STUDIES OF NUCLEOPHILE RING OPENING OF OXABICYCLIC SYSTEMS IN HIGHLY POLAR MEDIA: APPLICATION TO A TOTAL SYNTHESIS OF ANTITUMOR AGENT, (-)-EPOTHILONE B

by

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of a dissertation submitted by

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To my family, whose love and support
goes beyond what I can describe with words

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

LIST OF SCHEMES-CONTINUED

LIST OF SCHEMES-CONTINUED

LIST OF SCHEMES-CONTINUED

LIST OF ABBREVIATIONS

Ac……acetyl

acac…….acetylacetonyl

AIBN……..2,2'-azobisisobutyronitrile

9-BBN……9-borabicyclo[3.3.1]nonane

Bn……benzyl

BOC……tert-butoxycarbonyl

Bz……benzoyl

Cp……cyclopentadienyl

CSA…….10-camphorsulfonic acid

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

DCC…….1,3-dicyclohexylcarbodiimide

DDQ…….2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DEAD……...diethylazodicarboxylate

DHP……..3,4-dihydro-2H-pyran

Dibal-H…….diisobutylaluminum hydride

DMAP……..4-dimethylaminopyridine

DME…….ethylene glycol dimethyl ether

DMF…….N,N-dimethylformamide

DMS…….dimethyl sulfide

DMSO……..dimethyl sulfoxide

LIST OF ABBREVIATIONS-CONTINUED

HMPA…….hexamethylphosphoramide

Imid…….imidazole

KHMDS……..potassium bis(trimethylsilyl)amide

LDA……lithium diisopropylamide

LHMDS……..lithium bis(trimethylsilyl)amide

LPDE……..Lithium Perchlorate-Diethyl ether

mCPBA……...3-chloroperoxybenzoic acid

MEM……...2-methoxyethoxymethyl

MOM……...methoxymethyl

Ms……methanesulfonyl

NaHMDS…….sodium bis(trimethylsilyl)amide

NBS……..N-bromosuccinimide

NCS……..N-chlorosuccinimide

NIS……N-iodosuccinimide

NMM…….4-methylmorpholine

NMO…….4-methylmorpholine N-oxide

PCC……...pyridinium chlorochromate

PDC……...pyridinium dichromate

Piv……..pivaloyl

PMB……..4-methoxybenzyl

LIST OF ABBREVIATIONS-CONTINUED

PPTS……..pyridinium 4-toluenesulfonate

Ra-Ni……..Raney nickel

Red-Al……sodium bis(2-methoxyethoxy)aluminum hydride

TBAF……..tetra-n-butylammonium fluoride

TBDPS……tert-butyldiphenylsilyl

TBS…….tert-butyldimethylsilyl

TES…….triethylsilyl

Tf……trifluoromethanesulfonyl

TFA……trifluoroacetic acid

THF……tetrahydrofuran

THP……tetrahydropyranyl

TIPS……triisopropylsilyl

TMS……trimethylsilyl

TPAP……...tetra-n-propylammonium perruthenate

Trityl……triphenylmethyl

Ts……4-toluenesulfonyl

ABSTRACT

Polyketides constitute an important family of natural products, having a broad spectrum of biological activity such as antitumor, antibiotic, antifungal, or immunomodulatory action.[1] Many of these compounds possess polypropionates (units with alternating hydroxyl and methyl groups), reflecting their common biosynthesis that is found within nature. Their structural complexity and importance of these compounds as therapeutical agents have made them attractive targets for synthetic organic chemists.[1] Excellent chiral propionate reagents have been developed over the years, including many chiral auxiliaries to direct and promote stereoselectivity, but most recent, investigations have focused upon developing metal-catalyzed asymmetric ring opening. To achieve these results, transition metals (Ni, Pd, Pt) have been employed leading to synthetically useful transformations.

This dissertation describes an alternative methodology to the use of transition metal. Ring opening reaction *via* polar media methodology developed in the Grieco group was extended to the synthesis of polypropionates and the completion of the naturally occurring epothilones. The use of 5.0 M lithium perchlorate in ether as a reaction solvent was required to obtain direct bridgehead opening of oxabicyclic[3.2.1] compound. Many nucleophiles (silyl enol ether and silyl ketene acetal) were tested for ring opening, but minimal diastereoselectivity was achieved. The reaction was improved by changing the O-silyl group of the oxabicyclic[3.2.1]-silyl enol ether (from O-TBS to O-TBDPS). Addition of trimethylsilyl chloride (TMSCl) enhanced reaction when hindered nucleophile was employed. Chiral nucleophiles (silyl enol ether and silyl ketene acetal) were also attempted, but ring opening did not transpire. This thesis explains the conceptual development of direct ring-opening of [3.2.1]-oxabicyclic octene, explorating the scope, and proving the principle by the completion of the epothilones synthesis.

INTRODUCTION

Ring Opening of Oxabicyclic Systems in Highly Polar Media

Background

Synthetic organic chemists have paid considerable attention in recent years to the problem of achieving stereocontrol with respect to the construction of propionate-derived structural segments (units with alternating hydroxyl and methyl groups). The high level of activity in this area is in part due to the large number of important biologically active natural products which contain such segments, including (-)-epothilones and other macrolide antibiotics.[1] Polyketide-type natural products are attractive targets for total synthesis. Aside from the purely synthetic aspects, many of these polyketide natural products exhibit important biological activities, such as antifungal, antitumor, and antibacterial.[1] In recent years, tremendous progress has been reported in the development of powerful methods for carbon-carbon bond formation for the construction of polyoxygenated acyclic chain as well as cyclic tetrahydropyran building blocks. For example, the use of asymmetric aldol (*via* chiral auxiliary) to control absolute stereoinduction has found wide application in a variety of natural products over the last two decades.[2] Nontraditional approaches involving nitrile oxide dipolar additions[3] and epoxide rearrangements have also been reported.[4] Aside from these transformations, cycloaddition reactions, although widely studied for over three decades,[5] remain a focus of intense investigation in organic chemistry. Improvements in the Diels-Alder reaction of furans[6] and the interest in ring opening reactions of oxabicyclo[2.2.1] or [3.2.1] compounds have made oxabicyclic substrates attractive starting materials in organic

synthesis. Rigid polycyclic templates (structure **1**, Fig. 1.1) can be used to influence the stereoselectivity of functional group introduction or interconversion, followed by cleavage reactions such as oxidative cleavage of vicinal diols,[7] acid-induced skeletal rearrangements,[8] reductive elimination,[9] olefin cleavage,[10] Grob fragmentation,[11] hydrogen addition,[12] or transition metal-catalyzed alkylative ring- opening[13] given rise to

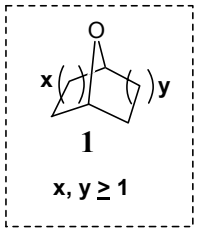


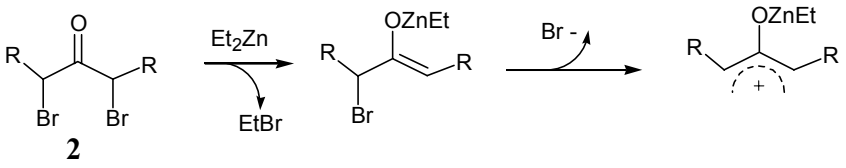
Figure 1.1: [2.2.1] and [3.2.1]-Oxabicyclic scaffold

simpler rings or acyclic chains. This approach has been a common strategy in the syntheses of many natural products. The analogous exploration in the context of oxabicyclic templates **1** has also increased as the new methods for their synthesis and ring opening of oxabicyclo[2.2.1] and [3.2.1] compounds has grown since the late seventies.

This dissertation is to give an overview of the general approaches that have been employed for the synthesis of oxabicyclic[2.2.1] compounds. In addition, a brief outline focussing on the preparation of a few of the oxabicyclic[3.2.1]heptene frameworks, and the most commonly used methods utilized to cleave one or more bonds within the oxabicyclic[3.2.1 and [2.2.1] frameworks. This report covers the work by many research groups and the work accomplished in the Grieco group in recent years.

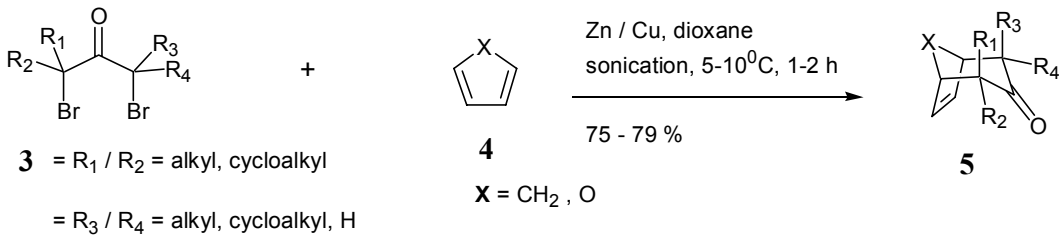
Cycloaddition of Furan Derivatives

Methods for the construction of oxabicyclic substrates of fundamental structure **1**, Figure 1.1, employing furan and substituted furans, have been the most widely investigated. Various research groups have used the furan nucleus with oxyallyl cations to produce compounds with the oxabicyclo[3.2.1]octene skeleton. Reviews on this reaction have been reported in the literature up to 1987.[14] The mechanism of the cycloaddition has been explained in detail by Hoffmann.[14d,e] A more recent development in the generation of oxyallyl cations from polybromoketones **2** has been the use of diethylzinc.[15] This procedure is convenient and amenable for the large-scale syntheses of



Scheme 1.1

oxabicyclic[3.2.1] compounds. In addition, the combination of cerium (III) chloride and tin (II) chloride has been very effective in inducing the [4+3] cycloaddition between furan and 2,4-dibromopentan-3-one **2**.[16] Sonication (**3** with **4**) has also been observed to improve yields in cycloadditions promoted by zinc-copper couple.[17]



Scheme 1.2

The cycoadditions of several oxyallyl cations are briefly outlined in Table 1.1.

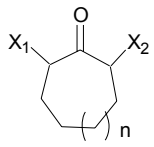
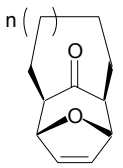
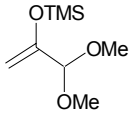
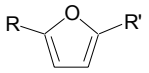
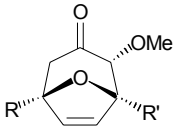
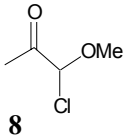
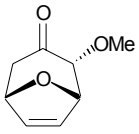
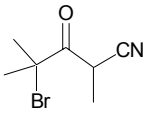
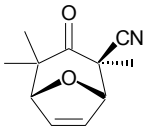
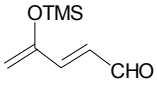
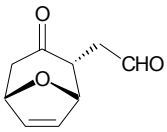
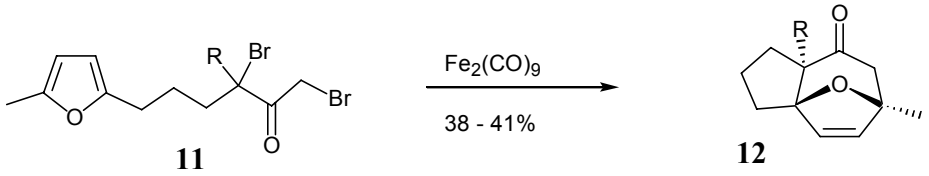
Entry	Oxyallyl Cation Precursor	Furan Derivative	Reaction Conditions	Oxabicyclic Product (Yield)
1	 **6a** X_1 = H, X_2 = Cl **6b** X_2 = X_2 = Br		A = 6a, Et_3N 3M $LiClO_4$ in ether B = 6b, $Fe_2(CO)_9$, reflux C = 6b, Zn-Cu	 n = 2, A (64%) n = 3, A (81%), B (35%) n = 4, A (11%), B (54%) n = 5, B (37%) n = 9, A (56%), B (52%)
2	 **7**	 R = R' = H R = H, R' = Me R = R' = Me	TMSOTf, $EtNO_2$, -78^0 C	 R = R' = H (67%) R = H, R' = Me (54%) R = R' = Me (78%)
3	 **8**		3M $LiClO_4$ in ether, Et_3N	 (44%)
4	 **9**		1. Ag_2O 2. Zn-Cu, MeOH	 (75%)
5	 **10**		$SnCl_4$, CH_2Cl_2, -78^{0}C	 (36%)

Table 1.1: [4+3] Cycloadducts.

Tricyclic oxa-bridged substrates can be readily assembled from cyclic oxyallyl cations derived from monohalogenated cyclic ketones **6a** and $LiClO_4$ / Et_3N (entry 1).[18] Dihalogenated cyclic ketones **6b** can also serve as cyclic oxyallyl cation precursors when treated with diiron nonacarbonyl,[19] or zinc-copper couple.[20] Cycloadditions of this type have been successful in producing oxatricyclic compounds where n = 2,3,4,5,9, however some adducts are mixtures of cis and trans isomers. Oxyallyl cations bearing oxygen substiuents have been synthesized from **7** and catalytic TMSOTf (entry 2).[21] Likewise, 2-chloroketone **8** was used in the presence of $LiClO_4$ / Et_3N (entry 3) to achieved a similar outcome, although the overall yield was low (44%).[22] Oxyallyl cations from 2-bromoketone **9** undergo cycloaddition with furan to give nitrile-substituted oxabicyclic[3.2.1] compounds (entry 4).[23] This methodology has been extended to conjugated oxyallyl cations derived from aldehyde **10** (entry 5).[24]

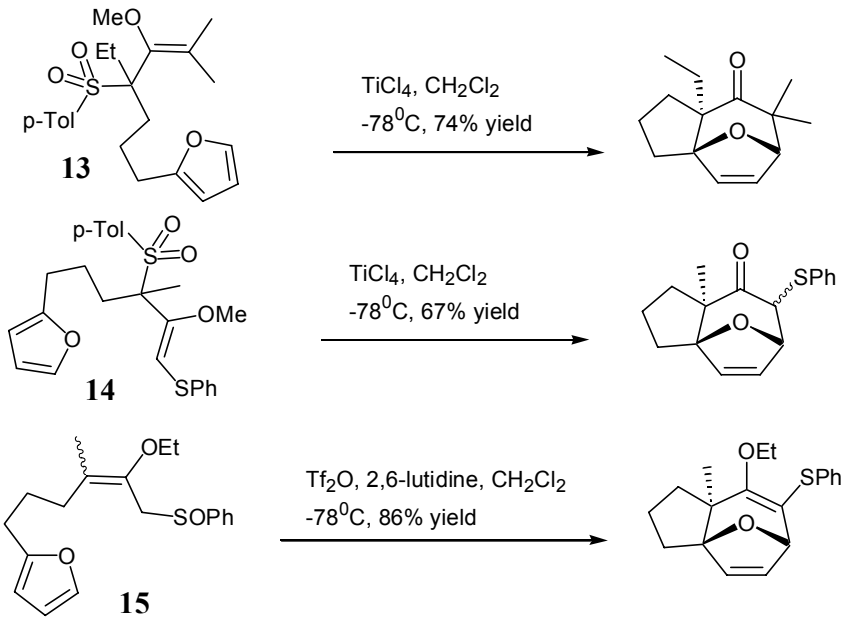
Further studies have been carried out on the of construction of oxabicyclo[3.2.1] framework utilizing furan by several research groups in recent years, although the yields were only modest. For example, furans tethered to α, α'-dibromoketones **11** undergo intramolecular [4+3] cycloadditions with diiron nonacarbonyl and with lithium perchlorate / triethylamine to give adduct **12**. The modest yields of adducts that were



Scheme 1.3

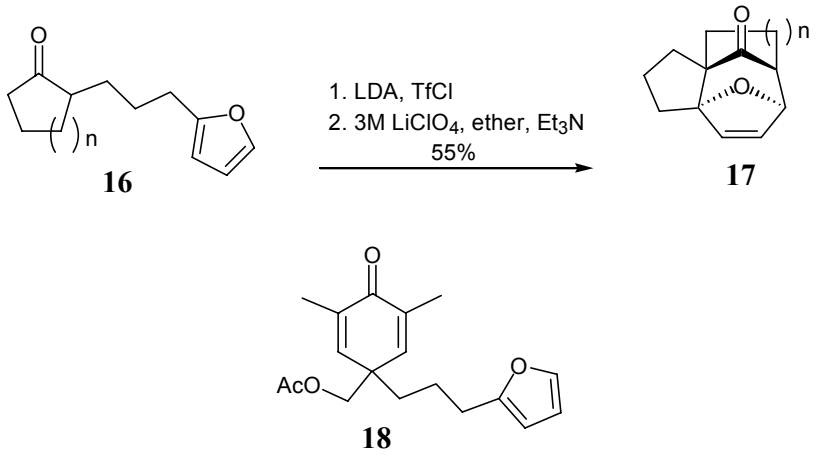
obtained motivated additional studies.[25a,b] Harmata has extensively examined intramolecular [4+3] cycloadditions using various oxyallyl cation precursors and also investigated the mechanism of the reaction.[26]

Under Lewis acid ($TiCl_4$ / CH_2Cl_2) conditions, alkoxy allylic sufone **13** generates an allylic cation for cycloaddition, scheme 1.4. Under the same reaction conditions, vinyl thioether **14** was found to generate an alkoxyvinyl thionium intermediate that undergoes cycloaddition with the tethered furan. Most recently, Harmata has shown that appropriately substituted allylic alcohols bearing a tethered furan generate vinylthionium ions in the presence of triflic anhydride which react to give [4+3] cycloadducts.[27] Harmata also found that the alkoxyallylic sulfoxide **15** undergoes a Pummerer rearrangement to yield the thionium intermediate, which undergoes an intramolecular cycloaddition in high yield (86%), Scheme 1.4.



Scheme 1.4

The construction of tetracyclic substrate **17** has been achieved by the intramolecular cycloaddition of a furan tethered to a cycloalkanone of **16** using conditions related to those developed by Föhlisch (Scheme 1.5).[23] As the ring size (greater than 5) of the oxyallyl cation increased, products arising from cycloaddition *via* the less strained *exo*-transition state predominated. Cycloadducts with six or eight member oxyallyl cation intermediates have also been successfully prepared, however a mixture of stereo isomers was observed.[28b] Cyclohexadienone **18** can be photogenerated for intramolecular cycloadditions when tethered to a furan.[29] However, the dienone precursors required substituents which provide the right electronic characteristics for the

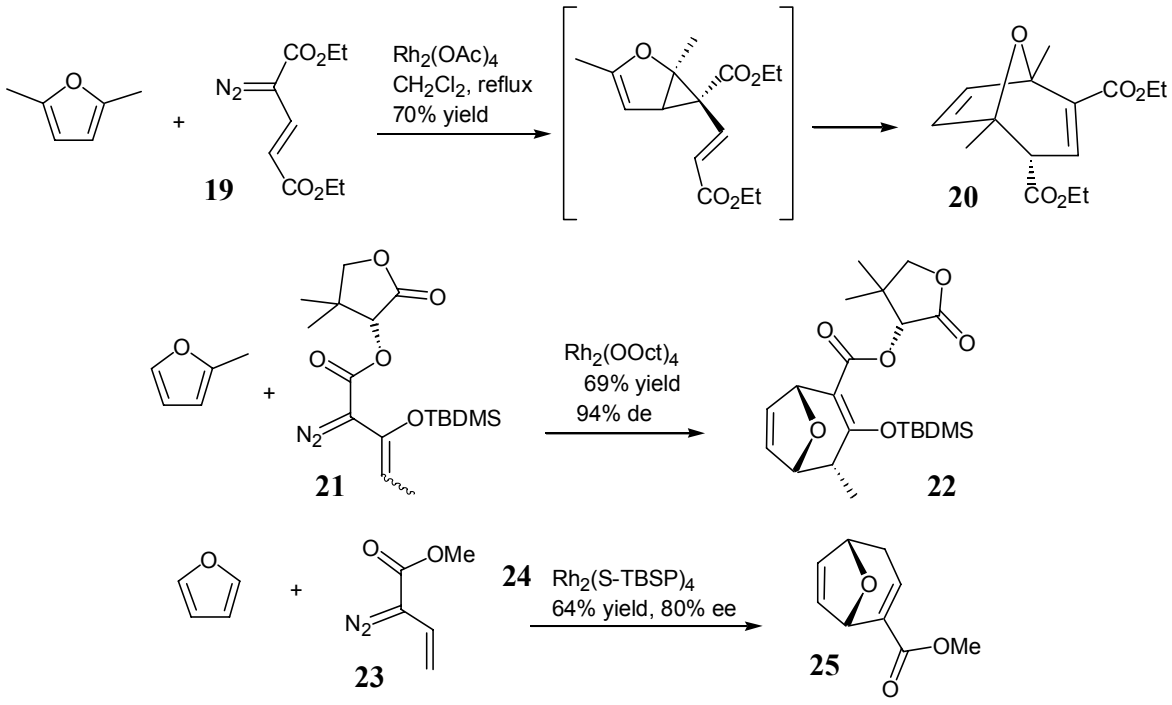


Scheme 1.5

photoconversion to the oxyallyl cations, thus limiting the versatility of this reaction.

In a recent study by Davies, rhodium carbenoids can also be used to react with furan derivatives to generate oxabicyclo[3.2.1] octadienes through the formation and rearrangement of divinyl cyclopropane intermediates.[30] Thus, treatment of 2,5-dimethylfuran with ester **19** leads to the adduct **20** (Scheme 1.6). Davies also reported a highly diastereoselective version of this reaction by incorporating chiral auxiliaries within

the carbenoid precursors.[30c] Consequently, the rhodium-catalyzed reaction of 2-methylfuran with vinyldiazomethane **21** provided cycloadduct **22** with 94% *de*. The products can be obtained in greater than 99% *de* after purification by column chromatography. In addition, an enantioselective cycloaddition was observed when the carbenoid was formed by the use of a chiral rhodium complex **24**. For example, decomposition of **23** by rhodium complex **24** in the presence of furan generated **25** with 80% *ee*, along with a triene containing side-product in 15-20% yield (Scheme 1.6). However the % *ee* dropped significantly when other vinyldiazo compounds were studied under the same conditions.[30c] With the steadily increasing number of syntheses of

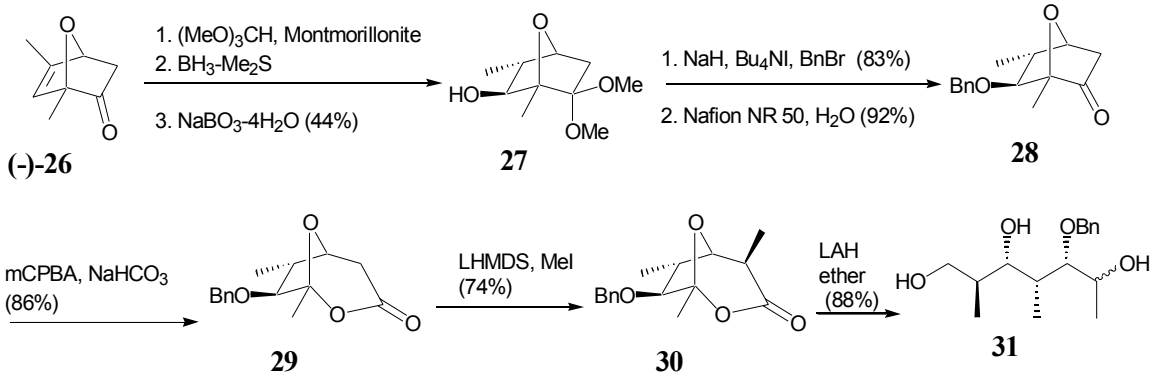


Scheme 1.6

polyketide biological products relies on readily available chiral building blocks, substrate **22** can be used for further elaboration.

Ring-Opening Chemistry of Oxabicyclic Compounds

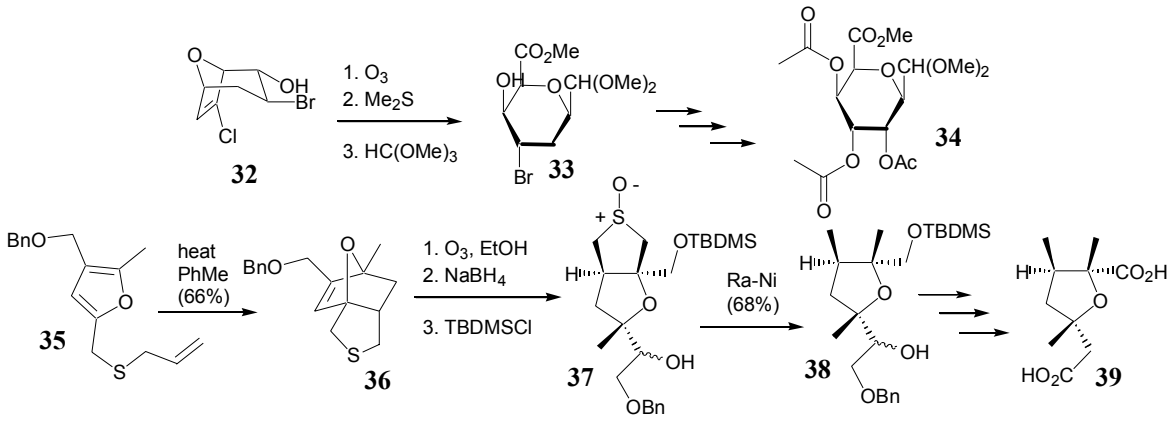
Over the past decade, ring-opening of oxabicyclic compounds has undergone significant growth as a result of the development of new methods to construct the oxabicyclo[3.2.1] structure.[6,14] Oxabicyclic substrates have been frequently used as precursors to highly substituted cyclic ethers, particularly tetrahydrofurans and tetrahydropyrans. This strategy relies on the selective cleavage of carbon-carbon bonds within the oxabicyclic framework. An examination of the literature reveals many methods used to cleave one or more bonds within the oxabicyclo[2.2.1] or [3.2.1] nucleus. For example, the Baeyer-Villiger ring cleavage of both [2.2.1] and [3.2.1] oxabicyclic compounds has been used as a key step in the synthesis of many natural products, including nonactic acid,[31] lilac alcohol,[32] the C_{21} to C_{27} subunit of rifamycin,[33] and many nucleosides.[34] More recently, Vogel has described the synthesis of many natural and unnatural sugars, as well as their derivatives, including D- and L-allose, D- and L-talose,[35] L-daunosamine,[36] and a variety of disaccharides.[37] As an illustration, Vogel used (-)-**26** (Scheme 1.7), prepared from 2,4-dimethylfuran, to show that a sequence involving stereoselective functionalization, fragmentation *via* Baeyer-Villiger



Scheme 1.7

oxidation and exhaustive reduction ($LiAlH_4$) constitutes a quick assembly of optically pure polypropionate arrays **31** with four contiguous stereocenters, scheme 1.7.[38]

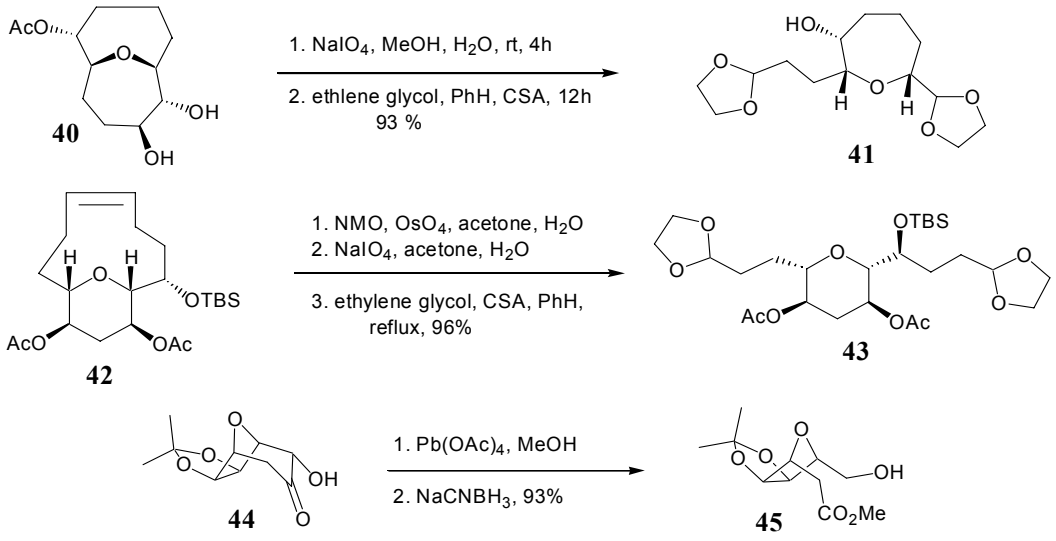
Ring opening which is complementary to that using the Baeyer-Villiger oxidation-hydrolysis sequence has also been documented. For example, carbon-carbon double bonds in oxabicyclic systems can be cleaved by ozonolysis.[10] Furthermore, tri-substituted olefins generate cyclic ethers bearing side chains with differentiated ends upon ozonolytic cleavage, thus allowing subsequent selective elaboration of each functional group. A recent approach to this concept was presented by Vogel in the recent synthesis of β-C-hexopyranosides **34**.[39] The [3.2.1]oxabicyclic vinyl chloride **32** was subjected to ozonolysis to produce a dialkylated tetrahydropyran **33** with differentially oxidized substituents at C_2 and C_6, scheme 1.8. This sequence of reactions was utilized in the synthesis of compound **34**. Another example is the use of bicyclic ether **36**, obtained from the intramolecular cycloaddition of **35**, which subjected to ozonolysis with a reductive work-up. Silyl protection provided alcohol **37** and reduction transformed the thioether linkage into the vicinal *cis* dimethyl groups found in nemorensic acid **39**.[40]



Scheme 1.8

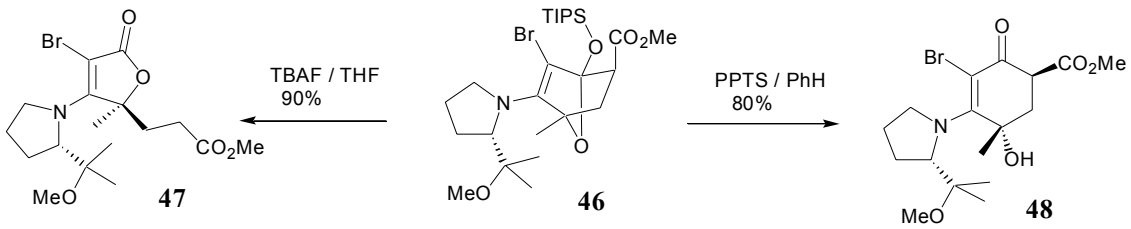
Many synthetic studies that have employed ozonolysis as a means for cleaving oxabicyclic substrates include Masamune's synthesis of avenaciolide,[41] Meinwald's studies toward pederin,[42] a recent synthesis of (+)-lauthisan by Cha,[43] and Ohno's syntheses of (+)-showdowmycin, (-)-cordycepin C, and (-)-6-azapseudouridine.[44]

Unsaturated oxabicyclic substrates can also be cleaved through their vicinal diol derivatives, as illustrated by the reaction of substrate **40** (Scheme 1.9).[45] Periodate cleavage of dihydroxy substrate **40** generated an unsymmetrical subunit useful for polyether construction. A similar reaction sequence was also a key step in the synthesis of **43**.[46] Furthermore, (α)-hydroxy ketone such as **44** offering yet another option for cabon-carbon bond cleavage. For example, Noyori's synthesis of showdomycin[47] demonstrated that α-hydroxy ketone **44**, available in greater than 98% *ee* from the parent



Scheme 1.9

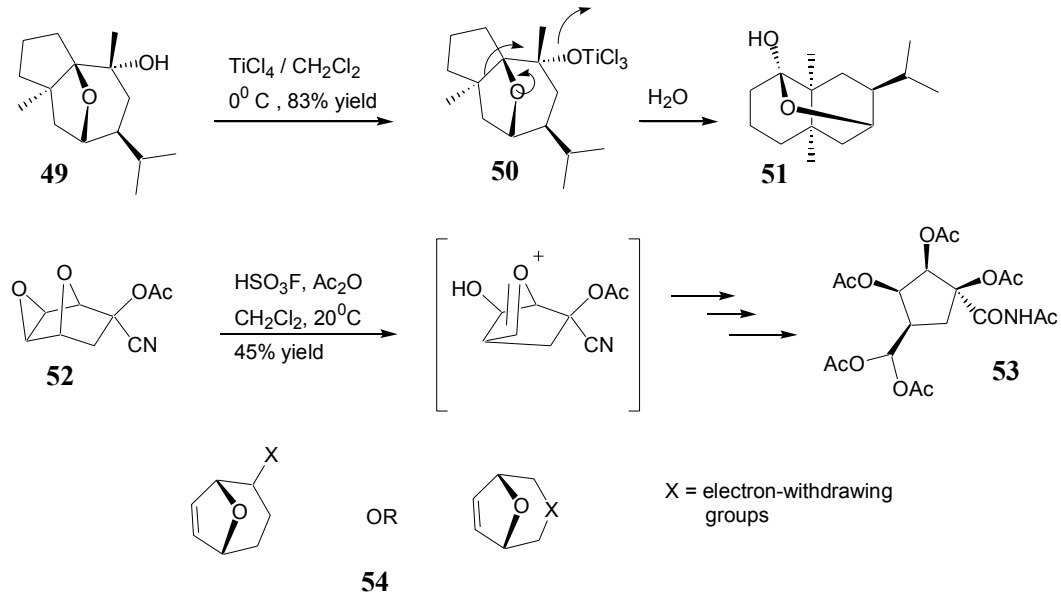
ketone, was cleaved by lead tetraacetate to provide an excellent yield of the hydroxyester **45**, Scheme 1.9. In addition to these carbon-carbon bond transformations (Baeyer-Villiger oxidation-hydrolysis, ozonolysis, and periodate cleavage of vicinal diol derivatives), a variety of strategies have been employed for ring-opening reactions of [2.2.1]- and [3.2.1]oxabicyclic compounds. Strategies like the retro-Dieckmann reaction,[48] whereas compounds bearing a β-hydroxycarbonyl motif (similar to **46**) undergo a retro-aldol ring cleavage. In the context of retro-Dieckmann / retro-aldol reaction, Schlessinger showed that a related complex such as **46** can be desilylated (*via* fluoride anion) to promote a retro-aldol reaction (Scheme 1.10) providing lactone **47**. It is interesting to note that treatment of the same substrate with PPTS (pyridinium 4-toluenesulfonate) led to oxygen bridge cleavage to give hydroxycyclohexenone **48**.[49]



Scheme 1.10

The oxygen bridge in oxabicyclo[2.2.1] and [3.2.1] compounds is an electron pair donor and a potential alkoxy leaving group. The cleavage of the ether bond in an oxabicyclic compound can be readily accomplished by various acidic or basic conditions. Such a reaction was exploited by Sammes for the synthesis of racemic cryptofauronol, in which treatment of **49** with Lewis acid induces rearrangement to a decalin ring system.[50] A similar rearrangement was observed by Vogel upon treatment of epoxidized oxanor-

bornane derivative **52** with acid (HSO_3F), Scheme 1.11.[51] In principle (structure **54**), numerous synthetic transformations such as acid-induced skeletal rearrangements,[50,51,54] base-induced ring openings,[52a,b] or β-elimination reaction[53a,b] have been applied (centered around the oxygen bridge) to the construction of polyoxygenated acyclic chain as well as cyclic (tetrahydropyran) substrates.

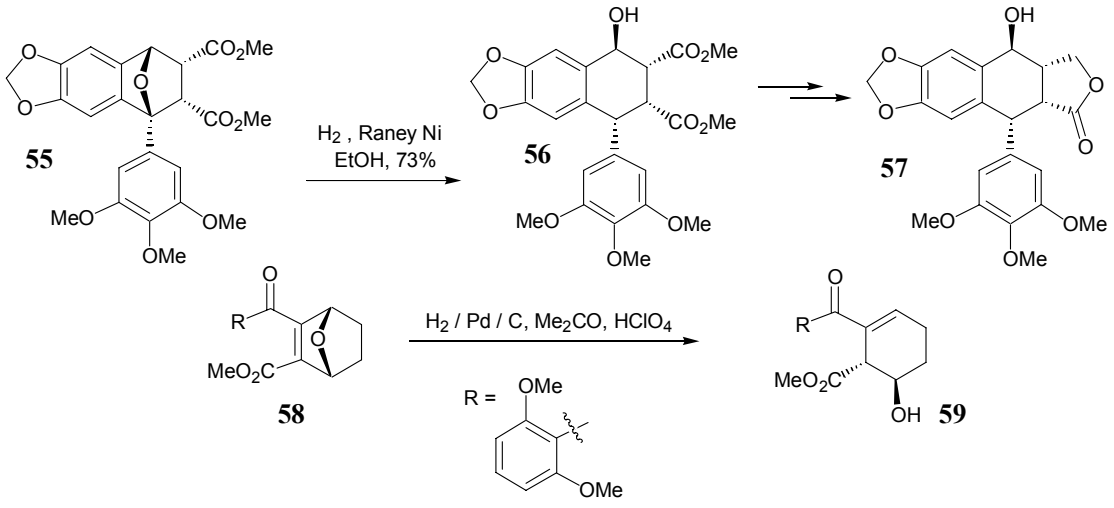


Scheme 1.11

Over the last decade, considerable effort has been made to find suitable nucleophile for ring-opening reaction, using the bridgehead oxygen as a leaving group, for installation of new functionalities. Numerous research groups have reported that oxabicyclo[2.2.1] and [3.2.1] compounds whose bridging oxygen atoms are in allylic or benzylic positions can be ring opened *via* various nucleophiles under different conditions. For example, in the special case of the oxabicyclic compounds with bridgehead carbons bearing aryl substituents, hydrogenolysis results in the cleavage of the bridging carbon-oxygen bonds.[55a] In the synthesis of isopicropodophyllin, the highly-substituted cyclo-

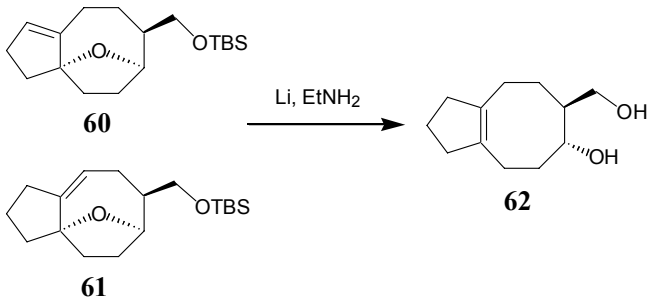
hexane ring in **56** was revealed by the hydrogenolysis of the oxabicyclo[2.2.1] framework of **55**, scheme 1.12.[55a]

A similar hydrogenolysis strategy was utilized for the synthesis of (-)-isopodophylotoxin.[55b] Furthermore, Whalley reported one case of a hydrogenation reaction that resulted in the *S_N2'* opening.[56] In the presence of acid ($HClO_4$), compound **58** was reductively ring opened to give **59** in quantitative yield, scheme 1.12.



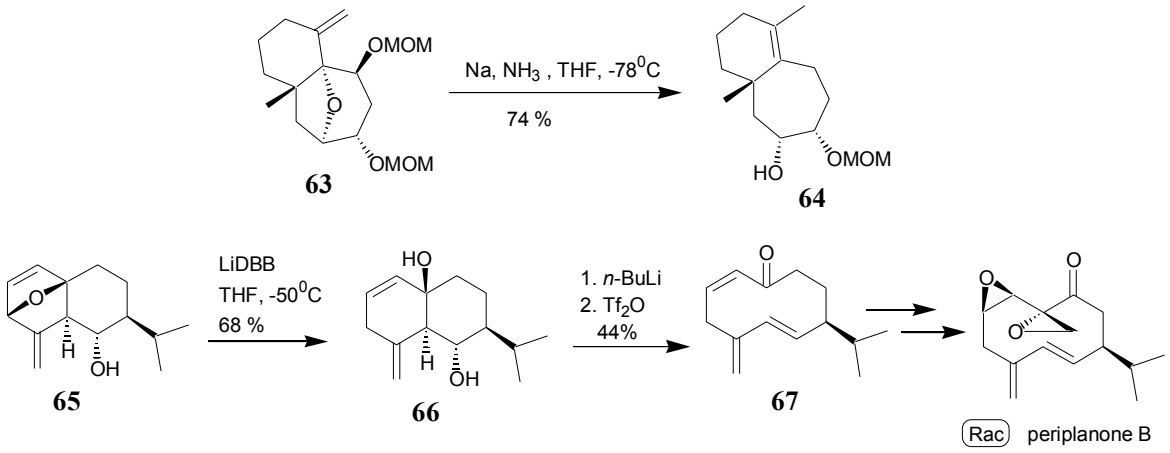
Scheme 1.12

Substrates whose bridging oxygen atoms are in allylic position such as compound **60** or **61** can be ring opened under dissolving metal conditions. Scheme 1.13 illustrates this methodology.[57] Another example of this type of reaction is the reaction of sodium



Scheme 1.13

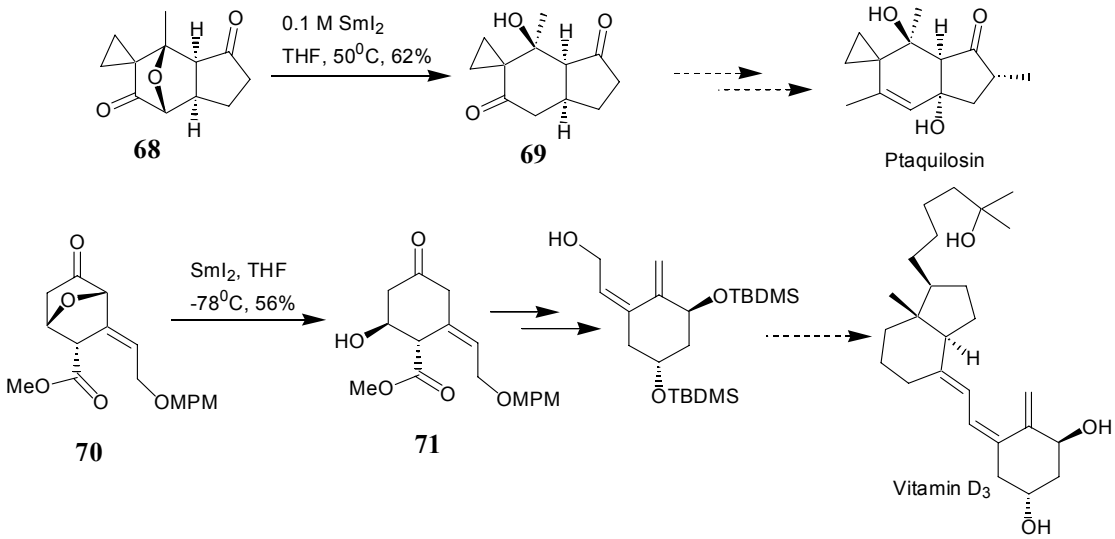
with the oxabicylic substrate **63** resulted in elimination of methoxymethoxide and reduction of the diene.[58] Only one olefinic product **64** was isolated (Scheme 1.14). This type of reductive ring opening can also be induced by single electron donor reagents such as LiDBB (lithium di-*tert*-butylbiphenylide). In De Clercq's formal total synthesis of periplanone B, intermediate **65** was reductively ring opened by treatment with LiDBB.[59] Subsequent Grob fragmentation of alcohol **66** led to decadienone **67** which was transformed into periplanone B (Scheme 1.14).



Scheme 1.14

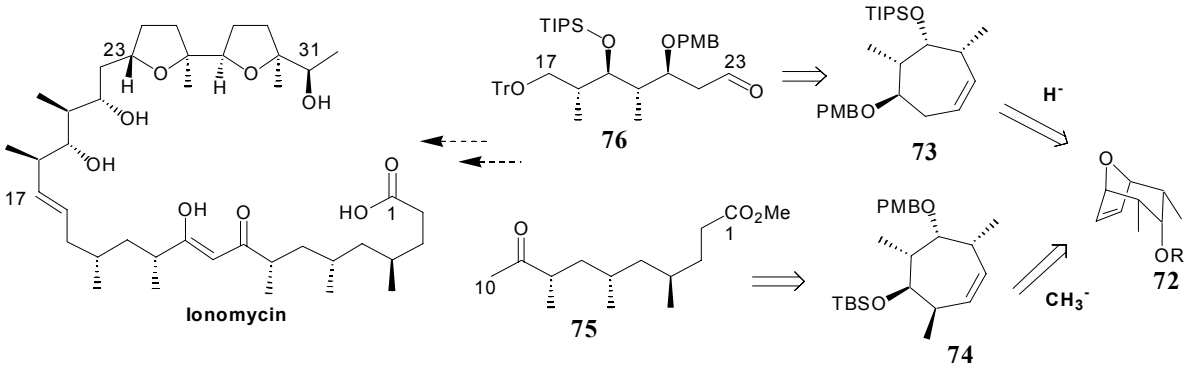
Samarium iodide is another useful metal that can be used to promote ring opening. This reductive ring opening was used by Padwa in synthetic studies toward ptaquilosin.[60] Treatment of **68** with SmI_2 generated **69** which contains the basic skeleton of the target molecule, scheme 15. It is noteworthy that the cyclopropyl substituent remained intact under the reaction conditions. Another example of this type of transformation was demonstrated by De Clercq's synthesis of a precursor to the A-ring of α-hydroxyvitamin D_3, scheme 1.15.[61] The samarium iodide promoted reduction of

substrate **70** led to ring opening to yield hydroxycyclohexenone **71**, which was subsequently transformed into Vitamin D_3.[61]



Scheme 1.15

Over the past decade, aside from many methods cited in this text (Schemes 1.7-1.15), Lautens and co-workers have demonstrated that metal-catalyzed asymmetric ring-opening reactions of *meso* oxabicyclic[3.2.1] alkenes can be carried out in high yield and typically higher than 90% *ee* with a variety of nucleophiles such as hydride, alcohols, alkylzincs, and malonates.[62] An example of this was the synthesis of the polyether antibiotic Ionomycin (Scheme 1.16).[63]



Scheme 1.16

The execution of the Ionomycin synthesis is shown in scheme 1.16. Lautens and Chiu demonstrated that DiBAL-H (diisobutylaluminum hydride) was the reagent of choice for the efficient reductive ring opening of an oxabicyclo[3.2.1] **72**. *S_N2'* delivery of hydride and methyl anion generate homoallylic protected alcohols such as **73** and **74** in good yield.[63] Subsequent manipulations of both compounds (**73** and **74**) including ring cleavage by ozonolysis afforded the terminally differentiated acyclic products such as ketone **75** and aldehyde **76**, which are the C_1 to C_{10} and the C_{17} to C_{23} subunits of ionomycin (scheme 1.16).

Over the years, Lautens and co-workers have shown that asymmetric ring-opening reactions of *meso* oxabicyclic alkenes (compounds similar to **72**) in the presence of transition metals, namely nickel, palladium, and rhodium[62] occur in high yield with high percent *ee*, and a very dependable way for *S_N2'* delivery of nucleophiles such as hydride, alcohols, alkylzincs, and malonates.[62] While this approach (asymmetric ring-opening reactions) provided rapid entry to functionalized cyclic skeletons, which are important for natural product synthesis, the predominant mode of action under these conditions have been shown to be *S_N2'* syn (Fig. 1.2).[62,63] There has been no example

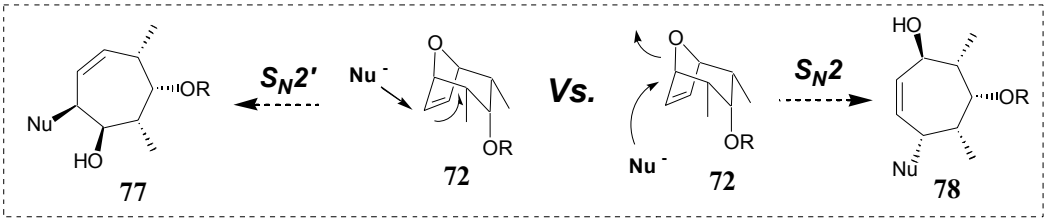


Figure 1.2: S_N2' *vs*. S_N2 reaction.

in the literature of nucleophilic S_N2 ring opening at the bridging oxygen (Fig. 1.2).[64]

Several years ago, the Grieco group set out to investigate the addition of nucleophiles to the bridghead of 8-oxa-bicyclo[3.2.1]octenes utilizing highly polar media, $LiClO_4$-Et_2O (LPDE), (Figure 1.3). The Grieco laboratories have been using lithium perchlorate diethyl etherate (LPDE)[65] as a highly polar media to influence many organic

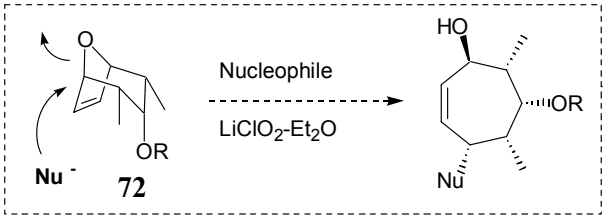
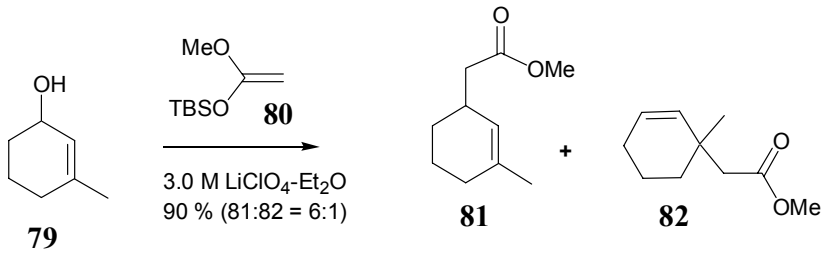


Figure 1.3: Bridgehead opening of 8-oxa-bicyclo[3.2.1]octenes.

tranformations. An example is the addition of nucleophiles such as silyl ketene acetal **80** to the cyclohexenols **79** in 3.0 M $LiClO_4$-Et_2O giving a mixture of products **81** and **82** (Scheme 1.17).[66] One possible explanation of this surprising result is the ability of the



Scheme 1.17

solvent (3.0 M $LiClO_4$-Et_2O) to stabilize the partial positive charge at the allylic position bearing the alcohol, thus giving rise to product **81** (Scheme 1.17). This result raises the question to whether oxabicyclic[3.2.1] system, which the oxabridge is at the allylic position (Figure 1.4), could undergo a ring opening event in the presence of lithium perchlorate diethyl etherate (LPDE). However, as depicted in scheme 1.18, attempts to

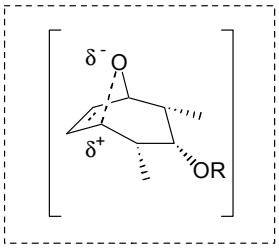
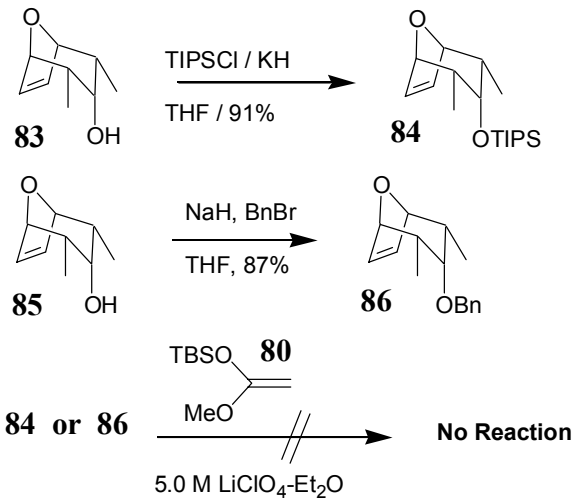


Figure 1.4: Allylic cation of oxabicyclic[3.2.1] system.

