STUDIES TOWARD THE COMPLETION OF THE C29-C51 SEGMENT OF SPONGISTATIN 1

DISSERTATION

Presented in Partial Fulfillment of the Requirements for
the Degree Doctor of Philosophy in the Graduate
School of The Ohio State University

By

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2008

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______________________________
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ABSTRACT

Spongistatin 1 (Altohyrtin A) is a marine natural product, which was isolated in 1993 from a species of Spongia in the Eastern Indian Ocean by Pettit and co-workers, and also from Hyrtios altum collected off the coast of Okinawa by Kobayashi and Kitagawa. This large macrocycle with 24 stereocenters boasts two spiroketals (AB and CD) in the C1-C28 segment, two highly functionalized tetrahydropyran rings (E and F), and a sensitive chlorodiene side chain in the C29-C51 segment, which is the focus of this dissertation. The biological activity of spongistatin 1 extends beyond the initially reported potent cytotoxicity in that it also aggressively inhibits cell growth in many cancer cell lines with IC$_{50}$ values in the pico- to nanomolar range, and has been shown to inhibit the growth of various fungi and yeasts. These results are attributed to spongistatin 1 binding to tubulin in a manner that inhibits microtubule formation.

Our efforts toward a concise synthesis of the C29-C51 segment of spongistatin 1 have resulted in an approach wherein three highly advanced intermediates are joined in two very convergent steps. One key intermediate, the vinyl iodide side chain, comprises the C45-C51 portion of our target; the second is the fully functionalized C38-C44 F ring methyl ester; and the third, the C29-C37 E segment sulfone, which later forms the E ring. In the first convergent step, the C44-C45 bond was formed via a B-alkyl Suzuki coupling to join the side chain and F ring. This was followed immediately by an α-sulfonyl anion addition to form the C37-C38 bond, which completes the carbon skeleton of the C29-C51 segment. Further transformations cyclized the E ring and installed the stereocenter at C38. Future work focuses on installing the double bond at C48-C49 to complete the side chain functionalization, followed by formation of the Wittig salt at C29 to join this segment with the C1-C28 unit and complete the total synthesis of spongistatin 1.
Dedicated to My Parents and
the Little Things in Life
ACKNOWLEDGMENTS

I wish to thank Professor Leo Paquette for extending to me the opportunity to work in his labs. His patience, guidance, and sense of humor are unsurpassed, and his undying enthusiasm to see a project through is both contagious and motivating. I greatly appreciate his advice, suggestions, and willingness to give me the freedom to try new ideas. Thanks are also in order for Professor David Hart and Professor James Stambuli for agreeing to serve on my dissertation committee.

I would also like to extend my gratitude to my family and friends, who have had to listen to so much for so long. First, to Dad for the introduction to organic chemistry, general directions for life, an appreciation for books, and late night chemistry conversations; to Mom, who listened to the successes, failures, and hilarious lab stories over very, very long phone calls; to John, who would drop everything when I needed a chat and a beer; to Dr. Mark Tierney, who still likes to think about chemistry and was always willing to help (unless it involved going into my lab); to Jack and Squirrelly Cat for forgiving the late returns home and forgotten meals; to Dr. Matthew Bedore and Mr. Sean Butler, the best lunch buddies you could hope to have and terrific labmates to boot; to Dr. Amy Hart, who had just as much fun as I did as part of the Spongistatin Death Squad; to Dr. Philip Weintraub for his assistance and further contributions to my book collection; and to all the great lab mates I have had, past and present, who number far too many to list, but without whom I would not have made it this far nor learned so much.
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<tr>
<td>α</td>
<td>alpha</td>
</tr>
<tr>
<td>[α]</td>
<td>specific rotation</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>Å</td>
<td>Ångstrom</td>
</tr>
<tr>
<td>br</td>
<td>broad (IR and NMR)</td>
</tr>
<tr>
<td>β</td>
<td>beta</td>
</tr>
<tr>
<td>9-BBN</td>
<td>9-borabicyclo[3.3.1]nonane</td>
</tr>
<tr>
<td>brsm</td>
<td>based on recovered starting material</td>
</tr>
<tr>
<td>n-Bu</td>
<td>normal-butyl</td>
</tr>
<tr>
<td>t-Bu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>Bz</td>
<td>benzoyl</td>
</tr>
<tr>
<td>°C</td>
<td>degrees Celsius</td>
</tr>
<tr>
<td>calcld</td>
<td>calculated</td>
</tr>
<tr>
<td>Cl</td>
<td>chloride</td>
</tr>
<tr>
<td>CSA</td>
<td>(1S)-(−)-10-camphorsulfonic acid</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift in parts per million</td>
</tr>
<tr>
<td>d</td>
<td>doublet (spectra); day(s)</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCC</td>
<td>N,N'‑dicyclohexylcarbodiimide</td>
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<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-1,4-benzoquinone</td>
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<tr>
<td>Dibal-H</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>Acronym</td>
<td>Full Form</td>
</tr>
<tr>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(N,N-dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>dppf</td>
<td>1,1'-bis(diphenylphosphino)ferrocene</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact ionization</td>
</tr>
<tr>
<td>ESI</td>
<td>positive ion electron spray ionization</td>
</tr>
<tr>
<td>equiv.</td>
<td>equivalent</td>
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<tr>
<td>Et</td>
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</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>g</td>
<td>gram(s)</td>
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<tr>
<td>GDP</td>
<td>guanine diphosphate</td>
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<tr>
<td>GI&lt;sub&gt;50&lt;/sub&gt;</td>
<td>concentration required for 50% growth inhibition, including correction for cell count at time zero</td>
</tr>
<tr>
<td>GTP</td>
<td>guanine triphosphate</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
</tr>
<tr>
<td>HMDS</td>
<td>hexamethyldisilazide</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectrometry</td>
</tr>
<tr>
<td>IBX</td>
<td>2-iodoxybenzoic acid</td>
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<tr>
<td>IC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>concentration required for 50% growth inhibition</td>
</tr>
<tr>
<td>imid</td>
<td>imidazole</td>
</tr>
<tr>
<td>iPr</td>
<td>iso-propyl</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant in Hz (NMR)</td>
</tr>
<tr>
<td>k</td>
<td>kilo</td>
</tr>
<tr>
<td>L</td>
<td>liter(s)</td>
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<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
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<td>--------------</td>
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<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>lut</td>
<td>lutidine</td>
</tr>
<tr>
<td>m</td>
<td>milli; multiplet (NMR)</td>
</tr>
<tr>
<td>μ</td>
<td>micro</td>
</tr>
<tr>
<td>M</td>
<td>molarity, moles per liter</td>
</tr>
<tr>
<td>mCPBA</td>
<td>meta-chloroperbenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MHz</td>
<td>megahertz</td>
</tr>
<tr>
<td>min</td>
<td>minute(s)</td>
</tr>
<tr>
<td>mol</td>
<td>mole(s)</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxymethyl</td>
</tr>
<tr>
<td>MPM</td>
<td>4-methoxyphenylmethyl (same as PMB)</td>
</tr>
<tr>
<td>Ms</td>
<td>methanesulfonyl</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry; molecular sieves</td>
</tr>
<tr>
<td>m/z</td>
<td>mass to charge ratio (MS)</td>
</tr>
<tr>
<td>n</td>
<td>nano</td>
</tr>
<tr>
<td>N</td>
<td>normality, grams per liter</td>
</tr>
<tr>
<td>NEP</td>
<td>N-ethyl piperidine</td>
</tr>
<tr>
<td>NMO</td>
<td>4-methylmorpholine N-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic reasonance</td>
</tr>
<tr>
<td>p</td>
<td>para</td>
</tr>
<tr>
<td>PDC</td>
<td>pyridinium dichromate</td>
</tr>
<tr>
<td>PG</td>
<td>undefined protecting group</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>Piv</td>
<td>pivalate</td>
</tr>
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<td>PMB</td>
<td>p-methoxybenzyl</td>
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<td>Definition</td>
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<tr>
<td>PMBz</td>
<td>p-methoxybenzoate</td>
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<td>PMP</td>
<td>p-methoxyphenyl</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>PPTs</td>
<td>pyridinium p-toluenesulfonate</td>
</tr>
<tr>
<td>py</td>
<td>pyridine</td>
</tr>
<tr>
<td>q</td>
<td>quartet (NMR)</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
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<td>s</td>
<td>singlet (NMR); second(s)</td>
</tr>
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<td>t</td>
<td>tertiary (tert)</td>
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<td>triplet (NMR)</td>
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<td>TBAI</td>
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</tr>
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<tr>
<td>TES</td>
<td>triethylsilyl</td>
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<td>Tf</td>
<td>trifluoromethanesulfonyl</td>
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<td>TIPS</td>
<td>triisopropylsilyl</td>
</tr>
<tr>
<td>Ts</td>
<td>p-toluenesulfonyl</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TPAP</td>
<td>tetrapropylammonium perruthenate</td>
</tr>
</tbody>
</table>
1.1 Introduction to Antimitotic Marine Macrocycles

In addition to spongistatin 1 (Figure 1.1), there exist a great number of marine-derived macrocycles that have demonstrated high levels of bioactivity. Many of these molecules, such as spirastrellolide A, \(^1\) (-)-lauimalide, \(^2\) and halichondrin B, \(^3\) have also been isolated from sponges (Figure 1.2). More specifically, these compounds share the key characteristic of being potent antimitotics.\(^{1c,2ab,3,4}\) Their interesting structure, potential use in treating cancer, and often difficult

\[ \text{Figure 1.1: Spongistatin 1.} \]
Figure 1.2: Sponge-derived antimitotics.
isolation have illicited a strong interest in the world of natural product synthesis. In this vein, we have undertaken the synthesis of spongistatin 1, which falls into the same categories of sponge origin, diverse structural design, and potent biological activity.

1.2 Isolation and Structure Determination

Spongistatin 1 was isolated in 1993 by two groups independent of each other. Pettit and coworkers, who named the isolate spongistatin 1, retrieved 13.8 mg from a 400 kg (wet weight) sample of *Spongia sp.* found in the Eastern Indian Ocean.\(^5\) Interestingly, Kobayashi and Kitagawa obtained 0.5 mg of what they named altohyrtin A from a 112 kg sample of a completely different sponge, *Hyrtios altum*, which was collected off the coast of Okinawa.\(^6\)

Further efforts by both groups\(^7\) led to the discovery of several additional related macrocycles. Furthermore, cinachyrolide A was also isolated in 1993 by Fusetani from yet another sponge of the genus *Cinachyra*.\(^8\) The discovery of the family of spongistatins in such a wide variety of sponges has led to the supposition that they may be created by a common bacteria rather than the sponges themselves.\(^9\)

The structural determination and preliminary stereochemical assignments were based on extensive NMR studies.\(^5,6,10\) Both groups reported the same structural assignment; however, their stereochemical assignments differed significantly (Figure 1.3). To further complicate the situation, Fusetani reported different stereochemistry for cinachyrolide A.\(^8\)

However, upon the total synthesis of spongistatin 2 by Evans\(^11\) in 1997 and the total synthesis of spongistatin 1 by Kishi\(^12\) in 1998, the stereochemistry was confirmed to match that proposed by Kobayashi and Kitagawa. This also proved that spongistatin 1 and altohyrtin A were in fact the same compound. As shown in Figure 1.4, many of the compounds were in fact identical.\(^9\)
Figure 1.3: Initially reported structures with differences in stereochemistry highlighted.
**Figure 1.4:** Part of the spongistatin family.

<table>
<thead>
<tr>
<th>Spongistatin 1</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>R&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Altohyrtin A)</td>
<td>Cl</td>
<td>OAc</td>
<td>OAc</td>
</tr>
</tbody>
</table>

| Altohyrtin B    | Br           | OAc          | OAc          |

| Spongistatin 2  | H            | OAc          | OAc          |
| (Altohyrtin C)  |              |              |              |

| Spongistatin 3  | Cl           | OH           | OAc          |

| Spongistatin 4  | Cl           | OAc          | OH           |
| (5-Desacetylatohyrtin A) |          |              |              |

| Spongistatin 6  | H            | OAc          | OH           |
| (Cinachyrolide A) |              |              |              |
1.3 Biological Activity of Spongistatin 1

Spongistatin 1 was immediately reported by both isolation groups as potently cytotoxic, showing an IC$_{50}$ of 0.01 ng/mL against KB cells,$^6$ an IC$_{50}$ of 0.1 ng/mL against L1210 murine leukemia cells,$^6$ and average GI$_{50}$ values of 2.5–3.5 x 10$^{-11}$ M against the NCI panel of 60 cancer cell lines.$^5$ Further work by Pettit showed that the mode of action was the inhibition of tubulin polymerization.$^{13}$ While there are a great number of natural products (and synthetic compounds) known to affect tubulin polymerization, not all do so in the same fashion. For example, the taxanes bind to tubulin and promote polymerization, while spongistatin 1 binds and inhibits polymerization. However, the end result is identical: treated cells are unable to undergo mitosis (and, hence, cell division) due to the fact that these compounds disturb the natural equilibrium of microtubule formation.$^{14}$

The exact binding site of spongistatin 1 on tubulin is not known. Studies have indicated that it likely binds near the vinca and nucleotide domains, since it noncompetitively inhibits the binding of vinca alkaloids and GDP/GTP exchange.$^{13}$

The interesting part about the antimitotic effects of spongistatin 1 are the varied roles it could potentially fill in treating diseases. The original work screening against cancer cell lines also led to the discovery by Russo et al. that spongistatin and other cytotoxic marine natural products induce apoptosis by a different mechanism of action than more common anti-cancer drugs such as vinblastine.$^{15}$ Further work may prove that this difference could be exploited to improve cancer treatment. Indeed, in the aforementioned study, spongistatin 1 showed an IC$_{50}$ of 1.0 nM against non small cell lung cancer A549 cells versus cisplatin, which gave an IC$_{50}$ of 250.0 nM.

Subsequent investigations have also shown that the impact spongistatin 1 has on microtubules also affords it great antifungal properties.$^{16}$ Minimal fungicidal concentrations (MFCs) as low as 3 μg/mL were expressed over a wide variety of fungi and yeasts, and good MFCs were even
obtained against strains resistant to current antibiotics, such as amphotericin B or ketoconazole. These results show a great deal of promise in treating the growing number of resistant strains that infect immunosuppressed patients.

1.4 Significant Structural Features Contributing to Biological Activity

Two groups have made analogs of spongistatin 1 in efforts to identify which structural features are responsible for its biological activity. As shown in Figure 1.5, Smith constructed “model trienes” utilizing a generic F ring and appending either the spongistatin 1 chlorinated side chain or the spongistatin 2 deschlorodiene side chain. Screening against six cancer cell lines showed the chlorinated side chain to be seven to 31 times more potent than the deschlorodiene. Impressively, the chlorinated side chain analog resulted in GI\textsubscript{50} values in the range of 0.25 to 0.70 μg/mL without the rest of the complex structure of the parent macrocycle, which indicates that it may be possible to greatly simplify the structure and still obtain an active compound.

Paterson produced analogs of the entire spongistatin 1 macrocycle, wherein either the E ring was dehydrated at C35 or the side chain was abbreviated at C46: both changes were made to ease synthesis (Figure 1.6). Again, these compounds were screened against a variety of cancer cell lines. Interestingly, the dehydrated E ring analog was 1.8 times more potent on average than the parent, while the abbreviated side chain analog was on average 10,000 times less potent, again highlighting the importance of the side chain. Also of note, no one to date has screened the C29-C51 segment alone, although the above two studies seem to indicate that the EF segment would be the region most responsible for activity.
Figure 1.5: Partial and full analogs of spongistatin 1.

Analogs by Smith:

Analogs by Paterson:
Together, the above results would indicate that not only is the side chain necessary for activity, but that the chlorine is of further benefit. However, for the sake of completeness, it should be noted that these findings are not in keeping with those of Uckun and coworkers, who have published a great deal focussing on the spiroketal unit as the main source of biological activity. Their conclusions were derived from modelling studies looking at the cavities of the tubulin heterodimer and identifying likely binding sites based on size, hydrophobicity and other characteristics. From the resulting information, they constructed SPIKET-P, a spiroketal unit that was designed to bind in a specific cavity found on tubulin (Figure 1.7), and which apparently showed inhibition of mitotic spindle formation at low nanomolar concentrations.

Although interesting, the work by Uckun fails to explain the great difference in activity within the spongistatin family, while the data clearly indicates reduced activity for the non-halogenated spongistatins. Furthermore, the spiroketal binding site as identified by Uckun does not necessarily reinforce the binding data collected by Pettit et al. in terms of affecting both the interactions with GTP and GDP and the binding of vinca alkaloids.

![Figure 1.6: Structure of SPIKET-P.](image)
CHAPTER 2

PREVIOUS SYNTHESES OF THE C29-C51 SEGMENT

2.1 Introduction to Previous Strategies

Analysis of the structure of spongistatin 1 shows obvious synthetic disconnects at the C1 lactone functionality and the C28-C29 double bond (Figure 2.1). In syntheses to date, the C28-C29 bond has been the key coupling point via a Wittig olefination to connect the ABCD and EF segments, followed by a macrolactonization to close the ring.⁹

Figure 2.1: Spongistatin 1, points of initial disconnect.
Differently, the EF segment (C29-C51) does not immediately lend any specific points of disconnect, which has led to the utilization of a range of strategies to construct this portion of the molecule. For the connection of the E ring and F ring (Figure 2.2), many groups have relied on an aldol addition to form either the C35-C36 \(^{18b,21,22,23,24}\) or C36-C37 \(^{25}\) bond. Alternatively, the addition of a C37 anion to a carbonyl at C38 has also been used. \(^{11,12b,26}\) As for the means of appending the side chain to the F ring, several different disconnects have been applied. Some groups built up the side chain in several steps, \(^{12b,18b,22,23,24,26a}\) while others attached the entire segment in one step at the end of the synthesis. \(^{11,21,25}\) The following sections will briefly cover the various strategies for assembling the C29-C51 segment, inclusive of the two syntheses of spongistatin 2.

