Synthetic Studies Toward Marine Natural Product Okadaic Acid and Its Analogs

Dissertation

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By

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Abstract

Okadaic acid is a potent and selective inhibitor of protein serine/threonine phosphatase 1 and 2A (PP1 and PP2A), and has been widely used as a laboratory tool for identifying and studying many essential cellular processes associated with the inhibition of protein phosphatases. In order to understand the structural basis of its activity toward protein phosphatases, an efficient and flexible total synthesis of okadaic acid was developed in the Forsyth group in 1997. This dissertation describes recent efforts to improve the synthetic approach toward okadaic acid and its analogs.

The first part of the work includes an efficient synthesis of C15-C38 fragment of okadaic acid and 29-desmethylokadaic acid, highlighted by the application of gold-catalyzed regiocontrolled spiroketalization to synthesize the central and tail spiroketal moieties. This method provides a reliable alternative to the conventionally used acid-catalyzed dehydrative cyclization approach. The second part of the dissertation describes a total synthesis of belizeanic acid, a structurally related analog of okadaic acid. The synthesis is based on the methods developed in our synthesis of okadaic acid, and will provide valuable materials for biological tests.
Dedication

This document is dedicated to my family.
Acknowledgments

First of all, I would like to thank Professor Forsyth for providing me the opportunity to work on the okadaic acid project, for offering me countless valuable advice and suggestions for my research, for supporting me in and out of the laboratory throughout the past five years, and most importantly, for helping me develop as an organic chemist. I will forever be grateful for that.

I would also like to thank the okadaic acid project members, Mr. Yucheng Pang, and Dr. Dan Wherritt. We spent lots of time discussing our research, sharing joy and disappointment about our project. Thank you for your teamwork!

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Fields of Study

Major Field: Chemistry
# Table of Contents

Abstract ........................................................................................................................................ii
Dedication .................................................................................................................................... iii
Acknowledgements ....................................................................................................................... iv
Vita ................................................................................................................................................ vi
List of Tables ................................................................................................................................ ix
List of Figures ............................................................................................................................ x
List of Schemes ........................................................................................................................... xi
List of Abbreviations ................................................................................................................... xiii

Chapter 1: Introduction ................................................................................................................ 1
  1.1 Isolation and Structure of Okadaic Acid ............................................................................ 1
  1.2 Biological Activities of Okadaic Acid .............................................................................. 2
  1.3 Okadaic Acid Class of Phosphatase Inhibitors ............................................................... 3
  1.4 SAR Data of Okadaic Acid and its Analogs ..................................................................... 6
  1.5 X-Ray Crystallographic Data for PP1-OA and PP2A-OA complex .............................. 9
  1.6 Total Syntheses of Okadaic Acid ..................................................................................... 13

Chapter 2: Objectives .................................................................................................................. 22
  2.1 Overall Project Objectives .............................................................................................. 22
  2.2 Specific Objectives of Dissertation Project .................................................................... 23
Chapter 3: Results and Discussion

3.1 Retrosynthetic Strategy of OA

3.2 Gold-catalyzed Spiroketalization

3.3 Synthesis of C15-C27 Fragment of OA

3.4 Synthesis of C28-C38 Fragment of OA

3.5 Coupling of C15-C27 and C28-C38 Fragments of OA

3.6 Synthesis of C15-C38 Fragment of 29-Desmethylokadaic Acid

3.7 Preliminary Studies on the Coupling of C1-C14 and C15-C27 Fragments

3.8 Total Synthesis of Belizeanic Acid

Chapter 4: Experimental

List of References

Appendix A: Selected NMR Spectra
List of Tables

1.1 Phosphatase Inhibition of Okadaic Acid Class of Inhibitors.................................6
List of Figures

1.1 The Structure of Okadaic Acid .................................................................1
1.2 Cyclic Conformation of Okadaic Acid .......................................................2
1.3 Structures of Okadaic Acid Class of Phosphatase Inhibitors .........................4
1.4 Structures of Okadaic Acid Related Analogs .............................................8
1.5 A. Stereo Representation of the Active Site of the PP1-OA Complex; B. Active Site of the PP1-OA Complex .................................................................10
1.6 The Active Site of PP2A-OA Complex .......................................................12
1.7 Structural Comparison of OA Binding to PP1 and PP2A .............................13
3.1 The Structure of Belizeanic Acid ..............................................................48
3.2 $^1$H NMR Spectra Comparison of Synthetic and Natural BA .....................55
List of Schemes

1.1 Isobe's Key OA Building Blocks ................................................................. 14
1.2 Isobe's Synthesis of OA's Spiroketal Moieties ........................................... 15
1.3 Stereoselective Reduction of C27 Ketone ................................................... 16
1.4 Forsyth's Key OA Building Blocks .............................................................. 17
1.5 Forsyth's Synthesis of OA’s Spiroketal Moieties ......................................... 18
1.6 Ley's Key OA Building Blocks .................................................................... 19
1.7 Ley's Synthesis of OA's Spiroketal Moieties ................................................ 20
2.1 Forsyth's Initial Approach Toward OA ......................................................... 23
3.1 Retrosynthetic Analysis of OA ....................................................................... 25
3.2 Gold Catalysis in Acetal Synthesis ................................................................. 27
3.3 Possible Pathways for C19 Spiroketal Formation ....................................... 28
3.4 Synthesis of OA's C15-C27 Fragment .......................................................... 29
3.5 Continued Synthesis of OA's C15-C27 Fragment ....................................... 30
3.6 Preparation of Coupling Partner III-4 ......................................................... 31
3.7 Possible Pathways for C34 Spiroketal Formation ....................................... 32
3.8 Previous Studies on [5,5] Spiroketal Formation ......................................... 33
3.9 Gold-Catalyzed Spiroketalization of Monopropargylic Triols .................... 34
3.10 Synthesis of OA's C28-C38 Fragment ....................................................... 36
3.11 Proposed Spiroketalization Mechanism .............................................. 37
3.12 Continued Synthesis of OA's C28-C38 Fragment .................................. 39
3.13 Initial Attempts on the Coupling of C19-C27 and C28-C38 Fragments of OA .40
3.14 Coupling of C15-C27 and C28-C38 Fragments of OA ......................... 41
3.15 Synthesis of C28 β-Keto Phosphonate ................................................. 44
3.16 Synthesis of C29 Aldehyde ................................................................. 45
3.17 Synthesis of C15-C38 Fragment of 29-Desmethylokadaic Acid ............. 46
3.18 Attempts on the Coupling of C1-C14 and C15-C27 Fragments of OA .... 47
3.19 Retrosynthetic Analysis of BA .............................................................. 50
3.20 Synthesis of BA’s C16-C27 Fragment ................................................... 51
3.21 Synthesis of BA’s C15-C38 Fragment ................................................... 52
3.22 Synthesis of BA’s C1-C14 Fragment .................................................... 53
3.23 Completion of the Synthesis of BA ....................................................... 54
### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>[α]</td>
<td>optical rotation</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>Arg</td>
<td>arginine</td>
</tr>
<tr>
<td>Asn</td>
<td>asparagine</td>
</tr>
<tr>
<td>Asp</td>
<td>aspartic acid</td>
</tr>
<tr>
<td>β</td>
<td>beta</td>
</tr>
<tr>
<td>BA</td>
<td>belizeanic acid</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>brsm</td>
<td>based on recovered starting material</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>calcld</td>
<td>calculated</td>
</tr>
<tr>
<td>CBS</td>
<td>oxazaborolidine developed by Corey, Bakshi, and Shibata</td>
</tr>
<tr>
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<td>cysteine</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shifts in ppm</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>Abbreviation</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>DME</td>
<td>dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>DSP</td>
<td>diarrhetic shellfish poisoning</td>
</tr>
<tr>
<td>EE</td>
<td>ethoxyethyl</td>
</tr>
<tr>
<td>ESI</td>
<td>electron spray ionization</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>Et$_2$O</td>
<td>diethyl ether</td>
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<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
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<td>glutamine</td>
</tr>
<tr>
<td>His</td>
<td>histidine</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectrometry</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
</tr>
<tr>
<td>IC$_{50}$</td>
<td>concentration at which enzyme activity decreases by 50%</td>
</tr>
<tr>
<td>Ile</td>
<td>isoleucine</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>$J$</td>
<td>coupling constant in NMR</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>kDa</td>
<td>kilodalton</td>
</tr>
<tr>
<td>KHMDS</td>
<td>potassium hexamethyldisilazide</td>
</tr>
<tr>
<td>Leu</td>
<td>leucine</td>
</tr>
<tr>
<td>LiDBB</td>
<td>lithium di-tert-butylbiphenylide</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>NaHMDS</td>
<td>sodium hexamethyldisilazide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>NOE</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>OA</td>
<td>okadaic acid</td>
</tr>
<tr>
<td>Phe</td>
<td>phenylalanine</td>
</tr>
<tr>
<td>PMB</td>
<td>para-methoxybenzyl</td>
</tr>
<tr>
<td>PMP</td>
<td>para-methoxyphenyl</td>
</tr>
<tr>
<td>PP1</td>
<td>protein phosphatase 1</td>
</tr>
<tr>
<td>PP2A</td>
<td>protein phosphatase 2A</td>
</tr>
<tr>
<td>PPTs</td>
<td>pyridinium p-toluenesulfonate</td>
</tr>
<tr>
<td>R&lt;sub&gt;f&lt;/sub&gt;</td>
<td>retention factor</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>SAR</td>
<td>structure-activity relationship</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Name</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Ser</td>
<td>serine</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBS</td>
<td>t-butyldimethylsilyl</td>
</tr>
<tr>
<td>TES</td>
<td>triethylsilyl</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>Thr</td>
<td>threonine</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>Trp</td>
<td>tryptophan</td>
</tr>
<tr>
<td>TsOH</td>
<td>p-toluene sulfonic acid</td>
</tr>
<tr>
<td>Tyr</td>
<td>tyrosine</td>
</tr>
<tr>
<td>Val</td>
<td>valine</td>
</tr>
</tbody>
</table>

xvi
Chapter 1: Introduction

1.1 Isolation and Structure of Okadaic Acid

![Okadaic Acid](image)

**Figure 1.1.** The Structure of Okadaic Acid

Okadaic Acid (OA, 1-I, Figure 1.1) is a cytotoxic polyether derivative of a C\textsubscript{38} fatty acid, and it was first isolated from *Halichondria okadai* Kadota, a black sponge commonly found along the Pacific coast of Japan, and *Halichondria melanodocia*, a Caribbean sponge collected in the Florida Keys.\textsuperscript{1} The name “okadaic acid” originates from the Japanese biologist Okada, whose name is associated with the classification of the particular species of the sponge *Halichondria* from which OA was originally isolated.\textsuperscript{2} Later on its biogenetic origin was found to be marine dinoflagellates *Prorocentrum lima, Dinophysis fortii,* and *Dinophysis acuminata,\textsuperscript{3,4} which frequently accumulate in sponges such as *H. okadaic,* and *H. melanodocia.*

The structure of okadaic acid was elucidated with x-ray crystallographic analysis of its o-bromobenzyl ester derivative by Van Engen and Clardy at Cornell University.\textsuperscript{1} It
contains 23 functionalized carbons that include 17 stereogenic centers and 3 spiroketals. X-ray crystallography\(^1\) and NMR experiments\(^5,6\) also revealed that okadaic acid adopts a cyclic conformation (Figure 1.2) in both solid state and CDCl\(_3\) solution. This pseudomacrolide conformation is facilitated by the hydrogen bond between C1 carboxylate and C24 hydroxyl, another hydrogen bond between C2 hydroxyl and C4 oxygen, both C8 and C19 spiroketals, the C14-C15 \textit{trans} alkene, and the C19-C26 \textit{trans} dioxadecalin system.

![Figure 1.2. Cyclic Conformation of Okadaic Acid](image)

### 1.2 Biological Activities of Okadaic Acid

Since its isolation in 1981, the biomedical and commercial importance of okadaic acid has been widely recognized. OA and its analogs were first identified as the toxins responsible for most human diarrhetic shellfish poisoning (DSP) related illnesses.\(^7\) DSP was discovered in 1976 when a mussel poisoning case occurred in northeastern Japan,\(^8\) and it is associated with eating bivalves such as mussels, scallops, or clam which have accumulated dinoflagellate toxins. The prominent symptoms are gastrointestinal disorders such as diarrhea, nausea, vomiting, and abdominal pain.\(^8\) DSP has wide
distribution over the world, and particularly in Japan and northwest Europe, it is a serious problem both to public health and to the shellfish industry.

Okadaic acid was also reported as a non-phorbol ester type tumor promoter on mouse skin.\(^9\) In 1980, Nishizuka identified the enzyme protein kinase C (PKC) as the receptor of the phorbol ester tumor promoters, and it was hypothesized that persistent activation of PKC by the phorbol esters leads to hyperphosphorylation of key proteins involved in cellular regulation.\(^10\) Since OA did not interact directly with PKC, its tumor promoting mechanism was illuminated by Bialojan and Takai when they reported that OA is a potent inhibitor against protein serine/threonine phosphatases 1 and 2A (PP1 and PP2A).\(^11\) In contrast to phorbol esters, which activate protein kinase C, OA inhibits the dephosphorylation of proteins, predominantly serine/threonine residues. Both types of tumor promoters eventually cause the accumulation of essentially the same phosphorylated proteins, some of which are involved in tumor promotion.\(^12\)

Since okadaic acid was discovered as an inhibitor of protein phosphatases, numerous biochemical/pharmacological studies have been carried out using OA as a probe. Many, if not all, of the observed biological activities of OA are now considered to be explainable by its inhibitory action against protein phosphatases.\(^13\)

1.3 Okadaic Acid Class of Phosphatase Inhibitors

In addition to okadaic acid, several other natural products have been characterized as additional members of the “okadaic acid class of phosphatase inhibitors”. These molecules include calyculin A (I-2),\(^14\) dephosphonocalyculin A (I-3),\(^15\) microcystin-LR
tautomycin (I-4),

cantharidin (I-6),
fostriecin (I-7),
thyrsiferyl 23-acetate (I-8), and spirastrellolide A (I-9) (Figure 1.3).
There are four major classes of protein serine/threonine phosphatases in the cytosol and nucleus of eukaryotic cells: types 1, 2A, 2B, and 2C. Most of the inhibitors have shown very potent inhibition against PP1 and PP2A (Table 1.1). For example, calyculin A (I-2), dephosphonocalyculin A (I-3), microcystin (I-4), and tautomycin (I-5) are all nanomolar inhibitors against both PP1 and PP2A, although none of them exhibits high selectivity toward PP1 or PP2A. While fostriecin (I-7) and thrysiferyl 23-acetate (I-8) have demonstrated high selectivity toward PP1 or PP2A, their activities are not as potent as other members in this class. Only okadaic acid (I-1) and newly reported
spirastrellolide A (I-9)\(^{21}\) are potent inhibitors toward both PP1 and PP2A, and also selective against PP2A over PP1. It’s also worth noting that most of these molecules showed very weak or no potency against PP2B or PP2C.

### Table 1.1. Phosphatase Inhibition of Okadaic Acid Class of Inhibitors\(^*\)

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>I-1(^{22})</th>
<th>I-2(^{14})</th>
<th>I-3(^{15})</th>
<th>I-4(^{16})</th>
<th>I-5(^{17})</th>
<th>I-6(^{18})</th>
<th>I-7(^{19})</th>
<th>I-8(^{20})</th>
<th>I-9(^{21})</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC(_{50}) against PP1 /nM</td>
<td>150</td>
<td>2.0</td>
<td>3.0</td>
<td>0.1</td>
<td>3.0</td>
<td>n/a</td>
<td>4000</td>
<td>n/a</td>
<td>50</td>
</tr>
<tr>
<td>IC(_{50}) against PP2A /nM</td>
<td>0.03</td>
<td>2.0</td>
<td>8.2</td>
<td>0.1</td>
<td>30</td>
<td>4-8</td>
<td>40</td>
<td>4k-16k</td>
<td>1</td>
</tr>
</tbody>
</table>

\(^*\)There are variations in the data available depending on the source of the enzymes and the nature of the assays.

Considering the structural diversity of protein phosphatase inhibitors, it’s remarkable that most of them share potent inhibitory activity. Also, the catalytic subunits of PP1 and PP2A are similar in size (37 and 36 kDa, respectively) and share 49% amino acid sequence identity, and therefore it’s intriguing that some of these natural products demonstrated high selectivity toward PP1 or PP2A. As okadaic acid is the leading compound of protein phosphatase inhibitors, numerous studies have been undertaken to understand its structural basis of inhibition of PP1 and PP2A.

### 1.4 SAR Data of Okadaic Acid and its Analogs

In 1992, Takai et al. reported some preliminary structure-activity relationship (SAR) data of okadaic acid on its affinity for PP1 and PP2A.\(^{23}\) They found that two closely related analogs of OA, acanthifolicin (I-10) and dinophysistoxin-1 (I-11) (Figure 1.4),
have similar activity against PP2A compared with OA, although dinophysistoxin-1 is slightly more potent than OA (19 nM vs. 30 nM). While removal of the C7 hydroxyl group (7-deoxy-OA, I-13) caused only a slight decrease (2.3-fold) in the affinity, esterification of the same hydroxyl group with palmitic acid resulted in more than 3000-fold decrease. A significant decrease in potency was also observed with saturation of the C14-C15 double bond (11-fold) and removal of the C2 hydroxyl group (30-fold). Additionally, the affinity of OA was essentially destroyed by either esterifying or removing the C1 carboxylate group, suggesting that the circular conformation of OA plays an important role in its inhibitory action.

In 2001, the Forsyth group determined the inhibitory activity of the C1-C27 (I-14) and C16-C38 (I-15) fragments of OA against PP1 and PP2A. While I-15 showed essentially no activity against either enzyme, I-14 had significantly weaker potency against PP1 and PP2A, indicating the importance of the C28-C38 hydrophobic domain for potent inhibition of protein phosphatases.

In 2007, the relative toxicity of dinophysistoxin-2 (I-12) compared with okadaic acid was also reported. It was determined that dinophysistoxin-2 is about 50% potent toward PP2A compared with OA. Since the only difference among OA, dinophysistoxin-1, and dinophysistoxin-2 is the methyl substituent at either C31 or C35 (Figure 1.4), their different affinity for protein phosphatases underlines the importance of these methyl groups in the interactions between the enzymes and the ligands.
Figure 1.4. Structures of Okadaic Acid Related Analogs
In 2007, a new okadaic acid analog, 19-epi-OA (I-16) was isolated from the marine dinoflagellate Prorocentrum Belizeanum. The only difference between OA and 19-epi-OA is the absolute configuration at C19, as it has an R configuration in OA and S configuration in 19-epi-OA. The two inhibitors have similar IC\textsubscript{50} values with PP2A, however, 19-epi-OA is about 10-fold weaker against PP1 compared with OA. As a result, 19-epi-OA is an even more selective protein phosphatase inhibitor than OA. The structural basis of the selectivity remains unclear, although the different conformations of 19-epi-OA and OA may be accountable.

More recently, Uemura et al. designed and synthesized another two analogs of OA, 24-epi-OA (I-17) and OA lactone (I-18). According to their biological assays, I-17 was more than 50 times weaker than OA against L1210 leukemia cells, which indicates that the absolute configuration of C24 hydroxyl might be important for the intramolecular hydrogen binding within OA. Moreover, the lactone I-18 had no cytotoxicity against P388 murine leukemia cells. Although I-18 possesses a fixed 18-membered macrocyclic core that resembles the conformation of OA, it loses the acidic carboxylate group, which may explain the loss of its binding activity.

### 1.5 X-ray Crystallographic Data for PP1-OA and PP2A-OA Complex

The crystal structure of a PP1-OA complex to a resolution of 1.9 Å was determined in 2001 by James et al. The structure reveals that both the ligand and the enzyme undergo little conformational change from their respective solid structure. In fact, the pseudocyclic conformation of OA is maintained in the active site of PP1 (Figure 1.5).
There are two types of interactions between OA and PP1: hydrophobic, and hydrogen bonding. The C28-C38 spiroketal moiety of OA is hydrophobic and binds into the hydrophobic groove of the protein. Trp-206 and Ile-130 in the hydrophobic groove appear to be the two most important residues in the hydrophobic interactions due to their proximity to the tail domain of OA (Figure 1.5 A). Other hydrophobic interactions occur between the C4-C16 region of OA and the PP1 residues Phe-276 and Val-250.

As for the hydrogen bonding interactions, the acid motif of OA accepts a hydrogen bond from the hydroxyl group of Tyr-272, and the importance of this interaction is
exemplified by the fact that mutation of Tyr-272 to Phe results in a 50-fold increase in the $K_i$ value.\textsuperscript{30} Other hydrogen bonding interactions occur between Arg-96 and the C2 hydroxyl of OA, as well as between Arg-221 and the C24 hydroxyl of OA.

The crystal structure also provided a possible explanation for the different inhibitory potential of OA on PP1 and PP2A.\textsuperscript{29} The primary difference in the active region between PP1 and PP2A is in the $\beta$12-$\beta$13 loop where PP1 contains the residues GEFD (residues 274-277) but PP2A has YRCG (residues 267-270) in the equivalent positions. James \textit{et al.} proposed that the enhanced affinity of OA with PP2A is likely caused by the differences in this $\beta$12-$\beta$13 loop, one of which is between Phe-276 of PP1 and Cys-269 of PP2A. The large phenyl ring of Phe-276 may inhibit entry of OA into the active site, overshadowing other favorable hydrophobic interactions (Figure 1.5). A smaller cysteine (Cys-269) is present at the equivalent position in PP2A, and may be the reason that OA has a higher affinity for PP2A. In fact, mutation of Phe-276 to cysteine in PP1 reduces the $K_i$ value for OA by 40-fold.\textsuperscript{30}

More recently, the crystal structure of a PP2A core enzyme bound to OA at 2.6 Å was reported by Shi \textit{et al.}\textsuperscript{31} OA exhibits a cyclic structure as in the PP1-OA complex, and it binds to the active site pocket of the catalytic subunit of PP2A (Figure 1.6). There are also both hydrophobic and hydrogen bonding interactions between OA and PP2A. The hydrophobic end of OA is located in a hydrophobic cage formed by four residues from PP2A, Gln-122, Ile-123, His-191, and Trp-200. Other hydrophobic interactions involve the residues from PP2A, Leu-243, Tyr-265, Cys-266, Arg-268, and Cys-269, and the C4-C16 region of OA (Figure 1.6).
The major hydrogen bonding interactions occur between the acid motif of OA and Tyr-265 of PP2A, the C2 hydroxyl of OA and Arg-89 of PP2A, the C4 oxygen of OA and Arg-89 of PP2A, as well as the C24 hydroxyl of OA and Arg-214 of PP2A (Figure 1.6).

Figure 1.6. The Active Site of PP2A-OA Complex\(^{31}\) (Reprinted from *Cell*, Vol. 127, Yigong Shi *et al.*, “Structure of Protein Phosphatase 2A Core Enzyme Bound to Tumor-Inducing Toxins”, 341-353, Copyright (2006), with Permission from Elsevier Ltd.)

Moreover, comparison of the structures of PP1-OA with PP2A-OA complex allows an alternative rationalization of OA’s strong preference for PP2A.\(^{31}\) Instead of focusing on the β12-β13 loop,\(^{29}\) Shi *et al.* argued that the major difference between the active sites of PP1 and PP2A is the hydrophobic cage (Figure 1.7). Compared with His-191 and Gln-122 from PP2A, Asp-197 and Ser-129 from PP1 form a more widely opened groove, and therefore its hydrophobic interaction with the hydrophobic end (C28-C38) of OA is weaker than that of PP2A. The recognition of this hydrophobic cage also helped to
explain the different affinity of OA, dinophysistoxin-1, and dinophysistoxin-2 toward PP2A.\textsuperscript{26}

![Figure 1.7. Structural Comparison of OA Binding to PP1 and PP2A](image)

**Figure 1.7.** Structural Comparison of OA Binding to PP1 and PP2A\textsuperscript{31} (Reprinted from *Cell*, Vol. 127, Yigong Shi *et al.*, “Structure of Protein Phosphatase 2A Core Enzyme Bound to Tumor-Inducing Toxins”, 341-353, Copyright (2006), with Permission from Elsevier Ltd.)

### 1.6 Total Syntheses of Okadaic Acid

There have been three total syntheses of okadaic acid reported until today, as well as other synthetic efforts toward OA. In 1986, Isobe, Ichikawa, and co-workers in Nagoya, Japan reported the first total synthesis of OA.\textsuperscript{32-36} According to Isobe’s synthetic plan, OA was disconnected into three fragments, the C1-C14 fragment **I-19**, the C15-C27 fragment **I-20**, and the C28-C38 fragment **I-21** (Scheme 1.1). The three fragments were coupled together following the order of **I-19 + [I-20 + I-21]**, and were based on successful additions of phenylsulfonyl stabilized carbanions upon aldehydes. Isobe’s
landmark synthesis of OA has 54 steps in the longest linear sequence, and an overall yield of ca. 0.01%.

**Scheme 1.1. Isobe's Key OA Building Blocks**

An important structural feature of OA is its three spiroketal-containing moieties, and therefore, a main focus of OA’s synthesis is to set up the three spiroketals efficiently. By far, cyclization of a preformed dihydroxyl ketone is the most commonly used strategy in spiroketal synthesis.\(^{37}\) Because most spiroketals in nature, as in the case of OA, possess the more stable configuration due to anomeric stabilization,\(^{38}\) equilibrium conditions would lead to the formation of the desired spiroketal center. In Isobe’s synthesis, the C8, C19, and C34 spiroketals were all formed using acid-catalyzed spiroketalization from
their corresponding hydroxyl ketone precursors, namely I-22, I-23, and I-25 (Scheme 1.2).\textsuperscript{33-35}

**Scheme 1.2.** Isobe's Synthesis of OA's Spiroketal Moieties

**A. The Synthesis of the C8 Spiroketal**

\[
\begin{align*}
\text{I-22} & \xrightarrow{\text{PPTs, MeOH}} \text{I-19}
\end{align*}
\]

**B. The Synthesis of the C19 Spiroketal**

\[
\begin{align*}
\text{I-23} & \xrightarrow{\text{H}_2, \text{Pd-C, EtOH, AcOH}} \text{I-24}
\end{align*}
\]

**C. The Synthesis of the C34 Spiroketal**

\[
\begin{align*}
\text{I-25} & \xrightarrow{\text{PPTs, EtOH}} \text{I-26}
\end{align*}
\]

Another important feature of Isobe’s synthesis is the installation of C27 stereocenter of OA after coupling of the C15-C27 fragment I-20 with the C28-C38 fragment I-21 (Scheme 1.3).\textsuperscript{36} Reduction of the C27 ketone I-27 with NaBH\textsubscript{4} gave the desired C27 carbinol I-28 with the natural product’s configuration as 27\textit{S}. The diastereoselectivity can be explained by a polar Felkin-Ahn model,\textsuperscript{39} as the addition of the hydride to the
carbonyl group of I-27 preferentially takes place in an antiperiplanar mode to the polar C26-O bond as illustrated in Scheme 1.3. This method was also utilized later on in both Forsyth’s and Ley’s synthesis of similar substrates.

