1.94 (m, 1H), 2.18 (s, 3H), 2.77 (m, 2H), 3.47 (m, 4H), 3.53 (m, 1H), 3.83 (s, 3H), 3.88 (m, 2H), 4.06 (m, 1H), 4.17 (m, 1H), 6.17 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.0, -4.9, -4.7, -4.6, -4.5, -4.4, -4.3, -3.0, 1.0, 10.2, 13.1, 13.2, 17.9, 18.0, 18.1, 18.1, 18.2, 20.2, 22.3, 22.7, 24.5, 25.2, 25.8, 26.0, 26.2, 26.3, 26.5, 29.7, 29.9, 34.0, 34.7, 38.0, 43.5, 51.9, 59.1, 69.3, 72.8, 75.5, 81.4, 105.9, 120.2, 121.3, 137.7, 151.0, 170.1, 172.4; MS (ESI+) for $C_{61}H_{120}O_{11}Si_5$ [M+Cs] calc 1301.673 found 1301.679.



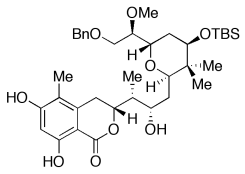
(+)-Teoc-Protected Hemiaminal 238 A 0 °C solution of (+)-carboxylic acid **237** (11.0 mg, 0.009 mmol) in anhydrous acetone (0.75 mL) was treated with triethylamine (3.1 µL, 0.023 mmol) followed by ethylchloroformate (2.0 µL, 0.021 mmol) and stirred at 0 °C for 30 min. The reaction mixture was then treated with a 0.62 M aqueous solution of NaN_3 (30 µL, 0.019 mmol), stirred at 0 °C for 2 h, poured into ice water (3 mL) and extracted with cold ether (5 x 3 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated at 30 °C. The residue was dissolved in toluene, dried again over Na_2SO_4, filtered, flushed with argon and set into a pre-heated 120 °C sand bath and stirred for 40 min. The reaction mixture was cooled to

50 °C and the solvent removed *in vacuo*. The residue was cooled to room temperature and charged with anhydrous DMF (50 µL). The solution was treated with β-trimethylsilylethanol (47 µL , 0.33 mmol) followed by copper(I) chloride (1.0 mg, 0.009 mmol), giving a pale green mixture. The reaction mixture stirred for 2 h giving a more intense green mixture that was diluted with water (2 mL) and ether (2 mL). The layers were separated and the aqueous layer was extracted with ether (4 x 2 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to clear oil. Purification by column chromatography (3.5% ether/ hexanes) afforded (+)-hemiaminal **238** (9.1 mg, 0.007 mmol) in 76% yield as clear oil. $[\alpha]^{25}_D$ = +30.3 (c = 0.25, CH_2Cl_2); IR (film) 3436, 2950, 2866, 1730, 1588, 1471, 1252, 1166, 1067, 836, 773; ^{1}H NMR (500 MHz, $CDCl_3$) δ -0.51 (s, 3H), -0.10 (s, 3H), 0.03 (m, 15H), 0.07 (s, 6H), 0.81 (m, 12H), 0.88 (s, 9H), 0.89 (m, 12H), 1.01 (m, 2H), 1.09 (m, 36H), 1.25 (m, 9H), 1.49 (m, 1H), 1.57 (m, 1H), 1.79 (m, 3H), 2.19 (s, 3H), 2.70 (m, 1H), 2.85 (dd, *J* = 10.5, 14.5 Hz, 1H), 3.32 (s, 3H), 3.41 (m, 1H), 3.52 (m, 1H), 3.84 (s, 3H), 3.86 (m, 1H), 3.95 (m, 2H), 4.12 (m, 1H), 4.22 (m, 1H), 4.90 (m, 1H), 5.30 (brs, 1H), 6.16 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.0, -4.8, -4.6, -4.4, -4.4, -1.5, 0.7, 1.0, 1.3, 10.4, 13.0, 13.1, 13.2, 13.3, 17.6, 17.8, 17.9, 18.0, 18.1, 22.7, 23.7, 25.8, 25.9, 26.0, 26.1, 26.2, 29.7, 31.0, 33.7, 38.2, 42.6, 51.7, 55.4, 63.1, 69.3, 72.9, 82.3, 105.9, 120.2, 121.5, 137.7, 150.9, 154.9, 157.0, 169.8; MS (ESI+)



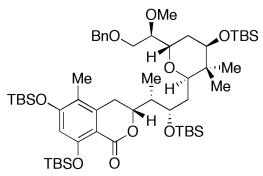
for $C_{66}H_{133}NO_{11}Si_6$ [M+Cs] calc 1416.7549 found 1416.753.

(+)-Alcohol 235 A room temperature solution of (+)-ketone **234** (103 mg, 0.091 mmol) in THF (2.2 mL) was treated with (R)-2-methyl-CBS-oxazaborolidine 1 M in toluene (0.18 mL, 0.18 mmol) followed by 1 M BH_3·THF in THF (0.18 mL, 0.18 mmol) and stirred for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$, diluted with CH_2Cl_2 and stirred for 15 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography (8% EtOAc/Hexanes) to give (+)-alcohol **235** (84 mg, 0.074 mmol) in 82% yield as clear oil. $[\alpha]^{21}_D$ = +30.6 (c = 0.26, CH_2Cl_2); IR (film) 3508, 2948, 2866, 1729, 1589, 1470, 1344, 1256, 1165, 1070, 881, 836, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ -0.43 (s, 3H), -0.11 (s, 3H), -0.08 (s, 6H), 0.81 (s, 9H), 0.88 (s, 3H), 0.91 (s, 3H), 0.92 (s, 9H), 0.99 (d, *J* = 6.5 Hz, 3H), 1.12 (m, 36H), 1.28 (m, 6H), 1.58 (m, 1H), 1.74 (m, 3H), 1.97 (m, 1H), 2.19 (s, 3H), 2.72 (m, 1H), 2.97 (dd, *J* = 10.5, 13.5 Hz, 1H), 3.50 (s, 3H), 3.53 (m, 1H), 3.61 (m, 3H), 3.81 (m, 4H), 3.92 (m, 1H), 3.98 (m, 1H), 4.05 (m, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 2H), 6.21 (s, 1H), 7.33 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.33, -5.09, -4.99, -4.22, 11.19, 12.95, 12.99, 13.17, 17.87, 17.88, 17.98, 18.01, 23.84, 25.75, 25.93, 29.71, 33.00, 34.88, 39.03, 45.73, 51.63, 58.42, 69.13, 70.69, 71.77, 72.32, 73.36, 77.25, 78.90, 81.92, 106.04, 119.85, 121.43, 127.43, 127.53, 127.58, 128.20, 128.23, 137.80, 138.21, 150.79, 154.95, 169.66;



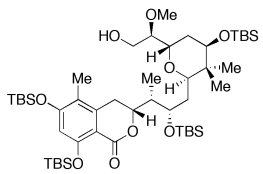
MS (ESI+) for $C_{62}H_{114}O_{10}Si_4$ [M+Cs] calc 1263.654 found 1263.652.

(+)-Lactone 243 To a 0 °C solution of (+)-silyl ether **235** (70 mg, 0.062 mmol) in DMF (1.0 mL) was added 1.0 M TBAF in THF (0.37 mL, 0.37 mmol) and the reaction stirred for 2 h at 0 °C. The reaction was quenched with saturated aqueous NH_4Cl, the layers were separated, and the aqueous layer was extracted with EtOAc (5 x 2 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to orange oil. Purification by column chromatography (25% EtOAc/ Hexanes to 40% EtOAc/Hexanes) provided the (+)-lactone **243** (32 mg, 0.048 mmol) in 77% yield as white waxy solid. $[\alpha]^{23}_D$ = +29.1 (c = 0.26, CH_2Cl_2); IR (film) 3378, 2929, 2857, 1661, 1619, 1496, 1470, 1374, 1253, 1172, 1102, 836, 775, 737, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.89 (s, 3H), 0.90 (s, 9H), 0.94 (s, 3H), 1.11 (d, *J* = 7.0 Hz, 3H), 1.50 (d, *J* = 15.3 Hz, 1H), 1.57 (m, 1H), 1.93 (m, 5H), 2.15 (m, 1H), 2.81 (dd, 12.3, 16.5 Hz, 1H), 2.98 (dd, *J* = 3.0, 16.5 Hz, 1H), 3.45 (s, 3H), 3.49 (q, *J* = 5.0, 8.6 Hz, 1H), 3.59 (m, 3H), 3.76 (dd, *J* = 3.5, 10.7 Hz, 1H), 4.04 (d, *J* = 10.0 Hz, 1H), 4.17 (q, *J* = 5.9, 10.7 Hz, 1H), 4.25 (brs, 1H), 4.48 (ddd, *J* = 3.0, 6.3, 12.3 Hz, 1H), 4.52 (d, *J* = 11.9 Hz, 1H), 4.58 (d, *J* = 11.9 Hz, 1H), 6.29 (s, 1H), 7.28 (m, 6H), 11.17 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.0, -4.3, 9.6, 10.5, 18.0, 25.0, 25.8, 28.1, 30.2, 32.3, 38.5, 42.8, 58.4, 69.0, 72.7, 72.7, 73.5, 80.5, 80.6, 82.6, 101.2, 101.4, 113.6, 127.7, 127.7, 128.4, 138.0, 139.8, 161.4, 162.2, 170.8; MS (ESI



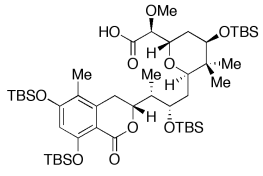
+) for $C_{37}H_{56}O_9Si$ [M+Cs] calc 805.2748 found 805.2814.

(+)-TBS ether To a 0 °C solution of (+)-triol **243** (31 mg, 0.046 mmol) in THF (0.4 mL) was added 2,6-lutidine (27 µL, 0.37 mmol) followed by TBSOTf (42 µL, 0.18 mmol). The reaction stirred for 2 h at 0 °C and was quenched with $NaHCO_3$ (0.4 mL) and diluted with CH_2Cl_2 (0.4 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 2 mL), the organics combined, dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (Hexanes to 5% EtOAc/Hexanes) gave (+)-TBS ether (39 mg, 0.038 mmol) in 83% yield as clear oil. $[\alpha]^{25}_D$ = +46.5 (c = 0.49, CH_2Cl_2); IR (film) 2955, 2930, 2857, 1725, 1592, 1568, 1472, 1360, 1252, 1166, 1069, 1005, 837, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.08 (s, 3H), 0.08 (s, 3H), 0.10 (s, 3H), 0.25 (s, 3H), 0.27 (m, 9H), 0.84 (s, 9H), 0.09 (s, 3H), 0.93 (s, 9H), 0.96 (s, 3H), 1.05 (s, 9H), 1.05 (s, 9H), 1.10 (d, *J* = 6.7 Hz, 3H), 1.65 (m, 2H), 2.00 (m, 3H), 2.05 (s, 3H), 2.60 (dd, *J* = 12.2, 16.1 Hz, 1H), 2.99 (m, 1H), 3.37 (m, 1H), 3.50 (s, 3H), 3.51 (m, 1H), 3.61 (m, 2H), 3.71 (dd, *J* = 3.6, 10.3 Hz, 1H), 4.01 (q, *J* = 5.5, 10.9 Hz, 1H), 4.13 (m, 1H), 4.26, (m, 1H), 4.56 (s, 2H), 6.34 (s, 1H), 7.28 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.9, -4.8, -4.4, -4.4, -4.3, -4.2, -4.2, -3.4, 9.0, 11.8, 18.0, 18.1, 18.3, 18.6, 25.2, 25.7, 25.8, 25.9, 29.9, 30.0, 33.1, 38.2, 40.1, 58.6, 68.7, 69.3, 69.6, 73.3, 73.5, 76.3, 77.2, 79.0, 80.7, 110.6, 110.7, 118.6, 127.4, 127.5, 128.3, 138.3, 141,2, 156.9, 158.3, 163.4; MS (ESI



+) for $C_{55}H_{98}O_9Si_4$ [M+Cs] calc 1147.5342 found 1147.5349.

(+)-Alcohol 244 A degassed solution of (+)-benzyl ether (41 mg, 0.040 mmol) in THF was purged with H_2 and treated with $Pd(OH)_2/C$ (11 mg). The reaction mixture stirred under H_2 pressure for 14 h and was filtered through Celite®, washed with EtOAc (15 mL), and concentrated to yellow oil. Purification by plug column (10% EtOAc/Hexanes) gave (+)-alcohol **244** (37 mg, 0.040 mmol) in quantitative yield as glassy white solids. $[\alpha]^{25}_D$ = +39.2 (c = 0.24, CH_2Cl_2); IR (film) 3460, 2955, 2930, 2885, 2857, 1708, 1592, 1567, 1472, 1360, 1253, 1166, 1069, 837, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 3H) 0.06 (s, 3H), 0.07 (s, 3H), 0.10 (s, 3H), 0.22 (s, 3H), 0.23 (s, 3H), 0.24 (s, 6H), 0.84 (s, 9H), 0.85 (s, 3H), 0.90 (s, 9H), 0.91 (s, 3H), 1.01 (s, 18H), 1.04 (d, *J* = 6.8 Hz, 3H), 1.70 (m, 2H), 1.91 (m, 2H), 1.99 (m, 1H), 2.07 (s, 3H), 2.74 (dd, *J* = 12.8, 16.4 Hz, 1H), 2.99 (m, 1H), 3.22 (m, 1H), 3.32 (m, 1H), 3.43 (m, 1H), 3.55 (s, 3H), 3.59 (m, 1H), 3.64 (m, 1H), 3.80 (m, 1H), 4.03 (m, 1H), 4.24 (m, 2H), 6.29 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.9, -4.6, -4.3, -4.2, -4.2, -4.1, -3.2, 8.6, 11.7, 18.0, 18.1, 18.3, 18.5, 24.8, 25.7, 25.9, 25.9, 25.9, 29.1, 30.8, 34.4, 38.4, 39.9, 59.2, 62.4, 67.9, 73.1, 76.3, 76.8, 77.2, 79.6, 81.0, 110.1, 110.5, 118.8, 141.7, 157.1, 158.6, 164.3; MS (ESI+) for $C_{48}H_{92}O_9Si$ [M+Cs] calc 1057.4873 found 1057.4695.

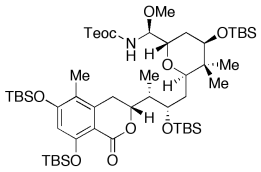


(+)-Acid 245 To a solution of oxalyl chloride (7.5 µL, 0.086 mmol) in CH_2Cl_2 (0.20 mL) at -78 °C was added DMSO (12.5 µL, 0.173 mmol). The resultant solution stirred at -78 °C for 30 min and was then treated dropwise with a solution of (+)-

alcohol **244** (40 mg, 0.043 mmol) in CH_2Cl_2 (0.2 mL) at -78 °C, followed by CH_2Cl_2 rinse (2 x 0.1 mL). The resulting cloudy white mixture stirred at -78 °C for 1 h and was treated with triethylamine (24.0 μL, 0.173 mmol) and stirred for 30 min at -78 °C. The reaction mixture was warmed to 0 °C for 40 min then warmed to room temperature for 20 min and quenched with saturated $NaHCO_3$. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 3 mL), the combined organic layers were dried over Na_2SO_4, filtered and concentrated. Filtration through a silica gel plug (Hexanes to 25% Ether/Hexanes) afforded the intermediate aldehyde (40 mg, 0.043 mmol), which was immediately taken on to the next step.

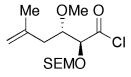
To a solution of the intermediate aldehyde (41 mg, 0.044 mmol) in *t*-BuOH (2.13 mL) was added 2-methyl-2-butene (0.11 mL, 1.065 mmol) followed by dropwise addition of a pre-made solution of $NaClO_2$ (60.2 mg, 0.533 mmol) in 0.05 M potassium biphthalate pH 4 buffer (2.13 mL). The yellow solution stirred for 1 h, gradually becoming clear and colorless. The reaction mixture was then diluted with brine and EtOAc and stirred for 5 min. The layers were separated and the aqueous layer was extracted with EtOAc (4 x 4 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (25% EtOAc/Hexanes) afforded (+)-acid **245** (38.5 mg, 0.041 mmol) in 93% yield over two steps. $[\alpha]^{25}_D$ = +53.3 (c = 0.26, CH_2Cl_2); IR (film) 3159, 2956, 2930, 2857, 1725, 1592, 1567, 1360, 1255, 1168, 1071, 1005, 837, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ -0.00 (s, 3H), -0.07 (s, 6H), 0.16 (s, 3H), 0.21 (s, 3H), 0.22 (s, 3H), 0.25 (s, 3H), 0.26 (s, 3H), 0.86 (s, 9H), 0.88 (s, 3H), 0.91 (s, 9H), 0.96 (d, *J* = 7.2 Hz, 3H), 0.99 (s, 3H), 1.00 (s, 9H), 1.01 (s, 9H), 1.55 (m, 1H), 1.83 (m, 2H), 2.04 (s, 3H), 2.18

(m, 2H), 2.82 (dd, *J* = 2.4, 16.8 Hz, 1H), 3.01 (dd, *J* = 13.2, 16.8 Hz, 1H), 3.40 (m, 1H), 3.43 (s, 3H), 3.61 (m, 1H), 3.75 (d, *J* = 3.7 Hz, 1H), 4.13 (m, 1H), 4.29 (m, 1H), 4.44 (dd, *J* = 3.6, 10.4 Hz, 1H), 6.28 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.9, -4.4, -4.2, -4.2, -2.8, 8.1, 11.7, 18.0, 18.3, 18.3, 18.5, 25.7, 25.9, 26.0, 26.0, 26.0, 26.2, 28.1, 31.6, 33.1, 37.0, 37.8, 58.4, 66.5, 73.3, 77.2, 77.5, 79.7, 83.2, 109.6, 110.3, 118.9, 142.1, 157.3, 158.9, 166.0, 172.6; MS (ESI+) for $C_{48}H_{90}O_{10}Si_4$ [M+Cs] calc 1071.4665 found 1071.4554.



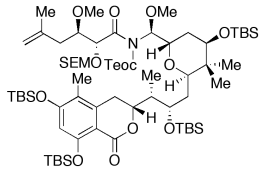
(+)-Teoc-Protected Hemiaminal 190 A 0 °C solution of (+)-carboxylic acid **245** (16.0 mg, 0.017 mmol) in anhydrous acetone (1.38 mL) was treated with triethylamine (5.7 µL, 0.041 mmol) followed by ethylchloroformate (3.6 µL, 0.037 mmol) and stirred at 0 °C for 30 min. The reaction mixture was then treated with a 0.62 M aqueous solution of NaN_3 (55 µL, 0.034 mmol), stirred at 0 °C for 2 h, poured into ice water and extracted with cold ether (5 x 3 mL). The combined extracts were dried over Na_2SO_4, filtered and concentrated at 30 °C. The residue was dissolved in toluene, dried again over Na_2SO_4, filtered, flushed with argon and set into a pre-heated 120 °C sand bath and stirred for 30 min. The reaction mixture was cooled to 50 °C and the solvent removed *in vacuo*. The residue was cooled to room temperature and charged with anhydrous DMF (0.1 mL). The solution was treated with β-trimethylsilylethanol (0.05 mL. 0.34 mmol) followed by copper(I) chloride (1.7 mg, 0.017 mmol), giving a pale green mixture. The reaction mixture stirred for 2 h

giving a more intense green mixture that was diluted with water (2 mL) and ether (2 mL). The layers were separated and the aqueous layer was extracted with ether (4 x 2 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to clear oil. Purification by column chromatography (10% ether/ hexanes) afforded (+)-hemiaminal **190** (13.5 mg, 0.013 mmol) in 76% yield as clear oil. $[\alpha]^{18}_D$ = +27.4 (c = 0.25, CH_2Cl_2); IR (film) 2955, 2857, 1726, 1592, 1568, 1472, 1351, 1250, 1167, 1069, 836, 776; ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.02 (s, 3H), 0.01 (s, 9H), 0.05 (s, 3H), 0.06 (s, 3H), 0.08 (s, 3H), 0.22 (s, 3H), 0.23 (s, 9H), 0.80 (s, 9H), 0.86 (s, 3H), 0.91 (s, 9H), 0.94 (m, 2H), 0.98 (s, 3H), 1.00 (s, 9H), 1.02 (s, 9H), 1.06 (d, *J* = 6.8 Hz, 3H), 1.47 (m, 1H), 1.62 (m, 1H), 1.82 (m, 1H), 1.95 (m, 1H), 2.07 (s, 3H), 2.26 (m, 1H), 2.60 (dd, *J* = 12.4, 16.4 Hz, 1H), 3.03 (m, 1H), 3.36 (s, 3H), 3.38 (m, 1H), 3.59 (m, 1H), 4.00 (m, 1H), 4.12 (m, 4H), 4.81 (m, 1H), 5.45 (m, 1H), 6.30 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.0, -4.9, -4.5, -4.4, -4.4, -4.3, -4.2, -3.5, -1.5, 8.8, 11.7, 17.5, 18.0, 18.1, 18.3, 18.5, 25.7, 25.8, 25.9, 26.0, 26.5, 29.4, 29.7, 31.4, 32.4, 37.3, 39.5, 55.8, 63.3, 67.4, 68.5, 73.3, 77.4, 79.3, 84.1, 110.6, 110.7, 118.5, 141.3, 156.8, 156.9, 158.2, 163.6; MS (ESI+) for $C_{53}H_{103}NO_{10}Si_5$ [M+Cs] calc 1186.5483 found 1186.5471.



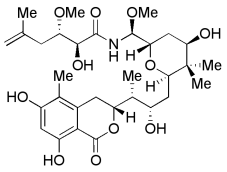
Acid Chloride 189 To a solution of (-)-carboxylic acid **137** (9.6 mg, 0.032 mmol) in CH_2Cl_2 (0.96 mL) was added 0.62 M pyridine in CH_2Cl_2 (0.20 mL), followed by 0.48 M $SOCl_2$ (0.20 mL). The reaction mixture stirred for 2 hours and the solvent was

removed under increased argon pressure, then concentrated further *in vacuo* at 30 °C. The material was suspended in d_6-benzene and analyzed by ^{1}H NMR to confirm the formation of acid chloride **189** then taken on immediately without further analysis as it showed significant moisture sensitivity. The NMR sample was transferred to an oven dried vial, the tube rinsed with anhydrous toluene, concentrated *in vacuo*, and dissolved in THF (0.32 mL) to make a 0.1 M solution that was used immediately in the next step. ^{1}H NMR δ -0.04 (s, 9H), 0.91 (ddd, m, 2H), 1.64 (s, 3H), 2.30 (dd, *J* = 4.4, 14.4 Hz, 1H), 2.37 (dd, *J* = 7.6, 14.4 Hz, 1H), 3.09 (s, 3H), 3.51 (ddd, *J* = 6.8, 9.6, 9.6 Hz, 1H), 3.76 (m, 2H), 4.36 (d, *J* = 5.6 Hz, 1H), 4.50 (q, *J* = 7.2, 14.8 Hz, 2H), 4.81 (m, 2H).



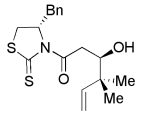
(+)-N-Acyl Hemiaminal 246 To a -78 °C solution of (+)-hemiaminal **190** (7.5 mg, 0.0071 mmol) in THF (0.28 mL) was added a solution of 2.0 M *i*-PrMgCl in THF (12.5 µL, 0.025 mmol) and stirred for 30 min. The reaction was then treated with a 0.1 M solution of acid chloride (142 µL, 0.0142 mmol), stirred at -78 °C for 30 min, then warmed to -40 °C and stirred for 45 min. The reaction was quenched with saturated aqueous NH_4Cl (0.2 mL), warmed to room temperature and diluted with CH_2Cl_2 (4 mL) and saturated aqueous NH_4Cl (4 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 3 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. Purification by column

chromatography (5% EtOAc/Hexanes) gave fully protected (+)-irciniastatin A **8** (8.3 mg, 0.0062 mmol) in 87% yield as well as recovered (+)-hemiaminal **190** (1.0 mg, 0.0009 mmol) in 13% yield. $[\alpha]^{23}_{D}$ = +42.8 (c = 0.21, CH_2Cl_2); IR (film) 3074, 2955, 2931, 2895, 2857, 2740, 2713, 1728, 1592, 1568, 1472, 1411, 1350, 1250, 1168, 1068, 938, 837, 776, 672 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) -0.05 (s, 9H), -0.04 (s, 3H), 0.03 (s, 3H), 0.04 (m, 15H), 0.21 (s, 3H), 0.22 (s, 6H), 0.23 (s, 3H), 0.76 (s, 9H), 0.81 (s, 3H), 0.83 (m, 2H), 0.89 (m, 12H), 1.00 (s, 9H), 1.01 (s, 9H), 1.08 (m, 5H), 1.62 (m, 1H), 1.67 (m, 1H), 1.74 (s, 3H), 1.77 (m, 1H) 1.95 (m, 1H), 2.13 (s, 3H) 2.00 (m, 1H), 2.20 (m, 1H), 2.29 (dd, *J* = 9.5, 14.5 Hz, 1H), 2.86 (dd, *J* = 12.5, 16.0 Hz, 1H), 3.05 (d, *J* = 15.5 Hz, 1H), 3.15 (d, *J* = 10.0 Hz, 1H), 3.27 (s, 3H), 3.34 (s, 3H), 3.54 (m, 3H), 3.62 (m, 2H), 4.09 (m, 1H), 4.18 (m, 1H), 4.29 (m, 2H), 4.64 (m, 2H), 4.76 (d, *J* = 11.5 Hz, 2H), 5.15 (d, *J* = 5.0 Hz, 1H), 5.64, (d, *J* = 5.0 Hz, 1H), 6.29 (s, 1H); δ ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.0, -4.9, -4.4, -4.3, -4.2, -4.2, -4.1, -3.3, -1.6, -1.5, -1.4, 1.0, 8.8, 11.9, 13.5, 13.5, 17.6, 18.0, 18.0, 18.1, 18.3, 18.6, 21.9, 22.8, 24.0, 25.7, 25.8, 25.9, 26.0, 29.7, 29.9, 30.3, 34.9, 38.8, 39.0, 40.4, 56.6, 58.1, 65.9, 66.1, 69.0, 72.7, 74.4, 75.3, 77.3, 79.6, 80.9, 95.8, 110.6, 110.8, 112.7, 119.0, 141.9, 142.6, 154.3, 156.7, 158.19, 163.7, 174.6; MS (ESI+) for $C_{67}H_{129}NO_{14}Si_6$ [M+Na] calc 1362.7926 found 1362.7686.



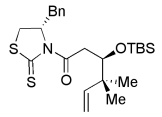
(+)-Irciniastatin A (8) To a sample of fully protected (+)-irciniastatin A **246** (7.5 mg, 0.006 mmol) in a polyethylene vial was added a prepared solution of TASF (23.1 mg,

0.084 mmol) in DMF (0.18 mL). The reaction was set in a 50 °C sand bath and stirred for 36 h. The reaction was quenched with saturated aqueous NH_4Cl (2 mL) and diluted with EtOAc (2 mL). The layers were separated and the aqueous layer was extracted with EtOAc (5 x 2 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (CH_2Cl_2 to 5% CH_2Cl_2/MeOH gradient) afforded (+)-irciniastatin A (**8**) (3.2 mg, 0.0052 mmol) 94% yield as white solids. $[\alpha]^{22}_D$ = +27.3 (c = 0.22, MeOH); IR (film) 3370, 2965, 2928, 2853, 1650, 1624, 1558, 1515, 1453, 1387, 1364, 1297, 1252, 1173, 1067, 967 cm^{-1}; ^1H NMR (500 MHz, MeOD) δ 0.89 (s, 3H), 0.96 (s, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.72 (m, 6H), 1.89 (m, 1H), 2.00 (m, 1H), 2.06 (m, 4H), 2.34 (dd, *J* = 9.5, 14.5 Hz, 1H), 2.85 (dd, *J* = 12.0, 17.0 Hz, 1H), 3.12 (dd, *J* = 3.0, 17.0 Hz, 1H), 3.19 (s, 3H), 3.34 (s, 3H), 3.49 (m, 1H), 3.58 (dd, *J* = 4.5, 11.0 Hz, 1H), 3.66 (ddd, *J* = 3.0, 3.0, 9.0 Hz, 1H), 3.93 (m, 2H), 4.34 (d, *J* = 2.5 Hz, 1H), 4.48 (ddd, *J* = 3.5, 6.0, 12.5 Hz, 1H), 4.71 (d, *J* = 12.0 Hz, 2H), 5.38 (d, *J* = 8.0 Hz, 1H), 6.23 (s, 1H); ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (s, 3H), 0.94 (s, 3H), 1.08 (d, *J* = 7.0 Hz, 3H), 1.61 (m, 2H), 1.73 (s, 3H), 1.81 (m, 2H), 1.98 (s, 3H), 2.05 (m, 1H), 2.16 (m, 1H), 2.38 (dd, *J* = 9.0, 14.5 Hz, 1H), 2.78 (m, 2H), 3.36 (s, 6H), 3.52 (m, 1H), 3.66 (m, 1H), 3.74 (m, 1H), 3.88 (m, 1H), 3.92 (m, 1H), 4.43 (m, 1H), 4.51 (m, 1H), 4.78 (s, 2H), 5.43 (t, *J* = 9.5 Hz, 1H), 6.33 (s, 1H), 7.12 (m, 1H), 11.03 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.0, 10.5, 13.7, 22.7, 23.0, 28.5, 29.6, 32.3, 37.6, 38.8, 42.6, 56.3, 57.8, 71.3, 72.9, 74.3, 78.4, 79.6, 80.6, 81.9, 100.8, 101.2, 113.1, 113.7, 139.5, 142.0, 162.0, 162.2, 170.7, 173.9; MS (ESI+) for $C_{31}H_{47}NO_{11}$ [M+Cs] calc 742.2203 found 742.2197.

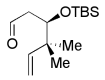


(+)-Alcohol 255 To a -78 °C solution of *N*-acetyl thiazolidinethione **254** (1.50 g, 5.97 mmol) in CH_2Cl_2 (19.1 mL) was added $TiCl_4$ (0.65 mL, 5.97 mmol) dropwise over 4 min. The orange solution was stirred for 20 min at -78 °C becoming an orange slurry. The reaction mixture was then treated with *i*-Pr_2NEt (2.1 mL, 11.9 mmol) dropwise over 5 min becoming purple in color. The thick purple solution stirred for 45 min at -78 °C and was then treated with a room temperature solution of the aldehyde **253** (878 mg, 8.95 mmol) in CH_2Cl_2 (4.1 mL), dropwise over 20 min. The purple reaction mixture was stirred at -78 °C for 2 h. The reaction was quenched with half-saturated aqueous NH_4Cl (20 mL) and warmed to room temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to green oil. Purification by column chromatography (15% EtOAc/Hexanes) afforded the desired (+)-alcohol diastereomer **255** (1.76 g, 5.04 mmol) in 85% isolated yield as well as the undesired diastereomer (240 mg, 0.69 mmol) in 12% isolated yield, giving an overall yield of 97% yield with 7.5:1 dr. $[\alpha]^{22}_D$ = +179.9 (c = 0.29, CH_2Cl_2); IR (film) 3544, 2965, 1693, 1455, 1436, 1364, 1341, 1318, 1293, 1264, 1192, 1165, 1136, 1043, 916, 746, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (s, 6H), 2.63 (br s, 1H), 2.87 (d, *J* = 11.5 Hz, 1H), 3.03 (dd, *J* = 10.3, 12.6 Hz, 1H), 3.20 (m, 2H), 3.38 (dd, *J* = 6.9, 11.5 Hz, 1H), 3.55 (dd, *J* = 1.4, 17.6 Hz, 1H), 3.96 (dd *J* = 1.4, 10.3 Hz, 1H), 5.08 (m, 2H), 5.37 (m, 1H), 5.87 (dd, *J* = 11.0, 17.6 Hz, 1H), 7.28 (m, 5H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 22.6, 23.2, 32.2, 36.9, 41.0, 41.6, 68.5, 74.2, 77.3, 113.5, 127.3, 128.9, 129.5, 136.5, 144.6, 173.7, 201.4; MS (ESI+) for $C_{18}H_{23}NO_2S_2$ [M+Na] calc 372.10 found 372.10.



(+)-TBS Ether To a yellow solution of (+)-alcohol (240 mg, 0.687 mmol) and 2,6-lutidine (0.32 mL, 2.47 mmol) in CH_2Cl_2 (1.7 mL) at 0 °C was added TBSOTf (0.32 mL, 1.37 mmol) dropwise over 3 min. The yellow solution was stirred at 0 °C for 30 min and the yellow solution was quenched with saturated aqueous $NaHCO_3$ (1.5 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 1 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (Hexanes to 3% EtOAc/ Hexanes) gave (+)-TBS ether (299 mg, 0.647 mmol) in 94% yield. $[\alpha]^{23}_D$ +191.5 (c = 0.25, CH_2Cl_2); IR (film) 2596, 2929, 2856, 1697, 1365, 1293, 1262, 1166, 1091, 1043, 835, 775, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.13 (s, 3H), 0.87, (s, 9H), 1.03 (s, 3H), 1.04 (s, 3H), 2.88 (d, *J* = 11.5 Hz, 1H), 3.04 (d, *J* = 10.7, 13.1 Hz, 1H), 3.33 (dd, *J* = 3.3, 13.1 Hz, 1H), 3.32 (dd, *J* = 7.7, 11.5 Hz, 1H), 3.36 (m, 2H), 4.24 (dd, *J* = 3.5, 6.3 Hz, 1H), 5.04 (m, 2H), 5.30 (m, 1H), 5.86 (dd, *J* = 10.8, 17.6 Hz, 1H), 7.29 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.6, -4.2, 18.4, 21.5, 24.7, 26.1, 32.1, 36.4, 42.3, 43.9, 68.7, 75.4, 112.6, 127.2, 128.9, 129.5, 136.6, 145.5, 173.0, 201.0; MS (ESI+) for $C_{24}H_{37}NO_2S_2Si$ [M+Na] calc 486.19 found 486.19.



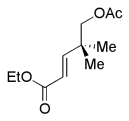
Aldehyde 249 To a green -78 °C solution of *N*-acyl thiazolidinethione (300 mg, 0.647 mmol) in CH_2Cl_2 (6.2 mL) was added a 1.0 M solution of diisobutylaluminum hydride in hexanes (1.30 mL, 1.30 mmol) dropwise over 10 min, giving a colorless solution. The reaction mixture was quenched with saturated aqueous Rochelle's salt (6 mL) and the reaction mixture was warmed to room temperature and stirred vigorously for 2 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (4% EtOAc/Hexanes) afforded aldehyde **249** (133 mg, 0.519 mmol) in 80% yield. The identity of the aldehyde product was confirmed by ^1H and immediately taken on to the next step.^1H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 3H) 0.04 (s, 3H), 0.89 (s, 9H), 0.99 (s, 3H), 1.00 (s, 3H), 2.43 (m, 1H), 2.59 (m, 1H), 3.98 (m, 1H), 5.02 (m, 2H), 5.82 (dd, *J* = 10.9, 17.5 Hz, 1H) 9.79 (s, 1H).

Aldehyde 259 To a 0 °C solution of 2,2-dimethyl-1,3-propane diol (**98**) (21.0 g, 201.6 mmol) in CH_2Cl_2 (129 mL) was added Et_3N (42.2 mL, 302.4 mmol) followed by a 1:1 v/v solution of acetic anhydride (21.9 mL, 231.8 mmol) and CH_2Cl_2 (21.9 mL)

dropwise over 60 min. The reaction stirred for 1 h at 0 °C and was warmed to room temperature and stirred for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (100 mL) giving pH 8 aqueous phase, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL) and the organic layers were combined, washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated to crude oil (23.8 g).

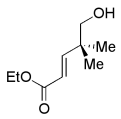
A separate flask containing CH_2Cl_2 (521 mL) at -78 °C was charged with oxalyl chloride (20.8 mL, 244 mmol) followed by dropwise addition a solution of DMSO (34.6 mL, 488 mmol) in CH_2Cl_2 (35 mL) over 20 min. The resultant solution evolved gas and stirred at -78 °C for 30 min. A sample of the above crude alcohol (23.8 g)was dissolved in CH_2Cl_2 (73 mL) and added dropwise to the reaction mixture at -78 °C over 30 min, followed by a rinse with CH_2Cl_2 (5 mL). The reaction formed a cloudy white solution and stirred at -78 °C for 30 min and was then treated with triethylamine (85 mL, 610 mmol) over 20 min at -78 °C. The reaction became thick and white slurry and was then warmed to 0 °C and was stirred for 30 min while additional CH_2Cl_2 (100 mL) was added to facilitate stirring. The reaction was warmed to room temperature for 30 min and quenched with saturated aqueous $NaHCO_3$ (100 mL), stirred for 5 min, diluted with water (100 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organics were dried with Na_2SO_4, filtered and concentrated. The crude material was diluted with ether (200 mL) and washed with copper(II) sulfate (200 mL), forming a light blue suspension. The layers were separated and the aqueous washed with ether (3 x 50 mL) and the combined organic layers were washed with brine (50 mL),

dried over Na_2SO_4, filtered and concentrated to orange oil. The product was vacuum distilled using a short path equipped with a vigreaux column under full vacuum at 80 °C to give aldehyde **259** (17.6 g, 122 mmol) in 61% yield over 2 steps. The identity of the aldehyde product was confirmed by ^1H NMR and taken forward immediately due to potential enone formation. ^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (s, 6H), 2.05 (s, 3H), 4.11 (s, 2H), 9.53 (s, 1H).

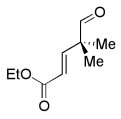


Enoate To a 0 °C slurry of NaH 60% oil dispersion (4.9 g, 123.1 mmol) in THF (125 mL) was added phosphonate (20.4 mL, 102.5 mmol) over 20 min, gradually giving a clear solution that stirred for 20 min at 0 °C. The clear solution was then treated with an orange solution of aldehyde (17.7 g, 123.1 mmol) in THF (83 mL) over 10 min. The reaction was stirred vigorously at 0 °C for 5 min then warmed to room temperature and stirred in a room temperature ultrasonic bath for 4 h. The reaction was quenched with saturated aqueous NH_4Cl and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined organic layers were washed with water (100 mL) and brine (100 mL) then dried over Na_2SO_4, filtered, and concentrated to yellow oil. The oil was purified by plug column chromatography (Hexanes to 10% EtOAc/Hexanes) to give pure enone (22.0 g, 102.6 mmol) in quantitative yield. IR (film) 2974, 1744, 1719, 1651, 1375, 1311, 1271, 1242, 1182, 1041 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 6H), 1.27 (t, J = 7.1 Hz, 3H), 2.03 (s, 3H), 3.88 (s, 2H), 4.17 (q, J = 7.1 Hz, 2H), 5.78 (d, J = 16.0 Hz,

1H), 6.90 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 20.7, 23.7, 37.1, 60.3, 71.2, 119.5, 153.8, 166.6, 170.7; MS (ESI+) for $C_{11}H_{18}O_4$ [M+Na] calc 237.1103 found 237.11.

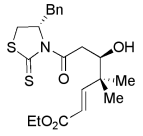


Alcohol A solution of enoate (22.0 g, 102 mmol) in reagent grade 99.5% absolute ethanol (203 mL) was treated with K_2CO_3 (42.5 g, 308 mmol) and stirred vigorously for 16 h. The reaction mixture was acidified to pH = 4 with 1 M HCl and diluted with CH_2Cl_2 (600 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (5 x 200 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (10% EtOAc/Hex) gave alcohol (15.9 g, 92.3 mmol) in 90% yield. IR (film) 3458, 2964, 2872, 1714, 1650, 1469, 1392, 1367, 1311, 1272, 1181, 1042, 998, 982, 912, 863, 727 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (s, 6H), 1.21 (t, *J* = 7.1 Hz, 3H), 2.99 (br s, 1H), 3.33 (s, 2H), 4.09 (q, *J* = 7.1 Hz, 2H), 5.73 (d, *J* = 16.1 Hz, 1H), 6.86 (d, *J* = 16.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 23.1, 39.0, 60.2, 70.6, 119.3, 155.4, 167.0; MS



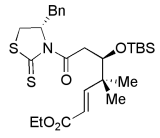
(ESI+) for $C_9H_{16}O_3$ [M+Na] calc 195.0997 found 195.1001

Aldehyde 260 A -78 °C solution of oxalyl chloride (5.9 mL, 69.6 mmol) in CH_2Cl_2 (300 mL) was treated dropwise with a solution of DMSO (9.9 mL, 139 mmol) in CH_2Cl_2 (10 mL). The resultant solution evolved gas and stirred at -78 °C for 20 min. A solution of alcohol (8.0 g, 46.4 mmol) was dissolved in CH_2Cl_2 (3 mL) and added dropwise to the reaction -78 °C over 5 min. The reaction mixture became a cloudy white solution and stirred at -78 °C for 45 min. The reaction mixture was then treated with triethylamine (19 mL, 139 mmol) and stirred for 15 min at -78 °C and was then allowed to warm to 0 °C and stirred for 40 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (50 mL), stirred 5 min diluted with water (50 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were washed with water (100 mL), brine (100 mL), dried over Na_2SO_4, filtered and concentrated. Purification by plug column chromatography (20% Et_2O/Hexanes) afforded the aldehyde **260** (7.5 g, 44.0 mmol) in 95% yield. The identity of aldehyde **260** was confirmed by ^1H NMR and immediately taken on to the next step. ^1H NMR (400 MHz, $CDCl_3$) δ .1.29 (m, 9 H), 4.21 (q, *J* = 7.2 Hz, 2H), 5.89 (d, *J* = 15.9 Hz, 1H), 6.96 (d, *J* = 15.9 Hz, 1H), 9.45 (s, 1H).



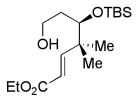
(+)-Alcohol 261 To a -78 °C solution of *N*-acetyl thiazolidinethione **254** (9.0 g, 35.1 mmol) in CH_2Cl_2 (114 mL) was added $TiCl_4$ (3.9 mL, 35.1 mmol) dropwise over 4 min. The orange solution was stirred for 15 min at -78 °C becoming an orange slurry. The

reaction mixture was then treated with *i*-Pr_2NEt (12.5 mL, 71.6 mmol) dropwise over 5 min becoming an opaque purple solution. The thick purple solution stirred for 40 min at -78 °C and was treated with a -78 °C solution of the aldehyde **260** (7.3 g, 43.0 mmol) in CH_2Cl_2 (22.9 mL), dropwise over 1 h. The purple solution was stirred at -78 °C for 1.5 h and the reaction was then quenched with half saturated NH_4Cl (100 mL) and warmed to room temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to yellow/green oil. Purification by column chromatography (10% to 20% EtOAc/Hexanes) afforded the desired isomer (+)-alcohol **261** (11.2 g, 24.8 mmol) in 75% yield as well as the undesired isomer (2.2 g, 5.2 mmol) in 15% yield for a total yield of 90% with 5:1 dr. $[\alpha]^{24}_D$ +109.1 (c = 0.24, CH_2Cl_2); IR (film) 3493, 2970, 1712, 1649, 1367, 1342, 1311, 1265, 1192, 1166, 1137, 1041, 747, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.10 (s, 6H), 1.26 (t, *J* = 7.1 Hz, 3H), 2.85 (d, *J* = 9.4 Hz, 1H), 3.00 (m, 1H), 3.14 (m, 3H), 3.36 (dd, *J* = 7.3, 11.4 Hz, 1H), 3.53 (d, *J* = 17.8 Hz, 1H), 4.00 (d, *J* = 9.4 Hz, 1H), 4.15 (q, *J* = 7.1, 14.2 Hz, 2H), 5.32 (ddd, *J* = 4.0, 7.0, 10.6, 1H), 5.82 (d, *J* = 16.0 Hz, 1H), 7.00 (d, *J* = 16.0 Hz, 1H) 7.26 (m, 3H), 7.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 22.5, 23.0, 32.2, 36.9, 41.1, 41.6, 60.3, 68.4, 73.8, 77.4, 119.9, 127.3, 128.9, 129.1, 129.4, 136.4, 154.4, 166.7, 173.3, 201.5; MS (ESI+) for $C_{21}H_{27}NO_4S_2Si$ [M+Na] calc 444.12



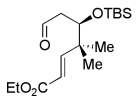
found 444.12.

(+)-TBS ether To a yellow solution of (+)-**261** alcohol (5.29 g, 12.55) and 2,6-lutidine (3.21 mL, 27.61 mmol) in CH_2Cl_2 (24.1 mL) at 0 °C was added TBSOTf (3.2 mL, 13.8 mmol) dropwise over 3 min. The yellow solution was stirred at 0 °C for 10 min and then warmed to room temperature and stirred for 2 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were washed with water (10 mL) and brine (10 mL) then dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (Hexanes to 8% EtOAc/Hexanes) gave (+)-TBS ether (5.73 g, 10.7 mmol) in 85% yield.$[\alpha]^{23}_D$ = +148.7 (c = 0.27, CH_2Cl_2); IR (film) 2956, 2929, 2895, 2856, 1715, 1650, 1294, 1259, 1191, 1166, 1092, 1041, 835, 777, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ -0.03 (s, 3H), -0.10 (s, 3H), 0.84 (s, 9H), 1.05 (s, 3H), 1.07 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 2.86 (d, *J* = 11.6 Hz, 1H), 3.00, (dd, *J* = 10.8, 13.1 Hz, 1H), 3.19 (dd, *J* = 3.2 Hz, 13.1 Hz, 1H), 3.32 (m, 3H), 4.15 (q, *J* = 7.2 Hz, 14.1 Hz, 2H), 4.30 (dd, *J* = 3.2, 6.8 Hz, 1H), 5.27 (ddd, *J* = 3.7, 6.8, 10.8 Hz, 1H), 5.80 (d, *J* = 16.0 Hz, 1H), 6.98 (d, *J* = 16.0 Hz, 1H), 7.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.8, -4.2, 14.3, 18.3, 22.0, 23.5, 26.0, 32.1, 36.4, 42.4, 43.7, 60.2, 68.6, 74.8, 77.3, 119.5, 120.1, 127.2, 128.9, 129.4, 136.5, 155.3, 157.6, 166.7, 172.3, 201.1; MS (ESI



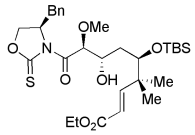
+) for $C_{27}H_{41}NO_4S_2Si$ [M+Na] calc 558.21 found 558.21.

(+)-Alcohol To a solution of *N*-acylthiazolidinethione (5.65 g, 10.54 mmol) in ether (55 mL) and MeOH (0.51 mL, 12.65 mmol) at -15 °C was added 2.0 M $LiBH_4$ solution in THF (6.32 mL, 12.65 mmol) over 5 min. The yellow solution stirred for 1.5 h at -15 °C. The reaction mixture was quenched with saturated aqueous Rochelle's salt at -15 °C (25 mL) and warmed to 0 °C over 30 min. then warmed to room temperature and stirred for 2 h. The layers were separated and the aqueous layer was extracted with ether (4 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (CH_2Cl_2 to 5% CH_2Cl_2/EtOAc) afforded the product (+)-alcohol (2.60 g, 7.89 mmol) in 75% yield. $[\alpha]^{22}_D$ = +20.8 (c = 0.25, CH_2Cl_2); IR (film) 3444, 2957, 2931, 2884, 2857, 1720, 1649, 1472, 1386, 1366, 1310, 1257, 1190, 1095, 1034, 1310, 1257, 1190, 1095, 1034, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.06 (s, 3H), 0.87 (s, 9H), 1.01 (s, 3H), 1.02 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.58 (m, 1H), 1.72 (m, 1H), 1.90 (br s, 1H), 3.59 (m, 2H), 3.65 (m, 1H) 4.14 (q, *J* = 7.1 Hz, 2H), 7.73 (d, *J* = 16.1 Hz, 1H), 6.99 (d, *J* = 16.1 Hz, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.1, -3.9, 14.2, 18.3, 22.8, 23.5, 26.0, 36.6, 42.4, 59.9, 60.2, 75.8, 118.7, 156.2, 167.0; MS (ESI+) for $C_{17}H_{34}O_4Si$ [M+Na] calc 353.21 found 353.21.



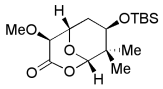
(+)-Aldehyde 262 To a -78 °C solution of oxalyl chloride (1.21 mL, 14.1 mmol) in CH_2Cl_2 (45 mL) was added a room temperature solution DMSO (2.0 mL, 28.3 mmol) in CH_2Cl_2 (2.0 mL). The resultant solution evolved gas and stirred at -78 °C for 20

min. A solution of (+)-alcohol (2.60 g, 7.86 mmol) in CH_2Cl_2 (25 mL) was added dropwise to the reaction mixture at -78 °C followed by a CH_2Cl_2 rinse (2 mL). The reaction formed a cloudy white solution and stirred at -78 °C for 30 min. The reaction mixture was treated with triethylamine (4.3 mL, 31.5 mmol) and stirred for 10 min at -78 °C, then warmed to 0 °C and stirred for 60 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL), stirred for 5 min, diluted with water(10 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (20% ether/hexanes) gave aldehyde **262** (2.54 g, 7.73 mmol) in 98%. The identity of aldehyde **262** was confirmed by ^1H NMR and taken on immediately to the next step.



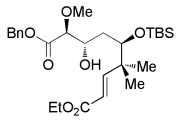
(-)-Alcohol 263 To a clear solution of methoxyglycolate **253** (1.45 g, 4.46 mmol) in CH_2Cl_2 (105 mL) at -78 °C was added $TiCl_4$ (0.72 mL, 6.56 mmol) over 3 min. and stirred for 15 min becoming and orange solution. The orange solution was then treated with (-)-sparteine (1.50 mL, 6.56 mmol) becoming an opaque purple solution and stirred for 45 min at -78 °C. The purple solution was treated with $TiCl_4$ (1.32 mL, 12.0 mmol) over 1 min and was immediately charged with a -78 °C solution of aldehyde (1.97 g, 6.00 mmol) in CH_2Cl_2 (14 mL). The reaction mixture stirred for 30 min and was quenched with saturated aqueous NH_4Cl and warmed to 0 °C. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL).

The combined organic layers were washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL) and then were dried over Na_2SO_4, filtered, and concentrated. HPLC analysis of the crude reaction product showed a 3.5/1.0/0.74 ratio of desired / undesired/undesired isomers. Purification by column chromatography (35% ether/ hexanes) afforded the desired (-)-alcohol **263** (1.90 g, 3.20 mmol) in 59% isolated yield. $[\alpha]^{23}_D$ = -115.2 (c = 0.25, CH_2Cl_2); IR (film) 3438, 2956, 2930, 2856, 1713, 1367, 1325, 1199, 836, 776, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.12 (s, 3H), 0.88 (s, 9H), 1.03 (s, 3H), 1.04 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.70 (m, 1H), 2.06 (m, 1H), 2.77 (m, 2H), 3.26 (m, 1H), 3.35 (s, 3H), 3.80 (m, 1H), 3.93 (m, 1H) 4.13 (q, *J* = 7.1, Hz, 2H), 4.35 (m, 2H), 5.00 (m, 1H), 5.74 (d, *J* = 16.0 Hz, 1H), 5.85 (d, *J* = 6.28 Hz, 1H), 7.04 (d, *J* = 6.28 Hz, 1H), 7.28 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.5, -3.6, 14.3, 18.2, 22.7, 23.2, 26.0, 37.5, 39.4, 42.9, 58.4, 60.2, 60.4, 71.2, 72.2, 75.7, 77.4, 82.1, 119.1, 127.5, 129.0, 129.2, 129.4, 155.8, 166.76, 172.5, 186.2; MS (ESI+) for $C_{30}H_{47}NO_7SSi$ [M+Na] calc 616.2740 found 616.2749.



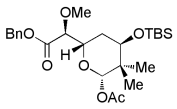
(+)-Dioxanone 248 To a solution of (-)-alcohol **248** (105 mg, 0.177 mmol) and pyridine (0.014 mL, 0.177 mmol) in CH_2Cl_2 (3.4 mL) at -78 °C was bubbled ozone @ 1 L/min for 0.5 min and the reaction stirred for 3 min. Ozone was bubbled again through the reaction mixture @ 1 L/min for 0.5 min and then the reaction mixture stirred for 3 min. Again, ozone was bubbled through the reaction mixture @ 1 L/min for 10 sec and the reaction mixture stirred for 5 min. Solid triphenylphosphine (139

mg, 0.530 mmol) was added to the reaction mixture at -78 °C and stirred for 10 min. The reaction mixture was warmed room temperature, purged with argon, and stirred for 2 h under inert atmosphere. The reaction mixture was then treated with imidazole (36 mg, 0.530 mmol) and stirred at room temperature for 18 h. The reaction mixture was concentrated and purification by column chromatography (Hexanes to 10% EtOAc/Hexanes) gave (+)-dioxanone **248** (22 mg, 0.0666) for a 38% yield.$[\alpha]^{20}_{D}$ = -82.5 (c = 0.28, CH_2Cl_2); IR (film) 2954, 2930, 2886, 2857, 1737, 1462, 1362, 1257, 1244, 1109, 1097, 984, 971, 880, 840, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.86 (s, 9H), 0.97 (s, 3H), 1.03 (s, 1H), 1.72 (dd, *J* = 5.2, 13.6 Hz, 1H), 2.09 (ddd, *J* = 6.2, 13.6, 13.6 Hz, 1H), 3.51 (m, 1H), 3.53 (s, 3H), 3.62 (dd, *J* = 5.2, 12.0 Hz, 1H), 4.39 (d, *J* = 6.2 Hz, 1H), 5.26 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.0, -4.3, 17.1, 17.9, 23.0, 25.6, 33.4, 40.7, 58.5, 67.4, 74.6, 78.2, 106.9, 164.8; MS (ESI +) for $C_{16}H_{30}O_5Si$ [2M+Cs] calc 683.3695 found 683.3695.