![Figure 2.2: EF segment of spongistatin 1.](image)

### 2.2 C29-C51 Segment of Spongistatin 2: Evans

The pioneering spongistatin 2 synthesis by Evans\(^{11}\) utilized the α-sulfonyl anion derived from \(2.3\) in an addition to the benzotriazole ketone \(2.2\) to make the connection between the E and F rings. Subsequent epoxidation across the C42-C43 olefin in the F ring allowed for a concise addition of the stannyl side chain unit \(2.1\) to complete the C29-C51 segment of spongistatin 2 (Scheme
This method was significantly convergent in that the E ring was added fully cyclized and functionalized prior to the installation of the complete side chain in one step. In his final approach for the total synthesis, Evans modified the order of connection. After the α-sulfonyle anion addition, the C29-C43 segment was converted to the Wittig salt **2.4** and then coupled to the ABCD portion to form the C28-C29 bond in **2.5**. The delicate side chain was then installed in the same fashion as noted before to afford **2.6** (Scheme 2.2).

**Scheme 2.1:** Initial synthesis of the C29-C51 segment by Evans.
Scheme 2.2: Final assembly strategy by Evans.
2.3 First Synthesis of Spongistatin 1: Kishi

In 1998, the first total synthesis of spongistatin 1 was published\textsuperscript{12b} employing a similar strategy to Evans in a different manner to build the C29-C51 segment. As shown in Scheme 2.3, Kishi also made the side chain disconnect at the C43-C44 bond, but transmetallated allyl stannane 2.7 and used the resulting cuprate in an addition to the F ring epoxide 2.8. This installed an abbreviated segment of the side chain (2.10) that was then elongated through an indium-mediated coupling to install the sensitive chlorodiene unit in 2.11. Subsequently, the C37-C38 bond was formed through addition of the Grignard reagent derived from vinyl iodide 2.9 to the aldehyde at C38 on the F ring to afford 2.12 (Scheme 2.4). After introduction of the methyl ketal at C37 through iodomethanolysis of the E ring olefin and radical-mediated removal of the iodine atom, followed by
protecting group manipulations, the hydroxyl group at C29 was converted to the Wittig salt in order to join the C29-C51 segment with the bis-spiroketal portion of spongistatin 1.

![Chemical Structures](image)

**Scheme 2.4:** Side chain completion by Kishi.

### 2.4 Introduction of the Aldol Addition: Crimmins

The approach of the Crimmins group\textsuperscript{21} utilized the allyl stannane method of Evans to install the side chain, but was one of the first groups to use an aldol addition to construct the C35-C36 bond and attach the E ring segment for later cyclization, a strategy which was subsequently applied by other groups.\textsuperscript{18b,22,23,24} The boron enolate of F ring ketone 2.14 was added to aldehyde 2.15, which underwent an acid-catalyzed cyclization to give the E ring (Scheme 2.5). The epoxide was then formed from the C42-C43 olefin, to which stannane 2.13 could then be added to complete the C29-C51 segment. Like Evans, the synthesis was actually completed by attaching the side chain to the F ring after the EF segment had been connected to the ABCD portion of spongistatin.
2.5 Two Aldols en Route to the C29-C51 Segment: Paterson

Although the same aldol disconnect was used for the F ring and E segment, Paterson also exploited the aldol addition to form the C46-C47 bond of the side chain.\textsuperscript{18b,22} Again, the boron enolate of the F ring ketone 2.17 was added to the E segment aldehyde 2.18 followed by cyclization of the E ring (Scheme 2.6). Following incorporation of the C44-C46 carbons of the side chain into the F ring intermediate, the exo-methylene at C45 was oxidatively cleaved to give the ketone, which was then converted to the boron enolate and added to aldehyde 2.16. The resulting ketone was then transformed back to the olefin to complete the side chain. To prepare the C29-C51 segment for addition to the ABCD portion, the primary chloride was converted to the Wittig salt.
2.6 The Second Spongistatin 2 Synthesis: Heathcock

Heathcock$^{23}$ also implemented the C35-C36 aldol disconnection, but used a novel Grignard addition to form the C44-C45 bond between the F ring and abbreviated side chain, which was then further functionalized. After formation of the boron enolate of 2.20 and addition to aldehyde 2.21, the E ring was cyclized (Scheme 2.7). At this point the alcohol at C44 was converted to the aldehyde and treated with Grignard reagent 2.19 to install the middle portion (C45-C48) of the side chain. The terminal alcohol at C48 was then transformed to the sequential aldehyde and treated with allyl magnesium bromide in the presence of ZnCl$_2$ to install the terminal diene.

Scheme 2.6: Key intermediates of synthesis by Paterson.
Another Application of Two Aldols: Ley

The synthesis of the C29-C51 segment of spongistatin 1 by the Ley group is very similar to that of the Paterson group, but with a modification to the method of side chain attachment. The F ring ketone was converted to the boron enolate and added to E segment aldehyde, followed by E ring cyclization (Scheme 2.8). However, instead of carrying an olefin at C45 through the first half of the synthesis as the masked ketone, Ley utilized a Weinreb amide, which was transformed to the methyl ketone after the E ring addition. The derived boron enolate was added to aldehyde, and the resulting ketone again underwent a Takai olefination to complete the side chain.
2.8 A Very Different Approach: Vogel

The work by Lemaire-Audoire and Vogel\textsuperscript{25} utilized a very different strategy to achieve the synthesis of the C29-C51 segment. While an aldol addition was used to connect the F ring and E segment, Vogel made the disconnection at the C36-C37 bond instead of the heavily exploited C35-C36 bond. Thus, the enolate of E segment aldehyde 2.25 was added to F ring aldehyde 2.24 (Scheme 2.9). After E ring cyclization, the F ring underwent a glycosidation reaction to install the side chain via allyl silane 2.23. The use of LDA to generate the enolate of 2.25 avoided the use of boranes; and since the resulting stereocenter was subsequently oxidized to the ketone to later form the E ring cyclic ketal, no selectivity was needed.
The Smith group has published two complete syntheses of the EF segment of spongistatin 1. The first approach used an anionic addition to join the E segment and F ring in conjunction with an allyl stannane addition to an F ring epoxide, much like Kishi, to append the side chain. The second approach utilized the same anion addition to form the C37-C38 bond, but with an interesting substitution reaction to install the side chain. To make the EF connection, dithiane 2.28 was deprotonated and added to F ring aldehyde 2.27 (Scheme 2.10). After E ring cyclization (2.29), the olefin in the F ring side chain was cleaved by ozonolysis with reductive workup to give the aldehyde, which was treated with Eschenmoser’s salt to give enal 2.30 (Scheme 2.11).
Reduction of the aldehyde and conversion of the resulting alcohol to the iodide gave intermediate 2.31. Cyanohydrin 2.26 was deprotonated and displaced the iodide to introduce the remainder of the side chain. To finish the C29-C51 segment, the alcohols at C29 and C49 were converted to the corresponding iodides. The iodide at C49 spontaneously eliminated to complete the side chain diene, and the iodide at C29 was converted to the Wittig reagent.

Scheme 2.10: Most recent generation synthesis from the Smith group.
**Scheme 2.11:** Installation of the side chain.
3.1 Retrosynthetic Analysis of C29-C51 Segment of Spongistatin 1: Paquette

The synthetic strategy employed by Paquette was to divide the C29-C51 segment into three key intermediates which would account for the complete carbon skeleton (Scheme 3.1). The C37-C38 disconnect would be accomplished via an anion addition to a carbonyl moiety, in the same vein as Kishi and Smith. Deprotonation of sulfone 3.3 would afford the necessary anion to add to a carbonyl electrophile at C38 derived from methyl ester 3.2. The entire side chain 3.1 would be appended to the F ring via a novel B-alkyl Suzuki coupling to form the C44-C45 bond. This highly convergent approach was also very flexible in that it allowed us to alter the order of connection, wherein we could construct either the C29-C44 subunit, which would then be coupled to the side chain, or build up the C38-C51 subunit, which could then be further extended with the E segment (Figure 3.1).27 Both possible routes will be addressed in detail in Chapters four and five, after the syntheses of the key intermediates have been discussed.
Figure 3.1: Alternative assembly routes from three key intermediates.

Scheme 3.1: C29-C51 approach by Paquette.
3.2 Original Synthesis of Chlorodiene Side Chain 3.1

Our approach\textsuperscript{27} to constructing the C45-C51 side chain unit began with \textit{R}-(+)-glycidol (Scheme 3.2). After pivalate protection, the epoxide was regioselectively opened with TMS-acetylide to afford 3.4. TBAF removed the terminal silyl group and I-9-BBN was used to install the vinyl iodide in 3.5 that would later be needed for the Suzuki coupling. The secondary alcohol was protected as the TBS ether and Dibal-H was employed to cleave the pivalate ester to give primary alcohol 3.6. The primary alcohol was then oxidized with TPAP to afford aldehyde 3.7, which was then coupled in an indium-mediated reaction with 2,3-dichloropropene to give 3.8. Subsequent treatment with Martin sulfurane gave the dehydrated triene product 3.1 with the terminal chlorodiene unit installed.

\textbf{Scheme 3.2:} Original synthesis of the chlorodiene side chain.
3.3 Original Synthesis of F Ring Methyl Ester 3.2

Synthesis of the C38-C44 F ring began with known lactone 3.10 derived from D- (+)-mannose in two steps: protection as the bis-isopropylidene acetal (3.9), followed by oxidation to 3.10 under standard Swern conditions as previously reported (Scheme 3.3). After α-methylation with LDA/MeI, treatment with SmI$_2$ afforded secondary alcohol 3.11. This material was protected as the PMB ether (3.12) using the corresponding trichloroacetimidate. A Tebbe olefination was used to install the exo-methylene, which was immediately subjected to a hydroboration-oxidation sequence to give the desired primary alcohol 3.13 in good yield. The ensuing pair of oxidations to the carboxylic acid were followed by treatment with diazomethane to form methyl ester 3.2.

3.4 Original Synthesis of E Segment Sulfone 3.3

The C29-C37 segment, which would later form the E ring, originally started with the mono-protection of 1,5-pentanediol as the TBDPS ether and oxidation to aldehyde 3.14 (Scheme 3.4). An Evans aldol addition utilizing the dibutylboron enolate, followed by TES protection of the resultant alcohol, gave intermediate 3.15 in high yield. Cleavage of the auxilliary afforded the intermediate terminal carbinol, which was oxidized to the corresponding aldehyde (3.16) with IBX. The second aldol in the series was performed using the Nagao protocol and followed by protection of the intervening alcohol as TBS ether 3.17. Subsequent reductive cleavage of the thiazolidinethione and further treatment with I$_2$/PPh$_3$ under standard conditions installed the primary iodide (3.18). The iodine was then displaced by sodium benzenesulfinatate at elevated temperatures to afford desired sulfone 3.3.
Scheme 3.3: Original synthesis of the F ring methyl ester.
Scheme 3.4: E segment original synthesis.
CHAPTER 4

FIRST ROUTE TOWARD THE C29-C51 SEGMENT: THE C29-C44 SUBUNIT

4.1 Retrosynthesis of the C29-C44 Subunit

The first route taken by the Paquette group focussed on the assembly of a C29-C44 subunit, which could then be joined with the fully elaborated side chain \(3.1\) via the aforementioned \(B\)-alkyl Suzuki coupling (Scheme 4.1). The key subunit would be the result of an addition of the sulfonyl anion of \(3.3\) to the acid chloride derived from the precursor to methyl ester \(3.2\). This approach was undertaken in two different studies, first by Kim\(^{31}\) and then Ciblat,\(^{27}\) which were the basis for future work on the project and will be discussed in detail in the following sections.

4.2 First Attempt Toward Construction of the C29-C44 Subunit

The initial work on the C29-C44 subunit by Kim\(^{31}\) proceeded with a different protecting group scheme than addressed in Chapter 3, but is useful background information as it laid the groundwork for the future efforts of Ciblat and even influenced how we approached modifications in the second route.

The investigations began with E segment sulfone \(4.1\), constructed via the same synthetic sequence as \(3.3\) from 1,5-pentanediol (Scheme 4.2). The addition partner would be aldehyde \(4.2\), differing from the previously detailed intermediate \(3.2\) by the C38 oxidation state and the PMP acetal in place of an isopropylidene ketal, and was also derived following a similar synthetic pathway.
Scheme 4.1: Retrosynthesis including the C29-C44 subunit.
Scheme 4.2: Completion of C29-C44 carbon skeleton.
Deprotonation of sulfone 4.1 with EtMgBr at an elevated temperature followed by the addition of HMPA and 4.2 afforded the addition product 4.3 in respectable yield. Oxidation of the resultant alcohol with IBX proceeded cleanly to afford 4.4; however, the subsequent oxidative cleavage of the sulfone to α-diketone 4.6 failed under numerous conditions (Scheme 4.3). The difficulty in obtaining this intermediate led to a sequence wherein alcohol 4.3 was converted to the acetate and subjected to reductive conditions to provide 4.5 with the hope that the olefin could be dihydroxylated and then oxidized to afford 4.6. However, the double bond in 4.7 was resistant to even stoichiometric amounts of OsO₄, which led to the abandonment of that route and highlighted the difficulties encountered with highly functionalized, hindered molecules. Further testing led to the discovery that Williams oxaziridine would, in fact, provide the desired 4.6 from β-ketosulfone 4.4. This step forward brought the synthesis of the C29-C44 subunit very close to completion. Unfortunately, no conditions could be found to selectively remove the secondary TBS in order to accomplish the E ring cyclization, product 4.7, without concomitant lost of the primary TBS (under basic conditions) or the acetal (under acidic conditions). However, the work shown here seemed to indicate that this strategy would be successful if the protecting groups were altered.

4.3 Second Attempt Toward Completion of the C29-C44 Subunit

The next push forward utilized the modified intermediates discussed in Chapter 3, as developed primarily by Ciblat.²⁷ The carboxylic acid precursor 4.8 to methyl ester 3.2 was converted to acid chloride 4.9 in situ with the Ghosez reagent (Scheme 4.4). Later, we found that the pentafluorophenyl ester 4.10 was as reactive an electrophile as 4.9, but significantly more stable and easy to handle. The use of these substrates rather than aldehyde 4.2 avoided the stability issues of the aldehyde itself and having to oxidize the alcohol, resulting from the addition, back to the ketone, which was needed for formation of the diketone.
Scheme 4.3: Termination of first efforts toward C29-C44 subunit.
With the F ring electrophiles in hand, deprotonation of 3.3 with nBuLi and subsequent addition to either 4.9 or 4.10 afforded the β-ketosulfone adduct 4.11 in high yield (Scheme 4.5). Treatment with Williams oxaziridine afforded the intermediate α-diketone, which, under acidic conditions, cyclized as desired to afford hemiketal 4.12. Since the isopropylidene protecting group was cleaved under the previous reaction conditions, the primary iodide (4.13) was installed under standard conditions, as it would be needed in a few steps for the Suzuki coupling.

At this point, the reduction of the C38 carbonyl was investigated. Under Luche conditions, a mixture of the desired product 4.14 and ketal migration product 4.15 was obtained; but the ratio could be controlled by reducing the time between the addition of the reagents (Scheme 4.6). If the time between the introduction of the CeCl₃ and NaBH₄ was 5 min, a 6:1 mixture of 4.14 to 4.15 was obtained; if the time was shortened to 10 sec, a 20:1 mixture in favor of the desired product was
formed. After methanolysis of 4.14 to give the methylketal and protection of the remaining alcohols as TMS ethers (4.16), the iodine was eliminated with DBU to afford the exo-methylene product and complete the C29-C44 subunit (Scheme 4.7).

\[ \text{Scheme 4.5: Second generation completion of C29-C44 carbon skeleton.} \]
Scheme 4.6: Completion of the C29-C44 subunit.
4.4 Efforts Toward Completion of the C29-C51 Segment

With the C29-C44 subunit constructed, the last major task at hand was the $B$-alkyl Suzuki coupling between side chain 3.1 and the $B$-alkyl intermediate generated from hydroboration of the aforementioned exocyclic olefin (Scheme 4.7). A variety of different bases, Pd(0) sources, solvents, and temperatures were screened in addition to altering the stoichiometry of the reactants, but to no avail.\(^{27}\) The lack of reaction could be the manifestation of a strong rate deceleration brought on by the sheer molecular weight of these substrates. However, there is little evidence that the hydroboration of the C29-C44 subunit actually proceeded prior to the attempted Suzuki coupling. Had additional material been available, a worthwhile effort would have been to screen other hydroboration reagents, followed by standard oxidative work-up, to see if this key step actually occurred, and if so, with what stereochemical outcome.\(^{32}\)

**Scheme 4.7:** Failure of first route to complete C29-C51 segment.
CHAPTER 5

SECOND ROUTE TOWARD THE C29-C51 SEGMENT: THE C38-C51 SUBUNIT AND ATTENDING SYNTHETIC MODIFICATIONS

5.1 Retrosynthetic Analysis of the Second Route

The key intermediate of the second route is the C38-C51 subunit,\textsuperscript{27} which is the Suzuki cross-coupling product of side chain 5.2 and the \textit{B}-alkyl intermediate derived from methyl ester 3.2 (Scheme 5.1). Subsequent addition of deprotonated E segment sulfone 5.1 would complete the C29-C51 carbon skeleton. Further manipulations would cyclize the E ring and complete the side chain unsaturation to conclude our efforts toward the EF segment of spongistatin 1.

5.2 Initial Modifications to the F Ring and Side Chain

At the outset of our work on the second route, we made several synthetic alterations to the construction of the F ring in order to ease scale-up, since material was also needed for ongoing efforts on the first route. Furthermore, we made one key adjustment to the side chain to avoid possible complications in later steps.

