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Synthetic Methods Development Towards the Total Synthesis of Chlorosulfolipids

Andres Villalpando
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SYNTHETIC METHODS DEVELOPMENT TOWARDS THE TOTAL SYNTHESIS OF CHLOROSULFOLIPIDS

A Dissertation

Submitted to the Graduate Faculty of the Louisiana State University and Agricultural and Mechanical College in partial fulfillment of the requirements for the degree of Doctor of Philosophy

in

The Department of Chemistry

by
Andres Villalpando
B.A., Whittier College, 2011
May 2016
Dedicated to my parents

and family for instilling

in me the value of education,

perseverance, hard work,

and faith.
ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

\[\alpha\]_{D}^{20} \quad \text{absolute optical rotation}

\text{^1H} \quad \text{proton NMR}

\text{^13C} \quad \text{carbon NMR}

Å \quad \text{angstrom}

Ac \quad \text{acetate, acetic}

acac \quad \text{acetylacetonate}

AD-mix \quad \text{asymmetric reagent mixture}

b \quad \text{broad}

Bn \quad \text{benzyl}

Boc \quad \text{tert-butoxycarbonyl}

Bu \quad \text{butyl}

CDCl\textsubscript{3} \quad \text{deuterated chloroform}

cm \quad \text{centimeter}

CSA \quad \text{camphorsulfonic acid}

δ \quad \text{chemical shift}

CSL \quad \text{chlorosulfolipid}

d \quad \text{doublet}

DABCO \quad \text{1,4-diazabicyclo[2.2.2.]octane}

DCM \quad \text{dichloromethane}

DDQ \quad \text{2,3-dicyano-5,6-dichloro-parabenoquinone}

DEAD \quad \text{diethyl azodicarboxylate}

DIAD \quad \text{diisopropyl azodicarboxylate}
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>DIBAL</td>
<td>diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DIPEA</td>
<td>N,N-diisopropylethylamine</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMP</td>
<td>Dess-Martin periodinane</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>FT-IR</td>
<td>Fourier transform infrared</td>
</tr>
<tr>
<td>g</td>
<td>gram</td>
</tr>
<tr>
<td>GCMS</td>
<td>gas chromatography mass spectrometry</td>
</tr>
<tr>
<td>HMDS</td>
<td>bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>HPLC</td>
<td>high-performance liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectrometry</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>IC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>half minimal inhibitory concentration</td>
</tr>
<tr>
<td>iPr</td>
<td>isopropyl</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
</tr>
<tr>
<td>JBCA</td>
<td>J-based configuration analysis</td>
</tr>
<tr>
<td>LAH</td>
<td>lithium aluminium hydride</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>M</td>
<td>molar</td>
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</table>
m .......................................................... multiple
mCPBA .................................................. meta-chloroperoxybenzoic acid
Me ........................................................ methyl
MeOH ........................................................ methanol
mg .......................................................... milligram
µg ........................................................... microgram
mL ........................................................... milliliter
mM .......................................................... millimolar
mmol ....................................................... millimol
n-Bu ........................................................ normal butyl
NBS ........................................................ N-bromosuccinimide
NCS ........................................................ N-chlorosuccinimide
NMO ........................................................ N-methylmorpholine N-oxide
NMR ........................................................ nuclear magnetic resonance
NOE ........................................................ nuclear Overhauser effect
Ns ........................................................... nosyl
p-Tol ........................................................ para-toluoyl
Ph ........................................................... phenyl
Piv ........................................................... pivaloyl
PMB ........................................................ para-methoxybenzyl
PMP ........................................................ para-methoxyphenyl
PNBA ....................................................... para-nitrobenzoic acid
ppm ........................................................ part per million
PPTS ................................................................. pyridinium para-toluenesulfonate
py ................................................................. pyridine
Red-Al ......................................................... sodium bis(2-methoxyethoxy)aluminiumhydride
rOe ............................................................. rotational nuclear Overhauser effect
s ................................................................. singlet
t ................................................................. triplet
TBAF ............................................................. tetra-N-butylammonium fluoride
TBDPS ........................................................... tert-butyldiphenylsilyl
TBHP .............................................................. tert-butyl hydroperoxide
TBS ............................................................... tert-butyldimethylsilyl
t-Bu ............................................................... tert-butyl
TEA .............................................................. triethylamine
TEMPO .......................................................... 2,2,6,6-tetramethylpiperidine-1-oxyl
TES ............................................................... triethylsilyl
Tf ................................................................. triflate, trifyl
TFA .............................................................. trifluoroacetic acid
THF .............................................................. tetrahydrofuran
THP .............................................................. tetrahydropyran
TLC .............................................................. thin layer chromatography
TMS ............................................................. trimethylsilyl
TPAP ............................................................ tetrapropylammonium perruthenate
Ts ............................................................... tosyl
UV .............................................................. ultraviolet
ABSTRACT

The focus of this dissertation is the development of a novel chlorination reaction utilizing a triphosgene-amine based mixture towards the total synthesis of chlorosulfolipids, a subclass of naturally occurring organohalogen natural products. This novel, mild chlorination reaction will be utilized under a global chlorination strategy to chlorinate multiple alcohol substituents in one synthetic operation. Chapter one details the history of chlorosulfolipids from the early stages of their isolation, relevant structural elucidation techniques, appropriate biosynthetic discoveries, and their biological relevance to a thorough investigation of the total syntheses completed to date. These compounds demonstrate a range of biological activities and have largely gone ignored by synthetic organic chemist for over 40 years since their discovery in freshwater microalga.

Chapter two describes our interest in chlorosulfolipids and the importance of developing a synthetic strategy to achieving the total synthesis of these natural products. This chapter introduces our novel chlorination methodology, utilizing a triphosgene-triethylamine mixture to convert unactivated aliphatic primary alcohols to their corresponding primary alkyl chlorides. An unanticipated result arose in which α-branched primary alcohols produced diethylcarbamates and secondary alcohols afforded a mixture of chlorination and diethylcarbamate products. Mechanistic studies revealed a competitive reaction pathway driven by steric.

In chapter three, the optimization for chlorinating secondary alcohols and α-branched primary alcohols is discussed. This chapter focuses on resolving the reactivity concerns posed by the triphosgene-triethylamine activation of primary alcohols. Herein, we discover that a triphosgene-pyridine mixture readily improves the reactivity of secondary alcohols and α-
branched primary alcohols to produce their corresponding alkyl chlorides. We also investigate the chlorination of racemic 1,3- and 1,6-diols in our initial attempts at a global chlorination.