(-)-Benzyl Ester 278 To a solution of *N*-acyloxazolidinethione (215 mg, 0.36 mmol) in CH_2Cl_2 (0.83 mL) and BnOH (0.37 mL, 3.6 mmol) was added DMAP (11 mg, 0.09 mmol) and imidazole (49 mg, 0.72 mmol) and the reaction mixture stirred for 2 h. The reaction mixture was concentrated and the crude material was purified by plug column chromatography (15% EtOAc/Hexane) to remove the chiral auxiliary and the amine bases. The material was then azeotroped with water at 55 °C until the remaining BnOH was gone and was purified again by column chromatography (15%

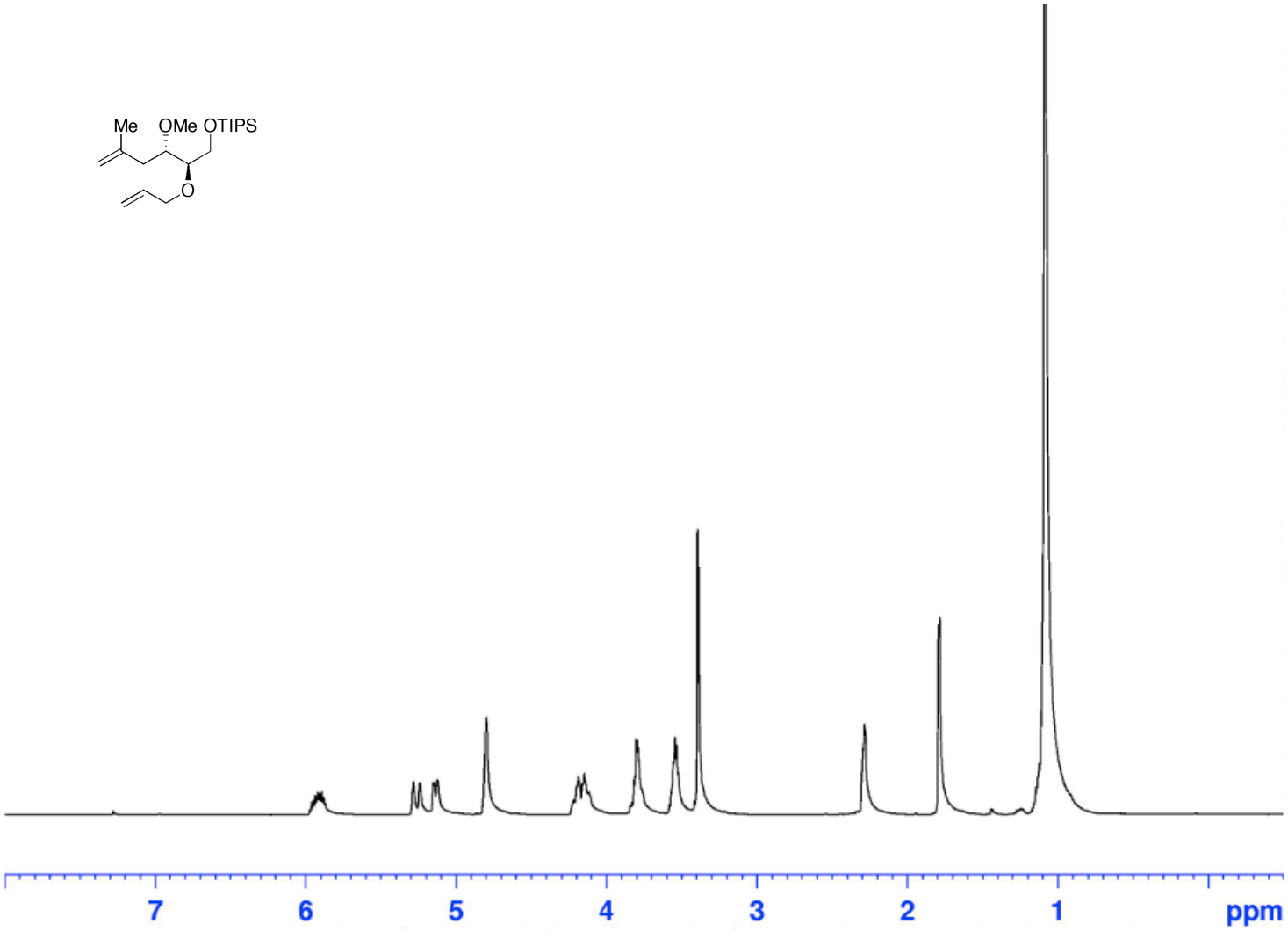
EtOAc/Hexanes) to give (-)-benzyl ester **278** (128 mg, 0.25 mmol) in 70% yield. [α] $^{20}_{D}$ = -17.4 (c = 0.25, CH_2Cl_2); IR (film) 3499, 2956, 2931, 2893, 2856, 1749, 1718, 1258, 1186, 1094, 837, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.87 (s, 9H), 0.94 (s, 3H), 0.96 (s, 3H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.56 (m, 1H), 1.74 (m, 1H), 3.40 (s, 3H), 3.65 (t, *J* = 5.6 Hz, 1H), 3.75 (d, *J* = 4.4 Hz, 1H), 3.92 (m, 1H), 4.16 (q, *J* = 7.0 Hz, 2H), 5.20 (s, 2H), 5.70 (d, *J* = 16.0 Hz, 1H), 6.99 (d, *J* = 16.0 Hz, 1H), 7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.4, -3.8, 14.2, 18.2, 22.7, 22.9, 26.0, 26.1, 37.1, 42.7, 58.7, 60.1, 66.7, 70.6, 76.3, 77.3, 84.0, 118.9, 128.5, 128.5, 128.6, 135.4, 155.9, 166.8, 170.2; MS (ESI+) for $C_{27}H_{44}O_7Si$ [M+Na] calc 531.2754 found 531.2746



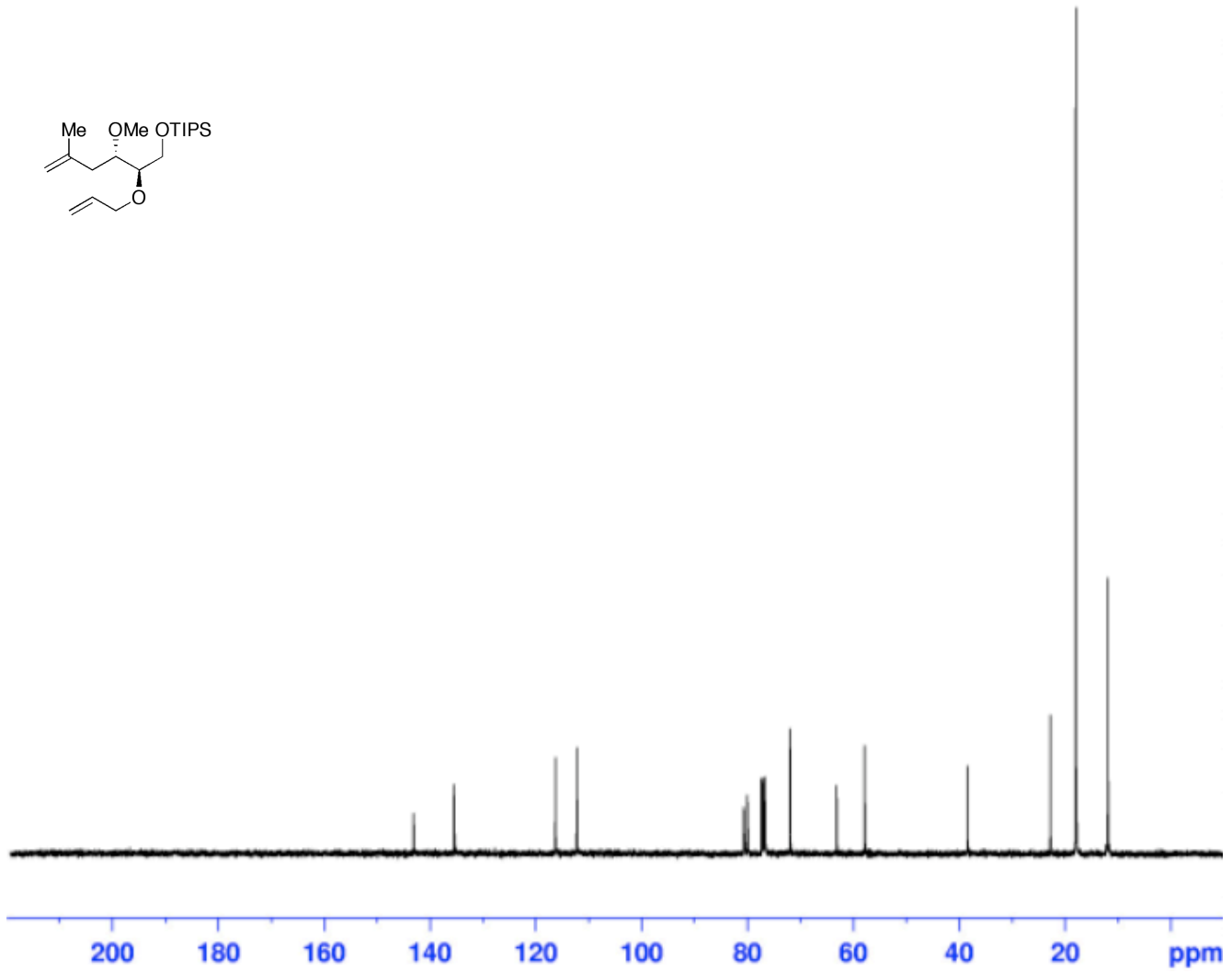
(-)-Lactol-Acetate 275 To a -78 °C solution of (-)-enoate **278** (120 mg, 0.24 mmol) in CH_2Cl_2 (2.26 mL) was bubbled ozone gas at 1L/min until the solution gave a persistent blue color (~ 1 min). The blue solution solution stirred at -78 °C for 2 min and was then charged with Et_3N (0.99 ml, 0.708 mmol), dropwise, producing a white plume of smoke and giving a clear solution immediately, The solution stirred at - 78 °C for 5 min and was connected to an argon line, purged over 5 min, then warmed to room temperature. After 1 h at room temperature the reaction was treated with pyridine (0.11 mL, 1.41 mmol), Ac_2O (0.067 mL, 0.71 mmol) and DMAP (2.9 mg, 0.024 mmol). The reaction stirred for 15 h and was quenched with saturated aqueous $NaHCO_3$ (2 mL). The layers were separated and the aqueous layer was

extracted with CH_2Cl_2 (3 x 3 mL), dried over Na_2SO_4, filtered and concentrated. Purification by plug column chromatography (8% EtOAc/Hexanes) gave (-)-lactol-acetate **275** (98 mg, 0.20 mmol) in 86% yield. $[\alpha]^{20}_D$ = -38.9 (c = 0.25, CH_2Cl_2); IR (film) 2955, 2930, 2885, 2857, 1753, 1462, 1390, 1371, 1228, 1186, 1148, 1085, 1059, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.03 (s, 3H), 0.87 (m, 12H), 0.97 (s, 3H), 1.34 (m, 1H), 2.08 (s, 3H), 2.16 (m, 1H), 3.45 (s, 3H), 3.66 (m, 1H), 4.01 (m, 1H), 4.32 (m, 1H), 5.05 (d, *J* = 12.2 Hz, 1H), 5.29 (d, *J* = 12.2 Hz, 1H), 5.79 (s, 1H), 7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.0, -4.5, 18.0, 18.6, 21.0, 21.5, 25.7, 25.8, 25.8, 29.6, 38.5, 58.9, 66.8, 72.7, 74.8, 82.8, 96.1, 128.3, 128.5, 135.4, 170.1, 169.4; MS (ESI+) for $C_{25}H_{40}O_7Si$ [M+Na] calc 503.2441 found 503.2482.

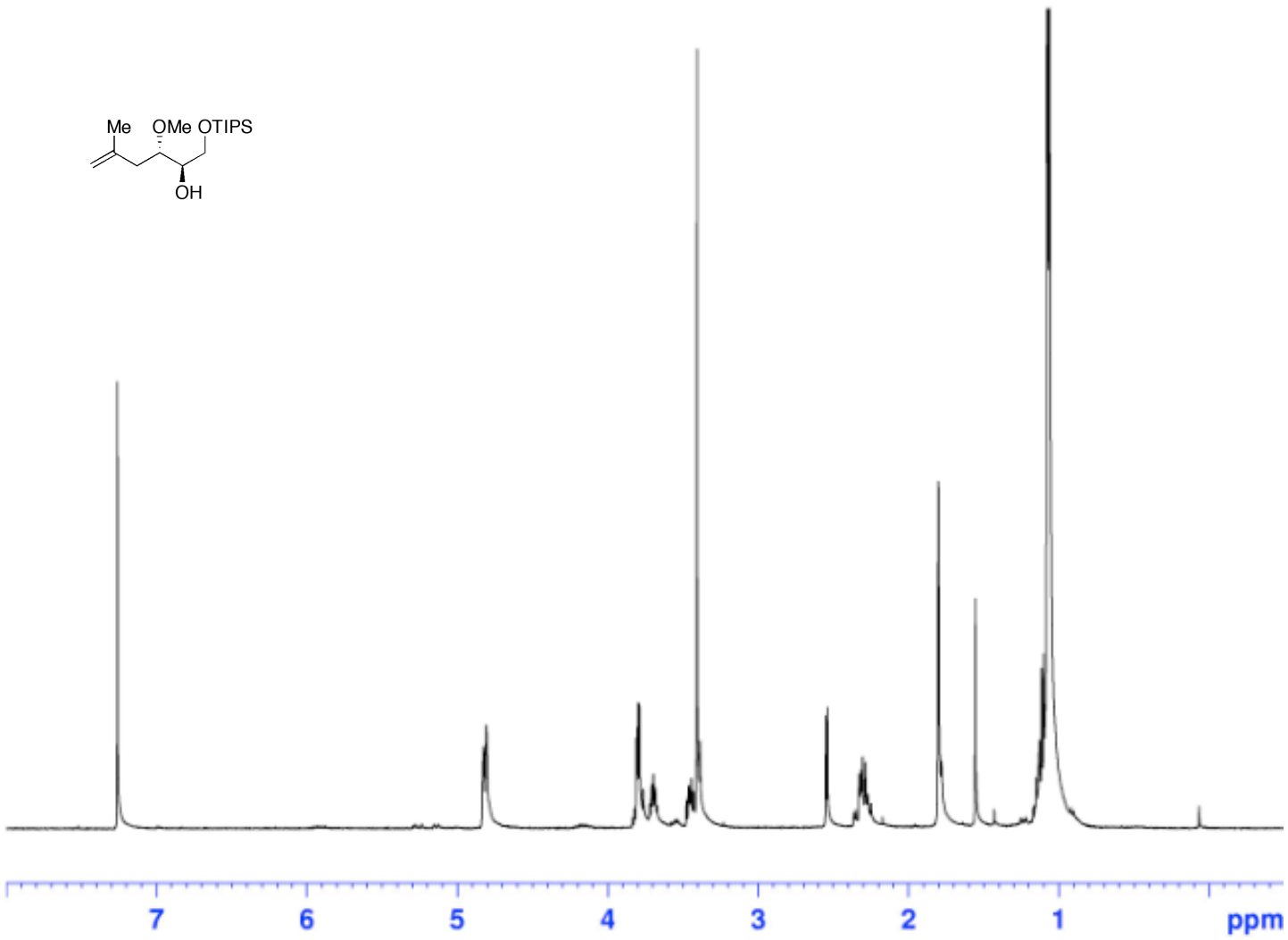
4.3 NMR Spectra



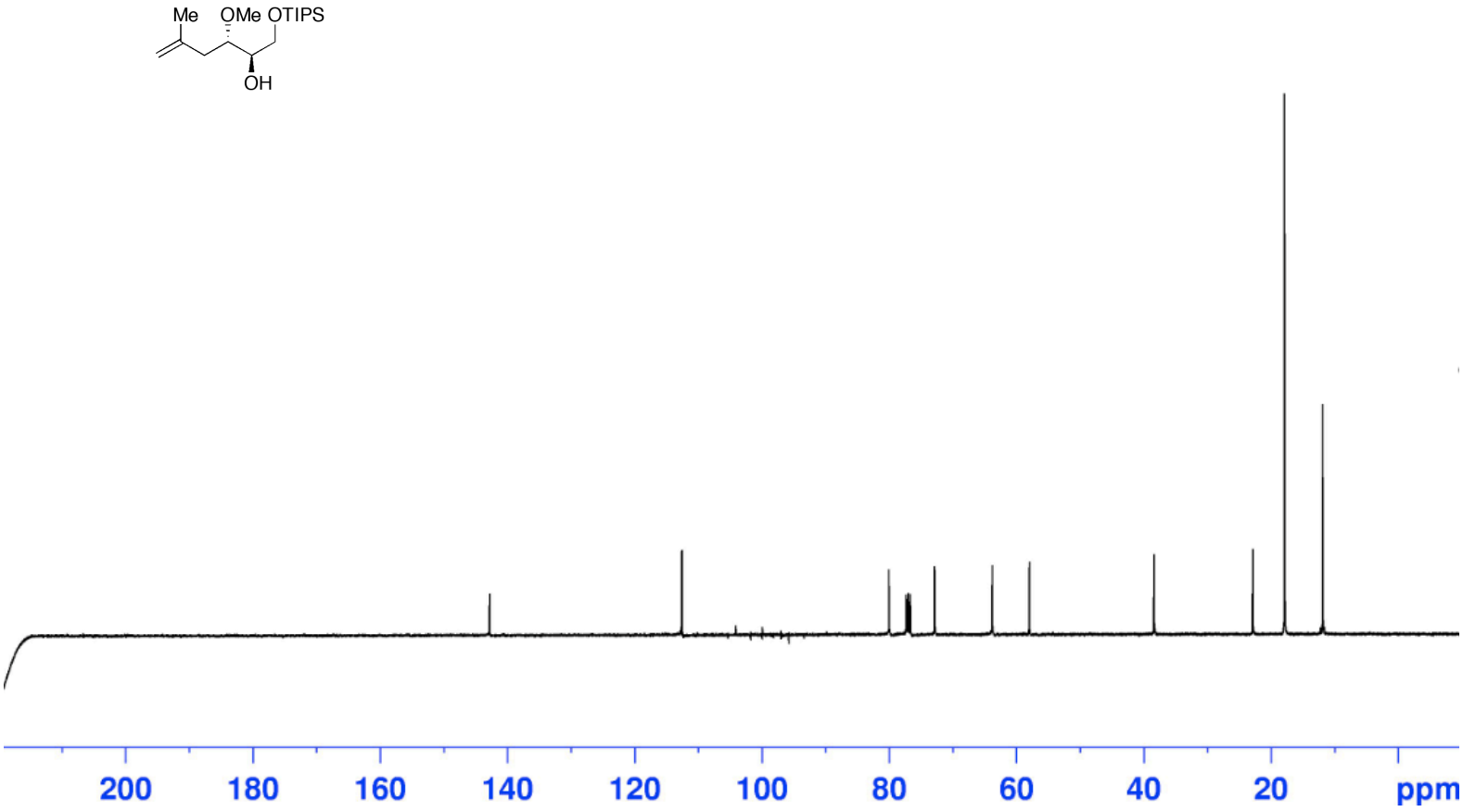
^{1}H NMR Spectrum: Methyl Ether, 300 MHz ($CDCl_3$)



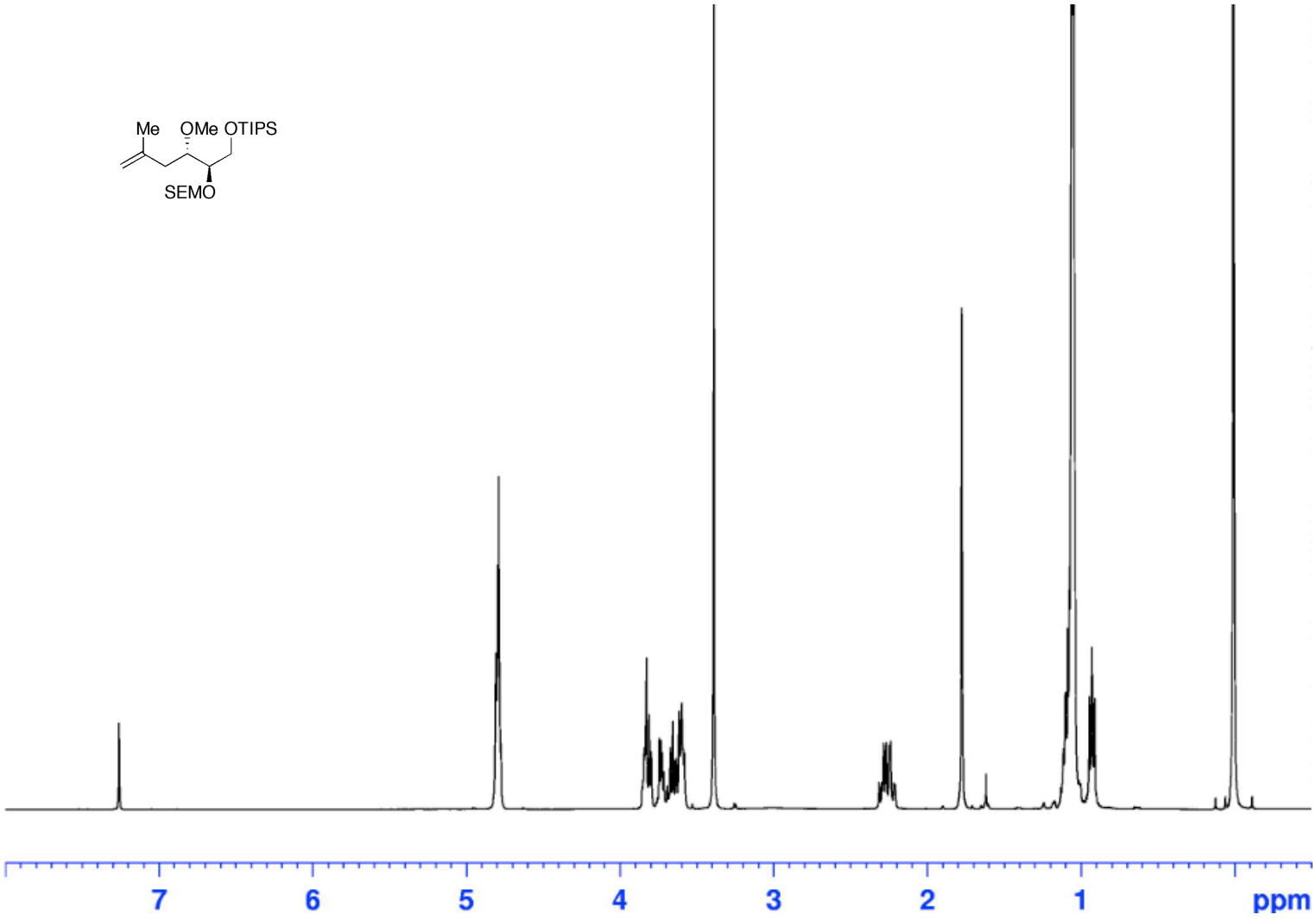
^{13}C NMR Spectrum: Methyl Ether, 100 MHz ($CDCl_3$)



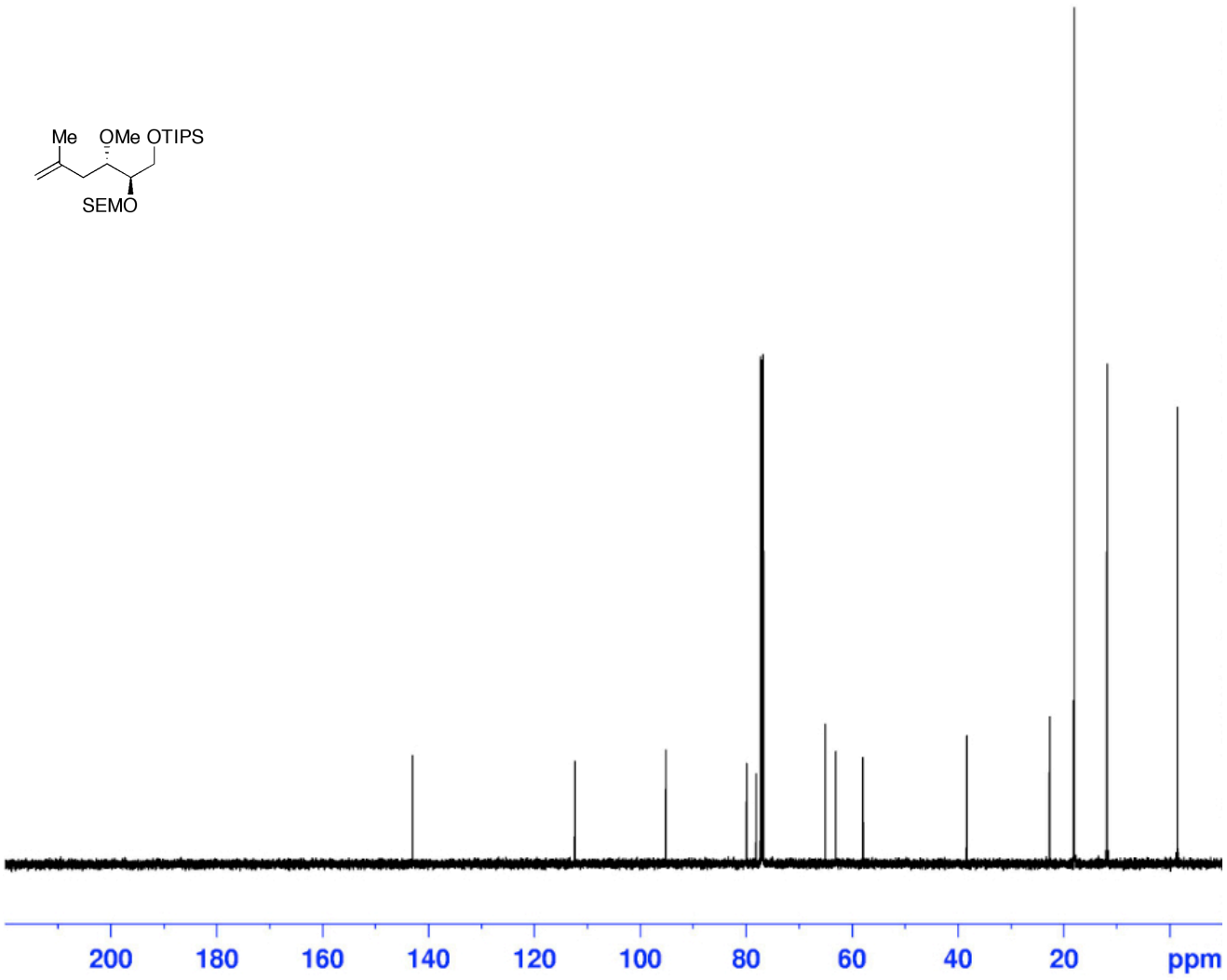
^{1}H NMR Spectrum: Alcohol **210**, 400 MHz ($CDCl_3$)



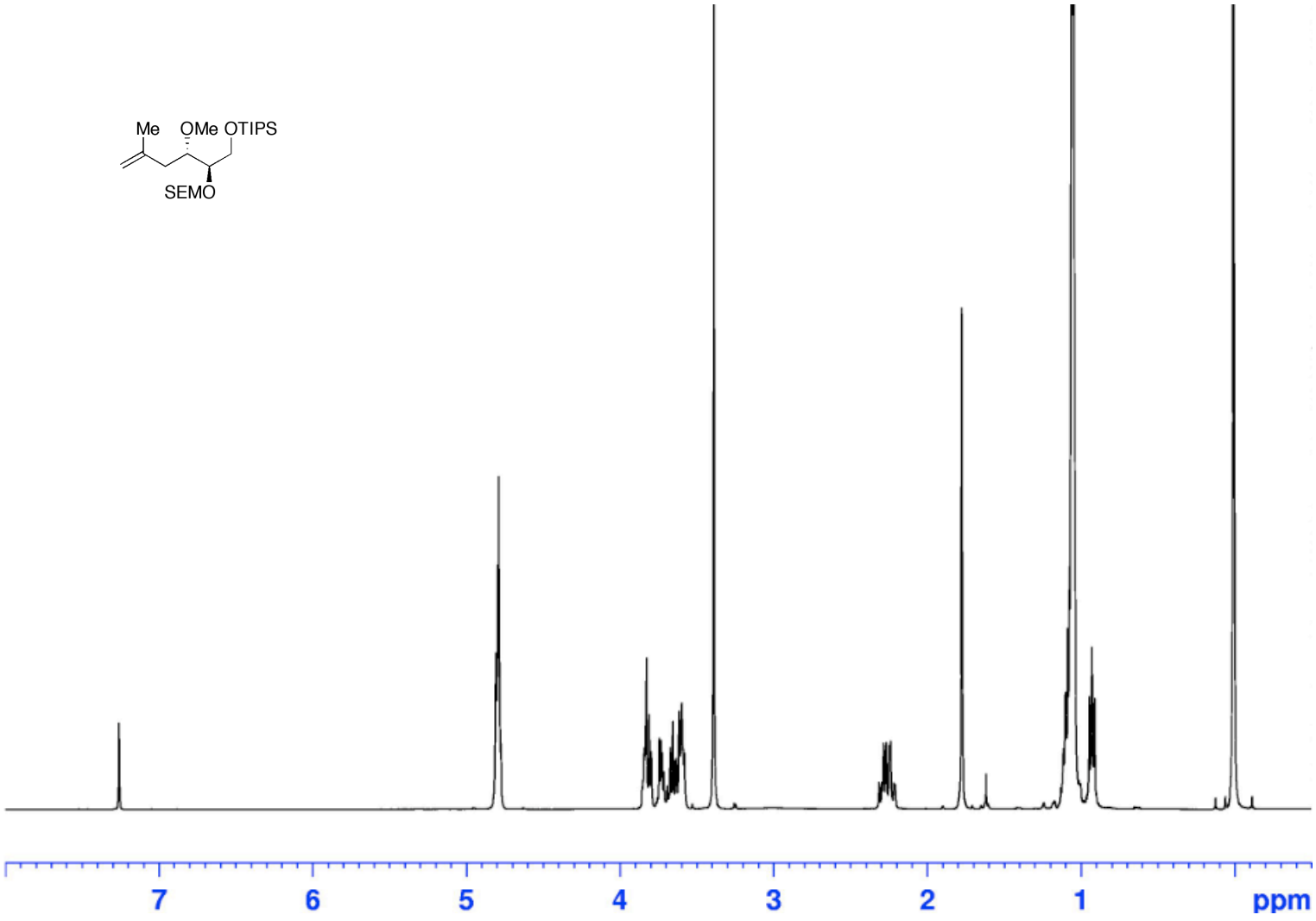
^{13}C NMR Spectrum: Alcohol **210**, 100 MHz ($CDCl_3$)



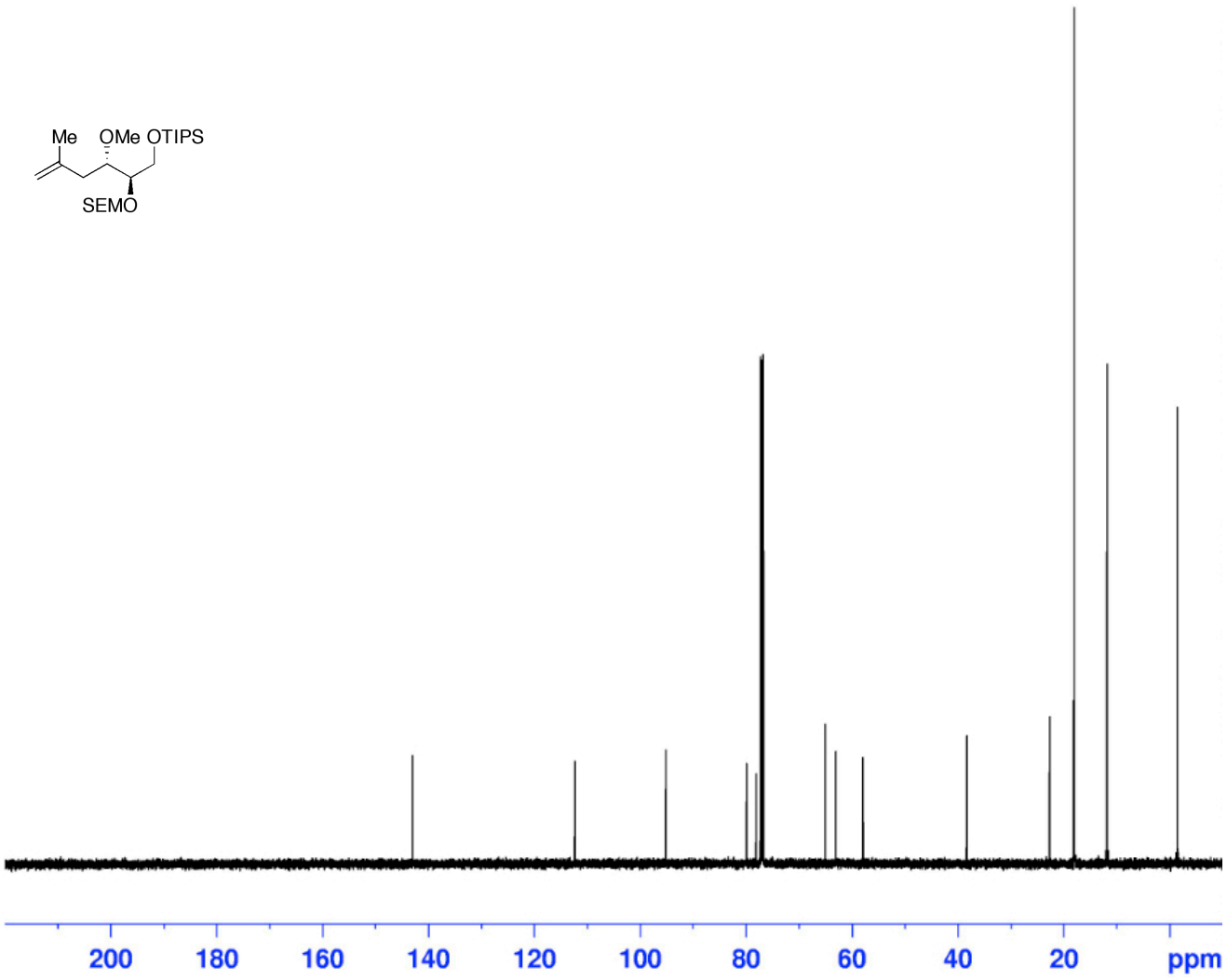
^{1}H NMR Spectrum: SEM Ether, 400 MHz ($CDCl_3$)



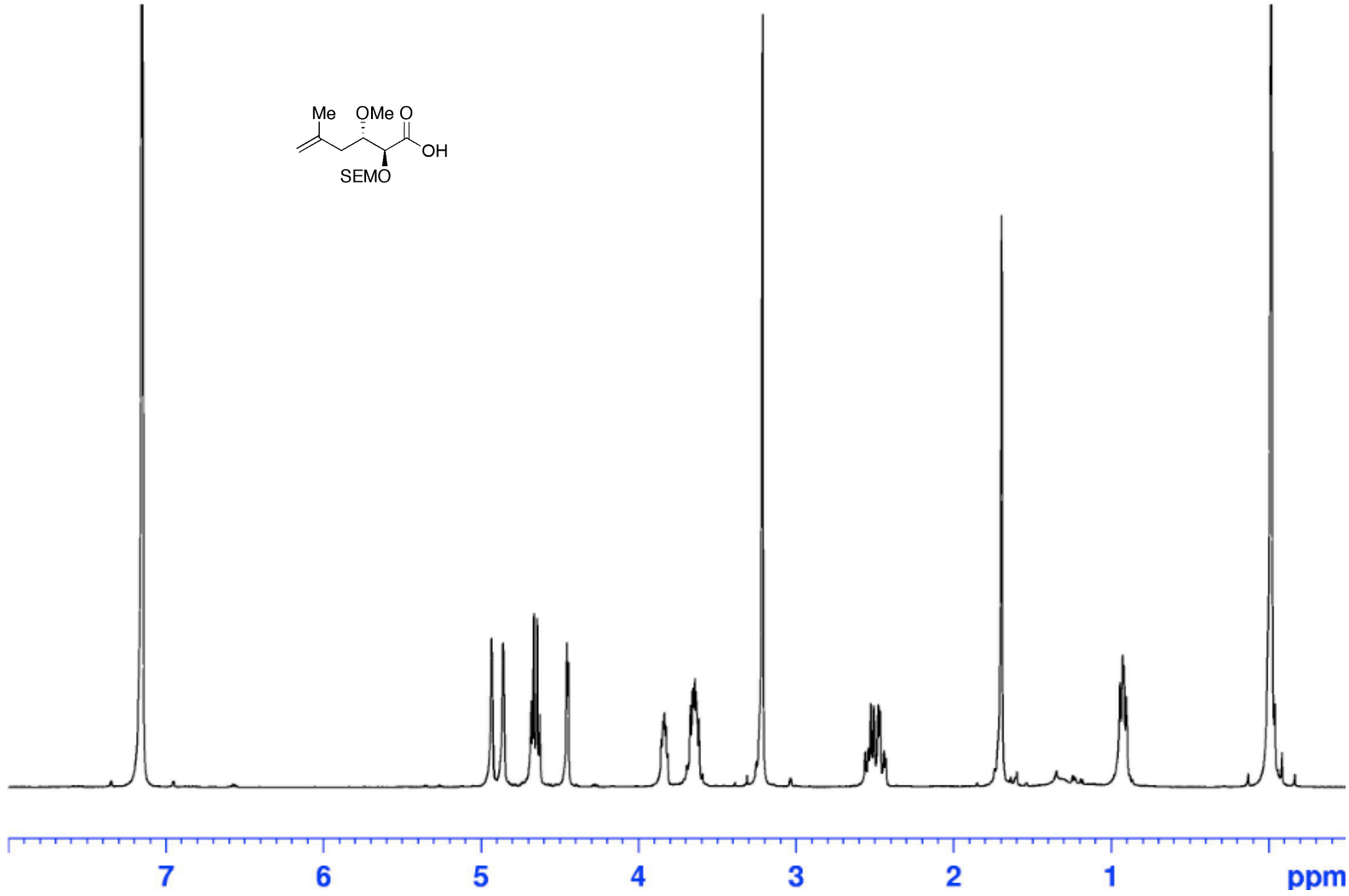
^{13}C NMR Spectrum: SEM Ether, 100 MHz ($CDCl_3$)



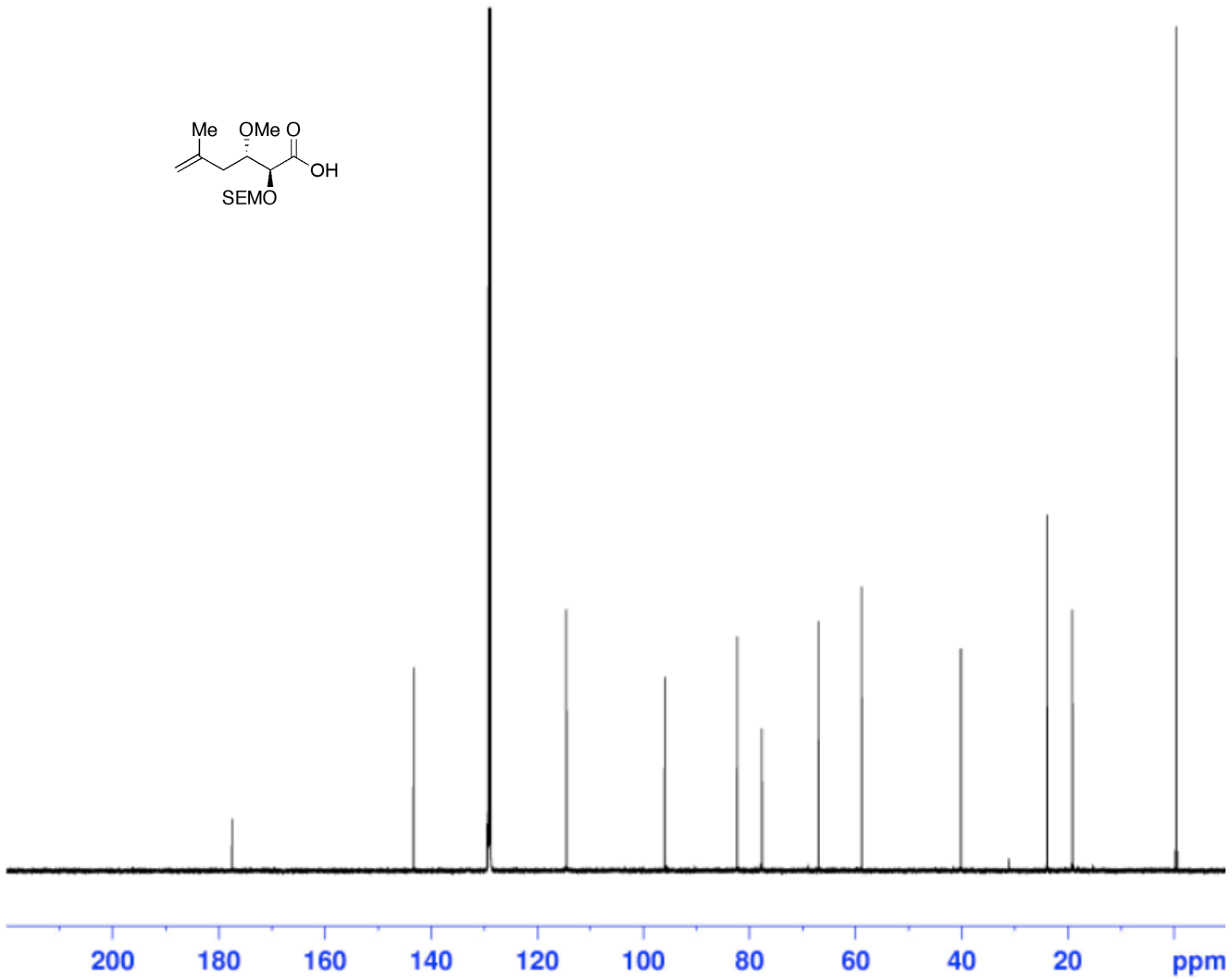
^{1}H NMR Spectrum: SEM Ether, 400 MHz ($CDCl_3$)



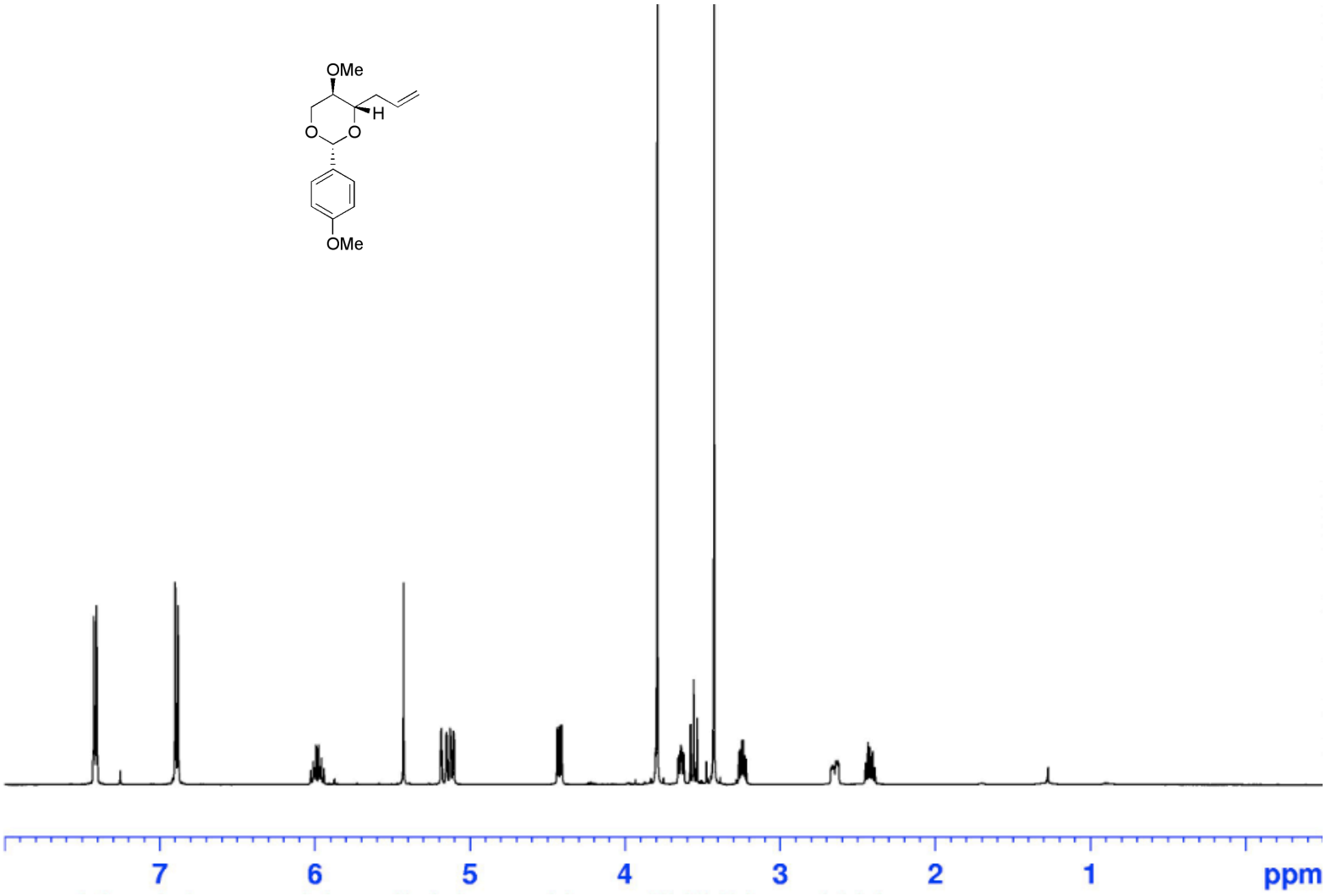
^{13}C NMR Spectrum: SEM Ether, 100 MHz ($CDCl_3$)



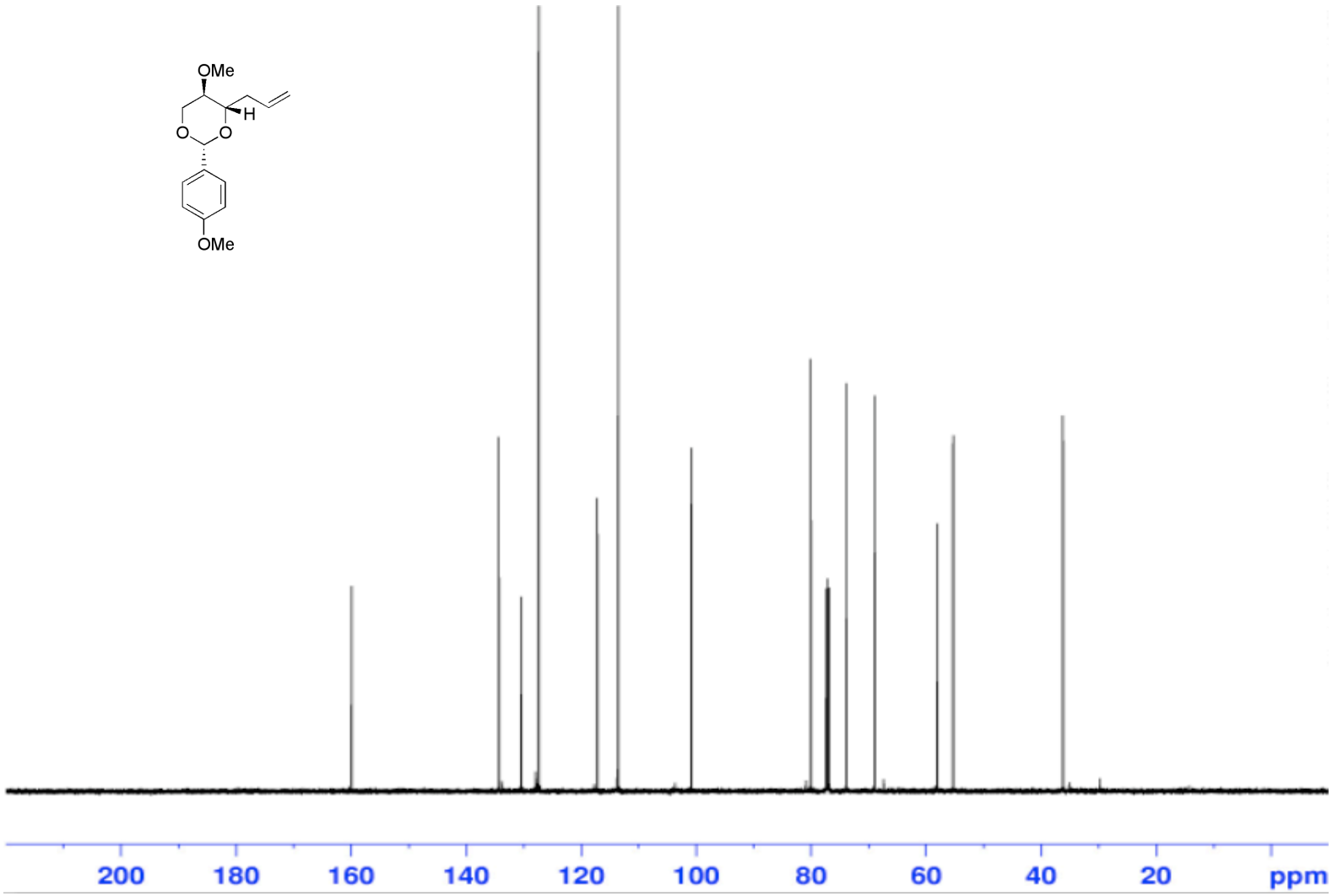
^{1}H NMR Spectrum: Acid **137**, 400 MHz (C_6D_6)



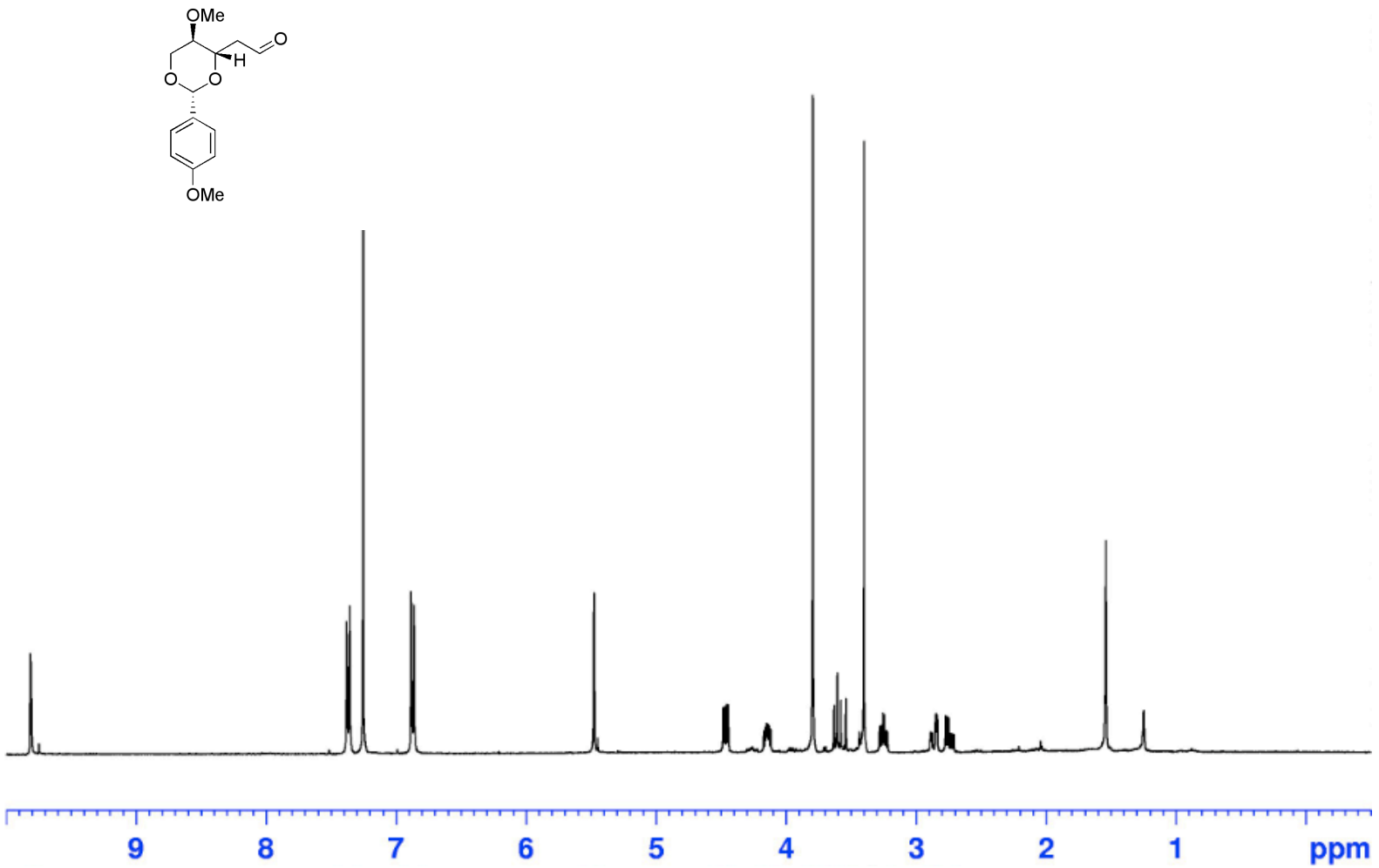
^{13}C NMR Spectrum: Acid **137**, 125 MHz (C_6D_6)



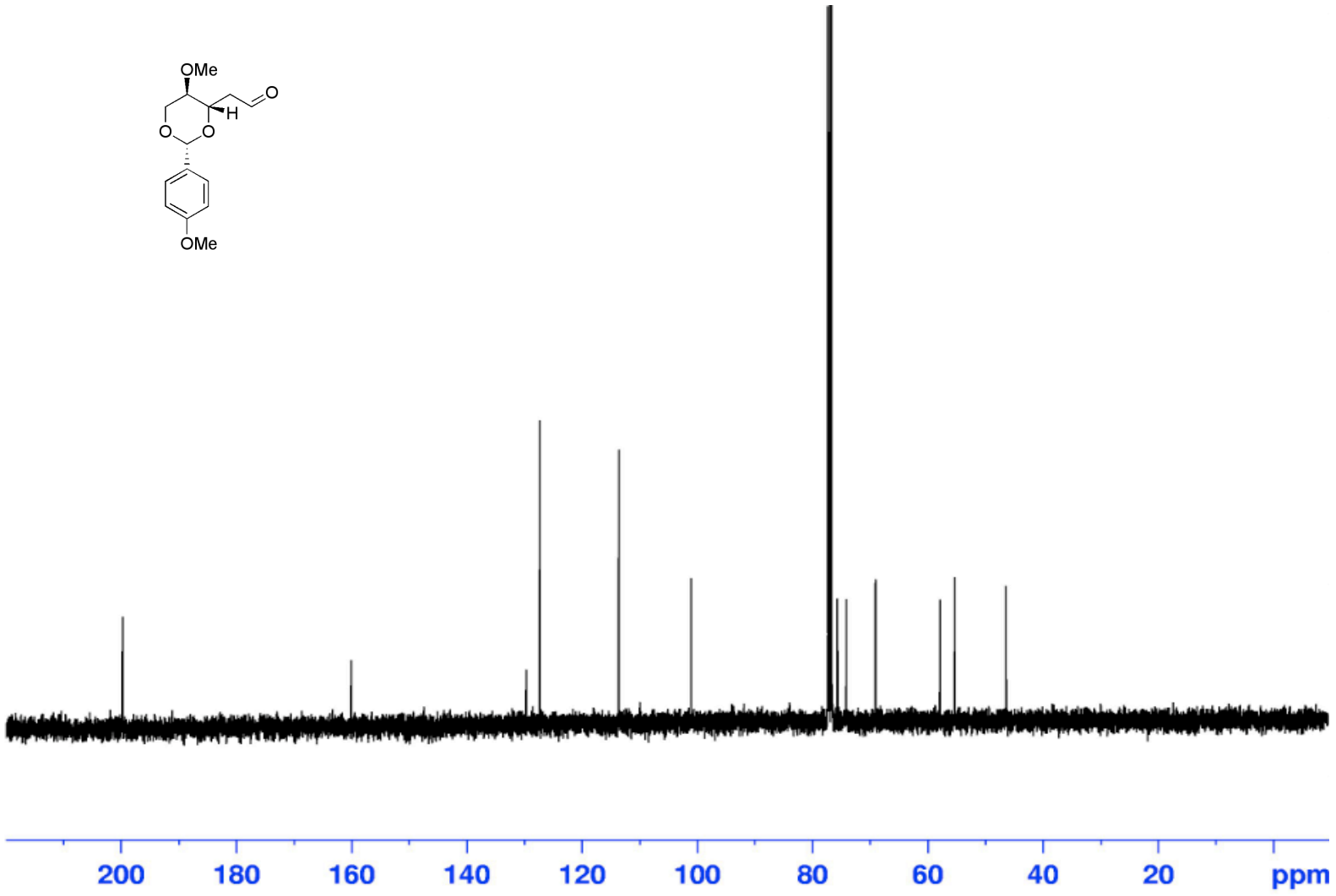
^{1}H NMR Spectrum: Methyl Ether, 500 MHz ($CDCl_3$)



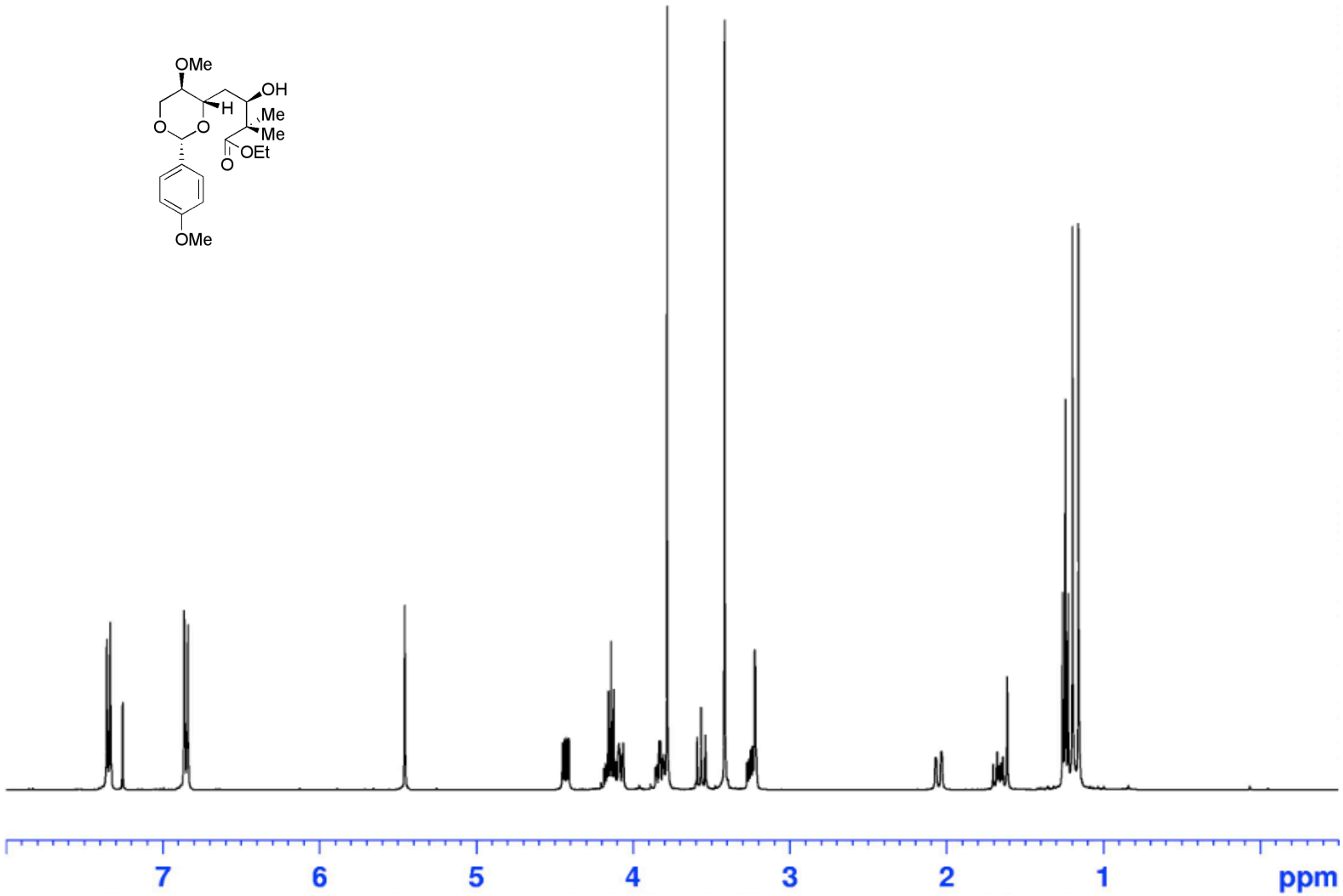
^{13}C NMR Spectrum: Methyl Ether, 125 MHz ($CDCl_3$)