Scheme 1.3. Stereoselective Reduction of C27 Ketone

In 1997, the Forsyth group at University of Minnesota reported their own total synthesis of OA. Similarly, Forsyth’s synthetic design utilized three highly functionalized fragments: I-29, I-30, and I-31, somewhat analogous to Isobe’s strategy (Scheme 1.4). While the C27-C28 bond was connected by a direct coupling of aldehyde I-30 with an unstabilized primary carbanion derived from I-31, the trans C14-C15 alkene was installed by a mild Horner-Wadsworth-Emmons olefination. In summary, Forsyth’s synthesis was accomplished in 26 steps and ca. 1.2% overall yield in the longest linear sequence, a significant improvement from Isobe’s synthesis. Moreover, Forsyth’s synthesis was designed to be efficient and flexible so that more rationally designed analogs of OA could be accessed for biological applications, as is demonstrated in this dissertation.
Scheme 1.4. Forsyth's Key OA Building Blocks

Forsyth’s group also utilized acid-catalyzed cyclizations to access all three spiroketals of OA (Scheme 1.5). While the synthesis of C8 spiroketal I-33 was induced by treatment of the linear (Z)-enone I-32 with TsOH, the acid source to form the C34 spiroketal I-37 was from the commercially obtained Pd(OH)$_2$ on carbon, which was originally used for the cleavage of the three benzyl ethers in I-36. The C19 spiroketal was formed at the end stage of the synthesis, with an acid-triggered spiroketalization of the C16 hydroxyl upon a masked ketone at C19 to provide the required (19R)-configuration in I-35.
At the end of 1998, Professor Steven Ley at Cambridge University reported a third total synthesis of OA.\textsuperscript{44} Retrosynthetically, Ley’s synthesis also utilized three key building blocks (Scheme 1.6), the C1-C14 (I-38), C15-C26 (I-39), and C27-C38 (I-40) fragments. The central and tail domains were coupled together by the nucleophilic attack of aluminium acetylide derived from I-40 to the electrophilic C26 center of I-39, and the second coupling utilized a modified Julia olefination\textsuperscript{45} to install the trans C14-C15 olefin. Ley’s synthesis has 29 steps in the longest linear sequence, and the overall yield is ca. 0.36%. 

\textbf{Scheme 1.5.} Forsyth's Synthesis of OA’s Spiroketal Moieties

\textbf{A. The Synthesis of the C8 Spiroketal}

\textbf{B. The Synthesis of the C19 Spiroketal}

\textbf{C. The Synthesis of the C34 Spiroketal}
Ley’s synthesis of OA’s spiroketal moieties was highlighted by several methods developed in their own laboratories (Scheme 1.7). Upon treatment with mild acid, the β-methoxy enol ether $\text{I-41}$ was activated to install the C9-C10 alkene of OA regioselectively along with the loss of one molecule of methanol, followed by the cyclization of C4 hydroxyl to form the C8 spiroketal $\text{I-42}$. In the case of C19 spiroketal $\text{I-44}$, liberation of the protected diol under acidic conditions allowed cyclization of in situ generated protonated enol ether in $\text{I-43}$ to deliver $\text{I-44}$. Another cascade of reactions was involved in the synthesis of C34 spiroketal $\text{I-46}$. Elimination of phenylsulfinic acid in $\text{I-}
45 was followed by removal of the acetonide group, protonation of the enol ether and final cyclization to give I-46.

**Scheme 1.7. Ley's Synthesis of OA's Spiroketal Moieties**

**A. The Synthesis of the C8 Spiroketal**

\[ \text{I-41} \longrightarrow \text{I-42} \]

**B. The Synthesis of the C19 Spiroketal**

\[ \text{I-43} \longrightarrow \text{I-44} \]

**C. The Synthesis of the C34 Spiroketal**

\[ \text{I-45} \longrightarrow \text{I-46} \]

In addition to the three total syntheses, there are also other reports of innovative fragmental synthesis of OA. Marko et al. reported some unique methodology toward the synthesis of the C30-C38 fragment and the C19-C26 dioxadecalin of OA.\(^{48-49}\) Professor Richard Schlessinger at University of Rochester has described their synthesis of the C1-C8,\(^{50}\) C9-C18,\(^{51}\) C19-C27,\(^{52}\) and C28-C38\(^{53}\) fragments of OA. Eustache et al. has
demonstrated their preparation of the C34 spiroketal using ring closing metathesis as a key step. More recently, Kelly et al. reported their effort toward the synthesis of the C19-C30 portion of OA.
Chapter 2: Objectives

2.1 Overall Project Objectives

The overall goal of this research project is to determine the structural basis of OA’s selective phosphatase inhibition. Based on extensive SAR studies and crystallographic data, the pharmacophore for phosphatase inhibition has been proposed: an acidic group, a proximal methyl group, two hydrogen bonding sites, $\beta_{12}$-$\beta_{13}$ loop-contacting region, and a hydrophobic segment. Although these elements may help to explain the potency of OA with both PP1 and PP2A, the elements of the pharmacophore that are responsible for its selective phosphatase inhibition are still poorly defined. Two hypotheses for the preferential selectivity for PP2A have arisen: the interactions between the $\beta_{12}$-$\beta_{13}$ loop of the enzymes and the C4-C16 region of OA proposed by James et al., and the interactions between the enzyme’s hydrophobic groove and OA’s tail spiroketal domain as explained by Shi et al. In order to define the structural elements for the selectivity, rationally designed analogs of OA will be synthesized and then assayed for their PP1 and PP2A activity, while the possible modification sites will be either the C4-C16 or the C28-C38 region of OA based on the hypotheses. Ultimately, this research will lead to the development of new, synthetically accessible inhibitors that display enhanced selectivity toward PP2A, but lack the structural complexity of okadaic acid, which can be utilized to better understand the cellular events mediated by those protein phosphatases.
2.2 Specific Objectives of Dissertation Project

While the convergent approach to OA developed in our laboratories\textsuperscript{40-42} could be readily applied to the synthesis of natural product analogs, improvements might still be needed to enhance the overall synthetic access to OA and its structural variants. One potential site for improvement is the coupling efficiency between the C16-C27 (II-1) and C28-C38 fragments (II-2, Scheme 2.1).\textsuperscript{41} The combined yield in the original OA synthesis is 53% yield, and the undesired 27\textit{R} cabinol (II-3) is the major product (\textit{dr} 2.5 : 1). Although II-3 could be converted into II-4 via an oxidation-reduction sequence, the overall yielding for the coupling and (27\textit{S}) alcohol installation is only moderate at 38%.

Scheme 2.1. Forsyth's Initial Approach Toward OA
Another difficulty encountered in the initial synthesis was at the mixed C19 methyl acetal.\textsuperscript{41} Although this masked ketone form allowed the stereoselective spiroketalization at C19 in the final stage of OA’s synthesis, it tends to cyclize prematurely upon the deprotection of C16 hydroxyl to give the undesired spiroketal II-6 in the presence of trace amount of acid (Scheme 2.1). To avoid this problem, a novel spiroketalization toward the C19 spiroketal will be attempted.

Recently, several OA derivatives have been identified from the marine dinoflagellate *Prorocentrum belizeanum* by Norte and co-workers, namely 19-\textit{epi}-okadaic acid,\textsuperscript{27} belizeanic acid,\textsuperscript{57} and corozalic acid.\textsuperscript{58} These molecules closely resemble the structure of OA and also maintain high level of potency against protein phosphatases. Another objective of this dissertation project is to complete the total synthesis of belizeanic acid based on our experiences in the synthesis of OA, which will not only help to confirm its initial structural assignment, but also provide valuable materials for parallel biological assays with other OA analogs.
Chapter 3: Results and Discussion

3.1 Retrosynthetic Strategy of OA

Scheme 3.1. Retrosynthetic Analysis of OA

Our revised synthetic strategy also disconnects OA into three fragments with comparable complexity (Scheme 3.1). The C14-C15 trans alkene of OA could be installed by the coupling between the C1-C14 arylsulfone III-2 and the C15-C38
aldehyde III-3, which has been demonstrated in both Isobe’s\textsuperscript{36} and Ley’s\textsuperscript{44} synthesis. The second disconnection happens at the C27-C28 bond, where the C15-C27 aldehyde III-4 and the C28-C38 iodide III-5 are joined together via the nucleophilic addition of a derived C28 organometallic species into the aldehyde III-4. Moreover, the spiroketal moieties in both III-4 and III-5 are synthesized by a novel gold-catalyzed spiroketalization.

3.2 Gold-catalyzed Spiroketalization

Transition metal catalyzed spiroketalization, pioneered by Utimoto,\textsuperscript{59} represents a highly atom-economical approach to the desired spiroketal ring system. The conventional approach toward spiroketals uses acid-catalyzed dehydrative cyclization of dihydroxyl ketones, as exemplified in the previous synthesis of OA’s spiroketal moieties.\textsuperscript{32-35, 40-42} Comparatively, utilization of an alkyne as an orthogonally reactive surrogate of a ketone is strategically advantageous as it often proceeds the spiroketal formation smoothly without requiring the use of additional protecting group manipulations or activating groups.\textsuperscript{60}

In addition to Pd\textsuperscript{59, 61-62} and Pt\textsuperscript{63-64} catalysts, Au catalysts recently have emerged as a reliable source in activating internal alkynes and promoting acetal formation under very mild conditions.\textsuperscript{65-67} Michelet and Genet reported the first example of gold catalysis to form bicyclic ketals (Scheme 3.2, eq 1),\textsuperscript{65} where treatment of bis-homopropargylic alcohol III-6 with 2 mol\% of AuCl in MeOH gave the bicyclic ketal III-7 in 99\% yield after only 30 minutes at room temperature. It’s noteworthy to mention that no addition of MeOH on the alkyne was observed, and replacing AuCl with Amberlyst 15 gave no
detectable product after 30 minutes at room temperature. The efficiency of gold catalysis was further exemplified by its application in both Forsyth’s synthesis of azaspiraicd’s A-D domain (Scheme 3.2, eq 2), and Trost’s synthesis of ushikulide A (Scheme 3.2, eq 3). The functionalized spiroketal moieties in both natural products were successfully synthesized from its linear precursors (III-8 and III-10) using AuCl as the catalyst, while other Ag, Hg, Pd, and Pt catalysts failed to give satisfactory results.

Scheme 3.2. Gold Catalysis in Acetal Synthesis

3.3 Synthesis of C15-C27 Fragment of OA

One inherent issue with the spiroketalization of dihydroxy alkynes is the potential poor regiocontrol as the cyclization can happen at either carbon of the triple bond. To
form the 1,6-dioxaspiro[4,5]decane ring system at the central domain of OA, both linear precursors, III-12 and III-13, can be utilized, where the triple bond locates at C19-C20 and at C18-C19, respectively (Scheme 3.3). In the case of III-12, the desired [4,5] spiroketal III-12-a is derived from the attack of the hydroxyls at C19 via a 5-exo/6-endo pathway (path a), while a similar 5-exo/6-endo pathway (path b) with hydroxyls attacking at C20 would lead to the formation of undesired [4,5] spiroketal III-12-b. On the other hand, the desired spiroketal III-13-a can be synthesized from the precursor III-13 (path a), while the other possible product III-13-b could only be formed by a 4-exo/7-endo pathway, considerably less favorable than the pathway leading to the desired product. So III-13 is chosen as the precursor for the spiroketalization toward OA’s C19 spiroketal.

**Scheme 3.3. Possible Pathways for C19 Spiroketal Formation**

The synthetic work started with the preparation of aldehyde III-21 using the procedures of Forsyth’s original OA synthesis$^{41}$ with slight modifications (Scheme 3.4).
The 1,3-diol of methyl α-D-glucopyranoside III-14 was selectively protected as benzylidene acetal, and the resulting diol was converted into epoxide III-15. Regioselective opening of the epoxide at C24 with sodium benzoate gave III-16 with the correct configuration at both C23 and C24.68

**Scheme 3.4. Synthesis of OA's C15-C27 Fragment**

The benzylidene group in III-16 was removed under acidic conditions, and the triol III-17 was converted into its tris-TMS ether derivative under standard conditions (Scheme 3.4). A one-pot procedure for C-glucosidation of methyl glycoside with allyl
trimethylsilane\textsuperscript{69} was performed to afford the propenylated product III-18, which was then converted into its anisylidene derivative III-19 with 59\% yield over 3 steps. The free hydroxyl in III-19 was protected as TBS ether quantitatively, after which a routine hydroboration-oxidation sequence gave the aldehyde III-21.

The next part of the synthesis (Scheme 3.5) began with treatment of aldehyde III-21 with Bestmann-Ohira reagent (III-22)\textsuperscript{70} and \( \text{K}_2\text{CO}_3 \) in MeOH, which afforded the terminal alkyne III-23 in 82\% yield. BF\(_3\)-mediated nucleophilic opening\textsuperscript{71} of oxirane III-24\textsuperscript{72} with the lithium acetylide generated from III-23 and \( \text{nBuLi} \) produced alcohol III-25 smoothly. Desilylation of III-25 with TBAF gave dihydroxy alkyne III-26 as the spiroketalization precursor.

**Scheme 3.5. Continued Synthesis of OA’s C15-C27 Fragment**
On the basis of previous reports, AuCl was selected as the catalyst for the spiroketalization reaction. Gratifyingly, the desired [4,5] spiroketal was formed after mixing III-26 with a catalytic amount of AuCl in CH₂Cl₂ (Scheme 3.5), and no [3,6] spiroketal like III-13-b was detected. Any acid cocatalyst was initially avoided here to prevent the removal of the anisylidene protecting group. However, the Lewis acidity of AuCl itself triggered partial removal of the protecting group, but the in situ liberated hydroxyl groups did not seem to affect the spiroketalization efficiency. Subsequent addition of TsOH to the reaction mixture helped to completely remove the anisylidene group to give diol III-27 in 81% yield.

The synthesis was then moved on to the preparation of III-4 (Scheme 3.6). Selective silyl protection of the primary hydroxyl of diol III-27 afforded secondary alcohol III-28, which was then oxidized to the corresponding ketone and converted into alkene III-29 under Wittig conditions. TBAF induced removal of the C27 silyl group gave primary alcohol III-30, which was oxidized into the sensitive β,γ-unsaturated aldehyde III-4 using Dess-Martin periodinane reagent immediately prior to use.

**Scheme 3.6. Preparation of Coupling Partner III-4**

![Scheme 3.6. Preparation of Coupling Partner III-4](image-url)
In summary, the C15-C27 fragment **III-27** was successfully synthesized from commercially available glucose derivative utilizing novel gold-catalyzed spiroketalization. Depending on different coupling strategies, this intermediate can be advanced into different coupling partners.

### 3.4 Synthesis of C28-C38 Fragment of OA

Similar with the C15-C27 fragment, the synthesis of the 1,7-dioxaspiro[5,5]undecane system in the tail domain of OA could be derived from two precursors, **III-31** and **III-32** (Scheme 3.7). In both cases, a 6-*exo*/6-*endo* cyclization pathway at C34 would lead to the formation of the desired [5,5] spiroketal **III-31-a** and **III-32-b** (path a), while the competing pathway involves a 5-*exo*/7-*endo* cyclization mode (path b), which results the formation of undesired [4,6] spiroketals at C33 (**III-31-b**) and C35 (**III-32-b**), respectively.

**Scheme 3.7.** Possible Pathways for C34 Spiroketal Formation
Moreover, preliminary results from both Utimoto\(^{59}\) and our group\(^{73}\) have demonstrated that metal-catalyzed spiroketalization of unbiased internal alkynes often yields selectively the [4,6] spiroketal instead of the [5,5] spiroketal (Scheme 3.8). In Utimoto’s case,\(^{59}\) PdCl\(_2\)-catalyzed spiroketalization of 4-nonyne-1,9-diol (III-34) gave the [4,6] spiroketal III-36 in 60% yield without the formation of [5,5] spiroketal III-35 (Scheme 3.8, eq 1).\(^{74}\) In our efforts toward the assignment of the C35 stereochemistry of dinophysistoxin-2,\(^{75}\) Dr. Ce Wang studied the gold-catalyzed spiroketalization to form the tail spiroketal of dinophysistoxin-2, similar with that of OA. She found that the undesired [4,6] spiroketal III-39 was the predominate product with little [5,5] spiroketal formation (Scheme 3.8, eq 2).

**Scheme 3.8.** Previous Studies on [5,5] Spiroketal Formation

\[ \begin{align*}
\text{III-34} & \xrightarrow{1\% \text{ PdCl}_2, \text{aq. MeCN, reflux, 60\%, only III-36}} \text{III-35} + \text{III-36} \\
\text{III-37} & \xrightarrow{\text{AuCl, MeOH, predominately III-39}} \text{III-38} + \text{III-39}
\end{align*} \]

In Trost’s synthesis of the [5,5] spiroketal III-10 of ushikulide A (Scheme 3.2),\(^{67}\) the desired regioselectivity was achieved by installing an inductively electron-withdrawing benzoyloxy group at the propargylic position, which changes the polarization of the two
acetylenic carbons and leads to the desired spiroketal. More recently, Aponick et al. demonstrated a gold-catalyzed spiroketalization of monopropargylic triols with good control of the size of ring formation. When triol III-40 was treated with gold(I) catalyst in the presence of AgOTf and molecular sieves, only [5,5] spiroketal III-41 was formed with 81% yield (Scheme 3.9, eq 1).

Scheme 3.9. Gold-Catalyzed Spiroketalization of Monopropargylic Triols

More interestingly, the relative 1,3-stereochemistry of the propargylic and nucleophilic hydroxyls within the triol has a significant influence on the outcome of the cyclization (Scheme 3.9). While treatment of 1,3-anti triol III-42 with gold catalysis
conditions as mentioned above afforded [5,5] spiroketal III-43 in 94% yield (Scheme 3.9, eq 2), exposure of 1,3-

syn triol III-44 with the same conditions gave a mixture of products, 31% of [5,5] spiroketal III-43, 30% of [4,6] spiroketal III-45, and 19% of [4,6] spiroketal III-46 (Scheme 3.9, eq 3). While no clear explanation was provided, these results certainly provide an alternative access to the C34 [5,5] spiroketal of OA.

The synthesis started with the preparation of diol III-49, a known material with the stereocenters from C29 to C31 correctly installed (Scheme 3.10). Silylation of commercially available methyl (S)-3-hydroxy-2-methylpropionate III-47, followed by reduction of the ester with DIBAL gave aldehyde III-48. Keck’s BF$_3$•Et$_2$O-mediated crotyl stannane addition$^{77}$ to III-48 followed by treatment with TBAF afforded diol III-49 in 85% overall yield. Selective protection of the primary hydroxyl using BnBr and KOH in refluxing benzene$^{78}$ gave benzyl ether III-50, while the remaining hydroxyl was protected as TES ether III-51. Ozonolysis of III-51 yielded aldehyde III-52 in 94% yield. Addition of the lithium acetylide derived from alkyne III-53 to III-52 afforded a mixture of epimers at the propargylic position C32 ($syn:anti = 1.5:1.0$). These were separated then treated with TsOH to generate 1,3-

syn triol III-56 and 1,3-

anti triol III-57 as the substrates for spiroketalization studies.
Scheme 3.10. Synthesis of OA’s C28-C38 Fragment

When 1,3-

\textit{syn} triol \textbf{III-56} was treated with AuCl, the undesired \([4,6]\) spiroketal (33\textit{S})-

\textbf{III-59} was formed as the major product, followed by the desired \([5,5]\) spiroketal \textbf{III-58},

and the \([4,6]\)-spiroketal (33\textit{R})-\textbf{III-60} in a 7.6:1.6:1.0 ratio (82% combined yield, Scheme

3.11). In contrast, the 1,3-\textit{anti} triol \textbf{III-57} gave the \([5,5]\) spiroketal \textbf{III-58} in 65% yield

with no \([4,6]\) spiroketal isolated. This divergent regioselectivity observed upon the

cyclization of \textbf{III-56} and \textbf{III-57} is consistent with that reported by Aponick.\textsuperscript{76}
Scheme 3.11. Proposed Spiroketalization Mechanism

AuCl (10 mol %)  
4 Å MS, THF, 0 °C  
82% combined yield  
III-58 : III-59 : III-60 = 1.6 : 7.6 : 1.0

AuCl (10 mol %)  
4 Å MS, THF, 0 °C  
65%
Based on these results, we proposed a mechanism for this type of gold-catalyzed spiroketalization (Scheme 3.11). The different results obtained from III-56 and III-57 suggest a kinetic preference for the C30 hydroxyl of III-56 versus the C30 hydroxyl of III-57 to participate in initial 5-\(\text{exo}\) addition at C33 of the alkyne. The 5-\(\text{exo}\) cyclization of III-56 would afford an enol ether gold intermediate B, protiodeauration of which followed by capture of the primary hydroxyl would lead to the spiroketalts III-59/60. However, an analogous 5-\(\text{exo}\) cyclization of III-57 has to proceed via a more sterically hindered all syn C30-C32 trisubstituted THF ring transition state (e.g., E, Scheme 3.11). Alternatively, the primary hydroxyl of III-57 likely initiates its spiroketalization via a less encumbered 6-\(\text{exo}\) oxy-auration.

The original C32 propargylic hydroxyl group of III-56 is retained in III-59/60, while that of III-57 is eliminated to give III-58. This may reflect a concerted loss of gold hydroxide from an \(\alpha\)-hydroxy vinyl gold species (e.g., G, Scheme 3.11), whereas an allylic hydroxy vinyl gold intermediate (e.g., B) undergoes simple protiodeauration. Isomerization of the resulting exocyclic allenyl ether intermediate H into a vinyl substituted oxacarbenium ion (I) followed by addition of the C30 hydroxyl affords III-58.

Once the dependence of spiroketalization regiocontrol on polyol stereochemistry was confirmed, an initial measure to enhance mass throughput was to convert syn-III-54 to anti-III-55 (Scheme 3.12). While attempts to invert the stereocenter at C32 via Mitsunobu reaction\(^79\) failed, III-54 was successfully converted into III-55 through an oxidation-asymmetric reduction\(^80\) sequence.
A more efficient route was then designed, where an asymmetric coupling of aldehyde \textbf{III-52} and alkyne \textbf{III-62} was performed using the protocol developed by Carreira.\textsuperscript{81} In the presence of Zn(OTf)\textsubscript{2} and amine base, along with (-)-N-methylephedrine (\textbf{III-63}) as a chiral additive, \textbf{III-52} and \textbf{III-62} were coupled together to give the propargylic alcohol \textbf{III-64} with the stereocenter at C32 correctly installed (Scheme 3.12). The same conditions were used to remove the silyl protecting groups and afford the desired spiroketal \textbf{III-58} upon gold catalysis. The introduction of the alkene into \textbf{III-58} would be...
inconsequential, as it was saturated along with the removal of the benzyl group under hydrogenolysis conditions to give alcohol III-65, iodination of which afforded the second coupling partner III-5.

### 3.5 Coupling of C15-C27 and C28-C38 Fragments of OA

Due to the undesired diastereoselectivity at installing the C27 stereocenter in Forsyth’s original coupling of the C15-C27 and C28-C38 fragments of OA, several modified coupling methods were initially attempted (Scheme 3.13).

**Scheme 3.13. Initial Attempts on the Coupling of C19-C27 and C28-C38 Fragments of OA**

Since the C27 ketone III-67 can be stereoselectively reduced to the desired C27 cabinol, the coupling between C27 Weinreb amide III-66 and C28 iodide III-5 was designed to form the C27 ketone to enhance the overall efficiency. While III-66 was successfully prepared from III-20 in 4 steps, the desired coupled product III-67 was never obtained. The lithium-iodine exchange did happen based on TLC observations, but
the nucleophilic attack on the C27 amide proved to be too challenging. Since it has been reported that Weinreb amides can be converted to ketones via a nonclassical Wittig reaction with phosphonium ylides, the coupling between Weinreb amide III-66 and the phosphonium ylide generated from III-68 and n-BuLi was then attempted. However, no successful result was obtained.


The unsuccessful attempts may be explained by the poor reactivity of the Weinreb amide, so the attention was turned back to the more electrophilic C27 aldehyde (Scheme 3.14). Considerable efforts have been made to couple the aldehyde III-4 and the iodide III-5 together using a similar procedure as reported in Forsyth’s original synthesis of
OA, where the iodide was treated with \( t\text{-BuLi} \) at -78 °C to undergo lithium-iodine exchange, followed by the addition of CeCl\(_3\) slurry to undergo transmetalation, and the resulting organocerium species was treated with aldehyde III-5 for nucleophilic addition. However, most of the attempts had very low conversion, unfavorable selectivity, along with byproduct formation, mainly caused by tert-butyl group added into the aldehyde. The low solubility of CeCl\(_3\) in either THF or Et\(_2\)O also made the operation difficult to handle, and the best result achieved was the formation of 19% undesired C27 alcohol III-69 with no desired product isolated.

At that time, a paper published by Bailey et al. came to our attention, as it described an efficient method for the preparation of primary alkyl lithium by lithium-halogen exchange based on their mechanistic studies. According to their studies, the success of the exchange depends critically on the choice of halide and solvent. Alkyl iodides rather than alkyl bromides should be used for the preparation of primary alkyllithiums due to their different exchange mechanisms. The best solvent choice for the lithium-iodine exchange is Et\(_2\)O-pentane, although the ratio is not crucial to the success. THF should be avoided as β-elimination and Wurtz-type coupling are the predominant reactions of \( t\)-BuLi with primary alkyl halides in THF solution. More importantly, they offered a reliable way to remove the excess \( t\)-BuLi after the exchange by simply warming the reaction mixture to room temperature, where the \( t\)-BuLi is consumed by rapid proton abstraction from diethyl ether, leaving a clean solution of the less reactive primary alkyllithium.

