Total Synthesis of Dinophysistoxin-2 and Its Analogues

DISSERTATION

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By

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Abstract

The thesis described here is synthetic effort towards marine natural PP1 and 2A inhibitor dinophysistoxin-2 (DTX-2) and its unnatural analogues. The first total synthesis of DTX-2 is completed here, which applies the previously developed coupling strategies and features a newly designed synthetic access to C1-C14 and C28-C38 segments. Sharpless Asymmetric Dihydroxylation (SAD) is applied to install the C2 stereochemistry, which gives unexpected diastereoselectivity and leads to the synthesis of 2-epi-DTX-2. 2-epi-DTX-2 exhibits greatly reduced potency towards PP1 and 2A, which indicated that the stereochemistry of C2 is crucial to the potency of DTX-2. To fully elucidate the structural basis of DTX-2’s inhibition to PP1 and 2A, a set of analogues is designed based upon preliminary SAR studies and X-ray crystal structure of DTX-2 bound to PP1 and 2A. C8 spiroketal moities of the shared 7-deoxy C1-C14 domain of DTX-2 is prepared via gold (I) catalyzed dehydro-spiroketalization process, which provides a rapid access to the designed analogues of DTX-2.
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Trygstad, T. M.; Pang, Y.; Forsyth, C. J. “Versatile synthesis of the C3-C14 domain of 7-
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Fields of Study

Major Field: Chemistry
# Table of Contents

Abstract .............................................................................................................................................. ii

Acknowledgement ............................................................................................................................... iii

Vita........................................................................................................................................................ iv

List of Tables ........................................................................................................................................ ix

List of Figures ....................................................................................................................................... x

List of Schemes ..................................................................................................................................... xi

List of Abbreviations ........................................................................................................................... xiii

Chapter 1: Introduction ......................................................................................................................... 1

1.1 Isolation and Structural Feature of Dinophysistoxin-2 ................................................................. 1

1.2 Biological Properties of DTX-2 ...................................................................................................... 2

1.3 Protein Serine/Threonine Phosphatase 1 and 2A .......................................................................... 4

1.4 X-ray Crystallography of OA Bound to PP1 and 2A ...................................................................... 4

1.5 DTX-2: Reduced Potency for PP2A Inhibition .............................................................................. 7

1.6 Previous Total Syntheses of Okadaic Acid ...................................................................................... 9

Chapter 2: Objective and Synthetic Strategy ....................................................................................... 16

2.1 Overall Project Objective ............................................................................................................... 16

2.2 Specific Objectives ....................................................................................................................... 16

Chapter 3: Total Synthesis of DTX-2 ................................................................................................. 18

3.1 Retrosynthetic Analysis of DTX-2 ............................................................................................... 18

3.2 Synthesis of C1-C14 Domain 63 ................................................................................................. 21
3.3 Construction of C2 Tertiary Hydroxyl Group via Sharpless Asymmetric Dihydroxylation and Synthesis of 64 .................................................................24
3.4 Synthesis of Bromide 65 ..................................................................................30
3.5 Construction of the Spiroketal Moiety in C15-C27 64 via Au(I) Catalysis ..........31
3.6 Model Studies upon the Construction of C14-C15 (E)-Alkene via Modified Julia Olefination ........................................................................................................32
3.7 Revised Synthetic Plan via Late-stage Au (I) Catalyzed Spiroketalization ........38
3.8 A 3rd Retrosynthesis towards DTX-2 Based on Our Previous Total Synthesis of OA .............................................................................................................41
3.9 Completion of the Total Synthesis of DTX-2 and 2-epi-DTX-2 .......................43
3.10 Inhibition of PP1 and PP2A by Synthetic DTX-2 (1) and 2-epi-DTX-1 (1a) ....47
3.11 Summary ........................................................................................................50
Chapter 4 Effort towards Designation and Synthesis of DTX-2 Analogues ............52
4.1 Designation and General Synthetic Plan of DTX-2 Analogues .......................52
4.2 Synthetic Plan of the Shared C1-C14 Domain of 7-deoxy DTX-2 Analogues ......55
4.3 Synthesis of C1-C14 Domain of 7-deoxy DTX-2 (171) via Au(I) Catalyzed Dehydro-spiroketalization Reaction ........................................................................57
4.4 Effort towards the Synthesis of 7-deoxy DTX-2 ..............................................62
4.5 Effort towards the Synthesis of C1-C14 Domain of DTX-2 .........................64
4.6 Summary ........................................................................................................65
References .............................................................................................................67
Appendix A: Experimental ....................................................................................77
Appendix B: NMR spectra

148
List of Tables

1.1 IC\textsubscript{50} (PP2A inhibition), LD\textsubscript{50} (ip, mouse) values for OA, DTX-1 and DTX-2, their ratios and 95% confidence intervals ........................................................................................................... 8

3.1 Model study towards modified Julia olefination ................................................................. 35

3.2 Model study towards modified Julia olefination between 134/135 and 130 ................. 37

3.3 Model studies of preparation of the precursor for gold catalyzed formation of C19 spiroketal of 1 ..................................................................................................................................................... 40

3.4 Calculated IC\textsubscript{50} values and relative potencies for natural OA (2), natural DTX-2 (Nat. 1), synthetic DTX-2 (Syn. 1), and synthetic 2-\textit{epi}-DTX-2 (1a) based on PP2A and PP1 inhibition ......................................................................................................................................................... 49

4.1 Okadaic acid derivatives inhibition to PP2A ........................................................................ 53
List of Figures

1.1 Structure of DTX-2 (1), OA (2), DTX-1 (3) and Originally Proposed 1 (4)..............1
1.2 Cyclic conformation of DTX-2 (1), OA (2) and DTX-1 (3).................................2
1.3 Ser/Thr hyperphosphorylation via activated PKC or inhibited PP1 and 2A ..........3
1.4 (A) Architecture of the PP1-OA complex with protein shown as ribbon representation;
(B) stereo representation of the active site of the PP1-OA complex .....................5
1.5 A schematic diagram describing the PP2A system........................................6
1.6 (A) Structural comparison of OA binding to PP2A (blue) and PP1 (yellow); (B) A
surface representation of OA binding to PP2A and PP1 .....................................7
1.7 Structures of DTX-1 and DTX-2 bound to the PP2A core enzyme ....................9
3.1 Anti-periplanar mode for the diastereoselectivity in converting 162 to 163 .........45
3.2 Inhibitory effects of natural OA (2), natural and synthetic DTX-2 (1), and synthetic 2-
epi-DTX-2 on (A) PP2A and (B) PP1 activity .....................................................48
3.3 Cyclic conformation of DTX-2 and proposed conformation of 2-epi-DTX-2 .........50
4.1 (A) Major interaction between PP1 and OA; (B) Major interaction between PP2A and
OA.......................................................................................................................54
4.2 Designed DTX-2 analogues with comparable bioactivities.............................55
4.3 Contrast of the synthetic efficiency of 211 and 216 .........................................66
List of Schemes

1.1 Retrosynthetic disconnection of three total syntheses of OA ........................................10
1.2 Isobe’s total synthesis of OA ..................................................................................11
1.3 Forsyth’s synthesis of C15-C38 domain of OA .....................................................12
1.4 Forsyth’s total synthesis of OA .............................................................................13
1.5 Ley’s total synthesis of OA ...................................................................................14
2.1 Mechanism of Au(I) catalyzed spiroketalization and its synthetic application ....18
3.1 Original retrosynthetic disconnection of DTX-2 (1) ..............................................20
3.2 Retrosynthesis of key intermediates 63, 64 and 65 ..............................................21
3.3 Synthetic access to lactone 67 ..............................................................................22
3.4 Synthetic access to alkyne 68 ..............................................................................23
3.5 Synthesis of C8 spiroketal in 63 ...........................................................................23
3.6 Empirical rules of SAD (left) and its application on substrate 63 .......................25
3.7 Previous applications of SAD on 1,1-disubstituted alkene ..............................26
3.8 Model studies of SAD on lactone 10 .................................................................27
3.9 Completion of synthesis of aldehyde 61 .............................................................29
3.10 Synthesis of bromide 65 ....................................................................................31
3.11 Synthesis of C15-C27 segment 112 .................................................................32
3.12 Mechanism of traditional (113-118) and modified Julia olefination (119-123) ..33
3.13 Preparation of sulfone 127 ................................................................................34
3.14 Synthesis of aldehyde 130 and sulfone 134/135 .............................................................. 36
3.15 Rationale to the unsuccessful modified Julia olefination ............................................. 38
3.16 2\textsuperscript{nd} retrosynthesis towards 1 via late-stage Au (I) catalyzed spiroketalization .... ... 38
3.17 Synthesis of C1-C17 domain 140 .................................................................................. 39
3.18 Rationale of side reactions between 111 and 140 ......................................................... 41
3.19 A third retrosynthetic disconnection of 1 ..................................................................... 42
3.20 Synthesis of aldehyde 157 .......................................................................................... 43
3.21 Synthesis of C15-C38 segment 156 ............................................................................. 44
3.22 Total synthesis of DTX-2 (1) ....................................................................................... 46
3.23 Total synthesis of 2-\textit{epi}-DTX-2 (1a) ......................................................................... 47
4.1 Retrosynthesis of DTX-2 analogues ............................................................................. 55
4.2 Previous synthesis of C7 spiroketal in 7-deoxy OA ..................................................... 56
4.3 Synthetic plan towards 171 ......................................................................................... 57
4.4 Synthesis of methyl ketone 182 .................................................................................. 58
4.5 Synthesis of 180a and 180b (Left); TLC of 191a and 191b (Right) ......................... 59
4.6 Determination of the absolute stereochemistry of 180a and 180b ...................... 60
4.7 Synthesis of 179 Au (I) catalyzed dehydro-spiroketalization .................................. 61
4.8 Proposed spiroketalization mechanism ................................................................. 62
4.9 Synthesis toward 7-deoxy DTX-2 ............................................................................. 63
4.10 Synthesis of 211 ...................................................................................................... 64
4.11 Synthetic effort towards 63 via Au (I) catalyzed dehydro-spiroketalization .......... 65
## List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>[α]</td>
<td>specific rotation</td>
</tr>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>BAIB</td>
<td>bis(acetoxy)iodobenzene</td>
</tr>
<tr>
<td>Br</td>
<td>broad (NMR)</td>
</tr>
<tr>
<td>brsm</td>
<td>Based on recovered starting materials</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>°C</td>
<td>degree Celsius</td>
</tr>
<tr>
<td>CBS</td>
<td>Corey-Bakshi-Shibata</td>
</tr>
<tr>
<td>CSA</td>
<td>10-camphorsulphonic acid</td>
</tr>
<tr>
<td>d</td>
<td>doublet (NMR); day(s)</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DIBAL</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(N,N-dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>EE</td>
<td>ethoxyethyl</td>
</tr>
<tr>
<td>ESI</td>
<td>electron spray ionization (MS)</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>g</td>
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<td>h</td>
<td>hour(s)</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectroscopy</td>
</tr>
<tr>
<td>HWE</td>
<td>Horner-Wadsworth-Emmons</td>
</tr>
<tr>
<td>i-</td>
<td>iso-</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant in Hz (NMR)</td>
</tr>
<tr>
<td>KHMDS</td>
<td>potassium hexamethyldisilazide</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>m</td>
<td>mili; multiplet (NMR)</td>
</tr>
<tr>
<td>M</td>
<td>molar</td>
</tr>
<tr>
<td>mCPBA</td>
<td><em>meta</em>-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MHz</td>
<td>megahertz</td>
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</tr>
<tr>
<td>mol</td>
<td>mole(s)</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectroscopy; molecular sieves</td>
</tr>
<tr>
<td>NaHMDS</td>
<td>sodium hexamethyldisilazide</td>
</tr>
<tr>
<td>NMO</td>
<td>4-methylmorpholine <em>N</em>-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>OA</td>
<td>okadaic acid</td>
</tr>
<tr>
<td>PP1</td>
<td>protein phosphatase 1</td>
</tr>
<tr>
<td>PP2A</td>
<td>protein phosphatase 2A</td>
</tr>
</tbody>
</table>
Ph  phenyl
PMB  para-methoxybenzyl
PMP  para-methoxyphenyl
Py  pyridine
q  quartet (NMR)
$R_f$  retention factor
s  singlet (NMR); second(s)
SAD  Sharpless Asymmetric Dihydroxylation
s-Bu  sec-butyl
$t$  tertiary
TBAF  tetrabutylammonium fluoride
TBAI  tetrabutylammonium iodide
TBDPS  $t$-butyldiphenylsilyl
TBS  $t$-butyldimethylsilyl
TES  triethylsilyl
TEMPO  (2,2,6,6-tetramethylpiperidin-1-yl)oxyl
THF  tetrahydrofuran
TLC  thin layer chromatography
TMS  trimethylsilyl
Ts  $p$-toluenesulfonyl
TsOH  $p$-toluenesulfonic acid
Chapter 1. Introduction

1.1 Isolation and Structural Feature of Dinophysistoxin-2

Dinophysistoxin-2 (DTX-2, 1) was polyketide algal toxin that was separated from extracts of poisoned mussels feeding on dinoflagellates of the genus Dinophysis in southwest Ireland. After the original report of the structure of DTX-2, it was assorted as an analogue of early discovered marine natural products okadaic acid (OA, 2) and dinophysistoxin-1 (DTX-1, 3). (Figure 1)

Figure 1. Structure of DTX-2 (1), OA (2), DTX-1 (3) and Originally Proposed 1 (4)

The structure of DTX-2 was later falsely revised to 4 (Figure 1.1) based upon the fact that the 35-Me in DTX-1 was also reported to show similar NOE correlations as those observed for DTX-2, indicating 1 and 3 should both have possessed (35R)-methyl group. However, after extensive NMR analyses on OA, DTX-1 and -2, Larsen et al finally deduced that the absolute stereochemistry of C35 in DTX-2 is (S) and is contrary to that in DTX-1. This deduction was further substantiated by the synthetic studies and NMR analyses of terminal spiroketal domain of DTX-2.
Except for the substituent on C31 and C35, 1-3 shares the same skeleton composed of 38 contiguous carbon atoms. Among the skeleton of 1-3 are 23 functionalized carbons that include 17 stereogenic centers, one carboxylic acid (C1), one trans-alkene (C14-C15) and three anomeric effect favored spiroketal moieties (C8, C19 and C35). These functionalities contribute to a cyclic conformation of DTX-2, which is demonstrated by both X-ray crystallography and extensive NMR either in the solid state or in solution. (Figure 1.2)\textsuperscript{7} This pseudomacrolide conformation of DTX-2 was further stabilized by intramolecular hydrogen bonding between C1 carboxylic acid and C24 hydroxyl group, and the one between C2 hydroxyl and C4 tetrahydropyran oxygen.

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{figure12.png}
\caption{Cyclic conformation of DTX-2 (1), OA (2) and DTX-1 (3)}
\end{figure}

1.2 Biological Properties of DTX-2

DTX-2 and its naturally occurred analogues are toxic. Digestion of shellfish contaminated by DTX-2 type compounds leads to diarrhetic shellfish poisoning (DSP), a type of food poisoning that induces nausea, vomiting and cramp.\textsuperscript{8} DSP has become a world wide hazard to human health, especially to people who eat shellfish as daily diet. During 1970s
and 1980s, more than ten thousand cases of DSP were reported in coastal countries of Asia, Europe and South America, which attracted public awareness in the detection of DSP toxins and related research.

In addition, Sугanuma and co-workers reported that OA, an analogue of DTX-2, is a non-phorbal type of tumor promoter. Their research showed that cancerous tumor growth was promoted by OA on the mouse skin after preliminary treatment with mutagens. The reason of the proliferation of the tumor cells was originally ascribed as the phorbal ester activation of protein kinase C (PKC) leading to hyperphosphorylation of key signaling proteins involved in cellular growth; however, Sугanuma’s studies excluded this possibility. In parallel with Sуганuma’s research, Bialojan and Takai discovered OA’s role as a strong inhibitor of protein phosphotase 1 and 2A (PP1 and PP2A), enzymes that have complementary activity of PKC. Later studies supported the hypothesis that the tumor growth promoted by OA was due to OA’s inhibition of PP1 and PP2A, which resulted in hyperphosphorylation equivalent to that caused by activated PKC (Figure 1.3). Because of resemblance of OA, DTX-1 and DTX-2, all of the three natural products are considered as tumor inducers.

![Figure 1.3](image_url) Ser/Thr hyperphosphorylation via activated PKC or inhibited PP1 and 2A
1.3 Protein Serine/Threonine Phosphatase 1 and 2A

Protein serine/threonine phosphatase (PPase) is a type of enzyme that catalyzing the hydrolysis of phosphorylated serine and threonine residues into a phosphate ion and serine and threonine with a free hydroxyl group. (Figure 1.3) The function of PPase is opposite to kinases and phosphorylases, which attach phosphate group on the substrate under the assistance of energetic molecules such as ATP. PPase presents in all eukaryotic cells and are important to the control of glycogen metabolism, muscle contraction, cell progression, neuronal activities, splicing of RNA, mitosis, cell division, apoptosis, protein synthesis, and regulation of membrane receptors and channels.

The biological function of PPase can be inhibited when binding DTX-2 type analogues (1-3, Figure 1). Takai and co-workers first reported OA’s selective inhibition of PP2A ($K_i = 30 \text{ pM}$) over PP1 ($K_i = 145 \text{ nM}$). Their research also showed that OA only weakly inhibits PP2B and does not inhibit PP2C. Compared to OA, DTX-1 and -2 also exhibit similar selectivity in the inhibition of PP2A over PP1. Although PP1 and PP2A are similar in size (37 and 36 kDa, respectively), they only share 49% amino acid sequence identity, which may account for their different affinity to DTX-2 type compounds.

1.4 X-ray Crystallography of OA Bound to PP1 and 2A

In 2001, James et al reported the crystal structure of OA bound to PP1 to a resolution of 1.9 Å. In the PP1-OA complex, PP1 presents three grooves (hydrophobic, C-terminal and acid) on its surface, among which lies the molecule of OA. When binding with PP1,
OA keeps its pseudomacrolide conformation stabilized by intramolecular hydrogen bonding between C1 carboxylate and C24 hydroxy group, which is the same as OA’s conformation in solid state and solution. (Figure 1.4A)

The crucial interactions between PP1 and OA can be classified as two types: hydrophobic interaction and hydrogen bonding. Trp-206 and Ile-133 in the hydrophobic groove are considered to have important interaction with the lipophilic tail of OA; whereas the C4 to C16 region of OA also exhibits hydrophobic interaction with PP1 residues Phe-276 and Val-250. On the other hand, the conserved acidic motif of OA accepts a hydrogen bond from the hydroxyl group of Tyr-272. Other hydrogen bonding interactions occur between Arg-96 and the C-2 hydroxyl of the inhibitor and between Arg-221 and the C-24 hydroxyl group of OA. (Figure 1.4B)

Figure 1.4 (A) Architecture of the PP1-OA complex with protein shown as ribbon representation; (B) stereo representation of the active site of the PP1-OA complex
In 2006, Shi and co-workers reported the co-crystal structure of OA bound to PP1 with a resolution of 2.6 Å\textsuperscript{18}. In PP2A-OA complex, the catalytic C subunit in PP2A core enzyme provides a similar active site as PP1 for binding OA, which prevents regulatory B subunit from binding with PP2A core enzyme and inhibits the normal dephosphorylation function of PP2A. (Figure 1.5) The co-crystal structure also demonstrated that both the protein and OA adopt conformation resemble to their individual solid-state structure.

![Figure 1.5 A schematic diagram describing the PP2A system. A, B, C, and OA denote the scaffolding subunit, regulatory subunit, catalytic subunit, and okadaic acid, respectively.](image)

The selective inhibition of okadaic acid to PP2A over PP1 was also rationalized by comparison of the crystal structure of OA-PP1 and OA-PP2A complexes. (Figure 1.6) Although many residues on PP2A active site that specifically recognize OA are conserved in PP1, the hydrophobic cage in the catalytic subunit of PP2A that accommodates the hydrophobic tail of OA is absent in PP1 (Figure 1.6A). By contrast the structure of OA bound to PP2A and PP1, His191, which contributes to one side of the hydrophobic cage of PP2A was replaced by Asp197 that is located further away from OA (Figure 1.6A). In addition, Gln122 of PP2A, whose aliphatic side chain contributes to another side of the hydrophobic cage, is replaced by Ser129 in PP1, leading to much diminished
capacity in mediating van der Waals interaction (Figure 1.6A). These substitutions of PP1 result in an open-ended groove, whereas PP2A contains a closed hydrophobic pocket that is more fitted in by the lipophilic tail of OA, leading to a better affinity to OA. (Figure 1.6B)

**Figure 1.6** (A) Structural comparison of OA binding to PP2A (blue) and PP1 (yellow); (B) A surface representation of OA binding to PP2A and PP1

### 1.5 DTX-2: Reduced Potency for PP2A Inhibition

Recently, DTX-2 was proved to be significantly less toxic in a mouse bioassay and was considered to be a weaker inhibitor of PP2A compared to OA and DTX-1. (Table 1.1)\(^9\) The reduced potency of DTX-2 resulted in the re-consideration of the stereochemistry of C35 in DTX-2 that was finally determined to be contrary to DTX-1 by extensive NMR comparisons among OA, DTX-1 and DTX-2.\(^5\) Molecular modeling of the docking of OA, DTX-1 and DTX-2 with the crystal structure of PP1 and PP2A predicted that the
reduced affinity of DTX-2 for PP2A might be due to axially oriented methyl on C35 that would show unfavorable interaction with His191 and Gln121 residues in the catalytic subunit of PP2A.

<table>
<thead>
<tr>
<th></th>
<th>IC$_{50}$ (ng/mL)</th>
<th>95% confidence interval</th>
<th>LD$_{50}$ (µg/kg)</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>OA (1)</td>
<td>2.87</td>
<td>2.51-3.27</td>
<td>194</td>
<td>141-266</td>
</tr>
<tr>
<td>DTX-2 (3)</td>
<td>5.96</td>
<td>5.42-6.55</td>
<td>364</td>
<td>290-456</td>
</tr>
<tr>
<td>Ratio OA/DTX-2 (%)</td>
<td>48</td>
<td>40-56</td>
<td>53</td>
<td>33-73</td>
</tr>
</tbody>
</table>

Table 1.1 IC$_{50}$ (PP2A inhibition), LD$_{50}$ (ip, mouse) values for OA, DTX-1 and DTX-2, their ratios and 95% confidence intervals.

The X-ray crystal structures of OA, DTX-1 and DTX-2 bound to PP2A provide an explanation for their relative affinities. All of the three natural toxins bound to the same surface pocket on the active site of the catalytic subunit Cα, and interactions between the toxins and Cα are very similar to each other. However, the methyl groups on C35 of DTX-1 and DTX-2 lead to the rearrangement of the hydrophobic pocket on Cα. The equatorial 35-methyl group of DTX-1 is angled away from Cα, and is partially buried upon binding. (Figure 1.7A, C) In contrast, the axial 35-methyl group of DTX-2 leads to steric clash between DTX-2 and His191 in the hydrophobic cage of Cα active site. (Figure 1.7B, D) The side chain of His191 is pushed away from the binding pocket and the
distance between Gln122 and His191 increases from 3.97 Å (PP1-DTX-1 complex) to 7.60 Å in the DTX-2 structure, which weakens the structural integrity of the hydrophobic cage. The open ended hydrophobic cage and the energy cost of displacing His191 would be expected to lead to a reduced toxicity and affinity of PP2A for DTX-2.

Figure 1.7 Structures of DTX-1 and DTX-2 bound to the PP2A core enzyme. (A) DTX-1 and (B) DTX-2 bound to the core enzyme. Magnified cartoon representations are shown of DTX-1 (C) and DTX-2 (D) in the hydrophobic cage of the binding site.

1.6 Previous Total Syntheses of Okadaic Acid

Because of their structural complexity and intriguing biological potencies, synthetic studies towards DTX-2, OA and DTX-2 have attracted interests from organic chemists. Among the three natural products, okadaic acid is the only molecule that has been totally synthesized. So far, three total syntheses towards okadaic acid has been completed.\textsuperscript{21-23} Surprisingly, all of the three total syntheses broke the skeleton of OA into three segments with comparable complexities. (Scheme 1.1)
In 1986, Isobe and co-workers completed the first total synthesis of OA with an overall yield of 0.01% through 54 steps in the longest linear sequence.\textsuperscript{21, 24-27} Their synthetic strategy features the application of sulfone chemistry to assemble the segments together. They successfully synthesized C15-C38 domain domain $^{15}$ through a three-step sequence: sulfonyl carbanion $^{14}$ was first added to aldehyde $^{13}$ followed by the oxidation of the resulting secondary alcohol and finally reductive removal of the sulfonyl group to afford ketone $^{15}$ that was converted to aldehyde $^{16}$ via a 7-step sequence. (Scheme 1.2)
To install the tertiary hydroxyl group on C2 of 2, Isobe et al applied a substrate chelation controlled hydroxymercurcation-demercuration process on 17 to prepare diol 18 that was then converted to lactone 19. Lactone 19 was opened by lithium acetylide generated from 20 to afford 21 that was then treated with MeLi and CuI to prepare (Z) and (E) enone 22. Acid-catalyzed removal of the ethoxyethyl group in 22 followed by spontaneous cyclization, lead to the formation of C8 spiroketal moiety in 23. Julia olefination was then applied to join 23 and 16 to afford 24 that was finally converted to OA (2) in four more steps. (Scheme 1.2)
In 1997, Forsyth et al developed an efficient and flexible total synthesis that is applicable to the preparation of an array of non-natural analogues of OA. Forsyth’s synthetic strategy provided significant improvement over previous work with fewer steps (26 steps in the longest linear sequence) and increased overall yield (1.7%).

Forsyth’s total synthesis started with glucose derivative in which the stereochemistry of C23 and C24 was converted via a two-step sequence: formation of exopoxide followed its regio-selective opening by BnONa. Aldehyde, representing the C15-C27 domain of OA and prepared from via steps sequence, then joined with organocerium reagent generated from bromide to afford. 30 was then converted to C15-C38 domain through five more steps. (Scheme 1.3)

Scheme 1.3 Forsyth’s synthesis of C15-C38 domain of OA.

The synthesis of C1-C14 fragment started with aldehyde in which the spiroketal moiety was assembled via using acid catalyzed cyclization that was similar to Isobe’s
method. The stereochemistry was installed by aldol reaction between Seebach’s lactate\(^{29}\) 32 and 33 followed by treatment of the product with Barton deoxygenation.\(^{30}\) The resultant 35 was converted to 36 upon the cleavage of PMB ether followed by Dess–Martin oxidation. 31 and 36 was then coupled via Horner-Wadsworth-Emmons reaction and the resultant enone was diastereoselectively reduced to allylic alcohol 38. The subsequent acid induced cyclization afforded C19 spiroketal in 39 that was finally converted to OA via a sequence of saponification and global debenzylolation. (Scheme 1.4)\(^{31}\)

**Scheme 1.4** Forsyth’s total synthesis of OA.

Ley’s total synthesis towards okadaic acid highlighted the methodology developed in his research group, such as the application of idiosyncratic diphenyl tetraoxadispiroketal
to install the stereochemistry of C2 and to protect α–hydroxy acid in 45.\textsuperscript{23} To couple the key intermediates, 41 was transmethylated to aluminum acetylide that was added to oxo-carbenium generated from sulfone 40. The resulting alkyne 42 was then converted to 43 via hydroboration-reduction sequence. The C15-C38 key intermediate 44, prepared from 43, was coupled with 45 to build the skeleton of OA through modified Julia olefination. The resultant 46 was finally converted to OA after manipulation of protecting groups. The synthetic track expanded in longest linear sequence of 24 steps with an overall yield of 1%.

Scheme 1.5 Ley’s total synthesis of OA.

Although the three total syntheses of OA shared similar tri-component strategy, they differed in their coupling method to build the skeleton of OA. Isobe and Ley pre-installed
the spiroketal moieties on C8, C19 and C34 before joining key intermediates together via sulfone chemistry; whereas Forsyth applied mild HWE reaction, leading to late stage construction of C19 spiroketal. The precedent synthetic studies towards OA provided sources and references in the synthesis of natural DTX-2 and designation of unnatural OA analogues.
Chapter 2. Objective and Synthetic Strategy

2.1 Overall Project Objective

The overall objective of this project is to define the structural basis of DTX-2 type toxin’s potent and selective inhibition to protein phosphotases. The reduced potency of DTX-2 towards PP2A indicates that structure amendment of the tail domain plays an important role in its potency, which makes this molecule as an important biomedical tool to fully elucidate the function of protein phosphotases. However, the limited natural resource\(^1\) of DTX-2 restricted related research, which make chemical synthesis a necessary access to this natural product.

A reliable total synthesis also benefits the designation of unnatural DTX-2 analogues. We aim to find an analogue of DTX-2 that selectively inhibits PP1 over PP2A in order to detect the difference in the structural basis of inhibition to PP1 and PP2A. Besides, recent studies showed that inhibition of PP2A led to proliferation of cells and promoted tumor growth\(^9\), which indicated that PP2A regulates the cell mitosis and is considered as a tumor suppressor. Designation of unnatural DTX-2 analogue that selectively inhibit PP1 may contribute to a better understanding of cell regulation by protein phosphotases, which underlies the anti-cancer leads.

2.2 Specific Objectives

The goal of this thesis research project was to develop an efficient and scalable total synthesis of DTX-2. The great resemblance of DTX-2 and OA allowed us to construct
the skeleton of DTX-2 by referring the previous synthesis of OA. However, careful examination of previously reported syntheses of the C1-C14 domains (23, Scheme 1.2; 36, Scheme 1.4; 45, Scheme 1.5) of OA suggested that the synthetic strategies towards this fragment alone might be dramatically improved. All of the previous OA syntheses take more than fifteen steps to construct C1-C14 domain by starting with highly functionalized compounds such as D-2-acetoxy-triacetylglucal, so the newly developed synthetic track towards C1-C14 domain of DTX-2 was planned to use simple commercial available compounds as starting materials. Additionally, optimization of reactions with modest yield and selectivity, such as the one applied Seebach’s lactate to construct the stereo center of C2, was also desired. (Scheme 1.4) Thus, the first specific objective of this research project was to develop an efficient synthesis of C1-C14 domain of DTX-2 to enhance synthetic access to DTX-2 and its unnatural analogues.

Besides an improved synthesis of C1-C14 domain, a newly developed methodology that apply AuCl to construct dioxaspiro[4.5]decane was planned to incorporate into the synthesis of DTX-2.32,33 This type of catalysis is based on the coordination between Au(I) and alkyne. (Scheme 2.1) Mechanically, Au(I) activated alkyne in 47 was first attacked by hydroxyl group to form enol ether 48. Under the catalysis of weak acid, 48 isomerized to oxocarbenium (49) that was attacked by a second hydroxyl group intramolecularly to afford dioxaspiro[4.5]decane 50. The successful applications in the synthesis of ABCD rings of azaspiracid (52)34 and spiroketal moiety of ushikulide A (54)35 provided an alternative access to the spiroketal moiety on C19 of DTX-2, which might shorten synthetic sequence of DTX-2.
One set of analogues of DTX-2 would be designed to probe the role of the lipophilic tail (C28-C38) in inhibition of PP1/2A, based on the X-ray crystal structure of OA/DTX-2 binding to PP1/2A.\textsuperscript{17,18} Previous SAR studies\textsuperscript{5,20} indicated that the substituent on tail domain may adjust or even reverse the selectivity of DTX-2’s inhibition to PP1/2A, which is anticipated that a reliable and efficient total synthesis would benefit the preparation of a series of rationally designed analogues of DTX-2. Moreover, structural alternation of DTX-2 may allow the application of newly developed methodology, leading to a faster access to the designed analogues.