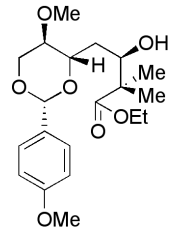
^{1}H Spectrum: Aldehyde **212**, 400 MHz ($CDCl_3$)



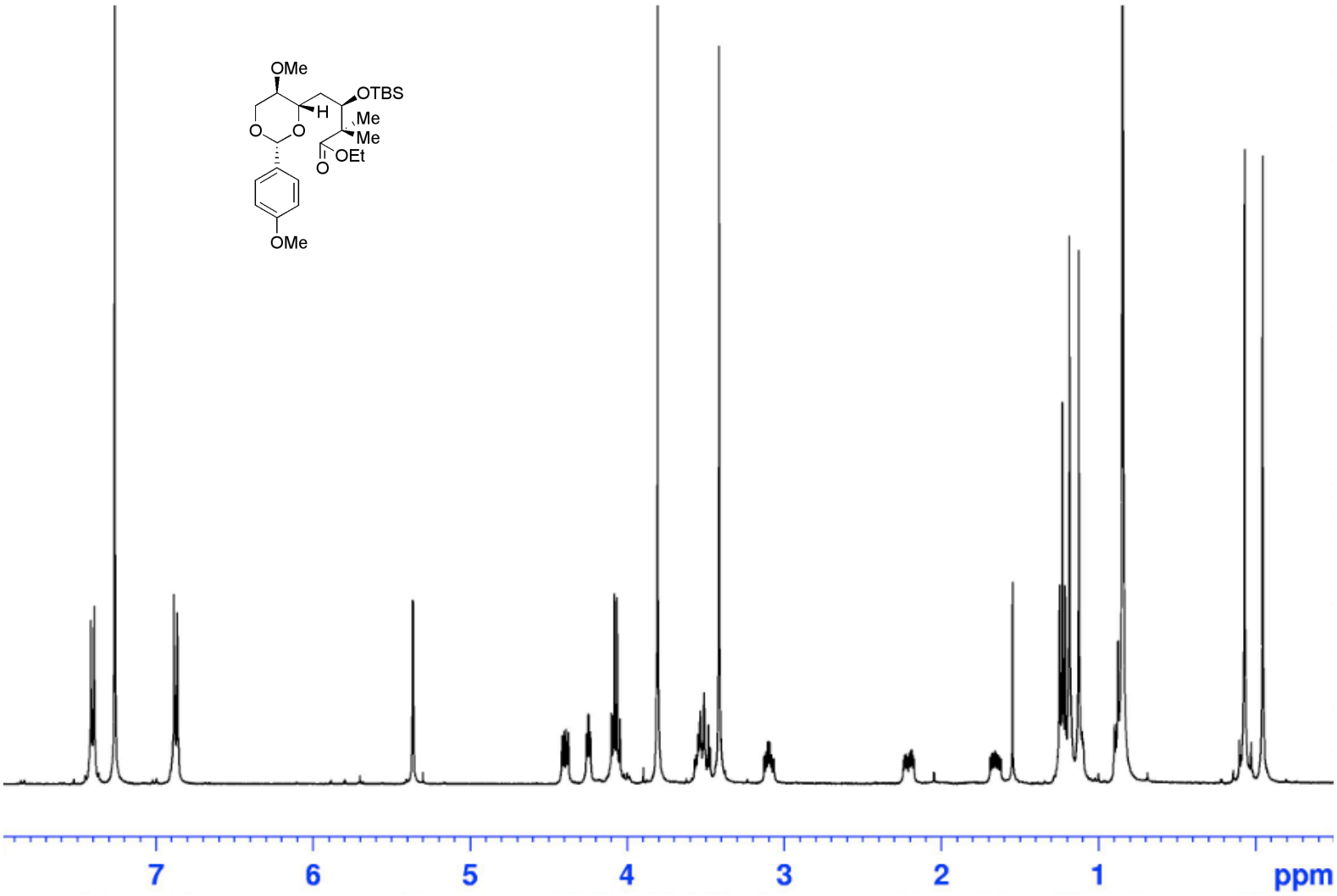
^{13}C Spectrum: Aldehyde **212**, 100 MHz ($CDCl_3$)



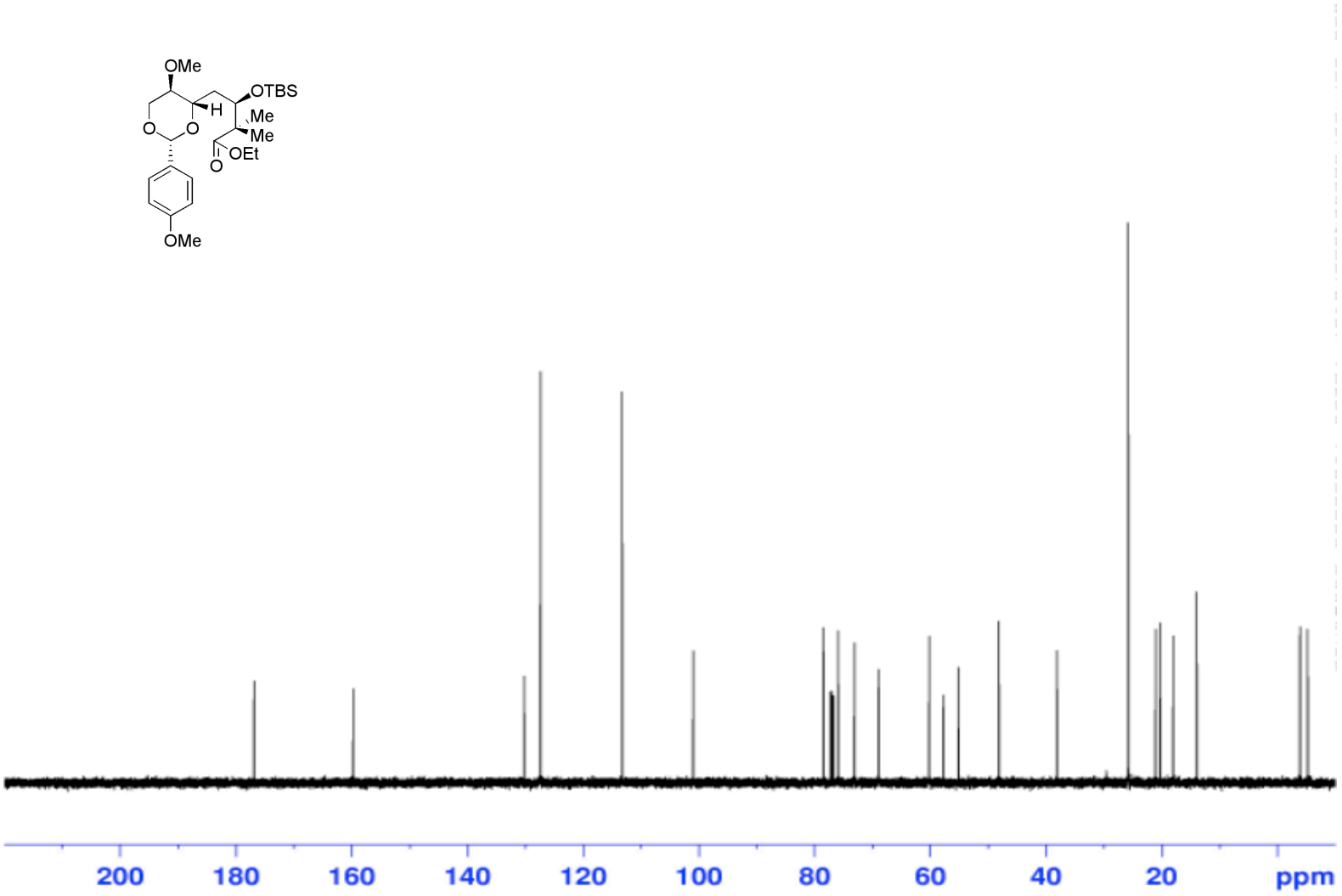
^{1}H Spectrum: Alcohol **213**, 400 MHz ($CDCl_3$)



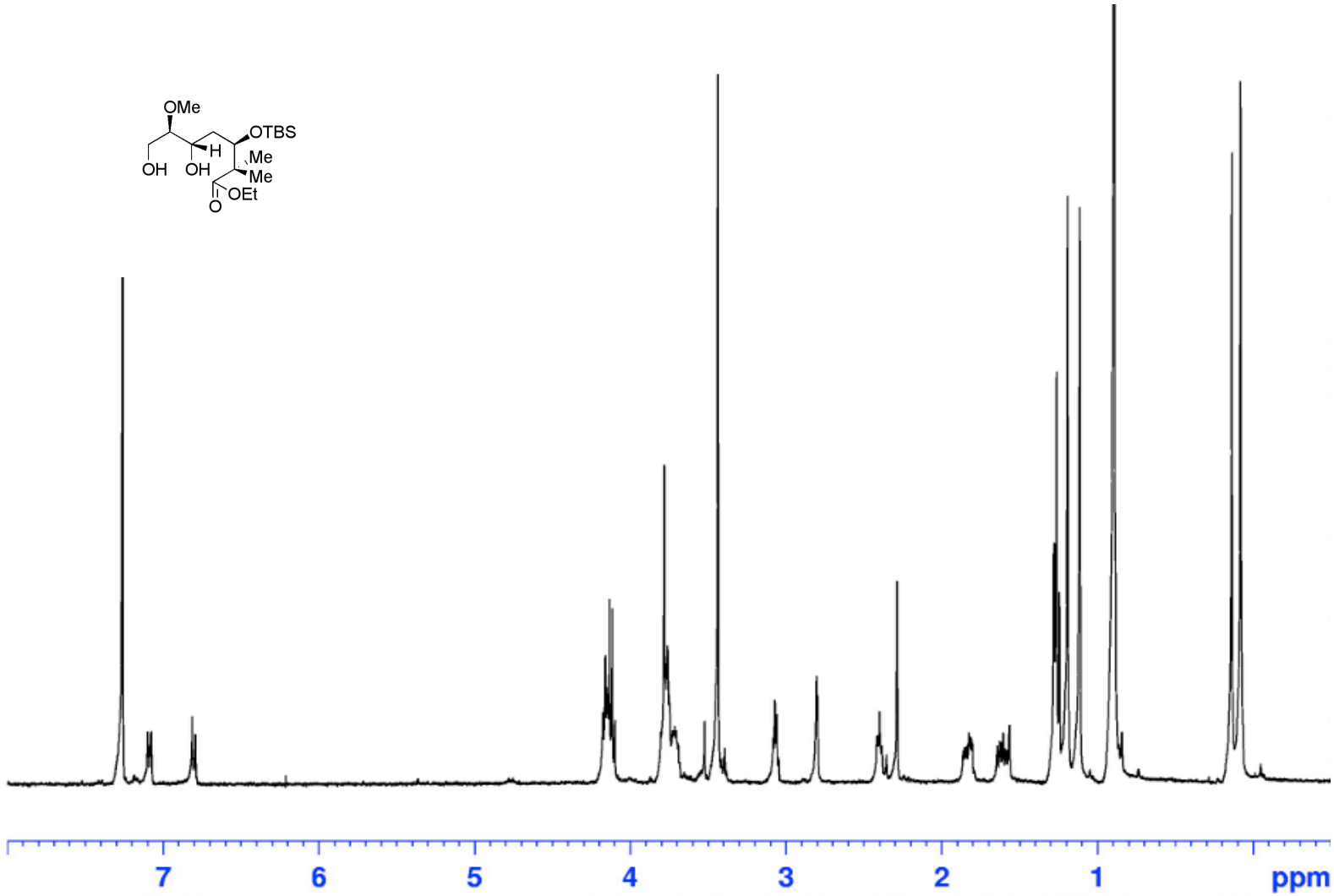
^{13}C Spectrum: Alcohol **213**, 100 MHz ($CDCl_3$)



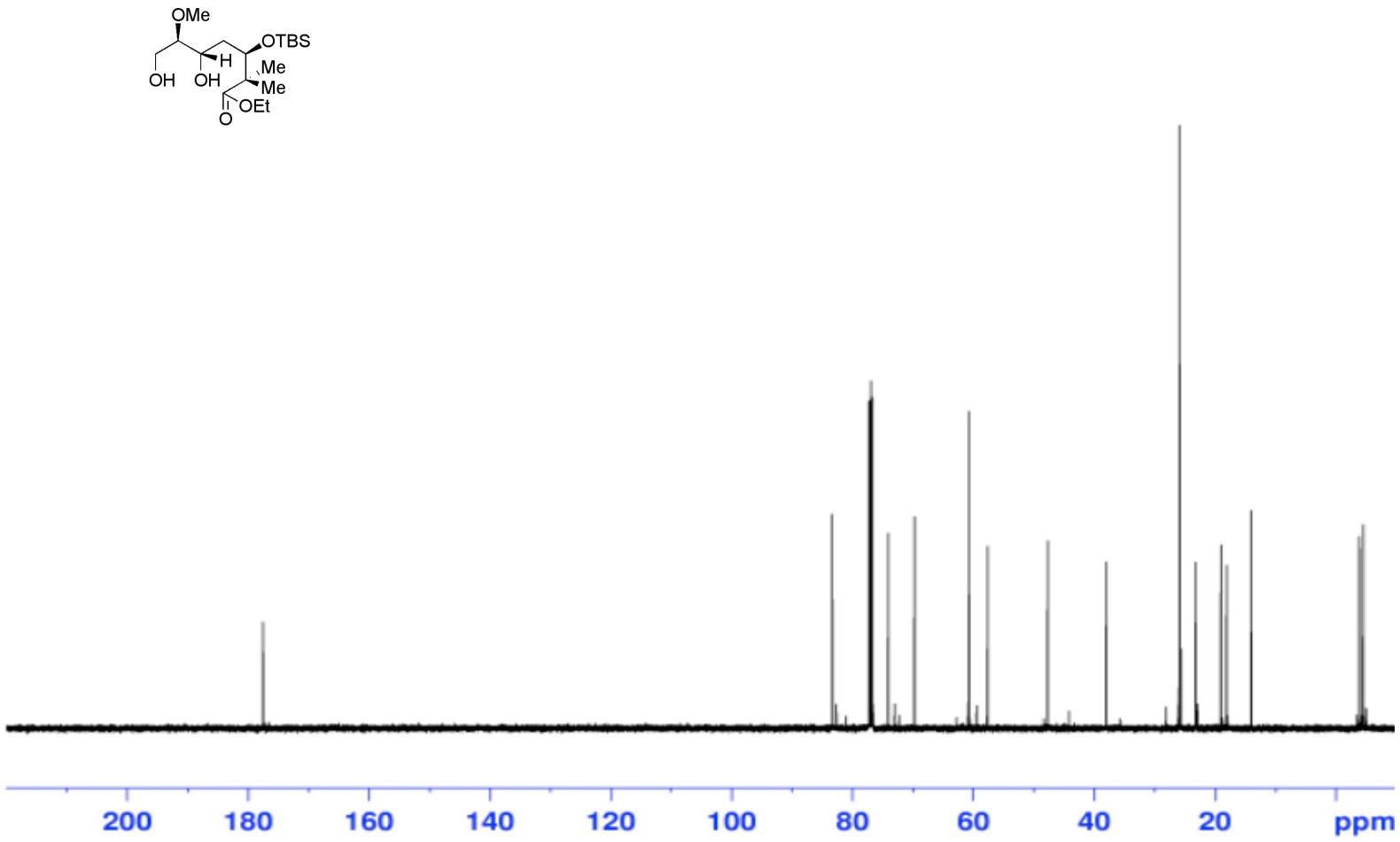
^{1}H Spectrum: TBS Ether, 400 MHz ($CDCl_3$)



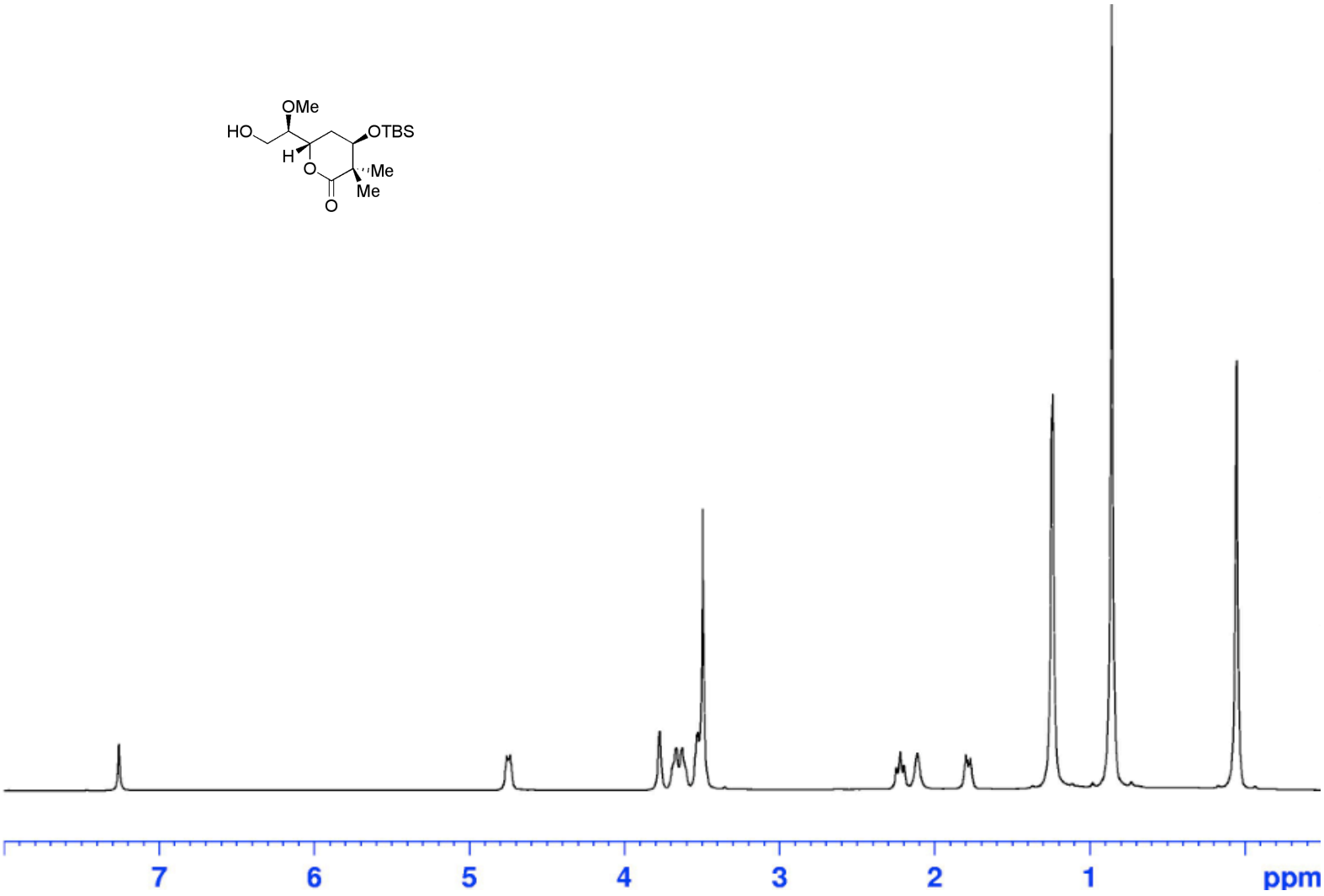
^{13}C Spectrum: TBS Ether, 125 MHz ($CDCl_3$)



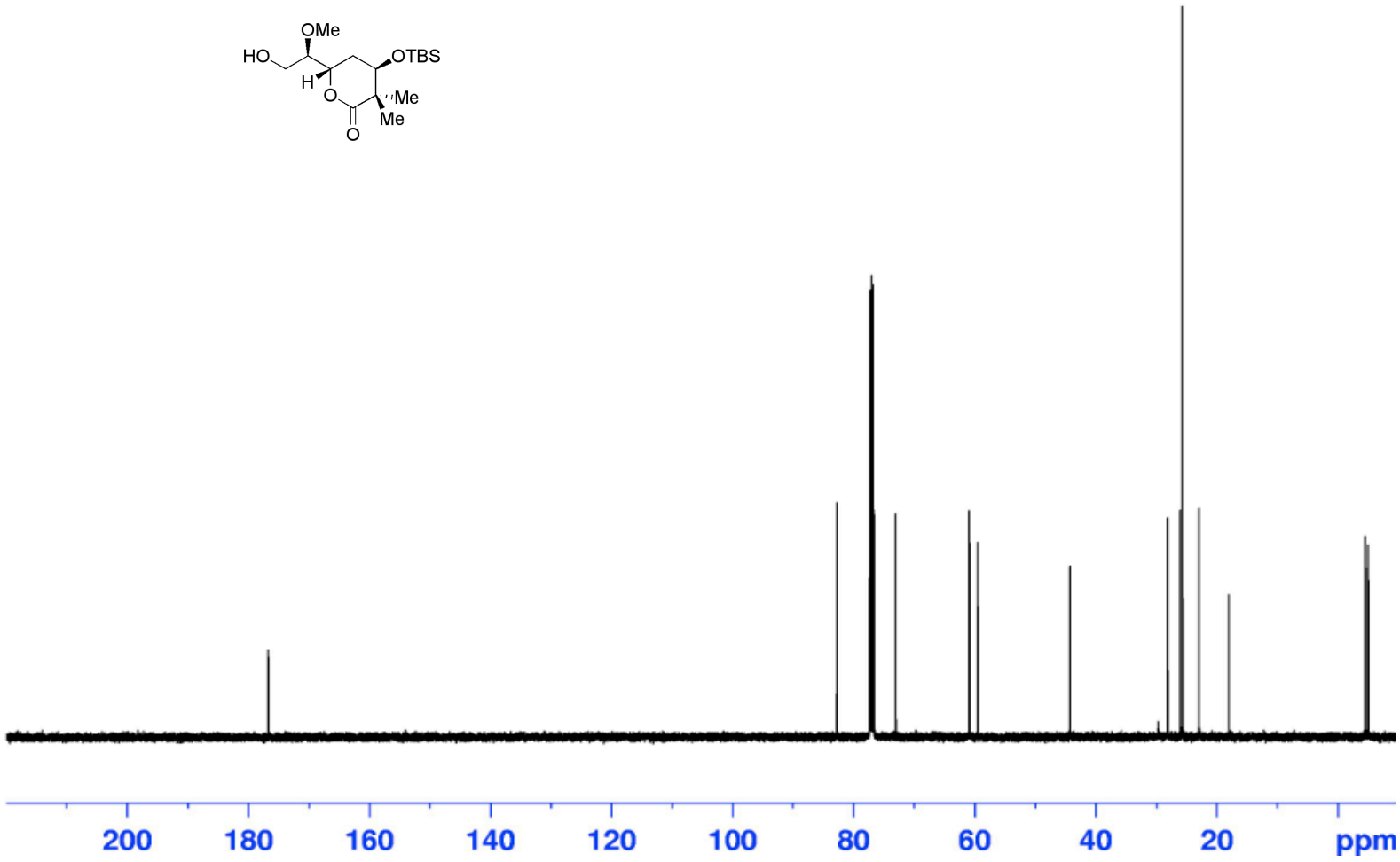
^{1}H Spectrum: 1,3-Diol, 100 MHz ($CDCl_3$)



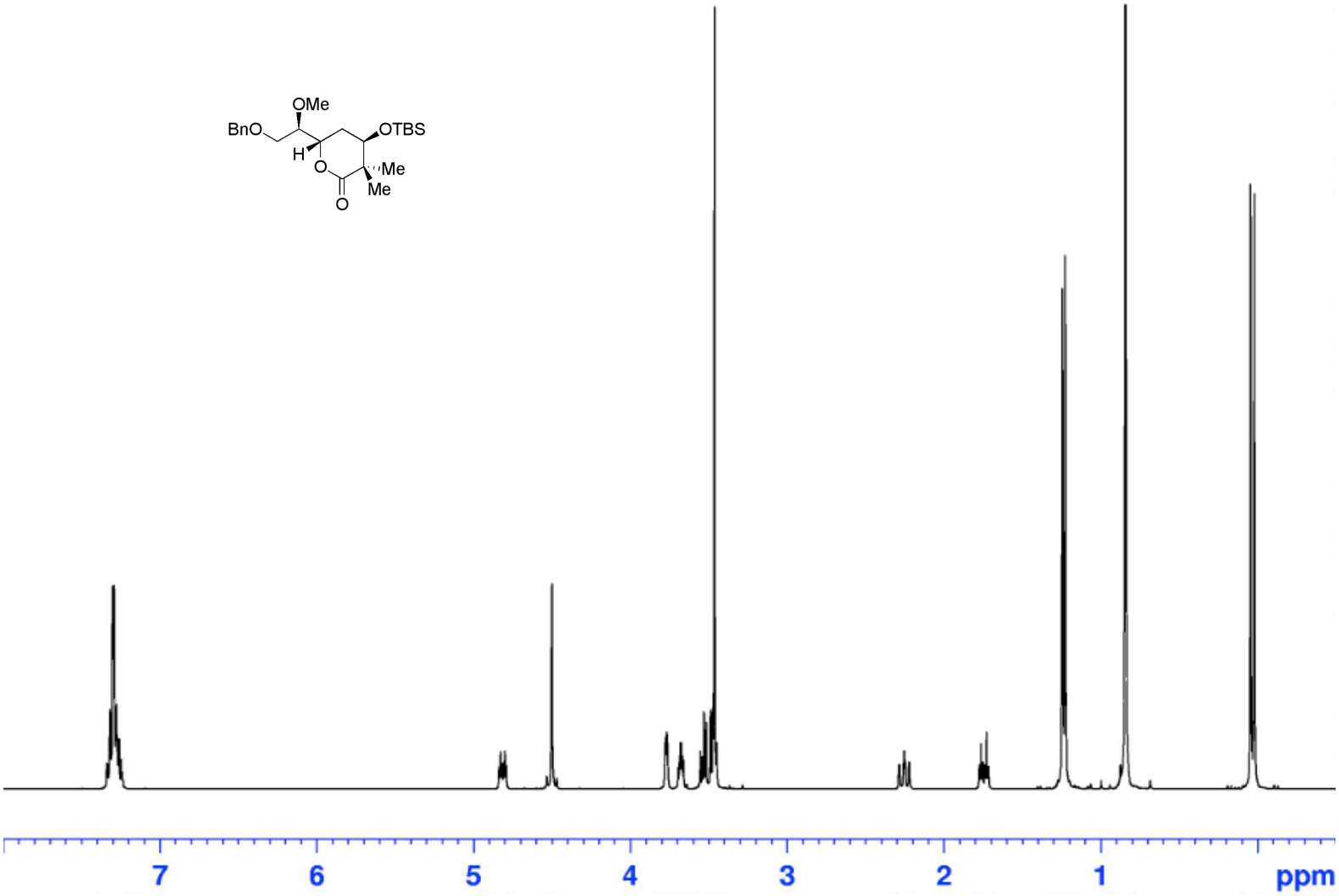
^{13}C Spectrum: 1,3-Diol, 125 MHz ($CDCl_3$)



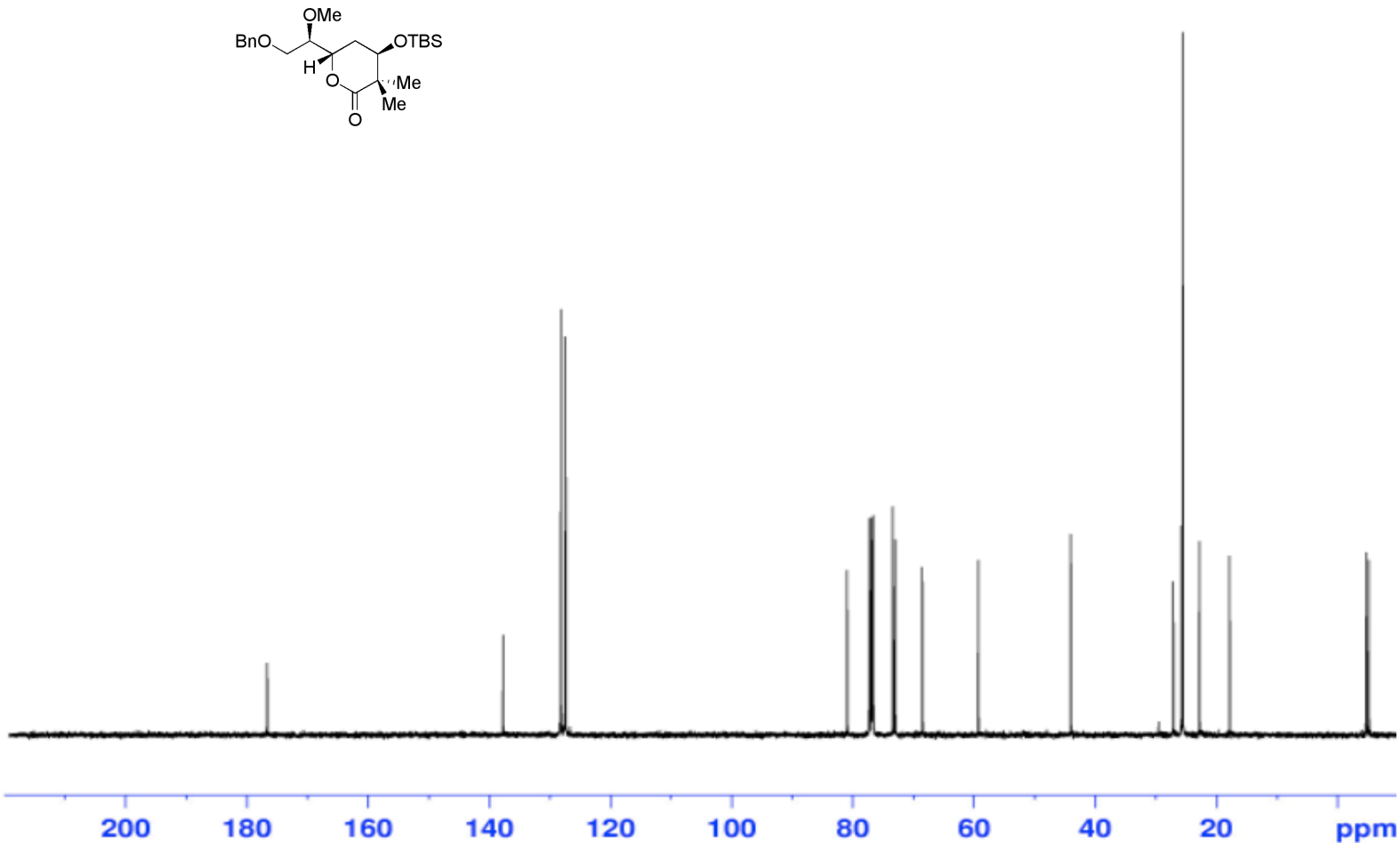
^{1}H Spectrum: Alcohol **214**, 500 MHz ($CDCl_3$)



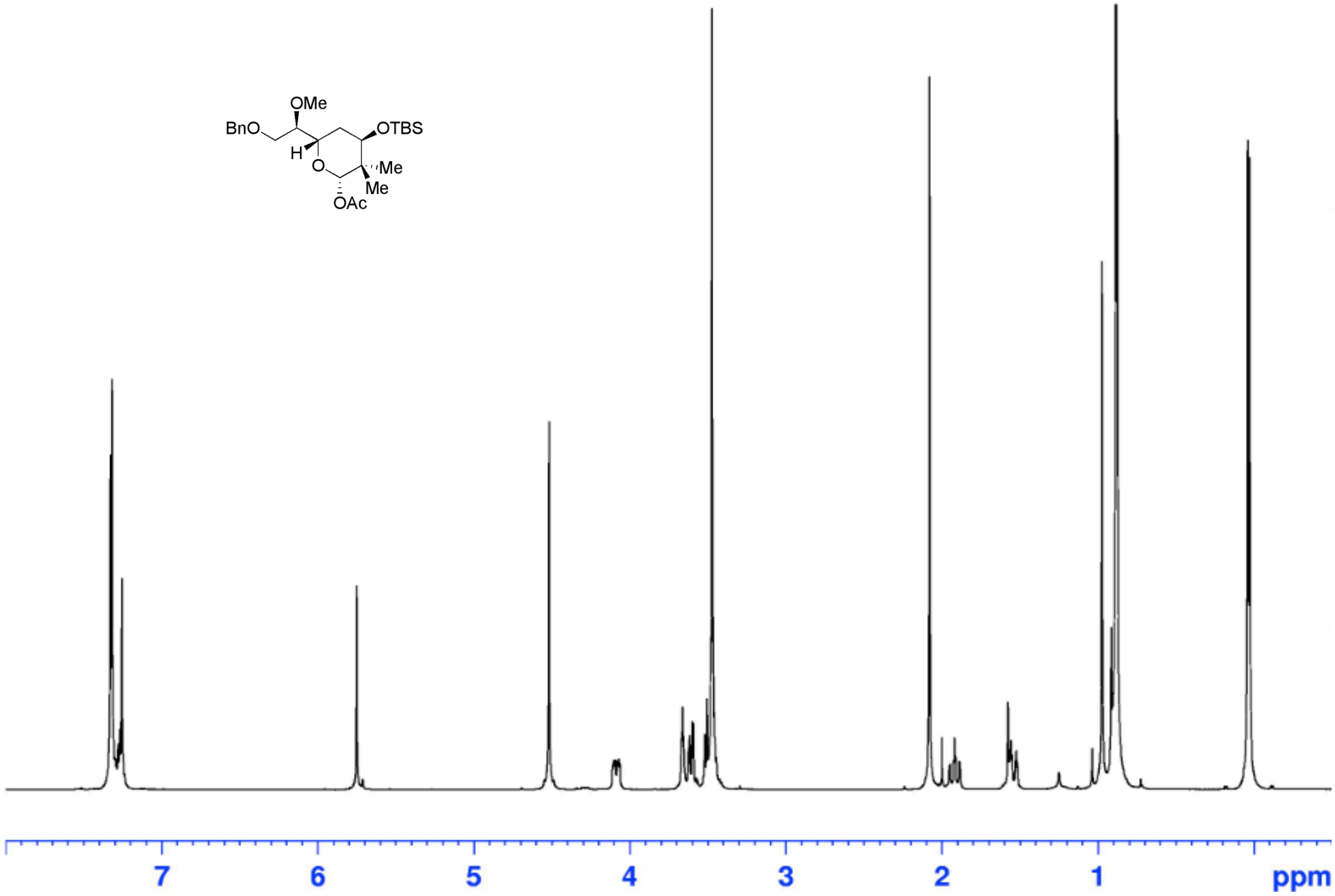
^{13}C Spectrum: TBS Ether **214**, 125 MHz ($CDCl_3$)



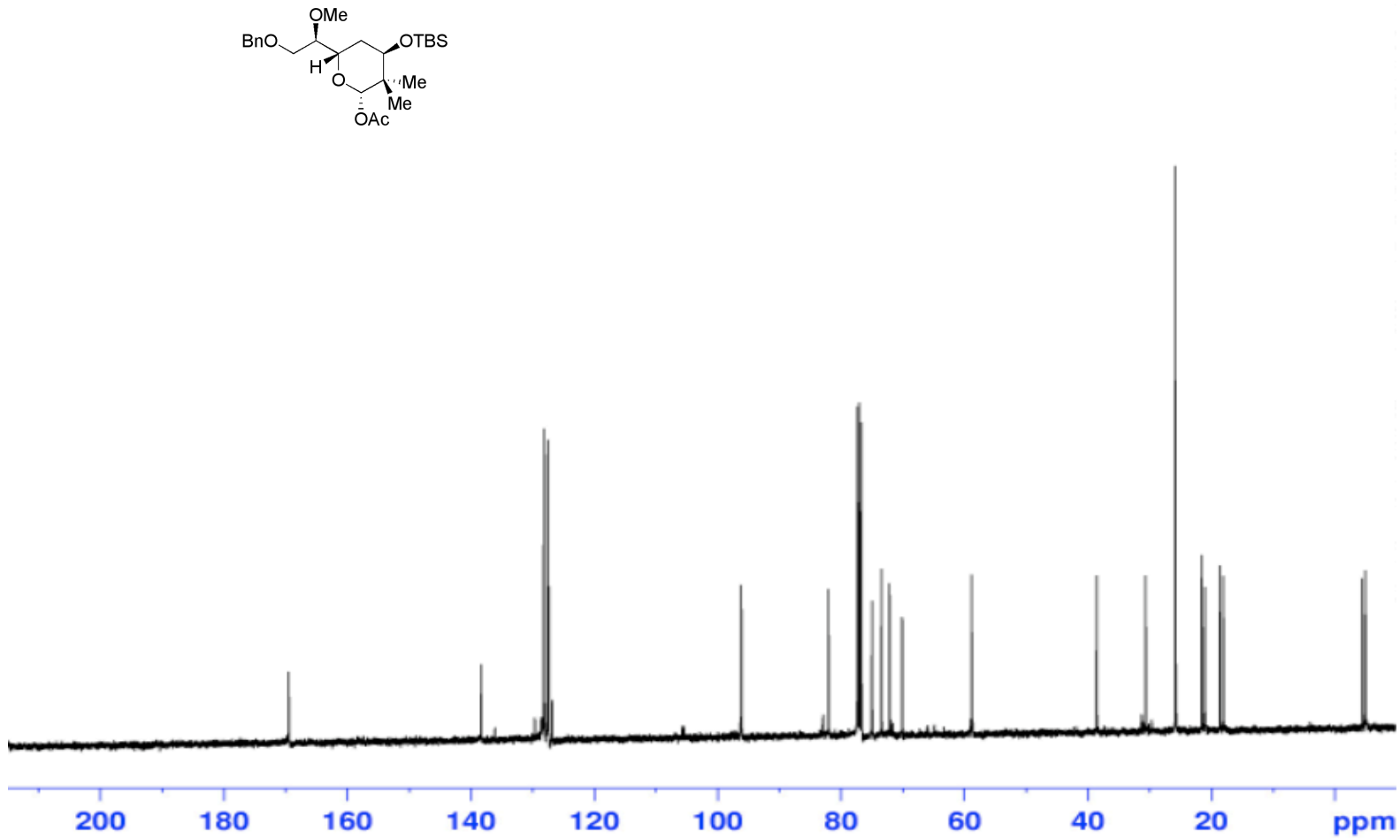
^{1}H Spectrum: Benzyl Ether **215**, 400 MHz ($CDCl_3$)



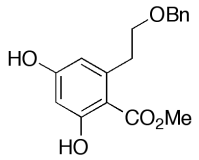
^{13}C Spectrum: Benzyl Ether **215**, 100 MHz ($CDCl_3$)

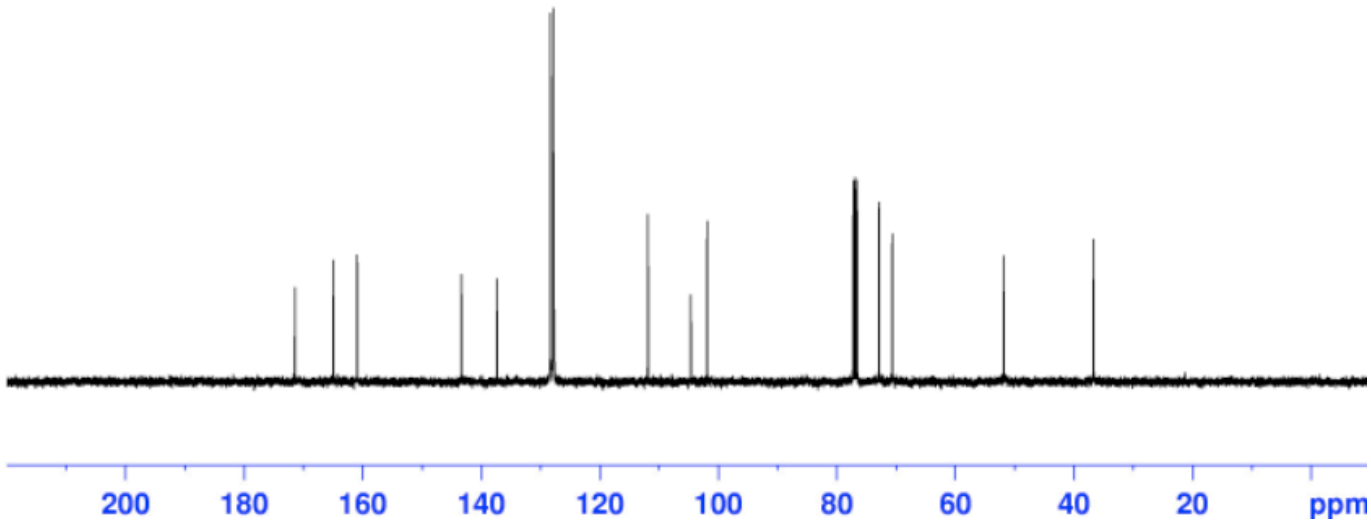


^{1}H Spectrum: Acetate **193**, 400 MHz ($CDCl_3$)

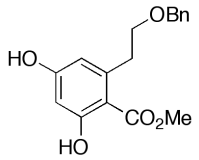


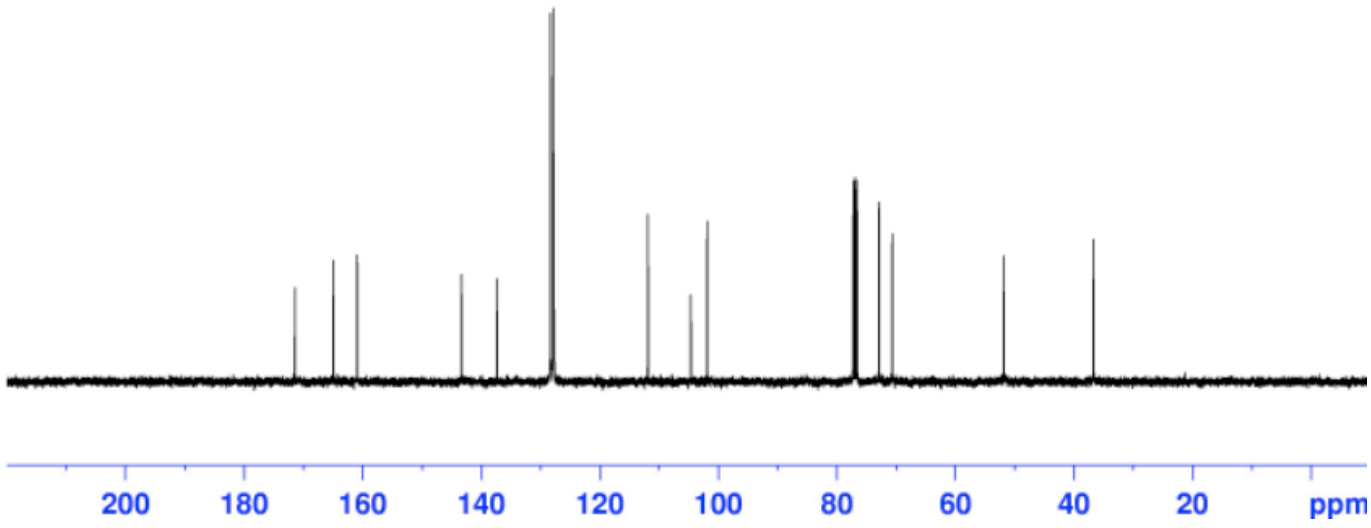
^{13}C Spectrum: Acetate **193**, 125 MHz ($CDCl_3$)



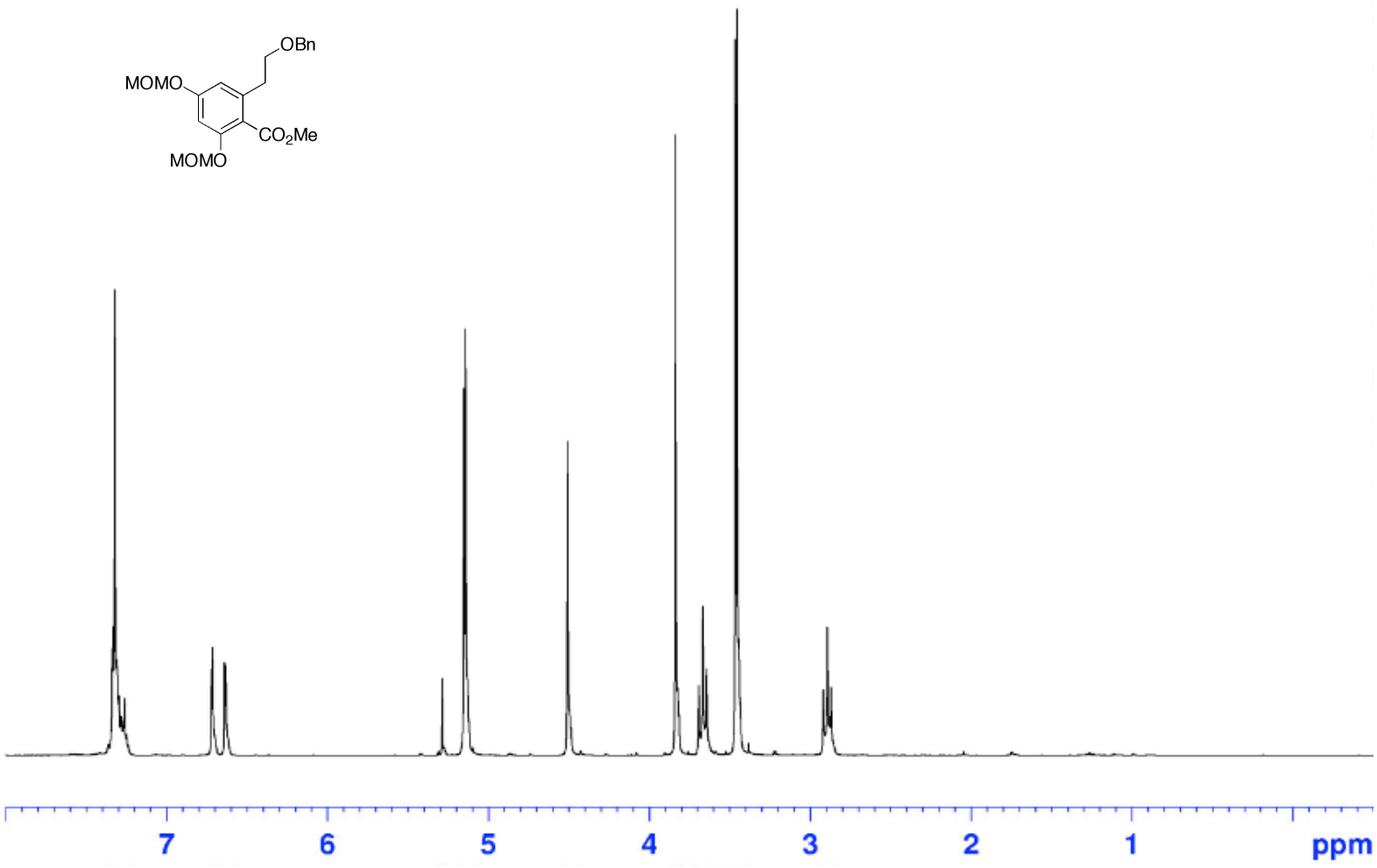


^{13}C NMR Spectrum: Catechol **218**, 100 MHz ($CDCl_3$)

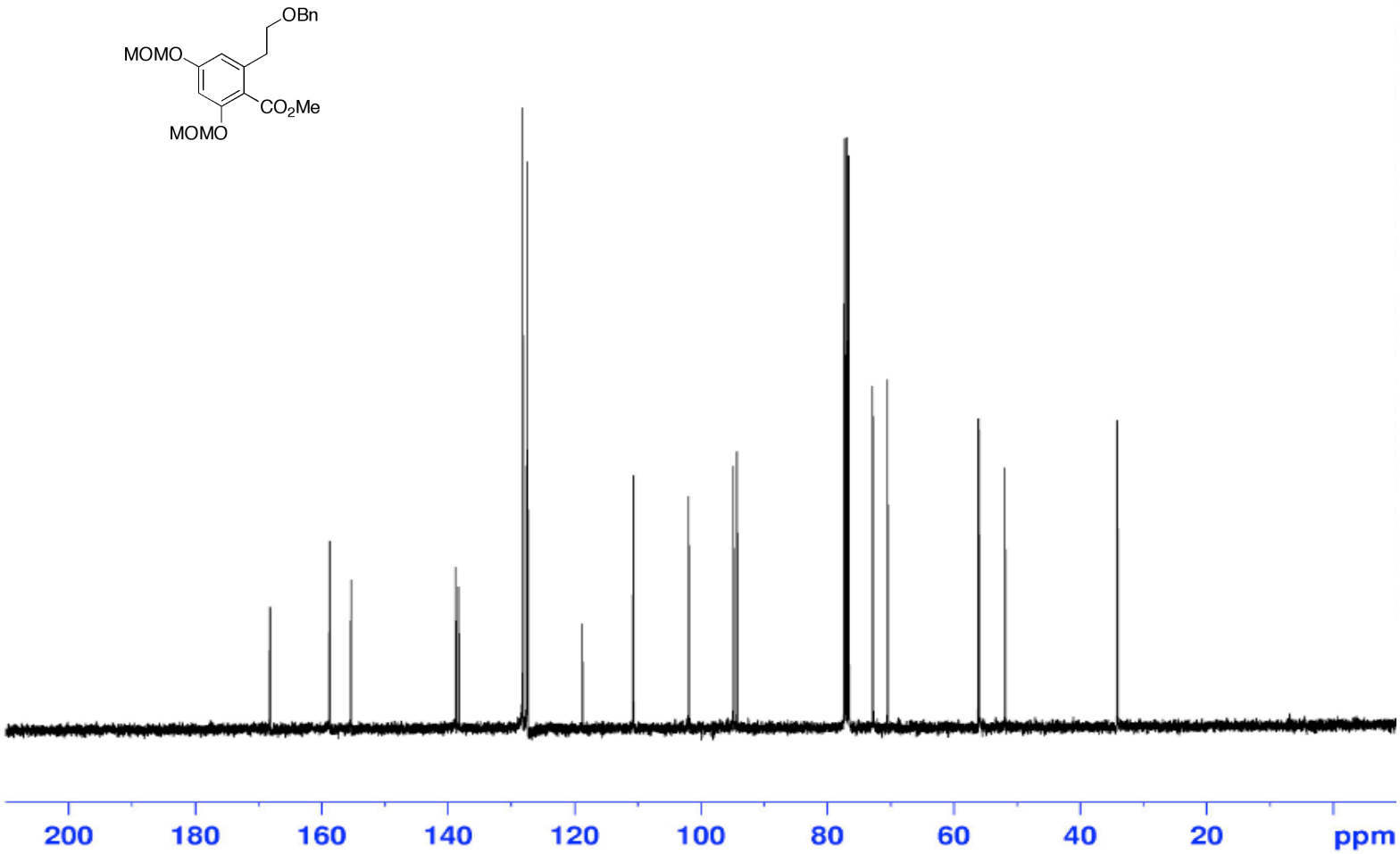




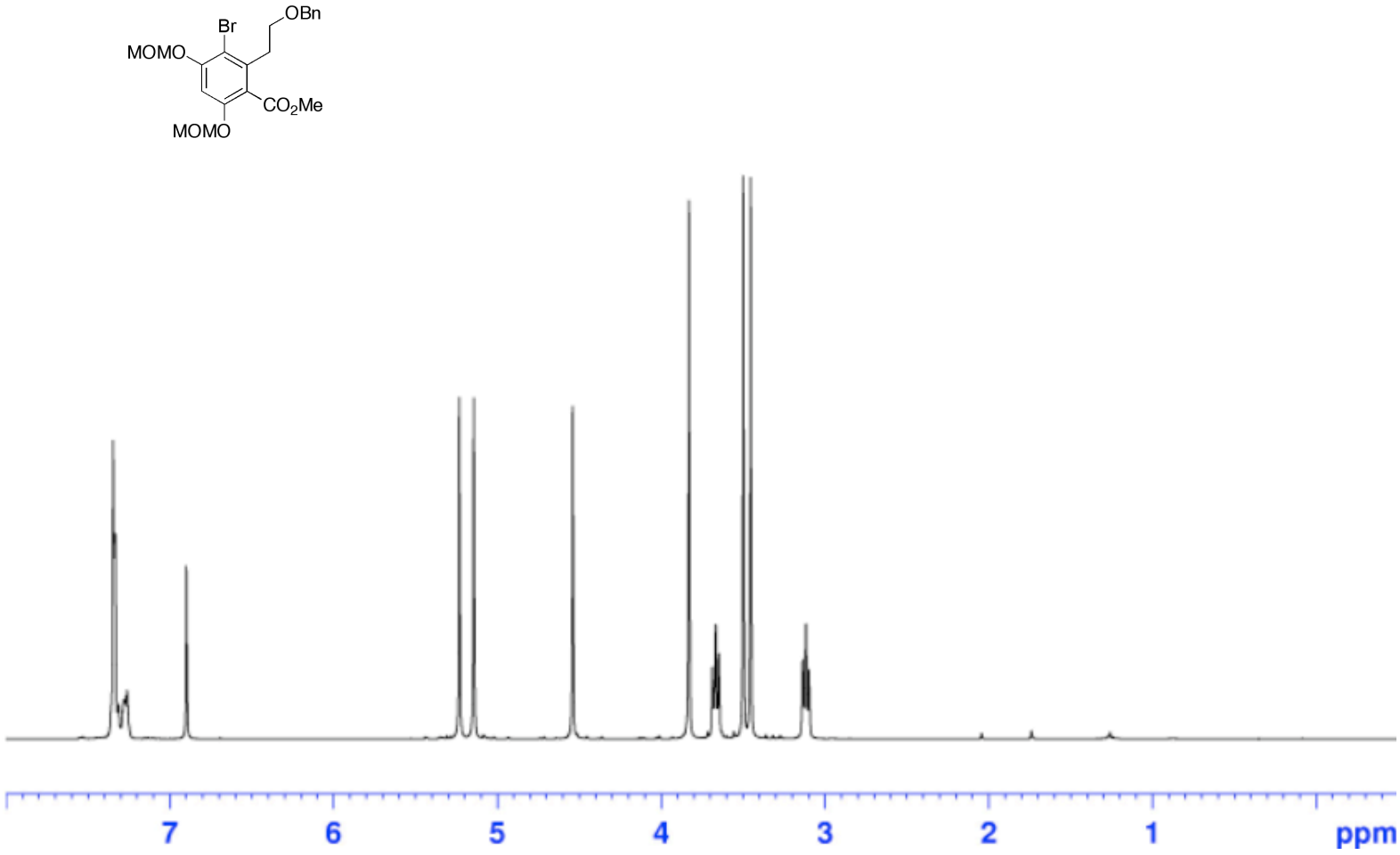
^{13}C NMR Spectrum: Catechol **218**, 100 MHz ($CDCl_3$)



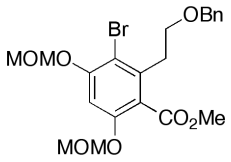
^{1}H NMR Spectrum: MOM Ether, 400 MHz ($CDCl_3$)