Accordingly, a revised procedure was attempted for the addition of the C28 carbanion derived from III-5 into the C27 aldehyde III-4 (Scheme 3.14). After the lithium-iodine
exchange, the reaction mixture was allowed to warm to room temperature for 30 minutes to decompose any residual tert-BuLi. Moreover, CeCl₃ was avoided to ease the operation, and a NaBH₄ reductive workup was used to convert any unreacted aldehyde III-4 into the corresponding alcohol, and to facilitate the product separation. Gratifyingly, a mixture of epimers at C27 was consistently obtained in 50% combined yield with a 2:1 ratio, favoring the natural product’s configuration. The undesired diastereomer III-69 was converted into III-70 using the traditional oxidation-reduction sequence. The overall yield for the coupling and stereochemistry correction at C27 is 48%, an improvement of Forsyth’s original approach (38%), which is also in line with the 52 and 47% yields in the other two OA total syntheses.

3.6 Synthesis of C15-C38 Fragment of 29-Desmethylokadaic Acid

The ultimate goal of our project is to provide synthetically more accessible analogs of okadaic acid for biological tests. According to the published crystallographic data for cocrystals of okadaic acid with PP1 and PP2A, the C29 methyl group of okadaic acid doesn’t appear to have any important binding interactions with the enzymes, so the 29-desmethylokadaic acid could serve as an important target in developing selective phosphatase inhibitors. Moreover, removal of the C29 methyl group will facilitate the coupling of the central and tail domain via a mild Horner-Wadsworth-Emmons olefination as demonstrated below.

The synthesis started with the preparation of C28 β-keto phosphonate III-73 (Scheme 3.15). The diol III-27 obtained from gold-catalyzed spiroketalization was protected as bis-TES ether, and the primary TES group was selectively cleaved to afford C27 primary
alcohol III-71. The free alcohol was oxidized into its corresponding aldehyde, which was further converted into the β-hydroxy phosphonate III-72 as a mixture of two diastereomers. Dess-Martin oxidation of III-72 afforded the β-keto phosphonate III-73.

Scheme 3.15. Synthesis of C28 β-Keto Phosphonate

On the other hand, the C29 aldehyde III-82 was also prepared using gold catalysis (Scheme 3.16). The aldol adduct III-74 was converted into Weinreb amide, and the free hydroxyl at C30 was protected as TBS ether III-75. Nucleophilic addition of lithium acetylide derived from III-62 into III-75 afforded the C32 ketone III-76 in 88% yield. Asymmetric reduction using (S)-oxazaborolidine III-61 gave the propargylic alcohol III-77, which was then treated with TsOH to afford the 1,3-anti triol III-78 as the spiroketalization precursor. Upon treatment of III-78 with AuCl, a mixture of products was obtained with 90% combined yield, the desired [5,5] spiroketal III-79 and the undesired [4,6] spiroketal III-80 with a 1.2:1.0 ratio. Compared with a similar substrate III-57, which gave predominately the [5,5] spiroketal (Scheme 3.11), the low regiocontrol in the case of III-78 may be explained by the smaller size of the C29
benzyloxymethyl group in III-78. Under hydrogenolysis conditions, III-78 was converted into the C29 alcohol III-81, which was then oxidized into the corresponding aldehyde III-82.

**Scheme 3.16. Synthesis of C29 Aldehyde**

Under Masamune-Roush conditions, the β-keto phosphonate III-73 and aldehyde III-82 were joined together to afford the (E)-enone III-83 (Scheme 3.17). The enone was reduced to the corresponding ketone using Stryker’s reagent, which was then further reduced using NaBH₄ to give the desired C27 carbinol III-84. The free hydroxyl at C27 was then protected as TBS ether III-85. Selective removal of the TES group in the
presence of the TBS group was achieved under acidic conditions to afford III-86, which was then converted into alkene III-87 using an oxidation-Wittig olefination sequence. In conclusion, an efficient synthesis of the C15-C38 fragment of 29-desmethylokadaic acid was developed utilizing a mild Horner-Wadworth-Emmons olefination as the coupling method.

Scheme 3.17. Synthesis of C15-C38 Fragment of 29-Desmethylokadaic Acid
3.7 Preliminary Studies on the Coupling of C1-C14 and C15-C27 Fragments

At this stage, synthetic studies on the coupling between the C1-C14 and C15-C27 fragments of OA were performed (Scheme 3.18).

Scheme 3.18. Attempts on the Coupling of C1-C14 and C15-C27 Fragments of OA

Our plan is to form the C14-C15 \textit{trans} alkene of OA via a modified Julia olefination,\textsuperscript{43} similar to the strategy used in Ley’s synthesis of OA.\textsuperscript{44} The core structure of the C1-C14 benzothiazol-2-yl sulfone III-88 was prepared using methods developed
by Dr. Ce Wang and Mr. Yucheng Pang in our group, while the C15-C27 aldehyde III-89 was synthesized from III-29 in 2 simple steps. However, the coupling between III-88 and III-89 under conditions described by Ley et al. failed to give the desired product III-90 (Scheme 3.18). Although switching the position of the sulfone and aldehyde within the coupling partners and replacing the sulfone substitute of benzothiazole with 1-phenyl-1H-tetrazole afforded a mixture of products in 31% yield, the major product was the C14-C15 cis alkene instead of the desired trans alkene (Scheme 3.18). More extensive studies on the Julia olefination between the C1-C14 and C15-C38 fragments of 29-desmethylokadaic acid were performed by Mr. Yucheng Pang in our group, and unfortunately, no reliable conditions to provide the desired coupling product were found.

3.8 Total Synthesis of Belizeanic Acid

Figure 3.1. The Structure of Belizeanic Acid

Belizeanic acid (BA, III-93, Figure 3.1), a novel metabolite belonging to the okadaic acid class of protein phosphatase inhibitors, was isolated from artificial cultures of the dinoflagellate Prorocentrum belizeanum in 2008. BA possesses a simplified version of
the okadaic acid skeleton, as the central C19 spiroketal of OA is replaced by an open form in BA (Figure 3.1). The relative stereochemistry of most stereocenters in BA is identical to OA, while the stereocenters at C16 and C19 were determined based on extensive molecular mechanics calculations and NMR data analysis.\textsuperscript{57} The C16 of BA has an \textit{S} configuration in contrast to the \textit{R} configuration in OA, and the C19 of BA also has an \textit{S} configuration in replacing the spirocarbon of OA.

Preliminary biological tests revealed that BA is a potent inhibitor of PP1, as \textit{in vitro} assays showed that BA has an IC\textsubscript{50} of 318 nM, whereas OA showed an IC\textsubscript{50} of 62 nM.\textsuperscript{57} BA’s activity against PP2A has yet to be reported. Moreover, molecular docking calculations of BA with PP1 active site complex suggested that the possible interactions might be different from those found in the aforementioned PP1/PP2A-OA complexes.\textsuperscript{29,31} Considering its interesting structural similarity with OA and its significant biological activities, it’s of our interest to target the synthesis of BA not only for its structural confirmation but also for more insightful biological tests.

The synthetic plan of BA utilized reliable fragment coupling methods developed in our synthesis of OA (Scheme 3.16), where the C1-C14 aldehyde \textbf{III-94} and the C15-C38 \(\beta\)-keto phosphonate \textbf{III-95} could be coupled together through a Horner-Wadworth-Emmons olefination.\textsuperscript{43} \textbf{III-95} is then disconnected into two pieces, the C16-C27 aldehyde \textbf{III-96} and the C28-C38 iodide \textbf{III-5}, which can be rejoined using the modified procedure developed in our synthesis of OA.
**Scheme 3.19.** Retrosynthetic Analysis of BA

The synthesis started with known aldehyde III-21 (Scheme 3.20).\(^1\) A Brown allylation\(^9\) of III-21 was utilized to install the stereocenter at C19, and the resulting hydroxyl was protected as TBS ether III-98. Hydroboration of III-98 followed by protection of the resulting hydroxyl afforded III-99. Regioselective cleavage of the anisylidene group in III-99 by DIBAL afforded the primary alcohol III-100 in relatively low yield (49%, 74% brsm), because longer reaction time or higher reaction temperature caused cleavage of the TBS ether at C16. Nevertheless, careful control of the reaction conditions helped to afford III-100 without losing too much material. Dess-Martin oxidation of III-100 gave aldehyde III-96 immediately before the coupling.
Using the previously established procedure, the C27 aldehyde **III-96** was coupled with C28 iodide **III-5** successfully to afford a mixture of two cabinols at C27 with a ratio of 1.0:1.4 favoring the undesired epimer (Scheme 3.21). After converting the undesired diastereomer **III-101-b** into the desired **III-101-a** using an oxidation-reduction sequence, the overall yield for the coupling and correction of C27 stereochemistry to afford **III-101-a** is 60%. The free hydroxyl in **III-101-a** was protected as TBS ether **III-102**, the PMB group of which was removed under oxidative conditions to give **III-103**. The C25 alkene of **III-104** was installed using a typical oxidation-Wittig olefination sequence. PPTs-mediated selective cleavage of the TBS ether at C16 of **III-104** provided the primary alcohol **III-105**, which was then converted into β-keto phosphonate **III-95** in...
three steps with 58% overall yield. **III-95** will participate in the incoming Horner-Wadsworth-Emmons olefination reaction.

Scheme 3.21. Synthesis of BA’s C15-C38 Fragment

![Scheme 3.21](image)

The synthesis of the C1-C14 fragment of BA started with **III-107** (Scheme 3.22), an intermediate prepared using the methods developed by Dr. Ce Wang and Mr. Yuchang Pang in our group.\(^9\) The acetonide group in **III-107** was removed under acidic conditions
to give diol III-108, which was converted into the α-hydroxy methyl ester III-109 in 3 steps with 70% overall yield. The remaining free hydroxyl in III-109 was masked as TES ether III-110, and the PMB group in III-110 was then removed using DDQ to afford III-111. Dess-Martin oxidation of III-111 gave the C14 aldehyde III-94 as the coupling partner with β-keto phosphonate III-95.

Scheme 3.22. Synthesis of BA’s C1-C14 Fragment
Scheme 3.23. Completion of the Synthesis of BA

Completion of the synthesis of BA began with a Horner-Wadsworth-Emmons olefination between III-94 and III-95 (Scheme 3.23). Under Masamune-Roush conditions, the complete carbon skeleton of BA was assembled by joining aldehyde III-94 and β-keto phosphonate III-95 to give (E)-ene III-112 in 80% yield. Regio- and stereoselective reduction of III-112 using the (R)-CBS/BH$_3$ combination proceeded smoothly to install the stereocenter at C16. TBAF-mediated removal of all four silyl groups in III-114 was then accomplished, and the basicity of TBAF/THF solution also induced the hydrolysis of the methyl ester to afford III-115 in 86% yield. Finally, lithium
di-tert-butylbiphenylide (LiDBB)\textsuperscript{95} was utilized for the controlled debenzylation at both C7 and C24, and belizeanic acid was afforded in 74% yield after isolation and purification. The proton NMR of synthetic BA matched well with that of natural BA (Figure 3.2), but unfortunately, no natural BA sample was available for more spectroscopical comparison.

Figure 3.2. \textsuperscript{1}H NMR Spectra Comparison of Synthetic (above) and Natural (bottom) BA
Chapter 4: Experimental

General Methods:

Unless otherwise noted, all reactions were carried out under an argon atmosphere in oven-dried glassware using standard syringe, cannula, and septa techniques. Dichloromethane, tetrahydrofuran, diethyl ether, toluene, and dimethylformamide were purified with Pure Solv. MD-6 solvent purification system. Triethylamine, diisopropylethylamine, acetonitrile, methanol were distilled from calcium hydride under argon or nitrogen. Benzene, dimethoxyethane was distilled from sodium/benzophenone ketyl under nitrogen. All other solvents were used as received. Analytical thin layer chromatography (TLC) was performed using 0.25 mm Silicycle silica gel 60 F254 plates. Preparative column chromatography was carried out using Silicycle SiliaFlash® P60 silica gel. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at the sodium D line (589 nm) in the solvent and concentration indicated. Infrared spectra (IR) spectra were recorded on a Perkin-Elmer FT-IR spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DPX 400 or 500 spectrometer. Chemical shifts were reported in ppm on the δ scale relative to residual CHCl₃ (δ = 7.26 for ¹H NMR and δ = 77.2 for ¹³C NMR) as an internal reference. ESI mass spectra were measured on a Bruker MicrOTOF instrument.
1-Deoxy-1-C-(3-butynyl)-a-D-3-O-benzyl-2-O-tert-butyldimethylsilyl-4,6-di-O-p-anisylidenealtropyranoside (III-23).

To a stirred solution of aldehyde III-21 (700 mg, 1.29 mmol) in MeOH (30 mL) under Ar was added potassium carbonate (356 mg, 2.58 mmol) followed by Bestmann-Ohira Reagent III-22 (371 mg, 1.93 mmol) at room temperature. The resulting yellow solution was allowed to stir for 16 h at room temperature before sat. aqueous NH₄Cl solution (10 mL) was added. Most of the MeOH was removed under vacuum, and the resulting residue was dissolved in ethyl acetate (20 mL), and then washed with saturated aqueous NaHCO₃ solution and brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated. Silica gel column chromatography (hexanes-ethyl acetate, 10:1, v/v) of the residue gave alkyne III-23 (571 mg, 1.06 mmol, 82%) as a colorless oil: Rf 0.74 (hexanes-ethyl acetate, 3:1, v/v); [a]²⁰D = -12° (c 1.80, CHCl₃); IR (neat): 2958, 2928, 2352, 2338, 1614, 1515, 1488, 1256, 1098, 1036 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.46 (d, J = 8.8 Hz, 2H), 7.35 (m, 5H), 6.92 (d, J = 8.8 Hz, 2H), 5.57 (s, 1H), 4.92 (d, J = 12 Hz, 1H), 4.64 (d, J = 12 Hz, 1H), 4.27 (dd, J = 4.8, 10 Hz, 1H), 4.11 (dd, J = 5.2, 14.8 Hz, 1H), 4.07 (d, J = 2.4 Hz, 1H), 4.03 (m, 1H), 3.89 (dd, J = 4.0, 10.8 Hz, 1H), 3.87 (s, 3H), 3.82 (m, 3H), 2.56 (m, 1H), 2.31 (m, 2H), 2.07 (m, 1H), 1.75 (m, 2H), 1.35 (m, 2H), 0.90 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 160.1, 138.7, 130.5, 129.4, 128.3, 127.6, 127.6, 117.4, 113.8, 113.7, 108.2, 102.2, 83.8, 78.3, 77.8,
74.9, 73.6, 70.9, 69.8, 68.8, 44.4, 36.3, 29.7, 28.1, 25.8, 25.1, 23.3, 22.4, 18.1, 15.7, 14.1,
-5.1, -5.0; HRMS (ESI⁺) calcd for C₃₁H₄₂NaO₆Si (M+Na⁺) 561.2643, found 561.2661.

1-Deoxy-1-C-[(R)-6-hydroxy-7-(4-methoxybenzyl)xyloxy]-3-heptynyl]-a-D-3-O-benzyl-2-O-tert-
butyldimethylsilyl-4,6-di-O-p-anisylidenealtropyranoside (III-25).

To a stirred solution of alkyne III-24 (571 mg, 1.06 mmol) in THF (20 mL) at -78 °C was added n-BuLi solution (0.51 mL, 2.5 M in hexanes, 1.27 mmol) dropwisely. The resulting solution was stirred for 30 min at – 78 °C, and then BF₃•Et₂O (0.16 mL, 1.27 mmol) was added followed by the solution of III-24 (823 mg, 4.24 mmol) in THF (10 mL) at -78 °C. The resultant solution was allowed to stir for 2 h at -78 °C before sat. aqueous NH₄Cl solution (10 mL) was added. The quenched solution was warmed to room temperature, and then diluted with ethyl acetate (30 mL). The separated aqueous layers were extracted with ethyl acetate (2×10 mL), and the combined organic layers were washed with H₂O and brine. The organic layers were dried over Na₂SO₄, filtered, and concentrated, and the resulting oil was generally used in next step without further purification. Silica gel column chromatography (hexanes-ethyl acetate, 10:1-5:1-2:1-1:1, v/v) provided an analytical sample of III-25 as a colorless oil: Rf 0.26 (hexanes-ethyl acetate, 3:1, v/v); [α]D²⁰ = -7.2° (c 1.0, CHCl₃); IR (neat): 3460, 2955, 2920, 2356, 2332,
1611, 1513, 1457, 1248 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\ 7.45\ (d, J = 8.8\ Hz, 2H), 7.37\ (m, 3H), 7.32\ (m, 2H), 7.26\ (m, 2H), 6.92\ (d, J = 8.4\ Hz, 2H), 6.90\ (d, J = 8.8\ Hz, 2H), 5.57\ (s, 1H), 4.92\ (d, J = 12\ Hz, 1H), 4.64\ (d, J = 12.4\ Hz, 1H), 4.51\ (m, 3H), 4.26\ (dd, J = 4.8, 10\ Hz, 1H), 4.11\ (dd, J = 4.8, 9.6\ Hz, 1H), 4.05\ (m, 1H), 4.03\ (m, 1H), 3.91\ (m, 1H), 3.84\ (s, 3H), 3.83\ (s, 3H), 3.78\ (m, 3H), 3.58\ (m, 1H), 3.48\ (m, 2H), 2.48\ (m, 1H), 2.42\ (m, 3H), 2.28\ (m, 2H), 1.68\ (m, 1H), 1.45\ (m, 1H), 0.90\ (s, 9H), 0.03\ (s, 3H), 0.01\ (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\ 160.1, 159.3, 138.8, 130.5, 130.1, 129.4, 128.3, 128.2, 127.9, 127.6, 113.9, 113.6, 102.2, 81.9, 78.5, 77.8, 76.2, 73.5, 73.1, 72.8, 72.3, 69.9, 69.1, 60.0, 55.3, 28.6, 25.8, 24.8, 23.9, 18.1, 16.0, 14.6, -5.1, -5.0; HRMS (ESI+) calcd for C\(_{42}H_{58}NaO_{9}Si\) (M+Na)\(^+\) 755.3586, found 755.3589.

![III-26](image)

1-Deoxy-1-C-\([(R)-6-hydroxy-7-(4-methoxybenzylxyloxy)-3-heptynyl]-a-D-3-O-benzyl-4,6-di-O-p-anisylidenealtropyranoside (III-26).

To a stirred solution of TBS ether III-25 (777mg, 1.06 mmol) in THF (20 mL) was added TBAF solution (1.27 mL, 1.0 M in THF, 1.27 mmol). The resulting solution was stirred for 1 h at room temperature before aqueous NH\(_4\)Cl solution (10 mL) and EtOAc (20 mL) were added. The separated aqueous layers were extracted with ethyl acetate and the combined organic layers were washed with H\(_2\)O and brine. The organic layers were
dried over Na₂SO₄, filtered, and concentrated, and the resulting oil was purified by silica gel column chromatography (hexanes-ethyl acetate, 1:1-ethyl acetate, 100%, v/v) to provide diol III-26 as colorless oil (508 mg, 0.82 mmol, 77% from III-23): R_f 0.18 (hexanes-ethyl acetate, 1:1, v/v); [α]_{D}^{20} = +18° (c 1.4, CHCl₃); IR (neat): 3424, 2908, 2358, 2341, 1614, 1515, 1455, 1250, 1173, 1100, 1034 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.44 (d, J = 8.8 Hz, 2H), 7.36 (m, 3H), 7.32 (m, 2H), 7.26 (m, 2H), 6.92 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 5.56 (s, 1H), 4.92 (d, J = 12.4 Hz, 1H), 4.64 (d, J = 12 Hz, 1H), 4.51 (s, 2H), 4.26 (dd, J = 5.2, 10.4 Hz, 1H), 4.11 (dd, J = 4.8, 9.6 Hz, 1H), 4.03 (m, 5H), 3.83 (s, 3H), 3.82 (s, 3H), 3.75 (dd, J = 10, 10Hz, 1H), 3.57 (dd, J = 4.0, 9.6 Hz, 1H), 3.46 (dd, 6.4, 9.6 Hz, 1H), 2.57 (d, 4.4 Hz, 1H), 2.48 (m, 1H), 2.42 (m, 2H), 2.34 (d, J = 5.2Hz, 1H), 2.28 (m, 2H), 1.77 (m, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ 160.1, 159.3, 138.7, 130.3, 130.0, 129.4, 128.3, 127.5, 127.4, 113.9, 113.7, 102.2, 81.5, 78.3, 77.8, 76.1, 73.7, 73.1, 72.8, 71.4, 69.7, 69.2, 60.3, 55.3, 27.9, 24.0, 15.7; HRMS (ESI+) calcd for C₃₆H₄₂NaO₉ (M+Na)⁺ 641.2721, found 641.2752.

C19 Spiroketal (III-27)

To a stirred solution of AuCl (70 mg, 0.30 mmol) in CH₂Cl₂ (10 mL) was added a solution of diol III-26 (0.96 g, 1.55 mmol) in CH₂Cl₂ (20 mL) by cannula. The resulting solution was stirred for 2 h at room temperature, upon which time TLC showed no
starting material left. A solution of TsOH•H₂O (18 mg, 0.094 mmol) in MeOH (12 mL) was then added into the flask, and the reaction was stirred for another 2 h, after which it was quenched with Et₃N (0.04 mL). The solvent was removed under vacuum, and the residue was purified by silica gel column chromatography (hexanes-ethyl acetate, 1:1-ethyl acetate, 100%, v/v) to give C19 spiroketal III-27 as a white solid (0.63 g, 1.26 mmol, 81% from III-26): mp 93-95 °C; Rf 0.16 (hexanes-ethyl acetate, 1:1, v/v); [α]²⁰<sub>D</sub> = +5.3° (c 1.2, CHCl₃); IR (neat): 3288, 2948, 2352, 1612, 1513, 1462, 1366, 1247, 1115, 1087, 1034 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.36 (m, 4H), 7.32 (m, 1H), 7.29 (m, 1H), 7.26 (m, 2H), 6.92 (d, J = 8.4 Hz, 2H), 4.86 (d, J = 12 Hz, 1H), 4.71 (d, J = 12 Hz, 1H), 4.54 (s, 2H), 4.33 (m, 1H), 4.13 (m, 1H), 3.98 (m, 1H), 3.87 (m, 1H), 3.83 (s, 3H), 3.59 (m, 2H), 3.51 (m, 2H), 3.38 (m, 1H), 2.82 (s, 1H), 2.14 (m, 1H), 2.03 (m, 1H), 1.90 (m, 5H), 1.78 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ 159.2, 138.3, 130.5, 129.3, 128.4, 127.8, 127.5, 113.8, 106.1, 78.0, 77.5, 76.6, 73.0, 72.03, 71.95, 69.4, 68.4, 59.7, 55.3, 36.7, 32.5, 26.5, 26.4; HRMS (ESI+) calcd for C₂₈H₃₆NaO₆ (M+Na)<sup>+</sup> 523.2302, found 523.2312.
C27 TBS Ether (III-28)

To a stirred solution of diol III-27 (230 mg, 0.46 mmol) in CH₂Cl₂ (12 mL) at 0 °C was added Et₃N (0.38 mL, 2.76 mmol), immediately followed by TBSCl (208 mg, 1.38 mmol) and DMAP (11 mg, 0.092 mmol). The resulting solution was allowed to warm to room temperature gradually and stirred for 14 h. After this time, the reaction mixture was diluted with CH₂Cl₂ (15 mL), and then quenched with saturated NaHCO₃ solution (10 mL). The separated organic layers were washed with H₂O and brine, and then dried over Na₂SO₄, filtered, and concentrated. The resulting residue was then purified by silica gel column chromatography (hexanes-ethyl acetate, 2:1, v/v) provided C27 TBS ether III-28 as a colorless oil (270 mg, 0.44 mmol, 95%): Rf 0.38 (hexanes-ethyl acetate, 2:1, v/v); [a]²₀_D = +10° (c 2.1, CHCl₃); IR (neat): 3410, 2950, 2359, 1612, 1513, 1457, 1362, 1248, 1110, 1069, 1038 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.35 (m, 4H), 7.28 (m, 2H), 7.25 (m, 1H), 6.87 (d, J = 8.8 Hz, 2H), 4.82 (d, J = 12.4 Hz, 1H), 4.71 (d, J = 12 Hz, 1H), 4.51 (s, 2H), 4.32 (m, 1H), 4.16 (d, J = 3.6 Hz, 1H), 4.07 (dd, J = 10, 10 Hz, 1H), 3.98 (dd, J = 6.0, 6.0 Hz, 1H), 3.84 (m, 1H), 3.81 (s, 3H), 3.77 (m, 1H), 3.73 (m, 1H), 3.48 (m, 3H), 2.76 (d, J = 1.2 Hz, 1H), 2.14 (m, 1H), 1.90 (m, 2H), 1.83 (m, 3H), 1.76 (m, 2H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 159.3, 138.8, 130.8, 129.4, 128.5, 127.8, 127.6, 113.9, 106.2, 78.5, 77.5, 76.7, 73.2, 72.6, 72.22, 72.17, 71.4, 69.0, 63.4, 55.5, 36.9, 32.8, 26.9, 26.6, 26.0, 18.3, -5.3, -5.4; HRMS (ESI+) calcd for C₃₄H₅₀NaO₇Si (M+Na)^+ 637.3167, found 637.3157.
**C25 Alkene (III-29)**

To a stirred room-temperature solution of alcohol **III-28** (120 mg, 0.195 mmol) in CH$_2$Cl$_2$ (20 mL) was added NaHCO$_3$ (1.64 g, 19.5 mmol), followed by the Dess-Martin periodinane reagent (1.24 g, 2.93 mmol). The resulting solution was allowed to stir for 14 h. After this time, the reaction mixture was diluted with CH$_2$Cl$_2$ (15 mL), and then quenched with H$_2$O (5 mL) and saturated aqueous Na$_2$S$_2$O$_3$ solution (15 mL), and the mixture was stirred until the organic layer became clear. The separated aqueous layers were extracted with CH$_2$Cl$_2$, and the combined organic layers were washed with H$_2$O and brine, and then dried over Na$_2$SO$_4$, filtered, and concentrated. The resulting residue was used for next step without further purification.