\textbf{Scheme 2.1} Mechanism of Au(I) catalyzed spiroketalization and its synthetic application
Chapter 3. Total Synthesis of DTX-2

3.1 Retrosynthetic Analysis of DTX-2

Our initial synthetic plan towards DTX-2 (1) was proposed as Scheme 3.1. In order to facilitate its application to analogue synthesis, we plan to minimize the number of transformations required to prepare each fragment, to install a maximal degree of functionality into each advanced synthetic intermediate so as to minimize the extent of post coupling transformations and to utilize chemoselective reactions to couple the fragments.

We planned to install the carboxylic acid moiety on C1 of 1 at late stage of the total synthesis by oxidation of primary hydroxyl group of 60. 60 would be disconnected at C14-C15 double bond into two segments: aldehyde 61 that representing C1-C14 domain and sulfone 62 that representing C15-C38 domain. The two key intermediates would be coupled via Julia-Kocienski olefination\textsuperscript{36} to construct the (E)-C14-C15 alkene in 60. The C1-C2 vicinal diol that protected as acetonide in 61 came from asymmetric dihydroxylation on intermediate 63, after the construction of C8 spiroketal moiety. Further retrosynthetic dissection would cleave 62 at C27-C28 carbon-carbon bond into aldehyde 64 and bromide 65. Aldehyde 64 represents the central core of 1–3, whereas 65 is unique to 1 in its methyl substitution at C35. Ideally, a direct coupling of aldehyde 64 with an unstabilized primary carbanion derived from 65 would generate the C27 carbinol and construct the back bone of 62 based upon the strategy optimized in the synthesis of OA.\textsuperscript{22,28}
Scheme 3.1 Original retrosynthetic disconnection of DTX-2 (1)

Synthesis of the three key intermediates involved the construction of spiroketal moieties in each segment. Based on their structural features, 63, 64 and 65 were designed to be prepared via three different methods. Based on previous synthesis of OA, the 1,7-dioxaspiro[5.5]undec-4-ene system in 63 would be generated from enone 66 that was treated with weak acid to cleave the silyl ethers and initiate the cyclization.\(^{31}\) In turn, 66 was derived from the opening of lactone 67 with the acetylide derived from alkyne 68. Aldehyde 64, representing C15-C27 domain of 1, would be prepared from 25, 27-diol 69 in which dioxaspiro[4.5]decane system was installed by treating alkyne 70 with AuCl. The spiroketal on C34 would form spontaneously from the triol generated by hydrogenation.
tion of the tris-benzyl ether 71 produced by joining of aldehyde 72 and β-ketophosphonate 73 via Horner-Wadsworth-Emmons reaction.

Scheme 3.2 Retrosynthesis of key intermediates 63, 64 and 65

3.2 Synthesis of C1-C14 Domain 63.

Synthesis of 64 started with (R)-glycidolyl PMB ether (74) in which the stereocenter represented C8 of 1. The epoxide in 74 was regioselectively opened by allyl magnesium bromide to afford 75, in which the resultant secondary hydroxyl group was then protected as benzyl ether. (Scheme 3.3) Ozonolysis followed by reductive work-up would afford
aldehyde 76. Keck methallylation\textsuperscript{37} of 76 installed stereogenic center of 3 in homoallylic alcohol 77 with almost quantitative yield and modest diastereoselectivity. The PMB ether of 77 was cleaved to generate 1,5-diol 15, which was oxidatively lactonized to 67 with TEMPO and BAIB.\textsuperscript{38}

\begin{align*}
\text{Scheme 3.3} & \text{ Synthetic access to lactone 67} \\
\end{align*}

Access to the coupling partner 68 of lactone 67 began with the mono-protected trans-2-buten-1,4-diol (79) that first underwent Sharpless Asymmetric Epoxidation\textsuperscript{39} to install the stereochemistry of C13 in 1. (Scheme 3.4) The resultant epoxide was then regioselectively opened by AlMe\textsubscript{3} in hexanes-CH\textsubscript{2}Cl\textsubscript{2} co-solvent to afford 1,2-diol 81.\textsuperscript{40} De-protonation followed by treatment with N-tosyl imidazole chemoselectively tosylated primary alcohol in 81 and the remaining secondary oxide anion intramolecularly replaced the newly generated tosylate to afford terminal epoxide 82.\textsuperscript{41} 82 was then opened from the less hindered site by lithium acetylide generated by treatment of TMS-acetylene with n-BuLi. TMS group in the resultant alcohol 83 was removed under basic condition and the hydroxyl group was silylated as TES ether.
Scheme 3.4 Synthetic access to alkyne 68

The newly devised synthesis of the C1-C14 domain 63 continued with opening of lactone 67 with the lithium acetylide generated from 68 to give ynone 84 that equilibrated with a semi-ketal conformation 85. (Scheme 3.5) C4 hydroxyl group in ynone format 84 could be protected by slow addition of TESCl. After silylation of the C4 alcohol, conjugate addition of methylcuprate installed the methyl group at C19 to afford E/Z-mixture of enones 86. Cleavage of the silyl ethers and spiroketalization using PPTS in CH2Cl2 and methanol yielded thermodynamically favored 63.

Scheme 3.5 Synthesis of C8 spiroketal in 63
3.3 Construction of C2 Tertiary Hydroxyl Group via Sharpless Asymmetric Dihydroxylation and Synthesis of 64

Our original synthesis of OA (2) utilized Seebach’s lactate pivalidene acetal (32) as the source of the C1-C2 α-hydroxy, α-methyl carboxylic acid (Scheme 1.4). Attempts to imbed this moiety within the okadaic acid intermediate 35 via late-stage alkylation at C2 of the lactate pivalidene enolate with C3 halides or sulfonates were uniformly unsuccessful. Instead, an aldol reaction was used with a C3 aldehyde (33) for C2-C3 bond formation. The facial selectivity of enolate addition was modest (2:1) and a subsequent Barton deoxygenation of the C3 alcohols (34) was required to complete the task. Thus, the combined yield was ca. 46% for forming the C1-C14 intermediate 35 from 33 and 34.

An alternative strategy was adopted for the early incorporation of the α-hydroxy, α-methyl carboxylate moiety in 1. This involved targeting spiroketal 61 (Scheme 3.1), the masked vicinal diol of which could be ultimately oxidized into the α-hydroxy carboxylic acid of 1. In the seminal total synthesis of 2, Isobe et al. installed the core vicinal diol of 19 (Scheme 1.2) via a substrate chelation controlled hydroxymercuriation process using a C2-C3 alkene. Since then, reagent controlled Sharpless asymmetric dihydroxylation (SAD) has been well established to provided reliable and empirically predictable facial selective vicinal dihydroxylations of alkenes.

We aimed to apply the SAD process with the C1-C2 alkene of 63 en route to 61. The facial selectivity by using commercial available AD-mix has been previously summarized by Sharpless. (Scheme 3.6) If 1,1-disubstituted alkenes served as substrates and were
placed as in Scheme 3.6, AD-mix-β tended to dihydroxylize the double bond from the top face whereas AD-mix-α dihydroxylized the double bond from the bottom face. In this case, to asymmetrically construct the vicinal diol in 87, 63 was originally proposed to be treated with AD-mix-β according to Sharpless’ empirical rules.

Scheme 3.6 Empirical rules of SAD (left) and its application on substrate 63

The structural complexity of 63 might contribute to the question about diastereoselectivity of SAD, though previous applications of SAD with terminal unsymmetrical disubstituted alkenes gives high yield and acceptable stereoselectivity. (Scheme 3.7)\textsuperscript{43, 44} In this context, SAD that use lactone 67 and its derivatives as substrates was introduced for model study.
Scheme 3.7 Previous applications of SAD on 1,1-disubstituted alkene

SAD was originally applied to 67 but undesired saponification occurred under the basic conditions because of the K$_2$CO$_3$ component of AD-mix. To buffer the basicity, three equivalence of NaHCO$_3$ was added besides AD-mix-β, but the condition was still too basic to keep the lactone untouched. Alternatively, lactone 67 was converted into mixed acetal 95 via a reduction–silylation sequence. (Scheme 3.8)
Scheme 3.8 Model studies of SAD on lactone 10

Application of AD-mix-β dihydroxylation on 95 generated the vicinal primary-tertiary diol 96 and its epimer 97 with an overall yield of 91%. 96 and 97 could be separated via column chromatography, indicating the conversion from 95 to 96 exhibited a diastereoselectivity of 9:1. It was anticipated that diol 97 would be the major diastereomer according to Sharpless’ empirical rules. However, after converting the major diol diastereomer 96 into the corresponding δ-lactone 98, it was found that the SAD reaction had given the opposite diastereoselectivity. This was determined by comparison of spectral data of 98 with those obtained previously by Isobe et al. The SAD was repeated with 95 but using AD-mix-α, which inverted the sense of diastereoselectivity to give a
3:1 diastereomeric ratio of diols 97 and 96, respectively. The major diastereomer was converted into a lactone (99) as before (Scheme 3.8). As a control reaction to probe potential inherent substrate bias, dihydroxylation of 95 using OsO$_4$ and pyridine-NMO in THF–H$_2$O was found to give a 1:1 ratio of diastereomeric diols in good yield.

The differential levels of diastereoselectivity with 95 and AD-mix-α versus AD-mix-β may represent mismatched versus matched diastereomeric transition states involving the pseudo-enantiomeric AD-mix ligands dihydroquinine and dihydroquinidine, respectively. The unexpected sense of diastereoselectivity in the SAD of 95 can be ascribed to the homoallylic tri-substituted oxane moiety reversing the π-facial selectivity generally predicted by the Sharpless empirical model for the AD-mix reagents. These results provide a caveat to the Sharpless’ empirical rules for the SAD facial selectivity with 95 and perhaps additional olefins of its type. Hale had reported modest levels of anomalous enantioselectivity in the SAD of achiral 1,1-disubstituted methyallyl alcohol derivatives.$^{45}$

Besides diastereoselectivity of SAD, chemoselectivity towards the two double bonds present in 63 arose as another problem. Compared with C1-C2 1,1-disubstituted alkene, C9-C10 double links to C8 spiroketal carbon, which decreased its electron density. It was anticipated that the relative electron-rich C1-C2 alkene would favor the electrophilic attack from Os (VIII) complex from AD-mix. Additionally, the bulky substitutions of C9-C10 alkene allowed little access of the large Os (VIII)-(DHQ)$_2$PHAL complex, whereas the less hindered C1-C2 terminal alkene might be dihydroxylized with a much faster rate. (Scheme 3.9)
Our prediction was confirmed by the result of treatment of AD-mix-α on 95. (Scheme 3.9) The major product 100 and its C2 epimer was prepared with a diastereomeric ratio of 3 : 1 and a combined yield of 95%; whereas products from dihydroxylation of C9-C10 alkene were not observed in this reaction. The two diastereomers were separable on flash chromatography and the major vicinal diol 100 was then protected as acetonide quantitatively. To complete the synthesis of 61, the PMB ether of 101 was oxidatively cleaved and the resultant primary alcohol was oxidized using the Dess-Martin periodinane reagent. This preparation of the C1-C14 domain shared by 1-3 was achieved in 13 linear steps and 15% overall yield from 74, which represents a significant improvement over our previous synthesis of the corresponding intermediate in 25 steps and 0.6% overall
yield from diethyl L-tartrate in the synthesis of 2. (15 % overall yield over 13 steps from 74).

3.4 Synthesis of Bromide 65

The synthesis of the C15-C38 domain 62 relied upon generation of the common central C15-C27 intermediate 64 and the unique C28-C38 bromide 65. The newly developed synthesis of the terminal C34 spiroketal domain of 1 necessarily deviated from those previous of 2.28 Whereas a Keck crotylation was used to set the vicinal C30 and C31 stereochemistry in our original synthesis of 2; the C29, C30, and C35 stereogenic centers in 1 were established reliably via Evans asymmetric aldol and alkylation processes. Imide 103, which was generated by auxiliary controlled α methylation of 102,48 provided access to the C33-C38 phosphonate 73 through a two-step sequence. (Scheme 3.10) On the other hand, the complementary C28-C32 aldehyde 72 was obtained from Evans’ aldol adduct 105.49 Reduction of 105 afforded a diol that was protected as bis-benzyl ether 105. The PMB ether of 105 was selectively cleaved and the resultant alcohol was oxidized to aldehyde 72. β-Ketophosphonate 73 was then coupled with 72.50 The resulting enone 71 was converted into the thermodynamically favored spiroketal 107 under a single reaction condition. Hydrogenation of 71 using Pearlman’s catalyst in ethanol saturated the alkene, cleaved the three benzyl ethers, and dehydratively spiroketalized the in situ generated keto-triol to 107 in 93% isolated yield. Thereafter, the residual alcohol was converted into bromide 65.51
3.5 Construction of the Spiroketal Moiety in C15-C27 64 via Au(I) Catalysis

The construction of C19 spiroketal was completed by my colleague Chao Fang. The synthesis started with \( \alpha-(D) \)-methyl glucopyranoside 108 that was converted to aldehyde 109 based upon our previous synthesis of 2. Treatment of aldehyde 109 with the Bestmann-Ohira reagent (8) and \( \text{K}_2\text{CO}_3 \) in methanol afforded terminal alkyne 9. \( \text{BF}_3 \)-mediated nucleophilic opening of epoxide 74 with the lithium acetylide generated from 111 followed by desilylation produced the diol 70. Treatment of spiroketalization precursor 70 with catalytic \( \text{AuCl} \) followed by \( p \)-toluenesulfonic acid in methanol constructed the C19 spiroketal and cleaved PMP acetal. The resultant diol 69 was converted to 112 via a 3-step sequence: selective silylation, oxidation and finally Wittig olefination.
Scheme 3.11 Synthesis of C15-C27 segment 112.

3.6 Model studies upon the construction of C14-C15 (E)-alkene via modified Julia olefination

Julia olefination is a reliable method to synthesize trans-1,2-disubstituted alkenes by starting with sulfonyl carbanion and aldehyde. The mechanism of this reaction involves the following steps: (1) nucleophilic addition of sulfonyl carbanion 113 to aldehyde 114; (2) esterification of the resultant alkoxide 115 and (3) elimination mediated Na-Hg. It is believed that the high E selectivity originates from the radical intermediate 117 that equilibrate to thermodynamically favored trans-alkene. (Scheme 3.12)

Compared to traditional method, modified Julia olefination replaced phenyl sulfoe with benzothiazole sulfoes, which avoids the use of poisonous Hg and greatly alters the reaction pathway. (Scheme 3.12) Unlike the phenyl sulfoes, the alkoxide intermediate 120 generated from 119 will transform to the sulfinate salt 122 via Smiles rearrangement.
122 will spontaneously eliminate sulfur dioxide and benzothiazolone producing the desired alkene 123. It is noticeable that the benzothiazole variation of the Julia olefination does not involve equilibrating intermediates. In this context, E/Z selectivity of this reaction is considered to be unpredictable.

Another variation of modified Julia olefination is Julia-Kocienski olefination in which tetrazole serves as alkylating reagent. It proceeds with the same mechanism as the benzothiazole sulfone above but gives better E/Z selectivity upon careful adjustment of reaction condition. In this context, it is necessary to manage a careful model study to optimize the reaction condition before applying modified Julia olefination to couple C1-C14 aldehyde 61 and C15-C38 sulfone 62 towards the total synthesis of 1.

We aimed to use C1-C14 aldehyde (61) and a sulfone (127, Scheme 3.13) representing C15-C27 segment of 1 to perform the model studies. It was anticipated that 127 could mimic the stereo-electronic properties of 62 and the optimized condition for the coupling

Scheme 3.12 Mechanism of traditional (113-118) and modified Julia olefination (119-123)
between 61 and 127 would be appropriate for joining 61 and 62. Sulfone 127 could be easily prepared from 112 via a three-step sequence. Oxidative cleavage of PMB ether in 112 afforded primary alcohol 124 that was then converted to thioether 126 via Mitsunobu reaction. Finally, 126 was oxidized to 1-phenyltetrazole sulfone 127 by using ammonium molybdate and hydrogen peroxide. Additionally, benzothiazole sulfone (128, Table 3.1) was also prepared via the same synthetic track.

Scheme 3.13 Preparation of sulfone 127

The detailed result concerning modified Julia olefination between sulfone 127/128 and aldehyde 61 was shown in Table 3.1. The general procedure involved deprotonation of sulfone 127/128 followed by treatment of aldehyde 61 to the resultant sulfonyl carbanion in different condition. It was noticeable that benzothiazole sulfone 128 was consumed upon the treatment of KHMDS and 61 in THF or DMF, but failed to give desired alkene 129 as a product. Replacement of 128 by 1-phenyltetrazole sulfone 127 led to the generation of a 1:2 mixture of E and Z isomers at C14-C15 double bonds of 129 with a combined yield of 15% to 30%. The two geometric isomers of 129 were not separable by
flash column chromatography or preparative TLC. The low yield and poor geometric selectivity indicated that 61 and 62 were not appropriate candidates in the construction of the skeleton of 1, leading to further investigation on the coupling strategies.

![Chemical structure](image)

<table>
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<th>Entry</th>
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<th>Condition</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BT</td>
<td>KHMDS, THF, -78 °C to 25 °C</td>
<td>Sulfone consumed, no 129 observed</td>
</tr>
<tr>
<td>2</td>
<td>BT</td>
<td>KHMDS, DMF, -60 °C to 25 °C</td>
<td>Sulfone consumed, no 129 observed</td>
</tr>
<tr>
<td>3</td>
<td>PT</td>
<td>NaHMDS, THF, -78 °C to 25 °C</td>
<td>15% yield, E/Z not determined</td>
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<tr>
<td>4</td>
<td>PT</td>
<td>KHMDS, THF, -78 °C to 25 °C</td>
<td>15% yield, E/Z not determined</td>
</tr>
<tr>
<td>5</td>
<td>PT</td>
<td>KHMDS, DMF, -60 °C to 25 °C</td>
<td>30% yield, E/Z = 1/2</td>
</tr>
<tr>
<td>6</td>
<td>PT</td>
<td>KHMDS, DME, -78 °C to 25 °C</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

Table 3.1 Model study towards modified Julia olefination (PT = 1-phenyltetrazole; BT = benzothiazole)

A character of Julia olefination is the exchangeable functionalities of aldehyde and sulfone, which means we can switch the roles of aldehyde and sulfone in Julia type olefinations without big change in the structure of the substrates. In this context, aldehyde 130 and sulfone 134/135, representing C15-C27 and C1-C14 domain of 1 respectively, were introduced into a second model study of modified Julia olefination. 130 could be easily
prepared from primary alcohol 124 via Parikh-Doering reaction.57 (Scheme 3.14) In turn, synthesis of 134/135 started with the oxidative cleavage of PMB ether in 101 and the resultant alcohol 131 was then converted to sulfones 134/135 via a Mitsunobu-oxidation sequence.

![Scheme 3.14 Synthesis of aldehyde 130 and sulfone 134/135.](image)

The representative results of modified Julia reaction between 134/135 and 130 were shown in Table 3.2. KHMDS followed by aldehyde 130 was treated with sulfones 134/135 in THF or DMF under different temperature. However, none of these conditions gave 129 as a product. 1-Phenyltetrazole sulfone 134 could be recovered after the reaction with 130, whereas benzothiazole sulfone 135 was consumed upon deprotonation by KHMDS.
Table 3.2 Model study towards modified Julia olefination between 134/135 and 130

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<th>Condition</th>
<th>Result</th>
</tr>
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<tbody>
<tr>
<td>1</td>
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<td>KHMDS, THF, -78 °C to 25 °C</td>
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<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>BT</td>
<td>KHMDS, THF, -78 °C to 25 °C</td>
<td>Sulfone consumed, no 129 observed</td>
</tr>
<tr>
<td>4</td>
<td>BT</td>
<td>KHMDS, DMF, -60 °C to 25 °C</td>
<td>Sulfone consumed, no 129 observed</td>
</tr>
</tbody>
</table>

The failure of modified Julia olefination between 134/135 and 130 might result from steric hindrance generated by di-substituted α-position of aldehyde 130. This hindrance prevented addition of sulfonyl carbanion 135 to aldehyde 130 and the desired product 129 was not accessible without the formation alkoxide intermediate 136. On the other hand, it was possible that sulfonyl carbanion generated 135 would have added to a second molecule and 135. The resultant adduct 137 would have transformed to byproduct 138 via an aromatization process, which might explain the solely consumption of benzothiazole sulfone in above model studies.
Scheme 3.15 Rationale to the unsuccessful modified Julia olefination

3.7 Revised Synthetic Plan via Late-stage Au (I) Catalyzed Spiroketalization

Scheme 3.16 2nd retrosynthesis towards 1 via late-stage Au (I) catalyzed spiroketalization
The unsuccessful application of modified Julia olefination as coupling strategy forced us to revise our synthetic plan. Based upon the successful Au(I) catalyzed construction of C19 spiroketal in C15-C27 domain of 1,\textsuperscript{52} a synthetic plan that would apply the same method as at late-stage of the total synthesis was proposed in Scheme 3.16. C19 spiroketal in 1 would be build after the assembly of all the skeleton carbons by treating alkyn-diol 139 with Au (I) salt. 139 would be bisected at C17-C18 carbon-carbon bond into epoxide 140 and terminal alkyne 141. The two segments would be joined via Lewis acid mediated opening of oxirane in 140 by lithium acetylide generated from 141.

The revised synthetic plan could utilize the prepared intermediates in previous studies towards 1. Synthesis of epoxide 140 started with aldehyde 61, which reacted with phosphonate 142 to give enone 143. Asymmetric reduction of 143 catalyzed by (-)-CBS catalyst to afford allylic alcohol 144. TBS group in 144 was then removed and the resultant 16,17-diol was converted to epoxide 140 under the treatment of NaH and \(N\)-tosyl imidazole in sequence.

![Scheme 3.17 Synthesis of C1-C17 domain 140](image-url)
Compared with the precursor to spiroketal 69, the proposed the substrate 139 for Au (I) catalyzed spiroketalization is more complex and functionalized, leading to the concern upon the synthetic accessibility to 139 and reliability of Au (I) catalyzed spiroketalization. To substantiate our retrosynthetic plan, we designed a model study which would apply 145 representing C1-C27 segment of 139 to perform Au (I) catalyzed C19 spiroketal formation. To synthesize 145, alkyne 111 was first treated with n-butyllithium followed by 140 and Lewis acid in sequence. (Table 3.3) BF3•OEt2 was utilized at -78 °C to mediate this reaction, which only led to partial decomposition of 111 and inseparable multiple products. (Entry 1, Table 3.3) Similar result was acquired by replacing BF3•OEt2 with lithium chloride at elevated temperature. (Entry 2, Table 3.3) A third trial that involved transmetalation from lithium acetylide to organo cuprate species was also performed, but no products were observed. (Entry 3, Table 3.3)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Temperature</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF3•OEt2 (1 eq.)</td>
<td>-78 °C</td>
<td>111 partially decomposed, multiple products</td>
</tr>
<tr>
<td>2</td>
<td>LiCl (10 eq.)</td>
<td>0 °C, 25 °C</td>
<td>111 decomposed, multiple products</td>
</tr>
<tr>
<td>3</td>
<td>CuCN (2.2 eq)</td>
<td>-78 °C, -20 °C</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

Table 3.3 Model studies of preparation of the precursor for gold catalyzed formation of C19 spiroketal of 1
The experimental results in Table 3.3 indicated that many side reactions were involved in joining 111 and 140, the reason of which was ascribed as the electronic effect of the double bond in 140. As shown in Scheme 3.18, Lewis acid (LA) activated the C-O bonds of oxirane in 146. Since electron double bond stabilize the \( \alpha \)-carbocation via resonance, the \( C_\alpha-O \) bond would be more activated and elongated than the \( C_\beta-O \) bond, and the nucleophilic lithium acetylide would selectively attack the \( \alpha \)-site of 148 via the \( S_N1 \) like mechanism to give 149. Additionally, 146 would undergo Meinwald rearrangement\(^{58} \) to afford 151 via the stabilized carbocation intermediate 150. 151 might further isomerize to conjugated aldehyde 153 and both intermediates would react with lithium acetylide 147 to give secondary alcohols 152 and 154 respectively. The reactions that generated 149, 152 and 154 completed with the desired \( \beta \)-alkynylation process, leading to a mixed products of the reaction between 111 and 140.

**Scheme 3.18** Rationale of side reactions between 111 and 140

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3.8 A 3\(^{rd} \) Retrosynthesis towards DTX-2 Based on Our Previous Total Synthesis of OA
The two previous unsuccessful synthetic plans forced us to find out reliable coupling strategies to construct the backbone of 1. The revised synthetic design of 1 featured reliable fragment coupling methods derived from our previous work on 2.22 The natural product 1 was designed to derive from enone 155 via a late-stage installation of the C19 spiroketal via a reduction–trans-ketalization sequence (Scheme 3.19). The two key intermediates, C1–C14 aldehyde 5 and C15–C38 β-keto phosphonate 6, could be coupled through a Horner–Wadsworth–Emmons reaction. The C15–C38 domain was dissected at the C27–28 bond into C27 aldehyde 7 and C28 bromide 8. Among the three key intermediates, 61 and 65 were applied in previous synthetic plans (Scheme 3.1, Scheme 3.16) towards 1, whereas aldehyde 157 would be freshly prepared but also relied on our previous synthetic studies towards 2 and its analogues.

Scheme 3.19 A third retrosynthetic disconnection of 1
3.9 Completion of the Total Synthesis of DTX-2 and 2-epi-DTX-2

Synthesis of 157 started with Grignard reaction of 109 and the resultant alcohol was oxidized to ketone 158. (Scheme 3.20) Treatment of 158 with camphorsulfonic acid (CSA) in methanol and toluene cleaved TBS ether, hydrolyzed the PMP acetal and dehydratively protected the ketone as mixed ketal at C19 in 159. After C27 primary alcohol of 159 was selectively protected as TBS ether, the remaining secondary alcohol was then oxidized to ketone in 160 that was then converted to methylene group via Wittig reaction. TBS ether was cleaved by TBAF and the result alcohol 161 was treated with Dess-Martin periodinane to form aldehyde 157 eventually.

Scheme 3.20 Synthesis of aldehyde 157
To synthesize C15-C38 domain, aldehyde 157 was joined with alkyl lithium generated from lithium-halogen exchange of bromide 65. (Scheme 3.21) The resultant mixture of epimeric alcohols 162 and 163 were separated and the absolute stereochemistry of 162 and 163 was determined via modified Mosher ester analysis. The undesired 162 was converted into desired 163 via an oxidation–reduction sequence based upon Isobe’s total synthesis of 2. This selectivity arose by electronic control of the hydride attack in antiperiplanar mode toward the carbonyl group as illustrated in Figure 3.1. After benzyla­tion of alcohol 163, the less hindered mono-substituted alkene in 164 was oxidized to aldehy­de 165 by treatment with OsO₄ and NaIO₄. A sequence of phosphonate anion addition and Dess–Martin periodinane oxidation converted 165 into β-ketophosphonate 156.
Figure 3.1 Anti-periplanar mode for the diastereoselectivity in converting 162 to 163

Only six steps from 61 and 156 were required to complete the first total synthesis of 1. First, aldehyde 61 and β-ketophosphonate 156 were joined in high yield to give (E)-enone 155 (Scheme 3.22). Diastereoselective ketone reduction using (S)-CBS catalyst\textsuperscript{60} converted 155 into the (16\textit{R})-alcohol 166, which upon treatment with acetic acid in THF and water underwent intramolecular transketalization and acetonide hydrolysis to yield diol 60. Sequential Parikh–Doering and Pinnick\textsuperscript{61} oxidations converted 60 into α-hydroxy acid 167. Finally, the three benzyl ethers in 167 were cleaved in THF at -78 °C using freshly prepared lithium di-\textit{tert}-butylbiphenylide LiDBB\textsuperscript{62} to provide 1. Moreover, 2-\textit{epi}-DTX-2 (1a) was also prepared in the same fashion as 1 by replacing 100 with 100a in the synthetic sequence. (Scheme 3.23) Confirmation of the identity of synthetic 1 with naturally occurring DTX-2 was obtained by LC-HRMS and \textsuperscript{1}H NMR analyses.
Scheme 3.22 Total synthesis of DTX-2 (1)
Scheme 3.23 Total synthesis of 2-epi-DTX-2 (1a)

3.10 Inhibition of PP1 and PP2A by Synthetic DTX-2 (1) and 2-epi-DTX-1 (1a)
Naturally-isolated DTX-2(1) and OA(2) were tested in parallel with synthetic 1 and 1a (2-epi-DTX-2) for PP2A and PP1 inhibition potential. All toxins were shown to inhibit each of these enzymes but with various degrees of potency (Figure 3.2). Although PP2A was always more sensitive than PP1, the relative order of potency of the toxins remained the same for both enzymes: nat. 2 > nat. 1 ≈ synthetic 1 > synthetic 1a. Respective IC₅₀ values (nM) for PP2A are 0.47, 0.99, 1.35, and 137, and for PP1 are 25.2, 76.4, 82.6, and 3100 (Table 3.4). The IC₅₀s for 2 on PP2A and PP1 is within the range of other published reports,¹¹,¹⁶,²⁰ as is the IC₅₀ for 1 (both natural and synthetic) on PP2A (3.5 nM).¹¹

Figure 3.2 Inhibitory effects of natural OA (2), natural and synthetic DTX-2 (1), and synthetic 2-epi-DTX-2 on (A) PP2A and (B) PP1 activity.

These studies indicate that the unnatural synthetic analog 2-epi-DTX-2 (1a) is at least 1 to 2 orders of magnitude less potent than 1 (101- and 38-fold for PP2A and PP1, respectively). That the C2 epimer of DTX-2 has such a remarkably reduced potency (IC₅₀ = 137 and 3114 nM for PP2A and PP1, respectively) indicates biogenetic optimization of
PPase inhibitory activity and the essential roles of detailed structural features within the C1-C12 domain for conferring biological activity of okadaic acid and its congeners.\textsuperscript{16}

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>PP2A IC\textsubscript{50} (nM)</th>
<th>95% Confidence Intervals</th>
<th>Rel. Potency</th>
<th>PP1 IC\textsubscript{50} (nM)</th>
<th>95% Confidence Intervals</th>
<th>Rel. Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nat. 2</td>
<td>0.47</td>
<td>0.40–0.54</td>
<td>1.000</td>
<td>25.2</td>
<td>18–35</td>
<td>1.000</td>
</tr>
<tr>
<td>Nat. 1</td>
<td>0.99</td>
<td>0.84–1.2</td>
<td>0.47</td>
<td>76.4</td>
<td>58–100</td>
<td>0.330</td>
</tr>
<tr>
<td>Syn. 1</td>
<td>1.4</td>
<td>1.1–1.6</td>
<td>0.35</td>
<td>82.6</td>
<td>55–120</td>
<td>0.305</td>
</tr>
<tr>
<td>2-epi-1 (1a)</td>
<td>140</td>
<td>110–180</td>
<td>0.003</td>
<td>3100</td>
<td>2100–4700</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Table 3.4 Calculated IC\textsubscript{50} values and relative potencies for natural OA (2), natural DTX-2 (Nat. 1), synthetic DTX-2 (Syn. 1), and synthetic 2-epi-DTX-2 (1a) based on PP2A and PP1 inhibition.