To address the latter, Smith had published\textsuperscript{26a} that the chlorodiene portion of the side chain was unstable to strongly basic conditions; furthermore, initial studies by Ciblat in our lab indicated similar instabilities.\textsuperscript{33} Since the plan of the second route appended the side chain prior to the E segment addition and subsequent chemistry, we wanted to proceed with a more robust species than 3.1.
We felt the simplest means of accomplishing this task would be to protect the alcohol in 3.8 rather than moving forward with the dehydration, which would allow us to unmask the hydroxyl group and install the desired diene at a later point in the synthesis. This plan would allow us to potentially avoid decomposition in later steps, such as the addition of the α-sulfonyl anion to install the E
segment, without having to completely retool the side chain synthesis. Thus, the C48 alcohol was protected as the TES ether to afford 5.2 in good yield (Scheme 5.2). Conveniently, the mixture of diastereomers was easily separated so we could later proceed with the major isomer alone to minimize difficulty in NMR interpretation.

In addition to modifying the side chain, we needed to be able to scale up production of F ring methyl ester 3.2; but the available synthetic pathway did not lend itself well to this. The first major obstacle was the diacetonide protection of D-mannose, ironically the very first step in the synthesis (Scheme 5.3). Although precedented in the literature, the original paper34 clearly indicates that a mixture of products, pyranose 3.9 and furanose 5.4, is formed and described the isolation of the desired pyranose by forming the 1-acetate derivative, recrystallization, and cleavage of the acetate. Additionally, there were no clear 1H NMR spectra available for either isomer.

Unfortunately, the direct recrystallization of the diacetonide mixture to separate the isomers was highly inefficient, affording a sub-25% yield of pure 3.9. This was frustrating because we were able to reproducibly obtain up to a 2.5:1 mixture of 3.9/5.4 on large scale by carefully controlling the reaction temperature, but could not effectively separate the desired pyranose form. Furthermore, carrying the mixture on through the Swern oxidation afforded a mixture of lactones that was incredibly difficult to separate by column chromatography and, hence, not practical on a large scale.

---

Scheme 5.2: Modification to improve stability of side chain.

![Scheme 5.2](image-url)
However, a fortuitous discovery showed that the lactones could be separated via a biphasic trituration using water and EtOAc. Hence, recrystallization of 3.9 and 5.4 as a mixture removed impurities from the protection step and both were then oxidized together. After standard work up, the mixture of isomeric lactones was triturated to afford the desired 3.10 in 90% yield based on the ratio of 3.9 in the original mixture. The biphasic trituration was effective because the furanone is significantly more soluble in EtOAc than 3.10; and while the triethylammonium salts from the Swern dissolved in the water layer, the pyranone formed a third layer in between and could easily be isolated by vacuum filtration. This eliminated the futile separation of the lactols, and neatly avoided having to purify 3.10 by column chromatography, thus making a large scale synthesis much more practical.

Scheme 5.3: Creating an F ring synthesis more amenable to large scale.

We were then able to proceed with the methylation and deoxygenation steps as before to afford alcohol 3.11 via 5.5 (Scheme 5.4). We did, however, find that preparing our own Sml₂
was not only significantly more cost effective, but the quality of the reagent was much more reliable and it could be made on any scale needed. This brings us to the point of protecting the secondary alcohol as the PMB ether. Originally, this was accomplished using PMB-trichloroacetimidate, which was highly inefficient due to the resultant tricholoracetamide that was effectively inseparable from the product (3.12). In general, this might not have been a problem, except that the subsequent Tebbe olefination to afford 5.6 (Scheme 5.5) then required an even greater excess of Tebbe reagent to accommodate the amide contaminant, which greatly increased the cost and hassle of work-up of that reaction. However, a fortuitous discovery of the PMBO-lepidine reagent shown in Scheme 5.4, coupled with modified reaction conditions, not only increased the yield of the protection to 80% from ~65%, but also greatly enhanced the ease of preparation of 3.12 since the lepidone byproduct is largely insoluble in many solvents. The details of this convenient means of installing a PMB ether will be discussed in Chapter 6.

Scheme 5.4: Further significant improvements to the F ring synthesis.
With lactone 3.12 in hand, the carbonyl was easily transformed in good yield into olefin 5.6 using the Tebbe reagent.\textsuperscript{39} The exocyclic olefin was fairly unstable; and, thus, was immediately submitted to a hydroboration/oxidation sequence to uneventfully afford 3.13. It should be noted that after changing the PMB protection conditions, only two equivalents of Tebbe reagent were needed versus four equivalents previously. Next, a Swern oxidation to the intermediate aldehyde was followed by a Lindgren-Kraus oxidation\textsuperscript{40} to the carboxylic acid, which was then converted to methyl ester 3.2 using diazomethane. To shorten the time involved, this set of transformations could be performed without purification between steps with no appreciable loss of yield. On large scale, we also found that the methyl ester could also be formed under alternative conditions, such as $i$Pr$_2$NEt/Mel\textsuperscript{41} or CsCO$_3$/Mel,\textsuperscript{42} although the yield for that individual step suffered somewhat, dropping to 58% from 87% using diazomethane. Furthermore, the conversion of 3.13 to 3.2 could be accomplished in a comparable 54% yield by oxidation with PDC, and subsequent treatment of the crude carboxylic acid with TMSCHN$_2$. Quantitatively, the overall yield of the 10-step sequence was increased to 19% with the above modifications from ~5% using the original methods. 

\textbf{Scheme 5.5:} Completion of modified F ring methyl ester synthesis.
5.3 Initial Completion of the C38-C51 Subunit

Our focus next moved to the transformation of 3.2 to 5.10, the desired substrate to test the Suzuki coupling (Schem 5.6). Treatment with 1 M HCl cleanly cleaved the remaining acetonide to afford diol 5.7, which was then converted to primary iodide 5.8 under standard conditions. The relatively unstable iodo alcohol was immediately converted to the TMS ether (5.9), which was chosen solely on the basis of minimizing steric bulk for the Suzuki coupling sequence. Subsequent exposure of 5.9 to DBU at elevated temperature gave desired exocyclic olefin 5.10 in good yield. Somewhat unstable, this intermediate did benefit from changing the solvent to PhH from DMF for ease of removal and could be, if necessary, stored overnight in the freezer with minimal degradation.

Scheme 5.6: Synthesis of F ring precursor to Suzuki coupling.
At this point, we were excited to press forward and determine if the Suzuki coupling would proceed and, if so, how stable the product would be to further synthetic transformations without the fully unsaturated side chain. Thus, **5.10** was hydroborated with 9-BBN to create the B-alkyl substituent *in situ* (Scheme 5.7). After the addition of K$_3$PO$_4$, side chain **5.2** and PdCl$_2$(dpdf) were added. An increase in overall yield was noted when the oily side chain was premixed neat with the palladium catalyst. Indeed, we were able to isolate coupled product **5.11** in 64% yield as a pure product. Higher yields (88%) of the C38-C51 subunit were obtained, but were contaminated with difficult to separate byproducts of the hydroboration.

As we looked forward, we opted to then replace the TMS ether with a less labile protecting group, in this case a TBS ether: The TMS group was cleaved under basic conditions and **5.12** was generated using TBSOTf, both steps occurring in good yield.

**Scheme 5.7:** Completion of the C38-C51 subunit and protecting group modification.
5.4 Addition of the E Segment to the C38-C51 Subunit

With a C38-C51 subunit that was at least stable to chromatography, we then approached the question of how to append the E segment via the planned α-sulfonyl anion addition. The assumption was made that a more reactive carbonyl electrophile was needed at C38, so we first worked with in situ generated acid chloride 5.14 or pentafluorophenyl ester 5.15, as both had served the first route well (Scheme 5.8). These intermediates were derived from carboxylic acid 5.13, which was reliably afforded by treatment of 5.12 with TMSOK.

Scheme 5.8: Synthesis of C38-C51 subunit electrophiles.
This allowed us to then screen conditions to deprotonate E segment sulfone 3.3, followed by the addition of 5.14 or 5.15 to give the desired product 5.16 (Scheme 5.9). Several different bases were tried in combination with acid chloride 5.14, but its instability prevented us from warming the reaction mixture above −40 °C, and no addition reaction took place below that temperature. To further alter variables, we tried additives such as HMPA, longer reaction times at lower temperatures, and changing the order of addition from the acid chloride solution to the deprotonated sulfone to addition of the deprotonated sulfone to the acid chloride. Furthermore, both 5.14 and 5.15 quickly decomposed in the presence of nBuLi. Alternatively, pentafluorophenyl ester 5.15 was much more stable in the presence of KHMDS or LiHMDS, and trace amounts of product were isolated when the reaction mixture was warmed to nearly 0 °C, but mostly decomposition was seen.

Scheme 5.9: Attempts to add α-sulfonyl anion.
We then made recourse to methyl ester 5.12 itself as precedent was found and, if plausible, this plan would eliminate having to convert the methyl ester to a “more reactive” intermediate. In initial attempts, we added the methyl ester to the sulfone deprotonated by nBuLi at \(-78^\circ C\) and mostly recovered both starting materials, which were of course difficult to separate. With a fair amount of material recovered, we changed the approach to the addition of base to the mixture of methyl ester and sulfone at \(-78^\circ C\). In this manner, we were able to obtain a near quantitative yield on a 20 mg scale using LiHMDS and warming the reaction mixture to \(-30^\circ C\) (Scheme 5.10). This success marked the completion of the carbon skeleton of the C29-C51 segment of spongistatin 1.

**Scheme 5.10:** Completion of the C29-C51 carbon skeleton.

### 5.5 Completion of the C29-C51 Backbone with Further Modified Intermediates

After the above achievement, we were faced with very little starting material for the C38-C51 subunit and a new concern: the C29 terminal TBDPS ether could likely prove difficult to selectively
remove later in the synthesis. Additionally, we also opted to alter the protecting group scheme on
the F ring to avoid the two steps needed to exchange the TMS ether for the TBS ether (5.12) by
choosing a group that would accommodate the Suzuki coupling and survive the remainder of the
synthesis.

For modification of the terminal protecting group of the E segment, we compared the
schemes employed previously by Kim (4.1) and Ciblat (3.3) and decided to proceed with a terminal
TBS as in 4.1, but maintain the other two protecting groups in 3.3, which would afford 5.1 (Scheme
5.11). This would hopefully be a more facile group to cleave at the end of the synthesis, and would
not interfere as the terminal TBS did for Kim since we would be removing a secondary TES rather
than a secondary TBS earlier in the synthesis to cyclize the E ring. The synthesis by Hart of the
modified E segment (Scheme 5.11) began with 1,5-pentanediol and followed the same synthetic
route outlined in Scheme 3.4.g

**Figure 5.1:** E segment protecting group schemes.
Scheme 5.11: Synthesis of modified E segment.
After addressing the E segment, we investigated further modification of the F ring. We needed a protecting group for the C42 hydroxyl that would not be so bulky as to interfere with the Suzuki coupling to append the side chain. Originally we had used a TMS ether, only to exchange it immediately after the coupling with a more robust group, which lengthened the synthesis. Ciblat had tested the Suzuki coupling with a variety of different protecting groups in this location (TMS, TBS, PMB) with vague results, but we felt that this was a necessary alteration. In order to simplify the overall synthesis, we opted for another PMB ether. If this group did not sterically interfere with the coupling of the side chain, it could also shorten the overall deprotection strategy at the end of the total synthesis. Paterson had utilized a bis-PMB pattern in his total synthesis of spongistatin 1, and demonstrated that both could be deprotected prior to the macrolactonization without affecting the outcome. Some concern existed over the protection conditions since our strategy using the PMBO-lepidine reagent called for a 2-day reaction time, and iodo alcohol 5.8 had previously shown some tendencies toward decomposition. Fortunately, the reaction proceeded without incident to afford 5.22 in 70% yield (Scheme 5.12). Even more promising, the ensuing

Scheme 5.12: Further modification of F ring and subsequent Suzuki coupling.
dehydroiodination, hydroboration, and Suzuki coupling afforded 5.23 in an improved yield. Due to the forthcoming push to then incorporate the E segment, we also decided to separate the diasteromers of side chain 5.2 and use only the major isomer in order to decrease the complexity of the NMR spectra.

The α-sulfonyl anion addition of the E segment was approached using the same conditions that we had developed earlier, which again afforded the desired product (5.24) in reproducibly good yield (Scheme 5.13). With a suitable amount of the C29-C51 skeleton available, we were then able to pursue the necessary functionalizations to cyclize the E ring and complete the segment.

**Scheme 5.13:** Incorporation of modifications into C29-C51 skeleton.

### 5.6 Functionalization of the C29-C51 Segment

The first of the transformations necessary to cyclize the E ring was oxidation of β-keto sulfone 5.24 to α-diketone 5.25. Initial attempts using conditions from the first route ([BuOK, Williams oxaziridine, THF, 0 °C]) with sulfone 5.15 met with failure, and did as well with 5.24, leading to decomposition. Many reactions at −78 °C also led to decomposition, so we were hesitant to try warmer conditions. The deprotonation itself appeared to take place with a wide variety of bases (KHMDS, NaH, tBuOK), but the anion was completely unreactive toward a variety of oxidants.
including $O_2^{45}$ and $(\text{BnOCO})_2O^{46}$ and to alkylation with MeI.\textsuperscript{47} Due to the side chain olefins, we were limited in terms of oxidants. Studies showed the molecule was stable to treatment with base (no oxidant present), and starting material could be quantitatively recovered when quenched even after stirring at room temperature for several hours. The oxidation was then tried again with Williams oxaziridine, but adding the reagent at 0 °C rather than –78 °C. Indeed, product was obtained with the yield optimized at a reaction time of 2 h; longer times led to decomposition (Scheme 5.14). Unfortunately, a 40% yield with 58% recovered starting material was the best result obtained. Although this step made material progression highly repetitive, it is likely more efficient than the alternative we would have pursued: reductive removal of sulfone, α-hydroxylation, and oxidation.

![Scheme 5.14: Key oxidation to α-diketone.](image)

The subsequent transformation was cyclization of the E ring via acid-catalyzed cleavage of the C33 TES ether. The obvious problem involved the other secondary TES ether on the side chain and the primary TBS ether at C29. As summarized in Table 5.1, we were able to selectively remove the desired TES group and effect cyclization with PPTs in MeOH/THF\textsuperscript{48} to afford 5.26a. Other conditions using $\rho$TsOH\textsuperscript{27} or acetic acid\textsuperscript{49} resulted in the loss of additional silyl groups.
α-Keto hemiketal 5.26a was then submitted to myriad conditions to form methyl ketal 5.27. There is precedent for this transformation under a variety of conditions; however, the gamut of conditions that we applied included acidic, Lewis acidic, and basic (a selection of which appear in Table 5.2), and all failed, many with loss of starting material. Although this lack of reactivity was seen in the first route, hence the reduction before methanolysis, we were hoping to preemptively methylate and avoid the potential hemiketal shift during the reduction of the C38 carbonyl (Scheme 4.6).

Forced to perform the reduction of the C38 ketone first, we made recourse to the Luche reduction conditions from the first route. However, we again found that previous conditions did not lead to success in the second route. Other than NaBH₄, the literature cited Dibal-H as a common reducing agent for ketones with a neighboring hemiketal. Unfortunately, changes in

<table>
<thead>
<tr>
<th>Acid/Solvent</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>pTsOH, HOCH₂CH₂OH/THF</td>
<td>34% 5.26c; no starting material recovered</td>
</tr>
<tr>
<td>2:2:1 AcOH/THF/H₂O</td>
<td>55% 5.26a; 13% 5.26b; 32% 5.26c</td>
</tr>
<tr>
<td>PPTs, MeOH/THF</td>
<td>77% 5.26a</td>
</tr>
</tbody>
</table>

*Table 5.1: Acidic conditions to cyclize E ring without loss of additional silyl groups.*

α-Keto hemiketal 5.26a was then submitted to myriad conditions to form methyl ketal 5.27. There is precedent for this transformation under a variety of conditions; however, the gamut of conditions that we applied included acidic, Lewis acidic, and basic (a selection of which appear in Table 5.2), and all failed, many with loss of starting material. Although this lack of reactivity was seen in the first route, hence the reduction before methanolysis, we were hoping to preemptively methylate and avoid the potential hemiketal shift during the reduction of the C38 carbonyl (Scheme 4.6).

Forced to perform the reduction of the C38 ketone first, we made recourse to the Luche reduction conditions from the first route. However, we again found that previous conditions did not lead to success in the second route. Other than NaBH₄, the literature cited Dibal-H as a common reducing agent for ketones with a neighboring hemiketal. Unfortunately, changes in
Table 5.2: Various conditions tested to form the α-keto methylketal.
solvent and temperature for both reducing agents resulted in either no reaction or degradation. Further searching for conditions to reduce hindered ketones afforded a combination of NaBH₄ and Amberlyst-15. Surprisingly, at room temperature the reaction was complete in 15 min to give 5.28 in 74% yield (Scheme 5.15). Although we have not yet proven the stereochemistry at C38, we have reason to believe the correct isomer (as shown) was formed since, in addition to our first route results, Evans has performed a similar reduction and obtained excellent diastereoselectivity without the use of a chiral reducing agent. Preliminary results have shown that the hemiketal of 5.28 can then be methylated under standard acidic conditions using PPTs/MeOH to afford 5.29, albeit as an inseparable mixture with the starting material.