To a stirred solution of methyltriphenylphosphonium iodide (296 mg, 0.73 mmol) in toluene (5 mL) under argon was added KHMDS solution (1.17 mL, 0.5M in toluene, 0.585 mmol). The resulting yellow solution was heated to 90 °C for 30 min and then cooled to room temperature before a solution of ketone from the previous step (0.195 mmol theor.) in toluene (5 mL) was added via cannula. The resulting solution was heated to 90 °C for 45 min and then recooled to room temperature before saturated aqueous NH$_4$Cl solution (5 mL) was added. The toluene was removed by rotary evaporation, and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, and then dried over Na$_2$SO$_4$, filtered, and concentrated. The resulting
residue was purified by silica gel column chromatography (hexanes-ethyl acetate, 20:1-10:1-5:1, v/v) to yield C25 alkene III-29 as a colorless oil (103 mg, 0.17 mmol, 86% from III-28): R\text{f} 0.70 (hexanes-ethyl acetate, 2:1, v/v); [a]\text{D}^{20} = +23^\circ (c 1.5, \text{CHCl}_3); \text{IR (neat):} 2950, 2360, 1513, 1456, 1248, 1095, 838 cm\textsuperscript{-1}; \text{^1H NMR} (\text{CDCl}_3, 400 MHz): \delta 7.39 (m, 2H), 7.30 (m, 4H), 7.25 (m, 1H), 6.87 (d, \text{J} = 8.8 Hz, 2H), 5.42 (dd, \text{J} = 2.0, 2.0 Hz, 1H), 5.06 (dd, \text{J} = 1.6, 2.0 Hz, 1H), 4.86 (d, \text{J} = 12 Hz, 1H), 4.75 (d, \text{J} = 12 Hz, 1H), 4.50 (d, \text{J} = 2.4 Hz, 2H), 4.32 (m, 2H), 4.16 (d, \text{J} = 9.2 Hz, 1H), 3.87 (dd, \text{J} = 6.0, 10.4 Hz, 1H), 3.80 (s, 3H), 3.77 (dd, \text{J} = 5.2, 10.4 Hz, 1H), 3.68 (m, 2H), 3.47 (m, 2H), 2.14 (m, 1H), 1.90 (s, 3H), 1.76 (m, 2H), 0.89 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); \text{^13C NMR} (\text{CDCl}_3, 100 MHz): \delta 159.3, 143.3, 139.4, 130.8, 129.4, 128.4, 127.6, 127.5, 113.9, 112.0, 106.1, 80.9, 78.5, 77.5, 76.7, 73.4, 73.1, 72.1, 71.1, 64.9, 36.9, 32.7, 27.1, 26.5, 26.1, 18.5, -5.19, -5.22; \text{HRMS (ESI+)} \text{calcd for C}_{35}\text{H}_{50}\text{NaO}_7\text{Si (M+Na)}^+ 633.3218, \text{found 633.3209.}

C27 Alcohol (III-30)

To a stirred room-temperature solution of TBS ether III-29 (21 mg, 0.034 mmol) in THF (1 mL) was added TBAF (0.052 mL, 1M in THF, 0.052 mmol), and then the resulting solution was stirred for 1 h at room temperature. After this time, the reaction mixture
was diluted with EtOAc (5 mL), and then quenched with saturated aqueous NH₄Cl solution (2 mL). The two layers were separated, and the aqueous layers were extracted with EtOAc, and the combined organic layers were washed with brine, and then dried over Na₂SO₄, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (hexanes-ethyl acetate, 1:1-1:2, v/v) to provide C27 alcohol **III-30** as a colorless oil (16 mg, 0.032 mmol, 94%): Rf 0.13 (hexanes-ethyl acetate, 2:1, v/v); [α]²⁰_D = +17° (c 1.4, CHCl₃); IR (neat): 3410 (br), 2947, 2357, 1513, 1456, 1247, 1086, 1036, 847 cm⁻¹;¹H NMR (CDCl₃, 400 MHz): δ 7.34 (m, 5H), 7.25 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 5.46 (dd, J = 2.0, 2.0 Hz, 1H), 5.12 (s, 1H), 4.87 (d, J = 11.6 Hz, 1H), 4.73 (d, J = 12 Hz, 1H), 4.50 (s, 2H), 4.42 (dd, J = 5.2, 10.0 Hz, 1H), 4.31 (dd, J = 4.8, 8.4 Hz, 1H), 4.04 (d, J = 9.2 Hz, 1H), 3.95 (ddd, J = 3.2, 11.6, 13.2 Hz, 1H), 3.80 (s, 3H), 3.73 (t, J = 9.6 Hz, 1H), 3.52 (m, 2H), 3.47 (dd, J = 2.8, 5.2 Hz, 2H), 2.13 (m, 1H), 1.90 (m, 6H), 1.76 (m, 2H);¹³C NMR (CDCl₃, 100 MHz): δ 159.3, 142.2, 139.1, 130.7, 129.4, 128.5, 127.6, 127.6, 113.9, 113.1, 106.1, 80.4, 78.5, 77.5, 73.6, 73.1, 72.1, 69.7, 61.6, 55.5, 36.8, 32.6, 26.9, 26.5; HRMS (ESI+) calcd for C₉₉H₃₆NaO₇ (M+Na)^+ 519.2353, found 519.2372.
**Hydroxylation (2S,3S,4R)-1-Benzyloxy-2,4-dimethylhex-5-ene-3-ol (III-50)**

To a stirred solution of diol **III-49** (108 mg, 0.75 mmol) in benzene (4 mL) under Ar was added powered KOH (104 mg, 1.86 mmol) and BnBr (0.13 mL, 1.1 mmol). The resulting solution was heated to reflux and then stirred for 2 h. The solution was allowed to cool to room temperature then filtered. After evaporation of solvents, the residue was purified by silica gel column chromatography (hexanes-ethyl acetate, 20:1-10:1-5:1-1:2, v/v) to isolate **III-50** as a colorless oil (96 mg, 0.41 mmol, 55%), as well as starting material **III-49** (30 mg, 0.21 mmol, 35%). Data for **III-50**: Rₐ 0.58 (hexanes-ethyl acetate, 3:1, v/v); [a]²⁰ = +8.0° (c 0.6, CHCl₃); IR (neat): 3468, 2972, 1699, 1652, 1456, 1096 cm⁻¹; 

1H NMR (CDCl₃, 400 MHz): δ 7.33 (m, 5H), 5.64 (ddd, J = 8.4, 10.0, 17.2 Hz, 1H), 5.06 (ddd, J = 0.8, 2.0, 17.2 Hz, 1H), 4.98 (dd, J = 2.0, 10.0 Hz, 1H), 4.53 (d, J = 12 Hz, 1H), 4.49 (d, J = 12 Hz, 1H), 3.56 (m, H), 3.54 (m, 1H), 3.52 (m, 1H), 2.59 (d, J = 2.8 Hz, 1H), 2.29 (m, 1H), 1.94 (m, 1H), 1.10 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 7.2 Hz, 3H); 13C NMR (CDCl₃, 100 MHz): δ 141.3, 138.1, 128.4, 128.4, 127.7, 127.6, 127.5, 114.6, 77.2, 77.2, 75.7, 73.4, 42.1, 35.4, 17.1, 9.8; HRMS (ESI+) calcd for C₁₅H₂₂NaO₂ (M+Na)⁺ 257.1512, found 257.1505.
(2S,3S,4R)-1-Benzyloxy-2,4-dimethyl-3-triethylsilyloxyhex-5-ene (III-51)

To a stirred solution of alcohol III-50 (162 mg, 0.69 mmol) in CH$_2$Cl$_2$ (6 mL) under argon was added imidazole (470 mg, 6.90 mmol), TESCl (0.58 mL, 3.46 mmol) and DMAP (17 mg, 0.14 mmol), and then the resulting solution was stirred at room temperature for 14 h. After this time, the reaction mixture was diluted with CH$_2$Cl$_2$ (15 mL), and then quenched with saturated NaHCO$_3$ solution (10 mL). The separated organic layers were washed with H$_2$O and brine, and then dried over Na$_2$SO$_4$, filtered, and concentrated. The resulting residue was then purified by silica gel column chromatography (hexanes-ethyl acetate, 50:1, v/v) provided TES ether III-51 as a colorless oil (218 mg, 0.63 mmol, 91%): R$_f$ 0.64 (hexanes-ethyl acetate, 10:1, v/v); [a]$^20$D = +3.5° (c 2.8, CHCl$_3$); IR (neat): 2958, 1652, 1456, 1112, 734 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.33 (m, 5H), 5.76 (ddd, $J = 8.0, 8.4, 17.2$Hz, 1H), 5.01 (ddd, $J = 1.2, 2.0, 17.2$Hz, 1H), 4.95 (ddd, $J = 0.8, 2.0, 9.6$ Hz, 1H), 4.52 (d, $J = 12$ Hz, 1H), 4.46 (d, $J = 12$Hz, 1H), 3.67 (dd, $J = 2.8, 7.6$Hz, 1H), 3.40 (dd, $J = 7.6, 8.8$ Hz, 1H), 3.24 (dd, $J = 6.4, 8.8$ Hz, 1H), 2.32 (m, 1H), 2.00 (m, 1H), 1.02 (d, $J = 6.8$ Hz, 3H), 0.96 (t, $J = 8.0$Hz, 9H), 0.86 (d, $J = 6.8$ Hz, 3H), 0.61(m, 6H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 142.1, 138.7, 128.3, 127.6, 127.4, 113.7, 77.2, 76.1, 73.7, 72.9, 42.7, 36.5, 17.1, 10.8, 7.1, 5.5; HRMS (ESI+) calcd for C$_{21}$H$_{36}$NaO$_2$Si (M+Na)$^+$ 371.2377, found 371.2368.
A stream of O$_2$/O$_3$ was bubbled through a stirred solution of alkene III-50 (138 mg, 0.40 mmol) in MeOH/CH$_2$Cl$_2$ (5 mL + 1 mL) at -78 °C until a faint blue color persisted. A stream of air was then bubbled through the solution until it became colorless again. Triphenylphosphine (156 mg, 0.44 mmol) was added and the solution was allowed to warm to room temperature and stir for 1 h. The solution was concentrated, and the resulting residue was purified by silica gel column chromatography (hexanes-ethyl acetate, 100:1-70:1-20:1, v/v) to give aldehyde III-51 as a colorless oil (131 mg, 0.37 mmol, 94%): $R_f$ 0.51 (hexanes-ethyl acetate, 10:1, v/v); $[\alpha]^{20}_D = +40^\circ$ (c 0.5, CHCl$_3$); IR (neat): 2956, 2876, 1723, 1456, 1102, 737 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 9.81 (d, $J$ = 1.2 Hz, 1H), 7.33 (m, 5H), 4.50 (d, $J$ = 12 Hz, 1H), 4.45 (d, $J$ = 12 Hz, 1H), 4.24 (dd, $J$ = 4.0, 4.8 Hz, 1H), 3.41 (dd, $J$ = 6.8, 9.2 Hz, 1H), 3.27 (dd, $J$ = 6.0, 8.4 Hz, 1H), 2.54 (m, 1H), 1.95 (m, 1H), 1.07 (d, $J$ = 6.8 Hz, 3H), 0.95 (t, $J$ = 8.0 Hz, 9H), 0.89 (d, $J$ = 6.8 Hz, 3H), 0.60 (m, 6H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 205.4, 128.6, 127.8, 127.8, 77.4, 73.2, 73.1, 72.9, 51.5, 37.4, 12.4, 9.5, 7.2, 5.4; HRMS (ESI+) calcd for C$_{20}$H$_{36}$NaO$_3$Si (M+Na)$^+$ 373.2169, found 373.2160.
C32 Propargyl Alcohols (III-54/55)

To a stirred solution of alkyne III-53 (153 mg, 0.72 mmol) in THF (1 mL) at -78 °C was added n-BuLi (0.43 mmol, 2.5M in hexanes, 1.08 mmol) dropwise, and the resulting solution was stirred for 30 min at -78 °C, after which the solution was allowed to warm to -30 °C and stir for 30 min. The flask was recooled to -78 °C, and then a precooled solution of aldehyde III-52 (126 mg, 0.36 mmol) in THF (2 mL) was cannulated into the flask. After 30 min at -78 °C, the solution was warmed to room temperature and stirred for 30 min. The solution was quenched with aqueous NH₄Cl solution, and then diluted with EtOAc (10 mL). The separated aqueous layers were extracted with EtOAc, and combined organic layers were washed with H₂O and brine, dried over anhydrous Na₂SO₄, filtered, and concentrated. The resulting oil was then purified by silica gel column chromatography (hexanes-ethyl acetate, 100:1-70:1-20:1-10:1, v/v) to give a mixture of two diastereomers (151 mg, 0.27 mmol, 75%). Diastereomeric ratio was determined as 1:1.5 anti:syn based on integration of 400-MHz ¹H NMR resonances at δ 4.02, and 3.97, respectively.

anti product III-55: Rᵣ 0.32 (hexanes-ethyl acetate, 10:1, v/v); [a]²⁰D = -2.3° (c 1.3, CHCl₃); IR (neat): 3430, 2953, 1600, 1456, 1417, 1239, 1107, 731 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.32 (m, 5H), 4.50 (s, 2H), 4.31 (m, 1H), 4.03 (t, J = 4.0Hz, 1H), 3.62 (t, J = 6.0Hz, 2H), 3.40 (dd, J = 6.8, 9.2Hz, 1H), 3.25 (dd, J = 6.8, 9.2Hz, 1H), 2.82 (d, J = 4Hz, 1H), 2.23 (m, 2H), 2.00 (m, 1H), 1.88 (m, 1H), 1.60 (m, 4H), 0.95 (m, 24H),
0.60(m, 6H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 138.8, 128.5, 127.8, 127.7, 127.6, 86.0, 77.4, 74.4, 73.6, 73.1, 65.7, 62.5, 43.9, 36.6, 32.3, 25.4, 18.8, 13.1, 12.5, 7.2, 7.0, 5.4, 4.6; HRMS (ESI+) calcd for C$_{32}$H$_{58}$NaO$_4$Si$_2$ (M+Na)$^+$ 585.3766, found 585.3759.

**syn product III-54**: R$_f$ 0.28 (hexanes-ethyl acetate, 10:1, v/v); [α]$^D_{20}$ = +0.7° (c 2.3, CHCl$_3$); $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.32 (m, 5H), 4.50 (d, $J = 12$ Hz, 1H), 4.47 (d, $J = 12$ Hz, 1H), 4.30 (t, $J = 5.6$ Hz, 1H), 3.97 (t, $J = 4.4$Hz, 1H), 3.61 (t, $J = 6.0$Hz, 2H), 3.46 (dd, $J = 6.0$, 9.2 Hz, 1H), 3.27 (dd, $J = 6.8$, 8.8 Hz, 1H), 2.22 (m, 2H), 2.03 (m, 1H), 1.93 (d, $J = 5.2$ Hz, 1H), 1.78 (m, 1H), 1.60 (m, 4H), 1.01 (d, $J = 6.8$ Hz, 3H), 0.95 (m, 21H), 0.60(m, 6H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 138.8, 128.5, 127.8, 127.6, 86.4, 81.2, 77.4, 74.9, 73.4, 73.2, 65.9, 62.5, 43.5, 38.3, 32.2, 25.3, 18.8, 13.3, 10.6, 7.2, 7.0, 5.6, 4.6; HRMS (ESI+) calcd for C$_{32}$H$_{58}$NaO$_4$Si$_2$ (M+Na)$^+$ 585.3766, found 585.3764.
Absolute configuration at C32 of III-54 and III-55 came from the conversion of III-56 to III-54-b, followed by analysis of their respective $^{13}$C NMR spectra according to Rychnovsky’s method (*J. Org. Chem.* 1993, 58, 3511).

![Chemical structures](image)

$^{13}$C NMR data for III-56: (CDCl$_3$, 100 MHz): $\delta$ 138.2, 128.4, 127.6, 127.6, 86.0, 80.6, 77.2, 76.3, 74.0, 73.3, 67.0, 62.3, 41.3, 36.9, 31.8, 24.9, 18.5, 13.1, 8.3;

$^{13}$C NMR data for III-54-b: (CDCl$_3$, 100 MHz): $\delta$ 138.7, 128.6, 127.8, 127.7, 99.7, 86.0, 78.7, 77.4, 74.9, 73.4, 71.5, 66.2, 62.6, 35.5, 35.1, 32.1, 30.2, 25.0, 19.5, 18.9, 14.8, 6.9; Among them, acetonide carbons resonate at 99.7, 30.2, and 19.5 ppm, indicating a syn 1,3-diol. Therefore, the other diastereomer III-55 must be an *anti* 1,3-diol.
1,3-Syn Triol (III-56)

To a stirred solution of III-54 (84 mg, 0.15 mmol) in MeOH (3 mL) at room temperature was added TsOH•H$_2$O (8.5 mg, 0.045 mmol), and the resulting solution was stirred for 1 h at room temperature, after which the solution was quenched with Et$_3$N (0.1 mL), and the solvent was removed under vacuum. The resulting oil was purified by silica gel column chromatography (dichloromethane-methanol, 20:1-10:1, v/v) to give III-56 as a colorless oil (49 mg, 0.15 mmol, 98%). Data for III-56: R$_f$ 0.29 (dichloromethane-methanol, 20:1, v/v); [a]$^20$D = +1.0° (c 0.8, CHCl$_3$); IR (neat): 3401, 2927, 1453, 1071, 973, 737, 699 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.32 (m, 5H), 4.50 (br, 1H), 4.48 (s, 2H), 3.84 (dd, $J = 4.8$, 4.8 Hz, 1H), 3.63 (dd, $J = 6.4$, 6.4Hz, 2H), 3.45 (m, 1H), 3.43 (dd, $J = 5.6$, 5.6Hz, 2H), 2.98 (br, 1H), 2.25 (dt, $J = 2.0$, 6.8Hz, 2H), 1.97 (m, 2H), 1.84 (m, 1H), 1.66 (m, 2H), 1.58 (m, 2H), 1.09 (d, $J = 6.8$Hz, 3H), 1.05 (d, $J = 6.8$Hz, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 138.2, 128.4, 127.6, 127.6, 86.0, 80.6, 77.2, 76.3, 74.0, 73.3, 67.0, 62.3, 41.3, 36.9, 31.8, 24.9, 18.5, 13.1, 8.3; HRMS (ESI+) calcd for C$_{20}$H$_{30}$NaO$_4$ (M+Na)$^+$ 357.2036, found 357.2062.
To a stirred solution of III-55 (70 mg, 0.12 mmol) in MeOH (3 mL) at room temperature was added TsOH•H₂O (6.1 mg, 0.03 mmol), and the resulting solution was stirred for 1 h at room temperature, after which the solution was quenched with Et₃N (0.1 mL), and the solvent was removed under vacuum. The resulting oil was purified by silica gel column chromatography (dichloromethane-methanol, 20:1-10:1, v/v) to give III-57 as a colorless oil (40 mg, 0.12 mmol, 96%). Data for III-57: R_f 0.28 (dichloromethane-methanol, 20:1, v/v); [a]_D^20 = +2.5° (c 2.0, CHCl₃); IR (neat): 3384(br), 2932, 1654, 1458, 1057, 698 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): d 7.32 (m, 5H), 4.49 (s, 2H), 4.38 (m, 1H), 4.06 (m, 1H), 3.63 (t, J = 6.0, 6.0Hz, 1H), 3.44 (m, 2H), 2.86 (d, J = 6.0Hz, 1H), 2.71 (d, J = 4.0Hz, 1H), 2.25 (dt, J = 2.0, 7.2Hz, 2H), 1.90 (m, 2H), 1.66 (m, 3H), 1.58 (m, 3H), 1.07 (m, 6H); ¹³C NMR (CDCl₃, 100 MHz): d 138.4, 128.6, 127.8, 127.7, 86.5, 80.8, 74.6, 74.2, 73.5, 66.7, 62.5, 41.3, 36.8, 32.0, 25.0, 18.7, 13.2, 10.6; HRMS (ESI+) calcd for C₂₀H₃₀NaO₄ (M+Na)⁺ 357.2036, found 357.2045.
Spiroketalts (III-58/59/60)

To a stirred solution of AuCl (3.4 mg, 0.015 mmol) and powered 4 Å MS in THF (1 mL) at 0 °C was cannulated the solution of triol III-56 (49 mg, 0.15 mmol) in THF (2 mL), and the resulting solution was stirred for 30 min at 0 °C, after which the solution was quenched with Et₃N (0.1 mL), and the solution was filtered through a pad of Celite. The solvent was removed under vacuum, and the resulting oil was then purified by silica gel column chromatography (hexanes-ethyl acetate, 10:1-8:1-3:1, v/v) to give spiroketal III-58 as colorless oil (6 mg, 0.02 mmol, 13%), spiroketal III-59 as a colorless oil (30 mg, 0.09 mmol, 61%) along with spiroketal III-60 (4 mg, 0.012 mmol, 8%).

Data for III-58: Rₜ 0.74 (hexanes-ethyl acetate, 3:1, v/v); [α]²⁰ D = -9.7° (c 1.5, CHCl₃); IR (neat): 2934, 1454, 1120, 1094, 1046, 1000, 898 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.32 (m, 5H), 5.90 (dd, J = 6.0, 10.0 Hz, 1H), 5.26 (d, J = 10.0 Hz, 1H), 4.50 (d, J = 12.4 Hz, 1H), 4.47 (d, J = 12 Hz, 1H), 3.91 (dt, J = 3.2, 11.6 Hz, 1H), 3.72 (dd, J = 2.8, 10.0 Hz, 1H), 3.61 (m, 1H), 3.43 (dd, J = 4.4, 9.2 Hz, 1H), 3.30 (dd, J = 6.8, 9.2 Hz, 1H), 2.00 (m, 2H), 1.90 (m, 1H), 1.56 (m, 6H), 1.21 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 138.8, 134.6, 129.3, 128.5, 128.4, 127.8, 127.7, 94.4, 77.4, 73.3, 72.8, 72.2, 61.3, 35.5, 35.4, 31.0, 25.4, 19.0, 15.5, 13.0; HRMS (ESI+) calcd for C₂₀H₂₈NaO₃ (M+Na)⁺ 339.1931, found 339.1918.
Data for **III-59**: R$_f$ 0.60 (hexanes-ethyl acetate, 3:1, v/v); [α]$^{20}_D$ = +78° (c 2.0, CHCl$_3$); IR (neat): 3500 (br), 2933, 1455, 1099, 1067, 964 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.32 (m, 5H), 4.50 (d, $J$ = 12 Hz, 1H), 4.49 (d, $J$ = 12 Hz, 1H), 3.96 (t, $J$ = 6.4 Hz, 1H), 3.89 (m, 1H), 3.73 (dt, $J$ = 3.2, 16 Hz, 1H), 3.55 (dd, $J$ = 4.8, 6.4 Hz, 1H), 3.39 (dd, $J$ = 6.0, 9.2 Hz, 1H), 3.25 (dd, $J$ = 6.8, 9.2 Hz, 1H), 3.08 (d, $J$ = 7.6 Hz, 1H), 2.17 (m, 2H), 1.96 (m, 3H), 1.80 (br, 1H), 1.68 (m, 3H), 1.52 (m, 1H), 1.39 (m, 1H), 0.97 (m, 6H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 138.8, 128.5, 128.5, 127.7, 127.6, 105.3, 84.6, 79.4, 77.4, 73.5, 73.3, 63.4, 43.9, 38.7, 34.4, 31.0, 29.5, 22.8, 14.3, 12.7; HRMS (ESI+) calcd for C$_{20}$H$_{30}$NaO$_4$ (M+Na)$^+$ 357.2036, found 357.2041.

Data for **III-60**: R$_f$ 0.40 (hexanes-ethyl acetate, 3:1, v/v); [α]$^{20}_D$ = -42° (c 0.4, CHCl$_3$); IR (neat): 3400 (br), 2890, 1379, 1066 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.32 (m, 5H), 4.50 (d, $J$ = 12 Hz, 1H), 4.48 (d, $J$ = 12 Hz, 1H), 4.00 (t, $J$ = 7.2 Hz, 1H), 3.85 (t, $J$ = 5.2 Hz, 1H), 3.80 (dd, $J$ = 2.4, 10.0 Hz, 1H), 3.59 (dt, $J$ = 3.6, 12.8 Hz, 1H), 3.39 (dd, $J$ = 5.2, 9.2 Hz, 1H), 3.23 (dd, $J$ = 6.8, 9.2 Hz, 1H), 2.17 (m, 2H), 2.01 (m, 1H), 1.78 (m, 1H), 1.70 (m, 4H), 1.43 (m, 2H), 1.11 (d, $J$ = 7.2 Hz, 3H), 1.07 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 138.8, 128.5, 127.7, 127.6, 111.0, 84.4, 81.2, 73.7, 73.3, 63.3, 44.1, 35.1, 34.2, 31.0, 29.8, 23.4, 14.9, 13.0; HRMS (ESI+) calcd for C$_{20}$H$_{30}$NaO$_4$ (M+Na)$^+$ 357.2036, found 357.2042.
Relative configuration of spiroketalts III-59 and III-60 were determined by NOE experiments as shown below. The assignment of proton resonances was completed by 2D-COSY experiments.

**C34 Spiroketal (III-58)**

To a stirred solution of AuCl (2.8 mg, 0.012 mmol) and powdered 4 Å MS in THF (1 mL) at 0 °C was cannulated the solution of triol III-57 (40 mg, 0.12 mmol) in THF (2 mL), and the resulting solution was stirred for 30 min at 0 °C, after which the solution was quenched with Et₃N (0.1 mL), and the solution was filtered through a pad of Celite. The solvent was removed under vacuum, and the resulting oil was purified was then purified...
by silica gel column chromatography (hexanes-ethyl acetate, 10:1-8:1-3:1, v/v) to give spiroketal III-58 as a colorless oil (24.5 mg, 0.08 mmol, 65%) with data matched with those reported above.

**Conversion of III-54 to III-55**

To a stirred room temperature solution of III-54 (137 mg, 0.24 mmol) in CH₂Cl₂ (10 mL) under argon was added NaHCO₃ (1020 mg, 12 mmol), followed by the Dess-Martin periodinane reagent (576 mg, 1.2 mmol). The resulting solution was stirred for 2 h at room temperature. After this time, the reaction mixture was diluted with CH₂Cl₂ (10 mL), and then quenched with H₂O (10 mL) and saturated Na₂S₂O₃ solution (10 mL), and the mixture was stirred until the organic layer became clear. The separated aqueous layers were extracted with CH₂Cl₂, and the combined organic layers were washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated. The resulting oil was purified by silica gel column chromatography (hexanes-ethyl acetate, 30:1, v/v) to provide the corresponding ketone as a colorless oil (121 mg, 0.22 mmol, 89%): Rᵓ 0.44 (hexanes-ethyl acetate, 10:1, v/v); [α]ᵢ^20_D = -3.5° (c 2.4, CHCl₃); IR (neat): 2954, 2876, 2209, 1672, 1455, 1238, 1107, 1008, 736 cm⁻¹; ^1H NMR (CDCl₃, 400 MHz): δ 7.32 (m, 5H), 4.48 (s,
2H), 4.30 (dd, $J = 4.0, 6.0\ Hz, 1H), 3.60 (dd, $J = 6.0, 8.4\ Hz, 2H), 3.43 (dd, $J = 6.8, 9.2\ Hz, 1H), 3.28 (dd, $J = 6.0, 9.6\ Hz, 1H), 2.73 (m, 1H), 2.33 (m, 2H), 1.91 (m, 1H), 1.60 (m, 4H), 1.17 (d, $J = 7.2\ Hz, 3H), 0.95 (m, 21H), 0.60(m, 6H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 190.9, 138.8, 128.4, 127.6, 127.6, 95.4, 80.6, 73.6, 73.0, 73.0, 62.2, 53.0, 38.4, 32.1, 24.6, 19.0, 12.4, 12.3, 7.2, 7.0, 5.6, 4.6; HRMS (ESI+) calcd for C$_{32}$H$_{56}$NaO$_4$Si$_2$ (M+Na)$^+$ 583.3609, found 583.3624.