The structural basis for the differential PPase inhibition by 1 and 1a may involve docking of both compounds at the active sites of the respective enzymes in either similar or considerably different conformations. For the former, the C2 hydroxyl and methyl substituents of 1 and 1a would be projected in opposite orientations. For 1a, this may cause the loss of potentially favorable contacts between the C2 hydroxyl and Tyr272 and Arg96, and between the C2 methyl group and His125 in PP1.\textsuperscript{17} Similar disruption of hydrogen bonding contacts between the C2 hydroxyl and Tyr265 and Arg89 in PP2A may occur.\textsuperscript{18}
The cyclic conformation of 1 that is crucial to its inhibition of PP1 and PP2A, is stabilized by intramolecular hydrogen bonding between C1 carboxylic acid and C24 hydroxyl group, and the one between C2 hydroxyl and C4 tetrahydropyran oxygen. (Figure 3.3) The reversed C2 chemistry in 1a may also break or change this pseudomacrolide conformation, which mismatches with the active site of PP1 and PP2A and leads to a decrease in potency.

3.11 Summary

An efficient total synthesis of DTX-2 (1) has been developed and executed based on the reliable fragment coupling methods derived from our previous work on 2. This strategy features a highly stereoselective 2-step construction of the central 1,6-dioxaspiro-[4.5]decane system by the tandem use of Corey’s CBS reduction and an acid-triggered trans-ketalization. In addition, this total synthesis highlights novel approaches to assem-
ble C1-C14 and C28-C38 domains. The overall efficiency of the assembly of 1 more than doubles that previously established for 2. Specifically, 2 was prepared in 1.7% overall yield spanning 26-steps in the longest linear sequence, whereas 1 is delivered in 3.6% yield over 21-steps by the chemistry outlined herein.

Au(I) catalyzed cyclization was applied to the construction of C19 spiroketal of 1, but the incorporation of this reaction into the total synthesis was not successful because of difficulties to join the segments. Modified Julia olefination was first applied to construct C14-C15 trans alkene in 1 but only gave low yield and poor E/Z selectivity. Attempt to apply Au (I) catalysis in late stage of the synthesis was interrupted due to failure in preparing the precursor (145) for the spiroketalization.

The freshly designed synthesis of C1-C14 domain of 1-3 was assembled from commercial available PMB ether of (R)-glycidol in 13 steps with a yield of 15%. The stereochimstry of C2 was generated via SAD on C1-C2 alkene of 63. The unexpected inversed diastereoselectivity of this reaction led to the synthesis of unnatural analogue 2-epi-DTX-2 (1a). The potency of 1a to PP1 and PP2A is much weaker than the natural 1, which indicates that the stereochemistry of C2 in DTX-2 is crucial for potent PPase inhibition.

The marriage of novel fragment assemblies with reliably established tri-component couplings described herein would provide access to further structural analogs derived from both 1 and the novel non-natural analog 2-epi-1. These unique molecules will facilitate studies to further elucidate the structural basis of selective PPase regulation and associated biological consequences.
Chapter 4. Effort towards Designation and Synthesis of DTX-2 Analogues

4.1 Designation and General Synthetic Plan of DTX-2 Analogues

Designation of DTX-2 analogues was based upon the X-ray crystal structure of OA bound to PP1/PP2A.\textsuperscript{17,18} It is anticipated that the skeleton of DTX-2 should not be altered since the pseudomacrolide conformation and the lipophilic tail domain of DTX-2 is crucial to its potency. The X-ray structure of OA-PP1/PP2A also elucidated the key interaction between active site on the surface of enzymes and functionalities of the inhibitor. As shown in Figure 4.1, several of OA’s functionality might be involved in direct interaction with both PP1 and PP2A, such as C1 carboxylate, C2 hydroxyl, C2 methyl, C10 methyl, C13 methyl, C24 hydroxyl, C25 methylene. Since DTX-2 and OA share all of these functionalities, it is anticipated that these functional groups must be retained in the designed analogues in order to keep their potency to PP1/PP2A.

Our hypothesis was confirmed by previous SAR studies by testing the inhibition effect of natural and unnatural analogues of OA(2) towards PP1 and PP2A. Some structural modifications about the C1-C14 domain of 2 have been shown to be tolerated (e.g. 7-deoxy\textsuperscript{16}, C9,10-episulfide\textsuperscript{63}), whereas others are not (2-deoxy, 2-oxo decarboxyl, and C1 methyl ester)\textsuperscript{16} with respect to retaining appreciable PPase activity. Moreover, fragments of OA and DTX-2, such as the C1-C27 and C15-C38 domain, only showed greatly reduced potency towards PP2A, which indicated the importance of integrity of OA/DTX-2’s skeleton with regard to its potency. (Table 4.1)
Table 4.1 Okadaic acid derivatives inhibition to PP2A.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>$K_i$ (pM)</th>
<th>%Inhibition (1.24 nmol/mL compound)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OA</td>
<td>30</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>OA-9,10-episulfide</td>
<td>47</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>14, 15-dihydro-OA</td>
<td>315</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>2-deoxy-OA</td>
<td>899</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>OA methyl ester</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>OA C1-C27 fragment</td>
<td>1300</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>OA C15-C38 fragment</td>
<td>-</td>
<td>99</td>
</tr>
</tbody>
</table>

OA and DTX-2 both selectively inhibit PP2A over PP1. To fully elucidate the structural basis of this phenomenon, we aim to find out a set of analogues of DTX-2 that selectively inhibit PP1 over PP2A. (Figure 4.2) As reported by Shi and co-workers, PP2A forms a close and tight hydrophobic cage to accommodate the tail domain, whereas PP1 only maintains a large and open-ended one. It is anticipated that adding alkyl functionalities on the tail domain might increase hydrophobic effect between the tail and the large hydrophobic cage in PP1 active site. Besides, we also attempt to add hydroxyl group on the tail domain in order to install hydrogen bonding with Asp197 and Ser 129 moities of PP1. Moreover, based on upon crystal structure of PP2A-DTX-2 complex, a bulky substituent on C35 of DTX-2 might decrease its affinity to PP2A without change its inhibition to PP1. Finally, to ease the synthesis, we decided to remove functionalities that have
no direct interactions with PP1 active site, such as methyl group on C29, hydroxyl groups on C7 and C27.

Figure 4.1 (A) Major interaction between PP1 and OA; (B) Major interaction between PP2A and OA.
Synthesis of these analogues would utilize our reliable coupling strategy developed in the total synthesis of DTX-2 and OA. (Scheme 4.1) It is noticeable that all of these analogues share the same C1-C14 domain (170) and our studies would start with the synthesis of this compound.

**Figure 4.2** Designed DTX-2 analogues with comparable bioactivities

**Scheme 4.1** Retrosynthesis of DTX-2 analogues

**4.2** Synthetic Plan of the Shared C1-C14 Domain of 7-deoxy DTX-2 Analogues
Compound 171 greatly resembles the C1-C14 domain of DTX-2 (61), whereas 171 misses the C7 hydroxyl group. This structural simplicity would allow a new and rapid synthetic access to this compound, especially the C7 spiroketal moiety.

The C1-C14 domains with different protecting groups were synthesized before. The first method applied acid-triggered cyclization process to convert TMS protected keto diol 173 to spiroketal 174, which was also applied in the synthesis of DTX-2 and OA. The second method applied double intramolecular hetero Michael addition (DIHMA) to construct C8 spiroketal, which convert 175 to 176 under the treatment of TsOH in toluene. The carbonyl group in 176 was converted to exo-methylene group via Wittig reaction and the resultant 177 then isomerized to 178 to install C9-C10 double bond. Both strategies only construct C3-C14 segment of 7-deoxy DTX-2 and utilized Seebach’s lactate to install C2 tertiary center. The two strategies both took more than thirteen steps to achieve fully functionalized C1-C14 domain.

Scheme 4.2 Previous synthesis of C7 spiroketal in 7-deoxy OA
We aimed to explore a more efficient pathway to prepare C1-C14 domain \((171)\). Based upon total synthesis of DTX-2 outlined in Chapter 3, C2 tertiary stereocenter would be constructed via SAD on compound \(179\). To install the central spiroketal in \(179\), triol \(180\) was treated with AuCl to trigger the dehydro-spiroketalization process.\(^{67}\) In turn, \(180\) was further disconnected at C9-C10 bond into alkyne \(181\) and methyl ketone \(182\). \(182\) would be joined with lithium acetylide generated from \(181\) to afford \(180\).

\[
\begin{align*}
\text{Scheme 4.3 Synthetic plan towards 171}
\end{align*}
\]

### 4.3 Synthesis of C1-C14 Domain of 7-deoxy DTX-2 (171) via Au(I) Catalyzed Dehydro-spiroketalization Reaction

The synthesis of \(171\) started with reduction of ester \(183\) to afford aldehyde \(184\).\(^{66}\) The C12 stereogenic center was installed via allylation of \(21\) to give the terminal alkene \(185\) in a 15:1 diastereomeric ratio based upon \(^1\)H NMR spectroscopy.\(^{68}\) Subsequent protection of the secondary alcohol \(185\) with TESCl gave \(186\). Alkene in \(186\) was oxidized to methyl ketone \(182\) via Wacker-Tsuji process.\(^{69}\) The silyl ether of C12 hydroxyl group
was partially cleaved due to the generation of HCl and the hydroxyl group at C12 in the by-product 187 was protected as TES ether to regenerate 182.

Scheme 4.4 Synthesis of methyl ketone 182

Synthesis of alkyne 181 started with commercial available 5-hexyn-1-ol (188), which was oxidized to aldehyde 189. (Scheme 4.5) Keck methallylation\(^\text{37}\) of 189 installed the C4 stereogenic center of 190 in homoallylic alcohol 181 and the resultant secondary hydroxyl group was then protected as TES ether. To join 181 and 182, 181 was first treated with \(n\)-BuLi and in situ generated lithium acetylide was added to methylketone 182 to afford a 1 : 1.3 mixture of diastereomers 191a \((R_f = 0.52)\) and 191b \((R_f = 0.34)\). The two epimers were separated and were then treated with TBAF to give triol 180a and 180b respectively.
To determine the absolute stereochemistry, 10,12-diol in 180a and 180b was first protected as acetonide to afford 192a and 192b respectively. (Scheme 4.6) Extensive NOE studies showed that the axial C12 H atom in 192a only correlated with axial CH₃ at the acetal carbon whereas C12 H atom in 192b correlated with C10 methyl group as a plus. This study indicated that 180a was a (10S)-triol whereas 180b was a (10R)-triol.
Scheme 4.6 Determination of the absolute stereochemistry of 180a and 180b

The spiroketal moiety in 179 was constructed via treatment of 180a and 180b with AuCl and molecular sieves separately. Surprisingly, the two C10 epimer presented different reactivity upon the treatment of AuCl. Whereas 1,3-anti triol 180a was converted to 179 exclusively with a yield of 90%, 1,3-syn triol 180b gave a mixture of 1,7-dioxaspiro[5.5]undec-4-ene (179) and 1,6-dioxaspiro[4.6]undecane (193/194) systems. The divergent regioselectivity observed upon cyclization of 180a and 180b is consistent with that reported by Aponick and previous synthetic studies in our group. This result confirms a mechanical explanation that developed by our group. This mechanism suggests that a kinetic preference for the C30 hydroxyl of 1,3-syn triol 180b versus the C30 hydroxyl of 1,3-anti triol 180a to participate in initial oxy-auration of the alkyne via 5-exo-dig addition at C9. (Scheme 4.8) The 5-exo-dig cyclization of 180a afforded enol-ether intermediate 197 that then isomerized to oxo-carbenium 198 to give
spirokets 193/194. In contrast, 5-exo-dig cyclization of 180a was hindered due to the unstable transition state 199 that resulted from axial oriented methyl group. Alternatively, C4 hydroxyl group initiated 6-exo-dig cyclization to afford enol ether gold intermediate 201. A molecule of water was removed from 201 and the resultant gold-allene complex isomerized to vinyl gold complex 203, leading to a second cyclization of C12 hydroxyl group and formation of spiroketal 179 eventually.

Scheme 4.7 Synthesis of 179 Au (I) catalyzed dehydro-spiroketalization
4.4 Effort towards the synthesis of 7-deoxy DTX-2

The first analogue of DTX-2(1) we planned to synthesize was 7-deoxy-DTX-2, which required aldehyde 171 and β-ketophosphonate 156 as key building blocks as proposed in Scheme 4.1. Whereas 156 has been prepared in the total synthesis of 1, 171 could be synthesized from 179. SAD of 179 afforded corresponding 1,2-diol with d.r. of 4.1 :1. The major product 205 was then protected as acetonide and PMB ether in 206 was oxidatively cleaved by DDQ. The resultant primary alcohol was oxidized via Dess-Martin oxidation to give aldehyde 171. (Scheme 4.9)
Parallel the success in the synthesis of 1 and 2, 171 and 156 was joined via HWE reaction to give enone 207. To construct the central spiroketal on C19, 207 was first reduced to by (S)-CBS catalyst to give allylic alcohol 208 that was then treated with the mixture of acetic acid, THF and water. However, this acid-catalyzed cyclization failed to produce 209, which indicated that the omission of C7 benzoxy group de-stabilized C8 spiroketal in 208 upon the treatment of acid. This hypothesis was confirmed by the fact that 206 decomposed upon the treatment of the same condition as that of 208.

Scheme 4.9 Synthesis toward 7-deoxy DTX-2
The above unsuccessful access to 7-deoxyl DTX-2 suggests that a less acidic condition should be applied to install C19 spiroketal. In addition, a change of the protecting groups of C1-C2 functionalities is also necessary since acetonide is usually removed under acidic condition. Consequently, we aim to install C1 carboxylic acid before the coupling of C1-C14 and C15-C38 domain, starting with conversion of 1,2-diol 205 to \( \alpha \)-hydroxy acid 210 via Heyns oxidation\(^7\). 210 was then esterified via the treatment with TMSCHN\(_2\) and the C2 hydroxyl group was silylated to afford 211. (Scheme 4.10)

**Scheme 4.10 Synthesis of 211**

4.5 Effort towards the Synthesis of C1-C14 Domain of DTX-2

The successful application of Au(I) catalyzed dehydro-spiroketalization in the synthesis of C1-C14 domain of 7-deoxyl DTX-2 encourages us to incorporate this strategy into the synthesis natural DTX-2 (1). The synthetic track started with homoallylic alcohol 77 in which the hydroxyl group was protected as TES ether followed by oxidative cleavage of PMB ether. The resultant primary alcohol was then converted 1,1-dibromide olefin 213 via a two-step sequence: Dess-Martin oxidation followed by Corey-Fuchs reaction\(^7\). 213 was then treated with \( n \)-BuLi and the *in situ* generated lithium acetylide was then joined with methylketone 182 to afford 214. After cleavage of the two TES ethers in 214, the resultant triol was treated with AuCl and molecular sieves; however, only trace
amount (less than 10%) of 63 was produced during this reaction. It is anticipated that the addition of benzoxy group at C7 hinders 6-exo-dig cyclization from C4 hydroxyl group to C8, which decelerate the catalytic cycle that leading to the formation of dioxaspiro[5.5]undec-4-ene system in 63.

![Scheme 4.11](image)

Scheme 4.11 Synthetic effort towards 63 via Au(I) catalyzed dehydro-spiroketalization

4.6 Summary

A set of analogues was designed here to fully elucidate the structural basis of OA/DTX-2’s inhibition to PP1/2A. We aim to design an unnatural analogue that selectively inhibits PP1 over PP2A based upon X-ray crystal structure of the binding complexes. The designed analogues shared a simplified C1-C14 domain that allowed the application of new methodologies in its preparation.

Au(I) catalyzed dehydro-spiroketalization process was successfully applied in the synthesis of 7-deoxyl C1-C14 domain of DTX-2. As a result, the overall efficiency of the assembly of 211 was greatly increase compared to that of 216 with comparable struc-
tural complexity. Specifically, \textbf{216} was prepared in 4.6\% overall yield spanning 16-steps in the longest linear sequence,\textsuperscript{64} whereas \textbf{211} is delivered in 25\% yield over 9-steps by the chemistry outlined in Chapter 4. (Figure 4.3) This synthetic plan provided efficient access towards DTX-2 analogues designed in Figure 4.2, whereas further synthetic studies are still necessary because of failure in the construction of C19 spiroketal of the designed analogues.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.3}
\caption{Contrast of the synthetic efficiency of \textbf{211} and \textbf{216}}
\end{figure}
References


Appendix A: Experimental

General Method

Unless noted otherwise, all oxygen and moisture-sensitive reactions were executed in oven-dried glassware sealed under a positive pressure of dry argon and moisture-sensitive solutions and anhydrous solvents were transferred via standard syringe and cannula techniques. Unless stated otherwise, all commercial reagents, were used as received. THF, diethyl ether, CH₂Cl₂, and toluene were were purified and dried under argon atmosphere on an Innovative Technologies Pure Solv. drying column; Et₃N, diisopropylethyl amine and pyridine were distilled from CaH₂. Flash chromatography was performed using Baker Flash silica gel 60 (40 mM); analytical TLC was performed using 0.25 mm EM silica gel 60 F254 plates that were visualized by UV irradiation (254 nm) and/or by staining with PAA stain (900 mL of 95% EtOH, 50 mL conc. H₂SO₄, 30 mL acetic acid, and 50 mL anisaldehyde). NMR spectra were obtained on either a 400 or 500 MHz Bruker Avance DPX instruments. Both ¹H and ¹³C NMR spectra were referenced to residual CHCl₃ (7.26 and 77.01 ppm respectively) and acquired at 300 K. High resolution mass spectra were taken on an Agilent 1200 HPLC interfaced with a Bruker MicroTOF ESI MS using sodium formate an internal standard. Infrared (IR) spectra were obtained via Perkin Elmer Spectrum RX1 spectrophotometer.
To a mixture of CuI (1.10 g, 5.78 mmol.) and diethyl ether (100 mL) at -20 °C was added 1.0 M solution of allylmagnesium bromide in diethyl ether (31 mL, 31 mmol) dropwise. After stirring for 30 min, a solution of (R)-2-(((4-methoxybenzyl)oxy)methyl)oxirane (5.62 g, 28.9 mmol.) in 20 mL of diethyl ether was added to the reaction mixture. After another 1 h stirring, 30 mL of saturated ammonium chloride solution was added to the reaction mixture and it was warmed to 25 °C. After the aqueous phase turned dark blue, the organic phase was separated and the aqueous phase was extracted with 100 mL of diethyl ether three times. The organic extracts were combined, dried over sodium sulfate, and filtered. Evaporation of the filtrate gave a light yellow oil which was then dissolved in 80 mL of THF. The solution was cooled to 0 °C and 2.2 g of a 60% suspension of NaH in mineral oil was added. The mixture was warmed to 25 °C and stirred for 1 h. After the reaction mixture was re-cooled to 0 °C, tetra-n-butylammonium bromide (0.50 g, 1.3 mmol) and benzyl bromide (4.2 mL, 35 mmol.) were added and the reaction mixture was warmed to 25 °C. After stirred for 16 h, 2 mL of methanol followed by 20 mL of saturated aqueous ammonium chloride solution were added. After the mixture was warmed to room temperature, THF was evaporated and the aqueous mixture was extracted with 120 mL of diethyl ether four times. The combined organic phase was washed with brine, dried over Na2SO4, filtered and concentrated. The
The residue was purified by flash chromatography (hexanes: EtOAc, 15:1, v/v) to give a colorless oil (7.80 g, 23.9 mmol, 84%, two steps): $R_f$ 0.60 (hexanes-ethyl acetate, 8:1, v/v); $[\alpha]_D^{20}$ +10.1 (c 0.50, CHCl$_3$); IR (neat): 3024, 2927, 2860, 1719, 1510, 1454, 1246, 1089, 1039, 822 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.33 (m, 5H), 7.28 (d, $J$ = 8.5 Hz, 2H), 6.88 (d, $J$ = 8.5 Hz, 2H), 5.79 (m, 1H), 5.00 (d, $J$ = 12 Hz, 1H), 4.95 (d, $J$ = 10 Hz, 1H), 4.68 (d, $J$ = 12 Hz, 1H), 4.55 (d, $J$ = 12 Hz, 1H), 4.49 (s, 2H), 3.81 (s, 3H), 3.60 (m, 1H), 3.55 (dd, $J$ = 10, 4.5 Hz, 1H), 3.50 (dd, $J$ = 10, 4.5 Hz, 1H), 2.15 (m, 2H), 1.66 (m, 2H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 159.2, 138.9, 138.5, 130.5, 129.2, 128.3, 127.8, 127.5, 114.7, 113.8, 77.6, 73.0, 72.5, 72.0, 55.3, 31.3, 29.7; HRMS caled for C$_{21}$H$_{26}$O$_3$Na $[M + Na]^+$: 349.1780; found : 349.1776.

**(R)-4-(benzyl)oxy)-5-(((4-methoxybenzyl)oxy)pentanal (76)**

To a mixture of (R)-1-(((2-(Benzyloxy)hex-5-en-1-yloxy)methyl)-4-methoxybenzene (6.80 g, 20.8 mmol), CH$_2$Cl$_2$ (120 mL) and methanol (60 mL) at -78 °C was bubbled with ozone until a light blue color showed up. The extra ozone was then blown out with argon and triphenylphosphine (5.47 g, 20.8 mmol) was added. The reaction mixture was warmed up to 25 °C and stirred for two more hours. The solvent was then evaporated and the residue was purified by chromatography (hexanes: ethyl acetate, 6:1, v/v) to get 76 (5.70 g 17.3 mmol, 83%) as a colorless oil:

$R_f$ 0.46 (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_D^{20}$ +23.2 (c 0.44, CHCl$_3$); IR (neat): 3024, 2927, 2860, 1719, 1510, 1454, 1246, 1089, 1039, 822 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.33 (m, 5H), 7.28 (d, $J$ = 8.5 Hz, 2H), 6.88 (d, $J$ = 8.5 Hz, 2H), 5.79 (m, 1H), 5.00 (d, $J$ = 12 Hz, 1H), 4.95 (d, $J$ = 10 Hz, 1H), 4.68 (d, $J$ = 12 Hz, 1H), 4.55 (d, $J$ = 12 Hz, 1H), 4.49 (s, 2H), 3.81 (s, 3H), 3.60 (m, 1H), 3.55 (dd, $J$ = 10, 4.5 Hz, 1H), 3.50 (dd, $J$ = 10, 4.5 Hz, 1H), 2.15 (m, 2H), 1.66 (m, 2H).
(4S,7R)-7-(benzyloxy)-8-((4-methoxybenzyl)oxy)-2-methylcycloct-1-en-4-ol (77)

A mixture of (R)-(+-1,1'-bi-2-naphthol (0.430 g, 1.50 mmol), Ti(Oi-Pr)₄ (0.44 mL, 1.50 mmol) and oven-dried powdered 4Å molecular sieves (7.2 g) in CH₂Cl₂ (20 mL) was heated at reflux for 1h. The red-brown mixture was cooled to room temperature and 76 (4.25 g, 12.9 mmol) in CH₂Cl₂ (10 mL) was added. After being stirred for 10 min, the contents were cooled to -78 °C, and 2-methyl-allyltri-n-butylstannane (6.00 g, 17.4 mmol) was added. The reaction was stirred for 10 min and then placed in a -20 °C freezer for 72 h. A solution of saturated NaHCO₃ (4 mL) was added and the mixture was stirred for 1 h. Na₂SO₄ (6.0 g, 42.2 mmol) was then added and the mixture was filtered through a plug of Celite and concentrated. The residue was purified by flash chromatography (hexanes-EtOAt, 4:1, v/v) to give 77 as a light yellow oil (4.98 g, 12.9 mmol, quant.):
$R_f$ 0.32 (hexanes-ethyl acetate, 4:1, v/v); IR (neat): 3444, 3067, 3022, 2918, 2856, 1644, 1614, 1586, 1454, 1302, 1247, 1173, 1089, 891, 739, 698 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.32 (m, 5H), 7.27 (d, $J = 8.5$ Hz, 1H), 6.88 (d, $J = 8.5$ Hz, 1H), 4.87 (s, 1H), 4.78 (s, 1H), 4.70 (d, $J = 11.5$ Hz, 1H), 4.57 (d, $J = 11.5$ Hz, 1H), 4.49 (s, 2H), 3.81 (s, 3H), 3.70 (m, 1H), 3.63 (m, 1H), 3.57 (dd, $J = 10$, 5 Hz, 1H), 3.52 (dd, $J = 10$, 5 Hz, 1H), 2.14 (m, 2H), 1.99 (brs, 1H), 1.77 (m,1H), 1.76 (s, 3H), 1.64 (m, 2H), 1.47 (m, 1H). $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 159.2, 142.9 138.8, 130.5, 129.3, 128.3, 127.9, 127.5, 113.8, 113.3, 78.3, 77.3, 73.1, 72.4, 72.0, 68.9, 55.3, 46.2, 33.0, 28.4, 22.4; HRMS calcd for C$_{24}$H$_{32}$O$_4$Na [M + Na]$^+$: 407.2198, found: 407.2231.

![Structure of (2R,5S)-2-(benzyloxy)-7-methyloct-7-ene-1,5-diol](image)

(2R,5S)-2-(benzyloxy)-7-methyloct-7-ene-1,5-diol (78)

To a mixture of 77 (2.00g, 5.20 mmol), tert-butanol (1.0 mL), pH = 7 buffer (4.0 mL) and CH$_2$Cl$_2$ (40 ml) at 25 °C was added 2,3-dichloro-5,6-dicyanobenzoquinone (1.77 g, 7.80 mmol). The mixture was stirred for 2 hours and saturated NaHCO$_3$ solution (80 mL) was added. The mixture was then diluted with 100 mL of diethyl ether and the organic phase was separated. The aqueous phase was further extracted with diethyl ether (5×50 mL) and the combined organic phase was dried over Na$_2$SO$_4$, filtered and concentrated. The residue was purified by chromatography (hexanes-EtOAc, 1:1, v/v) to give 78 (1.09 g, 4.16 mmol, 80%) as a light pink oil.
$R_f$ 0.25 (hexanes-ethyl acetate, 1:1, v/v); IR (neat): 3390, 3070, 3031, 2930, 2872, 1645, 1454, 1381, 1346, 1207, 1067, 890, 738, 698 cm$^{-1}; ^1$H NMR (CDCl$_3$, 500 MHz): δ 7.36 (d, $J = 4.5$ Hz, 4H), 7.30 (m, 1H), 4.89 (t, $J = 1.5$ Hz, 1H), 4.79 (d, $J = 1$ Hz, 1H), 4.63 (d, $J = 11.5$ Hz, 1H), 4.57 (d, $J = 11.5$ Hz, 1H), 3.71 (m, 2H), 3.57 (m, 2H), 2.18 (dd, $J = 13$, 3.5 Hz, 1H), 2.11 (dd, $J = 13$, 9 Hz, 1H), 1.95 (brs, 1H), 1.87 (brs, 1H), 1.75 (s, 3H), 1.73 (m, 1H), 1.60 (m, 1H), 1.50 (m, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 142.6, 138.4, 128.5, 127.9, 127.8, 113.6, 79.7, 71.6, 68.7, 64.2, 46.2, 32.7, 27.1, 22.4; HRMS calcd for C$_{16}$H$_{24}$O$_3$Na [M + Na]$^+$: 283.1623, found: 283.1629.

![Structure](image.png)

(3R,6S)-3-(benzyloxy)-6-(2-methylallyl)tetrahydro-2H-pyran-2-one (67)

To a solution of 78 (0.90 g, 3.40 mmol) in CH$_2$Cl$_2$ (30 mL) was added iodobenzene diacetate (2.74 g, 8.51 mmol) and 2,2,6,6-tetramethylpiperidine-1-oxyl (0.0265 g, 0.170 mmol). The reaction mixture was stirred for 12 hours and saturated Na$_2$S$_2$O$_3$ solution (10 mL) was added. Diethyl ether (60 mL) was then added to the mixture and organic phase was separated. The aqueous phase was then extracted diethyl ether (3 × 20 mL). The combined organic phase was washed with brine, dried over Na$_2$SO$_4$, concentrated and purified by flash chromatography (hexanes-ethyl acetate, 8:1, v/v) to give compound 67 (0.75 g, 4.61 mmol, 83%) as a colorless oil.