5.7 Future Work

With the desired methylketal available, we are then faced with the choice of attempting to finish the synthesis with the C38 hydroxyl group protected (5.29b), or not, as in 5.29a (Scheme 5.16). Kishi carried the free alcohol through the last few steps of his synthesis without incident. The next step would be deprotection of the terminal TBS ether at C29 and the secondary TES ester on C48 to give 5.30a or b. Subsequent treatment with iodine/PPh₃ according to Smith’s procedure should afford the primary iodide and concomitant formation of the terminal diene of the side chain (5.31a/b). Finally, conversion of the primary iodide to the Wittig salt 5.32a/b would complete our synthesis of the C29-C51 segment of spongistatin 1.
Scheme 5.15: Progress toward the desired methylketal.
Scheme 5.16: Projected end to the total synthesis of the C29-C51 segment.
CHAPTER 6

A MILD AND EFFICIENT MEANS FOR GENERATING PMB ETHERS

6.1 Introduction and Overview of Original Chemistry

There is a long history to the chemistry involving the conversion of 2-alkoxypyridines to \(N\)-alkyl-2-pyridones, such as that shown in Scheme 6.1.\textsuperscript{54} Recently, a paper utilized just such a transformation of a lepidine derivative in order to transfer a PMB group to form the corresponding ether.

\[
\begin{align*}
\text{R} & \quad \text{O} \quad \text{N} \\
\text{R} = \text{H, Me} \\
\text{R'}\text{CH}_2\text{X} & \quad \text{heat} \\
\text{O} & \quad \text{N} \\
\text{R'} & + \quad \text{R-X}
\end{align*}
\]

Scheme 6.1: Conversion of 2-alkoxypyridines to \(N\)-alkyl-2-pyridones.

As described in Chapter 5, we were in need of a mild and efficient PMB-protection method that would afford a much easier to purify product than obtained from the use of PMB-trichloroacetimidate \textsuperscript{6.1,36} (Scheme 6.1). The original method afforded the side product \textsuperscript{6.2}, which could not be fully separated from our desired product. Our searches led us to a paper by Dudley\textsuperscript{37} wherein he described the use of PMBO-lepidine derivative \textsuperscript{6.3} to effect the formation of PMB
ethers. Unfortunately, the original conditions utilized MeOTf to activate the reagent, and, in addition to affording a mediocre yield, we did not want to use MeOTf on large scale. However, reagent 6.3 is cost effective, simple to generate, and shelf stable. Furthermore, the allure of easily separated byproduct 6.4 spurred us on to find a novel set of conditions with which to employ PMBO-lepidine 6.3. Our modifications eventually utilized a mild acid in catalytic amounts to activate the reagent and yield byproduct 6.5, which is also generally insoluble. This allowed us to process material on a large scale and afforded a very clean product.

**Original method:**

\[
\text{R-OH} + \begin{array}{c} \text{NH} \\ \text{PMBO} \end{array} \begin{array}{c} \text{CCl}_3 \\ 6.1 \end{array} \xrightarrow{\text{TfOH or CSA}} \text{R-OPMB} + \begin{array}{c} \text{H}_2\text{N} \\ \text{CCl}_3 \end{array} 6.2
\]

\[
\text{Dudley's method:}
\]

\[
\text{R-OH} + \begin{array}{c} \text{CH}_3 \\ \text{PMBO} \end{array} \begin{array}{c} \text{6.3} \end{array} \xrightarrow{\text{MeOTf, MgO}} \text{R-OPMB} + \begin{array}{c} \text{CH}_3 \\ \text{O} \\ \text{N} \end{array} \begin{array}{c} \text{6.4} \end{array}
\]

**Our improved method:**

\[
\text{R-OH} + \begin{array}{c} \text{CH}_3 \\ \text{PMBO} \end{array} \begin{array}{c} \text{6.3} \end{array} \xrightarrow{\text{CSA (10 mol %)}} \text{R-OPMB} + \begin{array}{c} \text{CH}_3 \\ \text{O} \\ \text{N} \end{array} \begin{array}{c} \text{6.5} \end{array}
\]

**Scheme 6.2:** Options for PMB protection conditions.
The mechanism of action closely follows that of PMB-acetimidate: the nucleophile, in this case the alcohol to be protected, attacks the benzylic position of the reagent, which has been activated either by protonation with CSA or by methylation with MeOTf. Lepidone 6.5 (or 6.4 if methylated) is then formed as a neutral and highly polar byproduct (Scheme 6.3).

![Scheme 6.3: Mechanism of PMB protection using PMB-lepidine 6.3.](image)

6.2 Development of Conditions

For our substrate, secondary alcohol 3.11, the original conditions using 6.1 gave a reproducibly decent yield of approximately 65%; but a reasonably large amount of 6.2 could never be entirely removed (Table 6.1, Entry 1). This contaminant then consumed Tebbe reagent in the subsequent step, making the entire process more expensive and time consuming. The conditions proposed by Dudley afforded a meager 35% yield of 3.12 (Entry 2), so we attempted their alternate conditions employing K$_2$CO$_3$ (Entry 3). Unfortunately, only decomposition was seen. We then proceeded to try to substitute MeOTs for MeOTf, and no reaction took place. However, upon warming to 35 °C over an extended period of time, an 80% yield was obtained (Entry 4). The product was very easy to isolate: concentration of the reaction mixture followed by column chromatography. Interestingly, addition of MgO to the conditions using MeOTs resulted in absolutely no reaction.
(Entry 5). Trace acid in the MeOTs was likely catalyzing the reaction rather than by methylation, as MgO would scavenge any acid present. With this in mind, Peng suggested substituting CSA for the MeOTs since it worked well to catalyze the reaction with PMB-trichloroacetimidate 6.1. Indeed, we were able to obtain an increased yield of 3.12 (85%) with a lower reaction temperature (Entry 6).

### 6.3 Testing the Scope of Application

With what seemed to be a very effective and mild means to install a PMB ether available, we screened a wide variety of alcohols to determine what limitations, if any, existed to our method. Specifically, we chose substrates that were either hindered or could potentially suffer from acidic conditions. Table 6.2 shows a selection of the most hindered, complex, and potentially acid-sensitive alcohols tested using our PMBO-lepidine 6.3/CSA system. Entries 1, 2, and 5 show the successful protection of hindered secondary alcohols, while entries 4 and 6 show good yields for both simple and complex tertiary alcohols. We also included entry 5 due to the acid-labile acetonides, which were not harmed. Entries 3 and 6 demonstrate that allylic substrates are not subject to acid-catalyzed rearrangements under these reaction conditions. For comparative purposes, entries 1 and 5 were also subjected to our initial PMBO-lepidine 6.3/MeOTs system, and the products were formed in 65% and 93% yields, respectively.

Overall, our efforts have demonstrated that PMBO-lepidine 6.3 can be effectively activated with either MeOTs or especially a catalytic quantity of CSA to afford PMB ethers under mildly acidic conditions and with terrific ease of purification.
Table 6.1: Summary of conditions tested for protection of alcohol 3.11.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>6.1</strong>, CSA or TfOH, Et₂O, −10 to 10 °C</td>
<td>~65</td>
</tr>
<tr>
<td>2</td>
<td><strong>6.3</strong>, MeOTf, MgO, PhCH₃, 0 °C to rt</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td><strong>6.3</strong>, MeOTf, K₂CO₃, PhCH₃, 0 °C to rt</td>
<td>decomposition</td>
</tr>
<tr>
<td>4</td>
<td><strong>6.3</strong>, MeOTs, PhCH₃, 35 °C</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td><strong>6.3</strong>, MeOTs, MgO, PhCH₃, 35 °C</td>
<td>no reaction</td>
</tr>
<tr>
<td>6</td>
<td><strong>6.3</strong>, CSA, CH₂Cl₂, rt</td>
<td>85</td>
</tr>
</tbody>
</table>
### Table 6.2: Selection of alcohols protected with PMBO-lepidine 6.3/CSA.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Entry</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
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<td>1</td>
<td><img src="image2.png" alt="Product" /></td>
<td>48</td>
<td>95</td>
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<tr>
<td>TBDPSO</td>
<td>2</td>
<td>TBDPSO</td>
<td>96</td>
<td>91</td>
</tr>
<tr>
<td>Ph=CH=CH2</td>
<td>3</td>
<td>Ph=CH=CH2OPMB</td>
<td>24</td>
<td>94</td>
</tr>
<tr>
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</tr>
<tr>
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<td><img src="image6.png" alt="Product" /></td>
<td>48</td>
<td>quantitative</td>
</tr>
<tr>
<td><img src="image7.png" alt="Substrate" /></td>
<td>6</td>
<td><img src="image8.png" alt="Product" /></td>
<td>48</td>
<td>79</td>
</tr>
</tbody>
</table>
CHAPTER 7

EXPERIMENTALS

General Methods

Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR spectrometer. Mass spectral data were obtained with either electron impact (EI) ionization or positive ion electron spray (ESI) ionization. Optical rotations were measured on a Perkin Elmer 241 polarimeter using the sodium D line.

Proton nuclear magnetic resonance (\(^1\)H NMR) and carbon nuclear magnetic resonance (\(^{13}\)C NMR) spectra were recorded at 25 °C on Bruker spectrometers at 500, 400, or 300 and 125, 100, or 75 MHz, respectively. \(^1\)H chemical shifts are reported in ppm (δ) relative to the residual chloroform (δ 7.26) for spectra using CDCl\(_3\). Coupling constants are reported in Hertz (Hz). \(^1\)H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). \(^{13}\)C Chemical shifts are reported in ppm (δ) relative to the residual chloroform (δ 77.16) for spectra using CDCl\(_3\) as the solvent. For previously published compounds, only NMR data is provided.

All moisture sensitive reactions were run in oven-dried glassware under a dry nitrogen or argon atmosphere unless otherwise noted. Toluene (PhMe) and benzene (PhH) were distilled from sodium immediately before use. Tetrahydrofuran (THF) and diethyl ether (Et\(_2\)O) were distilled from sodium benzophenone ketyl immediately before use. Triethylamine (Et\(_3\)N), dichloromethane (CH\(_2\)Cl\(_2\)), diisopropylethylamine (iPrNEt), pyridine (py), acetonitrile (CH\(_3\)CN), and diisopropylamine (iPr\(_2\)NH) were distilled from calcium hydride immediately before use. Dimethylformamide (DMF)
and dimethylsulfoxide (DMSO) were dried over 4 Å molecular sieves. Hexamethylphosphoramide (HMPA) was distilled and stored over 4 Å molecular sieves. All other solvents and reagents were used as received unless otherwise indicated.

Thin-layer chromatography was performed on precoated silica gel 60 F254 aluminum sheets and the column chromatographic separations were performed with silica gel (40-63 μm).

**Iodo Diene Side Chain 5.2:** Hydroxy side chain 3.8 (167 mg, 0.40 mmol), imidazole (136 mg, 2.0 mmol), and DMAP (4.9 mg, 0.04 mmol) were taken up in DMF (0.17 mL) and cooled to 0 °C (ice). TESCl (0.12 mL, 0.60 mmol) was added and the reaction mixture was stirred for 10 min. The cold bath was removed and the reaction mixture was stirred for 1 h at 28 °C, quenched with H₂O (2 mL), and diluted with Et₂O (6 mL). The layers were separated and the aqueous phase was extracted with Et₂O (3 x 6 mL). The combined organics were dried (Na₂SO₄) and concentrated in vacuo to give a yellow oil. Column chromatography (1.5 x 17 cm silica; petroleum ether, 1% EtOAc/petroleum ether) afforded 5.2 as a clear, colorless oil (181 mg, 85%, 2:1 anti/syn). Major isomer (anti): ¹H NMR (400 MHz, CDCl₃) δ 6.07 (s, 1 H), 5.76 (s, 1 H), 5.20 (s, 1 H), 5.18 (s, 1 H), 4.06–4.02 (m, 1 H), 3.92–3.87 (m, 1 H), 2.78 (d, J = 14 Hz, 1 H), 2.67 (d, J = 14 Hz, 1 H), 2.28–2.17 (m, 2 H), 1.00–0.96 (m, 9 H), 0.88 (s, 9 H), 0.67–0.61 (m, 6 H), 0.14–0.11 (m, 6 H). ¹³C NMR (100 MHz, CDCl₃) δ 140.7, 128.6, 115.1, 110.1, 72.8, 71.3, 46.7, 41.5, 26.0 (3 C), 18.2, 7.21 (3 C), 5.22 (3 C), -3.8, -4.0. TOF MS ES+ [M+Na] calcd: 553.1198, obsd: 553.1206.

**2,3:4,6-Di-O-isopropylidene-α-mannopyranose 3.9 and Furanose Isomer 5.4:** D-(+)-Mannose (50.0 g, 0.278 mol) and p-toluenesulfonic acid monohydrate (5.29 g, 0.0278 mol) were dissolved in DMF (178 mL). The clear, yellow solution was cooled to –5 °C (ice/salt). 2-Methoxypropene (54 mL, 0.556 mol) was added dropwise over 25 min at –5 °C. The resulting solution was stirred for 2 h at –5 to –10 °C. The second portion of 2-methoxypropene (54 mL, 0.556 mol) was added dropwise over 30 min and the resulting solution was stirred for 2 h at –10 to –8 °C. The reaction mixture was
quenched at –8 °C by the addition of solid NaHCO₃ (18.4 g). The mixture was stirred for 15 min, the cold bath was removed, and the mixture allowed to warm to 10 °C. The mixture was filtered and the filtrate partitioned between Et₂O and H₂O (200 mL/200 mL). The aqueous layer was extracted with Et₂O (4 x 200 mL). The combined organic layers were washed with H₂O (10 x 100 mL), dried (Na₂SO₄), and concentrated in vacuo to give a white crystalline solid (55 g, 76%, 2.5:1 pyranose/furanose). The crude mixture of isomers was recrystallized from EtOAc/hexanes (x 3) to give the pure desired pyranose isomer 3.9 as clear, colorless, diamond-shaped crystals (24.1 g, 33%). For practical purposes, the two isomers were usually recrystallized together and carried on as a mixture to the next step: ¹H NMR (400 MHz, CDCl₃) δ 5.43 (d, J = 3.2 Hz, 1 H), 4.22–4.18 (m, 2 H), 3.89–3.71 (m, 4 H), 2.99 (m, 1 H), 1.55 (s, 3 H), 1.51 (s, 3 H), 1.43 (s, 3 H), 1.36 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 109.7, 99.9, 93.0, 76.3, 74.8, 72.8, 62.2, 61.8, 29.2, 28.3, 26.3, 19.0.

2,3:5,6-Di-O-isopropylidene-D-mannofuranose 5.4: ¹H NMR (400 MHz, CDCl₃) δ 5.38 (s, 1 H), 4.81 (dd, J = 3.6, 6.0 Hz, 1 H), 4.62 (d, J = 6.0 Hz, 1 H), 4.41 (dt, J = 6.8, 7.2 Hz, 1 H), 4.19 (dd, J = 3.6, 7.2 Hz, 1 H), 4.13–4.03 (m, 2 H), 2.64 (br s, 1 H), 1.47 (s, 3 H), 1.46 (s, 3 H), 1.38 (s, 3 H), 1.33 (s, 3 H).

2,3:4,6-Di-O-isopropylidene-D-mannopyranone 3.10: A solution of oxalyl chloride (9.5 mL, 109 mmol) in dry CH₂Cl₂ (130 mL) was cooled to –78 °C (acetone/CO₂). DMSO (15 mL, 217 mmol) was added dropwise over 10 min at –78 °C and the mixture was stirred for 15 min. A solution of mixed lactols 3.9 and 5.4 (9.41 g, 36.2 mmol, 1:2) in dry CH₂Cl₂ (47 mL) was added dropwise via cannula over 30 min and the reaction mixture was stirred for 1.5 h at –78 °C. Et₃N (45 mL, 326 mmol) was added dropwise over 10 min at –78 °C and the resulting mixture stirred for 1 h. The cold bath was removed and the yellow slurry allowed to warm to 25 °C with stirring over ~1.5 h. The mixture was washed with H₂O (1 x 200 mL). The aqueous layer was extracted with CH₂Cl₂ (2 x 100 mL) and the combined organic layers were dried (Na₂SO₄) and concentrated in vacuo to give a orange-yellow crystalline solid, which was purified by biphasic trituration with H₂O/EtOAc to yield the pure lactone.
3.10 as a fine white crystalline solid (3.02 g, 97%): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.75 (d, $J = 8.4$ Hz, 1 H), 4.60 (dd, $J = 6.4, 8.4$ Hz, 1 H), 4.12–4.04 (m, 2 H), 3.90–3.83 (m, 2 H), 1.56 (s, 3 H), 1.54 (s, 3 H), 1.46 (s, 3 H), 1.42 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 168.7, 113.0, 100.3, 76.9, 72.8, 72.3, 67.4, 61.6, 28.8, 26.8, 25.2, 18.9.

2,3:5,6-Di-O-isopropylidene-\textit{d}-mannofuranone: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.87 (dd, $J = 3.2$, 5.2 Hz, 1 H), 4.83 (d, $J = 5.2$ Hz, 1 H), 4.44 (ddd, $J = 4.0$, 5.6, 8.0 Hz, 1 H), 4.37 (dd, $J = 3.2$, 8.0 Hz, 1 H), 4.15 (dd, $J = 5.6$, 9.2 Hz, 1 H), 4.07 (dd, $J = 4.0$, 9.2 Hz, 1 H), 1.48 (s, 3 H), 1.47 (s, 3 H), 1.43 (s, 3 H), 1.39 (s, 3 H).

