Spring 1-1-2012

Development of a Novel Lewis Acid for Intramolecular Vinylogous Aldol Reactions, its Application to the Synthesis of (+)-Peloruside A, and Design and Synthesis of Lanthanide-Binding Nucleosides for Solution Phase Characterization of RNA by NMR

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Development of a Novel Lewis Acid for Intramolecular Vinylogous Aldol Reactions, its Application to the Synthesis of (+)-Peloruside A, and Design and Synthesis of Lanthanide-Binding Nucleosides for Solution Phase Characterization of RNA by NMR

by

Jeffrey A. Gazaille

B. S. Chemistry, University of Redlands, 2007

A thesis submitted to the Faculty of the Graduate School of the University of Colorado in partial fulfillment of the requirement for the degree of Doctor of Philosophy Department of Chemistry and Biochemistry 2012
This thesis entitled:

Development of a Novel Lewis Acid for Intramolecular Vinylogous Aldol Reactions, its Application to the Synthesis of (+)-Peloruside A, and Design and Synthesis of Lanthanide-Binding Nucleosides for Solution Phase Characterization of RNA by NMR

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Date ____________

The final copy of this thesis has been examined by the signatories, and we find that both the content and the form meet acceptable presentation standards of scholarly work in the above mentioned discipline.
Gazaille, Jeffrey Allyn (Ph.D., Chemistry)

Development of a Novel Lewis Acid for Intramolecular Vinylogenous Aldol Reactions, its Application to the Synthesis of (+)-Peloruside A, and Design and Synthesis of Lanthanide-Binding Nucleosides for Solution Phase Characterization of RNA by NMR

Thesis directed by Professor Tarek Sammakia

While in the Sammakia Lab, I have focused broadly on developing and applying new approaches to organic synthesis that increase the cache of methods for the synthesis and use of complex organic molecules. My research efforts can be classified into (i) the development and application of new methods for the synthesis of complex natural products, and (ii) the use of organic molecules as probes for problems in chemical biology. The application of the intramolecular vinylogenous aldol reaction with ATPH toward the synthesis of (+)-peloruside A, the development of the novel Lewis acid, ATNP, which promotes the vinylogenous aldol reaction of enolizable aldehydes with crotonate esters, and the design and synthesis of lanthanide binding nucleosides for inducing residual dipolar couplings will be discussed.
For Mom
Acknowledgements

Grad school is hard. It is extremely frustrating at times. The long hours, little pay, and diminishing job prospects for chemistry Ph.D.’s do little to help this perception. In spite of this, I’ve been able to have an unimaginably great experience here at CU and wouldn’t have changed a thing. This is completely due to the incredible network of advisors, colleagues, friends, and family that I’m fortunate enough to have. There, therefore, is no other way to begin this thesis than by thanking the people that have helped me get to this point in my life.

First and foremost, I want to thank the dear Lord baby Jesus, lyin’ there in his ghost manger, just lookin’ at his Baby Einstein developmental videos, learnin’ ‘bout shapes and colors. I would like to thank you for bringin’ me and my research advisor together, and also that I’ll no longer have to live in a frat house with kids that sound like idiot gang-bangers.

In all serious though, Tarek Sammakia has been the best teacher, research advisor, friend, and colleague I could have ever imagined. I would like to thank my former lab mates: Joe Abramite, Matt Sammons, Carolyn Chin, and Chenkang Mai for your insightful discussions and your friendship. To the new generation of Sammakians: Ryan Michael, Will Hartwig, Price Kirby, and Katelyn Chando, I will always consider you to be some of my best friends and I can’t imagine completing graduate school without you guys. To all of my other teachers and colleagues at CU, thank you so much!

Finally, I couldn’t have done this without the love and support of my mom and the rest of my family. Love you!
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Chapter 1

Toward the Synthesis of (+)-Peloruside A

1.1 Lewis Acids in Organic Synthesis

The importance of Lewis acids to the field of organic chemistry cannot be overstated. For decades, chemists have studied and observed the interactions of Lewis acids with Lewis bases to understand the diverse reactivity of these compounds. Their diligence has led to a vast collection of reactions that are indispensable to modern-day synthetic chemists. Understandably, reactions that form new C-C bonds are of greatest utility to practitioners of organic synthesis. As such, the Lewis acid-mediated addition of carbon nucleophiles to carbonyls continues to be an indispensable process used in organic synthesis.\textsuperscript{1} Even after intense study, the role of Lewis acids continues to expand and evolve as chemists devise new ways to render them catalytically active and increase the chemo-, regio, and stereoselectivities of the reactions in which they participate.

The low cost and availability of aluminum Lewis acids make them attractive and of substantial interest to the synthetic community. The traditional aluminum halides such as AlCl\textsubscript{3} and AlBr\textsubscript{3} have broad applications, but are most widely known for their ability to promote Friedel-Crafts reactions.\textsuperscript{2} When the halides bound to the

\begin{itemize}
  \item Yamamoto, H.; Editor \textit{Lewis Acids in Organic Synthesis}, Volume 2, \textbf{2000}.
\end{itemize}
aluminum are replaced by alkoxide ligands, a significant reduction in Lewis acidity occurs and a corresponding alteration in the type of reactivity they promote is observed. Arguably, the most famous application of an aluminum alkoxide Lewis acid in organic synthesis is the Al(Oi-Pr)$_3$ promoted Meerwein-Ponndorf-Verley reaction (Scheme 1.1).³

![Scheme 1.1 The Meerwein-Ponndorf-Verley Reaction](image)

**Bulky Aluminum Lewis Acids**

Aluminum alkoxide Lewis acids of this type often exist as complex, extended structures in solution.⁴ This intermolecular network decreases the Lewis acidity of the aluminum and introduces a variable that can lead to unpredictable outcomes when used in synthesis. When appropriately modifying the alkoxide ligands with very bulky substituents, monomeric structures are known to exist. This unique combination of increased Lewis acidity at the metal center and decreased accessibility has led to an abundance of interesting and previously unknown selectivities in various reactions. Yamamoto and coworkers have developed a class of these bulky aluminum-based Lewis acids where sterically hindered aluminum phenoxides are

---


used for inducing remarkable reactivities, specifically in reactions involving additions to carbonyls (Figure 1.1).  

\[ \text{Me}_3\text{Al} \]  

\[ \text{LaH}_2(\text{OC}_6\text{H}_3\text{Bu}^-\text{-2,6})_2 \]  

\[ \text{AlH}(\text{OC}_6\text{H}_3\text{Bu}^-\text{-2,6})_2(\text{OEt}_2) \]  

\[ \text{AlH}(\text{OC}_6\text{H}_3\text{Bu}^-\text{-2,6})_2(\text{OEt}_2) \]  

**Figure 1.1** Bulky Aluminum Based Designer Lewis Acids

In general, these reagents are easily prepared *in situ* from the reaction of Me₃Al with the appropriate phenol and are typically used without further purification. For example, aluminum tris(2,6-diphenylphenoxide) (ATPH, 1.2.2) is prepared by adding Me₃Al (1 equiv) to a solution of 2,6-diphenylphenol 1.2.1, (3 equiv) in toluene at room temperature with the rigorous exclusion of air and moisture (Scheme 1.2). The exception to this protocol is in the preparation of exceedingly bulky Lewis acids, such as aluminum tris(2,6-di-tert-butyl-4-methylphenoxide) 1.2.6 (ATD). In order to achieve this highly congested environment, 3 equivalents of the phenol 1.2.3 are added to LAH in ether. After liberation of H₂ and removal of Li[AlH₂(OC₆H₃t-Bu,₂,6)] 1.2.4 by fractional crystallization, the resulting [AlH(OC₆H₃t-Bu,₂,6)₂(OEt₂)]

---


1.2.5 is refluxed in toluene with an additional equivalent of phenol to provide the desired Lewis acid (Scheme 1.2).

**Scheme 1.2**  The Preparation of ATPH and ATD

Perhaps the most useful of Yamamoto’s designer aluminum Lewis acids is ATPH. The remarkable selectivities observed when it is used are hypothesized to be due to its unique structure and bulk. Crystal structures of ATPH bound to DMF reveal a pseudo $C_3$ symmetric, cup-shaped cavity with a propeller-like ligand array around the central aluminum atom (Figure 1.2). This unusual motif encapsulates the oxygen of a bound carbonyl and creates an extremely hindered environment at sites proximal to the binding site.
Some of the more notable uncommon reactions that ATPH promotes include discrimination of structurally or electronically similar substrates, 1,4-addition of nucleophiles to α,β-unsaturated carbonyl compounds, promotion of stereoselective Claisen rearrangements, and exo-selective Diels-Alder reactions. Of most interest to our group however, is its ability to access to δ-hydroxy-α,β-unsaturated esters via the vinylogous aldol reaction of α,β-unsaturated esters and aldehydes (Scheme 1.3).  

![Scheme 1.3](image)

Scheme 1.3 Some Interesting Selectivities when ATPH is used in Various Reactions

---

1.2 The Yamamoto Vinylogous Aldol Reaction

The aldol reaction is a versatile carbon-carbon bond forming transformation that is widely used and of great importance in organic synthesis. However, the control of the mixed aldol reaction between two different carbonyl compounds which present several possible sites for enolization is a challenging problem for synthetic chemists. Such reactions are normally carried out by converting the carbonyl compound, which is to serve as a nucleophile, to an enolate. This reactive nucleophile is then added to and allowed to react with the second carbonyl compound (Scheme 1.4).

![Scheme 1.4 Typical Procedure for Aldol Reactions](image)

The extension of this reaction to its vinylog (i.e., the vinylogous aldol reaction) is well known, and in its simplest form, proceeds via a dienolate and an aldehyde. The product, a δ-hydroxy-α,β-unsaturated carbonyl compound, is rich in functionality, and as this bond construction occurs in an uncommon position (between

---


the γ- and δ-carbons of the product), it offers novel strategic disconnections in synthetic planning (Scheme 1.5).

\[
\begin{align*}
\text{R}^1\text{H} \quad 1.5.1 & \quad + \quad \text{CH}_{\text{R}^2} \quad 1.5.2 & \quad \xrightarrow{\text{Vinylogous Aldol Reaction}} \quad \text{R}^1\text{OH} \quad 1.5.3 & \quad + \quad \text{CH}_{\text{R}^2} \quad 1.5.4 \\
\end{align*}
\]

**Scheme 1.5** The Vinylogous Aldol Reaction

Generating exclusively the γ-adduct 1.5.3 is a challenge to organic chemists. For example, when an α,β-unsaturated carbonyl such as cyclopentenone is treated with a thermodynamic, equilibrating base such as KOt-Bu it produces dienolate 1.6.2 (Scheme 1.6). When that enolate is trapped with an electrophile, the corresponding α-adduct 1.6.3 is the major product of the reaction. When that same α,β-unsaturated carbonyl is treated with a kinetic, non-equilibrating base such as LDA, enolate 1.6.5 is generated. Trapping of 1.6.5 with an electrophile primarily results in the production of α’-adduct 1.6.6 (Scheme 1.6).

**Scheme 1.6** Enolization/Trapping Strategies of Cyclopentenone
**ATPH-Mediated Vinylogous Aldol Reaction**

In recent years, this reaction has gained significant attention from the organic community, and an important advance was described by Hisashi Yamamoto with the use of the very bulky Lewis acid, aluminum tris(2,6-diphenylphenoxide) (ATPH). ATPH is used in reactions of lithium enolates and aldehydes, and it is thought to bind to both the dienolate and the aldehyde components of the reaction. Due to its bulk, it prevents reaction at the α-carbon of the dienolate, thereby forcing the reaction to occur at the distal γ-carbon (Scheme 1.7). Remarkably, Yamamoto has used ATPH to direct reactivity to the terminal carbon in substrates as large as hexaenolates derived from pentaenoates.

**Scheme 1.7** The Yamamoto Vinylogous Aldol Reaction

As a representative optimized example of Yamamoto’s procedure, pre-complexation of methyl crotonate 1.8.2 (2.0 equiv) and benzaldehyde 1.8.1 (1.0 equiv) with ATPH (3.3 equiv) was followed by treatment with a solution of LTMP (2.3 equiv) in THF at -78 °C under an argon atmosphere. After stirring of the mixture at this temperature for 30 min, quenching with aq. NH₄Cl, and purification by column chromatography on silica gel, aldol adduct 1.8.3 with exclusive E-configuration at the olefin was obtained in 97% yield (Scheme 1.8).
Yamamoto found that this reaction proceeds well in most cases where α,β-unsaturated aldehydes, ketones, and esters are used as coupling partners in the vinylogous aldol reaction with aldehydes. The exception to this is the case where α,β-unsaturated esters are used in the reaction with unbranched and enolizable aldehydes. For example, attempted vinylogous aldol reaction between methyl crotonate and valeraldehyde provides the desired product in a disappointing yield of only 22%. This is likely the result of the formation of a mixture of enolates which leads to a complex mixture of products and low yields of the desired compound (Table 1.1).
An additional requirement of the Yamamoto protocol is that the components must all be combined prior to the addition of the base. Attempts to conduct the reaction in a stepwise fashion wherein the enolate is first formed and the aldehyde then added provide significantly diminished yields (Scheme 1.9).

**Scheme 1.9**  Unsuccessful Stepwise Yamamoto Vinylogous Aldol
The Intramolecular Yamamoto Vinylogous Aldol Reaction

One can imagine the utility of an intramolecular reaction in the construction of macrolide-containing natural products. Some possible intramolecular vinylogous aldol retrosynthetic bond disconnections are shown in Figure 1.3. Possible target molecules include arenolide, RK-397, peloruside A, and laulimalide, all of which show interesting biological activities and structural motifs.

![Figure 1.3 Possible Target Molecules Utilizing an Intramolecular Vinylogous Aldol Reaction](image)

Mark Mitton-Fry and Joe Abramite, former graduate students in the Sammakia lab, hypothesized that if the aldehyde and α,β-unsaturated carbonyl compound must both be present and pre-complexed to ATPH prior to the addition of base, the method could be extended to the macroaldolization of crotonate esters to
rings of various size. Medium-membered rings of this nature are generally more difficult to make than their smaller or larger counterparts due to both entropic and enthalpic energy barriers they incur. Some of the more popular methods for medium-membered ring formation include macrolactonization and ring-closing metathesis, but these often provide moderate yields and are unable to create any new asymmetric carbons in the molecule. Abramite, however, demonstrated an intramolecular variation of the Yamamoto vinylogous aldol reaction using crotonate esters and non-enolizable aldehydes for the construction of 10- to 14-membered macrolides in good yields (up to 90%) and excellent remote diastereoselection (~20:1 dr) (Table 1.2).  

![Chemical Reaction Diagram]

<table>
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**Table 1.2** The Intramolecular Vinylogous Aldol Reaction

We wished to demonstrate the utility of the intramolecular vinylogous aldol reaction for the construction of macrolides in the context of natural products

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synthesis. We therefore targeted the polyoxygenated 16-membered macrolide pelorusside A for synthesis. This compound was chosen because it appeared to be amenable to efficient synthesis using the intramolecular vinylogous aldol method developed by Dr. Abramite, and because it displays potent antimitotic activity with low nanomolar activity against several cancer cell lines.12

1.3 Isolation, Characterization, and Biological Activity of (+)-Pelorusside A

Isolation and Characterization

Pelorusside A 1.4.1 is a polyoxygenated 16-membered macrolide natural product that was isolated from a marine sponge, *Mycale hentscheli*, found off the coast of New Zealand by Northcote and coworkers in 2000.13 The absolute configuration was determined by Debrabander and coworkers in their total synthesis of the antipode, (-)-pelorusside A.14

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In the isolation paper, Northcote and coworkers reported that (+)-peloruside A is cytotoxic against P388 murine leukemia cells at approximately 10 ng/mL (18 nM). Shortly thereafter, Miller and coworkers demonstrated that (+)-peloruside A is indeed a potent cytotoxin at low nanomolar concentrations (4-15 nM), inducing biochemical changes consistent with apoptosis in a variety of mammalian cell lines.\(^\text{12}\) It is proposed to have a mode of action that involves stabilizing microtubules during mitosis. This stabilization induces tubulin polymerization, causing cells to arrest at the G\(_2\)-M boundary of the cell cycle leading to apoptosis. Several drugs on the market including paclitaxel, vincristine, vinorelbine, vinblastine and many others in clinical trials take advantage of this tubulin-stabilizing strategy for cancer chemotherapy because of the rapid growth and division of cancer cells.

Peloruside was found to be not affected by the mutations that are known to affect the activity of the paclitaxel.\(^\text{15}\) Additionally, competition binding experiments

revealed that it does not bind to the taxane site in β-tubulin. In line with these results, peloruscide was found to synergize with other taxane site drugs in both polymerizing purified tubulin and cellular activity.\textsuperscript{16}

![Figure 1.5](image.png)

**Figure 1.5** Proposed Binding Site of (+)-Peloruside A from Ref. 16

In addition to the antimitotic activity, recent studies have shown that peloruscide protects cultured neurons against okadaic acid induced tau phosphorylation.\textsuperscript{17} The loss of tau function caused by misfolding, hyperphosphorylation, and sequestration of tau into insoluble aggregates, leads to axonal transport deficits with neuropathological consequences. These results suggest that peloruscide may also be considered a potential candidate for the treatment of tauopathies such as Alzheimers.


1.4 Previous Syntheses of (+)-Peloruside A

(+)-Peloruside A’s combination of potent biological activity and complex structure has led to intense interest by the synthetic organic community with six total syntheses reported to date.\(^\text{18}\) One of the challenges associated with the synthesis of peloruside A is the construction of the macrocycle, and all previous total syntheses have utilized a macrolactonization for this purpose. While macrolactonization has become a reliable method for the synthesis of medium- to large-membered rings, it can at times provide modest yields and there can be strategic advantages to other methods of macrocycle formation. Herein, we will briefly describe the most recent strategies used by the Evans, Hoye, and Jacobsen groups.

*The Evans Synthesis*

The Evans retrosynthetic analysis of (+)-peloruside A relies on the two highlighted aldol disconnections illustrated in Scheme 1.10. Based on prior work in the group, they anticipated that the C3 and C15 stereocenters would favorably influence the stereochemical outcome of these two major bond constructions.

The Evans synthesis of (+)-peloruside A commences with the protection of (S)-pantolactone 1.11.1 as a benzyl ether. Formation of the Weinreb amide is achieved by subjecting the lactone to a Lewis acid mediated nucleophilic ring opening with MeON(H)Me·HCl. Protection of the resulting free alcohol as a TES ether provides 1.11.2 in a 70% yield over three steps. Ketone 1.11.3 is prepared in a 97% yield after alkenyl lithium addition to the Weinreb amide. A highly diastereoselective zinc borohydride reduction of 1.11.3 is followed by TBS protection of the resulting hydroxyl group. Finally, oxidative cleavage of the alkene with ozone provides synthon 1.11.4 in an 80% yield over three steps (Scheme 1.11).
Scheme 1.11  Evans Forward Synthesis of (+)-Peloruside A (Part I)

The synthesis of ketone coupling partner 1.12.3 commenced with an aldol reaction of oxazolidinone 1.12.1 and a protected β-keto aldehyde to give alcohol 1.12.2 in 64% yield. Methylation of the free alcohol was achieved with methyl Meerwein and subsequent deprotection of the ketal under acidic conditions gave the desired ketone 1.12.3 in a 54% yield over three steps (Scheme 1.12).

Scheme 1.12  Evans Forward Synthesis of (+)-Peloruside A (Part II)

The aldol union of aldehyde 1.11.4 and ketone 1.12.3 was achieved in a highly diastereoselective fashion with 9-BBNOTf to give ketone 1.13.1 in an 82% yield. Subsequent 1,3-anti reduction of the ketone, regioselective protection of the least hindered alcohol as a TBS ether, methylation of the remaining alcohol, and a series of simultaneous deprotections and oxidations of the benzyl and TES ethers provided keto-aldehyde 1.13.2 in a 56% yield over five steps. A 1,5-anti aldol reaction produced ketone 1.13.3 in a high yielding and diastereoselective manner.
Protection of the alcohol as a silyl ether bearing a hydride enabled internal delivery of the hydride to give a 1,3-anti diisopropyl silylene. The silylene was then removed with TBAF and the desired alcohol was regioselectively methylated. Finally, the PMB ether was removed with DDQ to give a 58% yield of advanced intermediate 1.13.4 over 5 steps. To complete the synthesis, the chiral auxiliary was cleaved to give the carboxylic acid which was utilized in a macro lactonization to provide the desired macrocycle. A global deprotection with HCl resulted in formation of the natural product 1.4.1 in 45% yield over 3 steps (Scheme 1.13).

Scheme 1.13  Evans Forward Synthesis of (+)-Peloruside A (Part III)

The Hoye Synthesis

The Hoye group desired to apply a diastereoselective kinetic lactonization of a pseudo-symmetric azelaic acid derivative 1.14.2 and to capitalize on the versatility of relay ring-closing metathesis (RRCM) reactions. In their retrosynthetic analysis, they
hoped to affect a late-stage aldol coupling between the aldehyde acceptor 1.14.1 and methyl ketone donor 1.14.3. They planned to install the hindered Z-trisubstituted alkene in through RRCM of the silaketal 1.14.4. They envisioned the main aldehyde fragment 1.14.1 to arise from the C2-symmetric azelaic ester precursor 1.14.2.

Scheme 1.14  Hoye Retrosynthesis of (+)-Peloruside A

The synthesis of the first coupling fragment in the Hoye synthesis is presented in Scheme 1.15. Tertrol 1.15.2 was prepared from the ethylene ketal of dimethyl acetone dicarboxylate 1.15.1 by first utilizing a one-pot DIBAL-H reduction of both esters to give the intermediate 1,5-dialdehyde. Subsequent in situ double HWE homologation and Sharpless asymmetric dihydroxylation provided the desired compound 1.15.2. Exposure to catalytic aqueous HCl then promoted ketal metathesis by engagement of the C2 and C8 hydroxy groups to give a spirocyclic ketal as a single diastereomer. Installation of the methyl ethers found at C3 and C7 in peloruside A was achieved with Meerwein’s salt to provide 1.15.3. Transketalization
of 1.15.3 with ethanedithiol, MOM-ether protection of the C2/C8 diol, dithiolane removal, transesterification Otera’s catalyst smoothly and finally, use of hydrogen gas over Raney nickel provided a convenient route to C1-symmetric alcohol 1.15.4. Subsequent tetramethylguanidine promoted lactonization gave high levels of diastereoselectivity. Chemoselective reduction of the lactone was achieved with L-Selectride to provide a lactol, which was treated with prenyl bromide/indium. This sequence installed the gem-dimethylated C10 moiety, while simultaneously inducing relactonization. Removal of the two MOM groups, PMP acetal formation, and reprotection of the OH as a MOM ether gave 1.15.5. A series of functional/protecting group manipulations followed by the reinstatement of the C1 methyl ester and C11 aldehyde generation by ozonolysis completed the synthesis of 1.15.6 (Scheme 1.15).

Scheme 1.15  Hoye Forward Synthesis of (+)-Peloruside A (Part I)
To prepare the key RRCM substrate, 1.16.1 and 1.16.2 were sequentially loaded onto Ph₂SiCl₂. RRCM with Grubb’s 2nd Generation catalyst proceeded to give 1.16.3 in 38% yield over 2 steps. Efficient elaboration of 1.16.3 into the differentially protected diol derivative 1.16.4 was straightforward with desilylation and sequential TBS and PMB installations on the primary and secondary hydroxy groups, respectively. A modified Blaise reaction, wherein the reagent formed in situ from allyl 2-bromoacetate Zn⁰/Cp₂TiCl₂ converted the nitrile into an intermediate β-aminoenoate, the hydrolysis of which was achieved to afford the β-ketoester. The allyl ester was finally decarbalkoxylated with [Pd(PPh₃)₄] (HCO₂H, Et₃N) to give ketone 1.16.4 in a 36% yield over 6 steps (Scheme 1.16).

Scheme 1.16  Hoye Forward Synthesis of (+)-Peloruside A (Part II)

Conversion to the natural product was achieved by first coupling of 1.16.4 and 1.15.6 via a 1,5-anti aldol under conditions developed by Patterson to give 1.17.1 in a 64% yield. Reduction of the C13 ketone with Me₄NBH(OAc)₃ proceeded to give the 1,3-anti-diol which was then regioselectively methylated with Meerwein’s salt. Installation of a MOM ether at C11, removal of both PMB ethers, and saponification of the ester gave acid 1.17.2 in a high yielding manner. Yamaguchi
macrolactonization of the C15 alcohol followed by oxidation of the free C9 alcohol to the ketone was achieved with the Dess–Martin periodinane. Finally, the silyl and MOM ether protecting groups were sequentially removed by treatment first with HF·pyridine and then with 4N aqueous HCl to provide (+)-peloruside A in a 16% yield over 4 steps (Scheme 1.17).

Scheme 1.17  Hoye Forward Synthesis of (+)-Peloruside A (Part III)

The Jacobsen Synthesis

In the Jacobsen group’s synthetic plan, they wished to use their method of obtaining enantioenriched epoxides to serve as the key building blocks for the stereochemically complex macrocyclic framework. Like all previous total syntheses, they would employ a macrolactonization to form the macrocycle. Dissection of the seco-ester form of peloruside A into fragments of roughly equal size and complexity suggested aldehyde 1.18.2 and enone 1.18.3 as potentially useful late-stage intermediates. A second key strategic feature is a chiral-catalyst-controlled diastereoselective hetero-Diels–Alder reaction for the construction of intermediate
1.18.6. These fragments were envisioned to be prepared from enantioenriched epoxides which would control most of the developing stereocenters within the molecule (Scheme 1.18).

**Scheme 1.18** Jacobsen Retrosynthesis of (+)-Peloruside A

The Jacobsen synthesis of (+)-peloruside A began with a highly enantioselective Co-salen-catalyzed Payne rearrangement of meso-epoxy diol 1.19.1. Protection as the primary silyl ether in situ and subsequent alkylation of the secondary alcohol provided the bis-protected epoxide 1.19.2 in 56% yield over 3
steps. Epoxide **1.19.2** was subjected to a one-pot vinyl cuprate addition/methylation, followed by ozonolysis to provide aldehyde **1.19.3** in 66% overall yield. In an analogous manner, enantiopure aldehyde **1.19.6** was obtained from racemic epoxide **1.19.4** employing a sequence of a hydrolytic kinetic resolution, vinylation, alkylation, and ozonolysis (Scheme 1.19).

![Scheme 1.19](image)

**Scheme 1.19**  Jacobsen Forward Synthesis of (+)-Peloruside A (Part I)

Aldehyde **1.19.3** and diene **1.20.1** were engaged in a chiral chromium-catalyzed hetero-Diels–Alder reaction to give **1.20.2** in good yield and diastereoselectivity. Hydrogenation of **1.20.2** took place distereoselectively to provide **1.20.3** in 69% yield and 10:1 dr. Oxidation of the lactol and opening of the resulting lactone with N,O-dimethylamine HCl afforded Weinreb amide **1.20.4** which was protected as a TBS ether. Addition of isopropenylmagnesium bromide occurred with
cleavage of the acetate ester, which was then reprotected as the TBS ether to provide aldol coupling partner 1.20.5 (Scheme 1.20).

Scheme 1.20  Jacobsen Forward Synthesis of (+)-Peloruside A (Part II)

In Jacobsen’s approach to aldehyde 1.21.5, epoxide 1.21.1 was prepared in high ee then opened stereospecifically and regioselectively at the propargylic position. The resulting primary alcohol was protected as the TIPS ether to provide alkyne 1.21.2 in 72% yield over two steps. Silyl ether 1.21.2 was further elaborated to vinyl bromide 1.21.3 by a one-pot hydroboration/bromination/elimination/silyl deprotection sequence. Protection of the resultant primary alcohol as the benzyl ether provided compound 1.21.3 in 69% yield. Alcohol 1.21.4 was obtained in 5:1 dr and isolated in 64% yield by lithiation of 1.21.3 and its subsequent addition to aldehyde 1.19.6. The free alcohol of 1.21.4 was then protected as the PMB ether. The primary alcohol was selectively deprotected under aqueous acidic conditions and then oxidized with the Dess–Martin periodinane to provide aldehyde 1.21.5 in 58% yield over the three steps (Scheme 1.21).
**Scheme 1.21** Jacobsen Forward Synthesis of (+)-Peloruside A (Part III)

To begin the completion of the natural product, enone 1.20.5 and aldehyde 1.21.5 were coupled using a reductive aldol reaction. The primary TBS ether was then removed selectively using buffered HF-pyridine and the resulting alcohol was oxidized into aldehyde 1.22.1 in 38% yield over the three steps. Aldehyde 1.22.1 was then oxidized into the corresponding acid, and then subjected to DDQ to cleave the PMB ether and afford the macrolactonization precursor. The seco-acid was subjected to Yamaguchi conditions to provide the desired macrolactone. Finally, the benzyl protecting group was removed by transfer hydrogenolysis, and a subsequent global removal of the remaining protecting groups with aqueous HCl afforded (+)-peloruside A in 30% yield over the final 5 step sequence (Scheme 1.22).

**Scheme 1.22** Jacobsen Forward Synthesis of (+)-Peloruside A (Part IV)
1.5 Our Approach to the Total Synthesis of (+)-Peloruside A

As aforementioned, one of the many challenges associated with the synthesis of peloruside A is the construction of the macrocycle, and all previous total syntheses have utilized a macrolactonization for this purpose. While macrolactonization has become a reliable method for the synthesis of medium- to large-membered rings, it can at times provide modest yields, and there can be strategic advantages to other methods of macrocycle formation. Our lab has recently described the application of the Yamamoto vinylogous aldol reaction for the synthesis of medium-membered rings using non-enolizable aldehydes. These reactions proceed in good to excellent yields and with high levels of remote stereocontrol, and we wished to demonstrate the utility of this method in the context of natural product synthesis. The vinylogous aldol reaction, in one of its incarnations, produces an α,β-unsaturated ester, the alkene of which can be subjected to functionalization, and we targeted peloruside A for synthesis as this compound contains functionality that can be installed from the product of such an intramolecular vinylogous aldol reaction.

Retrosynthetic Analysis

We recognize that the most straightforward way of preparing the macrocycle in peloruside A via an intramolecular vinylogous aldol reaction would be to use aldehyde 1.23.2 as a cyclization precursor. After cyclization, the resulting alkoxide would potentially then cyclize onto the ketone to form the pyran functionality present
in the natural product. However, in both inter- and intramolecular cases, the Yamamoto vinylogous aldol reaction fails when the aldehyde coupling partner is unbranched and enolizable at the α-carbon. Clearly, the proposed aldehyde precursor bears an incompatible motif and another strategy needed to be developed to avoid this limitation (Scheme 1.23).

Scheme 1.23  Our Direct Retrosynthetic Analysis of (+)-Peloruside A

In order to avoid the use of an enolizable aldehyde in the macroaldolization step, Joe Abramite developed a strategy in which non-enolizable furfural derivative 1.24.3 would be utilized. Upon cyclization, this would provide a furyl alcohol 1.24.2 which could be subjected to the Achmatowicz oxidative rearrangement to provide a pyranone 1.24.1. This contains all the handles necessary to install the requisite functionality in the natural product (Scheme 1.24).
Our retrosynthetic analysis of (+)-peloruside A continues in Scheme 1.25 where crotonate ester 1.25.1 is envisioned to come from four commercially available fragments. As shown, the transformations required to convert these into to the β-hydroxy ketone 1.25.2, include a 1,3-anti reduction and selective functionalization of the C11-C13 diol. A disconnection at the C11-C12 linkage provides ketone 1.25.3 and aldehyde 1.25.4, which can be joined in a 1,5-anti aldol reaction. Ketone 1.25.3 can then prepared from a diastereoselective ene reaction between isobutylene and the aldehyde derived from protected (-)-ethyl lactate. A palladium catalyzed α-arylation reaction of substrates derived from methyl isobutyrate and 5-bromo-2-furoic acid would then give aldehyde 1.25.4 (Scheme 1.25).
Before embarking on the synthesis of (+)-peloruside A, Joe Abramite understood that an easily-prepared model system should be developed to test the key features of the synthetic plan. Therefore, intramolecular vinylogous aldol precursor 1.26.1 was prepared. Unfortunately, standard conditions developed by Abramite...
provided only 20% of the desired macrocycle 1.26.2. This material was isolated and subjected to the Achmatowicz oxidative rearrangement, which encouragingly provided a quantitative yield of pyranone 1.26.3. Isolation of the major side products in the Yamamoto intramolecular vinylogous aldol step indicated that enolization through the furan and subsequent addition to the aldehyde had occurred to provide dimeric products (Scheme 1.26).

**Scheme 1.26**  Intramolecular Vinylogous Aldol Reaction of Model System 1.26.1

To test the hypothesis that there was an undesired competitive enolization process occurring through the furan, a representative intermolecular reaction between methyl crotonate and 5-methyl furfural was examined. The results of this experiment were indeed in accordance with the hypothesis. Precomplexation of ATPH with the furfural does not block a bulky kinetic base like LTMP from deprotonating at its methyl terminus. The resulting extended enolate is free to add to other aldehydes in
solution, leading to the observed mixture of products. Although an undesired result in the current application, it is of note that this is a unique example of the utility of ATPH and is under further development (Scheme 1.27).

![Scheme 1.27 Enolization through a Furan with ATPH](image)

The enolization of the furan and subsequent low yielding cyclization of 1.26.1 could have potentially thwarted efforts toward the natural product by this method. However, examination of the proposed cyclization precursor 1.24.3 reveals that the offending site of enolization bares gem-dimethyl substitution. Because there are no enolizable protons in this position, the undesired reaction pathways could be avoided and it still could potentially be a successful method of preparing peloruside A.

A more representative model system 1.28.1 was, therefore, synthesized by Joe Abramite that bears an analogous gem-dimethyl substituent in the enolizable position. Upon application of the standard intramolecular vinylogous aldol reaction conditions, the desired macrocycle 1.28.2 was isolated in 87% yield, albeit in a relatively low 2:1 diastereoselectivity; however, we envisioned that increasing the rigidity and amount
of substitution along the backbone might improve the diastereoselectivity in the actual system (Scheme 1.28).

Scheme 1.28 Revised Model System for (+)-Peloruside A

Total Synthesis of (+)-Peloruside A

To begin the synthesis of (+)-peloruside A, Joe Abramite prepared aldehyde 1.29.3 in a sequence that I later repeated, as described below. 5-Bromo-2-furoic acid 1.29.1 was reduced with BH$_3$•THF to provide the corresponding alcohol which was protected as the TBS ether to provide bromofuran 1.29.2 in 94% yield over two steps (Scheme 1.29). Methyl isobutyrate was then subjected to α-arylation with bromofuran
1.29.2 under Hartwig’s conditions\textsuperscript{19} (Pd(dba)$_2$, P(r-Bu)$_3$, and Cy$_2$NLi) then reduced with DIBAL-H to provide aldehyde 1.29.3. This aldehyde was then coupled to ketone 1.30.4 using a 1,5-\textit{anti}-aldol reaction,\textsuperscript{20} as shown in Scheme 1.31.

![Scheme 1.29 Preparation of Aldehyde 1.29.3](image)

Ketone 1.30.3 was prepared from (-)-ethyl lactate by protection as the benzyl ether (benzyl trichloroacetimidate, catalytic TfOH), and reduction (DIBAL-H) to provide aldehyde 1.30.1 (Scheme 1.30). Subjection of this aldehyde to a chelation-controlled ene-reaction using 2-methyl propene as described by Mikami\textsuperscript{21} selectively provided alcohol 8 (>30:1 dr). Protection as the PMB ether (NaH, PMBCl) and oxidative cleavage (OsO$_4$, NaIO$_4$, 2,6-lutidine)\textsuperscript{22} provided methyl ketone 1.30.4 ready for coupling with aldehyde 1.29.3.


Scheme 1.30  Preparation of Ketone 1.30.3

The coupling of aldehyde 1.29.3 and methyl ketone 1.30.3 was accomplished using Evans’ conditions \((n\text{-Bu}_2\text{BOTf, }i\text{-Pr}_2\text{NEt})\)\(^{23}\) to provide 1.31.1 in 87\% yield and 7:1 diastereoselectivity (Scheme 1.31). Anti-selective hydroxyl-directed reduction \((\text{Me}_4\text{NBH(OAc)}_3)\)\(^{24}\) of 1.31.1 provided diol 1.31.2 which was protected as the diisopropyl silylene (1.31.3). Compound 1.31.3 was then treated with methyl lithium in the presence of HMPA followed by methyl iodide to provide 1.31.4 bearing a methyl ether at C-13 and a diisopropyl methyl silyl ether at C-11 as a single constitutional isomer to the limits of \(^1\text{H} \text{NMR} \) detection.\(^{25}\)

\(^{23}\) Evans, D. A.; Cote, B.; Coleman, P. J.; Connell, B. T. J. Am. Chem. Soc. 2003, 125, 10893.


Scheme 1.31 Preparation of Diisopropyl Methyl Silyl Ether 1.31.4

Deprotection of the C-16 PMB group (DDQ) resulted in simultaneous oxidation of the TBS ether at C-5 to provide hydroxy aldehyde 1.32.1. This fortuitous result is likely due to oxidation of the electron-rich furan by a mechanism similar to that of DDQ oxidation of a PMB ether to provide a silyl oxocarbenium ion which upon attack by water would provide the aldehyde (Scheme 1.32). Acylation with crotonic anhydride provided cyclization precursor 1.32.2 ready for the key intramolecular C-C bond forming reaction.

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We were pleased to find that subjection of compound \textbf{1.32.2} to the standard intramolecular vinylogous aldol reaction conditions (lithium 2,2,6,6-tetramethylpiperidine (LTMP), 2.0 equiv; aluminum tris- (2,6-diphenylphenoxide) (ATPH), 2.2 equiv; toluene/THF, -48 °C) provided the cyclized product in 86% yield as a 6:1 diastereomeric mixture. In order to determine the stereochemistry at C-5 of this material, the alkene was reduced (H$_2$, Pd/C, \textbf{1.33.2}) and the alcohol oxidized to provide ketone \textbf{1.33.3}. Reduction of the C-5-ketone with the (S)-CBS catalyst\textsuperscript{27} provided the C-5 R-alcohol (\textbf{1.33.4-R}) in greater than 25:1 diastereoselectivity while reduction with the (R)-CBS catalyst provided the C-5 S-alcohol (\textbf{1.33.4-S}) in 4:1 diastereoselectivity. The spectral data of \textbf{1.33.4-R} were identical to that of \textbf{1.33.2},

indicating that the product of the intramolecular vinylogous aldol reaction (1.33.1) bears the undesired configuration at C-5. While it is feasible that the stereochemistry at C-5 in compound 1.33.1 can be inverted, we instead studied a different cyclization precursor in order to directly obtain the desired stereochemical outcome as described below.