$R_f$ 0.36 (hexanes-ethyl acetate, 8:1, v/v); [α]$_D^{20}$ +96.0 (c 0.31, CHCl$_3$); IR (neat): 3074, 3031, 2936, 2860, 1747, 1650, 1454, 1378, 1312, 1249, 1192, 1129, 1057, 895,
738, 700 cm⁻¹ ¹H NMR (CDCl₃, 500 MHz): δ 7.37 (m, 5H), 4.91 (d, J = 12 Hz, 1H), 4.86 (s, 1H), 4.78 (s, 1H), 4.71-4.64 (m, 1H), 4.67 (d, J = 12 Hz, 1H), 3.96 (dd, J = 7, 5 Hz, 1H), 2.47 (dd, J = 12, 8 Hz, 1H), 2.24 (dd, J = 12, 6 Hz, 1H), 2.16 (m, 1H), 2.00 (m, 2H), 1.96 (s, 3H), 1.61 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 171.0, 140.4, 137.4, 128.5, 128.1, 128.0, 114.0, 78.4, 73.9, 72.7, 44.0, 26.9, 26.5, 22.7. HRMS calcd for C₁₆H₂₀O₃Na [M + Na]⁺: 283.1310; found: 283.1310

((2R,3R,6S)-3-(benzyloxy)-6-(2-methylallyl)tetrahydro-2H-pyran-2-yl)oxy)(tert-butyl)dimethylsilane (95)

To a solution of 67 (0.68 g, 2.61 mmol) in CH₂Cl₂ (22 mL) at -78 °C was added di-isopropylaluminum hydride (1M in toluene, 3.13 mL 3.13 mmol) dropwise. The solution was gradually warmed to -40 °C and was stirried at this temperature for 1 h. Methanol (1 mL), saturated sodium potassium tartrate solution (20 mL) and diethyl ether (30 mL) was added to the reaction mixture in sequence. The mixture was warmed to 25 °C and was stirred for 12 hours. The organic phase was separated and the aqueous phase was extracted with diethyl ether (4 × 20 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated. The colorless residue was then dissolved in 14 mL of dry dichloromethane. Imidazole (0.444g, 6.53 mmol), 4-dimethylaminopyridine (0.032 g, 0.261 mmol) and tert-butyl(dimethylchlorosilane (0.473g, 3.13 mmol) were also added to the solution in sequence. The mixture was stirred for 3 hours before saturated NH₄Cl so-
olution (10 mL) and diethyl ether (20 mL) was added. The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic phase was dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 30:1, v/v) to give 95 as a colorless oil (0.980 g, 2.60 mmol, 99%, two steps):

\[ R_f \, 0.50 \text{ (hexanes-ethyl acetate, 20:1, v/v); } \alpha_D^{25} = -4.8 \, (c \, 1.25, \, CHCl_3); \text{ IR (neat):} \]

3074, 3030, 2929, 2888, 2856, 1452, 1391, 1292, 1250, 1167, 1099, 1068, 1005, 892, 836, 733, 697 cm⁻¹; \( ^1H \text{ NMR (CDCl}_3, \, 500 \text{ MHz):} \, \delta \, 7.33 \, (m, \, 5H), \, 4.82 \, (d, \, J = 12 \, Hz, 1H), \, 4.77 \, (s, \, 1H), \, 4.73 \, (s, \, 1H), \, 4.65 \, (d, \, J = 12 \, Hz, \, 1H), \, 4.56 \, (d, \, J = 7 \, Hz, \, 1H), \, 3.54 \, (m, \, 1H), \, 3.16 \, (ddd, \, J = 12, \, 7, \, 5 \, Hz, \, 1H), \, 2.28 \, (dd, \, J = 14, \, 8 \, Hz, \, 1H), \, 2.12 \, (dd, \, J = 14, \, 5 \, Hz, \, 1H), \, 2.02 \, (m, \, 1H), \, 1.74 \, (s, \, 3H), \, 1.62 \, (m, \, 1H), \, 1.48 \, (m, \, 1H), \, 1.32 \, (m, \, 1H), \, 0.94 \, (s, \, 9H), \, 13C \text{ NMR (CDCl}_3, \, 125 \text{ MHz):} \, \delta \, 142.2, \, 139.1, \, 128.3, \, 127.7, \, 127.4, \, 112.6, \, 100.2, \, 78.2, \, 74.0, \, 72.7, \, 74.0, \, 72.7, \, 43.9, \, 30.7, \, 29.2, \, 25.8, \, 22.7, \, 18.1, \, -4.0, \, -5.1; \text{ HRMS calcd for C}_{22}H_{36}O_{3}SiNa [M + Na]^+: 399.2331; found: 399.2333.\]

![Chemical Structure](image)

(R)-3-((2S,5R,6R)-5-(benzyloxy)-6-((tert-butyldimethylsilyl)oxy)tetrahydro-2H-pyran-2-yl)-2-methylpropane-1,2-diol (96)

To a mixture of 95 (0.940g, 2.50 mmol), tert-butanol (12.5 mL) and water (12.5 mL) at 0 °C was added AD-mix-α (3.5 g). The mixture was stirred vigorously for 48 hours until when sodium sulfite (4.0 g) was added. The mixture was stirred at 25 °C for another
one hour and 20 mL diethyl ether was added. The organic phase was separated and the aqueous phase was extracted by diethyl ether (4 × 15 mL). The combined organic phase was dried over Na$_2$SO$_4$, filtered and concentrated. The residue was purified through column chromatography (hexanes-ethyl acetate, 4:1 to 2:1:1, v/v) to give 96 (0.701 g, 1.71 mmol, 68%) and 97 (0.236 g, 0.575 mmol, 23%) as colorless oil:

$$R_f 0.20 \text{ (hexanes-ethyl acetate, 2:1, v/v); } [\alpha]_D^{25} +6.7 \text{ (c 0.34, CHCl}_3\text{); IR (neat): 3415, 2929, 2857, 1650, 1454, 1392, 1252, 1170, 835 \text{ cm}^{-1}; }$$

$^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.33 (m, 5H), 4.73 (d, $J = 12$ Hz, 1H), 4.62 (d, $J = 12$ Hz, 1H), 4.59 (d, $J = 7$ Hz, 1H), 3.76 (m, 1H), 3.57 (dd, $J = 11$, 5 Hz, 1H), 3.43 (dd, $J = 11$, 8 Hz, 1H), 3.41 (s, 1H), 3.14 (ddd, $J = 12$, 7, 4.5 Hz, 1H), 2.29 (m, 1H), 2.04 (m, 1H), 1.81 (dd, $J = 14$, 8.5 Hz, 1H), 1.69 (dd, $J = 14$, 4 Hz, 1H), 1.59 (m, 1H), 1.51-1.36(m, 2H), 1.18 (s, 3H), 0.92 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 138.7, 128.3, 127.3, 127.5, 99.3, 78.0, 73.7, 72.5, 72.3, 69.3, 43.6, 31.7, 28.8, 25.7, 25.6, 25.2, 17.9, -4.5, -4.9; HRMS calcd for C$_{22}$H$_{38}$O$_5$SiNa [M + Na]$^+$: 433.2386; found: 433.2377.

(3R,6S)-3-(benzlyoxy)-6-(((R)-2,2,4-trimethyl-1,3-dioxolan-4-yl)methyl)tetrahydro-2H-pyran-2-one (98)

To a solution of 96 (0.560 g, 1.36 mmol) in CH$_2$Cl$_2$ (10 mL) was added 2,2-dimethoxypropane (1.01 mL, 0.852 g, 8.18 mmol) followed by pyridinium p-toluenesulfonate (18.3 mg, 0.068 mmol). The reaction mixture was stirred for 2.5 hours
until 0.5 mL of triethylamine was added. The solvent was evaporated and the residue was filtered through a pad of silica gel with hexanes-ethyl acetate (4:1, v/v). The obtained solution was concentrated and the residue was dissolved in THF (10 mL) and was treated with tetra-n-butylammonium fluoride solution (1.0 M in THF, 1.43mL, 1.43 mmol) dropwise within 1 hour. The mixture was stirred for another 0.5 hour and saturated ammonium chloride solution (5 mL) was added. THF was removed from the mixture and diethyl ether (20 mL) was added. The mixture was stirred for 10 min and the organic phase was separated. The aqueous phase was extracted with diethyl ether (3 × 15 mL). The combined organic phase was dried over Na₂SO₄, filtered and concentrated. The residue was filtered through a pad of silica gel with hexanes-ethyl acetate (2:1, v/v) and the obtained solution was concentrated. The residue was dissolved in CH₂Cl₂ (10 mL) followed by addition of NaHCO₃ (0.40g, 4.82 mmol), iodobenzene diacetate (0.526g, 1.63 mmol) and 2,2,6,6-tetramethylpiperidine-1-oxyl (12.0 mg, 0.077 mmol). The reaction was stirred for 12 hours before saturated Na₂S₂O₃ solution (3.0 mL) was added. Diethyl ether (20 mL) was added to the mixture and organic phase was separated. The aqueous phase was then extracted with diethyl ether (3 × 15 mL). The combined organic phase was washed with brine, dried over Na₂SO₄, concentrated and purified by flash chromatography (hexanes: ethyl acetate, 4:1, v/v) to give compound 10 (0.370 g, 1.11 mmol, 82%, three steps) as a colorless oil.

\[ R_f \ 0.34 \text{ (hexanes-ethyl acetate, 4:1, v/v);} \ \ [\alpha]_{\text{D}}^{25} +80.0 \text{ (c 0.40, CHCl}_{3})\text{; IR (neat):} \\
3058, 3028, 2928, 2930, 2868, 1745, 1454, 1379, 1246, 1209, 1118, 1058, 806, 739, 699 \text{ cm}^{-1}; \ \ ^1\text{H NMR (CDCl}_{3}, 500 \text{ MHz}):} \ \delta 7.36 \text{ (m, 5H),} 4.89 \text{ (d, J = 12 Hz, 1H),} 4.73 \text{ (m, 1H),} \]
4.66 (d, J = 12 Hz, 1H), 3.95 (dd, J = 7.5, 5 Hz, 1H), 3.86 (d, J = 9 Hz, 1H), 3.80 (d, J = 9 Hz, 1H), 2.12 (m, 1H), 2.02 (m, 2H), 1.92 (dd, J = 14, 8.5 Hz, 1H), 1.84 (dd, J = 14, 4 Hz, 1H), 1.38(s, 3H), 1.35(s, 6H); 13C NMR (CDCl3, 125 MHz) δ 170.6, 137.4, 128.5, 128.1, 128.0, 109.0, 79.6, 77.3, 46.0, 28.3, 27.2, 27.1, 26.6, 24.2; HRMS calcd for C19H26O5Na [M + Na]+: 357.1678; found : 357.1672.

![Chemical Structure](image)

triethyl(((2R,3S)-1-((4-methoxybenzyl)oxy)-2-methylhex-5-yn-3-yl)oxy)silane

(68)

To a solution of the residue (0.885 g, 3.56 mmol), imidazole (0.389 g, 5.70 mmol) and 4-dimethylaminopyridine (0.0435 g, 0.356 mmol) in CH2Cl2 (15 mL) was added chlorotriethylsilane (0.590 g, 0.66 mL, 3.92 mmol). The mixture was stirred for 30 min before saturated NH4Cl solution (6 mL) and diethyl ether (20 mL) were added. The organic phase was separated and the aqueous phase was extracted by diethyl ether (3 × 10 mL). The organic extracts were combined, dried over Na2SO4, filtered and concentrated. The residue was purified by flash column chromatography (hexanes: ethyl acetate, 16:1, v/v) to give 68 (1.290g, quantitative) as a colorless oil.

\[ R_f \text{ 0.66 (hexanes-ethyl acetate, 8:1, v/v); } [\alpha]_D^{25} +19.0 \text{ (c 0.64, CHCl}_3) \text{; IR (neat): 3310, 2955, 2910, 2876, 2119, 1613, 1514, 1462, 1247, 1085, 1007, 822, 742; } ^1H \text{ NMR (CDCl}_3\text{, 500 MHz): } \delta 7.25 \text{ (m, 2H), 6.87 (m, 2H), 4.44 (d, } J = 6.5 \text{ Hz, 1H), 4.40 (d, } J = 6.5 \text{ Hz, 1H), 3.84 (q, } J = 5.5 \text{ Hz, 1H), 3.81 (s, 3H), 3.51 (dd, } J = 9, 5.5 \text{ Hz, 1H), 3.33(dd, 1H) } \]
$J = 9, \ 6 \ \text{Hz, 1H}), \ 2.42 \ (\text{ddd, } J = 17, \ 6, \ 3 \ \text{Hz, 1H}), \ 2.33 \ (\text{ddd, } J = 17, \ 6, \ 3 \ \text{Hz, 1H}), \ 2.11 \ (\text{m, 1H}), \ 1.96 \ (t, \ J = 3 \ \text{Hz, 1H}), \ 0.96 \ (t, \ J = 8 \ \text{Hz, 1H}), \ 0.61 \ (q, \ J = 8 \ \text{Hz, 1H}); ^{13}\text{C NMR (CDCl}_3, \ 125 \ \text{MHz}) \ \\ \delta 159.0, \ 130.9, \ 129.1, \ 113.7, \ 81.9, \ 72.6, \ 72.5, \ 71.7, \ 69.8, \ 55.3, \ 38.5, \ 24.8, \ 13.8, \ 6.9, \ 5.1; \ \\ \text{HRMS calcd for C}_{21}\text{H}_{34}\text{O}_3\text{Na [M + Na]}^+: 385.2175; \ \\ \text{found: 385.2187.}

(2R,3S,8R,11S)-8-(benzyloxy)-11-hydroxy-1-((4-methoxybenzyl)oxy)-2,13-dimethyl-3-((triethylsilyl)oxy)tetracdec-13-en-5-yn-7-one (84)

To a stirred -78 °C solution of 68 (0.450 g, 1.24 mmol) in THF (15 mL) was added n-butyllithium (0.50 mL of a 2.5 M solution in hexanes, 1.25 mmol). After the mixture was stirred for 40 min, a solution of 67 (0.100 g, 0.384 mmol) in THF (3 mL) was added via cannula. After one hour, saturated aqueous NH$_4$Cl solution (8 mL) was added and the mixture was warmed to room temperature. The mixture was extracted with diethyl ether (3×20 mL) and the combined organic extracts were washed with water and saturated aqueous NaCl. The combined organic fraction was dried over Na$_2$SO$_4$, filtered and concentrated. The residue was chromatographed on silica gel (hexanes-ethyl acetate, 5:1, v/v) to give 84 (0.238g, 0.383 mmol, 99%) as colorless oil.

$R_f \ 0.58$ (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_D^{25} +51.8 \ (c \ 2.0, \ \text{CHCl}_3); \ \text{IR (neat): 3455, 3063, 3033, 2953, 2875, 1672, 1613, 1513, 1371, 1247, 1082 \ \text{cm}^{-1}; ^{1}\text{H NMR (CDCl}_3, \ 500 \ \text{MHz): 7.33-7.22 (m, 7H), 6.87 (m, 2H), 4.86 (t, } J = 1.5 \ \text{Hz, 1H), 4.76 (s,}}$
1H), 4.73 (d, J = 11.5 Hz, 1H), 4.44-4.36 (m, 3H), 3.93 (m, 2H), 3.80 (s, 3H), 3.69 (m, 1H), 3.46 (dd, J = 9.5, 6 Hz, 1H), 3.32 (dd, J = 9.5, 6 Hz, 1H), 2.66 (dd, J = 13, 6 Hz, 1H), 2.55 (dd, J = 13, 6 Hz, 1H), 2.14-2.04 (m, 4H), 1.86 (d, J = 3 Hz, 1H), 1.82 (m, 1H), 1.72 (s, 3H), 1.65 (m, 1H), 1.50 (m, 1H), 0.95 (m, 12H), 0.61 (q, J = 8 Hz, 6H); 13C NMR (CDCl₃, 125 MHz) δ 189.0, 159.1, 142.6, 137.5, 130.7, 129.1, 128.4, 128.0, 127.9, 113.7, 113.5, 95.5, 84.9, 80.5, 72.7, 72.3, 72.0, 71.5, 68.5, 55.3, 46.2, 38.8, 32.8, 28.6, 25.6, 22.4, 13.6, 6.8, 5.0; HRMS calcd for C₃₇H₅₄O₆Na [M + Na]⁺: 645.3587; found: 645.3594.

(2S,6R,8S,11R)-11-(benzylxy)-2-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-4-methyl-8-(2-methylallyl)-1,7-dioxaspiro[5.5]undec-4-ene (63)

To a solution of 84 (0.238 g, 0.861 mmol) in CH₂Cl₂ (4 mL) at room temperature was added imidazole (42 mg, 0.614 mmol) and 4-dimethylaminopyridine (2.3 mg, 0.019 mmol). A solution of chlorotriethylsilane (0.078 mL, 0.461 mmol) in CH₂Cl₂ (4 mL) was then added to the mixture dropwisely over 30 min. After stirring for 50 min, saturated aqueous NH₄Cl solution (3mL) was added. The mixture was extracted with diethyl ether (4 × 10 mL) and the combined organic phases were washed with water and saturated aqueous NaCl (5 mL), dried over Na₂SO₄, filtered, and concentrated. The residue was directly used for next step without further purification.
To a -78 °C suspension of CuI (0.440 g, 2.30 mmol) in diethyl ether (3 mL) under argon was added methyllithium (2.9 mL of a 1.6 M solution in diethyl ether, 4.6 mmol). The mixture was allowed to warm slowly to -30 °C until a clear and colorless solution formed. The solution was cooled to -78 °C, and a solution of crude TMS-protected 84 in diethyl ether (3 mL) was added via cannula. After 1.0 h, saturated aqueous NH₄Cl (5 mL) was added and the mixture was warmed to room temperature and stir until the aqueous became bright blue. The solution was extracted the diethyl ether (3 × 15 mL) and the combined organic phases were washed with water and saturated aqueous NaCl (10 mL), dried over Na₂SO₄, filtered, and concentrated to give crude 86 which was then dissolved in the mixture of dichloromethane (6 mL) and methanol (3 mL), and pyridinium p-toluenesulfonate (7.5 mg, 0.0279 mmol). After the solution was stirred at 25 °C for 4 hours, triethylamine (0.30 mL) was added. After the mixture was stirred for 10 min, the solvent was removed and the residue was purified via chromatography (hexanes-ethyl acetate, 10:1 to 8:1, v/v) to give 63 (0.112 g, 0.221 mmol, 57% based on 84) as colorless oil.

Rf 0.36 (hexanes-ethyl acetate, 8:1, v/v); [α]D²⁵ +30.2 (c 1.0, CDCl₃); IR (neat): 3058, 3026, 2932, 2860, 1609, 1521, 1250, 1098 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.30-7.23 (m, 7H), 6.86 (m, 2H), 5.20 (s, 1H), 4.72 (s, 1H), 4.68 (s, 1H), 4.62 (d, J = 12 Hz, 1H), 4.49 (d, J = 12 Hz, 1H), 4.43 (AB, J_AB = 11 Hz, 2H), 3.83-3.73 (m, 3H), 3.80 (s, 3H), 3.35 (dd, J = 9, 8 Hz, 1H), 3.28 (dd, J = 11.5, 4.5 Hz, 1H), 2.19 (dd, J = 14, 6 Hz, 1H), 2.11-1.99 (m, 3H), 1.92-1.81 (m, 3H), 1.74 (s, 3H), 1.67 (s, 3H), 1.25 (m, 1H), 1.01 (d, J = 6.5 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 159.0, 142.6, 139.0, 137.5, 131.0,
129.1, 128.1, 127.8, 127.4, 123.1, 113.7, 112.3, 96.2, 78.9, 72.7, 72.4, 71.4, 69.6, 67.8, 55.3, 44.1, 38.4, 33.1, 30.9, 24.4, 23.1, 23.0, 13.9; HRMS calcd for C\textsubscript{32}H\textsubscript{42}O\textsubscript{5}Na [M + Na\textsuperscript{+}]: 529.2930; found: 529.2930.

\[(R)-3-((2S,5R,6R,8S)-5-(benzyloxy)-8-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-10-methyl-1,7-dioxaspiro[5.5]undec-10-en-2-yl)-2-methylpropane-1,2-diol\]

To a mixture of 63 (0.112 g, 0.221 mmol), tert-butanol (1.2 mL) and water (1.2 mL) at 0 °C was added AD-mix-α (0.41 g). The mixture was stirred vigorously for 48 hours until when sodium sulfite (0.50 g) was added. The mixture was stirred at 25 °C for another one hour and 20 mL diethyl ether was added. The organic phase was separated and the aqueous phase was extracted by diethyl ether (5 × 5 mL). The combined organic phase was dried over Na\textsubscript{2}SO\textsubscript{4}, filtered and concentrated. The residue was purified through column chromatography (hexanes-ethyl acetate, 4:1 to 2:1 to 1:1, v/v) to give 100 (91 mg, 0.168 mmol, 76%) and 100\textsuperscript{a} (29 mg, 0.0536 mmol, 24%) as colorless oil:

Data for 100:

\[R_f \text{ } 0.32 \text{ (hexanes-ethyl acetate, 1:1, v/v)}; \ [\alpha]_{D}^{25} +20.5 \text{ (c } 1.0, \text{ CHCl}_{3}); \text{ IR (neat): } 3428, 3063, 3027, 2955, 2929, 2855, 1612, 1513, 1451, 1380, 1301, 1246, 1179, 1093, 1036, 964 \text{ cm}^{-1}; \text{ } ^1\text{H NMR (CDCl}_3, 500 MHz): } \delta 7.33-7.24 \text{ (m, 7H), } 6.86 \text{ (m, 2H), } 5.16 \text{ (s, 1H),} \]
4.59 (d, $J = 12.5$ Hz, 1H), 4.46-4.41 (m, 3H), 4.02 (s, 1H), 3.80 (s, 3H), 3.78 (m, 1H), 3.58 (dd, $J = 9$, 5 Hz, 1H), 3.51 (m, 2H), 3.46 (dd, $J = 11$, 4 Hz, 1H), 3.30-3.24 (m, 2H), 2.51 (brt, $J = 5$ Hz, 1H), 2.08 (m, 1H), 1.99 (dd, $J = 16$, 11 Hz, 1H), 1.93 (qd, $J = 12.5$, 3.5 Hz, 1H), 1.74 (s, 3H), 1.68-1.62 (m, 3H), 1.35 (m, 1H), 1.08 (s, 3H), 1.01 (d, $J = 6.5$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 159.2, 138.8, 138.0, 130.6, 129.4, 128.2, 127.7, 127.5, 122.3, 113.7, 96.3, 78.5, 72.9, 72.4, 71.8, 71.4, 69.8, 69.6, 67.2, 55.3, 44.3, 38.4, 32.4, 32.4, 25.2, 24.1, 23.0, 13.5; HRMS calcd for C$_{32}$H$_{44}$O$_7$Na [M + Na]$^+$: 563.2985; found: 563.2990.

Date for 100a:

$R_f$ 0.40 (hexanes-ethyl acetate, 1:1, v/v); $[\alpha]_{D}^{25}$ +14.5 (c 0.67, CHCl$_3$); IR (neat): 7.32-7.24 (m, 7H), 6.86 (m, 2H), 5.16 (s, 1H), 4.60 (d, $J = 12.5$ Hz, 1H), 4.48 (d, $J = 12.5$ Hz, 1H), 4.47 (d, $J = 11.5$ Hz, 1H), 4.41 (d, $J = 11.5$ Hz, 1H), 4.13 (brt, $J = 11.5$ Hz, 1H), 4.01 (s, 1H), 3.80 (s, 3H), 3.78 (m, 1H), 3.64 (dd, $J = 9$, 4.5 Hz, 1H), 3.50 (dd, $J = 9$, 6.5 Hz, 1H), 3.35 (d, $J = 9.5$ Hz, 1H), 3.26 (dd, $J = 12$, 9.5 Hz, 2H), 2.67 (brs, 1H), 2.09-1.91 (m, 3H), 1.86-1.76 (m, 3H), 1.74 (s, 3H), 1.60 (m, 3H), 1.44 (m, 2H), 1.14 (s, 3H), 1.01 (d, $J = 6.5$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 159.1, 138.8, 138.2, 130.6, 129.4, 128.2, 127.8, 127.5, 122.1, 113.7, 96.2, 78.5, 72.8, 72.2, 71.7, 71.5, 71.0, 70.0, 66.7, 55.3, 43.0, 38.6, 32.8, 32.2, 24.6, 24.1, 23.0, 13.8; HRMS calcd for C$_{32}$H$_{44}$O$_7$Na [M + Na]$^+$: 563.2985; found: 563.2988.
(2S,6R,8S,11R)-11-(benzylxy)-2-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-4-methyl-8-(((R)-2,2,4-trimethyl-1,3-dioxolan-4-yl)methyl)-1,7-dioxaspiro[5.5]undec-4-ene (101)

To a solution of 100 (0.091g, 0.168 mmol) in dichloromethane (2 mL) was added 2,2-dimethoxypropane (0.20 mL, 0.212g, 2.04 mmol followed by pyridinium p-toluenesulfonate (2.3 mg, 0.0084 mmol). The reaction was stirred for 2.5 hours until triethylamine (0.1 mL) was added. The solvent was evaporated on rotavapor and the residue was purified through column chromatography (hexanes-ethyl acetate, 10:1 to 7:1, v/v) to give 101 (94 mg, 0.168 mmol, quant.) colorless oil.

Rf 0.42 (hexanes-ethyl acetate, 4:1, v/v); [α]D 25 +11.8 (c 0.70, CDCl3); IR (neat): 3058, 3026, 2931, 2862, 1609, 1521, 1250, 1098 cm⁻¹; ¹H NMR (CDCl3, 500 MHz): δ 7.26 (m, 7H), 6.86 (d, J = 7 Hz, 2H), 5.15 (s, 1H), 4.61(d, J = 12 Hz, 1H), 4.48 (d, J = 12 Hz, 1H), 4.43 (d, J = 4 Hz, 1H), 3.78 (m, 2H), 3.78 (s, 3H), 3.72 (m, 1H), 3.65 (m, 2H), 3.35 (dd, J = 9, 8 Hz, 1 H), 3.24 (dd, J = 11.5, 8.5, 1H), 2.08 (m, 1H), 2.01 (m, 1H), 1.92 (qd, J = 12.5, 3 Hz, 1H), 1.80 (m, 2H), 1.73 (s, 3H), 1.66(m, 2H), 1.36 (s, 3H), 1.32 (s, 3H), 1.24 (s, 3H), 1.00(d, J = 7, 1H); ¹³C NMR (CDCl3, 125 MHz) δ 159.1, 139.0, 136.9, 130.9, 129.2, 128.1, 127.8, 127.4, 123.0, 113.7, 108.2, 95.9, 80.4, 78.8, 77.2, 75.0, 72.7, 72.2, 71.3, 69.8, 66.2, 55.3, 46.2, 38.5, 32.8, 32.4, 27.5, 27.0, 24.4, 24.3, 23.0, 13.8; HRMS calcd for C₃₅H₄₆O₇Na [M + Na]⁺: 603.3298; found: 603.3290.

93
(S)-2-((2S,6R,8S,11R)-11-(benzyloxy)-4-methyl-8-(((R)-2,2,4-trimethyl-1,3-dioxolan-4-yl)methyl)-1,7-dioxaspiro[5.5]undec-4-en-2-yl)propanal (61)

To a mixture of 101 (30 mg, 51 µmol), CH₂Cl₂ (5.0 mL), an aqueous NaH₂PO₄ buffer (pH = 7, 1.0 mL), and tert-butyl alcohol (0.30 mL) was added 2,3-dichloro-5,6-dicyanobenzoquinone (70 mg, 0.31 mmol). The reaction flask was placed in an aqueous bath and sonicated for 5 min. The mixture was diluted with diethyl ether (8 mL) and washed with saturated aqueous NaHCO₃ solution (2 mL). The aqueous phase was extracted with diethyl ether (3 × 2 mL) and the combined organic phases were washed with saturated aqueous NaCl (1.5 mL), dried over Na₂SO₄, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexanes-ethyl acetate, 5:1 to 3:2, v/v) to give colorless oil which was then dissolved in CH₂Cl₂ (3.0 mL). The solution was added NaHCO₃ (150 mg, 1.8 mmol) followed by the Dess–Martin periodinane (80 mg, 0.19 mmol). The mixture was stirred for 30 min before diethyl ether (4.0 mL) and 10% aqueous Na₂S₂O₃ and saturated aqueous NaHCO₃ (1.0 mL ea) were added. The mixture was stirred until the organic phase became clear and colorless. The separated aqueous phase was extracted with diethyl ether (3 × 2 mL), and the combined organic fractions were washed with saturated aqueous NaCl (1 mL), dried over Na₂SO₄, filtered, and
concentrated. Silica gel column chromatography (hexanes-ethyl acetate, 5:1, v/v) of the residue gave **61** (22 mg, 45 µmol, 90%) as a white crystalline solid:

\[ R_f 0.31 \text{ (hexanes-ethyl acetate, 4:1, v/v); } [\alpha]_D^{25} +29.2 \text{ (c 0.42, CDCl}_3\text{); IR (neat): } 3080, 3061, 3030, 2972, 2928, 2864, 1726, 1453, 1378, 1244, 1206, 1174, 1092, 1053, 1002, 977, 926, 856, 805, 735, 697 \text{ cm}^{-1}; \text{ }^1\text{H NMR (CDCl}_3\text{, 500 MHz): } \delta 9.98 \text{ (d, } J = 2 \text{ Hz, } 1\text{H}), 7.33-7.24 \text{ (m, } 5\text{H}), 5.17 \text{ (s, } 1\text{H}), 4.61 \text{ (d, } J = 12.5 \text{ Hz, } 1\text{H}), 4.47 \text{ (d, } J = 12.5 \text{ Hz, } 1\text{H}), 4.03 \text{ (ddd, } J = 11.5, 8.5, 3 \text{ Hz, } 1\text{H}), 3.85-3.79 \text{ (m, } 2\text{H}), 3.67 \text{ (d, } J = 8.5 \text{ Hz, } 1\text{H}), 3.24 \text{ (dd, } J = 11.5, 5 \text{ Hz, } 1\text{H}), 2.70 \text{ (m, } 1\text{H}), 2.10 \text{ (m, } 1\text{H}), 1.92-1.81 \text{ (m, } 3\text{H}), 1.75 \text{ (s, } 3\text{H}), 1.72-1.61 \text{ (m, } 3\text{H}), 1.37 \text{ (s, } 3\text{H}), 1.33 \text{ (s, } 3\text{H}), 1.31 \text{ (s, } 3\text{H}), 1.11 \text{ (d, } J = 7 \text{ Hz, } 3\text{H); }^1\text{C NMR (CDCl}_3\text{, 125 MHz) } \delta 204.5, 138.7, 136.1, 128.2, 127.8, 127.5, 123.3, 108.4, 96.1, 80.3, 78.5, 75.2, 71.4, 69.7, 66.7, 50.5, 45.8, 33.3, 32.1, 27.4, 27.1, 24.5, 24.2, 22.9, 10.5; \text{ HRMS calcd for } C_{27}H_{38}O_{6}Na \text{ [M + Na]}^+: 481.2566; \text{ found: 481.2566.}

\[
\begin{align*}
\text{BnO} & \quad \text{OPMB} \\
\text{OBn} & \\
\end{align*}
\]

**3S,4S)-3,5-bis(benzyloxy)-4-methylpentan-1-oxyl 4-methoxybenzyl ether (106)**

To a 0 °C solution of **105** (5.61 g, 13.1 mmol) in THF (120 mL) was added NaBH₄ (2.48 g, 65.7 mmol) followed by water (15 mL). The mixture was stirred for 14 hours before saturated NH₄Cl solution (30 mL) was added. The mixture was stirred for another hour and THF was removed on rotavapor. The aqueous phase was extracted with diethyl ether (4 × 50 mL) and the combined organic phase was dried over Na₂SO₄, filtered and concentrated. The residue was dissolved in THF (110 mL). After the solution was cooled
to 0 °C, NaH (60% in mineral oil, 2.78 g, 69.4 mmol) was added. The reaction mixture was warmed to room temperature and was stirred for 1 hour. After the reaction mixture was cooled to 0 °C, benzyl bromide (9.97 g, 6.9 mL, 57.8 mmol) and tetra-n-butylammonium iodide (4.27 g, 11.6 mmol) was added. The mixture was warmed to room temperature and was stirred for 72 hours before methanol (3 mL) was added. The mixture was stirred for another one hour and saturated NH₄Cl solution (20 mL) was added. THF was removed by rotavapor and aqueous phase was extracted with diethyl ether (4 × 50 mL). The combined organic phase was dried over Na₂SO₄, filtered, and concentrated. Silica gel column chromatography (hexanes-ethyl acetate, 10:1, v/v) of the residue gave product 106 (3.79 g, 8.73 mmol, 67%).

