APPROACHES TO MARINE-DERIVED POLYCYCLIC ETHER NATURAL PRODUCTS: FIRST TOTAL SYNTHESES OF THE ASBESTININS AND A CONVERGENT STRATEGY FOR BREVETOXIN A

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ABSTRACT

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Approaches to the Marine-derived Polycyclic Ether Natural Products: First Total Syntheses of the Asbestinins and a Convergent Strategy for Brevetoxin A
(Under the direction of Professor Michael T. Crimmins)

Glycolate aldol reactions and glycolate alkylations, followed by ring-closing metatheses, are used to prepare medium ring ethers used as building blocks for polycyclic ether containing natural products. Using the glycolate aldol/ring-closing metathesis strategy, an approach to a previously unprepared subclass of the C2–C11 cyclized cembranoids known as the asbestinins is described. An oxonene is efficiently synthesized and utilized as a manifold for an intramolecular Diels–Alder cycloaddition to form a hydroisobenzofuran moiety characteristic of the asbestinins. This tricyclic adduct represents the bulk of the framework of the asbestinins. Ultimately, the tricycle was progressed to two different natural products, 11-acetoxy-4-deoxyasbestinin D and asbestinin-12, via a late-stage divergent route. The completion of these natural products represented the first instance of preparing an asbestinin using chemical synthesis, and served to confirm the absolute configuration of the subclass.

Additionally, a glycolate alkylation/ring-closing metathesis strategy was used to prepare the B ring of brevetoxin A on multigram scale. Novel reactivity was discovered and exploited along this route. Namely, it was found that glycolate alkylation adducts can undergo direct Claisen condensation or reduction to the

aldehyde to provide useful synthons. The B ring has been progressed to the BCDE tetracycle in a convergent fashion, and portions of this supply have been carried forward to provide possible coupling partners for the GHIJ fragment in hopes of completing brevetoxin A in a convergent manner.

ACKNOWLEDGEMENTS

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Nearly every member I have overlapped with in the Crimmins laboratory contributed to me reaching this point, but several deserve special thanks. Dr. Brandon Brown and Dr. Jon Parrish were my mentors from day one, and I appreciate all they did to get me off on the right foot and show me how to still enjoy life while in graduate school. The third year is a crucial time for a Ph.D. candidate, and I was fortunate to be surrounded by a number of inspiring postdocs during this portion of my studies. Specifically, Dr. Franck Caussanel and Dr. Hilary Plake motivated me with their strong work ethic and were always there to lend advice. Dr. Hamish Christie brought the entire lab to a new level during his time here, and I was one of the many positively impacted by his contagious passion for science. I would also like to thank Dr. Aaron Smith and Matt Haley for their friendships and for making lab a fun place to be every single day. Special thanks are also extended to Danielle Jacobs for providing this dissertation, and many other things I have written during my time here, with her proofreading prowess.

During the latter half of my time here, I have had the privilege of being part of “Team Brevetoxin”. Many have contributed to this project, but I would like to specifically acknowledge Dr. Patrick McDougall and Luke Zuccarello for allowing me to join them on this task they have poured so much into and take part in the effort toward this natural product. It has been a privilege to be on the same team with such intelligent and talented chemists.

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LIST OF ABBREVIATIONS

Ac	Acetyl
Acac	Acetylacetonate
AIBN	Asobis(isobutyronitrile)
9-BBN	9-Borabicyclo[3.3.1]nonane
BHT	Butylated hydroxytoluene
Bn	Benzyl
Boc	*t*-Butyloxycarbonyl
Bu	Butyl
Bz	Benzoyl
COD	Cyclooctadiene
Cp	Cyclopentadienyl
CSA	Camphorsulfonic acid
Cy	Cyclohexyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexyl carbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DHP	Dihydropyran
DIAD	Diisobutyl azodicarboxylate
DMAP	4-Dimethylaminopyridine
DMDO	Dimethyldioxirane
DMF	Dimethylformamide
DMS	Dimethyl sulfide

DMSO	Dimethyl sulfoxide
Et	Ethyl
Hfacac	Hexafluoroacetylacetonate
HMDS	Hexamethyldisilazide
HMPA	Hexamethylphosphoramide
IBX	2-Iodoxybenzoic acid
Imid.	Imidazole
Ipc	Isopinocampheol
LDA	Lithium diisopropylamide
LiDBB	Lithium di-*tert*-butylbiphenylide
Lut.	Lutidine
m-CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
MEM	Methoxyethoxymethyl
Men	Menthyl
MOM	Methoxymethyl
MOP	Methoxypropyl
MS	Molecular Sieves
Ms	Methanesulfonyl
NBS	*N*-Bromo succinimide
NIS	*N*-Iodo succinimide
NMO	*N*-Methylmorpholine-*N*-oxide
NMP	*N*-Methylpyrrolidinone

PCC	Pyridinium chlorochromate
Ph	Phenyl
Piv	Pivaolyl
PMB	*p*-Methoxybenzyl
PPTS	Pyridinium *p*-toluenesulfonate
Pr	Propyl
Pyr.	Pyridine
Red-Al	Sodium bis(2-methoxyethoxy)aluminumhydride
TBDPS	*t*-Butyldiphenylsilyl
TBS	*t*-Butyldimethylsilyl
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMEDA	*N*,*N*,*N'*,*N'*-Tetramethylethylenediamine
TMS	Trimethylsilyl
TPAP	Tetrapropylammonium perruthenate
Tr	Triphenylmethyl
Ts	*p*-Toluenesulfonyl

Chapter I

An Aldol/Ring-Closing Metatheis/Intramolecular Diels–Alder Approach to the Asbestinins: Total Syntheses of 11-Acetoxy-4-deoxyasbestinin D and Asbestinin-12

A. Background

A wide array of C2–C11 cyclized cembranoid natural products have been isolated from marine sources.[1] These diterpenes are grouped into four categories: the cladiellins (eunicellins), the briarellins, the asbestinins, and the sarcodictyins. A biosynthetic pathway has been proposed by Faulkner relating each of these subclasses (Figure 1).[2] Beginning with the cembrane skeleton, C2–C11 cyclization provides the cladiellin framework. An intramolecular etherification of the cladiellin tricycle affords the tetracyclic framework of the briarellin subclass, and a 1,2-

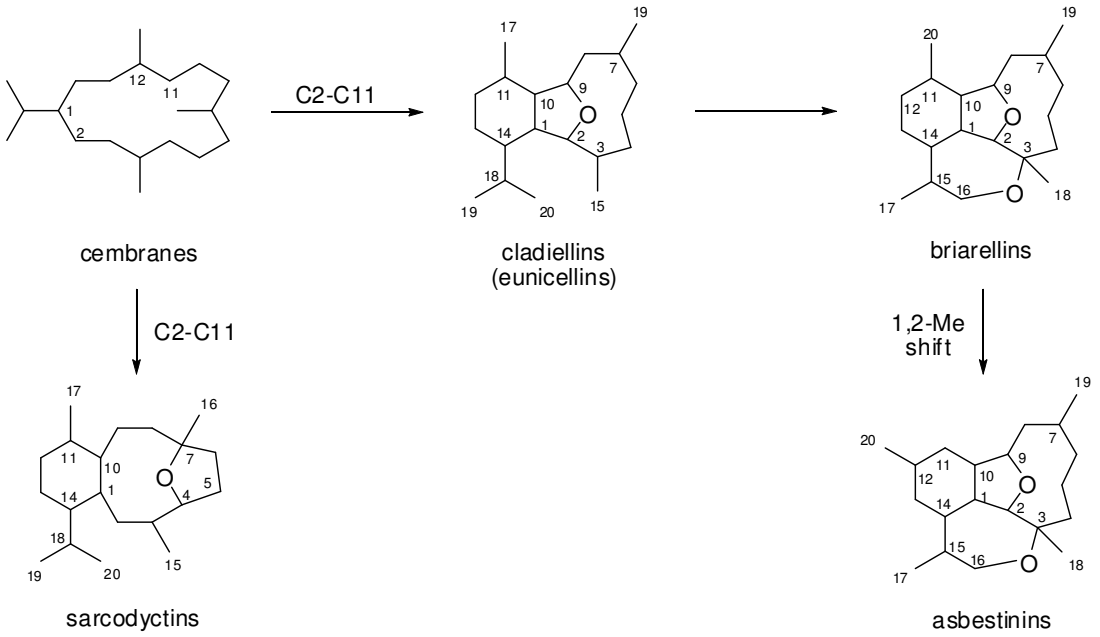


Figure 1. Proposed Biosynthesis

suprafacial methyl shift on the briarellin structure is further predicted to deliver the asbestinins. These speculations are corroborated by the isolation of a cembrane metabolite with cladiellin metabolites in *Alcyonium molle* and with asbestinin metabolites in *Briareum steckii*.[3] The sarcodictyins are also proposed to arise from a C2–C11 cyclization of the cembrane skeleton; however, in these systems, the cyclization results in a fused cyclohexyl and oxonane in place of the hydroisobenzofuran of the cladiellins, briarellins, and asbestinins. As a result of this significant structural variation of the sarcodyctins, the synthetic approaches to these molecules are quite different than those for the other three related subclasses.[4,5]

Eunicellin was the first reported member of the C2–C11 cyclized cembranoid natural products, isolated in 1968 by Djerassi and co-workers from the soft coral *Eunicella stricta* found off the coast of Banyuls-sur-Mer in France.[6] Since this discovery, over one hundred unique secondary metabolites of gorgonian octocorals have been characterized, including the first asbestinin in 1980[2] and the first briarellin in 1995.[7] The sum of these marine natural products provides a range of structural diversity. The natural role of these cembranoids is proposed, based upon mollusk and fish lethality assays, to involve predation deterrence.[7] Upon further investigation, several of the members of these subclasses have demonstrated remarkable pharmacological potential.[7-13] Particularly, these diterpenes have been shown to possess in vitro cytotoxicity against various cancer cell lines, anti-inflammatory properties, antimicrobial activities, and histamine and acetylcholine antagonism. The fascinating molecular architecture of these cembranoids, as well as their potential as therapeutic agents, has sparked much interest in the synthetic

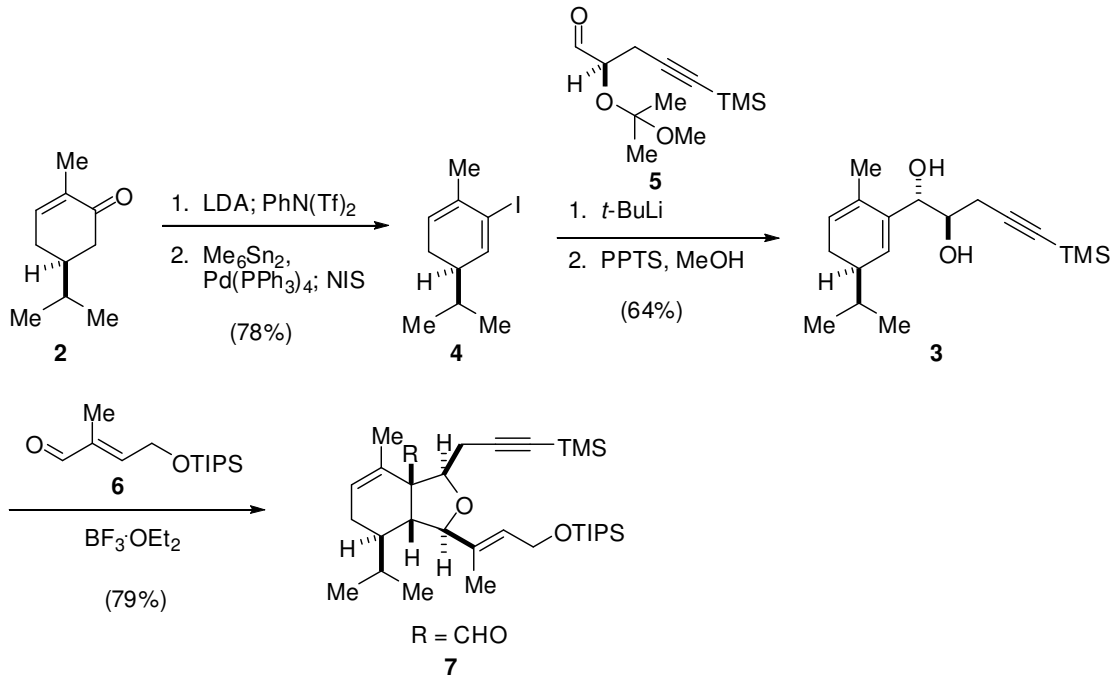
community over the past decade, resulting in a variety of approaches toward these challenging structural motifs and several total syntheses.

B. Previous Total Syntheses of C2–C11 Cyclized Cembranoids

1. Prins–pinacol Condensation–rearrangement

The first total synthesis of a cembranoid natural product was completed by Overman and co-workers, who reported the total synthesis of (-)-7-deacetoxyalcyonin acetate (**1**),[14] a cladiellin, in 1995.[15] The strategy relies upon the formation of the hydroisobenzofuran functionality via a Prins–pinacol condensation–rearrangement approach, which had been previously employed in the Overman laboratory to stereoselectively form tetahydrofurans.[16] (*S*)-Dihydrocarvone (**2**)[17] was utilized as the starting material to prepare dienyl diol **3** suitable for the proposed transformation (Scheme 1). Formation of the kinetic enol triflate,[18] followed by iodination[19] provided the dienyl iodide **4**.[20] Subsequent transmetalation and exposure to alkynyl aldehyde **5** (prepared in four steps from (*S*)-glycidyl pivalate)[21] provided diol **3** upon deprotection.[22] With the stage set for the key Prins–pinacol condensation–rearrangement, diol **3** was combined with enal **6** in the presence of $BF_3{\cdot}OEt_2$ to provide the hydroisobenzofuran **7** as a single diastereomer in 79% yield. The stereochemical outcome of this transformation is predicted to arise from transition state **8** (Figure 2). Following formation of the more stable (*E*)-oxocarbenium ion,[23] the molecule adopts the chair conformation necessary for the 6-endo cyclization process. Transition state **8** orients all substituents pseudoequatorially while also allowing the oxocarbenium ion to approach the diene

from the opposite face of the bulky isopropyl substituent.[16] The observed stereochemistry supports this model.



Scheme 1. Prins–pinacol Condensation–rearrangement

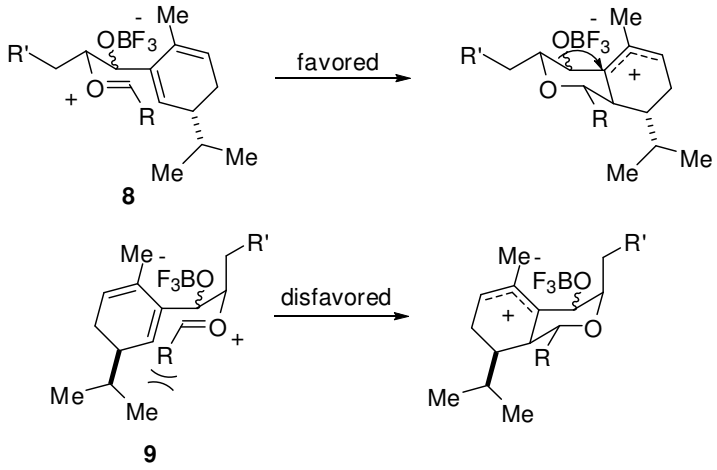
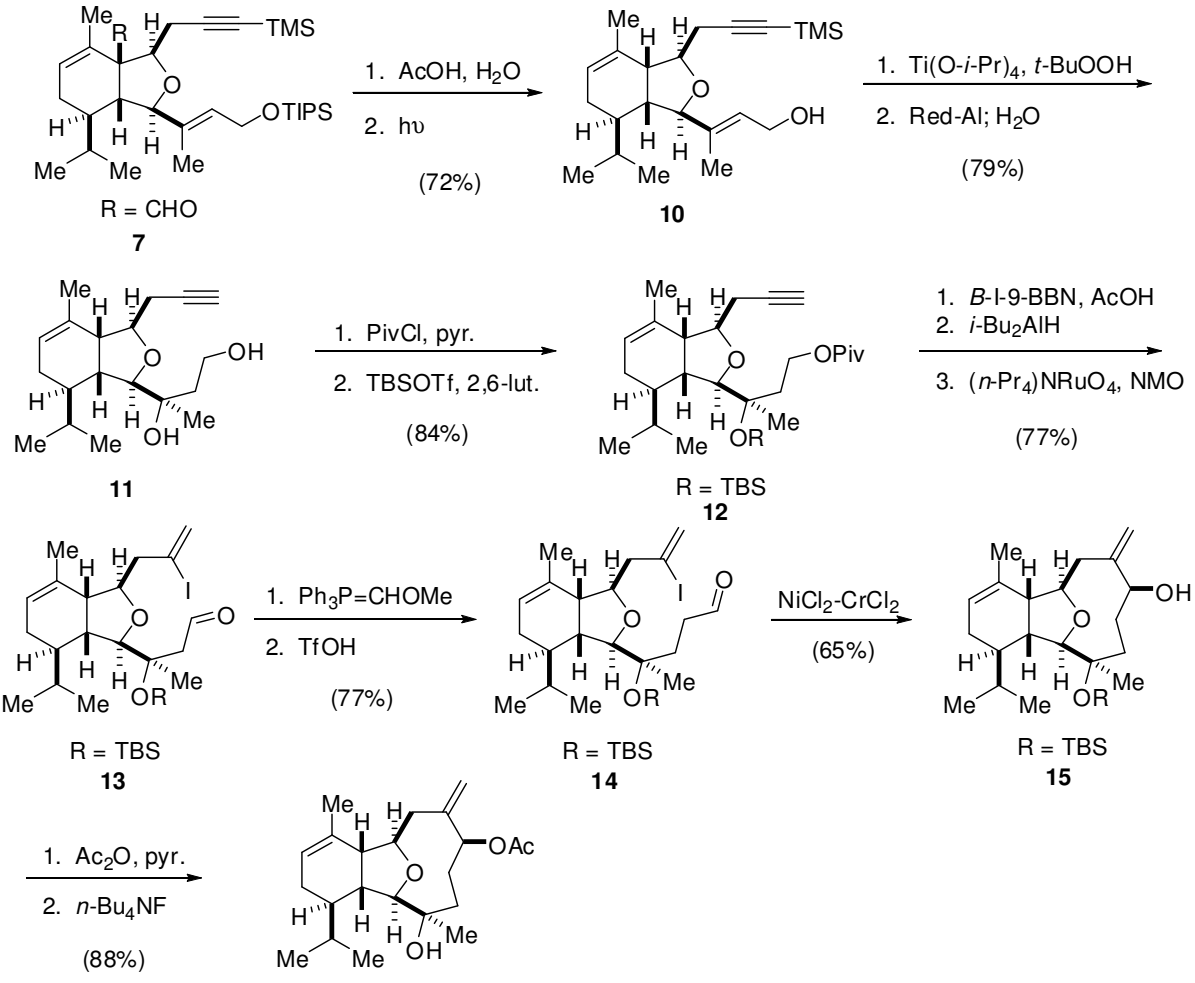


Figure 2. Transition States for Prins–pinacol Condensation–rearrangement

With the cyclohexene and tetrahydrofuran in place, attention was turned toward formation of the oxonane (Scheme 2). Removal of the primary silyl ether and

photochemical decarbonylation of the formyl group gave bicycle **10**.[24] The allylic alcohol was next exploited to achieve a Sharpless asymmetric epoxidation of the trisubstituted alkene,[25,26] and the epoxide was regioselectively reduced using bis(2-methoxy)aluminum hydride (Red-Al).[27-29] Addition of water produced NaOH, which also effected desilylation in one-pot delivering diol **11**. A series of protections



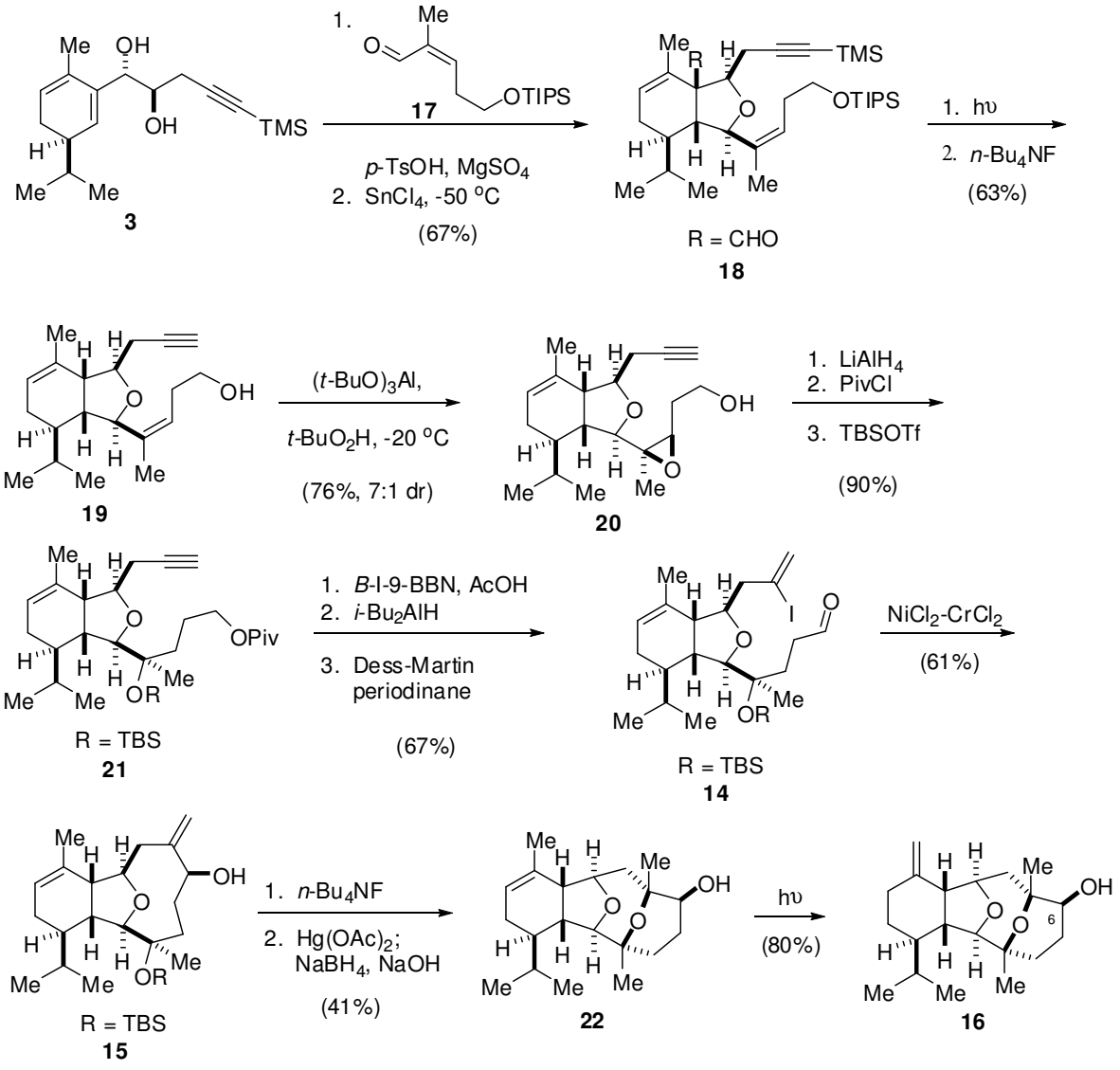
Scheme 2. Completion of (-)-7-Deacetoxyalcyonin Acetate

followed by iodoboration of the alkyne provided the vinyl iodide,[30] Reduction and oxidation revealed the aldehyde **13**,[31] which, following a one-carbon homologation, was utilized in an intramolecular Nozaki–Hiyama–Kishi coupling using $NiCl_2$–

$CrCl_2$.[32,33] Markedly, the resultant tricycle **15** was formed in 65% yield with high diastereoselection (>20:1 dr). Selective acetylation of diol **15**, with subsequent removal of the silyl ether, provided (-)-7-deacetoxyalcyonin acetate (**1**), marking the first successful total synthesis of a member of the C2–C11 cyclized cembranoid family.

The Overman laboratory next extended the Prins–pinacol condensation–rearrangement approach to a cladiellin of potential pharmacological utility. Sclerophytin A (**16**) was characterized as a tetracyclic diether and showed promising in vitro cytotoxicity against the L1210 leukemia cell line (1 ng/mL).[9,34,35] The strategy envisioned for sclerophytin A involved a Prins–pinacol approach, this time using a (Z)-α,β-unsaturated aldehyde as the nucleophile. The synthesis would provide the opportunity to assess the viability of using an aldehyde of this sort without observing isomerization of the alkene configuration, while accomplishing the first total synthesis of this therapeutically intriguing natural product. Utilizing diol **3** from the (-)-7-deacetoxyalcyonin acetate synthesis[15] and aldehyde **17** (prepared in four steps from 3-buten-1-ol),[36] a two step condensation and rearrangement procedure was employed (Scheme 3).[37,38] Condensation of the two components using acidic conditions provided an acetal that efficiently delivered bicycle **18** upon treatment with tin tetrachloride. The (Z)-olefin remained in tact throughout the cyclization with no stereomutation observed. Deformylation[24] and deprotection of the silyl protecting groups gave the allylic alcohol **19**, suitably poised for a substrate-controlled epoxidation. Treatment with $(t\text{-BuO})_3Al/t\text{-BuO}_2H$ provided a separable 7:1 mixture of epoxides, favoring the desired diastereomer **20**.[39] Opening of the epoxide and

sequential protection provided alkyne **21**. Refunctionalization to the Nozaki–Hiyama–Kishi candidate as before completed a more efficient synthesis of vinyl iodide **14**.[15,30] Upon treatment with $NiCl_2$–$CrCl_2$, the oxonane was formed, delivering the desired isomer of allylic alcohol **15** in good yield.[32,33] Deprotection of the tertiary silyl group and treatment with $Hg(OAc)_2$ followed by $NaBH_4$ provided diether **22** in moderate yield.[40] Photoisomerization to the exocyclic olefin gave the reported



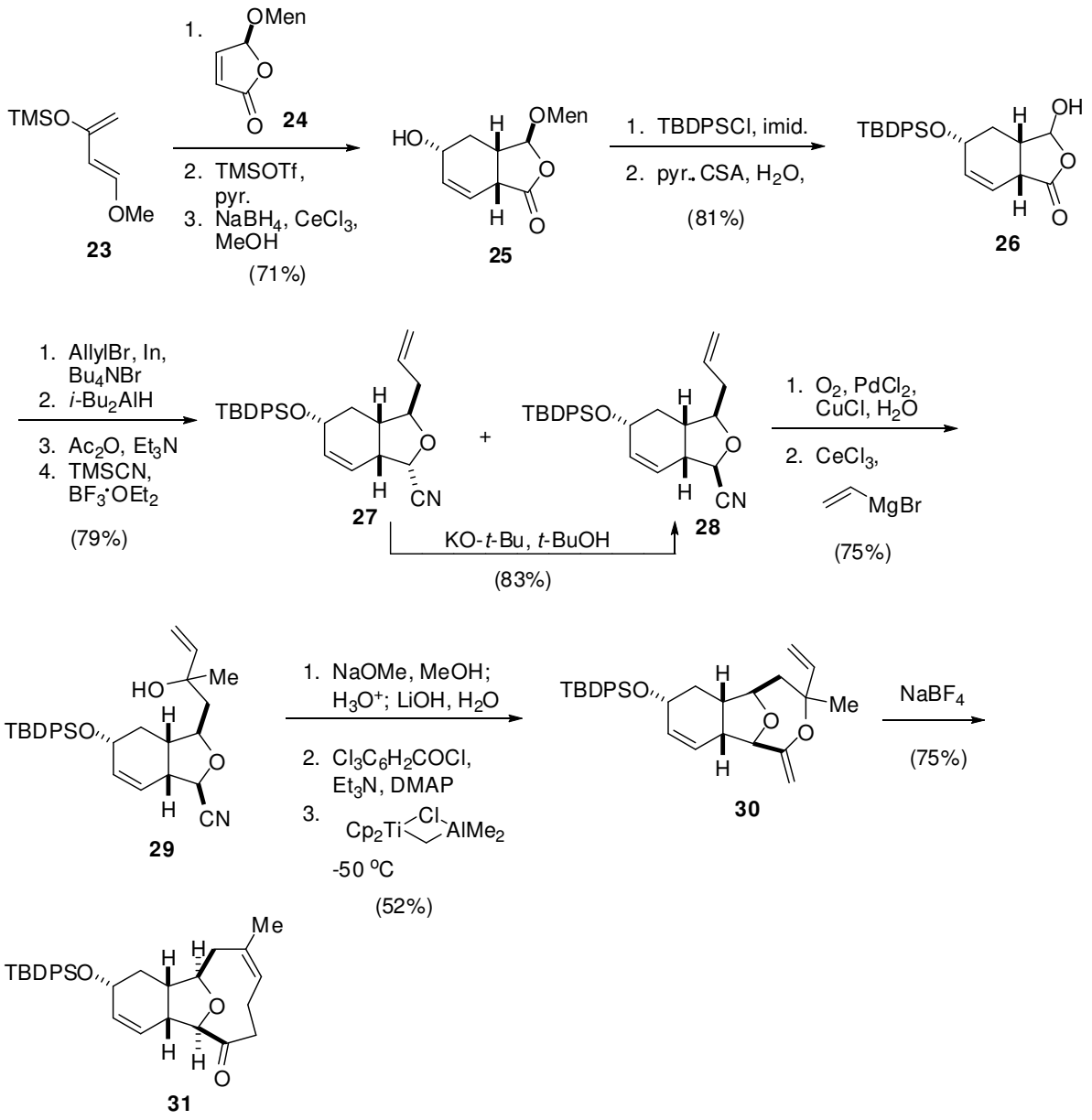
Scheme 3. Overman's Completion of Sclerophytin A

structure of sclerophytin A (**16**).[41,42] However, the data for the synthetic and natural material differed greatly.[13] The C6 epimer of tetracycle **16** was also prepared via oxidation[43] and reduction, but also failed to correlate with the natural product.

2. Claisen Rearrangement Strategy

Simultaneously, the Paquette group had made efforts to synthesize sclerophytin A (**16**) via a unique route.[13,34,35,44] Their strategy relied upon a Claisen rearrangement as the key step to provide the functionalized oxonane core of the natural product.[45] The synthesis commenced with a Diels–Alder cycloaddition involving the Danishefsky diene (**23**) and chiral dienophile **24** (Scheme 4).[46,47] The labile enolsilane was hydrolyzed[48] and the resultant enone was reduced under Luche conditions[49] to provide allylic alcohol **25** in good yield. Ensuing silylation of the allylic alcohol and hydrolysis of the menthyl ether delivered lactone **26**. Allylation of lactone **26** afforded a 13:1 ratio of adducts, favoring the desired diastereomer.[50] Reduction, acetylation, and treatment of the derived oxocarbenium ion with trimethylsilyl cyanide gave a 1:1 mixture of nitriles **27** and **28**.[51,52] Efficient conversion of nitrile **27** to nitrile **28** was achieved under alkaline conditions. Wacker oxidation[53] and vinylation provided tertiary alcohol **29** in 75% yield for two steps. Mild hydrolysis of the nitrile provided an acid,[54-56] which was used in a Yamaguchi lactonization to give the lactone.[57,58] A Tebbe methylenation provided the target diene **30** for the key Claisen rearrangement.[59] Gratifyingly, treatment of the mixture of dienes with sodium tetrafluoroborate in refluxing toluene provided the desired oxonene **31**, but at two distinctly different rates.[45] The noted variation in reaction

rate can be explained by examining the transition states for each rearrangement (Figure 3). The requisite chair conformations to access the desired rearranged product should both be accessible, however, transition state **30a** suffers from



Scheme 4. Claisen Rearrangement

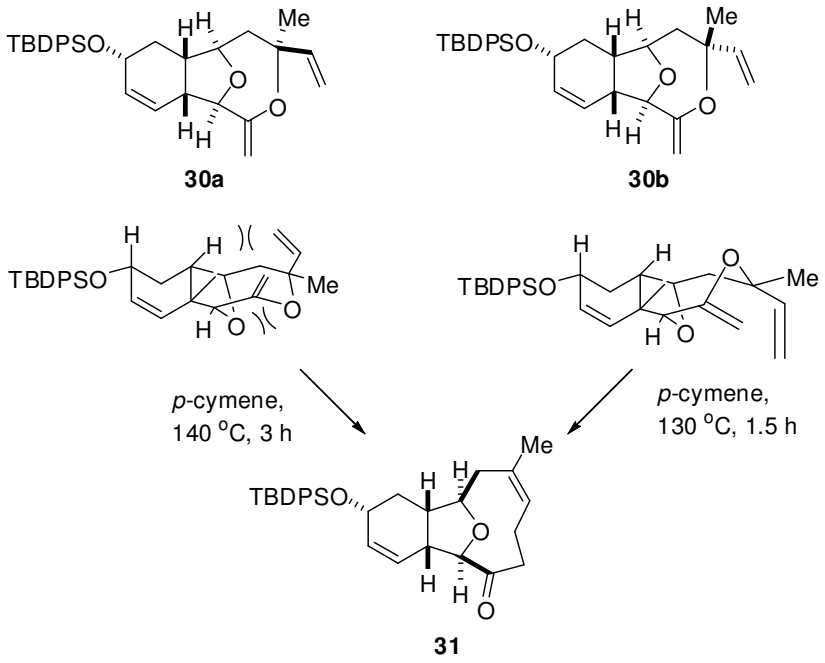
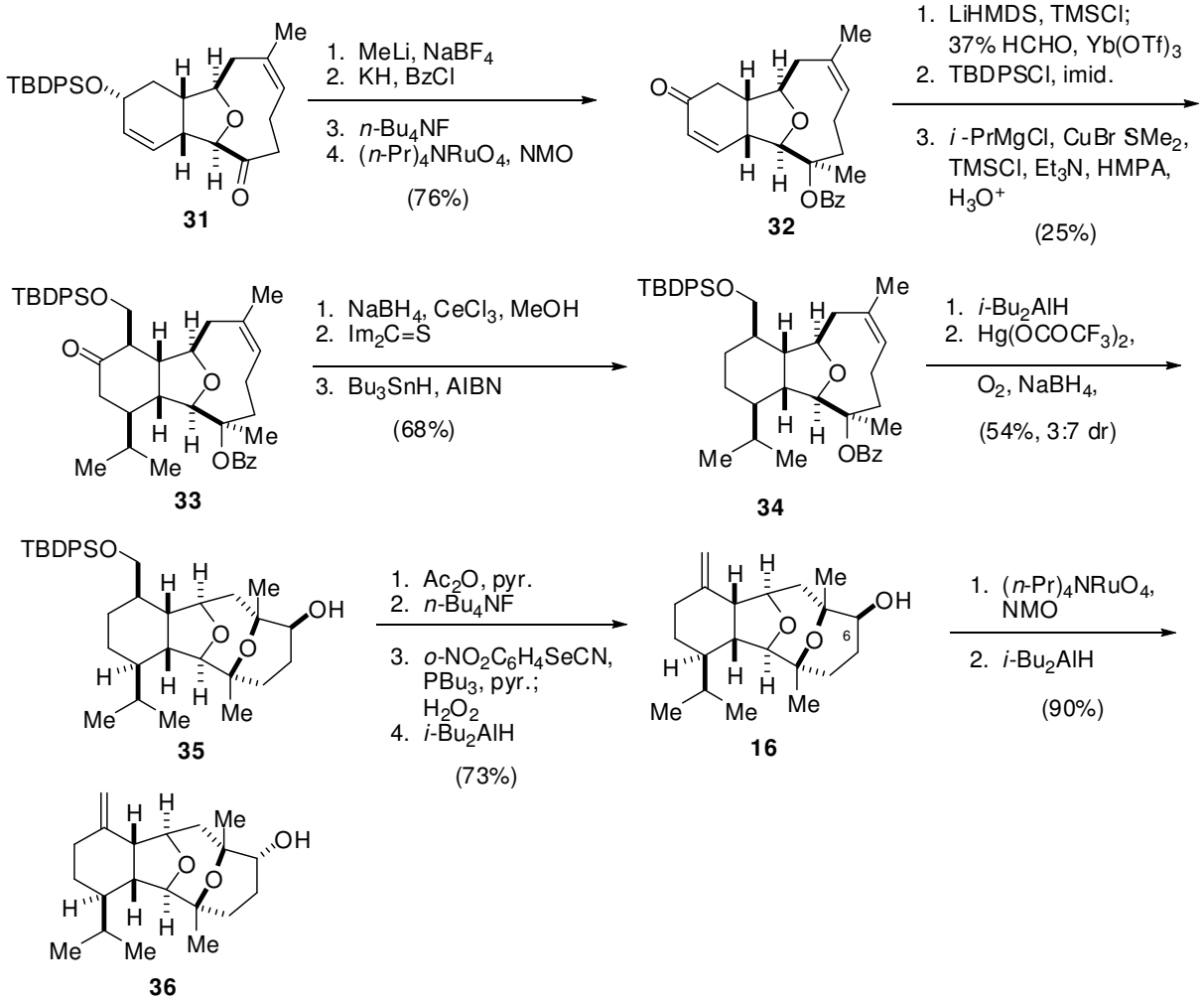


Figure 3. Claisen Rearrangement Transition States

enhanced steric interactions over its corresponding epimer **30b**, resulting in kinetically slower Claisen rearrangement.

With the formation of the oxonene completed, attention was turned toward properly functionalizing the six- and nine-membered rings. Diastereoselective alkylation of the ketone, protection of the resultant tertiary alcohol as a benzoate ester, removal of the silyl protecting group, and oxidation provided enone **32** (Scheme 5). Hydroxymethylation of the enone utilizing ytterbium triflate,[60] followed by silyl protection of the resultant alcohol delivered the silyl ether. Diastereoselective conjugate addition of isopropyl Grignard reagent completed the diterpene skeleton of sclerophytin A (**16**). A Luche reduction,[49] formation of the thiocarbonyl imidazole, and reduction under radical conditions served to deoxygenate the cyclohexyl unit giving ester **34**. Reduction of the benzoate ester,

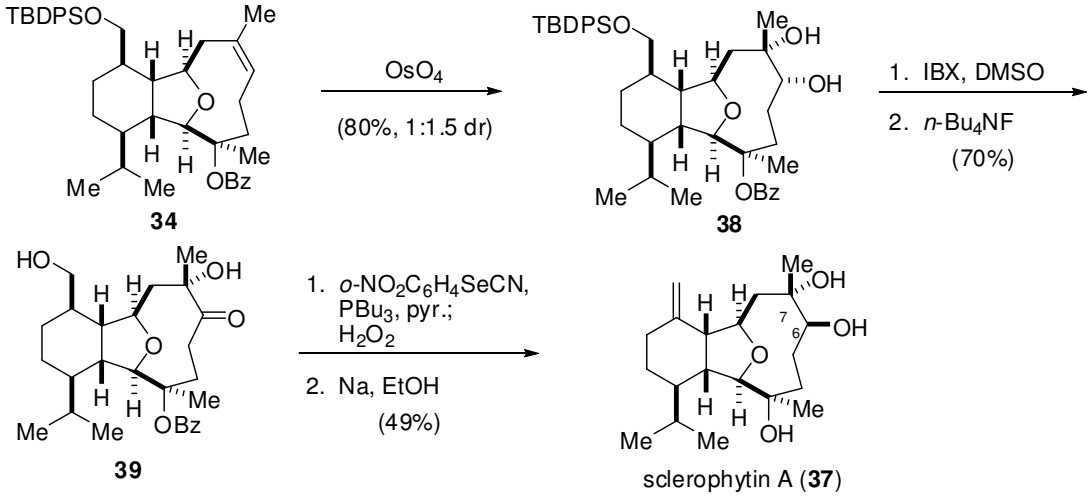
followed by oxymercuration and oxidative demercuration gave a 3:7 mixture of epimeric alcohols **35** in 54% yield, forming the final ring of the natural product.[61] Transient protection of the secondary alcohol as an acetate ester was followed by deprotection of the silyl ether and Grieco elimination.[62] Reduction of the acetate ester provided the purported structure of sclerophytin A (**16**). However, as expected based upon the Overman result, the spectroscopic data for this material differed significantly from that reported for the natural product.[9] Oxidation[31] and reduction of the secondary alcohol provided the C6 epimer **36**, which still did not match the data



Scheme 5. Paquette's Sclerophytin A Endgame

for the naturally isolated material. Additionally, tetracyle **16** was much less polar than an authentic sample of the natural compound.

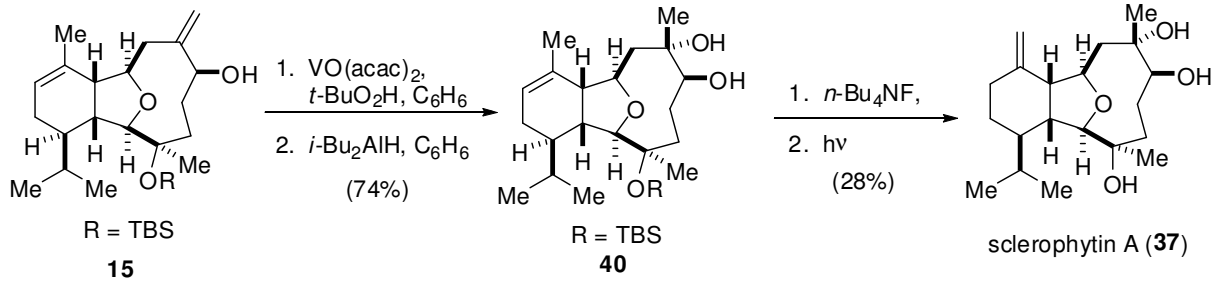
Armed with the knowledge that the true structure of the natural product was not merely an epimer, the Paquette group performed extensive NMR and literature investigation and proposed a new structure for sclerophytin A (**37**).[63] To access this material, in all of its C6 and C7 epimeric forms, alkene **34** was dihydroxylated using osmium tetraoxide to provide a nearly equal mixture of diastereomers (1.5:1 dr, Scheme 6).[64,65] Oxidation[66] and cleavage of the silyl ether with fluoride gave ketone **39**. Greico elimination was next executed.[62] Using one of three different reductive conditions, each of the four possible C6, C7 diastereomers of sclerophytin A (**37**) were accessed. Gratifyingly, triol **37** matched the data for the natural product, serving to establish the true structure of sclerophytin A.



Scheme 6. Paquette's Synthesis of Authentic Sclerophytin A

3. A Return to the Prins–pinacol Condensation–rearrangement

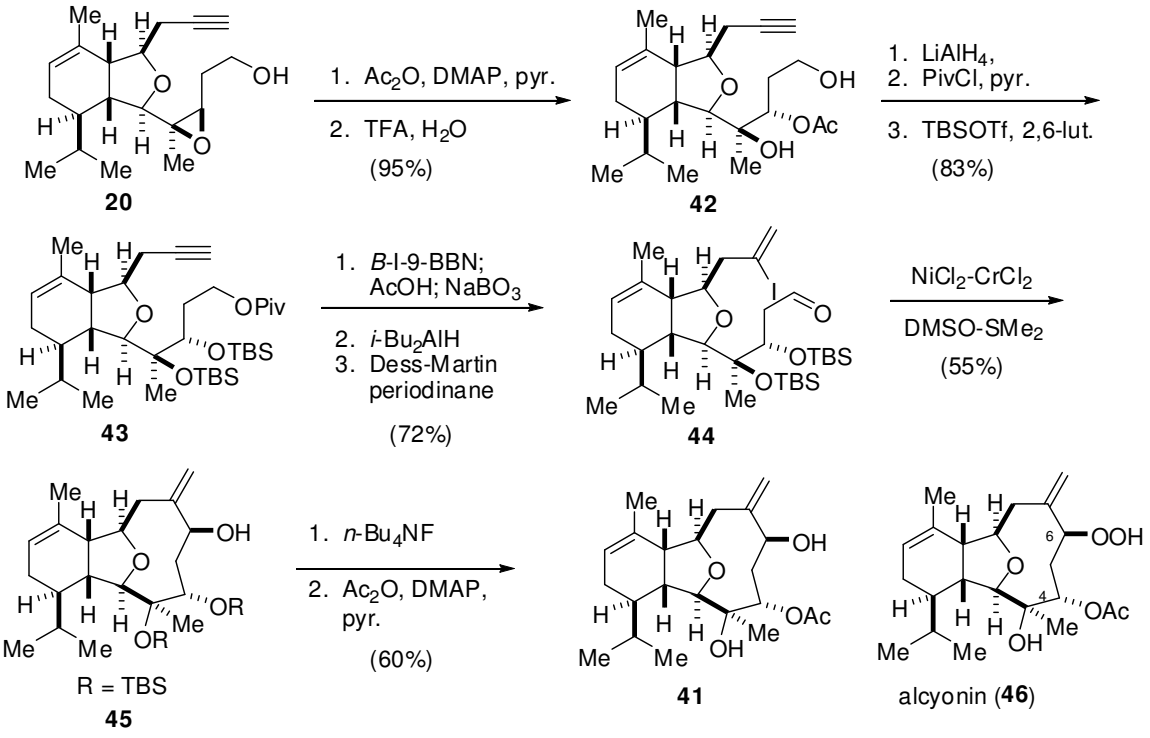
With knowledge of the reassignment of the structure by the Paquette group, the Overman laboratory had concurrently targeted authentic sclerophytin A (**37**) using an intermediate from their previous synthesis of the purported structure.[37,38,64] Hydroxyl-directed epoxidation of tricycle **15** gave 95% of the desired epoxide (Scheme 7).[67] Reductive opening of the epoxide[50] preceded cleavage of the silyl ether to give triol **40**. Finally, photochemical isomerization provided sclerophytin A (**37**), albeit in lower yield than the previous photoisomerization (vide supra, Scheme 3).[30]



Scheme 7. Overman's Synthesis of Authentic Sclerophytin A

In 2003, Overman applied the Prins–pinacol condensation–rearrangement approach to the synthesis of another cladiellin, alcyonin (**41**).[68] Protection of epoxide **20** (previously prepared in the synthesis of sclerophytin A, Scheme 2)[15,37,38] as its acetate ester and treatment with aqueous trifluoroacetic acid prompted a 6-exo opening of the epoxide to provide diol **42** (Scheme 8).[69-71] Reduction of the ester, selective protection of the primary alcohol as a pivalate ester, and protection of the resultant diol as silyl ethers provided alkyne **43**. Following iodoboration,[30,72,73] reduction of the ester, and oxidation[31] to provide the alkenyl iodide **44**, the Nozaki–Hiyama–Kishi protocol was used to form the oxonane **45**, again in excellent diastereoselectivity.[32,33] Fluoride-promoted cleavage of the silyl ethers and careful

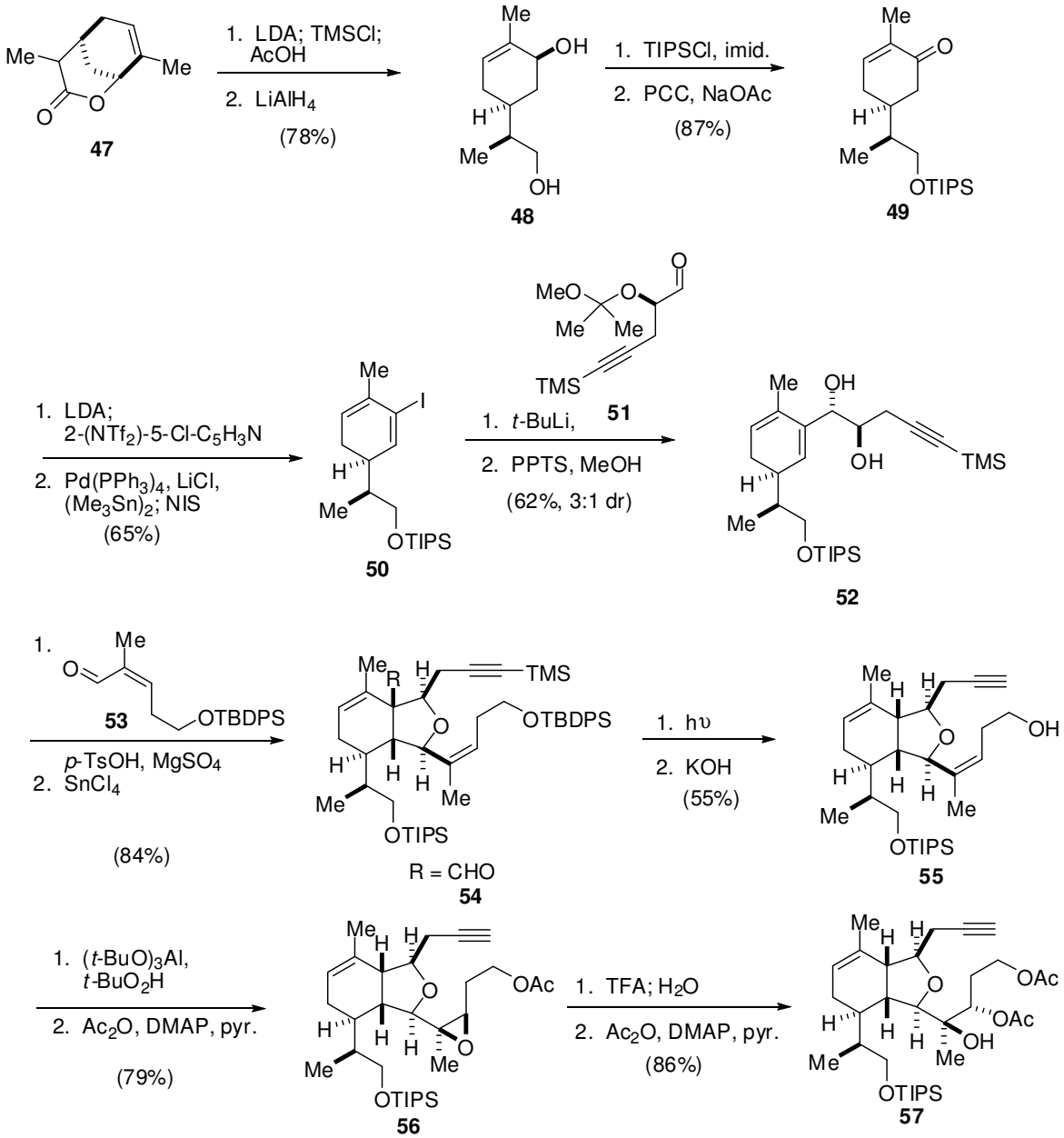
acetylation of the C4 hydroxyl provided the proposed structure of alcyonin (**41**). However, reminiscent of the sclerophytin A saga, the spectral data for the synthetic and natural material did not match. A C6 peroxide analog **46** was proposed by the Overman group based upon the observed spectral data and reactivity of the synthetic and natural molecules,[74-77] but no total synthesis of this reassigned compound has been achieved to date.



Scheme 8. Attempted Synthesis of Alcyonin

The Overman laboratory next turned its attention to the briarellin subclass of the C2–C11 cyclized cembrane natural products.[7,78,79] Again envisioning a Prins–pinacol reaction as the key step in forming the characteristic hydroisobenzofuran portion of the molecule (Scheme 9),[16] the synthesis commenced via protonolysis of the silyl ketene acetal of lactone **47** (prepared in two steps from (*S*)-(+)-carvone).[80,81] Reduction of the lactone gave diol **48**, which was selectively protected as a silyl

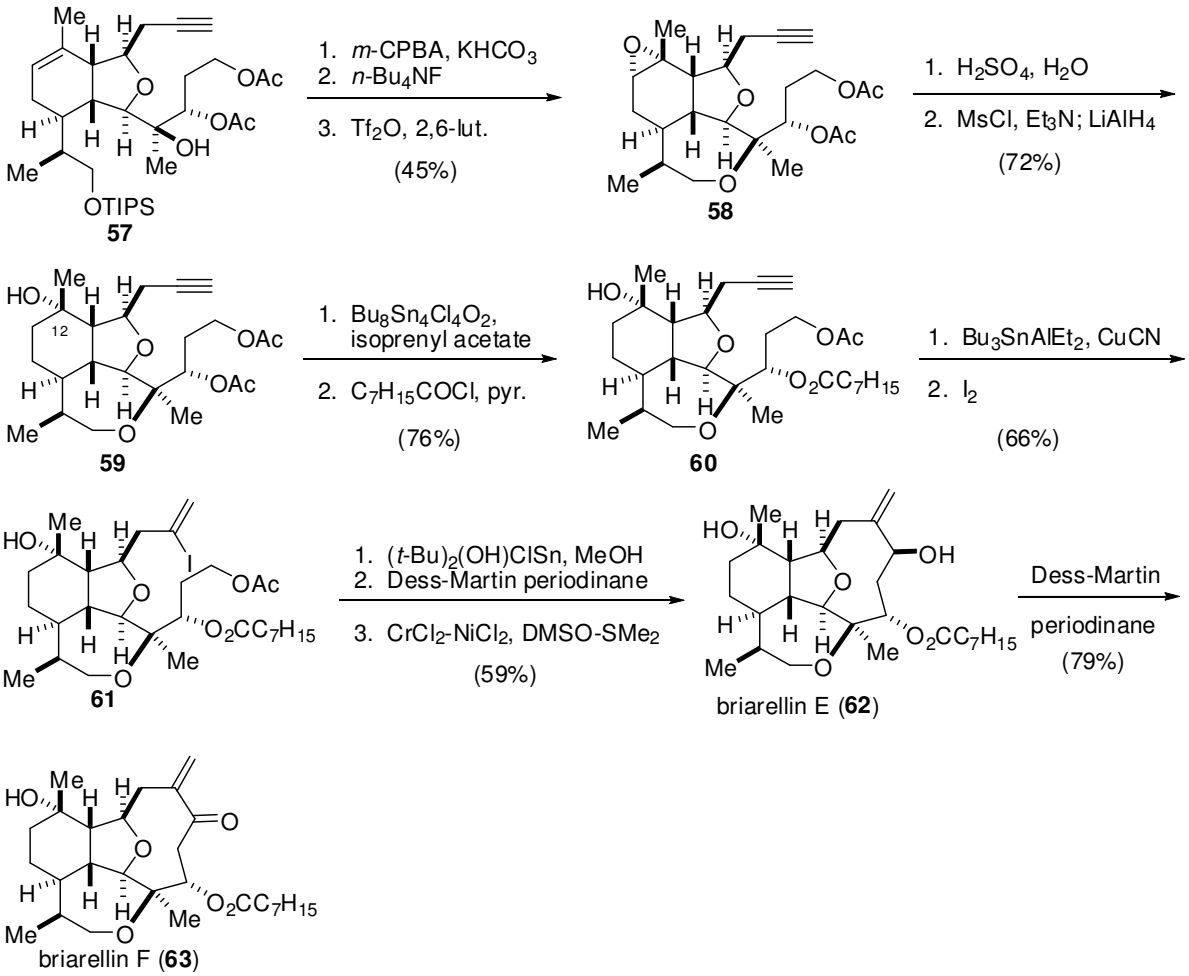
ether and oxidized to the corresponding enone **49**.[82] Synthesis of the enol triflate[18,83] preceded coupling with a tin reagent[19] followed by iodination to give dienyl iodide **50**.[20] The lithiated diene was then treated with chiral aldehyde **51** and gave the diol **52** in 62% yield (3:1 dr) following methanolysis of the acetal. The stage was set for the key Prins–pinacol condensation–rearrangement. Treatment of diol **52**



Scheme 9. Forming the Hydroisobenzofuran of the Briarellins

with acid in the presence of aldehyde **53**, followed by subjection of the condensed product to tin-catalyzed rearrangement conditions, provided the hydroisobenzofuran **54** in 82% yield as a single detectable diastereomer. Photolytic deformylation[24] and selective basic hydrolysis of the *t*-butyldiphenylsilyl and trimethylsilyl protecting groups gave alcohol **55**. Stereoselective epoxidation[84] and protection of the primary alcohol then allowed for acetate-assisted opening of the epoxide.[69] In the event, treatment with aqueous acid, followed by acetylation of the resultant alcohol efficiently provided alkyne **57**.

With two of the rings of the tetracyle formed, epoxidation of the trisubstituted olefin proceeded with good stereoselectivity, and attention was turned to the formation of the oxepane of the briarellin core (Scheme 10). Cleavage of the silyl ether and formation of the primary triflate under basic conditions triggered an intramolecular etherification, forming the third ring of the tetracyclic natural product. Next, to install the C12 carbinol, acid-catalyzed opening, followed by removal of the resultant C12 hydroxyl provided tricycle **59**. A two step procedure was next used to install the octanoyl side chain and provide ester **60**.[85] Stannylalumination–protonolysis and a subsequent iododestannylation incorporated the vinyl iodide for the Nozaki–Hiyama–Kishi reaction.[86] The acetate group was selectively removed using a tin reagent[87] and oxidation provided the aldehyde.[43] The cyclization again proceeded with complete stereoselection in 79% yield to provide briarellin E (**62**).[32,33] Oxidation of the allylic alcohol provided the enone, briarellin F (**63**).[43]

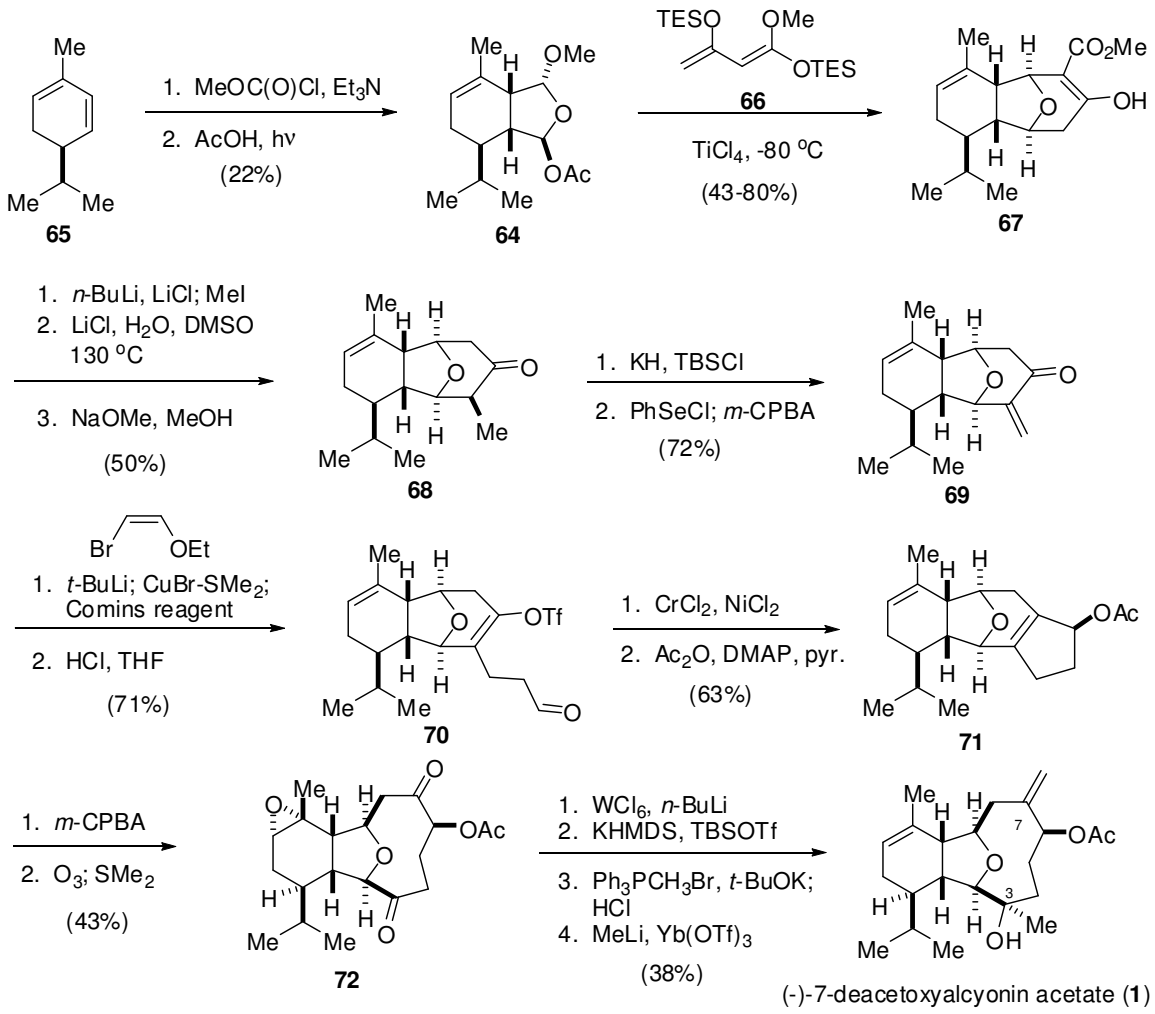


Scheme 10. Total Syntheses of Briarellins E and F

4. [4+3] Annulation Strategy

The Molander laboratory has developed a [4+3] annulation strategy amenable to the construction of the hydroisobenzofuran of the cembranoids.[88-90] (-)-7-Deacetoxyalcyonin acetate (**1**), previously synthesized by the Overman group, was chosen as the initial target for their investigations.[14,15] To prepare a dialdehyde surrogate, bis-acetal **64** was synthesized via a [2+2] cycloaddition of methoxy ketene and α-phellandrene (**65**),[91,92] followed by photochemical rearrangement (Scheme 11).[93,94] Treatment of this bis-acetal **64** with a bis-nucleophile **66** in the presence of

titanium tetrachloride effected the formal [4+3] addition in a single step, establishing five of the seven stereocenters of their target molecule. A diastereoselective methyl alkylation was followed by a Krapcho decarboxylation of the methyl ester, which also epimerized the newly-formed methyl stereocenter.[95] Since the stereochemistry of the methyl substituent was crucial for the subsequent silyl enol ether formation, the stereocenter of the minor diastereomer was epimerized to the necessary configuration under basic conditions. Formation of the silyl enol ether,[96] selenation, and selenoxide elimination delivered enone **69**.[97] Conjugate addition[98,99] and in situ formation of the vinyl triflate provided aldehyde **70** following hydrolysis.[83] A Nozaki–Hiyama–Kishi cyclization gave the cyclopentane in good yield as a mixture of diastereomers.[32,33] After a Mitsunobu reaction that served to transform the undesired cyclopentanol into the desired,[100] the merged material was progressed to the acetate ester **71**. The trisubstituted olefin was selectively protected as an epoxide, and the tetrasubstituted olefin cleaved under ozonolysis conditions, forming the nine-membered diketone **72**. The Sharpless tungsten reagent was used to reduce the epoxide and restore the trisubstituted olefin.[101] Finally, selective protection of the C3 ketone as the enol silane, methylenation of the C7 ketone, and subsequent hydrolysis of the silyl enol ether provided the ketone. Methylation provided (-)-7-deacetoxyalcyonin acetate (**1**)[14] as a single detectable diastereomer.[102]

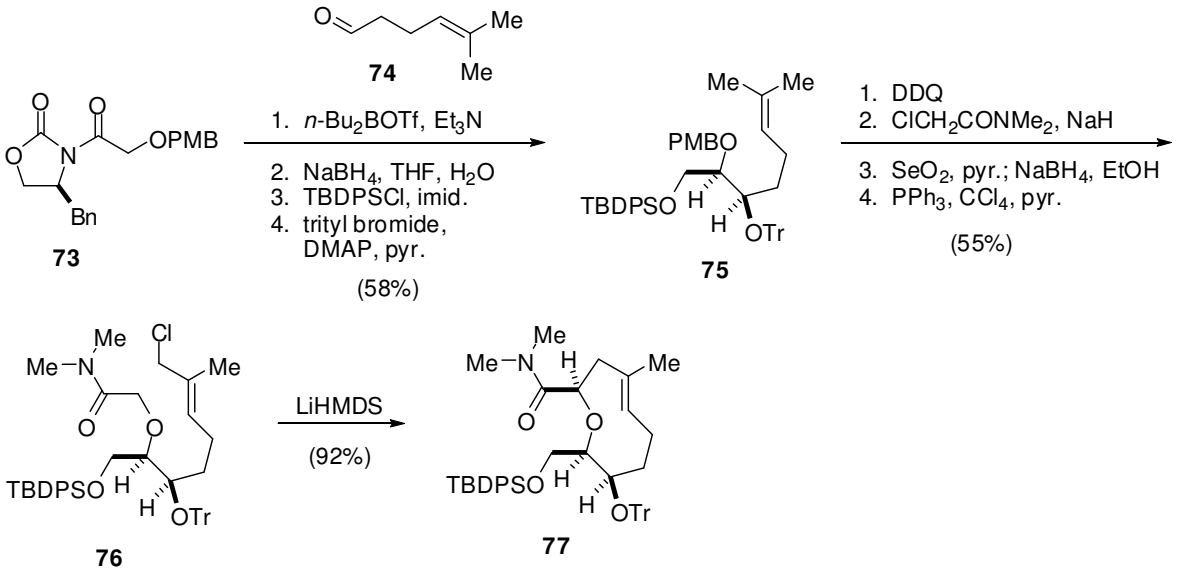


Scheme 11. Molander's Approach to the Cladiellins

5. Intramolecular Amide Enolate Alkylation

Each of the previous syntheses have targeted cembranoids containing a (*Z*)-olefin or lacking an endocyclic olefin within the nine-membered ring of the natural products. In 2006, the Kim laboratory reported a route to the more sensitive (*E*)-olefin containing cladiellins that are also ubiquitous in the isolation literature.[103] The proposed approach would involve an intramolecular amide enolate alkylation, which has been well-documented within their group for the efficient formation of medium

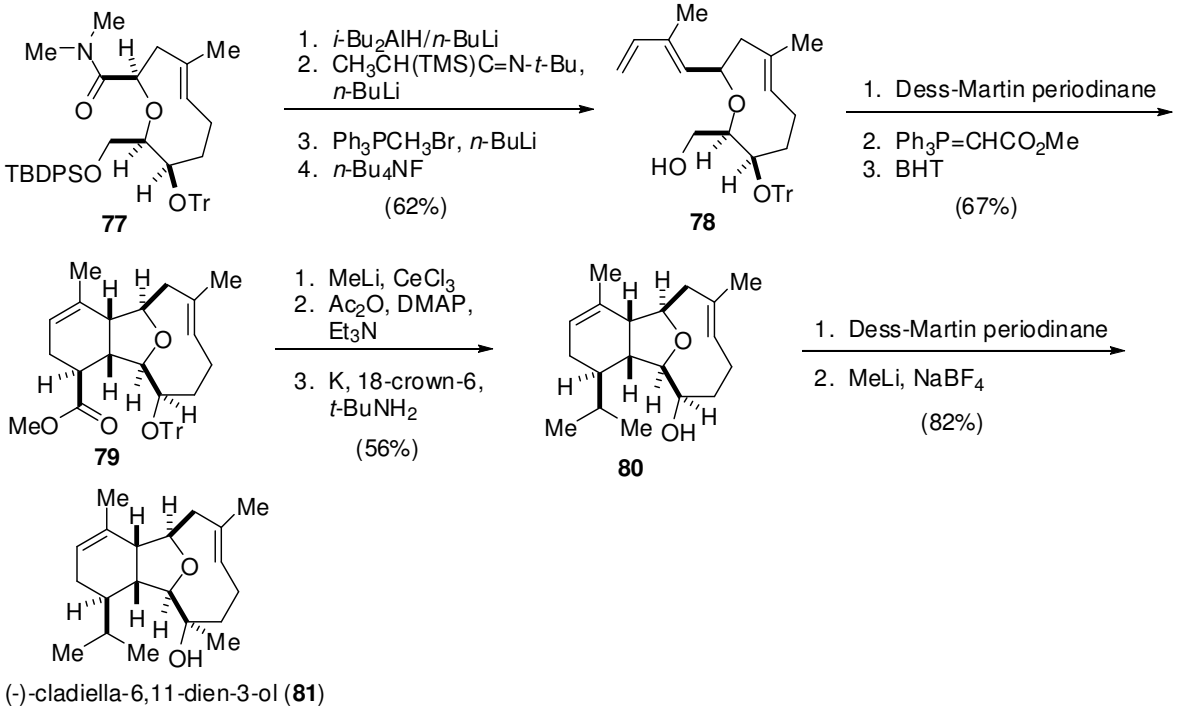
ring ethers.[104-106] Upon forming the oxonene via this process, an intramolecular Diels–Alder cycloaddition analogous to that reported in a previous synthesis by the Crimmins laboratory[107-110] would be used to form the remaining two rings of several cladiellin natural products. Their synthesis commenced with an asymmetric glycolate aldol reaction under Evans's dibutylboron triflate conditions (Scheme 12).[111-113] Reduction of the chiral auxiliary and sequential protection of the diol provided alkene **75**. Oxidative removal of the *p*-methoxybenzyl ether[114] and alkylation with an amide proceeded efficiently. Selective allylic oxidation[115] and chlorination of the resultant alcohol[116] afforded amide **76** prepared for the key intramolecular alkylation. In the event, treatment with lithium hexamethyldisilazide led to formation of the desired (*E*)-oxonene **77** in 92% yield as a single detectable diastereomer.[104-106]



Scheme 12. Formation of (*E*)-Oxonene

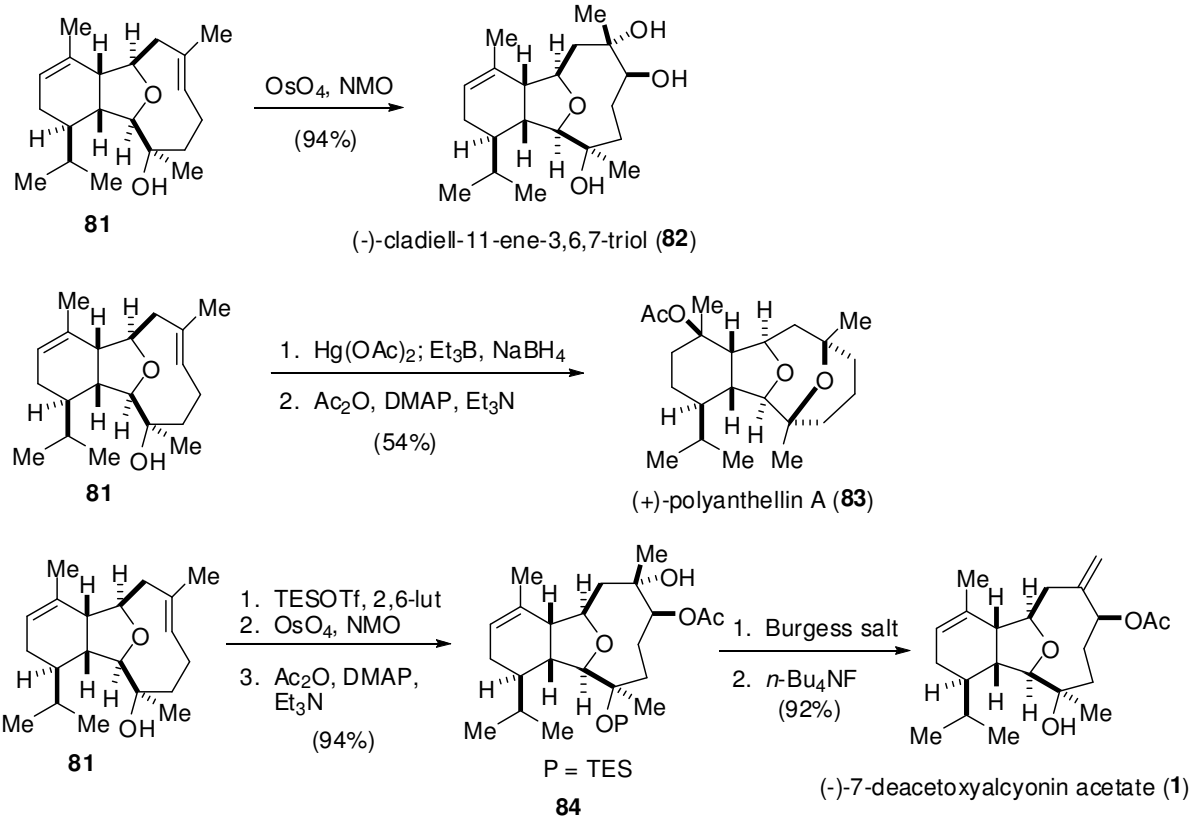
Following formation of the medium ring ether **77**, the functionalization to an appropriate Diels–Alder candidate commenced (Scheme 13). Reduction of the

amide to the aldehyde[117] and olefination by the Corey protocol gave an enal.[118] Methylenation and fluoride-promoted removal of the silyl ether gave alcohol **78**. Oxidation[43] and a stabilized Wittig reaction gave the intramolecular Diels–Alder substrate, which was treated with BHT in refluxing xylene to afford the desired tricycle **79** as a single detectable diastereomer via an exo-cycloaddition. Alkylation of the ester and protection of the tertiary alcohol as an acetate ester set the stage for a dissolving metal reduction to deoxygenate the ester and remove the trityl protecting group.[119] Oxidation[43] and methylation provided a single diastereomer of the tertiary alcohol in 82% yield over two steps, completing the total synthesis of (-)-cladiella-6,11-dien-3-ol (**81**),[35,120] which represents the first total synthesis of an (*E*)-olefin containing C2–C11 cyclized cembrane natural product.



