I. PARA-SILETANYLBENZYL (PSB) PROTECTING GROUP II. STEREOCONTROL OF 5,5-SPIROKETALS IN THE SYNTHESIS OF CEPHALOSPOROLIDES H, E, AND F

Sami Fahd Tlais

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I. PARA-SILETANYLBENZYL (PSB) PROTECTING GROUP

II. STEREOCONTROL OF 5,5-SPIROKETALS IN THE SYNTHESIS OF CEPHALOSPOROLIDES H, E, AND F

By

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A Dissertation submitted to the Department of Chemistry and Biochemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy

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This thesis is dedicated to my second half; Rasha, my daughter;

Yasmina, Father, and Mother
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LIST OF ABBREVIATIONS

Ac acetyl
Bn benzyl
t-Bu tertiary butyl
°C degrees Celsius
Calcd calculated (in mass spectrometry)
CBS Corey-Bakshi-Shibata reagent
CD circular dichroism
CI chemical ionization (in mass spectrometry)
CSA camphor-10-sulfonic acid
d doublet (spectral)
δ chemical shift, in parts per million relative to tetramethylsilane
DDQ 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
d e diastereomeric excess
d r diastereomeric ratio
DEAD diethylazodicarboxylate
DIBAL-H diisobutylaluminum hydride
DMAP N,N-4-dimethylaminopyridine
DMF dimethylformamide
DMP Dess-Martin periodinane
DMSO dimethylsulfoxide
ee enantiomeric excess
eq equation
EI electron ionization (in mass spectrometry)
equiv equivalent(s)
ESI electrospray ionization (in mass spectrometry)
Et ethyl
FT-IR Fourier-transformed infrared
g gram(s)
h hour(s)
HRMS high-resolution mass spectrometry
Hz hertz
IR infrared
J coupling constant reported in hertz (in NMR spectroscopy)
Imid. imidazole
IR infrared
KOH potassium hydroxide
LAH lithium aluminum hydride
m multiplet (spectral)
M moles per liter, mega
MS molecular sieves
mmol millimole(s)
mCPBA m-chloroperbenzoic acid
Me methyl
min  minute(s)
MOM  methoxymethyl
mp  melting point
MS  mass spectrometry
NMR  nuclear magnetic resonance
NOE  nuclear Overhauser effect
NOESY  nuclear Overhauser spectroscopy
PMB  p-methoxybenzyl
PSB  p-siletanylbenzyl
ppm  parts per million
PMP  p-methoxyphenyl
q  quartet (spectral)
rt.  room temperature
s  singlet (spectral)
t  triplet (spectral)
TBAF  tetrabutylammonium fluoride
TBAI  tetrabutylammonium iodide
TBDPS  tert-butyldiphenylsilyl
TBS  tert-butyltrimethylsilyl
TEMPO  2,2,6,6-tetramethyl-1-piperidinyloxy free radical
TES  triethylsilyl
Tf  trifluoromethanesulfonyl
TFA  trifluoroacetic acid
THF  tetrahydrofuran
TIPS  triisopropylsilyl
TMS  trimethylsilyl
Ts  p-toluenesulfonyl
ABSTRACT

Two independent topics are covered in this thesis. The first project covers the development of a new hydroxyl protecting group: para-siletanylbzyl (PSB). The para-siletanylbzyl (PSB) ether is electronically similar to the benzyl ether, yet deprotection of PSB was accomplished under mild oxidative conditions that are unique among cleavage protocols for arylmethyl ethers. A new reagent for installing the PSB group, PSB-OPT, was developed. PSB-OPT was used to synthesize PSB ethers starting with wide variety of alcohols.

The second project focuses on controlling the stereochemistry of oxygenated 5,5-spiroketalts using chelation effects. Stereocontrol of 5,5-spiroketalts is an important unsolved challenge in organic synthesis. We have developed a strategy in which chelation specifically of zinc salts (other protic and Lewis acids were less effective) between the spiroketal oxygen and appropriately positioned alcohol groups override normal biases in the preparation of 5,5-spiroketalts. This chelation approach was applied in the synthesis of cephalosporolides H, E, and F.
PART I*

PARA-SILETANYLBENZYL (PSB) PROTECTING GROUP

CHAPTER ONE: BACKGROUND ON THE SILETANE OXIDATION AND CLEAVAGE OF PARA-SILETANYLBENZYL (PSB) ETHERS

1. Overview

This chapter will cover a new entry in the growing arsenal of arylmethyl ether protecting groups: the para-siletanylbenzyl (PSB) group (Scheme 1). The PSB protecting group is electronically similar to the benzyl protecting group, yet cleavage of the PSB ether was accomplished under mild conditions — involving alkaline hydrogen peroxide — that are unique among cleavage protocols for arylmethyl ethers. Furthermore, the PSB group affords the user new flexibility in the implementation of protecting group strategies that revolve around multiple arylmethyl ether protecting groups.

Scheme 1. para-Siletanylbenzyl (PSB) ether

2. Development of para-Siletanylbenzyl (PSB) Group

In 2003, the Dudley Lab¹ illustrated the Tamao-type oxidation² of silacyclobutanes (siletanes),³ in which the strained organosiletane undergoes a rapid ring-opening reaction

promoted by aqueous fluoride to set the stage for eventual oxidation of the carbon–silicon bonds (Scheme 2). Organosiletanes are stable to routine purification, handling, and even acidic hydrolysis of silyl ethers. Because hydrolytic opening of the siletane ring occurs rapidly under the mildest of Tamao oxidation conditions, organosiletanes undergo carbossilane oxidations without affecting a pendant silyl ether and at rates comparable to even the most activated Tamao substrates. Notably, arylsiletanes provide convenient access to phenol derivatives without requiring the separate “priming” step of the Tamao–Fleming reaction, which often involves cleavage of an aryl–silicon bond.

![Scheme 2. Tamao-type oxidation of organosiletanes](image)

When functionalized at the para-position with an alkoxy methyl substituent, the arylsiletane oxidation provides easy access to labile para-hydroxy benzyl (PHB) ethers. From the perspective of protecting group strategies, the aforementioned para-(alkoxy methyl)-aryl siletane is more appropriately referred to as an alkyl PSB ether (PSB = para-siletanyl benzyl).

Jobron and Hindsgaul drew attention to the advantage of employing protected-PHB ethers in carbohydrate synthesis by introducing para-acetoxy benzyl (PAB) and para-
(tert-butyldimethylsilyl)oxybenzyl protecting groups, the cleavage of which is promoted by first cleaving the acetate ester or silyl ether, respectively. The use of protected-PHB ethers is well suited to carbohydrate synthesis; arylmethyl protecting groups offer minimal electronic impact on glycosyl donors, in contrast to more electron-withdrawing acetate esters and silyl ethers. Outside of glycosylation reactions, however, it is unclear how much is gained by employing protected-PHB protecting groups over direct use of an acetyl or silyl moiety, especially as formation of protected-PHB ethers has thus far only been demonstrated on primary alcohols.

Seeking to take advantage of siletane oxidation, the Dudley Lab set out to develop a new arylmethyl protecting group for alcohols. Scheme 3 summarizes the protection and deprotection processes. 

Scheme 3. Overview of protection/deprotection of alcohols using the para-siletanylbenzyl (PSB) protecting group

2.1. Synthesis of PSB Transferring Reagents (PSB-X)

A straightforward series of reactions sequentially provided PSB dimethyl acetal 3, PSB–OH 4, and PSB–Br 5 (Scheme 4). 

para-Bromobenzaldehyde dimethyl acetal (1) underwent Barbier
coupling with siletane 2 to furnish \textit{para}-siletanylbenzaldehyde dimethyl acetal (3) in 86–91% yield. Hydrolysis of 3 and reduction with DIBAL-H provided PSB–OH 4 in 87–95% yield over two steps. Finally, PSB–Br (5) was available in 95% yield by treating PSB–OH (4) with Appel’s conditions (Ph\textsubscript{3}P, CBr\textsubscript{4}, CH\textsubscript{2}Cl\textsubscript{2}).\textsuperscript{11}

\textbf{Scheme 4}. Synthesis of PSB transferring reagents

\textbf{2.2. Synthesis of PSB Ethers}

The first aspect of the development of the \textit{para}-siletanylbenzyl protecting group relates to the synthesis of PSB ethers from a collection of representative alcohols (Scheme 5). This collection comprises primary and secondary alcohols and phenols, which were protected with different PSB transferring reagents such as: PSB–OH, PSB–Br, and PSB(OMe)\textsubscript{2} (Scheme 4).

\textbf{Scheme 5}. Representative alcohols employed as test substrates

\textbf{2.2.1. Formation of Aryl PSB Ethers Using PSB–OH}

Conversion of phenols to the corresponding PSB ethers was best accomplished under Mitsunobu conditions (Scheme 6) using PSB–OH (4), providing ethers 11 (74%) and 12 (96%).
2.2.2. Formation of PSB Ethers Using PSB–Br

Arylmethylation using PSB–Br under basic conditions was less effective, due to competing silexane polymerization. Silver oxide-mediated etherification protocols delivered PSB ethers with limited efficiency (Table 1). Of the representative alcohols screened, only the simple primary alcohol (8) gave rise to the corresponding PSB ether 13 in good yield (up to 83%). Arylmethylation of phenol 6 was reasonably efficient at best (70%), whereas PSB ethers of secondary alcohols 9 and 10 were obtained in only up to 50% and 38% yields, respectively. Furthermore, these reactions were capricious, difficult to conduct successfully, and required freshly prepared silver oxide for best results. It can be concluded that PSB–Br 5 cannot provide the general solution for the synthesis of PSB ethers.

### Table 1

<table>
<thead>
<tr>
<th>ArOH</th>
<th>ArOPSB</th>
<th>X</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>11</td>
<td>Ph</td>
<td>74%</td>
</tr>
<tr>
<td>7</td>
<td>12</td>
<td>OMe</td>
<td>96%</td>
</tr>
</tbody>
</table>
Table 1. Formation of PSB ethers using PSB–Br

<table>
<thead>
<tr>
<th>entry</th>
<th>ROH</th>
<th>ROPSB</th>
<th>yield&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td><img src="Ph" alt="Ph" />OPSB <em>11</em></td>
<td>up to 70%</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td><img src="Ph" alt="Ph" />OPSB <em>13</em></td>
<td>up to 83%</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td><img src="Ph" alt="Ph" />OPSB <em>14</em></td>
<td>up to 50%</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td><img src="Cyclopentane" alt="Cyclopentane" />OPSB <em>15</em></td>
<td>up to 38%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yield of individual experiments highly dependent on the quality of 5, silver oxide, and other reaction variables.

2.2.3. Formation of secondary alkyl PSB ethers by reduction of dioxane acetals

Regioselective reduction of benzylidene acetals with DIBAL-H provided indirect access to secondary arylmethyl ethers, including PSB ethers (Scheme 7).<sup>10</sup> Condensation of 1,3-butanediol (16) with acetal 3 provided 1,3-dioxane 17 (quantitative yield), the reduction of 17 with DIBAL-H furnished PSB ether 18 in 97% yield.
2.2.4. Formation of alkyl PSB ethers from alkyl PBB ethers

In light of difficulties associated with the direct conversion of alcohols into PSB ethers using PSB–Br (19) (Table 1), a two-step process was developed to access PSB ethers indirectly from para-bromobenzyl (PBB) ethers, which are amenable to preparation using the Williamson ether synthesis. First, the alcohol was treated with sodium hydride and PBB–Br (19). With the PBB ether thus installed, conversion of the aryl bromide moiety to the corresponding arylsiletane was achieved under Barbier conditions to furnish the desired PSB ethers 13–15 (Scheme 5).

3. PSB Cleavage or Deprotection

Benzyl ethers are robust, yet they provide cleavage mechanisms unique among alkyl ethers, including hydrogenolysis, dissolving metal reduction, electron-transfer oxidation (i.e., DDQ oxidation), and acidic cleavage under a range of experimental conditions. Electronic tuning of
the aromatic ring provides an expanded range of valuable properties, resulting in a series of arylmethyl protecting groups that includes para-methoxybenzyl (PMB), dimethoxybenzyl (DMB), naphthylmethyl (NAP), para-bromobenzyl (PBB), and many others. PSB is a new technique by which the electric tuning of the aromatic ring could be controlled.

PSB cleavage started with Tamao-type oxidation of the arylsilane to generate intermediate PHB ether. In the cases of protected phenols, the alkaline oxidation conditions promoted expulsion of the free phenols. In cases of protected aliphatic alcohols, the intermediate PHB ethers were sufficiently stable to be isolated prior to cleavage. A separate step was then employed to release the free alcohol from the PHB ether. Conditions for cleaving PHB ethers had been reported elsewhere and include: DDQ, iron trichloride, sodium methoxide, and others. Of these, the Dudley Lab focused on the use of DDQ (conditions D) and iron trichloride (conditions E).

The PSB ethers were cleaved in one- or two-step protocols (Table 2) that involved standard Tamao conditions (conditions A). Alternatively, Woerpel’s method (conditions B) provided PHB ethers faster and in higher yield (compare entries 3 and 6 with 4 and 7), so this protocol is recommended for substrates that can withstand the more forcing conditions. PHB ethers released the original alcohols upon subsequent treatment with either iron trichloride or DDQ. Finally, as seen in entry 5, catalytic hydrogenolysis (conditions C) efficiently removed PSB ethers, as expected by analogy to electronically similar benzyl ethers.
**Table 2. One- and two-step cleavage of PSB ethers**

<table>
<thead>
<tr>
<th>entry</th>
<th>PSB ether</th>
<th>conditions&lt;sup&gt;a&lt;/sup&gt;</th>
<th>PHB ether (yield)</th>
<th>Alcohol (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="PSB ether 11" /></td>
<td>A</td>
<td>—</td>
<td>6 (89%)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="PSB ether 12" /></td>
<td>A</td>
<td>—</td>
<td>7 (86%)</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="PSB ether 13" /></td>
<td>A; D</td>
<td>20 (87%)</td>
<td>8 (90%)</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="PSB ether 13" /></td>
<td>B; E</td>
<td>20 (99%)</td>
<td>8 (99%)</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="PSB ether 13" /></td>
<td>C</td>
<td>—</td>
<td>8 (88%)</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="PSB ether 14" /></td>
<td>A; E</td>
<td>21 (84%)</td>
<td>9 (97%)</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="PSB ether 14" /></td>
<td>B; E</td>
<td>21 (99%)</td>
<td>9 (97%)</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="PSB ether 15" /></td>
<td>A; E</td>
<td>22 (85%)</td>
<td>10 (94%)</td>
</tr>
</tbody>
</table>

<sup>a</sup> See Supporting Information for details. Conditions A: 30% aqueous H$_2$O$_2$, KF, K$_2$CO$_3$, THF/MeOH, 50 °C; Conditions B: t-BuOOH, TBAF, DMF, 70 °C; Conditions C: H$_2$, 10% Pd/C, EtOH; Conditions D: DDQ, CH$_2$Cl$_2$; Conditions E: FeCl$_3$, CH$_2$Cl$_2$. 
The Dudley Lab introduced a new aryl methyl protecting group, which is the PSB group. PSB was successfully cleaved under mild oxidative conditions. But the main weakness of PSB protecting group was the installation step or the synthesis of PSB ether. A powerful and effective method for the synthesis of PSB ether should be developed.
CHAPTER TWO: SYNTHESIS OF A NEW REAGENT FOR MAKING PARA-SILETANYLBENZYL (PSB) ETHERS

1. Introduction

Protecting group strategies\textsuperscript{12,15} are indispensable to the general pursuit of synthetic polyketides,\textsuperscript{16} oligosaccharides,\textsuperscript{17,18} peptides,\textsuperscript{19} and other complex small molecule structures\textsuperscript{20} of potential relevance to human health. A desirable protecting group satisfies three main criteria: (1) installation (formation) of the protecting group must occur easily and in high yield; (2) the installed protecting group must render inert an otherwise reactive site during a synthetic sequence aimed at affecting other regions of the molecular system; and (3) removal (cleavage) of the protecting group must occur easily and under mild conditions at the appropriate point in the synthetic scheme. Orthogonal reactivity with other common protecting groups is especially valuable for highly functionalized systems.

PSB protection was not appropriately addressed in previously reported studies,\textsuperscript{6,10} which instead relied mostly on two-step protocols for preparing a limited range of PSB ethers. In order to make para-siletanylbenzyl (PSB) protecting group a desirable protecting group, PSB should satisfy the three main criteria, which were mentioned above. The Dudley Lab focused on the development of a new arylmethyl PSB transferring reagent that could be applicable to wide range of alcohols including primary, secondary, and tertiary alcohols.

Traditionally, preparation of arylmethyl ethers from alcohols is accomplished by one of two strategies: Williamson ether synthesis under basic conditions, or under acidic conditions using trichloroacetimidates.\textsuperscript{21} Neither strategy was found generally to be appropriate for making the PSB (para-siletanylbenzyl) ethers.\textsuperscript{6} Upon exposure to alkali metal alkoxides, such as are employed in the Williamson ether synthesis protocol, siletanes undergo ring-opening polymerization to give rise to carbosilane polymers.\textsuperscript{22,23,24} Under acidic conditions, arylsilanes are subject to protodesilylation.\textsuperscript{25}
Scheme 9. PSB and benzyl transferring reagents

A new arylmethylation strategy had to be developed in order to address these limitations, with an aim of eventually identifying a general method for making PSB ethers. Because trichloroacetimidates require acidic conditions that were not compatible with the aryl–silicon subunit, a search began for a reagent analogous to benzyl trichloroacetimidate (BTCA, Scheme 9) that could be activated by N-alkylation rather than by N-protonation. Initial efforts focused on the preparation of simple benzyl ethers,\textsuperscript{26} revealing that N-methylation of 2-benzylxoxypyridine\textsuperscript{27} leads to a reagent — 2-benzylxoxo-1-methylpyridinium triflate (Bn-OPT, 25)\textsuperscript{28} — that converts alcohols into benzyl ethers upon warming.\textsuperscript{29,30} Thus emerged a new benzyl ether synthesis, which has since been extended to include reagents for the preparation of PMB\textsuperscript{31,32} and halobenzyl ethers.\textsuperscript{33} Importantly, the new arylmethyl ether synthesis involves neutral conditions that are applicable to the formation of PSB ethers.

2. Summary for the Synthesis and Reactivity of Bn–OPT and Its Derivatives

2.1. Synthesis of Bn–OPT

The synthesis of Bn–OPT was accomplished by coupling 2-chloropyridine (28) with the potassium salt of benzyl alcohol (27) in refluxing toluene to yield 2-benzylxoxopyridine (29) followed by methylation (Scheme 10). The triflate salt 25 precipitates from the reaction mixture as a white, crystalline solid that is stable indefinitely to storage at room temperature or below. Bn–OPT (25) is now commercially available from Sigma-Aldich.\textsuperscript{34}
2.2. Benzylation of Alcohols Using Bn–OPT

Warming the Bn–OPT (25) in the presence of an alcohol gave the benzyl ether (Scheme 11). The best solvent was trifluorotoluene (PhCF₃). Magnesium oxide was typically added to the reaction as an acid scavenger. Primary and secondary alcohols were protected in high yields, where tertiary alcohols and phenols were more challenging substrates. This reagent has found synthetic use in several labs independent of Dudley’s Lab (Scheme 12).³⁵

Scheme 11. Bn–OPT reactivity with alcohols

2.3. Synthesis of Benzyl Esters Using Bn–OPT

In addition to the synthesis of benzyl ethers using Bn–OPT (25), Bn–OPT was used to synthesize benzyl esters (Scheme 13).³⁵
2.4. Halobenzyl and para-Methoxybenzyl Derivatives

Other derivatives of Bn–OPT salt were developed, such as halobenzyl pyridinium and PMB lepidinium salts (Scheme 14). PMB salt necessitated generation in situ due to its instability. The PMB salt precursor: PMB lepidine (PMB-L), which is stable at room temperature, is now commercially available from Sigma-Aldrich.36

Scheme 13. Benzylation of carboxylic acids

Scheme 14. Derivatives of Bn–OPT


My research was directed towards the synthesis of a siletane derivative of Bn–OPT (25), which could be used for installation of the PSB (para-siletanylbenzyl) protecting group (Scheme 9). The optimized synthesis of PSB–OPT (24) features an innovative technique for initiating the formation of Grignard reagents. PSB–OPT (24) was capable of delivering the PSB group onto a
wide range of alcohol substrates, including carbohydrates and secondary alcohols. Competition experiments illustrated the degree to which the PSB ethers were orthogonally compatible with other common protecting groups including MOM, TBS, PMB, and others.

3.1. Synthesis of PSB–OPT

The arylsiletanes employed in this methodology were prepared by coupling 1-chloro-1-methylsiletane (2) with the requisite aryl Grignard reagent or, similarly, with the aryl halide under Barbier conditions (Scheme 4). The applicability of Barbier conditions illustrates that arylsiletanes are stable to organomagnesium nucleophiles even at elevated temperature (refluxing THF). In contrast, organolithium reagents are not suitable for the preparation of arylsiletanes, because even substoichiometric amounts of most organolithium reagents promote anionic ring-opening polymerization of organosiletanes.22,23,24

PSB–OPT 24, like other oxypyridinium triflate reagents prepared in the Dudley Lab, was eventually synthesized by N-methylation of 2-PSBO-pyridine (PSB-OP, 31). Since the standard method for preparing 2-pyridyl ethers — potassium hydroxide-promoted nucleophilic aromatic substitution of 2-chloropyridine — was not compatible with the siletane ring (Scheme 15), alternative synthetic protocols were developed (vide infra).

Scheme 15. Nucleophilic substitution of 2-chloropyridine
Thus, nucleophilic aromatic substitution of 2-chloropyridine (28) with \textit{para}-bromobenzyl alcohol (32) and \textit{para}-iodobenzyl alcohol (33) was employed to provide aryl bromide 34 (97% yield) and aryl iodide 35 (92% yield), respectively (Scheme 16). Inclusion of 18-crown-6 in the reaction mixture increases the efficiency of this coupling process,\cite{27, 29, 30, 33} but this additive can be excluded without suffering a significant drop in the reaction yield if the potassium hydroxide pellets are thoroughly ground with a mortar and pestle prior to use. Aryl halides 34 and 35 were to be converted to the corresponding Grignard reagents for trapping with chlorosiletane 2.

![Scheme 16. Preparation of \textit{para}-halogenated 2-benzyloxy pyridines](image)

Initial attempts to generate aryl Grignard reagent 36 were unsuccessful using either aryl bromide 34 or iodide 35,\cite{37} but magnesium–iodide exchange with isopropyl Grignard \cite{38} furnished 36 (Scheme 17). Subsequent addition of chlorosiletane 2 afforded PSBO-pyridine (PSB-OP, 31) in 72% yield.

![Scheme 17. Synthesis of PSB–OP (31) from aryl iodide 35](image)

A weakness of the synthesis of 31 (precursor of 24) as outlined in Scheme 17 is that \textit{para}-iodobenzyl alcohol is prohibitively expensive\cite{39} compared to \textit{para}-bromobenzyl alcohol.\cite{40, 41} Although standard methods for preparing Grignard reagents\cite{42, 43, 44} failed for this
substrate (53 → 55), we identified a new protocol for activating magnesium turnings that enabled us to generate 36 from aryl bromide 34.

3.1.1. New Protocol for Activating Magnesium Turnings

The reaction protocol that provided reproducible amounts of arylsilethane 31 from 34 involved premixing aryl bromide 34 with a large excess (10 equiv) of unactivated magnesium turnings in THF, and then injecting dibromoethane (2 equiv) rapidly by syringe. Bubbles of gas emanated from the surface of the magnesium metal for approximately 30 min, after which time the formation of Grignard 36 was complete. Addition of chlorosilethane 2 then provided arylsilethane 31 in 55% yield (Scheme 18).

Scheme 18. Synthesis of PSB-OP (31) start with aryl bromide 34

This protocol might be successful because of localized heating that occurred selectively at the magnesium surface, promoting Grignard formation but not bimolecular reactions between combinations of aryl species (34 and 36). The localized heat then dissipates to the solvent and eventually to external cooling elements (water bath and reflux condenser). Such a procedure is likely scale-dependent and would have to be monitored and optimized carefully prior to preparing larger quantities of material, but in our hands it has provided 31 reproducibly on a ca. 1 mmol scale.

3.2. Generation and Recrystallization of PSB–OPT

Pyridyl ether 31 was dissolved in trifluorotoluene and treated with methyl triflate. After 30 min, the volatiles were removed in vacuo to leave crude PSB–OPT 24 as an oily residue, which was dissolved in trifluorotoluene and left standing in the freezer at –20 °C to provide crystalline 24 (mp 65°C) in 95% yield (Scheme 19). Alternatively, as outlined later in Table 3, the
activation of PSB–OP 31 with methyl triflate can be performed in situ, thus obviating the need to isolate PSB–OPT 24.