Chapter four details the stereospecific dichlorination of stereocomplementary 1,3-\textit{anti} and 1,3-\textit{syn} diols using a mixture of triphosgene-pyridine. 1,3-\textit{anti} diols readily reacted to produce the corresponding 1,3-\textit{anti} dichlorides. It was discovered that 1,3-\textit{syn} diols must be modified into monosilylethers in order to access the corresponding 1,3-\textit{syn} dichlorides. We also investigate the chlorination of stereocomplementary 1,3,5-triols to afford the 1,3,5-trichlorides in a global chlorination strategy introducing three C-Cl bonds.
CHAPTER ONE: A HISTORY OF CHLOROSULFOLIPIDS

1.1. Purpose

The purpose of this chapter is to give a comprehensive history of chlorosulfolipids, a class of natural products, whose structure are comprised of a long hydrocarbon backbone with multiple chlorine and sulfate substituents creating a synthetically challenging molecular architecture. Figure 1.1 depicts a few of the relevant chlorosulfolipids that have been synthesized to date. After being isolated in the 1960s, these natural products have gained synthetic interest in recent years, with multiple research laboratories developing creative total syntheses. This chapter will begin with the isolation of this subclass of naturally occurring organohalogens, followed by their isolation, biological relevance, relevant structural elucidation techniques and then a detailed account of reported total syntheses.

Figure 1.1 Examples of Chlorosulfolipids
1.2. Background Information

The first reported chlorosulfolipids (CSLs) were isolated from the freshwater microalgae *Ochromonas danica (O. danica)* in 1969 by Elovson and Vagelos.¹ These natural products went largely ignored by the synthetic organic community for over the ensuing 40 years. This was attributed to the synthetic challenges posed by the unique molecular structure of these compounds as well as the ambiguity of their absolute configuration since the available methods at the time could only deduce the planar structure of the compounds. It was not until more recently, with the advancement of characterization techniques, such as NMR, that the absolute configuration of these natural products could be elucidated, thus increasing interest among synthetic organic chemists. A number of these structurally unique natural products have been found to be components of algal membranes (1.1), protein kinase inhibitors (1.2), and the causative agents of Diarrhetic Shellfish Poisoning (1.3-1.5), making them a greater attraction to synthetic organic chemists.²

1.3. Isolation

1.3.1. Chlorosulfolipids from *Ochromonas danica*

Haines and Block first isolated compounds from the microalgae *O. danica* in 1962, discovering sulfated lipids.³ Further studies by the Haines group established that each lipid backbone contained two sulfate groups.⁴⁻⁵ Haines was unable to isolate and characterize these sulfated lipid compounds due to their hygroscopic and viscous properties. However, by cleaving the sulfate substituents to reveal diols, they successfully isolated and characterized the hydroxylated versions of the algal compounds. The first structure Haines and coworkers identified was 1,14-docosanediol disulfate 1.6 (Figure 1.2). Over the following few years the Haines group discovered that a number of the sulfolipid extracts from *O. danica* were
chlorinated. In 1969, the Haines group successfully elucidated the structure and absolute configuration of monochlorinated lipid 1.7 (Figure 1.2).  

![Figure 1.2 First elucidated sulfated structures](image)

Simultaneously, Elovson and Vagelos, isolated a number of polychlorodiols from *O. danica* while investigating its fatty acid biosynthesis. The compounds they extracted were a heterogeneous mixture of docosane (C22) and tetracosane (C24) disulfates. Through mass spectrometry they determined that these diols contained a chlorinated hydrocarbon backbone with up to six chloride atom substituents. Elovson and Vagelos observed that CSLs made up about 10-15% of the total lipid content in *O. danica* and roughly 3% of the dry weight of the cell. Further investigations conducted by Haines revealed the localization of CSLs in the cellular and flagellar membranes, constituting over 90 mol % of the total polar lipids found in the membranes.

### 1.3.2. Chlorosulfolipid Studies by Mercer and Davies

Beginning in the mid 1970s, Mercer and Davies discovered docosane CSLs from the alga *Tribonema aequale* (class Xanthophyceae). These compounds were structurally similar to those isolated from *O. danica*, bearing up to six chlorine atoms and two sulfate groups. GC-MS traces from both algal sources were identical, indicating that the same CSLs are found in multiple
algae. Mercer and Davies subsequently detected docosane CSLs in two other Xanthophyceae (*Botrydium granulatum* and *Monodus subterraneus*), two members of Chlorophyceae (*Elakatothrix viridis* and *Zygnema*), and a member of Cyanophyceae (*Nostoc*). In 1979, Mercer and Davies conducted a study in which they screened 30 algae species, twenty-two from freshwater sources and eight from marine sources, discovering CSLs in all freshwater algae but none in the marine algae, concluding that CSLs are widespread among freshwater species.

1.3.3. Chlorosulfolipids from *Poteriochromonas malhamensis*

After the isolation studies conducted from the mid 1960s to late 1970s, no new CSLs were reported until 1994, when the groups of Slate and Gerwick reported the isolation of malhamensilipin A from the alga *Poteriochromonas malhamensis*. This CSL displayed antimicrobial and antiviral activity as well as moderate pp60 protein tyrosine kinase inhibition (IC$_{50}$ = 35 μM). Slate and Gerwick were able to deduce the structural configuration of this compound via advances in NMR spectroscopy. The CSLs isolated from this alga were from the tetracosane (C24) family, however, the overall structure resembled those of the docosane (C22) family isolated from the alga *O. danica*.

1.3.4. Chlorosulfolipids from Adriatic Mussels

The groups of Ciminiello and Fattorusso were researching seafood toxins and collected the toxic contaminants of the Mediterranean mussel *Mytilus galloprovincialis* from the Adriatic coast of Italy in the late 1990s. From the digestive glands of these mussels, they were able to isolate three CSLs 1.3-1.5 between 2001 and 2004. These CSLs were determined to be the causative agents of Diarrhetic Shellfish Poisoning. Hexachlorosulfolipid 1.3 was the first CSL isolated and was found to be moderately cytotoxic. The latter two CSLs isolated 1.4-1.5, named undecachlorosulfolipid A and B, were the most structurally intriguing CSLs found to date,
containing eleven chlorine atoms, multiple hydroxyl groups and a sulfate group with nine contiguous stereogenic centers.