Scheme 13. Completion of First (*E*)-Olefin Containing Cladiellin

Seeking to further illustrate the versatility of their synthetic material, three other cembranoid natural products were targeted. Stereoselective dihydroxylation of tricycle **81** allowed access to (-)-cladiell-11-ene-3,6,7-triol (**82**) in 94% yield (Scheme 14).[121] A one-pot procedure was also developed involving oxymercuration of both olefins of (-)-cladiella-6,11-dien-3-ol (**81**) and demercuration to provide the tetracycle in 69% yield.[122] Acetylation of the resultant tertiary alcohol provided (+)-polyanthellin A (**83**),[78,123] marking the first total synthesis of this natural product. Finally, following protection of the tertiary alcohol of (-)-cladiella-6,11-dien-3-ol (**81**), stereoselective



Scheme 14. Versatile Syntheses of Several Natural Cladiellins

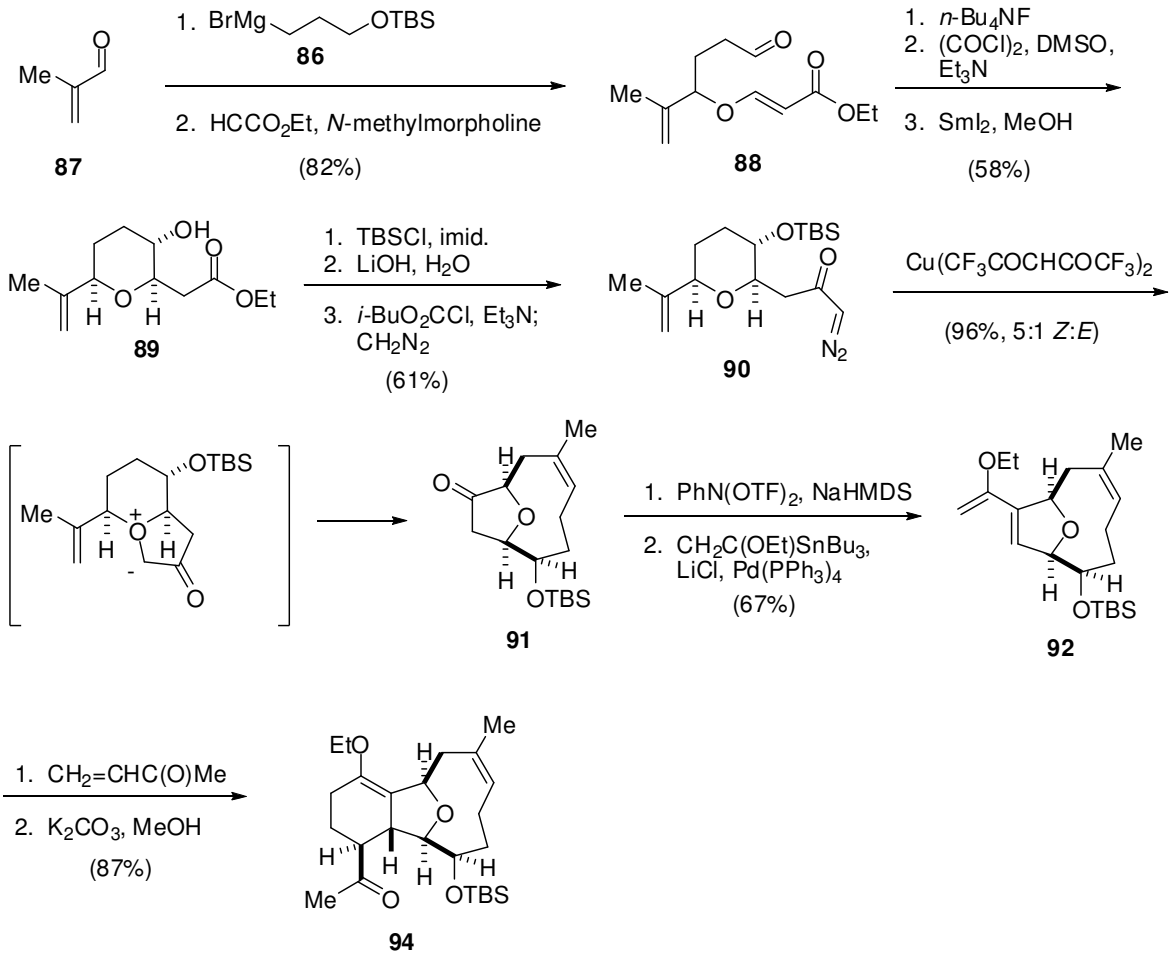
dihydroxylation and acetylation of the secondary alcohol gave tertiary alcohol **84**. Dehydration using Burgess salt provided the exocyclic olefin,[124] and removal of the

silyl protecting group afforded (-)-7-deacetoxyalcyonin acetate (**1**),[14,15,88] representing the third total synthesis of this natural product.

6. Wittig Rearrangement/Intermolecular Diels–Alder Strategy

In 2007, the Clark laboratory reported another unique approach to cladiellin diterpenes, hinging upon a [2,3]-sigmatropic rearrangement that would be used to form the five- and nine-membered rings of the tricycle. Following bicycle formation, an intermolecular Diels–Alder was envisioned to install the cyclohexyl moiety.[125] Vigulariol (**85**) was chosen as the initial target, a molecule possessing in vitro cytotoxicity against human-lung adenocarcinoma (IC_{50} = 18 nM).[126] To begin, a Grignard reagent **86** was added to methacrolein (**87**) to give a secondary alcohol (Scheme 15). The reported synthesis of vigulariol (**85**) is racemic due to the use of a racemic preparation of the secondary alcohol, but could be rendered enantioselective if a stereoselective method of preparing this alcohol was employed.[127] O-alkylation with ethyl propiolate gave enoate **88**.[128,129] Deprotection and Swern oxidation[130] gave the aldehyde. A samarium-mediated reductive cyclization delivered the tetrahydropyran **89** diastereoselectively,[131] and protection of the alcohol, followed by hydrolysis of the ester provided the acid. The acid was converted to the corresponding anhydride and treated with diazomethane to give diazo ketone **90**. At this point, the copper carbenoid of diazo ketone **90** was formed and an ensuing oxonium formation and [2,3]-Wittig rearrangement occurred to deliver the oxonene **91** of the cladiellins.[132,133] A 5:1 *Z*:*E* mixture of alkenes was obtained, but the material possessing the (*E*)-oxonene could be converted to the desired material using AIBN and ethanethiol.[134,135] The ketone appended to the

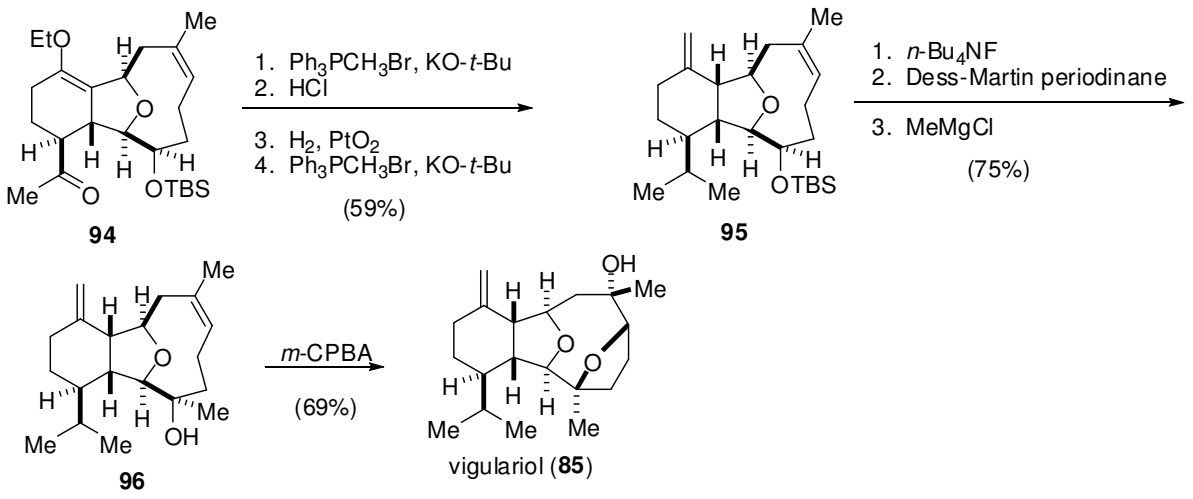
tetrahydrofuran was converted to a vinyl triflate and a Stille coupling was used to form the diene **92**.[136] Intermolecular Diels–Alder cycloaddition with methyl vinyl ketone (**93**) gave a 2:1 exo:endo mixture of isomers, which were equilibrated to the desired exo-adduct **94** under basic conditions.



Scheme 15. Intermolecular Diels–Alder

With the tricycle elaborated, the ketone **94** was methylenated, and the enol ether was hydrolyzed under acidic conditions (Scheme 16). Selective hydrogenation of the 1,1-disubstituted olefin was followed by methylenation of the ketone to give diene **95**. Deprotection of the silyl ether, oxidation to the ketone,[43] and addition of

methyl Grignard reagent efficiently provided alcohol **96**. Finally, an epoxidation with *m*-CPBA delivered the epoxide, which was opened intramolecularly by the tertiary alcohol to afford (±)-vigulariol (**85**).[126]



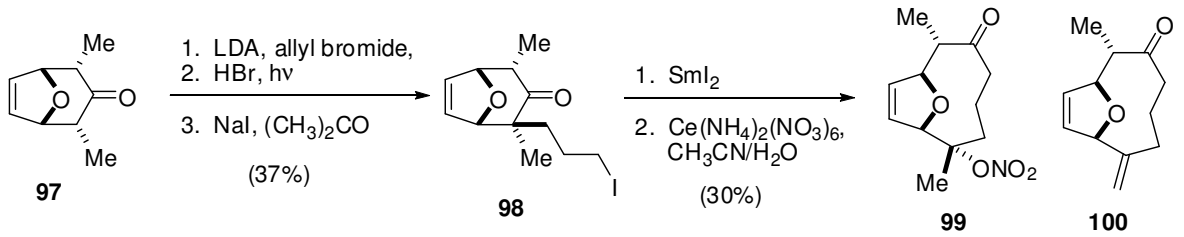
Scheme 16. Completion of (±)-Vigulariol

7. Miscellaneous Strategies

A variety of approaches leading to partial syntheses of cladiellins have been reported. Among these, some unique strategies have been elucidated adding to the methods for the synthesis of C2–C11 cyclized cembranoid natural products. Though none of the following attempts have resulted in a total synthesis, they provide valuable insight into several approaches that have shown promise in the setting of cladiellin, briarellin, and asbestinin syntheses, as well as some routes that have proven to be less amenable to these natural products.

Some of the earliest reported work involving cladiellins employed an annulation–fragmentation strategy for the formation of the five- and nine-membered rings of these cembranoids. The Hoffmann laboratory began with symmetrical ketone **97**[137] and performed a diastereoselective allylation in high yield (Scheme

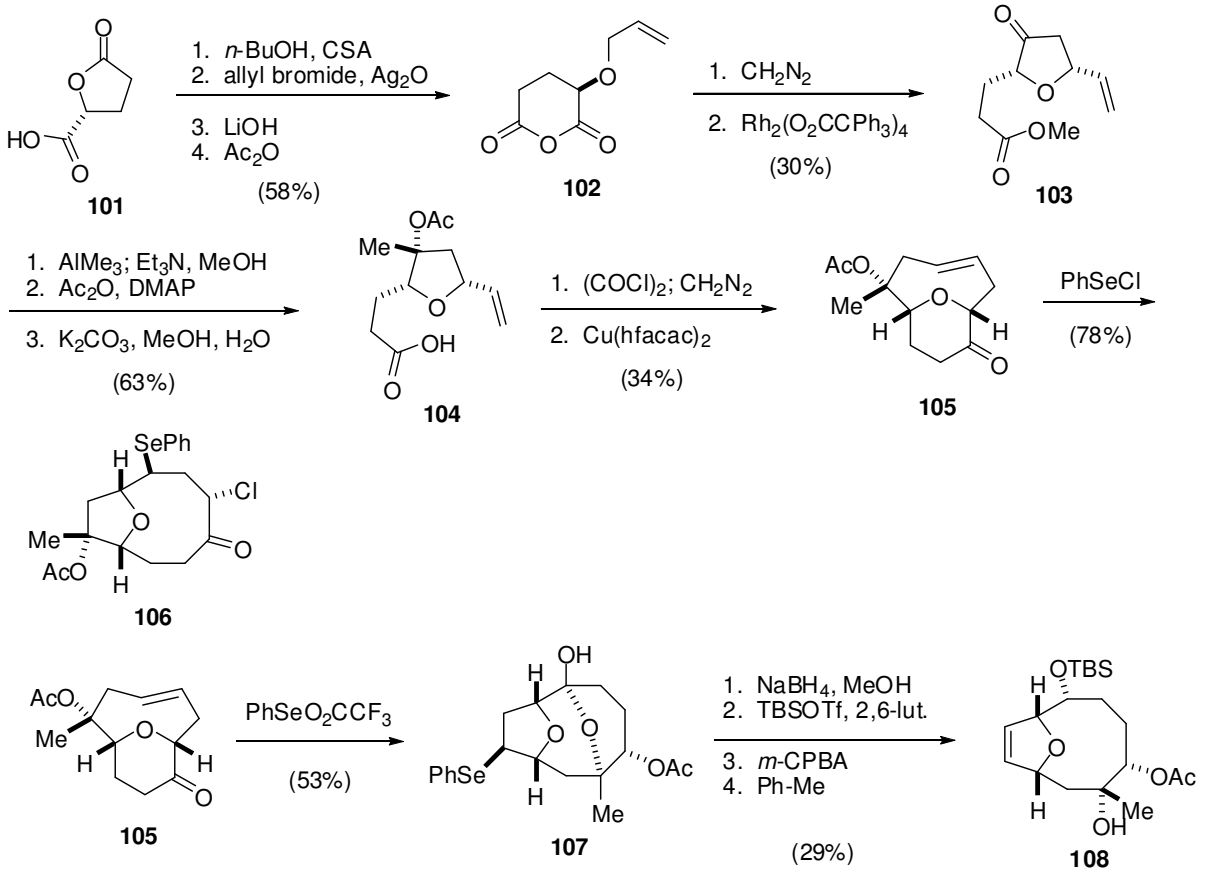
17).[138] Hydrobromination provided the alkyl bromide, which was uneventfully converted to the alkyl iodide **98** under Finkelstein conditions. A samarium-mediated Barbier-like cyclization provided the cyclopentanol,[139] which was fragmented using cerium(IV) ammonium nitrate to provide bicycles **99** and **100** in 27% yield and 7% yield, respectively.[140] No further efforts have been reported within the past decade utilizing this strategy.



Scheme 17. Annulation-Fragmentation Strategy

The Clark group reported an approach to a similar oxabicycloundecane core of the cladiellins in 2000. Their strategy featured a novel rearrangement to form the five- and nine-membered rings of these natural products. Beginning with (*R*)-γ-butyrolactone-γ-carboxylic acid (**101**),[141] acid-catalyzed ring opening of the lactone[142] was followed by allylation of the resultant secondary alcohol (Scheme 18).[143] Hydrolysis and acetylation afforded anhydride **102**. Treatment with diazomethane regioselectively opened the ring and formation of the rhodium carbenoid provided furanone **103** in 50% yield.[134,135,144] A diastereoselective methylation[145] preceded acetylation and hydrolysis to give acid **104**. Again, treatment with diazomethane followed by formation of the copper carbenoid set the stage for a spontaneous [2,3]-Wittig rearrangement to give bicycle **105**.[132,133] As the key step of the synthesis, bicycle **105** was treated with phenylselenyl chloride, which

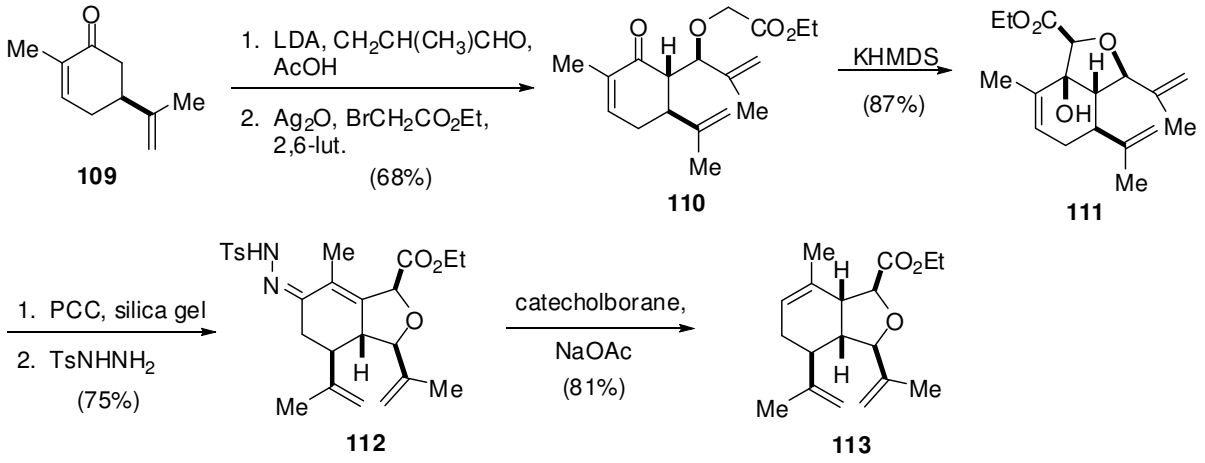
triggered a rearrangement to yield oxabicycloundecane **106** in 78% yield. Additionally, treatment of ketone **105** with phenylselenyl trifluoroacetate gave tricycle **107**, albeit in lower yield. Recently, in a separate publication, the Clark group reported that reduction of tricycle **107**, protection of the resultant secondary alcohol, and oxidative elimination o the selenide gave bicycle **108**, which represents a framework that could be used to complete a cladiellin natural product.



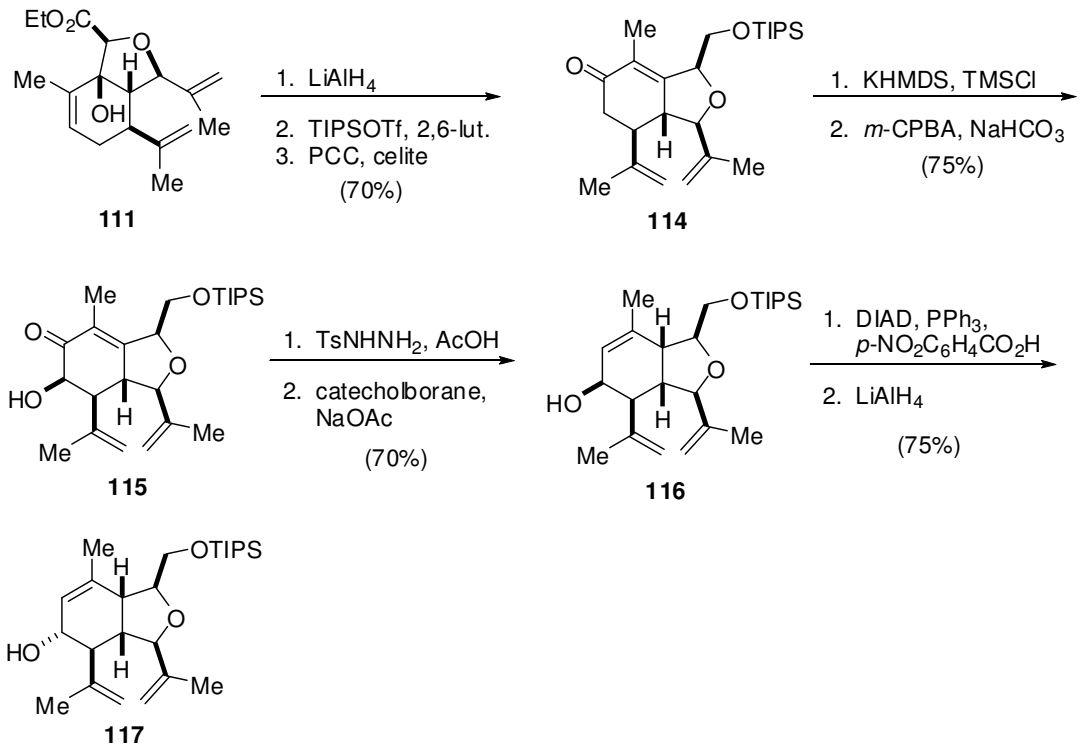
Scheme 18. Clark's Rearrangement Approach

The McIntosh laboratory has developed two strategies for the synthesis of the hydroisobenzofuran of the C2–C11 cyclized cembranoids. The first report relied upon a cycloaldol approach to form the furan portion of these molecules.[146]

Beginning with (*S*)-carvone (**109**), an aldol reaction[147] with methacrolein and Williamson etherification of the resultant alcohol provided ester **110** (Scheme 19).[82,148] An intramolecular aldol reaction delivered bicycle **111** in 87% yield. Oxidation gave the enone,[149] which was converted to the tosylhydrazone **112**. Reduction with catecholborane and heating the reaction gave the *cis*-fused isobenzofuran **113**.[150-152] A similar route was also developed to access natural products containing oxygenation at C13.[107,108,120,153] To this end, ester **111** was reduced to the primary alcohol, protected as a silyl ether, and allylic oxidization afforded the enone **114** (Scheme 20). Rubottom oxidation[154] gave predominantly the undesired configuration of the C13 alcohol **115** (7:1 dr), and formation of the tosylhydrazone proceeded smoothly. Reduction with catecholborane again and in situ allylic diazene rearrangement gave the trisubstituted olefin **116**,[150-152] and a Mitsunobu reaction gave the correct C13 configuration for bicycle **117**.[100] No further efforts utilizing this route have been reported since 2003.



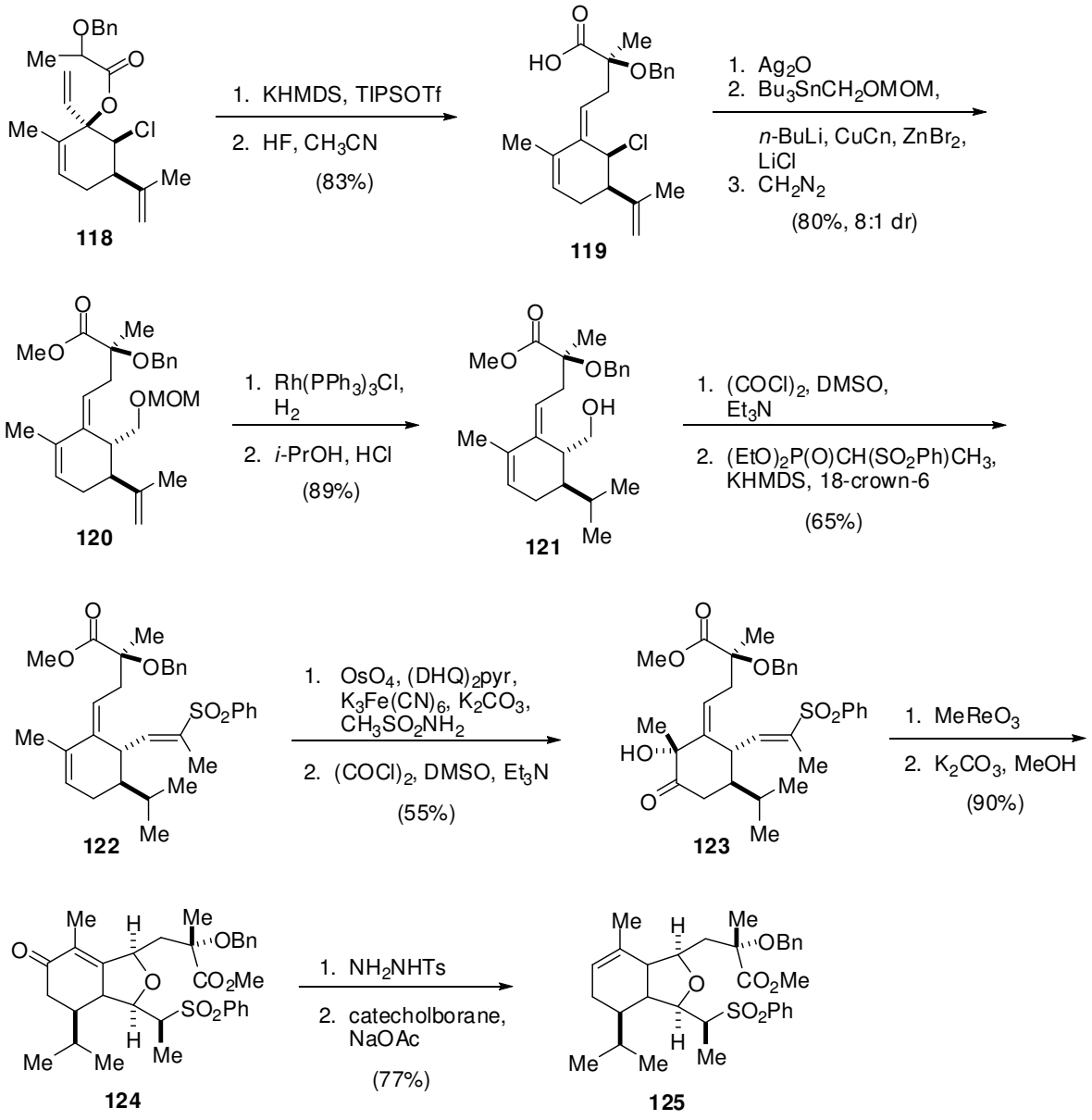
Scheme 19. Cycloaldol Route to the Isobenzofuran



Scheme 20. C13 Oxidized Isobenzofuran

The second route recently reported by the McIntosh group involves an Ireland–Claisen rearrangement (Scheme 21). The approach commenced with ester **118** (available in three steps from (*S*)-carvone).[155,156] Treatment with base in the presence of triisopropylsilyl triflate triggered the rearrangement to give acid **119** following deprotection.[157] Lactonization[158] set the stage for installation of an additional oxygen substituent via S_N2' addition of an alkoxy methyl copper nucleophile[159] and formation of the methyl ester **120**. Selective hydrogenation and cleavage of the methoxymethyl ether gave alcohol **121**. A Swern oxidation[130] and a Horner–Wadsworth–Emmons reaction provided sulfone **122**. Dihydroxylation[160] and oxidation[130] gave ketone **123**. Allylic alcohol transposition[161,162] preceded formation of the tetrahydrofuran **124** via subjection to alkaline conditions. Formation of the

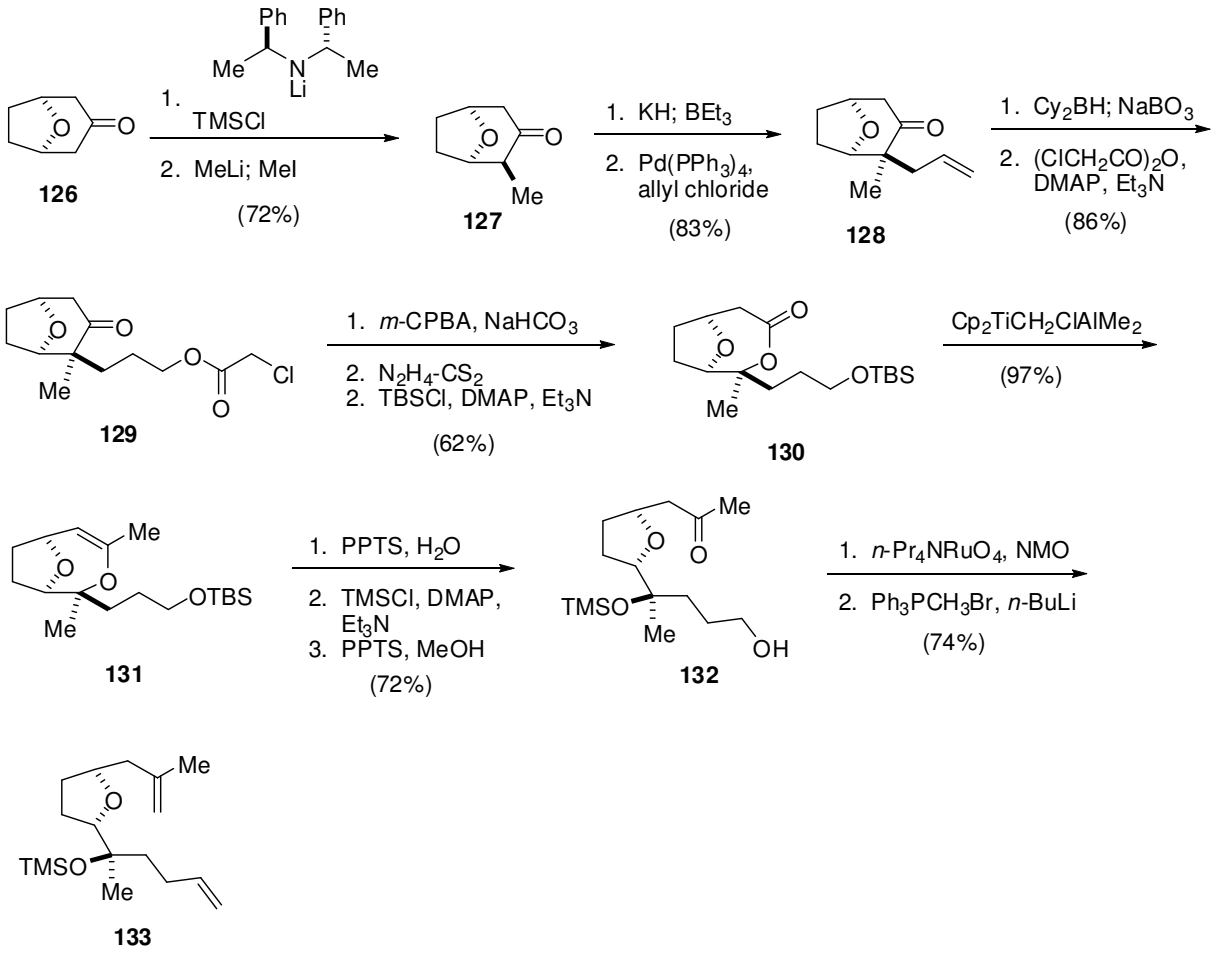
tosylhydrazone and reduction triggered an allylic diazene rearrangement once again to give bicycle **125**,[150-152] characteristic of the cladiellin subclass.



Scheme 21. Rearrangement Approach to the Cladiellins

In 2003, the Jung group reported efforts toward the initially reported structure of sclerophytin A (**16**).[9,34,35,163] Formation of the silyl enol ether of ketone **126** using a chiral base[164] and subsequent alkylation gave bicycle **127** (Scheme 22).[165] A

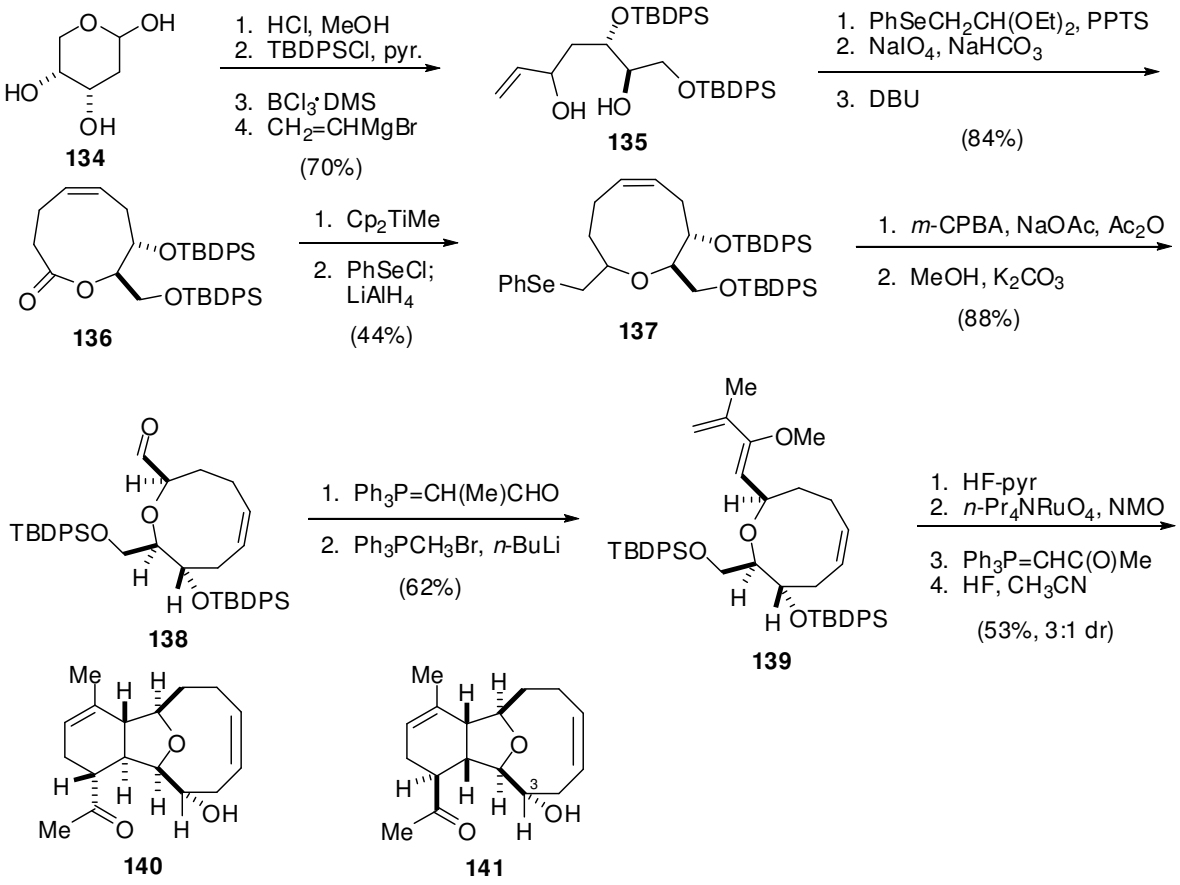
second alkylation using a palladium mediated coupling gave alkene **128** in 83% yield.[166,167] Hydroboration and oxidation of the terminal olefin[168] preceded protection of the resultant alcohol as an ester functionality. A Baeyer–Villiger oxidation provided the lactone,[169] from which the ester was removed[170] and the alcohol was protected as a silyl ether to give bicycle **130**. A Tebbe olefination proceeded in good yield,[59] however, the trisbustituted olefin **131** was isolated rather than the desired exocyclic olefin. The original synthetic plan involved a [3+2] cycloaddition reaction, but the inability to access the exocyclic olefin in good yield precluded this prospect, so the group redirected their strategy taking advantage of the alkene **131**. Hydrolysis of the enol ether provided the ketone, and the diol was bis-protected as silyl ethers. Selective removal of the primary silyl ether gave ketone **132**. Oxidation of the primary alcohol to the aldehyde[31] provided a substrate that was proposed to be suitable for a pinacol coupling.[171] However, no productive reaction could be achieved with the dicarbonyl. In an attempt to overcome this inactivity and form the nine-membered ring, methylenation of both carbonyls gave a diene **133** that was treated to the Grubbs second generation catalyst to attempt a ring-closing metathesis,[172] but again this was met with no success. Frustrated by the numerous roadblocks, this program was abandoned.



Scheme 22. Fragmentation Approach to the Furan

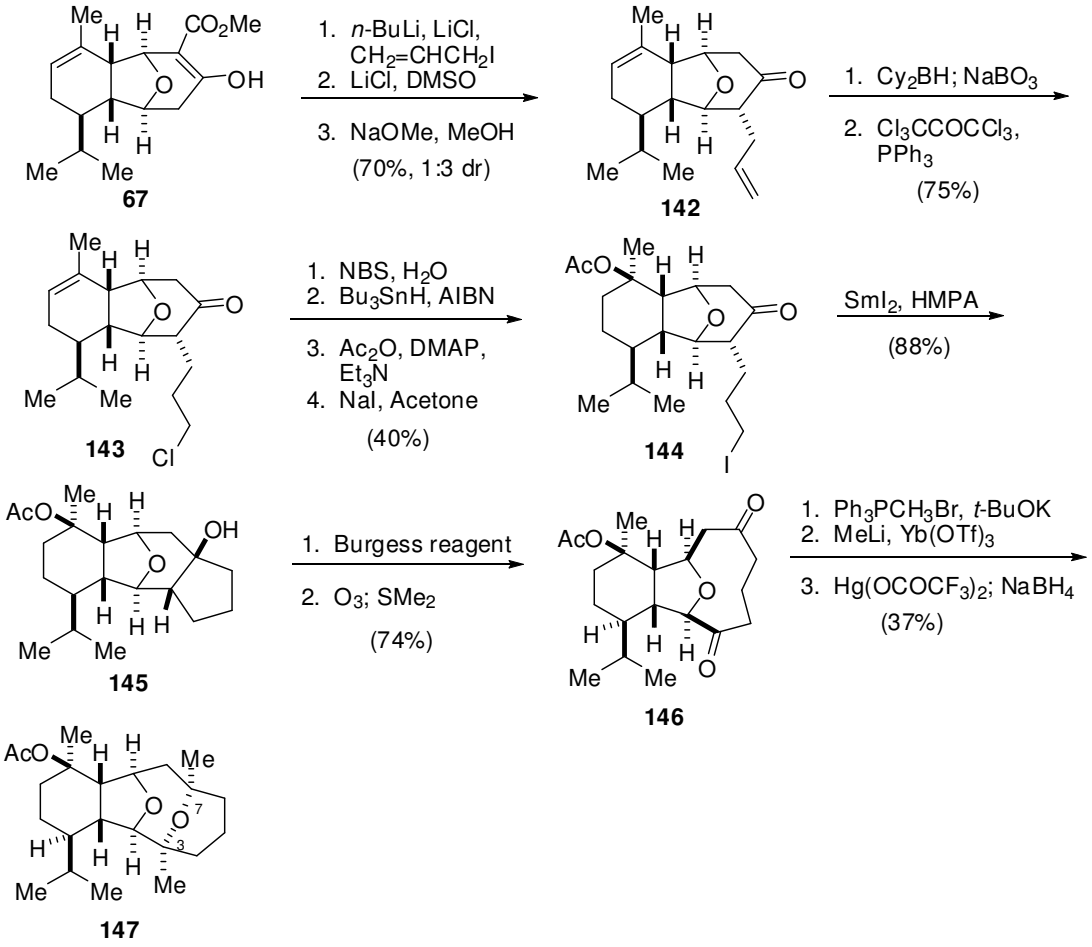
As alluded to earlier, the Holmes laboratory reported a route to cladiellin natural products that employed an intramolecular Diels–Alder cycloaddition (Scheme 23).[110] Their efforts were published shortly after the Crimmins laboratory divulged their synthesis of ophirin B.[107] The Holmes group has developed a Claisen rearrangement for accessing medium ring lactones.[173,174] Their synthesis commenced with the acid-catalyzed glycosidation of 2-deoxy-D-ribose (**134**),[175] followed by protection of the diol as silyl ethers. The acetal was demethylated[176,177] and treatment with a Grignard reagent gave diol **135**. Formation of the dioxepane[178] preceded oxidation of the selenide, which triggered a Claisen rearrangement to give

lactone **136**.[179] With an efficient route to lactone **136**, attention was turned toward preparing an appropriate Diels–Alder candidate. Methylenation[180] and selenation gave selenide **137**. Oxidation of selenide **137**, Pummerer rearrangement, and loss of methoxide gave aldehyde **138** as a single diastereomer.[181] A stabilized Wittig reaction gave the enal, and methylenation delivered triene **139**. Selective removal of the primary protecting group and oxidation gave the aldehyde,[31] which upon treatment with a stabilized Wittig reagent[182] formed the enone and spontaneously cyclized. Upon deprotection, tricycles **140** and **141** were isolated. However, the endo-adduct **140** was the major product of this cyclization (3:1 dr). This reversal of



Scheme 23. Cycloaddition Approach of Holmes

selectivity from the cladiellin and asbestinin syntheses from the Crimmins laboratory demonstrates the crucial nature of the C3 configuration and protecting group.[107-109] When the opposite configuration at C3 is employed, the endo-adduct is the dominant product, whereas the exo-adduct is favored when using the C3 epimer. The undesired result of the Diels–Alder cycloaddition brought an untimely end to this project.



Scheme 24. Samarium-mediated Cyclization to Polyanthellin A Diastereomer

Finally, the Molander group has reported a second route to the cladiellins that extends the [4+3] annulation strategy discussed earlier (Scheme 11).[88-90] Using tricycle **67** from their earlier synthesis (vide supra), an alkylation and Krapcho

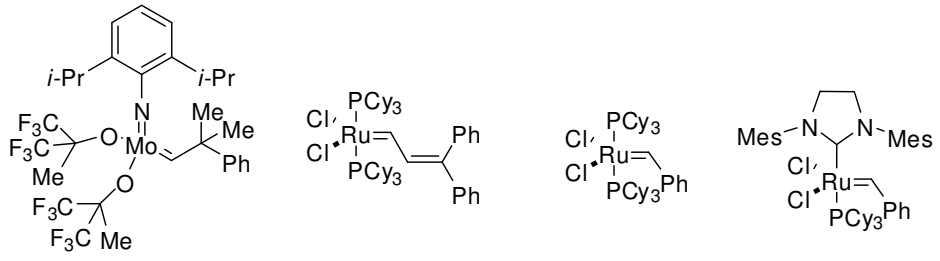
decarboxylation gave the ketone **142** as a mixture of epimers (3:1 dr),[95] which could be epimerized to the desired configuration under basic conditions (Scheme 24). Selective hydroboration and oxidation of the terminal olefin[168] was followed by chorination to give alkyl chloride **143**.[183] A three step sequence installed the tertiary acetate,[184-187] and the alkyl chloride was transformed into alkyl iodide **144**.[188] At this point, a key samarium iodide-mediated cyclization provided tetracycle **145**.[189] Dehydration[124] and ozonolysis gave the cladiellin skeleton **146**. Chemoselective methylenation was followed by alkylation.[102] At this point, oxymercuration and reduction[190] gave the 3,7-epimer of polyanthellin A **147**.[78]

C. Medium Ring Ether Synthesis via Ring-closing Metathesis

1. Catalyst Development

The olefin metathesis reaction is recognized as an efficient method for the construction of carbon–carbon bonds. Early efforts in this field utilized poorly defined catalyst systems that were difficult to employ and featured a narrow substrate scope due to functional group compatibility issues.[191] However, in 1990, the Schrock laboratory divulged a highly efficient catalyst system using molybdenum alkylidene complex **148**, which showed broader functional group than its predecessors (Figure 4).[192,193] As a result, this catalyst became widely-used among synthetic chemists for the formation of olefins, including medium ring ethers. However, the catalyst is not ideal due to its oxophilicity, rendering it highly air and moisture sensitive, as well as the difficulty in synthesizing the active catalyst.

Despite these drawbacks, the efforts of Schrock represent a major step forward in the history of olefin metathesis.



148 **149** **150** **151**

Figure 4. Olefin Metathesis Catalysts

Concurrently, the Grubbs laboratory focused efforts toward ruthenium-based alkylidene complexes they hoped to apply to olefin metathesis reactions.[194,195] Notably, catalysts **149** and **150** showed similarly high reactivity when compared to the Schrock system (Figure 4). Additionally, these catalysts demonstrated high thermal stability and broad functional group tolerance. Further, the ruthenium-based catalysts **149** and **150** showed lower air and moisture sensitivity than the Schrock systems. With the advent of a new catalyst species, featuring a 4,5-dihydroimidazol-2-ylidene ligand and coined the Grubbs second generation catalyst (**151**), the scope of potential products grew dramatically as the reactivity of the catalyst increased.[172] Di-, tri-, and tetrasubstituted olefins could efficiently be formed using catalyst **151**. Within the past decade, other novel ruthenium-based catalysts have been developed that have found great success in the ring-closing, ring-opening, and cross metathesis reactions.[196,197]

Early reports documented efficient formation of five-, six-, and seven-membered rings using the ruthenium-based catalyst systems, while the formation of

eight- and nine-membered rings remained more elusive due to unfavorable transannular interactions and entropic difficulties. To combat these challenges encountered in medium ring synthesis, extra rigidifying elements, such as cyclic constraints, have been employed successfully.[198-200] Grubbs demonstrated that such cyclic constraints greatly improve the efficiency of the formation of medium rings, due to the decreased rotational freedom of these dienes (Table 1).[201] However, the employment of these synthetic tactics greatly minimizes the utility of this reaction since the cyclic constraints are often not desired in the target molecule. In 1995, Grubbs reported the successful ring-closing metathesis of an eight-membered dipeptide lacking a cyclic constraint (Scheme 25).[201] The following year, the Hoveyda laboratory divulged the ring-closing metathesis of an even more simplified medium ring.[202] The success of these reactions is credited to the steric

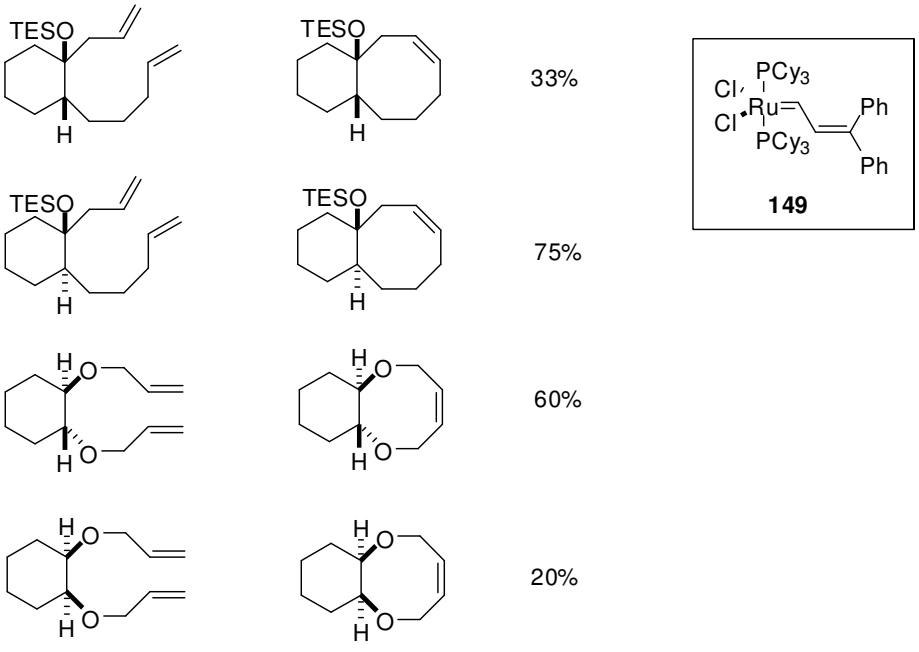
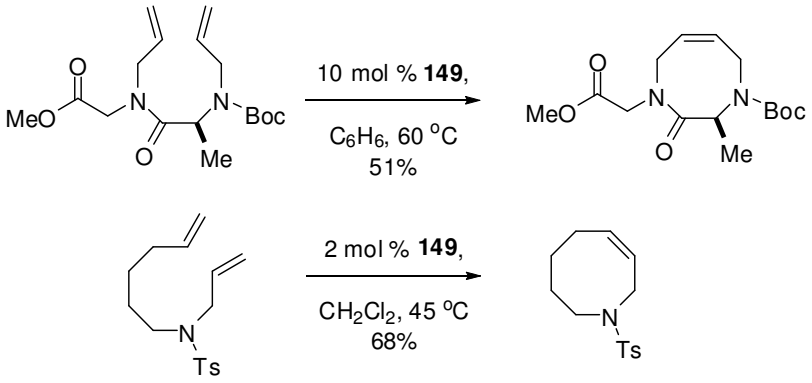


Table 1. Cyclic Constraints for Ring-closing Metathesis

and electronic requirements of the substituents on the respective dienes producing a rotamer that places the dienes in close proximity, favoring ring-closing metathesis. At the time, these served as very rare, but promising, examples of eight-membered ring formation via these processes.



Scheme 25. Early Ring-closing Metathesis Lacking Cyclic Constraint

2. Aldol/Ring-closing Metathesis in the Crimmins Laboratory

Around the same time that olefin metathesis was becoming more practical for target-directed synthesis, the Crimmins laboratory was developing auxiliary-based methodology for the synthesis of subunits of polyketide-containing natural products. Seeking to apply these reactions to the synthesis of medium ring ethers, efforts focused on the development of two distinct approaches to these cyclic units, namely a glycolate aldol or glycolate alkylation reaction, followed by ring-closing metathesis using the Grubbs catalysts. This approach was predicated on the expected gauche effect present in dienes derived from aldol adducts (Figure 5).[203] As demonstrated, the stabilizing interaction involving donation of the C-H σ orbital into the C-O σ^* orbital places the two olefins in a favorable conformation for ring-closing metathesis to occur. Alternatively, the dipole minimized conformation also leads to a

more favorable orientation for ring-closing metathesis. These acyclic conformational constraints were proposed to deliver medium ring ethers efficiently.

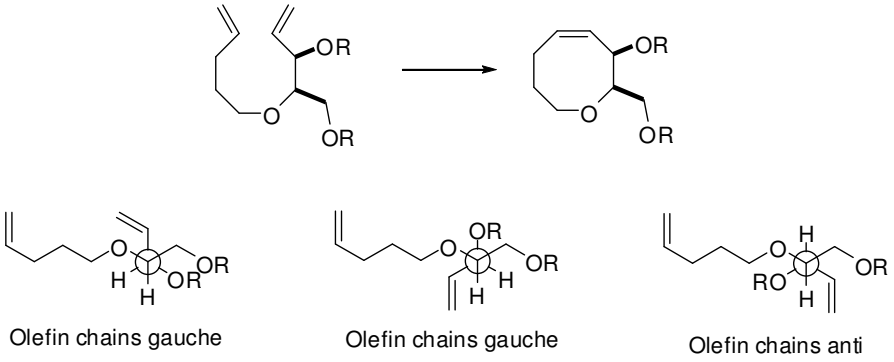


Figure 5. Acyclic Conformational Constraint via Gauche Effect

To synthesize the desired dienes, glycolate aldol reactions were utilized, allowing access to a variety of ring sizes by varying the chain length of the respective glycolate or aldehyde (Figure 6). Initially, the conditions developed by Evans using dibutylborontriflate for enolization were exploited in the asymmetric aldol additions.[111] Eventually, the Crimmins laboratory developed more cost efficient conditions using titanium tetrachloride, diisopropylethylamine, and later *N*-methyl pyrrolidinone for these additions, which proved to be applicable to a plethora of simple and complex oxazolidinone and oxazolidinethione glycolates to deliver the corresponding Evans-*syn* adducts in good yield and excellent diastereoselectivity.[204]

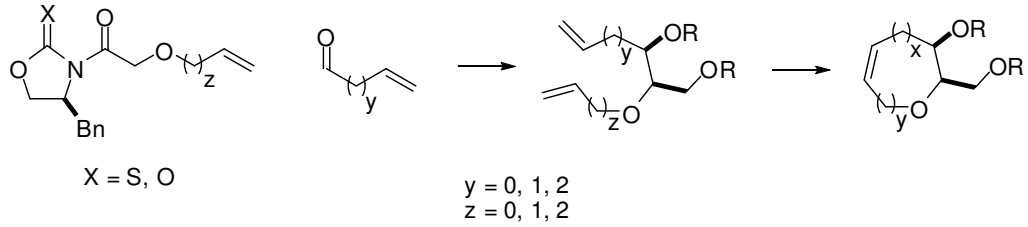
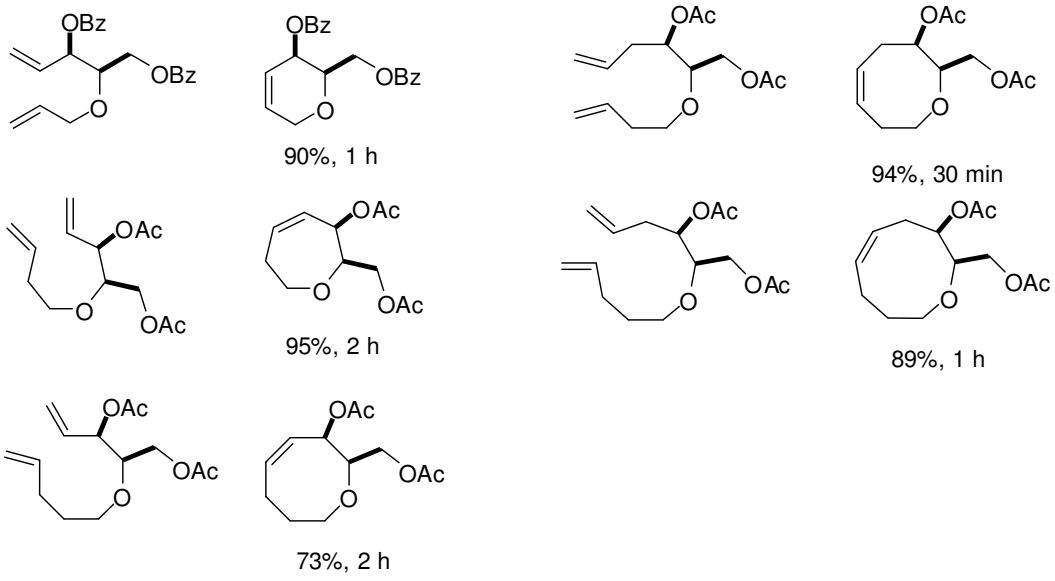


Figure 6. Aldol/Ring-Closing Metathesis Strategy

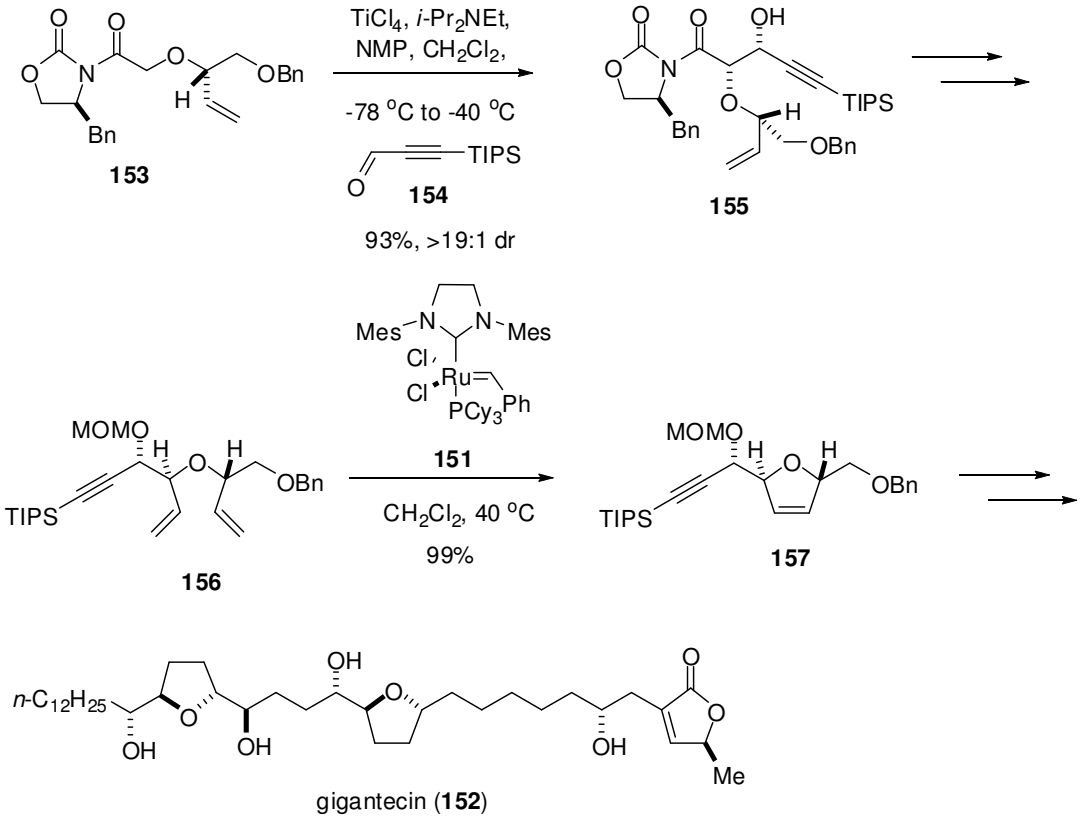
A systematic study examining the formation of six-, seven-, eight-, and nine-membered rings via ring-closing metathesis reactions of various aldol adducts was undertaken.[205] A variety of dienes accessible via Evans-*syn* glycolate aldol reactions were prepared and treated to Grubbs catalyst **150** in refluxing methylene chloride (Table 2). The results confirmed the hypothesis that the gauche effect present within these 1,2-dioxygenated compounds was sufficient to orient the olefins proximally and allow for small and medium ring ether formation. The desired unsaturated products were formed in less than two hours and were isolated in 73-95% yields.

Table 2. Small and Medium Ring Ether Formation



These findings concerning the glycolate aldol addition and the ring-closing metathesis reaction have been applied repeatedly in the setting of natural product synthesis in the Crimmins laboratory. The improved *syn* glycolate aldol conditions were applied to form two small rings in the total synthesis of gigantecin (**152**, Scheme 26).[206] The chlorotitanium enolate of complex glycolate **153** reacted with

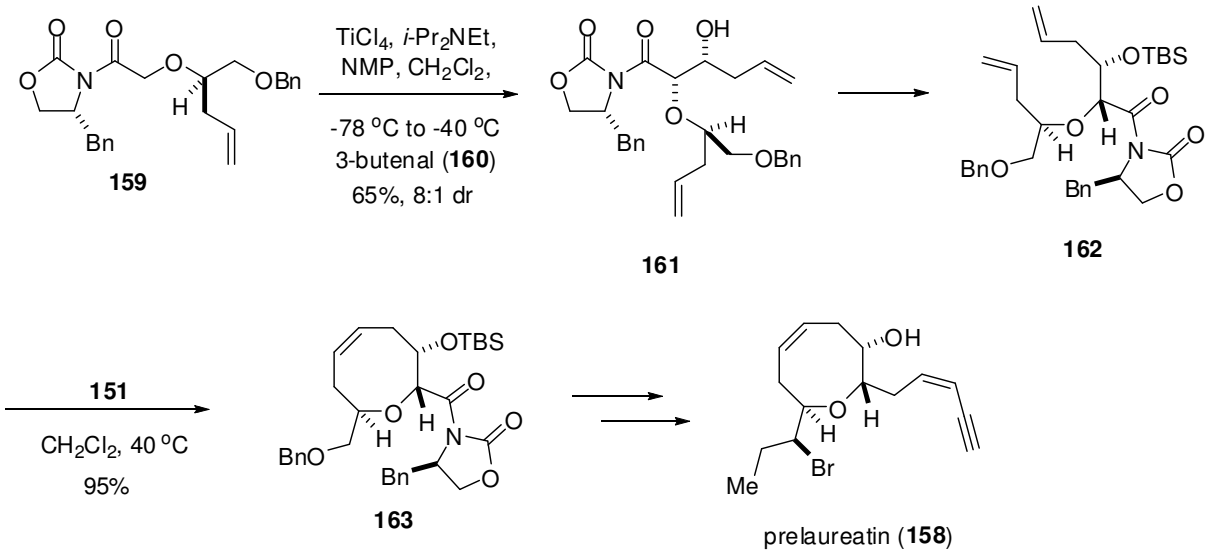
ynal **154** to provide the desired Evans-*syn* adduct **155** in 93% yield (>19:1 dr). Standard transformations prepared a diene **156** that served as a ring-closing metathesis candidate. Upon subjecting the diene **156** to the Grubbs second generation catalyst **151** in refluxing methylene chloride, the furan **157** was formed in nearly quantitative yield. Further manipulations afforded gigantecin (**152**).



Scheme 26. Total Synthesis of Gigantecin

In 2000, the Crimmins laboratory applied this aldol/metathesis approach to the synthesis of a medium ring ether natural product, prelaureatin (**158**, Scheme 27).[207] The use of titanium tetrachloride and diisopropylethylamine to form the corresponding enolate of glycolate **159**, followed by addition of 3-butenal (**160**), led to the desired aldol adduct **161** in good yield and good diastereoselectivity.

Protection of the secondary alcohol and treatment with catalyst **151** provided the oxocene **162** in 95% yield, which was carried on to prelaureatin (**158**). The aforementioned total syntheses represent a fraction of the natural products prepared in the Crimmins laboratory via the aldol/ring-closing metathesis strategy.



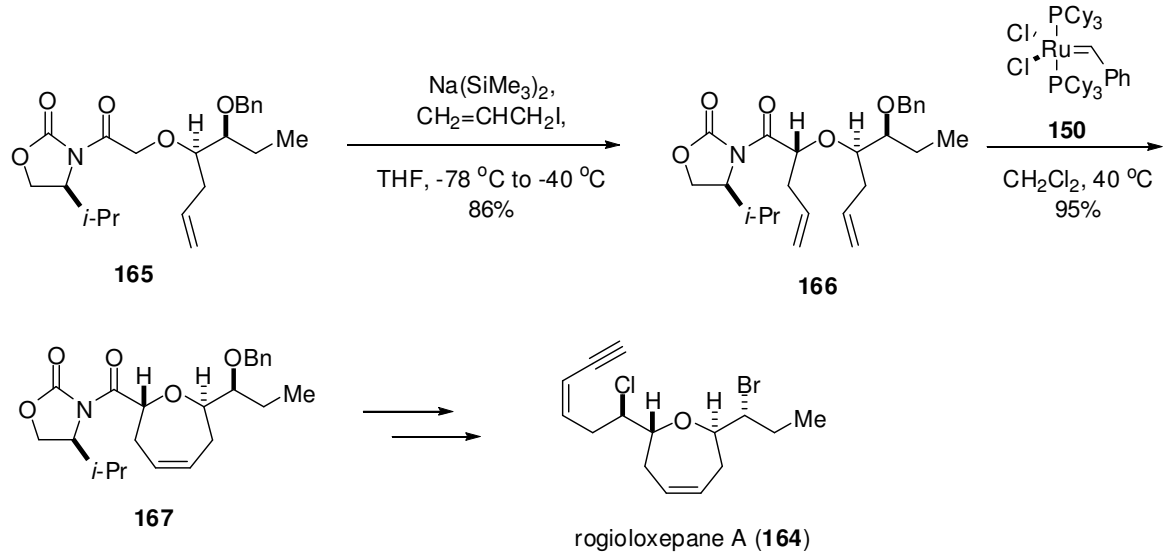
Scheme 27. Prelaureatin Total Synthesis

3. Alkylation/Ring-closing Metathesis in the Crimmins Laboratory

The Crimmins laboratory has also developed a useful extension to the Evans asymmetric alkylation which involves the formation of the sodium enolate of oxazolidinone glycolates and addition to a variety of electrophiles.[208] Most often, allylic iodides serve as electrophiles in the reaction, but other halides, such as propargylic bromides and benzyl iodomethyl ether have also been shown to deliver useful handles for natural product total synthesis. Silyl, benzyl, allyl, and alkyl protected glycolates perform well under these conditions providing the desired alkylation adducts in good yield and high diastereoselection. This alkylation strategy

has also been utilized to arrive at dienes useful for ring-closing metathesis to give small and medium ring ethers.

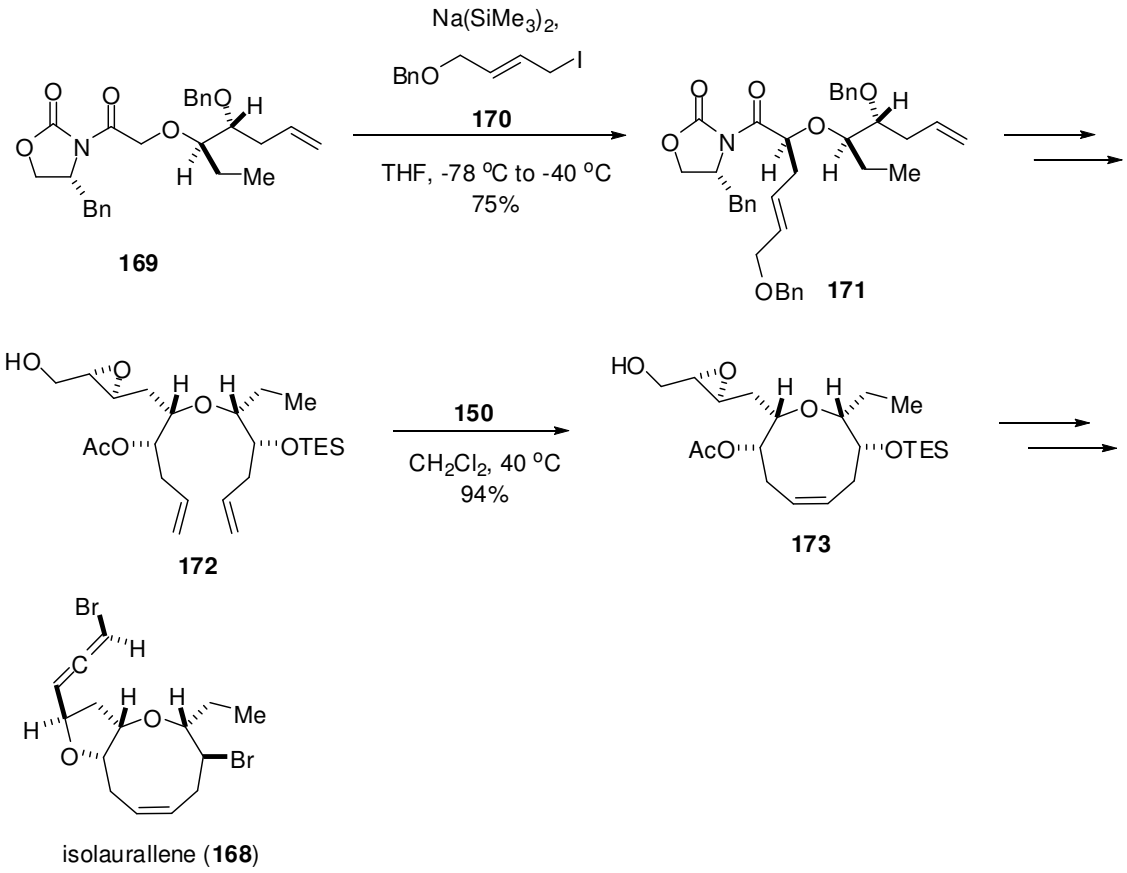
In 2003, the Crimmins laboratory divulged the total synthesis of rogioloxepane A (**164**) using the glycolate alkylation and ring-closing metathesis reactions as key steps (Scheme 28).[209] Alkylation of glycolate **165** with allyl iodide provided diene **166** in 86% yield as a single detectable diastereomer. Using Grubbs catalyst **150**, diene **166** underwent facile ring-closing metathesis to give the corresponding oxepene **167** in high yield. A series of manipulations provided rogioloxepane A (**164**).



Scheme 28. Total Synthesis of Rogioloxepane A

Crimmins and co-workers have also employed the alkylation/ring-closing metathesis strategy in the total synthesis of a medium ring ether-containing natural product, isolaurallene (**168**, Scheme 29).[210] The sodium enolate of complex oxazolidinone glycolate **169** was alkylated with allylic iodide **170** to give diene **171**. Several steps gave ring-closing metathesis candidate **172**, which was treated with

Grubbs catalyst **150** to efficiently deliver oxonene **173**. Medium ring ether **173** was carried on to isolaurallene (**168**).

