LARGE SCALE TOTAL SYNTHESIS OF APOPTOLIDINONE AND PROGRESS TOWARDS THE TOTAL SYNTHESIS OF AMMOCIDIN

A Dissertation

by

QINGSONG LIU

Submitted to the Office of Graduate Studies of
Texas A&M University
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

December 2006

Major Subject: Chemistry

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Approved by:

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Committee Members, Daniel Romo
Daniel A. Singleton
Heather H. Wilkinson
Head of Department, Emile Schweikert

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ABSTRACT

Large Scale Total Synthesis of Apoptolidinone and Progress Towards the Total Synthesis of Ammocidin.

(December 2006)

Qingsong Liu, B.S., Nankai University, P. R. China

Chair of Advisory Committee: Dr. Gary Sulikowski

Apoptolidin **1.1** was isolated in 1997 by Hayakawa and co-workers from a soil bacterium *Nocardiopsis* sp. during screening for specific apoptosis inducers. The primary biological test revealed that this polyketide macrolide induced apoptosis in cells transformed with the adenovirus type E1A oncognene, but not normal cells. This dissertation describes the latest studies in understanding of apoptolidin's biological activity mechanism and previous contributions towards its total synthesis. Synthesizing apoptolidinone **1.26** by an intra-molecular Horner-Wadsworth-Emmons approach featuring a Suzuki coupling, cross metathesis and two diastereoselective aldol reactions is discussed. 15 mg apoptolidinone is prepared via our previously developed intramolecular Suzuking coupling approach.

Ammocidin **3.1**, which was found to induce apoptosis in Ba/F3-v12 cells in an IL-3 free medium, is a specific apoptosis inducer discovered by Hayakawa and co-workers in 2001 from *Saccharothrix* sp. AJ9571. A strategy featuring Suzuki coupling, cross metathesis, Yamaguchi macrolactonization and three asymmetric aldol reactions was applied to the total synthesis of ammocidinone **3.6**, the aglycone of ammocidin. The preparation of the key building blocks was discussed in the following chapter: aldehyde **3.8** (C14-C19) was synthesized via Sharpless asymmetric epoxidation; ethyl ketone **3.9'**

(C20-C28) was prepared via Kobayashi and Crimmins's asymmetric aldol methodologies; aldehyde **3.14** (C7-C13) was generated by Brown crotylation and cross metathesis.

To my parents and my country

ACKNOWLEDGEMENTS

First of all, I would like to thank my research advisor, Professor Gary A. Sulikowski, for his guidance, patience and help during my four and half years of graduate school. Professor Sulikowski provided a world-class education that allowed me to learn from my failures, take pride in my successes, and finally become an enthusiastic chemist. I am also indebted to my committee members, Dr. Daniel Romo, Dr. Daniel Singleton, Dr. Heather H. Wilkinson, for their advice and assistance.

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More than anybody, my heartfelt appreciation goes to my girlfriend Jing Liu for enduring many hardships with me in the trenches, and for her understanding, especially during the two-year period after I moved to Vanderbilt University from Texas A&M University. A special thanks goes to my friends, Yao Zhang and Mingfeng Bai, who have provided a warm family atmosphere and made me feel right at home in Nashville.

I must thank my Mom and Dad, not only for their ceaseless love and sacrifices, but also for leading me to the natural sciences. Finally, great thanks goes to my motherland, People's Republic of China, who provided me a great fundamental education and the opportunity to study abroad cutting-edge modern-day science. For these reasons, this dissertation is dedicated to my parents and my country.

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CHAPTER I

INTRODUCTION TO APOPTOLIDIN: ISOLATION, BIOLOGICAL ACTIVITY AND PREVIOUS SYNTHESES

1.1 Apoptolidin: isolation and structure elucidation

Apoptosis, originated from Greek words *apo* and *ptosis*, meaning *from* and *fallings* respectively, was first introduced in the early 1970's to describe programmed cell death.[1] In contrast to necrosis, which is usually caused by injury, apoptosis is one of the most common regulated processes of cell death and essential to multi-cellular tissue's development and health. The main function of apoptosis is to dispose of unwanted cells including damaged and old cells without causing damage or effect of neighboring cells. Quite a few factors like DNA damage and oxidative stress can stimulate the apoptosis process by sending signals to the cell via special enzymes known as caspases through very complicated mechanisms that are still unclear. Apoptosis is an essential counterbalance to cellular proliferation. Defects in apoptosis can result in cancer, autoimmune diseases and spreading of viral infections. It has been shown that neurodegenerative disorders, AIDS and ischaemic diseases are caused or enhanced by apoptosis failure.[2] Therefore, a more detailed study of the mechanism of apoptosis could lead to significant advance in the clinical treatment of disease including cancer. a Selective apoptosis inducers can lead only certain types of tumor cells to apoptosis without affecting any other healthy ones and have attracted extensive attention in drug discovery in the past decade. In 1997, as a result of continuing efforts to discover

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This dissertation follows the style of *Journal of Organic Chemistry*.

cytotoxic agent: apoptolidin **1.1** from a culture of soil bacterial *Nocardiopsis* sp (Figure 1.1).[3]

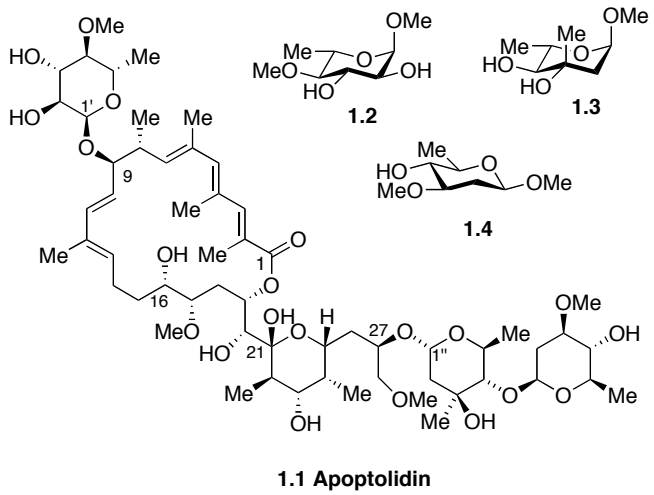


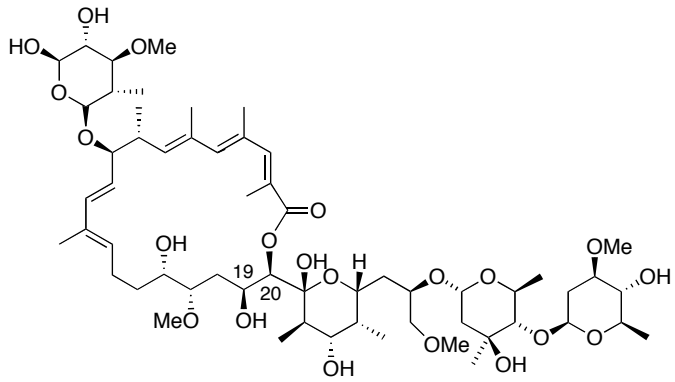
Figure 1.1 Structure of apoptolidin **1.1** and deoxy sugars **1.2**-**1.4**

The structure of apoptolidin was assigned based on the extensive NMR analysis and chemical degradation studies by Hayakawa in 1998.[4] A 218 mg sample of apoptolidin was isolated from fermentation culture broth of *Nocardiopsis* sp as a white powder. High resolution FABMS revealed that the molecular formula was $C_{58}H_{96}O_{21}$. Methanolysis of apoptolidin under acidic condition (1% HCl-MeOH, 50 °C, 30 min) led to the identification of three sugar units: 6-deoxy-4-*O*-methyl-L-glucose **1.2**, a disaccharide containing L-olivomycose **1.3** and D-oleandrose **1.4** attached at C(9) and C(27) respectively by comparing their derived methyl acetals to authentic samples. The aglycone structure was determined to consist of a 20-membered macrolactone and a fully substituted pyranose ring. The relative stereochemistry assignment of the aglycone was based on extensive two-dimensional NMR analysis. The aglycone absolute

stereochemistry at C(9) and C(27) were assigned through observed NOE enhancement between 1'-H and 9-H, C1''-H and C27-H.

1.2 Isolation of iso-apoptolidin and apotolidin B&C

In 2002 the Sulikowski and Wender groups independently identified a second major fermentation product in the apoptolidin culture broth, which was assigned the structure isoapoptolidin **1.5** (Figure 1.2).[5] Initially our group considered the possibility that isoapoptolidin was the C21 epimer of apoptolidin. However, following extensive two-dimensional NMR analysis we concluded that isoapoptolidin was actually a C(19) to C(20) acyl migration product. Both Wender's and Sulikowski's study showed that there existed an equilibrium between apoptolidin and isoapoptolidin. Our study showed that treatment of apoptolidin with methanolic triethylamine led to a 1.4:1 mixture of isomers.



1.5 isoapoptolidin

Figure 1.2 Structure of isoapoptolidin **1.5**

Wender demonstrated that in a cell environment apoptolidin and isoapoptolidin likey existe as an equilibrium mixture. In 2005, Wender's group reported the isolation of two new apoptolidin congeners, which they designated apoptolidin B and C (Figure 1.3).[6]

These newly discovered compounds were produced in amounts of 2-5 mg per liter of culture. High-resolution mass spectrometric analysis indicated the molecular formulas of apoptolidin $C_{58}H_{96}O_{20}$ and $C_{58}H_{96}O_{19}$ for apoptolidin B and C, respectively. The structure of these two compounds was established by two-dimensional NMR studies (COSY, TOCSY, HMQC, HMBC, ROSEY). Apoptolidin B proved to be a C(16), C(20) dideoxy derivative of apoptolidin and apoptolidin C a C(20) deoxy derivative. A study of the base liability of apotolidin B showed that it established an equilibrium (6:4 mixture) similar to apoptolidin (Dulbecco's phosphate-buffered saline pH 7.4) despite requiring two times longer to reach equilibrium relative to apoptolidin. Apoptolidin C, under the same conditions isomerized to a completely new compound, which has not been fully characterized.

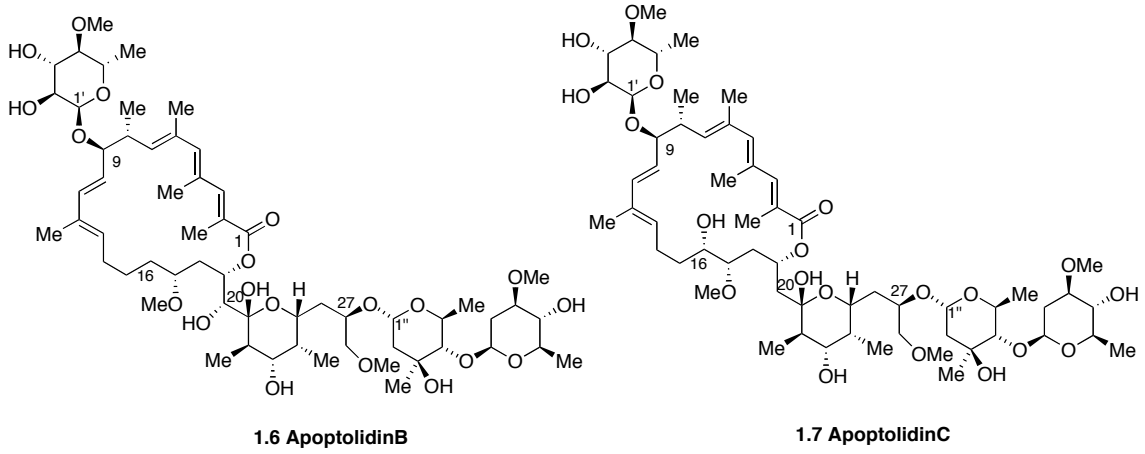


Figure 1.3 Structure of apoptolidin B (**1.6**) and C (**1.7**)

1.3 Biological activity study of apoptolidin and derivatives

1.3.1 Hayakawa's primary biological study of apoptolidin

As indicated by its name, apoptolidin is an apoptosis inducer. The primary biological assay conducted by Hayakawa showed that apoptolidin induced apoptotic cell

death in E1A and E1A/E1B19K transformed rat glial cells while not proving cytotoxic to normal cells including glial cells or H-ras- and v-src-transformed cells (Table 1.1).[3]

Table 1.1 Cytotoxicity of apoptolidin against normal and transformed cells[3]

Cell line	Oncogene	IC_{50} (ng/mL)
Glia		>100,000
RG-E1A-7	E1A	11
RG-E1A19K-2	E1A, E1B19K	10
RG-E1A54K-9	E1A, E1B54K	13
RG-E1-4	E1A, E1B19K, E1B54K	10
3Y1		>100,000
Ad12-3Y1	E1A, E1B19K, E1B54K	17
HR-3Y1	H-*ras*	>100,000
SR-3Y1	v-*src*	>100,000
SV-3Y1	SV40 large T antigen	>100,000

1.3.2 Khosla's biological target directed study of apoptolidin

Drugs that can selectively induce cancer cells to undergo apoptosis could play an important role in the development of new cancer therapy protocols. After apoptolidin's selective apoptosis ability was discovered, it drew extensive attention from researchers. To understand the mechanism of apopotosis of apoptolidin, Khosla and co-workers at Stanford University conducted a series of molecular and cell-based pharmacological

assays and proposed that apoptolidin's selective apoptosis activity was associated with its inhibition of F_0F_1-ATPase.[7] Their experiments showed that cell death induced by apoptolidin was independent of p53 status, which means it either acts downstream or independent of p53. In addition, the inhibition of apoptosis by BCL-2 and a caspase-9 specific inhibitor suggested that a mitochondria-dependent pathway was involved during the cell death signaling.[7b] To identify the target of apoptolidin, a structure comparison study was launched and revealed that apoptolidin's aglycone structure, apoptolidinone, has significant similarity with oligomycin A (**1.8**) and bafilomycin (**1.9),** which are both known ATPase inhibitors (Figure 1.4).[7c] These results prompted evaluation of the inhibition of apoptolidin against F_0F_1-ATPase, which led to the conclusion that F_0F_1-ATPase was the molecular target of apoptolidin.

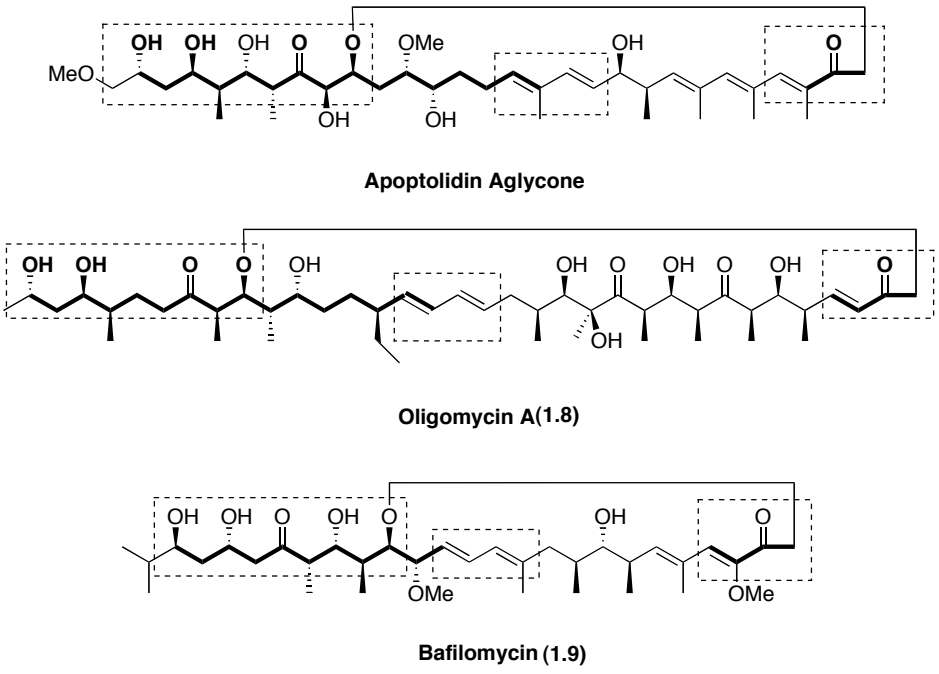
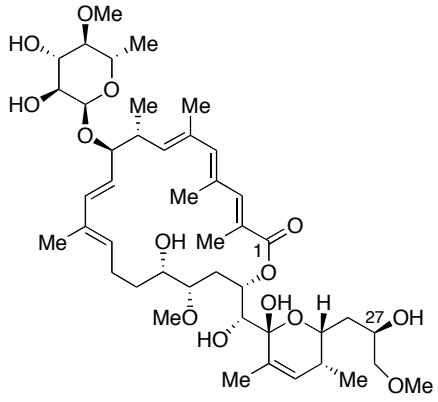


Figure 1.4 Structural similarity among apoptolidin, oligomycin and bafilomycin

Khosla proposed a metabolism-driven mechanism to explain the selective apoptosis induction of apoptolidin.[7a] According to his hypothesis, apoptolidin functions through inhibition of mitochondrial F_0F_1-ATPase in cells that demand a high level of ATP hydrolysis, which depends on mitochondrial activity. This model can explain the selectivity of apoptolidin in transformed cells over normal cells. Presumably, transformed cells demanding a high level of ATP require a higher aerobic mitochondrial metabolism can be signaled through the reduced mitochondrial ATP synthase caused by apoptolidin. While normal cells and transformed cells that require low level of ATP are resistant to apoptolidin-induced apoptosis. Further study of the mechanism of apoptosis is required to fully understand apoptolidin's biological activity.

During Khosla's structure comparison study, they found that apoptolidin derivative **1.10** (Figure 1.5) retained considerable activity against mitochondrial ATPase (one order less active than apoptolidin) but lost cellular cytotoxicity in vivo (1% active as apoptolidin). This observation suggests an alternative mechanism that apoptolidin may induce apoptosis by interfering with a secondary target.[7c]



1.10 Truncated Apoptolidin

Figure 1.5 Structure of truncated apoptolidin **1.10**

1.3.3 Wender's study of biological activity of apoptolidin derivatives

Since 2002, Wender's group has extensively investigated the biological activity of apoptolidin and its derivatives. Rresults of their study are summarized in the Table 1.2.[8]

Table 1.2: Summary of apoptolidin and derivatives biological activities in F_0F_1-ATPase and E1A transformed cells[8]

Compounds	GI_{50}(μM) Ad12-3Y1	GI_{50}(μM) 3Y1	IC_{50}(μM) F_0F_1-ATPase
1.1 (apoptolidin)	0.0065	>1.0	0.7
1.11 (C2'-OBz)	0.0036	>1.0	0.3
1.12 (C4'''-OAc,C23-OAc)	0.0095	>0.6	0.4
1.13 (C4'''-OAc)	0.0098	>1.0	0.8
1.14 (C16-OAc)	0.056	>1.0	0.8
1.15 (3'-OAc)	0.0027	>1.0	0.4
1.16 (C20-OAc)	0.011	>1.0	1.1
1.17 (C20-OMe)	0.012	>1.0	2.8
1.18 (C21-OMe)	0.016	>1.0	2.3
1.5 (isoapoptolidin)	0.009	>1.0	17
1.19 (macrolide, C20-OH)	5.4	>7.0	13
1.20 (macrolide, C20-OMe)	1.4	>5.0	16
1.21 (macrolide, C20-OBz)	2.4	>5.0	16
1.22 (δ-lactone)	>12	>12	190
1.23 (Diels-Alder adduct)	3.2	>5.0	2.3

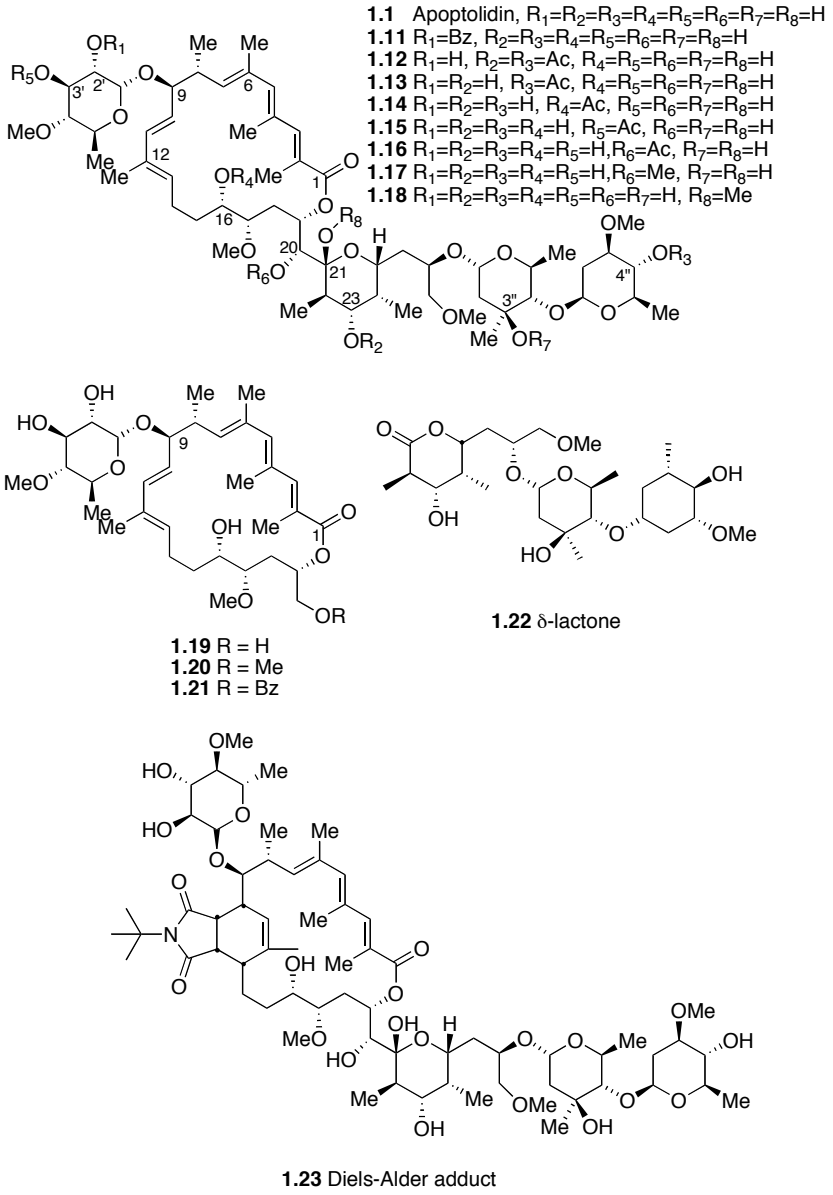


Figure 1.6 Structure of apoptolidin derivatives **1.11-1.23**

As described above, Khosla has proposed a hypothesis that apoptolidin's biological target is mitochondrial F_0F_1-ATPase and provided evidence to explain the relationship of cytotoxicity to this metabolic pathway. To explore the mechanism of apoptolidin and improve its therapeutic potential, Wender group prepared a series of

analogues **1.11**-**1.23** through chemical modification of apoptolidin, which is readily obtained by fermentation (Figure1.6).[8] The preliminary in vitro assay with F_0F_1-ATPase showed that modifications of hydroxyl groups with esters (**1.11**-**1.15**) and ethers (**1.16**-**1.18**) did not significantly effect the activity (Table 1.2). The greatest effect on activity observed across this series of analogs in this assay were methyl ethers C(20) (**1.17**) or C(21) (**1.18**). Isoapoptolidin (**1.5**) demonstrated a significant decrease in enzyme inhibitions with an over all 24-fold reduced potency. Although not as active as apoptolidin, derivatives **1.19**-**1.21** still retain activity compared to isoapoptolidin. However, the simple lactone **1.22** derived from oxidative cleavage of apoptolidin lost significant inhibition activity. To evaluate the importance of hydroxyl groups, Wender's group prepared compound **1.23** a Diels-Alder reaction product. Evaluation of **1.23** against F_0F_1-ATPase indicated that it was only 3 fold less active than apoptolidin and comparable to methyl ether **1.17** and **1.18**. Considering F_0F_1-ATPase assay is a cell free system and the unusual insensitivity of activity to widely varied structural change, they established a cell assay with normal 3Y1 and E1A and E1B transformed Ad12-3Y1 cells (identical to the same cell lines used by the Seto-Hayakawa group). In this assay apoptolidin showed its potency toward transformed Ad12-3Y1 cell (6.5 nM) and no effect on normal 3Y1 cell. While in cell free F_0F_1-ATPase inhibition test, it is much less potent (IC_{50} = 0.7 μM). They reasoned the 2-order magnitude difference in activity might reflect a difference in cellular uptake, chemical modification or cumulative effects in the 3 days cell-based assay. Acyl derivatives **1.11**-**1.16** were much more active in cell proliferation assay than in the cell free enzyme test. Furthermore, these analogues showed only a small difference relative to apoptolidin in terms of potency except **1.14**

(56 nM) (containing a C(16) Acetate). This exception (**1.14)** could be explained by one of three reasons: C(16) hydroxyl is important for activity; the increased steric demand affects the action of apoptolidin, or C(16) acetate might be a poor lipase substrate. The methyl ether **1.17** and **1.18** retained the same trend in the cell assay with the F_0F_1-ATPase enzyme assay, which demonstrated 3-4 fold less potency to apoptolidin. Surprisingly, isoapoptolidin **1.5** demonstrated almost the same activity against transformed cells with apoptolidin (9 nM vs 6.5 nM) while a great difference was observed in the enzymatic assay. This result is consistent with the observation that there is a facile equilibration between apoptolidin and isoapoptolidin. Without pyranose and disaccharide part, compounds **1.19**-**1.21** are about 20 fold less active than parent compounds in the enzymatic assay, while in E1A transformed cell they are almost 1000 times less potent than apoptolidin. Lactone **1.22** lost potency to both transformed cell and F_0F_1-ATPae. Diels–Alder adduct was 500 less active in transformed cells, however, it retained almost full activity against F_0F_1-ATPase. This indicated that the loss of activity in **1.19**-**1.21** was due to the binding affinity change to the biological target rather than a loss of cellular uptake. *Based on these data, Wender proposed that there might be a relevant secondary biological target of apoptolidin.*[8c]

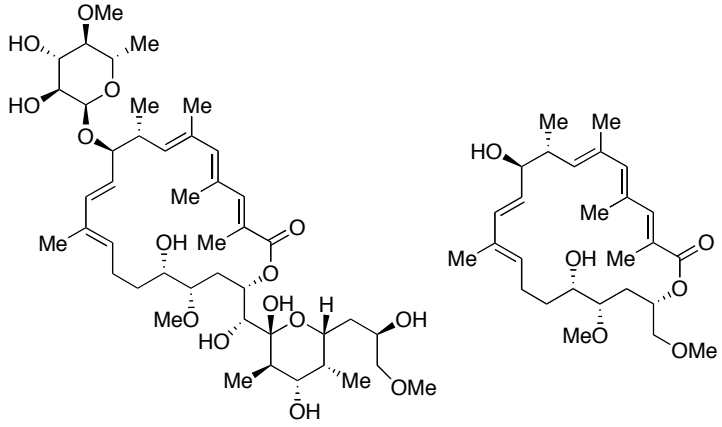
Wender also tested apoptolidin A, B and C in H292 cell line. The results are summarized below in Table 1.3. Apoptolidin B is more active than A to H292 cell. Apoptolidin C is less potent than B but more active than A.

Table 1.3 Growth inhibition assay result with H292 cells

Compounds	$GI_{50}(\mu M)$
Apoptolidin A (**1.1**)	0.032 ± 0.003
Apoptolidin B (**1.6**)	0.007 ± 0.004
Apoptolidin C (**1.7**)	0.024 ± 0.005

1.3.4 Nicolaou's biological study of apoptolidin and analogues

Nicolaou and co-workers at Scripps accomplished the first total synthesis of apoptolidin and investigated the biological activity of apoptolidin and some synthetic intermediates (Figure 1.7).[9] As summarized in Table 1.4, apoptolidin is the most active compound among these analogues. All the other analogues significantly lost their activity compared to apoptolidin (Table 1.4). These observations provide further evidence to Khosla's hypothesis that aglycone structure contributes the biological activity and carbohydrate side chain help cellular transport or binding to the cellular target.



1.24 **1.25**

Figure 1.7 Synthetic intermediates **1.24** and **1.25**

Table 1.4 Cytotoxicity of synthesized apoptolidin analogues against 1A9 human ovarian carcinoma cells

Entry	Compound	IC_{50} (μM)
1	Apoptolidin (**1.1**)	0.24
2	**1.24**	11.5
3	**1.20**	20.0
4	**1.25**	45.0

1.4 Previous studies toward total synthesis of apoptolidin

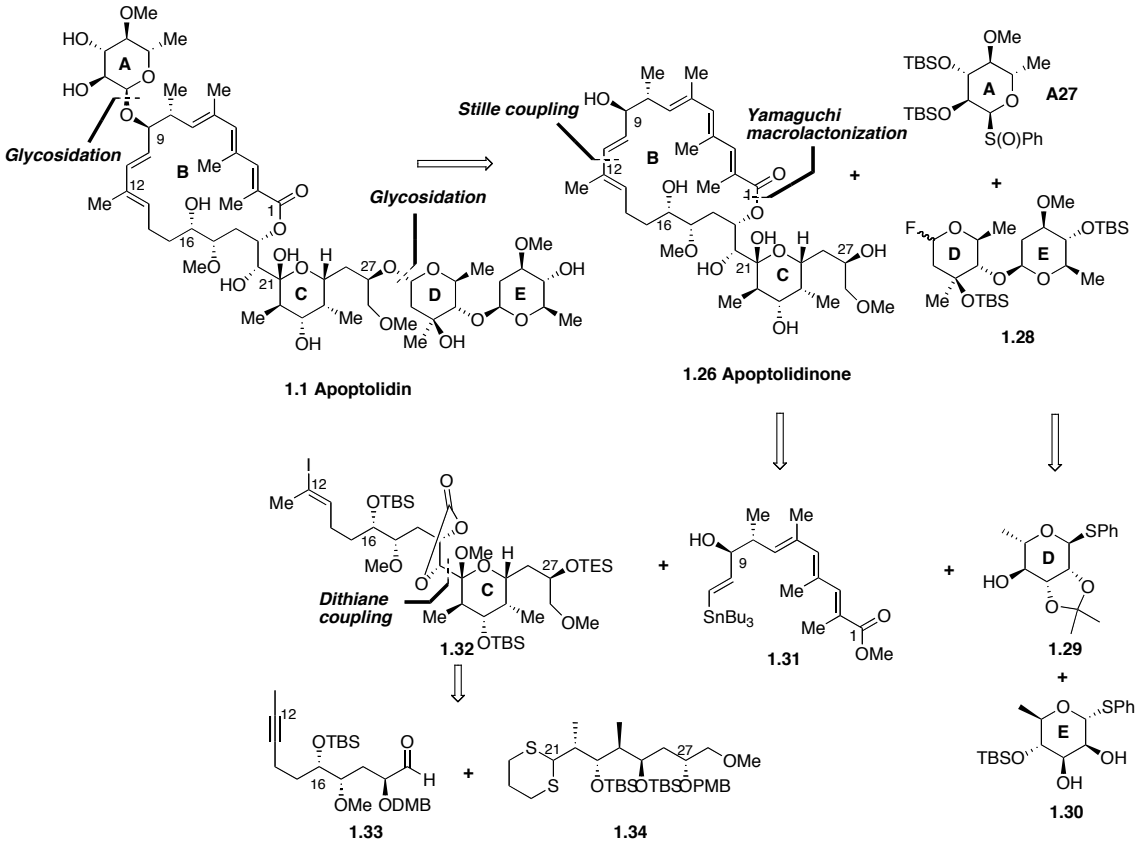
The complex structure and interesting biological activity of apoptolidin have drawn extensive attention from synthetic community. To date two total syntheses of apoptolidin and three total synthesis of apoptolidinone (aglycone structure) have been accomplished and multiple fragment syntheses have been reported. Some of these efforts will be discussed in this section.

1.4.1 K. C. Nicolaou's total synthesis of apoptolidin

In 2001, Nicolaou group completed the total synthesis of apoptolidin. Later in 2003, a revised synthesis route based on the same strategy was disclosed leading to an efficient total synthesis.[10] The total synthesis features a Stille coupling, Yamaguchi macrolactonization and a dithiane coupling reaction (later changed to a Horner-Wadsworth-Emmons reaction) to construct the 20-membered macrolactone ring (Scheme 1.1). The three sugar units were introduced at a very late stage of the total synthesis. The disconnection between C1 lactone and C11-C12 revealed **1.31** and **1.32** as key building

blocks. **1.32** was first prepared from **1.33** and **1.34** via dithiane coupling and later in the second generation it was constructed by Horner-Wadsworth-Emmons reaction.

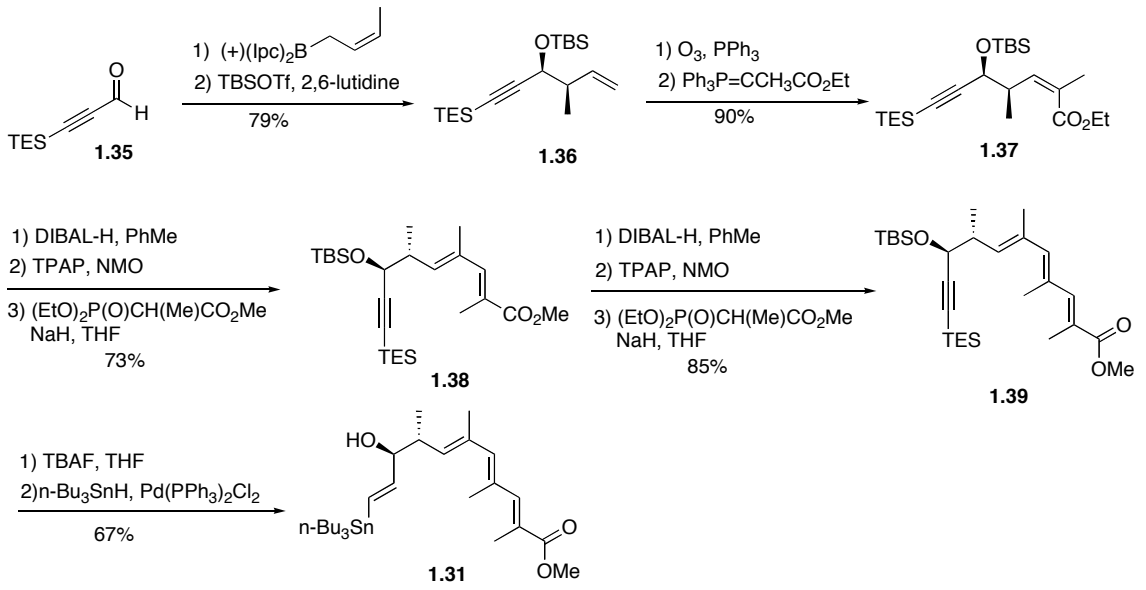
Scheme 1.1 Nicolaou's retrosynthetic analysis of apoptolidin **1.1**



The first generation synthesis of trienoate **1.31** was based on a strategy that utilized consecutive Wittig reactions (Scheme 1.2). Starting from known propargylic aldehyde **1.35**, Brown's asymmetric crotylation, TBS protection followed by ozonolysis of the terminal olefin and subsequent Wittig olefination provided ethyl ester **1.37**. DIBAL-H reduction, Ley oxidation followed by a Horner-Wadsworth-Emmons reaction afforded dienoate **1.38**. A second standard three-step sequence including reduction,

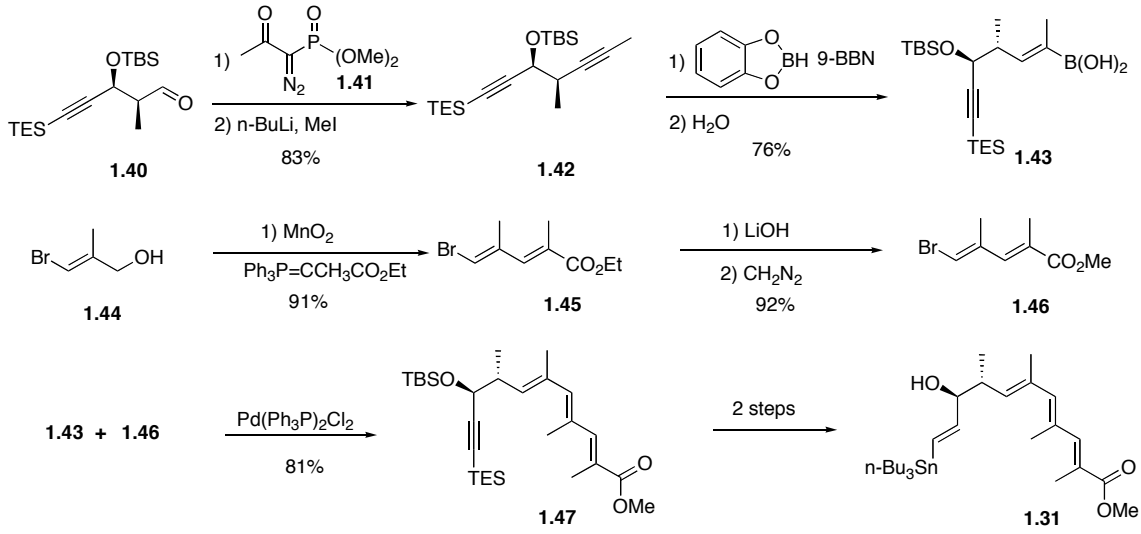
oxidation and HWE reaction furnished trienoate **1.39**. Finally deprotection followed by Pd(0) catalyzed hydrostannylation finished up the synthesis of **1.31**.

Scheme 1.2 Nicolaou's first generation synthesis of trienoate **1.31**



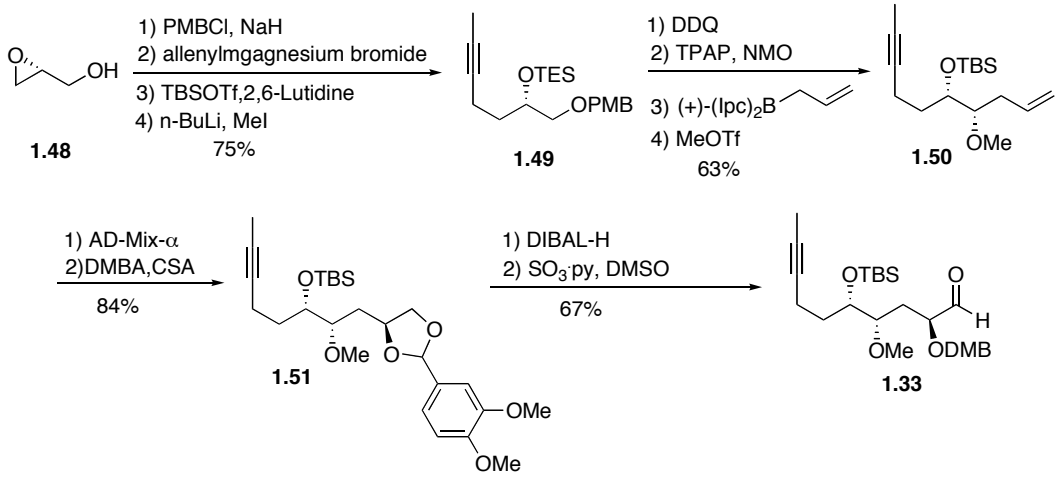
In 2003 the Nicolaou group reported a revised synthesis route to **1.31** based on a Suzuki coupling strategy (Scheme 1.3). This shorter sequence began with aldehyde **1.40**, which is available from the first generation synthesis. One carbon homologation with Ohira-Bestmann reagent **1.41** followed by methylation of terminal acetylene generated diyne **1.42**. Chemoselective hydroboration with catecholborane followed by aqueous hydrolysis afforded vinyl boronic acid **1.43**. The counterpart of the Suzuki coupling vinyl bromide **1.46** was prepared from known compound **1.44** with Wittig olefination. Trienoate **1.47** was obtained by coupling **1.43** and **1.46** together. Further elaboration introduced the vinyl tin moiety to afford **1.31**.

Scheme 1.3 Nicolaou's secondary generation synthesis of **1.31**



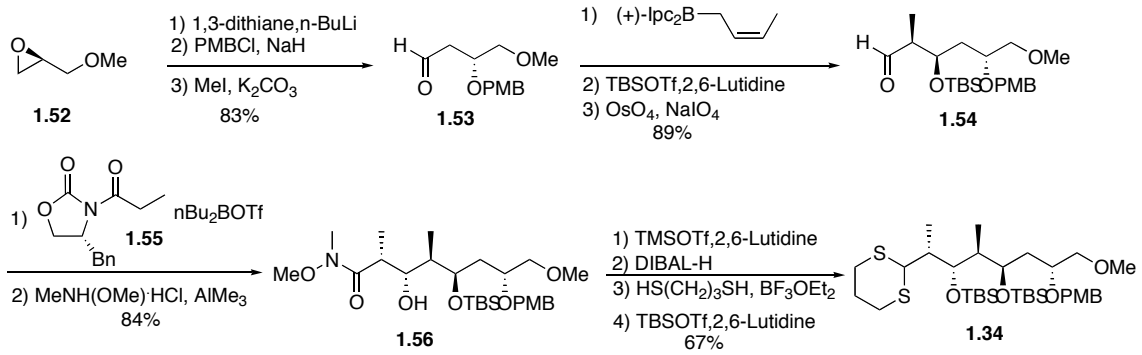
Nicolaou's first generation synthesis of fragment **1.32** (C12-C28) was based on a dithiane coupling reaction. Although two synthetic routes were developed to prepare the aldehyde part required for the dithiane coupling, only the more efficient synthetic sequence is summarized here (Scheme 1.4). The synthesis of aldehyde **1.33** began with commercial available (+)-glycidol **1.48**. Protection of the free hydroxyl group followed by epoxide opening with allenylmagnesium bromide, silylation of the newly generated hydroxyl group and methylation of the resultant terminal acetylene afforded compound **1.49**. DDQ removal of the PMB protecting group, Ley oxidation of the corresponding alcohol, asymmetric allylation followed by methylation of the newly formed hydroxyl group afforded **1.50**. Sharpless asymmetric dihydroxylation and benzylidene formation provided **1.51**. Finally, a reduction and oxidation sequence furnished desired aldehyde **1.33**.

Scheme 1.4 Nicolaou's synthesis fragment **1.33**



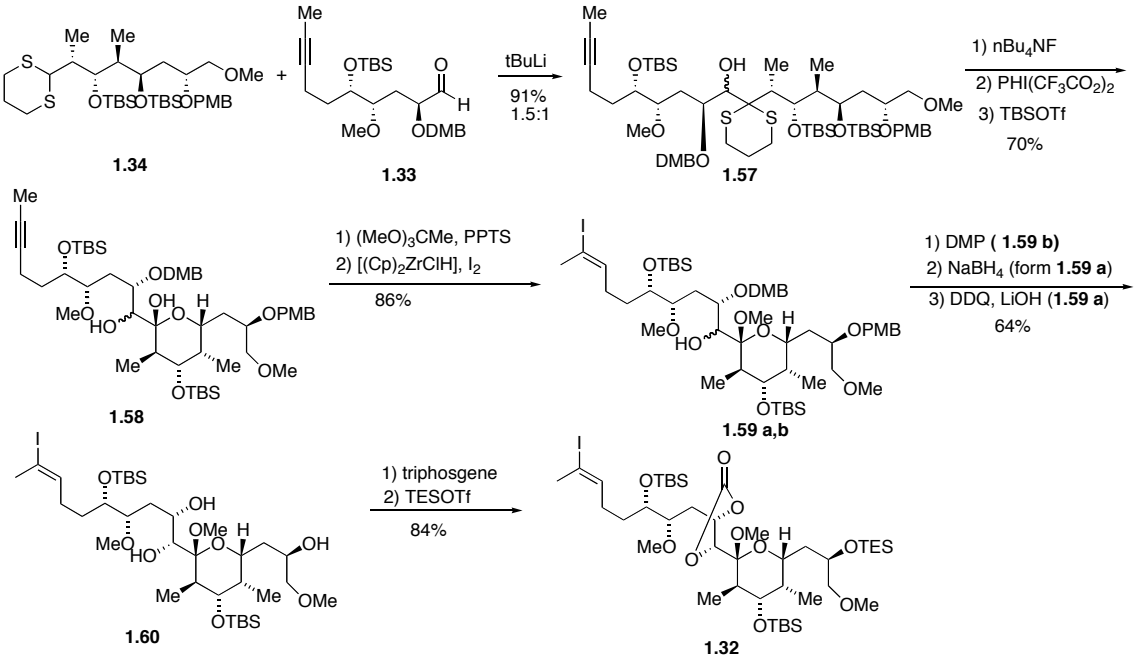
Dithiane **1.34** was prepared starting from the glycidol methyl ether **1.52**. 1,3-dithiane opening of the epoxide, PMB protection and dithiane hydrolysis afforded aldehyde **1.53** (Scheme 1.5). Brown asymmetric crotylation, silylation of the newly formed hydroxyl group followed by oxidative cleavage of the terminal alkene furnished aldehyde **1.54**. Evan's asymmetric aldol reaction and Weinreb amide displacement of the auxiliary generated amide **1.56**. Then TMS protection, DIBAL-H reduction, dithiane formation followed by silylation provided dithiane **1.34**.

Scheme 1.5 Nicolaou's synthesis fragment **1. 34**



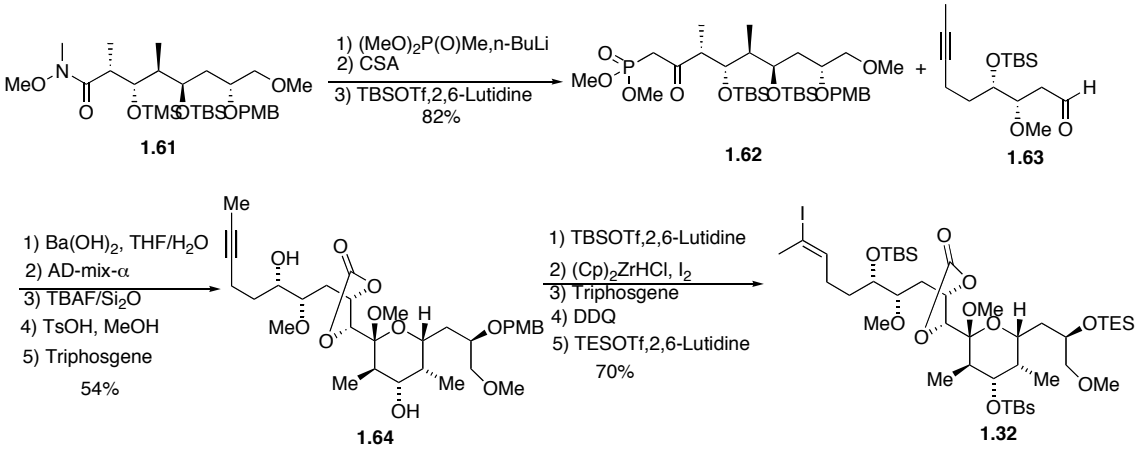
As designed, aldehyde **1.33** and dithiane **1.34** were coupled together by treatment with base (tBuLi) to provide a 1.5:1 mixture of diastereomers **1.57** (Scheme 1.6). Both of the disastereomers were taken forward. Hence, desilylation with TBAF, dithiane hydrolysis with Stork-Zhao's method and resilylation with TBSOTf afforded **1.58**. At this stage the stereochemistry of the C20 was assigned by converting **1.58** to C20-C21 carbonate with triphosgene. Then both isomers were protected as orthoester with trimethyl orthoacetate and the alkyne moiety was subjected to hydrozirconation and Zr-I exchange to furnish vinyl iodide **1.59**. At this point the unwanted C20 epimer was inverted through a standard oxidation-reduction sequence. Oxidative removal of DMB and PMB protecting groups followed by protection of the diol with triphosgene and silylation afforded southern part of the apoptolidin **1.32**.

Scheme 1.6 Nicolaou's completion synthesis of fragment **1.32**



An alternative route to synthesis of fragment A32 based on Horner-Wadsworth-Emmons reaction was later developed and summarized in Scheme 1.7. Weinreb amide **1.61**, which was an intermediate in the synthesis of fragment **1.34**, was converted to phosphonate **1.62** via a three-step sequence including phosphonate installation, desilyation and resilylation. HWE reaction between **1.62** and aldehyde **1.63**, which is readily available from **1.50** via oxidative cleavage of the terminal alkene, proceeded smoothly to form the trans olefin. Sharpless asymmetric dihydrolxyation, desilylation-cyclization, methylation of the newly formed hemiacetal and protection of the diol with

Scheme 1.7 Nicolaou's HWE strategy to synthesis of fragment **1.32**

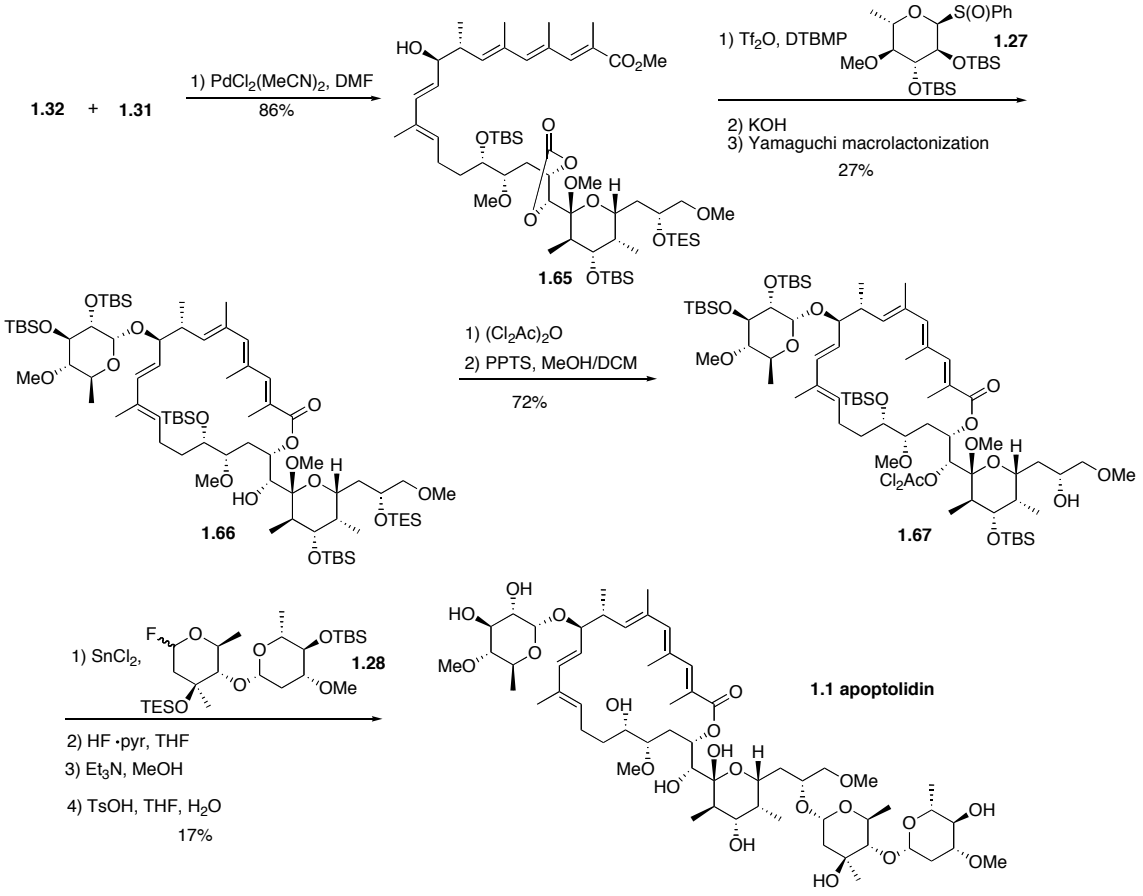


triphosgene furnished **1.64**. Silylation with TBSOTf, hydrozirconation and Zr-I exchange, reprotection of the diol with triphosgene, replacing the PMB group with TES protecting group afforded fragment **1.32**.

With both key fragment **1.32** and **1.31** in hand, Stille coupling connected them together and afforded ployene **1.65** (Scheme 1.8). Kahne's glycosylation with sugar **1.27** followed by KOH hydrolysis of C19–C20 carbonate and selective Yamaguchi

macrolactonization furnished macrolide **1.66**. Protection of the C20 hydroxyl followed by selective desilylation of C27 TES group provided **1.67** and set up the stage for the second glycosylation. Disaccharide **1.28** was attached to C27 via a Ti(II) mediated glycosylation. Finally, global desilylation with HF·Pyr, acetate saponification and acetal hydrolysis afforded the target molecule apoptolidin **1.1**.

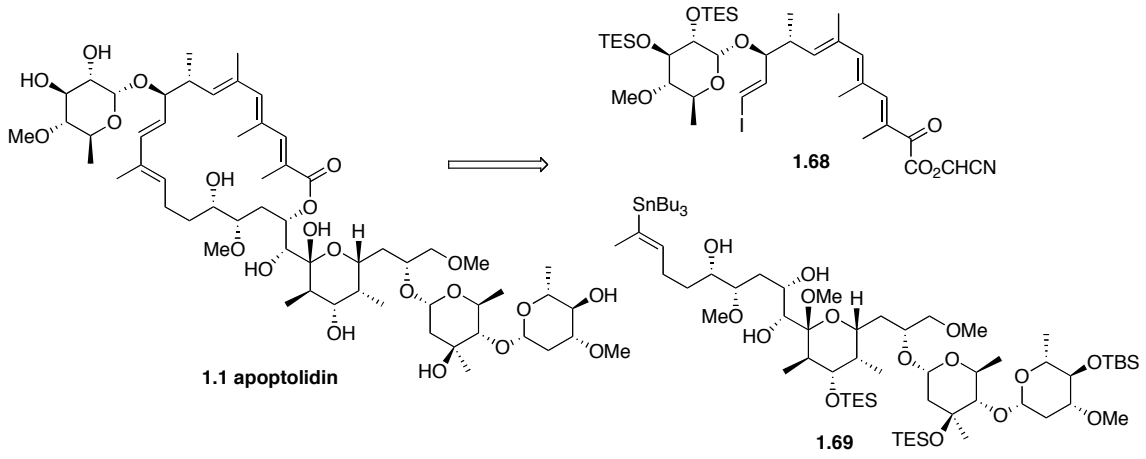
Scheme 1.8 Nicolaou's completion synthesis of apoptolidin **1.1**



1.4.2 Koert's total synthesis of apoptolidin

In 2001 Ulrich Koert accomplished the total synthesis of the aglycone structure of apoptolidin, apoptolidinone.[11] Three years later, they reported their total synthesis of apoptolidin.[12] Their synthesis feactures a strategy similar to Nicolaou's approach to construct the 20-membered macrolactone, which disconnected the macrolide from

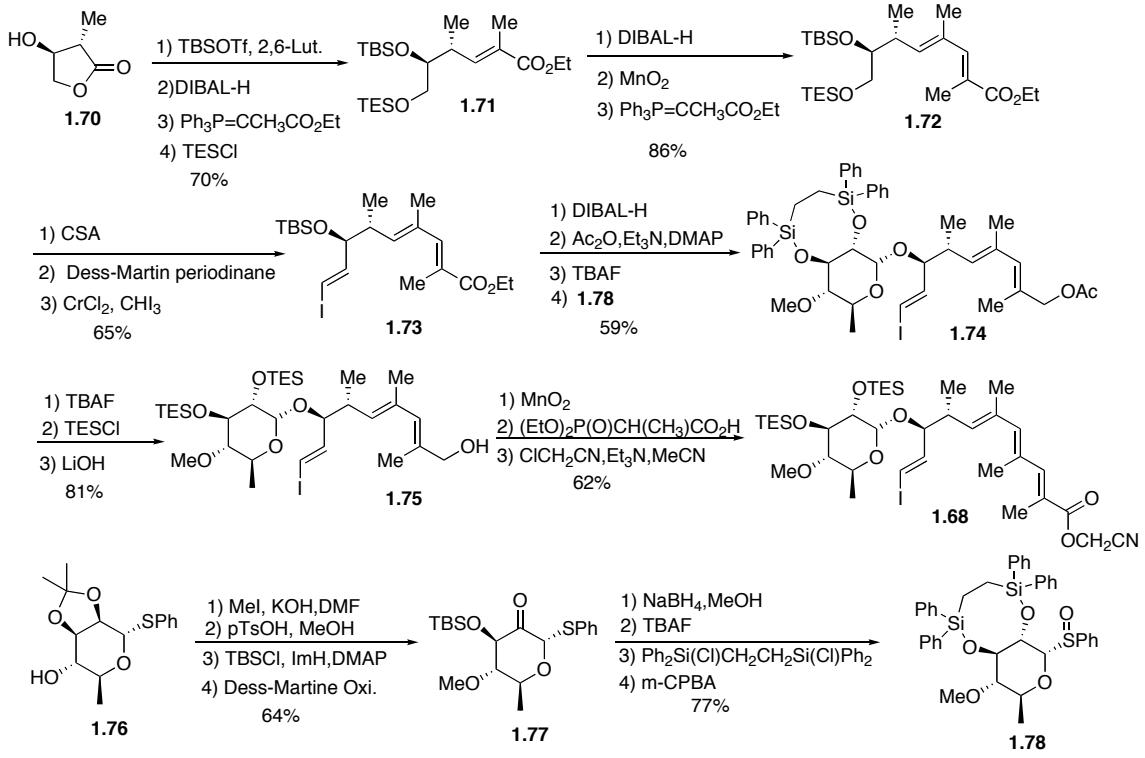
Scheme 1.9 Koert's restrosynthetic analysis of apoptolidin **1.1**



lactone part and C11-C12 bond. Regarding incorporation of the sugar moieties, they selected to introduce the sugar residues early during the course of the fragment synthesis. This strategy revealed northern half **1.68** and southern half part fragment **1.69** as key building blocks (Scheme 1.9). The synthesis of trienoate **1.68** was based on three consecutive Wittig type olefination reactions as Nicolaou applied in his first generation synthesis of trienoate **1.31** (Scheme 1.10). Starting from β-hydroxyl lactone **1.70**, silylation with TBSOTf, lactone reduction with DIBAL-H and Wittig olefination followed by silylation with TESCl provided bissilylated diol **1.71**. Then a standard three-step sequence including reduction, oxidation and Wittig olefination afforded dienoate

1.72. Selective removal of TES silyl ether with CSA, oxidation with Dess-Martin periodinane followed by Takai reaction introduced *E*-vinyl iodide **1.73**. The ethyl ester was reduced and the corresponding alcohol was acetylated. Desilylation followed by Kahne glycosylation with sulfoxide **1.78** afforded **1.68**. The glycosyl sulfoxide **1.78** was prepared from acetonide-protected L-rhamnose thioglycoside **1.76**. Methylation of the free hydroxyl, removal of the acetonide with PTSA, selective protection 4-hydroxyl as

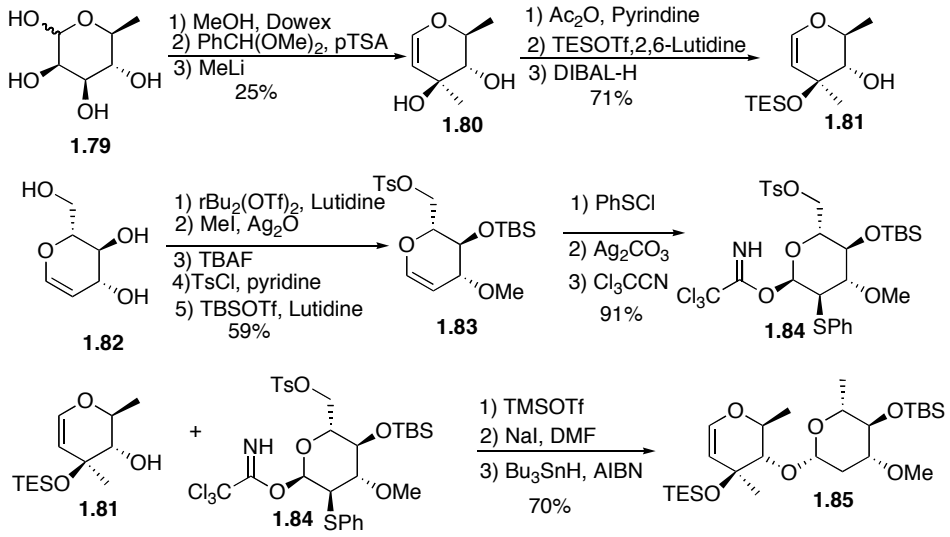
Scheme 1.10 Koert's synthesis of fragment **1.68**



TBS ether and Dess-Martin oxidation generated ketone **1.77**. Diastereoselective reduction of the ketone and desilylation furnished a diol, which was then transformed into SIBA-protected glycosylsulfoxide **1.78** by protection and oxidation.

The southeastern disaccharide was prepared from L-rhamnose **1.79** and D-glucal **1.82** (Scheme 1.11). methyl acetal formation followed by benzylidene protection of the 3,4-diol and treatment of excess MeLi afforded branched sugar **1.80**. Selective acylation of the secondary alcohol, protection of the tertiary alcohol as TES silyl ether followed by removal of the acetate protecting group furnished the left part of disaccharide **1.85**. The synthesis of the remaining sugar started from **1.82** and protection of the 4,6-diol. Methylation of the allylic alcohol, desilylation, tosylation followed by silylation again

Scheme 1.11 Koert's synthesis of disaccharide **1.85**

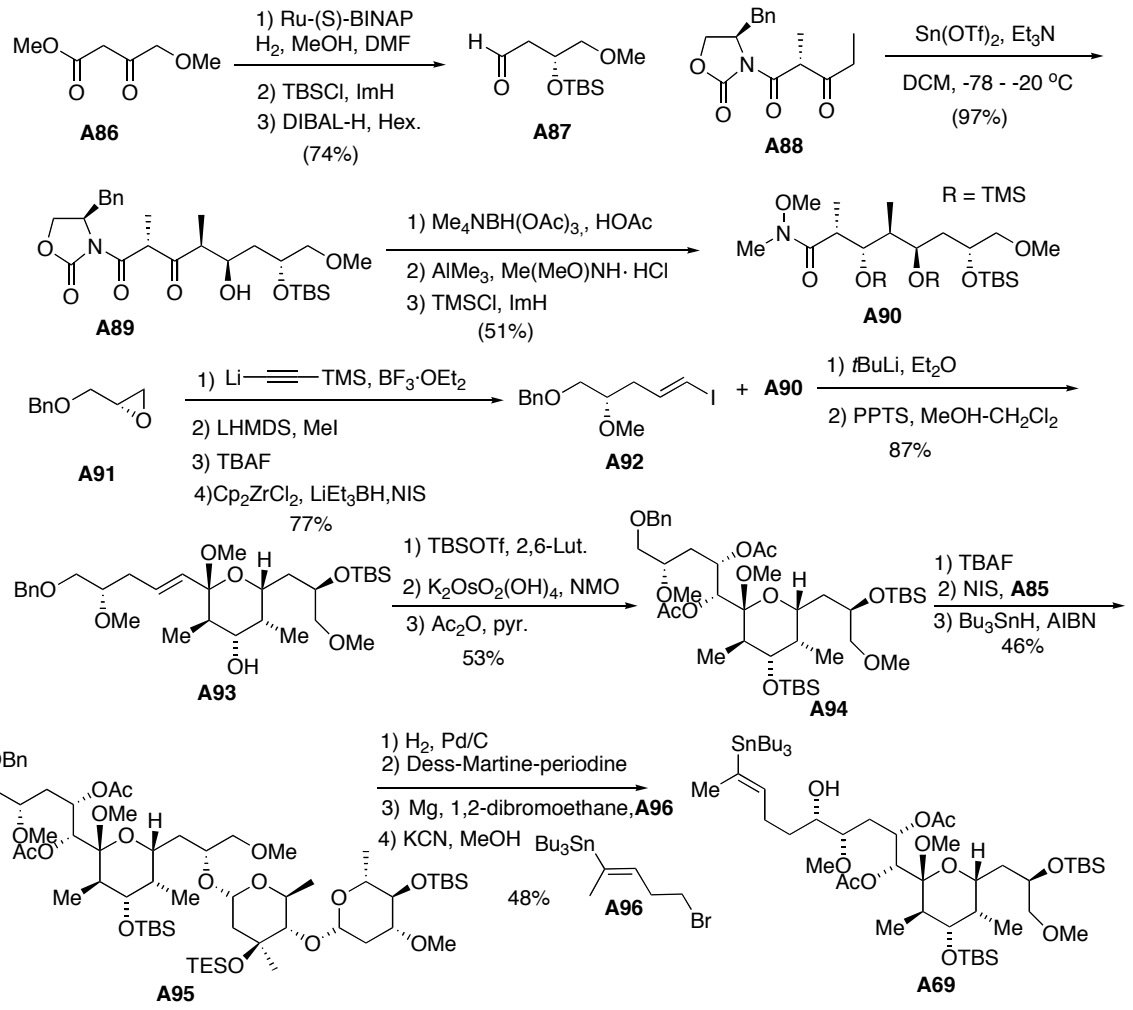


generated **1.83**. The precursor of the glycosyl donor **1.84** was obtained through a three-step reaction sequence including treatment of the **1.83** with PhSCl, Ag_2CO_3(aq) and NaH, Cl_3CCN subsequently. Finally, TMSOTf mediated coupling of **1.81** and **1.84** produced a disaccharide, which was reduced to afford **1.85**.

The synthesis of the southern half of apoptolidin began with β-ketoester **1.86**, which was subjected to Noyori's ruthenium catalyzed asymmetric hydrogenation,

silylation, DIBAL-H reduction to afford aldehyde **1.87** (Scheme 1.12). Evans aldol reaction with **1.88** produced alcohol **1.89**. Subsequently, anti-1,3-reduciton,

Scheme 1.12 Keort's synthesis of fragment **1.69**

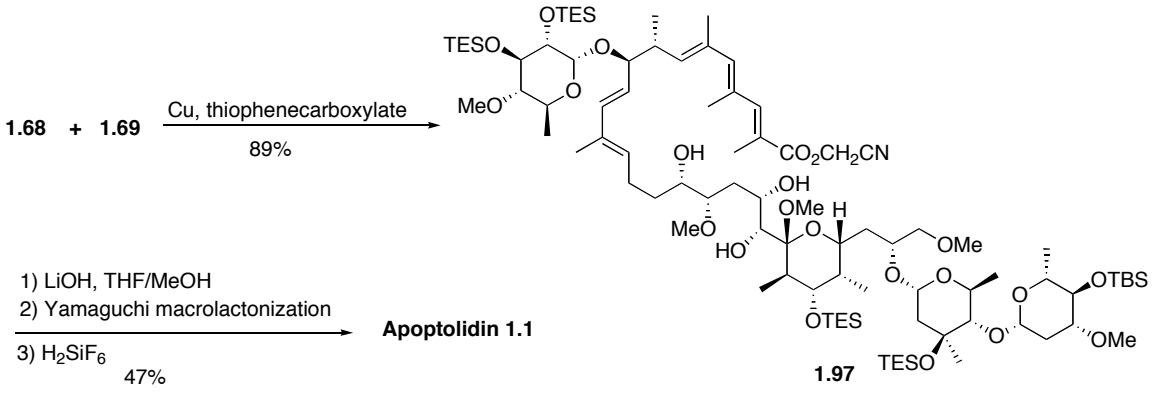


displacement of auxiliary with Weinreb amide and silylation of the free hydroxyl furnished **1.90**. Benzyl protected glycidol **1.91** was converted to E-vinyl iodide **1.92** via a four-step sequence including epoxide opening, methylation, desilylation, hydrozirconation and Zr-I exchange. After Lithium-Iodine change, compound **1.92** was coupled with Weinreb amide **1.90** to produce the corresponding ketone, which was

desilylated to cyclize to methyl hemiactal **1.93**. Silylation of the C27 hydroxyl group followed by Sharpless asymmetricdihydroxylation and acylation of the newly formed diol provided **1.94**. After desilylation, the disaccharide **1.85** was introduced to furnish **1.95** via NIS activation followed by reductive elimination of the iodide. Finally, reductive debenzylation, Dess-Martin oxidation, chelation-controlled Grignard addition and acetate hydrolysis provided C12-C28 fragment **1.69**.