1.4. Early Structural Elucidation

CSL 1.7 was the first to be structurally characterized by the Haines group in 1969. They determined the structure through mass spectrometry experiments (Figure 1.3). Cleavage of the sulfate groups revealed a diol that was readily isolated and characterized. They determined the absolute configuration of diol 1.8 through mass spectrometric fragmentation, with cleavage α to the oxygen, thus delivering a fragment of 14 carbon atoms, one chlorine atom, and two oxygen atoms. They secured structure assignment by subjecting the diol to base, which formed a cis-epoxide, thus confirming the presence of a vicinal chlorohydrin with syn configuration. They further confirmed their proposed absolute configuration by comparing the optical rotation of 1.7 to known standards.

![Figure 1.3 First elucidated Chlorosulfolipid](image)

Elovson and Vagelos were the first to determine the planar structure of danicalipin A (1.1) through chemical degradation and mass spectrometric studies in 1969. In order to accomplish this, they used a $^{36}$Cl-labeled CSL, which was obtained by growth of O. danica in a [$^{36}$Cl]HCl broth. Using $^{36}$Cl was necessary due to the fact that chlorine atoms do not promote mass spectrometry induced cleavage at the carbon to which they are attached. By using a $^{36}$Cl-labeled CSL, it allowed them to give the precise assignment of the six chlorine atoms to their
respective carbon atoms and also allowed them to estimate whether the chlorine atoms were displaced or eliminated during the chemical degradation steps. The key steps of their degradation study included base-promoted epoxide formations, conversion of the C2-dichloride into a ketone, an array of elimination, periodate cleavage, as well as inter- and intramolecular nucleophilic displacement steps. The intermediates of these reactions were analyzed through mass spectrometry to deduce the planar structure of danicalipin A.

1.5. Biosynthesis and Biological Relevance of *O. danica* Lipids

1.5.1. Biosynthesis

Several research groups, including Haines, Elovson, and Mercer, conducted independent biosynthetic studies in the 1970s to determine the origin of CSLs in *O. danica*. The Haines group conducted their studies based on $^{14}$C-labeled experiments. They determined that the aliphatic chain of CSLs are biosynthesized via normal fatty acid synthesis, due to the incorporation of $^{14}$C-labeled acetate and the integration of several $^{14}$C-labeled fatty acids, and then later functionalized with polar groups. Having incorporated oleic acid, they hypothesized that alkene hydration would introduce the C14 hydroxy group prior to aliphatic chain elongation and eventual reduction to the diol. Mercer obtained similar results to Haines, however, they discovered a key difference in that unsaturated fatty acids, such as oleic acid, were poorly incorporated. Given these results, Haines argued that chlorides must therefore be incorporated into a saturated hydrocarbon backbone, leading them to hypothesize incorporation of the chlorides via an enzymatic radical chlorination process. Elovson conducted $^{18}$O-labeled incorporation experiments by growing algae in $^{18}$O$_2$ enriched medium and discovered that the primary hydroxy group was derived by H$_2$O but the secondary hydroxy group resulted from molecular oxygen. These results confirmed that docosane 1,14-diol must be synthesized
via direct incorporation of a saturated carbon chain and not via oleic acid. Scheme 1.1 illustrates the overall consensus of the order of events based on the various biosynthetic studies conducted by the various groups. The order is as follows: fatty acid synthesis, docosanoic acid 1.9, 14-hydroxydocosanoic acid 1.10, docosane-1,14-diol 1.11, and then enzyme mediated transfer of the sulfate group from 3’-phosphoadenosine 5’-phosphosulfate (PAPS) to the diol as the final steps before enzymatic chlorination to provide the CSLs.17-22

Scheme 1.1 Proposed biosynthesis of Chlorosulfolipids
The incorporation of chlorine atoms along the bis-sulfated saturated hydrocarbon backbone is not well understood. The biosynthetic studies conducted by Haines, Elovson and Mercer concluded that enzymatic chlorination is the most likely mechanism to install the chlorine atoms. Using radiolabeling, Mercer’s group found that chlorination occurs stepwise, and observed that if a less chlorinated lipid is resubjected to the culture medium, it will continue to be chlorinated. It was later found improbable that enzymes such as haloperoxides would install chlorine atoms on unactivated carbons as these enzymes generate electrophilic chlorine. Haines hypothesized that perhaps chlorination occurred via free radical processes, however, enzymes capable of this process were unknown at the time of their studies. In conclusion, the mechanism for the biosynthetic chlorination of the bis-sulfated hydrocarbon backbone precursor to access CSLs remains a mystery.

1.5.2. Biological Relevance

The abundance of CSLs discovered in the membrane of *O. danica* suggests a structural role. Haines and coworkers discovered that CSLs make up over 90% of the polar lipids present in the flagellar membrane, while lacking phospholipids. A typical membrane bilayer seems unlikely since CSLs possess two charged sulfate groups; a terminal sulfate, as well as a sulfate two-thirds of the way down its carbon backbone thus placing a charged sulfate group in the middle of the hydrophobic region of the membrane. Hairpin-like structures have also been ruled out due to the bulkiness of the chloride and sulfate substituents, preventing the CSL from adopting sharp turns. Surprisingly, however, freeze fractures of the *O. danica* membrane revealed a bilayer structure. Haines group hypothesized that a divalent metal atom or a charged protein residue must be present to offset the negative charge of the sulfate group at physiological pH. The biological relevance of CSLs remains a mystery and as more information is discovered
the more it raises questions. Another intriguing discovery about CSLs are that they are toxic to brine shrimp and are associated with Diarrhetic Shellfish Poisoning, however, they are biosynthesized and incorporated into algal membranes in large quantities without compromising the health of those membranes.\textsuperscript{2, 12-14, 24}