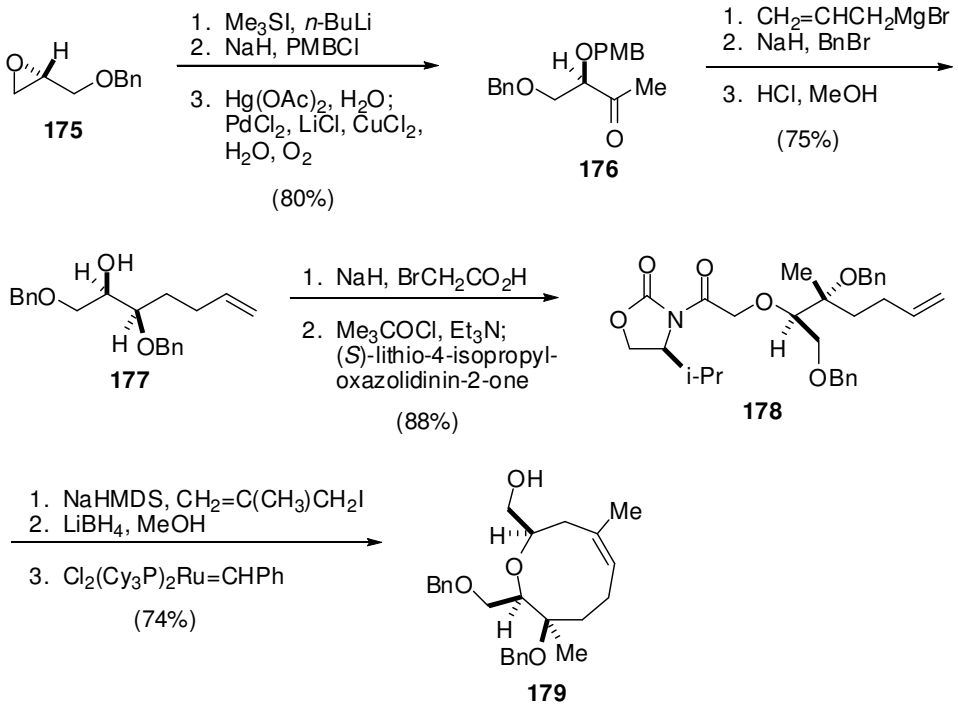


Scheme 29. Isolaurallene Total Synthesis

4. Total Syntheses of Eunicellin Diterpenes via Alkylation/Ring-closing Metathesis in the Crimmins Laboratory

As detailed, the Crimmins laboratory has extensively demonstrated the ability to form medium ring ethers[209,211-214] via the ring-closing metathesis reaction[172,195] of dienes generated by glycolate alkylation[208] and glycolate aldol reactions.[204,213,215,216] As an extension of these methods, a novel strategy was envisioned for the cembranoid natural products involving initial formation of the oxonene ring prior to the hydroisobenzofuran moiety. This would represent the first total synthesis at the

time to form the nine-membered ring prior to formation of either of the other two rings. The synthesis of these final two rings hinged upon an intramolecular Diels–Alder approach that would form the tricycle while concomitantly establishing the C1, C10, C13, and C14 stereocenters. Ophirin B (**174**)[120] was first targeted, representing the first C13, C18 oxygenated cladiellin to be prepared via total synthesis.[107,108] The synthesis commenced with the methylenation of (*S*)-benzylglycidyl ether (**175**)[217] followed by proection as a *p*-methoxybenzyl ether (Scheme 30). Wacker oxidation provided ketone **176** in 80% yield over three steps.[218,219] Chelation-controlled stereoselective alkylation and protection of the

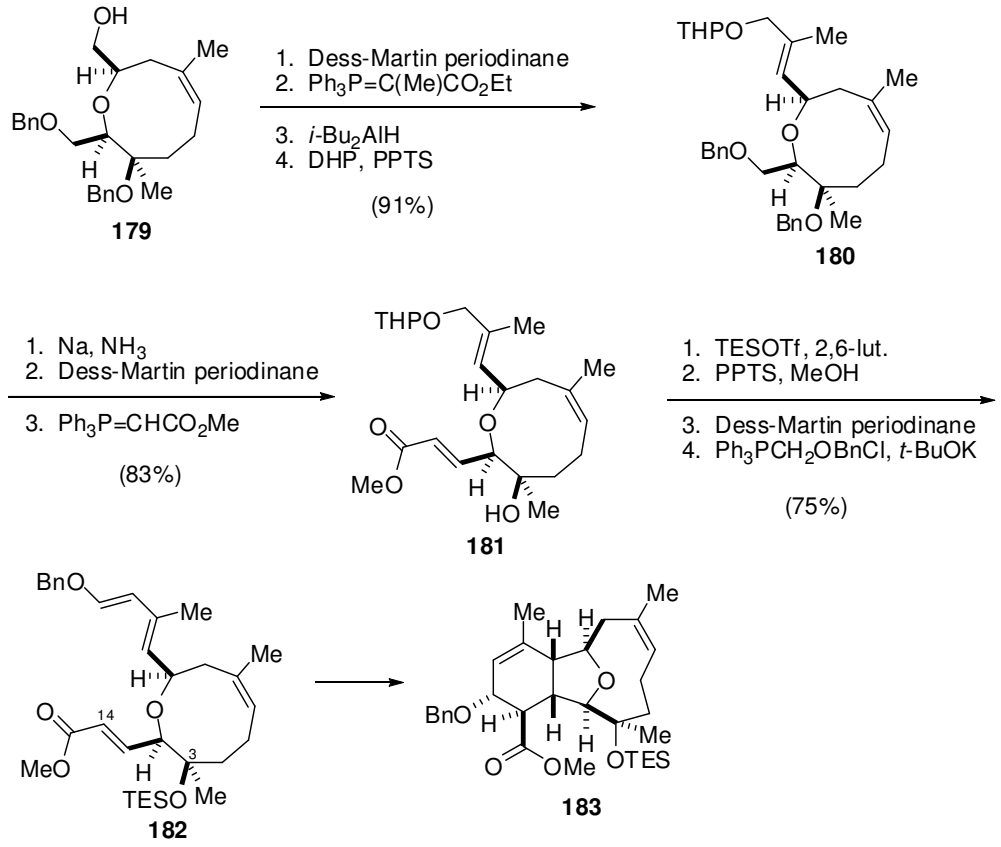


Scheme 30. Ophirin B Oxonene Formation

resultant alcohol as a benzyl ether preceded deprotection of the secondary alcohol under acidic conditions. Standard formation of the corresponding glycolic acid and glycolate provided imide **178**, prepared for a glylcolate alkylation. The sodium

enolate of imide **178** was alkylated with methyallyl iodide in 93% yield to provide a single detectable diastereomer of the diene.[208] Reduction of the chiral auxiliary and ring-closing metathesis efficiently provided the oxonene **179**.[172]

With the nine-membered ring **179** in hand, careful ordering was necessary for the installation of the diene and dienophile for the key Diels–Alder cycloaddition. To this end, an oxidation[43] and stabilized Wittig reaction provided the enoate, which was reduced to the allylic alcohol and protected as a tetrahydropyranyl ether to provide oxonene **180** (Scheme 31). Dissolving metal reduction of the benzyl ethers provided the diol, and the primary alcohol was oxidized[43] and treated with a stabilized Wittig reagent to give the enoate, which would be employed as the dienophile in the pending Diels–Alder reaction. The tertiary alcohol was protected as a triethylsilyl ether. The pyran was then removed under acidic conditions and the resultant alcohol was oxidized to the aldehyde.[31] Treatment with benzyloxymethyl-enetriphenylphosphorane gave tetraene **181** as a 3:1 mixture of E:Z isomers. Under ambient conditions, tetraene **182** underwent a spontaneous, highly exo-selective Diels–Alder cycloaddition. The minor isomer from the Wittig reaction could be photochemically recycled to the reactive tetraene **182**, providing an overall 78% yield of tricycle **183**.[220] The observed stereochemistry from the cycloaddition can be rationalized using transition states **182a** and **182b**, which demonstrate the importance of the C3 protecting group (Figure 7). Namely, the bulk at C3 has a significant steric interaction with the C14 proton and carbon in the endo case which is mitigated for the exo transition state. This hypothesis has been corroborated by varying the size of the C3 protecting group and observing the diastereoselectivity of



Scheme 31. Intramolecular Diels–Alder Cycloaddition

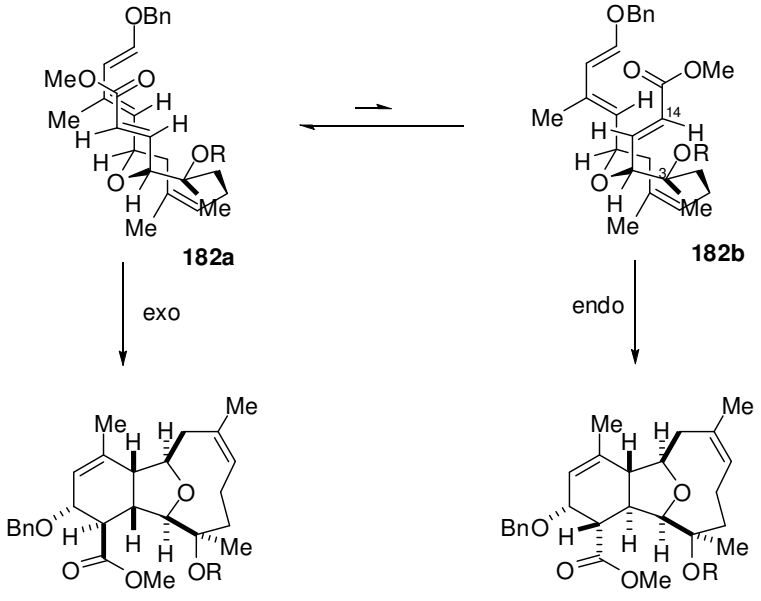
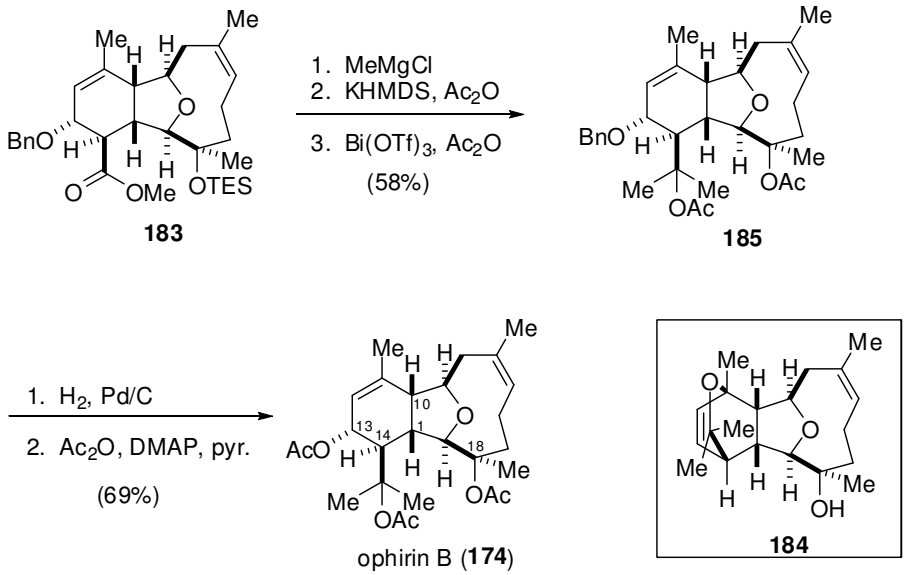


Figure 7. Diels–Alder Transition States

the cycloaddition. Additionally, the work of Holmes using C3 epimers (vide supra, Scheme 23) supports these selectivity models.[110]

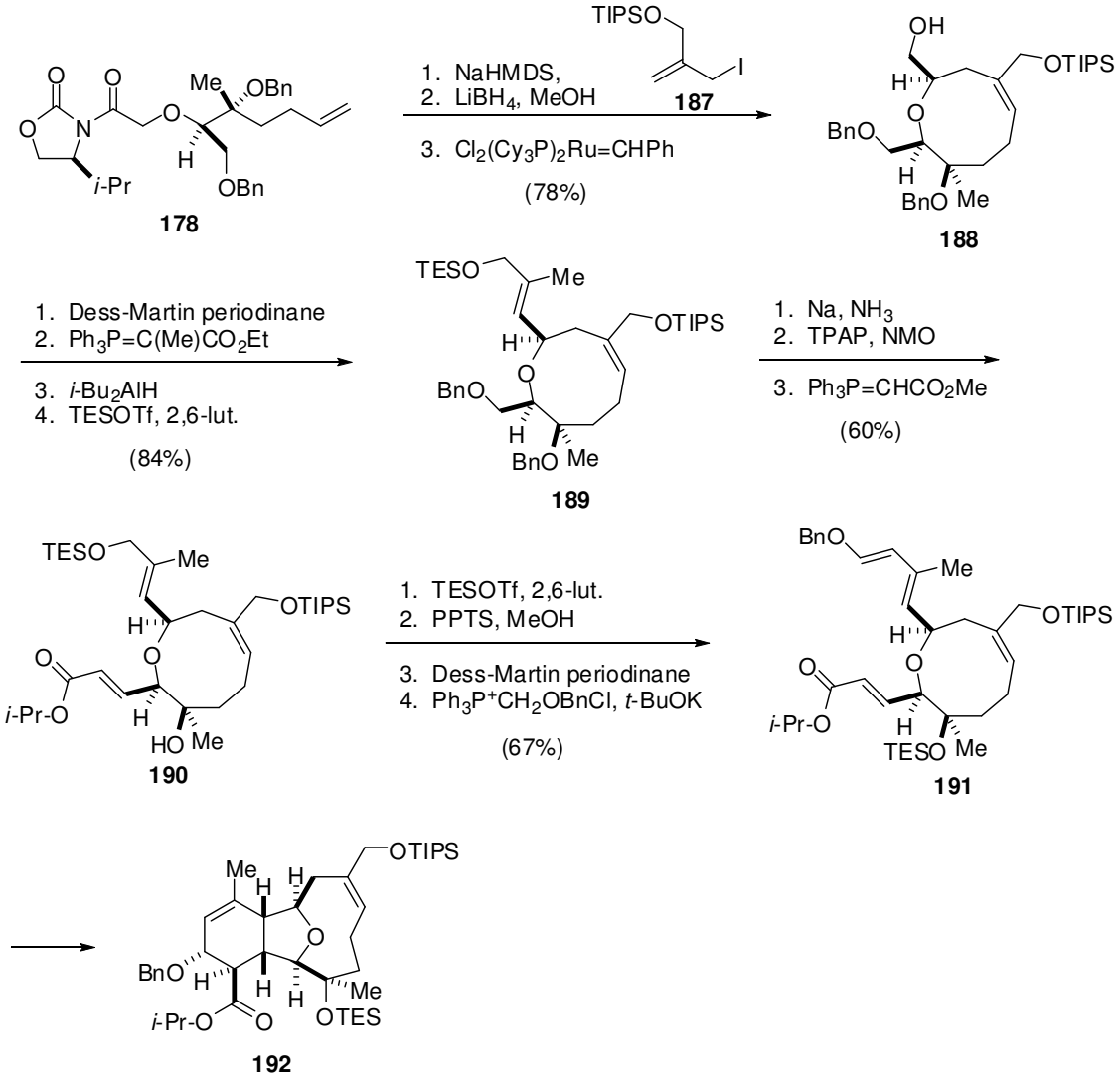
With the tricyclic core formed, alkylation of ester **183** delivered the tertiary alcohol (Scheme 32). A careful acetylation sequence was required to preclude formation of tetracycle **184**. Removal of the silyl ether provided the diol, and the C18 hydroxyl was selectively acetylated under basic conditions.[44] The C3 hydroxyl was then converted to its acetate ester **185** in the presence of a Lewis acid.[87,221] Finally, cleavage of the benzyl ether, and acetylation under basic conditions provided ophirin B (**174**), which possessed identical spectroscopic properties in all respects to the natural material.



Scheme 32. Completion of Ophirin B

During the course of the synthesis of ophirin B (**174**),[107,108] the Crimmins group pursued the synthesis of a biologically active cadiellin, astrogorgin (**186**).[120,153] Identical to ophirin B (**174**), except for an additional oxygenated stereocenter at C6, it was believed that astrogorgin (**186**) could be constructed utilizing a different

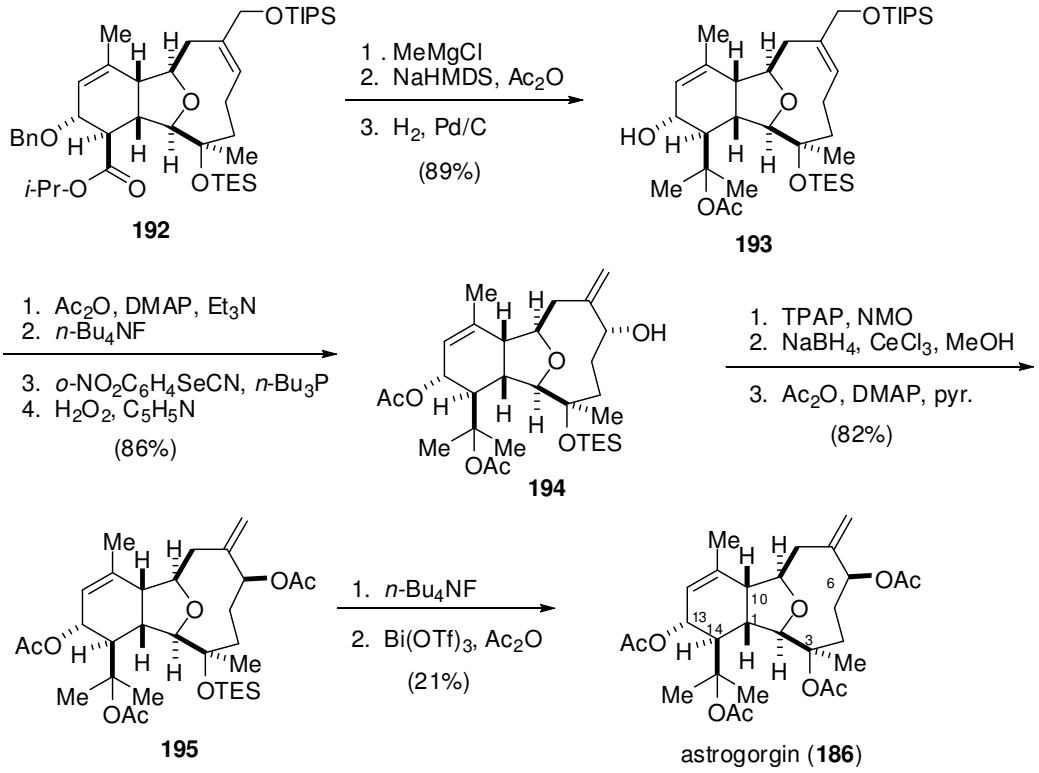
electrophile for the glyclolate alkylation reaction.[208] This electrophile would possess a latent synthetic handle that could be used to install the C6 stereocenter following construction of the tetracyle (Scheme 33). Alkylation, reduction and ring-closing metathesis each proceeded in greater than 90% yield to provided oxonene **188** (Scheme 33).[172] An identical sequence was utilized to install the diene and dienophile as was applied in the ophirin B (**174**) synthesis,[107,108] and the key



Scheme 33. Synthetic Approach to Astrogorgin

intramolecular Diels–Alder cycloaddition again proceeded under ambient conditions to provide tricycle **192** as a single diastereomer.

Upon completion of the tricycle **192**, methylation and acetylation of the C18 tertiary alcohol proceeded uneventfully, followed by careful hydrogenation of the benzyl ether (Scheme 34). Acetylation and deprotection of the allylic triisopropylsilyl protecting group provided an alcohol that was utilized in an allylic transposition to provide the epimeric C6 hydroxyl for astrogorgin (**186**).[222,223] An oxidation[23] and Luche reduction[49] delivered the desired C6 alcohol stereoselectively. Esterification, deprotection, and installation of the fourth and final acetate group was accomplished to provide astrogorgin (**186**), which was identical in all regards to the naturally isolated material.[120,153]

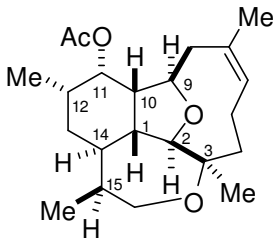


Scheme 34. Total Synthesis of Astrogorgin

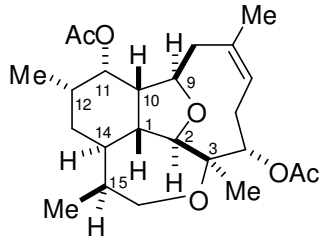
D. Total Syntheses of 11-Acetoxy-4-deoxyasbestinin D and Asbestinin-12

1. Background

The asbestinins represent the farthest evolved subclass from the original cembrane skeleton of the C2–C11 cyclized cembranoids (Figure 1). The first asbestinin was discovered and its structure elucidated in 1980.[2] For 25 years, no total synthesis of any member of this subclass had been reported. A diverse array of structures have been found within the asbestinins, which differ from the cladiellins and briarellins in that C12, C13, and C15 are never oxygenated and there is never a lactone moiety at C16.[1] This subclass features a range of biological activity, including antimicrobial, acetylcholine antagonism, and antitumor properties. Though an X-ray diffraction study of asbestinin-1 confirmed the relative stereochemistry of this subclass, some discrepancy exists in the literature regarding the absolute configuration of this family of natural products.[1,2] The biosynthetic hypothesis would suggest that the stereochemistry would correlate to that of the cladiellins and briarellins, but the isolation literature consistently portrays the enantiomer as the natural configuration.



11-acetoxy-4-deoxyasbestinin D (**196**)



asbestinin-12 (**197**)

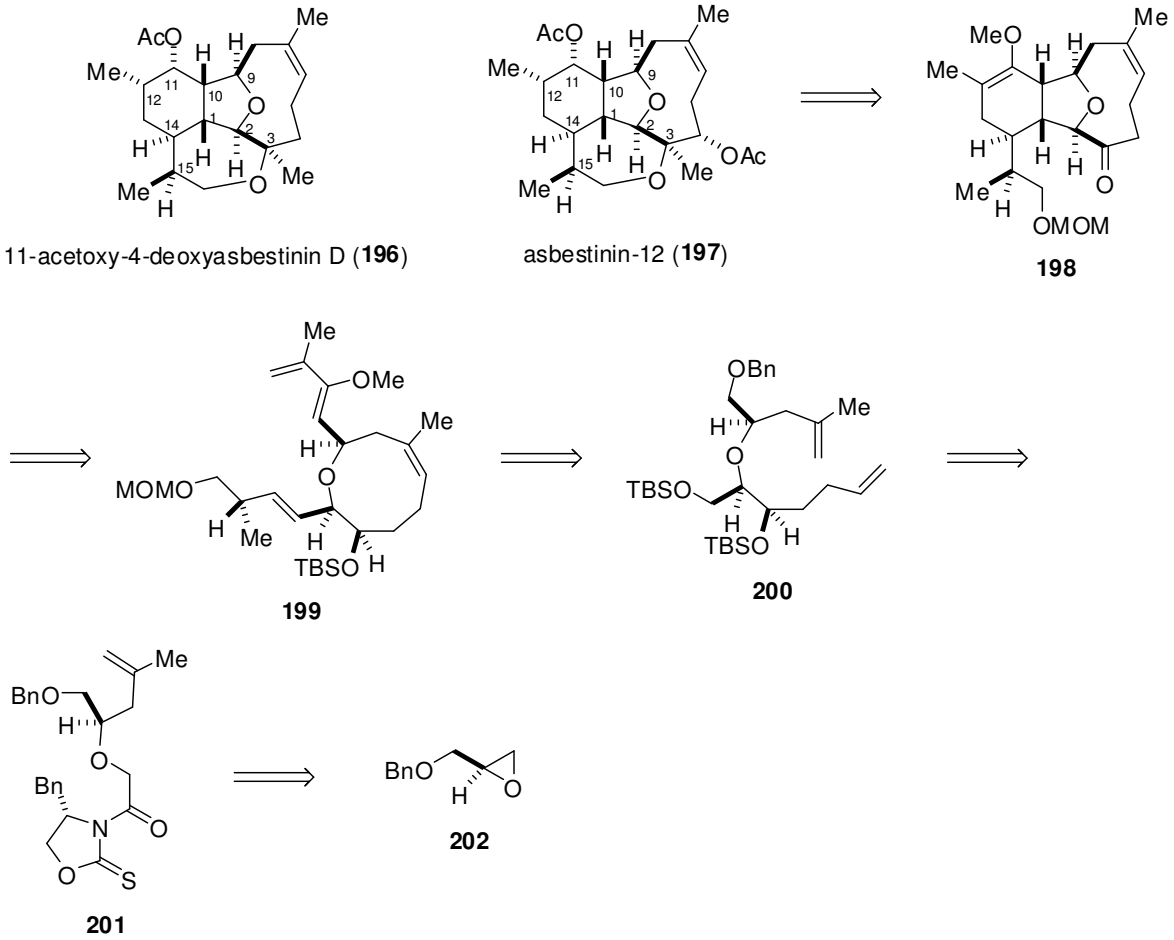
Figure 8. Targeted Asbestinins

11-Acetoxy-4-deoxyasbestinin D (**196**) was isolated in 1990 by Rodríguez and co-workers from *Briareum asbestinum* off the coast of Puerto Rico (Figure 8).[11] The title compound represented 0.072% of the dry weight of the isolated sponge. The natural product features a fascinating molecular structure, with nine contiguous stereocenters and a fully-substituted tetrahydrofuran. Further, 11-Acetoxy-4-deoxyasbestinin D (**196**) demonstrates strong antimicrobial activity against *Klebsiella pneumoniae* and cytotoxicity against CHO–K1 cells (ED_{50} = 4.82 μg/mL). A related member of this subclass, asbestinin-12 (**197**), features a similar structure with an additional stereocenter at C4,[224] which is more ubiquitious within the asbestinins. The sum of the biological benefits and structural intrigue, as well as the lack of a total synthesis of any member of this subclass piqued our interest in these two natural products. We set out to apply a strategy similar to that employed in the cladiellin syntheses in our laboratory,[107,108] this time targeting members of the asbestinin subclass, in hopes of verifying the viability of our plan and confirming the absolute configuration of the asbestinins.

2. Retrosynthetic Analysis

Strategically, ketone **198** was targeted as a point of divergence for the syntheses of 11-acetoxy-4-deoxyasbestinin D (**196**) and asbestinin-12 (**197**) (Scheme 35). The desire to apply the previously developed Diels–Alder strategy used for the cladiellins to complete the first total synthesis of a member of the asbestinin subclass of natural products resulted in selection of tetraene **199** as the Diels–Alder substrate. Tetraene **199** was an attractive Diels–Alder substrate in that it would incorporate the required stereochemistry of the C15 methyl group prior to the

Diels–Alder reaction. While the 2,3-substitution on the diene was viewed as a potential liability with regard to the possibility of the diene to adopt the required s-*cis* conformation, and the electronic character of the dienophile was less than optimal, the facility of the Diels–Alder reaction in the ophirin B (**174**) synthesis[107] provided optimism for the success of the Diels–Alder reaction of tetraene **199**. Thus, we set out to prepare tetraene **199** and investigate its performance in the designed cycloaddition. Tetraene **199** would be prepared from diene **200** by ring-closing metathesis followed by further functionalization. While construction of the diene metathesis substrate for the ophirin B and astrogorgin syntheses was accomplished



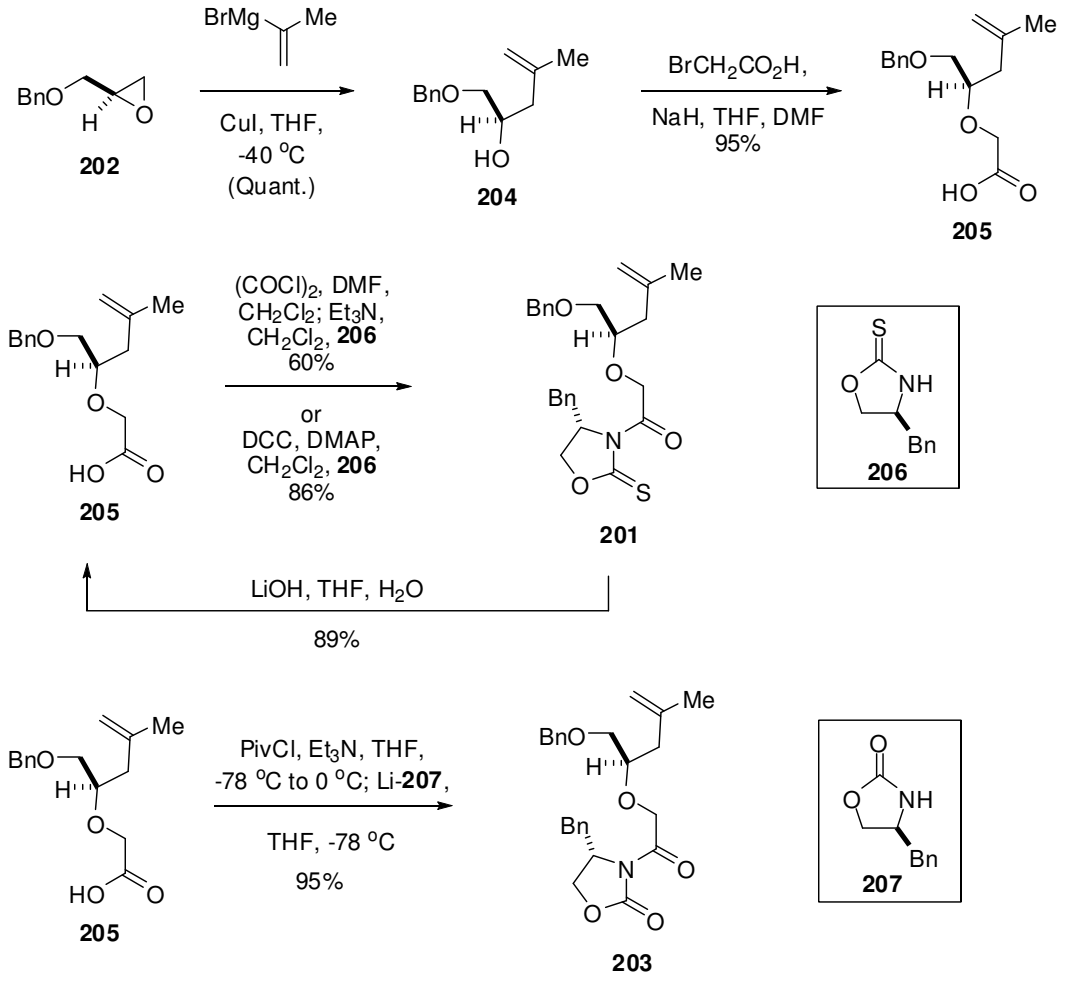
Scheme 35. Retrosynthetic Analysis

through the use of an asymmetric glycolate alkylation as the key step,[107,108,208] the strategy for the synthesis of diene **200** hinged upon the development and application of an asymmetric glycolate aldol reaction to establish the ether linkage stereochemistry of the oxonene precursor.[204,205] The required thioimide **201** for the aldol reaction would be prepared from (*R*)-benzyl glycidyl ether (**202**).

3. Oxonene Formation

An initial goal of this project was to probe the effectiveness of oxazolidinethione glycolate **201** and oxazolidinone glycolate **203** in the glycolate aldol reaction to determine which substrate was more useful for this transformation. The preparation of each of these glycolates commenced with a copper iodide-mediated propenyl Grignard addition to commercially available (*R*)-benzyl glycidyl ether (**202**).[225,226] A quantitative yield of the desired secondary alcohol **204** was routinely obtained, and alcohol **204** was transformed into the corresponding glycolic acid (Scheme 36). For this alkylation, three solvent systems were examined, tetrahhydrofun, *N*,*N*-dimethylformamide, and an equal mixture of the two aforementioned solvents. As has been previously observed, a 1:1 ratio of tetrahydrofuran and *N*,*N*-dimethylformamide provided the highest yields of acid **205**.[107,108] Attention was next turned to formation of the targeted glycolates **201** and **203** to probe the glycolate aldol reaction. The oxazolidinethione **201** was formed by either in situ acylation of the intermediate acid chloride with auxiliary **206** or standard peptide DCC coupling conditions. The latter method provided a higher yield of the glycolate **201** and also allowed for recovery of unreacted acid **205**, which was not

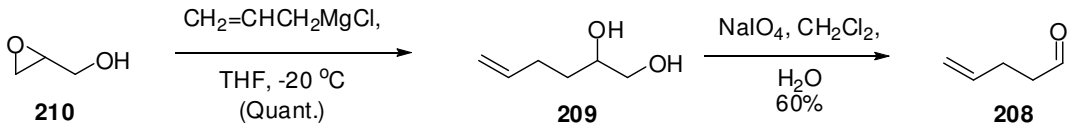
possible using the acid chloride route. Alternatively, for the oxazolidinone glycolate **203**, the mixed anhydride of acid **205** was formed and treated in situ with lithiated oxazolidinone **207**, providing glycolate **203** in high yield. It was also discovered that the oxazolidinethione glycolate **201** could be hydrolyzed to again provide glycolic acid **205** under basic conditions if a change of chiral auxiliary was desired following glycolate formation.



Scheme 36. Formation of the Glycolates

For the preparation of 4-pentenal (**208**), the aldehyde necessary for the proposed glycolate aldol reaction, we chose to utilize an oxidative cleavage of 5-

hexene-1,2-diol (**209**). To that end, racemic glycidol (**210**) was treated with allylmagnesium chloride to provide diol **209** (Scheme 37). Diol **209** was then subjected to sodium periodate to provide 4-pentenal (**208**) in good yield following purification via distillation. It was discovered that using unpurified aldehyde **208** led to poor results in the glycolate aldol reaction.

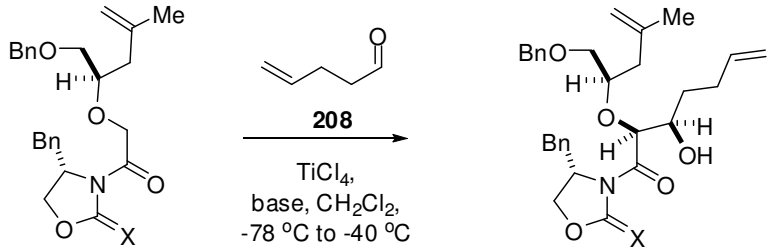


Scheme 37. 4-Pentenal Synthesis

The glycolate aldol reactions of thiomide **201** and imide **203** with 4-pentenal (**208**) were probed using three different enolization conditions (Table 3). Initially, the conditions that had previously been optimized for glycolate aldol reactions within the Crimmins laboratory were used;[207] namely, 1.0 equivalents of titanium tetrachloride were added to the cooled glycolates **201** and **203**, followed by 2.5 equivalents of *N,N*-diisopropylethylamine to form the chlorotitanium enolate. Also, the use of 1.0 equivalent of (-)-sparteine for enolization followed by the addition of 1.0 equivalent of *N*-methyl pyrrolidinone ten minutes prior to aldehyde addition were tested, but with limited success. Both methods exhibited higher reactivity and selectivity for the oxazolidinethione glycolate **201** when compared to the oxazolidinone glycolate **203**. Still, the results left room for improvement. Concurrently, more general conditions were being developed within our laboratory for use in the aldol addition of complex glycolates.[204] As part of this program, these modified conditions, involving initial enolization with *N*,*N*-diisopropylethylamine followed by the addition of 1.0 equivalent of *N*-methyl pyrrolidinone ten minutes prior to addition of the aldehyde, were tested

with glycolates **201** and **203**. The results obtained were very encouraging, providing a higher yield and selectivity for the desired adducts **211** and **212**. These conditions have proven general for a range of glycolates to give reproducibly higher yields and selectivities compared with previous methods. Though the oxazolidinone adduct **212** was obtained in higher yield than the corresponding thioimide **211**, for our purposes, we chose to proceed with the oxazolidinethione variant due to the higher diastereoselectivity obtained and resultant ease of purification of alcohol **211**.

Table 3. Base Screening for Glycolate Aldol Reaction



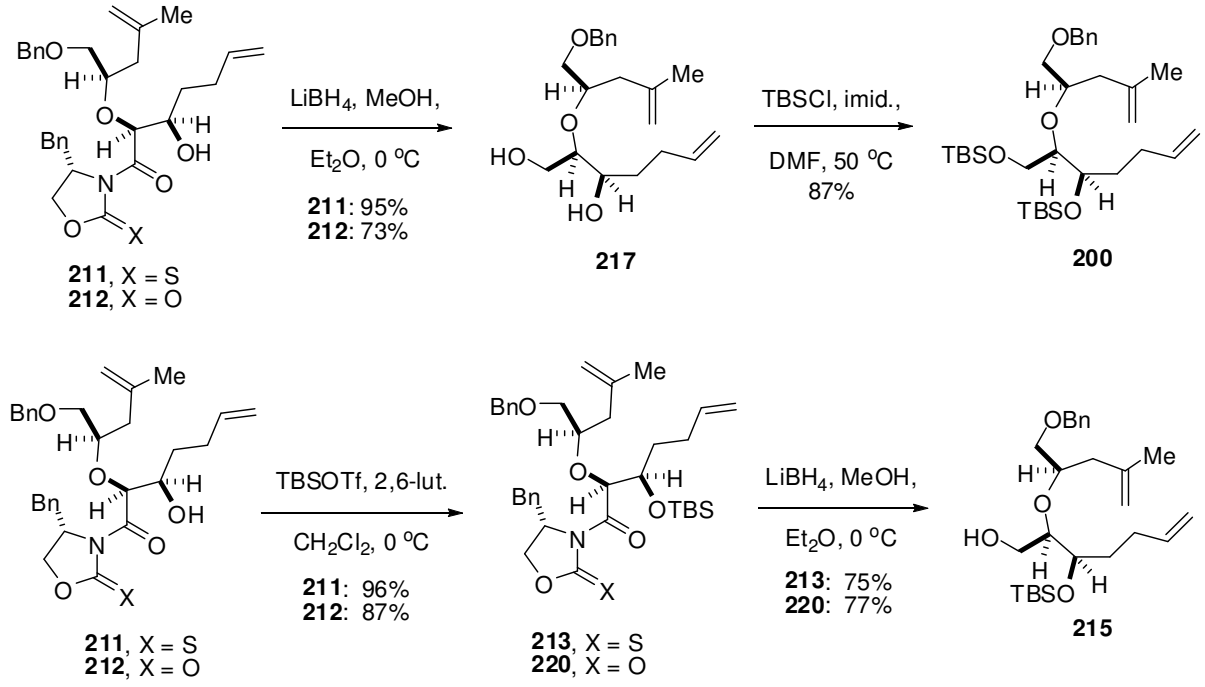
201: X = S
203: X = O

211: X = S
212: X = O

Base	211 Yield	211 dr	212 Yield	212 dr
i-Pr_2NEt	59%	90:10	18%	not measured
i-Pr_2NEt, NMP	70%	>95:5	78%	90:10
(-)-sparteine, NMP	18%	85:15	16%	not measured

With the α,ω-diene **211** in hand, the key ring-closing metathesis to complete the oxonene was probed. Treatment of aldol adduct **211** with the Grubbs second generation catalyst (**151**)[172] led mostly to recovered starting material and unidentified side products (Scheme 39). Protection of the secondary alcohol as the *t*-butyldimethylsilyl ether gave diene **213**, which did undergo ring-closing metathesis using the Grubbs second generation catalyst **151** in refluxing dichloromethane to form oxonene **214** (Scheme 38, 39). However, conversion was low, and loss of the protecting group was observed during the course of the reaction and purification. Other ring-closing metathesis candidates were also tested, including the reduced

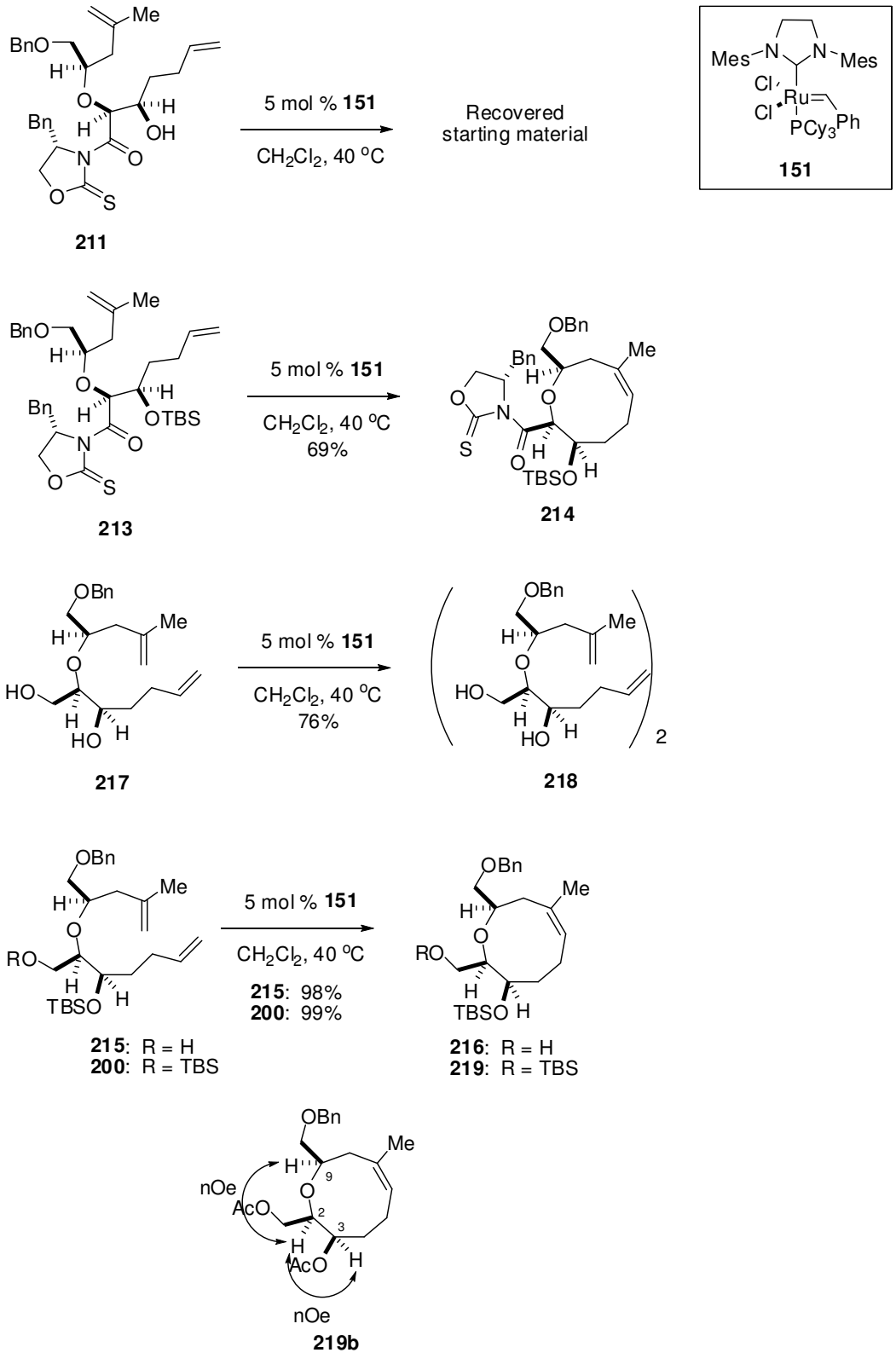
product of silyl ether **213**, as we hoped to investigate whether the sulfur atom in the chiral auxiliary was poisoning the catalyst, as has been previously observed. Treatment of alcohol **215** with ring-closing metathesis conditions led to a 98% yield of oxonene **216**. With this result in hand, we prepared diol **217** by reduction of aldol adduct **211**. However, under identical conditions, this substrate gave only dimer **218**. Finally, diol **217** was bis-protected as *t*-butyldimethylsilyl ethers and treated with the Grubbs second generation catalyst **151**. Excellent conversion to oxonene **219** was observed. Additionally, it was found that the concentration of the ring-closing metathesis of diene **200** could be increased from the traditionally-used 2 mM up to 10 mM. Though a seemingly small improvement, this finding paid dividends as throughput was greatly improved when processing material on larger scale as the



Scheme 38. Ring-closing Metathesis Candidates

project progressed. Following this modification, oxonene **219** could be isolated in 99% yield when 5 mol% of the catalyst **151** was used in refluxing dichloromethane. Two-dimensional ^{1}H NMR analysis (COSY, nOeSY) were performed on the bis-acetate version **219b** of oxonene **219**. This data corroborated that the desired configuration for the three stereocenters installed to this point was present, as strong nOe interactions were observed between the hydrogens on C2 and C9, and C2 and C3. The completion of oxonene **219** represents the first successful formation of a nine-membered ring in the Crimmins laboratory via the glycolate aldol/ring-closing metathesis strategy that resulted in a natural product total synthesis.

The sum of the results from the ring-closing metathesis studies can be rationalized via a conformational analysis of some of the possible rotamers of the diene (Figure 9). It is apparent from the data that the substituent at C3 is of utmost importance for the ring closure to proceed successfully. As previously described, gauche conformations place the olefins proximally allowing ring-closing metathesis to occur. In the case where C3 is a hydroxyl substituent (R = H, **217**), it is possible that the anti conformation is the least sterically encumbered, placing the two olefins distally. However, when C3 is a silyl ether (R = TBS, **200**, **215**), the steric interaction between the silyl ether and the ether linkage of the diene becomes more pronounced in the anti conformation, and the gauche conformations, particularly the dipole minimized conformation, become more readily accessible, leading to productive oxonene formation.



Scheme 39. Ring-closing Metatheses

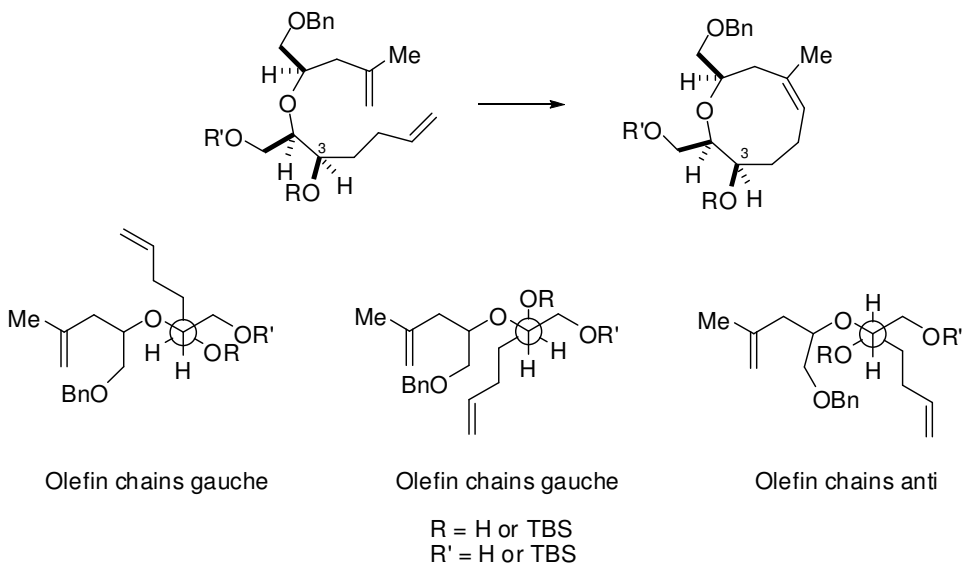
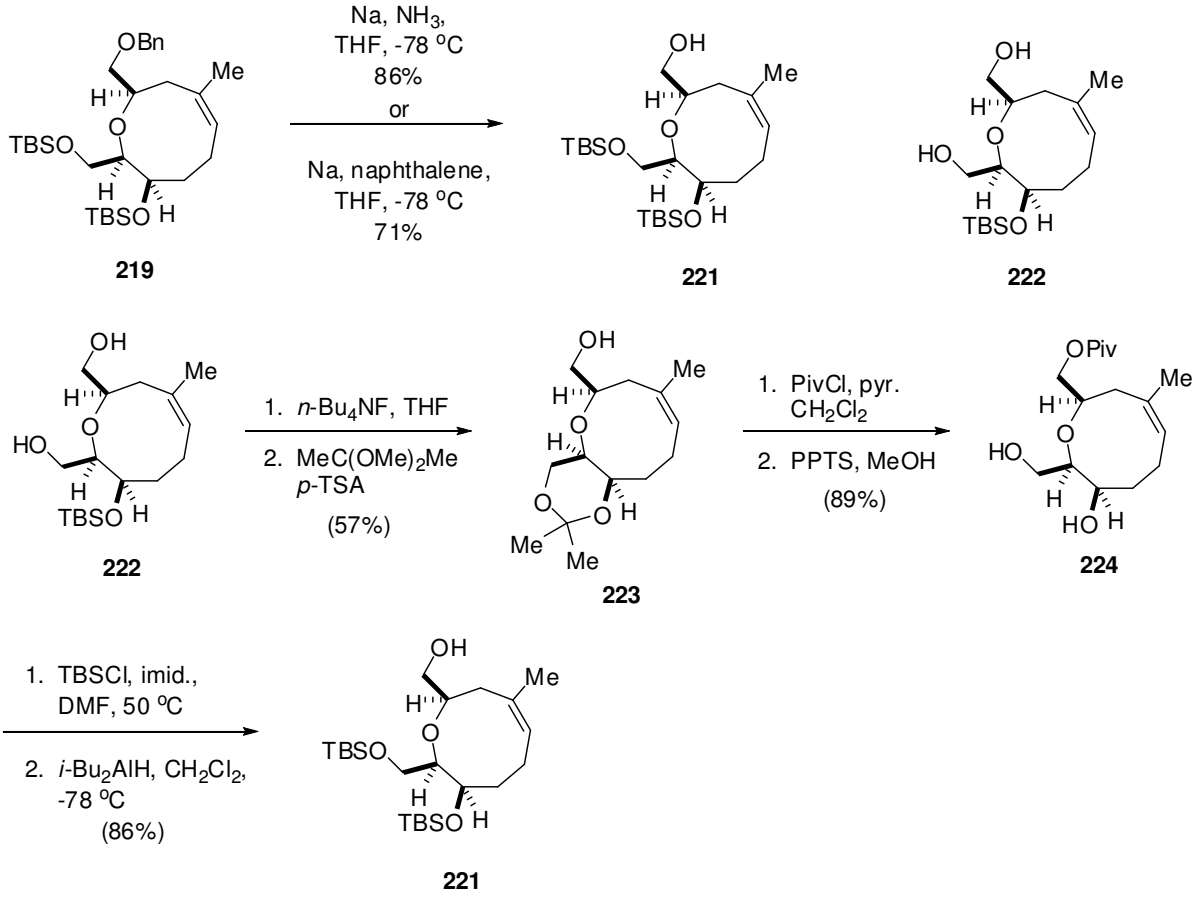


Figure 9. Conformational Analysis of Oxonene Formation

4. Synthesis of the Diels–Alder Candidate

Attention was next turned to installing the diene and dienophile necessary for the key intramolecular Diels–Alder cycloaddition. We chose to install the diene first. To that end, the cleavage of the benzyl ether was examined. Dissolving metal reductions of oxonene **200** using sodium naphthalene or sodium and liquid ammonia proved successful in accessing alcohol **221** in good yield (Scheme 40). Care had to be taken to ensure that the primary silyl group was not cleaved due to prolonged reaction times with these reductions producing diol **222**. A six step method for recycling diol **222** to the desired alcohol **221** was devised involving formation of the triol and protection of the 1,3-diol as an acetonide to give alcohol **223**. Protection of the primary alcohol **223** as a pivalate ester and deprotection of the acetonide afforded diol **224**. Bis-protection as *t*-butyldimethylsilyl ethers and reduction of the ester functionality intercepted alcohol **221**. Oxidative cleavage of the benzyl ether

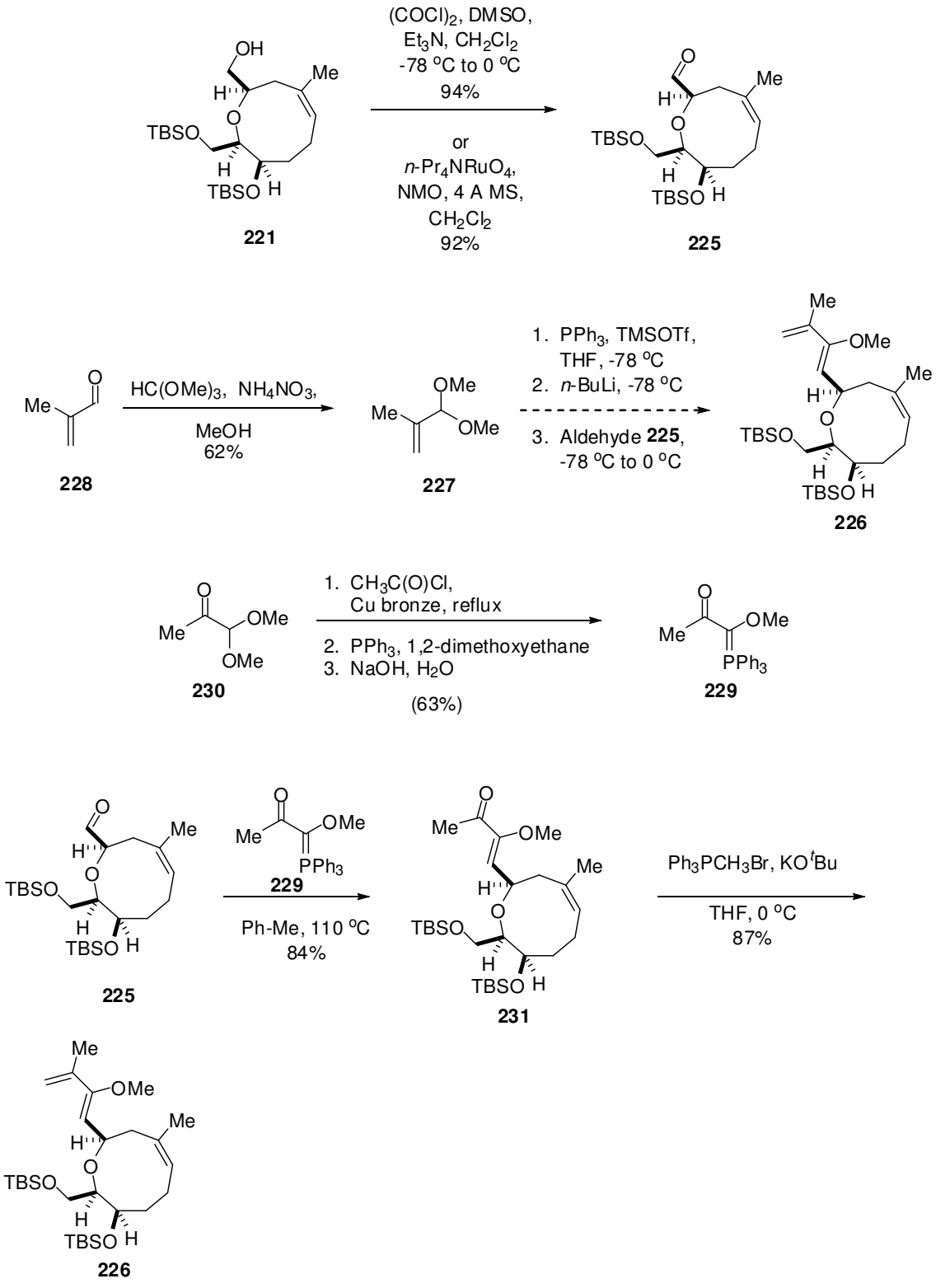
was also attemped using DDQ, but it was difficult to maintain the primary silyl ether within the slightly acidic reaction media. When using a basic buffer, such as sodium bicarbonate, the oxidation ceased to occur, and only starting material **200** was recovered. In the end, a sodium ammonia reduction became the most reproducible and scaleable method for transforming oxonene **200** into alcohol **221**.



Scheme 40. Benzyl Ether Cleavage

Oxidation of alcohol **221** was accomplished using Swern conditions[130] or *n*-Pr_4NRuO_4/NMO (Scheme 41).[31] The Swern oxidation was the most reproducible, regardless of scale. Dess-Martin periodinane was not useful in forming aldehyde **225**.[43] With aldehyde **225** in hand, a one-step procedure for installing the diene **226**

was attempted. 1-Alkyoxyallylphosphonium salts have been reported in the literature as useful substrates to effect a Wittig transformation, however, care must be exercised to maintain low temperatures to preclude allylic 1,3-rearrangement to afford 3-alkoxyphosphonium salts. However, if the salt is prepared from the corresponding acetal using a Lewis acid and triphenylphosphine at low temperature, it can be deprotonated in situ to form the ylide, and the aldehyde can be added to this solution to afford the Wittig adduct. This approach was reported by Kim and co-workers using similar acetals to the one we desired to employ, and the enol ether products were hydrolyzed to the corresponding enones.[227] The E:Z selectivity for the Wittig reactions were not reported due to the immediate hydrolysis of these adducts. With knowledge of this precedent, we prepared the dimethyl acetal **227** of methacrolein (**228**), and used the reported conditions in hopes of generating our desired diene **226**. However, all attempts to isolate the desired Wittig adducts using simple aliphatic or aromatic aldehydes, as well as complex aldehyde **225** proved fruitless. Though other methods exist in the literature for generating α-alkoxyallylphosphonates and phosphine oxides,[228] our concern with E:Z selectivity of these processes led us to try a two step method for installing the diene. The use of 1-methoxy-1-(triphenylphosphoranylidene)acetone (**229**) as a stabilized Wittig reagent had been reported to give excellent yield and complete E selectivity with aromatic aldehydes.[229] We prepared this reagent in three steps from pyruvic aldehyde dimethyl acetal (**230**). Formation of the α-chloro ketone was followed by displacement of the chloride with triphenylphosphine. Deprotonation of the resultant salt provided stabilized ylide **229**. Productive Wittig reaction was observed with a

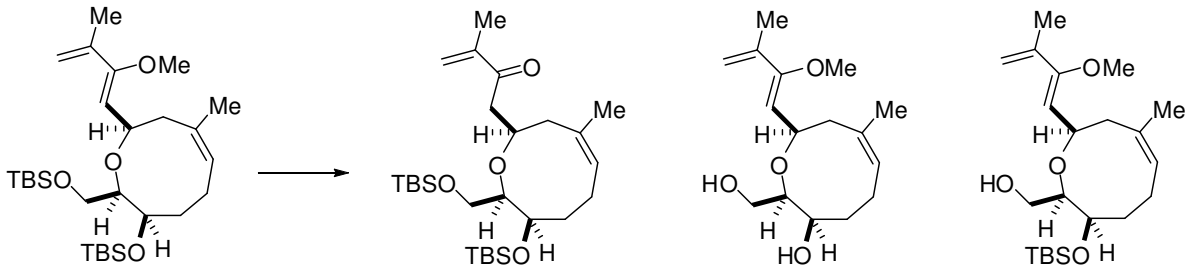


Scheme 41. Diene Installation

simple aliphatic aldehyde using ylide **229**. Gratifyingly, treatment of aldehyde **225** with ylide **229** in refluxing toluene led to an 84% yield of the desired enone **231** with complete E selectivity observed. Methylenation of enone **231** gave desired diene **226** in good yield.

Installation of the dienophile required selective deprotection of the primary silyl ether, oxidation of the resultant alcohol, and another olefination reaction to join the two pieces. Selective deprotection of diene **226** proved quite difficult.[230] A number of buffered hydrogen fluoride conditions were employed, but all attempts that led to selective deprotection also resulted in hydrolysis of the enol ether to yield enone **232** (Scheme 42). PPTS in protic solvent gave identical results. Tetrabutyl-

Table 4. Selective Deprotection Attempts

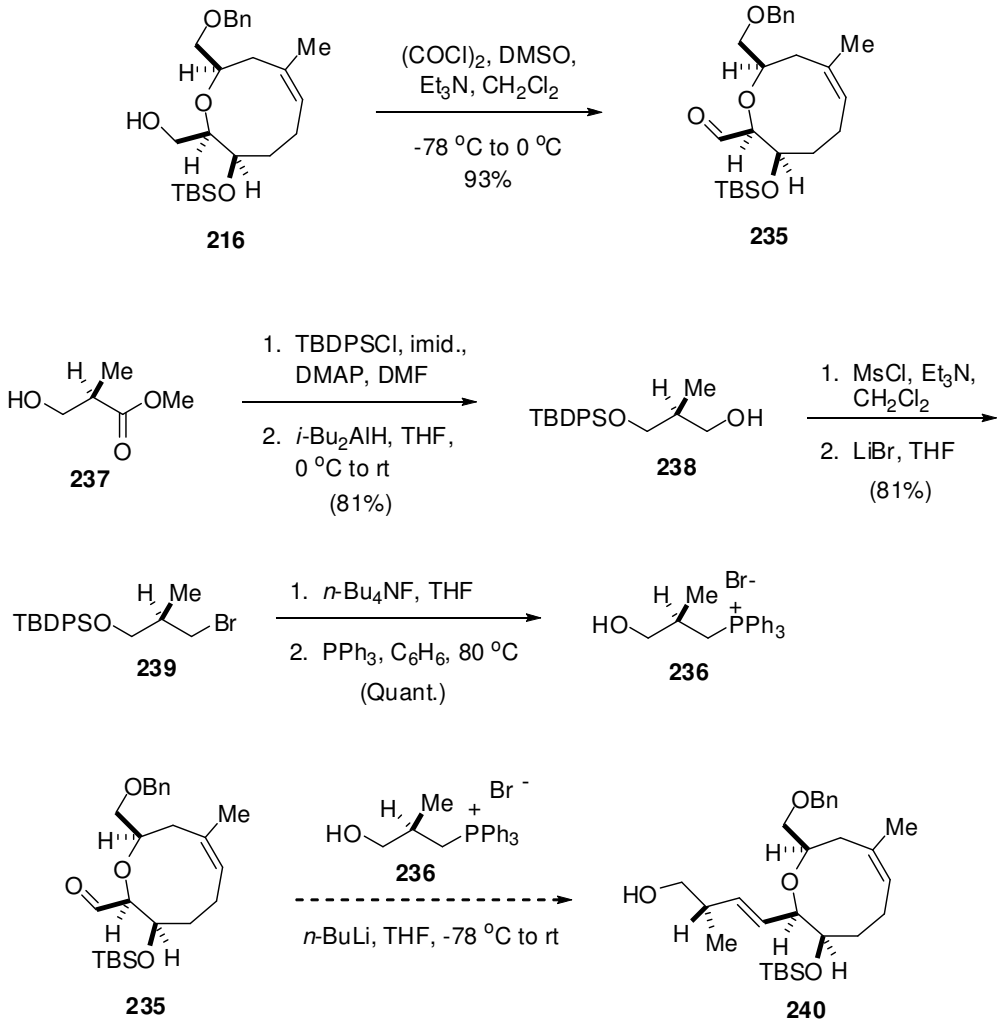


Conditions	226	232	233	234
PPTS, MeOH, $CH(OMe)_3$, CH_2Cl_2		▲		
HF:CH_3CN, CH_3CN, -20 °C		▲		
HF:pyr., pyr., THF		▲		
$Et_3N(HF)_3$, CH_3CN, 0 °C		▲		
n-Bu_4NF, THF, 0 °C			▲	
NaOH, EtOH, 78 °C			▲	
K_2CO_3, MeOH, 65 °C	▲			

ammonium fluoride at low temperature resulted in unselective deprotection to provide diol **233**. Sodium hydroxide in refluxing ethanol also gave diol **233**. Milder alkaline conditions, potassium carbonate in refluxing methanol, gave only recovered starting material **226**. The inability to access alcohol **234** led us to pursue initial installation of the dienophile prior to diene formation using alcohol **216**.

It was most expedient to use alcohol **216** (accessed in six steps from (*R*)-benzyl glycidyl ether (**202**)) to probe dienophile installation. Oxidation of alcohol **216** was accomplished using Swern conditions[130] to provide aldheyde **235** in high yield (Scheme 42). A Wittig reaction was targeted for dienophile formation. To that end, phosphonium salt **236** was prepared from Roche ester **237** in six steps. Protection and reduction of ester **237** gave alcohol **238**.[231] The alcohol **238** was then transformed into bromide **239** through the intermediate mesylate.[232] Finally, deprotection of the silyl ether gave the commercially available bromohydrin, which was converted to phosphonium salt **236** prepared for Wittig reaction. Kozikowski and co-workers have reported the use of phosphonium salt **236** to provide a Schlosser modified-type Wittig adduct favoring the E olefin due to the intramolecular alkoxide present during the reaction.[233] Since we desired the E olefin geometry as well, we attempted using this phosphonium salt with aldehyde **235**. Although the salt was effective in providing the E isomer when reacted with simple aldehydes, no olefination product **240** was observed using aldehyde **235**. Though we predicted a salt lacking the free hydroxyl would favor Z alkene formation, we still attempted using other protected Wittig substrates to investigate whether the free hydroxyl was leading to unproductive side reactions (Scheme 43). Transient in situ protection as

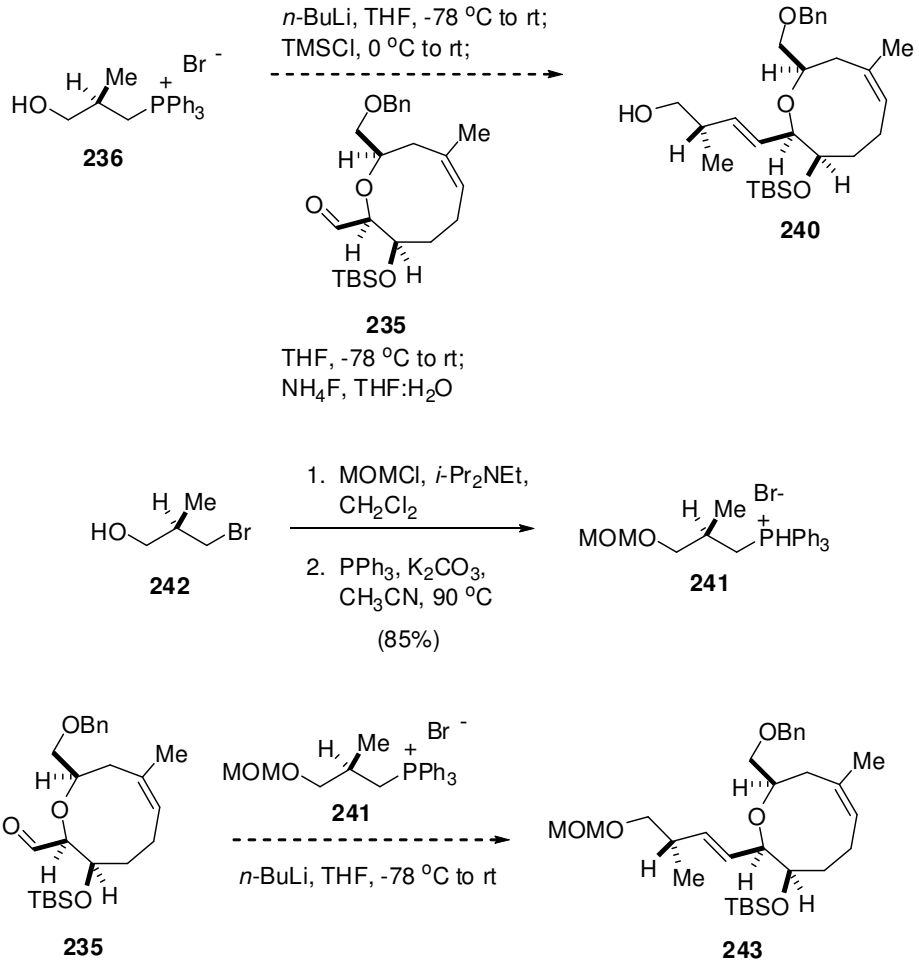
a silyl ether was attempted,[234] as well as use of the methoxymethyl ether variant **241** of phosphonium salt **236**, but none of the desired product **240** or **243** was obtained in any attempt.



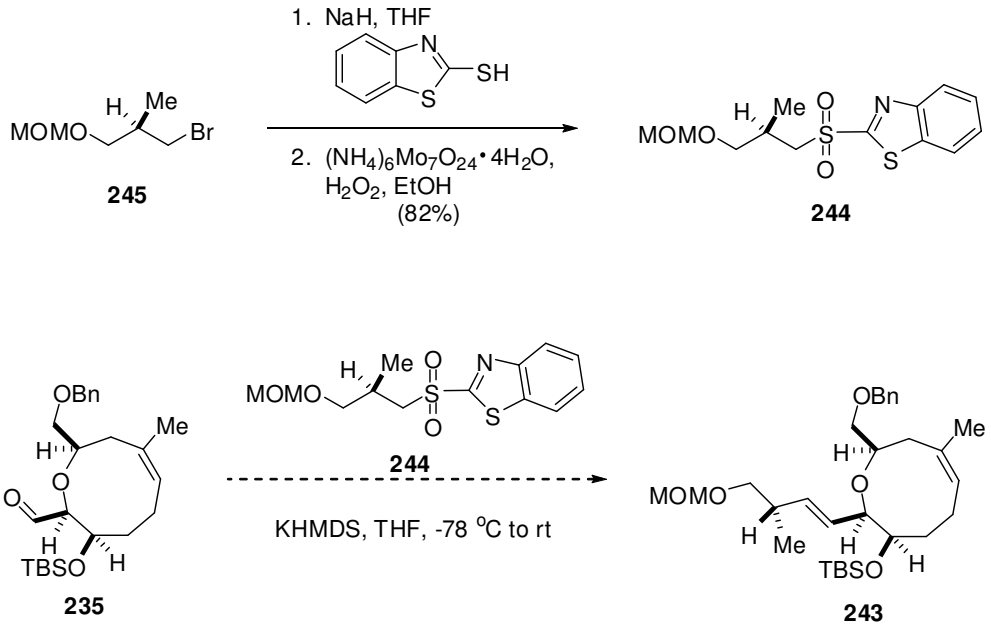
Scheme 42. Wittig Olefination Attempts

A modified Julia olefination was next investigated for installation of the dienophile, due to the efficiency and high E selectivity these reactions have displayed in the literature.[235] To that end, sulfone **244** was prepared in two steps from previously synthesized bromide **245** (Scheme 44). However, treatment of aldehyde **235** with the potassium anion of benzothiazole **244** did not provide any of the desired diene

243. Though discouraged by these results, we chose to attempt a cross-metathesis reaction, since this has found prior success in the Crimmins laboratory for joining two olefinic fragments.[236]

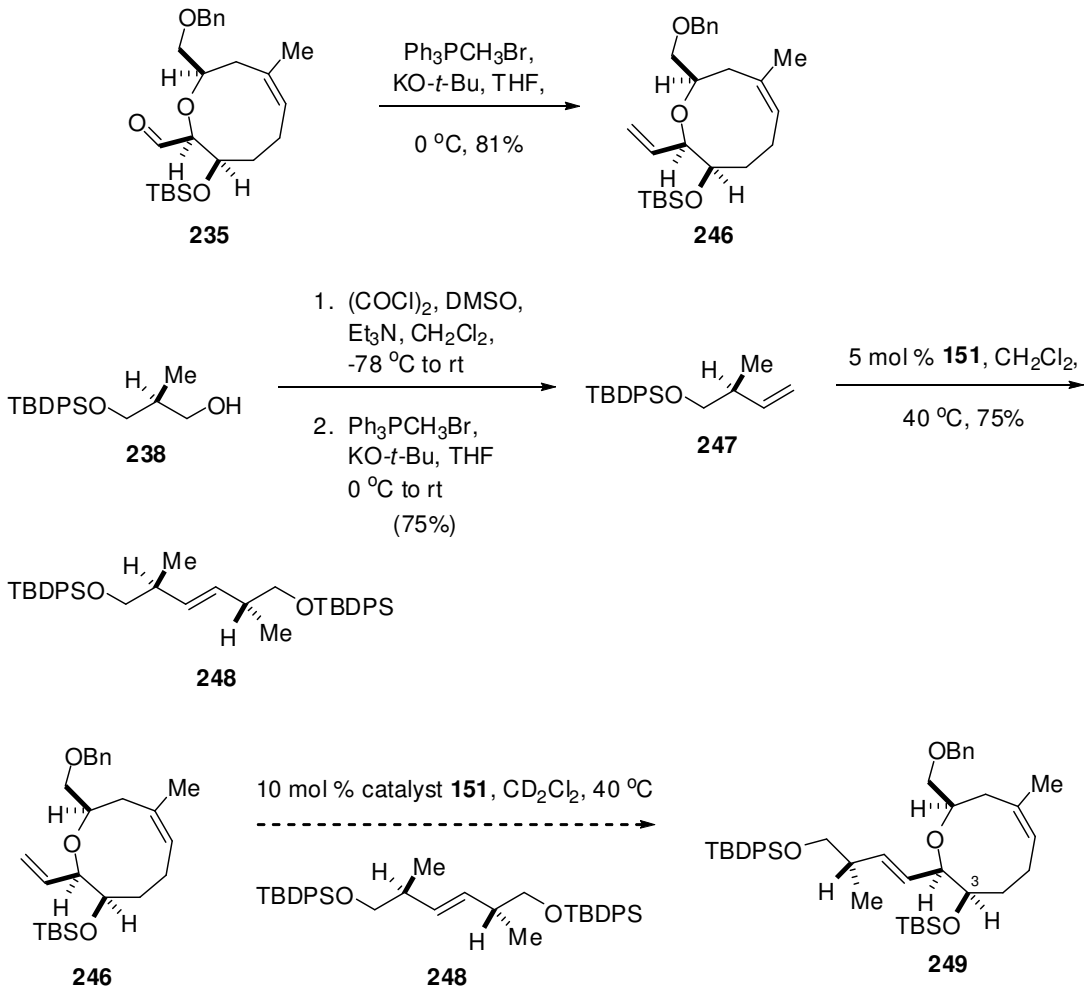


Scheme 43. Protected Wittig Attempts



Scheme 44. Modified Julia Attempt

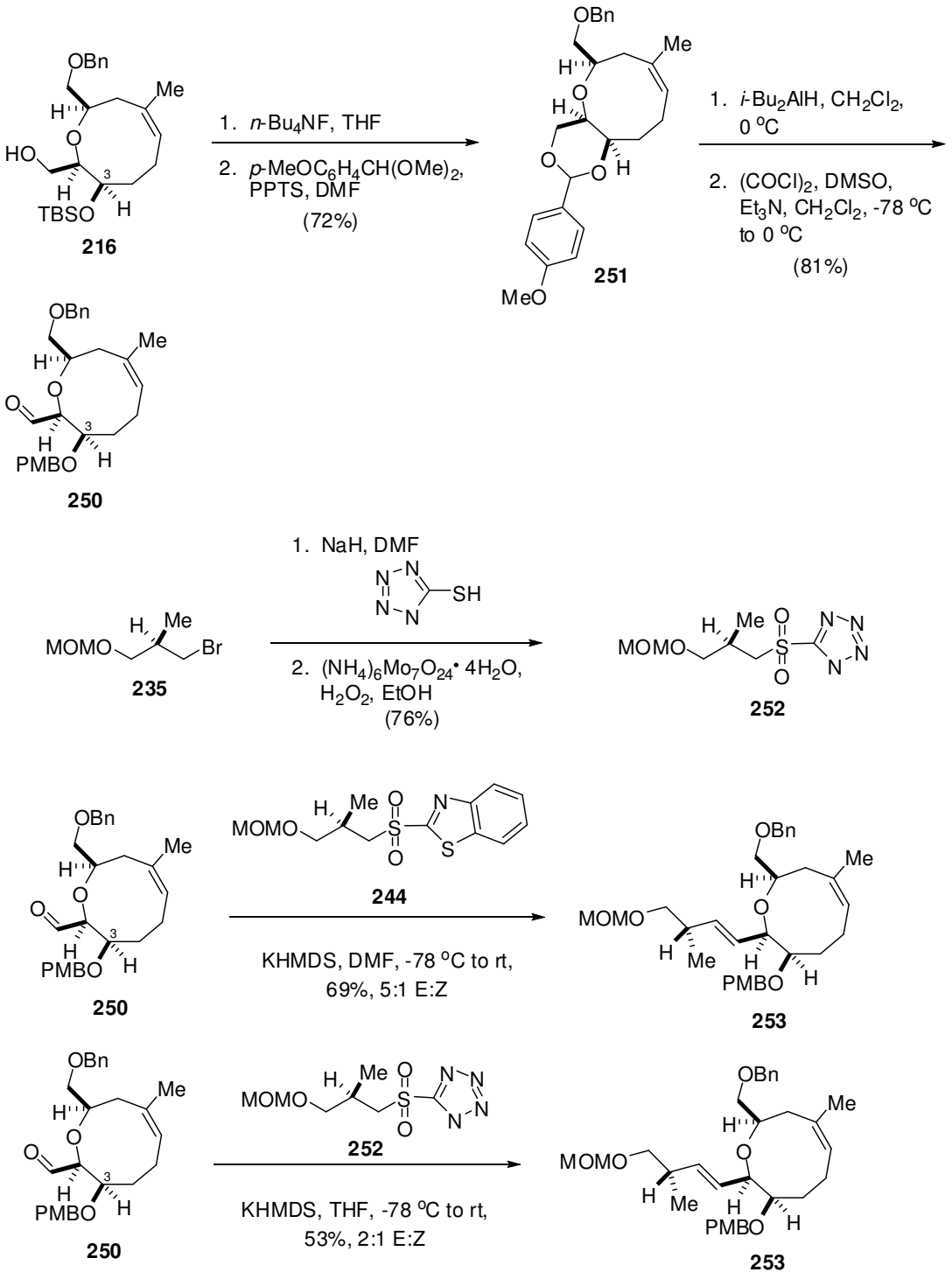
The two desired cross-metathesis coupling partners were prepared in a straightforward manner. Methylenation of aldehyde **235** gave diene **246** in 81% yield (Scheme 45). Alcohol **238** was oxidized[130] and methylenated to give alkene **247**. Homodimerization of alkene **247** with the Grubbs second generation catalyst **151** provided dimer **248** in good yield.[172] Unfortunately, combining alkene **248** and diene **246** in refluxing dichloromethane in the presence of catalyst **151** was not efficient in providing dienophile **249**.[237] At this point, we speculated that the steric bulk of the *t*-butyldimethylsilyl ether protecting group at C3 was impeding addition of the olefination reagents, precluding dienophile formation. We chose to install a less sterically encumbering protecting group at C3 to reattempt dienophile installation.