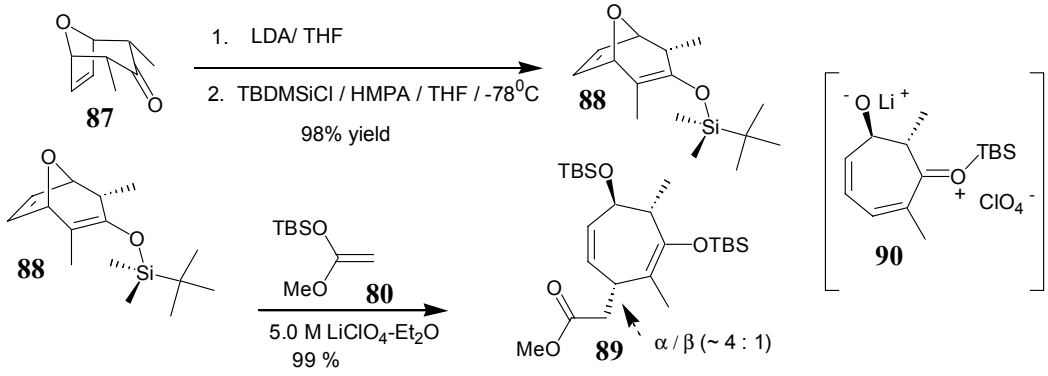
introduce substituents into the bridgehead position were met with many difficulties. For example, treatment of the protected alcohol **84** or **86** with nucleophile **80**, 1-methoxy-1-(*tert*-butyl- dimethylsiloxy)-ethylene, in 5.0 M LPDE gave no reaction.[67] Other nucleophiles (trimethylsilyl cyanide, trimethylsilyl azide, dimethyl-aluminum azide, and



Scheme 1.18

allyltrimethyl silane) were also examined but proved unsuccessful. The silyl group of the protected alcohol **84** was often removed when Lewis acid (BF_3-OEt_2, $TiCl_4$, or $MgBr_2$) was used.

Further studies were carried out and it was found that an additional π-system (double bond) was required to achieve ring-opening reaction (Scheme 1.19). When silyl enol ether **88** (a. LDA/THF with ketone **87**, b. HMPA/TBSCl) was subjected to 5.0 M LPDE in the presence of nucleophile **80**, ring opening at the bridging oxygen was achieved and gave rise to a mixture of cycloheptadienes **89** in high yield (Scheme 1.19).[67,68] It appeared that the success of the ring opening event, when a π-system (silyl

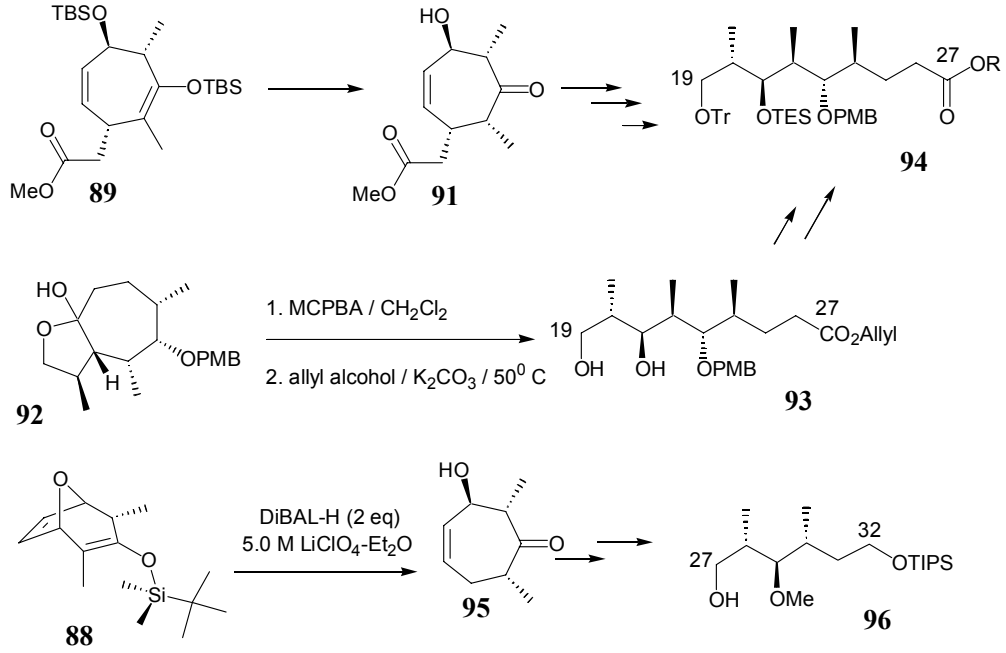


Scheme 1.19

enol ether **88**) was introduced, could be attributed to the flattening of the ring. Thus, allowing for better overlapping between the orbitals of the C-O bond and the extended π-system (double bond). Aside from the effective overlap with the σ^* orbital, the extra double bond in compound **88** introduced ring strain and provided some stabilization to the formation of the partial positively charged intermediate **90** (charge-separated intermediates that can be stabilized by highly polar solvent, 5.0 M LPDE).

Based on the success of LPDE mediated ring opening of silyl enol ether **88** (scheme 1.19) and the ability to desymmetrizing the oxabicyclic[3.2.1] core (**87**) to differentiate the two-enantiotopic bridgehead alkoxy leaving groups (enantioselective deprotonation with a chiral base),[69] two-advanced fragments of Scytophycin C (C_{19}-C_{26}

and C_{27}-C_{32}) were chosen and synthesized to showcase the established methodology.[67,68] The synthesis relied upon direct ring opening employing silyl ketene acetal **80** in 5.0 M LPDE (Scheme 1.20), followed by several delicate transformations that included an efficient synthesis of the keto-ester **91** *via* selective protonation of substrate **89** after ring opening with ketene acetal **80** (scheme 1.19), and Baeyer-Villiger oxidative ring expansion of the cyclic hemiketal **92** to complete the assembly of the carbon framework (C_{19}-C_{27}) of Scytophycin C.[67,68] Fragment **96** (C_{27}-C_{32}) was prepared in two steps (protection of the alchohol followed by ozonolysis of the olefin) from compound **95**, which was obtained through direct ring opening of silyl enol ether **88** using DiBAL-H (diisobutylaluminum hydride) as a nucleophile in 5.0 M LPDE (Scheme 1.20).[67,68]

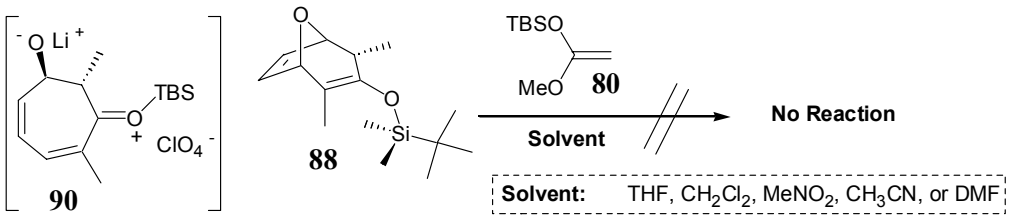


Scheme 1.20

Results and Discussion

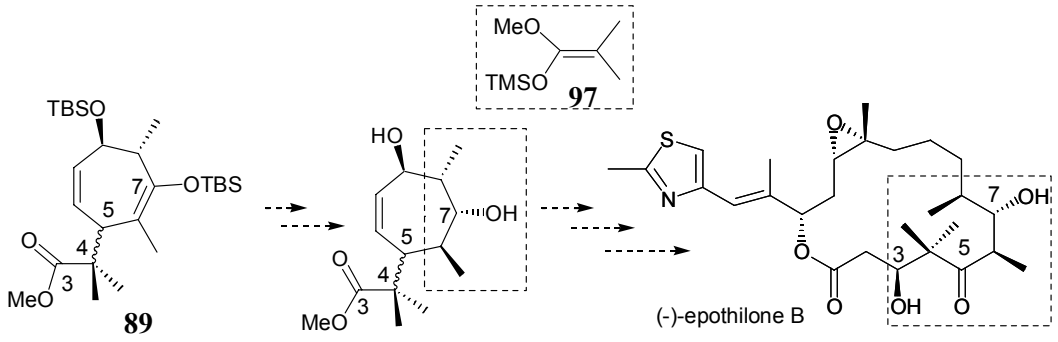
Scope and Studies of the Effect of Nucleophile

It became clear that ring opening of compound **88** can be realized using LPDE as a reaction solvent (Schemes 1.19, 1.20). In its absence (when a conventional solvent was used instead), reaction did not proceed (Scheme 1.21). It appeared that a highly polar solvent (LPDE) is required for the ring-opening event, which proceeds through polar



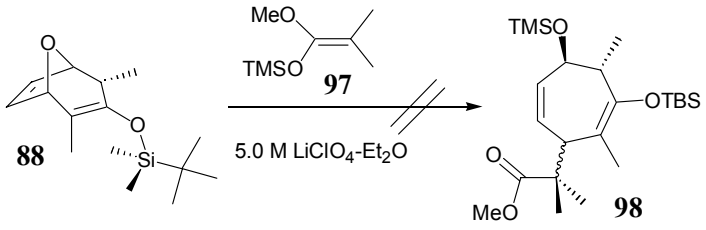
Scheme 1.21

transitions states[65] (involvement of charge-separated intermediates such as **90**, schemes 1.19 and 1.21). Given that ring opening can be obtained with unhindered silyl ketene acetal **80** (Scheme 1.19) in 5.0 M LPDE, and the success of this method to produce the two fragments (C_{19}-C_{26} and C_{27}-C_{32}) of Scytophycin C (Scheme 1.20), the decision was made to extend this methodological approach to other nucleophiles. Methyl trimethylsilyl dimethylketene acetal **97** (Scheme 1.22) was chosen to undergo testing because of the thought that the ring opening strategy (at the bridging oxygen) could potentially be employed to install the *gem*-dimethyl at the C_4 position of the natural product, (-)-epothilone B (Scheme 1.22).



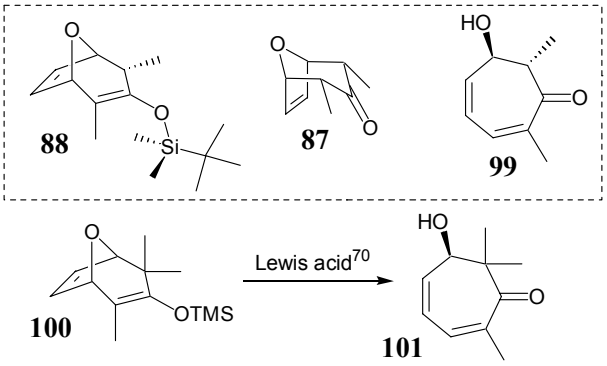
Scheme 1.22

With silyl enol ether **88** in hand, attempts were made to apply the ring opening methodology (using LPDE) toward the synthesis of cycloheptadienes **98**. However, these attempts were unsuccessful (Scheme 1.23). It was found that treating silyl enol ether **88** employing the previously developed conditions (Scheme 1.19) with TMS-dimethyl ketene acetal **97**, returned only starting material (Scheme 1.23). Prompted by the failure



Scheme 1.23

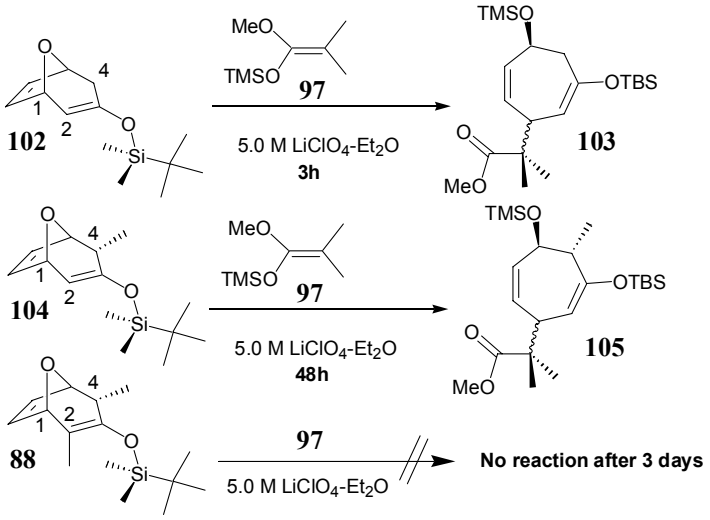
to achieve ring-opening reaction, Lewis acids such as BF_3-Et_2O, $TiCl_4$, $AlCl_3$, $ZrCl_4$, and TMSOTf were employed. Unfortunately, these efforts also proved to be ineffectual and many unwanted products were obtained. Starting material **88** was often recovered (low yield) with other unwanted products such as ketone **87** and the hydroxy enone **99** (Scheme 1.24). Isolation of **99** was not surprising because it has been shown that silyl-



Scheme 1.24

methyl enol ether **100** can be converted to the hydroxy ketone **101** in the presence of Lewis acids (Scheme 1.24).[70]

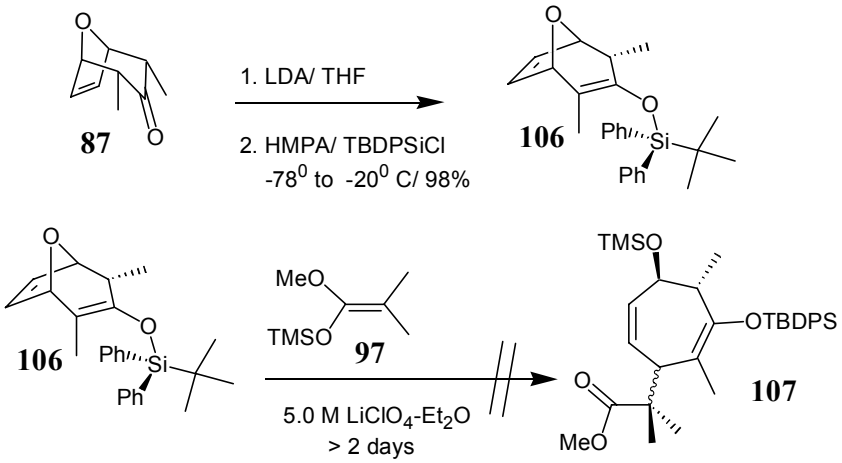
Based upon previous results[67] and control experiments, it appeared that steric effect played a major role in the ring-opening process. For example, silyl ketene acetal **97** reacted with substrate **102** (lack of the C_2 and C_4-methyl) to provide a mixture of cycloheptadienes **103** in 3 hours at room temperature (Scheme 1.25). Also, in this study, despite an extra methyl group at the C_4 position, enol ether **104** underwent ring opening



Scheme 1.25

in 48 hours under the same conditions. As mentioned earlier (Scheme 1.23), silyl enol ether **88** (methyl at C_2 and C_4) did not proceed to any appreciable degree, even after three days (Schemes 1.23 and 1.25).

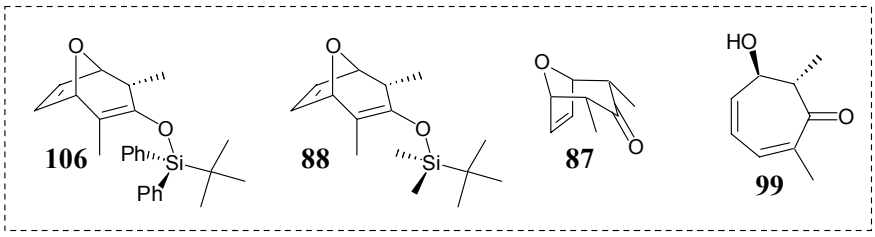
From this collection of information (Schemes 1.21, 1.23-1.25), the decision was to pursue a different approach, like changing the silyl-protecting group. This conceptual framework relied more upon robust silyl enol ether, *tert*-butyl-diphenylsilyl enol ether **106** (a. LDA/THF with ketone **87**, b. HMPA/ TBDPSiCl/ -78^{0}C/ 98%) was chosen for testing (Scheme 1.26). The thought that a more robust silyl enol ether **106** (with respect



Scheme 1.26

to compound **88**) might provide further stability. Thus, making it less prone to decomposition when forceful conditions are employed (longer reaction time and addition of Lewis acid). Also, an additional thought was that compound **106** might provide some added ring strain that could make ring opening event a more facile process. However, upon treatment of **106** with nucleophile **97** in 5.0 M LPDE, hardly any product was observed after several days (Scheme 1.26). In fact, reactions proceeded very sluggish at best. Despite repeated attempts, including the use of Lewis acids and changing the

reaction conditions to those similar to substrate **88** (Scheme 1.23), efforts proved unsuccesful. During the course of this study, all results were unsuccessful and revealed several methodological problems that may explain why the reaction had failed. For example, silyl ketene acetal **97** used for testing fell apart or polymerized when the reaction was prolonged in 5.0 M LPDE. This may be due to its instability in Lewis acid. Furthermore, in the absence of Lewis acid, the reaction failed to proceed. However, when Lewis acid was employed, too many side products were obtained (as mentioned earlier (Schemes 1.23, 1.24)). Nevertheless, this study showed that compound **106** was stable or even more so than the TBDM-silyl enol ether **88**. Ketone **87** or the hydroxy enone **99** (Scheme 1.27), the β-elimination product, was obtained when the reaction is prolonged in this study. This information indicated that perhaps a delicate balance between the stability and size of a nucleophile with a suitable Lewis acid had to be met. After screening most of the traditional Lewis acids,[70] and during the course of

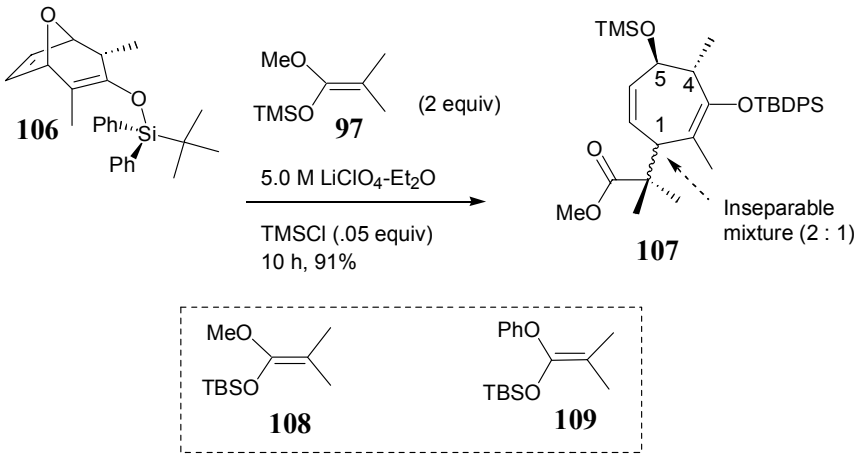


Scheme 1.27

synthesizing some of the potential nucleophiles (silyl enol ether and silyl ketene acetal)[71] by using trimethylsilyl chloride (TMSCl) as a trapping agent, it was decided to use trimethylsilyl chloride (TMSCl) as the Lewis acid catalyzed to promote ring opening. After all, the beneficial effects of added TMSCl on a variety of organic reactions is well-

documented,[72] and it is a lot milder than any of the additives (BF_3-Et_2O, $TiCl_4$, $AlCl_3$, $ZrCl_4$, and TMSOTf) that were used during the course of this study.

The result was dramatic when TMSCl (0.05 equiv) was employed. Upon treatment of *tert*-butyl-diphenylsilyl enol ether **106** with ketene acetal nucleophile **97** in 5.0 M LPDE in the presence of catalytic amount of TMSCl, clean conversion to the functionalized cycloheptadienes **107** (Scheme 1.28) was observed. The proton-NMR spectrum of the crude reaction mixture indicated an approximately 2:1 mixture of products (Scheme 1.28). This outcome was encouraging because ring opening was



Scheme 1.28

finally realized with dimethyl ketene acetal **97** in the presence of TMSCl. In attempts to improve upon the poor levels of facial selectivity, other silyl ketene acetals (**108** and **109**) were examined. However, efforts proved to be unsuccessful. For example, when the bulky, methyl *tert*-butyldimethylsilyl dimethyl ketene acetal **108** was employed the reaction did not proceed after two days. On the other hand, nucleophile **109** was found to be unstable and gave no desired product.

Upon further consideration of the results obtained using TMSCl as an additive to achieve ring opening, it became clear that silyl enol ether **88** (Fig. 1.5) was needed for further testing and for comparative purposes. The next objective was to test whether

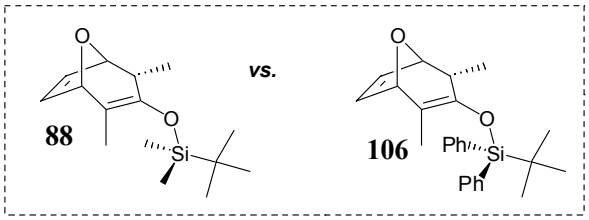
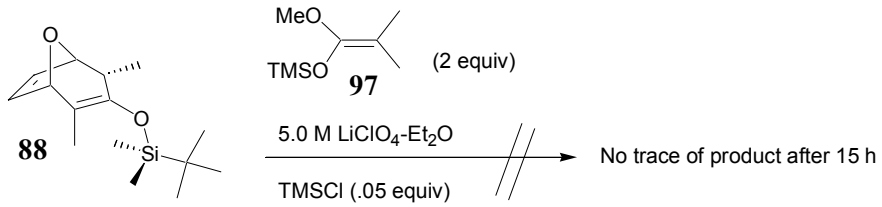


Figure 1.5: TBS-[3.2.1] enol ether *vs*. TBDPS-[3.2.1] enol ether.

substrate, TBS-[3.2.1] enol ether **88**, can be used for ring opening reaction under the same conditions, similar to compound **106** using nucleophile **97** and TMSCl as a Lewis acid. Careful investigation of the two compounds revealed that enol ether **106** was about three times in size and bulkier than compound **88**. The reason was the diphenyl substituents. Due to the severe size advantage that compound **106** had over **88**, one would predict that it exerts, if any, an additional ring strain that could make the ring opening a more favorable process. With this in mind, experiments were performed to investigate ways that selectivity could be controlled. To test this possibility, chlorotrimethylsilane (TMSCl) and silyl ketene acetal **97** were used for ring opening reactions with compound **88**. However, subjection of enol ether **88** to the 5.0 M LPDE with ketene acetal **97** in the presence of TMSCl (0.05 equiv) ring opening did not occur to any appreciable degree and starting material **88** was recovered (Scheme 1.29). In most cases, *tert*-butyl dimethyl silyl-enol ether **88** was recovered in good yield. Increasing the amount of Lewis acid (TMSCl) and longer reaction time only led to decomposition of

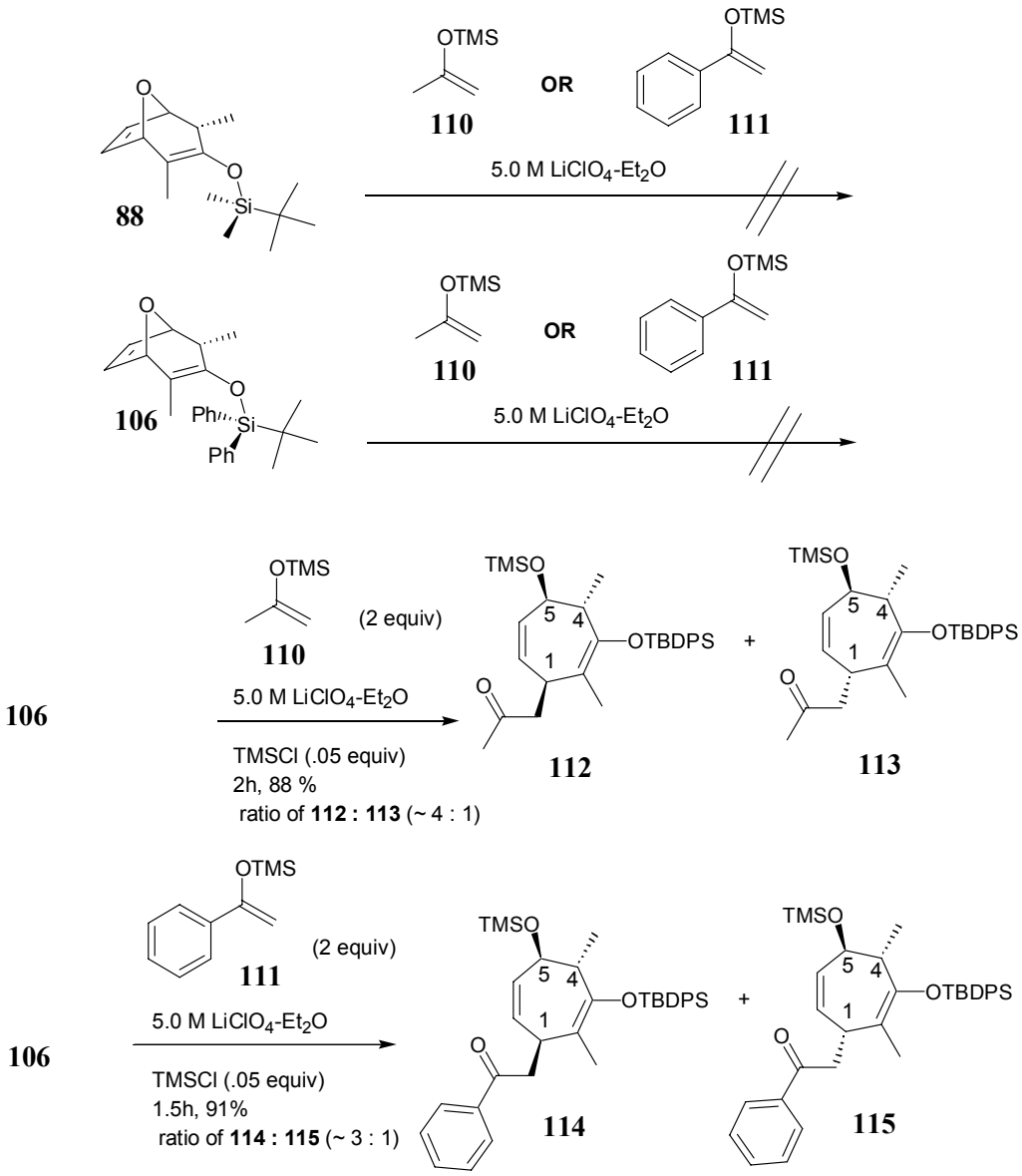
substrate **88**. It should also be mentioned that the nucleophile (hindered ketene acetal **97**) decomposed or polymerized when the reactions were prolonged. A dramatic contrast



Scheme 1.29

between TBS-[3.2.1] enol ether **88** and TBDPS-[3.2.1] enol ether **106** was noted in side by side control experiments. This phenomenon is not readily explained; however, one would expect based upon these observations, especially from a ring strain point of view, that subtrate **106** had just enough ring strain to override the instability and the steric nature of nucleophile **97**.

From previous work and control experiments,[67] Hunt and Grieco showed that ring opening did not occur for nucleophiles such as silyl enol ether **110** or **111** (scheme 1.30), unlike the outcome for the silyl ketene acetal **80** (scheme 1.19). Also, the same two nucleophiles (**110** and **111**) did not give rise to ring opening adducts (trace amount by TLC) when subjected for testing with TBDPS-enol ether **106**, scheme 1.30. However, starting material **106** was consumed (1.5-2 hrs) when TMSCl was used (Scheme 1.30). Interestingly, under the same condition employed (TMSCl (.05 eq)) for compound **88**, ring opening did not occur (Scheme 1.30).


OTMS
OR
OTMS
110
111
88
5.0 M LiClO4-Et2O
OTMS
OR
OTMS
110
111
106
Ph
Si
Ph
5.0 M LiClO4-Et2O
OTMS
(2 equiv)
110
106
5.0 M LiClO4-Et2O
TMSCl (.05 equiv)
2h, 88 %
ratio of 112 : 113 (~ 4 : 1)
TMSO
OTBDPS
+
TMSO
OTBDPS
112
113
OTMS
(2 equiv)
111
106
5.0 M LiClO4-Et2O
TMSCl (.05 equiv)
1.5h, 91%
ratio of 114 : 115 (~ 3 : 1)
TMSO
OTBDPS
+
TMSO
OTBDPS
114
115

Scheme 1.30

As shown in scheme 1.30, a mixture of products was generated when compound **106** was treated with trimethyl silyl enol ether **110** in 5.0M LPDE in the presence of TMSCl (.05 eq) at room temperature. Nucleophile **111** also gave rise to a mixture of cycloheptadienes **114** and **115** with excellent overall yield. The isomers can be separated *via* column chromatography. The relative stereochemistries at C_1 were obtained using the nuclear overhauser effect (nOe) measurements and decoupling experiments (Fig. 1.6).

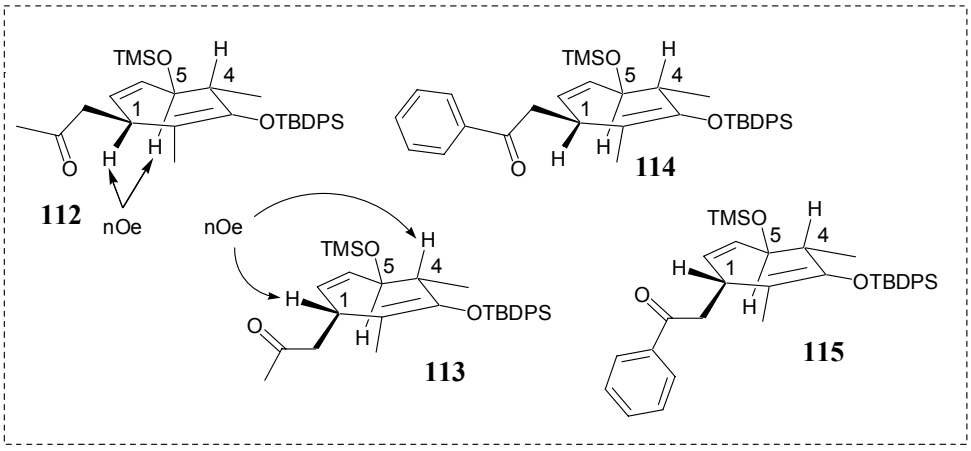
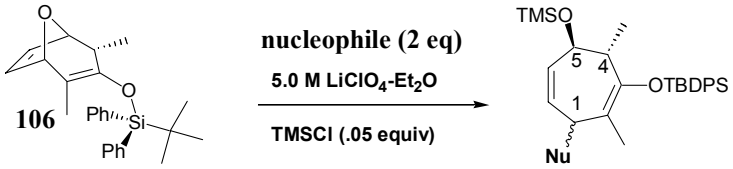
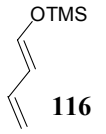
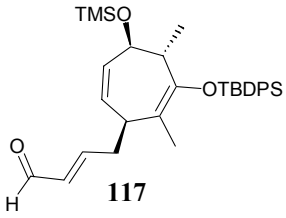
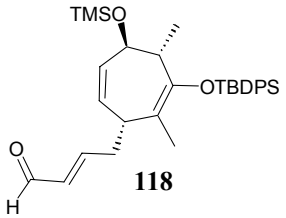
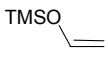
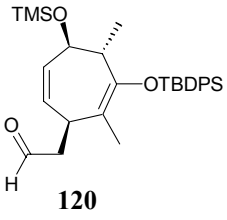
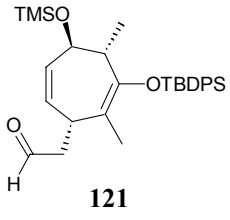
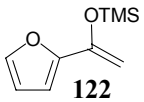
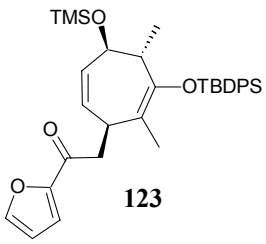
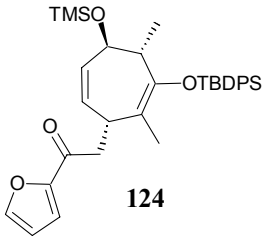


Figure 1.6: Nuclear overhauser effect (nOe) measurements.

Saturating the proton signal at C_1 of compounds **112** and **114** resulted in a positive nOe for the proton signal at C_5. This can be clearly seen in the nOe difference spectrum. Signal at C_5 was not found when C_1-proton was irradiated for isomers **113** and **115**, however, positive nOe enhancement for C_4-proton was detected.

Knowing that both hindered ketene acetal **97** and unreactive enol ether **110** or **111** can be used for ring opening (schemes 1.28 & 1.30), this methodological approach was extended to other nucleophilic reagents.[71] Under standard conditions in 5.0 M LPDE at room temperature, the reaction scope was investigated (Table 1.2). Trimethyl silyl enol



Entry	Nucleophile	Ratio (β: α)	product	time (hr)	(%)
1	 116	1.8 : 1	 117  118	1.5	84 %
2	 119	1.5 : 1	 120  121	1.5	81 %
3	 122	1 : 1	 123  124	1.5	86 %

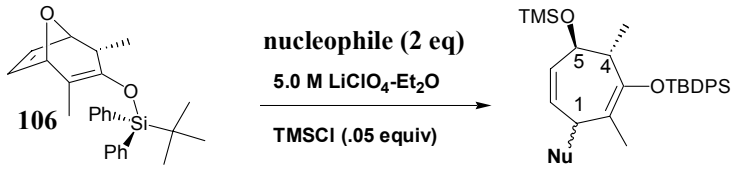
1. Ratio is determined by crude H-NMR, and relative stereochemistry was obtained by nOe measurements and careful decoupling.
2. Yield of isolated mixture.
3. In the absence of TMSCl, reactions did not proceed.

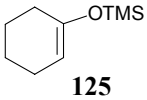
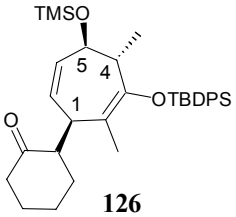
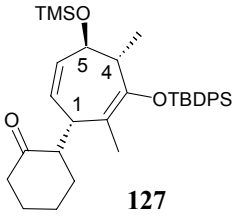
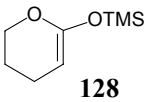
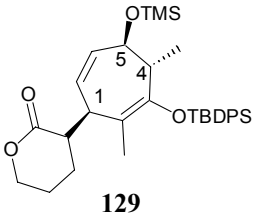
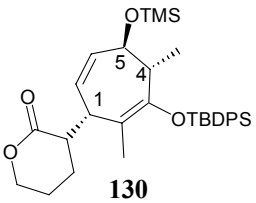
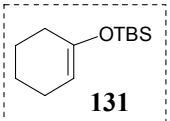
Table 1.2: Ring opening *via* enol ethers.

ethers such as **116**, **119**, and **122** all worked well when subjected to the reaction conditions (Table 1.2). Treatment of **106** with the conjugated diene silyl enol ether **116** in 5.0 M LPDE in the presence of TMSCl (.05 eq) resulted in rapid ring opening to generate products **117** and **118** with moderate facial selectivity (Table 1.2, entry 1). There was no trace of the cis-alkene. Trimethyl silyl enol ethers **119** and **122** proceeded in a similar manner under the same reaction conditions (entries 2 and 3). Either doubling the number of equivalents of the nucleophile or the TMSCl did not improve the isolated yield nor the facial selectivity. When trimethyl silyl chloride (TMSCl) was omitted from the reaction mixture, again no ring opening was observed and starting material **106** was recovered. Interestingly, even with the additive (.05 eq, TMSCl), the reaction did not work for compound **88** (*tert*-butyl-(2,4-dimethyl-8-oxa-bicyclo[3.2.1]octa-2,6-dien-3-yloxy)-dimethyl-silane). Although the results were somewhat discouraging, in terms of facial selectivity, the outcomes shown in table 1.2 were promising in term of the variety of functionalities that were able to be introduced. Since there was no change (~ 1:1) in facial selectivity for all three nucleophiles tested, it was assumed that by increasing the size of the R or the silyl-group within the nucleophile could make a difference.

Knowing that a quarternary (4^0) carbon atom can be installed *via* the hindered methyl trimethylsilyl dimethyl ketene acetal **97** (Scheme 1.28), an attempt was made to generate a *tri*-substituted product. Indeed, treatment of disubstituted silyl enol ether **125** and silyl ketene acetal **128** (prepared from the corresponding ketone and ester)[71] in 5.0 M LPDE in the presence of TMSCl (.05 eq) with **106** provided an inseparable mixture of products, (**126** & **127**) and (**129** & **130**) respectively in moderate yields (Table 1.3). The

relative stereochemistry at C_1 was determined by an nOe experiment (see Figure 1.6).



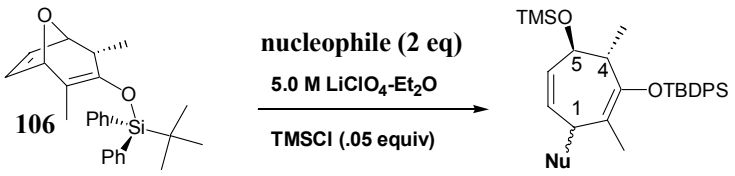
Entry	Nucleophile	Ratio (β: α)	product	time (hr)	(%)
1	 **125**	1.7 : 1	 **126**  **127**	9	66 %
2	 **128**	.8 : 1	 **129**  **130**	7.5	88 %
	 **131**				

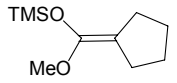
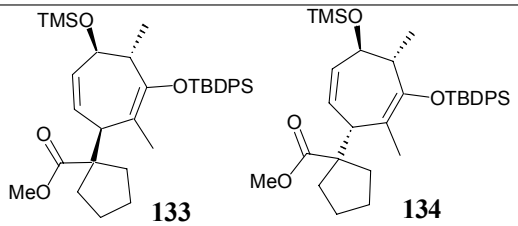
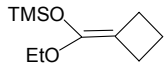
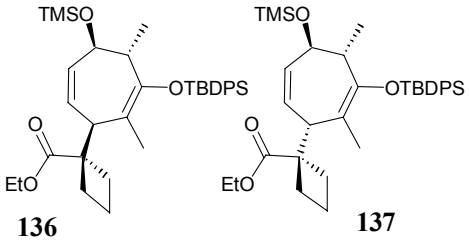
1. Ratio is determined by crude H-NMR, and relative stereochemistry was obtained by nOe measurements and careful decoupling.
2. Yield of isolated mixture.
3. In the absence of TMSCl, reactions did not proceed.

Table 1.3: Ring opening *via* cyclic ketene acetals and enol ethers.

Again, these nucleophiles gave no improvement in term of facial selectivity (~ 1:1) and did not proceed at all in the absence of TMSCl. TBS-cyclic enol ether **131** was also attempted in hopes to improve the selectivity, but ring opening did not transpire. Increasing the number of equivalents of TMSCl had a detrimental effect on the reaction.

The methodology was extended to the four and five membered ring nucleophiles **132** and **135** (Table 1.4). Though the reaction was unaffected in the absence of TMSCl, ring opening was achieved with ease (11-13 hrs) when nucleophiles **132** and **135** were



Entry	Nucleophile	Ratio (β: α)	product	time (hr)	(%)
1	 **132**	1 : 1.6	 **133** **134**	13	88 %
2	 **135**	1 : 1.4	 **136** **137**	11	92 %

1. Ratio is determined by crude H-NMR, and relative stereochemistry was obtained by nOe measurements and careful decoupling.
2. Yield of isolated mixture.
3. In the absence of TMSCl, reactions did not proceed.

Table 1.4: Ring opening *via* 4 and 5-membered ring ketene acetals.

employed. Lower the reaction temperature to zero degree showed no improvement in term of facial diastereoselectivity. In most cases, reaction was performed at room temperature.

Despite the success that has been realized (Schemes 1.28 & 1.30, Tables 1.2-1.4), in addition to the earlier results from Grieco and co-workers,[67,68] limitations still exist. For example, all nucleophiles (silyl-ketene acetal and enol ether) tested thus far provided nearly 1:1 facial selectivity, and many other nucleophiles such as trimethylsilyl cyanide, trimethylsilyl azide, dimethyl-aluminum azide, and allyltrimethyl silane did not work with the exception of DiBAL-H (diisobutylaluminum hydride).[67,68] There have been other accounts that indicated sterically hindered nucleophiles are not suitable for ring opening. For example, incorporating a chiral auxiliary into either the (TMS)-*N,O* ketene acetal **138** or **139**, treatment of the acylated oxazolidinones[73] with base (LDA) or the acylated sultams[74] with (NaHMDS or BuLi) produces an enolate followed by trapping reactions with TMSCl, did not work when employed for ring opening reactions. Similar result was observed for the (TMS)-*O,O* ketene acetal **140** which was synthesized from Corey's 8-phenylmenthyl propionate (Fig 1.7).[75] The difficulty of these nucleophiles (Fig 1.7) exist not only from the steric encumberance of the chiral auxiliary, but also their

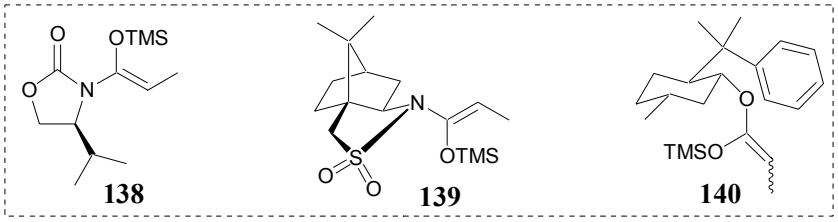
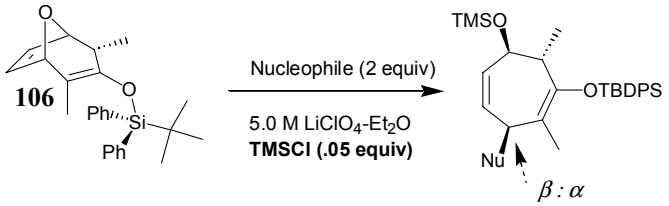


Figure 1.7: Chiral TMS-*N,O* (*O,O*) ketene acetal.

poor stability.[73,74] In general, no ring opening was observed when compound **138**, **139**, or **140** was treated with substrate **106** in 5.0 M LPDE in the presence of TMSCl. In several accounts, TMSCl was not used and ring opening did not transpire. In all cases, the precursors (chiral amide and ester) of **138**, **139** and **140** were recovered.

Mechanistic Considerations

Efforts to further refine the ring opening process employing highly polar media, 5.0 M $LiClO_4$-Et_2O, results (Schemes 1.23 & 1.25) clearly indicated that steric hinderance plays a major role in the ring-opening event. Due to the increased sensitivity of steric hinderance, and knowing that both the methyl trimethylsilyl dimethylketene acetal **97** and the (cyclohex-1-enyloxy)-trimethyl-silane **125** can be used for ring-opening (Scheme 1.28 and Table 1.3), the decision was to use (*tert*-butyldimethylsiloxy)-nucleophiles **131** & **141** for reaction to serve as a point of comparison for the purpose of reactivity as well as studying the effect of the substituents of silicon (trimethyl *vs*. *tert*-butyldimethyl), Table 1.5.

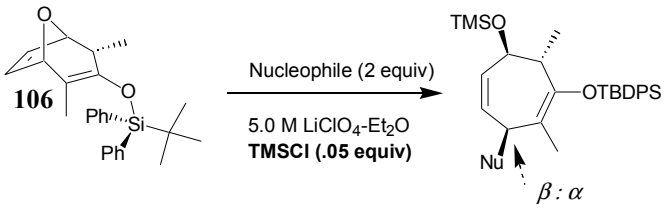


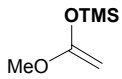
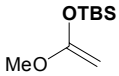
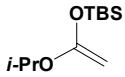
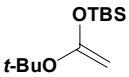
Nucleophile	Product (Nu)	Ratio (β:α)[1]	Time (h)	Yield[2]
TMSO, MeO, **97**	MeO, O	2 : 1	10 h	91 %
TBSO, MeO, **141**	No reaction after several days			
TMSO, **125**	O	1.7 : 1	9 h	66 %
TBSO, **131**	No reaction after several days			

1. Ratio is determined by crude H-NMR, and relative stereochemistry was obtained by nOe measurements and careful decoupling.
2. Yield of isolated mixture.

Table 1.5: TMS *vs*. TBS nucleophile.

The reaction scope is illustrated in Table 1.5. The hindered (*tert*-butyldimethylsiloxy) ketene acetal **141** or (*tert*-butyldimethylsiloxy) enol ether **131** failed to proceed even after several days under the standard conditions (5.0 M LPDE and TMSCl (.05 eq)), in sharp contrast to the less hindered (trimethylsiloxy) nucleophiles **97** and **125** (Scheme 1.28, Table 1.3 & 1.5). Due to the considerable difference in reactivity indicated above (Table 1.5), nucleophiles containing differentially protected silyls and substituents were examined (Table 1.6). Treatment of TBDP-silyl-enol ether **106** with a



Nucleophile	Ratio (β:α)[1]	Time (h)	Yield[2]
	1 : 1	< 1h	96%
	~ 1 : 1	~ 2.5h	94%
	~ 1 : 1	6h	93%
	incomplete conversion after 1 day		

1. Ratio is determined by crude H-NMR, and relative stereochemistry was obtained by nOe measurements and careful decoupling.
2. Yield of isolated mixture.

Table 1.6: Reactivity difference between hindered *vs*. unhindered nucleophile.

variety of ketene acetals hoping that by changing the silyl protecting group and the substituent, the selectivity would increase. However, as depicted in Table 1.6, the selectivity (~1:1) did not improve, only drop in the reaction rate as the size of the silicon

and the ketene acetal substituent (methyl to *t*-butyl) increased. Results from Table 1.5 and 1.6 suggested that TMS-enol ethers and TMS-ketene acetals behave much like a Lewis acid, and can activate the TBDP-silyl-enol ether **106** (*via* bridge head oxygen) more efficiently than the TBS-enol ethers or TBS-ketene acetals. This behavior is similar to the catalysis by trimethylsilyl triflate (TMSOTf) in several reactions of silyl enol ethers.[76] When the enol ether **106** is activated, the nucleophile can delivered from the top face of the molecule (*via* intramolecular) or from the bottom face with another nucleophile molecule to afford a mixture of products (Fig. 1.8).

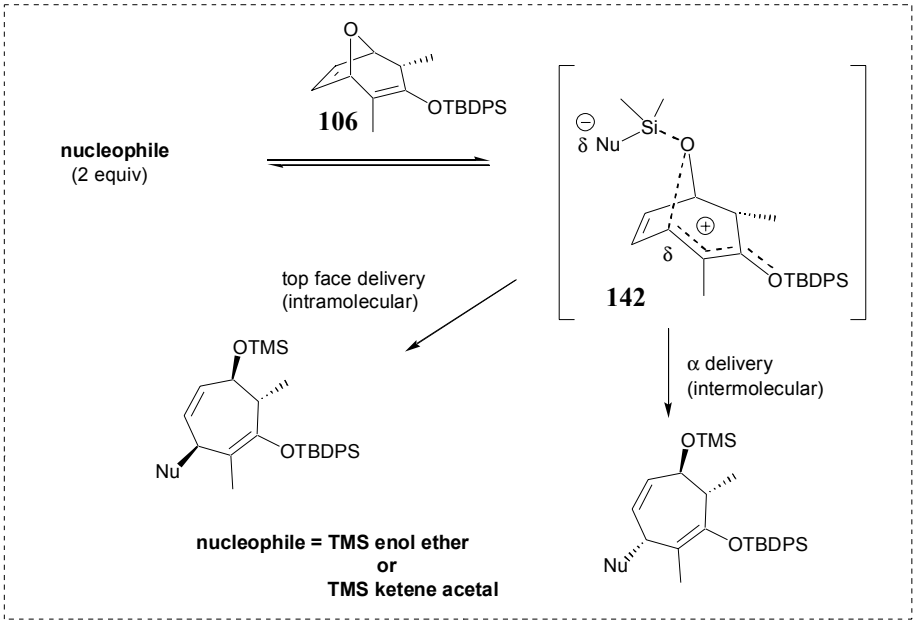


Figure 1.8: Intramolecular and intermolecular ring opening.

Nevertheless, the sluggish reaction of **106** with hindered or unreactive nucleophile can be accelerated by catalytic Me_3SiCl (TMSCl), raising the possibility that under the reaction condition, TMSCl can also complex with substrate **106** to provide a reactive intermediate **142** (stabilize in highly polar media, LPDE), which then reacts with the

nucleophile, giving rise to the adducts as well as to silyl group exchange. Presumable the chloride anion (produced *in situ*) promotes Si-O bond cleavage to generate a "naked" enolate in solution, which further enhances the nucleophilicity of otherwise unreactive nucleophile. It should be noted that nucleophiles (ketene acetals and enol ethers) used for ring opening reactions are bound to the trimethylsilyl (TMS) group, and with the presence of catalytic TMSCl, the silyl moiety serves as the chain carrier. Reason for this speculation is that the more hindered *tert*-butyldimethylsilyl ketene acetal **141** and enol ether **131** failed to react with **106** under similar conditions (Table 1.5).

Although many control experiments are still needed to fully understand the ring opening event and its full potential, the decision was shifted (with cycloheptadienes **107** in hand) to the synthesis of the natural product, (-)-epothilone B. Foreseeing that compound **107** (from ring opening *via* nucleophile **97**, Scheme 1.28) could potentially be used (with all the necessary carbon atoms needed) to generate the C_3-C_{11} fragment of the natural product, (-)-epothilone B (Fig. 1.9).

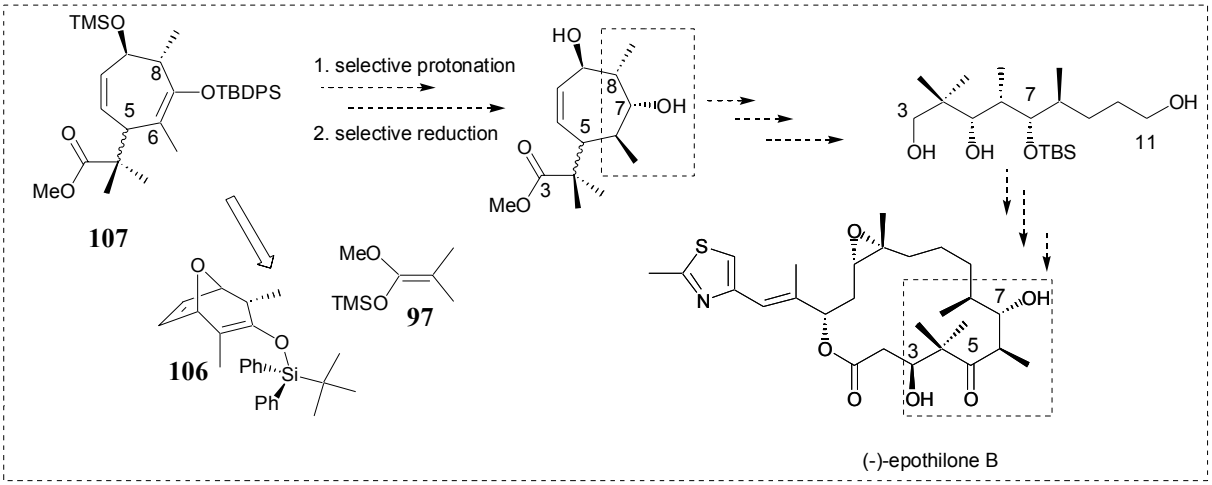


Figure 1.9: Synthetic strategy for Epothilone B.