1.6. Structure Elucidation Using \textit{J}-based Configurational Analysis

When CSLs were first discovered and isolated in the mid-1960s, there were no viable methods for deducing the configuration of complex acyclic molecules. The planar structure of one CSL was reported in 1970, however, it lacked stereochemical details.\textsuperscript{15} In the early 2000s, Ciminiello and Fattorusso realized they could possibly use Murata’s \textit{J}-based configuration analysis (JBCA),\textsuperscript{25} which was developed to define the configuration of acyclic polyoxygenated compounds, such as polyketides, to help deduce the configuration of CSLs. Murata’s \textit{J}-based configuration analysis is based on the measurement of homo (\textit{\textit{3}}\textit{J}_{\text{H,H}}) and heteronuclear (\textit{\textit{3}}\textit{J}_{\text{C,H}}, \textit{\textit{2}}\textit{J}_{\text{C,H}}) coupling constants between two heterosubstituted stereogenic centers.\textsuperscript{2, 25-26} Murata’s method determined that vicinal heteronuclear coupling constants (\textit{\textit{2}}\textit{J}_{\text{C,H}}) are dependent on the dihedral angle between the electronegative group on the carbon and its adjacent proton. When the electronegative substituent is \textit{gauche} to the vicinal proton, \textit{\textit{2}}\textit{J}_{\text{C,H}} is large, but when it is \textit{anti}, the coupling constant becomes small.\textsuperscript{25-26} These coupling constants in combination with nuclear Overhauser effect (nOe) or rotational nuclear Overhauser effect (rOe) data provide the solution confirmation as a Newman projection, thus allowing for the relative configurations of adjacent stereogenic centers to be determined.\textsuperscript{2, 26}

Ciminiello and Fattorusso used this method based on the assumption that reference values for hydroxlated systems could be used to deduce the configuration of chlorinated systems. However, in order for Murata’s method to work, reference values for the relevant coupling
constants must be available.\textsuperscript{26} Carreira’s group took it upon themselves to investigate the relevance of JBCA towards chlorinated systems.\textsuperscript{27} They were able to synthesize a unique library of trichlorohexanediols, with varying stereochemical configurations of 1,2,4- and 1,2,3-trichlorides. Upon synthesizing these compounds, they discovered that they readily crystallized allowing them to correlate NMR data with the configuration established through X-ray crystallographic analysis.\textsuperscript{27} These crystalline compounds were then analyzed for their relevant homo- and heteronuclear coupling constants. In order to correlate their data with specific dihedral angles, they needed a model system that would be conformationally rigid in solution. Carreira’s group found (1R, 2S, 4S)-4-tert-butyl-1,2-dichlorocyclohexane 1.13 to be a suitable system since this compound adopts a chair conformation in solution, allowing for the determination of the desired coupling constants for specific dihedral angles (Table 1.1).\textsuperscript{26}

\begin{table}[h]
\centering
\begin{tabular}{ccc}
\hline
\multicolumn{2}{c}{Table 1.1 Carreira’s investigation of dihedral angles on model system} \\
\hline
\includegraphics[width=0.4\textwidth]{model_system_diagram} & \hline
\end{tabular}
\begin{tabular}{cccc}
\hline
Coupling Constant & \multicolumn{1}{c}{Classification} \\
for 1.13 & \multicolumn{1}{c}{according to Murata} \\
\hline
\textsuperscript{3}J(H2,H3) & +2.9 Hz & Small \\
\textsuperscript{3}J(H2,C4) & +0.8 Hz & Small \\
\textsuperscript{3}J(H3,C1) & +4.7 Hz & Large \\
\textsuperscript{2}J(H2,C3) & +3.6 Hz & Small \\
\textsuperscript{2}J(H2,C2) & -4.5 Hz & Large \\
\hline
\end{tabular}
\end{table}
Upon analyzing model substrate 1.13, Carreira’s group was able to correlate the data for their library of crystalline trichlrides to be applicable towards the structural configuration of CSLs. Figure 1.4 shows the correlated data for the homo- and heteronuclear coupling constants for vicinal dichlorides and chlorohydrins as a function of the dihedral angle of the trichloride systems synthesized by Carreira’s group. As a comparison the values in parentheses represent Murata’s values for oxygenated systems. As demonstrated by Carreira’s work, the values for chlorinated systems and oxygenated systems are similar, proving that Ciminiello and Fattorusso accurately assumed Murata’s system could be utilized for determining the structural conformation of the CSLs.

![Figure 1.4 Carreira’s correlated coupling constant data for chlorinated systems](image)

This powerful method allowed for the determination of the solution conformation of CSLs by understanding the tendency of the lipids to avoid unfavorable syn-pentane like interactions and to maximize gauche orientations of vicinal polar groups. Figure 1.5 shows the solution conformation of hexachlorosulfolipid 1.3 determined by the coupling data correlated by Carreira. The Newman projection on the far right of the C13-C12 bond was determined to be favored because there is no NOe observed between the protons on C11 and C14. Further studies found that CSLs 1.1 and 1.2 adopt similar solution confirmations. Carreira’s work in
estimating reference values using their library of crystalline trichlorides further confirmed these conformational preferences among a variety of compounds.\textsuperscript{2, 30} Establishing a method to effectively determine the absolute configuration of these acyclic chlorinated compounds was an important achievement for the syntheses of CSLs. This work led to breakthroughs in assigning the relative and absolute configurations of a number of CSLs. In 2009, the groups of Gerwick, Haines, and Vanderwal collectively determined the relative and absolute configuration of CSL danicalipin A (1.1) using the Murata method in conjunction with the modified Mosher method.\textsuperscript{31} The Okino group isolated eight CSLs from \textit{O. danica}, including five that had not been previously isolated, and successfully determined the relative and absolute configurations of these compounds utilizing this method.\textsuperscript{34} In the following year, the Gerwick and Vanderwal groups revised the structure of malhamensisilipin A using the Murata and modified Mosher methods.\textsuperscript{32} The Murata method proved invaluable for the determination of the relative and absolute configurations of the CSLs, ultimately allowing for the onset of the total syntheses of these unique natural products.

Figure 1.5 Murata’s JBCA applied to Chlorosulfolipids using Carreira’s correlated data
1.7. Total Syntheses of Hexachlorosulfolipid

1.7.1. Carreira’s Synthesis of (±)-Hexachlorosulfolipid

In 2009, after more than 40 years after the first CSLs were discovered and isolated, the Carreira group completed the first total synthesis of a CSL by their construction of racemic hexachlorosulfolipid 1.3. Through preliminary experiments, Carreira’s group discovered that displacement of activated alcohol derivatives with chlorine proved problematic, especially when the carbinol was substituted with electron withdrawing groups, such as chlorine atoms. They also discovered that chlorinated aldehydes were troublesome intermediates as they underwent enolization, hydration or elimination readily. These results encouraged the Carreira group to discover viable methods for successfully crafting a synthetic route to CSL 1.3.