A copper (I) mediated Stille reaction coupled fragments **1.68** and **1.69** to provide **1.97**, which was then subjected to cyanomethyl ester hydrolysis and Yamaguchi macrolactonization to close the 20-membered macrolide (Scheme 1.13). Global deprotection with H_2SiF_6 completed the total synthesis of apoptolidin.

Scheme 1.13 Keort's completion synthesis of apoptolidin **1.1**

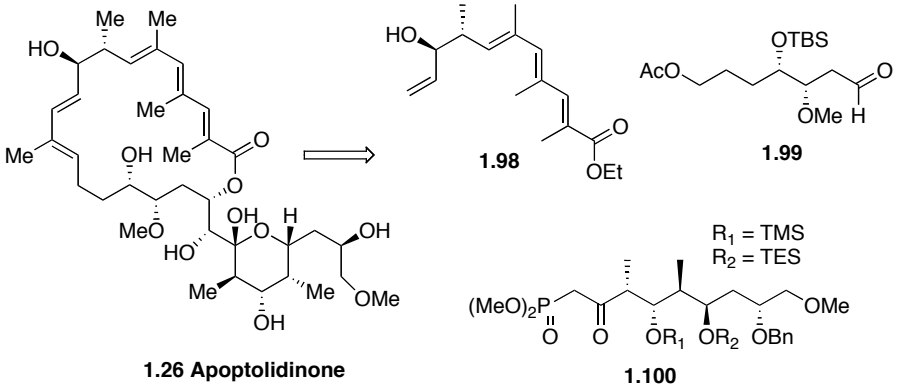


1.4.3 Crimmins's total synthesis of apoptolidinone and sugars

In late 2005 Crimmins and co-workers reported their total synthesis of apoptolidinone and later the individual sugar units.[13] Apoptolidinone, the aglycone of apoptolidin, was considered as a check-point en route to the total synthesis of

apoptolidin. In contrast to Nicolaou and Koert's synthesis, Crimmins disconnected the

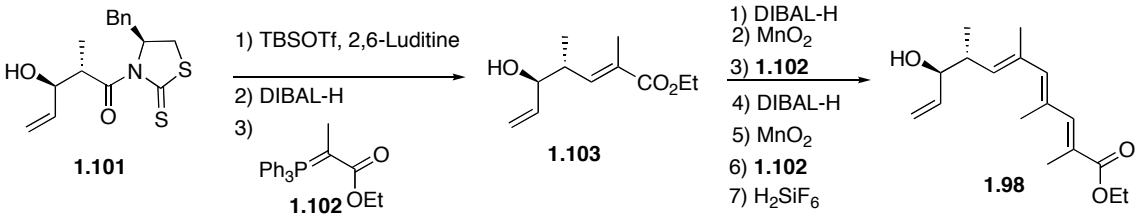
Scheme 1.14 Crimmins' retrosynthesis of apoptolidinone **1.26**



macrolide at the C10-C11 bond, which was proposed to be formed via a cross metathesis reaction. In the synthesis of lower part they adopted the same strategy as employed by Nicolaou, which introduced the C20–C21 diol by Horner-Wadsworth-Emmons olefination and Sharpless asymmetric dihydroxylation. The highlight of this synthesis was constructing 8 of 12 stereocenters via thiazolidinethione aided asymmetric methodology. The retrosynthesis of apoptolidinone is illustrated in Scheme 1.14.

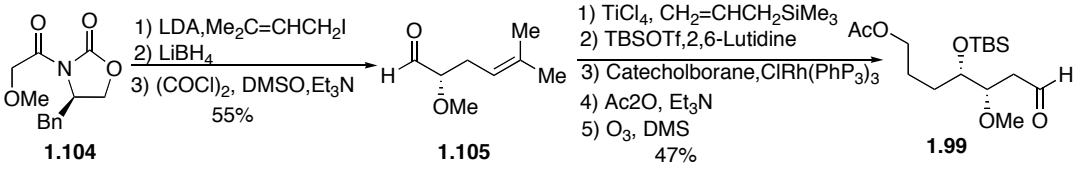
Crimmins' synthesis of trenoate **1.98** was similar to Koert's synthesis, which applied three consecutive Wittig type olefination reactions (Scheme 1.15). Starting from

Scheme 1.15 Crimmins' synthesis of trienoate **1.98**



known *anti*-aldol adduct **1.101**, silylation, reductive cleavage of the auxiliary and Wittig reaction afforded **1.103**. A sequence of two standard three-step reaction including reduction, oxidation and olefination completed the trienoate. Finally, desilylation with H_2SiF_6 delivered the upper fragment of apoptolidinone: **1.98**.

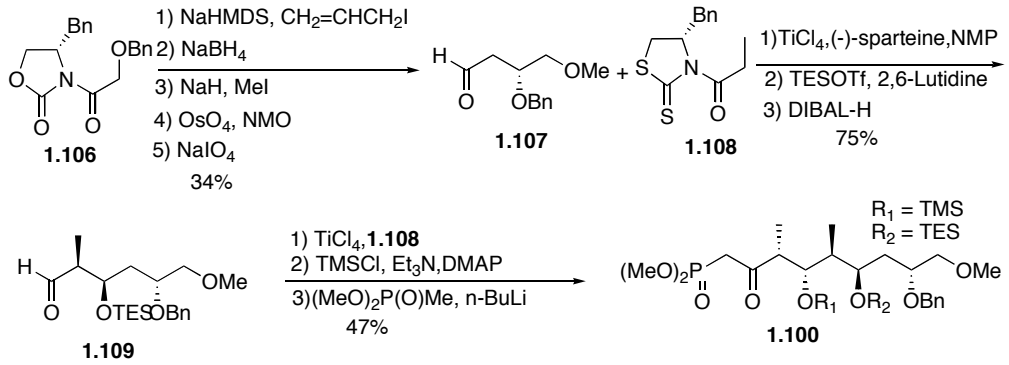
Scheme 1.16 Crimmins' synthesis of fragment **1.99**



The synthesis of aldehyde **1.99** commenced with glycolyl amide **1.104** (Scheme 1.16). Asymmetric alkylation followed by reductive cleavage of the auxiliary and Swern oxidation of corresponding alcohol afforded aldehyde **1.105**. Titanium mediated allylation provided a *syn*-diol via chelation-control. After silylation of the newly formed hydroxyl, ruthenium catalyzed hydroboration followed by acylation introduce the acetate in the right part of **1.99**. Finally, ozonolysis of the left terminal alkene finished up the synthesis of aldehyde **1.99**.

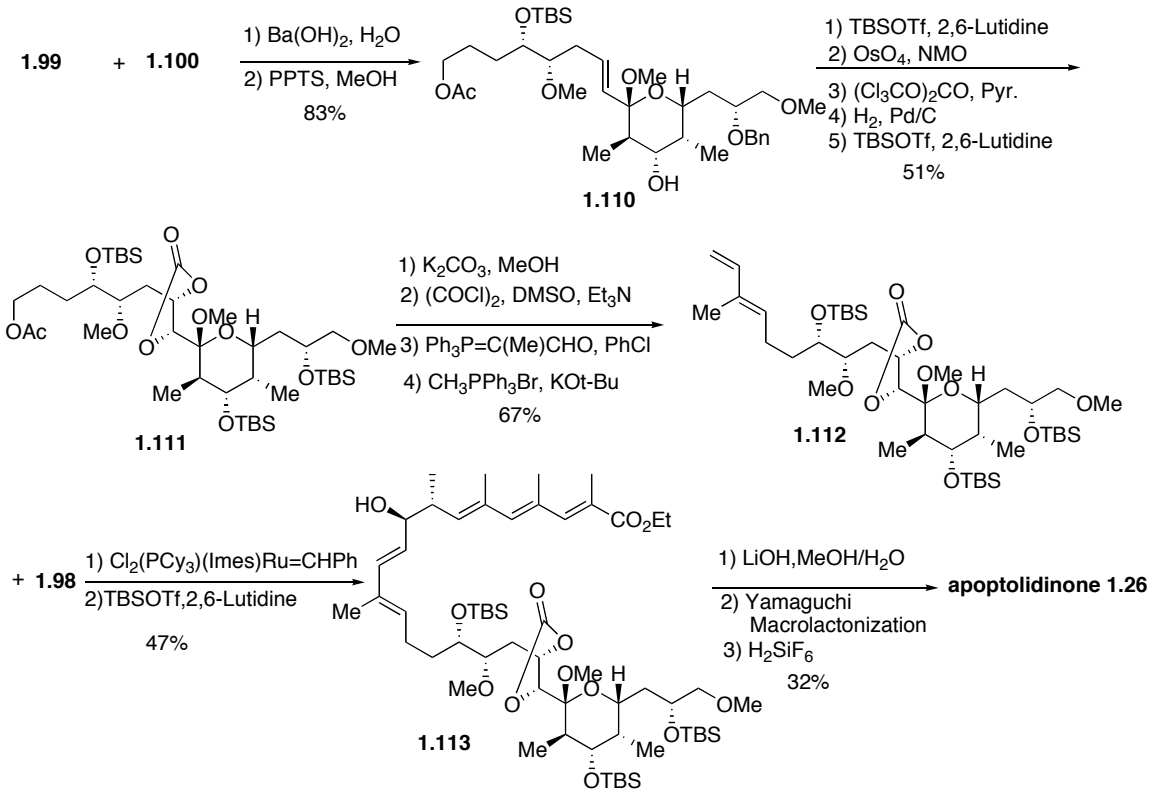
The preparation of ketophosphonate **1.100** began with chiral auxiliary **1.106** (Scheme 1.17). Asymmetric alkylation, reduction of auxiliary and subsequent methylation of the corresponding alcohol introduced the C27 stereocenter and terminal methyl ether. Asymmetric aldol with chiral thazolidinethione auxiliary **1.108** followed by silylation and reduction afforded aldehyde **1.109**. A second aldol reaction with **1.108** and silylation set up the stereocenter at C22 and C23. Finally, keotphosphonate **1.100** was obtained by displacement of the auxiliary with lithiodimethyl methylphosphonate.

Scheme 1.17 Crimmins' synthesis of fragment **1.100**



With all the building blocks in hand, they turned to the attention to the key coupling reactions. HWE reaction between aldehyde **1.99** and phosphonate **1.100** followed by desilyation afforded pyranose **1.110** (Scheme 1.18). Silylation followed by

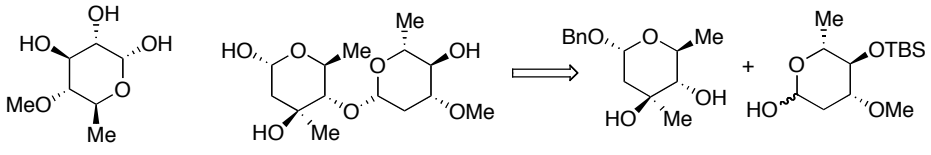
Scheme 1.18 Crimmins' completion synthesis of apoptolidinone **1.26**



dihydroxylation introduced C20 and C21 diol, which was subsequently protected as a carbonate. Converting benzyl ether to the more labile TES silyl ether was accomplished through two steps to furnished intermediate **1.111**. Hydrolysis of acetate followed by Swern oxidation set the stage for introducing diene required for cross metathesis. A Horner-Wadsworth-Emmons reaction followed by a Wittig reaction afforded diene **1.112**, which was then coupled with trienoate **1.98** via cross metathesis to form the C10-C11 bond. Silylation of the C9 hydroxyl with TBSOTf provided polyene intermediate **1.113**. Hydrolysis of the ethyl ester and C20-C21 carbonate followed by selective Yamaguchi macrolactonization closed the 20-membered macrolactone. Finally, global deprotection with H_2SiF_6 completed the total synthesis of apoptolidinone **1.26**.

Each of the three monosaccharide in apoptolidin is 6-deoxy sugar (scheme 1.19). Both Nicolaou's and Koert's synthesis took an approach to modify natural carbohydrates. In contrast, Crimmins group applied his *anti* glycolate aldol methodology to establish the C4 and C5 stereocenter in all sugar units and prepared them from simple building blocks.[14]

Scheme 1.19 Crimmins' retrosynthesis of sugar units

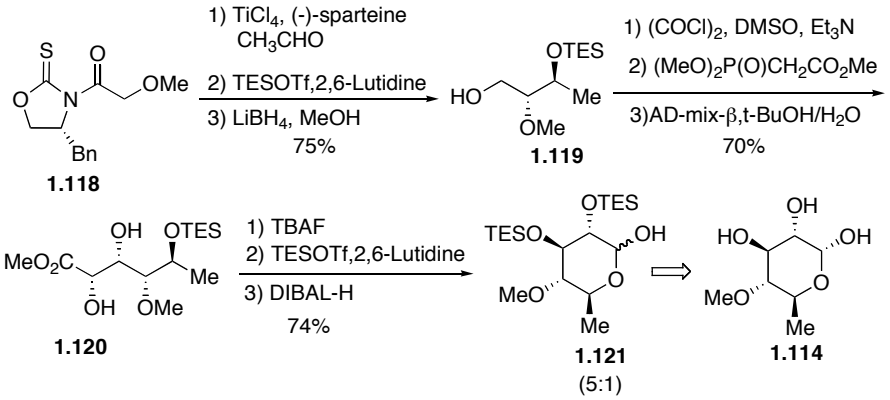


1.114 **1.115** **1.116** **1.117**

The preparation of sugar **1.114** commenced with an *anti* glycolate aldol reaction between *o*-methyl glycolyloxazolidinethione **1.118** and acetaldehyde (Scheme 1.20). After silylation and reductive removing of the auxiliary, the aldol adduct was converted

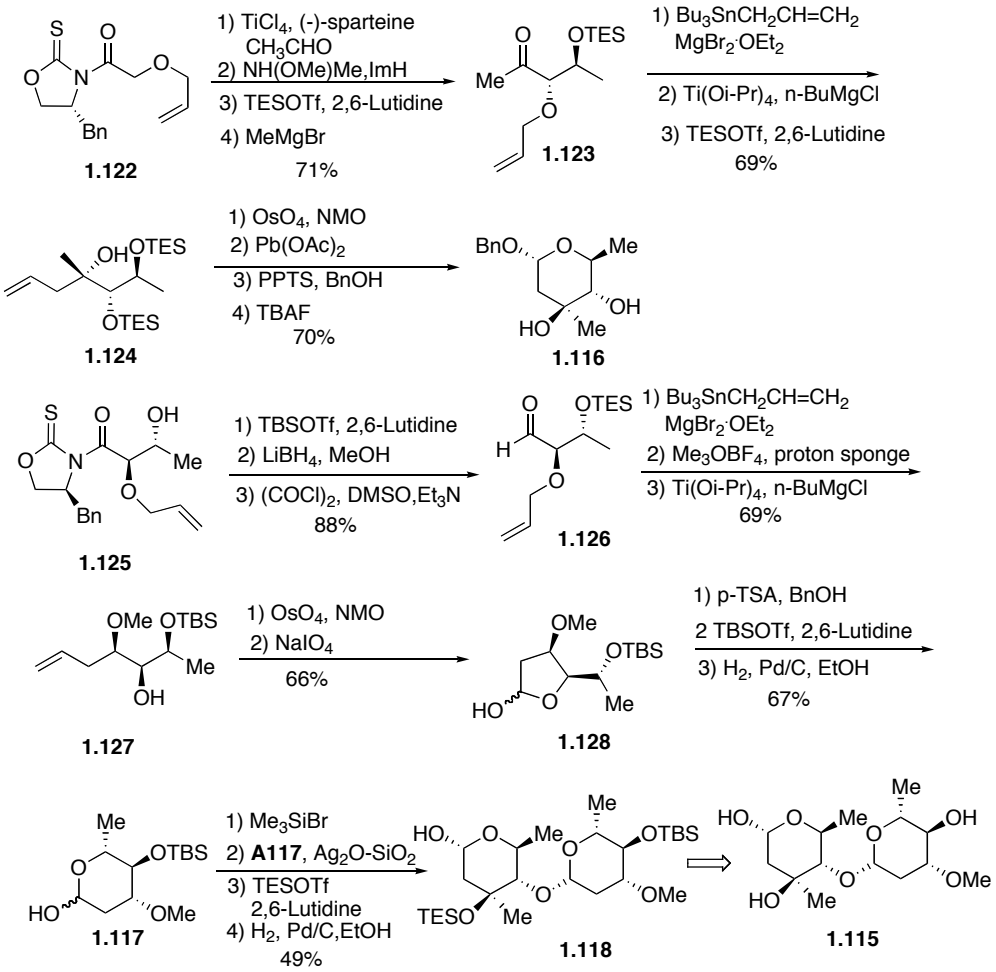
into primary alcohol **1.119**. Swern oxidation followed by Horner-Wadsworth-Emmons reaction provided α,β-unsaturated methyl ester, which in turn was subjected to Sharpless asymmetric dihydroxylation and afforded diol **1.120**. Desilylation simultaneously led to cyclization and furnished lactone, which was then resilylated and reduced to afford protected **1.114**: **1.121**.

Scheme 1.20 Crimmins' synthesis of sugar **1.114**



Disaccharide **1.115** is comprised of monosaccharide **1.116** and **1.117**. The synthesis of monosaccharide **1.116** began with allyl protected glycolyloxazolidinethione **1.122** (Scheme 1.21). Titanium chloride mediated anti aldol reaction with acetaldehyde set up the *anti*-1,2-diol, which was in turn converted to Weinreb amide. After silylation of the free hydroxyl group, methyl Grignard addition introduced methyl ketone **1.123**. The tertiary carbinol center was set up by chelation-controlled allylation with allyltributylstannane. Then the allyl protection group was replaced by TES silyl ether and afforded **1.124**. Oxidative cleavage of the terminal alkene followed by formation of benzyl acetal and desilylation provided the left hand of disaccharide **1.116**. The synthesis of right hand of **1.115** utilized the same strategy as **1.116**. Starting from aldol adduct

Scheme 1.21 Crimmins' synthesis of disaccharide **1.115**



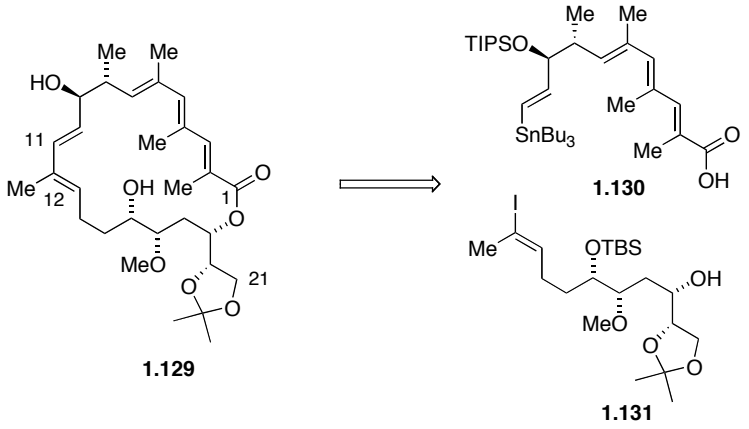
1.125, which was obtained from *ent*-**1.122** and acetaldehyde, was first protected as TBS silyl ether. Reductive removal of auxiliary followed by oxidation of the corresponding alcohol furnished aldehyde **1.126**. Chelation-controlled allylation and methylation of the corresponding homoallylic alcohol generated homoallylic methyl ether, which in turn was deallylated. Oxidative cleavage of the terminal alkene delivered hemiacetal **1.128**.Formation of the benzyl hemiacetal with BnOH followed by silylation and debenzylation provided the right part of the disaccharide **1.117**. Exposure of the hemiacetal **1.117** to Me_3SiBr generated glycosyl bromide, which was then coupled with

1.116 to form the disaccharide. Silylation followed by hydrogenolysis gave protected disaccharide **1.115**: **1.118**.

1.4.4 Toshima's synthesis of C1-C21 macrolide fragment and C12-C28 fragment

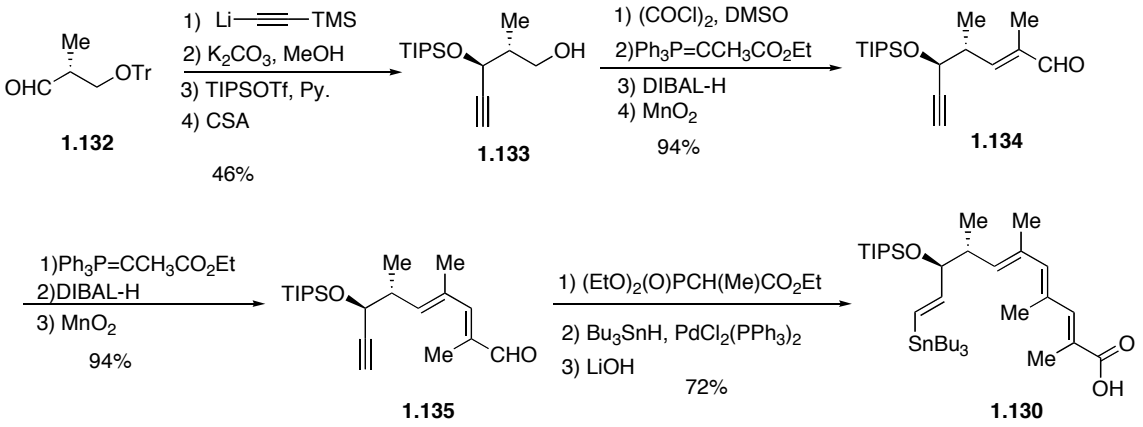
In 2001 Toshima and co-workers disclosed their synthesis of C1-C21 macrocyclic lactone **1.129** of apoptolidin.[15] Not surprisingly, Toshima selected a retrosynthetic disconnections form at the C1 lactone position and C11-C12 bond, which in the forward sense were to be formed by Yamaguchi macrolactonization and Stille coupling respectively. This synthetic strategy revealed intermediate **1.130** and **1.131** as key building blocks (Scheme 1.22).

Scheme 1.22 Toshima's retrosynthesis of macrolide C1-C21 **1.129**



Toshima's preparation of upper part of the **1.129** started from aldehyde **1.132**, which was obtained from methyl *R*-3-hydroxy-2-methylpropionate (Scheme 1.23). Addition of the lithium anion derived from trimethylsilylacetylene generated Cram-adduct as a major isomer (2:1), which was subjected to basic hydrolysis to remove TMS protective group. The propargyl alcohol was protected as TIPS silyl ether and the primary

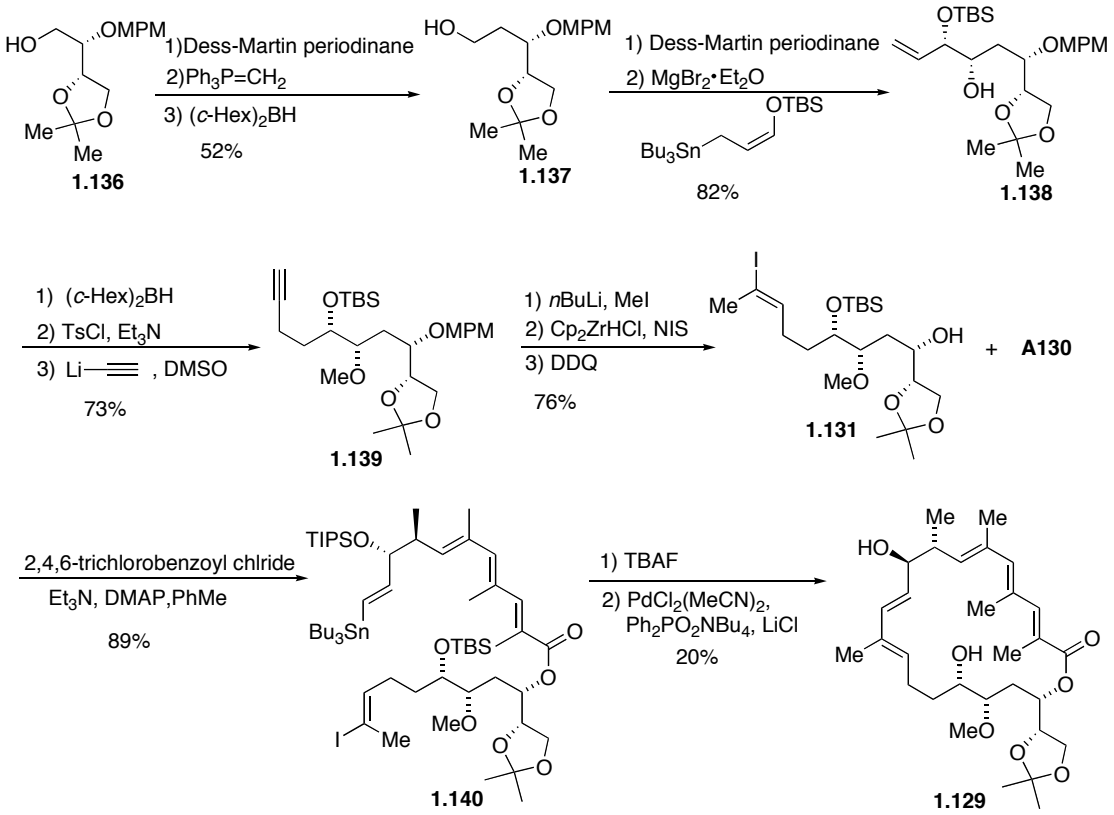
Scheme 1.23 Toshima's synthesis of fragment **1.130**



alcohol was released by removing trityl protection group under acidic condition to provided **1.133**. Swern oxidation followed by Wittig reaction introduced the first olefin of the trienoate. The resulting ethyl ester was then converted into aldehyde **1.134** via a standard two-step reaction sequence. Wittig olefination, reduction and oxidation introduced the second double bond and afforded aldehyde **1.135**. A Horner-Wadsworth-Emmons reaction completed the trienoate moiety. Palladium catalyzed regio- and stereoselective hydrostannylation introduced the *E*-vinyl tin required by Stille coupling. Finally, hydrolysis of the ethyl ester provided the desired acid **1.130**.

The construction of the lower part of the macrolide **1.131** began with alcohol **1.136**, which is readily prepared from diethyl L-tartrate (Scheme 1.24). One carbon homologation from **1.136** to **1.137** was accomplished via a three-step sequence consisting of Dess-Martin oxidation, Wittig olefination and hydroboration reaction. The *syn*-diol at C16 and C17 was introduced by $MgBr_2$ mediated crotylation of the corresponding aldehyde, which was obtained from oxidation of **1.137**. Then hydroboration of the alkene, tosylation of the corresponding alcohol and substitution of the tosylate with lithium anion

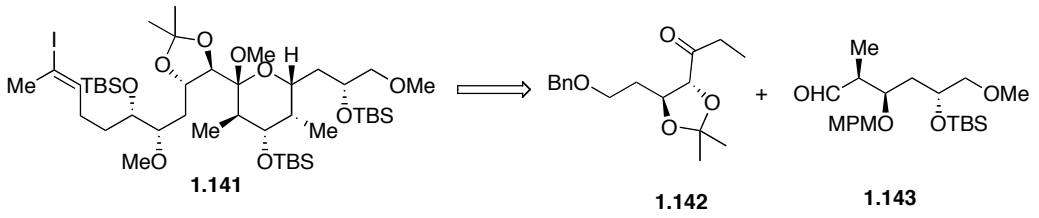
Scheme 1.24 Toshima's completion of macrolide **1.129**



of acetylene afforded terminal alkyne **1.139**. Methylation of the terminal alkyne with MeI followed by hydrozirconation and Zr-I exchange introduced E-vinyl iodide regio- and stereoselectively. Oxidative removal of MPM protecting group released the C20hydroxyl group and afforded **1.131**. Yamaguchi macrolactonization coupled acid **1.130** and alcohol **1.131** together to furnish **1.141**, which was then subjected to desilylation and intramolecular Stille coupling to complete the synthesis of macrolide **1.129**.

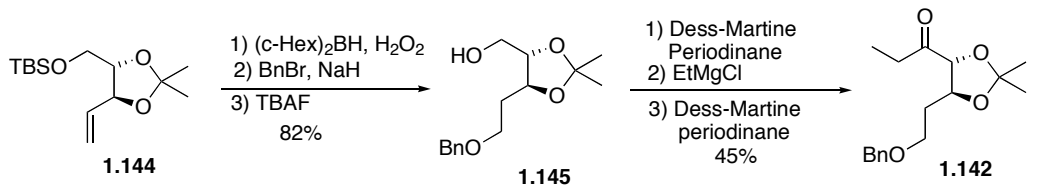
In 2004 Toshima's group reported their synthesis of fragment C12-C28 of apoptolidin featuring a tin (II) mediated highly diastereoselective aldol reaction.[16] This

Scheme 1.25 Toshima's retrosynthesis of fragment C12-C28 **1.141**



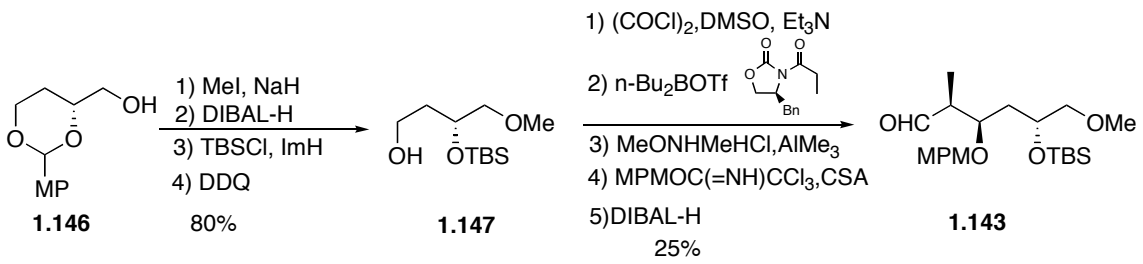
aldol approach led to the disconnection between C22 and C23 to reveal key building blocks ethyl ketone **1.142** and aldehyde **1.143** (Scheme 1.25).

Scheme 1.26 Toshima's synthesis of ethyl ketone **1.142**



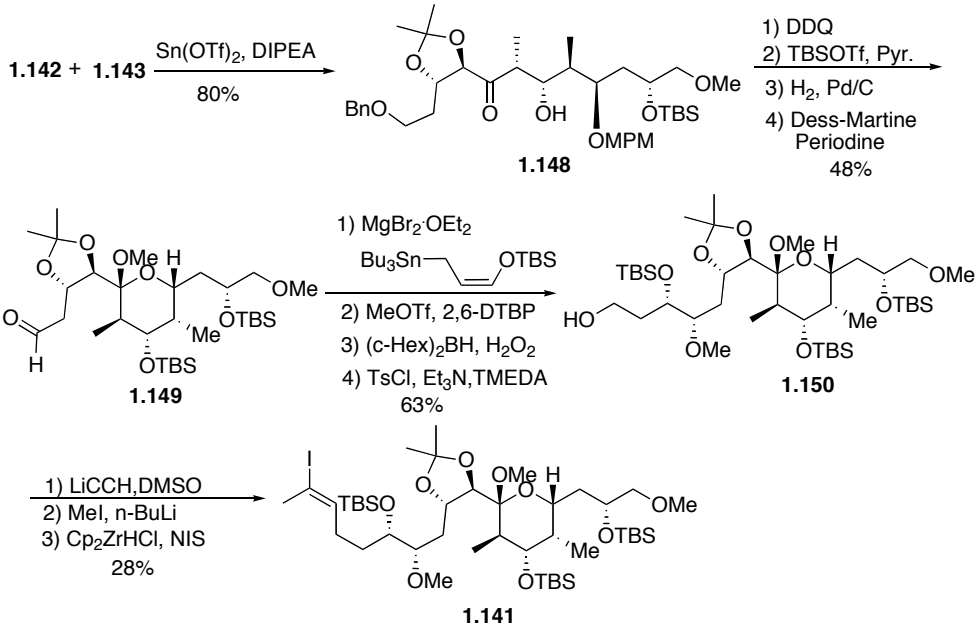
The preparation of ethyl ketone **1.142** commenced on dimethyl acetonide **1.144**, which was prepared from diethyl L-tartrate (Scheme 1.26). Hydroboration of the terminal, benzylation of the corresponding alcohol and disylation afforded **1.145**. The ethyl ketone **1.142** was obtained through Dess-martin oxidation, ethyl Grignard addition and reoxidation.

Scheme 1.27 Toshima's synthesis of aldehyde **1.143**



The construction of aldehyde **1.143** began with paramethoxybenzylidene acetal **1.146**, which was readily available from D-malic acid (Scheme 1.27). Methylation of the primary alcohol with MeI introduced C28 methyl ether. DIBAL-H reduction of the acetal released secondary alcohol, which was protected as a TBS ether. Finally oxidative debenzylation with DDQ afforded alcohol **1.147**. Swern oxidation followed by Evan's asymmetric aldol reaction set up the stereocenter at C24 and C25. Auxiliary was then replaced by Weinreb amide and free hydroxyl group resulting from aldol reaction was protected as PMB ether. At last the aldehyde **1.143** was obtained through reduction of Weinreb amide with DIBAL-H.

Scheme 1.28 Toshima's completion of fragment C12-C28 **1.141**

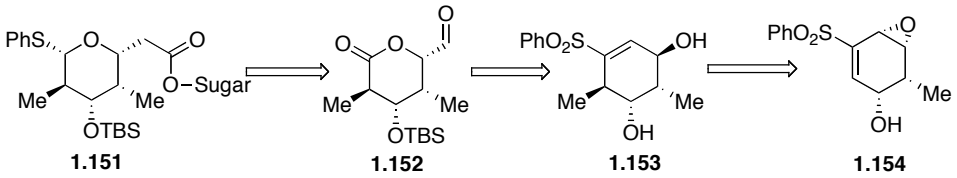


With fragment **A143** and **A144** in hand, they then exploited the aldol reaction. After several different Lewis acid-base combinations were screened, they found that

$Sn(OTf)_2$ with Hunig's base provided the best result to afford the *anti*-Feilkin-Anh product (Scheme 1.28). The aldol adduct **A149** was exposed to DDQ to remove the PMB ether and the resulting alcohol simultaneously cyclized to form pyranose, which was in turn protected as TBS silyl ether. Hydrogenolysis of benzyl ether followed by Dess-Martin oxidation afforded aldehyde **A150**. To introduce the C16 and c17 syn-diol, they adopted the same strategy as applied in their synthesis of C1-C21 macrolide that utilized $MgBr_2$ mediated crotylation. The newly formed allylic alcohol was methylated and the terminal alkene was subject to hydroboration-oxidation to furnish the primary alcohol, which was subsequently tosylated to give **A151**. Then the tosylate was replaced by lithium anion of acetylene. Methylation of the terminal alkyne, hydrozirconation and Zr-I exchange afforded *E*-vinyl iodide **A142**.

1.4.5 Fuchs' synthesis of C21-C26 fragment of apoptolidin

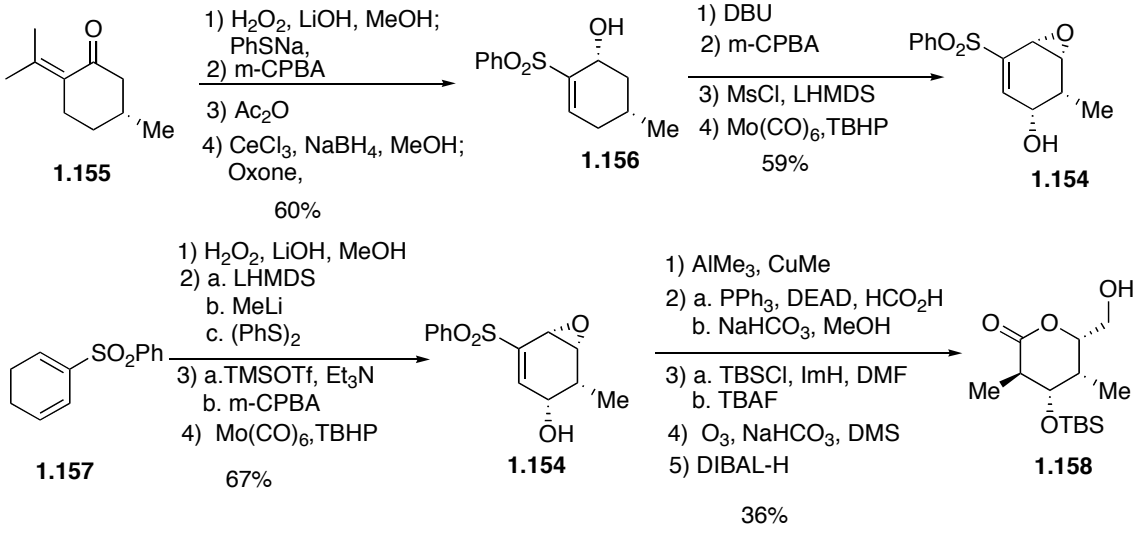
Scheme 1.29 Fuchs' retrosyntesis of C21-C26 pyranose **1.151**



In 2002 Fuchs group at Purdue University disclosed an approach to synthesis C21-C26 fragment of apoptolidin via an alkylative oxidation strategy.[17] The C21-C26 pyranose **1.151** could be obtained from epoixde **1.154** as shown in Scheme 1.29.

Fuch's synthesis started from *R*-pulegone **A156**. Basic epoxidation of **A156** followed by treatment of sodium thiophenoxide provided α-ketosulfide, which was in turn oxidized to the corresponding sulfoxide (Scheme 1.30). Pummerer elimination introduced the vinyl sulfide, which was subjected to Luche reduction and oxone oxidation to provided vinyl sulfone **1.156**. Double bond isomerization with DBU, epoxidation with m-CPBA followed by sequential treatment of MsCl and LHMDS afforded **1.154**. Considering the inefficiency of the synthesis, an alternative route was developed that began with dienyl sulfone **1.157**. Basic epoxidation followed by addition of LHMDS, MeLi, $(PhS)_2$ and TMSOTf sequentially generated a dienyl sulfide compound, which was finally treated with $Mo(CO)_6$ to afforded **1.154** in three operations.

Scheme 1.30 Fuchs's synthesis of C21-C26 fragment



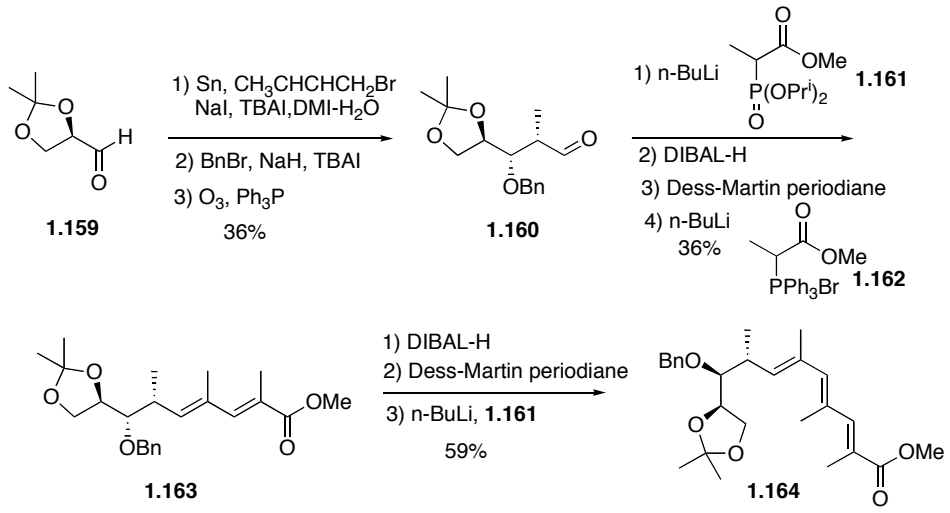
Comparing the initial study, the second approach is much shorter and more efficient. Treatment of epoxide **1.154** with trimethyl aluminum introduced the methyl group in a 1,4-addition mode. Mitsunobu reaction reversed the stereocenter at C25. Silylation of

the diol followed by selectively removing the less hindered C25 protecting group introduced the TBS silyl ether at C23. Finally, ozonolysis gave aldehyde, which was reduced to alcohol **1.158** for the storage purpose.

1.4.6 Loh's synthesis of C1-C11 fragment

In 2003 Loh reported a synthesis of fragment C1-C11 based on a strategy that introduced stereocenter at C8 and C9 diastereoselectively with Tin mediated allylation.[18] Their synthesis started from aldehyde **1.159**, which was readily available from D-mannitol (Scheme 1.31). A non chelation-controlled allylation give the *anti* relationship at the newly formed C-C bond, which was the required stereochemistry at C9. Hence,

Scheme 1.31 Loh's synthesis of C1-C11 fragment **1.164**



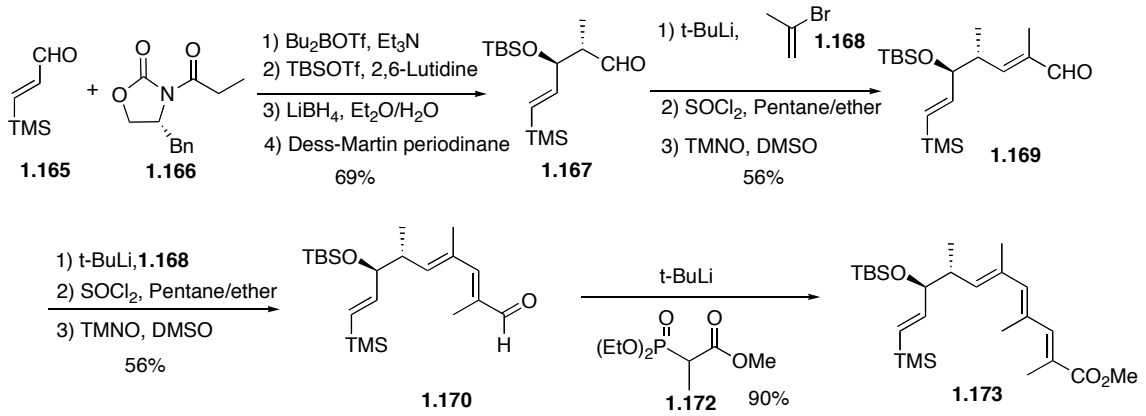
allylation of **1.159**, benzylation of the newly formed hydroxyl group followed by oxidative cleavage of the terminal alkene provided aldehyde **1.160**. The trienoate moiety was constructed by three sequential Wittig type olefination. As a result, Horner-

Wadsworth-Emmons reaction with **1.161**, DIBAL-H reduction of the resulting methyl ester and oxidation of the corresponding alcohol followed by another Wittig olefination with **1.162** generated diene **1.163**. Finally, another three-step sequence including reduction, oxidation, and HWE reaction completed the synthesis of C1-C11 fragment and provided methyl trienoate **1.164**.

1.4.7 Taylor's synthesis of fragment C1-C11 1.173

In 2004 Taylor at Norte Dame University disclosed a new route to prepare C1-C11 trienoate based on an iterative thionyl chloride rearrangement/oxidation strategy.[19]

Scheme 1.32 Taylor's synthesis of trienoate **1.173**

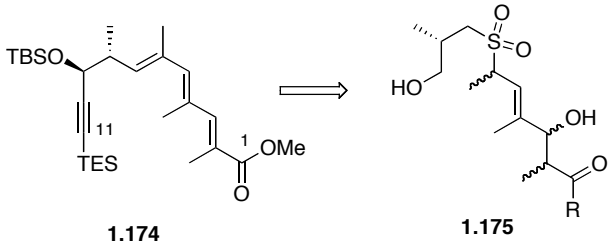


His synthesis began with Evans asymmetric aldol reaction with aldehyde **1.165** and auxiliary **1.166** (Scheme 1.32). Silylation of the aldol adduct followed by reductive removal of auxiliary and oxidation of the resulting alcohol provided aldehyde **1.167**. Addition of the vinyllithium reagent generated from 2-bromopropene afforded the secondary allylic alcohol. Thionyl chloride allylic rearrangement developed by Young in

the 1950s is a known method that can convert secondary allylic alcohols to their isomeric primary allylic chlorides strereospecifically. Hence, applying this methodology, the secondary allylic alcohol obtained from vinyllithium addition was treated with thionyl chloride and generated desired primary allylic chloride, which was subsequently oxidized to aldehyde **1.169** via Ganem oxidation. A second same three-step reaction sequence delivered aldehyde **1.170**. Finally, a Horner-Wadsworth-Emmons reaction with phosphonate **1.172** completed the synthesis of methyl trienoate **1.173**.

1.4.8 Vogel's synthesis of C1-C11 fragment 1.174

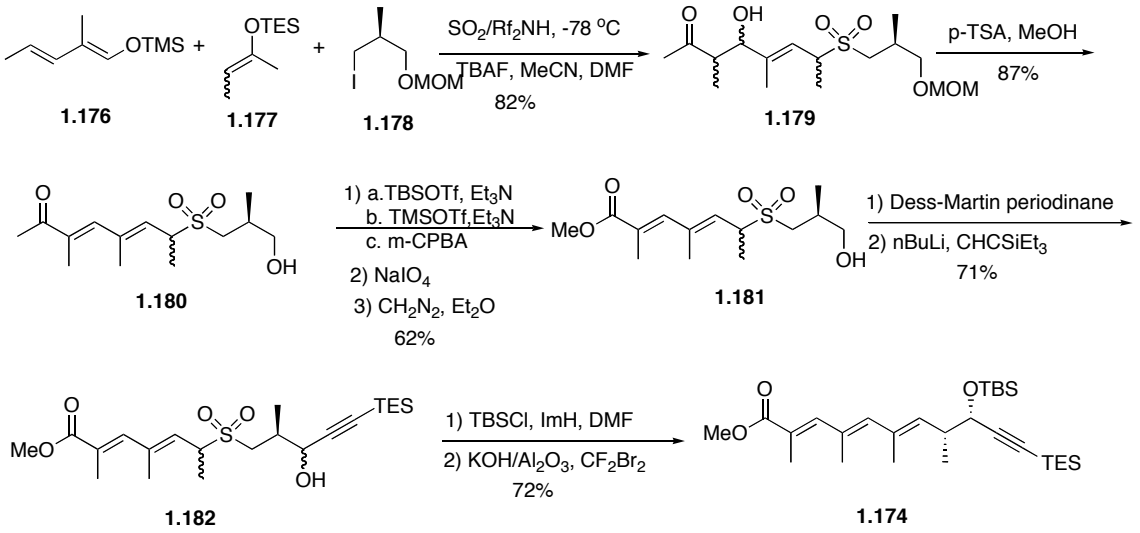
Scheme 1.33 Vogel's retrosynthesis of C1-C11 fragment



In 2005 Vogel at Switzerland disclosed a sulfur dioxide based approach to make C11-C12 fragment.[20] They envisioned that the trienoate moiety could be built up by the methodology that is sulfur dioxided mediated one pot, four-component synthesis of polyfunctional ε-alkanesulfonyl-γ,δ-unsaturated ketones developed by this group. This strategy revealed intermediate **1.175** as key building block, which can be converted to **1.174** via dehydration and Ramberg-Backlund reaction (Scheme 1.33).

Exposure of the diene **1.176** to SO_2 in the presence of Lewis acid generated Diels-Alder type adduct, which was then sequentially subjected to aldol reaction with silyl enol ether **1.177**, desilsylation and sulfone alkylation with **1.178** to provide stereomixture of **1.179** (Scheme 1.34). Acidic dehydration introduced C2-C3 double bond. The methyl ester **1.181** was obtained via oxidative cleavage of the α-hydroxyl ketone, which was generated by Silylation of the primary alcohol and Rubottom oxidation, followed by esterification of the corresponding carboxylic acid. Dess-Martin oxidation of the primary

Scheme 1.34 Vogel's synthesis of C1-C11 fragment **1.174**

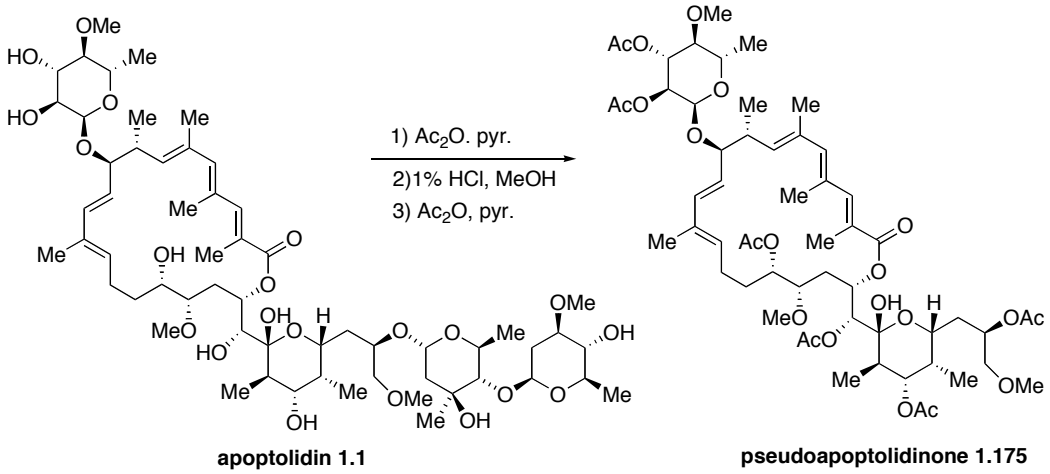


alcohol followed by lithium anion addition of the TES protected acetylene afforded **1.182**. After silylation of the secondary hydroxyl group resulting from the acetylene addition, under Chan's condition, Ramberg-Backlund reaction provided fragment **1.174** stereospecifically by losing SO_2.

1.5 Sulikowski's previous studies towards the total synthesis of apoptolidin

Our group's efforts towards a total synthesis of apoptolidin started in 1998. As described earlier, apoptolidin has a propensity to isomerize to iso-apoptolidin. To avoid this instability, we selected pseudoapoptolidinone **1.175** as our first synthetic target, a stable derivative of apoptolidinone and good candidate for chemical correlation with synthetic material. The preparation of pseudoapoptolidinone from apoptolidin is shown

Scheme 1.35 Sulikowksi's preparation of pseudoapoptolidinone **1.175**

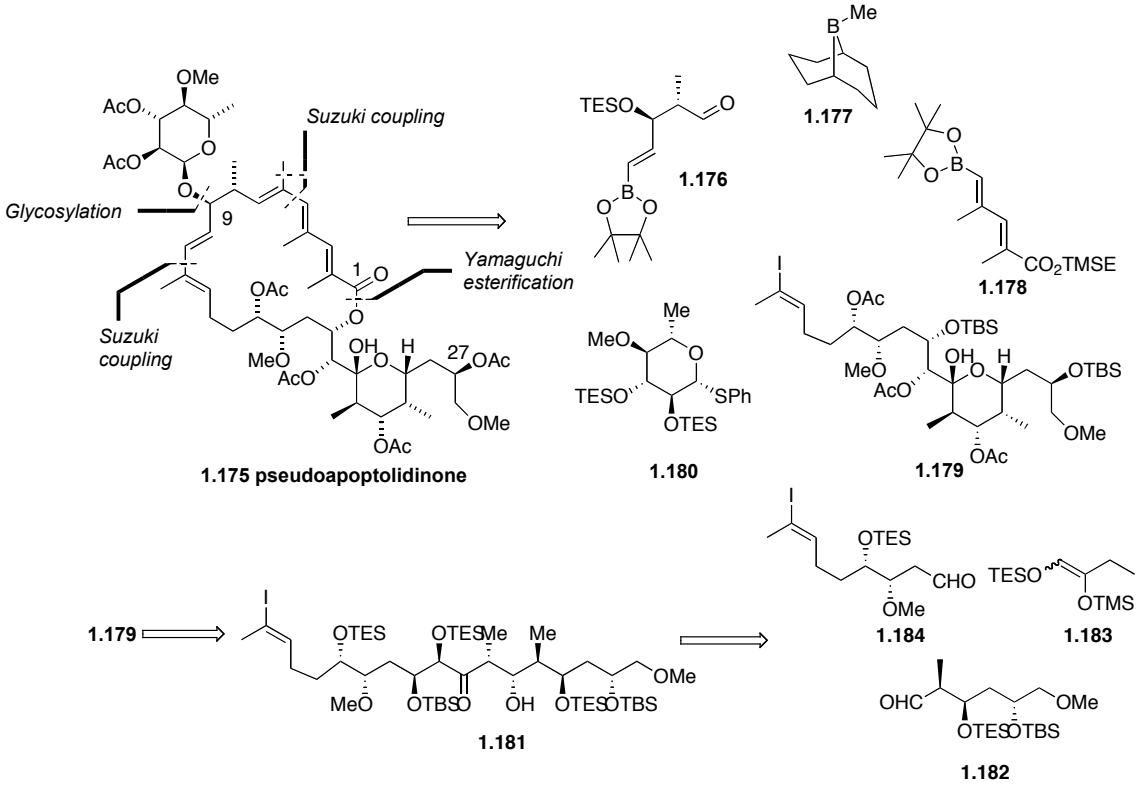


in Scheme 1.35. Acylation of the free hydroxyl groups afforded apoptolidin hexacetate,which was then subjected to selective methanolysis under acidic condition to remove the bottom disaccharide.[5a] At last acylation again to protect the C27 hydroxyl group resulting from hydrolysis to give **1.175**.

Retrosynthetically, we disconnected the C9 sugar bond first, which was going to be attached at proper time by chemical glycosylation (Scheme 1.36). The 20-membered macrolactone was disconnected into three major fragments (**1.176**, **1.178** and **1.179**),

which were going to be assembled together via three Suzuki couplings and Yamaguchi macrolactonization. The pyranose **1.179** was derived from**1.181**. Further disconnection of **1.181** at C19-C20 bond and C22-C23 bond revealed aldehyde **1.182**, **1.184** and silyl enol ether **1.183** as key building blocks. In a forward synthesis sense, a diastereoselective Mukaiyama aldol reaction and a lithium enolated mediated diastereoselective aldol reaction was going to assemble fragment **1.182**, **1.183** and **1.184** together and established the required stereochemistry.

Scheme 1.36 Sulikowski's retrosynthesis pseudoapoptolidinone **1.175**

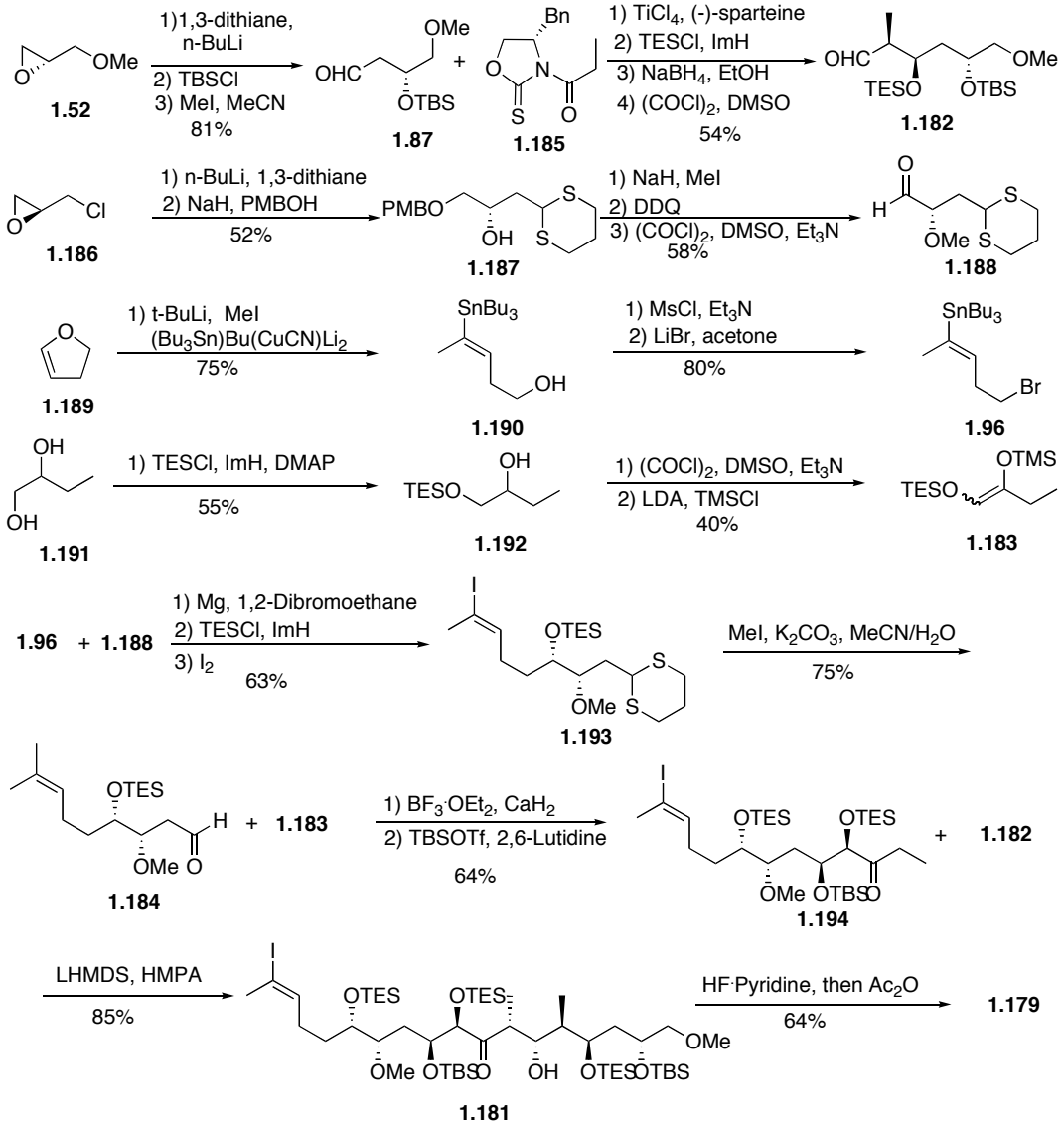


1.5.1 Sulikowski's synthesis of C12-C28 fragment: 1.179

Our synthesis of C12-C28 fragment commenced with synthesis of aldehyde**1.182** (Scheme 1.37). Exposure of the epoxide **1.52** to lithium anion of 1,3-dithiane followed

by silylation of the resulting secondary alcohol with TBS generated dithiane compound, which was in turn hydrolyzed to adehyde **1.87** with MeI. A Crimmins *syn* aldol with chiral auxiliary **1.185** established the C24-C25 stereocenter. The aldol adduct was converted into aldehdye **1.182** via a three-step sequence involving silyation of the hydroxyl group resulting from aldol reaction, reductive cleavage of the auxiliary and

Scheme 1.37 Sulikowski's secondary generation synthesis of C12-C28 fragment **1.179**



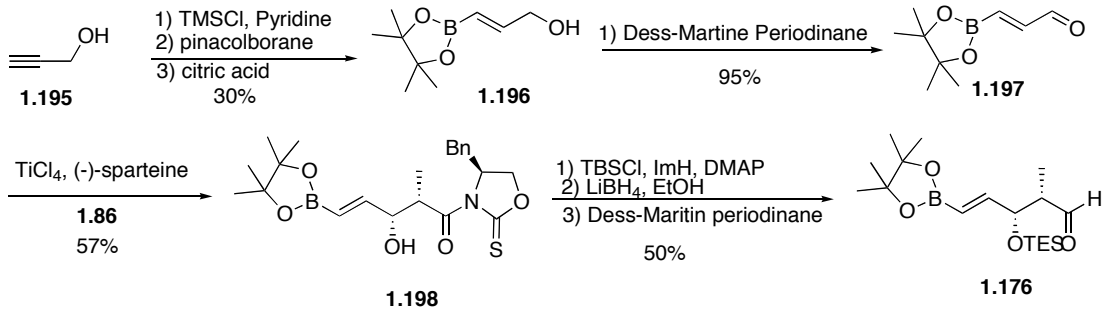
Swern oxidation of the corresponding primary alcohol. The preparation of aldehyde **1.184** began with epichlorohydrin **1.186**, which was subjected to epoxide opening with 1,3-dithiane followed by PMBOH opening of resulting epoxide to afford alcohol **1.187**. Methylation of the remaining secondary alcohol, oxidative removal of the PMB ether with DDQ and Swern oxidation of the corresponding primary alcohol provided aldehyde **1.188**. Here we adopted Ulrich Koert's strategy to establish the C16-C17 *syn* diol type stereochemistry via a chelating controlled Grignard addition. To that end, we prepared vinyl tin **1.96** based on Koert's procedure. Following Kocienski's procedure, 1,2-dihydrofuran **1.189** was converted to alcohol **1.190**, which was then transformed to bromide **1.96** via a standard two-step Finkelstein reaction sequence. With both bromide **1.96** and aldehyde **1.188** in hand, we then coupled them together via a chelation-controlled mode to afford a *syn* diol type product in a single isomer, which was in turn silylated and exposed to iodine to provide vinyl iodide **1.193**. Careful hydrolysis of dithiane gave aldehyde **1.184**. We then reached to the point to explore the Mukaiyama aldol reaction, which called for silyl enol ether **1.183** as a reaction partner. **1.183** was prepared from 1,2-butanediol **1.191**, which was first selectively silylated in the primary alcohol and afforded secondary alcohol **1.192**. Swern oxidation converted alcohol to ketone, which was then enolated with LDA and quenched with TMSCl to provide silyl enol ether **1.183**. Lewis acid $BF_3{\cdot}OEt_2$ promoted diastereoselective Mukaiyama aldol reaction furnished 4:1 mixture of two diastereomers, which could be separated in the later stage by normal flash chromatography or HPLC. TBS protection of the newly formed hydroxyl group generated ethyl ketone **1.194**. Then a double diastereoselective lithium enalote mediated aldol reaction proceeded smoothly to afford ketone **1.181** as a sole

isomer to establish C24-C25 stereocenter. Finally, global deprotection with HF·pyr completed the synthesis of C12-C28 fragment **1.179**.

1.5.2 Sulikowski's synthesis of fragments 1.176 and 1.178

Our preparation of aldehyde **1.176** began with propargyl alcohol **1.195**, which was first protected as TMS silyl ether (Scheme 1.38).[22, 23] Hydroboration followed by acidic desilylation using Vaultier's procedure provided allylic alcohol **1.196** in 30% yield stereo- and regioselectively. Dess-Martin oxidation of alcohol afforded aldehyde **1.197,** which then underwent Crimmins asymmetric aldol reaction to provide **1.198** with Evans *syn* stereoselectivity. Silylation of the aldol adduct with TBSCl, reductive removal of the auxiliary and Dess-martin oxidation gave aldehyde **1.176** in 50% yield over 3 steps.

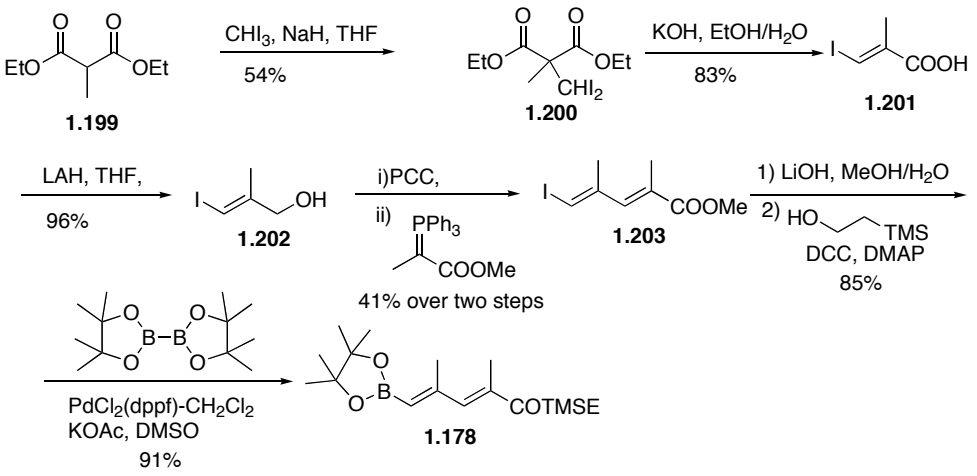
Scheme 1.38 Sulikowski's synthesis of aldehyde **1.176**



The synthesis of dienoate boronate **1.178** commenced on 2-methyl diethyl malonate **1.199** (Scheme 1.39). Alkylation with iodoform afforded **1.200**, which was subjected to decarboxylation and hydrolysis to give acid **1.201**. Reduction of acid furnished allylic alcohol **1.202**, which was subsequently oxidized and exposed to Wittig reaction to provide methyl ester **1.203**. Then the methyl ester was replaced by

trimethylsilylethyl ester, which was coupled with bis(pinacolato)diborane to give dienoate boronate **1.178**.