Scheme 19. Preferred synthesis of PSB–OPT 24

4. Formation of Alkyl PSB Ethers Using PSB–OPT

The viability of PSB–OPT and its immediate precursor, PSB-OP 31, as general reagents for the synthesis of PSB ethers is the key finding of our efforts. Dudley’s Lab findings using Bn–OPT 25 (Scheme 9, above) guided the development of PSB–OPT 24. A range of representative primary and secondary alcohols (Scheme 5) gave way to PSB ethers upon warming in the presence of PSB–OPT (Table 3, entries 1–5). 3-Phenylpropanol, a simple primary alcohol, was converted into the corresponding PSB ether in 90% by heating it at 80 °C in the presence of two equivalents of PSB–OPT (formed in situ from PSB–OP and methyl triflate) and magnesium oxide for 24 h (entry 1). PSB protection of secondary alcohols 1-phenylethanol and menthol each proceeded in 88% yield (entries 2 and 3). The Roche ester, which is susceptible to β-elimination of its oxygen functionality, was protected as a PSB ether (37 → 38, entry 4) in 71% yield. Additionally, glucose derivative 40 was prepared in 91% yield using a slightly larger excess (3.0 equiv) of preformed PSB–OPT 24 (entry 5).
**Table 3.** Formation of alkyl PSB ethers using PSB–OPT (24)\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alcohol</th>
<th>Ether</th>
<th>Yield(^b,c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>![Structure of ether 13]</td>
<td>90% (&gt;95%)(^{29})</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>![Structure of ether 14]</td>
<td>88% (83%)(^{29})</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>![Structure of ether 15]</td>
<td>88% (88%)(^{29})</td>
</tr>
<tr>
<td>4</td>
<td>![Structure of alcohol 37]</td>
<td>![Structure of ether 38]</td>
<td>71%(^d) (76–82%)(^{29})</td>
</tr>
<tr>
<td>5(^e)</td>
<td>![Structure of alcohol 39]</td>
<td>![Structure of ether 40]</td>
<td>91%(^d)</td>
</tr>
</tbody>
</table>

\(^a\) See experimental part for details; unless otherwise indicated, 2.0 equiv of 31, MeOTf, and MgO employed relative to ROH.  
\(^b\) Estimated by \(^1\)H NMR, unless otherwise noted; isolated material contaminated with varying amounts of di-PSB ether 41.  
\(^c\) Yield in parenthesis refers to synthesis of the corresponding benzyl ether using benzyl reagent 25, as reported in the literature.  
\(^d\) Isolated yield of pure material judged to be >95% pure by \(^1\)H NMR.  
\(^e\) For this experiment, triflate 24 was prepared and isolated prior to use and 3.0 equiv of 31 and MgO were employed relative to ROH.
5. Formation of PSB Esters Using PSB–OPT

Benzyl reagent 25 gave rise to benzyl esters upon reaction with carboxylic acids.\textsuperscript{48} Similar reactivity of oxypyridinium 24 is illustrated by the PSB esterification of acetylsalicylic acid in 84\% yield (Scheme 20).

![Scheme 20. Formation of PSB esters using PSB–OPT 24](image)

6. Cleavage of PSB Ethers

The cleavage of PSB ethers was previously described by the Dudley Lab;\textsuperscript{6} Tamao-type oxidation of the arylsiletane generates an intermediate PHB ether, which could be hydrolyzed directly or subsequently oxidized to release the alcohol. Cleavage of PSB ethers was already demonstrated in the previous study by a two step process. PSB ether 38 and 40 were cleaved in one-step protocol (Scheme 21) that involves standard Tamao conditions providing free alcohol 37 and 39 via a PHB ether intermediate prior to the addition of DDQ.

![Scheme 21. PSB deprotection](image)
7. Orthogonality and Reactivity Experiments

With the general method for the synthesis and cleavage of PSB ethers, it is important to know its compatibility with other protecting groups. In order to determine orthogonality with other common protecting groups, a series of competition experiments was performed (Table 4). The PSB ether of 3-phenylpropanol (8) was mixed with protected versions of 3-(p-anisyl)propanol (45) and treated under various protocols designed to cleave one protecting group or the other. The anisyl and phenyl tags are easily distinguishable by NMR spectroscopy, and we assume that their n-propyl chains provide essentially equivalent chemical platforms for studying the cleavage of the respective ethers. Entries 1 and 2 describe orthogonal reactivity of PSB and PMB ethers under oxidative conditions. The alkaline nucleophilic peroxide oxidation affects only PSB ether 13, whereas the charge-transfer oxidation of DDQ occurs preferentially at the electron-rich aromatic ring of the PMB ether. Similarly, MOM ether 44b withstands the Tamao oxidation but succumbs to aqueous hydrochloric acid, which does not affect the PSB ether (entries 3 and 4). As we showed in our original siletane oxidation study, TBS ethers survive the mild Tamao conditions, and they cleave under acidic hydrolysis conditions to which the PSB group is inert (entries 5 and 6). Finally, PSB ether 13 is recovered unchanged from a reaction mixture that cleaved the Troc carbonate of 44d (entry 8), but Troc carbonate 44d partially hydrolyzed on exposure to alkaline peroxide (entry 7).
Table 4. Orthogonality in the cleavage of PSB ethers with other common protecting groups

<table>
<thead>
<tr>
<th>Entry</th>
<th>PG (44)</th>
<th>Conditions</th>
<th>Recovered PSB 13</th>
<th>Recovered PG 44</th>
<th>Yield of PHB 20</th>
<th>Yield of 45</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PMB(44a)</td>
<td>H₂O₂, KF</td>
<td>—</td>
<td>96% (44a)</td>
<td>82%</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>PMB(44a)</td>
<td>DDQ</td>
<td>94%</td>
<td>—</td>
<td>—</td>
<td>96%</td>
</tr>
<tr>
<td>3</td>
<td>MOM(44b)</td>
<td>H₂O₂, KF</td>
<td>—</td>
<td>90% (44b)</td>
<td>85%</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>MOM(44b)</td>
<td>6N HCl</td>
<td>85%</td>
<td>—</td>
<td>—</td>
<td>86%</td>
</tr>
<tr>
<td>5</td>
<td>TBS(44c)</td>
<td>H₂O₂, KF</td>
<td>—</td>
<td>88% (44c)</td>
<td>72%</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>TBS(44c)</td>
<td>AcOH, H₂O</td>
<td>90%</td>
<td>—</td>
<td>—</td>
<td>98%</td>
</tr>
<tr>
<td>7</td>
<td>Troc(44d)</td>
<td>H₂O₂, KF</td>
<td>—</td>
<td>N.D.</td>
<td>—</td>
<td>N.D.²</td>
</tr>
<tr>
<td>8</td>
<td>Troc(44d)</td>
<td>Zn/AcOH</td>
<td>92%</td>
<td>—</td>
<td>—</td>
<td>90%</td>
</tr>
</tbody>
</table>

²Not determined

Implicit in this study is the assumption that these other protecting groups will equally survive removal of the intermediate PHB ethers. We consider this assumption to be quite sound in general, because each of these protecting groups (with the obvious exception of the PMB ether) can withstand conditions that cleave arylmethyl ethers. PMB ethers are known to be stable to FeCl₃ under the conditions that we use to cleave PHB ethers, so we chose to look specifically at cleavage of the PHB ether in the presence of the PMB ether using DDQ (Scheme 6). By controlling the reaction stoichiometry and temperature, we quickly obtained evidence to validate our assumption: the PHB ether was removed in 82% yield, whereas the PMB ether (44a) was recovered 85% yield.
Although not directly related to this orthogonality study, it is interesting to note that PHB ethers can be converted into PMB ethers (Scheme 23) under mild conditions that would not impact most other protected or unprotected alcohols. The ability to convert a given protecting group into an orthogonal protecting group during multi-step synthesis—as opposed to employing a deprotection/reprotection sequence—adds valuable flexibility to protecting group strategies based on the PSB ether.

Electronically, PSB ethers are similar to benzyl ethers. What differentiates PSB ethers from benzyl ethers is the siletane ring. Therefore, a thorough understanding of siletane reactivity will guide optimal incorporation of the PSB group in protecting group strategies for multi-step synthesis.

Based on Dudley’s review of the siletane literature and studies from the Denmark, Oshima, our and other research laboratories, a chart of siletane reactivity is outlined (Table 5). This Table is an abridged version of (and follows the same layout as) the reactivity profile chart published in Greene’s Protective Groups in Organic Synthesis. The entries for benzyl and TBS are reproduced for comparison.
Table 5. Reactivity of PSB, Bn, and TBS ethers under various reaction conditions

<table>
<thead>
<tr>
<th>conditions</th>
<th>Bn</th>
<th>PSB</th>
<th>TBS</th>
<th>conditions</th>
<th>Bn</th>
<th>PSB</th>
<th>TBS</th>
<th>conditions</th>
<th>Bn</th>
<th>PSB</th>
<th>TBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH 1, H₂O</td>
<td>L</td>
<td>L</td>
<td>H</td>
<td>Zn/AcOH</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>AlCl₃, rt</td>
<td>H</td>
<td>H</td>
<td>M</td>
</tr>
<tr>
<td>NaOMe</td>
<td>L</td>
<td>R</td>
<td>L</td>
<td>Na/NH₃</td>
<td>H</td>
<td>H</td>
<td>L</td>
<td>Br₂</td>
<td>M</td>
<td>M</td>
<td>L</td>
</tr>
<tr>
<td>R₃N</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>LiAlH₄</td>
<td>L</td>
<td>R</td>
<td>L</td>
<td>H₂O₂, pH 10</td>
<td>L</td>
<td>R</td>
<td>L</td>
</tr>
<tr>
<td>RLi</td>
<td>L</td>
<td>R</td>
<td>L</td>
<td>DIBAL-H</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>Quinone</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>RMgX</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>NaBH₄</td>
<td>L</td>
<td>R</td>
<td>L</td>
<td>150 °C</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>H₂/Pd</td>
<td>H</td>
<td>H</td>
<td>Hᵇ</td>
<td>Zn(BH₄)₂</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>N₂CHCO₂R,</td>
<td>L</td>
<td>R</td>
<td>L</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cu</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key: L: low reactivity; protecting group is stable under the reaction conditions. M: marginal reactivity; depends on exact reaction parameters. H: protecting group is removed. R: protecting group reacts, but the original functionality is not necessarily restored. Letters in italics are based on direct experimental evidence. Letters not in italics are based on circumstantial evidence. In reference 12, TBS ethers are estimated to be highly reactive towards H₂/Pd. We transcribed this estimation to remain true to the source but consider TBS ethers to be stable to these conditions. These conditions, along with potassium fluoride, are recommended for converting PSB ethers into PHB ethers for ensuing cleavage.

8. Conclusion

In conclusion, we have provided full details of the development of the para-siletanylbenzyl (PSB) ether as a new protecting group for alcohols. PSB ethers are conveniently prepared using the “mix-and-heat” protocol that the Dudley Lab reported previously for the synthesis of benzyl and para-halobenzyl ethers. PSB ethers are electronically similar to benzyl ethers, but cleavage occurs under conditions that are unique among benzyl ether derivatives. The methodology described herein broadens the utility of arylmethyl ethers as protecting groups for alcohols.

9. Experimental Part

¹H NMR and ¹³C NMR spectra were recorded on a 300 MHz spectrometer using CDCl₃ as the deuterated solvent. The chemical shifts (δ) are written in parts per million (ppm) relative to the residual CHCl₃ peak (7.26 ppm for ¹H NMR and 77.0 ppm for ¹³C NMR). The coupling constants (J) were reported in Hertz (Hz). IR spectra were recorded on FTIR spectrometer on NaCl discs. Mass spectra were acquired using electro spray ionization (ESI⁺) or chemical ionization (CI⁺). Yields refer to isolated material judged to be ≥95% pure by ¹H NMR spectroscopy following silica gel chromatography. The purifications were performed by flash
chromatography using silica gel. Magnesium oxide (MgO) was heated under vacuum (100 °C, 0.1 mmHg) overnight prior to use.

**Preparation of 2-(para-bromobenzyloxy)pyridine (34)**

A solution of 2-chloropyridine (28) (3 mL, 30 mmol), para-bromobenzyl alcohol (32) (5.0 g, 27 mmol), KOH (4.5 g, 80 mmol), and 100 mL of toluene was refluxed for 2-3 h with azeotropic removal of water (Dean-Stark trap) until all alcohol was consumed. After cooling the reaction mixture, the reaction mixture was quenched with 30 mL of water and extracted with 200 mL of ethyl acetate. The organic layer was washed with 50 mL of brine solution and dried over MgSO₄. Excess 2-chloropyridine was removed from the residue by bulb-to-bulb distillation (0.1 mmHg, 40 °C bath temperature) to leave 34 as a crude oil. Bulb-to-bulb distillation (0.1 mmHg, 150 °C bath temperature) provided 6.8 g (97%) of 34 as a white solid; mp=33 °C.33

**Preparation of 2-para-iodobenzyloxy pyridine (31)**

A solution of 2-chloropyridine (0.7 mL, 7.7 mmol), para-iodobenzyl alcohol (33) (1.5 g, 6.4 mmol), and KOH (1.0 g, 18 mmol) was heated at reflux for 2-3 h, with azeotropic removal of water (Dean-Stark trap) until all the starting alcohol was consumed. After cooling the reaction mixture, the reaction was quenched with 10 mL water and extracted with 50 mL of ethyl acetate. The organic layer was washed with 10 mL of brine solution, and dried over MgSO₄. Excess 2-chloropyridine was removed from the residue by bulb-to-bulb distillation (0.1 mmHg, 40 °C bath temperature) to leave 35 as a crude oil. Bulb-to-bulb distillation (0.1 mmHg, 180 °C bath temperature) then provided 1.8 g (92%) of 35 as a white solid; mp=35 °C.33

**Preparation of 2-para-siletanylbenzyloxy pyridine (31)**

A stirred solution of bis[2-(N,N-dimethylamino)ethyl] ether (2.7 mL, 14 mmol) in 15 mL of THF under nitrogen was cooled at 0 °C, and i-PrMgCl (1.0 M, 14 mL, 14 mmol) was added dropwise. After 30 min, iodide 35 (1.22 g, 3.93 mmol) in 5 mL of THF was added over 1.5 h at 0 °C. The solution was allowed to warm to rt over 1 h. After decreasing the temperature back to 0 °C, 1-chloro-1-methylsilacylclobutane (2) (1.7 mL, 14 mmol) was added, and the reaction mixture was warmed to room temperature and stirred for an additional 4 h. The reaction mixture was then diluted with 20 mL of diethyl ether, extracted with 5 mL of H₂O and washed with
brine. The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. 2-Benzylloxypyridine, a by-product of this reaction, is removed by bulb-to-bulb distillation at reduced pressure (0.1 mmHg, bath temp 100 °C), and the residual oil is further purified using silica gel chromatography (elution with 10% EtOAc in hexane) to give 760 mg (72%) of 31, white solid: mp=30 °C. ¹H NMR (300 MHz), δ 0.55 (s, 3H); 1.11-1.34 (m, 4H), 2.18 (m, 2H), 5.39 (s, 2H), 6.81 (d, 1H, J = 8.4 Hz), 6.88 (m, 2H), 7.49 (apparent d, 2H, J = 7.9 Hz), 7.65 (apparent d, 2H J = 7.9 Hz), δ 8.18 (d-d, 1H, J = 5.0, 1.3 Hz). ¹³C NMR (75 MHz) δ -1.71, 14.3, 18.2, 67.3, 111.2, 116.8, 127.3, 133.6, 138.0, 138.5, 138.6, 146.7, 163. HRMS (ESI⁺): calcd for C₁₆H₂₀NOSi 270.1314, found 270.1317.

**Preparation of 2-para-siletanylbenzyloxy pyridine (31) using Magnesium metal**

Magnesium turnings (2.0 g, 83.3 mmol) and aryl bromide 34 (525 mg, 1.98 mmol) were suspended in THF (32 mL) in a 250 mL, 3-neck round-bottomed flask equipped with a reflux condenser and a water bath in place to regulate the temperature (20-25 °C). Dibromoethane (0.5 mL, 5.8 mmol) was injected rapidly by syringe. Gaseous bubbles began to emanate from the surface of the magnesium metal, the physical appearance of which changed from shiny turnings to small, dull pieces. After 30 mins, the formation of the Grignard reagent 55 was complete. The resulting green suspension was slowly cooled to 0 °C and chlorosiletane 2 (170 μL, 1.38 mmol) was added. The solution was warmed up to room temperature and stirred for 4 h. Isolation and purification as above provided arylsiletane 31 (204 mg, 0.75 mmol) in 55% yield.

**2-para-siletanylbenzyloxy-1-methylpyridinium triflate (24)**

Pyridyl ether 31 (320 mg, 1.18 mmol) was dissolved in 2 mL of dry trifluorotoluene and treated with methyl triflate (138 μL, 1.21 mmol) at 0 °C. After warming to r.t. for 30 mins, the volatiles were removed under reduced pressure, which yielded 24 as an oily residue, which was redissolved in trifluorotoluene and left standing in the freezer at -20 °C provided 24 as a crystalline solid (488 mg) in 95% yield, (mp=65 °C). ¹H NMR (300 MHz), δ 0.55 (s, 3H), 1.13-1.33 (m, 4H), 2.19 (m, 2H), 4.08 (s, 3H), 5.56 (s, 2H), 7.41 (apparent t, 1H, J = 7.28 Hz), 7.51 (apparent d, 2H, J = 7.8 Hz), 7.67 (apparent t, 3H, J = 10.6 Hz), 8.33 (apparent td, 1H J = 8.1, 1.5 Hz), 8.5 (apparent dd, 1H, J = 1.2, 6.3 Hz). ¹³C NMR (75 MHz) δ -1.7, 14.2, 18.2, 42.1, 74.6,
112.1, 119.1, 127.9, 133.4, 134.2, 140.8, 143.9, 148.0, 159.7. HRMS (ESI\(^+\)): calcd for C\(_{17}\)H\(_{22}\)NOSi 284.1470, found 284.1468.

**Standard procedure for the formation of PSB ether using PSB-OP (31)**

An ice-cold mixture of PSB-OP (31) (2.0 equiv, 0.6 mmol), dry PhCF\(_3\) (2 mL), MgO (2.0 equiv, 0.6 mmol), and alcohol 8 (1 equiv, 0.3 mmol) was treated dropwise with methyl triflate (2.0 equiv, 0.6 mmol). After 30 min, the reaction mixture was warmed to room temperature and was stirred at 80-85 °C for 12 h until TLC analysis showed consumption of alcohol 8. The reaction mixture was cooled to room temperature and filtered through Celite. The filtrate was concentrated under vacuum and purified on silica gel (elution solvent 10% EtOAc/Hexane) to yield PSB ether 13 in 90% yield (see Table 3), admixed with varying amounts of (PSB)\(_2\)O (41).

1-Methyl-1-[4-(3-phenyl-propoxymethyl)-phenyl]-siletane (13)

![OPSB](image)

IR \(\nu_{max} cm^{-1}\) 2927, 2856, 1602, 1496, 1453 cm\(^{-1}\). \(^1\)H NMR (400 MHz) \(\delta\) 0.55 (s, 3H), 1.14-1.22 (m, 2H), 1.26-1.34 (m, 2H), 1.91-1.98 (m, 2H), 2.15-2.23 (m, 2H), 2.72 (apparent t, 2H, \(J = 8.0\) Hz), 3.50 (t, 2H, \(J = 7.3\) Hz), 4.52 (s, 2H), 7.16-7.19 (m, 2H), 7.25-7.29 (m, 3H), 7.40 (apparent d, 2H, \(J = 6.0\) Hz), 7.62 (apparent d, 2H, \(J = 6.0\) Hz). \(^1\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 1.5, 14.6, 18.5, 31.6, 32.6, 69.8, 73.1, 125.8, 127.4, 128.5, 128.6, 133.8, 138.0, 140.1, 142.2. HRMS: Calcd for C\(_{20}\)H\(_{24}\)OSi 310.1753, found: 310.1768.

1-Methyl-1-[4-(1-phenyl-thoxymethyl)-phenyl]-siletane 14

![OPSB](image)

IR \(\nu_{max} cm^{-1}\) 2971, 2928, 2864, 1451. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 0.56 (s, 3H), 1.14-1.31 (m, 4H), 1.48 (d, 3H, \(J = 6.6\) Hz), 4.52 (q, 1H, \(J = 6.4\) Hz), 4.48 (d, 1 H, \(J = 12.0\) Hz), 4.32 (d, 1H, \(J = 12.0\) Hz), 7.30-7.42 (m, 7H), 7.62 (apparent d, 2H, \(J = 7.8\) Hz). \(^1\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 1.5, 14.5, 18.5, 24.4, 70.4, 126.6, 127.4, 127.7, 127.9, 128.7, 133.8, 138.0, 140.2, 143.9. HRMS (ESI\(^+\)): calcd for C\(_{19}\)H\(_{26}\)OSi 296.1596, found 296.1601.
1-[4-(1S,2R,5R)-2-Isopropyl-5-methyl-cyclohexyloxyethyl]-phenyl]-1-methyl-siletane (15)

![Structure of 15](image)

IR $\nu_{\text{max}}$ cm$^{-1}$ 2954, 2922, 2867, 1455. $^1$H NMR (300 MHz), $\delta$: 0.55 (s, 3H), 0.73 (d, 3H, $J = 6.9$ Hz), 0.81-1.05 (m, 8H), 1.11-1.44 (m, 5H), 1.61-1.69 (m, 2H), 2.13-2.22 (m, 4H), 2.32 (m, 1H), 3.19 (dt, 2H, $J = 3.9, 10.5$ Hz), 4.41 (d, 1H, $J = 11.7$ Hz), 4.68 (d, 1H, $J = 11.7$ Hz), 7.39 (apparent d, 2H, $J = 7.8$ Hz), 7.61 (apparent d, 2H, $J = 7.8$ Hz). $^{13}$C NMR (75 MHz) $\delta$: 1.7, 14.4, 16.1, 18.2, 21.0, 22.4, 23.2, 25.5, 31.6, 36.1, 40.3, 48.3, 78.9, 127.2, 133.5, 137.5, 140.4. HRMS: Calcd. For C$_{21}$H$_{34}$OSi 330.2379, found 330.2377.

(R)-methyl-2-methyl-3-(4-(1-methylsiletan-1-yl)benzyloxy)propanoate (38)

![Structure of 38](image)

IR $\nu_{\text{max}}$ cm$^{-1}$ 1740. $^1$H NMR (300 MHz), $\delta$: 0.55 (s, 3H), 1.11-1.37 (m, 6H), 2.18 (m, 2H), 2.74-2.85 (m, 1H), 3.7 (s, 3H), 3.51 (d, 1H, $J = 5.8$ Hz), 3.48 (d, 1H, $J = 5.9$ Hz), 4.54 (s, 2H), 7.34 (apparent d, 2H, $J = 7.6$ Hz), 7.61 (apparent d, 2H, $J = 7.9$ Hz). $^{13}$C NMR (75 MHz) $\delta$: -1.7, 14.4, 14.0, 14.4, 1.2, 40.2, 51.7, 72.1, 73.0, 127.0, 133.6, 138.0, 139.5, 175.2. HRMS (ESI$^+$) calcd for C$_{16}$H$_{24}$NaO$_3$Si 315.1392, found 315.1391.

Synthesis of PSB ether (40) using PSB-OPT (24)

A mixture of PSB-OPT (24) (170 mg, 0.39 mmol), dry PhCF$_3$ (2 mL), MgO (16 mg, 0.387 mmol, vacuum dried), and alcohol 39 (61 mg, 0.13 mmol) was heated at 80-85 °C for 12 h. The reaction mixture was cooled to room temperature and filtered through Celite. The filtrate was concentrated under vacuum and purified on silica gel to yield 77 mg (92%) of PSB ether 40 as colorless oil; $[\alpha]^{22}_D = +22$ (c = 1M in CHCl$_3$). IR $\nu_{\text{max}}$cm$^{-1}$ 867.9, 1071.9, 1453.6, 1643.9, 2923.1, 3426.1. $^1$H NMR (300 MHz), $\delta$: 0.53 (s, 3H), 1.33-1.09 (m, 2H), 2.18 (m, 2H), 3.39 (s, 3H), 3.8-
3.54 (m, 6H), 3.99 (apparent t, 1H, J = 9.3 Hz), 4.5-4.44 (m, 2H), 4.84-4.62 (m, 7H), 5.01-4.97 (apparent d, 1H, J = 10.9 Hz), 7.14-7.11 (m, 2H), 7.38-7.25 (m, 10H), 7.59-7.57 (apparent d, 2H, J = 7.8 Hz). $^{13}$C NMR (75 MHz) δ -1.8, 14.37, 18.19, 55.14, 68.62, 70.12, 73.35, 74.96, 75.68, 77.73, 79.93, 82.13, 98.22, 127.35, 127.50, 127.59, 127.76, 127.84, 127.89, 128.08, 128.29, 128.32, 128.40, 133.55, 137.99, 138.20, 138.32, 138.86, 139.22, 177.02. HRMS (ESI$^+$); calcd for C$_{39}$H$_{46}$NaO$_6$Si 661.2961, found 661.2959.