From Scheme 1.2, their synthesis began with treatment of commercially available ethyl sorbate 1.15 with Et₄NCl₃ in a stereospecific anti-dichlorination reaction at the more electron rich alkene, followed by reduction of the ester using DIBAL and subsequent protection of the resulting primary alcohol with TBSCl. Diastereoselective dihydroxylation (dr = 5.6:1) using OsO₄ and NMO at the remaining alkene provided diol 1.16. Epoxide ring closure in a cyclodehydration reaction using triflic anhydride and DABCO followed by TBS deprotection with CSA in methanol resulted in cis-epoxide 1.17. Oxidation of the primary alcohol under Swern conditions afforded an epoxy aldehyde intermediate, which then underwent a Wittig reaction with phosphorane 1.18 to afford vinyl epoxide 1.19 (Z:E = 4.2:1). Treatment of epoxide 1.19 with TMSCl resulted in a mixture of diastereomers, with the major product assumed to contain the desired stereochemistry, therefore carried out to the completion of the natural product in a few steps. Stereospecific dichlorination of the alkene with Et₄NCl₃ followed by TBS deprotection, TEMPO oxidation, Takai chlorooolefination and sulfation completed the total
synthesis, leading to compound (±)-1.22. However, spectroscopic analysis of 1.22 in comparison to the published spectra of the natural product revealed the synthesis of a diastereomer of CSL 1.3.

After determining that the spectroscopic data of 1.22 did not match that of the natural product, they were able to pinpoint the source of the error. After examining NMR spectra, they discovered that 1.20 is the epimer of 1.19 at the allylic position, leading them to the conclusion that epoxide opening of 1.19 occurred with retention of configuration. As shown in Scheme 1.3, anchimeric assistance by one of the chlorides from the C2 or C3 position of 1.19 led to chloronium ion intermediates 1.23 or 1.24. The five membered chloronium ion intermediate 1.24 is expected to be favored over the four membered chloronium ion intermediate 1.23, however,
there is not sufficient data to distinguish between the two possible intermediates.\textsuperscript{29} Peterson and coworkers had previously reported this unexpected phenomenon of chloride participation in substitution reactions back in the 1960s and 1970s.\textsuperscript{35-37}

Scheme 1.3 Carreira’s revised approach to ($\pm$)-Hexachlorosulfolipid

The resulting retention of configuration from the epoxide ring opening revealed the anti-relationship between C4 and C5, however in the natural product C4 and C5 are syn to each other. Carreira hypothesized that the epoxide ring-opening step could easily be solved by switching the relative configuration of the epoxide at C5.\textsuperscript{29} However, it was unknown whether the trans-epoxide would react in the same manner to afford the retention of configuration product. Carreira’s revised approach to CSL 1.3 is shown in Scheme 1.4. Following a similar sequence, starting with ethyl sorbate 1.15 and undergoing stereospecific dichlorination of the alkene followed by ester reduction using DIBAL and epoxidation (dr = 1:1) of the alkene using m-CPBA produced trans-epoxide 1.25. The desired epoxide was separated from the undesired diastereomer via silica gel chromatography. Ley oxidation using NMO and TPAP followed by a
Wittig reaction using phosphorane \textbf{1.18} (Z:E = 7:1) gave \textbf{1.26}. Treatment of epoxide \textbf{1.26} with TMSCl resulted in a single product, with retention of configuration, leading to the proper \textit{syn}-chlorohydrin \textbf{1.27}. The same series of steps as in their first attempt from \textbf{1.27} completed the natural product with stereospecific dichlorination of the alkene (dr = 10:1), deprotection of the TBS, oxidation of the primary alcohol, Takai chloroolefination \textsuperscript{34} and finally sulfation led to CSL \textbf{1.3}. Spectroscopic data of this product matched that of the natural product, completing the first total synthesis of a CSL.\textsuperscript{29}

\begin{center}
\textbf{Scheme 1.4} Carreira’s total synthesis of (±)-Hexachlorosulfolipid
\end{center}

\textbf{1.7.2. Yoshimitsu’s Synthesis of (+)-Hexachlorosulfolipid}

In 2010, Yoshimitsu’s group completed one of the first enantioselective syntheses of a CSL, synthesizing (+)-hexachlorosulfolipid utilizing an epoxide deoxydichlorination methodology they developed.\textsuperscript{38-39} They discovered that stereospecific 1,2-deoxydichlorination of an epoxide can be achieved using three equivalents of NCS and PPh\textsubscript{3}, where \textit{cis}-epoxides
provided anti-1,2-dichlorides and trans-epoxides provided the syn-dichlorides. This reaction proceeded via inversion of both stereogenic centers. Scheme 1.5 shows the first part of their total synthesis of (+)-hexachlorosulfolipid. The synthesis began with epoxide 1.29 in a known sequence from commercially available starting materials. Treatment of the epoxide with NCS and PPh₃ in toluene at 90°C following their established protocol provided vicinal dichloride 1.30 as a single product in good yield. Removal of the pivaloyl protecting group using DIBAL, followed by oxidation of the resulting primary alcohol using Dess-Martin oxidation provided the aldehyde which subsequently underwent stereocontrolled allylation to afford anti-chlorohydrin 1.31 with a diastereoselectivity of 3.8:1 (anti/syn) in good yield. Efforts to directly displace the hydroxy group with chloride proved unfruitful. By converting the chlorohydrin into an epoxide 1.32 with NaH, this group was once again able to showcase their methodology. Treatment of epoxide 1.32 with their conditions using NCS and PPh₃ gave the all syn-chloro-stereotriad 1.33 as a single product in good yield. Allylic oxidation with selenium dioxide provided a mixture of diastereomers, favoring the undesired anti-isomer 1.34 (5:3). They were able to convert the anti-diastereomer 1.34 to the desired syn-isomer 1.35 in two steps by oxidizing the alcohol then doing a selective reduction with NaBH₄. Subsequent olefin cross metathesis with Grubbs 2nd generation catalyst and 2-butene provided E-alkene 1.36.