Scheme 45. Cross-Metathesis Attempt

A *p*-methoxybenzyl ether was installed at C3 in place of the *t*-butyldimethylsilyl ether present in aldehyde **235** (Scheme 46). Our synthesis of aldehyde **250** began with deprotection of the silyl ether of alcohol **216** (accessed in six steps from (*R*)-benzyl glycidyl ether (**202**)). The *p*-methoxyphenyl acetal **251** was formed under acidic conditions in 84% yield, and the acetal was reduced with complete regioselectivity to form the secondary *p*-methoxybenzyl ether. Oxidation under Swern conditions[130] delivered desired aldehyde **250**. Following preparation of the tetrazole **252** from bromide **235** in two steps, a Julia–Kocienski olefination was

attempted with aldehyde **250**, as was a modified Julia reaction using benzothiazole **244**. Each of these reactions led to productive olefination to give diene **253**, with the

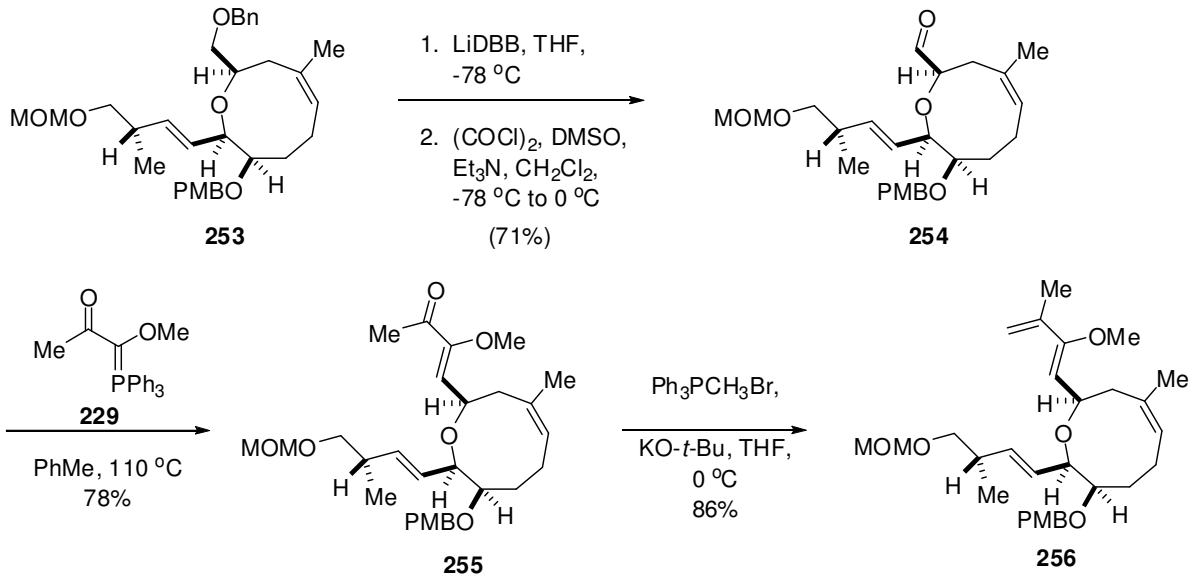


Scheme 46. Successful Julia Olefination

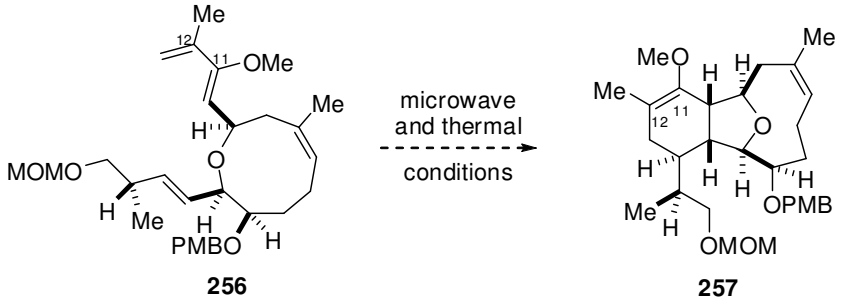
modified Julia substrate **244** performing better than the tetrazole **252**. These results support our hypothesis that it was indeed the bulk of the C3 protecting group preventing effective dienophile installation. With the dienophile installed, we targeted an installation of the diene that would allow us to test the viability of our intramolecular Diels–Alder strategy for the asbestinins.

Lithium di-*t*-butylbiphenylide was employed to selectively deprotect the benzyl ether of diene **253** in the presence of the *p*-methoxybenzyl ether (Scheme 47). Swern oxidation[130] of the resultant alcohol provided aldehyde **254**. The previously investigated two step procedure for diene installation was next utilized. First, a stabilized Wittig reaction using ylide **229** gave enone **255**,[229] which was methylenated to provide tetraene **256**, prepared for intramolecular Diels–Alder reaction. Unfortunately, subjection of oxonene **256** to conventional thermal as well as microwave conditions in an attempt to effect cycloaddition were unsuccessful (Scheme 48). At least two possible sources were postulated for the observed low reactivity. First, the 2,3-disubstituted diene hinders the rotation of the C11–C12 carbon–carbon bond due to the eclipsing interaction present in the necessary s-*cis* conformation of the diene. Second, the dienophile is significantly reduced in reactivity (compared to the dienophiles in the cladiellin series Diels–Alder reactions) because of the absence of an electron withdrawing group.[107,108] Since changes to the C11–C12 substitution seemed less straightforward to implement into our synthetic plan, we set out to revise our strategy utilizing a more activated dienophile still possessing the C11–C12 substituted diene. We postulated that this change in

electronics should allow for more facile cycloaddition, providing a substrate that could be converted into an asbestinin.



Scheme 47. Synthesis of the Diels–Alder Candidate

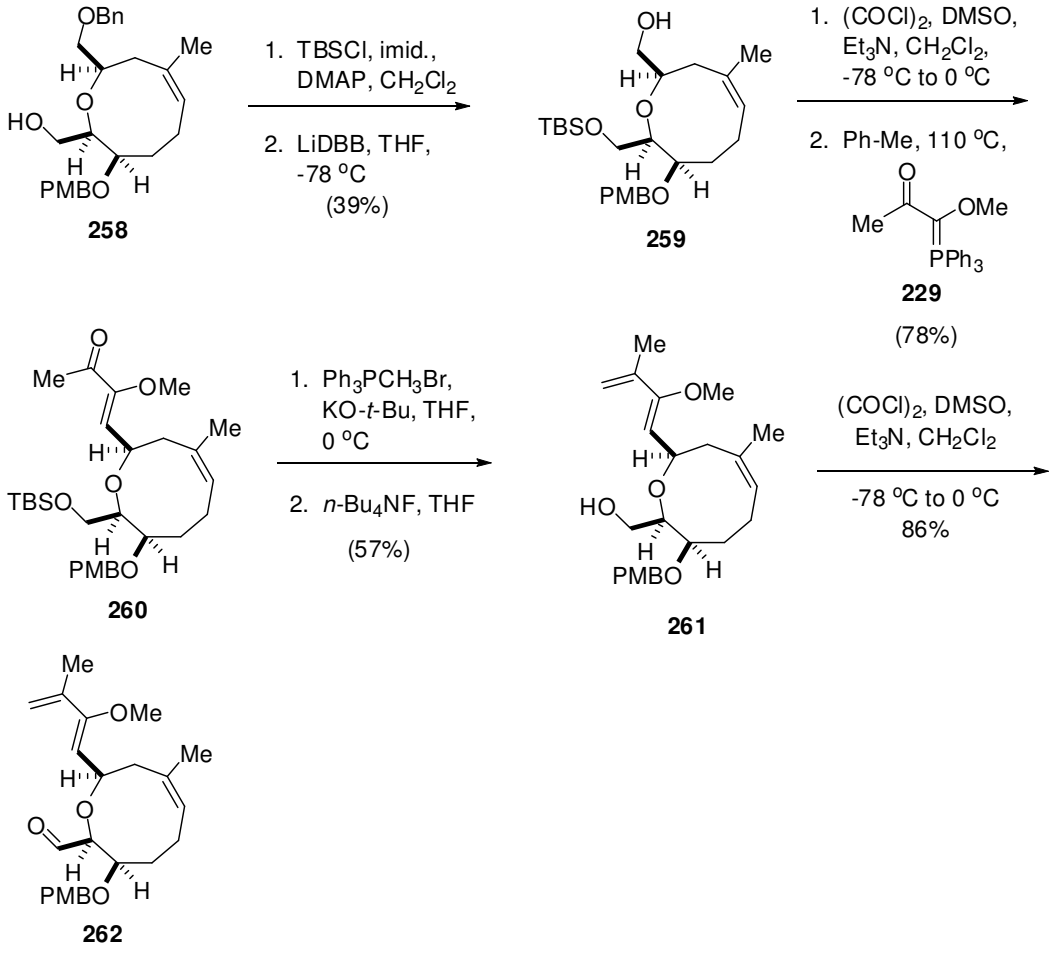


Scheme 48. Attempted Cycloaddition

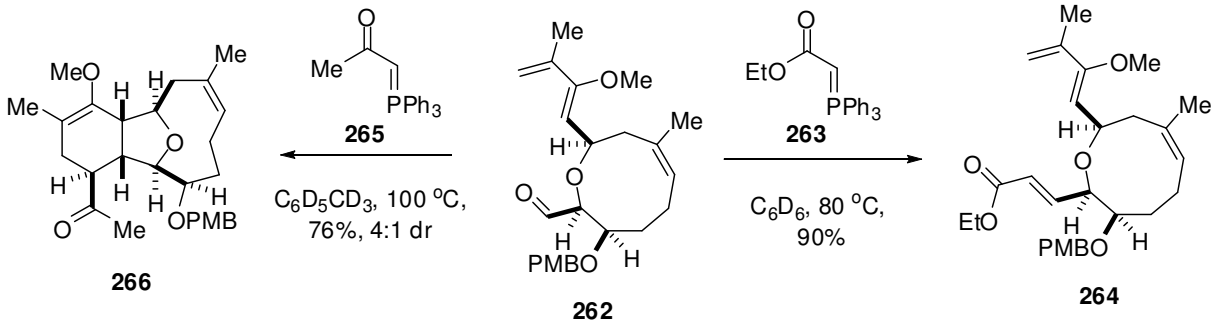
Rather than spend time optimizing our route to an activated Diels–Alder candidate, we chose to proceed in the most expedient fashion possible toward a proof of concept. So, previously prepared alcohol **258** was protected as a silyl ether, and the benzyl ether was reductively removed in the presence of the *p*-methoxybenzyl ether to give alcohol **259** in only 40% yield due to loss of some of the

primary silyl ether during the course of the reaction and workup (Scheme 49). Oxidation[130] and a Wittig reaction with ylide **229** provided enone **260**.[229] Diene formation and deprotection proceeded uneventfully to provide alcohol **261**, which upon oxidation gave aldehyde **262**.[130] With the stage set to attempt the Wittig reaction to prepare a more activated Diels–Alder candidate, two ylides were utilized for the olefination reaction. When ylide **263** was employed,[238] enoate **264** was isolated after refluxing in benzene for one hour. However, using (acetylmethylene)triphenylphosphorane (**265**),[182] intramolecular Diels–Alder cycloaddition ensued under the conditions of the Wittig reaction, presumably via intermediate enone to provide the desired tricycle **266** (76%, 4:1 dr) favoring the exo-diastereomer. This successful cycloaddition result served to confirm our hypothesis regarding the unfavorable electronics precluding reaction of the unactivated Diels–Alder candidate (Scheme 48). We rationalize the stereochemistry observed in this cycloaddition in an analogous manner to the cladiellin transition states (Figure 7, Figure 10).[108] Again, the exo-adduct is the favored product, but we hoped to improve the selectivity of this process by increasing the steric bulk at C3. This had been shown to be effective in the cladiellin case where the diastereoselection increased as the steric demand of the C3 substituent increased (Figure 11). Particularly, the selectivity obtained when C3 was a *p*-methoxybenzyl ether in the asbestinin case (4:1 dr) closely mirrored that obtained when C3 was a benzyl ether in the ophirin B synthesis (4.5:1 dr). Therefore, we chose to revise our approach to the asbestinins, ensuring a silyl ether was present at C3 in our modified

plan, since a silyl ether had demonstrated complete exo diastereoselection in the ophirin B case.



Scheme 49. Revised Synthesis of Cycloaddition Candidate



Scheme 50. Successful Intramolecular Diels–Alder Reaction

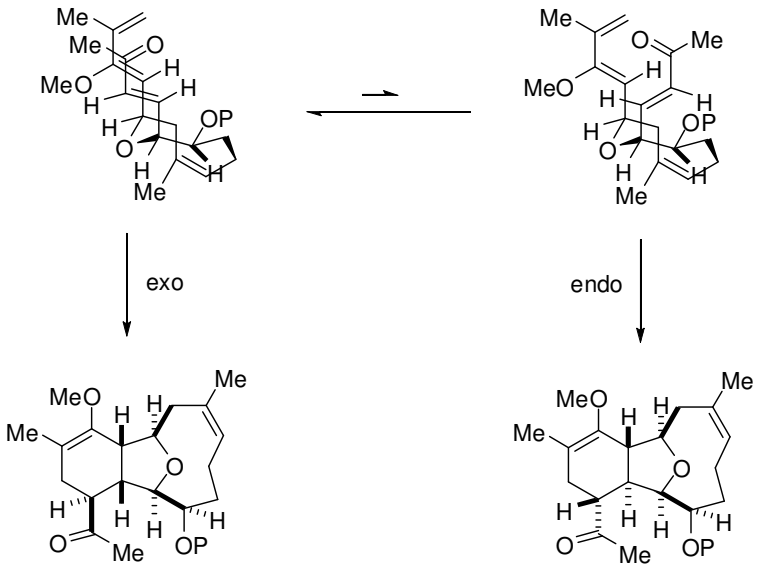


Figure 10. Asbestinin Cycloaddition Transition States

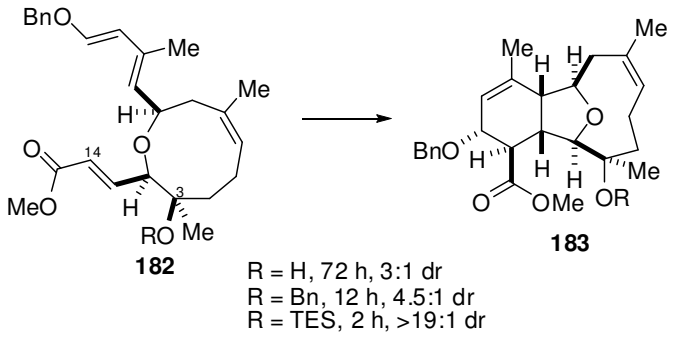
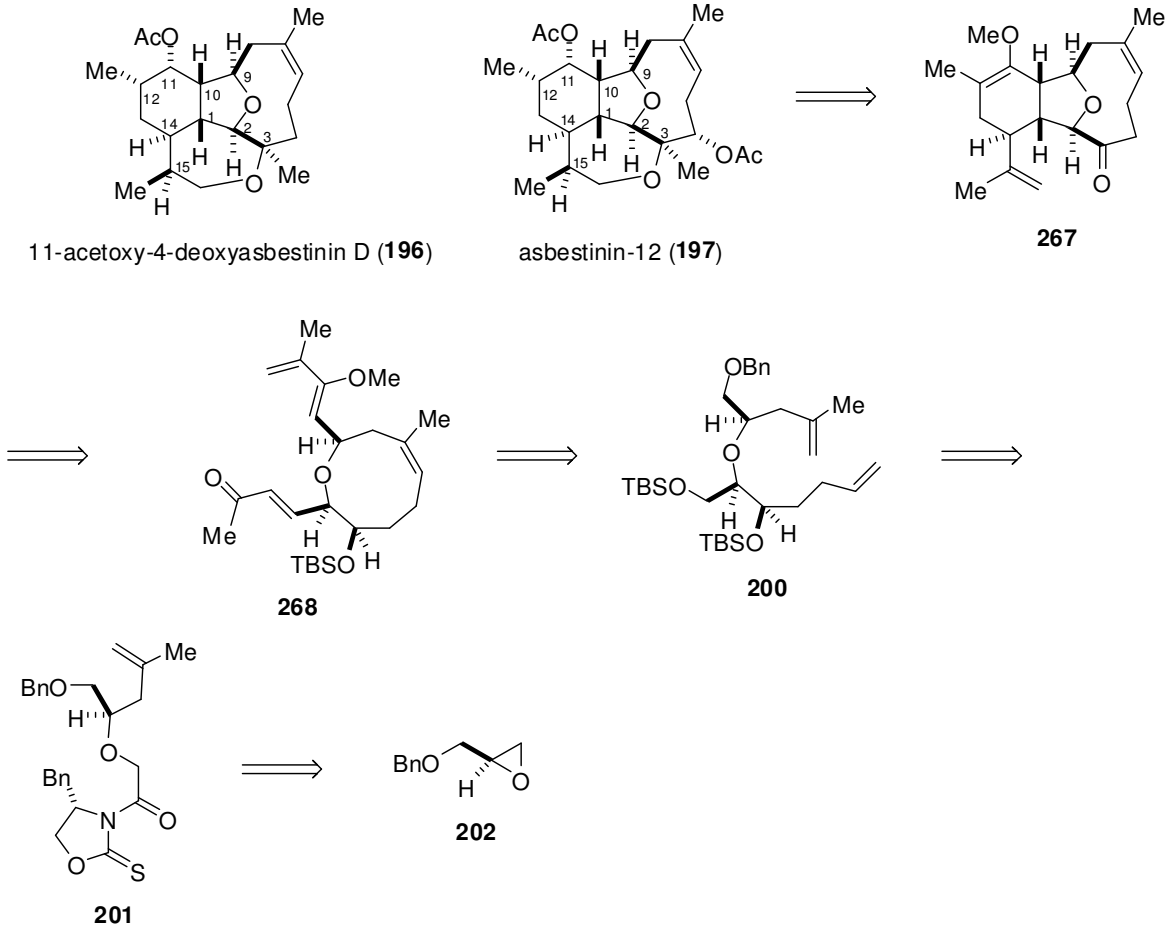


Figure 11. C3 Protecting Group Effects in the Ophirin B Synthesis

5. Revised Retrosynthesis

Armed with the knowledge gained from our investigations to this point, we set out to apply the activated Diels–Alder strategy to complete the synthesis of the asbestinins. Ketone **267** was targeted as a useful substrate for accessing the functionality of the five-, six-, and nine-membered rings of 11-acetoxy-4-deoxyasbestinin D (**196**) and asbestinin-12 (**197**). Triene **267** also features a handle that we envisioned to be useful for establishing the C15 stereochemistry of the

oxepane. An intramolecular Diels–Alder cycloaddition of tetraene **268**, with a silyl ether in place at C3 would be exploited to prepare the tricyclic framework. And, oxonene **268** would be constructed via a ring-closing metathesis of previously synthesized diene **200**, which was accessed via our glycolate aldol addition of thioimide **201**, derived from (*R*)-benzyl glycidyl ether (**202**).

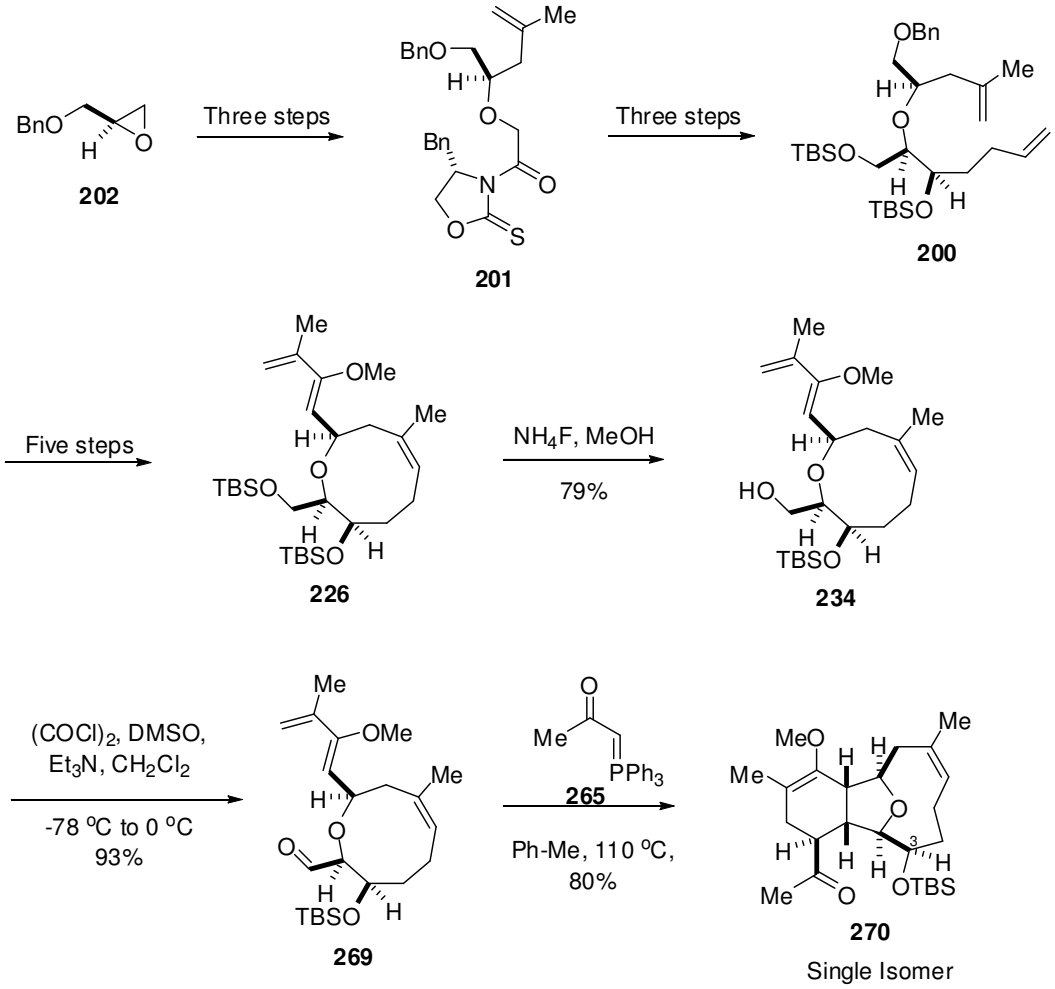


Scheme 51. Revised Retrosynthesis

6. Synthesis of the Revised Diels–Alder Substrate

Utilizing previously prepared triene **226**, accessible in 11 steps from commercially available material, the issue of selectively deprotecting the primary silyl ether was revisited (Table 4, Scheme 52). After attempting several of the previously

examined conditions once again, it was finally found that ammonium fluoride in methanol promoted highly efficient selective deprotection, providing alcohol **234** in 79% yield, with the remainder of the material representing recovered starting material **226** and diol **233** (which was able to be reprotected and recycled).[239] Following this important result, oxidation gave aldehyde **269** in high yield.[130]



Scheme 52. Selective Deprotection and Improved Cycloaddition

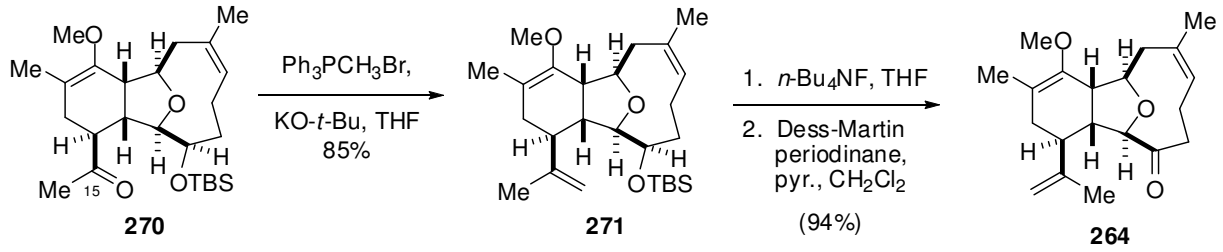
Utilizing ylide **265**, the aldehyde **269** underwent a Wittig reaction and again cyclized to the desired tricycle **270**, this time with a single isomer observable by NMR spectroscopy. This result is in agreement with our previous observations involving

the importance of the C3 protecting group, further supporting our transition state models (Figure 10).

7. Refunctionalization of the Six- and Nine-membered Rings

With an efficient, fourteen step route to tricycle **270**, attention was turned to refunctionalizing the six- and nine-membered rings with the substitution present within the asbestinin subclass. First, the ketone of cycloadduct **270** was methylenated to provide a handle for a hydroboration/oxidation protocol that would be used to provide the proper configuration at C15 at a later point (Scheme 53). Triene **271** was then deprotected and oxidized to give ketone **264**, the targeted point of divergence for the syntheses of 11-acetoxy-4-deoxyasbestinin D (**196**) and asbestinin-12 (**197**).[43] Two-dimensional ^{1}H NMR analysis (COSY, nOeSY) was performed at this point, since none of the previous substrates were amenable to confirming the stereochemistry obtained in the cycloaddition (Figure 12). Strong support was gleaned from this data that the desired configuration was the product of the Diels–Alder reaction. Namely, a nOe was observed between the hydrogens of C1 and C10 and C2 and C9. Further, the hydrogen of C2 was a singlet in the ^{1}H NMR, indicating that it does not couple with any other hydrogens. Via the Karplus equation, it can be deduced that it has a 90^{o} relationship with the C1 hydrogen, indicating a *trans* relationship between those two protons. The C14 configuration could not be definitively established from these data. However, ketone **264** was a solid, white compound following purification, and some time later, a suitable crystal was obtained for X-ray crystallographic analysis (Figure 13). The data obtained

confirmed that the desired configurations for the C1, C2, C9, C10, and C14 stereocenters were each as expected, definitively proving that the Diels–Alder cycloaddition proceeded to give the desired exo-adduct. Each of the five stereocenters matched the desired configuration for the asbestinin subclass. Additionally, this data corroborated speculation gained from previous two-dimensional analysis of asbestinin and cladiellin intermediates that the oxonene was oriented in a bowl shape with the top face (as drawn) representing the concave face. This conformational feature was present in the solid state, and we hoped to exploit this to execute a substrate-controlled diastereoselective reaction with the convex face of the oxonene.



Scheme 53. Synthesis of the Ketone

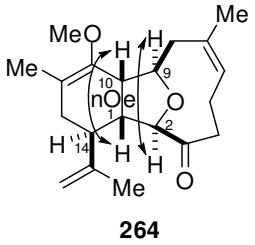


Figure 12. Two-dimensional NMR Data

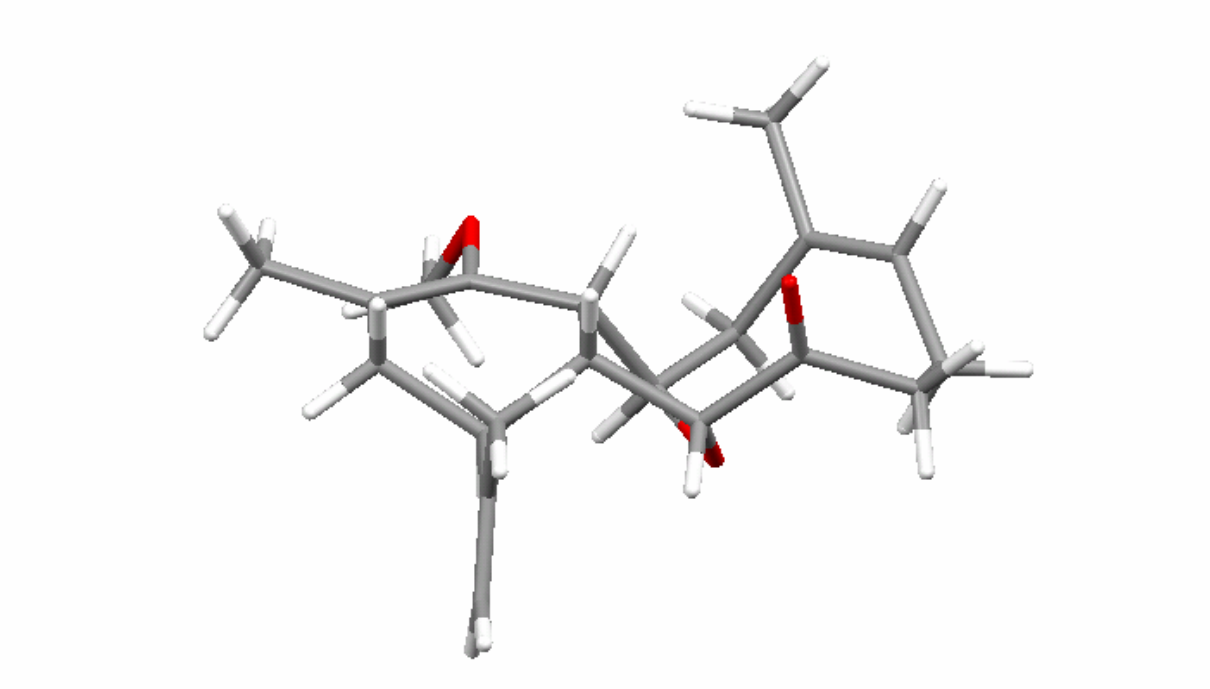
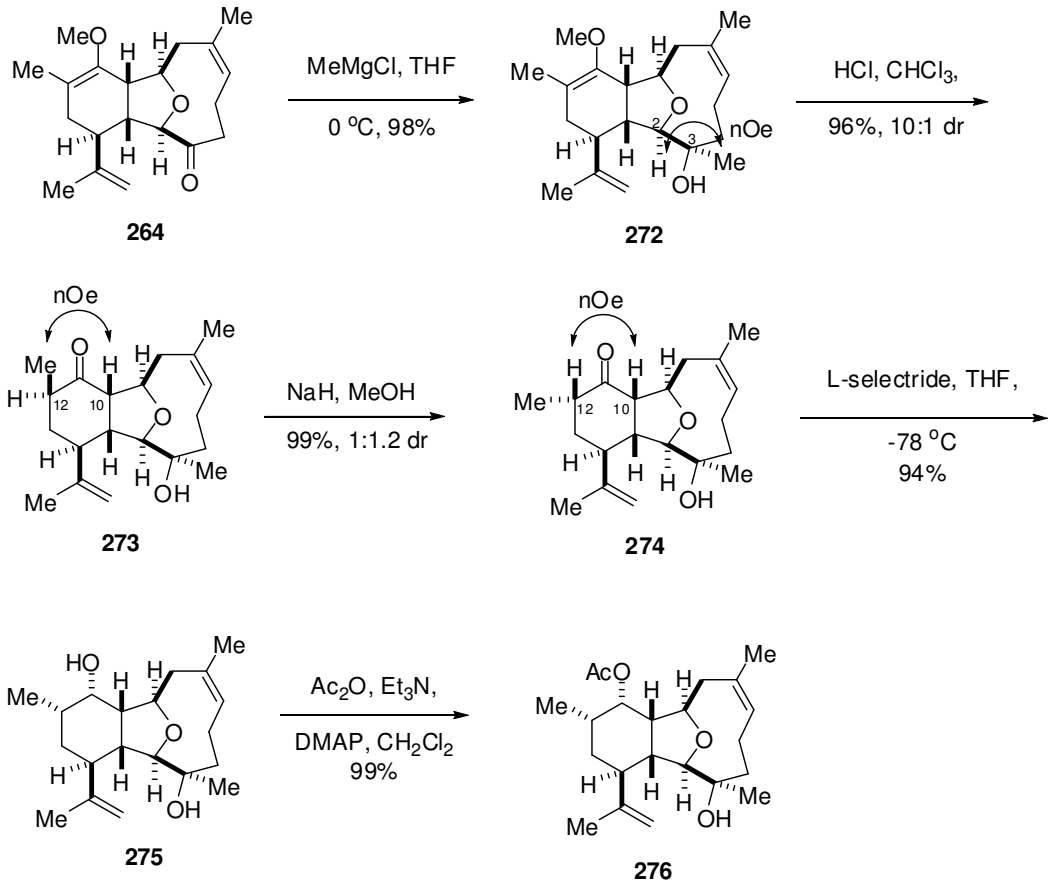


Figure 13. X-ray Crystallographic Data of the Ketone

A substrate-controlled diastereoselective methylation served to complete the functionalization of the oxonene (Scheme 54). As hoped, a single isomer of tertiary alcohol **272** was obtained, presumably via attack on the convex face of the oxonene. This stereochemical outcome was supported by two-dimensional ^{1}H NMR analysis (COSY, nOeSY), which showed a nOe between the newly installed methyl protons at C3 and the proton at C2 of the ring juncture, suggested a *cis* relationship between these two substituents.

Attention was then turned to functionalization of the cyclohexene (Scheme 54). Hydrolysis of the enol ether provided a 96% yield of a 10:1 mixture of α-methyl ketone diastereomers **273** and **274**, favoring the undesired configuration. Again, nOeSY spectroscopy was used to reveal a nOe interaction between the C12 methyl protons and the C10 proton in ketone **273**, while ketone **274** showed a similar nOe between the C12 proton and the C10 proton. Facile epimerization was achieved

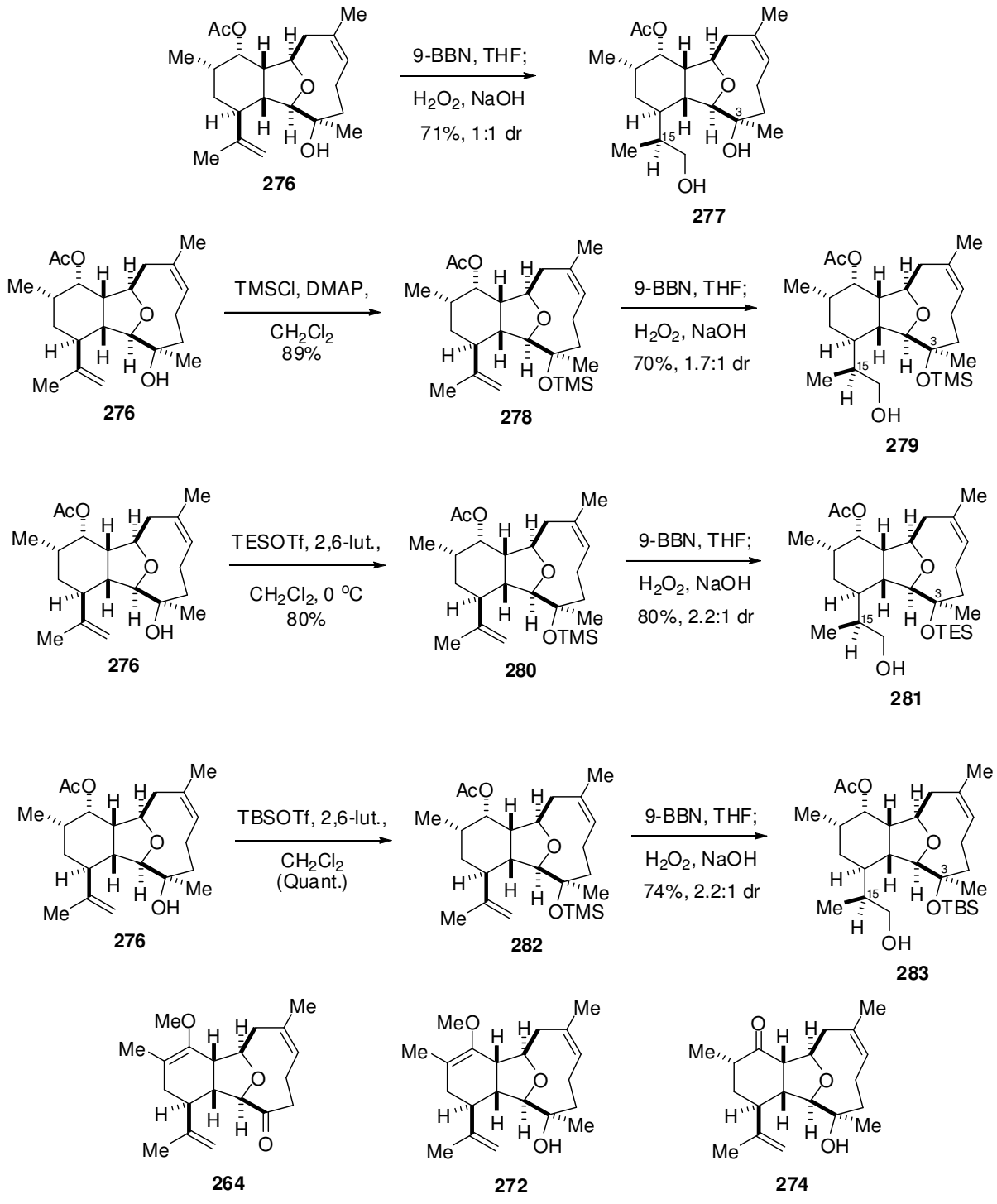
under alkaline conditions to provide a 1:1.2 mixture of diastereomers at equilibrium, favoring the undesired configuration. Two recycles allowed isolation of 83% of ketone **274** from enol ether **272**, along with 13% of ketone **273** remaining. Ensuing reduction of the ketone using sodium borohydride provided alcohol **275** in good yield with good diastereoselectivity (>4:1 dr) for the desired C11 stereocenter. However, using a bulkier hydride source, L-selectride, provided a single isomer of diol **275** in 94% yield. Selective acetylation of the secondary alcohol was trivial and proceeded in nearly quantitative yield to deliver alcohol **276**.



Scheme 54. Refunctionalization of the Six-membered Ring

8. Oxepane Formation to Complete 11-Acetoxy-4-deoxyasbestinin D

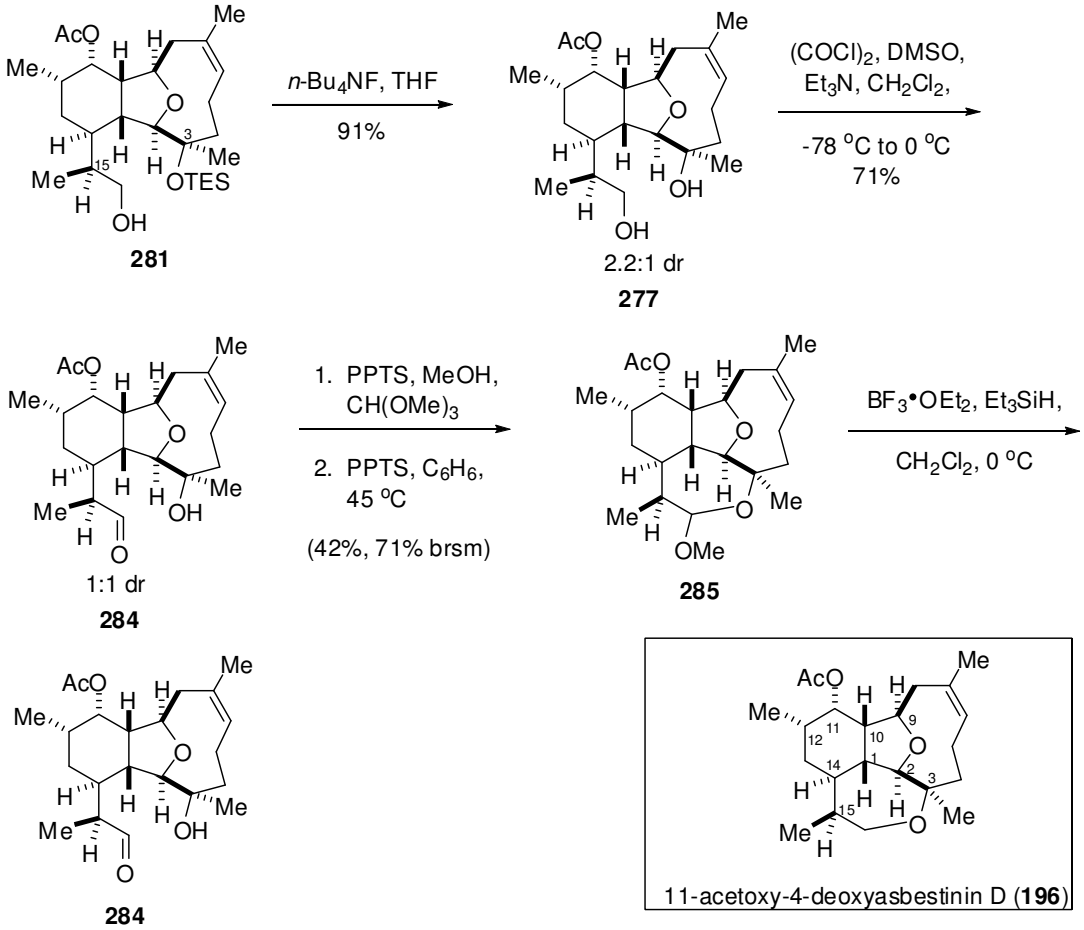
As previously mentioned, we had envisioned using a hydroboration/oxidation protocol to install the C15 stereocenter, hoping for a substrate-controlled diastereoselective reaction. The X-ray of ketone **264** revealed that, in the solid state, the 1,1-disubstituted olefin is oriented such that the face upon which we hoped to selectively operate appears unencumbered, while the undesired face of reactivity is shielded by the oxonene portion of the tricycle (Figure 13). We were hopeful that a similar low energy conformation would be operational in solution for diene **276**. Numerous substrate-controlled highly diastereoselective hydroborations exist in the literature involving the reaction of a variety of 1,1-disubstituted olefins with 9-BBN.[240-242] When diene **276** was treated with 9-BBN under ultrasonic conditions in THF, the starting material was consumed, and upon oxidation, alcohol **277** was isolated (Scheme 55). To our delight, chemoselective and regioselective hydroboration had been achieved, however, an equal amount of each C15 epimer was obtained. After attempting similar hydroborations on ketone **264**, alcohol **272**, and ketone **274** with no success, we turned our attention toward improving the reaction with diene **276**. Namely, we hoped to install a protecting group on the C3 alcohol that would impede addition for one face of the alkene by altering the energies of each transition state for the hydroboration step. A trimethylsilyl group was installed uneventfully. Hydroboration and oxidation of this substrate **278** did demonstrate modest diastereoselection (1.7:1 dr), but certainly left room for improvement. A triethylsilyl variant **280** was prepared, and provided a 2.2:1 dr under the hydroboration/oxidation conditions. A *t*-butyldimethylsilyl ether **282** was also formed, but exhibited identical diastereoselection to the triethylsilyl substrate **280**



Scheme 55. Hydroboration Studies

(2.2:1 dr) under the reaction conditions. Formation of *t*-butyldimethylsilyl ether **282** proceeded slowly due to the orientation of the C3 alcohol within the concave face of the oxonene. Predictably, a triisopropylsilyl ether could not be formed at a useful rate. Since this strategy seemed to have a modest ceiling of diastereoselectivity, we hoped to improve the ratio via epimerization of the corresponding aldehyde.

Diastereoenriched alcohol **277**, prepared via deprotection of alcohol **281**, was oxidized to the aldehyde **284** under Swern conditions (Scheme 56).[130]



Scheme 56. Reductive Etherification Strategy

Unfortunately, during the course of the reaction, the material epimerized to an equal ratio of C15 epimers. Despite this undesired result, we attempted to proceed via

aldehyde **284** to form the oxepane using a ketal cyclization/reductive etherification strategy that had found use in our approach to brevetoxin A.[214,243,244] To that end, the dimethyl ketal was formed. A solvent switch and heating of the dimethyl ketal gave mixed methyl ketal **285**. Unfortunately, reductive etherification of mixed ketal **285** resulted in isolation of aldehyde **284**, rather than natural product **196**, most likely due to adventitious water intercepting the oxocarbenium ion faster than hydride. Use of *i*-Bu_2AlH led only to reduction of the acetate ester.

A revised route to install the C15 methyl stereocenter diastereoselectively was devised envisioning hydrogenation of an exocyclic C15 1,1-disubstituted olefin following oxepane formation (Figure 14). It was proposed that the concave nature of the tetracycle would allow selective reaction from the convex face, providing the desired C15 configuration. To install the olefin and form the oxepane, we hoped to open the epoxide **286** of tricycle **276** with lithium diethylamide (Scheme 57).[245] The diol would then undergo an intramolecular etherification, and hydrogenation would provide 11-acetoxy-4-deoxyasbestinin D (**196**). Unfortunately, attempts to chemoselectively epoxidize the disubstituted olefin of diene **276** were unsuccessful, as the trisubstituted olefin reacted faster with *m*-CPBA to give epoxide **287**. Another method for installing the disubstituted epoxide was devised utilizing the Johnson–Corey–Chaykovsky reaction.[246,247] However, none of the desired epoxide **288** was isolated under these conditions. Finally, we envisioned using a modified dienophile for the intramolecular Diels–Alder reaction that would allow exocyclic olefin formation, while also providing a handle for oxepane cyclization. Again, our efforts

were thwarted as Wittig reaction with ylide **289** led to none of the desired tricycle **290** under the same conditions that were successful using ylide **265**.[248]

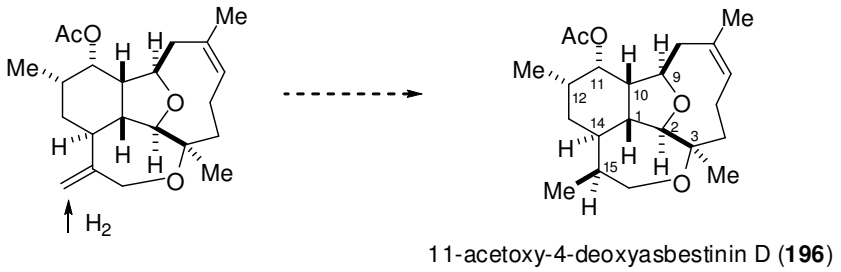
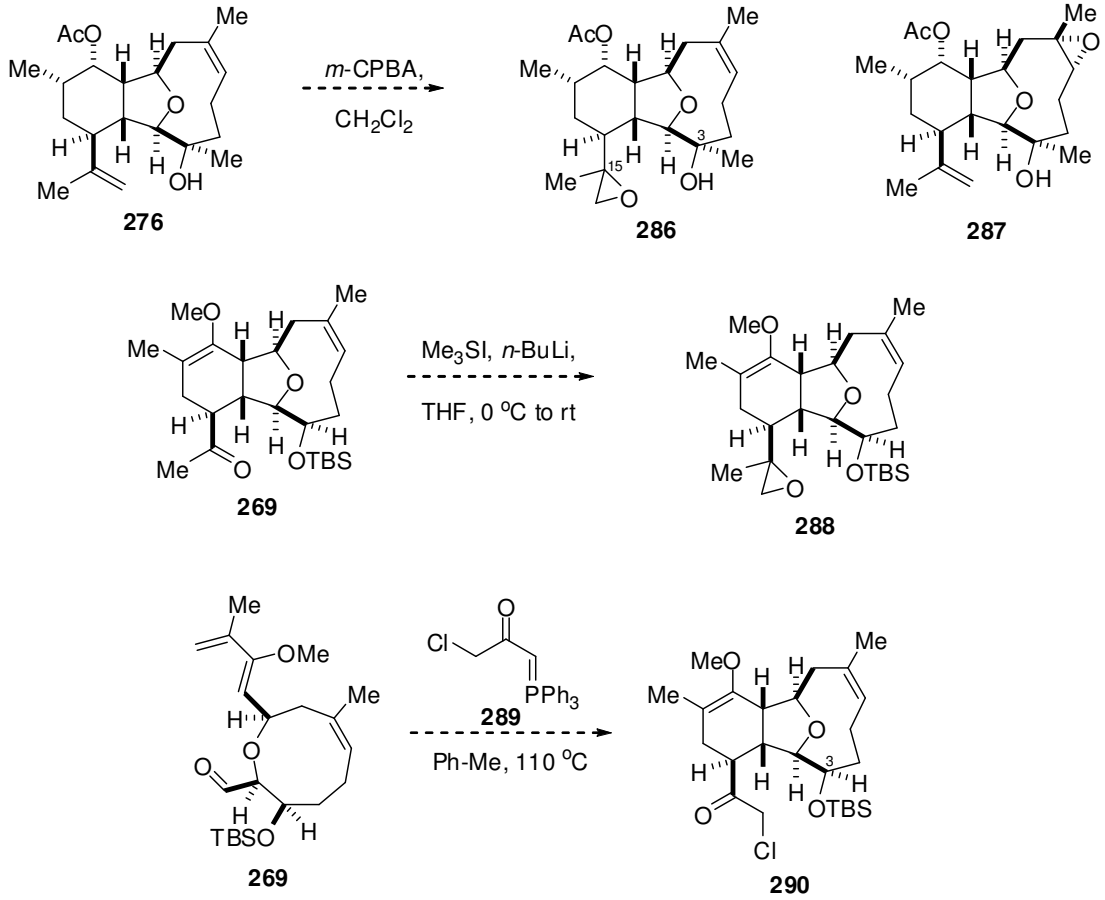


Figure 14. Hydrogenation Strategy

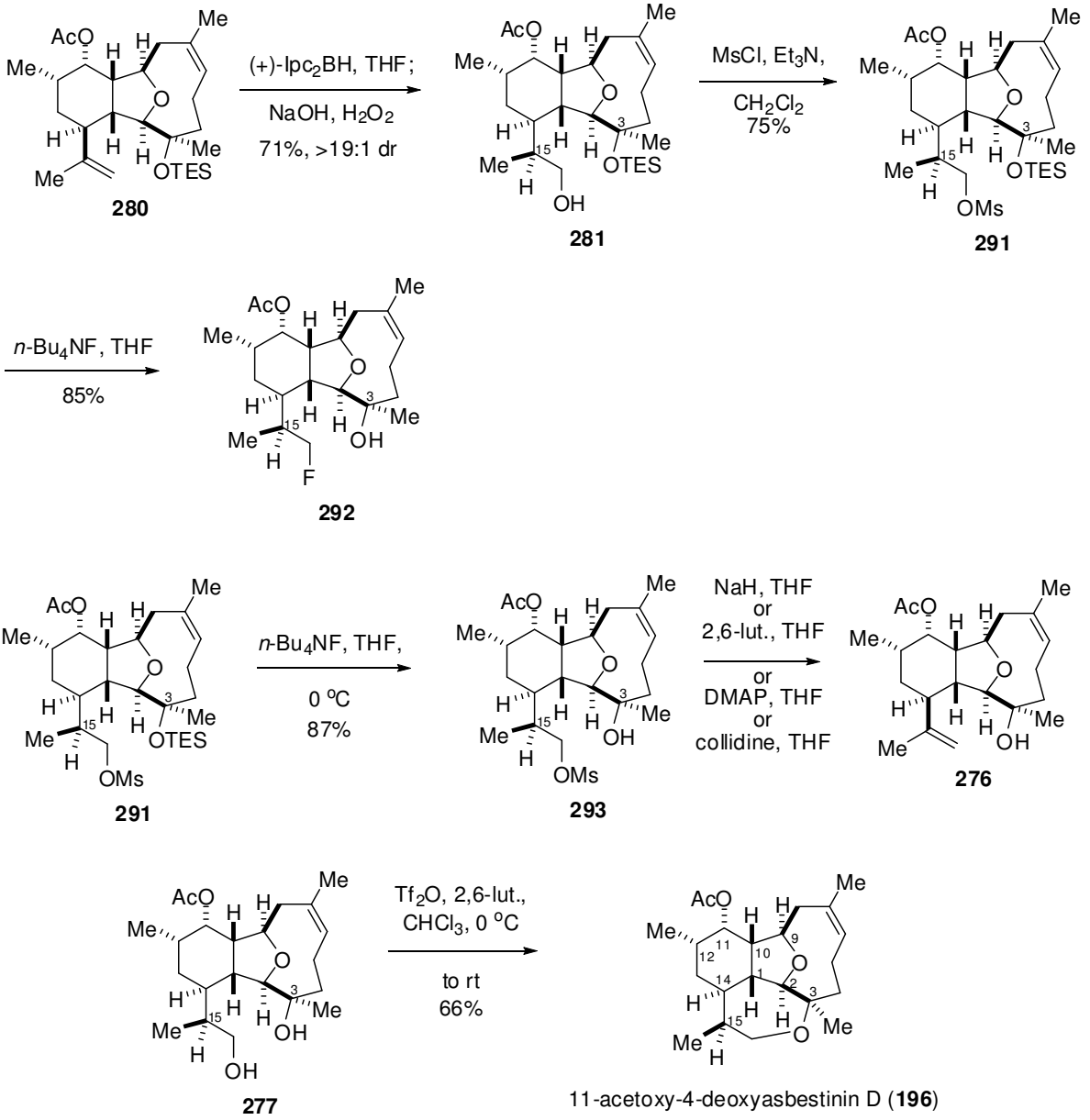


Scheme 57. Hydrogenation Strategy

With the previous routes for diastereoselectively installing the C15 stereocenter proving fruitless, we returned to the hydroboration/oxidation strategy.

Although chiral hydroborating agents generally give poor results for diastereoselectively hydroborating 1,1-disubstituted olefins, our lack of success with achiral variants led us to attempt using diisopinocampheylborane.[249] Much to our delight, treatment of diene **280** with (+)-diisopinocampheylborane, followed by alkaline oxidation gave diol **281** as a single detectable diastereomer (Scheme 58). This represents only the second example of the successful application of diisopinocampheylborane for the diastereoselective hydroboration of a 1,1-disubstituted alkene (Scheme 59).[250] Formation of the corresponding mesylate **291** was followed by deprotection of the silyl ether with fluoride, which we hoped would result in etherification via the intermediate alkoxide following deprotection. However, fluoride **292** was instead isolated from the reaction mixture. Alternatively, mesylate **291** could be deprotected at lower temperature, to provide alcohol **293**. But, upon treatment with a variety of bases (sodium hydride, 2,6-lutidine, 4-dimethylaminopyridine, collidine), only elimination product **276** was isolated. Overman has previously reported the formation of an oxepane in an analogous system for the total syntheses of briarellin E and F using an etherification that proceeds through the intermediate primary triflate (Scheme 10).[80] Application of the same conditions to diol **277** delivered 11-acetoxy-4-deoxyasbestinin D (**196**) in 66% yield, with the remainder of the material representing elimination product **276**. Whereas the Overman example required four days for complete reaction, the primary triflate of diol **277** took only four hours to cyclize, likely due to the extra rigidifying element present in our system of the closed oxonene. The synthetic material corresponded to the natural material in all regards.[11] Additionally, though

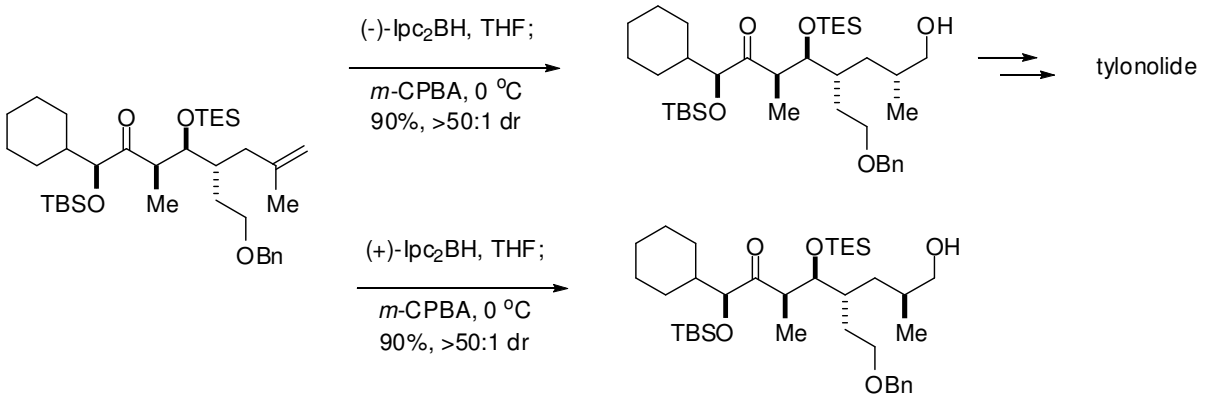
the optical rotation of the synthetic material ($[\alpha]^{26}_D$; $CHCl_3$ = -15) differed from the reported literature value ($[\alpha]^{29}_D$; $CHCl_3$ = -2.29), we were able to obtain a sample of the natural product from the Rodríguez laboratory at the University of Puerto Rico,



Scheme 58. Completion of 11-Acetoxy-4-deoxyasbestinin D

Río Piedras. Submission of the natural material to polarimetry under the same conditions used for the synthetic material provided a matching optical rotation ($[\alpha]^{26}_D$;

$CHCl_3$ = -15) to our synthetically prepared compound, further confirming the synthetic material was indeed 11-acetoxy-4-deoxyasbestinin D (**196**). This 26 step sequence from (*R*)-benzyl glycidyl ether (**202**) represents the first total synthesis of a member of the asbestinin subclass. Further, the optical rotations obtained for the synthetic and natural materials serve to confirm the absolute configuration of the asbestinin subclass, verifying that the biosynthetic proposal gives the proper configuration, rather than the enantiomer featured in the isolation literature.[1,2,11]

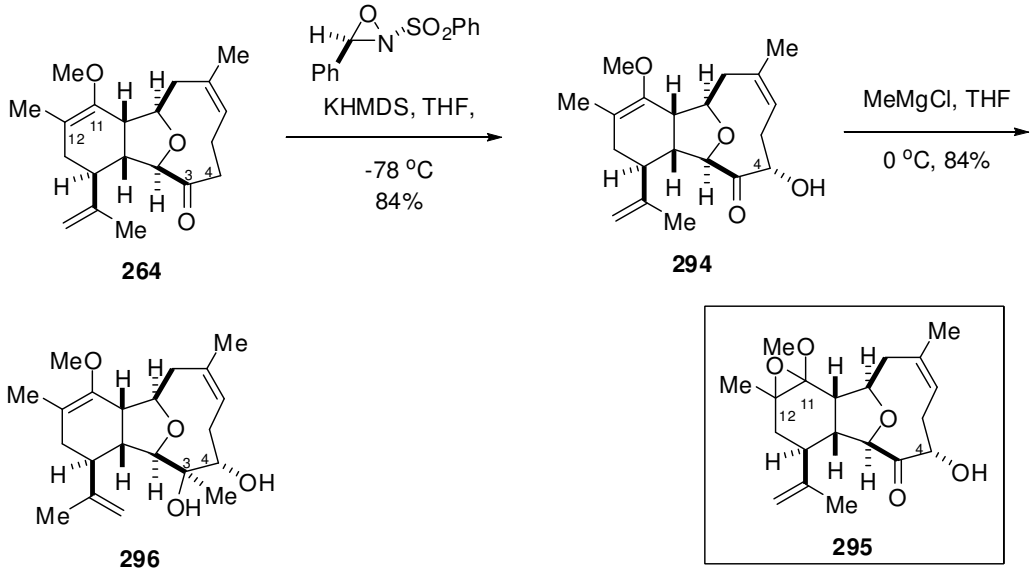


Scheme 59. Masamune's Chiral Hydroboration

9. Total Synthesis of Asbestinin-12

For the synthesis of asbestinin-12 (**197**),[224] we again hoped to exploit the inherent concavity of ketone **264** to perform a diastereoselective transformation. This time, an α-hydroxylation of the potassium enolate of ketone **264** using Davis oxaziridine provided the alcohol **294** as a single diastereomer (Scheme 60).[251-253] When a greater number of equivalents of the Davis reagent were employed, overoxidation was observed via epoxidation of the C11–C12 tetrasubstituted enol ether to provide a mixture of hydroxy epoxides **295** (1.3:1 dr). However, use of just more than stoichiometric oxaziridine and careful monitoring of the reaction could

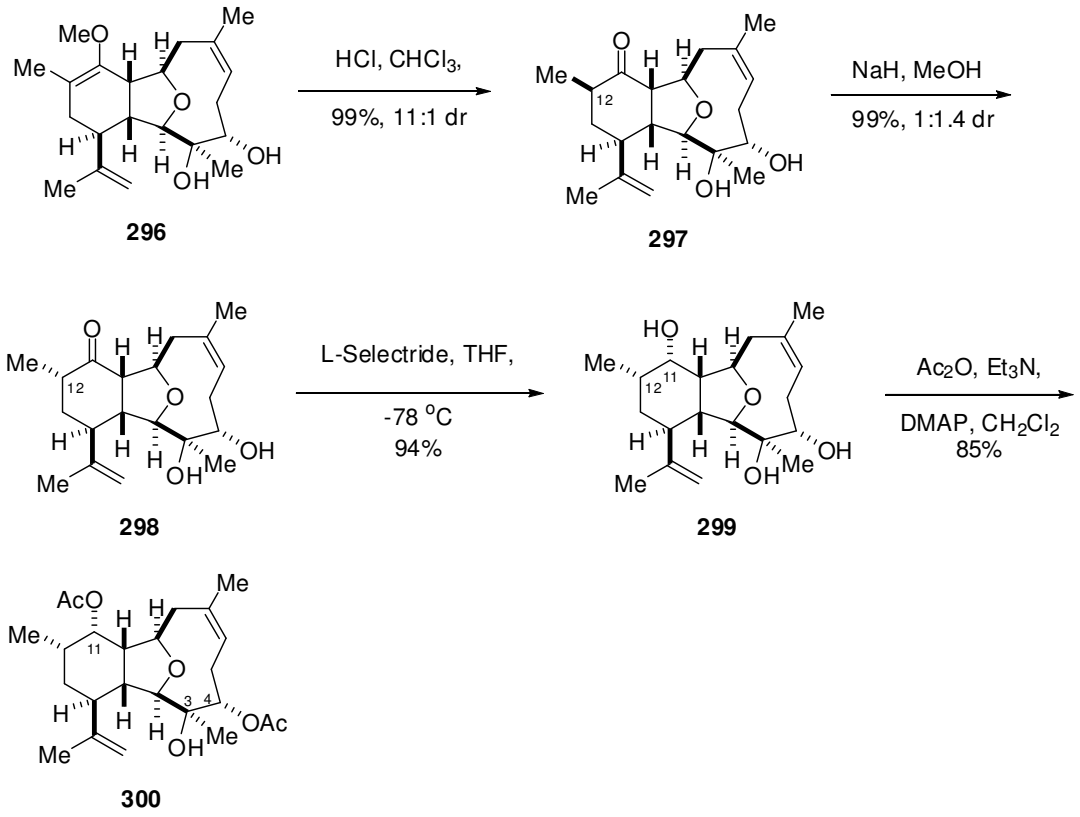
preclude formation of this undesired byproduct **295**. There was some concern that the presence of the C4 alcohol would adversely impact the diastereoselectivity of the subsequent alkylation via chelation of the carbonyl and hydroxyl to provide the epimeric C3 diol. Fortunately, this phenomenon was never observed. However, the conversion for this methylation was poor, perhaps due to competitive enolization of the C3 ketone, and prolonged reaction led to an unidentified byproduct. Attempted use of methyllithium (with or without sodium tetrafluoroborate) did not improve the yield of this reaction.[44,88,103] However, using a large excess of the Grignard reagent (20.0 eq), provided diol **296** as a single diastereomer in 84% yield.



Scheme 60. Hydroxylation and Grignard Reactions

Hydrolysis of enol ether **296** again provided the undesired C12 configuration of ketone **297** as the major product, in a similar ratio to that previously observed (Scheme 61). Epimerization was again facile under alkaline conditions and gave some of the desired C12 methyl configuration **298**. A single diastereomeric triol was obtained upon reduction of ketone **298** with L-Selectride, whereupon selective

protection of the secondary alcohols was accomplished in the presence of the tertiary alcohol providing diacetate **300**.

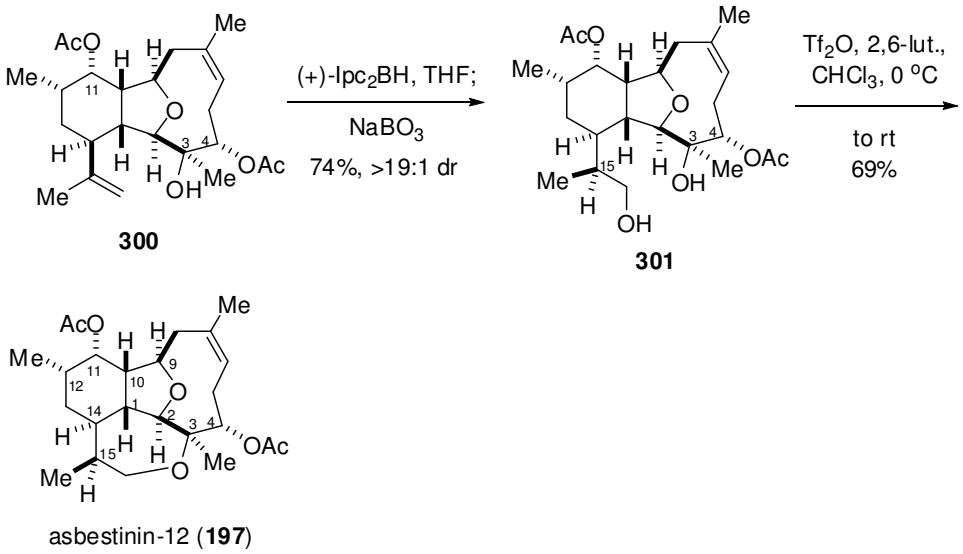


296 **297** **298** **299** **300**

Scheme 61. Formation of the Hydroboration Candidate

At this point, we hoped to examine the role of the C3 protecting group in the diastereoselectivity of the hydroboration. Earlier, the triethylsilyl ether **280** was ultimately employed as the hydroboration substrate for monitoring purposes (Scheme 58), but this was not necessary for diacetate **300**. Treatment of diene **300** with (+)-diisopinocampheylborane and oxidation provided the desired diol **301** as a single diastereomer in good yield,[249] confirming that the reagent controls the selectivity (Scheme 62). Oxidation with the milder sodium perborate conditions proved useful in this case to prevent hydrolysis of the labile C4 acetate.[73] Using

triflic anhydride and 2,6-lutidine,[80] asbestinin-12 (**197**) was obtained in good yield, with the remainder of the material representing elimination product **300**. All data reported for the natural material again corresponded well with the data for the synthetic material.[224]

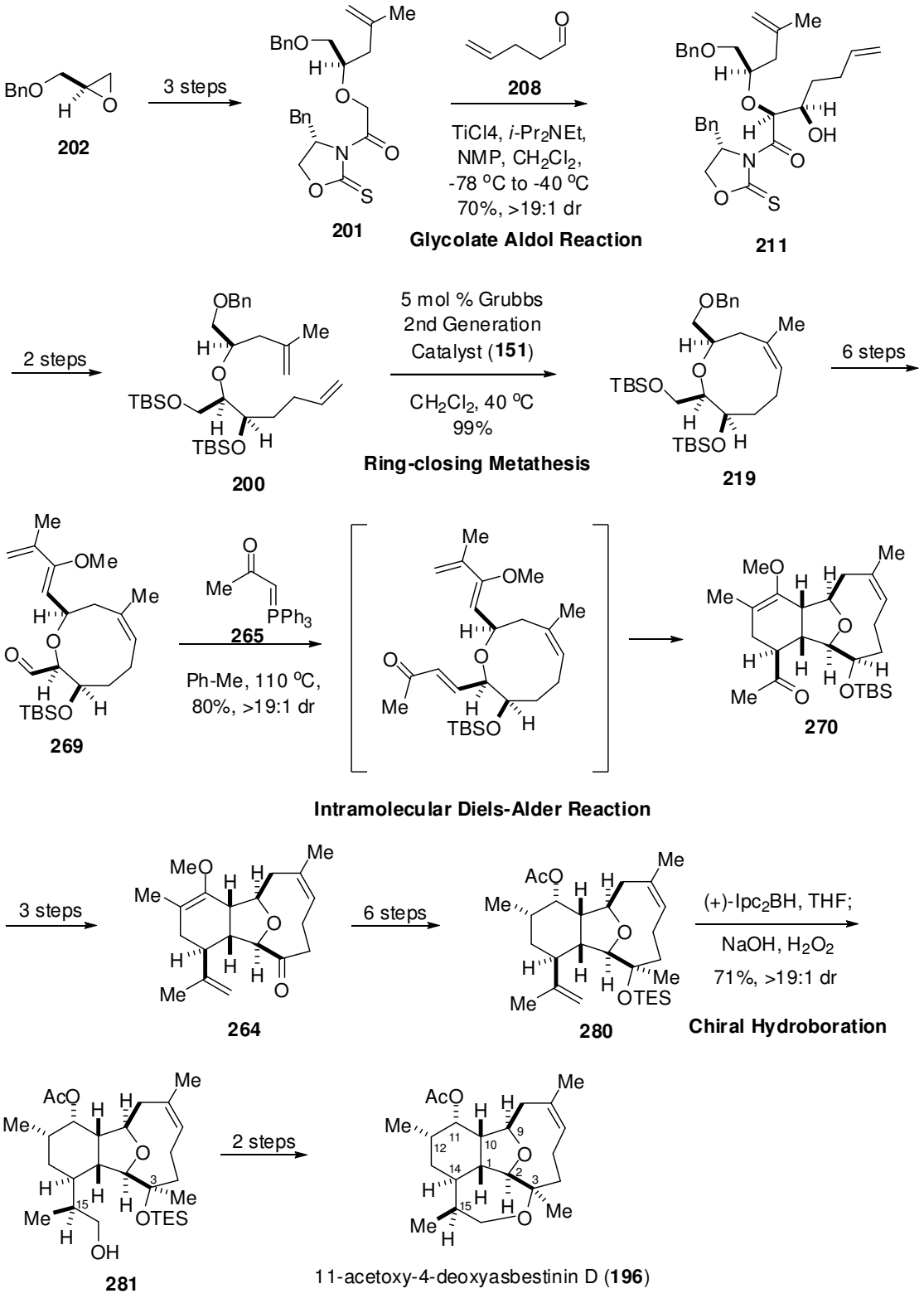


Scheme 62. Completion of Asbestinin-12

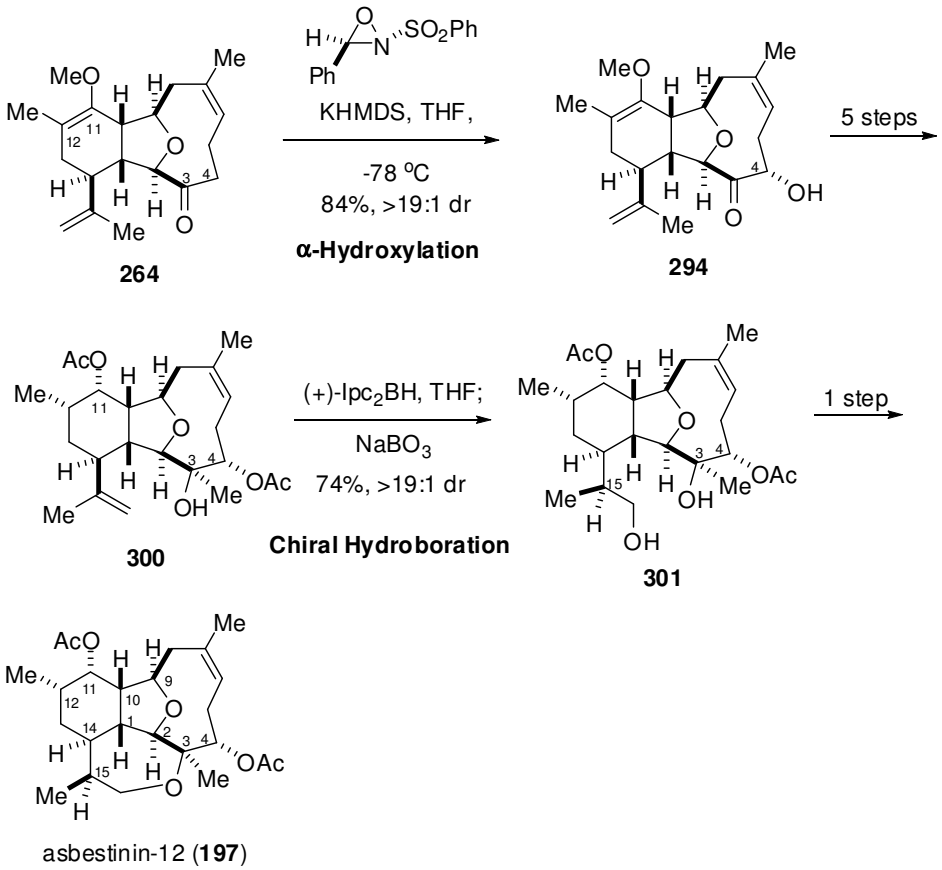
E. Summary

In summation, highly stereoselective syntheses of 11-acetoxy-4-deoxyasbestinin D (**196**) and asbestinin-12 (**197**) have been completed in 26 and 25 steps respectively. The strategy for completing these two molecules hinged upon the formation of an oxonene ring using an asymmetric gylcolate aldol reaction and subsequent ring-closing metathesis. This oxonene was used as a manifold for an intramolecular Diels–Alder cycloaddition to form the hydroisobenzofuran moiety. An α-hydroxylation was utilized to diverge the two routes. A chiral hydroborating reagent proved crucial in establishing the stereocenter at C15. These syntheses

stand as the first molecules of the asbestinin subclass to be prepared by chemical methods and serve to confirm the absolute configuration of the asbestinins.