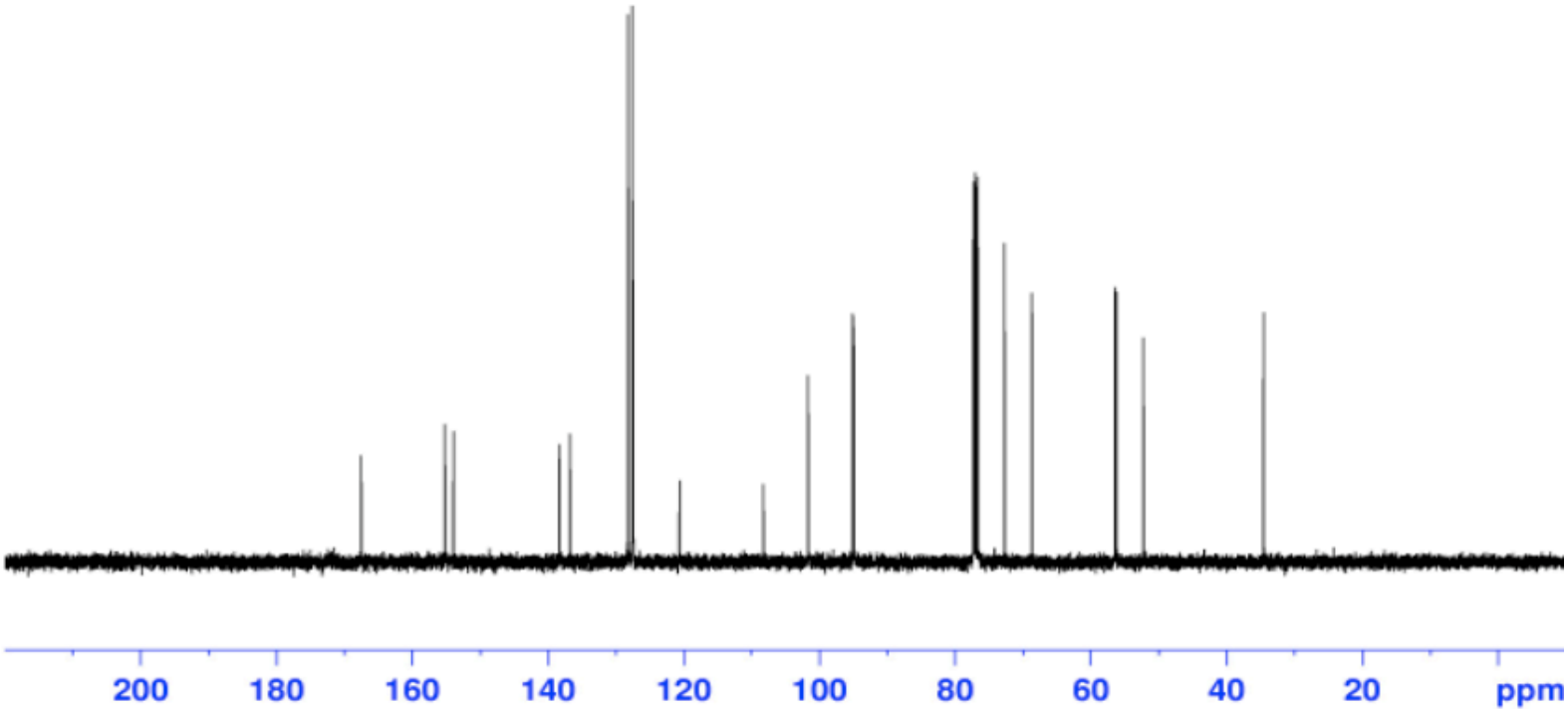


^{13}C NMR Spectrum: MOM Ether, 100 MHz ($CDCl_3$)

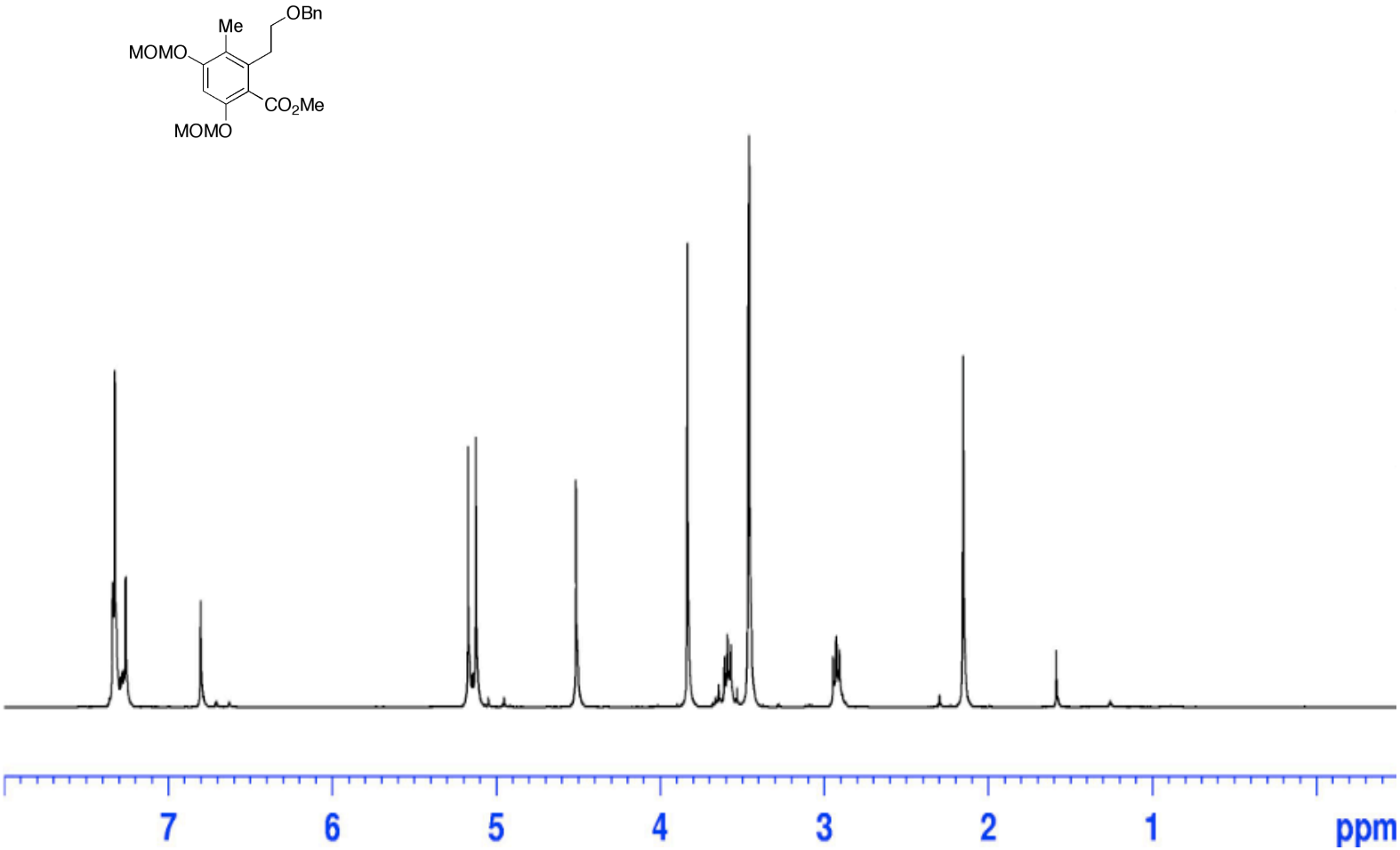


^{1}H NMR Spectrum: Aryl Bromide **219**, 400 MHz ($CDCl_3$)

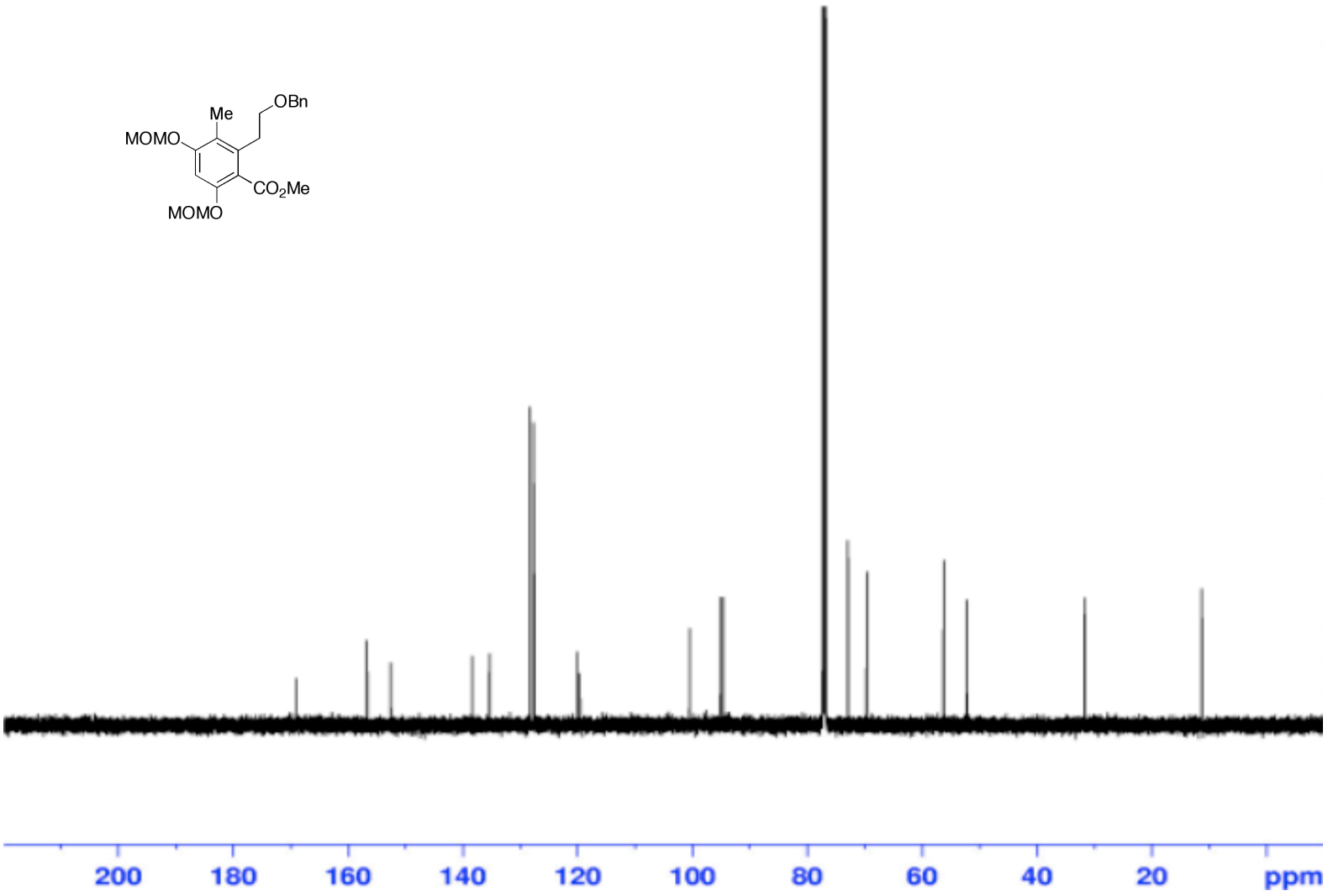




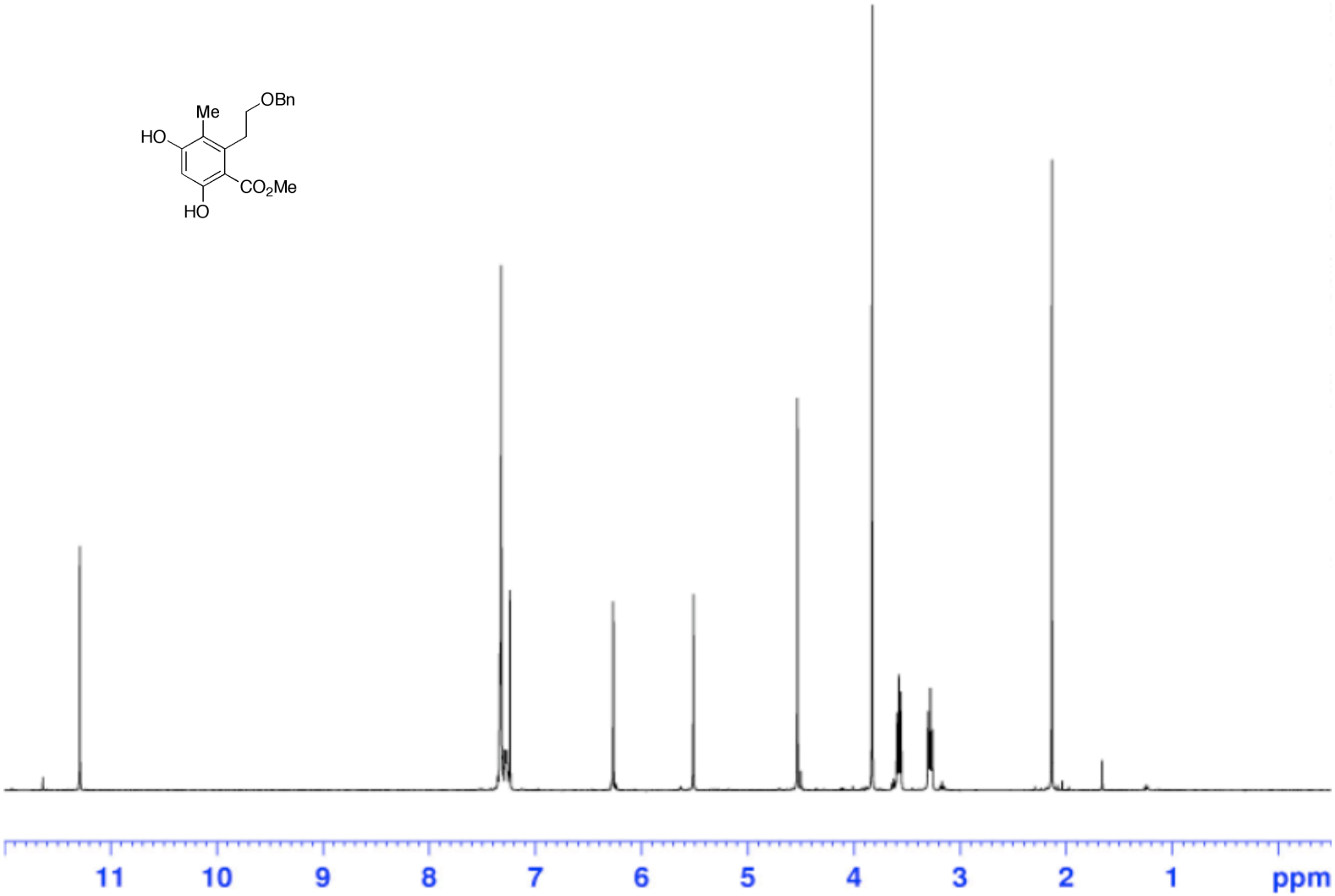
^{13}C NMR Spectrum: Aryl Bromide **219**, 100 MHz ($CDCl_3$)



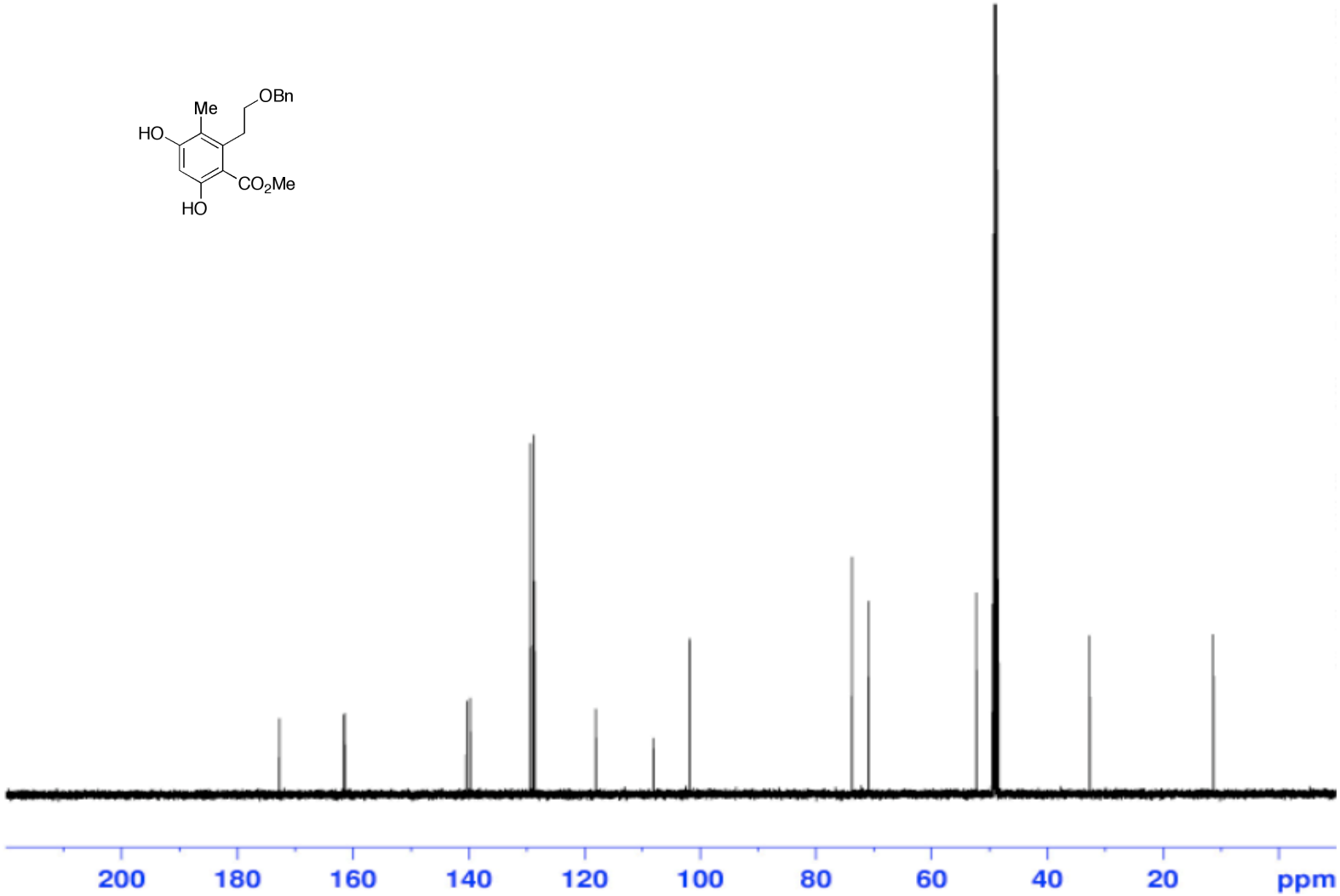
^{1}H NMR Spectrum: of Arene **220**, 400 MHz ($CDCl_3$)



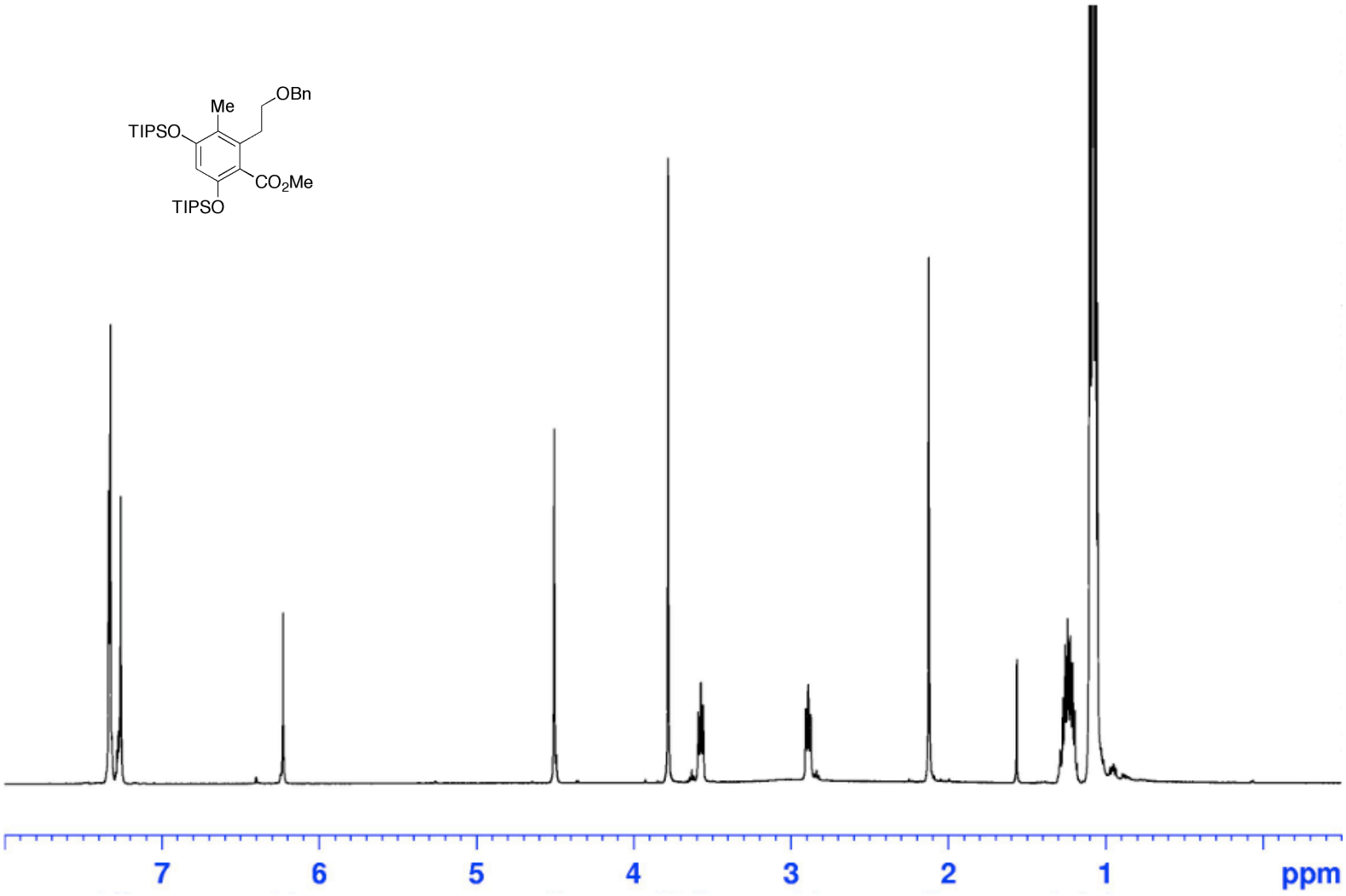
^{13}C NMR Spectrum: of Arene **220**, 100 MHz ($CDCl_3$)



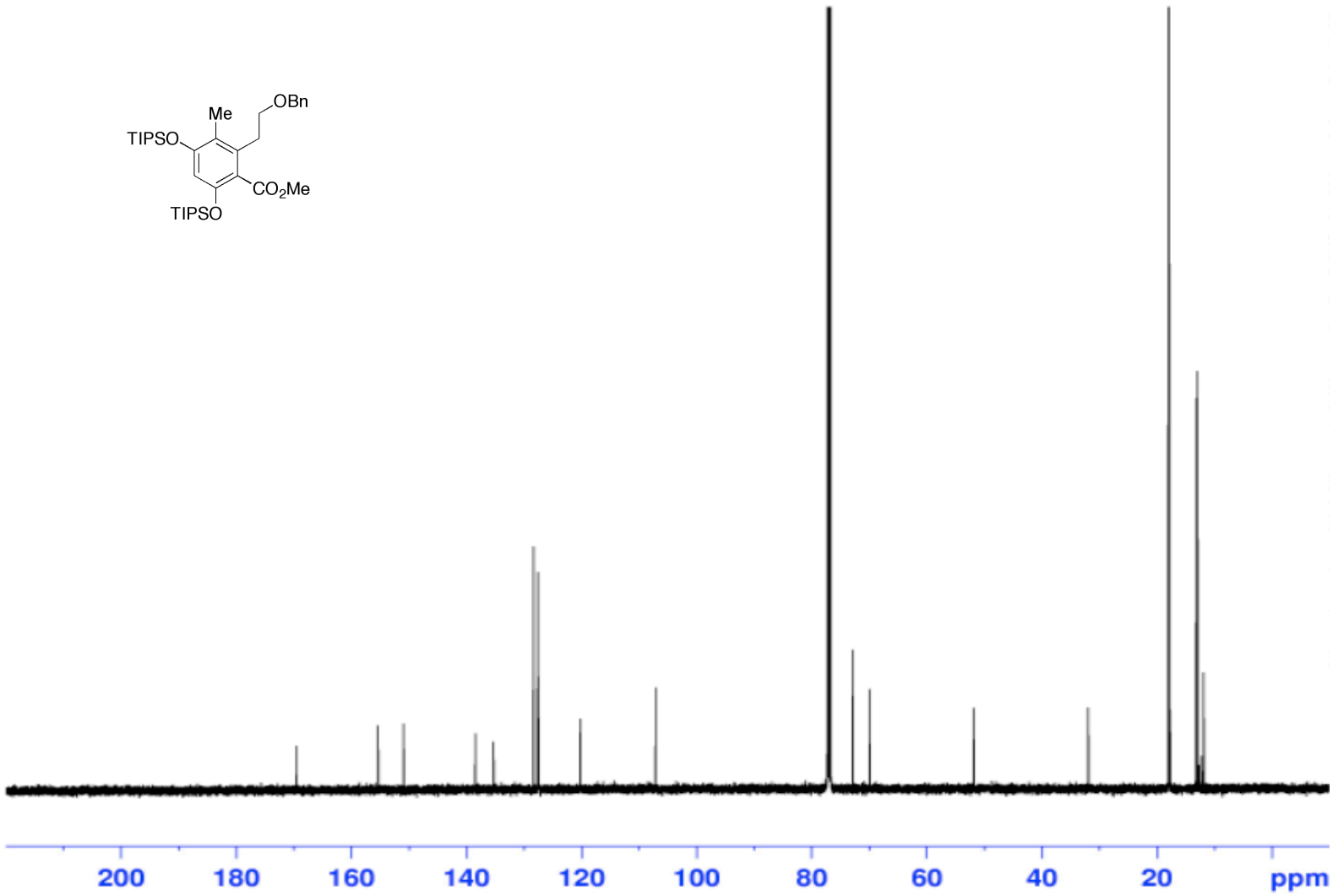
^{1}H NMR Spectrum: Catechol **221**, 400 MHz ($CDCl_3$)



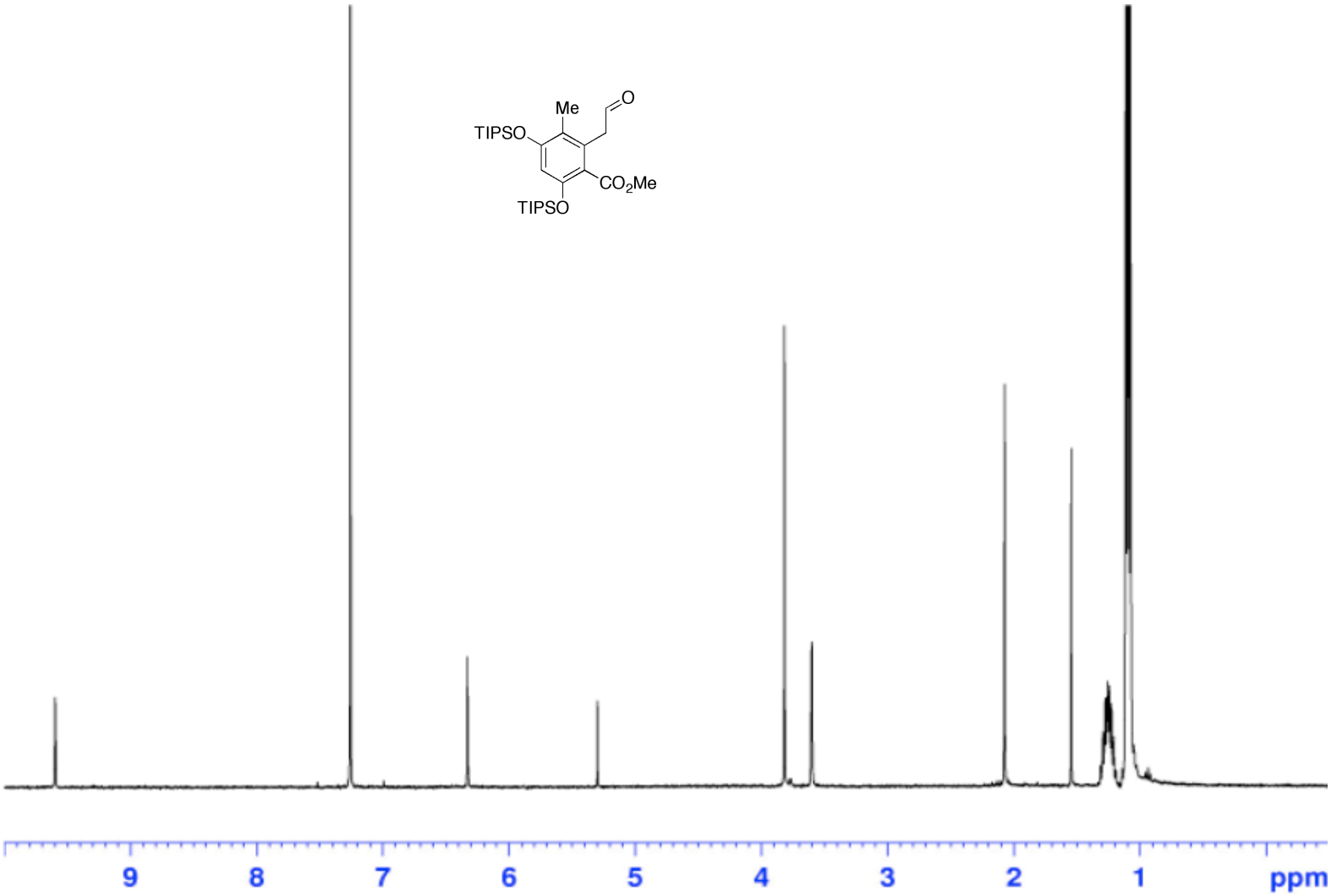
^{13}C NMR Spectrum: Catechol **221**, 100 MHz ($CDCl_3$)



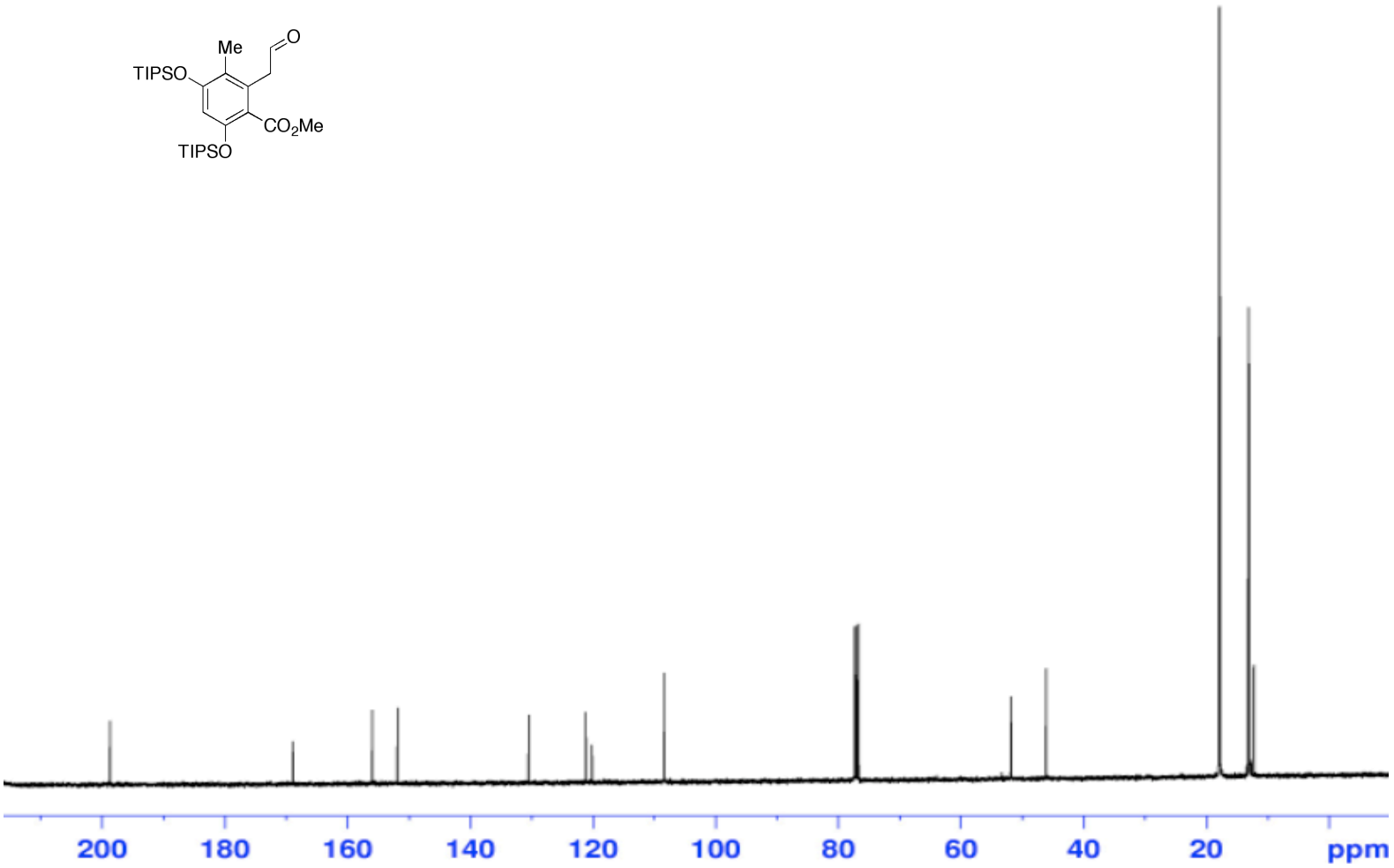
^{1}H NMR Spectrum: TIPS Ether, 400 MHz ($CDCl_3$)



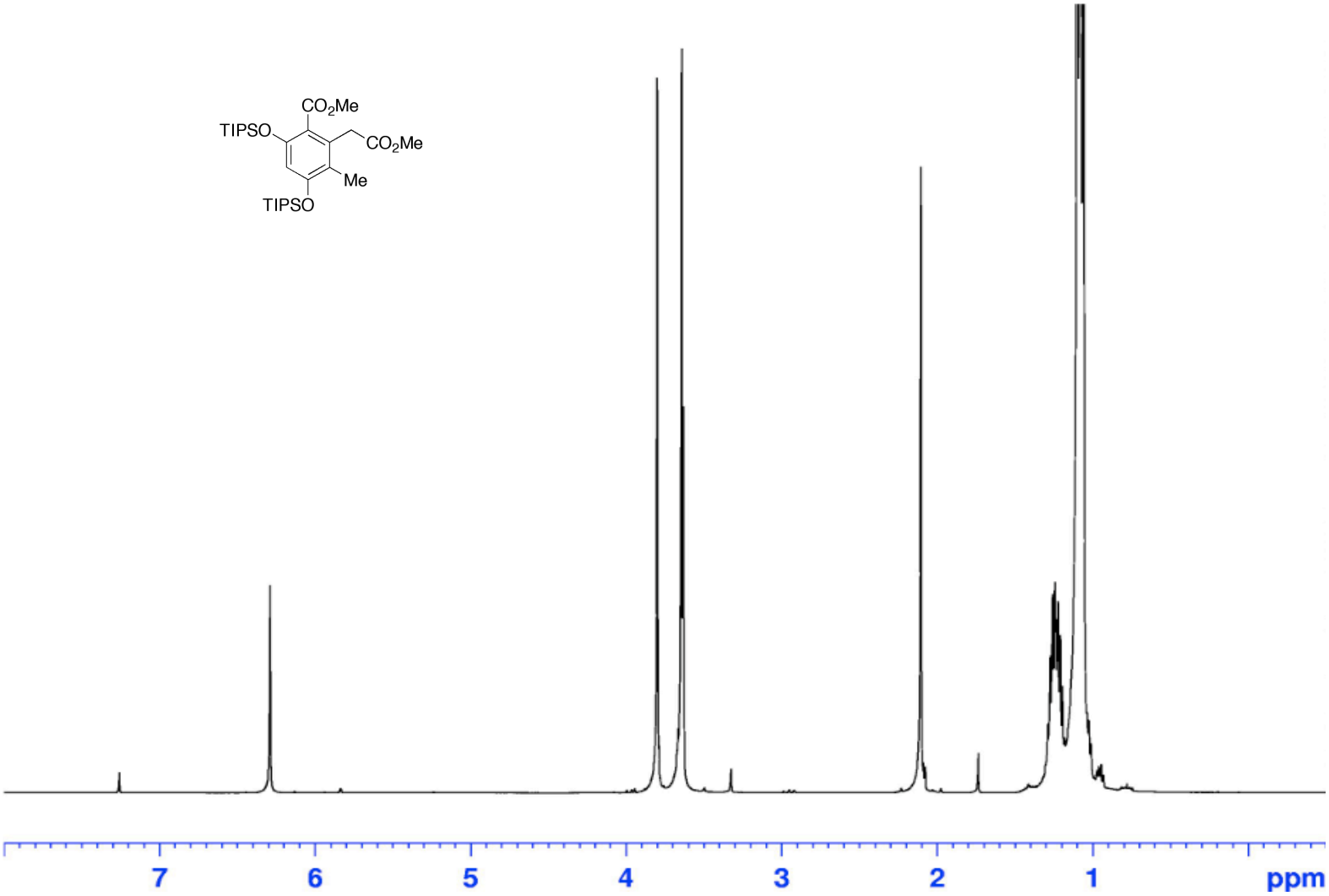
^{13}C NMR Spectrum: TIPS Ether, 100 MHz ($CDCl_3$)



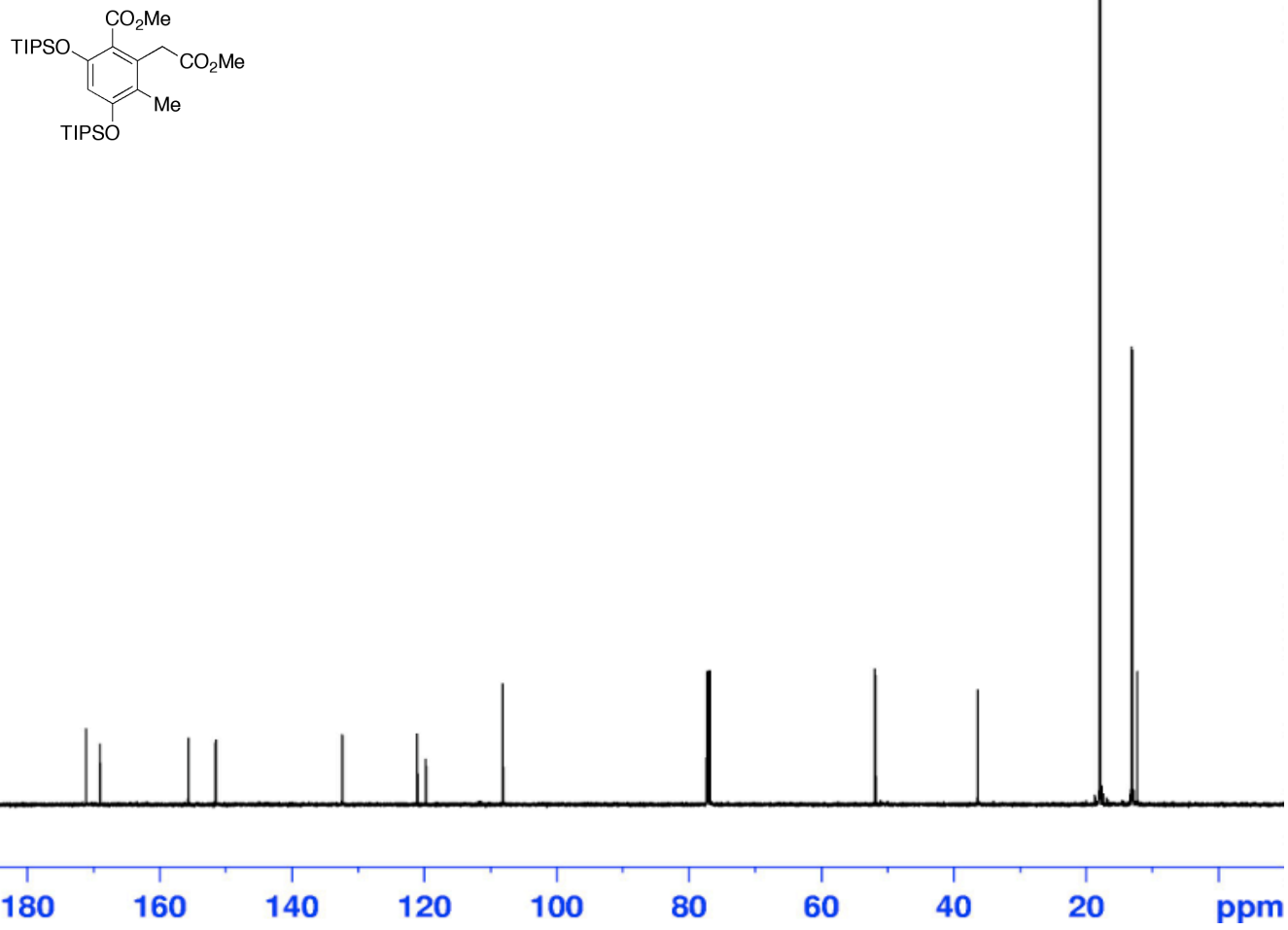
^{1}H NMR Spectrum: Aldehyde **158**, 400 MHz ($CDCl_3$)



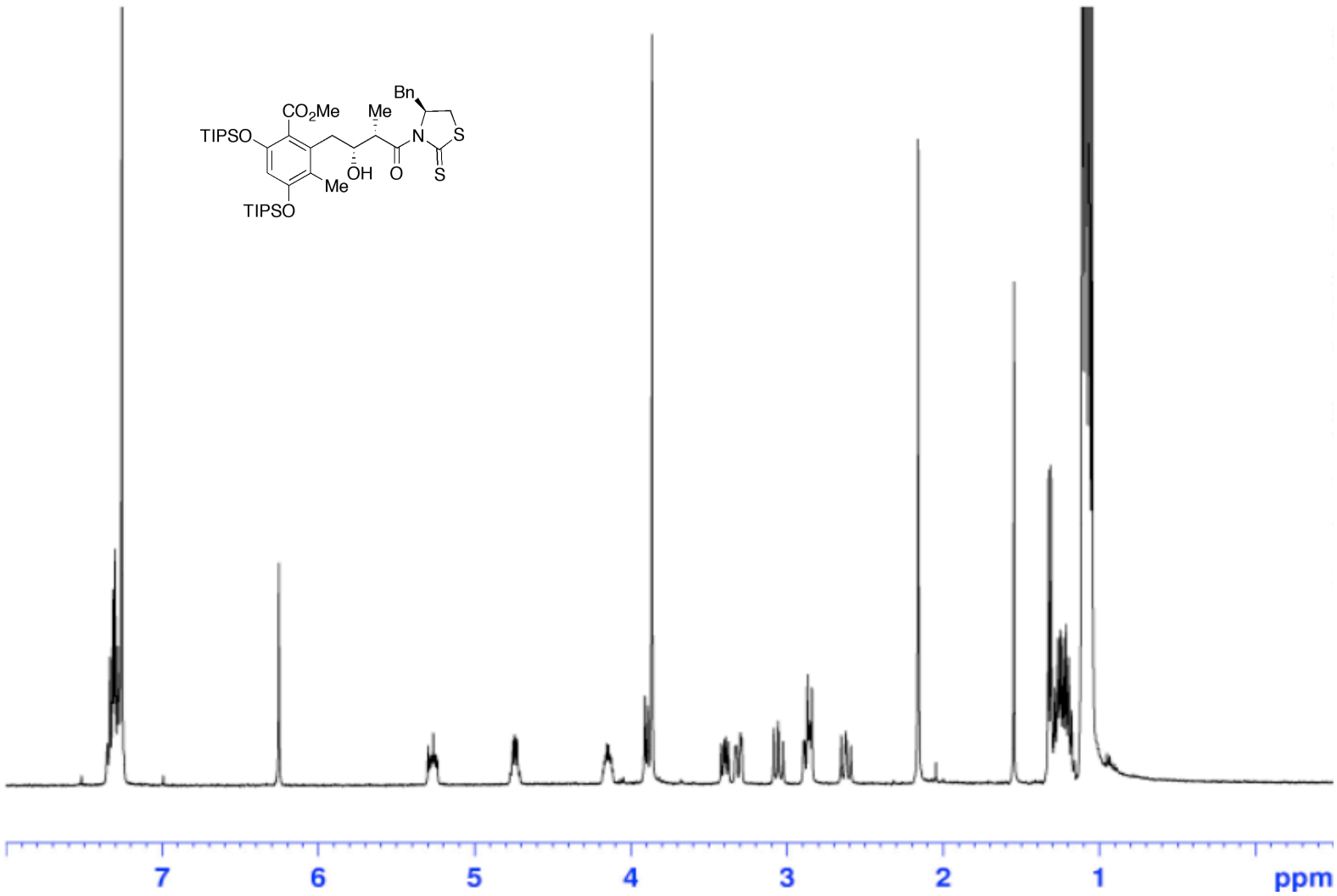
^{13}C NMR Spectrum: Aldehyde **158**, 100 MHz ($CDCl_3$)



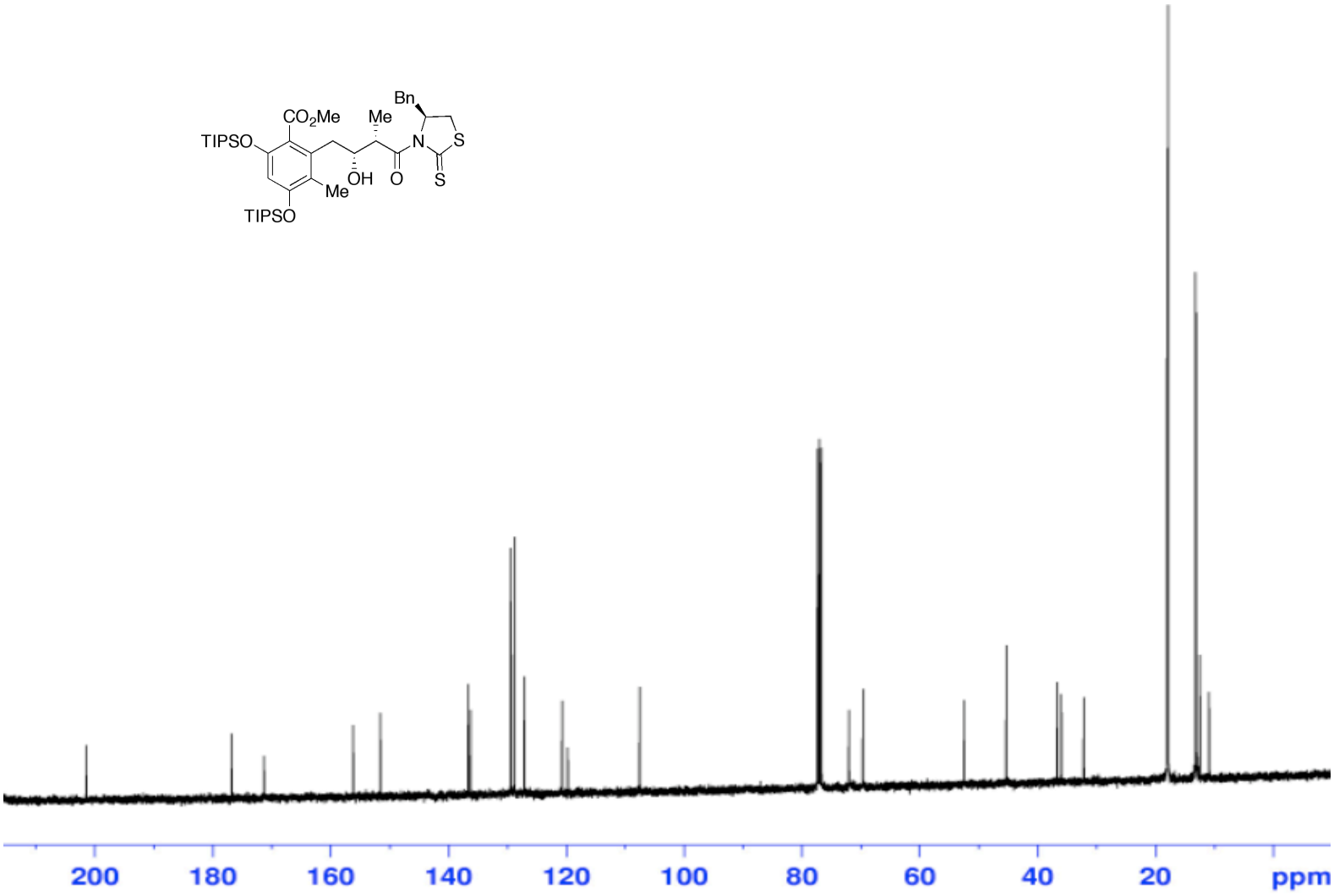
^{1}H Spectrum: TIPS Ether, 500 MHz ($CDCl_3$)



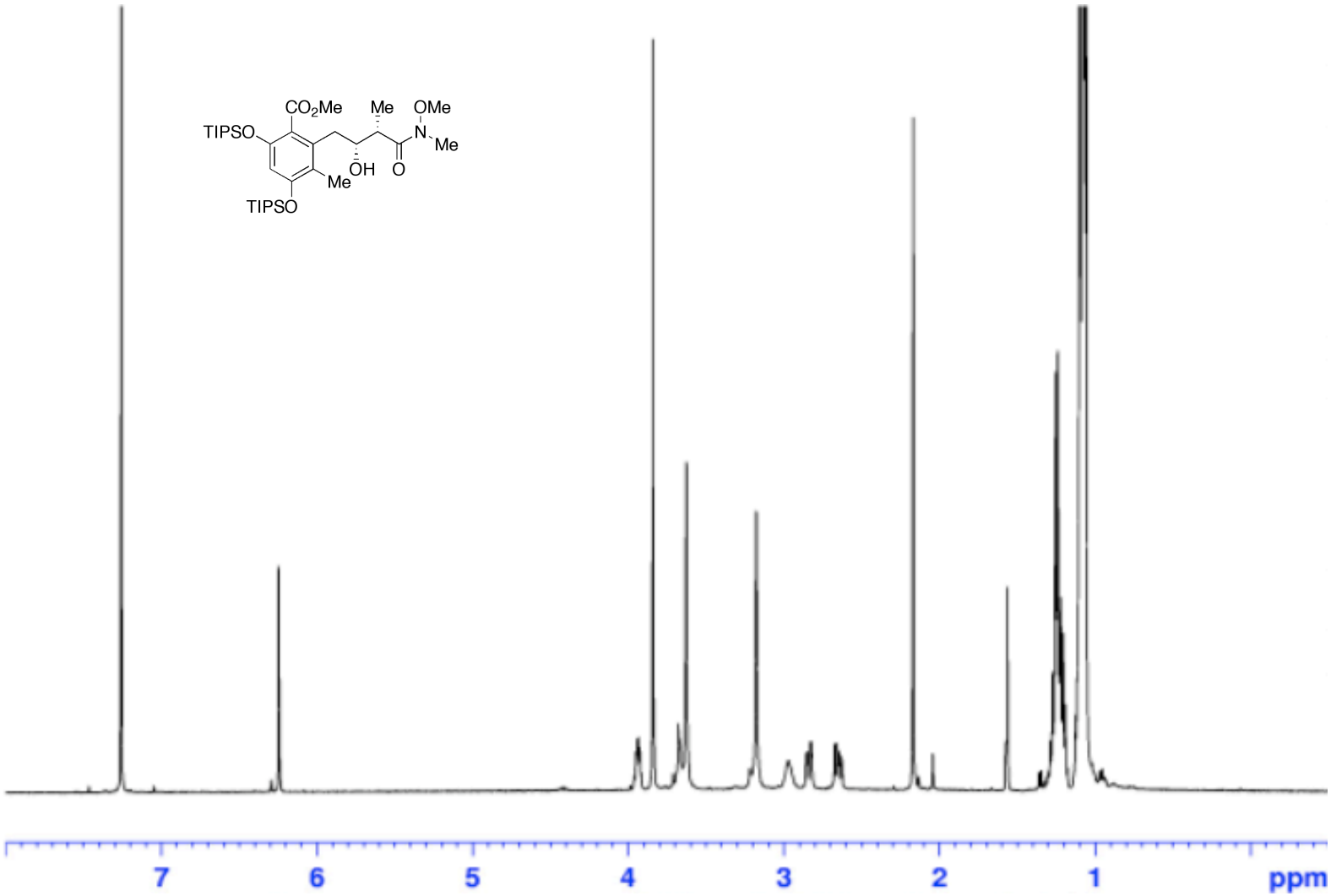
^{13}C Spectrum: TIPS Ether, 125 MHz ($CDCl_3$)



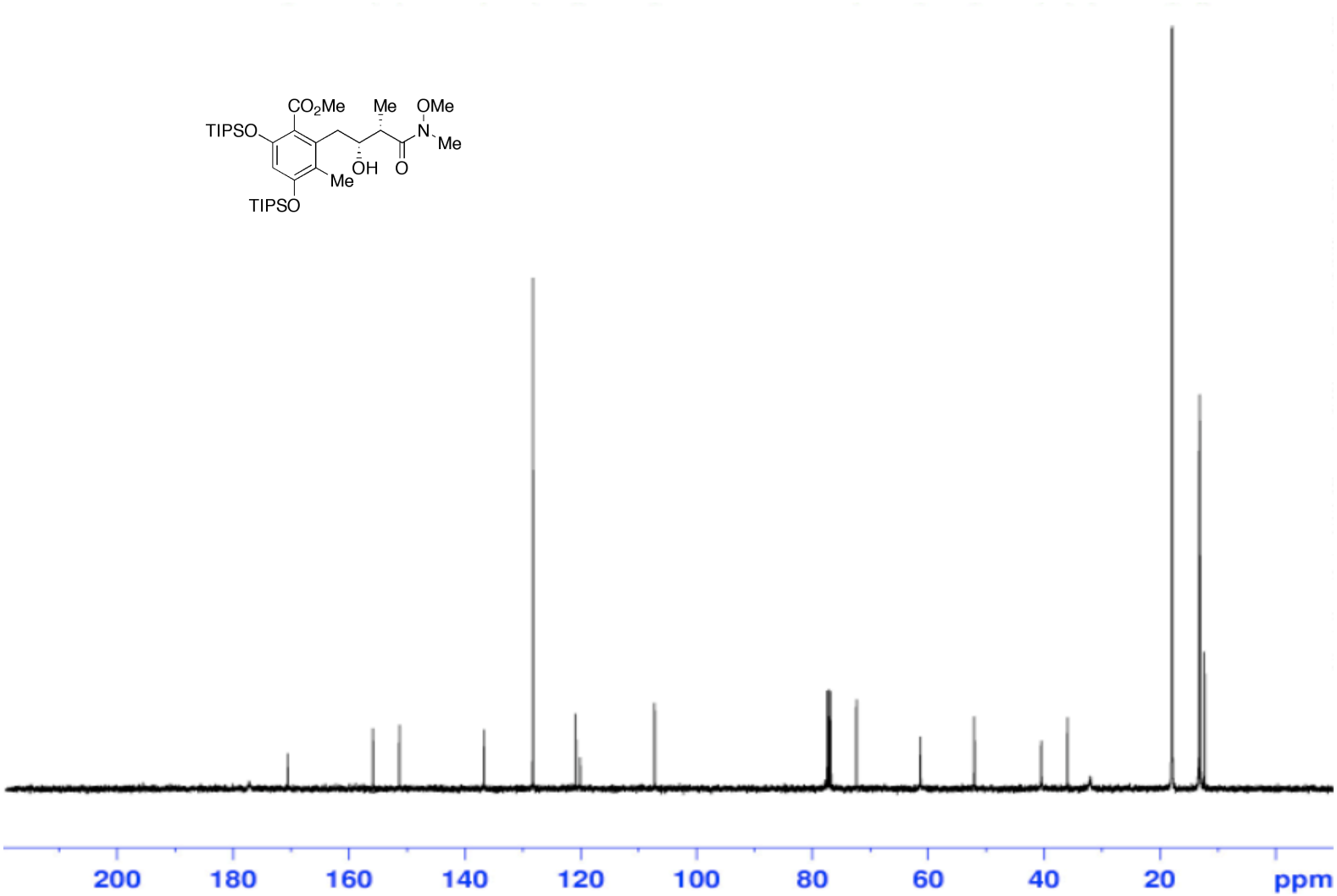
^{1}H Spectrum: Alcohol **223**, 400 MHz ($CDCl_3$)