**Scheme 1.33** Intramolecular Vinylogous Aldol Reaction of 1.32.2 and Proof of Stereochemistry
We reasoned that the stereochemistry of the cyclization could be dictated by the conformation of the forming macrocycle, and that a different conformation could provide the desired stereochemical outcome. We therefore studied cyclization of silylene 1.34.1, which was prepared from silylene 1.31.3 by subjection to DDQ. Again, this resulted in the simultaneous deprotection of the PMB ether and oxidation at C-5 to provide the corresponding hydroxy aldehyde as observed on compound 1.31.4. Acylation with crotonic anhydride then provided cyclization precursor 1.34.1. Subjection of compound 1.34.1 to our intramolecular vinylogous aldol reaction conditions provided macrolide 1.34.2 in 84% yield, again as a 6:1 diastereomeric mixture.

Scheme 1.34  Preparation of Macrolide 1.34.2

The stereochemistry of the C-5 alcohol in 1.34.2 was determined by chemical correlation as described for macrolide 1.33.1 in Scheme 1.33, and was found to have the desired S-configuration (Scheme 1.35). The alkene was reduced (H₂, Pd/C, 1.35.1) and the alcohol oxidized to provide ketone 1.35.2. Reduction of the C-5-ketone with the (S)-CBS catalyst provided the C-5 R-alcohol (1.35.3-R) in greater
than 25:1 diastereoselectivity while reduction with the (R)-CBS catalyst provided the C-5 S-alcohol (1.35.3-S) in 4:1 diastereoselectivity. The spectral data of 1.35.3-S were identical to that of 1.35.1, indicating that the product of the intramolecular vinylogous aldol reaction (1.34.2) bears the desired configuration at C-5.

Scheme 1.35  Stereochemical Determination of Macrocycle 1.34.2

With the desired macrocycle 1.34.2 in hand, the dihydroxylation of the C2-C3 alkene was examined. Subjection of compound 1.34.2 to dihydroxylation using the Upjohn conditions (OsO₄, NMO)²⁸ provided a 3:1 mixture of diastereomers which showed an intrinsic preference for the β-diol as drawn, which is the required configuration.

stereochemistry for the synthesis of the natural product. The stereochemistry of these triols was determined by reagent-controlled dihydroxylations using AD-mix. Treatment of 1.34.2 with AD-mix-β provided a >10:1 mixture of 1.36.1 and 1.36.2. In acyclic systems, AD-mix-β is known to produce the β-diol, as drawn in Scheme 1.36. On the other hand, AD-mix-α should provide the α-diol, and in the dihydroxylation of 1.34.2, a 1.4:1 mixture of 1.36.1 and 1.36.2 is produced. These results strongly support the assigned stereochemistry depicted in Scheme 1.36, where AD-mix-β provides matched diastereoselectivity (>10:1 dr) and AD-mix-α provides mismatched diastereoselectivity (1.4:1 dr).

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<th>β : α</th>
</tr>
</thead>
<tbody>
<tr>
<td>OsO₄, NMO, 0 °C, 15 h</td>
<td>95</td>
<td>3 : 1</td>
</tr>
<tr>
<td>AD-mix-β, 0 °C, 3 days</td>
<td>&gt; 95</td>
<td>&gt; 10 : 1     (matched)</td>
</tr>
<tr>
<td>AD-mix-α, 0 °C, 3 days</td>
<td>81</td>
<td>1.4 : 1     (mis-matched)</td>
</tr>
</tbody>
</table>

**Scheme 1.36** Dihydroxylation of the C2-C2 Alkene

In order to differentiate the hydroxyls in the resulting triol 1.36.1, the hydroxyl group at C-5 of 1.34.2 was protected as a TES ether and the alkene subjected to dihydroxylation using AD-mix-β to provide the diol bearing the natural

---

sterechemistry in a 12:1 diastereomeric ratio. The stereochemistry of the product was established by subjection of compound 1.37.1 to acidic deprotection conditions, the product of which had identical spectra to that of triol 1.36.1 with the desired stereochemistry. Interestingly, selective removal of the TES ether in the presence of the silylene could be accomplished with PPTS while cleavage of the silylene in preference to the TES ether could be accomplished using HF• pyridine in 75% yield (data not shown).

Scheme 1.37  Preparation of Diol 1.37.1 and Proof of Stereochemistry

The C-2 hydroxyl group was then selectively protected as the TBS ether (TBSCI, imidazole), and the C-3 alcohol was methylated (trimethyloxonium tetrafluoroborate, proton sponge) (1.38.2, Scheme 1.38). With the installation of the protected diol complete, we turned our attention to the Achmatowicz reaction. We found that subjection of compound 1.38.2 to mild acid (PPTS, MeOH / DMF) selectively removed the TES group in preference to the silylene and TBS ethers to provide the desired C-5 alcohol. After careful optimization, we found that subjection of this alcohol 1.38.3 to Achmatowicz reaction conditions (m-CPBA in the presence of trichloroacetic acid) with careful monitoring by TLC induced the oxidative
rearrangement and provided the desired pyranone \textbf{1.38.4} in 64% yield which is in good postion for conversion to the natural product.

\textbf{Scheme 1.38} Preparation of Pyranone \textbf{1.38.4}

We next turned our attention to the diastereoselective dihydroxylation of the C7-C8 alkene of pyranone \textbf{1.38.4}. In order to achieve the desired stereochemistry in the natural product, we required an oxidant to approach the molecule from the $\beta$-face. We were encouraged to discover that in similar systems, O’Doherty observed dihydroxylation under Upjohn conditions (OsO$_4$ cat., NMO) from the opposite face of a protected, pseudo-axial allylic alcohol (Scheme 1.39).\textsuperscript{30}

Scheme 1.39  Literature precedence for desired Stereochemistry in Dihydroxylation

To mimic the precedented system, the pyranone ketone 1.38.4 was quantitatively reduced to the α- (equatorial) position by axial attack of a hydride under Luche conditions (NaBH₄, CeCl₃(H₂O)₇) (1.40.1, data not shown). Acylated (1.40.2) and TES (1.40.3) ether protected derivatives of the hydroxyl group were also prepared by straightforward means to provide the dihydroxylation precursors shown in Scheme 1.40 but, surprisingly, there was no conversion of any of these precursors to the dihydroxylated product using catalytic OsO₄. This is likely due to the hindered environment around the alkene. Under more forcing, superstoichiometric conditions, we did observe conversion to the diol but, disappointingly, the undesired stereochemistry was the only product observed.
It was hypothesized that the conformation about the macrolide was a contributing factor to the steric hindrance and blocking the β-face of the pyranone and that by adjusting the constraints about the macrolide would affect its conformation and thereby make the desired face of the alkene more accessible to dihydroxylation. This strategy had worked previously in reversing the stereoselectivity of the intramolecular vinylogous aldol, and as such, silylene-free intermediates 1.41.1 and 1.41.2 were prepared (data not shown) and subjected to the superstoichiometric conditions as described above (Scheme 1.41). Unfortunately, the undesired stereochemistry was again the only observed product of the reaction and a more in depth look at this dihydroxylation was merited.

**Scheme 1.40** Dihydroxylation of the C$_7$-C$_8$ Olefin in Macrolides 1.40.1-3

**Scheme 1.41** Dihydroxylation of the C$_7$-C$_8$ Olefin in Macrolides 1.41.1-2
A closer examination of the system revealed the reason for the observed undesired stereoselectivity of the reaction. In order for a reagent to approach the alkene from the β-face, it must overcome an energetically unfavorable, developing syn-pentane interaction with the C-10 gem-dimethyl substituent \textbf{1.42.2}. The α-face of the alkene has a less disfavorable interaction with the anomeric hydroxyl and is, therefore, more accessible to attack.

\textbf{Scheme 1.42} Rationale for undesired stereochemical outcome of the dihydroxylation of \textbf{1.42.1}

We proposed a strategy in which a directed dihydroxylation by a C-6 axial alcohol to the top face could be utilized (Scheme 1.43). Previously, Donahoe developed a method to prepare all syn triols by taking advantage of the tendency for a TMEDA/OsO₄ complex to hydrogen bond the free hydroxyl and therefore deliver the reagent to the same face as the alcohol. Interestingly, these osmate esters do not cleave under standard workup conditions but instead require a harsher hydrolysis mediated by acidic methanol, reductive cleavage with Na₂SO₃, or ligand swap with excess ethylenediamine. We hoped the same tactic could be applied to our system and therefore prepared the C-6 axial “up” alcohol \textbf{1.43.1} by asymmetric reduction of the ketone with CBS catalyst (Scheme 1.43).
As shown in Scheme 1.44 below, even under directing conditions, our intermediates (1.44.1-4) are prone to undergo dihydroxylation on the bottom face of the molecule. All of our intermediates contain the C₉ hemiketal alcohol, and it is possible that the stereochemical outcome observed in this process is due to hydrogen bonding of the OsO₄-TMEDA complex with this alcohol, but it is likely due to its hindered environment. However, we cannot dismiss our previous hypothesis; the unfavorable interaction of the incoming osmium reagent with the gem-dimethyl group (a developing syn-pentane-like interaction) prevents dihydroxylation on the top face of the molecule despite having a directing group on that face. As such, studying intermediates containing the protected alcohol at C₉ would be a worthwhile endeavor.
Scheme 1.44  Dihydroxylation of the C7-C8 Olefin in Macrolides 1.44.1-4

Pyran Model System Studies

In order to preserve these valuable advanced intermediates, a model system was developed to mimic the actual system and its synthesis is described below (Scheme 1.45, other systems were also studied and are discussed in the experimental). 2-Furoic acid 1.45.1 was subjected to a Friedel-Crafts alkylation (AlCl3, t-BuCl)
installing what would become the gem-dimethyl substituent in the model system. A CuO mediated decarboxylation of acid 1.45.2 with heating provided 2-t-butylfuran (1.45.3) in 40% yield over 2 steps. Lithiation α- to the furan oxygen and subsequent trapping by propionaldehyde provided the desired furyl alcohol 1.45.4 in good yield. This was subjected to an Achmatowicz oxidative rearrangement, providing the desired pyranone 1.45.5 as the only detectable diastereomer.

![Scheme 1.45 Preparation of model system 1.45.5](image)

To study the applicability of the model system to the actual system, pyranone 1.45.5 was dihydroxylated under identical conditions (OsO₄/TMEDA) providing an osmate ester 1.46.1 of unknown stereochemistry. Reduction of the ketone with NaBH₄ provided alcohol 1.46.2, the stereochemistry of which could be ascertained by an analysis of coupling constants. We were pleased to find that system performed analogously to the actual system, giving the all syn triol. In obtaining data that our model system mimics the reactivity of that in the actual system, we continued studying the dihydroxylation under several different conditions as described below.
We wished to further study the hydroxyl directed dihydroxylation on the model system. In the actual system the pyranone ketone was stereoselectively reduced to the β-position using the CBS catalyst. The model system we had prepared was racemic and would therefore not be amenable to an enantioselective reduction. While possible to prepare an enantioenriched model system, it was simpler to pursue a hydroxyl-directed reduction of the racemic ketone. Evans had previously developed a method using Me₄N(OAc)₃BH whereby reduction cannot occur unless the reagent is bound to a directing alcohol. This is a method of choice for preparing 1,2- and 1,3-anti-diols and it is so selective that even acetone can be used as a solvent in the reaction without undergoing reduction to i-PrOH. We hoped that the C-9 hemiketal hydroxyl of 1.45.5 could act as the binding site, thereby delivering the hydride across the ring to the bottom side of the ketone, resulting in the desired up stereochemistry in 1.47.1 (Scheme 1.47).

**Scheme 1.46** Dihydroxylation of pyranone 1.45.5

**Scheme 1.47** Proposed directed reduction of ketone 1.45.5

![Scheme 1.46](image-url)  
**Scheme 1.47** Proposed directed reduction of ketone 1.45.5
When the model system was subjected to the proposed conditions, ketone 1.48.1 was isolated in good yield (Scheme 1.48). While we did not achieve the desired directed reduction to the underside of the ketone, we did observe a product that is consistent with 1,4-conjugate addition of the hydride into the alkene of the α,β-unsaturated ketone. We propose a mechanism that involves direction of the hydride into the alkene in a conjugate fashion followed by elimination of the hemiketal alcohol. To the best of our knowledge, this is a novel observation and although not applicable to our current system of interest, this reactivity could potentially have utility in the stereoselective, hydroxyl directed reduction of γ-hydroxy-α,β-unsaturated enones. The development and optimization of this reaction, however, is beyond the scope of this thesis research.

\[
\begin{array}{ccc}
\text{H} & \text{O} & \text{OH} \\
\text{H} & \text{O} & \text{OH} \\
\text{Me}_2\text{N(OAc)}_2\text{BH} & \text{Me}_2\text{N(OAc)}_2\text{BH} & \text{Me}_2\text{N(OAc)}_2\text{BH}
\end{array}
\]

Potential Utility:

\[
\begin{array}{ccc}
\text{H} & \text{O} & \text{OH} \\
\text{H} & \text{O} & \text{OH} \\
\end{array}
\]

Scheme 1.48  Directed reduction of ketone 1.45.5

As aforementioned, studying intermediates containing the protected alcohol at C9 would be a worthwhile endeavor. We, therefore, studied conditions (TMSCI, DMAP, imid., DMF) that would protect the very sterically hindered C-9 hydroxyl as a TMS ether 1.49.1. We hypothesized that the large silyl group would block the bottom face of the alkene and force the dihydroxylation to come from the top face
despite the developing syn pentane interaction it must overcome. Gratifyingly, stoichiometric dihydroxylation of the TMS ether 1.49.1 (OsO₄/TMEDA) provided a new product of unknown stereochemistry 1.49.2.

In order to prove the stereochemistry by coupling constant analysis, we reduced the ketone 1.49.2 with NaBH₄ (1.49.3, Scheme 1.49). The corresponding reduction in the actual system under these conditions provides the α-alcohol, and we expected the same outcome in the model system. However, with compound 1.49.2, NaBH₄ attacked from the α-face to provide alcohol 1.49.3 of β-stereochemistry. This was initial evidence of obtaining the desired stereochemistry in the dihydroxylation step because a bulky osmate ester on the α-face would hinder hydride attack from the α-face of the carbonyl and favor β-attack. A closer examination of the coupling constants of triol 1.49.4 indicated that we had indeed obtained the desired stereochemistry in the dihydroxylation.

Scheme 1.49  Synthesis of triol 1.49.4

With conditions identified that gave the desired stereochemistry of the dihydroxylation in the model system, we focused on their application to the actual system. Regrettably, none of the attempted protections of the hemiketal were
achieved (Scheme 1.50). It became clear that the hydroxyl of the actual system was more sterically hindered and could not be functionalized even under forcing conditions.

**Scheme 1.50** Attempted protection of 1.38.4

The significant challenges associated with conversion of the substrates that were studied to the natural product led us to investigate alternative strategies to complete the synthesis of (+)-peloruside A. Although we had devised a novel solution to the limitations of the intramolecular Yamamoto vinylogous aldol reaction, the current non-enolizable aldehyde strategy presented us with obstacles that would not have to be faced if a method existed for the use of enolizable aldehyde coupling partners (Scheme 1.51). Most notably, the diastereoselective dihydroxylation of the C7-C8 alkene and deoxygenation at C6 would be avoided. While we have not completely exhausted the set of conditions to prepare the target molecule by this route, we felt it necessary to step back and more closely examine the fundamental aspects of the Yamamoto vinylogous aldol reaction.
Scheme 1.51  Proposed Yamamoto intramolecular vinylogous aldol reaction with enolizable aldehyde coupling partner 1.51.1.

1.6 Experimental

All reactions were performed in oven-dried or flame-dried glassware under a dry nitrogen atmosphere. Toluene was washed with concentrated H$_2$SO$_4$, H$_2$O, 1 M NaOH, H$_2$O, dried over MgSO$_4$, filtered and distilled from CaH$_2$ under nitrogen prior to use. MeOH, CH$_2$Cl$_2$, Et$_3$N, 2,2,6,6-tetramethylpiperidine, 2,6-lutidine, and HMPA, were distilled from CaH$_2$ under nitrogen prior to use. DMF was distilled at reduced pressure from CaH$_2$. DMSO was distilled from CaH$_2$ and stored over 4 Å molecular sieves prior to use. THF and Et$_2$O were distilled from Na benzophenone ketyl under nitrogen prior to use. Crotonic anhydride was fractionally distilled at reduced pressure. 85% MCPBA was purified by dissolving in CH$_2$Cl$_2$ and washing with pH 7.5 phosphate buffer (1M). All other chemicals were used as received from the supplier. Cy$_2$NLi was purchased as a solid from Aldrich chemical company and
suspended in dry, distilled toluene (weighed and transferred in a glove bag under nitrogen) prior to use. Flash chromatography was performed using 60 Å silica gel (37-75 μ). $^1$H NMR spectra were recorded at either 400 MHz or 500 MHz in CDCl$_3$ using residual CHCl$_3$ (7.24 ppm) as the internal reference. $^{13}$C NMR spectra were recorded at 75 MHz or 100 MHz in CDCl$_3$ using residual CHCl$_3$ (77.26 ppm) as the internal reference. Infrared (IR) spectra were obtained as thin films on NaCl plates. Exact mass was determined using electrospray ionization.

$^{(5\text{-bromofuran-2-yl})\text{methoxy}}(\text{tert-butyl})\text{dimethylsilane (1.29.2)}$:

![Chemical diagram](attachment:image.png)

This reaction was performed according to the procedure of Joe Abramite.$^{31}$ Borane (500 mL of 1 M solution in THF, 0.5 mol, 2.0 equiv) was slowly added (over ~ 4 hours) to a solution of 5-bromo-2-furoic acid (49.6 g, 0.26 mol, 1.0 equiv) in THF (0.3 L) at 0 °C. The reaction was warmed to room temperature and stirred for 2 days. (Note: This reaction was also performed with BH$_3$$\cdot$SMe$_2$ and provided similar results.) The reaction was quenched by adding MeOH slowly at 0 °C until the evolution of H$_2$ gas subsided. The solution was warmed to room temperature; more MeOH (~200 mL) was added and the solution was stirred for 1 hr. The majority of

the solvent was removed under reduced pressure to provide a solution of the crude product in approximately 50 mL of solvent. A MeOH (200 mL) solvent exchange wherein MeOH was added then distilled at reduced pressure was performed twice to remove residual boron species as trimethylborate. A pentane (200 mL) solvent exchange was then performed twice to remove the residual MeOH. The crude bromo-furyl alcohol was carried on to the next step without purification. Note that warming this material or exposure to silica gel results in a mildly exothermic decomposition to provide a blue/black tarry substance.

TBSCl (43.1 g, 0.29 mol, 1.1 equiv), imidazole (21.3 g, 0.31 mol, 1.2 equiv), and DMAP (0.5 g, 4 mmol, 1 mol %) were added sequentially to a solution of the crude alcohol (assumed to be 0.26 mol, 1 equiv) in CH₂Cl₂ (1 L) at 0 °C. The reaction was warmed to room temperature and stir for approximately 1 hr, after which time TLC indicated complete conversion to the TBS ether. The reaction mixture was filtered through Celite, and the filtrate was washed with dilute HCl and brine, dried over MgSO₄, and concentrated under reduced pressure. The crude product was purified by flash chromatography (30:1 hexanes:EtOAc) to provide 5¹ (70 g, 0.24 mol, 94% over two steps).

¹H NMR (500 MHz; CDCl₃): δ 6.21 (d, J = 3.2, 1H), 6.19 (d, J = 3.2, 1H), 4.57 (s, 2H), 1.03 – 0.72 (m, 9H), 0.20 – -0.03 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 156.62, 121.33, 112.06, 110.12, 58.27, 26.10, 18.64, -4.99; HRMS (ESI) m/z calc’d for C₅H₄OBr [M - HOTBS]⁺: 158.9446; found: 158.9451.
Methyl 2-(5-((tert-butyldimethylsilyloxy)methyl)furan-2-yl)-2-methylpropanoate (1.29.2a)$^{31}$

A suspension of Cy$_2$NLi (66.7 mL of a 0.8 M suspension in toluene, 53.3 mmol, 1.6 equiv) was cannulated into a flask containing methyl isobutyrate (3.75 g, 36.7 mmol, 1.1 equiv) at 0 ºC. This mixture was stirred for 10 minutes and the resulting solution was cannulated into another flask containing bromofuran 1.29.2 (9.70 g, 33.3 mmol, 1.0 equiv) and Pd(dba)$_2$ (0.46 g, 0.5 mmol, 1.5 mol %). A solution of PrBu$_3$ (3.0 mL of 0.17 M in toluene, 0.5 mmol, 1.5 mol %) was added, and the reaction was then stirred at room temperature overnight (15 hours). The solvent was removed under reduced pressure, and a solution of 5:1 hexanes to EtOAc (~150 mL) was added to the crude mixture. This mixture was washed with 1 M HCl (3 x 100 mL), filtered through filter paper, and washed with water (100 mL), and brine (50 mL), dried over MgSO$_4$, and concentrated under reduced pressure. The crude material was purified by flash chromatography (gradient, hexanes to 10:1 hexanes:EtOAc) to provide 1.29.2a (7.7 g, 24.6 mmol, 90%).

$^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 6.15 (d, $J = 3.2$, 1H), 6.07 (d, $J = 3.2$, 1H), 4.60 (s, 2H), 3.66 (s, 3H), 1.54 (s, 6H), 0.92 – 0.86 (m, 9H), 0.08 – 0.05 (m, 6H). $^{13}$C NMR (100 MHz; CDCl$_3$): $\delta$ 157.28, 153.59, 108.13, 105.63, 77.56, 77.44, 77.24,
76.92, 58.42, 52.59, 43.65, 26.05, 24.76, 18.57, -5.00; HRMS (ESI) m/z calc’d for C\textsubscript{10}H\textsubscript{13}O\textsubscript{3} [M - HOTBS]\textsuperscript{+}: 181.0865; found: 181.0862.

2-(5-((tert-butyldimethylsilyloxy)methyl)furan-2-yl)-2-methylpropanal (1.29.3\textsuperscript{31}):

\[
\begin{array}{c}
\text{MeO} \quad \text{OTBS} \\
1.29.2a \quad \text{DIBAL-H} \quad \rightarrow \quad \text{OTBS} \\
\end{array}
\]

DIBAL-H (14.4 mL 1.0 M solution in hexanes, 14.4 mmol, 1.1 equiv) was added dropwise via cannula to a solution of ester 1.29.2a (4.1 g, 13.1 mmol, 1.0 equiv) in Et\textsubscript{2}O (50 mL) at -78 °C. The reaction was stirred for 1 hr at -78 °C, and then excess DIBAL-H was quenched with EtOAc (~20 mL). The reaction was then cannulated into a vigorously stirred solution of saturated Rochelle’s salt (50 mL). This biphasic mixture was stirred at room temperature for 2 hours, after which time the organic phase was separated, washed with brine, dried over MgSO\textsubscript{4}, and concentrated under reduced pressure. The crude material was purified by flash chromatography (30:1 hexanes:EtOAc) to provide aldehyde 1.29.3 (3.2 g, 11.5 mmol, 88%).

\[^1\text{H} \text{NMR (500 MHz; CDCl}_3\):} \quad \delta \text{ 9.48 (s, 1H), 6.17 (d, } J = 3.2, 1\text{H}, 6.11 (d, } J = 3.2, 1\text{H), 4.58 (s, 2H), } 1.39 (s, 6\text{H), 0.98 – 0.76 (m, 9H), 0.14 – -0.10 (m, 6H).} \] \[^{13}\text{C NMR (100 MHz; CDCl}_3\):} \quad \delta \text{ 200.41, 154.98, 154.79, 108.42, 107.39, 58.38, 48.21, 26.05, 20.67, 18.60, -5.00.} \]
(2S,3S)-2-(benzyloxy)-5-methylhex-5-en-3-ol (8)\textsuperscript{31}:

![Chemical reaction diagram]

Aldehyde 1.30.1 was prepared from (-)-ethyl lactate following known literature procedures (88\% over two steps).\textsuperscript{32} Aldehyde 1.30.1 was then converted to alcohol 1.30.2 via a known literature procedure (89\%, \textgreater 30:1 dr).\textsuperscript{21}

\textbf{(S)-ethyl 2-(benzyloxy)propanoate:} \textsuperscript{1}H NMR (500 MHz; CDCl\textsubscript{3}): \(\delta\) 7.42 – 7.25 (m, 5H), 4.68 (d, \(J = 11.6\), 1H), 4.43 (d, \(J = 11.6\), 1H), 4.26 – 4.13 (m, 2H), 4.03 (q, \(J = 6.9\), 1H), 1.42 (d, \(J = 6.9\), 3H), 1.28 (t, \(J = 7.1\), 3H).

\textbf{1.30.1:} \textsuperscript{1}H NMR (500 MHz; CDCl\textsubscript{3}): \(\delta\) 9.65 (d, \(J = 1.8\), 1H), 7.41 – 7.27 (m, 5H), 4.61 (q, \(J = 11.7\), 2H), 3.88 (qd, \(J = 1.8\), 7.0, 1H), 1.32 (d, \(J = 7.0\), 3H).

\textbf{1.30.2:} \textsuperscript{1}H NMR (500 MHz; CDCl\textsubscript{3}): \(\delta\) 7.37 – 7.26 (m, 5H), 4.88 – 4.73 (m, 2H), 4.66 (d, \(J = 11.5\), 1H), 4.45 (d, \(J = 11.5\), 1H), 3.69 – 3.60 (m, 1H), 3.44 (p, \(J = 6.2\), 1H), 2.42 (d, \(J = 3.8\), 1H), 2.26 – 2.13 (m, 2H), 1.76 (s, 3H), 1.23 – 1.18 (m, 3H);

\textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 142.95, 138.62, 128.69, 128.04, 127.97, 113.20, 77.92, 72.76, 71.37, 41.76, 22.70, 15.86; HRMS (ESI) \(m/z\) calcd for C\textsubscript{14}H\textsubscript{20}O\textsubscript{2}Na \([M+Na]^+\): 243.1361; found: 243.1360.

1-(((2S,3S)-2-(benzyloxy)-5-methylhex-5-en-3-yloxy)methyl)-4-methoxybenzene (1.30.2a)\textsuperscript{31}:

A solution of alcohol 1.30.2 (0.86 g, 3.9 mmol, 1.0 equiv) in DMF (5 mL) was slowly added via cannula to stirred mixture of \textit{p}-methoxybenzyl chloride (0.79 mL, 5.9 mmol, 1.5 equiv) and sodium hydride (0.24 g 60% in mineral oil, 5.9 mmol, 1.5 equiv) in DMF (5 mL) at 0 °C. The reaction was warmed to room temperature. After 4 hours, saturated NaHCO\textsubscript{3} (10 mL), water (20 mL), hexanes (20 mL), and EtOAc (5 mL) were added sequentially. The organic phase was separated, washed with water, 1 M CuSO\textsubscript{4} and brine, dried over MgSO\textsubscript{4}, and concentrated under reduced pressure. The crude product was purified by flash chromatography (gradient, hexanes to 10:1 hexanes:EtOAc) to provide olefin 1.30.2a (1.3 g, 3.8 mmol, 97%).

\textsuperscript{1}H NMR (500 MHz; CDCl\textsubscript{3}): δ 7.39 – 7.30 (m, 5H), 7.28 – 7.24 (m, 2H), 6.91 – 6.85 (m, 2H), 4.81 (d, J = 14.8, 2H), 4.64 (d, J = 11.9, 1H), 4.57 – 4.50 (m, 3H), 3.83 (s, 3H), 3.72 – 3.64 (m, 1H), 3.63 - 3.58 (m, 1H), 2.36 (dd, J = 3.8, 14.1, 1H), 2.25 (dd, J = 8.6, 14.2, 1H), 1.75 (s, 3H), 1.20 (d, J = 6.3, 3H). \textsuperscript{13}C NMR (100 MHz; CDCl\textsubscript{3}): δ 159.37, 143.46, 139.18, 131.17, 129.83, 128.59, 127.95, 127.74, 127.69, 113.91, 112.84, 79.43, 77.54, 75.79, 72.46, 71.55, 55.54, 38.49, 23.19, 15.44. [α]\textsubscript{D} = +20.7 (c 2.65, CHCl\textsubscript{3}). IR (cm\textsuperscript{-1}): 3068, 3032, 2935, 2864, 1612, 1513, 1454, 1174, 1092, 1037, 888, 821, 738, 698;
(4S,5S)-5-(benzyloxy)-4-(4-methoxybenzyloxy)hexan-2-one (1.30.3):}

\[
\begin{align*}
\text{PMBO} & \quad \text{OsO}_4, \text{NaIO}_4, 2,6\text{-lutidine} & \quad \text{PMBO} \\
1.30.2a & \quad \text{O} & \quad 1.30.3
\end{align*}
\]

2,6-Lutidine (0.77 mL, 6.6 mmol, 2.0 equiv), OsO\(_4\) (0.66 mL 0.1 M in water, 0.07 mmol, 2 mol %), and sodium periodate (2.82 g, 13.2 mmol, 4.0 equiv) were added sequentially to a solution of olefin 1.30.2a (1.12 g, 3.3 mmol, 1.0 equiv) in 3:1 dioxane:H\(_2\)O (32 mL) at room temperature. After stirring overnight (20 h), the reaction mixture was diluted with water (50 mL) and CH\(_2\)Cl\(_2\) (100 mL). The organic phase was separated, and the aqueous phases was extracted with CH\(_2\)Cl\(_2\) (2 x 50 mL). The combined organic phases were washed with brine, dried over MgSO\(_4\), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (gradient, hexanes to 2:1 hexanes:EtOAc) to provide ketone 1.30.3 (1.1 g, 3.1 mmol, 95%).

\(^1\)H NMR (500 MHz; CDCl\(_3\)): \(\delta 7.35 - 7.25\) (m, 5H), 7.21 - 7.16 (m, 2H), 6.86 - 6.79 (m, 2H), 4.54 (d, \(J = 11.9\), 1H), 4.47 (s, 2H), 4.46 - 4.41 (m, 1H), 4.10 - 4.03 (m, 1H), 3.77 (s, 3H), 3.64 (qd, \(J = 4.5, 6.4\), 1H), 2.68 - 2.62 (m, 2H), 2.09 (s, 3H), 1.14 (d, \(J = 6.4\), 3H). \(^{13}\)C NMR (100 MHz; CDCl\(_3\)): \(\delta 207.93, 159.46, 138.78, 130.80, 129.85, 128.63, 127.98, 127.86, 113.98, 94.66, 77.50, 76.48, 74.76, 72.76, 71.31, 55.53, 44.03, 31.37, 14.83.\) \([\alpha]\)_D \(= +7.0\) (c 0.690, CHCl\(_3\)). IR (cm\(^{-1}\)): 2933, 2857, 1716, 1612, 1513, 1248, 1091, 822, 740; HRMS (ESI) \(m/z\) calc’d for C\(_{21}\)H\(_{26}\)O\(_4\)Na [M+Na]\(^+\): 365.1729; found: 365.1718.
(3S,7S,8S)-8-(benzyloxy)-2-(5-((tert-butyldimethylsilyloxy)methyl)furan-2-yl)-3-hydroxy-7-(4-methoxybenzylloxy)-2-methylnonan-5-one (1.31.3)\textsuperscript{31}:

Diisopropylethylamine (0.71 mL, 4.1 mmol, 1.55 equiv) was added to a solution of ketone 1.30.3 (0.90 g, 2.6 mmol, 1.0 equiv) in Et\textsubscript{2}O (26 mL) at room temperature. This solution was cooled to approximately -100 °C (using a refrigerated Et\textsubscript{2}O/dry ice/liquid N\textsubscript{2} bath), and nBu\textsubscript{2}BOTf (3.7 mL 1 M in CH\textsubscript{2}Cl\textsubscript{2}, 3.7 mmol, 1.4 equiv) was added dropwise over ~3 min. Following the addition, the reaction was stirred for 30 min, after which time a solution of aldehyde 1.29.3 (0.89 g, 3.2 mmol, 1.2 equiv) in Et\textsubscript{2}O (7 mL) was slowly added (~ 1 hr) via cannula. The reaction was maintained between -100 °C and -90 °C for 5 hr, and then the addition of liquid nitrogen was ceased and the solution warmed to -78 °C and stirred for 1 hr. TLC indicated that the reaction was complete, and a solution of 6:1 MeOH to pH 7 buffer (33 mL) was added. The reaction mixture was warmed to 0 °C (ice bath), and the septum was removed and a solution of 2:1 MeOH to 30% H\textsubscript{2}O\textsubscript{2} (27 mL) was added dropwise via pipet over ~15 minutes in order to avoid an exotherm. The reaction was warmed to room temperature and stirred for 2 hours. The mixture was diluted with a solution of 1:1 hexanes to EtOAc (200 mL), and cooled in an ice bath. A dilute solution of aqueous K\textsubscript{2}CO\textsubscript{3} was then added dropwise over 15 minutes (caution, gas evolution!). This biphasic mixture was vigorously stirred for 2 hours, then the
organic phase was separated, washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (gradient, 10:1 to 2:1 hexanes:EtOAc) to provide alcohol **1.31.1** (1.43 g, 2.3 mmol, 87%, obtained as a ~6:1 mixture of diastereomers from which the minor diastereomer was removed in subsequent steps.).

**1H NMR** (500 MHz; CDCl₃): δ 7.34 – 7.25 (m, 5H), 7.16 (d, \( J = 8.7, \) 2H), 6.84 – 6.79 (m, 2H), 6.10 (d, \( J = 3.1, \) 1H), 5.96 (d, \( J = 3.1, \) 1H), 4.56 (s, 2H), 4.50 (d, \( J = 11.9, \) 1H), 4.44 (s, 2H), 4.42 (d, \( J = 11.9, \) 1H), 4.05 (dt, \( J = 4.6, 9.2, \) 1H), 3.78 – 3.73 (m, 4H), 3.61 (dd, \( J = 4.6, 6.4, \) 1H), 2.67 – 2.55 (m, 2H), 2.45 – 2.36 (m, 2H), 1.24 (s, 3H), 1.20 (s, 3H), 1.11 (d, \( J = 6.4, \) 3H), 0.88 – 0.85 (m, 9H), 0.06 – 0.03 (m, 6H). **13C NMR** (101 MHz, CDCl₃) δ 210.68, 160.01, 159.42, 153.20, 138.74, 138.66, 130.76, 130.67, 130.61, 129.85, 129.80, 128.59, 127.94, 127.92, 127.82, 113.95, 108.08, 106.04, 76.56, 76.44, 76.20, 74.79, 74.72, 74.67, 73.32, 72.79, 72.71, 71.27, 58.44, 55.49, 46.41, 46.18, 44.00, 43.94, 43.84, 40.26, 31.33, 26.08, 23.89, 23.78, 21.76, 21.51, 18.60, 14.79, 14.73, -4.92. \([\square]_D^1 = +2.7 (c 1.00, \text{CHCl}_3)\). **IR (cm}⁻¹):** 3503, 2932, 2858, 1715, 1614, 1514, 1463, 1380, 1249, 1079, 837. **HRMS (ESI) m/z** calc’d for C₃₆H₅₂O₇NaSi [M+Na]^+: 647.3380; found: 647.3384.
(3S,5S,7S,8S)-8-(benzyloxy)-2-(5-((tert-butyldimethylsilyloxy)methyl)furan-2-yl)-7-(4-methoxybenzyloxy)-2-methylnonane-3,5-diol (1.31.2)\textsuperscript{31}: 

\[ \text{Me}_4\text{NBH(OAc)}_3 \] (0.26 g, 1.0 mmol, 5.0 equiv) was added to a solution of acetonitrile (0.5 mL) and acetic acid (1.0 mL) at room temperature. After 10 min, the solution was cooled to -20 °C, and a solution of alcohol 1.31.1 (0.12 g, 0.2 mmol, 1.0 equiv) in acetonitrile (0.5 mL) was added via cannula. The reaction was stirred overnight (20 h) at -20 °C. A solution of saturated Rochelle’s salt (5 mL) was then added and reaction was stirred at room temperature for 10 min. The reaction mixture was extracted with CH\(_2\)Cl\(_2\) (2 x 10 mL). The combined organic extracts were washed with saturated NaHCO\(_3\) and brine, dried over MgSO\(_4\), filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (gradient, 5:1 to 2:1 hexanes:EtOAc) to provide diol 1.31.2 (0.12 g, 0.12 mmol, 93%).

\(^1\)H NMR (500 MHz; CDCl\(_3\)): \( \delta \) 7.37 – 7.26 (m, 6H), 7.19 – 7.14 (m, 2H), 6.86 – 6.80 (m, 2H), 6.10 (d, \( J = 3.1 \), 1H), 5.97 (d, \( J = 3.1 \), 1H), 4.60 (d, \( J = 5.2 \), 1H), 4.58 (d, \( J = 4.2 \), 1H), 4.56 (s, 2H), 4.49 – 4.45 (m, 1H), 4.39 (d, \( J = 10.9 \), 1H), 4.01 (s, 1H), 3.94 (dt, \( J = 4.2 \), 8.7, 1H), 3.79 – 3.77 (m, 4H), 3.76 – 3.69 (m, 2H), 2.62 (d, \( J = 4.2 \), 1H), 1.74 – 1.61 (m, 2H), 1.47 – 1.39 (m, 2H), 1.24 (s, 3H), 1.23 (s, 3H), 1.15 (d, \( J = 6.1 \), 4H), 0.90 – 0.83 (m, 9H), 0.08 – 0.03 (m, 6H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \)
165.36, 159.11, 155.41, 143.96, 138.89, 128.50, 128.08, 127.68, 124.49, 106.58, 106.23, 75.52, 75.37, 73.00, 71.39, 67.86, 67.08, 42.48, 41.73, 35.58, 34.93, 25.77, 19.47, 17.45, 17.30, 17.23, 17.15, 16.02, 13.42, 13.24, 6.89, 4.82. [α]_D = -13.1 (c 0.890, CHCl₃). IR (cm⁻¹): 3449, 2930, 2858, 1612, 1513, 1250, 1076, 837; HRMS (ESI) m/z calcd for C₃₆H₅₅O₇Si [M+H]⁺: 627.3717; found: 627.3731.