To a stirred solution of the ketone from the previous step (55 mg, 0.098 mmol, azeotropically dried with toluene under argon) in THF (2 mL) was added (S)-B-Me-oxazaborolidine (III-61, 0.20 mL, 0.20 mmol, 1M solution in toluene). The solution was then cooled to -30 °C, and BH$_3$•Me$_2$S (0.046 mL, 0.49 mmol) was added slowly. The resulting solution was stirred for 40 min at -30 °C, before it was quenched with 1 mL MeOH. Saturated NaHCO$_3$ solution and EtOAc was added, and the separated aqueous phase was extracted with EtOAc. The combined organic layers were then washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated to an oil, which was purified by silica gel column chromatography (hexanes-ethyl acetate, 30:1-20:1-10:1, v/v) to provide III-55 and III-54 (46 mg, 0.082 mmol, 83%) as a 6:1 mixture based on $^1$H NMR resonances at $\delta$ 2.84, and 5.85, with characterization data matching those reported above.
C32 Propargyl Alcohol (III-64)

Zn(OTf)_2 (567 mg, 1.56 mmol) was dried at 120 °C under vacuum overnight before the vacuum was released at room temperature. (-)-N-methylephedrine III-63 (308 mg, 1.72 mmol) was then added to the flask, and the mixture was then dried under vacuum for 30 min before the vacuum was released. Toluene (1 mL) and Et_3N (0.24 mL, 1.72 mmol) were added, and the resulting slurry was stirred from 2 h before neat alkyne III-62 (484 mg, 2.28 mmol) was added in one portion. After stirring for 1 h, the solution of aldehyde III-52 (160 mg, 0.46 mmol) in toluene (2 mL) was cannulated into the flask. The solution was stirred for 2 d at room temperature before saturated NaHCO_3 solution was added. The separated aqueous layers were extracted with EtOAc, and combined organic layers were washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated. The resulting oil was then purified by silica gel column chromatography (hexanes-ethyl acetate, 100:1-70:1-20:1-10:1, v/v) to give the propargyl alcohol III-64 as colorless oil (187 mg, 0.33 mmol, 73%). Data for III-64: R_f 0.32 (hexanes-ethyl acetate, 10:1, v/v); [α]_D^20 = -4.9° (c 5.5, CHCl_3); IR (neat): 3444, 2953, 2876, 1455, 1255, 1106, 836, 735 cm\(^{-1}\); ^1H NMR (CDCl_3, 400 MHz): δ 7.32 (m, 5H), 4.49 (s, 2H), 4.31 (m, 1H), 4.03 (t, J = 4.0 Hz, 1H), 3.62 (t, J = 6.0 Hz, 2H), 3.41 (dd, J = 6.8, 9.2 Hz, 1H), 3.26 (dd, J = 6.8, 9.2 Hz, 1H), 2.83 (d, J = 4 Hz, 1H), 2.23 (m, 2H), 2.00 (m, 1H), 1.88 (m, 1H), 1.60 (m, 4H), 0.95 (m, 15H), 0.90 (s, 9H), 0.62 (m, 6H), 0.05 (s, 6H); ^13C NMR (CDCl_3, 100
MHz): δ 138.8, 128.5, 127.7, 127.6, 86.0, 80.8, 74.3, 73.6, 73.1, 65.6, 62.8, 43.9, 36.6, 32.2, 26.1, 25.3, 18.7, 18.5, 13.1, 12.4, 7.2, 5.4, -5.1; HRMS (ESI+) calcd for C$_{32}$H$_{58}$NaO$_{4}$Si$_{2}$ (M+Na)$^+$ 585.3766, found 585.3729.

C28 Alcohol (III-65)

A mixture of III-58 (16 mg, 0.051 mmol) and 20% Pd(OH)$_2$ on carbon (3 mg, 0.02 mmol) in absolute ethanol (1 mL) was stirred vigorously under H$_2$ for 15 h, after which the mixture was filtered through a pad of Celite. The solvent was removed under vacuum, and the resulting oil was purified by silica gel column chromatography (hexanes-ethyl acetate, 8:1-3:1, v/v) to give III-65 as a colorless oil (9 mg, 0.04 mmol, 78%): R$_f$ 0.35 (hexanes-ethyl acetate, 3:1, v/v); [α]$^2$$_D$ = +67° (c 0.9, CHCl$_3$); IR (neat): 3400(br), 2937, 1456, 1111, 1044, 998, 876 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): δ 3.66 (dd, J = 3.2, 10.8 Hz, 2H), 3.56 (dd, J = 2.4, 10.0 Hz, 2H), 3.49 (dd, J = 6.4, 10.8 Hz, 1H), 2.04 (m, 1H), 1.85 (m, 3H), 1.58 (m, 6H), 1.42 (m, 4H), 1.13 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 7.2 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 95.9, 72.8, 65.2, 60.6, 37.8, 36.1, 30.5, 28.3, 26.7, 25.6, 19.0, 14.6, 11.6; HRMS (ESI+) calcd for C$_{13}$H$_{24}$NaO$_{3}$ (M+Na)$^+$ 251.1618, found 251.1614.
C28 Iodide (III-5)

To a stirred solution of III-65 (67 mg, 0.29 mmol) in CH$_2$Cl$_2$ (5 mL) under argon was added imidazole (40 mg, 0.59 mmol), PPh$_3$ (154 mg, 0.59 mmol), and I$_2$ (150 mg, 0.59 mmol) consecutively. The resulting solution was then stirred for 2 h at room temperature, after which the solution was diluted with CH$_2$Cl$_2$ (15 mL). The solution was washed with aqueous Na$_2$S$_2$O$_3$ solution and brine, dried over Na$_2$SO$_4$, filtered and concentrated into an oil, which was then purified by silica gel column chromatography (hexanes-ethyl acetate, 20:1, v/v) to give iodide III-5 as a colorless oil (95 mg, 0.28 mmol, 96%): $R_f$ 0.77 (hexanes-ethyl acetate, 3:1, v/v); [a]$^\text{D}_{20}$ = +43° (c 1.8, CHCl$_3$); IR (neat): 2936, 1456, 1235, 1102, 1044, 998, 978, 878 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): δ 3.63 (dt, $J$ = 2.8, 10.8 Hz, 2H), 3.41 (dd, $J$ = 2.4, 9.6 Hz, 1H), 3.25 (dd, $J$ = 2.8, 9.6 Hz, 1H), 3.11 (dd, $J$ = 6.0, 10.0 Hz, 1H), 2.04 (m, 1H), 1.85 (m, 2H), 1.56 (m, 6H), 1.42 (m, 5H), 1.15 (d, $J$ = 6.4 Hz, 3H), 0.93 (d, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 96.0, 74.7, 60.6, 36.0, 35.5, 30.3, 27.4, 26.4, 25.6, 18.9, 18.7, 13.7, 11.1; HRMS (ESI+) calcd for C$_{13}$H$_{23}$INaO$_2$ (M+Na)$^+$ 361.0635, found 361.0628.
(27S)-Alcohol (III-70)

To a stirred room-temperature solution of alcohol III-30 (24 mg, 0.048 mmol) in CH$_2$Cl$_2$ (2 mL) under argon was added NaHCO$_3$ (101 mg, 1.21 mmol), followed by the Dess-Martin periodinane reagent (102 mg, 0.242 mmol). The resulting solution was stirred for 1 h at room temperature. After this time, the reaction mixture was diluted with CH$_2$Cl$_2$ (5 mL), and then quenched with H$_2$O (2 mL) and saturated Na$_2$S$_2$O$_3$ solution (5 mL), and the mixture was stirred until the organic layer became clear. The separated aqueous layers were extracted with CH$_2$Cl$_2$, and the combined organic layers were washed with H$_2$O and brine, and then dried over Na$_2$SO$_4$, filtered, and concentrated. The resulting aldehyde III-4 was used for the next step without further purification.

To a stirred solution of iodide III-5 (111 mg, 0.328 mmol) in Et$_2$O (2 mL) at -78 °C under argon was added tBuLi (0.37 mL, 1.7 M in pentane, 0.62 mmol) dropwise, and the resulting solution was stirred for 5 min at -78 °C. After this time, the reaction mixture was allowed to warm to room temperature and stir for 30 min, and then recool to -78 °C. A solution of aldehyde III-4 (24 mg, 0.0483 mmol theor.) in Et$_2$O (2 mL) was added via cannula at -78 °C. After 45 min, saturated aqueous NH$_4$Cl solution was added, and the reaction mixture was allowed to warm to room temperature. EtOAc (5 mL) was added, and the two layers were separated. The aqueous layers were then extracted with EtOAc, and the combined organic layers were washed with brine, and then dried over
Na₂SO₄, filtered, and concentrated. The resulting residue was then dissolved in MeOH (2 mL), and then NaBH₄ (18 mg, 0.47 mmol) was added. The solution was stirred for 30 min at 0 °C, before it was quenched with aqueous NH₄Cl solution. Most of the MeOH was removed by rotary evaporation, and the resulting slurry was extracted with EtOAc, and the combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated to an oil, which was purified by silica gel column chromatography (hexanes-ethyl acetate, 10:1-5:1-3:1-2:1, v/v) to provide III-70 as a colorless oil (11 mg, 0.016 mmol, 32% from III-30) along with undesired diastereomer III-69 (6 mg, 0.009 mmol, 18% from III-30), as well as starting material III-30 (3 mg, 0.006 mmol, 13%).

Data for III-70: R_f 0.35 (hexanes-ethyl acetate, 2:1, v/v); [a]_D^{20} = +21° (c 1.0, CHCl₃); IR (neat): 3414 (br), 2947, 2358, 1589, 1456, 1121 cm⁻¹; ^1H NMR (CDCl₃, 400 MHz): δ 7.34 (m, 5H), 7.25 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 5.46 (dd, J = 2.0, 2.0 Hz, 1H), 5.06 (s, 1H), 4.86 (d, J = 12 Hz, 1H), 4.73 (d, J = 12 Hz, 1H), 4.50 (s, 2H), 4.32 (dd, J = 4.8, 8.4 Hz, 1H), 4.02 (t, J = 9.2 Hz, 1H), 3.91 (d, J = 9.2 Hz, 2H), 3.80 (s, 3H), 3.73 (m, 2H), 3.60 (m, 2H), 3.47 (dd, J = 2.8, 4.8 Hz, 2H), 3.26 (dd, J = 2.0, 12.4 Hz, 1H), 2.48 (s, 1H), 2.13 (m, 1H), 1.90 (m, 12H), 1.61 (m, 7H), 1.44 (m, 3H), 1.29 (m, 3H), 0.97 (d, J = 6.4 Hz, 3H), 0.92 (d, J = 7.2 Hz, 3H); ^13C NMR (CDCl₃, 100 MHz): δ 159.7, 142.2, 139.0, 130.8, 129.4, 128.5, 127.7, 127.6, 114.0, 106.5, 95.8, 77.4, 77.3, 75.3, 75.3, 73.1, 72.1, 70.4, 64.7, 55.5, 36.9, 36.2, 35.6, 32.7, 31.3, 30.7, 27.6, 27.1, 26.6, 26.5, 25.8, 19.0, 16.4, 10.9; HRMS (ESI+) calcd for C₄₂H₅₈NaO₉ (M+Na)^+ 729.3973, found 729.3957.
Conversion of (27R) III-69 to (27S) III-70

To a stirred room temperature solution of III-69 (6 mg, 0.008 mmol) in CH₂Cl₂ (1 mL) under argon was added NaHCO₃ (71 mg, 0.85 mmol), followed by the Dess-Martin periodinane reagent (54 mg, 0.13 mmol). The resulting solution was stirred for 1.5 h at room temperature. After this time, the reaction mixture was diluted with CH₂Cl₂ (5 mL), and then quenched with H₂O (2 mL) and saturated Na₂S₂O₃ solution (5 mL), and the mixture was stirred until the organic layer became clear. The separated aqueous layers were extracted with CH₂Cl₂, and the combined organic layers were washed with H₂O and brine, and then dried over Na₂SO₄, filtered, and concentrated. The resulting ketone was used for the next step without further purification.

To a stirred solution of the ketone from the previous step (8.49 µmol theor.) in MeOH (2 mL) at -20 °C was added NaBH₄ (6.4 mg, 0.17 mmol). The solution was stirred for 40 min at -20 °C, before it was quenched with aqueous NH₄Cl solution. Most of the MeOH was removed by rotary evaporation, and the resulting slurry was extracted with EtOAc, and the combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated to an oil, which was purified by silica gel column chromatography (hexanes-ethyl acetate, 5:1-3:1-2:1, v/v) to provide III-70 and III-69 (5.6 mg, 7.9 mmol, 93% from III-69) as a 9:1 mixture based on ¹H NMR resonances at δ 5.17 and 5.05 with characterization data matching those reported above.
To a stirred solution of diol **III-27** (160 mg, 0.32 mmol) in CH$_2$Cl$_2$ (6 mL) was added imidazole (217 mg, 3.2 mmol) followed by TESCl (0.27 mL, 1.6 mmol), and DMAP (8 mg, 0.064 mmol). The resulting solution was stirred for 1 h at room temperature, upon which time TLC showed no starting material left. The reaction mixture was diluted with CH$_2$Cl$_2$ and washed with saturated NaHCO$_3$ solution, and brine. The organic layers were dried, filtered, concentrated, and the resulting residue was used for next step without further purification.

To a solution of bis-TES ether (0.36 mmol theor.) in THF (5 mL) at -42 °C was added TBAF (0.72 mmol, 0.36 mmol, 0.5 M in THF) dropwisely. The resulting solution was stirred for 40 min at -42 °C before it was quenched with sat. NH$_4$Cl solution. The separated aqueous layers were extracted with EtOAc, and the combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexanes-ethyl acetate, 10:1-2:1, v/v) to give **III-71** as a colorless oil (170 mg, 77% from **III-27**): R$_f$ 0.22 (hexanes-ethyl acetate, 2:1, v/v); [α]$^2_0$D = -15° (c 1.8, CHCl$_3$); IR (neat): 3440, 2950, 2873, 1612, 1513, 1454, 1361, 1247 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.36 (m, 5H), 7.29 (m, 2H), 6.90 (d, $J = 8.4$ Hz, 2H), 4.83 (d, $J = 11.6$ Hz, 1H), 4.66 (d, $J = 12$ Hz, 1H), 4.57 (d, $J = 12$ Hz, 1H), 4.53 (d, $J = 12$ Hz, 1H), 4.33 (m, 1H), 4.25 (t, $J = 10$ Hz, 1H), 4.00 (m, 1H), 3.97 (m, 1H), 3.87 (m, 1H), 3.83 (s, 3H), 3.52 (m, 3H), 3.41 (dd, $J = 2.8, 9.6$ Hz, 1H), 3.36 (m, 1H), 3.09 (s, 3H), 2.65 (m, 1H), 2.54 (s, 3H), 1.80 (m, 2H), 1.50 (s, 3H), 1.30 (s, 18H), 1.20 (s, 3H), 0.95 (d, $J = 6.4$ Hz, 3H), 0.80 (t, $J = 6.4$ Hz, 3H), 0.70 (s, 6H), 0.20 (s, 9H).
1H), 2.10 (m, 2H), 1.88 (m, 5H), 1.76 (m, 2H), 0.94 (t, $J = 7.6$ Hz, 9H), 0.60 (m, 6H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 159.1, 146.9, 139.1, 130.6, 129.2, 128.1, 127.7, 127.3, 113.7, 105.9, 81.2, 73.0, 72.8, 71.9, 70.2, 70.1, 59.4, 55.3, 36.7, 32.6, 26.6, 26.3, 6.9, 5.0; HRMS (ESI+) calcd for C$_{34}$H$_{50}$NaO$_8$Si (M+Na)$^+$ 637.3167, found 637.3167.

C28 $\beta$-Hydroxy Phosphonate (III-72)

To a stirred room-temperature solution of III-71 (100 mg, 0.163 mmol) in CH$_2$Cl$_2$ (5 mL) was added NaHCO$_3$ (821 mg, 9.78 mmol), followed by the Dess-Martin periodinane reagent (414 mg, 0.98 mmol). The resulting solution was allowed to stir for 1 h. After this time, the reaction mixture was diluted with CH$_2$Cl$_2$, and then quenched with H$_2$O and saturated Na$_2$S$_2$O$_3$ solution. The resulting mixture was stirred until the organic layer became clear. The separated aqueous layers were extracted with CH$_2$Cl$_2$, and the combined organic layers were washed with H$_2$O and brine, and then dried over Na$_2$SO$_4$, filtered, and concentrated. The resulting aldehyde was used for next step without further purification.

To a stirred solution of methyl dimethylphosphonate (0.35 mL, 3.26 mmol) in THF (2 mL) at -78 °C was added $t$-BuLi (0.26 mL, 0.45 mmol) dropwise. The resulting solution was stirred for 45 min at -78 °C before a solution of the aldehyde prepared above (0.163
mmol theor.) in THF (5 mL) was cannulated into the flask. The resulting solution was stirred for 45 min at -78 °C before it was quenched with sat. NH₄Cl solution, and diluted with EtOAc. The separated aqueous layers were extracted with EtOAc, and the combined organic layers were washed with H₂O and brine, and then dried over Na₂SO₄, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (ethyl acetate, 100%, v/v) to yield III-72 as a colorless oil (90 mg, 75% from III-71): Rₐ 0.37 (ethyl acetate, 100%, v/v); [α]D²⁰ = -3° (c 1.0, CHCl₃); IR (neat): 2952, 1684, 1558, 1586, 1456, 1247, 1122, 1036 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ
7.36 (m, 5H), 7.29 (m, 2H), 6.90 (d, J = 8.4 Hz, 2H), 4.82 (dd, J = 4.4, 12 Hz, 1H), 4.69 (d, J = 12 Hz, 1H), 4.54 (m, 2H), 4.51 (m, 0.6H), 4.33 (m, 1H), 4.25 (m, 2H), 4.02 (m, 0.4H), 3.85 (s, 1.2H), 3.83 (s, 1.2H), 3.83 (s, 3H), 3.81 (d, J = 16Hz, 1.8H), 3.79 (d, J = 16Hz, 1.8H), 3.60 (m, 1H), 3.53 (m, 3H), 3.40 (m, 0.6H), 3.14 (m, 0.6H), 2.32 (m, 0.6H), 2.13 (m, 1H), 1.98 (m, 1H), 1.88 (m, 3H), 1.75 (m, 3H), 1.27 (m, 0.6H), 0.94 (m, 9H), 0.60 (m, 6H); ¹³C NMR (CDCl₃, 100 MHz): δ 159.1, 139.3, 135.7, 130.6, 129.2, 128.0, 127.7, 127.5, 127.2, 113.7, 105.9, 83.9, 79.7, 72.9, 72.8, 71.9, 71.6, 55.3, 36.7, 32.5, 26.8, 26.3, 6.9, 5.0, 5.0; HRMS (ESI+) calcd for C₃₇H₅₇NaO₁₁PSi (M+Na)⁺ 759.3300, found 759.3271.
C32 Weinreb Amide (III-75)

To a stirred suspension of N,O-dimethylhydroxylamine hydrochloride (159 mg, 1.63 mmol) in CH₂Cl₂ (2 mL) at 0 °C was added AlMe₃ (0.82 mL, 1.63 mmol, 2.0 M in hexanes). The resulting clear solution was stirred for 15 min at room temperature before it was recooled to -10 °C, and a solution of imide III-74 (208 mg, 0.54 mmol) in CH₂Cl₂ (3 mL) was cannulated into the flask. The solution was stirred for 1 h at -10 to 0 °C, 2 h at 0 °C and then 12 h at room temperature, before it was quenched with ice-cold 1 N HCl. More CH₂Cl₂ was added, and the mixture was stirred vigorously for 1 h. The separated aqueous layers were extracted with CH₂Cl₂, and the combined organic layers were washed with H₂O, saturated NaHCO₃ solution, and brine, dried over Na₂SO₄, filtered, and concentrated to a residue that was used for next step.

To a stirred solution of the Weinreb amide prepared above (0.54 mmol theor.) in CH₂Cl₂ (5 mL) at -20 °C was added 2,6-lutidine (0.38 mL, 3.24 mmol) followed by TBSOTf (0.25 mL, 1.08 mmol). The resulting solution was stirred for 2 h at -20 °C before it was quenched with saturated NaHCO₃ solution. The mixture was diluted with CH₂Cl₂, and washed with saturated NaHCO₃ solution, and brine, dried over Na₂SO₄, filtered, and concentrated. Silica gel column chromatography (hexanes-ethyl acetate, 20:1-10:1-5:1, v/v) of the residue gave III-75 (126 mg, 61% from III-74) as a colorless oil: Rf 0.61 (hexanes-ethyl acetate, 2:1, v/v); [α]²⁰D = -4° (c 8.0, CHCl₃); IR (neat): 2931, 2856, 1660, 1462, 1385, 1254, 998, 836, 777 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.31 (m, 5H), 4.50
(s, 2H), 4.07 (m, 1H), 3.62 (s, 3H), 3.50 (dd, J = 4.8, 10.4 Hz, 1H), 3.44 (dd, J = 4.4, 10 Hz, 1H), 3.11 (s, 3H), 1.17 (d, J = 6.8 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H);

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 138.5, 128.4, 127.9, 127.6, 73.6, 73.5, 73.1, 61.5, 39.2, 26.1, 26.0, 18.3, 14.4, -4.2, -4.6; HRMS (ESI$^-$) calcd for C$_{20}$H$_{35}$NaO$_4$Si (M+Na$^+$) 404.2228, found 404.2221.

**C32 Ynone (III-76)**

To a stirred solution of alkyne III-62 (301 mg, 1.41 mmol) in THF (2 mL) at -78 °C was added n-BuLi (0.54 mmol, 2.5M in hexanes, 1.35 mmol) dropwise, and the resulting solution was stirred for 30 min at -78 °C, after which the solution was allowed to warm to -30 °C and stir for 30 min. The flask was recooled to -78 °C, and then a solution of Weinreb amide III-75 (260 mg, 0.68 mmol) in THF (5 mL) was cannulated into the flask. After 30 min at -78 °C, the solution was warmed to 0 °C and stirred for 1 h. The solution was quenched with aqueous NH$_4$Cl solution, and then diluted with EtOAc. The separated aqueous layers were extracted with EtOAc, and combined organic layers were washed with H$_2$O and brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. The resulting oil was then purified by silica gel column chromatography (hexanes-ethyl acetate, 100:1-50:1-20:1, v/v) to III-76 (318 mg, 88%) as a colorless oil. $R_f$ 0.53 (hexanes-ethyl acetate, 10:1, v/v); $[\alpha]^{20}_{D} = -0.2^{\circ}$ (c 3.3, CHCl$_3$); IR (neat): 2929, 2856,
1677, 1579, 1472, 1255, 1104, 837, 776 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.35 (m, 5H), 4.56 (d, J = 12 Hz, 1H), 4.50 (m, 1H), 4.48 (d, J = 12 Hz, 1H), 3.62 (t, J = 6 Hz, 2H), 3.44 (dd, 1H), 3.40 (dd, 1H), 2.78 (m, 1H), 2.40 (t, J = 7.0 Hz, 2H), 1.65 (m, 4H), 1.12 (d, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.86 (s, 9H), 0.05 (s, 3H×4); ¹³C NMR (CDCl₃, 125 MHz): δ 190.3, 138.3, 128.5, 127.8, 94.8, 80.9, 73.5, 72.7, 71.3, 62.5, 51.7, 32.1, 26.1, 26.0, 24.6, 19.0, 18.5, 18.3, 9.2, -4.1, -4.8; HRMS (ESI+) calcd for C₃₀H₅₂NaO₄Si₂ (M+Na)⁺ 555.3296, found 555.3309.

C32 Propargyl Alcohol (III-77)

To a stirred solution of III-76 (132 mg, 0.25 mmol) in THF (3 mL) was added (S)-B-Me-oxazaborolidine (III-61, 0.49 mL, 0.49 mmol, 1M in toluene). The solution was then cooled to -30 °C, and BH₃•Me₂S (0.12 mL, 1.24 mmol) was added slowly. The resulting solution was stirred for 1 h at -30 °C, before it was quenched with 1 mL MeOH. Saturated NaHCO₃ solution and EtOAc was added, and the separated aqueous phase was extracted with EtOAc. The combined organic layers were then washed with brine, dried over Na₂SO₄, filtered, and concentrated to an oil, which was purified by silica gel column chromatography (hexanes-ethyl acetate, 30:1-20:1-10:1, v/v) to provide III-77 (130 mg, 98%) as a colorless oil: Rf 0.37 (hexanes-ethyl acetate, 10:1, v/v); [α]²⁰D = -5° (c 3.1, CHCl₃); IR (neat): 3436, 2929, 2857, 1577, 1471, 1254, 1104, 1029, 837, 777 cm⁻¹; ¹H
NMR (CDCl$_3$, 400 MHz): $\delta$ 7.35 (m, 5H), 4.54 (d, $J = 12$ Hz, 1H), 4.48 (d, $J = 12$ Hz, 1H), 4.28 (m, 2H), 3.62 (t, $J = 5.6$ Hz, 2H), 3.47 (d, $J = 6.0$ Hz, 2H), 2.82 (d, $J = 5.2$ Hz, 1H), 2.25 (m, 2H), 1.94 (m, 1H), 1.62 (m, 4H), 0.98 (d, $J = 6.8$ Hz, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.11 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H×2); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 138.4, 128.5, 127.8, 127.8, 85.9, 81.2, 73.5, 72.6, 72.0, 65.5, 62.8, 42.9, 32.2, 26.1, 26.1, 25.4, 18.8, 18.5, 18.3, 11.3, -4.1, -4.8, -5.1; HRMS (ESI+) calcd for C$_{30}$H$_{54}$NaO$_4$Si$_2$ (M+Na)$^+$ 557.3453, found 557.3435.