The completion of their synthesis is shown in Scheme 1.6 beginning with the dichlorination of E-alkene 1.36 following Marko-Maguire protocol for olefin dichlorination using KMnO₄ and BnEt₃NCl. This transformation led to pentachloride 1.37 as a mixture of diastereomers, with the desired disasteromer being produced in 38% and two other isomers making up 36%.
Scheme 1.5 Yoshimitsu’s synthesis of (+)-Hexachlorosulfolipid

They were able to separate these diastereomers via silica gel chromatography and continued with the desired diastereomer by protecting the free alcohol with an acetate group in quantitative yield producing 1.38. Silyl ether deprotection under acidic conditions followed by Dess-Martin oxidation afforded aldehyde 1.39 in good yield. Takai chloroolefination\textsuperscript{34} of the aldehyde followed by acetate deprotection using DIBAL and subsequent sulfation provided (+)-hexachlorosulfolipid.\textsuperscript{39} This synthesis highlighted Yoshimitsu’s novel epoxide ring opening dichlorination methodology and also confirmed the absolute configuration of the natural product as previously proposed by Ciminiello and Fattorusso.\textsuperscript{12}
1.7.3. Vanderwal’s Synthesis of Hexachlorosulfolipid

In 2013, the Vanderwal group successfully synthesized hexachlorosulfolipid 1.3 via a longest linear sequence of seven steps to its racemic form and eight steps to the enantioenriched form (Scheme 1.7).\textsuperscript{41} Crotyl alcohol 1.40 was treated with molecular chlorine and Et₄NCl (in situ generation of Mioskowski’s reagent\textsuperscript{33}, Et₄NCl₃) to afford \textit{anti}-dichloro alcohol, which was then oxidized with Dess–Martin periodinane to the aldehyde giving 1.41. Addition of the depicted bromoallylaluminum reagent\textsuperscript{42} to the aldehyde occurred with high diastereoselectivity (dr = 98:2) and treatment of the bromohydrin intermediate with aqueous NaOH provided \textit{cis}-epoxide (±)-1.42. They completed the racemic synthesis using (±)-1.42, however, in order to access the enantioenriched CSL they performed a kinetic resolution on the racemic epoxide through chlorinolysis using (\textit{R,R})-Denmark catalyst 1.43\textsuperscript{43-44} to provide (+)-1.42 with 87% ee. Alkene coupling partner 1.45 was synthesized in two steps from 8-bromo-1-octene 1.44 through the
formation of a Grignard reagent followed by Takai chloroolefination\textsuperscript{34} in good yield and with an $E:Z$ ratio of 93:7. One of the key steps of this synthesis was the $Z$-selective olefin cross metathesis between \textbf{1.42} and \textbf{1.45} using Grubbs cycloadamantyl catalyst \textbf{1.46}\textsuperscript{45-48} to afford $Z$-vinyl epoxide \textbf{1.47} under complete control of the olefin geometry.\textsuperscript{49} Although low yielding, due to catalyst deactivation by the vinyl epoxide, they were successfully able to generate the vinyl chloride in just one step. Epoxide ring opening via chlorinolysis using excess BF$_3$•OEt$_2$ and Et$_4$NCl resulted in $\text{syn}$-chlorohydrin \textbf{1.48} as a single product with inversion of stereochemistry.\textsuperscript{31, 50} The alkene was then dichlorinated using Mioskowski’s reagent\textsuperscript{33}, Et$_4$NCl, giving the $\text{syn}$-dichloride (dr = 93:7), which subsequently underwent sulfation to complete the synthesis of hexachlorosulfolipid \textbf{1.3}.

\begin{center}
\textbf{Scheme 1.7} Vanderwal’s total synthesis of (±)-Hexachlorosulfolipid
\end{center}
1.8. Total Syntheses of Danicalipin A

1.8.1. Vanderwal’s Synthesis of (±)-Danicalipin A

The Vanderwal group was initially interested in pursuing the total synthesis of hexachlorosulfolipid 1.3, however, a combination of failed reactions of chlorinated aldehyde electrophiles and the publication of the Carreira group total synthesis utilizing a similar alkene dichlorination strategy led the Vanderwal group to change their research focus towards synthesizing danicalipin A (1.1).2,31 They completed the synthesis of racemic danicalipin A in 2009, shortly after Carreira’s synthesis of racemic hexachlorosulfolipid. Vanderwal was able to access the different stereochemical configurations found in CSLs by optimizing a 1,2-dichlorination of Z-allylic alcohols using Mioskowski’s reagent33 (Et$_4$NCl$_3$). After experimentation, they observed that dichlorinations with Et$_4$NCl$_3$ of polychlorinated Z-olefins proceeded with anti stereoselectivity to afford syn-1,2-dichlorinations.51-52

Vanderwal’s synthesis of danicalipin A featured a Wittig reaction between phosphonium salt 1.52 and epoxy-aldehyde 1.55.31 Synthesis of the phosphonium salt 1.52 coupling partner began with known 11-bromoundecanal 1.49 which was treated with tBuNH$_2$ and NCS to afford α,α-dichloride 1.50 (Scheme 1.8). Subsequent reduction of the aldehyde with NaBH$_4$ followed by silyl ether protection with TBSCl resulted in 1.51. Iodination of 1.51 followed by treatment with PPh$_3$ gave pure phosphonium salt 1.52 to be used in the Wittig reaction. The aldehyde-coupling partner 1.55 was synthesized from unsaturated methyl ester 1.53. Exposure of the ester to Et$_4$NCl$_3$ led to stereospecific anti-1,2-dichlorination of the more electron rich alkene followed by diastereoselective dihydroxylation with OsO$_4$ and NMO at the remaining alkene to provide diol 1.54. Epoxide ring closure via regioselective nosylation and subsequent reduction of the ester with DIBAL gave cis-epoxy-aldehyde 1.55.
With both fragments synthesized, the coupling of phosphonium salt \( \text{1.52} \) and aldehyde \( \text{1.55} \) via a Wittig reaction with KHMDS afforded vinyl epoxide \( \text{1.56} \) as a 2.5:1 \( Z:E \) mixture (Scheme 1.9). At this point of the synthesis, the Vanderwal group first tried epoxide ring opening to access the chlorohydrin using TMSCl, however, this resulted in a mixture of diastereomers revealing a preference for the \textit{anti}-product, which corresponds to epoxide ring opening with retention of configuration at C13. This result hinted at anchimeric assistance by a chloride ion as discovered by Carreira’s synthesis of hexachlorosulfolipid. After much experimentation, they were unable to improve reaction conditions using a silyl chloride to access the desired diastereomer. However, they determined that the use of excess BF\(_3\)·OEt\(_2\) and Et\(_4\)NCl readily afforded the desired \textit{syn}-chlorohydrin \( \text{1.57} \) as a single product directly from the \( Z:E \) mixture of \( \text{1.56} \). Stereoselective \textit{anti}-1,2-iodochlorination of the alkene in \( \text{1.57} \) gave \( \text{1.58} \) with complete
regiocontrol but poor stereoselectivity (dr = 1.8:1). Radical deiodination using \( n\text{Bu}_3\text{SnH} \), followed by silyl ether deprotection and sulfation provided the completed synthesis of (±)-danicalipin A. The lower yield for the iodochlorination/deiodination sequence was attributed to the isolation of the pure stereoisomer not the reactivity, as both steps were efficient via crude NMR analysis. This completed synthesis allowed for the relative stereochemistry of danicalipin A to be analyzed via the \( J \)-based configurational analysis method. Vanderwal had hypothesized that CSLs 1.1-1.3 would have similar stereochemistries along their hydrocarbon backbones, however, analysis of danicalipin A 1.1 revealed that the configuration at C11 was opposite that of C11 in CSLs 1.2-1.3.