(4R,6S)-4-((2S,3S)-3-(benzyloxy)-2-(4-methoxybenzoyloxy)butyl)-6-(2-((5-((tert-butyldimethylsilyloxy)methyl)furan-2-yl)propan-2-yl)-2,2-diisopropyl-1,3,2-dioxasilinane (1.31.3)₃¹:

DMAP (0.205 g, 1.68 mmol, 0.2 equiv), triethylamine (2.9 mL, 21 mmol, 2.5 equiv), and dichlorodiisopropyl silane (2.27 mL, 12.6 mmol, 1.5 equiv) were added sequentially to a solution of diol 1.31.2 (5.26 g, 8.39 mmol, 1.0 equiv) in DMF (84 mL) at room temperature. The reaction was stirred at room temperature for 12 hours then quenched with saturated NaHCO₃. The mixture was diluted with 1:1 Hexanes/EtOAc and poured into water. The organic phase was separated, washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (gradient, CH₂Cl₂ to 10:10:1 CH₂Cl₂:hexanes:Et₂O) to provide silylene 1.31.3 (5.89 g, 7.97 mmol, 95%).
$^1$H NMR (500 MHz, CDCl$_3$) δ 7.32 – 7.25 (m, 5H), 7.21 – 7.15 (m, 2H), 6.85 – 6.79 (m, 2H), 6.08 (d, $J = 3.1$ Hz, 1H), 5.91 (d, $J = 3.1$ Hz, 1H), 4.59 – 4.51 (m, 3H), 4.48 – 4.42 (m, 2H), 4.39 (d, $J = 11.4$ Hz, 1H), 4.14 – 4.04 (m, 2H), 3.78 (s, 3H), 3.67 – 3.59 (m, 1H), 3.40 (dd, $J = 10.9$, 6.4 Hz, 1H), 1.87 (dt, $J = 14.4$, 7.3 Hz, 1H), 1.75 – 1.57 (m, 2H), 1.27 (dt, $J = 14.5$, 2.2 Hz, 1H), 1.23 (s, 3H), 1.19 (s, 3H), 1.14 (d, $J = 6.3$ Hz, 3H), 0.98 (dd, $J = 7.2$, 4.1 Hz, 6H), 0.92 (ddd, $J = 9.9$, 6.6, 3.3 Hz, 6H), 0.89 – 0.85 (m, 10H), 0.04 (d, $J = 2.2$ Hz, 6H). $^{13}$C NMR (100 MHz; CDCl$_3$): δ 160.58, 152.71, 139.08, 131.19, 129.71, 128.53, 128.00, 127.71, 113.87, 107.97, 105.71, 77.92, 77.48, 75.13, 73.89, 72.01, 71.11, 69.03, 58.54, 55.52, 41.27, 37.03, 34.67, 26.14, 24.46, 20.68, 17.24, 17.14, 17.06, 15.42, 13.96, 13.26, -4.89. $[\alpha]_D^{\text{D}} = +12.6$ (c 0.170, CHCl$_3$). IR (cm$^{-1}$): 2931, 2860, 1513, 1464, 1249, 1079, 837.

5-(2-((4S,6R)-6-((2S,3S)-3-(benzyloxy)-2-hydroxybutyl)-2,2-diisopropyl-1,3,2-dioxasilinan-4-yl)propan-2-yl)furan-2-carbaldehyde (1.34.1a)$^{31}$:

![Chemical Structure](image)

DDQ (4.3 g, 18.8 mmol, 2.3 equiv) was added to a solution of furan 1.31.3 (6.0 g, 8.1 mmol, 1.0 equiv) in 10:1 CH$_2$Cl$_2$ to H$_2$O (165 mL, biphasic). The solution was heated to reflux for 1 hour, then cooled to room temperature and quenched with saturated NaHCO$_3$ (150 mL). The organic phase was separated, washed with water and brine, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The
crude product was purified by flash chromatography (gradient, hexanes to 5:1 hexanes:EtOAc) to provide the desired hydroxy aldehyde 1.34.1a (2.9 g, 5.8 mmol, 72%).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 9.52 (s, 1H), 7.36 – 7.25 (m, 5H), 7.15 (d, \(J = 3.6\) Hz, 1H), 6.29 (d, \(J = 3.6\) Hz, 1H), 4.62 (d, \(J = 11.8\) Hz, 1H), 4.45 (d, \(J = 11.8\) Hz, 1H), 4.34 – 4.26 (m, 1H), 4.18 (dd, \(J = 9.9, 2.4\) Hz, 1H), 3.70 – 3.62 (m, 1H), 3.53 – 3.44 (m, 1H), 3.36 (d, \(J = 2.4\) Hz, 1H), 1.89 – 1.75 (m, 2H), 1.56 – 1.46 (m, 2H), 1.33 (s, 3H), 1.31 (s, 3H), 1.17 (d, \(J = 6.3\) Hz, 3H), 1.00 – 0.78 (m, 18H). \(^1\)C NMR (100 MHz; CDCl\(_3\)): \(\delta\) 177.39, 168.22, 138.80, 128.65, 128.05, 127.91, 109.21, 77.48, 74.13, 73.77, 71.80, 71.29, 42.22, 38.30, 35.39, 23.29, 21.58, 17.04, 17.02, 16.95, 16.80, 15.04, 13.67, 13.19. \([\alpha]_D = +16.5\) (c 0.280, CHCl\(_3\)). IR (cm\(^{-1}\)): 3489, 2943, 2866, 1680, 1512, 1464, 1385, 1248, 1107, 920, 803, 697; HRMS (ESI) \(m/z\) calc’d for C\(_{28}\)H\(_{42}\)O\(_6\)NaSi [M+Na]\(^+\): 525.2648; found: 525.2651.

\(\text{(E)}\)-\(((2S,3S)-3-(benzyloxy)-1-((4R,6S)-6-(2-(5-formylfuran-2-yl)propan-2-yl)-2,2-diisopropyl-1,3,2-dioxasilinan-4-yl)butan-2-yl) but-2-enoate (1.34.1)\(^{31}\):

\[\begin{align*}
\text{HO} & \quad \text{O} \\
\text{BnO} & \quad \text{Si-O} \\
\text{O} & \quad \text{Si-O} \\
\text{iPr} & \quad \text{iPr} \\
\text{Crotonic anhydride, Et\(_3\)N, DMAP} & \quad \text{Crotonic anhydride, Et\(_3\)N, DMAP} \\
\text{1.34.1a} & \quad \text{1.34.1}
\end{align*}\]

Triethylamine (1.1 mL, 7.9 mmol, 1.5 equiv) and DMAP (0.13 g, 1.0 mmol, 0.2 equiv) were added to a solution of alcohol 1.34.1a (2.63 g, 5.2 mmol, 1.0 equiv) and crotonic anhydride (1.0 mL, 6.8 mmol, 1.3 equiv) in CH\(_2\)Cl\(_2\) (50 mL) at 0 °C.
After 4 hours at 0 °C, the reaction was quenched with saturated NaHCO₃ (50 mL). The organic phase was separated, washed with water and brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (gradient, hexanes to 5:1 hexanes:EtOAc) to provide ester 1.34.1 (2.89 g, 5.1 mmol, 97%).

H NMR (500 MHz, CDCl₃) δ 9.53 (s, 1H), 7.38 – 7.27 (m, 5H), 7.16 (d, J = 3.6 Hz, 1H), 6.97 (dq, J = 13.7, 6.8 Hz, 1H), 6.28 (d, J = 3.6 Hz, 1H), 5.85 (dd, J = 15.5, 1.7 Hz, 1H), 5.04 – 4.96 (m, 1H), 4.63 (d, J = 12.0 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.15 (d, J = 9.0 Hz, 1H), 4.03 (dd, J = 13.9, 6.5 Hz, 1H), 3.71 – 3.62 (m, 1H), 2.03 (dt, J = 15.7, 5.4 Hz, 1H), 1.88 – 1.78 (m, 4H), 1.76 – 1.66 (m, 1H), 1.46 (d, J = 14.7 Hz, 1H), 1.28 (dd, J = 24.6, 7.7 Hz, 8H), 1.15 (d, J = 6.4 Hz, 3H), 0.97 (dd, J = 7.1, 3.2 Hz, 6H), 0.94 – 0.78 (m, 11H). C NMR (100 MHz; CDCl₃): δ 181.13, 177.43, 166.28, 145.31, 138.67, 128.60, 128.08, 127.89, 122.90, 109.19, 77.79, 77.48, 74.20, 73.66, 72.59, 71.11, 68.90, 42.13, 36.50, 34.20, 23.18, 21.59, 18.27, 17.00, 16.94, 16.82, 15.38, 13.81, 13.10. [α]D = +19.1 (c 0.067, CHCl₃). IR (cm⁻¹): 2938, 2865, 1717, 1681, 1511, 1467, 1251, 1107, 696; HRMS (ESI) m/z calc’d for C₃₂H₄₇O₇Si [M+H]⁺: 571.3091; found: 571.3108.

Macrolide 1.34.2:
A solution of cyclization precursor 1.34.1 (76 mg, 0.13 mmol, 1.0 equiv) in toluene (1.5 mL) was added to a stirred solution of freshly prepared ATPH* (0.29 mmol, 2.2 equiv) in toluene (1.5 mL) at -78 °C. After 20 minutes, the 1.34.1-ATPH solution was added dropwise via cannula (1 hour) to a stirred solution of LTMP** (0.40 mmol, 3.0 equiv) in THF (1.2 mL) and toluene (9.0 mL) at -78 °C. After 30 minutes at -78 °C, the ice bath was removed and saturated NH₄Cl (10 mL) was immediately added. The biphasic mixture was stirred vigorously for 20 minutes while warming to ambient temperature, then filtered through a small pad of Celite and rinsed with Et₂O (20 mL). The organic phase of the filtrate was separated and washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (gradient, 5:1 to 1:1 hexanes:EtOAc) to provide the desired macrocycle 1.34.2 (65 mg, 0.11 mmol, 85%, 5:1 dr).

*Preparation of ATPH: Me₃Al (0.15 mL 2.0 M solution in hexanes, 0.29 mmol, 2.2 equiv) was added to a stirred solution of 2,6-diphenylphenol (0.22 g, 0.88 mmol, 6.6 equiv) in toluene (1.5 mL) at room temperature. After 30 minutes, the ATPH solution was cooled to -78 °C and used as described in the cyclization procedure.

**Preparation of LTMP: nBuLi (0.25 mL 1.6 M solution in hexanes, 0.40 mmol, 3.0 equiv) was added to a stirred solution of 2,2,6,6-tetramethylpiperidine (0.77 mL, 0.47 mmol, 3.5 equiv) in THF (1.2 mL) at -78 °C. After 30 minutes and immediately before the cannulation step in the above procedure, the solution was diluted with cooled (ice bath) toluene (9.0 mL).
Macrolide 1.35.1 (Structure Proof):\textsuperscript{31}

A mixture of 1.34.2 (48 mg, 0.084 mmol, 1.0 equiv) and 5\% palladium on carbon (20 mg) in absolute EtOH was vigorously stirred under a hydrogen atmosphere (balloon) overnight at room temperature. The reaction mixture was
filtered through a pad of silica gel, which was washed with EtOAc, and then the resulting filtrate was concentrated under reduced pressure to provide macrolide 1.35.1 (47 mg, 0.082 mmol, 98%).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.33 – 7.20 (m, 5H), 6.10 (d, $J$ = 3.1, 1H), 5.99 (d, $J$ = 3.1, 1H), 5.20 – 5.12 (m, 1H), 4.58 – 4.43 (m, 3H), 4.09 (dd, $J$ = 5.1, 7.3, 1H), 3.99 – 3.91 (m, 1H), 3.82 (p, $J$ = 6.3, 1H), 2.33 – 2.11 (m, 2H), 1.98 – 1.50 (m, 9H), 1.27 (s, 3H), 1.23 (s, 3H), 1.16 (d, $J$ = 6.3, 3H), 1.06 – 0.77 (m, 14H).

**Ketone 1.35.2:**

Dess-Martin periodinane (70 mg, 0.16 mmol, 2.0 equiv) was added to a stirred solution of alcohol 1.35.1 (47 mg, 0.082 mmol, 1.0 equiv) and pyridine (79 uL, 0.98 mmol, 12.0 equiv) in CH$_2$Cl$_2$ (3.0 mL). The mixture was stirred overnight (14 h) at room temperature. The reaction was diluted with Et$_2$O (3.0 mL), then a 1:1 mixture of saturated NaHCO$_3$ and saturated Na$_2$S$_2$O$_3$ (5.0 mL) was added, and the reaction was stirred vigorously for 15 minutes. After the mixture was diluted further with Et$_2$O (15 mL), the organic phase was separated, washed with saturated NaHCO$_3$, deionized water and brine, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (10:1 hexanes:EtOAc) to provide ketone 1.35.2 (26 mg, 0.046 mmol, 56%).
Alcohol **1.35.3-S**:^{31}

(R)-2-Me-CBS-oxazaborolidine (84 µL of a 0.05 M solution in THF, 0.0042 mmol, 0.4 equiv) and BH$_3$•SMe$_2$ (105 µL of a 0.2 M solution in THF, 0.021 mmol, 2.0 equiv) were added sequentially to a solution of ketone **1.35.2** (6 mg, 0.01 mmol, 1.0 equiv) in THF (0.1 mL) at room temperature. After 20 min, the reaction was diluted with Et$_2$O (1.0 mL) and quenched with brine (1.0 mL). The organic phase was separated, dried over MgSO$_4$, filtered, and concentrated under reduced pressure to provide alcohol **1.35.3-S**, which has identical spectral data to **1.35.1** produced from the hydrogenation of **1.34.2**.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.33 – 7.20 (m, 5H), 6.10 (d, $J = 3.1$, 1H), 5.99 (d, $J = 3.1$, 1H), 5.20 – 5.12 (m, 1H), 4.58 – 4.43 (m, 3H), 4.09 (dd, $J = 5.1$, 7.3, 1H),
3.99 – 3.91 (m, 1H), 3.82 (p, J = 6.3, 1H), 2.33 – 2.11 (m, 2H), 1.98 – 1.50 (m, 9H), 1.27 (s, 3H), 1.23 (s, 3H), 1.16 (d, J = 6.3, 3H), 1.06 – 0.77 (m, 14H).

Macrolide 1.35.3-R:

(S)-2-Me-CBS-oxazaborolidine (84 uL of a 0.05 M solution in THF, 0.0042 mmol, 0.4 equiv) and BH$_3$•SMe$_2$ (105 uL of a 0.2 M solution in THF, 0.021 mmol, 2.0 equiv) were added sequentially to a solution of ketone 1.35.2 (6 mg, 0.01 mmol, 1.0 equiv) in THF (0.1 mL) at room temperature. After 20 min, the reaction was diluted with Et$_2$O (1.0 mL) and quenched with brine (1.0 mL). The organic phase was separated, dried over MgSO$_4$, filtered, and concentrated under reduced pressure to provide alcohol 1.35.3-R which had spectral properties that were different from 1.35.1 produced from the hydrogenation of 1.34.2.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.33 – 7.10 (m, 5H), 6.14 (d, J = 2.4, 1H), 6.01 (d, J = 3.2, 1H), 5.14 (s, 2H), 4.86 – 4.80 (m, 1H), 4.55 (d, J = 11.9, 2H), 4.46 (d, J = 12.0, 2H), 4.04 – 3.98 (m, 2H), 3.92 – 3.86 (m, 2H), 3.82 (s, 2H), 2.32 – 2.10 (m, 2H), 1.95 – 1.44 (m, 9H), 1.29 – 0.77 (m, 23H).
TES Ether 1.37.1a:

2,6-Lutidine (0.08 mL, 0.72 mmol, 3.0 equiv) and TESOTf (0.77 mL, 0.34 mmol, 1.5 equiv) were added sequentially to a solution of alcohol 1.34.2 (0.13 g, 0.23 mmol, 1.0 equiv) in CH₂Cl₂ (3 mL) at 0 °C. The ice bath was removed and the reaction allowed to warm to room temperature over a period of 20 min, then quenched with saturated NaHCO₃. The organic phase was separated, washed with water and brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (gradient, hexanes to 10:1 hexanes:EtOAc) to provide TES ether 1.37.1a (0.11 g, 0.21 mmol, 90%).

¹H NMR (500 MHz, CDCl₃) δ 7.34 – 7.23 (m, 5H), 6.64 (ddd, J = 15.2, 9.6, 5.2 Hz, 1H), 6.04 (t, J = 3.5 Hz, 1H), 5.94 (d, J = 3.2 Hz, 1H), 5.65 – 5.55 (m, 1H), 5.20 (td, J = 6.1, 3.0 Hz, 1H), 4.88 (dd, J = 8.9, 4.9 Hz, 1H), 4.57 (d, J = 11.8 Hz, 1H), 4.52 (d, J = 11.8 Hz, 1H), 4.14 (td, J = 9.6, 3.7 Hz, 1H), 3.89 (t, J = 6.5 Hz, 1H), 3.77 (p, J = 6.3 Hz, 1H), 2.71 (dtd, J = 13.5, 5.0, 1.8 Hz, 1H), 2.56 (dt, J = 14.3, 9.6 Hz, 1H), 1.95 (ddd, J = 15.2, 6.2, 3.1 Hz, 1H), 1.78 (ddddd, J = 20.7, 14.4, 6.2, 3.8 Hz, 2H), 1.57 – 1.48 (m, 1H), 1.24 (s, 3H), 1.20 (s, 3H), 1.16 (d, J = 6.4 Hz, 3H), 1.06 – 0.91 (m, 15H), 0.88 (t, J = 7.9 Hz, 10H), 0.57 – 0.48 (m, 6H). ¹³C NMR (75 MHz, CDCl₃) δ 165.36, 159.11, 155.41, 143.96, 138.89, 128.50, 128.08, 127.68, 124.49, 106.58, 106.23, 75.52, 75.37, 73.00, 71.39, 67.86, 67.08, 42.48, 41.73, 36.63, 35.58,
25.77, 19.47, 17.45, 17.30, 17.23, 17.15, 16.02, 13.42, 13.24, 6.89, 4.82; HRMS (ESI) m/z calc'd for C_{38}H_{61}O_{7}Si_{2} [M+H]^+: 685.3956; found: 685.3972.

Diol 1.37.1: \(^{31}\)

(DHQD)\(_2\)PHAL (23 mg, 0.12 mmol, 0.66 equiv), AD-mix-\(\beta\) (0.35 g), MeSO\(_2\)NH\(_2\) (45 mg, 0.45 mmol, 2.5 equiv), and OsO\(_4\) (45 \(\mu\)L 0.1 M solution in H\(_2\)O) were added sequentially to a solution of the TES ether 1.37.1a (0.10 g, 0.18 mmol, 1.0 equiv) in 1:1 tBuOH/H\(_2\)O (10 mL) at 0 \(^\circ\)C. After 2 days at 0 \(^\circ\)C, Na\(_2\)SO\(_3\) (250 mg) was added and the reaction was stirred vigorously at room temperature for 1 hr. EtOAc was then added, the layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with NaOH (2M), brine, and dried over MgSO\(_4\). The solvent was removed under reduced pressure and the crude material was purified by flash chromatography (2:1 hexanes:EtOAc) to provide diol 1.37.1 (0.10 mg, 0.17 mmol, 96%, 12:1 dr).

\(^1\)H NMR (500 MHz; CDCl\(_3\)): \(\delta\) 7.32 – 7.23 (m, 5H), 6.07 (d, \(J = 3.1\), 1H), 5.94 (d, \(J = 3.1\), 1H), 5.25 – 5.16 (m, 1H), 4.88 (dd, \(J = 6.2, 8.1, 1H\)), 4.56 (d, \(J = 11.8, 1H\)), 4.42 (d, \(J = 11.8, 1H\)), 4.11 (t, \(J = 6.5, 1H\)), 4.04 (t, \(J = 6.3, 1H\)), 4.02 – 3.93 (m, 1H), 3.86 – 3.79 (m, 1H), 3.44 – 3.33 (m, 1H), 2.97 (d, \(J = 2.9, 1H\)), 2.36 (d, \(J = 6.5, 1H\)), 2.04 – 1.95 (m, 1H), 1.95 – 1.86 (m, 2H), 1.83 – 1.72 (m, 2H), 1.55 – 1.46 (m, 1H), 1.23 (s, 4H), 1.22 (s, 4H), 1.19 (d, \(J = 6.3, 4H\)), 1.05 – 0.80 (m, 23H),
0.53 – 0.43 (m, 6H). $^{13}$C NMR (100 MHz; CDCl$_3$): δ 169.75, 160.56, 153.31, 138.63, 128.67, 128.07, 127.96, 108.34, 106.37, 77.78, 77.48, 75.87, 75.50, 74.78, 74.63, 71.33, 70.99, 66.85, 66.52, 41.77, 39.43, 37.32, 35.87, 29.98, 25.40, 21.65, 17.37, 17.14, 17.07, 15.96, 13.38, 13.23, 6.90, 4.75. $[^\alpha]_D = -29.3$ (c 0.067, CHCl$_3$). IR (cm$^{-1}$): 3436, 2953, 2868, 1733, 1462, 1246, 1087, 744; HRMS (ESI) m/z calc’d for C$_{38}$H$_{63}$O$_9$Si$_2$ [M+H]$^+$: 719.4011; found: 719.3995.

**TBS Ether 1.38.1:**

TBSCl (0.46 g, 3.1 mmol, 8.5 equiv) and imidazole (0.42 g, 6.2 mmol, 17.0 equiv) were added sequentially to a stirred solution of diol 1.37.1 (0.21 g, 0.36 mmol, 1.0 equiv) in DMF (8 mL) at 0 ºC. After 5 hr, the reaction was quenched with saturated NaHCO$_3$ (10 mL) and diluted with 5:1 hexanes / EtOAc (20 mL). The organic phase was separated, washed with water, CuSO$_4$ (1M) and brine, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (gradient, hexanes to 5:1 hexanes:EtOAc) to provide 1.38.1 (0.28 g, 0.34 mmol, 94%, ~10:1 regioisomeric ratio).

$^1$H NMR (500 MHz; CDCl$_3$): δ 7.32 – 7.19 (m, 5H), 6.08 (d, $J = 3.1$, 1H), 5.94 (d, $J = 3.1$, 1H), 5.34 – 5.28 (m, 1H), 4.88 (dd, $J = 5.7$, 9.1, 1H), 4.58 (d, $J = 11.8$, 1H), 4.50 (d, $J = 11.8$, 1H), 4.18 – 4.13 (m, 1H), 3.99 (t, $J = 7.5$, 2H), 3.85 –
3.80 (m, 1H), 3.33 – 3.26 (m, 1H), 2.90 (s, 1H), 2.10 – 2.02 (m, 1H), 1.88 (ddd, \( J = 5.0, 10.8, 15.3, 2H \)), 1.69 (dd, \( J = 7.7, 13.4, 2H \)), 1.49 – 1.40 (m, 1H), 1.25 – 1.22 (m, 6H), 1.14 (d, \( J = 6.3, 3H \)), 1.06 – 0.80 (m, 32H), 0.47 (ddd, \( J = 4.8, 7.9, 13.2, 6H \)), 0.04 (s, 3H), -0.01 (s, 3H). \(^{13}\)C NMR (100 MHz; CDCl\(_3\)): \( \delta \) 170.74, 160.80, 153.04, 138.99, 128.43, 127.92, 127.59, 108.64, 106.09, 77.48, 74.69, 74.20, 73.71, 71.01, 70.82, 66.72, 66.66, 41.80, 39.17, 36.51, 36.05, 26.00, 25.36, 21.54, 18.48, 17.39, 17.23, 17.10, 15.85, 13.30, 13.15, 6.94, 4.77, -4.57, -5.23. \([\alpha]_D = -40.5 \) (c 0.360, CHCl\(_3\)). IR (cm\(^{-1}\)): 3583, 2953, 2867, 1729, 1464, 1257, 1107, 839, 781, 743; HRMS (ESI) \( m/z \) calc’d for C\(_{44}\)H\(_{76}\)O\(_9\)NaSi\(_3\) [M+Na]\(^+\): 855.4695; found: 855.4656.

**Methyl Ether 1.38.2:**

![Diagram of Methyl Ether 1.38.2](image)

1,8-Bis(dimethylamino)naphthalene (proton sponge, 408 mg, 1.90 mmol, 20.0 equiv) and trimethyloxonium tetrafluoroborate (184 mg, 1.43 mmol, 15.0 equiv) were added sequentially to a stirred solution of alcohol 1.38.1 (67 mg, 0.095 mmol, 1.0 equiv) in CH\(_2\)Cl\(_2\) (5 mL) at room temperature. After 1 hour the reaction was quenched by adding saturated NaHCO\(_3\) (5 mL). The mixture was diluted with CH\(_2\)Cl\(_2\) (10 mL), and the organic phase was separated, washed with brine, dried over MgSO\(_4\), filtered, and concentrated under reduced pressure. The crude material was
purified by flash chromatography (hexanes then 5:1 hexanes:EtOAc) to provide macrolide 1.38.2 (56 mg, 0.080 mmol, 84%).

\[ ^1H \text{NMR (500 MHz; CDCl}_3\): } \delta 7.35 – 7.20 (m, 5H), 6.06 (d, \( J = 3.1 \), 1H), 5.97 (d, \( J = 3.1 \), 1H), 5.22 – 5.16 (m, 1H), 4.83 (dd, \( J = 4.1, 10.7, 1H \)), 4.58 (d, \( J = 12.1, 1H \)), 4.52 (d, \( J = 12.0, 1H \)), 4.08 – 4.02 (m, 2H), 3.98 – 3.87 (m, 2H), 3.44 (s, 3H), 2.86 – 2.78 (m, 1H), 2.01 – 1.92 (m, 1H), 1.93 – 1.80 (m, 3H), 1.78 – 1.70 (m, 1H), 1.60 – 1.51 (m, 1H), 1.27 (s, 3H), 1.21 (s, 3H), 1.12 (d, \( J = 6.3, 3H \)), 1.03 – 0.78 (m, 32H), 0.45 (qd, \( J = 3.2, 7.9, 6H \)), 0.06 – 0.04 (m, 3H), -0.02 – -0.05 (m, 3H).

\[ ^{13}C \text{NMR (100 MHz; CDCl}_3\): } \delta 171.08, 160.38, 153.46, 139.11, 128.42, 127.84, 127.50, 109.06, 106.59, 94.66, 79.74, 79.69, 77.48, 75.25, 74.27, 73.84, 70.69, 66.39, 65.82, 61.54, 41.81, 39.67, 36.32, 35.89, 26.13, 26.00, 25.09, 23.12, 18.43, 17.33, 17.18, 17.10, 15.77, 13.22, 13.12, 6.97, 4.81, -4.75, -4.93. \[ \alpha_D = -51.6 (c 0.212, CHCl}_3\).\]

\[ \text{IR (cm}^{-1}\): 2953, 2925, 2860, 1730, 1464, 1254, 1104, 838, 733; HRMS (ESI) \text{ m/z calc'd for C}_{45}H_{78}O_{9}NaSi}_{3} [M+Na]^+: 869.4851; found: 869.4836.\]

Alcohol 1.38.3: \[ ^{31}PPTS (1.2 mg, 0.005 mmol) was added to a solution of 1.38.2 (34 mg, 0.040 mmol) in 50:1 DMF / MeOH (3 mL) at 0 \({}^\circ\)C. The reaction was stirred for 20 h at 0 \({}^\circ\)C.\]
and then quenched with saturated NaHCO₃. The reaction was extracted with 5:1 hexanes/EtOAc (2 x 10 mL), and the combined organic phases washed with water, 1 M CuSO₄ and brine, and the aqueous layer back extracted with 5:1 hexanes/EtOAc. The organic phase was dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (gradient, hexanes to 5:1 hexanes:EtoAco) to provide alcohol 1.38.3 (26 mg, 0.035 mmol, 87%).

\[ 1^H \text{ NMR (500 MHz; CDCl}_3) \]: \( \delta \) 7.31 – 7.19 (m, 5H), 6.13 (d, J = 3.1, 1H), 5.97 (d, J = 3.1, 1H), 5.20 (q, J = 5.1, 1H), 4.80 (td, J = 3.9, 7.0, 1H), 4.56 – 4.49 (m, 2H), 4.28 (d, J = 6.2, 1H), 4.07 – 3.99 (m, 2H), 3.96 (t, J = 6.3, 1H), 3.51 (s, 3H), 3.19 (ddd, J = 3.3, 6.2, 9.7, 1H), 2.72 (d, J = 3.8, 1H), 2.03 – 1.94 (m, 3H), 1.83 – 1.77 (m, 2H), 1.56 – 1.48 (m, 1H), 1.28 (s, 3H), 1.20 (s, 3H), 1.17 (d, J = 6.3, 3H), 1.03 – 0.79 (m, 23H), 0.03 (s, 3H), -0.03 (s, 3H). \( ^{13} \text{C NMR (100 MHz; CDCl}_3) \): \( \delta \) 170.89, 160.62, 153.39, 139.15, 128.42, 127.71, 127.50, 108.32, 106.70, 82.33, 77.48, 75.76, 75.45, 75.25, 74.54, 70.75, 66.78, 66.46, 59.82, 41.70, 37.58, 37.32, 36.39, 26.00, 24.73, 23.30, 18.40, 17.29, 17.21, 17.07, 17.05, 16.03, 13.26, 13.10, -4.75, -5.08. \( [\alpha]_D \) = +6.7 (c 0.193, CHCl₃). IR (cm\(^{-1}\)): 3412, 2929, 2864, 1728, 1464, 1255, 1127, 862, 786; HRMS (ESI) m/z calc’d for C\(_{39}\)H\(_{65}\)O\(_9\)Si\(_2\) [M+H]\(^+\): 733.4167; found: 733.4158.

**Pyranone 1.38.4:**
*m*-CPBA (15 mg, 0.088 mmol, 1.3 equiv) was added to a solution of alcohol 1.38.3 (50 mg, 0.068 mmol, 1.0 equiv) in CH₂Cl₂ (10 mL) at room temperature. After stirring for 1 hr, trichloroacetic acid (0.7 mL 0.1 M solution in CH₂Cl₂, 0.005 mmol, 10 mol %) was added, and the reaction was stirred overnight (16 h). The reaction was quenched by adding saturated NaHCO₃ (5.0 mL). The organic phase was separated, washed with water and brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (5:1 hexanes:EtOAc) to provide pyranone 1.38.4 (33 mg, 0.044 mmol, 64%).

¹H NMR (500 MHz; CDCl₃): δ 7.36 - 7.24 (m, 5H), 6.96 (d, J = 10.4, 1H), 6.33 (s, 1H), 6.05 (d, J = 10.4, 1H), 5.30 (dd, J = 4.0, 9.6, 1H), 5.17 (d, J = 11.3, 1H), 4.77 (dd, J = 6.8, 9.9, 1H), 4.69 – 4.58 (m, 3H), 4.47 (d, J = 1.4, 1H), 4.28 – 4.21 (m, 1H), 4.16 (dd, J = 6.0, 9.6, 1H), 3.30 (s, 3H), 2.60 (dd, J = 10.2, 14.7, 1H), 2.31 – 2.12 (m, 3H), 1.62 (dd, J = 12.1, 15.6, 1H), 1.51 (d, J = 14.6, 1H), 1.16 (s, 3H), 1.09 – 0.95 (m, 15H), 0.91 (s, 9H), 0.86 (t, J = 7.3, 2H), 0.82 (s, 3H), 0.16 (s, 3H), 0.08 (s, 3H). ¹³C NMR (100 MHz; CDCl₃): δ 197.59, 171.74, 146.15, 138.88, 128.58, 128.00, 127.79, 99.13, 78.68, 77.48, 73.24, 72.73, 72.02, 71.63, 70.07, 67.49, 57.09, 43.61, 36.75, 33.75, 31.87, 29.98, 27.03, 26.29, 25.93, 22.22, 18.87, 17.83, 17.58, 17.21, 17.08, 16.15, 15.01, 14.69, 14.41, 14.27, -3.36, -4.62. [α]D = +15.2 (c 0.334, CHCl₃). IR (cm⁻¹): 3358, 2928, 2856, 1757, 1699, 1464, 1103, 838, 697; HRMS (ESI) m/z calc’d for C₃₉H₆₂O₉NaSi₂ [M-H₂O+Na]+: 753.3830; found: 753.3813.
Model System 1.45.1e:

**Alcohol 1.45.1a**

To a solution of aldehyde 1.45.1e (11.53 g, 40.8 mmol) in MeOH (200 mL) at 0 °C was added NaBH₄ (2.317 g, 61.2 mmol). The reaction was monitored by TLC and after consumption of the starting material the reaction was carefully quenched with 1 M HCl. After diluting with Et₂O (30 mL), the organic phase was separated, washed with deionized water and brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure. MeOH was added and then removed under reduced pressure. After repeating the MeOH exchange once more, the crude product was purified by flash chromatography (gradient 15:1 to 2:1 hexanes:EtOAc) to provide alcohol 1.45.1a (9.63 g, 33.9 mmol, 83%).

Rf = 0.65 (2:1 hexanes:EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 6.12 (d, J = 3.1 Hz, 1H), 6.00 (d, J = 3.1 Hz, 1H), 4.58 (s, 2H), 3.56 (d, J = 6.7 Hz, 2H), 1.41 (t, J = 6.7 Hz, 1H), 1.25 (s, 6H), 0.87 (s, 9H), 0.05 (s, 6H).

**Bis-TBS ether 1.45.1b**

To a stirring solution of 1.45.1a (15 g, 52.7 mmol) in 260 mL CH₂Cl₂ was added imidazole (4.67 g, 68.5 mmol, 1.3 equiv), DMAP (1.288 g, 10.55 mmol, 0.2
equiv) and TBSCI (9.54 g, 63.3 mmol, 1.2 equiv). The mixture was stirred at room temperature for 2 h, then 100 mL of water was added. The mixture was transferred to a separatory funnel. The aqueous layer was separated and extracted with ether (2x). The combined organic layers were then washed with water (2x), dried with MgSO₄ and filtered. The solvent was removed in vacuo and the residue was purified by column chromatography (60:1 hexanes:EtOAc with 0.5% Et₃N) to give 1.45.1b (19.48 g, 48.9 mmol, 93%) as a clear colorless liquid.

1H NMR (500 MHz, CDCl₃) δ 6.10 (d, J = 3.1 Hz, 1H), 5.94 (d, J = 3.1 Hz, 1H), 4.60 (s, 2H), 3.56 (s, 2H), 1.23 (s, 6H), 0.91 (s, 9H), 0.86 (s, 9H), 0.08 (s, 6H), -0.03 (s, 6H).

**Aldehyde 1.45.1c**

DDQ (5.54 g, 24.4 mmol, 1.0 equiv) was added to a solution of furan 1.45.1b (9.73 g, 24.4 mmol, 1.0 equiv) in 10:1 CH₂Cl₂ to H₂O (122 mL, biphasic). The solution was heated to reflux for 1 hour, then cooled to room temperature and quenched with saturated NaHCO₃ (150 mL). The organic phase was separated, washed with water and brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product (2:1 ratio of desired product versus open diketo form) was purified by flash chromatography (2:1 hexanes:CHCl₃) to provide the desired aldehyde 1.45.1c (4.7 g, 16.64 mmol, 68%).

Rf = 0.5 (CHCl₃); 1H NMR (500 MHz, CDCl₃) δ 9.51 (s, 1H), 7.14 (d, J = 3.6 Hz, 1H), 6.27 (d, J = 3.6 Hz, 1H), 3.60 (s, 2H), 1.28 (s, 6H), 0.79 (s, 9H), -0.08 (s, 6H).
Alcohol 1.45.1d

MeLi (18.24 mL, 29.2 mmol, 1.6 M solution in THF) was added to a stirred solution of aldehyde 1.45.1c (6.34 g, 22.45 mmol) in THF (112 mL) at -78 °C. After 1 hour, the reaction was quenched with saturated NH₄Cl (50 mL) and diluted with Et₂O (100 mL). The organic phase was separated, washed with deionized water and brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The crude product was purified by flash chromatography (15:1 hexanes:EtOAc) to provide alcohol 1.45.1d (6.04 g, 20.23 mmol, 90%).

Rf = 0.2 (15:1 hexanes:EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 6.08 (dd, J = 3.2, 0.6 Hz, 1H), 5.93 (d, J = 3.2 Hz, 1H), 4.84 – 4.77 (m, 1H), 3.53 (s, 2H), 1.80 (dd, J = 4.9, 1.7 Hz, 1H), 1.50 (d, J = 6.6 Hz, 3H), 1.21 (s, 6H), 0.82 (s, 9H), -0.07 (s, 6H).

Pyranone 1.45.1e

m-CPBA (4.19 g, 24.28 mmol, 1.2 equiv) was added to a solution of alcohol 1.45.1d (6.04 g, 20.23 mmol, 1.0 equiv) in CH₂Cl₂ (100 mL) at room temperature and the reaction was stirred overnight (16 h). The reaction was quenched by adding saturated NaHCO₃ (50 mL). The organic phase was separated, washed with water and brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (20:1 hexanes:EtOAc) to provide pyranone 1.45.1e (4.88 g, 15.52 mmol, 77%).

Rf = 0.30 (10:1 hexanes:EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 6.87 (d, J = 10.4 Hz, 1H), 6.01 (d, J = 10.4 Hz, 1H), 5.69 (s, 1H), 4.72 (q, J = 6.8 Hz, 1H), 4.21 (d, J = 9.3 Hz, 1H), 3.75 (s, 3H), 1.21 (s, 9H), -0.07 (s, 6H).
Hz, 1H), 3.22 (d, $J = 9.3$ Hz, 1H), 1.33 (d, $J = 6.8$ Hz, 3H), 1.20 (s, 3H), 0.90 (s, 9H), 0.77 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H).

Alcohol 1.45.1f

NaBH$_4$ (0.433 g, 11.45 mmol, 5.0 equiv) was added to a solution of 1.45.1e (0.72 g, 2.29 mmol, 1.0 equiv) and CeCl$_3$•7H$_2$O (5.12 g, 13.74 mmol, 6.0 equiv) in 1:1 MeOH to CH$_2$Cl$_2$ (50 mL) at -78 °C. After 20 min, the reaction was quenched by adding saturated NaHCO$_3$ (40 mL). Et$_2$O (100 mL) was added, the organic phase was separated, washed with deionized water and brine, dried over anhydrous MgSO$_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography (8:1 CH$_2$Cl$_2$:Et$_2$O) to provide alcohol 1.45.1f quantitatively.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.86 (dd, $J = 10.3$, 1.5 Hz, 1H), 5.76 (dd, $J = 10.3$, 2.2 Hz, 1H), 5.47 (s, 1H), 4.14 (d, $J = 9.2$ Hz, 1H), 3.82 (dq, $J = 8.9$, 6.2 Hz, 1H), 3.67 (tt, $J = 8.9$, 1.8 Hz, 1H), 3.15 (d, $J = 9.2$ Hz, 1H), 1.34 (dd, $J = 8.9$, 0.8 Hz, 1H), 1.27 (d, $J = 6.2$ Hz, 3H), 1.11 (s, 3H), 0.89 (s, 9H), 0.69 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H).
Thiocarbonate 1.45.1e:

![Chemical structure](image)

To a stirred solution of thiocarbonate **1.45.1f** (4 mg, 0.013 mmol), pyridine (4 µL, 0.051 mmol, 4 equiv), and DMAP (1.5 mg, 0.013 mmol, 1 equiv) in CH$_2$Cl$_2$ (1mL) at rt was added acid chloride (5 µL, 0.038 mmol, 3 equiv). The reaction was quenched by adding saturated NaHCO$_3$ (2 mL). The organic phase was separated, washed with deionized water and brine, dried over anhydrous MgSO$_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography (7:1 hexanes:EtOAc) to provide carbonate **1.45.1g** (5 mg, 0.011 mmol, 87%).