Scheme 63. Summary for 11-Acetoxy-4-deoxyasbestinin D



Scheme 64. Summary for Asbestinin-12

Chapter II

A Convergent Strategy for the Total Synthesis of Brevetoxin A

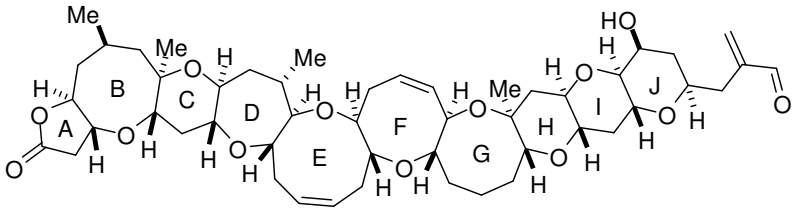
A. Background

In addition to the previously described C2–C11 cyclized cembranoids, marine sources also provide an assortment of *trans*-fused polycylic ethers (Figure 15).[254] These molecules, generally produced by algae called dinoflagellates, make up a class known as the ladder toxins, due to their ladder like structure and often toxic biological effects. In 1981, brevetoxin B became the first member of this class to be characterized.[255] Since this time, a number of other ladder toxins have been isolated and their structures elucidated. Each of the identified ladder toxins feature cylic ethers composed of five- to nine-membered rings, joined in a repeating *trans*/*syn*/*trans* pattern. The total number of rings within each molecule varies greatly, from hemibrevetoxin B (**302**)[256] possessing only four cyclic ethers and ten stereocenters, to maitotoxin, which features an impressive 32 ether rings and 98 stereocenters.[257]

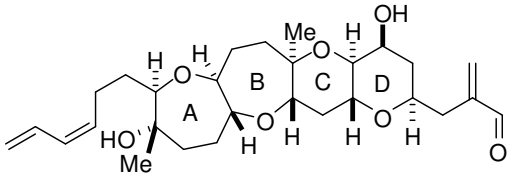
Beyond the fascinating complexity and uniformity of the structures of this class, the ladder toxins also display a range of biological properties. Many of the observed effects are harmful to humans, including strong ichthyotoxicity[255,258,259] and ciguatera poisoning.[260,261] These properties have been implicated as the potent component of the red tides, resulting in massive fish kills and human sickness upon

consumption of infected sea life.[262] Additionally, cases have been reported of some ladder toxins becoming aerosolized during red tides, resulting in respiratory irritation for those in the area. Despite these often harmful effects, some of the polycyclic ethers also feature beneficial biological effects, including antifungal properties[263] and tumor cytotoxicity, with IC_{50} values as low as 0.5 nM.[264,265]

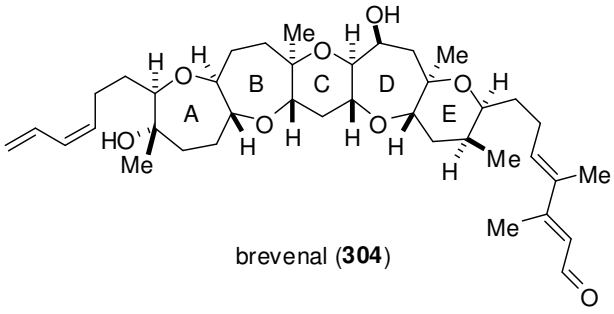
Due to the molecular intrigue, as well as the biological and ecological effects of *trans*-fused polycyclic ethers, a number of research groups have devoted effort toward the preparation of members of this class. Several total syntheses of these daunting natural products have resulted from these endeavors.[254,266] As part of this work, new synthetic strategies have been developed. The large number of steps



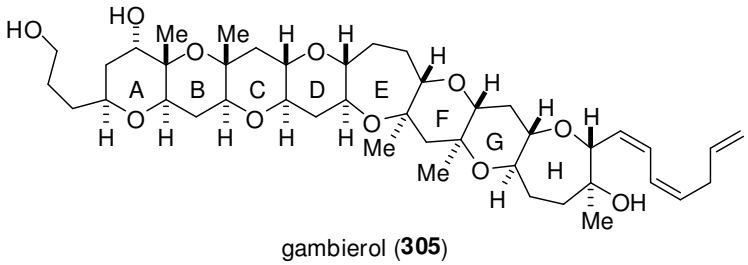
brevetoxin A (**303**)



hemibrevetoxin B (**302**)



brevenal (**304**)



gambierol (**305**)

Figure 15. *trans*-Fused Polycyclic Ethers

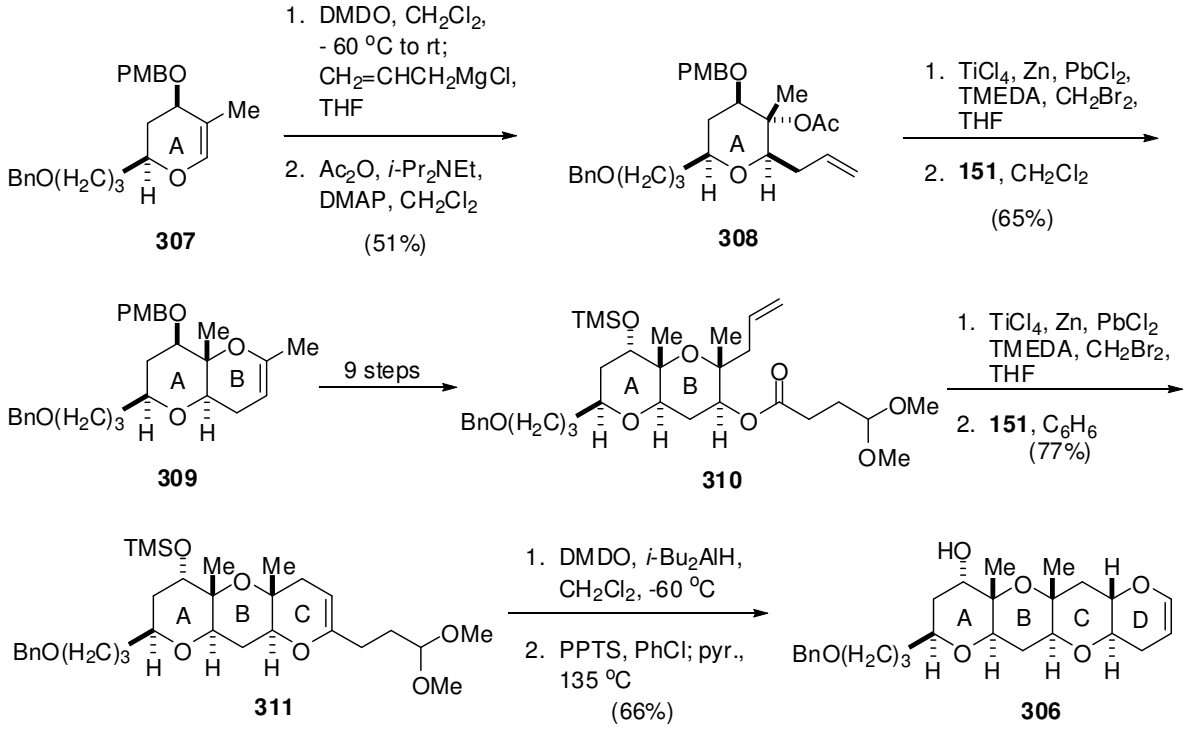
generally required to prepare these molecules demand high throughput, and strategies for decreasing the total, and longest linear, number of steps have been described.

B. Approaches to Polycyclic Ether Synthesis

1. Iterative Ring Formation

The most straightforward method for forming polycyclic ethers involves applying approaches to medium ring ether formation in an iterative fashion to construct each ring of the ladder toxins sequentially. Clearly, this strategy requires highly efficient formation of each ring, since there is no convergency to reduce the longest linear sequence. One of the most effective methods of forming polycyclic ethers in a linear fashion was developed by the Rainier laboratory, centered upon C-glycoside synthesis.[267] The strategy has been applied to the preparation of the ABCD **306**[268] and FGH[269] subunits of gambierol, a natural product that causes ciguatera (**305**).[270] Namely, an enol ether–olefin ring-closing metathesis route was exploited to build each of these subunits. Beginning with pyran **307**, an epoxidation and subsequent Grignard addition delivered the tertiary alcohol, which was acylated to provide alkene **308** in 51% yield over two steps (Scheme 65). The theme of opening enol ether epoxides with nucleophiles was repeatedly utilized to build handles for establishing the subsequent rings. Methylenation[271] and treatment with the Grubbs second generation catalyst (**151**)[172] gave the AB ring unit **309**, again possessing an enol ether ready for oxidation. Nine steps delivered ester **310**, which was again methylenated[271] and subjected to a ring-closing metathesis[172] to provide

the ABC ring system **311**. Epoxidation, in situ reduction, and cyclodehydration gave the ABCD fragment **306**[268]. Similar methods were employed to complete the FGH unit of gambierol (**305**).[269]

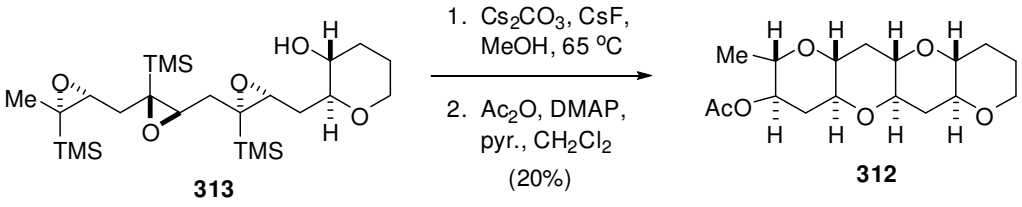


Scheme 65. Iterative Ladder Toxin Synthesis

2. Biomimetic Epoxide Opening

Nakanishi has proposed a biosynthetic pathway for the formation of polycyclic ethers involving a cascade of epoxide openings, with each epoxide opening simultaneously forming a new ring of the ladder toxins.[258] This sequential approach to the construction of marine ladder toxins has been examined by several research groups to test the probability of this hypothesis of origins.[272,273] One of the more refined approaches has been reported by the Jamison group. They have used a cascade opening of polyepoxides to form a tetrad of tetrahydropyrans, a unit which

is present in several of the ladder toxins.[274] Their strategy relies upon the use of trimethysilyl substituents on the epoxide, which serve to direct the cyclizations to favor the generation of tetrahydropyrans (6-endo) over the general bias for tetrahydrofuran formation (5-exo). Exemplary of their strategy is the formation of tetracycle **312** in one step from pyran **313** (Scheme 66). Pyran **313** was constructed using several iterations of the Shi epoxidation protocol to give the desired stereochemistry of each epoxide.[275] In the event, treatment with cesium carbonate and cesium fluoride in methanol at 65 °C provided the tetracycle, which was acylated to provide ester **312**. During the course of the reaction, the trimethylsilyl groups served to direct the epoxidation to form the desired ring size; these directing groups are also cleaved following cyclization, a feature absent in other biomimetic routes. Although the yield for this transformation is low (20% overall), three new C–O bonds and three new C–H bonds are formed in this example, translating to an average of 80% yield per bond formation.

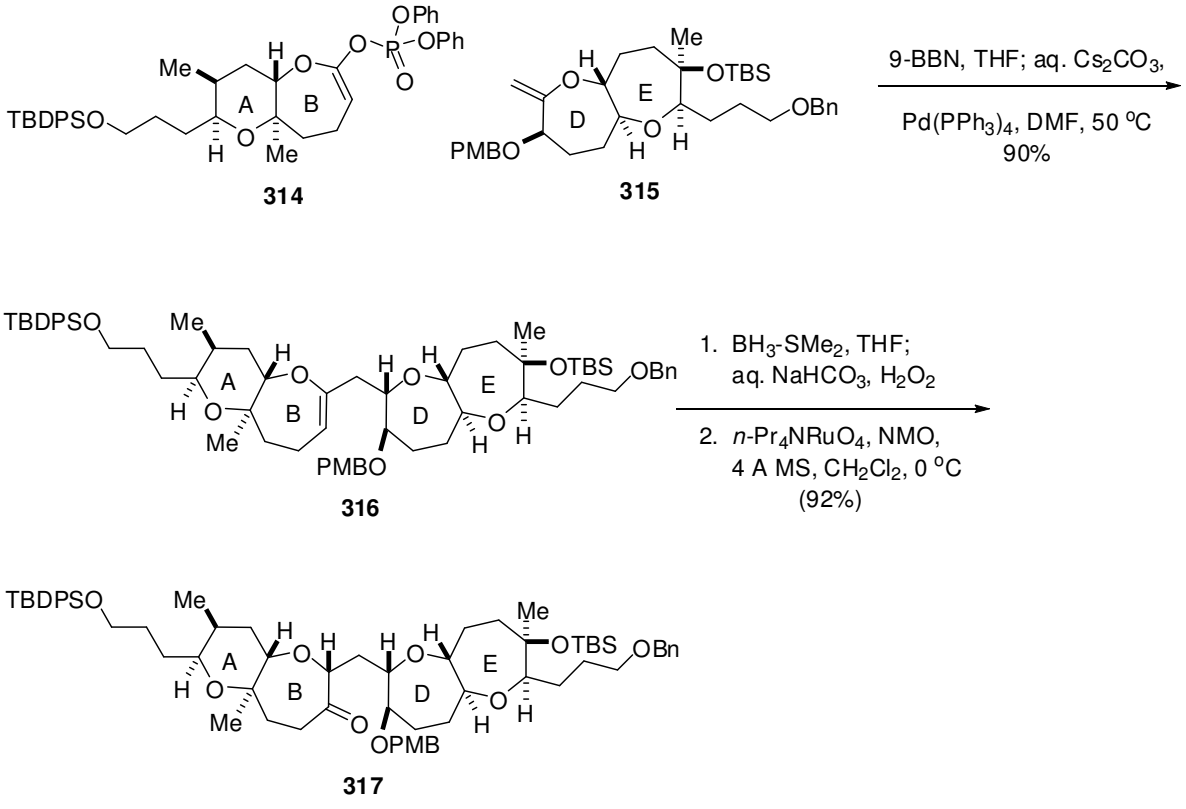


Scheme 66. Biomimetic Approach

3. [X + 1 + X] Approach

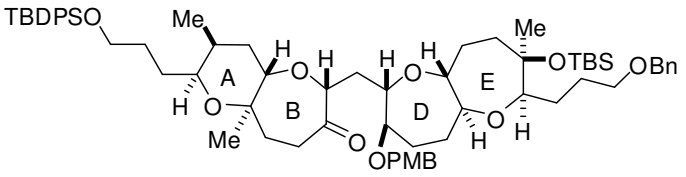
As previously mentioned, convergent strategies have gained popularity within the synthetic community for the construction of polycyclic ethers to shorten the longest linear sequence and thereby increase throughput. An example of this strategy was described by Sasaki in his synthesis of brevenal (**304**).[266,276,277]

Interestingly, brevenal (**304**) acts to competitively displace brevetoxin A (**303**) in rat brain synapses and antagonizes the toxic effects of its ten-ring counterpart. Due to this intriguing activity, as well as its potential utility for the treatment of cystic fibrosis, brevenal (**303**) has quickly garnered interest as a synthetic target. The Sasaki laboratory has applied their *B*-alkyl Suzuki strategy to couple two fragments and form the central ring of the natural product.[278] To that end, phosphate **314** and the hydroborated variant of alkene **315** were coupled under palladium-catalyzed conditions to afford tetracycle **316** (Scheme 67). A second hydroboration and oxidation of the B ring enol ether, followed by further oxidation of the resultant secondary alcohol, gave ketone **317** in good yield.



Scheme 67. [X + 1 + X] Strategy

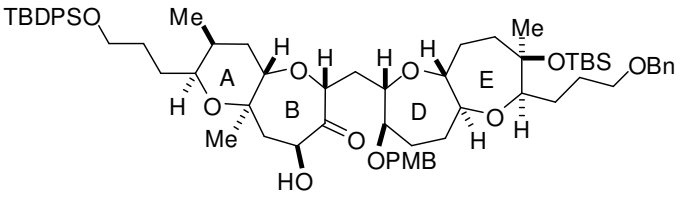
Installation of a secondary alcohol was next achieved in two steps (Scheme 68).[279] Protecting group manipulations and adjustment of the oxidation states of the



317

1. LiHMDS, TMSCl, Et_3N, THF, -78 °C
2. OsO_4, NMO, THF, H_2O

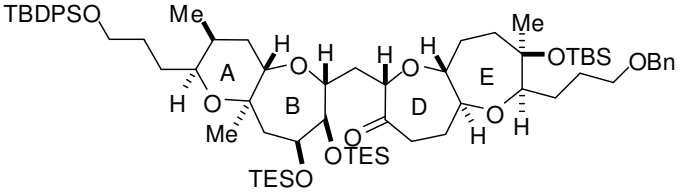
(87%)



318

1. *i*-Bu_2AlH, THF, -78 °C
2. TESOTf, Et_3N, CH_2Cl_2, 0 °C
3. DDQ, CH_2Cl_2/pH 7 buffer
4. *n*-Pr_4NRuO_4, NMO, 4 A MS, CH_2Cl_2

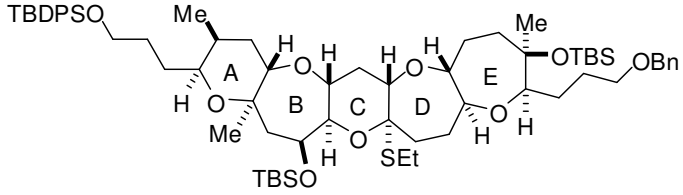
(67%)



319

1. EtSH, $Zn(OTf)_2$, THF
2. TBSOTf, Et_3N, CH_2Cl_2, 0 °C

(77%)

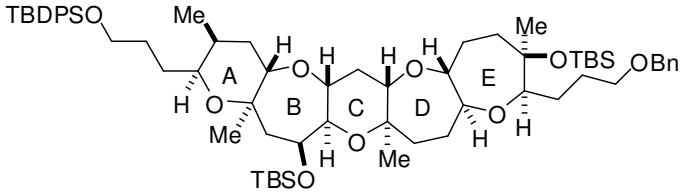


320

m-CPBA, CH_2Cl_2, -78 °C; $AlMe_3$, -78 °C

to 0 °C

92%



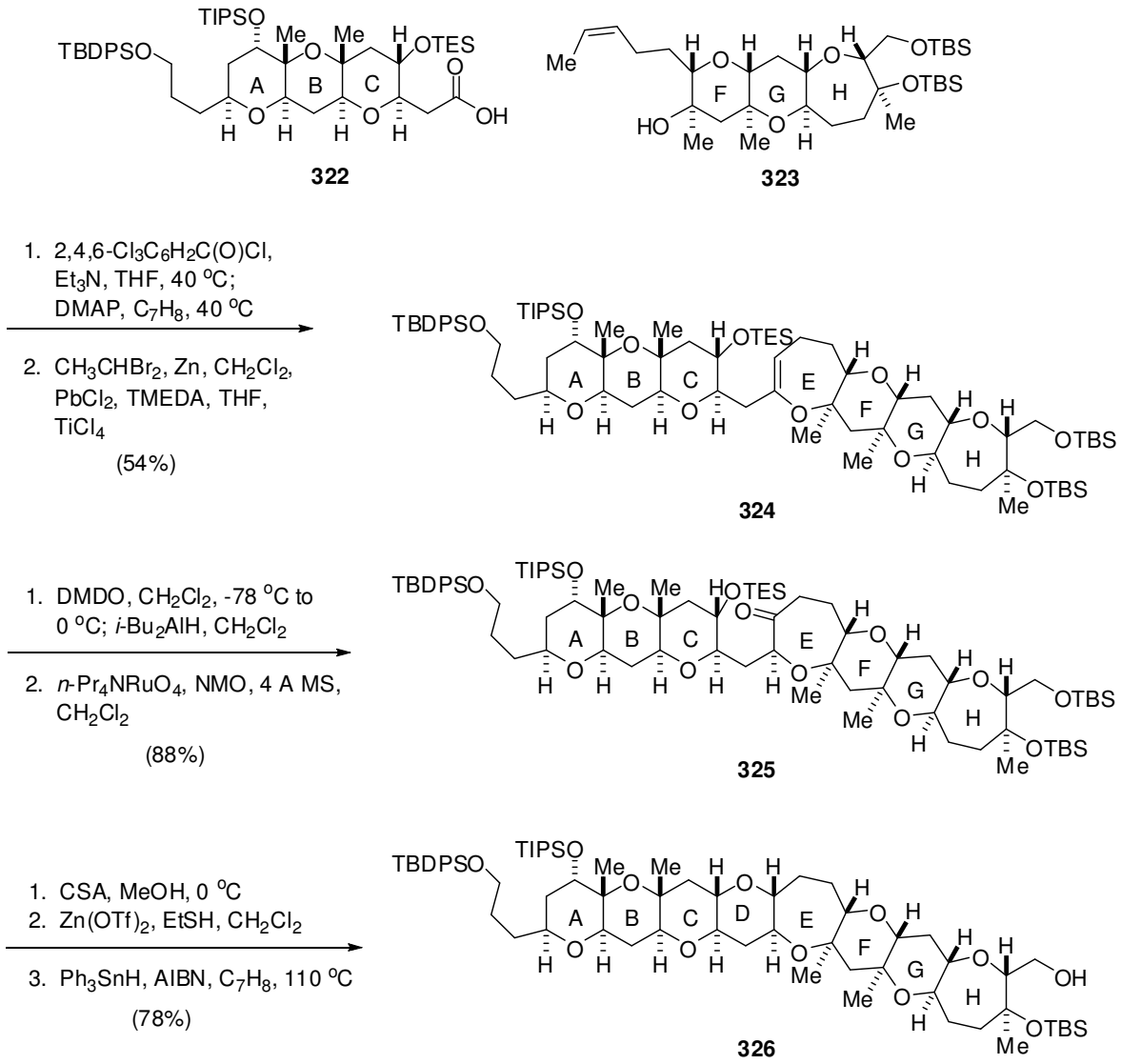
321

Scheme 68. Completion of the ABCDE Rings

alcohols on the B and D rings proceeded uneventfully. The triethylsilyl ethers were concomitantly cleaved under conditions used to form the dithioketal, and the alcohol spontaneously cyclized to form the mixed thioacetal.[280] Protection of the remaining secondary alcohol gave pentacycle **320**. Oxidation of sulfur and in situ alkylation of the resultant oxocarbenium ion provided polycycle **321** in 92% yield. All that remained was installation of the A and E ring sidechains, which was completed to achieve the first total synthesis of brevenal (**304**).[266,281]

4. [X + 2 + X] Strategy

The final convergent approach developed to date involves the coupling of two fragments and subsequent formation of two rings between the previously independent moieties. An example of this can also be found in the synthesis of gambierol (**305**) by Rainier.[282] After iterative formation of the ABC **322** and FGH **323** fragments,[268,269] the group sought to join the two fragments and complete the E ring, followed by formation of the D ring to complete the octacycle. To that end, acid **322** was esterified with alcohol **323** under Yamaguchi conditions (Scheme 69). Takai–Utimoto conditions were modified for direct formation of enol ether **324** from the ester in 60% yield.[283] With the E ring formed, attention was turned to installing the D ring to complete the octacyclic core. Epoxidation and in situ reduction of ketone **324** gave the alcohol, which was oxidized to provide ketone **325**. Deprotection, formation of the thioacetal,[280] and radical reduction completed the D ring, to give the framework **326** for gambierol (**305**). Eight more steps installed the side chains to complete the total synthesis of gambierol (**305**).



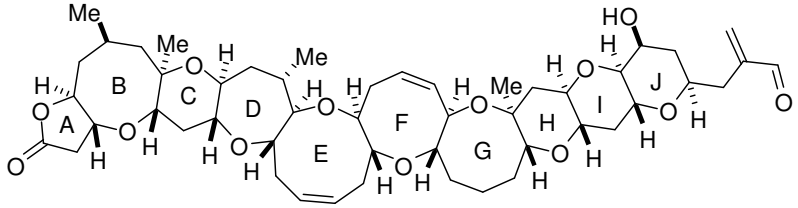
Scheme 69. Formation of the D and E Rings

C. Brevetoxin A

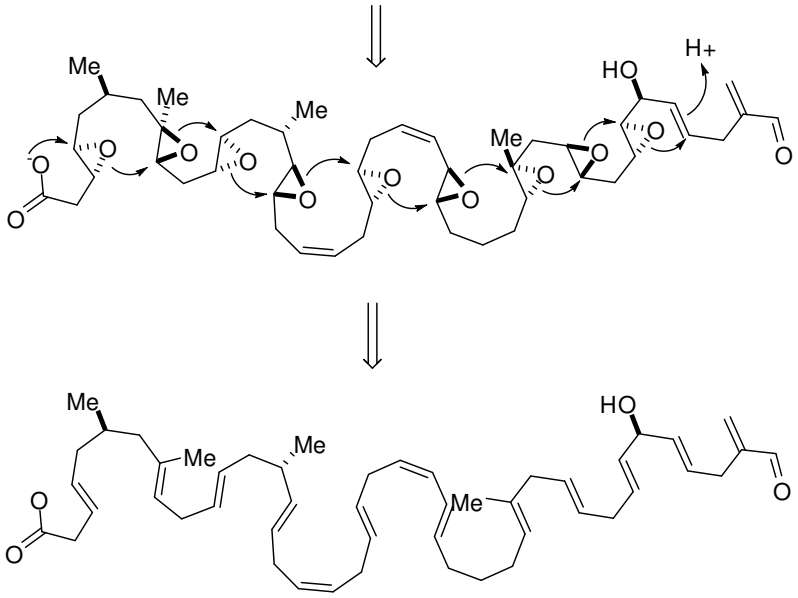
1. Characterization and Biological Activity

Brevetoxin A (**303**) was isolated in 1975 by Alam and co-workers from the dinoflagellate *Gymnodinium breve*.[284] This algal bloom has been implicated as the toxic component of the red tides in the Gulf of Mexico, causing massive fish kills.

The structure of brevetoxin A (**303**) was determined in 1986 via X-ray crystallographic analysis of its dimethyl ketal derivative.[285] The following year, extensive NMR and MS analyses were reported which corroborated the previous structural assignment.[286] Brevetoxin A (**303**) features a decacyclic structure with 22 stereocenters and four methyl substituents, two of which are angular. As with all ladder toxins, each ring is *trans*-fused. Interestingly, brevetoxin A (**303**) is the only



brevetoxin A (**303**)



Scheme 70. Biosynthetic Hypothesis for Brevetoxin A

polycyclic ether that possesses five-, six-, seven-, eight-, as well as nine-membered rings within the same molecule. The Nakanishi proposal for the biosynthesis of the ladder toxins is demonstrated below for the natural formation of brevetoxin A (**303**).[258] The decacycle is derived from a polyolefin via stereoselective

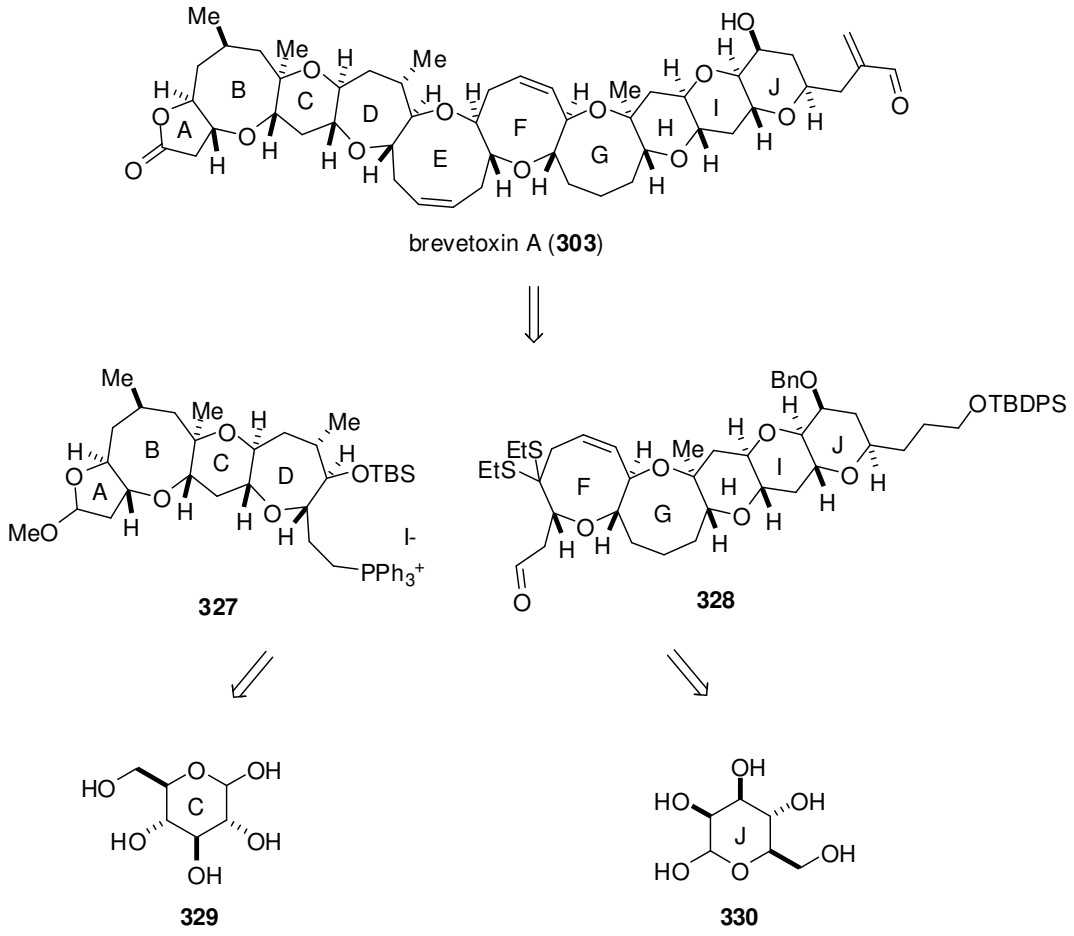
epoxidation of the nine *E*-olefins in the chain (Scheme 70). The polyepoxide is then opened in cascade fashion, initiated by cyclization of the five-membered lactone and concluding with protonation of the J ring.

In depth studies have been undertaken to elucidate the mode of action for brevetoxin A (**303**) within humans. The brevetoxins bind strongly with neurological sodium ion channels.[287] This binding causes the sodium channels to remain open, allowing a harmful influx of sodium ions. As a result, the parent organism is eventually asphyxiated, causing death. Based upon extensive calculations and binding studies with brevetoxin derivatives, the Baden laboratory has gained much insight into the binding of brevetoxin A (**303**) within the cell. Calculations have determined that two B ring conformers, five D ring conformers, three E ring conformers, and five G ring conformers are possible, giving a total of 48 possible conformations of the natural product within 6 kcal/mol of the global minimum.[288] Additionally, the F ring serves as a hinge point for the entire molecule, allowing the decacycle to fold nearly in half on itself. These calculations, as well as a number of synthetic manipulations on the natural material have elucidated which portions of brevetoxin A (**303**) are most crucial for binding. The sum of these results suggest that brevetoxin A (**303**) is a cigar-shaped molecule, about 30 Å in length, which binds primarily via hydrophobic and nonpolar solvation forces, potentially facilitated by hydrogen bond donors near the A ring lactone.[289] This greater understanding of the mode of action of the brevetoxins should prove useful in attempting to deal with this serious ecological concern.

2. Nicolaou's Total Synthesis of Brevetoxin A

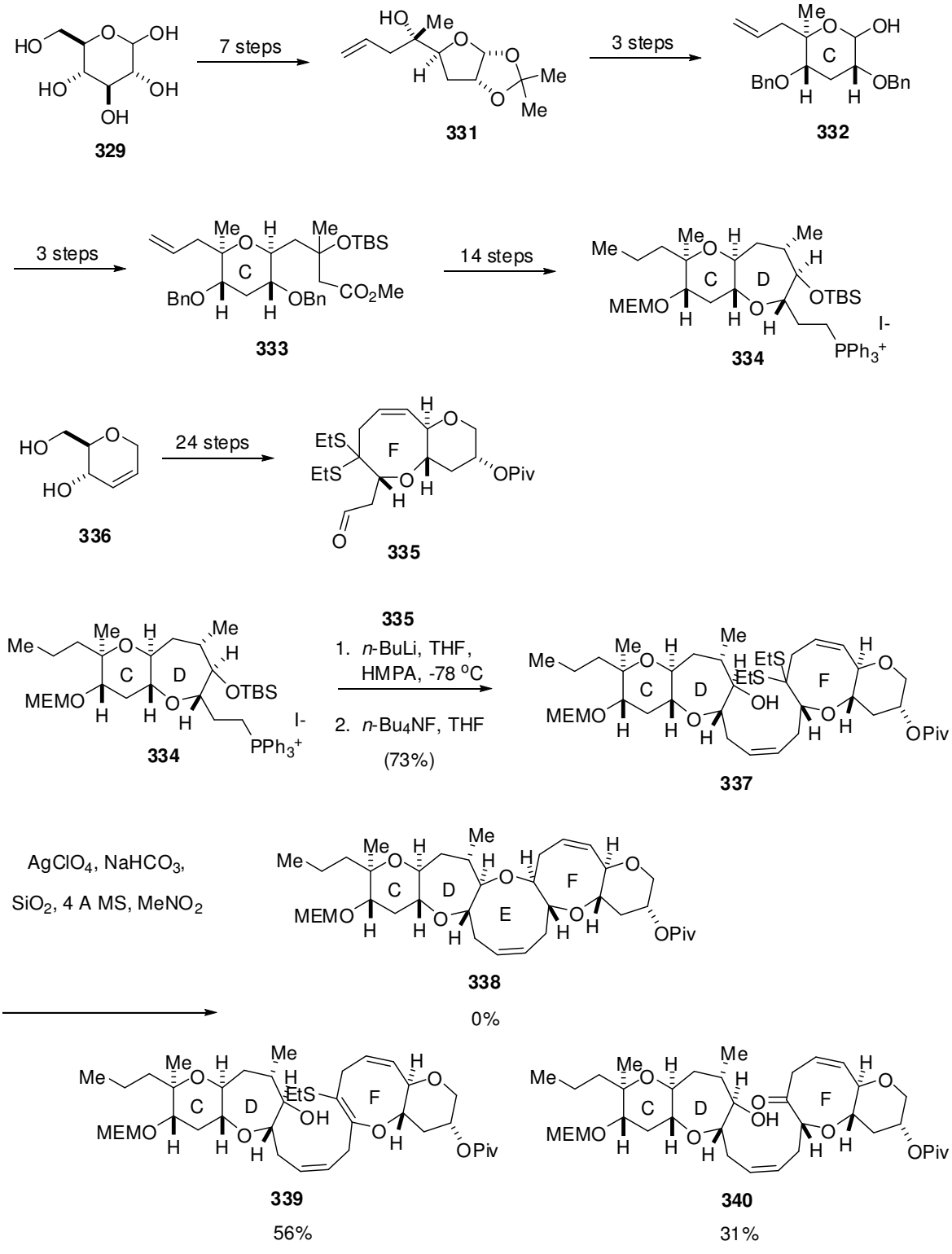
Naturally, the intriguing structure and biological properties of brevetoxin A (**303**) have sparked interest within the synthetic community. This molecule is clearly quite daunting, and some inherent question as to whether or not a molecule of this size and complexity could even be prepared via purely synthetic means existed from the outset. Undeterred, or possibly inspired by these challenges, the Nicolaou laboratory initiated a program targeting the brevetoxins in the 1980's. The group hoped to apply methods that they had developed specifically for the construction of oxygen-containing heterocycles to the total syntheses of the ladder toxins.

The Nicolaou group reported the total synthesis of the related undecacycle brevetoxin B in 1995,[145,290-295] and utilized a similar strategy for the preparation of brevetoxin A (**303**).[296-300] Strategically, the polycycle was envisioned to arise in a convergent [X + 1 + X] sense from the union of two fragments of similar complexity, the ABCD portion **327** and the FGHIJK fragment **328** (Scheme 71). The E ring was proposed to be formed via the coupling of these two fragments using a Wittig reaction and subsequent dithioketal cyclyization. For the ABCD fragment **327**, the B and D rings would be formed via a bis-lactonization of the C ring, derived from D-glucose (**329**). A late-stage lactonization would provide the A ring. The FGHIJ portion **328** would arise from a series of epoxide openings beginning with the J ring, derived from D-mannose (**330**), building the I and H rings in an iterative fashion. Wittig coupling and dithioketal cyclization would be exploited to establish the G and F rings.

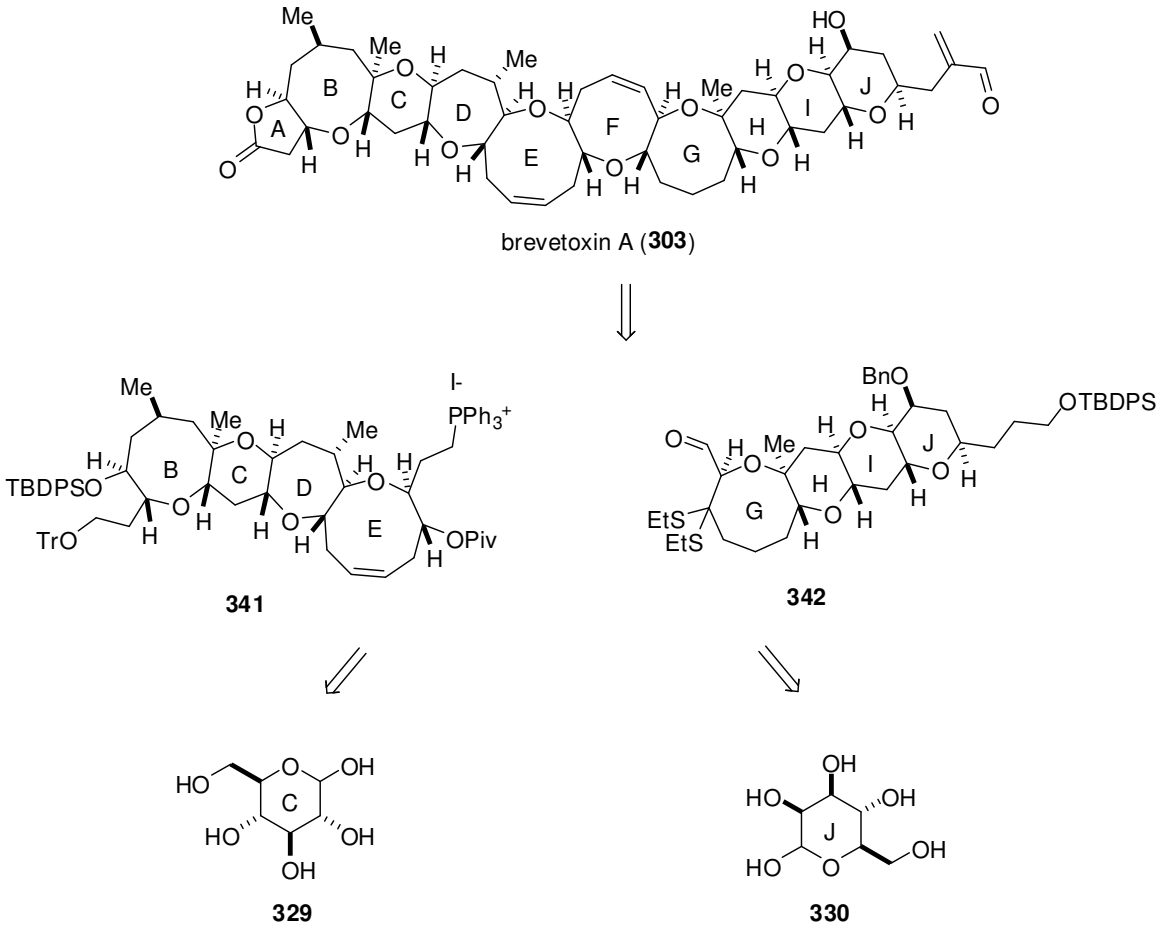


Scheme 71. Nicolaou's Retrosynthetic Analysis

To begin, tetrahydrofuran **331** was accessed in seven steps from D-glucose (**329**) via protection, oxygenations, deoxygenation, and alkylations (Scheme 72). Three steps delivered lactol **332**, which was converted in three steps to the C ring **333**. Fourteen steps were performed to prepare CD phosphonium salt **334**, to be used as a probe for the E ring formation. Similarly, F ring aldehyde **335** was synthesized in 24 steps from known diol **336**.[301] Union of fragments **334** and **335** was accomplished using a Wittig coupling to provide the diene in 82% yield. Deprotection provided the D ring alcohol **337**. However, upon subjecting the dithioketal **337** to the cyclization conditions developed in their laboratory, no E ring



Scheme 72. Attempted E Ring Formation Model

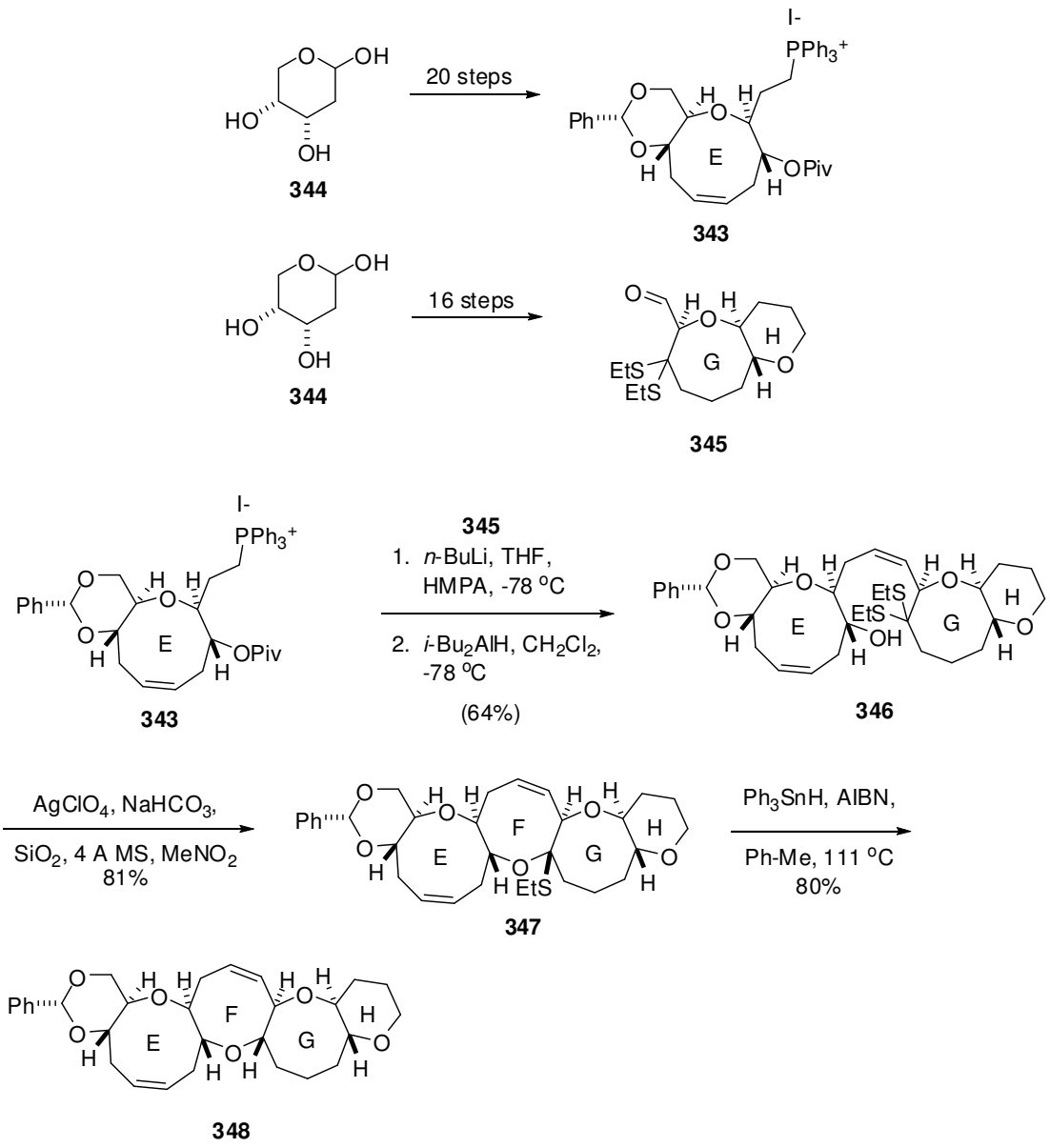


Scheme 73. Nicolaou's Revised Retrosynthesis

was formed.[280] Instead, elimination **339** and hydrolysis **340** products were isolated in 87% combined yield. Due to this setback, a new approach to brevetoxin A was envisioned that would involve formation of the F ring as the point of convergence (Scheme 73). It was thought that the smaller size of the F ring, an oxocene compared to the E ring oxonene, would facilitate the dithioketal cyclization. To that end, BCDE phosphonium salt **341** was targeted along with GHIJ aldehyde **342**.

To model the revised coupling strategy, E ring **343** was prepared in 20 steps from 2-deoxy-D-ribose (**344**, Scheme 74). Analogously, 16 steps delivered GH

aldehyde **345** from 2-deoxy-D-ribose (**344**). Again, Wittig coupling was effective in joining the two fragments and gave the diene in 77% yield. Deprotection provided a candidate for cyclization **346**, and this time, the conditions developed within the Nicolaou laboratory were effective for giving pentacycle **347**.[280] Radical reduction of



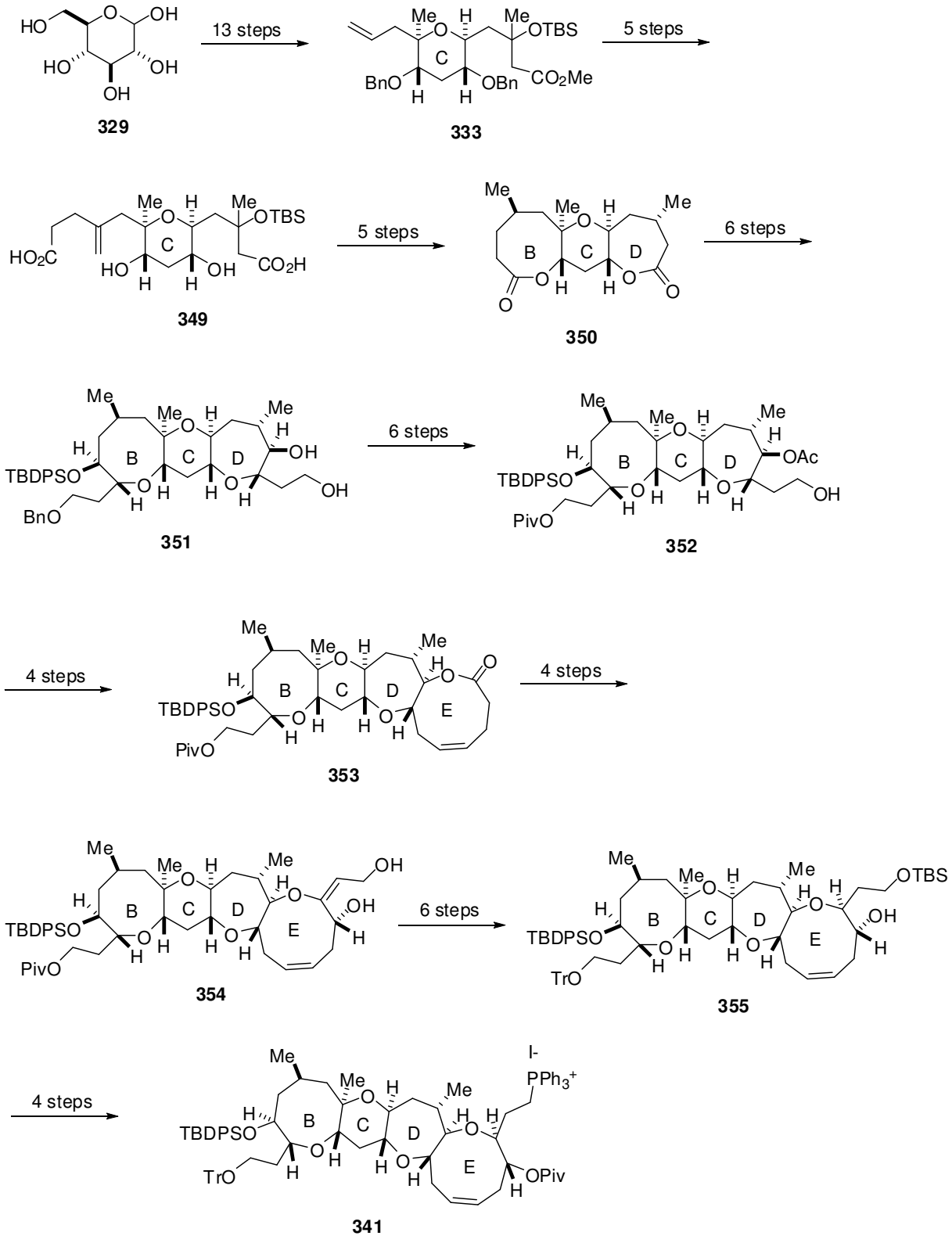
344 **343** **344** **345** **343** **346** **347** **348**

Scheme 74. Model of F Ring Formation

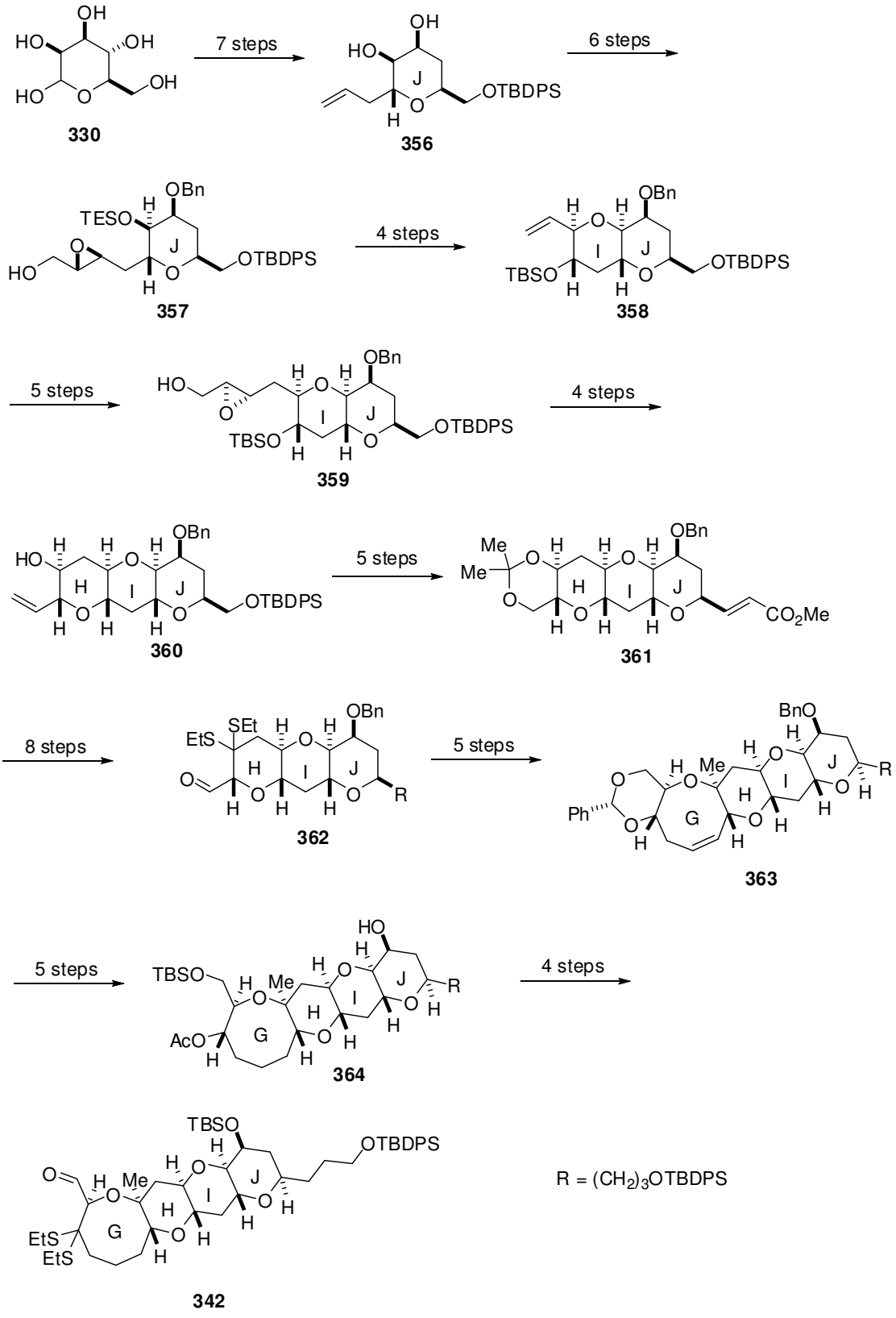
the mixed thioacetal delivered the EFGH fragment **348** in 80% yield as a single diastereomer.

With confidence in the main disconnection point chosen for brevetoxin A (**303**), the group set out to prepare BCDE fragment **341** and GHIJ aldehyde **342** to complete their total synthesis. Previously described C ring **333** was converted in five steps to diacid **349** (Scheme 75). A bis-lactonization closed the B and D rings and four more steps gave dilactone **350**. Six further steps were exploited to vary the oxidation states of the B and D rings and deliver triol **351**. Protecting group manipulations proceeded for the subsequent six steps to give alcohol **352**, and the lactone was formed to close the E ring and give access in four steps to lactone **353**. Four steps were utilized to prepared diene **354**, and alcohol **355** was accessed in six additional steps. Finally, the targeted phosphonium salt **341** was realized in four steps from alcohol **355**.

For the GHIJ aldehyde **342**, seven previously elucidated steps gave access to alkene **356** from D-mannose (**330**, Scheme 76).[293] Six further transformations delivered epoxide **357**, which was altered in four additional steps to give alkene **358**. Epoxide **359** was arrived upon in five steps from alkene **358**, and four more steps gave alkene **360** with the H ring in tact. Five manipulations gave acetonide **361**, and eight further steps provided the aldehyde **362**. The G ring was formed via a dithioketal cyclization and four additional steps to provide pentacycle **363**. Five steps delivered alcohol **364**, and four more transformations delivered targeted aldehyde **342**.



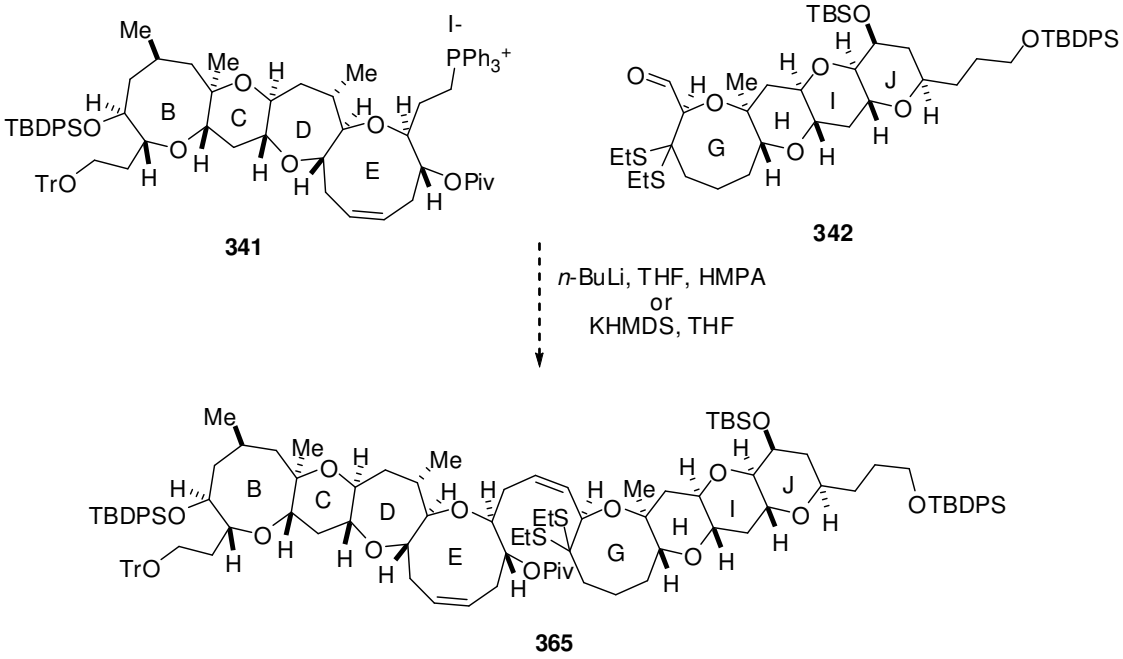
Scheme 75. BCDE Phosphonium Salt Synthesis



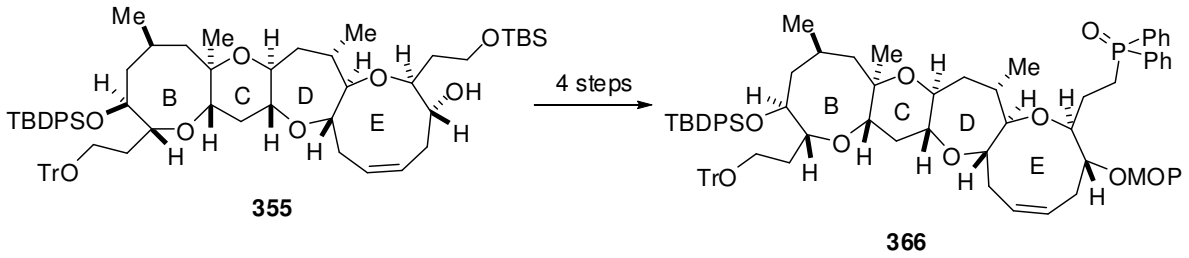
330 **356** **357** **358** **359** **360** **361** **362** **363** **364** **342**

Scheme 76. GHIJ Aldehyde Synthesis

With each of the desired coupling partners in hand, attention was turned to the union of these units and formation of the F ring. Unfortunately, unlike in the model system (Scheme 74), the Wittig reaction was unsuccessful in delivering the desired olefinic product **365** (Scheme 77). The methyl substituent of the GH ring juncture was implicated as the culprit, as it had been omitted in the successful model system (Scheme 74). The steric interactions of the ylide of phosphonium salt **341** and the aldehyde **342** precluded productive olefination. As a result, a less bulky ylide was targeted, and alcohol **355** was transformed into phosphine oxide **366** in four steps (Scheme 78). It was predicted via extensive modeling that a small, chelating protecing group, in this case methoxypropyl, would be necessary to obtain good *Z* selectivity for the olefination.

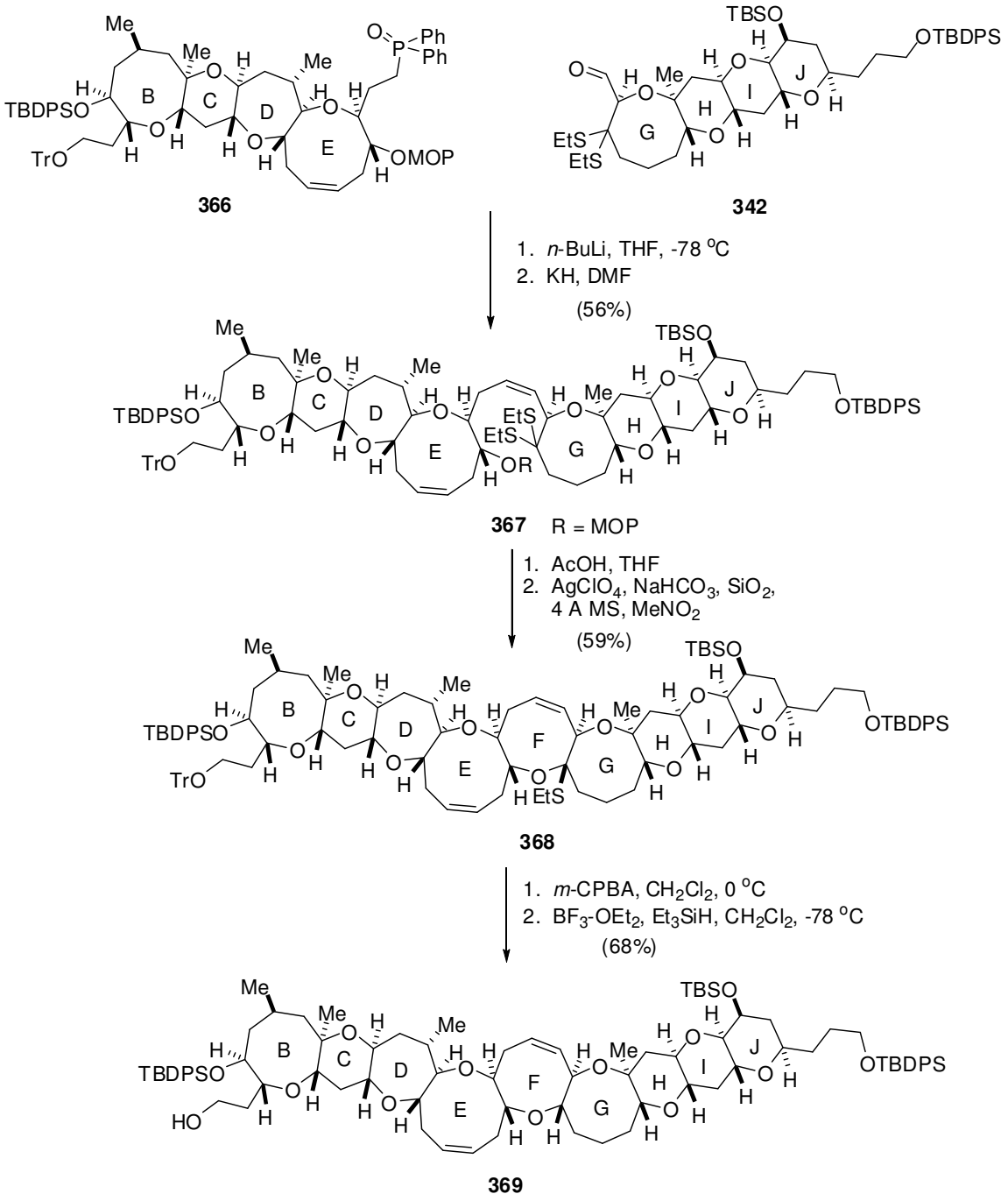


Scheme 77. Attempted Wittig Coupling

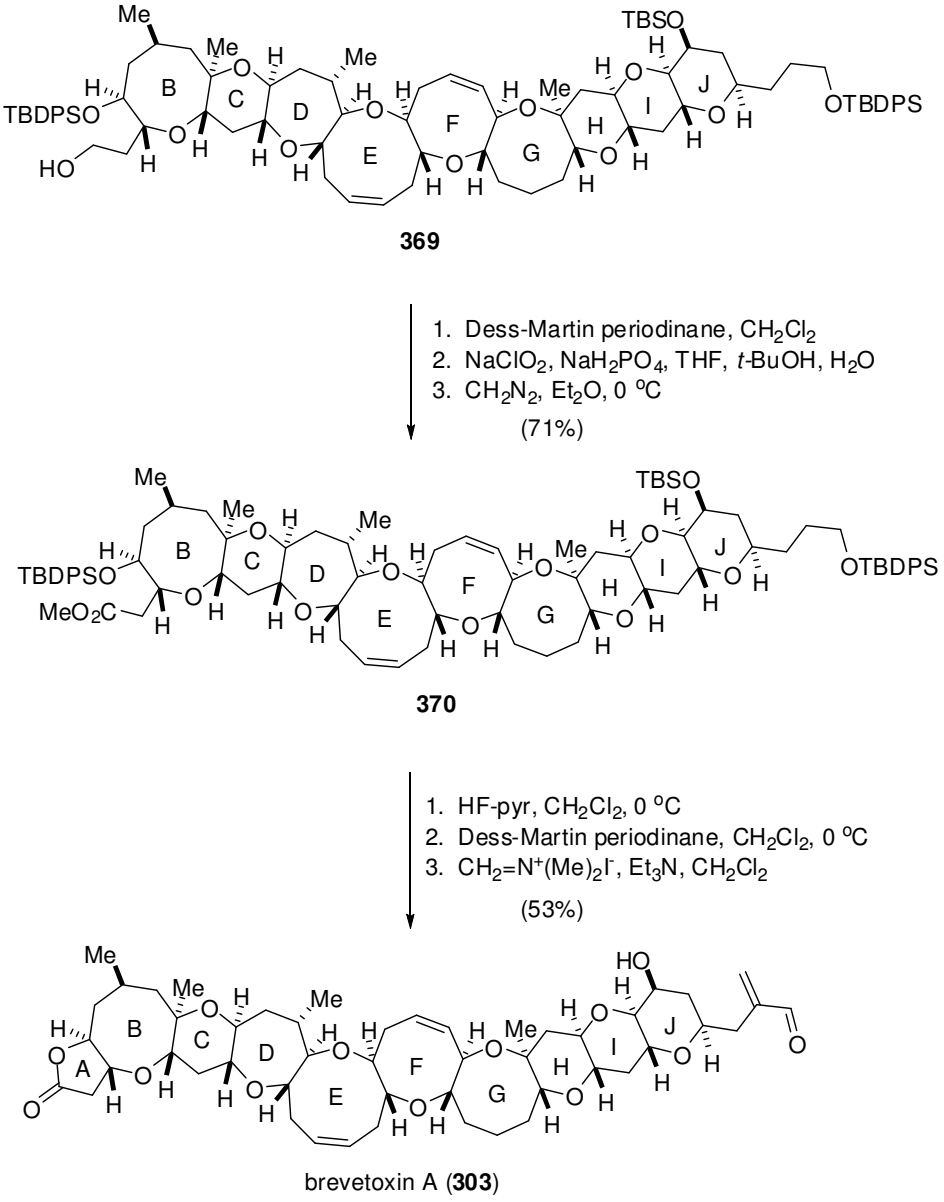


Scheme 78. Phosphine Oxide Formation

A Horner–Wittig coupling was employed to join the BCDE phosphine oxide **366** and GHIJ aldehyde **342** (Scheme 79). Base-induced elimination of the resultant adduct provided diene **367** in 56% yield over the two steps. Mild acidic conditions were useful in cleaving the ketal protecting group, and subjection to Nicolaou's hydroxyl dithioketal cyclization conditions resulted in formation of mixed thioacetal **368**.[280] Earlier investigations had revealed that radical reduction was not useful in removing the thioether, so a two-step oxidation and reduction protocol was exploited to deliver the fully functionalized F ring **369**. With the BCDEFGHIJ portion of brevetoxin A (**303**) constructed, formation of the A ring and the J ring sidechain were next targeted. The trityl protecting group had been cleaved during the reduction of the mixed thioacetal, so the primary alcohol was oxidized to the aldehyde[43] and then the acid, followed by formation of the methyl ester **370** (Scheme 80). Acidic removal of the silyl protecting groups also resulted in lactonization of the A ring. Careful oxidation of the primary alcohol on the J ring was carried out in the presence of the secondary alcohol,[43] and the resultant aldehyde was treated with Eschenmoser's salt to provide brevetoxin A (**303**),[302] which was identical in all regards to the natural material.[284]



Scheme 79. Formation of the BCDEFGHIJ Portion



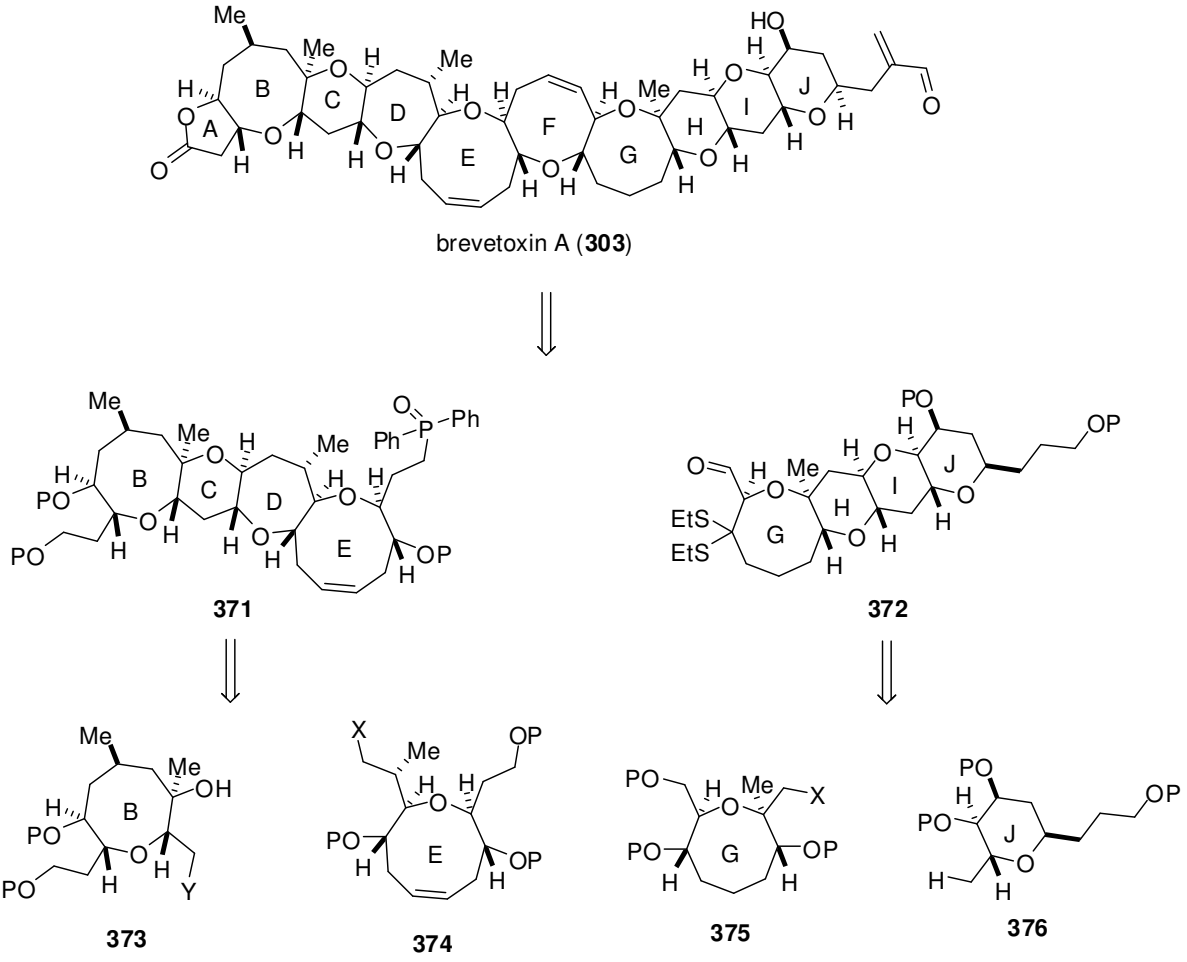
Scheme 80. Completion of Brevetoxin A

D. Previous Work in the Crimmins Laboratory Toward Brevetoxin A

1. Seminal Efforts Toward the BCDE Fragment

In 2000, the Crimmins laboratory began investigating the syntheses of the B and E rings of brevetoxin A (**303**). The original intent was to probe the efficiency with which the glycolate alkylation/ring-closing metathesis strategy would allow

access to subunits of the ladder toxins. In time, it was decided to pursue a total synthesis of this complex natural product. An [X + 1 + X] strategy highly analogous to the Nicolaou laboratory's endgame would be exploited to form the F ring (Scheme 81). This completion strategy was selected for at least two reasons; first, it divides the molecule into two fragments of very similar complexity, and second, the final steps worked out by the Nicolaou group have been demonstrated to be highly



Scheme 81. Retrosynthetic Analysis of Brevetoxin A

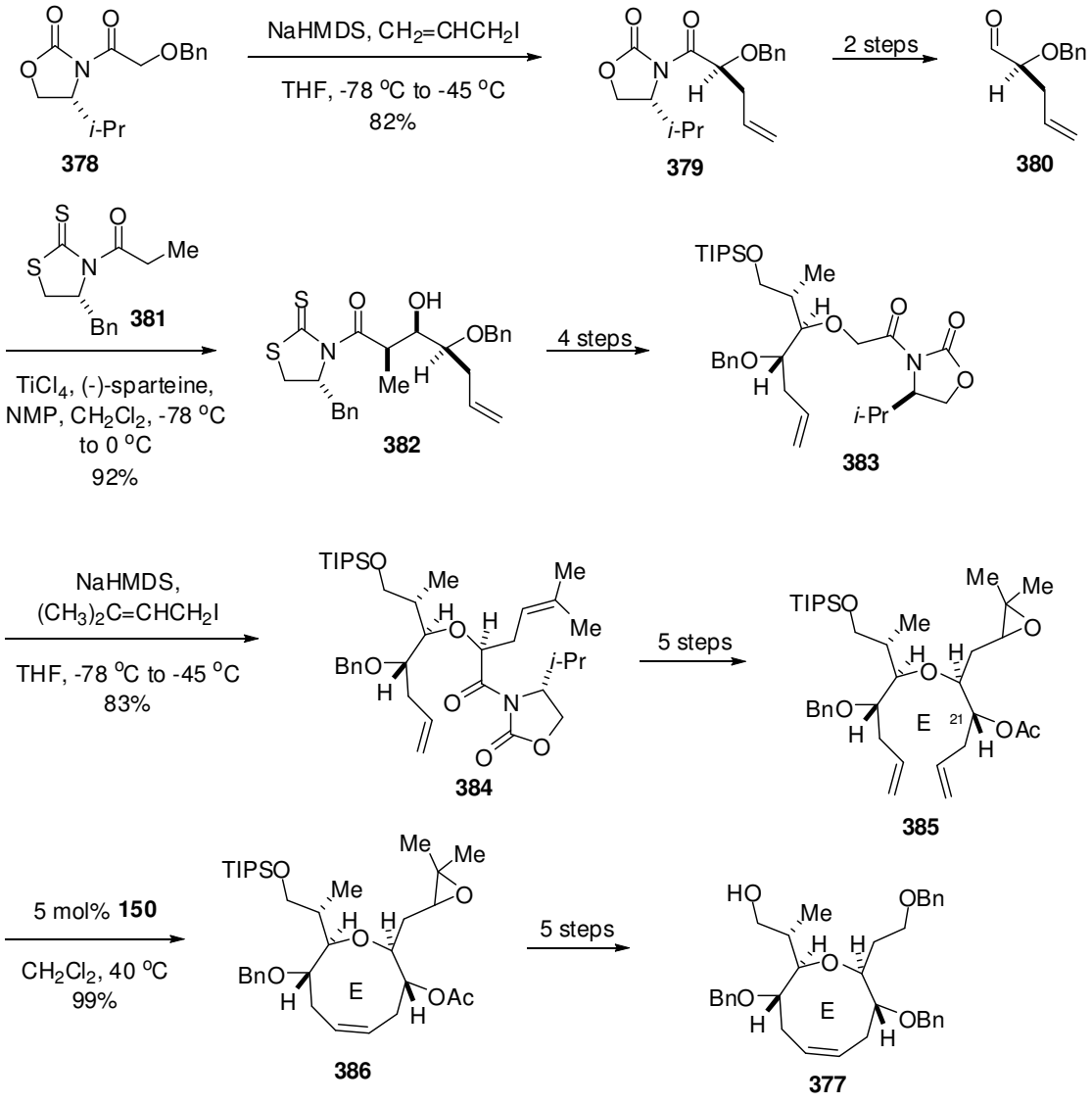
efficient.[300] The required BCDE **371** and GHIJ **372** fragments would arise from a novel, convergent [X + 2 + X] strategy to form the CD and HI rings from their

respective peripheral rings. The overall strategy hinged upon initial formation of the B **373**, E **374**, G **375**, and J **376** rings via methods developed in our laboratory.