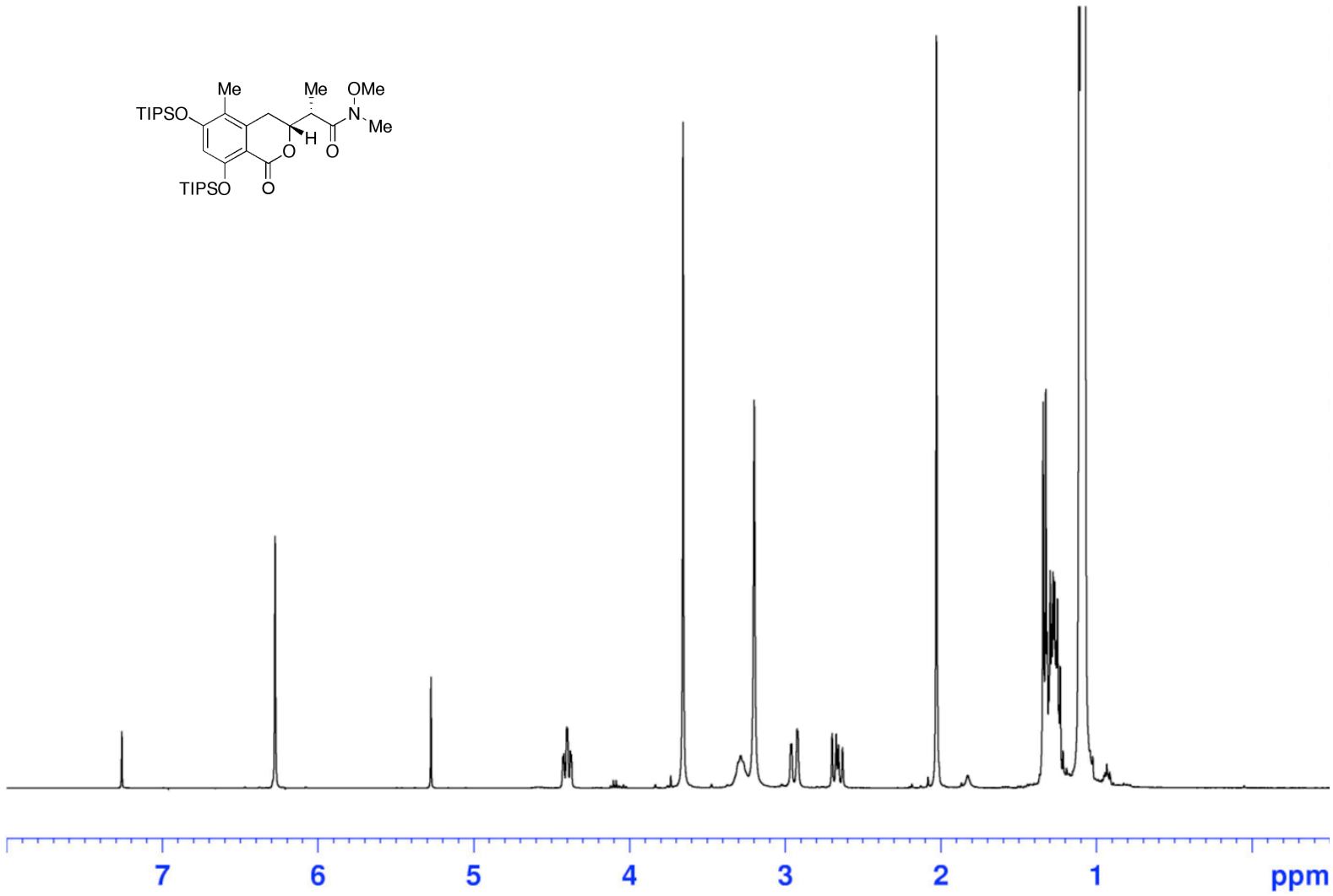
^{13}C Spectrum: Alcohol **223**, 100 MHz ($CDCl_3$)



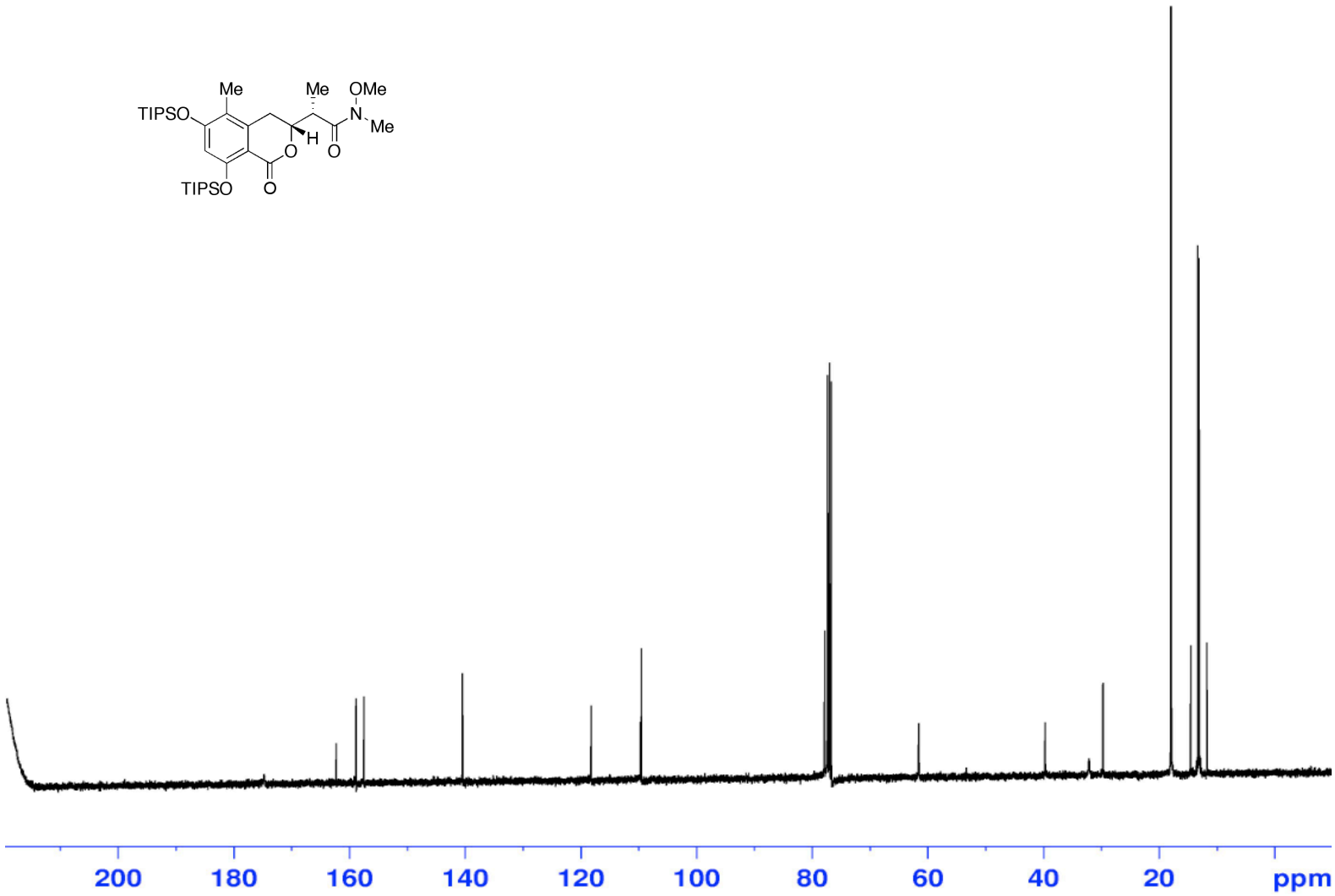
^{1}H Spectrum: Amide, 500 MHz ($CDCl_3$)



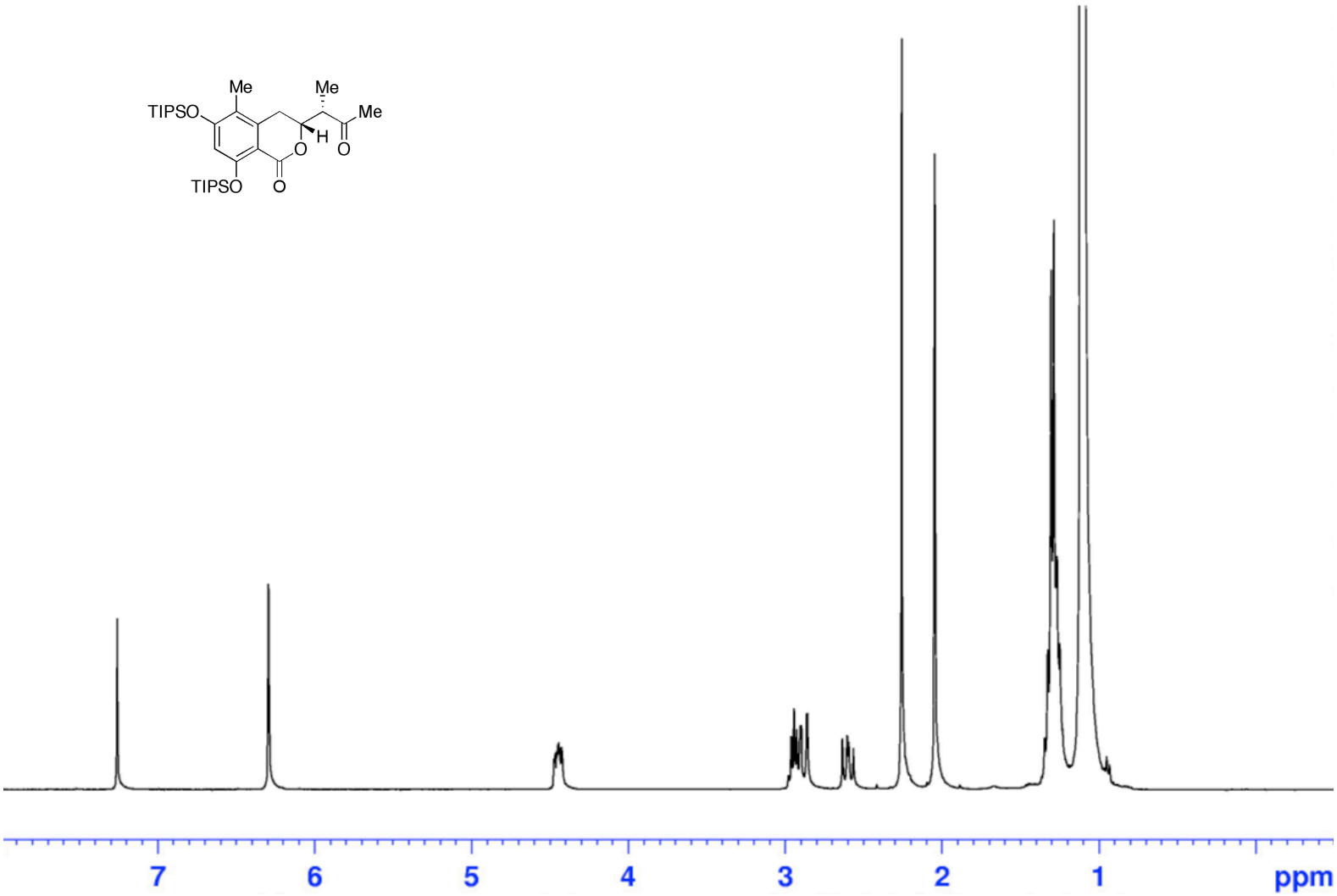
^{13}C Spectrum: Amide, 100 MHz ($CDCl_3$)



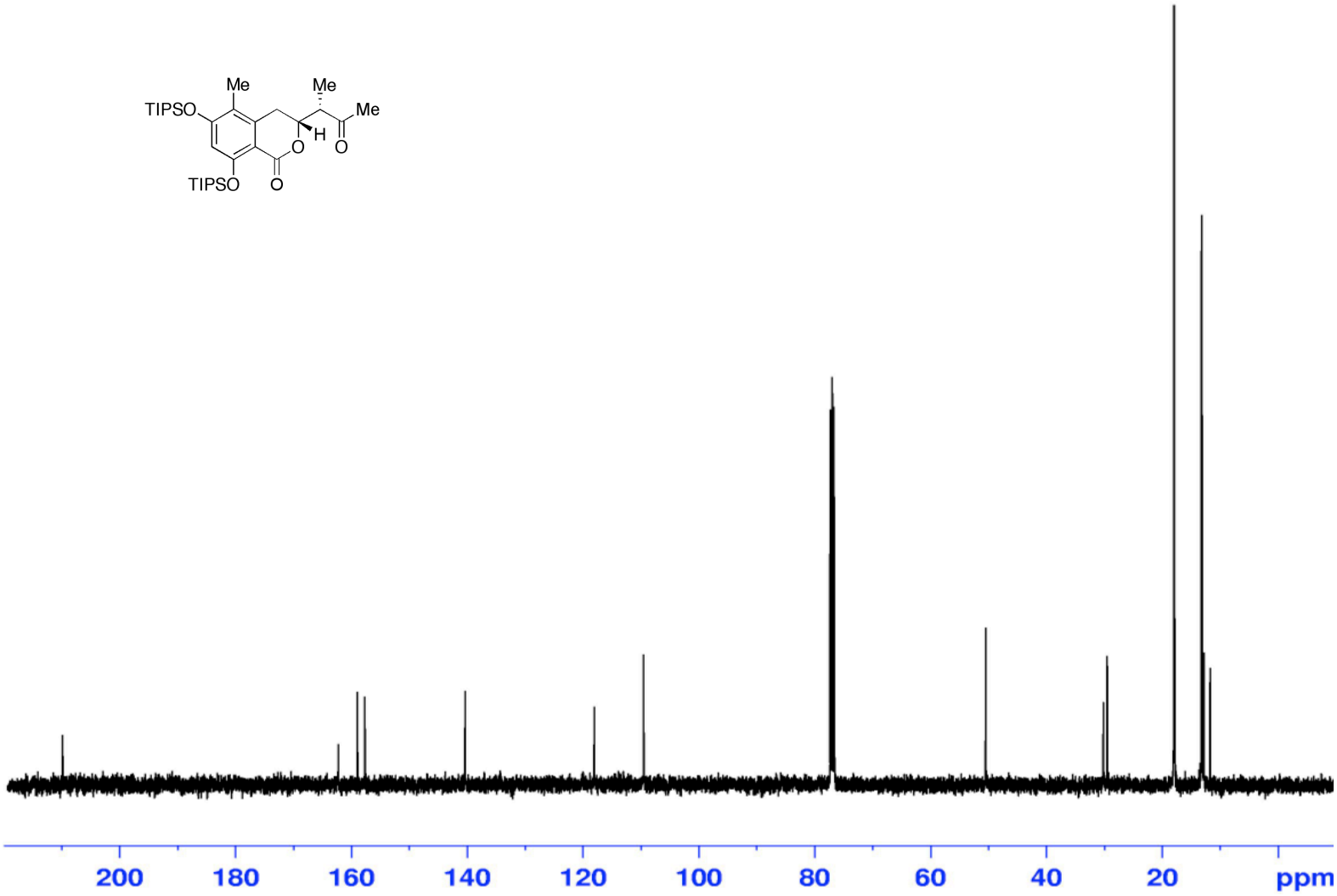
^{1}H NMR Spectrum: Lactone **224**, 400 MHz ($CDCl_3$)



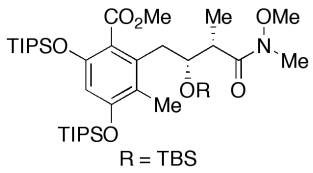
^{13}C NMR Spectrum: Lactone **224**, 100 MHz ($CDCl_3$)



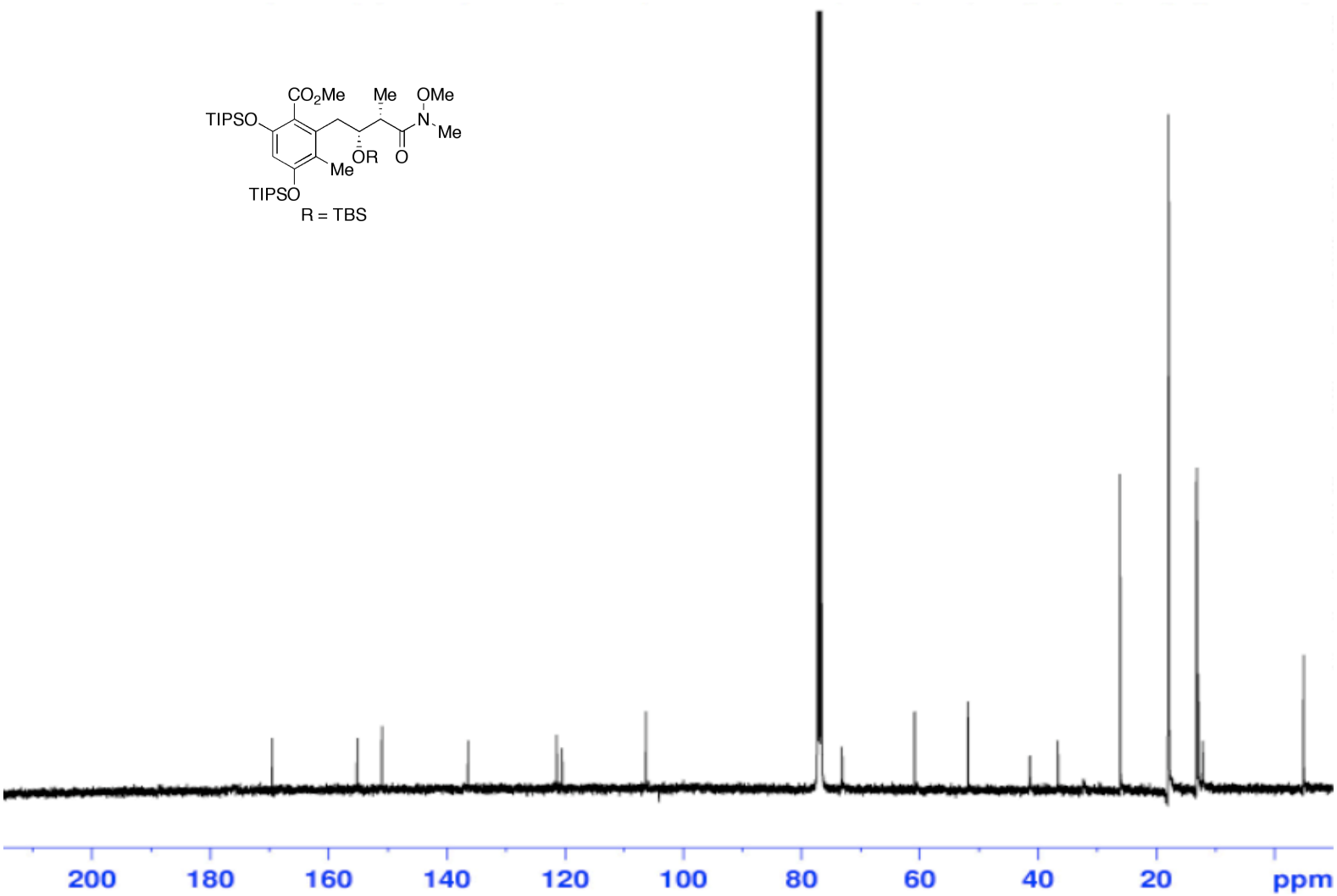
^{1}H NMR Spectrum: Ketone **225**, 400 MHz ($CDCl_3$)



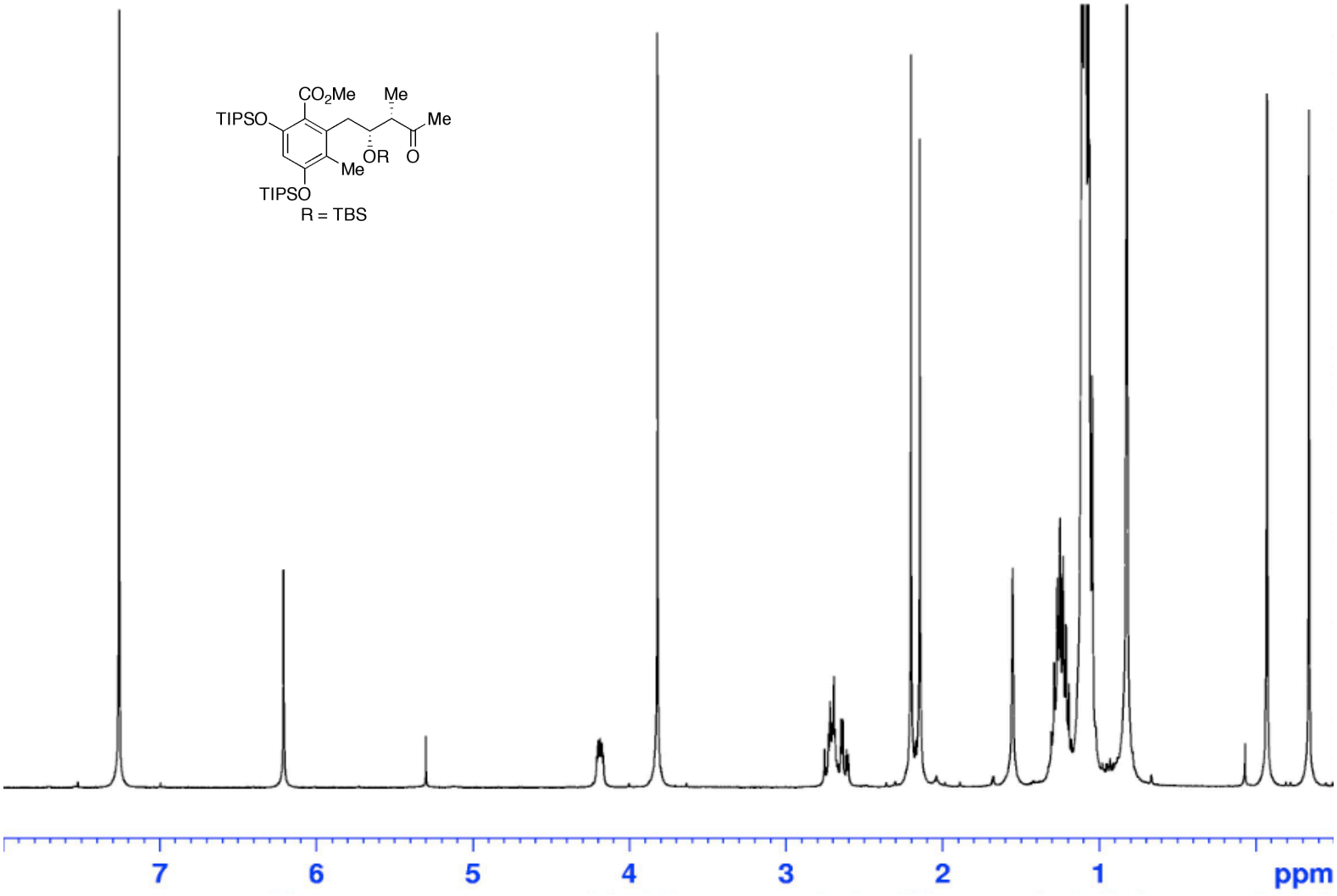
^{13}C NMR Spectrum: Ketone **225**, 100 MHz ($CDCl_3$)



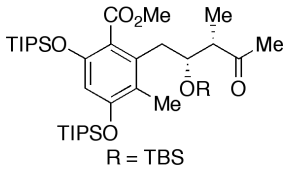
^{1}H Spectrum: TBS Ether **230**, 400 MHz ($CDCl_3$)

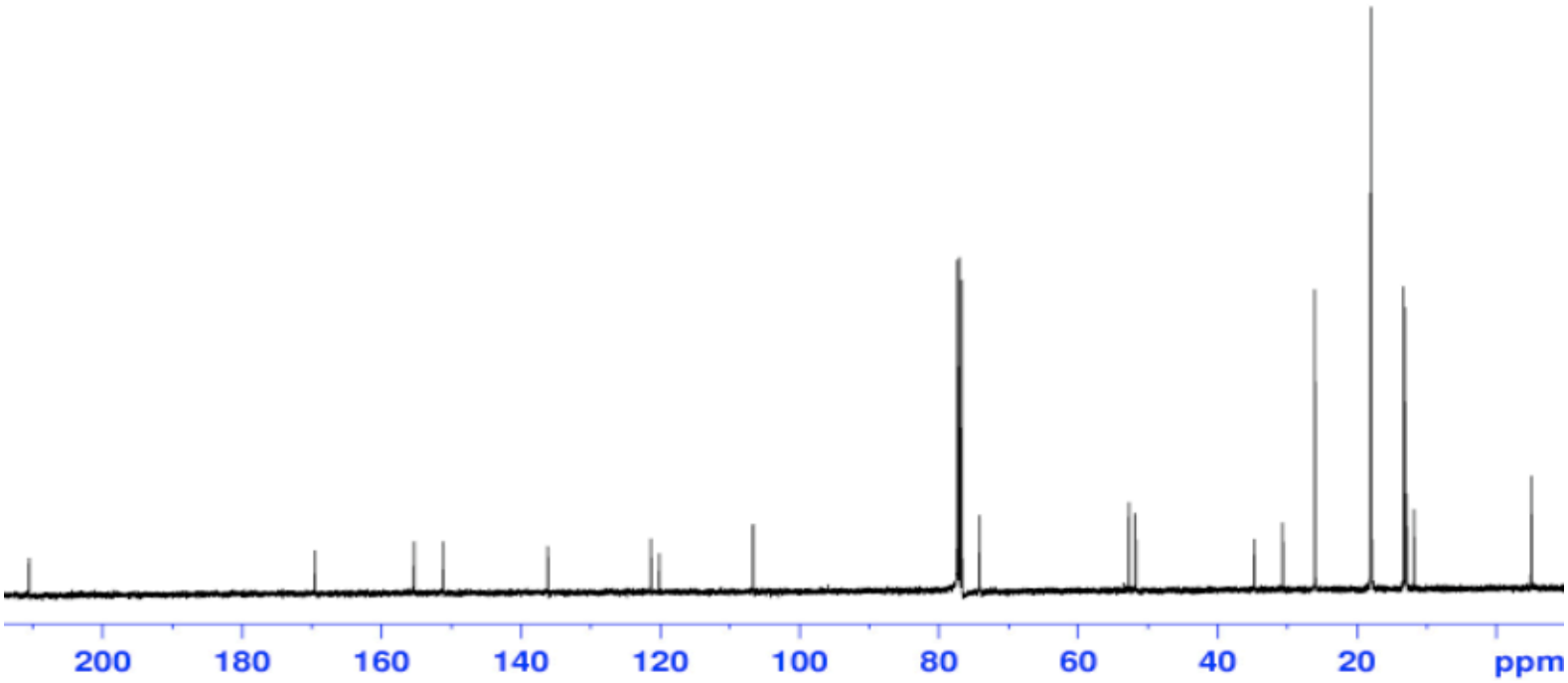


^{13}C Spectrum: TBS Ether **230**, 100 MHz ($CDCl_3$)

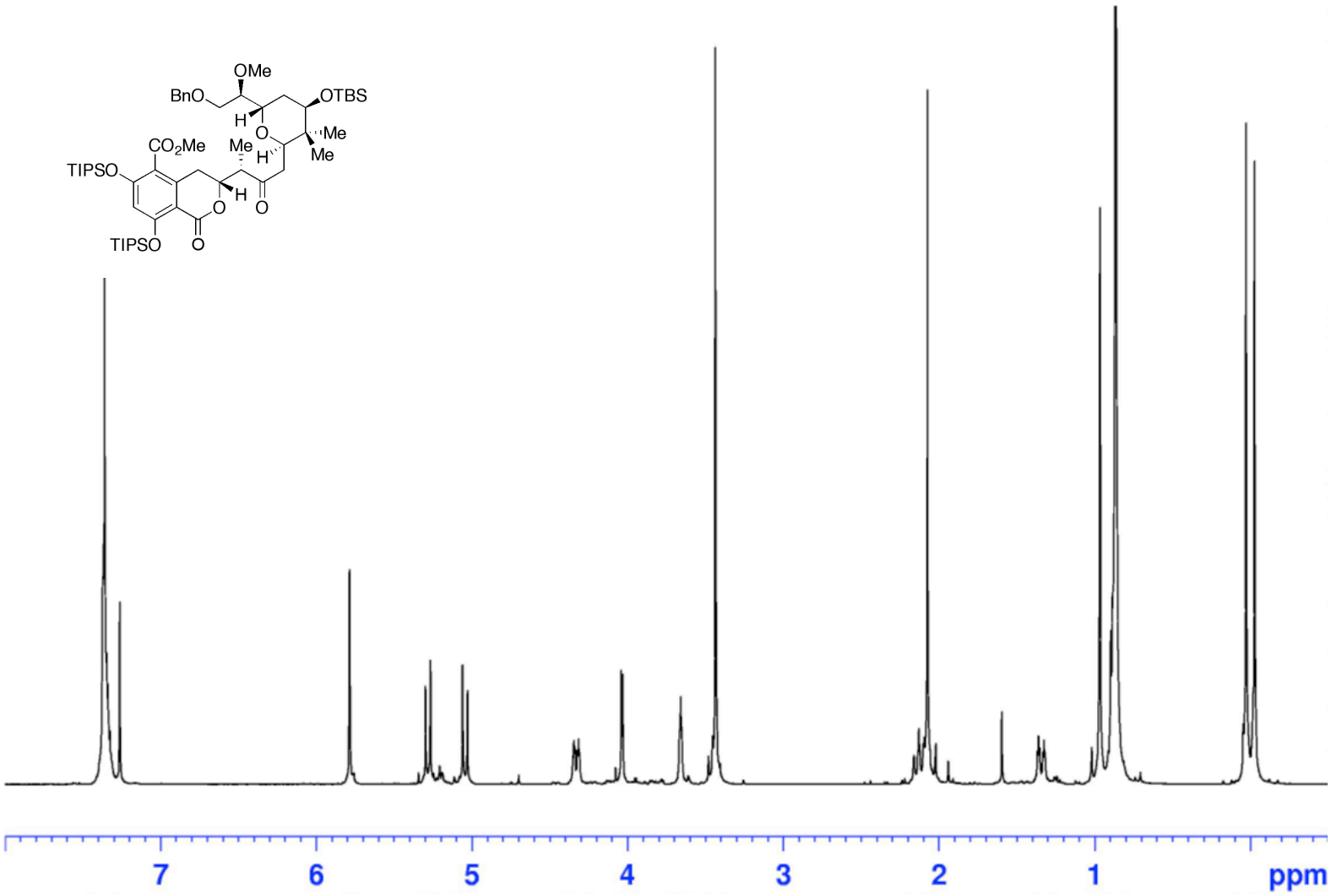


^{1}H Spectrum: Ketone **231**, 400 MHz ($CDCl_3$)

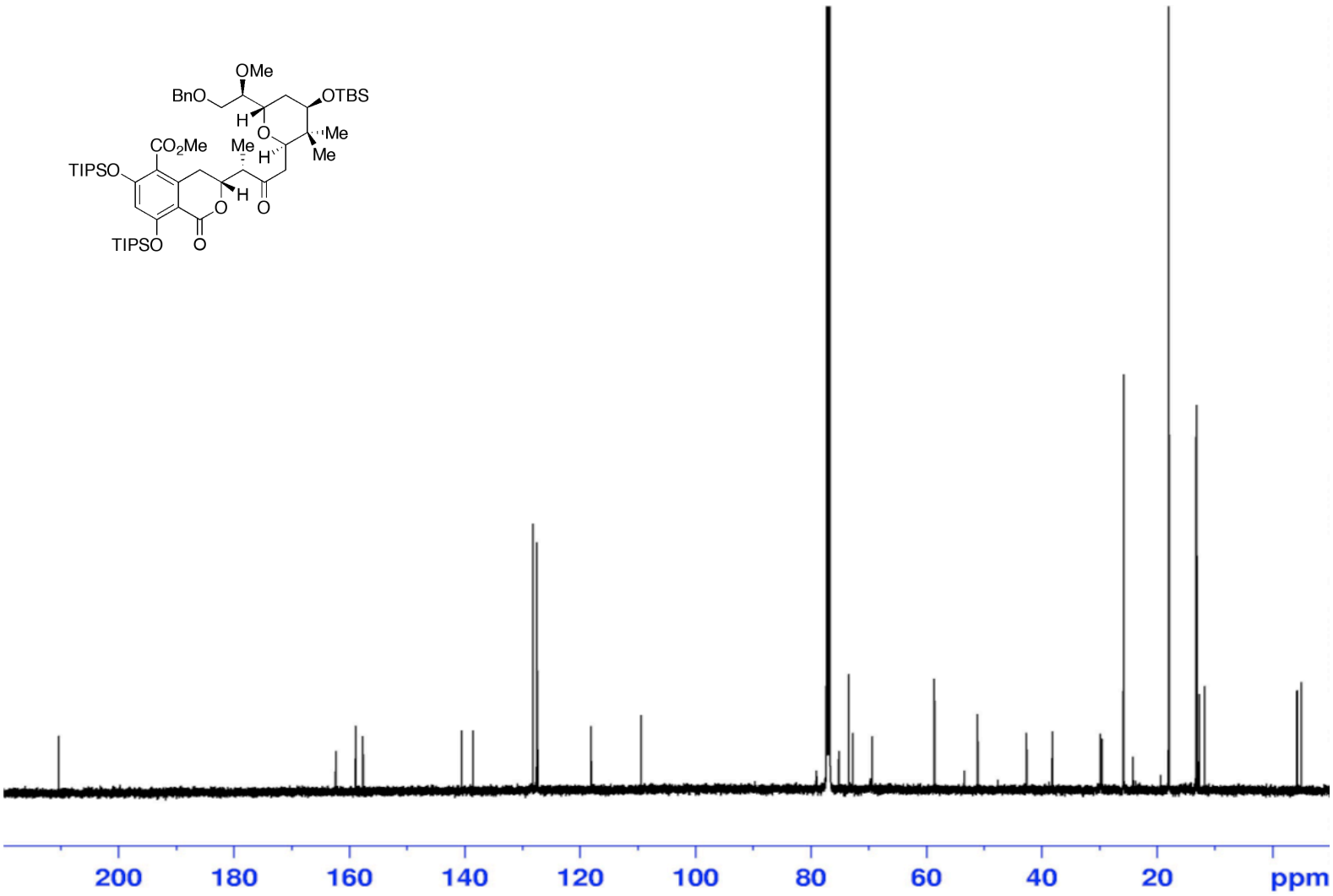




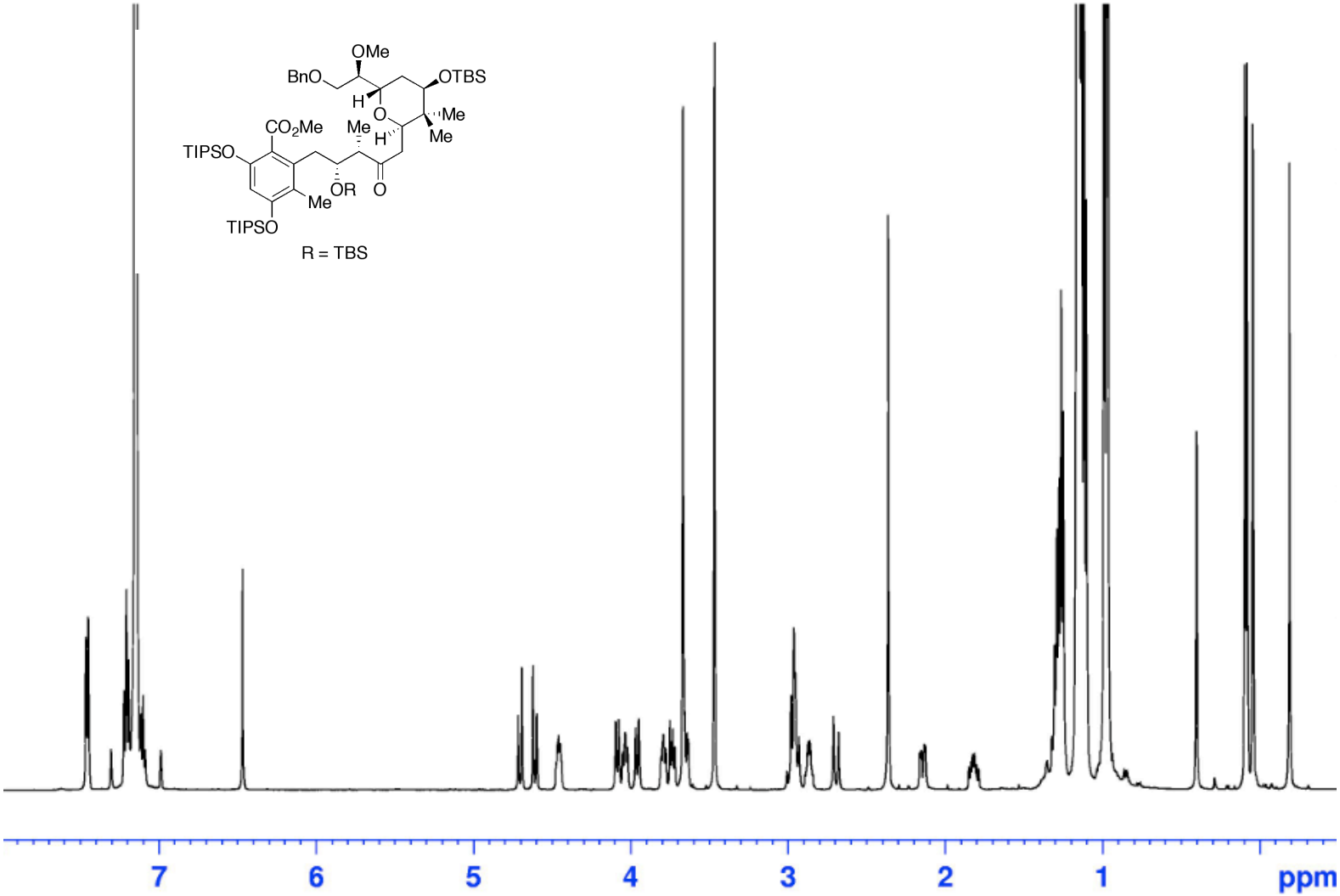
^{13}C Spectrum: Ketone **231**, 100 MHz ($CDCl_3$)



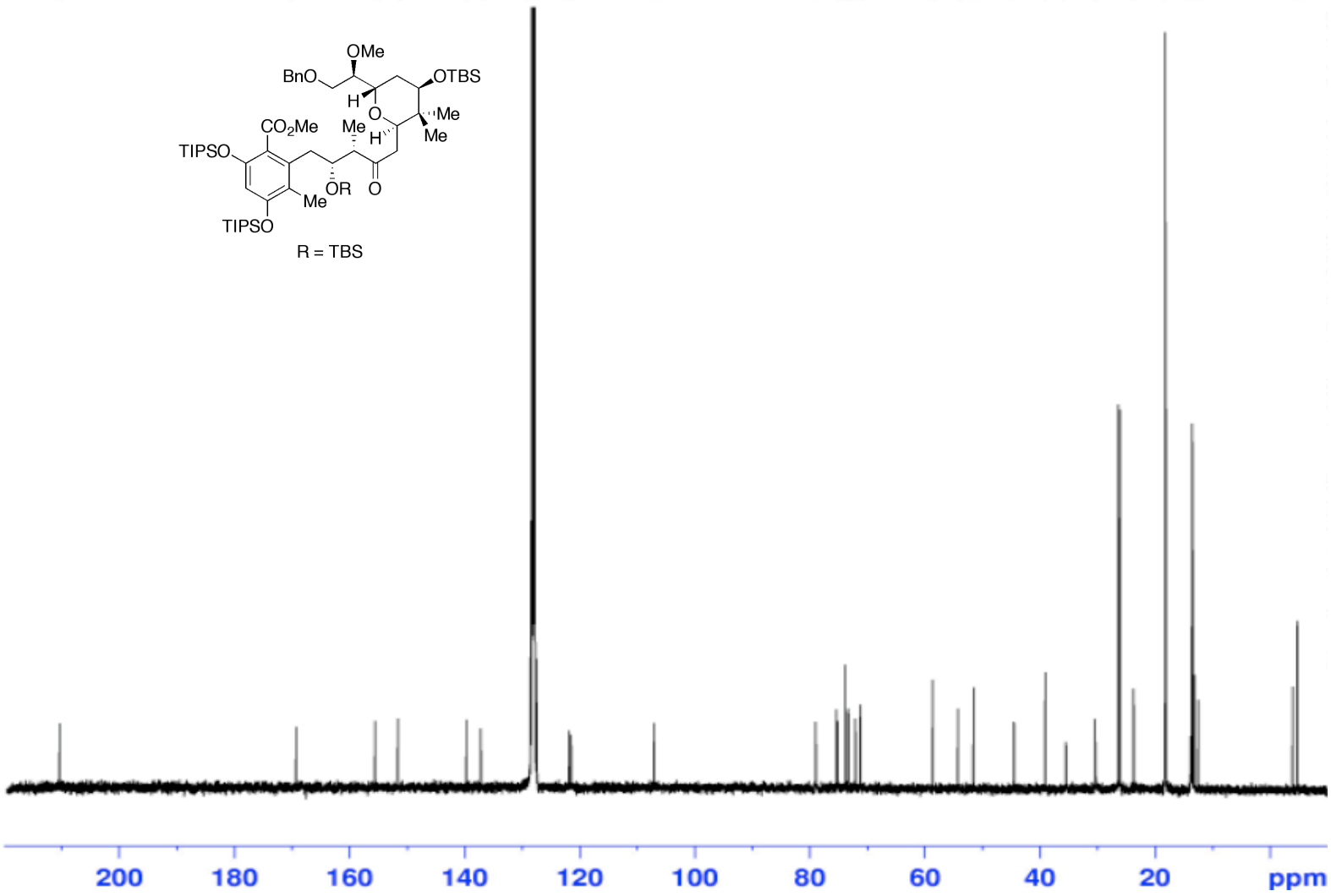
The ^{1}H Spectrum of Tetrahydropyran **233**; 400 MHz ($CDCl_3$)



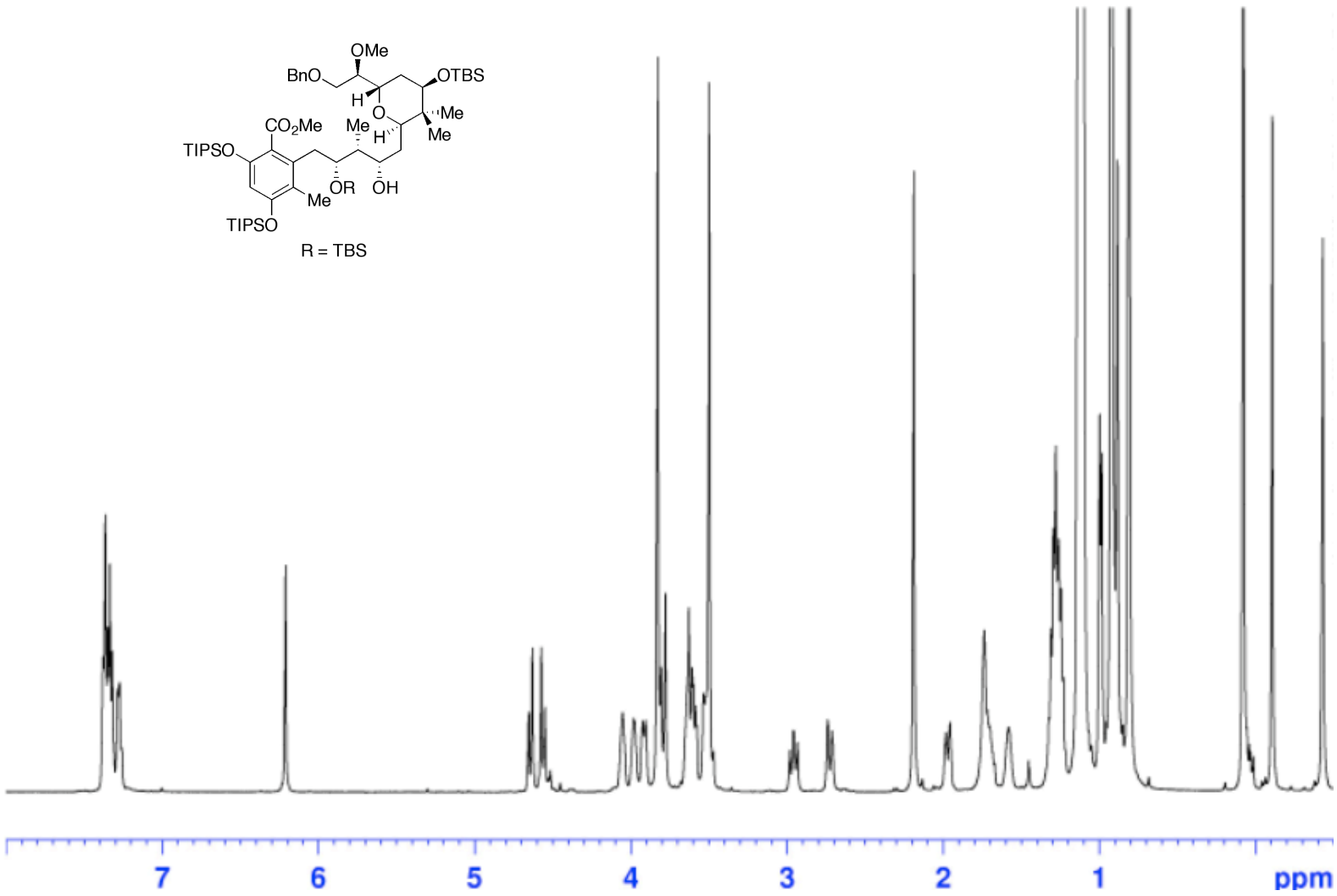
The ^{13}C Spectrum of Tetrahydropyran **233**; 125 MHz ($CDCl_3$)



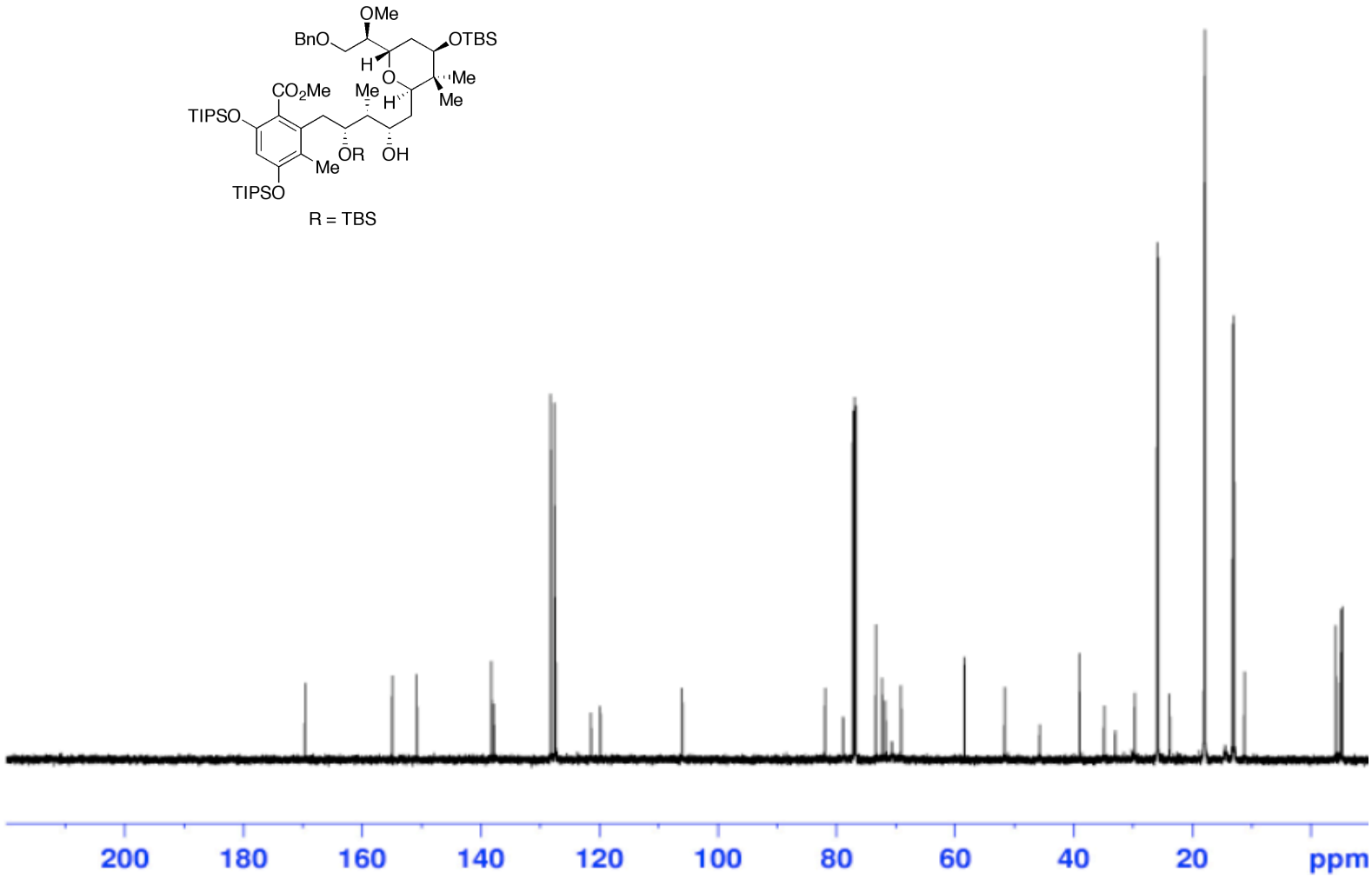
^{1}H Spectrum: Ketone **234**, 400 MHz (C_6D_6)



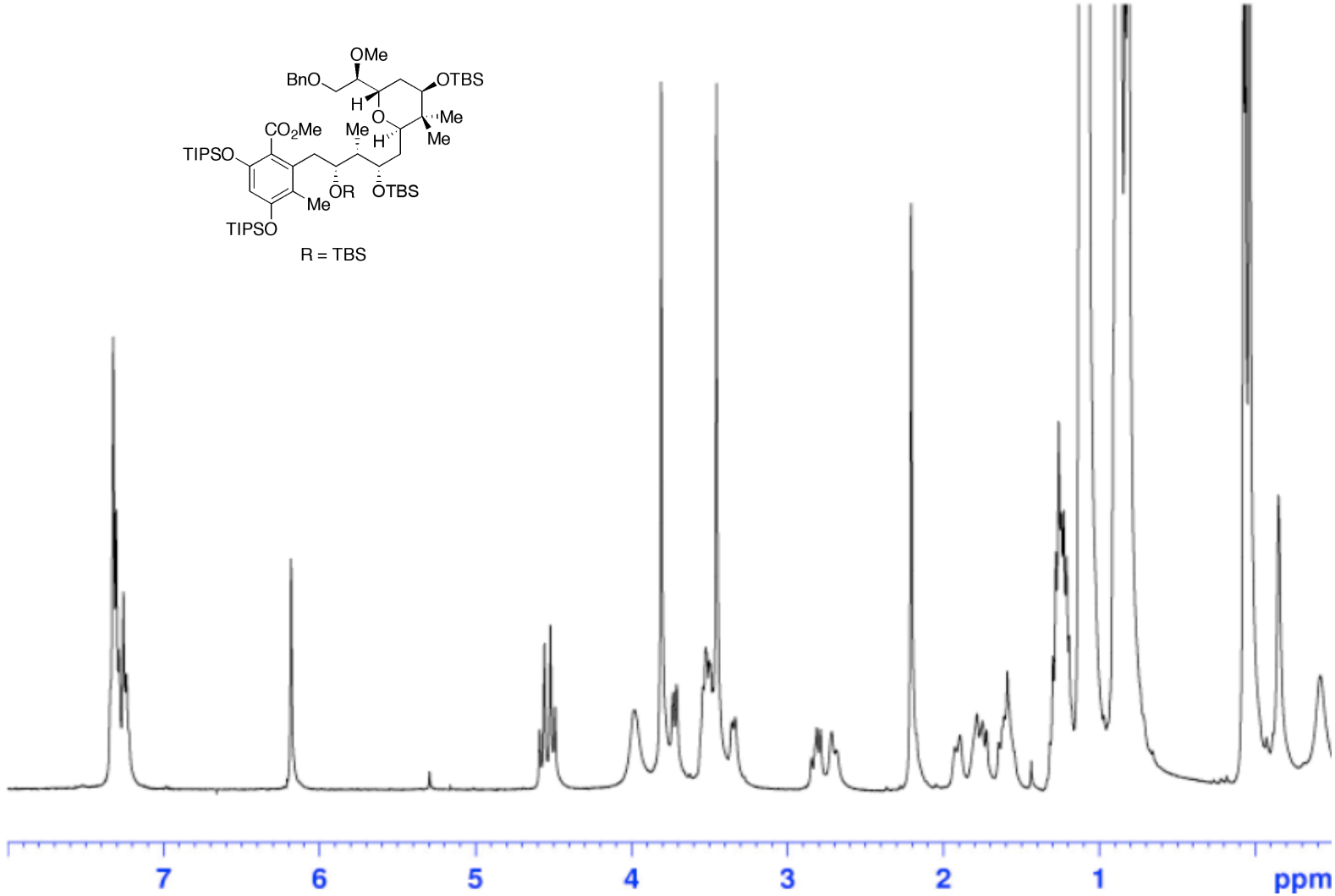
^{13}C Spectrum: Ketone **234**, 100 MHz (C_6D_6)



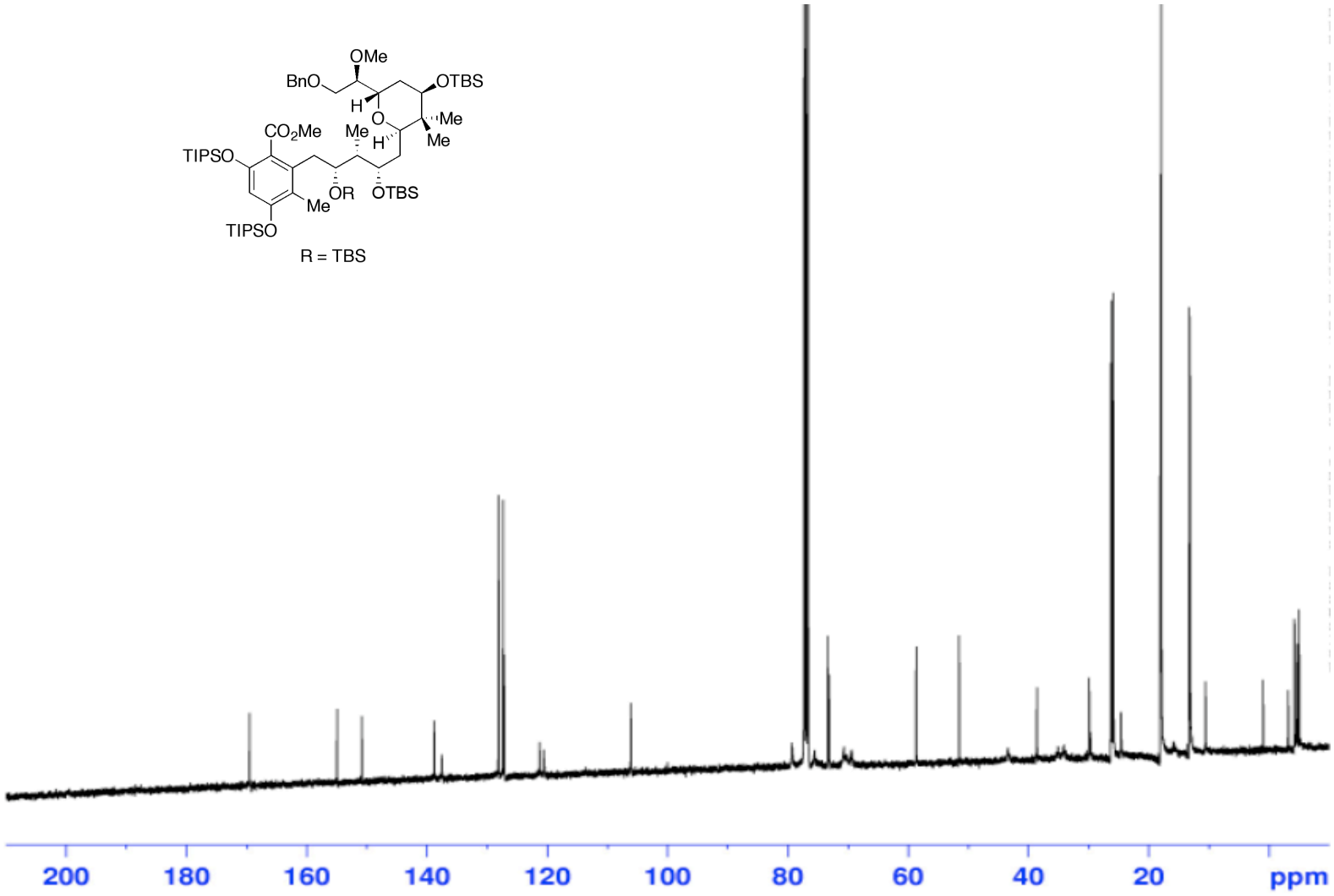
^{1}H Spectrum: Alcohol **235**, 500 MHz ($CDCl_3$)