R$_f$ = 0.15 (5:1 hexanes:EtOAc); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.34 – 7.29 (m, 5H), 6.07 (dd, $J$ = 10.4, 1.5 Hz, 1H), 5.95 (dd, $J$ = 10.4, 2.1 Hz, 1H), 5.63 (s, 1H), 5.47 (d, $J$ = 9.3 Hz, 1H), 4.35 (dq, $J$ = 9.6, 6.4 Hz, 1H), 4.22 (d, $J$ = 9.3 Hz, 1H), 3.23 (d, $J$ = 9.3 Hz, 1H), 1.34 (d, $J$ = 6.2 Hz, 3H), 1.19 (s, 3H), 0.95 (s, 9H), 0.79 (s, 3H), 0.15 (s, 3H), 0.13 (s, 3H).
Pyran 1.45.1h:

To a stirred solution of pyran 1.45.1f (0.01 g, 0.032 mmol), Et₃N (9 uL, 0.064 mmol), and DMAP (1 mg, 6 umol) in CH₂Cl₂ at rt was added Ac₂O (0.015 mL, 0.158 mmol). The reaction was quenched by adding saturated NaHCO₃ (3 mL). The organic phase was separated, washed with deionized water and brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The crude product was purified by flash chromatography (5:1 hexanes:EtOAc) to 279 (9 mg, 0.025 mmol, 79%).

¹H NMR (500 MHz, CDCl₃) δ 5.81 (dd, J = 10.4, 2.0 Hz, 1H), 5.76 (dd, J = 10.4, 1.5 Hz, 1H), 5.51 (s, 1H), 4.98 (dt, J = 9.4, 1.7 Hz, 1H), 4.18 (d, J = 9.2 Hz, 1H), 3.91 (td, J = 9.0, 3.0 Hz, 1H), 3.15 (d, J = 9.2 Hz, 1H), 2.05 (s, 3H), 1.64 (dqd, J = 15.0, 7.5, 3.0 Hz, 1H), 1.45 – 1.34 (m, 1H), 1.12 (s, 3H), 0.95 (t, J = 7.4 Hz, 3H), 0.88 (s, 9H), 0.70 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H).

Diene 1.45.1i:
To a solution of 1.45.1h (0.010 g, 0.027 mmol) in toluene (3 mL) was added Pd(PPh₃)₄ (6 mg, 5 umol), and ammonium formate (3.5 mg, 0.054 mmol). The reaction was refluxed for 3 hours, allowed to cool to room temperature, and quenched by adding saturated NaHCO₃ (3 mL). The organic phase was separated, washed with deionized water and brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The crude product was purified by flash chromatography (20:1 hexanes:EtOAc) to 1.45.1i (5 mg, 0.014 mmol, 53%).

¹H NMR (400 MHz, CDCl₃) δ 6.21 – 6.17 (m, 1H), 5.95 (d,  J = 3.2 Hz, 1H), 5.71 (t,  J = 7.2 Hz, 1H), 3.54 (q,  J = 9.4 Hz, 2H), 1.94 (pd,  J = 7.4, 1.4 Hz, 3H), 1.22 (d,  J = 3.3 Hz, 6H), 0.91 – 0.86 (m, 6H), 0.83 (s, 9H), -0.07 (d,  J = 4.5 Hz, 6H).

Compounds 1.45.1j-l

To a solution of alcohol 1.45.1f (0.311 g, 0.983 mmol) in CH₂Cl₂/MeOH (1:1, 5 mL) at rt was added PPTS (0.025 g, 0.098 mmol). After 1 hour, the reaction was quenched by adding saturated NaHCO₃ (5 mL). The organic phase was separated, washed with deionized water and brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The crude product was purified by flash chromatography (10:1 hexanes:EtOAc) to the desired product 1.45.1k.
\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.83 (d, \(J = 5.2\) Hz, 1H), 3.76 (dq, \(J = 9.9, 6.3\) Hz, 1H), 3.67 (t, \(J = 4.8\) Hz, 1H), 3.46 – 3.34 (m, 6H), 2.67 (d, \(J = 9.3\) Hz, 1H), 1.33 (d, \(J = 6.3\) Hz, 3H), 1.03 (d, \(J = 3.6\) Hz, 6H), 0.87 (s, 9H), 0.01 (s, 6H).

Thiocarbonate 1.45.1m:

\[ \text{1.45.1k} \quad \text{pyr., DMAP} \quad \text{1.45.1m} \]

To a stirred solution of thiocarbonate 1.45.1k (0.024 g, 0.073 mmol), pyridine (0.023 mL, 0.290 mmol, 4 equiv), and DMAP (0.2 mg, 1.5 umol, .02 equiv) in CH\(_2\)Cl\(_2\) (1 mL) at rt was added acid chloride (0.029 mL, 0.218 mmol, 3 equiv). The reaction was quenched by adding saturated NaHCO\(_3\) (2 mL). The organic phase was separated, washed with deionized water and brine, dried over anhydrous MgSO\(_4\), and concentrated under reduced pressure. The crude product was purified by flash chromatography (7:1 hexanes:EtOAc) to provide carbonate 1.45.1m (8 mg, 0.016 mmol, 22%).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.47 – 7.41 (m, 2H), 7.34 – 7.29 (m, 1H), 7.16 – 7.10 (m, 2H), 5.23 (dd, \(J = 9.9, 3.9\) Hz, 1H), 4.86 (d, \(J = 5.5\) Hz, 1H), 4.35 (dq, \(J = 9.9, 6.3\) Hz, 1H), 4.15 (dd, \(J = 5.5, 3.9\) Hz, 1H), 3.49 – 3.45 (m, 4H), 3.41 (d, \(J = 9.1\) Hz, 1H), 1.38 (d, \(J = 6.4\) Hz, 3H), 1.05 (d, \(J = 7.5\) Hz, 6H), 0.88 (s, 9H), 0.02 (d, \(J = 1.8\) Hz, 6H).
Model System 1.45.5

Carboxylic Acid 1.45.2:

To a stirred solution of 2-furoic acid 1.45.1 (1g, 8.92 mmol) in CH₂Cl₂ at 0 °C was added aluminum chloride (2.379 g, 17.84 mmol, 2 equiv) portionwise to keep the temperature below 10 °C. t-Butyl chloride (0.970 mL, 8.92 mmol, 1 equiv) was added gradually over 40 minutes. The mixture was allowed to warm to rt and stir for 1 hour. The reaction was quenched by pouring over ice, separating the organic layer, washed with water and brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product 1.45.2 was used without purification in the next step.

¹H NMR (500 MHz, CDCl₃) δ 11.02 (bs, 1H), 7.23 (d, J = 3.5 Hz, 1H), 6.16 (d, J = 3.5 Hz, 1H), 1.35 (s, 9H).

2-t-Butylfuran 1.45.3

To a stirred solution of carboxylic acid 1.45.2 (37.5 g, 223 mmol) in quinoline (68 mL) was added CuO (7.57 g, 95 mmol). The reaction flask was fitted with a distillation head and heated to 220 °C. The distillate was washed several times with 1M HCl to remove excess quinoline. CH₂Cl₂ was added and the organic phase was
separated, washed with water and brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give 1.45.3 (17.9 g, 144 mmol, 65%).

^1^H NMR (500 MHz, CDCl₃) δ 7.31 (dd, J = 1.8, 0.9 Hz, 1H), 6.27 (dd, J = 3.2, 1.8 Hz, 1H), 5.96 (dd, J = 3.2, 0.9 Hz, 1H), 1.29 (s, 9H).

**Alcohol 1.45.4**

To a stirred solution of furan 1.46.3 (17.93 g, 144 mmol) in THF (255 mL) at 0 °C was added n-BuLi (1.55 in hexanes, 93 mL, 144 mmol). The mixture was stirred for 30 minutes and which time a solution of propionaldehyde (7.99 g, 138 mmol) in THF (20 mL) was added dropwise. After 15 minutes, the reaction was quenched by adding saturated NaHCO₃ (100 mL) and diluted with Et₂O (200 mL). The organic phase was separated, washed with water and brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (9:1 hexanes:EtOAc) to provide alcohol 1.46.4 (19.61 g, 108 mmol, 78%).

Rf = 0.33 (7:1 hexanes:EtOAc); ^1^H NMR (500 MHz, CDCl₃) δ 6.10 (dd, J = 3.1, 0.6 Hz, 1H), 5.89 (d, J = 3.1 Hz, 1H), 4.56 (dd, J = 11.9, 6.7 Hz, 1H), 1.95 – 1.77 (m, 3H), 1.27 (s, 9H), 0.96 (t, J = 7.5 Hz, 3H).

**Pyranone 1.46.5**

m-CPBA (26.5 g, 118 mmol, 1.1 equiv) was added to a solution of alcohol 1.46.4 (19.61 g, 108 mmol, 1.0 equiv) in CH₂Cl₂ (540 mL) at room temperature and the reaction was stirred overnight (16 h). The reaction was quenched by adding
saturated NaHCO₃ (250 mL). The organic phase was separated, washed with water and brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (gradient 10:1 to 5:1 hexanes:EtOAc) to provide pyranone 1.46.5 (96:1 dr, 16.53 g, 83 mmol, 77%).

\[ R_f = 0.50 \text{ (2:1 hexanes:EtOAc)}; \] ¹H NMR (500 MHz, CDCl₃) δ 7.03 (d, \( J = 10.4 \text{ Hz, } 1\)H), 6.12 (d, \( J = 10.4 \text{ Hz, } 1\)H), 4.45 (dd, \( J = 7.2, 3.9 \text{ Hz, } 1\)H), 2.38 (s, 1H), 1.96 (dqd, \( J = 14.9, 7.5, 3.9 \text{ Hz, } 1\)H), 1.78 (dp, \( J = 14.5, 7.3 \text{ Hz, } 1\)H), 1.07 (s, 9H), 0.97 (t, \( J = 7.4 \text{ Hz, } 3\)H).

**Alcohol ##**

To a solution of ketone 1.45.5 (0.388 g, 1.959 mmol) in THF (10 mL) at -78 °C was cannulated a cooled solution of 1 M DIBAL-H in hexanes (2.55 mL, 2.55 mmol). The solution was stirred for 1.5 hours at which time EtOAc was added and stirred for an additional hour. The solution was cannulated into a vigorously stirred solution of saturated Rochelle’s salt and stirred for 2 hours. The organic layer was separated, dried over MgSO₄, and concentrated in vacuo. The crude product was then purified by recrystallization (CH₂Cl₂) to give the desired alcohol 1.45.5a a white solid (0.131 g, 1.76 mmol, 90%).

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$^1$H NMR (500 MHz, CDCl$_3$) δ 5.95 (dd, $J = 10.3$, 1.5 Hz, 1H), 5.89 (dd, $J = 10.3$, 2.1 Hz, 1H), 3.88 – 3.83 (m, 1H), 3.55 (td, $J = 8.7$, 3.0 Hz, 1H), 2.24 (s, 1H), 1.89 (dqd, $J = 15.0$, 7.5, 3.0 Hz, 1H), 1.56 – 1.47 (m, 1H), 1.38 (d, $J = 8.0$ Hz, 1H), 1.04 – 0.95 (m, 12H).

**Ketone 1.48.1:**

![Diagram of ketone 1.48.1](image)

Me$_4$NBH(OAc)$_3$ (0.37 g, 1.4 mmol, 5.0 equiv) was added to a solution of acetonitrile (0.5 mL) and acetic acid (1.0 mL) at room temperature. After 10 min, the solution was cooled to -20 °C, and a solution of ketone **1.45.5** (0.056 g, 0.280 mmol, 1.0 equiv) in acetonitrile (0.5 mL) was added via cannula. The reaction was allowed to stir overnight (20 h) at -20 °C. A solution of saturated Rochelle’s salt (5 mL) was added and reaction was allowed to stir at room temperature for 10 min. The reaction mixture was extracted with CH$_2$Cl$_2$ (2 x 10 mL). The combined organic extracts were washed with saturated NaHCO$_3$ and brine, dried over anhydrous MgSO$_4$, and concentrated under reduced pressure. The crude material was purified by column chromatography (gradient 20:1 to 10:1 hexanes:EtOAc) to provide keton **1.48.1** (0.18 g, 0.10 mmol, 36%).
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.80 (dd, $J = 4.0, 3.5$ Hz, 1H), 3.95 – 3.87 (m, 1H), 2.85 (td, $J = 3.7, 1.2$ Hz, 2H), 1.94 – 1.82 (m, 1H), 1.82 – 1.67 (m, 1H), 1.12 (s, 9H), 1.04 (t, $J = 7.4$ Hz, 3H).

**TMS Ether 1.49.1:**

To a solution of ketone 1.45.5 (0.99 g, 4.99 mmol) and imidazole (0.459 g, 6.74 mmol) in dry CH$_2$Cl$_2$ (16 mL) at 0 °C with stirring was added TMSCl (0.83 mL, 6.49 mmol) and DMAP (0.031 g, 0.25 mmol). The reaction mixture was allowed to warm to room temperature and was stirred for 18 h. Then, distilled water was added and the reaction mixture was extracted with CH$_2$Cl$_2$, dried, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexanes:EtOAc 40:1) afforded the desired TMS ether 1.49.1 quantitatively as a colorless oil.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.04 (d, $J = 10.5$ Hz, 1H), 6.08 (d, $J = 10.5$ Hz, 1H), 4.28 (dd, $J = 6.3, 4.2$ Hz, 1H), 1.93 (dd, $J = 14.9, 7.5, 4.2$ Hz, 1H), 1.88 – 1.79 (m, 1H), 1.00 (s, 9H), 0.96 (t, $J = 7.4$ Hz, 3H), 0.14 (s, 9H).
Alcohol 1.49.1a

To a solution of ketone 1.49.1 (0.05 g, 0.185 mmol) in THF (5 mL) at -78 °C was cannulated a cooled solution of 1 M DIBAL-H in hexanes (0.24 mL, 0.24 mmol). The solution was stirred for 15 minutes at which time EtOAc was added and stirred for an additional 10 minutes. The solution was cannulated into a vigorously stirred solution of saturated Rochelle’s salt and stirred for 10 minutes. Et₂O was added, the organic layer was separated, dried over MgSO₄, and concentrated in vacuo. The crude product 1.49.1a was then purified by flash chromatography (10:1 hexanes:EtOAc) to give the desired alcohol (0.040 g, 0.147 mmol, 79%).

¹H NMR (500 MHz, CDCl₃) δ 5.89 – 5.82 (m, 2H), 3.89 – 3.84 (m, 1H), 3.45 (ddd, J = 9.1, 7.1, 3.4 Hz, 1H), 1.85 (dqd, J = 15.1, 7.5, 3.4 Hz, 1H), 1.61 – 1.52 (m, 1H), 1.34 (d, J = 7.1 Hz, 1H), 1.00 (t, J = 7.4 Hz, 3H), 0.91 (s, 9H), 0.14 (s, 9H).

Osmate Ester 1.49.2:

OsO₄ (0.67 mL 0.5 M solution in CH₂Cl₂, 0.334 mmol, 2.0 equiv) was added to a solution of ketone 1.49.1 (0.045 g, 0.167 mmol, 1.0 equiv) and TMEDA (0.076
mL, 0.501 mmol, 3 equiv) in CH₂Cl₂ (1.0 mL) at -78 °C. After stirring at this temperature for 1.5 hr, the CH₂Cl₂ was removed under reduced pressure, and then THF (1 mL), H₂O (1 mL), and Na₂SO₃ (0.1 g) were added. This mixture was allowed to stir vigorously for 30 min. The mixture was extracted with CHCl₃ (3 x 2 mL), the combined organic extracts were washed with brine, dried over anhydrous CaCl₂, and concentrated under reduced pressure to provide osmate ester 1.49.2 (0.062 g, 0.097 mmol, 58%).

¹H NMR (500 MHz, CDCl₃) δ 4.96 (d, J = 4.6 Hz, 1H), 4.49 (dd, J = 4.6, 1.1 Hz, 1H), 4.08 (dd, J = 6.1, 4.9 Hz, 1H), 3.15 – 3.03 (m, 6H), 2.97 (s, 1H), 2.92 (s, 1H), 2.86 (s, 1H), 2.83 (s, 1H), 1.94 – 1.75 (m, 2H), 1.27 (dd, J = 13.2, 6.0 Hz, 3H), 1.16 (s, 9H), 0.22 (s, 9H).

Osmate Ester 1.49.3

NaBH₄ (4 mg, 0.113 mmol, 5.0 equiv) was added to a solution of 1.49.2 (0.015 g, 0.023 mmol, 1.0 equiv) in 1:2 MeOH to CH₂Cl₂ (1 mL) at 0 °C. After 20 min, the reaction was quenched by adding saturated NaHCO₃ (40 mL). Et₂O (100 mL) was added, the organic phase was separated, washed with deionized water and brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure to give the crude product 1.49.3 (yield not determined).
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.45 (d, $J = 4.7$ Hz, 1H), 4.09 – 4.00 (m, 2H), 3.62 (d, $J = 4.8$ Hz, 1H), 3.52 (t, $J = 7.0$ Hz, 1H), 3.18 – 3.05 (m, 4H), 2.97 (s, 3H), 2.90 (s, 3H), 2.89 (s, 3H), 2.84 (s, 3H), 1.88 – 1.69 (m, 3H), 1.13 (s, 9H), 0.99 (t, $J = 7.5$ Hz, 3H), 0.18 (s, 9H).

**Triol 1.49.4:**

Ethylenediamine (0.053 mL, 0.778 mmol, 50 equiv) was added to a solution of osmate ester 1.49.3 (.010 g, 0.016 mmol) in CH$_2$Cl$_2$ (1.5 mL) at room temperature. The reaction was allowed to stir for 1 hr, after which time dilute HCl (1.5 mL) and CH$_2$Cl$_2$ (2.0 mL) were added. The organic phase was separated, washed with saturated NaHCO$_3$ and brine, dried over anhydrous CaCl$_2$, and concentrated under reduced pressure. The crude product was purified by flash chromatography (gradient hexanes to 2:1 hexanes:EtOAc) to provide triol 1.49.4 (yield not determined).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.85 – 3.80 (m, 2H), 3.80 – 3.76 (m, 1H), 3.52 (td, $J = 7.2$, 1.4 Hz, 1H), 2.93 (d, $J = 8.5$ Hz, 1H), 2.76 (d, $J = 8.8$ Hz, 1H), 2.47 (d, $J = 6.2$ Hz, 1H), 1.95 – 1.87 (m, 1H), 1.80 – 1.59 (m, 5H), 1.50 (dt, $J = 13.8$, 5.3 Hz, 1H), 1.08 (s, 9H), 0.99 (t, $J = 7.5$ Hz, 3H), 0.20 (s, 9H).
Osmate Ester 1.46.1:

OsO$_4$ (1.82 mL 0.5 M solution in CH$_2$Cl$_2$, 0.908 mmol, 2.0 equiv) was added to a solution of ketone 1.45.5 (0.090 g, 0.454 mmol, 1.0 equiv) and TMEDA (0.206 mL, 1.362 mmol, 3 equiv) in CH$_2$Cl$_2$ (4.5 mL) at -78 °C. After stirring at this temperature for 1.5 hr, the CH$_2$Cl$_2$ was removed under reduced pressure, and then THF (2 mL), H$_2$O (2 mL), and Na$_2$SO$_3$ (0.5 g) were added. This mixture was allowed to stir vigorously for 30 min. The mixture was extracted with CHCl$_3$ (3 x 5 mL), the combined organic extracts were washed with brine, dried over anhydrous CaCl$_2$, and concentrated under reduced pressure to provide osmate ester 1.46.1 (0.17 g, 0.299 mmol, 66%).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.51 – 5.44 (m, 1H), 3.21 (dd, $J$ = 6.8, 3.2 Hz, 2H), 3.15 (dd, $J$ = 6.9, 3.3 Hz, 2H), 3.02 – 2.87 (m, 15H), 2.00 – 1.90 (m, 1H), 1.91 – 1.80 (m, 1H), 1.24 (s, 9H), 0.98 (t, $J$ = 7.4 Hz, 3H).
Chapter 2

Development of a Novel Lewis Acid for Intramolecular Vinylogous Aldol Reactions

2.1 The Development of ATNP

The Intermolecular Vinylogous Aldol Reaction

The aldol reaction is a versatile carbon-carbon bond forming transformation that is widely used and of great importance in organic synthesis. The extension of this reaction to its vinylog (i.e., the vinylogous aldol reaction) is well known, and in its simplest form, proceeds via a dienolate and an aldehyde. The product, a δ-hydroxy-α,β-unsaturated carbonyl compound, is rich in functionality, and as this bond construction occurs in an uncommon position (between the γ- and δ-carbons of the product), it offers novel strategic disconnections in synthetic planning. In recent years, the reaction has gained significant attention from the organic community, and an important advance was described by Hisashi Yamamoto with the use of the very bulky Lewis acid, aluminum tris(2,6-diphenylphenoxide) (ATPH 2.1.1, Scheme 1).


ATPH is used in reactions of lithium enolates and aldehydes, and it is thought to bind to both the dienolate and the aldehyde components of the reaction. Due to its bulk, it prevents reaction at the $\alpha$-carbon of the dienolate, thereby forcing the reaction to occur at the distal $\gamma$-carbon (Scheme 2.1).

**Scheme 2.1  Yamamoto Vinylogous Aldol Reaction with ATPH**

An important feature of the Yamamoto protocol is that the components must all be combined prior to the addition of the base; attempts to conduct the reaction in a stepwise fashion wherein the enolate is first formed then the aldehyde added provide significantly diminished yields. Because this reaction is not amenable to a two-step enolization/aldehyde addition protocol, if the aldehyde component is enolizable, there must be selectivity in the initial deprotonation step, otherwise a mixture of enolates will result, providing a mixture of products. While Yamamoto has described notable selectivity with many substrate combinations, in the case of crotonate esters, the reaction provides low yields when the aldehyde is enolizable and unhindered at the $\alpha$-
carbon. For example, attempted vinylogous aldol reaction between methyl crotonate and valeraldehyde provides the desired product in a yield of only 22% (Table 1, entry 1). This significantly limits the scope of this reaction, and we recently had a need to apply this method to an unbranched enolizable aldehyde. We, therefore, studied different Lewis acids to overcome this limitation.

**Scheme 2.2** Unsuccessful vinylogous aldol reaction with enolizable aldehyde

*Utilizing Enolizable Aldehydes*

In order to use enolizable aldehydes in this reaction, we required a Lewis acid that upon binding to an aldehyde renders it immune to enolization by bulky kinetic bases such as LDA or LTMP. We, therefore, studied a number of Lewis acids as surrogates for ATPH in a model vinylogous aldol reaction between methyl crotonate (2.2.2) and valeraldehyde (2.2.1) in search of one possessing the right combination of tight binding and bulk (Table 1). Under standard reaction conditions (addition of a cooled solution of LTMP (2.3 equivs) in THF to a toluene solution of the Lewis acid (3.3 equivs), ester (2 equivs) and aldehyde at -78 °C), none of the known Lewis acids
that we studied, including those devised by Yamamoto (MAD,\textsuperscript{36} MABR,\textsuperscript{37} MAT,\textsuperscript{38} ATD,\textsuperscript{39} Me-ATPH\textsuperscript{40}), were successful (Table 2.1).

![Lewis Acids Diagram]

Table 2.1  Vinylogous Aldol Reaction of an Enolizable Aldehyde with Various Known Lewis Acids

We considered the design features of ATPH and sought a Lewis acid with comparable bulk in the vicinity of the aluminum, but with extended “reach” such that, upon binding to an aldehyde, there is greater hindrance of the protons on the α-carbon and limited accessibility to base. We, therefore, considered replacing the phenyl


groups of ATPH with 2-naphthyl groups and devised aluminum tris(2,6-di-2-naphthylphenoxide) (ATNP) wherein the naphthyl groups should extend further forward toward the α-carbon of the aldehyde (Figure 2.1).

![Figure 2.1](image)

*Figure 2.1*  Extending the Reach of ATPH with Naphthyl Groups

To model this hypothesis, we began with the crystal structure of Yamamoto’s ATPH/methyl crotonate complex available from the Cambridge Crystallographic Data Centre CIF Depository. We added the corresponding 2-naphthyl groups and exchanged the ester for valeraldehyde and adjusted the complexation bond lengths and bond angles to the known values for ATPH-aldehyde complexes. We then minimized the energy of the structure (MM2 force field, see Experimental), to obtain a model of ATNP bound to valeraldehyde (Figure 2.2). In this model, the aluminum atom (light blue) of ATNP is shown coordinated to the oxygen (red) of valeraldehyde (carbons shown in yellow). The distal phenyl rings of the 2-naphthyl groups are shown in green and the enolizable protons are highlighted in blue. The aldehydic proton is also shown in blue; all other hydrogens have been omitted for clarity. This structure revealed that the additional reach of the 2-naphthyl groups indeed blocks the enolizable protons of the aldehyde.
The next task was to develop a synthesis of this hypothetical Lewis acid, ATNP. It was imagined that a Suzuki reaction would be employed to prepare the coupling product. Hence, we synthesized the corresponding naphthylboronic acid 2.3.2 in a straightforward manner by metalation of β-bromonaphthalene 2.3.1 with n-BuLi and trapping with trimethylborate (Scheme 2.3). We then examined an array of Suzuki coupling conditions as described in below for the coupling of boronic acid 2.3.2 with 2,6-dibromophenol 2.3.3. However, under the conditions initially examined, we were unable to obtain a yield higher than 29%.
Scheme 2.3  Synthesis of ATNP

It is known that electron rich aryl bromides, such as the phenol in this case, are less reactive than their electron deficient counterparts. We hypothesized that acylating the phenol, thereby reducing its electron density, would improve the yield and we therefore utilized 2.4.1 in the Suzuki reaction. Unfortunately, this reaction was low yielding under the conditions we examined and this substrate was abandoned (Scheme 2.4).
Boronic acids are often difficult to work with because of their tendency to dimerize and trimerize. The pinacol derivative 2.5.1 was consequently prepared and its use was investigated in the coupling reaction (Scheme 2.5).

It appeared that exchanging the phosphorous ligand to RuPhos significantly increased the yield of the reaction and it was assumed that the boronic acid might be as suitable of a coupling partner in this reaction as the pinacol ester 2.5.1. This turned out to be the case and conditions were ultimately developed (Pd(OAc)$_2$, RuPhos, K$_3$PO$_4$, toluene/H$_2$O, 100 °C) that provide the desired product in 98% yield. As in the
case of ATPH, ATNP (2.6.1) is prepared in situ immediately prior to use by stirring the corresponding phenol with trimethylaluminum (Scheme 2.6).

![Scheme 2.6](image)

**Scheme 2.6** Optimized preparation of ATNP

Gratifyingly, with ATNP using the conditions described in Scheme 1, the vinylogous aldol reaction of methyl crotonate (2.2.2) and valeraldehyde (2.2.1) proceeds cleanly to provide the desired γ-adduct (2.2.3) in 82% yield (Scheme 2.7). This is a substantial improvement over the 22% yield observed by Yamamoto using ATPH.

![Scheme 2.7](image)

**Scheme 2.7** The Use of ATNP in a Vinylogous Aldol Reaction with an Enolizable Aldehyde

With ATNP identified, we wished to optimize the reaction conditions and minimize the loading of methyl crotonate. Typically, two equivs of the crotonate are used by Yamamoto with approximately equal amounts of LTMP, and we wished to optimize this reaction using lower loadings of crotonate, which would require a
corresponding decrease in LTMP. We find that a modest decrease in yield is observed with the use of 1.5 equivs of crotonate (76%, Table 2.2, entry 2) and a more significant decrease with 1.1 equivs (60%, Table 2, entry 3). Neither slow addition of the base nor changing the order of addition such that the ATNP complexed substrates are added to the LTMP were beneficial (Table 2.2, entries 4 and 5). The reaction requires lower temperature to proceed cleanly; at -20 °C, the reaction produces greater amounts of byproducts and proceeds in 54% yield (Table 2.2, entry 6). Finally, inverse addition wherein ATNP complexed substrates are added to the LTMP was not advantageous and provided the product in 61% yield (Table 2.2, entry 7).

![Chemical reaction diagram]

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**Table 2.2** Optimization of Reaction Conditions – The mode of addition refers to the manner in which the complex and base were combined. std = cooled solution of LTMP added rapidly by cannula to ATNP-complex; slow std = cooled solution of
LTMP added dropwise by cannula to ATNP-complex; inverse = cooled solution of ATNP-complex added rapidly by cannula to LTMP.

Our optimized conditions are very similar to those of Yamamoto and consist of running the reaction at -78 °C using 2 equivs of the ester, 2.3 equivs of LTMP and 3.3 equivs of ATNP for every equiv of aldehyde. With these conditions identified, we studied the scope of the reaction with a variety of aldehydes. Our results are shown in the following tables.

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<td><img src="14" alt="Image" /></td>
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<tr>
<td>8</td>
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<td><img src="16" alt="Image" /></td>
<td>77</td>
<td>2.4:1 dr</td>
</tr>
</tbody>
</table>
Other unbranched, enolizable aliphatic aldehydes, such as heptanal (2.3.5) and hydrocinnamaldehyde (2.3.7), provided comparable results (76% and 82% yields, respectively, Table 2.3 entries 2 and 3). The α-branched aldehyde, cyclohexylcarboxaldehyde (2.3.9), was also an excellent partner and provided the product (2.3.10) in 96% yield (Table 2.3, entry 4). The reaction proceeded cleanly using pivaldehyde (2.3.11), a highly congested non-enolizable aldehyde (97%, Table 3 entry 5), and as expected, benzaldehyde (2.3.13) was an efficient reaction partner and provided the product in excellent yield (97%, Table 2.3 entry 6). We also studied oxygenation at the α- and β-position of the aldehyde and found that the reaction is tolerant of oxygenation in both positions with silyl as well as benzyl protecting groups. For example, the α-oxygenated substrate, triethylsiloxy acetaldehyde (2.3.15), provided the product in good yield (77%, Table 2.3, entry 7) while the α-benzylated substrates 2.3.17 and 2.3.19 also provided the products in yields of 77% and 87%
(Table 3, entries 8 and 9, respectively). Compounds **2.3.17** and **2.3.19** also provided the opportunity to study asymmetric induction with stereogenicity at the $\alpha$-position. We found that branching is required for high levels of selectivity; unbranched aldehyde **2.3.17** provided the product with a modest 2.4:1 dr while branched aldehyde **2.3.19** provided the product with a 10:1 dr (Table 3, entry 9 and 10, respectively). In both cases, the major isomer was the *anti*-diastereomer. In addition, we find that $\beta$-oxygenated substrates **2.3.21** and **2.3.23** provide the product in good chemical yield with no evidence of $\beta$-elimination, but with low to moderate levels of asymmetric induction (Table 3, entry 10, 65% yield, 1.3:1 dr; entry 11, 78% yield, 3.4:1 dr). Finally, cinnamaldehyde **2.3.25** provided the desired product in modest yield due to competitive conjugate addition (Table 3, entry 12).$^{41}$

We also wished to expand the scope of the nucleophiles in this reaction. First we examined the diastereoselectivity of the reaction when using an ester that would create a new stereocenter in the product. The homolog of methyl crotonate **2.8.3** was prepared via a Horner-Wadsworth-Emmons reaction (Scheme 2.8). The vinylogous aldol reaction of this substrate with benzaldehyde was studied and gratifyingly gave a 96% yield of the desired product **2.8.4** favoring the anti-stereochemistry.

**Scheme 2.8**  Vinylogous Aldol reaction of Ester **2.8.3**

---

We propose an open transition state for this reaction of the ATNP-aldehyde complex wherein the ATNP is on the side of the hydrogen of the aldehyde. Our model assumes that ATNP is larger than the phenyl group of the aldehyde and that antiperiplanar attack will occur. In the transition state leading to the major anti-product, there is a steric interaction between the methyl group of the enolate and the phenyl group of the aldehyde. In the transition state leading to the minor product, the corresponding interaction is between the methyl group and ATNP (Figure 2.3).

![Transition State of the Vinylogous Aldol Reaction of Ester 2.8.3](image)

**Figure 2.3** Transition State of the Vinylogous Aldol Reaction of Ester 2.8.3

The chemistry of the undesired side products derived from enolization through the furan in the original peloruside A model studies was also developed. Ester 2.9.2 was prepared\(^{42}\) and utilized in a vinylogous aldol reaction with ATNP and LTMP wherein enolization through the furan occurs. Reaction with benzaldehyde provides the doubly vinylogous aldol product 2.9.3 in 84% yield (Scheme 2.9). This reaction is also amenable to the enolizable aldehydes and proceeds in 70% yield with valeraldehyde.

Scheme 2.9  Preparation of Furyl Ester 2.9.2 and its use in the Vinylogous Aldol Reaction

2.2 Application of ATNP to the Synthesis of Macrolides

Synthesis of Substrates

With the use of ATNP as a Lewis acid with enolizable aldehydes developed in an intermolecular fashion, we wished to make this a feasible method for forming medium-membered rings with enolizable aldehyde partners. Before application of this method to a natural product synthesis, we conceived a series of model systems shown below (Scheme 2.10). These intramolecular vinylogous aldol precursors could be synthesized in similar fashions and give us the opportunity to study the formation of rings of various sizes, and the diastereoselectivities in their reactions.
A representative synthesis of an intramolecular precursor is shown below (Scheme 2.11) Starting with 2-iodobenzylalcohol 2.11.1, 2-iodobenaldehyde 2.11.2 was prepared in a straightforward manner by oxidation with PCC. Nucleophilic attack by methyl Grignard gave the corresponding secondary alcohol 2.11.3 without any detectable metal-halide exchange. The alcohol was then protected as a TBS ether 2.11.4 under standard conditions. The next step of the synthesis involved a tandem palladium catalyzed Heck arylation and alkene isomerization with hexenol. Once the Heck coupling is complete, the resulting alkene can equilibrate and migrate to the terminus to provide the enol. This enol then irreversibly tautomerizes to the aldehyde. The TBS ether is then cleaved under acidic conditions at 50 ºC to provide the free alcohol 2.11.6. The hydroxyl group was then acylated with crotonic anhydride to provide the corresponding precursor 2.11.7 for an intramolecular vinylogous aldol reaction with an enolizable aldehyde coupling partner.

Scheme 2.11 Synthesis of intramolecular vinylogous aldol precursor 2.11.7

*The Intramolecular Vinylogous Aldol Reaction*

After preparing the necessary substrates, we wished to apply the intramolecular vinylogous aldol reaction using ATNP to make medium-membered
lactones of 12- and 14-members. The results are shown below in Table 2.4. A control, non-enolizable substrate 2.4.12, which is known to undergo successful cyclizations with ATPH was carried out with ATNP demonstrating the utility of the new Lewis acid to promote these macroaldolizations. Both 12- and 14-membered ring systems were formed in good yields (79-94%) and in moderate levels of diastereoselectivity.

Table 2.4 The intramolecular vinylogous reaction of enolizable aldehydes

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield</th>
<th>Dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.4.3</td>
<td>2.4.4</td>
<td>81%</td>
<td>2.4.6</td>
</tr>
<tr>
<td>2.4.5</td>
<td>2.4.6</td>
<td>79%</td>
<td>2.4.8</td>
</tr>
<tr>
<td>2.4.7</td>
<td>2.4.8</td>
<td>90%</td>
<td>2.4.10</td>
</tr>
<tr>
<td>2.4.11</td>
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<td>94%</td>
<td>2.4.12</td>
</tr>
<tr>
<td>2.4.13</td>
<td>2.4.13</td>
<td>86%</td>
<td>15:1 dr</td>
</tr>
</tbody>
</table>

2.3 Future Directions

ATNP mediated additions to chiral aldehydes will also be studied in order to assess the diastereotopic face selectivity of the substrates in this reaction (Scheme 2.12). We have studied a single example of a chiral aldehyde bearing a stereocenter at the α-carbon, and found that the reaction provides a diastereomeric ratio of 10:1
favoring the *anti*-product (Table 2.3, entry 9; duplicated in Scheme 2.12). This is consistent with the polar Felkin-Anh model, as expected using an aluminum Lewis acid not capable of chelation. We suspect that this reaction will benefit from the steric effects of the ATNP as Heathcock has shown that increasing the substituents size of Lewis acid bound carbonyls will increase the stereoselectivity in nucleophilic additions to chiral substrates. We will study the substrates shown in Scheme 2.12 bearing alkyl and alkoxy groups at the α- and β-carbons using methyl crotonate as well as the homolog, 2.8.3.

Scheme 2.12  Additions to Chiral Aldehydes

As described above, we had initially studied the synthesis of peloruside A via a non-enolizable furfural derivative that was subjected to an intramolecular vinylogous aldol reaction to form the macrolide. This synthesis was problematic as the product must be subjected to an Achmatowicz rearrangement which produces a pyranone, and we experienced difficulty installing the requisite hydroxy and methoxy substituents with the correct stereochemistry on the pyranone. Proceeding through the furfural was required because our previous methods were not amenable to the use of enolizable aldehydes; however, the use of ATNP avoids these limitations and we have redesigned this synthesis to proceed in a more direct fashion. Our plan is heavily
influenced by our lessons from our work with the furfural system and is shown in Scheme 2.13 below.

We will begin with D-lyxose which is commercially available (current price is about $2.50/gram from Carbosynth) and which will be converted by a known procedure to TBS acetonide 2.13.1. This compound will then be subjected to Wittig olefination, deprotection and oxidative cleavage with periodate to provide enal 2.13.3. The aldehyde will then undergo an aldol reaction with methyl isobutyrate by a known procedure, reduced to the diol with lithium aluminum hydride, then oxidized (Dess-Martin periodinane) to keto aldehyde 2.13.4.

Scheme 2.13  Preparation of Aldehyde 2.13.4

As described above, ketone 1.30.3 will then undergo a 1,5-anti-aldol reaction with aldehyde 2.13.4 to merge the two fragments together. The product of the aldol reaction will then be subjected to a hydroxyl-directed anti reduction (Me₄N(OAc)₃BH), and protected as the isopropyl silylene 2.14.1 (Scheme 2.14). Deprotection of the PMB ether (DDQ) will be followed by acylation of the resulting alcohol with crotonic anhydride to give the crotonate ester (not shown). This compound will then undergo selective hydroboration/oxidation of the less hindered
and more reactive terminal alkene with a bulky hydroborating agent (9-BBN) to provide the primary alcohol which will be oxidized (Swern) to provide aldehyde 2.14.2 ready for the key intramolecular vinylogous aldol reaction. This will be conducted using our standard conditions, which are 2.3 equivalents of ATNP and 1.2 equivalents of LTMP at -78 °C. Of course, these conditions are amenable to optimization with respect to the number of equivalents of the reagents use, the temperature and time of the reaction and the solvent, and we will study the optimization of this reaction should our initial attempts prove unsuccessful or moderately successful. We anticipate obtaining the desired stereochemistry at the C-5 alcohol in the vinylogous aldol reaction based on our previous work using furfural substrate 1.34.1 and derivatives (data not shown) wherein we found that when the hydroxyl groups at C-11 and C-13 are engaged as a silylene, we obtain the desired stereochemical outcome at C-5. The stereochemistry was, however, reversed when these two alcohols were not protected in a cyclic array. In any event, if we obtain the undesired stereochemistry, we will perform the vinylogous aldol reaction on a substrate wherein the hydroxyl groups at C-11 and C-13 are not tied up as a silylene. Should this also fail we will then resort to an inversion (Mitsunobu or an oxidation / reduction sequence) to provide the desired stereochemistry. We do not anticipate the ketone at C9 to be problematic in the vinylogous aldol reaction as it is very hindered and significantly less electrophilic than the aldehyde.
Completion of the synthesis will then proceed by dihydroxylation of the enoate using the matched AD-mix-β reagent: again this transformation has precedence in our prior work using the furfural approach wherein these conditions provided the desired stereochemistry on compound 2.14.3 (Scheme 2.15). Silylation of the hydroxyl group at C-2 was found to be selective on our previous furfural-derived system, and will be followed by methylation using methyl Meerwein’s reagent and the mild base 2,6-di-tert-Butyl-pyridine so as to avoid any potential silyl migration. Removal of the benzyl ether and subsequent oxidation of the free hydroxyl would provide 2.15.1. Removal of the labile silylene in the presence of the TBS ether with HF in pyridine is well precedent, and we have observed this transformation on our furfural system. This will be followed by selective methylation of the hydroxyl group at C-13 with methyl Meerwein’s reagent and 2,6-di-tert-butylpyridine, a transformation which has precedent in the work of Debrabander. Protection of the alcohol as a TBS ether provides ketone 2.15.2. Installation of the alkene will be
accomplished using the known phosphonium salt 2.15.3 and will take advantage of Clark Still’s observation that Wittig reactions on α-alkoxy ketones selectively provide the Z- alkene geometry. Deprotection of the remaining acetonide will be followed by methylation of the more accessible hydroxyl group on C-7, a transformation that has precedence in the work of Taylor.

