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

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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 $\alpha$-allyloxy glycolylimides and aliphatic, unbranched aldehydes. Other suitably protected imides and $\alpha,\beta$-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.
ACKNOWLEDGEMENTS

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</tr>
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<td>HWE</td>
<td>Horner-Wadsworth-Emmons</td>
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</tr>
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<tr>
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<td>tetrapropylammonium peruthenate</td>
</tr>
<tr>
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</tr>
<tr>
<td>Ts</td>
<td>p-toluenesulfonyle</td>
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1.1 BACKGROUND

1.1.1. The aldol addition

The aldol addition reaction in its simplest form represents the union of the $\alpha$-carbon of a carbonyl group (1) with an aldehyde to generate $\beta$-hydroxy carbonyl products (3) (Scheme 1.1.1).\textsuperscript{1,2} The reaction itself is generally considered to be a two-stage process proceeding via base promoted deprotonation of the $\alpha$-C-H to generate the intermediate enol, enolate (2), or enolate equivalent (e.g. silyl enol ether, silyl ketene acetal). Subsequent attack of the nucleophilic $\alpha$-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,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 \(R^2\) (\(\upsilon\)-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 \(\text{syn}\) 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 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. 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. 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.

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,\textsuperscript{13,14} chiral catalysts\textsuperscript{15} or chiral auxiliaries.\textsuperscript{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").\textsuperscript{18} More importantly, since diastereomeric products are

\begin{center}
\textbf{Scheme 1.1.4. Chiral auxiliary mediated aldol additions}
\end{center}
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](image-url)
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.\(^\text{19}\) 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).\(^\text{20}\) 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 affording the syn glycolate aldol adducts with high diastereoselectivity.\(^\text{21}\) For example, formation of the titanium enolate of glycolate 23 using titanium tetrachloride and triethylamine followed by addition of the α-benzylxy aldehyde delivered the desired 1,2-syn

![Scheme 1.1.5](image-url)

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

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 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
elements for diastereoccontrol in aldol reactions. While this class of auxiliaries is more
commonly know for their ability to induce diastereoccontrol in propionate aldol additions, alkylating reactions and Diels-Alder additions, 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 glycolyl imides and aldehydes.

Like the propionate analogs, 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).

\[
\begin{eqnarray*}
\begin{align*}
&\text{Oxazolidinone glycolate aldol in the total synthesis of X-206 (Evans)}
\end{align*}
\end{eqnarray*}
\]

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 diastereoccontrol in propionate, acetate, 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 ($\text{Bu}_2\text{BOTf}$),
titanium tetrachloride is very inexpensive costing roughly 1/12th the price.\textsuperscript{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,\textsuperscript{26} \textit{N}-glycolyloxazolidinones can also be subjected to similar enolization conditions employing titanium tetrachloride and utilized in asymmetric \textit{syn} selective glycolate aldol additions. While (–)-sparteine is often employed as the base in these types of additions,\textsuperscript{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.\textsuperscript{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 \textit{i}-Pr\textsubscript{2}NEt and \textit{N}-methylpyrrolidinone (NMP) as an alternative amine base improved the yield to 72%.

![Scheme 1.1.9. Improved procedure for \textit{syn} glycolate aldol additions (Crimmins)](image)

Oxazolidinethione (16; Figure 1.1.1) mediated \textit{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).\textsuperscript{29} Upon switching to the oxazolidinethione auxiliary, the \textit{syn} adduct was provided with higher diastereoselectivity (95:5), though somewhat lower in yield.
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 1.1.10. Oxazolidinone vs. oxazolidinethione syn glycolate aldol additions (Crimmins)

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 \(\alpha\)-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.
A similar approach was reported by Ley and coworkers utilizing butane-2,3-diacetals of glycolic acid (43, Scheme 1.1.13). 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).

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). 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 (TiCl₄), 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.

![Scheme 1.1.14. Anti-glycolate addition of selone imides (Silks)](image)

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). 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, 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
appeared using $\alpha$-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). 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 $\alpha$-chiral aldehydes (Carter)](image)

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). These observations are similar to those reported by Silks, 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 through external activation of the aldehyde.

\[
\begin{align*}
\text{Scheme 1.1.17. } & \text{Anti propionate aldol additions (Heathcock)} \\
\text{A similar propionate aldol-type addition has more recently been described by Urpi using} & \\
\text{acetals as the enolate acceptor (Scheme 1.1.18). Exposure of the titanium enolates of } N- & \\
\text{propionylthiazolidinethione 56 to either a dimethyl or dibenzyl acetal in the presence of} & \\
\text{additional Lewis acid selectively generated the } \beta\text{-alkoxy derivatives (57) in good yields.} & \\
\text{Again, an open transition state (58) was postulated to explain the observed} & \\
\text{diastereoselectivity.} & \\
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 1.1.18. } & \text{Anti selective additions to acetals (Urpi)} \\
\text{Recent progress has been made by Evans to yield the anti diastereomers of propionate} & \\
\text{aldol additions using oxazolidinone, oxazolidinethione, and thiazolidinethione chiral} & \\
\text{auxiliaries. For example, formation of the magnesium enolate of propionate 59 using} & \\
\text{catalytic amounts of magnesium bromide diethyletherate led to the anti adducts (60) with} & \\
\text{excellent diastereoselection (Scheme 1.1.19). In contrast to the above examples, the} & \\
\text{reaction has been proposed to proceed via a closed boat-like transition state (61). The} & \\
\text{products are generally formed with high anti diastereoselectivity and in good yield. The} & \\
\end{align*}
\]
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. Efforts in this area have included the use of (−)-sparteine as a base to improve both the diastereoselectivity of the reaction and reaction yields. In addition, propionate aldol additions using oxazolidinethione and thiazolidinethione auxiliaries have yielded interesting results in terms of diastereoecontrol. 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. 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). Cyclization to the thiazolidinethione 63 readily occurred upon treatment of the amino alcohol 62 with carbon disulfide at elevated temperature. 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 thioimide 64
accomplished using \( N, N'-\text{dicyclohexylcarbodiimide (DCC)} \) 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 (\( \text{CH}_2\text{Cl}_2 \)) held at \(-78 \, ^\circ\text{C} \) 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 \textit{anti} products from the titanium enolates was based on the notion that activation of the aldehyde by an additional equivalent of Lewis acid may reverse the preference for \textit{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 \( \text{CaSO}_4 \) immediately prior to use) dissolved in \( \text{CH}_2\text{Cl}_2 \) was cooled to \(-78 \, ^\circ\text{C} \). An additional 2 equivalents of \( \text{TiCl}_4 \) was added to the aldehyde.

\[ \text{N} - \text{MeOAcThiazolidinethione} \]

\begin{equation}
\begin{array}{c}
\text{SN} \\
\text{S} \\
\text{Bn} \\
\text{O} \\
\text{OMe} \\
\text{TiCl}_4, \text{(-)-sparteine} \\
\text{CH}_2\text{Cl}_2, -78 \, ^\circ\text{C}
\end{array}
\end{equation}

\[ \text{via} \]

\begin{equation}
\begin{array}{c}
\text{SN} \\
\text{S} \\
\text{Bn} \\
\text{O} \\
\text{OMe} \\
\text{(=-)-sparteine, 65}
\end{array}
\end{equation}

\[ \min 67 \]

\textbf{Scheme 1.2.2.} Formation of the titanium enolates of \textit{N}-methoxyacetothiazolidinethione
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 this stage of the project, the relative configuration of the $\alpha$- and $\beta$-stereocenters were readily determined using the well known relationship between vicinal bond angle and coupling constants of the $\alpha$- and $\beta$-protons (Karplus relationship). As illustrated in Figure 1.2.1, hydrogen bonding of the $\beta$-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
through alteration of the reaction conditions were unsuccessful.

Oxazolidinone glycolylimide 69 was subsequently prepared according to literature procedures 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.

\[
\begin{array}{c}
\text{ON} \\
\text{O} \\
\text{Bn} \\
\text{OMe} \\
\text{Me} \\
\text{OH} \\
\text{OMe} \\
\end{array}
\xrightarrow{\text{TiCl}_4, (-)-\text{sparteine}; \text{acetaldehyde} + \text{TiCl}_4, \text{CH}_2\text{Cl}_2, -78\,^\circ\text{C}}
\begin{array}{c}
\text{ON} \\
\text{O} \\
\text{Bn} \\
\text{OMe} \\
\text{Me} \\
\text{OH} \\
\text{OMe} \\
\end{array}
+ \begin{array}{c}
\text{ON} \\
\text{O} \\
\text{Bn} \\
\text{OMe} \\
\text{Me} \\
\text{OH} \\
\text{OMe} \\
\end{array}
\sim 1:1
\]

**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.

\[
\begin{array}{c}
\text{HO} \\
\text{NH}_2 \\
\text{Bn} \\
\end{array}
\xrightarrow{\text{Et}_3\text{N}, \text{CH}_2\text{Cl}_2, 80\%}
\begin{array}{c}
\text{Cl} \\
\text{S} \\
\end{array}
\xrightarrow{\text{Cl-S}}
\begin{array}{c}
\text{S} \\
\text{Cl} \\
\end{array}
\xrightarrow{\text{Cl-COOMe}}
\begin{array}{c}
\text{O} \\
\text{S} \\
\text{N} \\
\text{Bn} \\
\end{array}
\]

**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
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).

\[
\begin{align*}
\text{L.A.} &\rightarrow \text{MeCHO} \\
\text{L.A.} = \text{lewis acid}
\end{align*}
\]

**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. Modifications to the stoichiometry of the TiCl4 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 dichlorodisopropoxide, trimethylsilyl trifluoromethanesulfonate (TMSOTf), and boron trifluoride-diethyl etherate (BF3·OEt2). All alternate Lewis acids provided the anti adducts with inferior selectivities when compared to TiCl4.

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 TiCl4 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 TiCl4 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-

<table>
<thead>
<tr>
<th>Aldehyde (R')</th>
<th>TiCl4:aldehyde (equiv)</th>
<th>Selectivity anti:all others</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂C-CHO</td>
<td>2.2 : 1.0</td>
<td>91:9</td>
</tr>
<tr>
<td></td>
<td>1.5 : 1.0</td>
<td>83:17</td>
</tr>
<tr>
<td>CHO</td>
<td>3.1 : 1.0</td>
<td>95:5</td>
</tr>
<tr>
<td></td>
<td>2.3 : 1.0</td>
<td>84:16</td>
</tr>
</tbody>
</table>

Table 1.2.1. Variation of additional TiCl4 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$_2$Cl$_2$) was premixed with the additional TiCl$_4$ in a separate flask held at -78 °C 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](image)

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

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Selectivity</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>methoxy glycolate (73)</td>
<td>86:14</td>
<td>62%</td>
</tr>
<tr>
<td>benzylxy glycolate (76)</td>
<td>70:30</td>
<td>55%</td>
</tr>
<tr>
<td>allyloxy glycolate (77)</td>
<td>97:3</td>
<td>84%</td>
</tr>
</tbody>
</table>

*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\textsuperscript{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 $\alpha$-alkoxy group for obtaining anti selectivity under these conditions.