Scheme 1.39 Sulikowksi's synthesis of dienoate boronate **1.178**

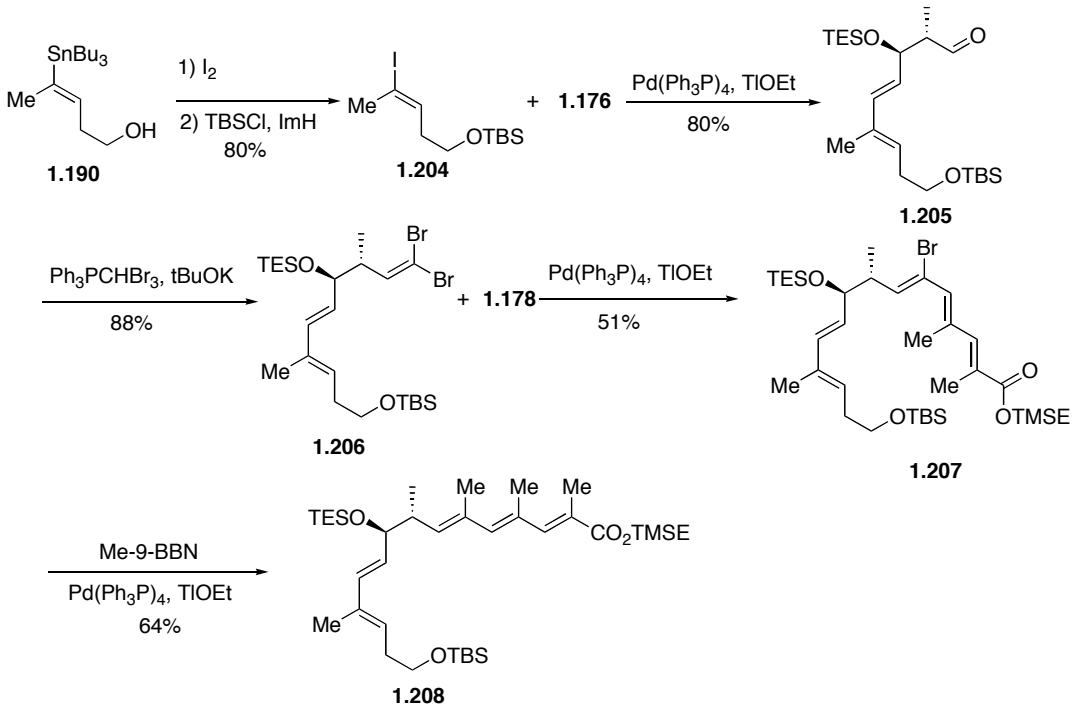


1.5.3 Sulikowski's model study of sequential Suzuki coupling

As designed, our end game strategy called for a sequential Suzuki coupling reaction to assemble those key building blocks together (Scheme 1.40). To explore this approach, we did a model study with a simplified lower vinyl iodide part **1.190**, which was an intermediate during the synthesis of vinyl tin **1.96**. Iodine-tin exchange followed by protection of the primary alcohol with TBS silyl ether afforded vinyl iodide **1.204**. With Roush modified Suzuki coupling condition, **1.204** coupled with vinyl boronate **1.176** smoothly to provided aldehyde **1.205**, which was then converted to vinyl dibromide **1.206**. The second Suzuki coupling attached vinyl boronate **1.178** to **1.206** strereoselectively to afford polyene **1.207**. Finally the third Suzuki coupling was carried out to methylate the C6 bromide with Me-9-BBN and furnished the desired trienoate

1.208. The sequential Suzuki coupling strategy with simple substrate proved to be successful.

Scheme 1.40 Sulikowski's model study of sequential Suzuki coupling

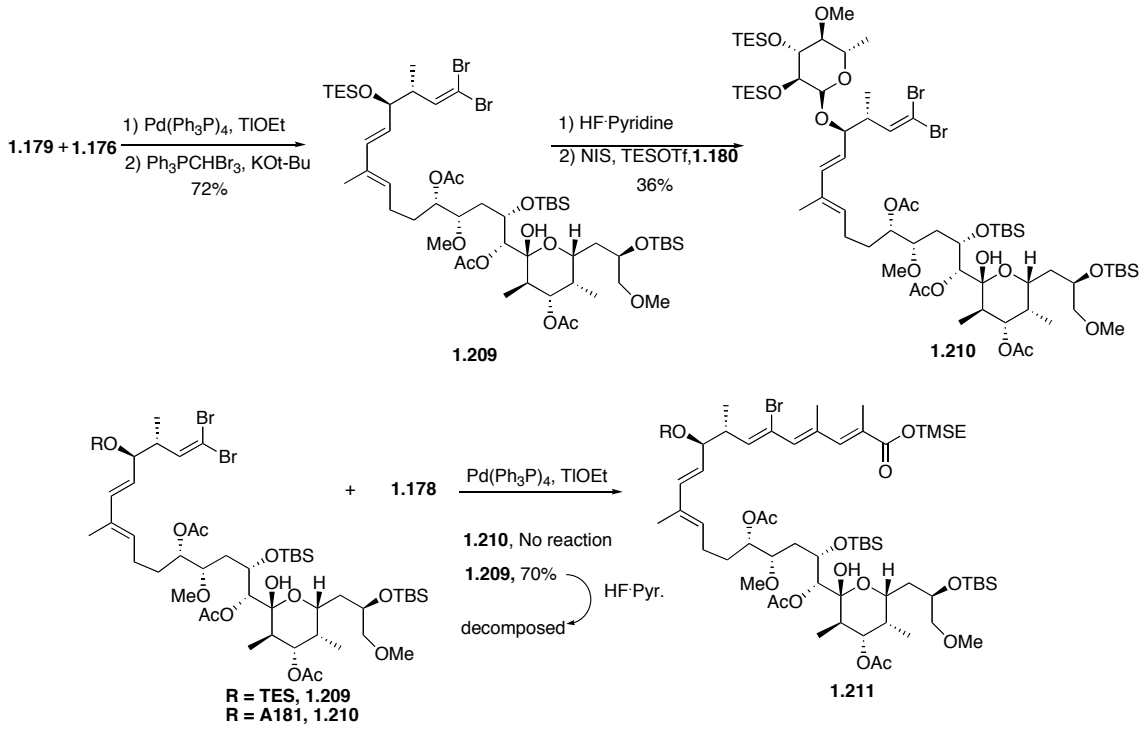


1.5.4 Sulikowski's studies toward first generation total synthesis of pseudoapoptolidinone

The model study described above indicated that the sequential Suzuki coupling approach might be effective in our total synthesis of pseudoapoptolidinone. At this point, we carried out the first Suzuki coupling between vinyl iodide **1.179** and vinyl boronate **1.176** and successfully obtained the coupling adduct, which was homologated to 1,1-geminal dibromide **1.209** in 72% yield over 2 steps (Scheme 1.41). After removal of C9 TES protecting group, glycosylation with sugar unit **1.180** upon activation with NIS and TESOTf afforded **1.210**. However, all attempts of the second Suzuki coupling between

vinyl boronate **1.178** and vinyl bromide**1.210** failed. We envisioned that the sugar in the C9 position might increase the steric effect. Therefore, a Suzuki coupling was carried out between **1.209** and **1.178** and the reaction proceeded smoothly to afford the coupled product **1.211**. However, all efforts to remove the C9 silyl protection group failed, probably due to the instability of the trienoate moiety. This failure led to our secondary generation total synthesis of apoptolidinone, which is going to be described in the next chapter.

Scheme 1.41 Sulikowski's studies towards completion synthesis of pseudoapoptolidinone **1.175**



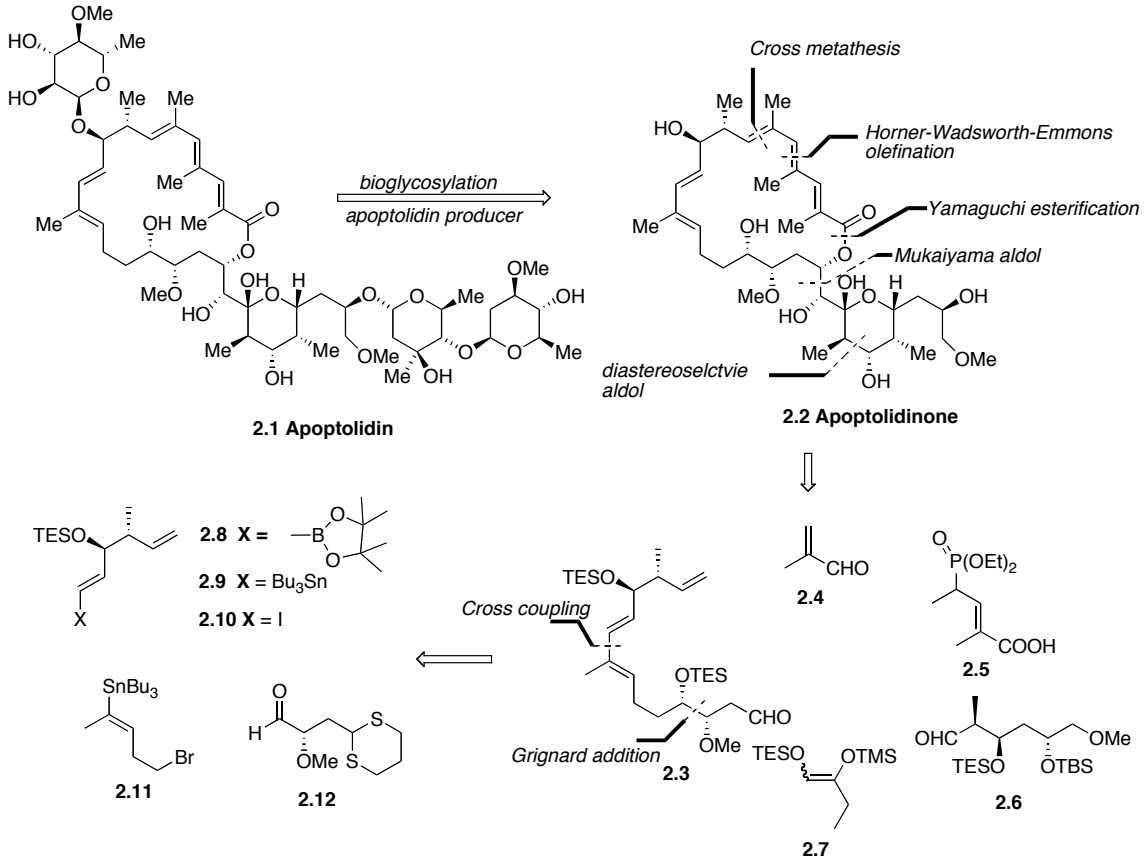
CHAPTER II

LARGE SCALE TOTAL SYNTHESIS OF APOPTOLIDINONE

2.1 Studies towards total synthesis of apoptolidinone: Horner-Wadsworth-Emmons approach

As described in the last chapter, the failed synthesis of pseudoapoptolidinone led us to reconsider our synthetic strategy directed toward apoptolidin itself. Based on the observation by K. C. Nicolaou and Ulrich Koert during their total synthesis of apoptolidin and our group's efforts to identify the isomerization product of apoptolidin, we realized that chemical glycosylation to attach the two sugar units would be

Scheme 2.1 Retrosynthetic analysis of apoptolidinone **2.2**



challenging. Therefore, biological glycosylation was considered, which would utilize glycosyltransferase *in vivo*.[23] This strategy revealed apoptolidinone **2.2** as our primary synthetic target. In contrast to our previous sequential Suzuki coupling approach, intramolecular Horner-Wadsworth-Emmons olefination, cross metathesis and Suzuki coupling reactions would serve as key transformations in the construction of the 20-membered macrolactone ring (Scheme 2.1). As before, C12-C28 was synthesized via our previous strategy, which featured a diastereoselective Mukaiyama aldol reaction and a lithium enolate mediated double diastereoselective aldol reaction.[21] These disconnections led to key intermediates aldehyde **2.3**, methacrolein **2.4**, phosphonate **2.5**, aldehyde **2.6** and silyl enol ether **2.7**. Fragment **2.6** and **2.7** were prepared following the procedure described in Chapter I. Further disconnection of fragment **2.3** called for a Suzuki coupling reaction and a Grignard addition reaction as key transformations. The *syn*-diol type stereochemistry at C16–C17 position was envisioned to be established via Grignard mediated addition of bromide **2.11** to aldehyde **2.12** in a chelation controlled fashion.[11] A palladium mediated cross coupling, either a Suzuki coupling[24] or a Stille coupling[25], would establish the C11-C12 bond employing building blocks **2.8**-**2.10**, which varies in the terminal groups.

2.2 A new approach to prepare aldehyde 2.12

The initial synthesis of fragment **2.12** began with (*S*)-epichlorohydrin **1.186**, which is very expensive. Therefore, a more practical method was required to enable the synthesis scalable. Hence, inexpensive (*S*)-malic acid **2.13** was considered as an alternative starting material. Fisher esterification of **2.13** provided dimethyl ester **2.14** in

85% yield (Scheme 2.2). β-hydroxy lactone **2.15** was obtained by $NaBH_4$ catalyzed broane regioselective reduction of dimethyl ester **2.14**[26a], which was followed by *in situ* acid mediated cyclization via the 1,2-diol intermediate.[26b] Next, an efficient methylation method was required to introduce the C17 methyl ether. Concerns here include

Scheme 2.2 New approach to aldehyde **2.12**

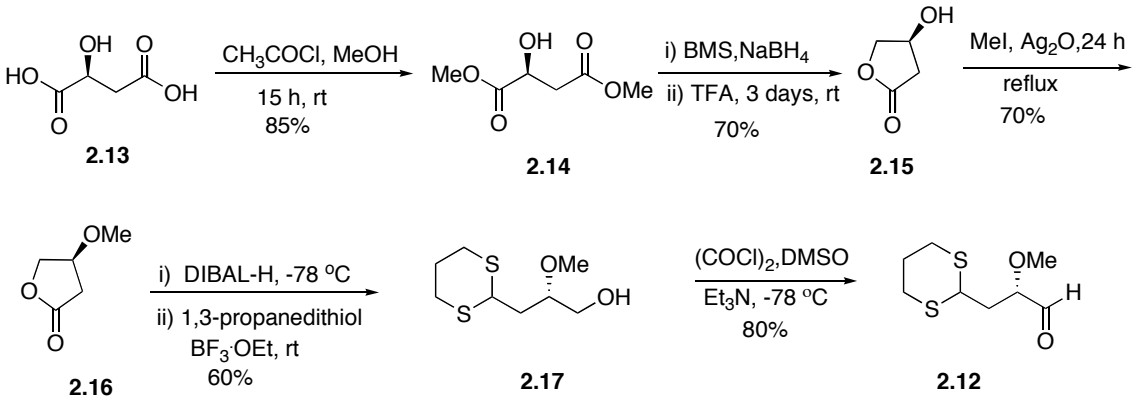


Table 2.1 Exploring methylation of **2.15**

Entry	Reaction Conditions	**2.16**
1	NaH (1.5 equiv), MeI (2 equiv), THF, 0°C-rt, 12h	Decomposed
2	NaH (1 equiv), MeI (1.5 equiv), THF, 0°C-rt, 5h	Decomposed
3	$Me_3O^+BF_4^-$, CH_2Cl_2, rt, 5h	No reaction
4	MeI (8 equiv), Ag_2O (1.1 equiv), CH_3CN, 80°C, 12h	17%
5	MeI (8 equiv), Ag_2O (1.1 equiv), CH_3CN, 40°C, 12h	34%
6	MeI (neat), Ag_2O (1.0 equiv), 40 °C, 12h	70%

potential for competing α-methylation of the lactone and competing beta elimination of

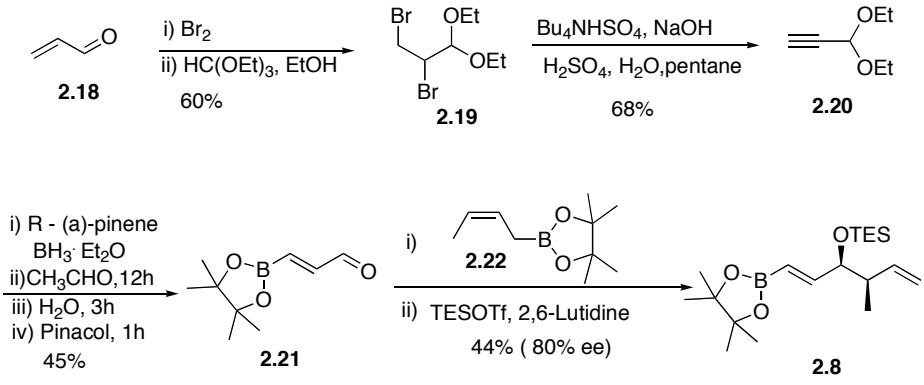
hydroxyl group. Initially, traditional basic conditions employing excess NaH and MeI were attempted (Table 2.1, Entry 1). Unfortunately, the reaction led to decomposition. Therefore, exactly one equivalent of base was used and the reaction was conducted at room temperature for 5 h instead of 12 h (Entry 2). However, again no product was obtained. Then our attention was turned to acidic conditions. Unfortunately, exposure of **2.15** to Meerwein's salt for 5 h at room temperature yielded only starting material (Entry 3). Therefore, mild neutral conditions were considered. Treatment of **2.15** with MeI and Ag_2O in refluxing acetonitrile at 80 °C for 12 h furnished 17% desired product (Entry 4).[27] It was suspected that the low yield might be due to the elevated reaction temperature, hence, the reaction was repeated and the temperature maintained at 40 °C. Under these conditions the yield improved (34%) with some starting material recovered (Entry 5).[28] To drive the reaction to completion, a neat reaction was examined, again maintaining a reaction temperature of 40 °C (Entry 6).[29] Under these conditions, a satisfactory yield (70%) was obtained. With methyl ether **2.16** in hand, the next goal was to prepare alcohol **2.17**. Reduction of lactone **2.16** with DIBAL-H followed by acetal formation with 1,3-propanedithiol afforded desired **2.17** in 60% yield over 2 steps.[30] Finally, Swern oxidation provided aldehyde **2.12** in 80% yield. In summary, this new approach started from inexpensive (*S*)-malic acid and furnished fragment **2.12** in 5 isolated steps with 20% overall yield. Later, we found that β-hydroxy lactone **2.15** was commerially available in kilogram quantities at a relatively low price (1 $/g, Louston International, Inc.). Thus our current approach to fragment **2.12** started from **2.15** instead of **2.13**.

2.3 Preparation of vinyl metal reagents 2.8, 2.9 and 2.10

2.3.1 Preparation of vinyl boronate 2.8

The synthesis of vinyl boronate **2.8** was based on a crotylation strategy. In the previous synthesis, aldehyde **2.21** was prepared from propargyl alcohol by hydroboration with pinacolborane. Long reaction time (4 days) and separation difficulty introduced by multiple stereoisomers from hydroboration prompted us to examine Hall's method for the preparation of **2.21**,[31] which started from propargyl aldehyde diethyl acetal **2.20**. The synthesis commenced with acrolein **2.18**, which was brominated and protected *in situ* as the diethyl acetal with triethyl orthoformate to provided dibormide **2.19** (Scheme 2.3).[32] Double elimination of dibromide afforded acetylene **2.20** in 68% yield. Then aldehyde

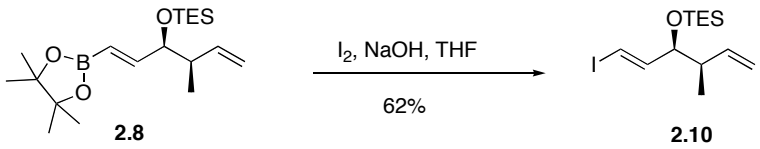
Scheme 2.3 Preparation of vinyl boronate **2.8**



2.21was obtained in 45% yield following Hall's procedure via stereo- and regioselective hydroboration, borane oxiation, boronate ester hydrolysis and pinacol boronate formation.[31] As planned, the stereogenic centers at C8 and C9 were installed using Roush's asymmetric crotylation reaction.[33] Under typical crotylation reaction conditions (3M NaOH for work up) no desired product was generated. It was envisioned that the

crotylation intermediate might not be stable enough to treatment with a 3M NaOH solution. Instead, 1 M NaOH was used in the hydrolysis process and analysis of the crude ^{1}HNMR showed the desired product was generated. However, after flash column chromatography purification, no product was obtained. This result indicated that the homoallylic alcohol resulting from crotylation was not stable in either strong basic conditions or weak acidic conditions. Finally, silylation of the resultant alcohol *in situ* with TESOTf led to isolation of the desired **2.8** in 44% yield over 2 steps without any apparent decomposition. Enantiomeric excess of **2.8** was determined to be 80% by chiral gas chromatography after converting vinyl boronate to vinyl iodide **2.10** (Scheme 2.4).[34] It was considered that Brown's asymmetric crotylation might improve the enantioselectivity of the addition process.[35] However, it was envisioned that 3M NaOH and H_2O_2 used in Brown's work up procedure might prove problematic due to the apparent instability of vinyl boronate under strongly basic condition.

Scheme 2.4 Synthesis of **2.10** from **2.8**



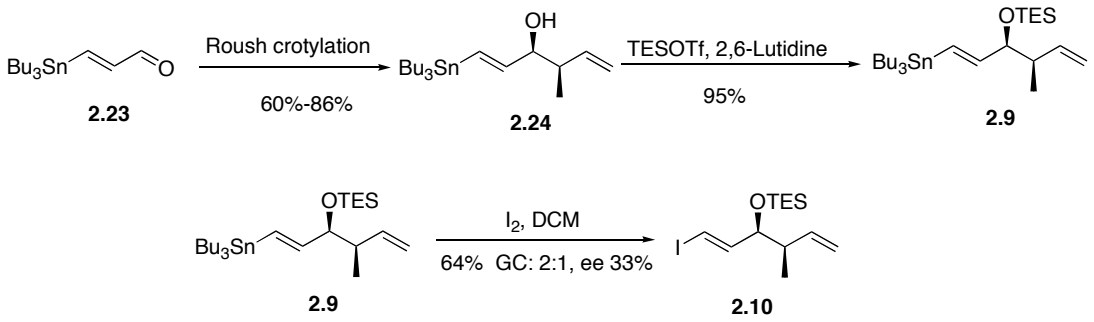
2.8 **2.10**

2.3.2 Preparation of vinyl tin 2.9

The synthesis of vinyl stannane **2.9** adopted the same strategy as the preparation of vinyl boronate **2.8**. The synthesis began with known aldehyde **2.23**, which was readily available from propargyl alcohol via hydrostannylation.[36] Under typical Roush

asymmetric crotylation condition, homoallylic alcohol **2.24** was afforded in 86% yield,

Scheme 2.5 Preparation of vinyl tin **2.9**



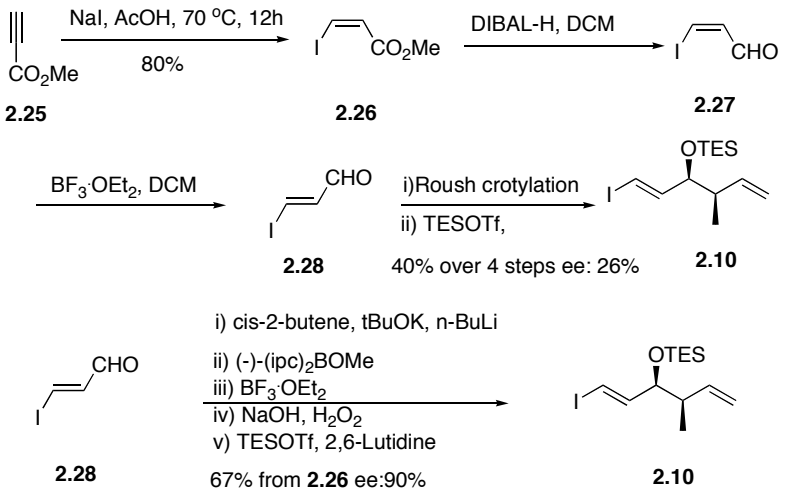
which was subsequently silylated to give **2.9** (Scheme 2.5). Again, the enantiometric excess of **2.9** was determined by chiral GC to be 33% after converting vinyl tin to vinyl iodide **2.10** via tin-iodine exchange. Although this route was more practical, the observed low enantioselectivity of the crotylation reaction rendered the procedure less useful.

2.3.3 Preparation of vinyl iodide 2.10

A new synthesis of vinyl iodide **2.10** was considered that still based on a crotylation strategy to establish the C8 and C9 stereogenic center. Starting from methyl propiolate **2.25**, hydroiodonaiton provided β-iodo methyl acrolate **2.26** in 80% yield (Scheme 2.6).[37] Carefully controlled DIBAL-H reduction of the methyl ester afforded aldehyde **2.27**, which in turn was subjected to isomerization in the presence of $BF_3{\cdot}OEt_2$ to generate *E* isomer of β-iodo acrolein **2.28** (*E:Z* = 10:1).[38] Neat aldehyde **2.28** underwent polymerization very quickly, therefore, after basic work up ($NaHCO_3$), **2.28**

was subjected to crotylation immediately in a solution of CH_2Cl_2 and protected from

Scheme 2.6 Preparation of vinyl iodide **2.10**



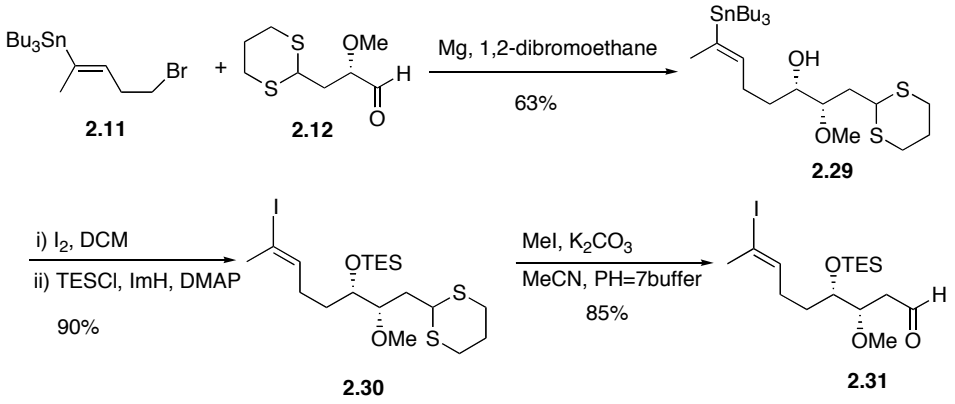
light. After silylated *in situ* with TESOTf, the desired vinyl iodide **2.10** was isolated in 40% yield over 4 steps from **2.26**. The enantiomeric excess was determined to be 26% by chiral GC. Brown's asymmetric crotylation provided a higher yield from **2.26** (67% over 4 steps) and high enantiomeric excess (90%).[38] Currently, 15 grams of **2.10** is produced using Brown's procedure.

2.4. Preparation of Suzuki coupling protocol 2.31

Triene aldehyde **2.3** was to be assembled using a standard Suzuki Cross coupling reaction and thus required vinyl iodide **2.31** as a reaction partner. Aldehyde **2.31** was prepared utilizing previously described chelation-controlled Grignard addition to establish the C16-C17 *syn* diol relationship.[21] Exposure of alkyl bromide **2.11** to magnesium metal in the presence of 1,2-diboromoethane followed by addition of

aldehyde **2.12** generated alcohol **2.29** in 63% yield as a sole isomer (Scheme 2.7). Our previous synthesis used 7 equivalents **2.11**. On larger scale (ca. 5 grams), we have successfully decreased **2.11** to 3 equivalents and maintained the high yield and

Scheme 2.7 Preparation of aldehyde **2.31**



diastereoselectivity. Iodine-tin exchange followed by *in situ* silylation of the secondary alcohol resulted vinyl iodide **2.30** in 90% yield over 2 steps. Hydrolysis of dithiane **2.30** with MeI and K_2CO_3 in the presence of pH=7 buffer was highly dependent on the reaction concentration.[39] After optimization, we determined a reaction concentration of 0.07 M at room temperature provided an 85% yield of aldehyde **2.31**.

2.5 Exploration of the cross coupling reaction to prepare aldehyde 2.3

2.5.1 Suzuki coupling between 2.31 and 2.8

Suzuki coupling between vinyl iodide **2.31** and vinyl boronate **2.8** proved challenging (Scheme 2.8 & Table 2.2). Under typical Roush modified Suzuki coupling reaction condition, which utilized TlOEt as base and $Pd(Ph_3P)_4$ as catalyst, both desired

product **2.3** and β-elimination product **2.32** were obtained (Entry1).[40] Presumably, this β-

Scheme 2.8 Suzuki coupling between **2.31**and **2.8**

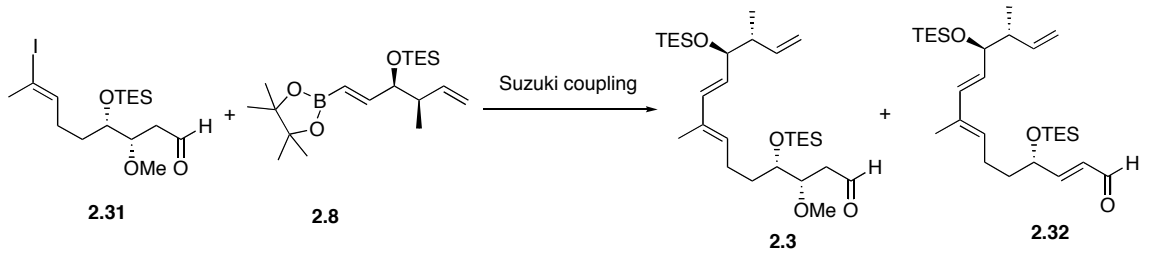


Table 2.2 Exploration of Suzuki coupling between 2.31 and 2.8

Entry	Reaction conditions	2.3	2.32	2.31
1	TlOEt(1.5 eq), $Pd(PPh_3)_4$, THF/H_2O(3:1),0.02 M, rt, 20 min,100 mg	44%	15%	0%
2	TlOEt(1.25 eq), $Pd(PPh_3)_4$, THF/H_2O(3:1),0.03 M, 0 °C, 40 min, 50 mg	89%	0%	0%
3	TlOEt(1.25 eq), $Pd(PPh_3)_4$, THF/H_2O(3:1),0.03 M, 0 °C, 2 h, 350 mg	36%	6%	28%
4	TlOEt(1.25 eq), $Pd(PPh_3)_4$, THF/H_2O(3:1),0.03 M, 0 °C for1.5 h then rt 5 min, 200 mg	45%	4%	20%
5	TlOEt(2.5 eq), $Pd(PPh_3)_4$, THF/H_2O(3:1),0.1 M, 0 °C for3 h then rt 10 min, 200 mg	25%	18%	16%
6	*TlOEt(1.25 eq), $Pd(PPh_3)_4$, THF/H_2O(3:1),0.02 M,rt, 15 min,200 mg-1g*	*82%*	0%	0%
7	Tl_2CO_3, $Pd(PPh_3)_4$, THF/H_2O(3:1), 0.02 M, rt, 1 h	37%	0%	0%
8	Tl_2CO_3, $Pd(PPh_3)_4$, THF, 0.02 M, rt, 1 h	0%	0%	100%
9	Tl_2CO_3, $Pd(PPh_3)_4$, THF/H_2O(3:1), 0.02 M, 0 °C, 2 h	19%	28%	0%
10	Tl_2CO_3, $Pd(PPh_3)_4$, THF/H_2O(3:1), 0.02 M, 10 °C, 1 h	30%	18%	0%
11	Tl_2CO_3, $Pd(PPh_3)_4$, THF, 0.02 M, 50 °C, 12 h	0%	0%	0%
12	Tl_2CO_3, $PdCl_2(dppf)_2{\cdot}CH_2Cl_2$, THF, 0.02 M, rt, 2 h	0%	0%	100%

Table 2.2 (continued)

Entry	Reaction conditions	2.3	2.32	2.31
13	Tl_2CO_3, $PdCl_2(dppf)_2$•CH_2Cl_2, THF/H_2O(3:1), 0.02 M, rt, 20 h	42%	0%	0%
14	Tl_2CO_3, $PdCl_2(dppf)_2$•CH_2Cl_2, THF/H_2O(3:1), 0.02 M, MW 50W, 5 min	0%	0%	100%
15	Tl_2CO_3, $PdCl_2(dppf)_2$•CH_2Cl_2, THF/H_2O(3:1), 0.02 M, 50 °C, 20 h	32%	0%	0%
16	TlOAc, $Pd(PPh_3)_4$,THF/H_2O(3:1), 0.02 M, rt,12 h	0%	0%	100%
17	KOAc, $PdCl_2(dppf)_2$•CH_2Cl_2, DMSO, 80 °C,2 h	0%	0%	0%

elimination was initiated by deprotonation of the acidic α-proton of the **2.3** aldehyde followed by elimination of β-methoxy group generating thermodynamically stable α,β-unsaturated aldehyde. To suppress this side reaction, the reaction was then conducted at lower temperature with a decreased amount of base. To our satisfaction the desired product was produced in 89% yield without the β-elimination byproduct (Entry 2). However, scaling up the reaction under the same condition resulted in incomplete coupling. Furthermore, extended reaction times resulted in β-elimination (Entry 3, 4). Attempts to increase the equivalents of base (1.25 equiv. – 2.5 equiv.) and reaction concentration (0.02 M – 0.1 M) provided the same result (Entry 5). Surprisingly, it was found that by decreasing the amount of base and lowering reaction concentration, good yield (87%) could be achieved by shortening the reaction time (less than 15 min). This condition worked well for reaction scales ranging from 200 mg to 1 g. This observation suggests that the coupling reaction occurs first and afterward the remaining base participates the elimination reaction. Tl_2CO_3 was also examined as a base. The advantage

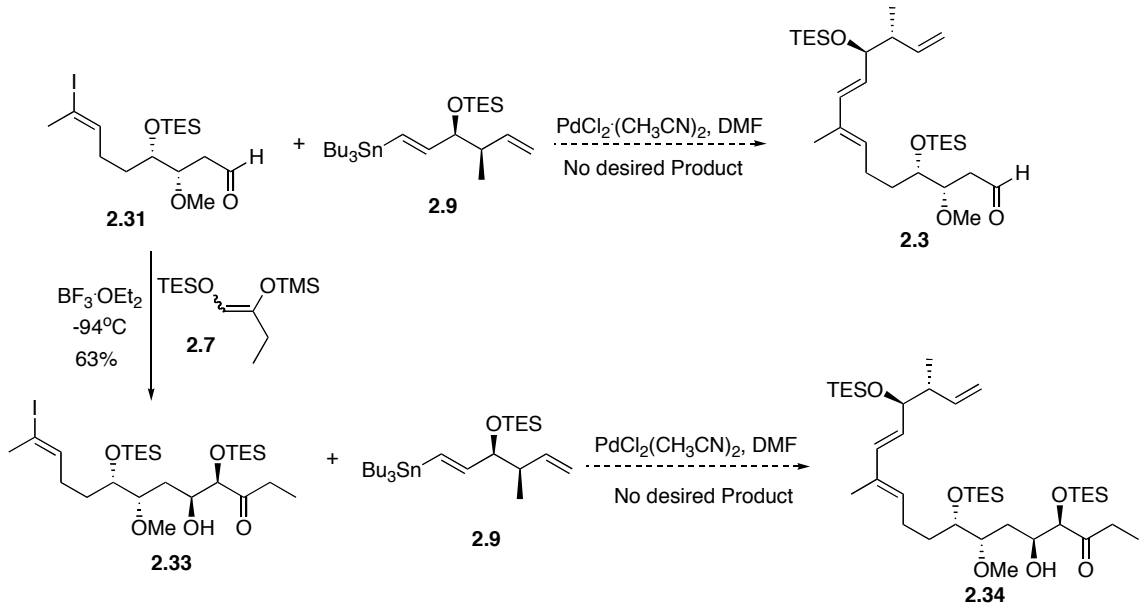
of Tl_2CO_3 over TlOEt is that this weaker base is soluable in organic solvents.[41] It was hoped that β-elimination side reaction could be avoided with weaker base. However, these conditions resulted in no reaction for these substrates either at room temperature or at elevated temperatures (Entry 8 and 11). In aqueous THF, the yield of **2.3** increased with increasing temperature (Entry 7, 9 and 10). Unfortunately, in these reactions, β-elimination could not be suppressed and the yield of the desired product was unacceptable. Screening Pd catalyst $Pd(Ph_3P)_4$ and $PdCl_2(dppf)_2{\cdot}CH_2Cl_2$ led to no reaction (Entry 12 and 14). Although it provided the desired product **2.3** without any byproduct in aqueous THF system at either room temperature or higher temperature, the low yield excluded these options (Entry 13 and 15). Microwave assisted reactions led to recovery of starting material (Entry 14). Changing base to TlOAc and using $Pd(Ph_3P)_4$ as catalyst in aqueous THF led to no reaction (Entry 16).[37] More harsh conditions, such as KOAc and $PdCl_2(dppf)_2{\cdot}CH_2Cl_2$ at 80 °C, resulted in decomposition of starting material.[24] In summary, entry 6 proved to be a mild and practical method to prepare large scale of fragment **2.3**.

2.5.2 Stille coupling between 2.31 and 2.9

In order to develop an efficient method to prepare fragment **2.3** we also explored Stille coupling reaction, which both Nicolaou and Koert applied in their total syntheses of apoptolidin. It was envisioned that Stille coupling would not require a base and β-elimination side reaction could be avoided. Under typical Stille condition $PdCl_2(dppf)_2{\cdot}(CH_3CN)_2$ as catalyst in DMF at room temperature no reaction was observed and starting material **2.31** was recovered (Scheme 2.9).[25] It was also reported that a free

alcohol in the molecule could be tolerated during Stille coupling and sometimes it facilitates the reaction. To examine the feasibility of this route, compound **2.33** was

Scheme 2.9 Stille coupling between **2.31** and **2.9**



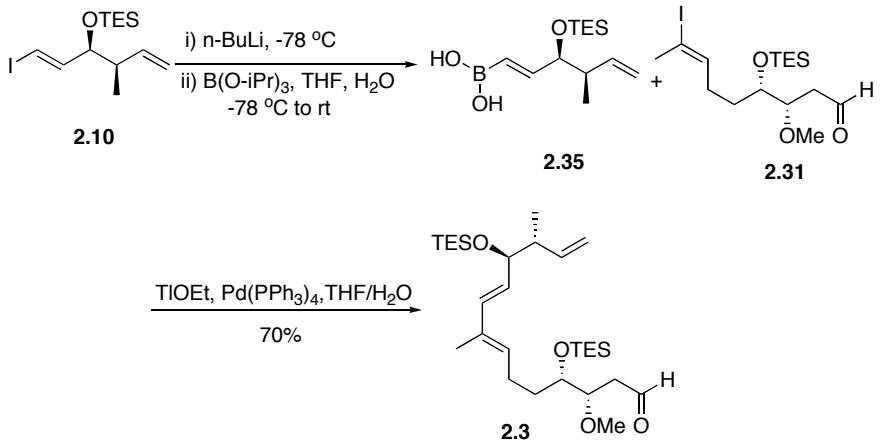
prepared via a diastereoselective Mukaiyama aldol reaction with silyl enol ether **2.7**. Unfortunately, Stille cross coupling did not take place on this substrate. One possible reason was that the trisubstituted olefin **2.31** or **2.33** was too hindered to react.

2.5.3 Suzuki coupling between 2.31 and 2.10

With aldehyde **2.31** and boronate ester **2.8** we had developed an efficient method to prepare fragment **2.3**. However, the low yield and enantioselectivity of reaction leading to **2.8** prevented scaling up of the synthesis. In order to make the synthesis more practical and suitable for large-scale synthesis, vinyl iodide **2.10** was prepared from methyl propiolate **2.25** in more than 50% yield over 5 steps as described above.

Converting vinyl iodide **2.10** to the vinyl boronic acid **2.35** was realized by lithium-

Scheme 2.10 Suzuki coupling between **2.31** and **2.10**



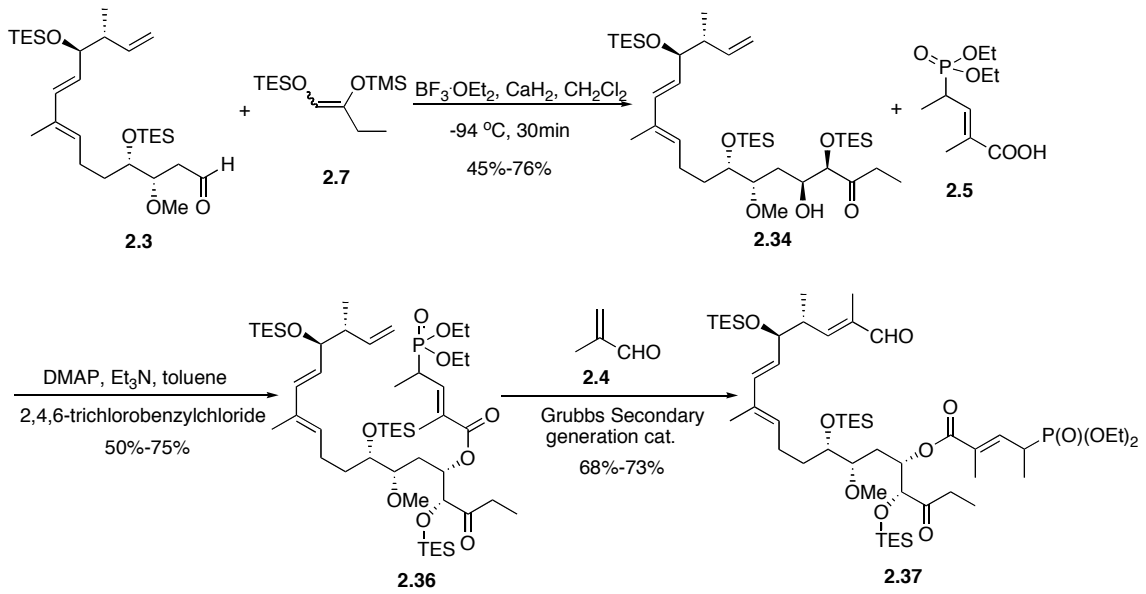
iodine exchange followed by *in situ* trapping with triisopropyl borate (Scheme 2.10).[42] Under Roush modified Suzuki coupling conditions, fragment **2.3** was generated in 70% yield on 100 mg to 1gram scale in 10 minutes without any β-elimination product observed. This observation supported our hypothesis that the β-elimination side reaction takes place after the Suzuki coupling. Therefore, the route starting from methyl propiolate **2.25** proved to be the most efficient approach to prepare aldehyde **2.3** on large scale.

2.6 End game strategy: exploring intramolecular Horner-Wadsworth-Emmons (HWE) reaction

In order to examine a unique approach to form the macrolactone of apoptolidin we planned to examine an intramolecular Horner-Wadsworth-Emmons reaction (HWE) that required preparation of phosphonate **2.37**. To this end, a second-generation synthesis

of C12-C28 fragment was adopted, which utilized diastereoselective Mukaiyama aldol reaction to establish the C16 and C17 stereocenters. Under the same conditions, $BF_3{\cdot}OEt_2$ mediated aldol reaction coupled aldehyde **2.3** and vinyl silyl enol ether **2.7** together and formed aldol adduct **2.34** in 45%-76% yield (dr: 5:1) (Scheme 2.11).[21] Acid **2.5**, which

Scheme 2.11 Preparation of fragment **2.37**

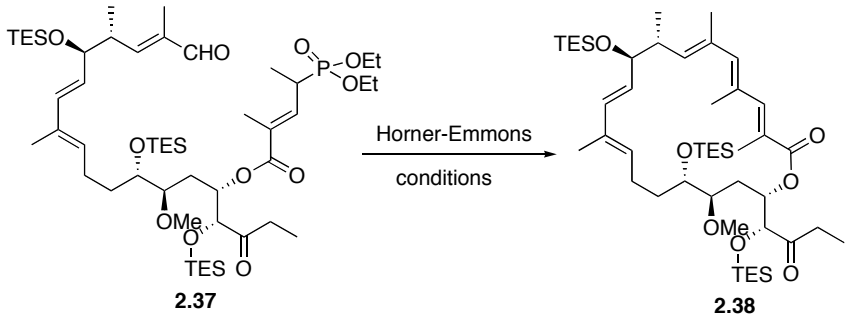


was prepared from methyl vinyl carbinol, was then attached to alcohol **2.34** by Yamaguchi esterification and afforded phosphonate **2.36** in 50%-75% yield. Finally, a cross metathesis with methacrolein **2.4** in the presence of Grubbs secondary generation catalyst introduced the α,β-unsaturated aldehyde **2.37** (*E:Z* = 10:1) to complete the HWE substrate.[43]

With aldehyde **2.37** in hand, the intramolecular Horner-Wadsworth-Emmons reaction was then investigated (Scheme 2.12). Treatment with n-BuLi in the presence of HMPA at a concentration of 0.01 M at 0 °C did not provided any desired product

(Entry1). Diluting the reaction mixture to 0.001 M still led to no reaction. Masamune-Roush modified condition, which utilized LiCl and DBU, yielded mostly the starting material (Entry 3).[44] Changing base to NaH resulted in no reaction or only a trace amount of product (Entry 4 and 5). When applying KOt-Bu as base, again no desired product was observed. In order to create a concentrated base environment, **2.37** was added to a solution of KOt-Bu by syringe pump over 12 h. This procedure still did not generate any cyclized product **2.38** (Entry 8). The reverse addition also failed (Entry 9). In all cases after base was added, color change was observed, indicating that deprotonation took place. Presumably, the failure of the cylization might be due to a conformational and/or stereo barrier.

Scheme 2.12 Horner-Wadsworth-Emmons reaction



2.37 **2.38**

Table 2.3 Intramolecular Horner-Wadsworth-Emmons reaction conditions

Entry	Reaction condition	**2.38**
1	n-BuLi, HMPA, THF, 0.01 M, 0 °C, 12 h	0%
2	n-BuLi, THF, 0.001 M, 0 °C, 12h	0%
3	LiCl, DBU, CH_3CN, 0.0005 M, rt, 36 h	No reaction

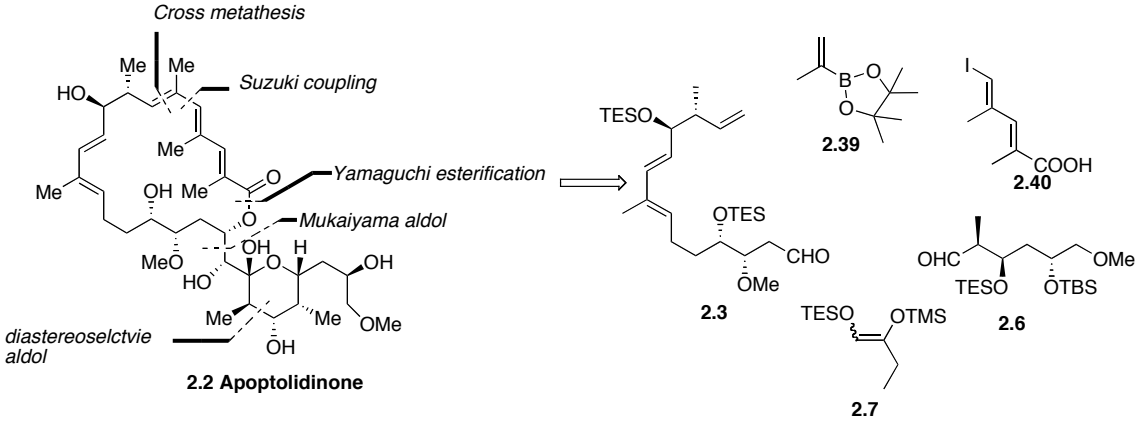
Table 2.3 (continued)

Entry	Reaction condition	**2.38**
4	NaH, THF, 0.005M, 0 °C 30 min then rt 3 h	0%
5	NaH, THF, 0.005M, 0 °C 30 min then rt 12 h	Trace amount
6	KOt-Bu, THF, 0.005 M, 0 °C 30 min then rt 3 h	0%
7	KOt-Bu, THF, 0.005 M, 0 °C 30 min then rt 12 h	0%
8	KOt-Bu, THF, rt, sm was added to a solution of base over 12 h	0%
9	KOt-Bu, THF, rt, base was added to a solution of sm over 12 h	0%

2.7 Large scale synthesis of apoptolidinone: intramolecular Suzuki coupling approach

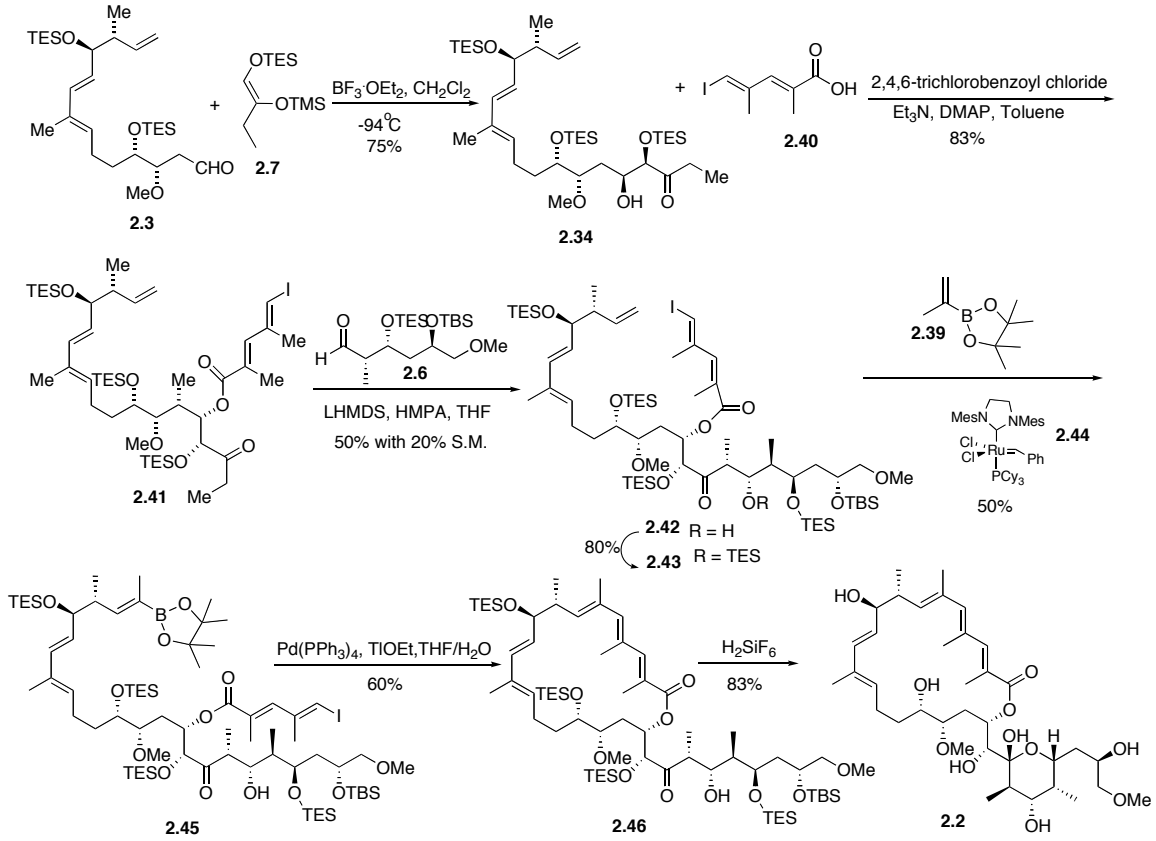
Failure of the intramolecular Horner-Wadsworth-Emmons approach forced examination of the previous intramolecular Suzuki coupling approach, which proved successful on small scale by Wu.[45] This strategy is similar to the intramolecular HWE approach. The only difference was that C5-C6 bond was to be formed by Suzuki coupling with fragment vinyl iodide **2.40** and vinyl boronate **2.39** in an intramolecular fashion. This retrosynthesis revealed aldehyde **2.3**, vinyl boronate **2.39**, carboxylic acid **2.40**, aldehyde **2.6** and silyl enol ether **2.7** as major building blocks (Scheme 2.13). Based on our previous studies, all these fragments could be prepared on multi-gram scale from readily available starting materials. This highly convergent route makes our goal of preparing 15-25 mg of apoptolidinone practical.

Scheme 2.13 Retrosynthetic analysis of apoptolidinone **2.2** based on intramolecular Suzuki coupling



The synthesis began with a Mukaiyama aldol reaction between aldehyde **2.3** and silyl enol ether **2.7**, which afforded diol type product **2.34** in 75% yield as an inseparable mixture of stereoisomers (Scheme 2.14). Yamaguchi esterification with acid **2.40**, which was obtained from hydrolysis of methyl ester **1.203**, provided ester **2.41** in 83% yield. At this stage three fractions were observed by TLC and were able to be separated by flash chromatograph column. The quantitative measurement demonstrated that the three isomers were produced in a ratio of 75:15:10. The NMR study indicated that the major isomer was the *anit, syn*-diastereomer **2.34**. Fraction C was determined to be a 1:1 mixture of two diastereomers based on NMR analysis. Minor fractions B and C were not fully characterized. Hence, the Mukaiyama aldol reactions between **2.3** and **2.7** generated all four possible stereoisomers in a ratio of 75:15:5:5. A lithium enolate mediated double diastereoselective aldol reaction between **2.41** and aldehyde **2.6** afforded aldol adduct **2.42** as a *single* isomer in 50% yield with 20% recovered starting

Scheme 2.14 Completion of the synthesis of apoptolidinone **2.2**



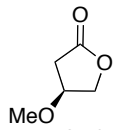
material. After silylation of the newly formed secondary hydroxyl group as TES ether, intermediate **2.43** was subjected to cross metathesis with vinyl boronate **2.39** in the presence of Grubbs secondary generation catalyst **2.44** and furnished vinyl pinacol boronate **2.45** in 50% yield (*E:Z*=10:1). Under Roush modified Suzuki coupling condition, the macorlide **2.46** was afforded. Finally, global deprotection delivered apoptolidinone **2.2**. Previously, HF·Pyridine was chosen as desilylation reagent, which afforded 40%-60% yield. Considering the instability of apoptolidinone under acidic conditions, a milder reagent, H_2SiF_6, was applied and the reaction afforded reproducible 80% yield.[46]

In summary this highly convergent synthesis provided apoptolidinone in 11 linear steps with 2.6% overall yield. With this synthesis route 15 mg apoptolidinone was prepared. The biological glycosylation study and biological activity test are in progress.

2.8 Experimental section

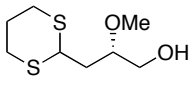
General procedures. Reagents were obtained from commercial suppliers, and where appropriate were purified prior to use. All reactions were carried out under a nitrogen or argon atmosphere using dry glassware that had been flame-dried under a stream of nitrogen, unless otherwise noted. All solvents were purified prior to use. Tetrahydrofuran and ethyl ether were distilled from sodium/benzophenone; dichloromethane and benzene were distilled from calcium hydride. Chloroform was washed twice with water, dried over potassium carbonate, refluxed, and distilled from phosphorus pentoxide. Triethylamine was distilled from calcium hydride and stored over sodium hydroxide. Reactions were monitored by thin-layer chromatography (TLC) using 0.25-mm E. Merck precoated silica gel plates. Visualization was accomplished with UV light and aqueous ceric ammonium molybdate solution, anisaldehyde stain or $KMnO_4$ followed by charring on a hotplate. Flash chromatography was performed with the indicated solvents using silica gel 60 (particle size 230-400 mesh) with the indicated solvent. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. Melting points are uncorrected unless otherwise noted. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 400, and 500 MHz spectrometers at ambient temperature. ^{1}H and ^{13}C NMR data are reported as δ values relative to tetramethylsilane or chloroform. Enantionmeric excess was determined by chiral GC analysis by Varian

3900 with chiral column (BETA DEX 120, 30 M x 0.25 mm, 0.25 μm film, column : # 17411-02B). High-resolution mass spectra were obtained at Texas A&M University Mass Spectrometry Service Center by Dr. Shane Tichy on an API QSTAR Pulsar Instrument. The single-crystal X-ray diffraction analysis was performed by Dr. Joseph Reibenspies at Texas A&M University using a Bruker Smart 1000 CCD single crystal X-ray diffractometer.



2.16

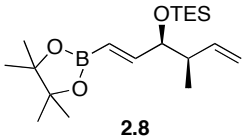
To a solution of **2.15** (5.23 g, 51.30 mmol) in MeI (50 mL) at room temperature was added Ag_2O (11.9g, 51.3 mmol, 1 equiv). The resultant mixture was stirred at 40 °C for 36 h, filtered through a celite pad, washed with ether, and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc 1:8-1:5) to afford 3.73g (63%) **2.16** as a colorless oil with 1.04 g (20%) recovered **2.15**: Observed physical properties were identical with those previously reported:[27] ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.37 (d, J = 3.2 Hz, 2H), 4.16 (m, 1H), 3.35 (s, 3H), 2.73 (dd, J = 18, 6.4 Hz, 2H)



2.17

To a solution of lactone **2.16** (730 mg, 6.29 mmol, 1 equiv) in CH_2Cl_2 (25 mL) at –78 °C was added DIBAL-H (1.68 mL, 9.5 mmol, 1.5 equiv) in CH_2Cl_2 (10 mL) dropwise. The resulting solution was stirred at –78 °C for 30 min before quenched with MeOH (5 mL). The mixture was allowed to warm to room temperature, poured into a saturated solution of potassium sodium tartrate (50 mL) and CH_2Cl_2 (200 mL) was added

to the solution. The mixture was stirred for 2 h two layers were separated and the aqueous solution was extracted with CH_2Cl_2 (50 mL x 3). The combined organic layers were dried over Na_2SO_4. The solvent was evaporated at 0 °C *in vacuo* and the residue was dissolved in CH_2Cl_2 (25 mL). 1,3 propanedithiol (2.45 mL, 25.16 mmol, 4 equiv) and $BF_3{\cdot}OEt_2$ (0.95 mL, 7.55 mmol, 1.2 equiv) were then added sequentially dropwise. The resulting solution was stirred at room temperature for 4 h. The reaction was quenched with H_2O (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (hexane/EtOAc, 2:1) to afford 0.785 g (60%) of the alcohol **2.17** as colorless oil: $[\alpha]_D^{25}$ +14.4° (c 5.2, $CHCl_3$); IR(neat) 3448, 2981,1425, 1113 cm^{-1}; ^1H NMR (300 MHz, C_6D_6): δ 4.18 (dd, J = 8.1, 6.3 Hz, 1H), 3.82 (ddd, J= 11.4, 6.0, 3.6 Hz, 1H), 3.65-3.50 (m, 2H), 3.47 (s, 3H), 2.99-2.82 (m, 4H), 2.21-2.04 (m, 2H), 1.96-1.83 (m, 2H); ^{13}C NMR (125MHz, C_6D_6): δ 78.1, 63.6, 57.8, 43.9, 37.1, 30.6, 30.4, 26.1; HRMS(ESI) *m/z* 231.0500 [$(M+Li)^+$ calculated for $C_8H_{16}O_2S_2Na$: 231.0483].



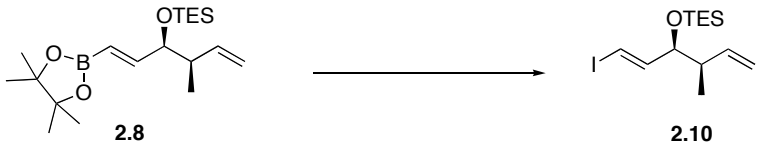
2.8

To as solution of tBuOK (48.5g, 433 mmol, 1.3 equiv) in THF (230 mL) at -78 °C was added cis-2-Butene (35.6 mL, 400 mmol, 1.2 equiv) through a cannula. After 5 min, n-BuLi (177 mL of 2.5 M solutions in hexanes, 333 mmol, 1 equiv) was added slowly so as to keep the internal temperature below -65°C. The reaction mixture was stirred at -78 °C for 1 h then -25 °C for 45 min before it was cooled down to -78°C. $B(O\text{-}iPr)_3$ (76.5

mL, 333 mmol, 1 equiv) was added slowly. The resultant solution was stirred at -78 °C for 30 min before quenched with 1 N HCl (130 mL). After warmed to rt, 1N HCl (460 mL) was added and stiring continued for 20 min. The solution was extracted with EtOAc (300 mL X 3). The combined organic layer was added 4 Å molecular sieves (50 g) and diethaolamine (25 mL, 266 mmol, 0.8 equiv). The resultant mixture was stirred under argon overnight and filtered. Solvents were removed *in vacuo* and white solid was obtained. Benzene (100 mL) was added to remove the unreacted diethanol amine. Recrystalization in ether-CH_2Cl_2 system afforded crotyl diethanol amine boronate complex 17.5 g (31%) as a white crystalline solid.

To a solution of the complex prepared above (765mg, 4.5 mmol, 4 equiv) in ether (10 mL) at room temperature was added diisopropyl tartrate (920 μL, 4.5 mmol, 4 equiv). After 15 min stirring, brine (10 mL) was added and the resultant solution was stirred at room temperature for 30 min before diluted with ether (10 mL), separated and extracted with ether (20 mL X 3). The combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to afforded crude product of **2.22**. The crude **2.22** was dissolved in toluene (12 mL) at room temperature and powdered 4 Å molecular sieves (4 g) were added. After 10 min, the mixture was cooled down to –78 °C and a solution of aldehyde **2.21** (220 mg, 1.2 mmol) in toluene (2 mL) was added dropwise. The resulting mixture was stirred at –78 °C for 12h. 1N NaOH solution (25 mL) was then added and the mixture was stirred for 2h at room temperature. The resultant cloudy mixture was diluted with brine (30 mL) and extracted with ether (50 mL x 3). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was dissolved in dichloromethane (8 mL) and cooled to –78 °C. 2,6-lutidine (0.2 mL, 1.6 mmol, 1.2 equiv)

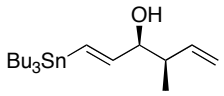
was added followed by TESOTf (0.28 mL, 1,2 mmol, 1 equiv). The reaction was stirred at –78 °C for 2 h before quenched with H_2O (2 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layer were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (hexane: EtOAc, 50:1) to afford 0.18g (43%) of homoallylic ether **2.8** as a colorless oil: $[\alpha]_D^{25}$ +7.0° (c 2.0, $CHCl_3$); IR (neat) 3018, 2953, 1738, , 1636, 1360, cm^{-1}; ^1H NMR (500 MHz, C_6D_6): δ 6.92 (dd, J = 18.0, 5.5 Hz, 1H), 5.96 (dd, J = 18.0, 1.0 Hz, 1H), 5.91-5.80 (m, 1H), 4.97-4.95 (m, 1H), 4.94-4.93 (m, 1H), 4.06 (dt, J = 6.0, 1.0 Hz, 1H), 2.31-2.25 (m, 1H)1.03 (s, 12H), 1.01 (d, J = 7.0 Hz, 3H), 0.96 (t, J = 8.0 Hz, 9H), 0.56 (dq, J = 8.0, 2.5Hz, 6H); ^{13}C NMR (125MHz, C_6D_6): δ 154.8, 141.1, 114.4, 83.0, 78.5, 44.3, 42.8, 42.7, 14.6, 7.1, 5.3; HRMS(ESI) *m/z* 359.2792 [$(M+Li)^+$ calculated for $C_{19}H_{37}BLiO_3Si$: 359.2765].



2.8 **2.10**

To a solution of **2.8** (40 mg, 0.11 mmol) in THF (2 mL) at room temperature was added NaOH (0.11 mL, 0.33 mmol of 3M solution, 3 equiv). After 10 min vigorous stirring, I_2 (0.11 mL, 0.22 mmol, 2 M, 2 equiv) in THF was added dropwise. The resultant solution was stirred for 2 h at room temperature before quenched with $Na_2S_2O_3$, extracted with CH_2Cl_2 (10 mL x 3), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc 150:1) to afford 24 mg (62%) **2.10** as a colorless oil: $[\alpha]_D^{25}$ -16.9° (c 1.4, $CHCl_3$); IR (neat) 2955, , 1455, 1238, 1072cm^{-1}; ^1H NMR(500 MHz, C_6D_6): δ 6.46 (dd, J = 14.5, 7 Hz, 1H), 6.02 (dd, J = 14.5, 1 Hz, 1H), 5.73 (m, 1H), 4.95 (m, 2H), 3.71 (ddd, J = 7, 5.5, 1 Hz, 1H), 2.12 (m,

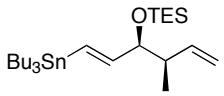
1H), 0.93 (m, 12H), 0.51 (q, J = 7.5Hz, 6H); ^{13}C NMR (125MHz, C_6D_6): δ 147.85, 140.20, 114.99, 79.17, 77.00, 44.10, 14,68, 7.01, 5.18. The enantiomeric excess of A216 was determined by chiral GC analysis of vinyl iodide **2.10** to be 80% (starting from 80 °C, 20 °C/min to 100 °C, then hold for 10 min, 0.5 °C/min to 120 °C, hold for 5 min, 0.1 °C/min to 139 °C, hold for 0 min, 20 °C/min to 220 °C hold for 0 min, totally 250 min, major isomer showed up at 61.06 min, minor isomer showed at 61.80 min starting from 80 °C, 20 °C/min to 100 °C, then hold for 10 min, 0.5 °C/min to 120 °C, hold for 5 min, 0.1 °C/min to 139 °C, hold for 0 min, 20 °C/min to 220 °C hold for 0 min, tonally 250 min, major isomer showed up at 61.06 min, minor isomer showed at 61.80 min)



2.24

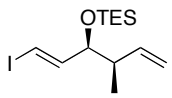
To a solution of **2.22** (360 mg, 1.2 mmol, 4 equiv) in toluene (5 mL) at room temperature, which was prepared following the procedure described in synthesis of **2.8** , was added 4 Å molecular sieves (1g). After 10 min, the reaction mixture was cooled down to –78 °C and **2.23** (103 mg, 0.3mmol) in toluene (2 mL) was added dropwise. The resultant solution was stirred at –78 °C for 16 h, quenched with 1N NaOH (8 mL) at –78 °C. The mixture was allowed to warm up to room temperature and continued to stir 1 h. After separated, it was extracted with ether, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc 30:1) to afford 104 mg (86%) **2.24** as a colorless oil: IR (neat) 3498, 2956, 1375cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.18 (dd, J = 19.0, 1.0 Hz, 1H), 6.03 (dd, J= 19.0, 5.5 Hz, 1H), 5.80 (m, 1H), 5.12-5.08 (m, 2 H), 4.0 (q, J = 5.0 Hz, 1 H), 2.41-2.37 (m, 1H), 1.65 (d, J = 5.5 Hz, 1H), 1.53-1.47(m, 6H), 1.35-1.27 (m, 6H), 1.04 (d, J = 7 Hz,

3H), 0.92-0.888 (m, 15H); ^{13}C NMR (125MHz, $CDCl_3$): δ148.2, 140.2, 128.9, 115.6, 78.1, 43.5, 29.1, 27.3, 14.6, 13.7, 9.5; HRMS (ESI) *m/z* 409.2108[$(M+Li)^+$ calculated for $C_{19}H_{38}OSn$ 409.2105]



2.9

To a solution of **2.24** (100 mg, 0.25 mmol) in CH_2Cl_2 (5 mL) at –78 °C was added 2,6-lutidine (90 μL, 0.75 mmol, 3 equiv) followed by TESOTf (113 μL, 0.50 mmol, 2 equiv.). The resultant solution was stirred at –78 °C for 1 h, quenched with saturated $NaHCO_3$ (5 mL), extracted with CH_2Cl_2 (10 mL x 3), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc 100:1) to afford 104 mg (86%) **2.9** as colorless oil: IR (neat) 2924, 1376, 1005cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.04 (d, J = 19 Hz, 1H), 5.93 (dd, J = 19, 6.5 Hz, 1H), 5.85-5.79 (m, 1H), 4.99 (dd, J =14, 1 Hz, 2H), 3.88 (t, J = 6.5Hz, 1H), 2.28-2.24 (m, 1H), 1.53-1.47 (m, 6H), 1.33-1.28 (m, 6H), 1.00 (d, J = 7 Hz, 3H), 0.95 (t, J = 8 Hz, 9H), 0.91-0.86 (m, 15H), 0.59 (qd, J = 8, 1 Hz, 6H); ^{13}C NMR (125MHz, $CDCl_3$): δ 149.8, 141.1, 128.3, 113.9, 80.5, 44.3, 29.1, 27.3, 15.0, 13.7, 9.5, 6.9, 5.0; After converting the vinyl tin to vinyl iodide **2.10** by treatment of iodine and $NaHCO_3$, the enantiomeric excess was determined to be 33% by chiral GC analysis (starting from 80 °C, 20 °C/min to 100 °C, then hold for 10 min, 0.5 °C/min to 120 °C, hold for 5 min, 0.1 °C/min to 139 °C, hold for 0 min, 20 °C/min to 220 °C hold for 0 min, totally 250 min, major isomer showed up at 61.06 min, minor isomer showed at 61.80 min)



2.10

A) Roush Crotylation[33]

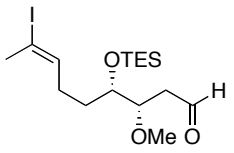
To a solution of **2.26** (1.13 g, 5 mmol) in CH_2Cl_2 at –78 °C was added DIBAL-H (1.0 mL, 6 mmol, 1.2 equiv) dropwise. The resultant solution was stirred at –78 °C for 30 min, quenched with MeOH (1 mL). Then the solution was poured into saturated Rochelle's salt (sodium potassium tartrate) solution (50 mL), diluted with CH_2Cl_2 (50 mL) and stiring continued for 1.5 h. The mixture was separated, aqueous layer was extracted with CH_2Cl_2 (50 mL x 3), and combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to about 30 mL. $BF_3{\cdot}OEt_2$ (0.85 mL, 6.7 mmol, 1.34 equiv) was added to this solution at room temperature and stirred 1.5 h while protected from light. The reaction was quenched with $NaHCO_3$, extracted with CH_2Cl_2, washed with $NaHCO_3$, brine, dried over Na_2SO_4, concentrated at 0 °C while kept off light *in vacuo* to about 5 mL. Then the solution was diluted with toluene (30 mL) and 4 Å molecular sieves (3 g) were added. After 10 min, the reaction was cooled to –78 °C and a solution of **2.22** (4.47 g, 15 mmol, 3 equiv) in toluene (10 mL) was added dropwise. The resultant slurry was stirred for 16 h before quenched with 1N NaOH (120 mL). After 1 h stirring, the mixture was diluted with brine (200 mL), extracted with ether, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL) at 0 °C and 2,6-lutidine (0.87 mL, 7.5 mmol, 1.5 equiv) was added. After 5 min, TESOTf (1.12 ml, 5 mmol) was added dropwise. The resultant solution was stirred at 0 °C for 1 h, quenched with H_2O, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered and concentrated *in vacuo*, The residue was purified by flash chromatography (Hexane/EtOAc 100:1 to

40:1) to afford 0.7g (40% over 4 steps) **2.10** as colorless oil. The enantiomeric excess was determined by chiral GC (starting from 80 °C, 20 °C/min to 100 °C, then hold for 10 min, 0.5 °C/min to 120 °C, hold for 5 min, 0.1 °C/min to 139 °C, hold for 0 min, 20 °C/min to 220 °C hold for 0 min, totally 250 min, major isomer showed up at 61.06 min, minor isomer showed at 61.80 min) to be 26%.