Scheme 2.15  Completion of Peloruside A

2.4  Experimental

All reactions were performed in oven-dried or flame-dried glassware under a dry nitrogen atmosphere. Toluene was washed with cold concentrated H$_2$SO$_4$, H$_2$O, 1 M NaOH, H$_2$O, dried over anhydrous MgSO$_4$, filtered and distilled from CaH$_2$ under nitrogen prior to use. CH$_2$Cl$_2$, Et$_3$N, and 2,2,6,6-tetramethylpiperidine were distilled from CaH$_2$ under nitrogen prior to use. THF and Et$_2$O were distilled from Na benzophenone ketyl under nitrogen prior to use. DMF was distilled from CaH$_2$ at
reduced pressure prior to use. Commercially available aldehyde substrates 2.2.1, 2.3.5, 2.3.7, 2.3.9, 2.3.11, 2.3.13, and 2.3.24 were distilled immediately before use. Non-commercially available aldehydes 2.3.15, 2.3.17, 2.3.19, 2.3.21, 2.3.23 and 2.3.24 were prepared according to standard literature procedures. All other chemicals were used as received from the supplier. Flash chromatography was performed using 60 Å silica gel (37-75 μm). 1H NMR spectra were recorded at 500 MHz in CDCl3 using residual CHCl3 (7.24 ppm) as the internal reference. 13C NMR spectra were recorded at 75 MHz in CDCl3 using residual CHCl3 (77.26 ppm) as the internal reference. Exact mass was determined using electrospray ionization on the sodiated ([M+Na]+) molecular ion.

\[
\begin{align*}
\text{HO-} & \quad \text{1. NaH} \quad \text{2. BuBr, TBAI} \\
2.3.1a & \rightarrow \quad \text{HO-} \quad \text{1. Oxalyl Chloride, DMSO} \quad \text{2. Et3N} \\
2.3.1b & \rightarrow \quad \text{H} \quad \text{OBn} \\
2.3.1c & 
\end{align*}
\]

3-(benzyl oxy)propan-1-ol 2.3.1c:

To a stirring solution of propane-1,3-diol 2.3.1a (2.89 g, 2.75 mL, 38.0 mmol) in THF (60 mL) at rt, was added NaH (60% dispersion in mineral oil, 1.745 g, 43.9 mmol) in portions. Upon completion of the addition, the suspension was stirred for 30 minutes at which time benzyl bromide (5g, 3.48 mL, 29.2 mmol) and TBAI

(tetrabutylammonium iodide, 1.080 g, 2.92 mmol) were added, the flask fitted with a condenser, and brought to reflux for 12 hours. The reaction mixture was cooled to room temperature, diluted with ether (50 mL), washed with saturated NaHCO₃, (25 mL) and brine (25 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo. The crude oil was then purified by flash chromatography (2% MeOH in CH₂Cl₂) to provide the desired alcohol (2.3.1b, 4.81 g, 29.1 mmol, 95%) as a colorless oil.

$^{1}$H NMR (500 MHz, CDCl₃) δ 7.37 – 7.25 (m, 5H), 4.51 (s, 2H), 3.77 (t, $J = 5.6$ Hz, 2H), 3.65 (t, $J = 5.8$ Hz, 2H), 1.89 – 1.81 (m, 2H); $^{13}$C NMR (75 MHz, CDCl₃) δ 138.30, 128.71, 127.97, 127.90, 73.55, 69.74, 62.28, 32.35.

3-(benzyloxy)propanal 2.3.1c:

To a solution of oxalyl chloride (3.44 g, 2.34 mL, 27.1 mmol) in CH₂Cl₂ (80 mL) at -78 °C was added DMSO (5.64 g, 5.12 mL, 72.2 mmol) in CH₂Cl₂ (10 mL) over 10 minutes. The reaction was allowed to stir an additional 15 minutes after which alcohol 2.3.1b (3.0 g, 18.05 mmol) in CH₂Cl₂ (5mL) was added. The reaction was allowed to stir for 1 hour at which time Et₃N (7.31 g, 10.15 mL, 72.2 mmol) was added and the cold bath removed, and reaction stirred overnight. The reaction mixture was poured into water (50 mL) and extracted with EtOAc (3 x 50 mL). The organic layers were combined then washed saturated NaHCO₃ (30 mL) and brine (25 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo. The crude oil was
then purified by flash chromatography (10:1 hexanes:EtOAc) to give the desired product 2.3.1c (2.74 g, 16.69 mmol, 92%) as a colorless oil.

\[ \text{H NMR (500 MHz, CDCl}_3\text{)} \delta 9.80 (t, \text{ } J = 1.8 \text{ Hz, 1H}), 7.41 - 7.27 (m, 5H), 4.54 (s, 2H), 3.82 (t, \text{ } J = 6.1 \text{ Hz, 2H}), 2.71 (td, \text{ } J = 6.1, 1.8 \text{ Hz, 2H}); \text{ ^13C NMR (75 MHz, CDCl}_3\text{)} \delta 201.38, 138.08, 128.70, 128.03, 127.95, 73.52, 64.08, 44.13. \]

**Alcohol 2.3.1d:**

TBSCI (1.0 g mmol, 6.63 mmol) in CH\(_2\)Cl\(_2\) (10 mL) was added to a stirred solution of 1,3-propanediol 2.3.1a (2.02 g, 1.92 mL, 26.5 mmol) and imidazole (13.27 mmol, 0.903 g) in DMF (1.5 ml) at 0 °C over 1 hour. The solution was allowed to warm to rt and stir for 16 hours. The reaction mixture was extracted with petroleum ether (3x 10 mL), the organic layers combined, washed with saturated NaHCO\(_3\) (20 mL) and brine (20 mL), dried over anhydrous MgSO\(_4\), and concentrated under reduced pressure on the rotary evaporator. The crude product was purified by flash chromatography (gradient20:1 hexanes:EtOAc to EtOAc) to provide the desired alcohol 2.3.1d (.356 g, 1.872 mmol, 28%) as a colorless oil.

\[ \text{H NMR (500 MHz, CDCl}_3\text{)} \delta 3.84 - 3.80 (m, 2H), 3.80 - 3.76 (m, 2H), 2.55 (bs, 1H), 1.81 - 1.70 (m, 2H), 0.88 (s, 9H), 0.06 (s, 6H); \text{ ^13C NMR (75 MHz, CDCl}_3\text{)} \delta 63.26, 62.80, 34.40, 26.13, 18.43, -5.24. \]
Aldehyde 2.3.1e:

To a solution of oxaly chloride (.336 g, 0.232 mL, 2.65 mmol) in CH₂Cl₂ (8 mL) at -78 ºC was added DMSO (.552 g, 0.502 mL, 7.07 mmol) in CH₂Cl₂ (1 mL) over 10 minutes and let stir an additional 15 minutes. Alcohol 2.3.1d (.336 g, 1.77 mmol) in CH₂Cl₂ (1 mL) was added and let stir for 1 hour at which time Et₃N (.715 g, 0.993 mL, 7.07 mmol) was added and the stirring solution was let warm to rt and stir overnight. The reaction mixture was poured into water (20 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were combined and washed saturated NaHCO₃ (15 mL) and brine (15 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo. The crude oil was then purified by flash chromatography (10:1 hexanes:EtOAc) to give the desired product 2.3.1e (.184 g, 0.977 mmol, 55%) as a colorless oil.

¹H NMR (500 MHz, CDCl₃) δ 9.78 (t, J = 2.1 Hz, 1H), 3.97 (t, J = 6.0 Hz, 2H), 2.58 (td, J = 6.0, 2.1 Hz, 2H), 0.86 (s, 9H), 0.04 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 202.30, 57.65, 46.82, 26.06, 18.47, -5.19.

Ester 2.3.15b

To a solution of α-hydroxy ester 2.3.15a (1 g, 0.926 mL, 9.61 mmol) in CH₂Cl₂ (19 mL), was added Et₃N (1.26 g, 1.76 mL, 12.49 mmol) at rt and then the reaction mixture was stirred for 30 min. The reaction mixture was cooled to 0 ºC and TESCl (1.59 g, 1.79 mL, 10.57 mmol) was added dropwise. The mixture was allowed
to warm to rt followed by stirring for 3 h. Saturated aqueous NaHCO₃ was poured into the mixture, the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over (MgSO₄) and concentrated to afford the crude product. Flash chromatography (20:1 hexanes/ethyl acetate) gave the desired product 2.3.15b.

^1H NMR (500 MHz, CDCl₃) δ 4.21 (s, 1H), 4.18 (q, J = 7.2 Hz, 1H), 1.26 (t, J = 7.1 Hz, 1H), 0.95 (t, J = 7.9 Hz, 3H), 0.63 (q, J = 8.0 Hz, 2H); ^13C NMR (75 MHz, CDCl₃) δ 171.94, 61.74, 61.01, 14.45, 6.87, 4.57.

**Aldehyde 2.3.15**

To a solution of ester 2.3.15a (1.5 g, 6.87 mmol) in hexanes/ether (10:1, 35 mL) at -78 ºC was added a -78 ºC solution of DIBAL-H (1 M solution in hexanes) (8.24 mL, 8.24 mmol) dropwise by cannula. The reaction mixture was stirred for 1.5 hr at -78 ºC at which time MeOH (10 mL) was added and let stir for 1 hour at -78 ºC. The reaction mixture was cannulated into a vigorously stirred saturated aqueous solution of Rochelle’s Salt (50 mL) and let warm to RT and stirred overnight. The organic layer was separated, washed with saturated NaHCO₃, (25 mL) and brine(25 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo. The crude oil was then purified by flash chromatography (20:1 hexanes:EtOAc) to give the desired aldehyde 2.3.15 (.465 g, 2.67 mmol, 39%) as a yellow oil.

^1H NMR (500 MHz, CDCl₃) δ 9.69 (t, J = 0.8 Hz, 1H), 4.19 (d, J = 0.8 Hz, 2H), 0.95 (t, J = 7.9 Hz, 9H), 0.63 (q, J = 8.0 Hz, 6H); ^13C NMR (75 MHz, CDCl₃) δ 202.62, 69.49, 6.85, 4.54.
(−)-(S)-Ethyl 2-(benzyloxy)propanoate 2.3.17b:

To a stirring solution of (R)-ethyl-2-hydroxybutyrate 2.3.17a (1 g, 8.47 mmol) and benzyl trichloroacetimidate (3.21 g, 12.7 mmol) in 19 mL of cyclohexane:CH₂Cl₂ (2:1) was added 0.075 mL of triflic acid. This solution was allowed to stir at room temperature for 36 h and then quenched with aqueous NaHCO₃. The organic layer was separated and the aqueous layer was washed three times with 20-mL portions of CH₂Cl₂. The organic layers were combined, dried over MgSO₄, and concentrated in vacuo. The resulting solid was filtered and washed with hexanes. The crude product was then purified by flash chromatography (12:1 hexanes:EtOAc) to give the desired ester 2.3.17b as a white solid (1.29 g, 79%).

¹H NMR (500 MHz, CDCl₃) δ 7.45 – 7.28 (m, 5H), 4.71 (d, J = 11.6 Hz, 1H), 4.46 (d, J = 11.6 Hz, 1H), 4.30 – 4.16 (m, 2H), 4.06 (q, J = 6.9 Hz, 1H), 1.45 (d, J = 6.9 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H).

(−)-(S)-2-(Benzyloxy)propanal 2.3.17:

To a solution of ester 2.3.17b (1.29 g, 6.21 mmol) in hexanes:ether (6:1, 35 mL) at -78 °C was cannulated a cooled solution of 1 M DIBAL-H in hexanes (6.83 mL, 6.83 mmol). The solution was stirred for 1.5 hours at which time MeOH (10 mL) was added and stirred for an additional hour. The solution was cannulated into a vigorously stirred solution of saturated Rochelle’s salt and stirred for 2 hours. The
organic layer was separated, dried over MgSO₄, and concentrated in vacuo. The crude product was then purified by flash chromatography (10:1 hexanes:EtOAc) to give the desired aldehyde 2.3.17 as a yellow oil (0.855 g, 5.21 mmol, 79%).

\[^1H\text{ NMR (500 MHz, CDCl}_3\delta 9.68 \ (d, J = 1.8 \text{ Hz}, 1\text{H}), 7.47 - 7.29 \text{ (m, 5H)}, 4.64 \ (q, J = 11.7 \text{ Hz}, 2\text{H}), 1.35 \ (d, J = 6.9 \text{ Hz}, 3\text{H}).\]

3-(tert-butyldimethylsiloxy)-butyrate 2.3.21b:

To a stirred solution of tert-butyldimethylsilyl chloride (TBSCI, 1.37 g, 9.08 mmol), DMAP (0.092 g, 0.757 mmol) and imidazole (0.67 g, 9.84 mmol) dissolved in dry DMF (15 mL) was added the ethyl ester 2.3.21a (1.0 g, 7.57 mmol). The solution was stirred for 14 hours and after addition of saturated NaHCO₃ aqueous solution (25 mL), the mixture was extracted with Et₂O (30 mL x 3), washed with H₂O, brine, dried over MgSO₄, and concentrated in vacuo. Crude material 2.3.21b was attained in quantitative yield and deemed pure enough for the next step.

\[^1H\text{ NMR (500 MHz, CDCl}_3\delta 4.36 – 4.21 \text{ (m, 1H)}, 4.20 – 4.04 \text{ (m, 2H)}, 2.48 \ (dd, J = 14.5, 7.7 \text{ Hz}, 1\text{H}), 2.37 \ (dd, J = 14.5, 5.3 \text{ Hz}, 1\text{H}), 1.27 \ (t, J = 7.2 \text{ Hz}, 3\text{H}), 1.20 \ (d, J = 6.1 \text{ Hz}, 3\text{H}), 0.87 \ (s, 9\text{H}), 0.07 \ (s, 3\text{H}), 0.05 \ (s, 3\text{H}).\]

3-(tert-Butyldimethylsiloxy)butanal 2.3.21:

To a solution of ester 2.3.21b (1.87 g, 7.57 mmol) in hexanes:ether (6:1, 38 mL) at -78 °C was cannulated a cooled solution of 1 M DIBAL-H in hexanes (8.33
mL, 8.33 mmol). The solution was stirred for 1.5 hours at which time MeOH (10 mL) was added and stirred for an additional hour. The solution was cannulated into a vigorously stirred solution of saturated Rochelle’s salt and stirred for 2 hours. The organic layer was separated, dried over MgSO₄, and concentrated in vacuo. The crude product was then purified by flash chromatography (40:1 petroleum ether:EtoAc) to give the desired aldehyde 2.3.21 as a yellow oil (1.50 g, 7.43 mmol, 98%).

\[ ^1H \text{ NMR (400 MHz, CDCl}_3 \text{) } \delta 9.81 (dd, J = 2.8, 2.1 \text{ Hz, 1H}), 4.36 (dqd, J = 12.3, 6.2, 5.0 \text{ Hz, 1H}), 2.56 (ddd, J = 15.7, 7.0, 2.8 \text{ Hz, 1H}), 2.47 (ddd, J = 15.7, 5.0, 2.1 \text{ Hz, 1H}), 1.24 (d, J = 6.2 \text{ Hz, 3H}), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). \]

**Ethyl-3-(Benzyloxy)butyrate 2.3.23b:**

To a stirring solution of ethyl-3-hydroxybutyrate 2.3.23a (1 g, 7.57 mmol) and benzyl trichloroacetimidate (9.08 mmol) in 21 mL of cyclohexane:CH₂Cl₂ was added 0.067 mL of triflic acid. This solution was allowed to stir at room temperature for 36 h and then quenched with aqueous NaHCO₃. The organic layer was separated and the aqueous layer was washed three times with 20-mL portions of CH₂Cl₂. The organic layers were combined, dried over MgSO₄, and concentrated in vacuo. The resulting solid was filtered and washed with hexanes. The crude product was then purified by flash chromatography (20:1 hexanes:EtoAc) to give the desired ester 2.3.23b (0.473 g, 93% BRSM).
\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 7.41 – 7.28\) (m, 5H), \(4.58\) (d, \(J = 11.6\) Hz, 1H), 
\(4.51\) (d, \(J = 11.6\) Hz, 1H), \(4.22 – 4.08\) (m, 2H), \(4.03\) (dp, \(J = 7.3, 6.1\) Hz, 1H), 
\(2.66\) (dd, \(J = 15.0, 7.3\) Hz, 1H), \(2.44\) (dd, \(J = 15.0, 5.7\) Hz, 1H), \(1.30 – 1.23\) (m, 6H).

**3-(Benzyloxy)butanal 2.3.23:**

To a solution of ester 2.3.23b (0.386 g, 1.734 mmol) in hexanes:ether (4:1, 10 mL) at -78 °C was cannulated a cooled solution of 1 M DIBAL-H in hexanes (1.91 mL, 1.908 mmol). The solution was stirred for 1.5 hours at which time MeOH (10 mL) was added and stirred for an additional hour. The solution was cannulated into a vigorously stirred solution of saturated Rochelle’s salt and stirred for 2 hours. The organic layer was separated, dried over MgSO\(_4\), and concentrated in vacuo. The crude product was then purified by flash chromatography (10:1 hexanes:EtOAc) to give the desired aldehyde 2.3.21 as a yellow oil (0.164 g, 0.920 mmol, 53%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 9.79\) (dd, \(J = 2.5, 1.9\) Hz, 1H), \(7.43 – 7.26\) (m, 5H), \(4.61\) (d, \(J = 11.6\) Hz, 1H), \(4.48\) (d, \(J = 11.6\) Hz, 1H), \(4.09\) (dqd, \(J = 7.4, 6.2, 5.0\) Hz, 1H), \(2.71\) (ddd, \(J = 16.4, 7.4, 2.5\) Hz, 1H), \(2.53\) (ddd, \(J = 16.4, 5.0, 1.9\) Hz, 1H), 
\(1.30\) (d, \(J = 6.2\) Hz, 3H).
1.4-bis-(tert-butyldimethylsilyloxy)but-2-ene 2.3.1g:

According to a literature procedure, a solution of 2-butene-1,4-diol 2.3.1f (1.5 g, 17.03 mmol) and imidazole (4.46 g, 3.41 mmol) in dry CH₂Cl₂ (45 mL) was cooled to 0 °C with stirring under argon atmosphere and a solution of tert-butyldimethylsilyl chloride (6.15 g, 40.9 mmol) and DMAP (0.416 g, 3.41 mmol) in dry CH₂Cl₂ (40 mL) at 0 °C was added via cannula. The reaction mixture was allowed to warm to room temperature and was stirred for 18 h. Then, distilled water (125 mL) was added and the reaction mixture was extracted with CH₂Cl₂, dried, filtered, and concentrated under reduced pressure. Purification by flash chromatography using EtOAc/hexanes (1:50) afforded the desired bi-protected alkene 2.3.1g (5.2 g, 96 %) as a colorless oil.

¹H NMR (500 MHz, CDCl₃) δ 5.56 (td, J = 3.3, 1.6 Hz, 2H), 4.24 (dd, J = 3.4, 0.8 Hz, 4H), 0.91 (s, 18H), 0.08 (s, 12H).

Aldehyde 2.3.1h:

According to a literature procedure, a solution of 2.3.1g (3.10 g, 9.78 mmol) in dry CH₂Cl₂ (49 mL) was cooled to -78 °C, and ozone was bubbled through until the solution turned blue. Nitrogen was then bubbled through the solution until the reaction mixture turned colorless. Triphenylphosphine (3.08 g, 11.74 mmol) was added, and the mixture was warmed to room temperature and stirred under nitrogen for 1.5 h. The solvent was removed in vacuo, and the residue was purified by flash

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chromatography (20:1 hexanes:EtOAc) to yield **2.3.1h** (1.63 g, 9.35 mmol, 96%) as a colorless oil.

$^1$H NMR (500 MHz, CDCl$_3$) δ 9.71 (t, J = 0.8 Hz, 1H), 4.23 (d, J = 0.8 Hz, 2H), 0.94 (s, 9H), 0.11 (s, 6H).

**Ester 2.3.1j:**

To a flask containing TBSCI (3.83 g, 25.4 mmol) and DMAP (3.10 g, 25.4 mmol) in DMF (51 mL) at 0 °C alcohol **2.3.1i** (3.0 g, 25.4 mmol) was added slowly and let stir 2 hours. The reaction was quenched with saturated ammonium chloride, extracted with hexanes (3x), washed with water, brine, dried over MgSO$_4$ concentrated in vacuo. The crude reaction was purified by flash chromatography (20:1) to give the product **2.3.1j** as a yellow oil (5.2 g, 22.38 mmol, 88%).

$^1$H NMR (500 MHz, CDCl$_3$) δ 4.32 (q, J = 6.7 Hz, 1H), 4.19 (qq, J = 10.8, 7.1 Hz, 2H), 1.41 (d, J = 6.8 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 0.91 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H).

**Aldehyde 2.3.1k:**

To a solution of ester **2.3.1j** (1.0 g, 4.30 mmol) in hexanes (22 mL) at -78 °C was cannulated a cooled solution of 1 M DIBAL-H in hexanes (4.73 mL, 4.73 mmol). The solution was stirred for 1.5 hours at which time MeOH (10 mL) was added and stirred for an additional hour. The solution was cannulated into a vigorously stirred
solution of saturated Rochelle’s salt and stirred for 2 hours. The organic layer was separated, dried over MgSO₄, and concentrated in vacuo. The crude product was then purified by flash chromatography (40:1 hexanes:EtOAc) to give the desired aldehyde 2.3.1k as a yellow oil (0.044 g, 0.169 mmol, 79%).

\[ ^1H \text{NMR (500 MHz, CDCl}_3 \delta 9.59 \text{ (d, } J = 1.3 \text{ Hz, } 1H), 4.07 \text{ (qd, } J = 6.9, 1.3 \text{ Hz, } 1H), 1.26 \text{ (d, } J = 6.9 \text{ Hz, } 3H), 0.90 \text{ (s, } 9H), 0.08 \text{ (d, } J = 6.2 \text{ Hz, } 6H). \]

![Chemical structure diagram](image)

(R)-2-hydroxy-3-methylbutanoic acid 2.3.19b

Acid 2.3.19b was prepared according to a literature procedure.²⁵ L-Valine 2.3.19a (1.60 g, 13.66 mmol) was placed into 3-necked flask, and water (10 mL) was added. The flask was fitted with two addition funnels and a stirrer-bar. In one addition funnel, was placed 2 N H₂SO₄ (7.50 mL). To the other addition funnel was added 2 N NaNO₃ (7.50 mL). The reaction vessel was cooled to 0 ºC, and the acid was added dropwise with stirring. After the L-valine dissolved, the sodium nitrite solution was added dropwise, and the rate of addition of the acid was adjusted similarly. After the addition was complete, the reaction was stirred at 0 ºC for 3 h and then allowed to stir at room temperature for 12 h. After this time, the reaction mixture was extracted with EtOAc (5 x 10 mL). The combined organic extracts were dried
(Na$_2$SO$_3$), filtered, and concentrated. The resulting crude solid was recrystallized twice from ether/petroleum ether to afford compound **2.3.19b** (0.92 g, 57% yield) as a white, crystalline solid.

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.30 (br s, 2H), 4.16 (d, $J = 3.6$, 1H), 2.09-2.19 (m, 1H), 1.05 (d, $J = 6.9$, 3H), 0.92 (d, $J = 6.9$, 3H).

**R**-methyl 2-hydroxy-3-methylbutanoate **2.3.19c**:

**Ester** **2.3.19c** was prepared in a similar manner to a procedure in the literature.$^{45}$ Refluxing a solution of (R)-2-hydroxy-3-methylbutanoic acid (5.0 g, 42.3 mmol) in MeOH (85 mL) with a catalytic amount of concentrated H$_2$SO$_4$ (.45 mL, 8.47 mmol) for 2 h. The reaction was concentrated in vacuo, diluted with ether (80 mL), and washed with saturated NaHCO$_3$, (80 mL) and brine (50 mL). The organic phase was dried (MgSO$_4$), filtered, and concentrated, which gave 4.24 g (76%) Methyl (R)-2-(Benzyloxy)-3-methylbutanoate **2.3.19c** as an oil with spectra that were consistent with the reported data.

$^1$H NMR (500 MHz, CDCl$_3$) δ 4.03 (dd, $J = 5.4$, 3.6 Hz, 1H), 3.78 (s, 3H), 2.64 (d, $J = 5.9$ Hz, 1H), 2.05 (heptd, $J = 6.9$, 3.5 Hz, 1H), 1.00 (d, $J = 6.9$ Hz, 3H), 0.84 (d, $J = 6.9$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 175.63, 75.28, 52.63, 32.40, 19.00, 16.24.

**R**-methyl 2-(benzyloxy)-3-methylbutanoate **2.3.19d**

Methyl (R)-2-hydroxy-3-methylbutanoate **2.3.19c** (1.0 g, 7.57 mmol) was dissolved in a solution of cyclohexane/CH$_2$Cl$_2$, (2:1, 19 mL). The reaction flask was
cooled to 0 °C, and benzyl 2,2,2-trichloroacetimidate (1.69 mL, 9.08 mmol) was added with stirring. To the resulting solution was added a catalytic amount of trifluoro-methanesulfonic acid (0.67 mL, 0.757 mmol). After 24 hours, the reaction was filtered, and the collected solid was rinsed with cyclohexane. The filtrate was washed with saturated NaHCO₃ (3 x 25 mL) and brine (25 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo. The crude oil was then purified by flash chromatography (20:1 hexanes:EtOAc). Pure methyl (R)-2-(benzyloxy)-3-methylbutanoate 2.3.19d (.858 g, 51% yield) was obtained as a colorless oil with spectra consistent with reported data.

\[ ^1H \text{ NMR (500 MHz, CDCl}_3\delta 7.41 – 7.25 (m, 5H), 4.68 (d, } J = 11.8 \text{ Hz, 1H), 4.36 (d, } J = 11.8 \text{ Hz, 1H), 3.73 (s, 3H), 3.68 (d, } J = 5.7 \text{ Hz, 1H), 2.13 – 2.00 (m, 1H), 0.94 (dd, } J = 12.1, 6.8 \text{ Hz, 6H).} \]

(R)-2-(benzyloxy)-3-methylbutanal 2.3.19:

To a solution of ester 2.3.19d (.858 g, 3.86 mmol) in hexanes/ether (10:1, 40 mL) at -78 °C was added a -78 °C solution of DIBAL-H (1 M solution in hexanes) (4.25 mL, 4.25 mmol) dropwise by cannula. The reaction mixture was stirred for 1.5 hr at -78 °C at which time MeOH (10 mL) was added and let stir for 1 hour at -78 °C. The reaction mixture was cannulated into a vigorously stirred saturated aqueous solution of Rochelle’s Salt (50 mL) and let warm to RT and stirred overnight. The organic layer was separated, washed with saturated NaHCO₃, (25 mL) and brine(25 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo. The crude oil
was then purified by flash chromatography (30:1 hexanes:EtOAc) to give the desired aldehyde 2.3.19 (0.531 g, 2.76 mmol, 72%) as a yellow oil.

^1H NMR (500 MHz, CDCl$_3$) $\delta$ 9.64 (d, $J = 2.7$ Hz, 1H), 7.42 – 7.26 (m, 5H), 4.67 (d, $J = 11.8$ Hz, 1H), 4.48 (d, $J = 11.8$ Hz, 1H), 3.46 (dd, $J = 5.8$, 2.7 Hz, 1H), 2.08 (qd, $J = 12.7$, 6.9 Hz, 1H), 0.98 (dd, $J = 9.3$, 6.9 Hz, 6H).

Methyl 2-(diethoxyphosphoryl)acetate 2.4.2

A stirred mixture of methyl bromoacetate 2.4.1 (2.85, 30.1 mmol) and triethylphosphite (5.0 g, 30.1 mmol) was heated at 60 °C for 2 h. After this time volatiles were removed in vacuo to give 2.4.2 as a colorless liquid (6.1 g, 29.0 mmol, 96%).

^1H NMR (400 MHz, CDCl$_3$), $\delta$  4.17  (qd, $J = 8.3$, 0.9 Hz, 4H), 3.75  (s,  3H), 2.96  (d, $J = 21.5$ Hz, 2H), 1.33 (td, $J = 7.0$, 0.5 Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$), $\delta$ 166.2 (d, $J = 5.4$ Hz), 62.5 (d, $J = 6.2$ Hz), 52.4, 34.0 (d, $J = 135.3$ Hz), 16.2 (d, $J = 6.2$ Hz).

Methyl 2-Butenoate 2.4.3

To a solution of NaH (60% in mineral oil, 0.571 g, 14.27 mmol) in THF (30 mL) was added dropwise the phosphonate 2.4.2 (3.0 g, 2.63 mL, 14.27 mL) at 0 °C. After 30 minutes, the aldehyde (0.638 g, 0.792 mL, 10.98 mmol) in THF (7 mL) was added dropwise. The resultant mixture was stirred for 1.5 h and then quenched with
water and ether. The organic phase was washed with saturated brine, dried over anhydrous MgSO₄, filtered, and the solvent was removed by evaporation under reduced pressure. Purification by flash chromatography (50:1 petroleum ether:EtOAc provided the desired ester (0.994 g, 8.71 mmol, 79%).

１Ｈ NMR (500 MHz, CDCl₃) δ 7.04 (dt, J = 15.7, 6.4 Hz, 1H), 5.83 (dt, J = 15.7, 1.7 Hz, 1H), 3.74 (s, 3H), 2.38 – 2.13 (m, 2H), 1.08 (t, J = 7.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 9.8, 25.1, 53.8, 122.2, 135.5, 174.2.

Furan-2-carboxylic acid methyl ester 2.5.2

A solution of 70% aqueous TBHP (1.5 mmol) was added dropwise to a solution of aldehyde 2.5.1 (1.0 mmol) and potassium iodide (0.05 mmol) in 5 mL of methanol over a period of 30 min and stirred at 65 °C. Progress of the reaction was monitored by TLC, and after completion of the reaction, the mixture was quenched with saturated aqueous Na₂S₂O₃, washed with brine, extracted with ethyl acetate, and dried over anhydrous Na₂SO₄. Removal of the solvent under vacuum afforded the crude product 2.5.2, which was purified by column chromatography using a hexane/ethyl acetate mixture.

１Ｈ NMR (300 MHz, CDCl₃) δ 7.03 – 6.88 (m, 1H), 6.10 – 5.85 (m, 1H), 3.79 – 3.62 (m, 3H), 2.25 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 157.02, 142.80, 119.29, 109.36, 108.32, 51.49, 13.73.
Naphthalen-1-yl-1-boronic acid 2.3.2

Following a modification of a literature procedure, a three-necked 1 L flask fitted with two dropping funnels, magnetic stirring bar, and low-temperature thermometer was charged with 1-bromonaphthalene (8.3 g, 40.0 mmol) under Argon. Dry THF (100 mL) was added, and the solution was cooled to -78 °C. To this solution was added n-butyllithium (25.0 mL of a 1.6 M solution, 40.0 mmol) dropwise through the first dropping funnel. The solution was stirred at -78 °C for 2 h whereupon trimethyl borate (6.3 g, 60.0 mmol) dissolved in 10 mL of dry THF was added dropwise through the second dropping funnel. The solution was allowed to warm to room temperature overnight. The reaction was quenched with dilute HCl (20%, 70 mL), and the reaction mixture was concentrated at 30 °C to 50% of its original volume by rotary evaporation and poured into H₂O. The resulted biphasic solution was extracted with Et₂O (2 X 50 mL). The ethereal solution was washed twice with H₂O and concentrated by rotary evaporation. The crude product was dissolved in 10% aqueous NaOH (80 mL) and extracted with Et₂O to remove liquid byproducts. The clear basic aqueous phase was collected and acidified by 10% HCl at 0 °C. Naphthalen-1-yl-1-boronic acid was collected as a white solid powder by filtration and washed with H₂O several times to remove HCl. It was dried at 20 °C under vacuum and used without further purification (92% isolated yield).

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\[ ^1 \text{H NMR (400 MHz, CDCl}_3 \text{)} \delta = 8.91 (s, 1H), 8.35 (d, 1H, J=8.2 \text{ Hz}), 8.11 (d, 1H, J=7.3 \text{ Hz}), 8.01 (d, 1H, J=8.2 \text{ Hz}), 7.96 (d, 1H, J=7.3 \text{ Hz}), 7.64 (m, 2H); \]^13 \text{C NMR (100 MHz, CDCl}_3 \text{)} \delta = 137.89, 135.88, 132.91, 130.68, 129.12, 127.89, 127.67, 127.37, 126.05

\[
\begin{array}{c}
\text{B-OH} \quad \overset{\text{pinacol, cyclohexane, reflux}}{\longrightarrow} \quad \text{B-O} \\
\text{2.3.2} \quad \text{2.5.1}
\end{array}
\]

**4,4,5,5-Tetramethyl-2-(naphthalen-2-yl)-1,3,2-dioxaborolane 2.5.1:**

Boronic Acid 2.3.2 (5.0 g, 10.82 mmol) and pinacol (4.09 g, 34.6 mmol) were dissolved in anhydrous cyclohexane (100 mL). The mixture was refluxed for 12 h at rt and concentrated under reduced pressure. The crude product was purified by recrystallization (hexanes), yielding the ester 2.5.1 in the form of white crystalline solid.

\[ ^1 \text{H NMR (400 MHz, CDCl}_3 \text{)} \delta = 8.37 (s, 1H), 7.88-7.81 (m, 4H), 7.52-7.44 (m, 2H), 1.38 (s, 12H); \]^13 \text{C NMR (100 MHz, CDCl}_3 \text{)} \delta = 136.2, 135.0, 132.8, 130.4, 128.6, 127.7, 127.0, 126.9, 125.8, 83.9, 24.9; mp = 62–65 °C.

\[
\begin{array}{c}
\text{OH} \quad \overset{\text{Ac}_{2}O, \text{pyr, DMAP, 25 °C}}{\longrightarrow} \quad \text{AcO} \\
\text{Br} \quad \text{2.3.3}
\end{array}
\]

**1-acetoxy-2,6-dibromobenzene 2.4.1:**

Following a modification on a literature procedure, a mixture of 2,6-dibromobenzene 2.3.3 (1.0 g, 3.97 mmol) and pyridine (3.21 mL, 39.7 mmol) was

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stirred in acetic anhydride (14.2 mL) at 80 °C for 4 hours under nitrogen atmosphere. The reaction mixture was evaporated under reduced pressure, and the residue was purified by recrystallization (CHCl₃, hexanes) to give the title compound 2.4.1 as a white solid (.243 g, .827 mmol) in 21% yield.

¹H NMR (500 MHz, CDCl₃) δ 7.55 (d, J = 8.1 Hz, 2H), 7.01 (t, J = 8.1 Hz, 1H), 2.40 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) 167.24, 146.3, 132.4, 128.2, 117.8, 20.5; IR (KBr, cm⁻¹) 1773, 1567, 1437, 1367, 1182, 1069, 1010, 900, 775, 729. mp = 46-47 °C.

1-acetoxy-2,6-di-2-napthylbenzene 2.4.2:

Open to the atmosphere, 1-acetoxy-2,6-dibromobenzene 2.4.1 (0.131 g, 0.447 mmol), 2-naphthalenylboronic acid 2.3.2 (0.169g, 0.983 mmol), KF (0.174 g, 2.99 mmol), Pd₂dba₃ (0.041 g, 0.045 mmol), and THF (5 mL) are added to a 10 mL RBF equipped with a stir bar. The vial is then capped with a septum, an argon inlet is attached, and the reaction mixture is gently sparged for about one minute. Then, a solution of the P(t-Bu)₃ in toluene is added by syringe, and the reaction mixture was stirred at room temperature for 2 days. At the conclusion of the reaction, the reaction mixture was diluted with Et₂O, filtered through a pad of silica gel with copious washings, concentrated, and purified by column chromatography on silica gel (40:1 hexanes:EtOAc) to give 2.4.2 as a white solid.

¹H NMR (500 MHz, CDCl₃) δ 7.97 (d, J = 1.3 Hz, 2H), 7.93 – 7.85 (m, 7H), 7.64 (dd, J = 8.5, 1.7 Hz, 2H), 7.57 – 7.44 (m, 8H), 1.73 (s, 3H).
2-(naphthalen-2-yl)-6-(naphthalen-7-yl)phenol 2.3.4:

To a solution of 2.4.2 in THF/MeOH (5 mL, 1:1) was added 4M aqueous NaOH (0.10 mL, 0.180 mmol). The solution was stirred for 1 hour at which time 4M aqueous HCl was carefully added until the solution was acidic. The mixture was diluted with water and extracted 3x with CH₂Cl₂. The organic layers were combined, dried (MgSO₄) and concentrated in vacuo to give the title compound 2.3.4.

¹H NMR (500 MHz, CDCl₃) δ 8.06 (d, J = 1.5 Hz, 2H), 7.97 (d, J = 8.5 Hz, 2H), 7.93 – 7.87 (m, 4H), 7.72 (dd, J = 8.5, 1.8 Hz, 2H), 7.58 – 7.48 (m, 4H), 7.42 (d, J = 7.6 Hz, 2H), 7.15 (t, J = 7.6 Hz, 1H), 5.61 (s, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 149.72, 135.05, 133.54, 132.68, 130.29, 128.79, 128.51, 128.15, 128.10, 127.73, 127.51, 126.41, 126.26, 120.92; Rf = 0.31 (hexanes/EtOAc 40:1); mp = 139-141°C.