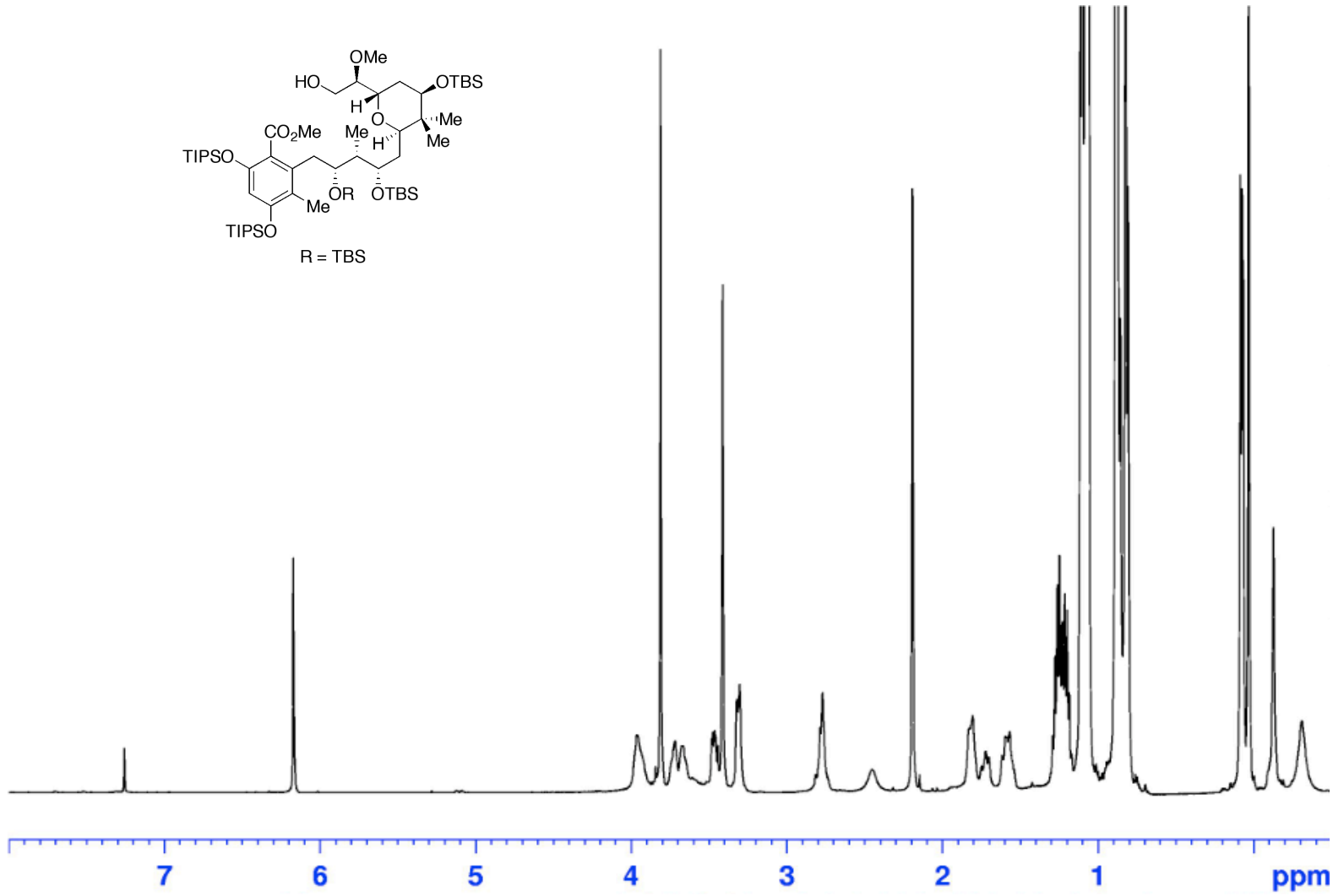
^{13}C Spectrum: Alcohol **235**, 100 MHz ($CDCl_3$)



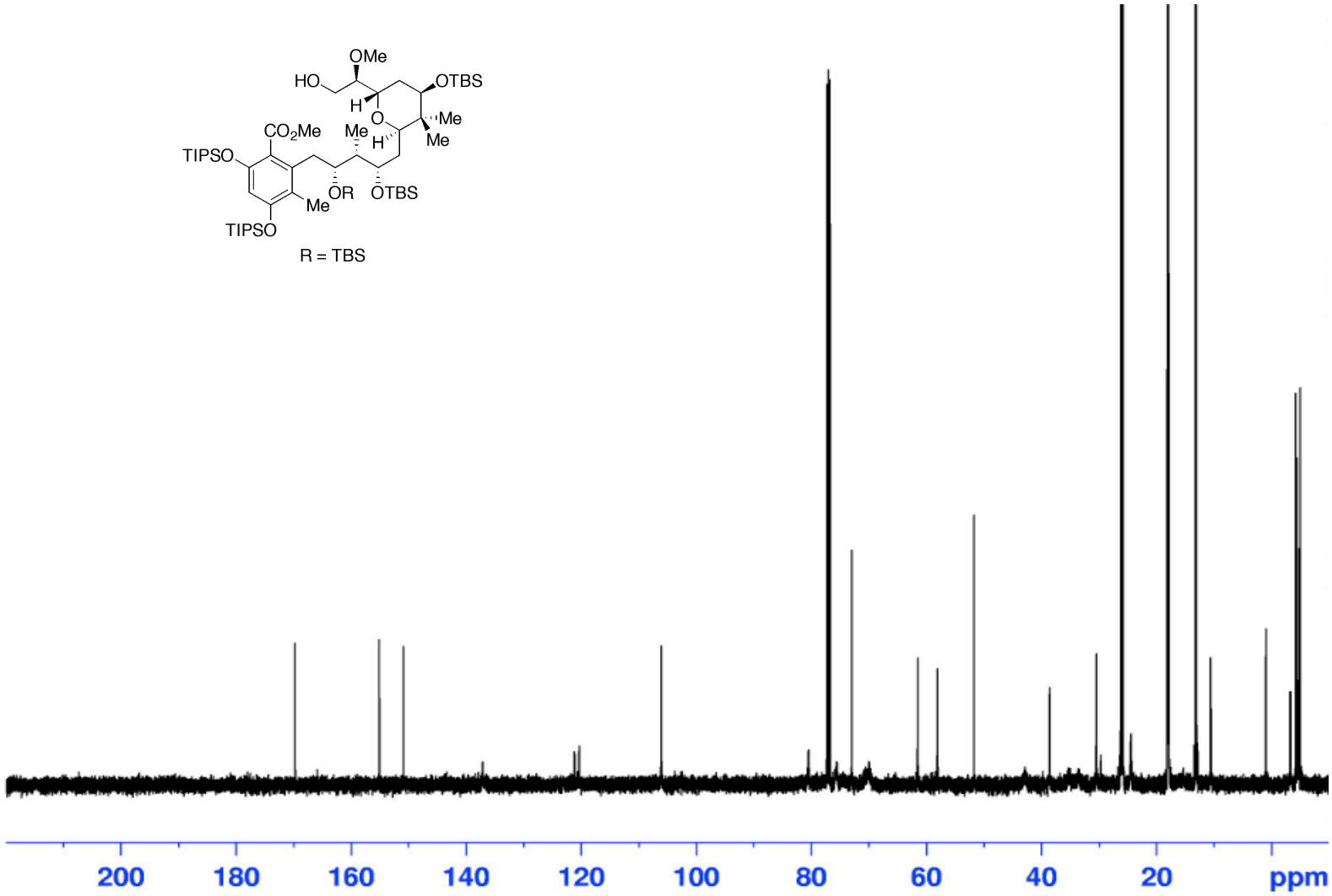
^{1}H Spectrum: TBS Ether, 500 MHz ($CDCl_3$)



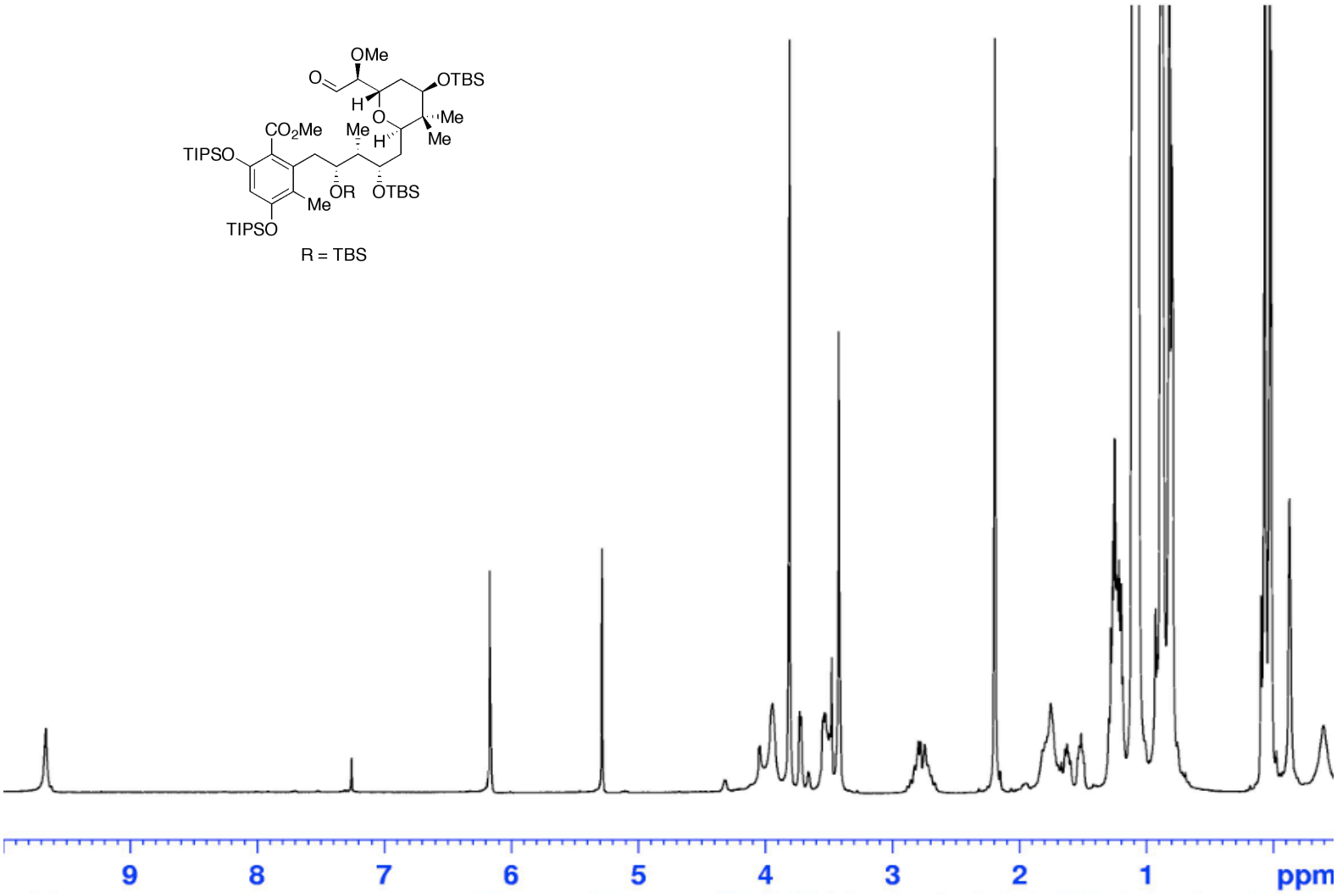
^{13}C Spectrum: TBS Ether, 125 MHz ($CDCl_3$)



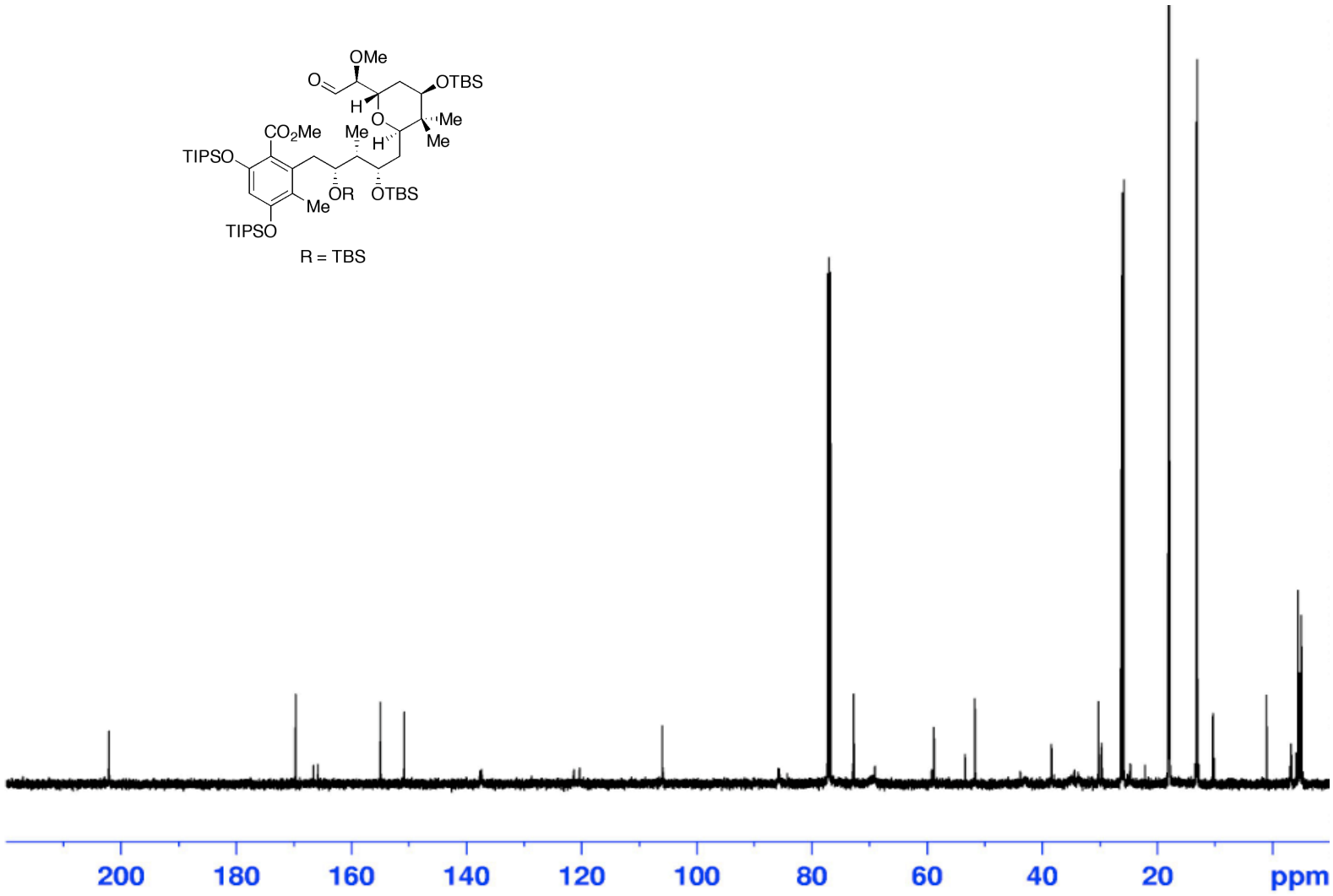
^{1}H Spectrum: Alcohol **236**, 500 MHz ($CDCl_3$)



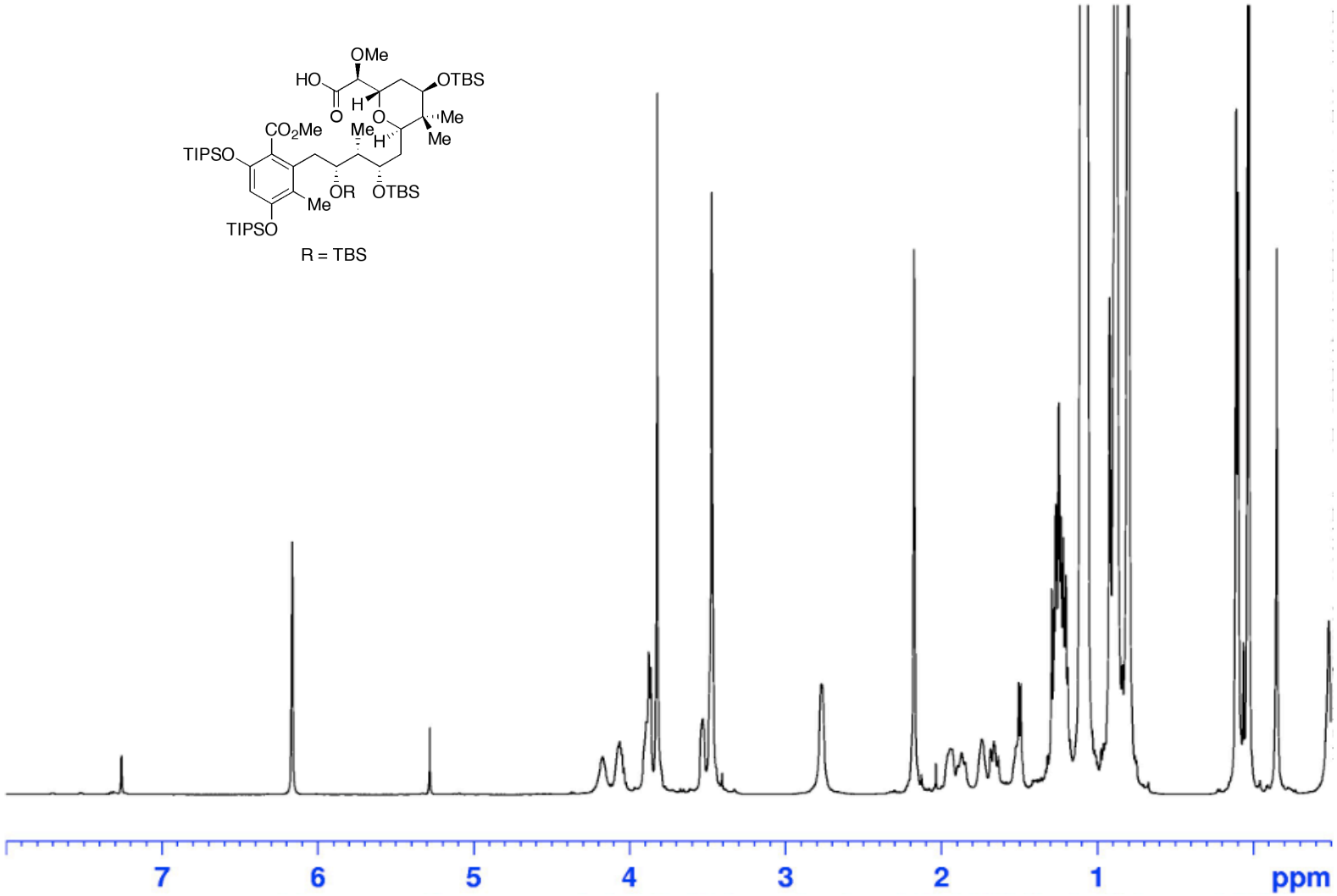
^{13}C Spectrum: Alcohol **236**, 125 MHz ($CDCl_3$)



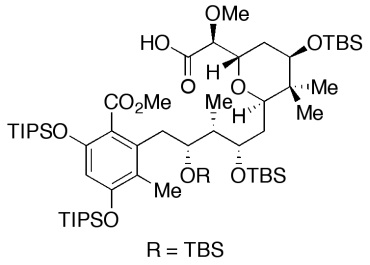
^{1}H Spectrum: Aldehyde, 500 MHz ($CDCl_3$)



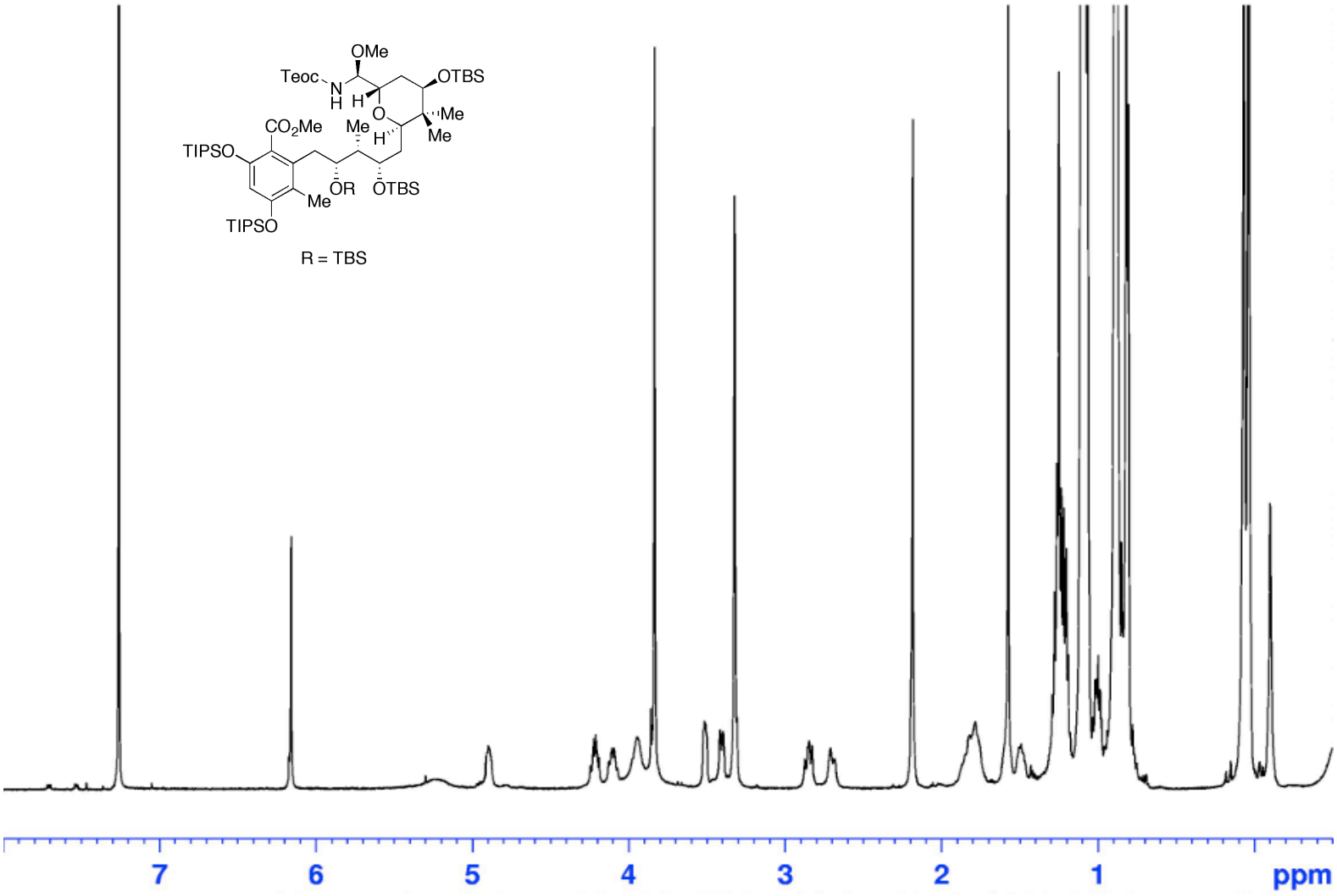
^{13}C Spectrum: Aldehyde, 125 MHz ($CDCl_3$)



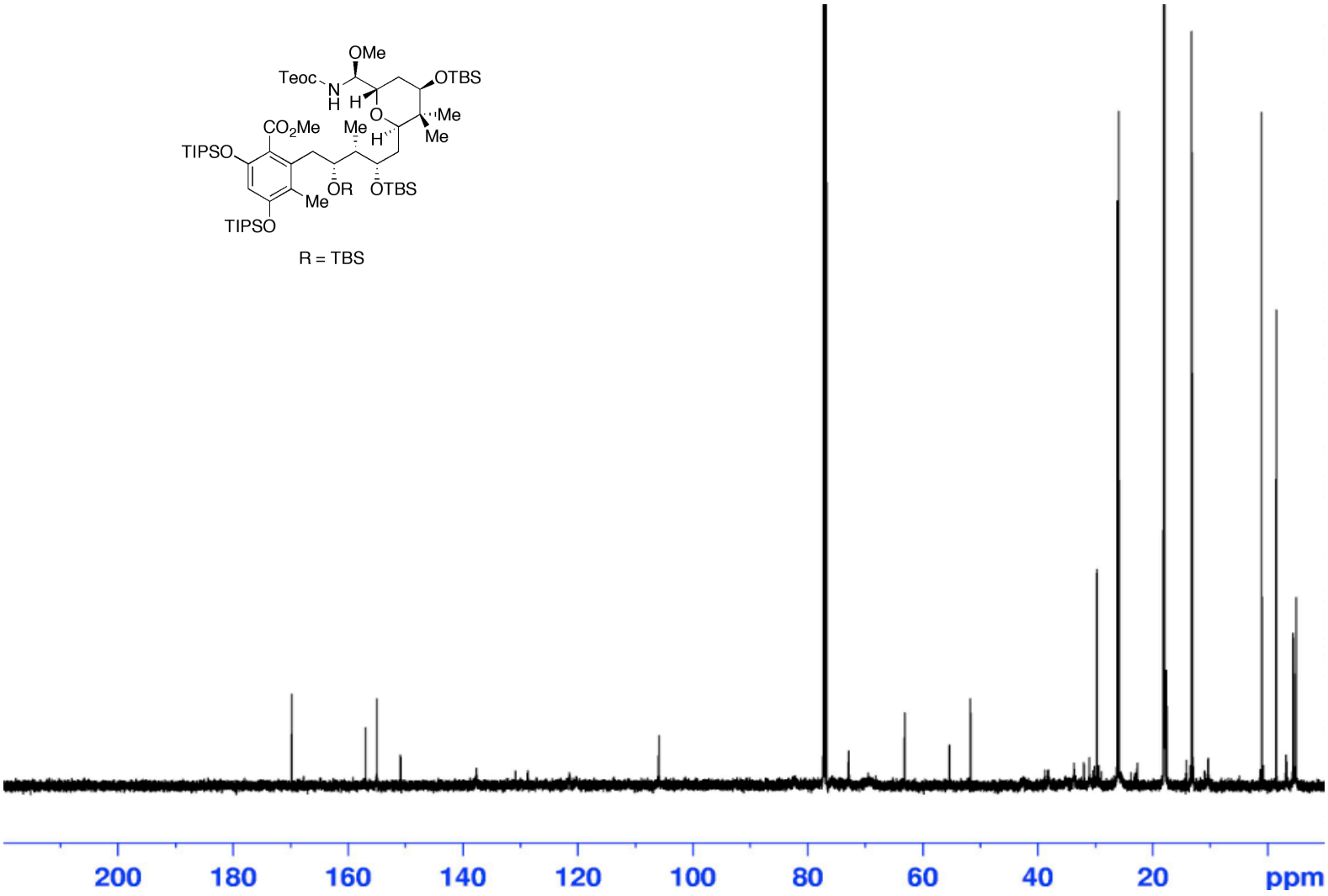
^{1}H Spectrum: Acid **237**, 500 MHz ($CDCl_3$)



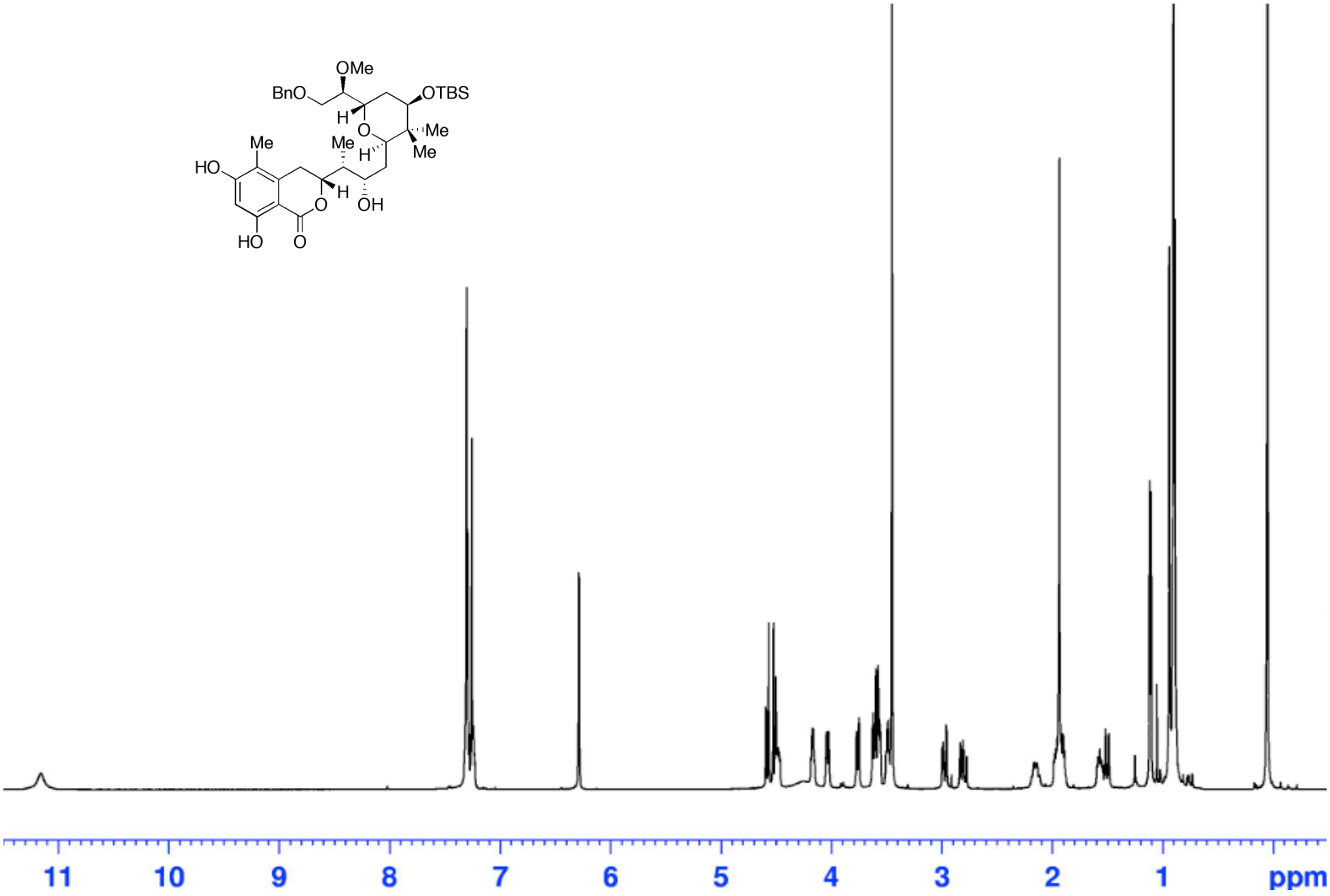
^{13}C Spectrum: Acid **237**, 125 MHz ($CDCl_3$)



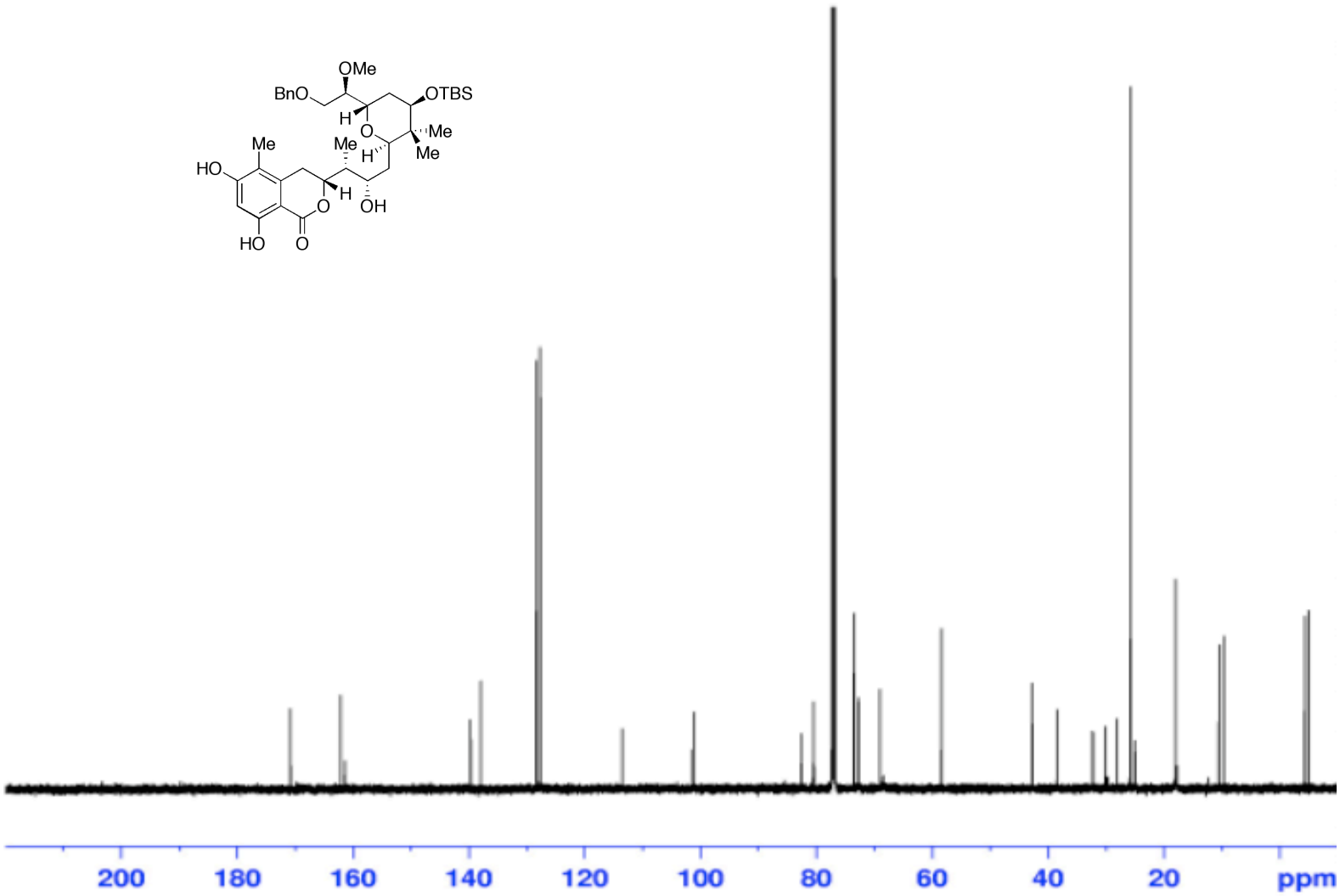
^{1}H Spectrum: Hemiaminal **239**, 500 MHz ($CDCl_3$)



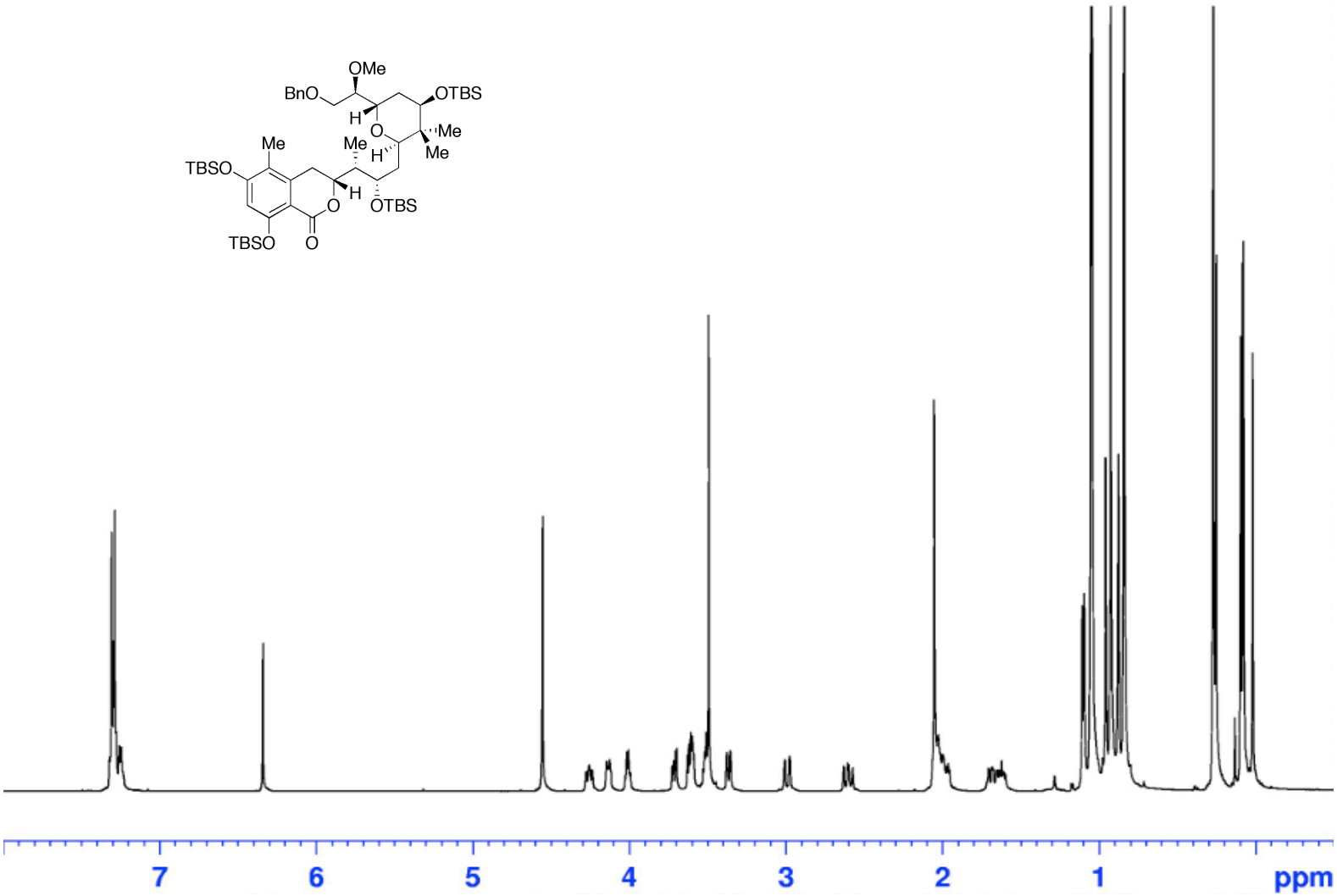
^{13}C Spectrum: Hemiaminal **239**, 125 MHz ($CDCl_3$)



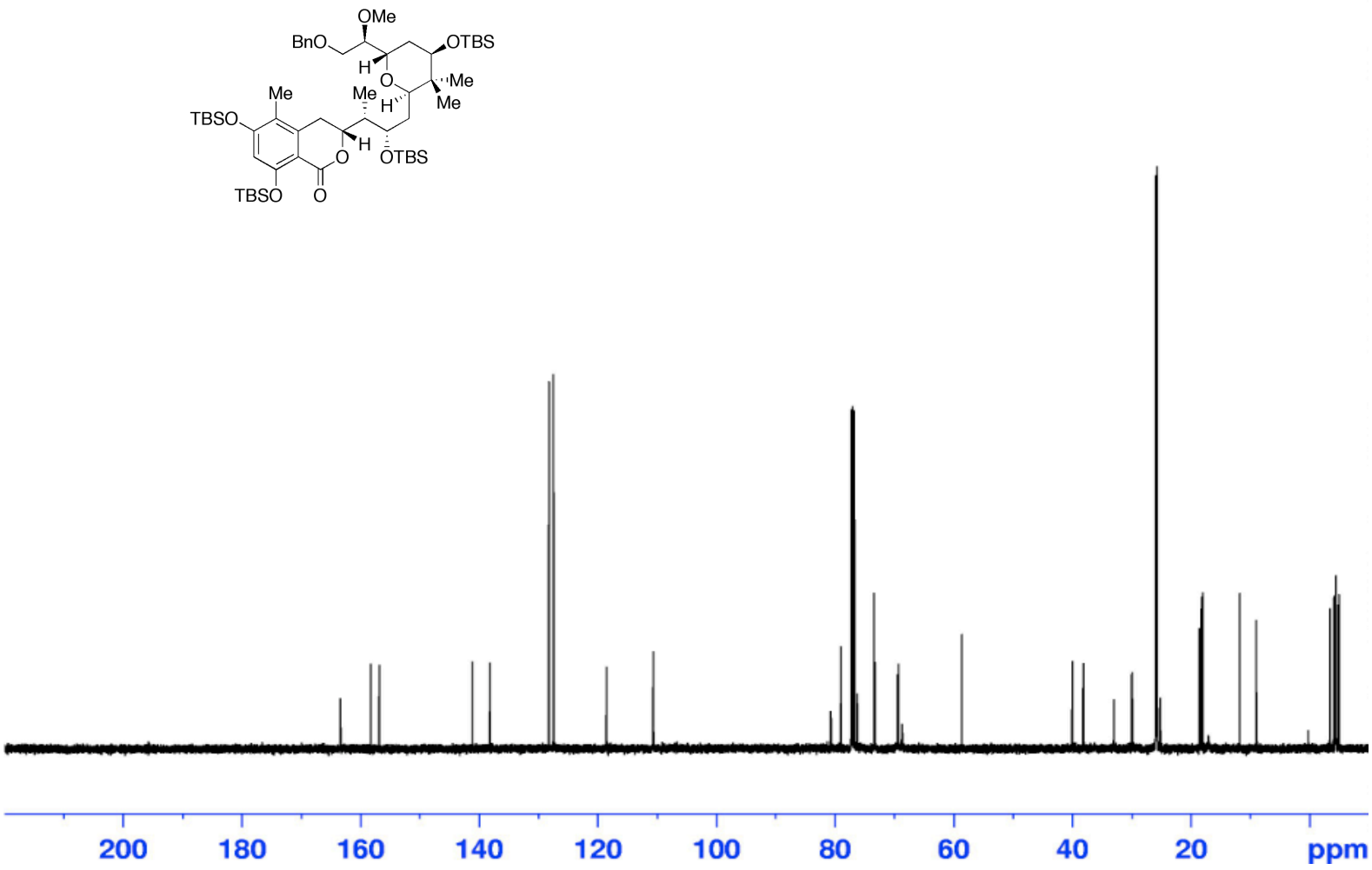
^{1}H Spectrum: Alcohol **243**, 500 MHz ($CDCl_3$)



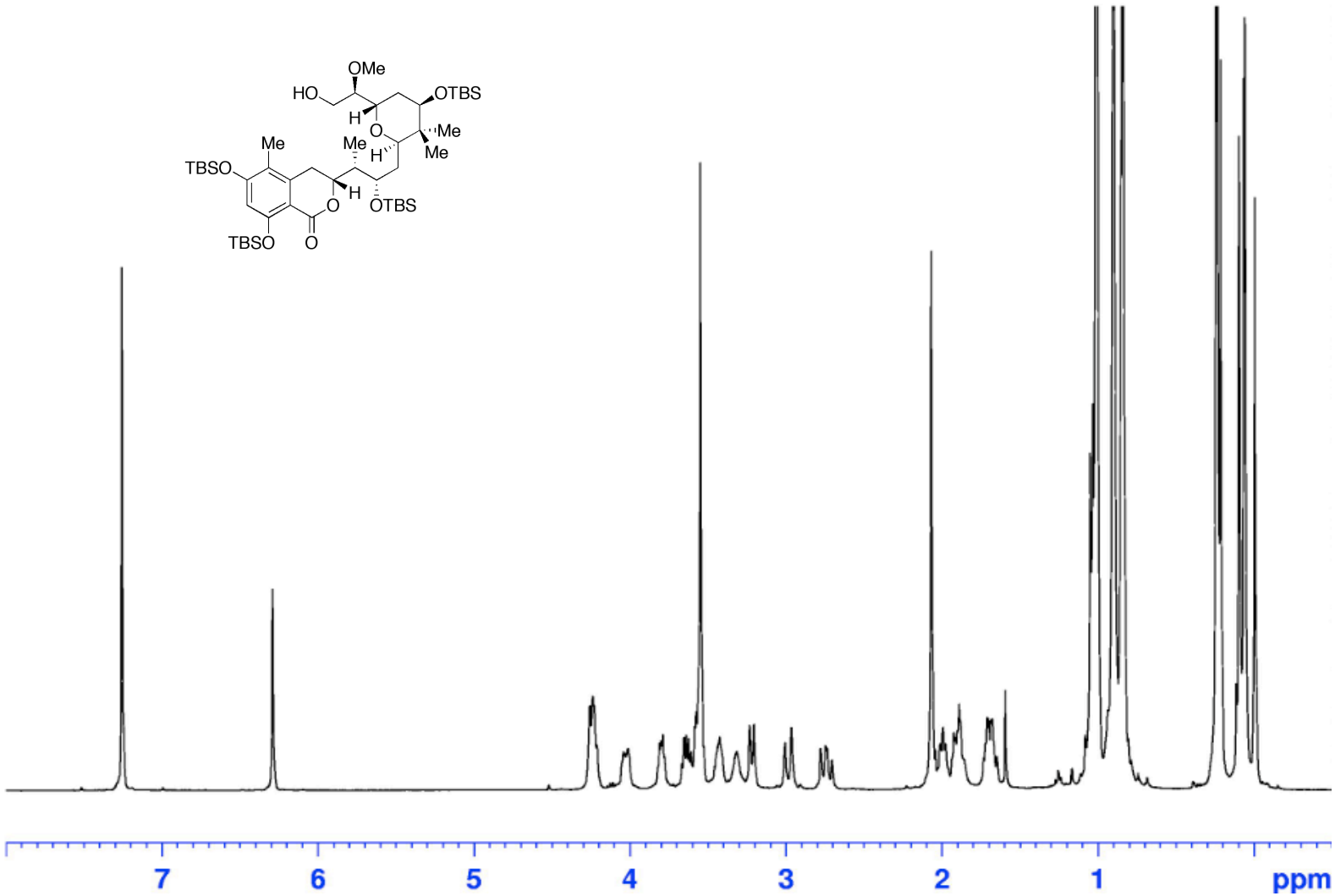
^{13}C Spectrum: Alcohol **243**, 125 MHz ($CDCl_3$)



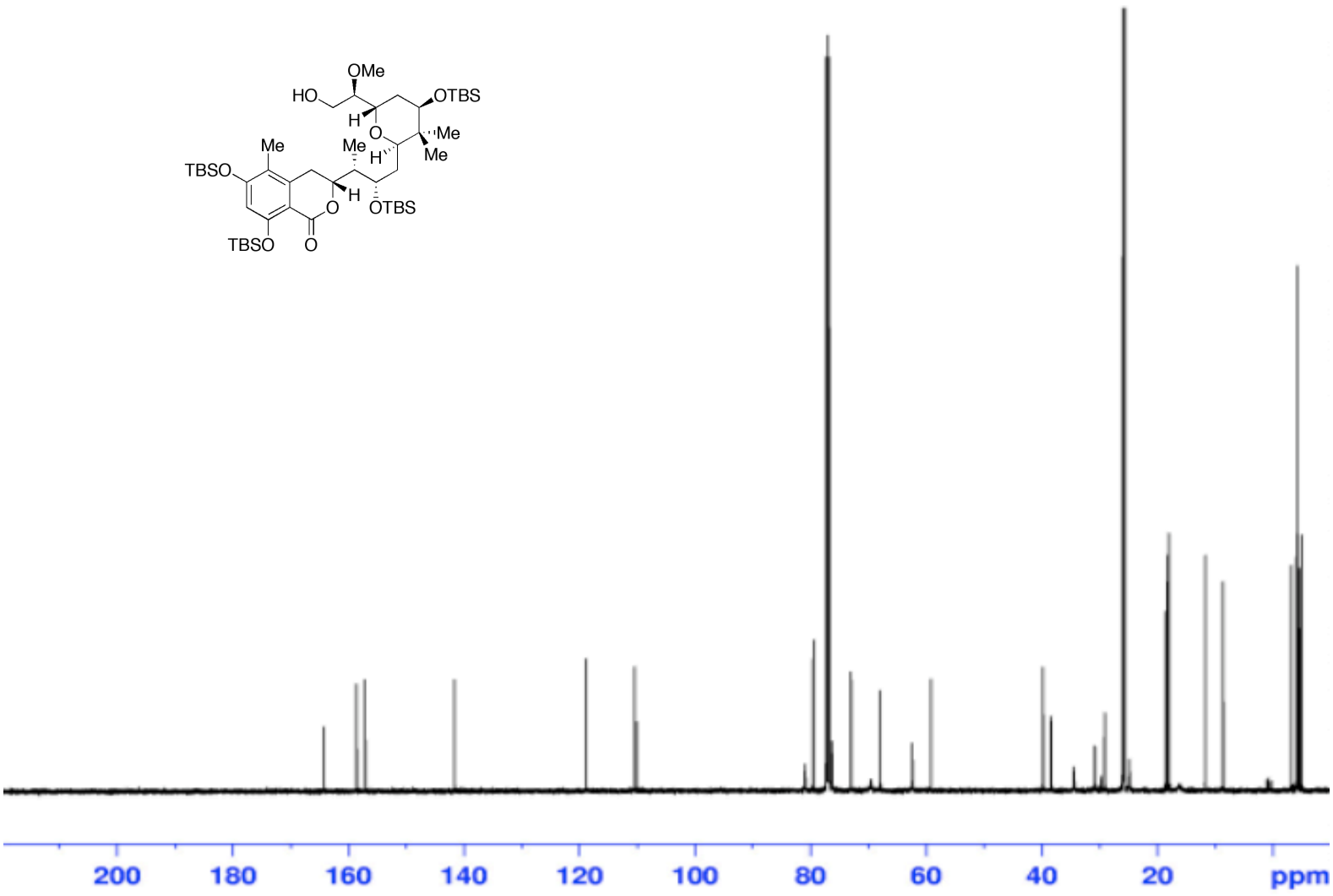
^{1}H Spectrum: TBS Ether, 500 MHz ($CDCl_3$)



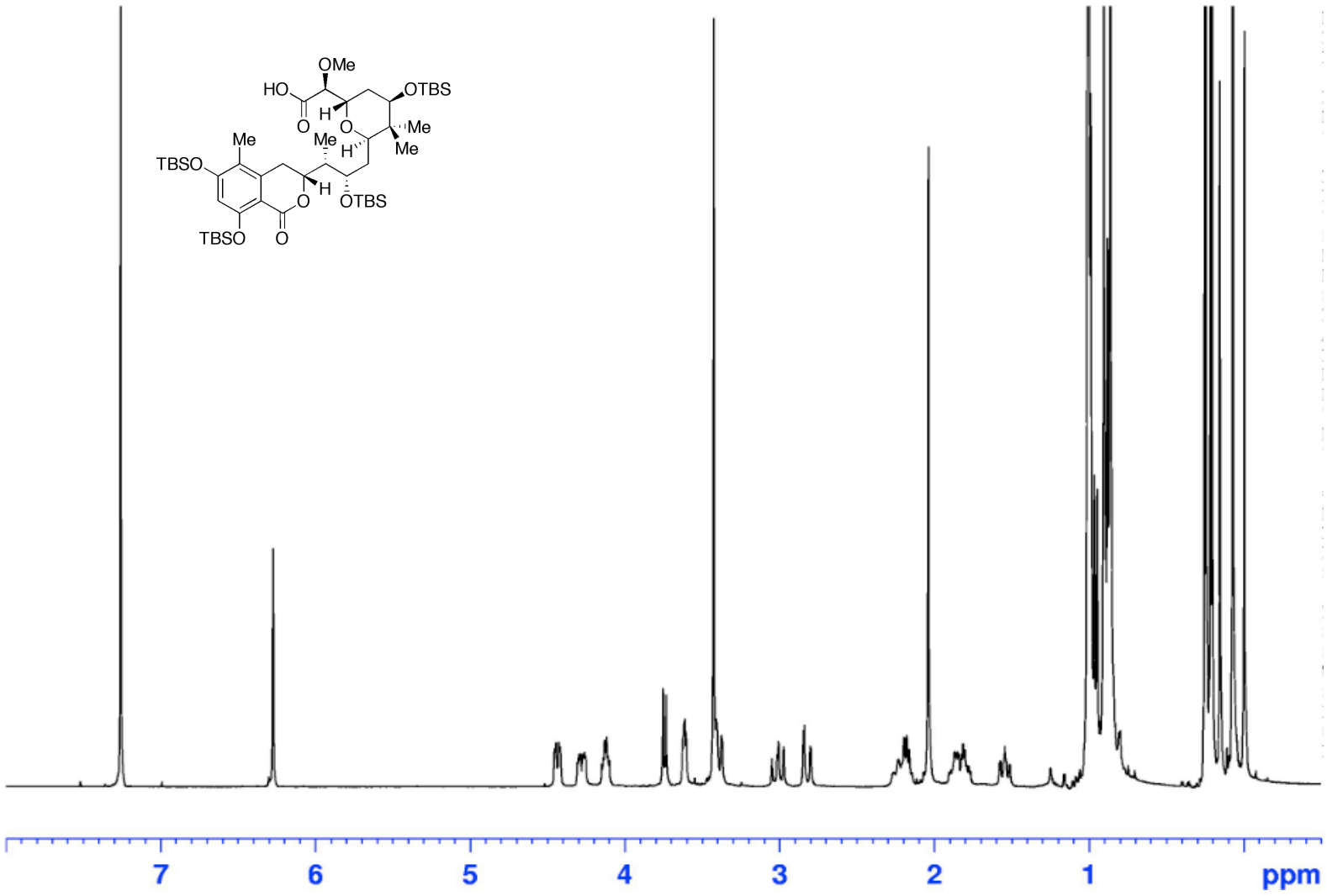
^{13}C Spectrum: TBS Ether, 125 MHz ($CDCl_3$)



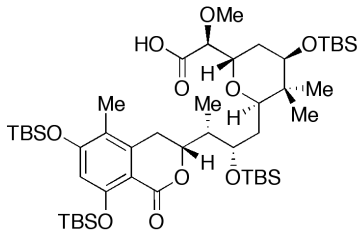
^{1}H Spectrum: Alcohol **244**, 400 MHz ($CDCl_3$)



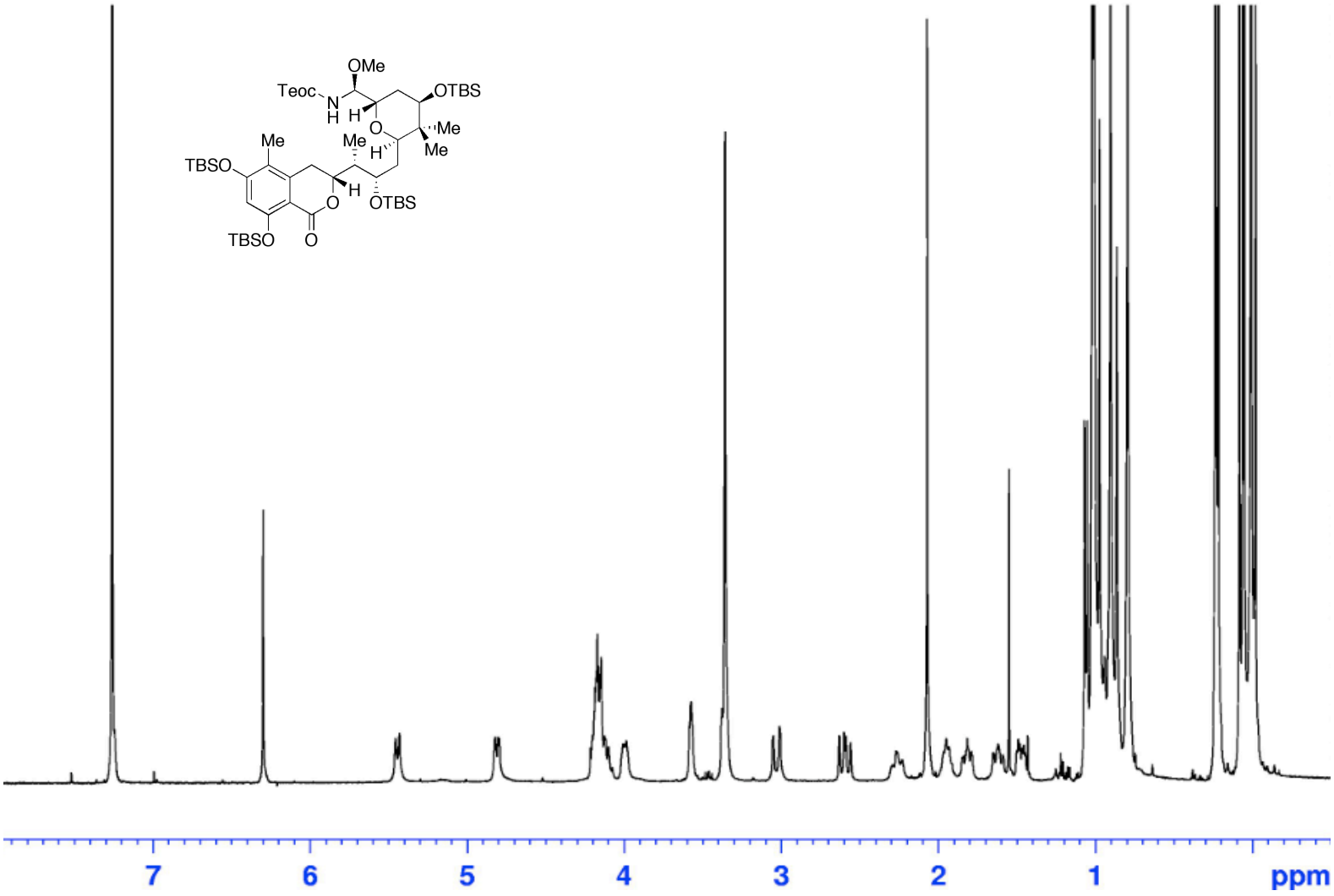
^{13}C Spectrum: Alcohol **244**, 125 MHz ($CDCl_3$)



