DEVELOPMENT OF ANTI-SELECTIVE ALDOL ADDITIONS AND A CONVERGENT ASSEMBLY OF POLYCYCLIC ETHERS: SYNTHESIS OF THE ABCDE FRAGMENT OF BREVETOXIN A

Patrick J. McDougall

A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Chemistry.

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Approved by:

Advisor: Professor Michael T. Crimmins

Reader: Professor Jeffrey S. Johnson

Reader: Professor Paul J. Kropp

ABSTRACT

Patrick J. McDougall

Development of Anti-Selective Aldol Additions and a Convergent Assembly of Polycyclic Ethers: Synthesis of the ABCDE Fragment of Brevetoxin A
(Under the direction of Professor Michael T. Crimmins)

Anti-selective aldol additions between the titanium enolates of *N*-glycolyl oxazolidinethiones and simple aldehydes are described. Variation to the Lewis acid stoichiometry of known *syn* aldol conditions led to a reversal of stereoselectivity favoring formation of one *anti* diastereomer. Highest selectivity and yield were observed using α-allyloxy glycolylimides and aliphatic, unbranched aldehydes. Other suitably protected imides and α,β-unsaturated or aromatic aldehydes were also viable reacting partners.

Application of the *anti* glycolate aldol additions toward the stereoselective synthesis of the BCDE fragment of the potent red tide neurotoxin brevetoxin A is also described. Synthesis of the B ring began with an *anti* aldol addition to set the C3 and C4 stereogenic centers. Further elaboration using glycolate alkylation and ring-closing metathesis reactions provided the B ring core. The E ring fragment likewise utilized *anti* aldol methodology to rapidly access a diene fragment needed to close the nine-membered ring.

A novel convergent coupling strategy was developed for the synthesis of the completed *trans*-fused BCDE tetracycle from the individual B and E units. This approach relied on a Horner-Wadsworth-Emmons reaction to join the two complex fragments. Enone reduction and subsequent cyclodehydration generated an intermediate endocyclic enol ether representing the B, C, and E rings. Elaboration of the enol ether intermediate via oxidation, cyclization of the D ring, and ketal reduction then provided the completed BCDE fragment.

A revised synthesis of this molecule was subsequently developed to provide the one-carbon homologated version needed for eventual completion of the natural product. The E ring revision is highlighted by a novel glycolate alkylation using bromoacetonitrile and several protecting group alterations. Significant improvements to the convergent assembly were realized during the revision, providing the BCDE fragment in significantly higher yield from the individual rings and in fewer synthetic steps. Finally, the A ring lactone was formed, providing the complete ABCDE pentacycle.

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LIST OF ABBREVIATIONS

9-BBN	9-borabicyclo[3.3.1]nonane
Ac	acetyl
Bn	benzyl
Bu	butyl
Bz	benzoyl
CSA	camphorsulfonic acid
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*-*N*'-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	diisobutylaluminum hydride
DIEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
Et	ethyl
HMPA	hexamethyl phosphoramide
HWE	Horner-Wadsworth-Emmons
Me	methyl
Mes	mesityl

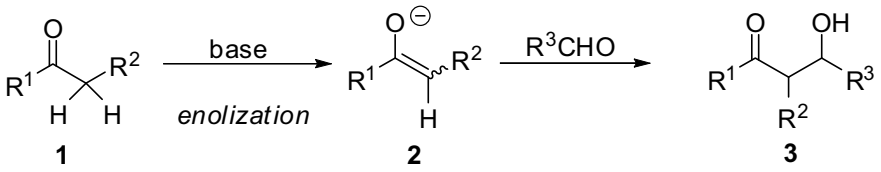
MOP	methoxypropyl
NMO	4-methylmorpholine *N*-oxide
NMP	1-Methyl-2-pyrrolidinone
Ph	phenyl
Piv	pivaloyl
PMB	*p*-methoxybenzyl bromide
PPTS	pyridinium *p*-toluenesulfonate
RCM	ring-closing metathesis
TBAF	tetrabutylammonium fluoride
TBS	*t*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Tr	trityl
Ts	*p*-toluenesulfonyl

CHAPTER 1: DEVELOPMENT OF CHIRAL AUXILIARY MEDIATED *ANTI* GLYCOLATE ALDOL ADDITIONS

1.1 BACKGROUND

1.1.1. The aldol addition

The aldol addition reaction in its simplest form represents the union of the α-carbon of a carbonyl group (**1**) with an aldehyde to generate β-hydroxy carbonyl products (**3**) (Scheme 1.1.1).[1,2] The reaction itself is generally considered to be a two-stage process proceeding via base promoted deprotonation of the α-C-H to generate the intermediate enol, enolate (**2**), or enolate equivalent (e.g. silyl enol ether, silyl ketene acetal). Subsequent attack of the



1 **2** **3**

Scheme 1.1.1. The aldol reaction

nucleophilic α-carbon on the electrophilic aldehyde leads to the cross-coupled product. This transformation is characterized by the generation of a new carbon-carbon bond with concomitant formation of up to two new stereogenic centers and, thus, represents one of the most powerful transformations available in organic synthesis.

Since the initial recognition by Wurtz in 1872,[1] the aldol addition has been the subject of intense investigations providing extensive information surrounding the substrate scope, reaction procedures, and mechanistic detail. Up until the mid-1970's, the aldol reaction was typically performed under protic conditions using a stoichiometric amount

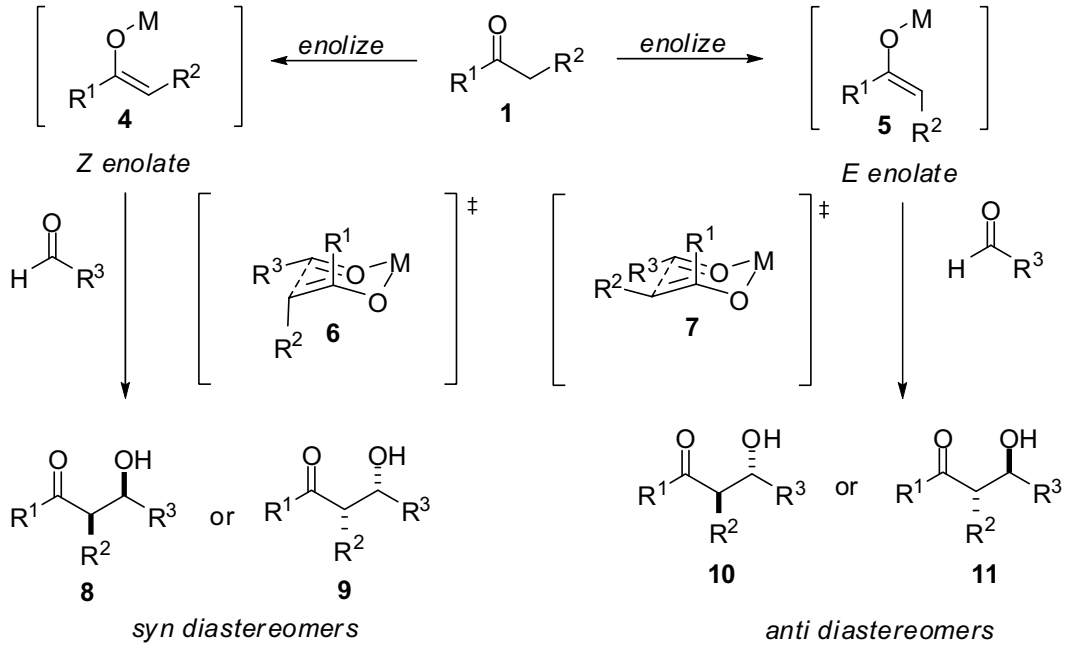
of hydroxide or alkoxide base. These reaction conditions favor reversible formation of the enolate and incur many limitations in terms of substrate versatility. For example, use of two reacting partners each capable of undergoing enolization under the reaction conditions would lead to complex mixtures of products resulting from self-condensation in addition to the desired cross aldol adduct. A major advance in cross-aldol chemistry came with the realization that stoichiometric amounts of a metal enolate can be formed prior to the addition of the aldehyde.[3,4] This allowed for enhanced substrate scope and, ultimately, increased stereocontrol over the new stereogenic centers. A number of Group I, II, III, and transition metals have been used to generate the reactive metal enolates. The more commonly employed metals are boron, titanium, lithium, zinc, zirconium, and tin.

1.1.2 Diastereoselectivity in aldol additions

With the advent of improved technologies for stoichiometric metal enolate generation, control over the configuration of the newly formed stereogenic centers became possible. Efforts to identify highly diastereoselective aldol reactions have occupied synthetic chemists for many years and have led to many well-behaved reactions. It had been observed throughout these studies that both the substrate and metal counterion can have a profound impact on the diastereoselectivity of the reaction.[3,5] As a result of this variable behavior, aldol additions can be classified into three categories depending on the stereochemical outcome of the reaction.[5]

In type I reactions, enolate geometry is found to directly influence the relative configuration of the newly formed stereogenic centers. As illustrated in Scheme 1.1.2, the generation of two distinct enolate geometries is possible. The *Z*-enolate (**4**), in which R^2 (α-substituent) is cis to the metal alkoxide, represents one possibility, and the *E* enolate (**5**) containing the trans orientation represents the other. Experimentally, *Z*-enolates predominantly lead to aldol adducts containing the *syn* diastereomeric relationship (**8**, **9**) and

the *E*-enolates provide the anti configuration (**10**, **11**). This trend is typically observed when using group I, II, or III metals. To account for the observed results, it has become commonplace to invoke a chair-like transition state (**6**, **7**), originally proposed by Zimmerman and Traxler[6] and later modified by Houk[7] and others.[5] Chelation of the aldehyde to the metal



Scheme 1.1.2. Product configuration as a function of enolate geometry

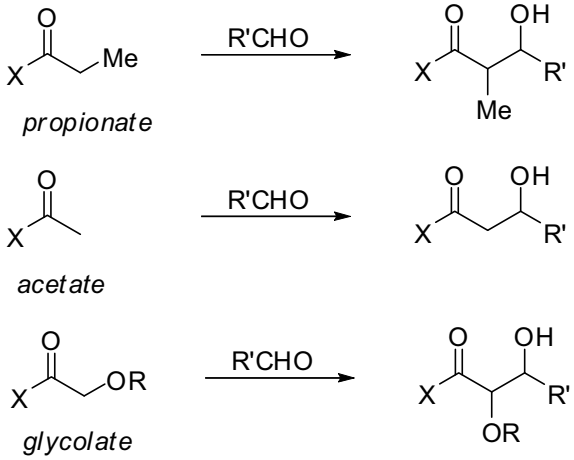
center has been proposed to not only organize the reacting partners into a predictable pericyclic transition state conformation, but also to activate the aldehyde toward nucleophilic addition. Positioning the aldehyde substituent in an equatorial position to minimize 1,3-diaxial steric interactions and orientation of the remaining components in the thermodynamically favored chair conformation completes the mechanistic picture for the observed diastereoselectivity.

In type II reactions, both *E*- and *Z*-enolate geometries lead to aldol products containing the *syn* configuration. These reactions are commonly observed using enol silane derivatives[8] and when using Lewis acids that have a low affinity for chelation.[9] The stereoselectivity of these reactions is generally thought to arise from an open, or acyclic

transition state.[10] In a similar sense, type III aldol reactions are characterized by the generation of *anti* products regardless of enolate geometry. These reactions represent only a small fraction of aldol chemistry and are uncommon.[11] Both open and closed transition states have been proposed.

1.1.3 Definitions of propionate, acetate, and glycolate aldol additions

Three separate subclasses of aldol additions are commonly encountered in organic synthesis and can be differentiated based on the substitution present at the α-carbon. Reactions involving substrates containing an α-methyl substituent are referred to as propionate aldol additions (Scheme 1.1.3). Those containing no substituent are referred to as acetate aldol additions and those with an α-alkoxy substituent are often called glycolate aldol additions. These three classes of aldol additions are widely employed in natural product synthesis depending on the desired product substitution.[12]



Scheme 1.1.3. Classification of aldol additions

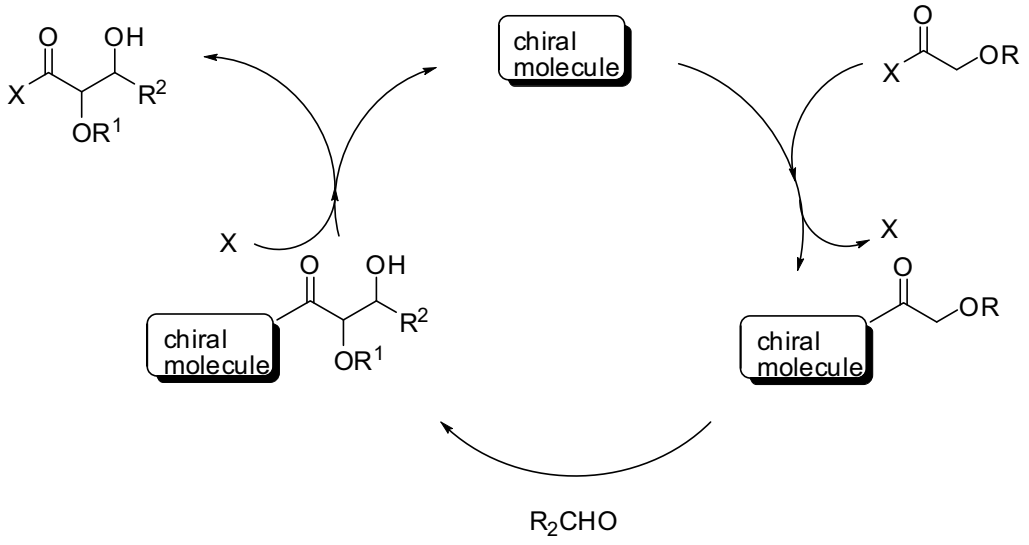
Glycolate aldol additions are particularly important for the stereoselective generation of a synthetically useful 1,2-diol unit. Based on the potential for facile functionalization of not only the free β-hydroxyl, but also the α-oxygen (via deprotection), glycolate aldol adducts are highly versatile intermediates for organic synthesis.

1.1.4 Asymmetric control using chiral auxiliaries

The diastereomeric relationship of the newly formed stereogenic centers in many aldol additions is generally believed to be a function of the enolate geometry and/or metal

counterion, as discussed previously. Control over the absolute configuration, however, is a far more complex situation that requires the addition of an optically active component to transfer chirality to the aldol adducts. Many approaches to this challenge have been developed over the past thirty years and include the use of stoichiometric chiral Lewis acids,[13,14] chiral catalysts[15] or chiral auxiliaries.[16,17]

Arguably, the latter option has been one of the more extensively studied and experimentally facile approaches to asymmetric control in aldol additions. A chiral auxiliary will be defined as a temporary chiral, non-racemic, organic component that is covalently attached to the substrate throughout the course of the aldol reaction *and* can be subsequently removed and recovered without compromising the auxiliary or substrate structure (see Scheme 1.1.4). This approach toward asymmetric aldol additions offers several advantages over other methods, such as those directed by chiral Lewis acids or chiral catalysts. For example, most synthetically useful chiral auxiliaries are simple to prepare from inexpensive enantiopure reagents that are readily available from naturally occurring sources ("chiral pool").[18] More importantly, since diastereomeric products are



Scheme 1.1.4. Chiral auxiliary mediated aldol additions

obtained (as opposed to enantiomeric mixtures) isolation of the desired isomer is often a far simpler task using simple chromatographic separations.[16]

1.1.4.1. Chiral auxiliary mediated *syn* glycolate aldol additions

The use of chiral auxiliaries to induce asymmetry for *syn* glycolate aldol additions has been studied by several research groups resulting in a number of effective methodologies. These acyclic substrates existing as either amides, imides, or esters invariably provide the *Z*-enolates upon enolization. Experimentally, there is an overwhelming preference for the formation of the *syn* diastereomers upon reaction with an aldehyde, thus classifying the additions as type I. Indeed, as is evidenced by the number of effective reaction technologies, selective generation of the *syn* diastereomers is a far simpler task than obtaining the *anti* isomers. Many different chiral auxiliaries have been effectively utilized, often as a result of successful use in the propionate counterparts. The majority of the more widely used auxiliaries are derived from either norephedrine or amino acids. Examples of several chiral auxiliaries previously utilized for *syn* glycolate aldol additions are illustrated in Figure 1.1.1.

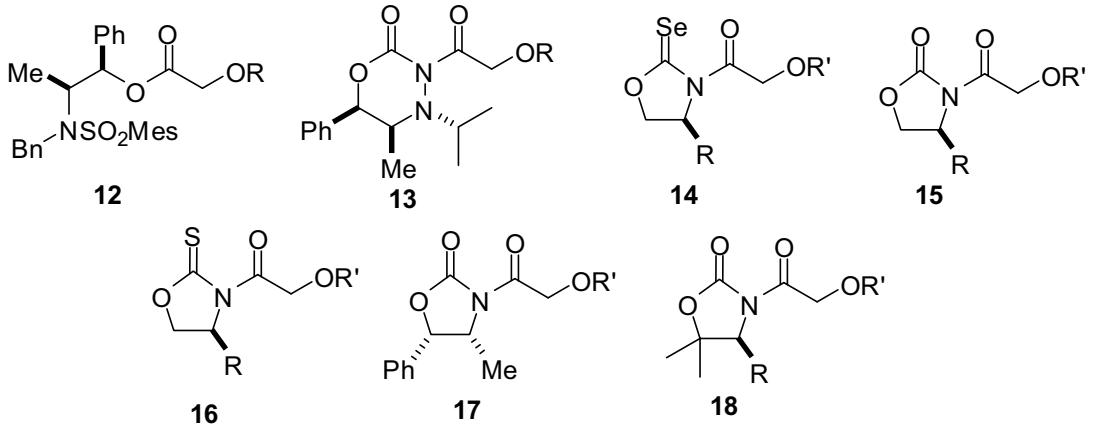
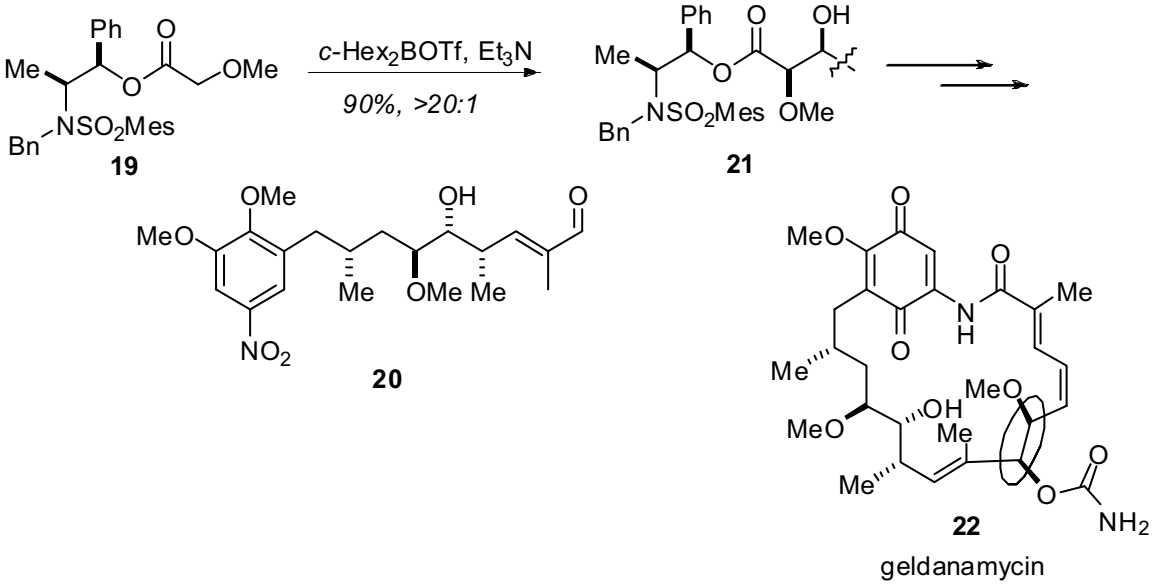


Figure 1.1.1. Common chiral auxiliaries for syn glycolate additions

1.1.4.1.1. Auxiliaries based on norephedrine

Andrus and coworkers have recently developed a highly *syn* selective glycolate aldol addition using Masamune norephedrine esters (**12**, Figure 1.1.1) as the chiral auxiliary component.[19] Initial formation of the boron enolate enabled the stereoselective generation of the *syn* aldol adducts from a variety of aliphatic, aromatic and α,β-unsaturated aldehydes in excellent yields and high diastereoselectivity. An illustrative example of an addition to a complex aldehyde is shown in Scheme 1.1.5, *en route* to their total synthesis of the natural product geldanamycin (**22**).[20] Aldol addition of methyl glycolate **19** to aldehyde **20** provided adduct **21** in 90% yield and >20:1 selectivity for the diastereomer shown.

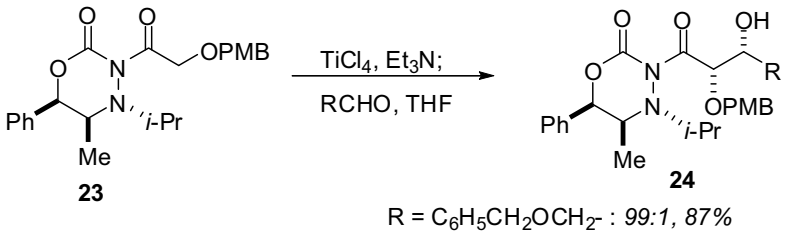
Similar to the Masamune auxiliary, another chiral auxiliary derived from the natural product norephedrine are the chiral oxadiazinones (**13**, Figure 1.1.1). Glycolylimides of these cyclic chiral components have recently been shown to be excellent substrates for



Scheme 1.1.5. *Syn* selective glycolate aldol in total synthesis of geldanamycin (Andrus)

affording the *syn* glycolate aldol adducts with high diastereoselectivity.[21] For example, formation of the titanium enolate of glycolate **23** using titanium tetrachloride and triethylamine followed by addition of the α-benzyloxy aldehyde delivered the desired 1,2-*syn*

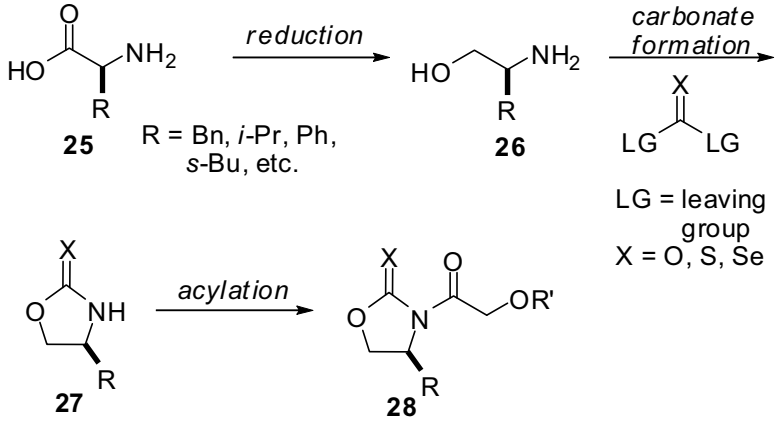
diol **24** with a 99:1 diastereomeric ratio and in good yield (Scheme 1.1.6). A wide range of aromatic, α,β-unsaturated, and aliphatic aldehydes have been successfully reacted under these conditions.



Scheme 1.1.6. Oxadiazinones in *syn* glycolate aldol additions (Hitchcock)

1.1.4.1.2. Auxiliaries derived from amino acids

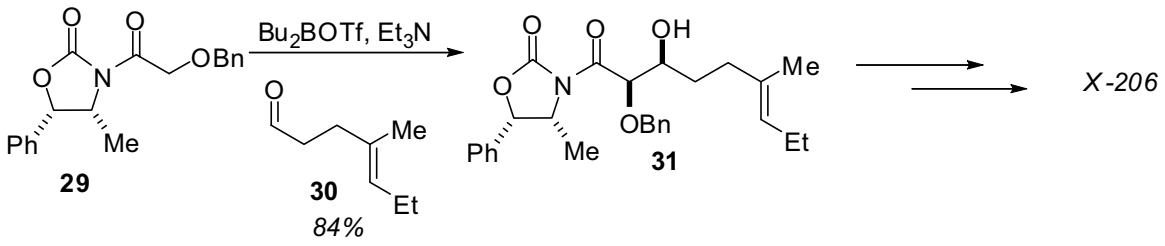
Undoubtedly, the most widely used auxiliaries for the three common classes of aldol additions (propionate, glycolate, and acetate) are centered on the oxazolidinone scaffold (**14**-**16**; Figure 1.1.1). These auxiliaries are readily available from the abundant and diverse class of amino acids and thus offer the opportunity for significant alterations at the chiral center of the auxiliary. Upon reduction[22,23] of the appropriate amino acid (**25**), the resulting amino alcohol (**26**) can be easily cyclized to various carbamate derivatives (**27**) depending on the reagent choice (Scheme 1.1.7). Acylation of the cyclic carbamate with an appropriate glycolic acid or acid chloride derivative forms the glycolylimides (**28**). Many variations to amino acid (i.e. R) and heteroatoms (X, O) of the general imide **28** are known and have been utilized as effective chiral



Scheme 1.1.7. Synthesis of oxazolidine-type chiral auxiliaries

elements for diastereocontrol in aldol reactions. While this class of auxiliaries is more commonly know for their ability to induce diastereocontrol in propionate aldol additions,[24] alkylation reactions and Diels-Alder additions,[25] their use in glycolate aldol additions have proven equally effective. The stereoselectivity of the additions is generally very high and the reaction is tolerant of a variety of glycolylimides and aldehydes.

Like the propionate analogs,[24] formation of the boron enolate of *N*-glycolyloxazolidinones is the more prevalent method for performing the *syn* diastereoselective glycolate aldol additions. Several applications to the synthesis of natural products can be found due, in part, to a high level of reaction versatility. For example, Evans total synthesis of the complex polyether antibiotic X-206 utilized a glycolate aldol addition between oxazolidinone **29** and aldehyde **30** as a key carbon-carbon bond forming reaction (Scheme 1.1.8).



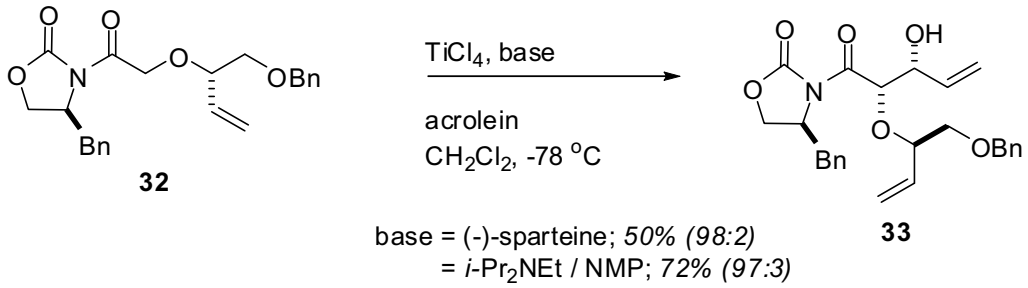
Scheme 1.1.8. Oxazolidinone glycolate aldol in the total synthesis of X-206 (Evans)

1.1.5 Crimmins approach to auxiliary-mediated *syn* aldol additions

Chiral auxiliary mediated aldol additions are a central theme to the work performed in the Crimmins laboratory. This work has focused on the use of the oxazolidinone (and related sulfur analogs) chiral auxiliaries to induce diastereocontrol in propionate,[26] acetate,[27] and glycolate aldol additions. In contrast to the widely-utilized boron-mediated additions, titanium tetrachloride is used as the stoichiometric Lewis acid to generate the titanium enolates. Use of this metal offers several advantages over boron and typically provides the aldol adducts in high diastereoselectivity and yields. In stark contrast to dibutylboron triflate (Bu_2BOTf),

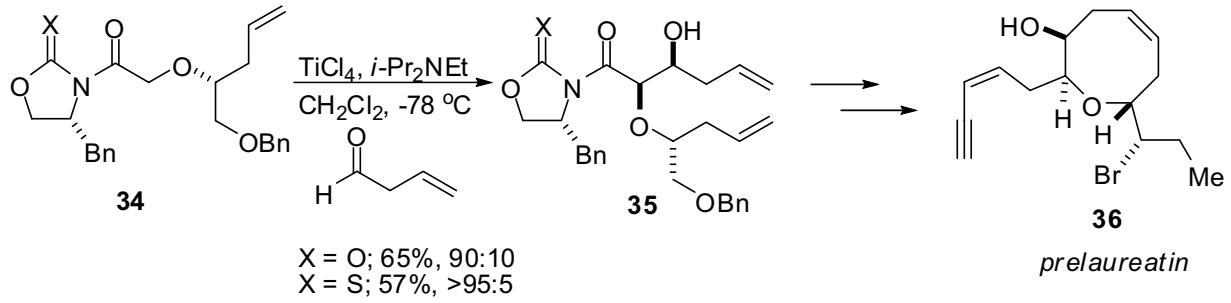
titanium tetrachloride is very inexpensive costing roughly 1/12th the price.[28] Furthermore, the oxidative workup common to boron mediated reactions can be avoided, which significantly improves the operational simplicity of the reaction.

In addition to the use of propionate substrates,[26] *N*-glycolyloxazolidinones can also be subjected to similar enolization conditions employing titanium tetrachloride and utilized in asymmetric *syn* selective glycolate aldol additions. While (–)-sparteine is often employed as the base in these types of additions,[26,29] subsequent work in the Crimmins laboratory has shown that alternative bases can have a significant impact on the isolated yields of the desired aldol adduct.[30] For example, the aldol addition of oxazolidinone imide **32** with acrolein employing (–)-sparteine as the base gave a 50% yield of the desired adduct **33** (Scheme 1.1.9). The combined use of *i*-Pr_2NEt and *N*-methylpyrrolidinone (NMP) as an alternative amine base improved the yield to 72%.



Scheme 1.1.9. Improved procedure for *syn* glycolate aldol additions (Crimmins)

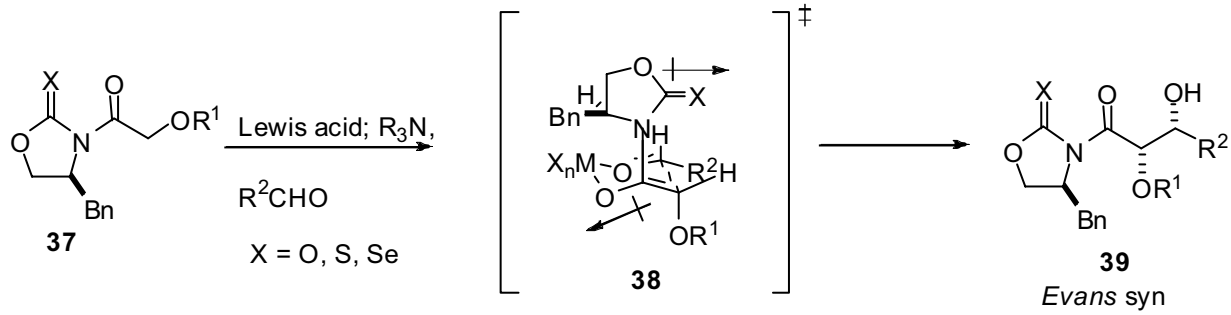
Oxazolidinethione (**16**; Figure 1.1.1) mediated *syn* glycolate aldol additions have also been explored by Crimmins, often leading to adducts in higher diastereoselectivity. For example, in the total synthesis of prelaureatin (**36**), aldol addition of butenal to the titanium enolate of the complex glycolate **34** using the oxazolidinone auxiliary delivered the aldol adduct **35** in ~90:10 stereoselectivity (Scheme 1.1.10).[29] Upon switching to the oxazolidinethione auxiliary, the *syn* adduct was provided with higher diastereoselectivity (95:5), though somewhat lower in yield.



Scheme 1.1.10. Oxazolidinone vs. oxazolidinethione *syn* glycolate aldol additions (Crimmins)

1.1.6 Proposed transition states for chiral oxazolidinone mediated *syn* glycolate aldol additions

The stereochemical outcome of oxazolidinone mediated glycolate aldol reactions is generally accepted to be the result of a Zimmerman-Traxler[6] chair transition state (Scheme 1.1.11), and is adopted from that proposed for propionate additions.[31] Formation of either the boron[24] or titanium *Z*-enolate[32] followed by chelation to the aldehyde forms the classic pericyclic closed transition state **38**. Orientation of the aldehyde substituent in a pseudo equatorial position and minimization of the carbonyl-carbonyl dipole interactions[33] leads to the corresponding syn diastereomer **39**. Based on the contribution made in this area by Evans,[24] this product is commonly referred to as the Evans *syn* product.



Scheme 1.1.11. Proposed transition state for *syn*-glycolate aldol additions

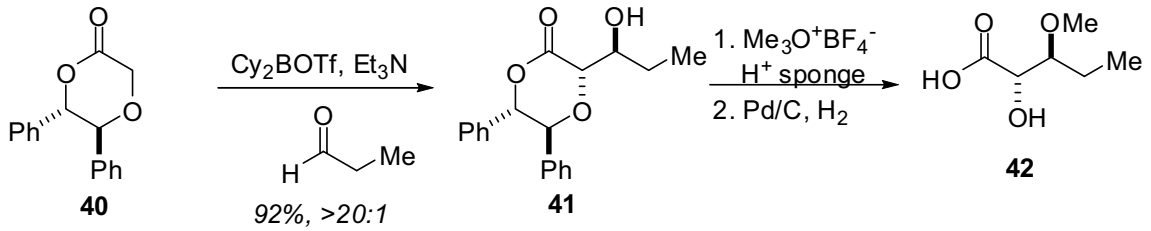
1.1.7 *Anti* diastereoselective glycolate aldol additions

In contrast to *syn* glycolate aldol additions, only limited examples of *anti* selective glycolate aldol additions mediated by chiral auxiliaries have been reported. The difficulty in accessing the *anti* isomers stems from the favorable formation of *Z*-enolates under typical enolization conditions[31] leading to an overwhelming preference for *syn* selectivity (see Scheme 1.1.11). Two general approaches have been employed in an effort to favor formation of the anti diastereomers; (1) selective generation of *E* enolates and (2) modification of reaction conditions to promote *anti* selective reactions from the Z-enolates (type III aldol reactions).

1.1.7.1. *E*-enolate formation

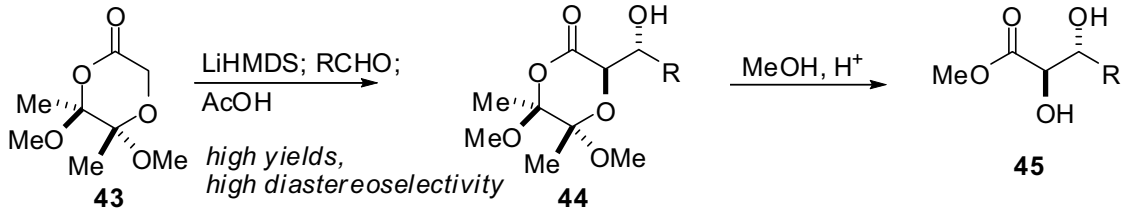
Two independent reports to selectively generate the *anti* glycolate diastereomers via formation of the *E*-metalloenolates were reported in early 2000. The researchers utilized cyclic substrates that were conformationally restricted to generation of the *E*-enolates upon deprotonation and therefore led to preferential formation of the *anti* diastereomers following the chair-transition state argument. Chiral oxapyrone (1,4-dioxinone) substrates serving as latent α-hydroxy esters have proven effective achieving this goal, controlling both the *anti* relationship (via *E*-enolate formation) and total relative (via resident stereogenic center(s)) configuration for the aldol adducts.

Andrus and coworkers have utilized diphenyl oxypyrone boron enolates **40** to give the *anti* aldol adducts in excellent yields and diastereoselectivity from a variety of aldehydes (Scheme 1.1.12).[34] For example, formation of the boron enolate of oxypyrone **40** gave the *anti* adduct **41** in >20:1 diastereomeric ratio. Removal of the auxiliary could be effected under reducing conditions, however, recovery of this chiral element was not possible and thus is not classified as a chiral auxiliary mediated aldol addition.



Scheme 1.1.12. Oxapyrone mediated anti aldol additions (Andrus)

A similar approach was reported by Ley and coworkers utilizing butane-2,3-diacetals of glycolic acid (**43**, Scheme 1.1.13).[35] In contrast to commonly employed soft enolization techniques, the lithium enolates were directly generated using lithium hexamethyldisilazide (LiHMDS) to give high selectivity for the *anti* isomers (**44**). The advantage of this substrate is the facile liberation of the *anti* adducts from the cyclic constraint under acidic conditions to give the 1,2-diols (**45**).



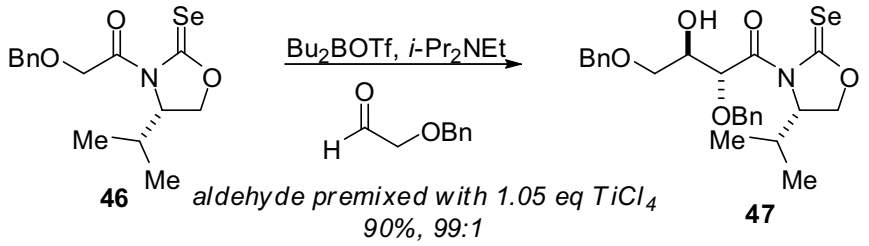
Scheme 1.1.13. *Anti* glycolate aldol addition of butane 2,3-diacetals (Ley).

1.1.7.2. *Anti* selectivity in acyclic substrates

The second approach involving modification of reaction conditions to disfavor formation of the *syn* diastereomers has been met with little success. These approaches have all relied on the oxazolidinone scaffold and are plagued with low selectivity and/or poor substrate versatility.

Silks and coworkers have shown that the chiral selone auxiliary **46** can provide *anti* aldol adducts (**47**) in high selectivity when reacted with α-alkoxy aldehydes (Scheme 1.1.14).[36] The authors noted that premixing the α-alkoxy aldehydes with additional Lewis acid was

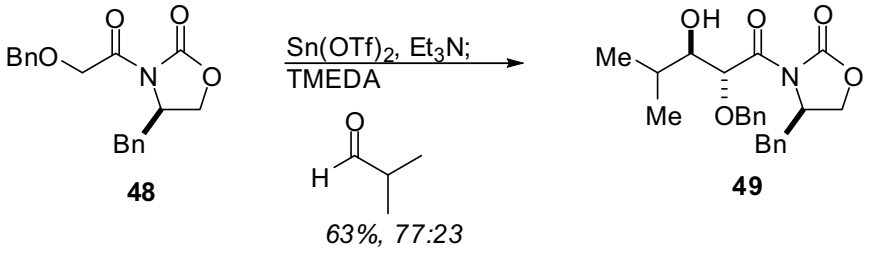
necessary to promote *anti* diastereoselectivity. However, if the aldehyde was not pre-complexed with additional Lewis acid ($TiCl_4$), little diastereoselection was observed. Of particular interest, both propionate and glycolate substrates could be utilized to form the *anti* adducts. The inability to afford *anti* aldol adducts with a general class of aldehydes, however, imposes a significant limitation on the substrate scope. Though no comment on possible transition states were made by the authors, it is reasonable that this external activation of the aldehyde precludes internal activation by the enolate bound metal, thereby favoring an open, or extended transition state.[9,10,37]



Scheme 1.1.14. *Anti*-glycolate addition of selone imides (Silks)

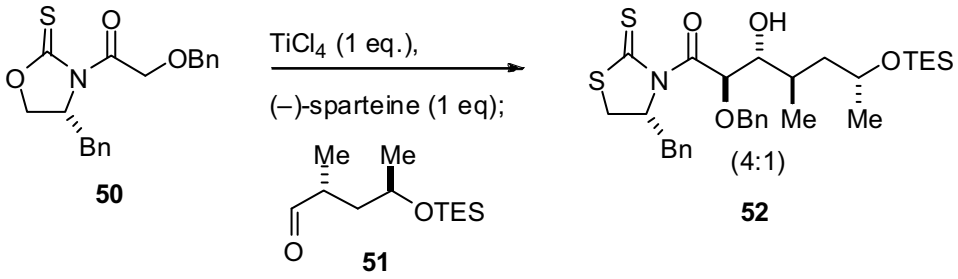
Evans and coworkers have also reported limited cases of an *anti* selective additions using tin (II) enolates of *N*-glycolyloxazolidinone imides (**48**) (Scheme 1.1.15).[38] However, only limited examples of this reaction are available and are characteristically poor yielding and moderately stereoselective (77:23). Nevertheless, an application of this methodology has appeared in the total synthesis of the natural product tautomycin,[39] a fact that is rather indicative of the void in effective *anti* glycolate aldol methodology.

It should also be noted that reports of *anti* selective glycolate aldol additions have



Scheme 1.1.15. *Anti* glycolate aldol additions using tin(II) enolates (Evans)

appeared using α-chiral aldehydes. These reactions proceed under typical aldol conditions that normally give rise to the *syn* adducts. For example, the aldol addition of thiazolidinethione benzyl glycolate **50** and aldehyde **51** proceeded to give the *anti* adduct **52** as the major diastereomer (4:1) under titanium mediated *syn* aldol conditions (Scheme 1.1.16).[40] Arguments favoring a boat transition state over the typical chair transition state have been postulated to explain the observed stereoselectivity. These reactions, however, are case dependent, and do not offer a solution to the long standing problem of obtaining *anti* selectivity in chiral auxiliary mediated aldol additions.



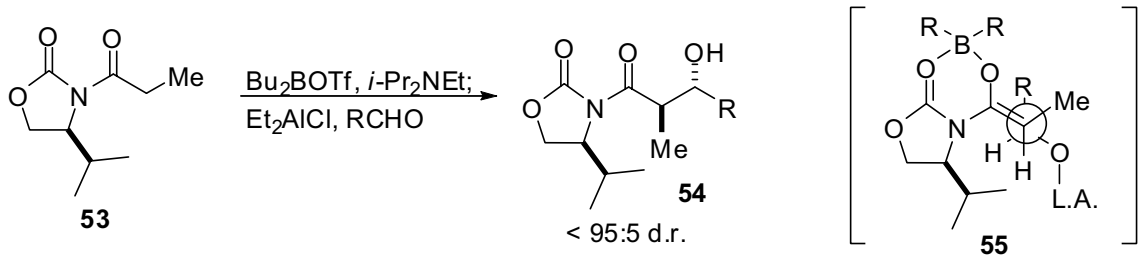
Scheme 1.1.16. *Anti* aldol additions with α-chiral aldehydes (Carter)

1.1.8 Chiral auxiliary mediated *anti* propionate aldol additions: an illustrative tool toward developing *anti* glycolate additions

Similar to *anti* glycolate aldol additions, *anti* diastereoselective propionate aldol additions have proven to be a considerably challenging venture. Three specific examples are discussed here as a prelude to the development of a general method to access *anti* glycolate aldol adducts.

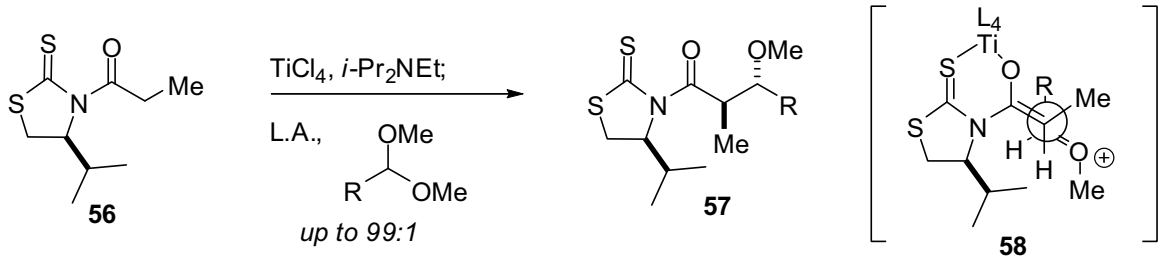
A report by Heathcock and coworkers demonstrated that additional Lewis acid premixed with an aldehyde prior to addition to the boron enolate of propionate **53** was observed to promote good selectivity for the *anti* isomers (**54**; Scheme 1.1.17).[41] These observations are similar to those reported by Silks,[36] though in the present case various aliphatic and aromatic aldehydes could be used. Based on the observed experimental results, it was

suggested by the authors that the reaction was occurring via the open transition state **55** through external activation of the aldehyde.



Scheme 1.1.17. *Anti* propionate aldol additions (Heathcock)

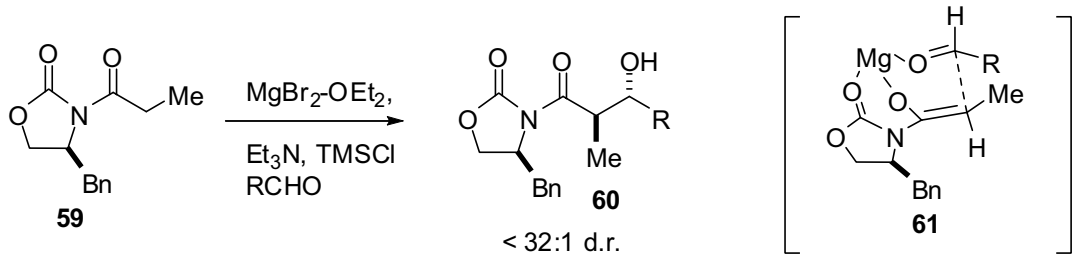
A similar propionate aldol-type addition has more recently been described by Urpi using acetals as the enolate acceptor (Scheme 1.1.18).[42] Exposure of the titanium enolates of *N*-propionylthiazolidinethione **56** to either a dimethyl or dibenzyl[43] acetal in the presence of additional Lewis acid selectively generated the β-alkoxy derivatives (**57**) in good yields. Again, an open transition state (**58**) was postulated to explain the observed diastereoselectivity.



Scheme 1.1.18. *Anti* selective additions to acetals (Urpi)

Recent progress has been made by Evans to yield the *anti* diastereomers of propionate aldol additions using oxazolidinone, oxazolidinethione, and thiazolidinethione chiral auxiliaries.[44,45] For example, formation of the magnesium enolate of propionate **59** using catalytic amounts of magnesium bromide diethyletherate led to the *anti* adducts (**60**) with excellent diastereoselection (Scheme 1.1.19). In contrast to the above examples, the reaction has been proposed to proceed via a closed boat-like transition state (**61**). The products are generally formed with high *anti* diastereoselectivity and in good yield. The

major limitation to this methodology, however, is that only aromatic and α,β-unsaturated aldehydes are viable enolate acceptors.



Scheme 1.1.19. *Anti* aldol additions of *N*-propionyl oxazolidinones (Evans)

1.2 DEVELOPMENT OF ANTI-SELECTIVE GLYCOLATE ALDOL ADDITIONS OF *N*-GLYCOLYLOXAZOLIDINETHIONES

1.2.1 Titanium enolates of oxazolidinones, oxazolidinethiones, and thiazolidinethiones: Crimmins aldol methodology

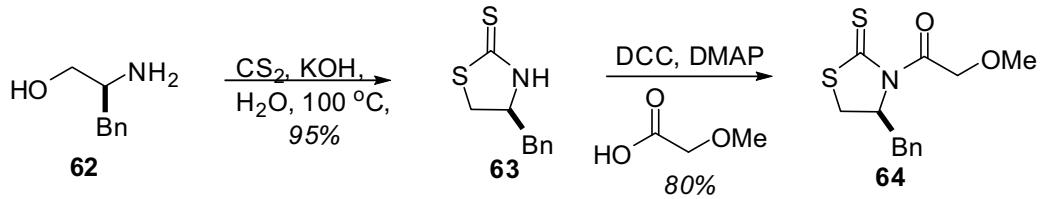
The continued development of oxazolidinone-based chiral auxiliary mediated aldol additions has been a significant focus of the Crimmins laboratory over the past eight years. In addition to the excellent progress made in the area of *syn* glycolate aldol additions discussed previously, much work has been performed to improve *syn* selective propionate aldol addition reactions using their respective titanium enolates.[46] Efforts in this area have included the use of (–)-sparteine as a base to improve both the diastereoselectivity of the reaction and reaction yields.[47] In addition, propionate aldol additions using oxazolidinethione[47] and thiazolidinethione[48] auxiliaries have yielded interesting results in terms of diastereocontrol. For example, it has been shown that access to either *syn* diastereomer from the same antipode of the oxazolidinethione or thiazolidinethione (see **63**, Scheme 1.2.1) auxiliary can be obtained simply by altering the reaction conditions.

Despite these advances in the *syn* selective aldol addition, selective generation of the *anti* isomers had remained elusive. Thus, a project aimed to afford the *anti* products using

the titanium promoted reactions of *N*-acylated chiral oxazolidinone-type substrates was developed. Specifically, the development of *anti* glycolate aldol additions was pursued with the ultimate goal of utilizing the adducts for natural product synthesis. Thus, the identification of a suitable auxiliary, substrate, and reaction conditions that would reverse the "normal" mode of reactivity that yields the *syn* diastereomers became the primary goals of the project.

1.2.2 Chiral auxiliary variants: Thiazolidinethione and oxazolidinone mediated additions

Studies began with the synthesis of *N*-glycolylthiazolidinethione substrates, primarily as a result of their excellent properties displayed in *syn* propionate aldol additions.[48] In addition to providing the *syn* adducts in high diastereoselection, the auxiliary holds many other advantages over the oxazolidinone chiral controller, including facile preparation from the corresponding amino acid, visual chromatography of the highly colored acylated substrates, and their versatility in subsequent transformations. Synthesis of the free thiazolidinethione auxiliary **63** began with the iodine promoted sodium borohydride reduction of phenylalanine to form the amino alcohol **62** (Scheme 1.2.1).[23] Cyclization to the thiazolidinethione **63** readily occurred upon treatment of the amino alcohol **62** with carbon disulfide at elevated temperature.[49] Preliminary studies focused on preparing the methoxy glycolate **64** due to the expected stability of the glycolyl ether. Thus, acylation of auxiliary **63** was readily

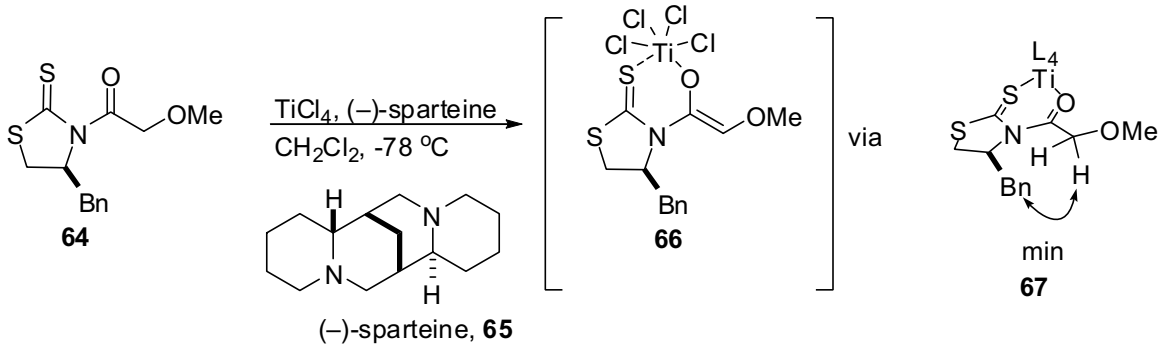


Scheme 1.2.1. Synthesis of α-methoxy thioiimide **64**

accomplished using *N, N'*-dicyclohexylcarbodiimide (DCC) in the presence of catalytic 4-dimethylaminopyridine (DMAP) to couple methoxyacetic acid directly to the auxiliary in good yield.

The highly effective "soft enolization" protocol developed previously in the laboratory employing titanium (IV) chloride and (–)-sparteine[26] was used to generate the intermediate titanium enolate **66** (Scheme 1.2.2). Specifically, to a solution of the imide **64** in dichloromethane (CH_2Cl_2) held at –78 ºC was added 1.1 equivalent of titanium (IV) chloride followed by addition of 1.1 equivalent of (–)-sparteine (**65**). A deep purple color resulted, suggestive of enolate formation. Based on previous literature reports,[31,32] it is highly probable that exclusive formation of the *Z*-enolate resulted due to minimized steric interactions of the substrate prior to deprotonation (see **67**, Scheme 1.2.2).

Initial approaches to selectively generate the *anti* products from the titanium enolates was based on the notion that activation of the aldehyde by an additional equivalent of Lewis

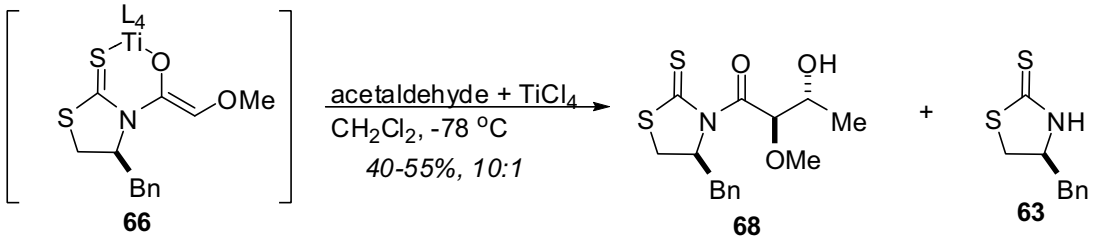


Scheme 1.2.2. Formation of the titanium enolates of *N*-methoxyacetothiazolidinethione

acid may reverse the preference for *syn* selective additions. This approach follows the observations of Heathcock[41] and Silks[36] discussed previously. In practice, a separate flask containing acetaldehyde (distilled from $CaSO_4$ immediately prior to use) dissolved in CH_2Cl_2 was cooled to –78 ºC. An additional 2 equivalents of $TiCl_4$ was added to the aldehyde

solution and immediately transferred via cannula to the enolate. After stirring the solution for 20 minutes, the reaction was quenched upon addition of saturated ammonium chloride.

Analysis of the crude reaction mixture by ^{1}H NMR indicated an *anti* selective reaction had occurred to give the adduct **68** with selectivities up to 10:1 (anti: all other isomers) (Scheme 1.2.3). While the configuration relative to the auxiliary could not be ascertained at



Scheme 1.2.3. Anti-selective reaction of *N*-glycolylthiazolidinethiones

this stage of the project, the relative configuration of the α- and β-stereocenters were readily determined using the well known relationship between vicinal bond angle and coupling constants of the α- and β-protons (Karplus relationship). As illustrated in Figure 1.2.1, hydrogen bonding of the β-hydroxyl group to the carbonyl induces a cyclic six-membered chair conformation, and thus, facile determination of the di-alkoxy configuration based on the dihedral angle between the indicated protons.[50] Typical coupling constants ranged from 6-9 Hz for the *anti* isomers and 2-4 Hz for the *syn* diastereomers, consistent with literature precedent.[51] Yields of these initial reactions typically ranged from 40-55%. The free auxiliary **63** (10-20%) was isolated as a major byproduct of the reaction, presumably formed during the reaction via deacylation of the starting material. Efforts to minimize this deacylation

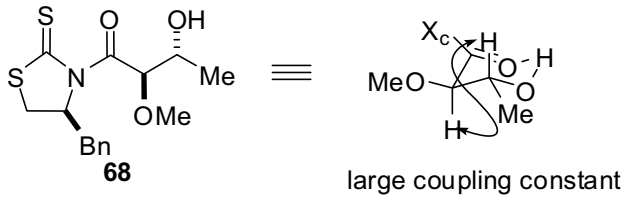
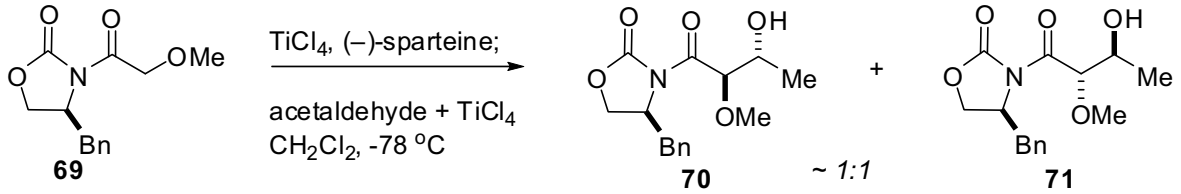


Figure 1.2.1. ^{1}H NMR analysis of anti adducts

through alteration of the reaction conditions were unsuccessful.

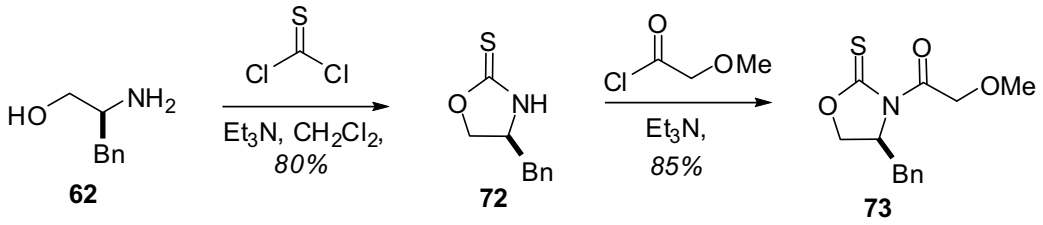
Oxazolidinone glycolylimide **69** was subsequently prepared according to literature procedures[52] and tested using the conditions optimized for the thiazolidinethione glycolate (Scheme 1.2.4). As expected from the enhanced stability of the *N*-acyl bond, no deacylation was observed during the course of the reaction. However, the diastereomeric ratio of *anti* products **70** and **71** was approximately 1:1 (determined by NMR analysis), in sharp contrast to the results obtained using the thiazolidinethione auxiliary.



Scheme 1.2.4. Attempted anti selective reactions of oxazolidinone substrates

1.2.3 Chiral auxiliary variants: Oxazolidinethione mediated additions

Based on the results obtained in the initial stages of the project, it was anticipated that the oxazolidinethione auxiliary **72** (Scheme 1.2.5) would provide the ideal characteristics for the aldol addition. It was reasoned that the enhanced stability of an *N*-acyloxazolidinethione (vs. thiazolidinethione) would minimize deacylation during the reaction while maintaining the thiocarbonyl moiety believed to be crucial for high selectivities.



Scheme 1.2.5. Synthesis of *N*-methoxyacetooxazolidinethione

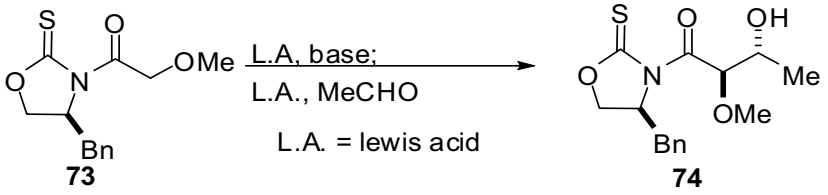
Formation of the oxazolidinethione auxiliary occurred upon treatment of the amino alcohol **62** with thiophosgene to provide the thiocarbamate **72** in good yield (Scheme

1.2.5).[26] In contrast to the thiazolidinethione and oxazolidinone auxiliaries, this auxiliary proved difficult to purify via recrystallization. However, after passing the crude material through a small pad of silica gel, the material could be acylated and purified as the thioimide. As with the thiazolidinethione auxiliary, acylation to form the methoxy glycolylimide **73** could be conducted using DCC and catalytic DMAP. However, for larger scale reactions use of the corresponding acyl chloride (available commercially or one step from methoxyacetic acid) was preferable. High, reproducible, yields could be secured using this procedure on scales approaching 200 mmole.

Upon applying the conditions used previously, high *anti* selectivities (~10:1) reminiscent of the thiazolidinethione mediated additions were observed. Additionally, in contrast to the thiazolidinethione auxiliaries, virtually no deacylation was detected during the course of the reaction (<3% by NMR analysis).

1.2.4 Reaction Optimization

Having secured a suitable chiral auxiliary for the titanium-mediated *anti* glycolate aldol addition, efforts shifted toward optimizing the reaction conditions to favor high selectivities and synthetically useful reaction yields. A standardized reaction between the methoxyimide **73** and acetaldehyde generating the *anti* adduct **74** was chosen for the ensuing studies (Scheme 1.2.6).



73 **74**

Scheme 1.2.6. Aldol addition for optimization studies

Among the optimization studies undertaken were a series of experiments designed to determine optimal enolization conditions. A variety of alternative bases were explored,

including diisopropylethylamine (DIEA), triethylamine, and tetramethylethylenediamine (TMEDA). In all cases yields for these reactions were significantly lower than with (–)-sparteine, in accord with previous observations.[26] Modifications to the stoichiometry of the $TiCl_4$ and base did not appear to have any influence on the reaction and a single equivalent (slight excess to ensure adequate quantities on small scale) of each was sufficient. Additionally, variations to the enolization time were explored, revealing an adequate time to ensure complete enolization prior to aldehyde addition.

Based on the known utility of the titanium enolates in oxazolidinone-mediated aldol additions, no examinations of alternative metalloenolates were performed. However, variations to both the nature and stoichiometry of the second Lewis acid component were examined. Among the Lewis acids tested were tin (IV) chloride, diethyl aluminum chloride, titanium dichlorodiisopropoxide, trimethylsilyl trifluoromethanesulfonate (TMSOTf), and boron trifluoride-diethyl etherate ($BF_3{\cdot}OEt_2$). All alternate Lewis acids provided the anti adducts with inferior selectivities when compared to $TiCl_4$.

One factor that was crucial to the reaction, however, was the stoichiometry of the additional titanium tetrachloride component, which was found to have a direct effect on the stereoselectivity of the reaction. For example, use of only 1.5 equivalents of the $TiCl_4$ relative to acetaldehyde delivered the *anti* adduct **74** in a 5:1 diastereomeric ratio. Upon increasing the amount of Lewis acid to 2.2 equivalents, the selectivity was improved to ~10:1 (Table 1.2.1). Increasing the amount of $TiCl_4$ further did not have any effect on the diastereoselectivity. It was later discovered that the nature of the aldehyde also influenced this effect, requiring an additional equivalent of Lewis acid when using α,β-

Aldehyde (R´)	$TiCl_4$:aldehyde (equiv)	Selectivity *anti*:all others
H_3C–CHO	2.2 : 1.0 1.5 : 1.0	91:9 83:17
	3.1 : 1.0 2.3 : 1.0	95:5 84:16

Table 1.2.1. Variation of additional $TiCl_4$ component.

unsaturated aldehydes. For example, increasing the equivalents of additional $TiCl_4$ from 2.3 to 3.1 when using acrolein improved the diastereoselection from 84:16 to 95:5.

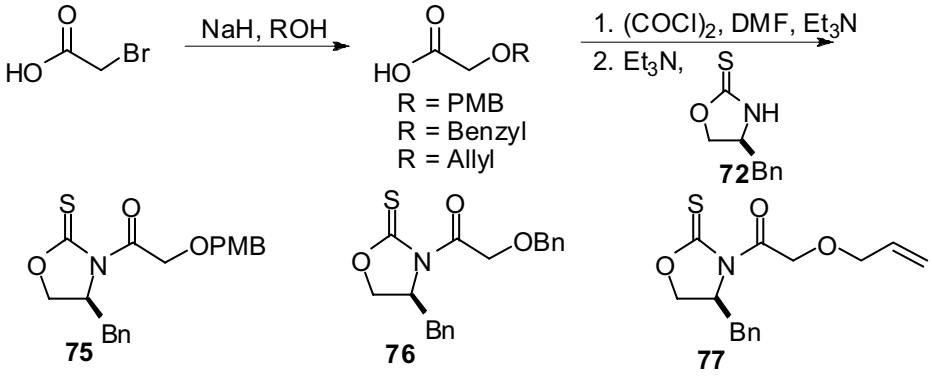
1.2.5 Development of a one-pot procedure

During the course of the investigation, it became apparent that the operational simplicity of the reaction could be significantly improved by developing a one-pot procedure. Throughout the optimization studies, a solution of the aldehyde (in CH_2Cl_2) was premixed with the additional $TiCl_4$ in a separate flask held at -78 ºC and immediately transferred via cannula to the preformed enolate. An alternative procedure was subsequently developed in which the "precomplexation" of the aldehyde would occur in situ provided the order of addition of reagents was carefully controlled. In practice, after formation of the enolate (1.1 equiv. $TiCl_4$ then 1.1 equiv. (–)-sparteine) for 40 minutes the additional $TiCl_4$ (2.1-3.0 equiv.) was added directly to the enolate. After brief stirring (<1 min) the neat aldehyde was added directly to the reaction vessel. The resulting aldol addition occurred very rapidly and the reactions were quenched within 20 min using ½ saturated ammonium chloride. Yields and selectivity were identical to those obtained using the previous method of premixing the additional Lewis acid and aldehyde in a separate flask. This modification to the original procedure has become the standard practice in the laboratory when performing *anti* glycolate aldol additions due to the simplicity of the experimental conditions.