INTRODUCTION

Total Synthesis of Antitumor Agent, (-)-Epothilone B

Background

Cancer is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells that invade and disrupt other tissues and spread to other areas of the body. There are two classes of factors, which can be responsible for the development of cancer, external factors (such as chemicals, radiation, and viruses) and internal factors (for example, immune conditions, hormones, and inherited genes). Causal factors may act together or in sequence, to initiate or promote carcinogenesis.[77a] Cancer is responsible for about 25% of all deaths in America. According to cancer statistics from NCI (National Cancer Institute), there were 1,284,900 new cancer cases in the year 2001, and an estimated half a million deaths were reported in 2002 (http://www.nci.nih.gov/statistics/datasources). The overall costs of cancer, which includes medical treatment, morbidity, and fatality costs are tremendous, usually over $100 billion dollars per year. Although revolutionary therapies have led to a decline in cancer death rates since 1991, cancer occurrence is on the rise and treatments are lasting longer, and the global costs of cancer drugs alone will likely increase to $35 billion dollars by 2010.[77a]

For years, the standard treatment for advanced colorectal cancer has been chemotherapy with a regimen containing 5-fluorouracil (5-FU) and leucovorin.[77b,78] However, the majority of patients who relapse or fail to respond after initial 5-FU-based therapy will eventually die of the disease, despite the recent availability of newer drugs

such as irinotecan, capecitabine, and oxaliplatin.[78] Thus, there continues to be a need for new treatments for this dreaded disease. In the last two decades, several anti-cancer agents have been discovered and developed. Prominent among them are two tubulin binding anticancer agents, taxol and taxotere. Both have occupied the attention of synthetic organic chemists and chemical biologists.[79a] More recently, chemists, biologists, and clinicians are switching their attention to a new and more potent class of anticancer agents called the epothilones (Figure 2.1).

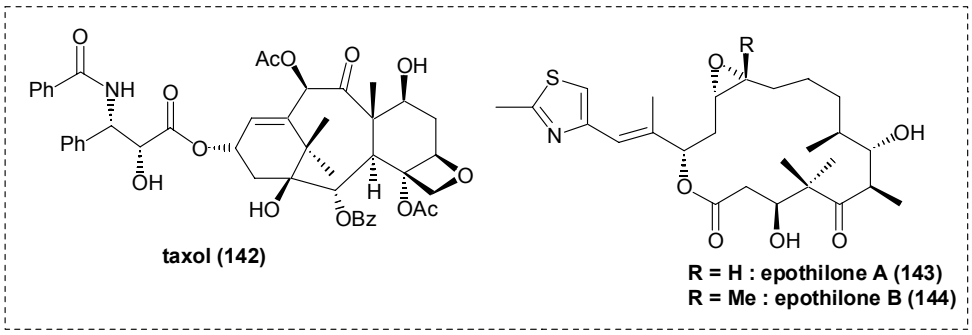


Figure 2.1: Anticancer agents (taxol and epothilone).

Since the discovery that the epothilones (Figure 2.1) possess a very high activity against cancer cells,[79b] as well as some advantages compared to the billion dollar anticancer drug Taxol^{R} in terms of potency and effectiveness against drug-resistant tumor cells, their total synthesis, structural modification and biological investigation became a very interesting synthetic target for many scientists all over the world. Epothilone is a 16-membered macrocyclic polyketide that was originally discovered in a screening program for secondary metabolites from myxobacteria by virtue of its selective antifungal activity against *Mucor hiemalis*.[80] Subsequently, it was also shown to possess potent cytotoxic activity against mammalian cells.[79,81]

Despite being structurally unrelated to the taxanes (Figure 2.1), epothilones are able to induce polymerization of tubulin dimers into microtubules in vitro.[81,82] Epothilones are more potent inducers of tubulin polymerization than paclitaxel,[82] and are also able to stabilize preformed microtubules against depolymerization with greater potency than paclitaxel.[81,82] Therefore, epothilones can inhibit cell proliferation by blocking the transition between the G2 and M phase of the cell cycle, and eventually, lead to apoptosis.[83]

One unexpected difference between taxol and epothilone was observed in promoting the assembly and stabilization of yeast microtubules. Taxol apparently failed to influence the dynamics of yeast microtubules in vitro, whereas epothilone B (**144**) bound to yeast tubulin and had an effect similar to that of Taxol on mammalian microtubules.[84] Compared to Taxol, the epothilone class of natural products holds several advantages: 1) the epothilones exhibit higher potencies in triggering α-and β-tubulin units to polymerize into hyper-stabilized microtubule assemblies;[85] 2) the epothilones are highly active against cell lines resistant to taxol and other anticancer agents[86] (> 35,000 fold higher potency than taxol in some cytotoxicity experiments), and are not sensitive to the induction of the P-glycoprotein drug-transport system, unlike the taxoids, which make it possible to overcome the acquired resistance in cancer chemotherapy;[87] 3) the epothilones are much more water-soluble than taxol (700 mg/L for epothilones *vs.* .25 mg/L for taxol, so it is convenient for formulation;[87] 4) epothilone D has lower toxicity than taxol in vivo;[87] and finally, 5) the epothilone structure is less complicated than taxol, which allows more concise synthetic routes for the total synthesis

of its analogues. With these significant superiorities over taxol, epothilones have become prominent in the search for new chemotherapeutic antitumor agents, and have been subjected to substantial efforts directed toward their synthesis.

Evolution of Epothilone Synthesis

Soon after the recognition of the importance of the epothilones, a number of research groups around the world began to develop strategies for their total synthesis.[88] Their remarkable biological activity and unique chemical structure, less complex than that of taxol, offer opportunities for the discovery and development of new synthetic methodology. The first total synthesis of this natural product was reported by the Danishefsky group in 1996.[88a] Since then, numerous total syntheses of epothilones have been published in the literature. Figure 2.2 illustrates and summarizes the most common methodologies and strategies toward the synthesis of epothilones. It should be noted that

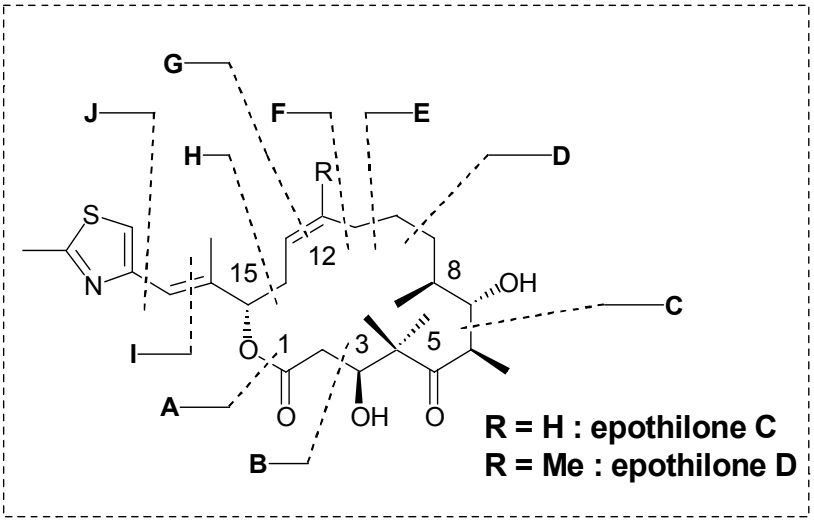


Figure 2.2: General Disconnections.

epoxidation of the olefin (C_{12}-C_{13}) of epothilone C and D can be achieved to generate epothilone A and B respectively with modest stereoselectivity.[88] According to a

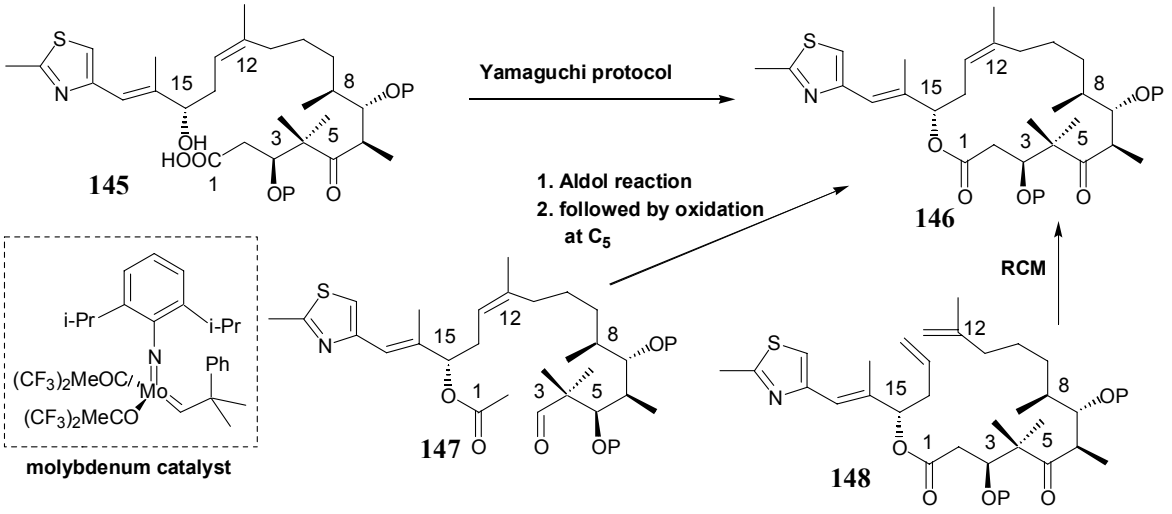
disconnection analysis, references to general strategies are indicated in the following table (Table 2.1).

Disconnection	Macro-lactonization	Aldol-rxn	Allyl-metallation	RCM	Wittig	Suzuki	Stille
A	95, 88f, 101						
B		89,90, 92,88f, 88e	102				
C		90,92, 95,88f, 97	91				
D				96			
E							94
F						95, 88e	90
G				98, 99	88f, 98, 102		
H			103, 104				
I					90,93, 100, 102		
J							105

Table 2.1: References to general disconnections.

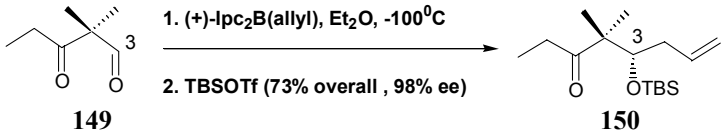
Macrolactonization is the most common strategy that has been adopted for cyclization of the sixteen membered ring. Danishefsky[95] and Nicolaou[88] both employed 2,4,6-trichlorobenzoyl chloride, Yamaguchi's reagent, for formation of the macrolide ring (Scheme 2.1). Utilization of the carbodiimide coupling reagent was reported by Mulzer.[100] These methods provided the 16-membered lactone in excellent yields. Construction of the C_{12}-C_{13} (Z) olefin has emerged as another attractive point of

convergence. Ring-closing metathesis (RCM) is one of the most successful and efficient methods used to construct a large macrolide ring. However, the epothilone synthesis yields a mixture of Z and E isomers in ~ 1:1 ratio. In general, this poor ratio could not be improved to give the desired Z-isomer, although a large number of conditions has been



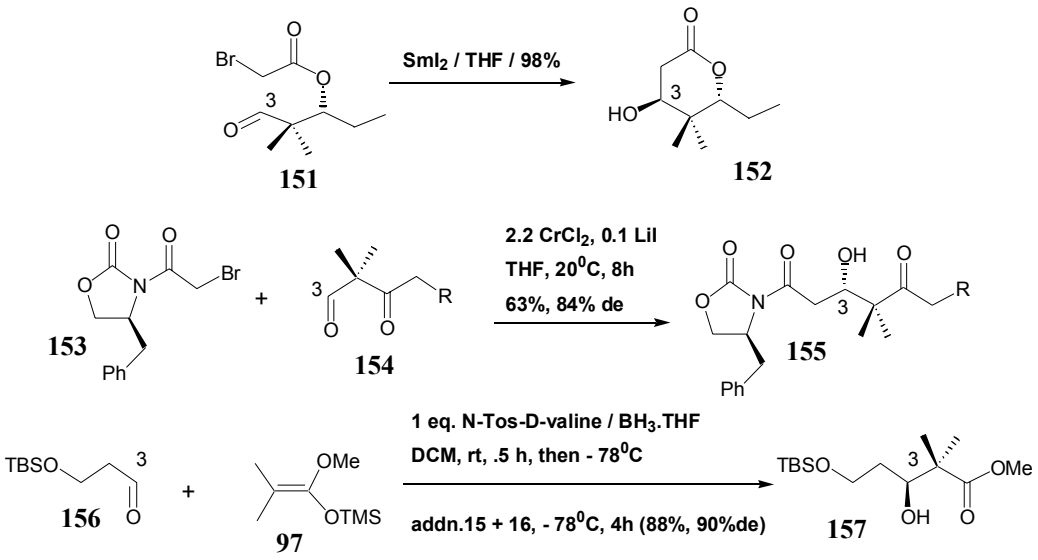
Scheme 2.1

developed.[106] A similar observation was recorded by May and Grieco using the same approach (molybdenum olefin-metathesis catlyst) to epothilone B.[88d] In the original paper by Danishefsky,[88a] macroaldolization was used. The acetate **147** was treated with potassium bis(trimethylsilyl)amide (KHMDS) in THF to generate the enolate, which reacted intramolecularly with the aldehyde moiety (C_3) to afford the cyclized products. However, the diastereoselectivity at C_3 was poor, and the alcohol at C_5 must be protected in order to avoid retroaldolization along the C_3-C_4 bond.



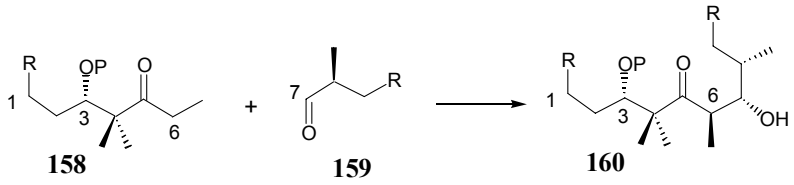
Scheme 2.2

To generate the C_3 chiral center with C_2-C_3 bond formation or C_3-C_4 bond formation, aldol reaction and allyboration are the major two approaches. The reaction of aldehyde **149** with allyl-(+)-Ipc_2B to generate the C_2-C_3 bond with high enantiomeric selectivity was first reported by Nicolaou (Scheme 2.2).[102] In addition to the intramolecular acetate aldol reaction mentioned earlier (Scheme 2.1), the intramolecular samarium mediated Reformatsky reaction was also used to introduce the C_3 chirality (Scheme 2.3).[89] Intermolecular acetate aldol was originally not very selective (3:1),[107] but a high degree of stereocontrol was achieved using the readily available 2-bromoacylated Evans oxazolidinone **153** for chromium(II)-mediated Reformatsky reaction to provide compound **155** in good yield and high selectivity.[108] An alternative route which exploits the elegant chemistry of Kiyooka was reported independently by Taylor[89] and Mulzer.[100] The reaction of a silylketene acetal **97** with propionaldehyde **156** under the influence of Kiyooka's chiral boron reagent provided the correct aldol adduct **157** in good yield and high *ee* (Scheme 2.3).



Scheme 2.3

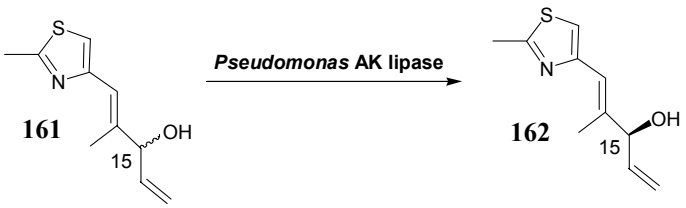
The formation of the C_6-C_7 bond and two adjacent stereocenters has been obtained through aldol chemistry. The aldol approach started with enolization of ketone **158**, followed by addition of aldehyde **159** to give the desired aldol product **160** in moderate yields (Scheme 2.4). [88c, 90, 103] The functional groups in the ketone fragment proved to be important for the selectivity. For example, in the case of the fully protected ketone [R = OP, P = TBS or $C(CH_3)_3$], selectivity ranged from 8:1 to 20:1. However, when C_1 was a free carboxylic acid or when there was a free hydroxyl at the C_3 position, the reaction was non-selective between the two syn adducts. Overall, the aldol reaction was the safest and most utilized method to obtain the correct stereocenters (C_6-C_7) by most research groups.



Scheme 2.4

To generate the C_{15} chiral center, Ti-BINOL-catalyzed allylation[103] and Brown's asymmetric allyboration were proven to be successful.[102] Enantioselective alkylation[90, 100] or hydroxylation[94] with Evans' auxiliary group was reported by several different groups. The chiral center at C_{15} was also accomplished by using a catalytic asymmetric cyanosilylation of an aldehyde.[88e] Panek demonstrated that an enzymatic kinetic resolution approach could be used to give the correct stereocenter at C_{15}.[91] This method involved a lipase-mediated separation of racemic homoallylic alcohols **161** (Scheme 2.5). Moreover, aldolase antibody catalyzed resolution was reported by Sinha to prepare the

C_{15} stereo-genic center with high *ee*, and the aldolase catalyzed asymmetric synthesis was also shown to be very effective.[96]



Scheme 2.5

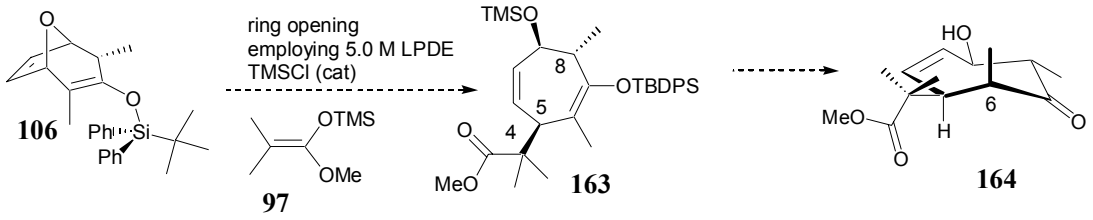
To date, several total and partial syntheses of the epothilones and analogs have been documented, and extensive Structure-Activity Relationship (SAR) studies have been carried out. The chemistry and biology have been reviewed and it has been shown that epothilone is the most potent antiproliferative agent among the naturally occurring tubulin polymerization promoters, with an activity from 2- to 10 fold greater than that of paclitaxel.[109] Coupled with its biological activity, epothilone's relatively simple structure has made it an interesting target for total synthesis.

As part of a continuing program to investigate the benefits of lithium perchlorate diethyl ether (LPDE) as a useful medium for organic synthesis, a highly convergent synthesis of epothilone B has been achieved. The synthesis features the direct bridgehead ring opening of an oxabicyclo-[3.2.1] ring system utilizing catalytic TMSCl in 5.0 M LPDE providing a functionalized cycloheptadiene as well as all the necessary carbon atoms needed for further elaboration into the C_3-C_{11} fragment of epothilone.

Results and Discussion

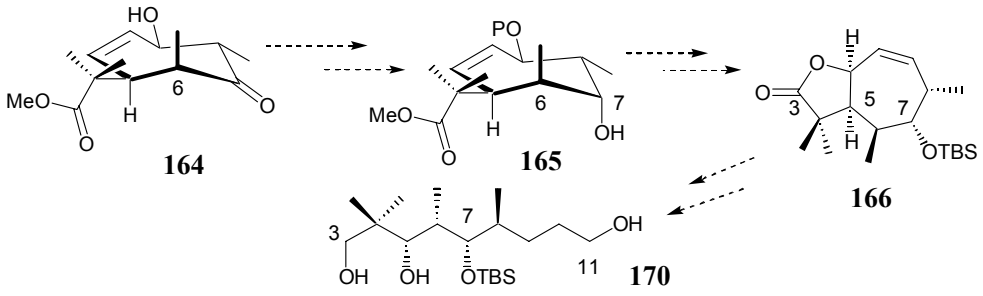
Analysis

The synthetic strategy for the preparation of the C_3-C_{11} (**167**) fragment of epothilone B centers around the direct ring opening of an oxabicyclo[3.2.1]octene (**106→163**) with a hindered silyl ketene acetal employing catalytic TMSCl in 5.0 M LPDE (Scheme 2.6). Through this reaction, the C_4 quaternary carbon atom (C_4) can be established. Subsequent selective protonation of the TBDP-silyl enol ether **163** provides the correct stereocenter at C_6 (**163→164**).



Scheme 2.6

Conversion of cycloheptenone **164** into fragment **167** requires several additional synthetic steps (Scheme 2.7). Compound **164** can be transformed into **166** as outlined in scheme 2.7: 1) the hydroxy ketone **164** could be protected and selectively reduced (C_7) to



Scheme 2.7

provide the correct stereocenter at C_7; and 2) cis-fused lactone **166** could be generated through an intramolecular lactonization using the intact skeleton of compound **165**. A

more pressing concern was to devise a strategy for sequential dealkylation of the methyl ester and cyclization (Figure 2.3). Assuming that these operations could indeed be effected, then lactone **166** could be used to access the stereochemically defined polypro-

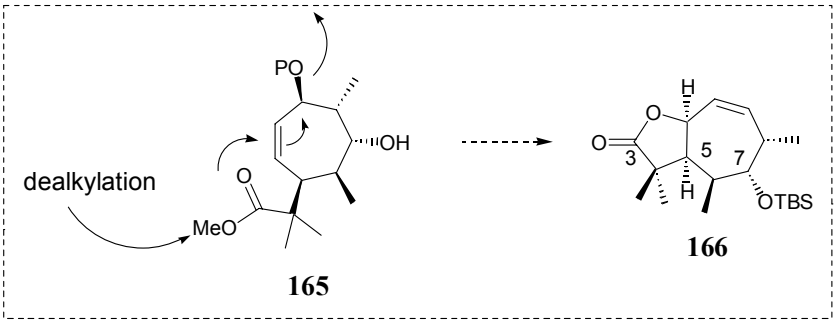
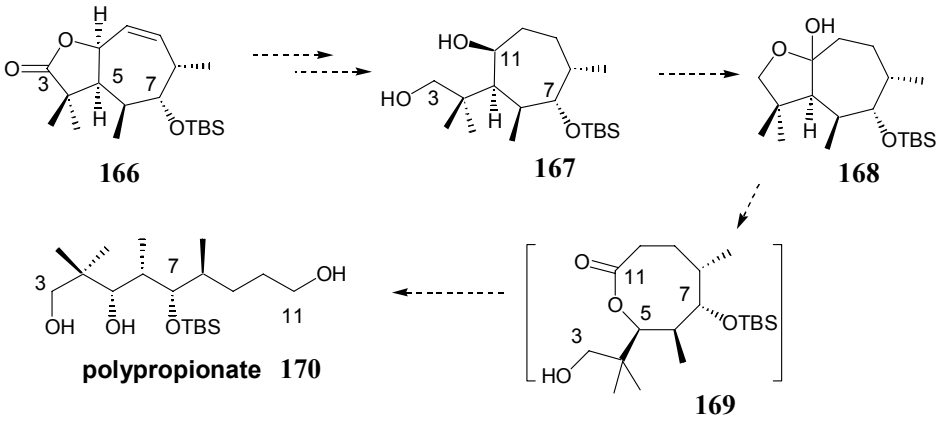


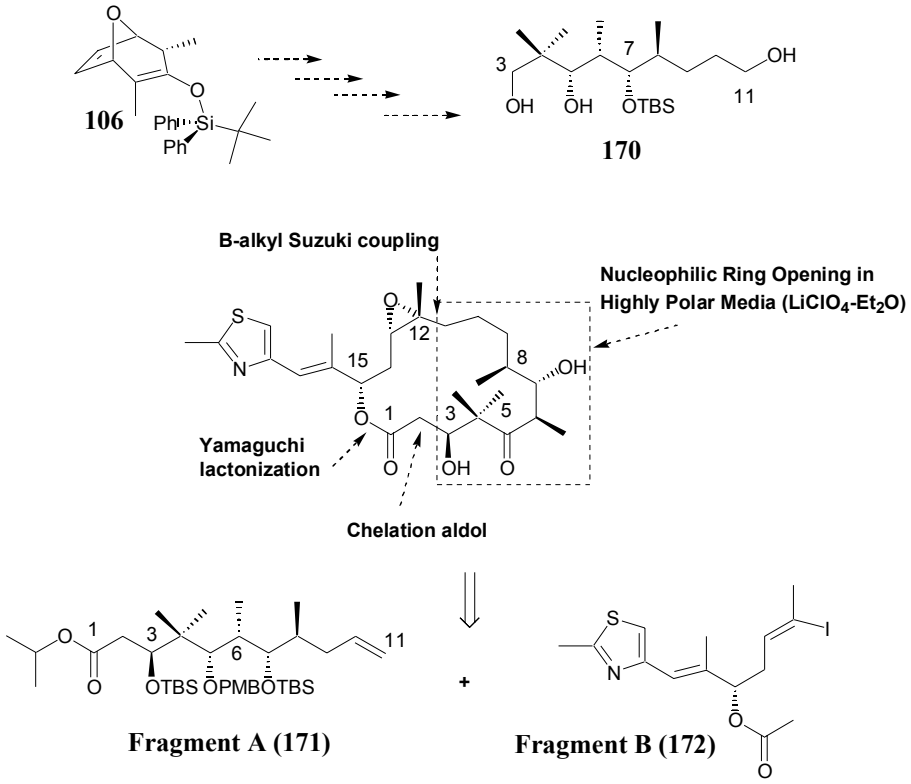
Figure 2.3: Lactone formation and dealkylation.

pionate fragment **170**. Completion of this polypropionate fragment was anticipated to be straightforward (Scheme 2.8). Hydrogenation of the olefin followed by a complete reduction would give rise to the diol (**166→167).** Access to hemiketal **168** was anticipated to arise from a selective oxidation of the C_{11} hydroxyl group. Direct oxidation of the secondary alcohol (C_{11}) would generate hemiketal **168**, thus avoiding protection of the primary hydroxyl group at C_3**.**



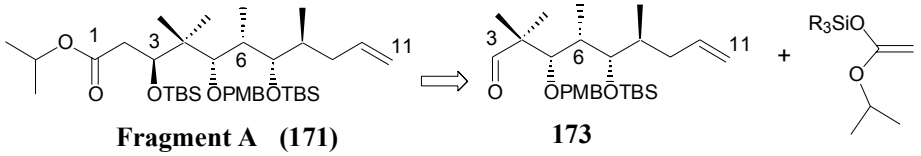
Scheme 2.8

Baeyer-Villiger oxidative ring expansion of **168** using the Grieco protocol[110] followed by reduction of the cyclic lactone intermediate **169** would provide fragment **170**. With the ready availability of polypropionate **170**, it was anticipated that (-)-epothilone B could be constructed by Suzuki coupling of fragment A with B followed by Yamaguchi macrolactonization (Scheme 2.9). The availability of fragment A was



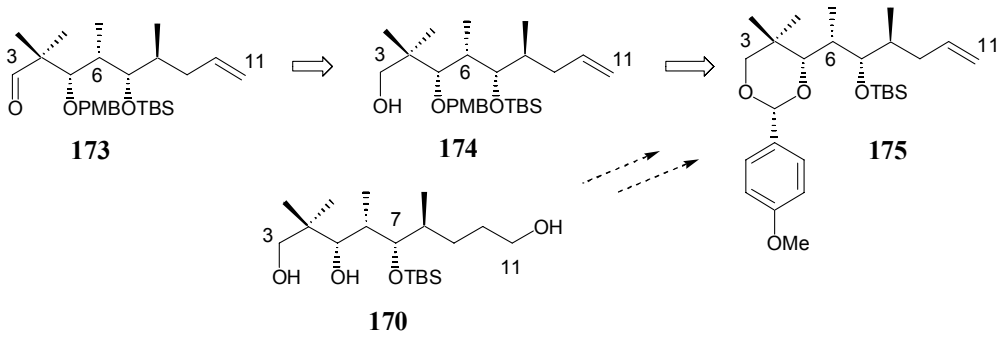
Scheme 2.9

envisioned to arise from a chelation controlled Mukaiyama aldol reaction between subunit **173** with isopropyl silyl ketene acetal to install the correct stereochemistry at C_3.



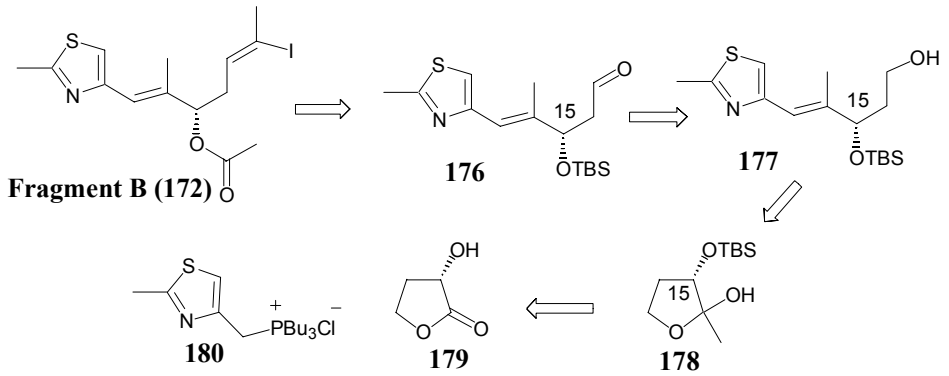
Scheme 2.10

The key aldehyde **173** can be easily obtained by oxidation (Dess-Martin periodiane) of alcohol **174** which is derived from selective reduction (DiBAlH) of the *p*-methoxy benzylidene acetal **175**. Compound **175** was expected to be available from triol **170** after protection of the 1,3-diol followed by introduction of the terminal olefin using Grieco's selenium chemistry (Scheme 2.11).



Scheme 2.11

As outlined in scheme 2.12, the known fragment B[88c] (**172**) can be achieved in good yield by coupling of the α-iodoalkyl ylide *via* Zhao's protocol[111] with aldehyde **176**



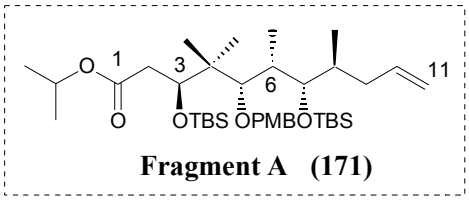
Scheme 2.12

In turn, the aldehyde intermediate can be obtained from oxidation of alcohol **177** (Dess-Martin reagent) following Schinzer's procedure.[88c] Compound **177** was anticipated to come from a Wittig reaction between the ylide derived from (2-methylthiazol-4-yl)

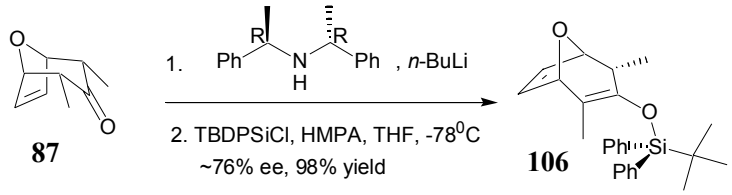
methyl tri-*n*-butyl-phosphonium chloride **180** with a mixture of cyclic hemiketal **178** and its open-chain hydroxy ketone. Ketal **178** can easily be obtained from hydroxylactone **179** (a. TBSCl / DCM / lutidine b. MeLi / Et_2O), which is commercially available.

Synthesis of Fragment A (171)

The construction of the optically active fragment A **(171)** commences with the racemic 8-oxabicyclo[3.2.1]oct-6-en-3-one **87**, which is readily available from the [4+3] cycloaddition of furan and 2-bromo-3-pentanone.[112] Subsequent desymmetrization of this racemic compound using a chiral amine[113] ([*R*-(*R**, *R**)]-(+)-bis(α)-methyl benzyl), *n*-BuLi, TBDPSiCl, HMPA) provided silyl enol ether **106** in 98% yield and ~76% ee (Scheme 2.13).



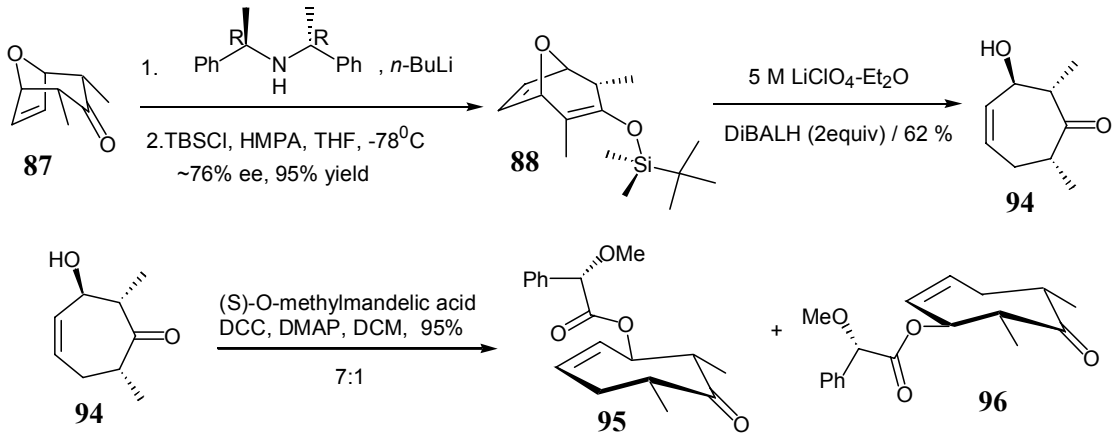
Fragment A (171)



Scheme 2.13

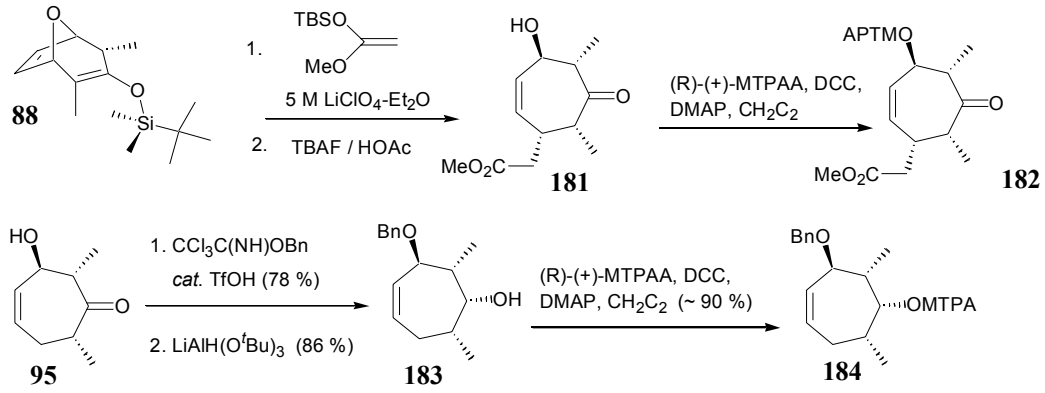
The enantiomeric excess of the desymmetrized compound **106** was determined in the same manner achieved for compound **88** (Scheme 2.14).[114c] Using the same chiral lithium-base, ([*R*-(*R**, *R**)]-(+)-bis(α)-methyl benzyl), to deprotonate ketone **87** and subsequence trapping with TBSCl provided enol ether **88.** Treatment of enol silane **88** with 2 equivalent of DiBALH in 5.0 M LPDE provided hydroxy ketone **94**. The absolute

stereochemistry of **94** was assigned by Mosher ester analysis. Esterification of the hydroxy ketone **94** with (S)-O-methylmandelic acid provided a separable mixture of esters **95** and **96** in 95% yield in a 7:1 ratio (Scheme 2.14).[114a,c]



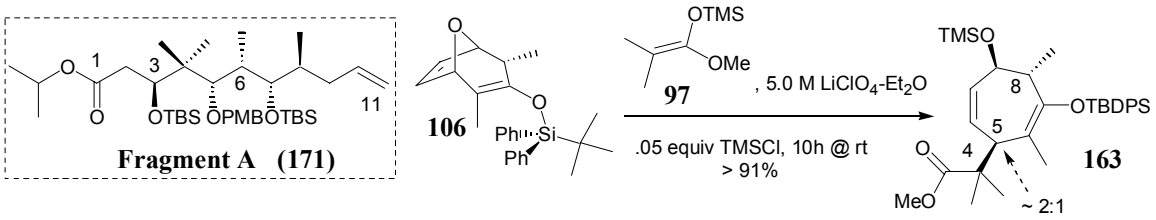
Scheme 2.14

In addition, the absolute configuration of **88** can be determined by Mosher ester analysis of the substrate **182** (Scheme 2.15), or esterification (DCC, DMAP) of alcohol **183** with Mosher acid [(*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid][114a,d] giving diastereomeric ester **184** in 90% yield after separation.[114d]



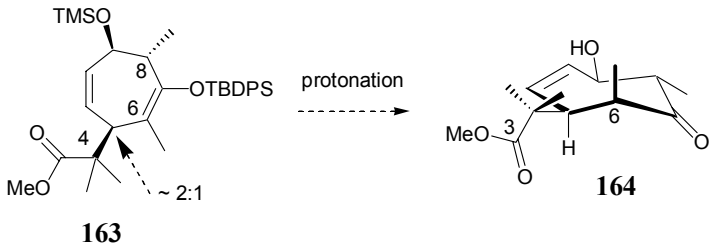
Scheme 2.15

With chiral enol ether **106** in hand, the established methodology (direct ring opening) was employed to introduce the *gem*-dimethyl at the C_4-position of fragment A (**171**). Treatment of silyl enol ether **106** with methyl trimethylsilyl dimethylketene acetal **97** (2 equiv) in 5.0 M $LiClO_4$-Et_2O in the presence of catalytic TMSCl (.05 equiv) provided a 91% yield of an inseparable mixture (~2:1) of **163** (Scheme 2.16). Although



Scheme 2.16

the selectivity of this step is modest, the result was welcomed at least with regard to the prospect that it provided for the construction of compound **164** (Scheme 2.17).



Scheme 2.17

At this stage, attention was directed at conversion of **163** into the hydroxy ketone **164** wherein the *t*-butyldiphenyl-silyl enol ether must be desilylated giving rise to the corresponding enolate, followed by selective protonation to give the correct stereocenter at the C_6-position of fragment A (**171**). Controlled experiments indicated that mixture **163** was quite stable unless TBAF (*tetra-n*-butylammonium fluoride) was used in the presence of acetic acid (Figure 2.4). However, the reaction produced mixture of products (difficult to separate) and the desired hydroxy ketone **164** was obtained in low yield.

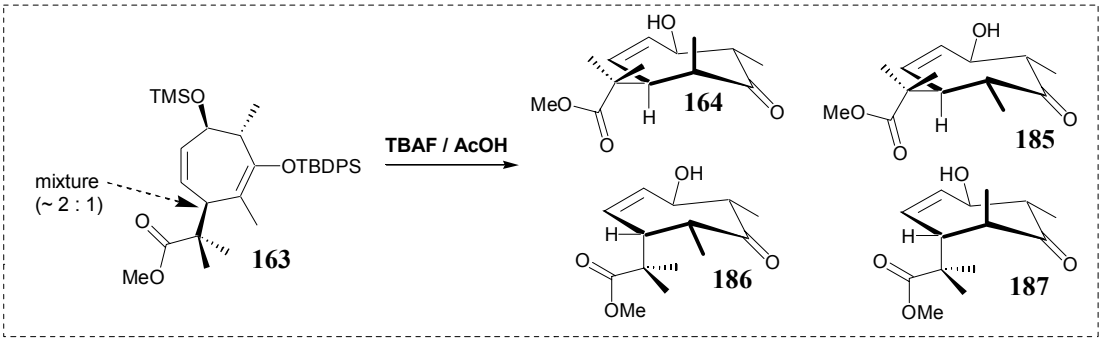
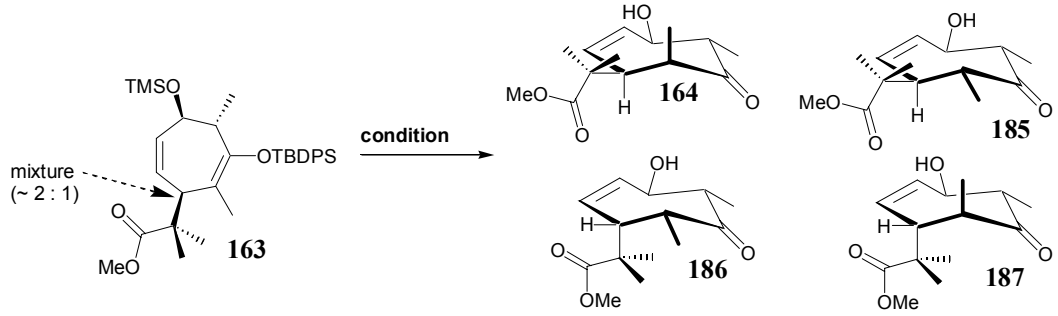
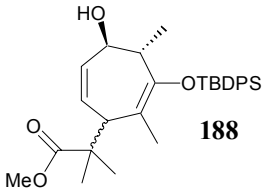


Figure 2.4: Protonation of TBDPS-enol ether.

Scheme 2.18 outlined a variety of conditions that were examined to remove water from TBAF solution, reasoning that trace of water could promote equilibration which can contribute to mixture of products. However, multiple efforts proved insufficient and only



Conditions	164: 185: 186	yield of mixture, %
1. TBAF / HOAc; 0^0C	1.2 : 1 : .9	96
2. TASF / proton source / -78^0C	3 : 1 : 1.6	88[a]
3. TBAF on Silica gel / proton source / -78^0C	1.7 : 1 : 1.2	91
4. TBAF 15% wt on alumina / proton source / -78^0C	8 : 1 : 3.8	79[a , b]
5. TBAF / molecular seives/ proton source / -78^0C	2.3 : 1 : 1.4	77[a , b]
6. HF.Pyridine / THF / rt	18 : 1 : 10	94
7. CsF / proton source / -78^0C	mostly mixture **188**	—
8. PPTS	mostly mixture **188**	—
9. CSA	mostly mixture **188**	—



proton source : HOAc or BHT

[a] very low yield when scaled up

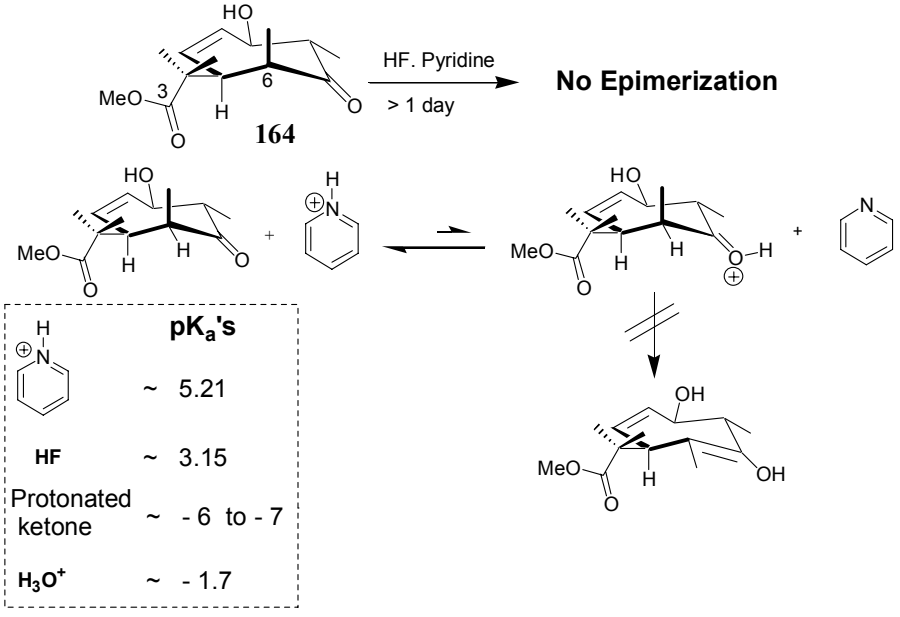
[b] several unknown products

187 not detected

Scheme 2.18

led to multiple products (entries 3-5, Scheme 2.18). Since quaternary ammonium fluorides are contaminated with water,[115] attention was directed toward Noyori's reagent, tris(dimethylamino)sulfonium difluorotrimethyl-siliconate (TASF).[116] However, selectivity did not improve (entry 2, Scheme 2.18). In view of factors such as fluoride anion, bulky proton donor, pKa's, and kinetic protonation that can influence the selectivity, hydrogen fluoride-pyridine (HF.py) was examined. When a mixture of **163** was exposed to excess HF.py (entry 6), the crude ^{1}H-NMR spectrum indicated an approximately 2:1 mixture of **164**:**186**, and revealed only trace amounts of **185** and **187**.

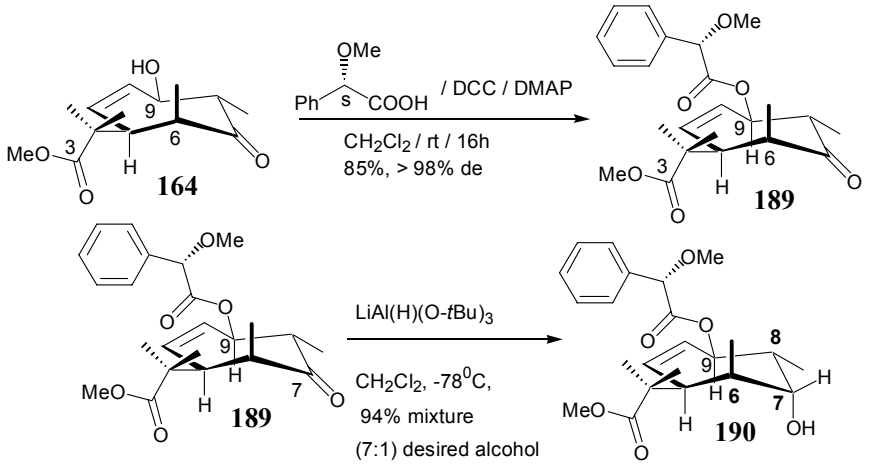
Under the reaction conditions (in HF.Py), it is reasonable to conclude that compound **164** can not be epimerized to the more stable hydroxy ketone **185**. For further testing, the hydroxy ketone **164** was re-submitted to the same reaction conditions for more than a day without any epimerization (Scheme 2.19). From the standpoint of



Scheme 2.19

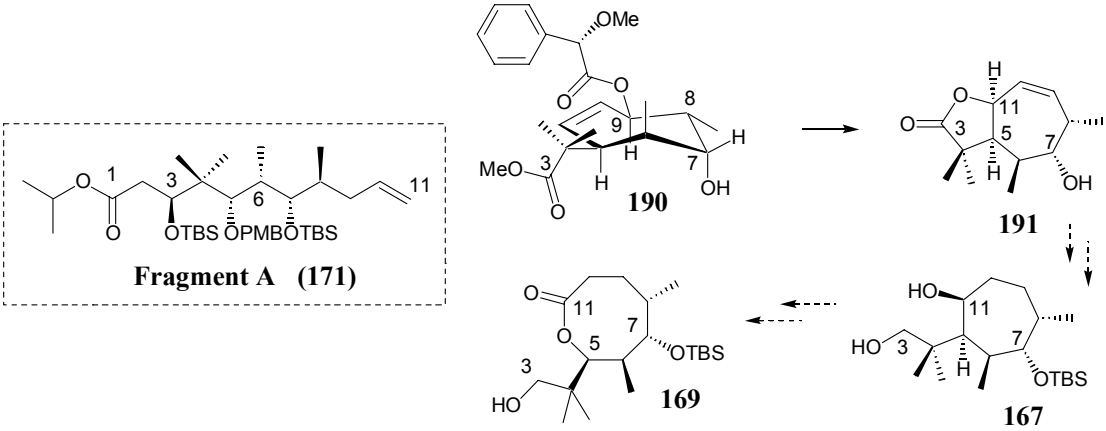
pKa's, the outcome was expected. Under this condition (in HF.py / THF), it is difficult for compound **164** to lose the equatorial hydrogen in the enolization of the ketone (Scheme 2.19). This stereoelectronic preference was postulated to be due to the requirement for continuous overlap between the C-H bond that is being broken and the π-orbital of the C=O group, a concept that was originally proposed by Corey and Sneen.[117] The optimal results from the standpoint of yield and selectivity of this critical event were accomplished using anhydrous HF.py (excess) in THF (Scheme 2.19). These conditions promoted desilylation and stereoselective protonation to provide the desired hydroxy ketone **164**, $[\alpha]_D^{25}$ - 43.6 (c 4.9, $CHCl_3$), in moderate yield (~50-55% in two steps).

The next phase involved the transformation of allylic hydroxy ketone **164** into a mandelate **189** (Scheme 2.20). Through this step, the (S)-O-methylmandelic ester served its purpose as both a resolving agent and protecting group. Not to mention, a potential leaving group was installed at C_9 for use in the latter stage of the synthesis. Esterification



Scheme 2.20

of allylic alcohol **164** with *(S)*-O-methylmandelic acid gave a diastereomeric mixture of esters (85%). Separation of diastereomers provided pure compound **189** in > 98% *de*, $[\alpha]_D^{25}$ +98.3 (c 1.7, $CHCl_3$). With ketone **189** in hand, the stage was set for reduction of the ketone moiety. This process was envisioned to occur from the top face of the molecule so as to give rise to the desired axial alcohol **190**, possessing the correct stereocenter at C_7 of fragment A. The bulky reducing agent LiAl(H)(O-*t*Bu)$_3$ at -78^0 C was able to accomplish this goal and provided compound **190** in 82% yield. With stereocenters C_6-C_8 of fragment A secured, it was appropriate to focus on the construction of lactone **191** (Scheme 2.21).

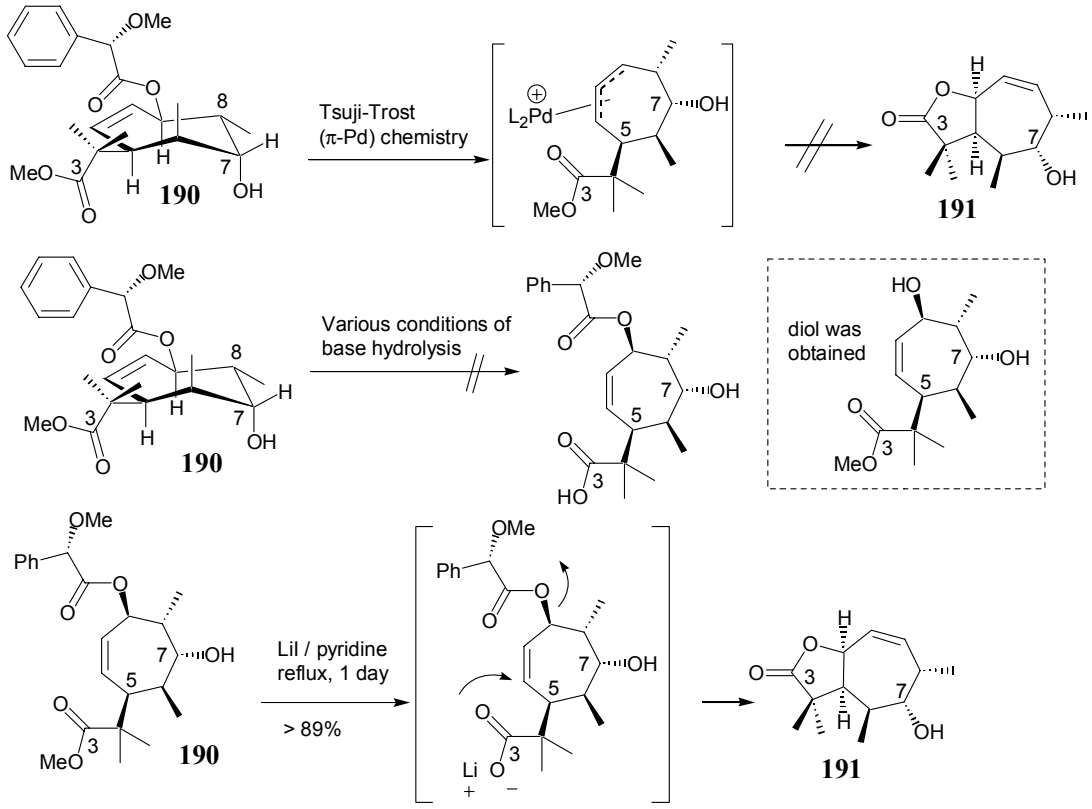


Scheme 2.21

Compound **191** is the key precursor to the 8-membered ring lactone **169** because its oxygen-bearing stereocenter at C_5 could be formed in a single step through a Baeyer-Villiger oxidation[118] *via* diol **167**. Needless to say, the C-O bond insertion at this position is crucial because it allows for a reductive ring opening of **169**, and the synthesis calls for a chelation controlled aldol at a latter stage to set the correct chirality

at C_3 of the natural product and in the end, the ketone moiety is required at this position (C_5) (Scheme 2.9).