**bis(2-para-Siletanylbenzyl) ether (41)**

![Structure of bis(2-para-Siletanylbenzyl) ether (41)](image)

$^1$H NMR (300 MHz), δ 0.55 (s, 6H), 1.12-1.34 (m, 8H), 2.19 (m, 4H), 4.58 (s, 4H), 7.41 (apparent d, 4H, J = 7.9 Hz), 7.63 (apparent d, 4H, J = 8.0 Hz). $^{13}$C NMR (75 MHz) δ -1.7, 14.3, 18.2, 72.0, 127.18, 133.6, 137.2, 139.5. HRMS (EI$^+$); calcd for C$_{22}$H$_{30}$O$_2$Si$_2$ 366.1835, found 366.1835.

**4-(1-methylsiletan-1-yl)benzyl-2-acetoxybenzoate (43)**

A mixture of PSB-OPT (24) (158 mg, 0.36 mmol, 2.1 equiv), 0.5 mL of dry PhCF$_3$, dry NEt$_3$ (0.05 mL, 0.4 mmol, 2.0 equiv), and carboxylic acid 42 (32 mg, 0.17 mmol) was heated at 83 °C for 12 h. The reaction mixture was cooled to room temperature, diluted with 5 mL of H$_2$O, and extracted with EtOAc (2 x 10 mL). The combined organic phase was washed with H$_2$O (10 mL) and brine (10 mL), dried over MgSO$_4$, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (elution with 2:3 EtOAc/hexane) to give 51 mg (93%) of PSB ester 43 as a colorless oil. IR $\nu_{max}$cm$^{-1}$ 1723, 1769. $^1$H NMR (300 MHz) δ 0.57 (s, 3H), 1.27 (m, 4H), 2.20 (m, 5H), 5.32 (s, 2H), 7.10 (d, 1H, J = 8.9 Hz), 7.31 (m, 1H), 7.46 (d, 2H, J = 7.8 Hz), 7.56 (m, 1H), 7.67 (d, 2H, J = 7.9 Hz), 8.07 (m, 1H). $^{13}$C NMR (75 MHz) δ -1.69, 14.30, 18.21, 20.70, 66.85, 123.21, 123.84, 125.97, 127.79, 131.77, 133.89, 136.70, 139.01, 150.71, 164.30, 162.56. HRMS (Cl$^+$); calcd for C$_{20}$H$_{23}$O$_4$Si 355.1366, found 355.1370.
Deprotection of compound 38

In a round bottom flask, compound 38 (105 mg, 0.359 mmol), K$_2$CO$_3$ (124 mg, 0.89 mmol), KF.2H$_2$O (85 mg, 0.9 mmol), and 3 mL of THF/MeOH (1:1) were mixed. At 0 °C, H$_2$O$_2$ (30% in H$_2$O, 30 equiv) was added dropwise. After 0.5 h, the reaction mixture was stirred at 50 °C for 3 h. The reaction mixture was extracted with CH$_2$Cl$_2$. The combined organic layers were concentrated under reduced pressure to afford a crude oil.

5 mL of CH$_2$Cl$_2$ and 0.15 mL of H$_2$O were added to the residue. At 0 °C, DDQ (122 mg, 0.538 mmol) was added. After 2 h from 0 °C to room temperature, the solution went from green color to orange color. The reaction was quenched with 2 mL of H$_2$O and extracted with CH$_2$Cl$_2$ (3 x 20 mL) followed by evaporation of CH$_2$Cl$_2$ under reduced pressure. Purification of the residue using bulb-to-bulb distillation at 40 °C (0.5 mmHg) provided 35 mg (83 %) of alcohol 37.

Deprotection of compound 40

In a round bottom flask, compound 40 (77 mg, 0.12 mmol), K$_2$CO$_3$ (52 mg, 0.37 mmol), KF.2H$_2$O (37 mg, 0.39 mmol), and 1.2 mL of THF/MeOH (1:1) were mixed. At 0 °C, H$_2$O$_2$ (30% in H$_2$O, 30 equiv) was added dropwise. After 0.5 h, the reaction mixture was stirred at 50 °C for 3 h. The reaction mixture was extracted with CH$_2$Cl$_2$. The combined organic layers were concentrated under reduced pressure to afford a crude oil.

The residue was dissolved in 0.5 mL of CH$_2$Cl$_2$, which was added dropwise to the solution of FeCl$_3$ (30 mg, 0.18 mmol) in 1 mL of CH$_2$Cl$_2$. After one hour, the reaction was quenched with H$_2$O and extracted with CH$_2$Cl$_2$ (3 x 20 mL). The organic layer was dried (MgSO$_4$) and concentrated under reduced pressure. Purification by silica gel column chromatography furnished 40 mg (72%) of alcohol 39.

Competition experiments:

Cleavage of the PMB 44a in presence of the PSB ether 13

A solution of DDQ (27 mg, 0.12 mmol) in CH$_2$Cl$_2$ (1 mL) was added dropwise at 0 °C over 5 min to a solution of 13 (31 mg, 0.10 mmol) and 44a (29 mg, 0.1 mmol) in 1.1 mL of CH$_2$Cl$_2$ and H$_2$O (9:1). After stirring for 30 min at room temperature, the reaction mixture was poured into a mixture of CH$_2$Cl$_2$ and water (3/1, 20 mL). The organic layer was separated and the aqueous
layer was extracted with CH$_2$Cl$_2$ (2 x 10 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated under reduced pressure to afford an orange residue. Purification by column chromatography (SiO$_2$, EtOAc/Hexanes: 20/80) afforded recovered 13 (29 mg, 96%) and the alcohol 45 (30 mg, 96%), respectively.

**Cleavage of the PSB ether 13 in presence of the PMB ether 44a**

**1-Oxidation of PSB ether**

KF⋅2H$_2$O (120 mg, 1.28 mmol) and K$_2$CO$_3$ (176 mg, 1.28 mmol) were added to a solution of 13 (160 mg, 0.51 mmol) and 44a (146 mg, 0.51 mmol) in a mixture of THF/CH$_3$OH (1:1, 8 mL) at 0 °C. H$_2$O$_2$ (610 mg of a 30% aqueous solution) was then added slowly. After heating at 50 °C for 1.5 h, the reaction was subjected to standard work up. Purification by column chromatography (SiO$_2$, gradient 10-20% EtOAc in hexanes) afforded 20 (101 mg, 82%) and recovered 44a (140 mg, 96%).

**2-Cleavage of PHB ether 20**

PMB ether 44a (33 mg, 0.12 mmol) was mixed with PHB ether 20 (37 mg, 0.15 mmol) in 2.2 mL of a mixture of H$_2$O and CH$_2$Cl$_2$ (1:10). At 0 °C, DDQ (35 mg, 0.152 mmol) was added to the solution, which was warmed up to room temperature for 1 h. The reaction was quenched with H$_2$O and extracted with CH$_2$Cl$_2$ (2 x 10 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated under reduced pressure to afford an orange residue. Purification by column chromatography (SiO$_2$, 10% EtOAc in hexanes) afforded recovered 44a (28 mg, 85%) and 8 (17 mg, 82%).

**Conversion of PHB-menthol 46 into PMB-menthol 46**

PHB-menthol 22 (39 mg, 0.14 mmol) was dissolved in 0.3 mL of methanol. At 0 °C, TMSCHN$_2$ (2.0 M, 0.34 mL, 0.68 mmol) was added to the solution, which was warmed up to room temperature and stirred for 24 h. Solvent evaporation afforded a residue which was purified by column chromatography on silica gel (elution with 5% EtOAc in Hexane) to give 38 mg (93%) of PMB-menthol 46.
Cleavage of the TBS ether (44c) in presence of the PSB ether (13)

PSB ether 13 (95 mg, 0.33 mmol) was mixed with TBS ether 44c (140 mg, 0.49 mmol) in 20 mL of AcOH, THF, and H₂O (3:1:1). The reaction mixture was stirred for 4 h, then quenched with saturated NaHCO₃ solution and extracted with Et₂O (3 x 15 mL). The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure to afford a crude oil. Purification by column chromatography (SiO₂, 2-40% of EtOAc in Hexane) afforded recovered 13 (86 mg, 90%), and 45 (82 mg, 98%).

Oxidation of the PSB ether (13) in presence of the TBS ether (44c)

PSB ether 13 (76 mg, 0.24 mmol), TBS ether 44c (86 mg, 0.30 mmol), KF.2H₂O (70 mg, 0.74 mmol), K₂CO₃ (83 mg, 0.60 mmol), and THF/CH₃OH (1:1, 2.6 mL) were mixed. At 0 °C, H₂O₂ (2.0 g, 30% aqueous solution) was added slowly. The solution was warmed up to room temperature followed by stirring for 12 h. The reaction mixture was extracted with CH₂Cl₂ (3 x 15 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure to afford a crude oil. Purification by column chromatography (SiO₂, gradient 2-40% EtOAc in hexanes) afforded 20 (42 mg, 72%) and recovered 44c (76 mg, 88%).

Cleavage of the MOM ether (44b) in presence of the PSB ether (13)

MOM ether 44b (64 mg, 0.3 mmol) and PSB ether 13 (66 mg, 0.21 mmol) were mixed with 2 mL of THF and HCl (3 mL, 6 M). The mixture was stirred for 4h, then quenched with NaHCO₃ at 0 °C. The solution was extracted with Et₂O (3 x 15 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure and afford a crude oil. Purification by column chromatography (SiO₂, gradient 2-40% EtOAc in Hexane) afforded 13 (56 mg, 85%) and recovered 45 (86 mg, 86%).

Oxidation of the PSB ether 13 in presence of the MOM ether 44b

KF.2H₂O (84 mg, 0.89 mmol), K₂CO₃ (43 mg, 0.31 mmol), MOM ether 44b (56 mg, 0.26 mmol), and PSB ether 13 (44 mg, 0.14 mmol) were mixed in 2.6 mL of THF/CH₃OH (1:1) at 0 °C. H₂O₂ (30% in H₂O, 30 equiv) was added slowly. After 0.5 h, the reaction mixture was stirred at 50 °C for 1.5-2 h. The reaction mixture was extracted with CH₂Cl₂ (3 x 15 mL). After the aqueous layer was removed, the organic phase was sequentially washed with 1.0 M aqueous
Na$_2$S$_2$O$_3$ (6 mL) and brine (6 mL). The organic phase was dried over MgSO$_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO$_2$, gradient 10-20% EtOAc in hexanes) afforded 20 (29 mg, 85%) and recovered 44b (51 mg, 90%).

**Cleavage of the Troc carbonate (44d) in presence of the PSB ether (13)**

PSB ether 13 (48 mg, 0.15 mmol), Troc carbonate 44d (70 mg, 0.20 mmol), and Zn metal (500 mg, 7.6 mmol) were mixed in 1 mL of CH$_3$COOH. The mixture was stirred for 8 h, then quenched with NaHCO$_3$ and extracted with Et$_2$O (3 x 15 mL). The organic layers were dried over MgSO$_4$, filtered, and concentrated under reduced pressure to afford a crude oil. Purification by column chromatography (SiO$_2$, 2% EtOAc in Hexane, then 40% EtOAc in Hexane) afforded 45 (30 mg, 90%) and recovered 13 (44 mg, 92%).

**1-methoxy-4-(3-(methoxymethyl)propyl)benzene (44b)**

We mixed NaH (200 mg, 60% silicon oil), 4 mL of THF, and alcohol 45 (191 mg, 1.4 mmol). After 0.5 h stirring, we added MOMCl (0.4 mL, 5.26 mmol), followed by stirring for 12 h. The reaction mixture was quenched with H$_2$O and extracted with Et$_2$O. The organic layer was dried under magnesium sulfate and solvent was evaporated under reduced pressure. After silica gel column, we got 44b in 48% yield (144 mg, 0.68 mmol); $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 1.88 (m, 2H), $\delta$ 2.65 (t, 2H, J=7.97 Hz), $\delta$ 3.54 (t, 2H, J=6.44 Hz), $\delta$ 3.78 (s, 3H), $\delta$ 3.37 (s, 3H), $\delta$ 4.63 (s, 2H), $\delta$ 6.83 (d, 2H, J=8.59 Hz), $\delta$ 7.11 (d, 2H, J=8.52 Hz); $^{13}$C-NMR $\delta$ 31.44, 31.59, 55.08, 55.16, 67.04, 96.44, 113.74, 129.23, 133.87, 157.77; HRMS (CI$^+$) found 210.12549 (M$^+$) (calcd for C$_{12}$H$_{18}$O$_3$ 210.12560).

**3-(4-methoxyphenyl)propyl-2,2,2-trichloroethyl carbonate (44d)**

We mixed alcohol 45 (305 mg, 1.8 mmol), 2 mL of pyridine and 0.3 mL of TMEDA. At 0 °C, we added 2.7 mL of Troc-Cl dropwise, then the solution warmed to room temperature. After stirring for 5 h, we quenched the reaction with NH$_4$Cl. We did the extraction with EtOAc followed by solvent evaporation under reduced pressure and silica gel column to get 44d in 31% yield (196 mg); $^1$H-NMR (300 MHz, CDCl$_3$), $\delta$ 2.01 (m, 2H), $\delta$ 2.68 (t, 2H, J=7.72 Hz), $\delta$ 3.79 (s, 3H), $\delta$ 4.24 (t, 2H, J=6.52 Hz), $\delta$ 6.84 (d, 2H, J=8.46 Hz), $\delta$ 7.11 (d, 2H, J=8.4 Hz); $^{13}$C-NMR $\delta$ 30.22, 30.78, 55.17, 68.39, 76.66, 94.48, 113.87, 129.24, 132.65, 153.94, 157.96; HRMS (CI$^+$) found 340.00296, calcd for C$_{13}$H$_{15}$C$_{13}$O$_3$ 340.00364.
PART II†‡

STEREOCONTROL OF 5,5-SPIROKETALS IN THE SYNTHESIS OF CEPHALOSPOROLIDES H, E, AND F

CHAPTER ONE: INTRODUCTION TO 5,5-SPIROKETALS

1. Overview

Spiroketal motifs are at the core structure of many biologically active compounds. The rigid spiroketal framework offers precision orientation of pendant functional groups, which likely supports precise interactions in complex biochemical systems. However, one must be able to install the core spiroketal stereochemistry efficiently in order to take advantage of its rigid three-dimensional shape. The anomeric effect can be predictably exploited in 6,6- and 5,6-systems, but it is less reliable in 5,5-systems.

The aim of the present work is to develop a synthetic strategy that would enable the asymmetric synthesis of β-oxygenated 5,5-spiroketalts using zinc metal chelation. Oxygenated 5,5-spiroketalts range from simple families such as the cephalosporolides to complex natural products such as norhalichondrin B (Scheme 24). Cephalosporolides H, E and F are the synthetic targets for the development of a stereocontrolled isomerization at the spirocenter in 5,5-spiroketalts.†§

† This part is a reproduced, modified, and expanded version of a published articles: Tlais, S. F.; Dudley, G. B. Stereocontrol of 5,5-Spiroketalts in the Synthesis of Cephalosporolide H Epimers. Organic Letters, 2010, 12, 4689-4701 and Tlais, S. F.; Clark, R. J.; Dudley, G. B. A striking exception to the chelate model for acyclic diastereocontrol: efficient access to a versatile propargyl alcohol for chemical synthesis. Molecules 2009, 14, 5216-5222.

‡ Structure numbering restarted in part II
2. Spiroketalts

2.1. Naming of Spiroketalts

There is some inconsistency in spiroketal numbering (i.e., [4.4]-spiroketal vs. 5,5-spiroketal). This is mainly due to conflicting desires to conform partially to IUPAC guidelines versus adhere to the accepted practice of naming bicyclic systems by counting the ring sizes independently (i.e., decalin is a fused 6,6-bicyclic system). This work focuses on ketals derived from two 5-membered spiro-fused oxygen heterocycles, which herein are termed 5,5-spiroketals. Alternatively, such ring systems have been called [4.4]-spiroketal derivatives, because the IUPAC name for two (five-membered) oxolane rings fused at C2 is 1,6-dioxaspiro[4.4]nonane (Scheme 25). Our preference is to follow the common practice of identifying the ring sizes independently and separated by a comma: 5,5-spiroketal refers to spiro-fused THF rings, and 6,6-spiroketal refers to spiro-fused THP (oxane) rings.
2.2. Spiroketal Conformation

The different conformations of 6,6 and 6,5-spiroketal systems have been widely studied.\textsuperscript{63} Large substituents on cyclohexane adopt an equatorial position to minimize steric interactions, but in cyclic ketal or spiroketals, alkoxy groups adjacent to an oxygen atom prefer axial positions due to anomeric stabilization energy (Scheme 26). Conformational preferences of cyclic ketals are mainly due to the anomeric effect, but there are other factors such as steric effect, intramolecular hydrogen bonding, and metal salt or cation chelation.

![Scheme 25. Types of spiroketals](image)

2.2.1. Anomeric Effect

The anomeric effect was originally defined as the preference for an electronegative substituent at the anomeric carbon in carbohydrates to be in an axial rather than an equatorial position.\textsuperscript{64,65} The modern definition includes carbohydrates and heterocyclic rings. The explanation of this criterion was initially attributed to the preference of unshared electron dipole alignment in the \( \alpha \)-conformation (Scheme 27), or to the destabilization of the equatorial conformation as a result of dipolar interaction. After thirteen years of the dipole theory, “rabbit-ear effect” theory was
proposed to be another explanation for the energy difference in cyclic ketal conformations. In this theory the instability in β-conformation was attributed to the repulsion of unshared electron pairs on nonadjacent atoms. Later, the stability of the α-conformation was attributed to the hyperconjugation or orbital overlap between a nonbonding oxygen orbital (n) with an anti-bonding (σ*) orbital of an adjacent carbon-oxygen bond. The alignment of non-bonding (n) orbital should be antiperiplanar with respect to the carbon-oxygen bond.  

Scheme 27. Development of anomeric effect theories

The calculated anomeric stabilization energy, which was performed by the Deslongchamps Group, is the range of 1.4-2.4 kcal.mol\(^1\) for each axial OR acetal in an unsubstituted 6,6-spiroketal.  

\(^{57}\) The stabilization energy can be doubled in the case of a double anomeric isomer (Scheme 28).
Scheme 28. Anomeric effect in the 6,6-spiroketal

2.2.2. Steric Effect

Steric interaction is one of the factors that can counteract anomeric stabilization energy. If the anomeric isomer produces a serious 1,3-diaxial interaction, then the non-anomeric isomer will be favored. Crimmins et al. showed the effect of sterics in the synthesis of spongistatin. Scheme 29 shows that the single anomeric isomer was more favored than the double anomeric isomer due to steric interactions.\(^\text{57}\)

Scheme 29. Steric effect in Crimmins’s synthesis of spongistatin

2.2.3. Hydrogen Bonding and Chelation Effect

Hydrogen bonding and chelation effect are other factors that can shift the equilibrium towards the non-anomeric isomer (Scheme 30). Chelation using Lewis acids such as zinc salts or cations such as Ca\(^{2+}\) ion may exert a more significant effect than hydrogen bonding. These chelation effects were tested in the synthesis of spongistatin, which has an interesting antitumor activity against human cancer cells, in three different laboratories.\(^\text{57}\) In Paterson’s and Evans’ synthesis, hydrogen bonding and metal chelation were used to shift the equilibrium towards the less
thermodynamically stable single anomeric isomer, but in Smith’s synthesis cation chelation was used to shift the equilibrium towards single anomeric S-configuration rather than single anomeric R-configuration.

Scheme 30. Chelation effect in spongistatin syntheses
3. Controlling the Stereochemistry of 5,5-Spiroketal Spirocenter in Different Syntheses

As mentioned earlier, the anomeric effect can be used to predict the more stable isomer of the unsubstituted 6,6 or 6,5-spiroketal under thermodynamic conditions, but it is less reliable for 5,5-spiroketal.\textsuperscript{66} The ease of prediction in 6,6 or 5,6-spiroketalts is mainly due to the rigidity of the chair conformation which helps in differentiating between the anomeric and non-anomeric conformation.\textsuperscript{67,68} Rapid pseudorotation, deformation, and puckering can be exhibited by five-membered rings.\textsuperscript{69} Moreover, the orbital overlap (n→σ\textsuperscript{*}), requires 180° antiperiplanar arrangement, which is less accessible in the bis-pseudoaxial conformation of 5,5-spiroketal than in bis-axial of 6,6-spiroketal.\textsuperscript{70} In summary, it can be concluded from all the above theoretical discussion that it is difficult to control the stereochemistry of the 5,5-spiroketal spirocenter.

This theoretical discussion is consistent with the literature experimental results.\textsuperscript{58,71,72} 5,5-Spiroketal have been synthesized as equimolar or nearly equimolar ratios of epimers at the spirocenter. The equilibrium sometimes shifts towards the isomer which has the alkyl group(s) at C-2 or C-7 anti to the spiro-oxygen (Scheme 31), as the Taber Group noted during their study of stability of ritterazine isomers.\textsuperscript{73} Although no general method has emerged, there are some limited successful approaches in controlling the spirocenter isomerization in different syntheses, some of which are featured in the following paragraphs.
Scheme 31. Syntheses of 5,5-spiroketalts with different ratios


The Solladié Group designed a method for controlling the stereochemistry in (2R,5S,7R)-2,7-dimethyl-1,6-dioxaspiro[4,4]nonane synthesis (Scheme 32). This method was based on chelation between sulfoxide and the spiro-oxygen using ZnBr₂. Spiroketalization under protic acidic conditions gave both isomers in a 1 : 1 ratio, but spiroketalization with ZnBr₂ led to the formation of the desired isomer in 95% de. Solladié attributed this selectivity to the chelation between sulfoxide and the nearest oxygen in the same tetrahydrofuran ring. Reduction of sulfoxide afforded (2R,5S,7R)-2,7-dimethyl-1,6-dioxaspiro[4,4]nonane.
Scheme 32. Zinc chelation between sulfoxide and spiro-oxygen

3.2. 5,5-Spiroketal in the Synthesis of Ritterazines and Cephalostatin 1

The Shair Group showed limited stereochemistry control of the 5,5-spiroketal during the synthesis of ritterazine F and G. They were able to prepare thermodynamic ritterazine G under thermodynamic conditions (MgSO₄ and heat), but they were less successful in preparing the contra-thermodynamic ritterazine H selectively (Scheme 33). The Shair Group was able to synthesize contra-thermodynamic cephalostatin 1, which belongs to the same family of ritterazine by using kinetic conditions through ring opening of cyclopropane and subsequent formation of 5,5-spiroketal (Scheme 33).⁷⁴,⁷⁵
3.3. 5,5-Spiroketal in the Synthesis of Norhalichondrin B

The Phillips Group controlled the 5,5-spiroketal stereochemistry in norhalichondrin B through thermodynamic conditions. β-Hydroxy 5,5-spiroketal was formed through a cascade cyclization which led to the formation of 6,6 and 5,5-spiroketals upon protective groups removal (Scheme 34).
3.4. 5,5-Spiroketals in the Synthesis of Hippuristanol

Recently, the Deslongchamps Group synthesized a contra-thermodynamic isomer hippuristanol (22-epi-hippuristanol) via Hg(II)-catalyzed spiroketalization in high yield. Treatment of 22-epi-hippuristanol with PPTS in CHCl₃, afforded both isomers in a 1 : 1.4 ratio favoring hippuristanol, which was unstable at room temperature. The difficulty of controlling the spirocenter stereochemistry was consistent with the contra-thermodynamic systems (Scheme 35).

![Scheme 35. 5,5-Spiroketal in hippuristanol synthesis](image)

4. Natural Products with β-Oxygenated 5,5-Spiroketal

Natural 5,5-spiroketals can be extremely challenging targets for stereoselective synthesis. In certain cases, such as norhalichondrin B (Scheme 36), the natural epimer is preferred, but such substrate biases are not always clear at the outset. The related cephalostatin 1 and ritterazines, for example, feature contra-thermodynamic 5,5-spiroketals, addressed in thoughtful studies by Shair, Taber, and Fuchs. In many cases, however, both 5,5-spiroketals epimers are encountered within the same natural product family (symbiospirols, ascospiroketals, and cephalosporolides). Cephalosporolides H, E and F are our targets, which will be used to stimulate a methodology for controlling the stereochemistry in 5,5-spiroketals.
Scheme 36. Natural products with β-oxygenated 5,5-spiroketal

4.1. Cephalosporolide E (2a) and Cephalosporolide F (2b)

Cephalosporolides E (2a) and F (2b) (Scheme 37) were isolated and characterized in 1985 by Ackland Group.\(^{62}\) Both compounds were extracted from commercial fermentation of fungus *Cephalosporium aplidicola*. Cephalosporolides E and F were characterized based on IR, NMR spectroscopy, and X-ray crystal analysis of E isomer.