![Scheme 1.9 Vanderwal’s synthesis of Danicalipin A](image)

The synthesis outlined in Schemes 1.8 and 1.9 was the Vanderwal group’s first generation approach to synthesizing the natural product, danicalipin A (1.1). They more recently
completed a second generation approach in 2014 (Scheme 1.10), utilizing some of the same chemistry as shown above in the Vanderwal synthesis of (+)-hexachlorosulfolipid (Scheme 1.7). Most notably they were able to reduce the number of steps to access 1.56 by utilizing a Z-selective olefin cross metathesis using Grubbs cycloadamantyl catalyst 1.46 that the group had previously optimized, instead of the previous Wittig reaction to couple two fragments which afforded a less selective Z-olefin. This coupling reaction was also used in their synthesis of hexachlorosulfolipid as shown in Scheme 1.7. Conversion of 1.56 to 1.57 was improved by using BF₃•OEt₃ at -78°C with a high concentration of Et₄NCl instead of 50 equivalents of Et₄NCl in the presence of BF₃•OEt₃, allowing them to isolate 1.57 in 73% yield as a single diastereomer (>20:1 dr). In their first generation synthesis they encountered problems with the iodination reaction of 1.57 to 1.58 only obtaining a dr = 1.8:1. However, in their second-generation synthesis they discovered that introduction of a TMS ether at the C14 hydroxyl, greatly improved diastereococontrol (dr = 95:5) of the iodochlorination reaction. Protection of the alcohol with TMSCl, followed by iodochlorination gave 1.58, which was then treated with CSA in methanol to reveal 1.59. Silyl ether deprotection followed by sulfation of the hydroxy groups completed the synthesis of danicalipin A (1.1). Overall their second generation approach produced a nine-step enantioselective synthesis whereas their first generation synthesis produced a 12-step racemic synthesis.

1.8.2. Matsuda’s Synthesis of (+)-Danicalipin A

The Matsuda group completed the synthesis of (+)-danicalipin A in 2011, almost simultaneously with the Yoshimitsu group, whose total synthesis will be discussed below. This group completed an asymmetric synthesis of the CSL and tested the racemic form as well as its two enantiomers for their toxicity in brine shrimp. They discovered that the absolute
configuration did not have any effect on its toxicity, finding that all three compounds revealed an LC$_{50}$ value of $\approx 2 \mu$g/mL in brine shrimp.$^{53}$

Matsuda’s synthesis featured a Wittig reaction between aldehyde 1.70 and phosphonium salt 1.63 as the convergent step (Scheme 1.11). The construction of phosphonium salt 1.63 underwent a similar procedure to that of Vanderwal’s synthesis above. Known aldehyde 1.60 was cleanly converted to $\alpha,\alpha$-dichloride 1.61 with NCS in the presence of catalytic pyrrolidine as a single product, without the formation of byproducts. Reduction of the dichloroaldehyde with DIBAL followed by protection of the resulting alcohol with TBSCI provided 1.62. Iodination of 1.62 and subsequent treatment with PPh$_3$ afforded the phosphonium salt coupling partner 1.63. The synthesis of the other coupling partner began from known epoxide 1.64, which underwent TEMPO oxidation followed by a Wittig reaction in a one-pot operation to give allylic epoxide.
Recrystallization of this epoxide intermediate improved the ee from 85% to over 99%. Epoxide ring opening via inversion of stereochemistry with thionyl chloride led to syn-chlorohydrin 1.66 in excellent yield as a single product. This epoxide ring opening was purposely carried out early in the synthesis to avoid an opening with retention of configuration via anchimeric assistance of a neighboring chloride as discovered by the Carreira group. Reduction of the ester with LiBH₄, TES protection of the alcohols, and Swern oxidation of the primary alcohol provided aldehyde 1.67. After extensive investigations, the diastereoselective α-chlorination of 1.67 with (R,R)-2,5-diphenylpyrroolidine 1.68 (Jørgensen catalyst) and bromoacetic acid was found to give the best diastereoselectivity of greater than 20:1 mono- to dichlorination. A subsequent Wittig reaction in a one-pot synthesis afforded α,β-unsaturated ester 1.69 in excellent yield. Ester reduction using LiBH₄ gave the primary alcohol, which then underwent TEMPO oxidation to afford the second coupling partner in aldehyde 1.70.