B) Brown Crotylation[35]

To a solution of **2.26** (5.18 g, 23 mmol) in CH_2Cl_2 (50 mL) at –78 °C was added DIBAL-H (4.5 mL, 25.2 mmol, 1.1 equiv) dropwise. The resultant solution was stirred at –78 °C for 30 min, quenched with MeOH (5 mL). Then the solution was poured into saturated Rochelle's salt (sodium potassium tartrate) solution (200 mL), diluted with CH_2Cl_2 (150 mL) and continued to stir for 1.5 h. The mixture was separated, aqueous layer was extracted with CH_2Cl_2 (150 mL x 3), and combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to about 30 mL. $BF_3{\cdot}OEt_2$ (3.8 mL, 30 mmol, 1.3 equiv) was added to this solution at room temperature and stirred 1.5 h protected from light. The reaction was quenched with $NaHCO_3$, extracted with CH_2Cl_2 (100 mL x 3), washed with $NaHCO_3$, Brine, dried over Na_2SO_4, concentrated at 0 °C while kept off light *in vacuo* to about 10 mL containing **2.28**. A solution of t-BuOK (3.7g, 33 mmol, 1 equiv) in THF (40 mL) at –78 °C was added cis-2-butene (10 mL, 20 equiv). After 5 min, n-BuLi (13.2 mL, 33 mmol) was added. The mixture was warmed up to –45 °C for 15 min. It was cooled down to –78 °C again and $(Ipc)_2BOMe$ (12.50 g, 39.50 mmol, 1.2 equiv) in ether (20 mL) was added. The resultant solution was stirred at –78 °C for 30 min then $BF_3{\cdot}OEt_2$ (5.6 mL, 44.2 mmol, 1.34 equiv) was added. After 15 min stirring, a solution of **2.28** was added in THF (10 mL) dropwise. The resultant solution

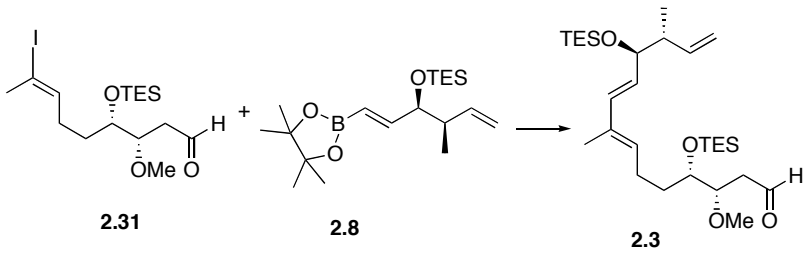
was stirred at –78 °C for 16 h before warmed up to room temperature. NaOH (40 mL, 115 mmol, 3M) and H_2O_2 (30%, 20 mL) were then added and the mixture was refluxed for 2 h. After separated, the aqueous layer was extracted with ether, dried over Na_2SO_4, concentrated *in vacuo*, The residue was purified by flash chromatography (Hexane/EtOAc 20:1) to afford 2.6 g product as colorless oil. It was then dissolved in CH_2Cl_2 (20 mL) at 0 °C. 2,6-lutidine (2.5 mL, 22 mmol, 2 equiv) was added followed by TESOTf (3.7 mL, 16.4 mmol, 1.5 equiv). The resultant solution was stirred at 0 °C for 1 h, quenched with H_2O (5 mL), extracted with CH_2Cl_2 (10 mL x 3), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc 100:1) to afford 3.1 g (38% over 4 steps) **2.10** as colorless oil. Enantiomeric excess was determined by chiral GC (starting from 80 °C, 20 °C/min to 100 °C, then hold for 10 min, 0.5 °C/min to 120 °C, hold for 5 min, 0.1 °C/min to 139 °C, hold for 0 min, 20 °C/min to 220 °C hold for 0 min, totally 250 min, major isomer showed up at 61.06 min, minor isomer showed at 61.80 min) to be 90%.



2.31

To a solution of **2.30**[45] (2.26 g, 4.37 mmol) in CH_3CN (48 mL) and pH=7 buffer (12 mL) at 0 °C was added K_2CO_3 (1.5 g, 11 mmol, 2.5 equiv) and MeI (2.7 mL, 43.7 mmol, 10 equiv). The resulting solution was stirred at 26.5 °C for 48 h before diluted with EtOAc (40 mL), washed with brine and dried over Na_2SO_4. The organic layer was filtered, concentrated, and residue was purified by flash chromatography (hexane:EtOAc, 20:1) to afford 1.58 g (85%) of the alcohol **2.31** as colorless oil: $[\alpha]_D^{25}$ –15.0° (c 5.4.,

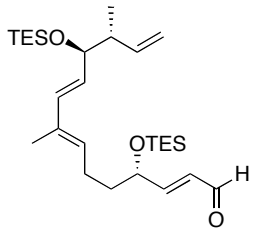
$CHCl_3$); IR(neat) 2953, 1724, 1375 cm^{-1}; ^1H NMR(500 MHz, C_6D_6): δ 9.47 (s, 1H), 6.14-6.10 (m, 1H), 3.68-3.62 (m, 2H), 3.04 (s, 3H), 2.31 (ddt, J=12.0, 3.5, 1.0Hz, 1H), 2.16-2.12 (m, 1H), 2.11 (s, 3H), 2.04-1.96 (m, 1H), 1.79-1.71 (m, 1H), 1.54-1.47 (m, 1H), 1.16-1.09 (m, 1H), 0.90 (t, J=8.0Hz, 9H), 0.50 (q, J = 8.0Hz, 6H); ^{13}C NMR (125MHz, C_6D_6): δ199.2, 141.0, 93.9, 78.8., 71.3, 57.5, 43.6, 30.9, 27.3, 27.2, 6.9, 5.2; HRMS(ESI) *m/z* 427.1131 [$(M+Li)^+$ calculated for$C_{16}H_{32}IO_3Si$: 427.1166].



2.31 **2.8** **2.3**

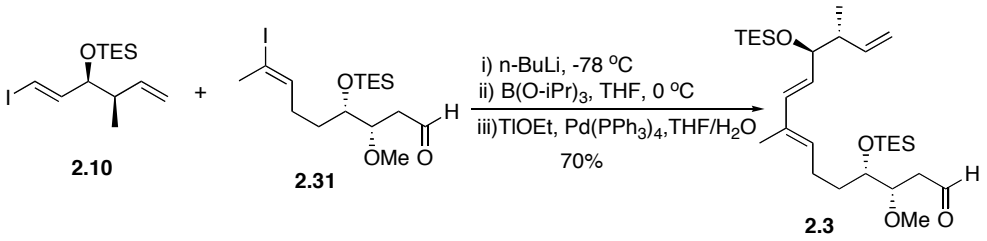
To a solution of aldehyde **2.31** (1.02 g, 2.4 mmol) and vinyl boronate **2.8** (1.3 g, 3.6 mmol, 1.5 equiv) in THF/H_2O (120 mL, 3:1, degassed by freezing in liquid nitrogen under vacuum followed by warmed up to room temperature and repeated three times) at room temperature was added $Pd(Ph_3P)_4$ (280 mg, 0.24 mmol, 0.1 equiv). The mixture was stirred for 5 min, and TlOEt (210 μL, 3 mmol, 1.25 equiv) was added via syringe. The reaction was kept at room temperature for 15 min, and then quenched with saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc (100 mL x 3), and the combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexanes:EtOAc, 30:1) to afford 1.03 g (82%) of **2.3** as a colorless oil: $[\alpha]_D^{25}$ –11.0° (*c* 1.2 , $CHCl_3$); IR (neat) 2960, 1731cm^{-1}; ^1H NMR (500 MHz C_6D_6): δ 9.53 (s, 1H), 6.27 (d, J = 15.5 Hz, 1H), 6.04-5.97 (m, 1H), 5.64 (dd, J = 15.5, 7.5 Hz, 1H), 5.51 (t, J = 7.0

Hz, 1H), 5.07-5.02 (m, 2H), 4.08 (t, J = 6.0 Hz, 1H), 3.83-3.79 (m, 1H), 3.72-3.68 (m, 1H), 3.10 (s, 3H), 2.42-2.37 (m, 2H), 2.36-2.29 (m, 1H), 2.21 (ddd, J = 16.5, 8.0, 2.0 Hz, 1H), 2.14 –2.06 (m, 1H), 1.74 (s, 3H), 1.73-1.66 (m, 1H), 1.36-1.28 (m, 1H), 1.11 (d, J = 6.5 Hz, 3H), 1.02 (t, J = 8.0 Hz, 9H), 0.95 (t, J = 8.0 Hz, 9H), 0.64 (dq, J = 8.0, 1.5 Hz, 6H), 0.56 (q, J = 8.0 Hz, 6H); ^{13}C NMR (125 MHz, C_6D_6): δ 199.5, 141.3, 135.6, 133.8, 132.2, 128.8, 114.2, 78.9, 78.0, 71.6, 57.6, 45.1, 43.7, 31.6, 25.2, 15.1, 12.6, 7.1, 7.0, 5.4, 5.3; HRMS (ESI) *m/z* 531.3869 [$(M+Li)^+$ calcd for $C_{29}H_{56}O_4Si_2Li$: 531.3877].

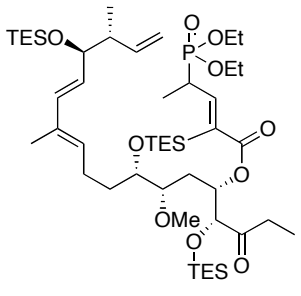


2.32

The byproduct of the Suzuki coupling was determined to be **2.32** as a colorless oil: $[\alpha]_D^{25}$ +19.2° (*c* 1.1, $CHCl_3$); IR (neat) 1696, 1457cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.59 (d, J = 8 Hz, 1H), 6.82 (dd, J = 15.5, 5 Hz, 1H), 6.31 (qd, J = 8, 1 Hz, 1H), 6.10 (d, J = 16 Hz, 1H), 5.87-5.80 (m, 1H), 5.54 (dd, J = 15.5, 7 Hz, 1H), 5.39 (t, J = 7 Hz, 1H), 5.0-4.97 (m, 2H), 4.47 (q, J = 5.5 Hz, 1H), 3.99 (t, J = 6.5 Hz, 1H), 2.31 (m, 1H), 2.23 (q, J = 7.5 Hz, 2H), 1.71 (s, 3H), 1.69 (q, J = 6.5 Hz, 2H), 1.0 (d, J = 7 Hz, 3H), 0.98 (q, J = 8 Hz, 18H), 0.64 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.5, 159.6, 141.0, 134.9, 134.0, 130.8, 130.7, 128.77. 114.1, 77.5, 71.1, 44.7, 37.0, 23.6,15.0, 12.6, 6.8, 6.7, 5.0, 4.8; HRMS (ESI) *m/z* 499.3617 [$(M+Li)^+$ calcd for $C_{28}H_{52}O_3Si_2Li$: 499.3615]

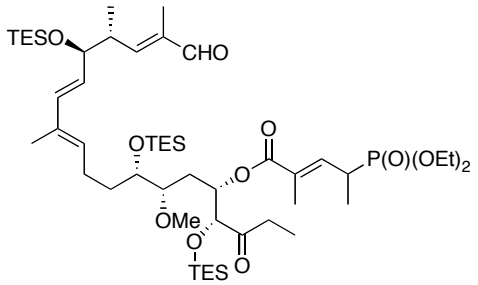


To a solution of **2.10** (140 mg, 0.4 mmol, 1.5 equiv) at –78 °C in THF (5 mL) was added n-BuLi (0.24 mL of 2.5 M solution in hexanes, 0.6 mmol, 2.25 equiv). After 2 h, $B(O\text{-}iPr)_3$ (140 μL, 0.6 mmol, 2.25 equiv) was added. The reaction mixture was warmed up to room temperature slowly and continued to stir overnight. The reaction was quenched with H_2O (5 mL), extracted with ether (10 mL x 3), dried over Na_2SO_4. The organic layer was filtered, concentrated *in vacuo*. The residue was added to a solution of **2.31** (110 mg, 0.27 mmol) in THF/H_2O (8 mL, 3:1) at room temperature. The resultant solution was degassed (by freezing in liquid nitrogen under vaccum followed by warming up to room temperature and repeated three times) and $Pd(PhP_3)_4$ (31 mg, 0.027 mmol, 0.1 equiv) was added. After 10 min, TlOEt (23 μL, 0.34 mmol, 1.25 equiv) was added. After 15 min the reaction was quenched with saturated $NaHCO_3$ (10 mL). The mixture was filtered through a celite pad, washed with EtOAc (20 mL), dried over Na_2SO_4. The organic layer was filtered and concentrated *in vacuo* and residue was purified by flash chromatography (Hexane/EtOAc, 20:1) to afford 100 mg (70%) of the alcohol **2.3** as colorless oil.



2.36

To a solution of **2.34** (154 mg, 0.21 mmol) in toluene (5 mL) was added **2.5** (100 mg, 0.4 mmol, 1.3 equiv). The reaction solution was then cooled to –78 °C and DMAP (384 mg, 3.15 mmol, 15 equiv), Et_3N (322 μL, 2.31 mmol, 11 equiv) and tricholro benzyl chloride (328 μL, 2.1 mmol, 10 equiv) was added sequentially. After 10 min, the reaction slurry was warmed up to room temperature and continued to stir overnight. The reaction was quenched with $NaHCO_3$ (10 mL), extracted with EtOAc (15 mL x 3), dried over Na_2SO_4. The organic layer was filtered, concentrated, and residue was purified by flash chromatography (Hexane/EtOAc, 3:1) to afford 150 mg (75%) of **2.36** as colorless oil: ^{1}H NMR (500 MHz C_6D_6): δ 6.99 (m, 1H), 6.30 (dd, J = 16, 4.4 Hz, 1H), 6.03 (m, 1H), 5.83 (m, 1H), 5.67 (dd, J = 15.6, 7.2Hz, 1H), 5.56 (m, 1H), 5.10-5.05 (m, 2H), 4.32(d, J = 4 Hz, 1H), 4.09 (t, J = 6.8Hz, 1H), 3.99-3.86 (m, 6H), 3.36-3.25 (m, 4H), 2.92-2.80 (m, 1H), 2.69-2.57 (m, 1H), 2.50-2.36 (m, 2H), 2.28-2.18 (m, 2H), 2.0 (m, 2H), 1.92-1.86 (m, 2H), 1.78 (s, 3H), 1.64 (s, 1H), 1.62-1.52 (m, 1H), 1.37 (s, 2H), 1.35-1.20 (m 4H), 1.15-0.95 (m, 40H), 0.71-0.58 (m, 18H); HRMS (ESI) *m/z* 965.6133[(M+Li)$^+$ calcd for $C_{49}H_{95}O_{10}PSi_3$ 965.6131].



2.37

To a solution of **2.36** (144 mg, 0.15 mmol) in CH_2Cl_2 (5 mL) at room temperature was added methacrolein **2.44** (62 μL, 0.75 mmol, 5 equiv) and Grubbs secondary generation catalyst (7 mg, 7.5 μmol, 0.05 equiv). The resultant solution was

refluxed at 45 °C (bath temperature) overnight. After cooled to room temperature, solvent was removed *in vacuo***.** The residue was purified by flash chromatography (Hexanes:EtOAc, 4:1 to 2:1) and afforded 110 mg (73%) of **2.37** as colorless oil: ^{1}H NMR (400 MHz C_6D_6): δ 9.35 (s, 1H), 7.01-6.87 (m, 1H), 6.35 (m, 1H), 6.11 (m, 1H), 5.68 (m, 1), 5.54 (m, 3H), 4.31 (dd, J = 13.2, 3.2Hz), 4.13-3.77 (m, 8H), 3.54-3.42 (m, 1H), 3.68-3.20 (m, 6H), 2.73-2.54 (m, 3H), 2.47-2.10 (m, 6H), 2.0 (m, 2H), 1.91-1.79 (m, 6H), 1.76-1.73 (m, 9H), 1.64-1.54 (m, 2H), 1.15-0.97 (m, 52H), 0.71-0.57 (m, 12H); HRMS (ESI) *m/z* 1007.6259[$(M+Li)^+$ calcd for $C_{51}H_{97}O_{11}PSi_3$ 1007.6236].

CHAPTER III

STUDIES TOWARDS THE TOTAL SYNTHESIS OF AMMOCIDINONE

3.1 Ammocidin: isolation and structure elucidation

Uncontrolled cell growth and differentiation in human tissues lead to cancer. Genetically, few mechanisms that lead to uncontrolled cell division and proliferation have been characterized. One such mechanism is that of a mutant gene, which is known as an oncogene leading to hyperactive cell growth. One example involves the gene Ras, found on chromosome 11, that functions like a switch in normal cells to regulate cell growth. When the receptor on the cell surface is initiated, it will be activated and transduce signals to initiate cell growth. When the ras signal is off, the cell growth cycle will stop. A mutant Ras will keep the cell growing regardless whether the receptor is stimulated or not, which may finally lead to the development of a cancerous cell. 30% of human cancers, especially colon and pancreas cancer are due to Ras mutations. In certain conditions, Ras can suppress an apoptosis process, which leads to programmed death of immortalized cells thus terminating the proliferation disorder and circumventing tumor formation. Therefore, a selective apoptosis-inducing reagent may be a useful anticancer drug to cells expressing mutant Ras. During their effort in searching for active apoptosis inducers with Ras dependent cell lines, a new promising cell-selective cytotoxic agent ammocidin **3.1** (Figure 3.1) was discovered.

In the course of screening for apoptosis inducer with Ras dependent Ba/F3-V12 cells, Hayakawa and co-workers isolated ammocidin from the culture broth of *Saccharothrix* sp. AJ9571 in 2001.[47] From a 10 liter culture broth 387 mg of ammocidin was isolated as a colorless powder. The molecular formula was determined to be

$C_{59}H_{96}O_{22}$ by high-resolution FAB-MS. Extensive NMR analysis and chemical degradation revealed the connectivity of the molecular structure of ammocidin. Furthermore, methanolysis of ammocidin under acidic conditions led to the identification of two sugar units: 6-deoxy-L-glucoside **3.2** a sugar determined to be located at C9 of the ammocidin aglycone, a disaccharide attached at C24 containing D-digitoxoside **3.3** and D-olivomycoside **3.4** interconnected through an alpha-glycoside linkage (Figure 3.1). The identity and absolute stereochemistry of three sugars units: **3.2**, **3.3**, and **3.4** were assigned by comparison to their derived methyl acetals to authentic samples. Unfortunately, the aglycone (ammocidinone) apparently did not survive the acidic degradation conditions. The HMQC, COSY, HMBC studies revealed that ammocidin consisted of a highly unsaturated 20-membered macrolactone containing two trisubstituted triene moieties and a fully substituted hemiketal pyranose.[48] The chemical

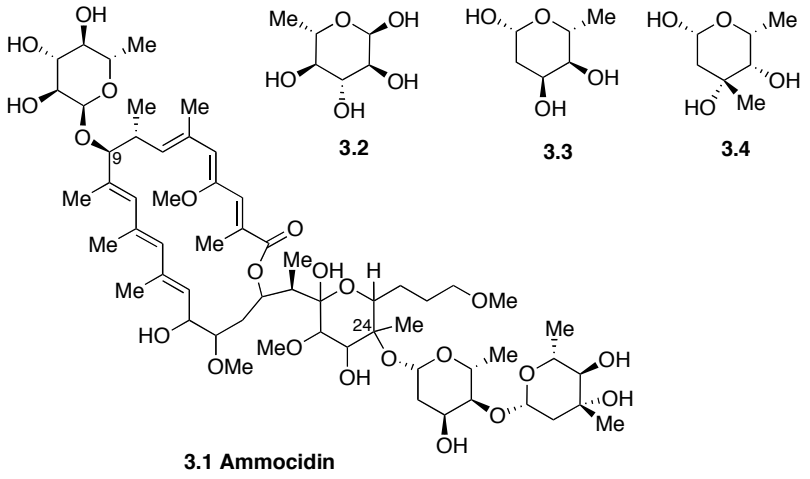


Figure 3.1 Structures of ammocidin **3.1** and deoxy sugars **3.2-3.4**

shifts of the five allylic methyl carbons and NOE correlations led to the configuration assignment of the two triene moieties as *E*. The complete relative and absolute stereochemistry of the aglycone (ammocidinone) was determined by two-dimensional NMR techniques. The absolute configuration of C9, assigned an ***S*** configuration, was determined by the observed NOE between C1' methine of the 6-deoxy-L-glucose sugar **3.2** (Figure 3.2).[49] The structural comparison studies between apoptolidin and ammocidin indicated that these two molecules share some similarities in terms of stereochemistry, specifically, the C8, C9 and C20 positions have the same absolute

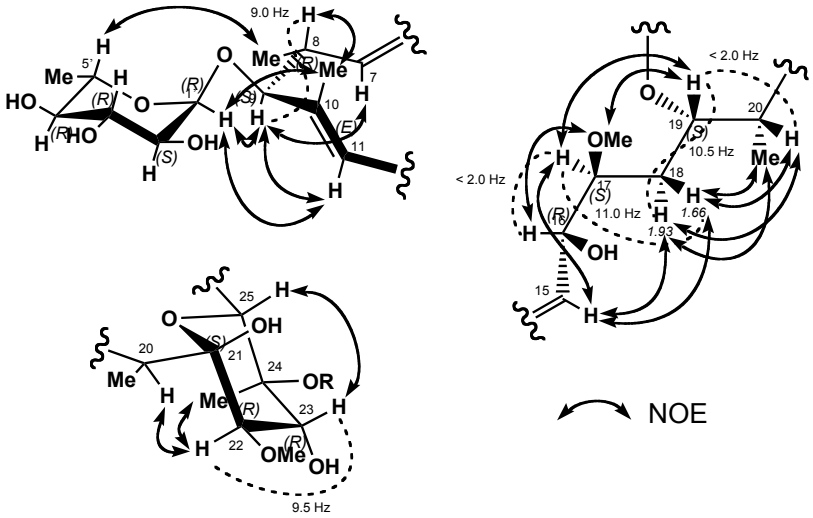


Figure 3.2 NOE studies of ammocidin structure

stereochemistry. Furthermore, the relative stereochemistry of C17-C19 and C21-C25 were determined to be identical, both the C22 methoxy in ammocidin and C22 methyl in apoptolidin occupy an equatorial position and both C24 methyl groups hold an axial orientation (Figure 3.2). However, the relative stereochemistry between C16-C17 in apoptolidin, have a *syn* relationship, while in ammocidin, they are *anti* to each other

(Figure 3.3). Unfortunately, the relationship of the C9, C17 and C21 positions remain unassigned.

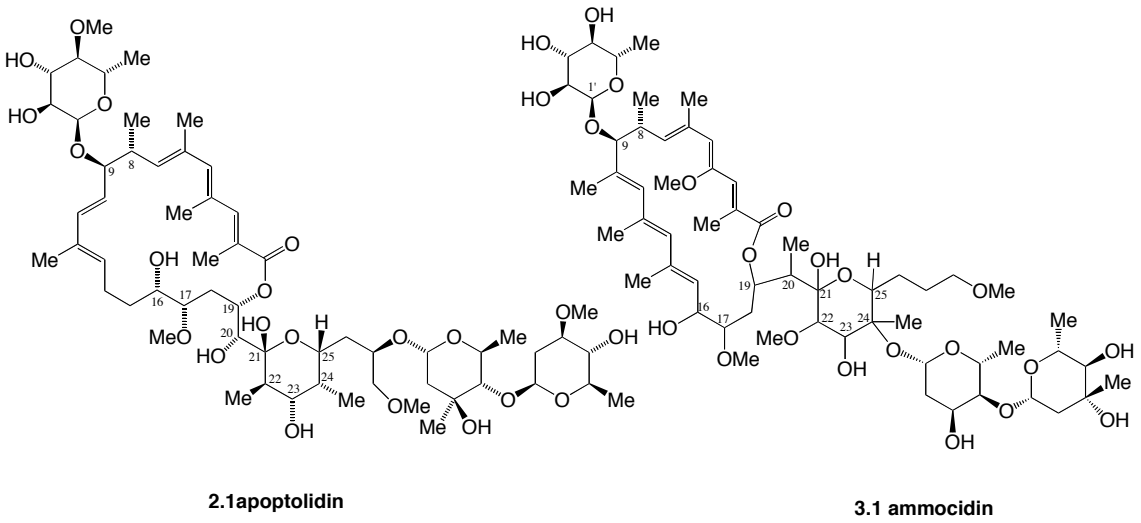


Figure 3.3 Structural similarities between apoptolidin **2.1** and ammocidin **3.1**

With the absolute configuration of C9, C17 and C21 unknown, 4 different stereoisomer of ammocidin were plausible. Based on the results obtained from the

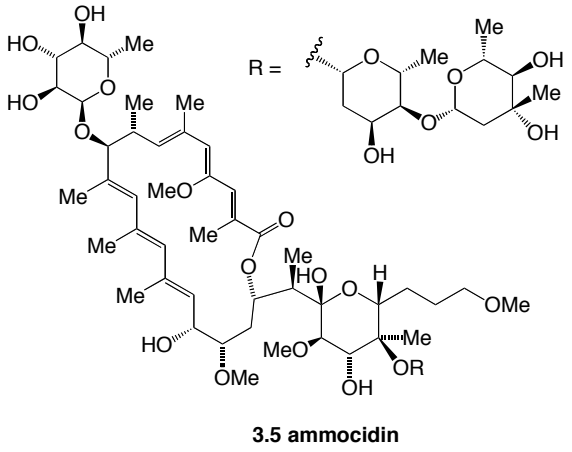


Figure 3.4 Proposed structure of ammocidin

spectroscopic studies conducted in Hayakawa group, and the known stereochemistry of apoptolidin, ammocidin was tentatively assigned the structure **3.5** (Figure 3.4).

3.2 Ammocidin: biological activity

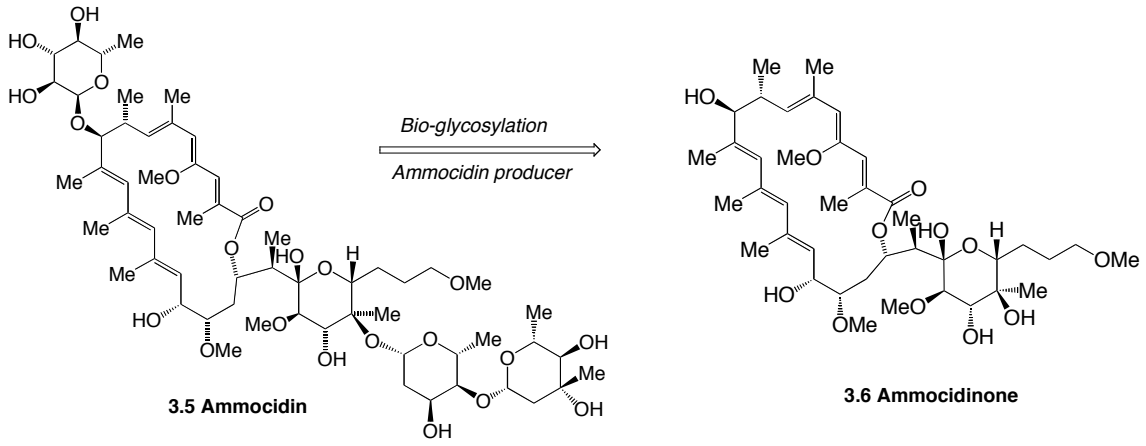
In IL-3 free medium the IL-3-dependent Ba/F3 pro-B cells undergoes apoptosis rapidly on treatment with ammocidin. However, Ras-dependent Ba/F3-V12 cells, bearing dexamethasone-inducible v-H-Ras, survive in the medium containing dexamethasone (Dex) in the absence of IL-3 when treated with ammocidin.[50] The primary biological assay showed that in an IL-3-free medium containing Dex (2×10^{-7} M) ammocidin induced apoptosis in Ba/F3-v12 cells with an IC_{50} of 66 ng/mL. However, in the presence of IL-3 and less than 100 μg/mL of ammocidin, only inhibition of the Ras-dependent Ba/F3-v12 cells growth was observed rather than apoptosis.[45] The anti-apoptotic function of Ras in Ba/F3 cells is believed to be mediated by mitogen-activated protein kinase (MAPK) and S6 kinase (S6K) pathway.[51] It is known that the phosphorylation of MAPK an S6K is induced by Ras. However, only 1 μg/mL of ammocidin could significantly reduce the phosphorylation lever of MAPK and S6K. These results indicated that the anti-apoptotic function of ammocidin in Ras-dependent cells is mediated by simultaneous inhibition of MAPK and S6K phosphorylaiton.[48]

3.3 Ammocidinone: a new synthetic target

The complex structure of ammocidin including two tri-substituted triene moieties and highly substituted pyranose unit combined with an interesting biological profile suggests ammocidin to be a worthy synthetic target. With the assignment of the absolute

stereochemistry of ammocidin incomplete, a highly convergent and flexible synthetic strategy was required that would allow for access to variable stereochemistry within its structure. As the first step toward the total synthesis of ammocidin we selected to develop a chemical synthesis of ammocidinone **3.6**, which can be further elaborated to ammocidin **3.5** by bioglycosylation with glycosyltranferase (Scheme 3.1).

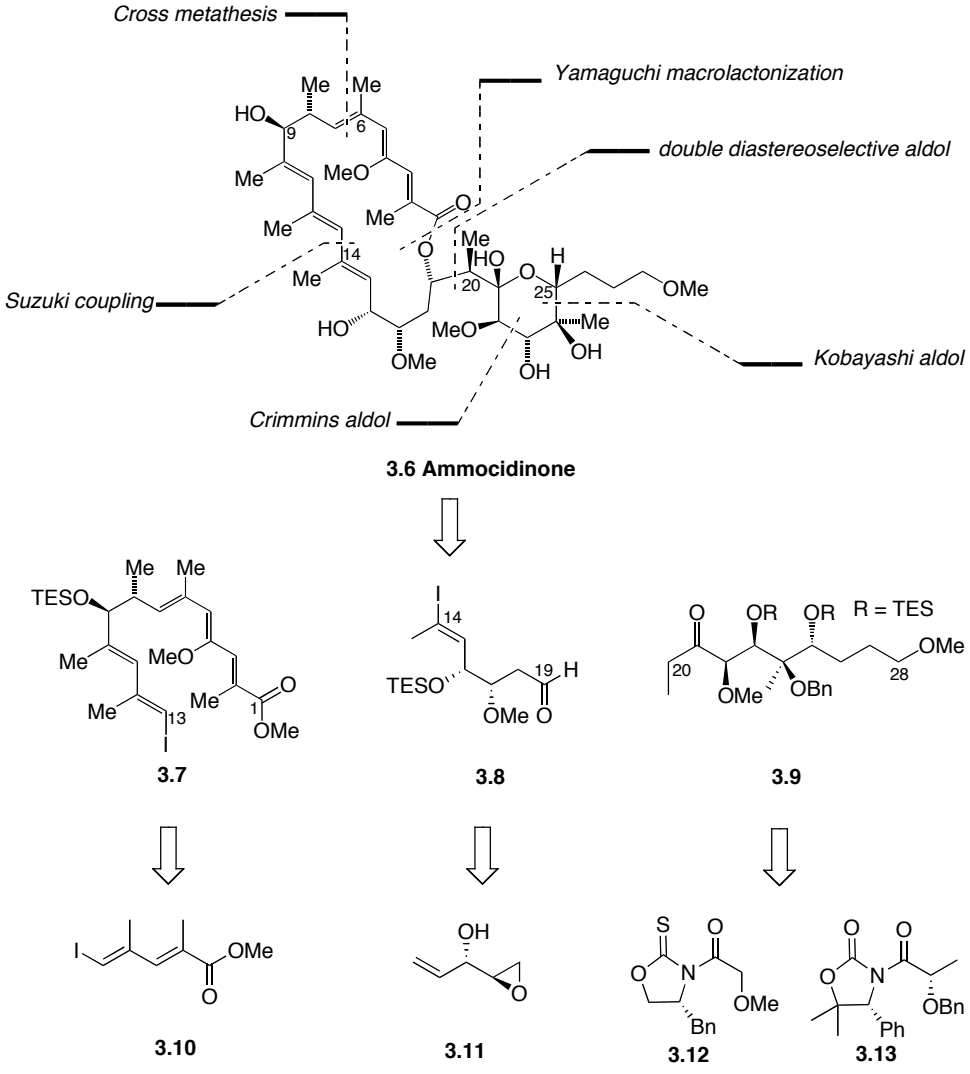
Scheme 3.1 Bio-glycosylation of ammocidinone **3.6**



Our primary goal of a projected total synthesis of ammocidin was assembly of the tentatively assigned structure of ammocidinone. Later work would focus on the utility of the natural product and it's derivatives to probe the mechanism of the selective apoptotic function of ammocidin and develop ammocidin related anticancer agents. To that end a highly convergent, efficient and flexible synthetic strategy was required for the chemical synthesis of ammocidinone. Retrosynthetically, the first three disconnections were identified at the lactone bond and C13-C14 and C19-C20 bonds (Scheme 3.2), which identified polyenoate **3.7** (C1-C13), vinyl iodide **3.8** (C14-C19) and ethyl ketone **3.9** (C20-C28) as key building blocks. In the forward sense, these three fragments will be

coupled through a diastereoselective aldol reaction between C19-C20, a Suzuki coupling between C13-C14, and a Yamaguchi macrolactonization. Fragment **3.7** would be derived from dienoate **3.10** by employing a Brown asymmetric crotylation methodology, a cross metathesis and Horner-Wadsworth-Emmons olefination reactions. Aldehyde **3.8** would

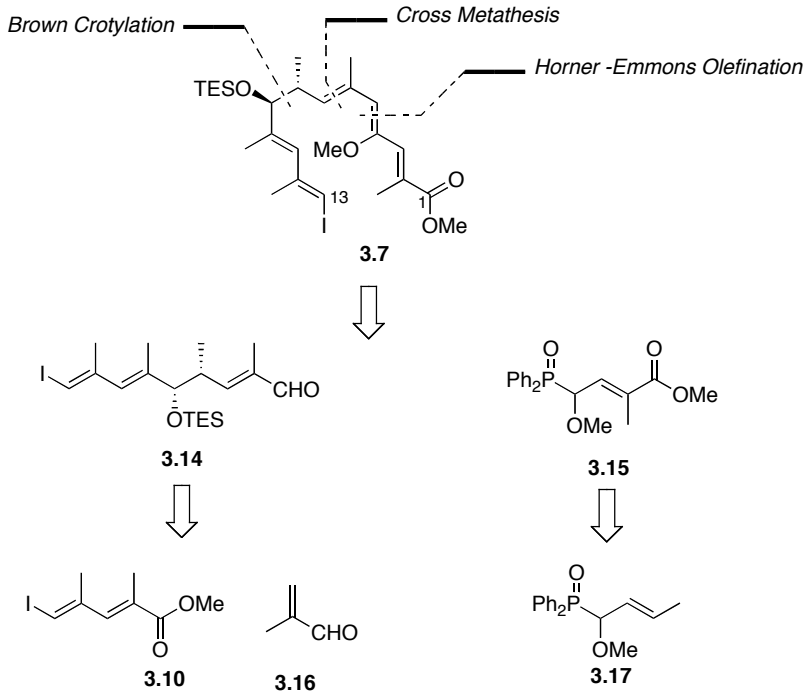
Scheme 3.2 Retrosynthetic analysis of ammocidinone **3.6**



be prepared from epoxide **3.11,** which could be obtained by a known Sharpless asymmetric epoxidation of 3-hydroxyl-1,4-pentadiene.[52] The pyranose ring in ammocidin would be introduced via ethyl ketone **3.9**. The four stereogenic centers in fragment C20-C28 would be established by two auxiliary based asymmetric aldol reactions. Crimmins glycolyloxazolidinethions **3.12** mediated aldol reaction will set up the *syn* diol at C22 and C23.[53] The *anti* diol and quaternary center at C24 position would be realized with Kobayashi's super-quats **3.13** aided aldol chemistry.[54] The flexibility of the synthetic route enable us to prepare the alternate isomers of fragments **3.8** and **3.9** if proven necessary.

3.4 Synthetic studies of fragment 3.7 (C1-C13)

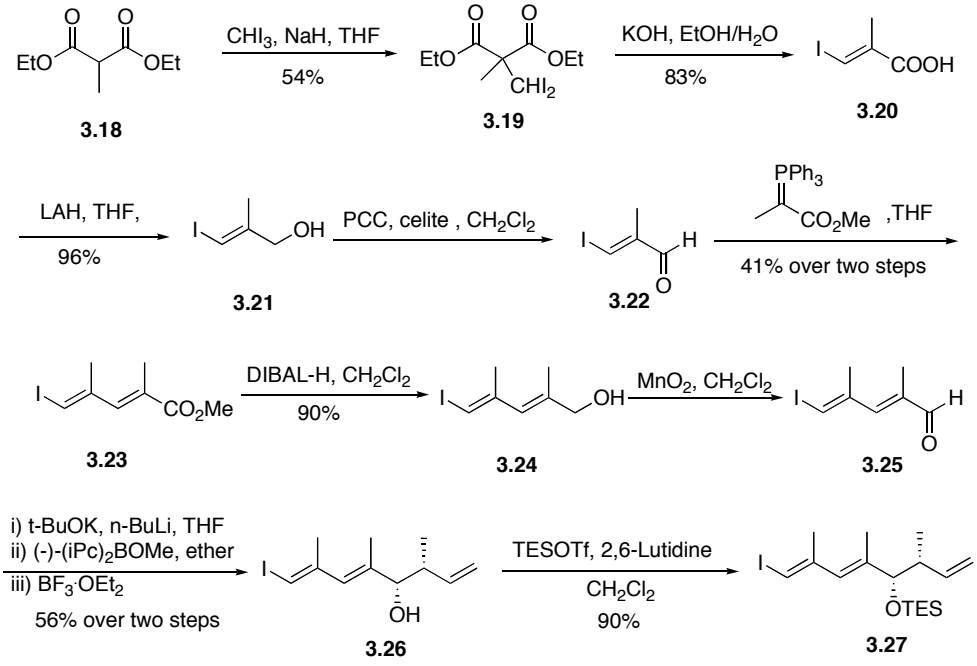
Scheme 3.3 Retrosynthetic analysis of fragment C1-C13 **3.7**



A highlight of our synthesis of fragment **3.7** was the combination of an asymmetric crotylation and cross metathesis strategy to provide aldehyde **3.14** instead of the traditional aldol-Wittig reaction sequence. This design identified dienoate **3.10** and aldehyde **3.16** as the key intermediates for assembly of aldehyde **3.14**. The 4-methoxy-dienoate was to be introduced by a Horner-Emmons reaction with known phosphine oxide **3.15** obtained from intermediate **3.17** (Scheme 3.3).[55]

3.4.1 Synthesis of aldehyde 3.14

Scheme 3.4 Synthesis of homoallylic alcohol **3.27**



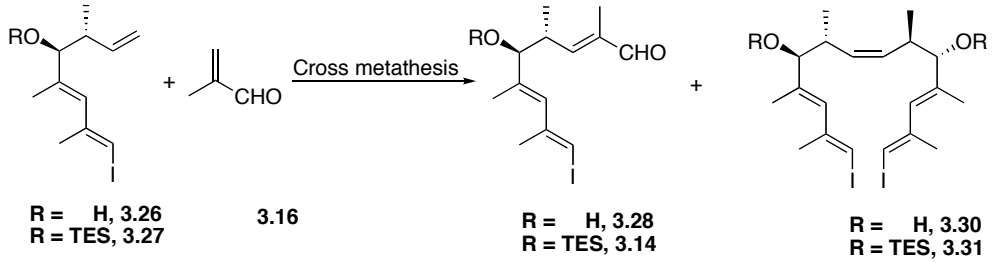
Our preparation of aldehyde **3.14** was adopted from a previously developed route to methyl ester **3.23** that had been developed during our synthesis of apoptolidinone (Scheme 3.4).[56] Starting from malonate **3.18**, following a known procedure, alkylation

with iodoform followed by basic hydrolysis with KOH provided acid **3.20**.[57] Reduction with LAH afforded allylic alcohol **3.21**, which was oxidized with PCC to provide aldehyde **3.22**.[56] A Wittig olefination reaction of **3.22** generated methyl dienoate **3.23**. With **3.23** in hand, we then focused on the introduction of the C8 and C9 stereocenters employing Brown's syn selective asymmetric crotylation. The reduction of methyl ester of **3.23** with DIBAL-H afforded allylic alcohol **3.24**, which was oxidized with MnO_2 to afford aldehyde **3.25**. Unfortunately, aldehyde **3.25** proved to be unstable with neat aldehyde undergoing rapid polymerization on exposure to light. Therefore, without any purification, aldehyde **3.25** was taken through reaction under Brown's conditions to afford homoallylic alcohols **3.26** in 56% yield over two steps.[35] After TES protection of the secondary alcohol **3.26**, terminal alkene **3.27** was suitably protected for the subsequent cross metathesis reaction.

With terminal alkenes **3.26** and **3.27** in hand, our efforts were directed towards cross metathesis with methacrolein **3.16** (Table 3.1). According to Grubbs general model for selectivity in olefin cross metathesis, terminal alkene **3.26** and **3.27** should be categorized as a type I olefin, which implies the alkene is a very reactive cross metathesis partners and can readily undergo homodimerization easily.[58] Methacrolein is categorized as a type III olefin, which does not show any homodimerization tendency during the cross metathesis reaction. Based on these empirical classifications, we anticipated that **3.26** or **3.27** would undergo cross metathesis with methacrolein smoothly. Unfortunately, in the presence of Grubbs secondary generation catalyst (Figure 3.5) and five equivalent methacrolein, **3.27** only provided 23% desired product with 30% recovered starting material (Entry 1). Homodimerization of **3.27** was observed during the reaction (**3.31**).

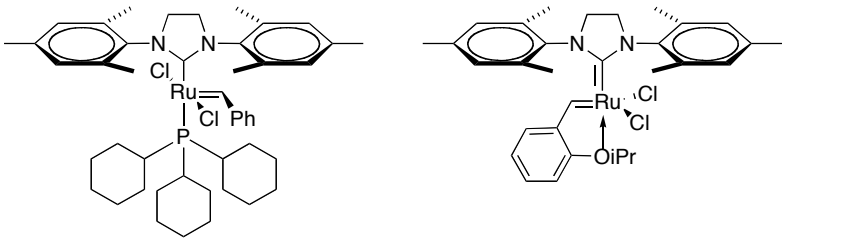
We envisioned that a silyl-protected ether might increase the steric bulk and decrease the activity of the terminal olefin, therefore, alcohol **3.26** was investigated. With excess amount of methacrolein, **3.26** provided only 15% cross metathesis product after reflux for 24 h in dichloromethane and the homodimer of **3.26** was not observed. According to Grubb's rule, type III olefins may require an excess amount of type I olefin partners in order to push the reaction to completion. One equivalent of methacrolein was then used

Table 3.1 Studies of cross metathesis



Entry*	**3.26/3.27**	**3.16**	Catalyst	**3.14/3.28**	**3.30/3.31**	Recovered **3.26/3.27**
1	**3.27**	5 equiv.	**3.32**	23% **3.14**	0% **3.31**	30% **3.27**
2	**3.27**	10 equiv.	**3.33**	35% **3.14**	0% **3.31**	60% **3.27**
3[a]	**3.27**	10 equiv.	**3.33**	66% **3.14**	0% **3.31**	10% **3.27**
4	**3.26**	10 equiv.	**3.32**	15% **3.28**	0% **3.30**	-
5	**3.26**	1 equiv.	**3.32**	0% **3.28**	13% **3.30**	-
6[b]	**3.26**	10 equiv.	**3.32**	21% **3.28**	0% **3.30**	-
7	**3.26**	10 equiv.	**3.33**	20% **3.28**	10% **3.30**	-

** All reactions were taken in CH_2Cl_2 at 40 °C for 24 h; a: yield was obtained after 3 cycles; b: 3.26 was added via syringe pump in 12 h.*



3.32 **3.33**

Grubbs seconary generation catalyst **Hoveyda-Grubbs seconary generation catalyst**

Figure 3.5 Structure of cross metathesis catalyst

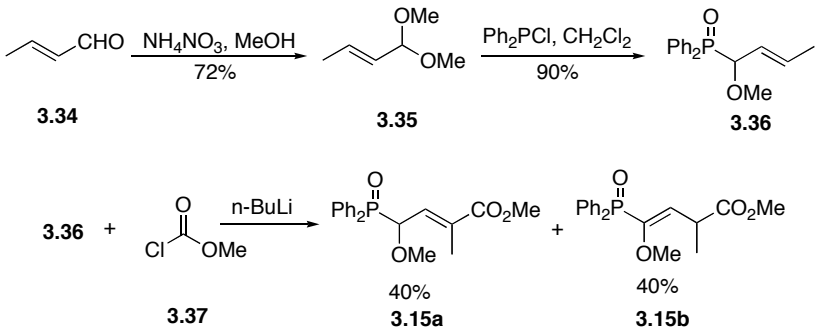
and homodimer product **3.30** was obtained in 13% without any cross metathesis product (Entry 5). This result indicated that terminal alkene **3.26** is reactive during the reaction and excess amount of type III olefin must be used to suppress the homodimerization. This led to adding **3.26** via syringe pump over 12 h in order to obtain optimal concentration conditions. Although the homodimerization of **3.26** was not observed, the reaction only afforded 21% yield with some amount of unreacted starting material (Entry 6). We then turned our attention to Hoveyda modified Grubbs catalyst (Figure 3.5), which is more reactive towards type III olefin.[59] A mixture of dimer and cross metathesis product was provided under Hoveyda's condition (Entry 7). This result indicated that catalyst **3.33** was more reactive than **3.32** for these reaction substrates. We then applied **3.33** to substrate **3.27** and a slightly high yield (35%) was obtained, but gratifyingly, dimerization was suppressed (0% **3.31**) and most of the unreacted starting material was recovered (60%)(Entry 2). After three cycles the yield improved to 66% (Entry 3).

3.4.2 Investigation of HWE reaction to complete synthesis of fragment 3.7

The synthesis of fragment phosphine oxide **3.15** was based on a known procedure (Scheme 3.5).[60] To this end, crotonaldehyde **3.34** was converted to dimethyl acetal **3.35**

with MeOH in the presence of NH_4NO_3.[61] Phosphine oxide **3.36** was obtained via

Scheme 3.5 Synthesis of phosphine oxide **3.15**



treatment of **3.35** with diphenyl phosphine chloride. A mixture of **3.15a** and double bond isomerized compound **3.15b** was furnished by quenching the lithium anion of **3.36** with methyl chloroformate **3.37**. A pure sample of **3.15** was obtained by a single recrystalization from toluene and hexanes. The structure of phosphine oxide **3.36** and **3.15** were verified by single X-ray analysis (Figure 3.6).

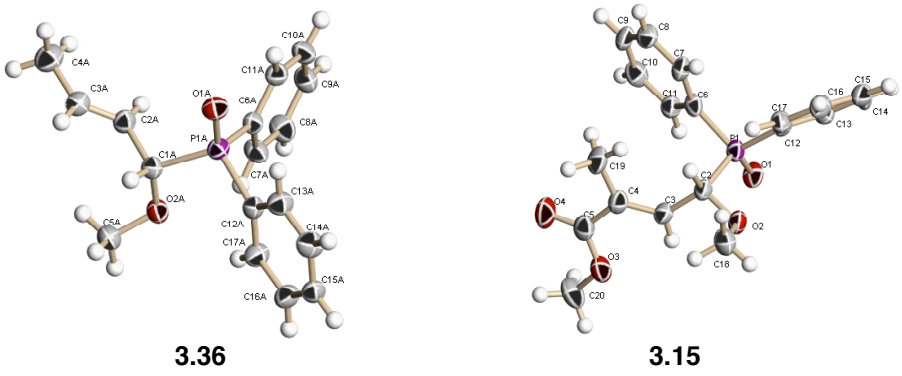
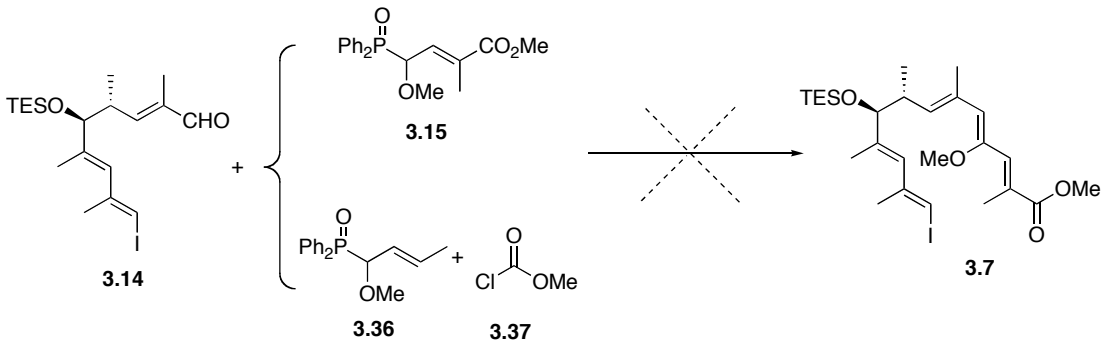


Figure 3.6 X-ray structure of **3.36** and **3.15**

With both aldehyde **3.14** and phosphine oxide **3.15** in hand, we were ready to assemble the top half part of ammocidinone **3.7**. Unfortunately, under typical Murrays' reproted conditions, no reaction occurred with either LDA or NaH as base (Scheme 3.6).[60]

Scheme 3.6 Studies of Horner-Wadsworth-Emmons olefination

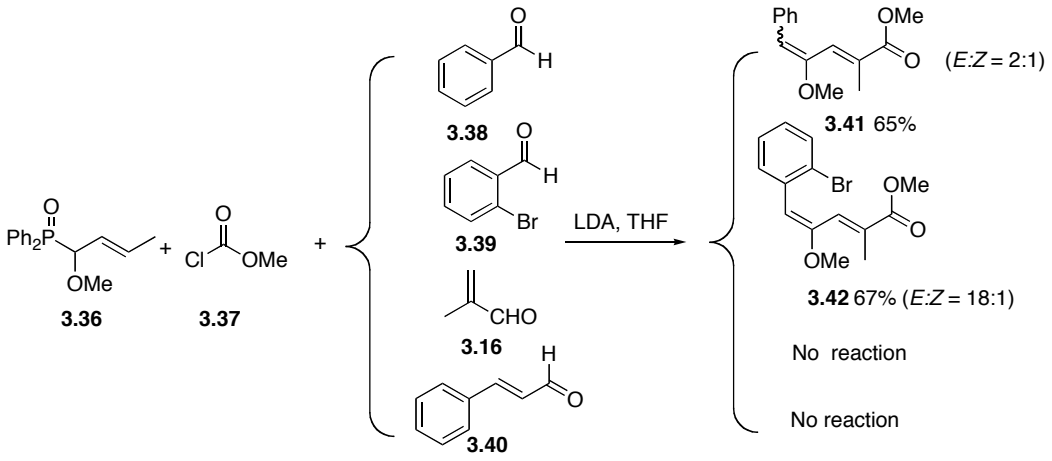


We then examined the generation of **3.15** *in situ* followed by olefination in a one pot reaction, which reportedly provided higher yields when compared to the corresponding two pot reaction sequence. However, we once again failed to obtain any desired product and recovered starting material was observed.

In order to explore the intermolecular Horner-wadsworth-Emmons reaction, we then conducted a model study with benzyl aldehyde **3.38** which was reported to be successful in Murrays' original publication (Scheme 3.7).[62] Under the same condition, the reaction afforded 65% yield with 2:1 (*E:Z*) stereoselectivity. We then selected 2-bromo-benzylaldehyde **3.39** as the reaction partner and again the reaction proceeded smoothly and provided the desired product in 67% yield with 18:1(*E:Z*) stereoselectivity based on NMR analysis. However, when methacrolein **3.16** or cinnamaldehyde **3.40** were

employed as substrates, no desired product was observed and only intermediate **3.15** was observed. With these results we suspect that the methodology does not extend to α,β-unsaturated aldehydes.

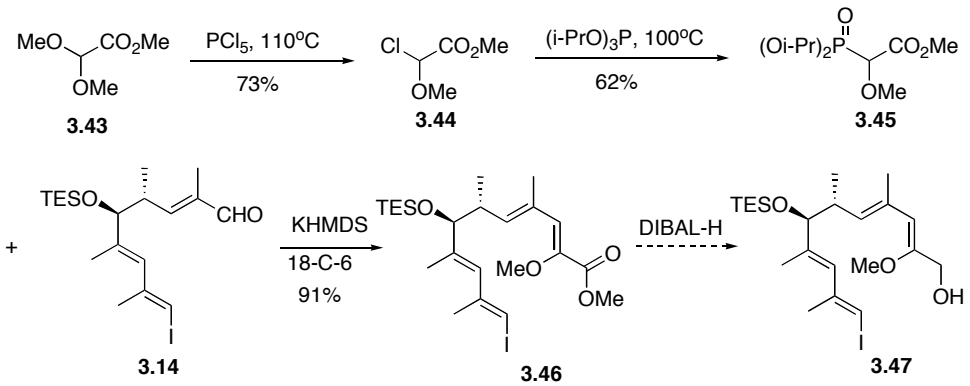
Scheme 3.7 Model study of Horner-Wadsworth-Emmons reaction



At this point we envisioned Murrays' methodology might not be suitable for the preparation of the trienoate moiety. Our attention was then directed to stepwise Horner-Wadsworth-Emmons reaction (Scheme 3.8). As has been illustrated in the total synthesis of bafilomycin A1 by Paterson and Roush, phosphonate **3.45** was a good starat for introduction of the dienoate moiety.[63] Following Roush's procedure, **3.45** was prepared from **3.43** by treatment of PCl_5 and $P(i\text{-}OPr)_3$ sequentially. To our satisfactory, Horner-Wadsworth-Emmons reaction between aldehyde **3.14** and phosphonate **3.45** afforded desired dienoate **3.46** in 91% yield with good stereoselectivity (95:5). Attempts to reduce the methyl ester with DIBAL-H failed to provide the desired allyl alcohol. Analysis of NMR data implied that some of the methyl enol ether was hydrolyzed during the work up procedure (sodium potassium tartrate solution was used). Efforts to conduct the DIBAL-

H reduction, MnO_2 allylic oxidation and Wittig reaction in one pot, which was protected from light, also did not provide any desired product **3.7**.

Scheme 3.8 Stepwise HWE approach to fragment **3.7**



At this stage, we envisioned that polyene **3.7** might not be stable to survive in the following reaction conditions, considering the fragment **3.7** would be introduced to target molecule by Suzuki coupling. Therefore, we decided to leave the elongation of **3.46** until the later stage of the synthesis.

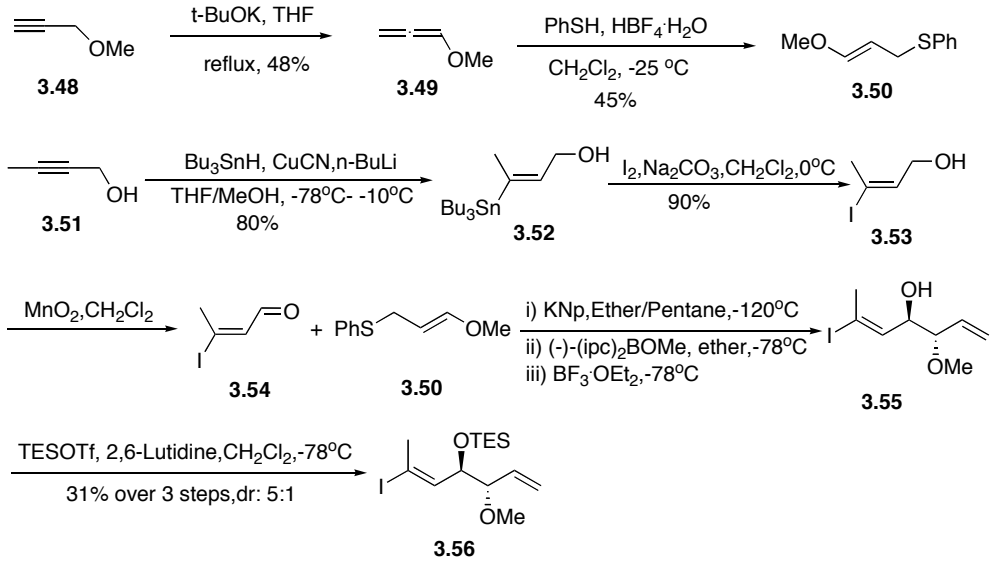
3.5 Synthesis of the fragment 3.8 (C14-C19)

3.5.1 *Anti*-crotylation approach to preparation of diene 3.56

A key consideration in designing a synthesis of aldehyde **3.8** was introduction of the *anti* relative stereochemistry between the C16 and C17 sbustituents. Possible methods for consideration in establishing this relative stereochemistry included an *anti*-aldol or crotylation reaction and nucleophilic opening of an enantiopure epoxide. We initially focused on application of an *anti*–crotylation reaction. Asymmetric crotylation reactions are well-established methods to establish two stereocenters located within a

homoallylic alcohol. Both Brown's pinene and Roush's tartrate mediated addition of (Z)-γ-alkoxyallylboronates to aldehydes can provide *syn*-diols with high selectivity.[33,35] However, due to the configurationally instability of the (E)-γ-alkoxyallyl anion, there are only a small number of examples reported in the literature that use crotylation methodology to establish *anti*-1,2-diols.[64]

Scheme 3.9 Preparation of diene **3.56**

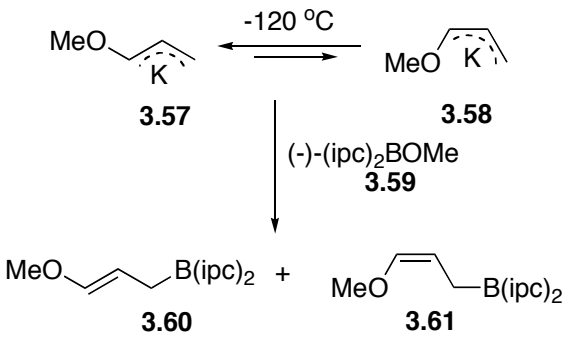


In 1985, Hoffmann and co-workers developed a procedure to prepare (Z)-γ-alkoxyallylboronates starting from (Z)-γ-alkoxyallylphenylsulfide (Scheme 3.9).[65] Later Nicholas adopted this strategy to produce (E)-γ-alkoxyallyldiisopinocampheylboranes which he subsequently utilized in an *anti*-crotylation of a cobalt complex of propiolaldehyde.[66] In the case of our projected stereoselective synthesis of **3.56**, we required aldehyde **3.54** that was prepared from methyl propargyl alcohol **3.51** according to the procedure shown in Scheme 3.9. To this end, a stereo- and regioselective

stannylcupration of alkyne **3.51** afforded vinyl tin **3.52**,[67] which was in turn converted into vinyl iodide **3.53** via halogen-tin exchange.[68] The allylic alcohol **3.53** was then oxidized to aldehyde **3.54** by MnO_2 and used directly without purification (neat aldehyde **3.54** undergoes rapid polymerization).

The chiral borane reagent required by the *syn* selective crotylation was prepared from methyl propargyl ether **3.48**. Treatment of **3.48** with KOt-Bu provided methyl allene ether,[69] which was then subjected to acid catalyzed phenyl thiol addition to afford

Scheme 3.10 Isomerization of (*E*)-γ-alkoxyallylic anion

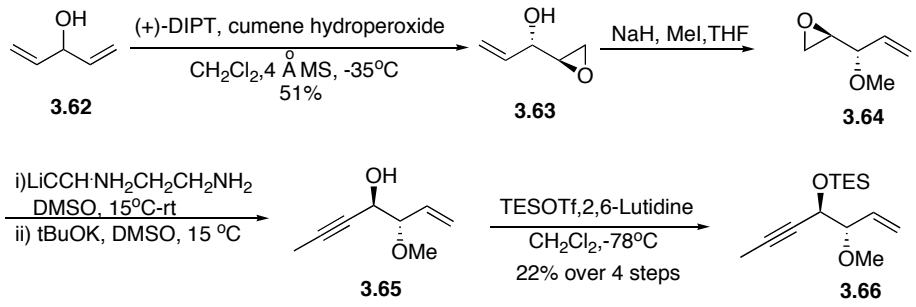


(Z)-γ-alkoxyallylphenylsulfide **3.50**.[65] Under Nicholas's conditions, crotylation followed by silylation of the newly formed hydroxyl group furnished fragment **3.56** as major isomer of an inseparable mixture of isomers. GC analysis and NMR analysis showed that the diastereoselectivity of the addition reaction was approximately 5:1. The observed low diastereoselectivity could be due to the instability of the (E)-γ-alkoxyallylic anion and/or the isomerization during quenching anion with borate **3.59** (Scheme 3.10).

3.5.2 Revised route to the synthesis of fragment 3.8

Despite the efficiency of the above route in terms of required transformations, a more stereoselective sequence was required to avoid production of a mixture of inseparable diastereomers. An alternative approach based on an epoxide opening strategy was then proposed (Scheme 3.11). Asymmetric epoxidation has been extensively studied and proven to be one of the most efficient methods for synthesizing chiral molecules. Adopting Sharpless asymmetric epoxidation (SAE) methodology to set stereocenters at C16 and C17,[70] the synthesis started from commercially available racemic 1,4-pentadien-3-ol **3.62**. A SAE reaction provided enantiopure α-hydroxyl-epoxide **3.63** in good

Scheme 3.11 Preparation of alkyne **3.66**



yield.[71] Methylation of alcohol **3.63** afforded methyl ether **3.64**.[72] Epoxide **3.64** was then treated with the ethylenediamine complex of lithium acetylide.[73] Isomerization of the crude terminal alkyne with KO^{t}Bu afforded the thermodynamically favored internal alkyne **3.65** as sole product. Crude secondary alcohol was then protected as TES silyl ether to afford **3.66** in 22% yield over 4 steps from **3.62**.

Our efforts were then directed towards conversion of the alkyne group to the *Z*-vinyl iodide group. Although many methodologies exist for this transformation,

palladium (0) catalyzed hydrostannylation drew our attention.[67] Pancrazi has systematically investigated addition of tin hydrides to alkynes and proposed an empirical model to help select proper reaction conditions. According to his study, the palladium(0) catalyzed hydrostannylation reaction of propargyl alcohol derivatives bearing a *R* substituent at the α position usually leads to the thermodynamically distal isomer as the major product (Figure 3.7). Based on this observation, we chose

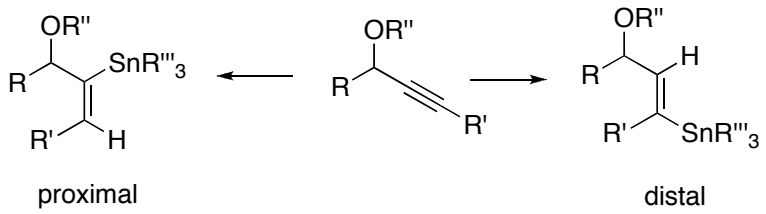
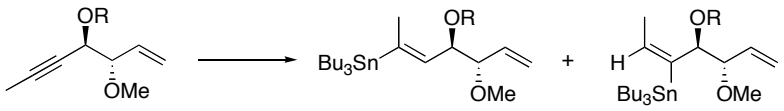


Figure 3.7 Model of regioselectivity of hydrostannylation

$PdCl_2(PPh_3)_2$ as our palladium source and conducted the reaction at room temperature (Table 3.2). Unfortunately, the reaction afforded poor regioselectivity and poor conversion (Entry 1). To suppress the undesired proximal isomer P1' the reaction temperature was decreased to 0 °C and $Pd(Ph_3P)_4$ was examined as the catalyst. The result showed that the ratio between those two regioisomers remained the same (Entry 2). Considering the mechanism, the first step of the reaction was believed to be *cis* addition to the alkyne. We speculated that by using a silyl protective group the steric bulk might favor the desired regioselectivity. However, with **3.66**, poor regioselectivity and conversion was observed with either $Pd(Ph_3P)_4$ or $PdCl_2(PPh_3)_2$ (Entry 3,4). Finally we turned our attention to stannylcupration. Surprisingly, using the procedure developed by

Pancrazi, the addition of excess MeOH (110 equiv.) provided excellent conversion, stereo and regioselectivity in 90% yield with **3.68** as the sole isomer (Entry 5).