![Scheme 1.2.7. Attempted anti propionate aldol addition](image)

1.2.7 Examination of reaction scope: Aldehyde versatility

A variety of aliphatic, aromatic, and $\alpha,\beta$-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 isobutyaldehyde gave lower selectivity (entry 3). With the exception of acrolein, $\alpha,\beta$-unsaturated and aromatic aldehydes also gave lower selectivities, though still favoring one major anti diastereomer (entries 4-6, 8, 10).
1.2.8 Characterization of aldol adducts

One complication frequently encountered with the \textit{anti} glycolate aldol additions, especially concerning the adducts of the O-allyl glycolylimide 77, was the inability to separate the major \textit{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\textsubscript{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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Aldehyde</th>
<th>Anti 1:Anti 2: syn</th>
<th>Yield (% isolated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>77</td>
<td>CHO</td>
<td>97:3:0</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>77</td>
<td>CHO</td>
<td>94:6:0</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>77</td>
<td>CHO</td>
<td>87:13:0</td>
<td>61</td>
</tr>
<tr>
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<td>77</td>
<td>CHO</td>
<td>95:5:0</td>
<td>58</td>
</tr>
<tr>
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<td>77</td>
<td>CHO</td>
<td>76:24:0</td>
<td>56</td>
</tr>
<tr>
<td>6</td>
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<tr>
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<td>73</td>
<td>CHO</td>
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</tr>
<tr>
<td>10</td>
<td>76</td>
<td>CHO</td>
<td>88:12:0</td>
<td>59</td>
</tr>
</tbody>
</table>

\textit{Table 1.2.3. Examination of various aldehyde components (yields of major diast.)}
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 $\alpha$-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](image)

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 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.
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 \( \alpha \)-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,\(^\text{10}\) Heathcock,\(^\text{41}\) and others. As illustrated in Figure 1.2.4, one equivalent of titanium may simultaneously coordinate to the enolate oxygen and the thiocarbonyl, while the second equivalent coordinates to the aldehyde and the \( \alpha \)-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.
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). 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. 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. A titanium bridge between the glycolyl ether and enolate oxygen atoms with the third

Figure 1.2.4. Proposed open transition state model

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 \textit{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 \((-\rangle\text{-sparteine followed by the addition of an additional titanium tetrachloride component immediately prior to the aldehyde leads to the formation of predominantly one \textit{anti} diastereomer in high selectivity and good reaction yields. Best results were obtained using \(O\text{-allyl, } N\text{-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.}

32
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 \textit{trans}-fused cyclic ethers of varying ring sizes.\textsuperscript{54} Since that time, many naturally occurring compounds sharing a similar structural array have been identified.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{58} protoceratin II is currently being investigated as an anticancer agent,\textsuperscript{59} and the recently discovered brevenal acts to inhibit the toxicity of the brevetoxins.\textsuperscript{60,61}
Due to their unique and challenging molecular architecture, the polycyclic ethers have received considerable attention in the synthetic community. 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 brevetoxin A in the mid to late 90’s, most of this progress has come within the last five years. Since then, ciguatoxin CTX3C, brevetoxin B, gymnocin, hemibrevetoxin B, and gambierol 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. 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). Since that time, several related brevetoxins (including brevetoxin B) have been isolated from the same organism. Structure elucidation occupied several research groups following the isolation and was initially incorrectly reported as a 5/6/6/7/11/8/6/6/6 ring system. The correct structure of brevetoxin A, which contains the 5/8/6/7/9/8/6/6/6 ring system, was finally secured by Shimizu in 1986 using X-ray crystallography. Pawlak and coworkers reached the same conclusion the following year using extensive NMR analysis.

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 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.\textsuperscript{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.\textsuperscript{79}

### 2.1.3 Brevetoxin A: Biological activity

The dinoflagellate now known as \textit{Karenia breve} (originally termed \textit{Gymnodinium breve} by Davis\textsuperscript{80} and later \textit{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.\textsuperscript{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\textsubscript{50} of 3-4 ng/mL.\textsuperscript{82} All natural and non-natural derivatives have demonstrated reduced toxicity.\textsuperscript{75}

The toxicology associated with the brevetoxins is complex and involves multiple receptors in the neuronal, pulmonary, and enzymatic regulatory systems.\textsuperscript{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).\textsuperscript{83} Binding to these membrane-associated potential-gated ion channels results in an influx of sodium ions.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{79} Indeed, it has been found experimentally that the lactone moiety is crucial for effective binding,\textsuperscript{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.\textsuperscript{82}

2.1.4 Proposed biosynthesis of Brevetoxin A

A truly remarkable biosynthetic pathway has been proposed for the formation of the ladder toxins.\textsuperscript{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 B64 and, shortly thereafter, brevetoxin A63,88-91 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
brevetoxin B via Wittig coupling and subsequent hydroxydithioketal cyclization. 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.

The stereoselective synthesis of medium ring ethers represents a considerable challenge in organic synthesis based on unfavorable entropic factors. 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. For the GHIJ fragment 94, a
hydroxydithioketal cyclization reaction would be utilized to form the eight membered G ring unit from the tricycle.

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 (available from D-glucose) to ultimately generate the tetrahydropyran fragment (C ring) in seven synthetic steps (Scheme 2.1.3). Further manipulation of the side chains was then required to install the requisite carbon framework to yield the dicarboxylic acid. The medium ring lactones (B and D rings) were subsequently generated upon double lactonization employing Yamaguchi’s conditions to give the bis-lactone. Stereoselective formation of the two exocyclic methyl groups was accomplished by first dehydrating the β-siloxy lactone to the cyclic enone, followed by a stepwise stereoselective double hydrogenation of the two olefins to give intermediate.

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

Elaboration of the bis-lactone to the BCD cyclic ether unit utilized a novel palladium-catalyzed transformation of the corresponding cyclic ketene acetal phosphates. Treatment
of lactone 103 with KHMDS and \((\text{PhO})_2\text{P(O)Cl}\) 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 \(\gamma,\delta\)-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)](image)

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).\(^9\) 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 ethers94 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.
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). 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 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

Scheme 2.1.8. Formation of the BCDE ring phosphine oxide
to the sulfone enabled reduction via the intermediate oxocarbenium ion using $\text{BF}_3\cdot\text{OEt}_2$ and $\text{Et}_3\text{SiH}$. 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, partial, and total syntheses 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. 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. Through the use of either Grubbs first or second 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. 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), 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.

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 addition103 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
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 \( \text{(90)} \) 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 \( \text{(132)} \) and GHIJ \( \text{(133)} \) 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
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](image)
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, 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 based on the Kulinkovich hydroxycyclopropanation reaction 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](image-url)
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 \(N\)-glycolyloxadazolidinones 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

\[
\text{PMBO} \quad \text{TIPSO} \quad \text{Me} \quad \text{O}\quad \text{OBn} \\
\text{HO} \\
151
\]

1. \((\text{COCl})_2, \text{DMSO, Et}_3\text{N}\)  
2. vinyl MgBr, THF, 0 °C  
76%, 3:1

\[
\text{PMBO} \quad \text{TIPSO} \quad \text{Me} \quad \text{O}\quad \text{OBn} \\
\text{Y} \quad \text{X} \\
152; X = \text{OH}, Y = \text{H}  
153; X = \text{H}, Y = \text{OH}
\]

catalyst 122  
\[(\text{CH}_2\text{Cl}_2) \quad 60 \text{ °C} \quad 75\%
\]

\[
\text{PMBO} \quad \text{TIPSO} \quad \text{Me} \quad \text{OH} \\
\text{BnO} \\
154
\]

+ \[
\text{PMBO} \quad \text{TIPSO} \quad \text{Me} \quad \text{OH} \\
\text{BnO} \\
155
\]

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 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 difficulty associated with a stereoselective reduction of a tri-substituted olefin in a ring system similar to oxocenes 154 and 155. 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).
reduction of 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), 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 2.2.7. 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.
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 \(\pi\)-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

<table>
<thead>
<tr>
<th>temperature</th>
<th>reaction time</th>
<th>d.r.</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 °C</td>
<td>10 min</td>
<td>3:1</td>
<td>95%</td>
</tr>
<tr>
<td>0 °C</td>
<td>30 min</td>
<td>8:1</td>
<td>N.D.</td>
</tr>
<tr>
<td>-50 °C</td>
<td>2 h</td>
<td>&gt;20:1</td>
<td>93%</td>
</tr>
</tbody>
</table>

*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 °C, where the reaction proceeded to give the desired product \textbf{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\textsuperscript{111} to give the ketone \textbf{139} in good yield (Scheme 2.2.9). A highly selective methyl Grignard addition to the ketone was observed to provide the tertiary alcohol \textbf{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 \textbf{138} in 98% yield.

\begin{scheme}
\centering
\includegraphics[width=0.8\textwidth]{scheme2_2_9}

\textbf{Scheme 2.2.9.} Completion of the B ring fragment
\end{scheme}
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.\textsuperscript{109} Beginning with the $\alpha$-benzyloxy glycolylimide \textbf{164}, an asymmetric alkylation\textsuperscript{100} with allyl iodide was performed to give the chiral aldehyde \textbf{165}, following reductive removal of the auxiliary (Scheme 2.2.10). Swern oxidation\textsuperscript{108} and subsequent \textit{syn} propionate aldol addition using the \textit{N}-propionyloxazolidinethione \textbf{166} gave the chiral diol \textbf{167} following reductive auxiliary removal. Protection of the primary alcohol as the silyl ether and alkylation using sodium bromoacetate

\begin{equation}
\text{O} \quad \text{O}
\begin{array}{c}
\text{OBn} \\
\text{164} \\
\text{1. NaHMDS,} \\
\text{2. NaBH}_4 \\
\text{3. (COCl)}_2, \text{Et}_3\text{N, DMSO, 78\%}
\end{array}
\end{equation}

\begin{equation}
\text{O} \quad \text{O}
\begin{array}{c}
\text{OBn} \\
\text{165} \\
\text{1. TiCl}_4, (-)-\text{sparteine} \\
\text{2. LiBH}_4, \text{MeOH} \\
\text{84\%}
\end{array}
\end{equation}

\begin{equation}
\text{O} \quad \text{O}
\begin{array}{c}
\text{OBn} \\
\text{166} \\
\text{1. i-Pr}_3\text{SiCl, imidazole} \\
\text{2. NaH, BrCH}_2\text{CO}_2\text{H} \\
\text{78\%}
\end{array}
\end{equation}

\begin{equation}
\text{O} \quad \text{O}
\begin{array}{c}
\text{TIPS} \\
\text{Me} \\
\text{168}
\end{array}
\end{equation}

\begin{equation}
\text{O} \quad \text{O}
\begin{array}{c}
\text{TIPS} \\
\text{Me} \\
\text{169}
\end{array}
\end{equation}

\begin{equation}
\text{O} \quad \text{O}
\begin{array}{c}
\text{TIPS} \\
\text{Me} \\
\text{149}
\end{array}
\end{equation}

\begin{equation}
\text{O} \quad \text{O}
\begin{array}{c}
\text{Me} \\
\text{167}
\end{array}
\end{equation}

\textbf{Scheme 2.2.10.} Previous synthesis of the E ring glycolate (Emmitte)

gave the carboxylic acid \textbf{168}. Formation of the glycolate \textbf{169} proceeded smoothly via the mixed pivaloyl anhydride.