Scheme 37. Structures of cephalosporolides E and F
Cephalosporolides B (3), C (4), D (5), and thiobiscephalosporolide (6) were also isolated from the same fungus, *Cephalosporium aplidicola* (Scheme 38). The Ackland Group proposed that cephalosporolides E and F could be derived from a ten-membered ring macrolactone cephalosporolide C (4) in two possible pathways. The first one, an intramolecular transesterification, leads to bassianolone (7), which can afford cephalosporolides E and F through spiroketalization. The Ackland Group tried unsuccessfully to mimic this route by converting cephalosporolide C into cephalosporolides E and F. The second pathway could start by hydrolysis of the macrolactone followed by tetrahydrofuran and lactone formation and end with spiroketalization. In 2004, other three 10-membered macrolides, which are similar in structure to cephalosporolide D (5) and cephalosporolides C (4), E (2a), and F (2b), were isolated from a different fungal source; entomopathogenic fungus§ *Cordyceps militaris*. In 2005, (+)-bassianolone (7), which was proposed as an intermediate in the biosynthesis of cephalosporolides E and F, was isolated from the fungus *Beauveria bassiana*. Upon treatment of bassianolone (7) with SiO₂, a thermodynamic mixture of cephalosporolides E and F was obtained. This study led to the first confirmation of the absolute configuration of cephalosporolides E and F.

§ A fungus that can act as a parasite of insects
4.1.1. Previous Syntheses of Cephalosporolides E and F

The first synthesis of cephalosporolides E and F was accomplished by the Ramana Group in 2009. Through their synthesis, they were able to confirm the absolute stereochemistry of both isomers. In fact, both isomers were synthesized simultaneously, followed by separation of both spiroketal isomers 13 and 14. The ratio of both isomers 13 and 14 was 1 : 1. Acetonide deprotection, lactol oxidation and dehydroxylation afforded cephalosporolides E and F enantiomers (Scheme 39). Although this route provides access to both cephalosporolides E and F, the lack of stereocontrol is a limitation.
In the same year, another synthesis was also reported by the Fernandes Group (Scheme 40). The main purpose was to synthesize bassianolone (7), but instead they observed formation of cephalosporolides E and F as a mixture, which was separated in the last step of the synthesis.
4.2. Cephalosporolides H and I and Penisporolides A and B

Cephalosporolides H (1) and I (1a)\textsuperscript{61} and penisporolides A (18) and B (19)\textsuperscript{84} were both isolated at the same time from derived fungus *Penicillium sp* (Scheme 41). These four spiroketals have the same core with a different tail at C-9. There is no reported biological activity for penisporolide A and B, whereas cephalosporolides H and I were found to inhibit of xanthine oxidase and 3α-hydroxysteroid dehydrogenase at <290 µM concentration. Xanthine oxidase catalyzes the reduction of oxygen into superoxide anion,\textsuperscript{85} which can lead to damage in the heart, brain, kidney, and liver.\textsuperscript{86} Inhibition of xanthine oxidase enzyme can help in reducing the risk of stroke or heart attack. 3α-Hydroxysteroid dehydrogenase plays an important role in the metabolism of steroid hormones providing protection against the flow of excess steroid hormones. It was also shown that non-steroidal and steroidal *anti*-inflammatory drugs inhibit 3α-hydroxysteroid dehydrogenase. Therefore, the compounds that inhibit 3α-hydroxysteroid dehydrogenase presumably are potential *anti*-inflammatory drugs.\textsuperscript{87}

**Scheme 41.** Reported structures of cephalosporolides H and I and penisporolides A and B
CHAPTER TWO: CHELATION-CONTROL OF OXYGENATED 5,5-SPIROKETALS

1. Overview

This chapter provides a new synthetic approach for controlling the stereochemistry of oxygenated 5,5-spiroketals using chelation effects. We envisioned a strategy in which chelation of metal salts across the two rings could be used to control the spiroketal stereochemistry. Prescribed access to 5,5-spiroketals would greatly facilitate the synthesis of complex and contrathermodynamic 5,5-spiroketals (Scheme 36, chapter 1). Preliminary development of this strategy, with an emphasis on the synthesis of the cephalosporolides H, E, and, F is described herein (Scheme 42).

![Scheme 42. Reported structures for cephalosporolides](image)

2. Asymmetric Synthesis of $\beta$-Oxygenated 5,5-Spiroketal Using Metal Chelation

Steric effect, not the anomeric effect, typically determines the stereochemistry at the spirocenter of 5,5-spiroketals. According to our central hypothesis, the steric effect can be overcome by the chelation of a free alcohol and a spiroketal oxygen (O-6) of the adjacent ring. This chelation would determine the dominant diastereomeric core in 5,5-spiroketals (Scheme 43).

![Scheme 43. Chelation hypothesis](image)
Spiroketal I and II, which are truncated models of cephalosporolide H, were used to test the chelation hypothesis (Scheme 44). Replacing the seven-carbon alkyl chain at C-9 in cephalosporolide H with a methyl group would allow the determination of the stereochemistry of the spirocenter by tracking the chemical shift of the methyl group with $^1$H NMR.\(^8\) The synthesis of spiroketals I and II will be discussed later in the chapter.

Scheme 44. Spiroketal I and II
Table 6. Controlled epimerization of β-oxygenated 5,5-spiroketalts

<table>
<thead>
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<th>entry</th>
<th>substrate</th>
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<th>R²</th>
<th>conditions</th>
<th>Ratio (a : b) ⁹</th>
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<td>H</td>
<td>H</td>
<td>A</td>
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<tr>
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<td>I</td>
<td>H</td>
<td>H</td>
<td>B</td>
<td>- ¹</td>
</tr>
<tr>
<td>3</td>
<td>I</td>
<td>H</td>
<td>H</td>
<td>C</td>
<td>68 : 32</td>
</tr>
<tr>
<td>4</td>
<td>I</td>
<td>H</td>
<td>H</td>
<td>D</td>
<td>95 : 05</td>
</tr>
<tr>
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<td>I</td>
<td>TBS</td>
<td>H</td>
<td>D</td>
<td>09 : 91</td>
</tr>
<tr>
<td>6</td>
<td>I</td>
<td>H</td>
<td>TBDPS</td>
<td>D</td>
<td>75 : 25</td>
</tr>
<tr>
<td>7</td>
<td>I</td>
<td>TBS</td>
<td>TBDPS</td>
<td>D</td>
<td>01 : &gt;20</td>
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<td>II</td>
<td>H</td>
<td>H</td>
<td>C</td>
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<tr>
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<td>H</td>
<td>D</td>
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<td>10</td>
<td>II</td>
<td>H</td>
<td>TBDPS</td>
<td>D</td>
<td>10 : 90</td>
</tr>
</tbody>
</table>

⁹Conditions A: MgCl₂, in CH₂Cl₂, rt, 12 h. B: BF₃•OEt₂ or TiCl₄, rt, 2h. C: 1% HCl in H₂O/MeOH, rt, 2 h. Conditions D: 1.1 equiv ZnCl₂ in CH₂Cl₂, rt, 12 h. Ratios estimated by ¹H NMR spectroscopic analysis of the product mixtures. ¹ Same as starting ratio. ² Decomposition

In the course of validating the chelation hypothesis, initial experiments involved treating β-oxygenated 5,5-spiroketal I with various Lewis and protic acid (Table 6). Mild Lewis acids such as MgCl₂ did not induce epimerization of I (entry 1), and strong Lewis acids including BF₃•OEt₂ and TiCl₄ promoted decomposition (entry 2). Protic acid had similar effects, but careful treatment of I (20a : 20b) with 1% HCl in MeOH led to 68 : 32 ratio in 2 hours (entry 3).

In contrast, zinc chloride (ZnCl₂) effectively catalyzed the equilibration between isomers a (Chelated isomer) and b (Non-chelated isomer). The role of chelation clearly emerges from
experiments on spiroketal I (Table 6), since spiroketal II (24a : 24b) afforded almost the same ratios upon treatment with protic acid (1% HCl in MeOH) and ZnCl$_2$ (entry 8 and 9).

*Either spiroketal epimer (I-a or I-b) can be produced in ≥15:1 dr by enabling or blocking chelation* (entries 4 and 7). Note that isomer I-a (23a) is not observed when silyl groups are positioned to disrupt chelation effects (entry 7), indicating that the reported structure of cephalosporolide H may be contra-thermodynamic. Considering the experiments recounted in entries 6 and 10, it can be concluded that a free hydroxyl group on the spiroketal ring (R$^1$ = H) provides the dominant chelation interaction, with a side-chain alcohol providing a secondary reinforcing role. Perhaps most instructive is to compare entries 6 and 7: silylation changes the selectivity from predominantly isomer I-a (22a) to exclusively isomer I-b (23b). What emerges from this study is a strategy for preparing either isomer of the reported cephalosporolide H spiroketal core.

3. Synthesis of I and II Spiroketals en Route to the Synthesis of Cephalosporolide H

The synthesis of the spiroketal systems I and II started with (D)-pantolactone (26), which was reduced with lithium aluminum hydride, and selective protection of the resulting triol using para-methoxyphenyl (PMP) acetal 27 provided dioxane 28 as reported previously (Scheme 45). Primary alcohol 28 was then oxidized to aldehyde 29 under Swern conditions; the unpurified aldehyde was immediately dissolved in anhydrous THF and treated with a solution of propynylmagnesium bromide.

![Scheme 45. Preparation of propargyl alcohol 30a and 30b as a mixture of diastereomers from pantolactone (26)](image-url)
Addition of propynyl Grignard to chiral aldehyde 29 provided a 3:1 mixture of two alcohol diastereomers (Scheme 46), the relative stereochemistry of which needed to be assigned. The Felkin–Anh model (Scheme 46, inset in oval) provides ambiguous guidance in this case, as two groups—namely, the gem-dimethyl quaternary center and the electronegative oxygen substituent—could reasonably be designated as the “large” group. Application of the Felkin–Anh model for predicting acyclic diastereoselection in the addition to aldehyde 29 is discussed below.

**Scheme 46.** Alternative Felkin–Anh models for predicting / assigning stereochemistry

### 3.1. Unusual Felkin Selectivity

To apply the Felkin-Anh model (Scheme 46), the three substituents on the aldehyde α-carbon (H, OR, and the quaternary carbon bearing the gem-dimethyl group) must be designated as “small” (S), “medium” (M), and “large” (L). Typically this designation is made based on the relative sizes of the three substituents (sterics), although there is a stereoelectronic preference for electronegative atoms to act “large” by creating local regions of high electron density that result in negative Coulombic interactions with the incoming nucleophile. Lewis basic substituents typically assume the “medium” position when chelating metal salts are present. Whichever is the relevant substrate conformation, the nucleophile (C₃H₅⁻) attacks along the Bürgi–Dunitz trajectory, passing closest to the “small” group and opposite from the “large” group.

** The products arising from the alternative conformations are sometimes referred to as “Felkin” and “anti-Felkin” products, although the Felkin–Anh model accounts for either
The reaction path represented in Scheme 46B (chelation control, \(29b \rightarrow 30b\)) appears quite reasonable, although it proved to be the minor pathway (\textit{vide infra}). Approach of the nucleophile from the side opposite the bulky quaternary center is consistent with steric considerations, and a five-membered ring chelation of magnesium(II) salts may provide a conformational bias in favor of \(29b\). The chelation-control model (\emph{i.e.,} Scheme 46B) is generally a good predictor of diastereoselectivity in the addition of Grignard reagents to \(\alpha\)-alkoxy aldehydes and ketones.\(^9^3\)

The reaction path represented in Scheme 46A (\(29a \rightarrow 30a\)) is favored (in the absence of chelation) on stereoelectronic grounds, as approach of the nucleophile from the side opposite the oxygen substituent minimizes Coulombic interactions between regions of high electron density surrounding the oxygen atom and the electron-rich nucleophile. For the reaction to proceed along this pathway, the five-membered ring chelation of magnesium(II) salts must be disrupted, and the stereoelectronic (Coulombic) shield provided by the electron-rich oxygen substituent must outweigh steric advantages of approaching opposite the bulky quaternary center. The major diastereomer produced in the reaction of propynylmagnesium bromide with aldehyde \(29\) was shown by X-ray crystallography to be \(30a\) (Scheme 47),\(^9^4\) which is the result of Felkin addition in the absence of chelation. This unpredicted result could prove quite useful for chemical synthesis.

\begin{center}
\textbf{Scheme 47.} Ball-and-stick representation of propargyl alcohol \(30a\) from X-ray analysis.
\end{center}

possibility. In this thesis, we use the term “chelation control” to indicate products arising from the electron-rich Lewis basic substituent occupying the “medium” position in the Felkin–Anh model.
Aldehyde 29 is available by oxidation of known pantolactone derivative 28 (Scheme 45). After clean addition of propynylmagnesium bromide, crystallization of the crude product mixture from ether provides monoprotected anti-1,2-diol 30a in 40% yield as a single diastereomer (Scheme 48) as measured by $^1$H- NMR spectroscopy. Slow evaporation of a dichloromethane solution of 30a provided crystals suitable for X-ray diffraction analysis (the result of which is shown in Scheme 47).

Scheme 48. The major diastereomer (30a) is highly crystalline.

Propargyl alcohol 30a is an ideal starting point for complex molecule synthesis. Both enantiomers of pantolactone (26) are commercially available, and 30a offers multiple and orthogonal functional handles for further manipulation. Propargyl alcohol 30a is highly crystalline, which is convenient for purification, storage, and handling of large quantities of material. As an indication of the potential utility of 30a in chemical synthesis, consider related alcohols in Scheme 49 that have been converted to the complex natural products; paclitaxel (Taxol) and peloruside.90,93

Scheme 49. Chiral, functionally rich small molecule building blocks for chemical synthesis.

Several factors may be involved in overriding the general tendency for chelation-controlled addition to $\alpha$-alkoxy aldehydes in this specific case (acetylide addition to aldehyde 29). Polar
coordinating solvents like THF often erode the diastereoselectivity of chelation-controlled additions, although we observed similar diastereoselectivities when conducting this particular reaction in other solvents. Hyperconjugative interactions (n → σ*) between the acetal oxygens attenuate their Lewis basicity as compared to typical ether linkages, resulting in weaker chelation from acetals, but chelation-controlled addition to α-(alkoxyalkyl)oxy aldehydes is known.\(^{95}\) Perhaps the best explanation comes from the analysis of an alternative illustration of the potential chelate (Scheme 50), which reveals a 1,3-diaxial interaction between the metal cation (with its associated ligands, not shown) and one of the two α-methyl substituents. Such a 1,3-diaxial interaction may disfavor and disrupt chelation.

**Scheme 50.** A diaxial interaction that may disrupt chelation in aldehyde 29

In the absence of chelation control, selectivity between the competing pathways (cf. Scheme 46A and 46B) arises from the balance of steric (favoring syn-isomer 30b) and stereoelectronic (favoring anti-isomer 30a) factors. Our study focused on the acetylide nucleophile derived from propyne.\(^{††}\) The steric profile of acetylide nucleophiles is minimal, which minimizes the impact of steric shielding from the large quaternary center.\(^{96}\) Meanwhile, the greater ionic character of acetylide organometallic reagents (sp-hybridized carbanions) as compared to most sp\(^2\)- and sp\(^3\)-hybridized carbanions probably translates into greater Coulombic interactions, which repel the electron-rich nucleophile from regions of high electron density. In summary, preparation of 30a in large quantities as a single diastereomer is not difficult. We attribute the observed stereochemistry to (a) a substrate that is ill-suited to chelation of metal salts, and (b) a small, electron-rich nucleophile that is more sensitive to stereoelectronic factors than steric factors.

\(^{††}\) Addition of a vinyl Grignard nucleophile to aldehyde 29 produced a complex mixture of products for which purification was not attempted.
3.2. Synthesis of Spiroketal II

With the pure propargyl alcohol 30a in hand, 30a was subjected to the alkyne zipper reaction\textsuperscript{97} followed by TBS protection to afford the silyl ether 32a. Homopropargyl silyl ether 32a was added to the commercially available (R)-propylene oxide (33) to give alkynyl alcohol 34a,\textsuperscript{98} which later was treated with AuCl in MeOH to provide spiroketal II in a mixture of 24a and 24b. More details about the gold cyclization will be discussed at the end of this chapter. The mixture of 24a and 24b was selectively silylated to afford 25a and 25b (Scheme 51).

Scheme 51. Synthesis of spiroketal II

3.3. Synthesis of Spiroketal I

Preparation of syn-propargyl alcohol 30b from \textit{anti}-propargyl alcohol 30a under Mitsunobu inversion conditions was unsuccessful. The inversion was performed over two steps through Swern oxidation followed by CBS reduction (Scheme 52). Pure propargyl alcohol 30b was subjected to zipper conditions to afford homopropargyl alcohol 31b, which was protected with
the TBS group. *syn*-Homopropargyl silyl ether 32b was added to (R)-1,2-propylene oxide (33) to afford *syn*-alkynol alcohol 34.

Scheme 52. Synthesis of homopropargyl alcohol 34b

Treatment of 34b with AuCl led to formation of spiroketal I as a diol mixture of 20a and 20b in 42 : 58 ratio. In the course of spiroketal isomerization study, protecting group manipulation was performed. TBDPS protection of I-(20a, 20b) afforded I-(22a, 22b) selectively (Scheme 53).

Scheme 53. Gold spiroketalization of homopropargyl alcohol 34b

On the other hand, treating alkyne 34b, cycloisomerization with *bis*-acetonitrile palladium(II) chloride in CH$_3$CN provided 5,5-spiroketal 21a and 21b, where the TBS ether was still intact.
with a 9:1 ratio favoring 21b. Both isomers were treated with TBAF to give diols 20a and 20b in 9:1 ratio. TBDPS protection of I-(21a, 21b) afforded I-(23a, 23b) (Scheme 54).

**Scheme 54.** Palladium spiroketalization of homopropargyl alcohol 34b

Both gold and palladium spiroketalization afforded spiroketal I in different ratios, which was used to test the zinc chelation hypothesis. More details about this spiroketalization will be discussed at the end of this chapter.

**4. Synthesis of Cephalosporolide H**

The synthesis of the reported structure of cephalosporolide H using the chelation approach started with a coupling of propargyl silyl ether 32b with (R)-1,2-epoxynonane (36a). This coupling afforded the internal alkyne 37, a key intermediate in the synthesis (Scheme 55).
Gold(I) chloride in MeOH induced cycloisomerization of alkyne 37 with concomitant cleavage of the PMP acetal and TBS ether to give 5,5-spiroketal 39a in 80% yield, but as a ca. 1:1 mixture with spiroketal epimer 39b (Scheme 56). Notably, exposure of this mixture to zinc chloride chelation effects for 8 h delivered spiroketal 39a as a single diastereomer in 86% yield. Magnesium oxide was included in this case as a protic acid scavenger. The protic acid scavenger helps suppress acid-catalyzed dehydration to furan by-products, which otherwise were detected in small quantities. Oxidation of spiroketal diol 39a (cf. Scheme 43, isomer I-a) was expected to provide cephalosporolide H, but spectroscopic data for lactone 1 did not match that reported for the natural product.

Retreating in the synthetic sequence to internal alkyne 37 (Scheme 56), cycloisomerization with bis-acetonitrile palladium(II) chloride in CH3CN provided 5,5-spiroketal 38, with the TBS ether being intact as a 9:1 mixture favoring the opposite (thermodynamic) spiroketal stereochemistry (cf. Scheme 56, isomer I-b). Desilylation with TBAF provided spiroketal 39b, still in a 9:1 ratio over 39a. TEMPO-catalyzed oxidation gave rise to diastereomerically pure lactone 1a in 68% yield; spectroscopic data aligned better with data reported for cephalosporolide H.

\[ 39b \rightarrow 1a \] is significantly faster than the oxidation \[ 39a \rightarrow 1 \], facilitating production of the more stable lactone \( 1a \)
Scheme 56. Synthesis of cephalosporolide isomers

5. Synthesis of C-9-epi-Cephalosporolide H Isomers

The reported spectroscopic data of cephalosporolide H did not match exactly with the two synthesized isomers 1 and 1a. Direct spectroscopic analysis using NOE and NOESY experiments conducted on both spiroketal epimers 1 and 1a was inconclusive in differentiating between the two epimers. Thus Xiang’s assignment of the relative stereochemistry of natural cephalosporolide H, which relied mainly on NOESY, is suspicious to us. C-9 Epimers were synthesized to reinspect the relative stereochemistry assignment. (S)-1,2-Epoxynonane (36b) was used to synthesize internal alkyne 40 which was subjected to gold cyclization giving spiroketal diol 41a and 41b in 95% yield in 32 : 68 ratio favoring 41b (Scheme 57). Both isomers were separated and subjected to TEMPO oxidation to afford both lactones 1b and 1c. Thermodynamic spiroketal 41b was isomerized into 41a (dr 15 :01) using ZnCl₂. It was noticed that spectroscopic data of 1 and 1a were quite similar to 1c and 1b respectively (Table 7).
Our stereochemical assignment of spirokets 1, 1a, 1b, and 1c is based on NMR correlations with the spiroketal resonances of cephalosporolides E and F, for which X-ray crystallographic data is available, and by analogy to the model systems I and II. Direct spectroscopic analysis using NOE and NOESY experiments conducted on both spirocenter epimers 1 and 1a was inconclusive. Most importantly, Xiang’s relative stereochemistry assignment of cephalosporolide H was made on the basis of NOESY cross peaks that we observed in both epimers. Therefore, we cannot be confident about the original stereochemical assignment. However, attempts to secure an authentic sample and/or copies of original NMR spectra from Xiang and co-workers were unsuccessful.

Seeking to draw conclusions about the true structure of the natural cephalosporolide H, we considered cephalosporolide H diastereomers 1, 1a, 1b, and 1c to be the most likely candidates, and we prepared all them as discussed above. Comparing the spectroscopic data of spirocenter epimers 1 and 1a and C-9 epimers 1b and 1c to the reported data of natural cephalosporolide H revealed that 1b is the strongest candidate to represent cephalosporolide H (Table 7). 1 and 1c were ruled out as one of possibilities because their NMR data and optical rotation did not match with the natural cephalosporolide H. 1a is very similar 1b to be ruled out on the basis of

Scheme 57. Synthesis of C-9-epi-cephalosporolide H isomers
comparison only to the reported data for cephalosporolide H. However, we note that 1b ([α]_D^{25} = +41.2, c 0.71, MeOH), corresponds to the same stereochemistry as the structure of cephalosporolide F enantiomer ([α]_D^{25} = +95.2, c 0.25, CHCl_3), the structure of which confirmed by X-ray.\(^\text{82}\)

In summary, we may not be able to assign definitively the true natural stereochemistry, but we can make the four isomers selectively, which was the goal of our efforts.

**Table 7.** Comparison between the synthesized isomers and reported \(^1\)H NMR and \(^13\)C NMR for cephalosporolide H

<table>
<thead>
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<th>reported data for natural cephalosporolide H</th>
<th>1</th>
<th>1a</th>
<th>1b</th>
<th>1c</th>
<th>(\Delta\delta) for 1a and 1b</th>
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<td></td>
<td>1a</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>[(\alpha)]_D^{25}</td>
<td>65</td>
<td>1b</td>
<td>1a</td>
<td></td>
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<tr>
<td>[(\alpha)]_D^{25}</td>
<td>= +41.2</td>
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<td>1b</td>
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<tr>
<td>[(\alpha)]_D^{25}</td>
<td>= -7.6</td>
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<tr>
<td>(^1)H NMR</td>
<td>(^13)C NMR</td>
<td>(^1)H NMR</td>
<td>(^13)C NMR</td>
<td>(^1)H NMR</td>
<td>(^13)C NMR</td>
<td>(^1)H NMR</td>
</tr>
<tr>
<td>5.01 (m)</td>
<td>180.8</td>
<td>5.07 (t)</td>
<td>180.6</td>
<td>5.03 (dd, d)</td>
<td>181</td>
<td>5.02 (dd)</td>
</tr>
<tr>
<td>4.26 (d)</td>
<td>115.5</td>
<td>4.29 (d)</td>
<td>115.1</td>
<td>4.29 (d, J = 3.8)</td>
<td>115.5</td>
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<tr>
<td>4.05 (m)</td>
<td>85.2</td>
<td>4.03 – 3.92 (m)</td>
<td>87.1</td>
<td>4.09–3.98 (m)</td>
<td>82.2</td>
<td>4.07–3.95 (m)</td>
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<tr>
<td>2.52 (d)</td>
<td>80.5</td>
<td>2.44 (d)</td>
<td>82.0</td>
<td>2.52 (dd)</td>
<td>80.6</td>
<td>2.49 (dd)</td>
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<tr>
<td>2.35 (d)</td>
<td>78.8</td>
<td>2.15 – 1.95 (m)</td>
<td>79.9</td>
<td>2.36 (dd)</td>
<td>79.0</td>
<td>2.33 (dd)</td>
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<tr>
<td>2.2–2.1 (m)</td>
<td>44.4</td>
<td>1.75 – 1.59 (m)</td>
<td>44.5</td>
<td>2.18 (m)</td>
<td>44.5</td>
<td>2.11–1.87 (m)</td>
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**Table 7.** Comparison between the synthesized isomers and reported $^1$H NMR and $^{13}$C NMR for cephalosporolide H.