\textit{\alpha}-Methyl Pyranone 5.5: A solution of LDA (43.4 mmol) in THF (26.0 mL) was added dropwise via cannula to a solution of pyranone 3.10 (8.62 g, 33.4 mmol) in THF (208 mL) over 25 min at –78 °C. The pale yellow solution was stirred for 15 min at –78 °C and for 1 h at –40 °C, cooled to –78 °C and MeI (10.4 mL, 167 mmol) was added dropwise over 20 min. The yellow solution was stirred for 15 min at –78 °C and for 1 h at –40 °C, cooled to –78 °C and the reaction mixture was quenched by the slow addition of pH 7.0 phosphate buffer (52 mL) and saturated aqueous NH$_4$Cl solution (26 mL). The cold bath was removed and the mixture allowed to warm with stirring until a smooth slurry was obtained, which was diluted with EtOAc (500 mL) and washed with brine (2 x 200 mL). The original aqueous layer was extracted with EtOAc (1 x 100 mL). The combined organic layers were dried (Na$_2$SO$_4$) and concentrated \textit{in vacuo} to give a pale yellow crystalline solid which was recrystallized from EtOAc/H$_2$O to yield the pure methylated product 5.5 as a fine, white crystalline solid (6.35 g, 70%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.19 (d, $J = 6.4$ Hz, 1 H), 4.13–4.06 (m, 2 H), 3.89–3.83 (m, 2 H), 1.69 (s, 3 H), 1.56 (s, 3 H), 1.46 (s, 6 H), 1.45 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.7, 112.2, 100.3, 82.7, 79.6, 73.7, 67.2, 61.7, 28.8, 27.4, 26.9, 26.2, 18.9, 14.5.
α-Deoxygenated Pyranone 3.11: A solution of 1,2-diiodoethane (310 mg, 1.1 mmol) in THF (28 mL) was deoxygenated with Ar (15 min) and transferred via cannula to a flask containing samarium powder (or chips) (331 mg, 2.2 mmol) under Ar, with stirring. The mixture slowly afforded a yellow green solution, which darkened to brown, and was stirred overnight to afford a deep blue solution of SmI$_2$.\textsuperscript{35}

A solution of methyl lactone 5.5 (100 mg, 0.37 mmol), HMPA (0.37 mL), and ethylene glycol (0.19 mL) in THF (4 mL) was deoxygenated with Ar (13 min) with stirring and treated via cannula with the above solution of SmI$_2$ to afford a grey mixture, which was poured into hexanes (30 mL). The slurry was filtered through a pad of Celite on a pad of silica gel (EtOAc). The filtrate was concentrated in vacuo to afford a pale yellow crystalline solid. Column chromatography (3.5 x 13 cm silica; 2:1 hexanes/EtOAc, 1:1 hexanes/EtOAc) afforded 3.11 as a pale yellow crystalline solid (71 mg, 88%): $^1$H NMR (400 MHz, CDCl$_3$) δ 4.01 (dd, $J = 10.4$, 5.2 Hz, 1 H), 3.96–3.89 (m, 1 H), 3.82 (t, $J = 10.4$ Hz, 1 H), 3.76 (t, $J = 9.2$ Hz, 1 H), 3.68 (t, $J = 9.2$ Hz, 1 H), 2.65–2.57 (m, 2 H), 1.55 (s, 3 H), 1.48 (d, $J = 7.6$ Hz, 3 H), 1.45 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 171.4, 100.3, 73.2, 72.5, 69.0, 61.5, 43.6, 28.9, 19.0, 14.9.

PMB Ether 3.12: A mixture of alcohol 3.11 (2.00 g, 9.25 mmol) and PMBO-lepidine 6.3 (5.14 g, 18.5 mmol) was taken up in a minimal amount of PhH, concentrated in vacuo and the flask flushed with Ar. The mixture was taken up in CH$_2$Cl$_2$ (18.5 mL) and treated with CSA (215 mg, 0.925 mmol) at 27 °C. The reaction mixture was stirred for 50 h, concentrated under reduced pressure and purified by column chromatography (5 x 10 cm silica; hexanes, 5:1 hexanes/EtOAc) to give 3.12 as a white crystalline solid (2.50 g, 80%): $^1$H NMR (400 MHz, CDCl$_3$) δ 7.26 (d, $J = 8.6$ Hz, 2 H), 6.90 (d, $J = 8.6$ Hz, 2 H), 4.80 (d, $J = 11.2$ Hz, 1 H), 4.60 (d, $J = 11.2$ Hz, 1 H), 4.04–4.00 (m, 1 H), 3.97–3.91 (m, 2 H), 3.84–3.80 (m, 1 H), 3.81 (s, 3 H), 3.49–3.46 (m, 1 H), 2.64 (quintet, $J = 7.4$ Hz, 1 H), 1.56 (s, 3 H), 1.48 (s, 3 H), 1.37 (d, $J = 7.3$ Hz, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 172.0, 159.2, 130.1, 129.7 (2 C), 113.9 (2 C), 99.8, 79.2, 73.7, 73.6, 68.7, 61.7, 55.3, 43.0, 29.0, 19.1, 15.8.
**Pyranyl Olefin 5.6:** A solution of PMB-protected alcohol 3.12 (10.1 g, 30.0 mmol) in 4:1 THF/py (180 mL/45 mL) was cooled to –78 °C (CO₂/acetone) and treated with a 0.67 M solution of Tebbe reagent in toluene (89.6 mL, 60.0 mmol) in portions. The red solution was stirred for 30 min at –78 °C, moved to a –10 °C bath (salt/ice) and stirred for 30 min. The cold bath was removed and the reaction mixture was stirred for 1.5 h at 28 °C, cooled to –10 °C and quenched by the dropwise addition of 20% aqueous NaOH solution (200 mL) to afford a brown-yellow mixture. After gas evolution ceased, the mixture was diluted with Et₂O (200 mL), allowed to warm to rt (~1 h), and filtered through a pad of Celite with Et₂O and H₂O. The separated aqueous layer was extracted with Et₂O (1 x 150 mL) and the combined organic layers were dried (MgSO₄) and concentrated in vacuo to give a dark brown oil. Rapid column chromatography (6.5 x 10 cm silica pretreated with 1% Et₃N/hexanes; hexanes, 3:1 hexanes/EtOAc) gave 5.6 as an orange-yellow oil (8.04 g, 80%), which was used immediately in the next step: ¹H NMR (400 MHz, CDCl₃) δ 7.29 (d, J = 8.4 Hz, 2 H), 6.88 (d, J = 8.4 Hz, 2 H), 4.82 (d, J = 10.8 Hz, 1 H), 4.57 (s, 1 H), 4.57 (d, J = 10.8 Hz, 1 H), 4.34 (d, J = 0.8 Hz, 1 H), 3.97 (dd, J = 10.4, 5.2 Hz, 1 H), 3.87 (t, J = 9.2 Hz, 1 H), 3.81 (s, 3 H), 3.80 (t, J = 10.4 Hz, 1 H), 3.32 (dt, J = 10.0, 5.2 Hz, 1 H), 3.16 (dd, J = 10.0, 8.8 Hz, 1 H), 3.83–2.31 (m, 1 H), 1.55 (s, 3 H), 1.45 (s, 3 H), 1.18 (d, J = 9.8 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 161.9, 159.4, 131.0, 129.9 (2 C), 113.9 (2 C), 99.6, 94.5, 81.2, 76.4, 74.2, 72.0, 62.7, 55.5, 39.8, 29.5, 19.5, 14.1.

**Primary Alcohol 3.13:** A solution of olefin 5.6 (3.70 g, 11.1 mmol) in dry THF (11 mL) was cooled to –10 °C (salt/ice) and treated with a 0.5 M solution of 9-BBN in THF (66.4 mL, 33.2 mmol). The reaction mixture was allowed to stir overnight (13 h) as the cold bath warmed to 30 °C. The reaction mixture was cooled to –10 °C and sequentially treated with H₂O (33 mL), 20% aqueous NaOH (33 mL), and 30% H₂O₂ (33 mL). The resulting opaque white slurry was stirred for 2 h at 0 °C and for 2 h at rt, adding H₂O as necessary to maintain stirring. The mixture was diluted with CH₂Cl₂ (250 mL) and H₂O (150 mL) and the separated aqueous layer was extracted with CH₂Cl₂ (3 x 50 mL). The
combined organic layers were dried (MgSO₄) and concentrated in vacuo to give a pale yellow oil. Purification by column chromatography (5 x 10 cm silica; hexanes, 1:1 hexanes/EtOAc) gave 3.13 as a white crystalline solid (3.42 g, 87%): ¹H NMR (300 MHz, CDCl₃) δ 7.27 (d, J = 8.7 Hz, 2 H), 6.87 (d, J = 8.7 Hz, 2 H), 4.82 (d, J = 14.6 Hz, 1 H), 4.55 (d, J = 14.6 Hz, 1 H), 3.90 (dd, J = 10.6, 5.4 Hz, 1 H), 3.80 (s, 3 H), 3.80–3.66 (m, 3 H), 3.57–3.50 (m, 1 H), 3.33–3.23 (m, 2 H), 3.16 (dd, J = 9.8, 8.7 Hz, 1 H), 1.98–1.94 (m, 1 H), 1.76–1.62 (m, 1 H), 1.53 (s, 3 H), 1.44 (s, 3 H), 0.95 (d, J = 6.5 Hz, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 159.2, 131.0, 129.7 (2 C), 113.7 (2 C), 100.0, 82.2, 81.2, 76.5, 74.1, 71.4, 63.5, 62.4, 55.3, 37.9, 29.3, 19.3, 13.1.

**Methyl Ester 3.2:** To a solution of (COCl)₂ (1.2 mL, 13.6 mmol) in CH₂Cl₂ (47.6 mL) at –78 °C (CO₂/acetonitrile) was added dropwise DMSO (1.45 mL, 20.4 mmol). The resulting solution was stirred for 30 min, treated in portions with a solution of alcohol 3.13 (0.48 g, 1.36 mmol) in CH₂Cl₂ (9.5 mL), and allowed to stir for 1 h at –78 °C and for 1 h at –50 °C (CO₂/CH₃CN). The reaction mixture was cooled to –78 °C and treated dropwise with Et₃N (5.7 mL, 40.8 mmol). The slurry was stirred for 2 h at –78 °C, the reaction mixture was quenched by the addition of H₂O (4.8 mL), and the mixture was allowed to warm to 28 °C. The clear orange solution was diluted with H₂O (50 mL) and the separated aqueous layer extracted with CH₂Cl₂ (2 x 20 mL). The combined organics were dried (Na₂SO₄) and concentrated in vacuo. The resulting pale yellow oily solid was dissolved in 10:1 tBuOH/H₂O (13 mL/1.3 mL), diluted with 2-methyl-2-butene (3 mL) and treated sequentially with Na₂HPO₄•H₂O (563 mg, 4.08 mmol) and NaClO₂ (738 mg, 8.16 mmol) at 28 °C. The reaction mixture became intensely yellow, which faded slowly, while the solution was stirred for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was taken up in a 1:1 mixture of saturated aqueous NH₄Cl solution and CH₂Cl₂ (40 mL). The separated aqueous layer was extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo to give a clear, colorless oil which was dissolved in Et₂O (19 mL), cooled to –10 °C (ice/NaCl), and treated dropwise with an ethereal solution of CH₂N₂ until the solution 71
remained yellow and gas evolution ceased. The reaction mixture was stirred for 20 min at 0°C and
for 2 h at 26 °C to give a pale yellow solution, which was concentrated in vacuo to give a yellow
oil that was purified by column chromatography (4.5 x 8.5 cm silica; hexanes, 4:1 hexanes/EtOAc,
2:1 hexanes/EtOAc) to give 3.2 as a colorless oil (0.32 g, 62%, 3 steps), which crystallized upon
standing: $^1$H NMR (300 MHz, CDCl$_3$) δ 7.27 (d, $J = 8.6$ Hz, 2 H), 6.87 (d, $J = 8.6$ Hz, 2 H), 4.81 (d,
$J = 11.0$ Hz, 1 H), 4.56 (d, $J = 11.0$ Hz, 1 H), 3.93–3.73 (m, 4 H), 3.80 (s, 3 H), 3.75 (s, 3 H), 3.30
(m, 1 H), 3.18 (m, 1 H), 2.01–1.92 (m, 1 H), 1.58 (s, 3 H), 1.44 (s, 3 H), 0.95 (d, $J = 6.6$ Hz, 3 H);
$^{13}$C NMR (75 MHz, CDCl$_3$) δ 169.7, 159.2, 130.8, 129.7 (2 C), 113.7 (2 C), 99.4, 81.8, 80.8, 75.8,

**Diol 5.7:** A solution of methyl ester 3.2 (60.5 mg, 0.159 mmol) in THF (0.61 mL) was treated with
1 N HCl (0.61 mL) at rt and the mixture was vigorously stirred for 2 h. The reaction mixture was
diluted with EtOAc (3 mL) and H$_2$O (0.5 mL), the layers were separated, and the aqueous layer was
extracted with EtOAc (3 x 3 mL). The combined organics were dried (Na$_2$SO$_4$) and concentrated
in vacuo to afford a clear colorless oil. Purification by column chromatography (2 x 7.5 cm silica;
CH$_2$Cl$_2$, 1% MeOH/CH$_2$Cl$_2$, 2.5% MeOH/CH$_2$Cl$_2$, 5% MeOH/CH$_2$Cl$_2$) gave 5.7 as a colorless oil
(46.6 mg, 86%); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.29–7.27 (m, 2 H), 6.90–6.87 (m, 2 H), 4.72–4.64
(m, 2 H), 3.90–3.62 (m, 4 H), 3.80 (s, 3 H), 3.76 (s, 3 H), 3.36–3.30 (m, 1 H), 3.16–3.10 (m, 1 H),
2.57 (br s, 2 H), 2.01–1.87 (m, 1 H), 0.99 (d, $J = 6.6$ Hz, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 170.4,
159.6, 130.5, 129.7 (2 C), 114.2 (2 C), 85.8, 81.1, 80.0, 74.5, 71.3, 62.7, 55.4, 52.4, 39.5, 12.9.

**Iodo TMS Ether 5.9 via Iodo Alcohol 5.8:** A solution of diol 5.7 (50 mg, 0.15 mmol) in PhH (2.5
mL) was treated with pyridine (0.06 mL, 0.74 mmol), triphenylphosphine (193 mg, 0.74 mmol), and
iodine (112 mg, 0.44 mmol) to give a brown slurry, which was heated at reflux with stirring for 2 h.
The resulting bright orange mixture was cooled to rt, diluted with H$_2$O (5 mL) and EtOAc (5 mL),
and washed with H$_2$O until no yellow solid remained (5 x 5 mL). The combined aqueous washings
were extracted with EtOAc (3 x 10 mL), and the combined organic layers were dried (Na$_2$SO$_4$) and evaporated under reduced pressure to give a cloudy, off-white oil. Column chromatography (1.5 x 14 cm silica; hexanes, 5% EtOAc/hexanes, 20% EtOAc/hexanes) gave 5.8 as a white oil which was used immediately.

A solution of the above alcohol was taken up in CH$_2$Cl$_2$/DMF (1.2 mL/0.1 mL), cooled to 0 °C, and treated with pyridine (0.12 mL, 1.47 mmol), DMAP (18 mg, 0.147 mmol), and trimethylsilyl chloride (0.09 mL, 0.735 mmol). The cold bath was removed and the reaction mixture was stirred for 1 h at 26 °C, quenched with water (1.5 mL), and diluted with CH$_2$Cl$_2$ (1.5 mL). The separated aqueous phase was extracted with CH$_2$Cl$_2$ (2 x 3 mL), and the combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo to give a slightly off-white oil. The crude product was purified by chromatography (1 x 16 cm silica gel; hexanes, 5% EtOAc/hexanes, 10% EtOAc/hexanes) to afford 5.9 as a colorless oil (66 mg, 86%), which solidified in the freezer: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.28 (d, J = 8.6 Hz, 2 H), 6.87 (d, J = 8.6 Hz, 2 H), 4.81 (d, J = 11.0 Hz, 1 H), 4.52 (d, J = 11.0 Hz, 1 H), 3.82 (s, 3 H), 3.78 (s, 3 H), 3.74 (d, J = 10.6 Hz, 1 H), 3.54 (dd, J = 13.2, 2.3 Hz, 1 H), 3.52 (s, 1 H), 3.27 (dd, J = 10.6, 6.8 Hz, 1 H), 3.16–3.06 (m, 2 H), 1.97 (m, 1 H), 0.89 (d, J = 6.6 Hz, 3 H), 0.21 (s, 9 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 169.6, 159.1, 130.3, 129.0 (2 C), 113.7 (2 C), 85.5, 81.1, 79.6, 75.9, 75.0, 55.2, 52.2, 40.0, 12.6, 7.0, 0.9 (3 C).