Table 3.2 Studies of hydrostannylation on **3.65/3.66**



3.65 R= H,
3.66 R= TES,

3.67 R= H,
3.68 R= TES,

3.69 R= H,
3.70 R= TES,

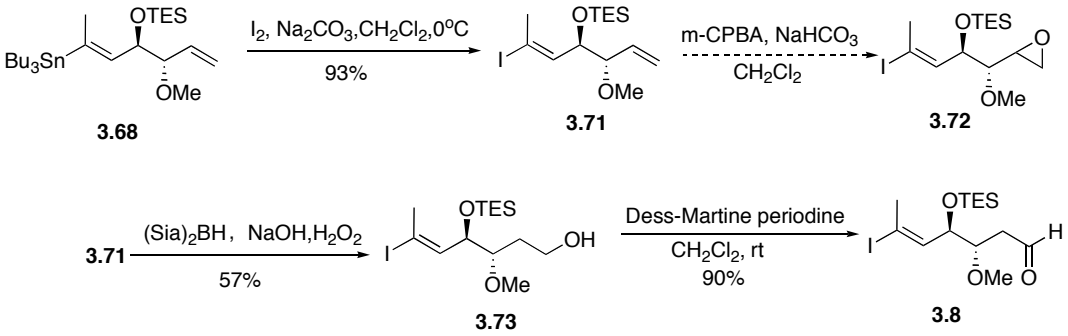
Entry	S.M.*	Reaction Condition	**3.67/3.68**	**3.69/3.70**	S.M.*
1	**3.65**	$PdCl_2(Ph_3P)_2$, Bu_3SnH,THF, rt	29%	9%	---
2	**3.65**	$Pd(Ph_3P)_4$, Bu_3SnH, THF, 0°C	18%	6%	---
3	**3.66**	$PdCl_2(Ph_3P)_2$, Bu_3SnH,THF, rt	14%	6%	58%
4	**3.66**	$Pd(Ph_3P)_4$, Bu_3SnH, THF, 0°C	20%	6%	60%
5	**3.66**	CuCN, Bu_3SnH, nBuLi, THF, MeOH, -78°C - -10°C	90%	Trace amount	0%

**Starting material*

With *Z*-vinyl tin **3.68** in hand, we then moved forward to finish up the synthesis. of fragment **3.8**. Iodine–tin exchange furnished vinyl iodide **3.71** in 93% yield (Scheme 3.12). Introduction of the aldehyde functionality was required to complete the synthesis Epoxide rearrangement to aldehydes or ketones catalyzed either by Lewis acid or base has been well studied recently.[74] Among Lewis acids examined erbium(III)triflate catalyzed regio and stereoselective epoxide opening was appealling.[75] This route called for regioselective epoxidation to set up the terminal epoxide. However, application of m-CPBA to **3.71** failed to provide the desired epoxide and interpretation of the crude NMR

spectroscopy revealed that epoxidation of the tri-substituted olefin was the major product. We then considered a hydroboration-oxidation sequence. A regio- aand chemoselective hydroboration was required to differentiate the two olefins. BH_3•DMS resulted in poor

Scheme 3.12 Completion synthesis of fragment **3.8**



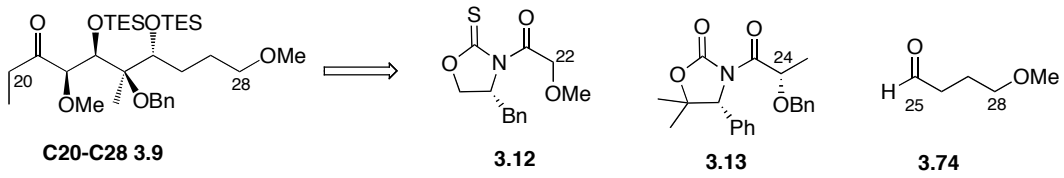
selectivity and poor yield. Considering steric effects, a more bulky borane reagent was needed. However, the application of 9-BBN led to an incomplete reaction and poor yield. Gratifyingly, disiamyl broane demonstrated good regioselectivity and an oxidative work up provided 57% yield without any other isomer. [76] Finally, oxidation of the corresponding alcohol with Dess-Martin periodinane completed the synthesis of aldehyde **3.8**. In summary, this synthetic route for fragment C14-C19 (**3.8)** was easy to conduct on large scale and provided the final 6-carbon aldehyde in good yield (9 linear steps, 5% overall yield).

3.6 Synthesis of fragment 3.9 (C20-C28)

The synthesis of fragment **3.9** C20-C28 relied on two consecutive asymmetric aldol reactions (Scheme 3.13). This approach enabled us to prepare all four possible

stereoisomers of ammocidin in a versatile manner. Introduction of the quaternary center at C24 position was considered one of the most challenging tasks in the total synthesis of

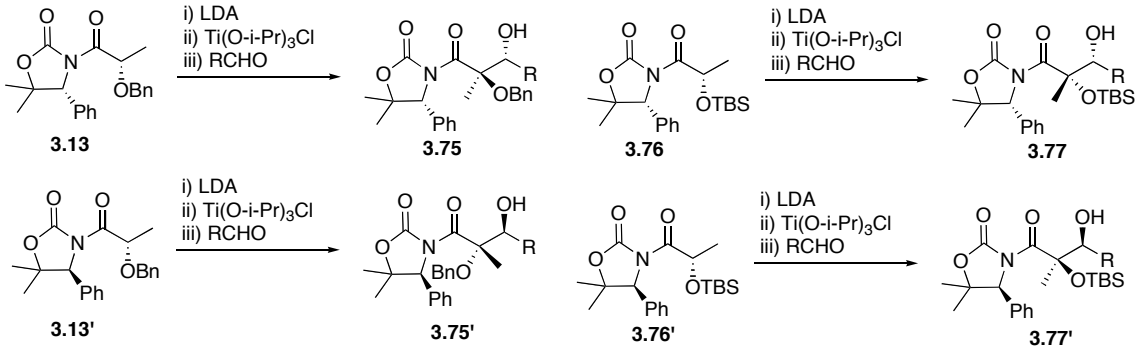
Scheme 3.13 Retrosynthetic analysis of fragment **3.9**



C20-C28 3.9 **3.12** **3.13** **3.74**

ammocidinone. There are only a limited number of methods available to establish a diol bearing a quaternary center stereoselectively. Among them the most practical approach is enantiolselective dihydroxylation developed by Sharpless.[77] However, regarding the *anti*-diol, which is required in our proposed ammocidinone, dihydroxylation usually affords low enantioselectivity. The other useful access to this kind of architecture is

Scheme 3.14 Stereoselectivity of SuperQuats facilitated aldol reaction



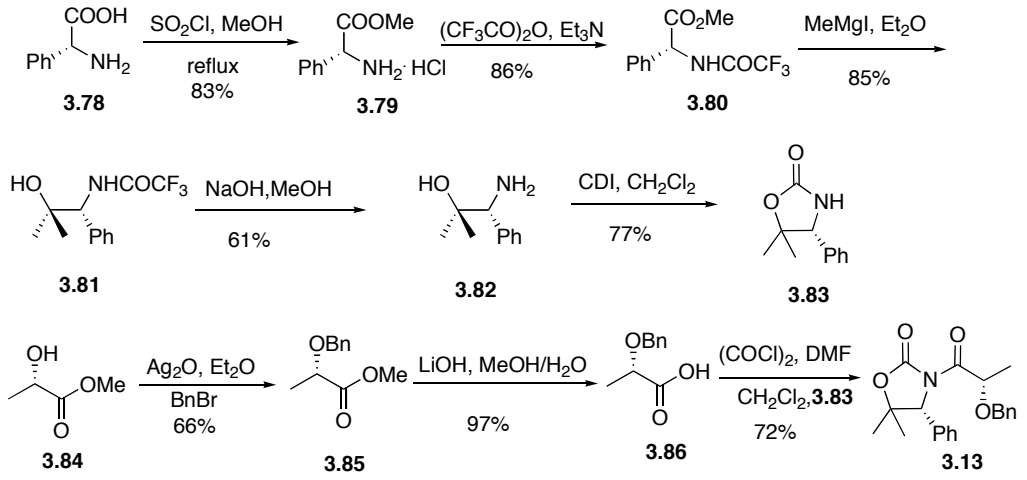
3.13 **3.75** **3.76** **3.77**

3.13' **3.75'** **3.76'** **3.77'**

stereoselective epoxide opening. The quaternary center demands a tri-substituted epoxide, which is difficult to open stereospecifically with nucleophiles. Recently Kobayashi developed an aldol reaction to prepare *syn* or *anti* diols asymmetrically facilitated by lactate derivatives bearing SuperQuats chiral auxiliary.[54] Diastereoselectivity of the aldol reaction could be controlled by varying the protecting groups of the SuperQuats auxiliary. Benzyl ether usually leads to *anti* diols, while TBS ether leads to *syn* diols. The enantioselectivity of the aldol reaction was controlled by the stereochemistry of phenyl substitutent in the SuperQuats auxiliary (Scheme 3.14). Relying on this methodology, in one single step the quaternary center at the C24 position and C25 hydroxyl group could be established stereoselectively. The other *syn* diol at C22 and C23 position was introduced by glycolate derivatives bearing Evans or Crimmins auxiliary. The ethyl ketone will be introduced in the final step.

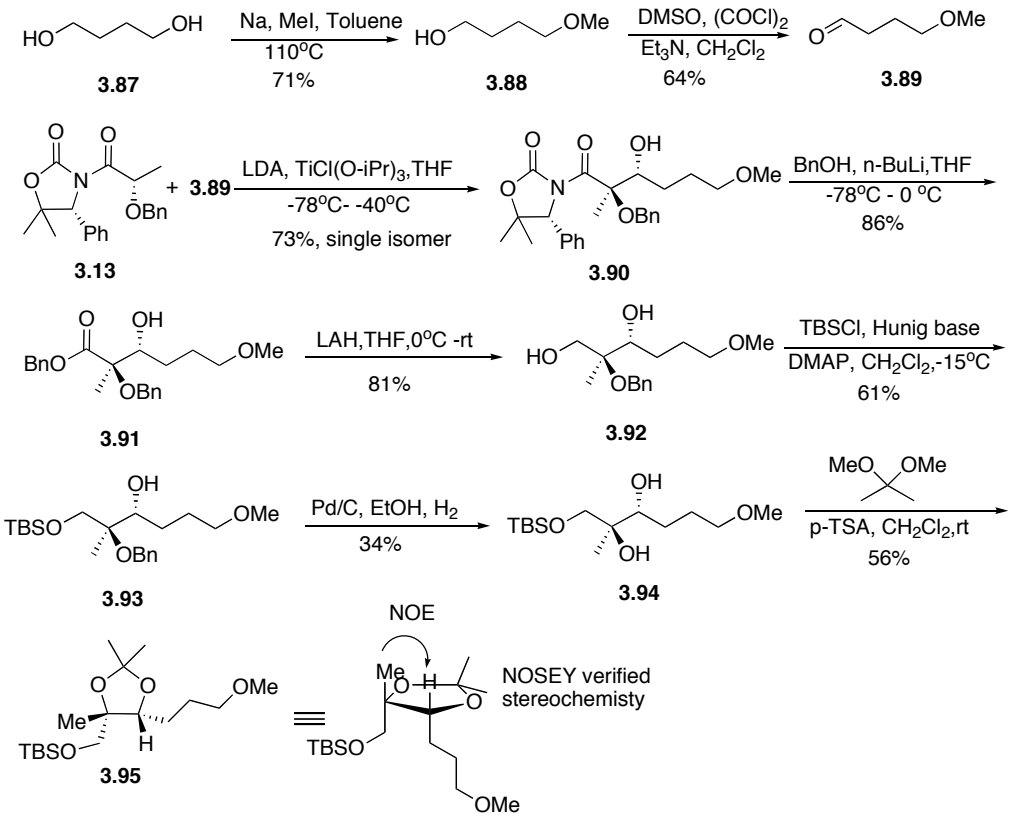
3.6.1 Exploration of Kobayashi aldol reaction to prepare 3.90

Scheme 3.15 Preparation of SuperQuats auxiliary **3.13**



The preparation of the SuperQuats auxiliary **3.13** required for the Kobayashi aldol reaction. The synthesis began with commercially available D-phenylglycine **3.78** (Scheme 3.15). The amino acid was esterified with thionyl chloride and methanol to give methyl ester **3.79** in good yield.[78] Protection of the amine with trifluoroacetic anhydride afforded amide **3.80**, which was then subjected to double Grignard addition with methylmagnesium iodide to provide tertiary alcohol **3.81**.[79] Hydrolysis of the trifluoroaceamide **3.81** under basic conditions gave rise to α-hydroxy amine **3.82**, which

Scheme 3.16 Approve stereochemistry for aldol product **3.90**



was in turn converted into oxazolidinone **3.83** with carbonyl diimidazole (CDI). The remaining part of the auxiliary came from (S)-methyl lactate. Protection of the secondary

alcohol of **3.84** with BnBr gave rise to benzyl ether **3.85**.[80] Then the methyl ester was hydrolyzed to furnish acid **3.86** in nearly quantitative yield.[81] Finally coupling SuperQuats **3.83** and acid **3.86** together provided auxiliary **3.13**.[53]

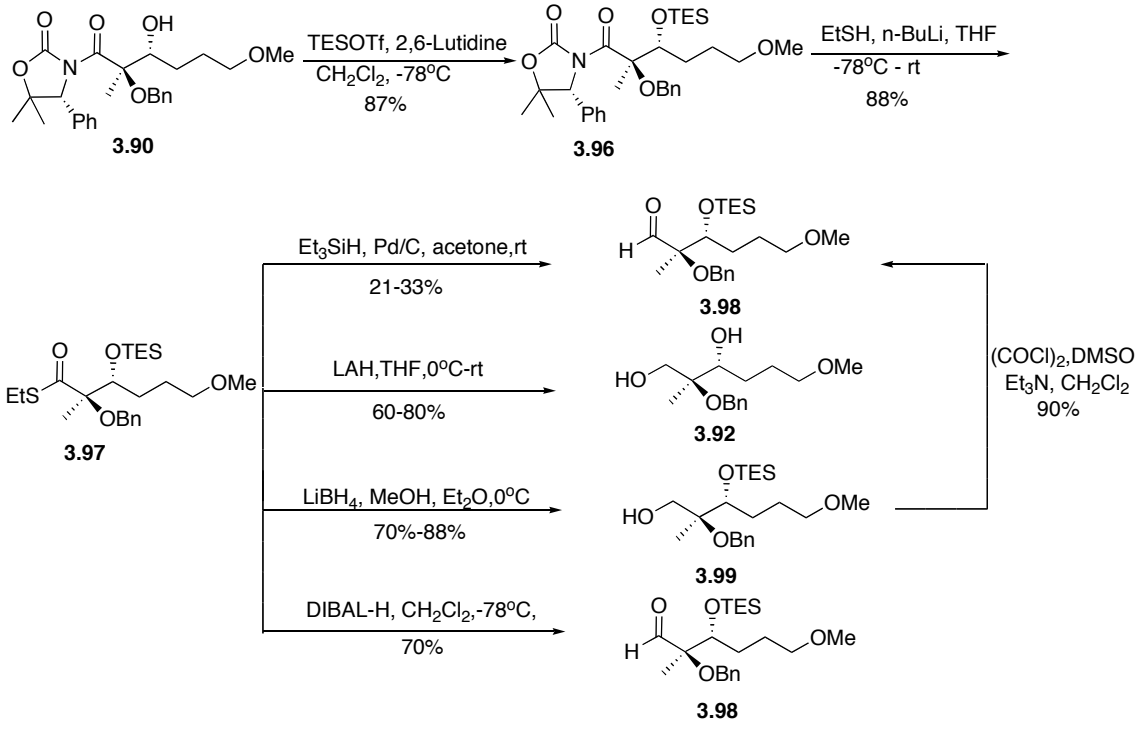
With SuperQuats auxiliaries in hand, the required aldehyde was needed for the Kobayashi aldol reaction. The aldehyde preparation began from 1,4-butanediol **3.87** (Scheme 3.16). Monomethylation with methyl idodide of the sodium salt of 1,4-butanediol afforded methyl ether **3.88** in good yield, which in turn was subjected toSwern oxidation to furnish aldehyde **3.89**. To our satisfaction, under the conditions developed by Kobayashi, the titanium enolate of SuperQuats auxiliary **3.13** coupled with aldehyde **3.89** smoothly and provided aldol adduct **3.90** in 73% yield as the sole isomer. The stereochemistry of **3.90** was determined by NOE analysis of acetonide ring **3.95**.[54] First, oxazolidinone was replaced by benzyl ester with lithium anion of benzyl alcohol. LAH reduction of the benzyl ester rendered diol **3.92**, which was selectively silylated with TBSCl to afford **3.93**. Reductive removal of the benzyl protective group by hydrogenolysis released the tertiary alcohol and the acetonide **3.95** was formed with 2,2-dimethoxypropane. The NOE analysis of acetonide B84 showed a strong signal between C(25) proton and C(24) methyl group, thus confirming the product was the 2,3-*anti* stereoisomer.

3.6.2 Studies towards elaboration of 3.90 to fragment 3.9

After completion of diol product **3.90**, introduction of stereocenters located at C22 and C23 position via Crimmins asymmetric glycolate aldol reaction was examined. First, the free hydroxyl group was protected as triethylsilyl ether **3.96** (Scheme 3.17).

Then SuperQuats auxiliary was replaced by lithium anion of ethyl thiol and afforded ethyl thiol ester **3.97**. The most common procedure employed in this kind of transformation was reduction of the ester followed by mild oxidation of the resulting alcohol. Unfortunately, LAH reduction of the ester **3.97** afforded diol **3.92** instead of **3.99**. A less reactive reducing reagent, lithium borohydride, was then examined and alcohol **3.99** was obtained. Swern oxidation of the resulting alcohol **3.99** provided the desired aldehyde **3.98** in high yield. However, a more efficient method was desired at this stage instead of a standard two-step sequence. Recently, Fukuyama developed a selective reduction procedure to convert thiol esters to aldehydes in one step applying

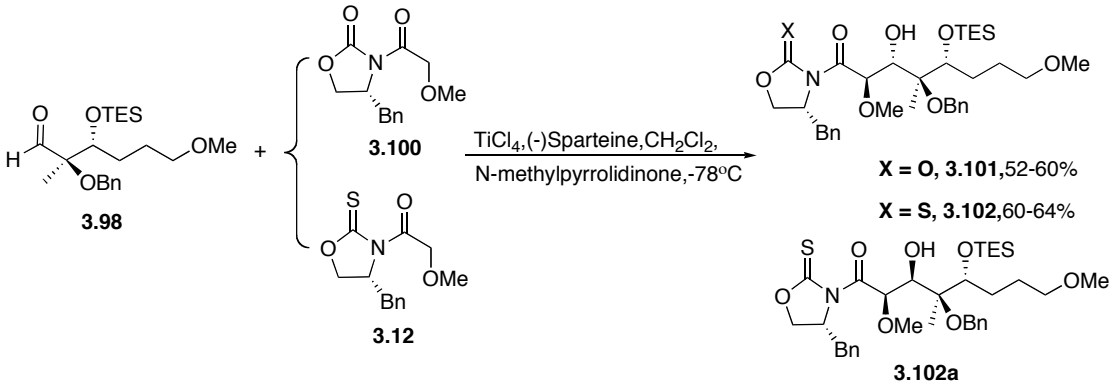
Scheme 3.17 Preparation of aldehyde **3.98**



Pd/C catalyzed hydrogenation in the presence of triethyl silane.[82] Unfortunately, this method only provided 21-33% yield of product along with unreacted starting material. Efforts to optimize the reaction and improve the conversion failed, possibly because of the steric hindrance from the α-tertiary center. Finally, we found that DIBAL-H (1.3 equiv.) provided desired aldehyde **3.98** in good yield.

With aldehyde **3.98** in hand, we set out to explore the Crimmins *syn* aldol reaction to set up the *syn* relationship at C22 and C23 position (Scheme 3.18). The reaction was first conducted with Evans N-glycolyloxazolidiones **3.100**, prepared from D-phenylglycine and methoxyacetic acid, and provided aldol adduct **3.101** in good yield (52%-60%) Under the same reaction condition, Crimmins glycolyloxazolidinethione auxiliary **3.12** afforded a slightly higher yield **3.102** (60%-64%).[83] Both **3.101** and **3.102** were obtained as a single isomer based on the NMR observation. Based on the Crimmins

Scheme 3.18 Crimmins *syn* glycolate aldol reaction



model, we predicted that the stereochemistry was the desired *syn* relationship, but single crystal X-ray analysis of the crystalline of **3.102** indicated that the C22-C23 stereocenters were actually of *anti*-stereochemistry (Figure 3.8). The stereochemistry of **3.101** was

determined to be *anti* relationship based on the NMR analysis comparison with **3.102**.

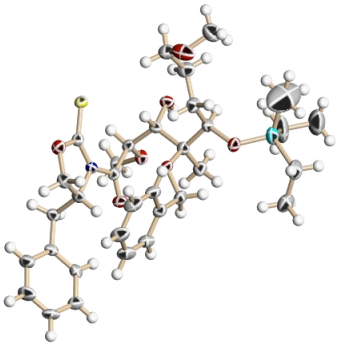


Figure 3.8 X-ray structure of aldol adduct **3.102**

This experimental observation can be rationalized based on the transition state models shown in Figure 3.6. According to Crimmins model, with one equivalent of Lewis acid $TiCl_4$, the reaction should proceed through a closed six-membered transition state and afford the desired *syn* aldol product **3.102a**. However, the unfavorable syn-

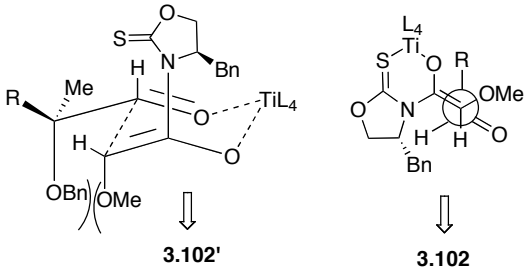


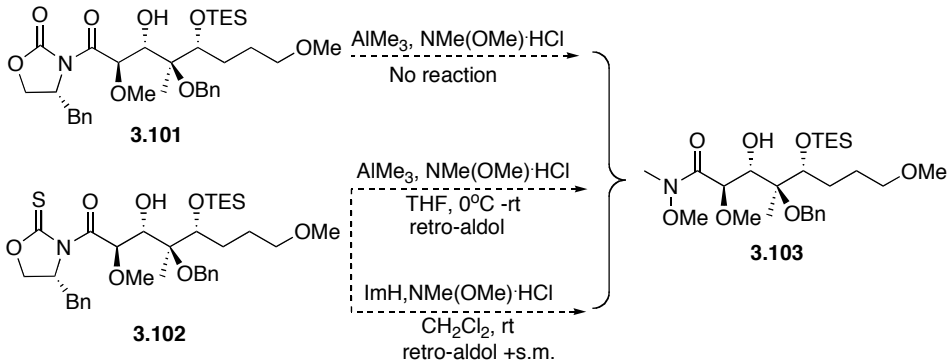
Figure 3.9 Rationalization of stereochemistry of aldol product **3.102**

pentane interaction between the benzyoxy on the steric bulky α quaternary stereocenter and the methoxy probably disfavors a closed transition state. Thus, we propose that the reaction proceeds through an open transition state, as suggested by Heathcock, to explain propionate *anti* aldol mediated by N-acyloxazolidinones (Figure 3.9).[84]

Although at this stage we did not obtain the desired aldol product **3.102a**, considering the generality of our synthetic strategy and the insignificance of the remaining chemistry on stereochemistry, we decided to continue with the undesired isomer **3.102** to investigate the remaining steps of the synthetic strategy. Our efforts were then directed towards introducing the ethyl ketone to complete the synthesis of fragment **3.9'**. Our initial design of the synthetic route was to convert the auxiliary to a Weinreb amide and subsequently the ethyl Grignard addition.

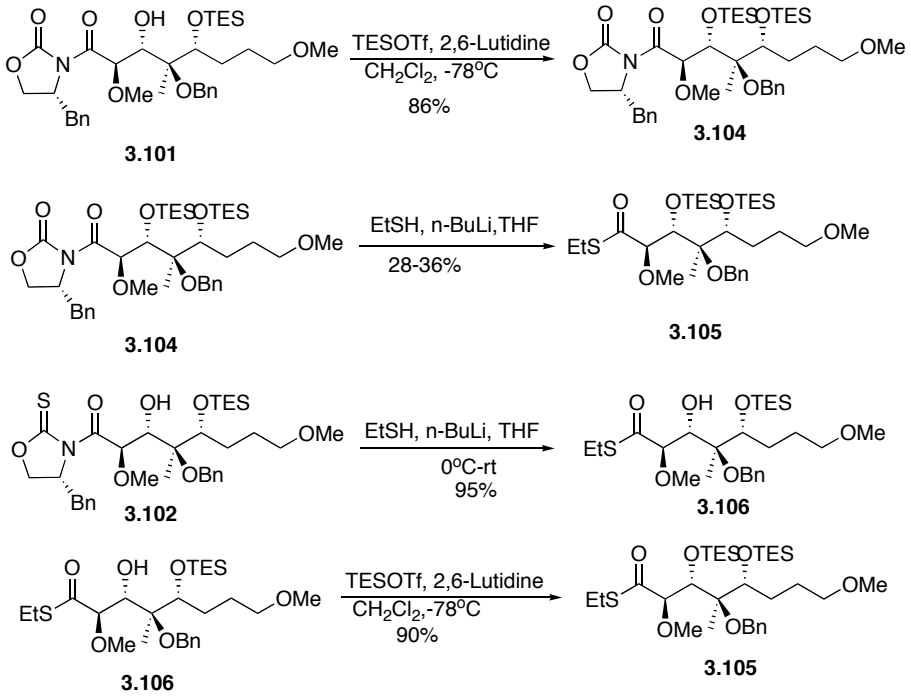
However, standard conditions to generate Weinreb amides led to no reaction, and recovery of most of the starting material was recovered (Scheme 3.19). We then turned to manipulation of thioxazolidnone **3.102** because it was reported that Crimmins

Scheme 3.19 Studies towards preparation of Weinreb amide **3.103**



oxazolidithione was more labile than Evan's oxazolidinone auxiliary and hence easier to be removed. Unfortunately, Lewis acid mediated replacement ($AlMe_3$, Weinreb salt) rendered aldehyde **B98** and auxiliary **3.100** via a retro-aldol reaction and all efforts to prevent retro-aldol reaction failed. Basic conditions developed by Crimmins provided a mixture of unreacted starting material and retro-aldol product.

Scheme 3.20 Preparation of ethylthioester **3.105**

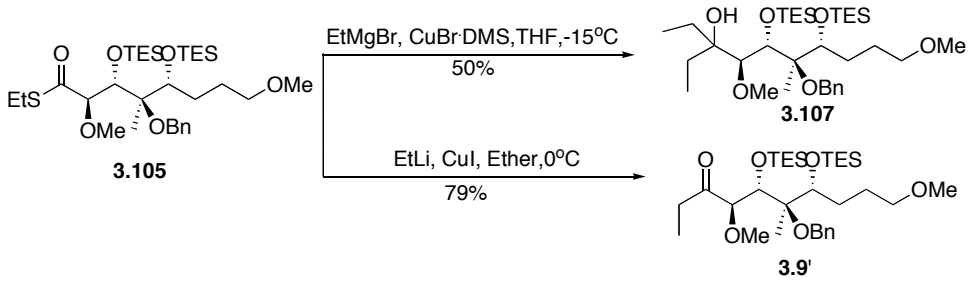


These failures led to an alternative strategy to introduce the ethyl ketone, an organocuprate catalyzed substitution of a thioester then drew our attention.[85] Protection of the free secondary hydroxyl group with TESOTf afforded silyl ether **3.104**, which was subjected to substitution with the lithium thioethoxide (Scheme 3.20). To our surprise, this reaction furnished desired thioester **3.105** in a low 28%-36% yield. Exchanging the lithium anion for potassium anion led to no reaction at all.[86] Presumably this poor yield

was due to the steric hindrance introduced by the TES silyl ether. Alternatively, starting from **3.102**, thioethoxide displacement of the auxiliary proceeded smoothly and afforded desired thioester **3.106** in 95% yield, which was silylated with TESOTf to provide **3.105**.

The formation of the ethyl ketone from the thiol ester **3.105** could be achieved by a couple of methods such as organo-cuprate catalyzed Grignard addition and organocuprate substitution. We initially attempted copper (I) catalyzed Grignard

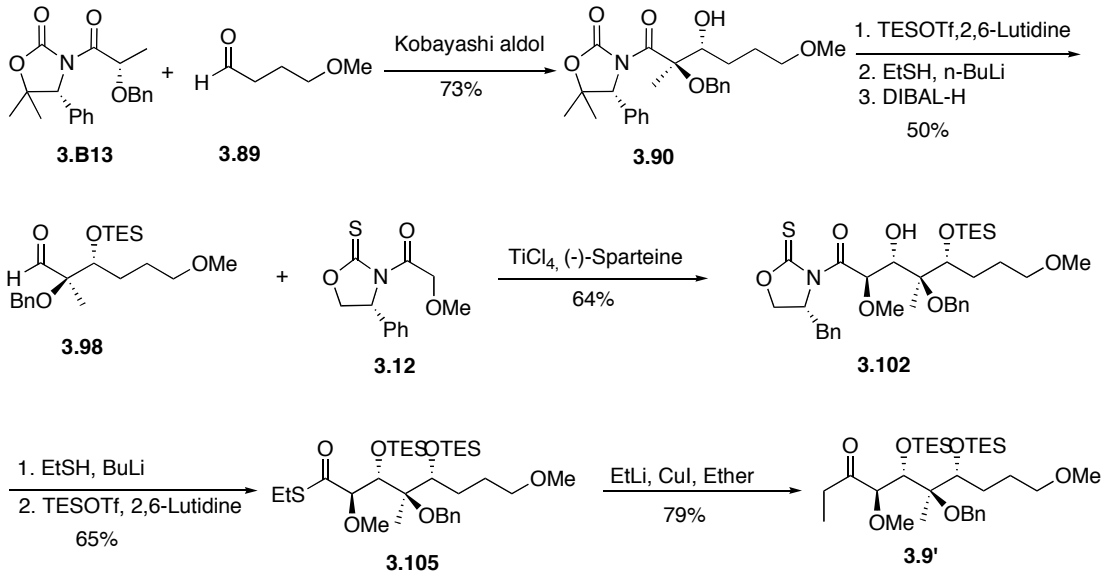
Scheme 3.21 Synthesis of ethyl ketone **3.9'**



substitution with ethylmagnesium bromide.[87] However, an over-addition product **3.107** was generated at -15°C (Scheme 3.21). Alternatively, we considered using of a Gilman reagent. But the reaction with lithium deethyl cuprate did not proceed at -15°C.[88] However, after the reaction temperature was warmed up to 0 °C, the desired ethylketone **3.9'** was provided in 79% yield.

In summary, the synthesis of fragment **3.9'** featured two consecutive aldol reactions and one cuprate addition reaction and was completed in 8 linear steps with a 12% overall yield (Scheme 3.22).

Scheme 3.22 Summary of synthesis of fragment **3.9'**

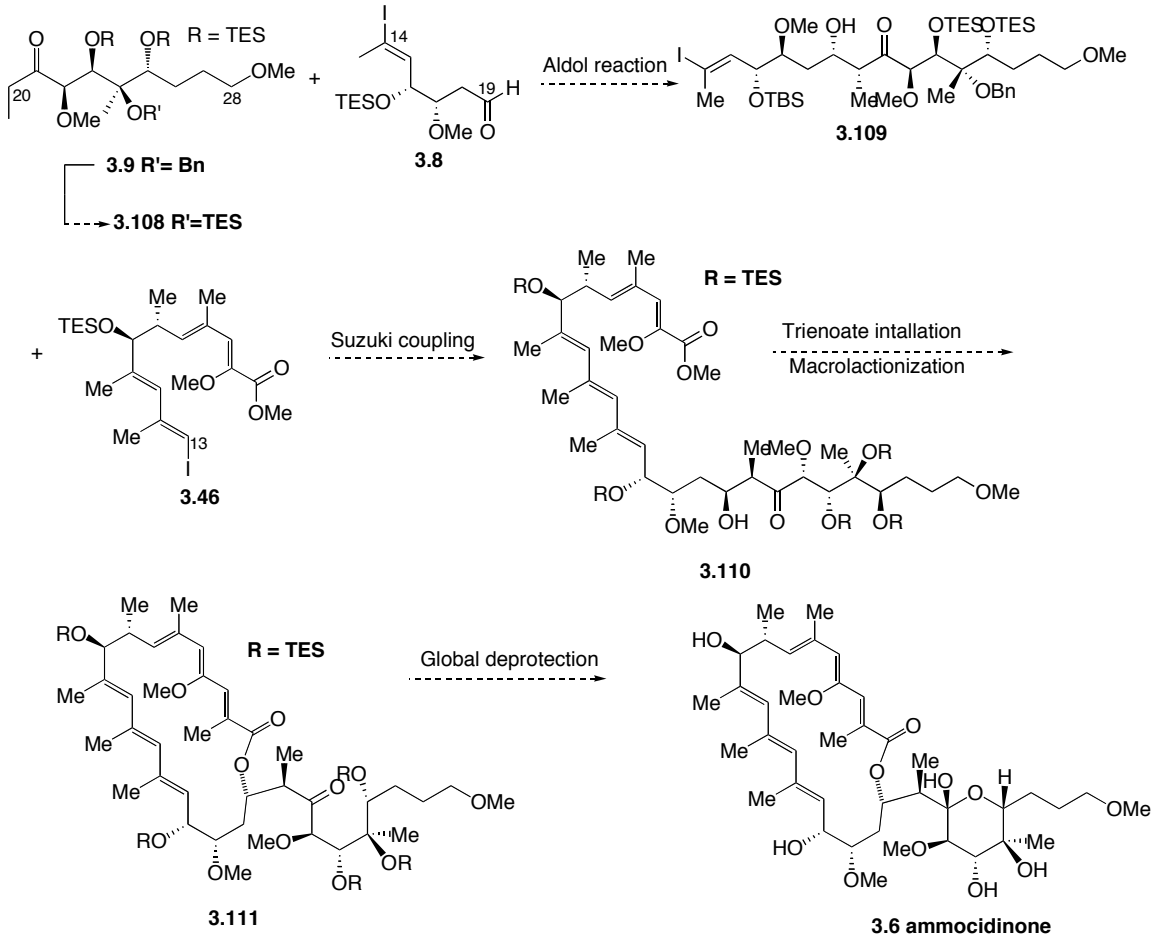


3.7 Conclusion: projected completion of ammocidinone

In conclusion, we have developed a highly convergent synthetic strategy to build ammocidinone **3.6**. Three key building blocks were prepared efficiently: fragment **3.9'** (C23 epimerized C20-C28) was synthesized by two consecutive asymmetric aldol reactions in 8 linear steps at 12% yield; fragment **3.8** (C14-C19) was built in 9 linear steps at 5% overall yield featuring a Sharpless asymmetric epoxidation and regioselective hydroboration reaction; fragment **3.46** was achieved via a Brown asymmetric crotylation, cross metathesis and Horner-Wadsworth-Emmons reaction. To complete the synthesis of ammoidinone **3.6**, we still require correction of the C23 stereocenter proper method. Possible solutions include examining different lewis acids mediated *syn* aldol reactions like nBu_2BOTf and $Sn(OTf)_2$ or employing asymmetric Mukaiyama aldol reaction.[89] With all building blocks in hand, an efficient strategy was required to assemble them together(Scheme 3.23). We envisioned that an $Sn(OTf)_2$ mediated aldol reaction would

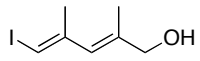
couple ethyl ketone **3.108**, which is derived from **3.9** via changing benzyl ether to TES silyl ether, and install the required stereochemistry.[90] Then a Suzuki coupling will attach fragment **3.46** to **3.109** and afford pentaene **3.110**. At this stage a reliable method is required to install the trienoate unit. Examining suitable reduction and oxidation conditions is necessary to avoid the unstability of the polyene system. Subsequently, macrolactonization will furnish the lactone **3.111**,[10] which finally will be subjected to global deprotection and simultaneously cyclization[45] to install the pyranose moiety and completed the total synthesis of ammocidinone.

Scheme 3.23 Projected completion of ammocidinone **3.6**



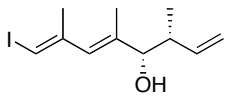
3.8 Experimental Section

General procedures. Reagents were obtained from commercial suppliers, and where appropriate were purified prior to use. All reactions were carried out under a nitrogen or argon atmosphere using dry glassware that had been flame-dried under a stream of nitrogen, unless otherwise noted. All necessary solvents were purified prior to use. Tetrahydrofuran and ethyl ether were distilled from sodium/benzophenone; dichloromethane and benzene were distilled from calcium hydride. Chloroform was washed twice with water, dried over potassium carbonate, refluxed, and distilled from phosphorus pentoxide. Triethylamine was distilled from calcium hydride and stored over sodium hydroxide. Reactions were monitored by thin-layer chromatography (TLC) using 0.25-mm E. Merck precoated silica gel plates. Visualization was accomplished with UV light and aqueous ceric ammonium molybdate solution, anisaldehyde or $KMnO_4$ stain followed by charring on a hot-plate. Flash chromatography was performed with the indicated solvents using silica gel 60 (particle size 230-400 mesh) with the indicated solvent system. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. Melting points are uncorrected unless otherwise noted. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 400, and 500 MHz spectrometers at ambient temperature. ^{1}H and ^{13}C NMR data are reported as δ values relative to tetramethylsilane or chloroform. High-resolution mass spectra were obtained at Texas A&M University Mass Spectrometry Service Center by Dr. Shane Tichy on an API QSTAR Pulsar Instrument. The single-crystal X-ray diffraction analysis was performed by Dr. Joseph Reibenspies of Texas A&M University using a Bruker Smart 1000 CCD single crystal X-ray diffractometer.



3.24

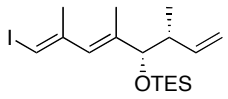
To a solution of **3.23** (532 mg, 2 mmol) in CH_2Cl_2 (20 mL) at -78°C was added DIBAL-H (2.2 mL, 2.2 mmol, 2.2 equiv) dropwise. After the addition was completed, the resulting solution was stirred at -78 °C for 1h before quenched with 1 mL MeOH. The mixture was poured into a 125 mL beaker containing 50 mL saturated Rochelle's salt (Sodium Potassium Tartrate) solution and stirred at room temperature for 1h. After separated, aqueous layer was extracted with CH_2Cl_2 (30 mL X 3). The combined organic layer was dried over Na_2SO_4, concentrated *in vacuo*. Residue was purified by flash chromatography (Hexanes: EtOAc, 2:1) to afford 400 mg (85%) of **3.24** as colorless oil: IR: (neat) 3314, 2912, 1439, 1260 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.07 (s, 1H), 5.91 (s, 1H), 4.06 (s, 2H), 1.95 (s, 3H), 1.76 (s, 3H), 1.55 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.2, 137.5, 125.4, 79.9, 68.2, 25.0, 15.4 ; HRMS (APCI) *m/z* 239.1771 [$(M+H)^+$ calcd for $C_7H_{11}IO$].



3.26

To a solution of t-BuOK (690 mg, 5.8 mmol, 2 equiv) in THF (15 mL) at -78 °C was added *cis*-2 butene (3 mL, 30 mmol, 10 equiv). After 5 min, n-BuLi (2.35 mL of 2.5 M solution in hexanes, 5.8 mmol, 2 equiv) was added dropwise. 5 min later, the reaction mixture was warmed up to -45 °C and stirred for 15 min. The reaction mixture was then cooled back to -78 °C and (-)-$(ipc)_2$BOMe (2.2 g, 7.0 mmol, 2.4 equiv) in ether (15 mL) was added via cannula. The resulting mixture was stirred at -78 °C for 30 min and

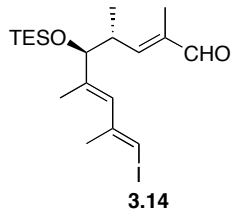
$BF_3{\cdot}OEt_2$ (1.1 mL, 7.9 mmol, 2.68 equiv) were added. In a meanwhile, to a solution of **3.24** (700 mg, 2.94 mmol) in CH_2Cl_2 (20 mL) at room temperature was added MnO_2 (21 g, 30 equiv/m). The resultant mixture was stired at room temperature for 2h before filtered through a short pad of celite and concentrated *in vacuo* to a solution of crude **3.25** in CH_2Cl_2 (ca. 1 mL). After $BF_3{\cdot}OEt_2$ was added 15 min, **3.25** in CH_2Cl_2 (1 mL) was added. The resulting mixture was stirred at -78 °C overnight and 10 mL NaOH (3 M) was added followed by 4 mL H_2O_2 (30% solution in H_2O). After refluxed at 60 °C for 2 h, it was cooled down to room temperature and separated, extracted with ether, dried over Na_2SO_4. After filtration and concentration *in vacuo*, the residue was purified by flash chromatography (Hexanes:EtoAc, 30:1) to afford 486 mg (56%) of **3.26** as colorless oil: $[\alpha]_D^{25}$ +8.1° (*c* 1.8, $CHCl_3$); IR (neat) 3410, 2973, 1451, 1296, 1008 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.03 (s, 1H), 5.88 (s, 1H), 5.75 (m, 1H), 5.06 (m, 2H), 3.89 (d, J = 8 Hz, 1H), 2.45 (m, 1H), 1.93 (s, 3H), 1.63 (bs, 1H), 1.04 (d, J = 8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3, 140.7, 138.6, 127.0, 114.8, 78.0, 79.8, 41.1, 25.1, 14.3, 14.2; HRMS (ESI) *m/z* 299.0486[$(M+Li)^+$ calcd for $C_{11}H_{17}IO$: 299.0484]. The enantiomeric excess of **3.26** was examined by $^{19}FNMR$ analysis after converting to Mosher ester with (*R*)-(+)-α-mehtyoxyl-α-(trifluoro-methyl)phenylacetic acid. (88% ee)



3.27

To a solution of **3.26** (210 mg, 0.72 mmol) in CH_2Cl_2 (5 mL) at -78 °C was added TESOTf (320 μL, 1.44 mmol, 2 equiv) and 2,6-lutidine (250 μL, 2.16 mmol, 3 equiv). The resultant solution was stirred at -78 °C for 3h, quenched with H_2O (5 mL), extracted

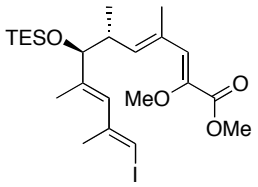
with CH_2Cl_2 (10 mL x 3), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexanes: EtOAc, 100:1) to afford 260 mg (90%) of **3.27** as colorless oil: $[\alpha]_D^{25}$ +4.2° (*c* 2.1, $CHCl_3$); IR: (neat) 2955, 1457, 1239, cm^{-1}; ^1H NMR (500 MHz $CDCl_3$): δ 5.97 (s, 1H), 5.74 (s, 1H), 5.67-5.60 (m, 1H), 4.99 (d, J = 17.5 Hz, 1H), 4.93 (d, J = 10.5 Hz, 1H), 3.73 (d, J = 7.5 Hz, 1H), 2.33 (m, 1H), 1.91 (s, 3H), 1.67 (s, 3H), 1.03 (d, J = 6.5 Hz, 3H), 0.95 (t, J = 8 Hz, 9H), 0.59 (q, J = 8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.5, 141.2, 139.9, 126.9, 113.6, 82.0, 79.4, 42.6, 15.0, 15.9, 13.7, 6.9, 4.9; HRMS (APSI) *m/z* 407.0594[$(M+Li)^+$ calcd for C17H31IOSi].



3.14

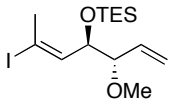
To a solution of **3.27** (180 mg, 0.44 mmol) in CH_2Cl_2 (3 mL) at room temperature was added methacrolein (180 μL, 2.2 mmol, 5 equiv) and Hoveyda-Grubbs secondary generation catalyst (27 mg, 0.044 mmol, 0.1 equiv). After degassed (by freezing in Liquid nitrogen under vacuum followed by warm up to room temperature, repeated three times), the resulting solution was refluxed at 40 °C overnight. After removed solvent *in vacuo*, the residue was purified by flash chromatography (Hexanes: EtOAc, 50:1) to afford 68 mg (38%, *E:Z* = 10:1) of **3.14** as colorless oil, after three this cycles, 130 mg (66%) of **3.14** was obtained: $[\alpha]_D^{25}$ -6.4° (*c* 1.8, $CHCl_3$); IR: (neat) 2955, 1689, 1457, 1258, 1154 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 9.36 (s, 1H), 6.28 (d, J = 10.5 Hz, 1H), 5.96 (s, 1H), 5.82 (s, 1H), 3.90 (d, J = 7 Hz, 1H), 2.88 (m, 1H), 1.89 (s, 3H), 1.76 (d, J =

1 Hz, 3H), 1.65 (d, J = 1 Hz, 3H), 1.1 (d, J = 6.5 Hz, 3H), 0.96 (t, J = 8 Hz, 9H), 0.62 (q, J = 8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.2, 156.5, 144.0, 139.0, 138.2, 127.3, 80.9, 79.9, 38.3, 29.7, 25.0, 15.5, 13.8, 9.3, 6.8, 4.8; HRMS (ESI) *m/z* 455.1459[$(M+Li)^+$ calcd for $C_{19}H_{33}IO_2Si$ 455.1455].



3.46

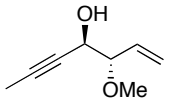
To a solution of **3.45** (89 mg, 0.33 mmol, 2.2 equiv) in THF (2 mL) at 0 °C was added 18-C-6 (85 mg, 0.32 mmol, 2.15 equiv) followed by KHMDS (0.6 mL of 0.5 M solution in toluene, 0.30 mmol, 2.0 equiv). After 30 min, **3.14** (67 mg, 0.15 mmol) was added in THF (1 mL). The resultant solution was then allowed to warm up to room temperature and continue to stir overnight. The reaction was quenched with NH_4Cl (sat. 5 mL), extracted with Ether (10 mL x 3), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexanes: EtOAc, 40:1) to afford 73 mg (91%) of **3.46** (*Z:E* = 100:6 based on NMR analysis) as colorless oil: $[\alpha]_D^{25}$ +22.5° (*c* 3.9, $CHCl_3$); IR: (neat) 2958, 1719, 1244, cm^{-1}; ^{1}H NMR (500 MHz $CDCl_3$): δ 6.88 (s, 0.06 H), 6.53 (s, 1H), 5.94 (s, 1H), 5.74 (s, 1H), 5.54 (d, J = 10 Hz, 1H), 3.79 (s, 3H), 3.80-3.75 (m, 1H), 3.64 (s, 3H), 2.70-2.65 (m, 1H), 1.96 (s, 3H), 1.88 (s, 3H), 1.64 (s, 3H), 1.0 (d, J = 6.5 Hz, 3H), 0.94 (t, J = 8 Hz, 9 H), 0.60 (q, J = 8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ; 165.3, 144.3, 142.9, 141.5, 139.8, 130.5, 129.5, 126.9, 81.8, 79.5, 60.2, 51.9, 37.6, 24.9, 16.4, 14.7, 13.7, 6.8, 4.8.



3.56

To a solution of naphthalene (533 mg, 4.16 mmol, 8 equiv) in dry THF (4 mL) at room temperature was added potassium metal (162 mg, 4.16 mmol 8 equiv) slowly. The reaction solution became green immediately. After 1 h stirring at room temperature, ether (1 mL) and pentane (1 mL) were added and the resultant solution was cooled to -120 °C with liquid nitrogen and pentane. A solution of (*E*)-1-methoxy-3-(phenylthio)-propene **3.50** (375 mg, 2.08 mmol, 4 equiv) and (-)-*B*-methoxydiisopinocampheyl-borance (658 mg, 2.08 mmol, 4 equiv) in dry THF (4 mL) was added via cannula. The resulting mixture was stirred at -120 °C for 1 h then -78 °C for 3 h before filtered through a short pad of celite under nitrogen quickly at -78 °C. $BF_3{\cdot}OEt_2$ (342 μL, 2.7 mmol, 5.2 mmol) was then added and the resulting solution was stirred at -78 °C for 15 min. Meanwhile, a solution of **3.53** (100 mg, 0.50 mmol) in CH_2Cl_2 (5 mL) at room temperature was added MnO_2 (3.5 g, 35 equiv/mass). The resultant black mixture was stirred at room temperature for 2 h before filtered though a celite pad and dried over Na_2SO_4 for 1 h. After filtration, the solution was concentrated *in vacuo* to a volume of 1 mL and the residue was diluted with dry THF (2 mL). The resultant solution was then cannulaed into the reaction solution prepared above at -78 °C and after 2 h the reaction mixture was allowed to warm up to room temperature overnight. The mixture was then concentrated under vacuum and the residue was dissolved in dry ether (15 mL) and then filtered into 25 mL round bottom flask. The resultant solution was then cooled down to 0 °C and dry ethanolamine (100 μL) was added and kept at this temperature for 1 h then room temperature for 24 h. After filtration and concentration, the residue was diluted

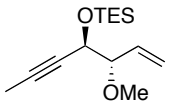
with dry CH_2Cl_2 (5 mL). 2,6-Lutidine (173 μL, 1.5 mmol, 3 equiv) and TESOTf (225 μL, 1 mmol, 2 euqiv) were added subsequently at -78 °C. The resultant solution was stirred at -78 °C for 30 min then 0 °C for 2 h. The reaction was quenched with H_2O (5 mL) and extracted with CH_2Cl_2 (20 mL x 3), dried Over Na_2SO_4. After concentrated in vacuum, the residue was purified by flash chromatography (Hexanes: EtOAc, 50:1) to afford 60 mg (31%) of **3.56** as colorless oil: $[\alpha]_D^{25}$ -21.6° (*c* 0.8, $CHCl_3$); IR (neat) 2953, 1639, 1460, 1239 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.22 (dd, J = 9, 1.5 Hz, 1H), 5.76 (m, 1H), 5.31 (d, J = 5 Hz, 1H), 5.29 (d, J = 12.5 Hz, 1H), 4.28 (dd, J = 9, 5 Hz, 1H), 3.50 (dd, J = 10.5, 7 Hz, 1H), 3.32 (s, 1H), 2.45 (s, 3H), 0.97 (t, J = 8 Hz, 9H), 0.63 (q, J = 8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.7, 135,4, 118.8, 96.5, 86.1, 72.3, 57.0, 28.7, 6.7, 4.9; HRMS (ESI) *m/z* 389.0929 [$(M+Li)^+$ calcd for $C_{14}H_{27}IO_2Si$: 389.0985].



3.65

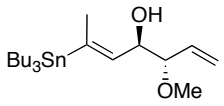
To a suspension of lithium acetylide ethylenediamine complex (3.9 g, 42.8 mmol, 2 equiv) in DMSO (40 mL) at 0 °C was added a solution of **3.64** (2.44 g, 21.4 mmol) in DMSO (20 mL). The solution was allowed to warm up to room temperature and continued to stir for 2 h. Then the reaction solution was diluted with ether and cooled down to 0 °C. H_2O (14 mL) was added followed by adjusting the pH to 3 with 5% HCl. Layers were separated and aqueous layer was extracted with ether (50 mL x 3), the combined organic layer was dried over Na_2SO_4. After concentration *in vacuo*, the residue was dissolved in DMSO (50 mL) and cooled down to 15 °C. t-BuOK (10 g, 85.6 mmol, 4 equiv) was added carefully. After 40 min, the reaction solution was diluted with ether (100 mL) and cooled down to 0 °C and carefully quenched with 3 M HCl (30 mL).

Layers were separated and aqueous layer was extracted with ether (100 mL x 3), the combined organic layer was washed with 1:1 mixture of $NaHCO_3$ and brine (200 mL), dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash chromatography (Pentane: ether, 4:1) to afford 1.8 g (60%) of **3.65** as colorless oil: $[\alpha]_D^{25}$ +66.4° (*c* 2.1, $CHCl_3$); IR (neat) 3419, 2920, 2361, 1422, 1132 cm^{-1}; ^1H NMR (500 MHz $CDCl_3$): δ 5.88-5.81 (m, 1H), 5.41 (d, J = 6.5 Hz, 1H), 5.394 (d, J = 14 Hz, 1H), 4.38 (s, 1H), 3.71 (dd, J = 7.5, 3.5 Hz, 1H), 3.38 (s, 3H), 2.45 (bs, 1H), 1.88 (d, J = 2 Hz, 3H),; ^{13}C NMR (125 MHz, $CDCl_3$): δ 133.9, 120.2, 851, 82.5, 64.9, 56.9, 31.2, 3.7; HRMS (ESI) *m/z* 147.0973 [$(M+Li)^+$ calcd for $C_8H_{12}O_2$: 147.0997].



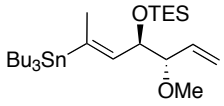
3.66

To a solution of **3.65** (280 mg, 2 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added 2,6-lutidine (0.7 mL, 6 mmol, 3 equiv) and TESOTf (1.12 mL, 5 mmol, 2.5 equiv). After 1 h, the reaction was quenched with H_2O (2 mL) and extracted with CH_2Cl_2 (10 mL x 3), dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash chromatography (Pentane: ether, 50:1) to afford 0.4 (79%) of **3.66** as colorless oil: $[\alpha]_D^{25}$ -27.9° (*c* 5.9, $CHCl_3$); IR (neat) 2953, 1450, 1194 cm^{-1}; ^1H NMR (500 MHz $CDCl_3$): δ 5.83-5.76 (m, 1H), 5.32-5.29 (m, 2H), 4.32 (dd, J = 5, 2 Hz, 1H), 3.59 (dd, J = 7, 5 Hz, 1H), 3.37 (s, 3H), 1.85 (d, J = 2 Hz, 3H), 0.97 (t, J = 8 Hz, 9H), 0.65 (qd, J = 8, 2.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.0, 118.9, 86.3, 81.2, 78.3, 65.8, 57.2, 6.7, 4.8, 3.7; HRMS (ESI) *m/z* 261.1870 [$(M+Li)^+$ calcd for $C_{14}H_{26}O_2Si$: 261.1862].



3.67

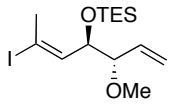
To a solution of **3.65** (140 mg, 1 mmol) in THF (10 mL) at room temperature was added $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol, 0.05 equiv) followed by Bu_3SnH (325 μL, 1.2 mmol, 1.2 equiv). The resultant solution was stirred for 30 min. Solvent was removed under *vacuo* and the residue was purified by the residue was purified by flash chromatography (Pentane: ether, 100:0-30:1) to afford 125 mg (29%) of **3.67** as colorless oil: $[\alpha]_D^{25}$ +2.93° (*c* 2.5, $CHCl_3$); ^{1}H NMR (500 MHz $CDCl_3$): δ 5.78-5.71 (m, 1H), 5.52 (d, J = 8 Hz, 1H), 5.34 (d, J = 10.5 Hz, 1H), 5.28 (d, J = 17.5 Hz, 1H), 4.68-4.65 (m, 1H), 3.61 (dd, J = 8, 3.5 Hz, 1H), 3.33 (s, 1H), 2.24 (d, J = 4.5 Hz, 1H), 1.91 (s, 3H), 1.51-1.45 (m, 6H), 1.34-1.28 (m, 6H), 0.90-0.87 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.3, 138.3, 134.3, 119.6, 85.6, 68.8, 56.4, 29.1, 27.3, 13.7, 9.1; HRMS (ESI) *m/z* 439.2216 [$(M+Li)^+$ calcd for $C_{20}H_{40}O_2Sn$: 439.2210].



3.68

To a solution of hexabutylditin (2.28 mL, 4.5 mmol, 7.6 equiv) in THF (5 mL) at -78 °C was added n-BuLi (1.8 mL, 4.5 mmol, 7.6 equiv) slowly. After 5 min it was warmed up to -40 °C (acetonitrile & dry ice) and stirred for 30 min. Then the solution was added to a suspension of CuCN (0.2 g, 2.24 mmol, 3.8 equiv) in THF (5 mL) at -78 °C. After 5 min, the mixture was warmed up to -40 °C and continued to stir for 30 min before cooled down to – 78 °C again and MeOH (1.2 mL) was added. After 5 min, the

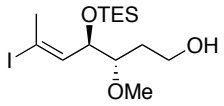
red slurry was warmed up to -10 °C (wet ice and acetone) and continued to stir for 30 min. Then a solution of **3.66** (150 mg, 0.59 mmol, 1 equiv) in THF (1 mL) was added at -78 °C and after 5 min it was warmed up to -10 °C and continued to stir for 6 h. The reaction mixture was then cooled down to -20 °C and MeOH (1.2 mL) was added. After 15 min, H_2O (1.2 mL) was added. After another 15 min stirring at -20 °C, the reaction mixture was diluted with ether (10 mL) and brine (10 mL), extracted with ether, dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash chromatography (Pentane: ether, 100:0 to 30:1) to afford 236 mg (73%) of **3.68** as colorless oil: $[\alpha]_D^{25}$ -8.1° (*c* 1.7, $CHCl_3$); IR (neat) 2955, 1461, 1113cm^{-1}; ^{1}H NMR (500 MHz $CDCl_3$): δ 5.81-5.74 (m, 1H), 5.54 (dd, J = 8.5, 2 Hz, 1H), 5.25-5.19(m, 2H), 4.58 (dd, J = 8.5, 4.5 Hz, 1H), 3.45 (dd, J = 7.5, 4.5 Hz, 1H), 3.29 (s, 3H), 1.88 (s, 3H), 1.56-1.43 (m, 6H), 1.35-1.28 (m, 6H), 0.95 (t, J = 7.5 Hz, 9H), 0.91-0.87 (m, 15H), 0.61(q, J = 7.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ141.1, 139.7, 135.8, 117.9, 86.9, 69.9, 56.7,29.0, 27.3, 13.6, 9.0, 6.7, 4.9.



3.71

To a solution of **3.68** (230 mg, 0.43 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added Na_2CO_3 (112 mg, 1.06 mmol, 2 equiv) and I_2 (270 mg, 1.06 mmol, 2 equiv). The resultant solution was stirred at 0 °C for 1 h before quenched with $Na_2S_2O_3$ (sat.). After separated, the aqueous layer was extracted with CH_2Cl_2 (10 mL x 3), dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash chromatography (Hexanes: EtOAc, 50:1) to afford 152 mg (92%) of **3.71** as colorless oil: $[\alpha]_D^{25}$ -21.6° (*c*

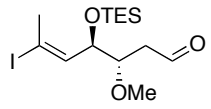
0.8, $CHCl_3$); IR (neat) 2953, 1639, 1416, 1193 cm^{-1}; ^1H NMR (500 MHz $CDCl_3$): δ 6.22 (dd, J = 9, 1.5 Hz, 1H), 5.76 (m, 1H), 5.31 (d, J = 5 Hz, 1H), 5.29 (d, J = 12.5 Hz, 1H), 4.28 (dd, J = 9, 5 Hz, 1H), 3.50 (dd, J = 10.5, 7 Hz, 1H), 3.32 (s, 1H), 2.45 (s, 3H), 0.97 (t, J = 8 Hz, 9H), 0.63 (q, J = 8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.7, 135.4, 118.8, 96.5, 86.1, 72.3, 57.0, 28.7, 6.7, 4.9; HRMS (ESI) *m/z* 389.0929 [$(M+Li)^+$ calcd for $C_{14}H_{27}IO_2Si$: 389.0985].



3.73

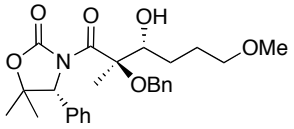
To a flame dried round bottom flask charged with BH_3·DMS (330 μL, 3.5 mmol, 5 equiv) was added 2-methyl-2-butene (890 μL, 8.4 mmol, 12 equiv) dropwise at -12 °C. After 15 min the reaction solution was warmed up to 0 °C and maintained at this temperature for 2 h before ether (2 mL) was added. The resulting homogenous solution was then stirred at 0 °C for 1 h and transferred to a solution of **3.71** (266 mg, 0.70 mmol) which has been pre-cooled to 0 °C via cannula. The resultant solution was stirred at 0 °C for 2 h before NaOH (7 mL, 2.5 M) and H_2O_2 (30% solution in H_2O, 5 mL) was added. After 20 min, the reaction mixture was warmed up to room temperature and continued to stir for 3 h. The two layers were separated and aqueous layer was extracted with Ether (20 mL x 3). The combined organic layer was then washed by brine, dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash chromatography (Hexanes: EtOAc, 5:1) to afford 160 mg (57%) of **3.73** as colorless oil: $[\alpha]_D^{25}$ -42.3° (*c* 5.1, $CHCl_3$); IR (neat) 2954, 1458, 1097 cm^{-1}; ^1H NMR (500 MHz $CDCl_3$): δ 6.23 (dd, J = 9, 1.5 Hz, 1H), 4.36 (dd, J = 9, 4.5 Hz, 1H), 3.78 (t, J = 5.5 Hz, 2H), 3.47 (s, 3H), 3.32

(m, 1H), 2.48 (d, J = 1.5 Hz, 3H), 1.76 (m, 2H), 1.60 (bs, 1H), 0.99 (t, J = 8 Hz, 9H), 0.63 (q, J = 8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.7, 96.3, 84.0, 71.7, 60.4, 59.0, 32.9, 28.5, 6.7, 4.8; HRMS (ESI) *m/z* 407.1108 [$(M+Li)^+$ calcd for $C_{14}H_{29}IO_3Si$: 407.1091].



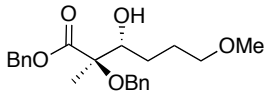
3.8

To a solution of **3.73** (30 mg, 0.075 mmol, 1 equiv) in CH_2Cl_2 (2 mL) at room temperature was added Dess-martin periodinane (65 mg, 0.15 mmol, 2 equiv). The resultant white slurry was stirred at room temperature for 1 h before evaporate solvent *in vacuo*. The residue was purified by flash chromatography (Hexanes: EtOAc, 5:1) to afford 160 mg (57%) of **3.8** as colorless oil: $[\alpha]_D^{25}$ -29.0° (*c* 2.7, $CHCl_3$); IR (neat) 2954, 1725, 1414, 1097cm^{-1}; ^{1}H NMR (500 MHz $CDCl_3$): δ 9.79 (t, J = 2 Hz, 1H), 6.17 (dd, J = 8.5, 1.5 Hz, 1H), 4.35 (dd, J = 8.5, 5 Hz, 1H), 3.60 (m, 1H), 3.43 (s, 3H), 2.60 (m, 2H), 2.45 (d, J = 1.5 Hz, 3H), 0.95 (t, J = 8 Hz, 9H), 0.60 (q, J = 8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.7, 141.4, 97.0, 80.0, 71.5, 58.7, 45.2, 28.6, 6.6, 4.7; HRMS (ESI) *m/z* 405.0715 [$(M+Li)^+$ calcd for $C_{14}H_{27}IO_3Si$: 405.0934].



3.90

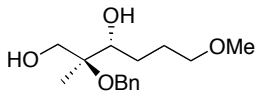
To a solution of diisopropyl amine (175 μL, 1.25 mmol, 1.6 equiv) in THF (4 mL) at 0 °C was added n-BuLi (470 μL, 1.17 mmol, 1.5 equiv). After 15 min, the reaction solution was cooled down to -78 °C and **3.13** (265 mg, 0.78 mmol) in THF (4 mL) was added. The resultant solution was stirred at -78 °C for 30 min before $TiCl(O\text{-}iPr)_3$(3.2 mL, 3.12 mmol, 4 equiv) was added. The resulting solution was then warmed up to –40 °C and stirred for 1 h. It was then cooled down to -78°C again and **3.89** (160 mg, 1.6 mmol, 2 equiv) in THF (4 mL) was added. The resultant solution was stirred at -40°C for 2 h before quenched with saturated NH_4Cl (5 mL), and stirred with celite for 30 min. The slurry was then filtered through a celite pad, washed with ether, dried over Na_2SO_4. The combined organic phase was filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexanes: EtOAc, 5:1) to afford 282 mg (79%) **3.90** as colorless oil: $[\alpha]_D^{25}$ -56.7° (*c* 1.0, $CHCl_3$); IR (neat) 2932, 1779, 1455, 1102 cm^{-1}; ^1H NMR (400 MHz C_6D_6): δ7.43 (d, J=7.6 Hz, 2 H), 7.23-6.96 (m, 8H), 4.94 (s, 1H), 4.82 (t,6.8 Hz, 1 H), 4.58 (d, J = 11.2 Hz, 1H), 4.53 (d, J = 11.2 Hz, 1 H), 3.25-3.10 (m, 2H), 3.05 (s, 3H), 1.90-1.57 (m, 4H), 1.81 (s, 3H),1.07 (s, 3H), 0.58 (s, 3 H); ^{13}C NMR (100 MHz, C_6D_6): δ 174.21, 152.02, 139.11, 137.19, 86.36, 81.60, 73.50, 72.31, 69.12, 66.96, 58.17,29.41, 28.11, 26.76,23.40, 17.00; HRMS (ESI) *m/z* 462.2471[$(M+Li)^+$ calcd for $C_{26}H_{33}NO_6$ 462.2468].



3.91

To a solution of BnOH (58 μL, 0.56 mmol, 2 equiv) in THF (2 mL) at -78 °C was added n-BuLi (168 μL, 0.42 mmol, 1.5 equiv). After 10 min, **3.90** (130 mg, 0.28 mmol)

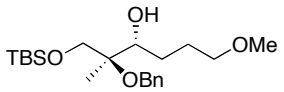
in THF (2 mL) was added dropwise. 10 min later, the reaction solution was warmed up to 0 °C and continued to stir 3 h. The reaction was quenched with saturated NH_4Cl (5 mL), extracted with CH_2Cl_2 (10 mL x 3), dried over Na_2SO_4. The organic phase was filtered, concentrated *in vacuo*. The residue was purified by flash chromatography (Hexanes: EtOAc, 6:1) to provide 90 mg (86%) **3.91** as colorless oil: : $[\alpha]_D^{25}$ +12.9° (*c* 2.8, $CHCl_3$); IR (neat) 2929, 1751, 1420, 1263cm^{-1}; ^{1}H NMR (500 MHz $CDCl_3$): δ 7.36-7.23 (m, 10H), 5.24 (d, J = 12.5 Hz, 1H), 5.18 (d, J = 12.5 Hz, 1H), 4.48 (d, J = 10.5 Hz, 1H), 4.44 (d, J = 10.5 Hz, 1H), 3.80 (d, J = 10.5 Hz, 1H), 3.34 (t, J = 5.5 Hz, 2H), 3.29 (s, 3H), 2.93 (bs, 1H), 1.80-1.73 (m, 1H), 1.67-1.59 (m, 2H), 1.52 (s, 3H), 1.46-1.39 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ173.0, 138.20, 135.6, 128.5, 128.4, 128.3, 128.2, 127.6, 127.5, 83.0, 75.8, 72.7, 66.9, 66.8, 58.5, 28.3, 26.6, 16.7; HRMS (ESI) *m/z* 379.2133[$(M+Li)^+$ calcd for $C_{22}H_{28}O_5$: 379.2097].