<table>
<thead>
<tr>
<th>$^1$H NMR</th>
<th>$^{13}$C NMR</th>
<th>$^1$H NMR</th>
<th>$^{13}$C NMR</th>
<th>$^1$H NMR</th>
<th>$^{13}$C NMR</th>
<th>$^1$H NMR</th>
<th>$^{13}$C NMR</th>
<th>$^1$H NMR</th>
<th>$^{13}$C NMR</th>
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<tbody>
<tr>
<td>1.65-1.23 (m)</td>
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<td>1.25 (br m)</td>
<td>41.7</td>
<td>1.55-1.47 (m)</td>
<td>42.3</td>
<td>1.79-1.28 (m)</td>
<td>41.8</td>
<td>1.54-1.25 (br m)</td>
<td>41.9</td>
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<tr>
<td>1.24 (s)</td>
<td>35.5</td>
<td>1.29 (s)</td>
<td>37.4</td>
<td>1.27 s</td>
<td>35.7</td>
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<td>37.2</td>
<td>1.25 (s)</td>
<td>35.3</td>
</tr>
<tr>
<td>1.19 (s)</td>
<td>33.8</td>
<td>1.21 (s)</td>
<td>36.3</td>
<td>1.22 s</td>
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<td>1.22 (s)</td>
<td>34.5</td>
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<td>0.84 (t)</td>
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<td>0.88 (t)</td>
<td>31.8</td>
<td>0.88 (t)</td>
<td>31.8</td>
<td>0.87 (t)</td>
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<td>22.5</td>
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<td>22.7</td>
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<td></td>
<td></td>
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<tr>
<td>18.1</td>
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<td>18.1</td>
<td>18.1</td>
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<td>0.0</td>
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<tr>
<td>14.0</td>
<td>14.1</td>
<td>14.1</td>
<td>14.1</td>
<td>14.1</td>
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<td></td>
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</tr>
</tbody>
</table>
6. Synthesis of Cephalosporolides E (2a) and F (2b)

During the asymmetric synthesis of cephalosporolide H, it was shown that chelation of zinc salts between the spiroketal oxygen and an appropriately positioned alcohol group overrides normal biases. Cephalosporolides E and F were targeted for the validation of this approach for controlling the spirocenter stereochemistry in 5,5-spiroketals. There are three main differences between cephalosporolides H, E, and F (Scheme 42): (a) E and F have methylene carbon at C-2 versus quaternary carbon in H; (b) E and F were isolated as mixture of isomers, but H was isolated as single isomer; (c) E and F have methyl group at C-9 versus seven carbon alkyl chain in H.

A new strategy was used to synthesize the homopropargyl silyl ether 42 which is similar to cephalosporolide H intermediate 32b. Homopropargyl alcohol 42 was converted into cephalosporolides E and F by using similar sequence of reactions to cephalosporolide H (Scheme 58).

Scheme 58. Comparison between cephalosporolide H and cephalosporolides E and F intermediates

Synthesis of cephalosporolides E and F started with the known alcohol 44, which was prepared from the commercially available diester 43 (Scheme 59). PMB protection of alcohol 44 followed by Sharpless dihydroxylation afforded diol 46. DDQ oxidation of PMB ether produced 1,3-dioxane 47. Protective groups manipulation led to the formation of primary alcohol 49, which was converted into homopropargyl silyl ether 42 over two steps; DMP oxidation and subsequent Ohira-Bestmann alkynyl formation.
Scheme 59. Synthesis of homopropargyl silyl ether 42

Coupling propargyl silyl ether 42 with the (R)-propylene oxide produced internal alkyne 51. Gold(I) chloride in MeOH induced cycloisomerization of alkyne 51 with concomitant cleavage of the PMP acetal and partially cleavage of TBS ether to give 5,5-spiroketal 52a and 52b in 45 : 55 ratio and 53a and 53b in 84 : 16 ratio, which was subsequently deprotected with TBAF (Scheme 60). Both spiroketals was contaminated with diastereomeric isomers at C-2 and C-3, which presumably resulted from Sharpless dihydroxylation. Exposure of diol 52a and 52b to zinc chloride chelation effects delivered spiroketal 52a as a single diastereomer admixed with diastereomer isomer at C-2 and C-3. TEMPO oxidation of diol crude 52a led to the formation of pure cephalosporolide E (2a). On the other hand, the mixture of diols 52a and 52b in 84 : 16 ratio was oxidized to afford cephalosporolides E (2a) and F (2b) respectively.
7. Addendum Gold-Catalyzed Alkyne-Diol Spiroketalization Towards the Synthesis of Cephalosporolides.

This section focuses on the cycloisomerization of alkyne diol to produce 5,5-spiroketal. The primary focus of the investigation was to control 5,5-spiroketal stereochemistry. However, synthesis of 5,5-spiroketal was a key challenge that was overcome along the way as described below.

Synthesis of spiroketals has received considerable attention, with the most progress having been made on systems that include at least one six-membered ring.\textsuperscript{108} 5,5-Spiroketals, particularly oxygenated 5,5-spiroketals such as are found in the cephalosporolides, are the focus of this study.

A variety of synthetic methods are available for the synthesis of 5,5-spiroketals, including cyclocondensation of ketone diols,\textsuperscript{72,89a} cycloisomerization of alkyne diols,\textsuperscript{99,100} oxidative spirocyclization,\textsuperscript{75,109,110} and others. Cyclocondensation of ketone diols is perhaps the most
straightforward and the most popular (Scheme 61), but the alternatives offer specific advantages. For example, the cycloisomerization of alkyne diols is more exothermic\(^8\) and atom economical,\(^{111}\) and non-polar alkyne π-bonds are more compatible than ketones (kinetically stable) towards a number of common reaction conditions. Conversely, the use of alkynes in the synthesis of spiroketals introduces regiochemistry concerns as to which of the two alkyne carbons becomes the spiroketal carbon, and the kinetic stability of alkynes must be overcome when alkyne reactivity is desired.

Scheme 61. Cyclocondensation and cycloisomerization for the synthesis of spiroketals

This section details the challenges and considerations involved in the cycloisomerization of alkynes to oxygenated spiroketals and outline our screening of various late transition metal catalysts and conditions that ultimately resulted in the acquisition of our target structures. Gold(I) chloride emerged as the best choice for the desired transformation.

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\(^8\) Energies calculated at the B3LYP/6-31G level
Key precedent for the desired cycloisomerization is recounted in Scheme 62, although many other methods are available\textsuperscript{98,112,113,114} and no consensus option has emerged. Utimoto studied the palladium-catalyzed cycloisomerization,\textsuperscript{99} reporting that a range of spiroketals are available in excellent yield (Scheme 62, Eq 1). However, regiochemistry is sometimes difficult to control, and De Brabander later found variability in reaction selectivity using the Utimoto conditions. Therefore, he suggested the preferred use of Ziese’s dimer, a platinum catalyst (Scheme 62, Eq 2), for such cyclizations.\textsuperscript{100} In an unrelated study that also bears on the current work, Aponick and co-workers described a gold-catalyzed cyclocondensation of alkyne diols to give substituted furans (Scheme 62, Eq 3).\textsuperscript{115}
Our objective, laid out in Scheme 63, was to initiate cycloisomerization with a 5-endo-dig cyclization of the homopropargyl alcohol 37, followed by 5-exo-trig cyclization onto the resulting dihydrofuran, while avoiding the kind of dehydration to furan reported by Aponick. The use of alkyne-diol cycloisomerization instead of ketone-diol cyclocondensation is important to the potential success of this approach because the β-alkoxy ketone (Scheme 63, inset) would be more prone to undesired elimination than homopropargyl ether 37. We addressed regiochemistry by blocking one of the alcohols as a ketal, thus favoring the initial 5-endo cyclization of the other. In this way, we aimed to ensure that the desired regioisomer could form with the expectation of ketal hydrolysis during the course of the reaction.
Table 8: Optimization for spiroketalization of anti-alkynol 34a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>II</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1% PdCl2, CH3CN, reflux, 1 h</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>1% PdCl2, CH3CN, rt, 1.5 h</td>
<td>54a/b</td>
<td>43%b</td>
</tr>
<tr>
<td>3</td>
<td>1% [Cl2Pt(CH2=CH2)]2, Et2O, rt, then CSA</td>
<td>-a</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>5% AuCl, CH2Cl2, rt, 6h</td>
<td>54a/b</td>
<td>36 %</td>
</tr>
<tr>
<td>5</td>
<td>5% AuCl, PPTS, CH2Cl2, rt, 14 h</td>
<td>54a/b</td>
<td>37 %</td>
</tr>
<tr>
<td>6</td>
<td>5% AuCl(PPh3)3, CH2Cl2, rt</td>
<td>-</td>
<td>-a</td>
</tr>
<tr>
<td>7</td>
<td>5% AuCl(PPh3)3, AgSbF6, CH2Cl2, 12 h rt</td>
<td>-</td>
<td>-a</td>
</tr>
<tr>
<td>8</td>
<td>5% AuCl3, CH2Cl2, 12h rt</td>
<td>-</td>
<td>-a</td>
</tr>
<tr>
<td>9</td>
<td>5% AuCl, MeOH, rt, 12h</td>
<td>24a/b</td>
<td>35 %</td>
</tr>
<tr>
<td>10</td>
<td>25% AuCl, MeOH, rt, 12 h</td>
<td>24a/b</td>
<td>68 %c</td>
</tr>
<tr>
<td>11</td>
<td>34% AuCl, CH3CN, rt, 4 h</td>
<td>55</td>
<td>18 %</td>
</tr>
</tbody>
</table>

*a complex mixture of products was observed. b no increase in yield after longer times. c another 25% of AuCl was added after 1 h.

Cycloisomerization of 37a to the spiroketal 24a/b or 54a/b was examined under a variety of conditions, some of which are featured in Table 8. Utimoto’s general conditions as reported (entry 1) resulted in decomposition of the substrate, but at room temperature the spiroketal was
observed in modest yield (entry 2). Reactions involving Ziese’s dimer were discouraging (eg, entry 2), but gold(I) chloride in methylene chloride (cf Eq 3) offered encouraging results. Other gold catalysts and solvents were screened, with the best results coming from a higher catalyst loading of gold(I) chloride in methanol (entry 10). The need for higher catalyst loading is tentatively ascribed to some form of instability of the gold catalyst in methanol, as pre-mixing the gold(I) chloride with methanol and aging this mixture prior to adding the substrate results in a less efficient reaction. This is not the first time that we observe the importance of order of addition in gold-catalyzed reaction in polar protic solvents, but nonetheless we were satisfied with these results for our current study. Furan 55, which presumably arises by analogy to Aponick’s cyclocondensation, was observed in varying amounts in many cases, although the use of methanol as a solvent seems to help suppress formation of the (undesired for our purposes) furan product.

Scheme 64. Gold spiroketalization in synthesis cephalosporolide H epimers

Treatment of 37 with 40 mol% gold(I) chloride in methanol resulted in cycloisomerization with simultaneous hydrolysis of the PMP acetal and cleavage of the silyl ether to give spiroketal diol 39a/b in 80% yield as a roughly 1:1 mixture of spiroketal epimers. epi-Alkynol 40 was also treated with AuCl in more dilute conditions led to 89% yield of spiroketal 41a/b (Scheme 64).
Two mechanistic alternatives are offered for the conversion of alkynyl alcohol to spiroketal diol, which is the focus of this report (Scheme 65). Path a, which we envisioned at the outset of our experimental designs, involves initial gold-catalyzed 5-endo-dig cyclization to dihydrofuran. Once the regiochemistry is established, any number of condensation pathways would converge on spiroketal. For example, protonation of the enol ether could assist in the solvolysis of the acetal, with simultaneous formation of spiroketal. Any carbenium intermediates could be intercepted reversibly by methanol. The acidity of the gold(I) chloride in methanol mixture is sufficient to hydrolyze the secondary silyl ether in a separate event; the reaction time was purposefully extended to allow for desilylation to reach full conversion.

A second mechanistic alternative, path b, cannot be ruled out at this time. Path b involves gold-activation of the alkyne followed by 5-exo-dig nucleophilic attack of the acetal oxygen. Methanolysis of the acetal and spirocyclization would quickly follow. Although this pathway seems unlikely to compete effectively with path a, a control experiment strongly suggests that
path b is feasible. We subjected terminal alkyne 32b to the same conditions and observed the formation of furan 56 in low yield, along with other products (Scheme 66).

Scheme 66. Terminal alkyne to interesting furan product

In conclusion, Gold(I) chloride effectively catalyzed the cycloisomerization of homopropargyl alcohols to spiroketals in good yield, despite potential regiochemical complications and elimination to furan by-products. Other late transition metal Lewis acids were less effective. This study provides yet another example of the advantages of gold catalysis in the activation of alkyne \( \pi \)-systems.

To summarize, we have shown that chelation of zinc salts between the spiroketal oxygen and an appropriately positioned alcohol group overrides normal biases in the preparation of 5,5-spiroketals, as illustrated by the stereocontrolled synthesis of both the reported structure of cephalosporolide H epimers (1a, 1b, 1c), E (2a), and F (2b). The use of zinc salts is important: weaker acids do not enable isomerization, and stronger acids promote decomposition, especially elimination to furans. This study provides new and valuable information for prescribing the chirality of the stereogenic core of 5,5-spiroketals.

8. Experimental Part

\(^1\text{H} \text{NMR} \) and \( ^{13}\text{C} \text{NMR} \) spectra were recorded using CDCl\(_3\) as the deuterated solvent. The chemical shifts (\( \delta \)) are reported in parts per million (ppm) relative to the residual CHCl\(_3\) peak (7.26 ppm for \(^1\text{H} \text{NMR} \) and 77.0 ppm for \(^{13}\text{C} \text{NMR} \) for all compounds with TMS as internal reference). The coupling constants (\( J \)) are reported in Hertz (Hz). IR spectra were recorded on a FT-IR spectrometer (100). Mass spectra were recorded using electron ionization (EI) or fast-atom bombardment (FAB). Melting points are uncorrected. Yields refer to isolated material judged to be \( \geq 95\% \) pure by \(^1\text{H} \text{NMR} \) spectroscopy following silica gel chromatography. All
chemicals were used as received unless otherwise stated. All solvents, solutions and liquid reagents were added via syringe. Tetrahydrofuran (THF) was purified by distillation over sodium and benzophenone. Methylene chloride (CH₂Cl₂) was distilled from calcium hydride (CaH₂). Methanol (MeOH) and acetonitrile (CH₃CN) were used without any purification. The n-BuLi solutions were titrated against a known amount of menthol dissolved in tetrahydrofuran using 1,10-phenanthroline as the indicator. All reactions were carried out under an inert nitrogen atmosphere unless otherwise stated. The purifications were performed by flash chromatography using silica gel F-254 (230-499 mesh particle size).

Oxalyl chloride (64 mmol, 5.5 mL) was added dropwise at −78 °C to a mixture of dry DMSO (85 mmol, 6.0 mL) in methylene chloride (72 mL). After 10 min, a solution of alcohol 28 (42.0 mmol, 10.6 g) in methylene chloride (39 mL) was added dropwise. After 30 min, triethylamine (30 mL) was added to the reaction mixture, which was warmed to ambient temperature over 15 min. The reaction was quenched with H₂O (100 mL) and extracted with methylene chloride (200 mL × 2). The combined organic layers were washed with saturated aqueous NaHCO₃ (100 mL). Evaporation of the organic solvent under reduced pressure afforded a pale yellow oil, which was mixed with ether (20 mL) and filtered through a small plug of silica gel with ether (100 mL). Evaporation of the volatile components under reduced pressure afforded 10.2 g of a pale yellow solid (consisting primarily of aldehyde 29), which was used without further purification in the next step.

The aforementioned crude mixture containing aldehyde 29 was dissolved in anhydrous THF (200 mL) cooled at 0 °C, and treated with a solution of propynylmagnesium bromide (0.5 M, 150 mL, 75 mmol). The reaction mixture was warmed to room temperature over 1.5 h. The reaction was quenched with saturated aqueous NH₄Cl (200 mL) and then extracted with ethyl acetate (300 mL). Evaporation of the volatile components under reduced pressure afforded a yellow oil, which was subsequently diluted with ether (15 mL). Shortly thereafter (within 5 min), white crystals began to form. The crystalline precipitate was collected by filtration, washed with
hexane (150 mL), and dried under reduced pressure to furnish 4.89 g (40% from 28) of alcohol 30a as a single diastereomer.

![Structural diagram of 30a]

White solid, mp = 105 °C; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.46 (m, 1H), 7.45 (m, 1H), 6.91 (m, 1H), 6.89 (m, 1H), 5.47 (s, 1H), 4.55 – 4.31 (m, 1H), 3.80 (s, 3H), 3.65 (d, $J = 4.4$ Hz, 1H), 3.63 (d, $J = 11.1$ Hz, 1H), 3.57 (d, $J = 11.2$ Hz, 1H), 2.33 (d, $J = 7.6$ Hz, 1H), 1.85 (d, $J = 2.2$ Hz, 3H), 1.30 (s, 3H), 0.93 (s, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 160.0, 130.9, 127.5, 113.6, 101.9, 87.0, 83.0, 79.5, 77.9, 62.7, 55.2, 32.5, 22.0, 19.5, 3.7; IR (neat): 3416, 3015, 2961, 2840, 1616, 1589, 1518, 1466, 1393, 1303, 1248, 1215, 1172, 1102; HRMS (ESI$^+$): calcd. for C$_{17}$H$_{22}$O$_4$Na 313.1416, found 313.1426.

Oxalyl chloride (12.5 mmol, 2.34 mL) was added dropwise at –78 °C to a mixture of dry DMSO (36 mmol, 2.6 mL) in CH$_2$Cl$_2$ (30 mL). After 10 min, a solution of alcohol 28 (12.0 mmol, 3.18 g) in CH$_2$Cl$_2$ (12 mL) was added dropwise. After 30 min, triethylamine (8 mL) was added to the reaction mixture, which was warmed to ambient temperature over 15 min. The reaction was quenched with H$_2$O (20 mL) and extracted with CH$_2$Cl$_2$ (60 mL). The combined organic layers were washed with saturated aqueous NaHCO$_3$ (20 mL). Evaporation of the organic solvent under reduced pressure afforded pale yellow oil, which was mixed with Et$_2$O (10 mL) and filtered through a small plug of silica gel with ether (100 mL). Evaporation of the volatile components under reduced pressure afforded 3 g of a pale yellow solid (aldehyde 29), which was used without further purification in the next step. The aforementioned crude mixture containing aldehyde 29 was dissolved in anhydrous THF (60 mL), cooled at 0 °C, and treated with a solution of propynylmagnesium bromide (0.5 M, 25 mL, 50 mmol). The reaction mixture was warmed to room temperature over 1.5 h. The reaction was quenched with saturated aqueous
NH₄Cl (20 mL), extracted with ethyl acetate (150 mL), washed with brine (30 mL), and dried over MgSO₄. Evaporation of the volatile components under reduced pressure afforded yellow oil. The purification of residue by silica gel column chromatography (20% ethyl acetate in hexane) gave (30a : 30b = 3 : 1) (2.9 g, 83 % yield) as yellow oil.

KH (30 % under mineral oil, 22 g) was washed free of oil with hexane (25 x 2 mL) and dried in vacuum. To the KH at room temperature, 1,3-diaminopropane (50 mL) was added and the mixture was stirred for 1 h. Propargylic alcohol 30a (1.5 g, 5.17 mmol) in diamine (5 mL) was added via cannula at 0 °C. After 10 h, the reaction was diluted with Et₂O ( 50 mL) and slowly quenched over ice and Et₂O (200 mL), then Et₂O layer was extracted, followed by addition of EtOAc (50 mL) and 10 % HCl (until pH = 6) to aqueous layer. The combined organic layers was washed with NaHCO₃ (50 mL), dried over MgSO₄, and concentrated under reduced pressure to afford crude homopropargyl alcohol 31a.

To a magnetically stirred solution of alcohol crude oil of 31a and imidazole (2.1 g, 30 mmol) in dry CH₂Cl₂ (28 mL), TBSCI (2.88 g, 19.1 mmol) was added at room temperature. After 24 h, the reaction was quenched with NaCHO₃ (20 mL), extracted with 50 mL of CH₂Cl₂, dried over MgSO₄, and concentrated under reduced pressure. The crude oil was purified using silica gel flash chromatography (10 % EtOAc in hexane) to afford alkyne 32a and silyl impurities which was removed under high vacuum (0.4 mmHg) at 120 °C using bulb to bulb distillation to afford pure alkyne 32a (1.89 g, 90 %).

KH (30 % under mineral oil, 22 g) was washed free of oil with hexane (25 x 2 mL) and dried in vacuum. To the KH at room temperature, 1,3-diaminopropane (50 mL) was added and the mixture was stirred for 1 h. Propargylic alcohol 30a (1.5 g, 5.17 mmol) in diamine (5 mL) was added via cannula at 0 °C. After 10 h, the reaction was diluted with Et₂O ( 50 mL) and slowly quenched over ice and Et₂O (200 mL), then Et₂O layer was extracted, followed by addition of EtOAc (50 mL) and 10 % HCl (until pH = 6) to aqueous layer. The combined organic layers was washed with NaHCO₃ (50 mL), dried over MgSO₄, and concentrated under reduced pressure to afford crude homopropargyl alcohol 31a.

To a magnetically stirred solution of alcohol crude oil of 31a and imidazole (2.1 g, 30 mmol) in dry CH₂Cl₂ (28 mL), TBSCI (2.88 g, 19.1 mmol) was added at room temperature. After 24 h, the reaction was quenched with NaCHO₃ (20 mL), extracted with 50 mL of CH₂Cl₂, dried over MgSO₄, and concentrated under reduced pressure. The crude oil was purified using silica gel flash chromatography (10 % EtOAc in hexane) to afford alkyne 32a and silyl impurities which was removed under high vacuum (0.4 mmHg) at 120 °C using bulb to bulb distillation to afford pure alkyne 32a (1.89 g, 90 %).

\[ \text{1H NMR (600 MHz, CDCl}_3) \delta 7.41 \text{ (app. t, 1H), 7.39 (m, 1H), 6.90 (m, 1H),} \\
\text{6.89 (m, 1H), 3.90 - 3.84 (m, 1H), 3.80 (s, 3H), 3.66 (d, } J = 11.3 \text{ Hz, 1H), 3.60 (d, } J = 11.8 \text{ Hz,} \]

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1H), 3.51 (d, J = 8.2 Hz, 1H), 2.64 (ddd, J = 16.9, 3.5, 2.7 Hz, 1H), 2.53 (ddd, J = 17.0, 6.8, 2.6 Hz, 1H), 2.14 (d, J = 6.4 Hz, 1H), 2.09 (t, J = 2.6 Hz, 1H), 1.22 (s, 3H), 1.00 (s, 3H); 13C NMR (150 MHz, CDCl3) δ 159.9, 131.0, 127.3, 113.5, 101.4, 85.2, 80.7, 79.1, 71.3, 69.5, 55.2, 32.5, 24.8, 22.5, 19.0; IR (Neat): 3466, 3298, 2954, 2839, 2280, 1615, 1518, 1464, 1391; HRMS (ESI+): calcd. for C17H22O4Na 313.1415, found 313.1435.