Dr. Kyle A. Emmitte initiated these efforts, developing a 20 step approach to oxonene **377**, as well as providing seminal results for the B ring synthesis. Following these findings, Dr. Patrick J. McDougall took on the task of improving routes to modified B and E rings, and developing a convergent [X + 2 + X] coupling strategy for the synthesis of the BCDE portion.[244] For the E ring, Dr. Emmitte utilized a glycolate alkylation to initiate the synthesis (Scheme 82).[208] Two steps transformed alkylation adduct **379** into aldehyde **380**, which was used in a thiazolidinethione propionate aldol reaction to give alcohol **382**.[215] Four further transformations provided glycolate **383**, which was alkylated with prenyl iodide to yield alkene **384**. Five further steps, including an asymmetric Brown allylation to set the C21 stereocenter,[303] delivered diene **385**, which was efficiently closed using the Grubbs catalyst **150** to provide oxonene **386**.[195,201] Five steps gave E ring **377**, which could be utilized in a coupling reaction with the B ring.

Dr. McDougall next developed two possible pathways to form the E ring of brevetoxin A (**303**). The second route to the E ring was predicated upon the *anti*-glycolate aldol methodology that Dr. McDougall had previously developed in the Crimmins laboratory (Scheme 83).[304] Using glycolic acid **387** from the previous E ring route, oxazolidinethione glycolate **388** was prepared and subjected to the optimized conditions for *anti*-aldol reaction with 3-butenal. This approach led to an E ring β-keto phosphonate **390**, which proved useful in a Horner–Wadsworth–Emmons reaction to couple to the B ring.[305,306] However, diene **390** was a truncated version

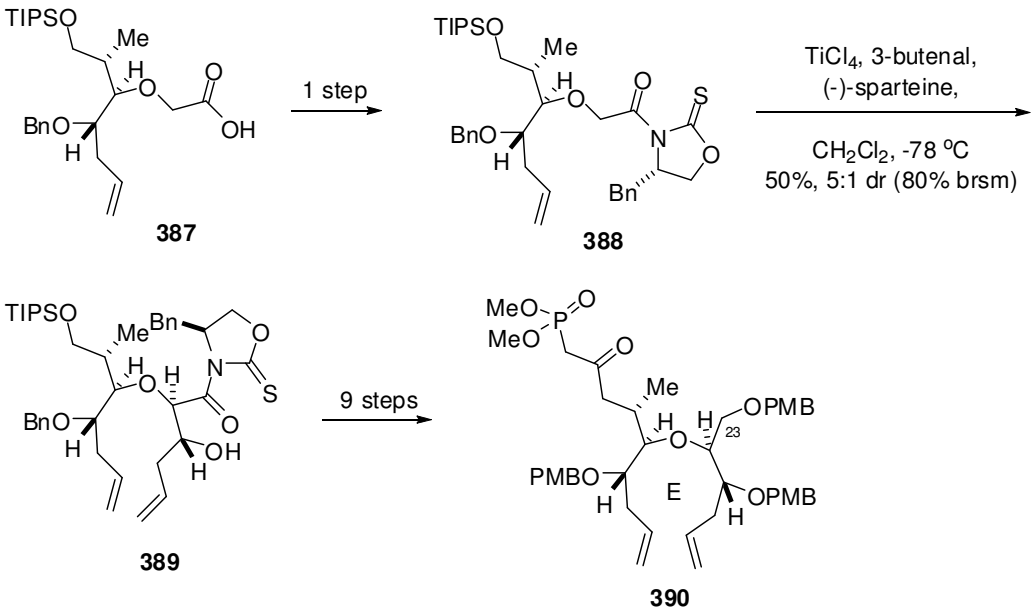
of the E ring, missing C24. It was determined that a homologated version of the E ring would be more amenable to the desired [X + 1 + X] convergent coupling strategy for the F ring formation. To that end, glycolate **391**, differing from previously



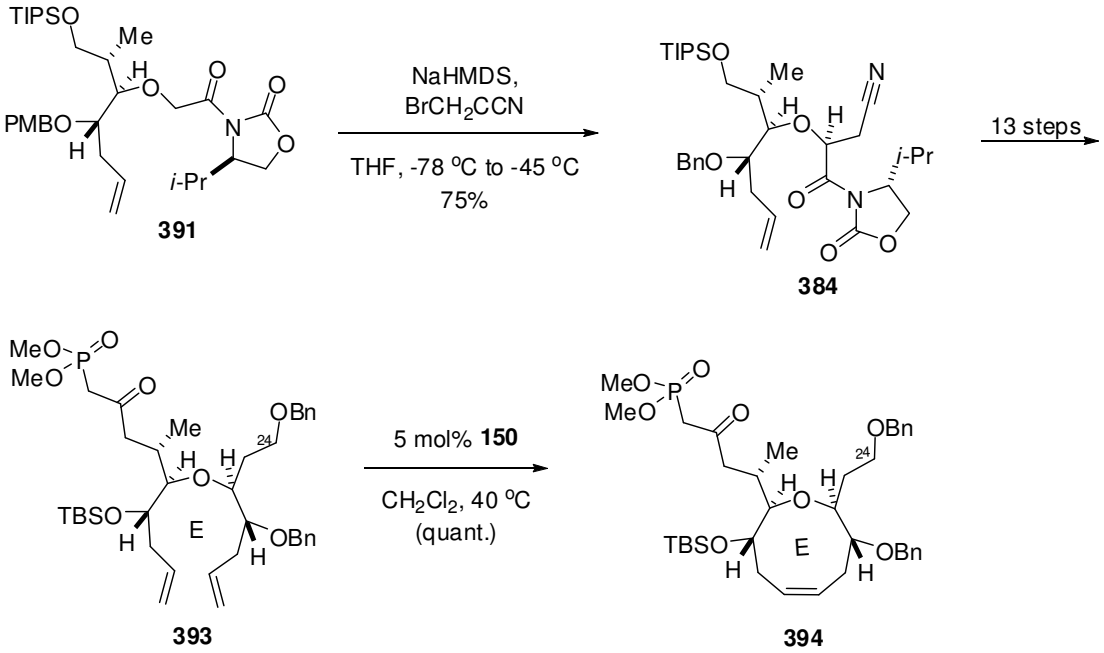
Scheme 82. Dr. Emmitte's E Ring Synthesis

prepared glycolate **383** only in the protecting group for the C16 hydroxyl moiety, was alkylated with bromoacetonitrile to afford nitrile **384** (Scheme 84). Thirteen steps provided diene **393**, prepared for ring-closing metathesis.[195,201] In the event, the

oxonene was formed, delivering phosphonate **394**. Both diene **389** and oxonene **394** were utilized for a convergent coupling with the B ring to form variants of the BCDE portion of brevetoxin A (**303**, vide infra).

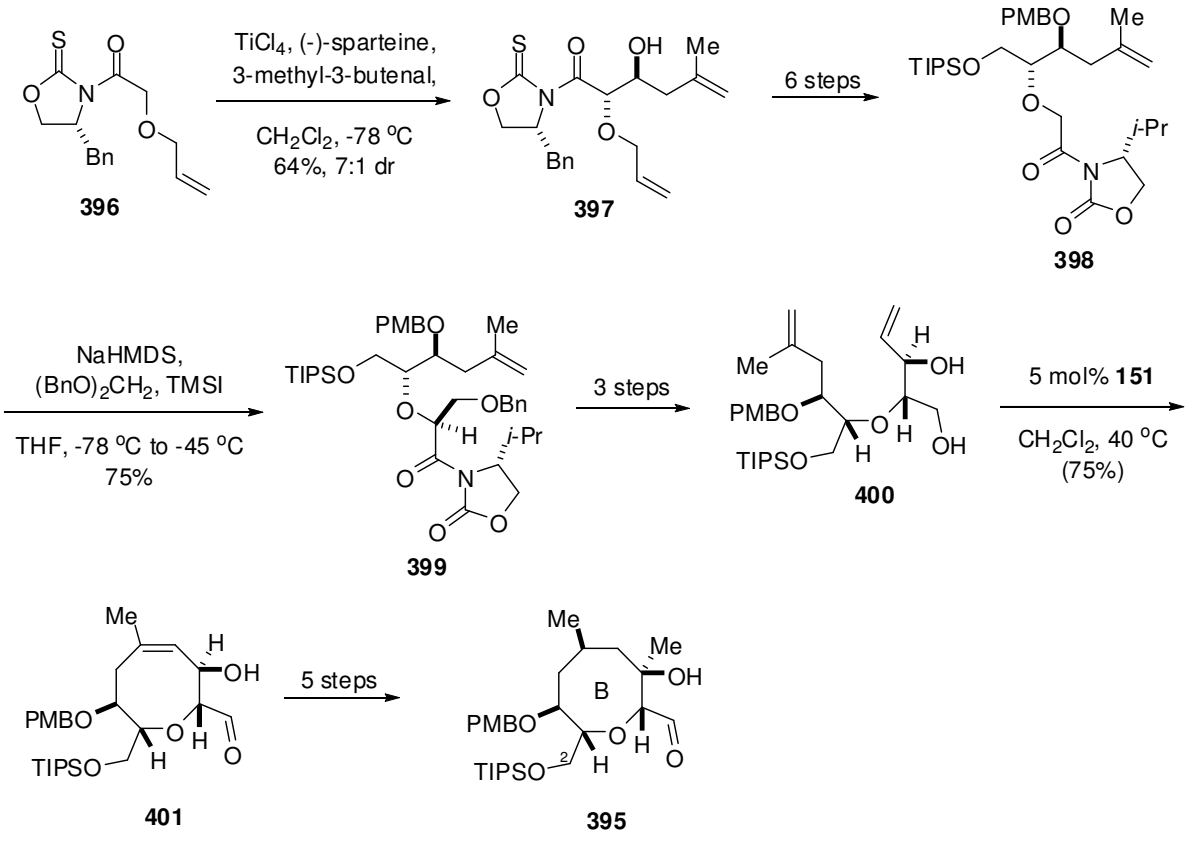


Scheme 83. Dr. McDougall's First Generation E Ring Synthesis



Scheme 84. Dr. McDougall's Second Generation E Ring Synthesis

For the B ring, Dr. McDougall built upon initial results obtained by Dr. Emmitte to develop an efficient strategy for oxocane **395** (Scheme 85). The approach commenced with an *anti*-glycolate aldol reaction of thioimide **396** with 3-methyl-3-butenal. Six steps provided glycolate **398**, a candidate for an asymmetric alkylation. Treatment of the sodium enolate of glycolate **398** with benzyl iodomethyl ether prepared in situ gave adduct **399**. Three steps delivered diene **400**, which upon treatment with the Grubbs second generation catalyst **151** yielded oxocene **401**.[172] Five further transformations led to B ring oxocane **395**, prepared for Horner–Wadsworth–Emmons coupling.



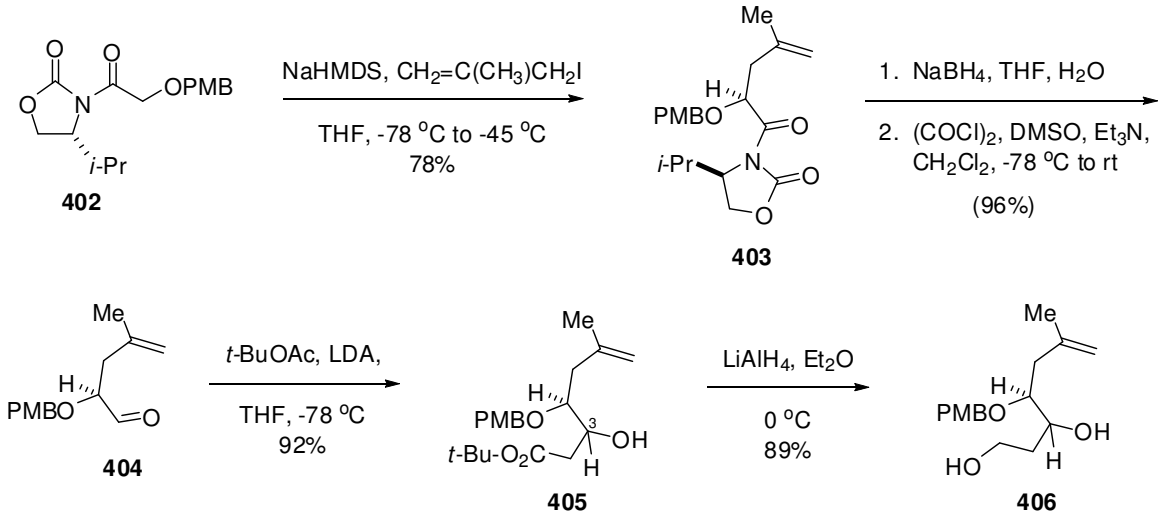
Scheme 85. Dr. McDougall's B Ring Synthesis

E. Prepartion of the BCDE and GHIJ Fragments

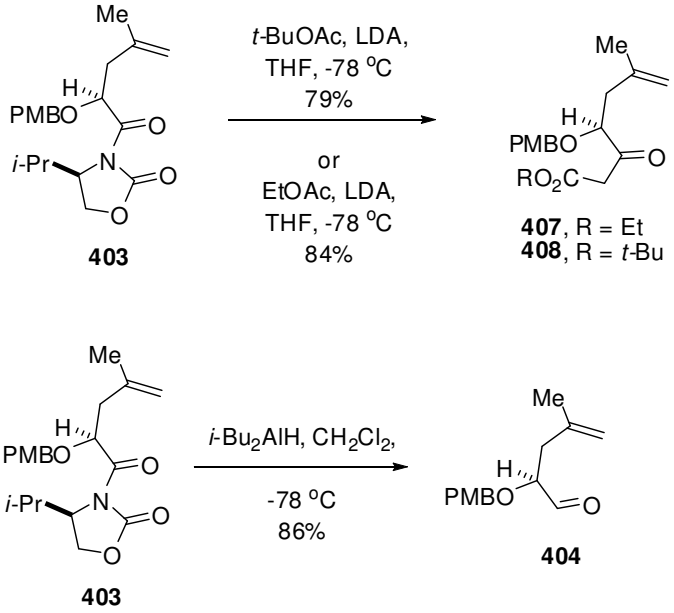
1. A Revised Route to a Homologated B Ring

The aforementioned B ring **395** was also truncated by one carbon (analogous to E ring **390**). Upon joining the effort toward brevetoxin A (**303**), my initial task was to develop an efficient, revised route to a homologated B ring, including C1, based upon Dr. McDougall's efforts. It was chosen to incorporate C1 at an early stage, essentially intercepting the previous route for the majority of the synthesis. To that end, a one-carbon homologated variant of glycolate **398** was targeted. A glycolate alkylation strategy was selected to replace the *anti*-glycolate aldol reaction used to initiate the previous route (Scheme 85). Alkylation of glycolate **402** with methallyl iodide provided the desired adduct in 78% yield (Scheme 86).[208] Reduction and oxidation[130] delivered aldehyde **404**, which was utilized in an aldol reaction with *t*-butyl acetate to give alcohol **405** as a mixture of C3 epimers. Reduction was accomplished using lithium aluminum hydride to provide diol **406**. In an effort to shorten the synthesis of diol **406**, and further examine the versatility of glycolate alkylation adducts, we investigated other useful transformations using imide **403**. After some optimization, it was found that very efficient Claisen condensation was possible using the lithium enolate of *t*-butyl acetate or ethyl acetate and imide **403** to yield β-keto ester **408** or **411** (Scheme 87). Additionally, it was discovered that *i*-Bu_2AlH reduction of alkylation adduct **403** allowed for direct access to aldehyde **404**. We propose that these manipulations are facilitated by the inductive effect of the ether oxygen, which increases the electrophilicity of the adjacent carbonyl. Since this discovery, these reactions have found use in other settings within our laboratory. The most direct route to the B ring involved use of β-keto ester **407**. Reduction

provided diol **406**, this time in three steps from glycolate **402** as opposed to the previous five step route (Scheme 88).



Scheme 86. Homologated Diol Synthesis

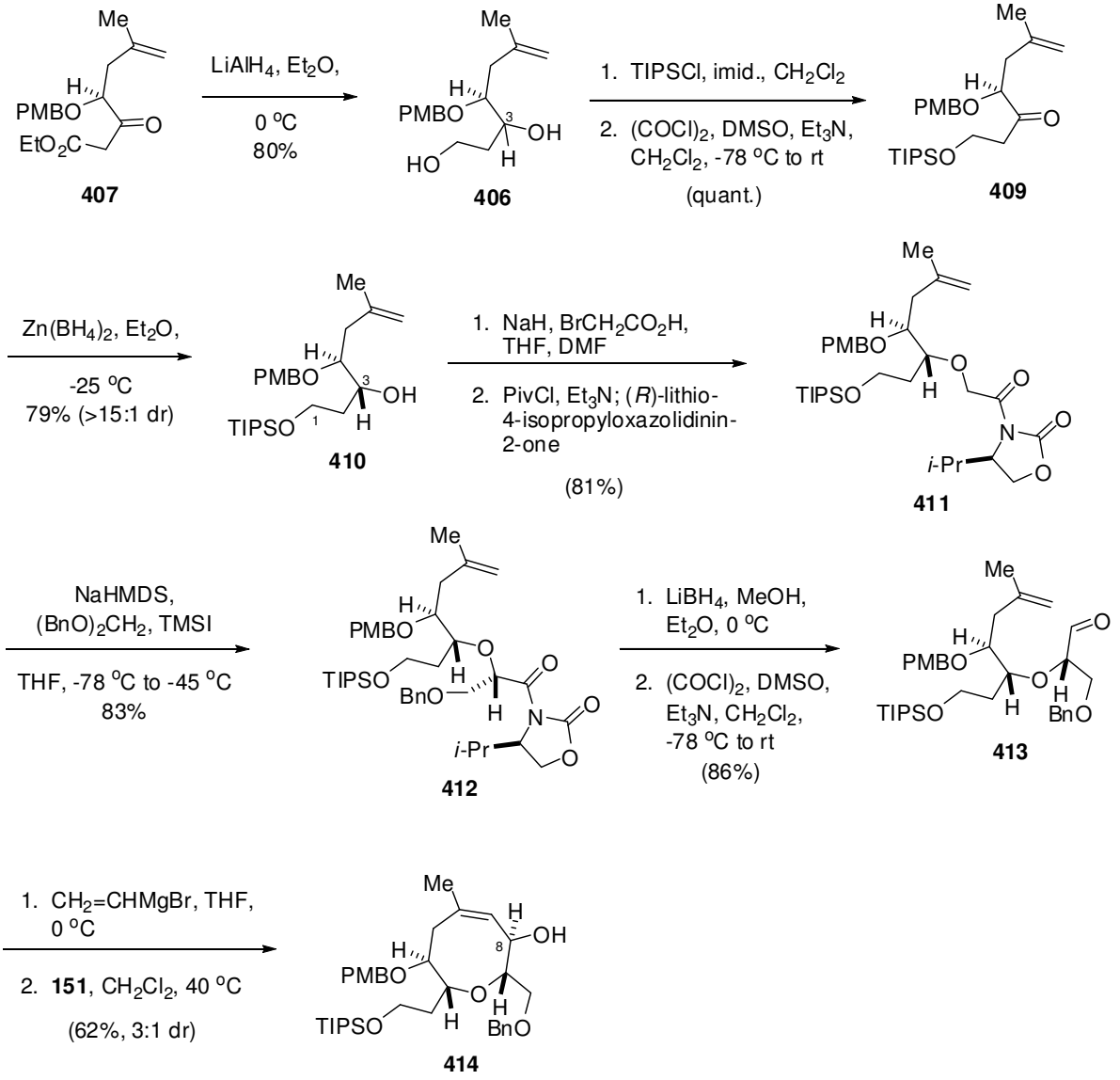


Scheme 87. Novel Glycolate Transformations

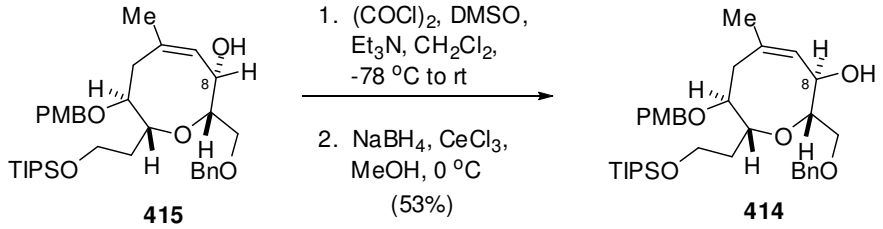
Selective protection of the primary alcohol of diol **406** was followed by oxidation to give ketone **409** (Scheme 88).[130] Chelation-controlled reduction

provided alcohol **410** in 79% yield (>15:1 dr).[307] It was not possible to effect direct diastereoselective reduction on β-keto ester **407**, likely due to favored formation of the zinc enolate. Alcohol **410** represents a one-carbon homologated variant of an intermediate from the previous B ring route. Formation of the glycolic acid and corresponding acylation to realize glycolate **411** proceeded uneventfully. Alkylation with benzyl iodomethyl ether afforded alkene **412**.[208] Reduction and oxidation served to deliver aldehyde **413**.[130] Direct reduction to the aldehyde was not possible in this case, presumably due to either the increased steric demand of the alkylation adduct or counterproductive participation of the benzyl ether oxygen. Vinyl Grignard addition gave a 3:1 inseparable mixture of diastereomers, favoring the desired C8 configuration. Although this center would later be oxidized, the configuration of the C8 alcohol had previously been demonstrated to be crucial for the impending hydrogenation to establish the C6 stereocenter. Ring-closing metathesis delivered oxocenes **414** and **415**. At this point, the C8 epimers were separable, and the minor diastereomer **415** could be recycled via a Swern oxidation[130] and Luche reduction (Scheme 89).[49]

With the oxocene in hand, the merged material was subjected to hydrogenation with Crabtree's catalyst at low temperature (Scheme 90).[308] Since hydrogenations of allylic alcohols with Crabtree's catalyst often proceed via direction from the hydroxyl group, it may appear counterintuitive that the C6 methyl and the C8 hydroxyl are *cis* to one another. However, there are examples of cyclopropanations and epoxidations of cyclooctenes proceeding to provide the

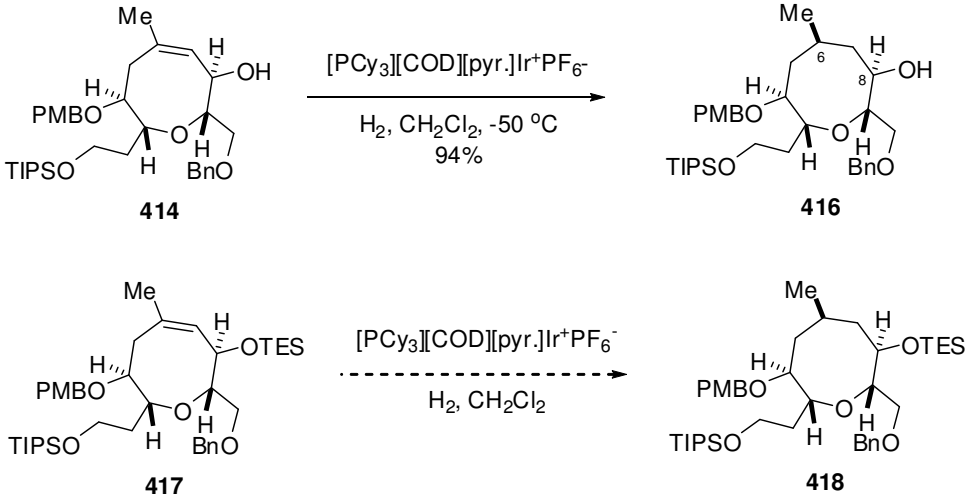


Scheme 88. Oxocene Synthesis



Scheme 89. Recycling the C8 Epimer

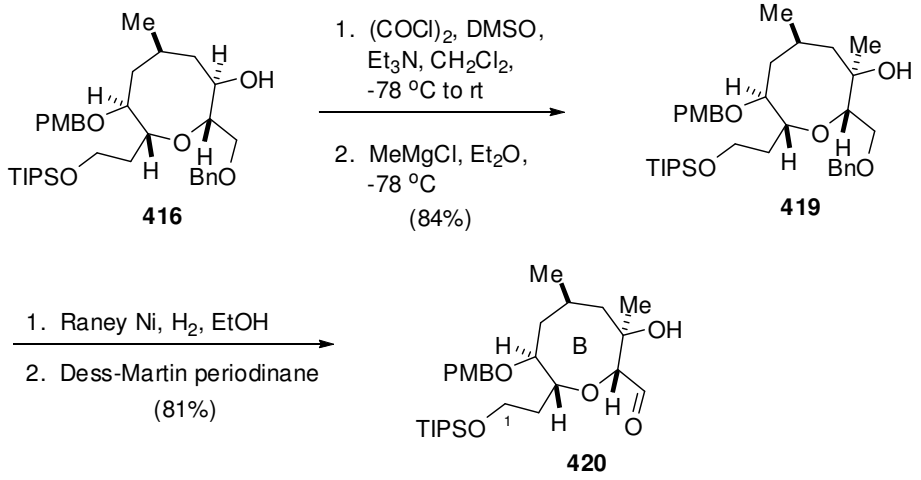
newly-formed ring *trans* to the alcohol.[309] As a probe of the role of the C8 oxygen, alcohol **414** was protected as a silyl ether and subjected to Crabtree's hydrogenation. In the event, no reaction was observed, even after several hours at ambient temperature. Whether responsible for a conformational or directing effect, the C8 hydroxyl is clearly important in this transformation. Oxidation[130] provided a ketone, which delivered a single diastereomer of tertiary alcohol **419** upon alkylation with methylmagnesium chloride (Scheme 91). Selective cleavage of the benzyl ether could be accomplished using lithium di-*t*-butylbiphenylide reduction or Raney nickel hydrogenation,[310] with the latter proving more amenable to larger scale. Dess–Martin oxidation provided aldehyde **420**,[43] a one-carbon homologated variant of aldehyde **395**. Aldehyde **420** was prepared in 18 steps and 9.8% overall yield,



Scheme 90. Diastereoselective Hydrogenation

compared to 17 steps and 8.8% overall yield for aldehyde **395**. Highlights of this route include the discovery of novel reactivity for glycolate alkylation adducts, use of the more economical Swern oxidation[130] in place of Dess–Martin periodinane at two

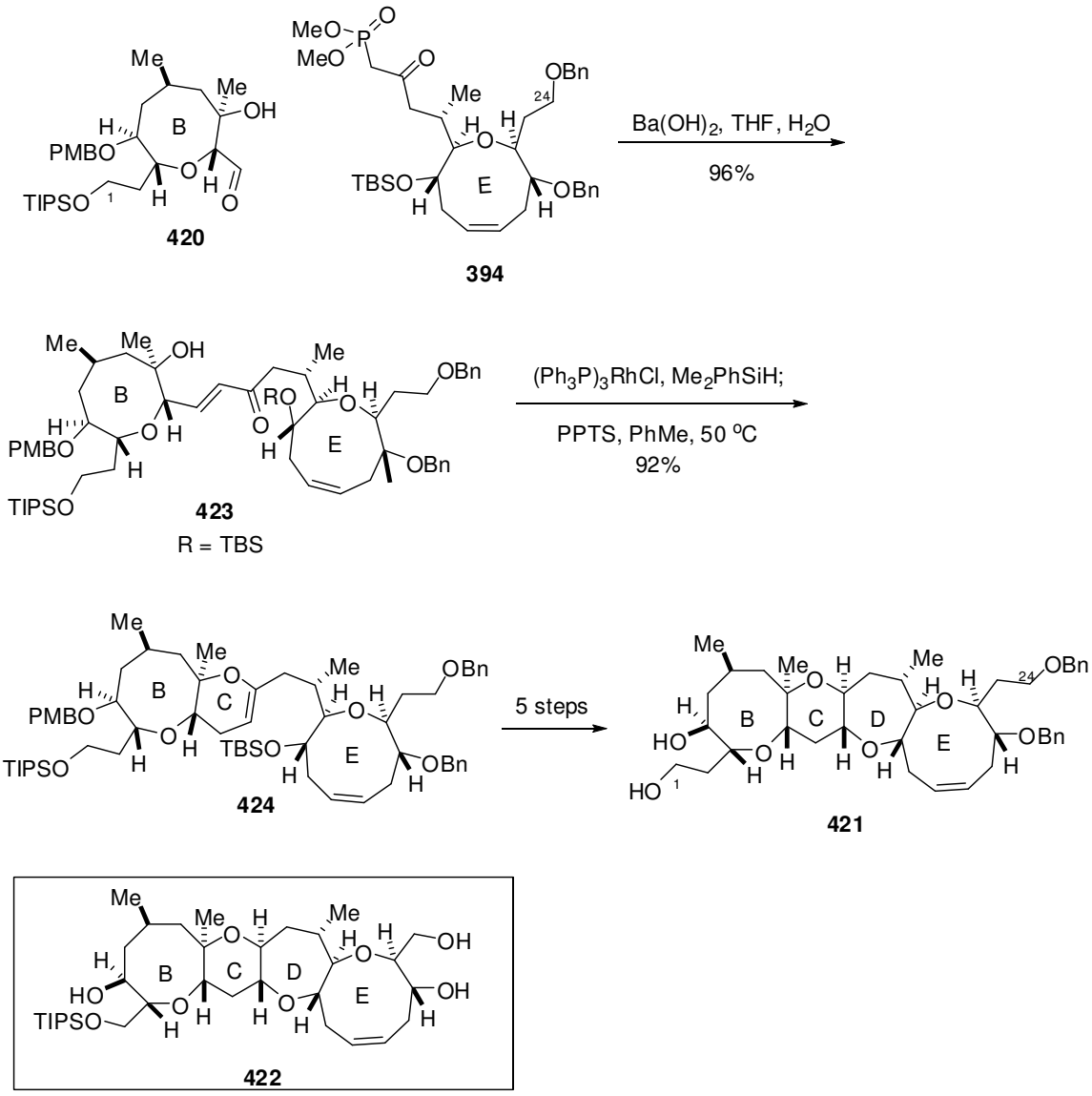
points,[43] and more practical conditions for removal of the benzyl ether on large scale.[310] The practicality and efficiency of this route is underscored by the preparation of 3.8 grams (7.2 mmol) of the B ring **420** in a single pass.



Scheme 91. Completion of the Homologated B Ring

2. Formation of the BCDE Fragment

After preparing multigram quantities of B ring aldehyde **420**, this material was passed on to Dr. Patrick J. McDougall, who progressed the B ring aldehyde **420** and the E ring phosphonate **394** to BCDE fragment **421**. The route utilized was based upon previous success forming BCDE fragment **422** in eleven steps from truncated B ring **395** and truncated E ring **390**. The homologated cyclic ethers **420** and **394** were joined via a Horner–Wadsworth–Emmons olefination using aqueous barium hydroxide (Scheme 92).[305,306] Cyclodehydration was accomplished using Wilkinson's catalyst, followed by heating with acid to give tricycle **424** in a single pot.[311] Oxidation, ketalization, and reduction led to diol **422** in five steps.[214] This route provided the BCDE tetracycle in four fewer steps from the B and E rings than the previous strategy for the truncated fragments.[244]



Scheme 92. Dr. McDougall's BCDE Formation

3. Formation of the GHIJ Fragment

The approach to the other half of brevetoxin A (**303**) was executed by J. Lucas Zuccarello, Dr. Pamela A. Cleary, and Dr. Jon D. Parrish. Dr. Cleary designed a first generation synthesis of the G ring,[312] while Dr. Parrish formed the J ring in an expedient fashion. With these results, Luke Zuccarello progressed these

fragments, while optimizing each step, to the GHIJ fragment **425** (Figure 16).[243] A similar Horner–Wadsworth–Emmons olefination/cyclodehydration approach was successful in forming the tetracycle **425**. Additionally, tetracycle **426** was accessed to provide a substrate with less robust protecting groups on the J ring, for more facile removal at a later stage. Efforts are also underway to intercept Nicolaou's silyl variant **342**.[296,297]

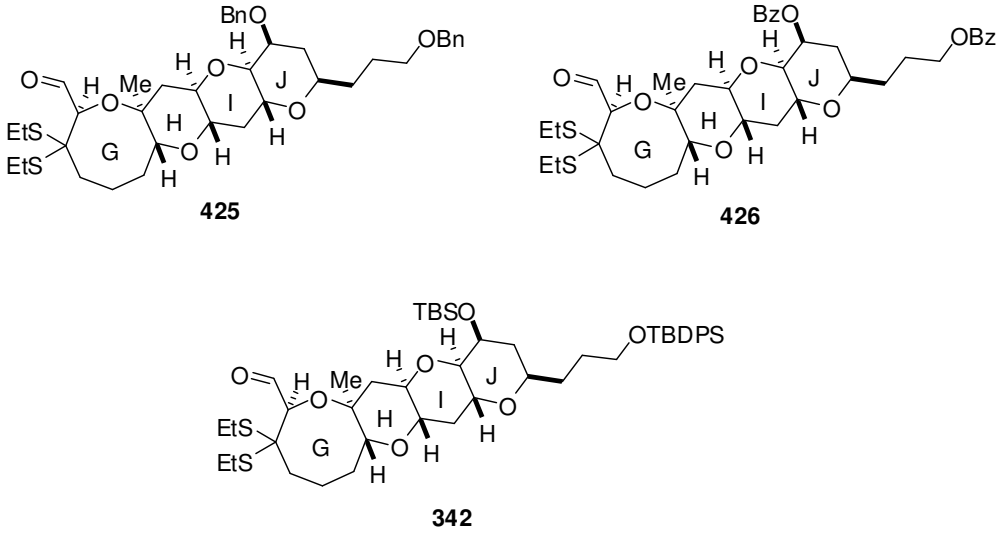
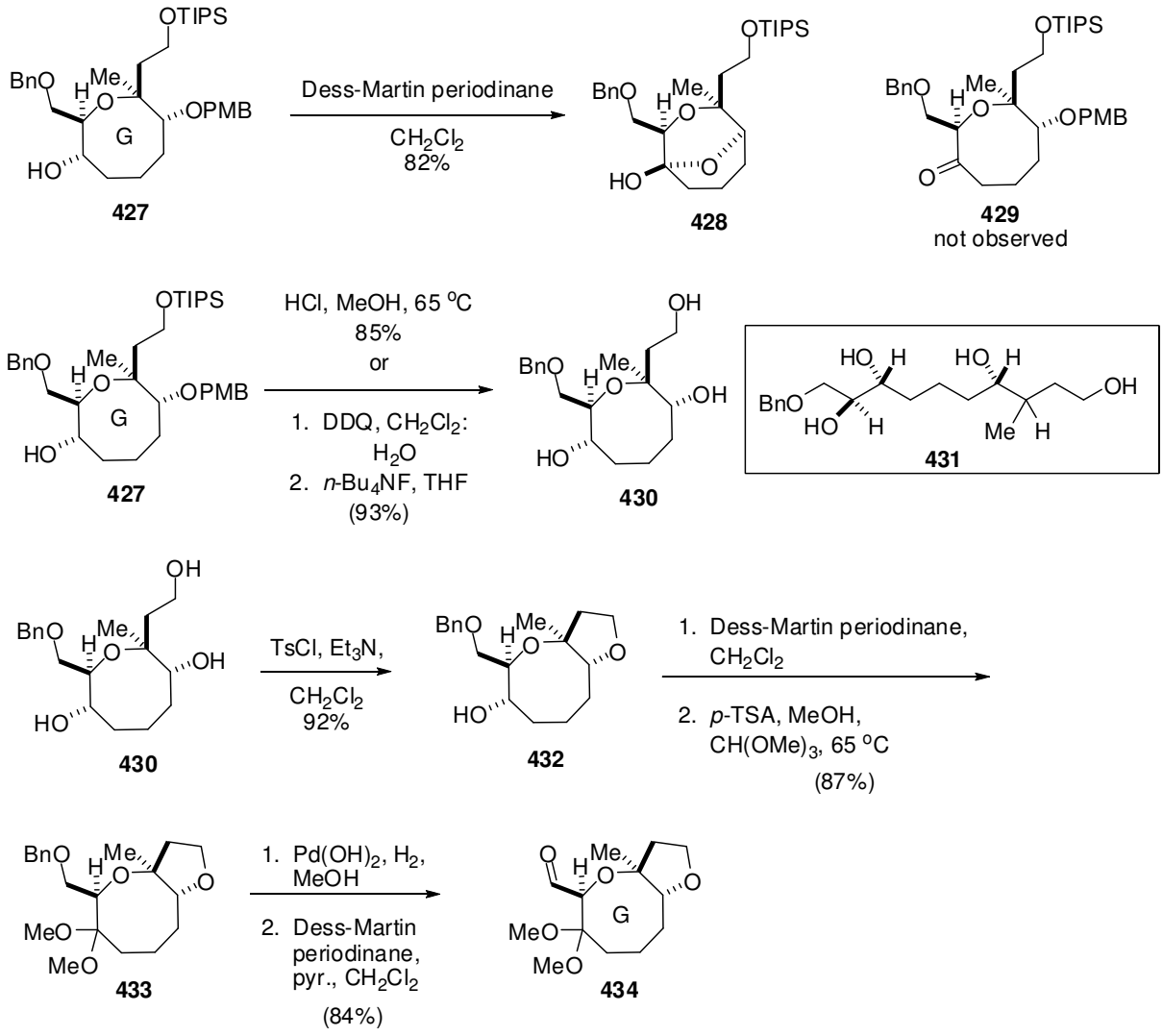


Figure 16. GHIJ Fragments

F. Model Studies of F Ring Formation

Upon attempting to model Wittig and Horner–Wittig strategies for the formation of the F ring using E and G ring fragments, a plethora of obstacles were encountered. Oxidation of alcohol **427**,[43] an intermediate from the G ring synthesis,[243] provided hemiketal **428**, with concomitant loss of the *p*-methoxybenzyl protecting group, instead of the desired ketone **429** (Scheme 93). To impede this cyclization so that we could access the ketal, we chose to install a cyclic constraint on the opposite side of the G ring. Triol **430** was accessed by acidic deprotection of

both the silyl and *p*-methoxybenzyl protecting group, or by oxidative deprotection of the aryl ether, followed by fluoride-mediated removal of the silyl ether. The latter route was more reproducible, as the acidic conditions gave a ring-opened product **431** upon extended reaction time. Treatment of triol **430** with *p*-toluenesulfonyl

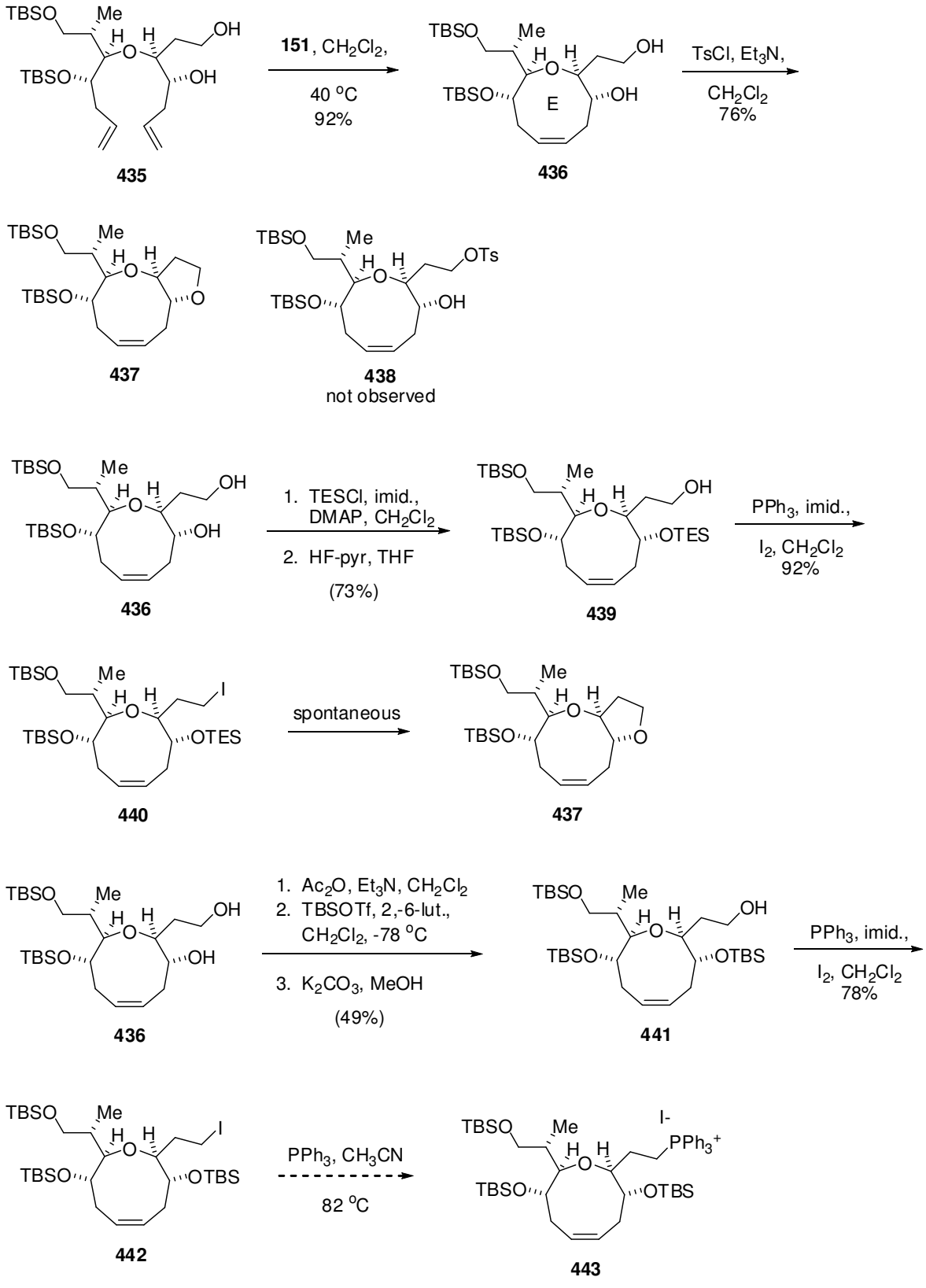


Scheme 93. G Ring Aldehyde for Model

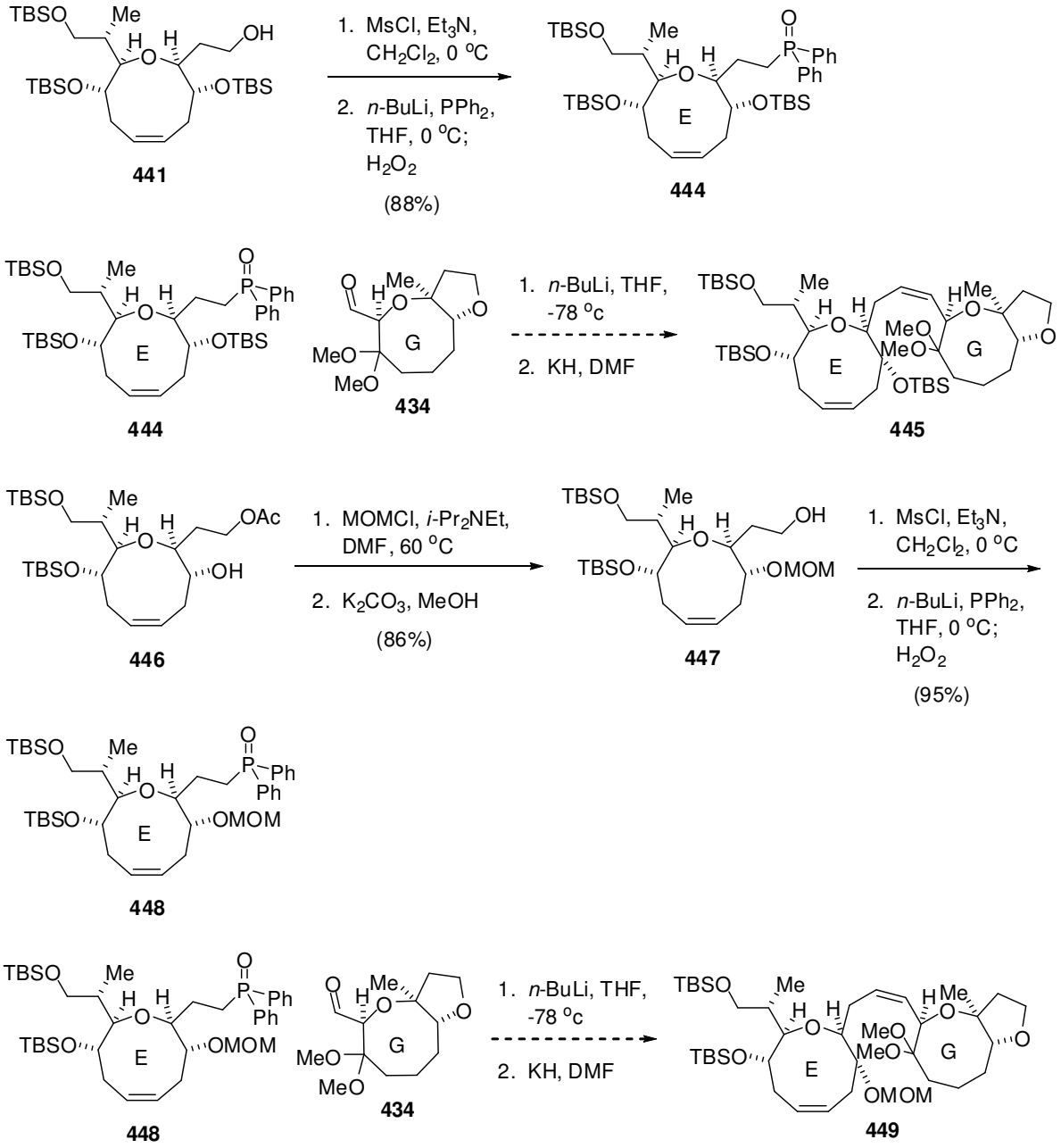
chloride caused spontaneous cyclization to give bicycle **432**. Oxidation provided the ketone, which was ketalized under acidic conditions to give dimethyl ketal **433**. Care had to be taken when handling ketal **433**, as some slightly acidic solvents caused

elimination to occur. As a result, all NMR's were taken in d_6-benzene. Finally, the benzyl ether was cleaved under hydrogenolysis conditions, and oxidation provided aldehyde **434**,[43] which we hoped to use in a Wittig or Horner–Wittig reaction.

The E ring model proved more difficult to work with. Diol **435**, an intermediate from the E ring **394** synthesis, was obtained from Dr. McDougall.[214] Ring-closing metathesis afforded oxonene **436** (Scheme 94).[195,201] We hoped to install a good leaving group on the primary alcohol, then protect the secondary alcohol. However, tosylation of the primary alcohol of diol **436** led only to furan **437**. The diol was bis-protected as triethylsilyl ethers and the primary silyl group was removed under acidic conditions. Formation of the primary iodide led to facile cyclization to the previously observed furan **437**, despite precedent in ladder toxin synthesis forming analogous silyl protected 1,4-halohydrins in high yield.[254] We returned to diol **436** and protected the primary alcohol as an ester, followed by protection of the secondary alcohol as a silyl ether. Methanolysis of the acetate group was followed by formation of the iodide **442**, which also formed furan **437**, though slower than the triethylsilyl variant **440**. Attempts to form the phosphonium salt **443** led to mixtures of cyclization and deprotection products. These undesired cyclizations served to thwart our efforts at a phosphonium salt for the time being, so we pursued a phosphine oxide variant for a Horner–Wittig olefination. To that end, mesylation and subsequent phosphine oxide formation delivered oxonene **444** in 88% from alcohol **441** (Scheme 95). Unfortunately, the lithium enolate of phosphine oxide **444** and aldehyde **434** did not react with one another, likely due to the size of the silyl ether on the E ring **444**. So, ester **446** was protected with a methoxymethyl ether, and



Scheme 94. Attempted Phosphonium Salt Formation



Scheme 95. Attempted Horner–Wittig Olefinations

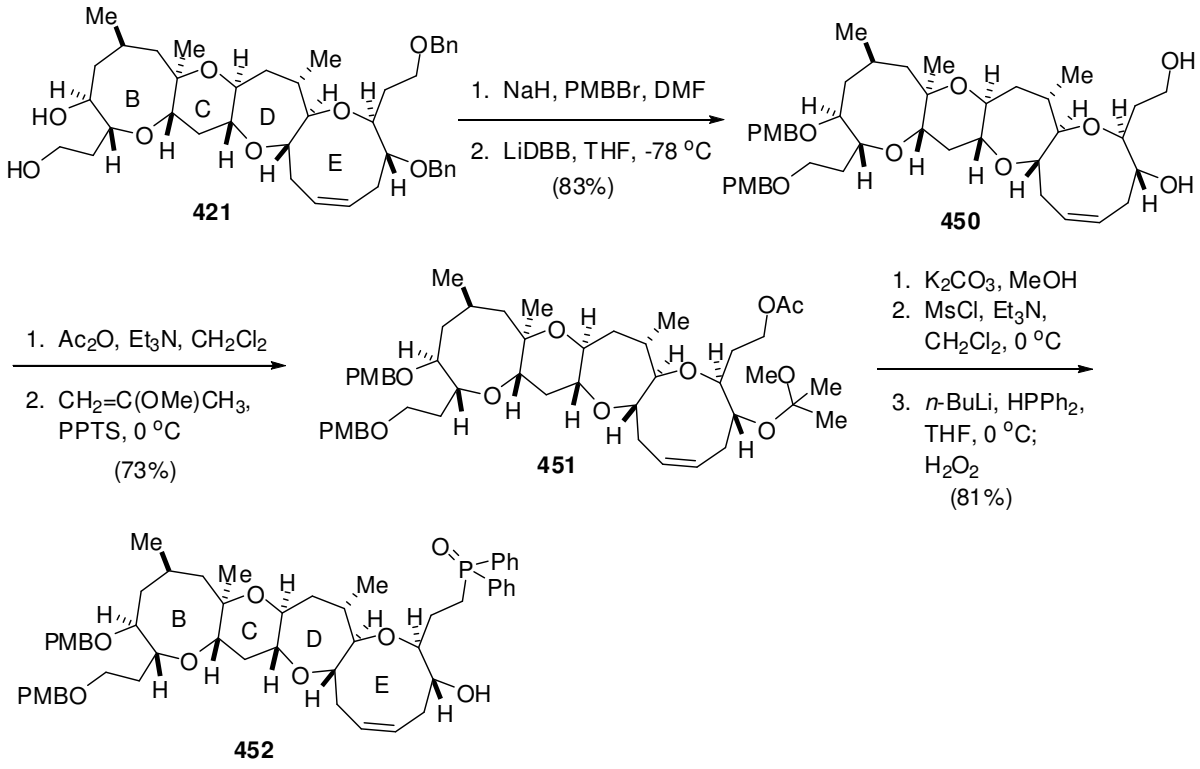
deprotection of the acetate gave alcohol **447**. Formation of the phosphine oxide **448** proceeded as before, and again, the subsequent Horner–Wittig reaction was unsuccessful. Discouraged by the time we had invested into these models that were diverging more and more from our complex system, we set out to prepare the BCDE

phosphine oxide with a methoxypropyl protecting group and the GHIJ aldehyde, fitted with a dithioketal, to mimic Nicolaou's olefination (Scheme 79).[296]

G. Progressing the BCDE Fragment

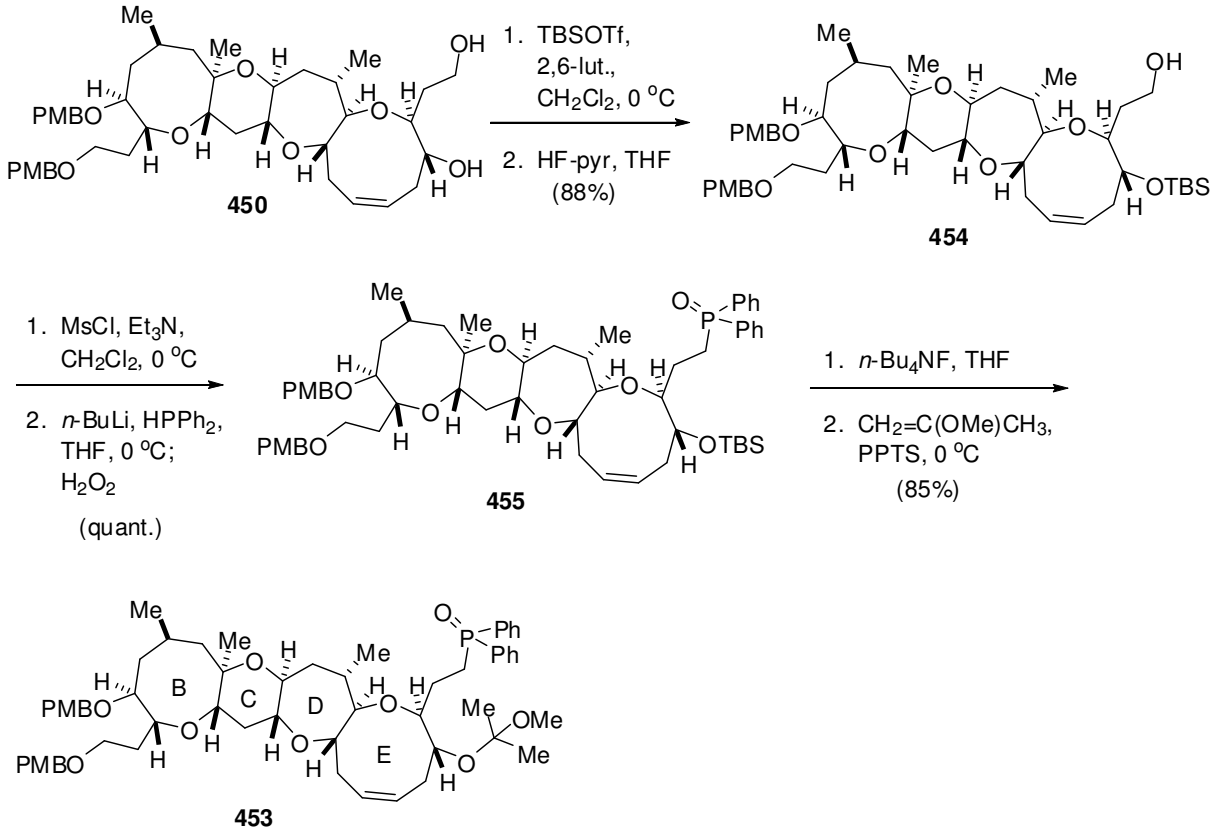
1. Preparation of the BCDE Coupling Partner

Following the attempted modeling of the F ring formation, I undertook the task of progressing the BCDE fragment **421** to some possible coupling partners for the GHIJ tetracycles **342**, **425**, and **426**. After some deliberation, it was decided that *p*-methoxybenzyl ethers would serve as useful protecting groups for the B ring diol during the formation of the F ring. Bis-protection of diol **421**, and reduction of the more electron poor benzyl ethers provided E ring diol **450** (Scheme 96). In order to install a methoxypropyl protecting group on the secondary alcohol, it was necessary to transiently protect the primary alcohol. To that end, the primary ester was accessed, followed by preparation of the desired ketal **451**. Alkaline solvolysis of the primary acetate and subsequent formation of the mesylate proceeded uneventfully. Formation of the phosphine oxide was successful; however, the oxidative workup also effected some hydrolysis of the acetal. Although the material could be reprotected, it was difficult to separate alcohol **452** from the excess diphenylphosphine oxide used in the reaction. To temporarily circumvent this difficulty, it was decided to form the acetal following synthesis of the phosphine oxide.

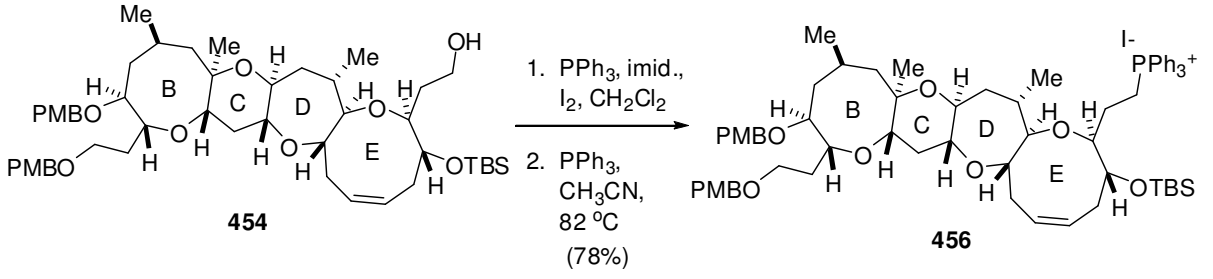


Scheme 96. Unprotected Phosphine Oxide Synthesis

To access the desired phosphine oxide **453** using one additional step, the bis-silyl ether was prepared, followed by selective acidic deprotection of the primary silyl ether to give alcohol **454** (Scheme 97). Synthesis of the phosphine oxide **455** proceeded in quantitative yield over the two steps. This intermediate **455** represents a potential coupling partner for the GHIJ aldehydes **342**, **425**, and **426**. At this point, the silyl ether could be cleaved using fluoride, and the resultant alcohol could be used without purification and delivered desired phosphine oxide **453** in good yield. Additionally, as a potential coupling partner for a Wittig reaction rather than a Horner–Wittig olefination, phosphonium salt **456** was accessed in two steps from alcohol **454**. With each of the BCDE coupling partners **453**, **455**, and **456**, the stage was set to probe the most efficient method for accessing the F ring olefin.



Scheme 97. BCDE Phosphine Oxide Formation

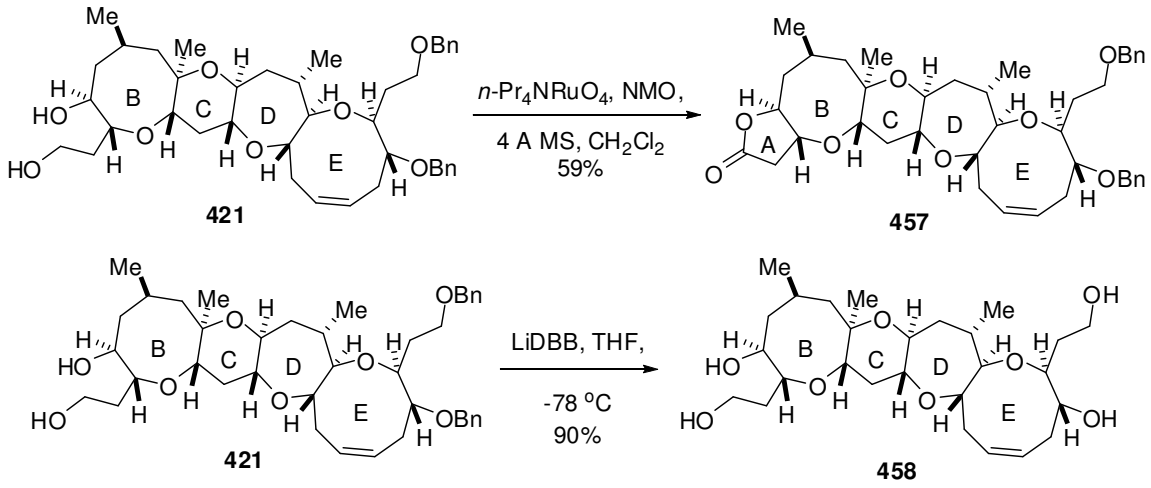


Scheme 98. Phosphonium Salt Formation

2. Analog Syntheses

Beyond the total synthesis of brevetoxin A (**303**), a second goal of this project involves accessing a variety of fragments and analogs of the brevetoxin structure that could provide further insight into the structure–activity relationships of this

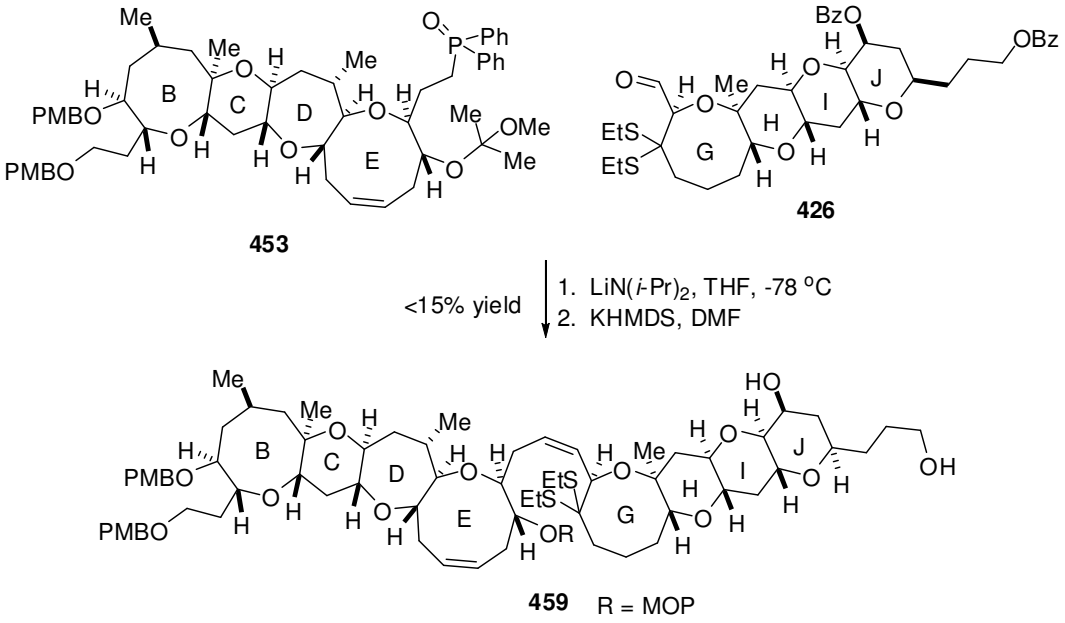
molecule. To facilitate these efforts, a collaboration was established with the Baden laboratory at the University of North Carolina at Wilmington. The Baden group has examined the biological properties of the ladder toxins for over two decades.[289,313] As an initial group of molecules to assay, we hoped to pass along several BCDE fragments. Oxidation of diol **421** delivered the A ring lactone, serving to form the pentacycle **457** useful for assays, as well as model the late-stage A ring formation (Scheme 99).[31] Oxidative deprotection of the benzyl ethers of pentacycle **457** was unsuccessful. Reduction of the benzyl ethers of diol **421** proceeded in high yield to give tetraol **458**. With these preliminary fragments in hand, diol **421**, pentacycle **457**, and tetraol **458** were sent to the Baden laboratory for testing, along with several GHIJ analogs. Although these compounds have not delivered results of high importance to date, they have paved the way for further collaboration in the hope of better understanding the ladder toxins.



Scheme 99. Analog Syntheses

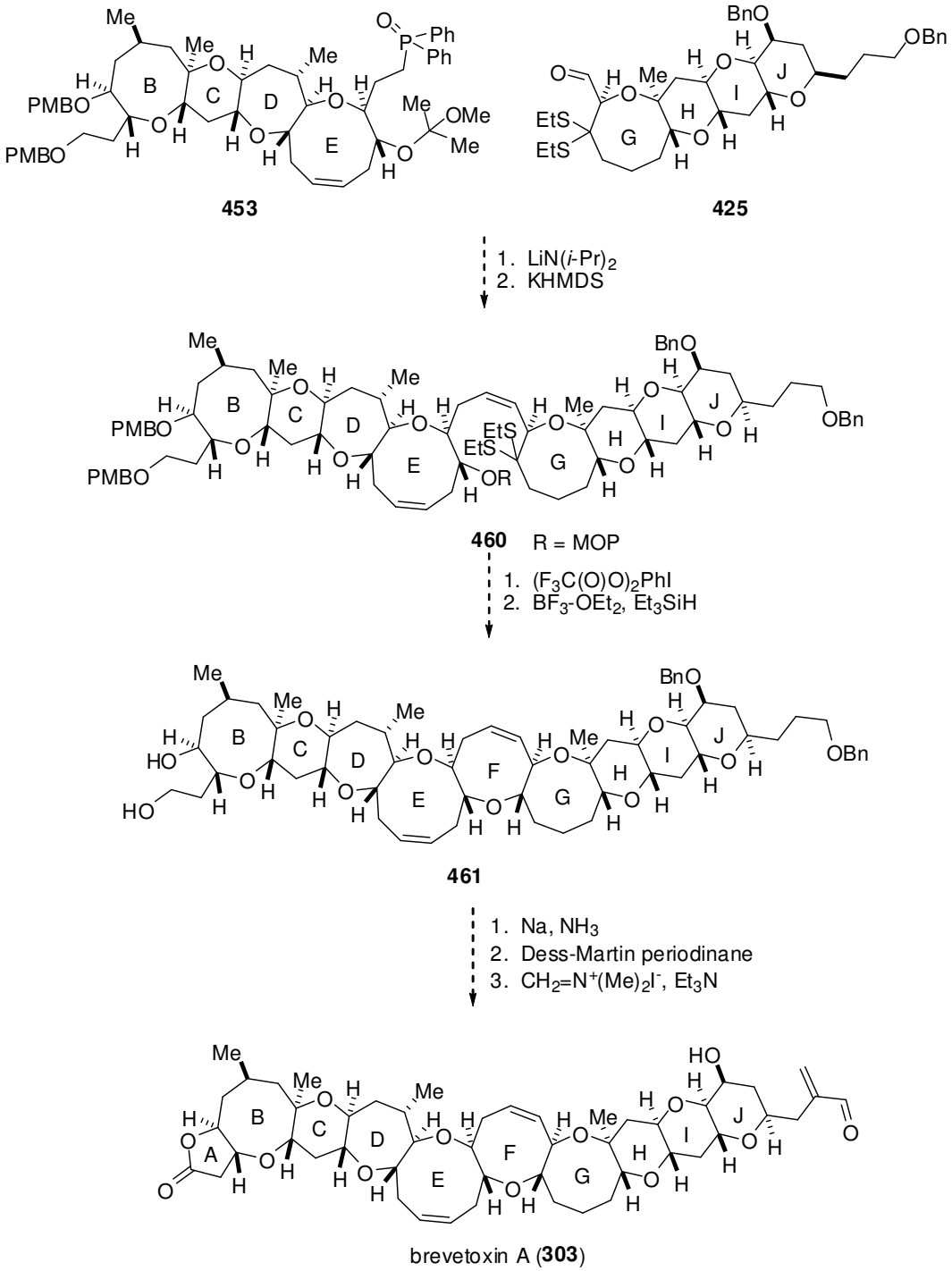
H. Union of the BCDE and GHIJ Fragments and Completion of Brevetoxin A

For the first attempt at coupling the BCDE and GHIJ fragments, phosphine oxide **453** and aldehyde **426** were chosen as substrates (Scheme 100). Use of *n*-butyllithium for the deprotonation of phosphine oxide **453** was difficult on small scale, as the resultant ylide was typically quenched by adventitious water prior to or during addition of aldehyde **426**. Since the use of superstoichiometric *n*-butyllithium would result in undesired alkylation and epimerization of aldehyde **426**, we chose to investigate the use of excess lithium diisoproplyamide for the deprotonation event. To ensure that the ylide of fragment **453** was indeed formed, lithium diisopropylamide was added to the substrate resulting in a yellow solution; the ylide was quenched with deuterium oxide, and ^{1}H NMR analysis of the resultant product provided evidence for incorporation of deuterium in the phosphine oxide, confirming that the ylide had been realized. Pushing forward, deprotonation of phosphine oxide **453** with lithium diisopropylamide followed by addition of a solution of aldehyde **426** provided a complex mixture of products. Inspection of the ^{1}H NMR spectrum of each of these adducts led us to speculate that addition had occurred, however a significant portion of the material featured free hydroxyls resulting from benzoate ester cleavage. Elimination of each of the coupled alcohols provided a very low yield of what we believe to be alkene **459**. However, the difficulties encountered with the esters in the initial addition caused us to pursue this strategy using a GHIJ fragment with more robust protecting groups on the J ring, namely aldehyde **425**, possessing benzyl ethers in place of benzoate esters (Scheme 101).



Scheme 100. Attempted Union of the Fragments

Future work will involve attempting the union of phosphine oxide **453** and aldehyde **425**, which we hope will allow the completion of the total synthesis of brevetoxin A (**303**) (Scheme 101). Following formation of diene **460**, we hope to effect deprotection of the acetal protecting group and form the mixed methoxyketal in one pot. These types of ring formations have previously been achieved with smaller rings.[314] Reduction of the resultant ketal should also result in deprotection of the *p*-methoxybenzyl ethers to provide nonacycle **461**. Removal of the benzyl ethers would then be followed by careful oxidation of the tetraol to deliver the A ring lactone and J ring aldehyde in one step. Finally, treatment with Eschenmoser's salt should provide brevetoxin A (**303**)[302]



Scheme 101. Proposed Completion of Brevetoxin A

I. Summary

In summary, a novel approach to the B ring **420** of brevetoxin A (**303**) has been devised and executed to prepare multigram quantities of the oxocane. Novel reactivity was discovered and exploited along this route, and several improvements were made on the previous strategy. This material has been progressed to tetracycle **421**, and portions of this supply have been carried forward to the phosphine oxides **453** and **455** and the phosphonium salt **456** (Scheme 97, 98). Current efforts are directed at union of the BCDE and GHIJ fragments and the ultimate completion of brevetoxin A (**303**).

Chapter III

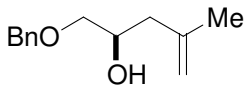
Experimental

A. Materials and Methods

Infrared (IR) spectra were obtained using a Jasco 460 Plus Fourier transform infrared spectrometer. Proton and carbon nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded on the following instruments: Bruker 400 (^{1}H at 400 MHz; ^{13}C at 100 MHz) and Bruker 500 (^{1}H at 500 MHz; ^{13}C at 125 MHz). Optical rotations were determined using a Jasco P1010 polarimeter. Thin layer chromatography (TLC) was conducted on silica gel F_{254} TLC plates purchased from Scientific Adsorbents, Inc. Flash column chromatography was carried out using silica gel (32 to 63 μm) purchased from Scientific Adsorbents, Inc. Diethyl ether (Et_2O), tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), and toluene were dried by being passed through a column of neutral alumina under nitrogen immediately prior to use. Alkylamines and benzene were distilled from calcium hydride immediately prior to use. Chloroform was washed and distilled over phosphorous pentoxide immediately prior to use. Dimethyl sulfoxide (DMSO) was distilled from calcium hydride under reduced pressure and stored over 4 Å molecular sieves. Anhydrous *N,N*-dimethylformamide (DMF) was purchased from Aldrich chemical company in 1L Sure/Seal™ bottles. Acetic anhydride was distilled and stored under a blanket of argon. Trifluoromethanesulfonic anhydride was distilled over phosphorous

pentoxide immediately prior to use. All other reagents and solvents were used as received from the manufacturer. All air and water sensitive reactions were preformed in flasks flame dried under positive flow argon and conducted under an argon atmosphere. Davis oxaziridine was prepared via the condensation of benzaldehyde and benzenesulfonamide, followed by oxidation according to literature precedent. Pivaloyl chloride was distilled and stored over 4Å molecular sieves. Zinc borohydride was prepared by stirring a solution of zinc chloride (1.0 M in Et_2O) with $NaBH_4$ for two days in Et_2O to prepare a 0.14M solution. Dess-Martin periodinane was prepared according to literature procedures and stored at -20 ºC.

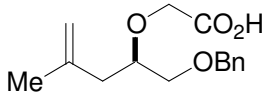
B. Procedures



Homoallylic alcohol 8. Into a flask equipped with a reflux condenser and an addition funnel was added freshly ground magnesium (10.55 g, 434.0 mmol). The flask and its contents were flame dried. 125 mL of THF and iodine (one crystal) were added to the flask. 2-bromopropene (50.00 g, 413.3 mmol) was added in 125 mL of THF to the addition funnel. Several drops of the 2-bromopropene solution were added to the flask via addition funnel and the solution was stirred until colorless. 350 mL of THF was added to the addition funnel and the solution was added dropwise to the flask. Following addition, 125 mL of THF was added to the flask, and the solution was stirred vigorously for 2 hours.