1,3-\textit{Anti} Triol (III-78)

To a stirred solution of III-77 (130 mg, 0.24 mmol) in MeOH (1 mL) at room temperature was added TsOH•H$_2$O (14 mg, 0.073 mmol), and the resulting solution was stirred for 1 h at room temperature, after which the solution was quenched with Et$_3$N (0.1 mL), and the solvent was removed under vacuum. The resulting oil was purified by silica gel column chromatography (dichloromethane-methanol, 20:1-10:1, v/v) to give III-78 as a colorless oil (71 mg, 95%). Data for III-78: R$_f$ 0.29 (Hexanes-Ethyl acetate, 1:1, v/v); $[\alpha]^{20}_D = +1^\circ$ (c 7.0, CHCl$_3$); IR (neat): 3368, 2936, 2866, 1455, 1062, 1027, 739, 699 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.32 (m, 5H), 4.57 (d, $J = 12$ Hz, 1H), 4.52 (d, $J = 11.6$ Hz, 1H), 4.35 (m, 2H), 3.67(m, 1H), 3.61 (t, $J = 6.4$ Hz, 2H), 3.48 (m, 2H), 3.45 (m, 1H), 3.21 (br, 1H), 2.28 (br, 1H), 2.24 (dt, $J = 1.6$, 6.8 Hz, 2H), 1.84 (m, 1H), 1.60 (m,
4H), 1.01 (d, J = 7.2 Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 138.0, 128.6, 128.0, 127.9, 86.2, 81.1, 73.6, 72.9, 70.8, 66.3, 62.3, 41.0, 31.8, 25.0, 18.7, 10.8; HRMS (ESI+) calcd for C\(_{18}\)H\(_{26}\)NaO\(_4\) (M+Na)\(^+\) 329.1723, found 329.1732.

Spiroketsals (III-79/80)

To a stirred solution of AuCl (1.4 mg, 0.006 mmol) and powered 4 Å MS in THF (1 mL) at 0 °C was cannulated the solution of triol III-78 (37 mg, 0.12 mmol) in THF (1 mL), and the resulting solution was stirred for 30 min at 0 °C, after which the solution was quenched with Et\(_3\)N (0.1 mL), and the solution was filtered through a pad of Celite. The solvent was removed under vacuum, and the resulting oil was then purified by silica gel column chromatography (hexanes-ethyl acetate, 10:1-8:1-3:1, v/v) to give spiroketal III-79 as colorless oil (17 mg, 49%), along with spiroketal III-80 as colorless oil (15 mg, 41%).

Data for III-79: R\(_f\) 0.80 (hexanes-ethyl acetate, 2:1, v/v); [\(\alpha\)]\(^{20}\)_D = -41° (c 1.7, CHCl\(_3\)); IR (neat): 2938, 2871, 1574, 1453, 1096, 1005, 896, 734 cm\(^{-1}\); \(^{1}\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.32 (m, 5H), 5.90 (dd, \(J = 5.5, 10.0\) Hz, 1H), 5.57 (dd, \(J = 1.0, 9.5\) Hz, 1H), 4.64 (d, \(J = 12\) Hz, 1H), 4.59 (d, \(J = 12\) Hz, 1H), 4.28 (m, 1H), 3.96 (dt, \(J = 2.5, 12.5\) Hz, 1H), 3.62 (m, 2H), 3.55 (dd, \(J = 5.5, 10.0\) Hz, 1H), 2.10 (m, 1H), 1.91 (m, 1H), 1.61 (m, 4H), 1.51
(m, 1H), 0.88 (d, J = 7.0 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 138.8, 134.2, 129.5, 128.5, 127.7, 127.7, 94.2, 73.4, 71.1, 68.7, 61.0, 35.1, 30.7, 25.2, 18.9, 12.8; HRMS (ESI+) calcd for C$_{18}$H$_{24}$NaO$_3$ (M+Na)$^+$ 311.1618, found 311.1612.

Data for III-80: R$_f$ 0.63 (hexanes-ethyl acetate, 2:1, v/v); [α]$^20_D$ = +79° (c 2.0, CHCl$_3$); IR (neat): 3420, 2927, 1456, 1045, 960, 885, 697 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.32 (m, 5H), 4.62 (d, J = 12 Hz, 1H), 4.53 (d, J = 11.5 Hz, 1H), 4.13 (dd, J = 2.0, 9.5 Hz, 1H), 3.88 (d, J = 12 Hz, 1H), 3.81 (t, J = 12.5 Hz, 1H), 3.59 (m, 3H), 3.37 (d, J = 10.5 Hz, 1H), 2.97 (m, 1H), 2.48 (dd, J = 8.5, 15 Hz, 1H), 1.79 (m, 1H), 1.70 (m, 4H), 1.40 (m, 2H), 1.05 (d, J = 7.5 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 137.1, 128.7, 128.2, 128.1, 112.6, 78.9, 76.3, 74.1, 69.4, 62.8, 37.9, 31.6, 31.2, 30.0, 23.3, 9.2; HRMS (ESI+) calcd for C$_{18}$H$_{26}$NaO$_4$ (M+Na)$^+$ 329.1723, found 329.1728.

C29 Alcohol (III-81)

A mixture of III-79 (25 mg, 0.087 mmol) and 20% Pd(OH)$_2$ on carbon (2 mg) in absolute ethanol (1 mL) was stirred vigorously under H$_2$ for 15 h, after which the mixture was filtered through a pad of Celite. The solvent was removed under vacuum, and the resulting oil was purified by silica gel column chromatography (hexanes-ethyl acetate, 8:1-3:1, v/v) to give III-81 as a colorless oil (14 mg, 81%): R$_f$ 0.39 (hexanes-ethyl
acetate, 3:1, v/v); [α]_D$^{20}$ = +49° (c 0.2, CHCl₃); IR (neat): 3398, 2936, 1577, 1438, 1046, 995 cm⁻¹; $^1$H NMR (CDCl₃, 400 MHz): δ 3.66 (ddd, 1H), 3.70 (m, 2H), 3.60 (m, 1H), 3.51 (m, 1H), 2.10 (m, 1H), 1.84 (m, 2H), 1.72 (m, 1H), 1.62 (m, 4H), 1.45 (m, 3H), 1.36 (m, 1H), 0.91 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (CDCl₃, 125 MHz): δ 95.7, 71.8, 64.9, 60.6, 35.7, 30.6, 28.3, 26.5, 25.4, 18.9, 11.9; HRMS (ESI+) calcd for C₁₁H₂₀NaO₃ (M+Na)$^+$ 223.1305, found 223.1293.

**C27 Enone (III-83)**

To a stirred room-temperature solution of III-72 (45 mg, 0.061 mmol) in CH₂Cl₂ (3 mL) was added NaHCO₃ (307 mg, 3.66 mmol), followed by the Dess-Martin periodinane reagent (155 mg, 0.37 mmol). The resulting solution was allowed to stir for 1 h. After this time, the reaction mixture was diluted with CH₂Cl₂, and then quenched with H₂O and sat. Na₂S₂O₃ solution. The resulting mixture was stirred until the organic layer became clear. The separated aqueous layers were extracted with CH₂Cl₂, and the combined organic layers were washed with H₂O and brine, and then dried over Na₂SO₄, filtered, and concentrated. The resulting residue was used for next step directly.

To a stirred room-temperature solution of III-73 prepared above (0.049 mmol estimated) in CH₃CN (0.5 mL) was added $i$-Pr₂EtN (11 µL, 0.064 mmol) and LiCl (4 mg, 0.098
mmol). The resulting suspension was allowed to stir for 30 min before a solution of III-82 (10 mg, 0.049 mmol) in CH$_3$CN (0.5 mL) was cannulated into the flask. The mixture was stirred for 14 h at room temperature before it was quenched with sat. NH$_4$Cl solution. EtOAc was added, and the separated aqueous layers were extracted with EtOAc, and the combined organic layers were washed with H$_2$O and brine, and then dried over Na$_2$SO$_4$, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (hexanes-ethyl acetate, 10:1-3:1, v/v) to yield III-83 as a colorless oil (30 mg, 61% from III-72): R$_f$ 0.39 (hexanes-ethyl acetate, 3:1, v/v); $[\alpha]^{20}_D = +2^\circ$ (c 0.6, CHCl$_3$); IR (neat): 2354, 1699, 1652, 1558, 1506, 1456 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.36 (m, 5H), 7.25 (m, 2H), 6.98 (dd, J = 2.8, 16 Hz, 1H), 6.89 (dd, J = 2.0, 16 Hz, 1H), 6.87 (d, J = 8.8 Hz, 2H), 4.76 (d, J = 12 Hz, 1H), 4.71 (t, J = 2.4 Hz, 1H), 4.65 (d, J = 12 Hz, 1H), 4.52 (dd, 2H), 4.35 (d, J = 2.0 Hz, 1H), 4.33 (m, 1H), 4.17 (t, J = 10 Hz, 1H), 3.81 (s, 3H), 3.57 (m, 2H), 3.49 (t, J = 4.4 Hz, 1H), 3.31 (dd, J = 3.2, 10 Hz, 1H), 3.11 (m, 1H), 2.10 (m, 3H), 1.86 (m, 6H), 1.70 (m, 4H), 1.58 (m, 4H), 1.44 (m, 4H), 0.94 (t, J = 8.0 Hz, 9H), 0.85 (d, J = 7.2 Hz, 3H), 0.60 (m, 6H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 200.0, 159.0, 149.2, 139.7, 130.8, 129.4, 128.2, 127.8, 127.3, 123.3, 114.0, 106.0, 96.3, 85.3, 74.0, 73.2, 73.0, 72.1, 71.4, 70.2, 69.6, 60.8, 55.5, 36.9, 35.6, 32.7, 30.7 30.0, 26.7, 26.4, 26.2, 25.5, 18.9, 12.0, 7.1, 5.2; HRMS (ESI+) calcd for C$_{46}$H$_{66}$NaO$_{10}$Si (M+Na)$^+$ 829.4317, found 829.4324.
C27 Alcohol (III-84)

The mixture of benzene (3 mL) and H₂O (1 drop) was degassed by standard Freeze-Pump-Thaw procedure, and then cannulated into [Ph₃PCuH]₆ (146 mg, 0.074 mmol). The resulting red solution was then added to III-83 (60 mg, 0.074 mmol) under argon, and the reaction mixture was stirred for 14 h at room temperature. The solution was then stirred for 1 h with open air, during which time the color changed from dark red into yellowish green. EtOAc and H₂O were added into the reaction mixture, and the separated aqueous layers were extracted with EtOAc. The combined organic layers were washed with H₂O and brine, and then dried over Na₂SO₄, filtered, and concentrated. The resulting residue was used for next step directly.

To a stirred -20 °C solution of the ketone prepared above (0.074 mmol theor.) in MeOH (2 mL) was added NaBH₄ (42 mg, 1.11 mmol). The reaction mixture was allowed to stir for 40 min at -20 °C before it was quenched with saturated NH₄Cl solution. EtOAc was added, and the separated aqueous layers were extracted with EtOAc, and the combined organic layers were washed with H₂O and brine, and then dried over Na₂SO₄, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (hexanes-ethyl acetate, 10:1-3:1-2:1, v/v) to yield III-84 as a colorless oil (48 mg, 80% from III-83): Rf 0.24 (hexanes-ethyl acetate, 3:1, v/v); [a]²⁰ₒ⁺ = +18° (c 1.8, CHCl₃); IR (neat): 2937, 2874, 1653, 1558, 1540, 1507, 1457, 1248, 1071, 1039, 837

96
cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.36 (m, 5H), 7.25 (m, 2H), 6.87 (d, J = 8.8 Hz, 2H), 4.84 (d, J = 12 Hz, 1H), 4.62 (d, J = 11.6 Hz, 1H), 4.52 (dd, 2H), 4.31 (m, 1H), 4.23 (t, J = 10 Hz, 1H), 4.09 (m, 1H), 3.88 (m, 1H), 3.80 (s, 3H), 3.77 (m, 1H), 3.63 (m, 2H), 3.53 (m, 1H), 3.49 (m, 2H), 3.42 (dd, 1H), 3.35 (m, 1H), 2.70 (s, 1H), 2.10 (m, 3H), 1.86 (m, 6H), 1.70 (m, 3H), 1.58 (m, 8H), 1.44 (m, 6H), 0.94 (m, 12H), 0.56 (m, 6H); ¹³C NMR (CDCl₃, 100 MHz): δ 159.3, 139.5, 139.0, 130.8, 129.4, 129.4, 128.5, 128.3, 127.8, 127.5, 113.9, 106.1, 95.8, 85.1, 74.3, 73.4, 73.0, 72.6, 72.1, 71.9, 71.3, 71.0, 70.1, 67.1, 60.7, 55.5, 36.8, 35.9, 32.8, 31.8, 30.9, 30.5, 29.9, 26.7, 26.5, 26.1, 25.7, 19.0, 18.2, 11.5, 7.0; HRMS (ESI+) calcd for C₄₆H₇₀NaO₁₀Si (M+Na)⁺ 833.4630, found 833.4615.

C₂₇ TBS Ether (III-85)

To a stirred solution of III-84 (60 mg, 0.074 mmol) in CH₂Cl₂ (2 mL) was added imidazole (100 mg, 1.48 mmol) followed by TBSCl (112 mg, 0.74 mmol), and DMAP (45 mg, 0.37 mmol). The resulting solution was stirred for 14 h before it was diluted with CH₂Cl₂. The organic solution was washed with saturated NaHCO₃ solution and brine, dried over anhydrous Na₂SO₄, filtered, and concentrated. Silica gel column chromatography (hexanes-ethyl acetate, 10:1-3:1-2:1, v/v) of the residue gave III-85 (45 mg, 66%) as a colorless oil along with III-84 (20 mg, 33%). Data for III-85: Rₜ 0.70
(hexanes-ethyl acetate, 3:1, v/v); [\alpha]^{20}_{D} = +14^\circ (c 1.2, \text{CHCl}_3); \text{IR (neat): } 2949, 1700, 1652, 1514, 1456, 1248, 1090, 834 \text{ cm}^{-1}; ^1H \text{ NMR (CDCl}_3, 400 \text{ MHz): } \delta 7.36 (m, 5H), 7.25 (m, 2H), 6.87 (d, J = 8.8 Hz, 2H), 4.84 (d, J = 12 Hz, 1H), 4.62 (d, J = 11.6 Hz, 1H), 4.52 (dd, 2H), 4.31 (m, 1H), 4.20 (t, J = 9.6 Hz, 1H), 4.09 (m, 1H), 3.94 (m, 1H), 3.83 (s, 3H), 3.68 (m, 3H), 3.55 (m, 2H), 3.50 (m, 3H), 2.06 (m, 2H), 1.85 (m, 6H), 1.72 (m, 2H), 1.56 (m, 5H), 1.40 (m, 6H), 0.90 (t, J = 6.8 Hz, 9H), 0.90 (s, 9H), 0.55 (m, 6H), 0.11 (s, 3H), 0.08 (s, 3H); ^13C \text{ NMR (CDCl}_3, 100 \text{ MHz): } \delta 159.4, 139.7, 130.9, 129.4, 128.2, 127.8, 127.6, 127.4, 113.9, 106.1, 95.7, 84.6, 73.4, 72.9, 72.5, 72.1, 71.7, 71.5, 71.1, 71.0, 60.6, 55.5, 37.0, 36.0, 32.7, 31.8, 30.6, 30.4, 29.1, 26.9, 26.6, 26.5, 26.2, 26.1, 25.9, 25.6, 19.0, 18.4, 11.4, 7.1, 5.2, -3.4, -3.9, -4.2; \text{HRMS (ESI+)} \text{ calcd for C}_{52}H_{84}NaO_{10}Si_{2} (M+Na)^{+} 947.5495, \text{ found 947.5516}.

C25 Alcohol (III-86)

To a stirred solution of III-85 (45 mg, 0.049 mmol) in CH$_2$Cl$_2$ (2 mL) at 0 °C was added TsOH (1.8 mg, 0.01 mmol). The resulting solution was stirred for 30 min at 0 °C before it was quenched with Et$_3$N. Most of the solvent was removed under rotary evaporation, and the residue was purified by silica gel column chromatography (hexanes-ethyl acetate, 10:1-3:1-2:1, v/v) to give III-86 (30 mg, 76%) as a colorless oil along with III-85 (10
mg, 22%). Data for III-86: Rf 0.20 (hexanes-ethyl acetate, 3:1, v/v); [α]_{D}^{20} = +18° (c 0.25, CHCl₃); IR (neat): 2949, 1700, 1653, 1558, 1506, 1456 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.36 (m, 5H), 7.25 (m, 2H), 6.87 (d, J = 8.8 Hz, 2H), 4.84 (d, J = 12 Hz, 1H), 4.68 (d, J = 12 Hz, 1H), 4.51 (s, 2H), 4.31 (m, 1H), 4.07 (m, 1H), 4.02 (d, J = 8.8 Hz, 1H), 3.88 (m, 3H), 3.80 (s, 3H), 3.72 (m, 1H), 3.66 (m, 2H), 3.57 (m, 1H), 3.48 (dd, J = 5.2, 6.0 Hz, 2H), 3.48 (d, J = 1.2 Hz, 1H), 2.10 (m, 2H), 1.88 (m, 6H), 1.74 (m, 2H), 1.53 (m, 6H), 1.40 (m, 5H), 0.88 (d, J = 6.8 Hz, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.01 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 159.6, 138.8, 131.0, 129.6, 128.5, 127.7, 113.9, 106.4, 95.5, 79.7, 74.3, 73.2, 72.7, 72.3, 71.6, 71.1, 70.5, 60.6, 55.5, 37.0, 36.0, 33.0, 31.5, 30.3, 29.1, 27.0, 26.6, 26.4, 26.1, 25.7, 18.9, 18.2, 11.3, -4.2, -4.3; HRMS (ESI+) calcd for C₄₆H₇₀NaO₁₀Si (M+Na)⁺ 833.4630, found 833.4624.

C25 Alkene (III-87)
To a stirred room-temperature solution of alcohol III-86 (30 mg, 0.037 mmol) in CH₂Cl₂ (2 mL) was added NaHCO₃ (310 mg, 3.7 mmol), followed by the Dess-Martin periodinane reagent (235 mg, 0.55 mmol). The resulting solution was allowed to stir for 14 h. After this time, the reaction mixture was diluted with CH₂Cl₂, and then quenched with H₂O and saturated aqueous Na₂S₂O₃ solution, and the mixture was stirred until the
organic layer became clear. The separated aqueous layers were extracted with CH₂Cl₂, and the combined organic layers were washed with H₂O and brine, and then dried over Na₂SO₄, filtered, and concentrated. The resulting residue was used for next step without further purification.

To a stirred solution of methyltriphenylphosphonium iodide (180 mg, 0.44 mmol) in toluene (1 mL) under argon was added KHMDS (0.67 mL, 0.5M in toluene, 0.33 mmol). The resulting yellow solution was heated to 90 °C for 30 min and then cooled to room temperature before a solution of ketone from the previous step (0.037 mmol theor.) in toluene (2 mL) was added via cannula. The resultant solution was heated to 90 °C for 1 h and then recooled to room temperature before saturated aqueous NH₄Cl solution was added. The toluene was removed by rotary evaporation, and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, and then dried over Na₂SO₄, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (hexanes-ethyl acetate, 20:1-10:1-5:1, v/v) to yield III-87 as a colorless oil (25 mg, 84% from III-86): Rf 0.58 (hexanes-ethyl acetate, 3:1, v/v); [α]²⁰° = +28° (c 1.6, CHCl₃); IR (neat): 2938, 1612, 1513, 1452, 1248, 1088, 996, 836 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.36 (m, 5H), 7.25 (m, 2H), 6.87 (d, J = 8.8 Hz, 2H), 5.41 (t, J = 1.6 Hz, 1H), 5.07 (s, 1H), 4.85 (d, J = 12 Hz, 1H), 4.72 (d, J = 12 Hz, 1H), 4.50 (m, 2H), 4.31 (m, 1H), 4.16 (d, J = 7.2 Hz, 1H), 4.04 (m, 2H), 3.80 (s, 3H), 3.63 (m, 3H), 3.55 (m, 2H), 3.47 (m, 2H), 2.10 (m, 2H), 1.88 (m, 6H), 1.74 (m, 3H), 1.53 (m, 7H), 1.40 (m, 5H), 0.90 (s, 9H), 0.88 (d, 3H), 0.07 (s, 3H), 0.06 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 159.4, 144.3, 139.4, 130.9, 129.3, 128.7, 127.6, 113.9, 112.1, 106.2, 95.6, 84.8, 78.6, 73.3, 73.1, 72.1, 71.8, 71.3, 70.9, 60.5, 55.5, 36.9, 35.9, 32.8, 31.8, 31.5, 30.4,
30.3, 28.8, 27.1, 26.6, 26.5, 26.2, 26.1, 25.7, 22.8, 19.0, 18.4, 14.4, 11.3, -4.0, -4.3;
HRMS (ESI+) calcd for C_{47}H_{70}NaO_{9}Si (M+Na)^+ 829.4681, found 829.4686.

C19 Alcohol (III-97)

To a stirred solution of B-chlorodiisopinocampheylborane (475 mg, 1.48 mmol) in Et₂O (5 mL) at -78 °C was added allylmagnesium bromide (1.48 mL, 1.48 mmol, 1.0 M in Et₂O). The resulting solution was stirred for 30 min before it was warmed to room temperature and stirred for 1 h. The solution of aldehyde III-21 (670 mg, 1.23 mmol) in Et₂O (5 mL) was cannulated into the flask at -78 °C before the solution was stirred for 2 h at -78 °C. The reaction mixture was then warmed to room temperature and stirred for 1 h before MeOH (2 mL), NaOH (3.7 mL, 1M in H₂O) and 30% H₂O₂ (0.84 mL) were added. The resulting mixture was heated to reflux for 1 h before saturated Na₂S₂O₃ solution was added. The separated aqueous layers were extracted with Et₂O, and the combined organic layers were then washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated. Silica gel column chromatography (hexanes-ethyl acetate, 20:1-10:1-5:1, v/v) of the residue gave C19 alcohol III-97 (485 mg, 82%) as a colorless oil: R_f 0.43 (hexanes-ethyl acetate, 3:1, v/v); [α]_{D}^{20} = -22° (c 1.9, CHCl₃); IR (neat): 3459, 2928, 1615, 1518, 1463, 1380, 1251, 1098, 835 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.44 (d, J = 8.8 Hz, 2H), 7.35 (m, 5H), 6.90 (d, J = 8.8 Hz, 2H), 5.81 (m, 1H), 5.55 (s,
1H), 5.14 (d, J = 0.8 Hz, 1H), 5.11 (d, J = 3.6 Hz, 1H), 4.90 (d, J = 12 Hz, 1H), 4.61 (d, J = 12 Hz, 1H), 4.25 (dd, J = 5.2, 10 Hz, 1H), 4.18 (dd, J = 5.2, 9.6 Hz, 1H), 4.03 (dd, J = 2.8, 9.6 Hz, 1H), 3.81 (s, 3H), 3.77 (m, 2H), 3.74 (m, 2H), 2.26 (m, 2H), 2.16 (m, 1H), 1.95 (d, J = 4.0 Hz, 1H), 1.67 (m, 2H), 1.55 (m, 2H), 1.28 (m, 2H), 0.88 (s, 9H), 0.01 (s, 3H), -0.02 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 160.3, 139.0, 135.0, 130.7, 128.5, 127.8, 118.2, 113.8, 102.4, 80.2, 78.0, 73.7, 72.4, 70.4, 70.0, 60.1, 55.5, 42.1, 34.0, 31.8, 26.0, 25.6, 22.8, 18.2, 14.3, -4.9; HRMS (ESI$^+$) calcd for C$_{33}$H$_{48}$NaO$_7$Si (M+Na$^+$) 607.3062, found 607.3032.

C19 TBS Ether (III-98)

To a stirred solution of III-97 (185 mg, 0.32 mmol) in CH$_2$Cl$_2$ (3 mL) was added imidazole (87 mg, 1.28 mmol) followed by TBSCl (95 mg, 0.63 mmol), and DMAP (8 mg, 0.06 mmol). The resulting solution was stirred for 2 h before it was diluted with CH$_2$Cl$_2$. The organic solution was washed with saturated NaHCO$_3$ solution and brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. Silica gel column chromatography (hexanes-ethyl acetate, 20:1, v/v) of the residue gave C19 TBS ether III-98 (226 mg, 100%) as a colorless oil: R$_f$ 0.78 (hexanes-ethyl acetate, 3:1, v/v); [a]$^{20}_{D}$ = -9° (c 7.5, CHCl$_3$); IR (neat): 2928, 1615, 1518, 1462, 1251, 1099, 836, 775 cm$^{-1}$; $^1$H
NMR (CDCl$_3$, 400 MHz): $\delta$ 7.44 (d, $J = 8.8$ Hz, 2H), 7.35 (m, 5H), 6.90 (d, $J = 8.8$ Hz, 2H), 5.80 (m, 1H), 5.55 (s, 1H), 5.04 (d, $J = 2.4$ Hz, 1H), 5.01 (s, 1H), 4.90 (d, $J = 12$ Hz, 1H), 4.61 (d, $J = 12$ Hz, 1H), 4.25 (dd, $J = 4.8$, 10 Hz, 1H), 4.11 (dd, $J = 4.8$, 9.6 Hz, 1H), 4.02 (dd, $J = 2.4$, 9.6 Hz, 1H), 3.82 (s, 3H), 3.76 (m, 4H), 3.63 (d, $J = 6.0$ Hz, 1H), 2.29 (m, 1H), 2.21 (t, $J = 6.4$ Hz, 2H), 1.58 (m, 2H), 1.46 (m, 1H), 0.90 (s, 9H), 0.88 (s, 9H), 0.05 (s, 6H), 0.04 (s, 3H), 0.00 (s, 3H), -0.03 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 160.3, 139.0, 135.5, 130.8, 128.5, 127.8, 127.8, 127.7, 116.9, 113.8, 102.4, 80.5, 78.1, 73.7, 72.5, 71.9, 70.1, 59.9, 55.5, 42.0, 34.0, 26.1, 26.0, 25.0, 18.3, 18.2, -4.2, -4.4, -4.9, -4.9; HRMS (ESI$^+$) calcd for C$_{39}$H$_{62}$NaO$_7$Si$_2$ (M+Na)$^+$ 721.3926, found 721.3906.