1.2.6 Examination of reaction scope: substrate versatility

After securing optimal reaction conditions, the scope of the reaction was explored using various substrates and aldehydes. Substrate versatility was highly desirable as it would significantly extend the utility of the aldol addition. Glycolylimides that possessed a removable protecting group were particularly sought to facilitate liberation of the α-hydroxy group following the aldol addition and enable differentiation of the 1,2-diol. Due to the Lewis

acidic reaction conditions, however, protecting group options for the α-hydroxy were limited. Formation of the requisite carboxylic acids were easily accomplished through an S_N2 reaction of the appropriate alkoxide and bromoacetic acid (Scheme 1.2.7). Coupling to the free auxiliary **72** was accomplished as before via the acyl chloride to give the glycolylimides **75**, **76**, and **77** .



Scheme 1.2.7. Substrate synthesis

While the PMB glycolate **75** suffered from rapid decomposition upon addition of the first equivalent of $TiCl_4$, the analogous benzyl glycolate **76** proved stable to the reaction conditions. However, in contrast to the methoxy glycolylimide **73**, lower selectivity and yield was observed. Nevertheless, the aldol adduct favoring one *anti* isomer (70:30) was obtained in 55% isolated yield (Table 1.2.2). Efforts to improve upon this ratio by altering the reaction conditions were unsuccessful.

In an effort to improve upon the diastereoselectivity of the reaction while offering a labile protecting group that was stable to the reaction conditions, the allyl protected glycolylimide **77** was examined. Gratifyingly, the

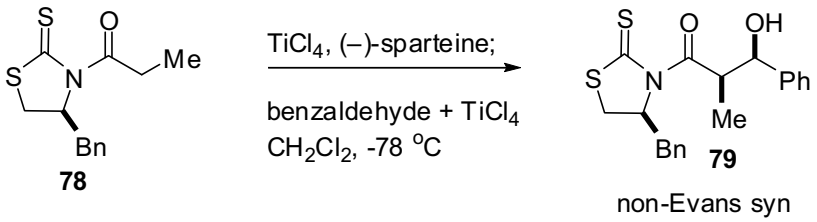
Substrate	Selectivity	Yield
methoxy glycolate (**73**)	86:14	62%
benzyloxy glycolate (**76**)	70:30	55%
allyloxy glycolate (**77**)	97:3	84%

Table 1.2.2. Variation of α-alkoxy functionality: aldol addition to acetaldehyde

yields and selectivity using this substrate was far superior to that previously observed with either the methyl or benzyl protected substrate. Excellent diastereoselectivity (97:3) and an 84% isolated yield was obtained using acetaldehyde as the enolate acceptor (Table 1.2.2).

1.2.6.1. Attempted *anti* aldol using *N*-propionylthiazolidinethiones

Based on the positive results obtained using the glycolyl substrates, an *anti* selective propionate aldol addition was attempted using the thiazolidinethione substrate **78**[48] (Scheme 1.2.7). However, only the non-Evans *syn* diastereomer **79** was produced under the optimized reaction conditions. This observation suggests the necessity of the α-alkoxy group for obtaining *anti* selectivity under these conditions.



Scheme 1.2.7. Attempted *anti* propionate aldol addition

1.2.7 Examination of reaction scope: Aldehyde versatility

A variety of aliphatic, aromatic, and α,β-unsaturated aldehydes were examined in an effort to explore the steric and electronic effects of the acceptor component (Table 1.2.3). In accord with the addition to acetaldehyde discussed previously, the *O*-allyl thioimide **77** delivered the *anti* adducts with the highest levels of diastereoselection and better yields that with either the *O*-methyl or benzyl substrates. With all substrates tested, reaction of aliphatic, unbranched aldehydes led to the *anti* adducts in higher yields (entries 1-2, 7, 9). Bulkier aldehydes, such as isobutyraldehyde gave lower selectivity (entry 3). With the exception of acrolein, α,β-unsaturated and aromatic aldehydes also gave lower selectivities, though still favoring one major *anti* diastereomer (entries 4-6, 8, 10).

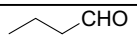
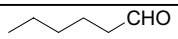
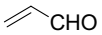
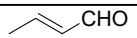
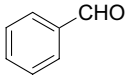
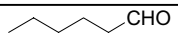
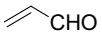
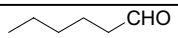
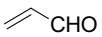
Entry	Substrate	Aldehyde	Anti 1:Anti 2: syn	Yield (% isolated)
1	**77**		97:3:0	74
2	**77**		94:6:0	74
3	**77**		87:13:0	61
4	**77**		95:5:0	58
5	**77**		76:24:0	56
6	**73**		65:24:11	56
7	**73**		88:12:0	64
8	**76**		74:26:0	48
9	**76**		84:11:5	63
10	**76**		88:12:0	59

Table 1.2.3. Examination of various aldehyde components (yields of major diast.)

1.2.8 Characterization of aldol adducts

One complication frequently encountered with the *anti* glycolate aldol additions, especially concerning the adducts of the *O*-allyl glycolylimide **77**, was the inability to separate the major *anti* isomer from small amounts of unreacted starting material using flash chromatography. Thus, for the purposes of characterizing the aldol adducts, most of the aldol products were reduced to the corresponding 1,3-diols using $LiBH_4$ and methanol.

1.2.9 Determination of the aldol adduct configuration

The determination of the relative configuration of the two new stereogenic centers created during the aldol addition was readily made through NMR analysis, as described

earlier. However, the configuration relative to the auxiliary was unknown throughout most of the project. A single crystal X-ray analysis of the *anti* product **74** resulting from the addition of methyl glycolate **73** and acetaldehyde (see Scheme 1.2.6) was obtained to ascertain the stereochemical relationship. As illustrated in Figure 1.2.3, the α-alkoxy group is oriented *syn* to the chiral auxiliary side chain (as drawn), and *anti* to the neighboring hydroxyl.

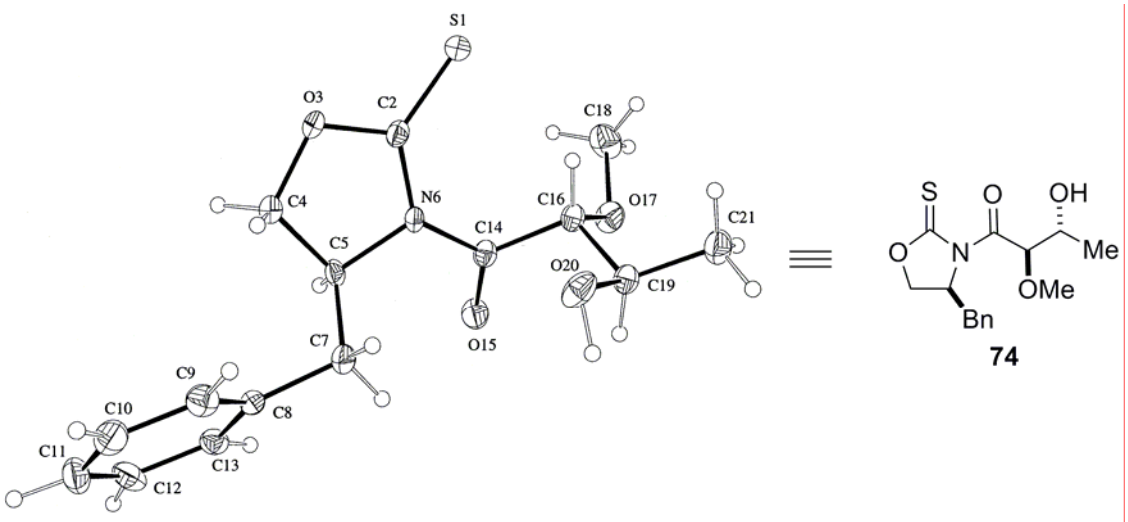
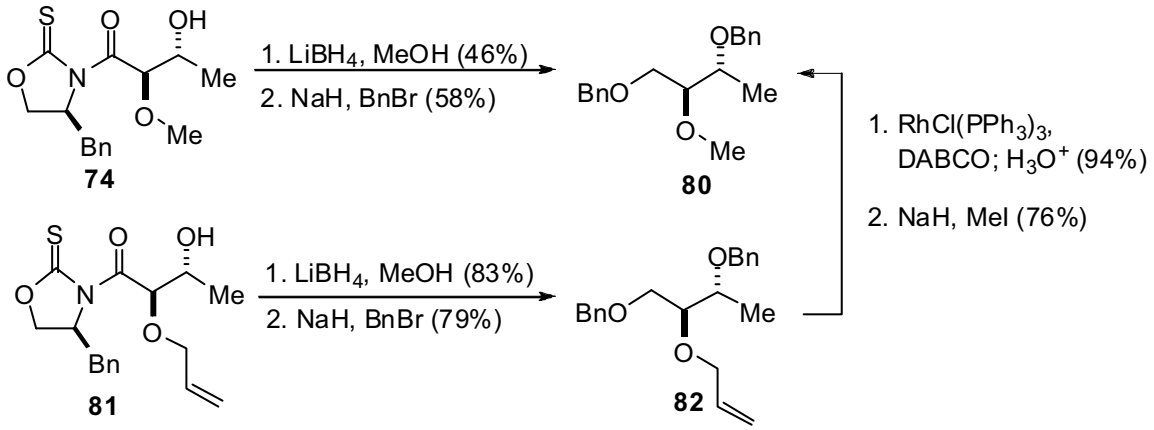


Figure 1.2.3. X-ray crystal structure of anti adduct **74**

Experiments were subsequently undertaken to confirm the configuration of the most successful *anti* additions; those of the allyl glycolate **77**. As such, aldol adduct **74**, for which the crystal structure was obtained, was converted to the dibenzyl ether **80** via reductive removal of the auxiliary and protection of the resultant 1,3-diol (Scheme 1.2.8). The corresponding adduct **81** obtained from the addition of the allyl glycolate **77** to acetaldehyde (see Table 1.2.2) was similarly manipulated to give allyl ether **82**. Removal of the allyl group[53] and methylation of the alcohol gave compound **80**. This compound was identical in all respects (^{1}H NMR, ^{13}C NMR, $[\alpha]^D$) to the material obtained from the adduct **74**, thus providing strong support for a general stereochemical assignment for these *anti* aldol adducts.



Scheme 1.2.8. Correlation of configuration of anti adducts

1.2.10 Proposed transition states

In light of the observed configuration of the aldol adducts, a transition state argument could be proposed to explain the observed diastereoselectivity. Several observations made during the course of the project were taken into account when developing the proposed transition state arguments. First, the necessity of additional Lewis acid prior to aldehyde addition suggested at least two metals were involved. Second, the lack of *anti* selectivity with the propionate substrates suggested metal coordination to the α-oxygen. Third, the enhanced selectivity using substrates possessing the thiocarbonyl moiety suggested strong coordination of one titanium to the sulfur atom.

One possible transition state is modeled after open transition states proposed by Noyori,[10] Heathcock,[41] and others. As illustrated in Figure 1.2.4, one equivalent of titanium may simultaneous coordinate to the enolate oxygen and the thiocarbonyl, while the second equivalent coordinates to the aldehyde and the α-alkoxy to give the ordered transition state structure **83**. Enolate facial selectivity would be controlled by the steric influence of the chiral auxiliary and the aldehyde facial bias could result from a minimization of steric interactions

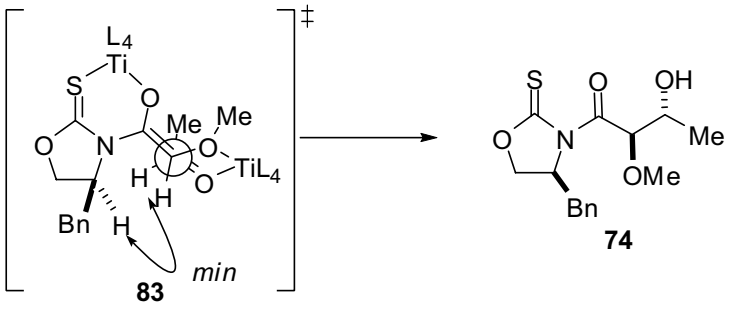


Figure 1.2.4. Proposed open transition state model

with the chiral auxiliary. Such an arrangement of reacting partners would lead to the observed *anti* aldol product **74**.

Alternatively, a boat-like transition state can be reasonably postulated to explain the *anti* selectivity. In this scenario, activation of the aldehyde in an intramolecular fashion using the titanium bound to the enolate oxygen forms a pericyclic structure **84** reminiscent of the widely proposed Zimmerman-Traxler transition state (Figure 1.2.5).[5,6] Additional coordination of the titanium enolate to the thiocarbonyl provides a rationale for enolate facial discrimination. Such interactions between the enolate metal and the thiocarbonyl moiety have been used to explain the diastereoselectivity in propionate aldol additions.[26] This three coordinate binding to titanium may also provide a rationale for the large excess of titanium tetrachloride that is needed. Chloride abstraction by the second equivalent may enable this highly ordered conformation, as proposed in oxazolidinethione propionate additions.[26] A titanium bridge between the glycolyl ether and enolate oxygen atoms with the third

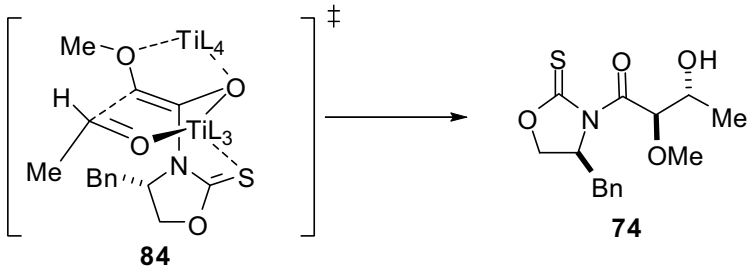


Figure 1.2.5. Proposed boat conformation transition state model

equivalent of titanium tetrachloride may also be involved.

1.3 SUMMARY

In summary, a highly *anti* diastereoselective aldol addition has been developed utilizing *N*-glycolylimides of the oxazolidinethione chiral auxiliary derived from phenylalanine. Use of the standard enolization protocol employing titanium tetrachloride and (–)-sparteine followed by the addition of an additional titanium tetrachloride component immediately prior to the aldehyde leads to the formation of predominantly one *anti* diastereomer in high selectivity and good reaction yields. Best results were obtained using *O*-allyl, *N*-glycolyloxazolidinethione and unbranched, aliphatic aldehydes, though the substrate versatility is quite broad. The reactions are proposed to proceed via either an open or boat-like transition state.

CHAPTER 2: STUDIES TOWARD THE TOTAL SYNTHESIS OF BREVETOXIN A: SYNTHESIS OF THE B AND E RING UNITS USING *ANTI* ALDOL METHODOLOGY

2.1 BACKGROUND

2.1.1 Polycyclic ethers: An introduction

A unique class of molecules commonly known as the ladder toxins represents some of the most challenging synthetic targets ever isolated from natural sources. The structural elucidation of the first of these intriguing molecules, brevetoxin B (**85**, Figure 2.1.1), in 1981 revealed an unprecedented molecular architecture consisting of repeating *trans*-fused cyclic ethers of varying ring sizes.[54] Since that time, many naturally occurring compounds sharing a similar structural array have been identified.[55,56] The number and size of the contiguously fused rings has been shown to vary greatly. For example, hemibrevetoxin B (**88**) contains only four fused ring systems, while gymnocin A (**89**) contains 14. The largest of the known polyethers, maitotoxin, contains 32 cyclic ethers and 98 stereogenic centers.[57]

The biological activity of this class of molecules can be generalized as extremely potent neurotoxins. This toxicology can impact the human population through the ingestion of contaminated seafood, often leading to serious neurological, gastrointestinal, and cardiovascular disorders.[55] Some polyethers, however, have been shown to be rather non-toxic and could have potential therapeutic benefits. For example, gambieric acid displays potent antifungal properties,[58] protoceratin II is currently being investigated as an anticancer agent,[59] and the recently discovered brevenal acts to inhibit the toxicity of the brevetoxins.[60,61]

Due to their unique and challenging molecular architecture, the polycyclic ethers have received considerable attention in the synthetic community.[62] An impressive number of research groups have published partial and/or total syntheses of various members of this family of natural products. With the exception of Nicolaou's groundbreaking syntheses of

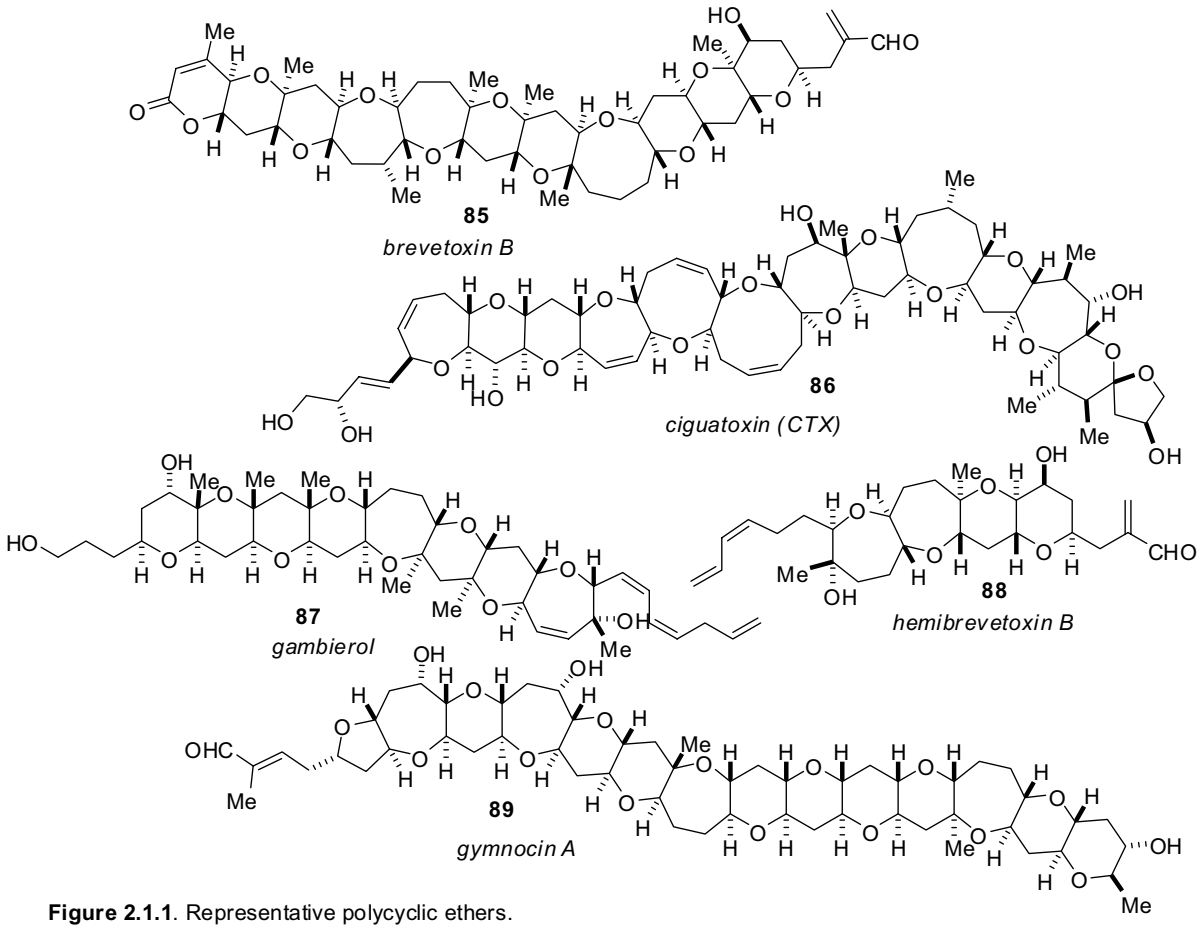


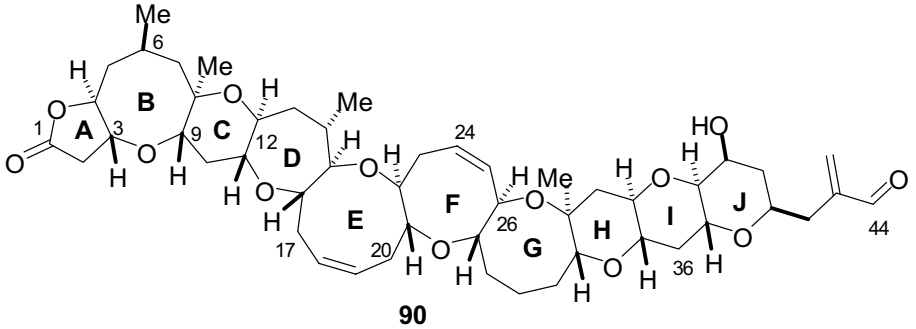
Figure 2.1.1. Representative polycyclic ethers.

brevetoxin A[63] and B[64] in the mid to late 90's, most of this progress has come within the last five years. Since then, ciguatoxin CTX3C (**86**),[65] brevetoxin B (**85**),[66] gymnocin (**89**),[67] hemibrevetoxin B (**88**),[68] and gambierol (**87**)[69-71] have all yielded to total synthesis efforts. *En route* to the total synthesis of these molecules, a number of strategies for the efficient construction of the repeating *trans-syn-trans*-fused cyclic ethers have been developed.[72,73] Several of these strategies will be discussed in Chapter 3.

2.1.2 Brevetoxin A: Structure elucidation

Arguably, one of the more daunting members of this class of molecules is the neurotoxic agent, brevetoxin A (**90**; Figure 2.1.2). Brevetoxin A (previously termed GB-1; also known as PbTx-1) was originally isolated in 1975 by Alam and coworkers from the marine dinoflagellate *Karenia breve* (formerly known as *Gymnodinium breve*).[74] Since that time, several related brevetoxins (including brevetoxin B) have been isolated from the same organism.[75] Structure elucidation occupied several research groups following the isolation and was initially incorrectly reported as a 5/6/6/7/11/8/8/6/6/6 ring system.[76] The correct structure of brevetoxin A, which contains the 5/8/6/7/9/8/8/6/6/6 ring system, was finally secured by Shimizu in 1986 using X-ray crystallography.[77] Pawlak and coworkers reached the same conclusion the following year using extensive NMR analysis.[78]

These combined efforts revealed a polyether backbone consisting of ten continuous *trans*-fused cyclic ethers and 22 stereogenic centers (Figure 2.1.2). Unique to the polyether subclass, every ring size from 5 to 9 membered, two of which are unsaturated, is represented in this natural product. Other structural features include four exocyclic methyl



90

Figure 2.1.2. Brevetoxin A

groups, two of which are present at ring junctions, a γ-lactone, and an exomethylene enal side chain. In the center of brevetoxin A lies a 9/8/8 fused ring system which imparts considerable conformational flexibility. The NMR signals for the E, F, and G rings have been demonstrated to be significantly broadened, indicating that the conformational changes take

place on the NMR time scale.[78] In fact, due to the flexibility imparted by the medium ring ethers, 48 conformations have been identified for brevetoxin A that are within 6 kcal/mol of the global minimum.[79]

2.1.3 Brevetoxin A: Biological activity

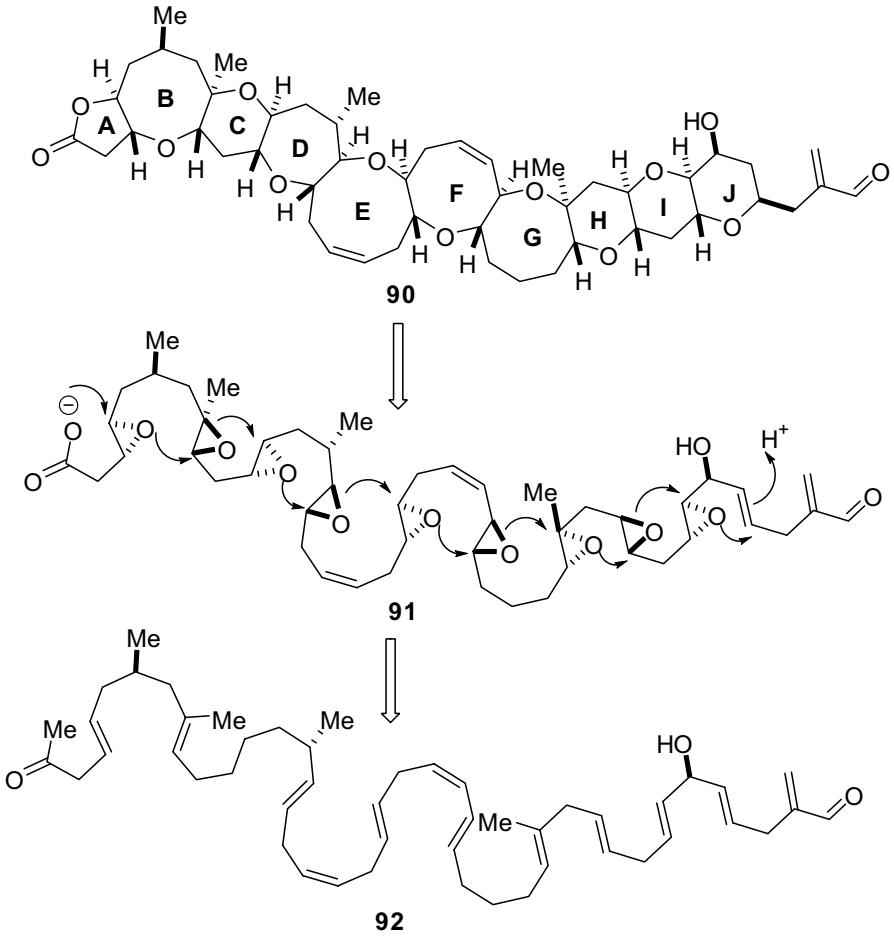
The dinoflagellate now known as *Karenia breve* (originally termed *Gymnodinium breve* by Davis[80] and later *Ptychodiscus brevis*) from which the brevetoxins were isolated are responsible for massive fish kills during the notorious red tide blooms occurring in the Gulf of Mexico. These blooms and their deleterious effects on marine populations have been documented since the mid-1800's. Human toxicity has also been reported due to the inhalation of aerosolized particles and from the ingestion of contaminated shellfish, though no fatalities have been reported.[81,82] Of the many brevetoxins that have been isolated from this organism, brevetoxin A has been shown to be the most potent ichthyotoxin displaying an LC_{50} of 3-4 ng/mL.[82] All natural and non-natural derivatives have demonstrated reduced toxicity.[75]

The toxicology associated with the brevetoxins is complex and involves multiple receptors in the neuronal, pulmonary, and enzymatic regulatory systems.[82] The extremely potent neurological effects have been shown to be the result of binding to site 5 of the α-subunit of voltage-sensitive sodium channels (VSSC).[83] Binding to these membrane-associated potential-gated ion channels results in an influx of sodium ions.[83,84] Based on the observed competitive binding of brevetoxin B, ciguatoxin, and brevetoxin A to the same binding site suggests these molecules share a similar pharmacophore.[79] A series of structure-activity relationship experiments using various derivatives of the brevetoxins have been performed to identify the structural requirements for efficient binding.[85] The results from these studies suggest a cigar-shaped molecule of ~30 Å is necessary for binding to site 5 of the receptor. A comparison of brevetoxins A and B suggest that the G-J (H-K in

brevetoxin B) rigid ring system and the A ring lactone moiety play key roles in the binding site. The B-F ring system, therefore, serves as a spacer region that does not directly bind to the VSSC.[79] Indeed, it has been found experimentally that the lactone moiety is crucial for effective binding,[85] indicative of possible hydrogen bond stabilization through the carbonyl group. The side chain, in contrast, does not appear to affect binding to the receptor, though the hydrophobic nature of the enal moiety may be important.[82]

2.1.4 Proposed biosynthesis of Brevetoxin A

A truly remarkable biosynthetic pathway has been proposed for the formation of the ladder toxins.[76] As illustrated for brevetoxin A (**90**), retrosynthetic disconnection of each



Scheme 2.1.1. Proposed biosynthesis of Brevetoxin A

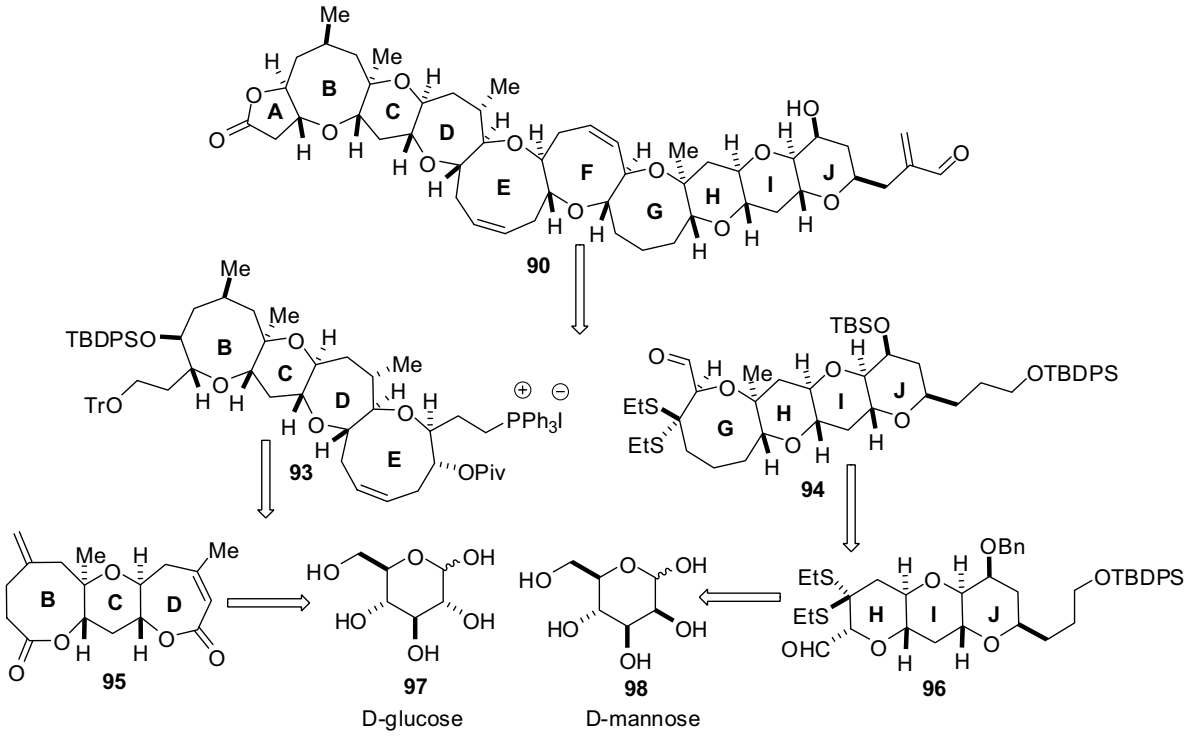
cyclic ether leads to the enantiopure polyepoxide **91** (Scheme 2.1.1). A cascading *endo*-selective epoxide opening event would then form the completed polyether array in a single operation. The requisite polyepoxide can be easily envisioned to come from the very simplified polyene **92** from a series of enantioselective epoxidations. The application of this incredibly rapid synthetic approach in the laboratory, however, would involve synthetic methods that are beyond the reach of synthetic chemists at the present time. Nevertheless, several research groups have reported reaction sequences generating up to four *trans*-fused cyclic ethers from corresponding epoxides.[86,87]

2.1.5 Nicolaou's total synthesis of Brevetoxin A

The combination of potent bioactivity and unique structure of the polyethers has attracted significant attention from the synthetic community. Based on the complexity and size of these molecules, the attempt at a total synthesis of any of these molecules is truly a daunting task. K.C. Nicolaou and coworkers demonstrated the power of modern organic chemistry in their landmark synthesis of both brevetoxin B[64] and, shortly thereafter, brevetoxin A[63,88-91] in the mid-1990's. As a pioneer in this area of polyether synthesis, the Nicolaou group developed several new methods for the synthesis of medium ring ethers and developed an efficient convergent coupling strategy to join two advanced fragments ultimately leading to the completed natural products.

2.1.5.1. Nicolaou's retrosynthetic analysis of brevetoxin A

A cursory examination of brevetoxin A reveals an ideal opportunity for a convergent approach that would divide the molecule into two fragments of roughly equal complexity. Such was the successful approach taken by Nicolaou, whose retrosynthetic division at the F ring gave the BCDE (**93**) and GHIJ (**94**) fragments (Scheme 2.1.2).[89] The coupling of these two units would mimic their successful fragment coupling employed in the synthesis of



Scheme 2.1.2. Nicolaou's retrosynthetic analysis of brevetoxin A

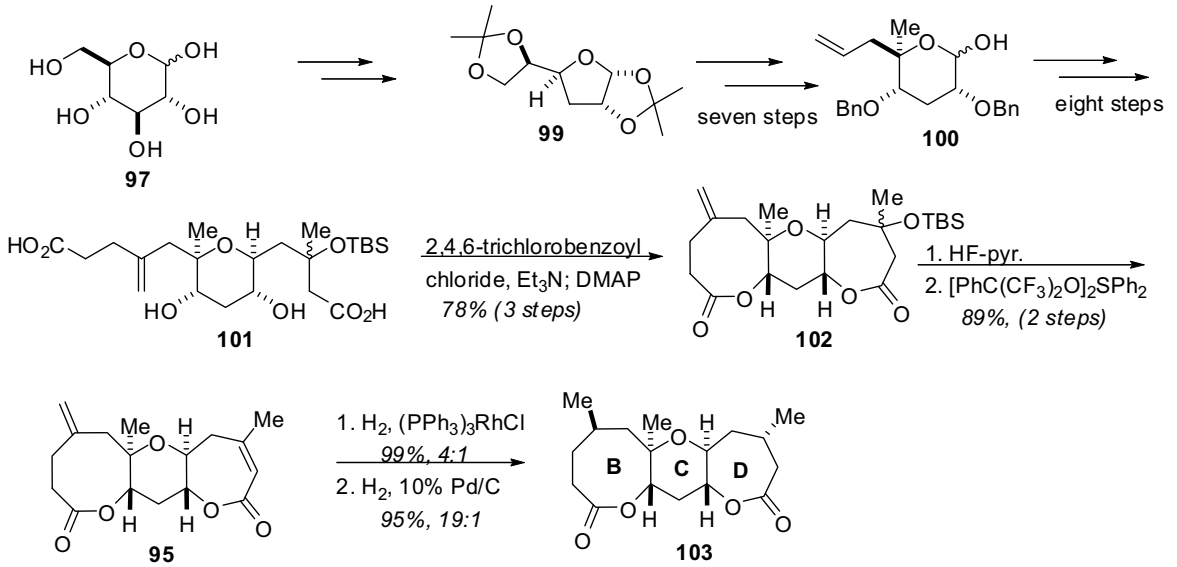
brevetoxin B via Wittig coupling and subsequent hydroxydithioketal cyclization.[64] These two fragments, in turn, were envisioned to ultimately arise from D-glucose (**97**) and D-mannose (**98**), respectively, using a linear synthetic approach. It should be noted that Nicolaou's original approach involved disconnection at the E ring and targeted the BCD and FGHIJK ring systems. However, a model system consisting of the CD and F rings demonstrated the inability to form the E ring oxonene using the hydroxydithioketal cyclization conditions.[88]

The stereoselective synthesis of medium ring ethers represents a considerable challenge in organic synthesis based on unfavorable entropic factors.[92] Novel methodology developed by Nicolaou for the efficient construction of medium ring ethers became key components in their construction of both the BCDE (**93**) and GHIJ (**94**) fragments. The BCDE fragment **93** was envisioned to come from the bis-lactone **95** using Nicolaou's improved procedures for palladium-mediated derivatization of medium ring lactones via intermediate cyclic ketene acetal phosphates.[93] For the GHIJ fragment **94**, a

hydroxydithioketal cyclization reaction[94] would be utilized to form the eight membered G ring unit from the tricycle **96**.

2.1.5.2. Nicolaou's synthesis of the BCDE fragment

The synthesis of the BCDE fragment commenced with the functionalization of the known tetrahydrofuran **99** (available from D-glucose (**97**)) to ultimately generate the tetrahydropyran fragment (C ring) **100** in seven synthetic steps (Scheme 2.1.3).[88,90] Further manipulation of the side chains was then required to install the requisite carbon framework to yield the dicarboxylic acid **101**. The medium ring lactones (B and D rings) were subsequently generated upon double lactonization employing Yamaguchi's conditions[95] to give the bis-lactone **102**. Stereoselective formation of the two exocyclic methyl groups was



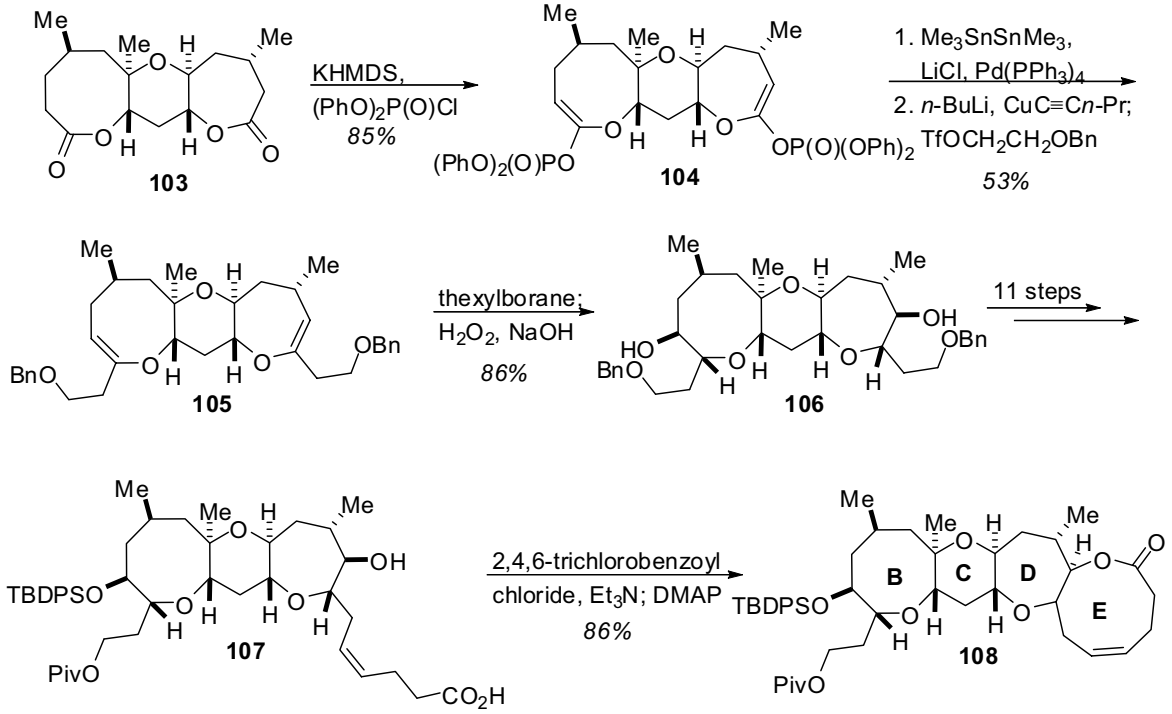
Scheme 2.1.3. Nicolaou's synthesis of the BCD bis-lactone

accomplished by first dehydrating the β-siloxy lactone **102** to the cyclic enone **95**, followed by a stepwise stereoselective double hydrogenation of the two olefins to give intermediate **103**.

Elaboration of the bis-lactone to the BCD cyclic ether unit utilized a novel palladium-catalyzed transformation of the corresponding cyclic ketene acetal phosphates.[93] Treatment

of lactone **103** with KHMDS and $(PhO)_2P(O)Cl$ gave the desired bis-cyclic ketene acetal phosphate **104** (Scheme 2.1.4). This intermediate was subsequently converted to the bis-vinylstannane under palladium catalysis. Further manipulation to the bis-enol ether **105** was accomplished via the mixed cuprate. Finally, stereoselective hydroboration using thexylborane completed the conversion to the fully saturated tricyclic ether **106**.

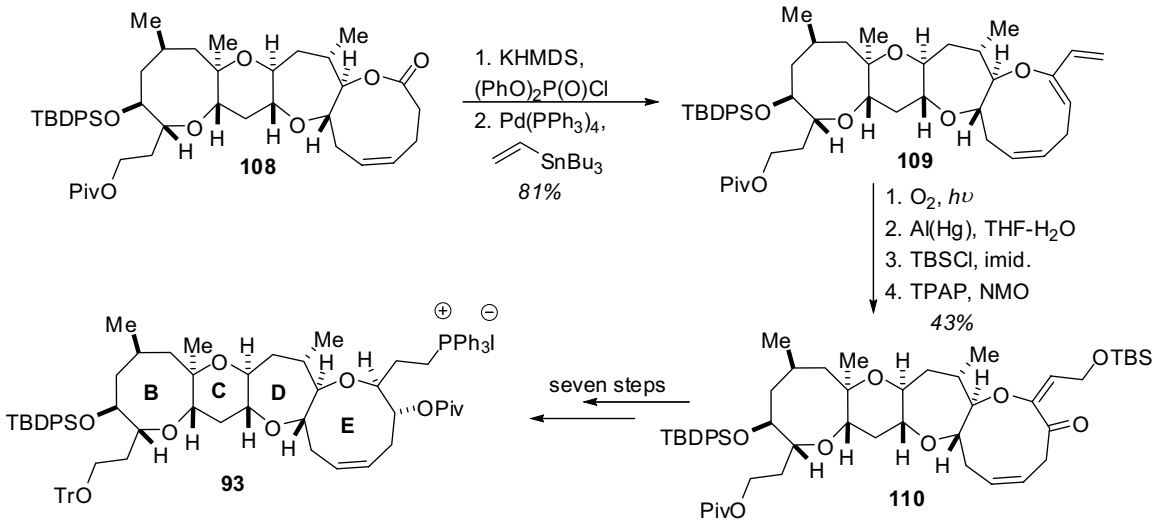
An eleven step sequence was then initiated to differentiate the two halves of the molecule, alter the protecting groups, and install the γ,δ-unsaturated carboxylic acid to generate intermediate **107** (Scheme 2.1.4). Cyclization under Yamaguchi conditions then delivered the nine-membered lactone **108**.



Scheme 2.1.4. Elaboration to form the E ring lactone (Nicolaou)

Similar to the B and D ring lactone manipulations, the E ring intermediate **108** was converted into the vinyl enol ether **109** via a cyclic ketene acetal phosphate (Scheme 2.1.5).[91] A subsequent [4+2] cycloaddition using singlet oxygen allowed for oxidation of the necessary carbon atoms to yield the ketone **110**, after further manipulation. A series of

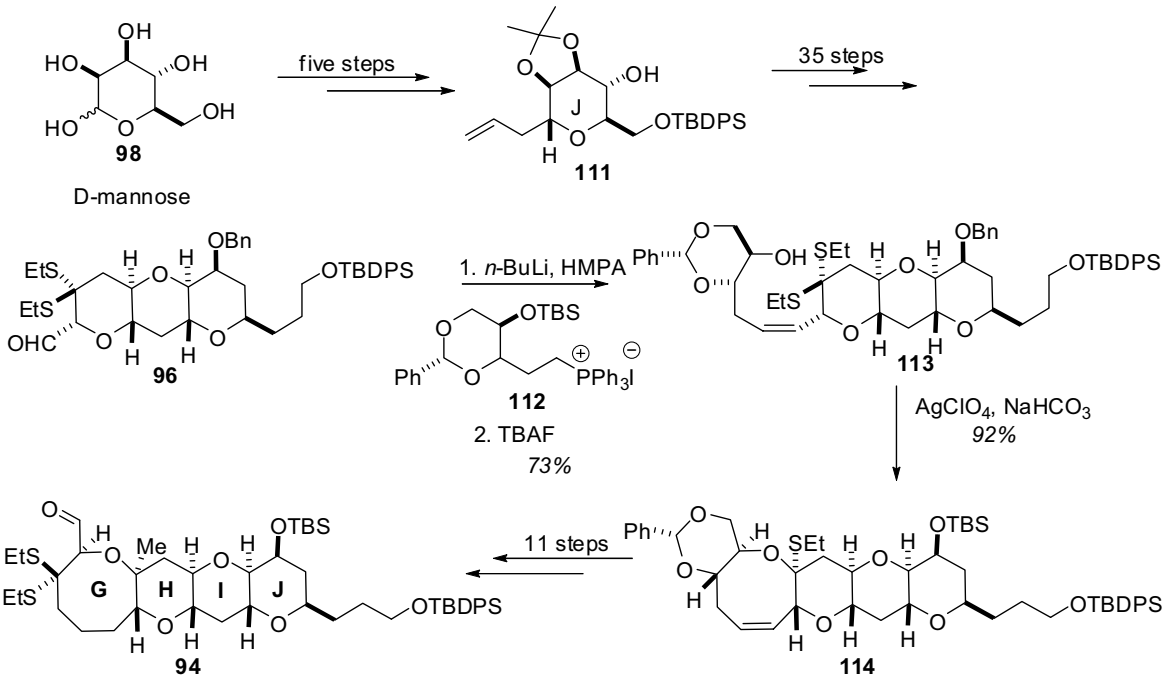
seven steps were then required to complete the BCDE phosphorane **93** in preparation for coupling to the GHIJ fragment.



Scheme 2.1.5. Nicolaou's completion of the BCDE fragment

2.1.5.3. Nicolaou's synthesis of the GHIJ fragment

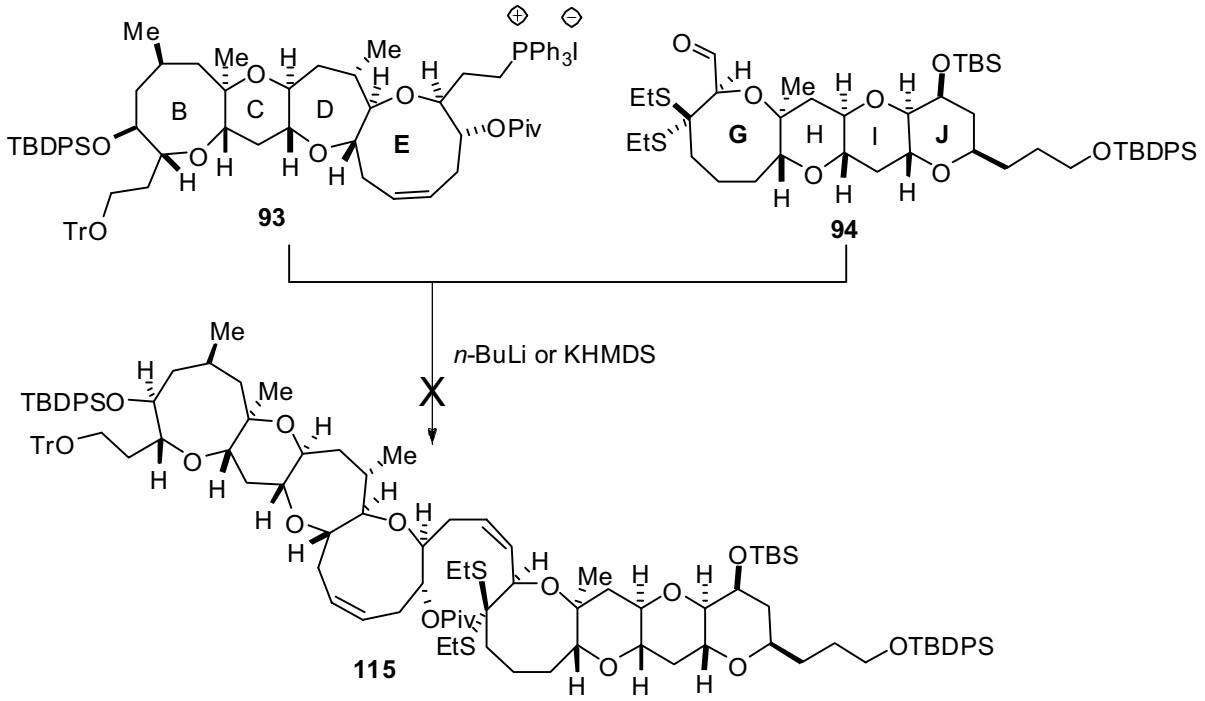
The synthesis of the GHIJ fragment centered on initial formation of the 6/6/6 tricycle, followed by formation of the G ring using their established hydroxydithioketal cyclization protocol.[90] Thus, D-mannose (**98**) was converted into the J ring fragment **111** in five synthetic steps (Scheme 2.1.6). Further manipulation of this material in a linear fashion relying on hydroxyepoxide cyclizations to generate the remaining tetrahydropyran units yielded the tricycle **96** in 35 additional steps. Coupling of the tricyclic aldehyde **96** to the phosphonium salt **112** proceeded to give the tetracycle precursor **113** in good yield following silyl deprotection. The hydroxydithioketal cyclization protocol developed by Nicolaou and coworkers for the formation of medium ring ethers[94] yielded the mixed thioketal **114** in excellent yield. Further manipulation of this fragment gave the GHIJ ring aldehyde **94** necessary for coupling to the BCDE unit and subsequent hydroxydithioketal cyclization to generate the F ring.



Scheme 2.1.6. Nicolaou's synthesis of the GHIJ ring fragment

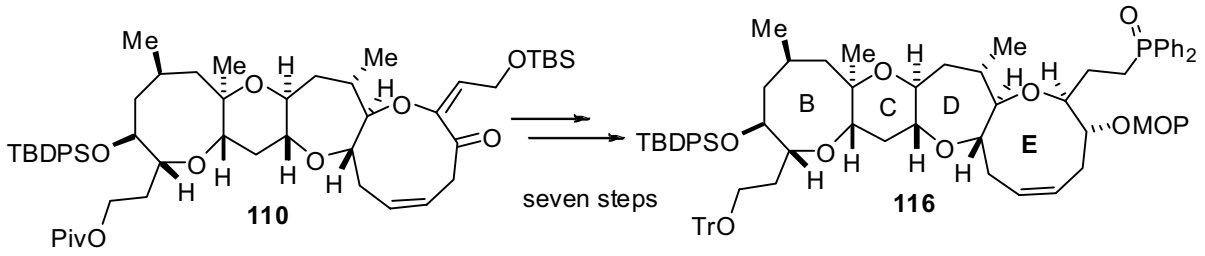
2.1.5.4. Coupling of the BCDE and GHIJ fragments and completion of Brevetoxin A

Initial coupling attempts between the BCDE phosphorane **93** and the GHIJ aldehyde **94** under various basic conditions failed to deliver the coupled intermediate **115** (Scheme 2.1.7).[91] It was reasoned that the steric bulk surrounding the aldehyde and phosphorane prevented reaction between the two units. Further model studies indicated that the use of Horner-Wittig reaction utilizing a diphenylphosphine oxide as the E ring coupling partner could relieve such steric barriers. Thus, preparation of the revised BCDE phosphine oxide **116** was accomplished from the same intermediate **110** prepared previously (Scheme 2.1.8). Importantly, use of the chelating protecting group, methoxypropyl (MOP), on the secondary alcohol adjacent to the phosphine oxide was shown to be important for obtaining a high Z/E ratio in model coupling studies.



Scheme 2.1.7. Attempted Wittig coupling of the two fragments

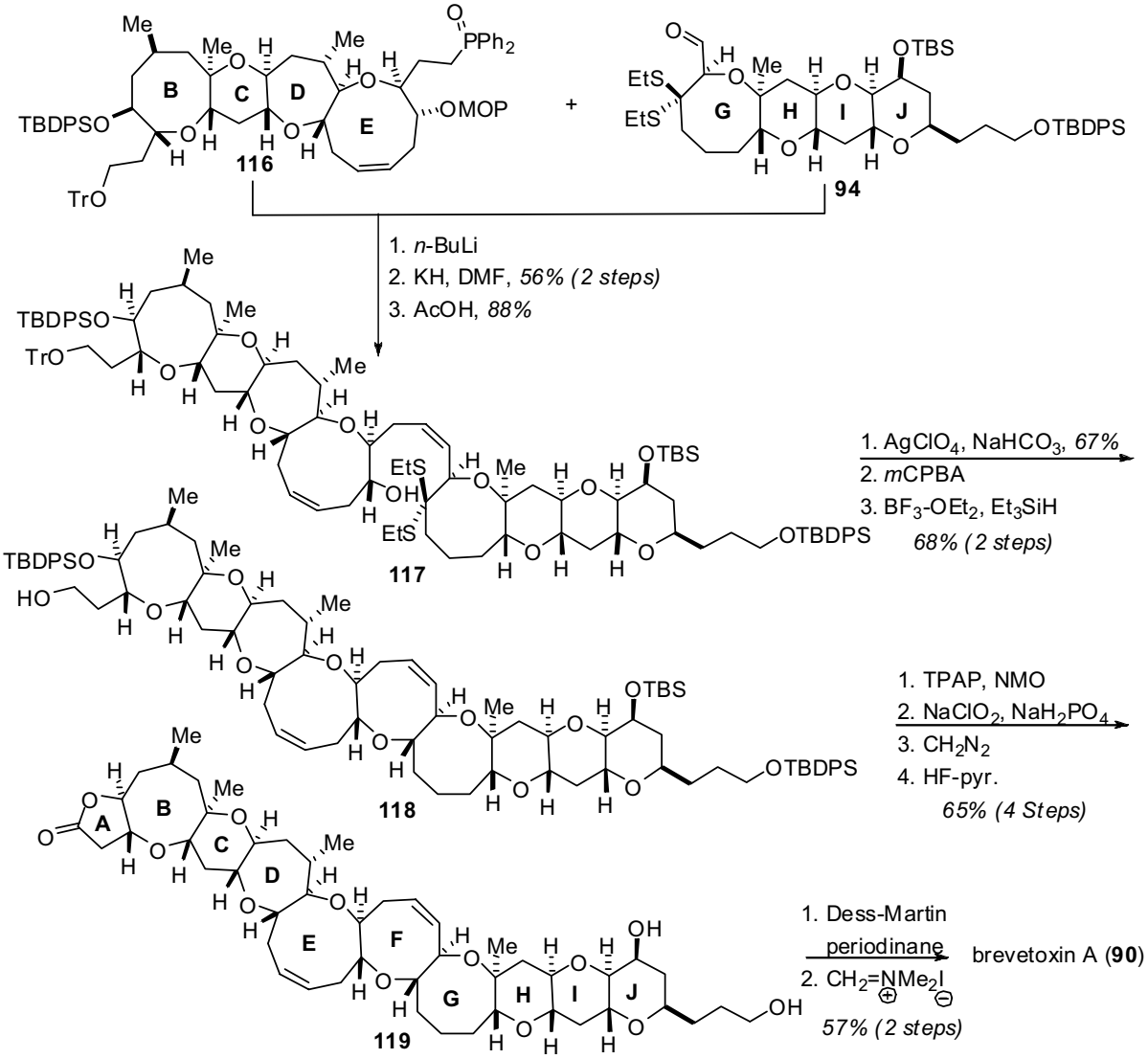
An efficient union of the two fragments **116** and **94** was eventually realized upon addition of the anion of the phosphine oxide to the aldehyde yielding a mixture of two diastereomeric (presumably *anti*) hydroxyphosphine oxides (Scheme 2.1.9). Addition of potassium hydride generated the *Z*-olefin in 56% yield over two steps. The MOP protected alcohol was



Scheme 2.1.8. Formation of the BCDE ring phosphine oxide

liberated with acetic acid to give hydroxydithioketal **117**. Closure of the F ring was accomplished in a manner similar to the G and E rings using the silver-promoted cyclization protocol. Reductive desulfurization under radical conditions in their model systems led to significant byproduct formation via participation of the F ring olefin. Thus, initial conversion

to the sulfone enabled reduction via the intermediate oxocarbenium ion using $BF_3 \cdot OEt_2$ and Et_3SiH. Concomitant loss of the trityl group led to the completed BCDEFGHIJ core **118**. Formation of the A ring lactone proceeded smoothly upon double oxidation of the primary alcohol, conversion of the resulting acid to the methyl ester, and removal of the TBDPS group to give the ABCDEFGHIJ unit **119**. Finally, exposure of the resultant diol to oxidation under Dess-Martin's conditions resulted in selective oxidation of the primary alcohol to the aldehyde. Reaction with Eschenmoser's salt gave brevetoxin A (**90**) that was identical in all respects to the natural material.



Scheme 2.1.9. Nicolaou's completion of brevetoxin A

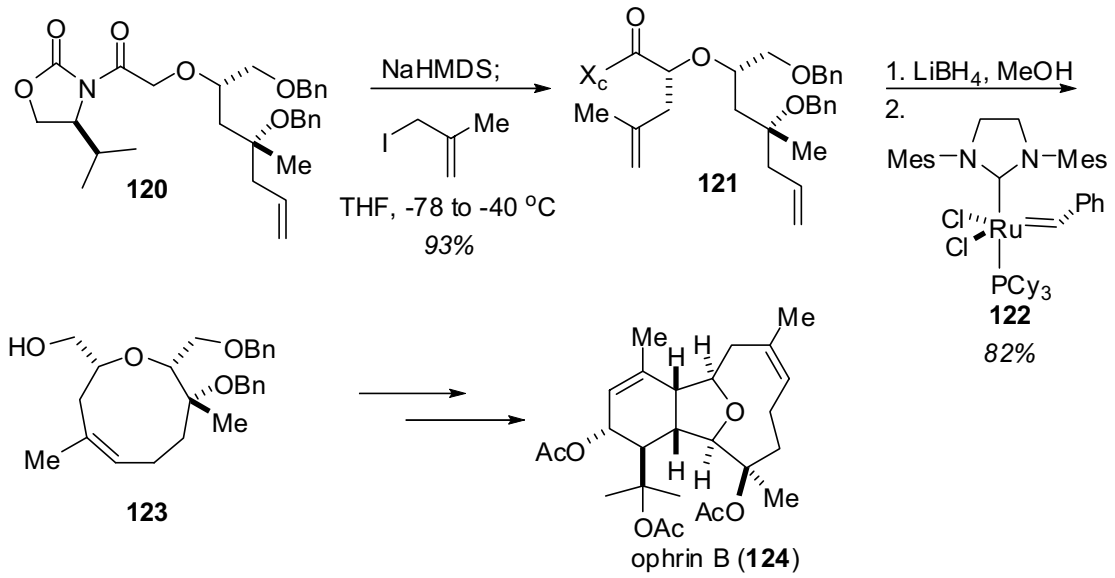
The completion of brevetoxin A by Nicolaou and coworkers was truly a monumental accomplishment in organic synthesis. Such a complex molecule required the development of new methodology for the synthesis of medium ring ethers and technology for the generation of contiguous *trans*-fused cyclic ethers. Since that time, many groups have reported strategies,[72] partial, and total syntheses[62] of related polycyclic ethers. Research into the efficient construction of this class of molecules remains a very active and rewarding area of organic synthesis.

2.1.6 A ring-closing metathesis approach to the synthesis of medium ring ethers: Crimmins methodology

One of the main areas of research in the Crimmins laboratory over the past seven years has been the design of new methodology for the synthesis medium ring ethers. The cornerstone of this technology is a ring-closing metathesis reaction of alkyl ether backbones terminating in two alkene functionalities.[96] Such an approach was made possible with the advent of highly efficient, stable, and functional group tolerant ruthenium carbene metathesis catalysts by Grubbs and coworkers in the mid to late 1990's.[97] Through the use of either Grubbs first[98] or second[99] generation catalysts, medium ring ethers of seven, eight, and nine atoms can be routinely prepared with extremely high efficiency.

The production of the precursor diene fragments for the ring closing metathesis chemistry relies primarily on chiral auxiliary mediated glycolate alkylation and aldol reactions developed in the Crimmins laboratory. A highly efficient, diastereoselective glycolate alkylation reaction using *N*-glycolyloxazolidinones was reported in 2000.[100] Enolization of the substrate using sodium hexamethyldisilazide followed by addition of an appropriate electrophile (typically allylic iodides) leads to the alkylation products in good yield and excellent diastereoselectivities. As exemplified in the total synthesis of ophrin B (**124**),[101] this alkylation approach readily generated the diene ether **121** from glycolate **120** in excellent

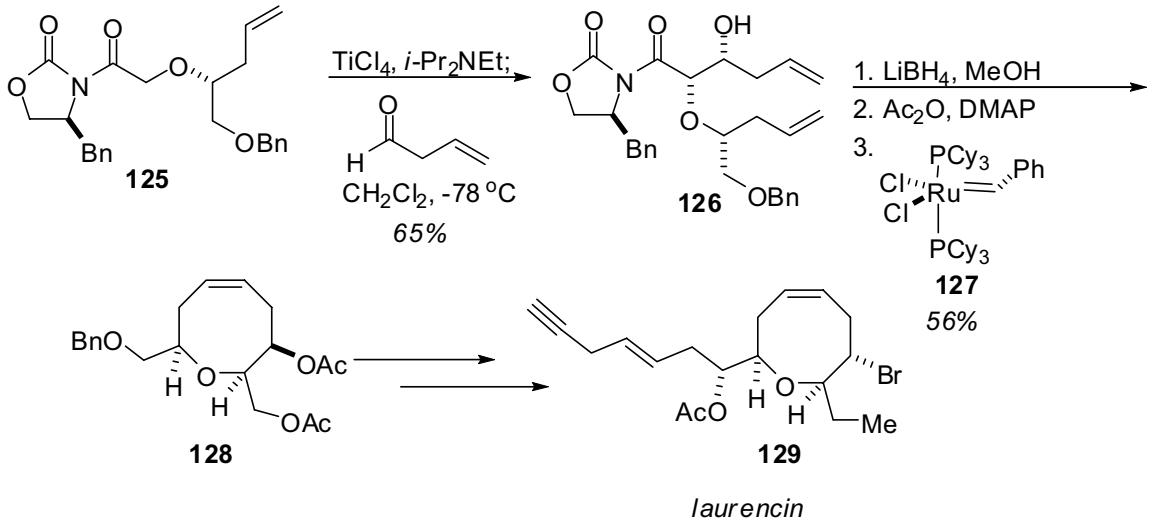
yield (Scheme 2.1.10). Ring closing metathesis with the Grubbs second generation catalyst (**122**) cleanly provided the nine-membered oxonene **123** which was carried forward to the natural product.



Scheme 2.1.10. Total synthesis of ophrin B: alkylation/RCM approach (Crimmins/Brown)

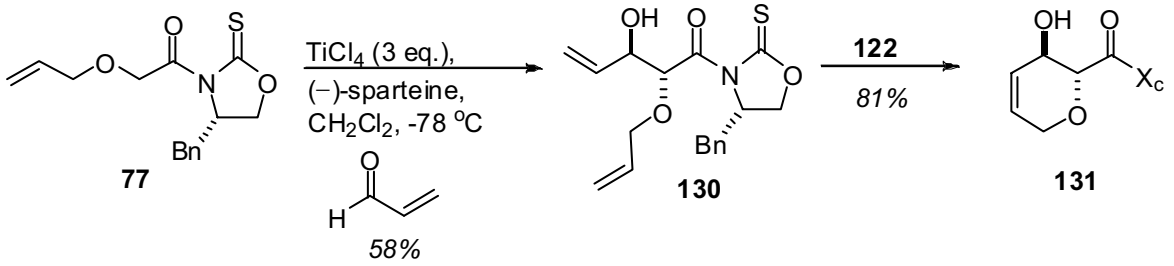
An alternative approach toward generating the diene ethers relies on glycolate aldol additions, again mediated by oxazolidinone-based chiral components.[102] Glycolate aldol additions utilizing the titanium enolates of oxazolidinone and oxazolidinethione glycolates were discussed in Chapter 1. An example of this approach applied to the formal synthesis of (+)-laurencin (**129**)[102] is illustrated in Scheme 2.1.11. *Syn* selective glycolate aldol reaction with glycolylimide **125** and 3-butenal directly generated the 1,2-*syn* aldol adduct **126** containing the two terminal alkenes. Reductive removal of the auxiliary, alcohol protection and ring-closing metathesis using the Grubbs first generation catalyst (**127**) provided the oxocene **128**, which was further elaborated to the natural product.