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

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\textsuperscript{103} using 3-butenal\textsuperscript{86}
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.

\[ X_c = \text{chiral auxiliary} \]

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

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, 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. 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.

Sasaki's \( \beta \)-alkyl Suzuki coupling approach

The \( \beta \)-alkyl Suzuki-reductive etherification approach developed by Sasaki and coworkers is one of the more effective convergent coupling strategies developed to date.\textsuperscript{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\textsuperscript{121} or phosphate\textsuperscript{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),\textsuperscript{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 3.1.2).

Scheme 3.1.2. Coupling strategies based on intermediate enol ether
Regioselective hydroboration/oxidation of the endocyclic enol ether then installed the oxygen functionality necessary to close the remaining cyclic ether. Protecting group 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 Ph₃SnH⁹⁴ 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 synthesis of gymnocin A (89).

Scheme 3.1.3. Sasaki’s total synthesis of gymnocin A
syntheses of several polycyclic ether molecules, including gambierol,\textsuperscript{69} and advanced intermediates of ciguatoxin.\textsuperscript{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.\textsuperscript{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](image)

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.\textsuperscript{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\textsuperscript{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-
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

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

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
Cp₂Ti[P(OEt)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 LiBHEt₃ (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 reagent¹¹¹ 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

1. Dess-Martin
2. TfOH, (MeO)₂CH
3. BF₃·OEt₂, Et₃SiH

52-67%
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$_2$AlH 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](image-url)
protecting groups gave the keto-alcohol 206 that was ultimately carried forward to the natural product using a mixed thio-ketal cyclization protocol (see Scheme 3.1.3).

3.1.1.4. Esterification/Sml$_2$ 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 Sml$_2$ 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 strategy](image-url)
(208).\textsuperscript{130} HWE reactions have been extensively demonstrated in complex systems leading to coupled products with high efficiency under very mild conditions.\textsuperscript{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\textsuperscript{134} was highly attractive to this sequence and ensured high substrate versatility. Furthermore, cyclodehydrations of $\delta$-hydroxy ketones were well known and could likewise occur under a variety of reaction conditions.\textsuperscript{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.

\textbf{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,\textsuperscript{108} TPAP/NMO,\textsuperscript{138} and CrO$_3$-pyridine.\textsuperscript{139} Ultimately, the use of the hypervalent iodide oxidant, Dess-Martin periodinane (213),\textsuperscript{111} gave the aldehyde 214 in the best yield (80-88\%) with minimal decomposition (Scheme 3.2.2).
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
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 Ibarra140 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](image-url)
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\textsuperscript{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.\textsuperscript{142} In particular, the hexameric triphenylphosphine copper hydride cluster ([PPh\textsubscript{3}CuH\textsubscript{6}]) commonly known as Stryker’s reagent\textsuperscript{143} has been effectively used as a mild reductant for $\alpha,\beta$-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 \textbf{219} in excellent yield (Scheme 3.2.4). No evidence of 1,2-reduction was observed. An alternative reduction protocol developed by Lipshutz\textsuperscript{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 \textbf{219} was highly acid sensitive and readily cyclized to the desired cyclic enol ether upon treatment with a mild acid source (CDCl\textsubscript{3}, PPTS, $p$-TsOH). In practice, subjection of the ketone to a catalytic amount of PPTS in CH\textsubscript{2}Cl\textsubscript{2} at 40 °C for 30 minutes (heating was required to drive the reaction to completion) the endocyclic enol ether \textbf{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 \textbf{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$_3$)$_3$RhCl$^{145}$) 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
transient epoxy enol ethers.\textsuperscript{112,128,148,149} Regioselective opening of the epoxide with a nucleophile (i.e. Me\textsuperscript{−}, H\textsuperscript{−}) then generates the desired alcohol (see example in Scheme 3.1.6).

The addition of DMDO to enol ether 220 at \( -78 \, ^\circ\text{C} \) 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.\textsuperscript{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\textsubscript{2}O or acetone present in the DMDO solutions). However, it was
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$_2$Cl$_2$) 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$_2$AlH)$^{71}$ 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 \( i-\text{Bu}_2\text{AlH} \) (>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)\textsuperscript{111} gave the two ketones 227 and 228 that were epimeric at the \(\alpha\)-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).\textsuperscript{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 \(\text{K}_2\text{CO}_3/\text{MeOH}\), 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\textsuperscript{155} and have been attempted in complex polyether synthesis.\textsuperscript{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](image)

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\(_2\)Cl\(_2\)\(^\text{156}\) 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](image)
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. 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, 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.
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$_3$SiH to give the completed BCDE ring fragment 233 as a single diastereomer in good yield.

![Chemical structures](image)

**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. 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. 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, 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\textsuperscript{103} to set four stereogenic centers and rapidly construct the B and E ring fragments.\textsuperscript{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

\[ R = \text{protecting group} \]

\[ R^1 = \text{TIPS} \]

\[ R^2 = \text{H} \]

\[ \text{anti aldol addition} \]

\[ 1\text{C homologation} \]

\[ 1\text{C homologation} \]

\[ \text{Figure 4.1.1. One carbon deficiency in the BCDE fragment} \]
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). 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.

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. 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 Emmitt.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 alkylation reaction would be utilized to generate compound 246 following the reductive auxiliary removal from alkylation adduct 247.
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 of the PMB glycolylimide 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 that was oxidized to the aldehyde under Swern conditions. 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. In addition to high, reproducible, yields and selectivities, the preparation of the propionate is considerably more facile. In the event, aldol addition with the prepared aldehyde 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,
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\textsuperscript{108} to provide the aldehyde in preparation for the asymmetric allylation reaction. Initially, the asymmetric allylation protocol developed by Brown\textsuperscript{117} using diisopinocampheylborane as the chiral element was examined. While these conditions were highly successful in the previous E ring synthesis (Emmitte),\textsuperscript{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\textsuperscript{163} were also examined. However, no significant amount of product was obtained after prolonged reaction times.

The presence of the $\alpha$-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$_3$·OEt$_2$ in the presence of allyltributytin also 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 °C. 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

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Selectivity</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>B(_ipc)$_2$</td>
<td>&gt;98:2</td>
<td>30%</td>
</tr>
<tr>
<td>MgBr</td>
<td>1:1</td>
<td>N.D.</td>
</tr>
<tr>
<td>SnBu$_3$, BF$_3$·OEt$_2$</td>
<td>4:1</td>
<td>50% + PMB dep.</td>
</tr>
<tr>
<td>SiMe$_3$, AlMe$_3$</td>
<td>---</td>
<td>no reaction</td>
</tr>
<tr>
<td>SnBu$_3$, AlMe$_3$</td>
<td>7:1</td>
<td>80%</td>
</tr>
</tbody>
</table>

*Table 4.2.1. Stereoselective allylation of the E fragment aldehyde*
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.

![Diagram showing separation process](image)

**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 $\gamma$-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.

![Chemical structure](image_url)

**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.
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](image)

**Figure 4.2.1.** Protecting group strategy for revised synthesis
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 aldehyde164 followed by subsequent oxidation to the acid 270 using sodium chlorite165 was utilized. Yields for this two step process, however, were moderate (average of 70%) and a more efficient process was desired.

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-butyllithium166 and the subsequent trapping with a one carbon electrophile, such as CO₂167 or CICO₂Me,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 CO₂ led only to reduction products, most likely due to difficulties in removing water completely from the gas (obtained from the sublimation of CO₂(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.

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 than 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 catalyst98 (127) to give the completed E ring fragment 276 in quantitative yield.
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](image)

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$_3$)$_3$RhCl$^{169}$ in the presence of a trialkysilane is known to give excellent selectivity for the 1,4-reduction product.$^{170}$ The product of the reaction is typically a
Table 4.2.2. Cyclodehydration conditions

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>[PPh₃CuH]₆, Me₂PhSiH; PPTS</td>
<td>65%</td>
</tr>
<tr>
<td>[PPh₃CuH]₆ (0.8 equiv); PPTS</td>
<td>82%</td>
</tr>
<tr>
<td>(PPh₃)₃RhCl, Me₂PhSiH; PPTS, toluene, 50 ºC</td>
<td>92%</td>
</tr>
</tbody>
</table>

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 (PPh₃)₃RhCl and excess Me₂PhSiH in toluene at 50 ºC 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$_2$AlH 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$_2$AlH requirements. Indeed, NMR analysis of the DMDO solutions that were thought to contain minimal amounts of acetone (approximately equal to DMDO concentration)\textsuperscript{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\textsuperscript{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$_2$Cl$_2$ 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$_2$AlH (~ 5 equiv.). A variety of other extraction solvents were also examined, including toluene,
pentanes, and CCl₄, 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-Bu₂AlH 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)

\[
\text{1. DMDO in pentanes/CH}_{2}\text{Cl}_{2}, \quad \text{CH}_{2}\text{Cl}_{2}, -78 \, ^{\circ}\text{C}; \quad \text{i-Bu}_{2}\text{AlH}, -78 \, ^{\circ}\text{C},
\]

\[
\text{2. Dess-Martin periodinane}
\]

\[
67\%, -3:1
\]

\[
111
\]

\[
\text{12}
\]

\[
\text{278}
\]

\[
\text{279}
\]

\[
\text{280}
\]

\[
\text{Scheme 4.2.12. Oxidation of the BCE enol ether.}
\]

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\textsuperscript{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% Et₂O/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 experiments to be conducted to avoid the loss of precious late-stage material. Many bases were examined, including NaOMe, LiOMe, imidazole, and KOt-Bu under various reaction conditions (temperature, solvent, etc) which all gave similar decomposition patterns (TLC
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 (H₂SiF₆). 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, 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
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.