Initially, the plan was to use π-Pd chemistry (Tsuji-Trost reaction)[119] (Scheme 2.22) to construct lactone **191** since hydroxyl **190** already posessed an excellent leaving group at C_9-position (an allylic acetate). However, there was some concern at the outset 6



Scheme 2.22

whether lactone **191** can be formed without prior conversion to the carboxylic acid. The desired carboxylic acid would require selective hydrolysis of the methyl ester in the presence of the unhindered allylic mandellic ester at the C_9 position. With this concern in mind, compound **190** was subjected to Tsuji-Trost reaction. However, as indicated in

scheme 2.22, it was found that without the presence of the carboxylic acid at C_3, the transformation did not work resulting in the loss of starting material **190** (Scheme 2.22). The strategy was abandoned when ester **190** could not be selectively hydrolyzed.

A similar 8-membered ring lactone (Figure 2.5) had previously been obtained by: 1) global base hydrolysis; 2) iodolactonization; 3) selective formation of the thionocarbonate; and 4) radical-induced *syn* elimination.[114c] This strategy had previously

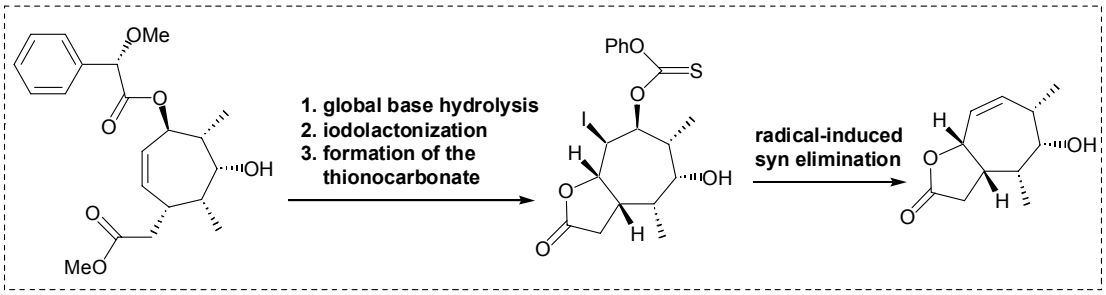
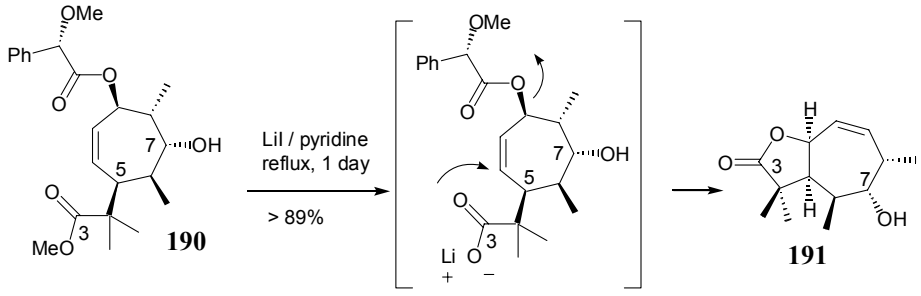
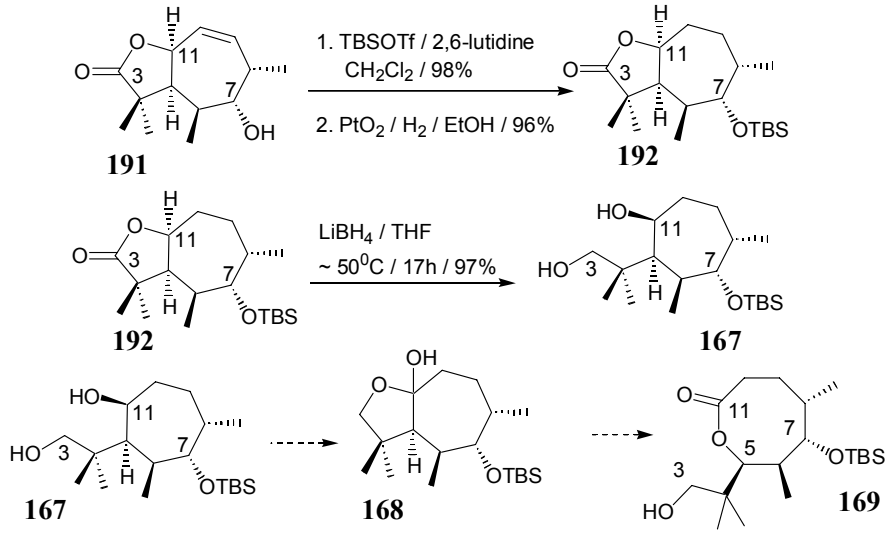


Figure 2.5: 8-membered ring lactone formation (earlier report).

been used in the Grieco group (Figure 2.5) for the synthesis of two-advanced fragments of Scytophycin C (C_{19}-C_{26} and C_{27}-C_{32}).[114c] However, the decision was made to pursue a different approach, and it was of considerable interest to ascertain whether dealkylation of the hindered ester could be achieved, allowing the Thorpe–Ingold effect (*gem*-dimethyl) to assist in the formation of the lactone **191**. After several failed attempts, the right conditions were found. Refluxing LiI in pyridine with **190** gave rise to the desired lactone **191** in excellent yield, $[\alpha]_D^{25}$ -14.3 (c 2.7, $CHCl_3$), (Scheme 2.22). Under the reaction conditions, it is reasonable to conclude that dealkylation occurs to generate a carboxylate anion intermediate, which can undergo a S_N2' reaction.



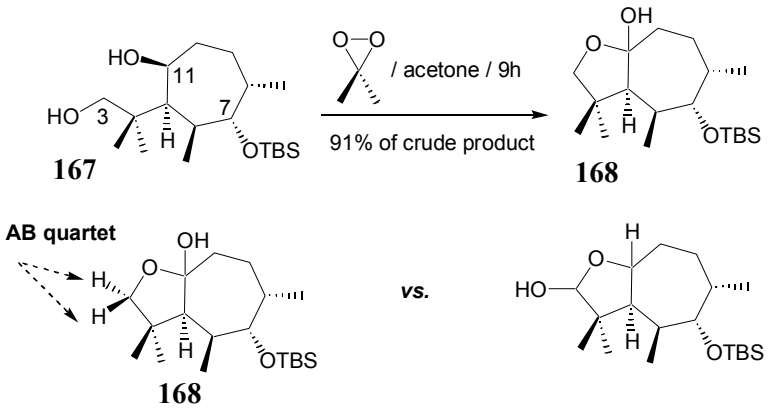
Having demonstrated that the formation of lactone **191** can be achieved in good yield, the stage was set for the conversion of lactone **191** into intermediate **169** *via* Baeyer-Villiger oxidation.[118] The construction of this 8-membered ring lactone **169** was accomplished as depicted in Scheme 2.23. The C_7-OH was protected as a silyl ether



Scheme 2.23

(TBSOTf, 2,6-lutidine) followed by hydrogenation using Adams' catalyst (PtO_2, H_2) in ethanol to provide the cis-fused lactone **192**, $[\alpha]_D^{25}$ -17.2 (c 3.1, $CHCl_3$). This lactone was reduced ($LiBH_4$) to afford diol **167** in 97% yield. With diol **167** in hand, attention was

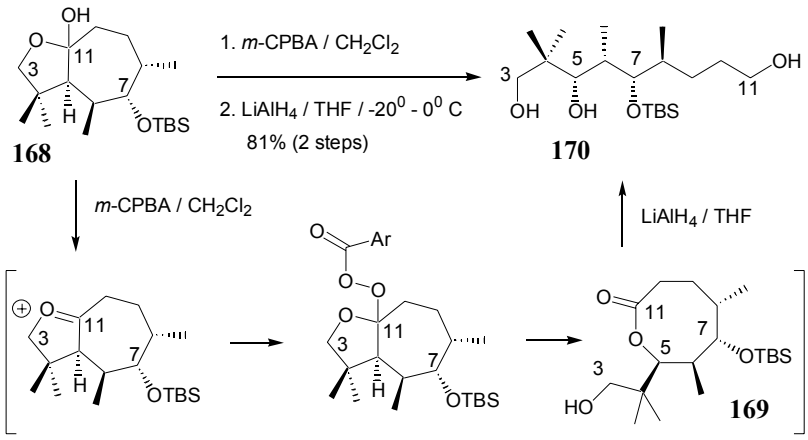
focused on oxidation of the secondary alcohol (C_{11}) in the presence of the hindered primary hydroxyl group. The attractiveness of the method lies in the fact that the cyclic hemiketal **168** can be directly subjected to the Baeyer-Villiger oxidation,[118] thus eliminating the protection-deprotection sequence as well as functional group transformations. After some experimentation and screening of the standard arsenal of oxidants, it was found that dimethyldioxirane[118] in actone was the reagent of choice to accomplish this critical task. Treatment of freshly prepared dimethyldioxirane with diol **167** in acetone resulted in a clean conversion to cyclic hemiketal **168** (Scheme 2.24). A clear AB quartet (H-NMR) indicated that the oxidation went the right way and



Scheme 2.24

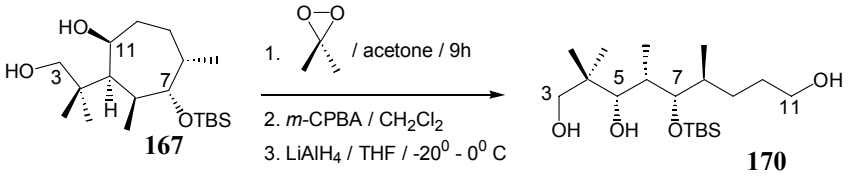
produced the right cyclic hemiketal **168**. Having demonstrated the direct conversion to the cyclic hemiketal, attention was focused on the Baeyer-Villiger ring expansion, a transformation that had previously been demonstrated in the Grieco laboratory[118] for the construction of eight-membered ring lactones.

As depicted (Scheme 2.25), cyclic hemiketal **168** was treated with *m*-chloroperoxybenzoic acid giving rise to crude lactone **169**, which was directly subjected



Scheme 2.25

to reduction ($LiAlH_4$) to afford triol **170**, $[\alpha]_D^{25}$ +9.5 (c 2.1, CH_2Cl_2), in good yield (81% for two steps). Gratifyingly, these conditions allow for the formation of triol **170** in a delicate set of transformations from diol **167** in good yield with only one purification process (Scheme 2.26).



Scheme 2.26

At this stage, it was anticipated that the triol fragment **170** would lend itself to the construction of the terminal olefin C_{10}-C_{11} so hydroboration, *via* a 9-BBN solution, could be used for Suzuki coupling with fragment B (Figure 2.6). The other end of this fragment would allow for the installation of the remaining stereocenter (C_3-hydroxyl) by a chelation controlled aldol. With the availability of triol **170**, conversion to fragment **175**

proved straightforward. As depicted in Scheme 2.27, the 1,3-diol was protected as its

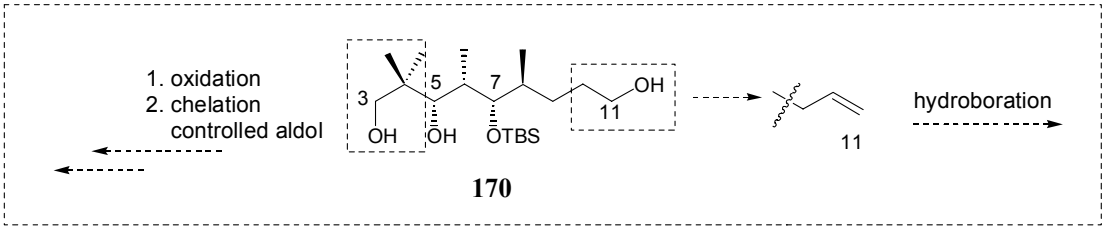
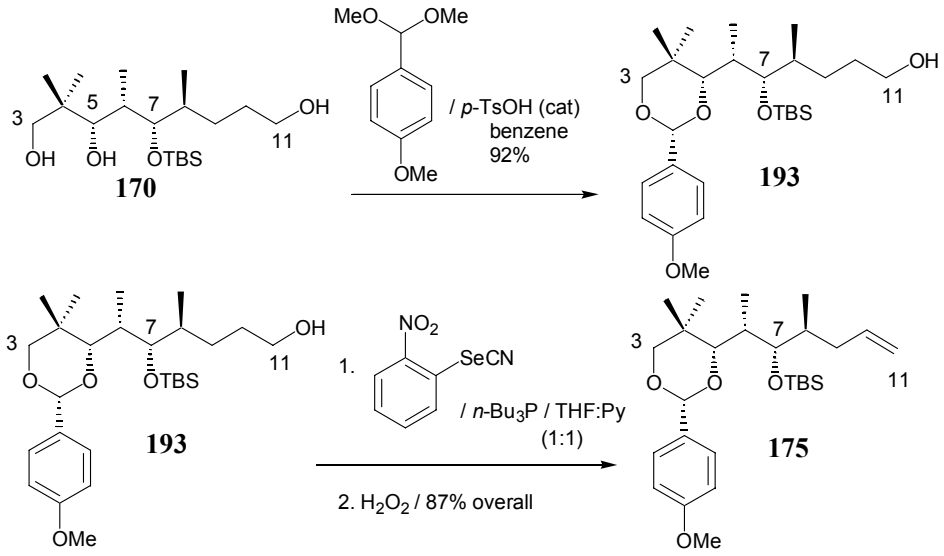


Figure 2.6: Triol functional group transformations.

p-methoxybenzylidene acetal (*p*-$MeOC_6H_4CH(OMe)_2$, *p*-TsOH), and the 1^0-hydroxyl group at C_{11} was transformed into the corresponding olefin. This versatile protecting group (benzylidene acetal) is well suited, since one of the two C-O bonds of the acetal can be selectively cleaved for further elaboration, and the plan was to use the resulting *p*-

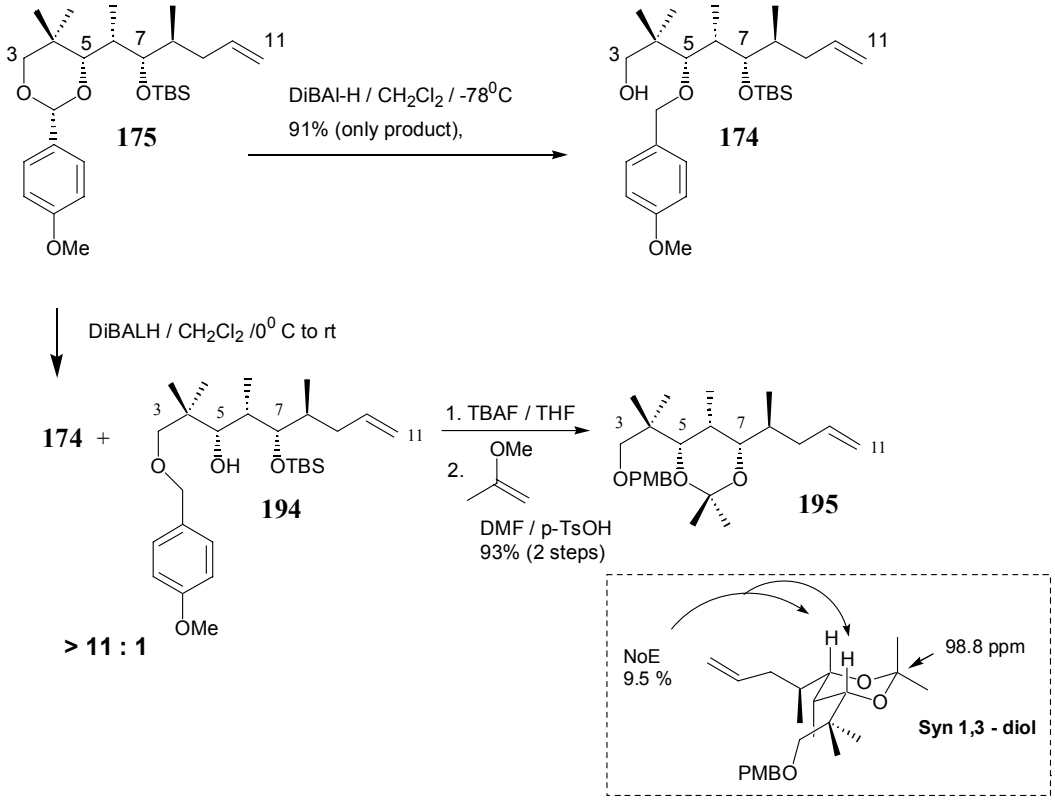


Scheme 2.27

methoxybenzyl ether at C_5 for the chelation controlled aldol to secure the final stereogenic center at C_3. With the formation of the acetal **193** ($[\alpha]_D^{25}$ +17.6 (c 1.8, CH_2Cl_2), attention was turned to the construction of the terminal olefin, which could be

obtained using Grieco's selenium chemistry.[121] As anticipated, treatment of **193** with *o*-nitrophenylselenocyanate and *n*-Bu_3P in co-solvent (THF/Pyridine/1:1) led cleanly to the corresponding selenide in good yield, which when subjected to oxidation-elimination proceeded smoothly to afford olefin **175**, $[\alpha]_D^{25}$ -35.03 (c 1.5, CH_2Cl_2), (Scheme 2.27).

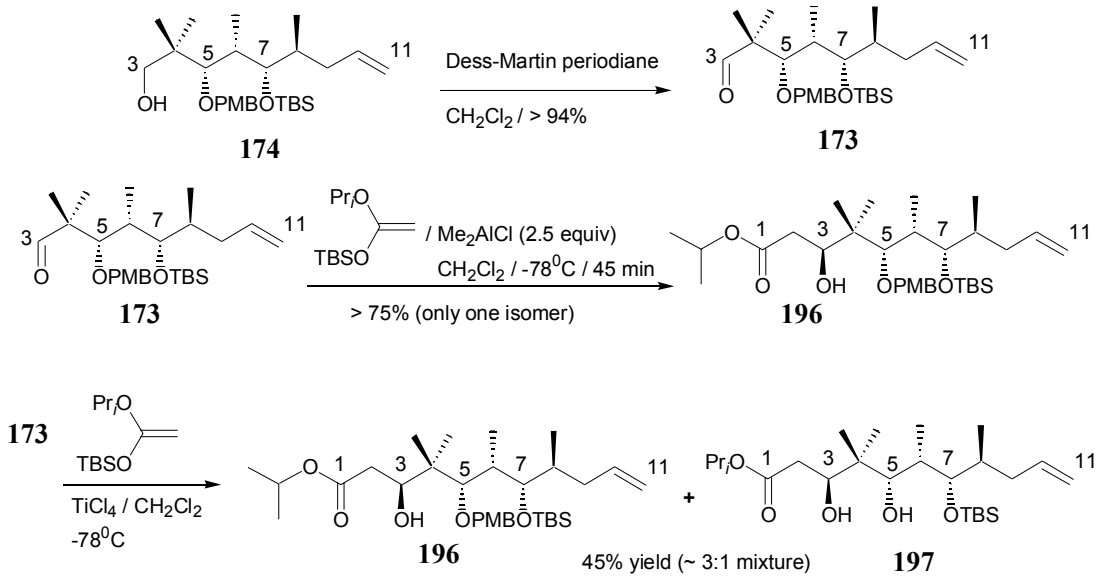
At this point, the synthesis called for a chelation controlled aldol to set the correct C_3 stereocenter of the molecule. It was anticipated that the pre-existing *para*-methoxybenzyl ether at C_5 would direct the process. The execution of this plan is shown in (Scheme 2.28). The acetal **175** was reduced regioselectively under Takano's protocol



Scheme 2.28

using DiBAL-H at –78^0 C,[122] which gave rise exclusively to the primary alcohol **174** in 91% yield. At higher temperature (0^0 C), the minor adduct **194** was observed and can

easily be transformed into the acetonide **195** for stereochemistry confirmation (C_5 and C_7).[123] The stage was set for incorporation of the aldol. The neopentyl alcohol **174** was converted into the corresponding aldehyde **173** *via* a Dess-Martin periodinane oxidation.[124] This crude aldehyde was subjected to chelation controlled aldol in the presence of dimethylaluminum chloride[125] (Scheme 2.29 & Figure 2.7) to afford only one diastereoisomer **196** (Scheme 2.29), $[\alpha]_D^{25}$ -3.1 (c .99, CH_2Cl_2). Titanium tetrachloride was also investigated, but the yield was low and the PMB-ether protecting group was cleaved under the reaction conditions. Use of $MgBr_2$ failed to promote the transformation and the neopentyl aldehyde **173** was recovered.



Scheme 2.29

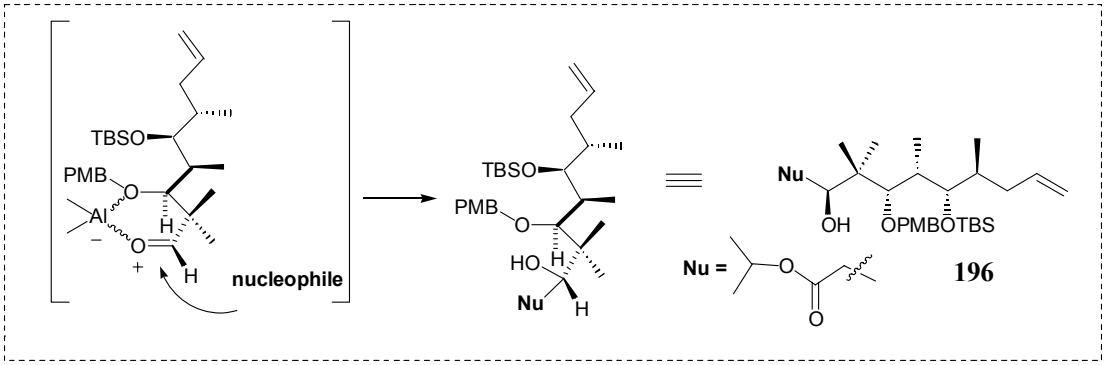


Figure 2.7: Chelation controlled aldol.

The stereochemical proof of the aldol addition process was readily determined. The strategy relied on intramolecular oxidative formation of the *p*-methoxybenzylidene acetal (PMP), which was accomplished by treatment of **196** under anhydrous conditions with DDQ.[126] A single diastereoisomer **198** was obtained and the stereochemistry was confirmed by nOe measurements (Figure 2.8). With the desired product in hand, it

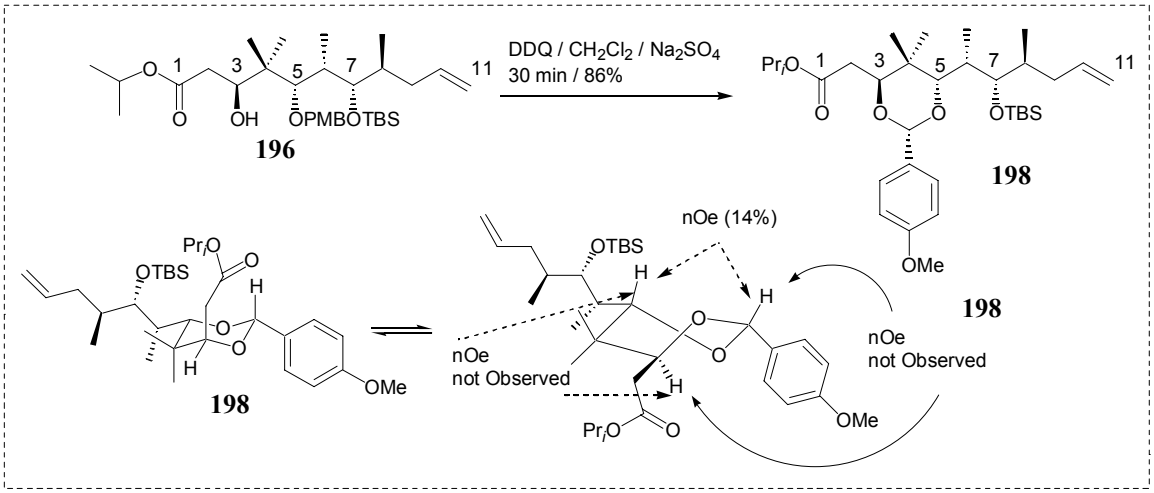
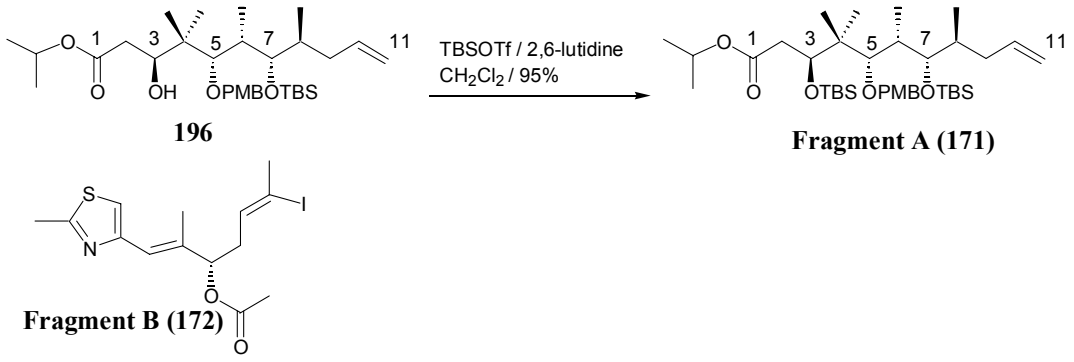


Figure 2.8: Confirmed stereochemistry of the aldol adduct.

remained only to protect the resulting alcohol **196** (Scheme 2.30) as a TBS-ether (TBSOTf, lutidine) affording fragment A (**171**), $[\alpha]_D^{25}$ -8.01 (c 1.8, CH_2Cl_2). With

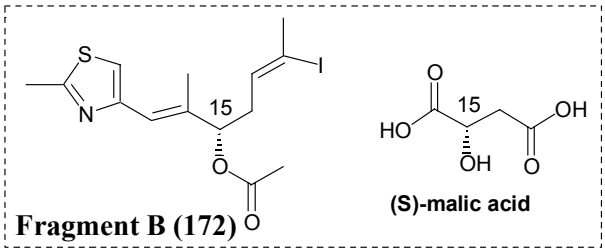
fragment A in hand, attention was turned to the construction of the vinyl iodide, fragment B, for coupling *via* a Suzuki reaction.



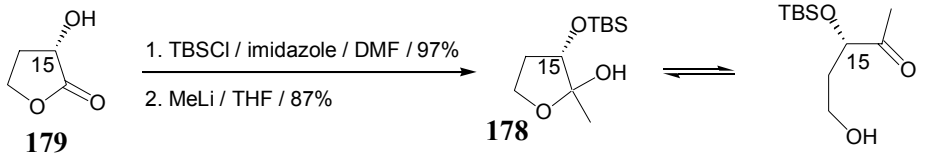
Scheme 2.30

Synthesis of Fragment B (172)

Recently, Schinzer and Shibasaki demonstrated a highly efficient route to fragment B (**172**).[88c, 88e] Both research groups employed a Wittig reaction to install the desired (Z)-vinyl iodide using iodomethyltriphenylphosphorane.[111] However, Schinzer and Shibasaki used different routes to obtain the key stereocenter at C_{15}. Rather than using (S)-malic acid as a source of chirality, Shibasaki demonstrated the usefulness of multifunctional asymmetric catalysis, such as a cyanosilylation of an aldehyde, to obtain the C_{15} chiral center.[88e]

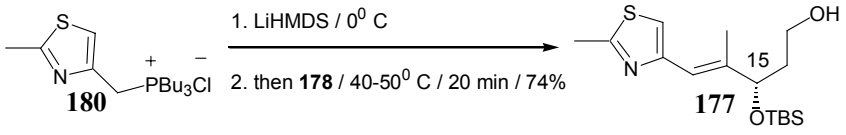


Readily available hydroxylactone **179**, (*S*)-(-)-α-Hydroxy-γ-butyrolactone, $[\alpha]_D^{25}$ -68 ^{0} (c 1.15, $CHCl_3$), served as the starting material for the construction of fragment B (**172**). As shown in (Scheme 2.31), the synthesis began with the protection of the C_{15}-



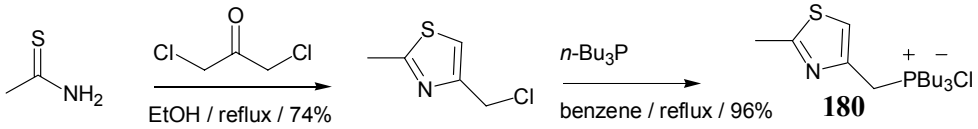
Scheme 2.31

OH (TBSCl, DMF, Im), followed by the addition of methyllithium to give **178** as a mixture of cyclic hemiketals and hydroxy ketone in 87 % yield.[88g] This mixture was subjected to a Wittig olefination using a slight modification of Schinzer's protocol,[88g] with tri-*n*-butyl phosphonium chloride **180** to afford the olefin **177** in good yield and excellent (E)-selectivity, $[\alpha]_D^{25}$ -32.7 (c 2.8, $CHCl_3$), (Scheme 2.32).[127] The (2-methylthiazol-4-yl)methyltri-*n*-butyl phosphonium chloride **180** was easily obtained through several routine steps. Condensation of thioacetamide and a solution of 1,3-



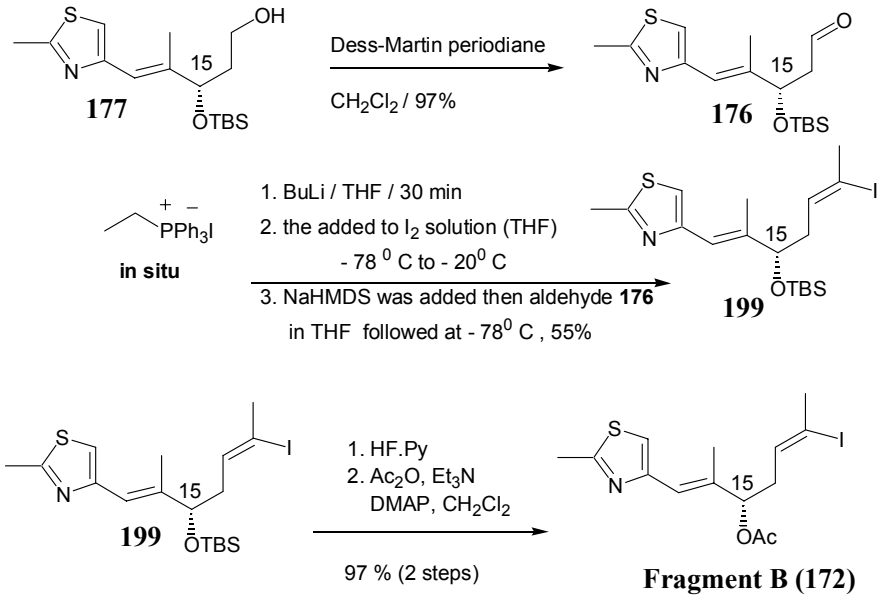
Scheme 2.32

dichloropropan-2-one in dry ethanol provided thiazole chloride in good yield (Scheme 2.33).[128] Application of Wang's protocol, the thiazole was reacted with tri-*n*-butylphosphine under reflux conditions for eight hours gave rise to a white solid **180** in 95% yield.[127]



Scheme 2.33

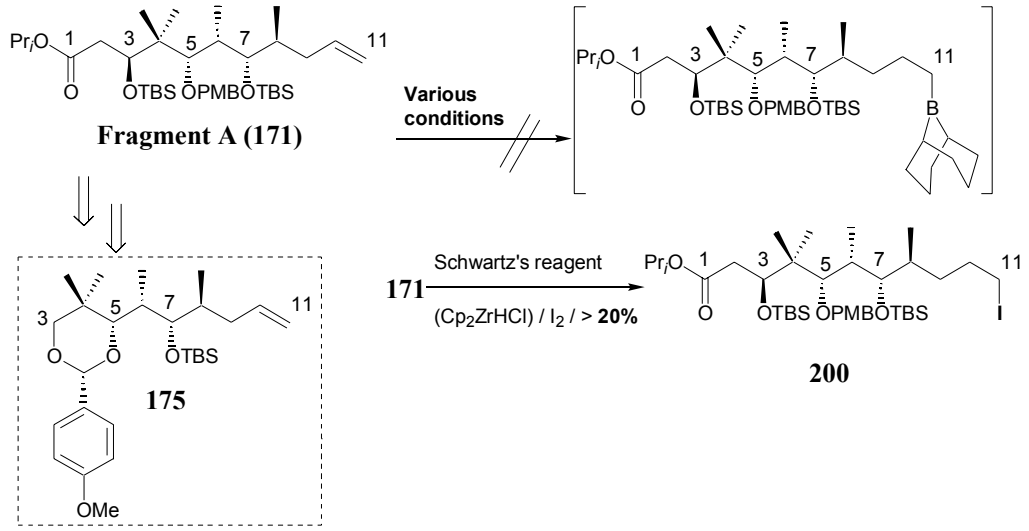
With compound **177** in hand, a few remaining steps were required to give fragment B **(172)**. The terminal hydroxyl group of compound **172** was subjected to oxidation (Dess-Martin periodiane) to provide aldehyde **176**,[88g] which was directly subjected to coupling with the α-iodoalkyl ylide, employing Zhao's protocol (Scheme 2.34).[111] The cis-vinyl iodide **199** was then treated with HF.pyridine to give alcohol **200**, which was protected as an acetate ester (Ac_2O, Et_3N, DMAP, CH_2Cl_2) to provide the known fragment B (**172**), $[\alpha]_D^{25}$ -24.3 (c 2.4, $CHCl_3$), lit. $[\alpha]_D^{25}$ -24.6 (c 1.2, $CHCl_3$),[88e, 88g] in 97% yield for two steps.



Scheme 2.34

Cross Coupling of Fragments A & B

With fragment A **(171)** in hand, the next step involved a hydroboration of the terminal olefin (C_{11}) for the Suzuki coupling. However, problems were encountered. Treatment of fragment A with 9-BBN (Scheme 2.35), proved unsuccessful and starting material was recovered in low yield. Despite repeated attempts, including the use of ultrasound,[129] raising the temperature, and changing reaction concentrations, efforts met with failure. One possible explanation for this is the potential for chelation by both

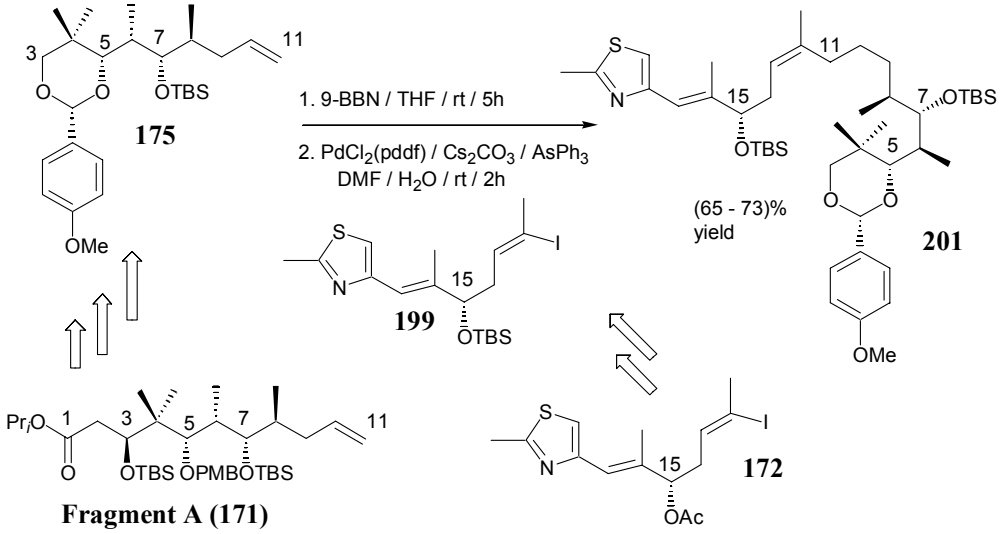


Scheme 2.35

the isopropyl ester (C_1) and the *p*-methoxybenzyl ether protecting group (C_5) to the electrophilic reagent (9-BBN). Or perhaps, the terminal olefin (C_{11}) of fragment A is not as accessible for hydroboration due to its many conformations in solution. Attempts were made to convert fragment A into the corresponding alkyl iodide **200** for further elaborations, but it was soon abandoned due to low yields (Scheme 2.35). With the availability of compound **175** and knowing that the stereogenic center at C_3 can be obtained through a chelation controlled aldol (Scheme 2.29), the decision was made to

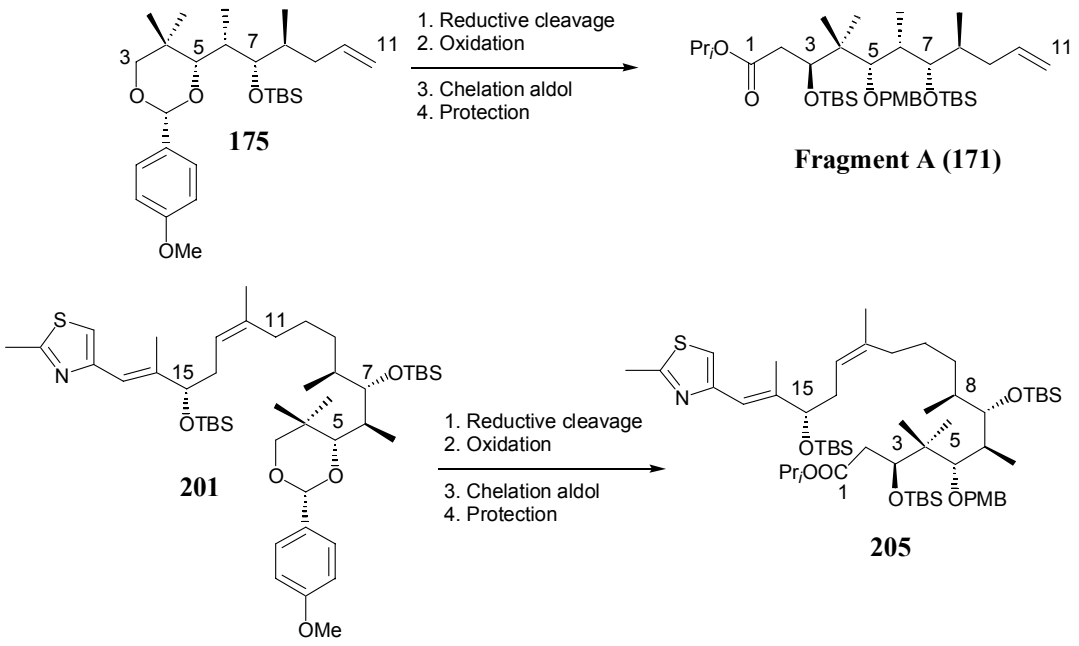
use the precursor of fragment A **(171)**, acetal **175**, for hydroboration bearing in mind that the same chemistry (**175➔171**) could probably be applied to the resulting coupling product **201** (Scheme 2.36).

Exposure of olefin **175** to 9-BBN solution for 5 hours at room temperature provided the borane alkyl intermediate, and the subsequent coupling reaction with vinyl iodide **199** in the presence of $PdCl_2$(dppf) gave the desired product **201**, $[\alpha]_D^{25}$ -16.3 (c .82, CH_2Cl_2), in good yield (65 –70%) (Scheme 2.36). The new route requires the C_{15}-



Scheme 2.36

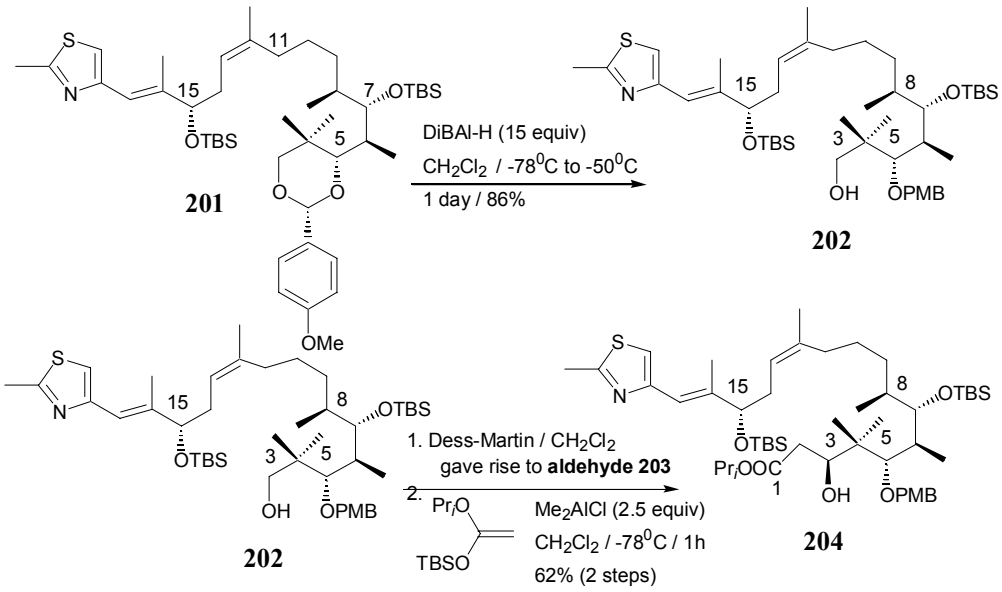
OTBS instead of the acetate protecting group because one of the two C-O bonds of the acetal **201** will be cleaved (*via* DiBAl-H) to give the corresponding primary alcohol. As was alluded to earlier, the same chemistry that was used in fragment A (**175➔171**) now will be applied to the resulting Suzuki adduct **201 (201➔205)**, scheme 2.37.



Scheme 2.37

Completion of (-)-Epothilone B

The synthesis of compound **204** from acetal **201** is summarized in (Scheme 2.38). The *p*-methoxy benzylidene group in **201** was cleaved regioselectively using DiBALH[122]



Scheme 2.38

(15 equiv) leading to primary alcohol **202** (86% yield, $[\alpha]_D^{25}$ +2.6 (c 1.3, CH_2Cl_2)), which upon subjecting to oxidation *via* Dess-Martin periodinane in CH_2Cl_2 afforded aldehyde **203**. Lewis acid, dimethyl aluminium chloride (2.5 equiv), was added dropwise to a cold (-78^0 C) solution of aldehyde **203** in CH_2Cl_2 to promote chelation between the *p*-methoxybenzyl ether (PMBO) and the aldehyde carbonyl. The nucleophile, TBS-isopropoxy ketene acetal, was then added giving rise to the aldol product 204 in 62% overall yield ($[\alpha]_D^{25}$ -2.2 (c 3.2, CH_2Cl_2)). The configuration at C_3 was determined by nOe measurements after DDQ oxidation[126] under anhydrous conditions to form the *p*-methoxybenzylidene acetal. The importance of the PMB ether-protecting group is without question here since it allowed for several key transformations (Figure 2.9). From

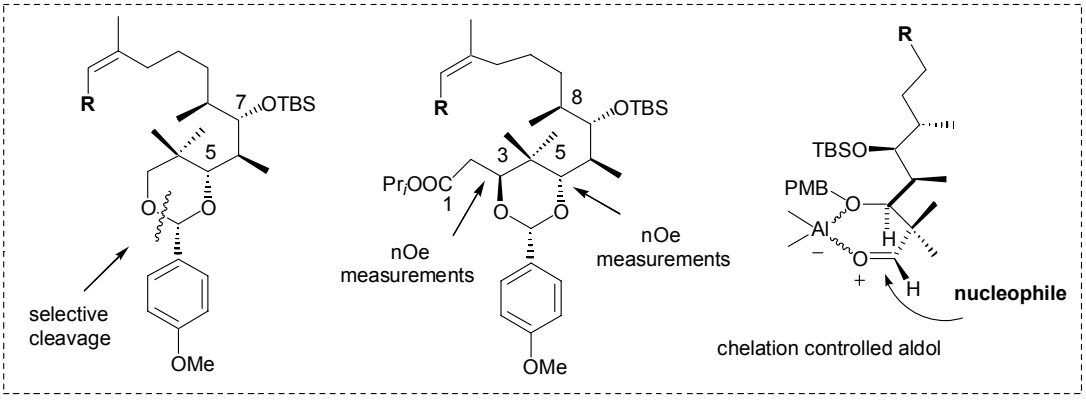
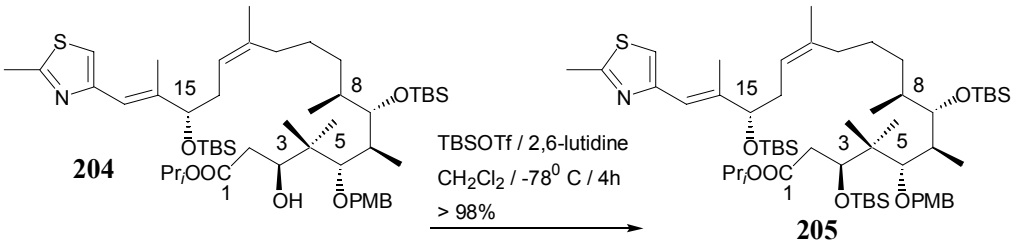


Figure 2.9: PMB ether-protection group.

selective cleavage of one of the C-O bonds of the acetal **201** to the nOe study and not to mention, it participated in the chelation controlled aldol which provided the desired product. Protection of the resultant alcohol **204** with TBSOTf in the presence of 2,6-lutidine afforded the fully protected intermediate **205** (Scheme 2.39).



Scheme 2.39

At this juncture, it should be emphasized that the isopropyl ester of compound **205** would, perhaps, be problematic for base saponification. However, from the outset, it was found that the TBS-isopropoxy ketene acetal (**A**) gave the best result (yield and selectivity) compared to the methyl TBS-ketene acetal (**B**) and the phenyl TBS-ketene acetal (**C**). For example, when ketene acetal **B** was employed for chelation controlled

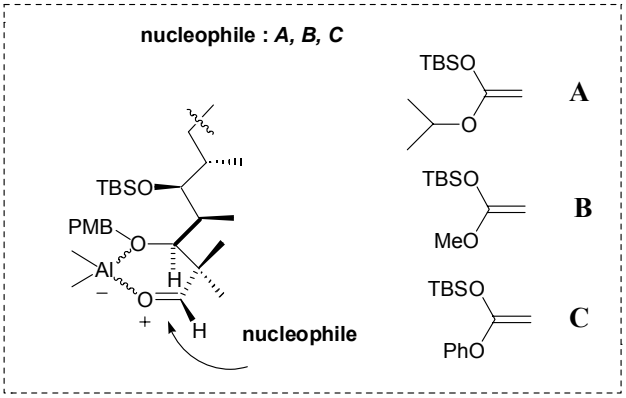
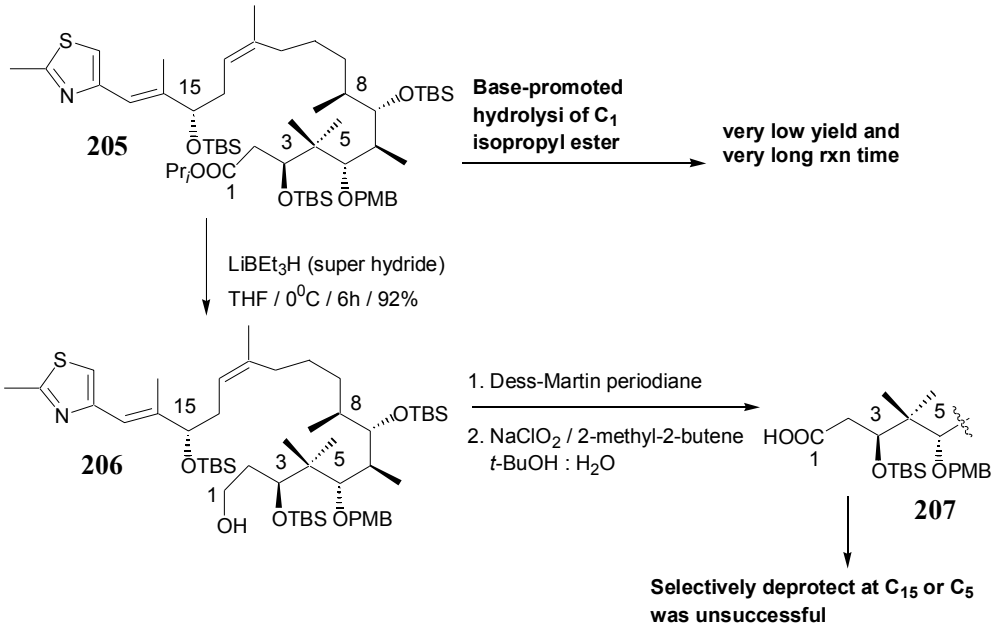


Figure 2.10: Examined of other ketene acetals.

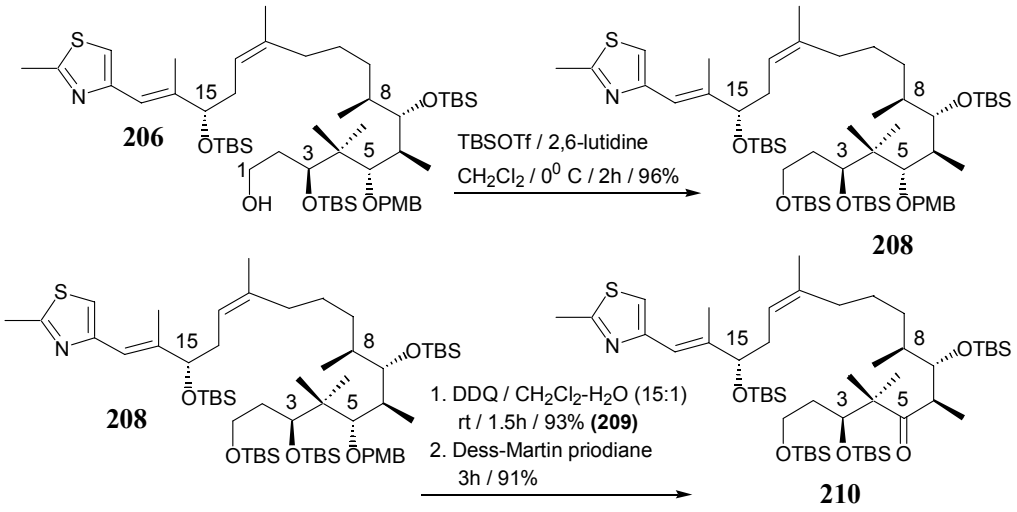
aldol, mixture of diastereomers was obtained in low yield. Nucleophile **C** was found to be unstable and not efficient. In any case, neopentyl aldehyde **203** was recovered. Indeed, base saponification met with difficulties (Scheme 2.40). Despite repeated attempts to hydrolyze compound **205**, efforts were consistently unsuccessful.[131]



Scheme 2.40

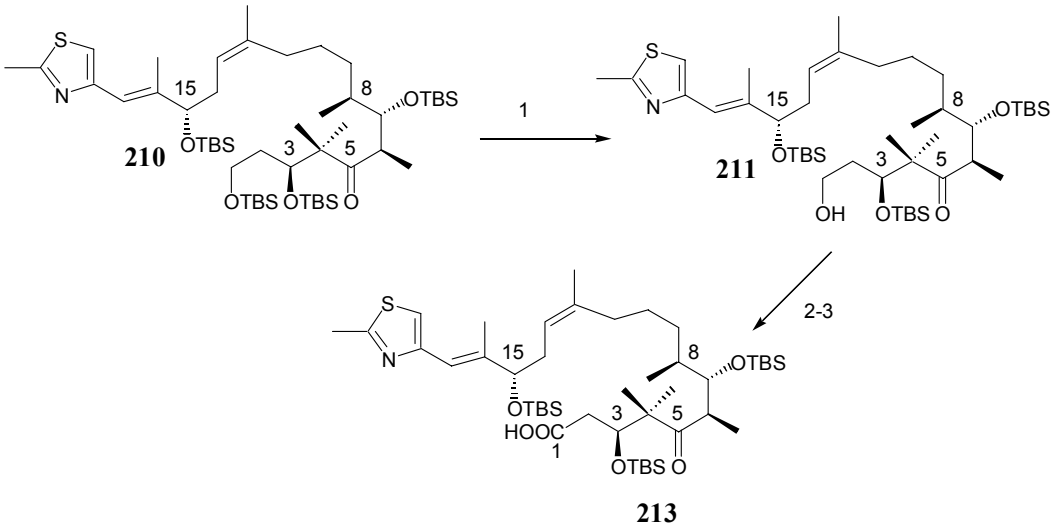
Frustrated by the lack of success, the decision was made to reduce the ester to the primary alcohol, knowing that it will eventually have to be oxidized to the carboxylic acid. Compound **205** was reduced, *via* superhydride ($LiBEt_3H$) (0^0C for 6 hours) and afforded primary alcohol **206**, $[\alpha]_D^{25}$ -2.6 (c 2.4, CH_2Cl_2), (Scheme 2.40) in 92% yield. Interestingly, it was found that with the carboxylic acid **207** (oxidation of **206** using Dess-Martin reagent followed by $NaClO_2$-NaH_2PO_4), all attempts to deprotect at C_{15}-OTBS selectively, setting up for Yamaguchi lactonization, cannot be done. Also the C_5-OPMB cannot be removed using DDQ in the presence of the carboxylic acid moiety at C_1. So with the realization that if the saponification proceeded smoothly, deprotection at C_{15} or C_5 is an issue (Scheme 2.40). Based on these results, the decision was made to protect the resulting alcohol after superhydride reduction. Compound **206** was treated

with TBSOTf and 2,6-lutidine in CH_2Cl_2 to give **208**, $[\alpha]_D^{25}$ -3.8 (c 2.5, CH_2Cl_2), in 96% yield (Scheme 2.41).