With the advent of the *anti* glycolate aldol addition[103] described in detail in Chapter 1, access to cyclic ethers containing the 1,2-*anti* hydroxyl relationship was possible. For example, *anti* aldol addition of acrolein to the allyl glycolylimide **77** gave the desired adduct



Scheme 2.1.11. Syn aldol/RCM approach to the synthesis of laurencin (Crimmins/Choy)

130 in 58% yield (Scheme 2.1.12). Upon exposure to Grubb's catalyst **122**, the desired dihydropyran **131** was obtained in 81% yield.



Scheme 2.1.12. *Anti* adol-RCM approach to cyclic ethers

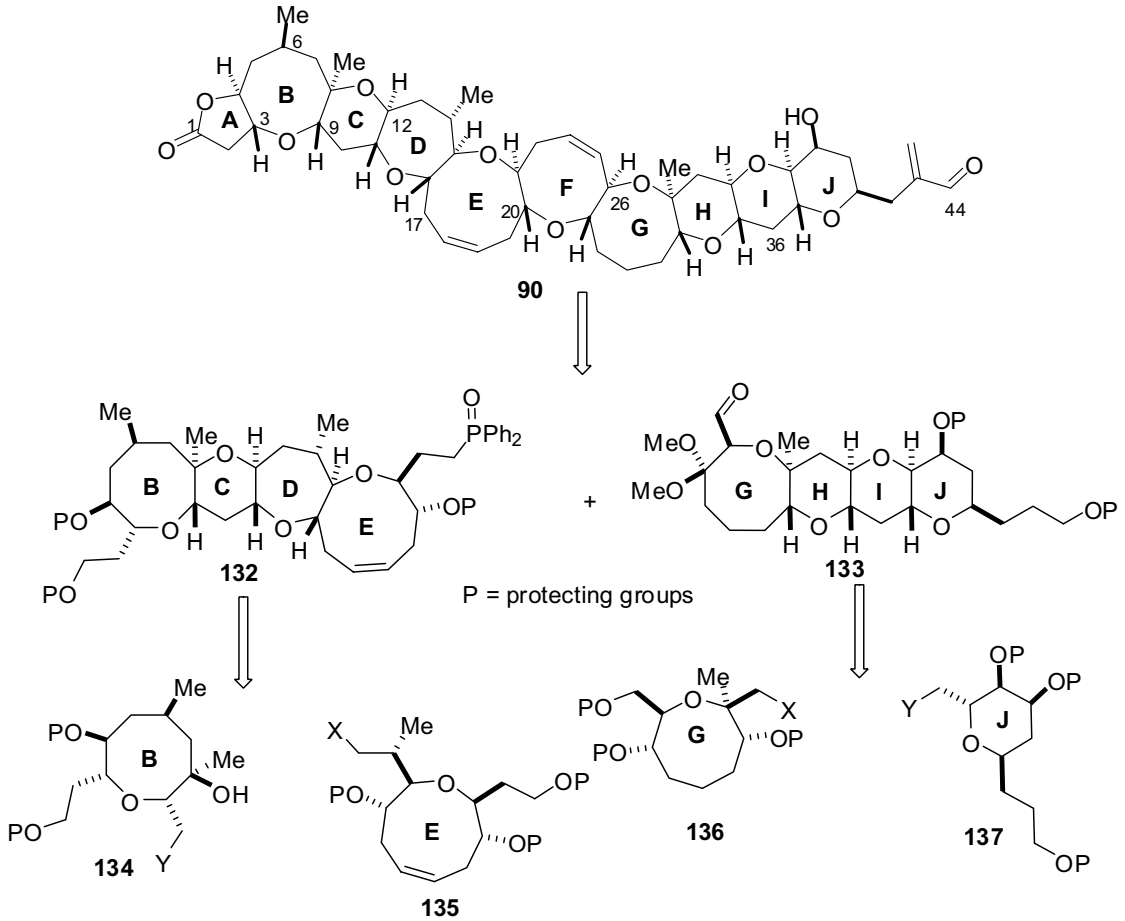
2.2 STUDIES DIRECTED TOWARD THE TOTAL SYNTHESIS OF BREVETOXIN A: 1ST GENERATION APPROACH OF THE B AND E RING UNITS

The technology developed in the Crimmins laboratory for the synthesis of medium ring ethers led to the development of a project aimed at the total synthesis of the marine ladder toxin, brevetoxin A. As is evident from the structure of this natural product, several medium ring ethers are represented, offering many opportunities to apply both the alkylation and aldol/ring-closing metathesis strategies described above.

2.2.1 Retrosynthetic analysis of Brevetoxin A

From a retrosynthetic viewpoint (Scheme 2.2.1), disconnection of brevetoxin A (**90**) at the F ring in a similar manner to Nicolaou's approach was decided upon for several reasons. First, the end game synthesis developed by Nicolaou was demonstrated to be highly efficient and required minimal synthetic operations. Second, disconnection at this ring divides the molecule into two fragments, the BCDE (**132**) and GHIJ (**133**) fragments that are similar in size and complexity. In contrast to the reported synthesis, however, a highly convergent method[72] for the preparation of these two fragments was envisioned.

It was anticipated that a convergent assembly could be employed that would enable the formation of the two inner ring systems (i.e. C and D, H and I) following union of the outer



Scheme 2.2.1. Retrosynthetic analysis of brevetoxin A

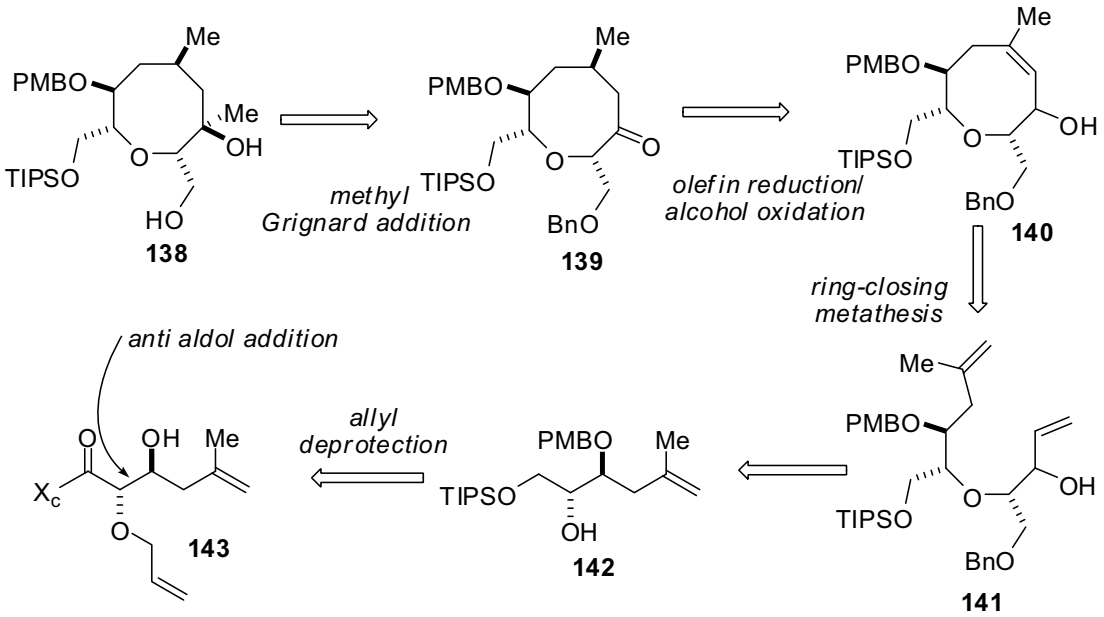
ring units (X+2+X approach (see Chapter 3)). For example, union of the B and E ring units **134** and **135** would be followed by subsequent iterative formation of the C and D ring units to complete the tetracycle **132**. Detailed discussion surrounding this convergent assembly will be presented in Chapter 3. Based on this analysis, the core medium ring ethers B (**134**), E (**135**), G (**136**), and J (**137**) were targeted.

2.2.2 Synthesis of the B ring fragment of Brevetoxin A

2.2.2.1. Retrosynthetic analysis of the B ring fragment: *Anti* glycolate aldol approach

An examination of the *trans*-fused ring junctions inherent to the polyether backbone suggests the potential application of the *anti* glycolate aldol addition for the efficient synthesis of this *trans* alkoxy relationship. Thus, the previously described methodology (Chapter 1) became instrumental for the synthesis of the B ring fragment.

A retrosynthetic analysis of the completed B ring fragment (**138**) containing the necessary hydroxyl protecting groups and functionality for eventual coupling to the E ring is

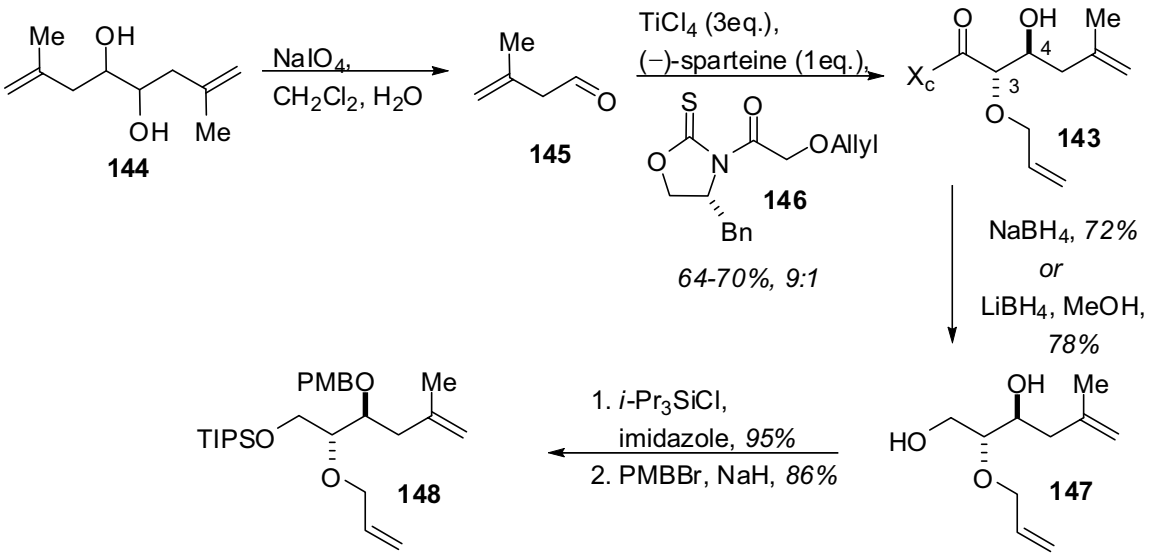


Scheme 2.2.2. Retrosynthetic analysis of the B ring fragment

shown in Scheme 2.2.2. The tertiary alcohol **138** was envisioned to arise from a methyl Grignard addition to the ketone **139**. This ketone would come from a stereoselective reduction of the tri-substituted allylic alcohol **140**, followed by oxidation of the secondary alcohol. The eight membered cyclic ether would be generated using a ring-closing metathesis reaction of the diene **141**. The diene would, in turn, be generated from the simplified 1,1-disubstituted alkene **142** that would ultimately arise from an *anti* glycolate aldol addition between the *O*-allyl glycolate (enantiomer of glycolate **77**) and 3-methylbutenal to generate the *anti* adduct **143**.

2.2.2.2. Synthesis of the B ring fragment

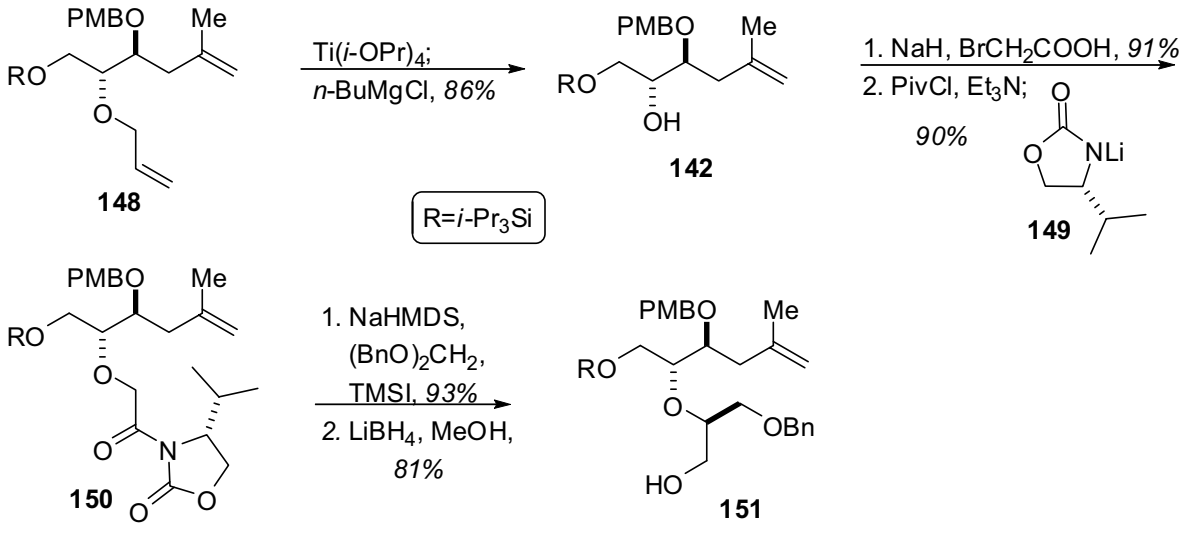
Synthesis of the B ring began with the newly developed *anti* glycolate aldol reaction to form the C3-C4 bond of brevetoxin A. The aldehyde acceptor needed for the synthesis, 3-methylbutenal (**145**), was prepared immediately prior to use via oxidative cleavage of the symmetrical diol **144** (Scheme 2.2.3).[104] Aldol addition of the chlorotitanium enolate of the α-allyloxy glycolylimide **146** with the aldehyde provided the adduct **143** in good



Scheme 2.2.3. Synthesis of the 1,2-*anti* alkoxy fragment

diastereoselectivity and 64-70% isolated yield. This reaction could be performed on large scale (~150 mmol) without significant loss of selectivity and/or yield. Reductive removal of the chiral auxiliary using either lithium or sodium borohydride gave diol **147** with which the primary alcohol was selectively protected as the triisopropylsilyl (TIPS) ether. Protection of the remaining secondary alcohol as the *p*-methoxybenzyl (PMB) ether then gave the fully protected intermediate **148**.

Selective removal of the allyl protecting group proved rather challenging due to the presence of the 1,1-disubstituted olefin. Standard methods for deprotection of allyl ethers, such as the use of Wilkinson's catalyst which acts to isomerize the allyl ether to the enol ether,[53] also suffered from reaction with the methallyl group. Ultimately, a highly efficient and selective deprotection was realized using titanium (IV) isopropoxide and *n*-BuMgCl at 0 ºC to give the free alcohol **142** (Scheme 2.2.4). This interesting deprotection procedure was developed by Cha and Lee[105] based on the Kulinkovich hydroxycyclopropanation reaction[106,107] and is believed to proceed via intermediate formation of the titanocyclopropane. Formation of the carboxylic acid using sodium bromoacetate, and subsequent coupling to (R)-lithio-4-isopropyl-2-oxazolidinone (**149**) via the mixed pivaloyl



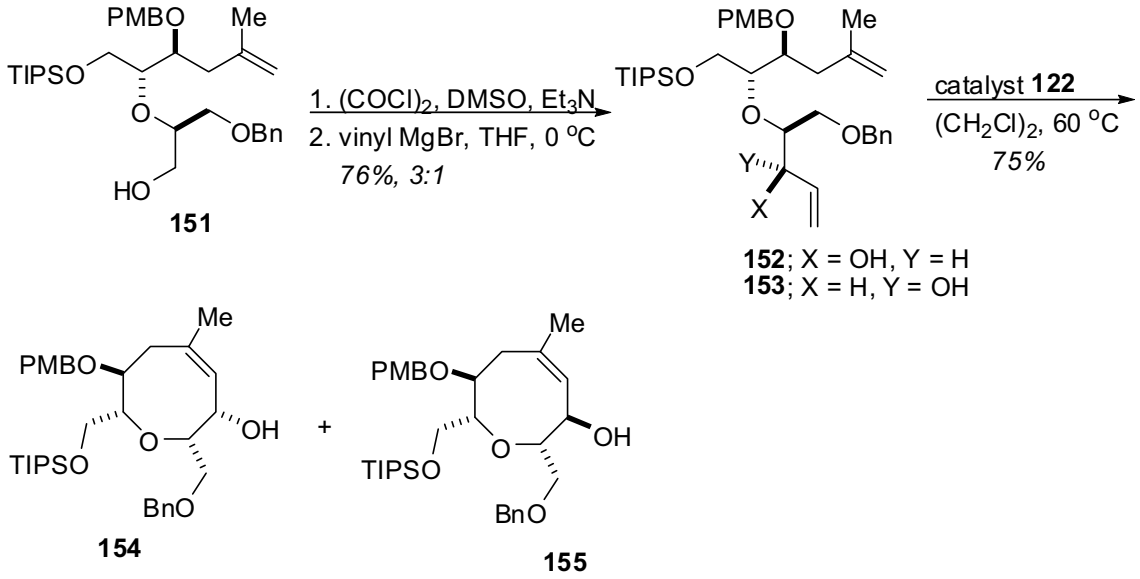
Scheme 2.2.4. Alkylation of the B ring fragment

anhydride provided the glycolylimide **150** in good overall yield.

The next stage of the synthetic sequence called for alkylation of the glycolate to install a one carbon unit. While the alkylation of *N*-glycolyloxazolidinones are typically conducted using allylic iodides, the use of benzyl iodomethyl ether (prepared immediately prior to use from formaldehyde dibenzyl acetal and iodotrimethylsilane) as the electrophilic partner can be accomplished under carefully controlled conditions.[100] Thus, formation of the sodium enolate of glycolate **150** using sodium hexamethyldisilazide followed by the addition of the electrophile gave the alkylation product in excellent yield as a single diastereomer (Scheme 2.2.4). Subsequent reductive removal of the auxiliary gave the primary alcohol **151**.

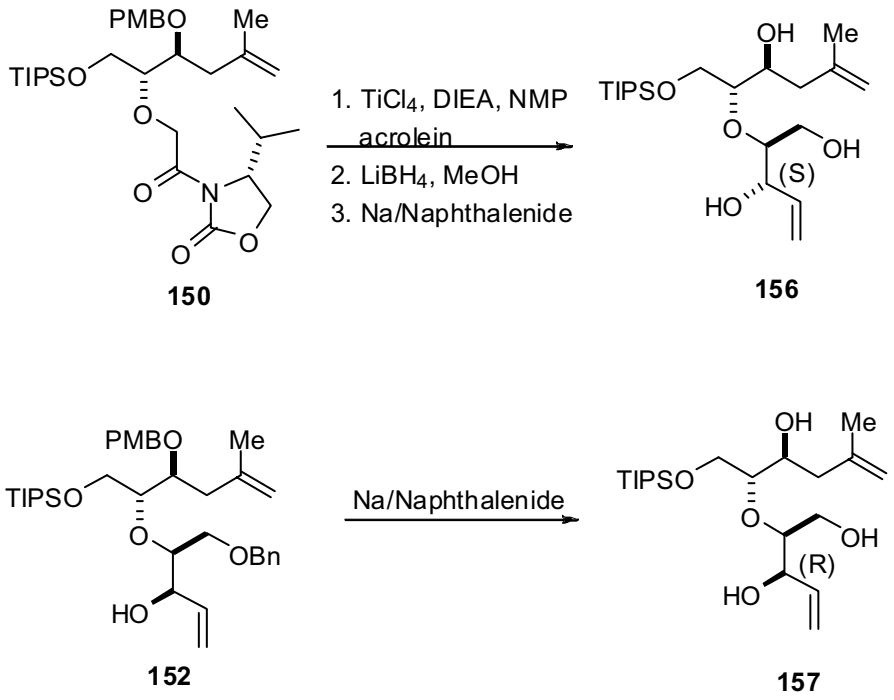
Oxidation of primary alcohol **151** under Swern conditions[108] gave the intermediate aldehyde which was immediately treated with vinyl magnesium bromide to give an inseparable 3:1 mixture of diastereomers **152** and **153** favoring compound **152** (Scheme 2.2.5). Ring-closing metathesis utilizing Grubbs' second generation catalyst (**122**)[99] cleanly furnished the separable oxocenes **154** and **155** in good yield.

Confirmation of the configuration of the allylic hydroxyl group resulting from the Grignard



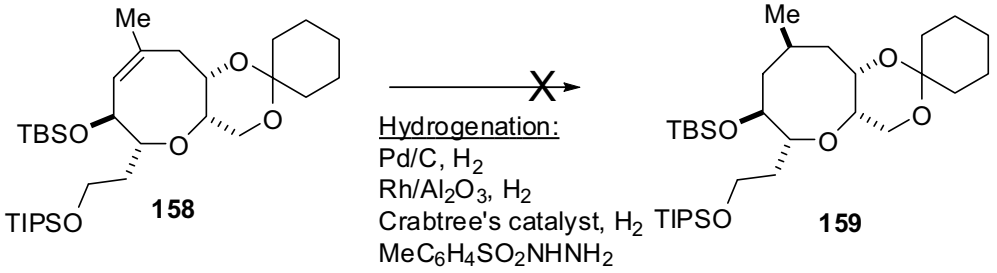
Scheme 2.2.5. Synthesis of the B ring oxocenes

addition was obtained rather circuitously using an Evans *syn* aldol addition between glycolylimide **150** with acrolein to yield the triol **156** following reductive removal of the auxiliary and PMB deprotection (Scheme 2.2.6). Compound **152**, obtained from the Grignard



Scheme 2.2.6. Determination of allylic hydroxyl configuration

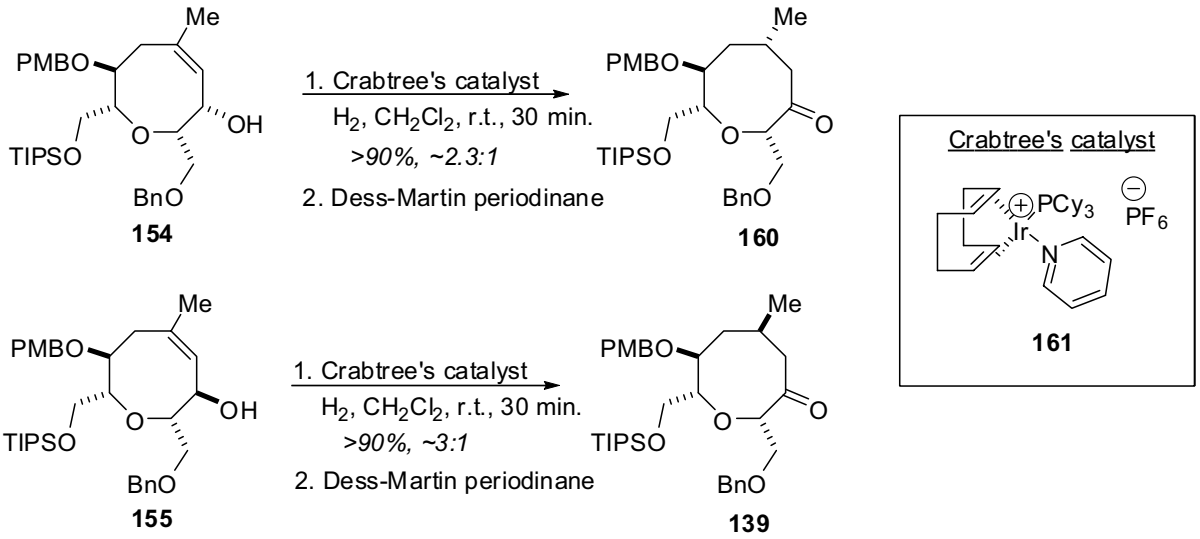
addition, was likewise converted to the triol **157** via deprotection of the PMB and benzyl ethers. The two compounds did not match by ^{1}H NMR analysis leading to the conclusion that the major isomer from the Grignard addition possessed the (R)-configuration at the allylic stereocenter as shown. Previous efforts aimed toward the synthesis of the B ring fragment by Dr. Kyle Emmitte hinted at the difficultly associated with a stereoselective reduction of a tri-substituted olefin in a ring system similar to oxocenes **154** and **155**.[109] For example, attempted reduction of compound **158** using a wide variety of reducing agents failed to give the desired oxocane **159**, typically yielding only unreacted starting material or decomposition byproducts (Scheme 2.2.7).



Scheme 2.2.7. A problematic hydrogenation (Emmitte)

Nonetheless, it was anticipated from the onset of this project that a substrate-controlled reduction of the endocyclic double bond present in intermediates **154** and **155** could be made viable to set the C6 stereogenic center. Initial testing of the reduction conditions of both oxocenes relied on the use of Crabtree's catalyst (**161**),[110] known for its ability to reduce hindered olefins. Surprisingly, hydrogenation of the olefin was accomplished within minutes for both oxocenes. This is in stark contrast to the previously tested substrate **158**, which is very similar in structure and steric environment.

Even more intriguing was the fact that upon independent subjection of each of the oxocenes **154** and **155** to the hydrogenation conditions two different saturated oxocanes possessing the opposite configuration at the C6 methyl group were formed (determined after

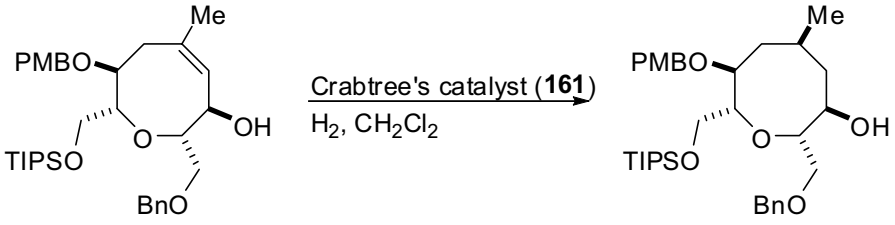


Scheme 2.2.8. Reduction of the endocyclic olefin

Dess-Martin periodinane[111] oxidation of the allylic hydroxyl to the ketones **160** and **139**) (Scheme 2.2.8). Upon confirmation of the C6 configuration by conversion of oxocane **139** to a known intermediate,[112] it was determined that hydrogenation of the major oxocene **155** proceeded from the desired π-face to give the desired C6 configuration in a 3:1 ratio. Likewise, oxocene **154**, which differed only at the allylic alcohol stereocenter, hydrogenated selectively from the undesired face to give the opposite C6 configuration in a ~2:1 ratio.

At first glance, these results seemed counterintuitive based on the known directing effects of allylic hydroxyl groups.[113] However, this discrepancy can be attributed to the conformational flexibility inherent to eight membered ring systems. In fact, there have been documented reports of similar selectivity occurring during directed cyclopropanation[114] and epoxidation[115] of medium ring allylic alcohols. Furthermore, a similar stereoselective hydrogenation of an eight membered endocyclic olefin of the ciguatoxin I ring has also been reported,[116] suggesting a conformational bias toward hydrogenation from the bottom face.

While the 3:1 selectivity was encouraging, failure to separate the diastereomers at this stage (and after several subsequent transformations) was cause for concern. Thus a series of experiments were undertaken to improve upon the selectivity. A major breakthrough was achieved upon simple variation of the reaction temperature. As shown in Table 2.2.1 a



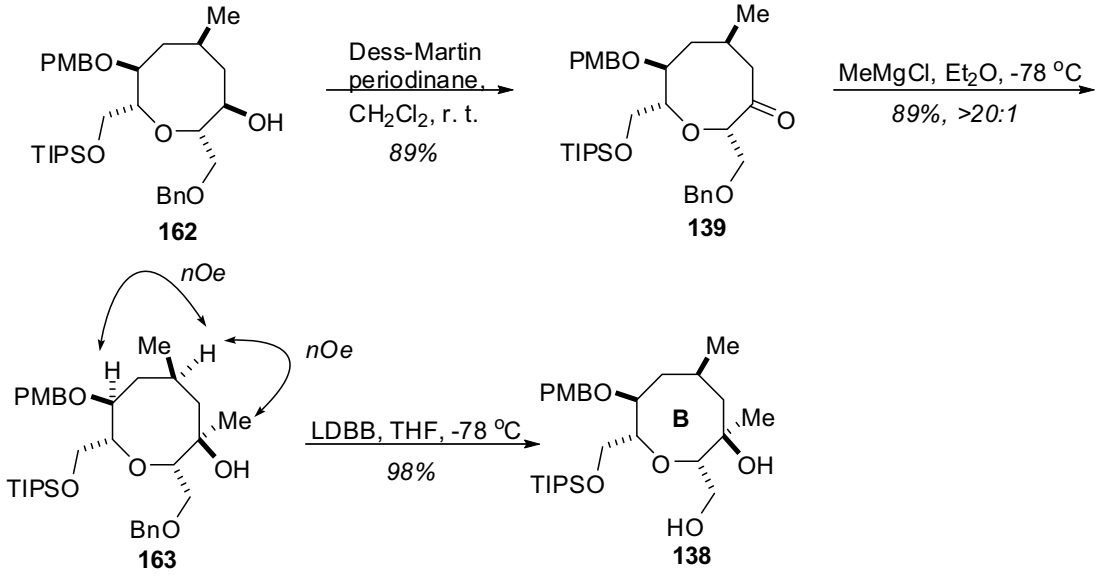
155 **162**

temperature	reaction time	d.r.	yield
25 °C	10 min	3:1	95%
0 °C	30 min	8:1	N.D.
-50 °C	2 h	>20:1	93%

Table 2.2.1. Reaction temperature vs. diastereoselectivity in oxocene reduction

inverse relationship between temperature and diastereoselectivity was observed. Optimal results were obtained at -50 ºC, where the reaction proceeded to give the desired product **162** in 93% yield as the only detectable stereoisomer.

To complete the synthesis of the B ring, the alcohol was oxidized using the Dess-Martin periodinane reagent[111] to give the ketone **139** in good yield (Scheme 2.2.9). A highly selective methyl Grignard addition to the ketone was observed to provide the tertiary alcohol



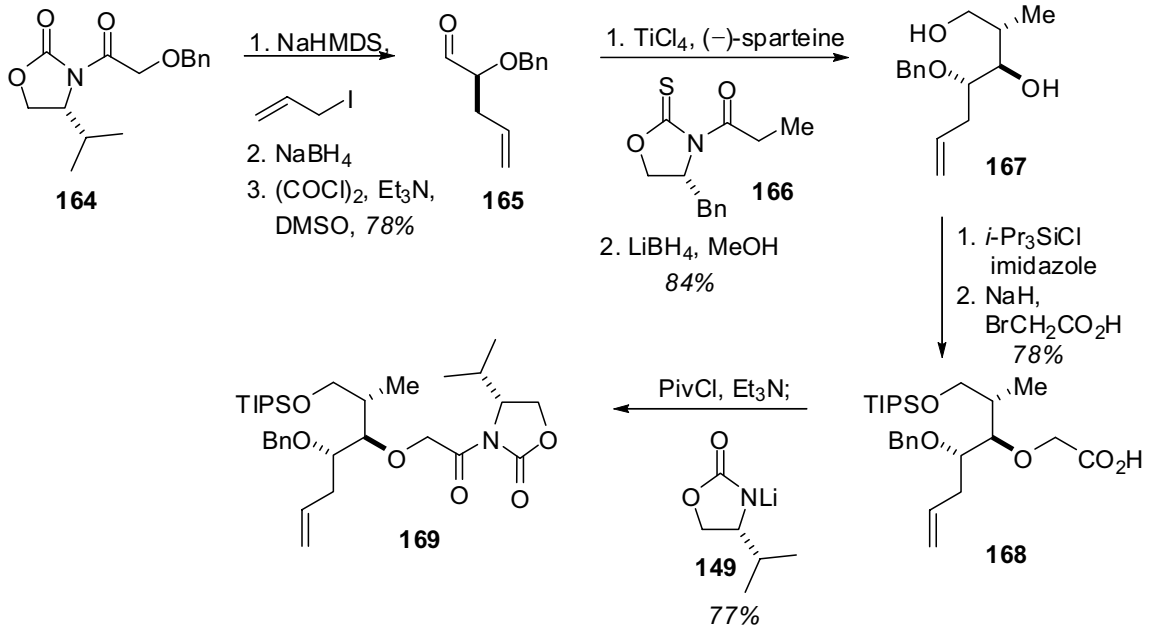
Scheme 2.2.9. Completion of the B ring fragment

163 in excellent yield as a single diastereomer. The configuration of the tertiary alcohol was established at this point using 2D-NMR studies and the examination of the nOe interactions. Finally, in preparation for eventual coupling to the E ring, the primary benzyl ether was selectively cleaved in the presence of the PMB ether using lithium 4,4'-di-*t*-butylbiphenylide (LDBB) to provide diol **138** in 98% yield.

2.2.3 Synthesis of the E ring fragment

2.2.3.1. Previous synthesis of the E ring fragment

The E ring fragment of brevetoxin A had been previously synthesized by a former member of the Crimmins group, Dr. Kyle Emmitte.[109] Beginning with the α-benzyloxy glycolylimide **164**, an asymmetric alkylation[100] with allyl iodide was performed to give the chiral aldehyde **165**, following reductive removal of the auxiliary (Scheme 2.2.10). Swern oxidation[108] and subsequent *syn* propionate aldol addition using the *N*-propionyloxazolidinethione **166** gave the chiral diol **167** following reductive auxiliary removal. Protection of the primary alcohol as the silyl ether and alkylation using sodium bromoacetate

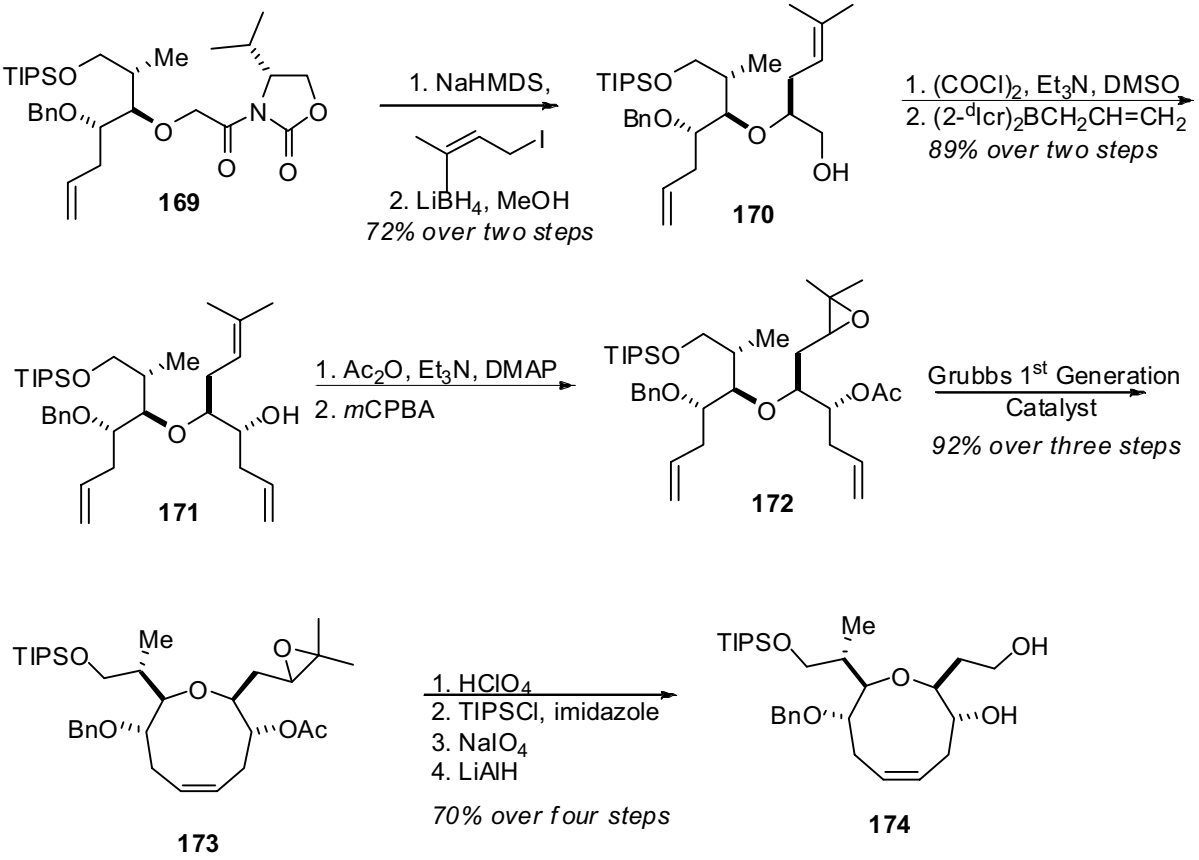


Scheme 2.2.10. Previous synthesis of the E ring glycolate (Emmitte)

gave the carboxylic acid **168**. Formation of the glycolate **169** proceeded smoothly via the mixed pivaloyl anhydride.

Conversion of the glycolate **169** into the desired E ring fragment required several synthetic operations. Alkylation of the sodium enolate of imide **169** with prenyl iodide generated the alcohol **170**, following reductive removal of the auxiliary (Scheme 2.2.11). Oxidation to the aldehyde followed by Brown allylation[117] delivered the diene **171** in good

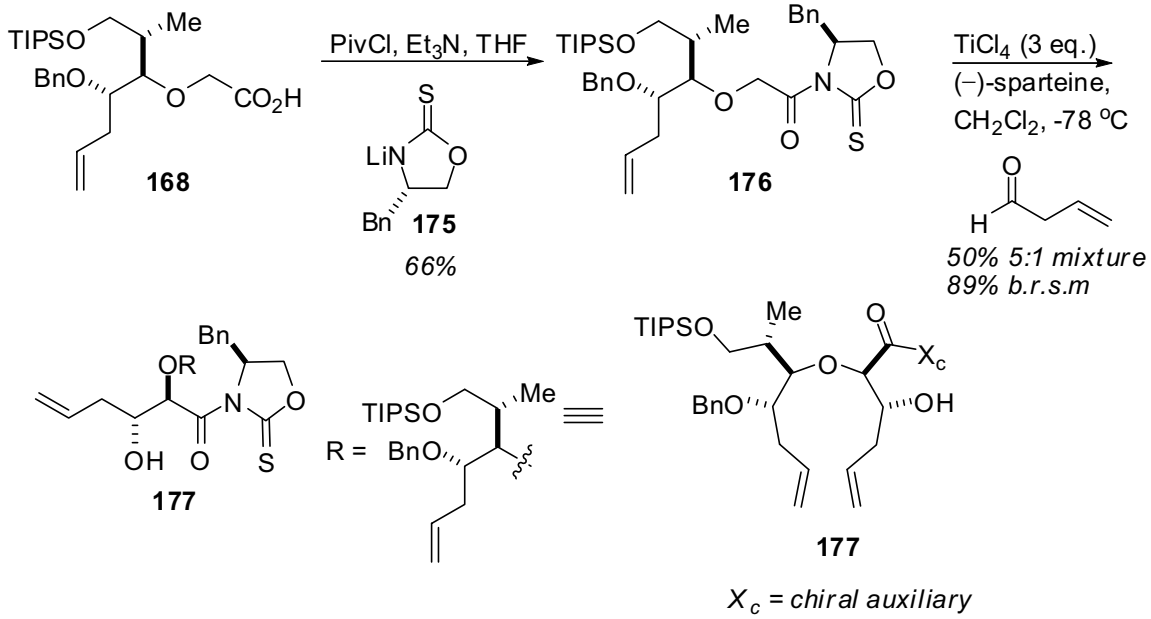
yield. After protection of the alcohol as the acetate and the tri-substituted olefin as the epoxide, ring closing metathesis completed the E ring core (**173**). Finally, a four step sequence was required to convert the epoxide to the intermediate diol **174**.



Scheme 2.1.11. Completion of the E ring (Emmitte)

2.2.3.2. An *anti*-aldol approach to the E ring fragment

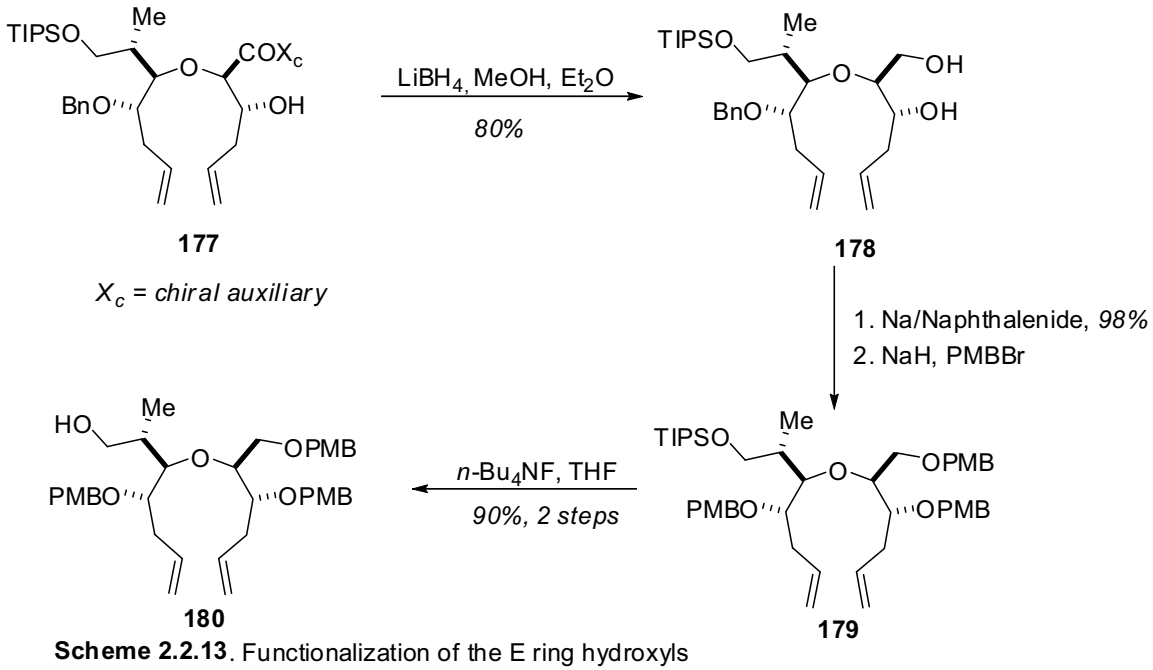
Re-examination of the right-hand portion of the E ring fragment revealed an opportunity to apply the *anti* glycolate aldol methodology to provide rapid access to a suitable diene fragment for closure of the nine-membered ring. Thus, formation of the requisite oxazolidinethione glycolate **176** proceeded readily from the previously synthesized carboxylic acid **168** and (*S*)-lithio-4-benzyl-2-oxazolidinethione (**175**) (Scheme 2.2.12). Subjection of the resulting thioimide to the standard *anti* aldol conditions[103] using 3-butenal[96]



Scheme 2.2.12. An *anti* aldol approach to the E ring fragment.

as the acceptor gave the desired product **177** in moderate yield as a 5:1 ratio of inseparable diastereomers. Interestingly, enolization of glycolate **176** (qualitative by formation of purple color) required significantly warmer temperatures (–40 ºC) than the simpler substrates tested during the methodological studies. This difficulty in enolization may explain the low product conversion. Despite the lower yield and selectivity, this represents an encouraging example of *anti* glycolate aldol additions using complex glycolylimides.

Reductive removal of the auxiliary using lithium borohydride provided the diol **178** as a mixture of stereoisomers in good yield (Scheme 2.2.13). Benzyl deprotection using sodium naphthalenide gave the free triol in excellent yield. Facile separation of the desired *anti* adduct was possible at this stage. Subsequent protection using *p*-methoxybenzyl bromide (PMBBr) yielded the tris-PMB ether **179**. Finally, removal of the TIPS protecting group was accomplished using tetrabutylammonium fluoride to provide alcohol **180** and set the stage for the elaboration to a coupling partner for the B ring unit.



Scheme 2.2.13. Functionalization of the E ring hydroxyls

2.3 SUMMARY

In summary, the completed syntheses of the B and E rings of the marine neurotoxin, brevetoxin A have been accomplished. Construction of these medium ring ethers utilized glycolate alkylation and aldol reactions that were previously developed in the Crimmins laboratory. The recently developed *anti* glycolate aldol addition described in Chapter 1 proved useful for the construction of both ring units, setting four of the required stereogenic centers for the completion of the natural product and providing rapid access to enantiopure metathesis precursors. The prepared intermediates were constructed in such a manner to allow facile derivatization for the exploration of novel coupling strategies to ultimately complete the BCDE tetracycle. These efforts are described in the following Chapter.

CHAPTER 3: DEVELOPMENT OF A CONVERGENT COUPLING STRATEGY FOR THE SYNTHESIS OF POLYCYCLIC ETHERS: COMPLETED SYNTHESIS OF THE BCDE FRAGMENT OF BREVETOXIN A

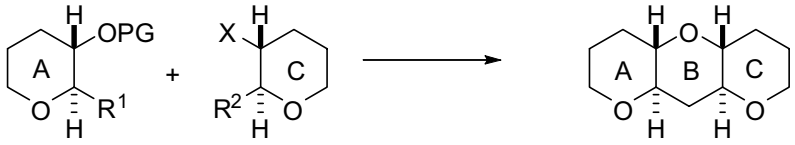
3.1 BACKGROUND: CONVERGENT COUPLING STRATEGIES

Due to the unique structure, potent biological activity, and limited availability of many polycyclic ether molecules, an extensive amount of chemical research has been conducted to achieve their total syntheses.[62] As with many total synthesis endeavors, many strategies for the efficient construction of the key structural element, the repeating *trans*/*syn*/*trans*-fused polycyclic ether, have emerged. The degree of variation in terms of ring sizes, number of fused rings, and substitution on the rings and ring junctions has sparked a significant number of unique and diverse methods for the preparation of polycyclic ether fragments. Interestingly, these strategies have been steadily increasing at an impressive rate in the past six years and continues to be an active and rewarding area of chemical synthesis.[72,73,118]

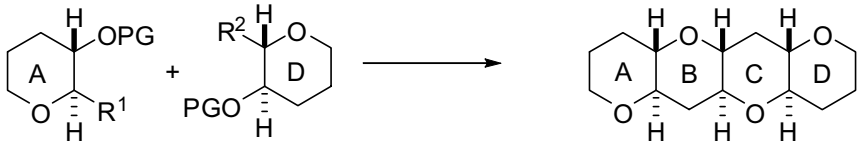
Based on the large size and high complexity of these molecules, the pivotal concerns regarding their synthesis relate to the efficiency and material throughput available with the synthetic approach. Total linear construction of the polyether framework becomes impractical as the size and complexity of the molecule increases. While a number of linear strategies have emerged for the synthesis of smaller fused systems,[119] most recent efforts have centered around the development of convergent strategies. In these approaches two complex cyclic ether subunits are coupled in a manner enabling the formation of additional ring(s) to complete the fused array. Such strategies have been categorized into two subsections.[72] First, in the [X+1+X] type strategy, the coupling of two cyclic ethers occurs in

a manner to allow for the construction of a third ring and complete a fused tricycle (Scheme 3.1.1). Alternatively, the [X+2+X] strategy couples two ring fragments in a manner to allow for the construction of two additional ring systems ultimately leading to a fused tetracyclic fragment. This later category is considerably more efficient and leads to cyclic ether fragments of higher molecular complexity. Thus, the majority of recent coupling strategies that have been developed have focused on the [X+2+X] approach.

The [X+1+X] Strategy



The [X+2+X] Strategy

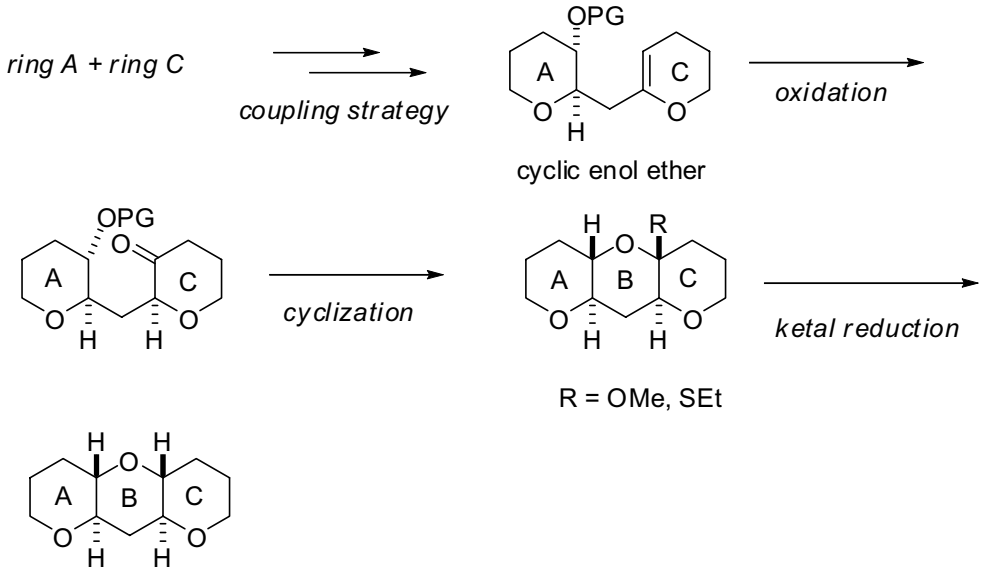


Scheme 3.1.1. Generalization of convergent coupling strategies (Inoue)

3.1.1 Convergent coupling strategies utilizing endocyclic enol ether intermediates

A number of the more successful convergent strategies share a common endocyclic enol ether intermediate (typically a dihydropyran) and differ primarily only in their approach toward its formation from the individual ring units (i.e. A and C; Scheme 3.1.2). Subsequent elaboration of the cyclic enol ether via oxidation of the olefin then installs a ketone functionality in a regio- and often stereoselective manner. Reductive closure of the final ring is readily accomplished using a reductive etherification approach via a mixed ketal to complete the fused array. Completion of the polycyclic fragments from dihydropyran units using this oxidation/reduction strategy has been extensively documented and is arguably

one of the more versatile, mild, and efficient methods for the convergent synthesis of polycyclic ethers.

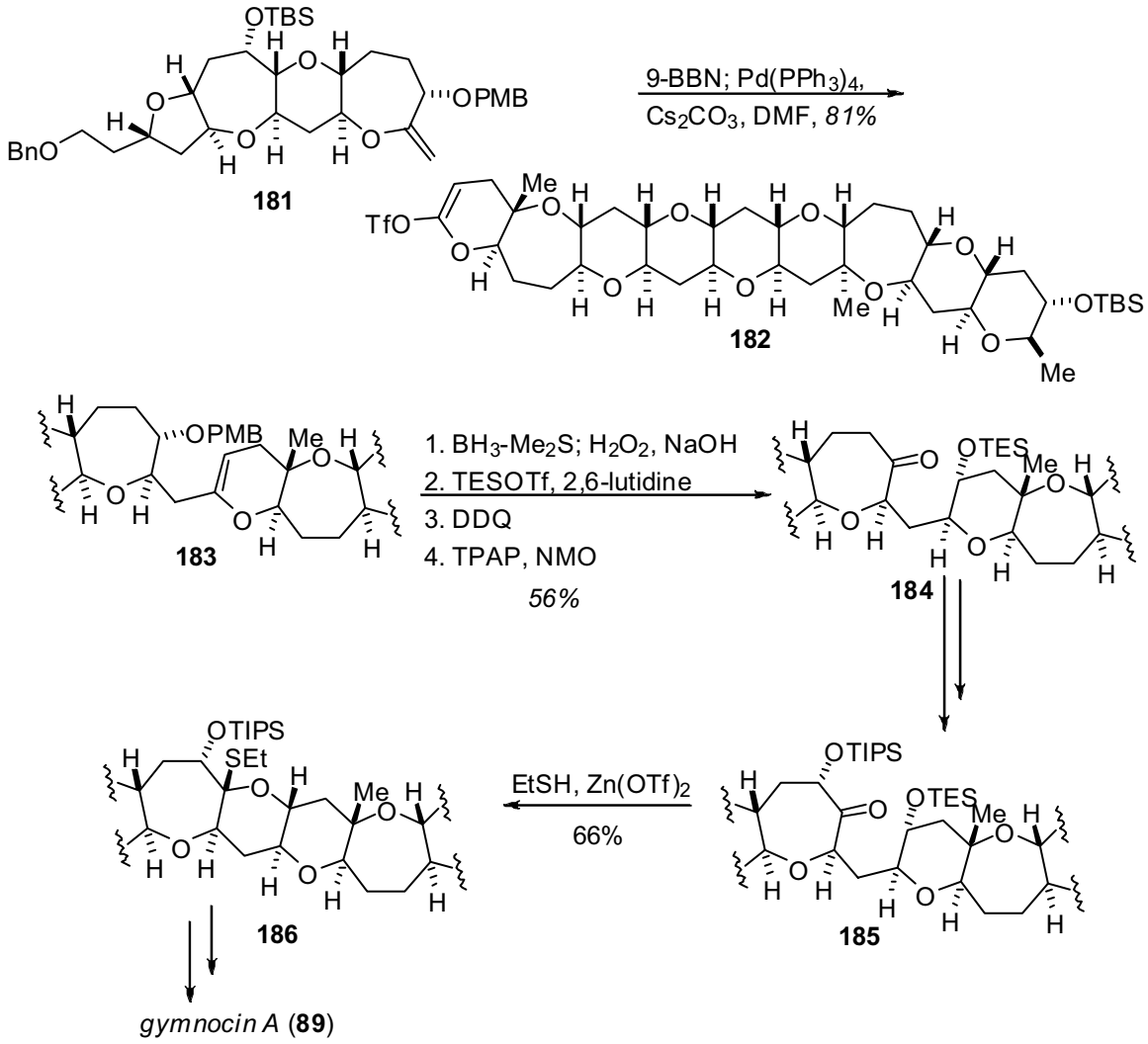


Scheme 3.1.2. Coupling strategies based on intermediate enol ether

3.1.1.1. Sasaki's β-alkyl Suzuki coupling approach

The β-alkyl Suzuki-reductive etherification approach developed by Sasaki and coworkers is one of the more effective convergent coupling strategies developed to date.[120] This example of an [X+1+X] strategy begins with the stereoselective hydroboration of one complex ring unit functionalized as an exocyclic enol ether to set one stereogenic center and generate a transient alkylborane. A palladium-catalyzed Suzuki coupling with another cyclic ether derivatized as the ketene acetal triflate[121] or phosphate[122] then joins the two ring systems in a highly efficient manner leading directly to an intermediate cyclic enol ether. As highlighted several times in their synthesis of gymnocin A (**89**),[67] this coupling strategy is extremely efficient and tolerant of a wide range of functional groups. For example, hydroboration of the complex tetracycle **181** followed by in situ palladium catalyzed Suzuki coupling with the enol triflate **182** led to the coupled product **183** in good yield (Scheme

3.1.3). Regioselective hydroboration/oxidation of the endocyclic enol ether then installed the oxygen functionality necessary to close the remaining cyclic ether. Protecting group



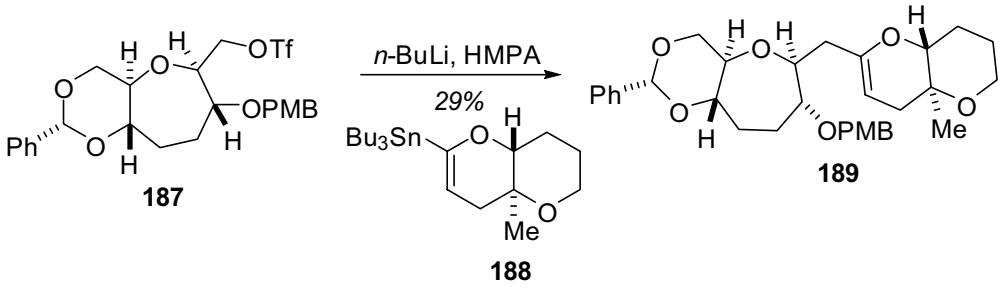
Scheme 3.1.3. Sasaki's total synthesis of gymnocin A

manipulations and oxidation of the secondary alcohol led to the keto-alcohol **184**, which, after conversion to intermediate **185**, underwent cyclization in the presence of ethanethiol and zinc triflate to form the thioketal **186**. Reduction using AIBN and Ph_3SnH[94] gave the cyclic ether which was ultimately converted to the natural product. The efficacy of this approach has been adequately demonstrated by Sasaki and has resulted in the total

syntheses of several polycyclic ether molecules, including gambierol,[69] and advanced intermediates of ciguatoxin.[123]

3.1.1.2. Vinylstannane/enol triflate couplings

A related [X+1+X] approach developed by Yamamoto utilized vinylstannanes and alkyl triflates to generate the coupled cyclic enol ether fragments.[124] For example, coupling of the bicyclic triflate **187** to the vinylstannane **188** in the presence of *n*-BuLi led to the enol ether **189** in 29% yield (Scheme 3.1.4). The utility of this strategy for the synthesis of naturally occurring polyethers has not been demonstrated, possibly due the low efficiency of the coupling event.

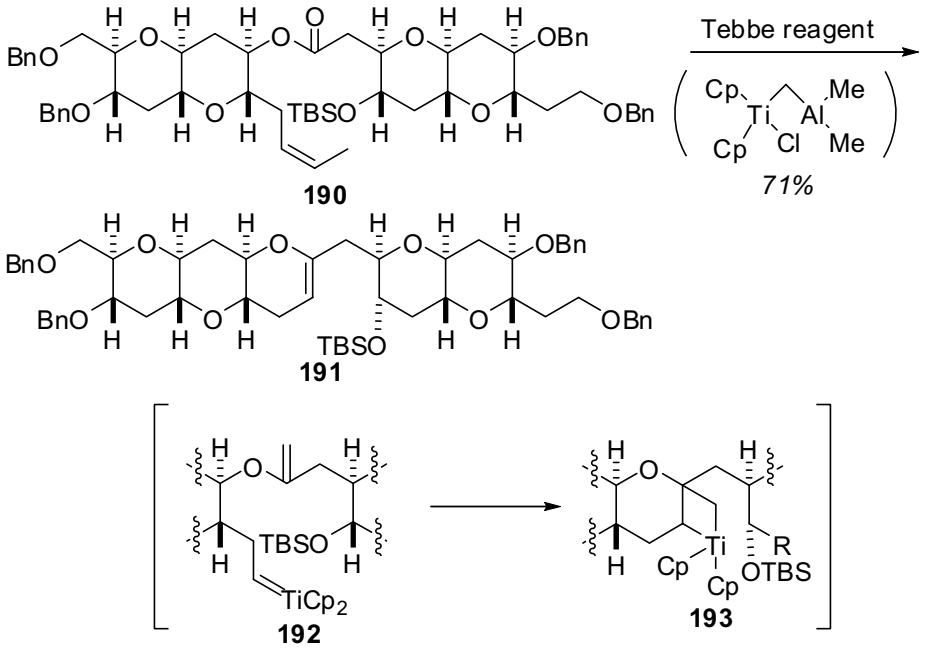


Scheme 3.1.4. Yamamoto's vinylstannane/triflate coupling

3.1.1.3. Esterification/ring-closing metathesis strategies

3.1.1.3.1. Nicolaou's titanium-mediated approach

In 1996 Nicolaou reported formation of an endocyclic enol ether using a titanium mediated ring-closing metathesis reaction.[125] Coupling of two complex ring fragments was accomplished through an esterification reaction of a carboxylic acid and an alcohol to give the intermediate ester **190** (Scheme 3.1.5). Subjection of this compound to the Tebbe reagent[126] led to the desired endocyclic enol ether **191** in 71% yield. This reaction sequence is believed to proceed through initial formation of the exo-methylene enol ether **192** followed by formation of the titanium alkylidene with a second equivalent of the Tebbe reagent. Ring-



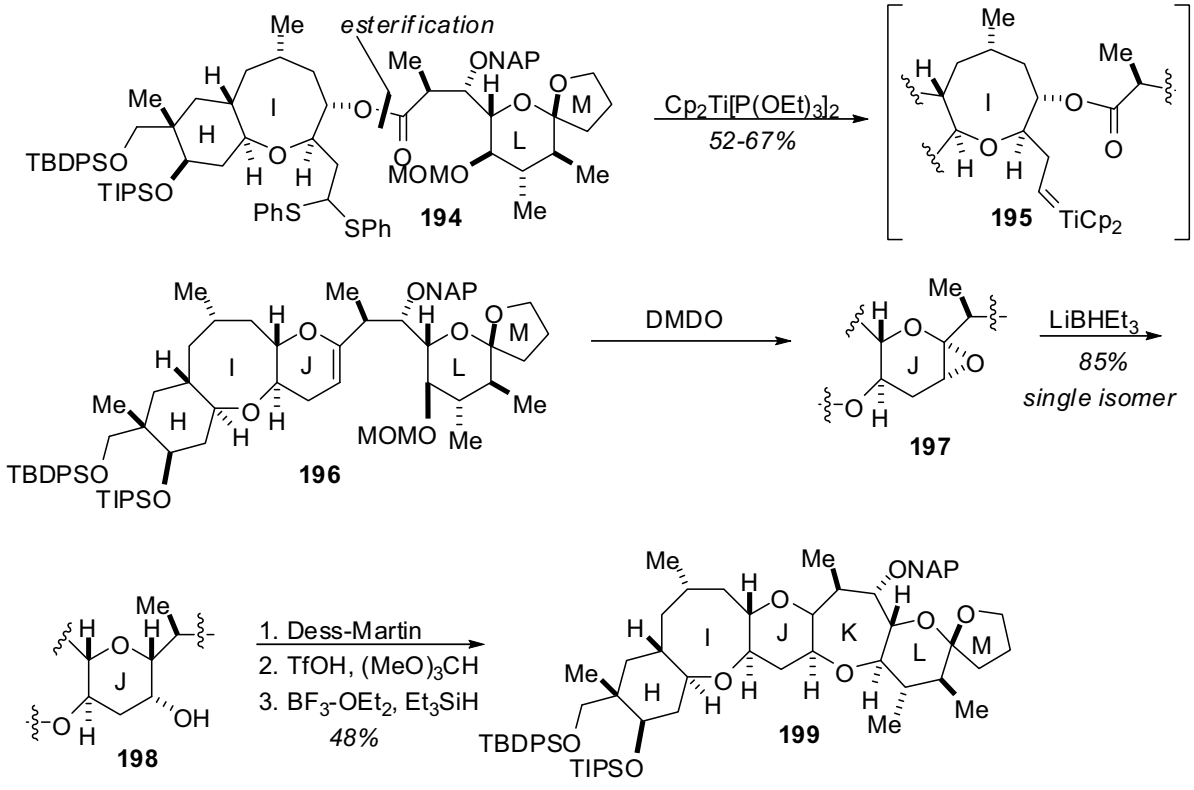
Scheme 3.1.5. Nicolaou's titanium-mediated formation of endocyclic enol ethers

closing metathesis via the intermediate titanocyclobutane **193** then produces the cyclic enol ether. In a manner similar to Sasaki's approach, conversion to the fused hexacyclic array was accomplished by a four step sequence involving hydroboration, oxidation of the resulting alcohol to the ketone, protecting group removal, and reductive etherification. Application of this strategy toward the synthesis of several ring fragments of maitotoxin has been reported.[127]

3.1.1.3.2. Hirama's direct carbonyl olefination approach

As an alternative to the powerful [X+2+X] coupling strategy offered by Nicolaou, Hirama and coworkers developed a ring-closing metathesis approach based on a direct carbonyl olefination using bis(phenylthio)acetal precursors.[112] This approach was applied directly toward the synthesis of ciguatoxin CTX3C after failing to obtain the cyclic enol ether using the Tebbe reagent. Coupling of two fragments under Yamaguchi esterification conditions led to the ester **194** in excellent yield (Scheme 3.1.6). Subjection of this compound to

$Cp_2Ti[POEt)_3]_2$ led to the desired enol ether **196** in moderate yield. Formation of the titanium alkylidene **195** is thought to precede insertion into the carbonyl moiety to generate an intermediate oxatitanacyclobutane (analogous to titanacyclobutane **193** in Scheme 3.1.5). In contrast to the hydroborative oxidations discussed previously, Hirama opted for an alternative method in an effort to improve the diastereoselectivity over the traditional hydroboration approach.[128] Oxidation of the enol ether using dimethyldioxirane (DMDO) led to the intermediate epoxide **197** as a single stereoisomer. Stereoselective reductive opening of the epoxide was explored using a variety of reducing agents. Ultimately, use of $LiBHEt_3$ (superhydride®) led to exclusive formation of the alcohol **198** with the desired configuration in excellent yield. Completion of the fused pentacyclic portion **199** was accomplished via oxidation of the alcohol to the ketone using Dess-Martin's reagent[111] followed by acid catalyzed cyclization to the seven-membered mixed methyl ketal. Reductive etherification of

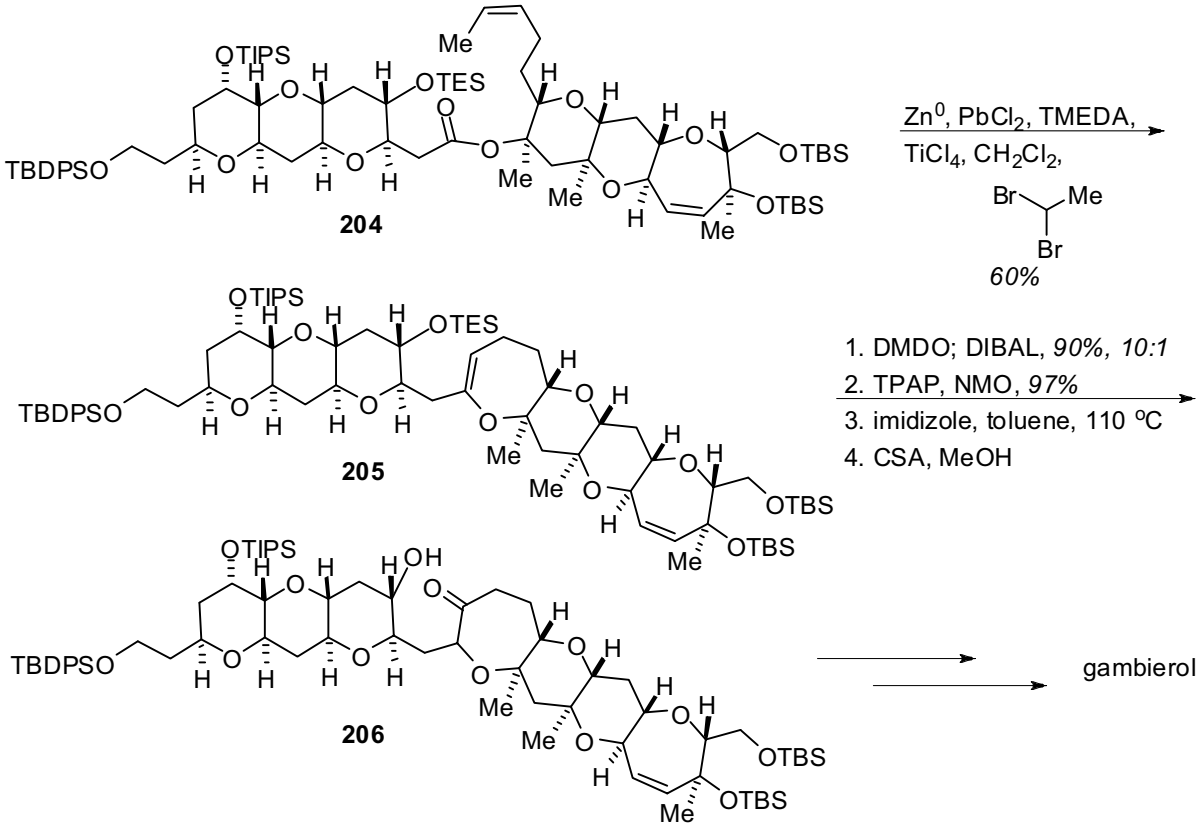


Scheme 3.1.6. Hirama's synthesis of the HIJKLM fragment of Ciguatoxin CTX3C

the ketal was readily accomplished upon exposure to BF_3•OEt_2 and triethylsilane.