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) 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.
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.

**Scheme 4.2.16.** Formation of the ABCDE lactone

**Figure 4.2.2.** nOe analysis of the ABCDE lactone

### 4.3 PROPOSED COMPLETION OF BREVENTOXIN 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
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). 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\textsubscript{3}-OEt\textsubscript{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
periodinane as the oxidant. Finally, methylation 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 (\(^1\text{H}, \text{ }^13\text{C}\) NMR, COSY, NOESY) spectra were recorded on the following instruments: Bruker model DRX 300 (\(^1\text{H} \text{ at } 300 \text{ MHz}; \text{ } ^13\text{C} \text{ at } 75 \text{ MHz})$, Bruker model DRX 400 (\(^1\text{H} \text{ at } 400 \text{ MHz}; \text{ } ^13\text{C} \text{ at } 100 \text{ MHz})$, and Bruker model DRX 500 (\(^1\text{H} \text{ at } 500 \text{ MHz}; \text{ } ^13\text{C} \text{ at } 125 \text{ MHz})$. Deuterated Chloroform was set to 7.24 ppm for \(^1\text{H}\) NMR and 77.0 ppm for \(^13\text{C}\). 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\(_2\)O), tetrahydrofuran (THF), and dichloromethane (CH\(_2\)Cl\(_2\)) 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\(^\text{TM}\) 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 °C. 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 CH₂Cl₂ was cooled to 0° C. Oxalyl chloride (61.7 mL, 123 mmole; 2.0 M in CH₂Cl₂) 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 auxiliary26 (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 CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and concentrated. Purification of the residue by flash column chromatography afforded 20.3 g (93%) of the allyl glycolate 77. (Recrystallization from Et₂O/Hex could be performed for enhanced purity.) ¹H NMR (CDCl₃, 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); \(^1^3^C\) NMR (CDCl\(_3\), 100 MHz) \(\delta\) 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\(_2\)Cl\(_2\)) 3065, 2988, 2687, 2308, 1714, 1424, 1366, 1328, 1266, 1024 cm\(^{-1}\); \([\alpha]\)^{22}_D +107° (c = 0.90, CH\(_2\)Cl\(_2\)).

Benzyl glycolate 76

See above procedure: \(^1^H\) NMR (CDCl\(_3\), 400 MHz) \(\delta\) 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); \(^1^3^C\) NMR (CDCl\(_3\), 100 MHz) \(\delta\) 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\(_2\)Cl\(_2\)) 3056, 2989, 2688, 2308, 1713, 1422, 1355, 1322, 1198 cm\(^{-1}\); \([\alpha]\)^{22}_D +96.7° (c = 0.55, CH\(_2\)Cl\(_2\)).

Methyl glycolate 73

See above procedure: \(^1^H\) NMR (CDCl\(_3\), 400 MHz) \(\delta\) 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); \(^1^3^C\) NMR (CDCl\(_3\), 100 MHz) \(\delta\) 184.7, 170.9, 134.9, 129.3, 129.0, 127.5, 73.96, 71.42, 59.71, 59.45, 37.52; IR (CH\(_2\)Cl\(_2\)) 3056, 2993, 2935, 2308, 1715, 1368, 1329, 1198 cm\(^{-1}\); \([\alpha]\)^{22}_D +114° (c = 0.95, CH\(_2\)Cl\(_2\)).
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$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$, 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$_2$Cl$_2$ 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 Na₂SO₄, and concentrated. Purification of the residue by column chromatography afforded the diol. Yields ranged from 83-97%.

Diols:

\[
\begin{align*}
\text{HO} & \quad \text{O} \\
\text{OH} & \quad \text{Me}
\end{align*}
\]

\(^1\)H NMR (CDCl₃, 400 MHz) \(\delta\) 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, \(J = 6.8\) Hz, 3H); \(^{13}\)C NMR (CDCl₃, 100 MHz) \(\delta\) 134.6, 117.4, 82.20, 71.14, 67.97, 61.13, 18.91; IR (CH₂Cl₂) 3586, 3053, 2984, 2308, 1424, 1266, 1096 cm⁻¹; \([\alpha]^{22}_D +5.8^\circ\) (c = 0.36, CH₂Cl₂).

\[
\begin{align*}
\text{HO} & \quad \text{O} \\
\text{OH} & \quad \text{Me}
\end{align*}
\]

\(^1\)H NMR (CDCl₃, 400 MHz) \(\delta\) 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 (CDCl₃, 100 MHz) \(\delta\) 134.6, 117.4, 81.35, 71.49, 70.85, 61.00, 35.07, 19.09, 13.97; IR (CH₂Cl₂) 3586, 3049, 2961, 2876, 2308, 1424, 1085 cm⁻¹; \([\alpha]^{26}_D + 9.5^\circ\) (c = 1.2, CH₂Cl₂).
$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 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) $\delta$ 134.6, 117.4, 81.33, 71.78, 70.86, 61.00, 32.93, 31.77, 25.58, 22.53, 13.96; IR (CH$_2$Cl$_2$) 3590, 2934, 2864, 1467, 1378, 1081 cm$^{-1}$; $[\alpha]^2$D$^2$ +6.5° ($c = 1.7$, CH$_2$Cl$_2$).

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 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) $\delta$ 134.5, 117.5, 79.18, 76.32, 70.61, 60.89, 29.65, 19.09, 17.90; IR (CH$_2$Cl$_2$) 3594, 3049, 2964, 2876, 2308, 1606, 1471, 1081 cm$^{-1}$; $[\alpha]^2$D$^2$ −3.0° ($c = 0.26$, CH$_2$Cl$_2$).

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 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) $\delta$ 136.7, 134.5, 117.6, 116.4, 81.08, 72.76, 71.19, 61.36; IR
(CH₂Cl₂) 3690, 3601, 3053, 2988, 2887, 2687, 2308, 1606, 1424, 1266, 1108, 1042 cm⁻¹; [α]_{D}^{25} +16.1° (c = 0.60, CH₂Cl₂).

\[\begin{align*}
\text{H NMR (CDCl₃, 400 MHz)} & \delta 5.96-5.86 (m, 1H), 5.81-5.72 (m, 1H), 5.54-5.47 (m, 1H) \\
& 5.30-5.25 (m, 1H), 5.20-5.16 (m, 1H), 4.29-4.26 (m, 1H), 4.17-4.08 (m, 2H), 3.77-3.68 (m, 2H), 3.36 (dd, J = 4.8, 4.8 Hz, 1H), 2.38 (bs, 1H), 2.23 (bs, 1H), 1.71 (d, J = 4.0 Hz, 3H); ^{13}\text{C NMR (CDCl₃, 100 MHz)} \delta 134.6, 129.6, 128.7, 117.5, 81.41, 72.87, 71.27, 61.54, 17.80; \text{IR (CH₂Cl₂) 3598, 3057, 2988, 2687, 2308, 1424, 1266 cm⁻¹; [α]_{D}^{26} –1.6° (c = 0.50, CH₂Cl₂).}
\end{align*}\]

\[\begin{align*}
\text{H NMR (CDCl₃, 400 MHz)} & \delta 7.38-7.24 (m, 5H), 5.78 (ddt, J = 17.2, 10.4, 6.0 Hz, 1H) \\
& 5.24-5.11 (m, 2H), 4.89 (d, J = 5.2 Hz, 1H), 4.00-3.90 (m, 2H), 3.73-3.63 (m, 2H), 3.51-3.48 (m, 1H), 3.08 (bs, 1H), 2.43 (bs, 1H); ^{13}\text{C NMR (CDCl₃, 100 MHz)} \delta 140.8, 134.4, 128.3, 127.7, 126.2, 117.6, 82.16, 74.02, 71.24, 61.38, 51.36; \text{IR (CH₂Cl₂) 3598, 2930, 2887, 2370, 1621, 1455, 1390, 1096, 1058 cm⁻¹.}
\end{align*}\]

\[\begin{align*}
\text{H NMR (CDCl₃, 400 MHz)} & \delta 7.37-7.28 (m, 5H), 4.62 (s, 2H), 3.86-3.75 (m, 3H), 3.35 (dt J = 4.4, 4.0 Hz, 1H), 2.46-2.34 (m, 2H), 1.50-1.44 (m, 3H), 1.34-1.24 (m, 6H), 0.87 (t, J = 6.8
\end{align*}\]
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$_2$Cl$_2$) 3690, 3601, 3053, 2988, 2934, 2308, 1606, 1424, 1266 cm$^{-1}$; $\left[\alpha\right]_{D}^{26} +13.8^\circ$ (c = 0.85, CH$_2$Cl$_2$).

![Chemical Structure](image)

$^1$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$_2$Cl$_2$) 3682, 3601, 2930, 2880, 1606, 1355, 1208, 1096 cm$^{-1}$; $\left[\alpha\right]_{D}^{26} +14.1^\circ$ (c = 0.75, CH$_2$Cl$_2$).

α-Methoxy glycolyl imide (73) adducts:

![Chemical Structure](image)

$^1$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$_2$Cl$_2$) 3053, 2984, 2937, 2308, 1718, 1366, 1328, 1197 cm$^{-1}$; $\left[\alpha\right]_{D}^{27} +276^\circ$ (c = 0.70, CH$_2$Cl$_2$).
$^1$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$_2$Cl$_2$) 3049, 2988, 2934, 2308, 1710, 1424, 1370, 1189 cm$^{-1}$; $[\alpha]^{23}_D$ +222° ($c = 0.70$, CH$_2$Cl$_2$).

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 Et₂O were added and the entire mixture was filtered through celite. The organic layer was separated and the aqueous layer extracted twice with Et₂O. The combined organic extracts were dried over MgSO₄. 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 CH₂Cl₂ 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 Na₂S₂O₃. The organic layer was separated and the aqueous layer extracted with a minimal amount of CH₂Cl₂. The combined organic extracts were washed with brine and dried over Na₂SO₄. 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 CH₂Cl₂ at -78 ºC
under an argon atmosphere was added TiCl₄ (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 CH₂Cl₂ was added dropwise. The resulting purple solution was stirred for an additional 1 h. A second batch of TiCl₄ (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 NH₄Cl. The organic layer was separated and the aqueous layer was extracted twice with CH₂Cl₂. The combined organic extracts were dried over Na₂SO₄, 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). ¹H NMR purified sample (400 MHz, CDCl₃) 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 Et₂O and methanol (0.053 mL, 1.32 mmole). The solution was cooled to 0 °C 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 CH₂Cl₂. The combined organic extracts were dried over Na₂SO₄ 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. ¹H NMR (400 MHz, CDCl₃) 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, 5.6, 3.6 Hz), 3.75-3.68 (m, 2H), 3.21 (dd, 1H, J = 10.4, 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); ¹³C NMR (400 MHz, CDCl₃) 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; [α]²⁸ D = –3.7 (c 2.4, CH₂Cl₂).