3.92

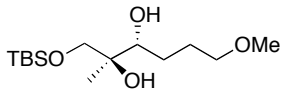
To a solution of **3.91** (90 mg, 0.24 mmol) in THF (4 mL) at 0 °C was added LAH (20 mg, 0.48 mmol, 2 equiv). After 10 min, the reaction mixture was warmed up to room temperature and continued to stir for 2 h. The reaction was quenched with NaOH (5 mL, 3 M) and H_2O (2 mL), extracted with ether (10 mL x 3), dried over Na_2SO_4. The combined organic layer was filtered, concentrated *in vacuo*. The residue was purified by flash chromatography (Hexanes: EtOAc, 1:2) to afford 52 mg (81%) diol **3.92** as colorless oil: $[\alpha]_D^{25}$ +19.0° (*c* 1.7, $CHCl_3$); IR (neat) 3366, 2926, 2360, 1459, 1130 cm^{-1}; ^{1}H NMR (400 MHz $CDCl_3$): δ 7.36-7.27 (m, 5H), 4.56 (s, 2H), 3.82-3.71 (m, 3H), 3.46

(t, J = 8Hz, 2H), 3.36 (s, 3H), 1.90-1.78 (m, 2H), 1.78-1.71 (m, 1H), 1.49-1.43 (m, 1H) 1.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8, 128.4, 127.5, 79.0, 75.9, 72.9, 65.2, 64.0, 58.6, 28.5, 27.2, 16.2; HRMS (ESI) *m/z* 275.1828[$(M+Li)^+$ calcd for $C_{15}H_{24}O_4$ 275.1835].



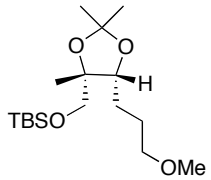
3.93

To a solution of **3.92** (52 mg, 0.19 mmol) in CH_2Cl_2 (2 mL) at –15 °C was added diisopropyl ethylamine (85 μL, 0.48 mmol, 2.5 equiv) and TBSCl (30 mg, 0.20 mmol, 1.05 equiv). The resultant solution was stirred at –15 °C for 4 h before quenched with H_2O (3 mL) and extracted with CH_2Cl_2 (10 mL x 3), dried over Na_2SO_4. After filtration and concentration *in vacuo*, the residue was purified by flash chromatography (Hexanes:EtoAc, 5:1) to afford 40 mg(55%) of **3.93** as colorless oil: $[\alpha]_D^{25}$ +9.5° (*c* 3.2, $CHCl_3$); IR (neat) 3366, 2926, 2360, 1459, 1130 cm^{-1}; ^{1}H NMR (500 MHz $CDCl_3$): δ7.34-7.25 (m, 5H), 4.63 (d, J = 11.5 Hz, 1H), 4.59 (d, J = 11.5 Hz, 1H), 3.76 (s, 2H), 3.74 (d, J = 11 Hz, 1H), 3.46-3.43 (m, 2H), 3.35 (s, 3H), 3.10 (bs, 1H), 1.93-1.85 (m, 1H), 1.80-1.74 (m, 1H), 1.69-1.64 (m, 1H), 1.50-1.42 (m, 1H), 1.25 (s, 3H), 0.92 (s, 9H), 0.08 (s, 3H), 0.7 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ139.6, 128.2, 127.2, 127.1, 78.9, 75.3, 72.9, 67.0, 64.7, 58.5, 28.2, 27.0, 25.8, 18.1, 16.2; HRMS (ESI) *m/z* 389.2650 [$(M+Li)^+$ calcd for $C_{21}H_{38}O_4Si$: 383.2618].



3.94

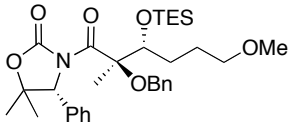
To a solution of **3.93** (40 mg, 0.10 mmol) in EtOH (3 mL) at room temperature was added Pd/C (11 mg of 10% wt mixture, 0.01 mmol, 0.1 equiv). The reaction flask was equipped with a Hydrogen gas balloon and stirred at room temperature for 16 h. The reaction mixture was filtered through a celite pad and washed with ether (10 mL). The combined organic layer was dried over Na_2SO_4. After filtration and concentration *in vacuo*, the residue was purified by flash chromatography (Hexanes: EtOAc, 4:1) to afford 10 mg (34%) of **3.94** as colorless oil: IR (neat) 3366, 2926, 2360, 1459, 1130 cm^{-1}; ^1H NMR (400 MHz C_6D_6): δ3.76 (d, J= 10 Hz, 1H), 3.58 (dd, J= 9.6, 4 Hz, 1H), 3.51(d, J = 10 Hz, 1H), 3.19 (t, J= 6 Hz, 2H), 3.08 (d, 5.2 Hz, 1H), 3.04 (s, 3H), 2.85 (s, 1H), 1.93-1.79 (m, 2H), 1.69-1.58 (m, 1H), 1.47-1.37 (m, 1H)1.14 (s, 3H), 0.92 (s, (H), -0.01 (s, 6H); ^{13}C NMR (100 MHz, C_6D_6): δ 76.6, 73.7, 73.0, 68.8, 58.2, 29.2, 27.7, 25.9, 20.2, 18.4.



3.95

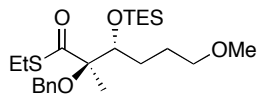
To a solution of **3.94** (10 mg, 0.034 mmol) in CH_2Cl_2 (2 mL) at room temperature was added p-TSA (2 mg, 3.4 μmol, 0.1 equiv) and 2,2-dimethoxy propane (10 μL, 50 μmol, 1.5 equiv). The resultant solution was stirred at room temperature for 1 h before quenched with saturated $NaHCO_3$ (3 mL). The mixture was separated, extracted with CH_2Cl_2 (10 mL x 3), dried over Na_2SO_4. After filtration and concentration *in vacuo*, the residue was purified by flash chromatography (Hexanes: EtOAc, 4:1) to afford 6 mg

(53%) of **3.95** as colorless oil: ^{1}H NMR (400 MHz C_6D_6): δ 3.80 (d, J = 9.6 Hz, 2H), 3.40 (d, 9.6 Hz, 1 H), 3.32-3.25 (m, 1H), 3.13 (s, 3 H), 1.97 (m, 1H), 1.86-1.79 (m, 2 H), 1.73-1.68 (m, 1H), 1.34 (s, 3 H), 1.32 (s, 3H), 0.95 (s, 9H), 0.009 (s, 3), 0.003 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ 106.8, 83.7, 81.8, 72.8, 65.9, 58.3, 29.0, 28.2, 26.7, 26.40, 26.0, 22.0, 18.3.



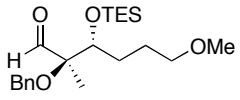
3.96

To a solution of **3.90** (320 mg, 0.70 mmol) in CH_2Cl_2 (10 mL) at -78 °C was added TESOTf (320 μL, 1.4 mmol, 2 equiv) and 2,6-Lutidine (240 μL, 2.1 mmol, 3 equiv). The resultant solution was stirred at -78 °C for 30 min the warmed up to 0 °C and stir for 2 h before quenched with H_2O (5 mL). Extracted with CH_2Cl_2 (10 mL x 3), dried over Na_2SO_4. After filtration and concentration *in vacuo*, the residue was purified by flash chromatography (Hexanes: EtOAc, 10:1) to afford 370 mg (90%) of **3.96** as colorless oil: $[\alpha]_D^{25}$ +9.7° (*c* 1.0, $CHCl_3$); IR(neat) 1954, 1456, 1118 cm^{-1}; ^{1}H NMR (400 MHz $CDCl_3$): δ 740-7.26 (m, 8H), 7.16 (m, 2H), 5.13 (s, 1H), 4.78 (d, J = 12 Hz, 1H), 4.69 (t, J = 4 Hz, 1H), 4.53 (d, J = 12 Hz, 1H), 3.27 (s, 3H), 3.26-3.23 (m, 2H), 1.76-1.68 (m, 1H), 1.58 (s, 3H), 1.56-1.47 (m, 3H), 1.43 (s, 3H), 0.95-0.88 (m, 12H), 0.52 (q, J = 8Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ; 175.8, 151.8, 138.7, 136.5, 128.6, 128.5, 128.2, 127.2, 127.1, 85.6, 81.7, 76.3, 72.8, 69.2, 67.0, 58.3, 29.8, 28.4, 26.5, 23.8, 16.4, 7.0, 5.4; HRMS (ESI) *m/z* 576.3339[$(M+Li)^+$ calcd for $C_{32}H_{47}NO_6Si$: 576.3333].



3.97

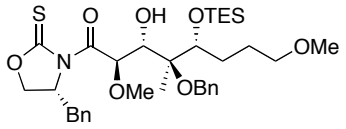
To a solution of EtSH (390 μL, 5.27 mmol, 3 equiv) in THF (5 mL) at -78 °C was added n-BuLi (1.4 mL, 3.52 mmol, 2 equiv). After 10 min, **3.96** (1 g, 1.76 mmol) in THF (10 mL) was added dropwise. The resultant solution was stirred at -78 °C for 10 min then warmed up to room temperature and continued to stir for 30 min. It was then diluted with ether (20 mL), washed with NaOH (10 mL of 1M solution) and brine (10 mL), dried over Na_2SO_4. After filtration and concentration *in vacuo*, the residue was purified by flash chromatography (Hexanes: EtOAc, 15:1) to afford 610 mg (79%) of **3.97** as colorless oil: $[\alpha]_D^{25}$ +29.0° (*c* 1.2, $CHCl_3$); IR (neat) 2954, 1875, 1454, 1120 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43-7.28 (m, 5H), 4.69 (d, J = 12 Hz, 1H), 4.61 (d, J = 12 Hz, 1H), 4.02 (t, J = 4 Hz, 1H), 3.35-3.32 (m, 2H), 3.30 (s, 3H), 2.84 (m, 2H), 1.72-1.68 (m, 2H), 1.61-1.53 (m, 2H), 1.47 (s, 3H), 1.26 (t, J = 4 Hz, 3H), 0.97 (t, J= 8 Hz, 9H), 0.62 (q, J = 8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.0, 138.7, 128.2, 127.2, 87.9, 77.7, 72.9, 66.6, 58.4, 29.7, 26.7, 22.7, 16.7, 14.4, 7.0, 5.4; HRMS (ESI) *m/z* 447.2583 [$(M+Li)^+$ calcd for $C_{23}H_{40}O_4SSi$ 447.2577].



3.98

To a solution of **3.97** (620 mg, 1.4 mmol) in CH_2Cl_2 (10 mL) at -78 °C was added DIBAL-H (2.3 mL, 2.3 mmol, 1.65 equiv). The resultant solution was stirred at -78 °C for 2 h before quenched with MeOH (2 mL). The reaction mixture was then poured into

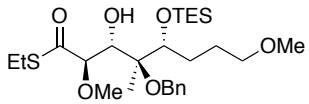
a saturated solution of Rochelle's salt (50 mL solution of sodium potassium tartrate in H_2O) and stirred at room temperature for 1 h. After separated, extracted with CH_2Cl_2 (10 mL x 3) and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash chromatography (Hexanes: EtOAc, 10:1) to afford 143 mg (90%) of **3.98** as colorless oil: $[\alpha]_D^{25}$ +58.5° (*c* 0.5, $CHCl_3$); IR (neat) 2954, 1737, 1453, 1116 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.63 (s, 1H), 7.37-7.28 (m, 5H), 4.58 (d, J = 12 Hz, 1H), 4.38 (d, J = 12 Hz, 1H), 3.97 (dd, J = 8, 4 Hz, 1H), 3.37 (t, J = 4Hz, 2H), 3.32 9(s, 3H), 1.78-1.69 (m, 2H), 1.62-1.54 (m, 2H), 1.33 (s, 3H), 0.93 (t, J = 8Hz, 9H), 0.60 (q, J = 8Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.0, 138.3, 128.3, 127.6, 127.5, 84.7, 75.7, 72.7, 66.5, 58.5, 29.3, 26.5, 12.8, 6.9, 5.3; HRMS (ESI) *m/z* 387.2584 [$(M+Li)^+$ calcd for $C_{21}H_{36}O_4Si$: 387.2543].



3.102

To a solution of **3.12** (53 mg, 0.2 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added $TiCl_4$ (0.2 mL, 0.2 mmol, 1 equiv). After 5 min, (-)-sparteine (46 μL, 0.2 mmol, 1 equiv) was added. 20 min later, the reaction slurry was cooled down to -78 °C and N-methyl-2-pyrrolidinone (20 μL, 0.2 mmol, 1 equiv) was added. After 10 min, **3.98** (100 mg, 0.26mmol, 1.3 equiv) was added in CH_2Cl_2 (2 mL). The resultant solution was stirred at -78 °C for 1 h, then 0 °C for 1 h, quenched with NH_4Cl (sat., 5 mL), extracted with CH_2Cl_2 (10 mL x 3), dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash chromatography (Hexanes: EtOAc, 5:1) to afford 80 mg (62%) of **3.102**

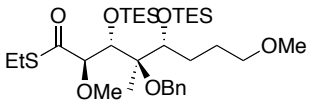
as colorless oil: $[\alpha]_D^{25}$ -4.8° (*c* 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.33-7.06 (m, 10H), 6.06 (d, J = 4 Hz, 1H), 4.84 (d, J = 8 Hz, 1H), 4.47 (dd, J = 8, 4 Hz, 1H), 4.34 (d, J = 8 Hz, 1H), 3.99 (m, 1H), 3.84 (t, J = 4 Hz, 1H), 3.79 (d, J = 8 Hz, 1H), 3.49 (s, 3H), 3.42 (t, J = 8 Hz, 2H), 3.36 (s, 3H), 3.22 (d, J = 8 Hz, 1H), 3.15-3.07 (m, 2H), 2.50 (dd, J = 12, 2 Hz, 1H), 1.88 (m, 2H), 1.68 (m, 2H), 1.51 (s, 3H), 0.97 (t, J = 8 Hz, 9H), 0.69 (q, J = 8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.9, 170.6, 139.4, 135.3, 129.3, 128.7, 128.3, 128.2, 127.5, 127.2, 81.8, 79.8, 77.9, 73.2, 73.0, 70.2, 66.4, 60.5, 59.0, 58.5, 37.3, 29.3, 27.3, 14.5, 7.1, 5.4; HRMS (ESI) *m/z* 652.3319 [$(M+Li)^+$ calcd for $C_{34}H_{51}NO_7SSi$: 652.3316].



3.106

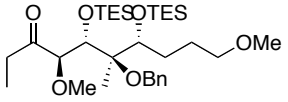
To a solution of EtSH (14 μL, 0.186 mmol, 5 equiv) in THF (1 mL) at -78 °C was added n-BuLi (45 μL, 0.111 mmol, 3 equiv). After 20 min, **3.102** (24 mg, 0.037mmol) in THF (1 mL) was added. The resultant solution was stirred at -78 °C for 2 h, quenched with NH_4Cl (sat., 2 mL), extracted with ether (10 mL x 3), dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash chromatography (Hexanes: EtOAc, 5:1) to afford 12 mg (63%) of **3.106** as colorless oil: $[\alpha]_D^{25}$ +33.0° (*c* 1.8, $CHCl_3$); IR (neat) 2951, 1686, 1378, 1191cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.33-7.21 (m, 5H), 4.73 (d, J = 11.5 Hz, 1H), 4.65 (d, J = 11.5 Hz, 1H), 4.03 (s, 2H), 3.97 (dd, J = 7, 3 Hz, 1H), 3.39 (s, 3H), 3.37 (t, J = 6.5 Hz, 2H), 3.32 (s, 3H), 2.99 (d, J = 3.5 Hz, 1H), 2.73 (m, 2H), 1.88-1.77 (m, 2H), 1.65-1.53(m, 2H), 1.40 (s, 3H), 1.18 (t, J = 7Hz, 3H), 0.97 (t, J = 8 Hz, 9H), 0.66 (q, J = 8 Hz, 6H) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.9, 139.5, 128.1,

127.2, 126.9, 87.4, 81.5, 77.2, 76.2, 73.0, 65.8, 58.9, 58.5, 29.5, 27.4, 22.5, 14.8, 14.2, 7.0, 5.4; HRMS (ESI) *m/z* [(M+Li)$^+$ calcd for].



3.105

To a solution of **3.106** (12 mg, 0.023 mmol) in CH_2Cl_2 (1 mL) at -78 °C was added 2,6-Lutidine (8 μL, 0.069 mmol, 3 equiv) followed by TESOTf (10 μL, 0.046 mmol, 2 equiv). The resultant solution was stirred at -78 °C for 3 h, quenched with H_2O (2 mL), extracted with CH_2Cl_2 (10 mL x 3), dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash chromatography (Hexanes: EtOAc, 10:1) to afford 13 mg (90%) of **3.105** as colorless oil: $[\alpha]_D^{25}$ +18.6° (*c* 2.0, $CHCl_3$); IR (neat) 2954, 1692, 1456, 1079^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ7.30-7.18 (m, 5H), 4.77 (d, J = 12 Hz, 1H), 4.67 (d, J = 12 Hz, 1H), 4.26 (d, J = 3.5 Hz, 1H), 3.97 (d, J = 3.5 Hz, 1H), 3.86 (dd, J = 7.5, 3 Hz, 1H), 3.44 (s, 3H), 3.38-3.33 (m, 2H), 3.32 (s, 3H), 2.68-2.60 (m, 1H), 2.40-2.32 (m, 1H), 1.84-1.73 (m, 2H), 1.58-1.45 (m, 2H), 1.45 (s, 3H), 1.05 (t, J = 7.5 Hz, 3H), 1.0 (t, J = 8 Hz, 9H), 0.94 (t J = 8 Hz, 9H), 0.67 (q, J = 8 Hz, 6H), 0.54 (q, J = 8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.1, 139.9, 127.8, 127.1, 126.6, 89.8, 82.4, 77.1, 76.9, 73.3, 66.1, 59.5, 58.4, 29.1, 27.5, 22.2, 14.3, 13.9, 7.1, 7.0, 6.8, 6.4; HRMS (ESI) *m/z* 635.3808[(M+Li)$^+$ calcd for $C_{32}H_{60}O_6SSi_2$: 635.3809].



3.9'

To a solution of suspension of CuI (30 mg, 0.16 mmol, 5 equiv) in ether (1 mL) at 0 °C was added EtLi (0.64 mL, 0.32 mmol, 10 equiv). After 15 min, **3.105** (20 mg, 0.032 mmol, 1 equiv) was added. The resultant solution was stirred at 0 °C for 20 min, quenched with NH_4Cl (sat.), extracted with ether, dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash chromatography (Hexanes: EtOAc, 10:1) to afford 15 mg (79%) of **3.9'** as colorless oil: $[\alpha]_D^{25}$ +14.6° (*c* 0.6, $CHCl_3$); IR (neat) 2955, 1711, 1456, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.31-7.21 (m, 5H), 4.75 (d, J = 12 Hz, 1H), 4.57 (d, J = 12 Hz, 1H), 4.26 (narrow d, 1H), 3.84 (dd, J = 8, 4 Hz, 1H), 3.79 (narrow d, 1H), 3.40-3.35 (m, 2H), 3.37 (s, 3H), 3.33 (s, 3H), 2.45-2.35 (m, 1H), 2.30-2.20 (m, 1H), 1.85-1.76 (m,1H), 1.73-1.69 (m, 1H), 1.46 (s, 3H), 1.03-0.96 (m, 18), 0.71-0.59 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.2, 139.3, 128.0, 127.54, 126.86, 89.4, 82.4, 77.5, 77.2, 73.2, 66.6, 58.9, 58.5, 32.7, 28.9, 27.5, 14.2, 7.1, 7.0, 6.7, 5.8, 5.6; HRMS (ESI) *m/z* 603.4084 [$(M+Li)^+$ calcd for $C_{32}H_{60}O_6Si_2$: 603.4089].

CHAPTER IV

SUMMARY

Apoptolidin, a specific apoptosis inducer, has attracted extensive attention from both biological and synthetic community for its interesting biological activity and complex architecture since its isolation in 1997 by Seto's group in Japan. Such interests has led to Khosla and Wender's work in Stanford University directed at identification of apoptolidin's biological target for causing apoptosis and quite a few synthetic studies towards total synthesis of apoptolidin as described in chapter I. To date, K. C. Nicolaou and Ulrich Koert have achieved two total syntheses of apoptolidin, respectively. Three groups including Koert, Crimmins and Sulikowksi group have completed the total synthesis of apoptolidinone. Several other fragments syntheses were also discussed in chapter I including our attempts towards total synthesis of pseudoapoptolidin.

Chapter II described our efforts towards total synthesis of apoptolidinone based on a strategy utilizing a cross metathesis and an intramolecular Horner-Wadsworth-Emmons reaction. Also a large-scale preparation of apoptolidinone for biological activity test via an intramolecular Suzuki coupling approach featuring asymmetric aldol reactions, Yamaguchi esterification reaction and intermolecular Suzuki coupling reaction was discussed in chapter II.

Ammocidin was another specific apoptosis inducer discovered by Seto's group. Since the isolation in 2001, its structure has not been fully assigned yet. The ambiguous structure and interesting biological activity of ammocidin drew our attention and hence led to our selecting ammocidinone as synthetic target. Chapter III mainly focused on our synthetic efforts to build three major building blocks of ammocidinone highlighted by

cross metathesis, Horner-Wadsworth-Emmons, asymmetric aldol and asymmetric expoxidation reactions.

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APPENDIX

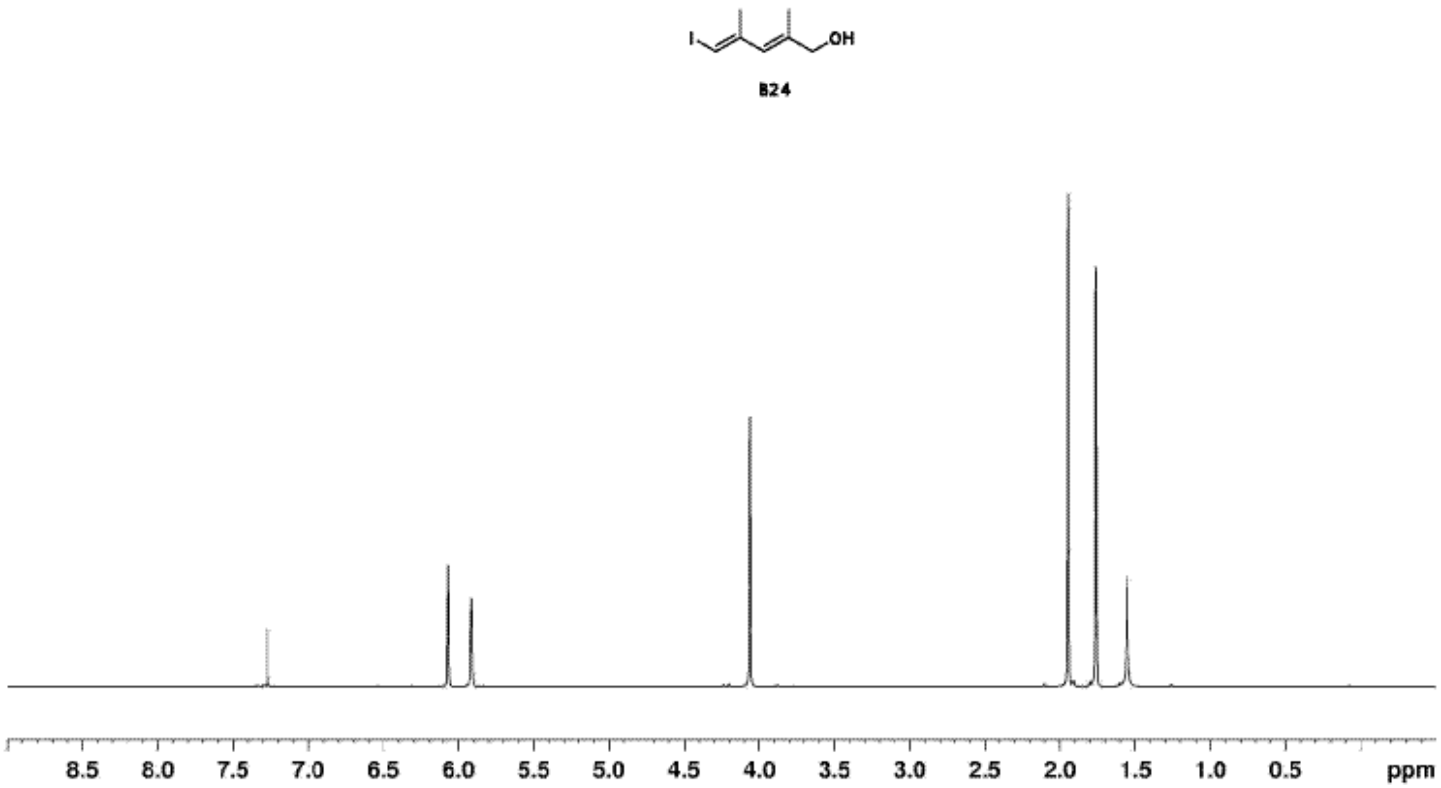

Figure 1a The 400 MHz ^{1}H NMR spectrum of **3.24** in $CDCl_3$.

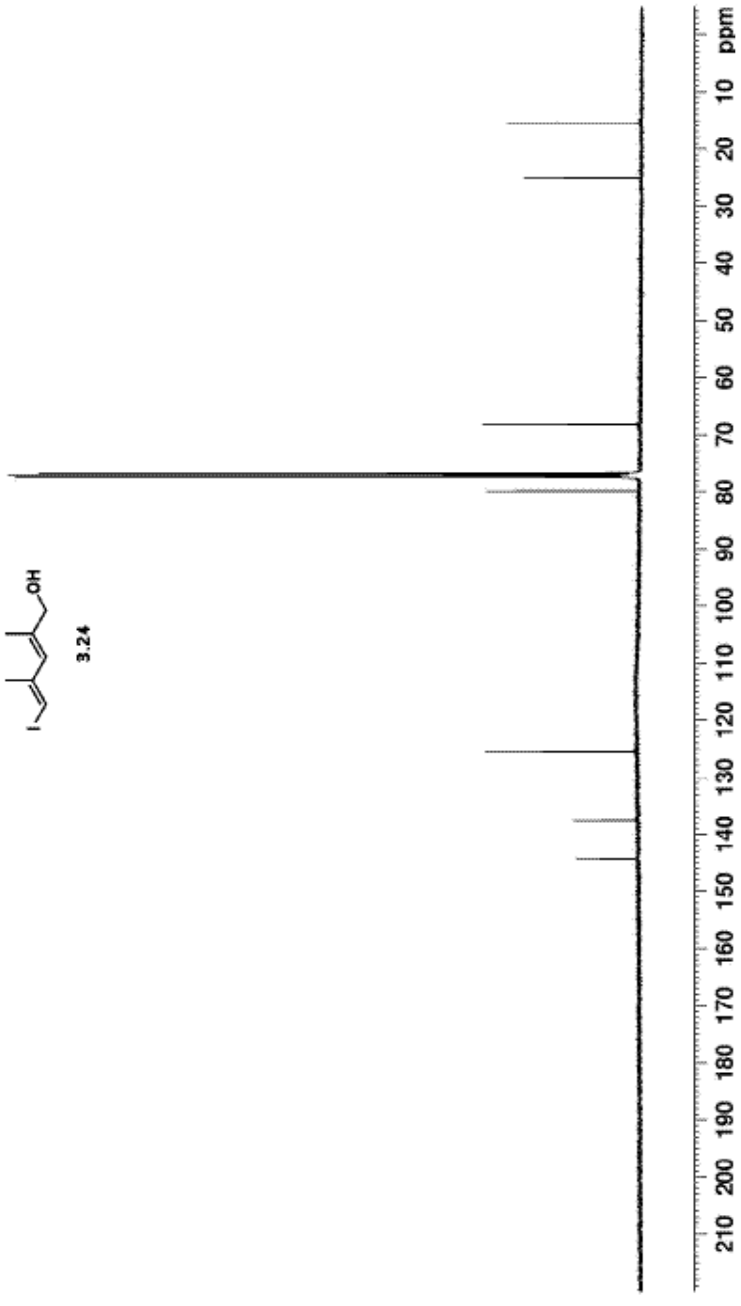

Figure 1b The 100 MHz ^{13}C NMR spectrum of **3.24** in $CDCl_3$.

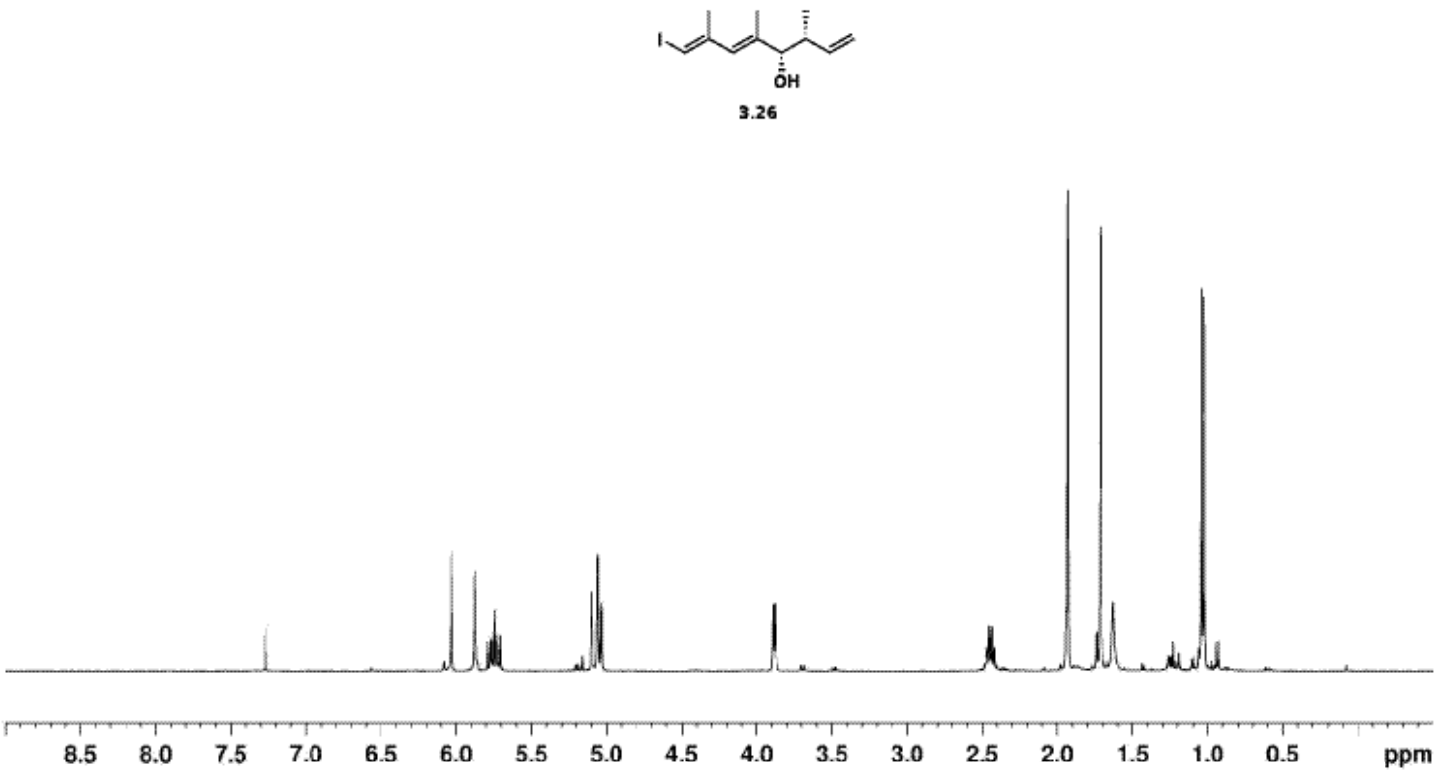

Figure B2a The 400 MHz ^{1}H NMR spectrum of **3.26** in $CDCl_3$.

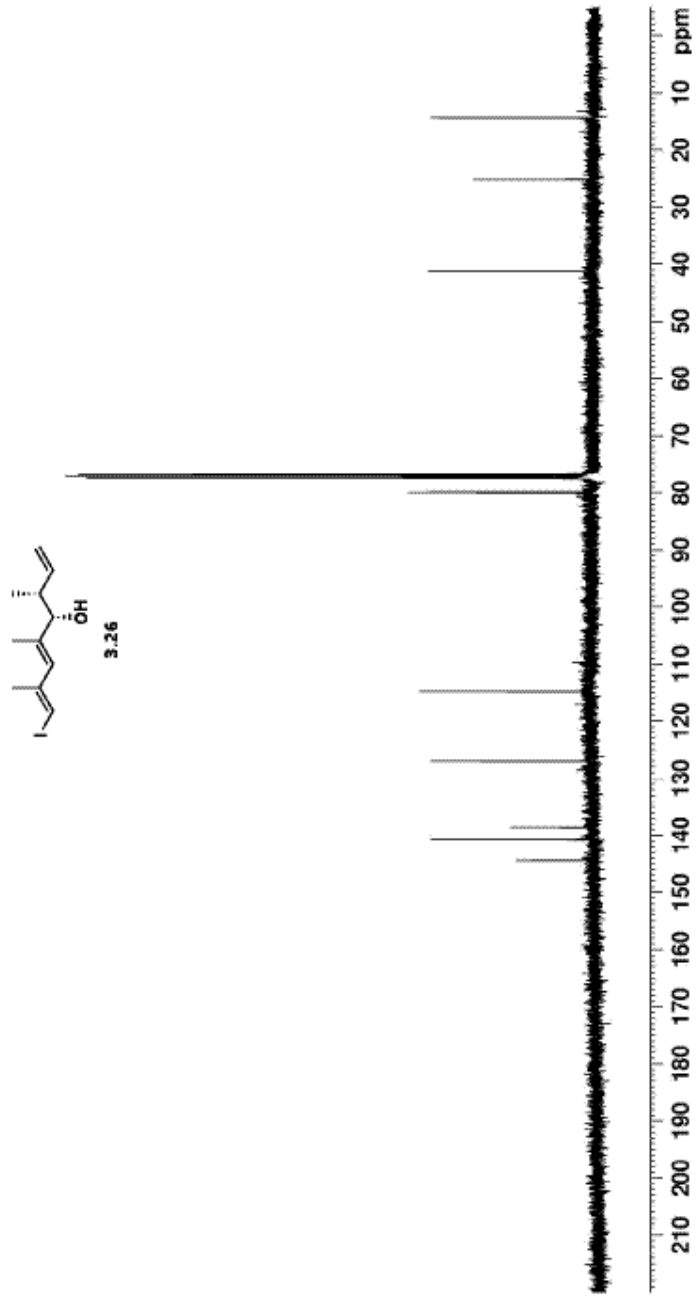

Figure 2b The 100 MHz ^{13}C NMR spectrum of **3.26** in $CDCl_3$.

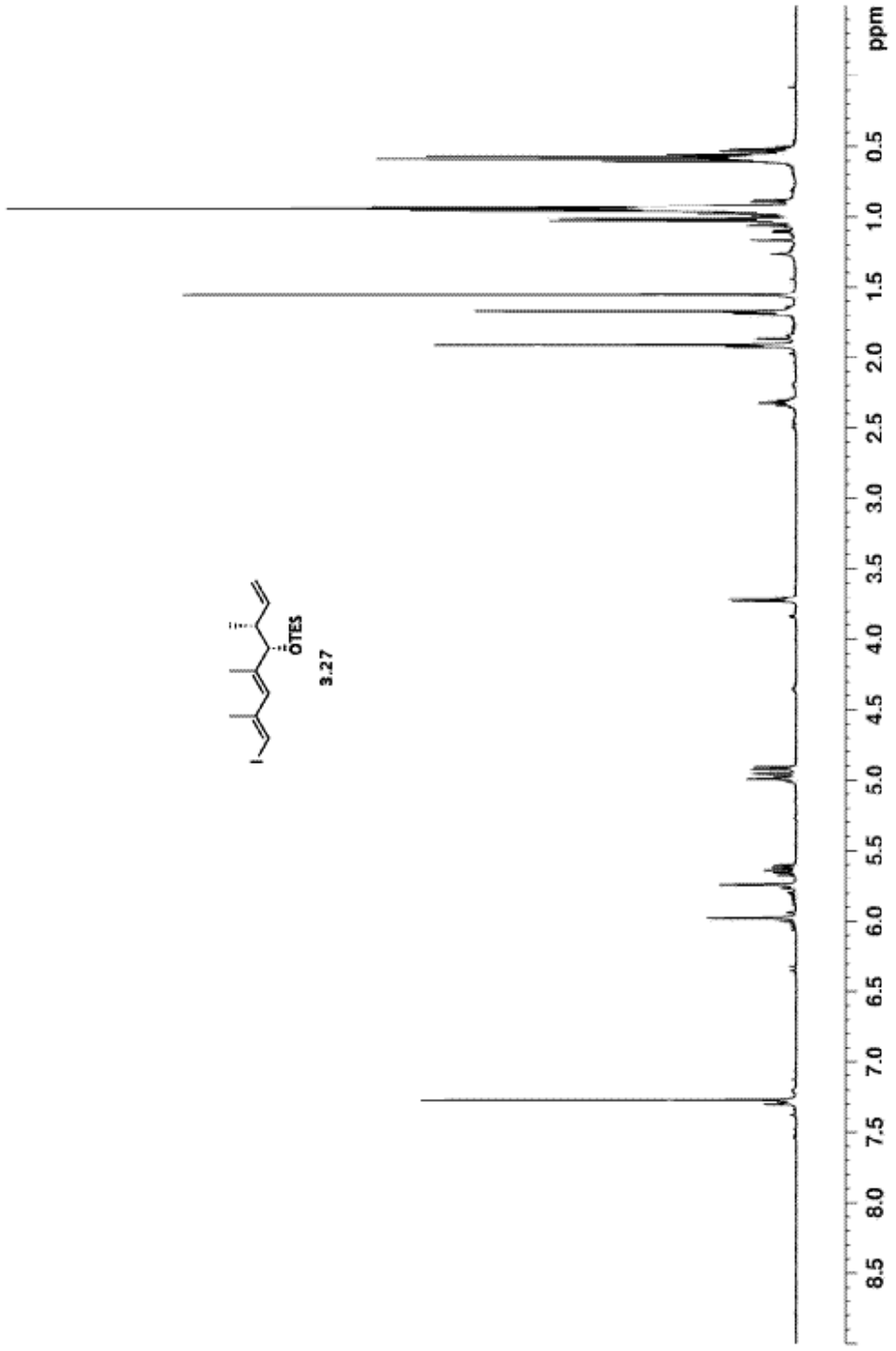

Figure 3a The 500 MHz ^{1}H NMR spectrum of **3.27** in $CDCl_3$.

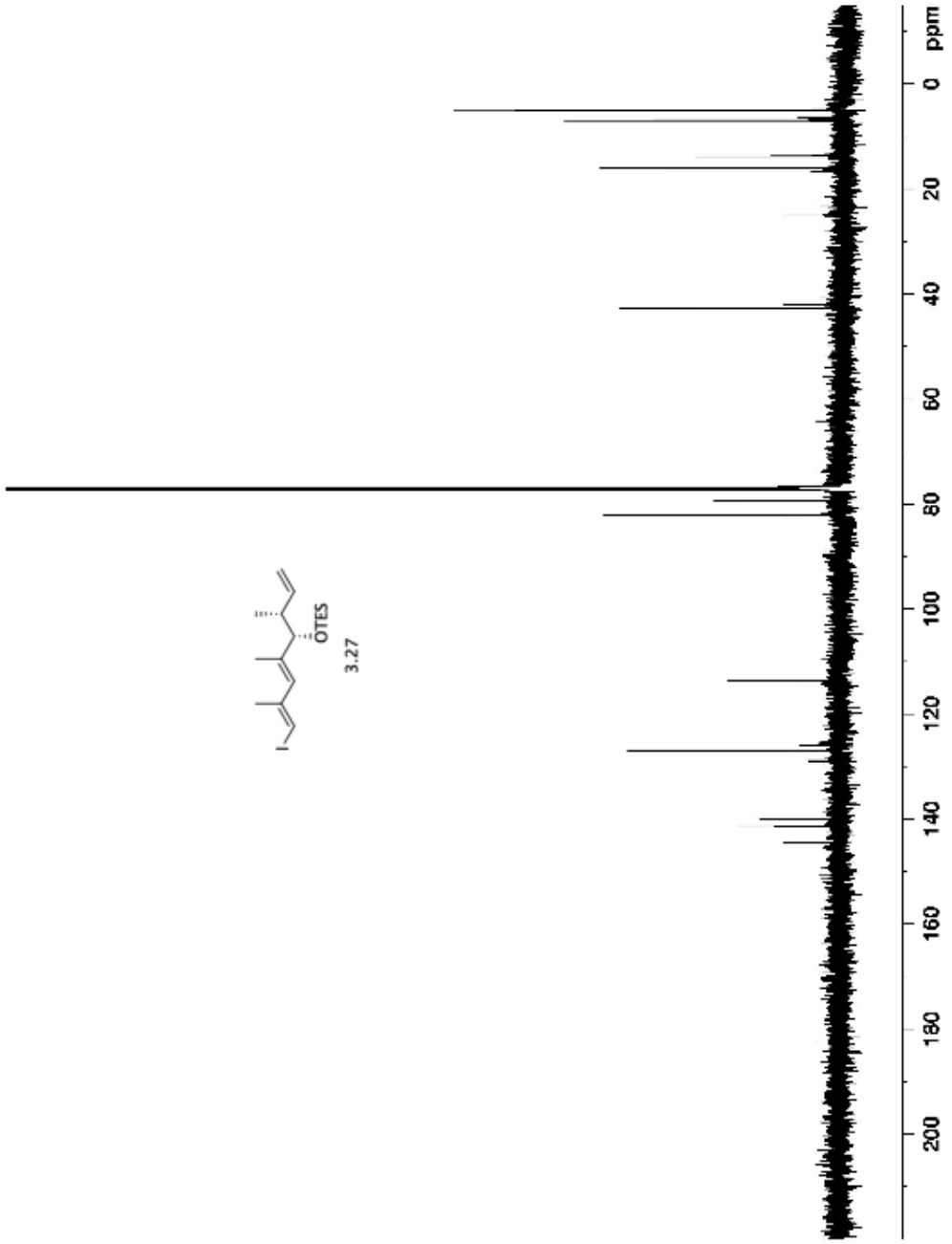

Figure 3b The 125 MHz ^{13}C NMR spectrum of **3.27** in $CDCl_3$.

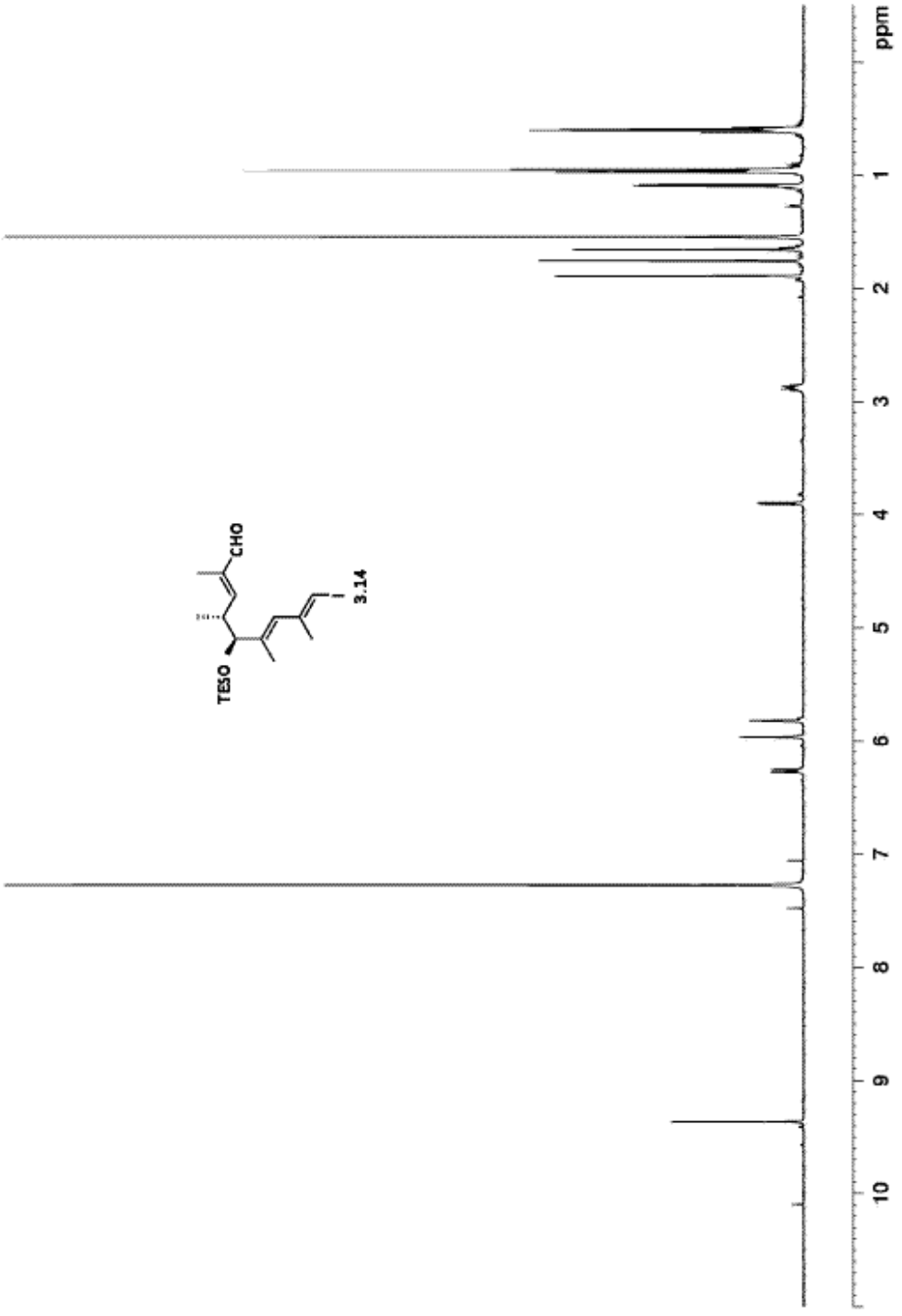

Figure 4a The 500 MHz ^{1}H NMR spectrum of **3.14** in $CDCl_3$.

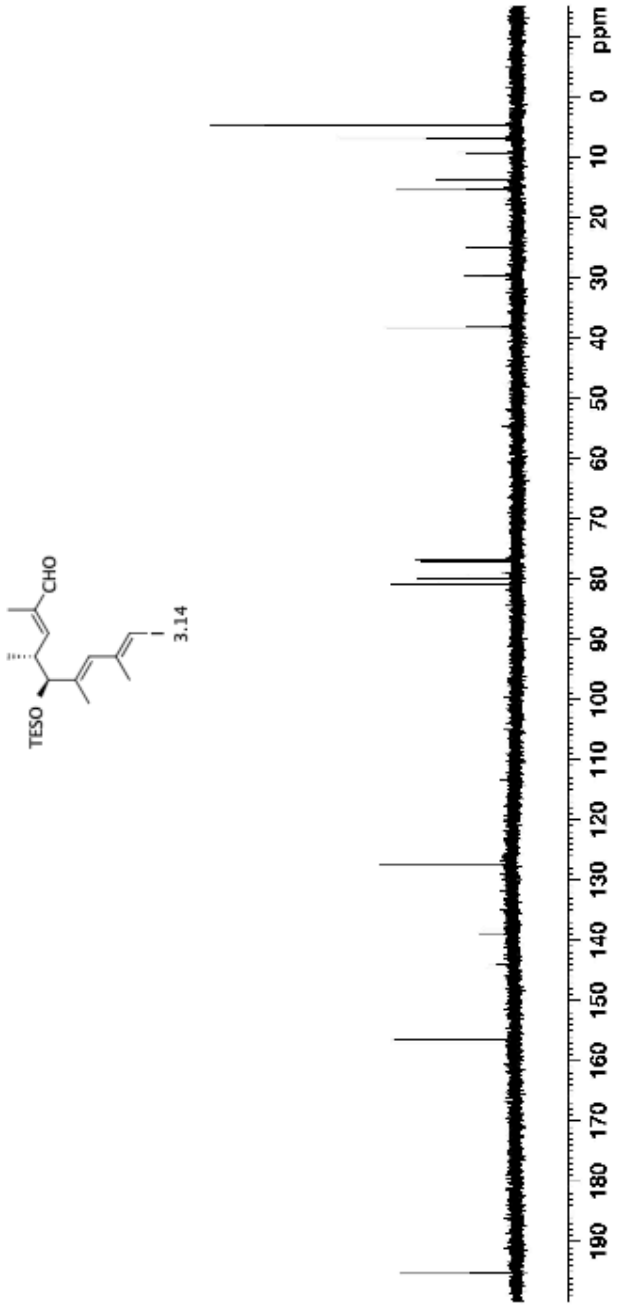

Figure 4b The 1250 MHz ^{13}C NMR spectrum of **3.14** in $CDCl_3$.

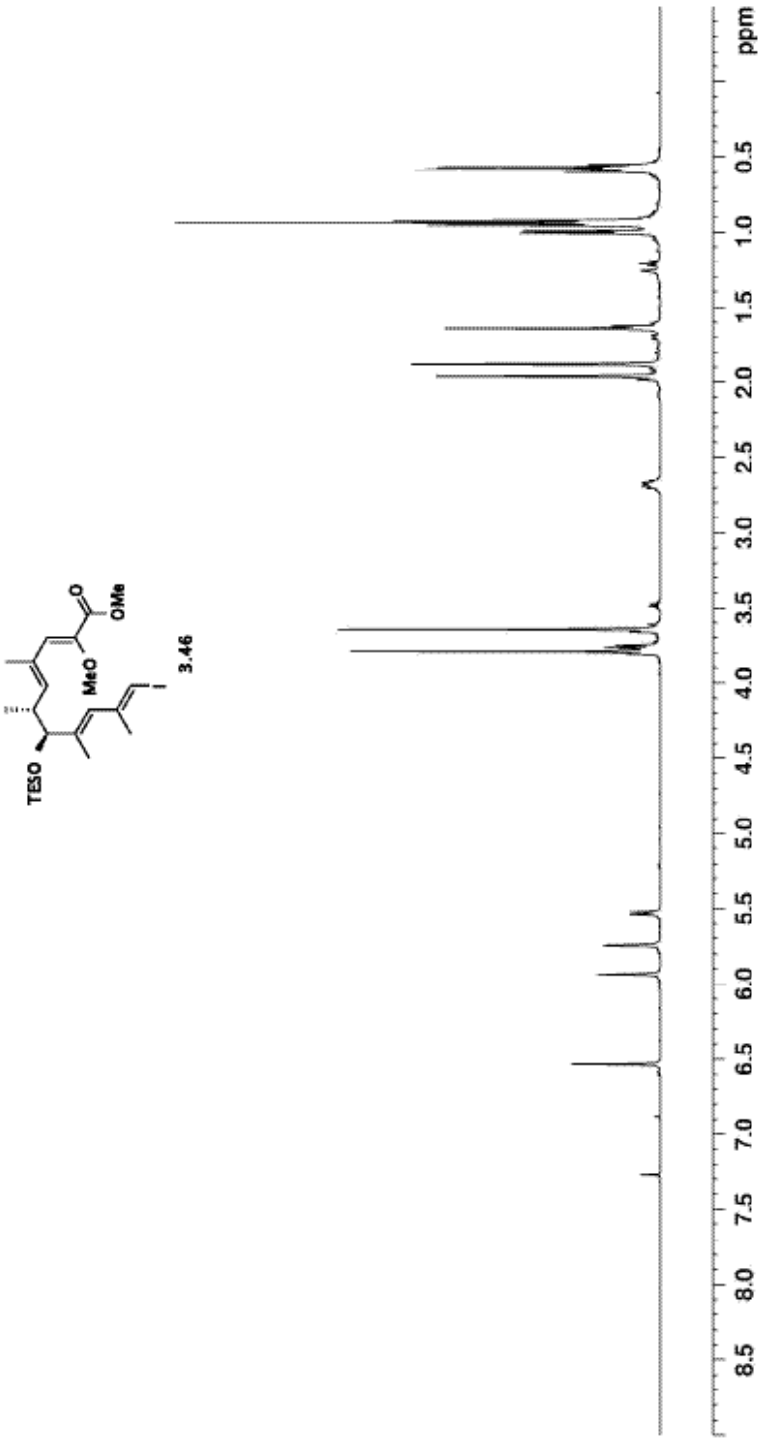

Figure 5a The 500 MHz ^{1}HNMR spectrum of **3.46** in $CDCl_3$.

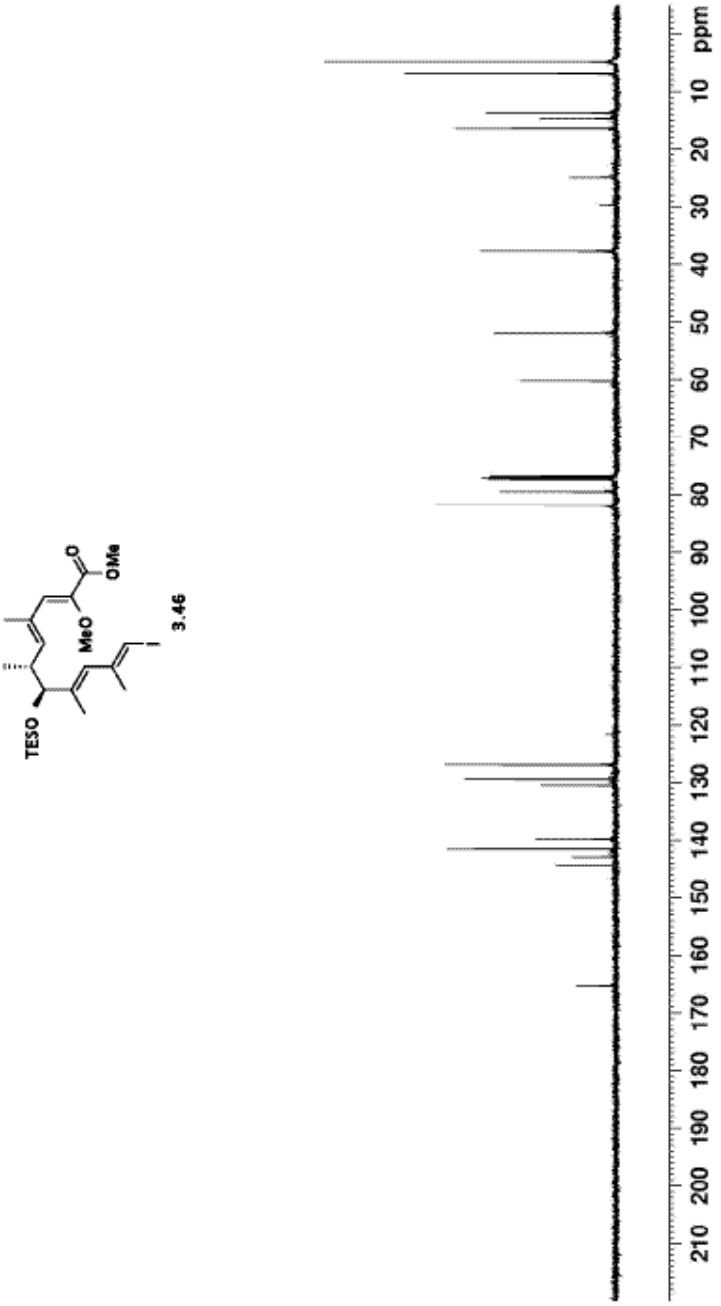

Figure 5b The 125 MHz ^{13}CNMR spectrum of **3.46** in $CDCl_3$.

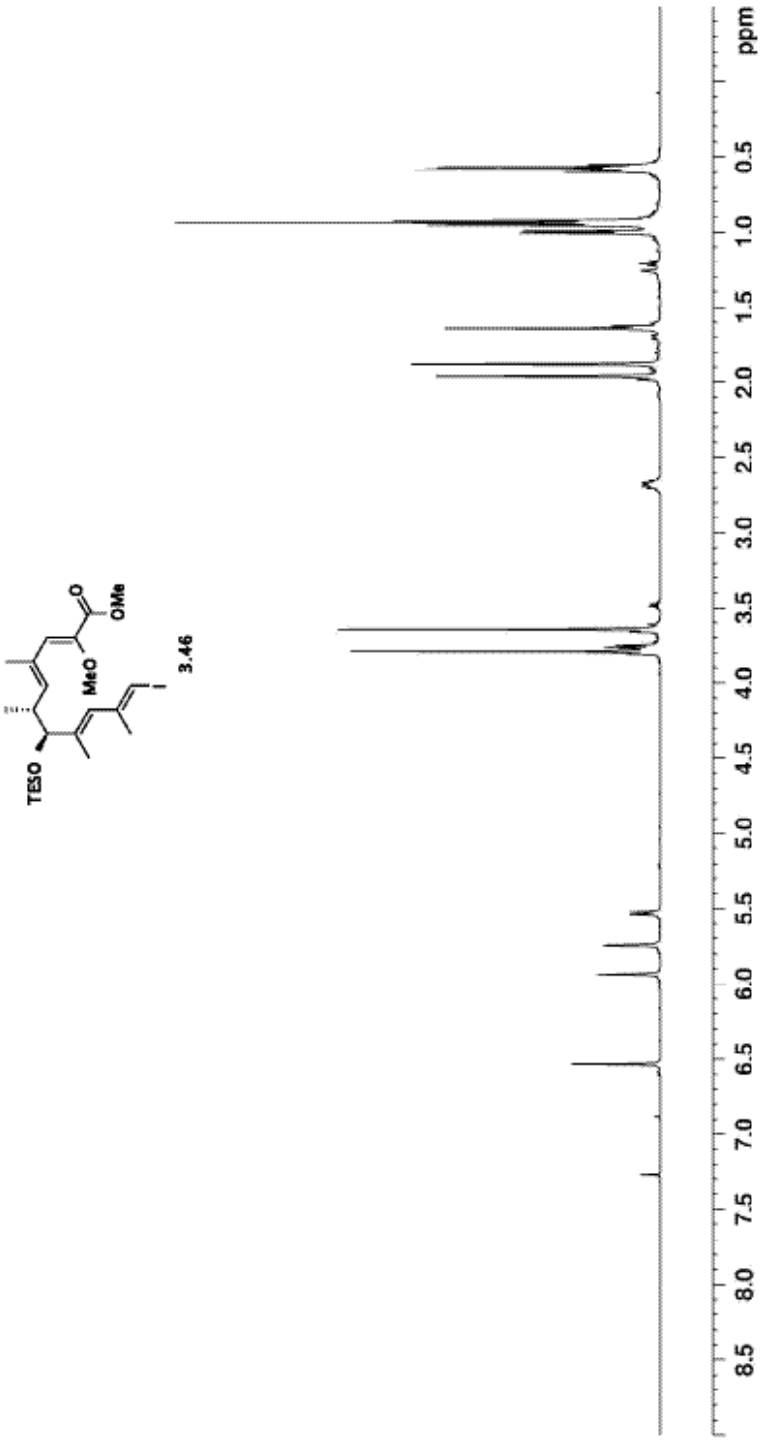

Figure 6a The 500 MHz ^{1}H NMR spectrum of **3.56** in $CDCl_3$.

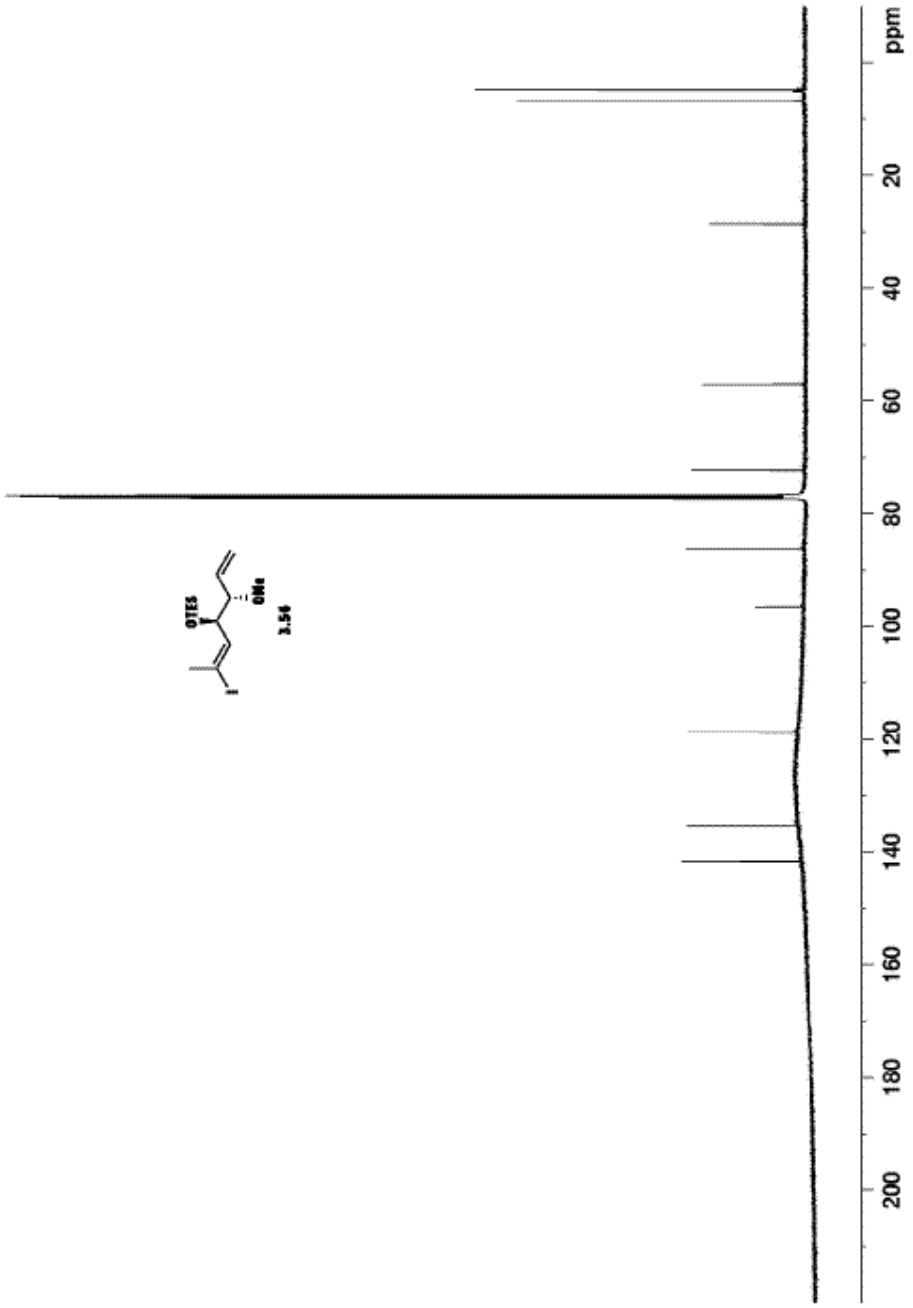

Figure 6b The 125 MHz ^{13}C NMR spectrum of **3.56** in $CDCl_3$.

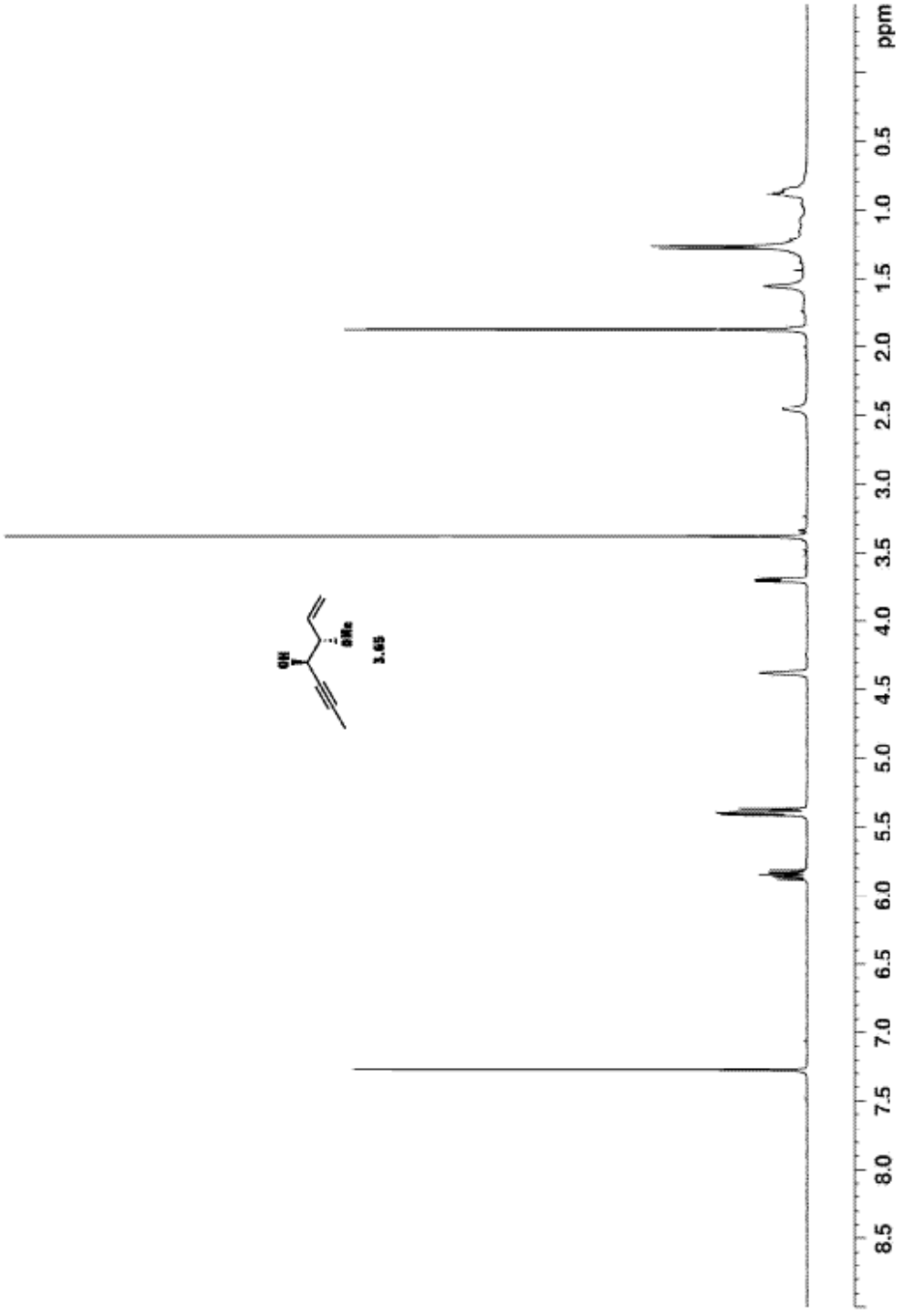

Figure 7a The 500 MHz ^{1}H NMR spectrum of **3.65** in $CDCl_3$.