3.1.1.3.3. Rainier's olefination/RCM approach to Gambierol

Rainier and coworkers developed a similar approach to those discussed above that was recently disclosed in their elegant synthesis of gambierol.[71] Again, a Yamaguchi esterification reaction was used to couple two complex fragments to obtain the ester **204** (Scheme 3.1.8). Initial explorations to generate the cyclic enol ether directly from the ester using the Takai-Utimoto reagent failed to give the desired product. Ultimately, the researchers discovered the use of 1,1-dibromoethane instead of 1,1-dibromomethane enabled the direct generation of the enol ether **205** in moderate yield. Epoxidation in a manner similar to Hirama (see Scheme 3.1.6) using DMDO was followed by reduction using *i*-Bu_2AlH to give the alcohol as a 10:1 mixture. Oxidation to the ketone and removal of the

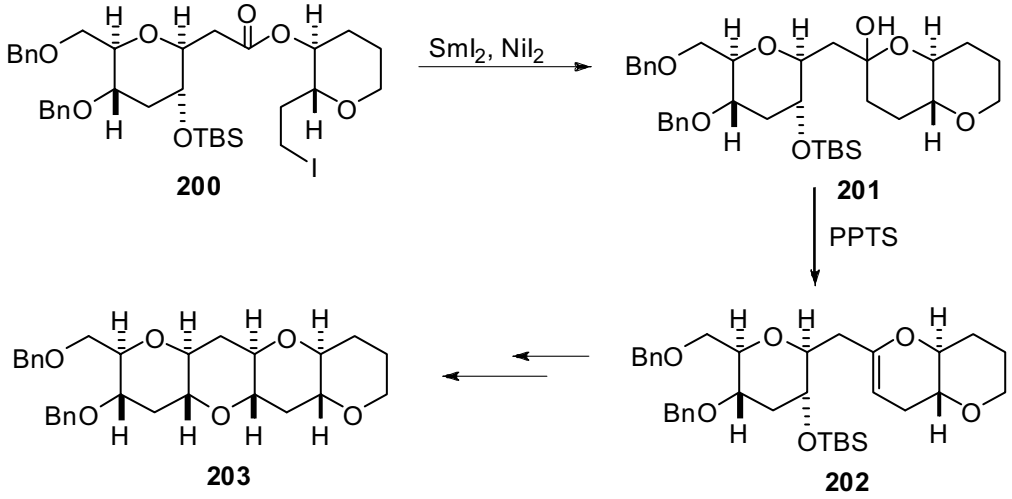


Scheme 3.1.8. Rainier's approach toward gambierol

protecting groups gave the keto-alcohol **206** that was ultimately carried forward to the natural product using a mixed thioketal cyclization protocol (see Scheme 3.1.3).

3.1.1.4. Esterification/SmI_2 promoted cyclization

Nakata and coworkers developed a unique [X+2+X] approach toward the generation of an intermediate enol ether via a samarium iodide cyclization of an alkyl iodide.[129] Again, an esterification reaction was used to couple two cyclic ether fragments to give the intermediate ester **200** (Scheme 3.1.7). Samarium iodide promoted nucleophilic attack of the alkyl iodide on the carbonyl group generated the cyclic hemiketal **201**. Addition of pyridinium *p*-toluenesulfonate (PPTS) promoted the endocyclic dehydration of the hemiacetal to the desired enol ether **202**. Application of the standard hydroboration, oxidation, and reductive etherification sequence then completed the tetracyclic fragment **203**.

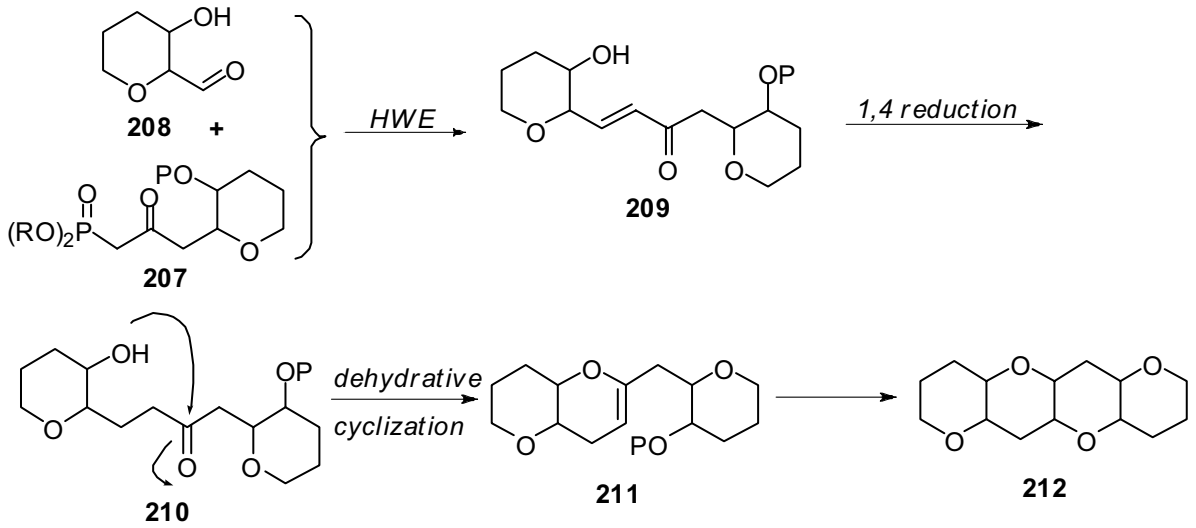


Scheme 3.1.7. Nakata's SmI_2 cyclization approach

3.2 A NOVEL CONVERGENT COUPLING STRATEGY BASED ON A HORNER-WADSWORTH EMMONS / CYCLODEHYDRATION SEQUENCE: STEREOSELECTIVE SYNTHESIS OF THE BCDE FRAGMENT OF BREVETOXIN A

In the ongoing studies aimed toward the synthesis of brevetoxin A, a novel [X+2+X] coupling strategy was envisioned that would likewise target an intermediate endocyclic enol ether upon joining two complex ring fragments. Several goals for a successful coupling strategy were addressed when considering the approach. First and foremost, a highly efficient coupling of two complex ring systems was needed that could occur under mild reaction conditions employing stable reactants and reagents. Second, conversion to the enol ether needed to be likewise highly efficient and require minimal synthetic operations. Third, the coupling strategy needed to be highly versatile to enable applications to not only the BCDE fragment, but to other polyether fragments as well.

The general reaction sequence for the coupling approach is illustrated in Scheme 3.2.1. To address the first concern, the key fragment coupling event would rely on the mild, versatile, and highly efficient Horner-Wadsworth-Emmons (HWE) reaction between one cyclic ether functionalized as the β-ketophosphonate (**207**) and the other as an aldehyde



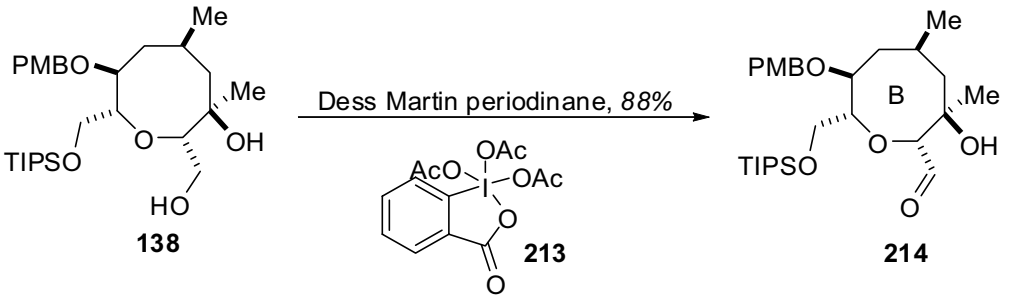
Scheme 3.2.1. Novel convergent coupling stratgey

(**208**).[130] HWE reactions have been extensively demonstrated in complex systems leading to coupled products with high efficiency under very mild conditions.[130-133] Furthermore, excellent selectivity for the *E*-olefin geometry and the opportunity for effective coupling using a 1:1 stoichiometry of coupling partners were very attractive attributes for the development of this convergent coupling strategy.

Conjugate reduction of the enone (**209**) to the saturated ketone (**210**) would then permit an acid-catalyzed *endo*-dehydration to deliver the desired cyclic enol ether intermediate (**211**), presumably via an intermediate hemiketal. The plethora of methods to effect conjugate reductions of enones[134] was highly attractive to this sequence and ensured high substrate versatility. Furthermore, cyclodehydrations of δ-hydroxy ketones were well known and could likewise occur under a variety of reaction conditions.[135-137] Conversion of the enol ether intermediate into a tetracyclic fragment (**212**) would be accomplished following the extensive literature precedent discussed earlier in this Chapter.

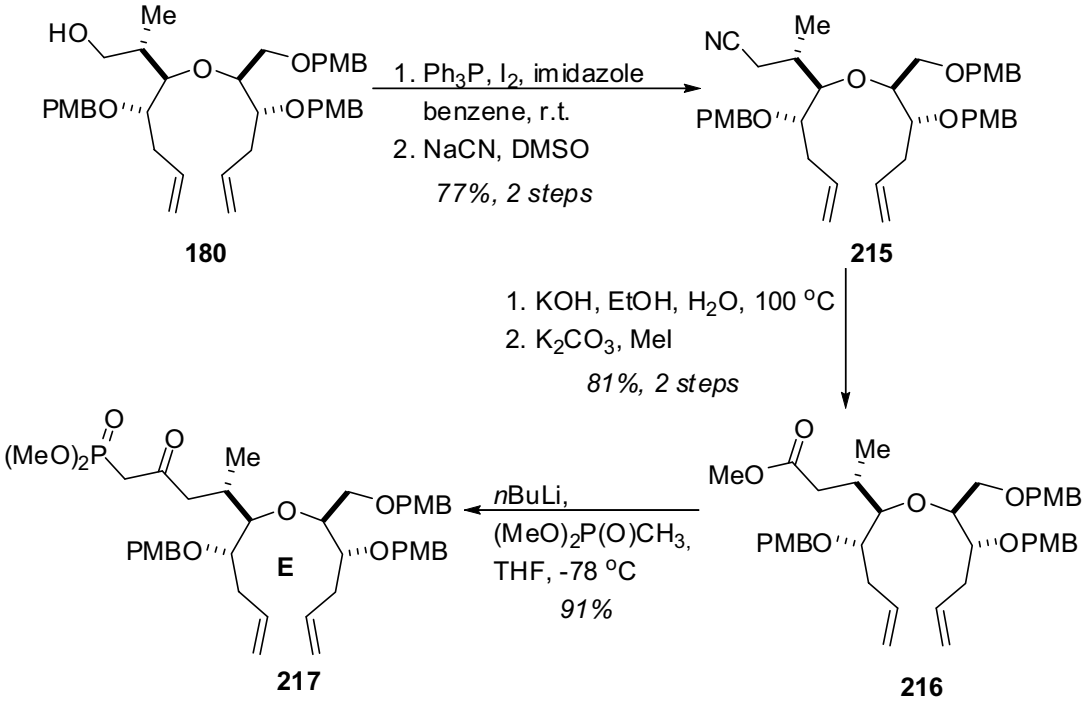
3.2.1 Preparation of the B and E ring fragments

In order to examine the planned coupling strategy, the required components needed to be synthesized from the previously completed B and E ring units (Chapter 2). Theoretically, formation of either the C or D ring cyclic enol ether could have been possible simply by altering the B and E ring coupling partners. Based on the suspected ease of the cyclodehydration event occurring to form a six-membered cyclic ether, however, formation of the C ring dihydropyran became the initial coupling approach. Thus, elaboration of the B ring intermediate **138** to the requisite aldehyde **214** was accomplished upon oxidation of the primary alcohol. Several conditions were examined, including Swern oxidation,[108] TPAP/NMO,[138] and CrO_3-pyridine.[139] Ultimately, the use of the hypervalent iodide oxidant, Dess-Martin periodinane (**213**),[111] gave the aldehyde **214** in the best yield (80-88%) with minimal decomposition (Scheme 3.2.2).



Scheme 3.2.2. Oxidation of the B ring diol

Formation of the required E ring phosphonate began with the homologation of the side chain of alcohol **180** by the initial conversion to the alkyl iodide using triphenylphosphine and iodine (Scheme 3.2.3). S_N2 displacement using sodium cyanide then generated the intermediate nitrile **215** in good yield. Nitrile hydrolysis required rather forcing conditions using potassium hydroxide at elevated temperature to give the desired carboxylic acid after several days. Alternative methods via partial reduction of the nitrile to the aldehyde using *i*-Bu_2AlH followed by oxidation to the carboxylic acid using sodium chlorite were faster but gave a lower yield. The acid was converted into the methyl ester **216** in preparation for the

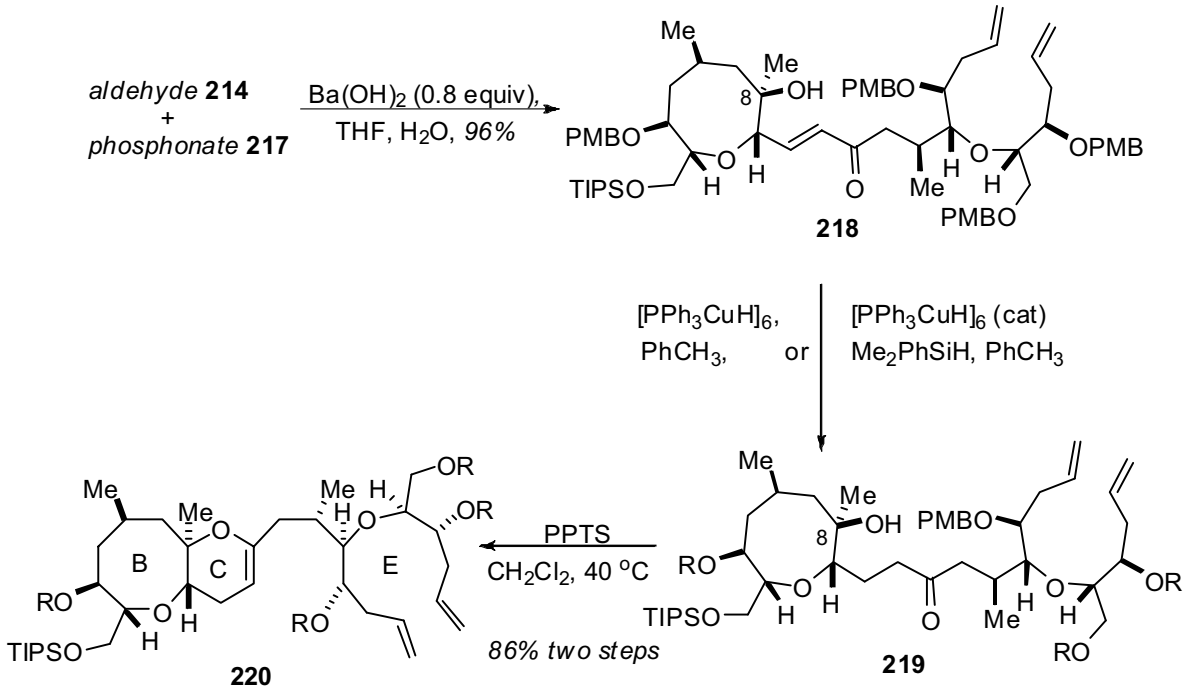


Scheme 3.2.3. Formation of the E fragment phosphonate

addition of lithiated dimethyl methyl phosphonate to yield the desired β-keto phosphonate **217** in excellent overall yield. The later sequence offered a rather efficient method for the preparation of the required E ring fragment and was readily amenable to large scale reactions.

3.2.2 Coupling and formation of the C ring enol ether

The Horner-Wadsworth-Emmons coupling between the two fragments **214** and **217** began using the mild, aqueous conditions employing barium hydroxide initially developed by Ibarra[140] and later explored with complex substrates by Paterson.[131] Thus, subjection of one equivalent of the phosphonate **217** to sub-stoichiometric $Ba(OH)_2$ followed by the addition of one equivalent of the aldehyde **214** cleanly provided enone **218** in high yield (typically >95%) with no detectable epimerization of the γ-center or evidence of the *Z*-isomer (Scheme 3.2.4). Use of these conditions fulfilled the first of the fundamental requirements for the convergent coupling strategy; mild reaction conditions using stable reactants and reagents,



Scheme 3.2.4. Formation of the BCE endocyclic enol ether

functional group tolerance, and high, reproducible yields.

The next stage of the coupling strategy required a selective conjugate reduction of the enone. A number of reagents were examined, including nickel boride[141] and DIBAL/HMPA. Unfortunately, these conditions gave no evidence for the 1,4-reduction product. Copper hydride reagents have been extensively studied as selective reagents for 1,4-reductions.[142] In particular, the hexameric triphenylphosphine copper hydride cluster ($[PPh_3CuH]_6$) commonly known as Stryker's reagent[143] has been effectively used as a mild reductant for α,β-unsaturated enones that gives very high selectivity for 1,4-reduction. In the present system, the use of stoichiometric amounts of Stryker's reagent gave the saturated ketone **219** in excellent yield (Scheme 3.2.4). No evidence of 1,2-reduction was observed. An alternative reduction protocol developed by Lipshutz[144] using a catalytic amount of Stryker's reagent and stoichiometric amounts of dimethylphenylsilane as a co-reductant was later found to provide the desired ketone with minimal loss in reaction yields. This method enabled the use of less of the air-sensitive Stryker's reagent and also resulted in easier purification of the ketone intermediate.

Most gratifyingly, ketone **219** was highly acid sensitive and readily cyclized to the desired cyclic enol ether upon treatment with a mild acid source ($CDCl_3$, PPTS, *p*-TsOH). In practice, subjection of the ketone to a catalytic amount of PPTS in CH_2Cl_2 at 40 °C for 30 minutes (heating was required to drive the reaction to completion) the endocyclic enol ether **220** was produced in excellent yield as a single regioisomer. Though no evidence of an intermediate hemiketal could be secured, addition of the C8 tertiary hydroxyl to the ketone is presumably followed by an *endo*-selective dehydration of the resulting hemiketal to give the desired product.

The sequence described above to form the cyclic enol ether **220** in three synthetic operations from the intermediate B and E fragments required minimal exploration in the laboratory and adequately demonstrated the power of the newly developed coupling

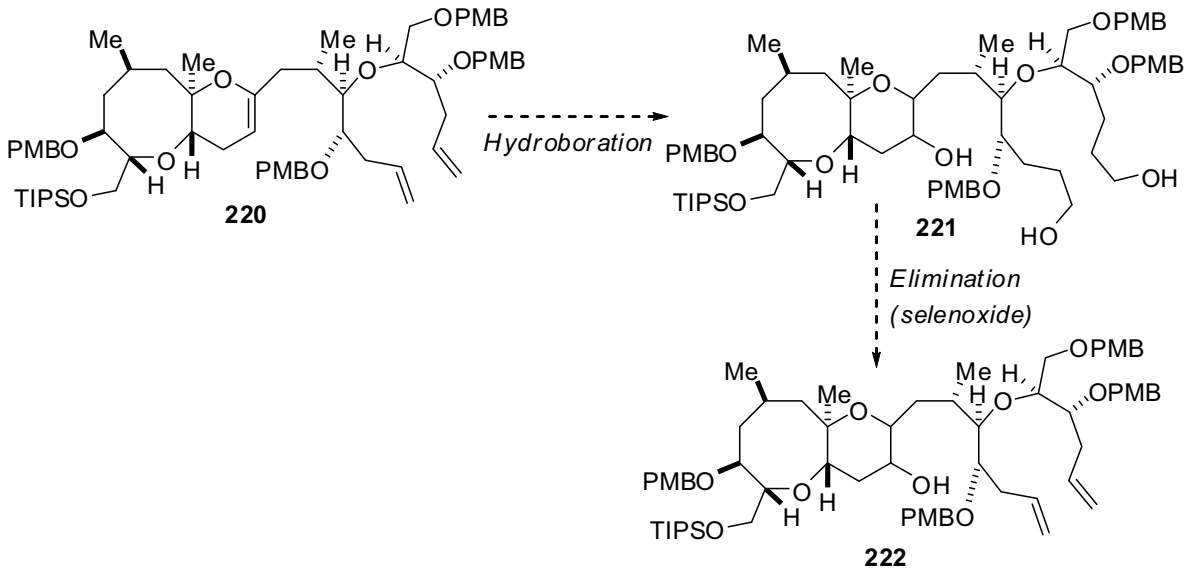
strategy. Large quantities of the enol ether could be routinely prepared, not only with the substrate illustrated in Scheme 3.2.4, but with all substrates examined during the course of this project.

3.2.3 Oxidation to the BCE ketone

In contrast to the facile preparation of the cyclic enol ether, the subsequent oxidation of the C ring enol ether **220** to a suitable precursor for D ring cyclization was highly problematic. It was anticipated during the planning stages of the synthesis that selective hydroboration of the enol ether in the presence of the E ring olefin(s) would be challenging. It was hoped that the more electron rich enol ether would undergo hydroboration at a faster rate, however competing steric factors favoring the more accessible E ring olefins were considered. In the event, attempts at obtaining the selective hydroboration reaction using a variety of reagents (9-BBN, BH_3-THF, catechol borane/$(PPh_3)_3RhCl$[145]) were unsuccessful, leading to complex product mixtures that lacked the characteristic vinyl protons (by NMR analysis).

It should be noted that one reason the E ring system was carried forward as the diene (as opposed to the closed oxonene) was to improve the hydroboration selectivity by decreasing the electron density of the olefins. Additionally, one potential solution to the hydroboration problem, as illustrated in Scheme 3.2.5, involved the non-selective hydroboration of all three olefins to deliver the triol **221**. Selective elimination of the two primary alcohols, possibly using the selenoxide elimination protocol developed by Grieco,[146] would then reform the E ring terminal olefins to generate the desired alcohol **222**.

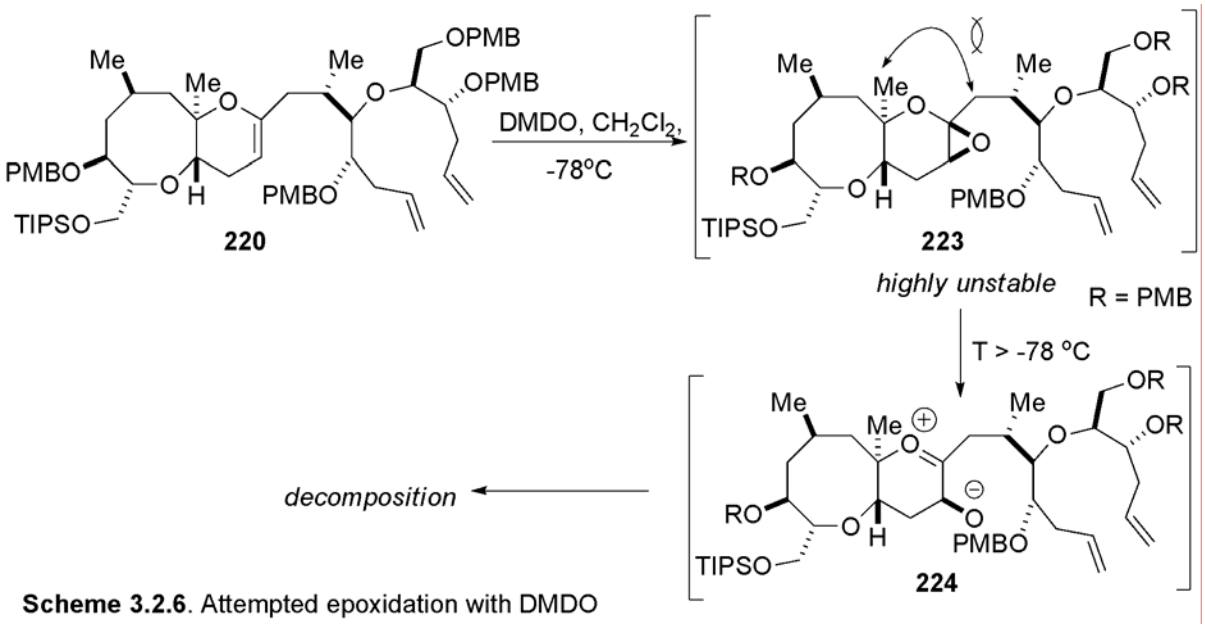
Before the hydroboration approach was explored further, an alternative chemoselective oxidation of the enol ether using freshly prepared solutions of dimethyldioxirane (DMDO)[147] was attempted. Several research groups studying polycyclic ether synthesis have been successful performing epoxidations of intermediate endocyclic enol ethers to generate the



Scheme 3.2.5. Potential solution to hydroboration problem

transient epoxy enol ethers.[112,128,148,149] Regioselective opening of the epoxide with a nucleophile (i.e. Me^-, H^-) then generates the desired alcohol (see example in Scheme 3.1.6).

The addition of DMDO to enol ether **220** at –78 °C immediately consumed the starting material, however, attempted detection or isolation of the glycal epoxide **223** was not possible. Thin layer chromatography and NMR analysis of the crude epoxidation reaction revealed multiple products, none of which could be reasonably assigned as the desired product. This observation was quite unexpected as most glycal epoxides seem to exhibit sufficient stability to enable removal of the acetone prior to the addition of a nucleophile.[112,150,151] It is suspected that the unusually sensitive nature of the epoxy enol ether **223** is due to the presence of a 1,3-diaxial steric interaction between the axially oriented methyl group and alkyl chain tethering the E ring system (Scheme 3.2.6). This destabilizing interaction may favor the highly reactive oxocarbenium ion **224** that could decompose via a number of pathways, including a 1,2-alkyl or hydride shifts or addition of an external nucleophile (H_2O or acetone present in the DMDO solutions). However, it was

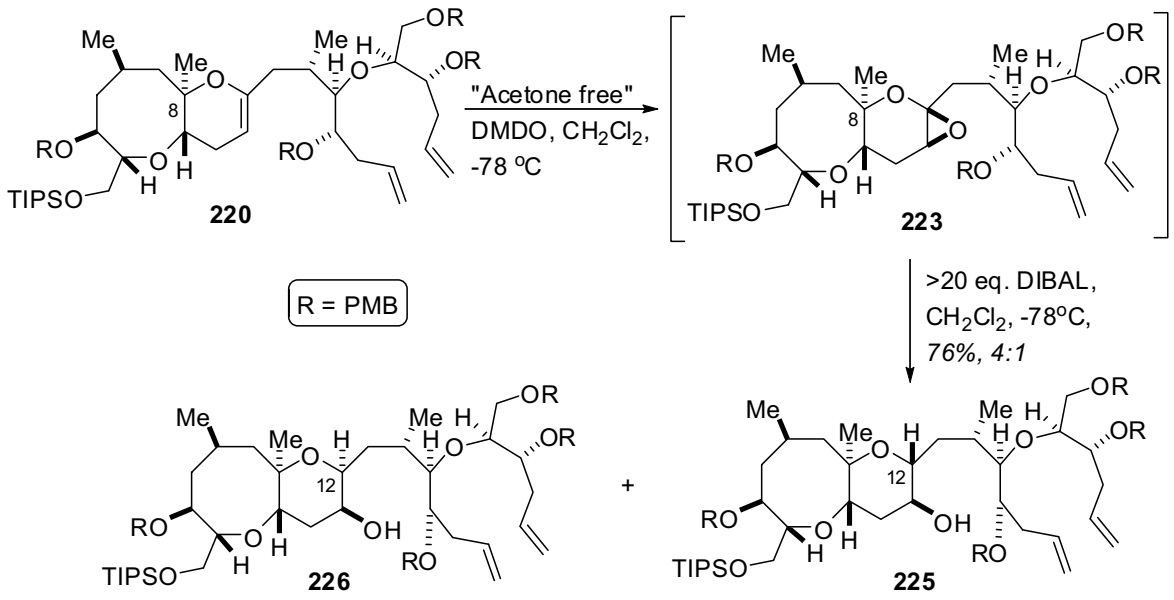


Scheme 3.2.6. Attempted epoxidation with DMDO

noted that all decomposition products that were isolated appeared to contain the E ring olefins (NMR analysis), suggesting a selective oxidation of the enol ether was occurring.

Based on the observed sensitivity of the epoxy enol ether, isolation and subsequent addition of a nucleophile was not a viable option. In searching for alternatives to this problem, it was suspected that an in situ reductive opening of the epoxide at low temperature may permit generation of the desired alcohol prior to decomposition. DMDO solutions, however, are prepared in acetone and would thus prevent such an in situ reduction protocol. Fortunately, DMDO solutions that contained concentrations of acetone that were lower than the concentration of DMDO itself had been reported and could be prepared using simple extraction techniques.[152,153] The initial acetone/water DMDO solutions were first extracted into chlorinated solvents (CH_2Cl_2) and subsequently washed using pH = 7 buffer solution to generate the “acetone free” DMDO solutions.

Application of this modified reagent in the present system again led to complete consumption of the enol ether **220** at low temperature (judged by TLC analysis) (Scheme 3.2.7). Immediate addition of a 1 M solution of diisobutylaluminum hydride (*i*-Bu_2AlH)[71] led to the isolation of two major products identified as the desired alcohols **225** and **226** in an

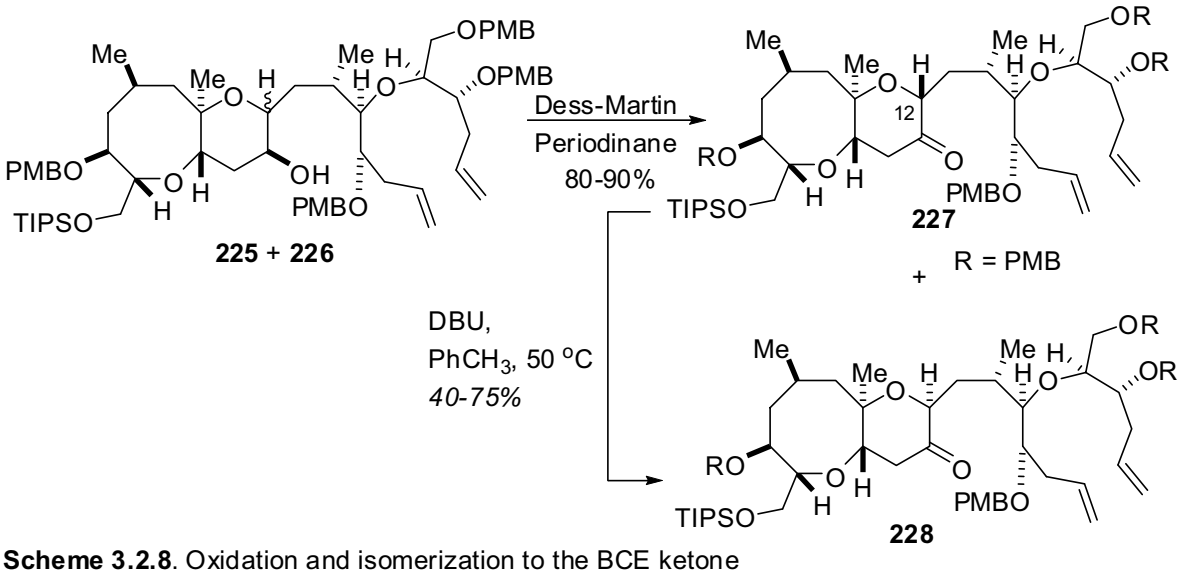


Scheme 3.2.7. Oxidation/reduction of the enol ether

approximate 4:1 ratio that were later determined to be epimeric at C12. Minor products believed to be alcohol diastereomers were also present in the reaction mixture and were carried through to the next step. Assignment of the configuration of the two major products was made upon analysis of the steric environment surrounding the enol ether. Specifically, the axial methyl group at C8 was expected to hinder oxidation from the bottom face of the enol ether. Furthermore, assuming hydride delivery from the same face as the oxidation, it was suspected that the major diastereomer **225** possessed the undesired configuration at C12.

While this protocol did offer a workable solution to the problem of the enol ether epoxidation, yields were irreproducible and significant decomposition products were often observed. Furthermore, a large excess of *i*-Bu_2AlH (>20 equivalents) was required to obtain the desired products. It was later discovered that these results were directly related to the quantity of acetone present in the DMDO solutions (see Chapter 4). Nonetheless, sufficient quantities of the desired alcohol intermediates could be secured to explore the remaining steps to complete the fused tetracycle.

Oxidation of the resultant alcohols using Dess-Martin periodinane (**213**)[111] gave the two ketones **227** and **228** that were epimeric at the α-stereocenter (C12), again presuming the undesired C12 configuration for the major compound **227** based on steric considerations (Scheme 3.2.8). Following extensive literature precedent, isomerization of the undesired C12 isomer to the desired compound **228** was effected with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[112,128,154] Despite repeated attempts to optimize the reaction conditions, the mass recovery for this transformation was often poor and results varied widely. Nevertheless, complete isomerization to the desired configuration could be achieved with an average recovery of 50% of the initial material. A variety of other bases, such as K_2CO_3/MeOH,

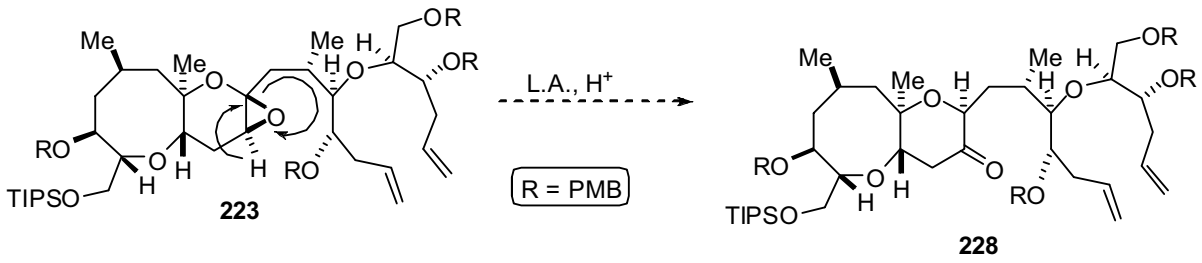


Scheme 3.2.8. Oxidation and isomerization to the BCE ketone

imidazole, and NaOMe were also examined and found to be inferior to DBU.

An intriguing reaction pathway that would circumvent the problematic in situ reduction and subsequent isomerization of the undesired C12 isomer was envisioned based on a 1,2-hydride shift of the intermediate epoxy enol ether **223** to deliver the ketone **228** directly in a stereospecific manner (Scheme 3.2.9). These reactions are known to occur in simple substrates[155] and have been attempted in complex polyether synthesis.[128] However, upon

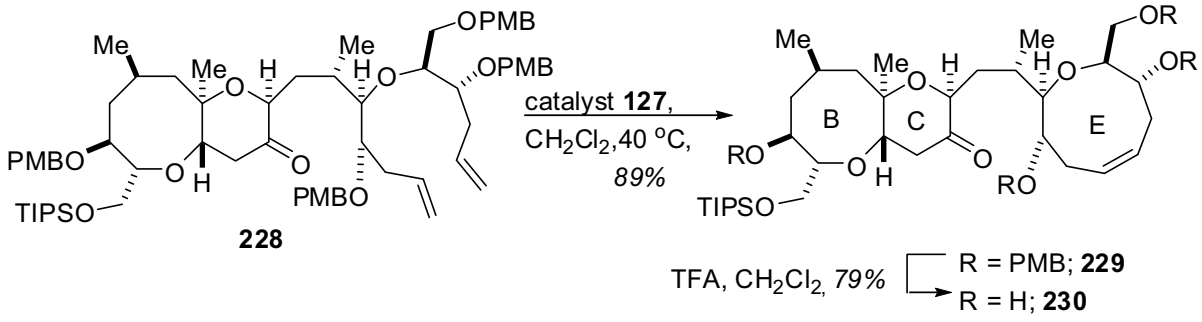
attempting an in situ hydride shift following the epoxidation using a variety of Lewis acids or protic acids, only decomposition products were observed that did not correlate to the desired ketone **228**.



Scheme 3.2.9. Attempted 1,2-hydride shift of epoxy enol ether

3.2.4 Completion of the BCDE fragment

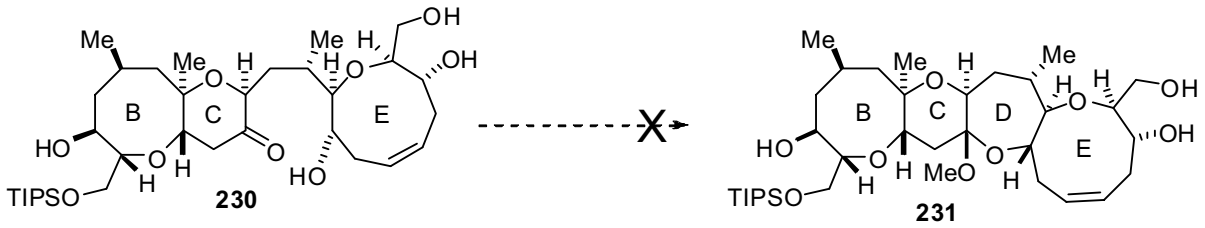
Olefin metathesis of the diene unit **228** using the Grubbs first generation catalyst (**127**)[98] cleanly closed the nine-membered E ring in excellent yield to give the intermediate ketone **229** (Scheme 3.2.10). Subsequent deprotection of all four PMB groups was examined in order to provide the keto-alcohol **230** necessary for cyclization of the final ring (D ring). Standard conditions employing 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) led to a complex mixture of products that was troublesome to purify. An alternative, acidic, cleavage protocol employing trifluoroacetic acid (TFA) in anhydrous CH_2Cl_2[156] led to the removal of all four PMB groups to give the tetraol. A small amount of deprotection of the primary silyl ether was also suspected, but this material could not be isolated, presumably due to the



Scheme 3.2.10. RCM and deprotection

hydrophilic nature of the fully deprotected intermediate.

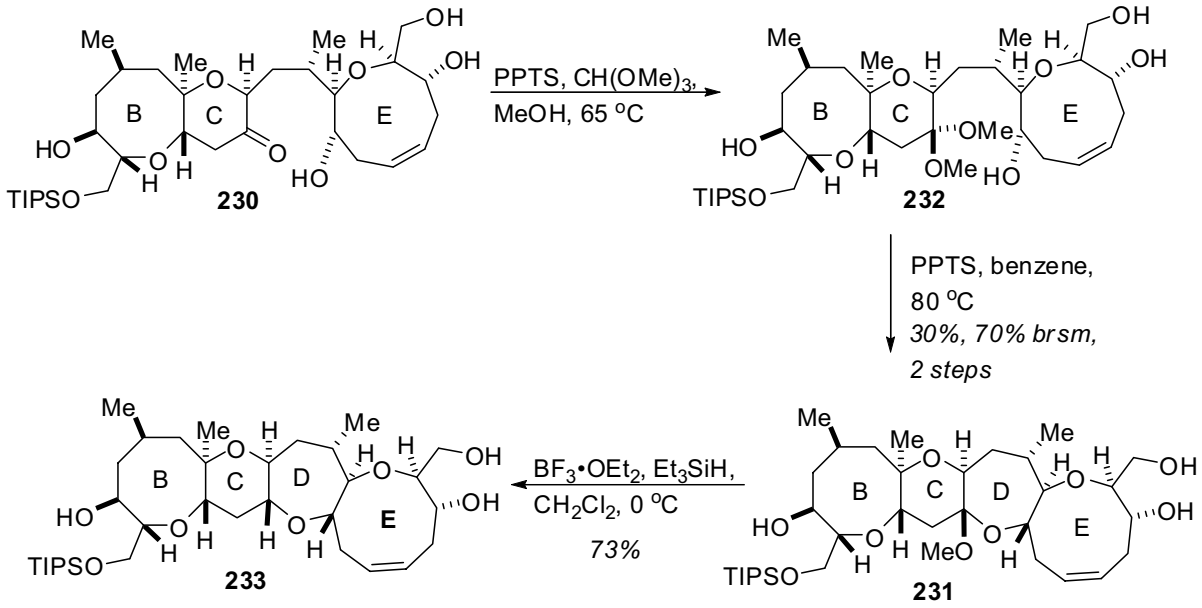
A major challenge facing the remaining synthetic operations was the closure of the seven-membered cyclic ether (D ring). Cyclization reactions of seven-membered rings are known to be unfavorable reactions due to a significant entropic penalty.[92] However, it was believed that the rigid scaffold created by the C and E ring cyclic ethers present in ketone **230** would aid in the cyclization due to an effective reduction of the available degrees of freedom . Several conditions were employed with the intention of forming the BCDE mixed methyl ketal **231** directly from the keto-alcohol **230** (Scheme 3.2.11). Following literature precedent,[128] use of trimethyl orthoformate ($(MeO)_3CH$) and an acid catalyst led only to protection of the 1,3-diol as the cyclic orthoester without concomitant formation of the cyclic ketal. Various acid sources (TFA, CSA, PPTS, etc.) in methanol also did not generate any of the desired cyclization product. Deprotection of the remaining alcohol via loss of the TIPS group under these acidic conditions was problematic using stronger acids.



Scheme 3.2.11. Attempted direct formation of the BCDE fragment

It was noted during the previous studies that formation of the dimethyl ketal from ketone **230** was occurring under certain reaction conditions. Therefore, a more indirect approach toward cyclization was envisioned that would target this dimethyl ketal as an isolable intermediate. It was anticipated that this two step procedure would favor the intramolecular reaction pathway by removal of the external nucleophile (methanol). In practice, initial formation of the dimethyl ketal **232** was accomplished using pyridinium *p*-toluenesulfonate (PPTS) and small amounts of trimethylorthoformate in methanol at reflux temperature

(Scheme 3.2.12). Upon workup and evaporation of the solvents, the crude material was dissolved in benzene and heated to reflux temperature in the presence of catalytic PPTS. Formation of the desired mixed methyl ketal **231** was observed (~30%) along with significant amounts of the ketone **230** (presumably from the addition of trace amounts of water to the oxocarbenium ion). Recovery of the ketone and re-subjection to the cyclization conditions was possible. Reduction of the mixed methyl ketal proceeded smoothly using BF_3•OEt and Et_3SiH to give the completed BCDE ring fragment **233** as a single diastereomer in good yield.

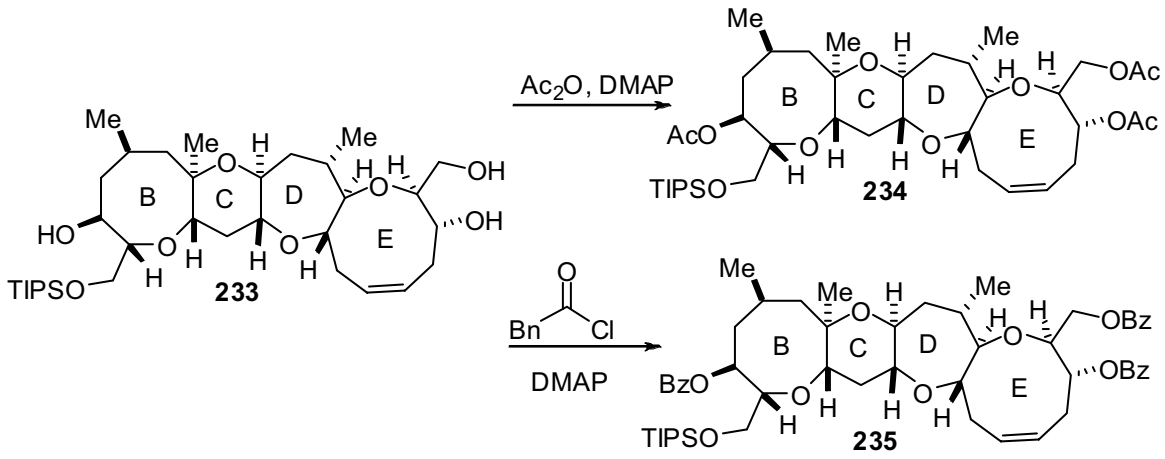


Scheme 3.2.12. Formation of the BCDE fragment

3.2.5 Stereochemical analysis using 2-D NMR

The semi-rigid scaffold that is characteristic of polycyclic ether fragments enables facile confirmation of the stereochemical arrangement based on observation of the through space interactions of nearby protons. These nuclear Overhauser effects (nOe's) have been instrumental in the structural confirmation and elucidation for many polyether

molecules.[157,158] In the present case, two-dimensional NMR analysis on the completed BCDE fragment **233** was not possible based on the multiple overlapping signals in the upfield region of interest. Protection of the triol as the tri-acetate derivative **234** did provide a well-resolved spectrum for 2D analysis (Scheme 3.2.13). In addition, the tri-benzoate derivative **235** was also targeted to gain additional NMR data to support the proposed structure of the BCDE fragment.



Scheme 3.2.13. Formation of the triacetate and tribenzoate derivatives

The combined 2D analysis on the protected derivatives showed several key interactions that strongly support the assigned configuration as shown. Illustrated in Figure 3.2.1 are the through space interactions that were detectable. Clearly, the relative configuration of the majority of the stereogenic centers are well defined based on this analysis.

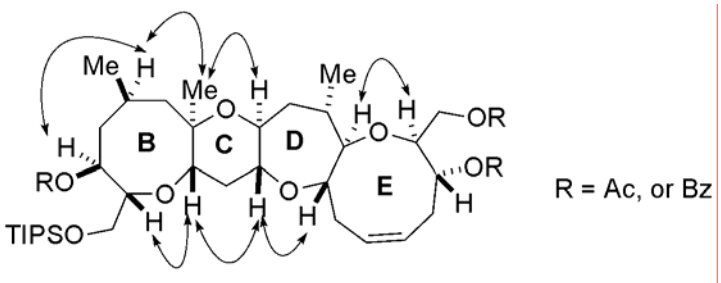


Figure 3.2.1. Key nOe interactions

3.3 SUMMARY

To summarize, the BCDE fragment was completed in only ten steps from the individual B and E ring systems using a novel convergent coupling strategy to rapidly access an endocyclic enol ether.[159] The crucial union of the two fragments was accomplished using a Horner-Wadsworth-Emmons reaction between a β-keto phosphonate and an aldehyde to deliver an intermediate enone. A subsequent 1,4-conjugate reduction and facile cyclodehydration of the intermediate δ-keto-alcohol generated the desired cyclic enol ether in a highly efficient manner. Elaboration of the enol ether was accomplished using a modified epoxidation/reduction protocol, followed by standard transformations to yield the completed BCDE tetracycle. This strategy has also been successfully applied by a fellow member of the Crimmins group to the completed synthesis of the GHIJ ring fragment of brevetoxin A,[160] providing an illustration of the versatility of this synthetic approach.

CHAPTER 4: REVISED SYNTHESIS OF THE BCDE FRAGMENT OF BREVETOXIN A

4.1 PROPOSED HOMOLOGATION OF THE BCDE FRAGMENT

The previous synthesis of the BCDE fragment **233** of brevetoxin A utilized two *anti* glycolate aldol additions[103] to set four stereogenic centers and rapidly construct the B and E ring fragments.[159] Use of this methodology, however, had a significant drawback when considering the completion of the synthesis of the natural compound. Upon reductive removal of the chiral auxiliary following aldol addition, the B and E carbon side chains were created, each containing a hydroxymethylene terminus (see Figure 4.1.1). However, when considering subsequent transformations toward the completed synthesis, formation of the A ring lactone **236** would necessitate a two carbon side chain. Likewise, the E ring side chain was envisioned to be ultimately transformed into the phosphine oxide in preparation for coupling to the G ring, again necessitating a two carbon chain.

It was originally anticipated that a late stage homologation of both of the side chains of

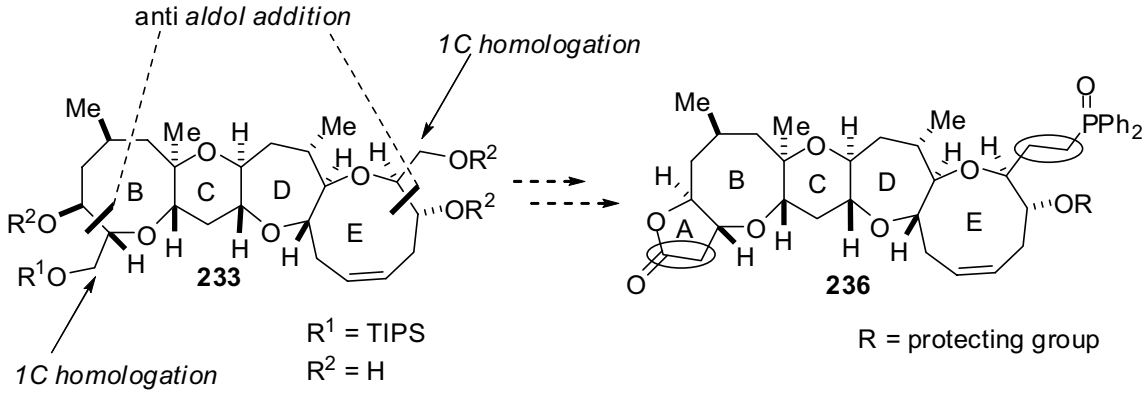
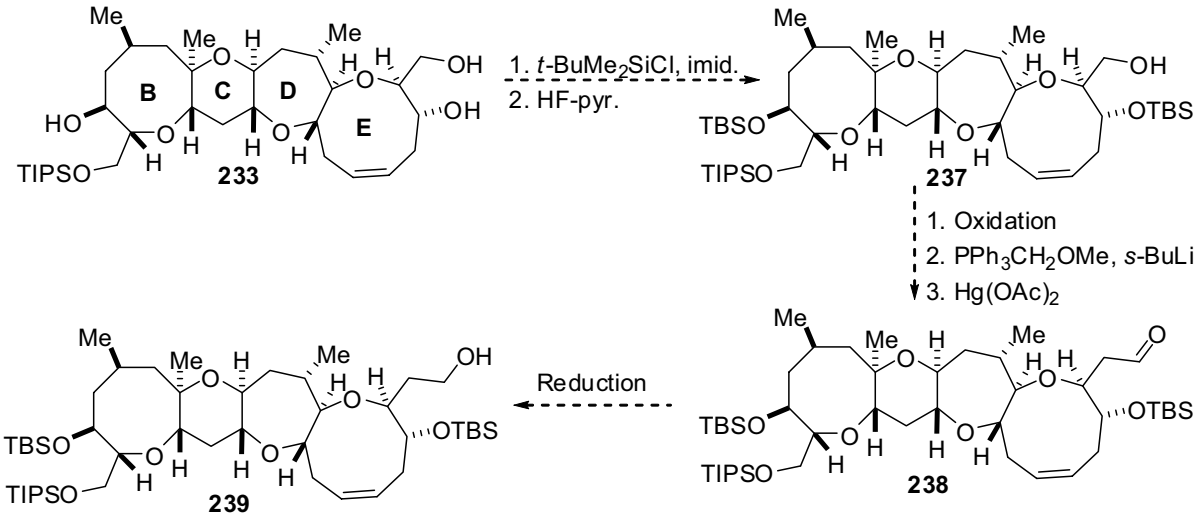


Figure 4.1.1. One carbon deficiency in the BCDE fragment

the BCDE fragment **233** could be employed. For example, upon protecting group manipulations to generate alcohol **237**, conversion to the aldehyde and subsequent methoxymethylene Wittig reaction should give the homologated aldehyde **238** upon treatment with mercuric (II) acetate (Scheme 4.1.1).[27] Reduction of the aldehyde would then deliver the homologated BCDE fragment **239** needed for formation of the phosphine oxide to couple with the GHIJ ring system (see retrosynthetic analysis; Scheme 2.1.2). A similar sequence of events could also be used to homologate the B ring side chain to ultimately form the A lactone.



Scheme 4.1.1. Strategy for chain homologation

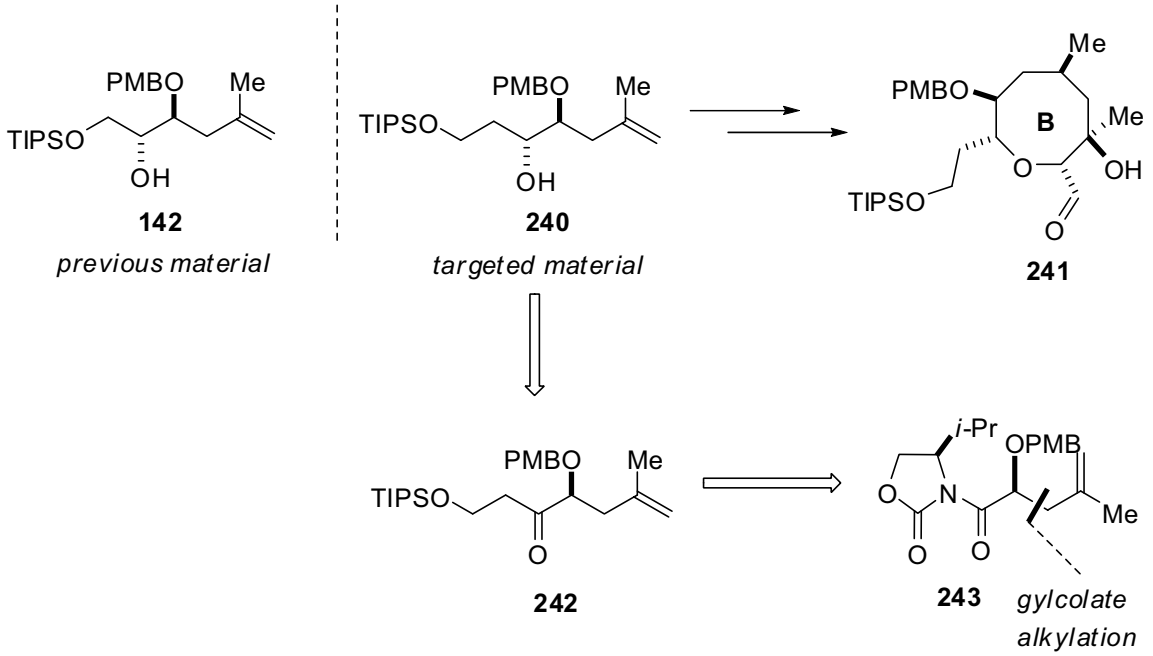
4.2 REVISION TO THE BCDE FRAGMENT

While the above strategy for a one carbon homologation seemed viable, the number of late stage synthetic manipulations needed to provide the required fragment would be problematic for high material throughput. Thus, a revision to the synthetic strategy seemed appropriate. Central to the planning for the revised synthesis was the early incorporation of the homologated side chains, yet keeping the synthetic sequence closely related to the previously successful approach. In addition, the scalability and efficiency of the new

synthetic route was a critical component to the planned revision. Significant quantities of both the BCDE and GHIJ fragments were desired in order to explore various end-game routes to complete the natural product. Thus, a goal of 20 mmole of each ring unit was set from the onset of the project.

4.2.1 Revised B ring synthesis

For the B ring fragment, it was predicted that alcohol **240**, which is simply the one carbon homologated version of the previously prepared alcohol **142**, could enter the original synthetic sequence to complete the homologated B ring aldehyde **241** (Scheme 4.2.1). Formation of the homologated alcohol would come from a glycolate alkylation to provide intermediate **243** followed by a substrate controlled stereoselective reduction of ketone **242** to provide the *anti* 1,2-diol relationship.[161] Efforts to provide the homologated B ring were conducted by another member of the Crimmins group, J. Michael Ellis. As predicted the homologated alcohol could be easily prepared using the glycolate alkylation strategy and the synthetic sequence to complete the B ring followed the previous route without complication.



Scheme 4.2.1. Homologated B ring synthesis

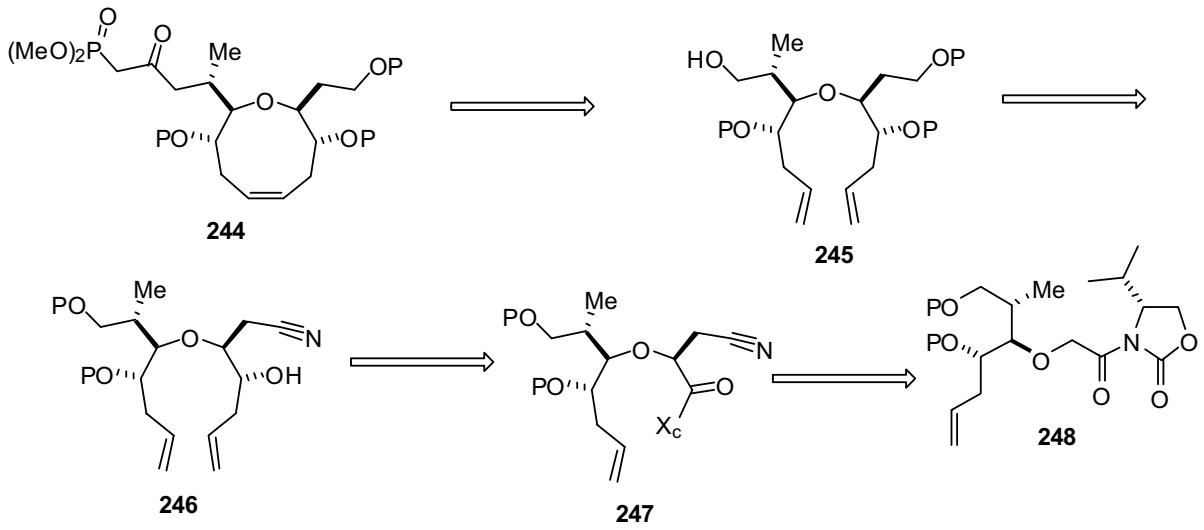
Several grams of the B ring aldehyde **241** were prepared in preparation for coupling to the revised E ring fragment.

4.2.2 Revised synthesis of the E ring fragment

4.2.2.1. Retrosynthetic analysis

In contrast to the B ring synthesis, installation of the E ring side chain via the anti aldol addition occurred at a later stage of the synthesis (see Chapter 2). The revised synthesis, therefore, was anticipated to follow the same initial synthetic sequence to arrive at a protecting group variant (**248**; see Scheme 4.2.2) of the known glycolylimide **169** (Scheme 2.2.10). Similar in design to the B ring revision, a glycolate alkylation reaction was anticipated for the stereoselective generation of the right half of the molecule. As illustrated in Chapter 2, a previous synthesis of the homologated E ring fragment utilizing a glycolate alkylation with prenyl iodide was achieved by Dr. Kyle Emmitte.[109] However, significant manipulations were necessary to convert the prenyl functionality into the desired side chain alcohol. Thus, an alternative alkylation strategy that could directly install a two carbon unit was sought to circumvent this lengthy process.