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 NaHCO₃, the aqueous layer was extracted three times with Et₂O The combined organic layers were dried over MgSO₄ and
concentrated in vacuo. Purification by flash chromatography gave 6.48 g (95%) of the desired silyl ether. \(^1\) H NMR (400 MHz, CDCl3) \(\delta\) 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, \(J = 14.0, \sim 0\) 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, CDCl3) \(\delta\) 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**

![PMB ether structure](image)

Preparation of PMBBBr: 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\(_2\)O 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 °C. After stirring for 10 min, a solution of 40 mL DMF and PMBBBr (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 °C with saturated
NH₄Cl, followed by the addition of ~500 mL saturated NH₄Cl and 500 mL Et₂O. The organic layer was separated and the aqueous layer extracted twice with Et₂O. The combined organic extracts were washed with H₂O, then brine, and dried over MgSO₄. Purification by flash chromatography gave 13.4 g (86%) of desired product 148: \(^1\)H NMR (400 MHz, CDCl₃) 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, \(\Delta v_{AB} = 24.8\) Hz), 4.19 (ddt, 1H, \(J = 12.8, 5.6, 1.6\) Hz), 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, CDCl₃) 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; \([\alpha]_{D}^{24} = +4.0\) (c 1.25, CH₂Cl₂).

Alcohol 142

The allyl ether 148 (9.06 g, 19.6 mmole) and 200 mL Et₂O were cooled to 0 °C 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 Et₂O) over one hour. Immediately following the addition the reaction was quenched with ~ 100 mL H₂O. 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 NH₄Cl. The aqueous layer was extracted twice with EtOAc and the combined extracts were dried over MgSO₄. Purification by flash chromatography gave 7.13 g (86%) of the desired alcohol 142 as a colorless oil. \(^1\)H NMR (400 MHz, CDCl₃) 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, \(\Delta v_{AB} = 23.2\) Hz), 3.82-3.80 (m, 1H), 3.77 (s, 3H), 3.79-3.75
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 NH₄Cl. The organic layer was separated and the aqueous layer was extracted twice with EtOAc. The combined extracts were dried over Na₂SO₄ and concentrated under reduced pressure. Purification by flash chromatography gave 7.37 g (91%) of the desired acid as a colorless oil. ¹H NMR (500 MHz, CDCl₃) 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, JAB = 11.5 Hz, ΔνAB = 15.0 Hz), 4.19 (AB, 2H, JAB = 17.5 Hz, ΔνAB = 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); ¹³C NMR (100 MHz, CDCl₃) δ 172.4, 159.5, 141.8, 129.8,
Glycolate 150

![Chemical structure](https://example.com/structure.png)

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 °C 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 °C, maintained at that temperature for 1 h and recooled to -78 °C.

A separate flask containing 30 mL THF and (R)-4-isopropyl-2-oxazolidinone (1.42 g, 11.0 mmole) was cooled to -78 °C. n-BuLi (6.33 mL, 10.1 mmole; 1.60 M in hexanes) was added dropwise over 20 min and stirred for an 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 °C for 1 h. The reaction was quenched using saturated NaHCO₃. The organic layer was separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over MgSO₄. Purification by flash chromatography yielded 4.48 g (90%) of the desired glycolate 150. ¹H NMR (400 MHz, CDCl₃) δ 7.24-7.21 (m, 2H), 6.82-6.79 (m, 2H), 5.00 (AB, 2H, J_AB = 18.3 Hz, Δν_AB = 11.2 Hz), 4.83 (s, 2H), 4.57 (AB, 2H, J_AB = 11.0 Hz, Δν_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), 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; [α]₂⁶⁺ = +15 (c 1.18, CH₂Cl₂).
0.93 (d, 3H, J = 7.0 Hz), 0.85 (d, 3H, J = 7.0 Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 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\(^{-1}\); \([\alpha]\)\(^{26}\) = -38 (c 1.41, CH\(_2\)Cl\(_2\)).

Alkylation adduct

![Alkylation adduct](image)

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 iodos(trimethyl)silane (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\(_4\)Cl. 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\(_3\)) \(\delta\) 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); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \delta 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\textsuperscript{-1}; \left[\alpha\right]^{24}_D = +43 (c 1.2, CH\textsubscript{2}Cl\textsubscript{2}).

Alcohol 151

To a solution of the alkylation adduct (3.96 g, 5.56 mmole) obtained above in 50 mL Et\textsubscript{2}O was added anhydrous methanol (0.334 mL, 8.34 mmole). The contents were cooled to 0 °C 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 °C, the reaction was quenched with saturated Na\textsuperscript{+}/K\textsuperscript{+} 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\textsubscript{4} and concentrated under reduced pressure. Purification by flash chromatography gave 2.65 g (81%) of the desired product 151 as a colorless oil. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \delta 7.34-7.22 (m, 7H), 6.84-6.81 (m, 2H), 4.79 (bs, 2H), 4.49 (AB, 2H, J\textsubscript{AB} = 11.6 Hz, \Delta v\textsubscript{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); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \delta 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\textsuperscript{-1}; \left[\alpha\right]^{24}_D = -6.6 (c 0.51, CH\textsubscript{2}Cl\textsubscript{2}).
Aldehyde

To a solution of oxalyl chloride (2.36 mL, 4.71 mmole; 2M in CH₂Cl₂) and 20 mL CH₂Cl₂ under an argon atmosphere at −78 ºC was slowly added a solution of DMSO (0.669, 9.43 mmole) and 4 mL CH₂Cl₂, 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 CH₂Cl₂ 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 H₂O. The organic layer was separated and the aqueous layer was washed with 100 mL each of saturated NaHSO₄, NaHCO₃, H₂O, and brine. The organic layer was dried over Na₂SO₄ 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

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/I₂ 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 NH₄Cl 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 MgSO₄, 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

The diene fragment obtained in the previous step (0.278 g, 0.454 mmole) was dissolved in 227 mL of CH₂Cl₂ and degassed using an argon purge for 1 h. Grubbs’ second generation catalyst (Cl₂(PCy₃)(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). ¹H NMR major
compound 155 (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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; [α]D²⁴ = +123 (c 0.51, CH₂Cl₂).

¹H NMR minor compound 154 (400 MHz, CDCl₃) 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 reaction¹⁷⁵ 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 CH₂Cl₂. After cooling to –78 °C, 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 CH₂Cl₂. The combined extracts were dried over Na₂SO₄, and concentrated under reduced pressure. Purification by flash chromatography gave 0.64 g (50%) of oxocene 155.
To a solution containing the oxocene 155 (0.384 g, 0.657 mmole) and 44 mL CH₂Cl₂ was added Crabtree’s catalyst ([PCy₃][COD][Pyr]Ir⁺PF₆⁻; 0.53 g, 0.066 mmole). The reaction flask was fitted with a hydrogen filled balloon and cooled to –50 °C (prior to H₂ 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 H₂ atmosphere for 2 h at -50 °C. 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. ¹H NMR (400 MHz, CDCl₃) 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), 3.65-3.46 (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); ¹³C NMR (100 MHz, CDCl₃) 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; [α]²⁵ = +43 (c 0.73, CH₂Cl₂).
To a solution of the alcohol 162 (0.360 g, 0.613 mmole) and 6 mL CH₂Cl₂ 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 Na₂S₂O₃ and NaHCO₃ the organic layer was separated and the aqueous layer extracted twice with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. Purification by flash chromatography gave 0.319 g (89%) of the desired ketone 139. ¹H NMR (400 MHz, CDCl₃) 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), 3.74-3.64 (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); ¹³C NMR (100 MHz, CDCl₃) 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; [α]24D = -37 ° (c 1.85, CH₂Cl₂).

Tertiary alcohol 163

To a solution of MeMgCl (0.313 mL, 0.940 mmole; 3 M in THF) and 5 mL Et₂O at -78 °C under an argon atmosphere was added a solution of the ketone 139 (0.110 g, 0.188 mmole) and 5 mL Et₂O dropwise. The reaction mixture was quenched after 10 min with saturated NH₄Cl 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 Na₂SO₄ 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\(_3\)) \(\delta\) 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, \(\Delta\nu_{AB} = 14.8\) 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\(_3\)) \(\delta\) 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\(_2\)Cl\(_2\)).

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\(_2\)O 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\(_2\)SO\(_4\) 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\(_3\)) \(\delta\) 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); ¹³C NMR (100 MHz, CDCl₃) 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; [α]²³° = +44 (c 0.73, CH₂Cl₂).

Aldehyde 214

To a solution of the diol (0.01 g, 0.060 mmole) and 0.6 mL CH₂Cl₂ 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 Na₂S₂O₃/NaHCO₃. The organic layer was separated and the aqueous layer extracted twice with CH₂Cl₂, dried over Na₂SO₄, 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 CH2Cl2 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 NH4Cl. The organic layer was separated and the aqueous layer extracted twice with EtOAc. The combined organic layers were dried over Na2SO4 and concentrated in vacuo. Purification by flash chromatography gave 3.47 g (71%) of the glycolate 176. 1H NMR (400 MHz, CDCl3) 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, JAB = 12.4 Hz, ΔνAB = ~ 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); 13C NMR (100 MHz, CDCl3) 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; [α]²⁵° = +55.2 (c 1.53, CH₂Cl₂).

Anti adduct 177

Preparation of the aldehyde: A flask containing 1,7-octadiene-4,5-diol¹⁰² (0.770 g, 5.42 mmole) and 5 mL CH₂Cl₂ 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 Na₂S₂O₃ and separation of the organic layer, the aqueous portion was extracted with minimal CH₂Cl₂. The combined organic fractions were dried over Na₂SO₄ 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 CH₂Cl₂ was cooled to -78 ºC under an argon atmosphere. Neat TiCl₄ (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 CH₂Cl₂ 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 recoupling the reaction to –78 ºC, additional TiCl₄ (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 NH₄Cl. The organic layer was separated and the aqueous layer extracted twice with CH₂Cl₂. The combined organic fractions were dried over Na₂SO₄ 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**

![Diol 178](image)

To a solution of the isomeric mixture obtained the previous reaction (1.86 g, 2.62 mmole), 10 mL Et₂O, and methanol (0.157 mL, 3.93 mmole) at 0 °C 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 °C 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 Na₂SO₄ 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. ¹H NMR major isomer (400 MHz, CDCl₃) 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, ∆ν_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); ¹³C NMR (100 MHz, CDCl₃) 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,
Preparation of Na/Naphthenol: 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 H₂O. Saturated NaHCO₃ 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 Na₂SO₄, 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). ¹H NMR major isomer (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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; [α]²⁵_D = +31.8 (c 1.34, CH₂Cl₂).
Tri-PMB silyl ether 179

To a solution of the triol (0.605 g, 1.40 mmole) and 7 mL dimethylformamide at 0 °C 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 NH₄Cl solution. The aqueous layer was extracted three times with Et₂O. The combined organic fractions were dried over Na₂SO₄ 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 NaHCO₃. The organic layer was separated and the aqueous layer extracted with EtOAc. The combined organic extracts
were dried over Na₂SO₄ and concentrated in vacuo. Purification by flash chromatography gave 0.801 g (90% over two steps) of the alcohol 180. ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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; [α]$_{D}^{22}$ = +17.7 (c 0.66, CH₂Cl₂).