\[ R_f \ 0.39 \ (\text{hexanes-ethyl acetate, 8:1, v/v}); \ [\alpha]_D^{25} \ -17.0 \ (c \ 0.70, \ CHCl_3) \]; IR (neat): 3080, 3057, 3027, 2921, 2856, 1613, 1513, 1454, 1362, 1302, 1248, 1092, 820, 736, 697 cm⁻¹; \(^1\)H NMR (CDCl₃, 500 MHz): \( \delta \) 7.33-7.21 (m, 12H), 6.86 (m, 2H), 4.47 (m, 4H), 4.42 (d, \( J = 12 \) Hz, 1H), 4.38 (d, \( J = 12 \) Hz, 1H), 3.80 (s, 3H), 3.73 (m, 1H), 3.53 (m, 3H), 3.34 (dd, \( J = 9, 7 \) Hz, 1H), 2.03 (m, 1H), 1.82 (m, 2H), 0.97 (d, \( J = 7 \) Hz, 1H); \(^1^3\)C NMR (CDCl₃, 125 MHz): \( \delta \) 159.2, 139.1, 138.7, 130.7, 129.3, 128.3, 128.3, 127.7, 127.6, 127.5, 127.4, 113.8, 77.2, 73.0, 72.7, 72.6, 72.5, 67.0, 55.3, 37.2, 32.1, 12.1; HRMS calcd for C₂₈H₃₄O₄Na [M + Na]⁺: 457.2355; found: 457.2360.

\[
\text{BnO} - \text{OBn} - \text{OH}
\]

(3S,4S)-3,5-bis(benzyloxy)-4-methylpentan-1-ol
To a mixture of 106 (2.64 g, 6.07 mmol), 1.0 mL tert-butanol, 5.0 mL pH = 7 buffer and dichloromethane (50 mL) at 25 °C was added 2,3-dichloro-5,6-dicyanobenzoquinone (3.18 g, 14.0 mmol). The mixture was stirred for 2 hours and saturated NaHCO₃ (50 mL) solution was added. The mixture was then diluted with diethyl ether (100 mL) and the organic phase was separated. The aqueous phase was further extracted with diethyl ether (3 × 50 mL) before the combined organic phase was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 1:1, v/v) to give the product (1.80 g, 5.72 mmol, 94%) as a light yellow oil.

\[ R_f \ 0.16 \text{ (hexanes-ethyl acetate, 4:1, v/v); } [\alpha]_{D}^{25} -20.0 \text{ (c 0.64, CHCl}_3\text{); IR (neat): 3407, 3084, 3056, 3029, 2921, 2874, 1496, 1454, 1362, 1206, 1066, 1028, 736, 697 \text{ cm}^{-1}; \]

\[ ^1\text{H NMR (CDCl}_3\text{, 500 MHz): } \delta 7.35-7.27 \text{ (m, 10H), 4.58 (d, } J = 11.5 \text{ Hz, 1H), 4.53 (d, } J = 11.5 \text{ Hz, 1H), 4.49 (s, 2H), 3.74 (m, 3H), 3.56 (dd, } J = 9, 6 \text{ Hz, 1H), 3.36 (dd, } J = 9, 6.5 \text{ Hz, 1H), 2.12 (m, 1H), 2.05 (brs, 1H), 1.77 (m, 2H), 1.01 (d, } J = 7 \text{ Hz, 3H); } ^{13}\text{C NMR (CDCl}_3\text{, 125 MHz): } \delta 138.6, 138.5, 128.4, 128.4, 127.9, 127.7, 127.7, 127.6, 79.2, 73.2, 72.3, 60.9, 36.8, 33.8, 12.8; \]


\[ \text{(3S, 4S)-3,5-bis(benzyloxy)-4-methypentanal (72)} \]

To a 0 °C solution of (3S,4S)-3,5-bis(benzyloxy)-4-methypentan-1-ol (1.80 g, 5.72 mmol) in dichloromethane (30 mL) was added DMSO (2.5 mL), diisopropylethylamine
(6.0 mL) and sulfur trioxide pyridine complex (2.00 g, 12.6 mmol). The solution was stirred for 1 h at 0 °C before saturated NH₄Cl solution (8 mL) and diethyl ether (60 mL) was added. The mixture was stirred for 5 min and the organic phase was separated. The aqueous phase was extracted with diethyl ether (3 × 30 mL). The combined organic phase was dried over Na₂SO₄, filtered, and concentrated. Silica gel column chromatography (hexanes-ethyl acetate, 10:1, v/v) of the residue gave product 72 (1.67 g, 5.34 mmol, 93%).

\[ R_f \ 0.61 \] (hexanes-ethyl acetate, 4:1, v/v); \[ [\alpha]_D^{25} -2.2 \] (c 0.67, CHCl₃); IR (neat): 3082, 3062, 3029, 2963, 2910, 2856, 2726, 1723, 1487, 1454, 1369, 1204, 1091, 736, 697 cm⁻¹; \(^1\)H NMR (CDCl₃, 500 MHz): \( \delta \) 9.77 (dd, \( J = 1.5, 1 \) Hz, 1H), 7.37-7.27 (m, 10H), 4.56 (d, \( J = 12 \) Hz, 1H), 4.52 (d, \( J = 12 \) Hz, 1H), 4.49 (d, \( J = 12 \) Hz, 1H), 4.46 (d, \( J = 12 \) Hz, 1H), 4.14 (m, 1H), 3.52 (m, 1H), 3.40 (m, 1H), 2.74 (m, 1H), 2.58 (m, 1H), 2.07 (m, 1H), 1.00 (d, \( J = 7 \) Hz, 1H); \(^{13}\)C NMR (CDCl₃, 125 MHz): \( \delta \) 201.5, 138.4, 128.4, 128.4, 127.7, 127.7, 127.6, 75.1, 73.1, 72.4, 72.0, 46.6, 37.7, 12.4; HRMS calcd for C₂₀H₂₄O₃Na [M + Na]⁺: 335.1623; found: 335.1620.

\[(S)-4\text{-benzyl-3-((S)-5-(benzyloxy)-2-methypentanoyl)oxazolidin-2-one (103)}\]

To a -78 °C solution of 102 (14.10 g, 38.4 mmol) in THF (200 mL) was added a solution of NaHMDS (2.0 M in THF, 20.0 mL, 40.0 mmol) dropwisely. The mixture of was
stirred at -78 °C for 2 hours before MeI (14.4 mL, 32.7 g, 230 mmol) was added. The mixture was stirred for another 2 h before saturated NH₄Cl (100 mL). The mixture was warmed to room temperature and THF was evaporated. The aqueous phase was extracted with diethyl ether (4 × 100 mL) before the combined organic phase was dried over Na₂SO₄, filtered and concentrated. The residue was purified by chromatography (hexanes-EtOAc, 5:1, v/v) to give 103 (11.70 g, 30.7 mmol, 80%) as light yellow oil.

\[ R_f 0.38 \text{ (hexanes-ethyl acetate, 4:1, v/v); } [\alpha]_D^{25} +56.4 \text{ (c 0.75, CHCl}_3) \]; IR (neat): 3021, 2930, 2857, 1779, 1696, 1454, 1385, 1210, 1100, 737, 699 cm⁻¹; \(^1\)H NMR (CDCl₃, 500 MHz): \( \delta \) 7.34-7.26 (m, 8H), 7.20 (d, \( J = 7.5 \) Hz, 1H), 4.64 (m, 1H), 4.49 (s, 2H), 4.12 (m, 2H), 3.75 (tq, \( J = 7, 7 \) Hz, 1H), 3.47 (m, 2H), 3.26 (dd, \( J = 13.5, 3.5 \) Hz, 1H), 2.76 (dd, \( J = 13.5, 9.5 \) Hz, 1H), 1.84 (m, 2H), 1.67 (m, 1H), 1.24 (d, \( J = 7 \) Hz, 1H); \(^{13}\)C NMR (CDCl₃, 125 MHz): \( \delta \) 177.0, 153.0, 138.6, 135.4, 129.5, 128.9, 128.4, 127.6, 127.5, 127.3, 77.2, 72.9, 70.3, 66.0, 55.3, 37.9, 37.5, 30.1, 27.4, 17.5; HRMS calcd for C₂₅H₄₀O₄Na [M + Na]⁺: 404.1838; found: 404.1837.

\[
\text{(S)-methyl 5-(benzyloxy)-2-methylpentanoate (104)}
\]

To methanol (70 mL) at 0 °C was added methylmagnesium bromide (1M in diethyl ether, 18.9 mL, 18.9 mmol) dropwise. After stirring for 15 min, 103 (5.40 g, 14.2 mmol) in methanol (20 mL) was cannulated into the flask and the reaction was stirred for 2 hours before saturated NH₄Cl solution (20 mL) was added. Methanol in the reaction mix-
ture was removed under vacuum and diethyl ether (100 mL) was added. The mixture was stirred for another 10 min and the organic phase was separated. The aqueous phase was extracted with diethyl ether (2 × 30 mL) before the combined organic phase was dried over Na₂SO₄, filtered and concentrated. The residue was purified by chromatography (hexanes-EtOAc, 15:1, v/v) to give 104 (2.82 g, 11.9 mmol, 84%) as light yellow oil.

\[ R_f 0.21 \text{ (hexanes-ethyl acetate, 20:1, v/v); } [\alpha]_{D}^{25} +14.7 \text{ (c 0.82, CHCl}_3\text{);} \text{ IR (neat): } 3084, 3056, 3028, 2947, 2857, 1736, 1454, 1360, 1169, 1101, 736, 698 \text{ cm}^{-1}; \text{ } ^1\text{H NMR (CDCl}_3\text{, 500 MHz): } \delta 7.34-7.27 \text{ (m, 5H), 4.49 (s, 2H), 3.66 (s, 3H), 3.46 (m, 2H), 2.46 (tq, } J = 7, 7 \text{ Hz, 1H), 1.71 (m, 1H), 1.61 (m, 2H), 1.55 (m, 1H), 1.16 (d, } J = 7 \text{ Hz, 1H); } \text{ ^13C NMR (CDCl}_3\text{, 125 MHz): } \delta 177.1, 138.6, 128.4, 127.6, 127.5, 72.9, 70.1, 51.5, 39.3, 30.4, 27.5, 17.1; \text{ HRMS calcd for } C_{14}H_{20}O_3Na [M + Na]^+: 259.1310; \text{ found: 259.1305.} \]

\[ \begin{align*}
\text{MeO} &\quad \text{O} \\
\text{O} &\quad \text{O} \\
\text{OBn} &\quad \text{O}
\end{align*} \]

\text{(S)-dimethyl (6-(benzyloxy)-3-methyl-2-oxohexyl)phosphonate (73)}

To a -78 °C solution of dimethyl methylphosphonate (1.53 g, 12.4 mmol) in THF (50 mL) was added \textit{n}-butyllithium (2.5 M in hexanes, 5 mL, 12.5 mmol). The solution was stirred at -78 °C for 1 hour before 104 (2.24 g, 9.5 mmol) in THF (20 mL) was cannulated into the reaction flask. The reaction mixture was stirred for one more hour before saturated NH₄Cl solution (20 mL) was added. The mixture was warmed to room temperature and was stirred for 15 min. After removal of THF from the mixture on vaccum, the residue was extracted with diethyl ether (4 × 60 mL). The combined organic phase was
dried over Na$_2$SO$_4$, filtered, and concentrated. Silica gel column chromatography (hexanes-ethyl acetate, 1:1 to 1:4, v/v) of the residue gave product 73 (3.68 g, 11.2 mmol, 91%) as a clear colorless oil.

$R_f$ 0.56 (hexanes-ethyl acetate, 1:5, v/v); $[\alpha]_D^{25} +7.9$ (c 0.58, CHCl$_3$); IR (neat): 3083, 3058, 3022, 2953, 2919, 2854, 1713, 1454, 1366, 1258, 1179, 1100, 1030, 876, 810, 740, 699 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.35-7.27 (m, 5H), 4.48 (s, 2H), 3.77 (dd, $J = 11.5$, 2 Hz, 6H), 3.46 (m, 2H), 3.11 (d, $J = 22.5$ Hz, 2H), 2.76 (ttq, $J = 7$ Hz, 1H), 1.77 (m, 1H), 1.60 (m, 2H), 1.45 (m, 1H), 1.11 (d, $J = 7$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 205.5, 138.5, 128.4, 127.6, 127.6, 72.9, 70.0, 53.0, 46.9, 40.2, 39.1, 29.1, 27.2, 16.0; HRMS calcd for C$_{16}$H$_{25}$O$_5$PNa [M + Na]$^+$: 351.1337; found: 351.1333.

(4$S,9$S,10$S$,$E$)-1,9,11-tris(benzyloxy)-4,10-dimethylundec-6-en-5-one (71)

To a 25 ºC solution of 73 (1.89 g, 5.76 mmol) in CH$_3$CN (20 mL) was added LiCl (0.285 g, 6.72 mmol) followed by diisopropylethylamine (1.2 mL, 6.72 mmol). The mixture was stirred for 15 min before 72 (1.60 g, 5.12 mmol) in 10 mL CH$_3$CN was cannulated into the reaction. The mixture was stirred for another 16 hours before saturated NH$_4$Cl solution (5 mL) was added. CH$_3$CN was removed from the mixture under vaccum and the residue was extracted with diethyl ether (4 x 60 mL). The combined organic phase was dried over Na$_2$SO$_4$, filtered, and concentrated. Silica gel column chromatogra-
phy (hexanes-ethyl acetate, 10:1, v/v) of the residue gave product 71 (2.55 g, 4.95 mmol, 97%) as a colorless oil.

\[ R_f \text{ 0.68 (hexanes-ethyl acetate, 4:1, v/v)}; [\alpha]_D^{25} -0.8 \text{(c 0.75, CHCl}_3\text{); IR (neat): 3081, 3051, 3021, 2962, 2909, 2855, 1693, 1667, 1632, 1620, 1538, 1454, 1360, 1099 cm}^{-1}; {^1}\text{H NMR (CDCl}_3\text{, 500 MHz): } \delta \text{ 7.36-7.26 (m, 15H), 6.87 (dt, } J = 15.5, 7.5 \text{ Hz, 1H), 6.20 (d, } J = 15.5 \text{ Hz, 1H), 4.54 (d, } J = 11.5 \text{ Hz, 1H), 4.74-4.45 (m, 5H), 3.71 (m, 1H), 3.49 (dd, } J = 9, 7 \text{ Hz, 1H), 3.44 (t, } J = 6 \text{ Hz, 2H), 3.36 (dd, } J = 9, 6 \text{ Hz, 1H), 2.72 (tq, } J = 7, 7 \text{ Hz, 1H), 2.50 (m, 1H), 2.43 (m, 1H), 1.99 (m, 1H), 1.74 (m, 1H), 1.58 (m, 2H), 1.45 (m, 1H), 1.08 (d, } J = 7 \text{ Hz, 3H), 0.98 (d, } J = 7 \text{ Hz, 3H); } {^{13}}\text{C NMR (CDCl}_3\text{, 125 MHz): } \delta \text{ 203.4, 143.9, 138.6, 138.5, 130.7, 128.4, 128.3, 127.7, 127.6, 127.6, 127.6, 127.5, 78.6, 73.1, 72.9, 72.5, 72.4, 70.2, 43.6, 37.4, 35.3, 29.7, 27.5, 16.7, 11.7; HRMS calcd for C}_{34}\text{H}_{42}\text{O}_4\text{Na [M + Na]}^+: 537.2981; found: 537.3015.}

\((S)-2-((2S,6R,11S)-11\text{-methyl-1,7-dioxaspiro[5.5]undecan-2-yl})\text{propan-1-ol (107)}\)

A mixture of 71 (2.50 g, 4.86 mmol) and 20% Pd(OH)$_2$ on carbon (0.30 g, 0.5 mmol) in absolute ethanol (50 mL) was stirred vigorously under 1 atm of H$_2$ for 15 h. The mixture was filtered through Celite with ethyl acetate. The filtrate was concentrated and the residue was purified by silica gel column chromatography (hexanes-ethyl acetate, 5:1, v/v) to give 107 (1.03 g, 4.52 mmol, 93%) as a clear, colorless oil.
$R_f$ 0.43 (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_{D}^{25}$ +63.6 ($c$ 0.68, CHCl$_3$); IR (neat): 3404, 2930, 2877, 1452, 1378, 1272, 1227, 1071, 1027, 990, 967, 947, 915, 865, 851, 800 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 3.82 (ddd, $J$ = 14.5, 5, 2.5 Hz, 1H), 3.75-3.56 (m, 4H), 2.82 (brt, $J$ = 5 Hz, 1H), 2.06 (m, 1H), 1.90 (m, 1H), 1.74 (m, 3H), 1.63 (m, 2H), 1.47 (m, 1H), 1.39 (td, $J$ = 12.5, 4 Hz, 1H), 1.31 (m, 2H), 1.21 (td, $J$ = 13.5, 4.5 Hz, 1H), 0.99 (d, $J$ = 7 Hz, 3H), 0.93 (d, $J$ = 7 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 98.4, 73.2, 66.4, 60.6, 39.0, 35.9, 32.2, 25.9, 25.8, 19.9, 18.7, 14.5, 11.9; HRMS calcd for C$_{13}$H$_{24}$O$_3$Na [M + Na]$^+$: 251.1623; found: 251.1622.

(2S,6R,11S)-2-((R)-1-bromopropan-2-yl)-11-methyl-1,7-dioxaspiro[5.5]undecane (65)

To a solution of 107 (0.851 g, 3.73 mmol), triphenylphosphine (1.23 g, 4.68 mmol) and triethylamine (1.1 mL, 7.80 mmol) in dichloromethane (20 mL) was added carbon tetrabromide (1.68 g, 5.07 mmol). The solution was stirred for 16 hours before saturated NH$_4$Cl solution (5 mL) and diethyl ether (30 mL) was added. The organic phase was separated and the aqueous phase was extracted with diethyl ether ($3 \times 30$ mL). The combined organic phase was dried over Na$_2$SO$_4$, filtered, and concentrated. Silica gel column chromatography (hexanes-ethyl acetate, 30:1, v/v) of the residue gave product 65 (1.029 g, 3.54 mmol, 95%) as a colorless oil:
\[ R_f \] 0.50 (hexanes-ethyl acetate, 20:1, v/v); \([\alpha]_D^{25} +67.2 \ (c \ 0.75, \ CHCl_3); \] IR (neat): 2942, 2873, 1462, 1378, 1270, 1239, 1211, 1194, 1171, 1067, 1027, 968, 948, 915, 866, 852, 738 \text{ cm}^{-1}; \] \(^1\)H NMR (CDCl\textsubscript{3}, 500 MHz): \(\delta\) 3.68 (m, 2H), 3.58 (dd, \(J = 10, 5 \text{ Hz, 1H})\), 3.57 (m, 1H), 3.37 (dd, \(J = 10, 7 \text{ Hz, 1H})\), 2.13 (m, 1H), 1.87 (m, 1H), 1.77 (m, 2H), 1.70 (m, 1H), 1.62 (m, 2H), 1.52 (m, 1H), 1.32-1.25 (m, 3H), 1.15 (td, \(J = 13.5, 4.5 \text{ Hz, 1H})\), 1.11 (d, \(J = 6.5 \text{ Hz, 3H})\), 0.99 (d, \(J = 7.5 \text{ Hz, 3H})\); \(^{13}\)C NMR (CDCl\textsubscript{3}, 125 MHz): \(\delta\) 97.9, 70.4, 60.5, 40.8, 38.2, 35.9, 32.3, 27.6, 25.7, 19.8, 18.8, 14.4, 14.2; HRMS calcd for C\textsubscript{13}H\textsubscript{23}O\textsubscript{2}BrNa [M + Na]\(^+\): 313.0779, 315.0759; found: 313.0771, 313.0745.

\[ \text{(2S,4R,4aR,6R,8aR)-4-(benzyloxy)-6-(but-3-en-1-yl)-6-methoxy-3-methyleneoctahydro} \]

\[ \text{pyrano-[3,2-b]} \text{pyran-2-yl)methanol (161)} \]

To the solution of 160 (0.890 g, 1.82 mmol) in THF (15 mL) was added tetrabutylammonium fluoride (1M in THF, 2.2 mL, 2.2 mmol). The mixture was stirred for 2 hours before saturated NH\textsubscript{4}Cl solution (10 mL) and diethyl ether (20 mL) was added. The organic phase was separated and the aqueous phase was extracted with diethyl ether (20 mL) three more times. The organic extracts were combined and dried over Na\textsubscript{2}SO\textsubscript{4}. After evaporation of the solvent, the residue was purified through column chromatography to get 161 (0.681 g, 1.82 mmol, quat.) as a white solid:
$R_f$ 0.10 (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_D^{25} -31.1$ (c 0.32, CHCl$_3$); IR (neat): 3453, 3083, 3032, 2956, 2873, 1643, 1545, 1354, 1130, 1100, 1043 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.33 (m, 5H), 5.86 (ddt, $J = 17$, 10, 6.5 Hz, 1H), 5.47 (t, $J = 1.5$ Hz, 1H), 5.13 (s, 1H), 5.05 (dq, $J = 17$, 1.5 Hz, 1H), 5.00 (dq, $J = 10$, 1.5 Hz, 1H), 4.92 (d, $J = 12$ Hz, 1H), 4.78 (d, $J = 12$ Hz, 1H), 4.04 (dt, $J = 9.5$, 1.5 Hz, 1H), 3.95 (t, $J = 10.5$ Hz, 1H), 3.50 (m, 3H), 3.22 (s, 3H), 2.08 (m, 2H), 1.96-1.76 (m, 5H), 1.59 (m, 2H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 142.1, 138.7, 138.2, 128.3, 127.5, 127.5, 114.6, 113.0, 99.2, 80.3, 77.5, 76.7, 74.1, 69.5, 61.4, 47.5, 34.8, 32.3, 27.9, 25.5; HRMS calcd for C$_{22}$H$_{30}$O$_5$Na [M + Na]$^+$: 397.1991; found: 397.2007.

(1S,3S)-1-((2S,4R,4aR,6R,8aR)-4-(benzyloxy)-6-(but-3-en-1-yl)-6-methoxy-3-methylenoctahydropyrano[3,2-b]pyran-2-yl)-3-((2S,6R,11S)-11-methyl-1,7-dioxaspiro[5.5]undecan-2-yl)butan-1-ol (163)

To a 0 °C solution of 161 alcohol (120 mg, 0.32 mmol) in CH$_2$Cl$_2$ (5 mL) was added NaHCO$_3$ (1.00 g, 11.9 mmol) followed by Dess-Martin periodinane (0.50 g, 1.18 mmol). The reaction was stirred for 1h before the addition saturated NaS$_2$O$_3$ solution (1 mL) followed by diethyl ether (10 mL). The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 5 mL). The combined organic phase was dried over Na$_2$SO$_4$, filtered and concentrated. The residue was passed through a pad of silica gel
with a mixture of hexanes and ethyl acetate (3:1, v/v) and the filtrate was concentrated. The residue was used for next step without further purification.

To a -78 °C solution of 65 (374 mg, 1.28 mmol) in diethyl ether (8 mL) was added t-butyllithium (1.7 M in pentane, 1.4 mL, 2.4 mmol) dropwise. The reaction was stirred at -78 °C before warmed to room temperature. After stirred at room temperature for 30 min, the mixture was re-cooled to -78 °C before a solution of 157 (crude, 0.32 mmol theor) in diethyl ether (2 mL) was added via cannula. After 30 min, saturated NH₄Cl solution (2 mL) was added before the mixture was warmed up to room temperature. The organic phase was separated and the aqueous phase was extracted with diethyl ether (4 × 3 mL). The combined organic phase was dried over Na₂SO₄, filtered, and concentrated. Silica gel column chromatography (hexanes-ethyl acetate, 8:1 to 2:1, v/v) of the residue gave 163 (39 mg, 0.0667 mmol) and 162 (51 mg, 0.0873 mmol, 48% combined yield) as colorless oil:

$$R_f 0.18 \text{ (hexanes-ethyl acetate, 4:1, v/v); } [\alpha]_D^{20} +3.1 \text{ (c 0.54, CHCl}_3); \text{ IR (neat): 3425, 3068, 3028, 2942, 2863, 1644, 1556, 1454, 1368, 1209, 1074, 1038 \text{ cm}^{-1}]; \text{ }^1\text{H NMR (CDCl}_3, 500 MHz): } \delta 7.33 \text{ (m, 5H), 5.87 (ddt, } J = 17, 10, 6.5 \text{ Hz, 1H), 5.47 (t, } J = 2 \text{ Hz, 1H), 5.07 (s, 1H), 5.06 (dd, } J = 17, 1.5 \text{ Hz, 1H), 4.99 (dd, } J = 10, 1.5 \text{ Hz, 1H), 4.90 (d, } J = 12 \text{ Hz, 1H), 4.81 (d, } J = 12 \text{ Hz, 1H), 3.94 (m, 3H), 3.67-3.55 (m, 3H), 3.44 (m, 2H), 3.23 (s, 3H), 2.88 (brs, 1H), 2.19-2.04 (m, 3H), 1.95-1.55 (m, 13H), 1.47 (d, } J = 12.5 \text{ Hz, 1H), 1.32-1.08 (m, 5H), 1.00 (d, } J = 7 \text{ Hz, 3H), 0.89 (d, } J = 6.5 \text{ Hz, 3H); } ^{13}\text{C NMR (CDCl}_3, 125 MHz): } \delta 142.4, 138.7, 138.2, 128.3, 127.5, 127.5, 114.6, 113.3, 99.2, 98.0, 85.1, 77.3, 73.7, 73.3, 70.2, 65.9, 60.4, 47.5, 36.8, 35.9, 34.8, 34.5, 32.4, 27.9, 26.9, 25.7,
25.6, 20.0, 19.0, 15.0, 14.4; HRMS calcd for C$_{35}$H$_{52}$O$_7$Na [M + Na]$^+$: 607.3611; found: 607.3615

(1R,3S)-1-((2S,4R,4aR,6R,8aR)-4-(benzyloxy)-6-(but-3-en-1-yl)-6-methoxy-3-methyleneoctahydropyrano[3,2-b]pyran-2-yl)-3-((2S,6R,11S)-11-methyl-1,7-dioxaspiro[5.5]undecan-2-yl)butan-1-ol (162)

$R_f$ 0.34 (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_D^{20}$ -4.1 (c 0.36, CHCl$_3$); IR (neat): 3456, 3068, 3028, 2942, 2870, 1643, 1454, 1358, 1213, 1094, 1044, 948, 914 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.44-7.30 (m, 5H), 5.85 (ddt, $J$ = 17, 10, 6.5 Hz, 1H), 5.52 (t, $J$ = 2 Hz, 1H), 5.10 (t, $J$ = 1.5 Hz, 1H), 5.05 (dd, $J$ = 17, 1.5 Hz, 1H), 4.98 (dd, $J$ = 10, 1.5 Hz, 1H), 4.91 (d, $J$ = 12 Hz, 1H), 4.80 (d, $J$ = 12 Hz, 1H), 4.18 (d, $J$ = 10 Hz, 1H), 4.12 (m, 1H), 4.01 (d, $J$ = 8 Hz, 1H), 3.67-3.48 (m, 5H), 3.42 (t, $J$ = 9.5 Hz, 1H), 3.22 (s, 3H), 2.90 (brs, 1H), 2.11-2.04 (m, 3H), 1.95-1.45 (m, 14H), 1.40-1.12 (m, 5H), 0.99 (d, $J$ = 7 Hz, 3H), 0.98 (d, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 142.7, 139.0, 138.2, 128.3, 127.5, 127.4, 114.5, 113.2, 99.1, 98.6, 83.0, 78.0, 77.2, 73.9, 73.3, 71.0, 68.4, 60.7, 47.5, 36.2, 36.1, 34.8, 33.2, 32.4, 31.9, 27.9, 26.1, 25.8, 24.5, 20.2, 18.7, 18.2, 14.6; HRMS calcd for C$_{35}$H$_{52}$O$_7$Na [M + Na]$^+$: 607.3611; found: 607.3616.
(2R,4aR,6S,8R,8aR)-8-(benzyloxy)-6-((1S,3S)-1-(benzyloxy)-3-((2S,6R,11S)-11-methyl-1,7-dioxaspiro[5.5]undecan-2-yl)butyl)-2-(but-3-en-1-yl)-2-methoxy-7-methyleneoctahydropyrano[3,2-b]pyran (164)

To a stirred 0 °C solution of 163 (39 mg, 0.0667 mmol) in THF (1.5 mL) was added 60% NaH (25 mg). The solution was stirred for 1h before the addition of benzyl bromide (50 µL, 0.422 mmol) followed by tetra-n-butylammonium iodide (5.0 mg, 0.0152 mmol). This mixture was allowed to warmed up to room temperature and stirred for 16 h. Diethyl ether (10 mL) and saturated aqueous NH₄Cl (1 mL) were added, and the separated organic phase was washed with water (1 × 3 mL) and saturated aqueous NaCl solution (2 × 3 mL). The aqueous phases were extracted with diethyl ether, and the combined organic phases were dried over Na₂SO₄, filtered, and concentrated. Silica gel column chromatography (hexanes-ethyl acetate, 8:1, v/v) of the residue gave 164 (42 mg, 0.0623 mmol, 93%) as colorless oil:

R_f 0.63 (hexanes-ethyl acetate, 4:1, v/v); [α]_D²⁵ +11.4 (c 0.67, CHCl₃); IR (neat): 3073, 3028, 2938, 2873, 1598, 1454, 1350, 1094 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.33 (m, 10H), 5.86 (ddt, J = 17, 10, 6.5 Hz, 1H), 5.47 (t, J = 1.5 Hz, 1H), 5.07 (dd, J = 18, 1.5 Hz, 1H), 5.05 (d, J = 1.5 Hz, 1H), 4.99 (dd, J = 10, 1.5 Hz, 1H), 4.86 (d, J = 12 Hz, 1H), 4.78 (d, J = 12 Hz, 1H), 4.65 (d, J = 11 Hz, 1H), 4.53 (d, J = 11 Hz, 1H), 4.36 (d, J = 7 Hz, 1H), 4.07 (d, J = 9.5 Hz, 1H), 3.92 (m, 1H), 3.69 (td, J = 10, 5 Hz, 1H), 3.62
(m, 1H), 3.53 (dd, \( J = 11, 5 \), Hz, 1H), 3.44 (t, \( J = 10 \) Hz, 1H), 3.40 (m, 1H), 3.24 (s, 3H), 2.19-2.02 (m, 3H), 1.95-1.55 (m, 13H), 1.47 (d, \( J = 12.5 \) Hz, 1H), 1.32-1.08 (m, 5H), 0.99 (d, \( J = 7 \) Hz, 3H), 0.86 (d, \( J = 6.5 \) Hz, 3H); \(^{13}\)C NMR (CDCl₃, 125 MHz): \( \delta \) 144.1, 138.9, 138.8, 138.3, 128.3, 128.3, 127.8, 127.6, 127.5, 114.5, 112.0, 99.1, 97.9, 83.9, 77.8, 75.9, 73.6, 73.4, 72.3, 70.8, 60.4, 47.4, 36.0, 35.5, 34.9, 34.0, 32.4, 28.0, 26.8, 25.8, 25.6, 20.0, 19.0, 15.3, 14.4; HRMS calcd for C₄₂H₅₈O₇Na [M + Na]$: 697.4080; found: 697.4065.

\[
\text{3-}((2S,4aR,6S,8R,8aR)-8-(benzyloxy)-6-((1S,3S)-1-(benzyloxy)-3-((2S,6R,11S)-11-methyl-1,7-dioxaspiro[5.5]undecan-2-yl)butyl)-2-methoxy-7-methyleneoctahydropyrano[3,2-b]pyran-2-yl)propanal (165)}
\]

To a stirred solution of 164 (39 mg, 0.578 mmol) in THF (1.5 mL) and H₂O (0.5 mL) was added sodium periodate (40 mg, 0.173 mmol), pyridine (1 \( \mu \)L) and OsO₄ (50 \( \mu \)L, 4% in water). The mixture was stirred for 2 h before 2 mL 20% Na₂S₂O₃ solution was added. The mixture was stirred for another 15 min and 10 mL diethyl ether was added. The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 \( \times \) 5 mL). The combined organic phase was dried over Na₂SO₄, filtered, and concentrated. Silica gel column chromatography (hexanes-ethyl acetate, 4:1, v/v) of the residue gave 165 (30 mg, 0.0443 mmol, 77%) as a colorless oil.
$R_f$ 0.18 (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_{D}^{25} +10.8 \text{ (c 0.50, CHCl}_3$); IR (neat): 
3080, 3037, 3027, 2961, 2711, 1728, 1454, 1386, 1363, 1273, 1213, 1092, 1040 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 9.80 (s, 1H), 7.33 (m, 10H), 5.43 (t, $J = 1.5$ Hz, 1H), 5.05 (s, 1H), 4.81 (d, $J = 12$ Hz, 1H), 4.74 (d, $J = 12$ Hz, 1H), 4.63 (d, $J = 11$ Hz, 1H), 4.53 (d, $J = 11$ Hz, 1H), 4.36 (d, $J = 7$ Hz, 1H), 4.07 (d, $J = 9.5$ Hz, 1H), 3.91 (m, 1H), 3.70-3.60 (m, 2H), 3.53 (dd, $J = 11$, 5 Hz, 1H), 3.41 (t, $J = 9.5$ Hz, 1H), 3.40 (m, 1H), 3.22 (s, 3H), 2.48 (dd, $J = 8$, 7 Hz, 1H), 2.14 (tt, $J = 12$, 5 Hz, 1H), 2.06 (m, 1H), 1.93 (m, 1H), 1.86-1.51 (m, 13H), 1.47 (d, $J = 12.5$ Hz, 1H), 1.31-1.09 (m, 5H), 0.99 (d, $J = 7.5$ Hz, 1H), 0.88 (d, $J = 7$ Hz, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 201.3, 144.0, 138.8, 138.7, 128.3, 127.8, 127.6, 127.5, 112.0, 98.7, 97.9, 83.6, 77.8, 76.3, 73.7, 73.4, 72.3, 70.6, 60.4, 47.5, 38.7, 36.0, 35.4, 34.0, 32.3, 32.2, 27.7, 26.7, 25.8, 25.5, 20.0, 19.0, 15.5, 14.4; HRMS calcd for C$_{41}$H$_{56}$O$_8$Na [M + Na]$^+$: 699.3873; found: 699.3867.

dimethyl (4-((2S,4aR,6S,8R,8aR)-8-(benzyloxy)-6-((1S,3S)-1-(benzyloxy)-3-((2S,6R,11S)-11-methyl-1,7-dioxaspiro[5.5]undecan-2-yl)butyl)-2-methoxy-7-methyleneoctahydropyran[3,2-b]pyran-2-yl)-2-oxobutyl)phosphonate (156)

To a stirred $-78$ °C solution of dimethyl methylphosphonate (40 µL, 0.37 mmol) in THF (1.5 mL) under argon was added tert-butyllithium (180 µL of a 1.7 M solution in pentane, 280 µmol) dropwise. The solution was stirred for 45 min before a solution of
165 (26 mg, 39 µmol) in THF (1 mL) was added slowly via cannula. The resultant pale yellow solution was stirred for an additional 45 min, at which time TLC showed no remaining 165. Saturated aqueous NaCl (1 mL) was added, and the mixture was allowed to warm to room temperature. THF was removed by rotary evaporation and the aqueous residue was extracted with diethyl ether (15 mL). The separated organic phase was washed with H₂O (2 × 3 mL) and saturated aqueous NaCl (2 × 3 mL). The combined aqueous phases were extracted with ethyl acetate, and the combined organic phases were dried over Na₂SO₄, filtered, and concentrated. The residue was filtered through silica gel with hexanes–ethyl acetate–triethylamine (1:5:0.3, v/v) and the filtrate concentrated to yield crude β-hydroxy phosphonate as oil, which was used without further purification.