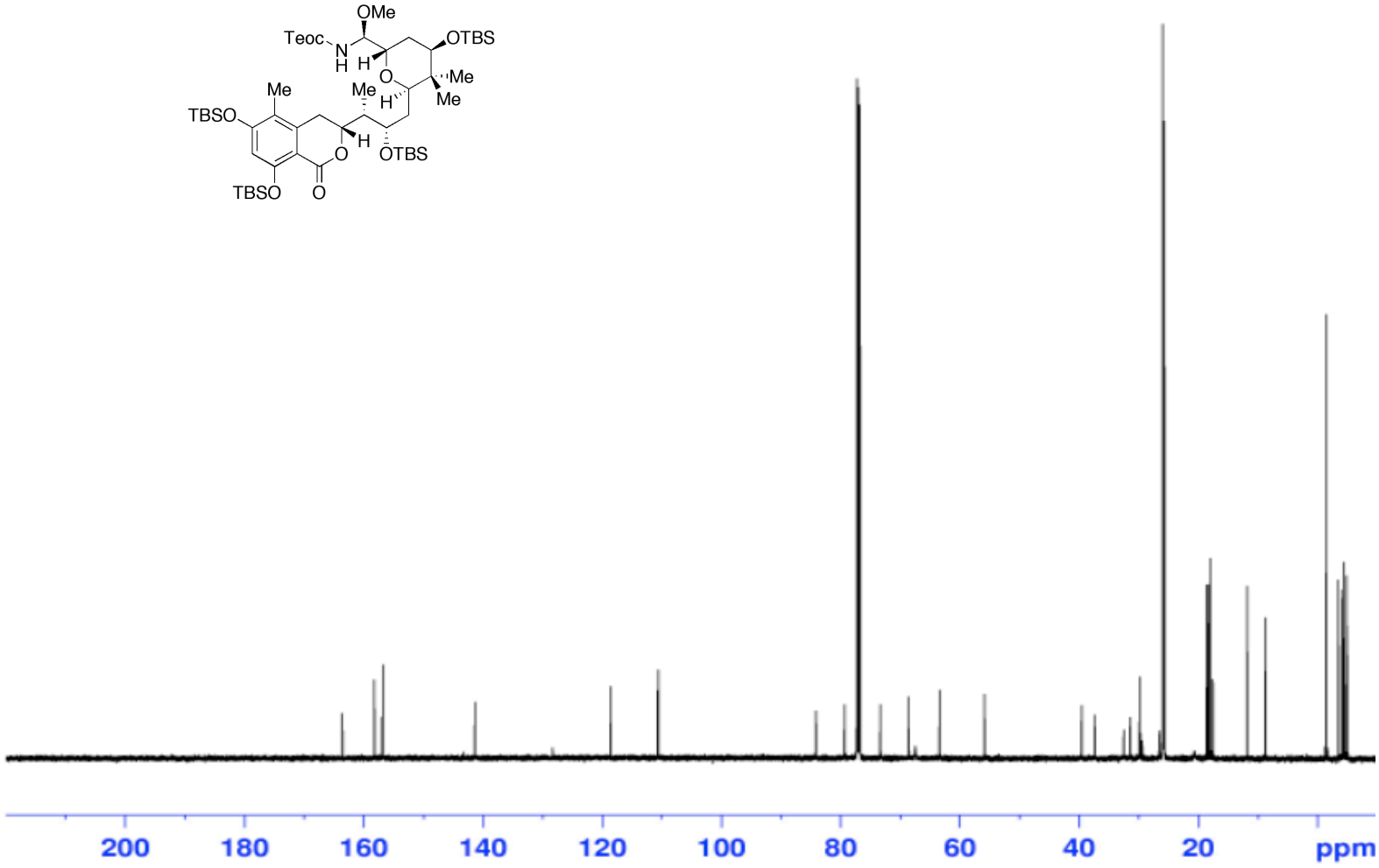
^{1}H Spectrum: Acid **245**, 400 MHz ($CDCl_3$)



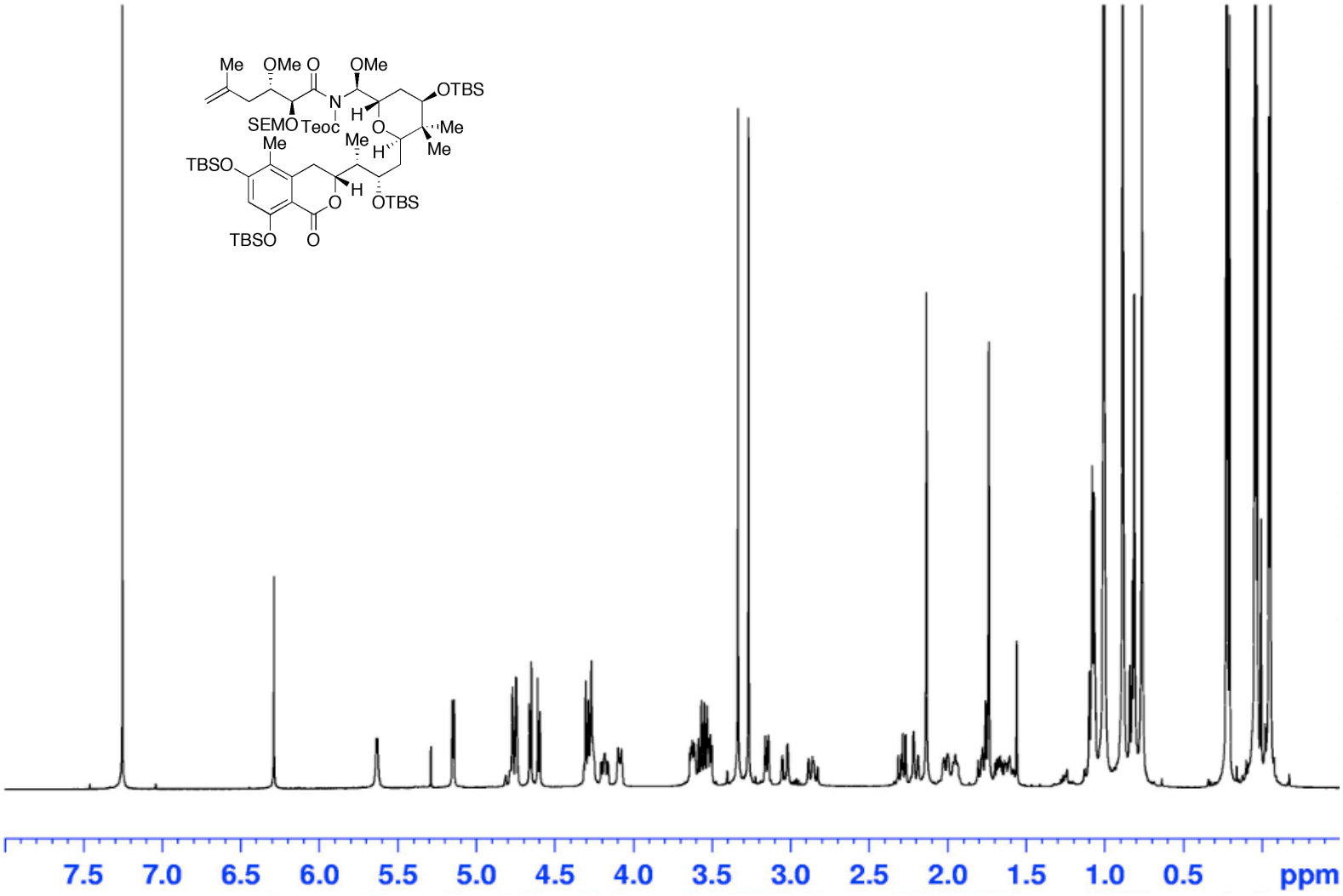
^{13}C Spectrum: Acid **245**, 125 MHz ($CDCl_3$)



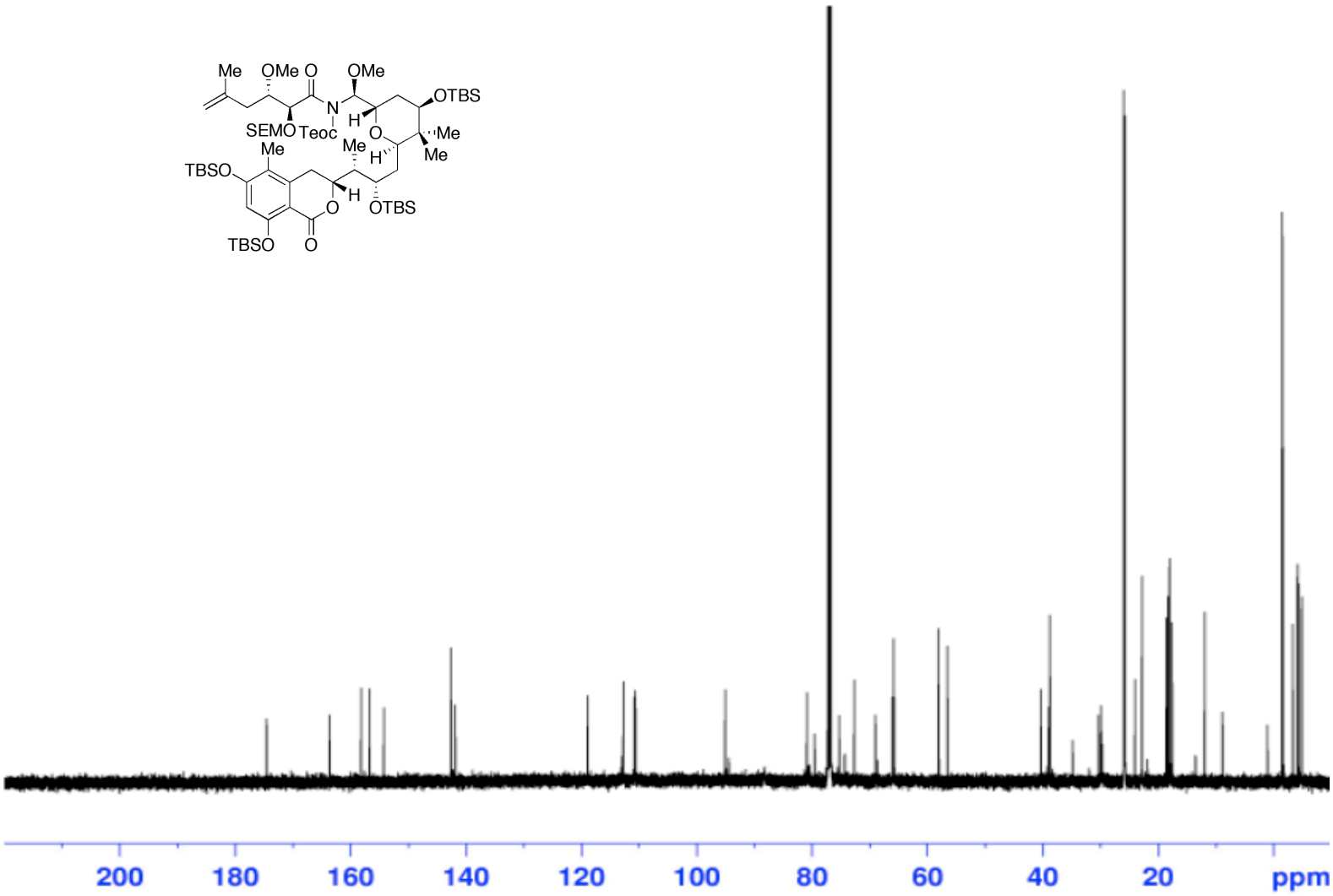
^{1}H Spectrum: Hemiaminal **190**, 400 MHz ($CDCl_3$)



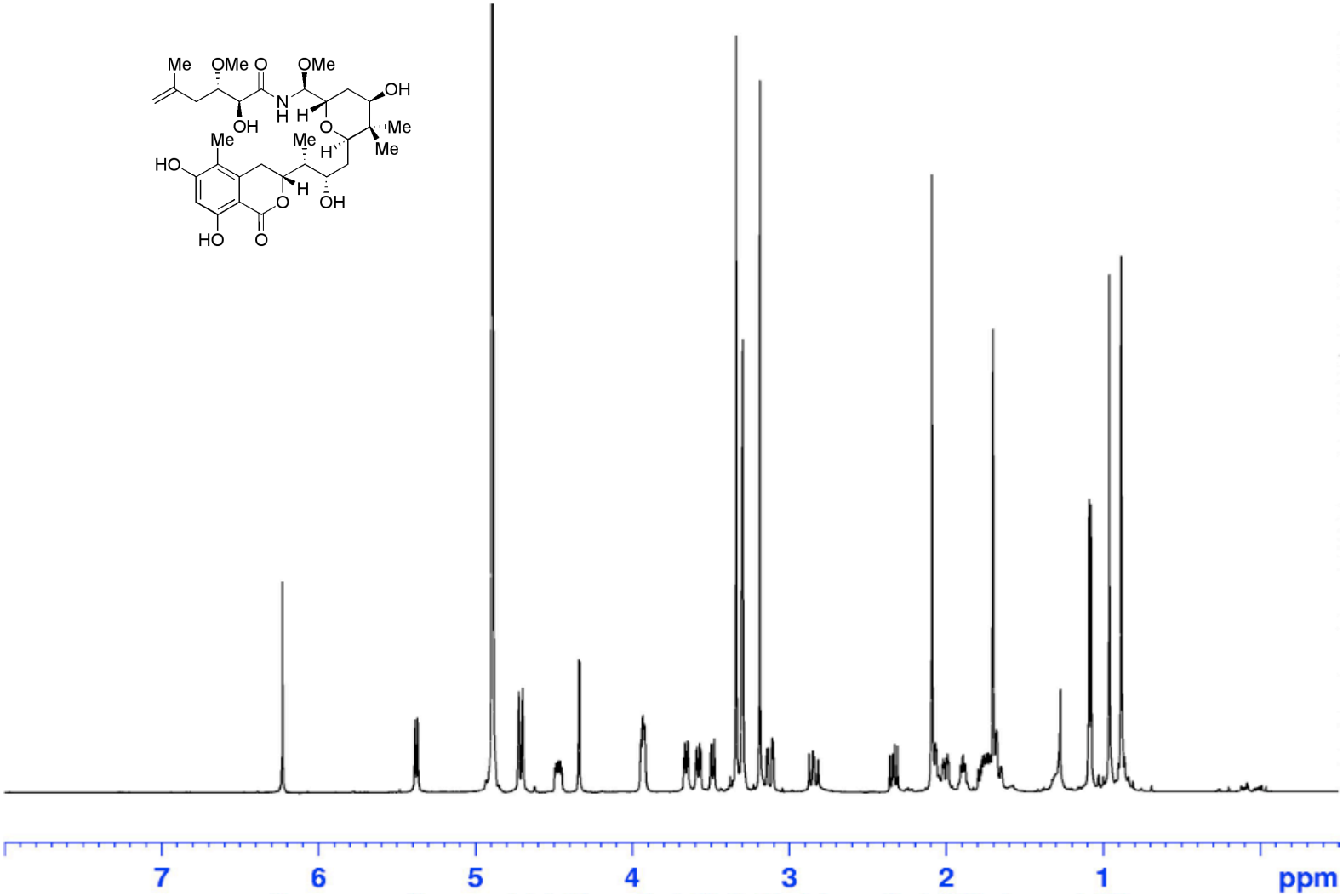
^{13}C Spectrum: Hemiaminal **190**, 125 MHz ($CDCl_3$)



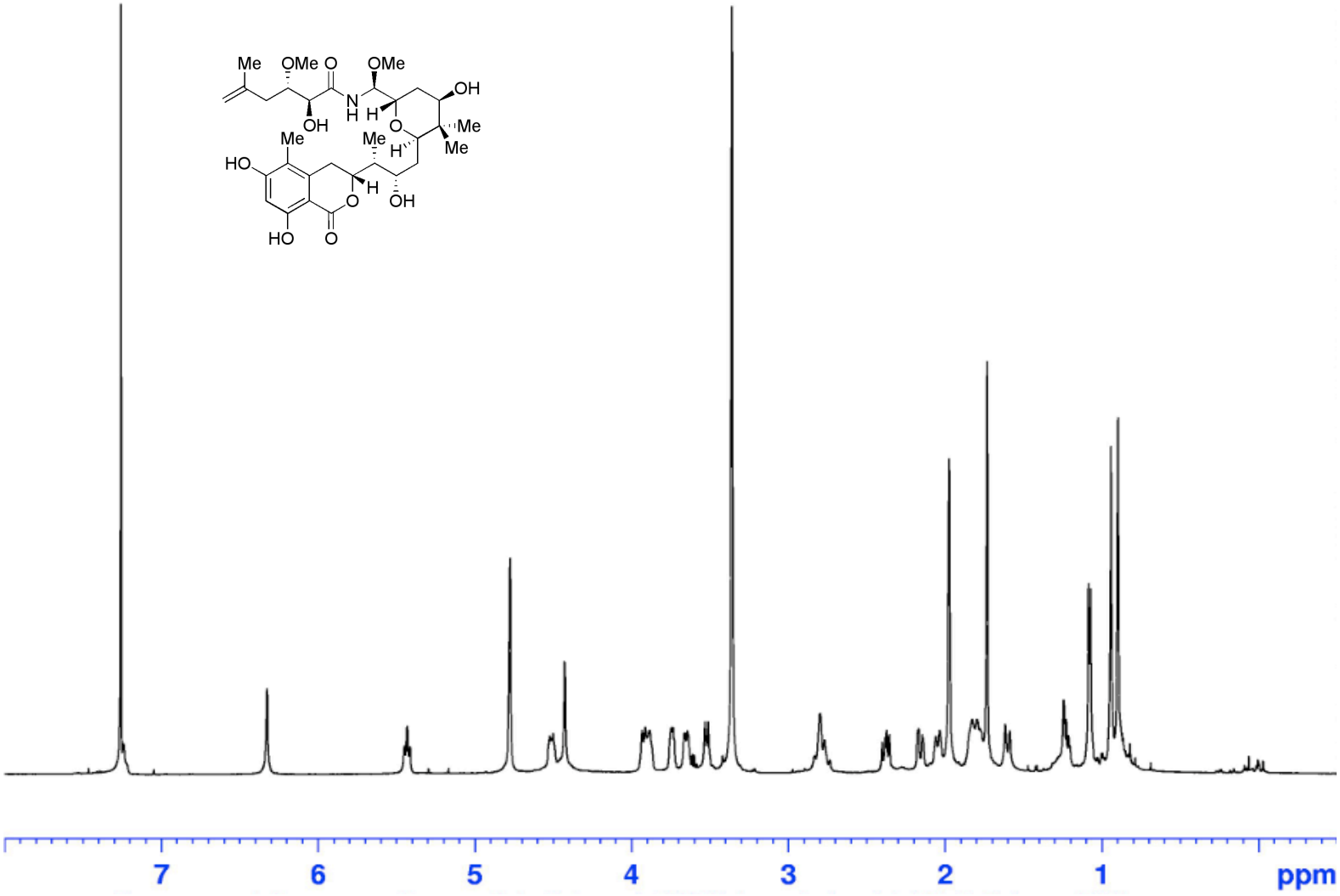
^{1}H Spectrum: Protected Irciniastatin A **246**, 500 MHz ($CDCl_3$)



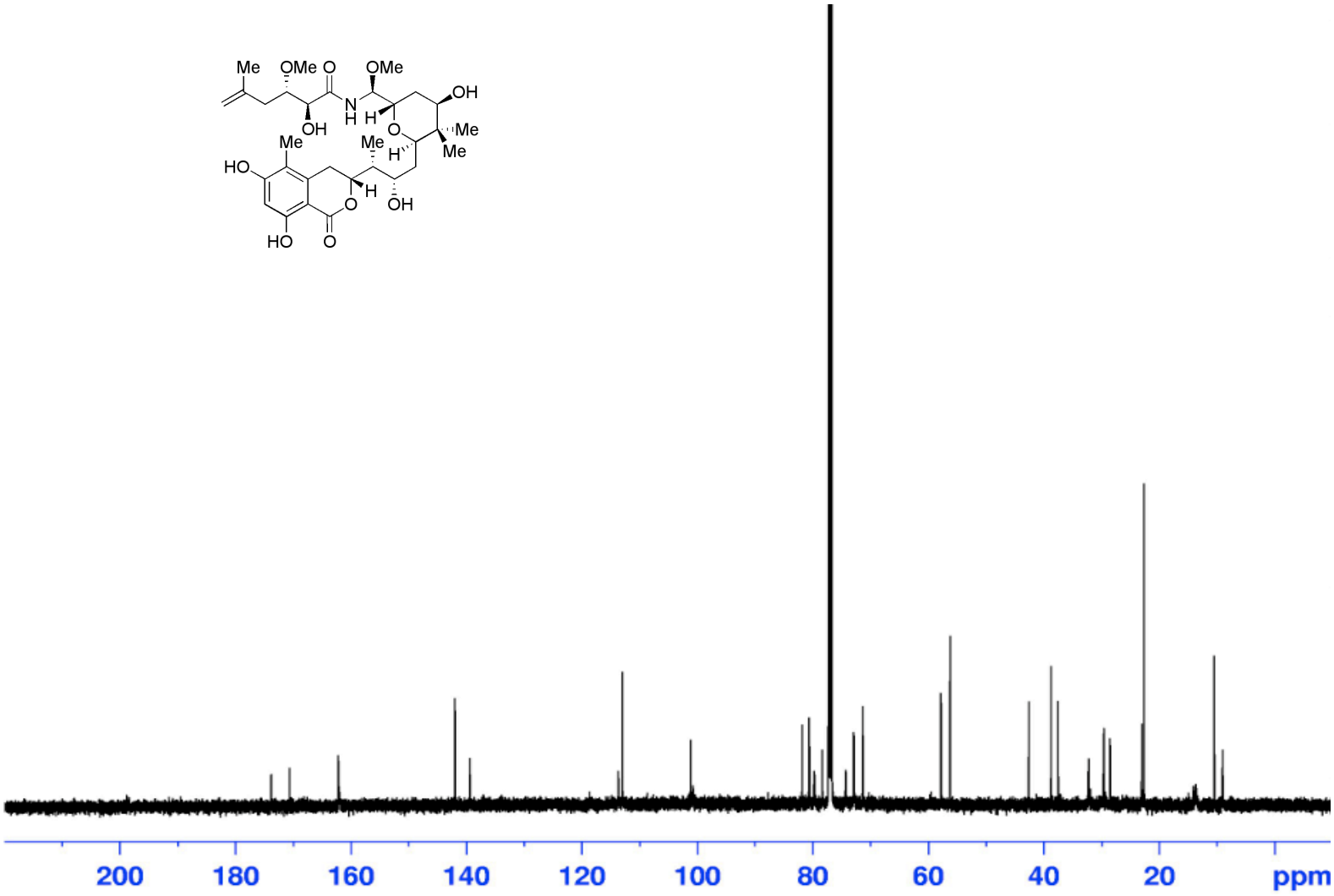
^{13}C Spectrum: Protected Irciniastatin A **246**, 125 MHz ($CDCl_3$)



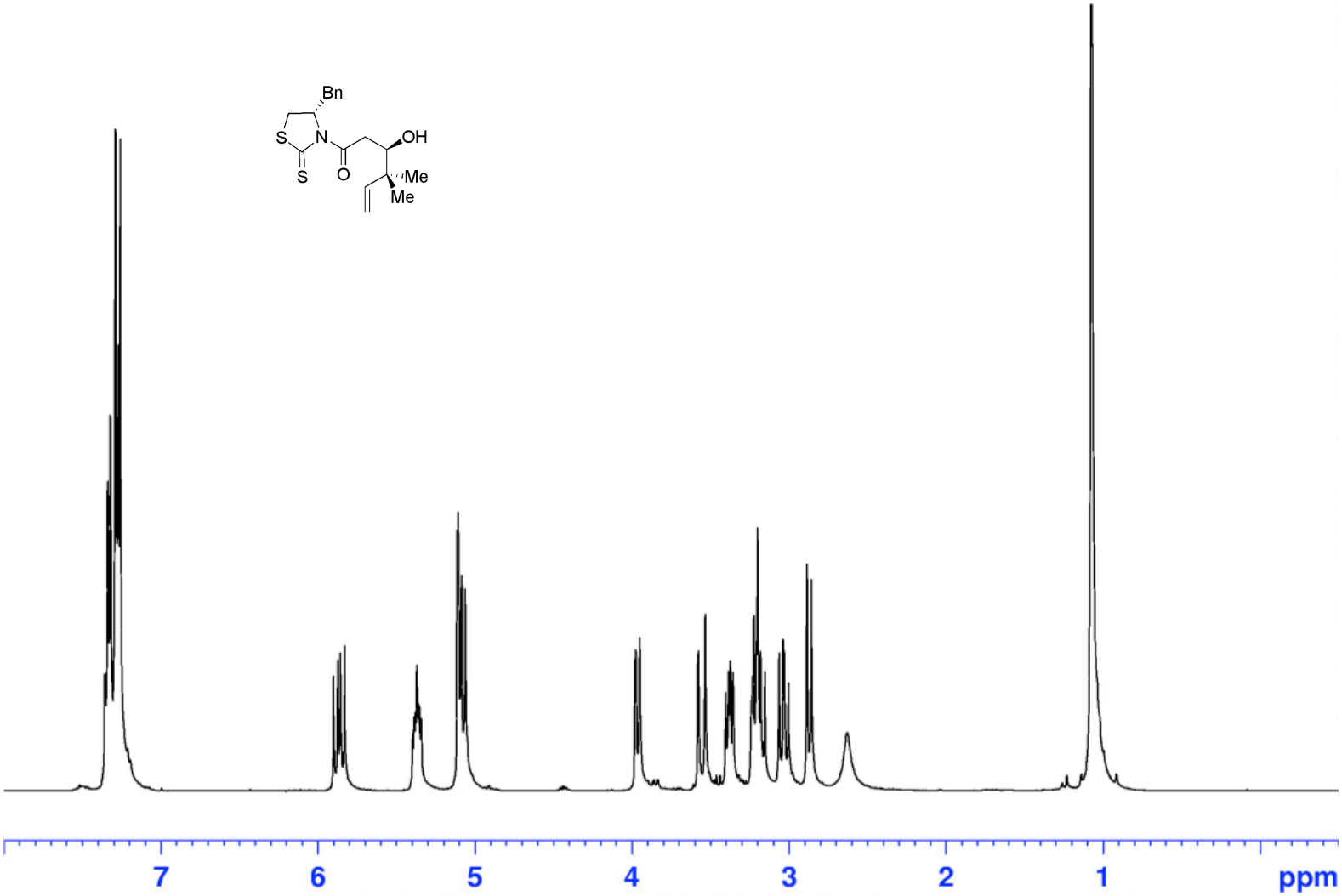
^{1}H Spectrum: Irciniastatin A (**8**), 500 MHz (MeOD)



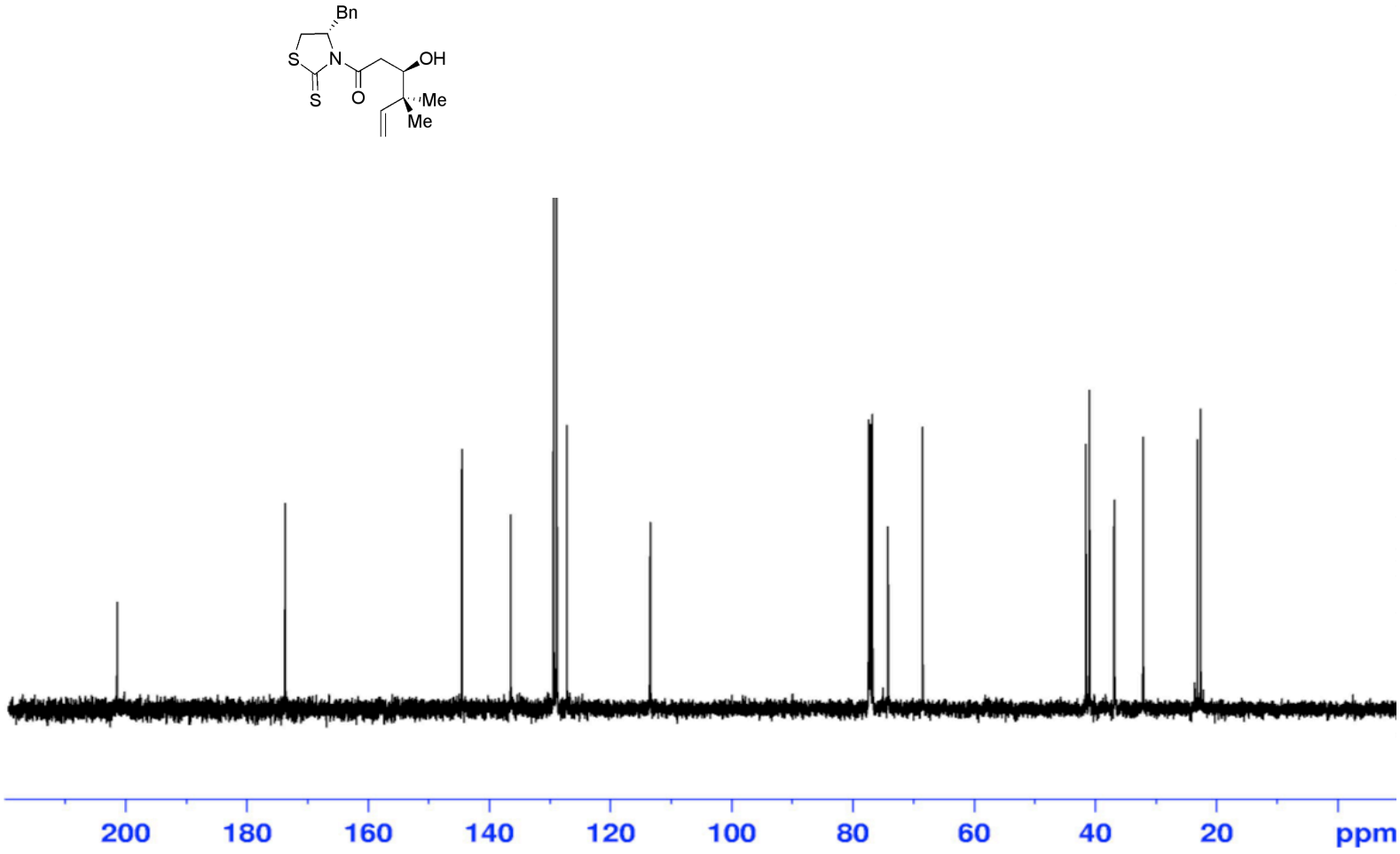
^{1}H Spectrum: Irciniastatin A (**8**), 500 MHz ($CDCl_3$)



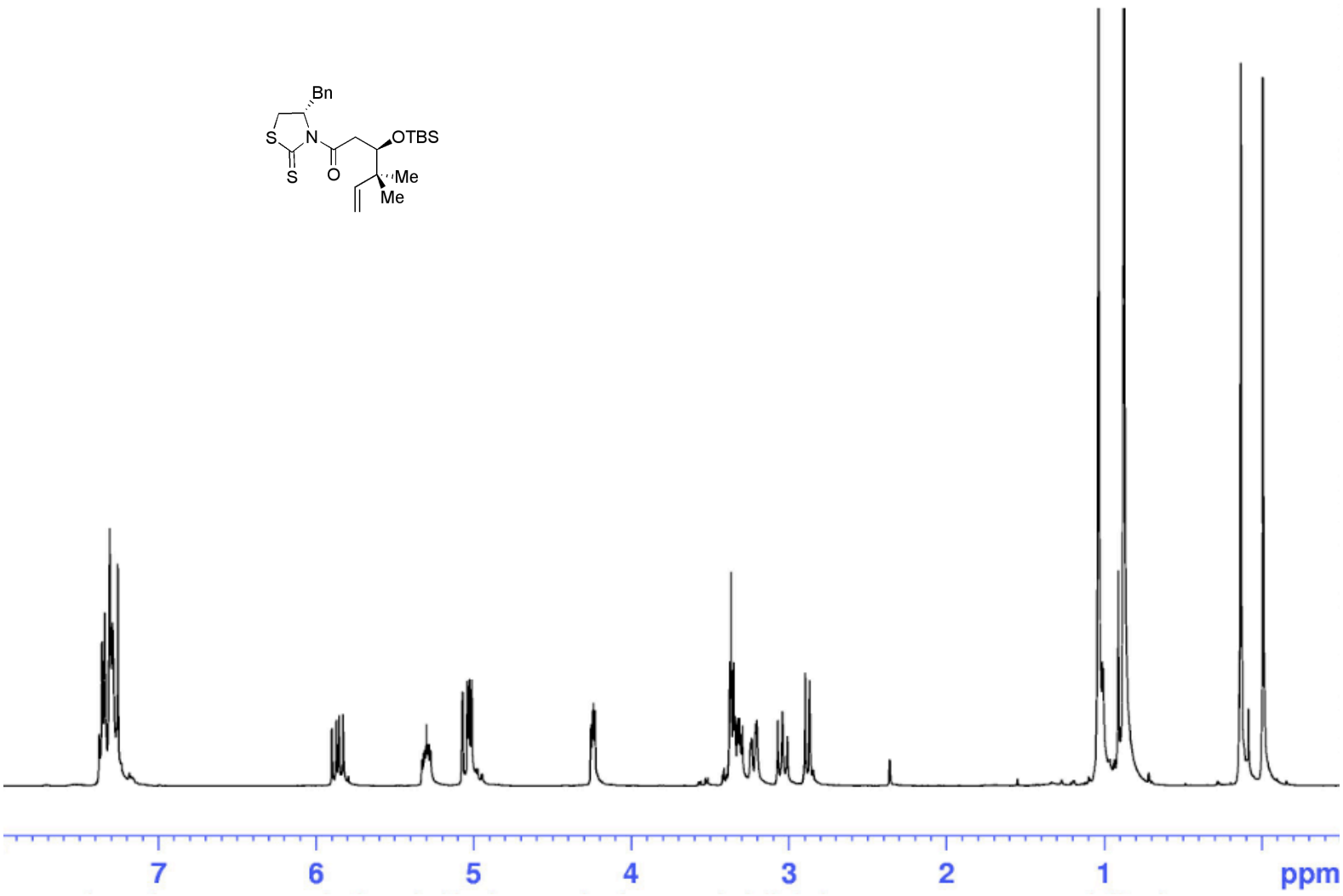
^{13}C Spectrum: Irciniastatin A (**8**), 125 MHz ($CDCl_3$)



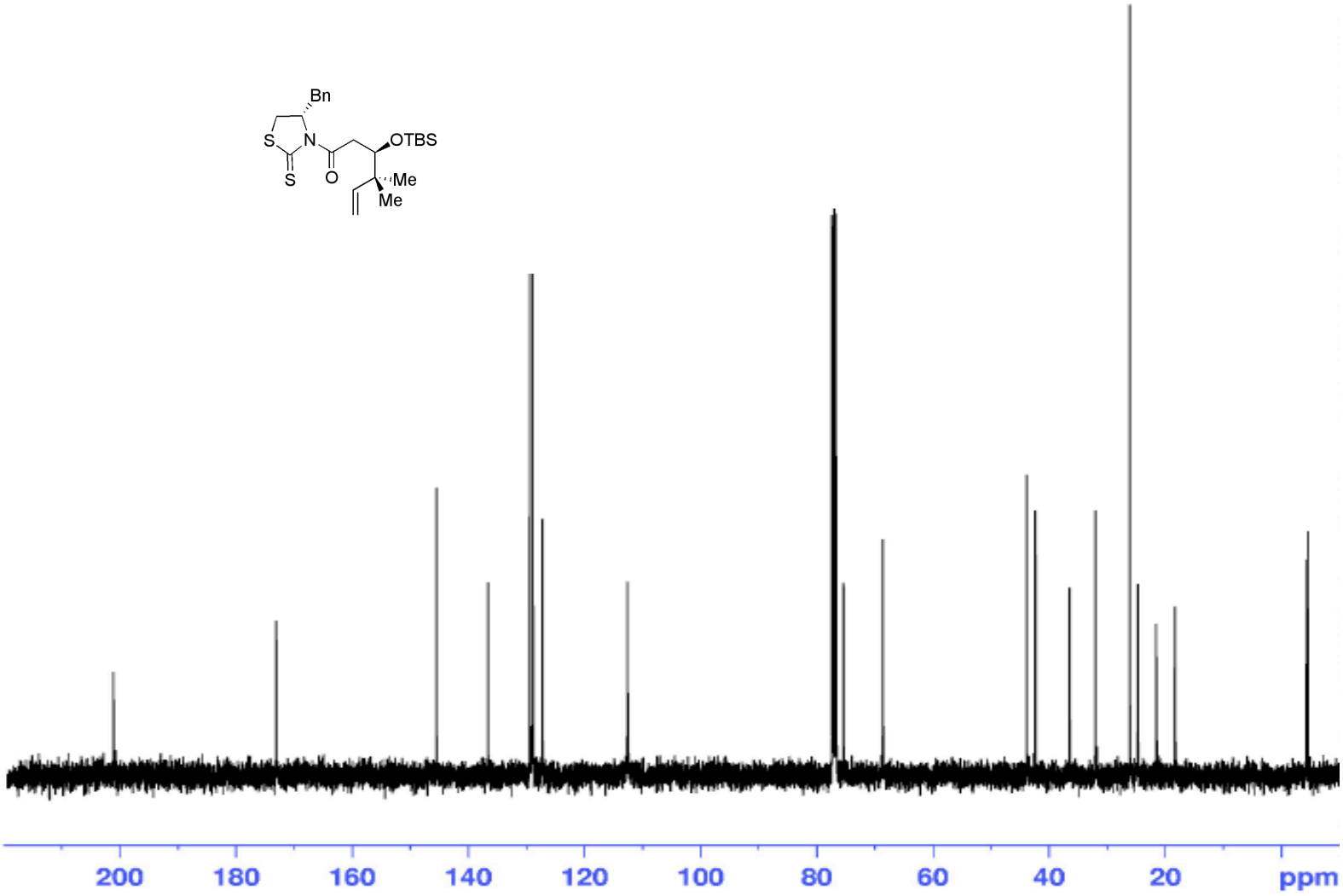
^{1}H Spectrum: Alcohol **255**, 400 MHz ($CDCl_3$)



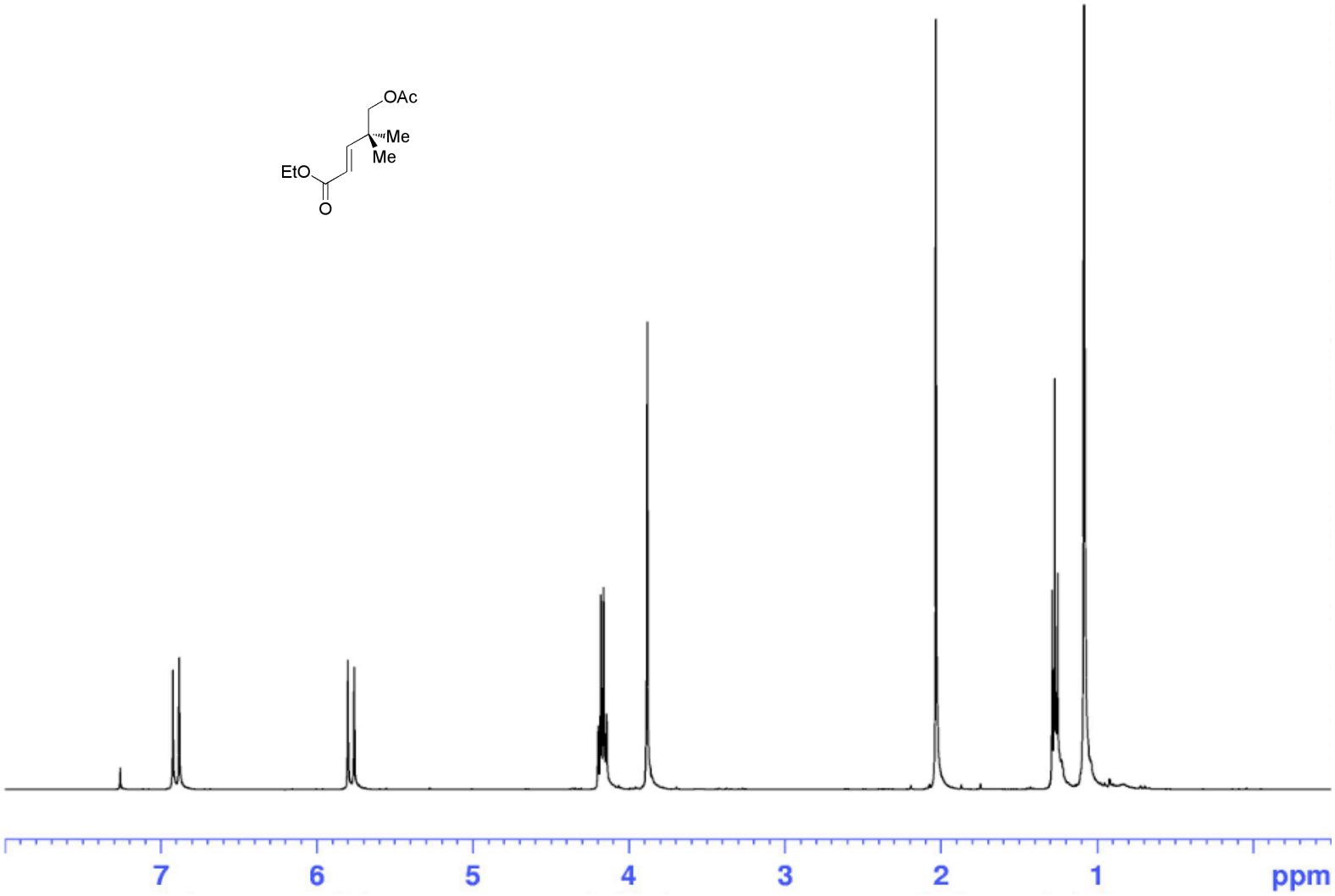
^{13}C Spectrum: Alcohol **255**, 100 MHz ($CDCl_3$)



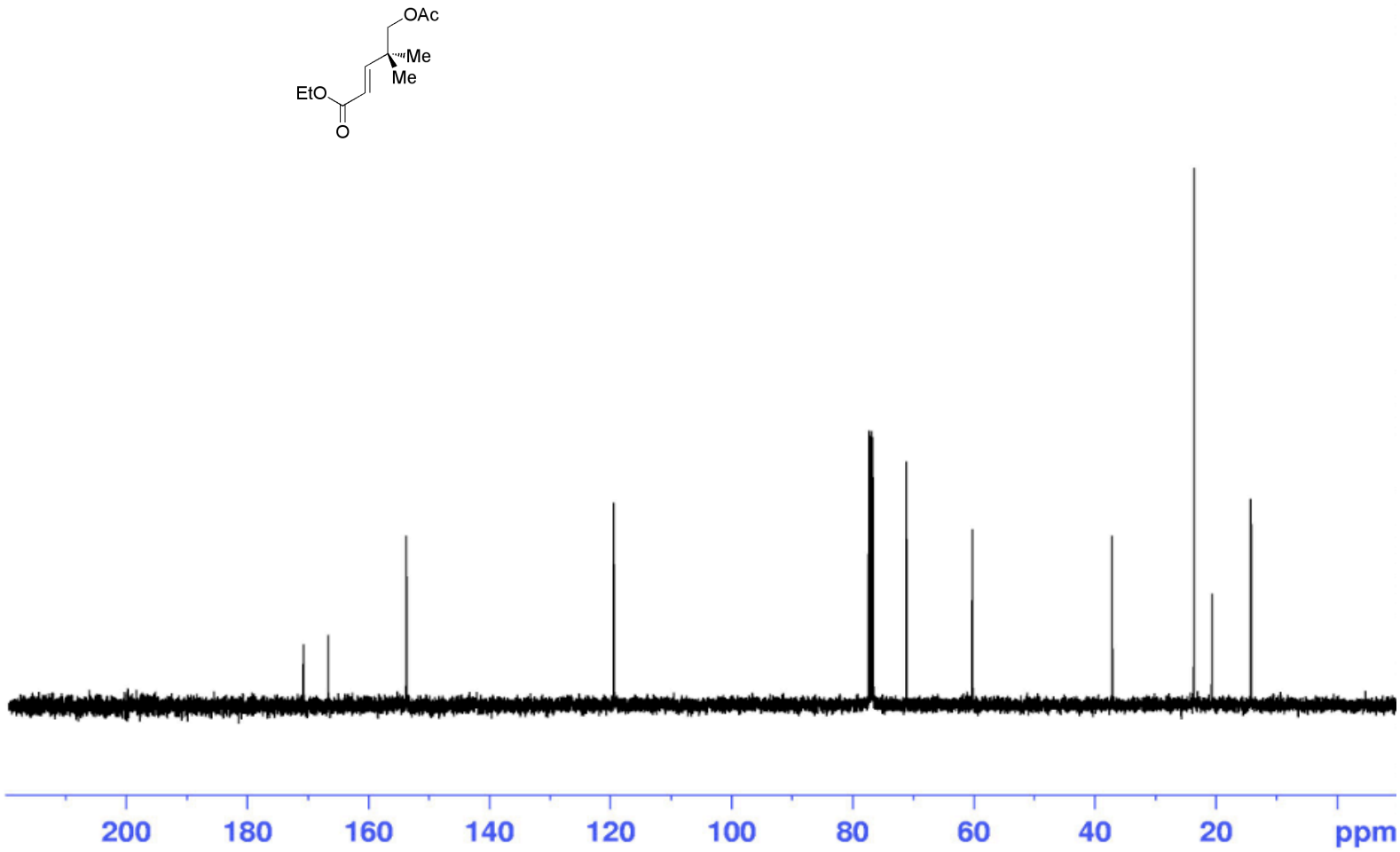
^{1}H Spectrum: TBS Ether, 400 MHz ($CDCl_3$)



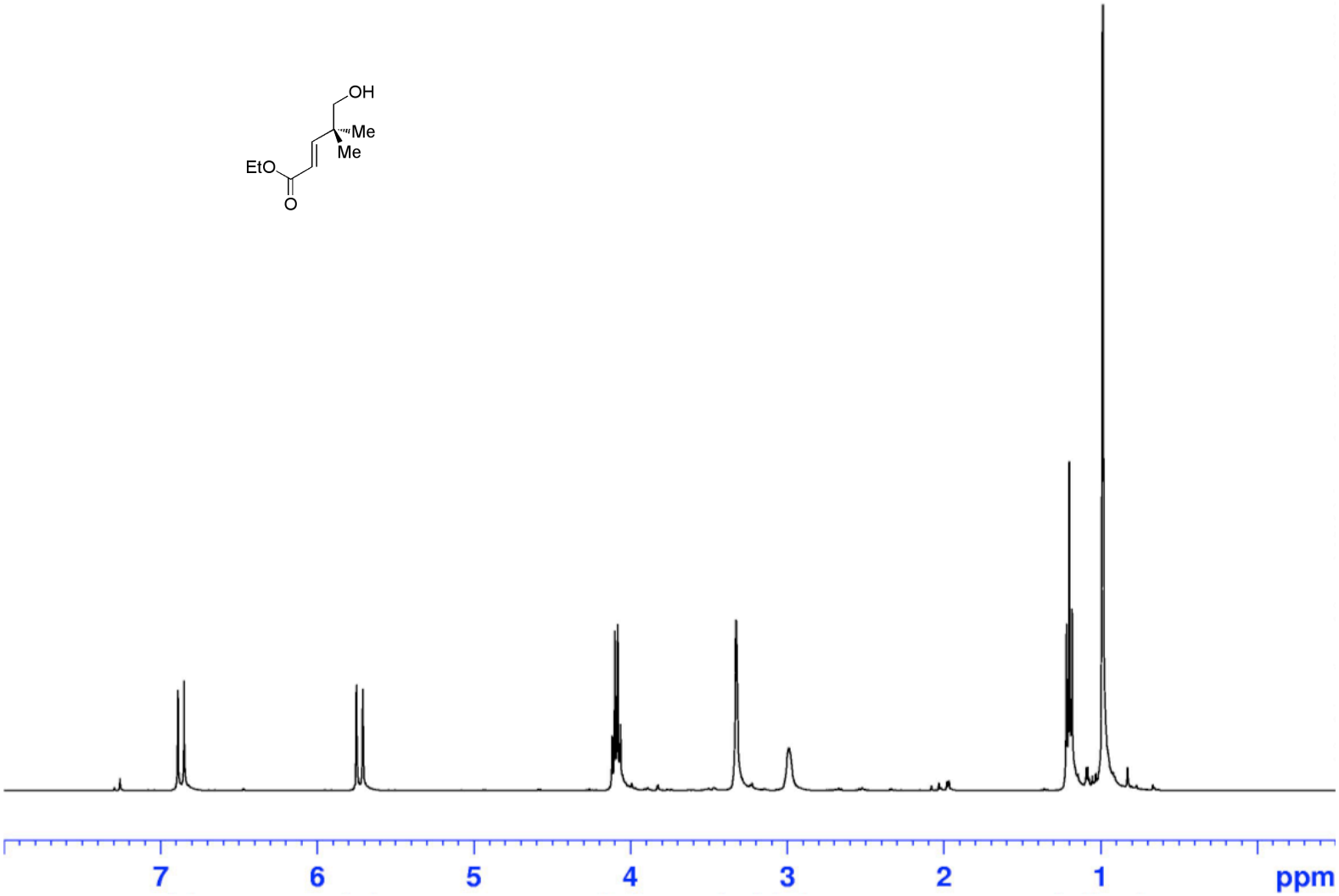
^{13}C Spectrum: TBS Ether, 100 MHz ($CDCl_3$)



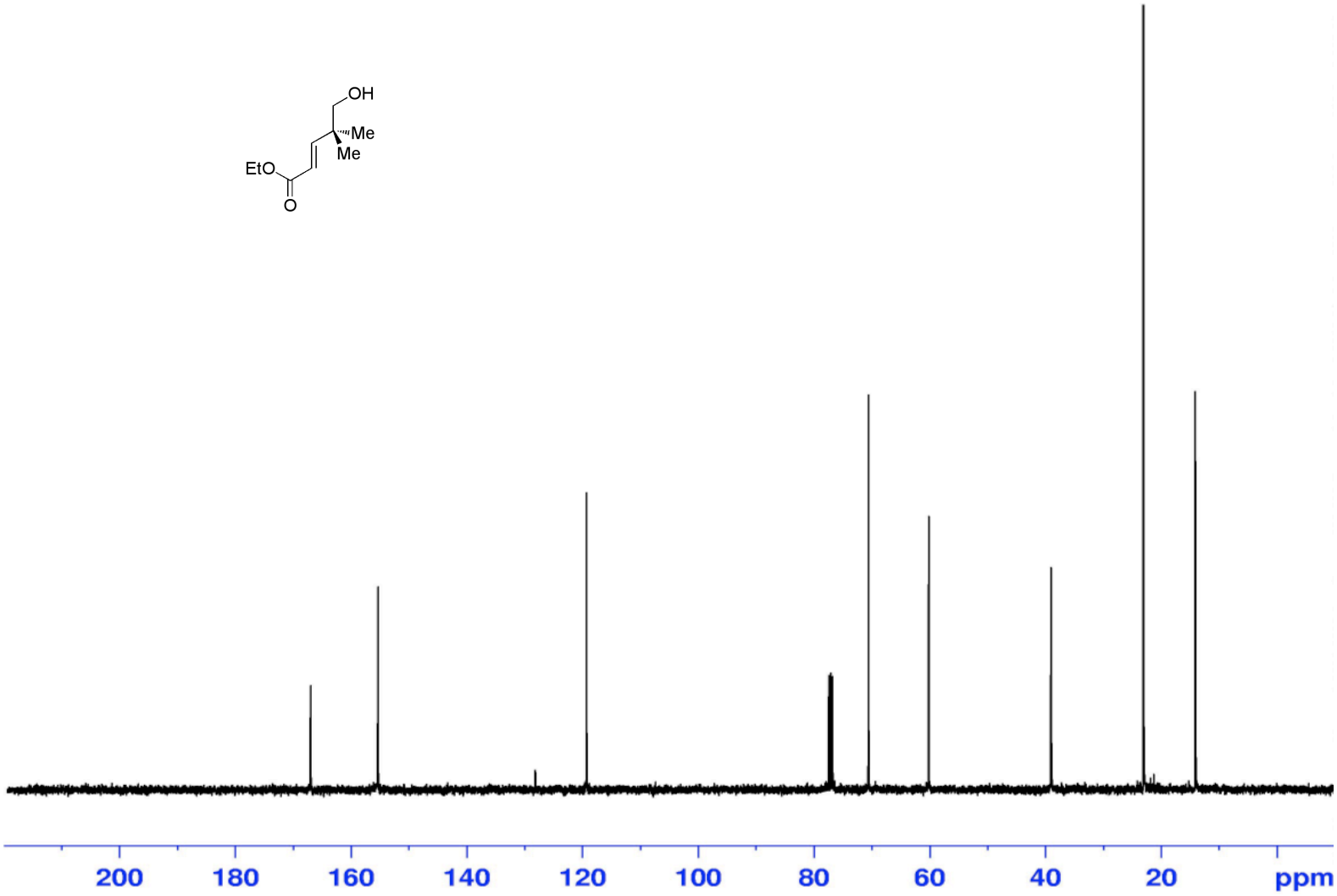
^{1}H Spectrum: Enoate **260**, 400 MHz ($CDCl_3$)



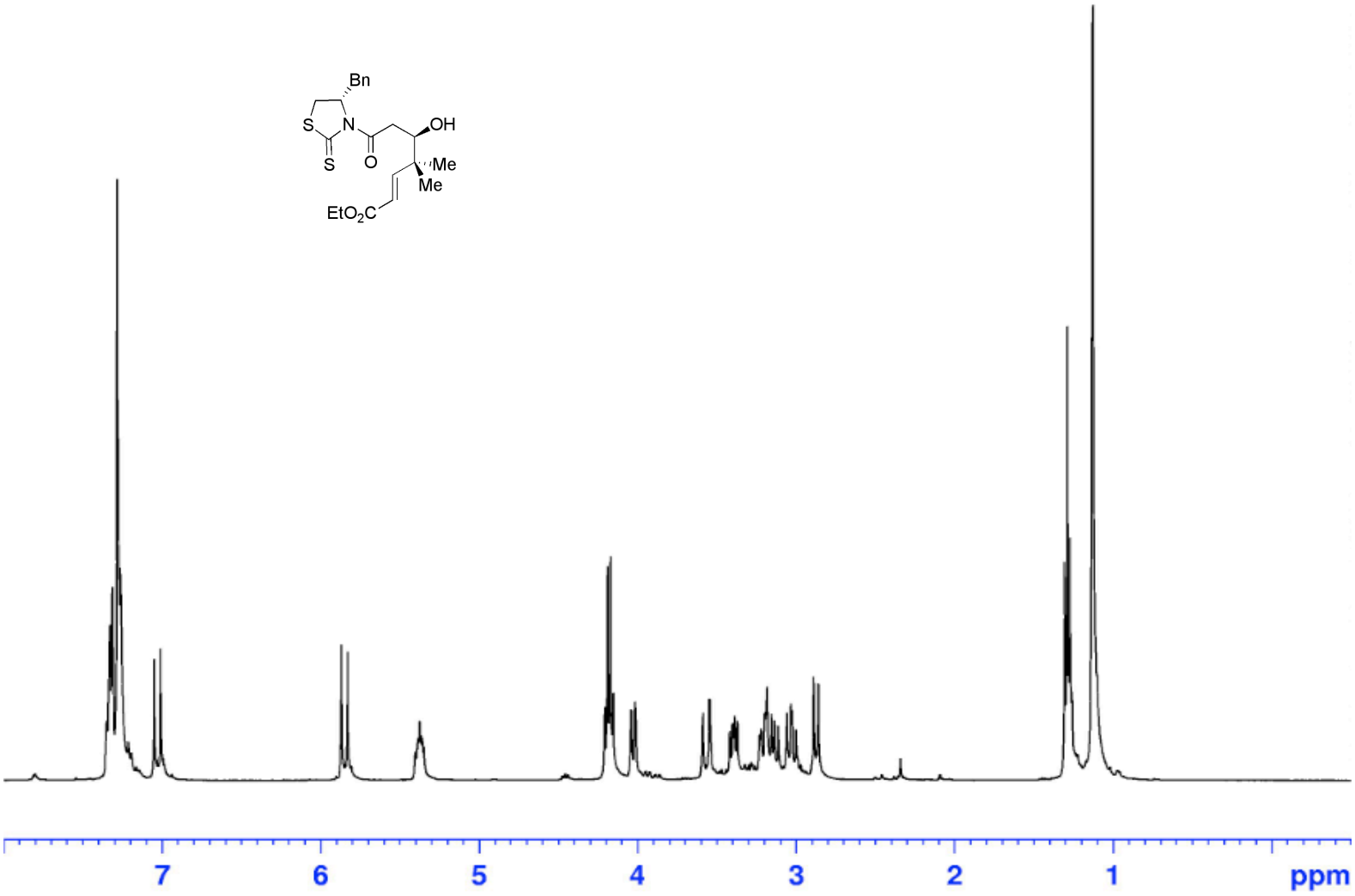
^{13}C Spectrum: Enoate **260**, 100 MHz ($CDCl_3$)