To a clear solution of alkyne 32a (1.36 g, 3.36 mmol) in THF (33 mL) stirring at -78 °C under a nitrogen atmosphere was added n-BuLi (3.3 M in hexane, 1.5 equiv). The solution immediately turned yellow. After 1h, freshly distilled neat BF3•Et2O (0.63 mL, 5.0 mmol) was added. After 6 minutes of BF3•Et2O addition, dry and neat (R)-(+)-propylene oxide (1 mL, 16.8 mmol) was added. The yellow solution stirred at -78 °C to 0 °C for 6 hours. The reaction was quenched with H2O (15 mL), and extracted with 50 mL of EtOAc, the aqueous layer mixed with saturated NH4Cl (50 mL) and extracted with 50 mL of EtOAc. The combined organic layers was washed with 50 mL of brine solution, dried under MgSO4, concentrated under reduced pressure to afford crude oil which was purified over silica gel (20 % EtOAc in hexane) to produce yellowish oil
34a (1.4 g, 90 %). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.42 (m, 1H), 7.40 (m, 1H), 6.90 (m, 1H), 6.88 (m, 1H), 5.41 (s, 1H), 3.91 (dt, $J = 3.7, 7.4$ Hz, 2H), 3.80 (s, 3H), 3.71 (d, $J = 7.4$ Hz, 1H), 3.62 (d, $J = 11.2$ Hz, 1H), 3.58 (d, $J = 11.3$ Hz, 1H), 2.73 – 2.63 (m, 1H), 2.45 – 2.37 (m, 2H), 2.34 – 2.26 (m, 1H), 2.03 (br s, 1H), 1.26 (d, $J = 6.1$ Hz, 3H), 1.18 (s, 3H), 0.95 (s, 3H), 0.93 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 159.9, 131.3, 127.3, 113.6, 113.6, 101.5, 85.1, 80.0, 79.4, 78.1, 71.0, 66.6, 55.3, 32.3, 29.6, 26.0, 25.94, 25.4, 24.8, 22.7, 22.2, 19.1, 18.1, -3.9, -4.1; IR (Neat): 3435, 2954, 2929, 2857, 2320, 1616, 1518, 1463, 1392; HRMS (ESI$^+$): for C$_{26}$H$_{42}$O$_5$SiNa 485.2699, found 485.2686.

AuCl (16 mg, 0.07 mmol) was added to a premixed 34a (130 mg, 0.28 mmol) and MeOH (10 mL) at room temperature, black color instantly appeared, after 1 h, another 15 mg of AuCl was added and stirred at room temperature for 12 h. The reaction mixture was filtered, mixed with 100 mg of silica gel, and concentrated under reduced pressure. The silica gel admixed with the crude reaction mixture was transferred into silica gel column (30 % EtOAc in hexane) to afford pure mixed products (24a : 24b = 72 : 28) (44 mg, 68 %).

24a and 24b mixture: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.57 (dd, $J = 16.2, 7.1$ Hz, 1H), 4.24 (dq, $J = 6.2, 12.6$ Hz, 1H), 4.17 – 4.06 (m, 2H), 3.86 (d, $J = 2.6$ Hz, 1H), 3.55 – 3.32 (m, 5H), 3.08 (br s, 1H), 2.95 (br d, $J = 9.3$ Hz, 1H), 2.65 (br s, 1H), 2.57 (br s, 1H), 2.31 (dd, $J = 12.5, 7.0$ Hz, 1H), 2.19 – 1.88 (m, 9H), 1.76 – 1.57 (m, 4H), 1.53 – 1.40 (m, 1H), 1.29 (d, $J = 6.1$ Hz, 3H), 1.22 (d, $J = 6.2$ Hz, 3H), 0.97 (s, 3H), 0.96 (s, 3H), 0.93 (s, 3H), 0.86 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 114.6, 113.0, 94.5, 91.7, 76.8, 74.8, 72.9, 72.1, 70.9, 70.8, 44.3, 44.1, 37.5, 37.3, 36.9, 34.0, 32.3, 31.6, 22.5, 21.5, 21.3, 20.99, 20.84, 18.8; IR (Neat): 3389, 3005, 2969, 2873, 1461, 1350; HRMS (ESI$^+$): calcd. for C$_{12}$H$_{22}$O$_5$SiNa 253.1416, found 253.1413.
To a magnetically stirred solution of alcohol 24a and 24b mixture (8 mg, 0.034 mmol) and imidazole (20 mg, 0.29 mmol) in dry CH₂Cl₂ (2 mL), TBDPSCl (30µl, 0.1 mmol) was added at room temperature. After 12 h, the reaction was quenched with NaCHO₃ (3 mL), extracted with 10 mL of CH₂Cl₂, dried over MgSO₄, and concentrated under reduced pressure. The crude oil was purified using silica gel flash chromatography (5 to 15% EtOAc in hexane) to afford 25a and 25b (11 mg, 69%).

**1H NMR (400 MHz, CDCl₃)** δ 7.77 – 7.59 (m, 1H), 7.52 – 7.31 (m, 2H), 4.34 – 4.11 (m, 1H), 3.96 (d, J = 2.2 Hz, 1H), 3.50 (d, J = 9.6 Hz, 1H), 3.31 (d, J = 9.6 Hz, 1H), 3.10 (d, J = 10.6 Hz, 1H), 2.21 – 2.05 (m, 1H), 2.05 – 1.95 (m, 1H), 1.21 (d, J = 6.1 Hz, 1H), 1.05 (s, 2H), 0.97 (s, 1H), 0.76 (s, 1H); **13C NMR (100 MHz, CDCl₃)** δ 135.7, 135.7, 133.6, 129.5, 129.5, 127.6, 127.5, 114.4, 91.7, 74.3, 72.7, 69.6, 44.3, 38.0, 33.9, 31.8, 26.8, 21.2, 21.11, 19.5, 19.4; IR (Neat): 3443, 3072, 2958, 2931, 2857, 1472, 1427; HRMS (ESI⁺): calcd. for C₂₈H₄₀O₄SiNa 491.2593, found 491.2587.

**1H NMR (400 MHz, CDCl₃)** δ 7.79 – 7.57 (m, 4H), 7.51 – 7.32 (m, 6H), 4.50 (dt, J = 7.1 9.4 Hz, 1H), 4.18 – 4.08 (m, 1H), 3.60 (d, J = 10.3 Hz, 1H), 3.56 (d, J = 7.2 Hz, 1H), 3.36 (d with br s overlap, J = 10.3 Hz, 2H), 2.33 (dd, J = 12.4, 7.0 Hz, 1H), 2.16 – 1.87 (m, 4H), 1.75 – 1.61 (m, 1H), 1.26 (d, J = 6.1 Hz, 3H), 1.08 (s, 9H), 0.94 (s, 3H), 0.79 (s, 3H); **13C NMR (100 MHz, CDCl₃)** δ 135.89, 135.65, 132.98, 132.72, 129.88, 129.78, 127.73, 127.72, 112.35, 90.34, 76.41, 71.34, 70.15, 43.76, 38.17, 37.59, 32.20, 29.69, 26.97, 23.12, 22.39, 19.29, 18.47; IR (Neat): 3443, 3072, 2958, 2931, 2857, 1472, 1427; HRMS (ESI⁺): calcd. for C₂₈H₄₀O₄SiNa 491.2593, found 491.2587.
PdCl₂ (1.5 mg, 0.008 mmol) was added to a premixed 34a (33 mg, 0.071 mmol) and CH₃CN (2 mL). The solution was stirred at room temperature for 1.5 h. The reaction mixture was concentrated under reduced pressure and transferred into silica gel column (1-5 % EtOAc in hexane) to afford pure mixed products (54a : 54b ~ 67 : 33) (10.5 mg, 43 %).

\[ \text{1H NMR (400 MHz, CDCl₃) \delta 4.49 (m, 1H) [Major], 4.18 (m, 1H) [Minor], 3.76 (d, J = 6.9 Hz, 1H) [Minor], 3.60 (d, J = 6.5 Hz, 1H) [Major], 3.49 (m, 1H), 3.39-3.30 (m, 2H), 3.31-2.20 (m, 1H), 2.15-1.86 (m, 4H), 1.68 (m, 1H), 1.43 (m, 1H), 1.29 (d, J = 6.1 Hz, 3H) [Major], 1.21 (d, J = 6.2 Hz, 3H) [Minor], 0.87 (s, 9H) [Minor], 0.86(s, 9H) [Major], 0.071 (d, J = 1.8 Hz, 6H) [Minor], 0.07(d, J = 7.4 Hz, 6H) [Major];} \]

\[ \text{13C NMR (100 MHz, CDCl₃) \delta 113.3, 112.8, 92.2, 89.9, 76.8, 74.4, 72.5, 71.6, 71.5, 71.4, 45.4, 45.1, 37.5, 37.2, 36.7, 36.7, 32.3, 31.8, 25.73, 25.70, 22.68, 22.4, 21.2, 21.0, 20.5, 19.73, 17.78, 17.70, -3.9, -4.0, -4.86, -4.95. HRMS (CI⁺): calcd. for C₁₈H₃₇O₄Si 345.2455, found 345.2455.} \]

AuCl (10 mg, 0.043 mmol) was added to a premixed 32a (126 mg, 0.31 mmol) and CH₂Cl₂ (10 mL) at room temperature. After 5 h, the reaction mixture was concentrated and transferred into silica gel column (30 % EtOAc in hexane) to afford furan 56 (30 mg, 35%).

\[ \text{1H NMR (400 MHz, CDCl₃) \delta 7.40 (d, J = 8.9 Hz, 2H), 6.91 (d, J = 16.24 Hz, 1H), 6.88 (d, J = 8.68 Hz, 2H), 6.71 (d, J = 16.24 Hz, 1H), 6.21 (d, J = 3.24 Hz, 1H), 6.12 (d, J = 3.24 Hz, 1H), 3.82 (s, 3H), 3.64 (d, J = 6.56 Hz, 2H), 1.62 (t, J = 6.60 Hz, 1H) 1.32 (s, 6H);} \]

\[ \text{13C NMR (100 MHz, CDCl₃) \delta 159.9, 159.1, 152.4, 129.9, 127.4, 125.8, 114.7, 114.1, 108.4, 106.9, 71.0, 55.2, 38.5, 23.4. HRMS (CI⁺): calcd. for C₁₇H₂O₃ 272.1412, found 272.1421.} \]
Oxalyl chloride (7.5 mmol, 0.65 mL) was added dropwise at -78 °C to a mixture of dry DMSO (12 mmol, 0.9 mL) in CH$_2$Cl$_2$ (9 mL). After 10 min, a solution of alcohol 30a/b (2.53 mmol, 736 mg) in CH$_2$Cl$_2$ (2 mL) was added dropwise. After 30 min, triethylamine (4 mL) was added to the reaction mixture, which was warmed to ambient temperature over 15 min. The reaction was quenched with H$_2$O (5 mL) and extracted with CH$_2$Cl$_2$ (20 mL). The combined organic layers were washed with saturated aqueous NaHCO$_3$ (15 mL). Evaporation of the organic solvent under reduced pressure afforded pale yellow oil, which was mixed with Et$_2$O (10 mL) and filtered through a small plug of silica gel with Et$_2$O (100 mL). Evaporation of the volatile components under reduced pressure afforded a pale yellow solid (consisting primarily of ketone 35), which was used without further purification in the next step. The yellow solid was dissolved in THF (27 mL) and mixed with (S)-CBS (1 M in Tolune, 1.51 mL). The solution was cooled to -40 °C. Then boron methyl sulfide complex (5 mmol, 0.45 mL) was added over 5-10 min. After 6 h, the reaction was quenched by slow dropwise addition of 4 mL of methanol. The solution was diluted with 50 mL of Et$_2$O and washed with saturated NH$_4$Cl (20 mL), saturated NaHCO$_3$ (20 mL), and brine (20 mL). The organic layer was dried over MgSO$_4$, filtered through silica gel, and concentrated under reduced pressure. Column chromatography (20 % ethyl acetate in hexanes) afforded yellowish oil alcohol 30b (558 mg, 76 %).

White solid, mp = 100 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.52 – 7.47 (m, 2H), 6.98 – 6.79 (m, 2H), 5.49 (s, 1H), 4.09 (s, 1H), 3.81 (s, 3H), 3.69 (d, $J =$ 11.3 Hz, 1H), 3.65 (d, $J =$ 11.3 Hz, 1H), 2.06 (s, 3H), 1.23 (s, 3H), 1.00 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 185.4, 160.1, 130.4, 127.5, 113.6, 101.2, 94.8, 88.5, 79.8, 78.6, 55.3, 33.6, 21.4, 19.3, 4.4; IR (Neat): 2965, 2853, 2212, 1665, 1616, 1518; HRMS (ESI$^+$): calcd. for C$_{17}$H$_{20}$O$_4$Na 311.1416, found 311.1259.
KH (30 % under mineral oil, 11 g) was washed free of oil with hexane (15 mL x 2) and dried under vacuum. To the KH at room temperature, 1,3-diaminopropane (32 mL) was added and the mixture was stirred for 1 h. Propargylic alcohol 30b (600 mg, 2.0 mmol) in 1,3-diaminopropane (4 mL) was added via cannula at 0 °C. After 10 h of stirring at 0 °C, the reaction was diluted with Et2O (10 mL) and slowly quenched over a mixture of ice and Et2O (150), the organic layer was extracted, followed by addition of EtOAc (30 mL) and 10 % HCl (until pH = 6) to aqueous layer. The combined organic layers was washed with NaHCO3 (20 mL), dried over MgSO4, and concentrated under reduced pressure to afford crude homopropargyl alcohol 31b. Silica gel chromatography purification (20 % EtOAc in hexane) afforded 13b (551 mg, 92 %). 1H NMR (400 MHz, CDCl3) δ 7.43 (d, J = 8.6 Hz, 1H), 6.91 (d, 1H), 5.55 (s, 1H), 3.95 – 3.87 (m, 1H), 3.81 (s, 2H), 3.72 (s, 1H), 3.67 (dd, J = 31.6, 11.1 Hz, 2H), 2.59 (dd, J = 9.2, 1.5 Hz, 1H), 2.54 – 2.43 (m, 2H), 2.05 (t, J = 2.6 Hz, 1H), 1.28 (s, 3H), 0.88 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 160.1, 130.6, 127.4, 113.6, 101.7, 83.2, 80.9, 79.1, 70.3, 67.7, 55.2, 32.5, 25.6, 21.6, 19.8; IR (Neat): 3553, 3289, 3006, 2989, 2840, 2706, 2318, 1615, 1517, 1393; HRMS (ESI+): calcd. for C_{17}H_{22}O_{4}Na 313.1416, found 313.1437.
To a magnetically stirred solution of alcohol 31b (1.0 g, 3.44) and imidazole (1.4 g, 20.6 mmol) in dry DMF (8 mL), TBSCl (1.5 g, 9.9 mmol) was added at room temperature. After 24 h, the reaction was quenched with H₂O (16 mL) and extracted with Et₂O (100 mL). The organic layer was washed with saturated solution of NH₄Cl, dried over MgSO₄, and concentrated under reduced pressure. The crude oil was purified using silica gel flash chromatography (10 % EtOAc in hexane) to afford alkyne 32b and silyl impurities which was removed under high vacuum (0.4 mmHg) at 120 °C using bulb to bulb distillation to afford pure yellowish oil 32b (1.29 g, 93 %).

To a clear solution of alkyne 32b (557 mg, 1.37 mmol) in THF (12 mL) stirring at -78 °C under a nitrogen atmosphere n-BuLi (1.8 M in hexanes, 1.5 equiv) was added. The solution immediately turned yellow. After 1h, freshly distilled neat BF₃•Et₂O (0.2 mL, 1.65 mmol) was added. After 6 minutes of BF₃•Et₂O addition, dry and neat (R)-(+)-propylene oxide (0.3 mL, 4.1 mmol) was added. The yellow solution stirred from -78 °C to 0 °C over 6 hours. The reaction was quenched with H₂O (8 mL), and extracted with 25 mL of EtOAc, the aqueous layer mixed with saturated NH₄Cl (25 mL) and extracted with 25 mL of EtOAc. The combined organic layers was washed with 25 mL of brine solution, dried under MgSO₄, concentrated under reduced
pressure to afford crude oil which was purified over silica gel (20 % EtOAc in hexane) to produce yellowish oil 34b (609 mg, 96 %). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.44 (d, $J = 8.7$ Hz, 2H), 6.88 (d, $J = 8.7$ Hz, 2H), 5.41 (s, 1H), 4.02 – 3.94 (m, 1H), 3.93 – 3.82 (m, 1H), 3.80 (s, 3H), 3.64 (d, $J = 4.3$ Hz, 1H), 3.58 (d, $J = 11.1$ Hz, 1H), 3.55 (d, $J = 11.3$ Hz, 1H), 2.66 (ddd, $J = 7.3, 5.9, 2.6$ Hz, 1H), 2.42 – 2.20 (m, 3H), 2.15 (br s, 1H), 1.25 (s, 3H), 1.24 (d, $J = 5.2$ Hz, 3H), 0.90 (s, 3H), 0.86 (s, 9H), 0.05 (s, 3H), -0.02 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 159.8, 131.2, 127.6, 113.4, 102.3, 85.2, 80.1, 80.0, 78.3, 71.3, 66.4, 55.2, 32.7, 29.4, 25.8, 25.2, 22.2, 22.1, 20.1, 18.1, -4.1, -4.3; IR (Neat): 3437, 2953, 2929, 2855, 2300, 1616, 1589, 1518, 1464, 1394, 1302; HRMS (ESI$^+$): calcd. for C$_{26}$H$_{42}$O$_5$SiNa 485.2699, found 485.2718.

AuCl (35 mg, 0.15 mmol) was added to a premixed 34b (200 mg, 0.43 mmol) and MeOH (18 mL) at room temperature, black color instantly appeared. After 6 h, the reaction mixture was filtered, mixed with 100 mg of silica gel, and concentrated under reduced pressure. The silica gel admixed with the crude reaction mixture was transferred into silica gel column (30 % EtOAc in hexane) to afford pure mixed products ($^{20}$a : $^{20}$b = 42 : 58) (45 mg, 45 %).

$^1$H NMR (400 MHz, CDCl$_3$) δ 4.26 (app t, 1H), 4.22 – 4.09 (m, 1H), 3.60 (d, $J = 3.1$ Hz, 1H), 3.51 (dd, $J = 11$ Hz, 4H), 2.19 – 1.92 (m, 5H), 1.77 – 1.62 (m, 1H), 1.32 (d, $J = 6.1$ Hz, 3H), 1.09 (s, 3H), 1.03 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 114.3, 91.0, 77.1, 73.2, 70.8, 44.0, 38.0, 36.4, 32.2, 23.8, 22.7, 21.0; HRMS (ESI$^+$): calcd. for C$_{12}$H$_{22}$O$_4$Na 253.1616, found 253.1430.
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.36 – 4.30 (m, 1H), 4.20 – 4.09 (m, 1H), 3.66 (d, $J = 10.6$ Hz, 1H), 3.62 (d, $J = 2.5$ Hz, 1H), 3.36 (d, $J = 10.6$ Hz, 1H), 2.41 (dd, $J = 14.3$, 5.4 Hz, 1H), 2.21 – 1.99 (m, 4H), 1.53 – 1.39 (m, 1H), 1.22 (d, $J = 6.1$ Hz, 3H), 1.04 (s, 3H), 1.03 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 113.5, 88.0, 74.1, 72.5, 68.7, 46.6, 37.5, 37.2, 32.2, 24.2, 21.8, 21.0; IR (Neat): 3294, 2944, 2867, 1578, 1463, 1384, 1367, 1244; HRMS (ESI$^+$): calcd. for C$_{12}$H$_{22}$O$_4$Na 253.1616, found 253.1430.

A solution of 34b (60 mg, 0.12 mmol) and PdCl$_2$(CH$_3$CN)$_2$ (4 mg, 0.0016 mmol) in CH$_3$CN (4 mL) was stirred at room temperature for 1.5 h. The reaction mixture was concentrated and the crude was purified by silica gel column chromatography (10% ethyl acetate in hexane) to afford 21a : 21b (1:9) admixed with some impurities. (21a : 21b) was dissolved in 1.5 mL THF, followed by addition of TBAF (1 M in THF, 0.26 mL). After 6 h, the reaction mixture was concentrated under reduced pressure, followed by column chromatography (30 % EtOAc in hexane) to afford (20a : 20b = 1:9) (14 mg, 34 % over 2 steps %).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.41 – 4.34 (m, 1H), 4.10 – 4.02 (m, 1H), 3.90 (dd, $J = 10.6$, 5.0 Hz, 1H), 3.50 (d, $J = 4.0$ Hz, 1H), 3.49 – 3.45 (m, 1H), 3.31 (dd, $J = 10.5$, 6.6 Hz, 1H), 2.10 (dd, $J = 3.7$, 1.9 Hz, 2H), 2.06 – 1.92 (m, 2H), 1.87 – 1.77 (m, 1H), 1.70 – 1.58 (m, 1H), 1.27 (d, $J = 6.1$ Hz, 3H), 1.07 (s, 3H), 0.99 (s, 3H), 0.93 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 113.2, 89.9, 76.5, 73.2, 71.8, 44.9, 38.3, 37.8, 32.3, 29.7, 25.8, 25.0, 22.6, 20.8, 18.0, -4.5, -4.5.
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.44 (ddd, $J = 5.6, 3.6, 2.2$ Hz, 1H), 4.22 – 4.11 (m, 1H), 3.70 (d, $J = 3.6$ Hz, 1H), 3.59 (d, $J = 6.4$ Hz, 1H), 3.40 (d, $J = 10.8$ Hz, 1H), 3.20 (br s, 1H), 2.36 (dd, $J = 14.0, 5.5$ Hz, 1H), 2.19 – 1.97 (m, 4H), 1.51 – 1.41 (m, 1H), 1.21 (d, $J = 6.2$ Hz, 3H), 1.03 (s, 3H), 1.01 (s, 3H), 0.91 (s, 9H), 0.09 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 113.4, 88.1, 74.2, 73.9, 72.1, 46.4, 37.5, 36.9, 31.9, 25.8, 23.9, 21.1, 20.0, 17.8, -4.3, -4.8; For Mixture 21a and 21b, IR (Neat): 3449, 2955, 2927, 2856, 1462, 1361, 1336, 1252, 1134, 1052; HRMS (ESI$^+$): calcd. for C$_{18}$H$_{36}$O$_4$SiNa 367.2280, found 367.2280.

To a magnetically stirred solution of alcohol (20a : 20b = 9:1) (10mg, 0.043 mmol) and imidazole (10 mg, 0.14 mmol) in dry CH$_2$Cl$_2$ (1.2 mL), TBDPSCl (17 µL, 0.065 mmol) was added at room temperature. After 12 h, the reaction was quenched with NaCHO$_3$ (3 mL), extracted with 10 mL of CH$_2$Cl$_2$, dried over MgSO$_4$, and concentrated under reduced pressure. The crude oil was purified using silica gel flash chromatography (5 to 15 % EtOAc in hexane) to afford 22a and 22b (17 mg, 83 %).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.73 – 7.65 (m, 1H), 7.46 – 7.33 (m, 2H), 4.31 – 4.23 (m, 1H), 4.21 – 4.09 (m, 1H), 3.86 (d, $J = 3.1$ Hz, 1H), 3.58 (d, $J = 9.4$ Hz, 1H), 3.37 (d, $J = 9.5$ Hz, 1H), 3.11 (d, $J = 11.0$ Hz, 1H), 2.17 (dd, $J = 13.3, 4.3$ Hz, 1H), 2.12 – 1.89 (m, 1H), 1.79 – 1.64 (m, 1H), 1.26 (d, $J = 6.1$ Hz, 1H), 1.12 (s, 1H), 1.04 (s, 2H), 1.02 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 135.7, 135.6, 133.9, 133.8, 129.5, 129.4, 127.6, 127.5, 113.9, 86.5, 76.6, 73.7, 70.9, 44.2, 38.6, 36.6, 38.6, 32.6, 28.6, 23.1, 21.2, 20.5, 19.4; IR (Neat): 3404, 3006, 2989,
2859, 2707, 2318, 1473, 1428, 1391, 1361; HRMS (ESI\(^+\)): calcd. for C\(_{28}H_{40}O_4SiNa\) 491.2593, found 491.2589.

\[
\begin{align*}
\text{HO} & \quad \text{TBDPS} \\
\text{OTBDPS} & \quad 22b
\end{align*}
\]
\(\text{\(^1\)H NMR (400 MHz, CDCl}_3\) \& 7.73 – 7.67 (m, 1H), 7.49 – 7.38 (m, 2H), 4.52 – 4.47 (m, 1H), 4.43 – 4.36 (m, 1H), 4.22 – 4.09 (m, 1H), 3.73 (d, J = 10.2 Hz, 1H), 3.66 (d, J = 2.7 Hz, 1H), 3.24 (d, J = 10.2 Hz, 1H), 2.41 (dd, J = 14.1, 5.3 Hz, 1H), 2.26 – 2.09 (m, 1H), 1.53 – 1.42 (m, 1H), 1.23 (d, J = 6.1 Hz, 1H), 1.07 (s, 2H), 1.00 (d, J = 7.5 Hz, 2H); \(^{13}\)C NMR (100 MHz, CDCl}_3\) \& 137.8, 135.7, 132.4, 132.27, 120.0, 129.9, 127.8, 127.7, 113.8, 87.9, 74.0, 72.4, 68.7, 46.4, 38.0, 37.3, 32.3, 26.8, 24.0, 23.0, 12.0, 19.1; IR (Neat): 3404, 3006, 2989, 2859, 2707, 2318, 1473, 1428, 1391, 1361; HRMS (ESI\(^+\)): calcd. for C\(_{28}H_{40}O_4SiNa\) 491.2593, found 491.2589.

\[
\begin{align*}
\text{TBSO} & \quad \text{OTBDPS} \\
\text{OH} & \quad \text{TBDPS} \quad \text{Imid, CH}_2\text{Cl}_2, \text{12 h} \\
(21a : 21b) & \quad \text{1:9}
\end{align*}
\]
\(\text{\(^1\)H NMR (400 MHz, CDCl}_3\) \& 7.70 – 7.64 (m, 4H), 7.60 – 7.55 [Minor] (m, 4H), 7.44 – 7.33 (m, 2H), 4.45 (ddd, J = 6.2, 4.0, 2.5 Hz, 1H), 4.18 (dd, J = 12.6, 6.3 Hz, 1H), 3.94 (d, J = 3.9 Hz, 1H), 3.57 (d, J = 9.3 Hz, 1H), 3.53 [Minor] (d, J = 9.5 Hz, 1H), 3.37 [Minor] (d, J = 9.4 Hz, 1H), 3.32 (d, J = 9.3 Hz, 1H), 2.37 (dd, J = 13.7, 5.6 Hz, 1H), 2.23 – 1.87 (m, 1H), 1.20 (d, J = 6.2 Hz, 3H), 1.06 (s, 3H), 1.04 (s, 9H), 1.01 (s, 3H), 0.97 [Minor] (s, 1H), 0.96 [Minor] (s, 1H), 0.86 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl}_3\) \& 135.76, 135.69, 134.17,

To a magnetically stirred solution of alcohol (21a : 21b = 9:1) (4 mg, 0.011 mmol) and imidazole (8 mg, 0.1 mmol) in dry CH\(_2\)Cl\(_2\) (1 mL), TBDPSCI (15 µL, 0.05 mmol) was added at room temperature. After 12 h, the reaction was concentrated under reduced pressure. The crude oil was purified using silica gel flash chromatography (1 % EtOAc in hexane) to afford mixture of 23a and 23b (1:9) (5 mg, 78 %).
134.01, 129.33, 127.48, 113.17, 83.46, 77.19, 74.07, 73.69, 71.11, 46.95, 38.38, 36.80, 34.67, 32.08, 31.61, 29.68, 29.06, 26.83, 25.86, 25.28, 22.69, 21.12, 20.93, 20.68, 20.25, 19.42, 17.78, 14.13, 11.46, -4.25, -4.87; HRMS (ESI\(^+\)): calcd. for C\(_{34}\)H\(_{54}\)O\(_4\)Si\(_2\)Na 605.34583, found 605.34676.