Enol Ether 5.10: Iodide 5.9 (60 mg, 0.115 mmol) was taken up in benzene (1.2 mL), treated with DBU (0.17 mL, 1.15 mmol), and heated at 65 °C for 5.5 h. The reaction mixture was concentrated under high vacuum and purified by column chromatography on silica gel treated with 2% triethyl amine/hexanes (20% EtOAc/hexanes) to give enol ether 5.10 as a clear, colorless oil that was used directly (41 mg, 90%): $^1$H NMR (CDCl$_3$, 300 MHz) δ 7.31–7.25 (m, 2 H), 6.91–6.86 (m, 2 H), 4.85 (d, J = 11.0 Hz, 1 H), 4.74–4.69 (m, 2 H), 4.53 (d, J = 11.0 Hz, 1 H), 4.16–4.12 (m, 1 H), 3.81 (s, 3 H), 3.79 (s, 3 H), 3.15–3.05 (m, 1 H), 2.18–2.01 (m, 2 H), 0.90 (d, J = 6.7 Hz, 3 H), 0.19 (s, 9 H).
Suzuki Adduct, 5.11: Enol ether 5.10 (41 mg, 0.104 mmol) was taken up in THF (0.21 mL), cooled to 0 °C (ice), treated with a 0.5 M solution of 9-BBN in THF (0.62 mL, 0.31 mmol), and stirred for 10 min. The cold bath was removed and the reaction mixture was stirred for 2 h at 26 °C. A 1:1 mixture of DMF (0.10 mL) and 3 M K$_3$PO$_4$ (0.10 mL, 0.31 mmol) was added, gas evolution occurred, and the mixture was stirred for 30 min. A neat mixture of 5.2 (83 mg, 0.16 mmol) and PdCl$_2$(dppf) (8.5 mg, 0.010 mmol) was allowed to stand for 30 min, then was taken up in DMF (0.52 mL). After another 30 min, this suspension was added to the above B-alkyl adduct to give an orange/brown slurry. The reaction mixture was stirred for 2.25 h and diluted with H$_2$O (1.5 mL) and Et$_2$O (10 mL). The separated aqueous layer was extracted with Et$_2$O (3 x 5 mL). The combined organics were dried and concentrated in vacuo to give a red-orange oil. Column chromatography on silica gel (1-5% EtOAc/petroleum ether) afforded 5.11 slightly contaminated with borane residues (53 mg, 64%); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.27 (d, $J$ = 8.6 Hz, 2 H), 6.87 (d, $J$ = 8.6 Hz, 2 H), 5.24 (s, 1 H), 5.19 (s, 1 H), 4.90 (s, 1 H), 4.88 (s, 1 H), 4.81 (d, $J$ = 11.0 Hz, 1 H), 4.52 (d, $J$ = 11.0 Hz, 1 H), 4.00–3.96 (m, 1 H), 3.80 (s, 3 H), 3.80–3.78 (m, 1 H), 3.72 (s, 3 H), 3.43–3.38 (m, 1 H), 3.33–3.27 (m, 1 H), 3.04 (dd, $J$ = 10.2, 8.4 Hz, 1 H), 2.53–2.38 (m, 3 H), 2.31–2.24 (m, 1 H), 2.15–2.01 (m, 2 H), 1.96–1.84 (m, 1 H), 0.97–0.83 (m, 21 H), 0.67–0.56 (m, 6 H), 0.17 (s, 9 H), 0.08 (s, 3 H), 0.02 (s, 3 H).

TBS Ether 5.12: Suzuki adduct 5.11 (21 mg, 0.0263 mmol) was taken up in 3:1 THF/MeOH (0.53 mL/0.18 mL) and treated with K$_2$CO$_3$ (7.3 mg, 0.053 mmol) at 27 °C. The reaction mixture was stirred vigorously for 3 h and diluted with EtOAc (2 mL) and saturated NaHCO$_3$ solution (2 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 2 mL). The combined organics were dried and concentrated in vacuo to give a pale yellow oil. Column chromatography on silica gel (10-20% EtOAc/hexanes) gave the desired free alcohol as pale yellow oil contaminated with borane residues; used immediately: $^1$H NMR (300 MHz, CDCl$_3$) δ 7.32–7.27 (m, 2 H), 6.93–6.89 (m, 2 H), 5.21 (s, 1 H), 5.18 (s, 1 H), 4.95 (s, 1 H), 4.90 (s, 1 H), 4.71 (d, $J$ = 11.0 Hz, 1 H), 4.63
(d, J = 11.0 Hz, 1 H), 3.98–3.94 (m, 1 H), 3.80 (s, 3 H), 3.79–3.76 (m, 1 H), 3.74 (s, 3 H), 3.64 (d, J = 10.5 Hz, 1 H), 3.44–3.32 (m, 2 H), 3.09 (dd, J = 10.3, 8.3 Hz, 1 H), 2.59–2.43 (m, 3 H), 2.29–1.94 (m, 3 H), 1.00–0.87 (m, 21 H), 0.64–0.56 (m, 6 H), 0.06 (s, 3 H), 0.00 (s, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 170.0, 159.4, 143.3, 140.8, 130.6, 129.7 (2 C), 115.7, 115.1, 114.3 (2 C), 86.3, 81.4, 79.9, 77.1, 74.9, 74.6, 74.4, 73.2, 55.5, 52.2, 43.1, 41.0, 39.5, 38.6, 26.2 (3 C), 18.4, 7.1 (3 C), 5.2 (3 C), -4.0, -4.5.

A solution of the above free alcohol in CH$_2$Cl$_2$ (0.66 mL) was treated with 2,6-lutidine (0.06 mL, 0.53 mmol) at 26 °C. The reaction mixture was cooled to –78 °C (CO$_2$/acetone), treated with TBSOTf (0.06 mL, 0.26 mmol), and stirred for 1 h at –78 °C. The flask was moved to a 0 °C bath (ice) and the reaction mixture was stirred for 30 min, quenched with saturated NaHCO$_3$ solution (1 mL), diluted with Et$_2$O (2 mL), and allowed to warm to 26 °C. The layers were separated and the aqueous layer was extracted with Et$_2$O (3 x 3 mL). The combined organic phases were dried (Na$_2$SO$_4$) and concentrated in vacuo. Column chromatography on silica gel (1-5% EtOAc/petroleum ether) afforded 5.12 as a clear, colorless oil (17.6 mg, 80%, 2 steps): [α]$_D$$_{20}$$^+$+43.4 (c 0.18, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.28–7.24 (m, 2 H), 6.89–6.85 (m, 2 H), 5.25 (s, 1 H), 5.19 (d, J = 0.8 Hz, 1 H), 4.88 (s, 1 H), 4.87 (s, 1 H), 4.79 (d, J = 11.2 Hz, 1 H), 4.51 (d, J = 11.2 Hz, 1 H), 4.01–3.97 (m, 1 H), 3.83–3.77 (m, 1 H), 3.80 (s, 3 H), 3.71 (s, 3 H), 3.61 (d, J = 10.6 Hz, 1 H), 3.42–3.36 (m, 1 H), 3.32–3.26 (m, 1 H), 3.05 (dd, J = 10.3, 8.4 Hz, 1 H), 2.58–2.29 (m, 4 H), 2.14–1.94 (m, 3 H), 0.99–0.83 (m, 30 H), 0.65–0.57 (m, 6 H), 0.11–0.06 (m, 9 H), 0.01 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 170.2, 159.0, 143.8, 140.9, 130.6, 129.0 (2 C), 114.7, 113.7 (2 C), 113.3, 86.1, 81.5, 81.3, 77.2, 75.5, 74.7, 73.8, 71.9, 55.3, 52.0, 40.9, 40.2, 39.3, 37.2, 26.1 (3 C), 25.9 (3 C), 18.0 (2 C), 7.0 (3 C), 5.1 (3 C), -3.5, -3.8, -4.28, -4.30; ESI HRMS [M+Na] m/z calcd: 863.4513; obsd: 863.4485.

Carboxylic Acid 5.13: Methyl ester 5.12 (36 mg, 0.043 mmol) in THF (2.0 mL) was treated with KOTMS (11 mg, 0.086 mmol) at 30 °C and stirred overnight (17 h). The reaction mixture was quenched with saturated aqueous NH$_4$Cl solution (6 mL) and diluted with Et$_2$O (10 mL). The
layers were separated and the aqueous layer was extracted with Et<sub>2</sub>O (3 x 10 mL). The combined organics were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo to give a cloudy, yellow oil. Column chromatography (0.5 x 9.5 cm silica; CH<sub>2</sub>Cl<sub>2</sub>, 2% MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) afforded 5.13 as a clear, colorless oil (28 mg, 78%): [α]<sub>D</sub><sup>20</sup> +2.76 (c 10.4, CHCl<sub>3</sub>); IR (thin film): 3394, 2924, 2868, 2826, 1734, 1507, 1458, 1270, 1228, 1091 cm<sup>-1</sup>; ¹H NMR (CDCl<sub>3</sub>, 400 MHz): diastereomeric mixture δ 7.27 (d, <i>J</i> = 8.4 Hz, 2 H), 6.87 (d, <i>J</i> = 8.0 Hz, 2 H), 5.21 (m, 2 H), 4.92 (m, 2 H), 4.78 (d, <i>J</i> = 11.2 Hz, 1 H), 4.52 (d, <i>J</i> = 11.2 Hz, 1 H), 3.99 (dd, <i>J</i> = 7.6, 4.4 Hz, 1 H), 3.82 (m, 1 H), 3.80 (s, 3 H), 3.65 (m, 1 H), 3.39 (m, 2 H), 3.08 (m, 1 H), 2.63 (m, 2 H), 2.47 (m, 2 H), 2.25 (m, 1 H), 2.09 (m, 2 H), 1.91 (m, 1 H), 1.04 (d, <i>J</i> = 6.4 Hz, 3 H), 0.85–1.00 (m, 27 H), 0.60 (m, 6 H), 0.15–0.00 (m, 12 H); ¹³C NMR (CDCl<sub>3</sub>, 100 MHz) diastereomeric mixture δ 159.11, 142.82, 140.30, 130.32, 128.91, 114.95, 114.85, 113.72, 85.99, 80.33, 75.46, 75.36, 75.05, 74.89, 72.93, 55.25, 43.60, 42.90, 40.54, 40.32, 39.16, 29.70, 26.04, 25.98, 25.90, 25.85, 18.21, 18.05, 17.99, 17.96, 13.24, 6.98, 5.08, 5.04, -3.55, -3.77, -4.12, -4.30, -4.57, -4.63; ESI HRMS [M+Na] m/z calcd for C<sub>42</sub>H<sub>75</sub>ClO<sub>8</sub>Si<sub>3</sub>: 849.4358, obsd: 849.4364.

**Acid Chloride 5.14:** Carboxylic acid 5.13 (12.2 mg, 0.015 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.15 mL) under Ar was cooled to 0 °C (ice/NaCl/H<sub>2</sub>O) and treated with the Ghosez reagent (2.3 mL, 0.018 mmol). The reaction mixture was stirred for 1.5 h at 0 °C, concentrated in vacuo, taken up in THF (0.15 mL), and used crude in the next step.

**Pentafluorophenyl Ester 5.15:** Crude carboxylic acid 5.13 (from 17.6 mg, 0.021 mmol of 5.12) in CH<sub>2</sub>Cl<sub>2</sub> (0.8 mL) was treated with DMAP (0.3 mg, 0.0021 mmol), DCC (8.6 mg, 0.0418 mmol) and pentafluorophenol (7.7 mg, 0.0418 mmol) at 27 °C. The reaction mixture was stirred 1.5 h, evaporated under reduced pressure, and purified by column chromatography (1.5 x 12 cm silica; hexanes, 10% EtOAc/hexanes) three times to afford 5.15 free of contaminants (10.8 mg, 52%, 2 steps): ¹H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.30–7.26 (m, 2 H), 6.90–6.87 (m, 2 H), 5.20–5.17 (m, 2 H),
4.91–4.89 (m, 2 H), 4.83 (d, \( J = 8.4 \text{ Hz} \), 1 H), 4.54 (d, \( J = 8.4 \text{ Hz} \), 1 H), 3.98–3.81 (series of m, 3 H), 3.81 (s, 3 H), 3.46–3.34 (series of m, 2 H), 3.15–3.10 (m, 1 H), 2.67–2.00 (series of m, 7 H), 1.00–0.81 (series of m, 30 H), 0.62–0.52 (m, 6 H), 0.11 (s, 6 H), 0.07 (s, 3 H), 0.01 (s, 3 H).

**α-Ketosulfone 5.16:** A neat mixture of methyl ester 5.12 (16.6 mg, 0.020 mmol) and sulfone 3.3 (31.4 mg, 0.039 mmol) was taken up in THF (0.20 mL), cooled to –78 °C (CO\(_2\)/acetone), and treated with a 0.85 M solution of LiHMDS in THF (0.05 mL, 0.039 mmol). The reaction mixture was allowed to warm with stirring to –30 °C over 4 h 45 min to afford a slightly yellow solution, and then stirred at –40 °C to –30 °C for 30 min. The reaction mixture was quenched with saturated aqueous NH\(_4\)Cl solution (1 mL), diluted with Et\(_2\)O (2 mL), and allowed to warm to rt. The separated aqueous layer was extracted with Et\(_2\)O (3 x 2 mL) and the combined organics were dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo to give a clear, colorless oil. Column chromatography (1.25 x 15.5 cm silica; hexanes, 5% to 10% Et\(_2\)O/hexanes) afforded 5.16 as a clear, colorless oil contaminated with 3.3 (43 mg, >100%): NMR data as a mixture of four diastereomers included in Appendix A; TOF MS ES\(^+\) [M+Na\(^+\)] calcd: 1627.8659, obsd: 1627.8636.

**Pentanal 5.17:**\(^44\) 1,5-Pentanediol (27.8 mL, 265.2 mmol) was dissolved in dry CH\(_2\)Cl\(_2\) (100 mL) in a round bottom flask under N\(_2\)(g) and cooled to 0 °C. Imidazole (6.8 g, 99.5 mmol) was added. TBSCI (10 g, 66.3 mmol) was dissolved in 100 mL CH\(_2\)Cl\(_2\) and added to the reaction mixture dropwise over 90 min via an addition funnel. The reaction mixture was warmed to rt over 12 h and transferred to a separatory funnel containing saturated aqueous NH\(_4\)Cl (100 mL) and CH\(_2\)Cl\(_2\) (100 mL). The separated aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 x 80 mL). The combined organic layers were washed with saturated aqueous NaCl solution, dried over MgSO\(_4\), filtered, and concentrated in vacuo. 5-(tert-Butyldimethylsilyloxy)pentan-1-ol (14.39 g, 99%) was isolated as a pale yellow oil: \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 3.63 (m, 4 H), 1.55 (m, 4 H), 1.42 (m, 2 H), 0.89 (s, 9 H), 0.042 (s, 3 H), 0.039 (s, 3H); \(^13\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 63.16, 62.96, 32.51, 26.01, 22.04, 18.41, -5.24.
A solution of (COCl)$_2$ (5.2 mL, 59.5 mmol) in CH$_2$Cl$_2$ (100 mL) was cooled to −78 °C and treated dropwise with a solution of DMSO (6.5 mL, 73.3 mmol) in CH$_2$Cl$_2$ (50 mL). The above alcohol (10 g, 45.8 mmol) was taken up in CH$_2$Cl$_2$ (50 mL) and added to the above solution. The reaction mixture was stirred for 15 min at −78 °C. Et$_3$N (16 mL, 114.5 mmol) was added slowly and the resulting mixture was stirred for 90 min at −78 °C and for 20 min after the cold bath was removed. The reaction mixture was poured into a separatory funnel containing a 1:1 mixture of saturated aqueous NH$_4$Cl solution and CH$_2$Cl$_2$. The separated aqueous layer was extracted with CH$_2$Cl$_2$ and the combined organics were washed with brine, dried (MgSO$_4$), and filtered through a plug of silica gel to afford 5.17 (9.5 g, 96%) as an oil: $^1$H NMR (CDCl$_3$, 400 MHz) δ 9.75 (t, $J$ = 1.6 Hz, 1 H), 3.61 (t, $J$ = 6.0 Hz, 2 H), 2.44 (td, $J$ = 7.2, 1.6 Hz, 2 H), 1.67 (quintet, $J$ = 7.6 Hz, 2 H), 1.53 (m, 2 H), 0.88 (s, 9 H), 0.03 (s, 6 H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 202.58, 62.55, 43.58, 32.08, 25.94, 18.61, 18.28, -5.37.

TES Protected Evans Aldol Adduct 5.18: (S)-4-Benzyl-3-propionyloxazolidin-2-one (4.49 g, 19.3 mmol) was stirred in dry CH$_2$Cl$_2$ (75 mL) in a flame-dried round bottom flask under N$_2$(g) and cooled to −78 °C. Neat Bu$_2$BOTf (5.8 mL, 23.1 mmol) was added in one portion. After 5 min, the bath was replaced with a 0 °C bath for 30 min. The solution was recooled to −78 °C and iPr$_2$NEt (5.4 mL, 30.8 mmol) was added. After being stirred at −78 °C for 10 min, the solution was warmed to 0 °C for 60 min, followed by recooling to −78 °C. Aldehyde 5.17 (5.0 g, 23.1 mmol) was dissolved in dry CH$_2$Cl$_2$ (75 mL) and added to the reaction mixture dropwise over 20 min via an addition funnel. The reaction mixture was stirred for 2 h at −78 °C and quenched at low temperature with pH 7 buffer. Over 30 min the reaction mixture was allowed to warm to rt and was extracted with CH$_2$Cl$_2$ (3 x 50 mL). The combined organic layers were washed with saturated NaCl solution, dried over MgSO$_4$, and concentrated in vacuo. Purification via flash column chromatography (20% EtOAc/hexanes) provided the Evans aldol product (7.25 g, 84%) as an inseparable mixture of diastereomers: $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.15–7.40 (m, 5 H), 4.70 (m, 1 H), 4.20 (m, 2 H), 3.94 (m, 1 H), 3.76
(qd, \( J = 6.8, 2.4 \) Hz, 1 H), 3.61 (t, \( J = 6.4 \) Hz, 2 H), 3.25 (dd, \( J = 13.2, 2.8 \) Hz, 1 H), 2.87 (d, \( J = 2.8 \) Hz, 1 H), 2.78 (dd, \( J = 13.2, 9.6 \) Hz, 1 H), 1.35–1.60 (m, 6 H), 1.25 (d, \( J = 7.2 \) Hz, 3 H), 0.88 (s, 9 H), 0.04 (s, 6 H); \(^{13}\)C NMR (CDCl\textsubscript{3}, 100 MHz) \( \delta 177.51, 171.20, 135.01, 129.93, 128.95, 127.41, 71.41, 66.14, 63.08, 60.36, 55.09, 42.12, 37.79, 33.59, 25.96, 21.01, 18.87, -5.30. \)

The above intermediate (8.3 g, 18.5 mmol) was dissolved in dry DMF (25 mL). Imidazole (3.1 g, 46.1 mmol) was added and TESCl (3.9 mL, 22.2 mmol) was added dropwise over 10 min. The reaction mixture was stirred at rt for 12 h and quenched by the addition of saturated NH\(_4\)Cl solution (50 mL) and Et\(_2\)O (50 mL). The aqueous layer was extracted with Et\(_2\)O (3 x 50 mL) and the combined organic layers were washed with H\(_2\)O (2 x 50 mL) and saturated NaCl solution (50 mL), dried over MgSO\(_4\) and concentrated \textit{in vacuo}. Flash column chromatography (5-10\% EtOAc/hexanes) provided the desired, major diastereomer 5.18 (8.85 g, 85\%) as an oil: \([\alpha]_D^{20} +29.7 \) (c 0.010, CHCl\textsubscript{3}); IR (thin film) 2952, 2935, 2877, 2858, 1785, 1703, 1461, 1382, 1349, 1237, 1209 cm\(^{-1}\); \(^1\)H NMR (CDCl\textsubscript{3}, 400 MHz) \( \delta 7.29 \) (m, 5 H), 4.62 (m, 1 H), 4.16 (m, 2 H), 4.01 (q, \( J = 5.2 \) Hz, 1 H), 3.86 (m, 1 H), 3.60 (td, \( J = 6.4, 2.4 \) Hz, 2 H), 3.29 (dd, \( J = 13.2, 3.2 \) Hz, 1 H), 2.76 (dd, \( J = 13.2, 9.6 \) Hz, 1 H), 1.50 (m, 4 H), 1.36 (m, 2 H), 1.25 (d, \( J = 6.8 \) Hz, 3 H), 0.95 (t, \( J = 8.0 \) Hz, 9 H), 0.89 (s, 9 H), 0.60 (q, \( J = 8.0 \) Hz, 6 H), 0.04 (s, 6 H); \(^{13}\)C NMR (CDCl\textsubscript{3}, 100 MHz) \( \delta 175.31, 153.02, 135.41, 129.50, 128.93, 127.31, 73.19, 65.98, 63.11, 62.67, 55.78, 43.07, 37.67, 35.54, 35.06, 33.14, 25.96, 21.67, 6.93, 5.14, -5.30, -5.32; \) ESI HRMS [M+Na] calcd for C\textsubscript{30}H\textsubscript{53}NO\textsubscript{5}Si\textsubscript{2}Na: 586.3360, obsd: 586.3359.