**C16 Alcohol**

To a stirred solution of **III-98** (482 mg, 0.69 mmol) in THF (7 mL) was added 9-BBN (2.76 mL, 1.38 mmol, 0.5 M in THF). The resulting solution was stirred for 14 h before EtOH (2 mL), NaOH (3.5 mL, 1M in H$_2$O) and 30% H$_2$O$_2$ (0.78 mL) were added. The resulting mixture was heated to 50 °C for 1 h before saturated Na$_2$S$_2$O$_3$ solution was added. The solution was then diluted with EtOAc, and the separated aqueous layers were extracted with EtOAc. The combined organic layers were then washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. Silica gel column chromatography (hexanes-ethyl acetate, 10:1-3:1, v/v) of the residue gave C16 alcohol (484 mg, 98%) as a
colorless oil: \( R_f 0.38 \) (hexanes-ethyl acetate, 3:1, v/v); \( [\alpha]^{20}_D = -11^\circ \) (c 2.2, CHCl\(_3\)); IR (neat): 3450, 2930, 1614, 1518, 1462, 1380, 1250, 1046, 834, 774 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta 7.44 \) (d, \( J = 8.8 \) Hz, 2H), 7.35 (m, 5H), 6.90 (d, \( J = 8.8 \) Hz, 2H), 5.55 (s, 1H), 4.90 (d, \( J = 12 \) Hz, 1H), 4.61 (d, \( J = 12 \) Hz, 1H), 4.23 (dd, \( J = 4.8, 10 \) Hz, 1H), 4.10 (dd, \( J = 5.2, 10 \) Hz, 1H), 4.02 (dd, \( J = 2.4, 9.6 \) Hz, 1H), 3.82 (s, 3H), 3.76 (m, 4H), 3.61 (m, 3H), 2.21 (m, 1H), 1.87 (br, 1H), 1.60 (m, 4H), 1.50 (m, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.06 (s, 6H), 0.05 (s, 3H), 0.00 (s, 3H), -0.03 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \( \delta 160.3, 139.0, 130.7, 128.5, 127.7, 113.8, 102.4, 80.5, 78.1, 73.7, 72.4, 72.1, 70.1, 63.3, 60.0, 55.5, 34.0, 33.3, 28.6, 26.1, 26.0, 25.1, 18.3, 18.2, -4.3, -4.3, -4.9, -4.9; HRMS (ESI\(^+\)) calcd for C\(_{39}\)H\(_{64}\)NaO\(_8\)Si\(_2\) (M+Na\(^+\)) 739.4032, found 739.4016.

![C16 TBS Ether (III-99)](image)

**C16 TBS Ether (III-99)**

To a stirred solution of C16 alcohol (484 mg, 0.67 mmol) in CH\(_2\)Cl\(_2\) (5 mL) was added imidazole (182 mg, 2.68 mmol) followed by TBSCl (202 mg, 1.34 mmol), and DMAP (16 mg, 0.13 mmol). The resulting solution was stirred for 1 h before it was diluted with CH\(_2\)Cl\(_2\). The organic solution was washed with saturated NaHCO\(_3\) solution and brine, dried over anhydrous Na\(_2\)SO\(_4\), filtered, and concentrated. Silica gel column chromatography (hexanes-ethyl acetate, 20:1, v/v) of the residue gave C16 TBS ether **III-**
99 (557 mg, 100%) as a colorless oil: R\textsubscript{f} 0.79 (hexanes-ethyl acetate, 3:1, v/v); [\textalpha\textsubscript{20}\textsuperscript{D} = -11° (c 2.9, CHCl\textsubscript{3}); IR (neat): 2929, 1615, 1518, 1462, 1380, 1252, 1098, 835, 774 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): \delta 7.44 (d, J = 8.8 Hz, 2H), 7.35 (m, 5H), 6.90 (d, J = 8.8 Hz, 2H), 5.55 (s, 1H), 4.88 (d, J = 12 Hz, 1H), 4.61 (d, J = 12 Hz, 1H), 4.23 (dd, J = 4.8, 10 Hz, 1H), 4.09 (dd, J = 5.2, 10 Hz, 1H), 4.01 (dd, J = 2.4, 9.6 Hz, 1H), 3.82 (s, 3H), 3.75 (m, 4H), 3.61 (m, 3H), 2.26 (m, 1H), 1.56 (m, 4H), 1.47 (m, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.87 (s, 9H), 0.05 (s, 3Hx2), 0.04 (s, 3H), 0.03 (s, 3H), -0.02 (s, 3H), -0.05 (s, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz): \delta 160.3, 139.0, 130.8, 128.5, 127.8, 127.8, 127.7, 113.8, 102.4, 80.6, 78.1, 76.8, 73.6, 72.5, 72.1, 70.1, 63.6, 59.9, 55.5, 34.4, 33.5, 29.0, 26.2, 26.0, 25.1, 18.5, 18.3, 18.2, -4.2, -4.3, -4.9, -4.9; HRMS (ESI\textsuperscript{+}) calcd for C\textsubscript{45}H\textsubscript{78}NaO\textsubscript{8}Si\textsubscript{3} (M+Na\textsuperscript{+}) 853.4897, found 853.4921.

**C27 Alcohol (III-100)**

To a stirred solution of **III-99** (184 mg, 0.22 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (6 mL) at 0 °C was added DIBAL-H (0.33 mL, 0.33 mmol, 1.0 M in toluene). The resulting solution was stirred for 2 h at 0 °C before it was quenched with MeOH. Saturated Na/K tartrate solution was added to the flask, and the mixture was stirred until the organic layers were clear. The separated aqueous layers were extracted with CH\textsubscript{2}Cl\textsubscript{2}, and the combined organic layers
were washed with H₂O and brine, dried over anhydrous Na₂SO₄, filtered, and concentrated. Silica gel column chromatography (hexanes-ethyl acetate, 20:1-10:1, v/v) of the residue gave C27 alcohol III-100 (90 mg, 49%) along with III-99 (62 mg, 34%): R₉ 0.54 (hexanes-ethyl acetate, 3:1, v/v); [α]D₂° = +18° (c 1.0, CHCl₃); IR (neat): 3435, 2928, 1578, 1441, 1251, 1095, 836 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.32 (m, 5H), 7.23 (d, J = 6.8 Hz, 2H), 6.86 (d, J = 7.6 Hz, 2H), 4.68 (d, J = 9.6 Hz, 1H), 4.57 (d, J = 10 Hz, 1H), 4.47 (d, J = 9.2 Hz, 1H), 4.44 (d, J = 9.2 Hz, 1H), 3.90 (m, 1H), 3.80 (s, 3H), 3.76 (m, 2H), 3.72 (m, 2H), 3.67 (m, 1H), 3.58 (m, 4H), 3.48 (d, J = 9.6 Hz, 1H), 2.12 (m, 1H), 2.01 (t, J = 5.6 Hz, 1H), 1.50 (m, 8H), 0.89 (s, 9H), 0.87 (s, 9H), 0.83 (s, 9H), 0.04 (s, 3H×2), 0.03 (s, 9H), 0.02 (s, 3H), -0.04 (s, 3H), -0.10 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 159.5, 138.7, 130.5, 129.9, 128.6, 128.1, 127.9, 114.0, 79.3, 76.5, 73.1, 73.0, 72.1, 71.5, 71.3, 68.5, 63.6, 63.0, 55.5, 34.3, 33.4, 29.0, 26.2, 26.1, 26.0, 25.2, 18.5, 18.3, 18.1, -4.2, -4.3, -4.7; HRMS (ESI⁻) calcd for C₄₅H₈₀NaO₈Si₃ (M+Na⁻) 855.5053, found 855.5027.

(27S)-Alcohol (III-101-a)

To a stirred room-temperature solution of III-100 (81 mg, 0.097 mmol) in CH₂Cl₂ (3 mL) under argon was added NaHCO₃ (407 mg, 4.85 mmol), followed by the Dess-Martin periodinane reagent (206 mg, 0.49 mmol). The resulting solution was stirred for 1 h at
room temperature. After this time, the reaction mixture was diluted with CH₂Cl₂ (5 mL), and then quenched with H₂O (2 mL) and saturated Na₂S₂O₃ solution (5 mL), and the mixture was stirred until the organic layer became clear. The separated aqueous layers were extracted with CH₂Cl₂, and the combined organic layers were washed with H₂O and brine, and then dried over Na₂SO₄, filtered, and concentrated. The resulting aldehyde III-96 was used for the next step without further purification.

To a stirred solution of iodide III-5 (150 mg, 0.47 mmol) in Et₂O (2 mL) at -78 °C under argon was added t-BuLi (0.52 mL, 1.7 M in pentane, 0.95 mmol) dropwise, and the resulting solution was stirred for 5 min at -78 °C. After this time, the reaction mixture was allowed to warm to room temperature and stir for 30 min, and then recool to -78 °C. A solution of aldehyde III-96 (0.097 mmol theor.) in Et₂O (2 mL) was added via cannula at -78 °C. After 45 min, saturated aqueous NH₄Cl solution was added, and the reaction mixture was allowed to warm to room temperature. EtOAc (5 mL) was added, and the two layers were separated. The aqueous layers were then extracted with EtOAc, and the combined organic layers were washed with brine, and then dried over Na₂SO₄, filtered, and concentrated. The diastereomeric ratio (1.0:1.4) of the mixture was determined based on ¹H NMR resonances at δ 3.28 and 3.38. Preliminary separation resulted the undesired diastereomer III-101-b (40 mg, 40%) and a mixture of desired product III-101-a with starting material aldehyde III-96 (37 mg), which was further separated later on.

To a stirred room temperature solution of III-101-b (40 mg, 0.038 mmol) in CH₂Cl₂ (3 mL) under argon was added NaHCO₃ (255 mg, 3.04 mmol), followed by the Dess-Martin periodinane reagent (130 mg, 0.31 mmol). The resulting solution was stirred for 1 h at room temperature. After this time, the reaction mixture was diluted with CH₂Cl₂ (5 mL),
and then quenched with \( H_2O \) (2 mL) and saturated \( Na_2S_2O_3 \) solution (5 mL), and the mixture was stirred until the organic layer became clear. The separated aqueous layers were extracted with \( CH_2Cl_2 \), and the combined organic layers were washed with \( H_2O \) and brine, and then dried over \( Na_2SO_4 \), filtered, and concentrated. The resulting ketone was used for the next step without further purification.

To a stirred solution of the ketone from the previous step (0.038 mmol theor.) in MeOH (3 mL) at -20 °C was added NaBH\(_4\) (14 mg, 0.38 mmol). The solution was stirred for 30 min at -20 °C, before it was quenched with aqueous NH\(_4\)Cl solution. Most of the MeOH was removed by rotary evaporation, and the resulting slurry was extracted with EtOAc, and then combined organic layers were washed with brine, dried over \( Na_2SO_4 \), filtered, and concentrated to an oil, which along with the mixture obtained above was purified by silica gel column chromatography (hexanes-ethyl acetate, 20:1-10:1, v/v) to provide \textbf{III-101-a} (61 mg, 60% combined) as a colorless oil.

Data for \textbf{III-101-a}: \( R_f \) 0.29 (hexanes-ethyl acetate, 10:1, v/v); [\( \alpha \)]\(_{20}^D\) = +14° (c 1.9, CHCl\(_3\)); IR (neat): 2952, 2837, 1514, 1471, 1252, 1099, 836, 775 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta \) 7.32 (m, 5H), 7.23 (d, \( J = 6.8 \) Hz, 2H), 6.86 (d, \( J = 7.6 \) Hz, 2H), 4.65 (d, \( J = 12.4 \) Hz, 1H), 4.57 (m, 3H), 3.99 (m, 1H), 3.84 (dd, \( J = 2.8, 8.8 \) Hz, 1H), 3.80 (s, 3H), 3.67 (m, 4H), 3.56 (m, 6H), 3.29 (dd, \( J = 2.0, 11.2 \) Hz, 1H), 2.01 (m, 2H), 1.90 (m, 3H), 1.81 (m, 1H), 1.65 (m, 3H), 1.53 (m, 8H), 1.40 (m, 8H), 1.08 (d, \( J = 6.4 \) Hz, 3H), 0.91 (d, \( J = 6.8 \) Hz, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.83 (s, 9H), 0.04 (s, 3Hxx2), 0.03 (s, 3H), 0.01 (s, 3H), -0.05 (s, 3H), -0.11 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \( \delta \) 159.5, 138.7, 130.7, 130.0, 128.6, 128.2, 127.9, 114.0, 95.8, 79.2, 75.4, 73.2, 72.6, 72.1, 72.0, 71.2, 66.4, 63.5, 60.5, 55.5, 36.8, 36.2, 34.2, 33.4, 31.6, 30.6, 28.8, 27.6, 26.7, 26.2, 26.1, 26.0, 25.7, 25.6, 108
19.0, 18.5, 18.3, 18.1, 16.5, 11.1, -4.2, -4.2, -4.7, -5.1; HRMS (ESI+) cale for 
C_{58}H_{102}NaO_{10}Si_3 (M+Na)^+ 1065.6673, found 1065.6624.

C27 TBS Ether (III-102)

To a stirred solution of III-101-a (61 mg, 0.058 mmol) in CH_2Cl_2 (2 mL) at -20 °C was 
added Et_3N (0.12 mL, 0.87 mmol) followed by TBSOTf (0.04 mL, 0.17 mmol). The 
resulting solution was stirred for 20 min at -20 °C before it was diluted with CH_2Cl_2. The 
organic solution was washed with saturated NaHCO_3 solution and brine, dried over 
anhydrous Na_2SO_4, filtered, and concentrated. Silica gel column chromatography 
(hexanes-ethyl acetate, 20:1, v/v) of the residue gave C27 TBS ether III-102 (58 mg, 
86%) as a colorless oil: R_f 0.49 (hexanes-ethyl acetate, 10:1, v/v); [a]^{20}_D = + 9.6° (c 2.2, 
CHCl_3); IR (neat): 2954, 1514, 1472, 1252, 1101, 1004, 836, 775 cm^{-1}; ^1H NMR (CDCl_3, 
400 MHz): δ 7.32 (m, 5H), 7.23 (d, J = 6.8 Hz, 2H), 6.86 (d, J = 7.6 Hz, 2H), 4.64 (d, J = 
12.4 Hz, 1H), 4.59 (d, J = 12.4 Hz, 1H), 4.51 (d, J = 11.2 Hz, 1H), 4.43 (d, J = 11.6 Hz, 
1H), 4.02 (t, J = 5.2 Hz, 1H), 3.96 (dd, J = 2.4, 11.6 Hz, 1H), 3.80 (s, 3H), 3.77 (dd, J = 
2.0, 7.6 Hz, 1H), 3.69 (m, 5H), 3.58 (m, 3H), 3.28 (dd, J = 2.0, 9.6 Hz, 1H), 2.01 (m, 
1H), 1.85 (m, 2H), 1.72 (m, 3H), 1.62 (m, 4H), 1.53 (m, 5H), 1.42 (m, 6H), 1.28 (m, 3H), 
1.05 (d, J = 6.8 Hz, 3H), 0.91 (d, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.87 (s, 9H), 0.84 (s,
9H), 0.09 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H×2), 0.02 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H), -0.05 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 159.2, 139.1, 131.0, 129.2, 128.5, 127.8, 127.6, 113.8, 95.6, 78.9, 75.7, 74.1, 73.3, 72.5, 72.4, 71.5, 71.0, 63.6, 60.5, 55.5, 36.5, 36.2, 34.1, 33.2, 31.7, 30.6, 28.9, 27.9, 26.9, 26.4, 26.2, 26.0, 25.7, 22.9, 19.0, 18.5, 18.3, 18.2, 17.5, 14.3, 11.5, -3.3, -3.9, -4.1, -4.3, -4.5, -5.1; HRMS (ESI+) calcd for C$_{64}$H$_{116}$NaO$_{10}$Si$_4$ (M+Na)$^+$ 1179.7538, found 1179.7478.

C25 Alcohol (III-103)

To a stirred solution of III-102 (46 mg, 0.04 mmol) in CH$_2$Cl$_2$ (1 mL) was added pH 7 buffer (0.5 mL), t-BuOH (0.25 mL), and DDQ (45 mg, 0.20 mmol). The resulting solution was stirred for 30 min before it was quenched with saturated NaHCO$_3$ solution. The separated aqueous layers were extracted with CH$_2$Cl$_2$, and the combined organic layers were washed with H$_2$O and brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. Silica gel column chromatography (hexanes-ethyl acetate, 20:1, v/v) of the residue gave III-103 (34 mg, 83%) as a colorless oil: R$_f$ 0.487 (hexanes-ethyl acetate, 10:1, v/v); [α]$^{20}$D $=$ +6.3° (c 2.6, CHCl$_3$); IR (neat): 3500, 2930, 2857, 1472, 1386, 1255, 1099, 836, 775 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.33 (m, 5H), 4.73 (d, $J$ = 12 Hz, 1H), 4.64 (d, $J$ = 11.6 Hz, 1H), 4.11 (m, 1H), 4.00 (m, 1H), 3.74 (dd, $J$ = 3.2, 8.8 Hz, 1H), 3.60 (s, 3H), 2.00 (s, 3H), 1.32 (s, 3H).
1H), 3.66 (m, 5H), 3.58 (m, 3H), 3.32 (dd, J = 2.0, 9.6 Hz, 1H), 3.13 (d, J = 3.6 Hz, 1H), 2.01 (m, 2H), 1.88 (m, 2H), 1.72 (m, 3H), 1.55 (m, 10H), 1.42 (m, 7H), 1.29 (m, 8H), 1.05 (d, J = 6.4 Hz, 3H), 0.91 (d, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.87 (s, 9H), 0.85 (s, 9H), 0.15 (s, 3H), 0.12 (s, 3H), 0.04 (s, 3H×2), 0.03 (s, 3H), 0.02 (s, 3H), -0.02 (s, 3H), -0.04 (s, 3H); 13C NMR (CDCl$_3$, 100 MHz): δ 138.9, 129.2, 128.5, 128.4, 127.9, 127.8, 113.8, 95.8, 79.9, 79.4, 75.6, 73.5, 72.3, 72.1, 71.4, 70.8, 67.4, 63.6, 60.5, 36.2, 34.8, 34.4, 33.5, 31.3, 30.6, 28.9, 27.7, 26.7, 26.4, 26.2, 26.1, 26.0, 25.8, 25.7, 19.0, 18.5, 18.3, 18.2, 18.2, 16.9, 11.3, -4.1, -4.2, -4.2, -4.6, -4.7, -5.1; HRMS (ESI+) calcd for C$_{56}$H$_{108}$NaO$_9$Si$_4$ (M+Na)$^+$ 1059.6963, found 1059.6996.

![III-104](image)

**C25 alkene (III-104)**

To a stirred room-temperature solution of **III-103** (34 mg, 0.033 mmol) in CH$_2$Cl$_2$ (2 mL) was added NaHCO$_3$ (416 mg, 4.95 mmol), followed by the Dess-Martin periodinane reagent (210 mg, 0.50 mmol). The resulting solution was allowed to stir for 14 h. After this time, the reaction mixture was diluted with CH$_2$Cl$_2$ (5 mL), and then quenched with H$_2$O (2 mL) and saturated aqueous Na$_2$S$_2$O$_3$ solution (5 mL), and the mixture was stirred until the organic layer became clear. The separated aqueous layers were extracted with CH$_2$Cl$_2$, and the combined organic layers were washed with H$_2$O and brine, and then
dried over Na$_2$SO$_4$, filtered, and concentrated. The resulting residue was used for next step without further purification.

To a stirred solution of methyltriphenylphosphonium bromide (141 mg, 0.40 mmol) in toluene (2 mL) under argon was added KHMDS solution (0.59 mL, 0.5M in toluene, 0.30 mmol). The resulting yellow solution was heated to 90 °C for 30 min and then cooled to room temperature before a solution of ketone from the previous step (0.033 mmol theor.) in toluene (2 mL) was added via cannula. The resultant solution was heated to 90 °C for 45 min and then recooled to room temperature before saturated aqueous NH$_4$Cl solution (3 mL) was added. The toluene was removed by rotary evaporation, and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, and then dried over Na$_2$SO$_4$, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (hexanes-ethyl acetate, 20:1-10:1, v/v) to yield **III-104** as a colorless oil (26 mg, 75% from **III-103**): R$_f$ 0.47 (hexanes-ethyl acetate, 10:1, v/v); $[\alpha]^{20}_D = +19^\circ$ (c 2.4, CHCl$_3$); IR (neat): 2929, 2856, 1472, 1255, 1090, 836m 775 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.33 (m, 5H), 5.27 (s, 1H), 5.14 (s, 1H), 4.62 (d, $J = 11.6$ Hz, 1H), 4.51 (d, $J = 11.6$ Hz, 1H), 4.16 (d, $J = 4.8$Hz, 1H), 3.97 (m, 1H), 3.90 (d, $J = 7.2$ Hz, 1H), 3.68 (m, 3H), 3.58 (m, 3H), 3.38 (t, $J = 7.2$ Hz, 1H), 3.28 (dd, $J = 2.0$, 10 Hz, 1H), 2.01 (m, 1H), 1.90 (m, 1H), 1.75 (m, 2H), 1.62 (m, 5H), 1.48 (m, 8H), 1.03 (d, $J = 6.4$ Hz, 3H), 0.91 (d, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 142.9, 138.5, 137.5, 137.4, 134.0, 133.8, 128.9, 128.7, 128.7, 128.5, 127.7, 111.8, 95.7, 83.3, 80.2, 79.1, 78.5, 75.5, 72.3, 72.1, 71.7, 63.6, 60.6, 36.2, 35.5, 34.9, 33.4, 33.2, 31.8, 31.2, 30.6, 28.8, 28.4, 27.8, 26.7, 112
26.3, 26.2, 26.0, 25.7, 25.5, 22.9, 19.0, 18.5, 18.4, 18.3, 16.8, 14.3, 11.2, -4.1, -4.2, -4.2, -4.6, -4.7, -5.1; HRMS (ESI+) calcd for C\textsubscript{57}H\textsubscript{108}NaO\textsubscript{8}Si\textsubscript{4} (M+Na)\textsuperscript{+} 1055.7013, found 1055.7030.

C\textsubscript{16} Alcohol (III-105)

To a stirred solution of III-104 (41 mg, 0.04 mmol) in MeOH (2 mL) under argon was added PPTs (8 mg, 0.03 mmol). The resulting solution was stirred for 4 h before it was quenched with 0.1 mL Et\textsubscript{3}N. The reaction mixture was concentrated under rotary evaporation, and the resulting residue was purified by silica gel column chromatography (hexanes-ethyl acetate, 20:1-10:1-5:1, v/v) to yield III-105 as a colorless oil (23 mg, 63%): R\textsubscript{f} 0.60 (hexanes-ethyl acetate, 3:1, v/v); [\text{a}]\textsuperscript{20}\text{D} = +16\degree (c 0.5, CHCl\textsubscript{3}); IR (neat): 3446, 2932, 1456, 1255, 1098, 830 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): \delta 7.33 (m, 5H), 5.27 (s, 1H), 5.15 (s, 1H), 4.62 (d, J = 11.6 Hz, 1H), 4.51 (d, J = 11.6 Hz, 1H), 4.17 (d, J = 4.8 Hz, 1H), 3.98 (m, 1H), 3.90 (d, J = 6.8 Hz, 1H), 3.70 (m, 3H), 3.58 (m, 3H), 3.38 (t, J = 7.2 Hz, 1H), 3.28 (dd, J = 2.0, 9.6 Hz, 1H), 2.01 (m, 1H), 1.90 (m, 1H), 1.75 (m, 5H), 1.62 (m, 6H), 1.48 (m, 6H), 1.40 (m, 4H), 1.03 (d, J = 6.4 Hz, 3H), 0.91 (d, 3H), 0.91 (s, 9H), 0.88 (s, 9H), 0.88 (s, 9H), 0.11 (s, 3H), 0.11 (s, 3H), 0.05 (s, 3H×2), 0.04 (s, 3H), 0.03 (s, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz): \delta 142.8, 138.4, 128.5, 127.7, 112.0, 113
95.8, 83.3, 80.4, 78.6, 78.3, 75.5, 72.3, 71.8, 63.4, 60.6, 35.6, 33.3, 32.7, 31.3, 30.6, 28.5, 28.3, 27.8, 26.7, 26.3, 26.2, 26.1, 25.7, 19.0, 18.4, 18.3, 16.9, 11.3, -4.2, -4.2, -4.6, -4.7; HRMS (ESI+) calcd for C$_{51}$H$_{94}$NaO$_8$Si$_3$ (M+Na)$^+$ 941.6149, found 941.6142.

![Chemical structure](image)

**C15 Keto Phosphonate (III-95)**

To a stirred room-temperature solution of **III-105** (23 mg, 0.025 mmol) in CH$_2$Cl$_2$ (2 mL) was added NaHCO$_3$ (105 mg, 1.25 mmol), followed by the Dess-Martin periodinane reagent (53 mg, 0.125 mmol). The resulting solution was allowed to stir for 1 h. After this time, the reaction mixture was diluted with CH$_2$Cl$_2$ (5 mL), and then quenched with H$_2$O (2 mL) and saturated aqueous Na$_2$S$_2$O$_3$ solution (5 mL), and the mixture was stirred until the organic layer became clear. The separated aqueous layers were extracted with CH$_2$Cl$_2$, and the combined organic layers were washed with H$_2$O and brine, and then dried over Na$_2$SO$_4$, filtered, and concentrated. The resulting aldehyde **III-106** was used for next step without further purification.

To a stirred solution of methyl dimethylphosphonate (0.054 mL, 0.5 mmol) in THF (1 mL) at -78 °C was added t-BuLi (0.26 mL, 0.45 mmol) dropwisely. The resulting solution was stirred for 30 min at -78 °C before a solution of **III-106** (0.025 mmol theor.) in THF (1 mL) was cannulated into the flask. The resulting solution was stirred for 1 h at
-78 °C before it was quenched with sat. NH₄Cl solution, and diluted with EtOAc. The separated aqueous layers were extracted with EtOAc, and the combined organic layers were washed with H₂O and brine, and then dried over Na₂SO₄, filtered, and concentrated. The resulting residue was used for next step without further purification.