2-(naphthalen-2-yl)-6-(naphthalen-7-yl)phenol 2.3.4:

To a dry 500 ml resealable tube equipped with a stirbar was added naphthalene-2-boronic acid 2.3.2 (11.47 g, 66.7 mmol), 2,6-dibromophenol 2.3.3 (5.6 g, 22.23 mmol), tripotassium phosphate (18.87 g, 89 mmol), RuPhos (2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl; 0.415 g, 0.889 mmol), and Pd(OAc)₂ (0.1g, 0.445 mmol). The vessel was evacuated and refilled with argon and
toluene (100 ml) and H₂O (10 ml) were added, and the vessel was sealed. The reaction mixture was heated to 100 ºC for 16 hours with stirring. The reaction was then cooled to room temperature and concentrated in vacuo. The crude reaction mixture was diluted with Et₂O, filtered through a pad of silica, washed with ether until the washings were clear, concentrated, and recrystallized from EtOAc/hexanes by dissolving in hot hexanes containing a minimal amount of EtOAc then allowing to cool. The mother liquor was concentrated and recrystallized as described above. The combined crystals provided 7.54g (98%) of a fluffy, white solid.

¹H NMR (500 MHz, CDCl₃) δ 8.06 (d, J = 1.5 Hz, 2H), 7.97 (d, J = 8.5 Hz, 2H), 7.93 – 7.87 (m, 4H), 7.72 (dd, J = 8.5, 1.8 Hz, 2H), 7.58 – 7.48 (m, 4H), 7.42 (d, J = 7.6 Hz, 2H), 7.15 (t, J = 7.6 Hz, 1H), 5.61 (s, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 149.72, 135.05, 133.54, 132.68, 130.29, 128.79, 128.51, 128.15, 128.10, 127.73, 127.51, 126.41, 126.26, 120.92; Rf = 0.31 (hexanes/EtOAc 40:1); mp = 139-141ºC.

**General Intermolecular Vinylogous Aldol Procedure:**

Preparation of ATNP (2.6.1): Me₃Al (0.457 mL, 0.914 mmol, 2.0 M solution in hexanes) was added to a stirred solution of 2,6-dinapthalphenol 2.3.4 (0.950 g, 2.74 mmol) in toluene (15 mL) at room temperature. After 20 minutes, the ATNP solution was cooled to -78 ºC and used as described in the vinylogous aldol procedure.

Preparation of LTMP: n-BuLi (0.398 mL, 0.637 mmol, 1.6 M solution in hexanes) was added to a stirred solution of 2,2,6,6-tetramethylpiperidine (TMP, 0.108
mL, 0.637 mmol) in THF (1.5 mL) at -78 °C. The cold bath was lowered and the solution allowed to stir for 10 minutes. The solution was cooled back to -78 °C and used as described below in the vinylogous aldol procedure.

The aldehyde (0.277 mmol) and ester (0.554 mmol) were added to a stirred solution of freshly prepared ATNP (0.914 mmol) in toluene (15 mL) at -78 °C (acetone/dry ice bath). After 20 minutes, a stirred solution of LTMP (0.638 mmol) in THF (1.5 mL) at –78°C was added via cannula to the ATPH-substrate solution. After 3 hours following the addition, saturated NH₄Cl (15 mL) was added, and the biphasic mixture was stirred vigorously for 30 minutes while warming to ambient temperature. The organic phase separated and the aqueous layer extracted with ether (3 times). The combined organic layers were washed with brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The reaction mixture was recrystallized from hexanes/chloroform to remove the majority of 2,6-dinapthalphenol (2.3.4). Purification of the crude product was achieved with flash chromatography (10:1 hexanes:EtOAc then 3:1 hexanes:EtOAc) to provide the desired product along with additional recovered 2,6-dinapthalphenol. The combined yield of recovered 2,6-dinapthalphenol was typically above 90%.

![Chemical structure](image_url)

(E)-methyl 5-hydroxynon-2-enoate (2.2.3)

Compound 2.2.3 was prepared from valeraldehyde 2.2.1 and methyl crotonate 2.2.2 in 82% yield after purification according to the general procedure.
Rf = 0.34 (hexanes/EtOAc 3:1); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.03 – 6.91 (m, 1H), 5.89 (dt, $J = 15.7, 1.2$ Hz, 1H), 3.74 (m, 1H), 3.72 – 3.68 (s, 3H), 2.39 (dd, $J = 13.1, 6.9, 4.5, 1.4$ Hz, 1H), 2.35 – 2.25 (m, 1H), 1.67 – 1.13 (m, 7H), 0.89 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 166.74, 145.53, 123.45, 70.57, 51.50, 40.17, 36.84, 27.74, 22.62, 14.03; HRMS (ESI) $m/z$ calc’d for C$_{10}$H$_{18}$O$_3$Na $[M+Na]^+$: 209.1154; found: 209.1156.

(E)-methyl 5-hydroxyundec-2-enoate (2.2.6)

Compound 2.3.6 was prepared from heptaldehyde 2.3.5 and methyl crotonate 2.2.2 in 76% yield after purification according to the general procedure.

Rf = 0.62 (hexanes/EtOAc 2:1); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.03 – 6.91 (m, 1H), 5.89 (dt, $J = 15.7, 1.4$ Hz, 1H), 3.79 – 3.72 (m, 1H), 3.71 (s, 3H), 2.50 – 2.24 (m, 2H), 1.54 (s, 1H), 1.50 – 1.16 (m, 10H), 0.86 (t, $J = 6.8$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 166.99, 145.80, 123.68, 70.82, 51.74, 40.42, 37.41, 32.02, 29.45, 25.79, 22.83, 14.31; HRMS (ESI) $m/z$ calc’d for C$_{12}$H$_{22}$O$_3$Na $[M+Na]^+$: 237.1467; found: 237.1462.

(E)-methyl 5-hydroxy-7-phenylhept-2-enoate (2.3.8)

Compound 2.3.8 was prepared from dihydrocinnamaldehyde 2.3.7 and methyl crotonate 2.2.2 in 82% yield after purification according to the general procedure.
Rf = 0.38 (hexanes/EtOAc 2:1); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.32 – 7.25 (m, 2H), 7.18 (dt, \(J = 3.1, 2.6\) Hz, 3H), 7.01 – 6.88 (m, 1H), 5.89 (dt, \(J = 15.6, 1.4\) Hz, 1H), 3.81 – 3.73 (m, 1H), 3.71 (s, 3H), 2.84 – 2.73 (m, 1H), 2.67 (dt, \(J = 13.8, 7.9\) Hz, 1H), 2.46 – 2.27 (m, 2H), 1.84 – 1.73 (m, 2H), 1.60 – 1.52 (m, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 166.94, 145.44, 141.80, 128.72, 128.64, 126.22, 126.22, 123.86, 70.04, 51.77, 40.58, 38.92, 32.19.

(E)-methyl 5-cyclohexyl-5-hydroxypent-2-enoate (2.3.10)

Compound 2.3.10 was prepared from cyclohexanecarboxaldehyde 2.3.9 and methyl crotonate 2.2.2 in 96% yield after purification according to the general procedure.

Rf = 0.42 (hexanes/EtOAc 3:1); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.05 – 6.93 (m, 1H), 5.90 (dt, \(J = 15.7, 1.4\) Hz, 1H), 3.71 (s, 3H), 3.53 – 3.45 (m, 1H), 2.42 (dddd, \(J = 14.5, 6.9, 3.8, 1.6\) Hz, 1H), 2.36 – 2.25 (m, 1H), 1.85 – 1.78 (m, 1H), 1.75 (tdd, \(J = 8.1, 5.9, 3.3\) Hz, 2H), 1.65 (dd, \(J = 12.6, 5.8, 3.3\) Hz, 2H), 1.47 (bs, 1H), 1.40 – 1.28 (m, 1H), 1.28 – 0.93 (m, 5H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 167.02, 146.52, 123.50, 75.00, 51.73, 43.52, 37.38, 29.35, 28.08, 26.64, 26.40, 26.25; HRMS (ESI) \(m/z\) calc’d for C\(_{12}\)H\(_{20}\)O\(_3\)Na [M+Na]\(^+\): 235.1310; found: 235.1299.
5-hydroxy-6,6-dimethyl-hept-2-enoic acid methyl ester (2.3.12)

Compound 2.3.12 was prepared from pivaldehyde 2.3.11 and methyl crotonate 2.2.2 in 97% yield in purification according to the general procedure.

Rf = 0.44 (hexanes/EtOAc 3:1); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.04 (ddd, $J =$ 15.6, 7.9, 6.7 Hz, 1H), 5.90 (dt, $J =$ 15.6, 1.4 Hz, 1H), 3.71 (s, 3H), 3.35 (d, $J =$ 10.3 Hz, 1H), 2.42 (ddt, $J =$ 14.6, 6.6, 1.9 Hz, 1H), 2.18 (ddddd, $J =$ 14.6, 10.3, 8.0, 1.3 Hz, 1H), 1.76 (s, 1H), 0.91 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 167.07, 147.84, 123.08, 78.55, 51.67, 35.24, 35.08, 25.83.

(E)-methyl 5-hydroxy-5-phenylpent-2-enoate (2.3.14)

Compound 2.3.14 was prepared from benzaldehyde 2.3.13 and methyl crotonate 2.2.2 in 97% yield after purification according to the general procedure.

Rf = 0.33 (hexanes/EtOAc 3:1); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.39 – 7.25 (m, 5H), 6.95 (dt, $J =$ 15.6, 7.3 Hz, 1H), 5.89 (dt, $J =$ 15.7, 1.4 Hz, 1H), 4.82 (dd, $J =$ 7.8, 5.2 Hz, 1H), 3.70 (s, 3H), 2.74 – 2.53 (m, 2H), 2.21 – 1.51 (bs, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 166.91, 145.12, 143.61, 128.90, 128.23, 125.96, 123.91, 73.38, 51.76, 42.08; HRMS (ESI) $m/z$ calc’d for C$_{12}$H$_{14}$O$_3$Na [M+Na]$^+$: 229.0841; found: 229.0848.
(E)-methyl 6-[(triethylsiloxy)-5-hydroxy-2-hexenoate (2.3.16)

Compound 2.3.16 was prepared from aldehyde 2.3.15 and methyl crotonate 2.2.2 in 77% yield after purification according to the general procedure.

\[ \text{Rf} = 0.22 \text{ (hexanes/EtOAc 5:1); } \text{H} \text{ NMR (500 MHz, CDCl}_3\text{) } \delta 6.98 \text{ (dt, } J = 15.6, 7.3 \text{ Hz, 1H), 5.90 \text{ (dt, } J = 15.7, 1.5 \text{ Hz, 1H), 3.83 – 3.72 \text{ (m, 1H), 3.71 (s, 3H), 3.61 (dd, } J = 9.9, 3.6 \text{ Hz, 1H), 3.43 (dd, } J = 9.9, 6.9 \text{ Hz, 1H), 2.48 (d, } J = 4.1 \text{ Hz, 1H), 2.40 – 2.30 \text{ (m, 2H), 0.94 (t, } J = 8.0 \text{ Hz, 9H), 0.59 (q, } J = 8.0 \text{ Hz, 6H); } ^{13}C \text{ NMR (75 MHz, CDCl}_3\text{) } \delta 163.96, 145.34, 123.45, 70.77, 66.40, 51.73, 36.19, 6.94, 4.55. \]

(E,5S,6R)-methyl 6-(benzyloxy)-5-hydroxyhept-2-enoate (2.3.18)

Compound 2.3.18 was prepared from 2.3.17 and methyl crotonate 2.2.2 in 77% yield and in a 2.4:1 anti:syn mixture of diastereomers after purification according to the general procedure.

Major isomer: \[ \text{Rf} = 0.23 \text{ (hexanes/EtOAc 3:1); } \text{H} \text{ NMR (500 MHz, CDCl}_3\text{) } \delta 7.43 – 7.27 \text{ (m, 5H), 7.08 – 6.91 \text{ (m, 1H), 6.00 – 5.89 \text{ (m, 1H), 4.63 (d, } J = 11.7 \text{ Hz, ...} \]
1H), 4.49 (d, J = 11.7 Hz, 1H), 3.85 (m, 1H), 3.73 (s, 3H), 3.59 – 3.50 (m, 1H), 2.42 – 2.34 (m, 2H), 2.11 (bs, 1H), 1.20 (d, J = 6.3 Hz, 3H).

Structure Proof:

\[
\text{Diol } 2.3.18a
\]

Ester 2.3.18, which was produced as a 2.4:1 mixture of diastereomers was subjected to ozonolysis and reduction according to a literature procedure to provide diol 2.3.18a as a 2.4:1 mixture.\textsuperscript{51} The spectroscopic data for the minor diastereomer of this mixture was consistent with that of the known syn diastereomer\textsuperscript{52} indicating that the anti-isomer is the major diastereomer in the reaction.

\[
\text{Ester } 2.3.2h
\]

Compound 2.3.2h was prepared from aldehyde 12.3.1h and methyl crotonate 2.2.2 in 54% yield after purification according to the general procedure.

\(^1\)H NMR (500 MHz, CDCl\textsubscript{3}) \ä 7.00 (dt, J = 15.6, 7.3 Hz, 1H), 5.92 (dt, J = 15.7, 1.5 Hz, 1H), 3.84 – 3.77 (m, 1H), 3.74 (s, 3H), 3.64 (dd, J = 10.0, 3.7 Hz, 1H),


3.46 (dd, J = 10.0, 6.7 Hz, 1H), 2.46 (d, J = 4.4 Hz, 1H), 2.41 – 2.35 (m, 2H), 1.02 – 0.79 (m, 9H), 0.08 (s, 6H); 

$^{13}$C NMR (75 MHz, CDCl$_3$) \( \delta \): 166.96, 145.31, 123.47, 70.74, 66.69, 51.73, 36.22, 26.09, 18.51, -5.13, -5.16.

**Ester 2.3.2**

Compound 2.3.2 was prepared from 2.3.1 and methyl crotonate 2.2.2 in 59% yield after purification in a 4:1 anti:syn mixture of diastereomers according to the general procedure.

$^1$H NMR (500 MHz, CDCl$_3$) \( \delta \): 7.03 (dt, J = 15.6, 7.3 Hz, 1H), 5.94 (dt, J = 15.7, 1.5 Hz, 1H), 3.81 (qd, J = 6.3, 3.7 Hz, 1H), 3.74 (s, 3H), 3.70 – 3.61 (m, 1H), 2.37 – 2.29 (m, 2H), 2.18 (bs, 1H), 1.12 (d, J = 6.3 Hz, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H).

**Ester 2.3.2**

Compound 2.3.2 was prepared from aldehyde 2.3.1 and methyl crotonate 2.2.2 in 59% yield after purification according to the general procedure.

$^1$H NMR (500 MHz, CDCl$_3$) \( \delta \): 7.01 (dt, J = 15.6, 7.4 Hz, 1H), 5.92 (dt, J = 15.7, 1.5 Hz, 1H), 4.07 – 3.97 (m, 1H), 3.96 – 3.88 (m, 1H), 3.83 (ddd, J = 10.2, 8.9, 3.9 Hz, 1H), 3.73 (s, 3H), 3.65 (d, J = 1.1 Hz, 1H), 2.49 – 2.32 (m, 2H), 1.76 – 1.62
(m, 2H), 0.91 (s, 9H), 0.09 (s, 3H), 0.09 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 145.88, 137.98, 123.38, 71.37, 62.99, 51.70, 40.45, 37.91, 26.08, 18.35, -5.31, -5.35.

(E,5S,6R)-methyl 6-(benzyloxy)-5-hydroxy-7-methyloct-2-enoate (2.3.20)

Compound 2.3.20 was prepared from 2.3.19 and methyl crotonate 2.2.2 in 87% yield after purification in a 10:1 anti:syn mixture of diastereomers according to the general procedure.

Rf = 0.22 (hexanes/EtOAc 5:1); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.38 – 7.30 (m, 4H), 7.28 (dd, $J$ = 10.2, 4.2 Hz, 1H), 7.05 – 6.95 (m, 1H), 5.90 (d, $J$ = 15.7 Hz, 1H), 5.86 (d, $J$ = 15.7 Hz, 1H), 4.67 (d, $J$ = 11.4 Hz, 1H), 4.61 (d, $J$ = 11.4 Hz, 1H, 3.90 – 3.82 (m, 1H), 3.71 (s, 3H), 3.23 – 3.16 (m, 1H), 2.47 (ddd, $J$ = 8.2, 5.3, 4.3 Hz, 1H), 2.44 – 2.33 (m, 1H), 1.90 (dq, $J$ = 13.5, 6.8 Hz, 1H), 1.02 (d, $J$ = 6.7 Hz, 3H), 0.96 (d, $J$ = 6.9 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 166.95, 146.42, 138.75, 128.74, 128.00, 127.88, 123.60, 87.61, 75.18, 71.32, 51.74, 35.57, 30.26, 20.19, 18.61; HRMS (ESI) m/z calc’d for C$_{17}$H$_{24}$O$_4$Na [M+Na]$^+$: 315.1572; found: 315.1567.

Structure Proof:
Compound 2.3.20 was protected as a TBS ether, subjected to ozonolysis and reduction to provide 2.3.20b. Authentic syn isomer, 2.3.20e, was prepared according to a literature procedure\textsuperscript{53} and provided different spectral data than 2.3.20b. This indicates that the anti-isomer is the major diastereomer in the reaction.

\[
\text{(E,5S,6R)-methyl-6-(benzyloxy)-5-(yloxy)(tert-butyl)dimethylsilane-7-methyloct-2-enoate (2.3.20a)}
\]

TBSCl (0.384 mmol, 0.058 g), imidazole (0.508 mmol, 0.034 g), and DMAP (0.025 mmol, 3 mg) were added to a stirred solution of 2.3.20 (0.127 mmol, 0.037 g) in DMF (6 ml) at 0 °C. The solution was allowed to warm to RT and stir for 6 days at which time TLC indicated consumption of the starting material. The reaction was diluted with Et\textsubscript{2}O (6 mL), washed with saturated NaHCO\textsubscript{3} and brine, dried over anhydrous MgSO\textsubscript{4}, and concentrated under reduced pressure. The crude product was purified by flash chromatography (25:1 hexanes:EtOAc) to provide the desired ester 2.3.20a (0.038 g, 0.094 mmol, 74%)

\[\text{Rf} = 0.75 \text{ (hexanes/EtOAc 5:1)}; [\alpha]_D^{24} = -12.4^\circ \text{ (c 0.034, CHCl}_3); ^1\text{H NMR (500 MHz, CDCl}_3) \delta 7.38 - 7.25 \text{ (m, 5H), 7.06 (dt, } J = 15.4, 7.5 \text{ Hz, 1H), 5.85 (dt, } J = 15.6, 1.4 \text{ Hz, 1H), 4.84 (d, } J = 11.2 \text{ Hz, 1H), 4.52 (d, } J = 11.2 \text{ Hz, 1H), 3.93 (dt, } J = 7.4, 3.7 \text{ Hz, 1H), 3.71 (s, 4H), 3.13 (dd, } J = 7.0, 3.6 \text{ Hz, 1H), 2.57 (dt, } J = 8.9, 7.7, 1.3 \text{ Hz, 1H), 2.39 (dddd, } J = 14.7, 7.1, 3.7, 1.5 \text{ Hz, 1H), 1.83 - 1.72 \text{ (m, 1H), 0.96 (dd, } J = 17.0, 6.7 \text{ Hz, 6H), 0.89 (s, 9H), 0.05 (d, } J = 11.1 \text{ Hz, 6H); ^13\text{C NMR (75}}
\]

MHz, CDCl\textsubscript{3}) \(\delta\) 167.08, 147.71, 139.34, 128.52, 127.89, 127.65, 122.93, 88.83, 75.28, 73.26, 51.62, 35.48, 30.45, 26.12, 20.55, 19.07, 18.28, -4.05, -4.23.

**Alcohol 2.3.20b**

A flask was charged with DCM (5 mL) and ester 2.2.20a (0.019 g, 0.046 mmol), and the solution was cooled to -78 °C in a dry ice-acetone bath. A stream of ozone from a Welsbach ozone generator was bubbled into the DCM solution until a persistent blue color of unreacted ozone was noticeable. The reaction mixture was allowed to warm to room temperature, and dry nitrogen was bubbled through for 1 minute to remove excess ozone. Borane dimethyl sulfide complex (0.017 g, 0.022 mL, 0.230 mmol) was added by syringe and the reaction mixture was allowed to stir at RT overnight. Aqueous HCl (5%, 5 mL) was added and the resulting mixture stirred vigorously for 30 minutes. Solid NaHCO\textsubscript{3} was carefully added (caution, gas evolution) and the organic layer was separated, washed with brine and dried over anhydrous MgSO\textsubscript{4}. The reaction mixture was filtered and concentrated to provide the crude product. Flash chromatography (10:1 hexanes:EtOAc) gave the desired alcohol (2.2.20b 8 mg, 0.024 mmol, 51%).

\[ R_f = 0.30 \text{ (hexanes/EtOAc 5:1)}; \]

\[ ^1H \text{ NMR (500 MHz, CDCl}_3) \delta 7.39 – 7.25 \text{ (m, 5H), 4.98 (d, } J = 10.8 \text{ Hz, 1H), 4.52 (d, } J = 10.8 \text{ Hz, 1H), 4.10 (td, } J = 4.9, 2.8 \text{ Hz, 1H), 3.87 (ddd, } J = 11.2, 7.8, 3.6 \text{ Hz, 1H), 3.63 (ddd, } J = 10.9, 6.8, 3.8 \text{ Hz, 1H), 3.14 (dd, } J = 8.8, 2.7 \text{ Hz, 1H), 1.96 – 1.83 \text{ (m, 1H), 1.81 – 1.66 \text{ (m, 2H), 0.99 (d, } J = 6.6 \text{ Hz, 3H), 0.92 (s, 8H), 0.89 (d, } J = 6.8 \text{ Hz, 3H), 0.10 (d, } J = 7.5 \text{ Hz, 6H); } ^13C \text{ NMR (75 MHz, CDCl}_3) \delta 128.61, 128.14, 127.85, 89.84, 76.07, 72.21, 58.63, 34.43, 30.95, 26.18, 20.19, 20.06, -4.09, -4.53. \]
(4R,5R)-5-(benzyloxy)-6-methylhept-1-en-4-ol (2.3.20c)

A solution of stannic chloride (0.061 mL, 36 mg, 0.138 mmol) in dry CH₂Cl₂ (6 ml) was cooled to -78 °C. To this solution was added dropwise a solution of (R)-2-(benzyloxy)-3-methylbutanal 2.3.19 (26.5 mg, 0.138 mmol) in CH₂Cl₂ (0.5 ml) via syringe over a 2-min period. The reaction was stirred for 3 min and allyltrimethylsilane (0.026 mL, 19 mg, 0.165 mmol) was added in one portion. After stirring at -78 °C for 15 min, the reaction mixture was quenched with water, allowed to warm to room temperature and extracted with ether. The ethereal layer was dried over MgSO₄ concentrated at reduced pressure, and purified by flash chromatography (15:1 hexanes/EtOAc) to afford 32 mg (49%) of a clear, colorless liquid, which was desired compound 2.3.20c.

Rᶠ = 0.22 (hexanes/EtOAc 10:1); [α]₂⁰⁵⁺D -5.5° (c 0.022, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.39 – 7.25 (m, 5H), 5.92 – 5.77 (m, 1H), 5.08 (dt, J = 3.5, 1.5 Hz, 2H), 4.64 (dd, J = 50.9, 11.1 Hz, 2H), 3.75 – 3.64 (m, 1H), 3.08 (dd, J = 5.6, 4.0 Hz, 1H), 2.33 – 2.23 (m, 3H), 2.03 – 1.91 (m, 1H), 0.98 (dd, J = 9.1, 6.9 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 138.70, 135.30, 128.70, 128.01, 127.98, 117.53, 86.40, 75.13, 71.20, 39.78, 30.29, 19.94, 18.28.
((4R,5R)-5-(benzyloxy)-6-methylhept-1-en-4-yloxy)(tert-butyl)dimethylsilane

(2.3.20d)

TBSCI (0.337 mmol, 0.051 g), imidazole (0.405 mmol, 0.028 g), and DMAP (0.013 mmol, 1.6 mg) were added to a stirred solution of 2.3.20c (0.067 mmol, 0.016 g) in DMF (1.5 ml) at 0 ºC. The solution was allowed to warm to RT and stir for 16 hours at which time TLC indicated consumption of the starting material. Et₂O (6 mL) was added, and the solution was washed with saturated NaHCO₃ and brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The crude product was purified by flash chromatography (gradient 80:1 to 10:1 hexanes:EtOAc) to provide 2.3.20d (0.010 g, 0.027 mmol, 41%).

Rf = 0.20 (hexanes/EtOAc 80:1); [α]D²⁴ -30.3º (c 0.034, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.37 – 7.27 (m, 5H), 5.92 – 5.79 (m, 1H), 5.09 – 4.97 (m, 2H), 4.69 (d, J = 11.7 Hz, 1H), 4.54 (d, J = 11.7 Hz, 1H), 3.83 (dd, J = 11.3, 5.0 Hz, 1H), 3.03 (t, J = 5.6 Hz, 1H), 2.41 (ddd, J = 12.5, 6.2, 4.8 Hz, 1H), 2.19 (dt, J = 14.2, 7.2 Hz, 1H), 1.91 (dq, J = 13.3, 6.7 Hz, 1H), 0.97 – 0.90 (m, 6H), 0.87 (s, 9H), 0.00 (d, J = 14.5 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 135.94, 128.43, 127.63, 127.44, 127.11, 116.97, 86.59, 73.75, 73.66, 38.14, 29.08, 26.18, 20.91, 18.62, 18.32, -4.09, -4.16.

Primary Alcohol (20e)

A flask was charged with DCM (2 mL) and ester 2.3.20d (6.7 mg, 0.019 mmol), and the solution was cooled to -78 ºC in a dry ice-acetone bath. A stream of ozone from a Welsbach ozone generator was bubbled into the DCM solution until a
persistent blue color of unreacted ozone was noticeable. The reaction mixture was allowed to warm to room temperature, and dry nitrogen was bubbled through for 1 minute to remove excess ozone. Borane dimethyl sulfide complex (7.3 mg, 0.009 mL, 0.096 mmol) was added by syringe and the reaction mixture was allowed to stir at RT overnight. Aqueous HCl (5%, 2 mL) was added and the resulting mixture stirred vigorously for 30 minutes. Solid NaHCO₃ was carefully added (caution, gas evolution) and the organic layer was separated, washed with brine and dried over anhydrous MgSO₄. The reaction mixture was filtered and concentrated to provide the crude product. Flash chromatography (10:1 hexanes:EtOAc) gave the desired alcohol (2.3.20b 4 mg, 0.011 mmol, 59%).

\[ \text{Rf} = 0.45 \text{ (hexanes/ EtOAc 5:1); } [\alpha]_D^{25} -35.8^\circ \text{ (c 0.026, CHCl}_3); \] \[ ^1H \text{ NMR (500 MHz, CDCl}_3) \delta 7.32 \text{ (d, } J = 4.4 \text{ Hz, 4H), 7.27 \text{ (dd, } J = 8.1, 4.1 \text{ Hz, 1H), 4.66 \text{ (d, } J = 11.5 \text{ Hz, 1H), 4.56 \text{ (d, } J = 11.5 \text{ Hz, 1H), 3.99 \text{ (dd, } J = 11.3, 5.2 \text{ Hz, 1H), 3.72 \text{ (bs, 2H), 3.10 \text{ (dd, } J = 6.7, 4.8 \text{ Hz, 1H), 2.45 \text{ (bs, 1H), 2.01 - 1.85 \text{ (m, 2H), 1.70 \text{ (ddd, } J = 14.5, 11.1, 4.9 \text{ Hz, 1H), 0.99 - 0.93 \text{ (m, 6H), 0.87 \text{ (s, 9H), 0.03 \text{ (d, } J = 16.8 \text{ Hz, 6H);}} \]

\[ ^{13}C \text{ NMR (75 MHz, CDCl}_3) \delta 138.95, 128.58, 127.82, 127.78, 86.82, 73.92, 72.66, 60.68, 35.51, 29.47, 26.11, 20.75, 19.20, 18.20, -4.11, -4.58. \]

(5,7-anti) methyl 7-[(tert-butyldimethylsilyl)oxy]-5-hydroxy-2E-octenoate 2.3.22

Compound 2.3.22 was prepared from aldehyde 2.3.21 and methyl crotonate 2.2.2 in 65% yield in a 1.3:1 anti:syn mixture of diastereomers after purification according to the general procedure.
Major isomer: \( R_f = 0.19 \) (hexanes/EtOAc 5:1); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.01 (dtd, \( J = 9.6, 7.3, 2.3 \) Hz, 1H), 6.00 – 5.81 (m, 1H), 4.23 (dd, \( J = 10.5, 4.5 \) Hz, 1H), 3.74 (s, 3H), 3.65 (s, 1H), 2.38 (m, 2H), 2.19 (s, 1H), 1.79 – 1.47 (m, 2H), 1.25 (d, \( J = 6.3 \) Hz, 3H), 0.90 (s, 9H), 0.10 (d, \( J = 3.8 \) Hz, 6H).

Structure Proof:

\[
\text{Diol 2.3.22a}
\]

Ester mixture 2.3.22 was deprotected using HF / pyridine to give 2.3.22a. Data of the resulting diol was then compared to known spectra for the syn diastereomer.\(^{54}\) These data were consistent with the minor diastereomer in our reaction. The major product in the vinylogous aldol reaction is the anti-diastereomer.

(5,7-anti) methyl 7-(benzyloxy)-5-hydroxy-2E-octenoate (2.3.24)

Compound 2.3.24 was prepared from aldehyde 2.3.23 and methyl crotonate 2.2.2 in 78% yield in a 3.4:1 anti:syn mixture of diastereomers after purification according to the general procedure.

\(^{54}\) Scott, M. S.; Luckhurst, C. A; Dixon, D. J. Org. Lett. 2005, 7, 5813.
Major isomer: \( R_f = 0.20 \) (hexanes/EtOAc 3:1); \(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 7.43 – 7.27 (m, 5H), 6.98 (ddd, \( J = 15.6, 8.3, 6.5 \) Hz, 1H), 5.88 (dt, \( J = 15.7, 1.4 \) Hz, 1H), 4.68 (d, \( J = 11.3 \) Hz, 1H), 4.41 (d, \( J = 11.4 \) Hz, 1H), 3.96 (dd, \( J = 8.7, 5.2 \) Hz, 1H), 3.82 (ddd, \( J = 12.3, 6.1, 3.1 \) Hz, 1H), 3.72 (s, 3H), 2.45 – 2.22 (m, 2H), 1.74 – 1.51 (m, 2H), 1.25 (d, \( J = 6.0 \) Hz, 3H).

Structure Proof:

Diol 2.3.24a

Ester 2.3.24 was reduced with H\(_2/Pd/C\) to give diol 2.3.24a. The resulting spectra were compared to that of the known syn- and anti-diols.\(^{55}\) This data was consistent with the major isomer of the vinylogous aldol reaction being the anti-diastereomer.

\((2E,6E)\)-methyl-5-hydroxy-7-phenylhepta-2,6-dienoate (2.3.26)

Compound 2.3.26 was prepared from aldehyde 2.3.25 and methyl crotonate 2.2.2 in 43% yield after purification according to the general procedure.

$R_f = 0.22$ (hexanes/EtOAc 3:1); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.40 – 7.25 (m, 5H), 6.99 (dt, $J = 15.6$, 7.4 Hz, 1H), 6.60 (d, $J = 15.9$ Hz, 1H), 6.21 (dd, $J = 15.9$, 6.6 Hz, 1H), 5.94 (dt, $J = 15.7$, 1.4 Hz, 1H), 4.44 (q, $J = 6.1$ Hz, 1H), 3.71 (s, 3H), 2.57 – 2.50 (m, 2H), 1.77 (bs, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 166.91, 144.79, 136.49, 131.45, 131.08, 128.87, 128.19, 126.81, 124.05, 71.79, 51.78, 40.38; HRMS (ESI) $m/z$ calc’d for C$_{14}$H$_{16}$O$_3$Na [M+Na]$^+$: 255.0997; found: 255.1000.

![Reaction scheme](image)

**Methyl (E)-(anti)-5-Hydroxy-4-methyl-5-phenylpent-2-enoate (2.8.4)**

Compound 2.8.4 was prepared from benzaldehyde 2.3.13 and 2.8.3 according to the general procedure. The product was isolated in 95% yield after purification and in a 15:1 diastereoselectivity favoring the anti-isomer.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.49 – 7.24 (m, 5H), 7.06 (dd, $J = 15.8$, 8.2 Hz, 1H), 5.92 (dd, $J = 15.8$, 1.1 Hz, 1H), 4.53 (dd, $J = 7.5$, 2.9 Hz, 1H), 3.75 (s, 3H), 2.79 – 2.54 (m, 1H), 1.95 (d, $J = 3.0$ Hz, 1H), 0.94 (d, $J = 6.9$ Hz, 3H). $^{13}$C NMR (75 MHz): $\delta$ 16.1, 44.4, 51.5, 77.9, 121.8, 126.6, 127.8, 128.4, 142.2, 150.8, 166.9.

![Reaction scheme](image)

**Alcohol 2.9.3**

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Compound 2.9.3 was prepared from benzaldehyde 2.3.13 and furan 2.9.2 in 84% yield after purification according to the general procedure.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.45 – 7.26 (m, 5H), 7.08 (d, J = 3.4 Hz, 1H), 6.18 (d, J = 3.4 Hz, 1H), 5.08 (ddd, J = 8.3, 4.8, 3.3 Hz, 1H), 3.87 (s, 3H), 3.23 – 2.98 (m, 2H), 2.12 (d, J = 3.2 Hz, 1H).

Alcohol 2.9.4

Compound 2.9.4 was prepared from valeraldehyde 2.2.1 and furan 2.9.2 in 72% yield after purification according to the general procedure.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.07 (d, J = 3.4 Hz, 1H), 6.21 (d, J = 3.3 Hz, 1H), 3.93 (m, 1H), 3.82 (s, 3H), 2.85 (dd, J = 15.1, 4.1 Hz, 1H), 2.75 (dd, J = 15.1, 8.1 Hz, 1H), 2.09 (bs, 1H), 1.61 – 1.12 (m, 6H), 0.86 (t, J = 7.1 Hz, 3H).

2-Iodobenzaldehyde (2.11.2):

According to a literature procedure,$^{56}$ to a solution of 2-iodobenzylalcohol 2.11.2 (1.31 g, 5.60 mmol) in DCM was added PCC (1.33 g, 6.16 mmol). After being stirred at room temperature for 2 h, the reaction solvent was removed in vacuum and

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the residue was dissolved with 30% EtOAc/hexane and filtered through a silica gel plug. Evaporation gave 1.26 g (97%) of 2.11.3 as a white solid.

\[ ^1H \text{ NMR (500 MHz, CDCl}_3 \text{)} \delta 10.08 (d, J = 0.6 \text{ Hz, 1H}), 7.96 (dd, J = 7.9, 0.8 \text{ Hz, 1H}), 7.89 (dd, J = 7.7, 1.8 \text{ Hz, 1H}), 7.48 (t, J = 7.5 \text{ Hz, 1H}), 7.32 - 7.28 (m, 1H); \]
\[ ^13C \text{ NMR (75 MHz, CDCl}_3 \text{)} \delta 196.03, 140.89, 135.71, 135.37, 130.50, 128.96, 100.93. \]

\[ \text{2-} (1'\text{-Methylethenyl)} - 1\text{-iodobenzene 2.11.4} \]

According to a literature procedure,\(^{57}\) a solution of 2-iodobenzaldehyde 2.11.3 (0.300 g, 1.29 mmol, 0 °C) in THF (6 mL) was treated with a 3 M solution of MeMgBr in THF (0.560 mL, 1.68 mmol). After 15 minutes, the reaction mixture was quenched with H\(_2\)O, extracted with Et\(_2\)O, dried over MgSO\(_4\), and evaporated. The crude material was purified by flash chromatography (5:1 pentane:Et\(_2\)O) to give 2.11.4 (0.298 g, 1.20 mmol, 98%).

\[ ^1H \text{ NMR (500 MHz, CDCl}_3 \text{)} \delta 7.81 (dd, J = 7.9, 1.2 \text{ Hz, 1H}), 7.58 (dd, J = 7.8, 1.7 \text{ Hz, 1H}), 7.39 (td, J = 7.7, 1.0 \text{ Hz, 1H}), 6.98 (td, J = 7.6, 1.7 \text{ Hz, 1H}), 5.08 (q, J = 6.4 \text{ Hz, 1H}), 1.47 (d, J = 6.4 \text{ Hz, 3H}); \]
\[ ^13C \text{ NMR (75 MHz, CDCl}_3 \text{)} \delta 147.4, 139.0, 128.9, 128.5, 126.2, 97.0, 73.4, 23.7. \]

---

TBS ether 2.11.5

To a stirring solution of alcohol 2.11.4 (0.278 g, 1.121 mmol) in DMF (6 mL) was added imidazole (0.153 g, 2.241 mmol), DMAP (0.027 g, 0.224 mmol) and TBSCl (0.253 g, 1.681 mmol). The mixture was stirred at room temperature for 2 h, then 15 mL of water was added. The mixture was transferred to a separatory funnel. The aqueous layer was separated and extracted with ether (2x). The combined organic layers were then washed with water, saturated NaHCO₃, brine, dried with MgSO₄ and filtered. The solvent was removed in vacuo and the residue was purified by column chromatography (hexanes) (2.11.5, 0.378 g, 1.043 mmol, 93%) as a clear colorless liquid.

¹H NMR (500 MHz, CDCl₃) δ 7.76 (d, J = 7.9 Hz, 1H), 7.59 (dd, J = 7.8, 1.5 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 6.94 (td, J = 7.7, 1.7 Hz, 1H), 5.00 (q, J = 6.2 Hz, 1H), 1.37 (d, J = 6.2 Hz, 1H), 0.92 (s, 3H), 0.07 (s, 1H), -0.02 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 149.00, 139.05, 128.84, 128.68, 127.36, 96.53, 74.82, 26.22, 26.13, 25.91, 18.46, -4.54, -4.65.

Aldehyde 2.11.6

nBu₄NBr (0.462 g, 1.434 mmol), NaOAc (0.146 g, 1.776 mmol), LiCl (0.030 g, 0.717 mmol), and Pd(OAc)₂ (0.015 g, 0.68 mmol) were added sequentially to a
stirred solution of 2.11.5 (0.248 g, 0.683 mmol) and 5-hexen-1-ol (0.085 mL, 0.717 mmol) in anhydrous DMF (4 mL). The mixture was heated to 50 °C. After 3 days at 50 °C, the reaction mixture was cooled to room temperature and diluted with EtOAc (10 mL) and hexanes (20 mL) resulting in a biphasic organic solution. The DMF-containing phase was separated and extracted with hexanes (10 mL). The combined hexanes/EtOAc extracts were washed with deionized water, 1.0 M CuSO₄, deionized water, 1.0 M NaOH, deionized water, and brine. After drying over anhydrous MgSO₄ and concentrating under reduced pressure, the crude product was purified by flash chromatography (30:1 hexanes:EtOAc) to afford aldehyde 2.11.6 (0.154 g, 0.046 mmol, 67%).