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 Na₂S₂O₃. The solution was diluted with Et₂O and the organic layer was separated. The aqueous layer was extracted twice with Et₂O and the combined organic layers were washed with brine, dried over Na₂SO₄, 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. ¹H NMR (400 MHz, CDCl₃) 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

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(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); \(^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 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**

\[
\begin{align*}
\text{Nitrile} & \quad \text{Me} \\
\text{PMBO} & \quad \text{OPMB} \\
\text{OPMB} & \quad \text{OPMB}
\end{align*}
\]

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\(_2\)O and water. The organic layer was separated and the aqueous layer was extracted twice with Et\(_2\)O. The combined organic extracts were washed with brine, dried over Na\(_2\)SO\(_4\), and concentrated in vacuo. Purification by flash chromatography gave 0.229 g (91%) of the desired nitrile **215**. \(^1\text{H} \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 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); \(^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 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\(_2\)Cl\(_2\)).
To a solution of the nitrile 215 (0.184 g, 0.286 mmole), 5 mL EtOH, and 2 mL H₂O 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 Et₂O and the combined extracts were dried over Na₂SO₄ and concentrated under reduced pressure. Purification by flash chromatography gave 0.161 g (85%) of the desired acid. ¹H NMR (400 MHz, CDCl₃) 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, Δν_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); ¹³C NMR (100 MHz, CDCl₃) 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; [α]D²⁴ = +5.3 (c 0.66, CH₂Cl₂).
To a solution of the carboxylic acid (0.407 g, 0.614 mmole) and 3 mL dimethylformamide was added anhydrous K$_2$CO$_3$ (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$_2$O and Et$_2$O. The organic layer was separated and the aqueous layer extracted twice with Et$_2$O. 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, $\Delta v_{AB}$ = 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$_2$Cl$_2$).
Phosphonate 217

\[
\begin{align*}
\text{(MeO)}_2P &= \text{Me} \\
\text{PMBO} &\cdots \text{OPMB} \\
\text{O} &\cdots \text{OPMB}
\end{align*}
\]

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 °C. 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 °C 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 °C. The reaction was then quenched with a saturated solution of NH₄Cl 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 Na₂SO₄ 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, CDCl₃) 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, Δν_{AB} = ~ 0), 4.42 (d, 1H, J = 11.0 Hz), 4.39 (AB, 2H, J_{AB} = 11.5 Hz, Δν_{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, Δν_{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, CDCl₃) 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\(_2\)Cl\(_2\)).

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 \(^\circ\)C 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\(_2\)O mixture was added to the phosphonate solution followed by the addition of an additional 0.5 mL of the THF/H\(_2\)O 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\(_2\)SO\(_4\) and concentrated under reduced pressure. Purification by flash chromatography gave 0.177g (96%) of the desired product \(218\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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, 1699, 1613, 1513, 1463, 1365, 1302, 1248, 1173, 1090 cm\(^{-1}\); \([\alpha]\)\textsubscript{D} = +26.6 (c 2.46, CH\(_2\)Cl\(_2\)). MS (ESI) for C\(_{68}\)H\(_{98}\)O\(_{13}\)Si [M + Na] calc. 1173.7, found 1173.6.

Ketone 219

![Ketone 219](image)

To a flask containing the enone 218 (0.177 g, 0.154 mmole) was added [PPh\(_3\)CuH]\(_6\) (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

![Enol ether 220](image)
The saturated ketone obtained above was dissolved in 5 mL CH₂Cl₂. 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. 

¹H NMR (400 MHz, C₆D₆) 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, JAB = 14.5 Hz, ΔνAB = 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); 

¹³C NMR (100 MHz, C₆D₆) 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; [α]²³D = +19.0 (c 1.05, CH₂Cl₂); MS (ESI) for C₆₈H₉₈O₁₂Si [M + 1] calc 1135.7, found 1135.8.

Alcohols 225 and 226
To a solution of the enol ether 220 (0.045 g, 0.040 mmole) and 1 mL CH$_2$Cl$_2$ 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$_2$Cl$_2$. The combined organic fractions were dried over Na$_2$SO$_4$ 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), 3.58-3.57 (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 (m, 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$_2$Cl$_2$); MS (ESI) for C$_{68}$H$_{100}$O$_{13}$Si [M + Na] calc 1175.7, found 1175.7.
To a flask containing an isomeric mixture of the alcohols (0.035 g, 0.030 mmole) and 2 mL CH₂Cl₂ 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 Na₂S₂O₅/NaHCO₃. The solution was poured into a separatory funnel and the organic layer was separated. The aqueous layer was extracted twice with CH₂Cl₂ and the combined extracts were dried over Na₂SO₄ 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 CH₂Cl₂). The reaction was heated to reflux for 15 h. After cooling the reaction, aqueous NH₄Cl was added and the organic layer was separated. The aqueous layer was extracted twice with CH₂Cl₂ and the combined extracts were dried over Na₂SO₄. Purification by flash chromatography gave 0.060 g (75%) of ketone 228 as a single stereoisomer with the desired configuration at C12. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz,
Ketone 229

A solution of anhydrous CH₂Cl₂ (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 (Cl₂(PCy₃)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. ¹H NMR (500 MHz, CDCl₃) 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 =
To a flask containing the tetra-PMB ether 229 (0.022 g, 0.0195 mmole) and 4 mL of anhydrous CH$_2$Cl$_2$ was added 0.1 mL trifluoroacetic acid. The resulting solution was allowed to stir for 1.5 h followed by dilution with additional CH$_2$Cl$_2$ and aqueous NaHCO$_3$. The organic layer was separated and the aqueous layer extracted twice with CH$_2$Cl$_2$. The combined organic extracts were dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by flash chromatography gave 0.010 g (79%) of the desired tetraol 230. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_9$Si [M + Na] calc. 665.4, found 665.4.
Mixed methyl ketal 231

![Mixed methyl ketal 231](image)

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$_2$Cl$_2$. Aqueous NaHCO$_3$ was added and the organic layer was separated. The aqueous layer was extracted twice with CH$_2$Cl$_2$ and the combined extracts were dried over Na$_2$SO$_4$. 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 °C 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$_2$SO$_4$ 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$_2$Cl$_2$ at 0 °C under an argon atmosphere was added triethylsilane (0.050 mL, 0.31 mmole) followed by BF$_3$·OEt$_2$ (0.010 mL, 0.079 mmole). The solution was allowed to stir at 0 °C for 15 min and quenched with aqueous NaHCO$_3$. The solution was diluted with CH$_2$Cl$_2$ and the organic layer was separated. The aqueous layer was extracted twice with CH$_2$Cl$_2$ and the combined extracts were dried over Na$_2$SO$_4$ 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$_6$D$_6$) 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$_8$Si [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 Et₂O and washed with aqueous NaHCO₃. The aqueous layer was extracted twice with Et₂O and the combined extracts were dried over Na₂SO₄. Purification by flash chromatography gave the desired tri-acetate 234. ¹H NMR (500 MHz, CD₃CN) 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, H12, 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); ¹³C NMR (125 MHz, CD₃CN) 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 C₄₀H₆₈O₁₁Si [M + 1] calc. 753.5, found 753.5.
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 CH₂Cl₂ and washed with aqueous NaHCO₃. The aqueous layer was extracted twice with CH₂Cl₂ and the combined extracts were dried over Na₂SO₄. Purification by flash chromatography gave the desired tribenzoate 235 which was further purified by semi-prep HPLC. ¹H NMR (500 MHz, CD₃CN) 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 C₅₅H₇₄O₁₁Si [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

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\text{O} \quad \text{N} \quad \text{OPMB}
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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 NH₄Cl. The organic layer was separated and the aqueous layer extracted twice with EtOAc. The combined organic fractions were dried over MgSO₄ 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). ¹H NMR (400 MHz, CDCl₃) δ 7.18-7.14 (band, 2H), 6.75-6.71 (band, 2H), 5.79 (dddd, \(J = 17.2, 10.0, 7.2, 7.2 \text{ Hz}, 1\text{H})\), 5.09-4.96 (band, 3H), 4.34 (AB, \(J_{AB} = 11.2 \text{ Hz}, \Delta v_{AB} = 40.1 \text{ Hz}, 2\text{H})\), 4.28 (ddd, \(J = 7.6, 3.6, 3.6 \text{ Hz}, 1\text{H})\), 4.10-4.02 (band, 2H), 3.64 (s, 3H), 2.50 (ddd, \(J = 14.0, 6.4, 4.8 \text{ Hz}, 1\text{H})\), 2.40 (ddd, \(J = 14.4, 7.2, 7.2 \text{ Hz}, 1\text{H})\), 2.14 (ds, \(J = 6.8, 3.6\text{Hz}, 1\text{H})\), 0.75 (d, \(J = 6.8 \text{ Hz}, 3\text{H})\), 0.71 (d, \(J = 7.2 \text{ Hz}, 3\text{H})\); ¹³C NMR (100 MHz, CDCl₃) 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\(_2\)Cl\(_2\)), 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\(_2\)O, and methanol (9.4 mL, 235 mmole) at 0 °C 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 °C 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\(_2\)SO\(_4\) and concentrated in vacuo. Purification by flash chromatography gave 37.4 g (93%) of the desired alcohol 250. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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\(_2\)Cl\(_2\)), MS (ESI) for C\(_{13}\)H\(_{18}\)O\(_3\) [M + Na] calc 245.1 found 245.1.
Into a 1 L flask equipped with a mechanical stirrer, addition funnel, and low-temperature thermometer was added 150 mL of CH$_2$Cl$_2$ and oxalyl chloride (49.7 mL, 99.3 mmol; 2.0 M in CH$_2$Cl$_2$). After cooling to −78 ºC, dimethylsulfoxide (9.40 mL, 132.4 mmol) in 150 mL of CH$_2$Cl$_2$ 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$_2$Cl$_2$ 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$_2$SO$_4$ 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$_2$Cl$_2$ 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 °C. After 10 minutes, aldehyde 251 (~ 66 mmol) in 20 mL of CH₂Cl₂ was added dropwise to the enolate solution. The reaction mixture was slowly warmed to –30 °C and maintained at that temperature for 2 hours. The reaction was quenched by the addition of 500 mL of half-saturated NH₄Cl and warmed to room temperature. The organic layer was separated and the aqueous layer extracted twice with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ 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: ¹H NMR (400 MHz, CDCl₃) 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, 6.0, 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); ¹³C NMR (100 MHz, CDCl₃) 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; [α]²³°D = –190 (c 2.7, CH₂Cl₂), MS (ESI) for C₂₆H₃₁NO₄S₂ [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 H₂O 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 Na₂SO₄. Purification by flash chromatography gave 10.3 g (78% over three steps) of diol 253. ¹H NMR (400 MHz, CDCl₃) δ 7.24-7.20 (band, 2H), 6.86-6.82 (band, 2H), 5.92 (ddddd, 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); ¹³C NMR (100 MHz, CDCl₃) 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; [α]²³_D = +39.9 (c 1.2, CH₂Cl₂), MS (ESI) for C₁₆H₂₄O₄ [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 CH₂Cl₂. 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 NaHCO₃ and the organic layer was separated. The aqueous layer was extracted twice with CH₂Cl₂ and the combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Purification by flash...
chromatography provided 21.7g (97%) of the silyl ether: ¹H NMR (400 MHz, CDCl₃) 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 (dddd, J = 4.0, 5.6, 8.0 Hz, 1H), 2.59-2.52 (m, 1H), 2.42 (dddd, 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); ¹³C NMR (100 MHz, CDCl₃) 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; [α]₂³° = +14.5 (c 5.6, CH₂Cl₂), MS (ESI) for C₂₅H₄₄O₄Si [M + Na] calc 459.3, found 459.3.