To a stirred room temperature solution of β-hydroxy phosphonate (39 µmol theor) in CH₂Cl₂ (1 mL) was added NaHCO₃ (120 mg, 1.4 mmol) and Dess–Martin periodinane reagent (60 mg, 0.14 mmol). The resultant mixture was stirred for 45 min, at which time TLC showed no remaining β-hydroxy phosphonate. Diethyl ether (15 mL), saturated aqueous NaHCO₃ (1 mL), and 10% aqueous Na₂S₂O₃ (1 mL) were added, and the mixture was stirred vigorously until the organic layer became clear. The separated organic phase was washed with H₂O (2 × 3 mL) and saturated aqueous NaCl (2 × 3 mL). The aqueous phases were extracted with diethyl ether, and the combined organic phases were dried over Na₂SO₄, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexanes–ethyl acetate, 1:2–1:5, v/v) to give 156 (21.4 mg, 27 µmol, 70% from 165) as a pale oil:
$R_f$ 0.36 (hexanes-ethyl acetate, 1:5, v/v); $[\alpha]_D^{25} +12.8$ (c 0.33, CHCl$_3$); IR (neat): 3080, 3060, 2925, 2850, 1713, 1591, 1454, 1123, 1089, 1029 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.33 (m, 10H), 5.43 (s, 1H), 5.04 (s, 1H), 4.83 (d, $J = 12.5$ Hz, 1H), 4.75 (d, $J = 12.5$ Hz, 1H), 4.64 (d, $J = 12$ Hz, 1H), 4.52 (d, $J = 12$ Hz, 1H), 4.35 (d, $J = 7$ Hz, 1H), 4.06 (d, $J = 9.5$ Hz, 1H), 3.92 (m, 1H), 3.78 (d, $J_{P,H} = 11.5$ Hz, 1H), 3.70-3.59 (m, 2H), 3.53 (m, 1H), 3.41 (m, 2H), 3.22 (s, 3H), 3.11 (d, $J_{P,H} = 22.5$ Hz, 6H), 2.65 (t, $J = 8$ Hz, 2H), 2.17-2.05 (m, 2H), 1.77-1.90 (m, 7H), 1.47-1.68 (m, 8H), 1.35-1.45 (m, 3H), 0.99 (d, $J = 6.5$ Hz, 3H), 0.87 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 201.1, 144.0, 138.8, 138.7, 128.3, 127.9, 127.6, 127.5, 127.5, 112.0, 98.7, 97.9, 83.8, 77.8, 76.1, 73.6, 73.4, 72.3, 70.6, 60.4, 53.1, 53.1, 47.5, 42.1, 41.0, 38.7, 36.0, 35.5, 34.0, 32.4, 32.2, 29.7, 29.0, 26.8, 25.8, 25.5, 20.0, 19.9, 15.4, 14.4; HRMS calcd for C$_{44}$H$_{63}$O$_{11}$PNa [M + Na]$^+$: 821.4006; found: 821.3983.

(6$R, E$)-6-((2$S, 8S, 11R$)-11-(benzyloxy)-4-methyl-8-(((R)-2,2,4-trimethyl-1,3-dioxolan-4-yl)methyl)-1,7-dioxaspiro[5.5]undec-4-en-2-yl)-1-((2$S, 4aR, 6S, 8R, 8aR$)-8-(benzyloxy)-6-((1$S, 3S$)-1-(benzyloxy)-3-((2$S, 6R, 11S$)-11-methyl-1,7-dioxaspiro[5.5]undecan-2-yl)butyl)-2-methoxy-7-methyleneoctahydropyrano[3,2-b]pyran-2-yl)hept-4-en-3-one (155)
To a stirred solution of 156 (20 mg, 25 µmol) in CH$_3$CN (0.6 mL) was added LiCl (5 mg, 0.12 mmol) followed by diisopropylethylamine (7 µL, 0.035 mmol). After stirring for 10 min, a solution of 61 (10.5 mg, 23 µmol) in CH$_3$CN (0.8 mL) was added. The resulting mixture became turbid after 10 min and was stirred for an additional 20 h. The mixture was diluted with diethyl ether (5 mL), washed with H$_2$O and saturated aqueous NaCl (0.5 mL ea), dried over Na$_2$SO$_4$, filtered, and concentrated. Silica gel column chromatography (hexanes–ethyl acetate, 5:1, v/v) of the residue gave 155 (25.2 mg, 22 µmol, 93%) as a clear, colorless oil:

$R_f$ 0.24 (hexanes-ethyl acetate, 4:1, v/v); [$\alpha$]$_{D}^{20}$ +10.5 (c 0.29, CHCl$_3$); IR (neat): 3082, 3064, 3025, 2931, 2844, 1674, 1629, 1454, 1378, 1239, 1208, 1090, 1026, 983, 912, 855, 813, 734, 698 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.37-7.26 (m, 15H), 7.08 (dd, $J = 16$, 7.5 Hz, 1H), 6.19 (d, $J = 16$ Hz, 1H), 5.43 (s, 1H), 5.16 (s, 1H), 5.04 (s, 1H), 4.85 (d, $J = 12.5$ Hz, 1H), 4.76 (d, $J = 12$ Hz, 1H), 4.64 (d, $J = 11$ Hz, 1H), 4.59 (d, $J = 12.5$ Hz), 4.52 (d, $J = 11$ Hz, 1H), 4.46 (d, $J = 12.5$ Hz, 1H), 4.35 (d, $J = 7$ Hz, 1H), 4.05 (d, $J = 10$ Hz, 1H), 3.91 (m, 1H), 3.80 (d, $J = 8.5$ Hz), 3.80 (m, 1H), 3.66 (d, $J = 8.5$ Hz, 1H), 3.71-3.59 (m, 3H), 3.54 (m, 1H), 3.40 (t, $J = 10$ Hz, 1H), 3.39 (m, 1H), 3.24 (dd, $J = 12$, 4 Hz, 1H), 3.19 (s, 3H), 2.56 (m, 3H), 2.14 (m, 2H), 2.03 (t, $J = 11$ Hz, 1H), 1.94 (td, $J = 13$, 3 Hz, 1H), 1.82-1.76 (m, 9H), 1.73 (s, 3H), 1.72-1.48 (m, 11H), 1.39 (s, 3H), 1.31 (s, 3H), 1.26 (s, 3H), 1.16 (d, $J = 7$ Hz, 3H), 0.99 (d, $J = 7$ Hz, 1H), 0.86 (d, $J = 7$ Hz, 1H); $^{13}$C NMR (CDCl$_3$, 125MHz) $\delta$ 199.2, 149.2, 144.0, 138.9, 138.8, 138.7, 136.5, 130.1, 128.3, 128.2, 127.9, 127.7, 127.6, 127.5, 127.5, 127.4, 123.1, 112.1, 108.3, 98.9, 97.9, 96.0, 83.9, 80.3, 79.0, 78.6, 78.2, 77.6, 77.6, 77.4, 75.8, 75.1, 73.7, 73.4, 72.3, 71.3, 70.6, 113
66.5, 60.4, 47.5, 46.1, 41.3, 36.0, 35.5, 34.5, 34.0, 33.4, 32.4, 32.3, 29.3, 27.5, 27.0, 26.8, 25.8, 25.5, 24.4, 24.3, 22.9, 20.0, 19.0, 15.5, 15.4, 14.4; HRMS calcd for C_{69}H_{94}O_{13}Na [M + Na]^+: 1153.6592; found: 1153.6580.

(2R)-3-((2S,6R,8S)-5-(benzyloxy)-8-((R,E)-4-((2R,4a'R,5R,6'S,8'R,8a'R)-8'-(benzyloxy)-6'-(1S,3S)-1-(benzyloxy)-3-((2S,6R,11S)-11-methyl-1,7-dioxaspiro[5.5]undecan-2-yl)butyl)-7'-methyleneoctahydro-3H,3'H-spiro[furan-2,2'-pyrano[3,2-b]pyran]-5-yl)but-3-en-2-yl)-10-methyl-1,7-dioxaspiro[5.5]undec-10-en-2-yl)-2-methylpropane-1,2-diol (60)

To a stirred solution of (S)-2-methyl-CBS-oxazaborolidine (200 µL of a 1.0 M solution in toluene, 0.20 mmol) in THF (0.6 mL) at 0 °C and under N₂ was added borane-tetrahydrofuran complex (140 µL of a 1 M solution in THF, 140 µmol) followed by a solution of 155 (12.0 mg, 10.6 µmol) in THF (0.35 mL). After 7 min, H₂O (200 µL) was added and the mixture was allowed to warm to room temperature. Diethyl ether (2 mL) was added and the mixture was washed with 5% aqueous HCl. The aqueous phase was extracted with diethyl ether (2 × 0.5 mL), and the combined organic phases were washed with H₂O and saturated aqueous NaCl (0.5 mL ea), dried over Na₂SO₄, filtered, and concentrated. The crude allylic alcohol (Rₗ 0.40; hexanes–ethyl acetate, 2:1, v/v) was filtered through silica gel with ethyl acetate, the filtrate was concentrated and then diluted.
with the mixture of THF (0.65 mL), acetic acid (0.50 mL) and H₂O (0.26 mL) in a 10 mL vial. The vial was then capped and the reaction was heated at 55°C for 40 hours before cooled down to room temperature. The solvent was removed by vaccum and the residue was purified through column chromatography (hexanes-ethyl acetate, 4:1 to 2:1) to give 60 (9.0 mg, 8.5 µmol, 80%) as white solid.

Rf 0.31 (hexanes-ethyl acetate, 2:1, v/v); [α]D²⁰ +30.5 (c 0.20, CHCl₃); IR (neat): 3399, 2920, 2852, 1644 1378, 1180, 1078, 964, 734, cm⁻¹;¹H NMR (CDCl₃, 500 MHz): δ 7.33-7.25 (m, 15H), 5.83 (dd, J = 15.5, 7.5 Hz, 1H), 5.60 (dd, J = 15.5, 7 Hz, 1H), 5.39 (t, J = 1.5 Hz, 1H), 5.15 (s, 1H), 5.02 (s, 1H), 4.81 (d, J = 12.5 Hz, 1H), 4.76 (d, J = 12.5 Hz, 1H), 4.66 (d, J = 11.5 Hz, 1H), 4.61 (d, J = 12.5 Hz, 1H), 4.58 (m, 1H), 4.51 (d, J = 11.5 Hz, 1H), 4.47 (d, J = 12.5 Hz, 1H), 4.30 (d, J = 7 Hz, 1H), 4.11 (brt, J = 11 Hz, 1H), 4.01 (d, J = 9.5 Hz, 1H), 3.90 (m, 1H), 3.69-3.58 (m, 4H), 3.53 (m, 2H), 3.46-3.35 (m, 3H), 3.24 (dd, J = 12, 4 Hz, 1H), 2.65 (brs, 1H), 2.43 (tq, J = 7.5, 7.5 Hz, 1H), 2.22-1.93 (m, 6H), 1.88-1.77 (m, 10H), 1.73 (s, 3H), 1.69-1.30 (m, 14H), 1.12 (s, 3H), 1.04 (d, J = 7.0 Hz, 3H), 0.99 (d, J = 7.5 Hz, 3H), 0.82 (d, J = 7.0 Hz, 3H);¹³C NMR (CDCl₃, 125MHz) δ 143.9, 138.8, 138.7, 137.9, 130.9, 128.3, 128.3, 128.2, 127.9, 127.8, 127.6, 127.5, 127.5, 122.5, 112.1, 105.6, 97.9, 96.4, 84.2, 79.0, 78.6, 77.6, 75.3, 73.4, 73.3, 72.7, 72.4, 72.2, 71.4, 70.6, 69.1, 67.4, 60.4, 43.9, 40.9, 37.2, 36.0, 35.7, 34.0, 33.4, 33.0, 32.5, 32.3, 30.7, 27.0, 26.7, 25.8, 25.2, 23.9, 23.0, 20.0, 19.0, 15.6, 15.0, 14.4; HRMS calcd for C₆₉H₉₄O₁₃Na [M + Na]⁺: 1083.6173; found: 1083.6155.

To a stirred solution of 60 (3.9 mg, 3.7 µmol), DMSO (0.05 mL) and diisopropylethylamine (0.10 mL) in CH$_2$Cl$_2$ (0.10 mL) was added sulfur trioxide pyridine complex (5.0 mg, 31.4 µmol). The mixture was stirred for 2 hours before saturated NH$_4$Cl solution (1 mL) and diethyl ether (2 mL) was added. After stirred for another 15 min, the organic phase was separated and the aqueous phase was extracted with diethyl ether (4 × 1 mL). The combined organic phase was dried over Na$_2$SO$_4$, filtered, and concentrated. The crude product was the dissolved in the mixture of t-butanol (0.25 mL) and water (0.05 mL) before NaH$_2$PO$_4$·2H$_2$O (7 mg, 44.9 µmol), 2-methyl-2-butene (0.2 mL) and NaClO$_2$ (4 mg, 44.2 µmol) was added in sequence. The mixture was stirred for 1 hour before saturated Na$_2$S$_2$O$_3$ solution (1 mL) was added. The mixture was stirred for another 20 min before the solution was acidified to pH = 2 with 1 M HCl. The mixture was then extracted with diethyl ether (6 × 1 mL) and the combined organic extract was dried over Na$_2$SO$_4$, filtered, and concentrated. Silica gel column chromatography (dichloro-
methane–methanol, 20:1, v/v) of the residue gave 167 (3.5 mg, 3.3 µmol, 89%) as a clear, colorless oil:

\[ R_f 0.48 \text{ (dichloromethane–methanol, 19:1, v/v); } [\alpha]_D^{25} +42.9 \text{ (c 0.22, CHCl}_3) \]; IR (neat): 3067, 3020, 2925, 2851, 1730, 1713, 1462, 1378, 1075, 1028, 965 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta 5.74 \text{ (dd, } J = 15, 8 \text{ Hz, } 1\text{H}), 5.61 \text{ (dd, } J = 15.5, 7.5 \text{ Hz, } 1\text{H}), 5.43 \text{ (s, } 1\text{H}), 5.13 \text{ (s, } 1\text{H}), 5.04 \text{ (s, } 1\text{H}), 4.88 \text{ (d, } J = 12.5 \text{ Hz, } 1\text{H}), 4.78 \text{ (d, } J = 12.5 \text{ Hz, } 1\text{H}), 4.66 \text{ (d, } J = 11.5 \text{ Hz, } 1\text{H}), 4.62 \text{ (m, } 1\text{H}), 4.60 \text{ (d, } J = 12.5 \text{ Hz, } 1\text{H}), 4.51 \text{ (d, } J = 11 \text{ Hz, } 1\text{H}), 4.47 \text{ (d, } J = 12.5 \text{ Hz, } 1\text{H}), 4.32 \text{ (d, } J = 7.5 \text{ Hz, } 1\text{H}), 4.05 \text{ (m, } 1\text{H}), 3.90 \text{ (m, } 1\text{H}), 3.69-3.52 \text{ (m, } 5\text{H}), 3.37 \text{ (ddd, } J = 11.5, 5, 2 \text{ Hz, } 1\text{H}), 3.25 \text{ (dd, } J = 12, 4 \text{ Hz, } 1\text{H}), 2.42 \text{ (tq, } J = 7.5, 7.5 \text{ Hz, } 1\text{H}), 2.22-1.93 \text{ (m, } 6\text{H}), 1.88-1.77 \text{ (m, } 10\text{H}), 1.72 \text{ (s, } 3\text{H}), 1.69-1.30 \text{ (m, } 14\text{H}), 1.35 \text{ (s, } 3\text{H}), 1.05 \text{ (d, } J = 7.0 \text{ Hz, } 3\text{H}), 0.99 \text{ (d, } J = 7.5 \text{ Hz, } 3\text{H}), 0.82 \text{ (d, } J = 7.0 \text{ Hz, } 3\text{H}); \(^{13}\)C NMR (CDCl\(_3\), 125MHz) \(\delta 176.4, 143.8, 139.0, 138.8, 138.7, 135.0, 131.3, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 122.2, 112.2, 105.8, 98.0, 96.6, 84.3, 79.3, 78.5, 77.9, 75.7, 75.6, 74.5, 73.5, 73.4, 72.5, 71.6, 71.3, 70.8, 68.4, 60.5, 43.8, 41.6, 37.4, 36.2, 35.8, 34.1, 32.9, 32.8, 32.5, 32.3, 32.1, 30.4, 29.5, 29.4, 27.5, 27.1, 26.9, 26.7, 25.9, 23.7, 23.2, 22.9, 22.8, 20.1, 19.2, 17.9, 16.0, 15.3, 14.5; HRMS caled for C\(_{65}\)H\(_{86}\)O\(_{13}\)Na [M + Na]\(^+\): 1097.5966; found: 1097.5958.
To a stirred –78 °C solution of 167 (2.1 mg, 1.9 µmol) in THF (0.2 mL) under argon was added a solution of lithium di-tert-butylbiphenylide (0.5 mL of 0.13 M solution in THF, 0.06 mmol). After stirring for 30 min, H₂O (0.2 mL) was added to the deep blue-green solution and the resulting colorless mixture was allowed to warm to room temperature. The THF was removed under a stream of argon, and the residue was diluted with H₂O (0.2 mL) and washed with hexanes (3 × 1 mL). The aqueous phase was cooled to 0 °C and was acidified to pH 2 with 0.5 M aqueous HCl, and extracted with diethyl ether (4 × 1 mL). The combined ether extracts were dried over Na₂SO₄, filtered, and concentrated. The residue was purified by silica gel column chromatography (dichloromethane-methanol, 18:1, v/v) to give 1 (1.0 mg, 1.3 µmol, 69%) as a colorless solid.

Rᶠ 0.24 (dichloromethane-methanol, 19:1, v/v); [α]D²⁵ +12.0 (c 0.075, CHCl₃); ¹H NMR (CD₃OD, 500 MHz): δ 5.84 (dd, J = 15.5, 8.5 Hz, 1H), 5.52 (dd, J = 15.5, 8 Hz, 1H), 5.36 (s, 1H), 5.29 (s, 1H), 4.62 (q, J = 7 Hz, 1H), 4.10 (m, 1H), 4.07 (m, 1H), 3.97 (d, J = 9 Hz, 1H), 3.75-3.62 (m, 3H), 3.51 (dd, J = 11, 5 Hz, 1H), 3.45-3.35 (m, 3H), 2.34 (q, J = 1.75 Hz, 1H), 2.20-2.15 (m, 2H), 2.00-1.95 (m, 3H), 1.90-1.16 (m, 23H), 1.75 (s, 3H), 1.34 (s, 3H), 1.07 (d, J = 7 Hz, 3H), 0.99 (d, J = 7 Hz, 3H), 0.95 (d, J = 7 Hz, 3H); ¹³C NMR (CDCl₃, 125MHz) δ 147.5, 140.0, 137.5, 132.4, 123.1, 112.1, 107.1, 99.3, 97.7,
86.4, 80.5, 78.1, 76.3, 75.0, 73.1, 72.0, 71.4, 69.5, 67.1, 61.4, 45.6, 43.4, 38.6, 38.1, 37.4, 35.3, 34.1, 33.4, 31.6, 28.6, 27.7, 27.6, 26.7, 23.1, 21.0, 20.1, 16.7, 14.7, 14.4; HRMS calcd for C_{44}H_{68}O_{13}Na [M + Na]^+: 827.4558; found: 827.4527.

(S)-3-((2S,5R,6R)-5-(benzyloxy)-6-(tert-butylidimethylsilyloxy)tetrahydro-2H-pyran-2-yl)-2-methylpropane-1,2-diol (96)

To a mixture of 95 (1.542 g, 4.10 mmol), tert-butanol (20 mL) and water (20 mL) at 0 °C was added AD-mix-α (5.74 g). The mixture was stirred vigorously for 24 hours until when sodium sulfite (6.2 g) was added. The mixture was stirred at 25 °C for another one hour and 20 mL diethyl ether was added. The organic phase was separated and the aqueous phase was extracted by diethyl ether (4 × 20 mL). The combined organic phase was dried over Na$_2$SO$_4$, filtered and concentrated. The residue was purified through column chromatography (hexanes-ethyl acetate, 4:1 to 2:1, v/v) to give 97 (0.156 g, 0.381 mmol, 9.3%) and 96 (1.391g, 3.39 mmol, 83%) as colorless oil:

$R_f$ 0.30 (hexanes-ethyl acetate, 2:1, v/v); $[\alpha]_D^{25} = +11.8$ (c 2.40, CDCl$_3$); IR (neat): 3416, 2929, 2858, 1648, 1456, 1396, 1252, 1170, 836 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) δ 7.33 (m, 5H), 4.74 (d, $J = 12$ Hz, 2H), 4.63 (m, 2H), 3.86 (t, $J = 11$ Hz, 1H), 3.74 (s, 1H), 3.42 (dd, $J = 11$, 5 Hz, 1H), 3.32 (dd, $J = 11$, 8 Hz), 3.16 (m, 1H), 2.31 (dd, $J = 8$, 5.5 Hz), 2.06 (m, 1H), 1.98 (dd, $J = 14.5$, 9.5 Hz, 1H), 1.60-1.41 (m, 4H), 1.22 (s, 3H), 0.95 (s, 9H), 0.17(m, 6H). $^{13}$C NMR (CDCl$_3$, 125MHz) δ 138.6, 128.3, 127.3, 99.4, 78.0, 119
73.5, 72.6, 72.3, 70.9, 42.1, 31.5, 28.8, 25.6, 23.9, 17.9, -4.5, -4.9. HRMS calcd for C_{22}H_{38}O_5SiNa [M + Na]^+: 433.2386; found: 433.2378.

(3R,6S)-3-(benzyloxy)-6-(((S)-2,2,4-trimethyl-1,3-dioxolan-4-yl)methyl)tetrahydro-2H-pyran-2-one (98)

To a solution of 96 (1.560 g, 3.80 mmol) in CH₂Cl₂ (20 mL) was added 2,2-dimethoxypropane (3.0 mL, 24.4 mmol) followed by pyridinium p-toluenesulfonate (37 mg, 0.14 mmol). The reaction mixture was stirred for 2.5 hours until 0.5 mL of triethylamine was added. The solvent was evaporated and the residue was filtered through a pad of silica gel with hexanes-ethyl acetate (4:1, v/v). The obtained solution was concentrated and the residue was dissolved in THF (20 mL) and was treated with tetra-n-butylammonium fluoride solution (1.0 M in THF, 3.90 mL, 3.90 mmol) dropwise within 1 hour. The mixture was stirred for another 0.5 hour and saturated ammonium chloride solution (5 mL) was added. THF was removed from the mixture and diethyl ether (20 mL) was added. The mixture was stirred for 10 min and the organic phase was separated. The aqueous phase was extracted with diethyl ether (3 × 25 mL). The combined organic phase was dried over Na₂SO₄, filtered and concentrated. The residue was filtered through a pad of silica gel with hexanes-ethyl acetate (2:1, v/v) and the obtained solution was concentrated. The residue was dissolved in CH₂Cl₂ (20 mL) followed by addition of NaHCO₃ (1.03 g, 12.3 mmol), iodobenzene diacetate (1.69 g, 5.25 mmol) and 2,2,6,6-
tetramethylpiperidine-1-oxyl (54 mg, 0.35 mmol). The reaction was stirred for 12 hours before saturated Na$_2$S$_2$O$_3$ solution (3.0 mL) was added. Diethyl ether (30 mL) was added to the mixture and organic phase was separated. The aqueous phase was then extracted with diethyl ether (3 × 25 mL). The combined organic phase was washed with brine, dried over Na$_2$SO$_4$, concentrated and purified by flash chromatography (hexanes: ethyl acetate, 4:1, v/v) to give compound 98 (0.956 g, 2.86 mmol, 75%, three steps) as a colorless oil.

$R_f$ 0.34 (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_{D}^{25} = +35.0$ (c 0.34, CDCl$_3$); IR (neat): 3058, 3027, 2928, 2930, 2868, 1745, 1454, 1379, 1246, 1209, 1118, 1058, 807, 738, 700 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.36 (m, 5H), 4.86 (d, $J = 12$ Hz, 1H), 4.82 (m, 1H), 4.06 (d, $J = 8.5$ Hz, 1H), 3.97 (t, $J = 6$ Hz, 1H), 3.72 (d, $J = 8.5$ Hz, 1H), 2.17-1.94 (m, 4H), 1.82 (dd, $J = 15$, 3.5 Hz, 1H), 1.69 (m, 1H), 1.41 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H).

$^{13}$C NMR (CDCl$_3$, 125MHz) $\delta$ 170.6, 137.3, 128.5, 128.1, 128.0, 109.2, 79.7, 76.5, 73.8, 72.8, 72.6, 44.8, 28.3, 27.2, 27.1, 26.8, 26.3. HRMS calcd for C$_{19}$H$_{26}$O$_5$Na [M + Na]$^+$: 357.1678; found: 357.1670.

(2S,6R,8S,11R)-11-(benzyloxy)-2-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-4-methyl-8-(((S)-2,2,4-trimethyl-1,3-dioxolan-4-yl)methyl)-1,7-dioxaspiro[5.5]undec-4-ene (101a)
To a solution of 100a (0.180 g, 0.332 mmol) in dichloromethane (3 mL) was added 2,2-dimethoxypropane (0.40 mL, 0.424 g, 4.08 mmol followed by pyridinium p-toluenesulfonate (4.6 mg, 0.0168 mmol). The reaction was stirred for 2.5 hours until triethylamine (0.1 mL) was added. The solvent was evaporated on rotavapor and the residue was purified through column chromatography (hexanes-ethyl acetate, 10:1 to 7:1, v/v) to give 101a (0.187 g, 0.332 mmol, quant.) colorless oil.