**1H NMR (500 MHz, CDCl₃)** δ 9.79 (t, J = 1.7 Hz, 1H), 7.55 (dd, J = 7.6, 1.3 Hz, 1H), 7.21 (td, J = 7.5, 1.4 Hz, 1H), 7.16 (td, J = 7.4, 1.6 Hz, 1H), 7.09 (dd, J = 7.5, 1.2 Hz, 1H), 5.08 (q, J = 6.3 Hz, 1H), 2.69 – 2.53 (m, 2H), 2.46 (td, J = 7.3, 1.7 Hz, 2H), 1.73 – 1.60 (m, 4H), 1.44 (ddd, J = 18.0, 8.7, 6.1 Hz, 2H), 1.38 (d, J = 6.3 Hz, 3H), 0.90 (s, 9H), 0.04 (s, 3H), -0.06 (s, 3H); **13C NMR (75 MHz, CDCl₃)** δ 202.81, 144.79, 137.44, 128.98, 126.78, 126.36, 126.00, 67.51, 44.09, 32.07, 31.32, 29.53, 27.28, 26.10, 22.26, 18.46, -4.48, -4.53.

![Structure of 2.11.6](image)

**2.11.6**

**HOAc:**

**2.11.7**

![Structure of 2.11.7](image)

**2.11.7**

To a solution of 2.11.6 (0.150 g, 0.448 mmol) in 1:1 THF/H₂O (2 mL) at room temperature was added HOAc (3 mL). The solution was stirred at 50 °C for 10 hours.
at which time saturated aqueous NaHCO$_3$ was carefully added until bubbling ceased. The mixture was extracted with Et$_2$O (2x) and washed with water and brine. After drying over MgSO$_4$ and concentrating under reduced pressure. The crude aldehyde 2.11.7 (0.094 g, 0.427 mmol, 95%) was used in the subsequent reaction because of instability to silica gel chromatography.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.77 (t, J = 1.7 Hz, 1H), 7.54 (dd, J = 7.6, 1.4 Hz, 1H), 7.26 – 7.19 (m, 2H), 7.14 (dd, J = 7.5, 1.4 Hz, 1H), 5.17 (q, J = 6.4 Hz, 1H), 2.74 – 2.59 (m, 2H), 2.46 (td, J = 7.3, 1.7 Hz, 2H), 1.72 – 1.58 (m, 5H), 1.50 (d, J = 6.4 Hz, 2H), 1.47 – 1.37 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 202.91, 143.49, 138.91, 129.57, 127.56, 126.74, 125.28, 66.39, 44.02, 32.32, 31.66, 29.38, 25.04, 22.14.

![Chemical structure](image)

Aldehyde 2.11.9

Triethylamine (0.253 mL, 1.78 mmol, 4.0 equiv) and DMAP (0.011 g, 0.09 mmol, 0.2 equiv) were added to a solution of alcohol 2.11.9 (0.099 g, 0.449 mmol, 1.0 equiv) and crotonic anhydride (0.133 mL, 0.899 mmol, 2.0 equiv) in CH$_2$Cl$_2$ (4.5 mL) at 0 ºC. After 2 hours at 0 ºC, the reaction was quenched with saturated NaHCO$_3$ (10 mL). The organic phase was separated, washed with water and brine, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (gradient, hexanes to 10:1 hexanes:EtOAc) to provide ester 2.11.9 (0.118 g, 0.409 mmol, 91%).
$^1$H NMR (500 MHz, CDCl$_3$) δ 9.77 (t, J = 1.7 Hz, 1H), 7.50 – 7.40 (m, 1H), 7.25 – 7.18 (m, 2H), 7.15 (dd, J = 6.2, 2.8 Hz, 1H), 6.99 (dq, J = 15.4, 6.9 Hz, 1H), 6.17 (q, J = 6.5 Hz, 1H), 5.88 (dd, J = 15.5, 3.2, 1.5 Hz, 1H), 2.80 – 2.59 (m, 2H), 2.45 (td, J = 7.4, 1.7 Hz, 2H), 1.88 (dd, J = 6.9, 1.7 Hz, 3H), 1.74 – 1.58 (m, 4H), 1.55 (d, J = 6.5 Hz, 3H), 1.43 (dt, J = 7.8, 4.7 Hz, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 202.95, 165.96, 144.98, 139.97, 139.34, 129.63, 127.91, 126.60, 126.02, 123.16, 68.64, 44.04, 32.58, 31.29, 29.40, 22.54, 22.18, 18.21.

Aldehyde 2.11.6a

$n$Bu$_4$NBr (0.682 g, 2.12 mmol), NaOAc (0.215 g, 2.62 mmol), LiCl (0.045 g, 1.058 mmol), and Pd(OAc)$_2$ (0.023 g, 1.101 mmol) were added sequentially to a stirred solution of 2.11.5 (0.365 g, 1.01 mmol) and 3-buten-1-ol (0.091 mL, 1.058 mmol) in anhydrous DMF (5 mL). The mixture was heated to 50°C. After 2 days at 50°C, the reaction mixture was cooled to room temperature and diluted with EtOAc (10 mL) and hexanes (20 mL) resulting in a biphasic organic solution. The DMF-containing phase was separated and extracted with hexanes (10 mL). The combined hexanes/EtOAc extracts were washed with deionized water, 1.0 M CuSO$_4$, deionized water, 1.0 M NaOH, deionized water, and brine. After drying over anhydrous MgSO$_4$ and concentrating under reduced pressure, the crude product was purified by flash chromatography (30:1 hexanes:EtOAc) to afford aldehyde 2.11.6a (0.169 g, 0.551 mmol, 55%).
$^1$H NMR (500 MHz, CDCl$_3$) δ 9.81 (t, J = 1.4 Hz, 1H), 7.56 (dd, J = 7.7, 1.3 Hz, 1H), 7.25 – 7.20 (m, 1H), 7.17 (td, J = 7.4, 1.5 Hz, 1H), 7.10 (dd, J = 7.5, 1.2 Hz, 1H), 5.10 (q, J = 6.3 Hz, 1H), 2.76 – 2.57 (m, 2H), 2.54 (td, J = 7.1, 1.4 Hz, 2H), 2.02 – 1.83 (m, 2H), 1.39 (d, J = 6.3 Hz, 3H), 0.90 (s, 9H), 0.05 (s, 3H), -0.05 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 202.21, 145.00, 136.49, 129.05, 126.91, 126.71, 126.22, 67.55, 43.78, 31.46, 27.32, 26.09, 23.66, 18.45, -4.50, -4.53.

**Alcohol 2.11.7a**

To a solution of 2.11.6a (0.169 g, 0.551 mmol) in 1:1 THF/H$_2$O (2 mL) at room temperature was added HOAc (3 mL). The solution was stirred at 50 °C for 10 hours at which time saturated aqueous NaHCO$_3$ was carefully added until bubbling ceased. The mixture was extracted with Et$_2$O (2x) and washed with water and brine. After drying over MgSO$_4$ and concentrating under reduced pressure. The crude aldehyde 2.11.7a (0.101 g, 0.525 mmol, 95%) was used in the subsequent reaction because of instability to silica gel chromatography.

$^1$H NMR (500 MHz, CDCl$_3$) δ 9.77 (t, J = 1.4 Hz, 1H), 7.55 (dd, J = 7.7, 1.4 Hz, 1H), 7.29 – 7.20 (m, 4H), 7.15 (dd, J = 7.5, 1.3 Hz, 1H), 5.19 (q, J = 6.4 Hz, 1H), 2.77 – 2.65 (m, 3H), 2.54 (td, J = 7.1, 1.4 Hz, 2H), 2.00 – 1.92 (m, 2H), 1.51 (d, J = 6.4 Hz, 5H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 202.40, 143.61, 138.00, 129.71, 127.73, 127.12, 125.56, 66.43, 43.66, 31.71, 24.98, 24.00.
Aldehyde 2.4.5:

Triethylamine (0.278 mL, 1.98 mmol, 4.0 equiv) and DMAP (0.012 g, 0.10 mmol, 0.2 equiv) were added to a solution of alcohol 2.11.7a (0.095 g, 0.495 mmol, 1.0 equiv) and crotonic anhydride (0.146 mL, 0.988 mmol, 2.0 equiv) in CH₂Cl₂ (4.5 mL) at 0 °C. After 2 hours at 0 °C, the reaction was quenched with saturated NaHCO₃ (10 mL). The organic phase was separated, washed with water and brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (gradient, hexanes to 20:1 hexanes:EtOAc) to provide ester 2.4.5 as colorless oil (0.072 g, 56%).

¹H NMR (500 MHz, CDCl₃) δ 9.79 (t, J = 1.4 Hz, 1H), 7.44 (dd, J = 7.0, 2.1 Hz, 1H), 7.26 – 7.18 (m, 2H), 7.18 – 7.13 (m, 1H), 6.99 (dq, J = 15.4, 6.9 Hz, 1H), 6.16 (q, J = 6.5 Hz, 1H), 5.91 – 5.84 (m, 1H), 2.83 – 2.66 (m, 2H), 2.53 (ddd, J = 8.9, 3.3, 1.7 Hz, 2H), 2.03 – 1.92 (m, 2H), 1.87 (dd, J = 6.9, 1.7 Hz, 3H), 1.55 (d, J = 6.6 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 202.41, 165.93, 145.08, 140.22, 138.22, 129.66, 127.96, 126.91, 126.03, 123.04, 68.60, 43.58, 31.79, 23.64, 22.56, 18.17.

TBS Iodobenzyl alcohol (2.11.5b)
To a stirring solution of 2-iodobenzylalcohol 2.11.1 (5.0 g, 21.36 mmol) in 100 mL DMF was added imidazole (2.18 g, 32 mmol, 1.5 equiv), DMAP (0.522 g, 4.27 mmol, 0.2 equiv) and TBSCl (3.54 g, 23.5 mmol, 1.1 equiv). The mixture was stirred at room temperature for 2 h, then 100 mL of water was added. The mixture was transferred to a separatory funnel. The aqueous layer was separated and extracted with ether (2x). The combined organic layers were then washed with water (2x), dried with MgSO\(_4\) and filtered. The solvent was removed in vacuo and the residue was purified by column chromatography (hexanes) (2.11.5b, 5.07 g, 68%) as a clear colorless liquid.

\[ R_f = 0.29 \text{ (hexanes); } ^1H \text{ NMR: (500 MHz, CDCl}_3\text{) } \delta 7.77 \text{ (dd, } J = 7.9, 1.3, 1H), 7.51 \text{ (d, } J = 7.7, 1H), 7.37 \text{ (t, } J = 7.5, 1H), 6.96 \text{ (t, } J = 7.8, 1H), 4.63 \text{ (s, } 2H), 0.97 \text{ (s, } 9H), 0.14 \text{ (s, } 6H); ^{13}C \text{ NMR: (75 MHz, CDCl}_3\text{) } \delta 143.1, 138.8, 128.7, 128.4, 127.6, 96.0, 69.6, 26.2, 18.6, -5.1. \]

\[
\begin{align*}
\text{TBSO} & \quad \text{Pd(OAc)}_2, \text{NaOAc} \\
\text{2.11.5b} & \quad \text{nBu}_4\text{NBr, LiCl} \\
& \quad \text{TBSO} \\
\end{align*}
\]

\[
\begin{align*}
\text{2.11.5b} & \quad \text{Pd(OAc)}_2, \text{NaOAc} \\
& \quad \text{nBu}_4\text{NBr, LiCl} \\
& \quad \text{TBSO} \\
\end{align*}
\]

4-[2-(tert-Butyldimethylsilyloxymethyl)phenyl]butyraldehyde (2.11.6b):

\[ \text{nBu}_4\text{NBr (1.94 g, 6.03 mmol), NaOAc (0.612 g, 7.46 mmol), LiCl (0.128 g, 0.301 mmol), and Pd(OAc)}_2 \text{ (0.064 g, 0.281 mmol) were added sequentially to a stirred solution of 2.11.5b (1.0 g, 2.87 mmol) and 3-buten-1-ol (0.259 mL, 0.3014 mmol) in anhydrous DMF (6 mL). The mixture was heated to 50 °C. After 3 days at 50 °C, the reaction mixture was cooled to room temperature and diluted with EtOAc} \]

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(10 mL) and hexanes (20 mL) resulting in a biphasic organic solution. The DMF-containing phase was separated and extracted with hexanes (10 mL). The combined hexanes/EtOAc extracts were washed with deionized water, 1.0 M CuSO₄, deionized water, 1.0 M NaOH, deionized water, and brine. After drying over anhydrous MgSO₄ and concentrating under reduced pressure, the crude product was purified by flash chromatography (30:1 hexanes:EtOAc) to afford aldehyde 2.11.6b (0.53 g, 1.83 mmol, 64%).

\[ ^1H \text{ NMR (500 MHz; CDCl}_3\text{): } \delta \text{ 9.76 (t, 1H, } J = 1.5 \text{ Hz), 7.42-7.38 (m, 1H), 7.22-7.17 (m, 2H), 7.14-7.10 (m, 1H), 4.72 (s, 2H), 2.64 (t, 2H, } J = 7.7 \text{ Hz), 2.48 (dt, 2H, } J = 1.5, 7.3 \text{ Hz), 1.96-1.89 (m, 2H), 0.92 (m, 2H), 0.09 (s, 6H).} \]

\[ ^13C \text{ NMR (100 MHz; CDCl}_3\text{): } \delta \text{ 202.5, 139.0, 138.7, 129.2, 127.7, 127.5, 126.5, 63.2, 43.7, 31.5, 26.2, 23.2, 18.7, -5.0.} \]

LRMS (ESI) \( m/z \) calc’d for C_{17}H_{28}O_{2}SiNa [M+Na]^+ \: 315.2; found: 315.1.

**Alcohol 2.11.7b:**

To a solution of 2.11.6b (0.20 g, 0.684 mmol) in 1:1 THF/H₂O (4 mL) at room temperature was added HOAc (5 mL). The solution was stirred for 10 hours at which time saturated aqueous NaHCO₃ was carefully added until bubbling ceased. The mixture was extracted with Et₂O (2x) and washed with water and brine. After drying over MgSO₄ and concentrating under reduced pressure, aldehyde 2.11.7b
(0.096 g, 0.539 mmol, 79%) was obtained. The crude product was used as is in the next subsequent steps because of decomposition on silica gel.

\[ \text{H NMR (400 MHz, CDCl}_3) \delta 9.77 (s, 1H), 7.36 (d, J = 6.9 Hz, 1H), 7.31 –
\]

\[ \text{7.07 (m, 3H), 4.72 (s, 2H), 2.81 – 2.65 (m, 2H), 2.54 (t, J = 7.0 Hz, 2H), 2.07 (bs,
\]

\[ \text{1H), 2.01 – 1.89 (m, 2H); } \]

\[ \text{C NMR (75 MHz, CDCl}_3) \delta 202.77, 139.87, 138.62,
\]

\[ 129.67, 128.93, 128.30, 126.73, 63.34, 43.63, 31.69, 23.67. \]

**Aldehyde 2.4.3**

Triethylamine (0.345 mL, 2.46 mmol, 10 equiv) and DMAP (0.006 g, 0.05 mmol, 0.2 equiv) were added to a solution of alcohol 2.11.7b (0.043 g, 0.246 mmol, 1.0 equiv) and crotonic anhydride (0.182 mL, 0.123 mmol, 5.0 equiv) in CH\(_2\)Cl\(_2\) (2.5 mL) at 0 °C. After 2 hours at 0 °C, the reaction was quenched with saturated NaHCO\(_3\) (10 mL). The organic phase was separated, washed with water and brine, dried over MgSO\(_4\), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (5:1 hexanes:EtOAc) to provide a colorless oil 2.4.3 (0.0265 g, 0.108 mmol, 44%).

\[ \text{H NMR (300 MHz, CDCl}_3) \delta 9.80 (t, J = 1.5 Hz, 1H), 7.39 (d, J = 7.3 Hz,
\]

\[ 1H), 7.33 – 7.17 (m, 4H), 7.03 (dq, J = 15.5, 6.9 Hz, 1H), 5.89 (dq, J = 15.6, 1.7 Hz,
\]

\[ 1H), 5.23 (s, 2H), 2.73 (dd, J = 8.9, 6.9 Hz, 2H), 2.53 (td, J = 7.3, 1.5 Hz, 2H), 2.05 –
\]

\[ 1.82 (m, 5H); } \]

\[ \text{C NMR (75 MHz, CDCl}_3) \delta 202.21, 145.58, 130.28, 129.74, 129.95,
\]

\[ 126.74, 122.64, 64.15, 43.68, 31.91, 23.66, 18.29. \]
**Aldehyde 2.11.6c:**

\( n\text{Bu}_4\text{NBr} \) (3.65 g, 11.34 mmol), NaOAc (1.151 g, 14.03 mmol), LiCl (0.240 g, 5.67 mmol), and Pd(OAc)_2 (0.121 g, 0.540 mmol) were added sequentially to a stirred solution of 2.11.4a (1.88 g, 5.40 mmol) and 3-methyl-3-buten-1-ol (0.572 mL, 5.67 mmol) in anhydrous DMF (11 mL). The mixture was heated to 50 °C. After 2 days at 50 °C, the reaction mixture was cooled to room temperature and diluted with EtOAc (10 mL) and hexanes (20 mL) resulting in a biphasic organic solution. The DMF-containing phase was separated and extracted with hexanes (10 mL). The combined hexanes/EtOAc extracts were washed with deionized water, 1.0 M CuSO_4, deionized water, 1.0 M NaOH, deionized water, and brine. After drying over anhydrous MgSO_4 and concentrating under reduced pressure, the crude product was purified by flash chromatography (40:1 hexanes:EtOAc) to afford aldehyde 2.11.6c (0.768 g, 2.506 mmol, 46%).

\(^1\)H NMR (500 MHz, CDCl_3) \( \delta \) 9.68 (dd, \( J = 2.3, 1.6 \text{ Hz, 1H} \), 7.48 – 7.33 (m, 1H), 7.24 – 7.15 (m, 2H), 7.13 – 7.04 (m, 1H), 4.73 (dd, \( J = 13.0, 3.2 \text{ Hz, 2H} \), 2.57 (qd, \( J = 13.8, 7.3 \text{ Hz, 2H} \)), 2.44 (ddd, \( J = 15.8, 5.2, 1.4 \text{ Hz, 1H} \)), 2.38 (dt, \( J = 19.8, 6.8 \text{ Hz, 1H} \)), 2.26 (ddd, \( J = 15.9, 7.6, 2.5 \text{ Hz, 1H} \)), 0.98 (d, \( J = 6.6 \text{ Hz, 3H} \)), 0.93 (s, 9H), 0.10 (s, 6H); \(^{13}\)C NMR (75 MHz, CDCl_3) \( \delta \) 202.59, 139.40, 137.48, 130.14, 127.79, 127.22, 126.64, 63.19, 50.82, 39.62, 29.60, 26.20, 20.45, 18.65, -5.00.
Aldehyde 2.11.7c

To a solution of 2.11.6c (0.260 g, 0.848 mmol) in 1:1 THF/H$_2$O (2 mL) at room temperature was added HOAc (3 mL). The solution was stirred for 10 hours at which time saturated aqueous NaHCO$_3$ was carefully added until bubbling ceased. The mixture was extracted with Et$_2$O (2x) and washed with water and brine. After drying over MgSO$_4$ and concentrating under reduced pressure, aldehyde 2.11.7c (0.162 g, 0.848 mmol, 99%) was obtained. The crude product was used as is in the next subsequent steps because of decomposition on silica gel.

$^1$H NMR (500 MHz, CDCl$_3$) δ 9.66 (s, 1H), 7.38 (d, J = 6.5 Hz, 1H), 7.24 (dd, J = 6.0, 2.9 Hz, 2H), 7.18 – 7.12 (m, 1H), 4.82 – 4.59 (m, 2H), 2.77 – 2.66 (m, 1H), 2.59 (dd, J = 13.7, 7.5 Hz, 1H), 2.52 – 2.37 (m, 3H), 2.37 – 2.27 (m, 2H), 1.00 (d, J = 6.4 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 203.07, 139.01, 138.39, 130.52, 128.93, 127.89, 126.82, 62.98, 50.79, 39.65, 29.86, 20.38.

Aldehyde 2.4.7

Triethylamine (0.289 mL, 2.06 mmol, 4.0 equiv) and DMAP (0.013 g, 0.103 mmol, 0.2 equiv) were added to a solution of alcohol 2.11.7b (0.099 g, 0.515 mmol,
1.0 equiv) and crotonic anhydride (0.153 mL, 1.03 mmol, 2.0 equiv) in CH$_2$Cl$_2$ (5 mL) at 0 °C. After 2 hours at 0 °C, the reaction was quenched with saturated NaHCO$_3$ (10 mL). The organic phase was separated, washed with water and brine, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography was purified by flash chromatography (30:1 hexanes:EtOAc) to provide a colorless oil (0.063 g, 0.242 mmol, 47%).

$^1$H NMR (500 MHz, CDCl$_3$) δ 9.70 (dd, $J = 2.2$, 1.6 Hz, 1H), 7.38 (dd, $J = 7.5$, 1.2 Hz, 1H), 7.29 (td, $J = 7.4$, 1.5 Hz, 1H), 7.24 (td, $J = 7.4$, 1.4 Hz, 1H), 7.21 – 7.17 (m, 1H), 7.02 (dq, $J = 15.5$, 6.9 Hz, 1H), 5.88 (dq, $J = 15.5$, 1.6 Hz, 1H), 5.32 – 5.07 (m, 2H), 2.68 (dd, $J = 13.9$, 7.2 Hz, 1H), 2.62 (dd, $J = 13.9$, 7.4 Hz, 1H), 2.47 (ddd, $J = 16.0$, 5.0, 1.4 Hz, 1H), 2.44 – 2.35 (m, 1H), 2.30 (ddd, $J = 16.0$, 7.8, 2.4 Hz, 1H), 1.89 (dd, $J = 6.9$, 1.7 Hz, 3H), 1.00 (d, $J = 6.5$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 202.43, 166.51, 145.59, 139.26, 134.42, 130.64, 130.32, 128.70, 126.87, 122.62, 64.05, 50.73, 39.82, 30.04, 20.33, 18.28.

6-[2-(tert-Butyldimethylsilyloxy)methyl]phenylhexanal 2.11.6d

$n$Bu$_4$NBr (1.94 g, 6.03 mmol), NaOAc (0.612 g, 7.46 mmol), LiCl (0.128 g, 3.01 mmol), and Pd(OAc)$_2$ (0.064 g, 0.287 mmol) were added sequentially to a stirred solution of 2.11.4a (1.0 g, 2.87 mmol) and 5-hexen-1-ol (0.357 ml, 3.01 mmol) in anhydrous DMF (6 mL). The mixture was heated to 50 °C. After 4 days at this temperature, the reaction mixture was to room temperature and diluted with EtOAc
(15 mL) and hexanes (30 mL) resulting in a biphasic organic solution. The DMF-containing phase was separated and extracted with hexanes (10 mL). The combined hexanes/EtOAc extracts were washed with deionized water, 1.0 M CuSO₄, deionized water, 1.0 M NaOH, deionized water, and brine. After drying over MgSO₄ and concentrating under reduced pressure, the crude product was purified by flash chromatography (30:1 hexanes:EtOAc) to afford aldehyde 2.11.6d (0.476 g, 1.48 mmol, 52%).

¹H NMR (500 MHz; CDCl₃): δ 9.75 (t, 1H, J = 1.8 Hz), 7.43-7.35 (m, 1H), 7.20-7.16 (m, 2H), 7.13-7.10 (m, 1H), 4.71 (s, 2H), 2.60-2.55 (m, 2H), 1.69-1.56 (m, 4H), 1.43-1.36 (m, 2H), 0.92 (s, 9H), 0.08 (s, 6H). ¹³C NMR (100 MHz; CDCl₃): δ 202.8, 139.7, 138.8, 129.0, 127.4, 127.3, 126.1, 63.2, 44.1, 32.1, 30.7, 29.4, 26.2, 22.2, 18.6, -5.0. LRMS (ESI) m/z calc’d for C₁₉H₃₂O₂SiNa [M+Na]⁺: 343.2; found: 343.2.

Alcohol 2.11.7d

To a solution of 2.11.6d (0.20 g, 0.684 mmol) in 1:1 THF/H₂O (3 mL) at room temperature was added HOAc (4 mL). The solution was stirred for 10 hours at which time saturated aqueous NaHCO₃ was carefully added until bubbling ceased. The mixture was extracted with Et₂O (2x) and washed with water and brine. After drying over MgSO₄ and concentrating under reduced pressure, the crude product was
purified by flash chromatography (3:1 hexanes:EtOAc) to afford aldehyde 2.11.7d (0.115 g, 0.557 mmol, 89%).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.77 (d, $J = 1.2$ Hz, 1H), 7.38 (d, $J = 7.3$ Hz, 1H), 7.28 – 7.09 (m, 3H), 4.72 (s, 2H), 2.79 – 2.56 (m, 2H), 2.45 (t, $J = 7.3$ Hz, 2H), 1.87 (bs, 1H), 1.66 (qd, $J = 15.3$, 7.7 Hz, 4H), 1.51 – 1.34 (m, 2H).

**Aldehyde 2.4.9**

A solution of Et$_3$N (1.04 mL, 7.42 mmol) and DMAP (0.018 g, 0.148 mmol) in CH$_2$Cl$_2$ (2 mL) was added to a stirred solution of alcohol 2.11.7d (.153 g, 0.742 mmol) and crotonic anhydride (0.550 mL, 3.71 mmol) in CH$_2$Cl$_2$ (5 mL) at 0 °C. After 4 hours at 0 °C, the reaction was concentrated under reduced pressure. EtOAc (5 mL) was added, and the organic solution was washed with saturated NaHCO$_3$, deionized water, and brine. The organic phase was dried over anhydrous MgSO$_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (10:1 hexanes:EtOAc) to provide ester 2.4.9 (0.183 g, 0.667 mmol, 90%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.76 (t, $J = 1.7$ Hz, 1H), 7.39 – 7.31 (m, 1H), 7.31 – 7.27 (m, 1H), 7.20 (t, $J = 6.6$ Hz, 2H), 7.08 – 6.94 (m, 1H), 5.87 (ddd, $J = 15.5$, 3.3, 1.6 Hz, 1H), 5.19 (s, 2H), 2.72 – 2.60 (m, 2H), 2.43 (td, $J = 7.3$, 1.7 Hz, 2H), 1.88 (dd, $J = 6.9$, 1.7 Hz, 3H), 1.64 (qd, $J = 15.4$, 7.6 Hz, 4H), 1.47 – 1.34 (m, 2H); $^{13}$C
NMR (75 MHz, CDCl₃) δ 202.81, 166.54, 145.44, 141.55, 133.76, 130.02, 129.64, 128.80, 126.36, 122.69, 64.21, 44.04, 32.55, 31.25, 29.36, 22.18, 18.25.

6-[2-(tert-Butyldimethylsilanyloxyethyl)phenyl]-2-methylhexan-3-ol (2.11.8)⁵⁸:

iPrMgBr (3.05 mL, 6.1 mmol, 2.0 M solution in Et₂O) was added to a stirred solution of aldehyde 2.11.6b (1.08 g, 4.1 mmol) in THF (40 mL) at 0 °C. After 1 hour, the reaction was quenched with saturated NH₄Cl (20 mL). The organic phase was separated, washed with deionized water and brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The product was purified by flash chromatography (10:1 hexanes:EtOAc) to provide a colorless oil 2.11.8 (0.78 g, 78%).

¹H NMR (400 MHz; CDCl₃): δ 7.42-7.38 (m, 1H), 7.21-7.12 (m, 3H), 4.74 (s, 2H), 3.42-3.34 (m, 1H), 2.68-2.54 (m, 2H), 1.85-1.40 (m, 5H), 1.31 (d, 1H, J = 5.0 Hz), 0.93 (s, 9H), 0.91 (d, 3H, J = 4.1 Hz), 0.88 (d, 3H, J = 4.0 Hz), 0.09 (s, 6H). ¹³C NMR (100 MHz; CDCl₃): δ 139.7, 138.8, 129.0, 127.3, 126.1, 76.8, 63.2, 34.4, 33.7, 32.3, 27.3, 26.2, 19.1, 18.6, 17.3, -5.0. LRMS (ESI) m/z calc’d for C₂₀H₃₆O₅SiNa [M+Na]⁺: 359.2; found: 359.2.

But-2-enoic acid 4-[2-(tert-Butyldimethylsilanyloxymethyl)phenyl]-1-isopropylbutyl ester 2.11.9:

A solution of Et₃N (1.665 mL, 11.85 mmol) and DMAP (0.058 g, 0.474 mmol) in CH₂Cl₂ (12 mL) was added to a stirred solution of alcohol 2.11.8 (0.798 g, 2.37 mmol) and crotonic anhydride (.731 g, 4.74 mmol) in CH₂Cl₂ (12 mL) at 0 °C. After 4 hours at 0 °C, the reaction was concentrated under reduced pressure. EtOAc (10 mL) was added, and the organic solution was washed with saturated NaHCO₃, deionized water, and brine. The organic phase was dried over anhydrous MgSO₄ and concentrated under reduced pressure. The crude product was purified by flash chromatography (30:1 hexanes:EtOAc) to provide a colorless oil (0.80 g, 83%).

¹H NMR (500 MHz; CDCl₃): δ 7.42-7.38 (m, 1H), 7.19-7.14 (m, 2H), 7.12-7.08 (m, 1H), 6.94 (dq, 1H, J = 6.9, 15.5 Hz), 5.83 (dq, 1H, J = 1.7, 15.5 Hz), 4.86-4.81 (m, 1H), 4.71 (s, 2H), 2.64-2.50 (m, 2H), 1.86 (dd, 3H, J = 1.7, 6.9 Hz), 1.86-1.78 (m, 1H), 1.65-1.49 (m, 4H), 0.92 (s, 9H), 0.89 (s, 3H), 0.87 (s, 3H), 0.08 (s, 6H).

¹³C NMR (100 MHz; CDCl₃): δ 166.7, 144.5, 139.3, 138.9, 129.0, 127.2, 127.1, 126.1, 123.3, 78.0, 63.0, 32.1, 31.8, 31.5, 26.7, 26.2, 18.8, 18.6, 18.2, 17.9, -5.0.

LRMS (ESI) m/z calc’d for C₂₄H₄₀O₃SiNa [M+Na]⁺: 427.32; found: 427.2.
But-2-enoic acid 4-(2-hydroxymethylphenyl)-1-isopropylbutyl ester 2.11.10:

TBAF (12.3 mL, 12.3 mmol, 1 M solution in THF) was added to a stirred solution of 2.11.9 (2.74 g, 8.2 mmol) in THF (80 mL) at 0 °C. After 45 minutes at 0 °C, the reaction was quenched with saturated NH$_4$Cl (20 mL). The organic phase was separated, washed with deionized water and brine, dried over anhydrous MgSO$_4$, and concentrated under reduced pressure. was purified by flash chromatography (10:1 hexanes:EtOAc) to provide a colorless oil 2.11.10 (99%).

$^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.35-7.32 (m, 1H), 7.25-7.13 (m, 3H), 6.94 (dd, 1H, J = 6.9, 15.5 Hz), 5.83 (dq, 1H, J = 1.7, 15.5 Hz), 4.88-4.82 (m, 1H), 4.72-4.62 (m, 2H), 2.77-2.56 (m, 2H), 1.85 (dd, 3H, J = 1.7, 6.9 Hz), 1.85-1.75 (m, 2H), 1.69-1.48 (m, 4H), 0.88 (s, 3H), 0.86 (s, 3H). $^{13}$C NMR (100 MHz; CDCl$_3$): $\delta$ 166.9, 144.8, 140.6, 138.5, 129.6, 128.6, 128.2, 126.4, 123.2, 77.8, 63.3, 32.3, 31.9, 31.5, 27.3, 18.8, 18.2, 17.8. LRMS (ESI) $m/z$ calc’d for C$_{18}$H$_{26}$O$_3$Na [M+Na]$^+$: 313.2; found: 313.1.

But-2-enoic acid 4-(2-formylphenyl)-1-isopropylbutyl ester 2.4.12

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Dess-Martin periodinane (1.02 g, 2.4 mmol) was added to a stirred solution of alcohol 2.11.10 (0.465 g, 1.6 mmol) in CH$_2$Cl$_2$ (16 mL). The mixture was stirred overnight (14 hours) at room temperature. The reaction was diluted with Et$_2$O (10 mL), then saturated NaHCO$_3$/Na$_2$S$_2$O$_3$ (15 mL, 1/1 mixture) was added, and the reaction was stirred vigorously for 15 minutes. After the mixture was diluted further with Et$_2$O (15 mL), the organic phase was separated and washed with saturated NaHCO$_3$, deionized water, brine, dried over anhydrous MgSO$_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography (20:1 hexanes:EtOAc) to provide a colorless oil 2.4.12 (0.42 g, 91%).

$^1$H NMR (400 MHz; CDCl$_3$): δ 10.22 (s, 1H), 7.79 (dd, 1H, J = 1.5, 7.7 Hz), 7.47 (dt, 1H, J = 1.5, 7.5 Hz), 7.34 (dt, 1H, J = 1.0, 7.5 Hz), 7.23 (d, 1H, J = 6.0 Hz), 6.93 (dq, 1H, J = 7.0, 15.6 Hz), 5.82 (dq, 1H, J = 1.7, 15.5 Hz), 4.86-4.80 (m, 1H), 3.08-2.93 (m, 2H), 1.86 (dd, 3H, J = 1.7, 7.0 Hz), 1.85-1.75 (m, 1H), 1.68-1.50 (m, 4H), 0.88 (s, 3H), 0.86 (s, 3H). $^{13}$C NMR (100 MHz; CDCl$_3$): δ 192.6, 166.7, 145.3, 144.7, 134.0, 133.9, 132.1, 131.2, 126.8, 123.2, 77.8, 32.6, 31.8, 31.3, 28.3, 18.8, 18.2, 17.8. IR (cm$^{-1}$): 2964, 2875, 1714, 1695, 1658, 1292, 1268, 1188, 754. HRMS (ESI) m/z calc’d for C$_{18}$H$_{24}$O$_3$Na [M+Na]$^+$: 311.1617; found: 311.1610.

**Alcohol 2.11.4e**

To a solution of 2-iodobenzaldehyde 2.11.3 (0.300 g, 1.29 mmol, 0 °C) in THF (6 mL) was treated with a 2.0 M solution of $i$-PrMgCl in Et$_2$O (0.84 mL, 1.68
mmol). After 15 minutes, the reaction mixture was quenched with H₂O, extracted with Et₂O, dried over MgSO₄, and evaporated. The crude material was purified by flash chromatography (10:1 hexanes:EtOAc) to give **2.11.4e** (0.052 g, 0.088 mmol, 7%).

^1^H NMR (500 MHz, CDCl₃) δ 7.82 (dd, J = 7.9, 1.2 Hz, 1H), 7.46 (dd, J = 7.8, 1.7 Hz, 1H), 7.37 (td, J = 7.7, 1.1 Hz, 1H), 6.97 (td, J = 7.7, 1.8 Hz, 1H), 4.71 (d, J = 5.6 Hz, 1H), 2.12 – 2.00 (m, 1H), 1.68 (s, 2H), 1.00 – 0.96 (m, 7H).

Ester **2.11.5e**

Compound **2.11.5e** was prepared from **2.11.4e** by following the procedure for the preparation of **2.11.9** and was purified by flash chromatography (40:1 hexanes:EtOAc) to provide a colorless oil (0.039 g, 66%).

^1^H NMR (500 MHz, CDCl₃) δ 7.82 (dd, J = 7.9, 1.1 Hz, 1H), 7.33 – 7.29 (m, 1H), 7.26 (dd, J = 7.8, 1.8 Hz, 1H), 7.02 (dq, J = 15.5, 6.9 Hz, 1H), 6.95 (td, J = 7.8, 1.8 Hz, 1H), 5.92 (dq, J = 15.5, 1.6 Hz, 1H), 5.77 (d, J = 6.0 Hz, 1H), 2.23 – 2.09 (m, 1H), 1.90 (dd, J = 6.9, 1.7 Hz, 3H), 0.98 (dd, J = 6.8, 5.3 Hz, 6H); ^1^C NMR (75 MHz, CDCl₃) δ 145.29, 143.08, 139.74, 129.35, 128.31, 127.76, 122.85, 98.83, 83.08, 33.47, 19.45, 18.31, 17.39.
Aldehyde 2.11.6e

$n\text{Bu}_4\text{NBr}$ (0.056 g, 0.174 mmol), NaOAc (0.018 g, 0.216 mmol), LiCl (3.7 mg, 0.087 mmol), and Pd(OAc)$_2$ (2 mg, 0.008 mmol) were added sequentially to a stirred solution of 2.11.5e (0.027 g, 0.083 mmol) and 3-butene-1-ol (0.0075 mL, 0.087 mmol) in anhydrous DMF (1 mL). The mixture was heated to 50°C. After 2 days at 50°C, the reaction mixture was cooled to room temperature and diluted with EtOAc (5 mL) and hexanes (10 mL) resulting in a biphasic organic solution. The DMF-containing phase was separated and extracted with hexanes (5 mL). The combined hexanes/EtOAc extracts were washed with deionized water, 1.0 M CuSO$_4$, deionized water, 1.0 M NaOH, deionized water, and brine. After drying over anhydrous MgSO$_4$ and concentrating under reduced pressure, the crude product was purified by flash chromatography (15:1 hexanes:EtOAc) to afford aldehyde 2.11.6e (0.012 g, 0.042 mmol, 50%).

$^1$H NMR (500 MHz, CDCl$_3$) δ 9.81 (t, J = 1.6 Hz, 1H), 7.36 – 7.31 (m, 1H), 7.23 – 7.18 (m, 2H), 7.17 – 7.13 (m, 1H), 6.98 (dq, J = 15.5, 6.9 Hz, 1H), 5.89 (dq, J = 15.5, 1.6 Hz, 1H), 5.81 (d, J = 7.6 Hz, 1H), 2.83 (ddd, J = 14.2, 9.7, 6.3 Hz, 1H), 2.73 (ddd, J = 14.1, 9.6, 6.2 Hz, 1H), 1.02 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 6.9 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 202.50, 165.89, 144.67, 138.84, 138.34, 129.15, 127.53, 126.76, 126.24, 122.87, 43.45, 34.07, 31.49, 29.70, 23.21, 19.20, 18.27, 17.99.
Alcohol 2.12.2

To a stirred solution of 2-bromoiodophenol 2.12.1 (0.227 mL, 1.77 mmol) in THF (9 mL) at -25 °C was added i-PrMgCl (2.0 M in Et₂O, 0.884 mL, 1.77 mmol). The solution was stirred for 45 minutes, crotonaldehyde (0.146 mL, 1.77 mmol) was added and the mixture warmed to rt and stirred for 10 minutes. The reaction was diluted with water, extracted 2x with Et₂O. The combined organic layers were then washed with brine, dried with MgSO₄ and filtered. The solvent was removed in vacuo and the residue was purified by column chromatography (25:1 hexanes:EtOAc) to give alcohol 2.12.2 (0.376 g, 1.654 mmol, 94%) as an off-white semi-solid.