Carboxylic acid 254

\[ \text{TIPSOMe} \]

\[ \text{PMBO} \]

\[ \text{OH} \]

\[ \text{CONH} \]

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 °C. 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% H₂SO₄. 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 Na₂SO₄ 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$_3$) $\delta$ 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, $\Delta v_{AB} = 22.1$ 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$_3$) $\delta$ 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$^{-1}$; [$\alpha$]$^2_{D} = -1.8$ (c 1.7, CH$_2$Cl$_2$), MS (ESI) for C$_{27}$H$_{46}$O$_6$Si [M + Na] calc 517.3, found 517.4.

**Glycolate 255**

![Glycolate 255](image)

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 $-78$ °C and pivaloyl chloride (4.29 mL, 34.8 mmole) was added dropwise. The reaction was warmed to 0 °C, stirred at that temperature for 1 h and recooled to $-78$ °C. To a separate flask containing (R)-4-isopropyl-2-oxazolidinone (**149**) (5.31 g, 41.1 mmole) and 80 mL THF at -78 °C 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 $-78$ °C the reaction was slowly warmed to 0 °C 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$_2$SO$_4$ and concentrated in
vacuo. Purification by flash chromatography gave 17.0 g (89%) of the glycolate 255. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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, \(\Delta v_{AB} = 36.6\) 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\(_3\)) \(\delta\) 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\(^{-1}\); \([\alpha]_{D}^{23} = -29\) (c 2.1, CH\(_2\)Cl\(_2\)), MS (ESI) for C\(_{33}\)H\(_{55}\)NO\(_7\)Si [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 °C. 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 °C. 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 °C. The reaction was quenched at that temperature using saturated NH\(_4\)Cl. The organic layer
was separated and the aqueous layer extracted twice with EtOAc. The combined organic fractions were washed with brine, dried over Na$_2$SO$_4$ 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), 4.43 (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, 2777, 1721, 1613, 1513, 1463, 1388, 1248, 1209, 1108 cm$^{-1}$; [α]$^{23}_{D} = -66$ (c 2.8, CH$_2$Cl$_2$), MS (ESI) for C$_{36}$H$_{56}$N$_2$O$_7$Si [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 Na₂SO₄ 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. ¹H NMR (400 MHz, CDCl₃) δ 7.23-7.20 (band, 2H), 6.86-6.83 (band, 2H), 5.87 (ddddd, 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, ΔνAB = 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 (ddddd, 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); ¹³C NMR (100 MHz, CDCl₃) 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; [α]₂¹D = −8.0 (c 0.5, CH₂Cl₂), MS (ESI) for C₂₉H₄₉NOSi [M + Na] calc 542.3, found 542.6.

Swern oxidation to the aldehyde

\[
\text{Me} \quad \text{O} \quad \text{N} \\
\text{BnO}^+ \quad \text{O} \quad \text{N} \\
\text{TIPSO}^{-} \quad \text{Me} \quad \text{O} \quad \text{N}
\]

Into a 300 mL flask equipped with an addition funnel and low-temperature thermometer under an argon atmosphere was added 50 mL of CH₂Cl₂ and oxalyl chloride (15.5 mL, 31.1 mmol; 2.0 M in CH₂Cl₂). After cooling to −78 °C, dimethylsulfoxide (2.94 mL, 41.4 mmol) in 50 mL of CH₂Cl₂ was added dropwise via an addition funnel to maintain a temperature < −65 °C. After stirring for 10 minutes, alcohol 256 (10.8 g, 20.7 mmol) in 50 mL of CH₂Cl₂ was added via addition funnel maintaining a temperature < −65 °C. 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 NaHCO₃, water, and brine. The organic layer was dried over Na₂SO₄ 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**

![Diene 257](image)

To a solution the aldehyde prepared in the previous step and 400 mL CH₂Cl₂ 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 CH₂Cl₂. The combined organic layers were concentrated in vacuo to give the crude diene 257.

**Lactone 262**

![Lactone 262](image)
To the crude material obtained above was added 100 mL methanol and 5 mL HCl (conc.). The resulting solution was heated to 65 °C for 3 h. After cooling the reaction mixture to room temperature, 100 mL each of CH₂Cl₂ and ½ saturated NaCl were added. The organic layer was separated and the aqueous layer extracted six times with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. Purification by flash chromatography gave 4.07 g (69%) of the desired isomer 262 along with 0.60 g (11%) of the undesired diastereomer. ¹H NMR (400 MHz, CDCl₃) 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 (ddd, 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); ¹³C NMR (100 MHz, CDCl₃) 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; [α]²¹D = +25 (c 0.35, CH₂Cl₂), MS (ESI) for C₁₅H₂₄O₅ [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 °C and allowed to stir under an argon atmosphere for 15 h. The reaction mixture was cooled and saturated NaHCO₃ was added along with Et₂O. The organic layer was separated and the aqueous layer extracted twice with Et₂O. The
combined organic layers were washed with brine and dried over Na$_2$SO$_4$. 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$_3$) $\delta$ 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 (ddddd, $J$ = 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$_3$) $\delta$ 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$_2$Cl$_2$), MS (ESI) for C$_{27}$H$_{52}$O$_5$Si$_2$ [M + Na] calc 535.3, found 535.5.

**Diol 264**

![Diol 264](image)

To a flask containing a solid addition funnel was added the lactone 263 (14.8 g, 28.8 mmole) and 300 mL Et$_2$O. 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$_2$O (slowly), 2 mL of 15% aq. NaOH, and 6 mL H$_2$O in that order. The resulting heterogeneous solution was filtered through a small pad of celite. The celite was washed with several portions of Et$_2$O 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$_3$) $\delta$ 5.86-
5.72 (band, 2H), 5.06-4.95 (band, 4H), 3.92 (dddd, \( J = 4.0, 8.0, 8.0, 12.4 \text{ Hz}, 1H \)), 3.86-3.82 (m, 1H), 3.82-3.80 (band, 2H), 3.67-3.57 (band, 3H), 3.53 (dddd, \( J = 3.0, 3.2, 3.2 \text{ Hz}, 1H \)), 3.45 (dd, \( J = 4.4, 10.4 \text{ Hz}, 1H \)), 3.41 (dd, \( J = 6.4, 10.0 \text{ Hz}, 1H \)), 2.37-2.21 (band, 3H), 2.04 (dddd, \( J = 4.0, 5.6, 9.6, 9.6 \text{ Hz}, 1H \)), 1.75-1.64 (band, 2H), 0.91 (d, \( J = 6.8 \text{ Hz}, 3H \)), 0.85 (s, 9H), 0.84 (s, 9H), 0.04 (3H), 0.03 (s, 3H), –0.01 (s, 6H); \(^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)) \( \delta 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\(_2\)Cl\(_2\)), MS (ESI) for C\(_{27}\)H\(_{56}\)O\(_5\)Si\(_2\) [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 °C. 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\(_4\)Cl. After the addition of 100 mL diethyl ether the organic layer was separated and the aqueous layer extracted twice with Et\(_2\)O. The combined organic layers were washed with brine, dried over Na\(_2\)SO\(_4\) and concentrated in vacuo. Purification by flash chromatography gave 2.52 g (98%) of the desired bis-benzyl ether 265. \(^1\text{H} \) NMR (400 MHz, CDCl\(_3\)) \( \delta 7.34-7.24 \) (band, 10H), 5.93-5.76 (band, 2H), 5.10-4.95 (band, 4H), 4.72 (d, \( J = 11.6 \text{ Hz}, 1H \)), 4.54 (d, \( J = 11.6 \text{ Hz}, 1H \)), 4.47 (AB, \( J = 12.0 \text{ Hz}, \Delta v_{AB} = 8.0 \text{ Hz}, 2H \)), 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); 13C 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; [α]23 D = + 17.3 (c 0.4, CH 2 Cl 2), MS (ESI) for C41H68O5Si2 [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 2 SO 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, CDCl₃) 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; $[\alpha]_{D}^{23} = +8.5$ (c 0.7, CH₂Cl₂), MS (ESI) for C₃₅H₅₄O₅Si [M + Na] calc 605.4, found 605.4.