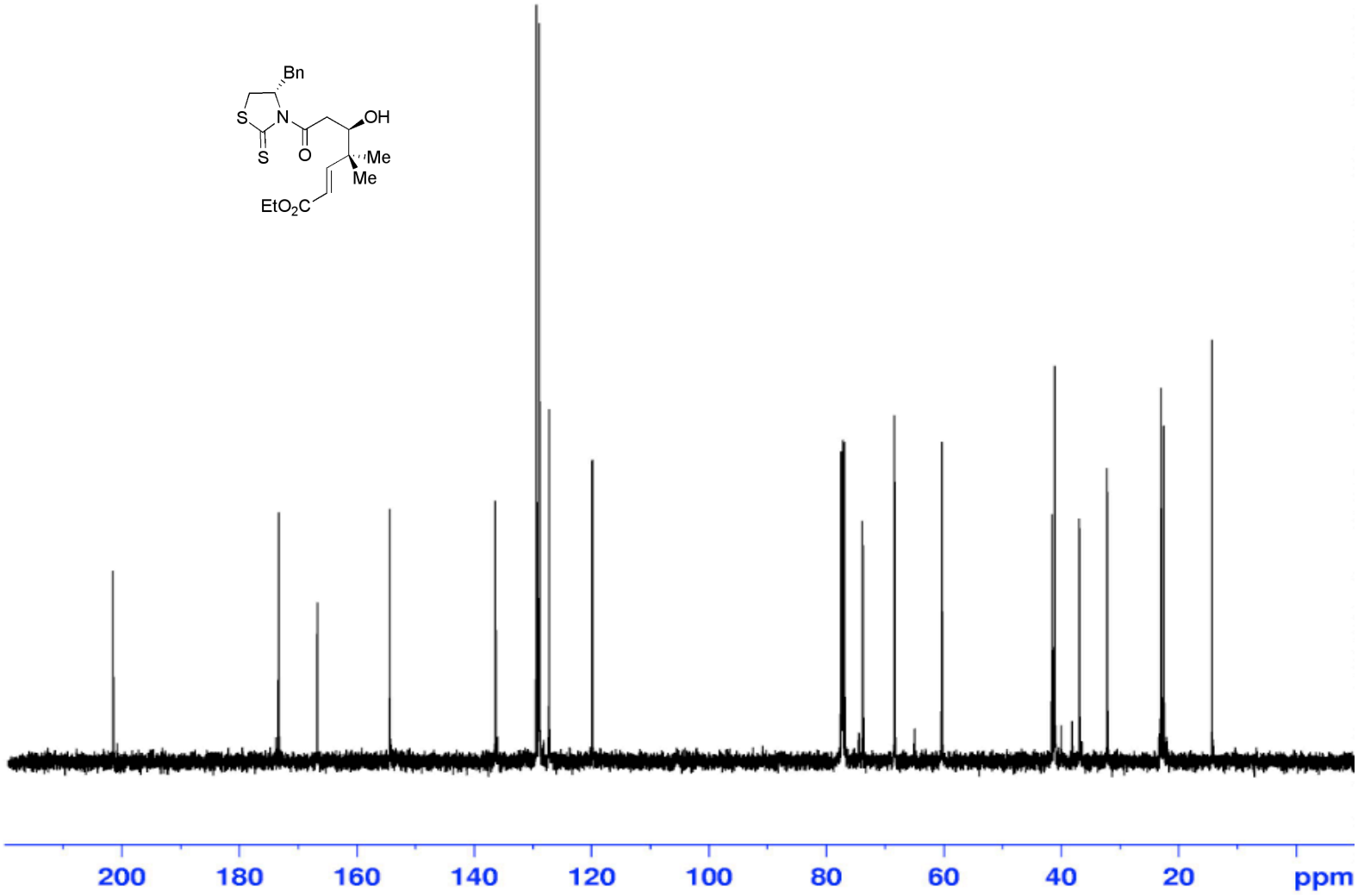
^{1}H NMR Spectrum: Alcohol, 400 MHz ($CDCl_3$)



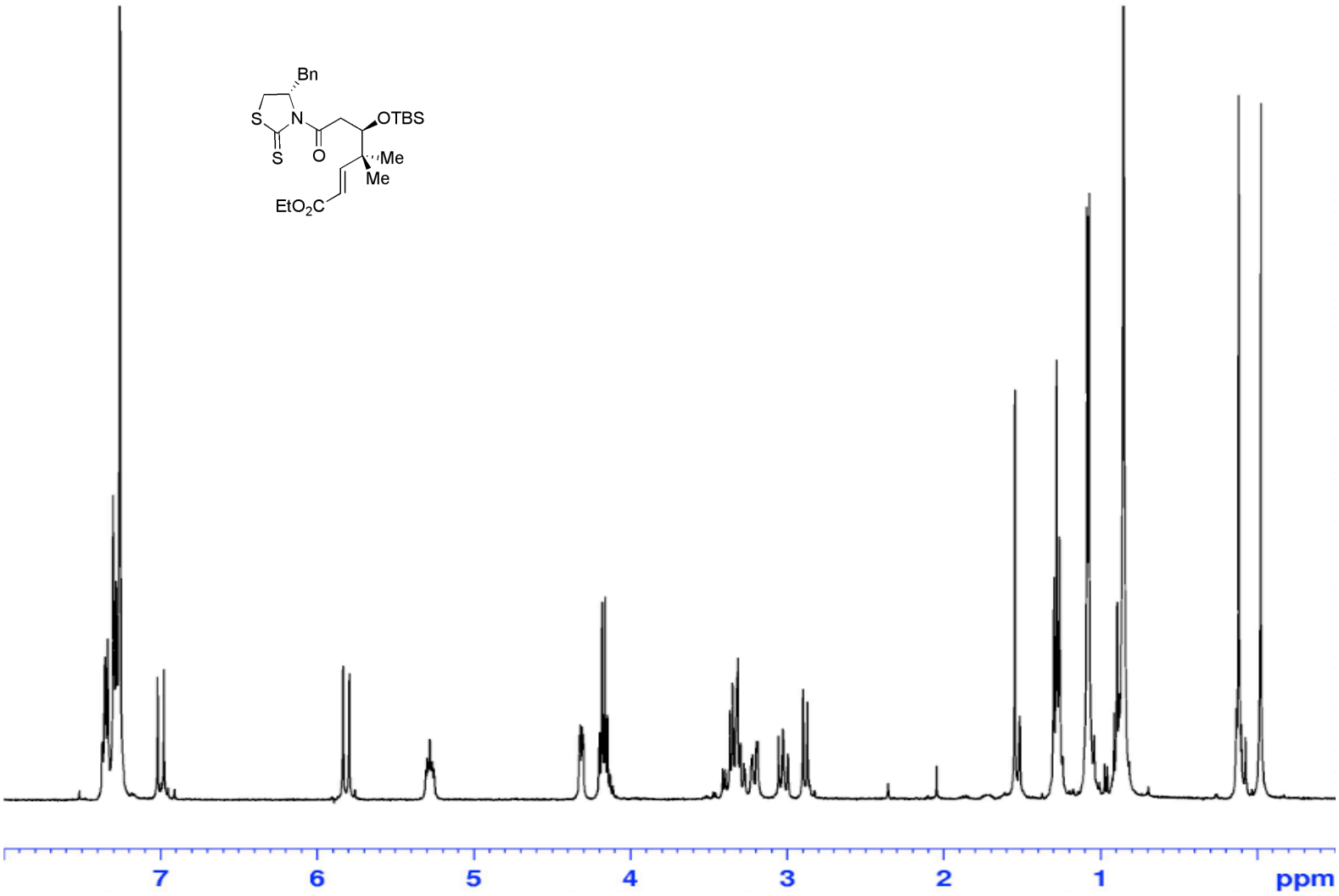
^{13}C NMR Spectrum: Alcohol, 100 MHz ($CDCl_3$)



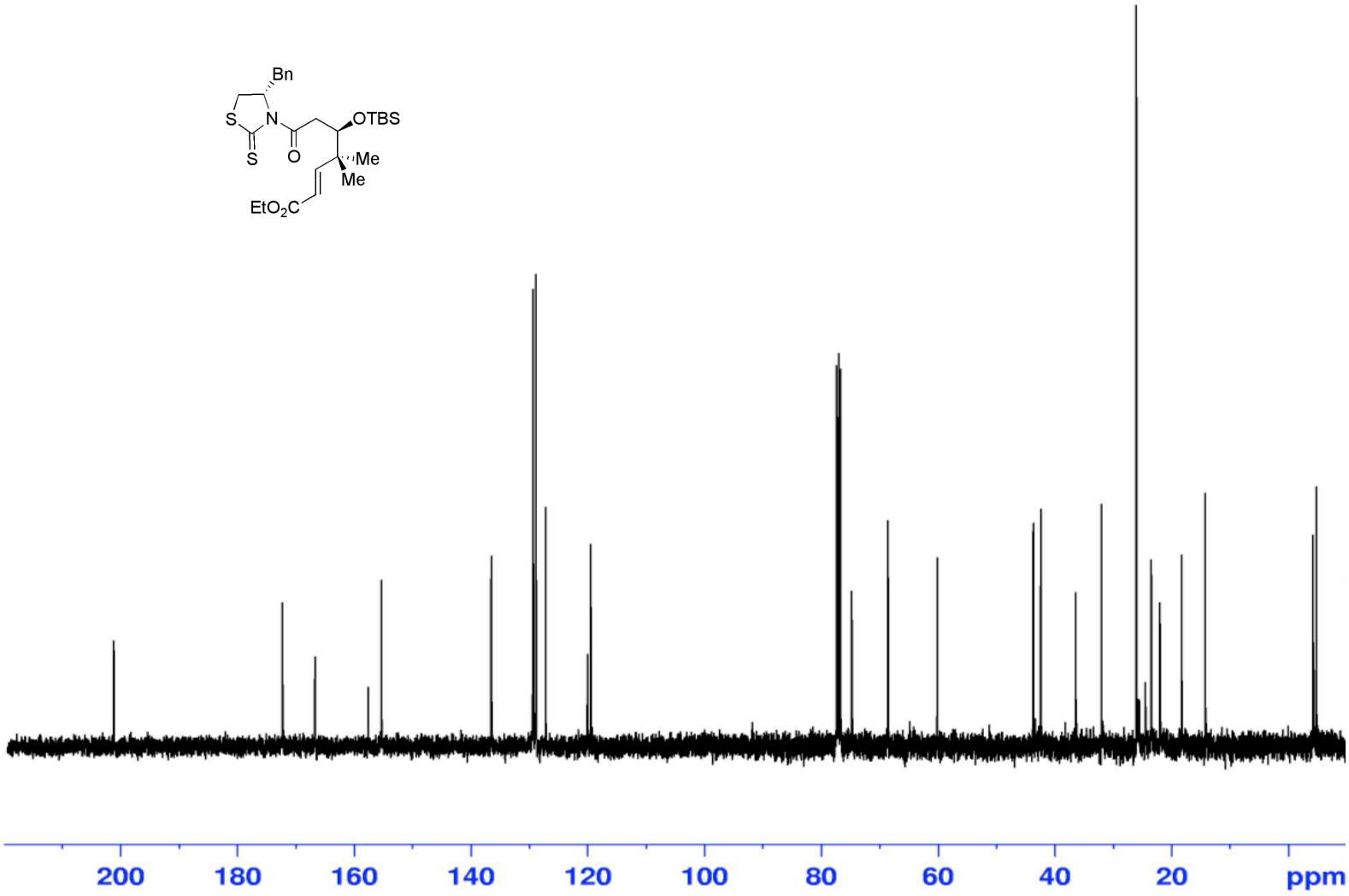
^{1}H NMR Spectrum: Alcohol **261**, 400 MHz ($CDCl_3$)



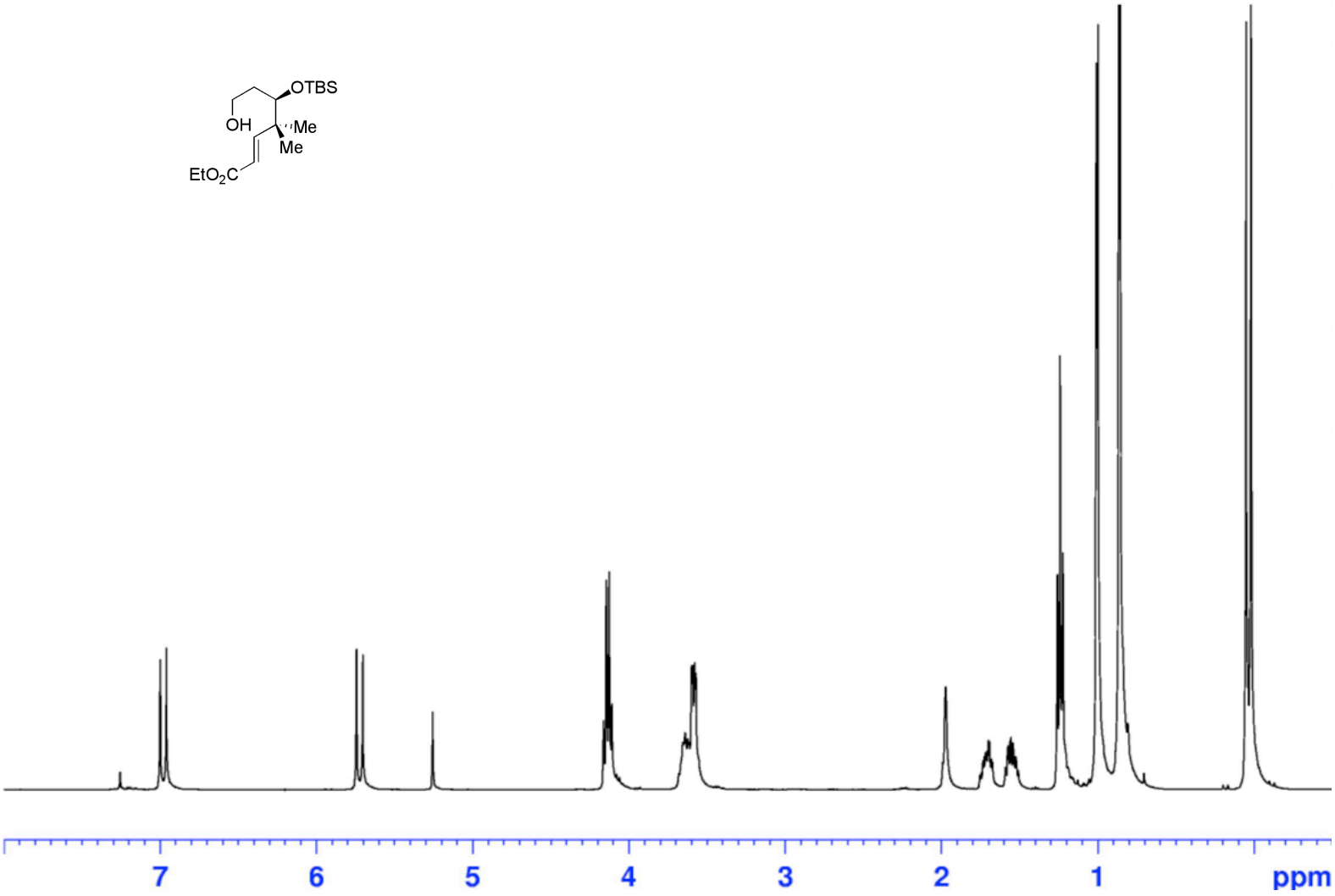
^{13}C NMR Spectrum: Alcohol **261**, 100 MHz ($CDCl_3$)



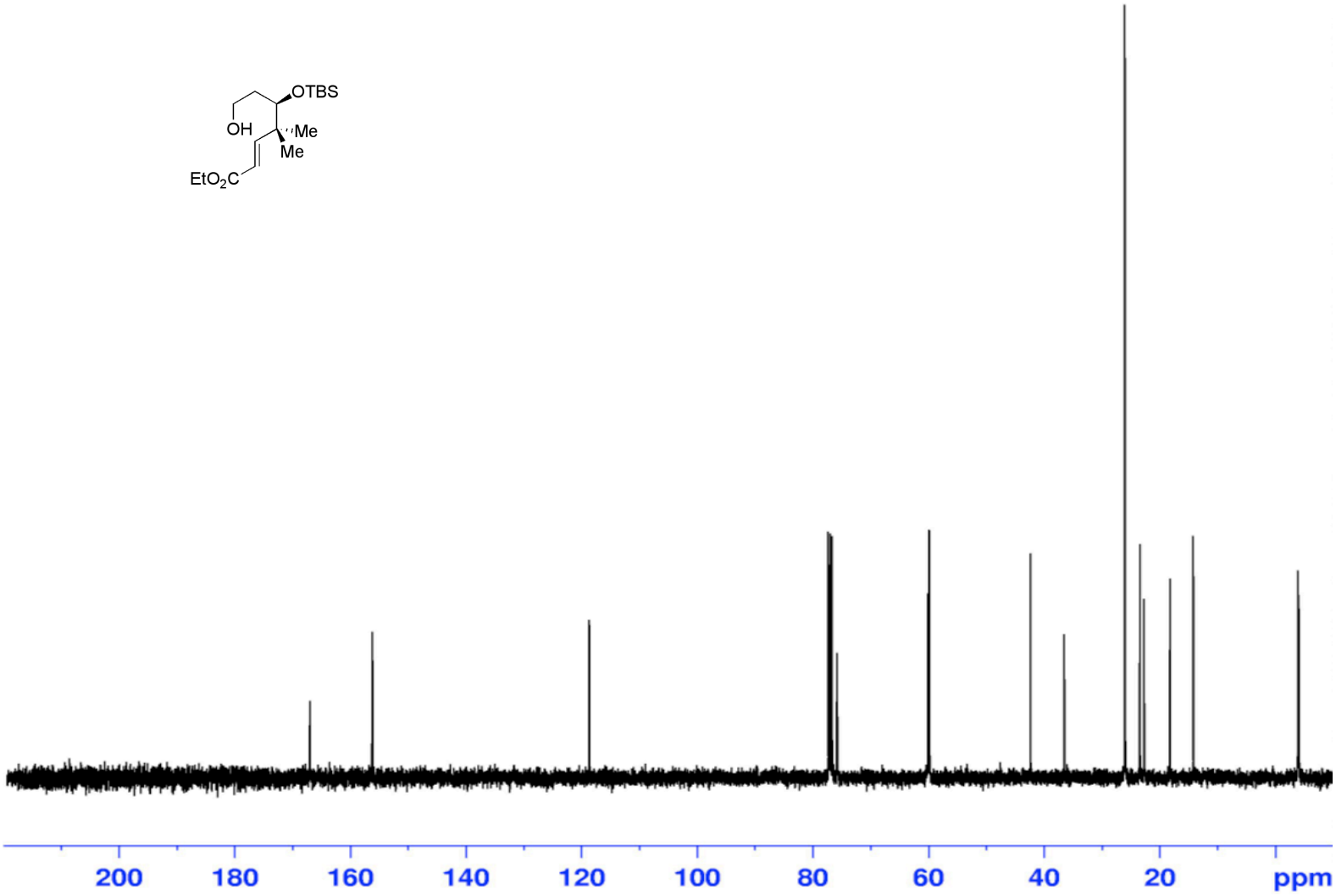
^{1}H NMR Spectrum: TBS Ether, 400 MHz ($CDCl_3$)



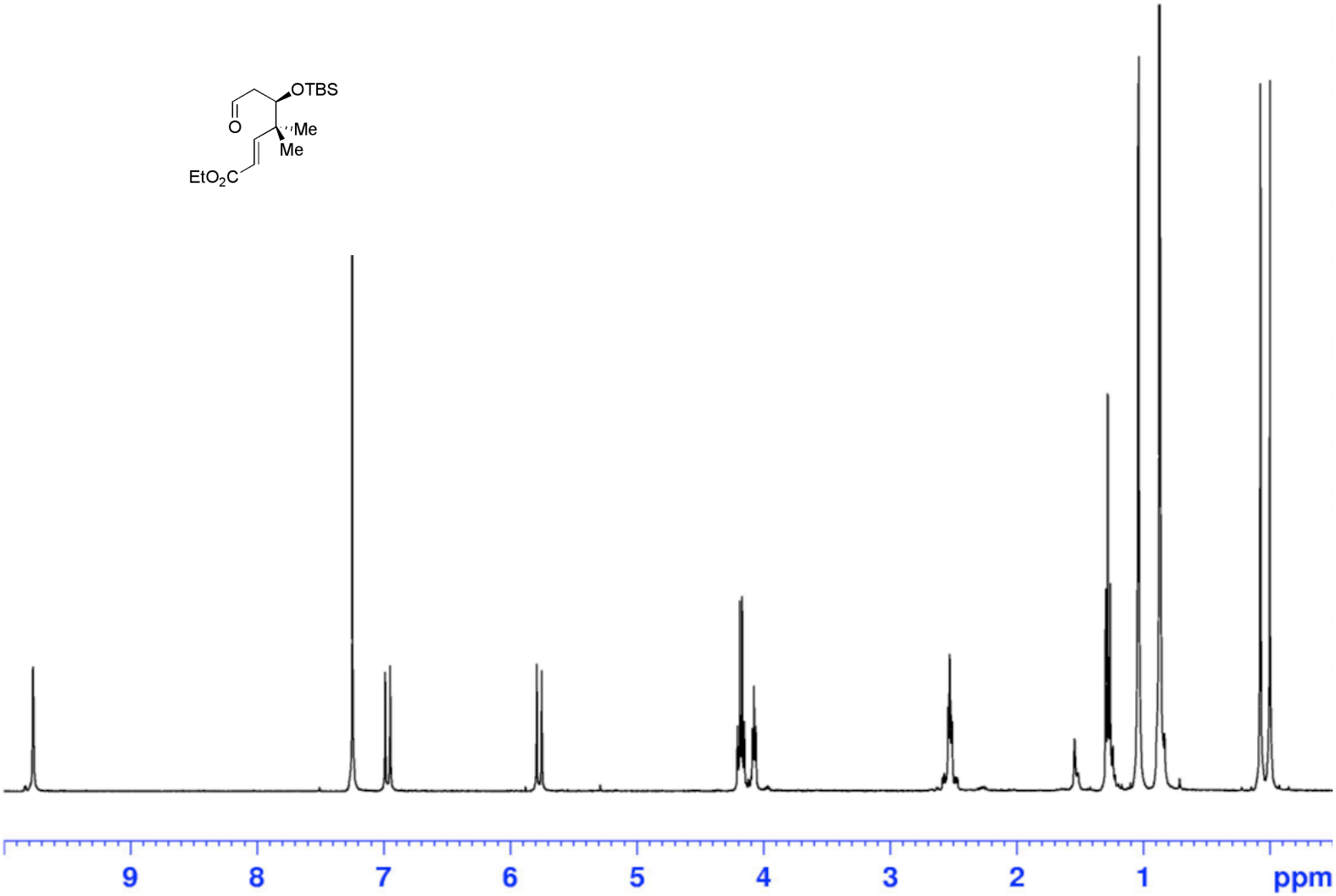
^{13}C NMR Spectrum: TBS Ether, 100 MHz ($CDCl_3$)



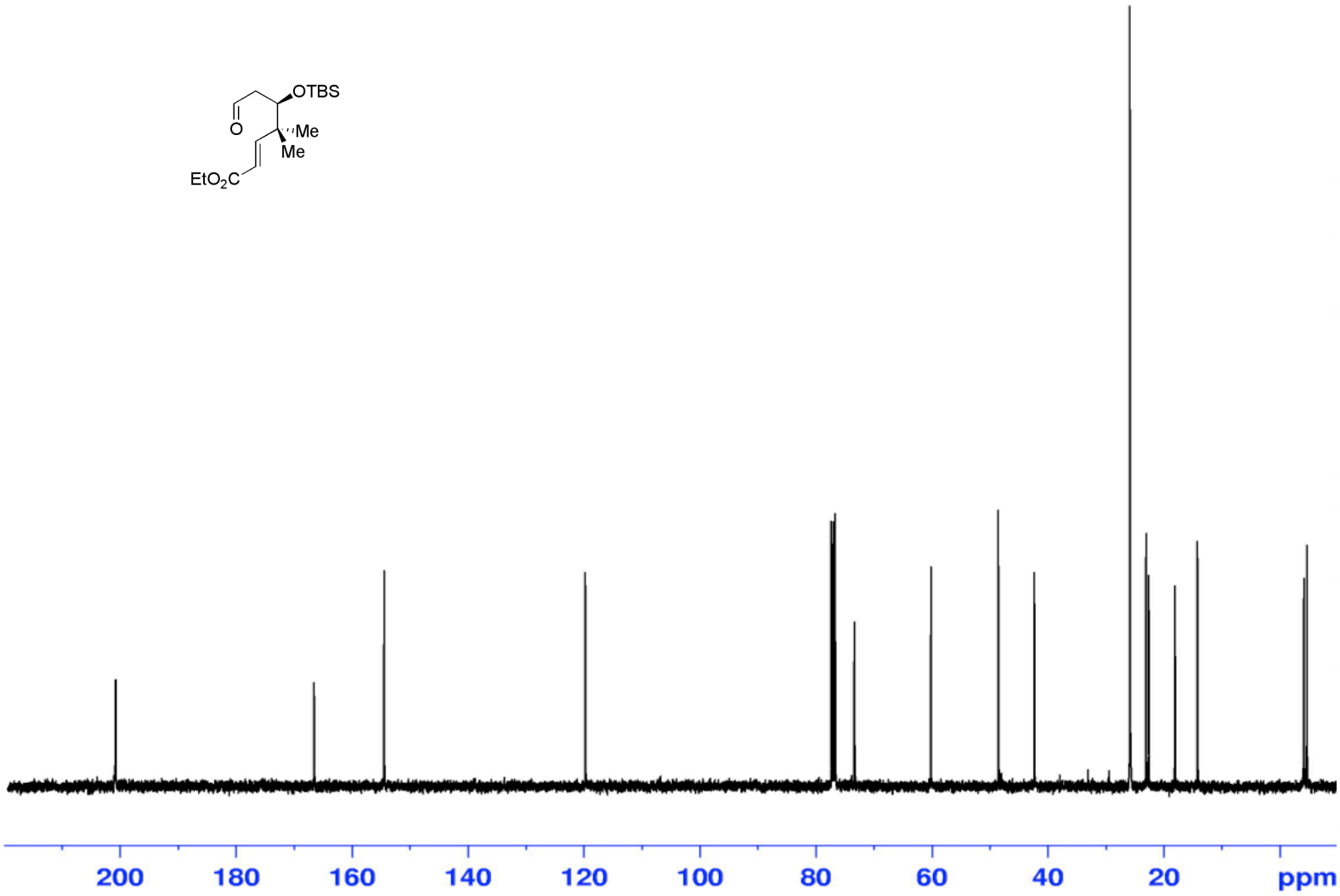
^{1}H NMR Spectrum: Alcohol, 400 MHz ($CDCl_3$)



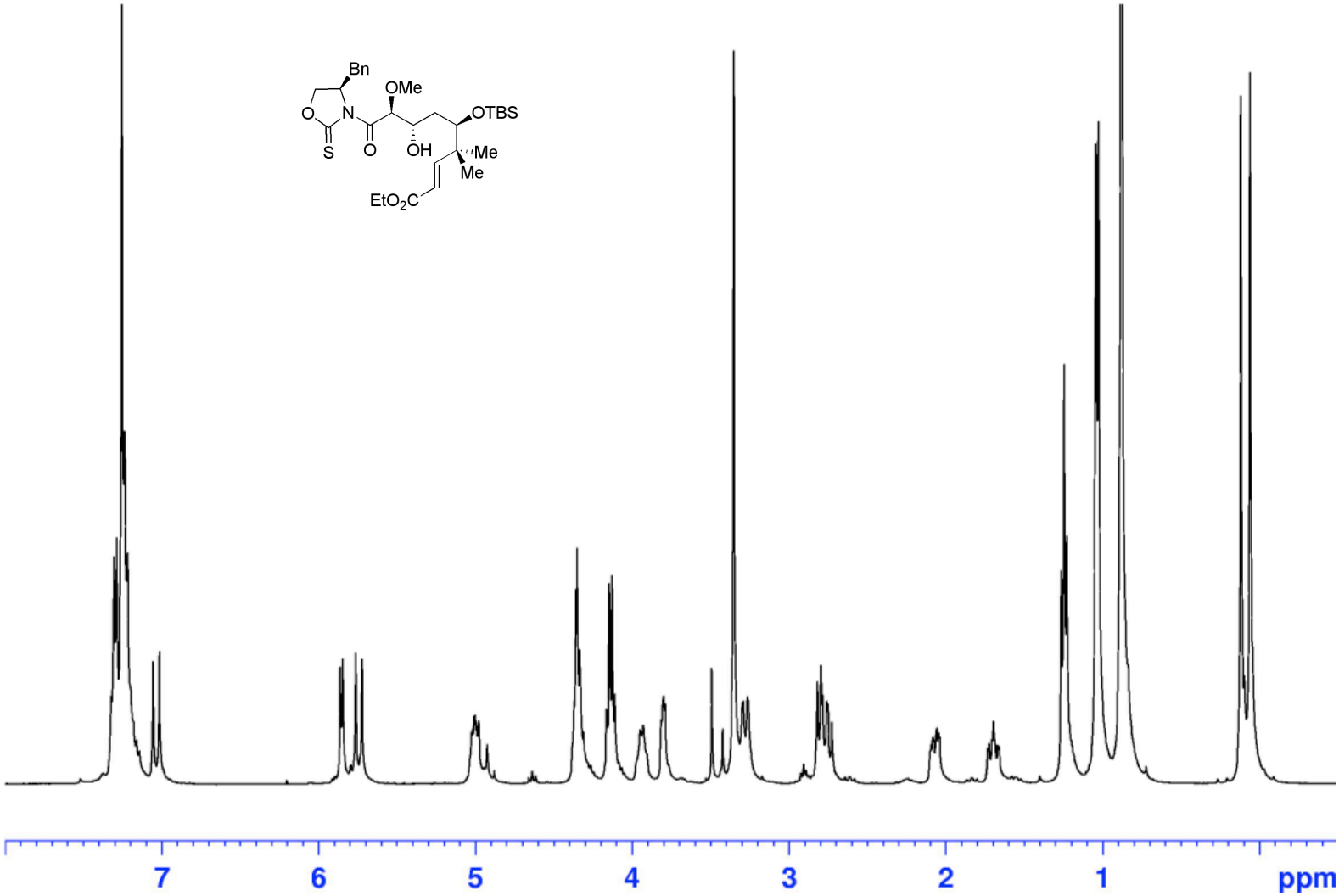
^{13}C NMR Spectrum: Alcohol, 100 MHz ($CDCl_3$)



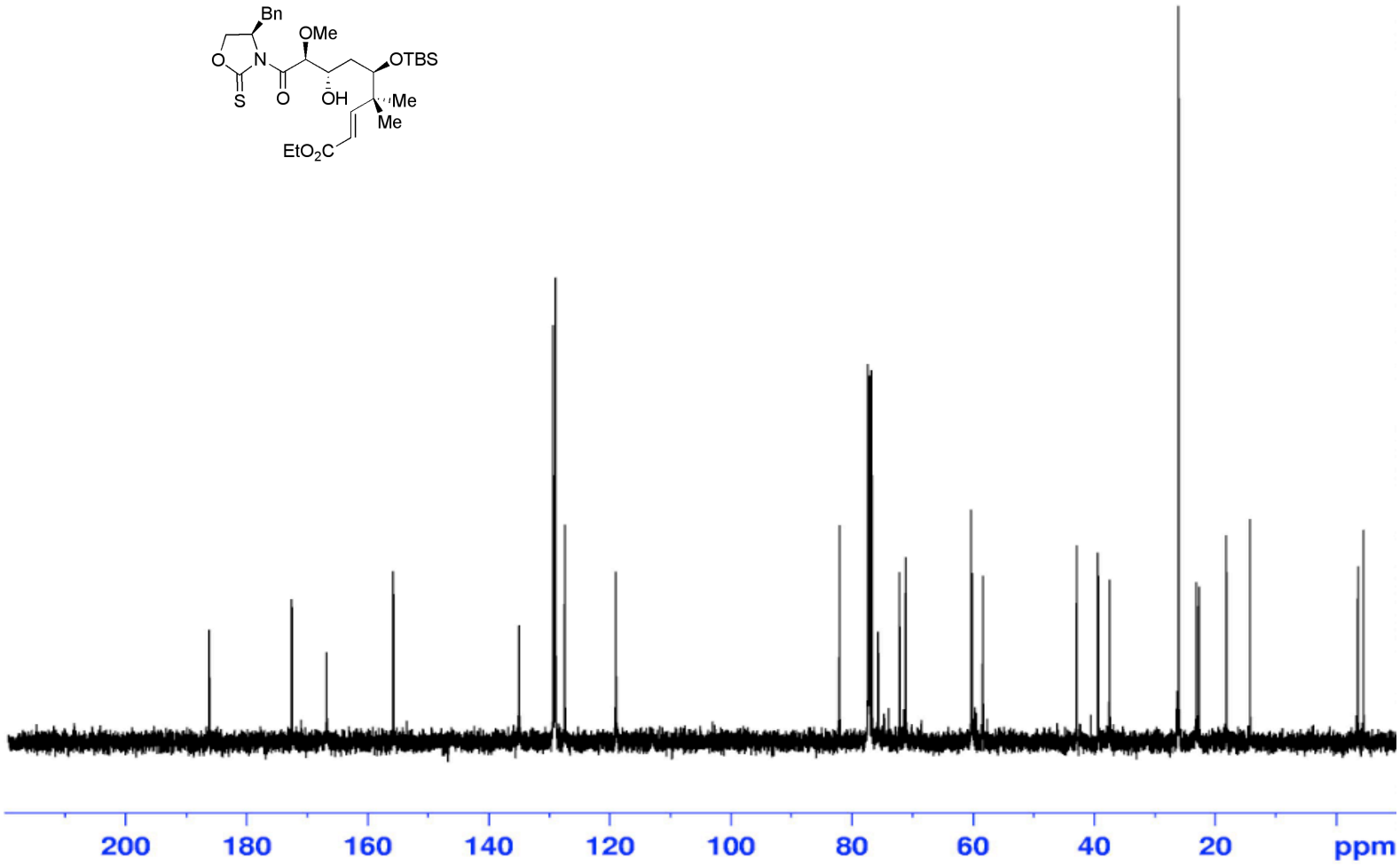
^{1}H NMR Spectrum: Aldehyde, 400 MHz ($CDCl_3$)



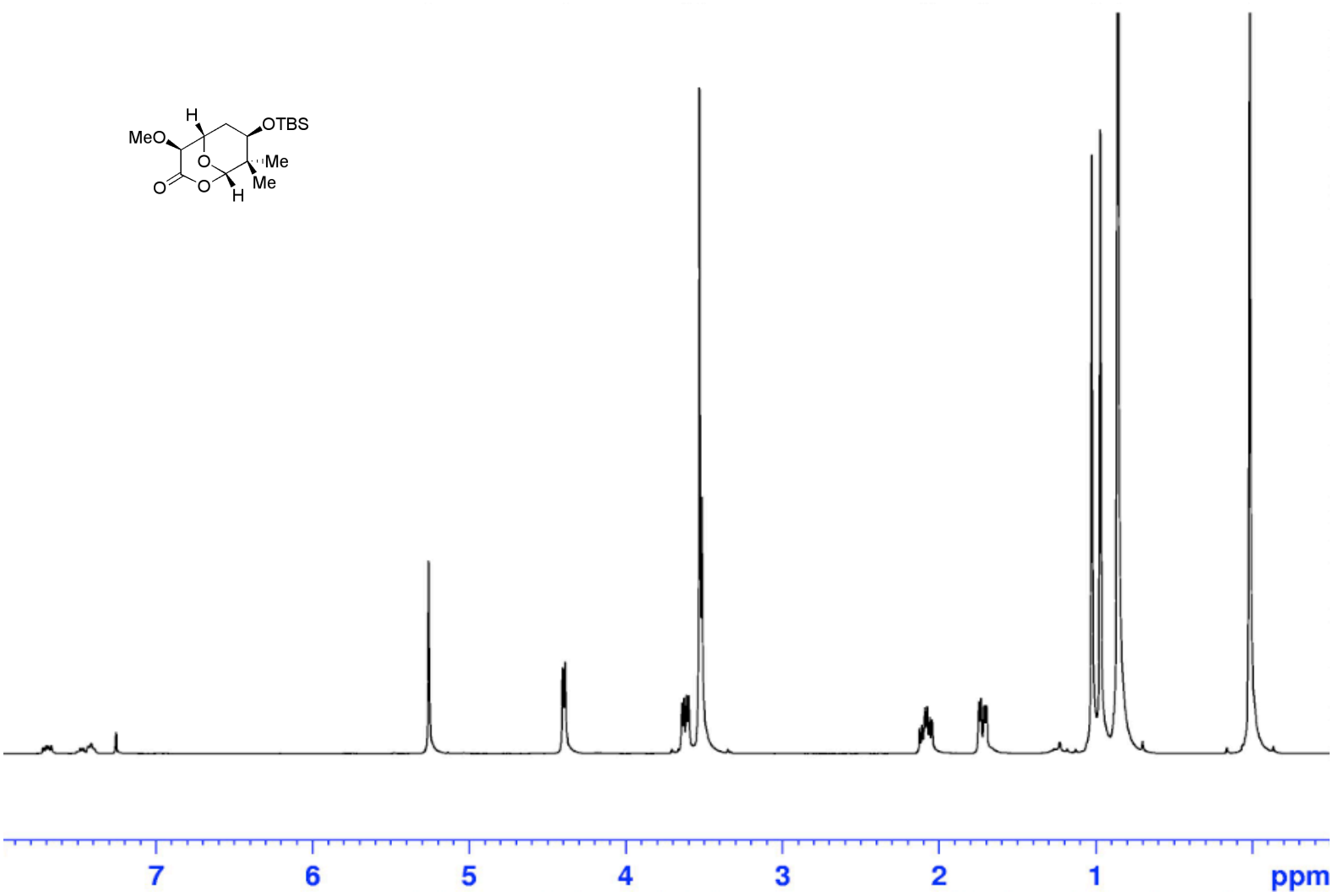
^{13}C NMR Spectrum: Aldehyde, 100 MHz ($CDCl_3$)



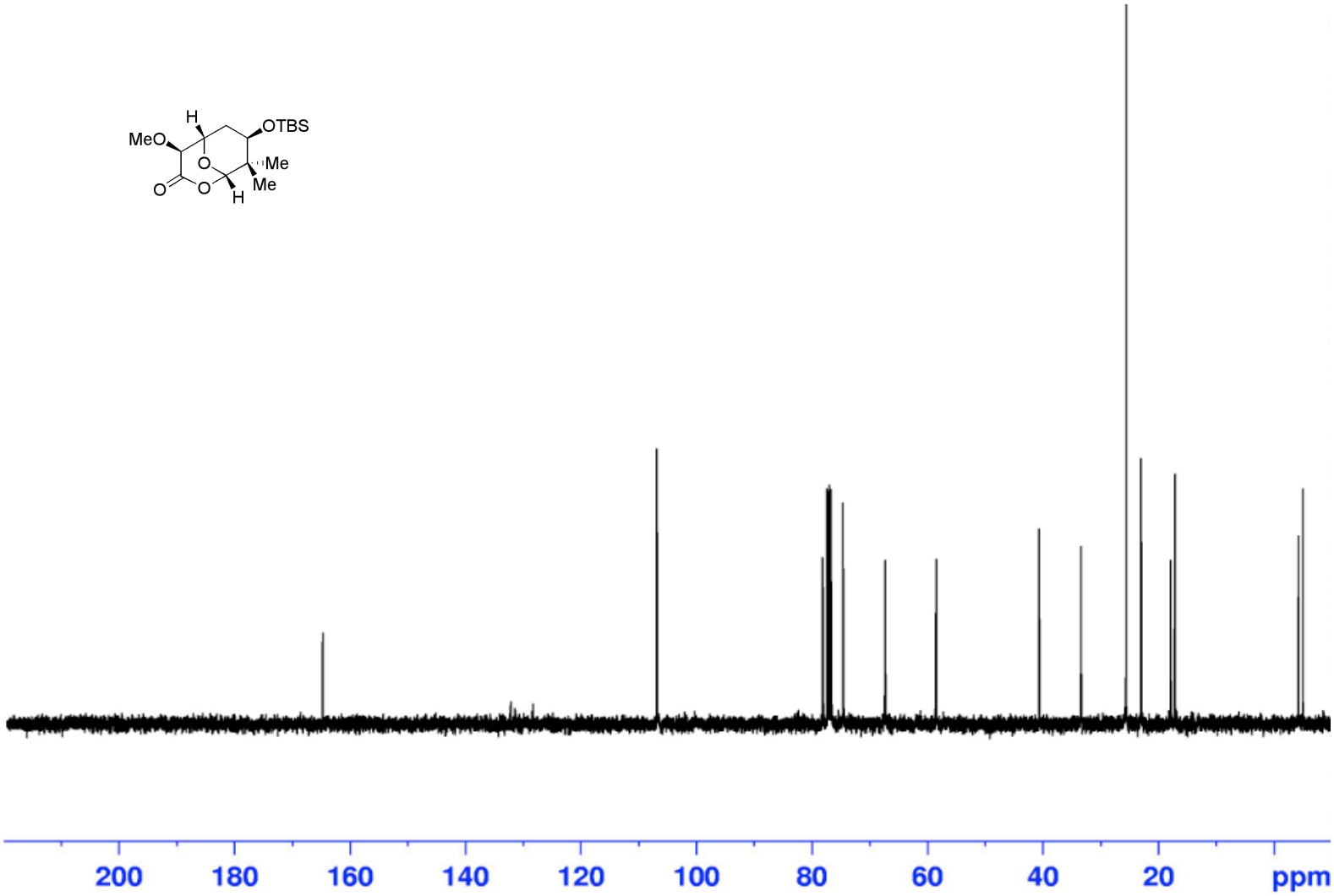
^{1}H NMR Spectrum: Alcohol **263**, 400 MHz ($CDCl_3$)



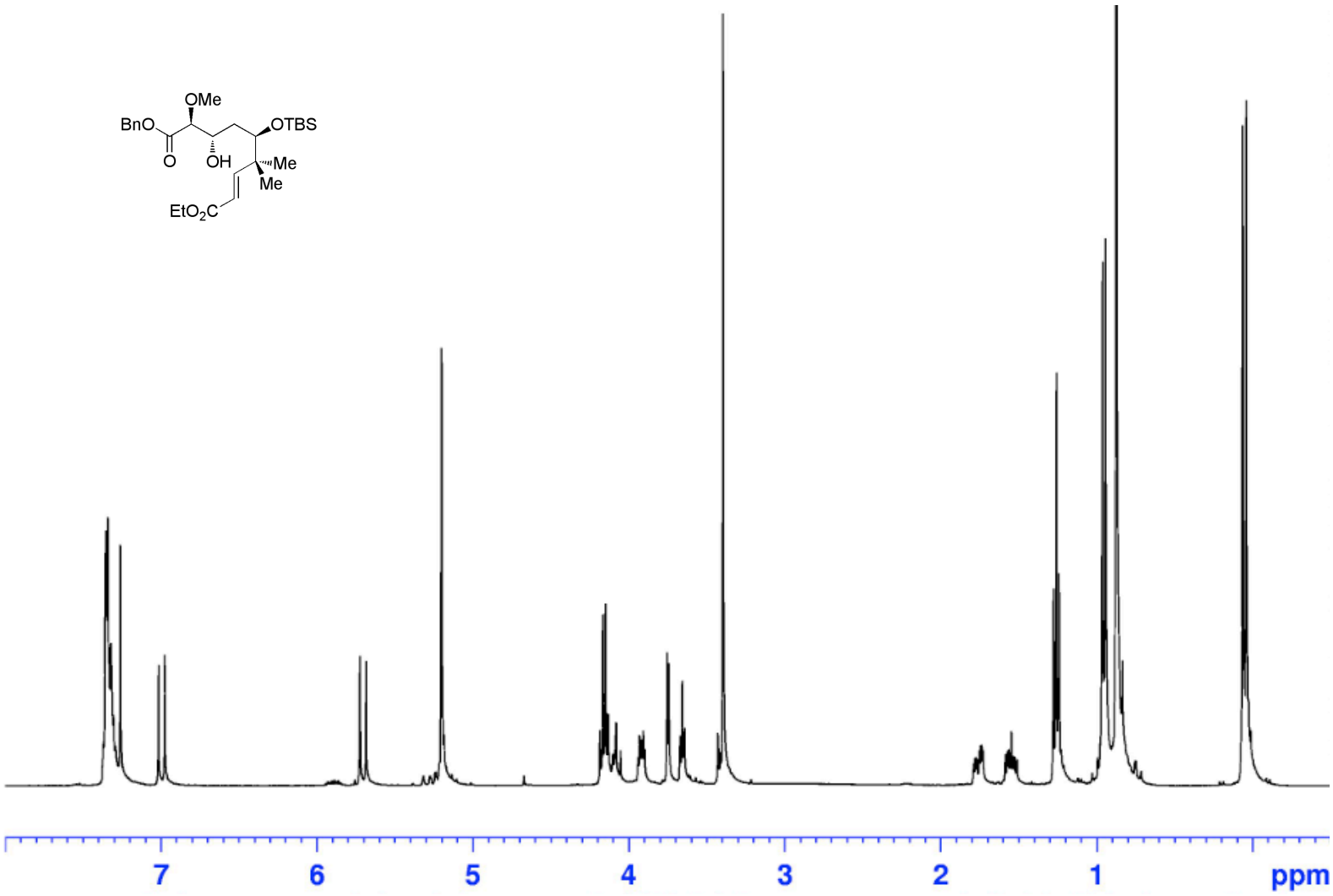
^{13}C NMR Spectrum: Alcohol **263**, 100 MHz ($CDCl_3$)



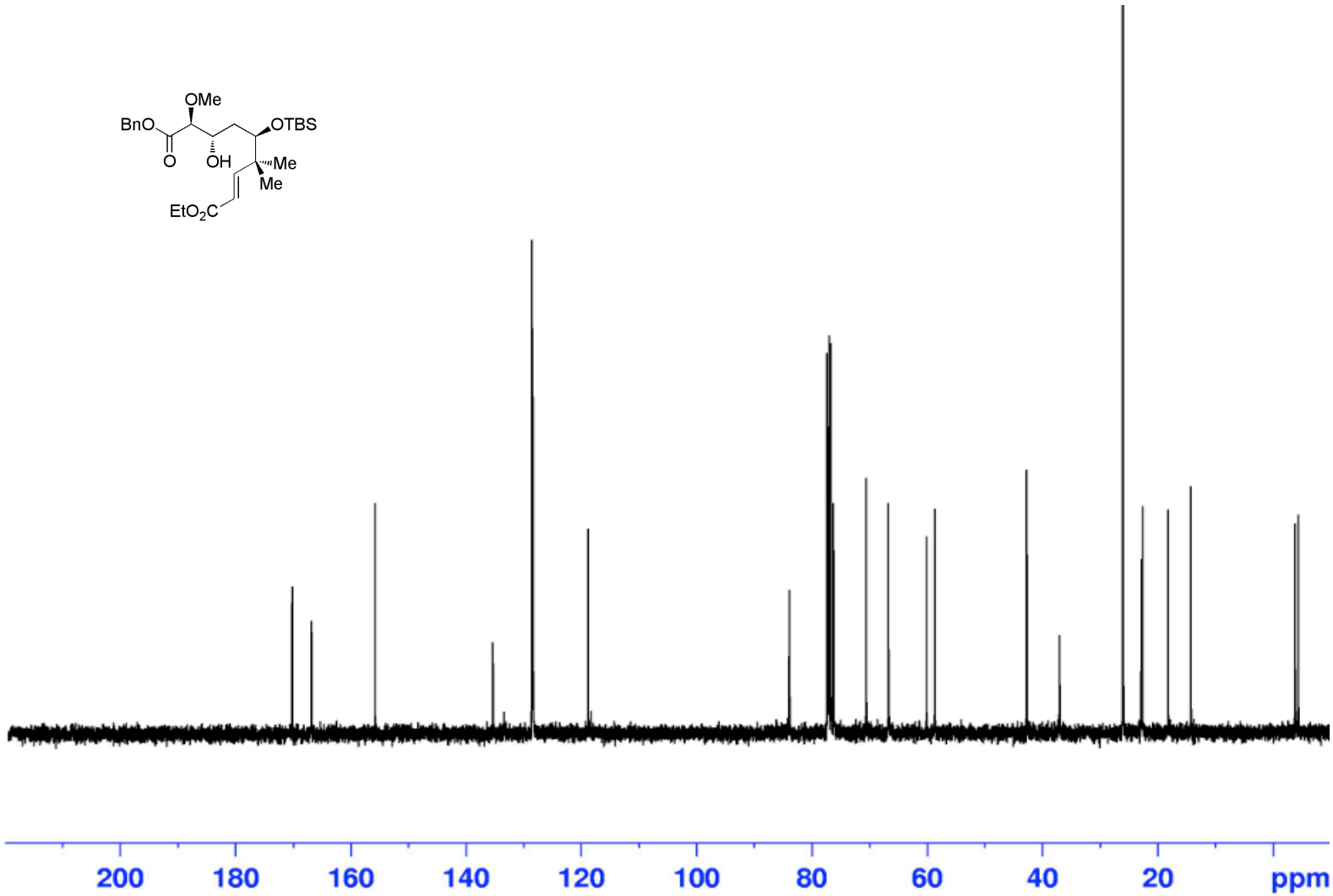
^{1}H Spectrum: Dioxanone **248**, 400 MHz ($CDCl_3$)



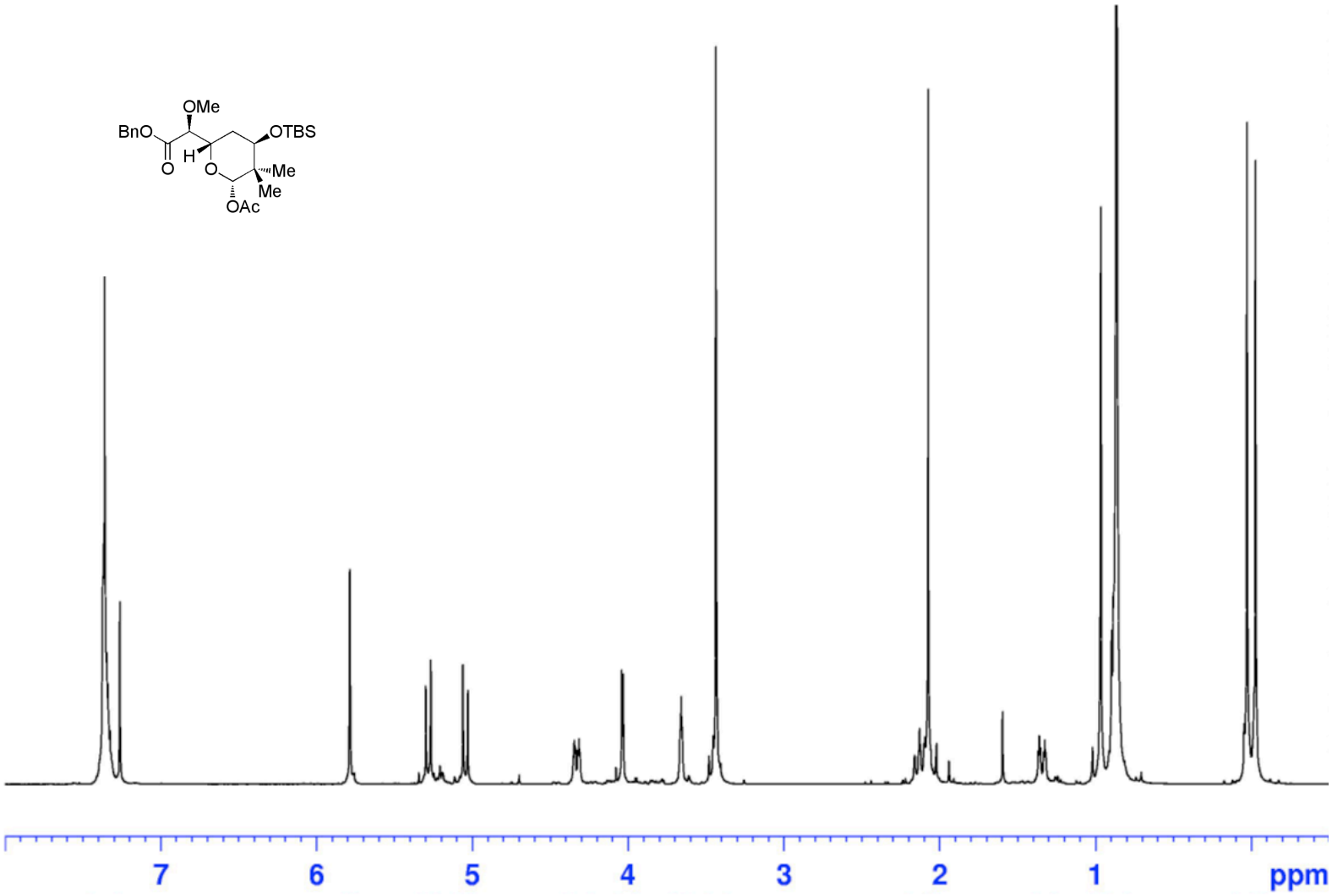
^{13}C Spectrum: Dioxanone **248**, 100 MHz ($CDCl_3$)



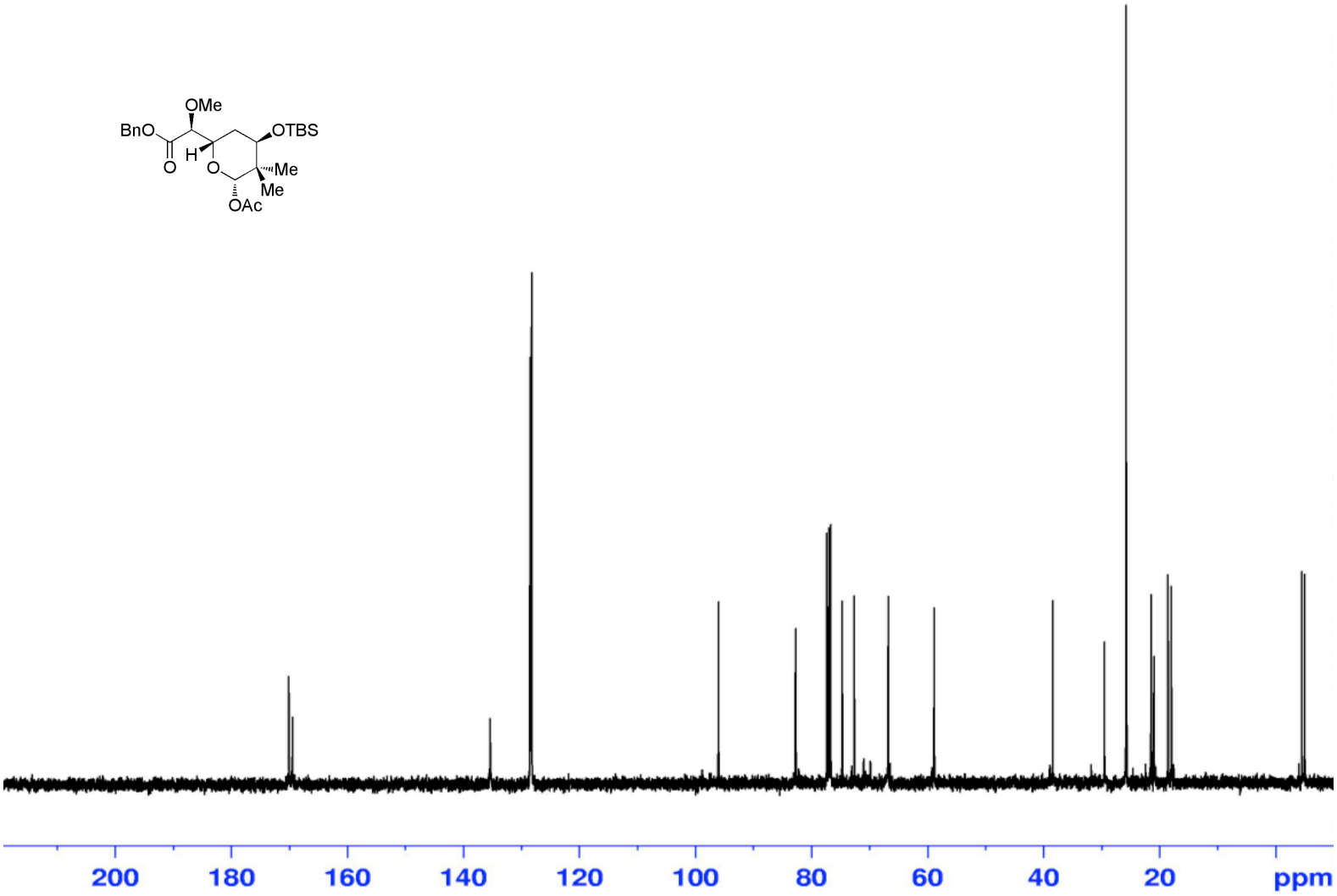
^{1}H Spectrum: Benzyl Ester **278**, 400 MHz ($CDCl_3$)



^{13}C Spectrum: Benzyl Ester **278**, 100 MHz ($CDCl_3$)



^{1}H Spectrum: Acetate **275**, 400 MHz ($CDCl_3$)



^{13}C Spectrum: Acetate **275**, 100 MHz ($CDCl_3$)