To a stirred room-temperature solution of the hydroxyl phosphonate prepared above (0.025 mmol theor.) in CH₂Cl₂ (2 mL) was added NaHCO₃ (210 mg, 2.5 mmol), followed by the Dess-Martin periodinane reagent (106 mg, 0.25 mmol). The resulting solution was allowed to stir for 1 h. After this time, the reaction mixture was diluted with CH₂Cl₂ (5 mL), and then quenched with H₂O (2 mL) and saturated aqueous Na₂S₂O₃ solution (5 mL), and the mixture was stirred until the organic layer became clear. The separated aqueous layers were extracted with CH₂Cl₂, and the combined organic layers were washed with H₂O and brine, and then dried over Na₂SO₄, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (hexanes-ethyl acetate, 5:1-2:1, v/v) to yield III-95 as a colorless oil (15 mg, 58% from III-105): Rf 0.31 (hexanes-ethyl acetate, 2:1, v/v); [α]²⁰D = +14° (c 1.4, CHCl₃); IR (neat): 2953, 2856, 1717, 1471, 1256, 1098, 1063, 836, 776 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.33 (m, 5H), 5.27 (s, 1H), 5.14 (s, 1H), 4.62 (d, J = 11.6 Hz, 1H), 4.51 (d, J = 11.6 Hz, 1H), 4.15 (d, J = 4.8 Hz, 1H), 3.98 (m, 1H), 3.89 (d, J = 6.8 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.70 (m, 3H), 3.58 (m, 1H), 3.37 (t, J = 7.2 Hz, 1H), 3.28 (dd, J = 2.0, 9.6 Hz, 1H), 3.10 (d, J = 22.4 Hz, 2H), 2.65 (t, J = 7.6 Hz, 2H), 2.01 (m, 1H), 1.90 (m, 1H), 1.75 (m, 4H), 1.65 (m, 4H), 1.55 (m, 6H), 1.40 (m, 5H), 1.03 (d, J = 6.4 Hz, 3H), 0.91 (d, 3H), 0.91 (s, 9H), 0.87 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), 0.03 (s, 3H), 0.03 (s, 3H), 0.03 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 201.9, 142.8, 138.4, 128.5, 127.7, 115
95.8, 83.2, 80.5, 78.6, 78.2, 75.5, 72.1, 71.2, 60.7, 53.3, 53.2, 42.1, 40.0, 36.2, 33.0, 31.2, 30.5, 30.2, 27.8, 26.7, 26.3, 26.1, 26.1, 25.7, 19.0, 18.4, 18.3, 18.2, 16.9, 11.2, -4.2, -4.2, -4.6, -4.7; HRMS (ESI+) calcd for C\textsubscript{54}H\textsubscript{99}O\textsubscript{11}P\textsubscript{3}Si\textsuperscript{+} (M+Na)\textsuperscript{+} 1061.6125, found 1061.6077.

C\textsubscript{1},C\textsubscript{2} Diol(III-108)

To a stirred solution of III-107 (87 mg, 0.15 mmol) in MeOH (4 mL) under argon was added TsOH (2.8 mg, 0.015 mmol). The resulting solution was stirred for 4 h before it was quenched with 0.1 mL Et\textsubscript{3}N. The reaction mixture was concentrated under rotary evaporation, and the resulting residue was purified by silica gel column chromatography (hexanes-ethyl acetate, 5:1-1:1, v/v) to yield III-108 as a colorless oil (53 mg, 65%): R\textsubscript{f} 0.10 (hexanes-ethyl acetate, 3:1, v/v); [\alpha]\textsubscript{D}\textsuperscript{20} = + 38° (c 0.4, CHCl\textsubscript{3}); IR (neat): 3448, 2931, 1583, 1441, 1246, 1095, 1035, 969 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz): δ 7.31 (m, 5H), 7.26 (d, J = 6.4 Hz, 2H), 6.86 (d, J = 8.0 Hz, 2H), 5.16 (s, 1H), 4.59 (d, J = 12 Hz, 1H), 4.45 (m, 3H), 4.04 (m, 1H), 3.80 (s, 3H), 3.58 (dd, J = 5.0, 9.0 Hz, 1H), 3.52 (m, 2H), 3.45 (dd, J = 5.0, 11.0 Hz, 1H), 3.28 (m, 2H), 2.49 (dd, J = 4.5 Hz, 1H), 2.01 (m, 3H), 1.80 (m, 2H), 1.72 (s, 3H), 1.62 (m, 3H), 1.35 (m, 1H), 1.08 (s, 3H), 1.10 (d, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz): δ 159.4, 139.0, 130.8, 129.6, 128.4, 127.9, 127.7, 122.5, 116
113.9, 96.5, 78.7, 73.1, 72.6, 72.0, 71.6, 70.0, 69.8, 67.4, 55.5, 44.5, 38.6, 32.6, 32.6, 25.3, 24.3, 23.2, 13.7; HRMS (ESI+) calcd for C_{32}H_{44}NaO_{7} (M+Na)^+ 563.2979, found 563.2963.

C1 Methyl Ester (III-109)

To a stirred solution of III-108 (53 mg, 0.098 mmol) in CH_{2}Cl_{2} (2 mL) under argon was added DMSO (1 mL), Et_{3}N (0.27 mL, 1.96 mmol) followed by SO_{3}·Py (156 mg, 0.98 mmol). The resulting solution was stirred for 30 min at room temperature before it was quenched with saturated NaHCO_{3} solution. The separated aqueous layers were extracted with CH_{2}Cl_{2}, and the combined organic layers were washed with H_{2}O and brine, and then dried over Na_{2}SO_{4}, filtered, and concentrated. The resulting residue was used for next step without further purification.

To a stirred solution of the aldehyde prepared above (0.098 mmol theor.) in t-BuOH (2 mL) and H_{2}O (1 mL) was added 2-methyl-2-butene (0.5 mL), NaH_{2}PO_{4} (176 mg, 1.47 mmol), followed by NaClO_{2} (89 mg, 0.98 mmol). The resulting solution was stirred for 1 h at room temperature before it was quenched with saturated NH_{4}Cl solution. The separated aqueous layers were extracted with EtOAc, and the combined organic layers
were washed with H₂O and brine, and then dried over Na₂SO₄, filtered, and concentrated. The resulting carboxylic acid was used for next step without further purification.

To a stirred solution of the acid prepared above (0.098 mmol, theor.) in benzene (1.2 mL) and MeOH (0.8 mL) was added TMSCHN₂ (0.15 mL, 0.29 mmol, 2.0 M in HA). The resulting reaction mixture was stirred for 30 min at room temperature before it was quenched with AcOH at 0 °C. The reaction mixture was concentrated under rotary evaporation, and the resulting residue was purified by silica gel column chromatography (hexanes-ethyl acetate, 10:1-5:1, v/v) to yield **III-109** as a colorless oil (39 mg, 70% from **III-108**): R₇ 0.33 (hexanes-ethyl acetate, 3:1, v/v); [a]²⁰D = + 40° (c 0.6, CHCl₃); IR (neat): 3446, 2931, 1747, 1576, 1437, 1246, 1093 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.31 (m, 5H), 7.26 (d, J = 6.4 Hz, 2H), 6.86 (d, J = 8.0 Hz, 2H), 5.15 (s, 1H), 4.70 (s, 1H), 4.59 (d, J = 9.6 Hz, 1H), 4.49 (d, J = 8.5 Hz, 1H), 4.47 (s, 2H), 3.87 (m, 1H), 3.78 (m, 1H), 3.70 (s, 3H), 3.31 (t, J = 9.0 Hz, 1H), 3.24 (dd, J = 4.5, 12 Hz, 1H), 2.07 (m, 1H), 2.02 (m, 2H), 1.85 (m, 4H), 1.70 (s, 3H), 1.62 (m, 2H), 1.40 (m, 1H), 1.36 (s, 3H), 1.30 (m, 2H), 1.04 (d, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ 176.6, 159.3, 139.0, 138.2, 131.1, 129.4, 128.4, 127.9, 127.6, 122.3, 113.9, 96.1, 78.6, 75.3, 72.8, 72.5, 71.6, 70.1, 68.3, 55.5, 52.5, 44.9, 38.7, 32.9, 32.2, 27.6, 24.1, 23.2, 13.9; HRMS (ESI+) calcd for C₃₃H₄₄NaO₈ (M+Na)⁺ 591.2928, found 591.2910.
C2 TES Ether (III-110)

To a stirred solution of III-109 (32 mg, 0.056 mmol) in CH$_2$Cl$_2$ (1 mL) was added imidazole (38 mg, 0.56 mmol) followed by TESCl (0.05 mL, 0.28 mmol), and DMAP (6.8 mg, 0.056 mmol). The resulting solution was stirred 24 h at room temperature before it was diluted with CH$_2$Cl$_2$. The organic solution was washed with sat. NaHCO$_3$ solution and brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. Silica gel column chromatography (hexanes-ethyl acetate, 10:1, v/v) of the residue gave III-110 (34 mg, 89%) as a colorless oil: $R_f$ 0.64 (hexanes-ethyl acetate, 3:1, v/v); $[\alpha]_{D}^{20} = +12^\circ$ (c 0.3, CHCl$_3$); IR (neat): 2952, 1743, 1514, 1455, 1248, 1096, 1008, 740 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.31 (m, 5H), 7.26 (d, $J$ = 6.4 Hz, 2H), 6.86 (d, $J$ = 8.0 Hz, 2H), 5.12 (s, 1H), 4.59 (d, $J$ = 12.4 Hz, 1H), 4.47 (d, $J$ = 12.4 Hz, 1H), 4.44 (s, 2H), 3.82 (m, 1H), 3.78 (s, 3H), 3.74 (m, 1H), 3.57 (s, 3H), 3.36 (t, $J$ = 8.8 Hz, 1H), 3.22 (dd, $J$ = 4.8, 12 Hz, 1H), 2.05 (m, 3H), 1.85 (m, 4H), 1.71 (s, 3H), 1.65 (m, 2H), 1.38 (s, 3H), 1.28 (m, 4H), 1.04 (d, $J$ = 6.8 Hz, 3H), 0.92 (m, 9H), 0.55 (m, 6H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 175.5, 159.2, 139.2, 137.1, 131.1, 129.3, 128.3, 127.9, 127.6, 123.3, 113.8, 96.0, 78.8, 75.8, 72.8, 72.6, 71.4, 69.7, 66.0, 55.4, 51.8, 48.2, 38.6, 33.0, 31.9, 31.8, 25.8, 24.4, 23.2, 22.8, 14.3, 14.1, 7.2, 6.3; HRMS (ESI+) calcd for C$_{39}$H$_{58}$NaO$_8$Si (M+Na)$^+$ 705.3793, found 705.3769.
C14 Alcohol (III-111)

To a stirred solution of III-110 (34 mg, 0.05 mmol) in CH₂Cl₂ (2 mL) was added pH 7 buffer (1 mL), t-BuOH (0.5 mL), and DDQ (56 mg, 0.25 mmol). The resulting solution was sonicated for 5 min before it was quenched with saturated NaHCO₃ solution. The separated aqueous layers were extracted with CH₂Cl₂, and the combined organic layers were washed with H₂O and brine, dried over anhydrous Na₂SO₄, filtered, and concentrated. Silica gel column chromatography (hexanes-ethyl acetate, 10:1-3:1, v/v, neutralized with 10% Et₃N) of the residue gave III-111 (23 mg, 82%) as a colorless oil: Rf 0.43 (hexanes-ethyl acetate, 3:1, v/v); [α]²⁰_D = +21° (c 0.1, CHCl₃); IR (neat): 3524, 2952, 2875, 1741, 1574, 1453, 1136, 1095, 1006, 742 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.31 (m, 5H), 5.12 (s, 1H), 4.59 (d, J = 12.5 Hz, 1H), 4.45 (d, J = 12.5 Hz, 1H), 3.90 (m, 2H), 3.83 (m, 1H), 3.71 (m, 1H), 3.60 (s, 3H), 3.21 (dd, J = 4.5, 11.5 Hz, 1H), 3.00 (t, J = 6.5 Hz, 1H), 2.12 (m, 1H), 2.02 (dd, J = 8.0, 14.0 Hz, 1H), 1.88 (m, 3H), 1.80 (m, 2H), 1.73 (s, 3H), 1.68 (m, 1H), 1.46 (s, 3H), 1.31 (m, 2H), 1.05 (d, J = 7.0 Hz, 3H), 0.92 (m, 9H), 0.59 (m, 6H); ¹³C NMR (CDCl₃, 125 MHz): δ 175.7, 138.6, 129.4, 128.4, 127.9, 127.6, 123.2, 95.7, 78.3, 75.8, 72.3, 71.5, 66.3, 51.8, 48.6, 39.8, 33.8, 31.6, 26.0, 24.8, 23.1, 14.3, 7.1, 6.4; HRMS (ESI⁺) calcd for C₃₁H₅₀NaO₇Si (M+Na)⁺ 585.3128, found 585.3231.
C14 Aldehyde (III-94)

To a stirred room-temperature solution of **III-111** (23 mg, 0.041 mmol) in CH₂Cl₂ (2 mL) was added NaHCO₃ (172 mg, 2.05 mmol), followed by the Dess-Martin periodinane reagent (87 mg, 0.204 mmol). The resulting solution was allowed to stir for 1 h. After this time, the reaction mixture was diluted with CH₂Cl₂ (5 mL), and then quenched with H₂O (2 mL) and saturated aqueous Na₂S₂O₃ solution (5 mL), and the mixture was stirred until the organic layer became clear. The separated aqueous layers were extracted with CH₂Cl₂, and the combined organic layers were washed with H₂O and brine, and then dried over Na₂SO₄, filtered, and concentrated. Silica gel column chromatography (hexanes-ethyl acetate, 10:1, v/v) of the residue gave **III-94** (17 mg, 74%) as a colorless oil: Rₛ 0.59 (hexanes-ethyl acetate, 3:1, v/v); [α]²⁰_D = +31° (c 0.6, CHCl₃); IR (neat): 2947, 1732, 1456, 1240, 1136, 741 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 9.95 (d, J = 2.4 Hz, 1H), 7.31 (m, 5H), 5.14 (s, 1H), 4.59 (d, J = 12.8 Hz, 1H), 4.45 (d, J = 12.4 Hz, 1H), 4.14 (m, 1H), 3.76 (m, 1H), 3.59 (s, 3H), 3.22 (dd, J = 4.8, 11.2 Hz, 1H), 2.65 (dt, J = 2.4, 7.6 Hz, 1H), 2.05 (m, 2H), 1.85 (m, 3H), 1.74 (s, 3H), 1.65 (m, 2H), 1.43 (s, 3H), 1.13 (d, J = 7.2 Hz, 3H), 0.92 (m, 9H), 0.55 (m, 6H); ¹³C NMR (CDCl₃, 100 MHz): δ 204.7, 175.6, 128.4, 128.0, 127.7, 123.6, 96.2, 78.6, 75.8, 71.5, 69.3, 66.5, 51.8, 50.8, 48.2, 33.3, 31.7, 26.0, 24.3, 23.1, 10.6, 7.1, 6.4; HRMS (ESI⁺) calcd for C₃₂H₅₂NaO₈Si (M+MeOH+Na)⁺ 615.3324, found 615.3310.
C16 Enone (III-112)

To a stirred room-temperature solution of III-95 (15 mg, 0.014 mmol) in CH$_3$CN (0.5 mL) was added i-Pr$_2$EtN (3.7 µL, 0.021 mmol) and LiCl (3 mg, 0.072 mmol). The resulting solution was allowed to stir for 30 min before a solution of III-94 (17 mg, 0.03 mmol) in CH$_3$CN was cannulated into the flask. The mixture was stirred for 2 d at room temperature before it was quenched with saturated NH$_4$Cl solution. EtOAc was added, and the separated aqueous layers were extracted with EtOAc, and the combined organic layers were washed with H$_2$O and brine, and then dried over Na$_2$SO$_4$, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (hexanes-ethyl acetate, 10:1, v/v) to yield III-112 as a colorless oil (17 mg, 80%): R$_f$ 0.72 (hexanes-ethyl acetate, 3:1, v/v); [a]$^{20}_{D}$ = +15$^\circ$ (c 1.7, CHCl$_3$); IR (neat): 2952, 1738, 1455, 1252, 1097, 1004, 836, 776, 736 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.33 (m, 10H), 6.99 (dd, $J = 7.6, 15.6$ Hz, 1H), 6.18 (d, $J = 15.6$ Hz, 1H), 5.27 (s, 1H), 5.14 (s, 1H), 5.12 (s, 1H), 4.62 (d, $J = 11.6$ Hz, 1H), 4.58 (d, $J = 12.8$ Hz, 1H), 4.51 (d, $J = 11.6$ Hz, 1H), 4.44 (d, $J = 12.4$ Hz, 1H), 4.15 (d, $J = 5.2$ Hz, 1H), 3.98 (m, 1H), 3.89 (d, $J = 7.2$ Hz, 1H), 3.82 (m, 2H), 3.70 (m, 3H), 3.57 (s, 3H), 3.37 (t, $J = 6.8$ Hz, 1H), 3.28 (dd, $J = 2.0, 10$ Hz, 1H), 3.22 (dd, 1H), 2.55 (m, 3H), 2.01 (m, 3H), 1.85 (m, 8H), 1.74 (s, 3H), 1.65 (m, 14H), 1.41 (s, 3H), 1.18 (d, $J = 6.8$ Hz, 3H), 1.03 (d, $J = 6.4$ Hz, 3H), 0.93 (d, 3H), 0.91 (m, 36H), 0.55 (m, 6H), 0.12 (s, 3H), 0.10 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H),
0.02 (s, 3H), 0.01 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 200.3, 175.4, 149.9, 142.8, 139.2, 138.5, 136.7, 130.3, 128.5, 128.3, 127.8, 127.7, 127.5, 123.4, 96.1, 95.7, 83.2, 78.8, 78.7, 78.4, 75.8, 75.5, 72.1, 71.2, 70.7, 66.1, 51.7, 48.4, 41.5, 36.2, 36.2, 33.1, 31.9, 31.2, 30.8, 30.0, 27.8, 26.7, 26.3, 26.2, 25.7, 23.1, 18.4, 18.3, 18.3, 16.8, 15.8, 11.2, 7.1, 6.3, -3.6, -3.8, -4.1, -4.3, -4.3; HRMS (ESI+) calcd for C$_{83}$H$_{140}$NaO$_{14}$Si$_{4}$ (M+Na)$^+$ 1495.9212, found 1495.9188.

### C16 Alcohol (III-114)

To a stirred 0 °C solution of ($R$)-2-methyl-CBS-oxazaborolidine (0.17 mL, 0.17 mmol, 1.0 M in toluene) in THF (1 mL) was added BH$_3$·Me$_2$S (0.12 mL, 0.12 mmol, 1.0 M in THF) followed a solution of III-112 (17 mg, 0.012 mmol) in THF (1 mL). The resulting solution was allowed to stir for 10 min at 0 °C before it was quenched by saturated NH$_4$Cl solution. EtOAc was added, and the separated aqueous layers were extracted with EtOAc, and the combined organic layers were washed with H$_2$O and brine, and then dried over Na$_2$SO$_4$, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (hexanes-ethyl acetate, 10:1, v/v) to yield III-114 as a colorless oil (15 mg, 88%): R$_f$ 0.55 (hexanes-ethyl acetate, 3:1, v/v); [α]$_D^{20}$ = +15° (c 0.8, CHCl$_3$); IR (neat): 2929, 1734, 1685, 1458, 1257, 1003, 909, 836, 732 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500
MHz): δ 7.33 (m, 10H), 5.82 (dd, J = 7.0, 15 Hz, 1H), 5.53 (dd, J = 6.5, 15 Hz, 1H), 5.27 (s, 1H), 5.14 (s, 1H×2), 4.62 (d, J = 12 Hz, 1H), 4.58 (d, J = 12.5 Hz, 1H), 4.51 (d, J = 11.5 Hz, 1H), 4.45 (d, J = 12.5 Hz, 1H), 4.16 (d, J = 4.5 Hz, 1H), 4.00 (m, 2H), 3.90 (d, J = 7.0 Hz, 1H), 3.88 (m, 1H), 3.77 (m, 1H), 3.72 (m, 3H), 3.59 (s, 3H), 3.37 (t, 1H), 3.25 (m, 2H), 2.40 (m, 1H), 2.01 (m, 3H), 1.90 (m, 2H), 1.80 (m, 4H), 1.71 (s, 3H), 1.65 (m, 8H), 1.52 (m, 9H), 1.43 (s, 3H), 1.12 (d, J = 7.0 Hz, 3H), 1.03 (d, J = 6.5 Hz, 3H), 0.93 (d, 3H), 0.91 (m, 36H), 0.55 (m, 6H), 0.12 (s, 3H), 0.10 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); 13C NMR (CDCl3, 125 MHz): δ 175.5, 143.2, 139.6, 138.6, 137.1, 133.7, 128.5, 128.3, 127.9, 127.6, 127.5, 123.6, 112.1, 96.1, 95.7, 83.2, 80.4, 78.9, 78.8, 78.4, 75.9, 75.5, 73.2, 72.4, 72.1, 71.7, 71.2, 71.0, 65.9, 60.6, 51.8, 48.3, 40.8, 36.2, 32.9, 32.1, 31.2, 30.6, 29.9, 27.8, 26.7, 26.3, 26.2, 26.0, 25.7, 24.4, 23.2, 19.0, 18.4, 18.3, 16.8, 16.5, 14.3, 11.2, 7.2, 6.4, 1.2, -3.6, -3.8, -4.2, -4.3; HRMS (ESI+) calcd for C83H142NaO14Si4 (M+Na)+ 1497.9369, found 1497.9270.
TBAF (0.5 mL, 0.5 mmol, 1.0 M in THF) was added into neat III-114 (8 mg, 0.005 mmol), and the resulting solution was allowed to stir for 2 d before it was quenched by saturated NH₄Cl solution. EtOAc was added, and the separated aqueous layers were extracted with EtOAc, and the combined organic layers were washed with H₂O and brine, and then dried over Na₂SO₄, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (dichloromethane-MeOH, 10:1, v/v) to yield III-115 as an amorphous solid (4.7 mg, 86%): Rₛ 0.54 (dichloromethane-MeOH, 10:1, v/v); [α]₂⁰ = +24° (c 0.4, MeOH); IR (neat): 3418, 2916, 2848, 1728, 1462, 1260, 1096, 900, 699 cm⁻¹; ¹H NMR (CD₃OD, 500 MHz): δ 7.33 (m, 10H), 5.81 (dd, J = 8.0, 15 Hz, 1H), 5.52 (dd, J = 7.0, 15.5 Hz, 1H), 5.27 (s, 1H), 5.17 (s, 1H), 5.00 (s, 1H), 4.76 (m, 2H), 4.58 (d, J = 12 Hz, 1H), 4.48 (d, J = 12 Hz, 1H), 4.03 (m, 3H), 3.89 (m, 1H), 3.74 (m, 3H), 3.61 (m, 2H), 3.17 (m, 2H), 2.33 (m, 1H), 2.01 (m, 3H), 1.90 (m, 7H), 1.74 (s, 3H), 1.62 (m, 6H), 1.55 (m, 6H), 1.40 (m, 5H), 1.25 (s, 3H), 1.08 (d, J = 6.5 Hz, 3H), 0.96 (d, 3H), 0.91 (d, 3H); ¹³C NMR (CD₃OD, 125 MHz): δ 144.7, 139.4, 139.4, 135.3, 134.2, 128.9, 128.8, 128.8, 128.7, 128.3, 128.2, 123.3, 111.4, 96.6, 85.0, 81.3, 80.0, 77.9, 76.3, 75.4, 74.1, 72.1, 68.7, 65.7, 61.0, 45.7, 42.4, 36.6, 36.3, 34.2, 33.9, 33.7, 31.7, 30.8, 29.0, 28.3, 27.0, 26.2, 26.1, 24.7, 22.7, 19.3, 16.4, 16.1, 10.6; HRMS (ESI+) calcd for C₅₈H₈₃NaO₁₄ (M+Na)⁺ 1049.5573, found 1049.5535.
**Belizeanic Acid (III-93)**

To a stirred – 78 °C solution of **III-115** (3.8 mg, .0038 mmol) in THF (0.5 mL) under argon was added a solution of lithium di-tert-butylbiphenylide (0.95 mL, 0.19 mmol, 0.2 M in THF). The resulting solution was allowed to stir for 30 min at – 78 °C before it was quenched by saturated NH₄Cl solution. EtOAc was added, and the separated aqueous layers were extracted with EtOAc extensively due to the high polarity of the product, and the combined organic layers were washed with brine, and then dried over Na₂SO₄, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (dichloromethane-MeOH, 10:1, v/v) to yield **III-93** as an amorphous solid (2.3 mg, 74%): Rf 0.51 (dichloromethane-MeOH, 5:1, v/v); [α]₂⁰D = + 14° (c 0.1, MeOH); literature⁵⁷: [α]₂⁰D = + 2.7° (c 0.073, MeOH); IR (neat): 3418, 2931, 1732, 1598, 1374, 1076, 1002 cm⁻¹; ¹H NMR (CD₃OD, 500 MHz): δ 5.81 (dd, J = 8.0, 15 Hz, 1H), 5.51 (dd, J = 7.5, 15.5 Hz, 1H), 5.28 (s, 1H), 5.27 (t, J = 2.0 Hz, 1H), 5.00 (s, 1H), 4.08 (m, 3H), 3.92 (m, 3H), 3.73 (m, 3H), 3.63 (m, 1H), 3.52 (m, 1H), 3.37 (m, 1H), 3.03 (t, J = 9.0 Hz, 1H), 2.33 (m, 1H), 1.99 (m, 3H), 1.80 (m, 5H), 1.75 (s, 3H), 1.71 (m, 2H), 1.63 (m, 4H), 1.55 (m, 8H), 1.41 (m, 5H), 1.35 (s, 3H), 1.29 (m, 2H), 1.10 (d, J = 7.0 Hz, 3H), 1.06 (d, J = 6.5 Hz, 3H), 0.94 (d, J = 7.0 Hz, 3H); ¹³C NMR (CD₃OD, 125 MHz): δ 146.9, 139.4, 135.1, 134.1, 122.8, 110.4, 97.2, 96.6, 85.0, 78.1, 76.4, 75.0, 74.0, 73.3, 72.6, 72.0, 68.7, 66.3, 60.9, 45.6, 42.4, 36.6, 34.2, 33.8, 33.7, 33.1, 32.7, 31.8, 30.8, 30.3, 126
29.1, 28.3, 27.7, 27.2, 27.0, 26.3, 26.1, 22.7, 19.4, 16.5, 16.3, 10.7; HRMS (ESI+) calcd for C_{44}H_{72}NaO_{14} (M+Na)^+ 847.4814, found 847.4826.
List of References


(74) De Brabander *et al.* reported\(^6\) that a similar reaction gave a mixture of \textbf{III-35} and \textbf{III-36} with a ratio of 1:2.5, with still the [4,6] spiroketal as the major product.


(92) Pang, Y.; Forsyth, C. J. Unpublished results.


Appendix A: Selected NMR Spectra