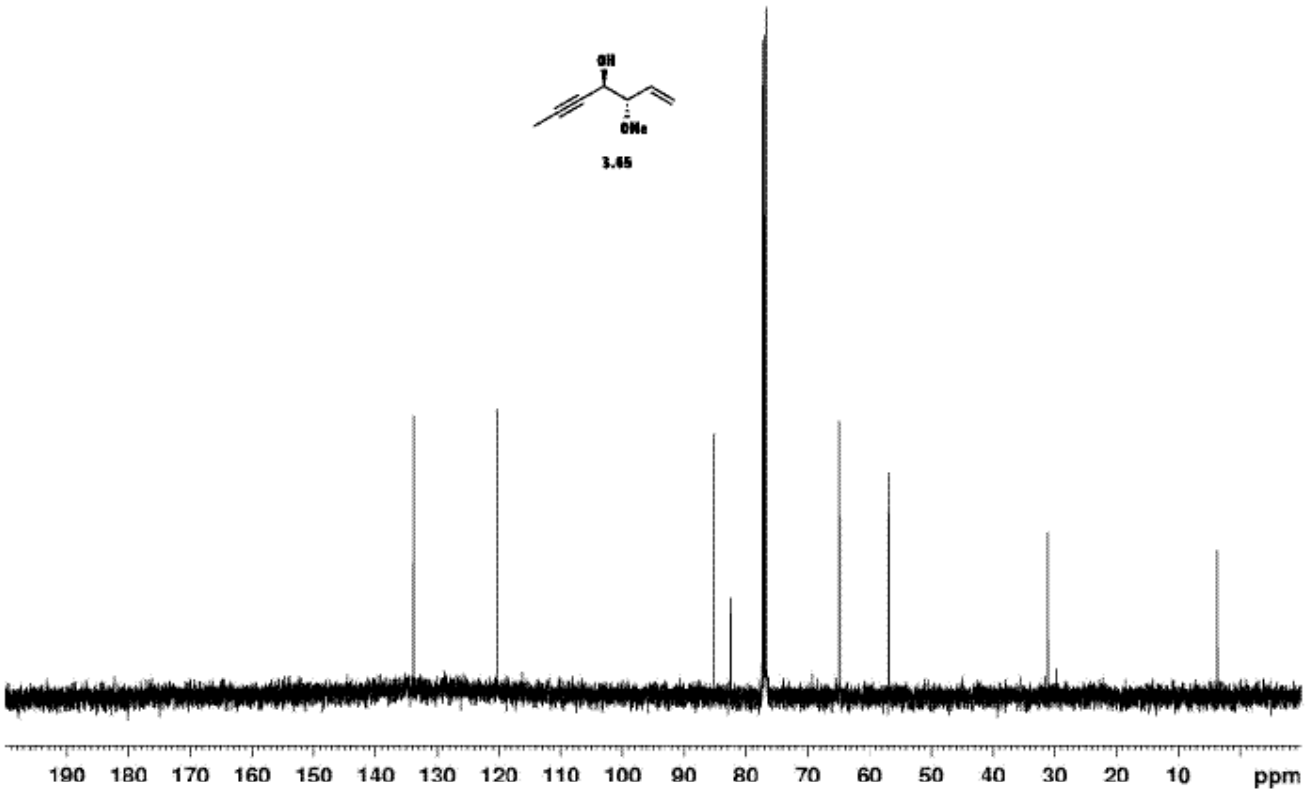

Figure 7b The 125 MHz ^{13}C NMR spectrum of phosphonate **3.65** in $CDCl_3$.

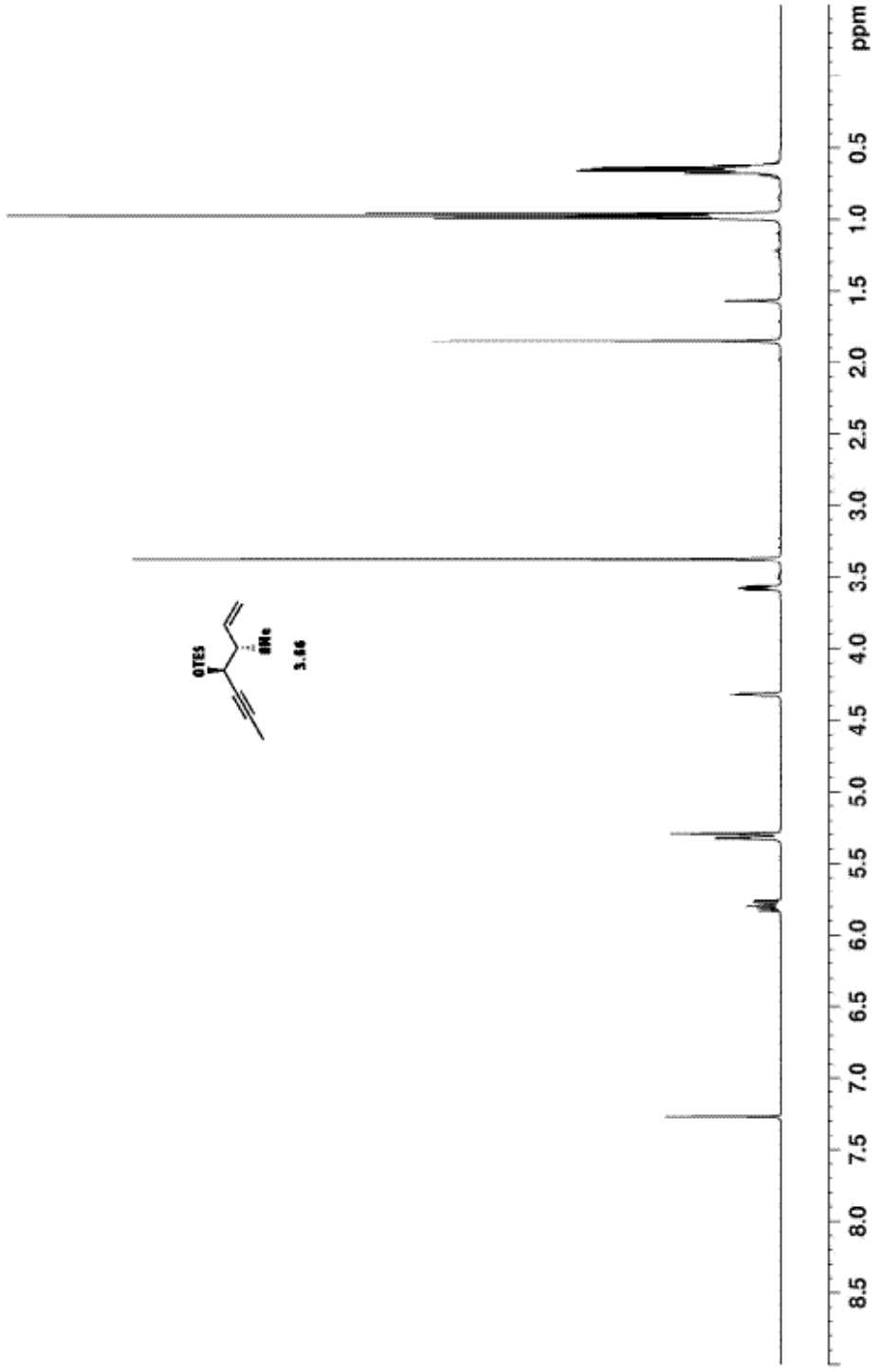

Figure 8a The 500 MHz ^{1}H NMR spectrum of **3.66** in $CDCl_3$.

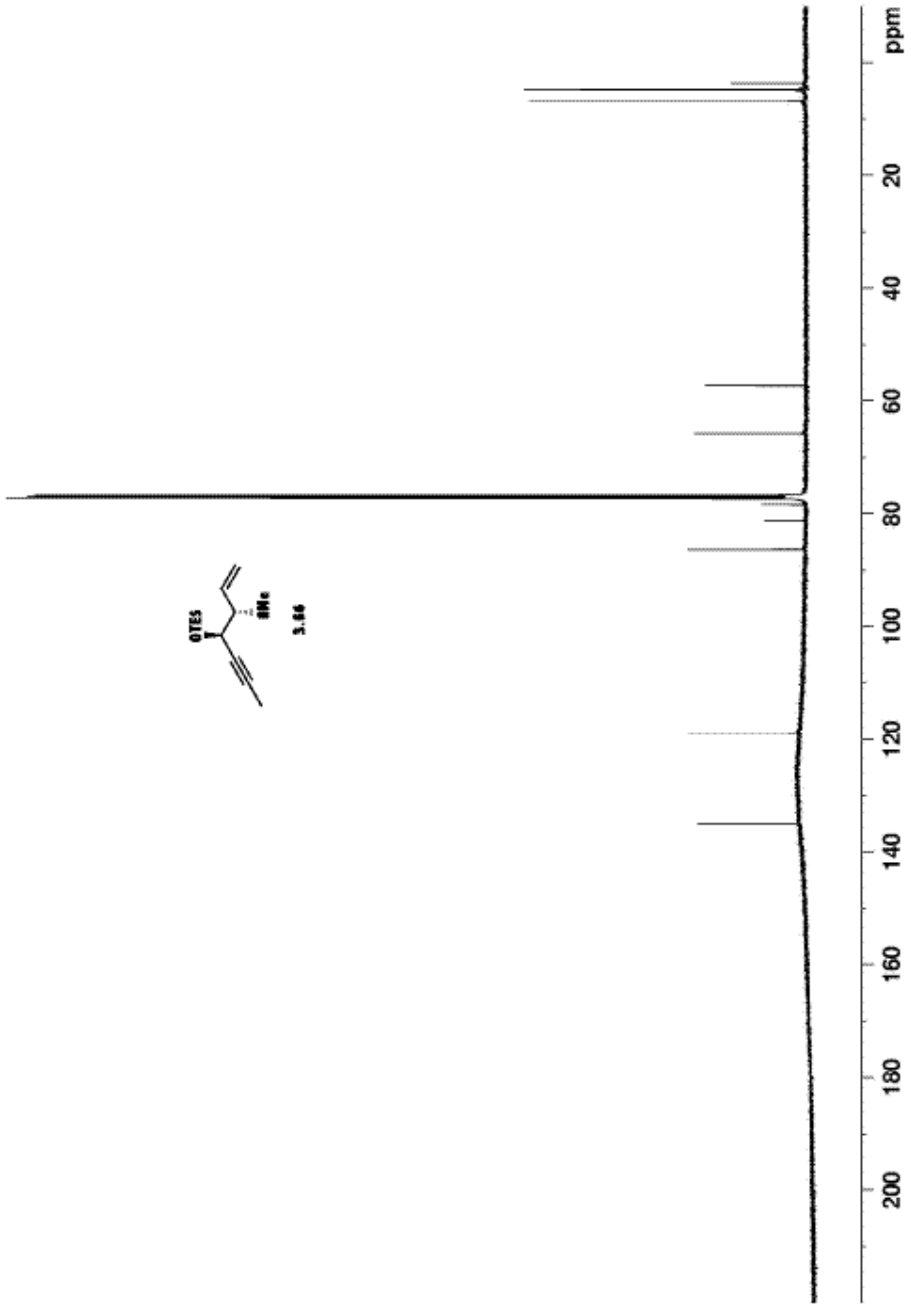

Figure 8b The 125 MHz ^{13}C NMR spectrum of **3.66** in $CDCl_3$.

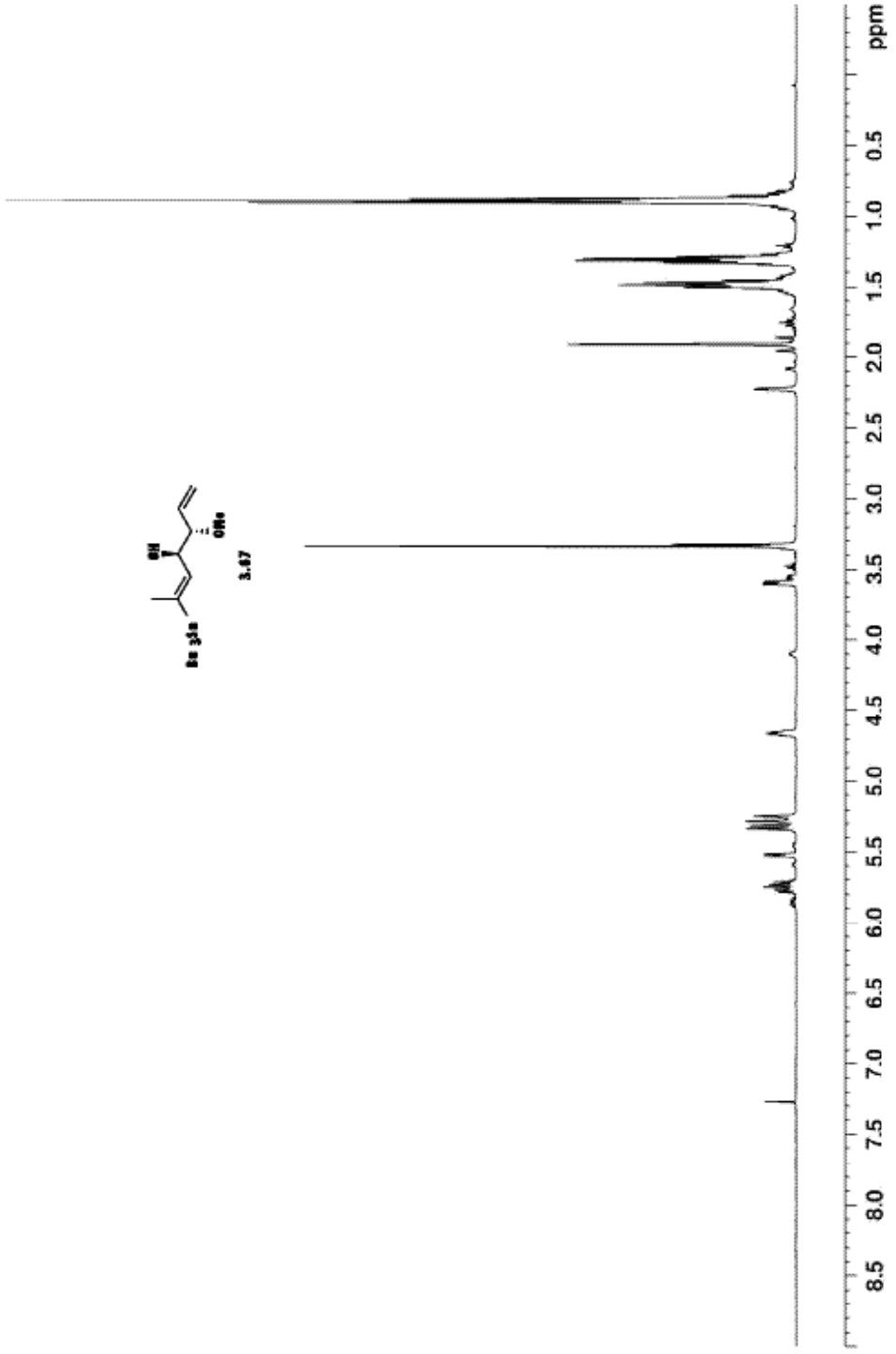

Figure 9a The 500 MHz ^{1}H NMR spectrum of ***3.67*** in $CDCl_3$.

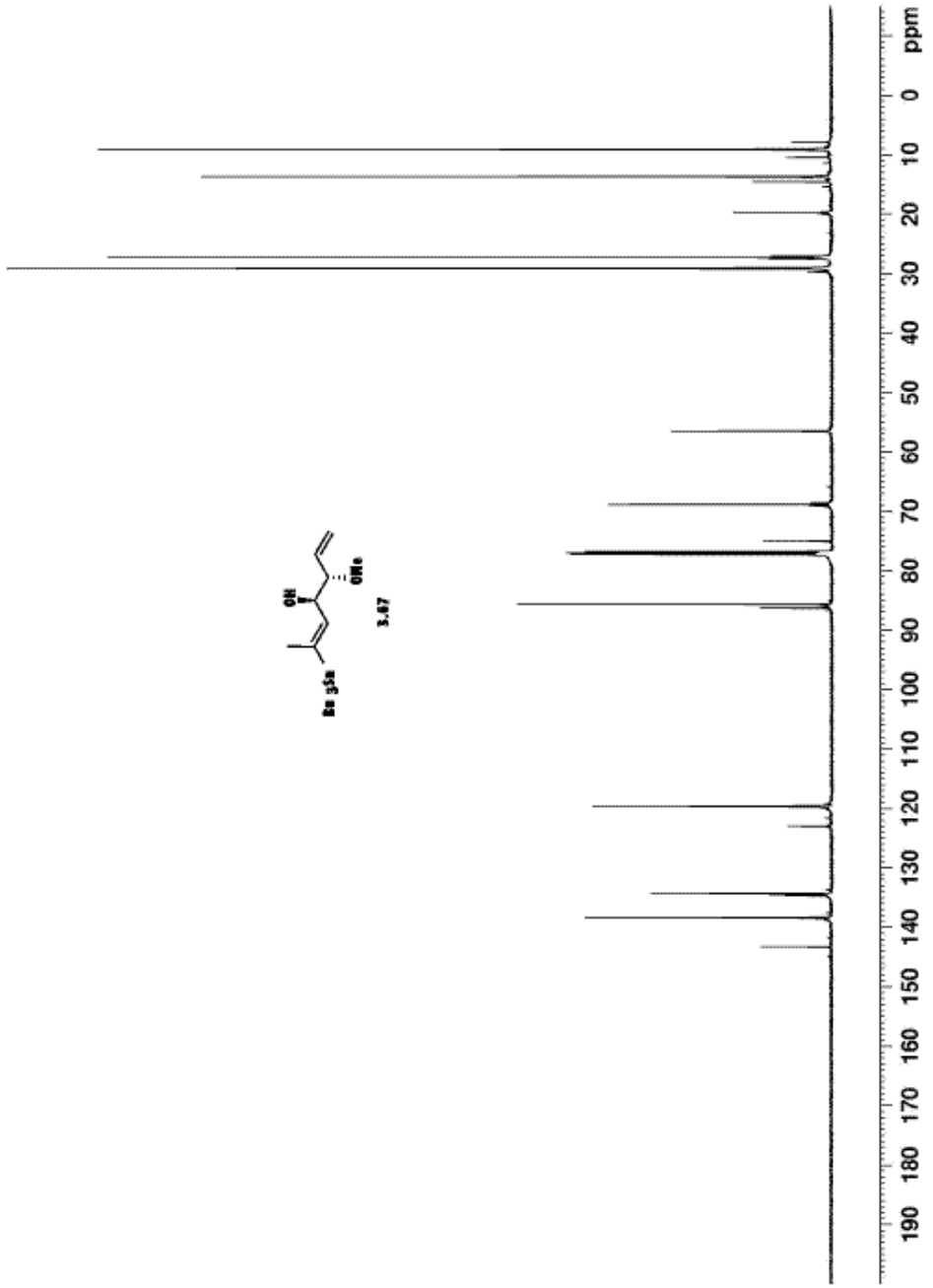

Figure 9b The 125 MHz ^{13}C NMR spectrum of **3.67** in $CDCl_3$.

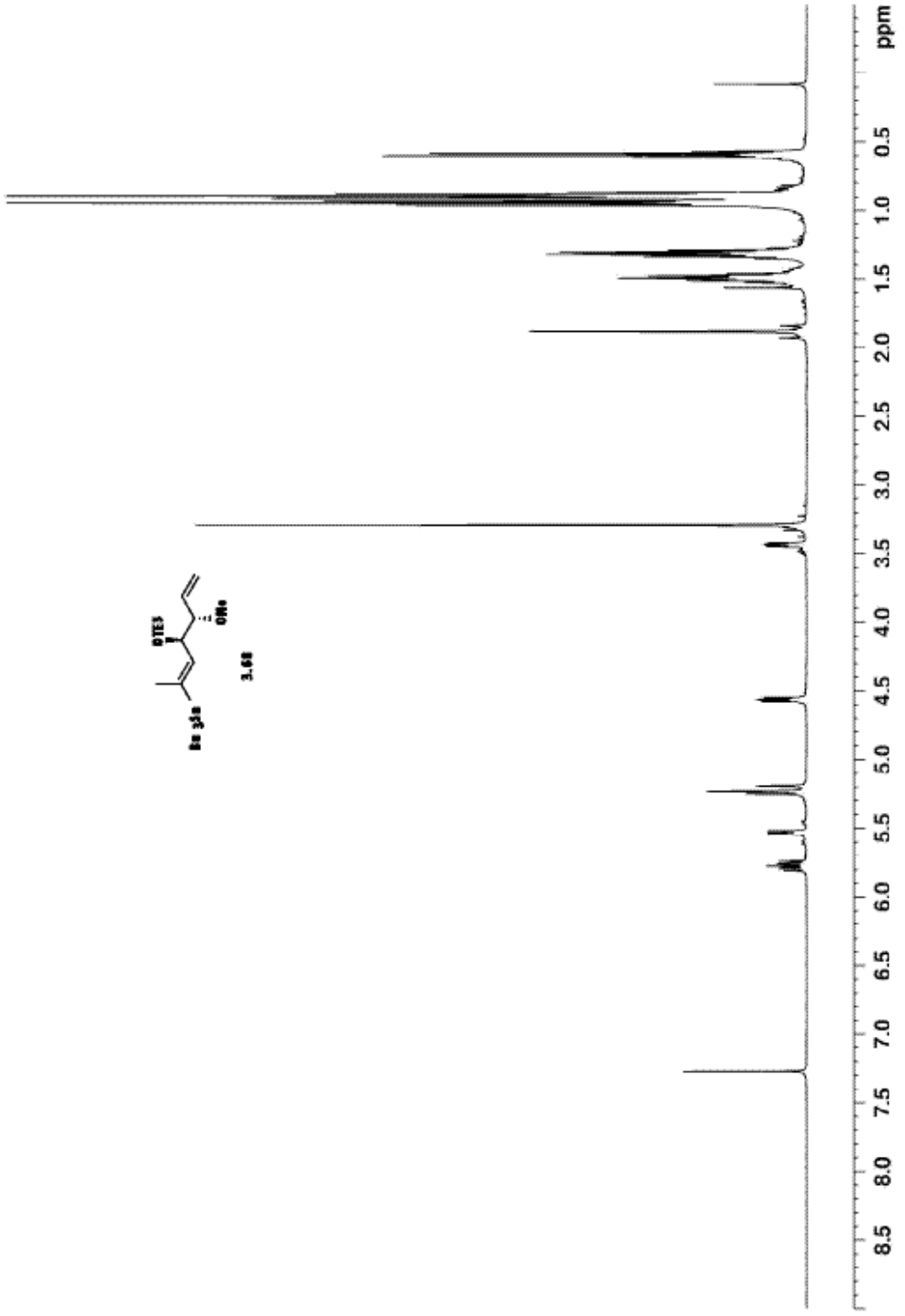

Figure 10a The 500 MHz ^{1}H NMR spectrum of **3.68** in $CDCl_3$.

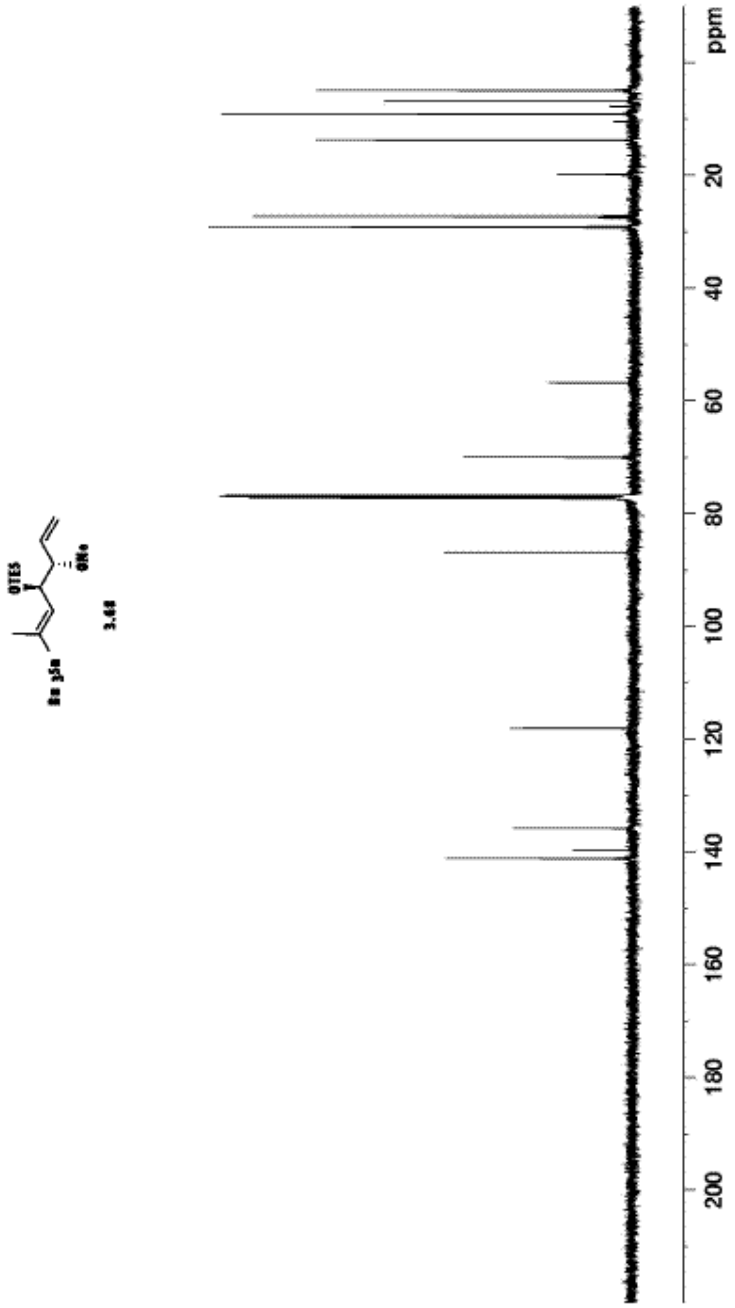

Figure 10b The 125 MHz ^{13}C NMR spectrum of **3.68** in $CDCl_3$.

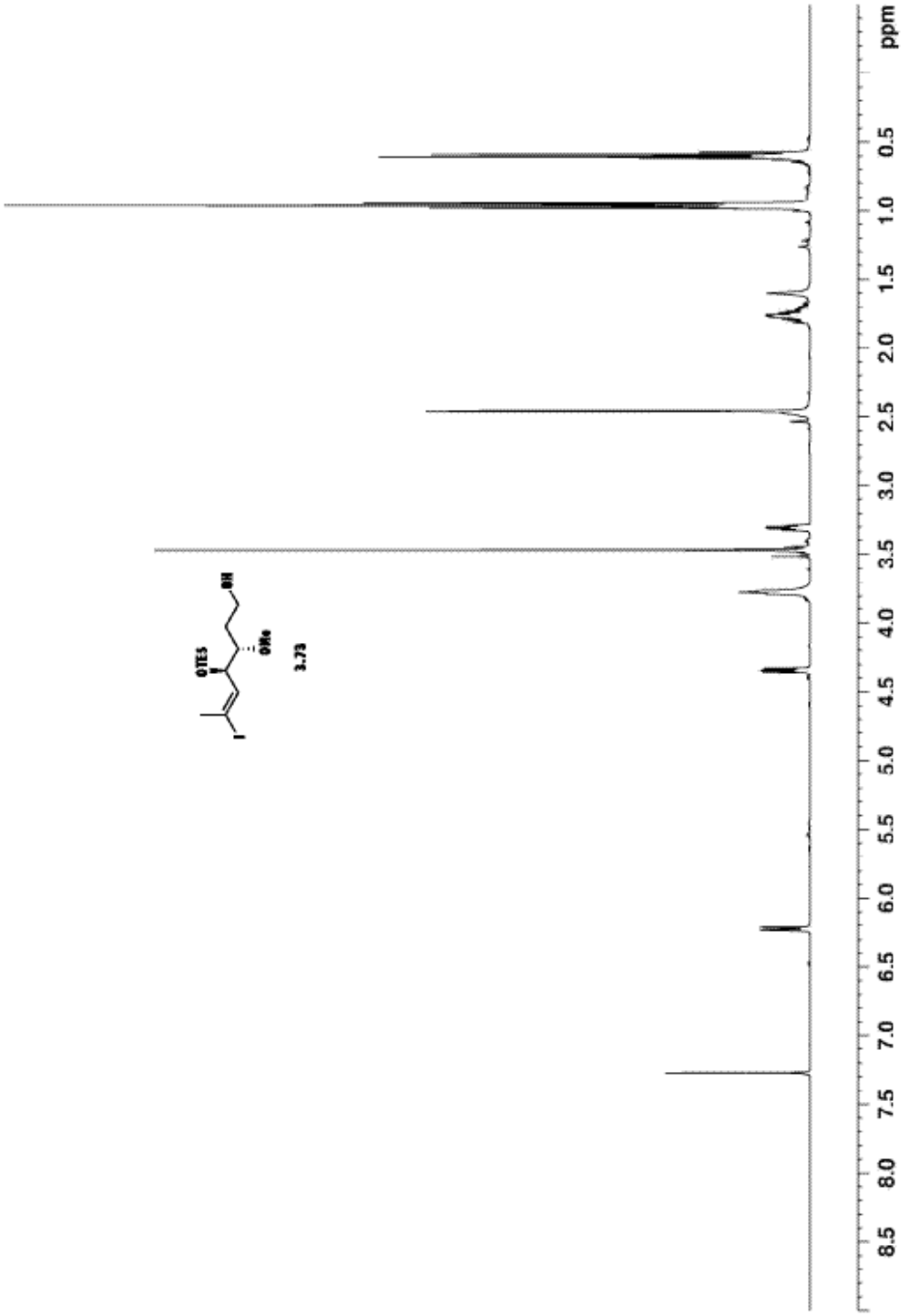

Figure 11a The 500 MHz ^{1}H NMR spectrum of **3.73** in $CDCl_3$.

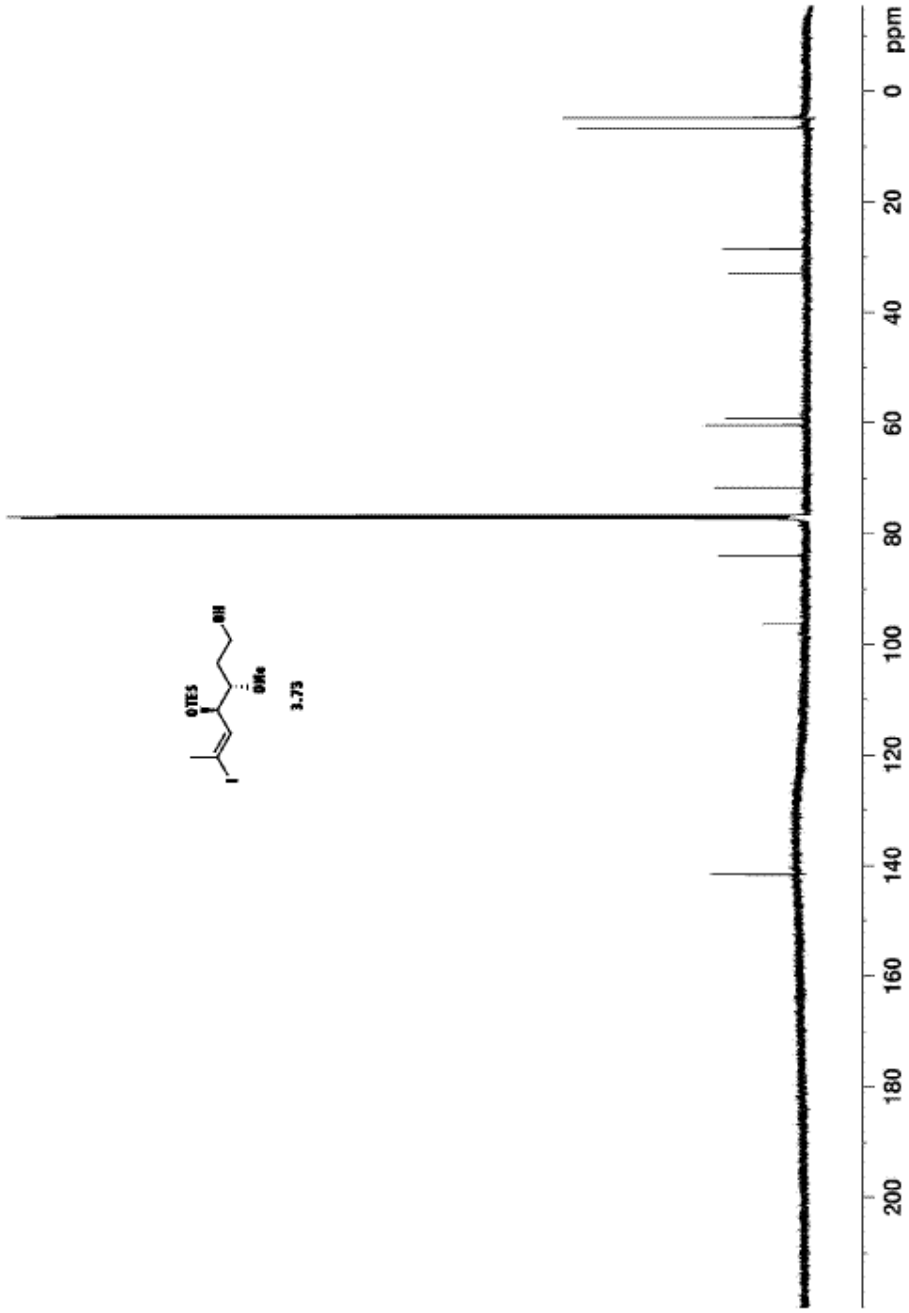

Figure 11b The 125 MHz ^{13}C NMR spectrum of **3.73** in $CDCl_3$.

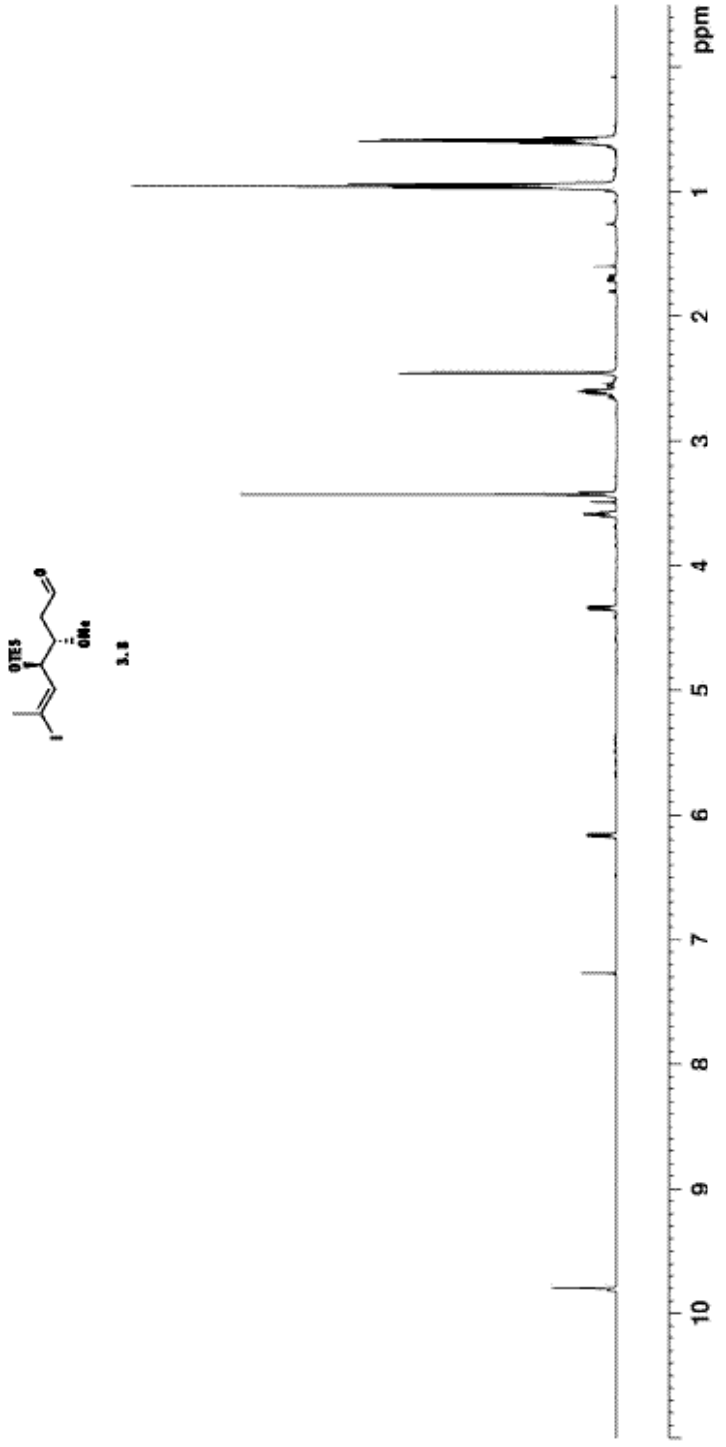

Figure 12a The 500 MHz ^{1}H NMR spectrum of **3.8** in $CDCl_3$.

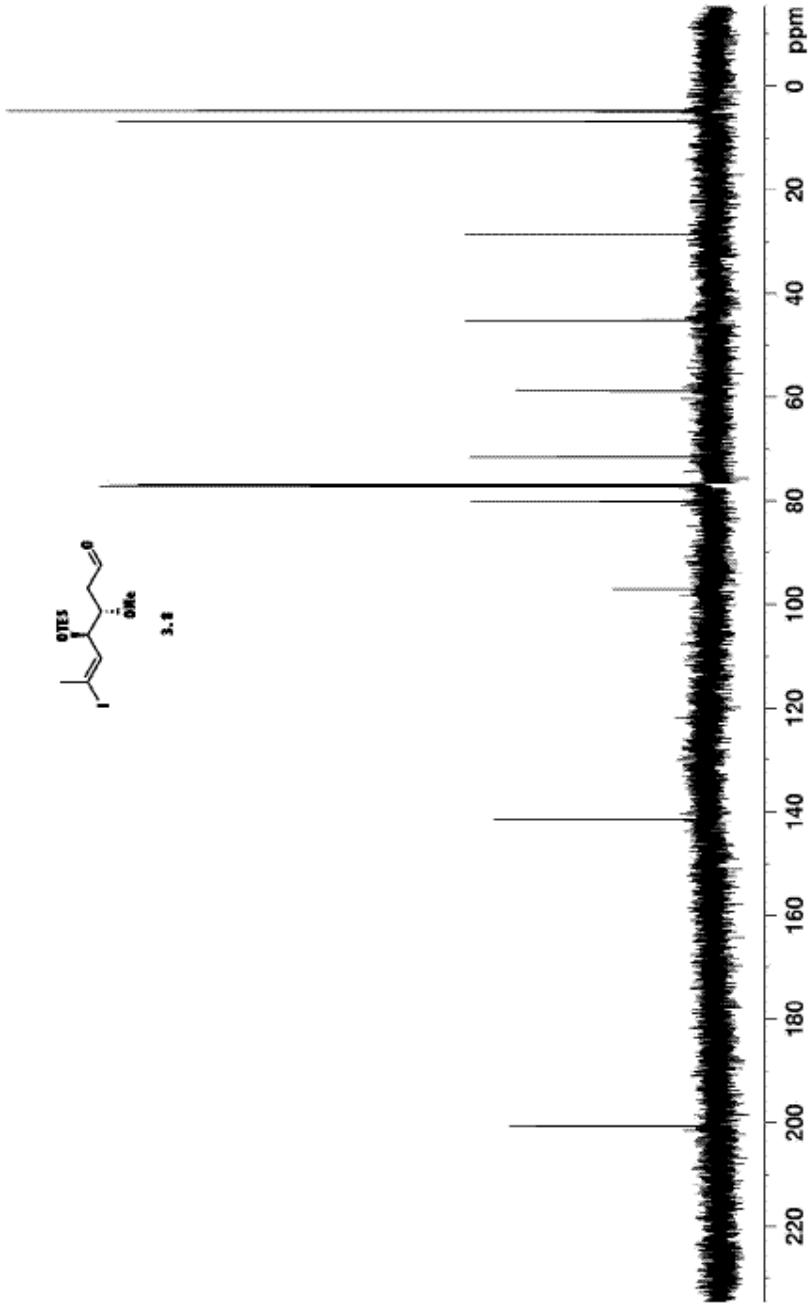

Figure 12b The 125 MHz ^{13}C NMR spectrum of **3.8** in $CDCl_3$.

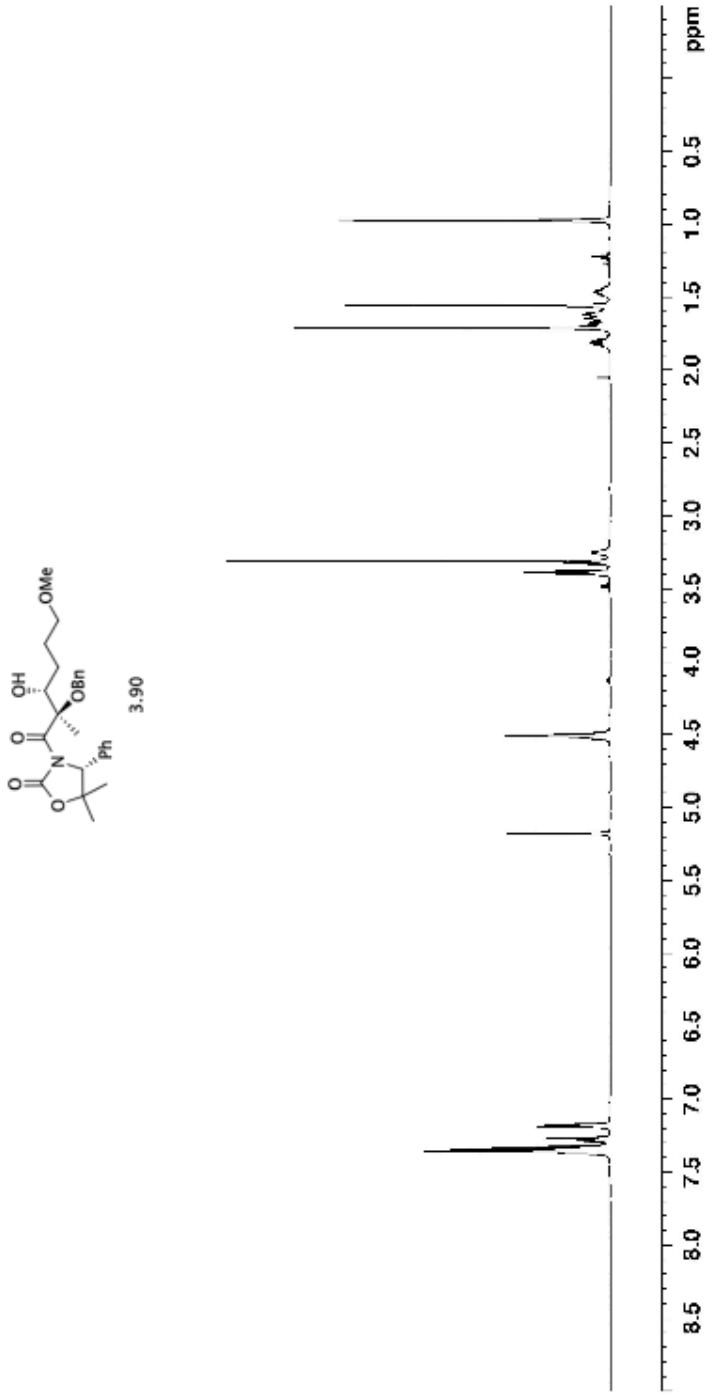

Figure 13a The 500 MHz ^{1}H NMR spectrum of **3.90** in $CDCl_3$.

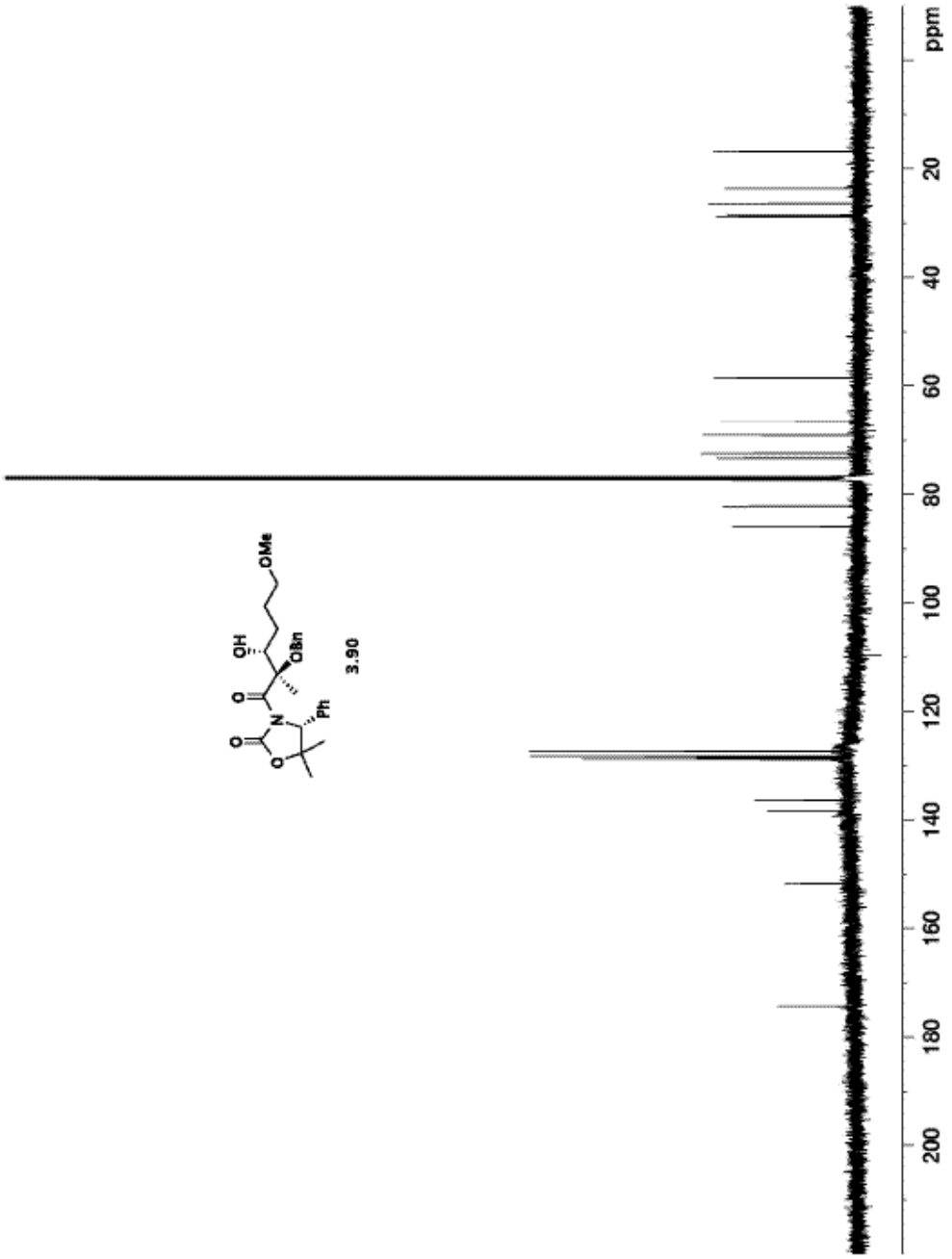

Figure 13b The 125 MHz ^{13}C NMR spectrum of **3.90** in $CDCl_3$.

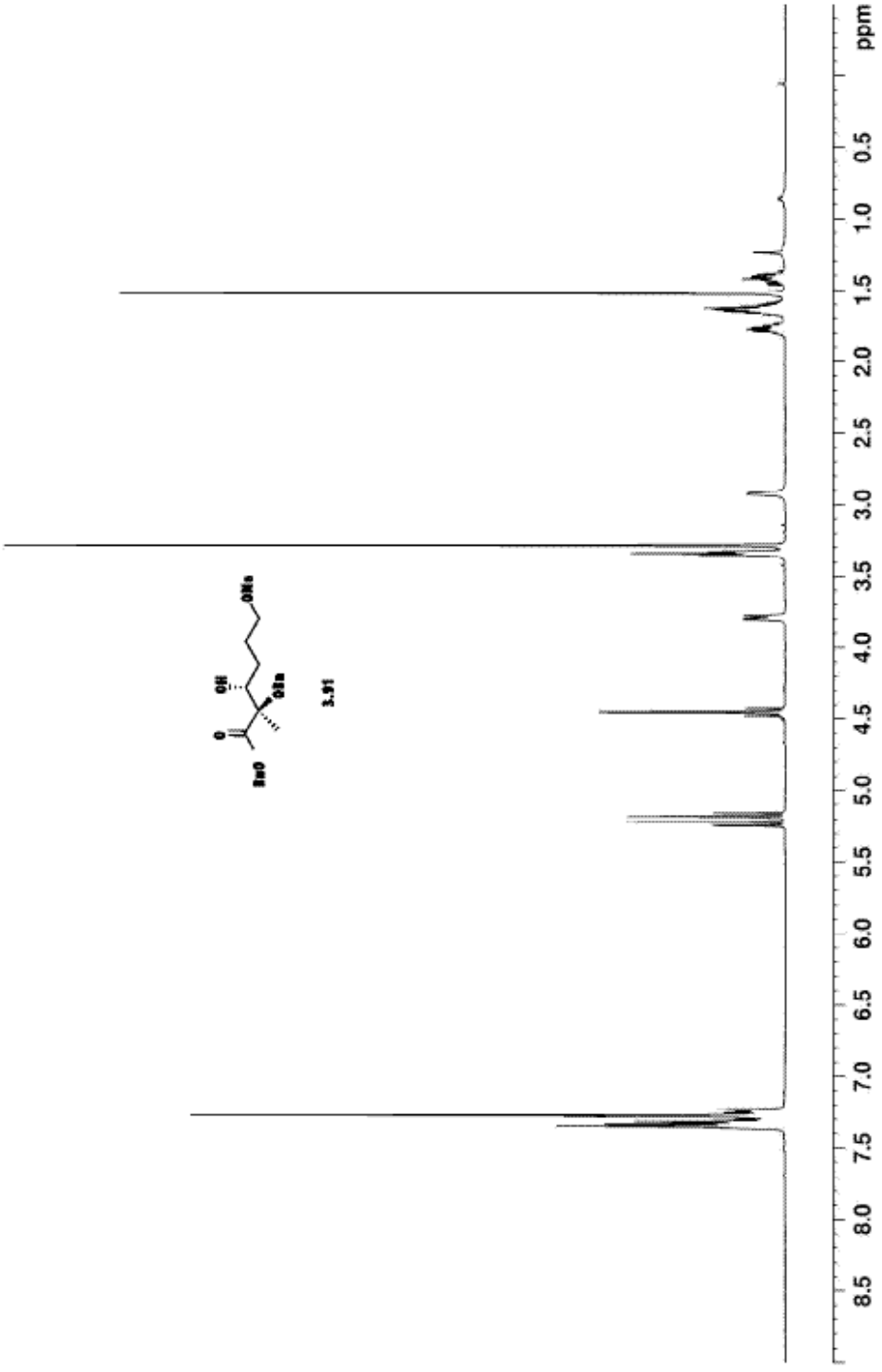

Figure 14a The 400 MHz ^{1}H NMR spectrum of **3.91** in $CDCl_3$.

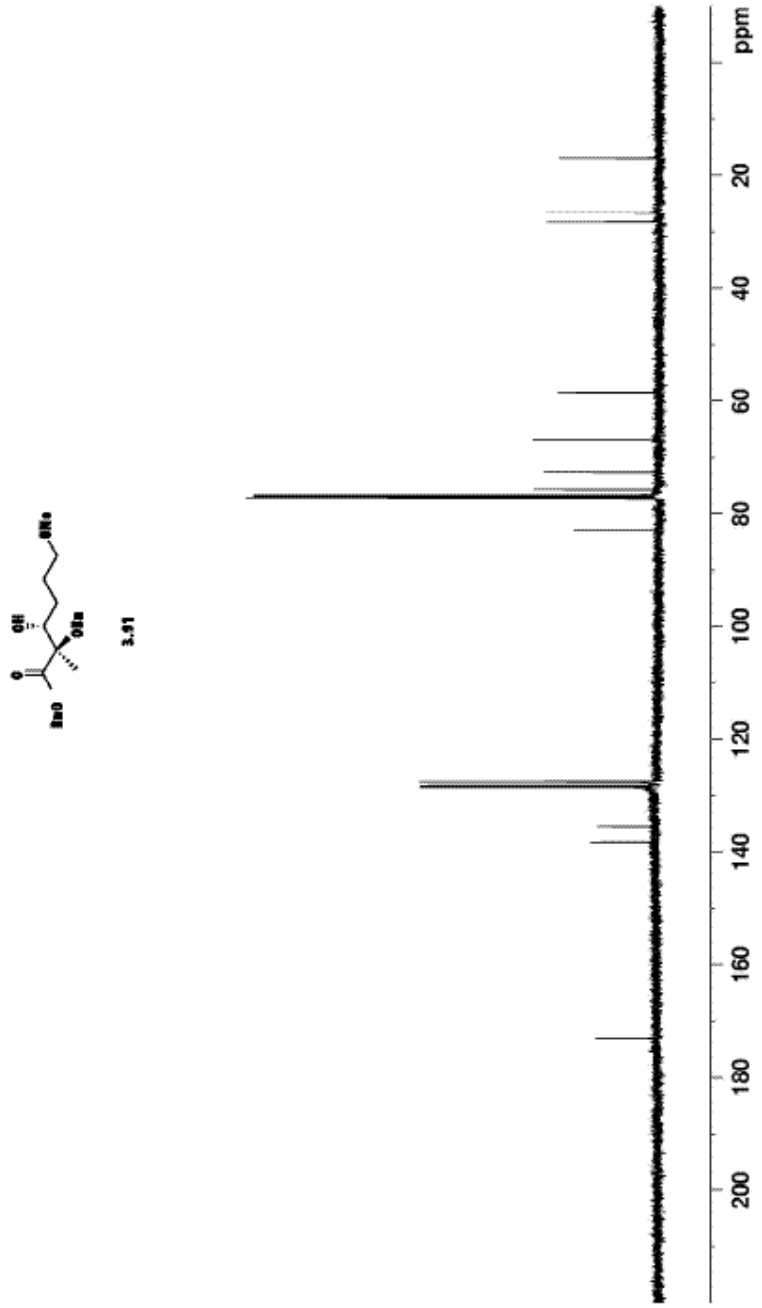

Figure 14b The 100 MHz ^{13}C NMR spectrum of **3.91** in $CDCl_3$.

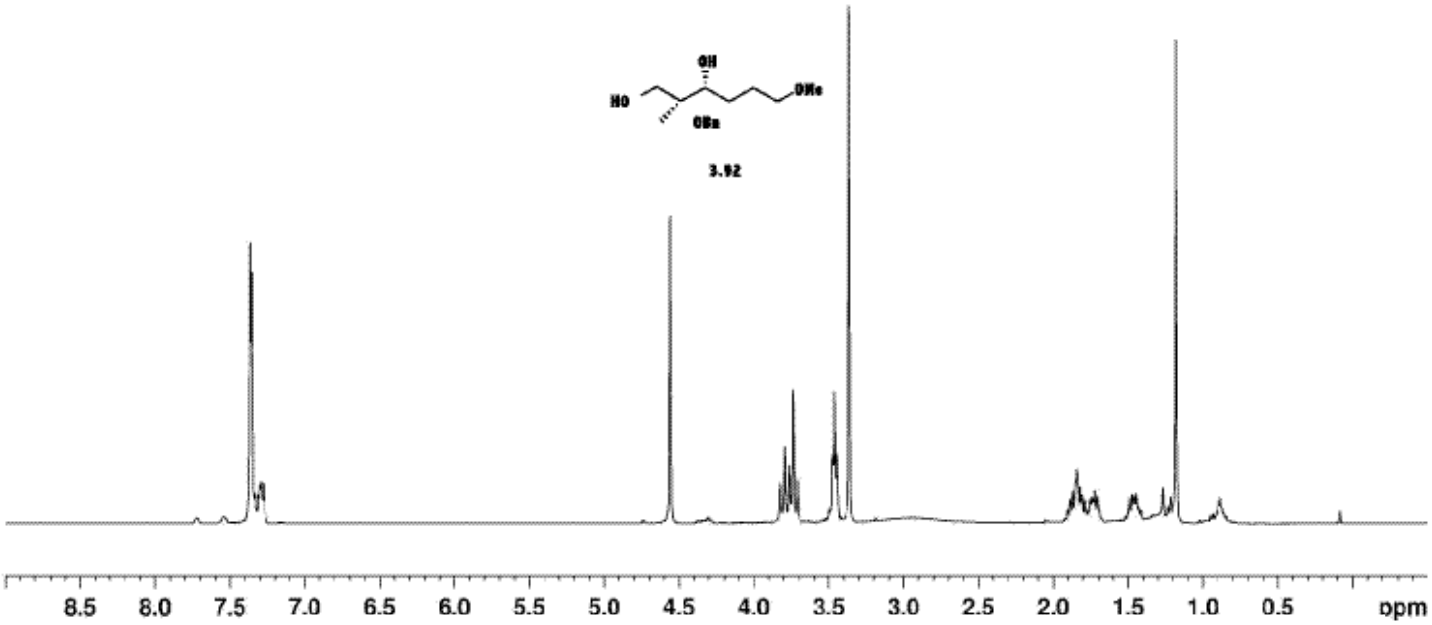

Figure 15a The 400 MHz ^{1}H NMR spectrum of **3.92** in $CDCl_3$.

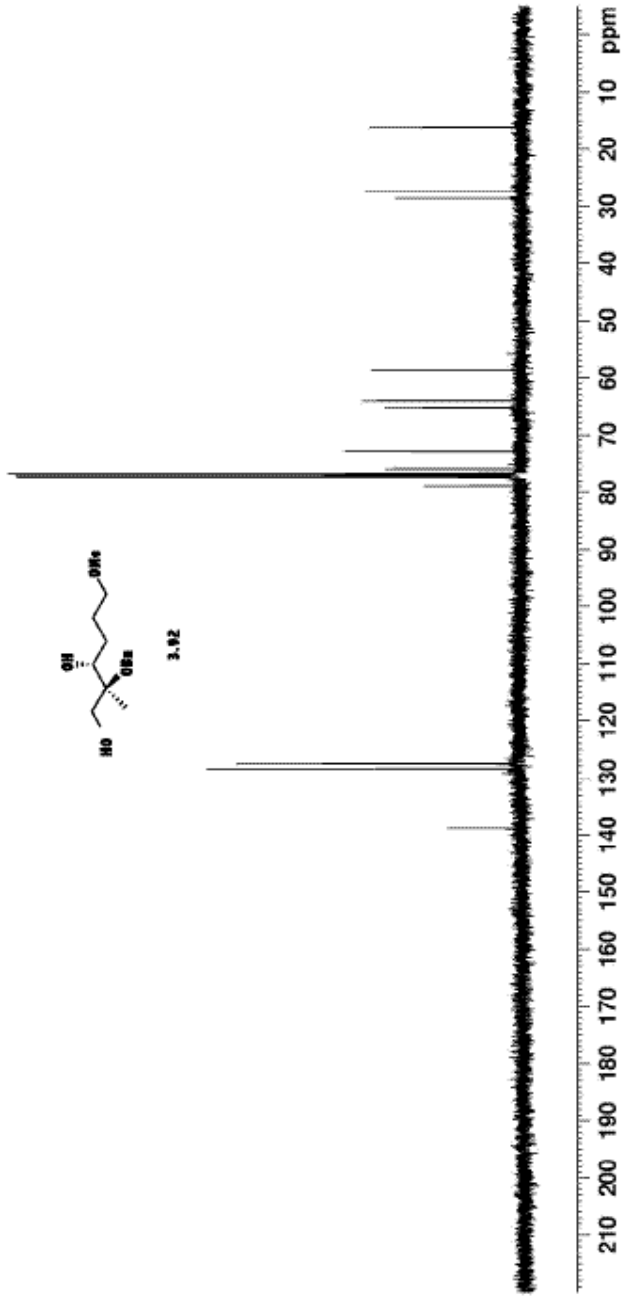

Figure B15b The 100 MHz ^{13}C NMR spectrum of **3.92** in $CDCl_3$.

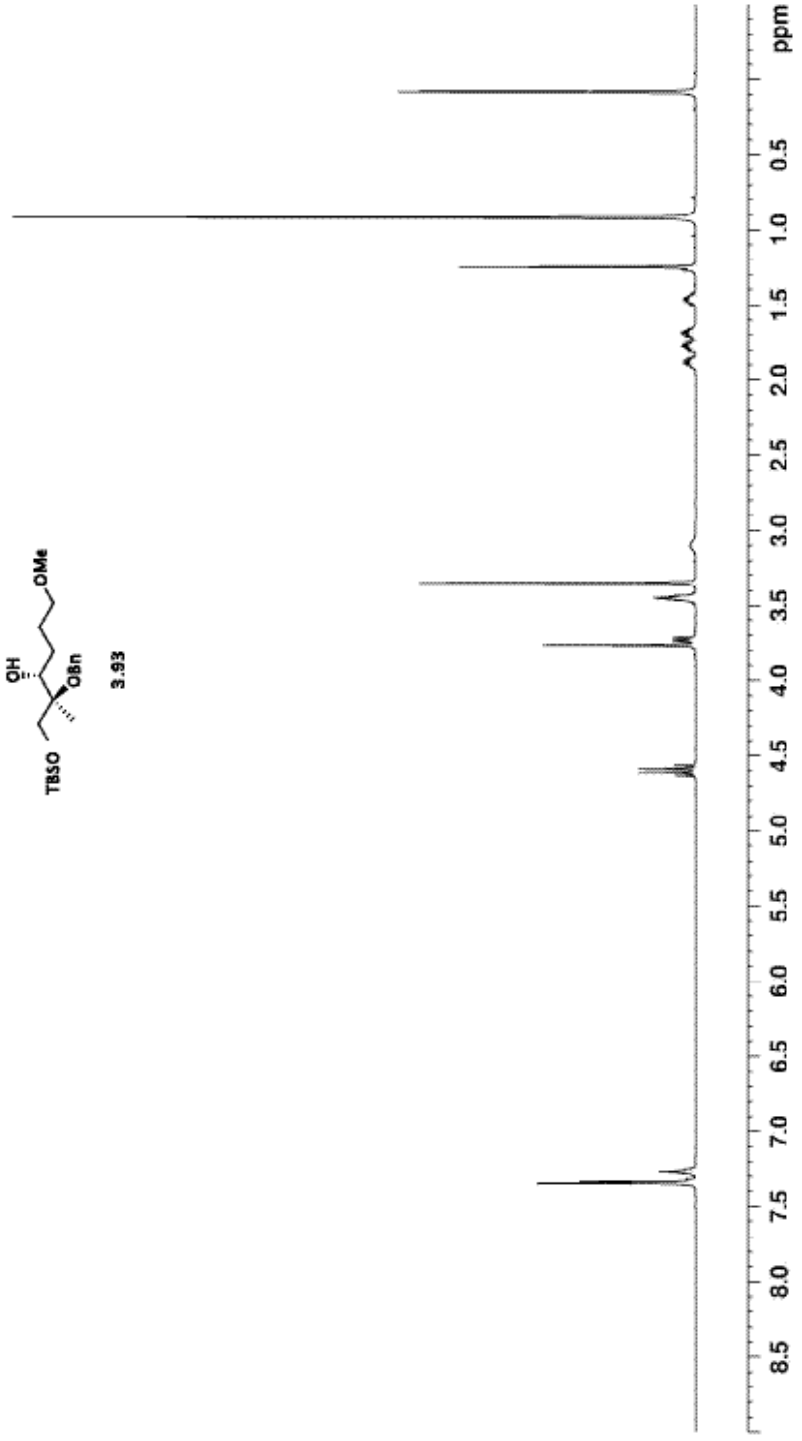

Figure 16a The 500 MHz ^{1}H NMR spectrum of **3.93** in $CDCl_3$.

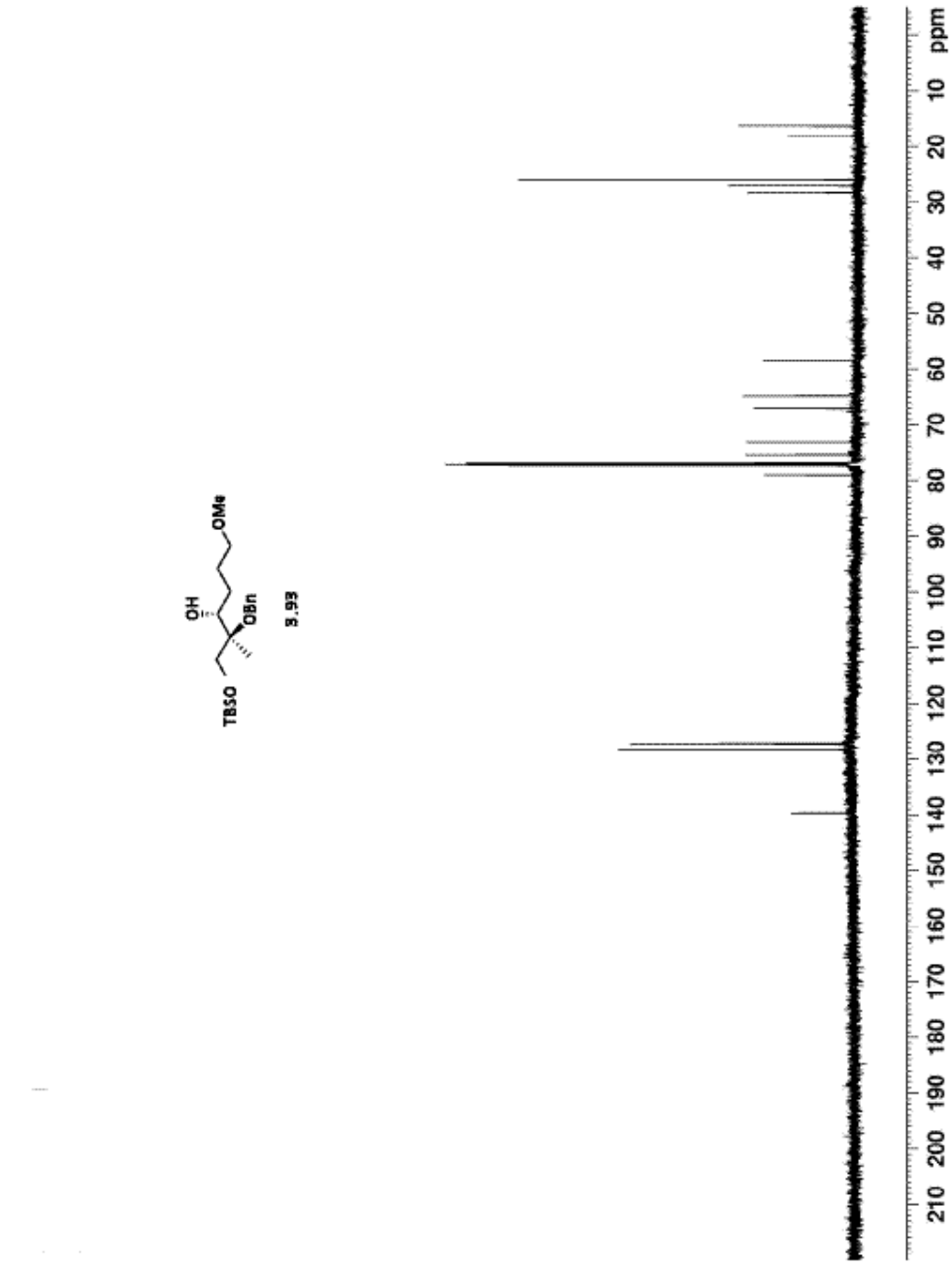

Figure 16b The 125 MHz ^{13}C NMR spectrum of **3.93** in $CDCl_3$.