^1^H NMR (500 MHz, CDCl₃) δ 7.54 (dd, J = 7.8, 1.5 Hz, 1H), 7.51 (dd, J = 8.0, 1.0 Hz, 1H), 7.33 (dd, J = 10.9, 4.2 Hz, 1H), 7.11 (td, J = 7.8, 1.6 Hz, 1H), 5.85 – 5.75 (m, 1H), 5.66 – 5.58 (m, 1H), 5.52 (d, J = 6.5 Hz, 1H), 2.02 (d, J = 2.3 Hz, 1H), 1.70 (d, J = 6.5 Hz, 3H); ^13^C NMR (75 MHz, CDCl₃) δ 142.41, 132.99, 131.83, 129.15, 128.46, 128.00, 122.66, 73.77, 29.96, 18.02.

Ketone 2.12.3

Dess-Martin periodinane (0.280 g, 0.661 mmol, 1.5 equiv) was added to a stirred solution of alcohol 2.12.2 (0.10 g, 0.440 mmol, 1.0 equiv) in CH₂Cl₂ (4 mL).
The mixture was stirred overnight (14 h) at room temperature. The reaction was diluted with Et<sub>2</sub>O (3.0 mL), then a 1:1 mixture of saturated NaHCO<sub>3</sub> and saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (5.0 mL) was added, and the reaction was stirred vigorously for 15 minutes. After the mixture was diluted further with Et<sub>2</sub>O (15 mL), the organic phase was separated, washed with saturated NaHCO<sub>3</sub>, deionized water and brine, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (25:1 hexanes:EtOAc) to provide ketone 2.12.3 (0.099 g, 0.044 mmol, 100%).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.57 (dd, J = 7.8, 1.7 Hz, 1H), 7.54 (dd, J = 8.0, 1.2 Hz, 1H), 7.35 (td, J = 7.7, 1.1 Hz, 1H), 7.14 (td, J = 7.7, 1.7 Hz, 1H), 5.83 (dqd, J = 13.9, 6.5, 0.9 Hz, 1H), 5.65 (ddq, J = 15.2, 6.5, 1.5 Hz, 1H), 5.55 (d, J = 6.5 Hz, 1H), 1.73 (ddd, J = 6.5, 1.3, 0.8 Hz, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 195.36, 148.67, 141.27, 133.52, 132.16, 131.26, 129.06, 127.36, 119.51, 18.91.

Ketone 2.12.5

To the TBS alkene 2.12.4 (0.112 g, 0.524 mmol) was added a solution of 9-BBN in THF (0.5M, 1.05 mL, 0.524 mmol) and stirred for 4 hours. To a sealed tube containing a solution of Bromide 2.12.3 (0.097 g, 0.403 mmol), PdCl<sub>2</sub>(dppf)·CH<sub>2</sub>Cl<sub>2</sub> (0.033 g, 0.040 mmol) and K<sub>2</sub>CO<sub>3</sub> in freshly distilled, degassed DMF (2 mL) was
added the trialkylborane solution. The reaction vessel was sealed, and heated to 50 °C for 8 hours. The reaction was then diluted with Et₂O then poured into water. The product was extracted with Et₂O, washed with water four times, and dried over MgSO₄. The crude product was purified by flash chromatography (40:1 hexanes:EtOAc) to provide ketone 2.12.5 (0.099 g, 0.273 mmol, 68%).

¹H NMR (500 MHz, CDCl₃) δ 7.36 (td, J = 7.5, 1.4 Hz, 1H), 7.33 – 7.30 (m, 1H), 7.27 – 7.19 (m, 2H), 6.70 (dq, J = 15.6, 6.8 Hz, 1H), 6.48 (dq, J = 15.7, 1.4 Hz, 1H), 3.58 (t, J = 6.6 Hz, 2H), 2.72 – 2.61 (m, 2H), 1.95 (dd, J = 6.8, 1.5 Hz, 3H), 1.61 – 1.40 (m, 4H), 1.40 – 1.27 (m, 4H), 0.89 (s, 9H), 0.04 (s, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 147.37, 141.64, 139.18, 133.20, 130.40, 130.21, 128.06, 125.44, 63.52, 33.45, 33.05, 31.98, 29.64, 26.24, 25.88, 18.80, 18.64, -5.00.

Alcohol 2.12.6:

To a solution of 2.12.5 (0.25 g, 0.69 mmol) in 1:1 THF/H₂O (0.5 mL) at room temperature was added HOAc (1 mL). The solution was stirred for 10 hours at which time saturated aqueous NaHCO₃ was carefully added until bubbling ceased. The mixture was extracted with Et₂O (2x) and washed with water and brine. After drying over MgSO₄ and concentrating under reduced pressure, the crude mixture was purified by flash chromatography (3:1 hexanes:EtOAc) to give ketone 2.12.6 (0.013 g, 0.053 mmol, 76%) was obtained.
$^1$H NMR (500 MHz, CDCl$_3$) δ 7.36 (td, J = 7.5, 1.4 Hz, 1H), 7.32 (dd, J = 7.6, 1.1 Hz, 1H), 7.25 (d, J = 7.4 Hz, 1H), 7.24 – 7.20 (m, 1H), 6.70 (dq, J = 15.6, 6.8 Hz, 1H), 6.48 (dq, J = 15.6, 1.4 Hz, 1H), 3.62 (t, J = 6.6 Hz, 2H), 2.72 – 2.61 (m, 2H), 1.95 (dd, J = 6.8, 1.5 Hz, 3H), 1.63 – 1.49 (m, 5H), 1.41 – 1.30 (m, 4H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 197.74, 147.39, 141.60, 139.13, 133.14, 130.41, 130.26, 128.11, 125.47, 63.18, 33.35, 32.89, 31.84, 29.46, 25.65, 18.77.

**Aldehyde 2.12.7**

Dess-Martin periodinane (0.043 g, 0.102 mmol, 1.5 equiv) was added to a stirred solution of alcohol 2.12.6 (0.17 g, 0.068 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (1 mL). The mixture was stirred overnight (14 h) at room temperature. The reaction was diluted with Et$_2$O (3.0 mL), then a 1:1 mixture of saturated NaHCO$_3$ and saturated Na$_2$S$_2$O$_3$ (5.0 mL) was added, and the reaction was stirred vigorously for 15 minutes. After the mixture was diluted further with Et$_2$O (15 mL), the organic phase was separated, washed with saturated NaHCO$_3$, deionized water and brine, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (20:1 hexanes:EtOAc) to provide ketone 2.12.7 (0.016 g, 0.065 mmol, 97%).

$^1$H NMR (500 MHz, CDCl$_3$) δ 9.76 (t, J = 1.8 Hz, 1H), 7.39 – 7.35 (m, 1H), 7.33 (dd, J = 7.6, 1.0 Hz, 1H), 6.49 (dq, J = 15.6, 1.5 Hz, 1H), 2.72 – 2.65 (m, 2H),
2.42 (td, J = 7.4, 1.8 Hz, 2H), 1.96 (dd, J = 6.8, 1.5 Hz, 3H), 1.69 – 1.54 (m, 4H), 1.41 – 1.31 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 203.03, 197.54, 147.36, 141.37, 139.10, 133.08, 130.45, 130.34, 128.22, 125.59, 44.04, 33.31, 31.66, 29.25, 22.08, 18.79.

**General Cyclization (Intramolecular Vinlylogous Aldol) Procedure:**

A solution of the substrate (0.5 mmol) in toluene (5 mL) was added to a stirred solution of freshly prepared ATPH (1.1 mmol) in toluene (5 mL) at -78°C (acetonitrile/dry ice bath). After 20 minutes, the ATPH-substrate solution was added dropwise via cannula (1 hour) to a stirred solution of LTMP (1.0 mmol) in THF (5 mL) and toluene (35 mL) at – 78°C. After 30 minutes following the addition, saturated NH$_4$Cl (25 mL) was added, and the biphasic mixture was stirred vigorously for 20 minutes while warming to ambient temperature. The mixture was filtered through a small pad of Celite, which was washed with Et$_2$O (50 mL). The organic phase of the filtrate was separated and washed with brine, dried over anhydrous MgSO$_4$, and concentrated under reduced pressure. Purification of the crude product was achieved with flash chromatography (10:1 hexanes:EtOAc then 3:1 hexanes:EtOAc) where 2,6-diphenylphenol was also recovered in good yield.

Preparation of ATPH: Me$_3$Al (0.55 mL, 1.1 mmol, 2.0 M solution in hexanes) was added to a stirred solution of 2,6-diphenylphenol (0.813 g, 3.3 mmol) in toluene (5 mL) at room temperature. After 30 minutes, the ATPH solution was cooled to -78°C and used as described in the cyclization procedure.
Preparation of LTMP: $n$BuLi (0.67 mL, 1.0 mmol, 1.50 M solution in hexanes) was added to a stirred solution of TMP (0.21 mL, 1.25 mmol) in THF (5 mL) at -78°C. After 30 minutes and immediately before the cannulation step in the cyclization procedure, the solution was diluted with cooled toluene (35 mL).

14-Hydroxy-8-isopropyl-5,6,7,8,13,14-hexahydro-9-oxabenzo-(E)-cyclododecen-10-one 2.4.13:

Compound 2.4.13 was prepared from 2.4.12 in 86% yield after purification using the general cyclization procedure. We could not detect any diastereomeric material by $^1$H NMR.

$^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.52 (br d, 1H, $J = 6.2$ Hz), 7.23-7.13 (m, 2H), 7.05 (br d, 1H, $J = 7.6$ Hz), 6.82 (ddd, 1H, $J = 5.4$, 10.9, 16.0 Hz), 5.49 (br d, 1H, $J = 15.7$ Hz), 5.08 (br d, 1H, $J = 9.4$ Hz), 4.63 (ddd, 1H, $J = 3.0$, 6.7, 10.0 Hz), 3.00-2.91 (br m, 1H), 2.64-2.52 (br m, 2H), 2.42 (br q, 1H, $J = 10.9$ Hz), 2.20-2.04 (br m, 1H), 2.03-1.98 (br d, 1H, $J = 1.8$ Hz), 1.92-1.74 (m, 2H), 1.54-1.42 (br m, 1H), 1.08-0.96 (br m, 1H), 0.94 (d, 3H, $J = 2.8$ Hz), 0.92 (d, 3H, $J = 2.9$ Hz). $^1$H NMR (T = 59°C, 500 MHz; CDCl$_3$): $\delta$ 7.52 (d, 1H, $J = 7.6$ Hz), 7.21 (dt, 1H, $J = 1.3$, 7.8 Hz), 7.16 (dt, 1H, $J = 1.5$, 7.2 Hz), 7.06 (d, 1H, $J = 7.7$ Hz), 6.78 (ddd, 1H, $J = 5.6$, 10.7, 16.1 Hz), 5.55 (d, 1H, $J = 15.9$ Hz), 5.11 (dt, 1H, $J = 2.8$, 10.3 Hz), 4.64 (ddd, 1H, $J = 3.0$, 6.6, 10.0 Hz), 3.00-2.92 (m, 1H), 2.69-2.55 (m, 2H), 2.45 (q, 1H, $J = 10.8$ Hz),
2.17-2.04 (m, 1H), 1.91-1.76 (m, 3H), 1.56-1.45 (br m, 1H), 1.16-1.06 (br m, 1H), 0.96 (d, 3H, J = 3.3 Hz), 0.94 (d, 3H, J = 3.3 Hz). $^1$H NMR (100 MHz; CDCl$_3$): $\delta$ 167.8, 144.4, 140.8, 139.7, 127.8, 126.7, 125.7, 124.9, 83.1, 70.5, 43.1, 32.3, 31.5, 31.0, 25.4, 19.1, 18.6. IR (cm$^{-1}$): 3431, 2962, 2875, 1712, 1645, 1247, 1034, 1003, 760. HRMS (ESI) $m/z$ calc'd for C$_{18}$H$_{24}$O$_3$Na [M+Na]$^+$: 311.1617; found: 311.1606.

Macrolactone 2.4.4

Compound 2.4.4 was prepared from 2.4.3 in 81% yield after purification using the general cyclization procedure. We could not detect any diastereomeric material by $^1$H NMR.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.32 – 7.23 (m, 1H), 7.17 (dd, J = 11.6, 4.3 Hz, 2H), 7.05 (ddd, J = 16.2, 9.1, 7.3 Hz, 1H), 5.92 (d, J = 15.8 Hz, 1H), 5.36 (d, J = 12.9 Hz, 1H), 5.20 (d, J = 12.9 Hz, 1H), 3.85 (dd, J = 14.5, 8.0 Hz, 1H), 2.81 (dt, J = 12.5, 6.3 Hz, 1H), 2.54 (td, J = 12.7, 5.3 Hz, 1H), 2.43 (td, J = 11.9, 3.8 Hz, 1H), 2.25 (dt, J = 12.2, 8.4 Hz, 1H), 1.82 – 1.46 (m, 3H), 1.40 – 1.29 (m, 1H), 1.29 – 1.18 (bs, 1H); $^1$C NMR (75 MHz, CDCl$_3$) $\delta$ 146.84, 142.36, 131.00, 130.18, 128.85, 126.21, 123.47, 71.54, 67.86, 42.14, 35.88, 33.21, 29.88.
Macrolactone 2.4.8

Compound 2.4.8 was prepared from 2.4.7 in 90% yield and ~2.5:1 dr after purification using the general cyclization procedure.

Major isomer: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.33 – 7.19 (m, 3H), 7.17 – 7.10 (m, 1H), 6.82 (ddd, J = 16.1, 9.6, 6.7 Hz, 1H), 5.95 (d, J = 15.9 Hz, 1H), 5.42 (d, J = 13.2 Hz, 1H), 5.14 (d, J = 13.3 Hz, 1H), 3.78 (dd, J = 15.2, 8.8 Hz, 1H), 2.63 (dd, J = 12.9, 3.4 Hz, 1H), 2.38 – 2.25 (m, 2H), 2.19 (dt, J = 11.1, 9.0 Hz, 1H), 1.73 – 1.65 (m, 1H), 1.36 (dd, J = 13.3, 10.8 Hz, 1H), 0.98 (d, J = 6.4 Hz, 3H); Mixture of isomers: $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 145.70, 134.39, 132.86, 131.22, 129.66, 129.34, 128.13, 127.92, 126.96, 126.60, 123.93, 121.81, 70.67, 68.46, 67.82, 67.12, 46.36, 42.12, 41.60, 41.34, 32.91, 19.82.

Macrolide 2.4.10

Compound 2.4.10 was prepared from 2.4.9 in 80% yield after purification using the general cyclization procedure. We could not detect any diastereomeric material by $^1$H NMR.
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.31 (dd, $J = 7.1$, 4.8 Hz, 2H), 7.23 (d, $J = 7.3$ Hz, 1H), 7.18 (t, $J = 7.4$ Hz, 1H), 6.87 (ddd, $J = 15.8$, 8.5, 7.3 Hz, 1H), 5.87 (d, $J = 15.8$ Hz, 1H), 5.30 (d, $J = 12.1$ Hz, 1H), 5.08 (d, $J = 12.1$ Hz, 1H), 3.69 (dd, $J = 10.4$, 3.9 Hz, 1H), 2.66 – 2.43 (m, 3H), 2.27 (dt, $J = 11.7$, 9.8 Hz, 1H), 1.76 – 1.34 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 165.79, 145.81, 143.46, 133.28, 131.20, 130.17, 129.29, 125.97, 124.14, 71.91, 66.66, 41.70, 34.71, 33.11, 31.89, 27.66, 26.19.

Macrolide 2.4.6

Compound 2.4.6 was prepared from 2.4.5 in 79% yield and 2:1 dr after purification using the general cyclization procedure.

Major diastereomer: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.26 – 7.12 (m, 4H), 6.94 (ddd, $J = 16.3$, 9.6, 6.6 Hz, 1H), 5.98 – 5.86 (m, 2H), 3.70 (dd, $J = 13.9$, 7.1 Hz, 1H), 3.00 – 2.91 (m, 1H), 2.79 – 2.71 (m, 1H), 2.71 – 2.60 (m, 1H), 2.39 – 2.21 (m, 2H), 1.91 – 1.75 (m, 3H), 1.60 (d, $J = 6.8$ Hz, 3H).

Macrocycle 2.4.11

Compound 2.4.11 was prepared from 2.11.7 in 94% yield and 4:1 dr after purification using the general cyclization procedure.
Major diastereomer: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.41 (d, J = 7.7 Hz, 1H), 7.35 – 7.26 (m, 1H), 7.26 – 7.17 (m, 2H), 6.91 (ddd, J = 16.2, 9.7, 6.7 Hz, 1H), 6.10 (q, J = 6.5 Hz, 1H), 5.90 (d, J = 15.8 Hz, 1H), 3.65 (qd, J = 7.6, 3.9 Hz, 1H), 2.61 – 2.50 (m, 2H), 2.32 – 2.20 (m, 2H), 1.74 (d, J = 6.5 Hz, 3H), 1.55 – 1.29 (m, 8H); Both diastereomers: $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 166.26, 144.99, 144.54, 143.07, 136.89, 131.56, 130.50, 129.39, 128.72, 128.22, 126.73, 125.98, 125.93, 124.91, 124.67, 100.23, 74.94, 71.98, 70.63, 70.44, 41.81, 41.53, 34.70, 34.24, 33.83, 32.69, 31.70, 31.58, 27.78, 27.66, 26.23, 25.60, 22.19, 18.55.
3.1 Introduction

The role of RNA in cellular processes recently underwent an expansion with the realization that many non-coding RNAs are not simply “transcriptional noise” but carry specific, often regulatory, functions. These discoveries continue to shape science’s perception of RNA’s role in biological functions and a better understanding of the functions of these RNAs will be greatly facilitated by improved methods for studying their structure and dynamics in solution.

NMR is currently the only method available for generating high-resolution structures of proteins and nucleic acids in solution. There have been tremendous advances in NMR methods that now make it possible to determine both the local and global structures of increasingly larger biomolecules. However, the specific physical properties of RNAs still present significant challenges for NMR solution structure determinations. First, the density of protons in RNA is relatively low compared to proteins; thus, the amount of information gained from a spectrum is also relatively low. Second, RNA often forms extended structures which are difficult to characterize using exclusively short-range Nuclear Overhauser Effect (NOE) interactions. Third, the functional sites of RNAs are often dynamic with many functionally important conformational changes occurring on relatively long

timescales, greatly broadening and complicating the spectra. Finally, since RNAs are
built from only four residues and a common sugar, there is a high degree of spectral
overlap in the NMR data.

*Residual Dipolar Couplings*

One important advance in macromolecular NMR in the last decade has been
the development of general methods for measuring Residual Dipolar Couplings
(RDCs) of molecules in solution. RDCs provide valuable information on both the
long-range structure and dynamics of macromolecules; however, these couplings
normally average to zero in isotropic solution. Thus, measurement of RDCs requires
partial alignment of the molecule relative to the magnetic field in order to be
observed. The observed RDCs for a rigid molecule can be described by the equation
where $\gamma_i$ is the gyromagnetic ratio of nucleus i, $r$ is the distance of the $P-Q$
internuclear vector, $S$ is the generalized order parameter, $A_a$ and $A_r$ are the axial and
rhombic components of the alignment tensor, and $\theta$ and $\phi$ are the polar coordinates
describing the orientation of the internuclear vector relative to the principle axis
system of the alignment tensor (Equation 3.1).

$$D_{PQ} \propto \gamma_P \gamma_Q S(1 / r^3)[A_a(3\cos^2 \theta - 1) + (3/2)A_r \sin^2 \theta \cos(2\phi)]$$

Equation 3.1

---

External techniques to induce anisotropy in RNA in solution and subsequently measure RDCs were the first to be developed. These processes involved adding Pf1 bacteriophages or liquid crystalline bicelles to the sample.\textsuperscript{61} When placed in a magnetic field, these disk-on-rod-like structures will align because of their anisotropic magnetic susceptibility. This induces a sterically uniform environment for the RNAs which will then align in the least sterically encumbering manner. The advantages of this method are the media will not bind nucleic acids and the media are stable to differing buffers and temperatures. However, the technique is limited because of the small degree of alignment.

![Diagram](image)

**Figure 3.1** External methods of inducting anisotropy

One approach that has been successfully used for alignment in proteins is the incorporation of so-called paramagnetic tags, which consist of a paramagnetic lanthanide atom bound to a strong chelating group site-specifically attached to a

biomolecule.\textsuperscript{62} In proteins, this can be done in 3 different ways: tagging an $N$- or $C$-terminal extension; extension by a peptide that is recognized by a metal binding protein such as CaM; or attaching a paramagnetic tag to the protein of interest, preferably via a cysteine residue (Figure 3.2).

![Figure 3.2](image)

**Figure 3.2** Paramagnetic tagging of proteins

### 3.2 Synthesis of Ligands

*Ligand Design Considerations*

We have studied analogous techniques for tagging RNA molecules with chelating groups that bind paramagnetic metals with very high affinities. By connecting a chelating group to the 5' end of RNA, different alignment tensors can then be induced by coordinating different paramagnetic lanthanide ions to the chelator.\textsuperscript{62} These paramagnetic labels can also be used to extract additional long-

range structural and dynamic information by analysis of pseudocontact shifts. Our goal is to develop efficient methods for applying these powerful paramagnetic tagging techniques to NMR studies of RNAs.

In our initial strategy, we considered several important design elements. First, the coordination strength of the chelator to the lanthanide is important because reversibility in binding is not conducive to the measurement of RDCs. The lanthanide itself is also a consideration, and we felt that one with a large magnetic susceptibility such as dysprosium would be a good initial candidate. The third important feature is to have as short of a linker as possible since longer linkers can lead to smaller degrees of alignment and less residual dipolar coupling. We also wished to use enzymatic synthesis of RNA in the presence of this chelator. In order to accomplish this, the recognition sites of the enzyme require a guanidine base, charge on the phosphate, and the 2′-hydroxyl to be present and these elements must also be present in the final chelator compound (Figure 3.3).

**Figure 3.3** Design Considerations

In our initial studies, we wished to examine how we would incorporate the ligand into the nucleotide and therefore chose to synthesize compounds with the general motif of **3.4.1**. Structures of this type would have at least six sites of
coordination to the metal (four carboxylates and two amines) and could foreseeably bind essentially irreversibly under the experimental conditions. The different linkers to be studied would be amenable to the proposed methods of incorporation to the nucleoside such as phosphorimidazolide coupling via an aliphatic amine, an azide/alkyne click-to-chelate strategy, and phosphoramidite coupling.

\[
\begin{align*}
\text{O}_2\text{C} & \quad \text{"LINKER"} \\
\text{O}_2\text{C} & \\
\text{O}_2\text{C} & \\
\text{\text{3.4.1}} & \\
\text{O}_2\text{C} & 
\end{align*}
\]

**Figure 3.4** First Generation Linker Framework Strategy

We recognize that while there is symmetry around the nitrogens in each of the proposed compounds above, once complexed to a metal a chiral complex is formed. After tethering to a chiral biomolecule, two diastereomeric compounds would result. Because diastereomeric compounds have different physicochemical properties this would result in a doubling of the resonances observed by NMR. This complicates the spectrum and makes extraction of RDC information difficult, hence would not be an effective chelator for us.\(^{62}\) One possible solution to this would be to prepare an inherently chiral chelator that would selectively bind as a single isomer. However, for the initial studies, we focused on the preparation and incorporation of linkers into achiral polyamine carboxylates.
The synthesis of the model chelators bearing different linkers is described below (Scheme 3.1). Starting with 1,3-diamino-2-propanol 3.1.1, the primary amines were tetra-alkylated and the secondary alcohol was oxidized to the ketone via the Swern oxidation. The resulting ketone 3.1.3 could then undergo a rearrangement with tosylmethyl isocyanide (TosMIC), giving primary nitrile 3.1.4 which could be reduced to the primary amine 3.1.5 using Pt₂O under H₂. Ketone 3.1.3 could also be utilized in a Horner-Wadsworth-Emmons olefination with 3.1.6 to give α,β-unsaturated primary amide 3.1.7. Reduction of this compound with Pd/C/H₂ provided the amide of interest, 3.1.8. Alcohol 3.1.2 could also be subjected to a Mitsunobu reaction, resulting in secondary azide 3.1.9. The azide itself could be studied for incorporation into the nucleoside but it was also reduced with Pd/C/H₂ to study incorporation of the resulting secondary amine 3.1.10. Finally, chelator 3.1.14 was prepared for study by first mono-Boc protecting triamine 3.1.11. The remaining
amines were tetra-alkylated as before and the Boc protecting group was removed with acid.

**Scheme 3.1** Synthesis of First Generation Chelators

The inherent difficulties in the synthesis of a lanthanide complex of a single diastereomer prompted us to explore an alternative wherein the stereochemistry at the metal center is controlled by a chiral, non-racemic ligand. After studying the
incorporation of molecules of various functionality into nucleosides (data not shown) it was determined that the azide functionality would be most readily linked by a click reaction.\textsuperscript{63} We, therefore, designed an inherently chiral chelator that would selectively bind as a single isomer with an azide linker, the synthesis of which is shown below (Scheme 3.2.3). 1,3-diamino-2-propanol 3.1.1 was tetra-alkylated with chiral amide 3.2.1 in excellent yield. The alcohol was then converted to the desired azide linker by a Mitsunobu reaction as before giving desired compound 3.2.3.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {3.1.1};
\draw[->] (0,-0.5) -- (0.5,-0.5) node[midway,above] {98\%};
\draw[->] (0.5,-0.5) -- (1,-0.5) node[midway,above] {KHCO$_3$};
\node at (1,0) {3.2.1};
\draw[->] (1,-0.5) -- (1.5,-0.5) node[midway,above] {62\%};
\draw[->] (1.5,-0.5) -- (2,-0.5) node[midway,above] {DIAD};
\node at (2,0) {3.2.3};
\end{tikzpicture}
\end{center}

\textbf{Scheme 3.2} Synthesis of 3.2.3

It is well known that lanthanide ions can promote the cleavage of RNA (Figure 3.6).\textsuperscript{64} In order for these lanthanide complexes to be useful as a means of inducing RDCs, the complexes must have a high degree of stability and/or inertness to dissociation under the NMR experimental conditions. In the case of 3.2.3, there are as many as 7 sites of coordination to the metal but lanthanides are known have up to 11 sites of coordination available.


In order to determine the stability of RNA in the presence of our complex, we monitored the interaction of our complex with a model RNA. Unfortunately, we found extensive degradation of RNA in preliminary studies conducted in the labs of our collaborator, Professor Art Pardi (Figure 3.7).
We suspected that the cause of instability of RNA towards our complex was due to the presence of an open coordination site, and sought to design a chiral ligand that would occupy as many sites of coordination on the metal as possible. Knowing that cyclic chelating ligands are among the most thermodynamically stable and kinetically inert lanthanide III complexes, we prepared 3.3.4 and 3.3.5 in order to try to prevent the degradation of the RNAs. Cyclen 3.3.1 was tris-alkylated with chiral amide 3.2.1. Degradation studies were carried out after methylating the remaining nitrogen and metallating with both dysprosium and thulium. Unfortunately, RNA degradation studies on the complex revealed that cleavage still occurs and we were faced with the need to develop a more chemically inert complex (Scheme 3.3).

Scheme 3.3. Third Generation Ligand Strategy and Model of 3.3.4
Among the many factors that can promote cleavage of RNA by lanthanides is the charge on the metal center. Therefore, we sought to design a complex that is overall neutral. We considered the same thermodynamically stable cyclic structure, but with carboxylate ligands in the place of amides. We prepared complex **3.4.5** by the route described below (Scheme 3.4). Cyclen was mono-protected with a formyl group, after which the remaining three amines were alkylated with **3.4.2**. No racemization was detected at the stereocenters in **3.4.3**. The benzyl esters and formyl group were then removed under acidic reducing conditions to provide **3.4.4**. Finally, metalation of the chelator with DyCl₃ gave complex **3.4.5**. Gratifyingly, subsequent degradation studies revealed that there was no detectable hydrolysis of the RNA.

![Scheme 3.4 Synthesis of Complex 3.4.5](image)

With a successful model substrate in hand, we focused on functionalizing the final amine with a linker for attachment to a GMP nucleotide for enzymatic incorporation into RNA. Unfortunately, we were unable to alkylate the remaining
secondary nitrogen after an exhaustive study. Our current progress on this fourth generation ligand strategy is shown in Scheme 3.5. We anticipate coupling to GMP via the free hydroxyl 3.5.5 with phosphoramidite chemistry or by the azide via a click reaction of 3.5.3 and 3.5.7. Full disclosure of RNA characterization is anticipated soon.

Scheme 3.5  Fourth Generation Ligand and Nucleoside Coupling Partner Strategy

3.3 Experimental

\[ \text{N-formycyclen 3.4.1} \]
Cyclen (5 g, 29 mmol) and \( N,N \)-dimethylformamide dimethylacetal (3.92 mL, 30.5 mmol) were dissolved in toluene (70 mL) and put into a flask equipped with a distillation apparatus under a nitrogen atmosphere. The methanol/toluene azeotrope formed was distilled until complete elimination of toluene had occurred. The resulting yellow oil (2a) was dried overnight at 70 ºC. It was then cooled to 0 ºC and a water/methanol mixture (1:1 v/v; 25 mL) was added dropwise. The mixture was warmed to room temperature and stirred for 24 h. The solvents were evaporated and the residue was re-dissolved in a minimum amount of acetonitrile, which was subsequently evaporated; this procedure was repeated twice to completely eliminate water. Addition of ether to the yellow oil precipitated a white solid (5.58 g, 95% yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.17 (s, 1H), 3.56 (t, \( J = 5.3 \) Hz, 2H), 3.52 – 3.47 (m, 2H), 2.86 – 2.76 (m, 6H), 2.72 – 2.65 (m, 6H).

\[\begin{array}{c}
\text{3.4.2a} \\
\text{O} \\
\text{Bn} \\
\text{OH} \\
\text{3.4.2} \\
\text{OTf} \\
\text{Bn} \\
\end{array}\]

**L-benzyl 2-(triflyloxy)propionate 3.4.2**

According to a variation of a literature procedure, a solution of benzyl lactate \(3.4.2\) \(a\) (5.0 g, 27.7 mmol) and pyridine (2.7 mL, 33.3 mmol) in CH\(_2\)Cl\(_2\) (45 mL) at 0 ºC was treated with triflic anhydride (8.61 g, 30.5 mmol) in CH\(_2\)Cl\(_2\) (45 mL) for 1 h. After removal of the pyridinium triflate salt by filtration, the crude product was purified by silica gel chromatography (5:1 hexanes/CH\(_2\)Cl\(_2\) to obtain benzyl 2-(triflyloxy)propionate \(3.4.2\) (6.91 g, 22.13 mmol, 80%).
Rf = 0.2 (5:1 hexanes/CH₂Cl₂); \(^1\)H NMR (500 MHz, CDCl₃) \(\delta 7.43 – 7.34\) (m, 2H), 5.31 – 5.24 (m, 1H), 1.72 (d, \(J = 7.0\) Hz, 1H).

\[ \text{1,4,7-Tris(benzyloxycarbonyl)methyl-10-formyl-1,4,7,10-tetraazacyclododecane} \]

3.4.3

To a stirred solution of \(N\)-formylcyclen 3.4.1 (0.668 g, 3.34 mmol) and diisopropylethylamine (2 mL, 11.68 mmol) in MeCN (17 mL) at 0 °C was added L-benzyl 2-(triflyloxy)propionate 3.4.2 (3.23 g, 10.34 mmol) in MeCN (10 mL). The solution was stirred for 3 hours and allowed to warm to RT. The crude product was obtained after removal of the solvent was extracted with water and CHCl₃. The organic layers were combined and dried over magnesium sulfate. Removal of the solvent afforded an orange residue. This crude product was purified by silica gel chromatography (1:1 hexanes/EtOAc) to obtain tribenzyl ester 3.4.3 (0.564 g, 0.821 mmol, 25%).

\(^1\)H NMR (500 MHz, CDCl₃) \(\delta 7.97\) (s, 1H), 7.40 – 7.28 (m, 15H), 5.14 – 5.09 (m, 6H), 4.23 – 4.15 (m, 1H), 3.85 – 3.73 (m, 1H), 3.68 – 3.61 (m, 2H), 3.52 (p, \(J = 7.2\) Hz, 2H), 3.17 (dt, \(J = 14.3, 4.8\) Hz, 1H), 2.92 (ddd, \(J = 14.0, 10.2, 3.7\) Hz, 1H), 2.88 – 2.52 (m, 9H), 2.44 – 2.34 (m, 2H), 1.26 – 1.20 (m, 9H); \(^{13}\)C NMR (75 MHz CDCl₃): \(\delta 14.94, 15.06, 15.16, 42.03, 47.32, 48.76, 49.37, 49.56, 50.13, 50.99, 52.66, \)
55.58, 58.76, 60.02, 65.83, 65.94, 66.05, 128.07, 128.15, 128.25, 128.44, 128.48, 135.68, 135.77, 135.80, 162.71, 173.02, 173.12, 173.17.

Tricarboxylic Acid 3.4.4

The tribenzyl ester 3.4.3 (0.138 g, 0.201 mmol) was hydrogenated overnight in 30% aqueous methanol containing 2 M HCl (1.5 mL of methanol and 0.5 mL of 2 M HCl) in the presence of Pd/carbon (10% Pd, 0.021 g, 0.020 mmol). The catalyst was filtered off and evaporation of the filtrate gave an off-white solid crude material 3.4.4.

\[^1\text{H} \text{NMR (500 MHz, D}_2\text{O)} \delta 4.36 – 4.27 (m, 1H), 4.05 – 3.95 (m, 1H), 3.81 – 3.53 (m, 2H), 3.41 (dd, J = 27.8, 13.6 Hz, 1H), 3.30 (t, J = 13.1 Hz, 1H), 3.14 (d, J = 5.6 Hz, 5H), 3.12 – 2.94 (m, 6H), 2.86 (dd, J = 32.8, 12.8 Hz, 4H), 2.68 (t, J = 11.1 Hz, 1H), 2.60 – 2.44 (m, 2H), 1.41 (d, J = 7.0 Hz, 3H), 1.11 (d, J = 5.9 Hz, 6H).\]

Compound 3.5.1
To a stirred solution of 3.4.3 (0.113 g, 0.165 mmol) in MeOH (1.3 mL) was added 2 M HCl in H₂O (0.46 mL, 0.928 mmol). The solution was stirred overnight and then concentrated in vacuo. The residue was dissolved in CHCl₃ and saturated solution of K₂CO₃ was carefully added to the vigorously stirred solution until effervescence ceased. The organic phase was separated, and the aqueous phase was extracted with CHCl₃. The combined organic phases were washed with water and brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (3% MeOH in CHCl₃) to provide 3.5.1 (0.109 g, 0.165 mmol, 100%).

¹H NMR (400 MHz, CDCl₃) δ 7.39 – 7.28 (m, 15H), 3.74 (q, J = 7.1 Hz, 1H), 3.55 (q, J = 7.1 Hz, 2H), 2.95 (bs, 2H), 2.83 (q, J = 9.7 Hz, 8H), 2.56 (d, J = 9.1 Hz, 4H), 2.43 (d, J = 18.8 Hz, 2H), 1.32 (d, J = 7.2 Hz, 6H), 1.25 (d, J = 7.0 Hz, 3H).

Compound 3.5.2

To a stirred solution of 3.5.1 (0.049 g, 0.074 mmol) and pyridine (0.030 mL, 0.369 mmol) in CH₂Cl₂ (1.5 mL) at 0 ºC was added chloroacetyl chloride (0.024 mL, 0.295 mmol). The cold bath was lowered and the solution allowed to warm to room temperature. After 30 minutes, the reaction was diluted with CHCl₃. The reaction was quenched with saturated NaHCO₃ and extracted (3x) with CHCl₃. The organic layers
were combined, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (1% MeOH in CHCl₃) to obtain **3.5.2** (0.0246 g, 0.033 mmol, 46%).

$^1$H NMR (400 MHz, CDCl₃) δ 7.40 – 7.28 (m, 15H), 5.19 – 5.03 (m, 6H), 4.53 – 4.41 (m, 1H), 4.02 – 3.90 (m, 2H), 3.75 – 3.61 (m, 3H), 3.57 – 3.46 (m, 2H), 3.34 (dt, J = 11.7, 5.3 Hz, 1H), 3.07 – 2.51 (m, 10H), 2.42 (dt, J = 5.2, 2.3 Hz, 1H), 2.37 – 2.28 (m, 1H), 1.23 (dt, J = 7.1, 2.3 Hz, 9H).

**Azide 3.5.3**

To a stirred solution of **3.5.2** (0.044 g, 0.059 mmol) in DMF (1.2 mL), was added sodium azide (7.7 mg, 0.118 mmol) and the reaction mixture was stirred overnight at room temperature. The solvent was removed under vacuum, and the residue was dissolved in EtOAc. The organic layer was washed three times with water and once with brine and then dried over MgSO₄ and evaporated under reduced pressure. The residue was purified by flash chromatography (2:1 hexanes/EtOAc) to give the title compound **3.5.3** (0.044 g, 0.059 mmol, 100%).

$^1$H NMR (500 MHz, CDCl₃) δ 7.40 – 7.28 (m, 15H), 5.18 – 5.04 (m, 6H), 4.29 (bs, 1H), 3.81 – 3.69 (m, 3H), 3.69 – 3.58 (m, 2H), 3.51 (dq, J = 20.6, 7.0 Hz,
2H), 3.22 – 3.12 (m, 1H), 2.95 – 2.54 (m, 10H), 2.43 (d, J = 13.4 Hz, 1H), 2.35 (d, J = 13.9 Hz, 1H), 1.34 – 1.15 (m, 9H).

Alkynyl Phosphoramidite 3.5.7

To a stirred solution of 2-cyanoethyl N,N-diisopropylchlorophosphoramidite 3.5.6 (1.0 g, 4.23 mmol) in THF (10 mL) at 0 ºC was added ethynylmagnesium bromide (0.5 M solution in THF, 8.45 mL, 1 equiv.). After 1 hour, the reaction was diluted with Et₂O and quenched with saturated NaHCO₃. The organic phase was separated, washed with water and brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (15:1 hexanes:EtOAc) to provide 3.5.7 (0.794 g, 3.51 mmol, 83%).

¹H NMR (500 MHz, CDCl₃) δ 3.96 – 3.82 (m, 2H), 3.83 – 3.62 (m, 2H), 3.13 (d, J = 1.7 Hz, 1H), 2.65 (t, J = 6.6 Hz, 2H), 1.23 (d, J = 6.8 Hz, 6H), 1.20 (d, J = 6.7 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 117.62, 92.55 (d, J = 7.7 Hz), 84.81 (d, J = 17.9 Hz), 61.13 (d, J = 17.9 Hz), 49.10 – 47.63 (m), 25.63 – 23.33 (m), 20.55 (d, J = 7.5 Hz); ³¹P NMR (122 MHz, CDCl₃) δ 96.68.
Bibliography


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