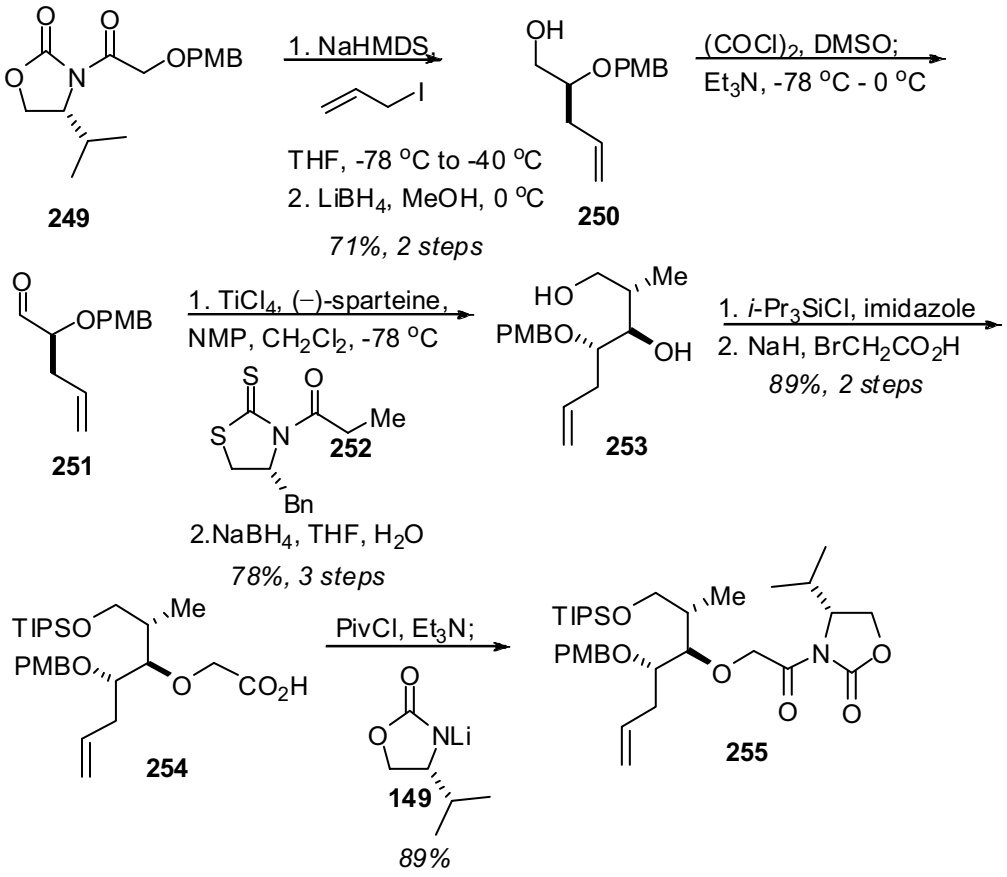
One attractive solution to this problem was the use of an acetonitrile alkylating agent, such as bromo- or iodoacetonitrile, to directly form the terminal nitrile **247** from a suitably protected glycolylimide **248** (Scheme 4.2.2). The completed phosphonate **244** could arise from alcohol **245** following the same homologation strategy used in the previous synthesis. This alcohol, in turn, was envisioned to come from the reduction of nitrile **246**. A stereoselective allylation reaction would be utilized to generate compound **246** following the reductive auxiliary removal from alkylation adduct **247**.



Scheme 4.2.2. Retrosynthetic analysis of the revised E ring

4.2.2.2. Revised synthesis of the E ring fragment

As noted in the previous synthesis of the E fragment, a late stage protecting group exchange of the secondary benzyl for a PMB ether was necessary. In an effort to circumvent this step and streamline the protecting group strategy, the PMB protecting group was utilized from the beginning of the revised synthesis. Thus, alkylation[100] of the PMB glycolylimide **249**[162] with allyl iodide was performed to give the alkylated product in 76% yield and excellent diastereoselectivity (>98:2) (Scheme 4.2.3). This reaction was performed twice on 250 mmole scale. Reductive removal of the auxiliary gave the primary alcohol **250** that was oxidized to the aldehyde **251** under Swern conditions.[108] While the previous synthesis utilized the oxazolidinethione auxiliary for the propionate aldol addition, subsequent work in the Crimmins laboratory has demonstrated the excellent properties of the analogous thiazolidinethione auxiliary.[48] In addition to high, reproducible, yields and selectivities, the preparation of the propionate **252** is considerably more facile. In the event, aldol addition with the prepared aldehyde **251** gave the desired adduct in excellent yield as a single detectable diastereomer. Purification of the aldol adduct from slight excess propionate used in the reaction was far more facile following auxiliary cleavage. Thus,

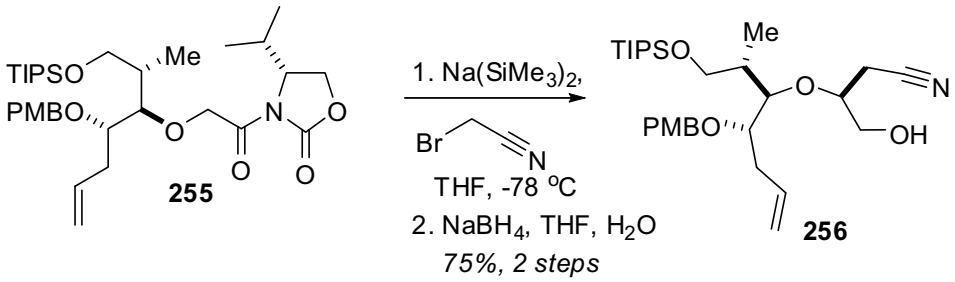


Scheme 4.2.3. Synthesis of the revised E ring glycolate fragment

reductive removal of the auxiliary with sodium borohydride gave the diol **253** in 78% over three synthetic transformations. This sequence was highly reproducible and could be performed on large scale (65 mmole) without any loss of stereoselectivity or yield. Subsequent protection as the primary triisopropylsilyl ether set the stage for an alkylation with sodium bromoacetate to give the carboxylic acid **254**. Conversion to the mixed pivaloyl anhydride followed by treatment with (*R*)-lithio-4-isopropyl-2-oxazolidinone (**149**) gave the desired imide **255** in high yield.

The next stage of the synthesis called for a novel glycolate alkylation using an activated, electrophilic, acetonitrile group. Initial efforts focused on the use of iodoacetonitrile and the sodium enolate of the glycolylimide **255**. Thus, formation of the enolate under standard conditions employing sodium hexamethyldisilazide (NaHMDS) was followed by the addition

of the electrophile. Complete consumption of the starting material was observed, however a complex mixture of products was obtained that did not correlate to the desired alkylation product. Upon switching to the less reactive bromoacetonitrile as the electrophile the desired alkylation product **256** was generated as a single detectable diastereomer in good yield (Scheme 4.2.4). Standard conditions employing sodium borohydride were used to subsequently remove the chiral auxiliary to provide primary alcohol **256** in good overall yield. Again, the alkylation proved readily amenable to larger scale reactions.

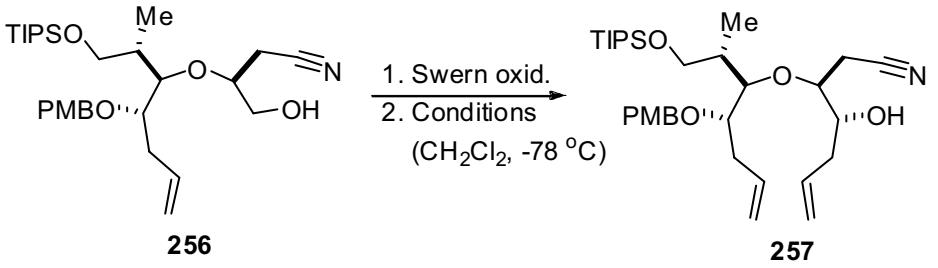


Scheme 4.2.4. Alkylation with bromoacetonitrile

Oxidation of the primary alcohol **256** was performed under Swern conditions[108] to provide the aldehyde in preparation for the asymmetric allylation reaction. Initially, the asymmetric allylation protocol developed by Brown[117] using diisopinocampheylborane as the chiral element was examined. While these conditions were highly successful in the previous E ring synthesis (Emmitte),[109] in the present system yields were low and efforts to improve the reaction outcome were largely unsuccessful (Table 4.2.1). As an alternative protocol utilizing asymmetric reagents, the allylation conditions described by Keck utilizing BINOL[163] were also examined. However, no significant amount of product was obtained after prolonged reaction times.

The presence of the α-stereogenic carbon suggested the possibility of a substrate-controlled asymmetric allylation using simple, achiral, allyl nucleophiles. Stereochemical models indicated that the product resulting from a Felkin-Ahn addition would be of the desired configuration, thus requiring a non-chelating Lewis acid for aldehyde activation. Not

surprisingly, use of allyl magnesium bromide gave a 1:1 mixture of diastereomers (Table 4.2.1). External activation of the aldehyde with $BF_3 \cdot OEt_2$ in the presence of allyltributytin also



256 **257**

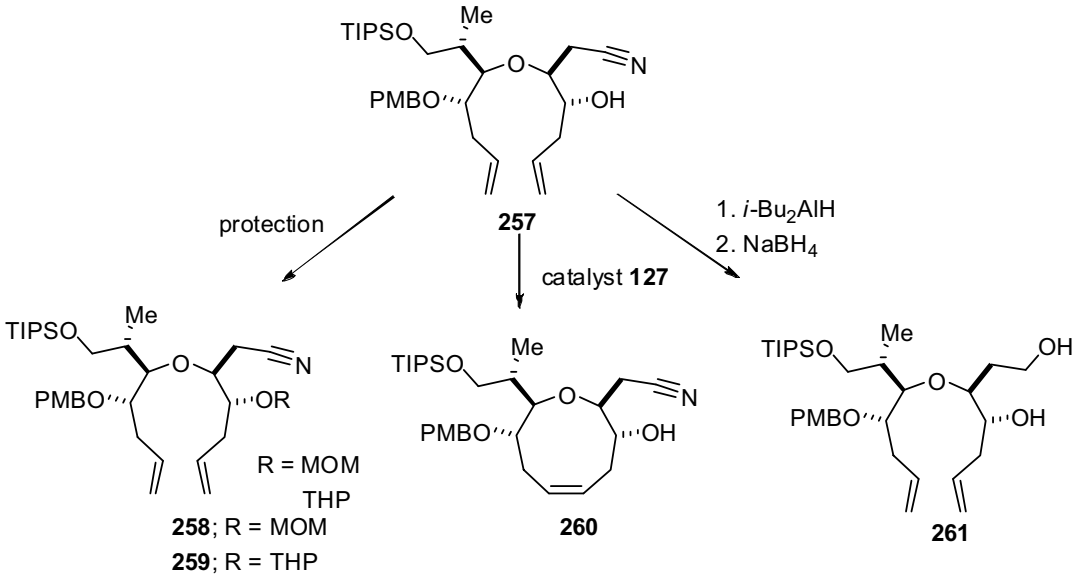
Conditions	Selectivity	Yield
$B(Ipc)_2$	>98:2	30%
MgBr	1:1	N.D.
$SnBu_3$, BF_3-OEt_2	4:1	50% + PMB dep.
$SiMe_3$, $AlMe_3$	---	no reaction
$SnBu_3$, $AlMe_3$	7:1	80%

Table 4.2.1. Stereoselective allylation of the E fragment aldehyde

led to the addition product in high yields (>80%) but with low diastereoselection (4:1). Partial loss of the PMB protecting group was also an undesired side effect. Subsequent screening of various Lewis acids revealed that trimethylaluminum delivered the product **257** with the highest levels of diastereoselection (>7:1) and in good yield. No loss of the PMB group was observed under these conditions. Use of the less-toxic allyltrimethylsilane as the nucleophile gave no reaction even at 0 ºC. The reaction sequence leading up to the homoallylic alcohol could be performed on large scale and consistently provided the product in good yield.

One problem resulting from the allylation, however, was the separation of the two diastereomers. Several subsequent conversions were attempted to improve

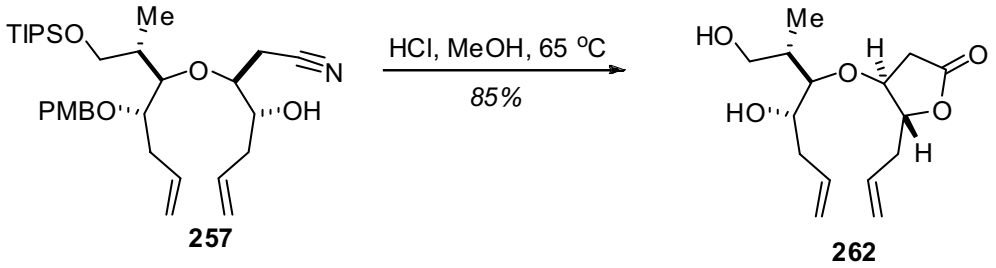
chromatographic separation, including protection of the resulting alcohol to deliver intermediates **258** and **259**, ring-closing metathesis to generate the oxonene **260**, and reduction of the nitrile to the diol **261** (Scheme 4.2.5). However, in every case, separation was exceedingly difficult.



Scheme 4.2.5. Attempted separation of diastereomers

It was reasoned that the high degree of conformational flexibility that was available in the acyclic substrate was responsible for the separation difficulties. Therefore, formation of the γ-lactone from the intermediate nitrile was examined. It was hoped that this transformation would accomplish several goals, including facile conversion of the nitrile to the desired alcohol (via reduction of the lactone) and separation of the diastereomers due to the cyclic constraint. In the event, treatment of the allylation product **257** with HCl in methanol at reflux temperature gave the lactone **262** in high yield (Scheme 4.2.6). Concomitant deprotection of both the silyl and PMB ethers could not be avoided. Separation of the two diastereomers was readily accomplished at this stage. In practice, the oxidation to the aldehyde, allyl addition, and hydrolysis to generate the lactone were accomplished without purification of

the intermediates allowing for a rapid, operationally simple, synthesis of the E fragment diene.



257 **262**

Scheme 4.2.6. Formation of the intermediate lactone

4.2.2.3. Completion of the E ring phosphonate

The sequence of events to install the necessary two carbon unit and generate the diene unit provided an excellent intermediate with which to probe the remaining E ring synthesis, as well as the BCDE coupling. Lactone **262** contained all the necessary stereogenic centers yet was completely amenable to protecting group manipulations. Thus, a large quantity of material (80 mmole) was carried through to this stage of the sequence and stored as the stable intermediate.

It was anticipated that the protecting group choice would be critical to a more efficient coupling and for enabling high material throughput. Based on the observed difficulty in the previous BCDE synthesis of removing all four PMB ethers while keeping the primary TIPS intact, an alternative protecting group strategy that would offer orthogonal deprotection options was sought. Specifically, an easily cleaved protecting group at C16 was desired to enable facile formation of the keto-alcohol necessary for D ring cyclization (Figure 4.2.1). In addition, use of protecting groups at C21 and C24 that would not be acid sensitive was desirable to enable more forcing reaction conditions to be used for the cyclization event.

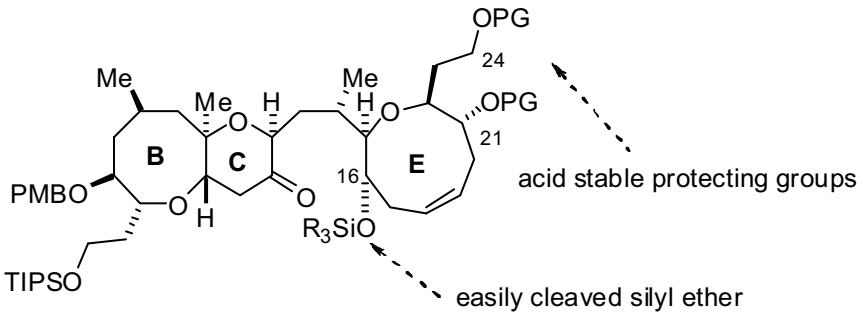
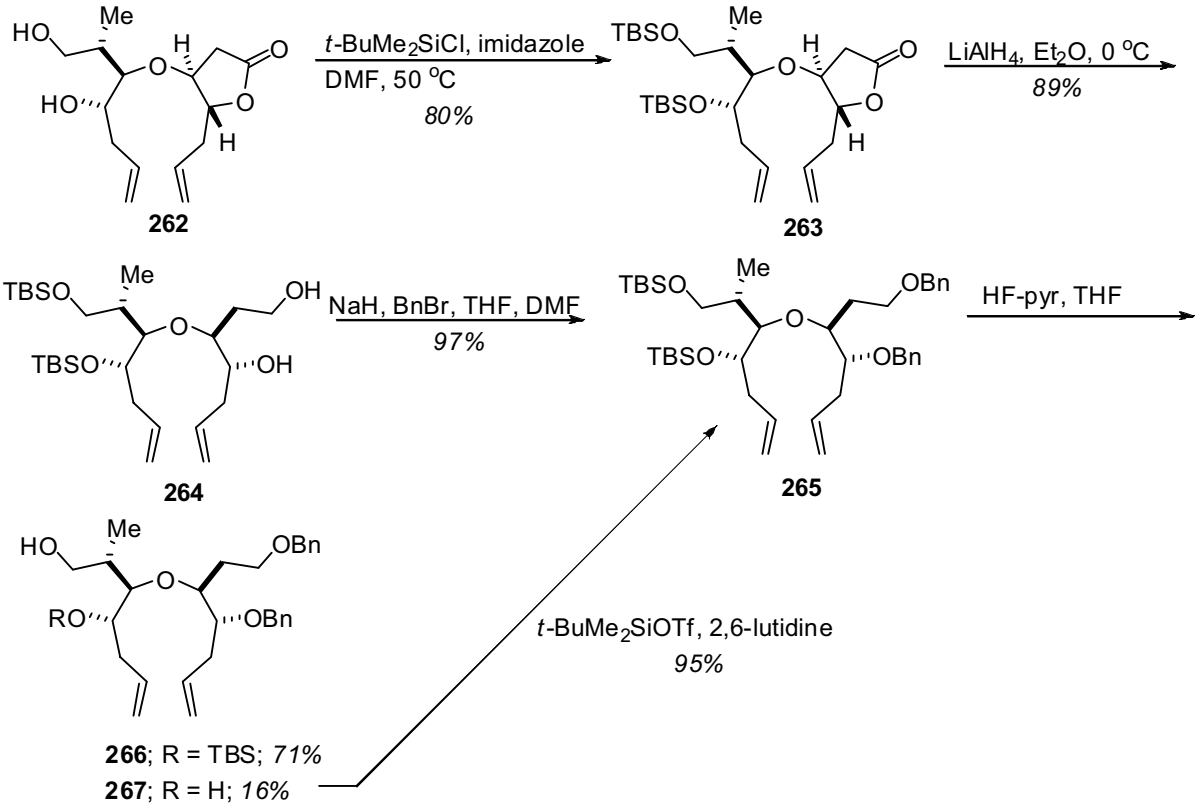


Figure 4.2.1. Protecting group strategy for revised synthesis

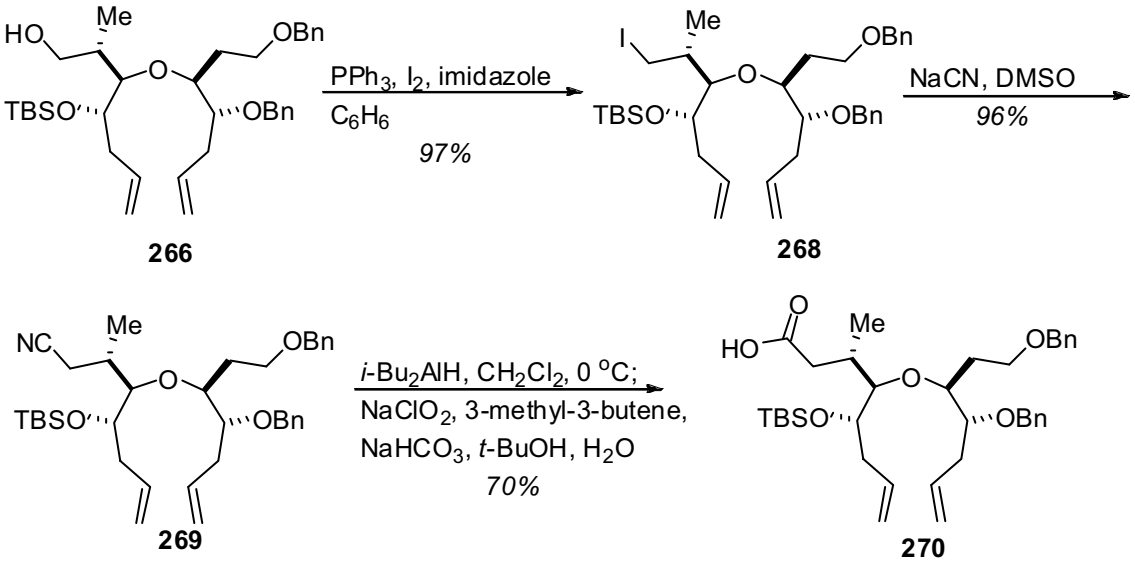
Protection of the diol **262** as the bis-TBS ether was initiated to give the compound **263** (Scheme 4.2.7). Subsequent reduction of the lactone using lithium aluminum hydride (LAH) then gave the diol **264** in excellent yield. Thus, use of the nitrile alkylation strategy enabled the formation of the requisite diol in only two synthetic operations. Protection of the resulting diol as the bis-benzyl ether led to the fully protected E ring fragment **265**. Selective



Scheme 4.2.7. E ring protecting group manipulations

deprotection of the primary TBS was best accomplished using HF-pyridine to give 71% of the desired alcohol **256** along with 16% of the diol **267**. Reformation of the bis-TBS ether **265** from the diol could be readily accomplished upon exposure to TBSOTf and 2,6-lutidine.

Formation of the iodide **268** from the primary alcohol **266** as in the previous synthesis was followed by displacement with cyanide (NaCN) to deliver the nitrile **269** in excellent overall yield (Scheme 4.2.8). One drawback to the use of the TBS protecting group for the secondary alcohol was the inability to hydrolyze the nitrile directly to the carboxylic acid **270** under strongly basic conditions. Therefore, a two-step procedure involving reduction to the intermediate aldehyde[164] followed by subsequent oxidation to the acid **270** using sodium chlorite[165] was utilized. Yields for this two step process, however, were moderate (average of 70%) and a more efficient process was desired.

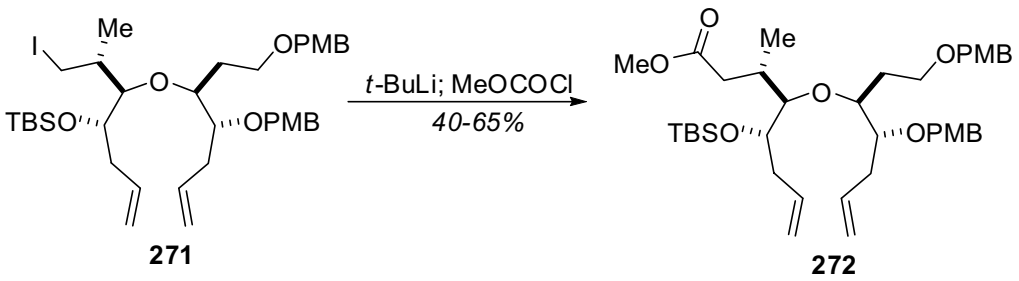


266 **268** **269** **270**

Scheme 4.2.8. Formation of the E ring acid

A direct conversion of the intermediate iodide **268** to the acid **270** or, ideally, the methyl ester seemed to be the most straightforward method to homologate the side chain and prepare for the methyl phosphonate addition. Examples involving the direct lithiation of primary alkyl iodides using *t*-butyllithium[166] and the subsequent trapping with a one carbon electrophile, such as CO_2[167] or $ClCO_2Me$,[168] were scarce, especially involving complex

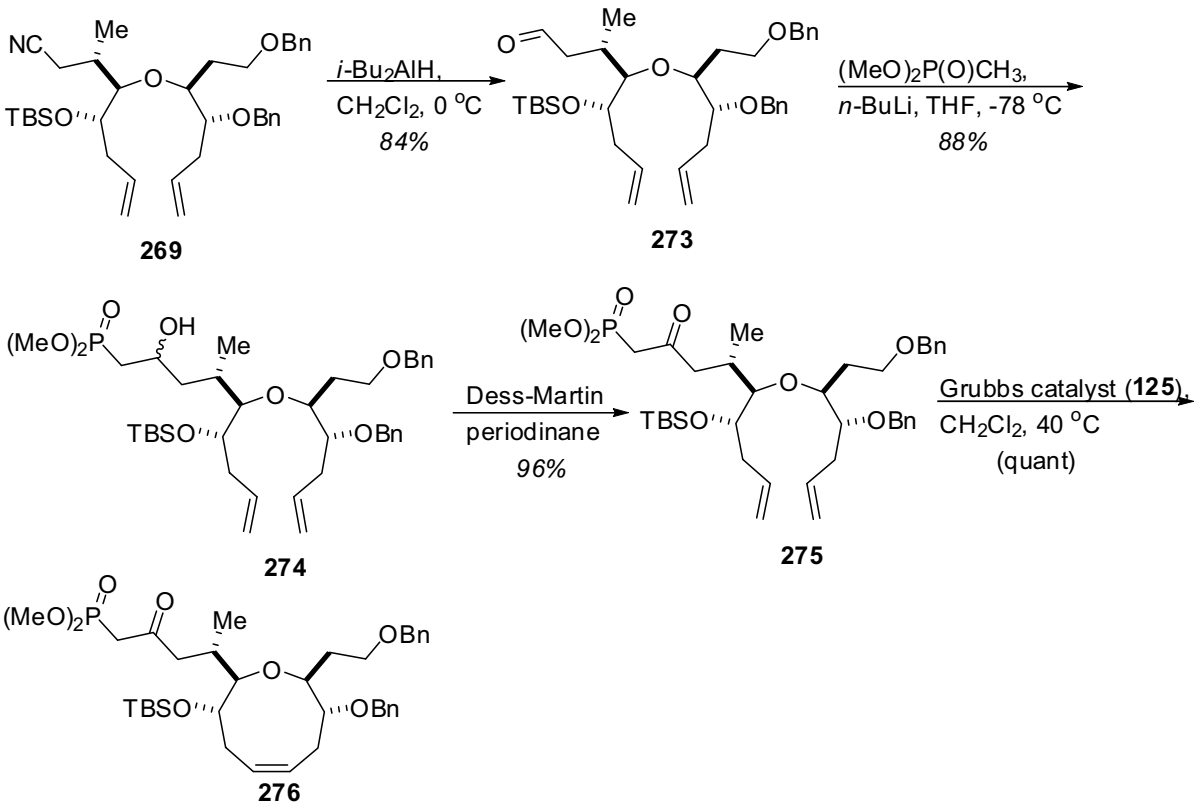
substrates with sensitive protecting groups. Subjection of the alkyl iodide **271** (see Scheme 4.2.9, note: PMB ethers used in place of Bn in earlier studies) to lithiation conditions employing *t*-BuLi, followed by the addition of water did reveal complete reduction of the alkyl iodide, thus providing evidence for the formation of the intermediate alkyl lithium. Attempts at trapping this intermediate, however, were largely unsuccessful. Use of CO_2 led only to reduction products, most likely due to difficulties in removing water completely from the gas (obtained from the sublimation of CO_2(s)). More directly, conversion to the methyl ester **272** was explored using methyl chloroformate as the electrophile (Scheme 4.2.9). While yields up to 65% were secured, these results were highly variable and often large quantities of the reduced product were obtained.



271 **272**

Scheme 4.2.9. Direct conversion to the methyl ester

As a result of the inconsistency observed in the above reaction, a more circuitous route was explored. Again, accessing the aldehyde **273** via the nitrile **269** enabled the direct addition of the lithiated dimethyl methyl phosphonate to give an inconsequential diastereomeric mixture of β-hydroxy phosphonates **274** in good yield (Scheme 4.2.10). Oxidation to the β-keto phosphonate **275** was readily accomplished using the Dess-Martin reagent.[111] While this route was two steps longer that the direct lithiation approach, the yields of the steps were highly reproducible and amenable to large scale synthesis. Finally, closure of the E ring was accomplished upon exposure to the Grubbs first generation catalyst[98] (**127**) to give the completed E ring fragment **276** in quantitative yield.



Scheme 4.2.10. Completion of the E ring phosphonate

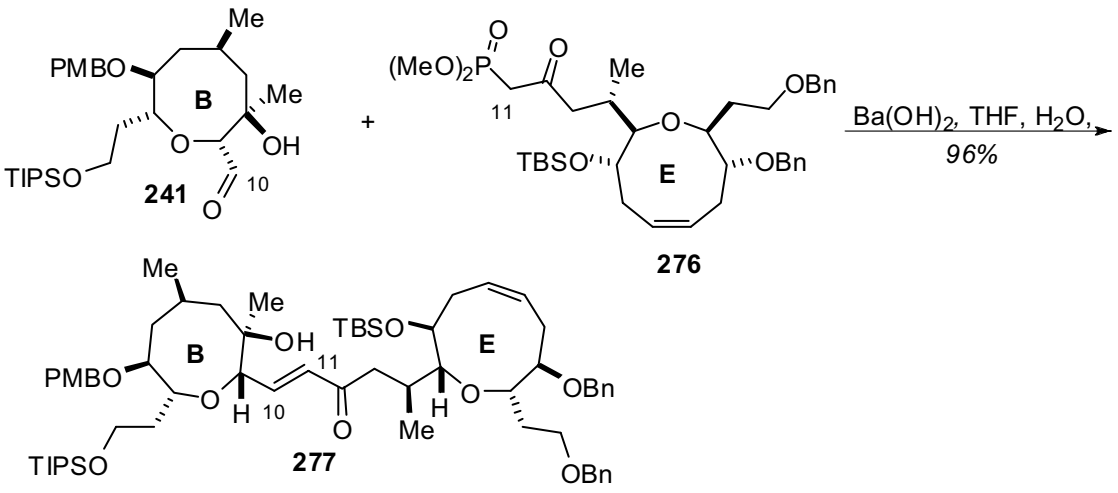
4.2.3 Revised synthesis of the BCDE fragment

4.2.3.1. Coupling and enol ether formation

A number of goals for the completion of the BCDE fragment from the individual B and E rings (**241** and **276**) were set early in the revised planning. While the earlier synthesis of the fragment (see Chapter 3) provided a template with which to focus the efforts, certain transformations needed significant improvements before sizable quantities of the BCDE fragment could be obtained. First, while the union of the two fragments and subsequent formation of the enol ether proved very reliable in the past, the oxidation of the enol ether was often problematic and gave irreproducible results. Second, the isomerization reaction to convert the undesired C12 α-ketone epimer into the desired compound was typically met with low mass recovery. Third, the cyclization of the D ring to form the mixed methyl ketal

was highly inefficient (~ 30%, 70% b.r.s.m.) and would necessitate many recycling operations in order to provide a significant quantity of the final fragment.

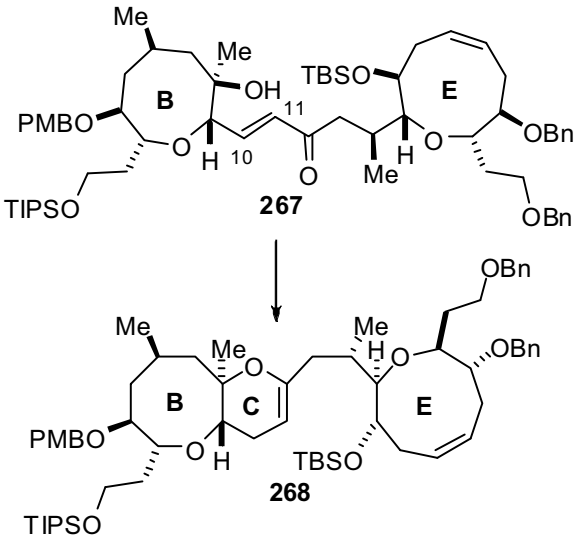
Union of the homologated B and E rings (**241** and **276**) proceeded smoothly using the previous conditions employing $Ba(OH)_2$ to give the enone **277** in excellent yield (Scheme 4.2.11). As before, this reaction was readily amenable to scale-up and gave the enone in high purity as a single olefin isomer (*E*).



Scheme 4.2.11. Coupling of the revised fragments

Reduction of the enone proceeded as before using catalytic Stryker's reagent and dimethylphenylsilane[144] to give the saturated ketone. Purification of the ketone, followed by subjection to acidic conditions provided the enol ether **278** in 65% overall yield (Table 4.2.2). Upon attempting the reduction using a stoichiometric amount of the copper hydride source, the yield was improved to 75%, though this was still significantly less than with the previous synthesis. The lower yield prompted an investigation into alternative 1,4-reduction methods that would provide the desired ketone in high yield and also obviate the need for preparation of large quantities of the highly air-sensitive Stryker's reagent.[143]

Conjugate reductions using catalytic amounts of the air-stable, commercially available Wilkinson's catalyst $(PPh_3)_3RhCl$[169] in the presence of a trialkylsilane is known to give excellent selectivity for the 1,4-reduction product.[170] The product of the reaction is typically a



Conditions	Yield
$[PPh_3CuH]_6$, Me_2PhSiH; PPTS	65%
$[PPh_3CuH]_6$ (0.8 equiv); PPTS	82%
$(PPh_3)_3RhCl$, Me_2PhSiH; PPTS, toluene, 50 °C	92%

Table 4.2.2. Cyclodehydration conditions

mixture of *E* and *Z* silyl enol ethers, which can be easily hydrolyzed to the desired saturated ketone.[171] It was reasoned that application of these conditions to the enone **277** may allow for a one-pot conversion to the C-ring enol ether that would obviate the need for purification of the intermediate ketone. Acid catalyzed cleavage of the silyl enol ethers and further acid-catalyzed cyclization to the cyclic enol ether **278** was anticipated to occur in a single operation following consumption of the starting enone. Indeed, subjecting enone **277** to a catalytic amount of $(PPh_3)_3RhCl$ and excess Me_2PhSiH in toluene at 50 °C led to consumption of the starting material with concomitant generation of two non-polar intermediates (suspected to be a mixture of silyl enol ethers by TLC analysis). It was also noted that direct formation of the desired cyclic enol ether **278** was occurring, albeit slowly. The addition of a catalytic amount of PPTS directly to the reaction mixture while maintaining the temperature at 50 ºC for 20 min led to a highly efficient transformation to the desired compound **278** (Table 4.2.2).

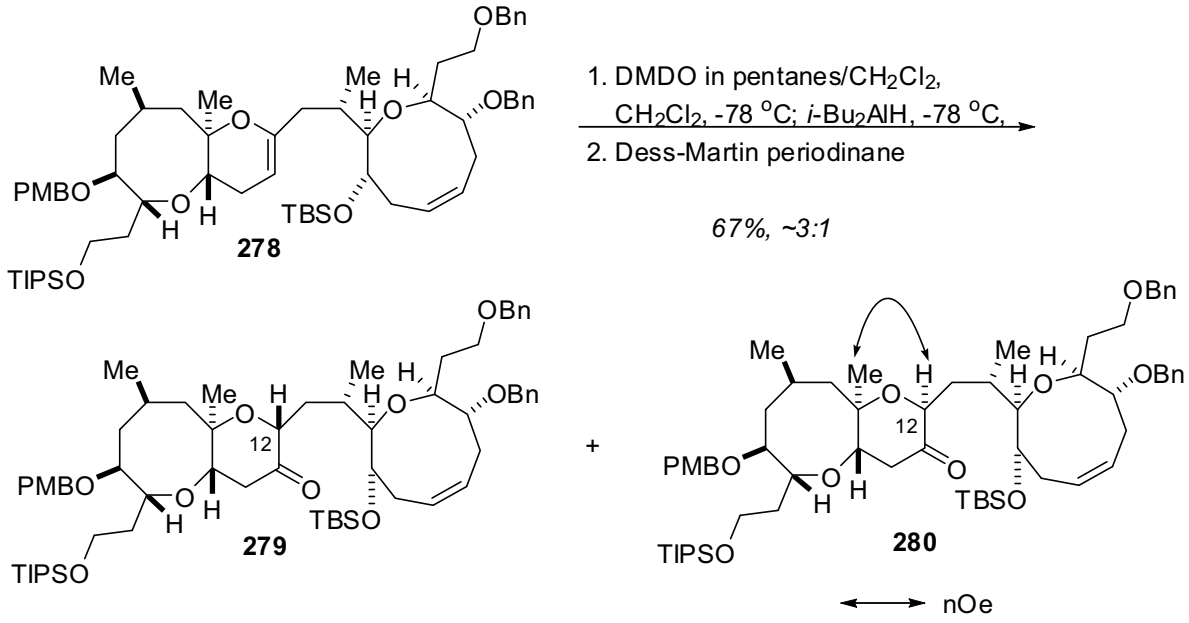
4.2.3.2. Enol ether oxidation: Modifications to DMDO preparation

The efficient and reproducible conversion of enol ether **278** to the diastereomeric mixture of alcohols using the in situ epoxidation/reduction protocol was extensively studied based on previously observed inconsistencies in the reaction. For example, upon following identical reaction conditions on the same batch of enol ether, yields ranging from 45-75% were obtained. Furthermore, the amount of *i*-Bu_2AlH that was needed for the complete conversion to the alcohols also varied considerably and always required a large excess of reagent (~20 equiv). It was reasoned that the inconsistent nature of the reaction was likely due to the quality of the DMDO reagent itself, which had to be prepared immediately prior to each reaction.

The in situ reduction protocol that was adopted for this transformation necessitated a low concentration of acetone relative to DMDO. Higher amounts of acetone in some of the DMDO solutions were believed to be responsible for the observed inconsistencies and high *i*-Bu_2AlH requirements. Indeed, NMR analysis of the DMDO solutions that were thought to contain minimal amounts of acetone (approximately equal to DMDO concentration)[152,153] often contained a large excess of acetone relative to DMDO (~20:1). To circumvent this problem, a simple modification to the originally reported procedure[152,153] was developed to deliver essentially acetone free DMDO solutions in a consistent and reproducible manner. Switching the extraction solvent from methylene chloride to a 4:1 mixture of pentanes/CH_2Cl_2 effectively increased the hydrophobic nature of the extraction solvent and, thus, decreased the amount of acetone remaining after subsequent aqueous washes. This also had the desirable effect of decreasing the number of washes that were needed and simplified the extraction procedure by using a less dense organic solvent mixture. Following the above protocol, DMDO solutions that were far superior for the oxidation of enol ether **278** were obtained, giving consistent reaction yields and requiring significantly less *i*-Bu_2AlH (~ 5 equiv.). A variety of other extraction solvents were also examined, including toluene,

pentanes, and CCl_4, but were found to give DMDO solutions that were inferior for the desired transformation. It should also be noted that these solutions were rather dilute would not be suitable for larger scale reactions.

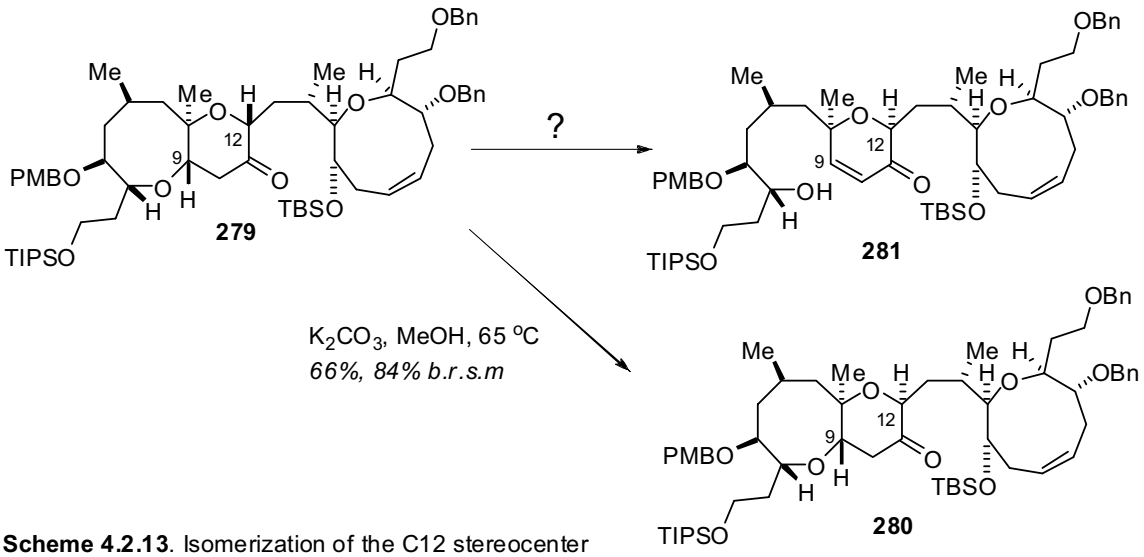
In practice, oxidation of the enol ether **278** using the aforementioned DMDO solutions followed by the in situ reduction with *i*-Bu_2AlH led to a diastereomeric mixture of secondary alcohols in good, reproducible yield (Scheme 4.2.12). The configuration of the diastereomers (three separate isomers were produced in sufficient quantities for detection)



Scheme 4.2.12. Oxidation of the BCE enol ether.

that were formed were not ascertained at this stage of the synthesis. However, it is likely that both the epoxidation and hydride addition selectively occurred from the top face of the enol ether opposite the axially disposed methyl group (see Chapter 3). Separation of the major components of the reaction followed by their subsequent oxidation using Dess-Martin periodinane[111] gave their respective ketones in good yield. Fortunately, separation of the two diastereomers by column chromatography could be readily accomplished using a diethyl ether/hexanes solvent mixture to provide the two ketone epimers **279** and **280** in an approximate 3:1 ratio favoring the undesired configuration at C12 (**279**).

The next challenge in the synthesis required finding an efficient method for the isomerization of the major C12 epimer **279** to the desired compound **280**. As observed in the previous synthesis of the BCDE fragment, significant loss of material was observed with the use of DBU. Unlike the previous case, however, multiple decomposition products could be observed upon TLC analysis. These decomposition products formed competitively with the isomerization and mass recovery of only 30% could be reliably secured. Reasons for the exceptional instability of the ketone to basic conditions are not entirely clear, however, is it suspected that β-elimination of the C9-oxygen bond to yield enone **281** could be a significant decomposition pathway (Scheme 4.2.13). An extensive experimentation of various reaction conditions was thus undertaken to find an alternative method for isomerization. Fortunately, separation of the two epimers was visible in the TLC analysis using 20% Et_2O/hexanes as the eluting solvent, thus enabling the rapid determination of the efficacy of the conditions. Furthermore, decomposition products were also visible by TLC enabling small scale



Scheme 4.2.13. Isomerization of the C12 stereocenter

experiments to be conducted to avoid the loss of precious late-stage material. Many bases were examined, including NaOMe, LiOMe, imidazole, and KO*t*-Bu under various reaction conditions (temperature, solvent, etc) which all gave similar decomposition patterns (TLC

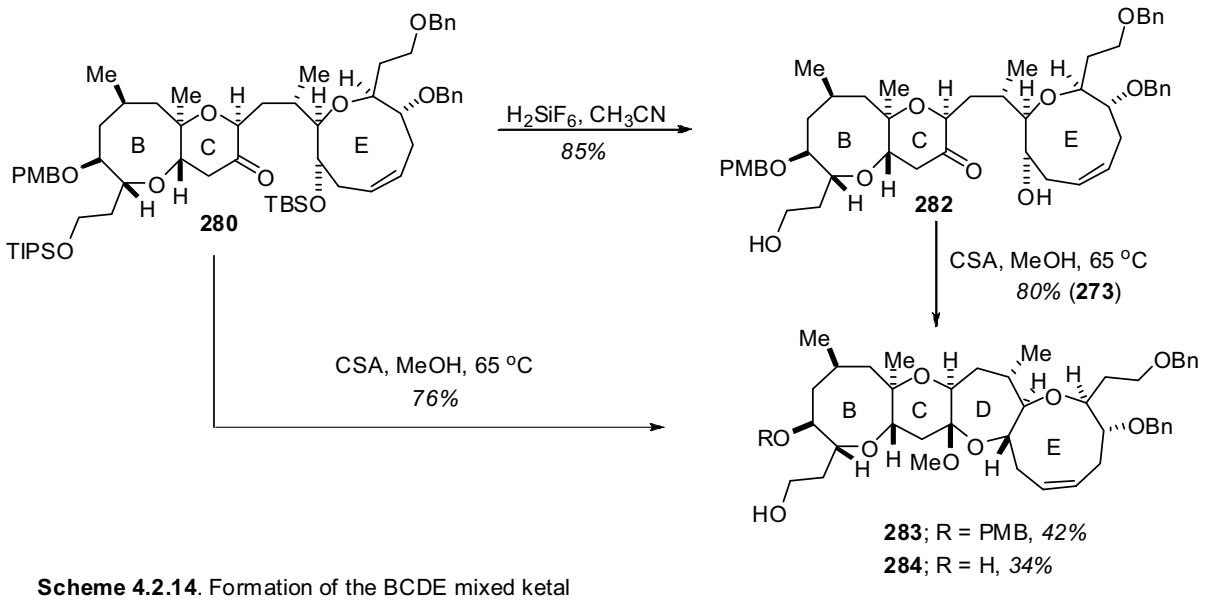
analysis). Isomerization under acidic conditions was also attempted, but in no case was any of the desired epimer detected. Remarkably, the use of potassium carbonate in methanol at reflux temperature provided the desired product **280** in significantly higher yield than with any other bases and was accompanied by only small amounts of decomposition. The reactions were typically stopped before isomerization was complete in order to minimize material loss. One cycle using these conditions could deliver close to 70% of the desired product along with 20% of the undesired, which could be separated and resubjected to the isomerization conditions.

4.2.3.3. D ring cyclization and completion of the ABCDE fragment

Removal of the TBS protecting group in preparation for the D ring cyclization was realized using aqueous fluorosilicic acid (H_2SiF_6).[172] Prolonged reaction times at 0 ºC were necessary to minimize the decomposition of the material. Concomitant loss of the primary TIPS group was also observed to give the keto-alcohol **282** (Scheme 4.2.14) in good yield. Other deprotection methods such as TBAF and HF/pyridine also resulted in competitive loss of both silyl groups but provided the desired diol in lower yield.

Previous work to close the remaining seven-membered ring as the mixed methyl ketal highlighted the difficulty associated with obtaining the desired product with high levels of conversion. Ultimately, a two-step process was required that first generated the dimethyl ketal from the keto-alcohol as an isolable intermediate. Subsequent treatment with an acid catalyst then provided the desired product in only a 30% yield along with recoverable keto-alcohol (70% b.r.s.m). In light of this low efficiency, an investigation into alternative methods for cyclization was undertaken with the revised keto-alcohol **282**.

In an attempt to follow literature precedent for a similar cyclization,[128] the keto-alcohol **282** was treated with a catalytic amount of PPTS and trimethylorthoformate. Interestingly, a stable intermediate was formed that corresponded to protection of the two free alcohols as



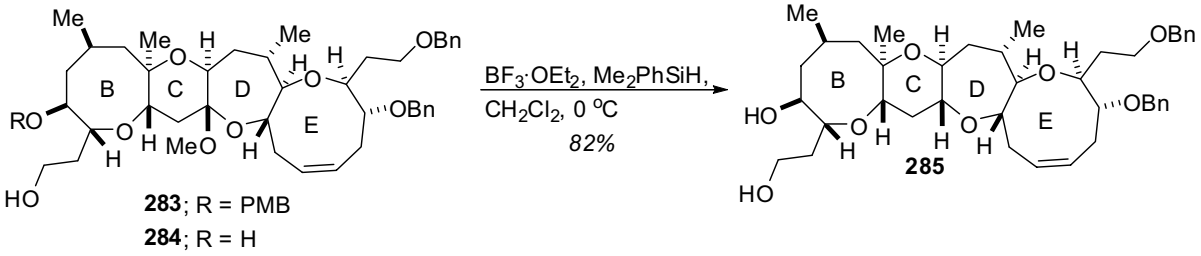
Scheme 4.2.14. Formation of the BCDE mixed ketal

their methyl orthoesters. The reaction was then attempted using the identical reaction conditions used before employing anhydrous methanol, small amounts of trimethylorthoformate and catalytic PPTS with the expectation of generating the dimethyl ketal. However, in addition to the formation of the dimethyl ketal, small amounts of the desired mixed methyl ketal product **283** was being generated directly under those conditions (see Scheme 4.2.14). Complete conversion to the desired ketal, however, could not be achieved. Upon switching to the stronger camphorsulfonic acid (CSA), a remarkably efficient cyclization to deliver mixed methyl ketal **283** as a single diastereomer in 80% yield (predicted configuration as shown) was observed (Scheme 4.2.14). These reaction conditions, which could not be used before due to loss of the primary TIPS protecting group (see Chapter 3), appeared ideally suited to the transformation and gave no detectable amounts of keto-alcohol **280**.

Based on this result, it was anticipated that removal of the two silyl groups and cyclization to the mixed ketal might occur in a single synthetic operation. If successful, formation of the tetracycle **283** could be accomplished in a single step from the protected precursor **280**, thus shortening the original sequence by two synthetic operations. Treatment

of the ketone **280** with CSA in methanol at reflux temperature did indeed lead to direct formation of the mixed ketal **283** (Scheme 4.2.14). Additional partial loss of the PMB was also observed to give the diol **284** as the major byproduct. A combined yield of 76% was secured, offering a significant improvement from the previous synthesis. Fortunately, this deprotection proved inconsequential to the synthesis as loss of the PMB group was observed in the subsequent reaction.

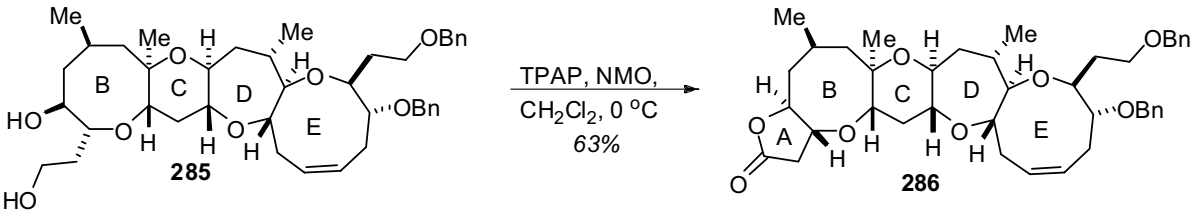
Reduction of both mixed methyl ketals **283** and **284** (R = PMB or H) using BF3·OEt2 and Me2PhSiH led to the formation of the BCDE fragment **285** in good yield and as a single detectable diastereomer (Scheme 4.2.15). Thus the completed fragment was obtained in only six synthetic transformations (7 including isomerization) from the individual fragments. Facile protecting group manipulations on the BCDE fragment were anticipated based on the highly stable nature of the tetracyclic polyether. Thus, significant quantities (>200 mg) of this BCDE fragment were prepared using the outlined synthetic route and stored at this stage for use.



283; R = PMB
284; R = H

Scheme 4.2.15. Formation of the BCDE fragment

In an effort to explore the formation of the A ring lactone, treatment of diol **285** with a catalytic amount of tetrapropylammonium perruthenate (TPAP) and stoichiometric quantities of 4-methylmorpholine *N*-oxide (NMO)[173] led to exclusive formation of the ABCDE lactone **286** in 63% yield (Scheme 4.2.16). No evidence of the oxidation of the secondary alcohol was observed.



Scheme 4.2.16. Formation of the ABCDE lactone

As in the previous synthesis, stereochemical confirmation of the ABCDE fragment **286** was obtained through extensive 2D-NMR analysis. Key nOe interactions are shown in Figure 4.2.1, which lend support for the proposed configuration as shown. Attempts at obtaining a suitable crystal for X-ray crystallographic analysis on the completed fragment were not successful. Protection of the diol as the bis-*p*-nitrobenzoate was also performed but, as before, no suitable crystals could be obtained.

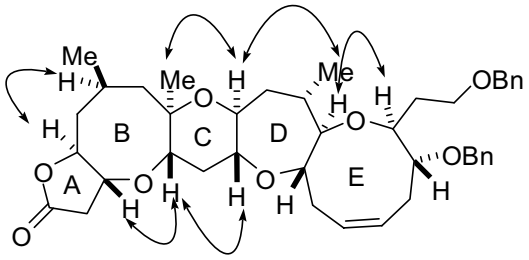
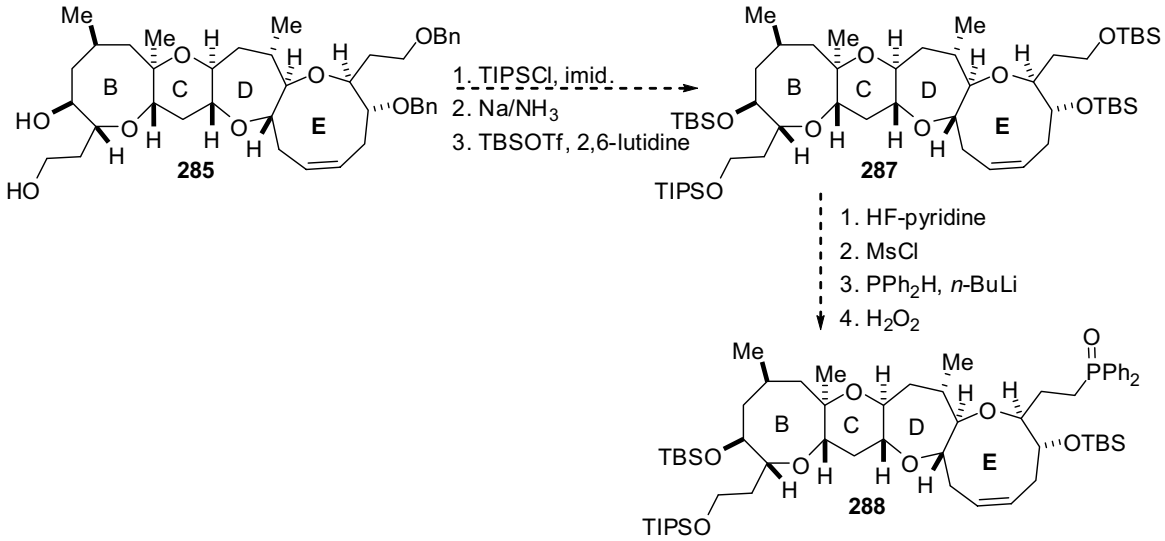


Figure 4.2.2. nOe analysis of the ABCDE lactone

4.3 PROPOSED COMPLETION OF BREVETOXIN A

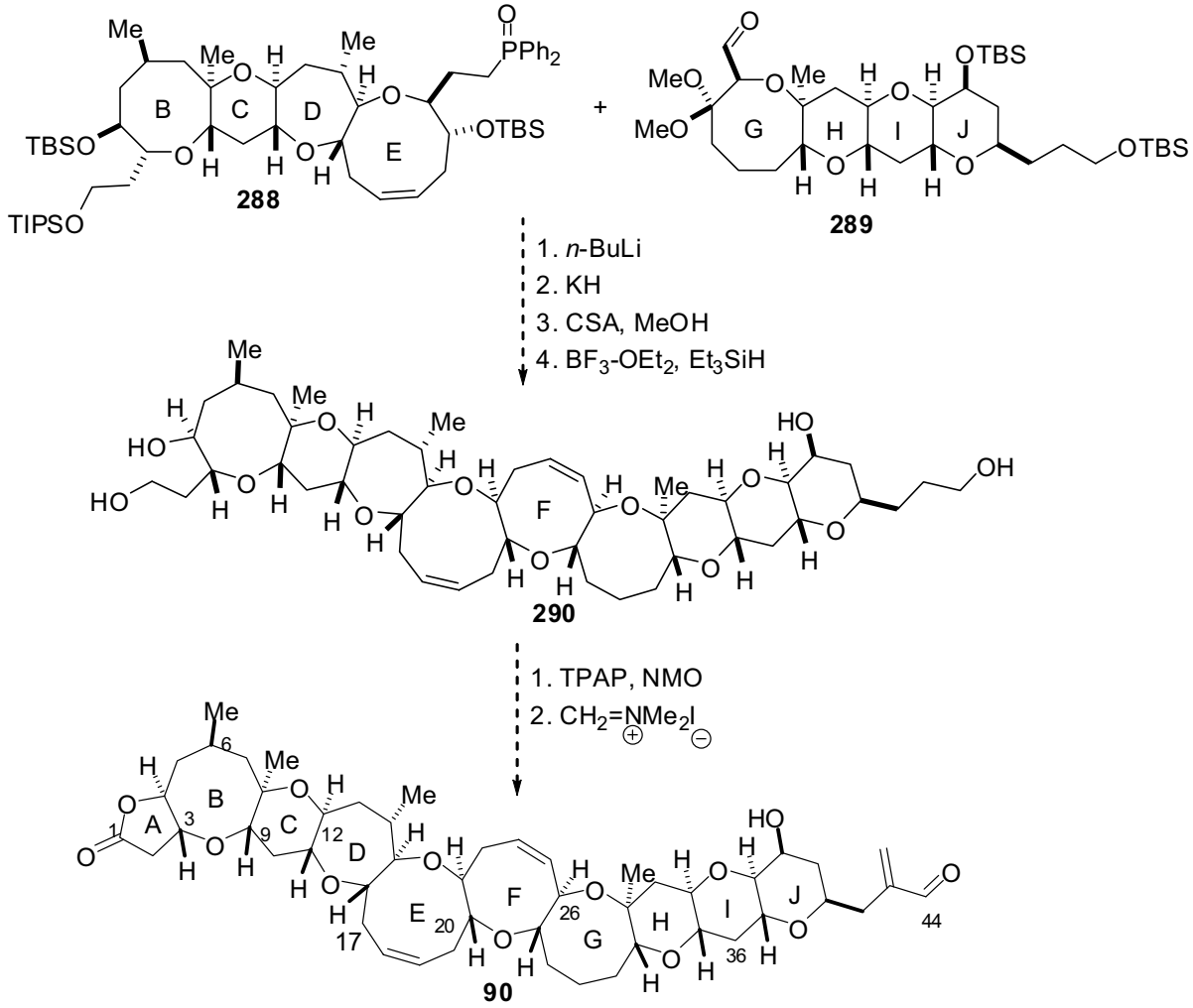
The completion of brevetoxin A is expected to occur through the coupling of the BCDE and GHIJ fragments using a Horner-Wittig reaction[174] between a BCDE phosphine oxide (**132**) and a GHIJ aldehyde (**133**) (see Chapter 2, Scheme 2.2.1). Formation of the required BCDE fragment from the diol **285** should be possible upon protection of the primary alcohol, deprotection of the benzyl ethers, and re-protection as the tris-silyl ether derivative **287** (Scheme 4.3.1). Selective deprotection of the primary TBS ether followed by formation of the phosphine oxide via the primary mesylate should deliver the coupling partner **288**.

The GHIJ fragment of brevetoxin A has previously been synthesized using a similar HWE coupling strategy.[160] Conversion to the GHIJ aldehyde **289** needed for the proposed coupling will occur using standard transformations. Base promoted Horner-Wittig coupling



Scheme 4.3.1. Proposed formation of the BCDE phosphine oxide

between fragment **288** and **289** is expected to deliver a diastereomeric mixture of α-hydroxy phosphine oxides that should generate the *Z*-olefin upon treatment with potassium hydride (Scheme 4.3.2).[91] While Nicolaou reported the necessity of a methoxypropyl protecting group on the secondary alcohol at C20, successful use of a silyl protecting group would significantly simplify the end-game strategy. In light of the highly efficient formation of the D ring mixed ketal, cyclization of the F ring system to the mixed methyl ketal is proposed to occur upon treatment with CSA in methanol at elevated temperatures. Reduction of the ketal as before using BF_3-OEt_2 and a silane source should provide the advanced intermediate **290**. Loss of all four silyl protecting groups is also anticipated either during the cyclization or the reduction reactions. As previously demonstrated, formation of the A ring lactone will be accomplished under TPAP/NMO oxidation conditions. It is also anticipated that the oxidation of the other primary alcohol will occur simultaneously to give the desired aldehyde. The oxidation of the secondary J ring alcohol is also possible under these conditions, though the rate of oxidation should be significantly lower than that of the primary hydroxyls due steric hindrance associated with the axially oriented J ring alcohol. In fact, Nicolaou was able to exploit this rate difference during the final stages of their synthesis using Dess-Martin



Scheme 4.3.2. Proposed completion of brevetoxin A

periodinane as the oxidant.[91] Finally, methylenation of the aldehyde using dimethyl(methylene)ammonium iodide (Eschenmoser's salt) should deliver the natural product **90**.

4.4 SUMMARY

In summary, a revised synthesis of the BCDE fragment of brevetoxin A has been developed. Modifications to the synthetic route of the E ring fragment were made, including

the development of a novel glycolylimide alkylation with bromoacteonitrile and efficient formation of the phosphonate, to give the completed fragment with a one carbon homologated side chain. Coupling of this fragment with a revised B ring unit gave an intermediate enol ether following the previous convergent coupling strategy. Several modifications to the previous approach toward the completion of the BCDE tetracycle were made to deliver the final product in higher overall yield in fewer synthetic operations. Finally, cyclization to form the A ring lactone was readily accomplished to provide the ABCDE fragment of brevetoxin A.

CHAPTER 5: EXPERIMENTAL

5.1 MATERIALS AND METHODS

Infrared (IR) spectra were obtained using a JASCO FT/IR 460-plus. Proton and carbon nuclear magnetic resonance (^{1}H, ^{13}C NMR, COSY, NOESY) spectra were recorded on the following instruments: Bruker model DRX 300 (^{1}H at 300 MHz; ^{13}C at 75 MHz), Bruker model DRX 400 (^{1}H at 400 MHz; ^{13}C at 100 MHz), and Bruker model DRX 500 (^{1}H at 500 MHz; ^{13}C at 125 MHz). Deuterated Chloroform was set to 7.24 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C. Deuterated benzene was set to 7.15 and 128 ppm, respectively. Optical rotations were determined using a JASCO P-1010 polarimeter. Mass spectra were obtained using a Micromass Quattro II (triple quad) with nano-electrospray ionization. Thin layer chromatography (TLC) was conducted on silica gel 60 F_{254} TLC plates purchased from EMD Chemicals, Inc. Flash chromatography was carried out using silica gel (60 Å, 40 to 63 μM) purchased from Sorbent Technologies, Inc. Diethyl ether (Et_2O), tetrahydrofuran (THF), and dichloromethane (CH_2Cl_2) were dried by passing through a column of neutral alumina under nitrogen immediately prior to use. Alkylamines, benzene, and toluene were distilled from calcium hydride immediately prior to use. Dimethyl sulfoxide (DMSO) was distilled under reduced pressure from calcium hydride and stored over 4Å molecular sieves. Anhydrous *N*,*N*-dimethylformamide (DMF) was purchased from Aldrich chemical company in 1L Sure/Seal™ bottles. Pivaloyl chloride was distilled and stored over 4Å molecular sieves. Titanium (IV) isopropoxide was distilled under reduced pressure and stored in a dark desiccator. Stryker's reagent was prepared according to literature procedures and stored in a glove box. Dess-Martin periodinane was prepared according to literature procedures and

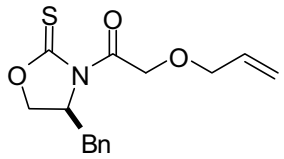
stored at -20 ºC. All other reagents and solvents were used as received from the manufacturer. All air and water sensitive reactions were performed in flasks flame dried under a positive flow of argon and conducted under an argon atmosphere.