General procedure for ZnCl\(_2\) isomerization

Substrate I or II (0.026 mmol) and ZnCl\(_2\) (4 mg, 1.1 mmol) were mixed with dry CH\(_2\)Cl\(_2\) (1 mL). After 12 h of stirring at room temperature, the reaction mixture was quenched with saturated solution of EDTA (0.1 mL) and saturated NaHCO\(_3\) (1 mL). The reaction mixture was extracted with CH\(_2\)Cl\(_2\) (3 mL) and dried over MgSO\(_4\). The reaction mixture was concentrated under reduced pressure and submitted to NMR analysis.
The following methyl substituted 5,5–spiroketalts illustrate the correlation between the $^1\text{H}$ NMR chemical shift of the methyl group and the stereochemistry of the spiroketal center. This well-established correlation, cited in reference 9 of the main text, was used to assign spiroketal stereochemistry in Table 6.

**Methyl group trans to oxygen substituent**


**Methyl group cis to oxygen substituent**


NMR study by screening wide range of spiroketalts


**Cephalosporolide E enantiomer**

Stereochemistry was confirmed by X-ray
MCPBA (75 %, 30 g) was dissolved in CH\textsubscript{2}Cl\textsubscript{2} (200 mL). After 30 min of stirring at room temperature, 1-Nonene (10 mL, 57.8 mmol) was added at 0 °C. The solution was warmed to room temperature over 6 h. The reaction mixture was cooled back to 0 °C, followed by quick filtration. The solution mixture was concentrated under reduced pressure, followed by bulb to bulb distillation at 50 °C at 0.4 mmHg to afford 36 (7.5 g, 91 %).

(R,R)-N,N-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (136 mg, 0.2 mmol) was charged to a 25 mL round bottomed flask. 1.2 mL of PhCH\textsubscript{3} and 24 µmL of acetic acid were added. After 30 min, the resulting brown solution was concentrated in vacuum to give a brown residue. Neat 36 (3.2 g, 0.022 mmol) with 7 mL of anhydrous Et\textsubscript{2}O were added to the round bottom flask at 0 °C. Water (0.2 mL, 0.011 mmol) was added dropwise. After 3 days of stirring at room temperature, the reaction solution was concentrated under reduced pressure, followed by bulb to bulb distillation to get 36a (1.2 g, 37%) in match with reported data.\textsuperscript{117}

To a clear solution of alkyne 32b (132 mg, 0.32 mmol) in THF (6 mL) stirring at -78 °C under a nitrogen atmosphere was added n-BuLi (2 M in hexanes, 1.5 equiv). The solution immediately turned yellow, and after 1h, freshly distilled neat BF\textsubscript{3}•Et\textsubscript{2}O (48 µL, 0.38 mmol) was added. After 6 minutes, dry and neat epoxy 36 (54 mg, 0.38 mmol) was added. The yellow solution stirred at -78 °C to 0 °C over 6 hours. The reaction was quenched with H\textsubscript{2}O (5 mL), and extracted with 10 mL of EtOAc, the aqueous layer mixed with saturated NH\textsubscript{4}Cl (5 mL) and extracted with 10 mL of EtOAc. The combined organic layers was washed with 10 mL of brine solution, dried under MgSO\textsubscript{4}, concentrated under reduced pressure to afford crude oil which was purified over silica gel (20 % EtOAc in hexane) to produce yellowish oil 37 (159 mg, 91 %, > 95 de. The minor diastereoisomer was not detected by NMR whereas addition of 32b to 36 gave 37 as a 1:1 mixture of diastereoisomers.

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\(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.44 (m, 1H), 7.43 (m, 1H), 6.89 (m, 1H), 6.88 (m, 1H), 5.41 (s, 1H), 3.97 (dt, \(J = 4.5, 7.0\) Hz, 1H), 3.80 (s, 3H), 3.72 – 3.66 (m, 1H), 3.64 (d, \(J = 4.3\) Hz, 1H), 3.58 (d, \(J = 11.0\) Hz, 1H), 3.55 (d, \(J = 11.1\) Hz, 1H), 2.69 – 2.63 (m, 1H), 2.43 – 2.34 (m, 2H), 2.31 – 2.25 (m, 1H), 2.02 (d, \(J = 4.3\) Hz, 1H), 0.91 – 0.84 (m, 16H), 0.05 (s, 3H), -0.03 (s, 3H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 159.9, 131.3, 127.7, 113.4, 102.4, 85.3, 80.1, 80.0, 78.4, 71.3, 70.1, 55.2, 36.3, 32.7, 31.8, 29.6, 29.2, 27.8, 25.9, 25.7, 25.2, 22.6, 22.1, 20.1, 18.1, 14.0, -4.1, -4.3; IR (3443, 2927, 2855, 1616, 1590, 1519, 1464, 1394, 1302; HRMS (ESI\(^+\)): calcd. for C\(_{32}\)H\(_{54}\)O\(_5\)SiNa 569.3638, found 569.3631.

AuCl (9 mg, 0.03 mmol) was added to a premixed 37 (50 mg, 0.091 mmol) and MeOH (5 mL) at room temperature, black color instantly appeared. After 4 h, the reaction mixture was filtered, mixed with 100 mg of silica gel, and concentrated under reduced pressure. The silica gel admixed with the crude reaction mixture was transferred into silica gel column (15% EtOAc in hexane) to afford pure product 39a and 39b in ratio (39a : 39b = 1:1) (23 mg, 80 %). (Different ratios (39a : 39b) were observed in different experiments. The ratio 39a / 39b decreases over time, indicating that 39b is thermodynamically preferred).

Mixture of diols 39a and 39b (24 : 76) (7 mg, 0.022 mmol), ZnCl\(_2\) (16 mg, 0.12 mmol), and acid scavenger MgO (20 mg, 0.5 mmol) were mixed with dry CH\(_2\)Cl\(_2\) (2 mL). After 8 h, the reaction mixture was filtered and quenched with saturated solution of EDTA (1 mL). The reaction mixture was extracted with CH\(_2\)Cl\(_2\) (10 mL), washed with NaHCO\(_3\) (5 mL), washed with brine (3 mL), and dried over MgSO\(_4\). The reaction mixture was concentrated under reduced
pressure and purified over silica gel (deactivated with Et$_3$N) to afford 39a (6 mg, 86 % yield, > 95% dr).

$^1$H NMR (600 MHz, CDCl$_3$) δ 4.26 (m, 1H), 3.98 (ddd, $J = 13.1, 9.4, 6.1$ Hz, 1H), 3.59 (d, $J = 3.1$ Hz, 1H), 3.51 (d, $J = 10.9$ Hz, 1H), 3.46 (d, $J = 10.9$ Hz, 1H), 2.15 (dd, $J = 13.4, 4.3$ Hz, 1H), 2.10 – 1.91 (m, 4H), 1.75 – 1.66 (m, 2H), 1.55 – 1.47 (m, 1H), 1.40 – 1.20 (m, 13H), 1.09 (s, 3H), 1.02 (s, 3H), 0.87 (t, $J = 7.0$ Hz, 4H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 114.1, 91.0, 81.3, 73.3, 71.1, 43.9, 38.0, 37.3, 36.1, 31.8, 30.6, 29.5, 29.2, 26.3, 23.4, 22.6, 20.9, 14.1; IR (Neat): 3280, 2926, 2857, 1461, 1334, 1108; HRMS (ESI$^+$): calcd. for C$_{18}$H$_{34}$O$_4$Na 337.2354, found 337.2354.

Mixture of 39a and 39b (39a peaks has been omitted): $^1$H NMR (400 MHz, CDCl$_3$) δ 4.39 – 4.33 (m, 1H), 4.07 – 3.97 (m, 1H), 3.67 (d, $J = 10.7$ Hz, 1H), 3.65 (d, $J = 2.9$ Hz, 1H), 2.44 (dd, $J = 14.3, 5.5$ Hz, 1H), 2.21 – 1.98 (m, 5H), 1.54 – 1.46 (m, 1H), 1.36 – 1.23 (m, 12H), 1.07 (s, 3H), 1.05 (s, 3H), 0.89 (t, $J = 6.8$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 113.2, 87.9, 78.3, 72.6, 69.7, 69.0, 46.4, 37.5, 36.9, 35.6, 31.8, 30.2, 29.7, 29.3, 25.8, 24.2, 22.7, 21.8, 14.1. IR (Neat): 3280, 2926, 2857, 1461, 1334, 1108; HRMS (ESI$^+$): calcd. for C$_{18}$H$_{34}$O$_4$Na 337.2354, found 337.2354.

Diol 39a (6 mg, 0.019 mmol) and PhI(OAc)$_2$ (30 mg, 0.093 mmol) were dissolved in CH$_2$Cl$_2$ (2 mL) followed by addition of TEMPO (2 mg, 0.013 mmol). After 18 h, the mixture was concentrated, followed by column chromatograph (10 % EtOAc in hexane) which afforded lactone 1 (4.8 mg, 81 %). $[\alpha] = -5$ (c = 0.7, MeOH) (reported value for cephalosporolide H: $[\alpha]=$
+57.6; $^1$H NMR (400 MHz, CDCl$_3$) δ 5.07 (t, $J = 4.9$ Hz, 1H), 4.29 (d, $J = 4.7$ Hz, 1H), 4.03 – 3.92 (m, 1H), 2.44 (d, $J = 14.1$ Hz, 1H), 2.15 – 1.95 (m, 4H), 1.75 – 1.59 (m, 2H), 1.29 (s, 3H), 1.25 (br m, 11H), 1.21 (s, 3H), 0.87 (t, $J = 6.9$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 180.6, 115.1, 87.1, 81.9, 79.8, 44.5, 41.7, 37.4, 36.3, 31.8, 30.9, 29.6, 29.2, 26.1, 24.9, 22.7, 18.3, 14.1; IR (Neat): 2998, 2927, 2856, 1774, 1457, 1439; HRMS (ESI$^+$): calcd. for C$_{18}$H$_{30}$O$_4$Na 333.2042, found 333.2036.

A solution of 37 (65 mg, 0.011 mmol) and PdCl$_2$(CH$_3$CN)$_2$ (4 mg, 0.015 mmol) in CH$_3$CN (6.5 mL) was stirred at room temperature for 1.5 h. The reaction mixture was concentrated and the crude was filtered over silica gel using 20 % EtOAc in hexane. After evaporation under reduced pressure, the resulted oil was subjected to bulb to bulb distillation under high vacuum (0.4 mmHg) to afford anisaldehyde at 70 °C and 38 (dr = 9:1) (21 mg, 42%) at 170 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 4.43 (ddd, $J = 5.6$, 3.7, 2.2 Hz, 1H)(major), 4.38 – 4.32 (m, 1H) (minor), 4.01 (p, $J = 6.5$ Hz, 1H), 3.70 (d, $J = 3.6$ Hz, 1H) (major), 3.59 (d, $J = 8.9$ Hz, 1H), 3.48 (d, $J = 3.9$ Hz, 1H) (minor), 3.40 (d, $J = 10.7$ Hz, 1H), 3.22 (m, 1H), 2.36 (dd, $J = 13.9$, 5.5 Hz, 1H), 2.19 – 2.05 (m, 2H), 2.04 – 1.91 (m, 2H), 1.37 – 1.20 (m, 16H), 1.05 (s, 1H) (minor), 1.03 (s, 5H), 1.01 (s, 5H), 0.99 (s, 1H) (minor), 0.91 (m, 12H), 0.09 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 113.2, 113.1, 89.9, 88.0, 80.6, 78.3, 74.0, 73.2, 72.1, 72.0, 46.2, 44.8, 38.0, 37.8, 37.6, 37.5, 36.6, 35.7, 31.8, 31.8, 31.6, 30.7, 29.9, 29.9, 29.7, 29.4, 29.2, 26.4, 25.9, 25.9, 25.7, 24.8, 23.8, 22.7, 20.6, 20.0, 18.0, 17.9, 14.1, 14.1, -4.3, -4.47, -4.55, -4.78; IR (Neat): 3460, 2928, 2857, 1463, 1362, 1334, 1251, 1131, 1108, 1047, 1021; HRMS (ESI$^+$): calcd. for C$_{24}$H$_{48}$O$_4$SiNa 451.3219, found 451.3209.
38 (de = 80%) (15 mg, 0.035 mmol) was dissolved in THF (2 mL), followed by addition of TBAF (1 M in THF, 0.1 mL). After 3 h, the reaction was quenched with H2O (2 mL) and extracted with Et2O (5 mL). The organic layer was dried over MgSO4, concentrated under reduced pressure, and purified over silica gel (5% EtOAc in hexane) to afford 39b (dr 1 : 9) (8 mg, 73%).

Diols 39b (dr 9: 1) (6 mg, 0.019 mmol) and PhI(OAc)2 (30 mg, 0.093 mmol) were dissolved in CH2Cl2 (1.5 mL) followed by addition of TEMPO (1 mg, 0.012 mmol). After 6 h, the mixture was concentrated under reduced pressure, followed by column chromatograph (10 % EtOAc in hexane) which afforded lactone 1a (4 mg, 68 %). [α]25D = +65 (c = 0.7, MeOH) (reported value for cephalosporolide H: [α]25D = +57.6); 1H NMR (400 MHz, CDCl3) δ 5.03 (ddd, J = 6.4, 3.8, 1.6 Hz, 1H), 4.29 (d, J = 3.8 Hz, 1H), 4.09 – 3.98 (m, 1H), 2.52 (ddd, J = 15.0, 6.4 Hz, 1H), 2.36 (dd, J = 15.0, 1.5 Hz, 1H), 2.18 – 1.97 (m, 3H), 1.55 – 1.47 (m, 1H), 1.27 (s, 12H), 1.22 (s, 3H), 0.88 (t, J = 6.9 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 181.0, 115.5, 85.2, 80.6, 79.0, 44.5, 42.4, 35.7, 35.5, 31.8, 30.1, 29.6, 29.2, 25.8, 23.1, 22.7, 18.1, 14.1; IR (Neat): 2926, 2856, 1778, 1462, 1390; HRMS (ESI+): calcd. for C18H30O4Na 333.2042, found 333.2033.
To a clear solution of alkyne 32b (565 mg, 1.4 mmol) in THF (26 mL) stirring at -78 °C under a nitrogen atmosphere was added n-BuLi (2.5 M in hexanes, 1.68 equiv). The solution immediately turned yellow, and after 1h minutes, freshly distilled neat BF$_3$•Et$_2$O (0.19 mL, 1.54 mmol) was added. After 6 minutes, dry and neat epoxy 19b (200 mg, 1.4 mmol) was added. The yellow solution stirred at -78 °C to 0 °C over 6 hours. The reaction was quenched with H$_2$O (10 mL), and extracted with 40 mL of EtOAc, the aqueous layer mixed with saturated NH$_4$Cl (20 mL) and extracted with 10 mL of EtOAc. The combined organic layers was washed with 20 mL of brine solution, dried under MgSO$_4$, concentrated under reduced pressure to afford crude oil which was purified over silica gel (20 % EtOAc in hexane) to produce yellowish oil 40 (596 mg, 78 %).

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.44 (d, $J = 8.6$ Hz, 2H), 6.88 (d, $J = 8.6$ Hz, 2H), 5.41 (s, 1H), 4.00 – 3.94 (m, 1H), 3.81 (s, 3H), 3.73 – 3.65 (m, 1H), 3.64 (d, $J = 4.1$ Hz, 1H), 3.57 (q, $J = 11.0$ Hz, 2H), 2.66 (dd, $J = 16.3, 7.2$ Hz, 1H), 2.44 – 2.22 (m, 3H), 1.99 – 1.85 (m, 1H), 1.52 (dd, $J = 14.1, 6.7$ Hz, 1H), 1.48 – 1.20 (m, 15H), 0.95 – 0.79 (m, 16H), 0.05 (s, 3H), -0.02 (s, 3H). $^{13}$C NMR (150 MHz, CDCl$_3$) δ 159.9, 131.4, 127.7, 113.5, 102.4, 85.3, 80.2, 80.1, 78.3, 71.3, 70.2, 55.3, 36.3, 32.8, 31.8, 31.6, 29.7, 29.3, 27.8, 25.9, 25.7, 25.3, 22.6, 22.1, 20.2, 18.1, 14.1, -4.1, -4.2. HRMS (ESI$^+$): calcd. for C$_{32}$H$_{54}$O$_5$SiNa 569.3638, found 569.3616.

AuCl (9 mg, 0.03 mmol) was added to a premixed 40 (50 mg, 0.091 mmol) and MeOH (10 mL) at room temperature, black color instantly appeared. After 6.5 h, the reaction mixture was quenched with Et$_3$N (0.2 mL). After solvent evaporation under reduced pressure, the crude
mixture was transferred into silica gel column (15% EtOAc in hexane) to afford pure product 41b (17 mg) and 41a (8 mg) (25 mg, 89%).

\[
\text{41a}
\]

\[
\text{41b}
\]

\[\begin{align*}
^1H \text{ NMR} (600 \text{ MHz, CDCl}_3) & \delta 4.31 - 4.24 (\text{m, 1H}), 4.18 - 4.10 (\text{m, 1H}), 3.67 (\text{d, } J = 3.3 \text{ Hz, 1H}), 3.50 (\text{d, } J = 10.9 \text{ Hz, 1H}), 3.47 (\text{d, } J = 10.9 \text{ Hz, 1H}), 2.17 (\text{dd, } J = 13.3, 4.3 \text{ Hz, 1H}), 2.14 - 1.97 (\text{m, 4H}), 1.55 - 1.22 (\text{m, 13H}), 1.08 (\text{s, 3H}), 1.03 (\text{s, 3H}), 0.88 (\text{t, } J = 7.1 \text{ Hz, 3H}). \\
^13C \text{ NMR} (150 \text{ MHz, CDCl}_3) & \delta 114.2, 90.8, 79.0, 73.7, 71.3, 43.9, 38.1, 35.6, 34.3, 31.8, 29.6, 29.6, 29.2, 26.0, 23.0, 22.6, 21.0, 14.1.
\end{align*}\]

\[\begin{align*}
^1H \text{ NMR} (400 \text{ MHz, CDCl}_3) & \delta 4.35 (\text{dd, } J = 4.4, 2.9 \text{ Hz, 1H}), 4.10 - 3.97 (\text{m, 1H}), 3.69 - 3.58 (\text{m, 2H}), 3.43 (\text{d, } J = 10.6 \text{ Hz, 1H}), 2.99 (\text{br s, 2H}), 2.44 (\text{dd, } J = 14.4, 5.6 \text{ Hz, 1H}), 2.24 - 1.87 (\text{m, 4H}), 1.85 - 1.70 (\text{m, 1H}), 1.26 (\text{s, 12H}), 1.05 (\text{s, 3H}), 1.04 (\text{s, 3H}), 0.87 (\text{t, } J = 6.8 \text{ Hz, 3H}). \\
^13C \text{ NMR} (100 \text{ MHz, CDCl}_3) & \delta 112.8, 87.4, 79.9, 72.6, 69.4, 45.9, 37.8, 37.7, 37.4, 31.8, 30.8, 29.6, 29.3, 26.0, 24.1, 24.1, 22.6, 21.8, 14.1.\text{Mixture of both isomers (41a and 41b), HRMS (ESI+): calcd. for C}_{18}\text{H}_{34}\text{O}_4\text{Na 337.2354, found 337.2359.}
\end{align*}\]

Diol 41b (16 mg, 0.05 mmol) and Phl(OAc)\(_2\) (80 mg, 0.25 mmol) were dissolved in CH\(_2\)Cl\(_2\) (5 mL) followed by addition of TEMPO (5.3 mg, 0.034 mmol). After 12 h, the mixture was concentrated, followed by column chromatograph (10 % EtOAc in hexane), which afforded lactone 1b (15 mg, 97%). \([\alpha]_D^{25} = +41.2 \text{ (c = 0.71, MeOH)} \) (reported value for cephalosporolide H: +57.6); \(^1H \text{ NMR} (400 \text{ MHz, CDCl}_3) \delta 5.02 (\text{ddd, } J = 6.3, 3.8, 1.6 \text{ Hz, 1H}), 4.30 (\text{d, } J = 3.8 \text{ Hz, 1H}), 3.71 - 3.45 (\text{m, 2H}), 1.68 - 1.36 (\text{m, 12H}), 1.09 (\text{s, 3H}), 1.05 (\text{s, 3H}), 0.87 (\text{t, } J = 6.8 \text{ Hz, 3H}). \]

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Hz, 1H), 4.07 – 3.95 (m, 1H), 2.49 (dd, \(J = 15.0, 6.3\) Hz, 1H), 2.33 (dd, \(J = 15.0, 1.5\) Hz, 1H), 2.11 – 1.87 (m, 4H), 1.79 – 1.67 (m, 1H), 1.28 (br m, 12H), 1.26 (s, 3H), 1.22 (s, 3H), 0.88 (t, \(J = 6.9\) Hz, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 181.0, 115.2, 85.0, 80.9, 80.4, 44.4, 41.8, 37.2, 37.0, 31.8, 30.6, 29.6, 29.2, 26.0, 23.1, 22.6, 18.1, 14.1\). HRMS (ESI\(^+\)): calcd. for C\(_{18}\)H\(_{30}\)O\(_4\)Na 333.2042, found 333.2021.

Diol 41a (6 mg, 0.019 mmol) and PhI(OAc)\(_2\) (30 mg, 0.093 mmol) were dissolved in CH\(_2\)Cl\(_2\) (2 mL) followed by addition of TEMPO (2 mg, 0.013 mmol). After 24 h, the mixture was concentrated, followed by column chromatograph (10 % EtOAc in hexane) which afforded lactone 1c (5 mg, 84 %). \([\alpha] = -7.65\) (c = 0.69, MeOH) (reported value for cephalosporolide H: + 57.6); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 5.10\) (t, \(J = 5.2\) Hz, 1H), 4.35 (d, \(J = 5.1\) Hz, 1H), 4.16 – 3.90 (m, 1H), 2.45 (d, \(J = 14.1\) Hz, 1H), 2.18 – 1.96 (m, 4H), 1.54 – 1.25 (m, 13H), 1.25 (s, 3H), 1.22 (s, 3H), 0.87 (t, \(J = 6.9\) Hz, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 180.8, 114.9, 86.7, 79.9, 79.6, 44.3, 41.9, 35.3, 34.5, 31.9, 29.9, 29.6, 29.2, 25.9, 25.4, 22.7, 18.4, 14.1\). HRMS (CI\(^+\)): calcd. for C\(_{18}\)H\(_{31}\)O\(_3\) 311.2222, found 311.2217.