Scheme 2.41

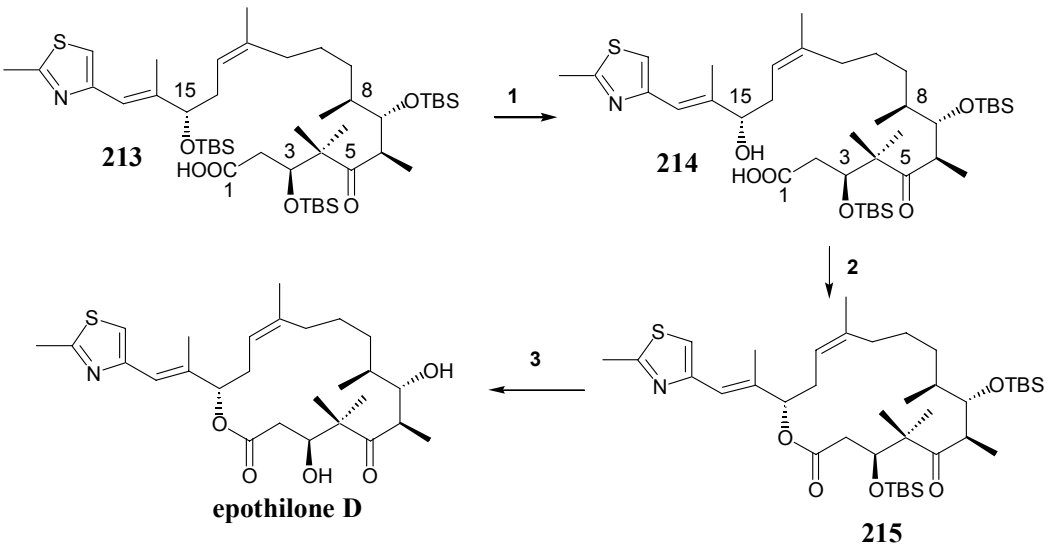
At this stage, all that remained to reach the known intermediate was to adjust a few functional groups. Removal of the PMB group at C_5 was performed first through oxidative cleavage with DDQ in aqueous CH_2Cl_2[126, 132] to give alcohol **209** in 93% yield. This alcohol **209** was then subjected to oxidation (Dess-Martin with excess buffered pyridine) which led to the tetrakis-silyl ether **210**, $[\alpha]_D^{25}$ -10.6 (c .52, $CHCl_3$), (Scheme 2.41). The completion of the total synthesis began with liberation of the primary alcohol by exposure to acidic methanol solution (CSA, CH_2Cl_2/MeOH) which provided alcohol **211** followed by two-step oxidation led to the known carboxylic acid **213** (Scheme 2.42) identical ([α], IR, MS, ^1H and ^{13}C NMR) to an intermediate from Nicolaou's synthesis of epothilone B.[102] Nicolaou and co-workers have shown that this precursor can be converted to (-)-epothilone B by a four-step sequence consisting of selective deprotection



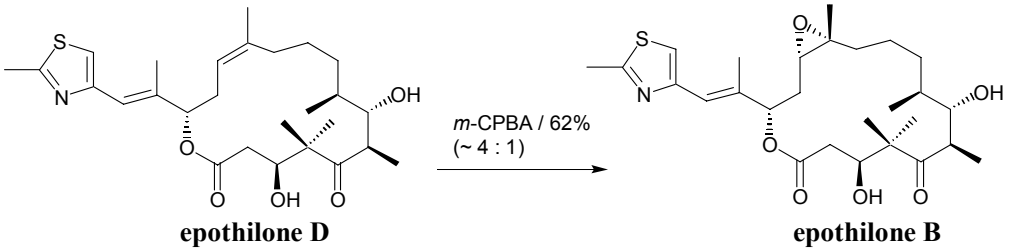
1. CSA / CH_2Cl_2 : MeOH (1:1) / 5h / 87%
2. Dess-Martin Periodiane / pyridine / CH_2Cl_2 (crude aldehyde 212)
3. $NaClO_2$ / 2-methyl-2-butene / *t*-BuOH : H_2O (94% , 2 steps)

Scheme 2.42

, Yamaguchi macrolactonization, global deprotection, and epoxidation. The carboxylic acid **213** has been previously converted to epothilone by Schinzer,[133] and Nicolaou[102] and thus represents a formal total synthesis of (-)-epothilone B. As highlighted in the following sections, the completion of the total synthesis began with removal of the C_{15}-OTBS ether (TBAF/THF) to provide the hydroxy acid **214**, $[\alpha]_D^{25}$ -10.9 (c 2.2, $CHCl_3$), in 75% yield. Macrolactonization proceeded smoothly using the Yamaguchi method[134] to give the 16-membered lactone **215** in 63% yield (Scheme 2.43). Deprotection of the C_3 and C_7 silyl ethers was carried out using excess buffered HF.py, providing epothilone D. Finally, incorporation of the C_{12}-C_{13} epoxide was carried out by exposure to *m*-CPBA, yielding epothilone B with a diastereoselectivity of ~ 4:1 and 62% yield (Scheme 2.43).

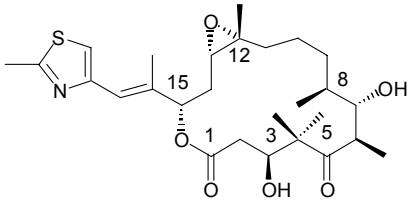


1. TBAF / THF / rt / 75% (**214**)
2. Yamaguchi's reagent / Et_3N / DMAP / toluene / 63% (**215**)
3. Excess buffered HF.pyridine / rt / 2 days / 94%



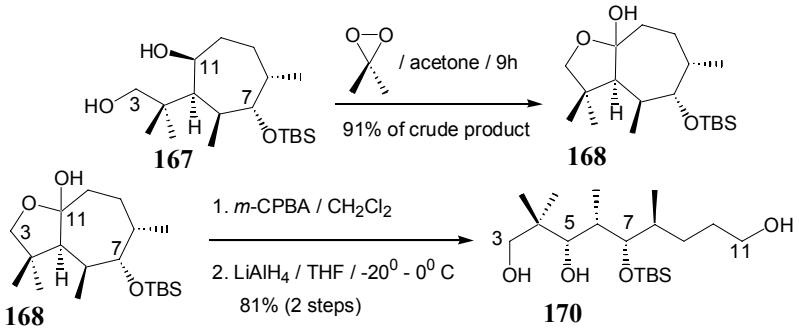
Scheme 2.43

Conclusions

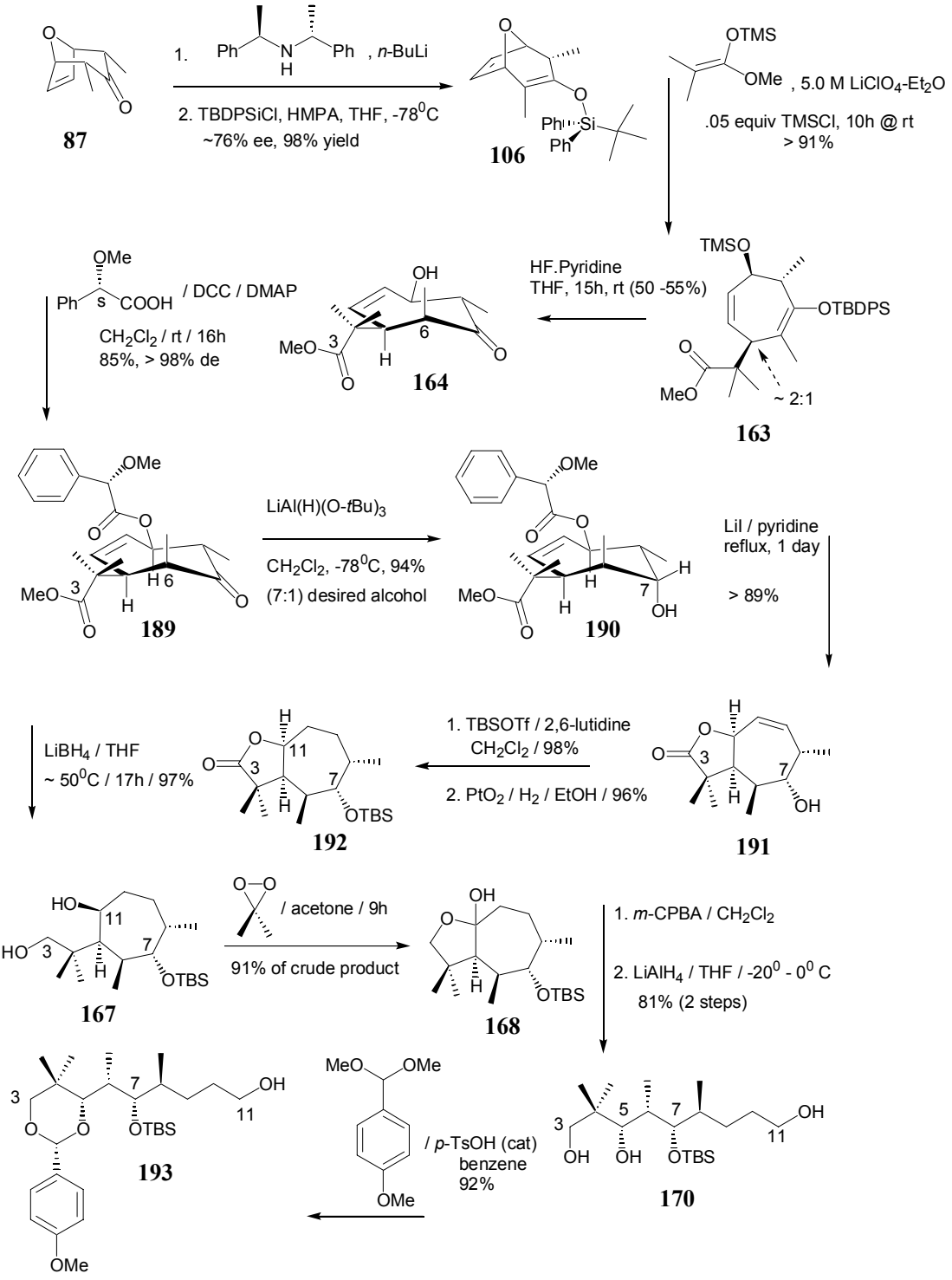


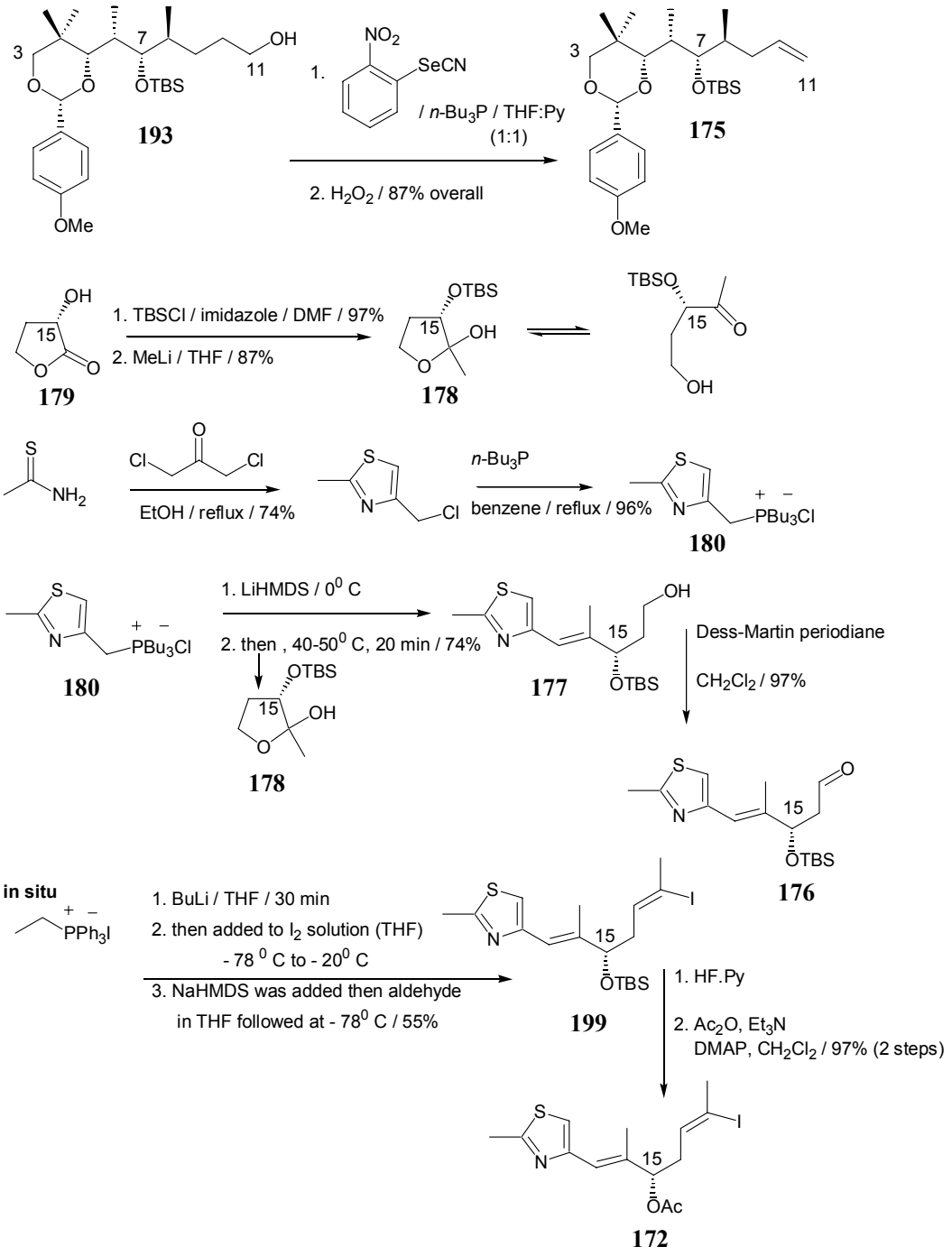
epothilone B

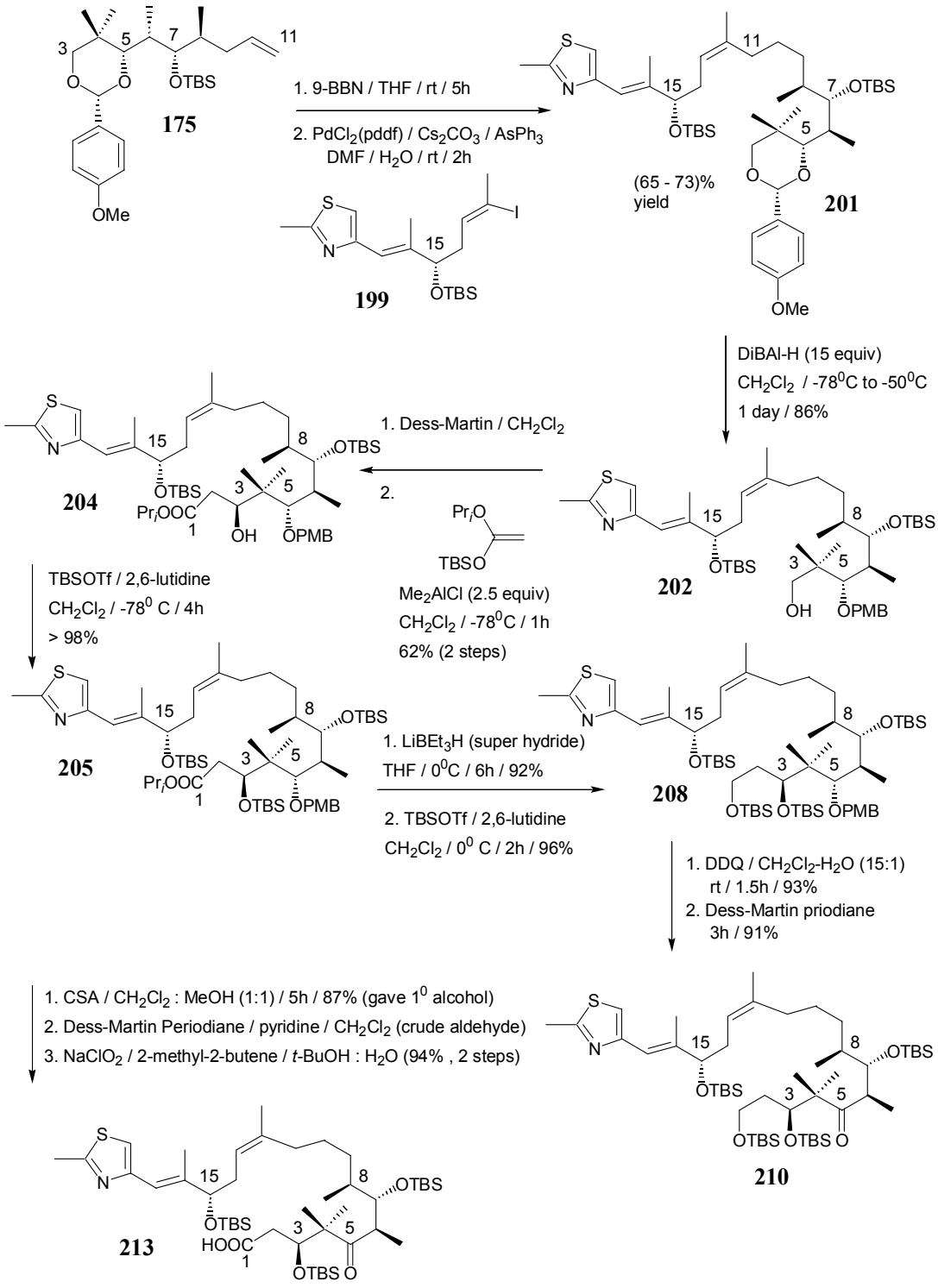
In summary, a total syntheses of **(-)-epothilone B** and **D** has been accomplished. The route is highlighted by the generation of silyl enol ether **106** using a chiral base for enantioselective deprotonation. Compound **106** was shown to be capable of undergoing direct bridgehead ring opening in LPDE with an assist from TMSCl leading to the formation of a functionalized cycloheptadiene **163** possessing not only the quaternary cabon atom at C_4, but all the necessary carbon atoms needed for further elaboration into the C_3-C_{11} fragment of epothilone. The synthesis features a Baeyer-Villiger oxidation of the cyclic hemiketal **168**, which was obtained *via* from a selective oxidation of diol **167**. Not only did this transformation install an important C-O bond at C_5, but also led to a chelation controlled aldol to set the correct chirality at C_3 and in the end, it transformed into the required ketone.

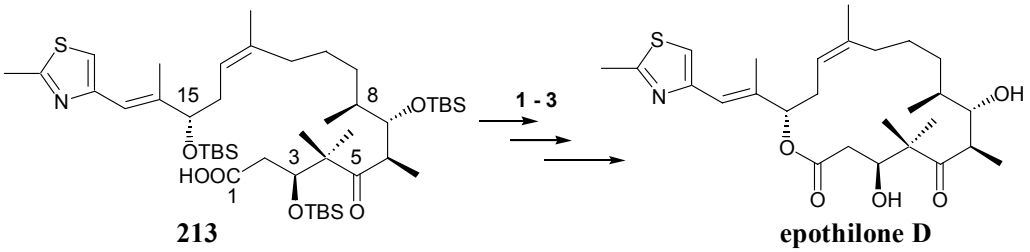


Overall Process



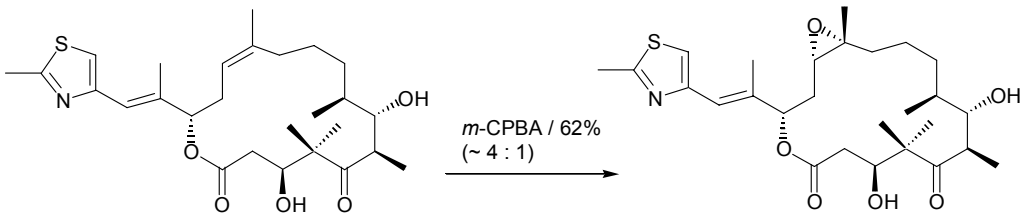

193
1. / n-Bu3P / THF:Py (1:1)
2. H2O2 / 87% overall
175
179
1. TBSCl / imidazole / DMF / 97%
2. MeLi / THF / 87%
178
180
1. LiHMDS / 0^0 C
2. then , 40-50^0 C, 20 min / 74%
177
Dess-Martin periodiane
CH2Cl2 / 97%
176
in situ
1. BuLi / THF / 30 min
2. then added to I2 solution (THF)
- 78 ^0 C to - 20^0 C
3. NaHMDS was added then aldehyde in THF followed at - 78^0 C / 55%
199
1. HF.Py
2. Ac2O, Et3N
DMAP, CH2Cl2 / 97% (2 steps)
172


175
1. 9-BBN / THF / rt / 5h
2. PdCl2(pddf) / Cs2CO3 / AsPh3
DMF / H2O / rt / 2h
199
(65 - 73)%
yield
201
DiBAl-H (15 equiv)
CH2Cl2 / -78°C to -50°C
1 day / 86%
202
1. Dess-Martin / CH2Cl2
2.
Me2AlCl (2.5 equiv)
CH2Cl2 / -78°C / 1h
62% (2 steps)
204
TBSOTf / 2,6-lutidine
CH2Cl2 / -78° C / 4h
> 98%
205
1. LiBEt3H (super hydride)
THF / 0°C / 6h / 92%
2. TBSOTf / 2,6-lutidine
CH2Cl2 / 0° C / 2h / 96%
208
1. DDQ / CH2Cl2-H2O (15:1)
rt / 1.5h / 93%
2. Dess-Martin priodiane
3h / 91%
210
1. CSA / CH2Cl2 : MeOH (1:1) / 5h / 87% (gave 1° alcohol)
2. Dess-Martin Periodiane / pyridine / CH2Cl2 (crude aldehyde)
3. NaClO2 / 2-methyl-2-butene / t-BuOH : H2O (94% , 2 steps)
213



213 **epothilone D**

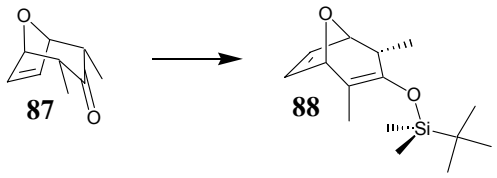
1. TBAF / THF / rt / 75%
2. Yamaguchi's reagent / Et_3N / DMAP / toluene / 63%
3. Excess buffered HF.pyridine / rt / 2 days / 94%



epothilone D **epothilone B**

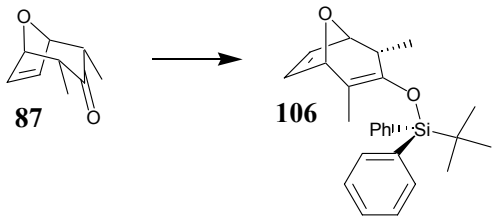
EXPERIMENTAL

General Procedures. Unless otherwise stated, solvents were dried by distillation under Argon, from sodium (Toluene, Benzene), sodium benzophenone ketyl (Ether, Tetrahydrofuran), CaH_2 (Methylene Chloride, DMF, MeCN, and *Tri*-ethyl amine, Chrolotrimethylsilane, *di*-isopropyl amine), and Mg (Methanol, Ethanol). DDQ was recrystallized from benzene before use. All other commercially available reagents were used without further purification unless specified otherwise. All reactions were performed in oven-dried glassware under Argon. Chromatography and chromatographic refers to flash column chromatography on silica gel. Analytical thin-layer chromatography (TLC) was performed on precoated glass-backed plates (Merck silica gel 60 F_{254}) and visualized by using either a UV lamp, phosphomolybdic acid (PMA), sulfuric acidic/anisaldehyde. Melting points (mp) are uncorrected. Optical rotations are reported in g/100 mL. Infrared spectra (IR) were measured as film on single-crystal silica plates and reported in wavenumbers (cm^{-1}). High-resolution mass spectra were obtained using electron ionization (EI). Proton and carbon nuclear magnetic resonance (^1H, ^{13}C NMR) spectra were recorded on a Bruker DPX-250, 300, or 500 MHz. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0) and peaks are reported as a singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). Peaks may also be described as broad (br).



(1S*,4S*,5S*)-*tert*-Butyl-(2,4-dimethyl-8-oxa-bicyclo[3.2.1]octa-2,6-dien-3-yloxy)-dimethyl-silane (88).

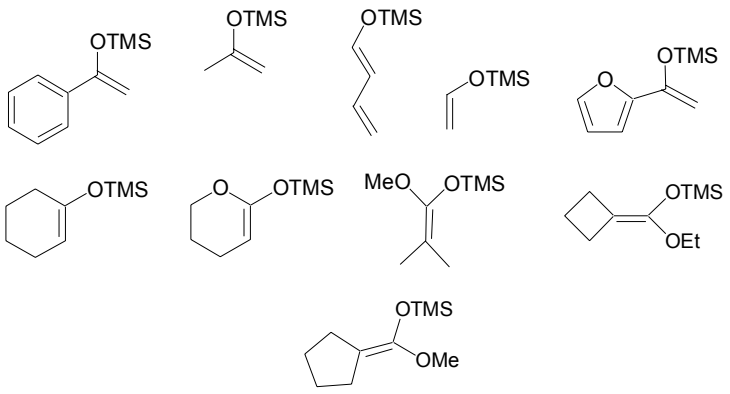
Diisopropylamine (773 μL, 5.52 mmol, 1.2 equiv) in 22.4 mL of THF at 0^0 C was treated with *n*-BuLi (2.21 mL, 5.52 mmol, 1.2 equiv). After 30 min, the reaction flask was cooled to -78^0 C before the addition of the ketone solution **87** (.7g, 4.61 mmol) in 2.8 mL of THF. Stirred for 1h at that temperature before the addition of HMPA (2.62 mL) followed by *tert*-butyldimethyl silyl chloride (5.52 mmol) in 1.4 mL of pentane. Dry ice was removed and stirred continuously for an additional hour. Saturated aqueous NH_4Cl and ether were added sequentially. The organic phase was washed with brine and dried (Na_2SO_4), filtered, and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 5% EtOAc-Hexanes) furnished 1.10 g of **88** (4.15 mmol, 90%): R_f 0.85 (EtOAc-Hexanes, 2:4); IR (neat) *v* 2931, 2858, 1670, 1473, 1311, 1255, 1179, 1052, 898, 838, 778 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.40 (d, J = 6.0 Hz, 1H), 5.70 (dd, J = 6.0, 1.8 Hz, 1H), 4.72 (dd, J = 6.3, 1.8 Hz, 1H), 4.45 (s, 1H), 3.20 (m, 1H), 1.51 (d, J = 2.1 Hz, 3H), .98 (s, 9H), .76 (s, 3H), .05 (s, 3H), -0.05 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 143.1, 139.2, 126.6, 117.0, 82.0, 80.0, 36.3, 26.6, 18.0, 12.3, 10.1, -4.1, -4.4; high resolution MS (EI): calcd for $C_{15}H_{26}O_2Si$ (M^+) *m/e* 266.1703, found 266.1702.



(1S*,4S*,5S*)-*tert*-Butyl-(2,4-dimethyl-8-oxa-bicyclo[3.2.1]octa-2,6-dien-3-yloxy)-diphenyl-silane (106) .

To a solution of diisopropylamine (4.92 mL, 35.10 mmol, 1.3 equiv) in dry THF (108 mL) was added dropwise *n*-BuLi (16.88 mL, 2.0 M in cyclohexane, 33.75 mmol, 1.25 equiv) at 0^0 C, stirred for 30 min, and then cooled to – 78^0 C. To this cold solution, was added dropwise a solution of [3.2.1] ketone **87**(4.11 g, 27.00 mmol) in THF (36 mL) over a period of 45 min *via* syringe pump. After complete addition, the mixture was stirred for an additional 30 min at the same temperature. HMPA (25 mL) was added *via* syringe pump over a period of 30 min, followed by TBDPSCl (9.11 mL, 35.1 mmol, 1.3 equiv) over a period of 45 min *via* syringe pump at – 78^0 C. The mixture was allowed to warm to – 50^0 C for 1 day. Saturated aqueous NH_4Cl and ether were added sequentially. The organic phase was washed with brine and dried (Na_2SO_4), filtered, and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 5% EtOAc-Hexanes) furnished 10.34 g of **106** (26.46 mmol, 98%): R_f 0.82 (EtOAc-Hexanes, 2:4); IR (neat) *v* 2931, 2856, 1668, 1467, 1427, 1310, 1180, 1112 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.76 - 7.67 (m, 4H), 7.44 - 7.34 (m, 6H), 6.64 - 6.61 (dd, J = 6.0, 1.7 Hz, 1H), 5.96 - 5.94 (dd, J = 6.0, 1.7 Hz, 1H), 4.78 - 4.75 (dd, J = 6.2, 1.7 Hz, 1H), 4.39 (d, J = 1.7 Hz, 1H), 2.60 - 2.56 (m, 1H), 1.30 (d, J = 2.0 Hz, 3H), 1.08 (s, 9H), .78 (d, J = 6.2

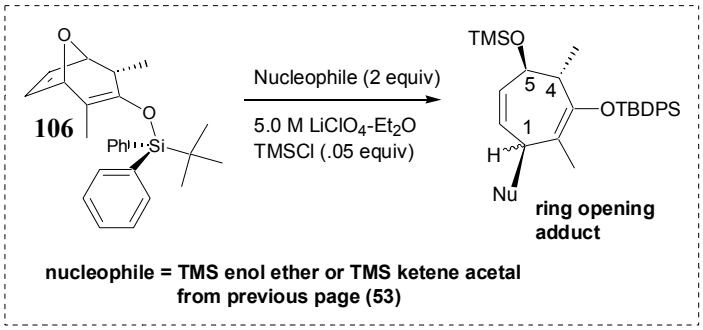
Hz, 3H); ^{13}C NMR (250 MHz, C_6D_6) δ 144.1, 139.2, 136.0, 135.9, 134.5, 134.3, 130.1, 130.0, 128.4, 127.4, 116.8, 82.3, 80.8, 36.7, 27.0, 20.0, 13.9, 11.3; high resolution MS (EI): calcd for $C_{25}H_{30}O_2Si$ (M^+) *m/e* 390.2016 , found 390.2015.



General Procedure

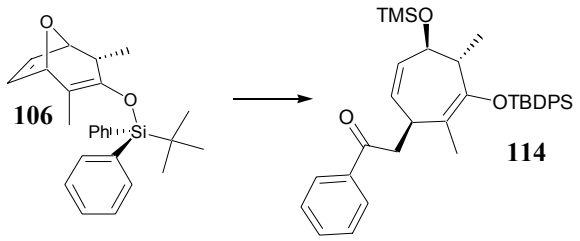
(a) House, H. O.; Czuba, L. J. *J. Org. Chem*. **1969**, 34, 2324-2336. (b) Some can be obtained from Aldrich. (c) To a stirred solution of lithium diisopropylamide [0.05 mol, prepared at 0^0C from diisopropylamine (5.05g, 0.05 mol) and *n*-BuLi (0.05 mol) in THF (50mL)] cooled at -78^0C is added over 10 min the appropriate ketone or ester (0.05 mol). The stirred solution is maintained at -78^0C for 30 min and TMSCl (0.1 mol, freshly distilled from CaH_2) is added during 10 min. After 15 min at this temperature, the mixture is allowed to warm to room temperature. After 1h, the mixture is concentrated on a rotary evaporator; a calcium chloride trap being placed between water pump and apparatus. The residue is washed with pentane, filtered, pentane evaporated, and the product is distilled under reduced pressure.

In many cases, considerable decomposition occurred during aqueous work up. Therefore, crude product was subjected directly to distillation after filtered and removal of solvent.



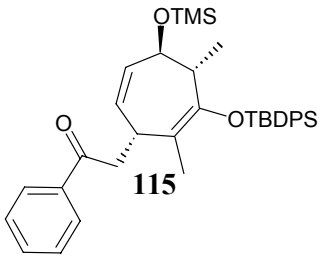
General Procedure ***(Representative procedure for the ring-opening reaction).***

TMSCl (.05 equiv), freshly distilled over CaH_2, is added to a stirred solution of (1S*,4S*,5S*)-*tert*-Butyl-(2,4-dimethyl-8-oxa-bicyclo[3.2.1]octa-2,6-dien-3-yloxy)-diphenyl-silane **106** (1 equiv) in 5.0 M $LiClO_4$-Et_2O (0.2 M in substrate) followed by 2 equiv of the appropriate nucleophile. After the mixture was stirred for an appropriate time, ether was added then quenched with water at 0^0 C. The product is isolated by partitioning between ether and water, combined organic layers were dried over Na_2SO_4, filtered, then concentrated in vacuo. The crude mixture was analyzed by ^{1}H-NMR for integration and nOe/decoupling (H, H-COSY) analysis. The relative stereochemistry at C_1 was determined by an nOe experiment, that is, by using the proton at C_1, C_4, and C_5 to observe, if any, enhancement when each proton was irradiated. In order to obtain analytical samples, the mixture was purified further on silica gel, Davisil silica gel (pH = 7), repeatedly with hexane-ether. In some cases, crude mixture is inseparable, and some minor products could not be isolated due to protonation of the silyl enol ether and the cleavage of a labile TMS-ether.



1S*-[3-(*tert*-Butyl-diphenyl-silanyloxy)-2,4S*-dimethyl-5S*-trimethyl-silanyloxy-cyclohepta-2,6-dienyl]-1-phenyl-ethanone (114).

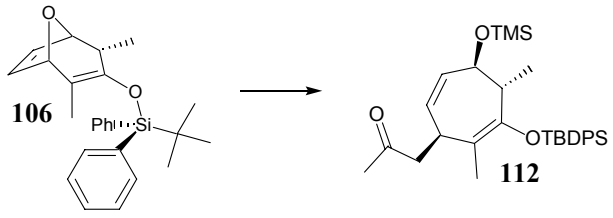
See general procedure. Crude ^{1}H-NMR spectroscopy indicated an approximately 3:1 (**114:115**) mixture of products. Relative stereochemistries were obtained by nOe measurements and careful decoupling (H, H-COSY). Flash column chromatography (Davisil silica gel, 2% EtOAc-Hexanes): R_f 0.92 (EtOAc-Hexanes, 2:4); IR (neat) ν 3050, 2957, 2930, 2857, 1682, 1598, 1558, 1472 cm^{-1}; ^{1}H NMR (C_6D_6, 300 MHz) δ 8.05 – 7.96 (m, 4H), 7.82 - 7.79 (m, 2H), 7.34 – 7.26 (m, 3H), 7.21 – 7.19 (m, 2H), 7.12 – 7.11 (m, 4H), 6.27 (dd, J = 11.3, 7.9 Hz, 1H), 5.57 (dd, J = 11.3, 6.7 Hz, 1H), 3.88 (dd, J = 17.3, 10.2 Hz, 1H), 3.78 (t, J = 5.9 Hz, 1H), 3.56 (ddd, J = 10.8, 6.9, 3.3 Hz, 1H), 2.97 (dd, J = 17.3, 3.3 Hz, 1H), 2.78 (m, 1H), 1.57 (s, 3H), 1.25 (s, 9H), 1.13 (d, J = 6.9 Hz, 3H), -0.06 (s, 9H); ^{13}C NMR (250 MHz, C_6D_6) δ 198.8, 147.5, 138.1, 137.9, 136.2, 136.1, 135.7, 134.8, 132.6, 130.2, 129.9, 129.8, 114.3, 71.3, 46.0, 45.0, 40.3, 27.4, 19.9, 19.4, 18.3, -0.12; high resolution MS (EI): calcd for $C_{36}H_{46}O_3Si_2$ (M^+) *m/e* 582.2987 , found 582.2985.



115

1R*-[3-(*tert*-Butyl-diphenyl-silanyloxy)-2,4S*-dimethyl-5S*-trimethyl-silanyloxy-cyclohepta-2,6-dienyl]-1-phenyl-ethanone (115).

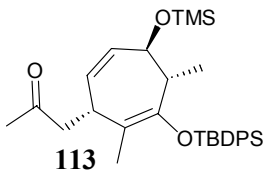
See general procedure. Flash column chromatography (Davisil silica gel, 2% EtOAc-Hexanes): R_f 0.90 (EtOAc-Hexanes, 2:4); IR (neat) *v* 3049, 2957, 2929, 2857, 1684, 1598, 1558, 1506, 1472, 1428 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 7.99 – 7.96 (m, 2H), 7.88 – 7.79 (m, 4H), 7.30 – 7.19 (m, 5H), 7.07 – 6.99 (m, 4H), 5.86 (dd, J = 11.7, 5.8 Hz, 1H), 5.50 (dd, J = 11.7, 6.0 Hz, 1H), 4.05 (t, J = 6.3 Hz, 1H), 3.64 (m, 1H), 3.06 (dd, J = 16.9, 9.8 Hz, 1H), 2.95 – 2.86 (m, 2H), 1.64 (s, 3H), 1.21 (s, 9H), 1.06 (d, J = 7.1 Hz, 3H), .06 (s, 9H); high resolution MS (EI): calcd for $C_{36}H_{46}O_3Si_2$ (M^+) *m/e* 582.2987 , found 582.2985.



106 **112**

1S*-[3-(*tert*-Butyl-diphenyl-silanyloxy)-2,4S*-dimethyl-5S*-trimethyl-silanyloxy-cyclohepta-2,6-dienyl]-propan-2-one (112).

See general procedure. The ratio of **112** and **113** was calculated from H^1-NMR integration (**112:113** ~ 4:1) mixture of products. Relative stereochemistries were obtained by nOe measurements and careful decoupling (H, H-COSY). Flash column chromatography (Davisil silica gel, Hexanes): R_f 0.95 (EtOAc-Hexanes, 2:4); IR (neat) *v* 3048, 2958, 2930, 2892, 2858, 1717, 1669, 1472, 1427 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 7.94 – 7.92 (m, 2H), 7.79 – 7.77 (m, 2H), 7.30 – 7.19 (m, 6H), 6.11 (dd, J = 11.2, 7.9 Hz, 1H), 5.57 (dd, J = 11.2, 6.5 Hz, 1H), 3.77 (t, J = 5.7 Hz, 1H), 3.29 (ddd, J = 17.2, 10.1, 7.1 Hz, 1H), 3.10 (dd, J = 16.9, 10.1 Hz, 1H), 2.73 (m, 1H), 2.38 (dd, J = 16.9, 3.3 Hz, 1H), 1.73 (s, 3H), 1.52 (s, 3H), 1.23 (s, 9H), 1.11 (d, J = 7.1 Hz, 3H), -0.03 (s, 9H); ^{13}C NMR (250 MHz, C_6D_6) δ 205.9, 147.4, 137.4, 136.4, 136.1, 136.0, 135.7, 134.8, 130.5, 129.9, 129.8, 114.0, 71.2, 49.3, 45.9, 39.7, 30.4, 29.9, 27.4, 27.0, 19.9, 19.2, 18.1, -0.05; high resolution MS (EI): calcd for $C_{31}H_{44}O_3Si_2$ (M^+) *m/e* 520.2828 , found 520.2829.

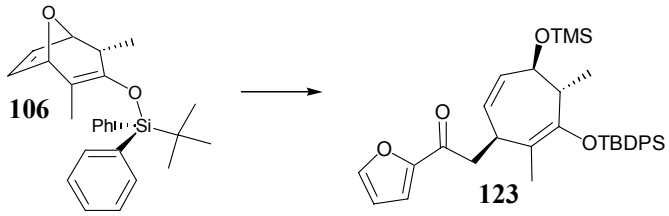


113

1R*-[3-(*tert*-Butyl-diphenyl-silanyloxy)-2,4S*-dimethyl-5S*-trimethyl-silanyloxy-cyclohepta-2,6-dienyl]-propan-2-one (113).

See general procedure. Flash column chromatography (Davisil silica gel, Hexanes): R_f 0.91 (EtOAc-Hexanes, 2:4); IR (neat) *v* 3048, 2959, 2930, 2900, 2850, 1716, 1669, 1540, 1488, 1472, 1456, 1428, 1361 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 7.97 – 7.95 (m, 2H), 7.87 – 7.83 (m, 2H), 7.30 – 7.21 (m, 6H), 5.74 (dd, J = 11.8, 5.9 Hz, 1H),

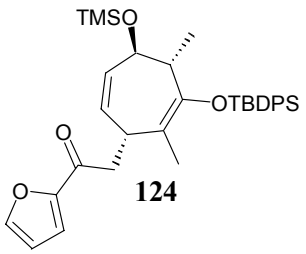
5.51 (dd, J = 11.8, 6.1 Hz, 1H), 4.02 (t, J = 6.3 Hz, 1H), 3.32 (m, 1H), 2.84 (m, 1H), 2.29 (m, 2H), 1.59 (s, 3H), 1.58 (s, 3H), 1.21 (s, 9H), 1.00 (d, J = 7.2 Hz, 3H), 0.08 (s, 9H); ^{13}C NMR (300 MHz, C_6D_6) δ 205.0, 148.9, 136.2, 136.0, 135.2, 135.0, 134.8, 133.5, 130.0, 129.9, 129.5, 125.8, 115.1, 71.5, 47.9, 46.0, 39.4, 30.4, 30.2, 29.6, 27.3, 20.1, 19.6, 18.1, 0.57; high resolution MS (EI): calcd for $C_{31}H_{44}O_3Si_2$ (M^+) *m/e* 520.2828 , found 520.2829.



1S*-[3-(*tert*-Butyl-diphenyl-silanyloxy)-2,4S*-dimethyl-5S*-trimethyl-silanyloxy-cyclohepta-2,6-dienyl]-1-furan-2-yl-ethanone (123).

See general procedure. Crude ^{1}H-NMR spectroscopy indicated an approximately 1:1 (**123:124**) mixture of products. Relative stereochemistries were obtained by nOe measurements and careful decoupling (H, H-COSY). Flash column chromatography (Davisil silica gel, 5% EtOAc-Hexanes): R_f 0.88 (EtOAc-Hexanes, 2:4); IR (neat) *v* 3048, 2956, 2953, 2857, 1731, 1674, 1471, 1428 cm^{-1}; ^{1}H NMR (C_6D_6, 300 MHz) δ 7.98 – 7.96 (m, 2H), 7.81 – 7.80 (m, 3H), 7.36 – 7.20 (m, 5H), 6.97 (d, J = 3.3 Hz, 1H), 6.89 (s, 1H), 6.20 (dd, J = 11.2, 7.9 Hz, 1H), 5.88 (dd, J = 3.3, 1.6 Hz, 1H), 5.57 (dd, J = 11.2, 6.5 Hz, 1H), 3.78 (m, 2H), 3.53 (m, 1H), 2.93 (dd, J = 16.9, 3.4 Hz, 1H), 2.78 (m, 1H), 1.57 (s, 3H), 1.24 (s, 9H), 1.12 (d, J = 6.9 Hz, 3H), -0.02 (s, 9H); ^{13}C NMR (250 MHz,

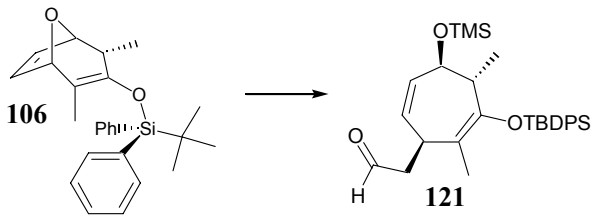
C_6D_6) δ 188.2, 154.0, 147.6, 145.3, 137.6, 136.1, 136.1, 135.8, 134.8, 130.4, 129.9, 129.8, 128.4, 115.8, 114.11, 112.0, 71.2, 46.0, 44.9, 39.8, 27.4, 27.0, 20.0, 19.3, 18.2, -0.12; high resolution MS (EI): calcd for $C_{34}H_{44}O_4Si_2$ (M^+) *m/e* 572.2772 , found 572.2778.



124

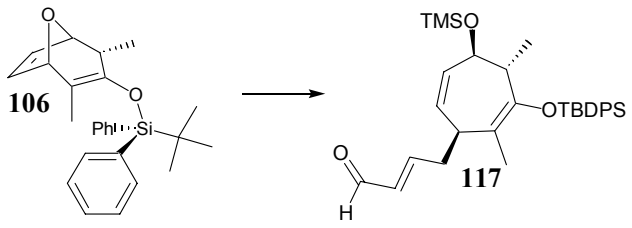
1R*-[3-(*tert*-Butyl-diphenyl-silanyloxy)-2,4S*-dimethyl-5S*-trimethyl-silanyloxy-cyclohepta-2,6-dienyl]-1-furan-2-yl-ethanone (124).

See general procedure. Flash column chromatography (Davisil silica gel, 5% EtOAc-Hexanes): R_f 0.85 (EtOAc-Hexanes, 2:4); IR (neat) *v* 2930, 2929, 2857, 1731, 1682, 1471, 1428, 1250, 1192, 1112 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 7.97 – 7.95 (m, 2H), 7.85 – 7.84 (m, 2H), 7.29 – 7.20 (m, 6H), 6.85 (d, J = 3.4 Hz, 1H), 6.80 (s, 1H), 5.82 (m, 2H), 5.48 (dd, J = 11.6, 5.9 Hz, 1H), 4.05 (t, J = 6.3 Hz, 1H), 3.53 (m, 1H), 3.04 (dd, J = 16.1, 10.1 Hz, 1H), 2.86 (m, 2H), 1.66 (s, 3H), 1.20 (s, 9H), 1.03 (d, J = 7.1 Hz, 3H), 0.06 (s, 9H); ^{13}C NMR (250 MHz, C_6D_6) δ 187.3, 153.7, 149.1, 145.6, 136.2, 136.0, 135.0, 134.9, 133.3, 130.0, 129.9, 129.6, 128.4, 116.1, 115.3, 112.2, 71.5, 46.2, 43.2, 40.0, 27.3, 20.0, 19.7, 18.1, 0.55; high resolution MS (EI): calcd for $C_{34}H_{44}O_4Si_2$ (M^+) *m/e* 572.2772 , found 572.2778.



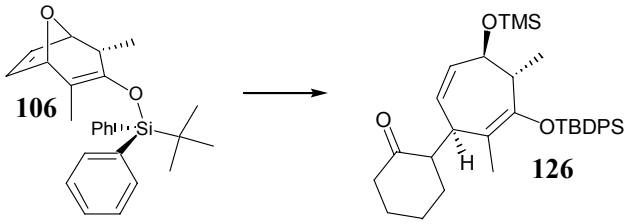
1S*-[3-(*tert*-Butyl-diphenyl-silanyloxy)-2,4S*-dimethyl-5S*-trimethyl-silanyloxy-cyclohepta-2,6-dienyl]-acetaldehyde (121).

See general procedure. The ratio of **120** and **121** was calculated from H^1-NMR integration (**120:121** ~ 1.5:1) mixture of products. Relative stereochemistries were obtained by nOe measurements and careful decoupling (H, H-COSY). Flash column chromatography, three times, (Davisil silica gel, 2% EtOAc-Hexanes): R_f0.91 (EtOAc-Hexanes, 2:4); IR (neat) ν 3233, 3048, 2930, 2857, 1723, 1666, 1618, 1452, 1330 cm^{-1}; ^{1}H NMR (C_6D_6, 500 MHz) δ 9.46 (dd, J = 2.1, .7 Hz, 1H), 7.91 – 7.89 (m, 2H), 7.79 – 7.76 (m, 2H), 7.31 – 7.19 (m, 6H), 5.84 (dd, J = 11.3, 7.6 Hz, 1H), 5.56 (dd, J = 11.3, 6.6 Hz, 1H), 3.73 (dd, J = 6.6, 5.6 Hz, 1H), 2.99 (dd, J = 12.7, 9.5, 3.9 Hz, 1H), 2.90 (ddd, J = 16.8, 9.5, 2.1 Hz, 1H), 2.71 (m, 1H), 2.27 (ddd, J = 16.8, 5.2, 1.3 Hz, 1H), 1.46 (s, 3H), 1.23 (s, 9H), 1.08 (d, J = 7.0 Hz, 3H), -0.03 (s, 9H); ^{13}C NMR (500 MHz, C_6D_6) δ 200.8, 147.9, 136.6, 136.04, 136.00, 135.6, 134.6, 130.7, 130.0, 129.9, 113.2, 71.0, 49.4, 46.0, 39.0, 27.2, 19.9, 19.1, 18.1, -0.12; high resolution MS (EI): calcd for $C_{30}H_{42}O_3Si_2$ (M^+) *m/e* 506.2665 , found 506.2672.



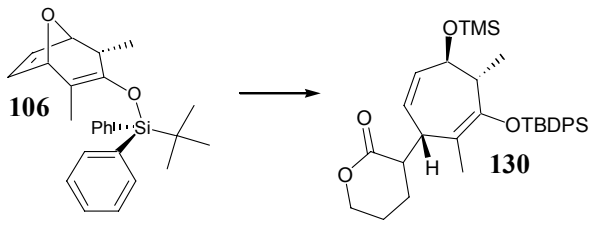
1S*-[3-(*tert*-Butyl-diphenyl-silanyloxy)-2,4S*-dimethyl-5S*-trimethyl-silanyloxy-cyclohepta-2,6-dienyl]-but-2E-enal (117).

See general procedure. Crude ^{1}H-NMR spectroscopy indicated an approximately 1.8:1 (**117:118**) mixture of products. Relative stereochemistries were obtained by nOe measurements and careful decoupling (H, H-COSY). Flash column chromatography, two times, (Davisil silica gel, Hexanes): R_f 0.89 (EtOAc-Hexanes, 2:4); IR (neat) *v* 3233, 3095, 3001, 2857, 1692, 1618, 1453, 1390, 1330 cm^{-1}; ^{1}H NMR (C_6D_6, 250 MHz) δ 9.41 (d, J = 7.6 Hz, 1H), 7.93 – 7.90 (m, 2H), 7.81 – 7.78 (m, 2H), 7.82 – 7.20 (m, 6H), 6.21 (m, 1H), 6.02 (dd, J = 15.6, 7.6 Hz, 1H), 5.54 (ddd, J = 17.4, 11.3, 6.2 Hz, 2H), 3.79 (t, J = 5.9 Hz, 1H), 2.79 – 2.59 (m, 2H), 2.50 – 2.42 (m, 1H), 2.30 – 2.20 (m, 1H), 1.51 (s, 3H), 1.24 (s, 9H), 1.12 (d, J = 7.0 Hz, 3H), -0.04 (s, 9H); ^{13}C NMR (250 MHz, C_6D_6) δ 192.5, 156.2, 147.9, 136.4, 136.02, 136.0, 135.5, 134.6, 134.2, 131.1, 130.0, 129.9, 113.7, 71.0, 46.1, 43.7, 38.2, 30.2, 27.3, 19.9, 19.4, 18.0, -0.09; high resolution MS (EI): calcd for $C_{32}H_{44}O_3Si_2$ (M^+) *m/e* 532.2820 , found 532.2829. The minor compound **118** could not be isolated after two attempts of column chromatography.