Wittig reaction between aldehyde 1.70 and phosphonium salt 1.63 followed by hydrogenation of the formed double bond and concurrent PMB deprotection with Pd(OH)₂ on carbon gave primary alcohol 1.71. TEMPO oxidation of the primary alcohol to afford the aldehyde followed by a Wittig reaction in a one-pot operation gave α,β-unsaturated ester 1.72 with an E:Z ratio of 10:1. Reduction of the ester with DIBAL followed by acetylation of the resulting alcohol using acetic anhydride then subsequent allylic substitution using nC₅H₁₁MgBr and Li₂CuCl₄ provided E-olefin 1.73. Removal of the silyl ethers with TBAF followed by stereospecific anti-dichlorination of the double bond using BnEt₃NCl-KMnO₄-TMSCl (Marko’s reagent) gave the desired dichloride in 39% yield as well as another anti-adduct in 28% yield (dr = 1.8:1). At this point, all spectral data matched that of the synthesis completed by Vanderwal. The asymmetric synthesis was completed after sulfation with ClSO₃H to give 1.1.
Scheme 1.11 Matsuda’s total synthesis of (+)-Danicalipin A

1.8.3. Yoshimitsu’s Synthesis of (+)-Danicalipin A

The Yoshimitsu group completed the synthesis of (+)-danicalipin A in 2011, almost simultaneously with the Matsuda group. One of the main features of this synthesis is the coupling reaction utilizing a 1,3-dipolar cycloaddition between an alkene and nitro compound.
This was a different approach to accessing danicalipin A, as the other two syntheses prior to their own utilized a Wittig reaction to couple an aldehyde and phosphonium salt.

The coupling reaction between alkene 1.77 and nitro compound 1.83 is shown in Scheme 1.12. Alkene 1.77 constructed from known cis-epoxide 1.74, which was synthesized from commercially available cis-2-nonen-1-ol via Sharpless asymmetric epoxidation with 80% ee. Protection of the primary alcohol with a pivalate ester followed by 1,2-deoxydichlorination with NCS and PPh₃ of the cis-epoxide provided anti-dichloride 1.75 as a single product. Reductive deprotection of the pivalate ester with DIBAL followed by Dess-Martin oxidation of the resulting alcohol gave aldehyde 1.76. This unstable aldehyde was immediately reacted with vinylmagnesium bromide giving a mixture of diastereomers (dr = 1.7:1) favoring the anti-isomer. Further attempts to increase the enantiomeric excess were successful through an enzymatic separation using Lipase PS IM Amano, increasing the ee from 80% to greater than 99% ee. Subsequent silyl ether protection of the secondary alcohol afforded 1.77, completing the synthesis of the alkene coupling partner.

The second coupling partner was synthesized from diene 1.78 (E:Z = 3:2), which was prepared via the Wittig methoxyolefination of commercially available 10-undecanal, shown in Scheme 1.12. Diene 1.78 was transformed to α-chloroaldehyde via chlorination with NCS followed by treatment of the crude reaction mixture with TFA. Subsequent treatment with t-BuNH₂ provided an enamine, which was further chlorinated with NCS in a one-pot operation, to give α,α-dichloroimine 1.79. Hydrolysis of the imine with 3N HCl followed by reduction of the aldehyde with NaBH₄ led to alcohol 1.80. Silyl ether protection with TBSOTf and 2,6-lutidine followed by ozonolysis of the alkene to the alcohol gave 1.81. Alcohol 1.81 was transformed into coupling partner 1.83 by iodination of the alcohol and subsequent substitution of 1.82 with NaNO₂.
Scheme 1.12 Yoshimitsu’s total synthesis of (+)-Danicalipin A
With both coupling partners synthesized, the Yoshimitsu group made numerous attempts to optimize reaction conditions for the desired diastereoselectivity. They found that the desired isoxazoline 1.84 was successfully prepared by slow addition of phenyl isocyanate\textsuperscript{59} into 1.77 and 1.83 in heating toluene to afford the desired anti-isomer in a 7.3:1 mixture at C13/C14. Reductive cleavage of the isoxazole moiety with Mo(CO)\textsubscript{6} led to a \(\beta\)-hydroxy ketone intermediate, which underwent diastereoselective reduction with Me\textsubscript{4}NBH(OAc)\textsubscript{3} to give anti-1,3-diol 1.85 (dr = 6:1). Double Appel reaction of the alcohols with 3 equivalents of NCS and PPh\textsubscript{3} afforded anti-1,3-dichloride 1.86 with inversion of stereochemistry at both asymmetric centers in 38% yield. They also isolated the C-11 epimer in 5% yield and an olefin, which was the major byproduct of the reaction in 40% yield. The synthesis was completed by deprotection of the silyl ethers and subsequent sulfation to give (+)-1.1.

1.9. Vanderwal’s Total Synthesis of Malhamensilipin A

The Vanderwal group successfully completed an enantioselective synthesis of malhamensilipin A (1.2) in 2010,\textsuperscript{50} shortly after its structural revision in a joint effort with the Gerwick\textsuperscript{32} group. The Vanderwal group had previously explored a syn-selective dichlorination of Z-allylic esters, however that would prove unsuitable for the synthesis of 1.2 due to the syn-anti relationship of C14-C16.

The synthesis of 1.2 began with known ester 1.87, which underwent Sharpless asymmetric dihydroxylation (>95% ee) at the alkene to give a diol intermediate, and subsequent semireduction of the alkyne using P-2 Ni/ethylenediamine gave Z-allylic diol 1.88 (Scheme 1.13). Selective nosylation of the \(\alpha\)-hydroxy group followed by alkene dichlorination (dr = >10:1) using Mioskowski’s reagent\textsuperscript{33} provided the desired syn-anti-stereotriad 1.89. This was unexpected as this reagent usually afforded a syn-syn-stereotriad with varying selectivity.\textsuperscript{51-52}
The selectivity for this particular case is not yet fully understood by the Vanderwal group. Base mediated cis-epoxidation followed by reduction of the ester with DIBAL set the stage for the Wittig coupling reaction. The resulting aldehyde was coupled to phosphonium salt 1.90, synthesized in the same fashion as previously reported by the Vanderwal group.31 This Wittig reaction afforded 1.91 with a Z:E geometry of 2:1 favoring the Z isomer. Chlorine induced epoxide ring opening using excess Et₄NCl and BF₃•OEt₂ as previously discovered by the Vanderwal group,31 provided stereospecific ring opening with inversion of stereochemistry to afford Z-syn-chlorohydrin 1.92 directly from the Z:E mixture. Diastereoselective dichlorination of the alkene with Et₄NCl gave 1.93 with a dr = 8:1. Silyl ether deprotection and simultaneous sulfation using chlorosulfonic acid delivered a bis-sulfate intermediate. