Total Synthesis of the EF Fragment of Spongistatin 1 en Route to a Spongistatin 1 Analog

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Abstract

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A major goal of the Leighton group is the synthesis of biologically relevant polyketide natural products. Among the most potent and chemically intriguing member of this class is spongistatin 1. This molecule has interested biologists and chemists for more than two decades. In this thesis, we report a highly practical and efficient synthesis of the EF fragment of spongistatin 1. This relied on the rapid introduction of a complex stereochemical array using double cross-metathesis/Sharpless asymmetric dihydroxylation reactions to quickly build the F-ring of spongistatin. The six contiguous stereocenters of the F-ring were established in just five steps. A new one-pot asymmetric strained-silane mediated allylation was developed that was greatly improved over previous methods in regards to practicality and substrate scope. This methodology was used to introduce the sensitive chlorodiene side chain. Finally, completion of the EF fragment led to the synthesis of a spongistatin 1 analog, using our previously developed redesigned ABCD fragment.
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<tr>
<td>9-BBN</td>
<td>9-borabicyclo[3.3.1]nonane</td>
</tr>
<tr>
<td>ADC</td>
<td>antibody drug conjugate</td>
</tr>
<tr>
<td>BnTCAI</td>
<td>benzyl trichloroacetimidate</td>
</tr>
<tr>
<td>CMAD</td>
<td>cross metathesis asymmetric dihydroxylation</td>
</tr>
<tr>
<td>CSA</td>
<td>camphorsulfonic acid</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>DIBAL</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>GI50</td>
<td>concentration causing 50% growth inhibition</td>
</tr>
<tr>
<td>HG-II</td>
<td>Hoveyda-Grubbs 2 catalyst</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>HPLC</td>
<td>high-performance liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>high-resolution mass spectrometry</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>lithium hexamethyldisilazide</td>
</tr>
<tr>
<td>LiDBB</td>
<td>lithium di-tert-butylbiphenylide</td>
</tr>
<tr>
<td>LiTMP</td>
<td>lithium tetramethylpiperidide</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
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</tr>
<tr>
<td>MS</td>
<td>molecular sieves</td>
</tr>
<tr>
<td>mCPBA</td>
<td>meta-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>NaHMDS</td>
<td>sodium hexamethyldisilazide</td>
</tr>
<tr>
<td>NMO</td>
<td>4-methylmorpholine N-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>OR</td>
<td>optical rotation</td>
</tr>
<tr>
<td>PG</td>
<td>protecting group</td>
</tr>
<tr>
<td>PMB</td>
<td>p-methoxybenzyl</td>
</tr>
<tr>
<td>PPTS</td>
<td>pyridinium p-toluenesulfonate</td>
</tr>
<tr>
<td>SAR</td>
<td>structure-activity relationship</td>
</tr>
<tr>
<td>TBAB</td>
<td>tetrabutylammonium bromide</td>
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<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBS</td>
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</tr>
<tr>
<td>TES</td>
<td>triethylsilyl</td>
</tr>
<tr>
<td>TESOTf</td>
<td>triethylsilyl trifluoromethanesulfonate</td>
</tr>
<tr>
<td>Tf</td>
<td>triflic</td>
</tr>
<tr>
<td>TFA</td>
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<tr>
<td>THF</td>
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<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
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Dedication

For my parents
Chapter 1 Introduction

Marine-derived non-aromatic polyketide natural products are an intensely studied class of molecules due to their diverse structures and potent biological activity. The high degree of chemical complexity has intrigued synthetic chemists for decades. Furthermore, the pharmacological properties of many polyketides promise extremely potent therapeutics, often as anticancer drugs. However, despite the high degree of interest, their development as therapeutics is limited by very low natural abundance. Synthetic chemistry is currently the sole source of these exciting compounds. Therefore, the development of new and efficient strategies and methodologies for the construction of polyketides remains a worthy endeavor.

Figure 1.1. Polyketides of interest to the Leighton group

The Leighton group has long been interested in the synthesis of polyketides and methodologies that enhance their facile synthesis.\textsuperscript{1–5} Because of the high degree of chemical complexity, we have focused on scalable and efficient syntheses in order to
produce useful amounts of a given target. The methodologies developed have largely focused on the facile introduction of complex stereochemical arrays. These have been used to successfully synthesize epothilone B, dictyostatin and other compounds with a step count greatly reduced compared to previous efforts.\textsuperscript{5–7} This has enabled the Leighton group to develop analogs and constructs as potentially useful therapeutics. The focus of this thesis will be on the development of an efficient synthesis of the EF fragment of spongistatin 1 and the completion of a spongistatin 1 analog.

\textbf{1.1. Spongistatin 1 background}

\textit{1.1.1. Bioactivity and isolation of the spongistatins}

Natural product collection initiatives in 1993 resulted in the independent isolation and characterization of three groups of similar macrolide polyketides, known as the spongistatins, cinachyrolides and the altohyrtins. These were collected from multiple taxa of marine sponge by the Pettit,\textsuperscript{8–11} Fusetani,\textsuperscript{12} and Kitagawa groups.\textsuperscript{13,14} It was hypothesized that a single group of symbiotic bacteria was responsible for their biosynthesis, due to the variety of sponges from which they were collected. Sponges, like most animals, do not possess the requisite biochemical machinery, polyketide synthases, needed to produce these natural products.\textsuperscript{15}

In regards to structure, the natural products were all extremely similar except for discrepancies in stereochemistry at the E-ring ketal and the AB and CD spiroketals. Kitagawa was able to obtain 7.6 mg from 112 kg of wet sponge and despite the extremely small quantity isolated, used this to determine the circular dichroism and NMR properties to assign the relative and absolute stereochemistry.\textsuperscript{14} The first synthesis of these compounds, by Evans, confirmed that spongistatin 2 and altohyrtin C were identical.\textsuperscript{16–19}
There are currently nine discovered members of the spongistatin family, with spongistatin 1 (1.1) being among the most active. The average GI<sub>50</sub> values were determined by testing each compound against the National Cancer Institute’s panel of 60 human cancer cell lines. The average value for spongistatin 1 is 0.13 nM, showing it has significantly more anti-proliferative activity than existing drugs like Taxol. It is worth noting that spongistatin 1 maintains excellent cytotoxicity against known chemoresistant cell lines. Additionally, it exhibits outstanding selectivity for the growth inhibition of cancer cells versus normal cells (10,000-fold). Key in vivo melanoma and ovarian xenograph models in mice show preliminary antitumor activity with minimal toxicity. Spongistatin 1 is an anti-mitotic agent, having a mechanism of action shared with other marine polyketides. During cell division, or mitosis, cells use microtubules to mediate the structural requirements for chromosomal redistribution. This accounts for the
increased activity against cancer cells, which generally reproduce at a faster rate than normal cells. Further studies suggest that spongistatin 1 shares a binding site with the Vinca alkaloids on β-tubulin.$^{23,24}$

1.1.2. SAR studies of spongistatin analogs

A few key conclusions can be derived from the nine members of the spongistatin family. Two critical structural elements are required for the most potent activity, the C5 acetate (1.1 vs. 1.3, 1.5 vs. 1.9) and the C50 chloride (1.1 vs. 1.2, 1.5 vs. 1.7). The importance of the diene sidechain was also demonstrated by Paterson who showed that analog 1.10 was completely inactive, despite maintaining the rest of the molecule (Figure 1.2).$^{25}$ Therefore, we decided on the EF fragment of spongistatin 1, with the chlorodiene sidechain, as the target of our efforts.

![Chemical Structure](image)

**Figure 1.2.** Paterson's truncated side chain analog 1.10

Additional studies have shown that the exact CD fragment is not critical to potency and may serve only as an architectural backbone to align the ABEF fragment. Accidental epimerization of the CD spiroketal on spongistatin 1 or 2 produced active
Because of the complexity of spongistatin 1, multiple research groups have tested whether a simplified version would be biologically active and simplify the synthesis. Various analogs which contained only the EF or AB fragments were only weakly bioactive. However, Smith synthesized analog 1.11 which contained the ABEF fragment but replaced the CD portion with a simple alkyl linker (Figure 1.3). This had been designed using molecular modeling of spongistatin 1, trying to emulate the geometric arrangement of the molecule and align the ABEF fragment in the correct conformation.

Analog 1.11 exhibited impressive (80-300 nM) inhibitory activity in a similar mechanism to spongistatin 1. Although this work provided the first proof-of-concept, the Leighton group, led by Dr. Linda Suen, embarked on the synthesis of an analog which would more closely resemble spongistatin 1 to retain more potency, yet at the same time would be simpler to synthesize.
1.1.3. Redesign of the CD spiroketal

Following the promising results of the Smith CD-deleted analog, the Leighton group sought to design a new version of the CD fragment that would be easier to synthesize but retain comparable potency. The natural CD spiroketal is singly anomeric where only one of the C-O bonds is in the favored axial position in the spiroketal system (Figure 1.4).

![CD spiroketal conformations](image)

This is the contrathermodynamic product. Typically, spiroketals are synthesized by the simple acid-catalyzed cyclization of a dihydroxy ketone, however, this most commonly leads to the thermodynamically favored doubly anomeric product. Although the CD fragment may represent a unique scenario where the singly anomeric spiroketal is especially stable, it has still proven a historical challenge to furnish. Several clever solutions have been utilized to create the CD spiroketal\(^\text{18,26,34–39}\) Many of these rely on the recycling and reequilibration of the undesired spiroketal or trying to kinetically control the spiroketalization and stopping partway. This represented a serious synthetic bottleneck. Additionally, it remained a sensitive functionality that could epimerize during the rest of the synthesis.

Therefore, the Leighton group envisioned spongistatin 1 analog 1.12 that has a redesigned CD fragment containing a stable and easy to synthesize doubly anomic
spiroketal that would retain the same overall geometry as the natural product (Figure 1.5). This would orient the ABEF fragment in the appropriate position and maintain spongistatin 1’s high bioactivity.

Additionally, new methods in the asymmetric silane-mediated crotylation to join the AB and CD fragments were developed. This built on our previous synthesis of the AB fragment and large stockpile of material. This served as an excellent proof of concept that strained-silane allylation is a powerful way to enantioselectively join two highly functionalized fragments in natural product synthesis. This will be referred to as spongistatin 1 analog and the redesigned spiroketal will be referred to as CD*, with the asterisk referring to any material with a redesigned D ring. This effort was successful and a large quantity of the new ABCD* fragment was prepared. The natural EF fragment of spongistatin 1 will be suitable towards coupling with either natural ABCD or our novel ABCD* fragment.
1.2. Previous syntheses of spongistatin

The astounding bioactivity of the spongistatin family immediately attracted the interested of the biomedical community. However, initial clinical testing was impeded by the severely limited supply of spongistatin from natural sources. Additionally, the synthetic community was interested to the spongistatins due to the opportunity to supply material for clinical studies and the unique synthetic challenge they posed.

Spongistatin 1 is a 42-member macrolactone with 24 stereocenters, two spiroketalts and two heavily functionalized tetrahydropyran subunits. The three most challenging aspects are arguably the synthesis of the singly-anomeric CD spiroketal, the introduction of a sensitive chlorodiene side chain and the construction of the F-ring, a tetrahydropyran with five stereocenters. To this date, seven research groups have completed syntheses of spongistatin 1 and/or 2: Evans,16–19 Kishi,26,41 Smith,34,35,42–50 Paterson,36,51–60 Crimmins,37,61–64 Healthcock,38,65–70 and Ley.39,71–74 However, in the pursuit of creating useful amounts of material, only the Heathcock and Smith groups have succeeded, creating 250 mg and 1 g of spongistatin 1 respectively.

Figure 1.5. Spongistatin 1 (1.1) and spongistatin 1 analog 1.12
As pioneered by the Evans group in the first reported synthesis of spongistatin 2, the Yamaguchi macrolactonization and Wittig olefination have been used to join the EF fragment with the ABCD fragment in all subsequent syntheses (Figure 1.6). In addition to the total syntheses, many more have been reported towards the EF fragment.\textsuperscript{75–83} This thesis will focus on the preparation of a novel EF fragment synthesis and therefore an overview of previously used strategies towards the synthesis of the EF fragment is warranted.
1.2.1. Strategies towards the preparation of the F-ring

The EF fragment contains 11 of the 24 stereocenters on spongistatin 1, nine of which reside on the two densely functionalized tetrahydropyran rings, E and F. Including the fully substituted F-ring, seven contiguous stereocenters are present on the molecule, presenting a serious challenge. Most of the synthetic effort on this fragment has been spent arranging the stereocenters on the F-ring and ensuring that it contains two handles to attach the chlorodiene sidechain and the E-ring.

The F-ring contains five stereocenters and requires at least one step mediated by a chiral reagent or catalyst. However, the protecting group manipulations and oxidation
state changes can easily stretch this into a very lengthy sequence. Setting multiple stereocenters sequentially through diastereoselective reactions serves to reduce the number of steps with using asymmetric reagents, but is often plagued by step-inefficiency.

The first approach by Evans was to set the C40 and C41 stereocenters with an asymmetric Mukaiyama aldol using a chiral tin-bisoxazoline complex. (Scheme 1.1).\textsuperscript{18} This was followed by a diastereoselective Mukaiyama aldol reaction. This was elaborated into glycal 1.18, which was posed to connect the pre-constructed E-ring and the sidechain by the later epoxidation of the glycal that will be discussed in a later section. This route involved a post-ABCD coupling introduction of the sidechain. This type of late-stage sidechain introduction was not utilized in later syntheses, due to the difficulties in the chemical manipulation of the ABCDEF fragment with various protecting and functional groups.

![Chemical Structure](image)

**Scheme 1.1.** Evan's route to F-ring glycal 1.18

The notable similarity of the F-ring to a sugar inspired the Heathcock group to utilize a chiral pool synthesis of F-ring 1.20 from commercially available sugar 1.19 in 11 steps (Scheme 1.2).\textsuperscript{70,84} Many non-ideal steps were used to produce this F-ring. This molecule contained all five stereocenters on the completed F-ring. Furthermore the C38
stereocenter was set next to a methyl ketone. Although the TIPS ether was not easy to elaborate into the sidechain, it did serve as an attachment point and enabled completion of the F-ring and side chain prior to coupling with the ABCD fragment. This methyl ketone was poised to participate in an aldol reaction that was used in multiple syntheses.

![Scheme 1](image)

**Scheme 1.2.** Heathcock's F-ring 1.20

The Paterson group made use of a diastereoselective boron-mediated aldol reaction to set another stereocenter of the F-ring.\(^{54}\) Starting with 1.21, which is derived from the commercially available Roche ester, and treating it with Cy₂BCl and acetaldehyde gave 1.22 (Scheme 1.3). This was elaborated into enoate 1.23 which underwent Sharpless asymmetric dihydroxylation to set two more stereocenters. The cyclization to close the tetrahydropyran ring created a 1:1 mixture of epimers at C43 that had to be equilibrated. This was eventually elaborated into F-ring 1.25. This compound had protecting group consistency, six stereocenters had been set, and a methyl ketone and a more functionalized sidechain attachment point were present. This synthesis was achieved in 18 steps, many of which were redox manipulations and protecting group switches.
Finally, the Smith group’s route to the EF fragment used a different E-F coupling strategy and required a slightly different F-ring. Two generations of this approach were used. The first route utilized the Petasis-Ferrier reaction of ester 1.26 to give ketone 1.27 (Scheme 1.4A). This reaction entails the methylation to an enol ether followed by Lewis acid promoted rearrangement. Following asymmetric α-hydroxylation using the Davis oxaziridine and isomerization of the methyl group at C40, this eventually led to aldehyde 1.28. This formed the cis-2,6-tetrahydropyran ring with the correct stereochemistry.

The second route utilized an organocatalytic aldol with propanal and subsequent Wittig olefination to form 1.30 (Scheme 1.4B). Sharpless asymmetric dihydroxylation, acid-catalyzed cyclization and protection gave lactone 1.31. This was reacted with cis-hexenyl Grignard to form a hemiketal. The hemiketal was reduced with triethylsilane to give the desired cis-2,6-tetrahydropyran 1.32. The hexenyl handle was later cleaved and elaborated into the side chain.
Finally, the Leighton group has recently reported a synthesis of the F-ring that made several key innovations that were used in this thesis work.\textsuperscript{86} We initially sought methyl ketone 1.33. This would provide the methyl ketone to perform an E-F coupling aldol and an ester to elaborate into the sidechain (Scheme 1.5). We envisioned this arising from 1.34 after decarboxylation of the β-keto ester and reduction of the C43 hemiketal, in analogy to previous precedent.\textsuperscript{87} Unraveling this shows the pseudo $C_2$-symmetric tetraol 1.35. This could come from dienone 1.36 via a double Sharpless asymmetric dihydroxylation and in turn from the cross-metathesis of 1.37 and 1.38.\textsuperscript{88} This cross-metathesis asymmetric dihydroxylation (CMAD) sequence would quickly build complexity and stereocenters.
Unfortunately the cross-metathesis between 1.37 and 1.38 was unsuccessful. However, we were able to furnish tetraol 1.40 from the CMAD sequence of diene 1.38 and t-butyl acrylate (Scheme 1.6). This compound was protected as an orthoester that desymmetrized the molecule to give 1.41. This was elaborated to β-keto ester 1.42, which upon cyclization gave hemiketal 1.43. This was successfully reduced to the desired cis-2,6-tetrahydropyran and the reaction conditions also protected the free alcohol at C42 and furnished the free carboxylic acid as 1.44. At this point, various protecting group manipulations and difficulties in transforming the methyl ester led to a successful but less than ideal synthesis of the F-ring. Nonetheless, it served to provide the starting point for our 2nd generation synthesis using the inherent $C_2$-pseudosymmetry in the F-ring.
1.2.2. E-F coupling strategy and boron-mediated aldol reactions

The most common approach to the E-F coupling is a selective boron-mediated aldol between an F-ring methyl ketone and an appropriate E-ring precursor aldehyde. This strategy was first used by Crimmins (Scheme 1.8) and followed by Paterson, Heathcock, and Ley. Although some attempts had been made previously using a lithium enolate, these were plagued by poor selectivity.

The aldol reaction of the boron enolate of methyl ketones with aldehydes is well known to give the 1,5-anti aldol product when the methyl ketone contains a β-alkoxy group (Scheme 1.7). Excellent diastereoselectivity is observed when the β-alkoxy group is a benzyl ether or a para-methoxybenzyl ether. Replacing the β-alkoxy group with a β-silyloxy group causes a complete loss of selectivity. This has been explained by DFT calculations on the preferred boat conformation of the transition state (Figure 1.8). The transition state is organized by a hydrogen bond between the aldehyde proton and the β-
alkoxy oxygen. Silyl ether groups cannot achieve this hydrogen bond because the oxygen is electron-poor and the high steric bulk of the silicon substituents. This explains the lack of selectivity when a silyl ether chosen as the β-hydroxy protecting group. In the transition state leading to the disfavored 1,5-syn, there is a steric clash between the cyclohexyl group on boron and the rest of the molecule. This model is highly predictive for simple systems, however it cannot explain systems with more complex stereochemical arrays.

Scheme 1.7. 1,5-anti aldol reaction

Figure 1.8. Hypothesized boron-aldol transition state

The EF fragment 1.47 has a 1,5-anti relationship between C35 and C39. This would suggest that the aldol reaction would be selective for the desired product. The F-ring also contains an α-hydroxy group at C38 which might complicate the reaction’s
selectivity. Additionally the aldehyde contains both α and β stereocenters. This makes the entire system too complex to rationalize using a simple model. Fortunately, the combination of stereoelectronic factors favors the desired 1,5-anti product as long as the C38 hydroxy is protected as a benzyl ether.

The advantage of this strategy is setting the alcohol stereocenter at C35 and leaving C37 in the desired ketone oxidation state. This reaction gave aldol product 1.47, which was deprotected and cyclized with acidic methanol to furnish metal ketal 1.48 with the correct stereochemistry at C37 and exposed the C35 alcohol for protection (Scheme 1.8). This strategy has proven to be reliable and selective and has been used with a variety of F-ring methyl ketones and E-ring aldehydes.

Scheme 1.8. The Crimmins group’s aldol reaction to join the E and F fragments

1.2.3. Chlorodiene sidechain installation approaches

The chlorodiene at C51 represents one of the most sensitive functionalities in spongistatin 1. In fact, its difficulty in handling most likely led many synthetic groups to initially target spongistatin 2, which contains a diene instead of the chlorodiene. This presents two challenges, the preparation of a chlorodiene and its introduction to an existing functional handle off of the F-ring.
The synthesis of a functionalized chlorodiene that contains the C47 stereocenter and a functional group handle to attach directly to the F-ring proved to be difficult. This approach was used by Evans in his spongistatin 2 synthesis and adapted in later syntheses for spongistatin 1.\textsuperscript{19,62} Aldehyde 1.49 was obtained in multiple steps using Evan’s chiral oxazolidinone auxiliary and underwent an indium promoted allylation and dehydration to give the chlorodiene 1.51 (Scheme 1.9). This was transformed using Trost’s palladium-catalyzed pi-allyl chemistry to obtain allyl stannane 1.52. This approach is highly convergent with regards to the respective complexity of the side chain and F-ring glycal.

![Scheme 1.9. Crimmins synthesis of allyl stannane 1.52](image)

With the allyl stannane in hand, the introduction of the entire sidechain was accomplished (Scheme 1.10). After coupling the EF glycal to the CD and AB fragments to give 1.53, the glycal was stereoselectively epoxidized with DMDO to form 1.54. This was reacted with a Lewis acid and allyl stannane 1.52 to give 1.55. This set the final two stereocenters on the F-ring from the epoxidation and selection addition of the allyl stannane side chain. Although this is an effective approach to the introduction of the side chain, there are some drawbacks. Performing any chemistry on the ABCDEF coupled material represents a loss of late-stage precious material. The addition of the allyl
stannane into the F-ring epoxide required more than a ten-fold excess of the allyl stannane that was not trivial to synthesize.

Multiple syntheses of spongistatin 1 relied on the use of chlorodiene aldehyde 1.60, for varying strategies. This sensitive compound has been synthesized using three different methods. Ley relied on the Johnson-Claisen reaction between orthoacetate 1.56 and alcohol 1.57 to give 1.58 (Scheme 1.11A).

The chloride was eliminated to give the enoate 1.59 which was reduced and reoxidized to give desired aldehyde 1.60. The second method used by Smith, allylated ethyl glyoxalate with 2,3-dichloropropene and aluminum to give 1.61 (Scheme 1.11B). This was mesylated and eliminated to give enoate 1.59, which was treated with the same reduction and oxidation procedure. The Paterson group used the Horner-Wadsworth-Emmons reaction of 2-chloroacrolein 1.62 which led directly to 1.59 (Scheme 1.11C). This was reduced with DIBAL and underwent a Swern oxidation to give the chlorodiene aldehyde 1.60.
Scheme 1.11. Syntheses of aldehyde 1.60 by the A) Ley, B) Smith and C) Paterson groups

This aldehyde proved to be successful in Paterson’s EF fragment synthesis by treating it with the boron-enolate of a methyl ketone (Scheme 1.12). Methyl ketone 1.63 and aldehyde 1.60 were successfully reacted with excellent selectivity to give 1.64. This compound required subsequent Lombardo methylation of the ketone to furnish the alkene. This is undesired as this reaction uses a complex mixture of metals, including toxic lead, and can often be difficult to reproduce.

Scheme 1.12. Boron-mediated aldol to install the chlorodiene sidechain

The Smith group utilized an umpolung approach with the appropriate nucleophile equivalent of the sidechain and an allyl halide (Scheme 1.13). Silyl cyanohydrin 1.65 was deprotonated with LiHMDS and added to allyl iodide 1.66 and desilylated to give 1.67. The allylic alcohol eventually was eliminated and the ketone was reduced
enantioselectively with CBS catalyst to give the desired sidechain. This was an efficient method to introduce the sidechain although it suffered from the need for post-introduction manipulations and the need to introduce another stereocenter with a stoichiometric asymmetric reagent. With the knowledge of previous syntheses successes and failures, we were posed to design a new and efficient route to the EF fragment.

![Chemical Reaction](image)

**Scheme 1.13.** Umpolung approach to sidechain installation

### 1.3. Development of spongistatin 1 as an anti-cancer therapeutic

Although the development of a highly efficient polyketide total synthesis highlights new synthetic methods and strategies, we were not simply interested in creating the most step-economical and efficient synthesis of spongistatin 1. Our ultimate goal is to develop a spongistatin 1 analog into an effective anti-cancer therapeutic. One approach to maximize the therapeutic potential of spongistatin 1 would be the use of targeted drug delivery, such as antibody drug conjugates (ADC). However, this will require the synthesis of multiple spongistatin 1 analogs. Each new linker design potentially requires a new analog. That is why having an extremely convergent and practical synthesis of spongistatin 1 analogs is vital. Fortunately, our previously
developed ABCD* synthesis is amenable to derivation to create ABCD* linker analogs. An efficient synthesis of the EF fragment is critical to provide material to complete the spongistatin 1 analogs.

ADCs function by coupling a drug to an antibody whose specific antigen is expressed exclusively or preferentially on tumor cells. This would deliver the drug specifically to tumor cells. This has the effect of significantly reducing the amount of required drug and severely reducing off-target toxicity therefore lessening the side effects common in many chemotherapy regiments. After the antibody binds to its antigen, the entire ADC enters the cell by endocytosis. Inside the cell, the antibody is degraded by proteases, which leave the drug-linker construct intact. Additionally, the ADC drug delivery strategy has been shown to alleviate drug efflux by the tumor cell that is mediated by the multidrug resistance-associated p-glycoprotein transmembrane pump. These multiple advantages have garnered the interest of chemists and biologists alike towards ADCs.

Despite the promising capabilities of ADCs, there are some challenges in their development. The drug molecule must have extremely high potency. Because of the cost and effort required to design and produce the antibody and linker a very powerful “warhead” must be attached. Additionally, the site of the linker on the drug must not be involved in the binding. Ideally, the linker site is located as far away as possible from the active binding pocket. Finally, the synthesis of the drug must be amenable towards the accommodation of the linker modification. This often presents a challenge in regards to functional group compatibility. Fortunately spongistatin 1 fulfills these criteria due to its
extreme potency and the presence of the CD fragment that isn’t directly involved in binding and is amenable to chemical modification.

By combining a scalable synthesis of a spongistatin 1 analog coupled with an ADC strategy we hope to advance it as a potential anti-cancer therapeutic. However, this dictated that our synthetic strategy be cognizant of linker compatibility. Based on numerous SAR studies, we decided to initially target the C15 position as a potential linker site. This was chosen as this region is not critical to tubulin binding and was incorporated into our previous ABCD* synthesis. These ABCD* linker analogs would be equally as amenable towards the coupling of the EF fragment. The following chapters will describe the synthesis of the EF fragment of spongistatin 1, the synthetic innovations realized, and the final synthesis of a spongistatin 1 analog.
1.4. References

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Chapter 2 Synthesis of the F-ring of the spongistatins

2.1. Introduction

Many of the obstacles encountered in the synthesis of spongistatin 1 (2.1) are found on the EF fragment that is composed of two tetrahydropyran rings, each packed with complex stereochemical arrays. The EF fragment is defined as the portion of the molecule between C29-C51. The degree of stereochemical complexity is denser than the ABCD fragment and poses a significant challenge. The F-ring is composed of a fully elaborated tetrahydropyran ring with five contiguous stereocenters that are adjacent to two additional stereocenters. A large portion of our effort was spent designing a scalable synthesis of a suitable F-ring that could be connected with both the E-ring and the chlorodiene side chain. Previous SAR studies suggest that the EF fragment is crucial to activity, with the chlorodiene variant being most potent. Therefore, we targeted the natural spongistatin 1 EF fragment for synthesis to be combined with our existing ABCD* material to furnish spongistatin 1 analog. This chapter will describe our new synthesis of spongistatin 1’s F-ring.
2.1.1. Retrosynthetic analysis of the EF fragment

One requirement of the synthesis of the EF fragment 2.3 was that it would be compatible towards coupling with the ABCD fragment 2.2. This entailed a Wittig reaction between C28 and C29 and a Yamaguchi macrolactonization between the C41 alcohol and the C1 carboxylic acid. This disconnection was first used by Evans and then in all subsequent syntheses.\(^\text{19}\) This necessitated having a triphenylphosphonium salt at C29 and a hydroxyl group at C41 on EF fragment 2.3. This fragment can be seen as being composed of three distinct pieces: The F-ring, the E-ring and the chlorodiene sidechain (Scheme 2.1).

Although there have been many approaches to introducing the sensitive chlorodiene side chain, as discussed, most suffer from step-inefficiency, yield or synthetic compatibility. We envisioned using an asymmetric allylation to join known chlorodiene aldehyde 2.4 with EF fragment silane 2.5 using Leighton group methodology.\(^\text{1,3}\) This silane would in turn come from the well-precedented aldol between methyl ketone 2.6 and aldehyde 2.7.\(^\text{37}\)
The protecting group strategy bears comment. The coupling of the EF and ABCD fragment and end-game chemistry is known to be compatible with TES groups and the synthesis was designed to accommodate this.\textsuperscript{42} However, the protecting group strategy on the EF fragment prior to ABCD coupling was more complex and will be discussed. With these two disconnects in mind, we set out to design an F-ring that would be amenable to both an aldol and an allylation reaction.
2.2. Preparation of protected allylic alcohol methyl ketone 2.6

F-ring methyl ketone 2.6 is the most stereochemically dense fragment in spongistatin 1. The desired fragment contains six contiguous stereocenters, five of which are contained on the ring. We wanted to avoid the three major downfalls of previous syntheses: multiple steps that require the use of chiral catalysts or reagents, nonstrategic protecting group manipulation, and redox adjustments. The methyl ketone at C37 was sought at the outset of the synthesis. However, we did not initially know what the best
functional handle at C43 would be. Two different functional handles were eventually used.

2.2.1. Retrosynthesis of F-ring methyl ketone 2.6

The strategy towards methyl ketone 2.6 relied on recognizing the element of \( C_2 \)-pseudosymmetry latent in the F-ring, as discussed in Chapter 1.\(^{86,95} \) Therefore we intercepted our previous synthesis using tetraol 2.10 (Scheme 2.2). This arises from the cross-metathesis asymmetric dihydroxylation (CMAD) sequence starting from commercially available diene 2.12. This would then undergo a desymmetrizing cyclization to set the methyl-containing stereocenter at C40. Whereas our first generation synthesis used an orthoacetate and benzyl protection to differentially protect alcohols and desymmetrize, we envisioned using a direct lactonization to arrive at lactone 2.9. This avoids complex protecting group manipulations and sets the C40 stereocenter. We then sought to install the C43 stereocenter via a methylenation and stereoselective hydroboration-Suzuki coupling sequence. This hydroboration reaction is known to give the desired \( cis \)-2,6-tetrahydropyran using a bulky borane.\(^{96} \) Following simple carbonyl manipulation at C37, we would arrive at F-ring methyl ketone 2.6. This sequence would allow us to install all six stereocenters in just five steps and protect all three alcohols with the same protecting group.
2.2. Optimization of cross-metathesis to afford dienoate **2.11**

Our previous synthesis of F-ring methyl ketone **2.6** utilized a double cross-metathesis reaction of diene **2.12** with t-butyl acrylate (Scheme 2.3). This reaction needed to work on decagram scale for two reasons. First, we had sought to produce a highly scalable and efficient synthesis of the EF fragment. Second, in more practical terms, a large amount of dienoate **2.11** would be required to fully test all downstream chemistry and have enough material to complete the synthesis. However, the existing procedure had problems with the catalyst loading of Hoveyda-Grubbs 2 catalyst (HG-II) and reaction time.\(^{97,98}\) Although a catalyst loading of 2.25 mol % compares favorably to most uses in total synthesis, we sought to further lower it because on this large scale, the catalyst represents a significant hurdle. Additionally, the reaction time was seven days, with requisite addition of acrylate and catalyst each day, which proved to be highly inconvenient.

A report by the Slugove group had shown that the cross-metathesis between alkyl terminal olefins and acrylates could be greatly improved in regards to catalyst loading and reaction rate by thoroughly removing oxygen and peroxides from the starting materials and using the acrylate in excess as the solvent.\(^{99}\) This appealed to us because it
provided a solution to our two key challenges in the improvement of the cross-metathesis reaction.

Combining diene 2.12 with a 20-fold excess of t-butyl acrylate with no additional solvent and adding the catalyst in three portions at 50 °C allowed the reaction to finish in just 5 hours with a 58% yield. Although this reaction results in a lower yield than the previous procedure, it is far more efficient in regards to reaction time. Additionally, the yield as a function of catalyst loading is illustrative. The original Tanis procedure results in 15.9 grams of desired product 2.11 per gram of HG-II, whereas the improved procedure results in 38.9 grams of 2.11 per gram of HG-II, a 2.5-fold increase.

![Scheme 2.3. Comparison of cross-metathesis procedures](image)

Several technical aspects should be noted. The t-butyl acrylate must be passed through an alumina column to remove peroxides and thoroughly sparged with nitrogen gas to remove dissolved oxygen. Additionally, the reaction must be run using a dry-ice condenser to avoid losing the highly volatile starting material 2.12. Finally, the reaction must be run under a constant stream of nitrogen with an outlet to remove the ethylene byproduct, lest it contribute to catalyst decomposition, and undesired metathesis.
pathways. This improved procedure was used to synthesize over 150 grams of dienoate 2.11 over the course of the project. With an efficient reaction to make 2.11 in place, we utilized the existing Sharpless asymmetric dihydroxylation to produce large amounts of desired tetraol 2.10 (Scheme 2.4). This reaction gave a 4.5:1 mixture of 2.10:2.10a after chromatography and was used in subsequent reactions as a mixture.

Scheme 2.4. Sharpless asymmetric dihydroxylation of 2.11

2.2.3. Lactonizations of tetraol 2.10

Previous attempts to cyclize tetraol 2.10 into lactone 2.14 were largely unsuccessful. Numerous base-promoted lactonizations resulted in poor yields and very poor reproducibility. Therefore, we focused on an acid-mediated cyclization to afford lactone 2.14. This would obviate the need to differentially and selectively protect a tetraol, which proved to be a difficult task using acetals or silyl acetals. Previous reaction attempts using trifluoroacetic acid (TFA) were able to produce a 1:1 mixture of 2.13 and epi-2.13 (Scheme 2.5). The lack of selectivity and the ester deprotection were undesired.
However, upon additional of an alcoholic co-solvent (ethanol), the reaction led to the desired lactone 2.14. The lactone was recovered with the $t$-butyl ester intact. The addition of the ethanol likely tempered the acidity of the reaction to prevent ester cleavage. Most importantly, lactone 2.14 was obtained as a 10:1 mixture with its C40 epimer epi-2.14. We hypothesize that ethanol provides a proton shuttle and nucleophile to render the cyclization reversible and allows generation of the thermodynamically favored product 2.14 that is the all-equatorial lactone (Figure 2.2). This product arises from 2.10. We hypothesize that the minor diastereomer of the tetraol 2.10a would give rise to lactones 2.14a and epi-2.14a. These sterically hindered products were not observed, suggesting that 2.10a does not react under these conditions. Therefore this reaction results in a partial resolution, upgrading the epimeric purity of the material substantially.

With an efficient route to a suitable lactone, we tackled the difficult challenge of installing appropriate protecting groups to three hydroxyl groups.
2.2.4. **Synthesis of benzyl lactone 2.15**

Previous attempts at protecting 2.14 proved to be generally difficult for three reasons. The first is that the molecule contains three secondary hindered hydroxyls. In particular, the C41-C42 diol is challenging to protect because after one protecting group is installed, the second alcohol becomes more hindered. The second problem is that this molecule contains α-hydroxy and β-hydroxy esters that are intolerant of highly basic conditions. α-Hydroxy carbonyls tend to epimerize and β-hydroxy carbonyls tend to eliminate hydroxide to give a conjugated carbonyl compound. Finally, t-butyl esters are sensitive to highly acidic conditions.

We initially envisioned using the benzyl ether protecting group because of the literature precedent of a benzyl group at C38 leading to good results in the boron-mediated aldol to join the E and F rings. We suspected that the classic sodium hydride and benzyl bromide conditions would be unsuitable due to aforementioned base sensitivity. Therefore we investigated alternative benzylation reactions to produce 2.15 (Scheme 2.6).
Various attempts at an efficient triple benzylation to provide 2.15 were plagued by a variety of problems. The Dudley reagent 2.17 is a neutral method for alcohol benzylation that operates through the thermal generation of benzyl cation as an ionic liquid.\textsuperscript{100} This reaction resulted in low yield (<30%) and incomplete conversion to the triply benzylated product. Additionally, large quantities of benzyl-related byproducts were formed which were extremely laborious to remove. Benzylation with benzyl trichloroacetimidate (BnTCAI) and triflic acid produced similar results.\textsuperscript{101}

Finally, benzyl bromide and silver (I) oxide successfully produced 2.15 in 50% yield.\textsuperscript{42} However, the reaction was not scalable above 500 mg, which would be untenable moving forward. We suspect this was due to the heterogeneity of the reaction mixture that often does not translate to large-scale reactions. This reaction also produced traces of tetrabenzyl lactone 2.16 that was almost inseparable from the desired product. Forcing the reaction to favor 2.16 was unsuccessful, suggesting that the \textit{t}-butyl ester was not compatible with the strongly electrophilic benzyl cation generated in this benzylation reaction. Therefore, we targeted another protecting group that will be compatible with the final ABCD-EF coupling, the TES group.

Scheme 2.6. Benzylation of triol 2.14
2.2.5. Attempts to synthesize TES protected F-ring 2.21

Silyl groups are ubiquitous in organic synthesis for their ease of introduction and removal. Lactone 2.14 proved to be incompatible with the strongly basic or strongly acidic/electrophilic conditions required for the introduction of benzyl groups. Silyl ether groups are often installed using a weak amine base under more mild conditions. Pleasingly, TES protection of triol 2.14 gave lactone 2.18 in 79% yield (Scheme 2.7). This allowed us to test a key step in our retrosynthesis, the methylenation of a protected lactone. The Petasis reagent (Cp₂TiMe₂) was chosen over the Tebbe Reagent (AlMe₃ + Cp₂TiCl₂) for its ease of use and synthesis, as well as its improved compatibility with acid-sensitive functional groups such as t-butyl ester and TES ether.¹⁰²,¹⁰³ This afforded enol ether 2.19 in 73% yield. Finally, we were in position to attempt the hydroboration-Suzuki sequence to install the sixth stereocenter on the F-ring.

Scheme 2.7. Attempts toward synthesis of tetrahydropyran 2.21

The hydroboration of acyclic enol ethers is typically unsuccessful due to the elimination of the resultant 1,2-oxoboron compound. This results in an olefin that can undergo further hydroboration. However, the hydroboration of exocyclic enol ethers is
well known to produce stable alkyl boron species that can be converted to either an alcohol via oxidation or engaged in a palladium-catalyzed Suzuki reaction with a suitable electrophile. Additionally, this reaction is highly stereoselective to favor the cis-2,6-tetrahydropyran when bulky boranes are used such as 9-BBN (Figure 2.3).

![Figure 2.3. Hydroboration of enol ether 2.19](image)

The reaction was monitored with $^{11}$B-NMR to observe the characteristic peak of a tri-alkyl borane, which was not observed. The reaction was extremely sluggish at 70 °C and 9-BBN decomposed at higher temperatures. It is common for the product of a Petasis methylenation to be contaminated with titanocene oxide byproducts even after precipitation with hexane, filtration and silica gel chromatography. Multiple purification methods were used to rigorously purify the enol ether, to no avail in the hydroboration. The recalcitrance of enol ether 2.19 to undergo hydroboration was presumably due to the steric hindrance of the TES groups. This type of hydroboration is known on highly substituted sugar lactones when protected by the less bulky benzyl groups. Therefore, we sought to synthesize a lactone that we could successfully benzylate by changing the nature of the problematic C37 carbonyl.

2.2.6. Attempts to synthesize a protected Weinreb amide

The Weinreb ketone synthesis is among the most effective methods for synthesizing ketones from other carbonyl compounds. In general, our strategy was to
convert the C37 ester to a Weinreb amide and then to a ketone. The carbonyl
manipulation step was therefore performed before the lactonization (Scheme 2.8). Tetraol
2.10 was cleanly protected as its double acetonide to give diester 2.22 in 82% yield. This
diester was then converted to diamide 2.23 in 71% yield by using the Weinreb amine salt
and i-PrMgCl to generate a magnesium amide in-situ. This was cyclized with TFA and
wet dichloromethane to give triol 2.24 in 71% yield that was not stable to silica gel
chromatography. All benzylation attempts proved to be equally as ineffective as for the t-
butyl ester variant 2.14. Nonetheless, it was TES protected to cleanly give 2.25, albeit in
poor yield (30%).

Scheme 2.8. Synthesis of Weinreb amide 2.25

We expected that a Weinreb amide would not be an idle participant during the
Petasis methylenation. Literature precedent reports that N,N-dialkyl amides are converted
to enamines, which would be hydrolyzed upon work up to give ketone-containing enol
erther 2.26. Instead, the reaction gave an equimolar mixture of the expected 2.26 and
the demethoxylated amide 2.27 (Scheme 2.9). This was unexpected as there are no
reports of a titanium reagent performing an N-O bond cleavage on a Weinreb amide.
However, this is not entirely inexplicable as the N-O bond is weak and titanium is highly oxophilic. Attempts to change this ratio to favor the desired product were unsuccessful. At this point, discouraged by the seemingly intractable protecting group issues, we proposed a new synthesis of the F-ring.

![Scheme 2.9. Methylenation of 2.25](image)

**Scheme 2.9. Methylenation of 2.25**

**2.3. Preparation of cis-hexenyl F-ring 2.28**

**2.3.1. Retrosynthesis of F-ring methyl ketone 2.28**

With a desire to quickly and efficiently synthesize the EF fragment we decided to use existing chemistry from the Smith route (Scheme 2.10). The *cis*-3-hexenyl fragment present on the left-hand side of the F-ring would eventually be converted into an allylic alcohol. Similarly, we envisioned introducing a hexenyl metal fragment to lactone 2.9, then silane reduction of 2.29. This would be followed by conversion to a Weinreb amide and a methyl ketone.
2.3.2. Synthesis of TES protected methyl ketone 2.33

Initial attempts to introduce the cis-hexenyl fragment as a Grignard reagent were unsuccessful, likely due to the same steric bulk that inhibited the hydroboration reaction. Fortunately, the more reactive hexenyl lithium cleanly afforded the desired hemiketal 2.30 in 87% yield (Scheme 2.11).

Based on our previous synthesis of the F-ring, we suspected and then observed that the TES-OTf and triethylsilane reduction of the hemiketal 2.30 would result in the
deprotection of the t-butyl ester. We thought this would be acceptable because a carboxylic acid is easily converted into a Weinreb amide. However, we also observed a deprotection of the adjacent TES ether at C38. This was likely due to the extremely acidic effect of the proximal, newly created carboxylic acid.

This effect was ameliorated by the subsequent addition of triethylamine, which re-silylated the alcohol using the excess TES-OTf and deprotonated the carboxylic acid, alleviating the proximal acid effect. However, upon workup and protonation of the carboxylate during isolation, the TES ether was simply deprotected again.

![Figure 2.4. Model α-silyloxy t-butyl esters](image)

This phenomenon was confirmed by treating two α-silyloxy t-butyl esters 2.34 and 2.35 with TES-OTf and triethylamine and observing the same desilylation to give mandelic acid and lactic acid, respectively (Figure 2.4). The carboxylate was instead protected in-situ as the methyl ester using TMS-CH$_2$N$_2$ before aqueous workup. This one-pot, three-step process produced methyl ester 2.31 in 37% yield. $^1$H-NMR coupling constants confirmed the geometry of the cis-2,6-tetrahydropyran. The yields for the conversion to the Weinreb amide 2.32 and subsequent methyl ketone 2.33 were both poor, which led to the conclusion that the extremely steric bulk of three TES groups interfered with the carbonyl manipulation steps as well.

In an attempt to improve the yield of the hemiketal reduction, a transesterification to the methyl ester with HCl in methanol was successfully performed. Therefore, we
decided to revisit the benzyl protecting group with the knowledge that the acid-sensitive t-butyl ester may be switched with the potentially less problematic methyl version before the benzylation.

2.3.3. Synthesis of methyl ketone 2.41

Being able to use the smaller benzyl protecting groups would likely alleviate the steric problems during the carbonyl manipulation towards the methyl ketone. Additionally, the benzyl group was expected to give excellent diastereoselectivity in the E-F aldol reaction. Because the initial lactonization of tetraol 2.10 was performed under alcoholic acid conditions, the natural conclusion was to combine the cyclization with the transesterification. However, as no transesterification to the ethyl ester was observed using TFA and ethanol, stronger conditions were required. TMS-Cl in methanol successfully afforded methyl ester 2.36 (Scheme 2.12). These particular conditions were chosen for two reasons. TMS-Cl, when heated in methanol produces anhydrous HCl in methanol. This is more convenient than using gaseous HCl and more reproducible than using commercial HCl in methanol that is difficult to titrate and purify. Additionally, upon reaction completion, the reaction mixture contains only volatile compounds (methanol, HCl and TMS-OMe) that can be easily removed by concentration. This proved to be necessary as 2.36 was not stable to silica gel chromatography; fortunately, it produced clean product.

We were exceedingly pleased to see that the benzylation of 2.36 with TriBOT 2.42 (Figure 2.5) and triflic acid was reproducible, clean and scalable and gave 2.37 in 62% yield over the two-step sequence. Additionally a mixture of doubly benzylated lactones was isolated in 9% yield that could be resubjected in similar conditions. TriBOT
is a recently introduced analogue of BnTCAI that offers several advantages. It contains three reactive benzyl fragments per molecule and in this case, only 1.2 equivalents of TriBOT were required, which is only slight excess, improving atom economy over BnTCAI. TriBOT is a bench-stable crystalline solid that can be synthesized on large scale and stored indefinitely. Finally, the byproduct, cyanuric acid, can be removed by a simple wash with aqueous sodium hydroxide, which proved necessary to facilitate product purification. With an effective route to a benzyl protected lactone, we proceeded with the rest of the synthesis.
Addition of cis-hexenyl Grignard afforded hemiketal 2.38. Using the alkyllithium compound caused over-addition to the methyl ester. Cerium and zinc –ate complexes of the organomagnesium compound were not reactive enough at -78 °C and caused epimerization of the C38 stereocenter at 0 °C. The four equivalents of the Grignard reagent were added slowly over five hours at -78 °C, lest it suffer from the same issues as the other metal species. The reduction with BF₃·OEt₂ and triethylsilane afforded tetrahydropyran 2.39 in 58% over the two-step sequence with no side-reaction of the benzyl ethers or the methyl ester. Conversion to Weinreb amide 2.40 and methyl ketone 2.41 went smoothly in 71% and 95% yields, respectively, avoiding the issues of the TES.
protected version. Finally with an efficient route to the appropriately protected methyl ketone 2.41, we were ready to test the boron-mediated aldol to join the E and F fragments. This route was used to produce over 5 grams of 2.41 in an overall yield of 8.9% in just 8 steps. Although the E-F coupling and downstream chemistry were moderately successful and will be discussed in Chapter 3, several issues caused us to revisit the original hydroboration-Suzuki route, using the new benzyl protected lactone.

2.4. Preparation of methyl ketone 2.43

2.4.1. Retrosynthesis of methyl ketone 2.43

Issues involving the inefficient and inconsistent conversion of the cis-3-hexenyl fragment into an allyl halide prompted a redesign of the methyl ketone. The sidechain would be brought in directly as a protected allylic alcohol to lactone 2.37, instead of an internal alkene. This would eliminate multiple problematic steps. Two strategies were devised. First, the allylic alcohol piece could be introduced to the lactone as an organometallic fragment and the resultant hemiketal 2.44 reduced (Scheme 2.13A). The second strategy was the most fruitful and was used to complete the synthesis of spongistain 1 analog; this was revisiting the original hydroboration-Suzuki route, albeit using the benzyl protected lactone 2.37 (Scheme 2.13B).
2.4.2. Synthesis of methyl ketone 2.43 via hemiketal reduction

Introduction of the appropriate allylic alcohol fragment relied on the synthesis of a suitable allyl halide. The Williamson ether synthesis with benzyl alcohol and Finkelstein halogen exchange of commercially available dichloride 2.46 provided allyl bromide 2.47 in 55% yield and 80% yield, respectively (Scheme 2.14). Attempts to lithiate or magnesate 2.47 were unsuccessful, likely due to the difficulty in generating allyl metal species. Instead, a one-pot Barbier process with zinc metal and TMS-Cl was used to generate hemiketal 2.44 cleanly. It should be noted that this reaction was chemoselective due to the increased reactivity of lactones compared to acyclic esters.
Various combinations of Lewis acids, reductants and solvents were used in the attempt to reduce the hemiketal. TMS-OTf, TES-OTf and BF$_3$•OEt$_2$ were used as Lewis acids. Triethylsilane and the more nucleophilic tributylsilane were used as reductants. Mixtures of dichloromethane, acetonitrile and propionitrile were used as solvents. Unfortunately, any reduction attempt led to a highly complex mixture that resulted in low yield and irreproducibility. We hypothesized that the oxocarbenium / homoallylic cation intermediate was performing non-productive pathways. Nonetheless, a small amount of 2.48 was obtained and successfully converted to methyl ketone 2.43. This led to the final synthesis of the methyl ketone, with proof that methyl ketone 2.43 could arise from methyl ester 2.48.

2.4.3. Synthesis of methyl ketone 2.43 via hydroboration-Suzuki coupling

After changing the C37 $t$-butyl ester to a methyl ester, we needed to rethink the Petasis methylenation. Whereas $t$-butyl esters are inert to the Petasis methylenation, methyl esters are converted to enol ethers. We decided to use this to our advantage and functionalize C37 at the same time as C43.
Lactone 2.37 was transformed into enol ether 2.51 with a 55% yield (Scheme 2.16). The typical Petasis methylenation uses at least two equivalents of the Petasis reagent because the by-product of the methylenation, titanocene oxide, can react with and consume the active titanium methylidene. However, due to the sluggish reactivity of the methyl ester, 3.5 equivalents were added. Under prolonged conditions, the newly created enol ether could undergo a side reaction with active titanium carbene, albeit slower than the desired reaction. Therefore, ethyl pivalate was added as a sink for excess reagent. This reaction was scalable although multi-gram scale reactions gave a large amount of the single enol ether 2.45 as a byproduct.

Vinyl bromide 2.50 was synthesized from commercially available 2,3-dibromopropene 2.49 in 52% yield (Scheme 2.15).

Vinyl bromide 2.50 was synthesized from commercially available 2,3-dibromopropene 2.49 in 52% yield (Scheme 2.15).

We envisioned a selective hydroboration at the exocyclic enol ether, with the methyl enol ether being hydrolyzed to the desired methyl ketone as the conclusion of the reaction. The hydroboration of 2.51 was successful and selective for the more reactive enol ether. Following Suzuki coupling with 2.50, the reaction mixture was hydrolyzed with aqueous HCl in THF to yield methyl ketone 2.43 in 49% isolated yield, even though the reaction created a complex mixture of products.
Because of the lower yields of the methylenation and hydroboration-Suzuki reactions, we synthesized enol ether 2.45 with 1.2 equivalents of Petasis reagent in a higher and more reliable yield of 75% (Scheme 2.17). This enol ether underwent the subsequent hydroboration-Suzuki reaction with a significantly higher 95% yield to provide methyl ester 2.48. After investigating multiple sources of palladium catalyst, the commercially available 3rd generation Buchwald precatalyst palladacycle with XPhos (XPhos Pd G3) performed the best. The methyl ester was converted to methyl ketone 2.43 with similar yields to the cis-hexenyl analogue.
Scheme 2.17. Synthesis of methyl ketone 2.43

The finalized eight-step sequence to methyl ketone 2.43 was conducted on decagram scale (Scheme 2.18).
2.5. Summary and Outlook

In this chapter, we detailed the retrosynthesis of the EF fragment and the preparation of the F-ring. The protecting group strategy and high level of stereochemical density on this ring proved to be a major synthetic challenge. We believe that methyl ketone 2.43 provides the most effective and convenient way to combine the F-ring, E-ring and chlorodiene sidechain. The longest linear sequence of this route was 8 steps in a combined overall yield of 11.4%. This is a significantly more step-economical approach compared to other routes to an F-ring methyl ketone. All six stereocenters on methyl ketone 2.43 were set in just five steps, only one of which required a chiral catalyst.
Although the overall yield was moderate, it was very convenient and was used to produce over 15 grams of methyl ketone. At this point, with a significant stockpile of methyl ketone, we were ready to tackle the E-F aldol reaction and subsequent sidechain installation.
2.6. Experimental Procedures

**General Information.** All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring and dry solvents unless otherwise indicated. Degassed solvents were purified by passage through an activated alumina column. t-Butyl acrylate was purified by passage through an activated alumina column and degassed with N₂. Et₃N was distilled from CaH₂. The synthesis of Cp₂TiMe₂, TriBOT and cis-3-hexenyl magnesium bromide were conducted as previously described, and all spectroscopic data were consistent with those reported for these compounds.¹⁰⁵,¹⁰⁹ Flash chromatography was performed with Silicycle SiliaFlash® P60 silica gel. pH 7 buffered silica gel was prepared by combining silica gel with 10% w/w dilute aqueous pH 7 phosphate buffer. Thin-layer chromatography (TLC) was carried out on glass backed silica gel TLC plates (250 mm) from Silicycle; visualization by UV light, KMnO₄ and/or ceric ammonium molybdenate (CAM). ¹H NMR spectra were recorded on a Bruker AVIII 300 (300 MHz), AVIII 400 (400 MHz), or AVIII 500 (500 MHz) spectrometer and are reported in ppm, relative to residual protonated solvent peak (CDCl₃, 7.26 ppm; C₆D₆, 7.16 ppm). Data are reported as follows: (bs= broad singlet, s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, td = triplet of doublets, q = quartet, p = quintet; coupling constant(s) in Hz; integration). Proton decoupled ¹³C NMR spectra were recorded on a Bruker AVIII 500 (126 MHz) spectrometer and are reported in ppm from CDCl₃ internal standard (77.16 ppm). Infrared spectra were recorded on a Perkin-Elmer Spectrum Two (Diamond ATR) IR spectrometer. Optical rotations were recorded on a Jasco DIP-1000
polarimeter. Mass Spectroscopy Data was obtained on a Waters XEVO G2-XS QTof mass spectrometer.

2.6.1. Preparation of tetraol 2.10.

To a solution of 3-methyl-1,4-pentadiene 2.12 (5.62 mL, 45 mmol, 1 equiv) in t-butyl acrylate (135 ml, 0.9 mol, 20 equiv) was added Hoveyda-Grubbs 2nd Generation catalyst (65.6 mg, 0.105 mmol, 0.23 mol %). The flask was fitted with a dry-ice condenser under constant nitrogen flow and the reaction mixture was heated to 50 °C. After 1.5 h, an additional portion of the HG-II catalyst (65.6 mg, 0.105 mmol, 0.23 mol %) was added. After 1.5 h, an additional portion of the HG-II catalyst (65.6 mg, 0.105 mmol, 0.23 mol %) was added. After 2 h, the reaction mixture was cooled to ambient temperature and concentrated. The residue was treated with toluene (100 mL) and the mixture was concentrated. The residue was purified by silica gel flash column chromatography (4% EtOAc/Hexanes) to yield dienoate 2.11 (7.55 g, 26.7 mmol, 58%) as a pale yellow oil. IR (thin film) 2977, 2933, 1713, 1614, 1392, 1318, 1153 cm\(^{-1}\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.76 (dd, \(J = 15.7, 7.0\) Hz, 2H), 5.73 (dd, \(J = 15.7, 1.3\) Hz, 2H), 3.17-3.08 (m, 1H), 1.47 (s, 18H), 1.20 (d, \(J = 6.9\) Hz, 3H). \(^13\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 165.9, 148.4, 123.2, 80.6, 38.5, 28.3, 18.6. HRMS (FAB+) calcd for \([\text{C}_{16}\text{H}_{26}\text{O}_4\text{H}^+]\) requires \(m/z\) 283.1904, found 283.1910.
To a mechanically-stirred solution of K$_3$Fe(CN)$_6$ (148 g, 450 mmol, 6 equiv), K$_2$CO$_3$ (62.1 g, 450 mmol, 6 equiv), NaHCO$_3$ (37.8 g, 450 mmol, 6 equiv) and CH$_3$SO$_2$NH$_2$ (14.3 g, 150 mmol, 2 equiv) in H$_2$O (750 mL) was added a solution of (DHQD)$_2$PHAL (3.00 g, 3.85 mmol, 0.05 equiv) in t-BuOH (500 mL). The mixture was cooled to 0 °C and K$_2$OsO$_4$ •2H$_2$O (1.10 g, 3.00 mmol, 0.04 equiv) was added, followed 10 minutes later by a solution of dienoate 2.11 (21.2 g, 74.9 mmol) in t-BuOH (250 mL). The bright orange suspension was stirred vigorously at 0 °C for 18 h. Solid Na$_2$SO$_3$ (94 g, 749 mmol, 10 equiv) was added and the reaction mixture was stirred for a further 45 min. The layers of the cold reaction mixture were separated, and the aqueous layer was extracted with EtOAc (3 x 150 mL). The combined organic layers were stirred with solid NaCl, the resulting brine layer was removed. The organic phase was washed with additional brine (350 mL), dried over Na$_2$SO$_4$, filtered and concentrated. The residue was purified by silica gel flash column chromatography (50% EtOAc/Hexanes) to yield tetraol 2.10 (16.4 g, 46.7 mmol, 62%) as the major product of a 4.5:1 mixture of diastereomers as a colorless gum that solidified to a colorless solid on standing. This mixture was used as is in the next step, but for the purposes of characterization, an analytically pure sample was obtained by careful flash chromatography. [$\alpha$]$_D^{21}$ $-12.7^\circ$ (c 0.56, CHCl$_3$). **IR** (thin film) 3473, 2978, 2934, 1716, 1394, 1288 cm$^{-1}$. **$^1$H NMR** (400 MHz, CDCl$_3$) $\delta$ 4.15 (dd, $J = 5.7, 3.0$ Hz, 1H), 4.12 (dd, $J = 5.7, 1.6$ Hz, 1H), 4.06 (dt, $J =$
8.4, 3.3 Hz, 1H), 3.99 (td, J = 8.9, 1.3 Hz, 1H), 3.55 (d, J = 8.5 Hz, 1H), 3.52 (d, J = 5.7 Hz, 1H), 3.34 (d, J = 5.7 Hz, 1H), 3.22 (d, J = 9.1 Hz, 1H), 2.26-2.14 (m, 1H), 1.50 (s, 18H), 1.07 (d, J = 7.0 Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 173.0, 83.5, 83.3, 75.0, 74.2, 72.2, 71.9, 40.0, 28.2, 13.1. HRMS (FAB+) calcd for [C$_{16}$H$_{30}$O$_8$H$^+$] requires m/z 351.2013, found 351.2018.

2.6.2. Preparation of enol ether 2.19

![Diagram of enol ether preparation](image)

To a solution of tetraol 2.10 (1.21 g, 3.45 mmol) in CH$_2$Cl$_2$ (8 mL) and EtOH (7 mL) was added TFA (2.60 mL, 34.5 mmol). The reaction was stirred for 24 h at rt, toluene was added and the reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography (90% EtOAc/Hexanes) on silica gel gave lactone 2.14 as a pale oil (667 mg, 2.42 mmol, 70% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.26 (dd, J = 10.4, 1.6 Hz, 1H), 4.18 (dd, J = 6.0, 1.6 Hz, 1H), 4.04 (dd, J = 9.9, 1.8 Hz, 1H), 3.63 (td, J = 10.3, 2.6 Hz, 1H), 3.55 (d, J = 2.1 Hz, 1H), 3.30 (d, J = 6.0 Hz, 1H), 2.99 (d, J = 2.7 Hz, 1H), 2.38 (m, 1H), 1.52 (s, 9H), 1.21 (d, J = 6.5 Hz, 3H).
Lactone 2.14 (500 mg, 1.80 mmol) was charged with dry pyridine (10 mL) and cooled to 0 °C. TES-Cl (2.0 mL, 11.7 mmol) was added dropwise. The reaction mixture was heated to 60 °C and stirred for 48 h. The reaction was slowly quenched by addition of NaHCO₃ (sat. aq.) (25 mL). The reaction mixture was extracted with (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated. The crude product was placed under high vacuum for 3 h to remove pyridine. Purification by flash column chromatography (3% EtOAc/Hexanes) on silica gel gave TES ether 2.18 as a clear oil contaminated with TES₂O (876 mg, 1.41 mmol, 79% yield). ¹H NMR (400 MHz, CDCl₃) δ 4.67 (dd, J = 10.3, 2.4 Hz, 1H), 4.22 (d, J = 2.4 Hz, 1H), 4.04 (d, J = 4.9 Hz, 1H), 3.70 (t, J = 4.6 Hz, 1H), 2.2-2.14 (m, 1H), 1.48 (s, 9H), 1.11 (d, J = 7.1 Hz, 3H), 0.99 – 0.93 (m, 20H), 0.72 – 0.57 (m, 19H).

To a solution of TES ether 2.18 (250 mg, 0.404 mmol) in toluene (3.2 mL) in a sealed-tube pressure apparatus was added Cp₂TiMe₂ (912 mg of a 27.7% w/w solution in toluene, 1.21 mmol). The pressure apparatus was sealed and heated at 80 °C in the dark overnight. The reaction was cooled to rt and hexane (12 mL) was added to precipitate the titanocene oxide byproduct. The reaction mixture was filtered over Celite and concentrated. Purification by flash column chromatography (0% → 4% EtOAc/Hexanes) on silica gel gave enol ether 2.19 as a yellow oil (184 mg, 0.30 mmol, 73% yield). ¹H NMR (400 MHz, CDCl₃) δ 5.47 – 5.06 (m, 1H), 4.44 (d, J = 3.5 Hz, 1H), 4.37 (d, J = 3.5
Hz, 1H), 4.22 (d, J = 3.1 Hz, 1H), 3.87 (m, 1H), 3.78 (m, 1H), 3.36 (m, 1H), 2.16 – 1.83 (m, 1H), 1.51 – 1.47 (m, 9H), 1.01 – 0.91 (m, 32H), 0.65 (m, 20H).

2.6.3. Preparation of methyl ketone 2.26

To a solution of tetraol 2.10 (1.2 g, 3.42 mmol) in CH₂Cl₂ (12 mL) and 2,2-dimethoxypropane (8.4 mL) was added PPTS (858 mg, 3.42 mmol). The reaction mixture was heated at 60 °C overnight. NaHCO₃ (sat. aq.) (20 mL) was added to quench the reaction. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. Purification by flash column chromatography (10% EtOAc/Hexanes) on silica gel gave acetonide 2.22 as a clear oil (1.21 g, 2.81 mmol, 82% yield). ¹H NMR (400 MHz, CDCl₃) δ 4.43 (dd, J = 7.8, 2.7 Hz, 1H), 4.17 (m, 3H), 2.07 – 1.97 (m, 1H), 1.49 (s, 9H), 1.48 (s, 9H), 1.44 (s, 6H), 1.43 (s, 6H), 1.00 (d, J = 6.9 Hz, 3H)
Acetonide 2.22 (260 mg, 0.604 mmol) and NH(OMe)Me·HCl (1.18 g, 12.1 mmol) were suspended in THF (15 mL) and cooled to -40 °C. i-PrMgCl (9 mL, 2M in THF) was added over 30 min via syringe pump at this temperature. The reaction mixture was allowed to warm to rt overnight. The reaction was quenched by addition of NH₄Cl (sat. aq.) (25 mL) and the layers were separated. The aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. Purification by flash column chromatography (50% EtOAc/Hexanes) on silica gel gave Weinreb amide 2.23 as a clear oil (187 mg, 0.462 mmol, 76% yield). ¹H NMR (400 MHz, CDCl₃) δ 4.7 – 4.44 (m, 4H), 3.77 (s, 3H), 3.75 (s, 3H), 3.22 (s, 6H), 2.13 – 2.06 (m, 1H), 1.45 – 1.36 (m, 12H), 0.99 (d, J = 7.0 Hz, 3H).

To a solution of Weinreb amide 2.23 (300 mg, 0.742 mmol) in wet CH₂Cl₂ (6 mL) was added TFA (2.8 mL, 37.1 mmol). The reaction mixture was heated to 40 °C in a sealed vial for 2 h. The reaction mixture was concentrated, benzene (2 mL) was added and re-concentrated. To the crude mixture was added CH₂Cl₂ (3 mL), MeOH (1 mL) and K₂CO₃ (300 mg, 2.23 mmol) and shaken for 5 min. The solution was filtered and concentrated to give lactone 2.24 as a white solid (139 mg, 0.527 mmol, 71% yield). This was used as is in subsequent reactions.
Lactone 2.24 (120 mg, 0.186 mmol), DMAP (5 mg, .037 mmol) and imidazole (152 mg, 2.22 mmol) were dissolved in DMF (1 mL). TES-Cl (0.25 mL, 1.49 mmol) was added dropwise and the reaction was heated to 60 °C and stirred overnight. The reaction was quenched by the addition of MeOH (0.15 mL), stirred 10 min and diluted with NaHCO$_3$ (sat. aq.) (5 mL). The aqueous reaction mixture was extracted with Et$_2$O (4 x 4 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated. Purification by flash column chromatography (0% → 20% EtOAc/Hexanes) on silica gel gave TES ether 2.25 as a pale oil (32 mg, 0.053 mmol, 30% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 4.68 (m, 2H), 4.05 (d, J = 5.1 Hz, 1H), 3.83 – 3.66 (m, 4H), 3.38 – 3.15 (m, 3H), 2.25 – 2.14 (m, 1H), 1.13 (d, J = 7.3 Hz, 3H), 1.01 – 0.82 (m, 27H), 0.73 – 0.54 (m, 18H).

To a solution of TES ether 2.25 (144 mg, 0.237 mmol) in toluene (2 mL) in a sealed-tube pressure apparatus was added Cp$_2$TiMe$_2$ (530 mg of a 28% w/w solution in toluene, 0.713 mmol). The pressure apparatus was sealed and heated at 80 °C in the dark overnight. The reaction was cooled to rt and hexane (10 mL) was added to precipitate the titanocene oxide byproduct. The reaction mixture was filtered over Celite and
concentrated. Purification by flash column chromatography (0% → 20% EtOAc/Hexanes) on silica gel gave methyl ketone 2.26 (41 mg, 0.071 mmol, 30% yield) and amide 2.27 (46 mg, 0.081 mmol, 34% yield). 2.26: ¹H NMR (400 MHz, CDCl₃) δ 4.41 (s, 1H), 4.29 (s, 1H), 4.14 (d, J = 2.3 Hz, 1H), 3.86 (m, 2H), 3.40 (t, J = 6.0 Hz, 1H), 2.25 (s, 3H), 1.99 – 1.90 (m, 1H), 1.01- 0.92 (m, 30H), 0.71 – 0.57 (m, 18H). 2.27: ¹H NMR (400 MHz, CDCl₃) δ 4.45 (s, 1H), 4.35 (s, 1H), 4.19 (s, 1H), 3.87 – 3.80 (m, 2H), 3.38 (t, J = 6.6 Hz, 1H), 2.86 (d, J = 5.0, 3H), 1.95 – 1.86 (m, 1H), 1.04 – 0.87 (m, 30H), 0.72 – 0.57 (m, 18H).

2.6.4. Preparation of methyl ketone 2.33

To a -78 °C solution of cis-3-hexenyl iodide (678 mg, 3.23 mmol) in Et₂O (12.5 mL) was added t-BuLi (5 mL, 1.35M in pentane) drop wise. After stirring for 5 min, the reaction was allowed to warm to 0 °C over 30 min. The reaction mixture was cooled to -78 °C and lactone 2.18 (1.00 g, 1.62 mmol) was added as a solution in Et₂O (2 mL) and the reaction stirred for 1.5 h at this temperature. NH₄Cl (sat. aq.) (10 mL) was added to quench the reaction and the layers were separated. The aqueous layer was extracted with Et₂O (2 x 5 mL). The combined organic layers were washed with NaHCO₃ (sat. aq.) (5 mL), dried over Na₂SO₄, filtered and concentrated. Purification by flash column
chromatography (0% \rightarrow 3\% \text{EtOAc/Hexanes}) on silica gel gave hemiketal 2.30 as a mixture of diastereomers as a pale oil (983 mg, 1.40 mmol, 87\% yield).

To a \(-78{\degree}\text{C}\) solution of hemiketal 2.30 (100 mg, 0.142 mmol) and \(\text{Et}_3\text{SiH}\) (0.25 mL, 1.56 mmol) in \(\text{CH}_2\text{Cl}_2\) (2.7 mL) was added TES-\text{OTf} (0.22 mL, 0.994 mmol) slowly. The reaction mixture was stirred at \(-78{\degree}\text{C}\) for 10 min, 0 °C for 1 h, then rt for 1.5 h. The solution was cooled to 0 °C and \(\text{Et}_3\text{N}\) (0.3 mL, 2.13 mmol) was added. The reaction was stirred at this temperature for 1 h. \(\text{MeOH}\) (0.5 mL) and TMS-\(\text{CH}_2\text{N}_2\) (0.71 mL, 2M in \(\text{Et}_2\text{O}\)) were added at 0 °C. The reaction mixture was stirred at this temperature for 30 min then at rt for 1 h, then diluted with \(\text{NaHCO}_3\) (sat. aq.) (5 mL) and \(\text{EtOAc}\) (5 mL). The layers were separated and the aqueous layer was extracted with \(\text{EtOAc}\) (3 x 5 mL). The combined organic layers were dried over \(\text{Na}_2\text{SO}_4\), filtered and concentrated. Purification by flash column chromatography (0\% \rightarrow 3\% \text{EtOAc/Hexanes}) on silica gel gave methyl ester 2.31 as a clear oil (34 mg, 0.053 mmol, 37\% yield). \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\) 5.40 – 5.24 (m, 2H), 4.40 (d, \(J = 2.5\) Hz, 1H), 3.72 (s, 3H), 3.40 – 3.21 (m, 3H), 2.95 (ddd, \(J = 10.6, 8.4, 2.3\) Hz, 1H), 2.12 (m, 1H), 2.01 (p, \(J = 14.5\) Hz, 2H), 1.95 – 1.82 (m, 2H), 1.76 – 1.65 (m, 1H), 1.51 – 1.39 (m, 1H), 1.34 – 1.19 (m, 1H), 1.02 – 0.85 (m, 33H), 0.75 – 0.55 (m, 18H).
Methyl ester 2.31 (330 mg, 0.512 mmol) and NH(OMe)Me·HCl (225 mg, 2.30 mmol) were suspended in THF (5.3 mL) and cooled to -40 °C. i-PrMgCl (2 mL, 2M in THF) was added over 30 min via syringe pump at this temperature. The reaction mixture was stirred at 0 °C for 1 h and at rt for 2 h. The reaction was quenched by the addition of NH₄Cl (sat. aq.) (8 mL) and the layers were separated. The aqueous layer was extracted with Et₂O (3 x 5 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. Purification by flash column chromatography (2% → 5% EtOAc/Hexanes) on silica gel gave Weinreb amide 2.32 as a clear oil (109 mg, 0.161 mmol, 32% yield).

To a -78 °C solution of Weinreb amide 2.32 (109 mg, 0.164 mmol) in THF (3 mL) was added MeLi (0.15 mL, 1.6 M in Et₂O). The reaction was stirred for 1 h at this temperature before another portion of MeLi (0.15 mL, 1.6 M in Et₂O) was added. The reaction was stirred for 1 h at -78 °C and quenched by the addition of NH₄Cl (sat. aq.) (3 mL). The layers were separated and the aqueous layer was extracted with Et₂O (2 x 2 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. Purification by flash column chromatography (0% → 2% EtOAc/Hexanes) on silica gel.
gave methyl ketone 2.33 as a clear oil (43 mg, 0.068 mmol, 41% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.56 – 5.07 (m, 2H), 4.12 (d, J = 2.4 Hz, 1H), 3.34 – 3.20 (m, 3H), 2.95 (ddd, J = 10.3, 8.1, 2.3 Hz, 1H), 2.22 (s, 3H), 2.17 – 1.77 (m, 5H), 1.77 – 1.67 (m, 1H), 1.50 – 1.37 (m, 1H), 1.02 – 0.92 (m, 33H), 0.72 – 0.59 (m, 18H).

2.6.5. Preparation of methyl ketone 2.41

Tetraol 2.10 (20.83 g, 59.40 mmol) was charged with methanol (300 mL) and TMS-Cl (37.7 mL, 297 mmol) was added slowly in sealed-tube pressure apparatus. The vessel was sealed and the reaction mixture was heated at 65 °C for 18 hrs. The reaction mixture was concentrated under reduced pressure, toluene (150 mL) was added and concentrated again.

To the crude mixture, TRIBOT (18.96 g, 47.52 mmol) and flame-dried MS 5Å (14.36 g) were added. 1,4-dioxane (585 mL) was added. Triflic acid (3.93 mL, 44.55 mmol) was added and the reaction mixture was stirred for 1 hr. Additional TRIBOT (14.22 g, 35.64 mmol) was added and the reaction mixture was stirred for 4 hrs. Additional TRIBOT (14.22 g, 35.64 mmol) was added and the reaction mixture was stirred for another 18 hrs. 1M NaOH (aq.) (45 mL) was added and stirred for 10 minutes. The reaction mixture was diluted with CH$_2$Cl$_2$ (450 mL) and filtered through Celite. The filtrate was washed with 2 x 100 mL 1M NaOH (aq.) and brine (150 mL), dried over
Na₂SO₄, filtered, and concentrated *in vacuo* to give the crude product as a yellow oil. Purification by flash column chromatography (5% → 10% → 20% → 30% EtOAc/Hexanes) on silica gel gave lactone 2.37 as a pale yellow oil (18.6 g, 36.8 mmol, 62% yield over two steps) as well as a mix of doubly benzylated lactones (1.9 g, 4.58 mmol, 9% yield). \([\alpha]_{D}^{23} = -43.6^\circ\) (c 1.00, CH₂Cl₂). **IR** (ATR) 3029, 2876, 1754, 1496, 1453, 1286, 1210 cm⁻¹. **¹H NMR** (500 MHz, CDCl₃) \(\delta 7.56 - 7.17\) (m, 20H), 5.06 (d, J = 11.2 Hz, 1H), 4.94 (d, J = 11.7 Hz, 1H), 4.80 (d, J = 11.1 Hz, 1H), 4.66 (d, J = 11.2 Hz, 1H), 4.52 (d, J = 11.2 Hz, 1H), 4.42 (d, J = 11.7 Hz, 1H), 4.38 (dd, J = 10.4, 2.2 Hz, 1H), 4.05 (d, J = 7.9 Hz, 1H), 4.03 (d, J = 2.2 Hz, 1H), 3.85 (s, 3H), 3.44 (dd, J = 9.8, 7.8 Hz, 1H), 2.33 – 2.22 (m, 1H), 0.78 (d, J = 6.6 Hz, 3H). **¹³C NMR** (126 MHz, CDCl₃) \(\delta 170.11, 169.66, 137.76, 137.31, 136.49, 128.89, 128.71, 128.66, 128.60, 128.57, 128.54, 128.51, 128.32, 128.20, 128.09, 81.86, 80.42, 79.87, 75.41, 74.51, 74.36, 73.17, 52.71, 35.65, 13.49. **HRMS** (ESI+) calcd for [C₆₂H₈₂O₉SiNa⁺] requires \(m/z\) 527.2046, found 527.2041.

![Diagram of chemical reaction](image)

To a -78 °C solution of lactone 2.37 (11.5 g, 22.7 mmol) in THF (120 mL) was added cis-3-hexenyl magnesium bromide (79 mL, 0.87M in THF) via addition funnel over 2 h. The reaction mixture was stirred at this temperature for 5 h. NH₄Cl (sat. aq.) (200 mL) was added to quench the reaction and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with
brine (150 mL), dried over Na$_2$SO$_4$, filtered and concentrated. The crude hemiketal 2.38 was used directly in the next step.

Crude hemiketal 2.38 was charged with dry MeCN (225 mL) and Et$_3$SiH (18.2 mL, 114 mmol) and cooled to -40 °C. BF$_3$·OEt$_2$ (11.1 mL, 90.8 mmol) was added dropwise, the reaction was warmed to 0 °C over 1 h and stirred at this temperature for 2 h. The reaction mixture was quenched by the addition of NaHCO$_3$ (sat. aq.) (300 mL) and EtOAc (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (150 mL), dried over Na$_2$SO$_4$, filtered and concentrated. Purification by flash column chromatography (0% → 5% → 10% EtOAc/Hexanes) on silica gel gave methyl ester 2.39 as a clear oil (7.26 g, 13.3 mmol, 58% yield over two steps). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.39 – 7.27 (m, 15H), 5.48 – 5.16 (m, 2H), 4.95 (d, J = 12.0 Hz, 1H), 4.90 (d, J = 10.9 Hz, 1H), 4.84 (d, J = 11.3 Hz, 1H), 4.62 (t, J = 9.9 Hz, 2H), 4.37 (d, J = 12.0 Hz, 1H), 4.06 (d, J = 2.8 Hz, 1H), 3.80 (s, 3H), 3.41 (dd, J = 10.3, 2.8 Hz, 1H), 3.32 – 3.06 (m, 3H), 2.22 – 1.90 (m, 4H), 1.85 – 1.75 (m, 1H), 1.57 (h, J = 4.5 Hz, 1H), 0.95 (t, J = 7.5 Hz, 3H), 0.68 (d, J = 6.5 Hz, 3H).
Methyl ester 2.39 (3.36 g, 5.89 mmol) and NH(OMe)Me·HCl (1.72 g, 17.6 mmol) were suspended in THF (68 mL) and cooled to -20 °C. i-PrMgCl (17.3 mL, 2M in THF) was added over 30 min via syringe pump at this temperature. The reaction mixture was stirred at -15 °C for 30 min and at °C for 30 min. The reaction was quenched by addition of NH₄Cl (sat. aq.) (75 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 75 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. Purification by flash column chromatography (10% → 20% EtOAc/Hexanes) on silica gel gave Weinreb amide 2.40 as a clear oil (2.51 g, 4.17 mmol, 71% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.44 – 7.11 (m, 15H), 5.45 – 5.21 (m, 2H), 5.00 – 4.77 (m, 3H), 4.62 (dd, J = 11.0, 8.1 Hz, 2H), 4.34 (d, J = 12.1 Hz, 1H), 4.27 (d, J = 2.8 Hz, 1H), 3.58 (s, 3H), 3.48 (s, 1H), 3.32 – 3.22 (m, 4H), 3.22 – 3.02 (m, 2H), 2.33 – 2.09 (m, 2H), 2.01 (dt, J = 14.8, 7.0 Hz, 3H), 1.86 – 1.72 (m, 1H), 1.65 – 1.51 (m, 2H), 1.27 (s, 1H), 0.94 (t, J = 7.5 Hz, 3H), 0.74 (d, J = 6.5 Hz, 3H).

To a -78 °C solution of Weinreb amide 2.40 (7.22 g, 12.0 mmol) in THF (144 mL) was added MeMgBr (8 mL, 3M in THF). The reaction mixture was stirred at 0 °C for 45 min. The solution was re-cooled to -78 °C and a second portion of MeMgBr (8
mL, 3M in THF) was added. The reaction mixture was stirred at 0 °C for 45 min. The reaction was quenched by addition of NH₄Cl (sat. aq.) (100 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 75 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. Purification by flash column chromatography (10% EtOAc/Hexanes) on silica gel gave methyl ketone 2.41 as a clear oil (6.35 g, 11.4 mmol, 95% yield). 1H NMR (400 MHz, CDCl₃) δ 7.37 – 7.29 (m, 15H), 5.39 – 5.19 (m, 2H), 4.94 – 4.75 (m, 3H), 4.61 (t, J = 11.3 Hz, 2H), 4.37 – 4.29 (m, 1H), 3.80 (d, J = 2.4 Hz, 1H), 3.36 – 3.20 (m, 2H), 3.20 – 3.05 (m, 2H), 2.19 – 2.03 (m, 1H), 2.03 – 1.92 (m, 3H), 1.88 – 1.75 (m, 1H), 1.60 – 1.45 (m, 2H), 0.93 (t, J = 7.5 Hz, 3H), 0.66 (d, J = 6.5 Hz, 3H).

2.6.6. Preparation of hemiketal 2.44

NaH (3.22 g, 80.5 mmol, 60% in mineral oil) was added to a flame-dried flask. Dry pentane (50 mL) was added and stirred for 5 min. The pentane was carefully removed by syringe. THF (110 mL) was added and the suspension was cooled to 0 °C. BnOH (8.5 mL, 82.4 mmol) was added and the reaction mixture was stirred at this temperature for 30 min before the addition of dry DMF (23 mL). The reaction mixture was refluxed at 80 °C for 30 min. 95 mL of this solution was transferred to an addition funnel and added to a 0 °C solution of dichloride 2.46 (5.5 mL, 47.5 mmol) in THF (31 mL) over 2 h. The reaction was allowed to warm to rt overnight. The reaction was
quenched by the addition of H$_2$O (100 mL). The solution was extracted with Et$_2$O:pentane (1:1, 3 x 75 mL). The combined organic layers were washed with H$_2$O (75 mL) and brine (75 mL), dried over MgSO$_4$, filtered and concentrated. Purification by flash column chromatography (0% → 2% Et$_2$O/Hexanes) on silica gel gave allyl chloride as a clear oil which was used directly in the next step (5.09 g, 26.0 mmol, 55% yield). Spectroscopic data was consistent with those previous reported in the literature.

The resultant allyl chloride (5.0 g, 25.4 mmol) was mixed with LiBr (4.40 g, 50.8 mmol) and TBAB (410 mg, 1.27 mmol) and stirred at 60 °C overnight. The mixture was diluted with Et$_2$O:pentane (1:5, 50 mL) and filtered over silica gel to give allyl bromide 2.47 as a clear oil (5.54 g, 23.0 mmol, 90% yield). Spectroscopic data was consistent with those previous reported in the literature.

Zn dust (156 mg, 2.38 mmol) was flame-dried under vaccum and covered with THF (6 mL). TMS-Cl (70 µL, .060 mmol) was added at rt and the mixture was stirred 15 min. Allyl bromide 2.47 (287 mg, 1.19 mmol) was added and the mixture was stirred another 15 min. Lactone 2.37 (300 mg, 0.595 mmol) was added as a solution in THF (1.2 mL) and the resultant mixture was stirred for 2 h. 0.1 M HCl (aq) (5 ml) was added. This was extracted with EtOAc (3 x 3 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated to give hemiketal 2.44 as a mix of diastereomers.
2.6.7. Preparation of methyl ketone 2.43

Sodium hydride (3.07 g, 76.7 mmol, 60% in mineral oil) was charged with dry THF (300 mL) and cooled to 0 ºC. BnOH (6.34 mL, 61.39 mmol) was added dropwise and stirred 1 h at rt. The reaction was cooled to 0 ºC, and 2,3-dibromopropene 2.49 was added dropwise and the reaction was warmed to rt over 18 hrs. The reaction was quenched with NH₄Cl (sat. aq.) (300 mL), the layers separated and the aqueous phase was extracted with 3 x 75 mL Et₂O. The combined organics layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated. Purification by flash column chromatography (0% → 1% EtOAc/Hexanes) gave vinyl bromide 2.50 as a clear oil (7.30 g, 32.17 mmol, 52%). IR (ATR) 3029, 2852, 1638, 1495, 1453, 1360, 1075, 897, 736, 697.¹H NMR (500 MHz, CDCl₃) δ 7.40 – 7.27 (m, 5H), 5.96 (s, 1H), 5.65 (s, 1H), 4.57 (s, 2H), 4.14 (s, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 137.66, 129.59, 128.61, 128.00, 127.94, 117.92, 74.13, 72.22.

To a solution of lactone 2.37 (918 mg, 1.82 mmol) in toluene (15 mL) in a sealed-tube pressure apparatus was added Cp₂TiMe₂ (5.77 g of a 24% w/w solution in toluene, 6.38 mmol) and ethyl pivalate (0.14 mL, 0.91 mmol). The pressure apparatus was sealed
and heated at 80 °C in the dark overnight. The reaction was cooled to rt and hexane (100 mL) was added to precipitate the titanocene oxide byproduct. The reaction mixture was filtered over Celite and concentrated. Purification by flash column chromatography (0% → 10% EtOAc/Hexanes) on silica gel gave enol ether 2.51 as a yellow oil (501 mg, 1.00 mmol, 55% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.41 – 7.27 (m, 15H), 4.91 (d, J = 11.1 Hz, 1H), 4.78 (dd, J = 14.0, 11.6 Hz, 2H), 4.65 (s, 2H), 4.58 (d, J = 11.1 Hz, 1H), 4.43 (d, J = 2.5 Hz, 1H), 4.38 (d, J = 11.9 Hz, 1H), 4.28 (d, J = 2.5 Hz, 1H), 3.98 (d, J = 8.1 Hz, 1H), 3.86 (d, J = 2.1 Hz, 1H), 3.64 (s, 3H), 3.45 (dd, J = 10.4, 2.1 Hz, 1H), 3.19 (dd, J = 9.9, 8.1 Hz, 1H), 2.24 – 2.09 (m, 1H), 0.70 (d, J = 6.6 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 159.39, 158.17, 138.58, 138.25, 137.76, 128.71, 128.53, 128.48, 128.44, 128.25, 128.07, 127.98, 127.82, 127.79, 94.28, 84.72, 82.64, 82.34, 81.38, 76.53, 74.97, 73.11, 72.20, 55.05, 37.55, 12.93. Low-Res MS (ESI+) calcd for [C$_{32}$H$_{36}$O$_5$SiNa+] requires m/z 523.25, found 523.55.

Enol ether 2.51 (1.70 g, 3.40 mmol) was charged with THF (19 mL) and cooled to 0 °C. 9-BBN (13.6 mL, 0.5 M in THF) was added and the reaction was stirred at this temperature for 6 h. 3M K$_3$PO$_4$ (aq) (3.4 mL) was degassed and added to the solution which was stirred at rt for 20 min. In a separate flask, Pd(dppf)Cl$_2$•CH$_2$Cl$_2$ (277 mg, 0.34 mmol) and vinyl bromide 2.50 (2.32 g, 10.2 mmol) were dissolved in degassed DMF (34
mL). This solution was added drop wise to the borane mixture and stirred overnight at rt. NaHCO$_3$ (sat. aq.) (15 mL) and H$_2$O (150 mL) were added. The resultant mixture was extracted with Et$_2$O (3 x 50 mL). The combined organic layers were concentrated. To this crude mixture were added THF (85 mL) and 1M HCl (aq) (5 mL) and this was stirred for 1 h. NaHCO$_3$ (sat. aq.) (80 mL) was added. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated. Purification by flash column chromatography (5% → 10% EtOAc/Hexanes) on silica gel gave methyl ketone 2.43 as a clear oil (1.06 g, 1.67 mmol, 49% yield). [α]$_D^{22}$ = −11.7º (c 1.00, CH$_2$Cl$_2$). IR (ATR) 3029, 2853, 1711, 1495, 1453, 1352, 1072 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.41 – 7.20 (m, 20H), 5.07 (s, 1H), 4.94 – 4.83 (m, 3H), 4.78 (d, J = 11.9 Hz, 1H), 4.65 (d, J = 11.0 Hz, 1H), 4.60 (d, J = 10.9 Hz, 1H), 4.48 (d, J = 11.9 Hz, 1H), 4.42 (d, J = 11.9 Hz, 1H), 4.31 (d, J = 11.8 Hz, 1H), 3.99 – 3.85 (m, 2H), 3.75 (s, 1H), 3.37 – 3.23 (m, 3H), 3.17 (t, J = 9.5 Hz, 1H), 2.69 (d, J = 15.0 Hz, 1H), 2.19 (s, 3H), 2.12 – 2.03 (m, 1H), 0.64 (d, J = 6.5 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 212.90, 142.90, 138.53, 138.42, 138.24, 136.67, 128.88, 128.71, 128.60, 128.57, 128.51, 128.46, 128.16, 127.95, 127.93, 127.87, 127.85, 127.58, 113.92, 86.45, 83.26, 83.05, 83.02, 78.16, 75.62, 75.12, 73.72, 72.95, 71.93, 38.05, 35.45, 27.94, 12.38. HRMS (ESI+) calcd for [C$_{41}$H$_{46}$O$_6$Na$^+$] requires m/z 657.3192, found 657.3195.
To a solution of lactone 2.37 (10.10 g, 20.03 mmol) in toluene (167 mL) in a sealed-tube pressure apparatus was added \( t \)-BuOAc (1.35 mL, 10.02 mmol) and \( \text{Cp}_2 \text{TiMe}_2 \) (20.8 g of a 24% w/w solution in toluene, 24.04 mmol). The pressure apparatus was sealed and heated at 80 °C overnight. The reaction was cooled to rt and hexane (600 mL) was added to precipitate the titanocene oxide byproduct. The reaction mixture was filtered over Celite and concentrated. Purification by flash column chromatography (5% \( \rightarrow \) 10% EtOAc/Hexanes) on silica gel gave enol ether 2.45 as a yellow oil (7.35 g, 14.64 mmol, 75%). \([\alpha]_{D}^{24} – 39.1^\circ \text{ (c 1.00, CH}_2\text{Cl}_2\)}. \textbf{IR (ATR)} 3029, 2873, 1757, 1735, 1657, 1495, 1453, 1355, 1283, 1207, 1107 cm\(^{-1}\). \textbf{\(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)\) \(\delta 7.38 – 7.27 \text{ (m, 15H), 4.92 (dd, J = 11.4, 5.5 Hz, 2H), 4.77 – 4.71 \text{ (m, 1H), 4.66 – 4.63 \text{ (m, 2H), 4.61 \text{ (s, 1H), 4.57 \text{ (d, J = 11.0 Hz, 1H), 4.39 \text{ (d, J = 11.9 Hz, 1H), 4.04 \text{ (d, J = 2.3 Hz, 1H), 3.98 – 3.92 \text{ (m, 1H), 3.85 \text{ (s, 3H), 3.67 \text{ (dd, J = 10.7, 2.3 Hz, 1H), 3.18 \text{ (dd, J = 10.0, 8.2 Hz, 1H), 2.27 – 2.17 \text{ (m, 1H), 0.70 \text{ (d, J = 6.6 Hz, 3H).}}} \right) \textbf{\(^{13}\text{C NMR\) (126 MHz, CDCl\(_3\)\) \(\delta 170.21, 156.64, 137.48, 137.11, 135.84, 127.88, 127.86, 127.59, 127.53, 127.48, 127.33, 127.28, 127.20, 127.12, 127.01, 126.92, 126.88, 126.72, 93.73, 83.37, 82.12, 80.22, 75.17, 74.16, 72.31, 72.16, 51.35, 36.23, 11.66.}} \textbf{HRMS (ESI\textsuperscript{+}) calcd for [C}\(_{31}\text{H}_{34}\text{O}_{6}\text{Na}\textsuperscript{+}] \text{ requires } m/z 525.2253, \text{ found 525.2255.}
A solution of enol ether 2.45 (7.20 g, 14.34 mmol) in THF (48 mL) was charged with 9-BBN (1.84 g, 15.06 mmol) and stirred for 1 h at rt. The reaction mixture was heated at 45 °C for 3 h and cooled to rt. 3M K$_3$PO$_4$ (aq) (12.0 mL) was degassed and added slowly to the borane solution which was stirred at rt for 20 min. In a separate flask, vinyl bromide 2.50 (3.58 g, 15.77 mmol) and XPhos Pd G3 (606 mg, 0.717 mmol) were dissolved in degassed DMF (72 mL). This solution was added dropwise to the borane mixture and the resultant mixture was stirred at rt overnight in the dark. The reaction was quenched by addition of water (500 mL), the layers separated, and the aqueous phase extracted with Et$_2$O (3 x 75 mL). The combined organic layers were washed with water (2 x 75 mL) and brine (1 x 75 mL). The combined aqueous layers were back-extracted with Et$_2$O (1 x 100 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated. Purification by flash column chromatography (5% → 10% EtOAc/Hexanes) on silica gel gave methyl ester 2.48 as a colorless oil (8.78 g, 13.49 mmol, 95% yield). [$\alpha$]$_D^{25}$ $-11.4^\circ$ (c 1.00, CH$_2$Cl$_2$). IR (ATR) 3028, 2851, 1756, 1731, 1651, 1602, 1495, 1453, 1358, 1283, 1207, 1164, 1072 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.42 – 7.21 (m, 20H), 5.08 (s, 1H), 4.95 – 4.82 (m, 4H), 4.62 (dd, J = 12.6, 11.0 Hz, 2H), 4.48 (d, J = 2.8 Hz, 2H), 4.34 (d, J = 12.0 Hz, 1H), 4.01 (d, J = 2.8 Hz, 1H), 3.92 (q, J = 13.1 Hz, 3H), 3.70 (s, 3H), 3.40 (dd, J = 10.4, 2.9 Hz, 1H), 3.36 – 3.14 (m, 2H), 2.63 (d, J = 15.0 Hz, 1H), 2.20 – 2.06 (m, 1H), 0.66 (d, J = 6.5 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 171.32, 143.05, 138.68, 138.48, 138.26, 136.97, 129.13, 129.01, 128.90, 128.55, 128.53, 128.51, 128.39, 128.24, 128.12, 128.11, 127.98, 127.86, 127.83, 127.75, 127.72, 127.49, 126.18, 126.16, 112.86, 86.67, 83.20, 82.06, 79.00, 76.56, 75.55, 75.14,
HRMS (ESI+) calcd for [C₄₁H₄₆O₇Na+] requires m/z 673.3141, found 673.3135.

Methyl ester 2.48 (7.88 g, 12.11 mmol) and NH(OMe)Me·HCl (3.54 g, 36.33 mmol) were charged with THF (140 mL) and cooled to -30 ºC. A solution of iPrMgCl (42.1 mL, 2M in THF) was added over 30 min by syringe pump at -30 ºC. The reaction mixture was allowed to warm to 0ºC and was stirred 45 min at this temperature. The reaction mixture was quenched by addition of NH₄Cl (sat. aq.) (100 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 75 mL) and the combined organic layers were dried over Na₂SO₄, filtered, and concentrated. Purification by flash column chromatography (30% EtOAc/Hexanes) on silica gel gave Weinreb amide 2.52 as a white gum (6.15 g, 9.05 mmol, 75% yield). [α]D₂⁵ –19.2° (c 1.00, CH₂Cl₂). IR (ATR) 3028, 2852, 1681, 1495, 1453, 1539, 1208, 1071 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.37 – 7.21 (m, 20H), 5.09 (s, 1H), 4.96 (s, 1H), 4.93 – 4.82 (m, 2H), 4.63 (t, J = 10.9 Hz, 1H), 4.32 (d, J = 12.0 Hz, 1H), 4.04 – 3.84 (m, 2H), 3.55 (s, 3H), 3.49 (dd, J = 10.3, 2.9 Hz, 1H), 3.19 (s, 3H), 2.63 (d, J = 14.8 Hz, 1H), 2.28 – 2.07 (m, 1H), 0.73 (d, J = 6.5 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 143.41, 138.81, 138.60, 138.34, 137.20, 129.13, 129.02, 128.94, 128.54, 128.53, 128.46, 128.38, 128.32, 128.16, 128.11, 128.09, 127.99, 127.96, 127.82, 127.70, 127.68, 127.44, 126.17, 112.72, 86.83,
HRMS (ESI+) calcd for \([\text{C}_{42}\text{H}_{49}\text{NO}_{7}\text{Na}^+]\) requires \(m/z\) 702.3407, found 702.3406.

Weinreb amide \(2.52\) (6.15 g, 9.05 mmol) was charged with THF (110 mL) and cooled to -78 °C. MeMgBr (5 mL, 3M in THF) was added and the reaction mixture was stirred 45 min at 0 °C. The reaction mixture was re-cooled to -78 °C. A second portion of MeMgBr (5 mL, 3M in THF) was added and the reaction mixture was stirred 30 min at 0 °C. The slurry was quenched by addition of NH\(_4\)Cl (sat. aq.) (100 mL), the layers separated, and the aqueous layer extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\), filtered, and concentrated. Purification by flash column chromatography (10% EtOAc/Hexanes) on silica gel gave methyl ketone \(2.43\) as a colorless oil (5.46 g, 8.60 mmol, 95% yield).

\section*{2.7. Spectral Data}
1H NMR (400 MHz, CDCl3)

[Diagram of a chemical structure with 2.14 indicated]
1H NMR (400 MHz, CDCl3)
13C NMR (126 MHz, CDCl3)

BnO\(\text{-}\)\(\text{Br} \quad 2.50\)
1H NMR (500 MHz, CDCl3)
13C NMR (126 MHz, CDCl3)

2.45
2.8. References


(50) Smith III, A. B.; Lin, Q.; Nakayama, K.; Boldi, A. M.; Brook, C. S.; McBriar, M.


Chapter 3 Synthesis of the EF fragment of spongistatin 1 and spongistatin 1 analog

3.1. Introduction

With a steady supply of the F-ring in hand, we were excited to test out the two key disconnects of the EF synthesis, the E-F coupling aldol and the installation of the chlorodiene sidechain. Fortunately, the literature suggested that the boron-mediated aldol would be successful as discussed in Chapter 1.\(^{24}\) The E and F-rings were successfully joined using this method. A new strained-silane asymmetric allylation methodology was developed during attempts to introduce the chlorodiene sidechain. This was used to complete the synthesis of EF fragment. Additionally, it expanded upon previous complex fragment couplings by allylation, previously reported by the Leighton group.\(^{3,33}\) The EF fragment was synthesized in 18 steps using practical and reliable chemistry. Four more steps furnished a spongistatin 1 analog containing the previously described ABCD* fragment.
3.1.1. Retrosynthesis of the EF fragment

Our strategy to the EF fragment 3.1 remained the same as that proposed in Chapter 2. A more detailed view follows (Scheme 3.1).

![Chemical structure](attachment:Scheme_3.1.png)

**Scheme 3.1. Retrosynthesis of 3.1**

We envisioned using a silane-mediated asymmetric allylation to join 3.3 and the chlorodiene aldehyde 3.2 to complete the side chain. This would set the final stereocenter and serve as a convergent route to the completed side chain. The allylic halide 3.3 that leads to a silane species would arise from the cyclization of aldol product 3.4, followed by protecting group manipulation and halogenation. Methyl ketone 3.5 and aldehyde 3.6 would be joined by the boron-mediated aldol used previously.\(^{61,112,113}\)
3.2. Preparation of allyl bromide 3.23 from methyl ketone 3.15

3.2.1. Synthesis of aldehyde 3.6

The first task towards examining the E-F aldol reaction was the preparation of aldehyde 3.6 (Scheme 3.2). Crimmins had previously used this aldehyde in his E-F coupling aldol.61 We decided to use the benzyl ether protecting group as on the F-ring to protect the right-hand side of the EF fragment, in order to simplify the deprotection strategy. However, we incorporated Leighton group strained-silane chemistry because of its advantages in simplicity and scalability. Selective mono-benzylation of 1,5-pentanediol 3.7, followed by Swern oxidation gave aldehyde 3.9 in 87% over the two-step sequence. This was subjected to a cis-crotylation with cis-crotyltrichlorosilane 3.11b and (R,R)-tridentate ligand 3.10 which afforded alcohol 3.12 in 79% yield.1 This was TES protected to give alkene 3.13 in quantitative yield. Finally, an Upjohn dihydroxylation, followed by cleavage with NaIO₄ afforded aldehyde 3.6 in 73% yield. This process was chosen over ozonolysis due to the latter’s incompatibility with benzyl ethers. Indeed, this route was used to produce over 17 grams of material in a single pass. With a large supply of aldehyde 3.6 in hand, we were ready to perform the key E-F coupling reaction.
3.2.2. Synthesis of TBS ether 3.18

At this point, we had completed our first approach to the F-ring and had a multigram supply of methyl ketone 3.15. We first tried similar aldol conditions to the Ley group using Cy$_2$BCl and triethylamine (Scheme 3.3). We were pleased to see that this reaction afforded β-hydroxy ketone 3.16 in 86% yield overall. However, the diastereoselectivity of this reaction was poor and gave only a 2.5:1 mixture of the desired C34-C35 syn product to the undesired anti product. This was surprising as examples using very similar substrates and conditions afforded 20:1 and 9:1 dr respectively.
The results of a boron-mediated aldol that uses 1,5-stereoinduction are notoriously difficult to rationalize when the methyl ketone contains both α and β-oxygenated stereocenters. Attempts to correct this ratio by changing temperature, solvent and base were unsuccessful. Fortunately, the two diastereomers were partially separable by careful column chromatography. This reaction was scalable due to a recent innovation in the purification described by the Ley group. The use of Cy₂BCl results in the production of Cy₂BOH as a byproduct, which is extraordinarily difficult to remove from the desired product. Previous efforts to solve this problem utilized oxidation to destroy the boron compound, however this produces cyclohexanol that can be equally as difficult to remove. Pleasingly, simply stirring the crude material with silica gel after an aqueous workup and before silica gel chromatography successfully removes the boron residues.

Partially purified β-hydroxy ketone 3.16 was subjected to the acid-mediated deprotection and cyclization to give methyl ketal 3.17 in 91% yield. At this stage, the syn and anti diastereomers were easier to separate by column chromatography and syn 3.17 was isolated cleanly. The overall yield of the syn diastereomer over this two-step sequence was 56%. This was protected as the TBS ether 3.18 in 81% yield. At this point, we had successfully joined the E and F rings and were ready to install the side chain after protecting group manipulation and the installation of an allylic halide at C47.
3.2.3. Synthesis of allyl bromide 3.23

With the E and F-rings successfully joined, we now turned our focus to the elaboration of the EF fragment. While benzyl groups were necessary to impart selectivity on the boron-mediated aldol reaction and survive the acid-catalyzed E-ring cyclization, they now posed a problem. There was no obvious method to remove the benzyl groups after installation of the chlorodiene side chain, so we decided to switch them to TES groups, analogous to the Smith route. The presence of the alkene precluded the use of simple hydrogenation with palladium. Reductive debenzylation with LiDBB afforded tetraol 3.19 in 82% yield (Scheme 3.4). Re-protection with TES-Cl gave TES ether 3.20 in 93% yield. TES ether was selected as the protecting group in order to intersect with a known EF fragment, ensuring compatibility for downstream chemistry with the later coupling of the EF and ABCD* fragments.
The next transformation was a one-pot ozonolysis and α-methylenation. Following ozonolysis and reductive quench with dimethyl sulfide, Eschenmoser salt was added with triethylamine to afford enal 3.21 in 54% yield. This reaction afforded a complex mixture containing an additional enal, which was identified as the trisubstituted alkene isomer. Additionally, this reaction proved difficult to reproduce on scale. Sudan III dye was used as a reaction progress indicator during the ozonolysis to attempt a more selective reaction, to no avail. Additionally, attempts to perform an alternative Lemieux–Johnson cleavage with OsO₄ and NaIO₄ were unsuccessful. Nonetheless, enal 3.21 was reduced with DIBAL to afford allyl alcohol 3.22 in 67% yield. This was smoothly transformed into allyl bromide 3.23 with an Appel reaction in 90% yield. This represented our first synthesis of the desired side chain allylation precursor. However, the difficulties in the transformation of the cis-hexenyl side chain into a usable allyl bromide had led us to devise the second F-ring route towards methyl ketone 3.5.
Scheme 3.4. Synthesis of allyl bromide 3.23

3.3. Preparation of allyl bromide 3.23 from methyl ketone 3.5

3.3.1. Synthesis of polyol 3.27

The final F-ring synthetic approach was designed to alleviate the issues presented in the previous section. The same approach to the synthesis of a polyol was used as before (Scheme 3.5). The boron-mediated aldol between methyl ketone 3.5 and aldehyde 3.6 was achieved in 84% yield and 11:1 dr to give 3.24. This was a notable improvement in diastereoselectivity over the previous aldol reaction (2.5:1 dr). This was a pleasant surprise as methyl ketones 3.15 and 3.5 are extremely similar. Separation of the syn and anti diastereomers was now facile at this stage. Pure syn 3.24 was cyclized to give methyl
ketal 3.25 in 70% yield. This was cleanly protected in 87% yield to give TBS ether 3.26. It should be noted that the next reaction required rigorous purification of 3.26 to remove any trace of 2,6-lutidine.

Debenzylation was performed to afford polyol 3.27 in 86% yield. At this stage, the material was notably obtained as a white solid. Therefore, this molecule was carefully crystallized by slow evaporation of a dichloromethane solution to provide X-ray crystallography quality material (Figure 3.1). This was crystallized by Dr. Dan Paley at the Shared Materials Characterization Laboratory. This crystal structure confirmed 10 of the 11 stereocenters on the EF fragment. At this point, we needed to transform polyol 3.27 into allyl bromide 3.23.
Figure 3.1 Molecular structure of 3.27 (one of two independent molecules shown). Blue, silicon; red, oxygen; black, carbon; white circles, hydrogen. C-H hydrogens and the minor positions of the disordered Si(tBu)Me$_2$ group are omitted for clarity.

3.3.2. Synthesis of allyl bromide 3.23

Polyol 3.27 posed a challenge in selectively functionalizing the five hydroxyl groups to eventually furnish 3.23. Fortunately, there was a difference in reactivity between the primary alcohols and secondary alcohols. We initially envisioned selectively brominating the allylic alcohol under Appel conditions and protecting the remaining four alcohols as TES groups. Unfortunately, this proved to be unfeasible. The primary alcohol
at C29 was more reactive than the allylic alcohol at C47 due to stereoelectronic factors, so the reaction resulted in 3.28, albeit in an inseparable mix with triphenylphosphine oxide (Scheme 3.6). Instead, we protected the C29 alcohol as a TES group to give 3.29 in 42% yield. Unfortunately, the bromination of this compound was unsuccessful.

Scheme 3.6. Attempted syntheses of 3.23

Finally, we devised a reliable route to 3.23 in four steps from polyol 3.27 (Scheme 3.7). The polyol was per-silylated and the primary TES ethers were selectively removed with potassium fluoride to give diol 3.30 in 74% yield. The C29 hydroxyl was selectively re-silylated with TES-Cl in 97% yield to afford allyl alcohol 3.22. This step was much more selective between the two primary alcohols compared to 3.27, likely due to the increased steric bulk from the TES groups near the allylic alcohol at C47. 3.22 was brominated as before to give allyl bromide 3.23 in 90% yield. This highly non-polar product was trivial to separate from the triphenylphosphine oxide byproduct and was obtained in high-yield reactions. With more 3.23 in hand, we were ready to develop a method that would be suitable for the side chain allylation.
3.4. Development of a one-pot asymmetric allylation

The Leighton group has been a pioneer in the asymmetric allylation of carbonyl compounds using strained silicon reagents.\textsuperscript{1,4,119–122} Sequential developments have improved allylations in regards to reactivity and ease-of-use. Commercially available EZ-crotyl reagents 3.31 require the isolation of a reactive silane complex by crystallization or air-free filtration and the use of an exogenous Lewis acid (Scheme 3.8A).\textsuperscript{4} This proves to be synthetically challenging and would require the formation and purification of an EF silane complex. This results in reduced yields especially on small scale. More recently however, former graduate student Dr. Linda Suen developed a methodology that does not require the isolation of a silane complex, using the tridentate ligand 3.10 and forming an \textit{in-situ} silane complex with DBU and trichlorosilane 3.11 (Scheme 3.8B).\textsuperscript{1} Addition of an aldehyde yields the homoallylic alcohol 3.32 in excellent yield and enantioselectivity. Despite this significant advance, this methodology still required the preformation and
isolation of an organotrichlorosilane, thus limited the scope and synthetic ease of the allylation procedure. The Suen methodology was successfully used to couple the AB and CD* fragments in high efficiency.\textsuperscript{33} The AB trichlorosilane was generated via the hydrosilylation of a diene and produced a clean trichlorosilane without purification.\textsuperscript{40}

\textbf{Scheme 3.8}. Previously developed allylations by the Leighton group: \textbf{A}) EZ-crotyl, \textbf{B}) tridentate ligands

Inspired by the application of this methodology towards coupling complex fragments, the Leighton group endeavored to develop a generalized procedure for telescoping the formation of allylic trichlorosilanes into an enantioselective allylation reaction. The most common method to synthesize allylic trichlorosilanes is the Benkeser-Furuya method followed by distillation or air-free filtration (Scheme 3.9).\textsuperscript{123,124} Filtration of an air-sensitive EF trichlorosilane was not appealing and distillation would be
impossible. It was hypothesized that the tridentate ligand 3.10 would be compatible with a wide variety of allylic trichlorosilanes, beyond the previously reported allyl and crotyl trichlorosilanes.

\[
\begin{align*}
\text{Cl}_2\text{R}_1\text{R}_2 & \quad \text{CuCl, HSiCl}_3 \\
\text{Et}_3\text{N} & \quad \text{Et}_2\text{O} \\
\text{Cl}_3\text{SiCl}_2\text{R}_1\text{R}_2
\end{align*}
\]

\[
\begin{align*}
3.33\text{a}: & \quad R_1 = R_2 = \text{H} \\
3.33\text{b}: & \quad R_1 = \text{Me}, R_2 = \text{H} \\
3.33\text{c}: & \quad R_1 = \text{H}, R_2 = \text{Me}
\end{align*}
\]

\[
\begin{align*}
3.11\text{a}: & \quad R_1 = R_2 = \text{H} \\
3.11\text{b}: & \quad R_1 = \text{Me}, R_2 = \text{H} \\
3.11\text{c}: & \quad R_1 = \text{H}, R_2 = \text{Me}
\end{align*}
\]

**Scheme 3.9.** Benkeser-Furuya synthesis of organotrichlorosilanes

Therefore, we envisioned performing the Benkeser-Furuya reaction on an allyl halide and directly adding tridentate ligand 3.10 and base to generate the desired silane complex *in-situ*, followed by the addition of aldehyde to yield the product (Scheme 3.10). This method would be amenable to a much greater range of allyl halides, especially those that are too high molecular weight to distill including 3.23. Former post-doctoral fellow Dr. Kevin Williamson and graduate student Makeda Tekle-Smith pioneered this methodology.

\[
\begin{align*}
\text{Cl}_2\text{R}_1\text{R}_2 & \quad 1. \text{CuCl, HSiCl}_3, \text{base} \\
& \quad 2. (R,R)-3.10, \text{base} \\
& \quad 3. R_2\text{CHO} \\
\text{OH} & \quad \text{CH}_2\text{Cl}_2
\end{align*}
\]

**Scheme 3.10.** One-pot alkylation using strained silane chemistry

3.4.1. **Optimization of the one-pot procedure**

The initial silylation of *trans*-crotyl chloride 3.33c into trichlorosilane 3.11c in dichloromethane was successful using copper (I) chloride and triethylamine (Scheme 3.11). This was notable because typical Benkeser-Furuya reactions typically use diethyl
ether as the solvent, generating a suspension. However, as previously shown in the optimization of asymmetric allylation methodology using tridentate ligand 3.10, the entire reaction mixture needed to be homogenous and therefore dichloromethane was used as the solvent as it can dissolve the generated ammonium salts. The success of the first step in the sequence was promising.

The next step was to test the complexation of (R,R)-3.10 with the generated trichlorosilane. Tridentate ligand and three equivalents of DBU were added and complex 3.34 was observed. Finally, addition of hydrocinnamaldehyde 3.35 produced the desired homoallylic alcohol 3.36 in 34% yield using this unoptimized one-pot procedure.

![Scheme 3.11](image)

**Scheme 3.11.** One-pot allylation to form 3.36

The reaction conditions were optimized with regards to base, catalyst and allyl halide choice (Tables 3.1, 3.2). It was confirmed that the reaction worked best using allyl bromides and copper (I) bromide. Additionally, it was found that the reaction required triethylamine for the silylation step and DBU for silane complexation step. At this point, the test substrate was changed to methallyl bromide because it is more similar to allyl
bromide 3.23. Following optimization, the substrate scope was significantly expanded to a wide variety of allyl bromides and aldehydes.

Table 3.1. Optimization of the copper catalyst

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<th>yieldb</th>
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<td>2</td>
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<td>66%</td>
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<td>5%</td>
<td>27%</td>
</tr>
</tbody>
</table>

*a*Unless otherwise noted, reactions were performed using 1 mmol allyl halide and 0.95 mmol hydrocinnamaldehyde. *b*Isolated yield.
3.5. Preparation of model coupling product 3.38

We decided to try a model coupling reaction in order to troubleshoot the key side chain allylation, expecting three key challenges initially. The first was that allyl bromide 3.23 was acid-sensitive because the TES groups. During the typical procedure for the one-pot allylation, the allyl bromide and trichlorosilane are dissolved in dichloromethane and added to a solution of triethylamine and copper (I) bromide. However, this would expose acid-sensitive 3.23 to the acidic trichlorosilane. A modified procedure was developed in which half of the triethylamine is added with the trichlorosilane and allyl bromide to prevent degradation. The second challenge was that chlorodiene 3.2 is very
unstable, so we wanted to test its stability under the reaction conditions. Finally, the allylation reactions are quenched with TBAF, which could remove the silyl groups on the EF fragment.

3.5.1 Synthesis of allyl bromide 3.43

We sought a model compound that contained sensitive primary TES ether and a methallyl bromide. Compound 3.43 was selected. Commercially available alcohol 3.39 was TES protected to give 3.40 in 94% yield (Scheme 3.12). This was epoxidized with mCPBA to give epoxide 3.41 in 75% yield. The epoxide was isomerized with LiTMP and Et$_2$AlCl to give allyl alcohol 3.42. The crude product was subjected to an Appel bromination to give allyl bromide 3.43 in 30% over two steps.

![Scheme 3.12. Synthesis of 3.43](image)

3.5.2 Synthesis of aldehyde 3.2

Although chlorodiene aldehyde 3.2 is known in the literature and has been used in multiple spongistatin 1 syntheses, all but one synthesis exclude experimental details on how to produce this sensitive compound. The reported Paterson route relied on the Horner-Wadsworth-Emmons reaction of 2-chloroacrolein. Unfortunately, the synthesis of
2-chloroacrolein using chlorine gas proved to be non-reproducible. Therefore, we envisioned a new synthesis of aldehyde 3.2 which skipped this step. Commercially available 2-chloro-2-propen-1-ol 3.44 was treated under a Swern oxidation (Scheme 3.13). The salts were crashed out with diethyl ether and the solution of 2-chloroacrolein underwent an air-free filtration and was treated with triethylphosphonacetate and NaHMDS. This avoids the isolation of 2-chloroacrolein and afforded ester 3.45 in 55% yield. The ester was reduced with DIBAL to give alcohol 3.46 in 74% yield. This was oxidized to give 3.2 in 89% yield and was used directly in the allylation reaction.

![Scheme 3.13. Synthesis of aldehyde 3.2](image)

Allyl bromide 3.43 and aldehyde 3.2 were combined under the modified allylation conditions. The amount of TBAF•3H₂O added at -40 °C was carefully controlled. The reaction was successful and afforded 3.47 in 63% yield and 90% ee (Scheme 3.14). With this promising result, we were finally ready to test the EF side chain allylation.
3.6. Introduction of the chlorodiene side chain and completion of EF fragment 3.51

3.6.1. Synthesis of allylation product 3.48

Initial observations during the reaction of 3.23 and aldehyde 3.2 showed the conversation to trichlorosilane was extremely sluggish at 0 °C (Scheme 3.15). Upon monitoring of the silylation step at room temperature, it was observed that the allyl bromide 3.23 was undergoing substantial decomposition. It was hypothesized that the EF allyl bromide might be too unstable under the reaction conditions. An EF allyl chloride variant might be a more suitable participant in this reaction.

However, as previously shown, the original trans-crotyl chloride gave much lower yields than the corresponding bromide. This was initially puzzling as both allyl halides undergo the silylation and ligand complexation steps with excellent conversion. Therefore, the natural conclusion was that the allylation step was the difference and was in turn caused by the presence or absence of Et₃N•HX salts. In order to solve the EF side
chain installation as well as substantially expand the substrate scope of the one-pot allylation methodology, conditions were optimized to enable chlorides as competent substrates. The Denmark group has previously reported problems with the reaction between aliphatic aldehydes and allyltrichlorosilane. This was hypothesized to result from the formation of an unreactive chlorohydrin derived from the aldehyde. In this case, the rate of allylation was improved by the addition of tetrabutylammonium bromide (TBAB).  

The addition of TBAB significantly improved the yield of the one-pot allylation when using an allyl chloride. It was found that the allylation step required the presence of bromide ions, whether from the substrate allyl bromide or added as an exogenous bromide source. The Et$_3$N•HCl salts generated in the silylation step might form the unreactive chlorohydrin. This advance served to greatly expand the substrate scope of this methodology to include the more stable and readily available allyl chlorides, as well as improve the yield when using allyl bromides. Although the discovery of TBAB would serve critical to the eventual success of the EF side chain allylation, the reaction did not initially work when using the EF allyl chloride and TBAB.

Eventually, several key advancements enabled the reaction to succeed. Initial results in the reaction of 3.23 and 3.2, gave 3.48 in 62% yield as a single diastereomer (Scheme 3.16). As previously discussed, addition of TBAB was found to improve the allylation step regardless of whether an allyl chloride or allyl bromide was used. Additionally, the methyl variant of the tridentate ligand 3.49 was used. This less-hindered version was more reactive and gave comparable stereoselectivity. Most importantly, the addition of excess 2,6-di-\textit{t}-butylpyridine was found to prevent acid-promoted
decomposition during the silylation. The E-ring methyl ketal is highly acid sensitive and was being degraded by the mild acid present during the one-pot allylation conditions. Although it was previously known that excess DBU or triethylamine would hinder the reaction, the extremely bulky 2,6-di-t-butylypyridine did not have this effect, instead only serving to successfully buffer the reaction. With this very promising result, we set out to redesign the allyl halide partner to reduce the overall step count.

Scheme 3.16. Synthesis of 3.48

3.6.2 Synthesis of EF fragment 3.53

Although the one-pot allylation was successful, the route to allyl bromide 3.23 had undesired protecting group manipulations both before and after the side chain allylation. Multiple silyl protection and deprotection steps reduced the step-economy of the route to 3.23. We would also need to convert the primary TES ether at C29 after the side chain allylation into a triphenylphosphonium salt. This would require a three-step sequence of deprotection, halogenation and phosphonium salt formation. During the expansion of the substrate scope of the one-pot allylation methodology, it was discovered
that the reaction was fully tolerant of a non-allylic primary chloride present on the allyl halide. Therefore, we saw an opportunity to streamline our synthesis by performing a double chlorination of diol 3.30. This was achieved using carbon tetrachloride and triphenylphosphine to give dichloride 3.48 in 87% yield (Scheme 3.17). The C29 primary chloride could be converted directly to the Wittig salt in one step. 3.50 was subjected to the same allylation conditions as 3.23 and afforded 3.51 in 52% yield, 94% based on recovered starting material. While this represented an impressive yield for such a complex fragment coupling, we wanted to optimize the reaction to make better use of this precious late state material.

Contemporaneous work by Makeda Tekle-Smith on a one-pot asymmetric allylation using propargyl chloride yielded an important realization. This silylation was also very sluggish and it was found that trichlorosilane was evaporating from the reaction mixture before it was consumed. Portion-wise addition of extra trichlorosilane during the reaction enabled efficient conversion. This strategy was applied to the coupling of 3.50 and 3.2 to solve the same problem. Additionally, the copper catalyst loading was increased to 25 mol % At this point, the allylation was optimized to give 3.51 in 71% yield, 94% brsm. TBS protection gave 3.52 in 90% yield. Finally, treatment with
triphenylphosphine and sodium iodide gave phosphonium salt 3.53 in 92% yield.\(^{54}\)

Scheme 3.17 Synthesis of Wittig salt 3.53

The route from methyl ketone 3.5 was used as the finalized version of the EF synthesis to give a few hundred milligrams of material. The synthesis of the EF fragment had a longest linear sequence of just 18 steps in 2% overall yield (Scheme 3.18). This represents the most step-economical synthesis of the EF fragment of spongistatin 1 to date. The two keys to this success were the rapid installation of the stereochemical array on the F-ring and the newly developed one-pot asymmetric allylation used to introduce the chlorodiene sidechain in a convergent and efficient manner.
Scheme 3.18 Synthesis of EF fragment 3.53
3.7. Preparation of spongistatin 1 analog 3.58

With an ample supply of both ABCD* and EF fragments, Makeda Tekle-Smith followed the original plan to couple them and complete the synthesis of spongistatin 1 analog. Using the exact EF fragment and a very similar ABCD fragment to the Smith route, she was able to closely follow literature precedent.\textsuperscript{48} ABCD* aldehyde 3.54 and EF Wittig salt 3.53 were successfully joined to form Wittig product 3.55 in 60\% yield, which is comparable to the yield using natural ABCD (Scheme 3.19). This underwent selective silyl deprotection with TBAF•3H\textsubscript{2}O to afford seco-acid 3.56 in 83\% yield. This was a slightly improved yield, likely due to the higher reliability of using solid TBAF•3H\textsubscript{2}O compared to the inconsistent commercially available TBAF in THF solution. Yamaguchi macrolactonization gave lactone 3.57 in 81\% yield. Finally, global deprotection with hydrofluoric acid produced spongistatin 1 analog 3.58 in 83\% yield. This was the first confirmation that the ABCD* fragment could be used to produce a new member of the spongistatin family.
Upon completion of the synthesis, we were eager to confirm its activity through biological testing. A 2-day cytotoxicity assay was performed using Ca46 lymphoma cells,
in collaboration with Dr. Dan Sackett at the National Institute of Health. The average GI$_{50}$ value was 0.065 nM over two assays. Although natural spongistatin 1 was not tested with this cell line, this was within the range of .04 nM to 1.1 nM observed over 60 cell lines. This confirmed that spongistatin 1 analog has potent cytotoxic activity. The synthesis of spongistatin 1 analog was completed and efforts are underway to synthesize more analogs that could be developed into antibody drug conjugates.

### 3.8. Summary, Conclusions and Outlook

Herein, we have described the synthesis of an EF Wittig salt suitable for coupling with any ABCD fragment. This was combined with the ABCD* fragment to successfully complete the synthesis of spongistatin 1 analog. The F-ring was prepared in large quantities in only eight steps. This validated the pseudosymmetric strategy to quickly build up stereochemical complexity.

The boron-mediated aldol reaction to connect the E and F-rings was high yielding and diastereoselective. This reaction introduced three more stereocenters to the molecule in a single step. The development of a one-pot asymmetric allylation led to a new generalized synthetic methodology with improved ease and scope over previous versions. This was successfully used to attach the side chain. This was a powerful proof of concept for the methodology, combining a heavily functionalized and sterically encumbered allyl halide with a very unstable aldehyde. This also represented the most efficient way to introduce the chlorodiene fragment. Additionally, a crystal structure of polyol 3.27 confirmed 10 of the stereocenters on the EF fragment.

The sequence from methyl ketone 3.5 to EF fragment 3.53 was achieved in 10 steps and 17% overall yield. This represents the most step-efficient route to the EF
fragment known. The longest linear sequence of the entire EF fragment synthesis was 18 steps and 2% overall yield. This route was highly efficient and was used to generate a few hundred milligrams of the EF Wittig salt. Just four more steps furnished spongistatin 1 analog. The biological testing results finally confirmed our structural hypothesis about the CD* spiroketal by proving that spongistatin 1 analog 3.58 has comparable biological activity to the natural spongistatin 1. With this knowledge, we have the capability to further our goal of developing spongistatin 1 analogs as potential therapeutics.
3.9. Experimental Procedures

**General Information.** All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring and dry solvents unless otherwise indicated. Degassed solvents were purified by passage through an activated alumina column. Et$_3$N and i-Pr$_2$NEt were distilled from CaH$_2$. Synthesis of cis-crotyl trichlorosilane, trans-crotyl chloride, tridentate ligands (R,R)-3.10 and (R,R)-3.49, and ABCD* 3.54 were conducted as previously described,$^{1,33}$ and all spectroscopic data were consistent with those reported for these compounds. Flash chromatography was performed with Silicycle SiliaFlash® P60 silica gel. pH 7 buffered silica gel was prepared by combining silica gel with 10% w/w dilute aqueous pH 7 phosphate buffer. Thin-layer chromatography (TLC) was carried out on glass backed silica gel TLC plates (250 mm) from Silicycle; visualization by UV light, KMnO$_4$ and/or ceric ammonium molybdenate (CAM). $^1$H NMR spectra were recorded on a Bruker AVIII 300 (300 MHz), AVIII 400 (400 MHz), or AVIII 500 (500 MHz) spectrometer and are reported in ppm, relative to residual protonated solvent peak (CDCl$_3$, 7.26 ppm; C$_6$D$_6$, 7.16 ppm; CD$_3$CN, 1.94 ppm; MeOH-d$_4$, 3.31 ppm). Data are reported as follows: (bs=broad singlet, s=singlet, d=doublet, t=triplet, m=multiplet, dd=doublet of doublets, ddd=doublet of doublet of doublets, ddt=doublet of doublet of triplets, td=triplet of doublets, q=quartet, p=quintet; coupling constant(s) in Hz; integration). Proton decoupled $^{13}$C NMR spectra were recorded on a Bruker AVIII 500 (126 MHz) spectrometer and are reported in relative to residual protonated solvent peak (CDCl$_3$, 77.16 ppm; C$_6$D$_6$, 128.06 ppm; CD$_3$CN, 1.32 ppm; MeOH-d$_4$, 49.00 ppm). Infrared spectra were recorded on a Perkin-Elmer Spectrum Two (Diamond ATR) IR spectrometer. Optical rotations were recorded on a Jasco DIP-1000 polarimeter. Mass
Spectroscopy data was obtained on a Waters XEVO G2-XS QToF mass spectrometer. X-ray crystallography data was collected on an Agilent SuperNova diffractometer using mirror-monochromated Cu Kα radiation.

3.9.1. Preparation of Aldehyde 3.6

NaH (3.25 g, 81.4 mmol, 60% in mineral oil) was to THF (100 mL) and cooled to 0 °C. A solution of 1,5-pentanediol 3.7 (49.5 g, 475 mmol) was dissolved in THF (100 mL) and added over 30 min to the NaH slurry by addition funnel. After stirring for 30 min at this temperature, a solution of BnBr (8.1 mL, 67.8 mmol) was dissolved in THF (100 mL) and added slowly by additional funnel to the reaction mixture that was stirred for 20 h at rt. H₂O (10 mL) was added to quench the reaction. The entire reaction mixture was concentrated to remove THF. The crude residue was partitioned between H₂O (500 mL) and EtOAc (125 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H₂O (6 x 100 mL), dried over Na₂SO₄ and concentrated to afford 3.8 contaminated with mineral oil. Spectroscopic data was consistent with that previously reported for this compound. This was used directly in the following reaction.
DMSO (8.7 mL, 122 mmol) was added dropwise to a -78 °C solution of oxalyl chloride (8.7 mL, 102 mmol) in CH₂Cl₂ (55 mL). The mixture was stirred for 10 min, then a solution of alcohol 3.8 dissolved in CH₂Cl₂ (110 mL) was added dropwise by additional funnel. The mixture was stirred at -78 °C for 30 min before Et₃N (56 mL, 407 mmol) was added dropwise. The reaction mixture was allowed to warm to rt and stirred another 30 min. Cold H₂O (50 mL) was added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 200 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated. Purification by flash column chromatography (10% → 15% EtOAc/Hexanes) on silica gel gave aldehyde 3.9 as a yellow oil (11.5 g, 59.8 mmol, 87% yield over two steps). Spectroscopic data was consistent with that previously reported for this compound.

(R,R)-3.10 (25.24 g, 86.90 mmol) was dissolved in CH₂Cl₂ (278 mL) and cooled to 0 °C. DBU (39.00 mL, 260.7 mmol) was added, followed by dropwise addition of cis-crotyl trichlorosilane 3.11b (14.6 mL, 95.60 mmol). The reaction was warmed to rt and stirred 1 h. The reaction was cooled to 0 °C and aldehyde 3.9 (15.87 g, 82.60 mmol) was
added dropwise and the reaction was stirred for 3 h at this temperature. The reaction was
concentrated, resuspended in Et₂O (40 mL) and stirred for 1 h to precipitate salts. The
reaction mixture was filtered, treated with TBAF (95 mL, 1M in THF) and stirred for 2 h.
1M HCl (aq.) (400 mL) was added and the mixture was extracted with Et₂O (3 x 400 mL).
The combined organic layers were washed with H₂O (2 x 100 mL) and NaHCO₃ (sat. aq)
(100 mL). The organic layers was dried over Na₂SO₄, filtered, and concentrated to afford
crude product. The aqueous layers were combined and treated with 1M NaOH (aq) (400
mL) and extracted with CH₂Cl₂ (3 x 400 mL). These organic layers were combined,
washed with H₂O (100 mL) and brine (100 mL), dried over Na₂SO₄, filtered and
concentrated to give recovered ligand. The crude product was purified by flash column
chromatography (0% → 30% EtOAc/Hexanes) on silica gel to give alcohol 3.12 as a
clear oil (16.2 g, 65.3 mmol, 79% yield, 97% ee). [α]D²⁵ +17.7° (c 1.00, CH₂Cl₂). IR
(ATR) 3420, 2934, 2859, 1738, 1638, 1453, 1363, 1098 cm⁻¹. ¹H NMR (500 MHz,
CDCl₃) δ 7.38 – 7.26 (m, 5H), 5.92 – 5.65 (m, 1H), 5.09 (d, J = 5.1 Hz, 1H), 5.06 (s, 1H),
4.50 (s, 2H), 3.53 – 3.44 (m, 3H), 2.27 (q, J = 6.6 Hz, 1H), 1.72 – 1.35 (m, 6H), 1.02 (d, J
= 6.8 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 141.13, 138.69, 128.47, 127.77, 127.63,
115.40, 74.70, 73.03, 70.43, 43.56, 33.84, 29.83, 22.93, 14.18. HRMS (ESI+) calcd for
[C₁₆H₂₄O₂Na⁺] requires m/z 271.1674, found 271.1667.
Alcohol (16.16 g, 65.06 mmol) was dissolved in CH$_2$Cl$_2$ (325 mL) and cooled to 0 °C. DMAP (794 mg, 6.50 mmol) and Et$_3$N (13.6 mL, 97.5 mmol) were added, and then TES-Cl (13.1 mL, 78.1 mmol) was added dropwise. The reaction was warmed to rt, stirred for 3 h, quenched with MeOH (2.62 mL, 65 mmol) and concentrated. The crude mixture was suspended in hexane and stirred for 20 min. The mixture was filtered and concentrated. Purification by flash column chromatography (0 → 5% EtOAc/Hexanes) on silica gel afforded TES ether 3.13 as a colorless oil (23.6 g, 64.35 mmol, 99%). $\left[\alpha\right]_D^{23}$ +15.8° (c 1.00, CH$_2$Cl$_2$). IR (ATR) 2951, 2910, 2874, 1639, 1454, 1413, 1360, 1237, 1100, 1006 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.38 – 7.27 (m, 5H), 5.93 – 5.76 (m, 1H), 5.00 (d, J = 6.9 Hz, 1H), 4.98 (s, 1H), 4.50 (s, 2H), 3.55 (q, J = 7.5 Hz, 1H), 3.46 (td, J = 6.6, 1.0 Hz, 2H), 2.41 – 2.16 (m, 1H), 1.67 – 1.24 (m, 6H), 0.96 (t, J = 7.8 Hz, 9H), 0.60 (q, J = 7.9 Hz, 6H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 141.55, 138.84, 128.47, 127.73, 127.59, 114.06, 76.16, 73.01, 70.58, 43.19, 33.87, 30.15, 22.24, 15.17, 7.17, 5.36. HRMS (ESI+) calcd for [C$_{22}$H$_{39}$O$_2$SiNa$^+$] requires m/z 363.2719, found 363.2715.

To a solution of alkene (23.6 g, 64.35 mmol) in THF (90 mL), acetone (90 mL) and pH 7 buffer (90 mL) was added OsO$_4$ (3.05 ml, 1.3 mmol, 4% in water) dropwise, followed by NMO (9.96 g, 85.00 mmol). The mixture was rapidly stirred for 24 h, then Na$_2$SO$_3$ (16.39 g, 130 mmol) in water (400 mL) was added and stirred for 1 h. The mixture was diluted with brine (200 mL) and extracted with EtOAc (3 x 400 mL). The
combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated to give crude diol 3.14 that was used directly in the next step.

Crude diol 3.14 was dissolved in THF (900 mL) and pH 7 buffer (230 mL), then NaIO$_4$ (27.8 g, 130 mmol) was added. After stirring for 20 h, the reaction was diluted with brine (1 L) and extracted with EtOAc (3 x 500 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated. Purification by flash column chromatography ($0 \rightarrow 5\%$ EtOAc/Hexanes) on pH 7 buffered silica gel afforded aldehyde 3.6 as a colorless oil (17.3 g, 47.45 mmol, 73% yield over two steps). $[\alpha]_D^2^4$ +35.93° (c 1.00, CH$_2$Cl$_2$). IR (ATR) 2938, 2874, 1724, 1454, 1360, 1238, 1101, 1030 cm$^{-1}$. $^1$H NMR (500 MHz, C$_6$D$_6$) $\delta$ 9.62 (s, 1H), 7.32 (d, J = 7.0 Hz, 2H), 7.20 (t, J = 7.6 Hz, 2H), 7.11 (t, J = 7.3 Hz, 1H), 4.34 (s, 2H), 4.01 – 3.94 (m, 1H), 3.29 (t, J = 6.2 Hz, 2H), 2.10 – 2.01 (m, 1H), 1.55 – 1.17 (m, 6H), 1.03 – 0.89 (m, 12H), 0.55 (q, J = 8.0 Hz, 6H). $^{13}$C NMR (126 MHz, C$_6$D$_6$) $\delta$ 203.32, 139.42, 128.59, 127.78, 127.70, 73.11, 72.13, 70.18, 51.39, 35.03, 30.22, 22.95, 7.63, 7.18, 5.52. HRMS (ESI+) calcd for [C$_{21}$H$_{36}$O$_3$SiNH$_4$+] requires m/z 382.2777, found 382.2781.

3.9.2. Preparation of TBS ether 3.18
Methyl ketone 3.15 (3.88 g, 6.97 mmol) was charged with Et₂O (30 mL) and cooled to –78 °C. Cy₂BCl (3.1 mL, 13.9 mmol) was added, followed by Et₃N (2.9 mL, 20.9 mmol). The reaction was warmed to 0 °C and stirred for 3 h to give an off-white slurry. The mixture was re-cooled to –78 °C and a solution of aldehyde 3.6 (7.64 g, 20.9 mmol) in Et₂O (5 mL) was added. The reaction was stirred 4 h at –78°C, 14 h at –60 °C, and then 1 h at 0 °C. The slurry was quenched by addition of NH₄Cl (sat. aq.) (100 mL), the layers separated, and the aqueous phase extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated in vacuo to ~50 mL. pH 7 buffered silica gel was added and the yellow solution was stirred at rt for 30 min, then filtered with EtOAc washings (3 x 100 mL) of the filter cake. The filtrate was concentrated to afford the crude product as a yellow oil. Purification by flash column chromatography (5% → 20% EtOAc/Hexanes) on pH 7 buffered silica gel gave 3.16 as a mix of diastereomers as a pale yellow oil (5.53 g, 6.0 mmol, 86% yield, 2.5:1 syn:anti). ¹H NMR (500 MHz, C₆D₆) δ 7.37 – 7.02 (m, 20H), 5.45 (dtd, J = 9.2, 6.4, 3.0 Hz, 2H), 4.87 (t, J = 11.3 Hz, 1H), 4.79 – 4.69 (m, 3H), 4.50 (t, J = 11.4 Hz, 1H), 4.43 (dd, J = 11.4, 3.6 Hz, 1H), 4.36 (s, 3H), 4.32 (d, J = 5.7 Hz, 1H), 4.22 (dd, J = 11.4, 4.7 Hz, 1H), 4.01 (q, J = 2.4 Hz, 1H), 3.92 – 3.86 (m, 1H), 3.45 (dd, J = 10.3, 2.5 Hz, 1H), 3.41 – 3.33 (m, 4H), 3.23 – 3.17 (m, 2H), 3.10 – 3.00 (m, 2H), 2.90 – 2.80 (m, 1H), 2.39 – 2.32 (m, 1H), 2.29 – 2.21 (m, 1H), 2.17 – 2.06 (m, 2H), 1.92 – 1.84 (m, 1H), 1.77 –
1.24 (m, 17H), 1.23 – 1.04 (m, 7H), 1.01 (d, J = 7.9 Hz, 12H), 0.85 (d, J = 6.9 Hz, 1H), 0.78 (d, J = 6.5 Hz, 1H), 0.76 – 0.69 (m, 4H), 0.64 (q, J = 8.0 Hz, 6H). This mixture was used directly in the next step.

Alcohol 3.16 (5.53 g, 6.0 mmol, 2.5:1 mix) was charged with dry MeOH (120 mL). Trimethylorthoformate (11.8 mL, 108 mmol) and PPTS (271 mg, 1.08 mmol) were added sequentially and the resulting mixture was stirred 2 h. The reaction was slowly quenched by addition of NaHCO$_3$ (sat. aq.) (150 mL) and the mixture extracted with EtOAc (3 x 125 mL). The combined organic layers were washed with brine (100 mL), dried over Na$_2$SO$_4$, filtered, and concentrated. Purification by flash column chromatography (10 → 25% EtOAc/Hexanes with 1% Et$_3$N) on silica gel afforded pure syn-methyl ketal 3.17 as a clear oil (3.20 g, 3.89 mmol, 56% yield of syn diastereomer over two steps).

A solution of TBS-OTf (0.29 mL, 1.26 mmol) and 2,6-Lutidine (1.47 mL, 12.6 mmol) in THF (4 mL) was cooled to −78°C and prestirred 10 min. The mixture was then added dropwise to a solution of alcohol 3.17 (515 mg, 0.63 mmol) in THF (30 mL) at −78°C. The reaction was stirred 1 h, then quenched by addition of NaHCO$_3$(sat. aq) (30 mL)
and diluted with EtOAc (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 \times 15 mL). The organic layers were combined, washed with brine (100 mL), dried over Na$_2$SO$_4$, filtered, and concentrated. Purification by flash column chromatography (2\% \rightarrow 10\% EtOAc/Hexanes with 1\% Et$_3$N) on silica gel afforded TBS ether 3.18 (476 mg, 0.51 mmol, 81\% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.62 – 6.81 (m, 20H), 5.31 (d, $J = 7.8$ Hz, 2H), 4.91 (d, $J = 11.7$ Hz, 1H), 4.86 – 4.73 (m, 2H), 4.65 – 4.45 (m, 4H), 4.18 – 4.09 (m, 1H), 3.98 – 3.86 (m, 1H), 3.80 (s, 1H), 3.58 – 3.46 (m, 3H), 3.24 – 3.02 (m, 7H), 2.34 – 2.25 (m, 2H), 2.07 – 1.18 (m, 19H), 0.88 (s, 9H), 0.44 (d, $J = 6.4$ Hz, 3H), 0.00 (d, $J = 9.1$ Hz, 6H).

3.9.3. Preparation of allyl bromide 3.23

To a $-78\,^\circ$C solution of TBS ether 3.18 (600 mg, 0.641 mmol) in THF (30 mL) was added LiDBB [(~0.48 M in THF) freshly prepared by sonication of Li granules (117 mg, 16.9 mmol) and 4,4-di-$t$-butyl-biphenyl (4.10 g, 15.4 mmol) in THF (35 mL) at 0 °C for 3.5 h] slowly via syringe. The reaction was stirred at $-78\,^\circ$C for 1 h, then at $-40\,^\circ$C for 2 h and finally $-20\,^\circ$C for 1 h. The reaction was then quenched by the addition of NH$_4$Cl (sat. aq.) (50 mL), diluted with ethyl acetate (50 ml) and warmed to room temperature. The aqueous phase was extracted with EtOAc (75 ml) and CH$_2$Cl$_2$ (2 \times 25 ml). The
combined organic extracts were dried over Na₂SO₄, filtered, and concentrated. Purification by flash column chromatography (1% to 10% MeOH/CH₂Cl₂) on silica gel afforded tetraol 3.19 (304 mg, 0.53 mmol, 82% yield) as an amorphous white solid. Spectroscopic data was consistent with that previously reported for this compound.

To a 0 °C solution of tetraol 3.19 (840 mg, 1.46 mmol) in dry DMF (81 ml) was added imidazole (2.98 g, 43.8 mmol). TES-Cl (4.9 mL, 28.9 mmol) was added dropwise over 15 min. The reaction mixture was stirred overnight at rt and diluted with Et₂O (75 mL). This mixture was slowly added to a stirred 0 °C solution of NaHCO₃(sat. aq) (100 mL). The layers were separated and the aqueous layer was extracted with Et₂O (3 x 50 mL). The combined organic layers were washed with H₂O (2 x 50 mL) and brine (50 mL). The combined aqueous layers were extracted with Et₂O (75 mL), which was added to the combined organic layers were all dried over Na₂SO₄, filtered and concentrated. Purification by flash column chromatography (0% → 2% EtOAc/Hexanes with 1% Et₃N) on silica gel afforded TES ether 3.20 as a clear oil (1.40 g, 1.36 mmol, 93% yield). Spectroscopic data was consistent with that previously reported for this compound.
A solution of **3.20** (265 mg, 0.242 mmol) in CH$_2$Cl$_2$ (18 mL) was cooled to -78 °C while flushing with O$_2$ over 5 min. The reaction solution was flushed with O$_3$ until the solution turned blue (~5 min.). The resulting solution was flushed with O$_2$ for 5 min to give a colorless solution. Et$_3$N (1.68 mL, 12.1 mmol) and Me$_2$S (0.17 mL, 2.42 mmol) were added. The solution was allowed to warm to rt overnight. Eschenmoser’s salt (224 mg, 1.21 mmol) was added and the reaction mixture was stirred for 16 h. The reaction was quenched by the addition of NaHCO$_3$(sat. aq) (15 mL) and the layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 10 mL). The combined organic layers were washed with H$_2$O (10 mL) and brine (10 mL), dried over Na$_2$SO$_4$, filtered and concentrated. Purification by flash column chromatography (0% → 4% EtOAc/Hexanes) on pH 7 buffered silica gel afforded enal **3.21** as a clear oil (134 mg, 0.132 mmol, 54% yield). Spectroscopic data was consistent with that previously reported for this compound.

To a -78 °C solution of enal **3.21** (150 mg, 0.147 mmol) in CH$_2$Cl$_2$ (18 mL) was added DIBAL (0.28 mL, 1M in hexanes) dropwise. The solution was stirred for 10, then
quenched with Rochelle’s Salt (sat. aq) (20 mL) and stirred vigorously at rt for 2 h. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 15 mL). The combined organic layers were washed with NaHCO₃(sat. aq) (25 mL), dried over Na₂SO₄, filtered and concentrated. Purification by flash column chromatography (0% → 7% EtOAc/Hexanes with 1% Et₃N) on silica gel afforded allyl alcohol 3.22 as a clear oil (101 mg, 0.10 mmol, 67% yield). Spectroscopic data was consistent with that previously reported for this compound.

To a 0 ºC solution of allyl alcohol 3.23 (77 mg, 0.075 mmol) in CH₂Cl₂ (3 mL) was added Et₃N (0.11 mL, 0.75 mmol), PPh₃ (59 mg, 0.225 mmol), and CBr₄ (75 mg, 0.225 mmol) sequentially. The reaction mixture was stirred at rt for 1 h, and then quenched by addition of NaHCO₃(sat. aq) (5 mL). The layers were separated and the aqueous layer was extracted with Et₂O (2 x 5 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. Purification by flash column chromatography (0% → 3% EtOAc/Hexanes with 1% Et₃N) on silica gel afforded allyl bromide 3.23 as a pale oil (73 mg, 0.067 mmol, 90% yield). Spectroscopic data was consistent with that previously reported for this compound.

3.9.4. Preparation of polyol 3.27
Methyl ketone 3.5 (5.23 g, 8.24 mmol) was charged with Et₂O (33 mL) and cooled to –78 °C. Cy₂BCl (3.6 mL, 16.48 mmol) was added, followed by Et₃N (3.42 mL, 24.72 mmol). The reaction was warmed to 0 °C and stirred for 3 h to give an off-white slurry. The mixture was re-cooled to –78 °C and a solution of aldehyde 3.6 (9.01 g, 24.72 mmol) in Et₂O (9 mL) was added. The reaction was stirred 4 h at –78°C, 14 h at –60 °C, and then 1 h at 0 °C. The slurry was quenched by addition of NH₄Cl (sat. aq.) (150 mL), the layers separated, and the aqueous layer extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated in vacuo to ~100 mL. pH 7 buffered silica gel was added and the yellow solution was stirred at room temperature for 30 min, then filtered with EtOAc washings (3 x 100 mL) of the filter cake. The filtrate was concentrated under reduced pressure to afford the crude product as a yellow oil. Purification by flash column chromatography (5% → 20% EtOAc/Hexanes) on pH 7 buffered silica gel gave 3.24 as a pale yellow oil (6.89 g, 6.88 mmol, 84% yield, 11:1 syn:anti). Major Diastereomer (syn): [α]D²⁰ −28.5° (c 2.00, CH₂Cl₂). IR (ATR) 3511, 3029, 2873, 1711, 1494, 1453, 1360, 1091, 1070 cm⁻¹. ¹H NMR (500 MHz, C₆D₆) δ 7.37 (d, J = 7.5 Hz, 2H), 7.28 – 7.35 (m, 5H), 7.14 – 7.24 (m, 8H), 7.00 – 7.13 (m, 10H), 5.29 (s, 1H), 5.05 (s, 1H), 4.85 (d, J = 11.0 Hz, 1H), 4.75 – 4.79 (m, 1H), 4.76 (d, J = 10.6 Hz, 1H), 4.73 (d, J = 11.0 Hz, 1H), 4.49 (d, J = 11.6 Hz, 1H), 4.44 (ABq, 2H,
$\Delta \nu_{AB} = 18.1$ Hz, $J_{AB} = 11.9$ Hz), 4.43 (d, $J = 11.5$ Hz, 1H), 4.36 (s, 2H), 4.22 (d, $J = 11.5$ Hz, 1H), 4.01 (ABq, 2H, $\Delta \nu_{AB} = 37.3$ Hz, $J_{AB} = 13.2$ Hz), 4.00 – 4.03 (m, 1H), 3.84 (d, $J = 2.5$ Hz, 1H), 3.45 (dd, $J = 17.2$, 9.8 Hz, 1H), 3.43 (td, $J = 9.4$, 2.5 Hz, 1H), 3.37 (dd, $J = 10.2$, 2.5 Hz, 1H), 3.34 (t, $J = 6.4$ Hz, 2H), 3.28 (d, $J = 1.4$ Hz, 1H), 3.21 (t, $J = 9.3$ Hz, 1H), 3.01 (dd, $J = 10.4$, 8.9 Hz, 1H), 2.75 (d, $J = 14.5$ Hz, 1H), 2.69 (dd, $J = 17.3$, 2.3 Hz, 1H), 2.35 (qq, $J = 10.1$, 6.4 Hz, 1H), 2.20 (dd, $J = 15.0$, 9.7 Hz, 1H), 1.54 – 1.75 (m, 5H), 1.42 (p, $J = 7.7$ Hz, 2H), 1.12 (d, $J = 7.0$ Hz, 3H), 1.01 (t, $J = 7.9$ Hz, 9H), 0.73 (t, $J = 7.9$ Hz, 3H), 0.63 (q, $J = 7.9$ Hz, 6H). $^{13}$C NMR (126 MHz, C$_6$D$_6$) $\delta$ 213.8, 144.8, 140.0, 140.0, 139.8, 139.7, 138.5, 129.3, 129.3, 129.2, 129.2, 129.1, 129.1, 128.9, 128.8 128.7, 128.6, 128.5, 128.4, 128.3, 128.3, 128.3, 128.2, 128.2, 128.2, 114.0, 87.2, 84.7, 84.2, 83.4, 78.9, 78.0, 75.9, 75.4, 74.1, 73.9, 73.7, 72.8, 71.2, 70.9, 45.9, 42.0, 38.9, 36.8, 35.7, 31.1, 23.2, 13.1, 8.1, 7.9, 6.4. HRMS (ESI+) calcd for $[C_{62}H_{82}O_9SiNa^+]$ requires $m/z$ 1021.5626, found 1021.5626.

Alcohol 3.24 (6.89 g, 6.90 mmol) was charged with dry MeOH (138 mL). Trimethylorthoformate (13.8 mL, 124 mmol) and PPTS (607 mg, 2.42 mmol) were added sequentially and the resulting mixture was stirred 2 h. The reaction was slowly quenched by addition of NaHCO$_3$ (sat. aq.) (175 mL) and the mixture extracted with EtOAc (3 x 125 mL). The combined organic layers were washed with brine (100 mL), dried over
Na$_2$SO$_4$, filtered, and concentrated. Purification by flash column chromatography (10 → 25% EtOAc/Hexanes with 1% Et$_3$N) on silica gel afforded hemiketal 3.25 as a clear oil (4.47 g, 5.00 mmol, 70% yield). [α]$^D_{20}$ +19.0º (c 2.0, CH$_2$Cl$_2$). IR (ATR) 3527, 3029, 2858, 1495, 1454, 1356, 1213, 1090, 1062, 1025 cm$^{-1}$. $^1$H NMR (500 MHz, C$_6$D$_6$) δ 7.40 (t, $J = 7.0$ Hz, 4H), 7.35 (d, $J = 7.0$ Hz, 2H), 7.31 (d, $J = 7.4$ Hz, 2H), 7.24 (d, $J = 7.0$ Hz, 2H), 7.00 – 7.21 (m, 15 H), 5.39 (s, 1H), 5.17 (s, 1H), 4.99 (d, $J = 11.2$ Hz, 1H), 4.92 (d, $J = 11.4$ Hz, 1H), 4.74 (d, $J = 11.4$ Hz, 1H), 4.58 (d, $J = 11.1$ Hz, 1H), 4.55 (d, $J = 11.6$ Hz, 1H), 4.47 (d, $J = 11.7$ Hz, 2H), 4.37 (d, $J = 12.1$ Hz, 1H), 4.36 (s, 2H), 4.22 (d, $J = 12.7$ Hz, 1H), 4.12 – 4.16 (m, 1H), 4.10 (d, $J = 12.7$ Hz, 1H), 3.90 – 3.96 (m, 1H), 3.87 (d, $J = 9.0$ Hz, 1H), 3.58 (td, $J = 9.0$, 2.6 Hz, 1H), 3.56 (s, 1H), 3.38 (t, $J = 6.1$ Hz, 2H), 3.27 (t, $J = 9.1$ Hz, 1H), 3.14 (dd, $J = 10.2$, 1.3 Hz, 1H), 3.06 (dd, $J = 10.5$, 8.7 Hz, 1H), 2.95 (s, 3H), 2.83 (d, $J = 14.1$ Hz, 1H), 2.49 (ABX, 2H, $\Delta v_{AB} = 22.8$ Hz, $J_{AB} = 15.3$ Hz, $J_{BX} = 3.3$ Hz, $J_{AX} = 2.1$ Hz), 2.32 (dd, $J = 14.9$, 9.4 Hz, 1H), 2.22 (ddt, $J = 16.7$, 10.4, 6.4 Hz, 1H), 1.76 – 1.83 (m, 1H), 1.67 – 1.75 (m, 2H), 1.65 (p, $J = 6.2$ Hz, 2H), 1.40 – 1.50 (m, 1H), 1.23 – 1.33 (m, 1H), 0.80 (d, $J = 7.1$ Hz, 3H), 0.71 (d, $J = 6.5$ Hz, 3H). $^{13}$C NMR (126 MHz, C$_6$D$_6$) δ 144.6, 140.2, 140.0, 140.0, 139.9, 139.7, 129.4, 129.2, 129.2, 129.1, 129.1, 128.9, 128.8, 128.7, 128.6, 128.5, 128.5, 128.4, 128.3, 128.3, 128.3, 128.3, 128.2, 128.2, 128.1, 115.1, 105.1, 87.7, 84.1, 80.9, 78.8, 77.6, 75.8, 75.5, 75.3, 74.1, 73.7, 72.6, 71.3, 70.9, 68.6, 48.0, 39.4, 38.5, 37.0, 33.8, 31.1, 30.8, 24.0, 13.8, 11.5. HRMS (ESI+) calcd for [C$_{57}$H$_{70}$O$_9$Na$^+$] requires m/z 921.4918, found 921.4922.
A solution of TBS-OTf (2.51 mL, 10.94 mmol) and 2,6-lutidine (4.23 mL, 36.48 mmol) in THF (24 mL) was cooled to −78°C and pre-stirred 5 min. The mixture was then added dropwise to a solution of hemiketal 3.25 (3.28 g, 3.65 mmol) in THF (180 mL) at −78°C. The reaction was stirred 1 h, then quenched by addition of NaHCO₃(sat. aq) (150 mL) and diluted with EtOAc (150 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 150 mL). The organic layers were combined, washed with brine (100 mL), dried over Na₂SO₄, filtered, and concentrated. Purification by flash column chromatography (10% EtOAc/Hexanes) on pH 7 buffered silica gel afforded TBS ether 3.26 as a pale yellow oil (3.15 g, 3.19 mmol, 87% yield). \([\alpha]_{D}^{21} +18.0^\circ \text{ (c 2.00, CH}_2\text{Cl}_2)\). IR (ATR) 3029, 2931, 2853, 1494, 1454, 1360, 1250, 1209, 1095, 1070, 1025 cm\(^{-1}\). \(^1\)H NMR (500 MHz, C\(_6\)D\(_6\)) δ 7.47 (d, \(J = 7.1\) Hz, 2H), 7.35 (t, \(J = 7.0\) Hz, 4H), 7.31 (d, \(J = 7.0\) Hz, 2H), 7.27 (d, \(J = 7.5\) Hz, 2H), 7.02 – 7.22 (m, 15 H), 5.38 (s, 1H), 5.16 (s, 1H), 5.07 (d, \(J = 11.3\) Hz, 1H), 4.88 (d, \(J = 11.4\) Hz, 1H), 4.80 (d, \(J = 11.5\) Hz, 1H), 4.67 (d, \(J = 11.2\) Hz, 1H), 4.53 (d, \(J = 11.2\) Hz, 2H), 4.44 (ABq, 2H, \(\Delta\nu_{AB} = 24.5\) Hz, \(J_{AB} = 12.5\) Hz), 4.36 (s, 2H), 4.31 – 4.36 (m, 1H), 4.19 (ABq, 2H, \(\Delta\nu_{AB} = 50.5\) Hz, \(J_{AB} = 13.2\) Hz), 3.86 (q, \(J = 3.1\) Hz, 1H), 3.65 (s, 1H), 3.55 (td, \(J = 7.7, 2.6\) Hz, 1H), 3.38 (t, \(J = 5.9\) Hz, 2H), 3.33 (t, \(J = 9.1\) Hz, 1H), 3.28 (d, \(J = 10.4\) Hz, 1H), 3.20 (s, 3H), 3.05 (dd, \(J = 10.4, 8.7\) Hz, 1H), 2.83 (d, \(J = 14.4\) Hz, 1H), 2.51 (dd, \(J = 15.5, 3.9\) Hz, 1H), 2.42 (dd, \(J = 14.7, 7.7\) Hz, 1H), 2.14 (tq, \(J = 10.2, 6.4\) Hz, 1H), 1.97 (dd, \(J = 15.0, 1.6\) Hz, 1H), 1.64 –
1.79 (m, 4H), 1.49 – 1.60 (m, 2H), 1.33 – 1.44 (m, 1H), 1.09 (s, 9H), 0.89 (d, J = 7.1 Hz, 3H), 0.76 (d, J = 6.5 Hz, 3H), 0.20 (s, 3H), 0.10 (s, 3H). $^{13}$C NMR (126 MHz, C$_6$D$_6$) δ 144.7, 140.2, 140.1, 129.2, 129.1, 129.1, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.3, 128.2, 128.1, 128.1, 114.7, 103.5, 87.9, 83.6, 80.4, 78.9, 77.6, 75.8, 75.7, 75.1, 74.6, 73.6, 72.8, 71.7, 71.0, 67.9, 47.9, 39.7, 39.2, 36.9, 33.8, 32.1, 31.1, 26.8, 24.0, 19.0, 13.9, 11.1, -3.6, -3.9. HRMS (ESI+) calcd for [C$_{63}$H$_{84}$O$_9$SiNa$^+$] requires m/z 1035.5782, found 1035.5789.

To a −78 °C solution of TBS Ether 3.26 (960 mg, 0.949 mmol) in THF (57 mL) was added LiDBB [(~0.48 M in THF) freshly prepared by sonication of Li granules (415 mg, 29.61 mmol) and 4,4-di-tert-butyl-biphenyl (7.28 g, 27.33 mmol) in THF (57 mL) at 0 °C for 3.5 h] slowly via syringe. The reaction was stirred at −78 °C for 2 h, then switched to a −30 °C bath and stirred for a further 16 h. The reaction was then quenched by the addition of NH$_4$Cl (sat. aq.) (150 mL), diluted with ethyl acetate (150 ml) and warmed to room temperature. The aqueous phase was extracted with ethyl acetate (75 ml) and methylene chloride (2 x 75 mL). The organic extracts were dried over Na$_2$SO$_4$, filtered, and concentrated. Purification by flash column chromatography (1% → 10% MeOH/CH$_2$Cl$_2$) on silica gel afforded polyol 3.27 as an amorphous white solid. (460 mg, 0.819 mmol 86% yield). X-ray quality crystals of 3.27 were obtained by slow evaporation
of a dichloromethane solution. $[\alpha]_D^{25} +22.2^\circ$ (c 1.00, MeOH). IR (ATR) 3316, 2942, 2831, 1448, 1401, 1402, 1113, 1023 cm$^{-1}$. $^1$H NMR (500 MHz, MeOH-d$_4$) $\delta$ 5.15 (d, J = 1.9 Hz, 1H), 5.02 (s, 1H), 4.25 – 4.17 (m, 1H), 4.08 (s, 2H), 3.86 (d, J = 2.8 Hz, 1H), 3.75 (s, 1H), 3.61 (t, J = 6.2 Hz, 2H), 3.41 – 3.34 (m, 4H), 3.32 (d, J = 10.3 Hz, 1H), 3.22 (s, 3H), 3.12 (d, J = 17.1 Hz, 2H), 2.70 (d, J = 14.5 Hz, 1H), 2.29 (dd, J = 14.6, 8.4 Hz, 1H), 2.10 (dd, J = 15.4, 3.9 Hz, 1H), 1.86 – 1.79 (m, 1H), 1.72 – 1.41 (m, 5H), 1.07 (d, J = 6.5 Hz, 3H), 0.96 (s, 9H), 0.93 (d, J = 7.1 Hz, 3H), 0.13 (s, 3H), 0.09 (s, 3H). $^{13}$C NMR (126 MHz, MeOH-d$_4$) $\delta$ 147.31, 113.49, 102.32, 79.98, 79.73, 79.60, 76.01, 71.90, 71.15, 67.99, 66.67, 62.85, 47.95, 47.76, 40.13, 39.48, 36.63, 33.79, 33.56, 31.43, 26.35, 23.58, 18.88, 13.50, 10.37, 9.23, -4.24, -4.65. HRMS (ESI+) calcd for $[C_{28}H_{54}O_9SiNa^+]$ requires m/z 585.3435, found 585.3443.

3.9.5. Preparation of 3.23

Polyol 3.27 (428 mg, 0.76 mmol) and 2,6-Lutidine (0.35 mL, 3.04 mmol) were suspended in CH$_2$Cl$_2$ (76 mL) and cooled to −78 °C. TES-Cl (0.067 mL, 0.40 mmol) was added dropwise and the reaction was stirred for 2 h at this temperature. An additional portion of TES-Cl (0.067 mL, 0.40 mmol) was added and the reaction mixture was stirred for another 2 h at this temperature. The reaction was quenched by the addition of
NaHCO$_3$(sat. aq) (50 mL) and the layers separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 50 mL) and EtOAc (50 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated. Purification by flash column chromatography (80% → 100% EtOAc/Hexanes) on pH 7 buffered silica silica gel afforded tetraol 3.29 as a clear oil (214 mg, 0.316 mmol, 42% yield). $^1$H NMR (300 MHz, C$_6$D$_6$) $\delta$ 5.26 (s, 1H), 5.17 (s, 1H), 4.40 – 4.10 (m, 4H), 3.90 (d, $J$ = 21.8 Hz, 2H), 3.62 (t, $J$ = 5.8 Hz, 2H), 3.53 – 3.37 (m, 3H), 3.20 (s, 3H), 2.87 – 2.57 (m, 1H), 2.32 (q, $J$ = 6.4 Hz, 3H), 2.20 – 2.06 (m, 1H), 1.87 (d, $J$ = 15.1 Hz, 1H), 1.80 – 1.22 (m, 5H), 1.13 – 1.00 (m, 18H), 0.94 (d, $J$ = 7.0 Hz, 3H), 0.83 (t, $J$ = 7.2 Hz, 3H), 0.63 (q, $J$ = 7.9 Hz, 6H), 0.22 (s, 3H), 0.13 (s, 3H).

To a 0 °C of polyol 3.27 (370 mg, 0.658 mmol) in DMF (36 mL) was added imidazole (1.57 g, 23.04 mmol) and TES-Cl (2.76 ml, 16.45 mmol). The solution was stirred overnight at 35 °C. The reaction mixture was diluted with Et$_2$O (100 mL), cooled to 0 °C and added to a stirring solution of NaHCO$_3$(sat. aq) (150 mL). The layers were separated and the aqueous layer extracted with Et$_2$O (3 x 50 mL). The organic layers were washed with water (2 x 50 mL) and brine (50 mL). The combined aqueous layers were extracted with Et$_2$O (75 mL). The combined organic extracts were dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo overnight. To the crude product was added THF (27 mL) and MeOH (82 ml). KF (2.86 g, 49.35 mmol) was added and stirred 8 h.
The reaction mixture was diluted with CH\textsubscript{2}Cl\textsubscript{2} (200 mL) and quenched with NaHCO\textsubscript{3} (sat. aq) (300 mL). The layers were separated, the aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 x 75 mL) and the combined organic layers dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, and concentrated. Purification by flash column chromatography (5% EtOAc/Hexanes with 1% Et\textsubscript{3}N) on silica gel afforded diol 3.30 as a colorless oil (440 mg, 0.487 mmol, 74% yield. [\alpha]_D^{22} +35.1^\circ$ (c 1.00, CH\textsubscript{2}Cl\textsubscript{2}). IR (ATR) 3421, 2952, 2876, 1459, 1414, 1378, 1237, 1079, 1006 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (500 MHz, C\textsubscript{6}D\textsubscript{6}) \( \delta \) 5.11 (d, \( J = 1.8 \) Hz, 1H), 5.02 (s, 1H), 4.32 – 4.21 (m, 3H), 3.97 (d, \( J = 2.9 \) Hz, 1H), 3.88 (s, 1H), 3.64 (t, \( J = 6.5 \) Hz, 1H), 3.60 – 3.49 (m, 3H), 3.44 – 3.38 (m, 3H), 3.13 (s, 3H), 2.74 – 2.65 (m, 2H), 2.34 (dd, \( J = 15.1, 3.7 \) Hz, 1H), 2.02 – 1.94 (m, 1H), 1.74 – 1.54 (m, 3H), 1.41 – 1.28 (m, 1H), 1.18 (t, \( J = 8.0 \) Hz, 9H), 1.13 – 1.03 (m, 27H), 1.00 (d, \( J = 7.2 \) Hz, 3H), 0.92 – 0.66 (m, 18H), 0.22 (s, 3H), 0.14 (s, 3H). \textsuperscript{13}C NMR (126 MHz, C\textsubscript{6}D\textsubscript{6}) \( \delta \) 148.71, 128.59, 111.94, 101.51, 82.08, 80.42, 77.68, 76.92, 71.59, 71.37, 67.69, 67.06, 62.64, 46.99, 40.27, 38.94, 37.60, 33.43, 33.10, 30.21, 26.18, 22.97, 18.41, 16.15, 10.75, 7.55, 7.45, 7.37, 6.19, 6.11, -4.10, -4.64. HRMS (ESI+) calcd for [C\textsubscript{46}H\textsubscript{96}O\textsubscript{8}Si\textsubscript{4}Na+] requires \( m/z \) 927.6029, found 927.6010.

Diol 3.30 (207 mg, 0.229 mmol) and 2,6-Lutidine (0.1 mL, 0.916 mmol) were dissolved in CH\textsubscript{2}Cl\textsubscript{2} (23 mL) and cooled to –78 °C. TES-Cl (0.021 mL, 0.126 mmol) was added dropwise and the reaction was stirred for 1.25 h at this temperature. An additional
portion of TES-Cl (0.021 mL, 0.126 mmol) was added and the reaction mixture was stirred for 2 h at this temperature. The reaction was quenched by the addition of NaHCO$_3$(sat. aq) (25 mL) and the layers separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 20 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated. Purification by flash column chromatography (3% → 20% EtOAc/Hexanes) on pH 7 buffered silica silica gel afforded allyl alcohol 3.22 as a clear oil (227 mg, 0.222 mmol, 97% yield).

3.9.6. Preparation of 3.43

\[ \text{OH} \]

3.39

\[ \text{OTES} \]

3.40

To a 0 ºC solution of 3-methyl-3-buten-1-ol 3.39 (10 mL, 99.2 mmol) in THF (107 mL) was added slowly a solution of TES-Cl (17.5 mL, 104 mmol) in THF (17 mL). The reaction mixture was allowed to warm to rt over 1.5 h. NH$_4$Cl (sat. aq.) (150 mL) and Et$_2$O (200 mL) were added to quench the reaction and the layers were separated. The aqueous layer was extracted with Et$_2$O (2 x 100 mL). The combined organic layers were dried over MgSO$_4$, filtered and concentrated to afford pure TES ether 3.40 (18.8 g, 93.6 mmol, 94% yield). Spectroscopic data was consistent with that previously reported for this compound.
To a 0 ºC solution of TES ether 3.40 (5.0 g, 25.0 mmol) in CH₂Cl₂ (150 mL) was added NaHCO₃ (5.58 g, 66.4 mmol) and mCPBA (7.81 g, 33.2 mmol, 73% purity). The reaction mixture was stirred at 0 ºC for 3 h and at rt for 30 min. H₂O (200 mL) and Et₂O (200 mL) were added and the layers were separated. The aqueous layer was extracted with Et₂O (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated. Purification by flash column chromatography (0% → 6% EtOAc/Hexanes) on silica gel afforded epoxide 3.41 as a clear oil (4.07 g, 18.8 mmol, 75% yield). Spectroscopic data was consistent with that previously reported for this compound.

To a 0 ºC solution of 2,2,6,6-Tetramethylpiperidine (20.4 mL, 120 mmol) in benzene (310 mL) was added n-BuLi (54 mL, 2.22M) dropwise. The resulting mixture was stirred 30 min, and then cooled to −78 ºC. Diethylaluminum chloride (25% in toluene, 62.3 mL, 114.6 mmol) was added slowly, and then the mixture was warmed to 0 ºC for 45 min. A solution of epoxide 3.41 (11.3 g, 52.1 mmol) in benzene (10 mL) was then added and the reaction mixture was stirred 3 h at 0 ºC. Upon completion, Rochelle’s
salt (sat. aq) (200 mL) was added and the mixture was stirred vigorously for 1 hr. The layers were separated, and the aqueous layer was extracted with Et₂O (3 x 75 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. The crude mixture was subjected to high-vaccum at 40 °C to remove 2,2,6,6-Tetramethylpiperdine. The resultant crude allyl alcohol 3.42 was used directly in the next step without further purification.

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\text{HO} \underset{\text{OTES}}{\begin{array}{c} \text{3.42} \\
\end{array}} \xrightarrow{\text{CBr}_4, \text{PPh}_3, \text{Et}_3\text{N}} \underset{\text{OTES}}{\begin{array}{c} \text{Br} \\
\end{array}} \text{3.43}
\]

To a 0 ºC solution of allyl alcohol 3.42 in CH₂Cl₂ (90 mL) was added Et₃N (6.4 mL, 46.2 mmol), PPh₃ (4.85 g, 18.5 mmol), and CBr₄ (6.13 g, 18.5 mmol) sequentially. The reaction mixture was stirred at rt for 1 h, and then quenched by addition of NaHCO₃(sat. aq) (90 mL). The layers were separated and the aqueous layer was extracted with Et₂O (2 x 50 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. Purification by flash column chromatography (0% → 2% EtOAc/Hexanes) on silica gel afforded allyl bromide 3.43 as a clear oil (4.37 g, 15.6 mmol, 90% yield). IR (ATR) 2953, 2875, 1640, 1458, 1413, 1381, 1238, 1208 cm⁻¹. ¹H NMR (500 MHz, CDCl₃) δ 5.22 (d, J = 1.2 Hz, 1H), 5.01 (q, J = 1.2 Hz, 1H), 4.01 (d, J = 0.8 Hz, 2H), 3.77 (t, J = 6.7 Hz, 2H), 2.44 (td, J = 6.7, 1.2 Hz, 2H), 0.96 (t, J = 8.0 Hz, 9H), 0.60 (q, J = 7.9 Hz, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 143.4, 116.8, 61.9, 37.4, 36.9, 7.0, 4.6. HRMS (APCI+) calcd for [C₁₁H₂₄OBrSi+] requires m/z 279.0780, found 279.0775.
3.9.7. Preparation of aldehyde 3.2

To a -78 °C solution of oxalyl chloride (5.6 mL, 65.2 mmol) in THF (106 mL) was added a mixture of DMSO (5.7 mL, 80.2 mmol) and THF (5 mL) dropwise. The reaction was allowed to warm to -40 °C over 30 min. Upon re-cooling to -78 °C, 2-chloro-2-propen-1-ol 3.44 (4.62 g, 50.2 mmol) was added and the reaction was allowed to warm to -40 °C over 1 h. Et$_3$N (36.3 mL, 261 mmol) was added and reaction was allowed to warm to rt over 1 h. Et$_2$O (50 mL) was added to precipitate salts. The mixture was air-free filtered into another flask. A second portion of Et$_2$O (50 mL) was used to rinse the reaction flask and filter cake. This clear solution of 2-chloroacrolein was kept at -78 °C under argon.

In a separate flask, triethylphosphonoacetate (6.6 mL, 33.1 mmol) was charged with THF (155 mL) and cooled to -78 °C. NaHMDS (36.6 mL, 1M in THF) was added dropwise, followed by addition of catechol (500 mg). The resultant blue solution was stirred for 15 min. The cold 2-chloroacrolein solution was added and the reaction mixture was stirred at -78 °C for 1.5 h, then overnight at -20 °C. The reaction was quenched by the addition of Et$_2$O (200 mL) and H$_2$O (175 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated. Purification by flash column chromatography (5% EtOAc/Hexanes) on silica gel afforded ester 3.45 as a yellow oil.
(2.95 g, 18.4 mmol, 55% yield). Spectroscopic data was consistent with that previously reported for this compound.

To a -78 °C solution of ester 3.45 (895 mg, 5.58 mmol) in CH₂Cl₂ (65 mL) was added DIBAL (22.3 mL, 1M in CH₂Cl₂). The reaction was stirred at this temperature for 1.5 h before quenching with Rochelle’s salt (sat. aq) (100 mL) and vigorously stirring for 4 h. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated. Purification by flash column chromatography (CH₂Cl₂) on silica gel afforded alcohol 3.46 as an unstable oil (665 mg, 4.13 mmol, 74% yield). This was dissolved in CH₂Cl₂ to form a 0.4M solution that was stable in the freezer. Spectroscopic data was consistent with that previously reported for this compound.

To a -78 °C solution of oxalyl chloride (0.74 mL, 8.60 mmol) in CH₂Cl₂ (4 mL) was added a solution of DMSO (1.27 mL, 17.2 mmol) in CH₂Cl₂ (17 mL). The reaction mixture was stirred at -78 °C for 5 min and a solution of alcohol 3.46 (10.75 mL, 0.4M in
CH$_2$Cl$_2$) was added and the resultant mixture was allowed to stir at this temperature for 15 min. Et$_3$N (3.6 mL, 25.8 mmol) was added and the reaction mixture was stirred at -78 ºC for 1 h. The reaction was quenched by the addition of H$_2$O (20 mL). The layers were separated and aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organic layers were washed with H$_2$O (3 x 10 mL), dried over Na$_2$SO$_4$, filtered and carefully concentrated to afford aldehyde 3.2 (446 mg, 3.83 mmol, 89% yield) that was used immediately in the subsequent reaction without further purification. Spectroscopic data was consistent with that previously reported for this compound.

In an argon-atmosphere glovebox, copper (I) chloride (1 mg, 0.0115 mmol) was placed in a 2-dram vial with a stir bar. The vial was capped with a septum and transferred out of the glove box. The vessel was then charged with CH$_2$Cl$_2$ (0.8 mL) and Et$_3$N (16.3 mg, 0.161 mmol), then cooled to 0 ºC. In a separate vial under Ar atmosphere, allyl bromide 3.43 (64 mg, 0.23 mmol) was charged with CH$_2$Cl$_2$ (0.8 mL), Et$_3$N (16.3 mg, 0.161 mmol), and HSiCl$_3$ (37.4 mg, 0.276 mmol) sequentially (base must be added first to prevent acid-mediated degradation). The solution was mixed, then transferred dropwise via syringe to the 0 ºC CuCl/Et$_3$N solution. The allyl bromide vial was then rinsed with CH$_2$Cl$_2$ (0.2 mL), this solution was added to the reaction flask, and the resulting mixture was stirred for 2 h at 0 ºC. A solution of the (R,R)-3.10 (66.8 mg, 0.23 mmol) and DBU (105 mg, 0.69 mmol) in CH$_2$Cl$_2$ (0.8 mL + 0.2 mL rinse) was then
added dropwise via syringe to the reaction mixture. The cooling bath was removed and the mixture was stirred 1 h at rt. The silane solution was then re-cooled to –40 °C and aldehyde 3.2 (53.4 mg, 0.46 mmol) was added. The reaction was stirred at 0 °C for 1 h. The reaction mixture was re-cooled to –40 °C and treated with TBAF•3H₂O (87 mg, 0.276 mmol) and stirred 1 h at –40 °C. The mixture was then passed through a silica plug with EtOAc and concentrated to give the crude product. Purification by flash column chromatography (10% EtOAc/Hexanes) on silica gel afforded alcohol 3.47 as a clear oil (46 mg, 0.145 mmol, 63% yield). The ee of the compound was determined to be 90% based on ¹⁹F analysis of the corresponding Moscher ester. [α]D²³ –1.2° (c 1.00, CH₂Cl₂).

**IR** (ATR) 3346, 2954, 2913, 2875, 1645, 1590, 1456, 1413, 1381, 1238 cm⁻¹. ¹H **NMR** (500 MHz, CDCl₃) δ 6.41 (dd, J = 14.9, 1.5 Hz, 1H), 6.16 (dd, J = 14.9, 5.1 Hz, 1H), 5.35 (s, 2H), 4.98 (d, J = 4.6 Hz, 2H), 4.42 (dq, J = 9.0, 4.4 Hz, 1H), 3.77 (t, J = 6.5 Hz, 2H), 2.64 (d, J = 3.2 Hz, 1H), 2.41 (dd, J = 14.1, 3.7 Hz, 1H), 2.32 (t, J = 6.4 Hz, 2H), 2.23 (dd, J = 14.1, 9.6 Hz, 1H), 0.96 (t, J = 7.9 Hz, 9H), 0.61 (q, J = 8.0 Hz, 6H). ¹³C **NMR** (126 MHz, CDCl₃) δ 143.6, 138.5, 137.1, 126.7, 115.6, 115.3, 69.4, 62.4, 45.3, 38.9, 6.9, 4.5. **HRMS** (ESI+) calcd for [C₁₆H₂₉O₂SiClNa⁺] requires m/z 339.1523, found 339.1531.
3.9.8. Preparation of EF fragment 3.53

In an argon-atmosphere glovebox, copper (I) bromide (0.9 mg, 0.0063 mmol) was placed in a flame-dried vial with a stir bar. The vial was capped with a septum and transferred out of the glove box. The vessel was then charged with CH$_2$Cl$_2$ (0.3 mL) and Et$_3$N (12 µL, 0.088 mmol), then cooled to 0 °C. In a separate vial under Ar atmosphere,
allyl bromide 3.23 (68 mg, 0.063 mmol) was charged with CH₂Cl₂ (0.3 mL) and cooled to 0 °C. 2,6-di-t-butylpyridine (82 µL, 0.378 mmol), and Cl₃SiH (7.7 µL, 0.076 mmol) were added sequentially. The solution was mixed, then transferred dropwise via syringe to the 0 °C CuBr/Et₃N solution. The resulting mixture was stirred for 5 h at 0 °C. To a solution of (R,R)-3.49 (15.6 mg, 0.063 mmol) and TBAB (4 mg, 0.0126 mmol) in CH₂Cl₂ (0.2 mL) was added DBU (28.3 µL, 0.189 mmol). This mixture was dropwise via syringe to the reaction mixture, rinsing with CH₂Cl₂ (0.1 mL). The resulting solution was stirred 2 h at 0 °C. The silane solution was then re-cooled to −78 °C and a solution of freshly prepared aldehyde 3.2 (44 mg, 0.378 mmol) in CH₂Cl₂ (0.2 mL) was added. The reaction was stirred at -10 °C for 12 h. The reaction mixture was cooled to −40 °C, treated with TBAF·3H₂O (76 µL, 1M in THF) and stirred 1 h at 0 °C. The mixture was then passed through a silica plug with EtOAc and concentrated to give the crude product. Purification by flash column chromatography (0% → 5% EtOAc/Hexanes) on pH 7 buffered silica gel afforded alcohol 3.48 as a clear oil (44 mg, 0.039 mmol, 62% yield). ¹H NMR (400 MHz, C₆D₆) δ 6.63 (d, J = 14.7 Hz, 1H), 6.40 (dd, J = 14.8, 4.2 Hz, 1H), 5.23 – 5.00 (m, 5H), 4.52 – 4.45 (m, 1H), 4.31 – 4.24 (m, 2H), 4.00 – 3.84 (m, 3H), 3.73 – 3.68 (m, 1H), 3.67 – 3.45 (m, 8H), 3.21 – 3.13 (m, 5H), 2.98 (d, J = 3.6 Hz, 1H), 2.63 – 2.49 (m, 3H), 2.33 – 2.23 (m, 2H), 2.07 – 1.26 (m, 9H), 1.17 (t, J = 8.1 Hz, 9H), 1.12 – 0.99 (m, 27H), 0.99 – 0.57 (m, 24H), 0.23 (s, 3H), 0.14 (s, 3H). HRMS (APCI+) calcd for [C₅₇H₁₁₅ClO₇Si₅Na+] requires m/z 1141.6974, found 1141.6985.
To a solution of diol 3.30 (392 mg, 0.432 mmol) in CH₂Cl₂ (9 ml) was added sequentially Et₃N (0.60 ml, 4.32 mmol), PPh₃ (566 mg, 2.16 mmol) and CCl₄ (0.84 ml, 8.64 mmol). The reaction was stirred overnight at rt and quenched by the addition of NaHCO₃ (sat. aq) (10 mL). The layers were separated and the aqueous layer was extracted with Et₂O (2 x 7 ml). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. Purification by flash column chromatography (0 → 2% EtOAc/Hexanes with 1% Et₃N) on silica gel afforded dichloride 3.50 as a colorless oil (357 mg, 0.379 mmol, 87% yield). [α]D²⁴ +31.5° (c 1.00, CH₂Cl₂). IR (ATR) 2952, 2876, 1648, 1459, 1415, 1377, 1238, 1078 cm⁻¹. ¹H NMR (500 MHz, C₆D₆) δ 5.29 (d, J = 1.5 Hz, 1H), 5.10 (s, 1H), 4.39 (d, J = 11.9 Hz, 1H), 4.23 – 4.17 (m, 2H), 3.98 – 3.94 (m, 1H), 3.86 (s, 1H), 3.57 – 3.48 (m, 3H), 3.46 (d, J = 10.6 Hz, 1H), 3.18 (td, J = 6.5, 2.1 Hz, 2H), 3.12 (s, 3H), 2.79 (dd, J = 13.8, 2.8 Hz, 1H), 2.45 (dd, J = 13.7, 8.7 Hz, 1H), 2.25 (dd, J = 15.2, 3.7 Hz, 1H), 1.96 – 1.91 (m, 1H), 1.68 – 1.50 (m, 5H), 1.14 (t, J = 8.0 Hz, 9H), 1.11 – 1.04 (m, 30H), 0.97 (d, J = 7.2 Hz, 3H), 0.84 – 0.70 (m, 18H), 0.21 (s, 3H), 0.15 (s, 3H). ¹³C NMR (126 MHz, C₆D₆) δ 144.12, 128.59, 115.64, 101.65, 81.02, 80.61, 77.65, 76.90, 71.62, 71.28, 67.33, 49.41, 46.94, 44.85, 40.19, 38.96, 37.54, 33.09, 32.46, 30.28, 26.16, 23.99, 18.40, 16.11, 10.68, 7.50, 7.47, 7.38, 6.23, 6.18, 6.13, -4.09, -4.56. HRMS (ESI⁺) calcd for [C₄₆H₉₄Cl₂O₇Si₄Na⁺] requires m/z 963.5351, found 963.5353.
In an argon-atmosphere glovebox, copper (I) bromide (2.5 mg, 0.017 mmol) was placed in a vial with a stir bar. The vial was capped with a septum and transferred out of the glove box. The vessel was then charged with CH$_2$Cl$_2$ (0.3 mL) and Et$_3$N (13.5 µL, 0.097 mmol, 1.4 equiv) and cooled to 0 ºC. In a separate vial under Ar atmosphere, dichloride 3.50 (65 mg, 0.069 mmol) was charged with CH$_2$Cl$_2$ (0.3 mL) and cooled to 0 ºC. 2,6-di-$t$-butyl pyridine (89.5 µL, 0.414 mmol) and Cl$_3$SiH (8.4 µL, 0.083 mmol) were added sequentially. The solution was mixed, and then transferred dropwise via syringe to the 0 ºC CuBr/Et$_3$N solution. The dichloride vial was then rinsed with CH$_2$Cl$_2$ (0.1 mL), this solution was added to the reaction flask, and the resulting mixture was stirred 5 h at 0 ºC. Additional Cl$_3$SiH (1.4 µL, 0.014 mmol) was added dropwise to the reaction flask, and the resulting mixture was stirred 4 h at 0 ºC. A solution of (R,R)-3.49 (17.1 mg, .069 mmol), TBAB (4.5 mg, 0.014 mmol) and DBU (31 µL, 0.207 mmol) in CH$_2$Cl$_2$ (0.2 mL + 0.1 mL rinse) was then added dropwise via syringe to the reaction mixture. The resulting mixture was stirred 2 h at 0 ºC. The silane solution was then cooled to -78 ºC and the freshly prepared chlorodiene aldehyde 3.2 (48.3 mg, 0.414 mmol) in CH$_2$Cl$_2$ (0.25 mL) was added dropwise. The reaction was then warmed to -10 ºC and stirred for 12 h. The reaction mixture was treated with TBAF•3H$_2$O (83 µL, 1M in THF) and stirred 2 h at 0ºC. The mixture was then passed through a pH 7 buffered silica plug with EtOAc and concentrated to give the crude product. Purification by flash column chromatography on pH 7 buffered silica (0% → 5% EtOAc/Hexanes) to give alcohol
3.51 as a clear oil (50 mg, 0.049 mmol, 71% yield, 94% yield brsm). [α]_D^{22} +33.9° (c 1.00, CH₂Cl₂). IR (ATR) 3469, 2953, 2876, 1643, 1590, 1459, 1414, 1378, 1238, 1093, 1006, 835, 727 cm⁻¹. H NMR (500 MHz, C₆D₆) δ 6.64 (d, J = 14.8 Hz, 1H), 6.42 (dd, J = 14.8, 4.2 Hz, 1H), 5.18 (s, 1H), 5.11 (s, 1H), 5.07 (s, 2H), 4.52 – 4.45 (m, 1H), 4.23 – 4.17 (m, 1H), 3.93 (d, J = 3.1 Hz, 1H), 3.86 (s, 1H), 3.73 – 3.68 (m, 1H), 3.62 – 3.56 (m, 3H), 3.18 (t, J = 6.5 Hz, 2H), 3.13 (s, 3H), 2.98 (d, J = 3.6 Hz, 1H), 2.62 (d, J = 6.7 Hz, 2H), 2.55 (dd, J = 13.5, 3.1 Hz, 1H), 2.33 – 2.24 (m, 2H), 2.07 – 1.98 (m, 1H), 1.70 (d, J = 14.8 Hz, 2H), 1.64 – 1.45 (m, 5H), 1.31 – 1.21 (m, 7H), 1.17 (d, J = 7.8 Hz, 9H), 1.13 – 1.04 (m, 30H), 0.95 (d, J = 7.4 Hz, 3H), 0.91 – 0.68 (m, 26H), 0.24 (s, 3H), 0.15 (s, 3H). C NMR (126 MHz, C₆D₆) δ 145.7, 138.9, 138.1, 125.8, 114.4, 113.9, 101.2, 82.3, 79.4, 77.0, 76.2, 71.2, 70.9, 70.4, 67.0, 46.7, 46.5, 44.4, 39.7, 38.6, 34.6, 32.7, 32.0, 31.6, 30.1, 29.0, 25.6, 25.3, 23.6, 22.7, 18.0, 16.3, 13.9, 11.3, 10.3, 7.2, 7.0, 6.9, 5.8, 5.6, 5.5, -4.1, -4.6. HRMS (ESI+) calced for [C₅₁H₁₀₀NCl₂O₅Si₄NH₄⁺] requires m/z 1040.6216, found 1040.6221.

A solution of 2,6-lutidine (268 µL, 2.30 mmol) and TBS-OTf (121 µL, 0.69 mmol) in THF (4.6 mL) was pre-mixed at room temperature for 15 min, then slowly added via syringe into a -78 °C solution of alcohol 3.51 (238 mg, 0.23 mmol) in THF (23 mL). The reaction was allowed to warm to 0 °C over 3 h, then quenched with NaHCO₃(sat.
aq) (50 mL) and extracted with Et₂O (3 x 50 mL). The combined extracts were washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated. Purification by flash column chromatography (0% → 2% EtOAc/Hexanes) on pH 7 buffered silica gel gave TBS ether 3.52 as a colorless oil (237 mg, 90% yield). \([\alpha]_D^{25} +31.2^\circ\) (c 1.00, CH₂Cl₂). **IR** (ATR) 2953, 2876, 1646, 1590, 1461, 1415, 1378, 1250, 1112, 1079, 1005, 833, 729 cm⁻¹. **¹H NMR** (500 MHz, C₆D₆) δ 6.56 – 6.41 (m, 2H), 5.23 – 5.10 (m, 3H), 5.07 (s, 1H), 4.52 (q, J = 6.1 Hz, 1H), 4.23 (d, J = 7.9 Hz, 1H), 3.98 – 3.92 (m, 1H), 3.89 (s, 1H), 3.63 – 3.44 (m, 4H), 3.17 (d, J = 12.7 Hz, 5H), 2.79 – 2.29 (m, 5H), 2.02 – 1.92 (m, 1H), 1.74 (t, J = 14.9 Hz, 1H), 1.67 – 1.52 (m, 4H), 1.22 – 1.01 (m, 5H), 0.98 (t, J = 7.2 Hz, 3H), 0.87 – 0.74 (m, 18H), 0.31 – 0.09 (m, 12H). **¹³C NMR** (126 MHz, C₆D₆) δ 144.0, 138.5, 128.2, 126.2, 115.5, 114.7, 101.3, 81.4, 80.7, 77.6, 77.3, 71.8, 71.4, 71.2, 66.9, 46.6, 46.1, 44.5, 40.1, 38.9, 32.3, 32.1, 30.1, 26.1, 25.8, 23.6, 18.2, 18.0, 15.7, 10.3, 7.5, 7.4, 7.3, 6.3, 6.2, 6.1, 5.4, -4.1, -4.3, -4.5, -4.6 **HRMS** (ESI+) calcd for \([C_{57}H_{114}Cl_8Si_5NH_4]^+\] requires m/z 1154.7081, found 1154.7080.

TBS ether 3.52 (235 mg, 0.206 mmol) was dissolved in MeCN (11.1 mL) and MeOH (1.2 mL). To this solution was added \(i\)-Pr₂NEt (72 µL, 0.413 mmol), NaI (458 mg, 3.08 mmol), and PPh₃ (2.16 g, 8.23 mmol). The resulting mixture was heated at reflux for 12 h. The reaction was cooled to rt and additional PPh₃ (1.08 g, 4.12 mmol)
was added. The reaction was heated to reflux for 8 h. The reaction was cooled to rt and concentrated. The residue was suspended in CH$_2$Cl$_2$ and filtered through a cotton plug, washing with CH$_2$Cl$_2$ (3X). The filtrate was concentrated. Purification by flash column chromatography (0% → 5% MeOH/CH$_2$Cl$_2$) on pH 7 buffered silica gel afforded Wittig salt 3.53 as a yellow foam (274 mg, 0.184 mmol, 92% yield). Spectroscopic data was consistent with that previously reported for this compound

3.9.9. Preparation of spongistatin 1 analog 3.58

Wittig salt 3.53 (90 mg, 0.06 mmol) was azeotroped with dry benzene (3x) and placed under vacuum for 24 h. Aldehyde 3.54 (90 mg, 0.06 mmol) was azeotroped with dry benzene (3x) and placed under vacuum for 24 h. The dried Wittig salt was charged with dry 10% HMPA/THF solution (0.63 mL) and cooled to -78 °C. LiHMDS (66 µL, 0.066 mmol) was added dropwise and the resultant orange solution was stirred 30 min at this temperature. A solution of the dried aldehyde in 10% HMPA/THF (0.45 mL) was
added dropwise to the reaction mixture. The yellow solution was allowed to warm to 0 °C over 1 h and stirred at 0 °C for 1 h. The reaction was quenched by the addition of a 4:1 mixture of NH₄Cl (sat. aq.) and Na₂S₂O₃ (sat. aq.) (5 mL). Et₂O (7 mL) was added the layers were separated. The aqueous layer was extracted with Et₂O (3 x 4 mL) and the combined organic layers were washed with NaHCO₃ (sat. aq.) (5 mL) and brine (5 mL), dried over MgSO₄, filtered and concentrated. Purification by flash column chromatography (10% → 40% EtOAc/Hexanes, then 0% → 10% MeOH/CH₂Cl₂) on pH 7 buffered silica gel afforded Wittig product 3.55 as a white solid (75 mg, 0.036 mmol, 60% yield). [α]D²⁷ +8.2° (c 1.00, CH₂Cl₂). IR (ATR) 3332, 2957, 2926, 2877, 288, 1636, 1462, 1419, 1372, 1259, 1080, 1020 cm⁻¹. ¹H NMR (500 MHz, C₆D₆) δ 6.55 – 6.42 (m, 2H), 5.63 (dd, J = 9.1, 3.5 Hz, 1H), 5.48 – 5.40 (m, 1H), 5.24 – 4.99 (m, 8H), 4.59 – 4.50 (m, 2H), 4.42 – 4.26 (m, 1H), 4.03 – 3.95 (m, 2H), 3.91 (s, 1H), 3.81 (td, J = 10.9, 5.3 Hz, 1H), 3.67 – 3.49 (m, 4H), 3.19 (s, 3H), 3.14 (s, 3H), 2.98 (dd, J = 9.1, 7.0 Hz, 1H), 2.93 (dd, J = 15.8, 3.9 Hz, 1H), 2.81 (dd, J = 17.1, 7.5 Hz, 1H), 2.77 – 2.65 (m, 2H), 2.61 – 2.48 (m, 3H), 2.47 – 2.32 (m, 3H), 2.29 – 2.20 (m, 2H), 2.14 – 1.90 (m, 6H), 1.83 – 1.73 (m, 6H), 1.69 – 1.59 (m, 2H), 1.51 – 1.17 (m, 29H), 1.18 – 1.00 (m, 72H), 0.97 – 0.77 (m, 16H), 0.71 – 0.60 (m, 5H), 0.29 (s, 12H), 0.26 (s, 3H), 0.18 (d, J = 3.5 Hz, 6H), 0.13 (s, 3H). ¹³C NMR (126 MHz, C₆D₆) δ 208.47, 170.64, 170.18, 168.84, 148.04, 144.40, 138.91, 138.89, 135.09, 129.36, 128.59, 126.55, 115.62, 115.11, 113.80, 101.63, 97.64, 97.26, 81.75, 80.76, 77.76, 77.40, 74.71, 73.19, 71.83, 71.65, 71.31, 70.77, 67.70, 67.01, 64.86, 64.71, 61.77, 60.00, 55.29, 49.14, 48.93, 47.90, 47.12, 46.98, 45.57, 42.80, 42.73, 42.43, 42.32, 40.44, 39.36, 39.09, 38.83, 37.73, 34.55, 32.99, 32.20, 32.17, 31.97, 30.33, 30.23, 29.85, 29.42, 29.29, 28.11, 27.17, 26.21, 23.14, 23.06, 21.36, 20.57, 18.57, 18.42, 18.10,
16.23, 14.35, 13.36, 12.99, 12.33, 10.78, 7.72, 7.65, 7.52, 7.46, 7.41, 6.25, 6.23, 6.15, 1.43, -4.00, -4.22, -4.44, -4.47. **HRMS** (ESI+) calcd for $[C_{109}H_{203}ClO_{21}Si_{7}NH_{4}^+]$ requires $m/z$ 2097.3234, found 2097.3267.

Wittig product **3.55** (68 mg, 0.033 mmol) was dissolved in THF (7 mL) and cooled to 0 °C. TBAF•3H$_2$O (99 µL, 1M in THF) was added in 6 portions over 1 h and stirring was continued at 0 °C for 3 h. The reaction was quenched by the addition of NH$_4$Cl (sat. aq.) (10 mL) and EtOAc (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (15 mL). The combined aqueous layers were back-extracted with CH$_2$Cl$_2$ (2 x 10 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated. Purification by flash column chromatography (0% → 5% MeOH/CH$_2$Cl$_2$) on silica gel afforded seco-acid **3.56** as a white solid (46 mg, 0.0274 mmol, 83% yield). $[\alpha]_D$$^{25}$ +25.4° (c 1.00, CH$_2$Cl$_2$). **IR** (ATR) 3448, 2951, 2930, 2876, 2860, 1734, 1590, 1551, 1461, 1371, 1241, 1182, 1144, 1106, 1077, 1027, 1004, 959, 895, 835, 775, 739 cm$^{-1}$. **$^1$H NMR** (500 MHz, C$_6$D$_6$) δ 6.56 – 6.40 (m, 2H), 5.63 (dd, J = 9.0, 3.5 Hz, 1H), 5.53 – 5.40 (m,
2H), 5.24 – 4.93 (m, 12H), 4.58 – 4.35 (m, 2H), 4.34 – 4.24 (m, 4H), 4.02 – 3.87 (m, 3H), 3.86 – 3.78 (m, 1H), 3.66 – 3.46 (m, 4H), 3.23 – 3.17 (m, 7H), 3.14 (s, 3H), 3.03 – 2.95 (m, 1H), 2.89 – 2.66 (m, 3H), 2.62 – 1.85 (m, 12H), 1.83 – 1.68 (m, 7H), 1.63 (d, J = 13.4 Hz, 2H), 1.55 – 1.39 (m, 3H), 1.39 – 0.76 (m, 93H), 0.67 (q, J = 7.9 Hz, 6H), 0.29 – 0.23 (m, 3H), 0.20 – 0.08 (m, 10H). 13C NMR (126 MHz, C6D6) δ 208.74, 170.11, 169.08, 167.37, 148.01, 144.36, 143.68, 138.91, 138.89, 135.05, 129.42, 126.55, 115.65, 115.12, 113.82, 101.69, 97.66, 97.55, 81.72, 81.16, 80.79, 77.82, 77.41, 76.90, 74.85, 73.25, 72.22, 71.83, 71.69, 71.33, 70.93, 67.67, 66.72, 64.86, 64.62, 61.69, 60.01, 55.75, 55.28, 53.32, 49.21, 49.01, 47.99, 47.11, 47.05, 45.24, 42.72, 42.41, 42.22, 40.64, 40.44, 39.00, 38.72, 37.67, 34.37, 32.94, 32.37, 32.23, 32.19, 30.23, 30.16, 30.09, 29.92, 29.85, 29.79, 29.70, 29.30, 28.11, 27.75, 26.23, 26.21, 25.13, 23.14, 21.33, 18.57, 18.44, 16.20, 16.06, 14.39, 13.43, 13.05, 10.79, 7.65, 7.52, 7.46, 7.25, 6.37, 6.25, 6.24, 6.15, 6.04, -4.01, -4.22, -4.41, -4.43, -4.46. HRMS (ESI+) calcd for [C88H155ClO21Si4NH4+] requires m/z 1713.0170, found 1713.0188.
Seco-acid **2.56** (40 mg, 0.023 mmol) was dissolved in toluene (2.3 mL) and \( i\)-Pr\(_2\)NEt (0.24 mL, 1.38 mmol) and 2,4,6-trichlorobenzoyl chloride (72 \( \mu \)L, 0.46 mmol) were added. This was stirred for 4 h at rt, then diluted with toluene (6.9 mL). The mixture was taken up into a 12 mL gas-tight syringe and added to a 90 °C solution of DMAP (141 mg, 1.15 mmol) in toluene (34 mL) over 24 h by syringe pump. The vial containing starting material which was sealed and stored at 0 °C was rinsed with toluene (2.3 mL) and added to the reaction at over 8 h by syringe pump. The starting material vial was rinsed with an additional portion of toluene (2.3 mL) and added to the reaction over 4 h by syringe pump. The reaction mixture was allowed to stir at 90 °C for 20 h. The reaction mixture was cooled to rt and diluted with Et\(_2\)O (50 mL). This was washed with NaHCO\(_3\) (sat. aq) (50 mL) and brine (50 mL). The combined aqueous layers were extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\), filtered and concentrated. Purification by flash column chromatography (10% \( \rightarrow \) 40% EtOAc/Hexanes) on silica gel afforded lactone **3.57** as a white solid (31 mg, 0.0186 mmol, 81% yield). 

[\( \alpha \)]\(_{D}^{24}\) +23.9° (c 1.00, CH\(_2\)Cl\(_2\)). **IR** (ATR) 2928, 2876, 2856, 1735, 1647, 1583, 1550, 1461, 1370, 1246, 1143, 1110, 1029, 1005, 961, 891, 835 775, 740 cm\(^{-1}\). **\( ^1\)H NMR** (500 MHz, C\(_6\)D\(_6\)) \( \delta \) 6.55 – 6.26 (m, 3H), 5.70 (d, J = 10.4 Hz, 1H), 5.41 (q, J = 7.7 Hz, 2H), 5.23 – 4.93 (m, 14H), 4.84 (q, J = 15.7 Hz, 1H), 4.41 (dq, J = 22.9, 12.2, 9.5 Hz, 6H), 4.03 – 3.74 (m, 5H), 3.64 – 3.39 (m, 5H), 3.28 – 3.05 (m, 10H), 2.68 (s, 1H), 2.61 – 2.46 (m, 5H), 2.45 – 2.05 (m, 5H), 2.11 – 1.54 (m, 16H), 1.55 – 0.54 (m, 162H), 0.32 – -0.02 (m, 17H). **\( ^{13}\)C NMR** (126 MHz, C\(_6\)D\(_6\)) \( \delta \) 208.78, 171.46, 170.32, 168.49, 148.19, 143.48, 142.76, 139.04, 138.89, 134.50, 130.01, 128.59, 126.53, 126.49, 126.38, 117.17, 116.20, 115.64, 115.21, 113.41, 101.80, 101.71, 97.70, 97.62, 97.07,
Lactone 3.57 (26 mg, 0.015 mmol) was dissolved in MeCN (1.08 mL) and cooled to -20 °C. A freshly prepared solution of HF in MeCN (1.08 mL) [prepared by mixing 48% aqueous HF (1.25 mL) and MeCN (5 mL)] was added over 2 h by syringe pump at -20 °C. The reaction was allowed to stir an additional 18 h at this temperature. The reaction was quenched by the dropwise addition of Et₃N (2.53 mL) and warmed to rt. The reaction mixture was diluted with a 2:1 mixture of EtOAc/CH₂Cl₂ (13 mL), then washed with NaHCO₃(sat. aq) (13 mL) and brine (13 mL). The combined aqueous layers were
extracted with a 2:1 mixture of EtOAc/CH$_2$Cl$_2$ (2 x 13 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated. Purification by flash column chromatography (0% $\rightarrow$ 5% MeOH/CH$_2$Cl$_2$) on silica gel afforded spongistatin 1 analog **3.58** as a white solid (15 mg, 0.0125 mmol, 83% yield). [$\alpha$]$_D^{22}$ $+18.2^\circ$ (c 0.50, MeOH).

**IR** (ATR) 3435, 2926, 2851, 1735, 1653, 1580, 1551, 1436, 1384, 1233, 1177, 1093, 1059, 894 cm$^{-1}$. **$^1$H NMR** (500 MHz, CD$_3$CN) $\delta$ 6.50 – 6.34 (m, 1H), 6.25 – 6.06 (m, 1H), 5.45 (d, $J = 6.9$ Hz, 2H), 5.36 (s, 1H), 5.33 – 5.11 (m, 3H), 5.07 (s, 1H), 4.97 – 4.79 (m, 6H), 4.81 – 4.67 (m, 1H), 4.48 – 4.22 (m, 3H), 4.21 – 4.08 (m, 2H), 4.08 – 3.96 (m, 1H), 3.93 – 3.47 (m, 4H), 3.47 – 3.31 (m, 1H), 3.27 (d, $J = 18.9$ Hz, 6H), 3.19 – 3.03 (m, 1H), 3.03 – 2.69 (m, 3H), 2.66 – 2.47 (m, 1H), 2.44 – 2.30 (m, 1H), 2.30 – 2.22 (m, 2H), 1.87 – 1.78 (m, 4H), 1.73 – 1.45 (m, 6H), 1.28 (d, $J = 13.7$ Hz, 11H), 1.14 (dd, $J = 7.0$, 2.7 Hz, 3H), 1.09 – 0.97 (m, 7H), 0.88 (d, $J = 7.1$ Hz, 1H), 0.84 – 0.73 (m, 6H). **$^{13}$C NMR** (126 MHz, CD$_3$CN) $\delta$ 210.67, 172.78, 171.60, 170.08, 148.06, 144.10, 139.24, 138.97, 135.80, 128.97, 126.86, 126.81, 99.25, 99.18, 99.13, 97.99, 81.09, 81.01, 80.34, 78.82, 78.56, 77.76, 74.86, 73.84, 73.16, 73.00, 71.49, 70.55, 69.38, 69.27, 69.16, 67.04, 64.71, 63.43, 62.58, 62.32, 60.69, 56.11, 55.51, 50.62, 48.14, 46.81, 45.11, 44.28, 44.04, 43.81, 42.94, 42.21, 40.41, 40.29, 40.14, 39.73, 39.64, 37.36, 37.29, 37.23, 36.77, 34.49, 33.78, 33.19, 32.64, 32.51, 30.35, 30.15, 30.07, 29.40, 27.72, 27.06, 23.39, 21.76, 21.00, 14.39, 13.10, 12.80, 12.24, 11.29. **HRMS** (ESI+) calcd for [C$_{63}$H$_{95}$ClO$_{20}$Na$^+$] requires $m/z$ 1229.6003, found 1229.5991.

**3.10. Spectral Data**
1H NMR (400 MHz, CDCl3)

![Chemical Structure](image)

**3.18**
13C NMR (126 MHz, C6D6)

![Chemical Structure](Image)

**3.26**
1H NMR (500 MHz, MeOH-d4)
1H NMR (500 MHz, CDCl3)

Br
OTES

3.43
1H NMR (400 MHz, C6D6)
$\text{OTES}$, $\text{OTBS}$, $\text{OH}$, $\text{TESO}$, $\text{Me}$, $\text{Cl}$, $\text{Me}$, $\text{OME}$, $\text{H}$, $\text{OTES}$, $\text{Cl}$, $\text{3.51}$
1H NMR (500 MHz, C6D6)

3.56
3.11. References

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