5.2 EXPERIMENTAL

5.2.1 *Anti* glycolate aldol additions

5.2.1.1. Substrate synthesis

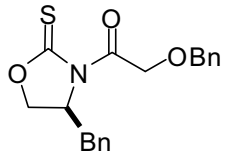
Allyl glycolate **77**



A dry round bottom flask containing allyloxyacetic acid (12.5 mL, 112 mmole), dimethylformamide (0.290 mL, 3.74 mmol), and 220 mL anhydrous CH_2Cl_2 was cooled to 0° C. Oxalyl chloride (61.7 mL, 123 mmole; 2.0 M in CH_2Cl_2) was added dropwise and the reaction mixture was allowed to warm to room temperature and stirred for 1 hour. Evaporation of most of the solvents gave the crude acyl chloride. To a separate dry flask was added the oxazolidinethione auxiliary[26] (14.5 g, 74.8 mmol) and triethylamine (31.3 mL, 224 mmole) in 200 mL THF. The solution was cooled to 0° C followed by dropwise addition of the crude acyl chloride. The solution was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched with 1 N HCl and the organic layer was separated. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. Purification of the residue by flash column chromatography afforded 20.3 g (93%) of the allyl glycolate **77**. (Recrystallization from Et_2O/Hex could be performed for enhanced purity.) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37-7.22 (band, 5H), 5.99 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.40-5.35 (m, 1H), 5.30-5.26 (m, 1H), 5.12-4.93 (band, 3H), 4.42-4.37 (band, 2H), 4.22-4.17 (band, 2H), 3.32 (dd, *J* = 13.2, 3.2

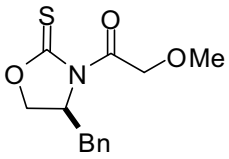
Hz, 1H), 2.82 (dd, *J* = 13.6, 10.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 184.7, 171.0, 134.6, 133.8, 129.4, 129.0, 127.5, 118.2, 72.47, 71.39, 59.76, 37.51; IR (CH_2Cl_2) 3065, 2988, 2687, 2308, 1714, 1424, 1366, 1328, 1266, 1024 cm^{-1}; $[\alpha]^{22}_D$ +107° (*c* = 0.90, CH_2Cl_2).

Benzyl glycolate **76**



See above procedure: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43-7.19 (band, 10H), 5.06 (dd, *J* = 37.6, 18.0 Hz, 2H), 4.68 (s, 2H), 4.39-4.32 (band, 2H), 3.29 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.84-2.76 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 184.7, 171.0, 137.2, 135.0, 129.4, 129.1, 128.5, 128.1, 128.0, 127.5, 73.56, 71.53, 71.40, 59.79, 37.56; IR (CH_2Cl_2) 3056, 2989, 2688, 2308, 1713, 1422, 1355, 1322, 1198 cm^{-1}; $[\alpha]^{22}_D$ +96.7° (*c* = 0.55, CH_2Cl_2).

Methyl glycolate **73**



See above procedure: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34-7.18 (band, 5H), 5.03-4.88 (band, 3H), 4.38-4.36 (band, 2H), 3.50 (s, 3H), 3.27 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.79 (dd, *J* = 13.6, 10.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 184.7, 170.9, 134.9, 129.3, 129.0, 127.5, 73.96, 71.42, 59.71, 59.45, 37.52; IR (CH_2Cl_2) 3056, 2993, 2935, 2308, 1715, 1368, 1329, 1198 cm^{-1}; $[\alpha]^{22}_D$ +114° (*c* = 0.95, CH_2Cl_2).

5.2.1.2. *Anti* aldol additions

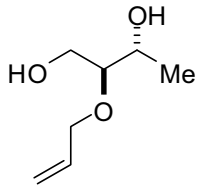
Typical procedure for anti aldol additions: **Method A**. To a dry round-bottom flask under an argon atmosphere was added the *N*-acyloxazolidinethione glycolate (0.172 mmol) and 5 mL dichloromethane. After cooling to -78°C, titanium (IV) chloride (0.023 mL, 0.206 mmol) was added dropwise and the solution was allowed to stir for 10 min. A freshly prepared 2M solution of (-)-sparteine in dichloromethane (0.103 mL, 0.206 mmol) was added to the mixture dropwise and the resulting solution was stirred for 40 min. Directly to the enolate was added the second batch of $TiCl_4$ (0.057 mL, 0.516 mmol, or 0.075 mL, 0.688mmol if aldehyde is α,β-unsaturated). After stirring for 1 min, freshly distilled aldehyde (0.224 mmol) was added to the reaction. The reaction was allowed to stir for 15 min and quenched with ½ saturated ammonium chloride. The organic layer was separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated *en vacuo*. Purification was performed using flash chromatography. **Method B**. See enolate formation above. To a separate dry flask was added 5 mL CH_2Cl_2 and $TiCl_4$ (0.057 mL, 0.516 mmol, or 0.075 mL, 0.688mmol) if aldehyde is α,β-unsaturated) and cooled to -78°C. Freshly distilled aldehyde (0.224 mmol) was added to the $TiCl_4$ solution and cold cannulated to the enolate after 10s. The resulting mixture was allowed to stir for 15 min and worked up as above.

Due to difficulties in separating *anti* aldol products from small amounts of unreacted starting material, the auxiliary was reductively cleaved to provide the aldol adducts as their corresponding 1,3-diols for characterization:

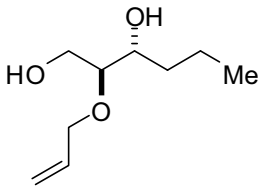
To a solution containing the inseparable mixture of starting material and aldol product and diethyl ether (0.1 M) at 0°C was added methanol (1.4 equiv) and lithium borohydride (1.4 equiv.; 2 M in THF). After stirring for 1 hour the reaction was quenched with Na^+/K^+ tartrate, warmed to room temperature, and allowed to stir for 1.5 h. The organic layer was extracted

with ethyl acetate and separated. The aqueous layer was saturated with NaCl and extracted multiple times with dichloromethane. The organic layers were combined, dried over Na_2SO_4, and concentrated. Purification of the residue by column chromatography afforded the diol. Yields ranged from 83-97%.

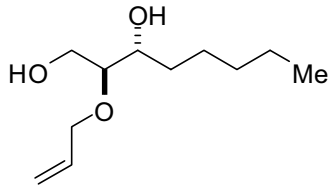
Diols:



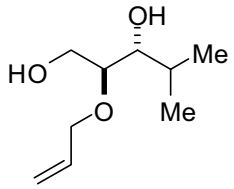
^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.88 (ddt, J = 17.2, 10.0, 6.0 Hz, 1H), 5.27-5.21 (m, 1H), 5.20-5.17 (m, 1H), 4.09-4.02 (m, 2H), 3.96-3.85 (m, 1H), 3.78-3.68 (m, 2H), 3.19 (dt, *J* = 4.8, 4.4 Hz, 1H), 3.01 (bs, 1H), 2.88 (bs, 1H), 1.18 (d, *J* = 6.8Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 134.6, 117.4, 82.20, 71.14, 67.97, 61.13, 18.91; IR (CH_2Cl_2) 3586, 3053, 2984, 2308, 1424, 1266, 1096 cm^{-1}; $[\alpha]^{22}_D$ +5.8° (*c* = 0.36, CH_2Cl_2).



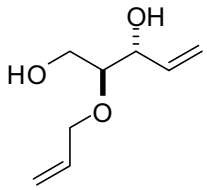
^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.90 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.29-5.23 (m, 1H), 5.18-5.15 (m, 1H), 4.11-4.05 (m, 2H), 3.82-3.70 (m, 3H), 3.25 (dt, *J* = 4.8, 4.0 Hz, 1H), 2.64 (bs, 2H), 1.56-1.34 (m, 4H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 134.6, 117.4, 81.35, 71.49, 70.85, 61.00, 35.07, 19.09, 13.97; IR (CH_2Cl_2) 3586, 3049, 2961, 2876, 2308, 1424, 1085 cm^{-1}; $[\alpha]^{26}_D$ + 9.5° (*c* = 1.2, CH_2Cl_2).



^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.90 (ddt, *J* = 17.2, 10.4, 6.0 Hz, 1H), 5.28-5.23 (m, 1H), 5.18-5.15 (m, 1H), 4.11-4.05 (m, 2H), 3.78-3.74 (m, 3H), 3.25 (dt, *J* = 4.8, 4.0 Hz, 1H), 2.69-2.64 (m, 2H), 1.49-1.42 (m, 3H), 1.36-1.26 (m, 5H), 0.90-0.84 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 134.6, 117.4, 81.33, 71.78, 70.86, 61.00, 32.93, 31.77, 25.58, 22.53, 13.96; IR (CH_2Cl_2) 3590, 2934, 2864, 1467, 1378, 1081 cm^{-1}; $[\alpha]^{26}_{D}$ +6.5° (*c* = 1.7, CH_2Cl_2).

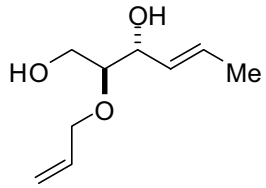


^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.90 (ddt, *J* = 17.2, 10.4, 6.0 Hz, 1H), 5.29-5.23 (m, 1H), 5.19-5.15 (m, 1H), 4.11-4.02 (m, 2H), 3.81-3.73 (m, 2H), 3.50 (dd, *J* = 5.2, 1.2 Hz, 1H), 3.43-3.38 (m, 1H), 2.57 (bs, 2H), 1.83-1.75 (m, 1H), 1.00 (d, *J* = 6.8 Hz), 0.89 (d, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 134.5, 117.5, 79.18, 76.32, 70.61, 60.89, 29.65, 19.09, 17.90; IR (CH_2Cl_2) 3594, 3049, 2964, 2876, 2308, 1606, 1471, 1081 cm^{-1}; $[\alpha]^{26}_{D}$ –3.0° (*c* = 0.26, CH_2Cl_2).

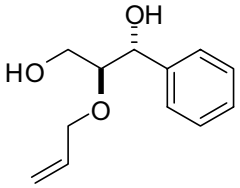


^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.93-5.85 (m, 2H), 5.39-5.17 (m, 4H), 4.38-4.33 (m, 1H), 4.17-4.08 (m, 2H), 3.79-3.70 (m, 2H), 3.40-3.36 (m, 1H), 2.56 (m, 1H), 2.27-2.24 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.7, 134.5, 117.6, 116.4, 81.08, 72.76, 71.19, 61.36; IR

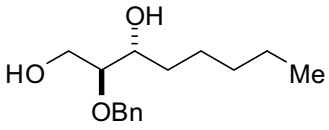
(CH_2Cl_2) 3690, 3601, 3053, 2988, 2887, 2687, 2308, 1606, 1424, 1266, 1108, 1042 cm^{-1}; $[\alpha]^{25}_D$ +16.1° (*c* = 0.60, CH_2Cl_2).



^1H NMR ($CDCl_3$, 400 MHz) δ 5.96-5.86 (m, 1H), 5.81-5.72 (m, 1H), 5.54-5.47 (m, 1H) 5.30-5.25 (m, 1H), 5.20-5.16 (m, 1H), 4.29-4.26 (m, 1H), 4.17-4.08 (m, 2H), 3.77-3.68 (m, 2H), 3.36 (dd, *J* = 4.8, 4.8 Hz, 1H), 2.38 (bs, 1H), 2.23 (bs, 1H), 1.71 (d, *J* = 4.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 134.6, 129.6, 128.7, 117.5, 81.41, 72.87, 71.27, 61.54, 17.80; IR (CH_2Cl_2) 3598, 3057, 2988, 2687, 2308, 1424, 1266 cm^{-1}; $[\alpha]^{26}_D$ –1.6° (*c* = 0.50, CH_2Cl_2).

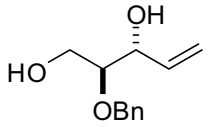


^1H NMR ($CDCl_3$, 400 MHz) δ 7.38-7.24 (m, 5H), 5.78 (ddt, *J* = 17.2, 10.4, 6.0 Hz, 1H), 5.24-5.11 (m, 2H), 4.89 (d, *J* = 5.2 Hz, 1H), 4.00-3.90 (m, 2H), 3.73-3.63 (m, 2H), 3.51-3.48 (m, 1H), 3.08 (bs, 1H), 2.43 (bs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.8, 134.4, 128.3, 127.7, 126.2, 117.6, 82.16, 74.02, 71.24, 61.38, 51.36; IR (CH_2Cl_2) 3598, 2930, 2887, 2370, 1621, 1455, 1390, 1096, 1058 cm^{-1}.



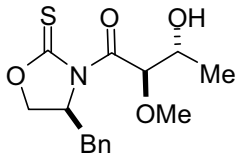
^1H NMR ($CDCl_3$, 400 MHz) δ 7.37-7.28 (m, 5H), 4.62 (s, 2H), 3.86-3.75 (m, 3H), 3.35 (dt *J* = 4.4, 4.0 Hz, 1H), 2.46-2.34 (m, 2H), 1.50-1.44 (m, 3H), 1.34-1.24 (m, 6H), 0.87 (t, *J* = 6.8

Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.0, 128.5, 128.0, 127.9, 81.45, 71.90, 61.06, 32.90, 31.78, 25.57, 22.55, 13.99; IR (CH_2Cl_2) 3690, 3601, 3053, 2988, 2934, 2308, 1606, 1424, 1266 cm^{-1}; $[\alpha]^{26}_D$ +13.8° (*c* = 0.85, CH_2Cl_2).

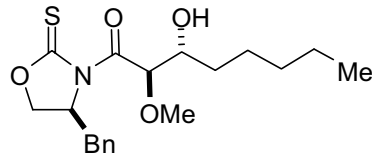


^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36-7.24 (m, 5H), 5.95-5.86 (m, 1H), 5.39-5.34 (m, 1H), 5.25-5.21 (m, 1H), 4.69-4.61 (m, 1H), 4.40-4.37 (m, 1H), 3.80-3.73 (m, 2H), 3.44 (dt, *J* = 4.8, 4.4 Hz, 1H), 2.63 (bs, 1H), 2.30 (bs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.8, 128.6, 128.5, 128.0, 127.9, 116.5, 81.25, 72.82, 72.22, 61.38; IR (CH_2Cl_2) 3682, 3601, 2930, 2880, 1606, 1355, 1208, 1096 cm^{-1}; $[\alpha]^{26}_D$ +14.1° (*c* = 0.75, CH_2Cl_2).

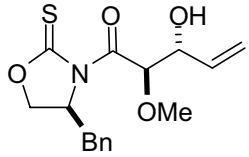
α-Methoxy glycolyl imide (**73**) adducts:



^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33-7.20 (m, 5H), 5.90 (d, *J* = 5.6 Hz, 1H), 5.08-5.02 (m, 1H), 4.39-4.36 (m, 2H), 4.17-4.14 (m, 1H), 3.40 (s, 3H), 3.26 (dd, *J* = 13.6, 3.6 Hz, 1H), 2.75 (dd, *J* = 13.2, 10.0 Hz, 1H), 2.66 (bd, *J* = 8.4 Hz, 1H) 1.34 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 186.0, 172.5, 134.8, 129.4, 129.0, 127.5, 82.70, 71.13, 69.44, 60.12, 58.52, 37.59, 19.33; IR (CH_2Cl_2) 3053, 2984, 2937, 2308, 1718, 1366, 1328, 1197 cm^{-1}; $[\alpha]^{27}_D$ +276° (*c* = 0.70, CH_2Cl_2).



^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34-7.21 (m, 5H), 5.93 (d, *J* = 6.8 Hz, 1H), 5.08-5.02 (m, 1H), 4.40-4.34 (m, 2H), 3.94-3.88 (m, 1H), 3.38 (s, 3H), 3.28 (dd, *J* = 13.6, 3.6 Hz, 1H), 2.75 (dd, *J* = 13.6, 10.0 Hz, 1H), 2.55 (d, *J* = 10.4 Hz, 1H), 2.02-1.55 (m, 2H), 1.41-1.23 (m, 6H), 0.89-0.85 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 186.2, 172.9, 134.9, 129.4, 129.0, 127.5, 81.96, 73.58, 71.07, 60.19, 58.41, 37.45, 33.67, 31.62, 25.15, 22.54, 13.97; IR (CH_2Cl_2) 3049, 2988, 2934, 2308, 1710, 1424, 1370, 1316, 1189 cm^{-1}; $[\alpha]^{23}_{D}$ +222° (*c* = 0.70, CH_2Cl_2).

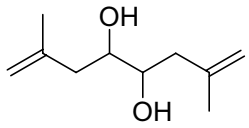


^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34-7.21 (m, 5H), 6.11-6.03 (m, 2H), 5.41-5.36 (m, 1H), 5.29-5.27 (m, 1H), 5.06-5.00 (m, 1H), 4.59-4.53 (m, 1H), 4.41-4.33 (m, 2H), 3.42 (s, 3H), 3.26 (dd, J = 13.2, 3.2 Hz, 1H), 2.89 (d, J = 9.6 Hz, 1H), 2.71 (dd, J = 13.6, 10.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 185.9, 171.7, 136.0, 134.9, 129.4, 129.1, 127.5, 117.2, 81.43, 73.55, 71.16, 60.19, 58.63, 37.66; IR (CH_2Cl_2) 3065, 2988, 2687, 2308, 1710, 1424, 1370, 1328, 1266, 1200 cm^{-1}; $[\alpha]^{23}_{D}$ +220° (*c* = 0.69, CH_2Cl_2).

5.2.2 1st Generation BCDE fragment synthesis

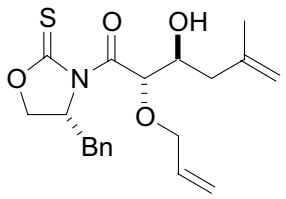
5.2.2.1. Synthesis of the B ring aldehyde

2,7-dimethylocta-1,7-diene-4,5-diol **144**[104]



To a solution of methallyl iodide (129 g, 709 mmole), glyoxal (49.9 g, 338 mmole; 40% aqueous sol.), 350 mL THF and 350 water was added powered tin (84.2 g, 709 mmole; 325 mesh). The solution was placed in a sonicator for 2 h. After the sonication, 400 mL of a 25 % aqueous KOH solution and 400 mL of Et_2O were added and the entire mixture was filtered through celite. The organic layer was separated and the aqueous layer extracted twice with Et_2O. The combined organic extracts were dried over $MgSO_4$. Purification by distillation under reduced pressure gave 57 g (99%) of the desired diol **144** as a mixture of stereoisomers.

Anti adduct **143**

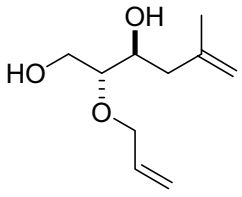


i) Preparation of the aldehyde: A solution of 2,7-dimethylocta-1,7-diene-4,5-diol (**144**) (0.233 g, 1.37 mmole) in 1 mL CH_2Cl_2 and 1 mL pH = 4 buffer was cooled to 0 ºC. Sodium periodate (0.293 g, 1.37 mmole) was added and the reaction mixture was stirred at 0 ºC for 30 min followed by 1 h at room temperature. The reaction was poured into a separatory funnel and washed with aqueous $Na_2S_2O_3$. The organic layer was separated and the aqueous layer extracted with a minimal amount of CH_2Cl_2. The combined organic extracts were washed with brine and dried over Na_2SO_4. The aldehyde (**145**) solution was then cooled to -78 ºC before use.

ii) Aldol addition: To a stirred solution of allyl glycolate **146** (see prep of enantiomer (**77)**; prepared from L-phenylalanine) (0.400 g, 1.37 mmole) in 14 mL anhydrous CH_2Cl_2 at -78 °C

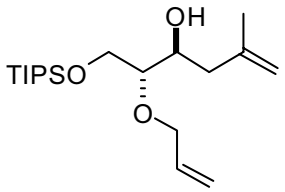
under an argon atmosphere was added $TiCl_4$ (0.166 mL, 1.51 mmole) dropwise. The resulting orange solution was allowed to stir for 10 min after which (–)-sparteine (0.347 mL, 1.51 mmole) dissolved in 3 mL CH_2Cl_2 was added dropwise. The resulting purple solution was stirred for an additional 1 h. A second batch of $TiCl_4$ (0.601 mL, 5.48 mmole) was added to the reaction immediately prior to addition of the aldehyde prepared above via cannula. After stirring for 30 min at –78 ºC, the reaction was quenched with saturated NH_4Cl. The organic layer was separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to give the crude product as a mixture of diastereomers (98:2 anti/anti, 89:11 anti/syn; by NMR analysis). Purification by flash chromatography gave an inseparable mixture of the product **143** (0.88 mmole) and small amounts of recovered starting material (64% of major diastereomer, 71% b.r.s.m.; determined by NMR analysis on mixture). On scale-up (117 mmole) the reaction yielded ~65% of the major diastereomer, with slightly lower selectivity (5:1). ^{1}H NMR purified sample (400 MHz, $CDCl_3$) δ 7.33-7.20 (m, 5H), 6.12 (d, 1H, *J* = 6.8 Hz), 5.94-5.85 (m, 1H), 5.28 (dd, 1H, *J* = 17.2, 1.2 Hz), 5.18 (dd, 1H, *J* = 12.5, 1.0 Hz), 5.05-4.98 (m, 1H), 4.87 (s, 1H), 4.84 (s, 1H), 4.36 (dd, 1H, *J* = 9.2, 2.8 Hz), 4.35-4.29 (m, 1H), 4.13-4.06 (m, 1H), 4.04-4.02 (m, 2H), 3.27 (dd, 1H, *J* = 13.2, 3.6 Hz), 2.74 (dd, 1H, *J* = 13.2, 10.0 Hz), 2.53 (dd, 1H, *J* = 14, 2.4 Hz), 2.52 (d, 1H, *J* = 9.2 Hz), 2.37 (dd, 1H, *J* = 14, 9.6 Hz), 1.78 (s, 3H).

Diol **147**



To the mixture of aldol adduct **143** (0.88 mmole) and unreacted starting material obtained in the previous step was added 5 mL of Et_2O and methanol (0.053 mL, 1.32 mmole). The solution was cooled to 0 ºC and lithium borohydride (0.660 mL, 1.32 mmole; 2 M in THF) was added slowly. After stirring for 1 h, the solution was quenched with 1N KOH and stirred for 2 h at room temperature. The organic layer was separated and the aqueous layer was saturated with NaCl and extracted five times with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography gave 0.128 g (78%) of the desired diol **147**, as well as recovered chiral auxiliary. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91-5.81 (m, 1H), 5.22 (ddd, 1H, *J* = 17.2, 3.2, 1.6), 5.13 (ddd, 1H, *J* = 10.4, 2.8, 1.2 Hz), 4.81 (m, 1H)), 4.74 (d, 1H, *J* = < 1.0 Hz), 4.10-3.99 (m, 2H), 3.86 (ddd, 1H, *J* = 9.6. 5.6, 3.6 Hz), 3.75-3.68 (m, 2H), 3.21 (dd, 1H, *J* = 10. 4.4 Hz), 2.91 (t, OH, *J* = 5.6 Hz), 2.77 (d, OH, *J* = 3.2 Hz), 2.31 (dd, 1H, *J* = 14, 3.2 Hz), 2.10 (ddd, 1H, *J* = 14, 10, 0.8 Hz), 1.70 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 142.2, 134.6, 117.2, 113.3, 81.2, 71.0, 69.2, 61.1, 41.9, 22.2; IR (film) 3398 (br), 3076, 2935, 1648, 1426, 1079 cm^{-1}; $[\alpha]^{28}_D$ = –3.7 (*c* 2.4, CH_2Cl_2).

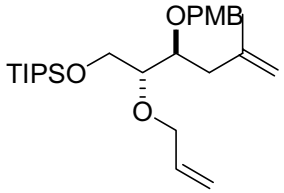
Silyl ether



To a solution of the diol **147** obtained in the previous step (3.69 g, 19.8 mmole) and 150 mL dimethylformamide was added imidazole (4.04 g, 59.4 mmole) followed by triisopropylsilyl chloride (4.36 mL, 19.8 mmole). The solution was allowed to stir for 15 h at room temperature. After dilution of the solution with aqueous $NaHCO_3$, the aqueous layer was extracted three times with Et_2O. The combined organic layers were dried over $MgSO_4$ and

concentrated in vacuo. Purification by flash chromatography gave 6.48 g (95%) of the desired silyl ether. ^{1} H NMR (400 MHz, CDCl3) δ 5.94-5.84 (m, 1H), 5.24 (d, 1H, *J* = 17.2 Hz), 5.14 (d, 1H, *J* = 10.4 Hz), 4.82 (d, 2H, *J* = 17.6 Hz), 4.17 (dd, 1H, *J* = 12.4, 5.2 Hz), 4.07 (dd, 1H, *J* = 12.8, 5.6 Hz), 3.92-3.80 (m, 3H), 3.35 (dd, 1H, *J* = 9.6, 5.2 Hz), 2.57 (d, 1H, *J* = 2.4 Hz), 2.35 (dd, 1H, *J* = 14.0, ~0 Hz), 2.18 (dd, 1H, *J* = 13.6, 10.4 Hz), 1.76 (s, 3H), 1.10-0.99 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 135.0, 117.0, 113.0, 81.5, 72.0, 70.2, 64.0, 41.4, 22.3, 17.9, 17.7, 11.8; IR (film) 3486 (br), 2942, 2867, 1739, 1643, 1462, 1376, 1247, 1091 cm^{-1}.

PMB ether **148**

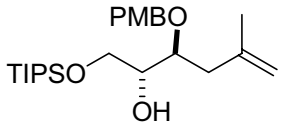


Preparation of PMBBr: To a flask containing *p*-methoxybenzyl alcohol (6.29 mL, 50.4 mmole) was added hydrobromic acid (~ 48% aqueous solution, 14.5 mL, 2.3 eq. by volume). The solution was allowed to stir for 15 min at room temperature. The reaction was then diluted with Et_2O and the aqueous layer separated. The organic layer was washed with aqueous $NaHCO_3$, then brine. The organic layer was dried over $CaCl_2$, concentrated in vacuo, and used immediately in the next reaction.

A solution of the alcohol 11.5 g, 33.6 mmole) in 40 mL DMF under an argon atmosphere was added slowly to a solution containing NaH (4.04 g, 100.9 mmole; 60% dispersion in mineral oil) and 100 mL DMF at 0 ºC. After stirring for 10 min, a solution of 40 mL DMF and PMBBr (6.30 g, 50.4 mmole) was added. The reaction was allowed to warm to room temperature and stirred for 2 h. The reaction was carefully quenched at 0 ºC with saturated

NH_4Cl, followed by the addition of ~500 mL saturated NH_4Cl and 500 mL Et_2O. The organic layer was separated and the aqueous layer extracted twice with Et_2O. The combined organic extracts were washed with H_2O, then brine, and dried over $MgSO_4$. Purification by flash chromatography gave 13.4 g (86%) of desired product **148**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.24-7.22 (m, 2H), 6.86-6.81 (m , 2H), 5.95-5.86 (m, 1H), 5.27-5.21 (m, 1H), 5.14-5.10 (m, 1H), 4.79 (s, 2H), 4.50 (AB, 2H, J_{AB} = 11.2 Hz, Δv_{AB} = 24.8 Hz), 4.19 (ddt, 1H, *J* = 12.8, 5.6, 1.6), 4.12 (ddt, 1H, *J* = 12.8, 5.6, 1.6 Hz), 3.82-3.73 (m, 3H), 3.78 (s, 3H), 3.55-3.51 (m, 1H), 2.35-2.27 (m, 2H), 1.72 (s, 3H), 1.13-1.02 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 143.2, 135.5, 130.9, 129.5, 116.5, 113.6, 112.6, 81.3, 77.4, 72.1, 71.9, 63.2, 55.2, 39.0, 22.9, 18.0, 11.9; IR (film) 2941, 2866, 1613, 1513, 1247, 1095 cm^{-1}; $[\alpha]^{24}_D$ = +4.0 (*c* 1.25, CH_2Cl_2).

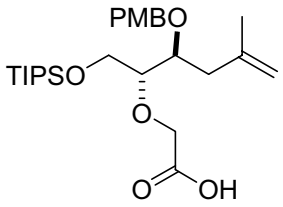
Alcohol **142**



The allyl ether **148** (9.06 g, 19.6 mmole) and 200 mL Et_2O were cooled to 0 ºC under an argon atmosphere. Ti(*i*-OPr)$_4$ (5.78 mL, 19.6 mmole) was added followed by syringe pump addition of *n*-BuMgCl (24.5 mL, 49.0 mmole; 2M in Et_2O) over one hour. Immediately following the addition the reaction was quenched with ~ 100 mL H_2O. The biphasic mixture was filtered through a small pad of celite and washed through with several portions of EtOAc. The organic layer was separated and washed with saturated NH_4Cl. The aqueous layer was extracted twice with EtOAc and the combined extracts were dried over $MgSO_4$. Purification by flash chromatography gave 7.13 g (86%) of the desired alcohol **142** as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.25-7.22 (m, 2H), 6.86-6.83 (m, 2H), 4.84 (bs, 2H), 4.52 (AB, 2H, J_{AB} = 10.8 Hz, Δv_{AB} = 23.2 Hz), 3.82-3.80 (m, 1H), 3.77 (s, 3H), 3.79-3.75

(m, 1H), 3.73-3.72 (m, 1H), 3.71-3.65 (m, 1H), 2.62 (d, 1H, *J* = 3.2 Hz), 2.39 (dd, 1H, *J* = 14.2, 4.0 Hz), 2.31 (dd, 1H, *J* = 14.2, 7.6 Hz), 1.78 (s, 3H), 1.15-1.03 (m, 21 H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 142.8, 130.7, 129.4, 113.7, 112.9, 77.6, 73.2, 72.0, 64.0, 55.1, 39.0, 22.9, 18.1, 17.89, 17.85, 11.9; IR (film) 2941, 1648, 1613, 1586, 1513, 1464, 1383, 1301, 1249, 1173, 1067 cm^{-1} ; $[\alpha]^{24}_D$ = +23 (*c* 1.16, CH_2Cl_2).

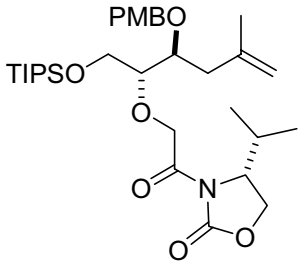
Carboxylic Acid



Sodium hydride (2.02 g, 50.6 mmole; 60 % in mineral oil; washed 3 times with hexanes) was dissolved in 10 mL THF and cooled to 0 ºC under an argon atmosphere. A solution of bromoacetic acid (2.82 g, 20.3 mmole) in 10 mL THF was added slowly and the resulting solution was allowed to stir for 10 min. The alcohol **142** prepared above (7.13 g, 16.9 mmole) was dissolved in 10 mL DMF and added slowly to the reaction. The reaction mixture was warmed to room temperature and stirred for 15 h. The reaction was then quenched with saturated NH_4Cl. The organic layer was separated and the aqueous layer was extracted twice with EtOAc. The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography gave 7.37 g (91%) of the desired acid as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22-7.20 (m, 2H), 6.86-6.83 (m, 2H), 4.84 (s, 1H), 4.79 (s, 1H), 4.53 (AB, 2H, J_{AB} = 11.5 Hz, Δv_{AB} = 15.0 Hz), 4.19 (AB, 2H, J_{AB} = 17.5 Hz, Δv_{AB} = 22.4 Hz), 3.80-3.76 (m, 1H), 3.78 (s, 3H), 3.72-3.66 (m, 2H), 3.51-3.48 (m, 1H), 2.33 (dd, 1H, *J* = 14.5, 8.0 Hz), 2.14 (dd, 1H, *J* = 14.0, 5.0 Hz), 1.70 (s, 3H), 1.15-1.08 (m, 3H), 1.05-1.02 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 159.5, 141.8, 129.8,

129.6, 113.8, 113.6, 84.8, 76.3, 72.3, 68.9, 63.3, 55.2, 38.6, 22.7, 17.8, 11.8; IR (film) 2943, 1766, 1731, 1613, 1513, 1463, 1351, 1248, 1110 cm^{-1}; $[\alpha]^{26}_{D}$ = +15 (*c* 1.18, CH_2Cl_2).

Glycolate **150**

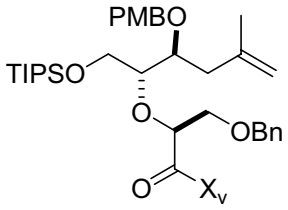


To a round-bottom flask containing 60 mL anhydrous THF and the carboxylic acid (4.06 g, 8.44 mmole) under an argon atmosphere was added triethylamine (1.29 mL, 9.28 mmole). The solution was cooled to -78 ºC and freshly distilled pivaloyl chloride (1.14 mL, 9.28 mmole) was added dropwise over a 20 min period. The solution was then warmed to 0 ºC, maintained at that temperature for 1 h and recooled to -78 ºC.

A separate flask containing 30 mL THF and (R)-4-isopropyl-2-oxazolidinone (1.42 g, 11.0 mmole) was cooled to -78 ºC. *n*-BuLi (6.33 mL, 10.1 mmole; 1.60 M in hexanes) was added dropwise over 20 min and stirred for and additional 20 minutes. The resulting solution was then transferred via cannula to the mixed anhydride prepared above. The resulting solution was allowed to stir at -78 ºC for 1 h. The reaction was quenched using saturated $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over $MgSO_4$. Purification by flash chromatography yielded 4.48 g (90%) of the desired glycolate **150**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.21 (m, 2H), 6.82-6.79 (m, 2H), 5.00 (AB, 2H, J_{AB} = 18.3 Hz, $\Delta\nu_{AB}$ = 11.2 Hz), 4.83 (s, 2H), 4.57 (AB, 2H, J_{AB} = 11.0 Hz, $\Delta\nu_{AB}$ = 21.9 Hz), 4.44-4.40 (m, 1H), 4.30-4.22 (m, 2H), 3.97-3.87 (m, 3H), 3.80 (s, 3H), 3.72-3.68 (m, 1H), 2.47-2.34 (m, 3H), 1.78 (s, 3H), 1.17-1.05 (m, 21H),

0.93 (d, 3H, *J* = 7.0 Hz), 0.85 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 159.0, 153.7, 142.9, 130.8, 129.3, 113.5, 112.5, 82.6, 77.8, 71.9, 71.0, 64.1, 63.8, 58.0, 55.1, 38.9, 28.2, 26.9, 22.7, 17.9, 17.7, 14.5, 11.7; IR (film) 2942, 2866, 1784, 1717, 1613, 1513, 1464, 1389, 1249, 1209 cm^{-1}; $[\alpha]^{26}_D$ = -38 (*c* 1.41, CH_2Cl_2).

Alkylation adduct

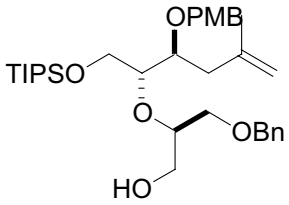


A flask containing a solution of freshly prepared sodium bis(trimethylsilyl)amide (12.0 mL, 8.97 mmole; 0.75 M in toluene/THF) and 30 mL THF under an argon atmosphere was cooled to -78 ºC. The glycolate **150** (3.54 g, 5.98 mmole) dissolved in 30 mL THF was added dropwise over 20 min and the solution was stirred at -78 ºC for 45 minutes.

A separate flask containing formaldehyde dibenzyl acetal (3.84 g, 17.9 mmole) under an argon atmosphere was cooled to 0 ºC. Dry iodotrimethylsilane (2.47 mL, 17.3 mmole) was added and the resulting mixture was stirred for 30 min. The solution was then transferred via cannula to the flask containing the enolate and stirred for 30 min. The reaction was quenched using saturated NH_4Cl. The organic layer was separated and the aqueous layer extracted twice with EtOAc. The combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography gave 3.96 g (93%) of the desired alkylation product as a single diastereomer (judged by NMR analysis). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22-7.14 (m, 7H), 6.77-6.75 (m, 2H), 5.65-5.63 (m, 1H), 4.73 (s, 2H), 4.55 (d, 1H, *J* = 12.0 Hz), 4.52 (d, 1H, *J* = 11.0 Hz), 4.48 (d, 1H, *J* = 12 Hz), 4.36 (d, 1H, *J* = 11 Hz), 4.26-4.24 (m, 1H), 3.96 (dd, 1H, *J* = 9.0, 2.5 Hz), 3.85-3.66 (m, 7H), 3.71 (s, 3H), 2.38 (dd, 1H, *J* = 14.5, 9.0 Hz), 2.22-2.17 (m, 2H), 1.66 (s, 3H), 1.03-0.93 (m, 21H),

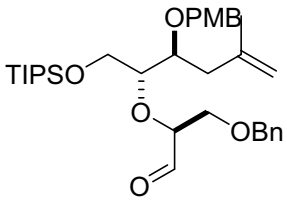
0.75 (d, 3H, *J* = 7.0 Hz), 0.66 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 159.0, 153.7, 143.2, 138.1, 130.9, 129.4, 128.1, 127.6, 127.4, 113.5, 112.4, 83.3, 79.2, 78.4, 73.3, 72.2, 71.3, 63.6, 63.4, 58.2, 55.2, 38.2, 28.1, 22.8, 17.9, 17.7, 14.5, 11.8; IR (film) 2941, 2866, 1781, 1715, 1613, 1513, 1463, 1387, 1301, 1247, 1109 cm^{-1}; $[\alpha]^{24}_D$ = +43 (*c* 1.2, CH_2Cl_2).

Alcohol **151**



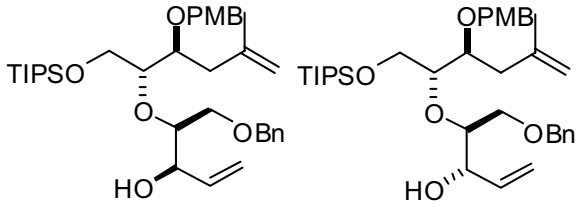
To a solution of the alkylation adduct (3.96 g, 5.56 mmole) obtained above in 50 mL Et_2O was added anhydrous methanol (0.334 mL, 8.34 mmole). The contents were cooled to 0 ºC under an argon atmosphere. Lithium borohydride (4.17 mL, 8.34 mmole; 2 M in THF) was added dropwise. After stirring for 1 h at 0 ºC, the reaction was quenched with saturated Na^+/K^+ tartrate and stirred for 3 h at room temperature. The organic layer was separated and the aqueous layer extracted twice with EtOAc. The combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography gave 2.65 g (81%) of the desired product **151** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.22 (m, 7H), 6.84-6.81 (m, 2H), 4.79 (bs, 2H), 4.49 (AB, 2H, J_{AB} = 11.6 Hz, Δv_{AB} = 19.2 Hz), 4.48 (s, 2H), 3.84-3.77 (m, 3H), 3.77 (s, 3H), 3.75-3.63 (m, 3H), 3.57-3.51 (m, 2H), 3.46 (dd, 1H, *J* = 10, 6.0 Hz), 3.40 (dd, 1H, *J* = 10, 5.6 Hz), 2.36 (dd, 1H, *J* = 14.4, 9.2 Hz), 2.21 (dd, 1H, *J* = 14.4, 3.2 Hz), 1.67 (s, 3H) 1.05-0.94 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 142.9, 138.1, 123.0, 129.8, 128.3, 127.6, 113.7, 112.8, 82.1, 81.6, 73.4, 71.8, 70.7, 63.4, 63.0, 55.2, 37.4, 22.7, 18.0, 11.8 ; IR (film) 2941, 2864, 1613, 1513, 1456, 1249, 1101 cm^{-1}; $[\alpha]^{24}_D$ = -6.6 (*c* 0.51, CH_2Cl_2).

Aldehyde



To a solution of oxalyl chloride (2.36 mL, 4.71 mmole; 2M in CH_2Cl_2) and 20 mL CH_2Cl_2 under an argon atmosphere at –78 ºC was slowly added a solution of DMSO (0.669, 9.43mmole) and 4 mL CH_2Cl_2, keeping the internal temperature < –65 ºC. After stirring for 10 min at –78 ºC, a solution of the alcohol **151** (1.84 g, 3.14 mmole) dissolved in 7 mL CH_2Cl_2 was added slowly, again keeping the temperature < –65 ºC. The resulting solution was stirred for 30 min followed by the dropwise addition of triethylamine (2.19 mL, 15.7 mmole). After warming the reaction mixture to room temperature, 150 mL of a 1:1 mixture of EtOAc / hexanes was added along with 100 mL H_2O. The organic layer was separated and the aqueous layer was washed with 100 mL each of saturated $NaHSO_4$, $NaHCO_3$, H_2O, and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was then passed through a small pad a silica gel and concentrated. The aldehyde was use immediately in the next reaction without further purification.

Dienes **152** and **153**



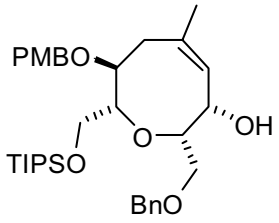
152 **153**

Preparation of vinyl magnesium bromide: To a flask fitted with a dry ice condenser and an addition funnel was added magnesium turnings (0.628 g, 25.8 mmole), 2 mL THF, and a small crystal of iodine. A solution of 2 mL THF and vinyl bromide (2.00 mL, 28.4 mmole) was

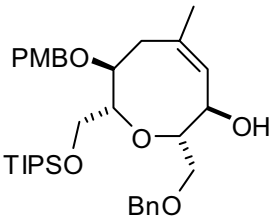
added to the addition funnel and added dropwise to the magnesium/I_2 solution at a rate to maintain reflux temperature. The mixture as allowed to stir for 30 min and diluted with additional THF to make a 1.4 M solution.

A flask containing 20 mL THF and freshly prepared vinyl magnesium bromide (6.73 mL, 9.42 mmole; 1.40 M in THF) was cooled to 0 ºC under an argon atmosphere. The aldehyde prepared in the previous step was diluted with 10 mL THF and added dropwise. After stirring for 5 min, saturated NH_4Cl was slowly added to the reaction mixture. The organic layer was separated and the aqueous layer extracted twice with EtOAc. The combined organic fractions were washed with saturated NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography gave 1.55 g (80% over two steps) of the desired products **152** and **153** as a 3:1 inseparable mixture of alcohol epimers favoring compound **152.**

Oxocenes **154** and **155**



154



155

The diene fragment obtained in the previous step (0.278 g, 0.454 mmole) was dissolved in 227 mL of CH_2Cl_2 and degassed using an argon purge for 1 h. Grubbs' second generation catalyst ($Cl_2(PCy_3)$(IMes)Ru=CHPh; 0.038 g, 0.045 mmole) was added to the reaction and the solution was heated to reflux under an argon atmosphere for 12 h. After cooling the reaction mixture to room temperature, air was bubbled through the solution for 2 h. Evaporation of the solvents and purification by flash chromatography gave 0.151 g of the major isomer **155** and 0.047 g of the minor isomer **154** (75% total). ^{1}H NMR major

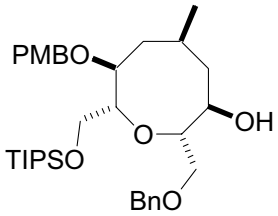
compound **155** (400 MHz, $CDCl_3$) δ 7.35-7.26 (m, 5H), 7.21-7.18 (m, 2H), 6.87-6.83 (m, 2H), 5.47 (d, 1H, *J* = 4.4 Hz), 4.64 (d, 1H, *J* = 12.0 Hz), 4.61 (d, 1H, *J* = 11.2 Hz), 4.46 (d, 1H, *J* = 12 Hz), 4.43-4.42 (m, 1H), 4.27 (d, 1H, *J* = 11.2 Hz), 3.87-3.84 (m, 2H), 3.78 (s, 3H), 3.71 (dd, 1H, *J* = 10, 5.6 Hz), 3.55-3.42 (m, 4H), 3.15 (d, 1H, *J* = 2 Hz), 2.63 (dd, 1H, *J* = 13.6, 2.8 Hz), 2.29 (dd, 1H, *J* = 13.6, 2.0 Hz), 1.86 (s, 3H), 1.08-0.99 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 137.6, 134.6, 130.3, 130.1, 129.4, 128.4, 127.8, 113.7, 83.4, 83.0, 78.7, 73.7, 72.5, 72.0, 70.8, 65.6, 55.1, 31.9, 26.4, 18.0, 11.9; IR (film) 2941, 2864, 1612, 1513, 1462, 1248, 1089 cm^{-1}; $[\alpha]^{24}_D$ = +123 (*c* 0.51, CH_2Cl_2).

^1H NMR minor compound **154** (400 MHz, $CDCl_3$) δ 7.32-7.26 (m, 5H), 7.20-7.18 (m, 2H), 6.84-6.82 (m, 2H), 5.62 (d, 1H, *J* = 3.8 Hz), 4.60-4.57 (m, 2H), 4.45 (d, 1H, *J* = 12.4 Hz), 4.37 (dd, 1H, *J* = 7.6, 2.8 Hz), 4.27 (d, 1H, *J* = 11.2 Hz), 3.89 (dd, 1H, *J* = 10, 1.6 Hz), 3.78 (s, 3H), 3.70-3.64 (m, 3H), 3.55-3.41 (m, 3H), 3.16 (d, 1H, *J* = 13.2 Hz), 2.93 (d, 1H, *J* = 3.6 Hz), 2.33 (dd, 1H, *J* = 13.6, 4.8 Hz), 1.83 (d, 3H, *J* = 1.2 Hz), 1.06-0.96 (m, 21H).

Mitsunobu reaction[175] to convert **154** to **155**:

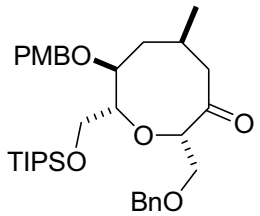
To a solution of alcohol **154** (0.101 g, 0.190 mmole) and 4 mL benzene under an argon atmosphere was added triphenylphosphine (0.249 g, 0.949 mmole), *p*-nitrobenzoic acid (0.159 g, 0.949 mmole), followed by diethylazodicarboxylate (DEAD) (0.209 mL, 1.33 mmole). The solution was allowed to stir for 1 h and the solvents were evaporated. Purification by flash chromatography gave the *p*-nitrobenzoate. The crude material was then dissolved in 2 mL CH_2Cl_2. After cooling to –78 ºC, DIBAL (0.400 mL; 1 M in hexanes) was added and the reaction was stirred for 30 min. The reaction was then quenched using saturated Na^+/K^+ and stirred overnight. The organic layer was separated and the aqueous layer extracted twice with CH_2Cl_2. The combined extracts were dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography gave 0.64 g (50%) of oxocene **155**.

Oxocane **162**



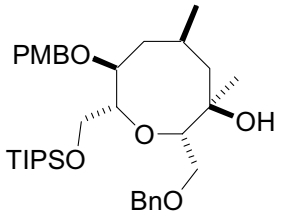
To a solution containing the oxocene **155** (0.384 g, 0.657 mmole) and 44 mL CH_2Cl_2 was added Crabtree's catalyst ($[PCy_3][COD][Pyr]Ir^+$ PF_6^-; 0.53 g, 0.066 mmole). The reaction flask was fitted with a hydrogen filled balloon and cooled to –50 ºC (prior to H_2 addition). The flask was evacuated under vacuum and filled with hydrogen. The procedure was repeated twice more and the reaction mixture was left to stir under an H_2 atmosphere for 2 h at -50 ºC. The hydrogen balloon was removed and the solution was warmed to room temperature. Evaporation of the solvents followed by purification by flash chromatography gave 0.359 g (93%) of the desired compound **162** as a single diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.25 (m, 5H), 7.22-7.18 (m, 2H), 6.86-6.83 (m, 2H), 4.59-4.48 (m, 3H), 4.27 (d, 1H, *J* = 11.2 Hz), 3.92 (dd, 1H, *J* = 10.0, 2.0 Hz), 3.89-3.87 (m, 1H), 3.78 (s, 3H), 3.75-3.70 (m, 1H), 3.65-3.3.46 (m, 4H), 3.30 (dt, 1H, *J* = 9.2, 2.8 Hz), 3.22 (d, 1H, *J* = 2.0 Hz), 1.96-1.72 (m, 4H), 1.70-1.60 (m, 1H), 1.09-1.01 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 137.6, 130.5, 129.3, 128.3, 127.7, 127.6, 113.7, 87.6, 83.9, 78.3, 74.2, 73.6, 73.2, 70.9, 65.5, 55.1, 46.1, 41.4, 27.6, 27.2, 17.9, 11.9 ; IR (film) 2941, 2864, 1613, 1513, 1462, 1384, 1301, 1248, 1091 cm^{-1}; $[\alpha]^{25}_D$ = +43 (*c* 0.73, CH_2Cl_2).

Ketone **139**



To a solution of the alcohol **162** (0.360 g, 0.613 mmole) and 6 mL CH_2Cl_2 at room temperature was added Dess-Martin periodinane (0.390 g, 0.920 mmole). The solution was allowed to stir for 1 h. After the addition of a 5:1 aqueous solution of $Na_2S_2O_3$ and $NaHCO_3$ the organic layer was separated and the aqueous layer extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography gave 0.319 g (89%) of the desired ketone **139**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.24 (m, 5H), 7.22-7.19 (m, 2H), 6.86-6.83 (m, 2H), 4.55 (d, 1H, *J* = 12.4 Hz), 4.48 (d, 1H, *J* = 11.6 Hz), 4.47 (d, 1H, *J* = 12.4 Hz), 4.34 (d, 1H, *J* = 11.6 Hz), 4.08-4.06 (m, 1H), 3.89-3.80 (m, 2H), 3.76 (s, 3H), 3.74-3.3.64 (m, 4H), 2.89-2.84 (m, 2H), 2.21 (dd, 1H, *J* = 16, 10 Hz), 1.97-1.92 (m, 1H), 1.57-1.49 (m, 1H), 1.13-1.02 (m, 21 H), 0.95 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.8, 159.0, 138.1, 129.9, 129.2, 128.1, 127.2, 127.1, 113.6, 88.3, 85.0, 76.8, 73.2, 72.7, 70.0, 64.0, 55.0, 48.7, 37.2, 27.7, 23.7, 17.8, 11.8; IR (film) 2941, 2866, 1701, 1612, 1513, 1461, 1361, 1301, 1248, 1110 cm^{-1}; $[\alpha]^{24}_D$ = -37 º (*c* 1.85, CH_2Cl_2).

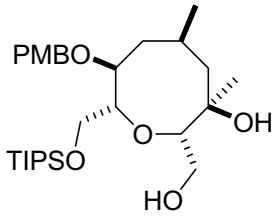
Tertiary alcohol **163**



To a solution of MeMgCl (0.313 mL, 0.940 mmole; 3 M in THF) and 5 mL Et_2O at -78 ºC under an argon atmosphere was added a solution of the ketone **139** (0.110 g, 0.188 mmole) and 5 mL Et_2O dropwise. The reaction mixture was quenched after 10 min with saturated NH_4Cl and allowed to warm to room temperature. The organic layer was separated and the aqueous layer extracted twice with EtOAc. The combined organic fractions were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography

gave 0.106 g (94%) of the desired compound **163** as a >20:1 diastereomeric mixture as detected by NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.25 (m, 5H), 7.22-7.19 (m, 2H), 6.86-6.83 (m, 2H), 4.51 (d, 1H, *J* = 10.8 Hz), 4.50 (AB, 2H, J_{AB} = 11.6 Hz, Δv_{AB} = 14.8 Hz), 4.30 (d, 1H, *J* = 10.8 Hz), 3.93-3.91 (m, 1H), 3.84-3.70 (m, 2H), 3.78 (s, 3H), 3.63-3.47 (m, 3H), 3.44 (s, 1H), 3.33-3.28 (m, 1H), 1.95-1.91 (m, 1H), 1.85-1.79 (m, 2H), 1.65-1.58 (m, 2H), 1.17 (s, 3H), 1.10-0.99 (m, 21H), 1.01 (d, 3H, *J* = 9.6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 137.4, 130.6, 129.3, 128.3, 128.3, 127.7, 127.6, 113.7, 88.2, 84.9, 78.1, 74.1, 73.6, 71.0, 70.8, 65.3, 55.1, 54.0, 42.9, 28.1, 26.9, 21.4, 18.0, 12.0; IR (film) 2942, 2865, 1612, 1513, 1382, 1297, 1248, 1089 cm^{-1} ; $[\alpha]^{25}_D$ = +42 (*c* 0.62, CH_2Cl_2).

Diol **138**

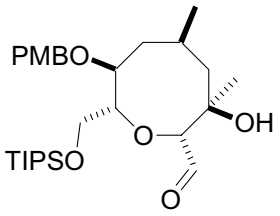


Preparation of LDBB: To a solution of 4,4'-di-*t*-butyl-biphenyl (3.0 g, 11.3 mmole) and 15 mL anhydrous THF under an argon atmosphere was added lithium metal (0.072 g, 10.2 mmole). The solution was placed in a sonicator maintained at 0 ºC for 3 h to make a 0.7 M solution of LDBB.

In a separate flask the benzyl ether **163** (0.118 g, 0.196 mmole) was dissolved in 3 mL THF and cooled to –78 ºC under an argon atmosphere. The LDBB solution was added until the reaction was complete as judged by TLC. The reaction was quenched by the slow addition of H_2O and allowed to warm to room temperature. Separation of the organic layer and extraction of the aqueous layer twice with EtOAc followed by drying of the combined extracts over Na_2SO_4 gave the crude material which was purified by flash chromatography to give 0.099 g (99%) of the desired diol **138**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16-7.14 (m,

2H) 6.84-6.81 (m, 2H), 4.51-4.46 (m, 2H), 4.18 (d, 1H, *J* = 11.2 Hz), 3.98 (dd, 1H, *J* = 10.0, 2.0 Hz), 3.86-3.80 (m, 1H), 3.76 (s, 3H), 3.63-3.57 (m, 3H), 3.40 (dd, 1H, *J* = 10.0, 1.0, Hz), 3.03-2.97 (m, 1H), 1.96 (bs, 1H), 1.87-1.83 (m, 1H), 1.71-1.55 (m, 4H), 1.11-1.05 (m, 21H), 1.10 (s, 3H), 1.07 (d, 3H, *J* = 4.8 Hz), 0.98 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 130.0, 129.5, 113.7, 89.3, 87.6, 78.8, 73.1, 70.3, 66.7, 63.5, 57.1, 55.1, 42.5, 28.1, 27.1, 21.3, 17.8, 11.8; IR (film) 3431, 2944, 2866, 1612, 1513, 1462, 1249, 1065 cm^{-1}; $[\alpha]^{23}_D$ = +44 (*c* 0.73, CH_2Cl_2).

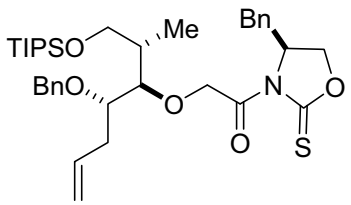
Aldehyde **214**



To a solution of the diol (0.031 g, 0.060 mmole) and 0.6 mL CH_2Cl_2 at room temperature was added Dess-Martin periodinane (0.038 g, 0.090 mmole). After stirring for 1 h at room temperature, the reaction was quenched by the addition of a 5:1 solution of $Na_2S_2O_3$/$NaHCO_3$. The organic layer was separated and the aqueous layer extracted twice with CH_2Cl_2, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography gave 0.027 g (88%) of the desired aldehyde **214** which was used immediately in the HWE coupling reaction.

5.2.2.2. Synthesis of the E fragment phosphonate

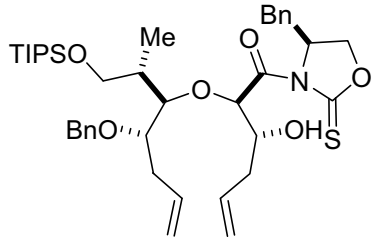
Glycolylimide **176**



To a solution of the carboxylic acid **168** (3.53 g, 7.60 mmole) and 50 mL anhydrous THF under an argon atmosphere was added triethylamine (1.16 mL, 8.36 mmole). The solution was cooled to –78 ºC and pivaloyl chloride (0.943 mL, 7.60 mmole) was added dropwise. The reaction was warmed to 0 ºC, stirred at that temperature for 1 h and recooled to -78 ºC. To a separate flask containing (S)-4-benzyl-2-oxazolidinethione (2.94 g, 15.2 mmole) and 25 mL CH_2Cl_2 at -78 ºC was added *n*-BuLi (6.08 mL, 15.2 mmole; 2.5 M in hexanes) dropwise. After stirring for 30 min, the lithiated auxiliary was cannulated to the anhydride. After stirring for 1 h at –78 ºC the reaction was quenched by the addition of saturated NH_4Cl. The organic layer was separated and the aqueous layer extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography gave 3.47 g (71%) of the glycolate **176**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.18 (m , 10H), 6.04-5.94 (m, 1H), 5.38 (d, 1H, *J* = 18.4 Hz), 5.21 (d, 1H, *J* = 18.4 Hz), 5.18 (dd, 1H, *J* = 17.2, 2.0 Hz), 5.10 (dd, 1H, *J* = 10.4, 2.0 Hz), 4.89-4.83 (m, 1H), 4.60 (AB, 2H, J_{AB} = 12.4 Hz, Δv_{AB} = ~ 0 Hz), 4.29 (dd, 1H, *J* = 9.6, 2.8 Hz), 4.25 (dd, 1H, *J* = 16.8, 9.2 Hz), 3.89-3.86 (m, 1H), 3.80-3.76 (m, 1H), 3.68-3.64 (m, 2H), 3.26 (dd, 1H, *J* = 13.2, 3.2 Hz), 2.64 (dd, 1H, *J* = 13.2, 10.0 Hz), 2.58-2.52 (m, 2H), 2.11-2.05 (m, 1H), 1.16-1.05 (m, 21H), 1.02 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.5, 170.9, 138.4, 135.3, 135.1, 129.2, 128.8, 128.1, 127.6, 127.3, 127.2, 116.7, 81.6, 79.8, 74.1, 71.8, 71.0, 65.6, 59.6,

37.2, 34.5, 17.9, 11.8; IR (film) 2940, 2864, 1717, 1456, 1365, 1325, 1204, 1129 cm^{-1}; $[\alpha]^{23}_D$ = +55.2 (*c* 1.53, CH_2Cl_2).

Anti adduct **177**

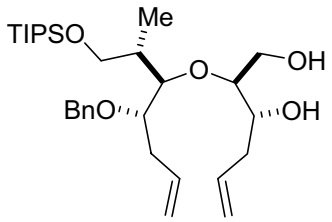


Preparation of the aldehyde: A flask containing 1,7-octadiene-4,5-diol[102] (0.770 g, 5.42 mmole) and 5 mL CH_2Cl_2 and 5 mL of pH = 4 buffer was cooled to 0 ºC. Sodium periodate (1.16 g, 5.42 mmole) was added to the solution and the reaction was stirred for 45 min at 0 ºC. The reaction was then warmed to room temperature and stirred for an additional 1.5 h. After the addition of saturated $Na_2S_2O_3$ and separation of the organic layer, the aqueous portion was extracted with minimal CH_2Cl_2. The combined organic fractions were dried over Na_2SO_4 and filtered. The resulting solution was cooled to –78 ºC.

A separated flask containing a solution of the glycolate **176** (3.47 g, 5.42 mmole) and 50 mL CH_2Cl_2 was cooled to -78 ºC under an argon atmosphere. Neat $TiCl_4$ (0.654 mL, 5.96 mmole) was added dropwise and the reaction was stirred for 10 min. A solution of (–)-sparteine (1.37 mL, 5.96 mmole) in 5 mL CH_2Cl_2 was added slowly to the reaction and the resulting solution was slowly warmed to –40 ºC and the temperature was maintained for 2 h. After recooling the reaction to –78 ºC, additional $TiCl_4$ (1.49 mL, 13.6 mmole) was added immediately prior to aldehyde transfer via cannula. The resulting solution was allowed to stir at –78 ºC for 20 min and quenched with ½ saturated NH_4Cl. The organic layer was separated and the aqueous layer extracted twice with CH_2Cl_2. The combined organic fractions were dried over Na_2SO_4 and concentrated in vacuo to provided the crude material.

Purification by flash chromatography gave 1.88 g (50%) of an inseparable 5:1 mixture of stereoisomers favoring the anti adduct **177** along with 1.35 g recovered starting material (80 % b.r.s.m.). Separation of the diastereomers was possible after removal of the chiral auxiliary.

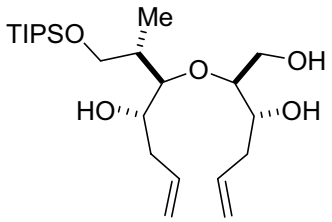
Diol **178**



To a solution of the isomeric mixture obtained the previous reaction (1.86 g, 2.62 mmole), 10 mL Et_2O, and methanol (0.157 mL, 3.93 mmole) at 0 ºC under an argon atmosphere was added lithium borohydride (1.97 mL, 3.96 mmole; 2M in THF). The reaction was allowed to stir for 1 h at 0 ºC followed by the addition of saturated Na^+/K^+ tartrate. The resulting mixture was stirred at room temperature for 15 h. The organic layer was separated and the aqueous layer extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography gave 0.194 g of pure minor isomer, 0.350 g pure major isomer **178** and 0.541 g of mixed product (80% total). Facile purification of the isomers was found after removal of the benzyl ether; mixed fractions were carried through to next reaction. ^{1}H NMR major isomer (400 MHz, $CDCl_3$) δ 7.33-7.26 (m, 5H), 5.93-5.85 (m, 1H), 5.78-5.72 (m, 1H), 5.14-5.00 (m, 4H), 4.55 (AB, 2H, J_{AB} = 11.6 Hz, Δv_{AB} = 13.8 Hz), 3.91-3.52 (m, 8H), 3.40 (d, 1H, *J* = 4.0 Hz), 2.96 (dd, 1H, *J* = 6.8, 4.4 Hz), 2.54-2.44 (m, 1H), 2.40-2.32 (m, 1H), 2.26-2.12 (m, 2H), 1.95-1.86 (m, 1H), 1.15-1.02 (m, 21H), 0.99 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 135.6, 135.5, 135.1, 128.3, 127.8, 127.6, 116.9, 116.7, 81.0, 80.9, 77.5, 72.2, 70.5, 66.0, 61.7, 38.2, 36.9, 34.6,

18.0, 11.9; IR (film) 2942, 2867, 1641, 1462, 1085, 1066 cm^{-1}; $[\alpha]^{25}_D$ = +1.0 (*c* 1.62, CH_2Cl_2).

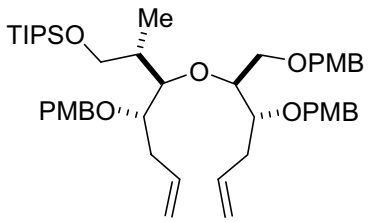
Triol



Preparation of Na/Napthelenide: To a solution of naphthalene (10.0 g, 78 mmole) and 80 mL THF under an argon atmosphere was added sodium metal (1.63 g, 70 mmole). The mixture was sonicated for 2 h to prepare a ~ 0.9 M solution.

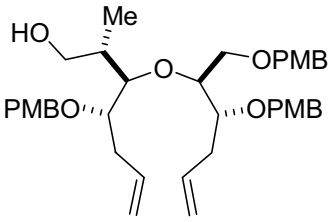
A separate flask containing the benzyl ether isomeric mixture (1.40 g, 2.69 mmole), 30 mL THF, and a glass stir bar under an argon atmosphere was cooled to 0 ºC. The Na/naphthalenide solution was added until the reaction was complete as judged by TLC. The reaction was then quenched by the slow addition of H_2O. Saturated $NaHCO_3$ was added and the organic layer was separated. The aqueous layer was extracted twice with EtOAc and the combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography gave 0.901 g of the major isomer and 0.229 g of the minor isomer (98% total yield). ^{1}H NMR major isomer (400 MHz, $CDCl_3$) δ 5.87-5.76 (m, 2H), 5.13-5.05 (m, 4H), 4.00-3.98 (m, 1H), 3.80-3.78 (m, 2H), 3.76-3.69 (m, 1H), 3.66-3.60 (m, 3H), 3.52 (dd, 1H, *J* = 10.8, 4.8 Hz), 3.39 (dd, 1H, *J* = 8.4, 4.8 Hz), 3.27 (bs, 1H), 3.20 (bs, 1H), 2.33-2.19 (m, 4H), 1.97-1.90 (m, 1H), 1.11-1.02 (m, 21H), 0.94 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.1, 134.8, 117.9, 117.5, 79.9, 78.2, 70.7, 70.5, 65.8, 62.9, 36.9, 36.8, 36.7, 17.93, 17.92, 12.1, 11.9; IR (film) 3306, 2939, 2864, 1638, 1456, 1083 cm^{-1} ; $[\alpha]^{25}_D$ = +31.8 (*c* 1.34, CH_2Cl_2).