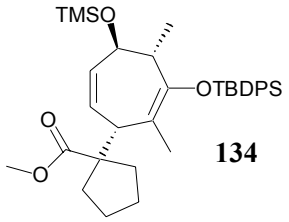
1S*-[3-(*tert*-Butyl-diphenyl-silanyloxy)-2,4S*-dimethyl-5S*-trimethyl-silanyloxy-cyclohepta-2,6-dienyl]-cyclohexanone (126).

See general procedure. The ratio of **126** and **127** was calculated from H^1-NMR integration (**126:127** ~ 1.7:1) mixture of products. Relative stereochemistries were obtained by nOe measurements and careful decoupling (H, H-COSY). Flash column chromatography, two times, (Davisil silica gel, 1% EtOAc-Hexanes): R_f 0.82 (EtOAc-Hexanes, 2:4); IR (neat) *v* 3048, 2930, 2857, 1708, 1664, 1618, 1450, 1429, 1390, 1330, 1250 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 7.97 – 7.94 (m, 2H), 7.83 – 7.80 (m, 2H), 7.28 – 7.19 (m, 6H), 5.98 (dd, J = 11.7, 6.9 Hz, 1H), 5.60 (dd, J = 11.7, 6.2 Hz, 1H), 3.90 (t, J = 6.1 Hz, 1H), 3.76 (t, J = 5.5 Hz, 1H), 2.85 (m, 1H), 2.42 (m, 1H), 2.24 (m, 1H), 2.10 (m, 1H), 1.82 – 1.59 (m, 2H), 1.52 (s, 3H), 1.47 – 1.29 (m, 2H), 1.24 – 1.23 (m, 12H), -0.04 (s, 9H); ^{13}C NMR (250 MHz, C_6D_6) δ 209.8, 148.8, 136.2, 136.0, 135.6, 134.9, 134.1, 130.5, 129.8, 129.7, 127.8, 114.1, 71.3, 53.4, 46.8, 42.7, 42.1, 31.9, 30.7, 30.2, 27.6, 27.4, 25.3, 23.0, 20.0, 18.9, 18.4, 14.3, -0.00; high resolution MS (EI): calcd for $C_{34}H_{48}O_3Si_2$ (M^+) *m/e* 560.3141 , found 560.3142. The minor compound **127** could not be isolated.



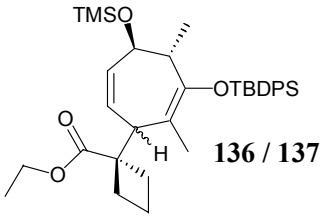
1R*-[3-(*tert*-Butyl-diphenyl-silanyloxy)-2,4S*-dimethyl-5S*-trimethyl-silanyloxy-cyclohepta-2,6-dienyl]-tetrahydro-pyran-2-one (130).

See general procedure. Crude ^{1}H-NMR spectroscopy indicated an approximately .8 : 1 (**129:130**) mixture of products. Relative stereochemistries were obtained by nOe measurements and careful decoupling (H, H-COSY) Flash column chromatography, three times, (Davisil silica gel, 5% EtOAc-Hexanes): R_f 0.76 (EtOAc-Hexanes, 2:4); IR (neat) *v* 2930, 2928, 2857, 1767, 1665, 1617, 1452, 1427, 1389, 1330, 1251 cm^{-1}; ^{1}H NMR (C_6D_6, 250 MHz) δ 7.89 – 7.85 (m, 2H), 7.77 – 7.73 (m, 2H), 7.26 – 7.17 (m, 6H), 5.76 (dd, J = 11.9, 6.1 Hz, 1H), 5.47 (dd, J = 11.9, 7.3 Hz, 1H), 4.33 (m, 1H), 3.62 (dd, J = 7.3, 5.1 Hz, 1H), 3.53 (t, J = 5.3 Hz, 1H), 2.91 – 2.69 (m, 3H), 1.50 (s, 3H), 1.19 (s, 9H), 1.20 - .95 (m, 4H), 1.04 (d, J = 6.3 Hz, 3H), -0.18 (s, 9H); high resolution MS (EI): calcd for $C_{33}H_{46}O_4Si_2$ (M^+) *m/e* 562.2919 , found 562.2935.



1R*-[3-(*tert*-Butyl-diphenyl-silanyloxy)-2,4S*-dimethyl-5S*-trimethyl-silanyloxy-cyclohepta-2,6-dienyl]-cyclopenpanecarboxylic acid methyl ester (134).

See general procedure. Crude ^{1}H-NMR spectroscopy indicated an approximately 1 : 1.6 (**133:134**) mixture of products. Relative stereochemistries were obtained by nOe measurements and careful decoupling (H, H-COSY) Flash column chromatography (Davisil silica gel, 1% EtOAc-Hexanes): R_f 0.85 (EtOAc-Hexanes, 2:4); IR (neat) ν 2954, 1727, 1692, 1641, 1428, 1250, 1197, 1112 cm^{-1}; ^{1}H NMR (C_6D_6, 250 MHz) δ 7.95 – 7.85 (m, 4H), 7.23 – 7.19 (m, 6H), 5.93 (ddd, J = 12.3, 7.3, 2.3 Hz, 1H), 5.58 (ddd, J = 12.3, 3.9, 2.1 Hz, 1H), 4.20 (m, 1H), 3.92 (m, 1H), 3.53 – 3.40 (m, 1H), 3.24 (s, 3H), 2.20 (m, 2H), 1.59 – 1.41 (m, 6H), 1.54 (s, 3H), 1.31 (d, J = 8.4 Hz, 3H), 1.18 (s, 3H), .14 (s, 9H); ^{13}C NMR (250 MHz, C_6D_6) δ 177.5, 148.5, 135.6, 134.9, 133.3**,** 132.2, 129.7, 129.6, 128.2, 119.7, 71.5, 56.5, 51.2, 47.5, 43.2, 37.5, 35.8, 27.1, 26.1, 25.4, 20.2, 18.1, 16.6, .39; high resolution MS (EI): calcd for $C_{35}H_{50}O_4Si_2$ (M^+) *m/e* 590.3248, found 590.3248.

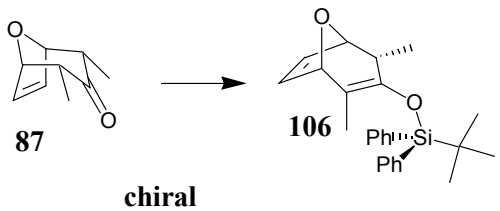


136 / 137

Inseparable Crude Mixture. 1-[3-(*tert*-Butyl-diphenyl-silanyloxy)-2,4-dimethyl-5-trimethylsilanyloxy-cyclohepta-2,6-dienyl]-cyclobutanecarboxylic acid ethyl ester (136 and **137).**

See general procedure. The ratio of **136** and **137** was calculated from H^1-NMR integration (**136:137** ~ 1:1.4) mixture of products. Relative stereochemistries were obtained by nOe measurements and careful decoupling (H, H-COSY). Flash column chromatography (Davisil silica gel, 1% EtOAc-Hexanes): R_f0.86 (EtOAc-Hexanes, 2:4);

IR of mixture,**136** & **137**, (neat) *v* 3048, broad 2956, 2895, 2858, 1725, 1724, 1658, 1589, 1428, 1365, 1251 cm^{-1}; high resolution MS (EI): calcd for $C_{35}H_{50}O_4Si_2$ (M^+) *m/e* 590.3258, found 590.3248.

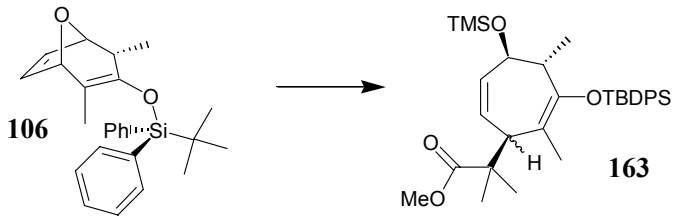


chiral

(-)-(1S,4S,5S)-*tert*-Butyl-(2,4-dimethyl-8-oxa-bicyclo[3.2.1]octa-2,6-dien-3-yloxy)-diphenyl-silane (106) .

To a solution of chiral amine, [R-(R^*, R^*)]-(+)-bis(α-methylbenzyl)amine, (8.01 mL, 35.10 mmol, 1.3 equiv) in dry THF (108 mL) was added dropwise *n*-BuLi (13.5 mL, 2.0 M in cyclohexane, 33.75 mmol, 1.25 equiv) at 0^0 C, stirred for 30 min, and then cooled to – 78^0 C. To this cold solution, was added dropwise a solution of [3.2.1] ketone (4.11 g, 27.00 mmol) in THF (36 mL) over a period of 45 min *via* syringe pump. After complete addition, the mixture was stirred for an additional 30 min at the same temperature. HMPA (25 mL) was added *via* syringe pump over a period of 30 min, followed by TBDPSCl (9.11 mL, 35.1 mmol, 1.3 equiv) over a period of 45 min *via* syringe pump at – 78^0 C. The mixture was allowed to warm to – 50^0 C for 1 day. Saturated aqueous NH_4Cl and ether were added sequentially. The organic phase was washed with brine and dried (Na_2SO_4), filtered, and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 5% EtOAc-Hexanes)

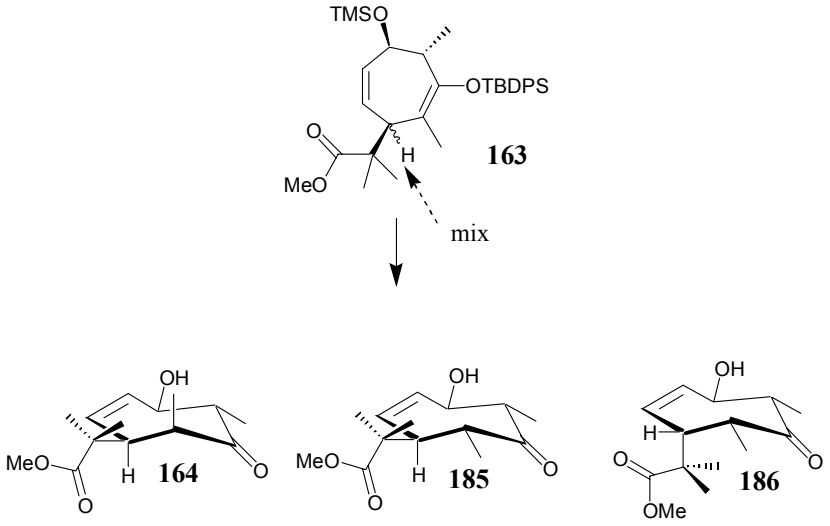
furnished 10.34 g of **106** (26.46 mmol, 98%, ~76 %ee): R_f 0.82 (EtOAc-Hexanes, 2:4); $[\alpha]_D^{25}$ -31.6 (c 3.5, $CHCl_3$); IR (neat) *v* 2931, 2856, 1668, 1467, 1427, 1310, 1180, 1112 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.76 - 7.67 (m, 4H), 7.44 - 7.34 (m, 6H), 6.64 - 6.61 (dd, J = 6.0, 1.7 Hz, 1H), 5.96 - 5.94 (dd, J = 6.0, 1.7 Hz, 1H), 4.78 - 4.75 (dd, J = 6.2, 1.7 Hz, 1H), 4.39 (d, J = 1.3 Hz, 1H), 2.60 - 2.56 (m, 1H), 1.30 (d, J = 2.0 Hz, 3H), 1.08 (s, 9H), .78 (d, J = 7.3 Hz, 3H); ^{13}C NMR (250 MHz, C_6D_6) δ 144.1, 139.2, 136.0, 135.9, 134.5, 134.3, 130.1, 130.0, 128.4, 127.4, 116.8, 82.3, 80.8, 36.7, 27.0, 20.0, 13.9, 11.3; high resolution MS (EI): calcd for $C_{25}H_{30}O_2Si$ (M^+) *m/e* 390.2016 , found 390.2015.



Crude mixture (163).

TBDP-Silyl enol ether (.815 g, 2.09 mmol) in 10.5 mL of 5.0 M $LiClO_4$-Et_2O at room temperature. Dropwise addition of nucleophile, ketene acetal, (.89 mL, 4.38 mmol, 2.0 equiv) followed by TMSCl solution (51.70 μL, 2.0 M in CH_2Cl_2, .105 mmol, .05 equiv). After 15 h at room temperature, the reaction mixture was diluted with Et_2O and quenched with aqueous $NaHCO_3$. The aqueous solution was washed with Et_2O (3X), the organic solution was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel (Davisil), elution with 2.5% EtOAc-Hexanes) to obtain 1.07 g (~2:1 inseparable mixture of β:α ,

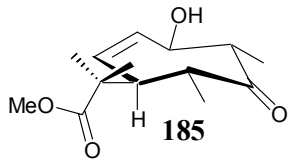
1.90 mmol, 91%). Residue was eluted through a short pad of Davisil and Na_2SO_4 to absorb excess water and ready for the next step: R_f 0.94 (EtOAc-Hexanes, 2:4).



(-)-(1S,2Z,4R,5S,7S)-2-(4-Hydroxy-5,7-dimethyl-6-oxo-cyclohept-2-enyl)-2-methyl-propionic acid methyl ester (164) .

To a plastic container containing a solution of TBDPS-enol ether (1.08 g, 1.93 mmol) in dry THF (19 mL) at 0^0 C was added HF.pyridine (7 mL). The resulting mixture was allowed to warm to room temperature over 18 h. The mixture was diluted with Et_2O and quenched by slowly adding saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with aqueous $CuSO_4$, dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by flash chromatography (silica gel, 25% EtOAc-Hexanes) afforded products **164**, **185**, **186** (18:1:10) respectively (461.39 mg, 1.81 mmol, 94%): **164** R_f 0.31 (EtOAc-

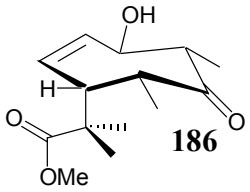
Hexanes, 2:4); $[\alpha]_D^{25}$ -43.6 (c 4.9, $CHCl_3$); IR (neat) *v* 3492, 2976, 2935, 2852, 1730, 1715, 1694, 1454, 1392, 1253 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.97 (ddd, J = 11.5, 5.5, 2.3 Hz, 1H), 5.78 (ddd, J = 11.5, 6.3, 2.5 Hz, 1H), 3.95 (dt, J = 10.3, 2.5 Hz, 1H), 3.68 (s, 3H), 2.89 (dq, J = 13.1, 3.8 Hz, 1H), 2.79 (q, J = 6.9 Hz, 1H), 2.36 (d, J = 6.2 Hz, 1H), 1.15 (s, 3H), 1.22 (s, 3H), 1.14 (d, J = 6.5 Hz, 3H), 1.01 (d, J = 6.9 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 211.9, 177.1, 136.8, 127.1, 77.2, 71.3, 52.0, 49.2, 48.9, 46.7, 45.1, 24.3, 23.6, 12.7, 11.4; high resolution MS (EI): calcd for $C_{14}H_{22}O_4$ (M^+) *m/e* 254.1526 , found 254.1518.



185

(1S,2Z,4R,5S,7R)-2-(4-Hydroxy-5,7-dimethyl-6-oxo-cyclohept-2-enyl)-2-methyl-propionic acid methyl ester (185).

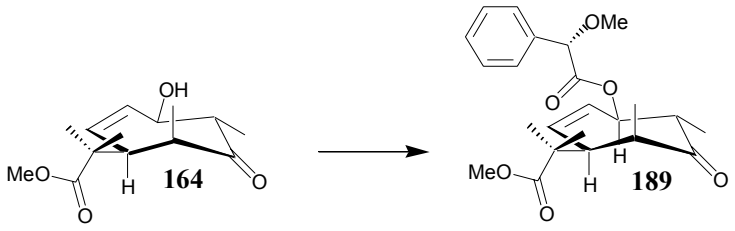
R_f 0.29 (EtOAc-Hexanes, 2:4); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.88 (dd, J = 12.3, 4.5 Hz, 1H), 5.57 (dd, J = 12.3, 5.9 Hz, 1H), 4.09 (m, 1H), 3.70 (s, 3H), 3.00 (p, J = 6.8 Hz, 1H), 2.78 (p, J = 7.2 Hz, 1H), 2.65 (t, J = 5.7 Hz, 1H), 1.83 (br s, 1H), 1.26 (s, 3H), 1.25 (s, 3H), 1.21 (d, J = 6.8 Hz, 3H), 1.09 (d, J = 6.9 Hz, 3H) ; ^{13}C NMR (500 MHz, $CDCl_3$) δ 212.3, 177.6, 134.3, 129.8, 70.3, 53.7, 52.0, 49.5, 46.9, 45.9, 24.6, 21.7, 16.9, 14.1.



186

(1R,2Z,4R,5S,7R)-2-(4-Hydroxy-5,7-dimethyl-6-oxo-cyclohept-2-enyl)-2-methyl-propionic acid methyl ester (186).

R_f 0.22 (EtOAc-Hexanes, 2:4); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.11 (dd, J = 11.6, 5.8 Hz, 1H), 5.72 (ddd, J = 11.6, 6.9, 2.2 Hz, 1H), 3.79 – 3.76 (m, 1H), 3.71 – 3.67 (m, 1H), 3.69 (s, 3H), 3.65 – 3.60 (m, 1H), 2.66 – 2.58 (m, 1H), 1.76 (br d, J = 5.6 Hz, 1H), 1.31 (s, 3H), 1.30 (s, 3H), 1.22 (d, J = 6.2 Hz, 3H), 1.02 (d, J = 7.0 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 212.1, 177.5, 131.5, 131.1, 73.3, 52.0, 49.4, 49.2, 45.0, 44.1, 25.1, 24.5, 13.9, 11.1.

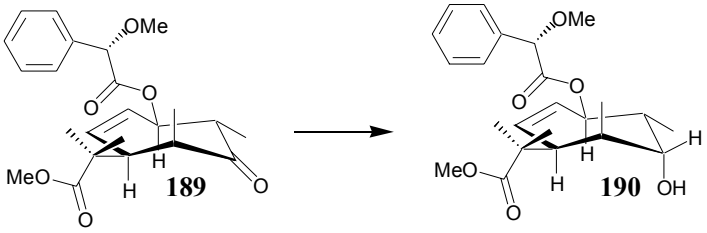


164 **189**

(+)-(1S,2Z,4R,5S,7S)-2-[4-((2S)-Methoxy-2-phenyl-acetoxy)-5,7-dimethyl-6-oxo-cyclohept-2-enyl]-2-methyl-propionic acid methyl ester (189).

DCC (327 mg, 1.58 mmol, 1.4 equiv), DMAP (28.30 mg, .226 mmol, .2 equiv), and chiral acid, (S)-(+)-α-Methoxyphenylacetic acid, (226 mg, 1.36 mmol, 1.2 equiv) were added to a cold (0^0 C) solution of hydroxy ketone (.287 g, 1.13 mmol) in 5.6 CH_2Cl_2. Stirring was continued for 13 h allowing to warm to room temperature. The

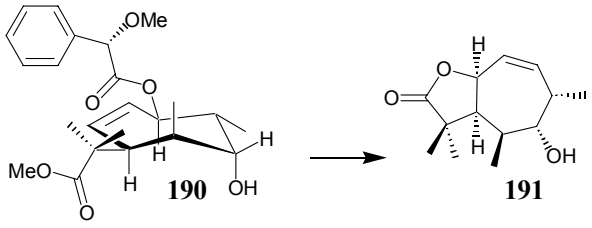
reaction mixture was diluted with ether and eluted through a short pad of Celite and silica gel, concentrated under reduced pressure to afford the crude product which was subjected to flash column chromatography (silica gel, 10% EtOAc-Hexanes) afforded product showed above **189** (391.13 mg, .97 mmol, 86%, >98%ee): R_f 0.55 (EtOAc-Hexanes, 2:4); $[\alpha]_D^{25}$ +98.3 (c 1.7, $CHCl_3$); IR (neat) ν 2978, 2931, 2854, 1748, 1731, 1703, 1454, 1379, 1256, 1175, 1113, 1006 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.45 (m, 2H), 7.37 (m, 3H), 5.76 (ddd, J = 11.6, 6.2, 2.4 Hz, 1H), 5.48 (dt, J = 11.6, 2.4 Hz, 1H), 5.20 (d, J = 11.0 Hz, 1H), 4.80 (s, 1H), 3.67 (s, 3H), 3.44 (s, 3H), 3.00 (dq, J = 13.1, 4.5 Hz, 1H), 2.83 (q, J = 6.8 Hz, 1H), 2.45 (d, J = 5.6 Hz, 1H), 1.21 (s, 3H), 1.20 (s, 3H), .98 (d, J = 6.8 Hz, 6H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 210.2, 176.9, 169.7, 135.8, 132.5, 128.9, 128.7, 128.6, 127.1, 82.6, 77.1, 72.8, 57.4, 52.1, 49.2, 46.6, 46.4, 45.0, 24.6, 23.4, 12.7, 11.6; high resolution MS (EI): calcd for $C_{23}H_{30}O_6$ $(M + Na)^+$ *m/e* 425.1932 , found 425.1940.



(+)-(1S,2Z,4R,5R,6R,7S)-2-[6-Hydroxy-4-((2S)-methoxy-2-phenyl-acetoxy)-5,7-dimethyl-cyclohept-2-enyl]-2-methyl-propionic acid methyl ester (190).

A solution of tri-*tert* butyloxy-lithium aluminum-hydride (.97 mL, .97 mmol, 1.2 equiv) was added dropwise to a cold (- 78^0 C) solution of ketone (.325 g, .807 mmol) in dry THF (4 mL). After 6 h at that temperature, the reaction mixture was diluted with

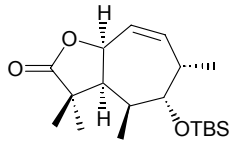
ether and quenched with aqueous NaK tartrate. The layers were separated, the aqueous phase was extracted with Et_2O, and the combined organic solutions were dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography (silica gel, elution with 25% EtOAc-Hexanes) furnished 306.85 mg (~ 7:1) of the desired alcohol (.76 mmol, 94%): R_f 0.36 (EtOAc-Hexanes, 2:4); $[\alpha]_D^{25}$ +27.4 (c 2.7, $CHCl_3$); IR (neat) *v* 3520, 2969, 2893, 1742, 1718, 1704, 1459, 1372, 1224 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.47 – 7.31 (m, 5H), 5.76 (dt, J = 11.3, 3.0 Hz, 1H), 5.53 (ddd, J = 11.0, 6.6, 2.2 Hz, 1H), 5.32 (dq, J = 11.0, 1.7 Hz, 1H), 4.78 (s, 1H), 3.66 (s, 3H), 3.57 (dd, J = 6.4, 2.0 Hz, 1H), 3.43 (s, 3H), 3.23 (d, J = 6.6 Hz, 1H), 2.04 – 1.85 (m, 3H), 1.18 (s, 3H), 1.15 (s, 3H), .92 (d, J = 6.9 Hz, 3H), .82 (d, J = 6.9 Hz, 3H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 178.3, 169.8, 136.2, 133.7, 128.6, 128.5, 128.2, 127.0, 82.7, 79.1, 72.8, 57.4, 51.9, 44.9, 41.8, 37.5, 33.9, 25.4, 22.1, 15.4, 13.2; high resolution MS (EI): calcd for $C_{23}H_{32}O_6$ $(M + Na)^+$ *m/e* 427.2098, found 427.2097.



(-)-(1S,2Z,4S,5S,6S,7S)-5-Hydroxy-3,3,4,6-tetramethyl-3,3a,4,5,6,8a-hexahydro-cyclohepta[b]furan-2-one (191).

LiI solid was heated under *vac* for 15 min at 70^0 C. After recooled to room temperature, alcohol above (77.8 mg, .19 mmol) in dry pyridine (1.92 mL) was added. The reaction flask was heated at reflux for 1 day. The oil bath was removed, reaction

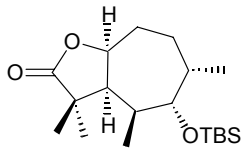
mixture was diluted with ether and quenched with water. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with aqueous $CuSO_4$, dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by flash chromatography (silica gel, 25-35% EtOAc-Hexanes) afforded 38.39 mg (.17 mmol, 89%): mp 103-106^0 C; R_f 0.17 (EtOAc-Hexanes, 2:4); $[\alpha]_D^{25}$ -14.3 (c 2.7, $CHCl_3$); IR ($CDCl_3$ solution) ν 2954, 2858, 1736, 1666, 1471, 1390, 1252, 1191, 1156 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.73 (ddd, J = 12.8, 5.2, 2.9 Hz, 1H), 5.46 (ddd, J = 12.8, 4.2, 1.3 Hz, 1H), 5.19 (m, 1H), 3.88 (m, 1H), 2.94 (dd, J = 5.6, 3.1 Hz, 1H), 2.65 (m, 1H), 2.26 (ddd, J = 14.3, 7.3, 3.1, 1H), 1.37 (s, 3H), 1.28 (s, 3H), 1.20 (d, J = 7.5 Hz, 3H), 1.01 (d, J = 7.3 Hz, 3H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 181.6, 135.1, 122.2, 78.2, 74.7, 45.6, 43.5, 37.3, 36.0, 26.1, 19.5, 18.0, 12.6; high resolution MS (EI): calcd for $C_{13}H_{20}O_3$ (M^+) *m/e* 224.1414, found 224.1412.



(-)-(1S,2Z,4S,5S,6S,7S)-5-(*tert*-Butyl-dimethyl-silanyloxy)-3,3,4,6-tetramethyl-3,3a,4,5,6,8a-hexahydro-cyclohepta[b]furan-2-one.

Freshly distilled 2,6-lutidine (17.2μL, .15 mmol, 2.5 equiv) was added to a cold (0^0) solution of hydroxy lactone (13.2 mg, .059 mmol) in CH_2Cl_2 (1 mL) followed by TBSOTf (16.4 μL, .071 mmol, 1.2 equiv). Stirring was continued for 3 h at 0^0 C. Saturated aqueous NH_4Cl and ether were added sequentially. The organic phase was

washed with brine and dried (Na_2SO_4), and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 5-10% EtOAc-Hexanes) furnished 19.58 mg (.058 mmol, 98%): R_f 0.85 (EtOAc-Hexanes, 2:4); $[\alpha]_D^{25}$ -21.6 (c 1.9, $CHCl_3$); IR (neat) *v* 2955, 2928, 2872, 2855, 1770, 1467, 1395, 1322, 1250, 1200 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.65 (ddd, J = 12.8, 4.9, 2.9 Hz, 1H), 5.42 (ddd, J = 12.8, 4.2, 1.3 Hz, 1H), 5.17 (m, 1H), 3.85 (t, J = 4.6 Hz, 1H), 2.99 (dd, J = 5.6, 2.9 Hz, 1H), 2.57 (m, 1H), 2.13 (ddd, J = 14.2, 7.4, 3.0 Hz, 1H), 1.34 (s, 3H), 1.24 (s, 3H), 1.09 (d, J = 7.4 Hz, 3H), 1.00 (d, J = 7.3 Hz, 3H), .92 (s, 9H), .08 (s, 3H), .06 (s, 3H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 181.7, 135.7, 121.4, 78.5, 75.5, 45.7, 43.4, 37.9, 36.8, 29.7, 25.9, 19.5, 18.8, 18.2, 12.6, -4.1, -4.9.

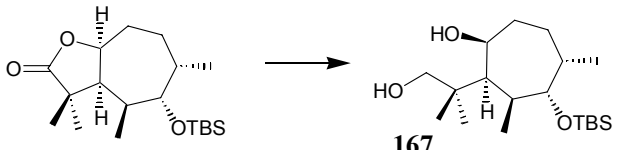


192

(-)-(1S,4S,5S,6S,7S)-5-(*tert*-Butyl-dimethyl-silanyloxy)-3,3,4,6-tetramethyl-octahydro-cyclohepta[b]furan-2-one (192).

Lactone (8.60 mg, .025 mmol) and PtO_2 (spatula tip) in a 5 mL flask were flushed with argon (3X), then 1 mL of dry EtOH was added, followed by a balloon of H_2. After 15 h, ether was added and eluted through a short pad of Celite, concentrated in vacuo. Purification of the residue by flash chromatography (silica gel, 20% EtOAc-Hexanes) afforded product indicated above (8.17 mg, .024 mmol, 96%): R_f 0.85 (EtOAc-Hexanes, 2:4); $[\alpha]_D^{25}$ -17.2 (c 3.1, $CHCl_3$); IR (neat) *v* 2955, 2858, 1736, 1471, 1389, 1361, 1252,

1191, 1155, 1123 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.75 (ddd, J = 16.3, 10.1, 6.2 Hz, 1H), 3.66 (m, 1H), 2.76 (dd, J = 6.2, 2.3 Hz, 1H), 2.36 (m, 1H), 1.98 – 1.69 (m, 3H), 1.56 – 1.39 (m, 2H), 1.32 (s, 3H), 1.95 (s, 3H), .98 (d, J = 7.5 Hz, 3H), .94 (d, J = 7.2 Hz, 3H), .91 (s, 9H), .05 (s, 3H), .04 (s, 3H)**;** ^{13}C NMR (300 MHz, $CDCl_3$) δ 182.4, 80.0, 77.9, 44.8, 43.1, 38.6, 37.8, 30.6, 29.7, 26.3, 25.9, 23.9, 20.9, 19.4, 18.2, 13.6, -4.1, -4.8.

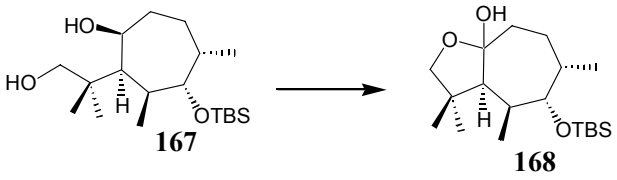


192 **167**

(-)-(1S,2S,3S,4S,5S)-4-*tert*-Butyl-dimethyl-silanyloxy)-2-(2-hydroxy-1,1-dimethyl-ethyl)-3,5-dimethyl-cycloheptanol (167).

A solution of $LiBH_4$ (18.2 μL, 2.0 M in THF, .036 mmol, 1.5 equiv) was added dropwise to a solution of lactone (7.3 mg, .021 mmol) in THF (.45 mL). The reaction mixture was heated to 50^0 C for 17 h. Recooled to 0^0C before quenched with water and saturated aqueous potassium carbonate. The mixture was diluted with Et_2O, layers were separated, and the combined organic solutions were dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography (silica gel, elution with 30% EtOAc-Hexanes) furnished 7.02 mg (.0203 mmol, 97%) of the diol: R_f 0.23 (EtOAc-Hexanes, 2:4); $[\alpha]_D^{25}$ -7.4 (c 2.4, $CHCl_3$); IR (neat) *v* 3251, 2955, 2928, 2867, 1690, 1468, 1387, 1361, 1251, 1061 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 4.25 (br, 1H), 3.55 (br, 4H), 3.20 (d, J = 11.0 Hz, 1H), 2.33 (m, 1H), 2.06 – 1.93 (m, 2H), 1.91 – 1.80 (m, 2H), 1.51 (m, 2H), 1.17 (d, J = 7.5 Hz, 3H), 1.13 (s, 3H), .96 (s, 3H), .92 (br s, 12H), .06 (s, 3H), .04 (s, 3H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 77.9, 71.3, 69.0, 45.2, 39.3, 38.7, 38.6, 37.4, 27.9,

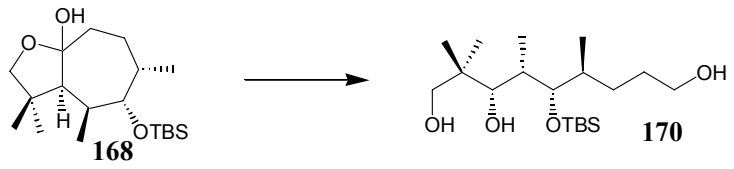
26.4, 26.0, 25.5, 21.4, 18.4, 16.4, -3.0, -3.9; high resolution MS (EI): calcd for $C_{19}H_{40}O_3Si$ $(M - H_2O - C_4H_9)^+$ *m/e* 269.1938, found 269.1937.



167 **168**

Crude cyclic hemiketal (**168**).

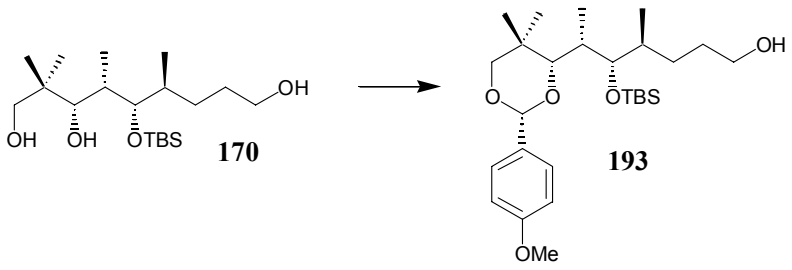
Freshly prepared solution of dioxirane (.92 mL, ~.1 M in acetone, .092 mmol, 1.1 equiv) was added dropwise to a 10 mL flask containing (28.7 mg, .084 mmol) of the diol. Stirred at room temperature for 9 h before concentrated in reduced pressure to provide 26.19 mg (.076 mmol, 91%) of the crude cyclic hemikal (A clear AB quartet was indicated: very clean based on ^{1}H NMR). The **crude residue** was diluted with CH_2Cl_2 (1 mL) and ready for the next step: R_f 0.70 (EtOAc-Hexanes, 2:4); IR (neat) *v* 3330, 2963, 2888, 1459, 1374, 1133 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.89 – 3.77 (AB q, J = 8.2 Hz, 2H), 3.68 – 3.54 (m, 2H), 2.24 – 2.09 (m, 3H), 1.90 – 1.62 (m, 3H), 1.05 (s, 3H), 1.05 (s, 3H), 1.02 (d, J = 7.2 Hz, 3H), .95 (d, J = 6.5 Hz, 3H), .90 (s, 9H), .06 (s, 3H), .04 (s, 3H).



(+)-(3S,4S,5S,6S)-5-(*tert*-Butyl-dimethyl-silanyloxy)-2,2,4,6-tetramethyl-nonane-1,3,9-triol (170).

m-CPBA solid (.076 mmol, ~78% purity, 1 equiv) was added in one portion to a solution of crude cyclic hemiketal prepared above (26.19 mg, .076 mmol) in CH_2Cl_2 (1 mL) at 0^0 C. The reaction flask was covered with aluminum foil and stirred for 3-4 h at room temperature. Diluted with ether, quenched with 10% sodium sulfite, organic phase was washed with brine and dried (Na_2SO_4), combined solvents were removed under reduced pressure to provide crude lactones. THF (1 mL) was added then cooled to - 20^0 C. $LiAlH_4$ solution (76 μL, .076 mmol, 1.0 M in THF, 1 equiv) then added to this solution at that same temperature, the mixture was stirred for 1 h, allowed to warm to 0^0 C, and quenched by addition of saturated NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by flash chromatography (silica gel, 50% EtOAc-Hexanes) afforded 22.32 mg (.062 mmol, 81% in two steps) of the triol: R_f 0.21 (EtOAc-Hexanes, 1:1); $[\alpha]_D^{25}$ +9.5 (c 2.1, CH_2Cl_2); IR (neat) *v* 3356, 2955, 2929, 2856, 1471, 1385, 1253, 1046 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.64 (m, 3H), 3.56 (dd, J = 4.5, 3.3 Hz, 1H), 3.47 (m, 2H), 2.45 (br s, 3H), 1.97

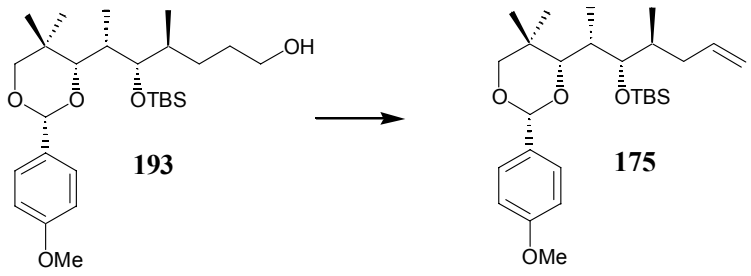
(dd, J = 6.8, 2.8, 1H), 1.78 – 1.40 (m, 4H), 1.19 – 1.08 (m, 1H), .96 (d, J = 8.2 Hz, 3H), .94 (d, J = 8.5 Hz, 3H), .92 (br s, 15H), .10 (s, 3H), .09 (s, 3H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 82.2, 77.2, 73.1, 62.7, 39.2, 36.9, 36.0, 30.6, 29.7, 28.8, 26.1, 23.4, 20.1, 18.3, 16.6, 9.3, -3.6, -4.3; high resolution MS (EI): calcd for $C_{19}H_{42}O_4Si$ $(M + Na)^+$ *m/e* 385.2747 , found 385.2750.



(+)-(5S)-(*tert*-Butyl-dimethyl-silanyloxy)-(6S)-[(2R)-(4-methoxy-phenyl)-5,5-dimethyl-[1,3]dioxan-(4S)-yl]-(4S)-methyl-heptan-1-ol (193).

Para-anialdehyde dimethylacetal (35.5 μL, .208 mmol, 3 equiv) was added dropwise to a solution of triol (25.2 mg, .0695 mmol) in dry benzene (1 mL) at room temperature, followed by several small crystals of *p*-TsOH. The reaction mixture was stirred for 45 min, at which time TLC indicated completion of the reaction. The mixture was diluted with Et_2O and quenched with saturated aqueous $NaHCO_3$. The aqueous solution was washed with Et_2O (3X), the organic solution was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, elution with 15% EtOAc-Hexanes) to obtain 30.74 mg (.064 mmol, 92%): R_f 0.42 (EtOAc-Hexanes, 1:5); $[\alpha]_D^{25}$ +17.6 (c 1.8, CH_2Cl_2); IR

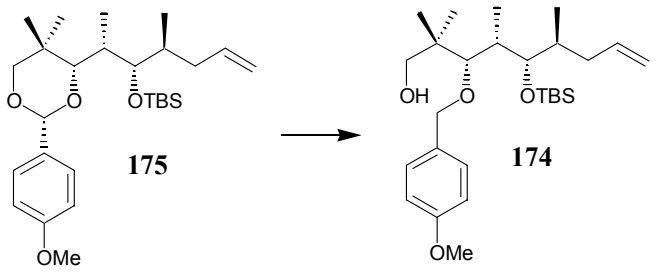
(neat) *v* 3417, 2954, 2930, 2856, 1614, 1518, 1462, 1392, 1360, 1302, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.43 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 5.42 (s, 1H), 3.80 (s, 3H), 3.65 – 3.61 (m, 3H), 3.57 – 3.52 (m, 2H), 3.41 (t, J = 3.7 Hz, 1H), 1.95 (m, 1H), 1.71 – 1.55 (m, 3H), 1.36 – 1.26 (m, 2H), 1.17 (s, 3H), 1.01 (d, J = 7.1 Hz, 3H), .93 (d, J = 7.2 Hz, 3H), .89 (s, 9H), .77 (s, 3H), .05 (s, 3H), .02 (s, 3H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 159.7, 131.7, 127.4, 113.5, 101.4, 83.9, 80.7, 79.9, 63.5, 55.2, 37.7, 36.6, 34.0, 31.3, 28.1, 26.1, 22.3, 20.2, 18.4, 18.3, 11.4, -3.8, -4.0; high resolution MS (EI): calcd for $C_{27}H_{48}O_5Si$ $(M + Na)^+$ *m/e* 503.3157 , found 503.3169.



(-)-(5S)-(*tert*-Butyl-dimethyl-silanyloxy)-(6S)-[(2R)-(4-methoxy-phenyl)-5,5-dimethyl-[1,3]dioxan-(4S)-yl]-(4S)-methyl-heptene (175).

1^0 alcohol (25.1 mg, .052 mmol)in dry THF and pyridine (1 mL total, 1:1) was treated sequentially with solid selenocyanate (35.5 mg, .156 mmol, 3 equiv) and *n*-Bu_3P (39.0 μL, .156 mmol, 3 equiv) at room temperature. After 30 min, at which time TLC

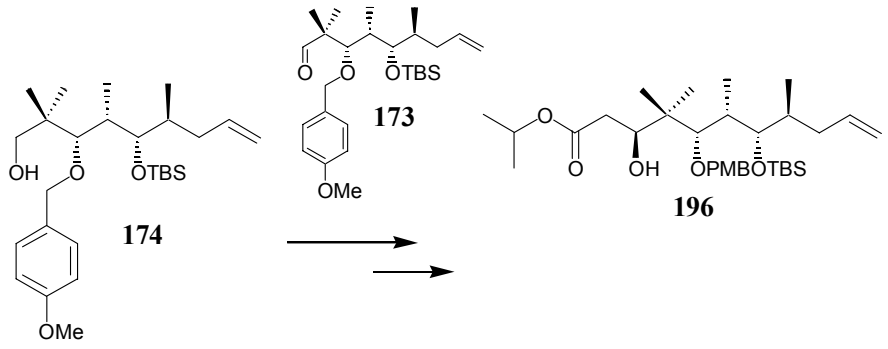
indicated completion of the reaction. The solvent was evaporated and residue was taken up in dry ether and filtered through a short pad of silica gel. After concentrated in vacuo, the residue (selenide) was diluted in dry THF (1mL), then H_2O_2 (.2 mL, of 30% solution) was added at 0^0 C. The reaction mixture was warmed to room temperature and stirred for 5 h. Saturated aqueous $NaHCO_3$ and ether were added sequentially. The organic phase was washed with brine and dried (Na_2SO_4), and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 10% EtOAc-Hexanes) furnished 20.93 mg (.045mmol, 87% in two steps): R_f 0.77 (EtOAc-Hexanes, 1:4); $[\alpha]_D^{25}$ -35.03 (c 1.5, CH_2Cl_2); IR (neat) ν 2941, 2856, 1640, 1614, 1589, 1518, 1467, 1391, 1359, 1302, 1249 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.42 (d, J = 7.8 Hz, 2H), 6.89 (d, J = 7.8 Hz, 2H), 5.69 (m, 1H), 5.42 (s, 1H), 4.95 (m, 2H), 3.81 (d, J = 1.1 Hz, 3H), 3.68 – 3.56 (m, 3H), 3.43 (m, 1H), 2.35 (m, 1H), 1.97 (m, 1H), 1.78 (m, 2H), 1.19 (s, 3H), 1.02 (dd, J = 7.2, .8 Hz, 3H), .91 (br s, 12H), .78 (s, 3H), .07 (s, 3H), .04 (s, 3H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 159.7, 138.5, 131.7, 127.4, 115.4, 113.4, 101.4, 83.8, 80.5, 79.9, 55.2, 37.8, 36.8, 36.3, 34.0, 26.2, 22.3, 20.2, 18.3, 18.2, 11.4, -3.7, -4.0; high resolution MS (EI): calcd for $C_{27}H_{46}O_4Si$ $(M + Na)^+$ *m/e* 485.3082 , found 485.3063.



(+)-(3S,4R,5S,6S)-5-(*tert*-Butyl-dimethyl-silanyloxy)-3-(4-methoxy-benzyloxy)-2,2,4,6-tetramethyl-non-8-en-1-ol (174).

DiBALH solution (.82 mL, 1.0 M in Hexanes, .82 mmol, 5 equiv) was added dropwise to a solution of olefin (75.9 mg, .164 mmol) in 5.5 mL of CH_2Cl_2 at -78^0 C. After 3 h, the reaction mixture was quenched with aqueous NaK tartrate, and the mixture was diluted with Et_2O. The layers were separated, the aqueous phase was extracted with Et_2O, and the combined organic solutions were dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography (silica gel, elution with 10% EtOAc-Hexanes) furnished 69.36 mg (.149 mmol, 91%) of the alcohol: R_f 0.52 (EtOAc-Hexanes, 1:4); $[\alpha]_D^{25}$ +8.2 (c 1.7, CH_2Cl_2); IR (neat) ν 3446, 2956, 2868, 1640, 1612, 1586, 1514, 1468, 1302, 1250, 1173 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.26 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 5.76 (ddd, J = 16.8, 10.1, 6.5 Hz, 1H), 5.00 (br m, 2H), 4.62 – 4.37 (AB q, J = 10.8 Hz, 2H), 3.48 (dd, J = 7.4, 1.6 Hz, 1H), 3.28 (d, J = 1.4 Hz, 1H), 2.25 (dd, J = 13.2, 6.6 Hz, 1H), 2.04 (m, 1H), 1.80 (m, 2H), 1.02 (d, J = 7.4 Hz, 3H), 1.00 (s, 3H), .97 (d, J = 6.6 Hz, 3H), .94 (s, 9H), .89 (s, 3H), .10 (s, 3H), .08 (s, 3H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 159.3, 138.0, 130.4, 129.3, 115.6, 113.9, 87.0, 80.1, 74.5, 71.3,

55.3, 40.8, 37.4, 36.8, 35.5, 26.4, 23.9, 20.9, 18.6, 17.9, 12.0, -3.0, -3.4; high resolution MS (EI): calcd for $C_{27}H_{48}O_4Si$ $(M + Na)^+$ *m/e* 487.3214 , found 487.3220.

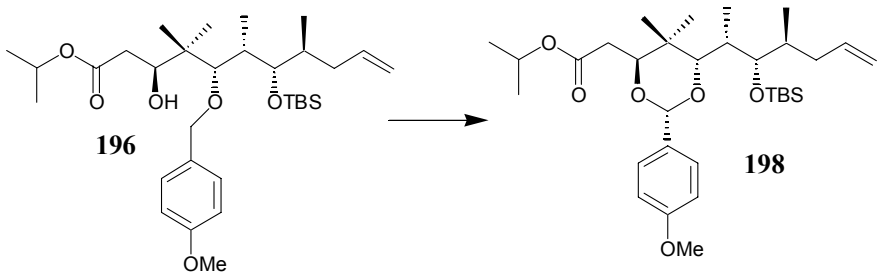


(-)-(3S,5S,6R,7S,8S)-7-(*tert*-Butyl-dimethyl-silanyloxy)-3-hydroxy-5-(4-methoxy-benzyloxy)-4,4,6,8-tetramethyl-undec-10-enoic acid isopropyl ester (196).

Dess-Martin periodinane (54 mg, .127 mmol, 2 equiv) reagent was added in one portion to the alcohol solution (29.5 mg, .064 mmol) in CH_2Cl_2 (1.2 mL) at room temperature. After 2.5 h, the reaction mixture was transferred to a short pad of silica gel (Davisil) and Na_2SO_4, mixture was eluted with 6% ether:hexanes, concentrated under reduced pressure to afford **crude aldehyde 173** 27.84 mg (.060 mmol, 94%): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 9.64 (s, 1H), 7.24 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.75 (ddd, J = 16.7, 10.1, 6.4 Hz, 1H), 5.01 (m, 2H), 4.55 – 4.39 (AB q, J = 10.8 Hz, 2H), 3.81 (s, 3H), 3.50 (m, 2H), 2.24 (m, 1H), 2.00 – 1.71 (m, 3H), 1.12 (s, 3H), 1.08 (s, 3H), .97 - .93 (br s, 15H), .07 (s, 3H), .069 (s, 3H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 206.2, 159.2, 137.9, 130.6, 129.0, 115.7, 113.8, 83.9, 79.1, 74.4, 55.3, 51.9, 37.9, 37.2, 35.6, 26.3, 20.6, 18.6, 18.3, 17.8, 11.7, -3.2, -3.4.

Crude aldehyde above (27.84 mg , .060 mmol) was taken up in dry CH_2Cl_2 (.8 mL) and cooled to – 78^0 C before the addition of Lewis Acid, dimethylaluminum

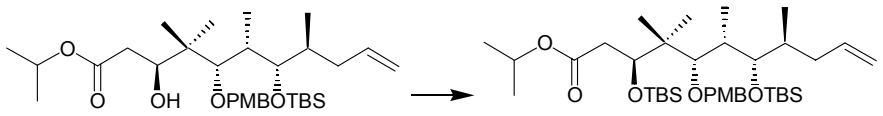
chloride, (85.3 μL, 1.0 M on hexanes, .15 mmol, 2.5 equiv). After 5 min at that temperature, TBS-ketene acetal was added dropwise (.072 mmol, 1.2 equiv). Stirred at – 78^0 C for 45 min, then quenched by dropwise addition of saturated NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by flash chromatography (silica gel, 6% EtOAc-Hexanes) afforded 25.42 mg (.045 mmol, 75%) of compound indicated above: R_f 0.49 (EtOAc-Hexanes, 1:4); $[\alpha]_D^{25}$ -3.1 (c .99, CH_2Cl_2); IR (neat) ν 3484, 2958, 2931, 2868, 1726, 1639, 1612, 1586, 1514, 1466, 1385, 1364, 1301, 1250, 1180 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.25 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.75 (ddd, J = 16.8, 10.2, 6.3 Hz, 1H), 5.13 - 4.97 (m, 3H), 4.62 - 4.38 (AB q, J = 10.3 Hz, 2H), 4.16 (dd, J = 9.2, 3.5 Hz, 1H), 3.80 (s, 3H), 3.48 (dd, J = 6.7, 1.8 Hz, 1H), 3.36 (d, J = 1.6 Hz, 1H), 2.45 – 2.21 (m, 3H), 2.14 – 2.03 (m, 1H), 1.91 – 1.72 (m, 2H), 1.25 (d, J = 6.2 Hz, 6H), 1.06 (d, J = 7.1 Hz, 3H), .98 (s, 3H), .97 (d, J = 6.1 Hz, 3H), .94 (s, 9H), .85 (s, 3H), .11 (s, 3H), .08 (s, 3H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 172.5, 159.3, 137.9, 130.3, 129.4, 115.7, 113.9, 87.0, 80.3, 74.7, 73.1, 67.9, 55.3, 42.6, 37.9, 37.1, 37.0, 35.7, 26.4, 21.9, 21.8, 21.6, 20.7, 18.6, 17.8, 12.1, -2.9, -3.3; high resolution MS (EI): calcd for $C_{32}H_{56}O_6Si$ $(M + Na)^+$ *m/e* 587.3736 , found 587.3744.



[(6S)-[(2S)-(*tert*-Butyl-dimethyl-silanyloxy)-(1S),(3S)-dimethyl-hex-5-enyl]-(2S)-(4-methoxy-phenyl)-5,5-dimethyl-[1,3]dioxan-(4S)-yl]-acetic acid isopropyl ester (198).