Diol 41b (7 mg, 0.022 mmol), ZnCl\(_2\) (16 mg, 0.12 mmol), and acid scavenger MgO (100 mg, 0.5 mmol) were mixed with dry CH\(_2\)Cl\(_2\) (2 mL). After 8 h, the reaction mixture was filtered and quenched with saturated solution of EDTA (1 mL). The reaction mixture was extracted with CH\(_2\)Cl\(_2\) (10 mL), washed with NaHCO\(_3\) (5 mL), washed with brine (3 mL), and dried over MgSO\(_4\). The reaction mixture was concentrated under reduced pressure and purified over silica gel (deactivated with Et\(_3\)N) to afford 41a (5 mg, 71 % yield, dr 15 : 1).
Alcohol 44 (1.63 g, 7 mmol) was mixed with NaH (60% in oil, 500 mg) and 50 mL of THF. After 30 min of stirring at room temperature, PMB-Cl (1.92 mL, 14 mmol) and catalytic amount of TBAI (50 mg) was added. The mixture was refluxed for 12 h. The reaction was quenched with 10 ml of H$_2$O at 0 °C, and extracted with Et$_2$O (100 mL). After solvent evaporation, the reaction crude was purified using bulb to bulb distillation by distilling off the impurities 140 °C at 0.4 mmHg. PMB ether 45 was resulted as yellowish oil (1.58 g, 64%).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.30 – 7.20 (m, 2H), 6.92 – 6.78 (m, 2H), 5.48 (apparent t, $J$ = 3.7 Hz, 2H), 4.44 (s, 2H), 3.80 (s, 3H), 3.61 (t, $J$ = 6.9 Hz, 2H), 3.45 (t, $J$ = 7.0 Hz, 2H), 2.31 (dd, $J$ = 11.1, 6.8 Hz, 2H), 2.22 (dd, $J$ = 11.3, 6.6 Hz, 2H), 0.89 (s, 9H), 0.04 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 159.1, 130.5, 129.2, 128.6, 128.4, 113.7, 113.7, 72.4, 69.7, 63.1, 55.1, 36.3, 33.1, 25.9, 18.3, -5.3. HRMS (Cl$^+$): calcd. for C$_{20}$H$_{35}$O$_3$Si 351.2356, found 351.2352.

A mixture of AD-mix α (3 g), CH$_3$SO$_2$NH$_2$ (285 mg, 3 mmol), t-BuOH (10 mL), and H$_2$O (10 mL) was stirred for 15 min at 0 °C, and then alkene 45 (700 mg, 2.0 mmol) was added. After 1 days of stirring at 0 °C, another 1 g of AD-mix α was added. After 3.5 days as an overall time, Na$_2$SO$_3$ (4 g) and EtOAc (50 mL) were added to the reaction mixture, which was stirred for 30 min at room temperature. The organic layer was extracted and washed with NH$_4$Cl and brine solution. Solvent evaporation under reduced pressure afforded crude oil. The oil was purified with silica gel using 20% EtOAc in hexane to produce yellow oil 46 (562 mg, 73%).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.29 – 7.23 (m, 2H), 6.90 – 6.84 (m, 2H), 5.60 – 5.29 (m, 2H), 4.44 (s, 2H), 3.80 (s, 3H), 3.61 (t, $J$ = 6.9 Hz, 2H), 3.45 (t, $J$ = 7.0 Hz, 2H), 2.36 – 2.26 (m, 2H), 2.25 – 2.14 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 159.1, 130.5, 129.3, 129.2, 128.6, 128.4, 113.7, 113.7, 72.4, 69.7, 63.1, 55.1, 36.3, 33.1, 25.9, 18.3, -5.3. HRMS (Cl$^+$): calcd. for C$_{20}$H$_{37}$O$_3$Si 385.2410, found 385.2409.
A solution of diol 46 (400 mg, 1.04 mmol) in CH$_2$Cl$_2$ (26 mL) and MS (1g) was stirred for 1 h. DDQ (450 mg, 1.47 mmol) was added to reaction the mixture at 0 °C. After 2 h of stirring from 0 °C to room temperature, the reaction mixture was quenched with 1 M Na$_2$S$_2$O$_3$ solution and extracted with diethyl ether (100 mL). The organic layer was washed with saturated NaHCO$_3$ solution and brine, dried with anhydrous sodium sulfate and concentrated in vacuo to provide crude oil, which purified over silica gel. PMP acetal 47 (254 mg) was isolated in 63 % yield.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.49 – 7.31 (m, 2H), 7.01 – 6.74 (m, 2H), 5.49 (s, 1H), 4.29 (ddd, $J$ = 11.3, 5.0, 1.2 Hz, 1H), 3.99 – 3.90 (m, 1H), 3.90 – 3.81 (m, 2H), 3.80 (s, 3H), 2.97 (d, $J$ = 2.8 Hz, 1H), 2.00 – 1.85 (m, 1H), 1.82 – 1.50 (m, 3H), 0.90 (s, 9H), 0.07 (s, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 159.95, 131.04, 127.40, 113.57, 113.55, 101.17, 79.92, 72.06, 66.69, 60.74, 55.28, 34.34, 26.67, 25.90, 18.22, -5.44, -5.46. HRMS (Cl$^+$): calcd. for C$_{20}$H$_{35}$O$_5$Si 383.2254, found 383.2246.

To a magnetically stirred solution of alcohol 47 (230 mg, 0.6 mmol) and imidazole (204 mg, 3.0 mmol) in dry DMF (3 mL), TBSCl (286 mg, 1.88 mmol) was added at room temperature. After 24 h, the reaction was quenched with H$_2$O (5 mL) and extracted with Et$_2$O (30 mL). The organic layer was washed with saturated solution of NH$_4$Cl, dried over MgSO$_4$, and concentrated under reduced pressure. The crude oil was purified using silica gel flash chromatography (1 % EtOAc in hexane) to afford silyl ether 48 (245 mg, 82%).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.43 – 7.37 (m, 2H), 6.89 – 6.84 (m, 2H), 5.42 (s, 1H), 4.31 – 4.22 (m, 1H), 3.97 – 3.86 (m, 2H), 3.80 (s, 3H), 3.85 – 3.64 (m, 2H), 1.94 – 1.75 (m, 2H), 1.69 – 1.58 (m, 1H), 1.57 – 1.49 (m, 1H), 0.90 (s, 9H), 0.85 (s, 9H), 0.05 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), -0.02 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 159.83, 131.29, 127.59, 113.40, 101.45,
Compound 48 (1.35 g, 2.5 mmol) was dissolved in a mixture of dry THF (13 mL). The mixture was then treated with a solution of the HF-pyridine complex (0.4 mL, ca. 12.5 mmol of HF). The resulting solution was stirred at room temperature for 3 h. The reaction mixture was diluted with EtOAc (10 mL). The mixture was slowly quenched at 0 °C with saturated NaHCO₃. After extracted of EtOAc layer, the aqueous layer was extracted with another 10 mL of EtOAc. The combined organic layers was subsequently washed with saturated NH₄Cl, NaHCO₃, and dried over MgSO₄. After evaporation under reduced pressure, the crude oil was purified with silica gel (elution 20 % EtOAc in hexane) to yield alcohol 49 (150 mg, ≥ 99%). ¹H NMR (400 MHz, CDCl₃) δ 7.39 (apparent d, J = 8.7 Hz, 2H), 6.95 – 6.79 (m, 2H), 5.44 (s, 1H), 4.29 (dd, J = 11.4, 4.0 Hz, 1H), 4.03 – 3.85 (m, 3H), 3.80 (s, 3H), 3.84 – 3.71 (m, 2H), 2.26 (t, J = 5.4 Hz, 1H), 2.02 – 1.82 (m, 2H), 1.79 – 1.67 (m, 1H), 1.52 (dd, J = 13.2, 1.4 Hz, 1H), 0.87 (s, 9H), 0.07 (s, 3H), 0.01 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 159.9, 130.9, 127.5, 113.5, 101.7, 80.0, 72.5, 66.9, 59.9, 55.2, 34.5, 25.8, 25.6, 18.0, -4.4, -5.0. HRMS (Cl⁺): calcd. for C₂₀H₄₅O₃Si 383.2254, found 383.2265.

DMP (0.21 mmol, 90 mg) was added to solution of alcohol 49 (40 mg, 0.1 mmol), excess of NaHCO₃ (200 mg), and 2 mL of CH₂Cl₂. The reaction mixture was allowed to warm up over 1 h. The mixture was filter over silica gel to afford aldehyde 50 (39 mg, > 98%). ¹H NMR (400 MHz, CDCl₃) δ 9.80 (dd, J = 2.9, 1.6 Hz, 1H), 7.42 – 7.32 (m, 2H), 6.96 – 6.80 (m, 2H), 5.45 (s, 1H), 4.38 (dt, J = 4.8, 7.4 Hz, 1H), 4.29 (dd, J = 11.4, 3.9 Hz, 1H), 3.98 – 3.85 (m, 2H), 3.79 (s, 3H), 2.75 (ddd, J = 16.0, 4.5, 1.6 Hz, 1H), 2.56 (ddd, J = 16.0, 7.5, 3.0 Hz, 1H), 1.86 (ddd, J = 24.8,
12.3, 5.0 Hz, 1H), 1.52 (dd, \( J = 13.2, 1.4 \) Hz, 1H), 0.94 – 0.79 (m, 9H), 0.06 (s, 6H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 201.3, 159.9, 130.8, 127.4, 113.5, 101.4, 79.1, 69.1, 66.8, 55.2, 46.6, 25.7, 25.2, 18.0, -4.5, -5.0. HRMS (Cl\(^+\)): calcd. for C\(_{20}\)H\(_{33}\)O\(_5\)Si 381.2097, found 381.2091.

Dimethyl-1-diazo-2-oxopropylphosphonate (Ohira Bestmann) (0.26 mmol, 50 mg) was added to premixed solution of the aldehyde 50 (0.1 mmol, 40 mg) and K\(_2\)CO\(_3\) (0.43 mmol, 60 mg) in 4 mL of MeOH. After 12h of stirring at room temperature, the reaction mixture was concentrated and transferred into the column of silica gel. Elution of 1% EtOAc in hexane afforded alkyne 42 (30 mg, 80%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.40 (d, \( J = 8.7 \) Hz, 2H), 6.88 (d, \( J = 8.8 \) Hz, 2H), 5.46 (s, 1H), 4.28 (dd, \( J = 11.4, 4.0 \) Hz, 1H), 4.02 – 3.86 (m, 3H), 3.80 (s, 3H), 2.60 (ddd, \( J = 16.7, 4.4, 2.7 \) Hz, 1H), 2.34 (ddd, \( J = 16.8, 6.5, 2.7 \) Hz, 1H), 1.97 (t, \( J = 2.6 \) Hz, 1H), 1.88 (ddd, \( J = 23.5, 12.5, 5.0 \) Hz, 1H), 1.56 – 1.45 (m, 1H), 0.89 (s, 9H), 0.11 (s, 3H), 0.05 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 159.9, 131.1, 127.5, 113.5, 101.4, 81.8, 79.0, 72.5, 69.8, 66.9, 55.2, 25.8, 25.7, 22.7, 18.1, -4.6, -4.6. HRMS (Cl\(^+\)): calcd. for C\(_{21}\)H\(_{33}\)O\(_4\)Si 377.2148, found 377.2152.

To a clear solution of alkyne 42 (69 mg, 0.18 mmol) in THF (2 mL) stirring at -78 °C under a nitrogen atmosphere was added n-BuLi (1.8 M in hexanes, 2.7 equiv). The solution immediately turned yellow, and after 1h minutes, freshly distilled neat BF\(_3\)•Et\(_2\)O (62 µL, 0.5 mmol) was added. After 6 minutes, dry and neat excess of R-propylene oxide (0.1mL) was added. The yellow solution stirred at -78 °C to 0 °C over 2.5 hours. The reaction was quenched with NaHCO\(_3\) (3 mL), and extracted with 10 mL of EtOAc, the aqueous layer mixed with saturated NH\(_4\)Cl (10 mL) and extracted with 10 mL of EtOAc. The combined organic layers was washed with 10 mL of brine solution, dried under MgSO\(_4\), concentrated under reduced pressure to afford
crude oil which was purified over silica gel (15 % EtOAc in hexane) to produce colorless oil 51 (75 mg, 96 %). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.47 – 7.31 (m, 2H), 6.96 – 6.78 (m, 2H), 5.45 (s, 1H), 4.34 – 4.23 (m, 1H), 3.98 – 3.83 (m, 4H), 3.80 (s, 3H), 2.63 – 2.52 (m, 1H), 2.42 – 2.22 (m, 2H), 1.94 – 1.80 (m, 1H), 1.55 – 1.47 (m, 1H), 1.23 (d, \(J = 6.1\) Hz, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.04 (s, 3H). \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 159.9, 131.1, 127.5, 113.5, 101.4, 80.3, 79.3, 77.8, 72.8, 66.9, 66.5, 55.2, 29.5, 25.8, 23.0, 22.2, 18.1, -4.6, -4.6. HRMS (CI\(^+\)): calcd. for C\(_{24}\)H\(_{39}\)O\(_5\)Si 435.2567, found 435.2573.

AuCl (6 mg, 0.025mmol) was added to a premixed 51 (26 mg, 0.059 mmol) and MeOH (6 mL) at room temperature, black color instantly appeared. After 5 h, the reaction mixture was quenched with Et\(_3\)N (0.1 mL). After solvent evaporation under reduced pressure, the crude mixture was transferred into silica gel column (10-70% EtOAc in hexane) to afford 52a and 52b in ratio 45 : 55 (5.5 mg) and 53a and 53b in ratio 16 : 84. Both isomers admixed with diastereomers from the Sharpless dihydroxylation at C-2 and C-3.

Mixture of TBS ether isomers 53a and 53b were diluted in 0.5 mL of THF was treated with TBAF (1M, 0.05 mL). After 2 h of stirring at room temperature, the reaction mixture was concentrated and transferred into silica gel column to afford 52a and 52b (3 mg) in same ratio (8.5 mg, <71% overall yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.41 – 4.33 (m, 1H), 4.27 (dd, \(J = 12.8, 6.8\) Hz, 1H)[52b], 4.23 – 4.04 (m, 2H), 3.89 (dt, \(J = 4.9, 10.1\) Hz, 1H), 3.82 – 3.72 (m, 1H), 2.46 (dd, \(J = 14.3, 6.3\) Hz, 1H).
1H, 2.23 – 1.87 (m, 6H), 1.80 – 1.67 (m, 1H). 1.31 (d, \(J = 6.0 \text{ Hz}, 3\H)\) [52a], 1.28 (d, \(J = 6.2 \text{ Hz}, 3\H)\) [52b], 1.22 (d, \(J = 6.2 \text{ Hz}, 3\H)\) [52c], 1.20 (d, \(J = 6.2 \text{ Hz}, 3\H)\) [52d]. \(^{13}\text{C} \text{ NMR} (101 \text{ MHz, CDCl}_3) \delta 114.5, 113.7, 113.6, 83.8, 81.2, 81.0, 77.2, 76.1, 74.8, 74.3, 73.3, 72.5, 60.7, 60.5, 60.3, 45.4, 44.9, 43.8, 37.8, 34.4, 33.1, 32.6, 30.8, 23.0, 21.1, 21.0. HRMS (Cl\(^{+}\)): calcd. for C\(_{10}\)H\(_{15}\)O\(_4\) 202.1283, found 202.1285.

\(^{1}\text{H} \text{ NMR} (400 \text{ MHz, CDCl}_3) \delta 4.35 \text{ (dd, } \(J = 8.6, 5.0 \text{ Hz, 1H}), 4.32 – 4.04 (m, 2H), 3.85 – 3.72 (m, 1H), 2.63 (s, 1H), 2.33 \text{ (dd, } \(J = 13.6, 5.8 \text{ Hz, 1H}), 2.25 – 1.87 (m, 6H), 1.75 – 1.61 (m, 1H), 1.42 – 1.39 (m, 1H)[\text{Minor}], 1.32 (d, \(J = 6.2 \text{ Hz, 3H}[\text{Minor}], 1.28 (d, \(J = 6.1 \text{ Hz, 3H}], 1.20 (d, \(J = 6.2 \text{ Hz, 3H}[\text{Minor}], 1.18 (d, \(J = 6.1 \text{ Hz, 3H}[\text{Minor}], 0.89 (s, 9H), 0.05 (d, \(J = 2.6 \text{ Hz, 6H}). \(^{13}\text{C} \text{ NMR} (100 \text{ MHz, CDCl}_3) \delta 116.3, 114.0, 113.7, 81.4, 77.2, 76.1, 74.8, 73.1, 72.2, 61.6, 61.4, 45.1, 44.3, 38.3, 37.6, 32.5, 32.0, 25.7, 22.9, 14.0, -4.7, -5.0. HRMS (Cl\(^{+}\)): calcd. for C\(_{16}\)H\(_{33}\)O\(_4\)Si 317.2148, found 317.2140.

Diol 52a and 52b in 16 : 84 ratio (5 mg, mmol) and PhI(OAc)\(_2\) (30 mg, 0.093 mmol) were dissolved in CH\(_2\)Cl\(_2\) (1.5 mL) followed by addition of TEMPO (2 mg, 0.013 mmol). After 12 h, the mixture was concentrated, followed by column chromatograph (20 % EtOAc in hexane) which afforded lactone 2b (2.5 mg) (contaminated with diastereomers at C-2 and C-3) and 2a (1mg) contaminated with 2b in 71%. The spectroscopic data was in match with the reported data. \(^{1}\text{H} \text{ NMR} (400 \text{ MHz, CDCl}_3) \delta 5.09 \text{ (ddd, } \(J = 6.6, 4.4, 2.1 \text{ Hz, 1H}), 4.80 (t, \(J = 4.4 \text{ Hz, 1H}), 4.30 – 4.12 (m, 1H), 2.79 – 2.64 (m, 2H), 2.51 (dd, \(J = 14.9, 6.7 \text{ Hz, 1H}), 2.33 (dd, \(J = 14.9, 2.0 \text{ Hz,}
1H), 2.20 – 1.94 (m, 3H), 1.79 – 1.67 (m, 1H), 1.28 (d, J = 6.2 Hz, 3H). 13C NMR (100 MHz, CDCl3) δ 175.7, 115.5, 83.8, 76.9, 76.5, 42.2, 36.9, 36.0, 32.4, 22.8. HRMS (Cl+) : calcd. for C10H15O4 199.0970, found 199.0966.

Diol 52a and 52b (4 mg, 0.019 mmol), ZnCl2 (10 mg, 0.075 mmol), and acid scavenger MgO (100 mg, 0.5 mmol) were mixed with dry CH2Cl2 (1 mL). After 12 h, the reaction mixture was filtered and quenched with saturated solution of NaHCO3. The reaction mixture was extracted with EtOAc (10 mL), and dried over MgSO4. The reaction mixture was concentrated under reduced pressure to afford crude 52a (3 mg, dr > 20 : 1). The crude 52a was subjected to oxidative conditions: PhI(OAc)2 (30 mg, 0.093 mmol) and CH2Cl2 (1.5 mL) followed by addition of TEMPO (2 mg, 0.013 mmol). After 12 h, the mixture was concentrated, followed by column chromatograph (20 % EtOAc in hexane), which afforded lactone 2a (1.7 mg, <43% over 2 steps). The spectroscopic data was in match with the reported data. 1H NMR (600 MHz, CDCl3) δ 5.15 (t, J = 5.9 Hz, 1H), 4.91 – 4.86 (m, 1H), 4.23 – 4.15 (m, 1H), 2.77 – 2.69 (m, 1H), 2.66 (dd, J = 18.6, 1.6 Hz, 1H), 2.45 (d, J = 14.3 Hz, 1H), 2.16 – 2.00 (m, 5H), 1.49 – 1.40 (m, 3H), 1.20 (d, J = 6.2 Hz, 4H). 13C NMR (151 MHz, CDCl3) δ 115.1, 83.3, 77.4, 75.1, 41.8, 37.6, 34.3, 31.4, 29.7, 20.9. HRMS (Cl+) : calcd. for C10H15O4 199.0970, found 199.0966.
22b
ZnCl$_2$ treatment
REFERENCES


36 Also now commercially available: Sigma–Aldrich product number 701440.

37 Multiple attempts to prepare Grignard reagent 55 using activated magnesium turnings under standard conditions were unsuccessful. Insertion does not occur at room temperature, and it appears as though magnesium insertion into the benzylic carbon–oxygen bond occurs upon prolonged heating, based on recovery of bis-siletane from the crude reaction mixture.

\[
\begin{align*}
\text{Si} & \\
\text{Si} & \\
\text{bis-siletane} \\
\end{align*}
\]


39 Sigma–Aldrich list pricing: 523496-5g, $104.00 ($4.87/mmol); see [http://www.sigmaaldrich.com](http://www.sigmaaldrich.com)

40 Sigma–Aldrich list pricing: 187054-50g, $151.50 ($0.57/mmol); see [http://www.sigmaaldrich.com](http://www.sigmaaldrich.com)

41 Note that the Sigma–Aldrich list price of siletane 28 (411582-5g, $145.50, $3.54/mmol) is comparable to that of TBS–OTf (226149-5g, $52.60, $2.78/mmol); see [http://www.sigmaaldrich.com](http://www.sigmaaldrich.com)


45 Grignard formation does not initiate spontaneously even when using magnesium turnings that were preactivated with iodine and/or dibromoethane.
A reflux condenser was included in the experimental setup as a precaution; solvent reflux was never definitively observed in this experiment.

Further exploration of this protocol is underway and will be reported in due course.


84 Li, X.; Sattler, I.; Lin, W. J. Antibiot. 2007, 60, 191.


88 Spiroketal stereochemistry assigned by ¹H NMR using diagnostic NMR resonances of the spiroketal methyl group. To quote from ref 88c (below), “CH3... when cis to the oxygen of the second ring resonates at lower field than when trans to the oxygen... of the second ring.” For further discussion and analysis of this spectroscopic trend, see Supporting Information, ref 82 and (a) Brimble, M. A.; Bryant, C. J. Chem. Commum. 2006, 4506. (b) Occhiato, E. G.; Guarna, A.; De Sarlo, F.; Scarpi, D. Tetrahedron: Asymm. 1995, 6, 2971. (c) Nishiyama, T.; Woodhall, J. F.; Lawson, E. N.; Kitching, W. J. Org. Chem. 1989, 54, 2183. For the seminal identification of this NMR correlation, see: (d) Francke, W.; Reith, W.; Sinnwell, V. Chem. Ber. 1980, 113, 2686. For independent confirmation of this trend by X-ray analysis, see ref 82.

89 This preference for the large tert-alkyl group to orient trans to the spiroketal oxygen is not unusual in 5,5-spiroketal systems, although this trend is not sufficiently reliable as to be predictive. See ref. 88a, 88c and Occhiato, E. G.; Guarna, A.; De Sarlo, F.; Scarpi, D. Tetrahedron: Asymm. 1995, 6, 2971.


92 Electronegative atoms (e.g., oxygen) are often good Lewis bases, so manipulation of the system in either direction (–OR as “large” or “medium” group) is frequently possible by promoting or disrupting chelation of metal salts; see reference 91 for discussion.


94 CCDC 748703 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html/ or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033; E-Mail: deposit@ccdc.cam.ac.uk.

Our lab has documented and exploited the minimal steric profile of acetylide nucleophiles in the olefination of hindered aldehydes and ketones; see: Engel, D.A.; Dudley, G.B. Org. Lett. **2006**, *8*, 4027–4029.


BIOGRAPHICAL SKETCH

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Education and Professional Development

*Florida State University, Tallahassee, FL*
January 2006 to February 2011
PhD in organic chemistry, 5th year, GPA 3.92
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Under the supervision of Professor Rick L. Danheiser

Honors and Awards
Nominated as outstanding Teaching assistant by the program for instructional excellence at FSU (2008 and 2011)

Teaching
TA for Organic One recitation (CHM 2211) at FSU (summer 2007, fall 2007, fall 2009, fall 2010).
TA for Organic Two Lab (CHM2211L) at FSU (fall 2006, spring 2007, summer 2008).
TA for Organic Survey (CHM 2200L) at FSU (summer 2009, spring 2010, summer 2010).
TA for General Chemistry (CHM1045L) at FSU (spring 2006, summer 2006).
TA for Advanced Analytical as a part of a voluntary activity done by the Student Government Association at the Lebanese University (fall 2005).

**Publications**


Tlais, S. F.; Clark, R. J.; Dudley, G. B. A striking exception to the chelate model for acyclic diastereocontrol: efficient access to a versatile propargyl alcohol for chemical synthesis. *Molecules* **2009**, *14*, 5216-5222.


**Presentations and Posters**