Tri-PMB silyl ether **179**



To a solution of the triol (0.605 g, 1.40 mmole) and 7 mL dimethlformamide at 0 ºC under an argon atmosphere was added slowly NaH (0.560 g, 14.0 mmole; 60% dispersion in mineral oil). The mixture was allowed to stir for 10 min before the addition of freshly prepared PMBBr (1.02 mL, 7.0 mmole; see synthesis of compound **148** for PMBBr prep.) The reaction was warmed to room temperature and stirred for 15 h before slowly quenching with a saturated NH_4Cl solution. The aqueous layer was extracted three times with Et_2O. The combined organic fractions were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography gave an inseparable mixture of the desired product **179** and unreacted PMBBr which was carried forward to the next reaction.

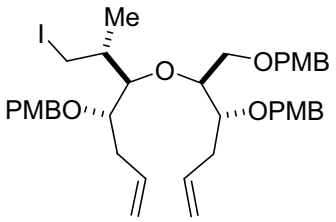
Alcohol **180**



The mixture containing fragment **179** and excess PMBBr prepared in the previous step was dissolved in 10 mL THF. Tetrabutylammonium fluoride (TBAF) (2.1 mL, 2.1 mmole; 1M in THF) was added and the reaction mixture was stirred at room temperature for 1 h. The reaction was diluted with EtOAc and washed with saturated $NaHCO_3$. The organic layer was separated and the aqueous layer extracted with EtOAc. The combined organic extracts

were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography gave 0.801 g (90% over two steps) of the alcohol **180**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.15 (m, 6H), 6.87-6.79 (m, 6H), 5.90-5.73 (m, 2H), 5.08-4.98 (m, 4H), 4.51-4.39 (m, 6H), 3.90-3.95 (m, 1H), 3.81-3.77 (m , 1H), 3.78 (s, 3H), 3.770 (s, 3H), 3.769 (s, 3H), 3.65-3.52 (m, 5H), 3.47-3.42 (m, 1H), 3.15 (dd, 1H, *J* = 7.2, 6.4 Hz), 2.44-2.21 (m, 4H), 2.00-1.94 (m, 1H), 0.91 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 158.9, 158.8, 135.6, 135.2, 130.7, 130.6, 129.5, 129.3, 129.1, 128.9, 128.8, 116.5, 116.3, 113.6, 113.4, 80.7, 79.3, 78.9, 78.7, 72.8, 71.9, 71.5, 69.6, 65.4, 54.8, 37.0, 35.9, 35.6, 11.8; IR (film) 3451, 2933, 1612, 1513, 1463, 1301, 1247, 1173, 1083, 1034 cm^{-1}; $[\alpha]^{22}_D$ = +17.7 (*c* 0.66, CH_2Cl_2).

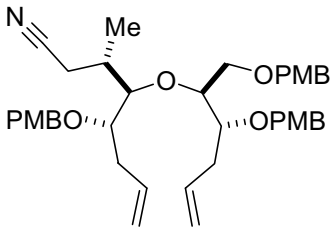
Iodide



To a solution of the alcohol **180** (0.293 g, 0.462 mmole) and 5 mL anhydrous benzene under an argon atmosphere was added imidazole (0.047 g, 0.692 mmole), triphenylphosphine (0.182 g, 0.692 mmole) and iodine (0.152 g, 0.500 mmole). The reaction mixture was allowed to stir for 1 h at room temperature and quenched by the addition of saturated $Na_2S_2O_3$. The solution was diluted with Et_2O and the organic layer was separated. The aqueous layer was extracted twice with Et_2O and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography gave 0.293 g (85%) of the desired alkyl iodide that was used immediately in the next reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.18 (m, 6H), 6.90-6.84 (m, 6H), 5.93-5.81 (m, 2H), 5.13-5.02 (m, 4H), 4.55 (d, 1H, *J* = 11.2 Hz), 4.49-4.52 (m, 5H), 3.90-3.87

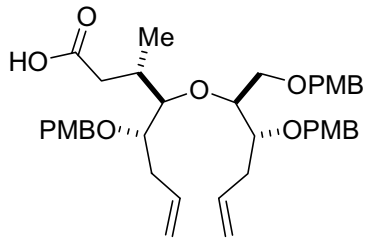
(m, 1H), 3.81-3.77 (m, 10H), 3.69-3.58 (m, 4H), 3.37 (dd, 1H, *J* = 9.6, 6.0 Hz), 3.13 (dd, 1H, *J* = 9.6, 6.0 Hz), 2.47-2.40 (m, 1H), 2.38-2.26 (m, 3H), 1.95-1.90 (m, 1H), 1.14 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 158.97, 158.94, 135.58, 135.55, 130.8, 130.7, 130.2, 129.4, 129.3, 129.2, 116.7, 116.6, 113.7, 113.5, 80.3, 80.0, 79.4, 79.3, 72.9, 72.0, 71.6, 69.5, 55.1, 37.3, 35.8, 35.2, 16.7, 14.7.

Nitrile **215**



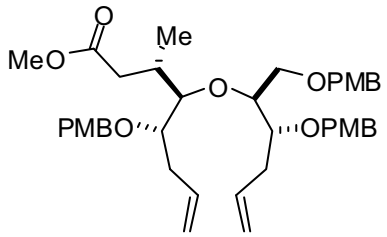
To a flask containing the iodide (0.293 g, 0.393 mmole) and 0.5 mL anhydrous dimethylsulfoxide was added sodium cyanide (0.096 g, 1.97 mmole; use extreme caution when handling this reagent). The reaction mixture was allowed to stir for 15 h followed by dilution with Et_2O and water. The organic layer was separated and the aqueous layer was extracted twice with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography gave 0.229 g (91%) of the desired nitrile **215**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.19 (m, 6H), 6.92-6.83 (m, 6H), 5.90-5.80 (m, 2H), 5.14-5.04 (m, 4H), 4.53-4.43 (m, 6H), 3.80-3.77 (m, 10H), 3.71-3.69 (m, 1H), 3.66-3.58 (m, 4H), 2.50 (dd, 1H, *J* = 16, 6.0 Hz), 2.46-2.21 (m, 6H), 1.13 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 159.1, 135.2, 134.9, 130.6, 130.5, 129.9, 129.4, 129.2, 129.1, 119.6, 117.1, 116.8, 113.7, 113.63, 113.60, 80.0, 79.5, 79.4, 79.4, 72.9, 72.1, 71.6, 69.5, 55.1, 35.8, 35.4, 32.4, 22.1, 15.0; IR (film) 2934, 2241, 1613, 1513, 1463, 1301, 1248, 1173, 1085, 1035 cm^{-1}; $[\alpha]^{18}_D$ = +10.2 (*c* 1.01, CH_2Cl_2).

Carboxylic Acid



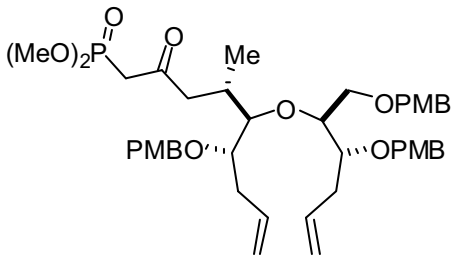
To a solution of the nitrile **215** (0.184 g, 0.286 mmole), 5 mL EtOH, and 2 mL H_2O was added KOH (0.313 g, 4.90 mmole). The solution was heated to reflux temperature for 7 days. The reaction was cooled and acidified with 1N HCl. The aqueous layer was extracted three times with Et_2O and the combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography gave 0.161 g (85%) of the desired acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.20 (m, 6H), 6.89-6.84 (m, 6H), 5.90-5.81 (m, 2H), 5.11-5.02 (m, 4H), 4.56 (d, 1H, *J* = 8.8 Hz), 4.97 (AB, 2H, J_{AB} = 9.2 Hz, Δv_{AB} ~ 0 Hz), 4.47-4.41 (m, 3H), 3.87-3.85 (m, 1H), 3.80-3.78 (m, 9H), 3.71 (t, 1H, *J* = 2.8 Hz), 3.69-3.66 (m, 1H), 3.64-3.62 (m, 2H), 3.60-3.57 (m, 1H), 2.61 (dd, 1H, *J* = 12.4, 4.4 Hz), 2.49-2.43 (m, 1H), 2.39-2.30 (m, 4H), 2.26 (dd, 1H, *J* = 12.4, 6.8 Hz), 1.09 (d, 3H, *J* = 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.3, 159.1, 159.0, 158.9, 135.7, 135.5, 130.73, 130.66, 130.1, 129.4, 129.3, 129.2, 116.7, 116.6, 113.6, 113.5, 80.8, 80.0, 79.4, 79.2, 72.8, 72.1, 71.5, 69.6, 55.1, 38.7, 35.9, 35.4, 31.7, 15.6; IR (film) 2934, 1705, 1613, 1513, 1463, 1301, 1248, 1173, 1085, 1035 cm^{-1}; $[\alpha]^{24}_D$ = +5.3 (*c* 0.66, CH_2Cl_2).

Methyl ester **216**



To a solution of the carboxylic acid (0.407 g, 0.614 mmole) and 3 mL dimethylformamide was added anhydrous K_2CO_3 (0.424 g, 3.07 mmole) and methyl iodide (0.191 mL, 3.07 mmole). The reaction mixture was allowed to stir at room temperature for 30 min, followed by the addition of H_2O and Et_2O. The organic layer was separated and the aqueous layer extracted twice with Et_2O. The combined organic extracts were washed with brine and dried over $MgSO_4$. Purification by flash chromatography gave 0.593 g (95%) of the desired methyl ester **216**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.18 (m, 6H), 6.88-6.81 (m, 6H), 5.90-5.78 (m, 2H), 5.09-4.99 (m, 4H), 4.54 (d, 1H, *J* = 8.8 Hz), 4.48 (AB, 2H, J_{AB} = 9.2 Hz, Δv_{AB} = 13.1 Hz), 4.44-4.38 (m, 3H), 3.86-3.83 (m, 1H), 3.79 (s, 3H), 3.78 (s, 6H), 3.69-3.61 (m, 2H), 3.64 (s, 3H), 3.60-3.59 (m, 2H), 3.57-3.54 (m, 1H), 2.51 (d, 1H, *J* = 12.4, 4.8 Hz), 2.46-2.41 (m, 1H), 2.38-2.25 (m, 4H), 2.20 (d, 1H, *J* = 12.4, 6.8 Hz), 1.03 (d, 3H, *J* = 5.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 159.1, 158.98, 158.94, 157.9, 135.9, 135.6, 130.9, 130.8, 130.3, 129.35, 129.27, 129.19, 116.6, 116.5, 113.64, 113.56, 80.8, 80.2, 79.5, 79.2, 72.8, 72.1, 71.5, 69.8, 55.2, 51.3, 49.10, 49.09, 38.8, 35.9, 35.4, 31.9, 15.7; IR (film) 2931, 1734, 1612, 1513, 1463, 1247, 1172, 1081, 1034 cm^{-1}; $[\alpha]^{25}_D$ = +12.2 (*c* 0.79, CH_2Cl_2).

Phosphonate **217**

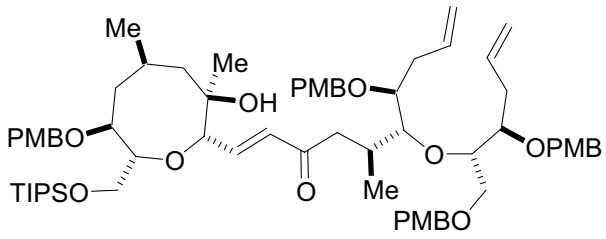


A flask containing a solution of 6 mL anhydrous THF and dimethyl methyl phosphonate (0.217 mL, 2.00 mmole) under an argon atmosphere was cooled to –78 ºC. A solution of *n*-BuLi (0.760 mL, 1.90 mmole; 2.5 M in hexanes) was added slowly to the phosphonate and the resulting solution was stirred at –78 ºC for 1 h. A solution of the methyl ester **216** (0.129 g, 0.191 mmole) and 3 mL THF was slowly added to the lithiated phosphonate and allowed to stir for 1 h at –78 ºC. The reaction was then quenched with a saturated solution of NH_4Cl and warmed to room temperature. The organic layer was separated and the aqueous layer extracted twice with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography gave 0.134 g (91%) of the desired β-keto phosphonate **217**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23-7.16 (m, 6H), 6.86-6.79 (m, 6H), 5.90-5.75 (m, 2H), 5.08-4.98 (m, 4H), 4.51 (d, 1H, J = 11.0 Hz), 4.45 (AB, 2H, J_{AB} = 11.5 Hz, $\Delta\nu_{AB}$ = ~ 0), 4.42 (d, 1H, J = 11.0 Hz), 4.39 (AB, 2H, J_{AB} = 11.5 Hz, $\Delta\nu_{AB}$ = 9.6 Hz), 3.80-3.77 (m, 1H), 3.77 (s, 3H), 3.758 (s, 3H), 3.756 (s, 3H), 3.73 (d, 3H, J = 0.5 Hz), 3.70 (d, 3H, J = 0.5 Hz), 3.65-3.61 (m, 2H), 3.60-3.55 (m, 2H), 3.52-3.49 (m, 1H), 2.88 (ABX, 2H, J_{AB} = 22.5 Hz, J_X = 14.0 Hz, $\Delta\nu_{AB}$ = 55.1 Hz), 2.73 (dd, 1H, J = 17.5, 5.0 Hz), 2.49 (dd, 1H, J = 17.5, 7.5 Hz), 2.44-2.38 (m, 1H), 2.36-2.30 (m, 3H), 2.27-2.22 (m, 1H), 0.96 (d, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.43, 201.38, 159.1, 159.0, 158.9, 135.8, 135.5, 130.8, 130.7, 130.2, 129.27, 129.20, 129.18, 116.6, 116.5, 113.6, 113.5, 80.9, 80.3, 79.5, 79.3, 72.7, 72.0, 71.4, 69.8, 55.1, 52.83, 52.82, 52.78, 52.77, 48.6, 41.6, 40.6,

35.9, 35.4, 30.5, 15.7; IR (film) 2934, 1713, 1612, 1513, 1458, 1248, 1174, 1033 cm^{-1}; $[\alpha]^{24}_D$ = +11.9 (*c* 1.15, CH_2Cl_2).

5.2.2.3. Synthesis of the BCDE tetracycle

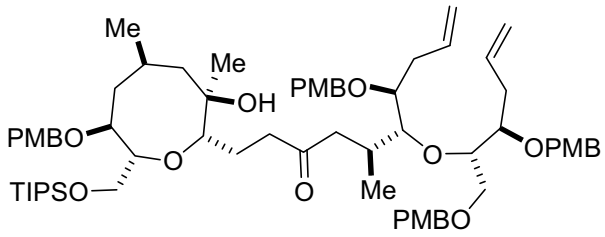
Enone **218**



To a solution of the E fragment phosphonate **217** (0.123 g, 0.160 mmole) in 0.4 mL THF was added $Ba(OH)_2$ (0.040 g, 0.128 mmole; predried @ 120 ºC for 2 h). The solution was allowed to stir at room temperature for 30 min. A solution of the aldehyde **214** (0.153 mmole) and 0.4 mL of a 40:1 THF/H_2O mixture was added to the phosphonate solution followed by the addition of an additional 0.5 mL of the THF/H_2O mixture. After stirring for 30 min, the reaction was diluted with EtOAc and filtered through a small pad of celite. The filtrate was washed with aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography gave 0.177g (96%) of the desired product **218**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23-7.17 (m, 8H), 6.91 (dd, 1H, *J* = 16.0, 4.5 Hz), 6.86-6.80 (m, 8H), 6.34 (dd, 1H, *J* = 16.0, 1.5 Hz), 5.90-5.76 (m, 2H), 5.07-4.98 (m, 4H), 4.54-4.33 (m, 8H), 4.30 (d, 1H, *J* = 2.5 Hz), 3.86-3.84 (m, 1H), 3.81 (dd, 1H, *J* = 10.5, 3.5 Hz), 3.78-3.77 (m, 12H), 3.73 (dd, 1H, *J* = 10.5, 5.0 Hz), 3.70 (dd, 1H, *J* = 3.5, 3.5 Hz), 3.65 (ddd, 1H, *J* = 8.0, 5.0, 4.0 Hz), 3.62-3.47 (m, 5H), 2.73 (dd, 1H, *J* = 16.0, 4.5 Hz), 2.47-2.22 (m, 6H), 1.96-1.89 (m, 3H), 1.67-1.61 (m, 1H), 1.59-1.56 (m, 1H), 1.47 (s, 1H), 1.10-0.98 (m, 30H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.8, 159.0, 158.96, 158.87, 158.82, 144.6, 136.0, 135.6, 130.83, 130.80, 130.4, 130.3,

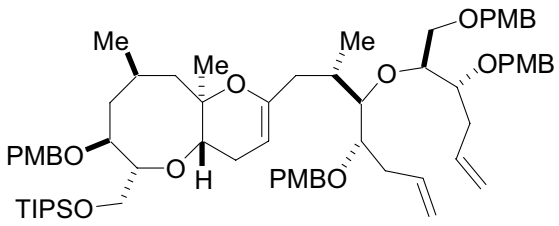
130.2, 129.28, 129.23, 129.20, 129.16, 116.5, 116.3, 113.63, 113.61, 113.49, 113.48, 86.4, 86.1, 81.1, 80.4, 79.4, 79.1, 78.0, 74.1, 72.7, 72.0, 71.3, 70.8, 69.7, 64.7, 55.1, 53.1, 44.5, 40.7, 35.8, 35.3, 31.1, 27.7, 27.1, 21.9, 17.94, 17.93, 15.9, 11.8; IR (film) 3487, 2939, 2864, 1736, 1669, 1613, 1513, 1463, 1365, 1302, 1248, 1173, 1090 cm^{-1}; $[\alpha]^{24}_{D}$ = +26.6 (*c* 2.46, CH_2Cl_2). MS (ESI) for $C_{68}H_{98}O_{13}Si$ [M + Na] calc. 1173.7, found 1173.6.

Ketone **219**



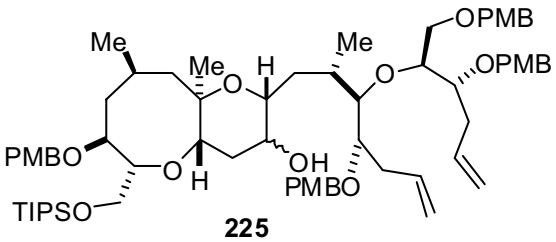
To a flask containing the enone **218** (0.177 g, 0.154 mmole) was added $[PPh_3CuH]_6$ (Stryker's reagent)[176] (0.030 g, 0.015 mmole) using a glove box. The flask was sealed prior to removal from the glove box. After the addition of 1.5 mL of degassed toluene and dimethylphenyl silane (0.036 mL, 0.231 mmole) the reaction mixture was stirred at room temperature under an argon atmosphere for 3 h. Air was then bubbled through the solution for 15 min and the solution was filtered through a small pad of silica gel and celite. The solvents were evaporated to yield the crude ketone **219** which was used in the next reaction without further purification.

Enol ether **220**

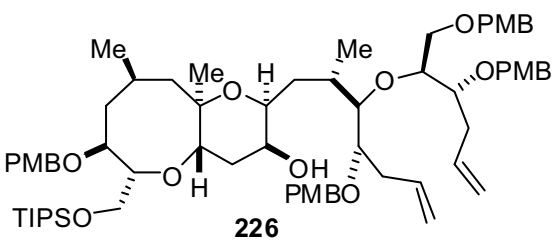


The saturated ketone obtained above was dissolved in 5 mL CH_2Cl_2. A catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) (~ 20 mg) was added and the reaction mixture was heated to reflux temperature for 1 h. The reaction was cooled and the solvents were evaporated. Purification of the residue by flash chromatography gave 0.143 g (82%) of the desired enol ether **220**. ^{1}H NMR (400 MHz, C_6D_6) δ 7.31-7.19 (m, 8H), 6.82-6.76 (m, 8H), 6.11-5.94 (m, 2H), 5.23-4.96 (m, 4H), 4.67 (d, 1H, *J* = 14.5 Hz), 4.56 (d, 1H, *J* = 15.5 Hz), 4.53 (d, 1H, *J* = 14.5 Hz), 4.48-4.43 (m, 3H), 4.37 (AB, 2H, J_{AB} = 14.5 Hz, Δv_{AB} = 25.1 Hz), 4.23-4.20 (m, 2H), 3.96 (dd, 1H, *J* = 13.0, 3.0 Hz), 3.92-3.85 (m, 2H), 3.80 (dd, 1H, *J* = 12.5, 6.5 Hz), 3.76-3.67 (m, 4H), 3.50-3.46 (m, 1H), 3.39-3.34 (m, 1H), 3.320 (s, 3H), 3.315 (m, 9H), 2.76-2.69 (m, 1H), 2.65-2.58 (m, 1H), 2.56-2.38 (m, 4H), 2.36-2.30 (m, 1H), 2.19 (dd, 1H, *J* = 20.0, 12.5 Hz), 2.01 (dd, 1H, *J* = 16.5, 10.5 Hz), 1.96-1.87 (m, 4H), 1.65-1.57 (m, 1H), 1.30 (s, 3H), 1.29 (d, 3H, *J* = 6 Hz), 1.18-1.07 (m, 21H), 1.00 (d, 3H, *J* = 7.5 Hz); ^{13}C NMR (100 MHz, C_6D_6) δ 159.7, 159.58, 159.56, 150.7, 137.0, 136.5, 131.7, 131.6, 131.2, 131.0, 129.6, 129.5, 129.47, 129.46, 128.5, 116.6, 116.4, 114.07, 114.00, 113.97, 113.92, 94.4, 88.8, 82.7, 82.1, 81.4, 80.3, 79.8, 78.6, 77.5, 73.2, 72.2, 71.9, 71.0, 70.6, 66.0, 54.7, 53.2, 42.7, 39.6, 36.2, 35.8, 32.8, 28.3, 27.5, 27.0, 18.3, 17.1, 16.0, 12.3; IR (film) 2937, 2864, 1613, 1513, 1463, 1301, 1248, 1172, 1104, 1036 cm^{-1}; $[\alpha]^{23}_D$ = +19.0 (*c* 1.05, CH_2Cl_2); MS (ESI) for $C_{68}H_{98}O_{12}Si$ [M + 1] calc 1135.7, found 1135.8.

Alcohols **225** and **226**



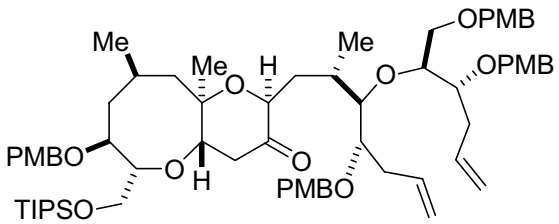
225



226

To a solution of the enol ether **220** (0.045 g, 0.040 mmole) and 1 mL CH_2Cl_2 at -78 ºC under an argon atmosphere was added freshly prepared "acetone free" dimethyl dioxirane[152,153] until the starting material was consumed as judged by TLC. To the same reaction flask was added diisobutylaluminum hydride (0.70 mL, 0.70 mmole; 1 M in hexanes). The reaction was immediately quenched with a saturated solution of Na^+/K^+ tartrate, warmed to room temperature, and stirred for 2 h. The organic layer was separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic fractions were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography gave 0.027 g of an isomeric mixture **225** (correlates to undesired configuration at C12 and hydroxyl epimers) and 0.008 g (76% total) of one pure isomer **226** (correlates to desired configuration at C12). ^{1}H NMR **226** (correct configuration at C12) (500 MHz, $CDCl_3$) δ 7.22-7.16 (m, 8H), 6.84-6.79 (m, 8H), 5.90-5.76 (m, 2H), 5.05-4.95 (m, 4H), 4.53 (d, 1H, *J* = 11.0 Hz), 4.47 (d, 1H, *J* = 10.5 Hz), 4.44-4.36 (m, 5H), 4.29 (d, 1H, *J* = 11.0 Hz), 3.85 (dd, 1H, *J* = 8.5, 5.0 Hz), 3.81-3.76 (m, 14 H), 3.67-3.64 (m, 2H), 3.62-3.57 (m, 7H), 3.30-3.21 (m, 2H), 2.42-2.39 (m, 1H), 2.34-2.30 (m, 2H), 2.28-2.24 (m, 1H), 2.12-2.07 (m, 1H), 1.88 (bm, 1H), 1.82-1.76 (m, 2H), 1.72-1.52 (m, 5H), 1.10 (s, 3H), 1.09-1.02 (m, 21H), 0.98 (d, 3H, *J* = 7.0 Hz), 0.94 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 159.1, 159.0, 158.9, 136.4, 135.9, 131.1, 131.0, 130.6, 130.5, 129.5, 129.4, 129.3, 129.2, 116.5, 116.2, 113.72, 113.66, 113.57, 86.5, 82.5, 80.5, 79.6, 79.4, 79.1, 78.5, 76.2, 72.8, 72.1, 71.5, 70.9, 69.9, 69.8, 68.9, 65.1, 55.3, 55.2, 54.5, 42.7, 35.9, 35.8, 35.3, 30.8, 29.7, 28.3, 26.9, 18.05, 18.04, 18.02, 15.6, 15.2, 12.0; IR (film) 2928, 2870, 1612, 1513, 1459, 1382, 1305, 1247, 1171, 1078, 1038 cm^{-1}; $[\alpha]^{24}_D$ = +6.1 (*c* 0.3, CH_2Cl_2); MS (ESI) for $C_{68}H_{100}O_{13}Si$ [M + Na] calc 1175.7, found 1175.7.

Ketone **228**

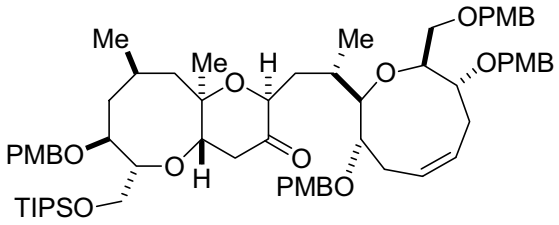


To a flask containing an isomeric mixture of the alcohols (0.035 g, 0.030 mmole) and 2 mL CH_2Cl_2 was added Dess-Martin periodinane (0.025 g, 0.060 mmole). The reaction was stirred for 30 min and quenched with a 5:1 aqueous solution of $Na_2S_2O_3/NaHCO_3$. The solution was poured into a separatory funnel and the organic layer was separated. The aqueous layer was extracted twice with CH_2Cl_2 and the combined extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography gave 0.030 g (87%) of inseparable ketone isomers.

To a flask containing a mixture of the C12 epimers (0.092 g, 0.080 mmole) was added a solution of DBU (0.1 M in CH_2Cl_2). The reaction was heated to reflux for 15 h. After cooling the reaction, aqueous NH_4Cl was added and the organic layer was separated. The aqueous layer was extracted twice with CH_2Cl_2 and the combined extracts were dried over Na_2SO_4. Purification by flash chromatography gave 0.060 g (75%) of ketone **228** as a single stereoisomer with the desired configuration at C12. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22-7.16 (m, 8H), 6.85-6.79 (m, 8H), 5.90-5.75 (m, 2H), 5.05-4.95 (m, 4H), 4.53 (d, 1H, *J* = 11.0 Hz), 4.49-4.36 (m, 6H), 4.29 (d, 1H, *J* = 11.0 Hz), 3.89-3.86 (m, 2H), 3.81 (dd, 1H, *J* = 10.0, ~0 Hz), 3.78 (s, 3H), 3.77 (s, 3H), 3.76 (m, 6H), 3.75-3.72 (m, 1H), 3.66-3.63 (m, 1H), 3.58-3.53 (m, 5H), 3.27-3.26 (m, 2H), 2.78 (dd, 1H, *J* = 16.0, 6.0 Hz), 2.42-2.37 (m, 2H), 2.33-2.23 (m, 3H), 1.93 (bm, 1H), 1.86-1.80 (m, 2H), 1.68-1.56 (m, 4H), 1.46-1.41 (m, 1H), 1.26 (s, 3H), 1.10-1.04 (m, 21H), 1.01 (d, 3H, *J* = 7.0 Hz), 0.92 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 207.4, 159.2, 159.0, 158.95, 158.93, 136.4, 135.9, 131.1, 131.0, 130.5, 130.3, 129.6, 129.4, 129.28, 129.26, 116.4, 116.2, 113.76, 113.66, 113.57, 113.56, 87.9, 83.3, 82.4, 80.5, 79.6, 79.4, 78.2, 75.7, 72.9, 72.8, 72.1, 71.6, 71.0, 69.9, 64.9, 55.26, 55.23, 53.5, 43.9, 42.8, 35.9, 35.1, 33.4, 30.3, 29.7, 28.2, 26.7, 18.0, 15.4, 14.8, 11.9; IR (film) 2927, 2864, 1725, 1613, 1586, 1513, 1463, 1381, 1301, 1248, 1173, 1094 cm^{-1}; MS (ESI) for $C_{68}H_{98}O_{13}Si$ [M + Na] calc. 1173.7, found 1173.6.

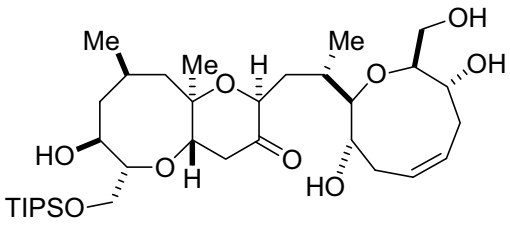
Ketone **229**



A solution of anhydrous CH_2Cl_2 (10 mL) and the diene **228** (0.031 g, 0.027 mmole) was heated to reflux under an argon atmosphere for 5 min to degas the solvent. The solution was cooled and Grubb's 1st generation catalyst ($Cl_2(PCy_3)_2Ru$=CHPh; ~ 3mg) was added. The reaction was reheated to reflux temperature and stirred for 4 h. The reaction was then cooled to room temperature, opened to air, and allowed to stir for 3 h. After evaporation of the solvents, the crude material was purified by flash chromatography to give 0.027 g (89%) of the intermediate **229**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22-7.18 (m, 6H), 7.09-7.07 (m, 2H), 6.84-6.78 (m, 8H), 5.75-5.65 (m, 2H), 4.53 (d, 1H, *J* = 10.5 Hz), 4.50-4.61 (m, 3H), 4.31-4.27 (m, 3H), 4.18 (d, 1H, *J* = 11 Hz), 3.86 (dd, 1H, *J* = 9.5, 3.0 Hz), 3.80 (dd, 1H, *J* = 9.0, 1.0 Hz), 3.79-3.72 (m, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.765 (s, 3H), 3.74 (s, 3H), 3.68 (dd, 1H, *J* = 11.0, 6.0 Hz), 3.63-3.60 (m, 1H), 3.59-3.55 (m, 2H), 3.50 (dd, 1H, *J* = 10.5, 3.0 Hz), 3.33 (dd, 1H, *J* = 6.5, 2.5 Hz), 3.32-3.21 (m, 3H), 2.76 (dd, 1H, *J* = 16.0, 6.0 Hz), 2.68-2.60 (m, 2H), 2.37 (dd, 1H, *J* = 16.0, 11.0 Hz), 2.34-2.24 (m, 2H), 2.03 (bm, 1H), 1.83-1.80 (m, 2H), 1.73-1.52 (m, 5H), 1.23 (s, 3H), 1.08-1.02 (m, 21H), 0.98 (d, 3H, *J* = 7.5 Hz), 0.80 (d, 3H, *J* =

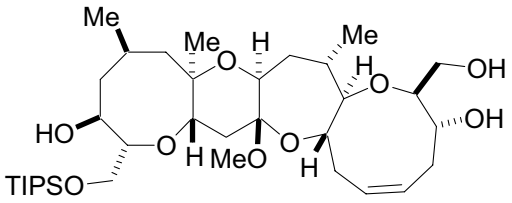
7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.2, 159.3, 159.12, 159.10, 130.9, 130.8, 130.5, 129.5, 129.3, 129.2, 128.2, 127.0, 113.8, 113.84, 113.77, 113.72, 113.66, 87.9, 87.0, 83.3, 82.2, 80.5, 78.3, 75.7, 73.4, 72.7, 71.10, 70.98, 70.6, 69.8, 65.0, 55.29, 55.28, 55.27, 55.2, 53.6, 43.9, 42.8, 33.1, 32.6, 29.7, 28.2, 27.0, 26.9, 26.7, 18.06, 18.05, 15.3, 14.2, 12.0; IR (film) 2972, 2863, 1724, 1613, 1513, 1463, 1301, 1248, 1172, 1096 cm^{-1}; $[\alpha]^{24}_D$ = +10 (*c* 0.185, CH_2Cl_2); MS (ESI) for $C_{66}H_{94}O_{13}Si$ [M + Na] calc. 1145.7, found 1145.7.

Tetraol **230**



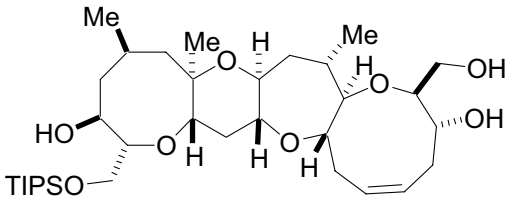
To a flask containing the tetra-PMB ether **229** (0.022 g, 0.0195 mmole) and 4 mL of anhydrous CH_2Cl_2 was added 0.1 mL trifluoroacetic acid. The resulting solution was allowed to stir for 1.5 h followed by dilution with additional CH_2Cl_2 and aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer extracted twice with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography gave 0.010 g (79%) of the desired tetraol **230**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84-5.76 (m, 2H), 3.97-3.95 (m, 2H), 3.91 (t, 1H, *J* = 6.5 Hz), 3.81-3.78 (m, 2H), 3.73-3.70 (m, 3H), 3.65-3.60 (m, 1H), 3.25 (dd, 1H, *J* = 8.5, 8.0), 3.15-3.13 (m, 2H), 2.75-2.68 (m, 2H), 2.73 (dd, 1H, *J* = 16, 6.0 Hz), 2.38 (dd, 1H, *J* = 16.0, 10.5 Hz), 2.16-2.11 (m, 2H), 2.02 (bm, 1H), 1.87 (bs, 1H), 1.75-1.61 (m, 6H), 1.27 (s, 3H), 1.14-1.03 (m, 24H), 0.93 (d, 3H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.8, 127.8, 127.7, 88.6, 85.5, 85.2, 83.2, 76.4, 75.6, 73.2, 72.2, 69.7, 67.7, 61.9, 53.4, 46.7, 44.0, 33.7, 32.8, 32.2, 31.0, 29.7, 28.4, 26.6, 17.89, 17.88, 15.7, 15.4, 11.7; IR (film) 3407, 2927, 2866, 1723, 1456, 1248, 1094 cm^{-1}; MS (ESI) for $C_{35}H_{64}O_9Si$ [M + Na] calc. 665.4, found 665.4.

Mixed methyl ketal **231**



To a solution of the ketone **230** (2.3 mg, 0.0036 mmole) and 0.5 mL anhydrous methanol under an argon atmosphere was added a catalytic amount of PPTS. The solution was heated to reflux temperature for 2 h. The reaction was cooled and diluted with CH_2Cl_2. Aqueous $NaHCO_3$ was added and the organic layer was separated. The aqueous layer was extracted twice with CH_2Cl_2 and the combined extracts were dried over Na_2SO_4. The solution was filtered and concentrated in vacuo to give the crude dimethyl ketal. To this crude material was added 0.5 mL benzene and a catalytic amount of PPTS. The reaction was heated to 60 ºC for 1 h under argon. After cooling and dilution with EtOAc, aqueous $NaHCO_3$ was added and the organic layer was separated. The aqueous layer was extracted twice with additional EtOAc and the combined extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography gave 0.8 mg (35%) of the desired mixed methyl ketal **231** and 1.2 mg ketone **230** (70% b.r.s.m.). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88-5.84 (m, 1H), 5.74-5.68 (m, 1H), 4.45 (dt, 1H, *J* = 7.0, > 1 Hz), 3.92-3.85 (m, 2H), 3.82 (dd, 1H, *J* = 10.0, 6.0 Hz), 3.75-3.71 (m, 2H), 3.68 (dd, 1H, *J* = 3.5, <1.0 Hz), 3.62-3.55 (m, 1H), 3.57 (dd, 1H, *J* = 11.5, 6.5 Hz), 3.44-3.40 (m, 2H), 3.28-3.23 (m, 1H), 3.25 (s, 3H), 2.99 (dd, 1H, *J* = 9.5, 6.5 Hz), 2.72 (bm, 1H), 2.58 (bm, 1H), 2.37 (bm, 2H), 2.27 (dd, 1H, *J* = 12.5, 5.5 Hz), 2.17 (bm, 2H), 1.87-1.49 (m, 7H), 1.39 (dd, 1H, *J* = 12, 12 Hz), 1.11 (s, 3H), 1.08-1.04 (m, 21H), 1.01 (d, 3H, *J* = 7.0 Hz), 0.97 (d, 3H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 130.3, 125.1, 97.8, 88.0, 85.1, 82.5, 76.2, 75.8, 72.2, 69.7, 67.9, 62.6, 54.6, 48.0, 46.9, 38.2, 36.1, 33.2, 28.3, 26.7, 19.6, 17.92, 17.90, 17.87, 15.2, 11.7.

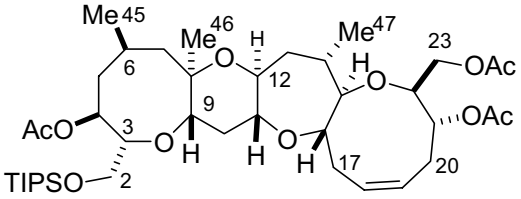
BCDE fragment **233**



To a solution of the mixed methyl ketal **231** (2.0 mg, 0.0030 mmole) and 0.5 mL CH_2Cl_2 at 0 ºC under an argon atmosphere was added triethylsilane (0.050 mL, 0.31 mmole) followed by $BF_3{\cdot}OEt_2$ (0.010 mL, 0.079 mmole). The solution was allowed to stir at 0 ºC for 15 min and quenched with aqueous $NaHCO_3$. The solution was diluted with CH_2Cl_2 and the organic layer was separated. The aqueous layer was extracted twice with CH_2Cl_2 and the combined extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography gave 1.4 mg (73%) of the desired tetracycle **233** as a single diastereomer. ^{1}H NMR (500 MHz, C_6D_6) δ 5.92-5.87 (m, 1H), 5.85-5.79 (m, 1H), 3.91 (dd, 1H, *J* = 10, 5.5 Hz), 3.85 (dd, 1H, *J* = 10, 7.0 Hz), 3.78 (bm, 1H), 3.70-3.66 (m, 2H), 3.60-3.53 (m, 2H), 3.44-3.40 (m, 2H), 3.31 (ddd, 1H, *J* = 15, 6.0, 6.0 Hz), 3.20-3.16 (m, 2H), 2.86 (bs, 1H), 2.82-2.74 (m, 2H), 2.58-2.53 (m, 1H), 2.41-2.38 (m, 1H), 2.24 (ddd, 1H, *J* = 12, 5.0, 5.0 Hz), 2.16-2.07 (m, 2H), 2.01 (ddd, 1H, *J* = 15, 11, 4.5 Hz), 1.95-1.88 (m, 2H), 1.85-1.83 (m, 2H), 1.78-1.62 (5H), 1.25 (s, 3H), 1.11-1.03 (m, 24H), 0.95 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.4, 127.3, 92.0, 86.1, 84.3, 83.0, 82.0, 81.4, 76.4, 75.8, 71.7, 68.9, 68.2, 63.9, 54.5, 46.4, 36.7, 36.2, 35.2, 29.7, 28.4, 26.7, 22.7, 21.5, 17.90, 17.88, 16.2, 11.7; MS (ESI) for $C_{34}H_{62}O_8Si$ [M + Na] calc. 649.4, found 649.4.

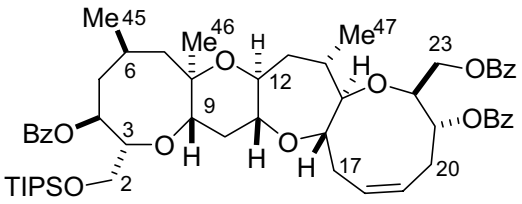
5.2.2.4. 2-D Analysis of Completed BCDE Fragment

Triacetate **234**



The triacetate derivative was also formed to enable further 2D analysis: To a solution of the triol **233** (~2 mg) and acetic anhydride was added an excess of 4-(dimethylamino)pyridine. The reaction was allowed to stir for 3 h at room temperature. The reaction was diluted with Et_2O and washed with aqueous $NaHCO_3$. The aqueous layer was extracted twice with Et_2O and the combined extracts were dried over Na_2SO_4. Purification by flash chromatography gave the desired tri-acetate **234**. ^{1}H NMR (500 MHz, CD_3CN) δ 5.68-5.65 (m, 1H, H18), 5.63-5.59 (m, 1H, H19), 4.83-4.79 (m, 1H, H21), 4.64 (ddd, 1H, H4, *J* = 12, 12, 2.5 Hz), 4.04-4.03 (m, 2H, H23a,b), 3.70 (dd, 1H, H2a, *J* = 10.5, 1.5 Hz), 3.64 (ddd, 1H, H22, *J* = 8.0, 4.0, 4.0 Hz), 3.60-3.56 (m, 1H, H16), 3.57 (dd, 1H, H2b, *J* = 11, 6.0 Hz), 3.52 (dd, 1H, H9, *J* = 12, 5.0 Hz), 3.45-3.40 (m, 1H, H3), 3.34 (ddd, 1H, H12, *J* = 10, 10, 1.0 Hz), 3.27 (dd, 1H, H15, *J* = 9.0, 3.5 Hz), 2.93 (ddd, 1H, H11, *J* = 12, 9.5, 4.5 Hz), 2.61 (bm, 1H, H17a), 2.53-2.47 (bm, 1H, H20a), 2.42-2.35 (bm, 1H, H20b), 2.31-2.25 (bm, 1H, H17b), 2.21 (ddd, 1H, H10a, *J* = 11.5, 4.0, 4.0 Hz), 2.13-2.10 (m, 1H), 1.99-1.95 (m, 1H), 1.98 (s, 3H, Ac), 1.97 (s, 3H, Ac), 1.92 (s, 3H, Ac), 1.89-1.75 (m, 3H), 1.51-1.39 (m, 4H), 1.15 (s, 3H, Me47, *J* = 7.5 Hz)), 1.12 (s, 3H, Me46), 1.07-1.03 (m, 21H, TIPS), 0.95 (d, 3H, Me45, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, CD_3CN) δ 171.3, 170.7, 170.4, 129.5, 127.8, 86.7, 84.0, 83.2, 82.1, 76.4, 73.2, 72.6, 69.9, 65.6, 65.1, 55.0, 44.1, 36.6, 36.5, 35.9, 28.4, 27.7, 21.6, 21.3, 21.2, 20.9, 18.28, 18.27, 16.4, 12.7; IR (film) 2926, 2866, 1742, 1461, 1371, 1239, 1100 cm^{-1}; MS (ESI) for $C_{40}H_{68}O_{11}Si$ [M + 1] calc. 753.5, found 753.5.

Tribenzoate **235**

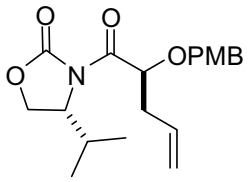


To a solution of the triol **233** (~2 mg) and pyridine (0.5 mL) was added benzoyl chloride (0.1 mL) and an excess of 4-(dimethylamino)pyridine (DMAP). The reaction was allowed to stir for 15 h at room temperature. The reaction was diluted with CH_2Cl_2 and washed with aqueous $NaHCO_3$. The aqueous layer was extracted twice with CH_2Cl_2 and the combined extracts were dried over Na_2SO_4. Purification by flash chromatography gave the desired tribenzoate **235** which was further purified by semi-prep HPLC. ^{1}H NMR (500 MHz, CD_3CN) δ 7.99-7.92 (m, 6H, HBz), 7.62-7.57 (m, 3H, HBz), 7.48-7.42 (m, 6H, HBz), 5.75-5.68 (m, 2H, H18, H19), 5.26 (bm, 1H, H21), 4.91 (ddd, 1H, H4, *J* = 12, 12, 3.0 Hz), 4.42 (dd, 1H, H23a, *J* = 12, 4.0 Hz), 4.36 (dd, 1H, H23b, *J* = 12, 4.5 Hz), 4.05 (ddd, 1H, H22, *J* = 7.5, 4.5, 4.5 Hz), 3.78-3.75 (m, 1H, H2a), 3.68-3.63 (m, 3H, H2b, H3, H16), 3.59 (dd, 1H, H9, *J* = 12, 5.0 Hz), 3.42 (dd, 1H, H15, *J* = 8.5, 3.5 Hz), 3.37 (ddd, 1H, H12, *J* = 11, 11, 2.0 Hz), 2.98 (ddd, 1H, H11, *J* = 12, 9.0, 4.0 Hz), 2.73-2.63 (bm, 2H, H17a, 20a), 2.61-2.55 (bm, 1H, H20b), 2.36-2.31 (bm, 1H, H17b), 2.26 (ddd, 1H, H8a, *J* = 9.0, 9.0, 4.5 Hz), 2.21-2.18 (m, 1H, H14), 2.10-1.95 (m, 1H, H6), 1.91-1.78 (m, 3H, H4a,b, H11a), 1.54-1.40 (m, 4H, H8b, H6a,b, 11b), 1.17 (d, 3H, Me47, *J* = 7.5 Hz), 1.15 (s, 3H, Me46), 1.04-0.97 (m, 24H, TIPS, Me45). MS (ESI) for $C_{55}H_{74}O_{11}Si$ [M + Na] calc. 961.5, found 961.2.

5.2.3 2nd Generation synthesis and synthesis of the ABCDE Lactone

5.2.3.1. Synthesis of the E fragment phosphonate

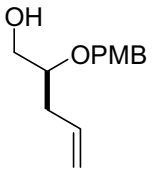
Alkylation of glycolylimide **249**



A 3 L flask equipped with a mechanical stirrer, addition funnel and a low temperature thermometer containing a solution of freshly prepared sodium bis(trimethylsilyl)amide (453 mL, 358 mmole; 0.79 M in toluene/THF) and 700 mL THF under an argon atmosphere was cooled to -78 ºC. The glycolate **249** (73.31 g, 239 mmole) dissolved in 300 mL THF was added dropwise over 40 min. maintaining a T< –65 ºC. The resulting solution was stirred at -78 ºC for an additional 45 minutes. Neat allyl iodide (109 mL, 1.19 mol) was added to the reaction flask. The solution was warmed to –40 ºC and maintained at that temperature for 2 h. The reaction was quenched using saturated NH_4Cl. The organic layer was separated and the aqueous layer extracted twice with EtOAc. The combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography gave 62.9 g (76%) of the desired product as a single diastereomer (judged by NMR analysis). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-7.14 (band, 2H), 6.75-6.71 (band, 2H), 5.79 (dddd, *J* = 17.2, 10.0, 7.2, 7.2 Hz, 1H), 5.09-4.96 (band, 3H), 4.34 (AB, J_{AB} = 11.2 Hz, $\Delta\nu_{AB}$ = 40.1 Hz, 2H), 4.28 (ddd, *J* = 7.6, 3.6, 3.6 Hz, 1H), 4.10-4.02 (band, 2H), 3.64 (s, 3H), 2.50 (ddd, *J* = 14.0, 6.4, 4.8 Hz, 1H), 2.40 (ddd, *J* = 14.4, 7.2, 7.2 Hz, 1H), 2.14 (ds, *J* = 6.8, 3.6Hz, 1H), 0.75 (d, *J* = 6.8 Hz, 3H), 0.71 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 158.9, 153.1, 132.7, 129.4, 129.2, 117.5, 113.2, 75.9, 71.6, 63.5, 57.7, 54.7, 37.0, 28.0, 17.3, 14.3; IR (film) 2964, 1779, 1709, 1613, 1513, 1388, 1301, 1247, 1206, 1104,

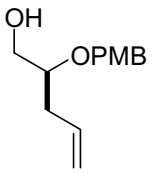
1033 cm^{-1}; $[\alpha]^{23}_D$ = -97 (*c* 7.7, CH_2Cl_2), MS (ESI) for $C_{19}H_{25}NO_5$ [M + Na] calc 370.2, found 370.2.

Alcohol **250**



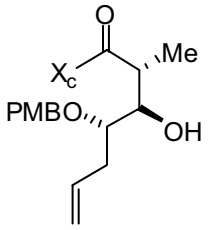
To a solution of the alkylation adduct (62.9 g, 181 mmole), 1 L Et_2O, and methanol (9.4 mL, 235 mmole) at 0 ºC under an argon atmosphere was added lithium borohydride (118 mL, 235 mmole; 2M in THF) slowly over 30 min. The reaction was allowed to stir for 2 h at 0 ºC followed by the addition of saturated Na^+/K^+ tartrate. The resulting mixture was stirred at room temperature for 3 h. The organic layer was separated and the aqueous layer extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography gave 37.4 g (93%) of the desired alcohol **250**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.22 (band, 2H), 6.86-6.83 (band, 2H), 5.79 (dddd, *J* = 14.0, 10.0, 7.2, 7.2 Hz, 1H), 5.11-5.03 (band, 2H), 4.48 (AB, J_{AB} = 11.2 Hz, $\Delta\nu_{AB}$ = 31.3 Hz, 2H), 3.72 (s, 3H), 3.61-3.56 (m, 1H), 3.51-3.45 (band, 2H), 2.78 (bs, 1H), 2.37-2.23 (band, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 134.1, 130.3, 129.0, 116.9, 113.5, 78.7, 70.9, 63.6, 54.9, 35.1; IR (film) 3434 (b), 2934, 1613, 1513, 1464, 1301, 1248, 1174, 1077, 1035 cm^{-1}; $[\alpha]^{23}_D$ = +13.7 (*c* 11, CH_2Cl_2), MS (ESI) for $C_{13}H_{18}O_3$ [M + Na] calc 245.1 found 245.1.

Aldehyde **251**



Into a 1 L flask equipped with a mechanical stirrer, addition funnel, and low-temperature thermometer was added 150 mL of CH_2Cl_2 and oxalyl chloride (49.7 mL, 99.3 mmol; 2.0 M in CH_2Cl_2). After cooling to –78 ºC, dimethylsulfoxide (9.40 mL, 132.4 mmol) in 150 mL of CH_2Cl_2 was added dropwise via an addition funnel to maintain a temperature < –65 ºC. After stirring for 10 minutes, alcohol **250** (14.7 g, 66.2 mmol) in 150 mL of CH_2Cl_2 was added via addition funnel maintaining a temperature < –65 ºC. After stirring for 30 minutes, triethylamine (46.1 mL, 331 mmol) was added dropwise. The cooling bath was removed and the reaction was allowed to warm to room temperature over 30 min. The reaction mixture was washed with 400 mL each water, 1M HCl, saturated $NaHCO_3$, water, and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The aldehyde was quickly filtered through a small plug of silica gel, concentrated, and used immediately in the next reaction.

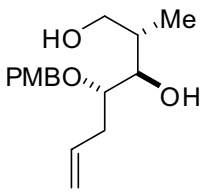
Aldol Addition



A 1L flask equipped with a mechanical stirrer containing the thiazolidinethione propionate **252** (21.6 g, 81.4 mmol) and 600 mL of CH_2Cl_2 was cooled to 0 ºC. $TiCl_4$ (10.7 mL, 97.7 mmol) was added dropwise to the solution. After stirring for 10 minutes, (–)-sparteine (22.5 mL, 97.7 mmol) was added dropwise. After 30 minutes, *N*-methylpyrrolidinone (9.40 mL,

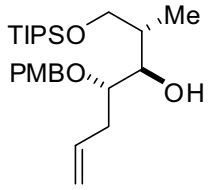
97.7 mmol) was added dropwise and the resulting solution was cooled to –78 ºC. After 10 minutes, aldehyde **251** (~ 66 mmol) in 20 mL of CH_2Cl_2 was added dropwise to the enolate solution. The reaction mixture was slowly warmed to –30 ºC and maintained at that temperature for 2 hours. The reaction was quenched by the addition of 500 mL of half-saturated NH_4Cl and warmed to room temperature. The organic layer was separated and the aqueous layer extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography was performed, however, the desired product (single diastereomer by NMR analysis) could not be effectively separated from the excess thiazolidinethione propionate. Thus, the mixture was carried forward to the next reaction. Analysis of a pure sample: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.24 (band, 7H), 6.86-6.84 (band, 2H), 5.92 (dddd, *J* = 17.6, 10.4, 7.2. 7.2 Hz, 1H), 5.22 (ddd, *J* = 10.4, 6.8, 4.0 Hz, 1H), 5.20-5.08 (band, 2H), 4.61 (dddd, *J* = 6.8, 6.8, 6.8, 4.0 Hz, 1H), 4.54 (d, *J* = 11.2 Hz, 1H), 4.40 (d, *J* = 11.2 Hz, 1H), 3.95 (dd, *J* = 7.6, 4.0 Hz, 1H), 3.74 (s, 3H), 3.37 (ddd, *J* = 7.6, 5.2, 5.2 Hz, 1H), 3.13 (dd, *J* = 13.2, 3.6 Hz, 1H), 3.11-3.05 (band, 2H), 2.99 (dd, *J* = 13.2, 10.4 Hz, 1H), 2.76 (d, *J* = 11.6 Hz, 1H), 2.57-2.51 (m, 1H), 2.46-2.39 (m, 1H), 1.25 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.7, 178.2, 159.2, 136.2, 134.3, 129.8, 129.5, 129.3, 128.7, 127.1, 117.4, 113.7, 77.7, 72.7, 71.1, 68.2, 55.1, 39.7, 36.6, 34.2, 31.7, 11.8; IR (film) 3499, 2934, 1690, 1612, 1512, 1455, 1342, 1249, 1164, 1034 cm^{-1}; $[\alpha]^{23}_D$ = –190 (*c* 2.7, CH_2Cl_2), MS (ESI) for $C_{26}H_{31}NO_4S_2$ [M + Na] calc 508.2, found 508.2.

Alcohol **253**



To a flask containing the impure aldol adduct (~ 46 mmole), 225 mL THF and 75 mL H_2O was added sodium borohydride (3.51 g, 92.8 mmole). The resulting solution was allowed to stir for 1 h at ambient temperature. The reaction was quenched with saturated Na^+/K^+ tartrate and allowed to stir for 15 h. The organic layer was separated and the aqueous layer extracted twice with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. Purification by flash chromatography gave 10.3 g (78% over three steps) of diol **253**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.20 (band, 2H), 6.86-6.82 (band, 2H), 5.92 (dddd, *J* = 7.6, 7.6, 10.4, 17.2 Hz, 1H), 5.17-5.07 (band, 2H), 4.55 (d, *J* = 10.8 Hz, 1H), 4.35 (d, *J* = 10.8 Hz, 1H), 3.78-3.75 (m, 1H), 3.75 (s, 3H), 3.60-3.51 (band, 2H), 3.47-3.43 (m, 1H), 3.20-3.10 (band, 2H), 2.54-2.48 (m, 1H), 2.43-2.36 (m, 1H), 2.01-1.93 (m, 1H), 0.87 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 134.7, 130.3, 129.3, 117.0, 113.7, 78.6, 73.6, 71.2, 66.9, 55.1, 35.3, 34.3, 10.0; IR (film) 3348, 2936, 1612, 1513, 1467, 1304, 1249, 1090 cm^{-1}; $[\alpha]^{23}_D$ = +39.9 (*c* 1.2, CH_2Cl_2), MS (ESI) for $C_{16}H_{24}O_4$ [M + Na] calc 303.2, found 303.2.

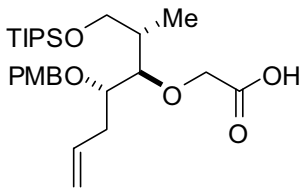
Silyl Ether



Into a 500 mL flask under an argon atmosphere was placed diol **253** (14.3 g, 51.1 mmol), imidazole (6.96 g, 102 mmol) and 300 mL CH_2Cl_2. Triisopropylsilyl chloride (11.3 mL, 51.1 mmol) was added via syringe and the solution was allowed to stir for 15 h at room temperature. To the reaction mixture was added saturated $NaHCO_3$ and the organic layer was separated. The aqueous layer was extracted twice with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash

chromatography provided 21.7g (97%) of the silyl ether: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.21 (band, 2H), 6.87-6.83 (band, 2H), 5.97 (dddd, *J* = 6.8, 6.8, 10.0, 17.2 Hz, 1H), 5.19-5.14 (m, 1H), 5.10-5.07 (m, 1H), 4.58 (d, *J* = 11.2 Hz, 1H), 4.38 (d, *J* = 10.8 Hz, 1H), 3.88-3.82 (band, 2H), 3.78-3.75 (m, 1H), 3.77 (s, 3H), 3.47 (ddd, *J* = 4.0, 5.6, 8.0 Hz, 1H), 2.59-2.52 (m, 1H), 2.42 (ddd, *J* = 6.0, 6.0, 13.6 Hz, 1H), 2.03-1.97 (m, 1H), 1.17-1.03 (band, 21H), 0.97 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 134.9, 130.5, 129.4, 117.0, 113.7, 78.4, 75.0, 71.3, 69.5, 55.1, 34.9, 34.3, 17.96, 17.94, 17.87, 17.86, 17.84, 11.85, 11.73, 11.71, 10.5; IR (film) 3504, 2942, 2865, 1613, 1513, 1463, 1248, 1090 cm^{-1}; $[\alpha]^{23}_D$ = + 14.5 (*c* 5.6, CH_2Cl_2), MS (ESI) for $C_{25}H_{44}O_4Si$ [M + Na] calc 459.3, found 459.3.

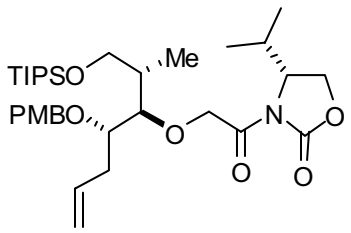
Carboxylic acid **254**



Into a 200 mL flask was placed sodium hydride (60% dispersion in mineral oil, 5.96 g, 149 mmol). The sodium hydride was washed with pentanes (3X) to remove the mineral oil, and an argon purge was used to remove any remaining hexanes. Dimethylformamide (50 mL) was added to the washed sodium hydride and the resulting solution was cooled to 0 ºC. Bromoacetic acid (10.4 g, 74.6 mmol) in 25 mL of THF was added slowly. The solution was then stirred for 10 minutes, followed by the addition of the alcohol (21.7 g, 49.7 mmol) in 25 mL of THF. The reaction was allowed to warm to room temperature and stirred for 15 h. The reaction was quenched by the dropwise addition of water and acidified with cold 10% H_2SO_4. The mixture was poured into a separatory funnel and extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography gave 22.7 g

(92%) of the desired acid **254**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.20 (band, 2H), 6.85-6.82 (band, 2H), 5.86 (dddd, *J* = 7.2, 7.2, 10.0, 17.2 Hz, 1H), 5.13-5.07 (m, 1H), 5.07-5.04 (m, 1H), 4.51 (AB, *J* = 11.2 Hz, Δv_{AB} = 22.1 Hz, 2H), 4.34 (d, *J* = 16.8 Hz, 1H), 4.10 (d, *J* = 17.2 Hz, 1H), 3.77 (s, 3H), 3.70 (ddd, *J* = 4.0, 4.0, 7.6 Hz, 1H), 3.58-3.55 (band, 2H), 3.51 (dd, *J* = 6.4, 10.0 Hz, 1H), 2.46-2.37 (band, 2H), 1.93-1.87 (m, 1H), 1.14-1.01 (band, 21H), 0.96 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 159.4, 135.0, 129.6, 129.4, 117.0, 113.8, 85.0, 79.4, 71.9, 70.6, 65.8, 55.1, 37.9, 34.0, 17.94, 17.92, 17.91, 12.9, 11.9; IR (film) 2942, 1766, 1732, 1613, 1513, 1463, 1248, 1107 cm^{-1}; $[\alpha]^{23}_{D}$ = – 1.8 (*c* 1.7, CH_2Cl_2), MS (ESI) for $C_{27}H_{46}O_6Si$ [M + Na] calc 517.3, found 517.4.

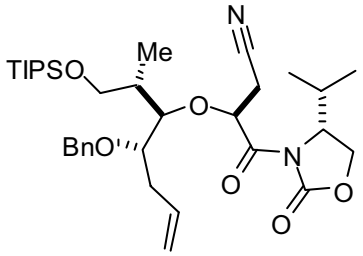
Glycolate **255**



To a solution of carboxylic acid **254** (15.6 g, 31.6 mmole) and 160 mL anhydrous THF under an argon atmosphere was added triethylamine (4.85 mL, 34.8 mmole). The solution was cooled to –78 ºC and pivaloyl chloride (4.29 mL, 34.8 mmole) was added dropwise. The reaction was warmed to 0 ºC, stirred at that temperature for 1 h and recooled to –78 ºC. To a separate flask containing (R)-4-isopropyl-2-oxazolidinone (**149**) (5.31 g, 41.1 mmole) and 80 mL THF at -78 ºC was added *n*-BuLi (15.2 mL, 37.9 mmole; 2.5 M in hexanes) dropwise. After stirring for 30 min, the lithiated auxiliary was cannulated to the anhydride. After stirring for 1 h at –78 ºC the reaction was slowly warmed to 0 ºC and quenched by the addition of saturated $NaHCO_3$. The organic layer was separated and the aqueous layer extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in

vacuo. Purification by flash chromatography gave 17.0 g (89%) of the glycolate **255**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.21 (band, 2H), 6.84-6.81 (band, 2H), 5.91 (dddd, *J* = 7.2, 7.2, 10.4, 17.2 Hz, 1H), 5.09 (dd, *J* = 2.0, 17.2 Hz, 1H), 5.02 (dd, *J* = 1.6, 10.0 Hz, 1H), 4.83 (AB, *J* = 18.0 Hz, Δv_{AB} = 36.6 Hz, 2H), 4.47 (AB, *J* = 11.6 Hz, $\Delta v_{AB} \approx 0$ Hz, 2H), 4.32 (ddd, *J* = 4.0, 8.0, 8.0 Hz, 1H), 4.16-4.15 (m, 2H), 3.76 (s, 3H), 3.73-3.66 (band, 2H), 3.60-3.57 (band, 2H), 2.49 (dddd, *J* = 7.2, 7.2, 7.2, 7.2 Hz, 1H), 2.42-2.33 (m, 2H), 1.98 (dddd, *J* = 6.4, 6.4, 13.2, 13.2 Hz, 1H), 1.11-1.00 (m, 21H), 0.97 (d, *J* = 7.2 Hz, 3H), 0.86 (d, *J* = 7.2 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 158.9, 153.7, 135.7, 130.7, 129.2, 116.5, 113.5, 82.0, 79.6, 72.1, 71.4, 65.7, 64.1, 58.0, 55.1, 37.4, 34.7, 28.1, 17.9, 17.8, 14.5, 12.2, 11.8; IR (film) 2941, 2865, 1783, 1721, 1513, 1463, 1388, 1249, 1209, 1093 cm^{-1}; $[\alpha]^{23}_{D}$ = –29 (*c* 2.1, CH_2Cl_2), MS (ESI) for $C_{33}H_{55}NO_7Si$ [M + Na] calc 628.4, found 628.4.