Alcohol **196** (11.5 mg, .020 mmol) in dried CH_2Cl_2 (.4 mL). Solid Na_2SO_4 (65 mg) was added in one portion to the stirring solution. Stirring continued for 10 min, then 1.1eq of DDQ (6.7 mg, .022 mmol) was added. After 30 min at room temperature, the reaction flask was quenched with $NaHCO_3$ (aq), and diluted with Et_2O. The layers were separated, the aqueous phase was extracted with Et_2O, and the combined organic solutions were dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography (silica gel, elution with 3% EtOAc-Hexanes) furnished 9.67 mg (.0172 mmol, 86%) of the acetal: R_f 0.59 (EtOAc-Hexanes, 1:4); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.37 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 5.79 (s, 1H), 5.76 – 5.60 (m, 1H), 5.08 – 4.91 (m, 3H), 4.13 (dd, J = 10.5, 5.0 Hz, 1H), 3.97 (br s, 1H), 3.80 (s, 3H), 3.41 (t, J = 3.5 Hz, 1H), 3.06 (dd, J = 13.9, 10.6 Hz, 1H), 2.59 (dd, J = 13.9, 5.0 Hz, 1H), 2.39 – 2.32 (m, 1H), 1.99 – 1.90 (m, 1H), 1.84 – 1.74 (m, 2H), 1.30 (s, 3H), 1.21 (q, J = 6.2 Hz, 6H), 1.02 (d, J = 7.2 Hz, 3H), .91 (br s, 12H), .79 (s, 3H), .07 (s, 3H), .04 (s, 3H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 171.0, 159.7, 138.4, 131.7, 127.4, 115.5, 113.4, 94.6, 81.1,

80.5, 77.4, 77.2, 68.1, 55.2, 37.6, 36.9, 36.2, 36.1, 34.3, 26.1, 23.1, 22.2, 21.8, 21.7, 18.3, 11.7, -3.7, -4.0.

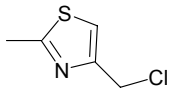


196 **Fragment A (171)**

(-)-(3S,5S,6S,7S,8S)-3,7-Bis-(*tert*-butyl-dimethyl-silanyloxy)-5-(4-methoxy-benzyloxy)-4,4,6,8-tetramethyl-undec-10-enoic acid isopropyl ester (171) .

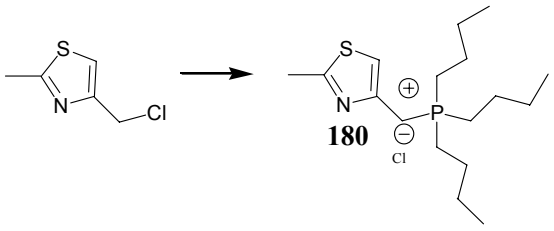
2,6-lutidine (9.54 μL, .082 mmol, 4 equiv) was added to a solution of alcohol (11.5 mg, .0204 mmol) in dry CH_2Cl_2 (.4 mL) at – 78^0 C, followed by dropwise of TBSOTf (18.65 μL, .0814 mmol, 4 equiv). After 1 h at that temperature, the mixture was quenched by addition of saturated NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by flash chromatography (silica gel, 2% EtOAc-Hexanes) to give 13.16 mg of the desired product (.019 mmol, 95%): R_f 0.81 (EtOAc-Hexanes, 1:4); $[\alpha]_D^{25}$ -8.01 (c 1.8, CH_2Cl_2); IR (neat) ν 2955, 2928, 2856, 1732, 1683, 1616, 1516, 1467, 1439, 1362, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.27 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 5.73 (ddd, J = 17.1, 11.5, 7.8 Hz, 1H), 4.99 (m, 3H), 4.59 – 4.41 (AB q, J = 10.6 Hz, 2H), 4.45 (m, 1H), 3.80 (s, 3H), 3.53 (d, J = 7.9 Hz, 1H), 3.38 (br s, 1H), 2.73 (dd, J = 16.8, 4.2 Hz, 1H), 2.32 (dd, J = 16.8, 5.4 Hz, 1H), 2.30 (m, 1H), 2.09 (m, 1H), 1.89 – 1.78 (m, 2H), 1.22 (d, J = 3.1 Hz, 3H), 1.20 (d, J = 3.2 Hz, 3H), 1.00 - .89 (m, 30H), .07 - .03 (m, 12H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 172.1, 158.8, 138.2, 131.5, 128.4, 128.4, 115.4, 113.7, 83.3, 80.6, 73.9,

73.5, 67.7, 55.3, 45.2, 39.9, 37.3, 36.7, 35.1, 26.4, 26.1, 21.8, 21.7, 20.4, 19.9, 18.7, 18.3, 18.1, 12.3, -3.1, -3.3, -3.8, -4.5; high resolution MS (EI): calcd for $C_{38}H_{70}O_6Si_2$ $(M + Na)^+$ *m/e* 701.4593, found 701.4609.



4-Chloromethyl-2-methyl-thiazole.

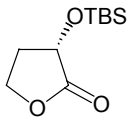
A solution of 1,3-dichloropropan-2-one (9.7 g, 76.38 mmol) and thioacetamide (5.73 g, 76.38 mmol) in dry ethanol (53.5 mL) was heated under argon for 6 h and then concentrated under reduced pressure. The dark residue was dissolved in water, and quenched with aqueous solution of $NaHCO_3$. The aqueous solution was washed with Et_2O (3X), the organic solution was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by distillation (bp: 96^0 C, 0.10 Torr) to obtain 8.34 g (56.52 mmol, 74%) of the thiazole as light yellow oil, which was identical in every respect with the described compound.[27] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.13 (s, 1H), 4.65 (s, 2H), 2.71 (s, 3H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 166.9, 151.7, 116.9, 40.8, 19.2; high resolution MS (EI): calcd for C_5H_6ClNS (M^+) *m/e* 146.9909 , found 146.9909.



180

Tri-*n*-butyl[(2-methyl-1,3-thiazol-4-yl)methyl]phosphonium chloride (180).

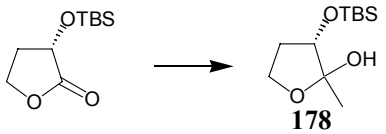
To a solution of 4-Chloromethyl-2-methyl-thiazole (8.12 g, 55.07 mmol) in dry benzene (70.60 mL) was added tri-*n*-butylphosphane (13.41 mL, 55.07 mmol, 1 equiv) under argon, and the reaction mixture was heated to reflux for 10 h. The mixture was concentrated under reduced pressure and the residue crystallized with dry ether to give 18.50 g (52.87 mmol, 96%) of the title compound: mp 83 – 86^0 C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.69 (br d, J = 3.1 Hz, 1H), 4.33 (d, J = 14.5 Hz, 2H), 2.62 (s, 3H), 2.38 (m, 6H), 1.44 (m, 12 H), .89 (t, J = 7.1 Hz, 9H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 166.8, 142.9 (d, ^{2}J = 9.9 Hz), 119.9 (d, ^{3}J = 9.2 Hz), 23.8 (d, J = 16.3 Hz), 23.5 (d, J = 4.6 Hz), 22.7 (d, ^{1}J = 48.1 Hz), 19.3 (d, ^{1}J = 46.7 Hz), 19.1, 13.3; high resolution MS (EI): calcd for $C_{17}H_{33}OClNPS$ $(M - HCl)^+$ *m/e* 313.1993 , found 313.1993.



(-)-(3S)-3-(*tert*-Butyl-dimethyl-silanyloxy)-dihydro-furan-2-one.

To a solution of (S)-α-hydroxybutyrolactone (5.00 g, 48.98 mmol) and imidazole (6.67 g, 97.96 mmol, 2 equiv) in dry DMF (64 mL) was added TBSCl (9.60 g, 63.67 mmol, 1.3 equiv) at 0^0 C, and the mixture was stirred for 3 h. The reaction was quenched with saturated aqueous NH_4Cl, extracted with ether, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash column chromatography (silica gel, 5% EtOAc-Hexanes) furnished 10.28 g of TBS-ether (47.59 mmol, 97%): R_f 0.49 (EtOAc-

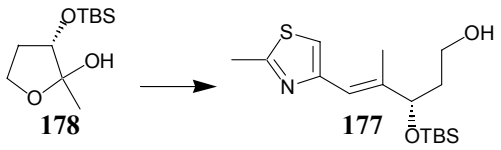
Hexanes, 1:5); $[\alpha]_D^{25}$ -30.3 (c 10.7, $CHCl_3$); IR (neat) *v* 2943, 2909, 2857, 1787, 1464, 1362, 1253, 1153 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.40 (dt, J = 12.4, 3.4 Hz, 2H), 4.19 (ddd, J = 15.6, 9.2, 6.4 Hz, 1H), 2.46 (m, 1H), 2.23 (ddd, J = 17.4, 12.4, 8.6 Hz, 1H), .92 (s, 9H), .18 (s, 3H), .15 (s, 3H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 175.8, 68.2, 64.7, 32.4, 25.7, 18.2, -4.7, -5.2; high resolution MS (EI): calcd for $C_{10}H_{20}O_3Si$ $(M + H)^+$ *m/e* 217.1261 , found 217.1260.



178

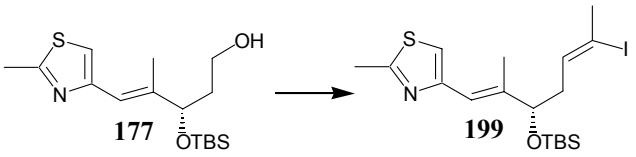
(3S)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-methyl-tetrahydro-furan-2-ol (178).

MeLi (33.73 mL, 1.6 M in Et_2O, 53.96 mmol, 1.2 equiv) was added dropwise to a solution of (-)-(3S)-3-(*tert*-Butyl-dimethyl-silanyloxy)-dihydro-furan-2-one (9.73 g, 44.97 mmol) in 225 mL of THF at – 78^0 C, and the reaction was stirred for 2 h at the same temperature. The cooling bath was removed, and saturated aqueous NH_4Cl was added rapidly. Aqueous NaK tartrate was added dropwise, and the mixture was diluted with Et_2O. The layers were separated, the aqueous phase was extracted with Et_2O, and the combined organic solutions were dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography (silica gel, elution with 20% EtOAc-Hexanes) affording 8.88 g (38.22 mmol, 85%) of the alcohol: mp 54 – 57^0 C; R_f 0.24 (EtOAc-Hexanes, 1:5); IR (neat) *v* 3316 br, 1460, 1250, 1115, 1050, 1030 cm^{-1}; high resolution MS (EI): calcd for $C_{11}H_{24}O_3Si$ $(M + H_2O)^+$ *m/e* 214.1389, found 214.1389.



(-)-(3S,4E)-3-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-5-(2-methyl-thiazol-4-yl)-pent-4-en-1-ol (177).

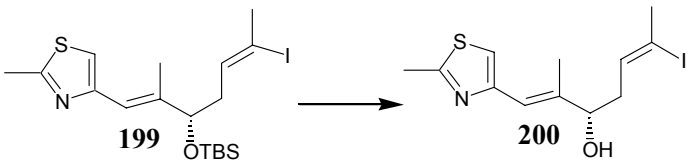
To a solution of Tri-*n*-butyl[(2-methyl-1,3-thiazol-4-yl)methyl]phosphonium Chloride (8.56 g, 24.46 mmol, 2 equiv), and (3S)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-methyl-tetrahydro-furan-2-ol (2.84 g, 12.23 mmol) in dry THF (56 mL) was added dropwise a solution of LiHMDS (28.13 mL, 1 M in THF, 28.13 mmol, 2.3 equiv) at 0^0 C over a period of 45 min *via* syringe pump. After 5 min the cooling bath was removed and the reaction mixture was heated to 60^0 C for 40 min. After recooling to room temperature, the mixture was diluted with ether and quenched by addition of saturated aqueous NH_4Cl, the organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by flash chromatography (silica gel, 20-30% EtOAc-Hexanes) to give 2.96 g (9.05 mmol, 74%): R_f 0.23 (EtOAc-Hexanes, 1:3); $[\alpha]_D^{25}$ -32.7 (c 2.8, $CHCl_3$); IR (neat) ν 3356, 2952, 2907, 2855, 1656, 1505, 1466, 1253, 1184, 1073 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.94 (s, 1H), 6.53 (s, 1H), 4.39 (dd, J = 7.2, 5.0 Hz, 1H), 3.75 (m, 2H), 2.72 (s, 3H), 2.02 (s, 3H), 1.93 – 1.77 (m, 2H), .092 (s, 3H), .011 (s, 3H), .04 (s, 3H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 164.8, 152.9, 141.8, 118.7, 115.4, 77.2, 60.5, 38.2, 25.8, 19.2, 18.1, 14.4, -4.6, -5.2; high resolution MS (EI): calcd for $C_{16}H_{29}O_2NSSi$ (M^+) *m/e* 327.1681 , found 327.1688.



(+)-(1E,3S,5Z)-4-[3-(*tert*-Butyl-dimethyl-ilanyloxy)-6-iodo-2-methyl-hepta-1,5-dienyl]-2-methyl-thiazole (199).

Dess-Martin periodinane (659 mg, 4.01 mmol, 1.3 equiv) was added to a solution of alcohol, (-)-(3S,4E)-3-(tert-Butyl-dimethyl-silanyloxy)-4-methyl-5-(2-methyl-thiazol-4-yl)-pent-4-en-1-ol, (1.01g, 3.08 mmol) in CH_2Cl_2 (14 mL). The mixture was stirred for 45 min at room temperature. The solvent was removed under reduced pressure, diluted with organic solvent (~ 10% EtOAc/Hexanes), and eluted through a short column containing silica gel, Davisil, and Na_2SO_4. Concentrated in vacuo to give .97 g of crude aldehyde (2.98 mmol, 97%). *n*-BuLi (2.98 mL, 2.0 M in cyclohexane, 5.96 mmol, 2 equiv) was added at 0^0 C to a stirred suspension of ethyl triphenylphosphonium iodide (5.96 mmol, 2 equiv) in THF (28 mL). After 30 min at 0^0 C, the resulting red ylide solution was added dropwise *via* cannula to a rapidly stirred solution of iodine (1.44 g, 5.66 mmol, 1.9 equiv) in THF (40 mL) at -78^0 C. The resulting yellow suspension was stirred vigorously for 15 min at that same temperature and for 30 min at -40^0 C. A solution of NaHMDS (5.66 mL, 1.0 M in THF, 5.66 mmol, 1.9 equiv) was added dropwise at that same temperature. After 30 min at -40^0 C, a solution of aldehyde prepared earlier in THF (14 mL) was added dropwise. The mixture was stirred for 1h at -40^0 C and quenched by dropwise addition of saturated NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined

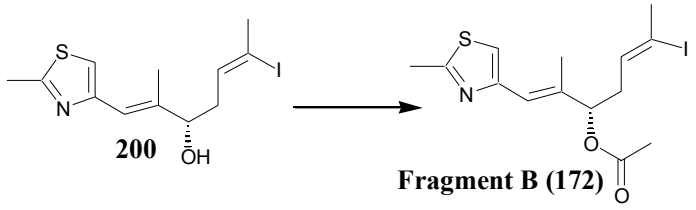
organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by flash chromatography (silica gel, 5% EtOAc-Hexanes) afforded 759.66 mg (1.64 mmol, 55%) of vinyl iodide: R_f 0.85 (EtOAc-Hexanes, 2:4); $[\alpha]_D^{25}$ +14.8 (c 2.4, $CHCl_3$), lit. $[\alpha]_D^{25}$ +14.2 (c 1.63, $CHCl_3$)[131a]; IR (neat) *v* 2953, 2926, 2893, 2854, 1650, 1506, 1470, 1461, 1427, 1360, 1250, 1183 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.95 (s, 1H), 6.50 (s, 1H), 5.46 (ddd, J = 8.1, 6.6, 1.4 Hz, 1H), 4.22 (t, J = 6.4 Hz, 1H), 2.72 (s, 3H), 2.48 (d, J = 1.0 Hz, 3H), 2.37 (m, 2H), 2.03 (d, J = .9 Hz, 3H), .90 (s, 9H), .07 (s, 3H), .02 (s, 3H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 164.9, 153.0, 141.9, 132.1, 118.8, 115.2, 102.3, 77.3, 43.7, 33.7, 25.8, 19.2, 18.2, 14.1, -4.7, -5.0; high resolution MS (EI): calcd for $C_{18}H_{30}OINSSi$ (M^+) *m/e* 463.0958 , found 463.0862.



(-)-(1E,3S,5Z)-6-Iodo-2-methyl-1-(2-methyl-thiazol-4-yl)-hepta-1,5-dien-3-ol (200).

To a solution of **199** (.365 g, .787 mmol) in THF (5 mL) was added HF.pyridine (1 mL) at 0^0 C. After 10 h, the mixture was diluted with Et_2O and quenched with saturated aqueous $NaHCO_3$. The aqueous solution was washed with Et_2O (3X), the organic solution was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, elution with 10% EtOAc-Hexanes) to obtain .269g (.771 mmol, 98%): R_f 0.48 (EtOAc-Hexanes, 2:4); $[\alpha]_D^{25}$ -8.7 (c 4.5, $CHCl_3$), lit. $[\alpha]_D^{25}$ -8.4 (c 0.85, $CHCl_3$)[131a]; IR (neat) *v* 3334, 2947,

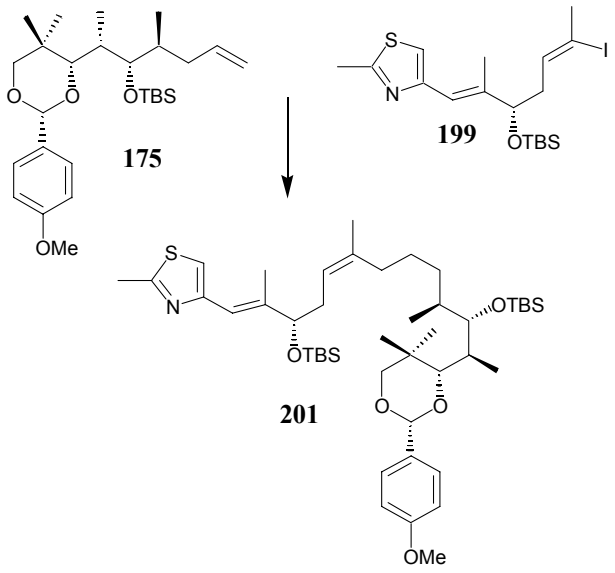
2914, 2848, 1650, 1508, 1426, 1374, 1288, 1188, 1150 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.96 (s, 1H), 6.57 (s, 1H), 5.54 (dd, J = 6.6, 1.2 Hz, 1H), 4.28 (t, J = 6.6 Hz, 1H), 2.71 (s, 3H), 2.51 (d, J = 1.1 Hz, 3H), 2.45 (m, 2H), 2.06 (d, J = 1.0 Hz, 3H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 164.7, 152.6, 141.5, 131.4, 119.1, 115.8, 103.3, 76.4, 42.5, 33.7, 19.1, 14.5; high resolution MS (EI): calcd for $C_{12}H_{16}ONIS$ $(M + H)^+$ *m/e* 350.0093 , found 350.0076.



(-)-(1E,3S,5Z)-6-Iodo-2-methyl-1-(2-methyl-1,3-thiazol-4-yl)-1,5-heptadien-3-yl Acetate (172).

A solution of alkene **200** (23 mg, .066 mmol) in CH_2Cl_2 (1.5 mL) were added triethylamine (12 μL, .13 mmol, 2 equiv), acetic anhydride (37 μL, .26 mmol, 4 equiv), and then small amounts of DMAP. The mixture was stirred at room temperature for 6 h, and saturated aqueous NH_4Cl was added to the mixture followed by the addition of AcOEt. The organic layer was separated, and the aqueous phase was further extracted with AcOEt. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel (elution with 15% EtOAc-Hexanes) to obtain **172** (25 mg, .063 mmol, 96%): R_f 0.65 (EtOAc-Hexanes, 2:4); $[\alpha]_D^{25}$ -24.3 (c 2.4, $CHCl_3$), lit. $[\alpha]_D^{25}$ -24.6 (c 1.2, $CHCl_3$)[131a] ; IR (neat) *v* 2947, 2915, 1734, 1656, 1501, 1426, 1368, 1233 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.97 (s, 1H), 6.53 (s,

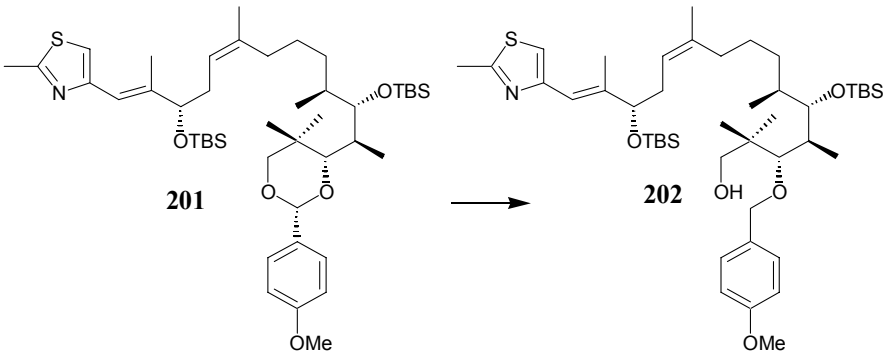
1H), 5.41 (dd, J = 6.6, 1.4 Hz, 1H), 5.34 (t, J = 6.6 Hz, 1H), 2.71 (s, 3H), 2.56 – 2.53 (m, 2H), 2.49 (d, J = 1.2 Hz, 3H), 2.08 (br s, 6H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 170.1, 164.7, 152.4, 137.0, 130.3, 120.6, 116.4, 103.6, 77.3, 40.4, 33.7, 21.2, 19.2, 14.9; high resolution MS (EI): calcd for $C_{14}H_{18}O_2NIS$ $(M + H)^+$ *m/e* 392.0186, found 392.0181.



(-)-4-{(3S),(11S)-Bis-(*tert*-butyl-dimethyl-silanyloxy)-(12S)-[(2R)-(4-methoxy-phenyl)-5,5-dimethyl-[1,3]dioxan-(4S)-yl]-2,6,(10S)-trimethyl-trideca-(1E),(5Z)-dienyl}-2-methyl-thiazole (201).

Olefin (45.5 mg, .0983 mmol) in dry flask was added 9-BBN (.492 mL, .5 M in THF, .246 mmol, 2.5 equiv). In a separate flask, the vinyl iodide (36.6 mg, .079 mmol) was dissolved in DMF (.9 mL). Cs_2CO_3 (2 equiv with respect to the olefin, .197 mmol, 64 mg) was then added with vigorous stirring followed by sequential addition of $AsPh_3$ (.15 equiv with respect to the olefin, 4.6 mg, .015 mmol), $PdCl_2(dppf)_2$ (.2 equiv with respect to the olefin, 16.2 mg, .0197 mmol), and H_2O (100μL). The flask was flushed

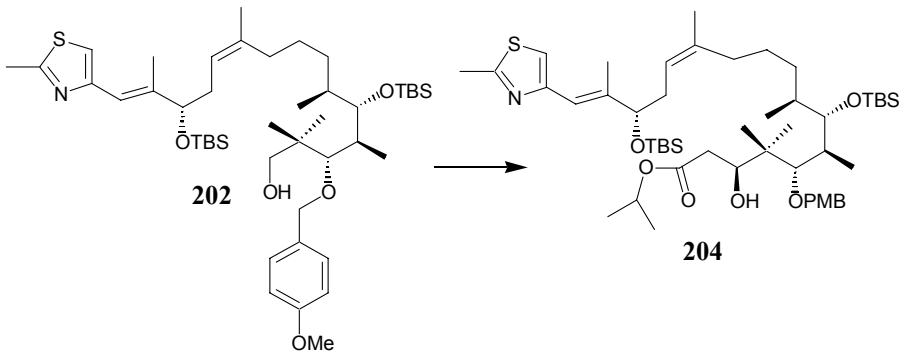
with argon for 10 min while stirring. After 5 h at room temperature, TLC indicated completion of the olefin. This borane solution was added to the vinyl iodide mixture prepared above *via* cannula, then rinsed with small amount of THF. The reaction quickly turned dark brown in color and slowly became pale yellow after 2 h, , at which time TLC indicated completion of the reaction. The reaction was then quenched by dropwise addition of saturated NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by flash chromatography (silica gel, 5% EtOAc-Hexanes) to give 58.22 mg (.073 mmol, 74%) of the coupling product: R_f 0.52 (EtOAc-Hexanes, 1:5); $[\alpha]_D^{25}$ -16.3 (c .82, CH_2Cl_2); IR (neat) *v* 2954, 2927, 2854, 1614, 1588, 1507, 1462, 1443, 1390, 1359, 1302, 1249 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.39 (d, J = 8.6 Hz, 2H), 6.91 (s, 1H), 6.87 (d, J = 8.6 Hz, 2H), 6.45 (s, 1H), 5.41 (s, 1H), 5.10 (t, J = 7.0 Hz, 1H), 4.07 (t, J = 6.3 Hz, 1H), 3.79 (s, 3H), 3.60 (AB q, J = 11.0 Hz, 2H), 3.59 (br s, 1H), 3.39 (t, J = 4.0 Hz, 1H), 2.71 (s, 3H), 2.41 (m, 1H), 2.28 – 2.17 (m, 2H), 1.99 (s, 3H), 1.97 – 1.87 (m, 5H), 1.63 (s, 3H), 1.57 – 1.30 (m, 2H), 1.16 (s, 3H), .99 (d, J = 7.1 Hz, 3H), .90 (d, J = 6.9 Hz, 3H), .89 (s, 9H), .87 (s, 9H), .76 (s, 3H), .043 (s, 3H), .037 (s, 3H), .01 (s, 3H), .00 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 164.3, 159.7, 153.2, 142.6, 137.0, 131.7, 127.9, 127.3, 121.3, 118.6, 114.8, 113.8, 113.5, 101.3, 84.6, 80.8, 79.8, 79.0, 55.2, 41.9, 37.3, 37.2, 35.3, 34.0, 32.5, 32.4, 31.6, 29.7, 27.2, 26.4, 26.1, 25.8, 25.6, 24.7, 23.5, 22.6, 22.2, 20.0, 19.1, 18.3, 18.2, 17.9, 14.1, 13.9, 11.2, -3.8, -3.9, -4.7, -4.9; high resolution MS (EI): calcd for $C_{45}H_{77}O_5NSSi_2$ $(M+Na)^+$ *m/e* 822.4951 , found 822.4959.



(+)-(3S,4R,5S,6S,10Z,13S,14E)-5,13-Bis-(*tert*-butyl-dimethyl-silanyloxy)-3-(4-methoxy-benzyloxy)-2,2,4,6,10,14-hexamethyl-15-(2-methyl-thiazol-4-yl)-pentadeca-10,14-dien-1-ol (202).

DiBALH solution (.915 mL, 1.0 M in hexanes, .915 mmol, 15 equiv) was added dropwise to a solution of acetal (48.6 mg, .061 mmol) in dry CH_2Cl_2 (3.9 mL) at – 78^0 C. Allowed to warm to – 50^0 C for 1 day. At 0^0 C, aqueous NaK tartrate was added dropwise, and the mixture was diluted with Et_2O. The layers were separated, the aqueous phase was extracted with Et_2O, and the combined organic solutions were dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography (silica gel, elution with 10-15% EtOAc-Hexanes) furnished 42.09 mg (.0525 mmol, 86%) of the alcohol: R_f 0.26 (EtOAc-Hexanes, 1:5); $[\alpha]_D^{25}$ +2.6 (c 1.3, CH_2Cl_2) ; IR (neat) ν 3415, 2953, 2927, 2855, 1613, 1586, 1514, 1466, 1387, 1360, 1301, 1249, 1180, 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.25 (d, J = 8.6 Hz, 2H), 6.92 (s, 1H), 6.87 (d, J = 8.6 Hz, 2H), 6.47 (s, 1H), 5.13 (t, J = 6.6 Hz, 1H), 4.61 – 4.35 (AB q, J = 10.5 Hz, 2H), 4.08 (t, J = 5.9 Hz, 1H), 3.80 (s, 3H), 3.54 (d, J = 10.8 Hz, 1H), 3.46 (dd, J = 4.2, 2.3 Hz, 1H), 3.31 (d, J = 10.7 Hz, 1H), 3.26 (br s, 1H), 2.72 (s, 3H), 2.23 (m, 2H), 2.03 (m, 2H), 1.99 (s, 3H), 1.66

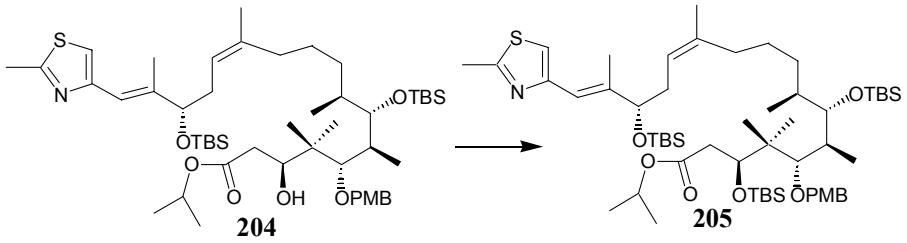
(s, 3H), 1.58 – 1.12 (m, 6H), 1.01 (d, J = 7.1 Hz, 3H), .99 (s, 3H), .96 (d, J = 6.9 Hz, 3H), .92 (s, 9H), .89 (s, 9H), .87 (s, 3H), .09 (s, 3H), .07 (s, 3H), .05 (s, 3H), .00 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 164.4, 159.2, 153.1, 142.7, 136.8, 130.6, 129.2, 121.6, 118.5, 114.9, 113.9, 87.5, 80.5, 78.9, 74.4, 71.3, 55.2, 40.8, 37.6, 37.0, 35.4, 32.5, 31.4, 26.5, 26.4, 25.8, 23.9, 23.5, 22.6, 20.8, 19.1, 18.6, 18.2, 17.7, 14.0, 11.8, -3.1, -3.3, -4.6, -4.9; high resolution MS (EI): calcd for $C_{45}H_{79}O_5NSSi_2$ $(M + Na)^+$ *m/e* 824.5115 , found 824.5115.



(-)-(3S,5S,6S,7S,8S,12Z,15S,16E)-7,15-Bis-(*tert*-butyl-dimethyl-silanyloxy)-3-hydroxy-5-(4-methoxy-benzyloxy)-4,4,6,8,12,16-hexamethyl-17-(2-methyl-thiazol-4-yl)-heptadeca-12,16-dienoic acid isopropyl ester (204).

To a solution of alcohol **202** (68.5 mg, .0853 mmol) in dry CH_2Cl_2 (1.7 ml) was added Dess-Martin reagent (72.6 mg, .171 mmol, 2 equiv) at room temperature. After 2 hours of constant stiring, the reaction mixture was transferred to a short column of silica gel (Davisil) and Na_2SO_4 then eluted with ~ 8% EtOAc / Hexanes. Concentrated in vacuo and purified by flash column chromatography (silica gel, elution with 5% EtOAc-Hexanes) to obtain 64.17 mg of aldehyde **203** (.0802 mmol, 94 %). Aldehyde **203** was

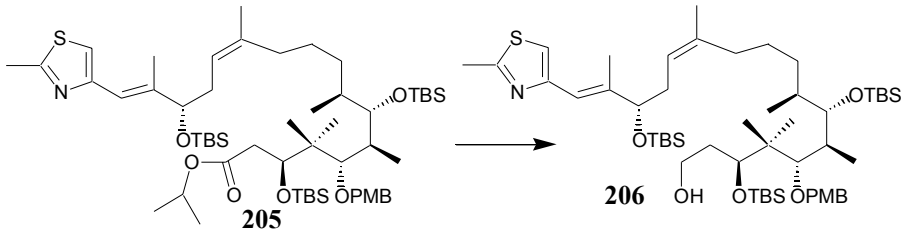
taken up in dry CH_2Cl_2 (2.5 mL) then cooled to – 78^0 C. Me_2AlCl (213 μL, 1.0 M in hexanes, .213 mmol, 2.5 equiv) was added dropwise to this cold aldehyde solution. After 5 min, TBS-isopropyl ketene acetal (.171 mmol, 2 equiv) was added at that temperature. Reaction mixture was diluted with ether and quenched with H_2O after 1 hour of stirring. The aqueous solution was washed with Et_2O (3X), the organic solution was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, elution with 11% EtOAc-Hexanes) to obtain 44.87 mg (.0497 mmol, 62%): R_f 0.44 (EtOAc-Hexanes, 1:5); $[\alpha]_D^{25}$ -2.2 (c 3.2, CH_2Cl_2); IR (neat) *v* 3492, 2955, 2929, 2855, 1728, 1658, 1613, 1586, 1514, 1470, 1385, 1360, 1301, 1250, 1181 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.25 (d, J = 8.6 Hz, 2H), 6.92 (s, 1H), 6.85 (d, J = 8.6 Hz, 2H), 6.46 (s, 1H), 5.13 (t, J = 7.0 Hz, 1H), 5.05 (sept, J = 6.3 Hz, 1H), 4.62 – 4.35 (AB q, J = 10.3 Hz, 2H), 4.14 (m, 1H), 4.08 (t, J = 6.5 Hz, 1H), 3.88 (d, J = 2.6 Hz, 1H), 3.79 (s, 3H), 3.45 (dd, J = 3.1, .9 Hz, 1H), 3.34 (br s, 1H), 2.71 (s, 3H), 2.40 – 2.29 (m, 2H), 2.28 – 2.19 (m, 1H), 2.08 (m, 1H), 2.00 (s, 3H), 1.99 – 1.97 (m, 2H), 1.66 (s, 3H), 1.48 – 1.36 (m, 4H), 1.24 (d, J = 6.2 Hz, 6H), 1.16 – 1.11 (m, 2H), 1.04 (d, J = 7.1 Hz, 3H), .97 (d, J = 6.9 Hz, 3H), .96 (s, 3H), .93 (s, 9H), .89 (s, 9H), .84 (s, 3H), .10 (s, 3H), .07 (s, 3H), .05 (s, 3H), .00 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.5, 164.3, 159.2, 153.2, 142.5, 136.7, 130.3, 129.3, 121.6, 118.6, 114.9, 113.8, 87.5, 80.7, 79.0, 74.5, 73.2, 67.8, 55.2, 42.5, 37.9, 37.8, 36.6, 35.4, 32.5, 31.7, 29.7, 26.5, 26.4, 25.8, 23.5, 21.9, 21.8, 21.4, 20.8, 19.2, 18.6, 18.2, 17.5, 14.0, 11.8, -3.0, -3.3, -4.7, -4.9; high resolution MS (EI): calcd for $C_{50}H_{87}O_7NSSi_2$ $(M + Na)^+$ *m/e* 924.5632 , found 924.5639.



(-)-(3S,5S,6S,7S,8S,12Z,15S,16E)-3,7,15-Tris-(*tert*-butyl-dimethyl-silanyloxy)-5-(4-methoxy-benzyloxy)-4,4,6,8,12,16-hexamethyl-17-(2-methyl-thiazol-4-yl)-heptadeca-12,16-dienoic acid isopropyl ester (205).

2,6-lutidine (32 μL, .276 mmol, 5 equiv) was added dropwise to a solution of alcohol **204** (49.8 mg, .0552 mmol) in dry CH_2Cl_2 (1.3 mL) at – 78^0 C, followed by 4 equiv of TBSOTf (50.6 μL, .221 mmol). After 4 hours at that temperature, the mixture was quenched by dropwise addition of saturated NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by flash chromatography (silica gel, 5-10% EtOAc-Hexanes) afforded product indicated (55.00 mg, .0541 mmol, 98%): R_f 0.64 (EtOAc-Hexanes, 1:5); $[\alpha]_D^{25}$ -4.72 (c 3.7, CH_2Cl_2); IR (neat) ν 2955, 2930, 2856, 1725, 1613, 1514, 1471, 1375, 1299, 1250, 1182, 1076 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.29 (d, J = 8.6 Hz, 2H), 6.92 (s, 1H), 6.87 (d, J = 8.6 Hz, 2H), 6.46 (s, 1H), 5.12 (t, J = 6.7 Hz, 1H), 4.98 (sept, J = 6.2 Hz, 1H), 4.59 (d, J = 10.6 Hz, 1H), 4.45 (t, J = 5.1 Hz, 1H), 4.38 (d, J = 10.7 Hz, 1H), 4.08 (t, J = 6.4 Hz, 1H), 3.80 (s, 3H), 3.49 (d, J = 6.8 Hz, 1H), 3.34 (br s, 1H), 2.76 – 2.72 (m, 1H), 2.71 (s, 3H), 2.32 – 2.24 (m, 3H), 2.11 – 1.99 (m, 2H), 2.00 (s, 3H), 1.66 (s, 3H), 1.43 (m, 2H), 1.20 (t, J = 6.3 Hz, 6H), 1.14 – 1.07 (m, 4H), .96 (d, J = 6.9 Hz, 3H), .91 (br s, 9H), .89 (br s, 12H),

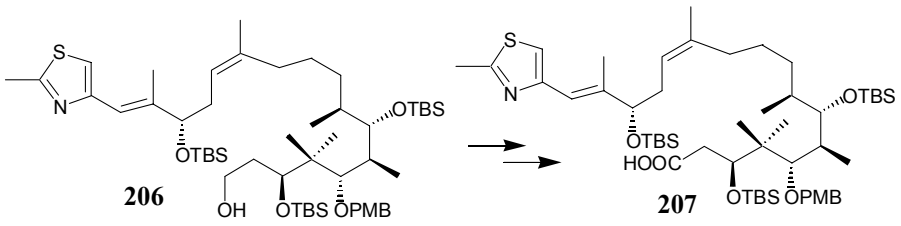
.88 (br s, 9H), .85 (br s, 6H), .064 - .062 (br s, 9H), .05 (s, 3H), .03 (s, 3H), .01 (s, 3H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 172.1, 164.3, 158.7, 153.2, 142.6, 136.9, 131.6, 128.4, 121.4, 118.6, 114.9, 113.6, 83.6, 81.1, 79.0, 73.5, 73.4, 67.6, 55.2, 45.2, 39.9, 37.6, 36.9, 35.3, 32.6, 31.1, 26.5, 26.4, 26.1, 25.9, 23.5, 22.6, 21.8, 21.7, 20.2, 19.5, 19.2, 18.6, 18.3, 18.2, 17.9, 14.1, 13.9, 12.0, -3.1, -3.3, -3.8, -4.5, -4.6, -4.9; high resolution MS (EI): calcd for $C_{56}H_{101}O_7NSSi_3$ $(M)^+$ *m/e* 1015.6610, found 1015.6607.



(-)-(3S,5S,6S,7S,8S,12Z,15S,16E)-3,7,15-Tris-(*tert*-butyl-dimethyl-silanyloxy)-5-(4-methoxy-benzyloxy)-4,4,6,8,12,16-hexamethyl-17-(2-methyl-thiazol-4-yl)-heptadeca-12,16-dien-1-ol (206).

To a solution of ester **205** (54.2 mg, .0533 mmol) in 1.1 mL of THF at 0^0 C was added $LiBEt_3H$ (.320 mmol, 320 μL, 6 equiv). After 6 hours at that temperature, the mixture was diluted with Et_2O and quenched with saturated aqueous $NaHCO_3$. The aqueous solution was washed with Et_2O (3X), the organic solution was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, elution with 25% EtOAc-Hexanes) to obtain 47.11 mg (.049 mmol, 92%): R_f 0.30 (EtOAc-Hexanes, 1:5); $[\alpha]_D^{25}$ -2.6 (c 2.4, CH_2Cl_2); IR (neat) *v* 3416, 2954, 2929, 2855, 1778, 1659, 1614, 1586, 1514, 1471, 1387, 1360, 1301, 1249, 1180, 1076 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26 (d, J = 8.5 Hz, 2H),

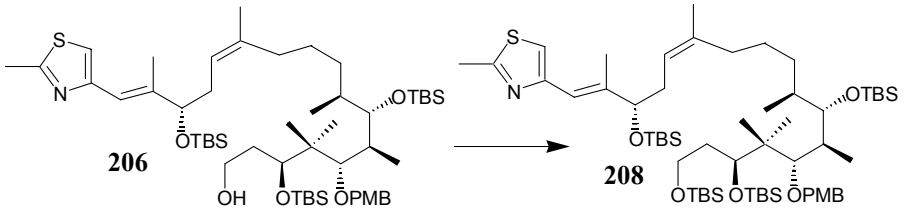
6.93 (s, 1H), 6.87 (d, J = 8.5 Hz, 2H), 6.47 (s, 1H), 5.14 (t, J = 6.7 Hz, 1H), 4.60 – 4.37 (AB q, J = 10.8 Hz, 2H), 4.09 (t, J = 6.1 Hz, 1H), 3.85 (dd, J = 3.2, 2.9 Hz, 1H), 3.80 (s, 3H), 3.74 (m, 1H), 3.65 (m, 1H), 3.52 (d, J = 5.2 Hz, 1H), 3.32 (br s, 1H), 2.72 (s, 3H), 2.25 (m, 2H), 2.05 – 1.98 (m, 2H), 1.99 (s, 3H), 1.67 (s, 3H), 1.65 – 1.59 (m, 2H), 1.42 (m, 2H), 1.27 – 1.10 (m, 4H), .97 (d, J = 6.7 Hz, 3H), .96 (d, J = 6.9 Hz, 3H), .91 (br s, 9H), .90 (br s, 9H), .89 (br s, 12H), .88 (s, 3H), { .08, .06, .05, .01 (m, 18H) }; ^{13}C NMR (500 MHz, $CDCl_3$) δ 162.8, 158.8, 153.0, 142.9, 137.0, 131.7, 128.4, 121.4, 118.4, 114.8, 113.6, 83.9, 80.8, 79.0, 73.8, 73.7, 60.8, 55.2, 45.4, 45.4, 37.7, 36.9, 36.5, 35.4, 32.7, 31.3, 26.5, 26.4, 26.2, 25.9, 23.6, 20.7, 20.1, 19.1, 18.6, 18.5, 18.2, 17.9, 14.0, 11.9, -3.1, -3.3, -3.4, -3.7, -4.6, -4.9; high resolution MS (EI): calcd for $C_{53}H_{97}O_6NSSi_3$ (M + Na^+ *m/e* 982.6216 , found 982.6242.



(3S,5S,6S,7S,8S,12Z,15S,16E)-3,7,15-Tris-(tert-butyl-dimethyl-silanyloxy)-5-(4-methoxy-benzyloxy)-4,4,6,8,12,16-hexamethyl-17-(2-methyl-thiazol-4-yl)-heptadeca-12,16-dienoic acid (207).

Dess-Martin (2 eq, 23 mg, .054 mmol) was added in one portion to a stirring solution of alcohol above (25.9 mg, .027 mmol) in dried CH_2Cl_2 (2.5 mL) and pyridine (59 μL). Stirred at room temperature for 1 hr then transferred to a short column of Davisil, Na_2SO_4, and eluted with 20 % ether-hexanes. Extracted with H_2O, combine

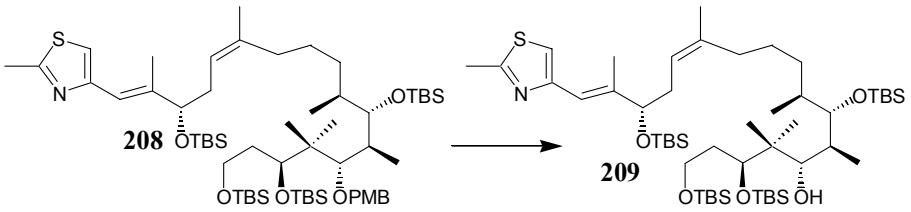
organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give crude aldehyde in quantitative yield. To a solution of the above crude aldehyde in *tert*-butyl alcohol (.6 mL) and 2,3-dimethyl-but-2-ene (.6 mL) was added a solution of $NaClO_2$ (12.3 mg, .135 mmol, 5 equiv) and NaH_2PO_4 (12.3 mg) in water (.12 mL). The mixture was stirred for 1 hr and then diluted with ether. The layers were separated, the aqueous phase was extracted with Et_2O, and the combined organic solutions were dried over $NaSO_4$, filtered, and concentrated. Flash column chromatography (silica gel, elution with 30% EtOAc-Hexanes) furnished 25.26 mg (.026 mmol, 96%) of the carboxylic acid: R_f 0.10 (EtOAc-Hexanes, 1:5); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27 (d, J = 8.5 Hz, 2H), 6.95 (s, 1H), 6.86 (d, J = 8.5 Hz, 2H), 6.64 (s, 1H), 5.17 (t, J = 7.2 Hz, 1H), 4.62 – 4.37 (AB q, J = 10.7 Hz, 2H), 4.25 (br m, 1H), 4.19 (dd, J = 4.4, 5.0 Hz, 1H), 3.80 (s, 3H), 3.52 (br m, 1H), 3.18 (s, 1H), 2.72 (s, 3H), 2.63 (br d, J = 16.3 Hz, 1H), 2.44 – 2.40 (dd, J = 16.2, 7.4 Hz, 1H), 2.26 – 1.93 (m, 4H), 1.96 (s, 3H), 1.69 (s, 3H), 1.61 – 1.52 (m, 2H), 1.26 (br s, 6H), 1.25 – 1.11 (m, 4H), .97 (d, J = 6.1 Hz, 3H), .93 (d, J = 7.3 Hz, 3H), .91 (s, 9H), .89 (s, 9H), .88 (s, 9H), { .09, .06, .04, .00 (m, 18H) }; ^{13}C NMR (500 MHz, $CDCl_3$) δ 175.2, 165.4, 158.8, 152.5, 144.1, 137.5, 131.6, 128.5, 121.3, 117.9, 114.4, 113.6, 84.7, 80.1, 79.2, 74.2, 73.7, 55.2, 45.5, 39.0, 38.3, 36.9, 35.3, 32.7, 32.3, 31.9, 29.7, 26.7, 26.4, 26.2, 25.823.5, 22.7, 20.5, 20.4, 18.6, 18.5, 18.4, 18.3, 17.0, 14.1, 14.0, 11.3, -3.3, -3.4, -3.7, -4.3, -4.7, -5.0.



(-)-(1E,3S,5Z,10S,11S,12S,13S,15S)-2-Methyl-4-[3,11,15,17-tetrakis-(*tert*-butyl-dimethyl-silanyloxy)-13-(4-methoxy-benzyloxy)-2,6,10,12,14,14-hexamethyl-heptadeca-1,5-dienyl]-thiazole (208).

2,6-lutidine (38.3 μL, .332 mmol, 4 equiv) was added dropwise to a solution of alcohol **206** (79.7 mg, .083 mmol) in dry CH_2Cl_2 (1.6 mL) at – 78^0 C, followed by 3 equiv of TBSOTf (57.1 μL, .249 mmol). After 2 hours at that temperature, the mixture was quenched by dropwise addition of saturated NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by flash chromatography (silica gel, 3% EtOAc-Hexanes) afforded product indicated (85.65 mg, .0797 mmol, 96%): R_f 0.62 (EtOAc-Hexanes, 1:5); $[\alpha]_D^{25}$ -3.8 (c 2.5, CH_2Cl_2); IR (neat) ν 2955, 2929, 2855, 1614, 1514, 1471, 1462, 1387, 1360, 1301, 1250, 1180, 1093 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.26 (d, J = 8.5 Hz, 2H), 6.92 (s, 1H), 6.86 (d, J = 8.5 Hz, 2H), 6.47 (s, 1H), 5.12 (t, J = 6.8 Hz, 1H), 4.60 – 4.39 (AB q, J = 10.8 Hz, 2H), 4.09 (t, J = 6.4 Hz, 1H), 3.90 (m, 1H), 3.81 (s, 3H), 3.68 (m, 1H), 3.59 (m, 1H), 3.50 (d, J = 6.9 Hz, 1H), 3.40 (br s, 1H), 2.72 (s, 3H), 2.25 (m, 2H), 2.04 – 1.99 (m, 1H), 2.00 (s, 3H),

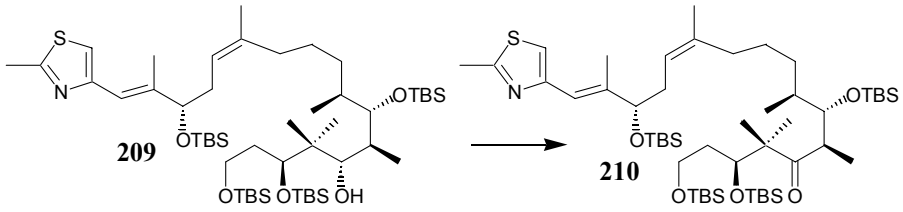
1.87 (m, 1H), 1.68 – 1.60 (m, 2H), 1.67 (s, 3H), 1.43 (m, 1H), 1.31 – 1.21 (m, 4H), 1.12 (m, 1H), .98 (d, J = 6.9 Hz, 3H), .97 (d, J = 6.8 Hz, 3H), .91 (s, 9H), .90 (s, 9H), .89 (s, 9H), .88 (s, 9H), .86 (s, 3H), .84 (s, 3H), { .08, .06, .05, .03, .01 (m, 24H) }; ^{13}C NMR (500 MHz, $CDCl_3$) δ 164.4, 158.7, 153.2, 142.7, 136.9, 131.9, 128.3, 121.4, 118.6, 114.9, 113.6, 83.2, 81.3, 79.0, 73.8, 73.4, 61.6, 55.3, 45.4, 37.5, 36.9, 36.8, 35.3, 32.7, 31.0, 30.3, 29.7, 26.4, 26.3, 26.0, 25.9, 23.6, 20.0, 19.8, 19.2, 18.7, 18.5, 18.3, 18.2, 18.1, 13.9, 12.3, -3.0, -3.1, -3.3, -3.8, -4.6, -4.9, -5.2; high resolution MS (EI): calcd for $C_{59}H_{111}O_6NSSi_4$ $(M + Na)^+$ *m/e* 1096.7087 , found 1096.7107.



(-)-(3S,5S,6S,7S,8S,12Z,15S,16E)-1,3,7,15-Tetrakis-(*tert*-butyl-dimethyl-silanyloxy)-4,4,6,8,12,16-hexamethyl-17-(2-methyl-thiazol-4-yl)-heptadeca-12,16-dien-5-ol (209).

Freshly prepared solution of DDQ (.017 mmol, 2.1 ml, .008 M in CH_2Cl_2, 1.2 equiv) was added dropwise to a solution of O-PMB ether **208** (15 mg, .0140 mmol) in 1.7 ml (total) CH_2Cl_2 /H_2O (15 : 1) at 0^0 C. After 1.5 h at room temperature, the mixture was quenched by dropwise addition of saturated $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by flash chromatography (silica gel, 5% EtOAc-Hexanes) afforded product **209** (12.52 mg, .0131 mmol, 93%): R_f 0.47 (EtOAc-Hexanes, 1:5); $[\alpha]_D^{25}$ -7.3 (c 2.96, CH_2Cl_2); IR (neat)

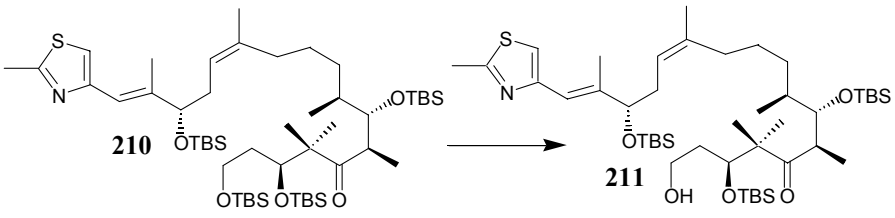
v 3460, 2954, 2926, 2854, 1471, 1386, 1360, 1253, 1081 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.91 (s, 1H), 6.46 (s, 1H), 5.12 (t, J = 6.8 Hz, 1H), 4.08 (t, J = 6.4 Hz, 1H), 3.88 (m, 1H), 3.67 (m, 1H), 3.58 (m, 1H), 3.49 (br d, J = 6.9 Hz, 1H), 3.39 (br s, 1H), 2.70 (s, 3H), 2.23 (m, 2H), 2.03 – 1.97 (m, 2H), 1.99 (s, 3H), 1.86 (m, 1H), 1.66 (s, 3H), 1.59 (m, 1H), 1.42 – 1.11 (m, 6H), .97 - .95 (d, J = 6.7 Hz, 6H), .90 (s, 9H), .89 (s, 9H), .88 (s, 9H), .86 (s, 9H), .85 (s, 3H), .82 (s, 3H), { .07, .05, .04, .01, -.002 (m, 24H) }; ^{13}C NMR (500 MHz, $CDCl_3$) δ 157.8, 152.3, 141.8, 136.1, 120.5, 117.7, 114.0, 82.3, 80.5, 72.9, 72.6, 60.8, 44.5, 36.6, 36.1, 36.0, 34.5, 31.8, 30.2, 29.5, 28.9, 25.6, 25.4, 25.1, 25.0, 22.7, 19.1, 18.9, 18.3, 17.8, 17.6, 17.41, 17.39, 17.27, 13.1, 11.4, -3.96, -3.99, -4.2, -4.6, -5.5, -5.8, -6.1.