$R_f$ 0.43 (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_D^{25} = +24.2$ (c 1.1, CDCl$_3$); IR (neat):
3058, 3026, 2930, 2861, 1611, 1512, 1247, 1095 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.32-7.24 (m, 7H), 6.86 (m, 2H), 5.18 (s, 1H), 4.61 (d, $J = 12.5$ Hz, 1H), 4.49 (d, $J = 12.5$ Hz, 1H), 4.44 (d, $J = 2$ Hz, 2H), 3.80-3.67 (m, 6H), 3.64 (d, $J = 8$ Hz, 1H), 3.34 (t, $J = 8.5$ Hz, 1H), 3.26 (dd, $J = 12$, 4.5 Hz, 1H), 2.11 (m, 1H), 2.04 (dd, $J = 16.5$, 11.5 Hz, 1H), 1.92 (qd, $J = 12.5$, 4 Hz, 1H), 1.83-1.76 (m, 3H), 1.73 (s, 3H), 1.62 (dd, $J = 13$, 6 Hz, 2H), 1.37 (s, 3H), 1.33 (s, 3H), 1.27 (s, 3H), 1.03 (d, $J = 7$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125MHz) δ 159.1, 139.0, 137.2, 130.9, 129.2, 128.1, 127.7, 127.4, 123.0, 113.7, 108.8, 96.2, 80.5, 78.7, 73.6, 72.7, 72.4, 71.3, 69.7, 66.4, 55.3, 45.9, 38.4, 32.8, 32.7, 27.3, 27.2, 26.3, 24.4, 23.0, 13.8; HRMS calcd for C$_{35}$H$_{48}$O$_7$Na [M + Na]$^+$: 603.3298; found: 603.3292.
(S)-2-((2S,6R,8S,11R)-11-(benzyloxy)-4-methyl-8-((S)-2,4,trimethyl-1,3-dioxolan-4-yl)methyl)-1,7-dioxaspiro[5.5]undec-4-en-2-yl)propanal (61a)

To a mixture of 101a (30 mg, 51 µmol), CH₂Cl₂ (5.0 mL), an aqueous NaH₂PO₄ buffer (pH = 7, 1.0 mL), and tert-butyl alcohol (0.30 mL) was added 2,3-dichloro-5,6-dicyanobenzoquinone (70 mg, 0.31 mmol). The reaction flask was placed in an aqueous bath and sonicated for 5 min. The mixture was diluted with diethyl ether (8 mL) and washed with saturated aqueous NaHCO₃ solution (2 mL). The aqueous phase was extracted with diethyl ether (3 × 2 mL) and the combined organic phases were washed with saturated aqueous NaCl (1.5 mL), dried over Na₂SO₄, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexanes–ethyl acetate, 5:1 to 3:2, v/v) to give a colorless oil which was then dissolved in CH₂Cl₂ (3.0 mL). The solution was added NaHCO₃ (150 mg, 1.8 mmol) followed by the Dess–Martin periodinane (80 mg, 0.19 mmol). The mixture was stirred for 30 min before diethyl ether (4.0 mL) and 10% aqueous Na₂S₂O₃ and saturated aqueous NaHCO₃ (1.0 mL ea) were added. The mixture was stirred until the organic phase became clear and colorless. The separated aqueous phase was extracted with diethyl ether (3 × 2 mL), and the combined organic fractions were washed with saturated aqueous NaCl (1 mL), dried over Na₂SO₄, filtered, and concentrated. Silica gel column chromatography (hexanes–ethyl acetate, 5:1, v/v) of the residue gave 61a (17 mg, 35 µmol, 69%, two steps) as a white crystalline solid.

R_f 0.70 (hexanes-ethyl acetate, 4:1, v/v); [α]D²⁵ = +16.1 (c 0.18, CDCl₃); IR (neat): 3066, 3035, 2924, 2852, 1727, 1604, 1454, 1378, 1245, 1209, 1089, 1051 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 9.92 (d, J = 2.5 Hz, 1H), 7.32-7.24 (m, 5H), 5.20 (s, 1H), 4.61 (d, J
= 12 Hz, 1H), 4.47 (d, J = 12 Hz, 1H), 4.10 (m, 1H), 3.89 (d, J = 8.5 Hz, 1H), 3.80 (m, 1H), 3.71 (d, J = 8.5 Hz, 1H), 3.26 (dd, J = 11.5, 4.5 Hz, 1H), 2.71 (m, 1H), 2.09 (dd, J = 14, 11.5 Hz, 1H), 1.90-1.71 (m, 4H), 1.71 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H), 1.29 (s, 3H), 1.11 (d, J = 7 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125MHz) δ 204.3, 138.8, 136.4, 128.2, 127.8, 127.5, 123.3, 108.9, 96.3, 80.3, 78.5, 73.6, 71.4, 69.2, 66.7, 50.5, 46.0, 33.1, 32.7, 27.2, 27.1, 26.4, 24.3, 23.0, 10.4; HRMS calcd for C$_{27}$H$_{38}$O$_6$Na [M + Na]$^+$: 481.2566; found: 481.2575.

(6R,E)-6-((2S,8S,11R)-11-(benzyloxy)-4-methyl-8-(((S)-2,2,4-trimethyl-1,3-dioxolan-4-yl)methyl)-1,7-dioxaspiro[5.5]undec-4-en-2-yl)-1-((2S,4aR,6S,8R,8aR)-8-(benzyloxy)-6-((1S,3S)-1-(benzyloxy)-3-((2S,6R,11S)-11-methyl-1,7-dioxaspiro[5.5]undecan-2-yl)butyl)-2-methoxy-7-methyleneoctahydropyrano[3,2-b]pyran-2-yl)hept-4-en-3-one (155a)

To a stirred solution of 156 (15 mg, 18 µmol) in CH$_3$CN (0.6 mL) was added LiCl (5 mg, 0.12 mmol) followed by diisopropylethylamine (7 µL, 0.035 mmol). After stirring for 10 min, a solution of 61a (8.6 mg, 18 µmol) in CH$_3$CN (0.8 mL) was added. The resulting mixture became turbid after 10 min and was stirred for an additional 20 h. The mixture was diluted with diethyl ether (5 mL), washed with H$_2$O and saturated aqueous NaCl (0.5 mL ea), dried over Na$_2$SO$_4$, filtered, and concentrated. Silica gel column chro-
matography (hexanes–ethyl acetate, 5:1, v/v) of the residue gave 155a (18.2 mg, 16 µmol, 89%) as a clear, colorless oil:

$R_f$ 0.18 (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_{D}^{20} = +13.3$ (c 0.33, CDCl$_3$); IR (neat): 3082, 3060, 3025, 2931, 2852, 1674, 1629, 1454, 1378, 1239, 1208, 1090, 1026, 983, 912, 856, 734, 698 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.34-7.24 (m, 15H), 7.07 (dd, $J$ = 16, 7.5 Hz, 1H), 6.21 (d, $J$ = 16 Hz, 1H), 5.43 (s, 1H), 5.20 (s, 1H), 5.04 (s, 1H), 4.86 (d, $J$ = 12.5 Hz, 1H), 4.76 (d, $J$ = 12 Hz, 1H), 4.64 (d, $J$ = 11.5 Hz, 1H), 4.59 (d, $J$ = 12.5 Hz), 4.52 (d, $J$ = 11.5 Hz, 1H), 4.46 (d, $J$ = 12.5 Hz, 1H), 4.35 (d, $J$ = 7 Hz, 1H), 4.06 (d, $J$ = 9.5 Hz, 1H), 3.91 (m, 1H), 3.81 (m, 3H), 3.66 (m, 2H), 3.64 (m, 1H), 3.55 (m, 1H), 3.41 (m, 2H), 3.26 (m, 1H), 3.19 (s, 3H), 2.59 (m, 3H), 2.14 (m, 1H), 2.08-1.90 (m, 2H), 1.82-1.48 (m, 20H), 1.73 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3H), 1.26 (s, 3H), 1.18 (d, $J$ = 7 Hz, 3H), 0.99 (d, $J$ = 7 Hz, 3H), 0.86 (d, $J$ = 7 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125MHz) δ 199.2, 149.1, 144.01, 139.0, 138.8, 136.7, 130.1, 128.3, 128.2, 127.9, 127.8, 127.6, 127.5, 127.4, 123.1, 112.0, 108.8, 99.0, 97.9, 96.2, 83.9, 80.4, 78.6, 78.5, 75.9, 73.7, 73.4, 72.3, 71.2, 70.9, 70.6, 68.0, 66.5, 60.4, 47.5, 46.0, 41.4, 36.0, 35.5, 34.7, 34.0, 33.1, 32.8, 32.4, 29.4, 27.3, 27.2, 26.8, 26.2, 25.8, 25.5, 24.4, 23.0, 20.0, 19.0, 15.5, 15.4, 14.4; HRMS calcd for C$_{69}$H$_{94}$O$_{13}$Na [M + Na]$^+$: 1153.6592; found: 1153.6581.

![Chemical Structure](image-url)
(2S)-3-((2S,6R,8S)-5-(benzoyloxy)-8-((R,E)-4-((2R,4a'R,5R,6'S,8'R,8a'R)-8'-(
(benzoyloxy)-6'-(1S,3S)-1-(benzoyloxy)-3-((2S,6R,11S)-11-methyl-1,7-
dioxa[5.5]undecan-2-yl)butyl)-7'-methyleneoctahydro-3H,3'H-spiro[furan-2,2'-
pyran[3,2-b]pyran]-5-yl)but-3-en-2-yl)-10-methyl-1,7-dioxa[5.5]undec-10-en-
2-yl)-2-methylpropane-1,2-diol (60a)

To a stirred solution of (S)-2-methyl-CBS-oxazaborolidine (180 µL of a 1.0 M solu-
tion in toluene, 0.18 mmol) in THF (0.6 mL) at 0 °C and under N₂ was added borane-
tetrahydrofuran complex (140 µL of a 1 M solution in THF, 140 µmol) followed by a so-
lution of 155a (16.5 mg, 14.6 µmol) in THF (0.35 mL). After 7 min, H₂O (200 µL) was
added and the mixture was allowed to warm to room temperature. Diethyl ether (2 mL)
was added and the mixture was washed with 5% aqueous HCl. The aqueous phase was
extracted with diethyl ether (2 × 0.5 mL), and the combined organic phases were washed
with H₂O and saturated aqueous NaCl (0.5 mL ea), dried over Na₂SO₄, filtered, and con-
centrated. The crude allylic alcohol 166a (Rf 0.40; hexanes–ethyl acetate, 2:1, v/v) was
filtered through silica gel with ethyl acetate, the filtrate was concentrated and then diluted
with the mixture of THF (0.65 mL), acetic acid (0.50 mL) and H₂O (0.26 mL) in a 10 mL
vial. The vial was then capped and the reaction was heated at 55°C for 40 hours before
cooled down to room temperature. The solvent was removed by vacuum and the residue
was purified through column chromatography (hexanes-ethyl acetate, 4:1 to 2:1) to give
155a (11.6 mg, 10.8 µmol, 74%) as white solid.

Rf 0.31 (hexanes-ethyl acetate, 2:1, v/v); [α]D²⁰ = +28.4 (c 0.25, CHCl₃); IR (neat):
3387, 3087, 3061, 3023, 2953, 2925, 2864, 2854, 1491, 1455, 1379, 1250, 1206, 1078,
1026, 964, 913, 735, 698 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.34-7.24 (m, 15H), 5.83 (dd, J = 15.5, 7.5 Hz, 1H), 5.59 (dd, J = 15.5, 7 Hz, 1H), 5.39 (t, J = 1.5 Hz, 1H), 5.15 (s, 1H), 5.02 (s, 1H), 4.81 (d, J = 12.5 Hz, 1H), 4.75 (d, J = 12.5 Hz, 1H), 4.66 (d, J = 11.5 Hz, 1H), 4.61 (d, J = 12.5 Hz, 1H), 4.58 (m, 1H), 4.51 (d, J = 11.5 Hz, 1H), 4.47 (d, J = 12.5 Hz, 1H), 4.30 (d, J = 7 Hz, 1H), 4.11 (s, 1H), 4.02 (d, J = 9.5 Hz, 1H), 3.91 (m, 1H), 3.69-3.53 (m, 6H), 3.37 (m, 2H), 3.24 (m, 2H), 2.54 (m, 1H), 2.44 (q, J = 7.5 Hz, 1H), 2.22-1.93 (m, 6H), 1.73 (s, 3H), 1.69-1.30 (m, 14H), 1.16 (s, 3H), 1.04 (d, J = 7.0 Hz, 3H), 0.99 (d, J = 7.5 Hz, 3H), 0.83 (d, J = 7.0 Hz, 3H); ¹³C NMR (CDCl₃, 125MHz) δ 144.1, 138.8, 138.7, 138.1, 134.8, 130.9, 128.3, 128.2, 128.2, 127.9, 127.9, 127.6, 127.5, 127.5, 122.4, 112.0, 105.5, 97.9, 96.4, 84.1, 79.0, 78.6, 77.7, 75.3, 73.4, 73.3, 72.5, 72.4, 72.2, 71.3, 70.6, 70.4, 67.4, 60.4, 42.7, 41.0, 37.4, 36.0, 35.7, 34.0, 33.4, 33.1, 32.4, 32.3, 31.9, 30.8, 27.0, 26.7, 25.8, 24.9, 24.7, 23.8, 23.0, 20.0, 19.0, 15.7, 15.1, 14.4; HRMS calcd for C₆₉H₉₄O₁₃Na [M + Na]⁺: 1083.6173; found: 1083.6158.

To a stirred solution of 60a (4.5 mg, 4.2 µmol), DMSO (0.05 mL) and diisopropylethylamine (0.10 mL) in CH$_2$Cl$_2$ (0.10 mL) was added sulfur trioxide pyridine complex (5.0 mg, 31.4 µmol). The mixture was stirred for 2 hours before saturated NH$_4$Cl solution (1 mL) and diethyl ether (2 mL) was added. After stirred for another 15 min, the organic phase was separated and the aqueous phase was extracted with diethyl ether (4 × 1 mL). The combined organic phase was dried over Na$_2$SO$_4$, filtered, and concentrated. The crude product was the dissolved in the mixture of t-butanol (0.25 mL) and water (0.05 mL) before NaH$_2$PO$_4$·2H$_2$O (7 mg, 44.9 µmol), 2-methyl-2-butene (0.2 mL) and NaClO$_2$ (4 mg, 44.2 µmol) was added in sequence. The mixture was stirred for 1 hour before saturated Na$_2$S$_2$O$_3$ solution (1 mL) was added. The mixture was stirred for another 20 min before the solution was acidified to pH = 2 with 1 M HCl. The mixture was then extracted with diethyl ether (6 × 1 mL) and the combined organic extract was dried over Na$_2$SO$_4$, filtered, and concentrated. Silica gel column chromatography (dichloromethane–methanol, 20:1, v/v) of the residue gave 167a (3.5 mg, 3.3 µmol, 78%) as a clear, colorless oil:

$R_f$ 0.22 (dichloromethane-methanol, 19:1, v/v); $[\alpha]_D^{25} = +19.2$ (c 0.33, CHCl$_3$); IR (neat): 3066, 3021, 2924, 2853, 1738, 1713, 1462, 1378, 1180, 1078, 1027, 964, 734, 697 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.33-7.24 (m, 15H), 5.81 (dd, $J = 15.5$, 7.5 Hz, 1H), 5.59 (dd, $J = 15.5$, 7 Hz, 1H), 5.44 (s, 1H), 5.14 (s, 1H), 5.04 (s, 1H), 4.79 (m, 2H), 4.67 (d, $J = 11$ Hz, 1H), 4.60 (d, $J = 12.5$ Hz, 1H), 4.57-4.51 (m, 2H), 4.46 (d, $J = 12.5$ Hz, 1H), 4.32 (d, $J = 7.5$ Hz, 1H), 4.23 (brt, $J = 10$ Hz, 1H), 4.03 (d, $J = 9.5$ Hz, 1H), 3.92 (m, 1H), 3.68-3.52 (m, 5H), 3.38 (dd, $J = 11.5$, 3 Hz, 1H), 3.23 (dd, $J = 12$, 4 Hz, 1H), 2.44
(dd, $J = 14.5, 9.5$ Hz, 1H), 2.33 (q, $J = 7.5$ Hz, 1H), 1.73 (s, 3H), 1.39 (s, 3H), 1.07 (d, $J = 7$ Hz, 3H), 0.99 (d, $J = 7$ Hz, 3H), 0.83 (d, $J = 7$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125MHz) δ 175.6, 143.7, 138.8, 138.7, 138.3, 130.9, 128.3, 128.2, 127.9, 127.8, 127.6, 127.5, 122.2, 112.4, 105.6, 97.9, 96.4, 84.2, 78.8, 78.4, 77.9, 75.3, 73.4, 73.2, 72.4, 71.9, 71.3, 70.6, 66.9, 60.4, 42.7, 41.1, 37.2, 36.0, 35.6, 34.0, 33.2, 32.9, 32.3, 31.9, 30.6, 29.6, 29.5, 29.4, 29.3, 29.1, 27.2, 27.0, 26.8, 25.8, 24.9, 24.8, 23.7, 23.0, 22.7, 20.0, 19.0, 15.8, 15.1, 14.4, 14.1; HRMS calcd for C$_{65}$H$_{86}$O$_{13}$Na [M + Na]$^+$: 1097.5966; found: 1097.5960.


To a stirred $-78$ °C solution of 167a (1.5 mg, 1.3 µmol) in THF (0.2 mL) under argon was added a solution of lithium di-tert-butylbiphenylide (0.4 mL of 0.13 M solution in THF, 0.05 mmol). After stirring for 30 min, H$_2$O (0.2 mL) was added to the deep blue-green solution and the resulting colorless mixture was allowed to warm to room temperature. The THF was removed under a stream of argon, and the residue was diluted with H$_2$O (0.2 mL) and washed with hexanes (3 × 1 mL). The aqueous phase was cooled to 0
°C and was acidified to pH 2 with 0.5 M aqueous HCl, and extracted with diethyl ether (4 × 1 mL). The combined ether extracts were dried over Na₂SO₄, filtered, and concentrated. The residue was purified by silica gel column chromatography (dichloromethane-methanol, 18:1, v/v) to give 1a (0.7 mg, 0.9 µmol, 67%) as a colorless solid.

Rf 0.09 (dichloromethane-methanol, 19:1, v/v); [α]D²⁵ = +10.8 (c 0.07, CHCl₃); ¹H NMR (CDCl₃, 500 MHz): δ 5.78 (dd, J = 15, 8 Hz, 1H), 5.54 (dd, J = 15, 8 Hz, 1H), 5.44 (s, 1H), 5.32 (s, 1H), 5.14 (s, 1H), 4.49 (q, J = 7 Hz, 1H), 4.21 (d, J = 10 Hz, 1H), 4.00 (m, 1H), 3.65 (m, 2H), 3.55 (m, 1H), 3.45 (dd, J = 7.5 Hz, 1H), 3.42 (t, J = 10 Hz, 1H), 3.40 (m, 1H), 2.33 (q, J = 7 Hz, 1H), 2.23-1.30 (m, 20H), 1.77 (s, 3H), 1.48 (s, 3H), 1.07 (d, J = 7 Hz, 3H), 0.99 (d, J = 7.5 Hz, 3H), 0.95 (d, J = 6.5 Hz, 1H); ¹³C NMR (CD₃OD, 125MHz) δ 147.4, 137.8, 132.0, 123.7, 112.2, 107.1, 99.3, 97.7, 86.4, 80.7, 79.5, 75.0, 73.3, 72.1, 71.4, 67.0, 61.4, 38.6, 38.1, 37.4, 35.3, 34.3, 34.2, 33.3, 31.6, 28.6, 27.7, 26.7, 25.3, 23.2, 21.0, 20.1, 16.8, 14.7, 14.4; HRMS calcd for C₄₄H₆₈O₁₃Na [M + Na]⁺: 827.4558; found: 827.4545.

(S)-2-methylnon-1-en-8-yn-4-ol (190)

A mixture of (R)-(+)1,1’-bi-2-naphthol (2.88 g, 10 mmol), Ti(Oi-Pr)₄ (2.93 mL, 10 mmol) and oven-dried powdered 4Å molecular sieves (36 g) in CH₂Cl₂ (200 mL) was heated at reflux for 1h. The red-brown mixture was cooled to room temperature and 189 (9.0 g, 93.6 mmol) in CH₂Cl₂ (20 mL) was added. After being stirred for 10 min, the contents were cooled to -78 °C, and 2-methyl-allyltri-n-butylstannane (38.7 g, 112.3 mmol)
was added. The reaction wash stirred for 10 min and then placed in a -20 °C freezer for 72 h. A solution of saturated NaHCO$_3$ (25 mL) was added and the mixture was stirred for 1 h. Na$_2$SO$_4$ (18.0 g, 126.6 mmol) was then added and the mixture was filtered through a plug of Celite and concentrated. The residue was purified by flash chromatography (hexanes-EtOAc, 4:1, v/v) to give 190 as a light yellow oil (12.80 g, 84.1 mmol, 90\%):

\[ R_f 0.60 \text{ (hexanes-ethyl acetate, 8:1, v/v); } [\alpha]_D^{20} -14.8 \text{ (c 1.0, CHCl}_3); \text{ IR (neat): 3417, 3305, 3075, 2934, 2871, 2117, 1650, 1454, 1376, 1259, 1082, 996, 893, 635, 529 cm}^{-1}; \]

\[ ^1\text{H NMR (CDCl}_3, 500 MHz): } \delta 4.89 \text{ (s, 1H), 4.80 \text{ (s, 1H), 3.75 \text{ (m, 1H), 2.26-2.20 \text{ (m, 3H), 2.11 \text{ (dd, } J = 14, 9 \text{ Hz, 1H), 1.95 \text{ (t, } J = 2.5 \text{ Hz, 1H), 1.76 \text{ (s, 3H), 1.74-1.69 \text{ (m, 2H), 1.63 \text{ (m, 3H); } ^13\text{C NMR (CDCl}_3, 125 MHz)} \delta 142.8, 113.8, 84.5, 68.6, 68.3, 46.4, 36.2, 24.9, 22.5, 18.6; HRMS calcd for } \text{C}_{10}\text{H}_{16}\text{ONa [M + Na}^+\text{]: 175.1099; found: 175.1090.} \]

(\text{S})\text{-triethyl((2-methylnon-1-en-8-yn-4-yl)oxy)silane (181)}

To a solution of 190 (0.900 g, 5.92 mmol), imidazole (1.01 g, 14.8 mmol) and 4-dimethylaminopyridine (0.072 g, 0.59 mmol) in CH$_2$Cl$_2$ (15 mL) was added chlorotriethylsilane (0.98 g, 0.66 mL, 6.51 mmol). The mixture was stirred for 30 min before saturated NH$_4$Cl solution (6 mL) and diethyl ether (20 mL) were added. The organic phase was separated and the aqueous phase was extracted by diethyl ether (3 \times 20 mL). The organic extracts were combined, dried over Na$_2$SO$_4$, filtered and concentrated. The residue
was purified by flash column chromatography (hexanes: ethyl acetate, 16:1, v/v) to give \textbf{181} (1.44 g, 5.40 mmol, 91\%) as a colorless oil.

\( R_f \) 0.56 (hexanes-ethyl acetate, 20:1, v/v); \([\alpha]^2_0\) -6.3 (c 1.2, CHCl\(_3\)); IR (neat): 3313, 3075, 2954, 2912, 2877, 2119, 1456, 1415, 1376, 1239, 1090, 1035, 1010, 926, 891, 742, 631 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 4.78 (s, 1H), 4.72 (s, 1H), 3.84 (m, 1H), 2.21 (m, 4H), 1.93 (t, \(J = 2.5\) Hz, 1H), 1.73 (s, 3H), 1.68-1.44 (m, 4H), 0.96 (t, \(J = 8\) Hz, 9H), 0.60 (q, \(J = 8\) Hz, 6H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 142.7, 112.9, 84.5, 70.4, 68.3, 46.2, 35.8, 24.3, 23.0, 18.6, 6.9, 5.1; HRMS calcd for C\(_{16}\)H\(_{30}\)ONa [M + Na]\(^+\): 289.1964; found: 289.1957.

\(\text{182}\) and \(\text{187}\)

\(\text{(4S,5R)}\)-6-\((\text{4-methoxybenzyl})\)oxy-\(5\)-methyl-4-\((\text{triethylsilyl})\)oxyhexan-2-one (182)

\(\text{(4S,5R)}\)-\(4\)-hydroxy-6-\((\text{4-methoxybenzyl})\)oxy-\(5\)-methylhexan-2-one (187)

To the mixture of PdCl\(_2\) (10.6 mg, 0.060 mmol), CuCl (0.079 g, 0.80 mmol), DMF (4.5 mL) and water (0.6 mL) was blown in O\(_2\) from balloon. After 20 min, a solution of \textbf{186} (0.22 g, 0.60 mmol) in DMF (1.5 mL) was added to the mixture. The mixture was stirred for 6 hours before water (15 mL) and concentrated ammonium hydroxide solution (0.5 mL) was added. The mixture was stirred for another one hour before diethyl ether (15 mL) was added. The aqueous phase was separated and the aqueous phase was ex-
tracted with diethyl ether (3×7 mL) and the combined organic extracts were washed with saturated aqueous NaCl (10 mL). The combined organic fraction was dried over Na₂SO₄, filtered and concentrated. The residue was chromatographed on silica gel (hexanes-ethyl acetate, 10:1 to 2:1, v/v) to give 182 (0.137 g, 0.374 mmol, 62%) and 187 (0.048 g, 0.180 mmol, 30%, 92% in total) as colorless oil.

Data for 182:

\[ R_f \ 0.36 \text{ (hexanes-ethyl acetate, 8:1, v/v); } [\alpha]_D^{20} -8.7 \text{ (c 1.1, CHCl}_3\text{); IR (neat): 3100, 3062, 3032, 2995, 2956, 2911, 2876, 1716, 1613, 1586, 1514, 1462, 1416, 1359, 1302, 1248, 1172, 1079, 1038, 1006, 821, 741, 581, 518 \text{ cm}^{-1}; \]

\[ ^1H \text{ NMR (CDCl}_3\text{, 500 MHz): } \delta 7.24 \text{ (d, } J = 6.5 \text{ Hz, 2H), 6.87 \text{ (d, } J = 6.5 \text{ Hz, 2H), 4.42 \text{ (d, } J = 11.5 \text{ Hz, 1H), 4.36 \text{ (d, } J = 11.5 \text{ Hz, 1H), 3.81 \text{ (s, 3H), 3.38 (dd, } J = 9, 7 \text{ Hz, 1H), 3.23 (dd, } J = 9.5, 6 \text{ Hz, 1H), 2.56 (dd, } J = 16, 8 \text{ Hz, 1H), 2.46 (dd, } J = 16, 4 \text{ Hz, 1H), 2.11 (s, 3H), 0.93 (t, } J = 8 \text{ Hz, 9 H), 0.59 (q, } J = 8 \text{ Hz, 6H);} \]

\[ ^{13}C \text{ NMR (CDCl}_3\text{, 125 MHz) } \delta 208.0, 159.1, 130.7, 129.1, 113.7, 72.7, 72.0, 70.1, 55.3, 47.5, 39.5, 31.4, 12.6, 6.9, 5.01; \]


Data for 187:

\[ R_f 0.24 \text{ (hexanes-ethyl acetate, 2:1, v/v); } [\alpha]_D^{20} -27.9 \text{ (c 1.1, CHCl}_3\text{); IR (neat): 3468, 2964, 2906, 2858, 1712, 1613, 1514, 1460, 1413, 1360, 1302, 1248, 1173, 1082, 1034, 820 \text{ cm}^{-1}; \]

\[ ^1H \text{ NMR (CDCl}_3\text{, 500 MHz): } \delta 7.24 \text{ (d, } J = 6.5 \text{ Hz, 2H), 6.87 \text{ (d, } J = 6.5 \text{ Hz, 2H), 4.43 (s, 2H), 4.02 (m, 1H), 3.80 (s, 3H), 3.56 (d, } J = 3.5 \text{ Hz, 1H), 3.49 (m, 2H), 2.58 (d, } J = 6 \text{ Hz, 2H), 2.18 (s, 3H), 1.87 (m, 1H), 0.91 (d, } J = 7 \text{ Hz, 3H);} \]

\[ ^{13}C \text{ NMR (CDCl}_3\text{,} \]
125 MHz) δ 209.4, 159.3, 130.1, 129.3, 113.9, 73.5, 73.0, 71.5, 55.3, 48.1, 38.3, 31.0, 13.7; HRMS calcd for C$_{15}$H$_{22}$O$_4$Na [M + Na]$^+$: 289.1416; found: 289.1403.

(5S,7S,13S)-3,3,15,15-tetraethyl-5-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-7-methyl-13-(2-methylallyl)-4,14-dioxa-3,15-disilaheptadec-8-yn-7-ol (191a)

To a stirred -78 ºC solution of 181 (0.400 g, 1.50 mmol) in THF (5 mL) was added n-butyllithium (0.60 mL of a 2.5 M solution in hexanes, 1.5 mmol). The mixture was stirred at -78 ºC before warmed to 0 ºC. The mixture was then cooled to -78 ºC again after 40 minutes and a solution of 182 (0.185 g, 0.486 mmol) in THF (3 mL) was added via cannula. After one hour, saturated aqueous NH$_4$Cl solution (15 mL) was added and the mixture was warmed to room temperature. The mixture was extracted with diethyl ether (3×10 mL) and the combined organic extracts were washed with water and saturated aqueous NaCl. The combined organic fraction was dried over Na$_2$SO$_4$, filtered and concentrated. The residue was chromatographed on silica gel (hexanes-ethyl acetate, 20:1 to 7:1, v/v) to give 191a (0.106 g, 0.164 mmol, 34%) and 191b (0.136 g, 0.210 mmol, 43%, 77% in total) as colorless oil:
Data for **191a**:

$R_f$ 0.53 (hexanes-ethyl acetate, 8:1, v/v); $[\alpha]_D^{20}$ -11.2 (c 1.6, CHCl$_3$); IR (neat): 3493, 3070, 2954, 2936, 2913, 2877, 1613, 1514, 1456, 1378, 1247, 1169, 1139, 1086, 1038, 1005, 886, 819, 743 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.24 (d, $J = 6.5$ Hz, 2H), 6.87 (d, $J = 6.5$ Hz, 2H), 4.85 (s, 1H), 4.76 (s, 1H), 4.69 (s, 1H), 4.68 (m, 1H), 4.47 (d, $J = 12$ Hz, 1H), 4.37 (d, $J = 12$ Hz, 1H), 3.83 (s, 3H), 3.22 (m, 2H), 2.19 (m, 2H), 2.14 (m, 2H), 1.72 (s, 3H), 1.68-1.54 (m, 5H), 1.43-1.38 (m, 2H), 1.41 (s, 3H), 1.00 (t, $J = 8$ Hz, 9H), 0.95 (t, $J = 8$ Hz, 9H), 0.88 (d, $J = 7$ Hz, 3H), 0.71 (q, $J = 8$ Hz, 6H), 0.59 (q, $J = 8$ Hz, 6H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 159.1, 142.8, 130.6, 128.9, 113.7, 112.8, 83.6, 73.2, 72.6, 72.3, 70.5, 67.7, 55.3, 46.1, 41.2, 39.8, 36.2, 31.4, 24.7, 23.0, 19.0, 10.5, 7.0, 6.8, 5.3, 5.1; HRMS calcd for C$_{37}$H$_{66}$O$_5$Si$_2$Na [M + Na]$^+$: 669.4346; found:669.4333.