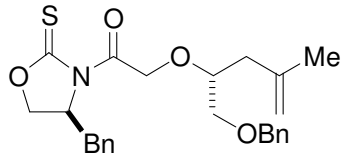
Into a flask equipped with an addition funnel and a low-temperature thermometer was added cuprous iodide (3.58 g, 18.8 mmol) in 375 mL of THF. The solution was cooled to –35 °C. The solution of 2-propenylmagnesium bromide was

transferred via cannula to the addition funnel and added dropwise to yield a yellow solution. (*R*)-benzylglycidyl ether (**5**) (28.66 mL, 187.4 mmol) was added to the addition funnel in 200 mL of THF. The epoxide was added dropwise, and the solution was stirred at –35 °C for 1 hour. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and then warmed to room temperature. The resultant mixture was filtered through celite, yielding a blue solution. The layers were separated and the organic layer was washed with brine. The aqueous portions were extracted twice with a 1:1 solution of EtOAc/hexanes. The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (25% EtOAc/Hexanes) provided 38.22 g (99%) of the alcohol as a colorless oil.



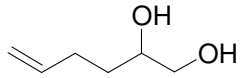
Glycolic acid 9. Into a flask equipped with an addition funnel was added sodium hydride (60% dispersion in mineral oil, 23.95 g, 598.6 mmol). The sodium hydride was rinsed with pentane three times, diluted in 100 mL of THF, and cooled to 0 °C. Bromoacetic acid (41.58 g, 299.3 mmol) was added to the addition funnel in 100 mL of THF and added dropwise to the flask. The solution was warmed to room temperature and stirred for 1 hour. The flask was again cooled to 0 °C, and the previous secondary alcohol **8** (41.16 g, 199.5 mmol) was added to the addition funnel in 200 mL of DMF. The solution of alcohol was added to the flask dropwise. Following addition, the reaction was warmed to room temperature and allowed to stir overnight. The reaction was quenched by the addition of saturated aqueous NH_4Cl and diluted with diethyl ether. The solution was acidified to pH 3-4 by the addition of

10% H_2SO_4, then extracted. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (10% then 25% EtOAc/Hexanes) provided 49.71 g (95%) of the acid as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75 (s, 3H), 2.13 (dd, *J* = 14.0, 6.0 Hz, 1H), 2.27 (dd, *J* = 14.0, 7.1 Hz, 1H), 3.48 (dd, *J* = 10.0, 8.5 Hz, 1H), 3.54 (dd, *J* = 10.1, 2.9 Hz, 1H), 3.71 (m, 1H), 4.10 (d, *J* = 17.3 Hz, 1H), 4.28 (d, *J* = 17.3 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.77 (d, *J* = 0.8 Hz, 1H), 4.85 (dd, *J* = 1.6, 1.6 Hz, 1H), 7.29-7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 40.0, 68.2, 72.2, 73.6, 79.6, 114.3, 127.9, 128.1, 128.6, 136.7, 140.8, 172.2; IR (film) 3483 (br), 3201 (br), 2917, 1733 (str), 1454, 1454, 1364, 1205, 1129 cm^{-1}; $[\alpha]^{25}_D$ = -25.0 (c = 1.30, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{15}H_{21}O_4$ $[M + 1]^+$: 265.14, found: 265.2.



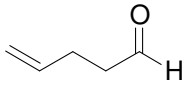
Oxazolidinethione glycolate 6. A flask was charged with the glycolic acid **9** (49.13 g, 185.9 mmol) and (*4S*)-4-benzyl-1,3-oxazolidine-2-thione (39.52 g, 204.5 mmol) in 150 mL of CH_2Cl_2. The solution was cooled to 0 ^{o}C. Dicyclohexylcarbodiimide (38.35 g, 185.9 mmol), 4-dimethylaminopyridine (1.14 g, 9.33 mmol), and 35 mL of CH_2Cl_2 were added to the solution and the mixture was warmed to room temperature. The yellow solution was stirred 4 hours, then cooled to 0 ^{o}C, and filtered. The filtrate was washed with CH_2Cl_2. The combined organic portions were washed with saturated aqueous $NaHCO_3$, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were washed with

brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (25% EtOAc/Hexanes) provided 70.13 g (86%) of the glycolate as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81 (s, 3H), 2.31 (dd, *J* = 14.1, 6.7 Hz, 1H), 2.44 (dd, *J* = 14.3, 6.8 Hz, 1H), 2.64 (dd, *J* = 13.3, 10.2 Hz, 1H), 3.26 (dd, *J* = 13.3, 3.2 Hz, 1H), 3.64 (m, 2H), 3.93 (m, 1H), 4.23 (dd, *J* = 7.7, 7.7 Hz, 1H), 4.31 (dd, *J* = 9.3, 2.4 Hz, 1H), 4.54 (s, 2H), 4.79 (s, 1H), 4.83-4.90 (m, 1H), 4.83 (s, 1H), 5.23 (d, *J* = 18.3 Hz, 1H), 5.34 (d, *J* = 18.3 Hz, 1H), 7.17-7.36 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 37.3, 40.3, 59.8, 71.2, 71.9, 73.3, 73.5, 77.7, 113.1, 127.4, 127.5, 127.6, 128.4, 129.0, 129.4, 135.1, 138.1, 142.1, 171.4, 184.7; IR (film) 2924, 1712 (str), 1361, 1324, 1206, 1124 cm^{-1}; $[\alpha]^{22}_D$ = +93 (c = 0.26, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{25}H_{30}NO_4S$ $[M + 1]^+$: 440.18, found: 440.3.

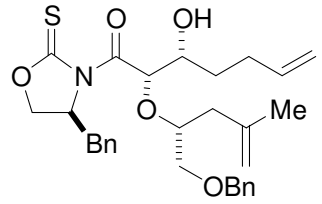


Hex-5-ene-1,2-diol. Into a flask equipped with a mechanical stirrer, an addition funnel, and a low temperature thermometer was added allylmagnesium chloride (2.0 M in THF, 800.0 mL, 1.600 mol) and 800 mL of THF. The solution was cooled to –20 °C. Glycidol (35.40 mL, 533.3 mmol) in 800 mL of THF was added dropwise via addition funnel keeping the temperature at –20 °C. The mixture was stirred 1 hour at –20 °C, then quenched by the addition of saturated aqueous NH_4Cl. The organic layer was washed with brine, and the combined aqueous extracts were washed twice with 50% EtOAc/Hexanes. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column

chromatography (10% then 50% EtOAc/Hexanes) provided 57.16 g (93%) of the diol as a colorless oil.

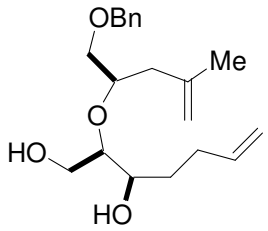


Pent-4-enal. Into a flask equipped with a mechanical stirrer was added hex-5-ene-1,2-diol (65.31 g, 562.2 mmol), 800 mL of CH_2Cl_2, and 800 mL of water. Sodium periodate (240.52 g, 1.1245 mol) was added to the biphasic solution which was stirred for one hour. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$. The organic layer was washed twice with 10% $Na_2S_2O_3$ in water, then dried over Na_2SO_4. The volume was reduced to 100 mL in vacuo at 0 ^oC. Purification via distillation (bp: 96 ^oC, 760 mm Hg) gave 29.33 g (63%) of the aldehyde as a colorless liquid.



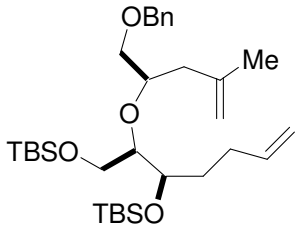
Glycolate Aldol Adduct 11. Into a flask equipped with an addition funnel was added glycolate **6** (28.63 g, 65.13 mmol) and 435 mL of CH_2Cl_2. The solution was cooled to –78 ^oC and titanium tetrachloride (7.50 mL, 68.4 mmol) was added dropwise via addition funnel. The solution was stirred 10 minutes at –78 ^oC and *N, N*-diisopropylethylamine (26.92 mL, 162.8 mmol) was added dropwise to give a purple solution that was stirred at –78 ^oC for 2.5 hours. *N*-methylpyrrolidinone (6.57 mL, 68.3 mmol) was added to the solution via addition funnel and stirred for 10 minutes. 4- pentenal was added dropwise via addition funnel and stirred at –78 ^oC for 2 hours. The solution was warmed to –40 ^oC for 1 hour, then quenched by the

addition of half saturated aqueous NH_4Cl and warmed to room temperature. The aqueous layer was extracted twice with CH_2Cl_2, then the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (20% then 50% EtOAc/Hexanes) provided 23.61 g (70%) of the alcohol as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.67-1.78 (m, 2H), 1.80 (s, 3H), 2.01 (dd, *J* = 13.2, 11.1 Hz, 1H), 2.15 (ddd, *J* = 14.9 , 7.1, 7.1 Hz, 1H), 2.20-2.36 (m, 3H), 2.41 (dd, *J* = 14.0, 7.9 Hz, 1H), 3.20 (dd, *J* = 13.3, 2.8 Hz, 1H), 3.51 (dd, *J* = 10.3, 2.7 Hz, 1H), 3.68 (dd, *J* = 10.3, 7.6 Hz, 1H), 3.92-4.01 (m, 2H), 4.14 (dd, *J* = 9.4, 2.1 Hz, 1H), 4.19 (ddd, *J* = 9.3, 9.3, 9.3 Hz, 1H), 4.47 (d, *J* = 12.3 Hz, 1H), 4.53 (d, *J* = 12.3 Hz, 1H), 4.77 (m, 1H), 4.84 (s, 1H), 4.86 (s, 1H), 4.98 (d, *J* = 10.2 Hz, 1H), 5.05 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.83 (dddd, *J* = 17.0, 10.3, 3.6, 3.6 Hz, 1H), 6.34 (d, *J* = 2.0 Hz, 1H), 7.08-7.35 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 29.9, 33.2, 36.7, 40.7, 60.9, 70.6, 72.5, 73.1, 74.2, 78.7, 80.8, 114.0, 114.9, 127.22, 127.24, 127.5, 128.4, 128.9, 129.3, 135.6, 138.0, 138.1, 141.6, 172.2, 185.2; IR (film) 3458 (br), 2924, 1712 (str), 1446, 1361, 1324, 1206, 1128 cm^{-1}; $[\alpha]^{23}_D$ = **+**25 (c = 0.43, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{30}H_{38}NO_5S$ $[M + 1]^+$: 524.24, found: 524.3.



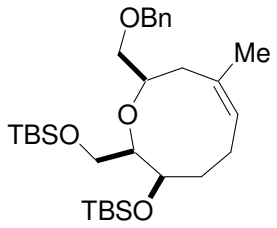
Dien diol 14. Into a flask equipped with an addtion funnel was added alcohol **11** (19.89 g, 38.01 mmol) in 380 mL of Et_2O. Methanol (3.08 mL, 76.0 mmol) was

added, and the solution was cooled to 0 °C. Lithium borohydride (2.0 M in Et_2O, 38.01 mL, 76.03 mmol) was added dropwise via addition funnel, and the solution was stirred 1.5 hours at 0 °C. The reaction was quenched by the addition of aqueous NaOH (380 mL, 190 mmol) and stirred 15 minutes at room temperature. The layers were separated and the aqueous was washed three times with Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (20% EtOAc/Hexanes) gave 11.96 g (95%) of the diol as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51-1.60 (m, 2H), 1.75 (s, 3H), 2.08-2.19 (m, 2H), 2.26 (ddd, *J* = 14.4, 7.8, 7.8 Hz, 1H), 2.36 (dd, *J* = 14.0, 6.5 Hz, 1H), 2.72 (br s, 1H), 3.32 (m, 1H), 3.47 (dd, *J* = 10.0, 7.9 Hz, 1H), 3.56-3.61 (m, 3H), 3.75 (br s, 1H), 3.77 (br s, 1H), 3.90 (dddd, *J* = 7.0, 7.0, 7.0, 2.6 Hz, 1H), 4.56 (s, 2H), 4.77 (s, 1H), 4.84 (s, 1H), 4.96 (ddd, *J* = 10.2, 1.9, 0.7 Hz, 1H), 5.03 (ddd, *J* = 17.1, 3.5, 1.6, 1H), 5.82 (dddd, *J* = 16.9, 10.2, 6.7, 6.7 Hz, 1H), 7.29-7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 29.8, 32.5, 41.2, 62.7, 71.2, 72.9, 73.6, 76.7, 83.0, 114.0, 114.8, 127.9, 128.1, 128.6, 137.1, 138.3, 141.7; IR (film) 3436 (br), 2921, 1641, 1454, 1092 cm^{-1}; $[\alpha]^{24}_D$ = -11 (c = 0.32, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{20}H_{30}O_4Na$ $[M + Na]^+$: 357.20, found: 357.3.

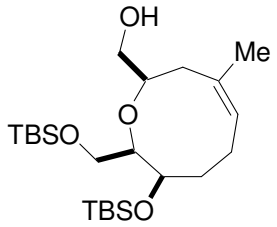


Diene 5. A flask was charged with the 1,3-diol **14** (11.96 g, 35.76 mmol) and 140 mL DMF. Imidazole (18.26 g, 268.2 mmol) and 4-dimethylaminopyridine (437 mg, 3.58 mmol) were added to the solution, followed by

tert-butyldimethylsilyl chloride (13.48 g, 89.40 mmol). The solution was warmed to 50 °C and stirred overnight. The reaction was quenched by the addtion of saturated aqueous NH_4Cl, cooled to room temperature, and diluted with Et_2O. The layers were separated, and the aqueous portion was washed twice with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (1% EtOAc/Hexanes) provided 17.42 g (86%) of the diene as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.107 (s, 3H), 0.112 (s, 3H), 0.93 (s, 9H), 0.95 (s, 9H), 1.29 (dddd, *J* = 14.7, 9.9, 9.9, 5.0 Hz, 1H), 1.74-1.82 (m, 1H), 1.82 (s, 3H), 1.98 (m, 1H), 2.18-2.28 (m, 1H), 2.24 (dd, *J* = 13.8, 7.9 Hz, 1H), 2.39 (dd, *J* = 13.8, 4.6 Hz, 1H), 3.45 (dd, *J* = 9.7, 6.2 Hz, 1H), 3.45-3.50 (m, 1H), 3.61 (dd, *J* = 10.6, 7.9 Hz, 1H), 3.69 (dd, *J* = 9.8, 4.6 Hz, 1H), 3.70-3.75 (m, 1H), 3.82-3.88 (m, 1H), 3.89 (dd, *J* = 10.6, 2.2 Hz, 1H), 4.59 (s, 2H), 4.82 (s, 1H), 4.85 (m, 1H), 4.98 (dd, *J* = 10.2, 1.9 Hz, 1H), 5.05 (ddd, *J* = 17.0, 3.3, 1.5 Hz, 1H), 5.85 (dddd, *J* = 16.9, 10.2, 6.6, 6.6 Hz, 1H), 7.27-7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.5, -5.3, -4.6, -4.3, 18.0, 18.2, 23.0, 25.8, 25.86, 25.92, 25.93, 30.6, 30.9, 41.4, 62.8, 71.9, 72.7, 73.2, 77.2, 83.3, 113.0, 114.3, 127.4, 127.5, 128.2, 138.6, 138.8, 142.6; IR (film) 2929, 1463, 1255, 1095 cm^{-1}; $[\alpha]^{24}_D$ = +35.7 (c = 1.24, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{32}H_{58}O_4Si_2Na$ $[M + Na]^+$: 585.38, found: 585.5.

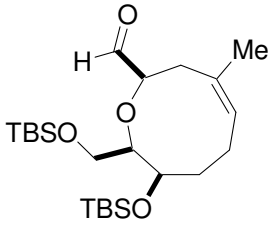


Oxonene 18. Into a flask equipped with a reflux condenser was added diene **5** (16.56 g, 29.24 mmol) and 2.9 L CH_2Cl_2. The solution was brought to reflux for 30 minutes, followed by the addtion of Grubbs' catalyst (1.25 g, 1.47 mmol) and stirring three hours at reflux. The solution was cooled to room temperature and concentrated in vacuo. Purification by flash column chromatography (1% EtOAc/Hexanes) provided 15.53 g (99%) of the oxonene as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.03 (s, 9H), 0.88 (s, 9H), 0.89 (s, 9H), 1.42 (dddd, *J* = 3.9, 3.9, 13.5, 13.5 Hz, 1H), 1.73 (m, 1H), 1.79 (s, 3H), 1.86 (m, 1H), 1.98 (d, *J* = 14.02 Hz, 1H), 2.44 (dd, *J* = 14.2, 7.9 Hz, 1H), 2.81 (dddd, *J* = 13.2, 13.2, 13.2, 4.4 Hz , 1H), 3.29-3.35 (m, 2H), 3.38 (m, 1H), 3.54 (dd, *J* = 13.6, 8.9 Hz, 1H), 3.67 (dd, *J* = 11.0, 8.5 Hz, 1H), 3.92 (dd, *J* = 11.1, 2.4 Hz, 1H), 3.96 (m, 1H), 4.56 (s, 2H), 5.34 (dd, *J* = 11.4, 5.3 Hz, 1H), 7.27-7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.2, -5.1, -4.8, 18.1, 18.3, 25.3, 25.8, 25.9, 26.0, 26.1, 32.2, 36.1, 61.8, 67.7, 73.0, 73.4, 77.9, 84.3, 126.1, 127.5, 127.6, 128.3, 134.7, 138.4; IR (film) 2928, 1471, 1254, 1089 cm^{-1}; $[\alpha]^{24}_D$ = +33.6 (c = 1.16, CH_2Cl_2); MS (electrosray ionization) calculated for $C_{30}H_{54}O_4Si_2Na$ $[M + Na]^+$: 557.35, found: 557.4.



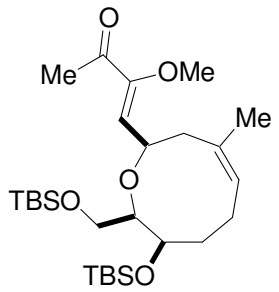
Primary alcohol 37. Into a flask equipped with a cold finger condenser, cooled to –78 °C, and a stir bar was added oxonene **18** (4.03 g, 7.52 mmol) and 210 mL of THF. The solution was cooled to –78 °C, and 105 mL of ammonia was condensed into the flask. Freshly cut sodium metal (3.46 g, 150 mmol) was added

to the solution yielding a blue color. After 15 minutes at –78 °C, the reaction was quenched by the addition of saturated aqueous NH_4Cl. The ammonia was allowed to evaporate at room temperature, and the layers were separated. The aqueous portion was washed three times with Et_2O, dried over Na_2SO_4 and concentrated in vacuo. Purification via flash column chromatography (5% EtOAc/Hexanes) gave 2.86 g (86%) of the alcohol as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.02 (s, 3H), 0.09 (s, 3H), 0.10 (s, 3H), 0.86 (s, 9H), 0.91 (s, 9H), 1.44 (m, 1H), 1.49 (d, *J* = 10.6 Hz, 1H), 1.70 (dddd, *J* = 13.8, 13.8, 5.3, 2.0 Hz, 1H), 1.78 (s, 3H), 1.90 (m, 1H), 2.39 (dd, *J* = 14.1, 9.9 Hz, 1H), 2.77 (dddd, *J* = 13.0, 13.0, 13.0, 5.4 Hz, 1H), 3.33 (m, 1H), 3.44-3.52 (m, 2H), 3.59 (m, 1H), 3.73 (dd, 10.0, 10.0 Hz, 1H), 3.88 (ddd, *J* = 6.6, 3.5, 3.5 Hz, 1H), 3.97 (ddd, *J* = 8.8, 3.2, 3.2 Hz, 1H), 4.01 (dd, *J* = 10.5, 2.1 Hz, 1H), 5.35 (dd, *J* = 11.8, 5.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.5, -5.3, -5.0, -4.9, 18.0, 18.5, 25.6, 25.78, 25.79, 26.0, 31.6, 35.0, 62.5, 67.7, 68.0, 81.2, 85.8, 125.9, 133.9; IR (film) 3477 (br), 2929, 1463, 1255, 1089 cm^{-1}; $[\alpha]^{24}_D$ = +26.9 (c = 2.44, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{23}H_{48}O_4Si_2Na$ $[M + Na]^+$: 467.30, found: 467.4.

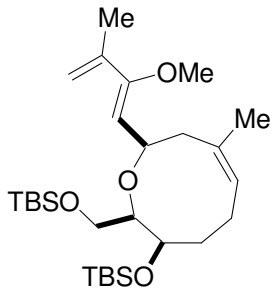


Aldehyde. A flask was charged with oxalyl chloride (2.0 M in CH_2Cl_2, 3.52 mL, 7.04 mmol) and 40 mL of CH_2Cl_2 and cooled to –78 °C. Dimethylsulfoxide (1.00 mL, 14.1 mmol) in 8 mL of CH_2Cl_2 was added dropwise, and the solution was stirred 2 minutes. The primary alcohol **37** (2.85 g, 6.40 mmol) and 16 mL CH_2Cl_2 were

added dropwise to the mixture and allowed to stir 30 minutes at –78 °C. Triethylamine (4.46 mL, 32.0 mmol) was added dropwise and stirred 5 minutes at –78 °C, followed by warming to 0 °C for 1 hour. The reaction was quenched by the addition of cold water. The organic portion was washed with cold saturated aqueous $NaHCO_3$, then water. The combined aqueous portions were washed with CH_2Cl_2. The combined organic extracts were then washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (5% EtOAc/Hexanes) provided 2.64 g (94%) of the aldehyde as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.02 (s, 3H), 0.06 (m, 6H), 0.86 (s, 9H), 0.89 (s, 9H), 1.46 (dddd, *J* = 13.6, 13.6, 4.2, 4.2 Hz , 1H), 1.74-1.85 (m, 1H), 1.79 (s, 3H), 1.89 (m, 1H), 2.06 (d, *J* = 14.3 Hz, 1H), 2.50 (dd, *J* = 14.1, 10.2 Hz, 1H), 2.76 (dddd, *J* = 13.1, 13.1, 13.1, 4.1 Hz, 1H), 3.49 (d, *J* = 10.0 Hz, 1H), 3.49-3.53 (m, 1H), 3.78 (dd, *J* = 10.9, 8.7 Hz, 1H), 3.89 (ddd, *J* = 10.3, 3.7, 3.7 Hz, 1H), 3.95 (dd, *J* = 16.5, 1.6 Hz, 1H), 5.39 (dd, *J* = 11.3, 5.3 Hz, 1H), 9.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.3, -5.1, -4.9, -4.7, 18.1, 18.3, 24.9, 25.8, 25.9, 32.5, 34.0, 62.3, 67.6, 83.6, 85.6, 127.5, 132.8, 204.5; IR (film) 2929, 1737 (str), 1473, 1254, 1086 cm^{-1}; $[\alpha]^{24}_D$ = +84 (c = 0.48, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{23}H_{46}O_4Si_2Na$ $[M + Na]^+$: 443.28, found: 443.4.

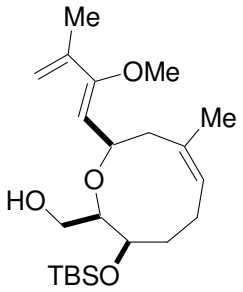


Enone. Into a flask equipped with a reflux condenser was added the aldehyde (2.70 g, 6.10 mmol), 60 mL of toluene, and 1-Methoxy-1-(triphenyl-l5-phosphanylidene)-propan-2-one (**21**) (6.37 g, 18.3 mmol). The solution was brought to reflux overnight, then cooled to room temperature. The mixture was concentrated in vacuo, then purified by flash column chromatography (5% EtOAc/Hexanes) to provide 2.59 g (84%) of the enone as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.02 (s, 6H), 0.85 (s, 18H), 1.42 (dddd, *J* = 13.4, 13.4, 3.8, 3.8 Hz, 1H), 1.69 (d, *J* = 14.0 Hz, 1H), 1.70-1.78 (m, 1H), 1.79 (s, 3H), 1.85 (m, 1H), 2.42 (s, 3H), 2.71 (dd, *J* = 13.8, 9.1 Hz, 1H), 2.77 (dddd, *J* = 13.1, 13.1, 13.1, 4.5 Hz , 1H), 3.34 (dd, *J* = 5.9, 5.9 Hz, 1H), 3.62-3.68 (m, 1H), 3.64 (s, 3H), 3.91 (dd, *J* = 11.4, 2.2 Hz, 1H), 3.96 (ddd, *J* = 11.4, 3.7, 3.7 Hz, 1H), 4.21 (dd, *J* = 8.7, 8.7 Hz, 1H), 5.34 (dd, *J* = 11.5, 5.4 Hz, 1H), 6.20 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.2, -5.04, -5.01, -4.97, 18.1, 18.2, 25.4, 25.79, 25.81, 25.86, 26.0, 32.2, 39.4, 59.7, 61.6, 74.2, 84.0, 126.3, 131.7, 134.1, 151.5, 195.0; IR (film) 2929, 1687 (str), 1471, 1253, 1086 cm^{-1}; $[\alpha]^{24}_{D}$ = -48.6 (c = 1.46, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{27}H_{52}O_5Si_2Na$ $[M + Na]^+$: 535.32, found: 535.5.

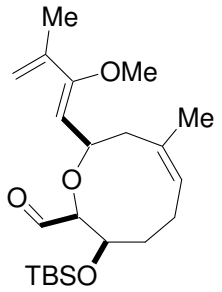


Triene 38. A flask was charged with methylenetriphenylphosphine bromide (6.59 g, 18.5 mmol) and 15 mL of THF and cooled to 0 °C. Potassium *tert*-butoxide

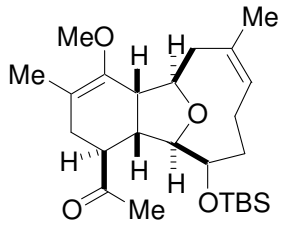
(1.0 M in THF, 14.8 mL, 14.8 mmol) was added to the heterogeneous mixture to give a yellow homogeneous solution. After stirring 30 minutes at 0 °C, the enone (1.89 g, 3.69 mmol) in 20 mL of THF was added dropwise and stirred 30 minutes at 0 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl, warmed to room temperature, and diluted with Et_2O. The layers were separated and the aqueous portion was washed twice with Et_2O, dried over Na_2SO_4, and concentrated in vacuo. Purification via flash column chromatography (5% EtOAc/Hexanes) gave 1.63 g (87%) of the diene as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.038 (s, 3H), 0.045 (s, 3H), 0.06 (s, 3H), 0.87 (s, 9H), 0.89 (s, 9H), 1.43 (m, 1H), 1.72 (d, *J* = 14.1 Hz, 1H), 1.74 (m, 1H), 1.82 (s, 6H), 1.85 (m, 1H), 2.72 (dd, *J* = 14.1, 9.7 Hz, 1H), 2.84 (dddd, *J* = 13.0, 13.0, 13.0, 4.6 Hz, 1H), 3.39 (dd, *J* = 6.5, 4.7 Hz, 1H), 3.57 (s, 3H), 3.67 (dd, *J* = 11.2, 8.9 Hz, 1H), 3.95 (dd, *J* = 11.2, 2.1 Hz, 1H), 4.02 (ddd, *J* = 11.5, 3.6, 3.6 Hz, 1H), 4.19 (dd, *J* = 8.9, 8.9 Hz, 1H), 5.00 (s, 1H), 5.24 (d, *J* = 1.5 Hz, 1H), 5.30 (d, *J* = 8.6 Hz, 1H), 5.34 (dd, *J* = 11.4, 5.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.1, -4.97, -4.96, -4.9, 18.2, 18.3, 19.6, 25.5, 25.9, 26.0, 26.3, 32.3, 40.3, 59.9, 61.8, 67.8, 74.5, 83.6, 113.4, 118.7, 125.9, 134.8, 137.2, 154.6; IR (film) 2928, 1463, 1253, 1086 cm^{-1}; $[\alpha]^{24}_D$ = -31 (c = 0.38, CH_2Cl_2)**;** MS (electrospray ionization) calculated for $C_{28}H_{54}O_4Si_2Na$ $[M + Na]^+$: 533.35, found: 533.5.



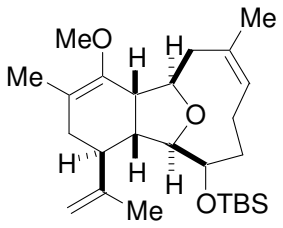
Primary alcohol 40. A flask was charged with triene **38** (1.55 g, 3.03 mmol) and 30 mL of methanol. Ammonium fluoride (2.25 g, 60.6 mmol) was added to the solution and stirred overnight. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ and diluted with Et_2O. The layers were separated and the aqueous portion was washed twice with Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (5% EtOAc/Hexanes) provided 940 mg (79%) of the alcohol as a colorless oil, as well as 240 mg (16%) of recovered starting diene: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.07 (s, 3H), 0.88 (m, 9H), 1.49 (dddd, *J* = 14.5, 14.5, 6.0, 6.0 Hz, 1H), 1.72 (d, *J* = 14.2 Hz, 1H), 1.82 (s, 3H), 1.83 (s, 3H), 1.85-1.94 (m, 2H), 2.38 (dd, *J* = 7.8, 4.2 Hz, 1H), 2.65 (dd, *J* = 15.0, 10.5 Hz, 1H), 2.73 (m, 1H), 3.52-3.59 (m, 1H), 3.58 (s, 3H), 3.65 (m, 1H), 3.83 (ddd, 11.1, 7.9, 4.6 Hz, 1H), 4.10 (ddd, *J* = 11.5, 3.9, 3.9 Hz, 1H), 4.21 (dd, *J* = 9.1, 9.1 Hz, 1H), 5.04 (d, *J* = 0.5 Hz, 1H), 5.17 (d, *J* = 8.6 Hz, 1H), 5.27 (m, 1H), 5.37 (dd, *J* = 11.5, 5.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.1, -4.9, 18.1, 19.8, 25.4, 25.8, 26.2, 31.8, 40.2, 59.9, 61.2, 68.7, 75.1, 81.4, 114.4, 117.2, 125.9, 134.6, 137.1, 155.7; IR (film) 3435 (br), 2928, 1644, 1444, 1247, 1085 cm^{-1}; $[\alpha]^{22}_D$ = -13 (c = 0.31, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{22}H_{40}O_4SiNa$ $[M + Na]^+$: 419.26, found: 419.3.



Aldehyde. A flask was charged with oxalyl chloride (2.0 M in CH_2Cl_2, 1.20 mL, 2.40 mmol) and 15 mL of CH_2Cl_2 and cooled to –78 °C. Dimethylsulfoxide (341 µL, 4.80 mmol) in 3 mL of CH_2Cl_2 was added dropwise, and the solution was stirred 2 minutes. The primary alcohol **40** (865 mg, 2.18 mmol) and 6 mL of CH_2Cl_2 were added dropwise to the mixture and allowed to stir 30 minutes at –78 °C. Triethylamine (1.52 mL, 10.9 mmol) was added dropwise and stirred 5 minutes at –78 °C followed by warming to 0 °C for 1 hour. The reaction was quenched by the addition of cold water. The organic portion was washed with cold saturated aqueous $NaHCO_3$, then water. The combined aqueous portions were washed with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (5% EtOAc/Hexanes) provided 797 mg (93%) of the aldehyde as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.09 (m, 6H), 0.89 (m, 9H), 1.57-1.77 (m, 3H), 1.81 (s, 3H), 1.82 (s, 3H), 1.87 (m, 1H), 2.69-2.81 (m, 2H), 3.54 (s, 3H), 4.09 (d, *J* = 4.8 Hz, 1H), 4.21-4.27 (m, 1H), 4.23 (d, *J* = 9.0 Hz, 1H), 5.03 (d, *J* = 0.5 Hz, 1H), 5.24 (m, 1H), 5.30 (d, *J* = 8.6 Hz, 1H), 5.35 (dd, *J* = 11.3, 5.6 Hz, 1H), 9.81 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.1, -4.8, 18.1, 19.7, 24.6, 25.7, 26.2, 33.9, 39.6, 59.8, 69.4, 74.8, 85.9, 114.3, 117.1, 126.0, 134.3, 137.0, 155.5, 202.5; IR (film) 2925, 1735 (str), 1462, 1255, 1083 cm^{-1}; $[\alpha]^{22}_D$ = -11 (c = 0.33, CH_2Cl_2).

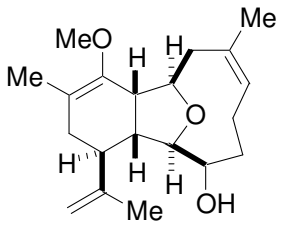


Tricycle 41. Into a flask equipped with a reflux condenser was added the previous aldehyde (664 mg, 1.68 mmol), 17 mL of toluene, and 1-(Triphenyl-l5-phosphanylidene)-propan-2-one (**28**) (1.61 g, 5.05 mmol). The solution was brought to reflux overnight, then cooled to room temperature. The mixture was concentrated in vacuo, then purified by flash column chromatography (5% then 10% EtOAc/Hexanes) provided 583 g (80%) of the ketone as a colorless oil: ^{1}H NMR (400 MHz, C_6D_6, 60 ^{o}C) δ 0.007 (s, 3H), 0.011 (s, 3H), 0.89 (s, 9H), 1.56-1.65 (m, 1H), 1.62 (s, 3H), 1.84 (s, 3H), 1.86 (s, 3H), 1.87-2.02 (m, 3H), 2.12 (m, 1H), 2.29 (dd, *J* = 17.2, 6.5 Hz, 1H), 2.67 (m, 1H), 2.70 (d, *J* = 14.4 Hz, 1H), 2.89 (ddd, *J* = 6.9, 3.6, 3.6 Hz, 1H), 3.10 (m, 1H), 3.22 (m, 1H), 3.26 (s, 3H), 4.02 (dd, *J* = 8.4, 3.7 Hz, 1H), 4.20 (ddd, *J* = 10.4, 4.5, 4.5 Hz, 1H), 4.45 (ddd, *J* = 4.9, 2.5, 2.5 Hz, 1H), 5.49 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6, 60 ^{o}C) δ –4.8, -4.7, 16.2, 18.2, 23.0, 26.1, 27.6, 28.2, 28.5, 33.1, 39.0, 40.1, 41.2, 46.7, 56.7, 73.3, 80.4, 84.3, 113.3, 130.0, 131.2, 149.1, 207.4; IR (film) 2927, 1712 (str), 1445, 1360, 1251, 1088 cm^{-1}; $[\alpha]^{22}_{D}$ = +40.8 (c = 1.10, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{25}H_{43}O_4Si$ $[M + 1]^+$: 435.29, found: 435.3.



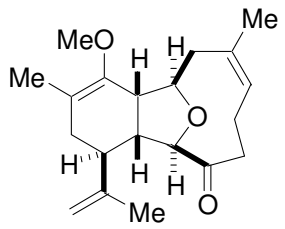
Triene 42. A flask was charged with methylenetriphenylphosphine bromide (2.30 g, 6.43 mmol) and 10 mL of THF. Potassium *tert*-butoxide (1.0 M in THF, 5.14 mL, 5.14 mmol) was added to the heterogeneous mixture to give a yellow

homogeneous solution. After stirring 30 minutes, ketone **41** (559 mg, 1.29 mmol) in 15 mL of THF was added dropwise and stirred 3 hours. The reaction was quenched by the addition of saturated aqueous NH_4Cl and diluted with Et_2O. The layers were separated and the aqueous portion was washed twice with Et_2O, dried over Na_2SO_4,, and concentrated in vacuo. Purification via flash column chromatography (5% EtOAc/Hexanes) gave 468 mg (85%) of the alkene as a colorless oil: ^{1}H NMR (400 MHz, C_6D_6, 60 ^{o}C) δ 0.016 (s, 3H), 0.022 (s, 3H), 0.93 (s, 9H), 1.58-1.68 (m, 1H), 1.65 (s, 3H), 1.75 (s, 3H), 1.81 (s, 3H), 1.90 (m, 1H), 2.04 (dd, *J* = 17.2, 5.6 Hz, 1H), 2.05-2.17 (m, 2H), 2.24 (dd, *J* = 7.1, 5.5 Hz, 1H), 2.60 (dd, *J* = 12.0, 6.1 Hz, 1H), 2.60-2.71 (m, 1H), 2.72 (d, *J* = 14.2 Hz, 1H), 2.82 (dd, *J* = 13.5, 6.4 Hz, 1H), 2.97 (m, 1H), 3.32 (s, 3H), 4.07-4.16 (m, 2H), 4.44 (m, 1H), 4.83 (m, 1H), 4.85 (m, 1H), 5.56 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6, 60 ^{o}C) δ –4.8, -4.6, 16.1, 18.3, 21.3, 23.2, 26.2, 27.6, 33.0, 38.9, 40.7, 42.1, 43.0, 57.0, 73.7, 80.3, 84.6, 110.6, 114.8, 129.5, 131.7, 148.6, 149.0; IR (film) 2928, 1706, 1644, 1452, 1254, 1086 cm^{-1}; $[\alpha]^{25}_D$ = +22.3 (c = 1.32, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{26}H_{45}O_3Si$ [M + 1]$^+$: 433.31, found: 433.4.



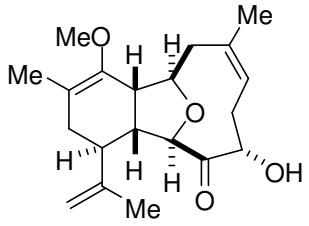
Secondary alcohol. A flask was charged with the previous alkene **42** (410 mg, 0.948 mmol) and 10 mL of THF. Tetrabutylammonium fluoride (1.0 M in THF, 1.90 mL, 1.90 mmol) was added to the solution and stirred 4 hours. Saturated

aqueous NH_4Cl was added and the solution was diluted with Et_2O. The layers were separated and the aqueous portion was washed twice with Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification via flash column chromatography (10% EtOAc/Hexanes) provided 283 mg (95%) of the alcohol as a colorless oil: ^{1}H NMR (400 MHz, C_6D_6, 60 ^{o}C) δ 1.60 (s, 3H), 1.61 (s, 3H), 1.71-1.85 (m, 2H), 1.79 (s, 3H), 1.90-2.08 (m, 4H), 2.11 (dd, *J* = 14.5, 3.9 Hz, 1H), 2.40 (ddd, *J* = 9.5, 9.5, 5.7 Hz, 1H), 2.69 (ddd, *J* = 10.2, 7.2, 2.6 Hz, 1H), 2.85-2.92 (m, 2H), 3.07 (m, 1H), 3.30 (s, 3H), 3.70 (m, 1H), 4.16 (dd, *J* = 4.4, 2.7 Hz, 1H), 4.31 (ddd, *J* = 7.1, 3.5, 3.5 Hz, 1H), 4.78-4.82 (m, 2H), 5.67 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6, 60 ^{o}C) δ 16.1, 19.9, 25.7, 28.2, 32.5, 35.4, 37.8, 42.6, 42.8, 44.3, 57.9, 73.4, 82.3, 85.9, 111.7, 115.7, 129.6, 134.3, 148.2, 150.0; IR (film) 3445 (br), 2918, 1695, 1638, 1448, 1221, 1053 cm^{-1}; $[\alpha]^{25}_D$ = +100 (c = 0.67, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{20}H_{30}O_3Na$ $[M + Na]^+$: 341.21, found: 341.4.



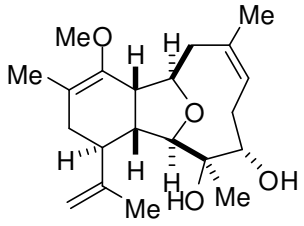
Ketone 43. A flask was charged with the secondary alcohol (300 mg, 0.866 mmol) and 17 mL of CH_2Cl_2. Pyridine (351 µL, 4.33 mmol) followed by Dess-Martin periodinane (735 mg, 1.73 mmol) were added to the solution and stirred 15 minutes. The reaction was quenched by the addition of $Na_2S_2O_3/NaHCO_3$ (5:1 v:v) and the layers were separated. The aqueous portion was washed twice with CH_2Cl_2 and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo.

Purification via flash column chromatography (10% EtOAc/Hexanes) gave 290 mg (98%) of the ketone as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64 (s, 6H), 1.78 (s, 3H), 1.93 (dd, *J* = 16.3, 4.6 Hz, 1H), 2.02 (dd, *J* = 14.4, 5.4 Hz, 1H), 2.05-2.18 (m, 2H), 2.24 (ddd, *J* = 11.2, 11.2, 4.7 Hz, 1H), 2.35 (ddd, *J* = 12.1, 12.1, 5.6 Hz, 1H), 2.51 (dd, *J* = 7.3, 7.3 Hz, 1H), 2.73 (d, *J* = 14.1 Hz, 1H), 2.82 (ddd, *J* = 12.4, 4.6, 4.6 Hz, 1H), 2.89 (dd, *J* = 11.8, 7.1 Hz, 1H), 3.10 (dddd, *J* = 12.2, 12.2, 12.2, 5.5 Hz, 1H), 3.49 (s, 3H), 4.06 (s, 1H), 4.30 (ddd, *J* = 8.0, 5.4, 3.3 Hz, 1H), 4.77 (s, 2H), 5.53 (dd, *J* = 10.8, 6.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.9, 19.0, 26.0, 26.4, 35.1, 37.3, 41.3, 42.0, 42.1, 42.6, 58.6, 85.1, 87.7, 112.7, 117.2, 126.9, 134.3, 146.7, 148.6, 214.0; IR (film) 3070, 1705 (str), 1448, 1202, 1119, 1032 cm^{-1}; $[\alpha]^{25}_{D}$ = -10.3 (c = 1.44, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{20}H_{28}O_3Na$ $[M + Na]^+$: 339.19, found: 339.3.



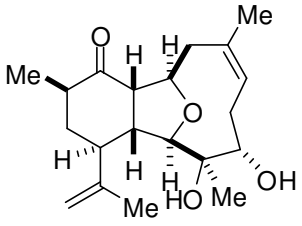
Secondary alcohol 51. A flask containing the ketone **43** (280 mg, 0.885 mmol) in 20 mL of THF was cooled to -78 °C. Potassium hexamethyldisilazide (0.5 M in toluene) was added dropwise, and the solution was allowed to stir for one hour at -78 °C. Davis oxaziridine (278 mg, 1.062 mmol) was added in 10 mL of THF to the enolate, and the solution was allowed to stir 45 minutes at -78 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl. The mixture was diluted with Et_2O and the layers were separated. The aqueous portions were washed three

times with Et_2O, dried over Na_2SO_4 and concentrated in vacuo. Purification via flash column chromatography (10% EtOAc/Hexanes) gave 245 mg (84%) of the alcohol as a white solid: ^{1}H NMR (400 MHz, C_6D_6, 60 ^{o}C) δ 1.54 (s, 3H), 1.56 (s, 3H), 1.67 (s, 3H), 1.80 (dd, *J* = 16.5, 4.9 Hz, 1H), 1.95 (m, 1H), 2.03 (dd, *J* = 14.0, 8.3 Hz, 1H), 2.20-2.31 (m , 2H), 2.44 (m, 1H), 2.61 (dd, *J* = 6.3, 6.3 Hz, 1H), 2.76 (m, 1H), 3.03 (dd, *J* = 11.4, 7.6 Hz, 1H), 3.14 (br d, *J* = 9.6 Hz, 1H), 3.23 (s, 3H), 4.22 (ddd, *J* = 10.1, 10.1, 3.7 Hz, 1H), 4.30 (m, 1H), 4.59 (s, 1H), 4.74 (s, 1H), 4.78 (s, 1H), 5.30 (dd, *J* = 7.5, 7.5 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6, 60 ^{o}C) δ 16.0, 19.5, 24.8, 34.9, 35.3, 39.9, 42.0, 42.8, 43.7, 57.8, 79.2, 83.6, 84.1, 112.7, 116.7, 121.8, 138.7, 147.1, 149.0, 214.4; IR (film) 3419 (br), 2912, 1715 (str), 1447, 1051 cm^{-1}; $[\alpha]^{24}_D$ = +55.3 (c = 6.50, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{20}H_{28}O_4$ [M + Na]$^+$: 355.19, found: 355.3.



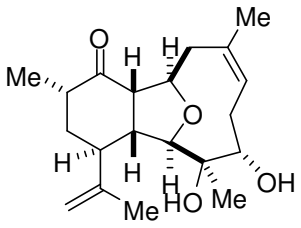
Diol 52. A flask was charged with methylmagnesium chloride (3.0 M in THF, 6.42 mL, 19.3 mmol) and 24 mL of THF. The solution was cooled to 0 ^{o}C and the ketone **51** (320 mg, 0.963 mmol) was added in 8 mL of THF dropwise. The solution was stirred 30 minutes, then quenched with saturated aqueous NH_4Cl, warmed to room temperature, and diluted with Et_2O. The layers were separated and the aqueous portion was washed twice with Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification via flash column

chromatography (20% EtOAc/ Hexanes) provided 278 mg (83%) of the alcohol as a white solid: ^{1}H NMR (400 MHz, C_6D_6, 60 ^{o}C) δ 1.28 (s, 3H), 1.59 (s, 3H), 1.65 (s, 3H), 1.78 (s, 3H), 1.91 (dd, *J* = 16.8, 5.1 Hz, 1H), 1.99-2.09 (m, 2H), 2.13 (dd, *J* = 14.6, 4.4 Hz, 1H), 2.20-2.31 (m, 2H), 2.40 (ddd, *J* = 9.7, 9.7, 5.2 Hz, 1H), 2.56 (ddd, *J* = 10.3, 7.4, 2.7 Hz, 1H), 2.76-2.85 (m, 2H), 3.12 (m, 1H), 3.29 (s, 3H), 3.51 (dd, *J* = 7.5, 4.3 Hz, 1H), 4.13 (d, *J* = 2.6 Hz, 1H), 4.27 (ddd, *J* = 7.4, 4.4, 2.9 Hz, 1H), 4.83 (s, 2H), 5.68 (dd, *J* = 10.7, 6.7 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6, 60 ^{o}C) δ 16.0, 19.6, 24.3, 27.7, 35.1, 36.1, 38.0, 42.9, 43.4, 44.1, 58.0, 76.5, 77.4, 82.5, 87.5, 112.5, 115.8, 126.0, 135.9, 147.8, 149.7; IR (film) 3437 (br), 2910, 1445, 1376, 1118, 1092, 1050 cm^{-1}; $[\alpha]^{24}_D$ = +82 (c = 0.34, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{21}H_{32}O_4Na$ $[M + Na]^+$: 371.22, found: 371.4.



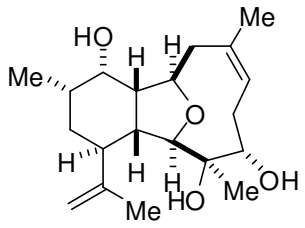
Ketone 53. A flask was charged with diol **52** (220 mg, 0.631 mmol), 10 mL of $CHCl_3$, and 450 µL of water. Hydrochloric acid (12 M, 450 µL, 5.4 mmol) was added to the biphasic solution and stirred for 2 hours. The reaction was quenched by the slow addition of saturated aqueous $NaHCO_3$ and diluted with CH_2Cl_2. The layers were separated and the aqueous portion was washed twice with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (20% EtOAc/Hexanes) gave 192 mg (91%) of the ketone as a white solid and 16 mg (8%) of the (*4S*)-product (**#**) as a

colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, 60 ^{o}C) δ 1.06 (d, *J* = 6.6 Hz, 3H), 1.08 (s, 3H), 1.58 (ddd, *J* = 13.0, 13.0, 13.0 Hz, 1H), 1.69 (s, 3H), 1.89 (s, 3H), 1.88-1.99 (m, 2H), 2.08 (m, 1H), 2.33 (br s, 1H), 2.46 (ddd, *J* = 15.0, 12.3, 2.8 Hz, 1H), 2.48-2.60 (m, 2H), 2.63 (dd, *J* = 11.7, 7.6 Hz, 1H), 2.83-3.06 (m, 3H), 3.53 (br dd, *J* = 6.9, 6.9 Hz, 1H), 4.09 (s, 1H), 4.36 (ddd, *J* = 9.5, 3.2, 3.2 Hz, 1H), 4.86 (s, 2H), 5.76 (dd, *J* = 10.6, 6.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 60 ^{o}C) δ 14.5, 18.6, 24.4, 27.9, 35.9, 36.9, 39.3, 42.1, 46.8, 47.9, 54.4, 76.3, 77.0, 80.5, 89.2, 113.4, 125.0, 137.0, 146.3, 210.9; IR (film) 3523 (br), 2925, 1705 (str), 1450, 1184, 1071 cm^{-1}; $[\alpha]^{22}_{D}$ = +35 (c = 0.37, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{20}H_{30}O_4Na$ $[M + Na]^+$: 357.20, found: 357.3.



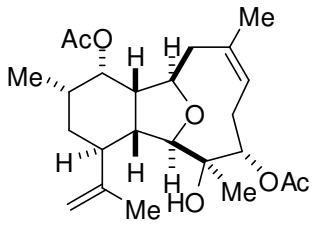
Ketone 54. Into a flask containing the previous ketone **53** (242 mg, 0.724 mmol) and 24 mL of methanol was added catalytic sodium hydride. After stirring 15 minutes, the reaction was quenched by the slow addition of saturated aqueous NH_4Cl and diluted with Et_2O. The layers were separated and the aqueous portion was washed twice with Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (20% EtOAc/Hexanes) gave 103 mg (42%) of the ketone as a colorless oil and 139 mg (58%) of the (*4R*)-product as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$, 60 ^{o}C) δ 1.02 (d, *J* = 6.8 Hz, 3H), 1.21 (s, 3H), 1.62 (ddd, *J* = 14.2, 9.2, 5.5, Hz, 1H), 1.73 (s,

3H), 1.77 (s, 3H), 1.94-2.09 (m, 3H), 2.35-2.55 (m, 4H), 2.72-2.81 (m, 2H), 2.95 (ddd, *J* = 13.3, 11.4, 7.5 Hz, 1H), 3.04 (ddd, *J* = 7.6, 7.6, 7.6 Hz, 1H), 3.53 (dd, *J* = 7.4, 3.0 Hz, 1H), 3.77 (d, *J* = 5.7 Hz, 1H), 4.60 (m, 1H), 4.84 (s, 1H), 4.90 (s, 1H), 5.65 (dd, *J* = 10.7, 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 60 ^{o}C) δ 15.0, 20.2, 22.7, 27.9, 34.7, 34.8, 37.2, 40.2, 41.2, 45.0, 53.5, 76.1, 76.2, 77.2, 87.3, 112.1, 125.8, 134.5, 147.0, 211.9; IR (film) 3459 (br), 2930, 1710 (str), 1448, 1377, 1048 cm^{-1}; $[\alpha]^{21}_{D}$ = +54 (c = 1.9, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{20}H_{30}O_4Na$ $[M + Na]^+$: 357.20, found: 357.3.



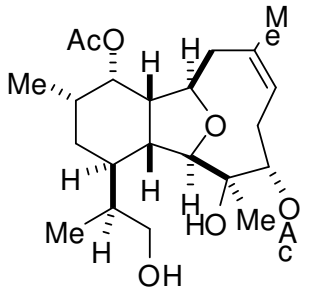
Triol. Into a flask charged with the ketone **54** (158 mg, 0.472 mmol) was added 5 mL of THF. The solution was cooled to –78 ^{o}C and L-Selectride® (1.0 M in THF, 567 µL, 0.567 mmol) dropwise. The reaction was stirred 10 minutes, then quenched by the addition of sodium hydroxide (3 M, 288 µL, 0.864 mmol) and hydrogen peroxide (30%, 566 µL, 5.184 mmol). The mixture was stirred three hours at room temperature, then diluted with CH_2Cl_2. The layers were separated and the aqueous portions were washed twice with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (50% EtOAc/Hexanes) gave 148 mg (94%) of the alcohol as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$, 60 ^{o}C) δ 0.99 (d, *J* = 6.1 Hz, 3H)1.29 (s, 3H), 1.38 (m, 1H), 1.73 (s, 3H), 1.83 (s, 3H), 1.98 (dd, *J* = 14.6, 3.9 Hz, 1H), 2.06 (m, 1H),

2.13-2.28 (m, 3H), 2.61 (s, 2H), 2.78 (d, J = 14.4 Hz, 1H), 3.00 (ddd, J = 11.6, 8.2, 8.2, Hz, 1H), 3.65 (m, 1H), 3.78 (s, 1H), 3.92 (d, J = 7.0 Hz, 1H), 4.37 (d, J = 2.5 Hz, 1H), 4.75 (s, 1H), 4.84 (s, 1H), 5.64 (dd, J = 9.8, 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 60 ^{o}C) δ 16.9, 21.6, 22.9, 28.2, 28.4, 31.4, 34.4, 38.3, 39.5, 41.3, 45.5, 72.2, 75.9, 76.9, 79.8, 88.0, 110.7, 125.8, 134.2, 149.1; IR (film) 3382 (br), 2912, 1440, 1366, 1052 cm^{-1}; $[\alpha]^{21}_{D}$ = +2.8 (c = 3.2, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{20}H_{32}O_4Na$ $[M + K]^+$: 375.33, found: 375.2.



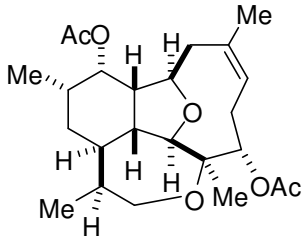
Diester 55. Into a flask containing the triol (122 mg, 0.363 mmol) in 10 mL of CH_2Cl_2 was added triethylamine (253 µL, 1.81 mmol) and 4-dimethylaminopyridine (4.4 mg, 0.036 mmol). Acetic anhydride (103 µL, 1.09 mmol) was added to the solution and stirred for firve hours. The reaction was quenched using saturated aqueous NH_4Cl and the layers were separated. The aqueous portions were washed twice with CH_2Cl_2, dried over Na_2SO_4 and concentrated in vacuo. Purification via flash column chromatography (20% EtOAc/Hexanes) gave 130 mg (85%) of the ester as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$, 60 ^{o}C) δ 0.90 (d, J = 7.0 Hz, 3H), 1.24 (s, 3H), 1.47 (m, 1H), 1.63 (ddd, J = 13.5, 8.8, 4.1 Hz, 1H), 1.71 (s, 3H), 1.79 (s, 3H), 1.90 (dd, J = 14.8, 3.6 Hz, 1H), 1.91-2.08 (m, 2H), 2.04 (s, 3H), 2.07 (s, 3H), 2.25-2.34 (m, 2H), 2.61-2.68 (m, 2H), 2.77 (d, J = 14.9 Hz, 1H), 3.12 (ddd, J = 12.9, 11.5, 8.2 Hz, 1H), 3.90 (d, J = 6.4 Hz, 1H), 4.19 (d, J = 2.6 Hz, 1H), 4.75 (m 1H),

4.76 (s, 1H), 4.84 (s, 1H), 5.16 (dd, *J* = 4.1, 4.1 Hz, 1H), 5.70 (dd, *J* = 11.2, 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 60 ^{o}C) δ 16.5, 20.9, 21.1, 21.3, 23.5, 28.3, 29.6, 29.8, 32.9, 37.9, 39.2, 42.1, 43.8, 73.7, 75.5, 78.7, 79.6, 87.6, 111.1, 125.2, 134.9, 148.3, 170.51, 170.54; IR (film) 3362 (br), 2933, 1734 (str), 1448, 1374, 1238 (str), 1038 cm^{-1}; $[\alpha]^{22}_{D}$ = +18 (c = 3.1, $CHCl_3$); MS (electrospray ionization) calculated for $C_{24}H_{36}O_6Na$ $[M + Na]^+$: 443.24, found: 443.3.



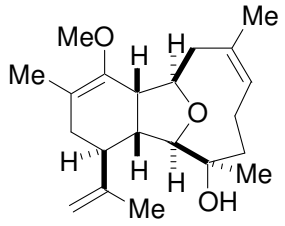
Diol 56. A flask was charged with alkene **55** (16.1 mg, 38.3 μmol) in 1 mL of THF. (+)-Diisopinocampheylborane (33.1 mg, 115 μmol) was added to the solution and allowed to stir 30 minutes. The reaction was quenched by the addition of 1 mL of water and sodium perborate tetrahydrate (53.0 mg, 345 μmol) and allowed to stir for three hours, then diluted with brine and Et_2O. The layers were separated and the aqueous portion was washed twice with Et_2O, dried over Na_2SO_4, and concentrated in vacuo. Purification via flash column chromatography (10% then 30% EtOAc/Hexanes) gave 12.3 mg (74%) of the diol as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (d, *J* = 6.0 Hz, 3H), 8.87 (d, *J* = 6.9 Hz, 3H), 1.02 (m, 1H), 1.17 (m, 1H), 1.38 (s, 3H), 1.70-1.92 (m, 5H), 1.81 (s, 3H), 2.06 (m, 1H), 2.10 (s, 3H), 2.11 (s, 3H), 2.90 (br s, 1H), 2.46 (dd, *J* =10.3, 8.1 Hz, 1H), 2.69 (d, *J* = 14.8 Hz, 1H), 3.15 (ddd, *J* = 13.5, 11.5, 7.7 Hz, 1H), 3.53-3.62 (m, 3H), 3.87 (d, *J* = 10.7 Hz,

1H), 4.04 (s, 1H), 4.89 (d, *J* = 7.6 Hz, 1H), 5.18 (d, *J* = 3.3 Hz, 1H), 5.65 (dd, *J* = 10.3, 4.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 18.4, 21.2, 21.5, 21.8, 23.3, 24.7, 28.3, 29.4, 30.9, 32.5, 36.6, 38.0, 41.0, 45.7, 65.0, 73.8, 75.7, 77.8, 79.9, 88.7, 125.2, 133.9, 171.4, 171.6; IR (film) 3392 (br), 2926, 1735 (str), 1375, 1244 (str), 1024 cm^{-1}; $[\alpha]^{21}_D$ = -11 (c = 0.40, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{24}H_{38}O_7Na$ $[M + Na]^+$: 461.25, found 461.4.



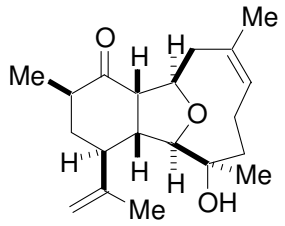
Asbestinin-12 (2). A flask charged with diol **56** (13.7 mg, 31.2 μmol) in 1.6 mL of $CHCl_3$ was cooled to 0 °C. 2,6 lutidine (18.2 μL, 0.156 mmol) followed by trifluoromethanesulfonic anhydride (5.80 μL, 34.4 μmol) were added to the solution and allowed to stir 30 minutes at 0 °C. The solution was warmed to room temperature for 4 hours, then quenched via the addition of saturated aqueous NH_4Cl. The mixture was diluted with $CHCl_2$ and the layers were separated. The aqueous portion was washed three times with CH_2Cl_2, dried over Na_2SO_4, and concentrated in vacuo. Purification via flash column chromatography (15% EtOAc/Hexanes) gave 9.0 mg (69%) of asbestinin-12 as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, *J* = 7.1 Hz, 3H), 0.92 (d, *J* = 7.2 Hz, 3H), 1.00 (ddd, *J* = 13.4, 3.3, 1.7 Hz, 1H), 1.42 (s, 3H), 1.51 (ddd, *J* = 3.8, 3.8, 3.8 Hz, 1H), 1.62 (m, 2H), 1.79 (s, 3H), 1.85 (dd, *J* = 14.6, 4.5 Hz, 1H), 1.98 (ddd, *J* = 10.8, 3.1, 3.1 Hz, 1H), 2.02 (m, 1H), 2.10 (s, 3H), 2.12 (s, 3H), 2.26 (ddd, *J* = 11.0, 11.0, 11.0 Hz, 1H),

2.68 (d, *J* = 15.1 Hz, 1H), 3.19 (ddd, *J* = 13.8, 11.1, 7.4 Hz, 1H), 3.49 (dd, *J* = 13.3, 3.8 Hz, 1H), 3.85 (d, *J* = 13.1 Hz, 1H), 3.93 (d, *J* = 9.1 Hz, 1H), 4.10 (ddd, *J* = 3.4, 3.4, 3.4 Hz, 1H), 4.87 (d, *J* = 7.4 Hz, 1H), 5.28 (dd, *J* = 4.9, 2.9 Hz, 1H), 5.74 (dd, *J* = 10.8, 6.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.8, 18.2, 19.3, 21.3, 21.6, 29.6, 31.3, 31.4, 33.4, 36.9, 37.6, 38.3, 40.8, 44.9, 67.8, 73.6, 76.7, 79.2, 81.7, 91.3, 126.7, 131.6, 170.8, 171.3; IR (film) 2926, 1737 (str), 1459, 1377, 1231, 1088 cm^{-1}; $[\alpha]^{21}_{D}$ = -22 (c = 0.29, $CHCl_3$); MS (electrospray ionization) calculated for $C_{24}H_{36}O_6$ $[M + Na]^+$: 443.24, found: 443.3.



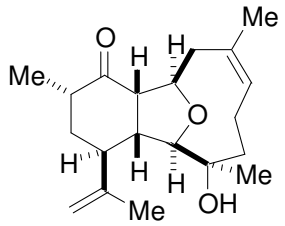
Tertiary alcohol 44. A flask was charged with methylmag-nesium chloride (3.0 M in THF, 3.47 mL, 10.4 mmol) and 70 mL of THF. The solution was cooled to 0 °C and the ketone **43** (659 mg, 2.08 mmol) was added in 35 mL of THF dropwise. The solution was stirred 30 minutes, then quenched with saturated aqueous NH_4Cl, warmed to room temperature, and diluted with Et_2O. The layers were separated and the aqueous portion was washed twice with Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification via flash column chromatography (10% EtOAc/ Hexanes) provided 678 mg (98%) of the alcohol as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 3H), 1.66 (s, 3H), 1.69 (s, 3H), 1.69-1.79 (m, 1H), 1.85-1.96 (m, 2H), 1.90 (s, 3H), 2.00 (m, 1H), 2.17 (m, 2H), 2.28 (ddd, *J* = 11.2, 11.2, 4.5 Hz, 1H), 2.43 (dd, *J* = 11.7, 6.9 Hz, 1H), 2.75 (dd, *J* = 7.1,

7.1 Hz, 1H), 2.95 (d, *J* = 14.7 Hz, 1H), 3.07-3.24 (m, 2H), 3.52 (s, 3H), 3.87 (s, 1H), 4.18 (ddd, *J* = 8.6, 3.3, 3.3 Hz, 1H), 4.82 (s, 1H), 4.83 (m, 1H), 5.84 (dd, *J* = 10.9, 6.0 Hz, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8, 19.0, 27.1, 28.3, 28.9, 35.2, 36.7, 38.8, 41.8, 42.9, 45.0, 58.6, 75.3, 83.4, 89.4, 113.0, 116.7, 128.7, 136.5, 147.0, 149.1; IR (film) 3511 (br), 2914, 1447, 1119, 1058 cm^{-1}; $[\alpha]^{24}_D$ = +74 (c = 0.42, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{21}H_{32}O_3Na$ $[M + Na]^+$: 355.23, found: 355.3.



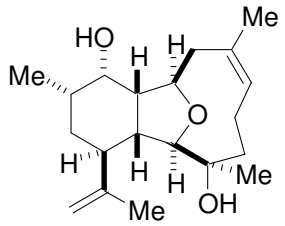
Ketone 45. A flask was charged with alcohol **44** (678 mg, 0.255 mmol), 20 mL of $CHCl_3$, and 2.5 mL of water. Hydrochloric acid (12 M, 2.50 mL, 30.0 mmol) was added to the biphasic solution and stirred for 2 hours. The reaction was quenched by the slow addition of saturated aqueous $NaHCO_3$. The layers were separated and the aqueous portion was washed twice with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (10% then 25% EtOAc/Hexanes) gave 562 mg (87%) of the ketone as a white solid and 58 mg (9%) of the (*4S*)-product (**#**) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 3H), 1.07 (d, *J* = 6.6 Hz, 3H), 1.59 (dd, *J* = 25.8, 13.0 Hz, 1H), 1.69 (s, 3H), 1.71-1.78 (m, 1H), 1.85-2.03 (m, 4H), 1.93 (s, 3H), 2.48 (ddd, *J* = 12.3, 12.3, 2.8 Hz, 1H), 2.59 (dddd, *J* = 11.7, 11.7, 6.5, 6.5 Hz, 1H), 2.69 (dd, *J* = 12.0, 7.0 Hz, 1H), 2.91-2.97 (m, 2H), 3.07 (m, 1H), 3.13 (ddd, *J* = 11.9, 11.9, 6.4 Hz, 1H), 3.94 (s, 1H), 4.36 (ddd, *J* = 9.9, 3.1, 3.1 Hz, 1H), 4.86 (m, 2H),

5.83 (dd, *J* = 11.5, 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 18.5, 27.2, 28.4, 28.7, 35.2, 38.5, 39.0, 41.8, 46.0, 48.7, 54.1, 74.8, 80.5, 91.3, 113.4, 128.3, 136.6, 146.2, 211.7; IR (film) 3514 (br), 2928, 1702 (str), 1453, 1377, 1184, 1076 cm^{-1}; $[\alpha]^{24}_D$ = +40 (c = 0.18, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{20}H_{30}O_3Na$ $[M + Na]^+$: 341.21, found: 341.3.



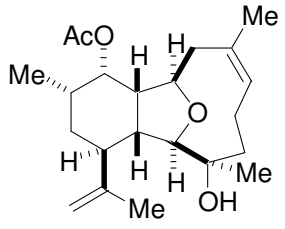
Ketone 46. Into a flask containing the previous ketone **45** (551 mg, 1.73 mmol) and 17 mL of methanol was added catalytic sodium hydride. After stirring 15 minutes, the reaction was quenched by the slow addition of saturated aqueous NH_4Cl and diluted with Et_2O. The layers were separated and the aqueous portion was washed twice with Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (10% then 25% EtOAc/Hexanes) gave 246 mg (45%) of the ketone as a colorless oil and 303 mg (55%) of the (*4R*)-product (**#**) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (d, *J* = 6.8Hz, 3H), 1.14 (s, 3H), 1.59-1.71 (m, 2H), 1.77 (s, 3H), 1.80-1.87 (m, 1H), 1.88 (s, 3H), 1.92-1.99 (m, 1H), 2.01 (dd, *J* = 14.8, 3.7 Hz, 1H), 2.11 (ddd, *J* = 13.9, 8.6, 7.1 Hz, 1H), 2.34 (s, 1H), 2.47 (ddd, *J* = 8.6, 8.6, 5.5 Hz, 1H), 2.58 (ddq, *J* = 21.7, 7.0, 7.0 Hz, 1H), 2.83 (ddd, *J* = 7.8, 7.8, 7.8 Hz, 1H), 2.84-2.93 (m, 2H), 3.02 (ddd, *J* = 8.1, 8.1, 4.6 Hz, 1H), 3.72 (d, *J* = 4.6 Hz, 1H), 4.58 (ddd, *J* = 6.3, 3.3, 3.3 Hz, 1H), 4.89 (d, *J* = 0.7 Hz, 1H), 4.92 (d, *J* = 1.3 Hz, 1H), 5.71 (dd, *J* =

11.3, 5.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 20.0, 25.3, 28.5, 28.9, 34.7, 36.5, 38.4, 40.7, 40.9, 45.9, 53.3, 74.7, 77.7, 89.1, 112.7, 129.2, 134.2, 146.9, 212.9; IR (film) 3443 (br), 2928, 1710 (str), 1642, 1446, 1376, 1081 cm^{-1}; $[\alpha]^{24}_D$ = +92 (c = 0.19, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{20}H_{30}O_3Na$ [M + Na]$^+$: 341.21, found: 341.4.



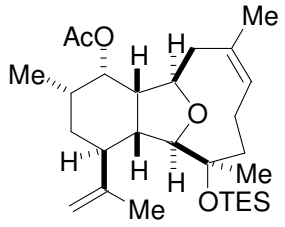
Diol. Into a flask charged with the ketone **46** (523 mg, 1.64 mmol) was added 16 mL of THF. The solution was cooled to –78 °C and L-Selectride® (1.0 M in THF, 1.97 mL, 1.97 mmol) dropwise. The reaction was stirred 10 minutes, then quenched by the addition of sodium hydroxide (3 M, 1.0 mL, 3.0 mmol) and hydrogen peroxide (30%, 2.0 mL, 18 mmol). The mixture was stirred three hours at room temperature, then diluted with Et_2O. The layers were separated and the aqueous portions were washed twice with Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (25% EtOAc/Hexanes) gave 493 mg (94%) of the alcohol as a white solid: ^{1}H NMR (400 MHz, C_6D_6, 60 °C) δ 0.95 (d, *J* = 7.0 Hz, 3H), 1.19 (m, 1H), 1.28 (s, 3H), 1.33 (m, 2H), 1.56 (m, 1H), 1.64-1.73 (m, 2H), 1.70 (s, 3H), 1.75 (s, 3H), 1.77-1.94 (m, 2H), 1.89 (m, 1H), 2.19 (ddd, *J* = 7.8, 4.2, 4.2 Hz, 1H), 2.69-2.92 (m, 4H), 3.42 (s, 1H), 3.91 (d, *J* = 7.5 Hz, 1H), 4.24 (dd, *J* = 6.7, 3.8 Hz, 1H), 4.86 (s, 1H), 4.88 (d, *J* = 1.3 Hz, 1H), 5.52 (dd, *J* = 11.0, 6.1 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6, 60 °C) δ 17.2,

22.0, 24.6, 28.4, 28.8, 29.7, 31.8, 38.5, 38.6, 39.8, 42.6, 45.9, 72.2, 74.7, 80.0, 89.5, 110.6, 130.0, 132.3, 149.8; IR (film) 3329 (br), 2921, 1439, 1373, 1088 cm^{-1}; $[\alpha]^{25}_D$ = +5.7 (c = 0.46, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{20}H_{32}O_3Na$ [M + Na]$^+$: 343.23, found: 343.3.



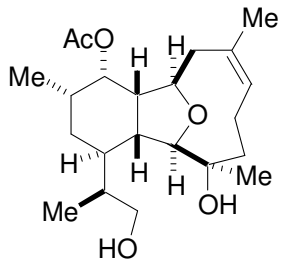
Ester 47. Into a flask containing the secondary alcohol (406 mg, 1.27 mmol) in 26 mL of CH_2Cl_2 was added triethylamine (707 µL, 5.07 mmol) and 4-dimethylaminopyridine (16.0 mg, 0.127 mmol). Acetic anhydride (240 µL, 2.53 mmol) was added to the solution and stirred overnight. The reaction was quenched using saturated aqueous NH_4Cl and the layers were separated. The aqueous portions were washed twice with CH_2Cl_2, dried over Na_2SO_4 and concentrated in vacuo. Purification via flash column chromatography (25% EtOAc/Hexanes) gave 453 mg (99%) of the ester as a colorless oil: ^{1}H NMR (400 MHz, C_6D_6, 60 ^{o}C) δ 0.87 (d, *J* = 7.0 Hz, 3H), 1.25 (s, 3H), 1.37 (ddd, *J* = 13.7, 6.2, 4.1 Hz, 1H), 1.50-1.69 (m, 4H), 1.66 (s, 3H), 1.67 (s, 3H), 1.74 (dd, *J* = 14.6, 3.9 Hz, 1H), 1.77-1.92 (m, 2H), 1.81 (s, 3H), 2.32 (ddd, *J* = 4.9, 4.9, 4.9 Hz, 1H), 2.66-2.78 (m, 3H), 2.89 (m, 1H), 3.88 (d, *J* = 6.6 Hz, 1H), 4.25 (dd, *J* = 7.0, 3.8 Hz, 1H), 4.83 (s, 1H), 4.85 (d, *J* = 1.3 Hz, 1H), 5.22 (dd, *J* = 5.1, 3.7 Hz, 1H), 5.51 (dd, *J* = 11.1, 6.0 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6, 60 ^{o}C) δ 16.8, 20.7, 21.5, 24.9, 28.4, 29.7, 30.1, 30.2, 38.1, 38.8, 39.7, 43.0, 44.2, 73.8, 74.7, 79.7, 89.3, 111.1, 130.0, 132.6, 149.2, 170.0; IR (film)

3465(br), 2924, 1737 (str), 1450, 1374, 1237, 1039 cm^{-1}; $[\alpha]^{25}_D$ = +42.2 (c = 1.32, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{22}H_{35}O_4$ $[M + 1]^+$: 363.25, found: 363.4.