**Heptanal 5.19:**\(^{44}\) The prepared aldol adduct 5.18 (15.3 g, 27.1 mmol) was stirred in THF (300 mL). H\(_2\)O (1.2 mL, 67.5 mmol) was added and the reaction mixture was cooled to 0 °C. LiBH\(_4\) (1.5 g, 67.7 mmol) was cautiously added in one portion. The reaction mixture was stirred at 0 °C for 5 h and allowed to warm to rt over 12 h, quenched with 1 N NaOH (60 mL), diluted with EtOAc (90 mL), and stirred for 15 min. The separated aqueous layer was extracted with EtOAc (2 x 80 mL). The combined organic layers were washed with saturated NaCl solution (80 mL), dried over MgSO\(_4\),
filtered and concentrated in vacuo. Flash column chromatography (15% EtOAc/hexanes) provided the corresponding alcohol (8.26 g, 78%) as a clear oil: \([\alpha]_D^{20} +1.8 \ (c \ 0.030, \ CHCl_3); \) IR (thin film) 3362, 2954, 2876, 1462, 1414, 1384, 1360, 1254, 1099, 1006 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 3.77 (m, 1 H), 3.68 (m, 1 H), 3.61 (t, \(J = 5.9 \) Hz, 2 H), 3.52 (m, 1 H), 2.81 (dd, \(J = 5.6, 3.7 \) Hz, 1 H), 1.95 (m, 1 H), 1.4–1.6 (m, 6 H), 0.96 (t, \(J = 7.8 \) Hz, 9 H), 0.89 (s, 9 H), 0.81 (d, \(J = 7.0 \) Hz, 3 H), 0.62 (q, \(J = 7.8 \) Hz, 6 H), 0.05 (s, 6 H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 76.33, 66.20, 63.04, 39.57, 33.02, 32.23, 25.95, 22.69, 18.35, 11.93, 6.88, 5.12, -5.32; ESI HRMS [M+Na] calcd for C\(_{20}\)H\(_{46}\)O\(_3\)Si\(_2\)Na: 413.2883, obsd: 413.2882.

The above alcohol (232 mg, 0.593 mmol) in CH\(_2\)Cl\(_2\) (5 mL) was treated with Dess-Martin periodinane (288 mg, 0.889 mmol) in one portion. After being stirred at rt for 45 min, the reaction mixture was quenched by the addition of sodium thiosulfate doped NaHCO\(_3\) (10 mL). CH\(_2\)Cl\(_2\) (10 mL) was added and the biphasic solution stirred vigorously until two clear layers were present. The separated aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 x 10 mL) and the combined organic layers were washed with saturated NaCl solution (20 mL), dried over MgSO\(_4\), filtered and concentrated in vacuo to yield heptanal 5.19 (205 mg, 89%) which could be used without any further purification: \([\alpha]_D^{20} +17.2 \ (c \ 0.007, \ CHCl_3); \) IR (thin film) 2954, 2936, 2877, 1728, 1462, 1414, 1255, 1101 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 9.78 (d, 1 H, \(J = 0.9 \) Hz), 4.11 (td, 1 H, \(J = 6.5, 3.6 \) Hz), 3.60 (t, 2 H, \(J = 6.3 \) Hz), 2.44 (qdd, 1 H, \(J = 6.9, 3.7, 0.7 \) Hz), 1.52 (m, 4 H), 1.41 (m, 1 H), 1.29 (m, 1 H), 1.05 (d, 3 H, \(J = 7.0 \) Hz), 0.94 (t, 9 H, \(J = 8.0 \) Hz), 0.89 (s, 9 H), 0.58 (q, 6 H, \(J = 8.1 \) Hz), 0.04 (s, 6 H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 205.37, 72.26, 62.88, 51.39, 34.51, 32.82, 25.95, 22.19, 18.34, 7.71, 6.86, 5.13, -5.31, -5.32; ESI HRMS [M+Na] calcd for C\(_{20}\)H\(_{44}\)O\(_3\)Si\(_2\)Na: 411.2727, obsd: 411.2724.

**TBS Protected Nagao Adduct 5.20:**\(^{44}\) In a drybox, a flame-dried round bottom flask was charged with Sn(OTf)\(_2\) (3.86 g, 9.26 mmol). Dry CH\(_2\)Cl\(_2\) (35 mL) was added and the mixture cooled to −50 °C. N-Ethyl piperidine (1.27 mL, 9.26 mmol) was added followed by the addition of (R)-1-(4-isopropyl-2-thioxothiazolidin-3-yl)ethanone (1.49 g, 9.26 mmol) in CH\(_2\)Cl\(_2\) (4 mL). The solution was stirred
at −50 °C for 3 h and cooled to −78 °C. Heptanal 5.19 (1.28 g, 3.29 mmol) was added in CH₂Cl₂ (4 mL). After being stirred at −78 °C for 2.5 h, the reaction mixture was quenched by the addition of pH 7 buffer and warmed to rt. The separated aqueous layer was extracted with CH₂Cl₂ (3 x 25 mL). The combined organic layers were washed with saturated NaCl solution (30 mL), dried over MgSO₄, and concentrated in vacuo. Purification of the crude oil by flash column chromatography (10-25% EtOAc/hexanes) provided the Nagao adduct (1.2 g, 62%) as a yellow oil and a mixture of product and (R)-1-(4-isopropyl-2-thioxothiazolidin-3-yl)ethanone: [α]D²⁰ –169.8 (c 0.002, CHCl₃); IR (thin film) 3514, 2956, 2934, 2876, 1698, 1463, 1372, 1255, 1165, 1094 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 5.16 (t, J = 6.8 Hz, 1 H), 4.33 (dt, J = 8.9, 3.2 Hz, 1 H), 3.87 (m, 1 H), 3.59 (t, J = 6.4 Hz, 2 H), 3.50 (dd, J = 11.4, 8.0 Hz, 1 H), 3.44 (A of ABX, J_AB = 7.5 Hz, J_{AX} = 3.3 Hz, 1 H), 3.35 (B of ABX, J_{AB} = 7.4 Hz, J_{BX} = 8.9 Hz, 1 H), 3.30 (br s, 1 H), 3.00 (d, J = 11.5 Hz, 1 H), 2.36 (sextet, J = 6.8 Hz, 1 H), 1.44–1.65 (m, 5 H), 1.26 (m, 2 H), 1.05 (d, J = 6.8 Hz, 3 H), 0.96 (d, J = 6.9 Hz, 3 H), 0.94 (t, J = 8.0 Hz, 9 H), 0.92 (d, J = 6.9 Hz, 3 H), 0.88 (s, 9 H), 0.60 (q, J = 8.0 Hz, 6 H), 0.03 (s, 6 H); ¹³C NMR (CDCl₃, 100 MHz) δ 202.94, 172.66, 76.79, 71.53, 70.92, 62.90, 44.14, 40.34, 34.31, 32.92, 32.23, 30.85, 30.62, 25.95, 21.89, 19.05, 18.33, 17.78, 6.90, 5.38, -5.29; ESI HRMS [M+Na] calcd for C₂₈H₅₇NO₄S₂Si₂Na: 614.3165, obsd: 614.3146.

The above Nagao product (1.2 g, 2.03 mmol) was dissolved in dry CH₂Cl₂ (15 mL) in a flame-dried round bottom flask under N₂(g) and cooled to −78 °C. 2,6-Lutidine (0.47 mL, 4.06 mmol) was added, followed by the dropwise addition of TBSOTf (0.65 mL, 2.84 mmol). After being stirred at −78 °C for 4.5 h, the reaction mixture was quenched by addition to a separatory funnel containing saturated NH₄Cl solution and CH₂Cl₂. The separated aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL) and the combined organic layers were washed with saturated NaCl solution, dried over MgSO₄ and concentrated in vacuo. Purification of the crude material by flash column chromatography (5-25% EtOAc/hexanes) provided 5.20 (740 mg, 52%) as an oil, and the separable C34 diastereomer: [α]D²⁰ –87.9 (c 0.002, CHCl₃); IR (thin film) 2954, 2929, 2856, 1698, 1478, 1462, 1372, 1255, 1169, 1097 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 5.08 (t, J = 7.0 Hz, 1 H), 4.37 (dt, J = 7.4, 4.1 Hz, 1 H), 3.71
(q, J = 5.3 Hz, 1 H), 3.59 (m, 3 H), 3.44 (dd, J = 11.4, 7.8 Hz, 1 H), 3.08 (dd, J = 17.6, 4.2 Hz, 1 H),
3.01 (d, J = 11.4 Hz, 1 H), 2.37 (sextet, J = 6.7 Hz, 1 H), 1.63 (m, 1 H), 1.52 (m, 4 H), 1.45 (m, 2 H),
1.05 (d, J = 6.8 Hz, 3 H), 0.95 (m, 15 H), 0.89 (s, 9 H), 0.85 (s, 9 H), 0.60 (q, J = 6.9 Hz, 6 H), 0.06
(s, 3 H), 0.05 (s, 6 H), 0.01 (s, 3 H); 13C NMR (CDCl3, 100 MHz): δ 202.52, 172.04, 73.22, 71.63,
69.70, 63.25, 44.37, 42.95, 34.62, 33.42, 30.75, 30.72, 25.98, 25.92, 21.05, 19.11, 18.35, 18.17,
17.87, 10.67, 7.06, 5.38, -4.21, -4.47, -5.27; ESI HRMS [M+Na] calcd for C28H57NO4S2Si2Na:
728.4030, obsd: 728.4010.

Iodide 5.21:44 A solution of 5.20 (75 mg, 0.106 mmol) in THF (1 mL) was stirred and cooled to 0
°C. H2O (5 µL, 0.265 mmol) was added, followed by the cautious addition of LiBH4 (6 mg, 0.265
mmol) in one portion. The reaction mixture was stirred at 0 °C for 4 h, warmed slowly to rt over
12 h, and cautiously quenched with 1 N NaOH (2 mL). EtOAc (5 mL) was added and the reaction
mixture stirred for 15 min. The separated aqueous layer was extracted with EtOAc (2 x 10 mL) and
the combined organic layers were washed with saturated NaCl solution (10 mL), dried over MgSO4,
and concentrated in vacuo. Flash column chromatography (5-25% EtOAc/hexanes) provided the
resulting alcohol (44.3 mg, 76%) as an oil: [α]D20 +3.8 (c 0.002, CHCl3); IR (thin film) 3451, 2952,
2929, 2258, 1472, 1462, 1255, 1102, 1029, 1005 cm−1; 1H NMR (CDCl3, 400 MHz) δ 3.87 (q, J =
6.3 Hz, 1 H), 3.77 (m, 2 H), 3.68 (m, 1 H), 3.60 (t, J = 5.5 Hz, 2 H), 2.23 (br s, 1 H), 1.84 (m, 2 H),
1.72 (m, 1 H), 1.50 (m, 5 H), 1.28 (m, 1 H), 0.95 (t, J = 7.9 Hz, 9 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.58
(q, J = 8.0 Hz, 6 H), 0.10 (s, 3 H), 0.05 (s, 3 H), 0.04 (s, 6 H); 13C NMR (100 MHz, CDCl3) δ 72.77,
72.46, 63.04, 60.06, 40.85, 35.74, 33.21, 25.96, 25.92, 22.69, 21.71, 18.35, 18.01, 9.93, 7.01, 5.47,

The above alcohol (2.66 g, 4.84 mmol) was dissolved in dry PhH (30 mL) in a flame-dried round
bottom flask under N2(g). Imidazole (1.6 g, 24.2 mmol) was added, followed by the addition of PPh3
(1.5 g, 5.81 mmol). Lastly, I2 (1.5 g, 5.81 mmol) was added in 3 portions over 5 min. The reaction
mixture was stirred for 1 h at rt, quenched by the addition of Na2S2O3 doped NaHCO3, and stirred
until two clear layers were observed. The mixture was extracted with CH$_2$Cl$_2$ (3 x 20 mL) and the combined organic layers were washed with saturated aqueous NaCl solution (30 mL), dried over MgSO$_4$, and concentrated in vacuo. Hexanes (15 mL) were added and the mixture was frozen for 15 min. The triphenylphosphine oxide was removed by filtration and the organic layer was concentrated in vacuo to yield 5.21 (2.88 g, 90%) as an oil; [α]$_D^{20}$ –0.5 (c 0.0502, CHCl$_3$); IR (thin film) 2952, 2928, 2856, 1462, 1384, 1254, 1101, 1030, 1005 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) δ 3.80 (m, 1 H), 3.69 (m, 1 H), 3.61 (t, $J$ = 6.8 Hz, 2 H), 3.16 (t, $J$ = 7.2 Hz, 2 H), 2.08 (m, 2 H), 1.61 (m, 1 H), 1.49 (m, 4 H), 1.31 (m, 2 H), 0.96 (t, $J$ = 8.0 Hz, 9 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.89 (m, 3 H), 0.60 (q, $J$ = 8.0 Hz, 6 H), 0.08 (s, 3 H), 0.05 (s, 6 H), 0.02 (s, 3 H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 74.05, 72.21, 63.12, 41.01, 38.81, 35.06, 33.33, 29.72, 29.68, 26.00, 25.92, 25.72, 22.71, 21.54, 7.07, 5.49, -2.93, -4.03, -4.23, -5.26; ESI HRMS [M+Na] calcd for C$_{28}$H$_{63}$IO$_3$Si$_3$Na: 681.3028, obsd: 618.3024.

Sulfone, 5.1:$^{44}$ Iodide 5.21 (2.86 g, 4.34 mmol) was dissolved in dry DMF (40 mL) in a flame-dried round bottom flask under N$_2$(g). Sodium phenylsulfinate (7.1 g, 43.4 mmol) was added in one portion. The reaction mixture was warmed at 60 °C for 2 h, cooled to rt, and transferred to a separatory funnel containing 1:1 half saturated NH$_4$Cl solution and Et$_2$O (60 mL). The mixture was extracted with Et$_2$O (3 x 30 mL) and the combined organic layers were washed with H$_2$O (2 x 25 mL) and saturated NaCl solution (25 mL), dried over MgSO$_4$, and concentrated in vacuo. The crude oil was purified by flash column chromatography (5-10% EtOAc/hexanes) to yield sulfone 5.1 (2.1 g, 72%) as a clear oil; [α]$_D^{20}$ +0.5 (c 0.0551, CHCl$_3$); IR (thin film) 3066, 2953, 2856, 1471, 1462, 1447, 1389, 1361, 1318, 1308, 1255, 1149, 1089, 1006 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400MHz) δ 7.90 (d, $J$ = 5.6 Hz, 2 H), 7.65 (t, $J$ = 6.0 Hz, 1 H), 7.56 (t, $J$ = 6.4 Hz, 2 H), 3.71 (m, 1 H), 3.62 (m, 1 H), 3.59 (t, $J$ = 5.2 Hz, 2 H), 3.16 (td, $J$ = 9.2, 3.6 Hz, 1 H), 3.08 (td, $J$ = 10.0, 4.4 Hz, 1 H), 1.90 (m, 2 H), 1.48 (m, 4 H), 1.40 (m, 1 H), 1.21 (m, 2 H), 0.91 (t, $J$ = 6.0 Hz, 9 H), 0.89 (s, 9 H), 0.84 (s, 9 H), 0.81 (d, $J$ = 5.2 Hz, 3 H), 0.51 (q, $J$ = 6.0 Hz, 6 H), 0.05 (s, 6 H), -0.01 (s, 3 H), -0.07 (s, 3 H);
$\mathrm{^{13}C}$ NMR ($\mathrm{CDCl}_3$, 100 MHz) $\delta$ 139.23, 133.54, 129.24, 128.09, 72.13, 71.72, 62.95, 52.11, 40.97, 31.95, 29.72, 29.68, 29.38, 25.99, 25.86, 22.71, 21.97, 18.37, 7.02, 5.45, -4.37, -4.52, -5.26; ESI HRMS [M+Na] calcd for C$_{34}$H$_{68}$O$_5$Si$_3$Na: 695.3993, obsd: 695.3990.