Data for **191b**:

$R_f$ 0.34 (hexanes-ethyl acetate, 8:1, v/v); $[\alpha]_D^{20}$ -16.1 (c 1.1, CHCl$_3$); IR (neat): 3450, 3070, 2954, 2936, 2906, 2876, 1613, 1514, 1456, 1408, 1370, 1296, 1247, 1169, 1089, 1038, 1005, 886, 819, 743 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.23 (d, $J = 6.5$ Hz, 2H), 6.87 (d, $J = 6.5$ Hz, 2H), 4.76 (s, 1H), 4.70 (s, 1H), 4.43 (m, 2H), 4.27 (m, 1H), 4.18 (s, 1H), 3.82 (m, 1H), 3.80 (s, 3H), 3.39 (dd, $J = 9$, 8 Hz, 1H), 3.25 (dd, $J = 9$, 5 Hz, 1H), 2.31 (m, 1H), 2.22-2.11 (m, 4H), 1.90 (dd, $J = 14$, 7 Hz, 1H), 1.76 (dd, $J = 14.5$, 5 Hz, 1H), 1.72 (s, 3H), 1.62-1.42 (m, 4H), 1.44 (s, 3H), 0.97 (t, $J = 8$ Hz, 9H), 0.96 (t, $J = 8$ Hz, 9H), 0.91 (d, $J = 7$ Hz, 3H), 0.64 (q, $J = 8$ Hz, 6H), 0.59 (q, $J = 8$ Hz, 6H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 159.2, 142.8, 130.4, 129.1, 113.8, 112.8, 84.8, 82.8, 72.7, 72.1,
71.9, 70.5, 67.0, 55.3, 46.1, 43.8, 38.7, 36.1, 30.9, 24.6, 23.0, 18.9, 12.6, 7.0, 6.9, 5.2, 5.1; HRMS calcd for \(C_{37}H_{66}O_5Si_2Na\) \([M + Na]^+\): 669.4346; found: 669.4337.


To a solution of 191a (60.1 mg, 0.092 mmol) in THF (0.7 mL) was added tetra-\(n\)-butylammonium fluoride solution (1.0 M in THF, 0.28 mL, 0.28 mmol) dropwise. The mixture was stirred for 30 min before saturated ammonium chloride solution (4 mL) was added. THF was removed from the mixture on rotavapor and diethyl ether (7 mL) was added. The mixture was stirred for 10 min and the organic phase was separated. The aqueous phase was extracted with diethyl ether (5 × 4 mL). The combined organic phase was dried over Na\(_2\)SO\(_4\), filtered and concentrated. The residue was purified by flash column chromatography (hexanes: ethyl acetate, 2:1 to 1:2, v/v) to give 180a (34.7 mg, 0.083 mmol, 90%) as a colorless oil:

\(R_f\) 0.16 (hexanes-ethyl acetate, 2:1, v/v); [\(\alpha\)]\(_D\)\(^{20}\) -29.2 (c 0.67, CHCl\(_3\)); IR (neat): 3364, 3073, 2954, 2924, 1612, 1514, 1441, 1367, 1292, 1248, 1180, 1081, 1031, 927, 890, 815 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.24 (d, \(J = 6.5\) Hz, 2H), 6.88 (d, \(J = 6.5\) Hz, 2H), 4.99 (s, 1H), 4.88 (s, 1H), 4.79 (s, 1H), 4.45 (AB, \(J_{AB} = 11.5\) Hz, 2H), 4.24 (m, 1H), 4.17 (brs, 1H), 3.81 (s, 3H), 3.77 (m, 1H), 3.60 (dd, \(J = 9.5, 4\) Hz, 1H), 3.46 (dd, \(J = 9, 7.5\) Hz, 1H), 2.26 (m, 2H), 2.19 (dd, \(J = 13.5, 3.5\) Hz, 1H), 2.10 (dd, \(J = 13.5, 9\) Hz,
1H), 1.84 (m, 1H), 1.76 (s, 3H), 1.71 (m, 2H), 1.61 (m, 4H), 1.47 (s, 3H), 0.91 (d, \( J = 7 \) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \( \delta \) 159.4, 142.7, 129.6, 129.4, 113.9, 113.5, 84.2, 83.5, 75.9, 74.7, 73.2, 68.2, 55.3, 46.3, 46.2, 38.7, 36.2, 31.5, 24.9, 22.4, 18.8, 13.9; HRMS calcd for C\(_{25}\)H\(_{38}\)O\(_3\)Na [M + Na]\(^+\): 441.2617; found: 441.2611.

(2R,3S,5R,11S)-1-((4-methoxybenzyl)oxy)-2,5,13-trimethyltetradec-13-en-6-yn-3,5,11-triol (180b)

To a solution of 191b (0.128 g, 0.198 mmol) in THF (1 mL) was added tetra-\(n\)-butylammonium fluoride solution (1.0 M in THF, 0.5 mL, 0.50 mmol) dropwise. The mixture was stirred for 30 min before saturated ammonium chloride solution (5 mL) was added. THF was removed from the mixture on rotavapor and diethyl ether (10 mL) was added. The mixture was stirred for 10 min and the organic phase was separated. The aqueous phase was extracted with diethyl ether (5 \( \times \) 5 mL). The combined organic phase was dried over Na\(_2\)SO\(_4\), filtered and concentrated. The residue was purified by flash column chromatography (hexanes: ethyl acetate, 2:1 to 1:2, v/v) to give 180b (77.0 mg, 0.184 mmol, 93%) as a colorless oil:

\( R_f \) 0.16 (hexanes-ethyl acetate, 2:1, v/v); \([\alpha]_D^{20} \) -12.1 (c 0.83, CHCl\(_3\)); IR (neat): 3370, 3073, 2955, 2924, 2876, 1612, 1583, 1514, 1441, 1367, 1292, 1248, 1180, 1081, 1031, 927, 890 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz): \( \delta \) 7.23 (d, \( J = 6.5 \) Hz, 2H), 6.88 (d, \( J = 6.5 \) Hz, 2H), 4.87 (s, 1H), 4.79 (s, 1H), 4.44 (AB, \( J_{AB} = 11.5 \) Hz, 2H), 4.04 (brs, 1H), 3.98
(brs, 1H), 3.94 (m, 1H), 3.80 (s, 3H), 3.74 (m, 1H), 3.56 (dd, \(J = 9.5, 4.5\) Hz, 1H), 3.45 (dd, \(J = 9.5, 7.5\) Hz, 1H), 2.24 (t, \(J = 7\) Hz, 2H), 2.19 (dd, \(J = 13.5, 3.5\) Hz, 1H), 2.10 (dd, \(J = 13.5, 9\) Hz, 1H), 1.96 (m, 2H), 1.82 (dd, \(J = 14.5, 2.5\) Hz, 1H), 1.75 (s, 3H), 1.71 (m, 1H), 1.61-1.51 (m, 3H), 1.52 (s, 3H), 0.91 (d, \(J = 7\) Hz, 3H).

\(^{13}\text{C NMR} (\text{CDCl}_3, 125\text{ MHz}) \delta 159.4, 142.7, 129.8, 129.3, 113.9, 113.5, 85.4, 82.8, 74.4, 73.6, 73.1, 68.2, 67.6, 55.3, 46.2, 46.1, 38.6, 36.2, 29.7, 24.9, 22.4, 18.7, 13.7; \text{HRMS calcd for } C_{25}H_{38}O_5Na [M + Na]^+: 441.2617; \text{found: 441.2613.}

\[ \text{(2S,6S,8S)-2-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-4-methyl-8-(2-methylallyl)-1,7-dioxaspiro[5.5]undec-4-ene (179)} \]

Dry THF (2 mL) was added to a pear like flask containing gold(I) chloride (5 mg, 0.022 mmol) and activated MS-4Å (0.30 g). After stirring for 10 minutes, the mixture was cooled to 0 °C and a solution of 180a (0.180 g, 0.430 mmol) in dry THF (3 mL) was added. After stirred for 2 hours, the mixture was filtered through a short plug of silica with ether (40 mL). The solution of crude product was concentrated, and then purified by flash chromatography (hexanes: ethyl acetate, 16:1, v/v) to give 179 as a colorless oil (36.7 mg, 88 %).

\( R_f \) 0.56 (hexanes-ethyl acetate, 8:1, v/v); [\( \alpha \)]\(_D\)\(^{20}\) -0.6 (c 0.60, CHCl\(_3\)); IR (neat): 3071, 3033, 2934, 2854, 1682, 1650, 1614, 1586, 1514, 1454, 1378, 1301, 1248, 1201, 1172,
1091, 1037, 980, 889, 820 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.26 (d, J = 6.5 Hz, 2H), 6.87 (d, J = 6.5 Hz, 2H), 5.34 (s, 1H), 4.74 (s, 1H), 4.71 (s, 1H), 4.45 (AB, J_AB = 12 Hz, 2H), 3.86-3.71 (m, 3H), 3.80 (s, 3H), 3.29 (t, 1H), 2.22 (dd, J = 13.5, 6 Hz, 1H), 2.06 (dd, J = 14, 7.5 Hz, 1H), 1.97-1.91 (m, 2H), 1.86-1.77 (m, 2H), 1.70 (s, 3H), 1.69 (s, 3H), 1.59 (m, 3H), 1.48 (td, J = 13, 4 Hz, 1H), 1.12 (m, 1H), 1.01 (d, J = 7 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 159.2, 142.9, 135.9, 131.0, 129.3, 125.1, 113.8, 112.3, 95.0, 72.8, 72.6, 69.0, 68.8, 55.4, 45.1, 38.8, 35.3, 33.4, 30.6, 23.2, 23.1, 19.1, 14.1; HRMS calcd for C₂₅H₃₆O₄Na [M + Na]⁺: 423.2511; found: 423.2512.

(R)-3-((2S,6S,8S)-8-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-10-methyl-1,7-dioxaspiro[5.5]undec-10-en-2-yl)-2-methylpropane-1,2-diol (205)

To a mixture of 179 (0.225 g, 0.562 mmol), tert-butanol (3.0 mL) and water (3.0 mL) at 0 °C was added AD-mix-α (0.91 g). The mixture was stirred vigorously for 48 hours until when sodium sulfite (1.0 g) was added. The mixture was stirred at 25 °C for another one hour and 20 mL diethyl ether was added. The organic phase was separated and the aqueous phase was extracted by diethyl ether (5 × 6 mL). The combined organic phase was dried over Na₂SO₄, filtered and concentrated. The residue was purified through column chromatography (hexanes-ethyl acetate, 4:1 to 2:1 to 1:1, v/v) to give 205 (0.181 g, 0.416 mmol, 74%) and 205a (0.044 g, 0.101 mmol, 18%, 92% overall) as colorless oil:
$R_f$ 0.16 (hexanes-ethyl acetate, 2:1, v/v); $[\alpha]_D^{20}$ -12.1 (c 0.56, CHCl$_3$); IR (neat): 3467, 3118, 3066, 3036, 2930, 2865, 2845, 1724, 1680, 1612, 1513, 1455, 1382, 1300, 1248, 1180, 1084, 1038, 972, 905, 835 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.26 (d, J = 6.5 Hz, 2H), 6.88 (d, J = 6.5 Hz, 2H), 5.28 (s, 1H), 4.48 (d, J = 11.5 Hz, 1H), 4.43 (d, J = 11.5 Hz, 1H), 4.05 (t, J = 11 Hz, 1H), 3.80 (s, 3H), 3.75 (ddd, J = 11, 7.5, 3.5 Hz, 1H), 3.58 (dd, J = 9, 5.5 Hz, 1H), 3.50 (d, J = 11 Hz, 1H), 3.41 (dd, J = 9, 6.5 Hz, 1H), 3.30 (d, J = 10.5 Hz, 1H), 1.99 (m, 1H), 1.93-1.85 (m, 2H), 1.75-1.72 (m, 2H), 1.68 (s, 3H), 1.59 (d, J = 15, 1.5 Hz, 2H), 1.48 (d, J = 13, 4 Hz, 2H), 1.1 (s, 3H), 0.99 (d, J = 6.5 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 159.2, 136.1, 130.6, 129.4, 124.1, 113.7, 113.7, 95.0, 72.9, 72.5, 69.7, 69.2, 68.2, 55.3, 45.1, 38.5, 35.1, 32.2, 31.9, 25.3, 22.8, 18.6, 13.3; HRMS calcd for C$_{25}$H$_{38}$O$_{6}$Na [M + Na]$^+$: 457.2566; found:457.2552.

(5S,6S,8S)-3-((2S,6S,8S)-8-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-10-methyl-1,7-dioxaspiro[5.5]undec-10-en-2-yl)-2-methylpropane-1,2-diol (205a)

$R_f$ 0.20 (hexanes-ethyl acetate, 2:1, v/v); $[\alpha]_D^{20}$ -13.8 (c 0.56, CHCl$_3$); IR (neat): 3458, 3066, 3029, 2932, 2850, 1682, 1613, 1513, 1454, 1378, 1301, 1247, 1205, 1180, 1088, 1038, 967, 907, 835 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.26 (d, J = 6.5 Hz, 2H), 6.86 (d, J = 6.5 Hz, 2H), 5.29 (s, 1H), 4.48 (d, J = 12 Hz, 1H), 4.43 (d, J = 12 Hz, 1H), 4.20 (s, 1H), 4.16 (t, J = 11 Hz, 1H), 3.80 (s, 3H), 3.75 (ddd, J = 11, 7.5, 3.5 Hz, 1H), 3.40 (dd, J = 9, 6.5 Hz, 1H), 1.95 (m, 1H), 1.92-1.85 (m, 2H), 1.75-1.72 (m, 2H), 1.66 (s, 3H), 1.59 (d, J = 15, 1.5 Hz, 2H), 1.48 (d, J = 13, 4 Hz, 2H), 1.1 (s, 3H), 0.99 (d, J = 6.5 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 159.2, 136.1, 130.6, 129.4, 124.1, 113.7, 113.7, 95.0, 72.9, 72.5, 69.7, 69.2, 68.2, 55.3, 45.1, 38.5, 35.1, 32.2, 31.9, 25.3, 22.8, 18.6, 13.3; HRMS calcd for C$_{25}$H$_{38}$O$_{6}$Na [M + Na]$^+$: 457.2566; found:457.2552.
3.66 (dd, J = 9, 4.5 Hz, 1H), 3.42 (dd, J = 9, 7 Hz, 1H), 3.36 (dd, J = 11, 5 Hz, 1H), 3.28 (dd, J = 11, 7 Hz, 1H), 2.70 (brt, J = 6.5 Hz, 1H), 1.97-1.78 (m, 4H), 1.68 (s, 3H), 1.60 (m, 2H), 1.50 (dd, J = 15, 1.5 Hz, 1H), 1.40 (dd, J = 15, 1 Hz, 1H), 1.29 (m, 2H), 1.16 (s, 3H), 1.00 (d, J = 7 Hz, 3H); 13C NMR (CDCl3, 125 MHz) δ 159.1, 136.2, 130.7, 129.4, 123.9, 113.7, 94.9, 72.8, 72.3, 71.8, 71.2, 69.3, 67.6, 55.3, 43.6, 38.8, 35.1, 32.8, 31.7, 24.5, 22.8, 18.5, 13.7; HRMS calcd for C25H38O6Na [M + Na]+: 457.2566; found: 457.2555.

(2S,6S,8S)-2-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-4-methyl-8-((R)-2,2,4-trimethyl-1,3-dioxolan-4-yl)methyl)-1,7-dioxaspiro[5.5]undec-4-ene (206)

To a solution of 205 (22 mg, 0.0507 mmol) in dichloromethane (1 mL) was added 2,2-dimethoxypropane (0.10 mL, 0.106g, 1.02 mmol followed by pyridinium p-toluenesulfonate (1.2 mg, 0.00438 mmol). The reaction was stirred for 2.5 hours until triethylamine (0.1 mL) was added. The solvent was evaporated on rotavapor and the residue was purified through column chromatography (hexanes-ethyl acetate, 15:1 to 10:1, v/v) to give 206 (24 mg, 0.0506 mmol, quant.) colorless oil.

Rf 0.45 (hexanes-ethyl acetate, 8:1, v/v); [α]D20 +24.2 (c 0.50, CHCl3); IR (neat): 2975, 2934, 2860, 1608, 1514, 1453, 1377, 1298, 1247, 1206, 1183, 1096, 1051, 979, 907, 838, 815 cm⁻¹; 1H NMR (CDCl3, 500 MHz): δ 7.25 (d, J = 12 Hz, 2H), 6.87 (d, J =
12 Hz, 2H), 5.28 (s, 1H), 4.44 (AB, $J_{AB} = 7$ Hz, 2H), 3.85 (d, $J = 9$ Hz, 1H), 3.80 (s, 3H), 3.78 (m, 1H), 3.71 (dd, $J = 9.5$, 5 Hz, 1H), 3.67 (d, $J = 9$ Hz, 1H), 3.65 (ddd, $J = 11$, 8, 4 Hz, 1H), 3.29 (dd, $J = 9$, 8 Hz, 1H), 1.95 (m, 1H), 1.90 (m, 1H), 1.82 (tt, $J = 13.5$, 3.5 Hz, 1H), 1.76 (dd, $J = 17$, 3 Hz, 1H), 1.71 (d, $J = 6.5$ Hz, 2H), 1.69 (s, 3H), 1.55 (m, 3H), 1.43 (td, $J = 13$, 4.5 Hz, 1H), 1.38 (s, 3H), 1.33 (s, 3H), 1.25 (s, 3H), 0.99 (d, $J = 6.5$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 159.1, 135.0, 130.8, 129.2, 124.8, 113.7, 108.1, 94.5, 80.4, 75.1, 72.7, 72.3, 69.0, 67.0, 55.3, 47.0, 38.7, 35.1, 32.8, 31.9, 27.6, 27.0, 24.5, 22.9, 18.9, 13.7; HRMS calcd for C$_{28}$H$_{42}$O$_6$Na [M + Na]$^+$: 497.2879; found: 497.2885.

![Chemical structure](image)

(S)-2-((2S,6S,8S)-4-methyl-8-(((R)-2,2,4-trimethyl-1,3-dioxolan-4-yl)methyl)-1,7-dioxaspiro[5.5]undec-4-en-2-yl)propanal (171)

To a mixture of 206 (19 mg, 40 µmol), CH$_2$Cl$_2$ (4.0 mL), an aqueous NaH$_2$PO$_4$ buffer (pH = 7, 0.8 mL), and tert-butyl alcohol (0.15 mL) was added 2,3-dichloro-5,6-dicyanobenzoquinone (45 mg, 0.20 mmol). The reaction flask was placed in an aqueous bath and sonicated for 5 min. The mixture was diluted with diethyl ether (7 mL) and washed with saturated aqueous NaHCO$_3$ solution (2 mL). The aqueous phase was extracted with diethyl ether ($3 \times 2$ mL) and the combined organic phases were washed with saturated aqueous NaCl (1.5 mL), dried over Na$_2$SO$_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexanes–ethyl acetate, 5:1 to
3:2, v/v) to give a colorless oil which was then dissolved in CH₂Cl₂ (3.0 mL). The solution was added NaHCO₃ (120 mg, 1.43 mmol) followed by the Dess–Martin periodinane (60 mg, 0.143 mmol). The mixture was stirred for 30 min before diethyl ether (4.0 mL) and 10% aqueous Na₂S₂O₃ and saturated aqueous NaHCO₃ (1.0 mL ea) were added. The mixture was stirred until the organic phase became clear and colorless. The separated aqueous phase was extracted with diethyl ether (3 × 2 mL), and the combined organic fractions were washed with saturated aqueous NaCl (1 mL), dried over Na₂SO₄, filtered, and concentrated. Silica gel column chromatography (hexanes–ethyl acetate, 8:1, v/v) of the residue gave 171 (11.3 mg, 32 µmol, 82%, two steps) as colorless oil.

\[ R_f \, 0.60 \text{ (hexanes-ethyl acetate, 4:1, v/v); } [\alpha]_{D}^{20} -13.8 \text{ (c 0.56, CHCl}_3\); \text{ IR (neat): } 2975, 2935, 2872, 2728, 1727, 1682, 1453, 1378, 1240, 1211, 1182, 1148, 1119, 1050, 978, 907, 855, 832, 809 \text{ cm}^{-1}; \text{ } ^1\text{H NMR (CDCl}_3, 500 MHz): } \delta \, 9.89 \text{ (d, } J = 2.5 \text{ Hz, 1H), 5.32 \text{ (s, 1H), 4.02 (ddd, } J = 11, 8, 4 \text{ Hz, 1H), 3.84-3.80 (m, 2H), 3.69 (d, } J = 7.5 \text{ Hz, 1H), 2.51 (qdd, } J = 7, 7, 2.5 \text{ Hz, 1H), 1.99 (dd, } J = 16, 11 \text{ Hz, 1H), 1.89-1.77 (m, 2H), 1.71 \text{ (s, 3H), 1.60 (m, 2H), 1.44 (m, 1H), 1.37 (s, 3H), 1.33 \text{ (s, 3H), 1.31 (s, 3H), 1.21 (m, 1H), 1.11 (d, } J = 7 \text{ Hz, 3H); } ^{13}\text{C NMR (CDCl}_3, 125 MHz) } \delta \, 204.6, 134.4, 125.2, 108.5, 94.9, 80.5, 75.5, 69.1, 67.6, 51.1, 46.8, 34.9, 33.6, 31.8, 27.8, 27.2, 24.8, 22.9, 18.9, 10.7; \text{ HRMS calcd for C}_{20}\text{H}_{32}\text{O}_{5}\text{Na }[M + Na]^+ : 375.2147; \text{ found: 375.2140.} \]
(R,E)-1-((2S,4aR,6S,8R,8aR)-8-(benzyloxy)-6-((1S,3S)-1-(benzyloxy)-3-((2S,6R,11S)-11-methyl-1,7-dioxaspiro[5.5]undecan-2-yl)butyl)-2-methoxy-7-methyleneoctahydropyran[3,2-b]pyran-2-yl)-6-((2S,6S,8S)-4-methyl-8-(((R)-2,2,4-trimethyl-1,3-dioxolan-4-yl)methyl)-1,7-dioxaspiro[5.5]undec-4-en-2-yl)hept-4-en-3-one (207)

To a stirred solution of 156 (28 mg, 34 µmol) in CH$_3$CN (0.5 mL) was added LiCl (7 mg, 0.17 mmol) followed by diisopropylethylamine (10 µL, 0.050 mmol). After stirring for 10 min, a solution of 171 (10 mg, 28.4 µmol) in CH$_3$CN (1.0 mL) was added. The resulting mixture became turbid after 10 min and was stirred for an additional 20 h. The mixture was diluted with diethyl ether (5 mL), washed with H$_2$O and saturated aqueous NaCl (0.5 mL ea), dried over Na$_2$SO$_4$, filtered, and concentrated. Silica gel column chromatography (hexanes–ethyl acetate, 5:1, v/v) of the residue gave 207 (27.0 mg, 26 µmol, 93%) as a clear, colorless oil:

$R_f$ 0.26 (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_D^{20}$ -14.2 (c 0.45, CHCl$_3$); IR (neat): 3087, 3062, 3030, 2934, 2871, 1732, 1694, 1678, 1624, 1454, 1378, 1209, 1115, 1080, 1045, 981, 911, 854, 734, 698 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.36-7.25 (m, 10H), 7.00 (dd, $J = 16$, 8 Hz, 1H), 6.16 (d, $J = 16$ Hz, 1H), 5.43 (s, 1H), 5.29 (s, 1H), 5.04 (s, 1H), 4.85 (d, $J = 12$ Hz, 1H), 4.76 (d, $J = 12$ Hz, 1H), 4.64 (d, $J = 12.5$ Hz, 1H), 4.51 (d, $J = 12.5$ Hz, 1H), 4.35 (d, $J = 7$ Hz, 1H), 4.07 (m, 1H), 3.91 (m, 1H), 3.84 (d, $J = 8.5$ Hz, 144
1H), 3.82 (m, 1H), 3.72 (m, 1H), 3.67 (d, $J = 9$ Hz, 1H), 3.60 (m, 1H), 3.53 (dd, $J = 11$, 5 Hz, 1H), 3.42 (t, $J = 9.5$ Hz, 1H), 3.50 (m, 1H), 3.20 (s, 3H), 2.58 (m, 2H), 2.49 (qdd, $J = 6.5$ Hz, 1H), 2.15 (m, 2H), 1.94-1.73 (m, 13H), 1.59 (m, 7H), 1.38 (s, 3H), 1.32 (s, 3H), 1.26 (s, 3H), 1.17 (d, $J = 7$ Hz, 3H), 0.99 (d, $J = 7.5$ Hz, 3H), 0.86 (d, $J = 7$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 199.2, 149.0, 144.0, 138.8, 138.7, 134.6, 128.3, 127.9, 127.6, 127.5, 125.0, 112.0, 108.2, 99.0, 97.9, 94.7, 83.9, 80.3, 77.7, 75.9, 75.2, 73.7, 73.4, 72.3, 70.6, 70.4, 67.2, 60.4, 47.6, 46.9, 41.6, 36.0, 35.5, 34.9, 34.6, 34.0, 33.5, 32.4, 31.8, 29.7, 27.6, 27.0, 26.8, 25.8, 25.5, 24.5, 22.8, 21.0, 20.0, 19.0, 18.8, 15.8, 15.4, 14.4, 14.2; HRMS calcd for C$_{62}$H$_{88}$O$_{12}$Na [M + Na]$^+$: 1047.6173; found: 1047.6197.

(R)-2-hydroxy-3-((2S,6S,8S)-8-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-10-methyl-1,7-dioxaspiro[5.5]undec-10-en-2-yl)-2-methylpropanoic acid (210)

To a mixture of 205 (20 mg, 0.046 mmol), 5% Pt/C (9 mg), NaHCO$_3$ (8 mg, 0.095 mmol) was bubbled in O$_2$ at 70 °C. After stirred for 3 days, the mixture was cooled to room temperature and was filtered through a pad of Celite. The filtrate was then acidified to pH = 3 through addition of HCl. The resultant cloudy mixture was extracted with diethyl ether (5 × 3 mL), and the combined organic fractions were washed with saturated aqueous NaCl (1 mL), dried over Na$_2$SO$_4$, filtered, and concentrated. Silica gel column
chromatography (CH$_2$Cl$_2$-methanol, 50:1 to 20:1, v/v) of the residue gave 210 (12.0 mg, 0.027 mmol, 59%, 89% brsm) and 205 (6 mg, 0.014 mmol, 30%) as colorless oil.

$R_f$ 0.50 (CH$_2$Cl$_2$-methanol, 19:1, v/v); $[\alpha]_D^{20} + 1.6$ (c 0.93, CHCl$_3$); $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.26 (d, $J = 12$ Hz, 2H), 6.87 (d, $J = 12$ Hz, 2H), 5.55 (brs, 1H), 5.26 (s, 1H), 4.52 (d, $J = 11.5$ Hz, 1H), 4.42 (d, $J = 11.5$ Hz, 1H), 3.99 (t, $J = 11$ Hz, 1H), 3.80 (s, 3H), 3.73 (ddd, $J = 10.5$, 7, 3.5 Hz, 1H), 3.54 (dd, $J = 9$, 6.5 Hz, 1H), 3.37 (dd, $J = 9$, 6.5 Hz, 1H), 2.13 (dd, $J = 15$, 2 Hz, 1H), 2.02 (m, 1H), 1.89 (dd, $J = 16$, 11 Hz, 1H), 1.80-1.70 (m, 3H), 1.68 (s, 3H), 1.60-1.45 (m, 5H), 1.38 (s, 3H), 0.92 (d, $J = 7$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 177.3, 159.2, 136.8, 132.3, 130.4, 129.7, 123.7, 113.8, 113.7, 95.4, 76.2, 72.8, 71.8, 69.5, 69.1, 55.3, 44.2, 38.1, 35.0, 31.5, 31.2, 29.7, 27.2, 22.8, 18.2, 12.7; HRMS calcd for C$_{26}$H$_{35}$O$_7$ [M - H]$: 447.2388; found: 447.2387.

(R)-methyl 3-((2S,6S,8S)-8-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-10-methyl-1,7-dioxaspiro[5.5]undec-10-en-2-yl)-2-methyl-2-((triethylsilyl)oxy)propanoate (211)

To a solution of 210 (28 mg, 0.0624 mmol) in benzene (1 mL) was added TMSCHN$_2$ (2.0 M in hexanes, 0.050 mL, 0.10 mmol) at 0 °C. After stirred for 30 min, the mixture was added acetic acid (0.05 mL) and was then warmed to room temperature. The solvent was then evaporated and the residue was dissolved in CH$_2$Cl$_2$ (1 mL). Imidazole (34 mg,
0.5 mmol) and chlorotriethylsilane (30 mg, 0.03 mL, 0.2 mmol) was added in sequence. The mixture was stirred for 10 hours before saturated NH₄Cl solution and diethyl ether (3 mL) was added. The organic phase was separated and the aqueous phase was extracted with diethyl ether (4 × 2 mL), and the combined organic fractions were washed with saturated aqueous NaCl (1 mL), dried over Na₂SO₄, filtered, and concentrated. Silica gel column chromatography (hexanes-ethyl acetate, 20:1, v/v) of the residue gave 211 (31 mg, 54 µmol, 87%) as colorless oil.

\[ R_f \] 0.50 (hexanes-ethyl acetate, 15:1, v/v); \([\alpha]_D^{25} -4.0 \ (c \ 1.0, \ CHCl_3); \) IR (neat): 2975, 2933, 2860, 1740, 1608, 1514, 1453, 1377, 1298, 1247, 1206, 1183, 1096, 1051 cm\(^{-1}\); \(^{1}\)H NMR (CDCl₃, 500 MHz): \(\delta\) 7.27 (d, \(J = 13 \) Hz, 2H), 6.87 (d, \(J = 13 \) Hz, 2H), 5.25 (s, 1H), 4.45 (s, 2H), 3.80 (s, 1H) 3.79 (m, 2H), 3.59 (s, 3H), 3.31 (t, \(J = 9 \) Hz, 1H), 2.04 (dd, \(J = 14, 7.5 \) Hz, 1H), 1.97 (m, 2H), 1.76 (m, 2H), 1.72 (dd, \(J = 14, 5 \) Hz, 1H), 1.67 (s, 3H), 1.41 (m, 1H), 1.39 (s, 3H), 1.02 (d, \(J = 6.5 \) Hz, 3H), 0.93 (t, \(J = 7 \) Hz, 9H), 0.58 (q, \(J = 7 \) Hz, 6H); \(^{13}\)C NMR (CDCl₃, 125 MHz) \(\delta\) 175.5, 159.1, 135.1, 131.0, 129.1, 125.0, 113.7, 94.5, 75.7, 72.6, 72.5, 68.8, 66.7, 55.3, 51.5, 48.8, 38.6, 35.0, 32.9, 31.3, 29.7, 25.8, 22.8, 18.8, 13.9, 7.0, 6.2; HRMS calcd for C₃₂H₅₂O₇Na [M + Na]⁺: 599.3380; found: 599.3369.
Appendix B: NMR Spectra
176
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SPW3 10.000000 sec
SPW4 10.000000 sec

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| HH02             | 46.00 μsec    |
| F12               | 1.0000000 mHz|
| F121              | 12.5000000 mHz|
| NPOD             | 50.06000000 mHz|

--- F2 Parameters ---
| S2                | 13.50001111 MHz|
| DIR               | 1.00000000 Hz|
| FO                | 1.00000000 Hz|
| PC                | 3.00000000 Hz|