Diene 48. A flask was charged with ester **13** (64.0 mg, 0.176 mmol) in 2 mL of CH_2Cl_2 and cooled to 0 °C. 2,6-lutidine (62 µL, 0.53 mmol) and triethylsilyl trifluoromethanesulfonate (60 µL, 0.27 mmol) were added sequentially and stirred for 1 hour at 0 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl, warmed to room temperature and the layers were separated. The aqueous portions were washed twice with CH_2Cl_2, dried over Na_2SO_4 and concentrated in vacuo. Purification via flash column chromatography (5% EtOAc/Hexanes) gave 67 mg (80%) of the alkene as a colorless oil: ^1H NMR (400 MHz, C_6D_6, 60 °C) δ 0.62 (q, *J* = 7.8 Hz, 6H), 0.83 (d, *J* = 5.8 Hz, 3H), 1.00 (t, *J* = 7.9 Hz, 9H), 1.38 (ddd, *J* = 13.9, 3.1, 3.1 Hz, 1H), 1.55-1.65 (m, 2H), 1.57 (s, 3H), 1.71 (s, 3H), 1.73-1.89 (m, 4H), 1.79 (s, 3H), 1.86 (s, 3H), 2.20 (dd, *J* = 7.1, 4.6 Hz, 1H), 2.63 (d, *J* = 13.9 Hz, 1H), 2.68 (m, 1H), 2.96 (dd, *J* = 8.8, 8.8 Hz, 1H), 3.03 (d, *J* = 5.3 Hz, 1H), 3.97 (d, *J* = 10.4 Hz, 1H), 4.08 (d, *J* = 1.63 Hz, 1H), 4.88 (s, 1H), 4.94 (m, 1H), 5.19 (m, 1H), 5.44 (dd, *J* = 10.6, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6, 60 °C) δ 7.3, 7.5, 18.2, 20.7, 23.1, 23.5, 26.7, 28.5, 28.9, 29.5, 38.5, 39.2, 39.5, 41.4, 44.8, 74.1, 78.4, 79.4, 88.3, 110.1, 130.5, 130.9, 149.4, 170.5; IR (film) 2957, 1739 (str), 1462, 1373, 1235,

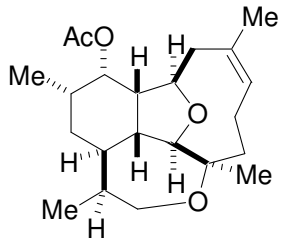
1116, 1048 cm^{-1}; $[\alpha]^{23}_D$ = -33 (c = 0.43, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{28}H_{48}O_4SiNa$ $[M + Na]^+$: 499.32, found: 499.4.



Diol 50. A flask was charged with diene **48** (10.4 mg, 21.8 µmol) in 500 µL of THF. (+)-Diisopinocampheylborane (24.0 mg, 83.2 µmol) was added to the solution and allowed to stir 30 minutes. The reaction was quenched by the addition of sodium hydroxide (3 M, 130 µL, 0.390 mmol), then hydrogen peroxide (30%, 260 µL, 2.29 mmol). The biphasic solution was stirred three hours, then diluted with brine and Et_2O. The layers were separated and the aqueous portion was washed twice with Et_2O, dried over Na_2SO_4, and concentrated in vacuo. For purification purposes, the product and isopinocampheol were carried on to the next reaction as a mixture. In a separate experiment, purification via flash column chromatography (10% EtOAc/Hexanes) gave the alcohol as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.59 (q, *J* = 7.8 Hz, 6H), 0.81 (d, *J* = 6.5 Hz, 3H), 0.94 (t, *J* = 7.9 Hz, 9 H), 1.01 (d, *J* = 6.7 Hz, 3H), 1.22 (d, *J* = 15.3 Hz, 1H), 1.47 (s, 3H), 1.59-1.94 (m, 9H), 1.77 (s, 3H), 2.08-2.18 (m, 2H), 2.10 (s, 3H), 2.52 (ddd, *J* = 12.2, 12.2, 8.3 Hz, 1H), 2.66 (m, 2H), 3.41 (dd, *J* = 10.9, 5.3 Hz, 1H), 3.63 (m, 1H), 3.78 (d, *J* = 10.7 Hz, 1H), 3.93 (s, 1H), 5.14 (m, 1H), 5.48 (dd, *J* = 11.2, 5.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.8, 6.9, 7.0, 15.8, 18.3, 21.2, 22.9, 26.7, 28.3, 28.5, 29.8, 32.9, 38.1, 38.7, 38.9, 44.4,

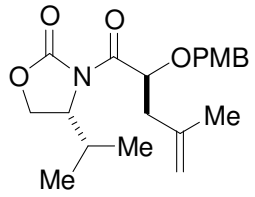
66.5, 73.9, 78.2, 78.8, 87.3, 130.0, 130.7, 171.4; IR (film) 3446 (br), 2957, 1737 (str), 1457, 1374, 1237, 1137, 1117, 1043 cm^{-1}; $[\alpha]^{26}_D$ = +2.3 (c = 0.68, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{28}H_{50}O_5SiNa$ $[M + Na]^+$: 517.33, found: 517.5.

Into a flask containing the alcohol **15** in 500 µL of THF was added tetrabutylammonium fluoride (1.0 M in THF, 63 µL, 63 µmol). The solution was stirred 1 hour, then quenched by the addition of saturated aqueous NH_4Cl and diluted with Et_2O. The layers were separated and the aqueous portion was washed three times with Et_2O, dried over Na_2SO_4, and concentrated in vacuo. Purification via flash column chromatography (30% EtOAc/Hexanes) gave 5.1 mg (64% over two steps) of the diol as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 0.82 (d, *J* = 6.0 Hz, 3H), 0.86-0.99 (m, 1H), 0.88 (d, *J* = 6.9 Hz, 3H), 1.17 (d, *J* = 9.8 Hz, 1H), 1.42 (s, 3H), 1.64 (dd, *J* = 13.9, 8.4 Hz, 1H), 1.75-1.85 (m, 6H), 1.79 (s, 3H), 1.93 (m, 1H), 2.09-2.13 (m, 1H), 2.10 (s, 3H), 2.34 (br s, 1H), 2.49 (dd, *J* = 8.7, 8.7 Hz, 1H), 2.60 (dd, *J* = 21.1, 11.0 Hz, 1H), 2.69 (d, *J* = 14.4 Hz, 1H), 3.46 (dd, *J* = 11.6, 5.5 Hz, 1H), 3.53 (dd, *J* = 11.5, 11.5 Hz, 1H), 3.78 (d, *J* = 10.2 Hz, 1H), 4.04 (s, 1H), 5.18 (d, *J* = 3.7 Hz, 1H), 5.52 (dd, *J* = 10.7, 5.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 1.0, 14.1, 18.4, 21.2, 23.0, 28.4, 29.4, 29.7, 29.8, 30.9, 37.9, 38.1, 42.2, 45.7, 65.4, 74.0, 75.1, 79.9, 89.1, 130.1, 171.4; IR (film) 3355 (br), 2925, 1736 (str), 1455, 1381, 1237, 1017 cm^{-1}; $[\alpha]^{26}_D$ = +33 (c = 0.39, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{22}H_{36}O_5K$ $[M + K]^+$: 419.36, found: 419.4.



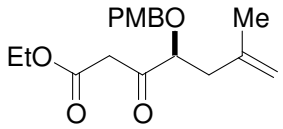
11-acetoxy-4-deoxyasbestinin D (1). A flask charged with diol **50** (8.9 mg, 24 μmol) in 1.1 mL of THF was cooled to 0 °C. 2,6 lutidine (13.6 μL, 0.117 mmol) followed by trifluoromethanesulfonic anhydride (5.8 μL, 34 μmol) were added to the solution and allowed to stir 45 minutes at 0 °C. The solution was warmed to room temperature for 4 hours, then quenched via the addition of saturated aqueous NH_4Cl. The mixture was diluted with Et_2O and the layers were separated. The aqueous portion was washed three times with Et_2O, dried over Na_2SO_4, and concentrated in vacuo. Purification via flash column chromatography (10% EtOAc/Hexanes) gave 5.5 mg (66%) of 11-acetoxy-4-deoxyasbestinin D as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (d, *J* = 7.1 Hz, 3H), 0.92 (d, *J* = 7.2 Hz, 3H), 1.01 (m, 1H), 1.35 (s, 3H), 1.52 (ddd, *J* = 13.5, 13.5, 9.7 Hz, 1H), 1.61 (m, 1H), 1.75 (s, 3H), 1.75 (m, 2H), 1.84-2.08 (m, 5H), 2.10 (s, 3H), 2.34 (ddd, *J* = 10.4, 10.4, 10.4 Hz, 1H), 2.50 (br d, *J* = 14.8 Hz, 1H), 2.55 (ddd, *J* = 14.5, 10.3, 4.8 Hz, 1H), 3.48 (dd, *J* = 13.2, 3.2 Hz, 1H), 3.86 (d, *J* = 15.2 Hz, 1H), 3.87 (d, *J* = 8.7 Hz, 1H), 4.10 (ddd, *J* = 5.5, 2.9, 2.9 Hz, 1H), 5.31 (dd, *J* = 5.1, 2.8 Hz, 1H), 5.47 (dd, *J* = 8.1, 8.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.0, 17.9, 21.3, 23.4, 26.1, 28.9, 31.3, 31.5, 37.3, 37.5, 38.0, 38.5, 40.5, 45.8, 67.9, 73.5, 76.4, 81.0, 92.2, 128.7, 130.8, 171.3; IR (film) 2926, 1737 (str), 1459, 1377, 1231, 1088 cm^{-1}; $[\alpha]^{26}_D$ = -15 (c = 0.17, $CHCl_3$); MS (electrospray ionization) calculated for $C_{22}H_{35}O_4$ $[M + 1]^+$: 363.25, found: 363.2.

An authentic sample of 11-acetoxy-4-deoxyasbestinin D was provided by Dr. Abimael D. Rodríguez (University of Puerto Rico, Río Piedras),[3] purified in the same manner as described above, and an optical rotation was obtained under identical conditions: $[\alpha]^{25}_{D}$ = -15 (c = 0.10, $CHCl_3$). The ^1H NMR (500 MHz, $CDCl_3$) spectrum of the authentic sample also mirrored the synthetic material.



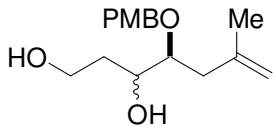
Alkylation Adduct. Into a flask equipped with an addition funnel and a low-temperature thermometer was added sodum bis(trimethylsilyl)amide (0.78 M in toluene/THF, 321.86 mL, 251.05 mmol) and 400 mL of THF. The solution was cooled to –78 ^oC and glycolate **2** in 200 mL of THF was added dropwise via addition funnel keeping the temperature below –65 ^oC. The resultant solution was stirred 30 minutes at –78 ^oC, then methallyl iodide (90.66 mL, 836.8 mmol) was added dropwise via addition funnel. The soludtion was stirred 5 minutes at –78 ^oC, then warmed to –45 ^oC for 1 hour. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and then warmed to room temperature. The layers were separated and the aqueous was extracted twice with EtOAc. The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (10% then 20% EtOAc/Hexanes) provided 47.07 g (78%) of the alkene as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 0.82 (d, *J* = 6.9 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H), 1.78 (s, 3H), 2.27 (m, 1H), 2.40 (dd, *J* = 13.9, 8.8 Hz, 1H), 2.51 (dd, *J* = 13.9, 4.0 Hz, 1H), 3.78 (s, 3H), 4.18 (m, 2H), 4.34 (m, 1H), 4.45 (AB,

J_{AB} = 11.3 Hz, Δv_{AB} = 27.3 Hz, 2H), 4.82 (s, 2H), 5.26 (dd, *J* = 4.0, 8.8 Hz, 1H), 6.82 (d, *J* = 6.6 Hz, 2H), 7.24 (d, *J* = 6.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 17.7, 22.2, 28.3, 41.0, 55.1, 58.1, 63.8, 72.2, 75.4, 113.46, 113.52, 129.5, 129.8, 140.9, 153.4, 159.2, 172.7; IR (film) 2964, 2360, 1779 (str), 1709 (str), 1514 (str), 1248 cm^{-1}; $[\alpha]^{21}_D$ = -75.0 (c = 2.75, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{20}H_{27}NO_5Na$ $[M + Na]^+$: 384.18, found: 384.2.



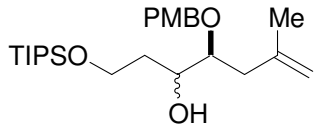
β-Keto Ester. Into a flask equipped with an addition funnel and a low temperature thermometer was added diisopropylamine (50.52 mL, 360.5 mmol) and 285 mL of THF. The solution was cooled to 0 °C and *n*-butyl lithium (2.5 M in hexanes, 143.04 mL, 357.60 mmol) was added dropwise via addition funnel. After 10 minutes at 0 °C, the solution was cooled to –78 °C and ethyl acetate (35.21 mL, 360.5 mmol) was added dropwise via addition funnel and stirred for 1 hour. The alkene dissolved in 145 mL of THF was added dropwise and the reaction mixture was stirred 1 hour at –78 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and then warmed to room temperature. The layers were separated and the aqueous was extracted twice with ethyl acetate. The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (5% then 10% EtOAc/Hexanes) provided 38.31 g (84%) of the ester as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ β-keto ester 1.24 (t, *J* = 7.1 Hz, 3H), 1.72 (s, 3H), 2.34-2.47 (m, 2H), 3.55 (AB, J_{AB} = 16.1 Hz, Δv_{AB} = 35.0 Hz, 2H), 3.78 (s, 3H), 4.03 (dd, *J* = 7.5, 5.5 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H),

4.47 (AB, J_{AB} = 11.1 Hz, Δv_{AB} = 26.6 Hz, 2H), 4.78 (s, 1H), 4.84 (s, 1H), 6.86 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 8.6 Hz, 2H); β-enol ester 1.30 (t, *J* = 7.1 Hz, 3H), 1.68 (s, 3H), 2.34-2.47 (m, 2H), 3.78 (s, 3H), 3.93 (dd, *J* = 8.1, 4.8 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.45 (AB, J_{AB} = 11.4 Hz, Δv_{AB} = 100.3 Hz, 2H), 4.76 (s, 1H), 4.80 (s, 1H), 5.30 (s, 1H), 6.86 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 8.6 Hz, 2H), 12.04 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.1, 22.4, 39.9, 42.2, 44.7, 55.1, 60.1, 61.1, 71.2, 72.3, 82.8, 88.7, 113.2, 113.6, 113.7, 114.0, 129.1, 129.4, 129.5, 129.6, 140.5, 141.3, 159.2, 159.4, 167.2, 172.7, 176.8, 205.0; IR (film) 2980, 2938, 1747 (str), 1719 (str), 1651, 1613 (str), 1515 (str), 1465, 1250 (str) cm^{-1}; $[\alpha]^{22}_D$ = -45.3 (c = 5.50, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{18}H_{24}O_5Na$ $[M + Na]^+$: 343.15, found: 343.2.

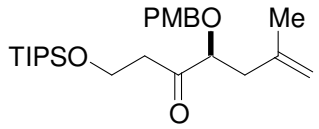


Diol. A flask equipped with an addition funnel was charged with lithium aluminum hydride (9.08 g, 239 mmol) and 1.00 L of Et_2O. The suspension was cooled to 0 °C and ester **3** (38.31 g, 119.6 mmol) in 200 mL of Et_2O was added dropwise. The solution was allowed to stir for 1 hour at 0 °C, then the reaction was quenched by the slow addition of 9.08 mL of H_2O, 9.08 mL of 15% sodium hydroxide, and 18.16 mL of H_2O. After warming to room temperature, the suspension was filtered through celite and the salts were washed with ethyl acetate. The organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (40% EtOAc/Hexanes) provided 26.7 g (80%) of

the diol as a colorless oil: IR (film) 3390 (br), 2937, 1613, 1514 (str) cm^{-1}; MS (electrospray ionization) calculated for $C_{16}H_{24}O_4Na$ $[M + Na]^+$: 303.16, found: 303.2.

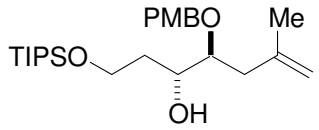


Silyl Ether. A flask was charged with the diol (22.21 g, 79.22 mmol) and 320 mL of CH_2Cl_2. Imidazole (16.18 g, 237.7 mmol) and triisopropylsilyl chloride (18.63 mL, 87.14 mmol) were added sequentially. The solution was allowed to stir overnight, then quenched by the addition of saturated aqueous NH_4Cl. The layers were separated, and the aqueous was washed twice with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (10% EtOAc/Hexanes) provided 34.59 g (100%) of the alcohol as a colorless oil: IR (film) 3492 (br), 2943 (str), 2866 (str), 1514, 1249 (str) cm^{-1}; MS (electrospray ionization) calculated for $C_{25}H_{44}O_4SiNa$ $[M + Na]^+$: 459.29, found: 459.4.



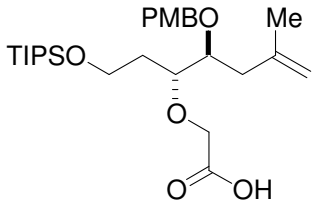
Ketone. A flask was charged with oxalyl chloride (2.0 M in CH_2Cl_2, 59.41 mL, 118.8 mmol) and 300 mL of CH_2Cl_2 and cooled to –78 °C. Dimethylsulfoxide (14.06 mL, 198.02 mmol) in 75 mL of CH_2Cl_2 was added dropwise, and the solution was stirred 2 minutes. The alcohol (34.59 g, 79.21 mmol) and 125 mL CH_2Cl_2 were added dropwise to the mixture and allowed to stir 30 minutes at –78 °C. Triethylamine (55.20 mL, 396.04 mmol) was added dropwise and stirred 5 minutes at –78 °C, followed by warming to room temperature for 1 hour. The reaction was

quenched by the addition of water. The organic portion was washed with saturated aqueous $NaHCO_3$, then water. The combined aqueous portions were washed with CH_2Cl_2. The combined organic extracts were then washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (5% EtOAc/Hexanes) provided 34.43 g (100%) of the ketone as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 21H), 1.71 (s, 3H), 2.3-2.43 (m, 2H), 2.67-2.82 (m, 2H), 3.77 (s, 3H), 3.93-4.02 (m, 3H), 4.45 (AB, J_{AB} = 11.3 Hz, Δv_{AB} = 65.8 Hz, 2H), 4.77 (s, 1H), 4.81 (s, 1H), 6.85 (d, J = 8.6 Hz, 2H), 7.24 (d, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7, 17.8, 22.3, 39.8, 40.6, 55.0, 58.5, 71.9, 83.2, 113.3, 113.6, 129.38, 129.42, 140.9, 159.2, 210.9; IR (film) 2043 (str), 2866 (str), 1719 (str), 1613, 1514 (str), 1464, 1250 (str), 1099 (str) cm^{-1}; $[\alpha]^{22}_D$ = -24.1 (c = 5.45, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{25}H_{42}O_4SiNa$ $[M + Na]^+$: 457.28, found: 457.3.



Alcohol. Into a flask equipped with an addition funnel and a low temperature thermometer was added ketone **4** (35.96 g, 82.73 mmol) in 800 mL of Et_2O. The solution was cooled to –40 °C and $Zn(BH_4)_2$ (~0.14 M in Et_2O, 335 mL, 47 mmol) was added dropwise via addition funnel. The mixture was warmed to –25 °C and stirred for 15 minutes. The reaction was quenched by the addition of 33.5 mL of saturated aqueous NaCl. The mixture was warmed to room temperature, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (5% EtOAc/Hexanes) provided 28.52 g (79%) of the alcohol as a colorless oil: ^1H

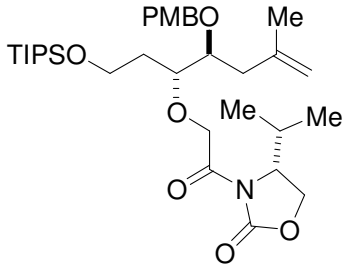
NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 21H), 1.71-1.84 (m, 2H), 1.77 (s, 3H), 2.25-2.37 (m, 2H), 3.36 (br s, 1H), 3.54-3.60 (m, 1H), 3.77 (s, 3H), 3.84-4.01 (m, 3H), 4.55 (s, 2H), 4.82 (s, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 7.26 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7, 17.9, 22.9, 33.8, 38.9, 55.1, 62.7, 72.0, 72.8, 80.2, 112.8, 113.6, 129.4, 130.8, 142.8, 159.1; IR (film) 3493 (br), 2943 (str), 2866 (str), 1613, 1514 (str), 1464, 1249 (str) cm^{-1}; $[\alpha]^{22}_D$ = +12 (c = 3.4, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{25}H_{44}O_4SiNa$ $[M + Na]^+$: 459.29, found: 459.4.



Glycolic Acid. A flask equipped with an addition funnel was charged with sodium hydride (60% dispersion in mineral oil, 6.59 g, 165 mmol). The solid was rinsed with pentane three times, diluted in 55 mL of DMF, and cooled to 0 °C. Bromoacetic acid (9.16 g, 65.9 mmol) in 25 mL of THF was added dropwise, then allowed to stir 10 minutes. The alcohol **5** (23.97 g, 54.89 mmol) was added via addition funnel in 30 mL of THF, and the solution was warmed to room temperature and stirred overnight. The mixture was then cooled to 0 °C and quenched by the addition of saturated aqueous NH_4Cl and diluted with Et_2O. The layers were separated, and the aqueous portion was extracted twice more using Et_2O. The combine organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (10% then 50% EtOAc/Hexanes) provided 24.4 g (90%) of the acid as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 21H), 1.67 (m, 1H), 1.71 (s, 3H), 1.78 (m, 1H), 2.19 (dd, *J* =

14.4, 4.4 Hz, 1H), 2.36 (dd, J = 14.5, 8.3 Hz, 1H), 3.48 (ddd, J = 4.3, 4.3, 2.1 Hz, 1H), 3.77 (s, 3H), 3.77-3.88 (m, 3H), 4.22 (AB, J_{AB} = 17.1 Hz, Δv_{AB} = 22.6 Hz, 2H), 4.55 (AB, J_{AB} = 11.5 Hz, Δv_{AB} = 8.3 Hz, 2H), 4.79 (s, 1H), 4.81 (s, 1H), 6.84 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 8.5 Hz, 2H), 10.80 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7, 17.8, 22.5, 33.6, 38.0, 54.9, 59.6, 68.1, 71.8, 78.3, 80.1, 113.0, 113.6, 129.5, 129.6, 142.0, 159.2, 173.4; IR (film) 3074 (br), 2943 (str), 2866 (str), 1763, 1732 (str), 1613, 1514 (str), 1464, 1249 (str) cm^{-1}; $[\alpha]^{21}_D$ = +14 (c = 1.8, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{27}H_{46}O_6SiK$ $[M + K]^+$: 533.41, found: 533.3.

ii.) Acylation of the acid to yield glycolate **6**

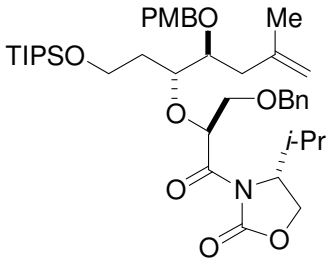


Complex Glycolate. Into a flask fitted with an addition funnel was added the glycolic acid (24.36 g, 49.24 mmol) in 350 mL of THF. The solution was cooled to –78 °C and triethylamine (7.55 mL, 54.2 mmol) was added to the solution, followed by dropwise addition of pivaloyl chloride (6.68 mL, 54.16 mL). The mixture was warmed to 0 °C and stirred for 1 hour, then cooled to –78 °C.

In a separate flask equipped with an addition funnel was added (4*S*)-4-Isopropyl-oxazolidin-2-one (8.27 g, 64.0 mmol) and 175 mL of THF. The solution was cooled to –78 °C, and *n*-butyl lithium (2.3 M in hexanes, 25.69 mL, 59.09 mmol) was added dropwise, and stirred for 30 minutes.

The lithiated oxazolidinone was then transferred via cannula into the mixed anhydride and the mixture was stirred for 1 hour at –78 °C followed by warming to 0 °C for 45 minutes. The reaction was quenched using saturated aqueous NH_4Cl, then warmed to room temperature. The layers were separated and the aqueous was washed twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (10% then 20% EtOAc/Hexanes) provided 27.6 g (90%) of the glycolate as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (d, *J* = 6.9 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H), 1.05 (s, 21H), 1.68-1.78 (m, 1H), 1.73 (s, 3H), 1.85 (dddd, *J* = 9.5, 9.5, 4.6, 4.6 Hz, 1H), 2.18 (dd, *J* = 14.5, 4.7 Hz, 1H), 2.34-2.43 (m, 2H), 3.72-3.78 (m, 1H), 3.77 (s, 3H), 3.79-3.86 (m, 2H), 3.90 (ddd, *J* = 9.7, 9.7, 4.7 Hz, 1H), 4.17-4.23 (m, 2H), 4.36 (ddd, *J* = 7.9, 4.0, 4.0 Hz, 1H), 4.54 (AB, J_{AB} = 11.2 Hz, Δv_{AB} = 53.4 Hz, 2H), 4.77 (s, 2H), 4.78 (AB, J_{AB} = 18.0 Hz, Δv_{AB} = 28.1 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 14.5, 17.9, 22.8, 26.9, 28.1, 33.8, 38.9, 55.1, 58.0, 59.7, 64.1, 70.5, 71.7, 78.8, 79.2, 112.5, 113.5, 129.3, 130.8, 142.8, 153.8, 158.9, 170.0; IR (film) 2942, 2867, 1785 (str), 1719 (str), 1613, 1514 (str), 1464, 1389, 1302, 1251 cm^{-1}; $[\alpha]^{25}_D$ = -18.7 (c = 14.4, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{33}H_{55}NO_7SiNa$ $[M + Na]^+$: 628.36, found: 628.3.

e.) B fragment alcohol **7**

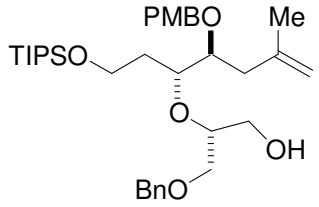


Alkylation Adduct. A flask equipped with an addition funnel was charged with sodum bis(trimethylsilyl)amide (0.78 M in toluene/THF, 77.45 mL, 60.41 mmol) and 200 mL of THF. The solution was cooled to –78 °C and glycolate **6** (24.40 g, 40.27 mmol) in 200 mL of THF was added dropwise via addition funnel keeping the temperature below –65 °C. The resultant solution was stirred 1 hour at –78 °C.

In a separate flask, formaldehyde dibenzyl acetal (25.85 mL, 120.8 mmol) was cooled to 0 °C, and iodotrimethylsilane(16.62 mL, 116.8 mmol) was added and allowed to stir 30 minutes.

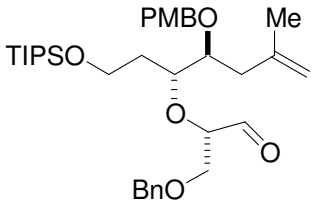
The benzyl iodomethyl ether was then added to the enolate, and the solution was allowed to stir for 1 hour at –78 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and then warmed to room temperature. The layers were separated, and the aqueous was extracted twice with Et_2O. The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (5% then 10% EtOAc/Hexanes) provided 23.98 g (83%) of the benzyl ether as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.66 (d, *J* = 6.9 Hz, 3H), 0.77 (d, *J* = 7.0 Hz, 3H), 1.04 (s, 21H), 1.60 (m, 1H), 1.73 (s, 3H), 1.82 (m, 1H), 2.17 (dd, *J* = 15.0, 3.8 Hz, 1H), 2.22 (m, 1H), 2.57 (dd, *J* = 14.7, 9.1 Hz, 1H), 3.52 (dd, *J* = 8.8, 8.8 Hz, 1H), 3.60 (ddd, *J* = 9.0, 3.7, 4.1 Hz, 1H), 3.70 (dd, *J* = 10.4, 4.0 Hz, 1H), 3.72 (s, 3H), 3.79 (dd, *J* = 4.4, 4.4 Hz, 1H), 3.83 (m, 2H), 3.88 (dd, *J* = 9.1,

3.0 Hz, 1H), 3.94 (m, 1H), 4.18 (ddd, J = 8.4, 3.2, 3.2 Hz, 1H), 4.47 (AB, J_{AB} = 11.9 Hz, Δv_{AB} = 89.5 Hz, 2H), 4.55 (AB, J_{AB} = 11.9 Hz, Δv_{AB} = 21.5 Hz, 2H), 4.80 (s, 2H), 5.58 (dd, J = 5.7, 4.1 Hz, 1H), 6.81 (d, J = 8.6 Hz, 2H), 7.17-7.30 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 14.1, 17.3, 17.7, 22.6, 27.7, 34.6, 37.4, 54.7, 57.7, 59.8, 63.1, 71.0, 71.6, 72.9, 78.8, 79.4, 81.1, 111.9, 113.2, 127.0, 127.2, 127.8, 128.7, 130.5, 137.7, 142.9, 153.3, 158.7, 170.4; IR (film) 2942, 2866, 1780 (str), 1715, 1514, 1388, 1248 (str) cm^{-1}; $[\alpha]^{25}_D$ = -34 (c = 1.9, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{41}H_{63}NO_8SiNa$ $[M + Na]^+$: 748.42, found: 748.4.



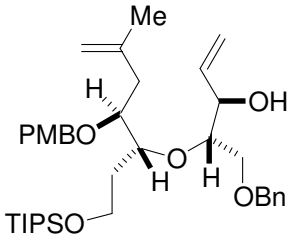
Primary Alcohol. To a solution of the benzyl ether (21.55 g, 29.68 mmol) and methanol (1.81 mL, 44.52 mmol) in 300 mL of Et_2O at 0 °C was added lithium borohydride (2.0M in THF, 22.26 mL, 44.52 mmol) dropwise via addition funnel. After stirring for 1 hour at 0 °C, MeOH (1.81 mL, 44.52 mmol) was added. The solution was quenched by the addition of saturated sodium potassium tartrate, warmed to ambient temperature, and stirred for 2 hours. The layers were separated, and the aqueous was extracted twice with Et_2O. The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (10% EtOAc/Hexanes) provided 15.28 g (86%) of the alcohol as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (s, 21H), 1.68 (m, 1H), 1.77 (s, 3H), 1.83 (m, 1H), 2.24 (dd, J = 14.6, 5.2 Hz, 1H), 2.46 (dd, J = 14.6, 8.5 Hz, 1H), 3.32 (br s, 1H), 3.54 (dd, J = 9.6, 6.0 Hz, 1H), 3.59-3.67 (m, 2H), 3.69 (ddd, J = 8.3, 4.3,

1.5 Hz, 1H), 3.75-3.88 (m, 4H), 3.78 (s, 3H), 4.02 (m, 1H), 4.55 (s, 2H), 4.58 (AB, J_{AB} = 11.5 Hz, Δv_{AB} = 25.5 Hz, 2H), 4.85 (s, 2H), 6.88 (d, J = 8.6 Hz, 2H), 7.27-7.39 (m, 7H)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 17.9, 22.7, 34.8, 38.0, 54.9, 59.6, 63.0, 70.2, 71.5, 73.1, 76.7, 79.1, 79.5, 112.6, 113.5, 127.2, 127.3, 128.1, 129.3, 130.0, 138.1, 142.5, 159.0; IR (film) 3450 (br), 2942 (str), 2865 (str), 1514, 1249, 1093 (str) cm^{-1}; $[\alpha]^{23}_D$ = +17 (c = 4.7, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{35}H_{56}O_6SiNa$ $[M + Na]^+$: 623.37, found: 623.3.



Aldehyde. A flask was charged with oxalyl chloride (2.0 M in CH_2Cl_2, 18.45 mL, 36.89 mmol) and 150 mL of CH_2Cl_2 and cooled to –78 °C. Dimethylsulfoxide (4.37 mL, 61.49 mmol) in 30 mL of CH_2Cl_2 was added dropwise, and the solution was stirred 2 minutes. The alcohol **7** (14.78 g, 24.60 mmol) and 60 mL CH_2Cl_2 were added dropwise to the mixture and allowed to stir 30 minutes at –78 °C. Triethylamine (17.14 mL, 123.0 mmol) was added dropwise and stirred 5 minutes at –78 °C, followed by warming to room temperature for 1 hour. The reaction was quenched by the addition of water. The organic portion was washed with saturated aqueous $NaHCO_3$, then water. The combined aqueous portions were washed with CH_2Cl_2. The combined organic extracts were then washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by passing through a short plug of silica (10% EtOAc/Hexanes) provided 14.44 g (99%) of the aldehyde as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 21H), 1.66-1.78 (m, 1H), 1.73 (s, 3H), 1.88

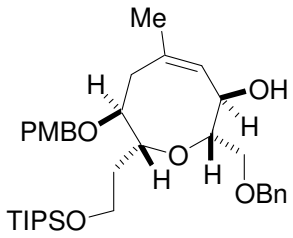
(m, 1H), 2.25 (dd, J = 14.4, 4.5 Hz, 1H), 2.44 (dd, J = 14.4, 8.3 Hz, 1H), 3.69 (ddd, J = 8.2, 4.6, 1.7 Hz, 1H), 3.72-3.88 (m, 2H), 3.79 (s, 3H), 3.84-3.91 (m, 2H), 3.98 (m, 1H), 4.13 (ddd, J = 4.4, 4.4, 1.3 Hz, 1H), 4.53 (AB, J_{AB} = 11.4 Hz, Δv_{AB} = 31.1 Hz, 2H), 4.55 (AB, J_{AB} = 12.2 Hz, Δv_{AB} = 14.6 Hz, 2H), 4.80 (s,1H), 4.82 (s, 1H), 6.87 (d, J = 6.8 Hz, 2H), 7.21-7.48 (m, 7H), 9.77 (d, J = 1.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 17.9, 22.7, 34.4, 38.7, 55.1, 59.7, 69.7, 71.4, 73.4, 78.7, 79.7, 84.6, 112.7, 113.6, 127.5, 127.6, 128.2, 129.3, 130.4, 137.7, 142.6, 159.0, 202.6; IR (film) 2942 (str), 2865 (str), 1734 (str), 1613, 1514, 1463, 1249 (str), 1096 (str) cm^{-1}; $[\alpha]^{23}_D$ = +4.0 (c = 1.9, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{35}H_{54}O_6SiNa$ $[M + Na]^+$: 621.36, found: 621.4.

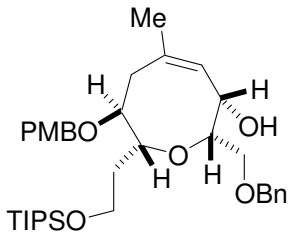


Diene. A flask fitted with an addition funnel and dry ice/acetone filled condenser was charged with freshly ground magnesium (3.65 g, 150 mmol) and the system was flame dried. The solid was suspended in 12 mL of THF, and one crystal of iodine was added to the suspension. Vinyl bromide (11.64 mL, 165 mmol) in 12 mL of THF was added dropwise via addition funnel until the mixture began to reflux. The halide was added at a rate to maintain reflux until addition was complete. The solution was stirred for 30 minutes upon completion of addition, then diluted with 83 mL of THF.

In a separate flask equipped with an addition funnel, the previously prepared vinyl magnesium bromide (1.4 M in THF, 52.71 mL, 73.79 mmol) was added to 160 mL of

THF. The solution was cooled to 0 °C and the aldehyde (14.73 g, 24.60 mmol) was added dropwise via addition funnel. The solution was stirred for 5 minutes, then the reaction was quenched by the slow addition of saturated aqueous ammonium chloride. After dilution with Et_2O, the layers were separated, and the aqueous portion was extracted twice more with Et_2O. The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (10% EtOAc/Hexanes) provided 12.99 g (86%) of a colorless oil consisting of a 3:1 inseparable mixture of alcohol epimers, favoring the configuration shown: IR (film) 3437 (br), 2942 (str), 2866 (str), 1613, 1514 (str), 1463 (str), 1365, 1303, 1249 (str), 1093 cm^{-1}; MS (electrospray ionization) calculated for $C_{37}H_{58}O_6SiNa$ $[M + Na]^+$: 649.39, found: 649.4.

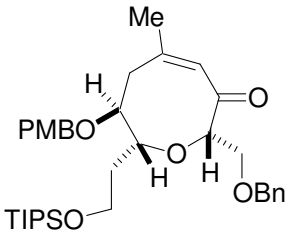




Oxocenes. A flask equipped with a reflux condenser was charged with the diene (11.31 g, 18.06 mmol) in 1.800 L of CH_2Cl_2. The solution was refluxed for 30 minutes while purging the system with argon. The vessel was cooled to room temperature and $(Cl_2(PCy_3)(Imes)Ru{=}CHPh$ (765 mg, 0.903 mmol) was added. The solution was stirred at reflux overnight, then cooled to room temperature. Evaporation of the solvents and purification via flash column chromatography (10% then 25% EtOAc/Hexanes) provided a separable mixture 5.58 g (52%) and 1.95 g (19%%) of the oxocenes as a colorless oil: **Major epimer:** ^1H NMR (400 MHz, $CDCl_3$) δ 1.07 (s, 21H), 1.52 (dddd, J = 14.4, 9.8, 4.9, 4.9 Hz, 1H), 1.86 (s, 3H), 2.10

(m, 1H), 2.32 (d, J = 12.1 Hz, 1H), 2.67 (dd, J = 13.5, 2.9 Hz, 1H), 3.10 (br s, 1H), 3.43 (ddd, J = 8.8, 4.3, 4.3 Hz, 1H), 3.50 (m, 1H), 3.64 (m, 1H), 3.69-3.87 (m, 4H), 3.77 (s, 3H), 4.38 (m, 1H), 4.48 (AB, J_{AB} = 11.1 Hz, Δv_{AB} = 122.3 Hz, 2H), 4.57 (AB, J_{AB} = 12.1 Hz, Δv_{AB} = 46.9 Hz, 2H), 5.46 (d, J = 4.4 Hz, 1H), 6.87 (d, J = 8.3 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 7.27-7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 17.8, 26.0, 31.8, 36.8, 54.87, 54.89, 70.7, 71.2, 71.9, 73.3, 77.5, 82.2, 82.6, 113.4, 127.46, 127.53, 128.2, 129.0, 129.7, 130.2, 134.7, 137.6, 158.9; IR (film) 3465 (br), 2942, 2865, 1613, 1514 (str), 1464, 1302, 1249 cm^{-1}; $[\alpha]^{21}_D$ = +95.5 (c = 8.94 CH_2Cl_2); MS (electrospray ionization) calculated for $C_{35}H_{54}O_6SiNa$ [M + Na]$^+$: 621.36, found: 621.3.

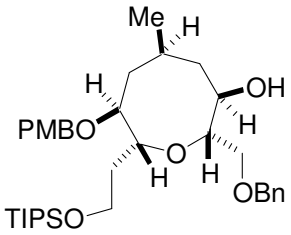
Minor epimer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 21H), 1.50 (m, 1H), 1.83 (s, 3H), 2.13 (m, 1H), 2.36 (dd, J = 13.5, 5.7 Hz, 1H), 2.73 (br s, 1H), 3.08 (d, J = 12.5 Hz, 1H), 3.40 (m, 1H), 3.54-3.72 (m, 4H), 3.76-3.86 (m, 2H), 3.81 (s, 3H), 4.38 (d, J = 6.6 Hz, 1H), 4.48 (AB, J_{AB} = 11.3 Hz, Δv_{AB} = 101.7 Hz, 2H), 4.54 (AB, J_{AB} = 12.1 Hz, Δv_{AB} = 23.8 Hz, 2H), 5.56 (dd, J = 7.5, 1.1 Hz, 1H), 6.86 (d, J = 6.7 Hz, 2H), 7.21-7.38 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.0, 18.0, 26.8, 33.9, 37.1, 55.2, 59.9, 69.9, 71.0, 71.5, 73.7, 79.5, 80.3, 82.0, 113.7, 125.5, 127.72, 127.75, 128.4, 129.4, 130.4, 137.7, 139.3, 159.1; IR (film) 3445 (br), 2941, 2865, 1612, 1514, 1463, 1248 cm^{-1}; $[\alpha]^{23}_D$ = +84 (c = 0.47 CH_2Cl_2); MS (electrospray ionization) calculated for $C_{35}H_{54}O_6SiNa$ [M + Na]$^+$: 621.36, found: 621.4.



Enone. A flask was charged with oxalyl chloride (2.0 M in CH_2Cl_2, 2.91 mL, 5.81 mmol) and 25 mL of CH_2Cl_2 and cooled to –78 °C. Dimethylsulfoxide (688 µL, 9.69 mmol) in 5 mL of CH_2Cl_2 was added dropwise, and the solution was stirred 2 minutes. The alcohol (2.32 g, 3.87 mmol) and 10 mL CH_2Cl_2 were added dropwise to the mixture and allowed to stir 30 minutes at –78 °C. Triethylamine (2.70 mL, 19.4 mmol) was added dropwise and stirred 5 minutes at –78 °C, followed by warming to room temperature for 1 hour. The reaction was quenched by the addition of water. The organic portion was washed with saturated aqueous $NaHCO_3$, then water. The combined aqueous portions were washed with CH_2Cl_2. The combined organic extracts were then washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (10% EtOAc/Hexanes) provided 1.47 g (64%) of the enone as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 21H), 1.75 (m, 1H), 1.86 (m, 1H), 1.94 (s, 3H), 2.54 (d, *J* = 16.7 Hz, 1H), 2.65 (dd, *J* = 16.8, 7.6, Hz, 1H), 3.50 (m, 1H), 3.67-3.76 (m, 2H), 3.79 (s, 3H), 3.82-3.92 (m, 3H), 4.24-4.31 (m, 2H), 4.47-4.58 (m, 3H), 5.80 (s, 1H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.22 (d, *J* = 8.7 Hz, 2H), 7.24-7.35 (m, 5H);); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 18.0, 27.5, 35.8, 36.8, 55.17, 55.18, 59.9, 70.2, 72.3, 73.4, 78.5, 82.5, 87.2, 113.7, 126.0, 127.38, 127.42, 128.2, 129.4, 129.5, 138.1, 146.5, 159.2, 203.4; IR (film) 2942, 2865, 1668, 1514, 1250 cm^{-1}; $[\alpha]^{24}_D$ = -7.5 (c = 2.4 CH_2Cl_2); MS (electrospray ionization) calculated for $C_{35}H_{52}O_6SiNa$ $[M + Na]^+$: 619.34, found: 619.2.

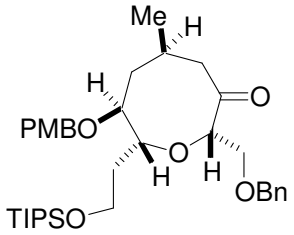
The resultant enone 1.17 g (1.96 mmol) was dissolved in 10 mL of methanol and cooled to 0 °C. Cerium chloride heptahydrate (740 mg, 1.96 mmol) was added,

followed by sodium borohydride (74 mg, 2.0 mmol). The solution was stirred for five minutes, then quenched by the addition of 1M HCl and diluted with Et_2O. After warming to room temperature, the layers were separated, and the aqueous fraction was extracted twice with Et_2O. The combined organic extracts were then washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (10% EtOAc/Hexanes) provided 950 mg (82%) of oxocene **8** as a colorless oil.



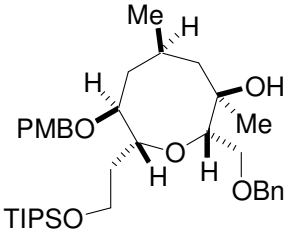
Oxocane. To a solution of oxocene **8** (5.58 g, 9.32 mmol) in 93 mL of CH_2Cl_2 was added Crabtree's catalyst ($[PCy_3][COD][Pyr]Ir^+PF_6^-$; 188 mg, 0.233 mmol). The mixture was cooled to –50 °C and fitted with a hydrogen balloon. The flask was purged under vacuum and filled with hydrogen five times. The solution was allowed to stir overnight under an atmosphere of hydrogen. The balloon was removed and the solution was warmed to room temperature. Evaporation of the solvents and purification via flash column chromatography (10% EtOAc/Hexanes) provided 5.24 g (94%) of the oxocane as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03-1.14 (m, 24H), 1.55 (dddd, J = 13.8, 9.5, 4.6, 4.6 Hz, 1H), 1.67-1.81 (m, 2H), 1.83-2.02 (m, 3H), 2.08 (m, 1H), 2.96 (br s, 1H), 3.26 (ddd, J = 8.8, 8.8, 2.7 Hz, 1H), 3.63-3.72 (m, 2H), 3.72-3.80 (m, 3H), 3.78 (s, 3H), 3.82-3.87 (m, 2H), 4.44 (AB, J_{AB} = 11.1 Hz, $\Delta\nu_{AB}$ = 84.2 Hz, 2H), 4.56 (AB, J_{AB} = 12.0 Hz, $\Delta\nu_{AB}$ = 32.8 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 7.26 (d, J = 8.6 Hz, 2H), 7.27-7.46 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

11.8, 17.9, 26.8, 27.7, 37.3, 40.1, 45.3, 55.0, 59.6, 70.6, 72.4, 73.0, 73.4, 81.5, 82.3, 83.0, 113.5, 127.5, 127.6, 128.3, 129.1, 130.4, 137.6, 158.9; IR (film) 3461 (br), 2943, 2865, 1613, 1514, 1463, 1249 cm^{-1}; $[\alpha]^{21}_D$ = +38.0 (c = 8.10 CH_2Cl_2); MS (electrospray ionization) calculated for $C_{35}H_{56}O_6SiNa$ $[M + Na]^+$: 623.37, found: 623.3.



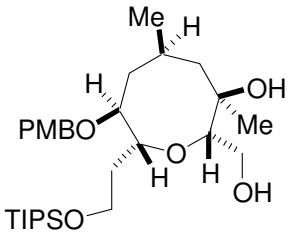
Ketone. A flask was charged with oxalyl chloride (2.0 M in CH_2Cl_2, 6.54 mL, 13.1 mmol) and 50 mL of CH_2Cl_2 and cooled to –78 °C. Dimethylsulfoxide (1.55 mL, 21.8 mmol) in 10 mL of CH_2Cl_2 was added dropwise, and the solution was stirred 2 minutes. The oxocane (5.24 g, 8.72 mmol) and 20 mL CH_2Cl_2 were added dropwise to the mixture and allowed to stir 30 minutes at –78 °C. Triethylamine (6.08 mL, 43.6 mmol) was added dropwise and stirred 5 minutes at –78 °C, followed by warming to room temperature for 1 hour. The reaction was quenched by the addition of water. The organic portion was washed with saturated aqueous $NaHCO_3$, then water. The combined aqueous portions were washed with CH_2Cl_2. The combined organic extracts were then washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (10% EtOAc/Hexanes) provided 4.94 g (95%) of the ketone as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, *J* = 6.7 Hz, 3H), 1.07 (s, 21H), 1.53 (ddd, *J* = 5.3, 11.9, 16.5 Hz, 1H), 1.77 (m, 1H), 1.84 (m, 1H), 1.95 (m, 1H), 2.23 (dd, *J* = 15.4, 9.1 Hz, 1H), 2.87 (dd, *J* = 15.4, 4.6 Hz, 1H), 2.98 (m, 1H), 3.43 (m, 1H), 3.67 (dd, *J* = 10.0,

2.6 Hz, 1H), 3.77 (m, 1H), 3.79 (s, 3H), 3.83-3.89 (m, 3H), 4.03 (dd, J = 4.3, 2.7 Hz, 1H), 4.42 (AB, , J_{AB} = 11.8 Hz, Δv_{AB} = 46.5 Hz, 2H), 4.54 (AB, J_{AB} = 12.3 Hz, Δv_{AB} = 22.3 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 7.22 (d, J = 8.6 Hz, 2H), 7.24-7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 17.9, 23.7, 27.6, 36.3, 37.3, 48.8, 55.0, 59.8, 69.6, 72.8, 73.3, 80.3, 80.8, 88.0, 113.6, 127.2, 127.3, 128.1, 129.1, 129.8, 138.0, 159.0, 211.8; IR (film) 2940, 2865, 1699, 1514, 1457, 1248 cm^{-1}; $[\alpha]^{23}_D$ = -33 (c = 2.6 CH_2Cl_2); MS (electrospray ionization) calculated for $C_{35}H_{54}O_6SiNa$ $[M + Na]^+$: 621.36, found: 621.4.



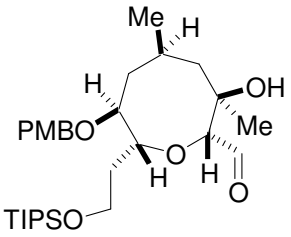
Tertiary Alcohol. Into a flask equipped with an addition funnel was added methylmagnesium chloride (3.0 M in THF, 13.75 mL, 41.24 mmol) and 200 mL of E_2O. The solution was cooled to –78 °C, and ketone **10** (4.94 g, 8.25 mmol) in 200 mL of Et_2O was added dropwise via addition funnel. The mixture was allowed to stir for 20 minutes at –78 °C. The reaction was quenched by the addition of saturated aqueous ammonium chloride and allowed to warm to room temperature. The layers were separated and the aqueous portion was extracted twice with EtOAc. The combined organic extracts were then washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (10% EtOAc/Hexanes) provided 4.42 g (88%) of the alcohol as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (d, J = 6.4 Hz, 3H), 1.07 (s, 21H), 1.18 (s, 3H), 1.51-1.73 (m, 3H), 1.83-1.95 (m, 3H), 2.03 (m, 1H), 3.22 (m, 1H), 3.28 (br s, 1H), 3.62-3.69 (m,

3H), 3.73-3.87 (m, 3H), 3.80 (s, 3H), 4.44 (AB, J_{AB} = 11.1 Hz, Δv_{AB} = 74.9 Hz, 2H), 4.52 (AB, J_{AB} = 11.7 Hz, Δv_{AB} = 24.8 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.27-7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 18.0, 21.8, 27.0, 27.6, 37.3, 41.5, 53.0, 55.1, 59.8, 70.7, 70.8, 73.6, 74.2, 82.0, 82.1, 82.9, 113.6, 127.6, 127.8, 128.4, 129.2, 130.5, 137.3, 159.0; IR (film) 3481 (br), 2943, 2865, 1613, 1514, 1463, 1249 cm^{-1}; $[\alpha]^{22}_D$ = +42 (c = 1.9 CH_2Cl_2); MS (electrospray ionization) calculated for $C_{36}H_{58}O_6SiNa$ $[M + Na]^+$: 637.39, found: 637.3.



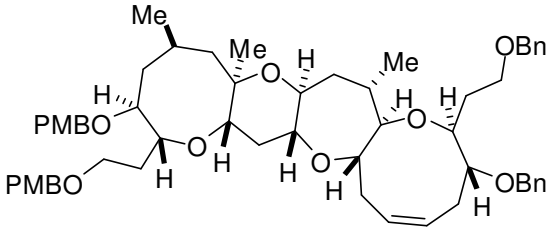
Primary Alcohol. To a solution containing tertiary alcohol (3.70 g, 6.01 mmol) in 120 mL of EtOH was added Raney Nickel (2800 slurry in H_2O, 18.76 mL). The reaction flask was fitted with a hydrogen filled balloon. The flask was evacuated under vacuum and filled with hydrogen. The procedure was repeated twice more, and the reaction mixture was allowed to stir under an atmosphere of H_2 overnight. The hydrogen balloon was removed and the suspension was filtered through celite. The filtrate was washed several times with ethanol while ensuring that the solid was not allowed to become dry. The solvent was concentrated in vacuo and the product was purified by flash column chromatography (30% EtOAc/Hexanes) to provide 2.98 g (95%) of the diol as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, J = 6.7 Hz, 3H), 1.07 (s, 21H), 1.15 (s, 3H), 1.51 (m, 1H), 1.56 (d, J = 12.9 Hz, 1H), 1.72 (m, 1H), 1.78-1.93 (m, 3H), 2.04 (m, 1H), 2.24 (br s, 1H), 3.17 (ddd, J = 8.4, 8.4, 2.7 Hz, 1H), 3.64 (m, 1H), 3.72-3.80 (m, 3H), 3.78 (s, 3H), 3.80-3.91 (m, 2H), 4.41 (AB, J_{AB}

= 11.2 Hz, Δv_{AB} = 72.7 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 17.9, 21.7, 27.4, 27.5, 36.7, 41.0, 54.4, 55.1, 59.8, 63.3, 70.4, 74.3, 81.4, 82.4, 86.0, 113.6, 129.2, 130.4, 159.0; IR (film) 3389 (br), 2944, 2866, 1613, 1514, 1463, 1384, 1302, 1249 cm^{-1}; $[\alpha]^{23}_D$ = +36 (c = 4.4 CH_2Cl_2); MS (electrospray ionization) calculated for $C_{29}H_{52}O_6SiNa$ $[M + Na]^+$: 547.34, found: 547.4.



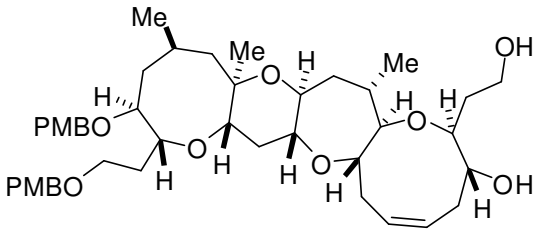
B Ring Aldehyde. To a solution of the diol (280 mg, 0.534 mmole) in 5 mL of CH_2Cl_2 was added Dess-Martin periodinane (339 mg, 0.800 mmol). After stirring 1 hour at room temperature, the reaction was quenched via the addition of a 5:1 solution of saturated aqueous $Na_2S_2O_3$/$NaHCO_3$. The layers were separated and the aqueous layer was washed twice with CH_2Cl_2. The combined organic extracts were then dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (25% EtOAc/Hexanes) provided 238 mg (85%) of the aldehyde 11 as a colorless oil. ^{1}H NMR (500 MHz, C_6D_6) δ 9.88 (s, 1H), 7.22-7.19 (band, 2H), 6.83-6.80 (band, 2H), 4.39 (d, *J* = 11.5 Hz, 1H), 4.16 (d, *J* = 11.5 Hz, 1H), 4.05 (s, 1H), 3.93 (ddd, *J* = 5.0, 9.5, 9.5 Hz, 1H), 3.84 (ddd, *J* = 4.0, 7.0, 10.5 Hz, 1H), 3.76 (ddd, *J* = 2.5, 7.0, 9.5 Hz, 1H), 3.29 (s, 3H), 3.17 (m, 1H), 2.40 (s, 1H), 2.09 (dddd, *J* = 3.0, 7.0, 9.5, 9.5 Hz, 1H), 1.91-1.85 (band, 2H), 1.78 (ddd, *J* = 3.0, 3.0, 15.5 Hz, 1H), 1.66 (dddd, *J* = 3.5, 5.0, 9.0, 13.5 Hz, 1H), 1.51-1.42 (band, 2H), 1.17 (s, 3H), 1.12-1.04 (band, 21H), 0.89 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz,

C_6D_6) δ 205.0, 159.7, 130.9, 129.41, 129.40, 128.5, 128.1, 127.9, 114.1, 89.9, 83.3, 82.3, 74.4, 70.8, 60.1, 54.7, 53.2, 41.2, 37.4, 27.8, 27.1, 22.9, 18.3, 18.2, 12.3; IR (film) 3447, 2942, 2865, 1732, 1612, 1513, 1462, 1381, 1301, 1249, 1094 cm^{-1}; $[\alpha]^{25}_D$ = +35 (c = 0.35, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{29}H_{51}O_6Si$ $[M + H]^+$: 523.35, found: 523.4.



BCDE Tetraaryl Ether. Into a flask containing a stir bar was added the diol (87 mg, 0.13 mmol) in 3 mL of DMF. The mixture was cooled to 0 °C prior to addition of sodium hydride (60% dispersion in mineral oil, 26 mg, 0.64 mmol). Freshly prepared *p*-methoxybenzyl bromide (57 µL, 0.38 mmol) was added to the solution. After stirring for 10 minutes at 0 °C, the reaction mixture was warmed to room temperature and allowed to stir for 14 hours. The reaction was quenched by the slow addition of saturated NH_4Cl, and diluted with Et_2O. The layers were separated, and the aqueous portion was extracted three more times with Et_2O. The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (25% EtOAc/Hexanes) provided 106 mg (91%) of the ether as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, *J* = 6.6 Hz, 3H), 1.12 (s, 6H), 1.32-1.69 (m, 6 H), 1.70-2.02 (m, 5H), 2.04-2.26 (m, 3H), 2.33 (m, 1H), 2.44 (m, 2H), 2.56 (m, 1H), 2.87 (dd, *J* = 7.8, 7.8 Hz, 1H), 3.02 (dd, *J* = 9.3, 9.3 Hz, 1H), 3.28-3.58 (m, 11 H), 3.74 (s, 6H), 4.22-4.60 (m, 8H), 5.66 (m, 2H),

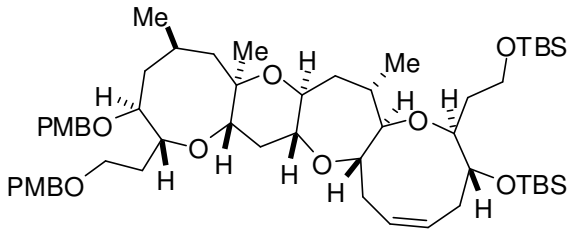
6.82 (m, 4H), 7.14-7.36 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.5, 21.0, 26.7, 28.0, 33.6, 34.2, 34.4, 34.6, 34.9, 42.3, 54.1, 55.1, 64.6, 66.4, 66.6, 68.9, 70.6, 71.2, 72.3, 72.7, 75.7, 80.7, 81.9, 82.1, 82.2, 82.3, 82.7, 82.9, 113.5, 113.6, 127.3, 127.4, 127.5, 127.7, 128.17, 128.23, 129.2, 129.4, 130.2, 130.5, 138.1, 138.3, 158.9, 159.0; IR (film) 2954, 2925, 1609, 1516 (str), 1455, 1242 (str) cm^{-1}; $[\alpha]^{22}_D$ = -15 (c = 0.73, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{57}H_{74}O_{10}Na$ $[M + Na]^+$: 941.52, found: 941.6.



BCDE Diol. Preparation of LiDBB: A reaction vessel was charged with 4,4'-di-*t*-butylbiphenyl (3.17g, 11.9 mmol) and 10.8 mL of THF. Freshly cut lithium metal (75 mg, 10.8 mmol) was added to the solution and the heterogenous mixture was placed in a sonicating bath. The solution was sonicated at 0 ^oC for two hours to provide a 1.0 M solution of LiDBB.

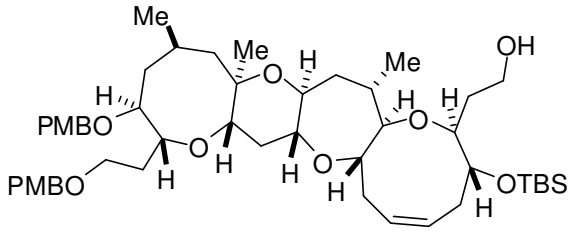
To a flask equipped with a stir bar was added the BCDE ether (106 mg, 0.12 mmol) and 5 mL of THF. The mixture was cooled to -78 ^oC, and the solution of LiDBB (3.0 mL, 3.0 mmol, 1.0 M in THF) was added. After stirring for 10 minutes at -78 ^oC, the reaction was quenched by the addition of saturated NH_4Cl, diluted with Et_2O, and warmed to room temperature. The layers were separated, and the aqueous portion was extracted three more times with Et_2O. The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (25% to 75% EtOAc/Hexanes) provided 75 mg (89%) of the diol as

a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (d, *J* = 7.0 Hz, 3H), 1.15 (s, 3H), 1.18 (d, *J* = 7.4 Hz, 3H), 1.39-1.72 (m, 6 H), 1.73-2.02 (m, 5H), 2.10-2.27 (m, 3H), 2.35-2.87 (m, 6H), 2.91 (ddd *J* = 15.7, 12.1, 4.3 Hz, 1H), 3.06 (dd, *J* = 10.6, 10.6 Hz, 1H), 3.23-3.40 (m, 3H), 3.42-3.61 (m, 5H), 3.68-3.84 (m, 3 H), 3.784 (3, 3H), 3.789 (s, 3H), 4.39 (AB, J_{AB} = 11.0 Hz, Δv_{AB} = 72.3 Hz, 2H), 4.41 (AB, J_{AB} = 11.2 Hz, Δv_{AB} = 8.7 Hz, 2H), 5.73 (m, 2H), 6.85 (d, *J* = 2.9 Hz, 2H), 6.87 (d, *J* = 2.9 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H), 7.26 (d, *J* = 11.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.5, 21.4, 26.8, 28.1, 33.7, 34.5, 35.9, 36.1, 36.6, 42.4, 54.1, 55.2, 59.3, 64.9, 66.7, 68.9, 70.8, 72.4, 73.2, 75.9, 81.4, 82.05, 82.14, 82.3, 83.0, 86.4, 92.0, 113.6, 113.7, 127.7, 128.0, 129.3, 129.6, 130.3, 130.6, 159.0, 159.1; IR (film) 3395 (br), 2929, 1612, 1514 (str), 1458, 1303, 1249 (str) cm^{-1}; $[\alpha]^{20}_D$ = 15 (c = 1.5, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{43}H_{62}O_{10}Na$ $[M + Na]^+$: 761.42, found: 761.5.



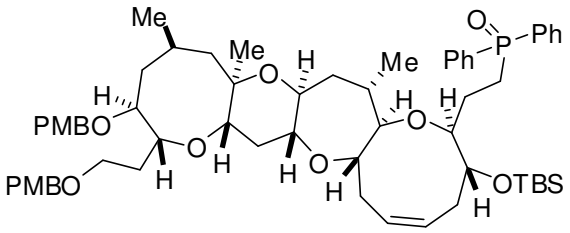
BCDE Bis Silyl Ether. To a round-bottomed flask equipped with a stir bar was added the diol (62 mg, 0.092 mmol) in 5 mL CH_2Cl_2. The solution was cooled to 0 ^{o}C, and 2,6 lutidine (43 µL, 0.37 mmol) was added, followed by *t*-butyldimethylsilyl trifluoromethanesulfonate (64 µL, 0.28 mmol). The solution was stirred for 1 hour, then quenched by the addition of saturated NH_4Cl and warmed to room temperature. The layers were separated, and the aqueous portion was extracted three more times

with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (10% EtOAc/Hexanes) provided 79 mg (96%) of the ether as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.03 (s, 3H), 0.07 (s, 3H), 0.09 (s, 3H), 0.87 (s, 9H), 0.90 (s, 9H), 1.00 (d, J = 7 Hz, 3H), 1.15 (s, 3H), 1.16 (d, J = 7.3 Hz, 3H), 1.38-1.73 (m, 7H), 1.73-1.96 (m, 4H), 2.11-2.33 (m, 3H), 2.33-2.50 (m, 3H), 2.54 (m, 1H), 2.92 (ddd, J = 12.0, 9.8, 4.0 Hz, 1H), 3.07 (dd, J = 10.6, 10.6 Hz, 1H), 3.34-3.68 (m, 11H), 3.791 (s, 3H), 3.794 (s, 3H), 4.40 (AB, J_{AB} = 11.0 Hz, Δv_{AB} = 72.6 Hz, 2H), 4.41 (AB, J_{AB} = 11.4 Hz, Δv_{AB} = 0.0 Hz, 2H), 5.66 (m, 2H), 6.85 (d, J = 3.7 Hz, 2H), 6.87 (d, J = 3.7 Hz, 2H), 7.22 (d, J = 9.4 Hz, 2H), 7.27 (d, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.54, -5.52, -4.9, -4.5, 16.5, 17.8, 18.0, 20.6, 25.67, 25.69, 26.7, 28.0, 33.6, 34.0, 34.2, 34.7, 37.4, 42.3, 54.1, 55.1, 58.5, 66.6, 69.0, 70.6, 72.3, 75.6, 75.7, 81.4, 82.1, 82.2, 82.9, 83.0, 113.5, 113.6, 126.1, 129.1, 129.2, 129.4, 130.2, 130.5, 158.9, 159.0; IR (film) 2955, 2928, 2855, 2360, 1613, 1514 (str), 1462, 1361, 1306, 1250 (str) cm^{-1}; $[\alpha]^{20}_D$ = -14 (c = 1.5, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{55}H_{90}O_{10}Si_2Na$ $[M + Na]^+$: 989.60, found: 989.7.



BCDE Primary Alcohol. A reaction vessel with a stir bar was charged with the bis silyl ether (66 mg, 0.068 mmol) in 3 mL of THF. Hydrogen fluoride-pyridine (150 µL, 65% hydrogen fluoride in pyridine) was added, and the solution was stirred

for 1.5 hours at room temperature. The reaction was quenched via the slow addition of saturated $NaHCO_3$ and diluted with Et_2O. The layers were separated, and the aqueous portion was extracted three more times with Et_2O. The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (25% EtOAc/Hexanes) provided 50 mg (86%) of the alcohol as a colorless oil, along with 9 mg (14%) of the starting bis silyl ether: ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 0.98 (d, J = 6.7 Hz, 3H), 1.14 (s, 3H), 1.19 (d, J = 7.5 Hz, 3H), 1.38-1.54 (m, 3H), 1.55-1.64 (m, 3H), 1.65-1.82 (m, 4H), 1.83-1.98 (m, 3H), 2.14 (m, 1H), 2.19-2.36 (m, 4H), 2.50 (m, 1H), 2.62 (m, 1H), 2.91 (dd, J = 8.6, 8.6 Hz, 1H), 3.06 (dd, J = 9.6, 9.6 Hz, 1H), 3.36 (m, 2H), 3.42-3.49 (m, 2H), 3.50-3.63 (m, 4h), 3.71 (m, 1H), 3.792 (s, 3H), 3.796 (s, 3H), 3.82 (m, 2H), 4.39 (AB, J_{AB} = 11.0 Hz, Δv_{AB} = 74.0 Hz, 2H), 4.41 (AB, J_{AB} = 11.5 Hz, Δv_{AB} = 7.5 Hz, 2H), 5.68 (m, 2H), 6.85 (d, J = 3.1 Hz, 2H), 6.87 (d, J = 3.1 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.8, -4.3, 16.6, 17.9, 21.3, 25.8, 26.8, 28.1, 33.7, 34.7, 35.1, 35.5, 42.4, 54.2, 55.23, 55.24, 60.0, 66.8, 69.0, 70.8, 72.4, 73.8, 75.8, 82.2, 82.3, 82.4, 82.6, 83.0, 85.6, 113.6, 113.7, 126.8, 128.7, 129.3, 129.6, 130.3, 130.7, 159.0, 159.1; IR (film) 2956, 2929, 2853, 1613, 1514 (str), 1463, 1303, 1250 (str), 1173 cm^{-1}; $[\alpha]^{20}_D$ = 1.8 (c = 0.84, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{55}H_{94}NO_{10}Si_2$ $[M + NH_4]^+$: 870.56, found: 870.6.

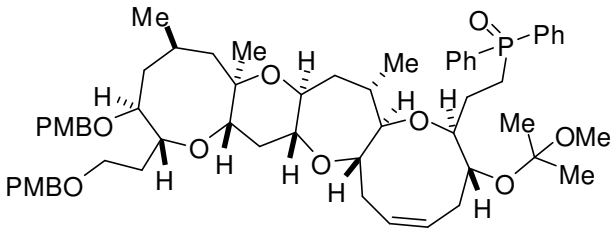


BCDE Silyl Protected Phosphine Oxide. The previously prepared alcohol (26 mg, 0.030 mmol) in 1 mL CH_2Cl_2 was added to a flask with a stir bar. The solution was cooled to 0 ^oC, and triethylamine (17 µL, 0.12 mmol) was added, followed by methanesulfonyl chloride (5.0 µL, 0.061 mmol). The solution was stirred for 15 minutes, then quenched by the addition of saturated NH_4Cl and warmed to room temperature. The layers were separated, and the aqueous portion was extracted three more times with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (25% EtOAc/Hexanes) provided 28 mg (100%) of the mesylate as a colorless oil.

Prepartion of lithium diphenylphosphide: To a reaction vessel with a stir bar was added diphenylphosphine (165 µL, 0.948 mmol) in 2.5 mL of THF. The solution was cooled to 0 ^oC, and *n*-butyllithium (652 µL, 1.043 mmol, 1.6 M in hexanes) was added, resulting in a bright red solution. The mixture was warmed to room temperature and stirred for 30 minutes.

The previously prepared mesylate (28 mg, 0.030 mmol) was added to a flask in 1 mL of THF and 50 µL of hexamethylphosphoramide. The solution was cooled to 0 ^oC, and the lithium diphenylphosphide (800 µL, 0.304 mmol, 0.38 M in THF) was added until a red color persisted for several minutes. The reaction was quenched via the addition of 1 mL of water, then 100 µL of 30% H_2O_2 were added to the

solution and warmed to room temperature. After dilution with Et_2O, 10% $Na_2S_2O_3$ was used to wash the organic layer. The aqueous layer was extracted five times further with Et_2O. The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (50% EtOAc/Hexanes) provided 29 mg (94%) of the phosphine oxide as a colorless semi-solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.05 (s, 3H), 0.04 (s, 3H), 0.83 (s, 9H), 0.97 (d, *J* = 7.4 Hz, 3H), 0.98 (s, 3H), 1.14 (s, 3H), 1.26 (dd, *J* = 6.4, 6.4 Hz, 1H), 1.38-1.56 (m, 4 H), 1.56-1.73 (m, 3H), 1.74-1.95 (m, 6H), 2.08-2.37 (m, 5H), 2.44 (m, 1H), 2.61 (m, 1H), 2.89 (dd, *J* = 7.8 Hz, 1H), 3.06 (dd *J* = 10.4 Hz, 1H), 3.24-3.40 (m, 4H), 3.44 (dd *J* = 11.0, 4.5 Hz, 1H), 3.50-3.61 (m, 3H), 3.68 (br s, 1H), 3.79 (s, 6H), 4.39 (AB, J_{AB} = 11.0 Hz, Δv_{AB} = 72.3 Hz, 2H), 4.41 (AB, J_{AB} = 12.7 Hz, Δv_{AB} = 0.0 Hz, 2H), 5.67 (m, 2H), 6.86 (d, *J* = 7.9 Hz, 4H), 7.23 (d, *J* = 7.7 Hz, 2H), 7.26 (d, *J* = 6.7 Hz, 2H), 7.41-7.55 (m, 6H), 7.73 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.7, -4.3, 16.5, 17.9, 21.2, 24.7, 24.8, 25.8, 26.9, 28.1, 33.7, 34.7, 35.2, 36.0, 42.5, 54.2, 55.23, 55.25, 66.7, 69.0, 70.8, 72.4, 73.4, 75.9, 82.2, 82.36, 82.39, 83.0, 113.6, 113.7, 127.0, 128.48, 128.54, 128.6, 128.7, 129.3, 129.6, 130.3, 130.7, 130.8, 130.9, 131.0, 131.6, 131.7, 159.0, 159.1; IR (film) 2952, 2925, 2855, 1516 (str), 1451, 1245 (str) cm^{-1}; $[\alpha]^{20}_D$ = 5.8 (c = 0.68, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{61}H_{86}O_{10}PSi$ [M + 1]$^+$: 1037.57, found: 1037.6.



BCDE Acetal Protected Phosphine Oxide. A reaction vessel with a stir bar was charged with the silyl protected phosphine oxide (56 mg, 0.055 mmol) in 2 mL of THF. Tetrabutylammonium fluoride (163 µL, 0.163 mmol, 1.0 M in THF) was added, and the solution was stirred for three hours at room temperature. The reaction was then concentrated in vacuo.

The crude hydroxyphosphine oxide from the previous step was dissolved in 3 mL of 2-methoxypropene in a reaction vessel with a stir bar at 0 ^{o}C. Pyridinium *p*-toluenesulfonate (50 mg, 0.20 mmol) was added, and the mixture was stirred for 1 hour. The reaction was quenched via the slow addition of saturated $NaHCO_3$, then warmed to room temperature. The mixture was extracted five times with CH_2Cl_2, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (100% EtOAc then 100% Acetone) provided 48 mg (90%) of the phosphine oxide as a pale white semi-solid: ^{1}H NMR (400 MHz, C_6D_6) δ 0.96 (d, *J* = 7.4 Hz, 3H), 1.08 (d, *J* = 7.4 Hz, 3H), 1.22 (s, 3H), 1.27 (s, 3H), 1.28 (s, 3H), 1.38 (m, 1H), 1.52 (m, 1H), 1.65-1.90 (m, 8H), 1.98 (m, 2H), 2.12 (m, 2H), 2.26-2.55 (m, 6H), 2.62 (dd, *J* = 12.3, 12.3 Hz, 1H), 2.79 (ddd, *J* = 12.1, 9.1, 4.3 Hz, 1H), 2.96-3.09 (m, 2H), 3.13 (s, 3H), 3.29 (s, 3H), 3.31 (s, 3H), 3.42-3.57 (m, 4H), 3.58-3.76 (m, 4H), 3.96 (dd, *J* = 4.4, 4.4 Hz, 1H), 4.31 (AB, J_{AB} = 11.4 Hz, Δv_{AB} = 100.0 Hz, 2H), 4.36 (s, 2H), 5.89 (ddd, *J* = 10.5, 10.5, 6.5 Hz, 1H), 6.00 (ddd, *J* = 10.8, 10.8, 7.3 Hz, 1H), 6.78 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 7.02 (m, 6H), 7.20 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 7.81 (m, 4H); ^{13}C NMR (100 MHz, C_6D_6) δ 16.8, 22.4, 25.2, 25.4, 27.1, 28.3, 29.4, 29.5, 34.5, 35.2, 36.1, 37.0, 42.7, 49.2, 54.7, 54.9, 66.8, 69.7, 70.8, 72.8, 73.4, 75.9, 82.0, 82.3, 82.4, 82.7, 83.5, 127.2, 127.9, 128.1,

128.3, 128.5, 128.6, 128.66, 128.75, 129.66, 129.70, 131.0, 131.08, 131.10, 131.15, 131.19, 131.3, 131.4; IR (film) 2929, 2862, 1514, 1463, 1439, 1249, 1180 cm^{-1}; $[\alpha]^{20}_{D}$ = 18 (c = 0.61, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{59}H_{79}O_{11}PNa$ $[M + Na]^+$: 1017.53, found: 1017.6.

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