**Bis-PMB Iodide 5.22:** A mixture of iodo alcohol 5.8 (0.950 g, 2.11 mmol), PMBO-lepidine 6.3 (1.77 g, 6.33 mmol), and CSA (49.0 mg, 0.211 mmol) in CH$_2$Cl$_2$ (10 mL) was stirred for 43.5 h at rt. The resulting slurry was diluted with a small amount of CH$_2$Cl$_2$ and loaded directly onto the column (silica gel; 5:1 to 4.5:1 hexanes/EtOAc), which afforded 5.22 as a slightly off-white semisolid (0.85 g, 70%): $[\alpha]_D^{25}$ +30.0 (c 0.09, CHCl$_3$); IR (neat) 2954, 2917, 1745, 1612, 1514, 1249 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.28–7.24 (m, 4 H), 6.89–6.88 (m, 4 H), 4.86 (d, $J = 10.7$ Hz, 1 H), 4.84 (d, $J = 10.7$ Hz, 1 H), 4.68 (d, $J = 10.7$ Hz, 1 H), 4.60 (d, $J = 10.7$ Hz, 1 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.78 (s, 3 H), 3.72 (d, $J = 10.7$ Hz, 1 H), 3.49 (dd, $J = 2.6$, 10.8 Hz, 1 H), 3.28–3.24 (m, 1 H), 3.17–3.13 (m, 1 H), 2.05–1.97 (m, 1 H), 0.95 (d, $J = 6.6$ Hz, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 169.7, 159.6, 159.5, 130.4, 130.1, 129.7 (2 C), 129.6 (2 C), 114.1 (2 C), 114.0 (2 C), 85.3, 82.3, 81.2, 78.9, 75.2, 75.1, 55.42, 55.40, 52.3, 40.2, 12.6, 6.5; ESI HRMS [M+Na] calcd: 593.1012, obsd: 593.0999.

**Bis-PMB Suzuki Product 5.23:** A solution of iodide (93 mg, 0.16 mmol) in PhH (1.6 mL) was treated with DBU (0.24 mL, 1.6 mmol) and the mixture was heated at 60 °C for 4 h. The solvent was removed under reduced pressure to give a pale yellow mixture, which was purified by column chromatography (2 x 10 cm silica treated with 2% Et$_3$N/hexanes; hexanes, 20% EtOAc/hexanes) to afford the enol ether as a semi-opaque, colorless oil (62 mg, 87%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.31–7.20 (m, 4 H), 6.90–6.85 (m, 4 H), 4.79–4.65 (m, 4 H), 4.54 (d, $J = 11.2$ Hz, 1 H), 4.50 (d, $J = 11.2$ Hz, 1 H), 3.99–3.96 (m, 2 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.77 (s, 3 H), 3.25–3.21 (m, 1 H), 2.12–2.04 (m, 1 H), 0.96 (d, $J = 6.8$ Hz, 3 H).

A solution of enol ether (62 mg, 0.14 mmol) in THF (0.28 mL) was cooled to 0 °C (ice/NaCl) and treated with a 0.5 M solution of 9-BBN in THF (0.84 mL, 0.42 mmol). The reaction mixture was
stirred for 15 min at 0 °C and for 2.5 h at 26 °C. Gas evolution occurred upon addition of 9-BBN. A neat mixture of sidechain (110 mg, 0.21 mmol) and PdCl$_2$(dpff) (17 mg, 0.021 mmol) was allowed to stand for 30 min at 26 °C before dilution with DMF (0.74 mL) and another 30 min of standing. To the hydroboration flask was added a 1:1 mixture of 3 M aqueous K$_3$PO$_4$ solution (0.14 mL, 0.42 mmol) and DMF (0.14 mL). The resulting mixture was stirred for 30 min and treated with the sidechain/PdCl$_2$(dpff) mixture to give a dark brown reaction mixture, which was stirred for 2 h at 26 °C and gradually lightened to a red-orange color. The reaction mixture was diluted with H$_2$O (3 mL) and Et$_2$O (20 mL). The separated aqueous layer was extracted with Et$_2$O (3 x 10 mL) and the combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo to give a red oil. After purification twice by column chromatography (2 x 9 cm silica; petroleum ether, 1% EtOAc/petroleum ether, 2% EtOAc/petroleum ether, 5% EtOAc/petroleum ether, 10% EtOAc/petroleum ether) the desired coupled product 5.23 was obtained as a clear, nearly colorless oil (98 mg, 82%): $[\alpha]_D^{25}$ –10.2 (c 0.85, CHCl$_3$); IR (neat) 2953, 2929, 2877, 2857, 2359, 1748, 1638, 1613, 1586, 1514, 1250 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.26–7.23 (m, 4 H), 6.88–6.85 (m, 4 H), 5.19 (s, 1 H), 5.18 (s, 1 H), 4.91 (s, 1 H), 4.86 (s, 1 H), 4.82 (d, $J$ = 10.8 Hz, 2 H), 4.60 (d, $J$ = 7.2 Hz, 1 H), 4.57 (d, $J$ = 7.6 Hz, 1 H), 3.98–3.95 (m, 1 H), 3.801 (s, 3 H), 3.797 (s, 3 H), 3.797 (s, 3 H), 3.80–3.73 (m, 1 H), 3.73 (s, 3 H), 3.61 (d, $J$ = 10.8 Hz, 1 H), 3.47–3.42 (m, 1 H), 3.30–3.20 (m, 2 H), 2.65 (d, $J$ = 14 Hz, 1 H), 2.95 (d, $J$ = 15.2 Hz, 1 H), 2.43 (d, $J$ = 13.6 Hz, 1 H), 2.28 (dd, $J$ = 9.6, 14 Hz, 1 H), 2.25–2.19 (m, 1 H), 2.00–1.93 (m, 1 H), 1.92–1.86 (m, 1 H), 0.96–0.86 (m, 21 H), 0.61–0.55 (m, 6 H), 0.53 (s, 3 H), -0.02 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.2, 159.5, 159.4, 143.5, 141.0, 130.7, 130.6, 129.6 (2 C), 129.4 (2 C), 114.8, 114.02 (2 C), 113.99 (2 C), 113.6, 86.1, 82.8, 81.3, 79.2, 75.2, 74.9, 74.4, 72.1, 55.5, 55.4, 52.1, 41.0, 40.4, 39.2, 37.3, 26.1 (3 C), 22.2, 18.2, 7.12 (3 C), 5.26 (3 C), -4.13, -4.30; ESI HRMS [M+Na] calcd: 869.4223, obsd: 869.4185.

**β-Ketosulfone, 5.24:** A mixture of 5.23 (104 mg, 0.12 mmol) and 5.1 (162 mg, 0.24 mmol) in THF (1.2 mL) was cooled to –78 °C (CO$_2$/acetone) and treated with a 1.0 M solution of LiHMDS in THF
(0.25 mL, 0.25 mmol) to afford a yellow solution, which was stirred for 2 h at –78 to –70 °C. The bath was allowed to warm to –40 °C over 1 h and then to –28 °C over 20 min. The reaction mixture was stirred for 1 h 15 min at –35 °C to –20 °C, quenched by the addition of saturated aqueous NH₄Cl solution (1 mL), diluted with Et₂O (2 mL), and allowed to warm to rt. The separated aqueous layer was extracted with Et₂O (4 x 4 mL) and the combined organics were dried (Na₂SO₄) and concentrated in vacuo to give a yellow oil. Column chromatography (2 x 9 cm silica; petroleum ether, 1% EtOAc/petroleum ether, 2% EtOAc/petroleum ether, 5% EtOAc/petroleum ether) gave 5.24 as a clear colorless oil (120 mg, 67%), recovered 5.1 (86 mg, 53%), and recovered 5.23 (25 mg, 24%). ¹H NMR/¹³C NMR: mixture of diastereomers, see Appendix A; IR (neat) 2950, 2857, 1731, 1639, 1614, 1586, 1514 cm⁻¹; ESI HRMS [M+Na] calcd: 1510.8081, obsd: 1510.8102.

α-Diketone 5.25: A solution of sulfone 5.24 (13 mg, 0.0085 mg) in THF (0.14 mL) was cooled to 0 °C (ice/NaCl), and treated with an 0.5 M solution of KHMDS in Tol (22 µL, 0.011 mmol) to give an intensely yellow solution and stirred 28 min at 0 °C. A solution of Williams’ oxaziridine (14 mg, 0.043 mmol) in THF (0.10 mL, 0.10 mL rinse) was added dropwise and the yellow color faded quickly to a very pale yellow. The reaction mixture was stirred for 2 h at 0 °C, quenched with saturated aqueous NH₄Cl solution (0.5 mL), diluted with Et₂O (2 mL), and allowed to warm to rt. The separated aqueous layer was extracted with Et₂O (3 x 2 mL) and the combined organics were dried (MgSO₄) and concentrated in vacuo to afford a yellow semi-solid. Purification twice by column chromatography (1 x 14 cm silica; petroleum ether, 2% EtOAc/petroleum ether, 5% EtOAc/petroleum ether) gave starting material 5.24 (7.5 mg, 58%) as a nearly colorless oil and 5.25 as a semi-opaque, nearly colorless oil (4.6 mg, 40%): [α]D²⁵ –5.6 (c 0.16, CHCl₃); IR (neat) 2955, 2927, 2856, 1731, 1613, 1514, 1463, 1250 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.26–7.22 (m, 4 H), 6.88–6.84 (m, 4 H), 5.19 (s, 1 H), 5.17 (s, 1 H), 4.82 (d, J = 10.4 Hz, 4 H), 4.58 (d, J = 10.4 Hz, 2 H), 4.28–4.22 (m, 2 H), 4.13–3.94 (m, 2 H), 4.13–3.94 (m, 2 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.80–3.74 (m, 1 H), 3.72–3.48 (m, 3 H), 3.29–3.18 (m, 2 H), 3.02–2.97 (m, 1 H), 2.89–2.83 (m, 1 H), 2.65–2.57 (m, 2 H), 2.36 (d, J = 13.2 Hz, 1 H), 2.29–2.32 (m, 1 H), 2.13–2.07.
(m, 1 H), 1.84–1.78 (m, 1 H), 1.65–1.21 (series of m, 7 H), 0.98–0.79 (m, 51 H), 0.62–0.47 (m, 12 H), 0.05 (s, 6 H), 0.06 (s, 6 H), -0.01 (s, 3 H), -0.05 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 200.0, 195.8, 159.5, 159.4, 143.0, 141.0, 130.7, 130.6, 129.6 (2 C), 129.3 (2 C), 114.9, 114.1 (2 C), 114.03 (2 C), 113.98, 86.2, 83.1, 79.2, 79.0, 75.3, 74.9, 74.6, 72.0, 71.8, 69.1, 63.3, 55.5, 55.4, 42.6, 42.2, 41.0, 39.11, 39.06, 37.5, 35.4, 33.5, 29.9, 26.14 (3 C), 26.07 (3 C), 26.03 (3 C), 21.7, 18.5, 18.1 (2 C), 7.21 (3 C), 7.13 (3 C), 5.63 (3 C), 5.26 (3 C), -4.16, -4.25, -4.28 (2 C), -5.12, -5.14; ESI HRMS [M+Na] calcd: 1384.7942, obsd: 1384.8062.

**α-Ketohemiketal 5.26a:** To a solution of diketone 5.25 (5.7 mg, 0.0042 mmol) in MeOH/THF (0.42 mL/0.28 mL) was added PPTs (1.5 mg, 0.0084 mmol) and the reaction mixture was stirred for 2.5 h at rt, quenched by the addition of py (0.1 mL), and diluted with brine (1 mL) and Et$_2$O (2 mL). The separated aqueous layer was extracted with Et$_2$O (3 x 2 mL) and the combined organics were dried (Na$_2$SO$_4$) and concentrated *in vacuo* to give a pale yellow residue. Column chromatography (1 x 11 cm silica gel; hexanes to 4:1 hexanes/ETOAc) afforded 5.26a as a nearly colorless residue (4.0 mg, 77%): $^1$H NMR (400 MHz, CDCl$_3$) δ 7.26–7.23 (m, 4 H), 6.87–6.84 (m, 4 H), 5.82 (s, 1 H), 5.82 (s, 1 H), 5.18 (br s, 1 H), 5.16 (br s, 1 H), 4.98 (br s, 1 H), 4.84 (d, $J$ = 10.4 Hz, 1 H), 4.82 (br s, 1 H), 4.80 (d, $J$ = 10.4 Hz, 1 H), 4.58 (d, $J$ = 10.4 Hz, 2 H), 4.33–4.26 (m, 1 H), 4.25 (d, $J$ = 10.8 Hz, 1 H), 4.05–4.01 (m, 1 H), 3.96–3.93 (m, 1 H), 3.80 (s, 6 H), 3.74–3.71 (m, 1 H), 3.62 (t, $J$ = 6.4 Hz, 2 H), 3.57–3.55 (m, 1 H), 3.31–3.22 (m, 2 H), 2.64 (br d, $J$ = 14 Hz, 1 H), 2.57 (br d, $J$ = 15.6 Hz, 1 H), 2.38 (br d, $J$ = 13.6 Hz, 1 H), 2.25 (dd, $J$ = 14, 10 Hz, 1 H), 2.17–2.08 (m, 3 H), 1.85 (dd, $J$ = 13.6, 10.4 Hz, 1 H), 1.66–1.58 (m, 2 H), 1.44–1.35 (m, 2H), 0.96–0.79 (series of m, 42 H), 0.59–0.52 (m, 6 H), 0.12–0.08 (series of m, 18 H); TOF MS ES [M+Na] calcd: 1269.7052, obsd: 1269.7072.

**α-Hydroxyhemiketal 5.28:** A solution of 5.26a (6.1 mg, 0.0049 mmol) in THF (0.25 mL) was treated with Amberlyst-15 (7 beads) followed immediately by NaBH$_4$ (1.8 mg, 0.048 mmol) at rt. The reaction mixture was stirred for 40 min, filtered through a pad of Celite (EtOAc), and concentrated to give a white solid. Column chromatography (1 x 11

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in vacuo to give an off-white residue. Column chromatography (1 x 11.5 cm silica; hexanes, 4:1 hexanes/EtOAc) gave 5.28 as a colorless residue (4.5 mg, 74%): [α]D24 -7.8 (c 0.23, CHCl3); IR (neat) 3456, 2953, 2927, 1514, 1463, 1250, 1098 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.27-7.24\) (m, 4 H), 6.87–6.84 (m, 4 H), 5.34 (s, 1 H), 5.18 (s, 1 H), 5.15 (s, 1 H), 4.93 (s, 1 H), 4.84 (d, \(J = 10.4\) Hz, 1 H), 4.81 (d, \(J = 10.4\) Hz, 1 H), 4.57 (d, \(J = 10.4\) Hz, 2 H), 4.26–4.19 (m, 1 H), 3.97–3.92 (series of m, 2 H), 3.797 (s, 3 H), 3.795 (s, 3 H), 3.73–3.71 (m, 1 H), 3.62–3.59 (m, 2 H), 3.50–3.44 (m, 2 H), 3.39 (d, \(J = 6.8\) Hz, 1 H), 3.25–3.16 (m, 2 H), 2.65 (d, \(J = 14\) Hz, 2 H), 2.44 (d, \(J = 6.8\) Hz, 1 H), 2.40 (d, \(J = 12.8\) Hz, 1 H), 2.25 (dd, \(J = 14, 9.6\) Hz, 1 H), 2.11–1.96 (m, 2 H), 1.92–1.85 (m, 2 H), 1.78–1.72 (m, 1 H), 1.70–1.10 (series of m, 7 H), 1.01–0.79 (series of m, 42 H), 0.63–0.54 (m, 6 H), 0.10–0.04 (m, 18 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 159.4, 159.3, 144.3, 140.9, 131.0, 130.8, 129.6 (2 C), 129.2 (2 C), 114.9, 114.1, 114.0 (2 C), 113.9 (2 C), 98.6, 86.7, 83.1, 78.9, 78.6, 75.0, 74.9, 74.7, 73.9, 73.0, 72.0, 66.3, 63.2, 55.44, 55.39, 41.2, 39.0, 38.8, 38.4, 37.2, 33.0, 32.1, 31.4, 29.5, 26.13 (3 C), 26.05 (3 C), 25.9 (3 C), 22.8, 22.1, 18.5, 18.2, 18.0, 7.16 (3 C), 5.25 (3 C), -4.25 (2 C), -4.74, -4.85, -5.10 (2 C); TOF MS ES+ [M+Na] calcd: 1271.7208, obsd: 1271.7111.

\(\alpha\)-Hydroxymethylketal 5.29: A solution of 5.28 (5.4 mg, 0.0043 mmol) in MeOH (0.22 mL) was treated with PPTs (a few small crystals, ~1 mg) at rt and stirred for 30 min. The reaction mixture was quenched with py (0.05 mL) and diluted with brine (1 mL) and Et\(_2\)O (2 mL). The separated aqueous layer was extracted with Et\(_2\)O (3 x 2 mL) and the combined organics were dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo to afford a pale yellow residue. Column chromatography (1 x 12 cm silica; hexanes, 4:1 hexanes/EtOAc) gave 5.29 as a mixture with 5.28 (3.4 mg). \(^1\)H NMR of mixture, see Appendix A. TOF MS ES+ [M+Na] calcd: 1285.7365, obsd: 1285.7281.
LIST OF REFERENCES


31. Kim, J., Unpublished work.


33. Ciblat, S., Unpublished work.


APPENDIX A

\(^1\text{H} \text{ NMR AND SELECT } ^{13}\text{C} \text{ NMR SPECTRAL DATA}\)
precursor to 5.12
HO\(\sim\)\(\sim\)\(\sim\) OTBS

precursor to 5.17
precursor to 5.21
5.29 (with starting material 5.28)