(-)-(3S,6R,7S,8S,12Z,15S,16E)-1,3,7,15-Tetrakis-(*tert*-butyl-dimethyl-silanyloxy)-4,4,6,8,12,16-hexamethyl-17-(2-methyl-thiazol-4-yl)-heptadeca-12,16-dien-5-one (210).

To a solution of alcohol **209** (11 mg, .0115 mmol) in dry CH_2Cl_2 (.4 ml) was added pyridine (19 μL, .0345 mmol, 3 equiv) followed by Dess-Martin reagent (14.6 mg, .0345 mmol, 3 equiv) at room temperature. After 4 hours of constant stiring, the reaction mixture was transferred to a short column of silica gel (Davisil) and Na_2SO_4 then eluted with ~ 8% EtOAc / Hexanes. Concentrated in vacuo and purified by flash column

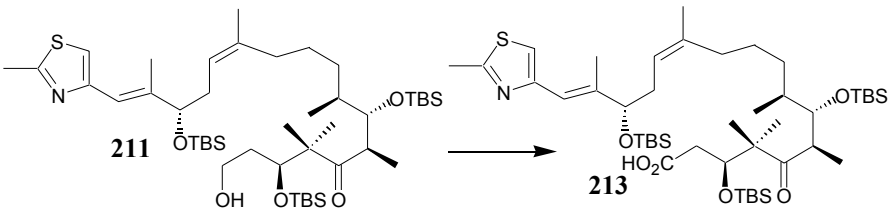
chromatography (silica gel, elution with 5% EtOAc-Hexanes) to obtain ketone **210** (9.971 mg, .0105 mmol, 91 %): R_f 0.52 (EtOAc-Hexanes, 1:10); $[\alpha]_D^{25}$ -10.6 (c .52, $CHCl_3$); IR (neat) *v* 2954, 2929, 2884, 2856, 1693, 1471, 1462, 1387, 1360, 1255, 1184, 1094 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.92 (s, 1H), 6.47 (s, 1H), 5.12 (t, J = 6.8 Hz, 1H), 4.08 (t, J = 6.7 Hz, 1H), 3.88 (dd, J = 7.4, 2.6 Hz, 1H), 3.76 (dd, J = 7.1, 1.7 Hz, 1H), 3.66 (ddd, J = 9.5, 8.9, 5.0 Hz, 1H), 3.57 (dd, J = 7.5, 1.9 Hz, 1H), 3.13 (qd, J = 6.7 Hz, 1H), 2.72 (s, 3H), 2.23 (m, 2H), 1.99 (s, 3H), 1.96 – 1.91 (m, 2H), 1.66 (s, 3H), 1.53 – 1.24 (m, 6H), 1.21 (s, 3H), 1.03 (d, J = 6.7 Hz, 3H), 1.01 (s, 3H), .90 - .88 (br m, 39H), .084 - .00 (m, 24H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 218.2, 164.3, 153.2, 142.5, 136.7, 121.5, 118.6, 114.9, 79.0, 74.0, 61.0, 53.6, 45.0, 38.9, 38.1, 35.3, 32.6, 31.0, 26.2, 26.1, 26.0, 25.8, 24.5, 23.5, 19.4, 19.2, 18.5, 18.3, 18.28, 18.2, 17.5, 13.9, -3.7, -3.8, -4.0, -4.7, -4.9, -5.2; high resolution MS (EI): calcd for $C_{51}H_{101}O_5NSSi_4$ $(M + Na)^+$ *m/e* 974.6387 , found 974.6375.



(-)-(3S,6R,7S,8S,12Z,15S,16E)-3,7,15-Tris-(*tert*-butyl-dimethyl-silanyloxy)-1-hydroxy-4,4,6,8,12,16-hexamethyl-17-(2-methyl-thiazol-4-yl)-heptadeca-12,16-dien-5-one (211).

To compound **210** (35.7 mg, .0377 mmol) dissolved in MeOH-CH_2Cl_2 (1:1, 1.4 mL) was added CSA (8.73 mg, .0377 mmol, 1 equiv) at 0^0 C. The mixture was stirred

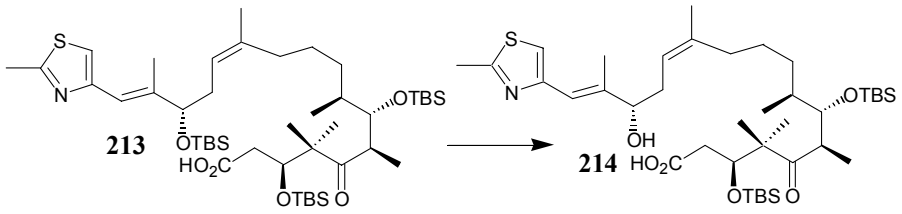
for 4 h and then deluted with CH_2Cl_2 and quenched with saturated aqueous $NaHCO_3$. The layers were separated, the aqueous phase was extracted with Et_2O, and the combined organic solutions were dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography (silica gel, elution with 20% EtOAc-Hexanes) furnished 27.50 mg (.0328 mmol, 87%) of the alcohol **211**: R_f 0.30 (EtOAc-Hexanes, 1:10); $[\alpha]_D^{25}$ -9.7 (c .46, $CHCl_3$); IR (neat) ν 3417, 2954, 2884, 2855, 1682, 1471, 1462, 1386, 1360, 1255, 1185, 1083, 986 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.91 (s, 1H), 6.45 (s, 1H), 5.13 (t, J = 6.9 Hz, 1H), 4.09 – 4.05 (m, 2H), 3.79 (br d, J = 7.0 Hz, 1H), 3.64 (t, J = 6.5 Hz, 2H), 3.12 (qd, J = 7.0, 6.5 Hz, 1H), 2.71 (s, 3H), 2.23 (m, 2H), 1.99 (s, 3H), 2.03 – 1.91 (m, 2H), 1.65 (s, 3H), 1.54 – 1.26 (m, 5H), 1.22 (s, 3H), 1.20 – 1.11 (m, 2H), 1.06 – 1.05 (br s, 6H), .90 - .86 (m, 30H), .10 (s, 3H), .06 (s, 9H), .04 (s, 3H), -.004 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 219.5, 164.4, 153,1, 142.6, 136.7, 121.6, 118.6, 114.9, 79.0, 73.1, 60.2, 53.7, 45.9, 45.1, 38.8, 38.4, 35.3, 32.5, 30.8, 26.2, 26.0, 24.9, 23.5, 19.1, 18.5, 18.3, 17.7, 15.6, 13.9, -3.6, -3.8, -3.9, -4.7, -4.9; high resolution MS (EI): calcd for $C_{45}H_{87}O_5NSSi_3$ $(M + Na)^+$ *m/e* 860.5489 , found 860.5510.



(-)-(3S,6R,7S,8S,12Z,15S,16E)-3,7,15-Tris-(*tert*-butyl-dimethyl-silanyloxy)-4,4,6,8,12,16-hexamethyl-17-(2-methyl-thiazol-4-yl)-5-oxo-heptadeca-12,16-dienoic acid (213).

To a solution of alcohol **211** (86.4 mg, .102 mmol) and dry pyridine (.22 mL) and CH_2Cl_2 (5 mL) was added Dess-Martin reagents (65.8 mg, .153 mmol, 1.5 equiv) at room temperature. The mixture was stirred for 2.5 h and then diluted with ether; the precipitate was separated by filtration and washed with ether. The filtrate was washed with saturated aqueous $NaHCO_3$-$Na_2S_2O_3$ (1:1), dried over Na_2SO_4, filtered through a short pad of silical gel, and concentrated under reduced pressure to afford the crude aldehyde. To a solution of the above crude aldehyde in *tert*-butyl alcohol (2.3 mL) and 2,3-dimethyl-but-2-ene (2.3 mL) was added a solution of $NaClO_2$ (46.4 mg, .51 mmol, 5 equiv) and NaH_2PO_4 (46 mg) in water (.5 mL). The mixture was stirred for 45 min and then diluted with ether. The layers were separated, the aqueous phase was extracted with Et_2O, and the combined organic solutions were dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography (silica gel, elution with 35% EtOAc-Hexanes) furnished 81.74 mg (.0959 mmol, 94%) of the carboxylic acid **213**: R_f 0.3 (EtOAc-Hexanes, 1:5); $[\alpha]_D^{25}$ -2.6 (c 3.5, $CHCl_3$), lit. $[\alpha]_D^{25}$ -2.9 (c 0.8, $CHCl_3$)[102]; IR (neat) ν 3423, 2955, 2929, 2856, 1712, 1509, 1472, 1388, 1360, 1294, 1254, 1188, 1082 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.93 (s, 1H), 6.58 (s, 1H), 5.16 (t, J = 7.0 Hz, 1H), 4.40 (dd, J = 6.6, 3.1 Hz, 1H), 4.12 (m, 1H), 3.75 (dd, J = 5.8, 2.0 Hz, 1H), 3.13 (qd, J = 7.1, 6.5 Hz, 1H), 2.71 (s, 3H), 2.45 (dd, J = 16.6, 3.3 Hz, 1H), 2.31 (dd, J = 16.5, 6.8 Hz, 1H), 2.25 – 2.04 (m, 3H), 1.95 (s, 3H), 1.93 – 1.86 (m, 2H), 1.67 (s, 3H), 1.50 – 1.34 (m, 4H), 1.18 (s, 3H), 1.13 (s, 3H), 1.07 (d, J = 6.8 Hz, 3H), .89 - .87 (m, 30H), { .13, .08, .07, .04, .03, -.01 (m, 18H) }; ^{13}C NMR (300 MHz, $CDCl_3$) δ 218.1, 175.6, 165.1, 152.7, 143.5, 137.0, 121.6, 118.1, 114.5, 79.1, 73.3, 53.8, 44.5, 40.0, 39.2, 35.3, 32.5, 31.4, 26.2, 26.0, 25.8, 25.3, 23.5,

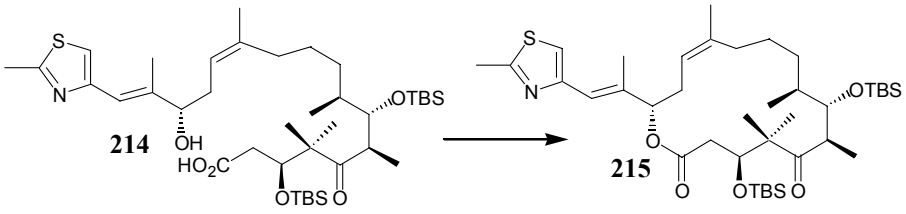
18.9, 18.7, 18.5, 18.2, 16.8, 15.7, 14.0, -3.8, -4.0, -4.1, -4.6, -4.7, -5.0; high resolution MS (EI): calcd for $C_{45}H_{85}O_6NSSi_3$ $(M + Na)^+$ *m/e* 874.5305, found 874.5305.



(-)-(3S,6R,7S,8S,12Z,15S,16E)-3,7-Bis-(*tert*-butyl-dimethyl-silanyloxy)-15-hydroxy-4,4,6,8,12,16-hexamethyl-17-(2-methyl-thiazol-4-yl)-5-oxo-heptadeca-12,16-dienoic acid (214).

TBAF (.466 mL, .466 mmol, 1M in THF, 5 equiv) was added to a stirring solution of **75** (75.6 mg, .0932 mmol) in 2 mL of THF at room temperature. The reaction mixture was stirred for 10 h at room temperature and then quenched by addition of saturated aqueous NH_4Cl and extracted with ether. The organic phase was washed with brine and dried (Na_2SO_4), and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 50% EtOAc-Hexanes) furnished seco acid **214** (52.72 mg, .0699 mmol, 75%): R_f 0.48 (EtOAc-Hexanes, 1:1); $[\alpha]_D^{25}$ -10.9 (c 2.2, $CHCl_3$), lit. $[\alpha]_D^{25}$ -10.4 (c 0.4, $CHCl_3$)[102] ; IR (neat) *v* 3320, 2955, 2928, 2855, 1729, 1713, 1696, 1462, 1360, 1255, 1088 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.97 (s, 1H), 6.71 (s, 1H), 5.18 (t, J = 7.1 Hz, 1H), 4.41 (br dd, J = 6.0, 3.7 Hz, 1H), 4.17 (t, J = 6.3 Hz, 1H), 3.78 (br d, J = 6.1 Hz, 1H), 3.12 (qd, J = 7.0, 6.4 Hz, 1H), 2.75 (s, 3H), 2.46 (dd, J = 16.5, 3.2 Hz, 1H), 2.36 – 2.32 (m, 3H), 2.19 – 2.12 (m, 1H), 1.99 (s, 3H), 2.02 – 1.94 (m, 1H), 1.72 (s, 3H), 1.57 – 1.31 (m, 5H), 1.20 (s, 3H), 1.15 (s, 3H), 1.06 (d, J = 6.7 Hz, 3H), .92

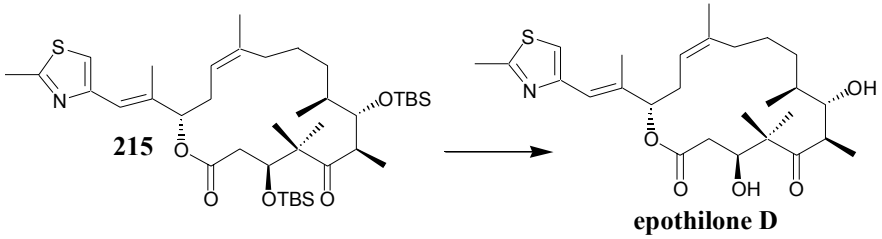
- .86 (m, 21H), { .11, .08, .07, .05 (m, 12H) }; ^{13}C NMR (250 MHz, $CDCl_3$) δ 217.9, 174.8, 165.2, 152.5, 142.2, 139.4, 120.3, 118.6, 115.1, 73.4, 53.9, 44.6, 40.0, 39.2, 34.2, 32.5, 31.4, 26.3, 26.2, 26.0, 23.6, 23.4, 19.1, 18.7, 18.5, 18.2, 16.9, 16.0, 14.7, -3.8, -4.0, -4.1, -4.6.



(-)-(4S,7R,8S,9S,13Z,16S)-4,8-Bis-(*tert*-butyl-dimethyl-silanyloxy)-5,5,7,9,13-pentamethyl-16-[(E)-1-methyl-2-(2-methyl-1,3-thiazol-4-yl)-ethenyl]-oxacyclohexadec-13-ene-2,6-dione (215).

To a solution of hydroxy acid **214** (37.6 mg, .0509 mmol) in THF (2 mL) were added Et_3N (80 µL, .509 mmol, 10 equiv) and 2,4,6-trichlorobenzoyl chloride (84.8 µL, .611 mmol, 12 equiv). The mixture was stirred at room temperature for 30 min, diluted with toluene (6.75 mL), and added dropwise over a period of 3h to a solution of DMAP (247 mg, 2.04 mmol, 40 equiv) in toluene (40 mL). After complete addition, the mixture was stirred for an additional 2 h and concentrated in vacuo. Purification of the residue by silica gel flash chromatography (silica gel, 20% EtOAc-Hexanes) furnished **215** (23.1 mg, .0321 mmol, 63%): R_f 0.38 (EtOAc-Hexanes, 1:10); $[\alpha]_D^{25}$ -12.3 (c 1.1, $CHCl_3$), lit. $[\alpha]_D^{25}$ -11.8 (c 0.8, $CHCl_3$)[102] ; IR (neat) *ν* 2953, 2928, 2855, 1742, 1694, 1462, 1378, 1254, 1158 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.97 (s, 1H), 6.58 (s, 1H), 5.16 (t, J

= 8.1 Hz, 1H), 4.97 (d, J = 9.9 Hz, 1H), 4.02 (d, J = 9.5 Hz, 1H), 3.89 (d, J = 8.9 Hz, 1H), 3.03 (qd, J = 7.0, 6.5 Hz, 1H), 2.81 (d, J = 16.6 Hz, 1H), 2.72 (s, 3H), 2.71 – 2.63 (m, 2H), 2.50 –2.41 (m, 1H), 2.10 (s, 3H), 2.09 – 2.02 (m, 2H), 1.74 – 1.69 (m, 2H), 1.67 (s, 3H), 1.63 – 1.47 (m, 3H), 1.20 (s, 3H), 1.14 (s, 3H), 1.10 (d, J = 6.7 Hz, 3H), .97 (d, J = 7.0 Hz, 3H), .95 (s, 9H), .85 (s, 9H), .11 (br s, 6H), .07 (s, 3H), -.11 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 215.1, 171.2, 164.9, 152.5, 140.7, 138.7, 119.1, 119.0, 115.9, 79.8, 76.3, 53.4, 39.1, 32.4, 31.9, 31.4, 29.7, 27.5, 26.4, 26.2, 26.0, 24.6, 24.3, 23.1, 19.3, 18.7, 18.6, 17.8, 15.4, -3.3, -3.7, -5.6; high resolution MS (EI): calcd for $C_{39}H_{69}O_5NSSi_2$ (M^+) *m/e* 719.4421, found 719.4417.

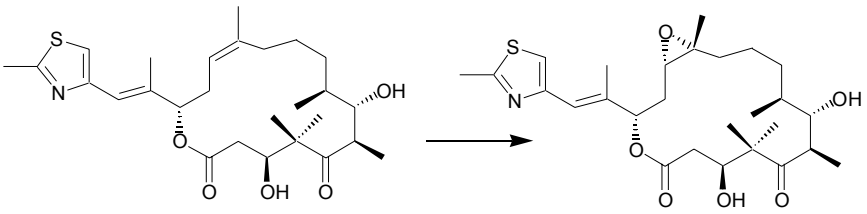


epothilone D

(-)-(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[(E)-1-methyl-2-(2-methyl-1,3-thiazol-4-yl)-ethenyl]-oxacyclohexadec-13-ene-2,6-dione (Epothilone D).

To a plastic container containing a solution of **77** (27.4 mg, .0380 mmol) in THF (1.8 mL) and pyridine (.55 mL) was added HF.pyridine (1.1 mL) at 0^0 C. Reaction mixture was allowed to warm to room temperature over 24 hours. At 0^0 C the mixture was quenched by slowly adding saturated aqueous $NaHCO_3$, then diluted with ether. The layers were separated, the aqueous phase was extracted with Et_2O, and the combined

organic solutions were dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography (silica gel, elution with 50% EtOAc-Hexanes) furnished 16.26 mg (.033 mmol, 87%) of **epothilone D**: R_f 0.12 (EtOAc-Hexanes, 1:3); $[\alpha]_D^{25}$ -89.7 (c .57, $CHCl_3$), lit. $[\alpha]_D^{25}$ -91.5 (c 0.3, $CHCl_3$)[102] ; IR (neat) ν 3499, 2933, 1732, 1687, 1506, 1466, 1376, 1335, 1293, 1251, 1187, 1149 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.95 (s, 1H), 6.57 (s, 1H), 5.20 (dd, J = 9.6, 1.1 Hz, 1H), 5.13 (dd, J = 10.0, 4.8 Hz, 1H), 4.28 (br d, J= 10.8 Hz, 1H), 3.72 (br s, 1H), 3.43 (br s, 1H), 3.15 (qd, J = 6.5, 2.5 Hz, 1H), 3.05 (br s, 1H), 2.69 (s, 3H), 2.63 (dt, J = 15.1, 9.9 Hz, 1H), 2.45 (dd, J = 14.6, 11.1 Hz, 1H), 2.35 – 2.27 (m, 1H), 2.29 (dd, J = 14.6, 2.5 Hz, 1H), 2.22 (br d, J = 15.0 Hz, 1H), 2.06 (s, 3H), 1.90 – 1.85 (m, 1H), 1.77 – 1.67 (m, 1H), 1.66 (s, 3H), 1.34 (s, 3H), 1.31 – 1.25 (m, 4H), 1.18 (d, J = 6.8 Hz, 3H), 1.07 (s, 3H), 1.01 (d, J = 7.0 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 220.6, 170.4, 165.0, 152.0, 139.2, 138.5, 120.9, 119.3, 115.6, 78.9, 74.1, 72.3, 53.5, 41.7, 39.6, 38.4, 32.5, 31.7, 31.6, 25.4, 22.9, 19.0, 18.1, 15.8, 15.8, 13.4; high resolution MS (EI): calcd for $C_{27}H_{41}O_5NS$ (M^+) *m/e* 491.2693, found 491.2705.



epothilone D **epothilone B**

(-)-(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[(E)-1-methyl-2-(2-methyl-1,3-thiazol-4-yl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (Epothilone B).

To a solution of epothilone D (9 mg, 18.29 μmol) in dry CH_2Cl_2 (1mL) was added *m*-CPBA (6.86 mg, 27.44 μmol, 1.5 equiv, 70% purity) at – 18^0 C. The reaction mixture was stirred for 4.5 h at the same temperature and then diluted with CH_2Cl_2 and quenched with saturated aqueous $NaHCO_3$. The organic phase was washed with brine and dried (Na_2SO_4), and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 75% EtOAc-Hexanes), followed by prep plate (1:1 EtOAc-Hexanes) furnished epothilone B (7.52 mg, 14.82 μmol, 81%): mp 91-93^0 C, lit. mp 93^0 C[102] ; R_f .2 (4% MeOH / CH_2Cl_2); $[\alpha]_D^{25}$ -35.8 (c .55, MeOH), lit. $[\alpha]_D^{25}$ -34.3 (c 0.2, MeOH)[102]; ^{1}H NMR ($CDCl_3$, 350 MHz) δ 6.98 (s, 1H), 6.61 (s, 1H), 5.41 (dd, J = 7.9, 3.0 Hz, 1H), 4.26 (br s, 2H), 3.77 (br s, 1H), 3.30 (qd, J = 7.0, 4.0 Hz, 1H), 2.80 (dd, J = 7.4, 4.5 Hz, 1H), 2.71 (s, 3H), 2.64 (s, 1H), 2.54 (dd, J = 14.2, 10.0 Hz, 1H), 2.35 (dd, J = 13.5, 2.7 Hz, 1H), 2.16 – 2.07 (m, 1H), 2.08 (s, 3H), 1.90 (dd, J = 15.5, 8.0 Hz, 1H), 1.77 – 1.66 (m, 3H), 1.55 – 1.44 (m, 2H), 1.44 – 1.34 (m, 2H), 1.38 (s, 3H), 1.28 (s, 3H), 1.17 (d, J = 7.0 Hz, 3H), 1.08 (s, 3H), 1.00 (d, J = 7.0 Hz, 3H); high resolution MS (EI): calcd for $C_{27}H_{41}O_6NS$ (M^+) *m/e* 507.2646, found 507.2655.

REFERENCES

1. For reviews of synthetic efforts in the macrolide antibiotic area, see: (a) Paterson, I.; Mansuri, M.M. *Tetrahedron* **1985**, *41*, 3569. (b) Masamune, S.; McCarthy, P. *In Macrolide Antibiotics*, Omura, S., ed.; Academic Press: New York, **1984**, p. 127.

2. (a) Evans, D. A. *Aldrichimica Acta*, **1982**, 15, 25. (b) Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichimica Acta*, **1997**, 30, 3. (c) Yanagisawa. A in *Comprehensive Asymmetric Catalysis* (Eds.: Jacobsen, N. E.; Pfaltz. A.; Yamamoto. H, Springer, Berlin, **2000**, chapter. 27.

3. Bode, J. W.; Fraefel, N.; Muri. D.; Carreira, E. M. *Angew. Chem*. **2001**, 113, 2128.

4. (a) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc*. **1993**, 115, 12208. (b) Jung, M. E.; Hofffmann. B.; Rausch. B.; Contreras, J. M. *Org. Lett*, **2003**, 5, 3159.

5. (a) Hoffmann, H. M. R. *Angew. Chem*. **1973**, 85, 877; *Angew. Chem. Int. Ed. Engl*. **1973**, 12, 819. (b) Noyori. R.; Hayakawa. Y. *Org. React*. **1983**, 29, 163. (c) Hoffmann, H. M. R. *Angew. Chem*. **1984**, 96, 29; *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 1. (d) Mann. J. *Tetrahedron* **1986**, 42, 4611. (e) Rigby, H. J.; Pigge, F. C. *Org. React*. **1997**, 51, 351. (f) Harmata. M.; Rashatasakhon. P, *Tetrahedron* **2003**, 59, 2371.

6. (a) Hosomi. A.; Tominaga. Y. In *Comprehensive Organic Synthesis*; Trost. B.; Fleming. I., Eds.; Pergamon: Oxford, UK.; **1991**; Vol. 5, Chapter 5.1, p 593. (b)

Hoffmann, H . M. R. *Angew. Chem., Int. Ed. Engl*. **1984**, 23, 1. (c) Noyori. R.; Hayakawa. Y. *Org. React*. **1983**, 29, 163.

7. Alvarez. E.; Diaz, M. T.; Perez. R.; Martin, J. D. *Tetrahedron Lett*. **1991**, 32, 2241.

8. (a) Sammes, P. G.; Street, L. J. *J. Chem. Soc. Chem. Commun*, **1983**, 666. (b) Sammes, P. G. ; Street, L. J.; Whitby, R. J. *J. Chem. Soc. Perkin. Trans 1*. **1986**, 281.

9. Jung, M. E.; Street, L. J. *J. Am. Chem. Soc*. **1984**, 106, 8327.

10. (a) Lautens. M.; Stammers, T. A. *Synlett*, **2002**, 1993. (b) Lautens. M.; deFrutos. O.; Stammers, T. A. *Tetrahedron Lett*. **1999**, 40, 8317-8321.

11. (a) Grieco, P. A.; Zelle, R. E.; Lis. R.; Finn. J. *J. Am. Chem. Soc*. **1983**, 105, 1403. (b) Grieco, P. A.; Zelle, R. E.; Lis. R.; Finn. J. *J. Am. Chem. Soc*. **1986**, 108, 5908.

12. Forsey, S. P.; Rajapaksa. D.; Taylor, N. J.; Rodrigo. R. *J. Org. Chem*. **1989**, 54, 4280.

13. (a) Duan, J. P.; Cheng, C. H. *Tetrahedron Lett*, **1993**, 34, 4019. (b) Moinet. C.; Fiaud, J. C. *Tetrahedron Lett*, **1995**, 36, 2051.

14. (a) Mann. J. *Tetrahedron Asymm*. **1986**, 42, 4611. (b) Rigby, J. H.; Pigge, F. C *Org. React*. **1997**, *51*, 351. (c) Noyori. R.; Hayakawa. Y. *Org React*, **1983**, 29, 163. (d) Hoffmann, H. M. R. *Angew. Chem. Int. Ed. Engl*. **1973**, 12, 819. (e) Hoffmann, H. M. R.; Clemens, K. E.; Smithers, R. H. *J. Am. Chem. Soc*. **1972**, 94, 3940.

15. Mann. J. ; Barbosa, L. A. *J. Chem. Soc. Perkin. Trans*, **1992**, 1, 787.

16. Fukuzawa. S. ; Fukushima. M. ; Fujinami. T. ; Sakai. S. *Bull. Chem. Soc. Jpn*, **1989**, 62, 2348.

17. (a) Joshi, N. N. ; Hoffmann, H. M. R. *Tetrahedron Lett*, **1986**, 27, 687. (b) Hoffmann, H. M. R. ; Eggert. U.; Gibbels. U.; Giesel. K.; Koch. O.; Lies.R. ; Rabe. J. *Tetrahedron*, **1988**, 44, 3899.

18. Herter. R. ; Föhlisch. B. *Synthesis*, **1982**, 976.

19. Takaya. H. ; Makino. S. ; Hayakawa.Y. ; Noyori. R. *J. Am. Chem. Soc*, **1978**, 100, 1765.

20. Vinter, J. G. ; Hoffmann, H. M. R. *J. Am. Chem. Soc*, **1973**, 95, 3051.

21. (a) Murray, D. H. ; Albizati, K. F. *Tetrahedron Lett*, **1990**, 31, 4109. (b) Föhlisch. B. ; Sendelbach. S. ; Bauer. H. *Liebig. Ann. Chem*, **1987**, 1.

22. Föhlisch. B. ; Krimmer. D. ; Gerlach. E. ; Kashammer.D. *Chem Ber*, **1988**, 121, 1585.

23. (a) Föhlisch. B. ; Herter. R. ; Wolf. E. ; Stezowske, J. J. *Chem. Ber*, **1982**, 115, 355. (b) Herter. R. ; Föhlisch. B. *Synthesis* **1982**, 976.

24. Ohno. M. ; Mori. K. ; Hattori. T. ; Eguchi. S. *J. Org. Chem*, **1990**, 55, 6086.

25. (a) Noyori. R. ; Nishizawa. M. ; Shimizu. F. ; Hayakawa. Y. ; Maruoka. K. ; Hashimoto. S. ; Yamamoto. H. ; Nozaki. H. *J. Am. Chem. Soc*, **1979**, 101, 220. (b) Fohlisch. B. ; Herter. R. *Chem Ber*, **1984**, 117, 2580.

26. (a) Harmata. M. ; Gamlath, C. B. *J. Org. Chem*, **1988**, 53, 6154. (b) Harmata. M. ; Gamlath, C. B. ; Barnes, C. L. *Tetrahedron Lett*, **1990**, 31, 5981. (c)

Harmata. M. ; Fletcher, V. R. ; Claassen II, R. J. *J. Am. Chem. Soc*, **1991**, 113, 9861. (d) Harmata. M. ; Elahmad. S. *Tetrahedron Lett*, **1993**, 34, 789. (e) Harmata. M. ; Elomari. S. *Tetrahedron Lett*, **1996**, 37, 783. (f) Harmata. M. ; Elahmad. S. ; Barnes, C. L. *J. Org. Chem*, **1994**, 59, 1241.

27. Harmata. M. ; Jones, D. E. *Tetrahedron Lett*, **1996**, 37, 783.

28. (a) Harmata. M. ; Elahmad. S. *Tetrahedron Lett*, **1993**, 34, 789. (b) Harmata. M. ; Elomari. S. ; Barnes, C. L. *J. Am. Chem. Soc*, **1996**, 118, 2860.

29. Schultz, A. G. ; Macielag. M. ; Plummer. M. *J. Org. Chem*, **1988**, 53, 391.

30. (a) Davies. H. ; Clark, D. M. ; Smith, T. K. *Tetrahedron Lett*, **1985**, 26, 5659. (b) Davies. H. ; Clark, D. M. ; Alligood, D. B. ; Elband, G. R. *Tetrahedron*, **1987**, 43, 4265. (c) Davies. H. ; Ahmed. G. ; Churchill, M. R. *J. Am. Chem. Soc*, **1996**, 118, 10774.

31. Arco. M. ; Trammell, M. H. ; White, J. D. *J. Org. Chem*, **1976**, 41, 2075.

32. Hoffmann, H, M. R. *Angew. Chem. Int. Ed. Engl*, **1984**, 23, 1.

33. Jung, M. E. ; Street, J. J. *J. Am. Chem. Soc*, **1984**, 106, 8327.

34. Sato. T. ; Hayakawa. Y. ; Noyori. R. *Bull. Chem. Soc. Jpn*, **1984**, 57, 2515.

35. (a) Auberson. Y. ; Vogel. P. *Helv. Chim. Acta*, **1989**, 72, 278. (b) Nativi. C. ; Reymond, J. L. ; Vogel. P. *Helv. Chim. Acta*, **1989**, 72, 882.

36. Warm. A. ; Vogel. P. *J. Org. Chem*, **1986**, 51, 5348.

37. Bimwala, R. M. ; Vogel. P. *J. Org. Chem*, **1992**, 57, 2076.

38. Sevin, A. F. ; Vogel. P. *J. Org. Chem*, **1994**, 59, 5920.

39. Fattori. D. ; Vogel. P. *Tetrahedron Lett*, **1993**, 34, 1017.

40. Klein, L. L. *J. Am. Chem. Soc*, **1985**, 107, 2573.

41. Murai. A. ; Takahashi. K. ; Taketsuru. H. ; Masamune. T. *J. Chem. Soc. Chem. Commun*, **1981**, 221.

42. Meinwald. J. *Pure & Appl. Chem*, **1997**, 49, 1275.

43. Kim. H. ; Ziani-Cherif. C. ; Oh. J. ; Cha, J. K. *J. Org. Chem*, **1995**, 60, 792.

44. Ohno. M. ; Ito. Y. ; Arita. F. ; Shibata. T. ; Adachi. K. ; Sawai. H. *Tetrahedron*, **1984**, 40, 145.

45. Alvarez. E. ; Zurita. D. ; Martin, J. D. *Tetrahedron Lett*, **1991**, 32, 2245.

46. (a) Alvarez. E. ; Diaz, M. T. ; Rodriguez, M. L. ; Martin, J. D. *Tetrahedron Lett*, **1990**, 31, 1629. (b) Zarraga. M. ; Martin, J. D. *Tetrahedron Lett*, **1991**, 32, 2249.

47. Sato. T. ; Hayakawa. Y. ; Noyori. R. *Bull. Chem. Soc. Jpn*, **1984**, 57, 2515.

48. Kozikowske, A. P. ; Ames. A. *J. Am. Chem. Soc*, **1981**, 103, 3923.

49. Schlessinger, R. H. ; Pettus, R. R. *J. Org. Chem*, **1994**, 59, 3246.

50. (a) Sammes, P. G. ; Street, L. J. *J. Chem. Soc. Chem. Commun*, **1983**, 666. (b) Sammes, P. G. ; Street, L. J. ; Whitby, R. J. J. *Chem. Soc. Perkin. Trans I*, **1986**, 281.

51. Le Drian. C. ; Vogel. P. *Helv. Chim. Acta*, **1987**, 70, 1703.

52. (a) Takahashi. T. ; Iyobe. A. ; Arai. Y. ; Koizumi. T. *Synthesis*, **1989**, 189. (b) Kinder Jr, F. R. ; Bair, K. W. *J. Org. Chem*, **1994**, 59, 6965.

53. (a) Guildford. A. ; Turner, R. W. *J. Chem. Soc. Chem. Commun*, **1983**, 466. (b) Molander, G. A. ; Eastwood, P. R. *J. Org. Chem*, **1995**, 60, 4559.

54. Stohrer. I. ; Hoffmann, H. R. *Tetrahedron*, **1992**, 48, 6021.

55. (a) Forsey, S. P. ; Rajapaksa, D. ; Taylor, N. J. ; Rodrigo, R. *J. Org. Chem*, **1989**, 54, 4280. (b) Pelter, A. ; Ward, R. S. ; Li, Q. ; Pis, J. *Tetrahedron Asymm*. **1994**, 5, 909.

56. Borthwick, A. D. ; Curry, D. J. ; Poynton, A. ; Whalley, W. B. ; Hooper, J. W. *J. Chem. Soc. Perkin. Trans l.* **1980**, 2435.

57. Harmata, M. ; Elahmad. S. ; Barnes, C. L. *J. Org. Chem*, **1994**, 59, 1241.

58. Williams, D. R. ; Benbow, J. W. ; McNutt, J. G. ; Allen, E. E. *J. Org. Chem.* **1995**, 60, 833.

59. Cauwberghs, S. G. ; De Clerq, P. J. *Tetrahedron Lett*. **1988**, 29, 6501.

60. Padwa, A. ; Sandanayaka, V. P. ; Curtis, E. A. *J. Am. Chem. Soc*. **1994**, 116, 2667.

61. De Schrijver. J. ; De Clerq, P. J. *Tetrahedron Lett*, **1993**, 34, 4369.

62. (a) Lautens, M.; Rovis, T. *Tetrahedron* **1998**, *54*, 1107. (b) Lautens, M.; Rovis, T. *J. Am. Chem. Soc.* **1997**, *119*, 11090. (c) Lautens, M.; Renaud, J. L.; Hiebert, S. *J. Am. Chem. Soc*. **2000**, *122*, 1804. (d) Lautens, M.; Fagnou, K.; Rovis, T. *J. Am. Chem. Soc.* **2000**, *122*, 5650. (e) Lautens, M.; Colucci, J. T.; Hiebert, S.; Smith, N. D.; Bouchain, G. *Org. Lett*. **2002**, *4*, 1879.

63. Lautens, M.; Colucci, J. T.; Hiebert, S.; Smith, N. D.; Bouchain, G. *Org. Lett*. **2002**, *4*, 1879.

64. (a) Barbosa, L. C. A.; Rubinger, M. M. M.; Mann, J.; Mansell, H. L. Tetrahedron 1996, 52, 11297. (b) Lautens, M.; Chiu, P.; Ma, S.; Rovis, T. *J. Am. Chem. Soc.* **1995**, *117*, 532.

65. For the use of highly polar media to promote organic reactions, see: (a) Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc*. **1990**, *112*, 4595. (b) Grieco, P. A. *Aldrichim. Acta* **1991**, *24*, 59. (c) Grieco, P. A. Organic Chemistry in Lithium Perchlorate/Diethyl Ether. *In Organic Chemistry: Its Language and Its State of the Art*; Kisakurek, V., Ed.; VCH: Basel, 1993; p 133.

66. Grieco, P. A.; Colins, J. L.; Henry, K. J. Jr. *Tetrahedron Letters* **1992**, *33*, 4735.

67. Hunt, K. W.; Grieco, P. A. *Org. Lett*. **2001**, *2*, 481.

68. Hunt, K. W.; Grieco, P. A. *Org. Lett*. **2002**, *4*, 245.

69. For review articles, see: (a) O'Brien, P. *J. Chem. Soc., Perken Trans.1* **2001**, 95. (b) Cox, P. J.; Simpkins, N. S. *Tetrahedron*: *Asymmetry* **1991**, *2*, 1. (c) Simpkins, N. S. *Chem. Soc. Rev*. **1990**, *19*, 335.

70. (a) Hoffmann, M. R.; Stohrer, I. *Tetrahedron* **1992**, *48*, 6021. (b) Fohlisch, B.; Sendelbach, S. *Liebigs Ann. Chem*. **1987**, 1-5.

71. (a) House, H. O.; Czuba, L. J. *J. Org. Chem*. **1969**, 34, 2324-2336. (b) **General Procedure:** To a stirred solution of lithium diisopropylamide [0.05 mol, prepared at 0^0C from diisopropylamine (5.05g, 0.05 mol) and *n*-BuLi (0.05 mol) in THF (50mL)] cooled at -78^0C is added over 10 min the appropriate ketone or ester (0.05 mol). The stirred solution is maintained at -78^0C for 30 min and TMSCl (0.1 mol, freshly distilled from CaH_2) is added during 10 min. After 15 min at this temperature, the mixture is allowed to warm to room temperature. After 1h, the mixture is concentrated on a rotary evaporator; a calcium chloride trap being placed between water pump and apparatus. The residue is washed with

pentane, filtered, pentane evaporated, and the product is distilled under reduced pressure. In many cases, considerable decomposition occurred during aqueous work up. Therefore, crude product was subjected directly to distillation after filtered and removal of solvent.

72. Dilman, D. A.; Ioffe, L. S. *Chem. Rev*. **2003**, *103*, 733.

73. (a) Evans, D. A. *Asymmetric Synthesis*, **1984**, Vol. 3, pp. 1-110, Academic Press, New York. (b) Evans, D. A. ; Gage, D. A. *Organic Syntheses*, **1989**, 68, 77. (c) Evans, D. A. *Aldrichimica Acta*, **1982**, 53, 23. (c) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc*. **1981**, *103*, 2127.

74. (a) Oppolzer, W. ; Chapuis, C. ; Bernardinelli, G. *Helv. Chim. Acta*, **1984**, 67, 1397. (b) Oppolzer, W.; Blagg, J.; Rodriguez, E.; Walther, E. *J. Am. Chem. Soc*. **1990**, *112*, 2767. (c) Mekelburger, H. B.; Wilcox, C, in Comprehensive Organic Synthesis, B. M. Trost and I. Fleming Ed., Pergamon Press, 1991, vol. 2, chap. 1.4. (d) Oppolzer, W. ; Loher, H. J. *Helv. Chim. Acta*, **1981**, 64, 2808. (e) Oppolzer, W. *Tetrahedron*, **1987**, 43, 1969.

75. Corey, E. J.; Ensley, M. E. *J. Am. Chem*. **1975**, *97*, 6908.

76. Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899.

77. (a) Muir, C. S. *Cancer Res*. **1990**, 50, 6441. (b) Graf, W.; Pahlman, L.; Bergstrom, R. *Br J. Cancer* **1994**, 70, 559.

78. Nordic Gastrointestinal Tumor Adjuvant Therapy Group. *J Clin Oncol*, **1992**, 10, 904.

79. (a) Hofle, G.; Bedorf, H.; Steinmetz, H.; Schomburg, D.; Gerth, K.; Reichenbach, H. *Angew. Chem. Int. Ed*. **1996**, 35, 1567. (b) Bollag, D.; McQueney, P.; Zhu, J. *Cancer Res*, **1995**, 55, 2325.

80. Hofle, G.; Bedorf, H.; Gerth, K: Epothilones A and B: Antifungal and cytotoxic compounds from Sorangium cellulosum. Production, physico-chemical and biological properties. *J. Antibiot* (Tokyo), **1996**, 49, 560.

81. Bollag, D.; McQueney, P.; Zhu, J. *Cancer Res*, **1995**, 55, 2325.

82. Kowalski, R.; Giannakakou, P.; Hamel, E. *J. Biol. Chem*, **1997**, 272, 2534.

83. Nicolau, K. C.; Roschangar, F.; Vourloumis, D. *Angew. Chem. Intl. Ed*. **1998**, 37, 2014, and references cited therein.

84. Bode, C. J.; Gupta, M. L.; Reiff, E. A.; Suprenant, K. A.; Georg, G. I.; Himes, R. H. *Biochemistry* **2002**, 41, 3870.

85. Hofle, G.; Bedorf, H.; Steinmetz, H.; Schomburg, D.; Gerth, K.; Reichenbach, H. *J. Antibiot*. **1996**, 49, 560.

86. Chou, T. C.; Ahang, X. G.; Balog, A.; Su, D. S.; Meng, D.; Savin, K.; Bertino, J. R.; Danishefsky, S. *J. Proc. Natl. Acad. Sci. USA* **1998**, 95, 9642.

87. Gianakakou, P.; Sackett, D. L.; Kang, Y. K.; Zhan, Z.; Bters, J.T. M.; Fojo, T.; Poruchynsky, M. S. *J. Biol. Chem*. **1997**, 27, 17118.

88. (a) Balog, A.; Meng, D.; Kamenecka, T.; Bertinato, P.; Su, D.; Sorensen, E. J.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2801. (b) Yang, Z.; He, Y.; Vourloumis, D.; Vallberg, H.; Nicolaou, K.C. *Angew. Chem., Int. Ed. Engl.*

1997, *36*, 166. (c) Schinzer, D.; Limberg, A.; Bauer, A.; Bohm, O. M.; Cordes, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 523. (d) May, S.A.; Grieco, P.A. *J. Chem. Soc., Chem. Commun*. **1998**, 1597. (e) Sawada, D.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 209. (f) Martin, H. J.; Drescher, M.; Mulzer, J. *Angew. Chem., Int. Ed*. **2000**. *39*, 581. (g) Schinzer, D.; Limberg, A.; Schieber , *J. Chem. Eur. J*. **1999**, 5, 2492.

89. Taylor, R. E.; Chen, Y.; Galvin, G. M.; Hilfiker, K. A. *J. Org. Chem*. **1998**, 63, 9580.

90. Lee, C. B.; Wu, Z.; Zang, F.; Chappell, M.D.; Stachel, S. J.; Chou, T. C.; Danishefsky, S. J. *J. Am. Chem. Soc*. **2001**, 123, 5249.

91. Zhu, B.; Panek, J. S. *Eur. J. Org. Chem*. **2001**, 1701.

92. Hindupur, R. M.; Panicker, B.; Valluri, M.; Avery, M. A. *Tetrahedron Lett*. **2001**, 42, 7341.

93. Martin, H.; Drescher, M.; Mulzer, J. *Angew. Chem. Int. Ed*. **2000**, 39, 581.

94. White, J. D.; Carter, R. G. *J. Am. Chem. Soc*. **2001**, *123*, 5407.

95. Balog, A.; Harris, C.; Savin, K.; Zhang, X.; Chou, T. C.; Danishefsky, S. J. *Angew. Chem. Int. Ed*. **1998**, 37, 2675.

96. Sun, J.; Sinha, S.C. *Angew. Chem. Int. Ed*. **2002**, 41, 1381.

97. Koch, G.; Loiseleur, O.; Fuentes, D.; Jantsch, A.; Altmann, K. *Org. Lett*. **2002**, 4, 3811.

98. Furstner, A.; Mathes, C.; Lehmann, C. W. *Chem. Eur. J*. **2001**, 7, 5299.

99. Kalesse, M.; Quitschalle, M.; Claus, E.; Gerlach, K.; Pahl, A.; Meyer, H. H. *Eur. J. Org. Chem*. **1999**, 2817.

100. Mulzer, J.; Karig, G.; Pojarliev. P. *Tetrahedron Lett*. **2000**, 41, 7635.

101. Nicolaou, K. C.; Sarabia, F.; Ninkovic, S.; Finlay, M. R.; Boddy, C. N. *Angew. Chem. Int. Ed*. **1998**, 37, 81.

102. Nicolaou, K.C.; He, Y.; Vourloumis, H.; Vallberg, F.; Roschangar, F.; Sarabia, S.; Ninkovic, Z.; Yang, J. I. *J. Am. Chem. Soc.* **1997**, *119*, 7974.

103. Taylor, R.E.; Haley, J. D. *Tetrahedron Lett*. **1997**, 38, 2061.

104. Nicolaou, K.C.; He, Y.; Vourloumis, H.; Vallberg, F.; Roschangar, F.; Sarabia, S.; Ninkovic, Z.; Yang, J. I. *J. Am. Chem. Soc.* **1997**, *119*, 7960

105. Nicolaou, K. C.; Hepworth, D.; King, N. P.; Finlay, M. R. V.; Scarpelli, R.; Pereira. M. A.; Bollbuck, B.; Bigot, A.; Werschkun, B.; Winssinger, N. *Chem. Eur. J*. **2000**, 6, 2783.

106. Balog, A.; Meng, D.; Kamenecka, T.; Bertinato, P.; Su, D.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem.Soc*. **1997**, 119, 2733.

107. Chakraborty, T. K.; Dutta, S. Tetrahedron Lett. 1998, 39, 101.

108. T. Gabriel.; Wessjohann, L. A. *Tetrahedron Lett*. **1997**, 38, 1363.

109. Altmann, K. H. *Curr.Opin. Chem. Biol*, **2001**, 5, 424.

110. Hunt, K. W.; Grieco, P. A. *Org. Lett*. **2000**, *2*, 1717.

111. Chen, J.; Wang, T.; Zhao, K. *Tetrahedron Letters*. **1994**. *35*, 2827.

112. For reviews on [4 + 3] cycloaddition chemistry, see: (a) Rigby, J. H.; Pigge, F. C [4+3] cycloaddition reactions. *Org. React*. **1997**, *51*, 351. (b) Harmata, M.

Heteroatom-stabilized allylic cations in [4 + 3] cycloaddition reactions. *Recent Res. Dev. Org. Chem*. **1997**, *1*, 523. (c) Harmata, M. Intramolecular [4 + 3] cycloaddition reactions. *Adv. Cycloaddit*. **1997**, *4*, 41.

113. For review articles, see: (a) O'Brien, P. *J. Chem. Soc., Perken Trans.1* **2001**, 95. (b) Cox, P. J.; Simpkins, N. S. *Tetrahedron*: *Asymmetry* **1991**, *2*, 1. (c) Simpkins, N. S. *Chem. Soc. Rev*. **1990**, *19*, 335.

114. (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc*. **1973**, *95*, 512. (b) Trost, B. M. *J. Org. Chem.* **1986**, *51*, 2370. (c) Hunt, K. W.; Grieco, P. A. *Org. Lett*. **2002**, *4*, 245. (d) Zemribo, R.; Grieco, P. A. Postdoctoral Research (unpublished results).

115. (a) Kent, P. W.; Yound, R. C. *Tetrahedron* **1971**, *27*, 4057. (b) Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc*. **1982**, *104*, 1025.

116. Noyori, R.; Nishida, L.; Sakato, J. *J. Am. Chem. Soc*. **1983**, *105*, 1598 and references cited therein.

117. Corey, E. J.; Sneen, R. A. *J. Am. Chem. Soc*. **1956**, *78*, 6269.

118. Hunt, K. W.; Grieco, P. A. *Org. Lett*. **2000**, *2*, 1717.

119. (a) Tsuji. J. *Palladium Reagents and Catalysis*: Innovations in organic Synthesis, Wiley, **1995**. (b) Trost, B. M. *Acc. Chem. Res*. **1980**, *13*, 385.

120. Selective oxidation of secondary alcohol, see: Arterburn, B. J. *Tetrahedron*. **2001**, *57*, 9765. Preparation of dimethyldioxirane, see: (a) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res*. **1989**, *22*, 205. (b) Adam, W. *Chem. Ber*. **1991**, *124*, 2377.

121. Grieco, P. A.; Gilman. S.; Nishizawa. M. *J. Org. Chem*. **1976**, *41*, 1485.

122. Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett*. **1983**, 1593.

123. Good references for the observed chemical shifts for the acetonide carbons, see: (a) Rychnovsky, S. D.; Skalizky, D. J. *Tetrahedron Lett*. **1990**, *31*, 945. (b) Evans, D. A. *Tetrahedron Lett*. **1990**, *31*, 7099.

124. (a) Dess, D. B.; Martin, J. C. *J. Org. Chem*. **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc*. **1991**, *113*, 7277.

125. Evans, D. A. *J. Am. Chem. Soc*. **2001**, *123*, 10840.

126. (a) Yonemitsu, O.; Yoshioka, T. *Tetrahedron Lett*. **1984**, *47*, 5393. (b) Yonemitsu, O.; Yoshioka, T. *Tetrahedron Lett*. **1982**, *8*, 885.

127. Thiazolylphosphonium salt **59** has independently been used by a research group in China for the synthesis of the C_7-C_{21} segment of epothilone **A**.; Liu, Z.Y.; Yu, C. Z.; Wang, R. F.; Li, G. *Tetrahedron Lett*. **1998**, *39*, 5261.

128. (a) Gasteiger, J.; Herzig, C. *Tetrahedron* **1981**, *15*, 2607. (b) Marzoni, G. J. *Heterocycl. Chem*. **1986**, *23*, 577.

129. Brown, H. C.; Racherla, U. S. *Tetrahedron Lett*. **1985**, *26*, 2187.

130. For an excellent review, see: Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457.

131. Similar problem with base hydrolysis of ester, see: (a) Shibasaki, M.; Kanai, M.; Sawada, D. *J. Am. Chem. Soc*. **2000**, *122*, 10521. (b) White, J. D.; Carter, R. G. *J. Am. Chem. Soc*. **2001**, *123*, 5407.

132. Trost, B. M.; Chulbom, L. *J. Am. Chem. Soc*. **2001**, *123*, 12191.

133. Schinzer, D.; Bauer, A.; Schieber, J. *Chem. Eur. J.* **1999**, *5*, 2492.

134. Similar macrolactonization procedure, see: Shibasaki, M.; Kanai, M.; Sawada, D. *J. Am. Chem. Soc*. **2000**, *122*, 10521.