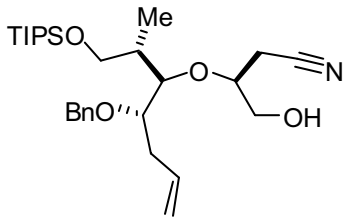
Alkylation with bromoacetonitrile



A 500 mL flask equipped with an addition funnel containing 150 mL anhydrous THF and sodium hexamethyldisilazide (36.2 mL, 29.0 mmole; 0.8 M in toluene/THF) was cooled to –78 ºC. Glycolyl imide **255** (11.7 g, 19.3 mmole) dissolved in 50 mL THF was added dropwise over 30 min. via the addition funnel. The resulting solution was allowed to stir for an additional 30 min. at –78 ºC. Bromoacetonitrile (5.38 mL, 77.3 mmole) was added dropwise to the enolate producing a deep red color. The reaction was allowed to stir for 1 h at –78 ºC. The reaction was quenched at that temperature using saturated NH_4Cl. The organic layer

was separated and the aqueous layer extracted twice with EtOAc. The combined organic fractions were washed with brine, dried over Na_2SO_4 and concentrated in vacuo to provide the crude material. Purification by flash chromatography gave 18.4 g of an inseparable mixture of product and unreacted glycolate. Facile separation of the product was possible after removal of the chiral auxiliary. Analysis of a pure sample: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.21 (band, 2H), 6.85-6.83 (band, 2H), 5.90 (dddd, *J* = 6.4, 6.4, 9.6, 16.8 Hz, 1H), 5.44 (dd, *J* = 6.4, 6.4 Hz, 1H), 5.12-5.02 (band, 2H), 4.38 (AB, J_{AB} = 10.8 Hz, $\Delta\nu_{AB}$ = 61.5 Hz, 2H), 4.05 (ddd, *J* = 4.4, 4.4, 7.6 Hz, 1H), 3.90 (dd, *J* = 4.0, 9.2 Hz, 1H), 3.78 (s, 3H), 3.78-3.76 (m, 1H), 3.70 (d, *J* = 9.6 Hz, 1H), 3.65-3.56 (band, 2H), 3.33 (dd, *J* = 8.8, 8.8 Hz, 1H), 2.79-2.72 (band, 2H), 2.69-2.61 (m, 1H), 2.30-2.23 (band, 2H), 1.83 (dddd, *J* = 8.0, 8.0, 15.6, 15.6 Hz, 1H), 1.16 (d, *J* = 6.8 Hz, 3H), 1.10-1.03 (band, 21H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.74 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 159.1, 153.7, 136.5, 136.4, 130.5, 129.0, 116.3, 113.6, 85.6, 82.2, 76.1, 72.5, 65.7, 63.7, 58.2, 55.3, 37.7, 33.5, 28.0, 22.9, 18.0, 17.8, 15.0, 14.6, 11.8; IR (film) 2941, 2865, 1777, 1721, 1613, 1513, 1463, 1388, 1248, 1209, 1108 cm^{-1}; $[\alpha]^{23}_D$ = –66 (*c* 2.8 , CH_2Cl_2), MS (ESI) for $C_{35}H_{56}N_2O_7Si$ [M + Na] calc 667.4, found 667.6.

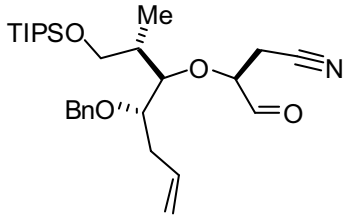
Alcohol **256**



To a solution of the product mixture obtained in the above reaction (~ 28 mmole), 40 mL THF and 10 mL water was added sodium borohydride (2.13 g, 56.3 mmole). The reaction was allowed to stir for 2 h at room temperature followed by the addition of saturated Na^+/K^+ tartrate. The resulting mixture was stirred at room temperature for 15 h. The organic layer

was separated and the aqueous layer extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography gave 11.0 g (75% over two steps) of the desired alcohol **256** as a single diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.20 (band, 2H), 6.86-6.83 (band, 2H), 5.87 (dddd, *J* = 7.2, 7.2, 10.0, 17.2 Hz, 1H), 5.09 (dd, *J* = 1.6, 16.8 Hz, 1H), 5.05-5.02 (m, 1H), 4.51 (AB, *J* = 11.2 Hz, Δv_{AB} = 6.20 Hz, 2H), 3.82-3.74 (m, 3H), 3.77 (s, 3H), 3.63 (ddd, *J* = 2.0, 3.2, 8.0 Hz, 1H), 3.59-3.52 (band, 2H), 3.44-3.37 (band, 2H), 2.66 (dd, *J* = 6.4, 16.8 Hz, 1H), 2.53 (dd, *J* = 5.6, 16.8 Hz, 1H), 2.48-2.40 (m, 1H), 2.36-2.30 (m, 1H), 1.80 (dddd, *J* = 7.2, 7.2, 14.0, 14.0 Hz, 1H), 1.08-1.04 (band, 21H), 1.02 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 135.63, 135.59 129.5, 117.8, 116.8, 113.7, 80.6, 79.3, 75.9, 72.1, 65.8, 61.8, 55.1, 38.6, 34.2, 20.4, 18.0, 13.5, 11.8; IR (film) 3457, 2941, 1613, 1513, 1463, 1248, 1086 cm^{-1}; $[\alpha]^{21}_D$ = –8.0 (*c* 0.5, CH_2Cl_2), MS (ESI) for $C_{29}H_{49}NO_5Si$ [M + Na] calc 542.3, found 542.6.

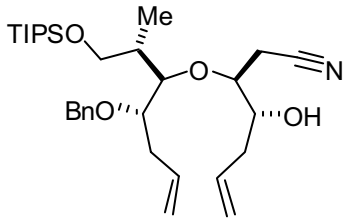
Swern oxidation to the aldehyde



Into a 300 mL flask equipped with an addition funnel and low-temperature thermometer under an argon atmosphere was added 50 mL of CH_2Cl_2 and oxalyl chloride (15.5 mL, 31.1 mmol; 2.0 M in CH_2Cl_2). After cooling to –78 ºC, dimethylsulfoxide (2.94 mL, 41.4 mmol) in 50 mL of CH_2Cl_2 was added dropwise via an addition funnel to maintain a temperature < –65 ºC. After stirring for 10 minutes, alcohol **256** (10.8 g, 20.7 mmol) in 50 mL of CH_2Cl_2 was added via addition funnel maintaining a temperature < –65 ºC. After stirring for 30 minutes, triethylamine (14.4 mL, 103.5 mmol) was added dropwise. The cooling bath was removed

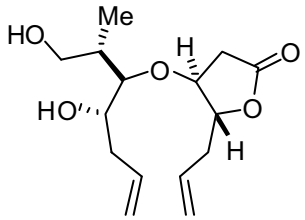
and the reaction was allowed to warm to room temperature over 30 min. The reaction mixture was washed with 200 mL each water, 1M HCl, saturated $NaHCO_3$, water, and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The aldehyde was quickly filtered through a small plug of silica gel, concentrated, and used immediately in the next reaction.

Diene **257**



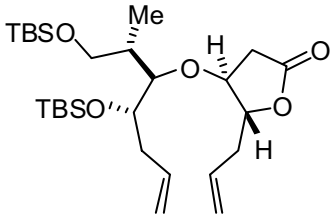
To a solution the aldehyde prepared in the previous step and 400 mL CH_2Cl_2 at –78 ºC under an argon atmosphere was added allyl tri-*n*-butyltin (7.01 mL, 22.7 mmole). Trimethylaluminum (41.2 mL, 82.4 mmole; 2M in toluene) was added slowly over 1 h via syringe pump. After the addition was complete, 20 mL methanol was added slowly and the reaction mixture warmed to 0 ºC. 400 ml of a 1 N HCl solution was added slowly. The organic layer was separated and the aqueous layer extracted twice with CH_2Cl_2. The combined organic layers were concentrated in vacuo to give the crude diene **257**.

Lactone **262**



To the crude material obtained above was added 100 mL methanol and 5 mL HCl (conc.). The resulting solution was heated to 65 ºC for 3 h. After cooling the reaction mixture to room temperature, 100 mL each of CH_2Cl_2 and ½ saturated NaCl were added. The organic layer was separated and the aqueous layer extracted six times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purfication by flash chromatography gave 4.07 g (69%) of the desired isomer **262** along with 0.60 g (11%) of the undesired diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85-5.68 (band, 2H), 5.18-5.09 (band, 4H), 4.54 (ddd, *J* = 2.4, 6.8, 6.8 Hz, 1H), 4.20 (ddd, *J* = 2.4, 2.4, 4.8 Hz, 1H), 3.73 (dddd, *J* = 3.2, 3.2, 3.2, 8.4 Hz, 1H), 3.53-3.48 (m, 1H), 3.45-3.36 (band, 2H), 2.73-2.67 (band, 2H), 2.60 (dd, *J* = 2.8, 18.0 Hz, 1H), 2.54 (d, *J* = 3.6 Hz, 1H), 2.42-2.31 (band, 3H), 2.15 (ddd, *J* = 8.0, 8.0, 14.0 Hz, 1H), 1.91 (m, 1H), 0.88 (*J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 134.7, 131.5, 119.4, 118.3, 85.1, 79.9, 71.2, 64.3, 37.4, 37.1, 36.6, 35.1, 12.0; IR (film) 3426, 2932, 1774, 1642, 1412, 1364, 1175, 1035 cm^{-1}; $[\alpha]^{21}_D$ = +25 (*c* 0.35, CH_2Cl_2), MS (ESI) for $C_{15}H_{24}O_5$ [M + Na] calc 307.2, found 307.1.

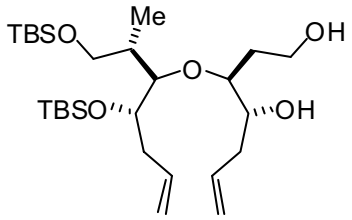
Bis-TBS Ether **263**



To a solution of the diol **262** (2.89 g, 10.2 mmole) in 20 mL dimethylformamide was added imidazole (2.08 g, 30.5 mmole) followed triisopropylsilyl chloride (3.38 g, 22.4 mmole). The reaction mixture was heated to 80 ºC and allowed to stir under an argon atmosphere for 15 h. The reaction mixture was cooled and saturated $NaHCO_3$ was added along with Et_2O. The organic layer was separated and the aqueous layer extracted twice with Et_2O. The

combined organic layers were washed with brine and dried over Na_2SO_4. The crude extract was concentrated under reduced pressure and purified by flash chromatography to give 4.18 g (80%) of the bis-TBS ether **263.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87-5.70 (band, 2H), 5.18-5.13 (band, 2H), 5.06-5.00 (band, 2H), 4.54 (ddd, *J* = 2.0, 6.4, 6.4 Hz, 1H), 4.43-4.40 (m, 1H), 3.81 (dddd, *J* = 2.8, 2.8, 4.8, 4.8 Hz, 1H), 3.50 (ddd, *J* = 0, 2.8, 4.8 Hz, 1H), 3.44 (dd, *J* = 4.4, 10.0 Hz, 1H), 3.36 (dd, *J* = 7.6, 10.0 Hz, 1H), 2.61 (d, *J* = 1.6 Hz, 1H), 2.60 (s, 1H), 2.41-2.33 (band, 2H), 2.27-2.23 (band, 2H), 1.79-1.72 (m, 1H), 0.87 (s, 9H), 0.85 (s, 9H), 0.81 (d, *J* = 7.2 Hz, 3H), 0.03-0.02 (band, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 135.5, 131.6, 119.1, 116.7, 85.0, 79.9, 76.5, 74.4, 65.0, 37.5, 37.24, 37.17, 34.6, 25.74, 25.66, 18.1, 17.8, 12.1, –4.5, –4.7, –5.6; IR (film) 2955, 2929, 2857, 1786, 1643, 1472, 1255, 1204, 1086 cm^{-1}; $[\alpha]^{24}_D$ = +6.6 (*c* 2.5, CH_2Cl_2), MS (ESI) for $C_{27}H_{52}O_5Si_2$ [M + Na] calc 535.3, found 535.5.

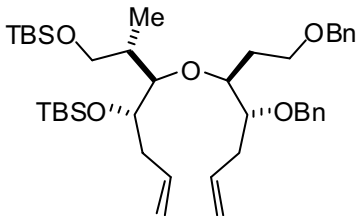
Diol **264**



To a flask containing a solid addition funnel was added the lactone **263** (14.8 g, 28.8 mmole) and 300 mL Et_2O. The resulting mixture was cooled to –20 ºC. Lithium aluminum hydride (2.0 g, 52.6 mmole) was added to the addition funnel and added slowly to the reaction mixture over 30 min. To the reaction mixture was added 2 mL H_2O (slowly), 2 mL of 15% aq. NaOH, and 6 mL H_2O in that order. The resulting heterogeneous solution was filtered through a small pad of celite. The celite was washed with several portions of Et_2O until all product was removed from the solids. The filtrate was concentrated and purified by flash chromatography to give 13.1 g (88%) of the diol **264**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86-

5.72 (band, 2H), 5.06-4.95 (band, 4H), 3.92 (dddd, *J* = 4.0, 8.0, 8.0, 12.4 Hz, 1H), 3.86-3.82 (m, 1H), 3.82-3.80 (band, 2H), 3.67-3.57 (band, 3H), 3.53 (ddd, *J* = 3.0, 3.2, 3.2 Hz, 1H), 3.45 (dd, *J* = 4.4, 10.4 Hz, 1H), 3.41 (dd, *J* = 6.4, 10.0 Hz, 1H), 2.37-2.21 (band, 3H), 2.04 (ddd, *J* = 4.8, 7.6, 12.8 Hz, 1H), 1.88 (dddd, *J* = 4.0, 5.6, 9.6, 9.6 Hz, 1H), 1.75-1.64 (band, 2H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.85 (s, 9H), 0.84 (s, 9H), 0.04 (s,3H), 0.03 (s, 3H), –0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 135.2, 116.8, 116.6, 80.4, 80.0, 74.9, 69.3, 65.6, 58.8, 38.9, 37.0, 36.5, 31.2, 26.0, 25.99, 25.97, 25.89, 25.87, 25.86, 18.21, 18.19, 13.3, –4.24, –4.53, –5.45; IR (film) 3399, 2929, 1642, 1471, 1256, 1080 cm^{-1}; $[\alpha]^{23}_D$ = –7.8 (*c* 0.6, CH_2Cl_2), MS (ESI) for $C_{27}H_{56}O_5Si_2$ [M + Na] calc 539.4, found 539.4.

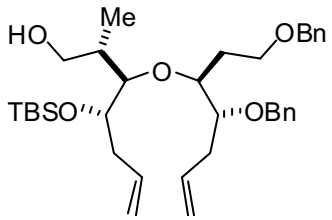
Bis-benzyl ether **265**



To a 100 mL flask containing the diol **264** (3.87 g, 7.49 mmole) and 20 mL dimethylformamide under an argon atmosphere was added benzyl bromide (2.67 mL, 22.5 mmole). The resulting solution was cooled to 0 ºC. Sodium hydride (1.50 g, 37.5 mmole) was added in one portion and the resulting reaction mixture was warmed to room temperature and stirred for 15 h. The reaction was slowly quenched using saturated NH_4Cl. After the addition of 100 mL diethyl ether the organic layer was separated and the aqueous layer extracted twice with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography gave 2.52 g (98%) of the desired bis-benzyl ether **265**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.24 (band, 10H), 5.93-5.76 (band, 2H), 5.10-4.95 (band, 4H), 4.72 (d, *J* = 11.6 Hz, 1H), 4.54 (d, *J* = 11.6 Hz, 1H), 4.47 (AB, *J* = 12.0 Hz, $\Delta\nu_{AB}$ = 8.0 Hz, 2H), 3.92-3.85 (band, 2H), 3.69 (ddd, *J* =

2.0, 4.8, 7.2 Hz, 1H), 3.61-3.56 (band, 3H), 3.52 (dd, *J* = 7.6, 10.0 Hz, 1H), 3.45, (dd, *J* = 5.6, 9.6 Hz, 1H), 2.45-2.36 (band, 2H), 2.29-2.21 (band, 2H), 2.34-1.97 (m, 1H), 1.90-1.81 (band, 2H), 0.93-0.86 (band, 21H), 0.063-0.007 (band, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 138.6, 136.4, 136.0, 128.3, 128.1, 127.6, 127.5, 127.4, 127.2, 116.5, 116.4, 81.2, 79.5, 77.6, 75.3, 72.1, 67.6, 65.8, 38.2, 37.8, 35.7, 30.1, 26.0, 25.98, 25.97, 18.3, 18.1, 12.8, –4.1, –4.4, –5.30, –5.33; IR (film) 2928, 2857, 1641, 1471, 1360, 1254, 1091 cm^{-1}; $[\alpha]^{23}_D$ = + 17.3 (*c* 0.4, CH_2Cl_2), MS (ESI) for $C_{41}H_{68}O_5Si_2$ [M + Na] calc 719.5, found 719.5.

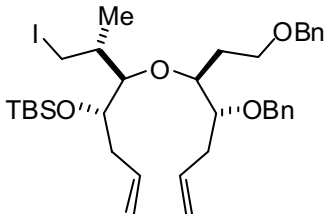
Alcohol **266**



To a solution of the bis-TBS ether **265** (23.4 g, 33.6 mmole) and 150 mL THF at room temperature was added hydrogen fluoride-pyridine (15 mL; 65% HF in pyridine). The resulting solution was allowed to stir for 3 h. The reaction was quenched with saturated $NaHCO_3$. The organic layer was separated and the aqueous layer extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography gave 14.08 g (72%) of the primary alcohol **266** and 2.48 g (16%) of the diol **267**. Diol **267** could be converted to the bis-TBS ether **265** upon treatment with TBSOTf and 2,6-Lutidine. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.25 (band, 10H), 5.90 (dddd, *J* = 7.2, 7.2, 10.0, 17.2 Hz, 1H), 5.81 (dddd, *J* = 7.2, 7.2, 10.4, 17.2 Hz, 1H), 5.15-5.00 (band, 4H), 4.70 (d, *J* = 11.6 Hz, 1H), 4.58 (d, *J* = 11.6 Hz, 1H), 4.50 (s, 2H), 3.95 (ddd, *J* = 2.0, 5.2, 7.2 Hz, 1H), 3.90 (ddd, *J* = 2.0, 5.6, 5.6 Hz, 1H), 3.67 (ddd, *J* = 1.6, 5.2, 7.2 Hz, 1H), 3.64-3.49 (band, 5H), 2.72 (bs, 1H), 2.49-2.39 (band, 2H), 2.35-2.24

(band, 2H), 2.02-1.85 (band, 3H), 0.99 (d, *J* = 7.2 Hz, 3H), 0.93 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 138.3, 135.8, 135.6, 128.3, 128.12, 128.11, 127.7, 127.5, 127.3, 116.8, 116.7, 81.4, 81.1, 76.97, 75.4, 72.8, 72.2, 67.1, 65.0, 38.6, 37.2, 35.5, 30.3, 25.9, 18.0, 13.3, –4.2, –4.6; IR (film) 3445, 2928, 2857, 1641, 1471, 1455, 1361, 1254, 1094 cm^{-1}; $[\alpha]^{23}_D$ = + 8.5 (*c* 0.7, CH_2Cl_2), MS (ESI) for $C_{35}H_{54}O_5Si$ [M + Na] calc 605.4, found 605.4.

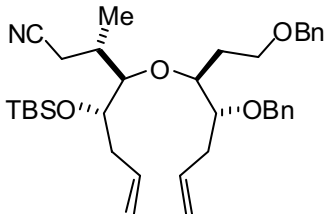
Iodide **268**



To a solution of the alcohol **266** (2.57 g, 4.41 mmole) and 40 mL anhydrous benzene under an argon atmosphere was added imidazole (0.450 g, 6.62 mmole), triphenylphosphine (1.50 g, 5.73 mmole) and iodine (1.45 g, 5.73 mmole). The reaction mixture was allowed to stir for 1 h at room temperature and quenched by the addition of saturated $Na_2S_2O_3$. The solution was diluted with Et_2O and the organic layer was separated. The aqueous layer was extracted twice with Et_2O and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography gave 2.96 g (97%) of the desired alkyl iodide **268**. This compound was found to be slightly light sensitive and was protected accordingly. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.24 (band, 10H), 5.88 (dddd, *J* = 7.2, 7.2, 10.0, 16.8 Hz, 1H), 5.80 (dddd, *J* = 7.2, 7.2, 10.8, 17.6 Hz, 1H), 5.13-4.99 (band, 4H), 4.69 (d, *J* = 11.6 Hz, 1H), 4.56 (d, *J* = 11.6 Hz, 1H), 4.51 (AB, *J* = 12.0 Hz, $\Delta\nu_{AB}$ = 13.9 Hz, 2H), 3.91 (ddd, *J* = 1.6, 7.2, 7.2 Hz, 1H), 3.84 (ddd, *J* = 2.4, 4.8, 7.2 Hz, 1H), 3.67 (ddd, *J* = 1.6, 4.8, 7.2 Hz, 1H), 3.61-3.56 (band, 2H), 3.52 (dd, *J* = 2.8, 4.0 Hz, 1H), 3.35 (dd, *J* = 6.0, 9.6 Hz, 1H), 3.14 (dd, *J* = 6.8, 9.6 Hz, 1H), 2.48-2.35 (band, 2H), 2.30-2.22

(band, 2H), 2.00-1.92 (band, 2H), 1.88 (dddd, *J* = 7.2, 7.2, 14.0, 14.0 Hz, 1H), 1.09 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.10 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 138.4, 135.7, 135.6, 128.3, 128.1, 127.7, 127.5, 127.3, 117.1, 116.7, 81.8, 81.2, 77.4, 74.8, 72.9, 72.1, 67.0, 38.5, 37.9, 35.4, 30.4, 26.0, 18.1, 16.9, 14.5, –4.0, –4.4; IR (film) 2928, 2856, 1640, 1454, 1360, 1254, 1199, 1093 cm^{-1}; $[\alpha]^{20}_D$ = + 8.74 (*c* 3.8, CH_2Cl_2), MS (ESI) for $C_{35}H_{53}IO_4Si$ [M + H] calc 693.3, found 693.2.

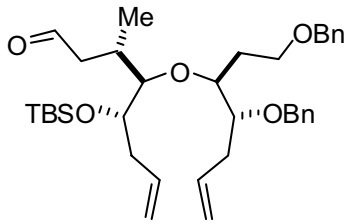
Nitrile **269**



To a flask containing iodide **268** (2.96 g, 4.27 mmole) and 10 mL anhydrous dimethylsulfoxide was added sodium cyanide (0.418 g, 8.54 mmole; use caution when handling this reagent). The reaction mixture was allowed to stir for 15 h followed by dilution with Et_2O and water. The organic layer was separated and the aqueous layer was extracted twice with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography gave 2.42 g (96%) of the desired nitrile **269**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.26 (band, 10H), 5.86 (dddd, *J* = 7.2, 7.2, 10.0, 17.6 Hz, 1H), 5.75 (dddd, *J* = 6.8, 6.8, 10.4, 16.8 Hz, 1H), 5.11-4.99 (band, 4H), 4.58 (AB, *J* = 11.6 Hz, $\Delta\nu_{AB}$ = 36.2 Hz, 2H), 4.48 (s, 2H), 3.87 (ddd, *J* = 2.4, 6.4, 6.4 Hz, 1H), 3.83 (ddd, *J* = 1.0, 6.0, 6.0 Hz, 1H), 3.61 (ddd, *J* = 1.0, 6.0, 6.0 Hz, 1H), 3.57-3.49 (band, 2H), 3.44 (dd, *J* = 3.6, 3.6 Hz, 1H), 2.46 (dd, *J* = 6.0, 16.8 Hz, 1H), 2.47-2.13 (band, 6H), 1.92-1.80 (band, 2H), 1.11 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 138.2, 135.6, 135.0, 128.3, 128.2, 127.7, 127.6, 127.5, 127.4, 119.4, 117.4, 116.9, 81.2, 81.0, 77.3, 74.7, 72.9, 72.1, 66.8, 39.1, 35.2, 32.6, 30.5,

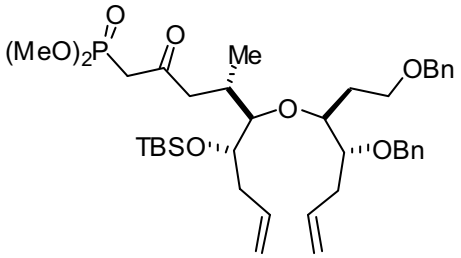
25.9, 22.2, 18.0, 15.7, –4.3, –4.5; IR (film) 2929, 2857, 1641, 1455, 1361, 1254, 1096 cm^{-1}; $[\alpha]^{23}_D$ = + 6.1 (*c* 3.2, CH_2Cl_2), MS (ESI) for $C_{36}H_{53}NO_4Si$ [M + Na] calc 614.4, found 614.4.

Aldehyde **273**



A solution of nitrile **269** (7.58 g, 12.8 mmole) in 100 mL CH_2Cl_2 under an argon atmosphere was cooled to 0 ºC. Diisobutylaluminum hydride (38.5 mL, 38.5 mmole; 1M in hexanes) was added dropwise to the solution and the resulting mixture was allowed to stir at 0 ºC for 3 h. The reaction was quenched with a saturated solution of Na^+/K^+ tartrate and the resulting heterogeneous solution was vigorously stirred for 2 h at room temperature. The organic layer was separated and the aqueous layer extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography gave 6.17 g (81%) of the aldehyde **273**. ^1H NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 1H), 7.36-7.24 (band, 10H), 5.87 (dddd, *J* = 6.8, 6.8, 10.0, 17.2 Hz, 1H), 5.83-5.75 (m, 1H), 5.13-4.98 (band, 4H), 4.63 (AB, *J* = 11.6 Hz, Δv_{AB} = 48.2 Hz, 2H), 4.48 (s, 2H), 3.88-3.81 (band, 2H), 3.68 (ddd, *J* = 1.6, 5.2, 7.2 Hz, 1H), 3.61-3.51 (band, 2H), 3.40 (dd, *J* = 2.8, 3.6 Hz, 1H), 2.60 (dd, *J* = 4.4, 16.0 Hz, 1H), 2.47-2.37 (band, 3H), 2.31-2.21 (band, 3H), 1.95-1.84 (band, 2H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4, 138.9, 138.3, 135.7, 135.6, 128.3, 128.1, 127.6, 127.50, 127.48, 127.3, 116.9, 116.8, 82.7, 81.1, 77.3, 74.4, 72.8, 72.1, 67.0, 48.4, 38.5, 35.5, 30.2, 29.7, 25.9, 18.0, 16.2, –4.2, –4.4; IR (film) 2955, 2856, 1725, 1641, 1454, 1361, 1254, 1095 cm^{-1}; $[\alpha]^{23}_D$ = +5.6 (*c* 1.9, CH_2Cl_2), MS (ESI) for $C_{36}H_{54}O_5Si$ [M + Na] calc 617.4, found 617.2.

Phosphonate **275**



i) Formation of the β-hydroxy phosphonate

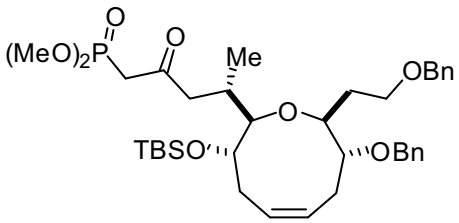
A flask containing dimethyl methyl phosphonate (10.8 mL, 100 mmole) and 300 mL anhydrous THF was cooled to –78 ºC. *n*-Butyl lithium (40 mL, 100 mmole; 2.5 M in hexanes) was added dropwise to the solution over 15 min. The resulting mixture was allowed to stir for 1 h. The aldehyde **273** (6.17 g, 10.4 mmole) prepared in the previous step was dissolved in 50 mL THF and added slowly to the lithiated phosphonate solution. After stirring at –78 ºC for 20 minutes the reaction mixture was warmed to 0 ºC and quenched with saturated $NaHCO_3$. The solution was diluted with EtOAc and the organic layer was separated. The aqueous layer was extracted twice with EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography gave 7.19 g (96%) of the desired phosphonate as a mixture of β-hydroxy epimers.

ii) Formation of the β-keto phosphonate

The β-hydroxy phosphonate mixture obtained in the previous step (2.38 g, 3.31 mmole) was dissolved in 20 mL CH_2Cl_2. Dess-Martin periodinane (1.68 g, 3.97 mmole) was added in a single portion and the resulting mixture was allowed to stir at room temperature for 20 min. The reaction was then quenched using a saturated solution of 5:1 $Na_2S_2O_3/NaHCO_3$. The organic layer was separated and the aqueous layer extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in

vacuo. Purification by flash chromatography gave 2.27 g (96%) of the desired β-keto phosphonate **275**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.21 (band, 10H), 5.89-5.73 (band, 2H), 5.09-4.95 (band, 4H), 4.60 (AB, *J* = 11.6 Hz, Δv_{AB} = 52.3 Hz, 2H), 4.45 (AB, *J* = 12.0 Hz, Δv_{AB} = 12.3 Hz, 2H), 3.82-3.76 (band, 2H), 3.75 (d, *J* = 3.2 Hz, 3H), 3.72 (d, *J* = 3.2 Hz, 3H), 3.66 (ddd, *J* = 2.0, 5.6, 7.6 Hz, 1H), 3.59-3.49 (band, 2H), 3.37 (dd, *J* = 2.8, 4.0 Hz, 1H), 2.99 (dd, *J* = 14.0, 33.2 Hz, 1H), 2.94 (dd, *J* = 13.6, 32.8 Hz, 1H), 2.73 (dd, *J* = 4.4, 17.2 Hz, 1H), 2.52 (dd, *J* = 8.8, 17.6 Hz, 1H), 2.43-2.31 (band, 3H), 2.29-2.17 (band, 2H), 1.92-1.80 (band, 2H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.15, 201.08, 139.0, 138.5, 136.0, 135.7, 128.3, 128.1, 127.6, 127.5, 127.4, 127.2, 116.8, 116.7, 82.7, 81.2, 77.4, 74.8, 72.8, 72.1, 67.2, 52.94, 52.87, 52.81, 48.6, 42.1, 40.8, 38.5, 35.6, 30.5, 30.2, 26.0, 18.1, 15.9, –4.2, –4.5; IR (film) 2954, 1715, 1640, 1454, 1361, 125, 1030 cm^{-1}; $[\alpha]^{23}_D$ = + 3.9 (*c* 3.3, CH_2Cl_2), MS (ESI) for $C_{37}H_{57}O_8PSi$ [M + Na] calc 739.4, found 739.2.

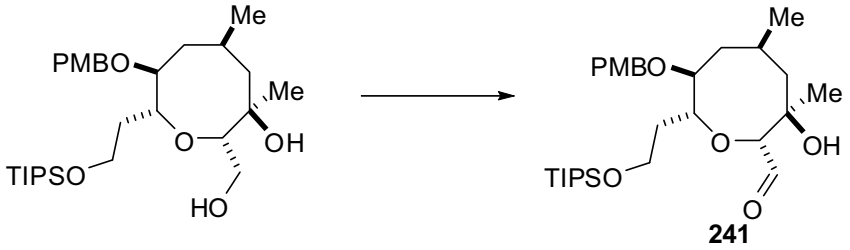
Phosphonate **276**



A flask equipped with a reflux condenser containing the diene fragment (3.54 g, 4.94 mmole) and 1 L CH_2Cl_2 was heated to 40 ºC for 10 min. under an argon purge in order to degas the solvent. After cooling to room temperature, Grubbs second generation catalyst (**122**) (0.203 g, 0.247 mmole) was added and the reaction mixture was reheated to 40 ºC under an argon atmosphere. After stirring for 4 h, the reaction was cooled to room

temperature and quenched using air bubbling for 2 h. The solvent was evaporated an the crude residue was purified by flash chromatography to give 3.40 g (quant.) of the desired oxonene **276**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.21 (band, 10H), 5.73-5.61 (band, 2H), 4.62 (d, *J* = 11.6 Hz, 1H), 4.41 (s, 2H), 4.36 (d, *J* = 11.6 Hz, 1H), 3.83 (ddd, *J* = 1.6, 5.6, 5.6 Hz, 1H), 3.71 (d, *J* = 5.2 Hz, 3H), 3.68 (d, *J* = 5.2 Hz, 3H), 3.64 (m, 1H), 3.56-3.47 (band, 2H), 3.42 (ddd, *J* = 7.6, 7.6, 7.6 Hz, 1H), 3.36 (dd, *J* = 2.4, 6.0 Hz, 1H), 2.97 (dd, *J* = 13.6, 33.2 Hz, 1H), 2.92 (dd, *J* = 14.0, 33.2 Hz, 1H), 2.71-2.54 (band, 4H), 2.38-2.28 (band, 2H), 2.10 (ddd, *J* = 5.6, 5.6, 13.2 Hz, 1H), 1.96 (dddd, *J* = 4.4, 8.0, 10.8, 14.4 Hz, 1H), 1.82 (dddd, *J* = 5.6, 5.6, 7.6, 13.6 Hz, 1H), 0.87 (s, 9H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.74, 200.68, 138.41, 138.36, 128.3, 128.18, 128.17, 127.6, 127.5, 127.4, 127.3, 126.4, 85.6, 80.5, 78.2, 72.9, 72.8, 70.9, 66.7, 52.8, 52.7, 52.65, 49.02, 49.00, 41.9, 40.6, 32.7, 31.5, 30.7, 25.9, 25.70, 25.68, 17.8, 14.3, –4.4, –4.9; IR (film) 2954, 2856, 1716, 1496, 1454, 1362, 1258, 1097, 1030 cm^{-1}; $[\alpha]^{23}_{D}$ = –6.3 (*c* 2.4, CH_2Cl_2), MS (ESI) for $C_{37}H_{57}O_8PSi$ [M + Na] calc 711.4, found 711.2.

5.2.3.2. Synthesis of the B ring aldehyde



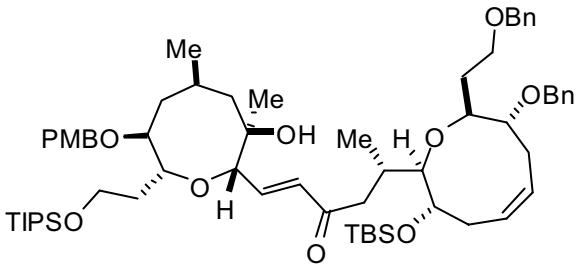
241

To a solution of the B-ring diol (0.280 g, 0.534 mmole) in 5 mL CH_2Cl_2 was added Dess-Martin periodinane (0.339 g, 0.800 mmole). The resulting solution was allowed to stir for 1 h and quenched with a 5:1 $Na_2S_2O_3$/$NaHCO_3$ solution. The organic layer was separated and the aqueous layer extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by

flash chromatography gave 0.238 g (85%) of the aldehyde **241**. ^{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 (ESI) for $C_{29}H_{50}O_6Si$ [M + H] calc 523.3, found 523.4.

5.2.3.3. Synthesis of the ABCDE lactone

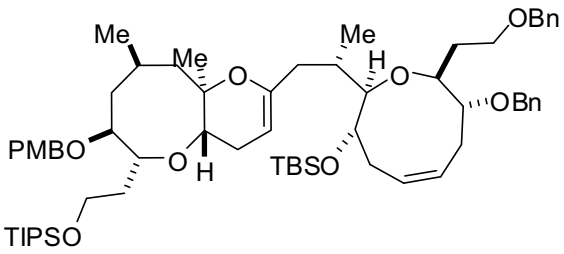
Enone **277**



To a solution of the E ring phosphonate **276** (0.123 g, 0.160 mmole) in 0.4 mL THF was added $Ba(OH)_2$ (0.040 g, 0.128 mmole; predried @ 120 ºC for 2 h). The solution was allowed to stir at room temperature for 30 min. A solution of the B ring aldehyde **241** (0.153 mmole) and 0.4 mL of a 40:1 THF/H_2O mixture was added to the phosphonate solution followed by the addition of an additional 0.5 mL of the THF/H_2O mixture. After stirring for 30 min., the reaction was diluted with EtOAc and filtered through a small pad of celite. The filtrate was washed with aqueous $NaHCO_3$. The organic layer was separated and the

aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography gave 0.177g (96%) of the desired product **277**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.21 (band, 12H), 6.90 (dd, *J* = 5.2, 16.4 Hz, 1H), 6.87-6.83 (band, 2H), 6.26 (dd, *J* = 1.2, 16.0 Hz, 1H), 5.72 (ddd, *J* = 6.0, 10.4, 10.4 Hz, 1H), 5.63 (ddd, *J* = 5.6, 10.4, 10.4 Hz, 1H), 4.63 (d, *J* = 11.6 Hz, 1H), 4.51 (d, *J* = 11.2 Hz, 1H), 4.42 (s, 2H), 4.36 (d, *J* = 11.6 Hz, 1H), 4.35 (d, *J* = 11.2 Hz, 1H), 4.24 (dd, *J* = 1.0, 4.4 Hz, 1H), 3.92 (dd, *J* = 4.8, 4.8 Hz, 1H), 3.78 (s, 3H), 3.78-3.68 (band, 2H), 3.66-3.60 (band, 2H), 3.56 (ddd, *J* = 5.6, 9.2, 9.2 Hz, 1H), 3.48 (m, 1H), 3.43 (ddd, *J* = 6.4, 9.2, 9.2 Hz, 1H), 3.36 (dd, *J* = 2.0, 4.8 Hz, 1H), 3.30 (ddd, *J* = 3.2, 8.0, 8.0 Hz, 1H), 2.74 (dd, *J* = 4.0, 16.0 Hz, 1H), 2.71-2.63 (band, 2H), 2.44 (dd, *J* = 8.8, 24.4 Hz, 1H), 2.45-2.39 (m, 1H), 2.31 (ddd, *J* = 5.2, 5.2, 10.0 Hz, 1H), 2.15 (ddd, *J* = 5.6, 5.6, 12.4 Hz, 1H), 2.03-1.85 (band, 6H), 1.79 (s, 1H), 1.68-1.56 (band, 2H), 1.50 (d, *J* = 12.8 Hz, 1H), 1.09-1.01 (band, 24H), 0.99 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.0, 159.1, 144.5, 138.43, 138.36, 130.8, 130.5, 129.1, 128.7, 128.3, 128.2, 127.73, 127.72, 127.5, 126.2, 113.7, 86.5, 86.3, 82.1, 81.8, 80.2, 77.8, 74.0, 73.7, 72.8, 71.0, 70.8, 66.9, 60.2, 55.2, 53.2, 44.6, 41.1, 37.3, 32.5, 32.4, 30.6, 27.8, 27.0, 26.2, 25.8, 21.8, 18.0, 17.9, 14.8, 11.9, –4.3, –4.7; IR (film) 2928, 2863, 1674, 1613, 1513, 1460, 1379, 1301, 1249, 1097 cm^{-1}; $[\alpha]^{21}_D$ = + 14.6 (*c* 1.4, CH_2Cl_2), MS (ESI) for $C_{64}H_{100}O_{10}Si_2$ [M + Na] calc 1107.7, found 1107.5.

Enol ether **278**



Stryker's reduction:

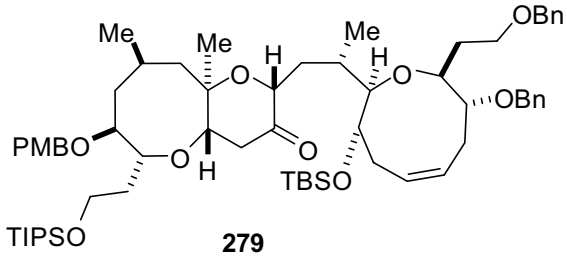
To a flask containing the enone **277** (1.24 g, 1.14 mmole) and $[PPh_3CuH]_6$ (2.23 g, 1.14 mmole) was added 10 mL toluene (degassed) and 0.100 mL H_2O (degassed). The reaction mixture was heated to 50 ºC and stirred for 15 h under an argon atmosphere. The reaction mixture was cooled and air was bubbled through the mixture for 2 h to quench the excess reagent. The entire reaction mixture was then directly purified by flash chromatography. After evaporation of the solvents, the material was dissolved in 5 mL CH_2Cl_2. A catalytic amount of PPTS was added and the reaction mixture was heated to 40 ºC for 30 min. After cooling the reaction, the mixture was purified directly using flash chromatography to give 1.00 g (82%) of the desired enol ether **278**.

Wilkinson's reduction:

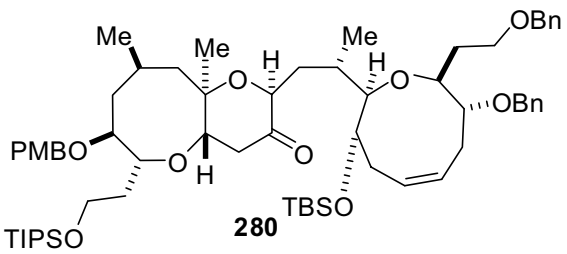
To a flask containing the enone **277** (0.379 g, 0.349 mmole) and 3 mL toluene maintained under an argon atmosphere was added diemethylphenylsilane (0.270 mL, 1.75 mmole) and $(PPh_3)_3RhCl$ (Wilkinson's catalyst; 0.016 g, 0.017 mmole). The flask was heated to 50 ºC and the reaction monitored by TLC. After consumption of the starting material, pyridinium *p*-toluene sulfonate (0.050 g) was added and the reaction mixture stirred at 50 ºC for 10 min. The solvents were evaporated and the crude material was purified using flash chromatography to give 0.342 g (92%) of the desired enol ether **278**. ^{1}H NMR (400 MHz, C_6D_6) δ 7.33-7.31 (band, 2H), 7.23-7.06 (band, 10H), 6.82-6.79 (band, 2H), 5.96 (ddd, *J* = 5.6, 10.4, 10.4 Hz, 1H), 5.86 (ddd, *J* = 6.0, 10.4, 10.4 Hz, 1H), 4.44-4.34 (band, 5H), 4.20 (d, *J* = 4.4 Hz, 1H), 4.17 (d, *J* = 3.6 Hz, 1H), 3.95-3.83 (band, 4H), 3.71-3.55 (band, 5H), 3.51 (dd, *J* = 5.2, 5.2 Hz, 1H), 3.30 (s, 3H), 3.14 (ddd, *J* = 1.0, 10.8, 10.8 Hz, 1H), 2.92 (ddd, *J* = 1.0, 10.8, 10.8 Hz, 1H), 2.71 (ddd, *J* = 1.0, 10.8, 10.8 Hz, 1H), 2.51-2.39 (band, 2H), 2.28-2.23 (band, 3H), 2.19-2.07 (band, 4H), 1.97-1.89 (band, 5H), 1.64-1.57 (band, 2H), 1.34 (s, 3H), 1.51-1.10 (band, 21H), 1.06 (d, *J* = 7.2 Hz, 3H), 1.00 (s, 9H), 1.00-0.98 (m, 3H), 0.11

(s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 159.6, 150.8, 139.47, 139.38, 131.2, 129.4, 128.5, 127.7, 127.6, 127.5, 114.0, 93.7, 86.2, 83.5, 82.7, 81.52, 81.48, 79.2, 77.4, 73.6, 73.1, 71.0, 70.8, 67.2, 60.5, 54.7, 53.2, 42.7, 40.3, 38.0, 33.73, 33.68, 31.7, 28.3, 27.4, 26.9, 26.4, 26.2, 18.33, 18.26, 17.2, 13.9, 12.4, –4.0, –4.5; IR (film) 2927, 2863, 1677, 1609, 1513, 1455, 1385, 1303, 1249, 1098 cm^{-1}; $[\alpha]^{21}_D$ = + 10.1 (*c* 0.8, CH_2Cl_2), MS (ESI) for $C_{64}H_{100}O_9Si_2$ [M + Na] calc 1091.7, found 1091.5.

Ketones **279** and **280**



279



280

i) <u>Oxidation/reduction of the enol ether:</u>

Preparation of "acetone free" DMDO[152,153]: An acetone/water solution of dimethyldioxirane was prepared according to literature procedures beginning with 60 mL acetone.[147] Directly to the solution was added 5 mL CH_2Cl_2 and 20 mL pentane. The solution was poured into a separatory funnel and washed four times with ~100 mL phosphate buffer (pH = 7). The organic layer was dried over magnesium sulfate, filtered and cooled to –78 ºC under an argon atmosphere. Solutions were approximately 0.1 M in DMDO.

To a solution of the enol ether **278** (0.157 g, 0.147 mmole) and 1 mL CH_2Cl_2 at –78 ºC under an argon atmosphere was added the freshly prepared "acetone free" dimethyldioxirane solution until the starting material was consumed as judged by TLC. To the same reaction flask was added diisobutylaluminum hydride (0.735 mL, 0.735 mmole; 1 M in hexanes). The reaction was immediately quenched with a saturated solution of Na^+/K^+ tartrate, warmed to room temperature, and stirred for 15 h. The organic layer was separated and the aqueous

layer was extracted twice with CH_2Cl_2. The combined organic fractions were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography gave a mixture of alcohol diastereomers that was carried through directly to the next reaction.

ii) Dess-Martin oxidation to the ketone:

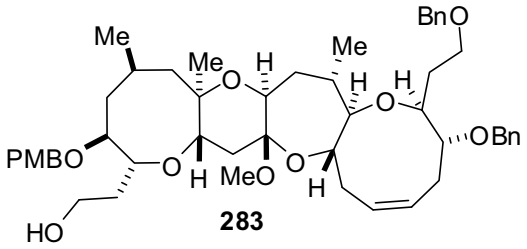
To a flask containing an isomeric mixture of the alcohols (0.136 g, 0.125 mmole) and 1 mL CH_2Cl_2 was added Dess-Martin periodinane (0.080 g, 0.188 mmole). The reaction was stirred for 30 min and quenched with a 5:1 aqueous solution of $Na_2S_2O_3/NaHCO_3$. The solution was poured into a separatory funnel and the organic layer was separated. The aqueous layer was extracted twice with CH_2Cl_2 and the combined extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (15% Et_2O/Hexanes) gave 0.080 g of the major ketone **279** and 0.027 g (67% total) of the minor ketone **280**. ^{1}H NMR (**279**) (400 MHz, $CDCl_3$) δ 7.33-7.21 (band, 12H), 6.87-6.84 (band, 2H), 5.72-5.66 (band, 2H), 4.64 (d, *J* = 12.4 Hz, 1H), 4.47 (d, *J* = 11.2 Hz, 1H), 4.44 (AB, *J* = 12.0 Hz, Δv_{AB} = 14.5 Hz, 2H), 4.40 (d, *J* = 12.0 Hz, 1H), 4.28 (d, *J* = 11.2 Hz, 1H), 4.08 (dd, *J* = 2.8, 10.0 Hz, 1H), 3.88 (ddd, *J* = 5.2, 10.0, 10.0 Hz, 1H), 3.79 (s, 3H), 3.79-3.77 (m, 1H), 3.73-3.61 (band, 2H), 3.58-3.47 (band, 5H), 3.03-2.96 (band, 2H), 2.78 (m, 1H), 2.63-2.53 (band, 2H), 2.35-2.30 (band, 2H), 2.09-2.03 (band, 4H), 1.90 (dddd, *J* = 6.0, 6.0, 7.0, 13.6 Hz, 1H), 1.80-1.70 (band, 4H), 1.57-1.54 (band, 2H), 1.42-1.35 (band, 2H), 1.14 (s, 3H), 1.10-1.01 (band, 24H), 0.89 (s, 9H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.09 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.4, 159.1, 138.5, 138.4, 130.5, 129.2, 128.5, 128.3, 127.7, 127.6, 127.4, 127.3, 127.0, 113.7, 83.2, 82.5, 82.0, 80.5, 78.8, 78.2, 77.1, 73.8, 72.9, 71.8, 71.5, 70.5, 67.1, 60.1, 55.3, 49.5, 41.9, 41.1, 36.7, 34.5, 34.0, 31.0, 28.2, 28.1, 26.0, 25.3, 20.5, 18.0, 15.0, 12.0, –4.3, –4.7; IR (film) 2928, 2863, 1729, 1613, 1513, 1454, 1381, 1359, 1303, 1249, 1093 cm^{-1}; $[\alpha]^{26}_D$ = + 49 (*c* 2.3, CH_2Cl_2), MS (ESI) for $C_{64}H_{100}O_{10}Si_2$ [M + Na] calc 1107.7, found 1107.7.

^{1}H NMR (**280**) (400 MHz, $CDCl_3$) δ 7.35-7.25 (band, 10H), 7.21-7.19 (band, 2H), 6.86-6.83 (band, 2H), 5.74-5.63 (band, 2H), 4.60 (d, *J* = 11.6 Hz, 1H), 4.49 (d, *J* = 11.2 Hz, 1H), 4.43 (s, 2H), 4.39 (d, *J* = 11.6 Hz, 1H), 4.30 (d, *J* = 11.2 Hz, 1H), 3.84-3.79 (band, 2H), 3.79 (s, 3H), 3.75-3.68 (band, 3H), 3.63 (m, 1H), 3.57-3.48 (band, 3H), 3.41-3.38 (band, 2H), 3.08 (ddd, *J* = 1.0, 8.8, 8.8 Hz, 1H), 2.82 (dd, *J* = 6.0, 15.6 Hz, 1H), 2.72 (ddd, *J* = 1.0, 12.0, 13.0 Hz, 1H), 2.61 (ddd, *J* = 1.0, 12.0, 13.0 Hz, 1H), 2.36-2.28 (band, 2H), 2.13-1.87 (band, 5H), 1.84-1.78 (band, 3H), 1.68-1.50 (band, 4H), 1.39 (dddd, *J* = 3.6, 3.6, 8.8, 8.8 Hz, 1H), 1.26 (s, 3H), 1.13-1.02 (band, 21H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.86 (s, 9H), 0.79 (d, *J* = 7.2 Hz, 3H), 0.07 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.5, 159.2, 138.8, 138.7, 130.4, 129.3, 128.2, 128.1, 127.6, 127.5, 127.34, 127.28, 127.0, 113.7, 86.9, 82.7, 82.6, 81.4, 79.3, 75.7, 73.3, 72.8, 72.7, 71.0, 70.7, 67.0, 59.7, 55.2, 53.5, 43.5, 42.6, 37.0, 33.8, 33.2, 31.54, 31.50, 31.4, 28.0, 26.7, 26.4, 25.9, 22.6, 18.08, 18.06, 18.02, 17.94, 15.5, 13.5, 12.0, –4.2, –4.8; IR (film) 2928, 2864, 1725, 1609, 1513, 1461, 1385, 1303, 1249, 1092 cm^{-1}; $[\alpha]^{23}_D$ = +5.8 (*c* 0.6, CH_2Cl_2), MS (ESI) for $C_{64}H_{100}O_{10}Si_2$ [M + Na] calc 1107.7, found 1107.7.

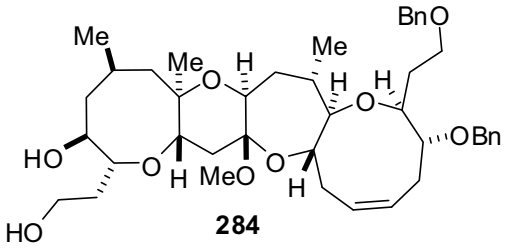
iii) Isomerization of C12 stereocenter, ketone **279** to ketone **280** conversion

To a flask containing the major, undesired ketone isomer **279** (0.155 g, 0.142 mmole) was added 10 mL anhydrous methanol and a small amount of K_2CO_3. The reaction was heated to reflux and monitored by TLC. After a ratio of ~ 4:1 desired to undesired was achieved the reaction was cooled to room temperature and quenched with saturated NH_4Cl. After the addition of CH_2Cl_2 the organic layer was separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (15% Et_2O/Hex) gave 0.102 g (66%) of the ketone **280** with the desired configuration at C12 and 0.034 g (84% b.r.s.m) of the ketone **279**.

Mixed methyl ketals **283** and **284**



283



284

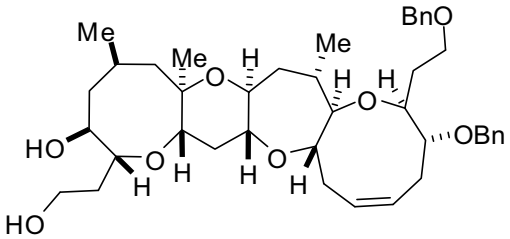
To a solution of the ketone **280** (0.095 g, 0.087 mmole) and 0.5 mL anhydrous methanol under an argon atmosphere was added a catalytic amount of camphorsulfonic acid. The solution was heated to reflux temperature for 3 h. The reaction was cooled and diluted with CH_2Cl_2. Aqueous $NaHCO_3$ was added and the organic layer was separated. The aqueous layer was extracted twice with CH_2Cl_2 and the combined extracts were dried over Na_2SO_4. The solution was filtered and concentrated in vacuo. Purification by flash chromatography gave 0.030 g (42%) of the PMB protected mixed methyl ketal **283** and 0.021 g (34%; 76% total) of the deprotected mixed methyl ketal **284**.

^{1}H NMR ketal **283** (500 MHz, C_6D_6) δ 7.31-7.28 (band, 4H), 7.18-7.14 (band, 6H), 7.10-7.05 (band, 2H), 6.81-6.78 (band, 2H), 6.04 (ddd, *J* = 5.5, 10.5, 10.5 Hz, 1H), 5.86 (ddd, *J* = 6.0, 10.5, 10.5 Hz, 1H), 4.43 (d, *J* = 11.5 Hz, 1H), 4.39 (d, *J* = 11.0 Hz, 1H), 4.31 (AB, *J* = 12.0 Hz, Δv_{AB} = 20.2 Hz, 2H), 4.20 (d, *J* = 11.5 Hz, 1H), 4.11 (d, *J* = 11.0 Hz, 1H), 4.11 (m, 1H), 3.77 (ddd, *J* = 5.5, 5.5, 5.5 Hz, 1H), 3.72-3.68 (band, 2H), 3.60-3.48 (band, 6H), 3.33 (dd, *J* = 5.0, 5.0 Hz, 1H), 3.30 (s, 3H), 3.16 (s, 3H), 3.04 (ddd, *J* = 1.5, 10.5, 10.5 Hz, 1H), 2.97 (ddd, *J* = 1.0, 10.0, 10.0 Hz, 1H), 2.76 (ddd, *J* = 5.0, 11.0, 15.0 Hz, 1H), 2.64-2.59 (band, 2H), 2.27 (ddd, *J* = 5.5, 5.5, 12.0 Hz, 1H), 2.21 (m, 1H), 2.16-2.06 (band, 2H), 2.00 (m, 1H), 1.89 (m, 1H), 1.83-1.63 (band, 6H), 1.49 (ddd, *J* = 7.5, 7.5, 7.5, 12.0 Hz, 1H), 1.35 (dd, *J* = 2.0, 14.0 Hz, 1H), 1.22 (s, 3H), 1.22 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 159.8, 139.3, 131.0, 129.7, 128.53, 128.50, 127.7, 127.62, 127.60, 114.0, 97.9, 88.8, 84.2, 83.1, 82.5, 81.8, 81.1, 75.9, 73.2, 71.2, 70.8, 70.7, 70.5, 66.9, 59.4,

54.80, 54.79, 54.5, 48.0, 42.6, 36.7, 36.3, 34.5, 34.1, 31.9, 31.6, 28.3, 27.0, 22.1, 16.0; IR (film) 3466, 2923, 1613, 1513, 1454, 1381, 1299, 1248, 1069 cm^{-1}; $[\alpha]^{22}_D$ = – 1.7 (*c* 1.7, CH_2Cl_2), MS (ESI) for $C_{50}H_{68}O_{10}$ [M + Na] calc 851.5, found 851.5.

^{1}H NMR ketal **284** (500 MHz, C_6D_6) δ 7.34-7.32 (band, 4H), 7.22-7.14 (band, 4H), 7.10-7.05 (band, 2H), 6.06 (ddd, *J* = 6.0, 10.5, 10.5 Hz, 1H), 5.88 (ddd, *J* = 6.0, 10.5, 10.5 Hz, 1H), 4.43 (d, *J* = 12.0 Hz, 1H), 4.31 (AB, *J* = 12.0 Hz, Δv_{AB} = 20.2 Hz, 2H), 4.20 (d, *J* = 11.5 Hz, 1H), 4.13 (m, 1H), 3.78-3.75 (band, 2H), 3.67 (m, 1H), 3.63 (dd, *J* = 5.0, 12.0 Hz, 1H), 3.57-3.48 (band, 4H), 3.38 (ddd, *J* = 1.0, 8.5, 8.5 Hz, 1H), 3.34-3.28 (band, 2H), 3.28 (s, 3H), 2.98 (ddd, *J* = 1.0, 11.5, 11.5 Hz, 1H), 2.75 (ddd, *J* = 5.5, 11.5, 11.5 Hz, 1H), 2.65-2.56 (band, 2H), 2.50 (bm, 2H), 2.29-2.25 (band, 2H), 2.15-2.06 (band, 2H), 2.00 (m, 1H), 1.90 (dddd, *J* = 6.0, 6.0, 6.0, 6.0 Hz, 1H), 1.86-1.56 (band, 7H), 1.35 (dd, *J* = 1.0, 15.5 Hz, 1H), 1.23 (s, 3H), 1.21 (d, *J* = 7.5 Hz, 3H), 0.92 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.3, 128.52, 128.50, 127.7, 127.62, 127.60, 98.0, 88.8, 85.6, 82.4, 82.1, 81.2, 75.95, 75.94, 75.8, 73.1, 71.2, 70.60, 70.56, 66.9, 59.3, 54.8, 48.4, 48.09, 48.07, 37.4, 36.3, 34.5, 34.3, 32.0, 31.6, 28.7, 27.3, 27.0, 22.0, 15.9; IR (film) 3398, 2923, 1454, 1364, 1329, 1216, 1067 cm^{-1}; $[\alpha]^{22}_D$ = – 25 (*c* 1.0, CH_2Cl_2), MS (ESI) for $C_{42}H_{60}O_9$ [M + Na] calc 731.4, found 731.4.

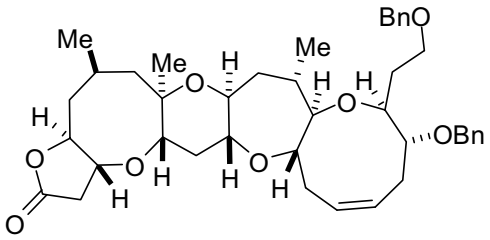
BCDE fragment **285**



Both ketals obtained in the previous step underwent reduction to the corresponding bis-diol **285** (i.e. ketal **283** was reduced with concomitant loss of the PMB group). Representative procedure: To a solution of the mixed methyl ketal **283** (0.039 g, 0.0055 mmole) and 0.5 mL

CH_2Cl_2 at 0 ºC under an argon atmosphere was added dimethyphenylsilane (0.100 mL). Redistilled $BF_3{\cdot}OEt_2$ (0.020 mL) was added dropwise to the reaction mixture and the solution was allowed to stir at 0 ºC for 15 min, followed by the addition of aqueous $NaHCO_3$. The solution was diluted with CH_2Cl_2 and the organic layer was separated. The aqueous layer was extracted twice with CH_2Cl_2 and the combined extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography gave 0.029 g (78%) of the desired tetracycle **285** as a single diastereomer. ^{1}H NMR (500 MHz, C_6D_6) δ 7.28-7.25 (band, 4H), 7.18-7.14 (band, 4H), 7.10-7.06 (band, 2H), 5.96 (ddd, *J* = 10.0, 10.0, 10.0 Hz, 1H), 5.81 (ddd, *J* = 10.0, 10.0, 10.0 Hz, 1H), 4.42 (d, *J* = 12.0 Hz, 1H), 4.30 (AB, *J* = 12.0 Hz, $\Delta\nu_{AB}$ = 14.7 Hz, 2H), 4.19 (d, *J* = 12.0 Hz, 1H), 3.79-3.71 (band, 4H), 3.60 (dd, *J* = 2.5, 9.0 Hz, 1H), 3.56-3.46 (band, 5H), 3.38-3.36 (band, 2H), 2.96-2.92 (band, 2H), 2.57 (dd, *J* = 12.0, 12.0 Hz, 1H), 2.46 (ddd, *J* = 5.5, 5.5, 12.5 Hz, 1H), 2.37-2.32 (band, 2H), 2.22-2.11 (band, 3H), 1.96-1.86 (band, 4H), 1.78-1.65 (band, 6H), 1.22 (s, 3H), 1.19 (d, *J* = 7.5 Hz, 3H), 0.98 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.20, 139.17, 128.9, 128.52, 128.51, 127.8, 127.6, 89.1, 84.9, 83.0, 82.9, 82.6, 80.6, 75.9, 75.8, 73.1, 71.3, 69.7, 66.9, 59.5, 55.3, 48.4, 37.7, 36.3, 35.73, 35.66, 35.1, 34.2, 28.7, 27.3, 21.7, 16.7; IR (film) 3397, 2924, 1454, 1366, 1069 cm^{-1}; $[\alpha]^{23}_D$ = – 40 (*c* 1.6, CH_2Cl_2), MS (ESI) for $C_{41}H_{58}O_8$ [M + Na] calc 701.4, found 701.3.

ABCDE lactone **286**



To a solution of the diol **285** (0.010 g, 0.015 mmole) in 1.5 mL CH_2Cl_2 at 0 ºC under an argon atmosphere was added 4-methylmorpholine *N*-oxide (0.020 g). A catalytic amount of

tetrapropylammonium perruthenate (TPAP) was added to the reaction mixture and the solution was allowed to stir at 0 ºC for 2 h. The solvents were evaporated and the crude residue was purified by flash chromatography to give 0.0063 g (63%) of the desired lactone **286**. ^{1}H NMR (500 MHz, C_6D_6) δ 7.29-7.26 (band, 4H), 7.18-7.13 (band, 4H), 7.11-7.05 (band, 2H), 5.94 (ddd, *J* = 6.5, 10.5, 10.5 Hz, 1H), 5.81 (ddd, *J* = 7.0, 10.0, 10.0 Hz, 1H), 4.42 (d, *J* = 12 Hz, 1H), 4.31 (AB, *J* = 12.0 Hz, Δv_{AB} = 19.6 Hz, 2H), 4.19 (d, *J* = 12.0 Hz, 1H), 3.81 (ddd, *J* = 5.5, 5.5, 5.5 Hz, 1H), 3.69 (dddd, *J* = 4.5, 4.5, 4.5, 8.5 Hz, 1H), 3.62 (dd, *J* = 3.0, 8.5 Hz, 1H), 3.56 (m, 1H), 3.51-3.42 (band, 4H), 3.09 (ddd, *J* = 8.0, 8.0, 10.0 Hz, 1H), 2.97-2.87 (band, 2H), 2.75 (dd, *J* = 4.5, 11.5 Hz, 1H), 2.57 (dd, *J* = 12.5, 12.5 Hz, 1H), 2.44-2.32 (band, 2H), 2.38 (dd, *J* = 8.0, 17.0 Hz, 1H), 2.25-2.20 (band, 1H), 2.20 (dd, *J* = 10.5, 17.0 Hz, 1H), 2.10 (ddd, *J* = 3.5, 11.0, 14.0 Hz, 1H), 1.97-1.87 (band, 3H), 1.82-1.77 (band, 2H), 1.74 (ddd, *J* = 2.5, 5.0, 14.5 Hz, 1H), 1.66 (ddd, *J* = 11.5, 11.5, 11.5 11.5 Hz, 1H), 1.40-1.35 (m, 1H), 1.27 (dd, *J* = 10.0, 15.0 Hz, 1H) 1.19 (d, *J* = 7.5 Hz, 3H), 0.93 (s, 3H), 0.75 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 171.3, 139.21, 139.15, 128.9, 128.54, 128.51, 127.7, 127.65, 127.63, 127.4, 88.6, 86.9, 84.6, 84.1, 83.3, 83.1, 82.9, 80.4, 76.7, 73.1, 71.4, 69.6, 66.9, 52.8, 43.2, 37.5, 36.5, 36.1, 35.7, 35.1, 34.0, 27.6, 27.5, 27.0, 21.7, 15.0; IR (film) 2925, 1788, 1455, 1375, 1321, 1260, 1207, 1107 cm^{-1}; $[\alpha]^{26}_{D}$ = – 58 (*c* 0.33, CH_2Cl_2), MS (ESI) for $C_{41}H_{54}O_8$ [M + H] calc 675.4, found 675.3.

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