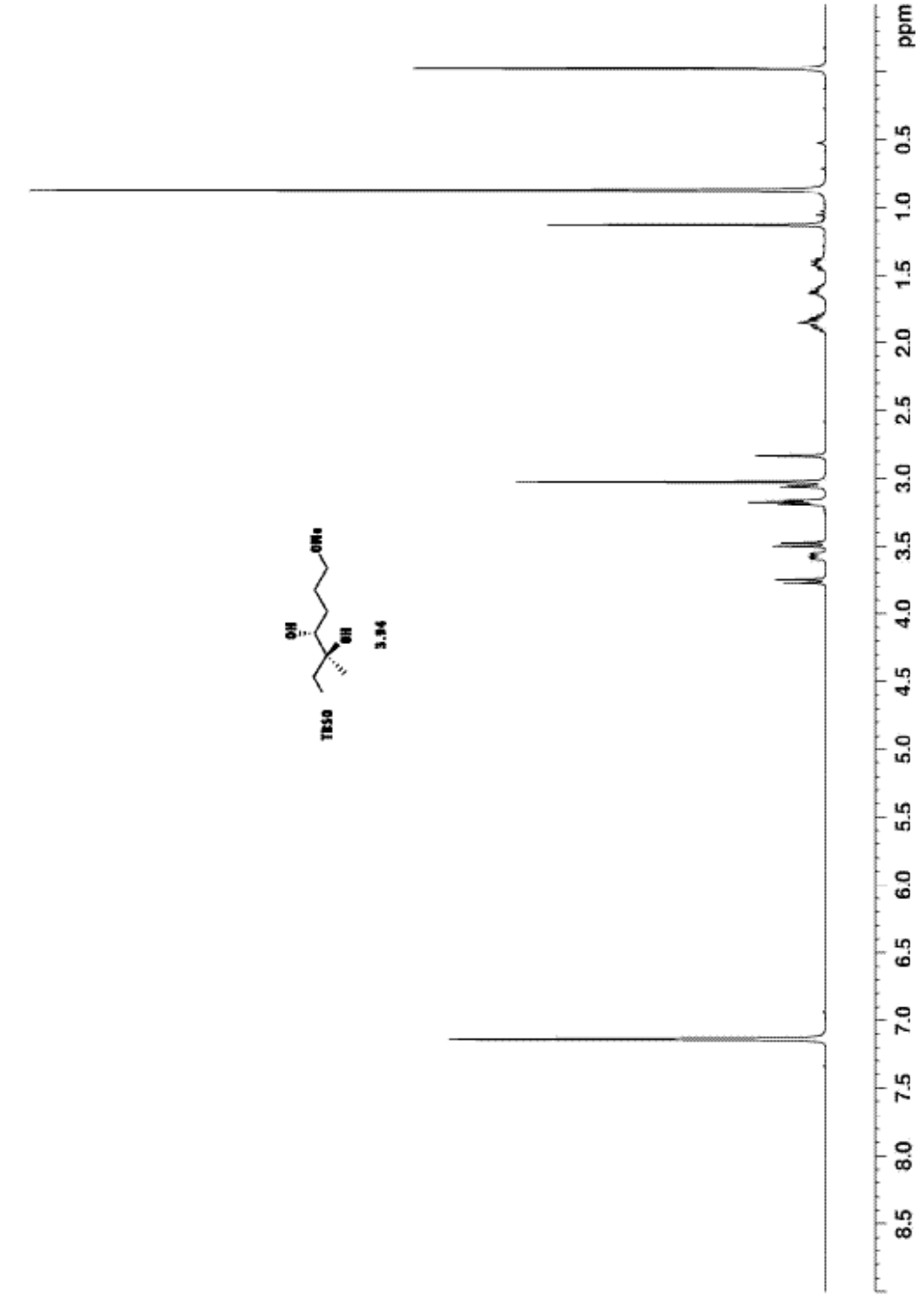

Figure 17a The 400 MHz ^{1}H NMR spectrum of **3.94** in $CDCl_3$.

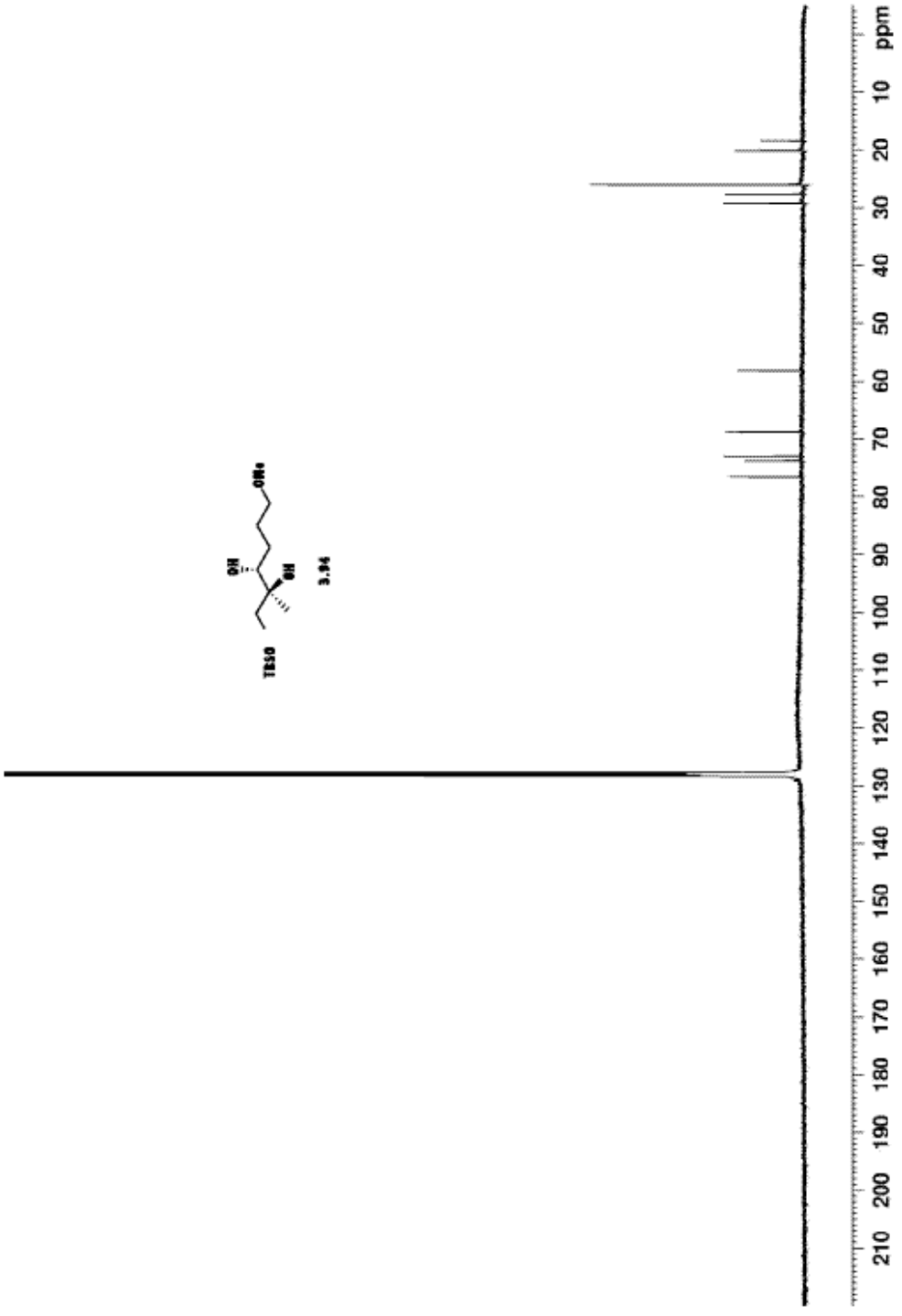

Figure 17b The 100 MHz ^{13}C NMR spectrum of **3.94** in $CDCl_3$.

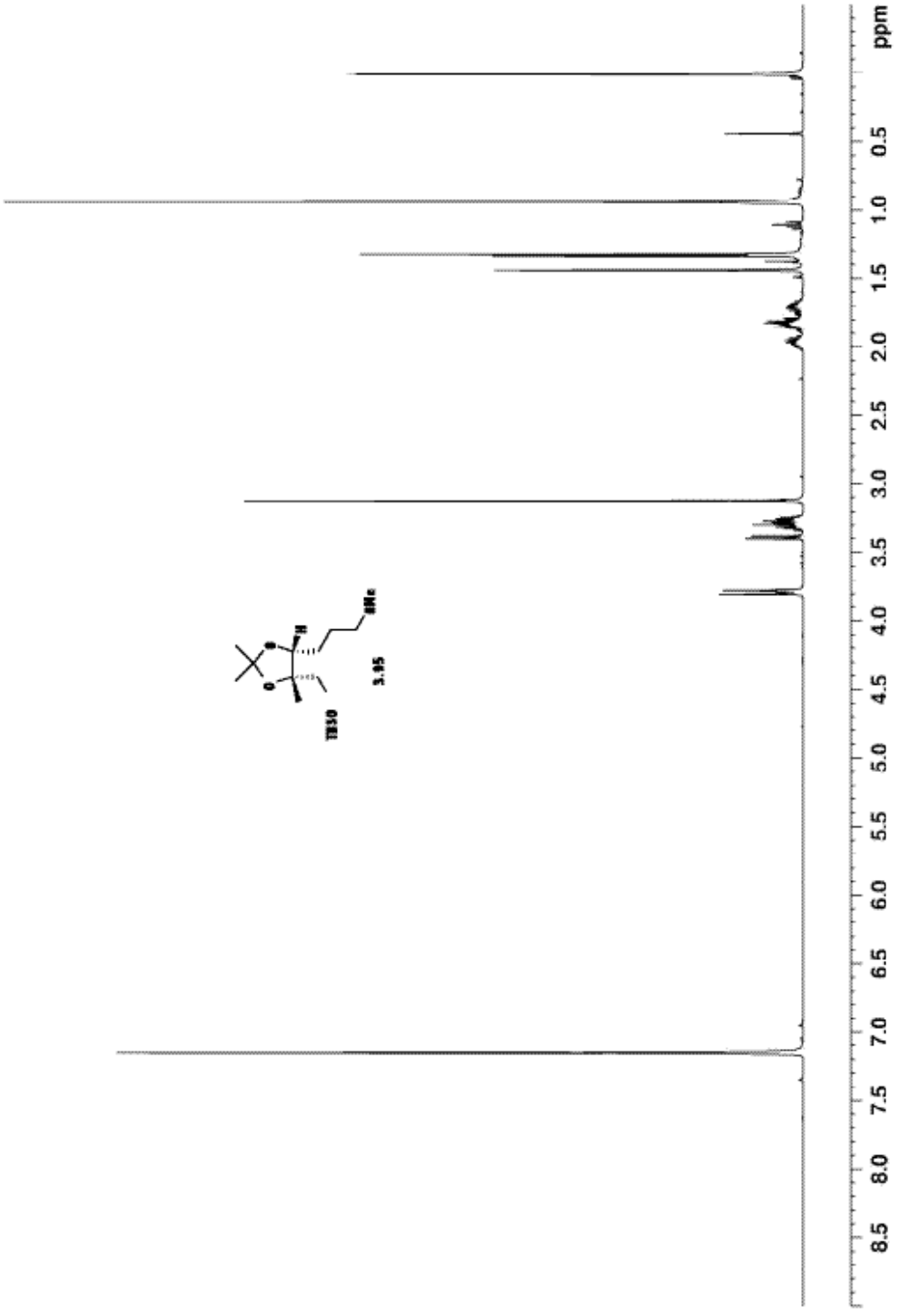

Figure 18a The 400 MHz ^{1}H NMR spectrum of **3.95** in $CDCl_3$.

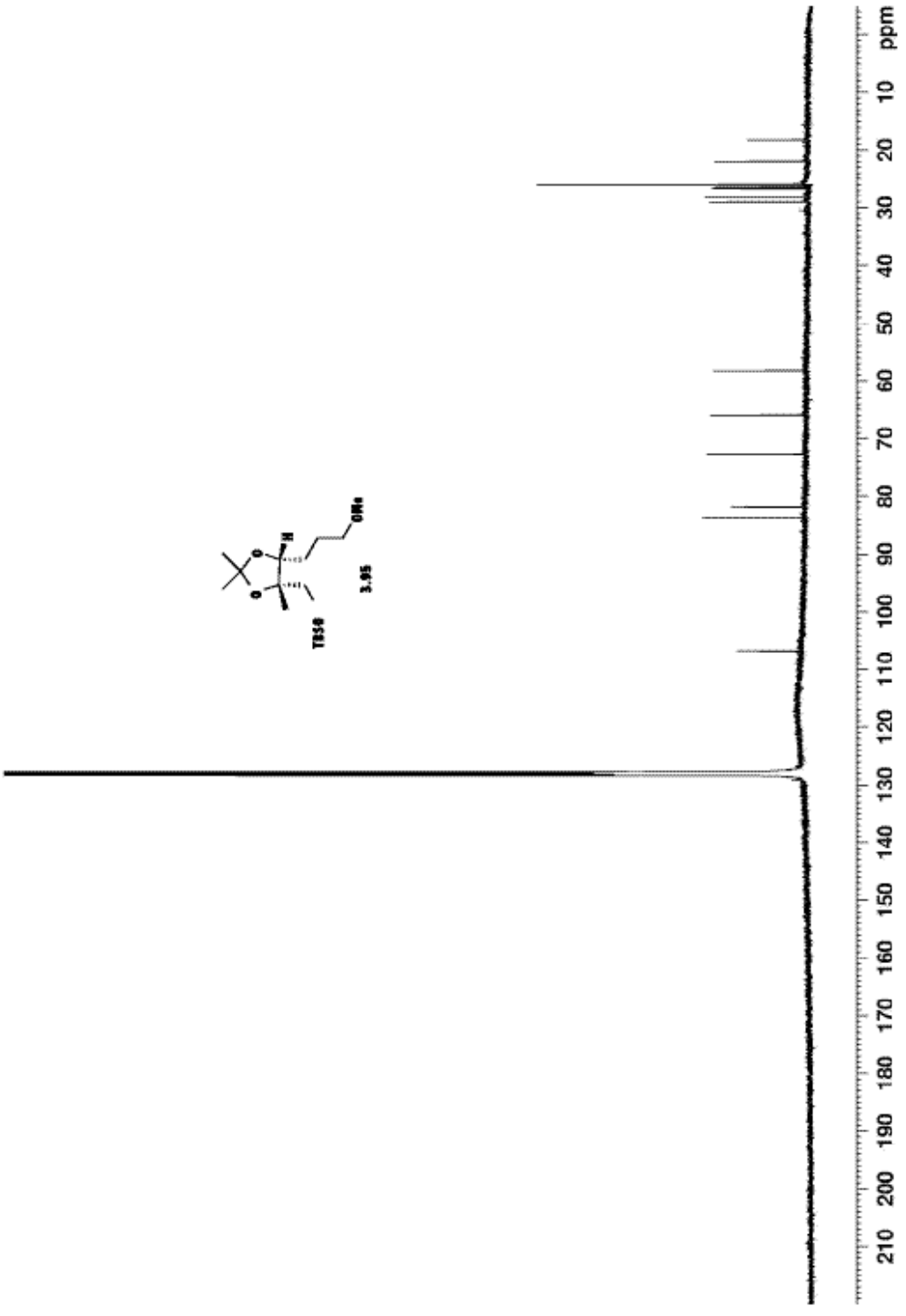

Figure 18b The 100 MHz ^{13}C NMR spectrum of **3.95** in $CDCl_3$.

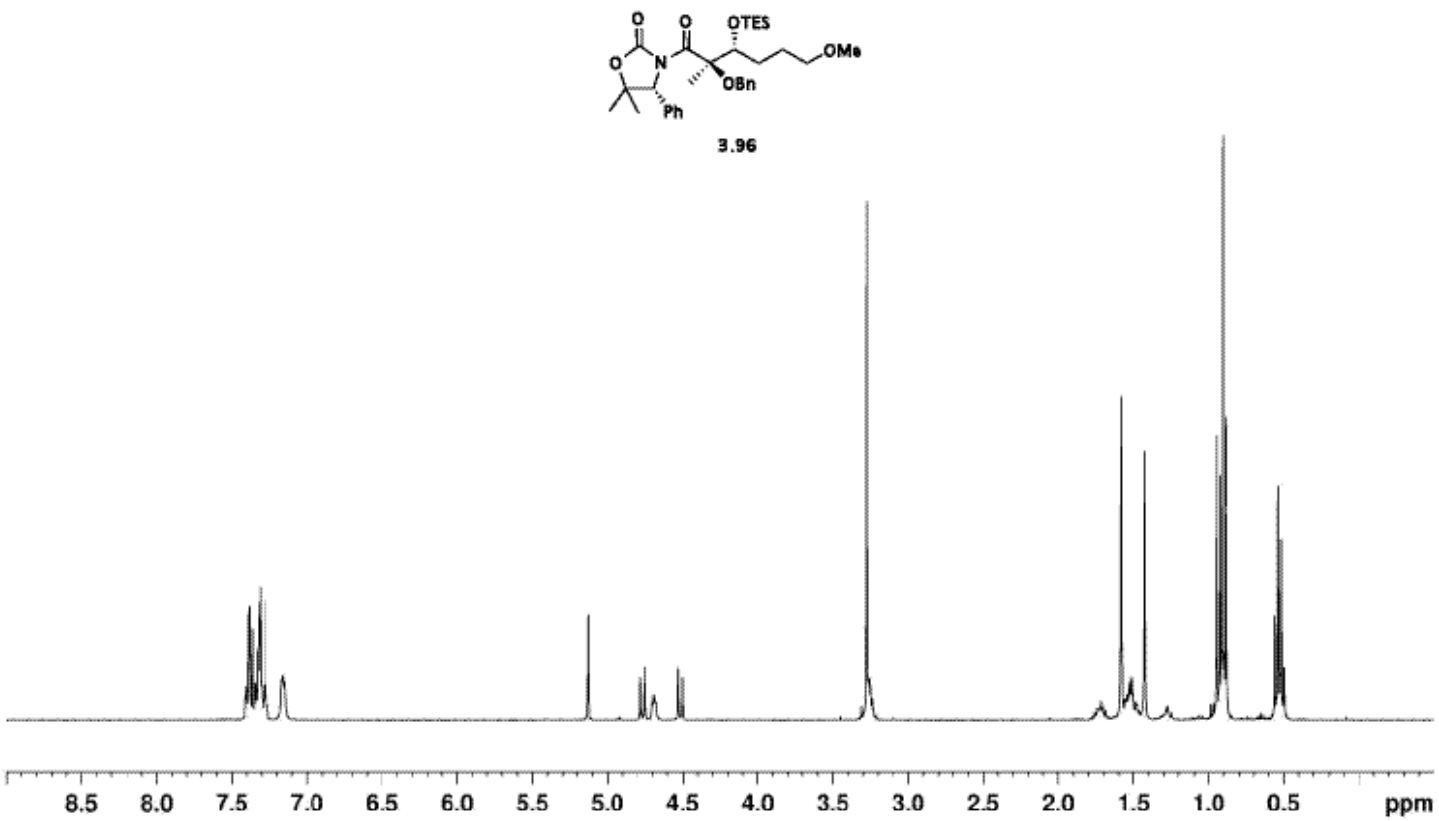

Figure 19a The 400 MHz ^{1}H NMR spectrum of **3.96** in $CDCl_3$.

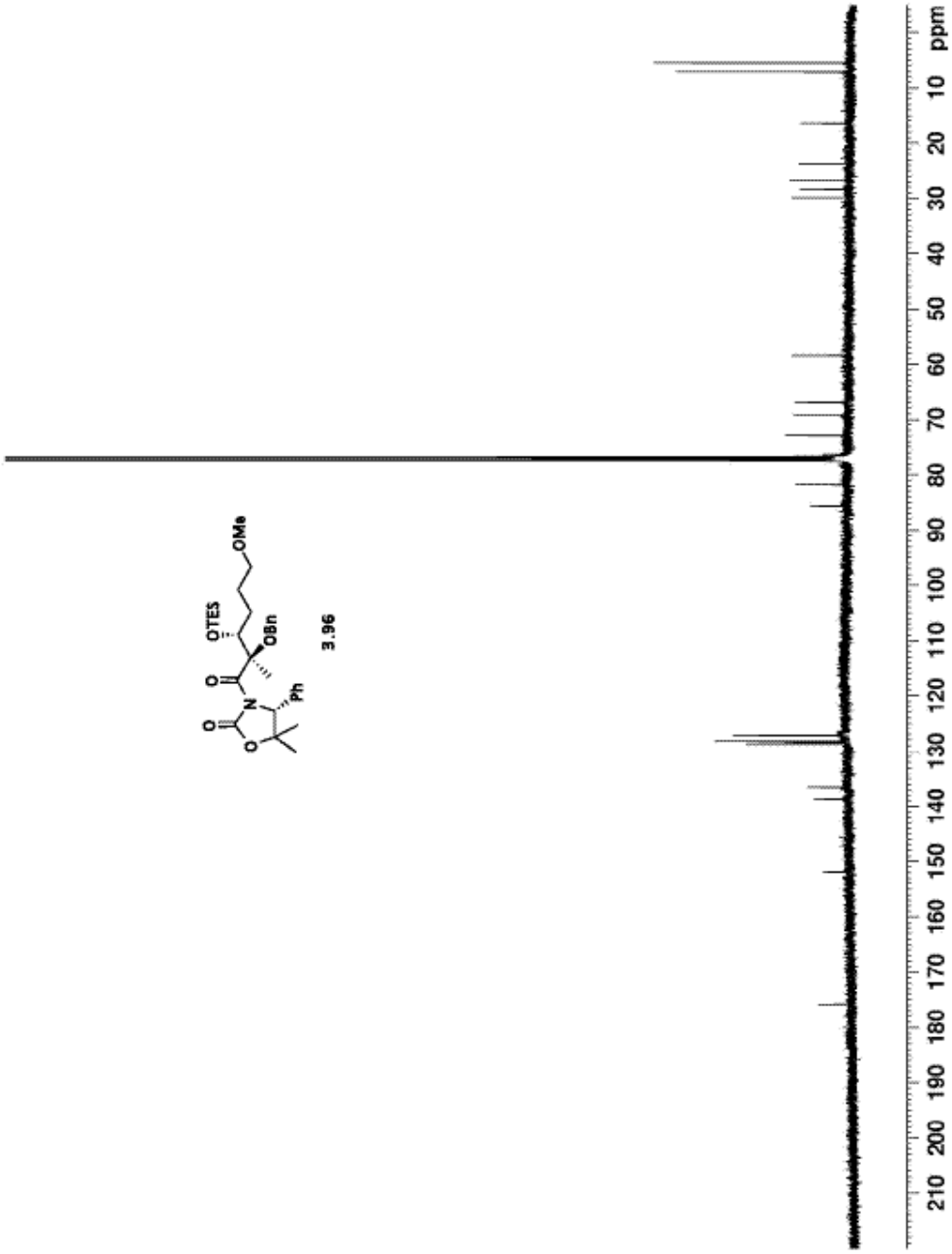

Figure 19b The 100 MHz ^{13}C NMR spectrum of **3.96** in $CDCl_3$.

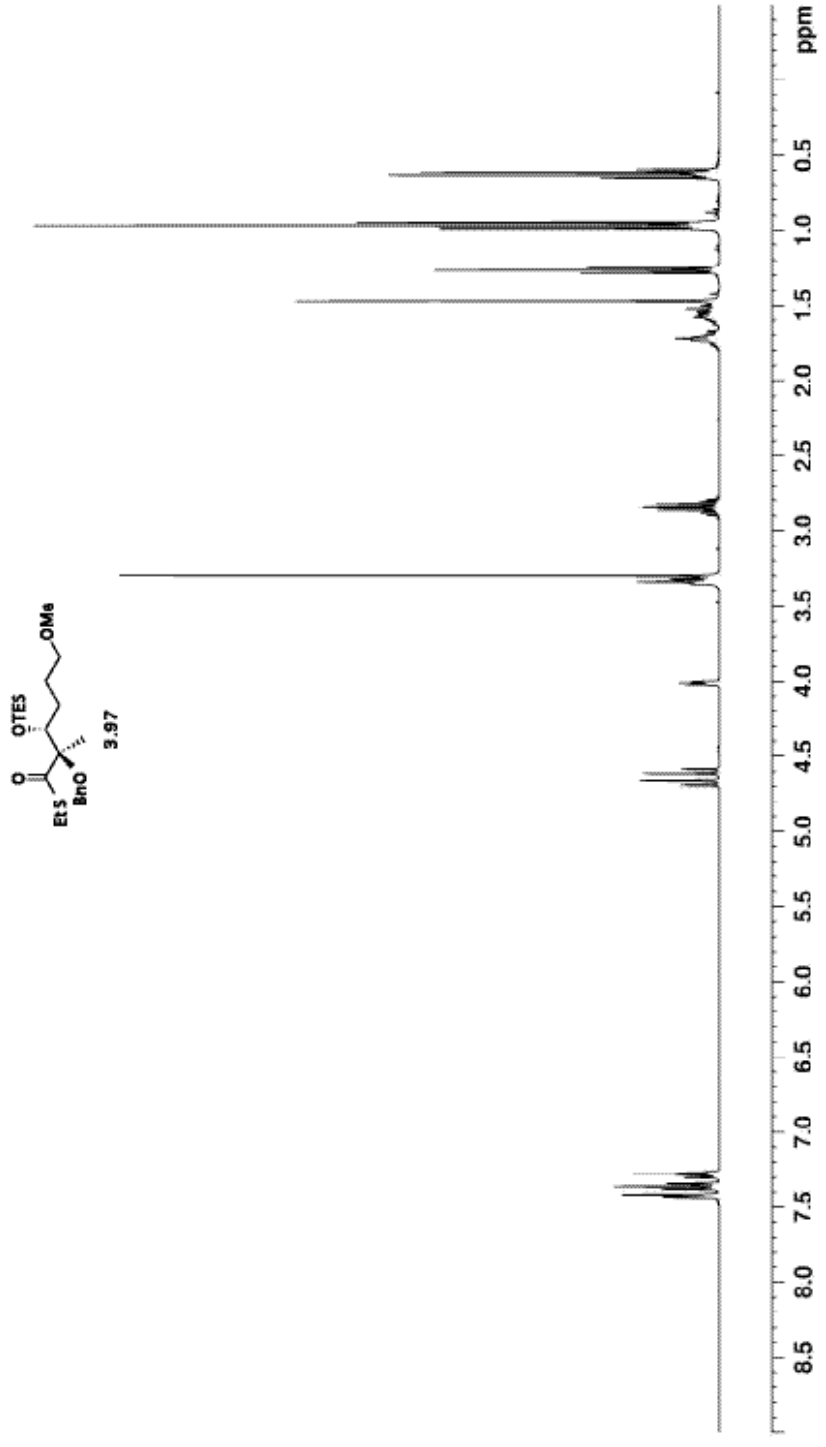

Figure 20a The 400 MHz ^{1}H NMR spectrum of **3.97** in $CDCl_3$.

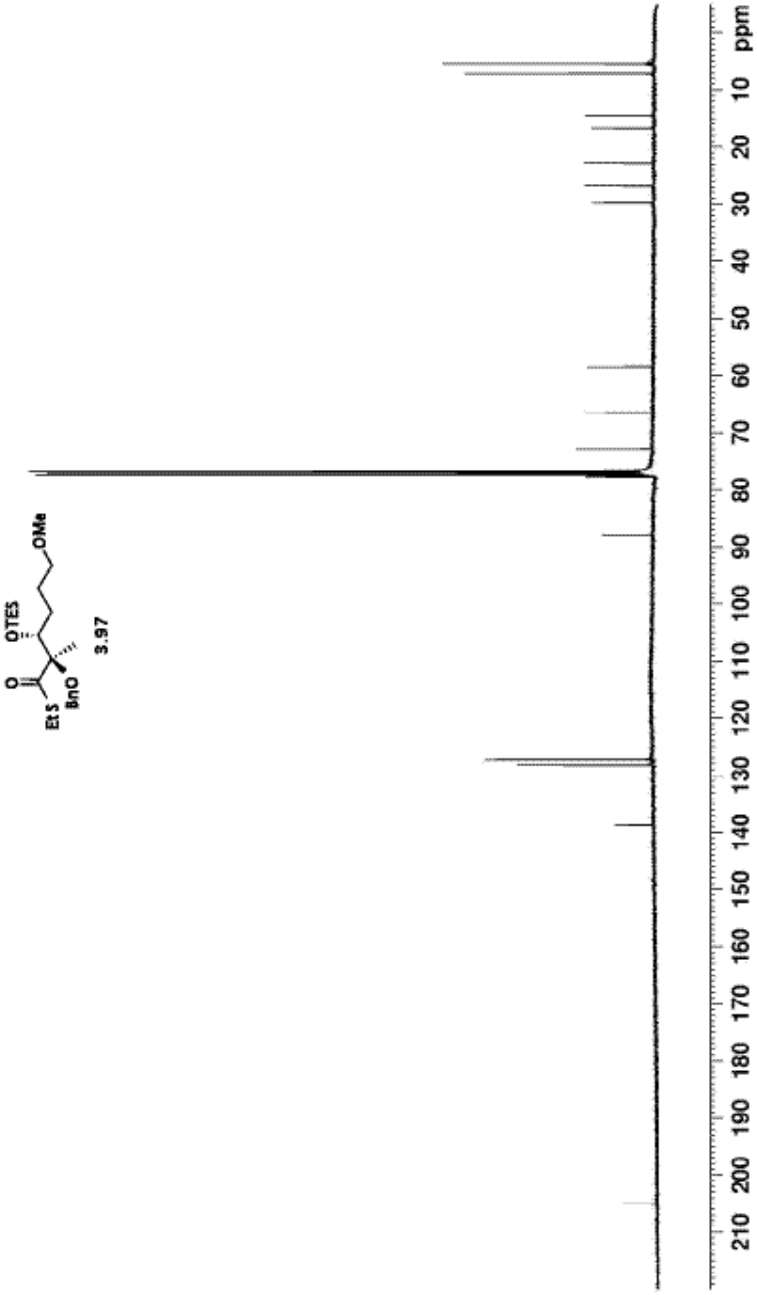

Figure 20b The 100 MHz ^{13}C NMR spectrum of **3.97** in $CDCl_3$.

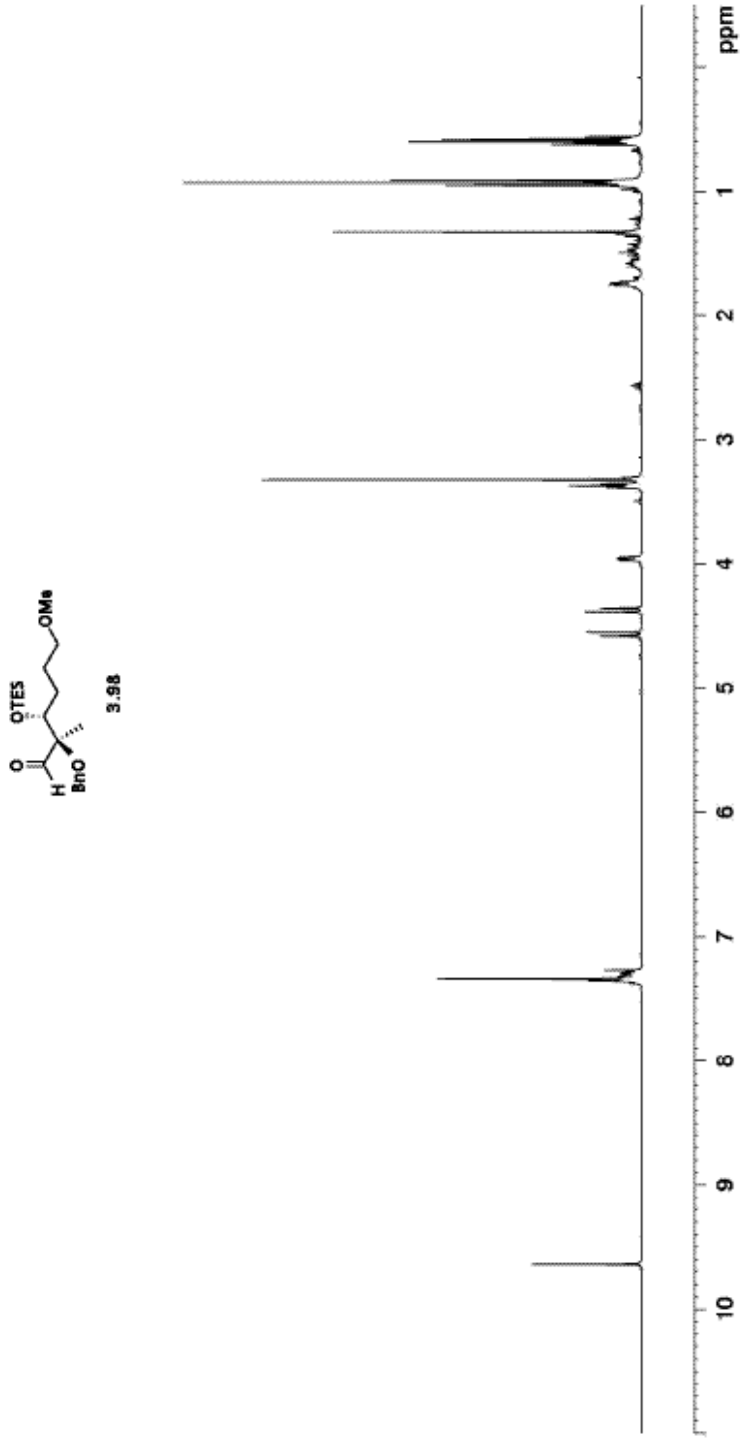

Figure 21a The 400 MHz ^{1}H NMR spectrum of **3.98** in $CDCl_3$.

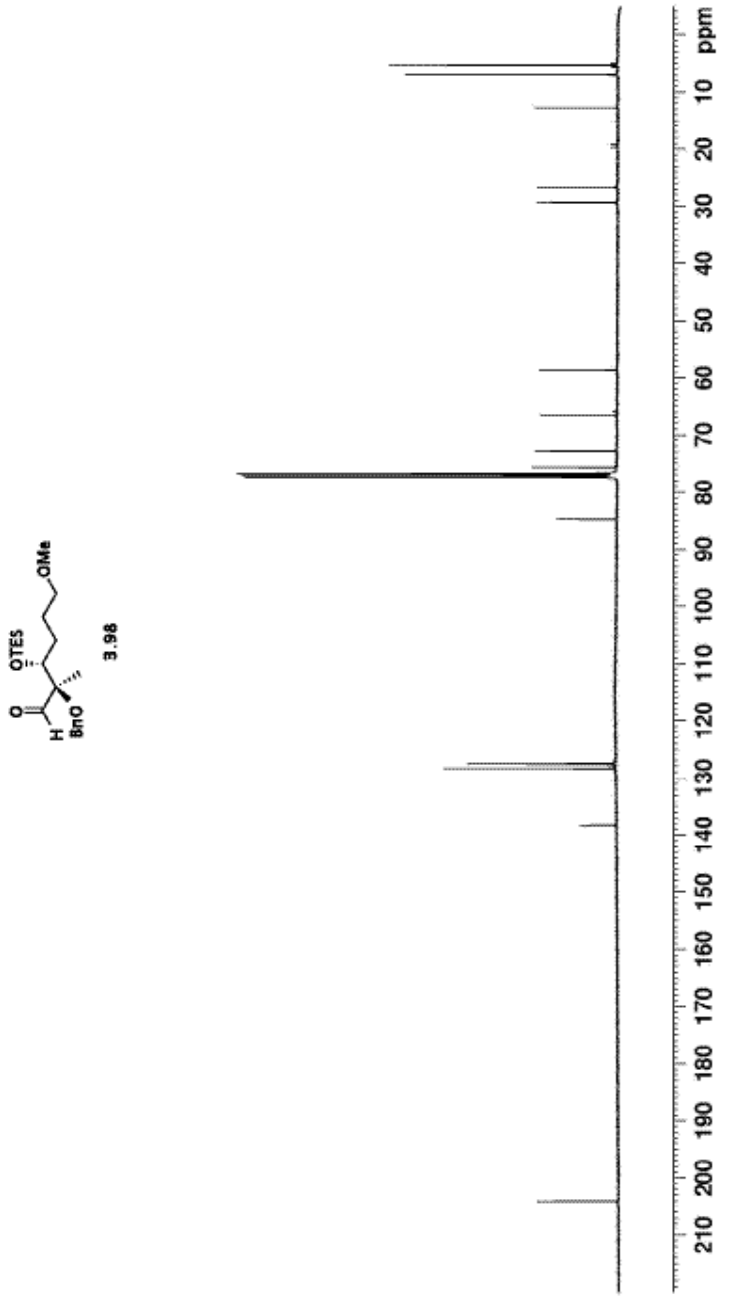

Figure 21b The 100 MHz ^{13}C NMR spectrum of **3.98** in $CDCl_3$.

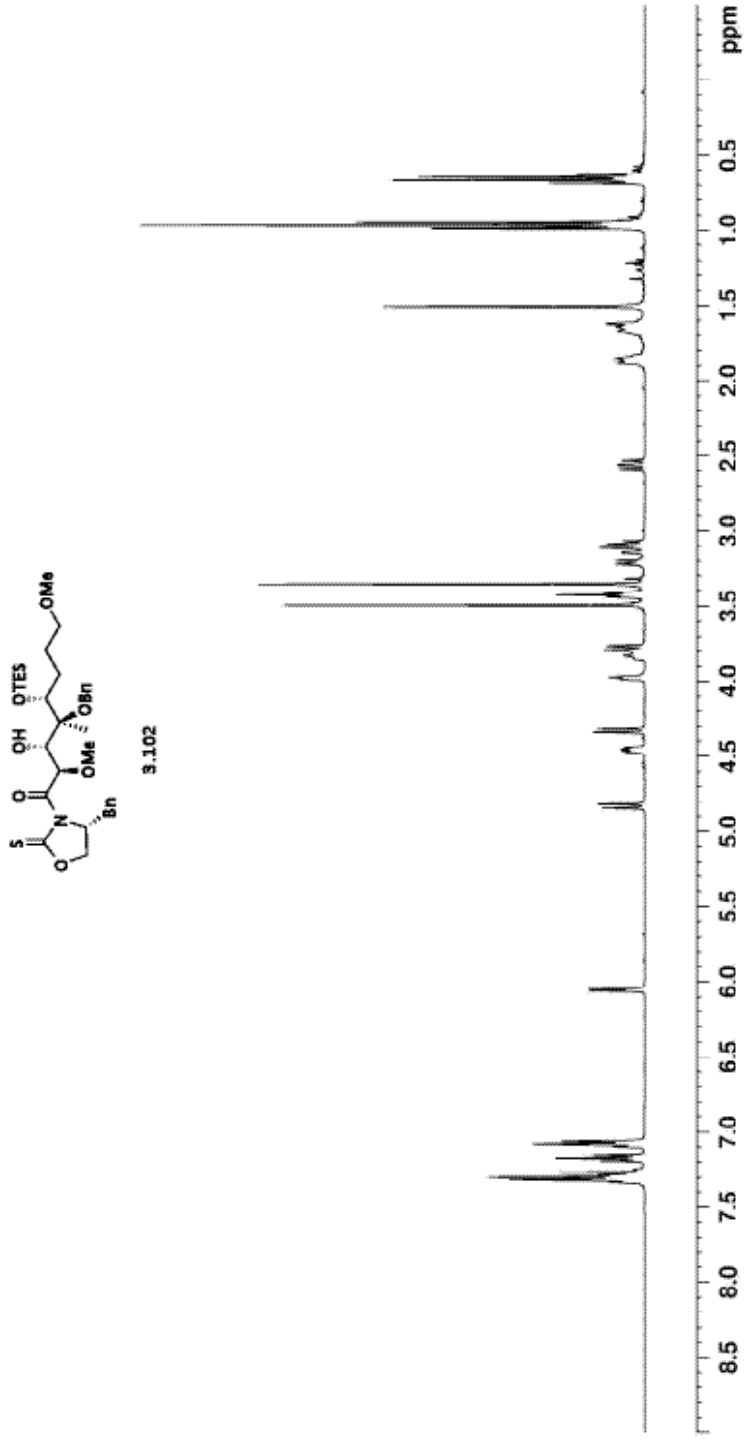

Figure 22a The 400 MHz ^{1}H NMR spectrum of **3.102** in $CDCl_3$.

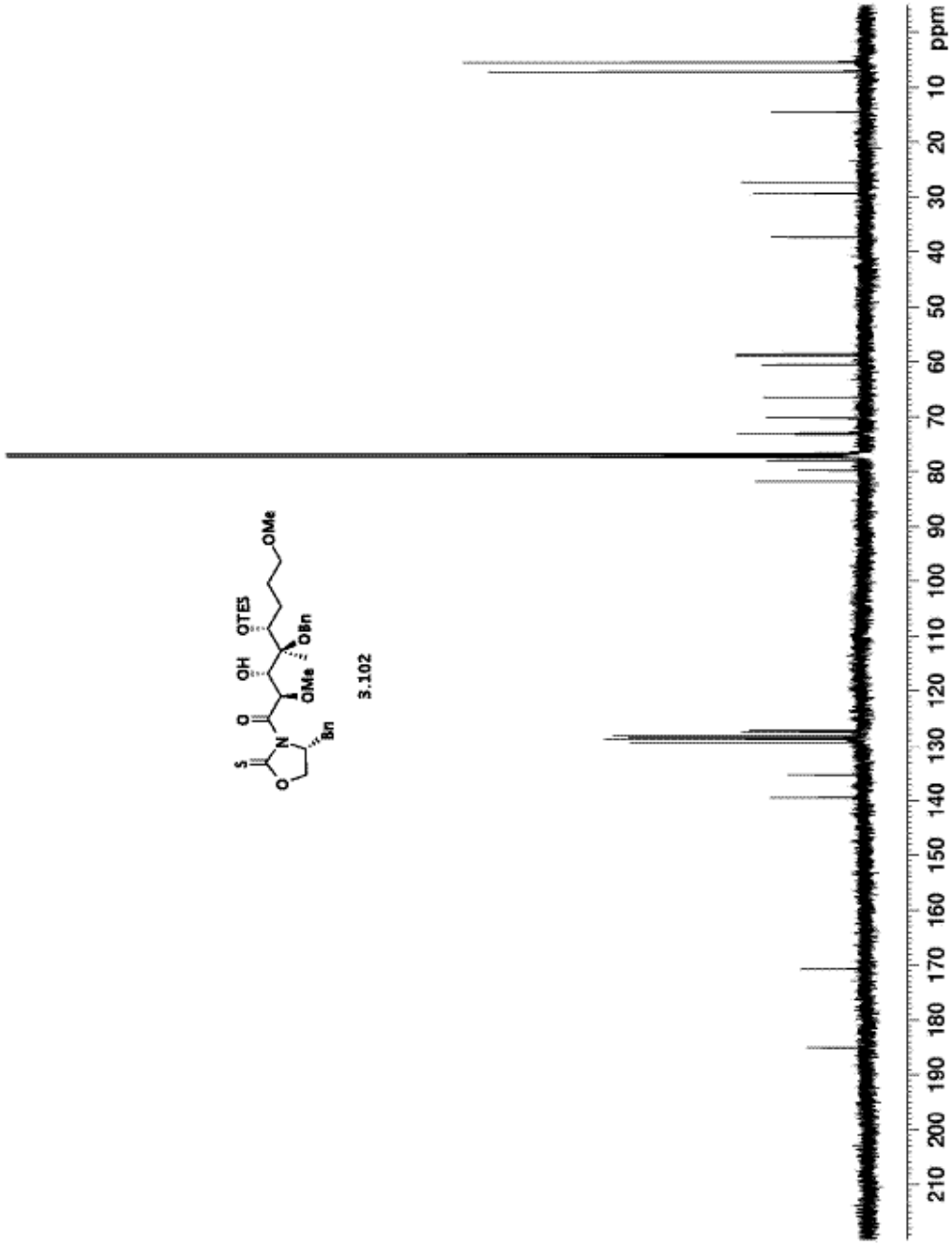

Figure 22b The 100 MHz ^{13}C NMR spectrum of **3.102** in $CDCl_3$.

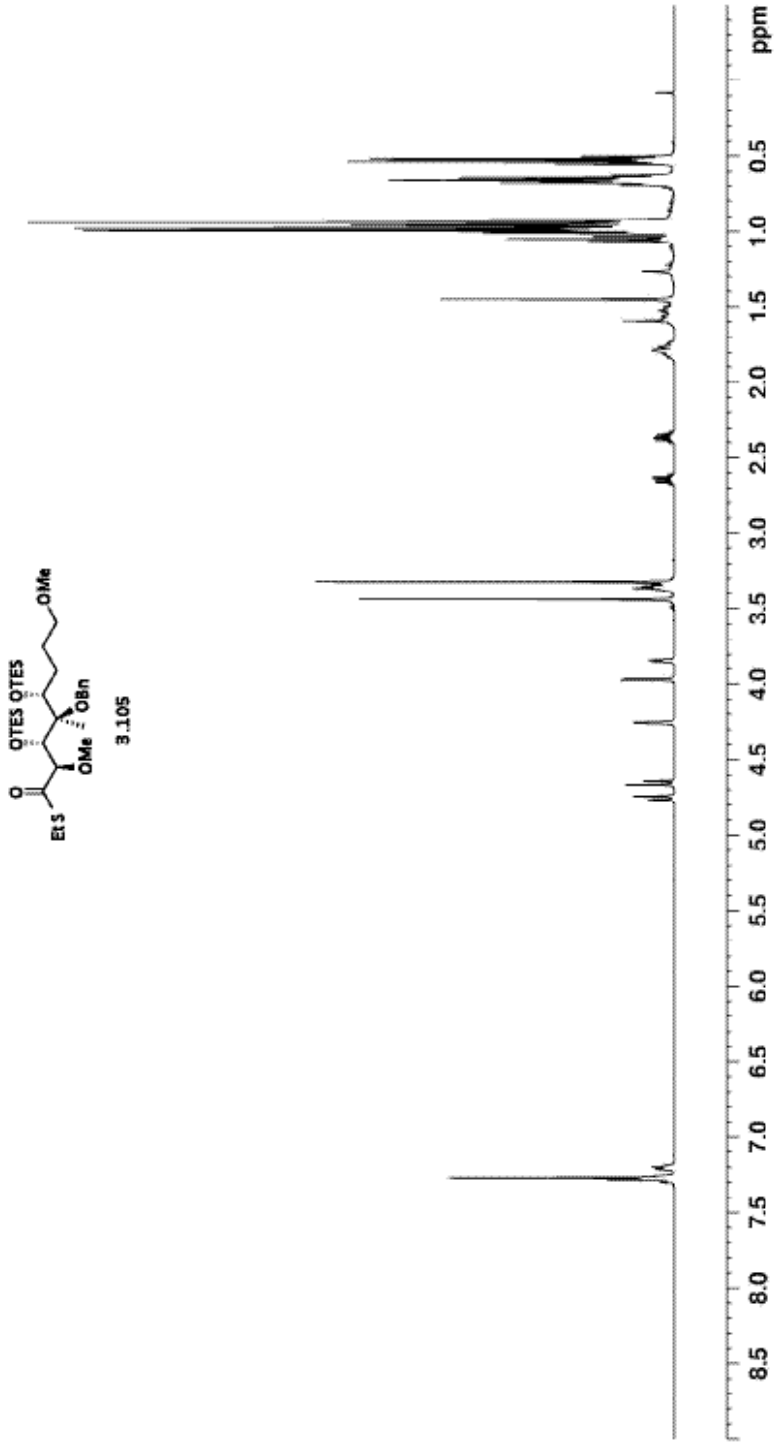

Figure 23a The 500 MHz ^{1}H NMR spectrum of **3.105** in $CDCl_3$.

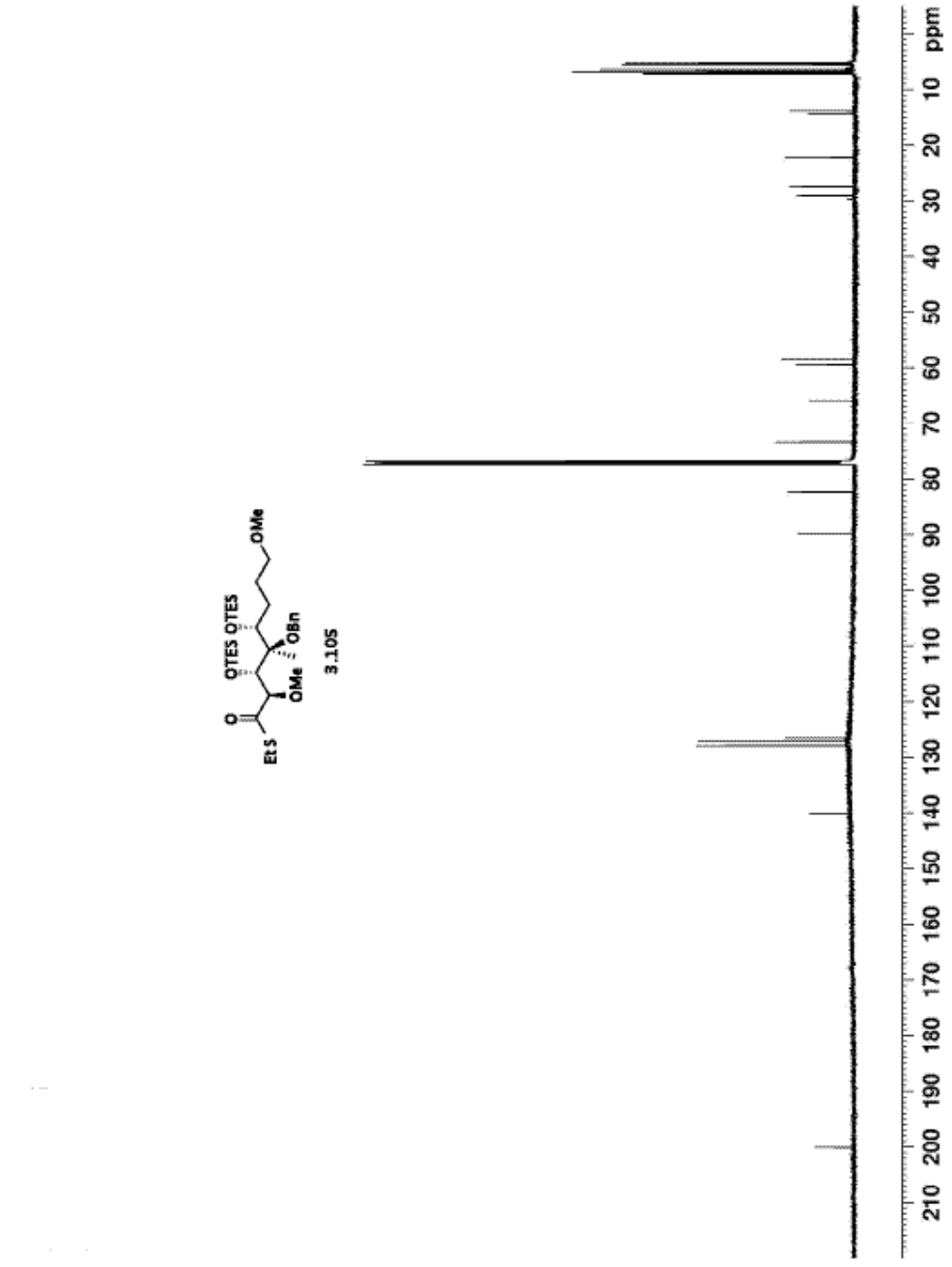

Figure 23b The 125 MHz ^{13}C NMR spectrum of **3.105** in $CDCl_3$.

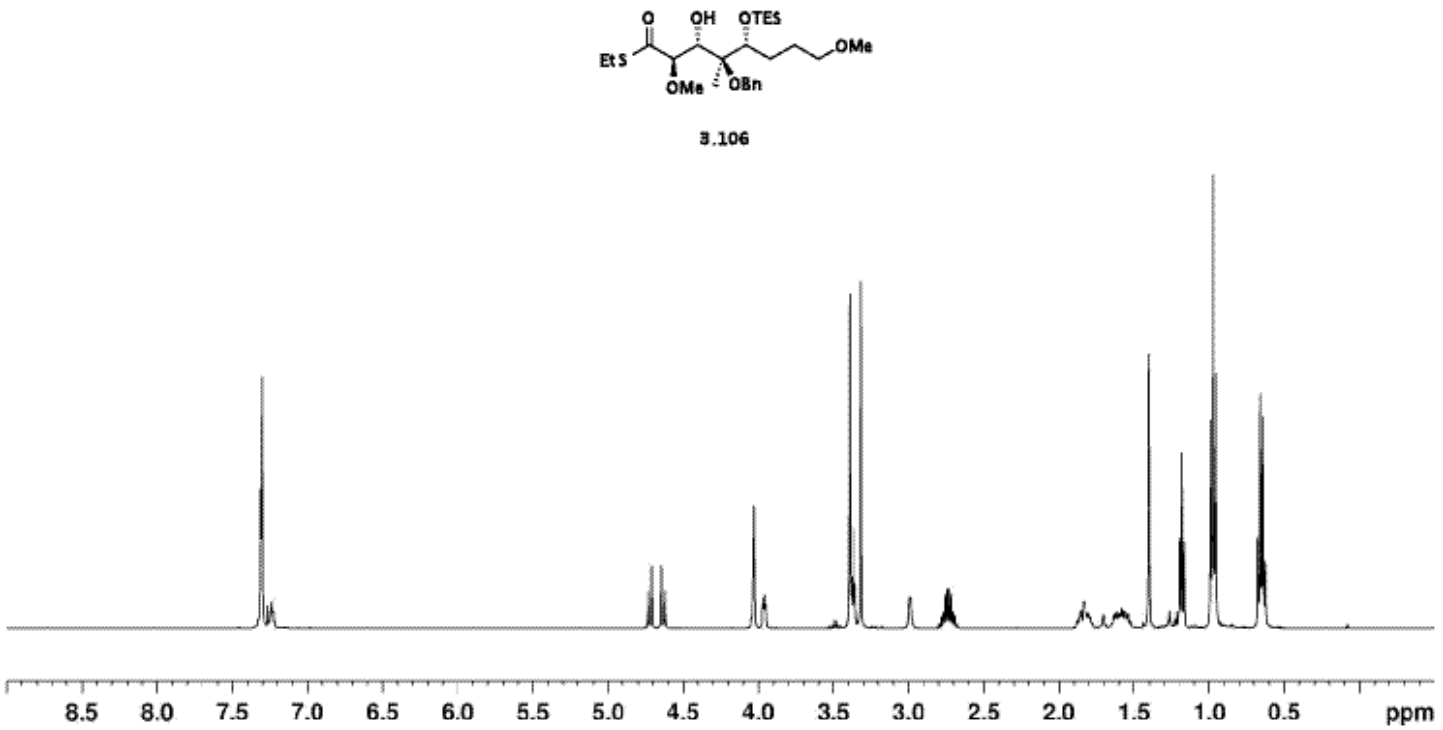

Figure 24a The 500 MHz ^{1}HNMR spectrum of **3.106** in $CDCl_3$.

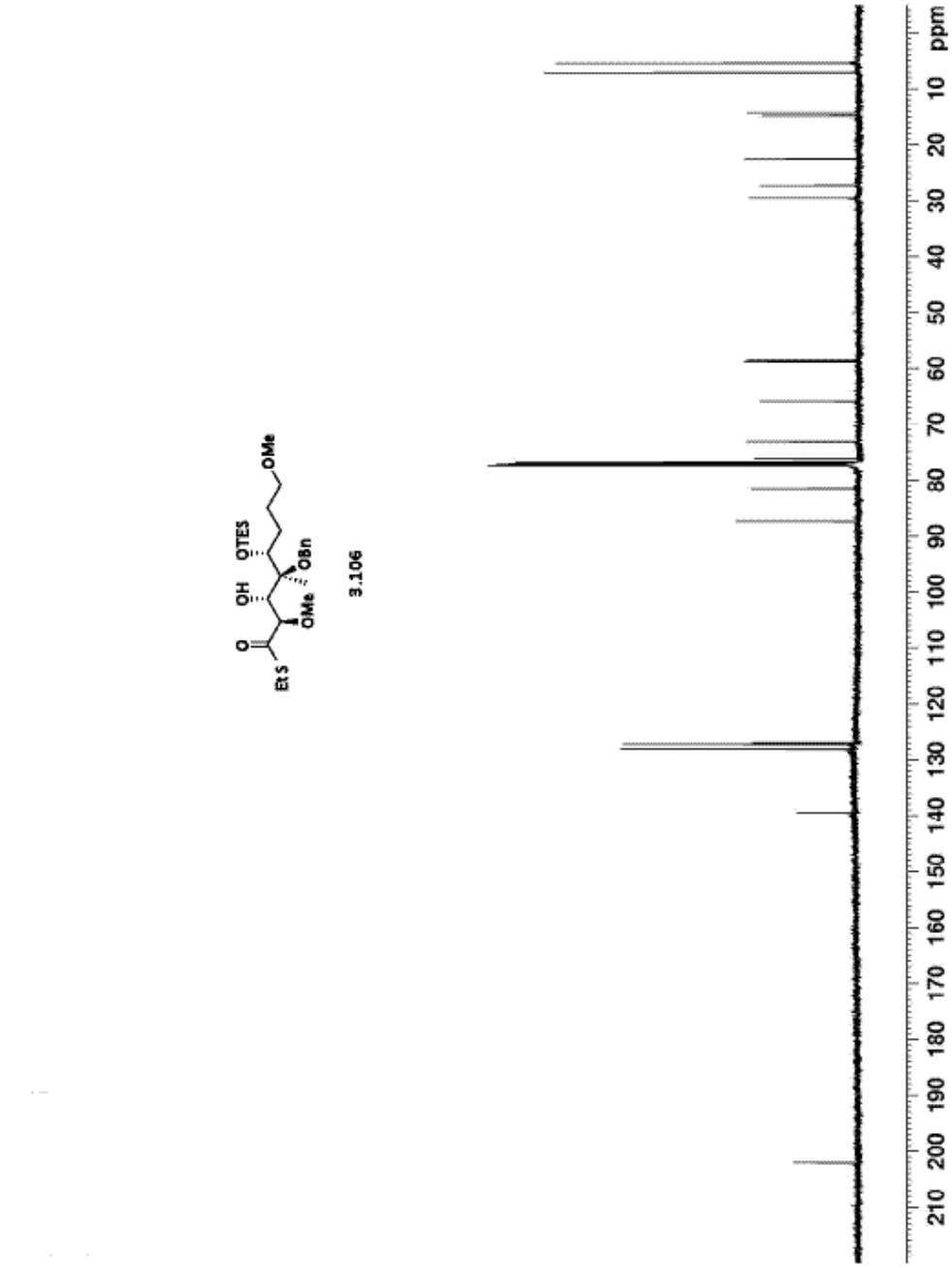

Figure 24b The 125 MHz ^{13}C NMR spectrum of **3.106** in $CDCl_3$.

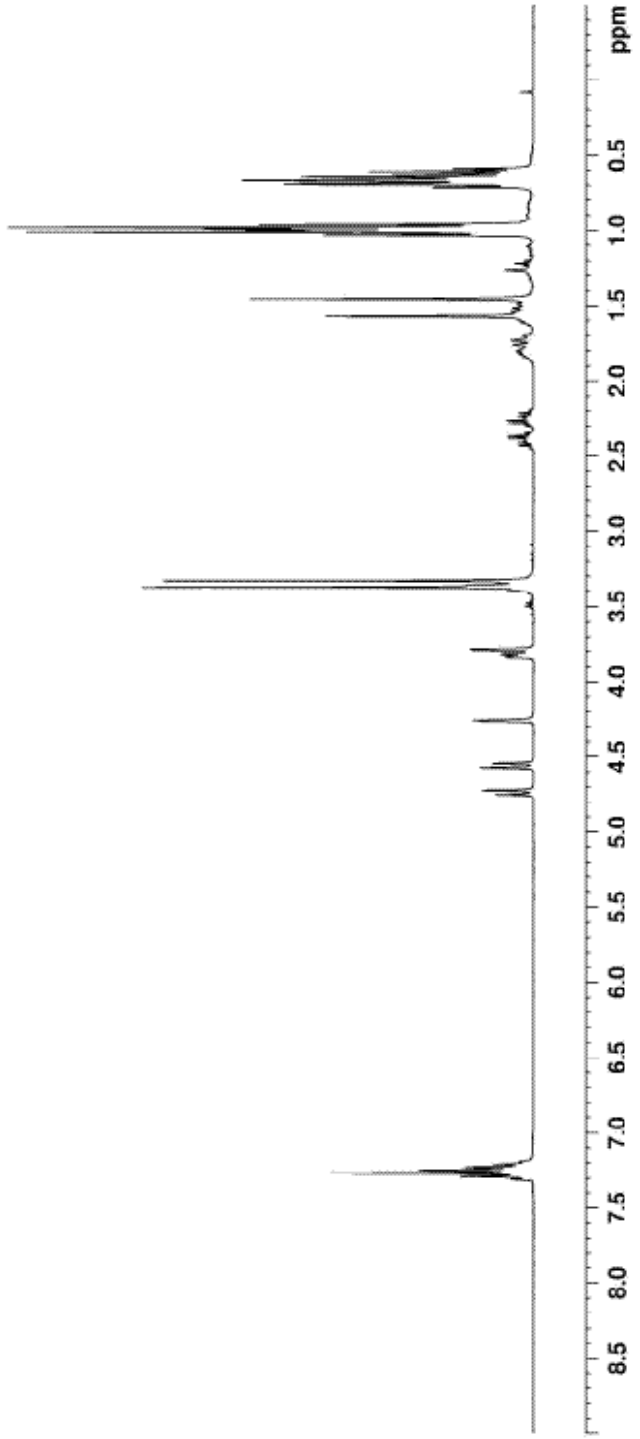

Figure 25a The 400 MHz ^{1}H NMR spectrum of **3.9'** in $CDCl_3$.

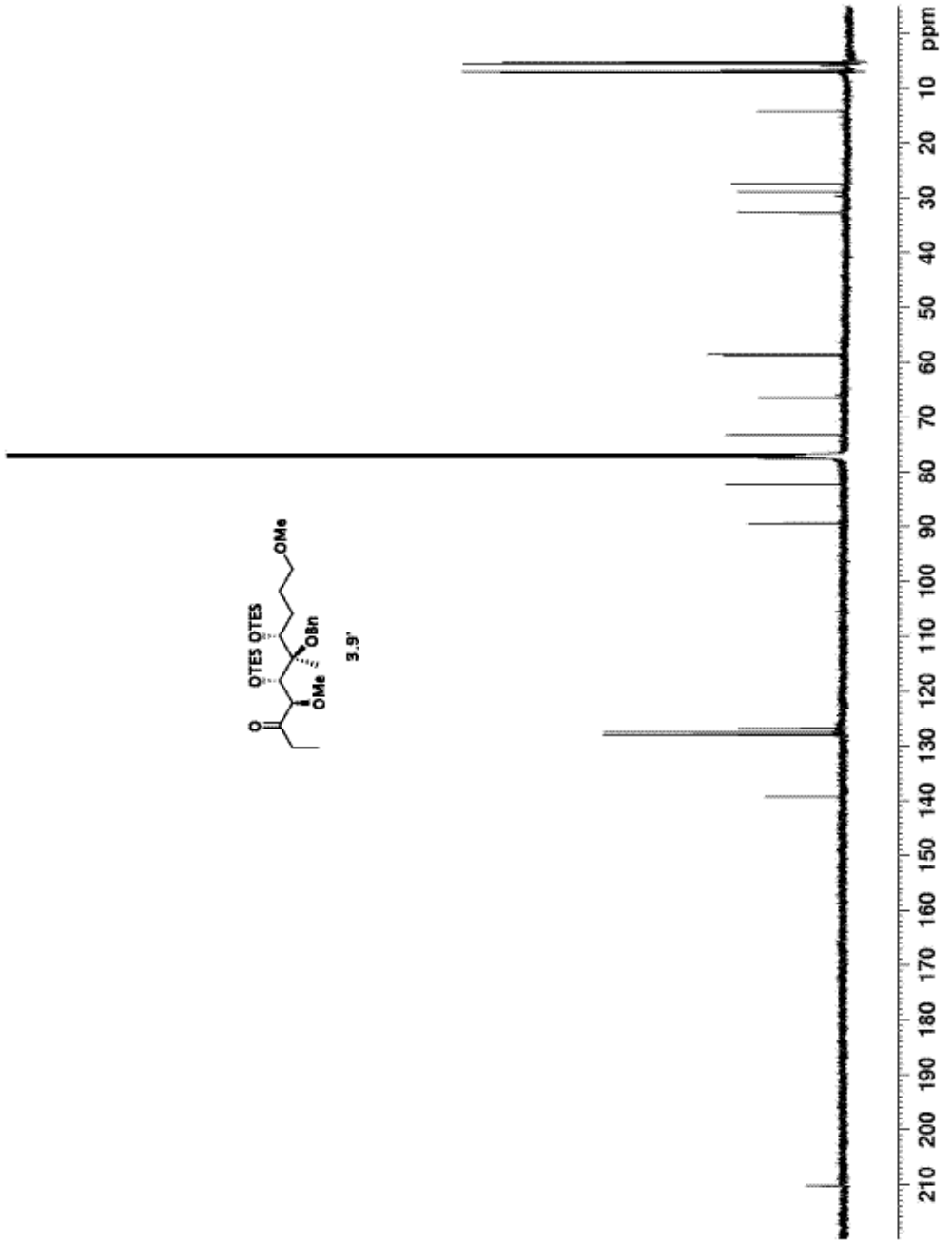

Figure 25b The 125 MHz ^{13}C NMR spectrum of **3.9'** in $CDCl_3$.

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