**Iodide 268**

![Iodide 268](image)

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 Na₂S₂O₃. The solution was diluted with Et₂O and the organic layer was separated. The aqueous layer was extracted twice with Et₂O and the combined organic layers were washed with brine, dried over Na₂SO₄, 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, CDCl₃) δ 7.35-7.24 (band, 10H), 5.88 (ddddd, J = 7.2, 7.2, 10.0, 16.8 Hz, 1H), 5.80 (ddddd, 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, ΔνAB = 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$^{-1}$; [$\alpha$]$^2$D = + 8.74 (c 3.8, CH$_2$Cl$_2$), MS (ESI) for C$_{35}$H$_{53}$IO$_4$Si [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$_2$O and water. The organic layer was separated and the aqueous layer was extracted twice with Et$_2$O. The combined organic extracts were washed with brine, dried over Na$_2$SO$_4$, 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, $\Delta v_{AB} = 36.2$ 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,
A solution of nitrile 269 (7.58 g, 12.8 mmole) in 100 mL CH₂Cl₂ 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 CH₂Cl₂. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. Purification by flash chromatography gave 6.17 g (81%) of the aldehyde 273. ¹H NMR (400 MHz, CDCl₃) 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, Δνₐₘ = 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); ¹³C NMR (100 MHz, CDCl₃) 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; [α]⁺²³ = +5.6 (c 1.9, CH₂Cl₂), MS (ESI) for C₃₆H₅₄O₅Si [M + Na] calc 614.4, found 614.4.
Phosphonate 275

\[
\begin{align*}
\text{Formation of the } \beta\text{-hydroxy phosphonate} & \\
\text{A flask containing dimethyl methyl phosphonate (10.8 mL, 100 mmole) and 300 mL anhydrous THF was cooled to } -78 \, ^\circ\text{C. } n\text{-Butyl lithium (40 mL, 100 mmole; 2.5 M in hexanes) was added dropwise to the solution over 15 min. The resulting mixture was allowed to stir for 1 h. The aldehyde 273 (6.17 g, 10.4 mmole) prepared in the previous step was dissolved in 50 mL THF and added slowly to the lithiated phosphonate solution. After stirring at } -78 \, ^\circ\text{C for 20 minutes the reaction mixture was warmed to } 0 \, ^\circ\text{C and quenched with saturated NaHCO}_3. \text{ The solution was diluted with } \text{EtOAc and the organic layer was separated. The aqueous layer was extracted twice with EtOAc and the combined organic layers were washed with brine, dried over Na}_2\text{SO}_4, \text{ and concentrated in vacuo. Purification by flash chromatography gave 7.19 g (96%) of the desired phosphonate as a mixture of } \beta\text{-hydroxy epimers. }
\end{align*}
\]

\[i) \text{ Formation of the } \beta\text{-keto phosphonate} \]

The } \beta\text{-hydroxy phosphonate mixture obtained in the previous step (2.38 g, 3.31 mmole) was dissolved in 20 mL CH}_2\text{Cl}_2. \text{ 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}_2\text{S}_2\text{O}_3/\text{NaHCO}_3. \text{ The organic layer was separated and the aqueous layer extracted twice with CH}_2\text{Cl}_2. \text{ The combined organic layers were washed with brine, dried over Na}_2\text{SO}_4 \text{ 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, $\Delta v_{AB} =$ 52.3 Hz, 2H), 4.45 (AB, J = 12.0 Hz, $\Delta v_{AB} =$ 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, 1250 cm$^{-1}$; [α]$^{23}_{D} = +3.9$ (c 3.3, CH$_2$Cl$_2$), MS (ESI) for C$_{37}$H$_{57}$O$_8$PSi [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$_2$Cl$_2$ was heated to 40 °C 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 °C 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$_3$) $\delta$ 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, 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$_3$) $\delta$ 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}$; [a]$^{23}_D = $ $-6.3$ (c 2.4, CH$_2$Cl$_2$), MS (ESI) for C$_{37}$H$_{57}$O$_8$PSi [M + Na] calc 711.4, found 711.2.

5.2.3.2. Synthesis of the B ring aldehyde

![Chemical structure](image)

To a solution of the B-ring diol (0.280 g, 0.534 mmole) in 5 mL CH$_2$Cl$_2$ 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$_2$S$_2$O$_3$/NaHCO$_3$ solution. The organic layer was separated and the aqueous layer extracted twice with CH$_2$Cl$_2$. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. Purification by
flash chromatography gave 0.238 g (85%) of the aldehyde 241. $^1$H NMR (500 MHz, C$_6$D$_6$) 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 (ddd, $J = 3.0, 7.0, 9.5, 9.5$ Hz, 1H), 1.91-1.85 (band, 2H), 1.78 (ddd, $J = 3.0, 3.0, 15.5$ Hz, 1H), 1.66 (ddd, $J = 3.5, 5.0, 9.0, 13.5$ 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$_6$D$_6$) 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$^{-1}$; [α]$^{25}_D = + 35$ (c 0.35, CH$_2$Cl$_2$), MS (ESI) for C$_{29}$H$_{50}$O$_6$Si [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$_2$O mixture was added to the phosphonate solution followed by the addition of an additional 0.5 mL of the THF/H$_2$O 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$_2$SO$_4$ 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$^{-1}$; $[\alpha]^{21\circ}$D = + 14.6 (c 1.4, CH$_2$Cl$_2$), MS (ESI) for C$_{64}$H$_{100}$O$_{10}$Si$_2$ [M + Na] calc 1107.7, found 1107.5.

Enol ether 278

![Enol ether structure](image-url)
**Stryker's reduction:**

To a flask containing the enone 277 (1.24 g, 1.14 mmole) and [PPh₃CuH]₈ (2.23 g, 1.14 mmole) was added 10 mL toluene (degassed) and 0.100 mL H₂O (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 CH₂Cl₂. 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 dimethylphenylsilane (0.270 mL, 1.75 mmole) and (PPh₃)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. 

¹H NMR (400 MHz, C₆D₆) 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), 3.30 (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$_6$D$_6$) 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$^{-1}$; $[\alpha]_D^{21} = + 10.1$ (c 0.8, CH$_2$Cl$_2$), MS (ESI) for C$_{64}$H$_{100}$O$_9$Si$_2$ [M + Na] calc 1091.7, found 1091.5.

Ketones 279 and 280

i) Oxidation/reduction of the enol ether:

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$_2$Cl$_2$ 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$_2$Cl$_2$ 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$_2$Cl$_2$. The combined organic fractions were dried over Na$_2$SO$_4$ 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$_2$Cl$_2$ 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$_2$S$_2$O$_3$/NaHCO$_3$. The solution was poured into a separatory funnel and the organic layer was separated. The aqueous layer was extracted twice with CH$_2$Cl$_2$ and the combined extracts were dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by flash chromatography (15% Et$_2$O/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, $\Delta v_{AB}$ = 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, 2H), 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$^{-1}$; [α]$^D_{26}$ = + 49 (c 2.3, CH$_2$Cl$_2$), MS (ESI) for C$_{64}$H$_{100}$O$_{10}$Si$_2$ [M + Na] calc 1107.7, found 1107.7.
\[ ^1H \text{NMR (280)} \text{ (400 MHz, CDCl}_3\text{)} \delta \ 7.35-7.25 \text{ (band, 10H), 7.21-7.19 \text{ (band, 2H), 6.86-6.83 (band, 2H), 5.74-5.63 (band, 2H), 4.60 \text{ (d, } J = 11.6 \text{ Hz, 1H), 4.49 \text{ (d, } J = 11.2 \text{ Hz, 1H), 4.43 (s, 2H), 4.39 \text{ (d, } J = 11.6 \text{ Hz, 1H), 4.30 \text{ (d, } J = 11.2 \text{ Hz, 1H), 3.84-3.79 \text{ (band, 2H), 3.79 (s, 3H), 3.75-3.68 \text{ (band, 3H), 3.63 \text{ (m, 1H), 3.57-3.48 \text{ (band, 3H), 3.41-3.38 \text{ (band, 2H), 3.08 \text{ (ddd, } J = 1.0, 8.8, 8.8 \text{ Hz, 1H), 2.82 \text{ (dd, } J = 6.0, 15.6 \text{ Hz, 1H), 2.72 \text{ (ddd, } J = 1.0, 12.0, 13.0 \text{ Hz, 1H), 2.61 \text{ (ddd, } J = 1.0, 12.0, 13.0 \text{ Hz, 1H), 2.36-2.28 \text{ (band, 2H), 2.13-1.87 \text{ (band, 5H), 1.84-1.78 \text{ (band, 3H), 1.68-1.50 \text{ (band, 4H), 1.39 \text{ (dddd, } J = 3.6, 3.6, 8.8, 8.8 \text{ Hz, 1H), 1.26 (s, 3H), 1.13-1.02 \text{ (band, 21H), 0.96 \text{ (d, } J = 6.8 \text{ Hz, 3H), 0.86 \text{ (s, 9H), 0.79 \text{ (d, } J = 7.2 \text{ Hz, 3H), 0.07 \text{ (s, 3H), 0.02 \text{ (s, 3H); } ^{13}C \text{NMR (100 MHz, CDCl}_3\text{)} \delta 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]_{D}^{23} = +5.8 (c 0.6, CH\text{Cl}_2), MS (ESI) for C_{64}H_{100}O_{10}Si_{2} [M + Na] \text{ 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$_2$CO$_3$. 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$_4$Cl. After the addition of CH$_2$Cl$_2$ the organic layer was separated and the aqueous layer was extracted twice with CH$_2$Cl$_2$. The combined extracts were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Purification by flash chromatography (15% Et$_2$O/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

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 CH₂Cl₂. Aqueous NaHCO₃ was added and the organic layer was separated. The aqueous layer was extracted twice with CH₂Cl₂ and the combined extracts were dried over Na₂SO₄. 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.

¹H NMR ketal 283 (500 MHz, C₆D₆) 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, ΔνAB = 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); ¹³C NMR (125 MHz, C₆D₆) 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,
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
CH₂Cl₂ at 0 ºC under an argon atmosphere was added dimethyphenylsilane (0.100 mL). Redistilled BF₃·OEt₂ (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 NaHCO₃. The solution was diluted with CH₂Cl₂ and the organic layer was separated. The aqueous layer was extracted twice with CH₂Cl₂ and the combined extracts were dried over Na₂SO₄ and concentrated in vacuo. Purification by flash chromatography gave 0.029 g (78%) of the desired tetracycle 285 as a single diastereomer. ¹H NMR (500 MHz, C₆D₆) 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, ΔνAB = 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); ¹³C NMR (125 MHz, C₆D₆) 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; [α]²³D = −40 (c 1.6, CH₂Cl₂), MS (ESI) for C₄₁H₅₈O₈ [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 CH₂Cl₂ 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 °C 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$_6$D$_6$) 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, $\Delta \nu_{AB} = 19.6$ Hz, 2H), 4.19 (d, $J = 12.0$ Hz, 1H), 3.81 (ddd, $J = 5.5, 5.5, 5.5$ Hz, 1H), 3.69 (ddddd, $J = 4.5, 4.5, 4.5, 8.5$ 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, $J = 11.5, 11.5, 11.5$ 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$_6$D$_6$) 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$^{-1}$; $[\alpha]^{26}_{\text{D}} = -58$ (c 0.33, CH$_2$Cl$_2$), MS (ESI) for C$_{41}$H$_{54}$O$_8$ [M + H] calc 675.4, found 675.3.
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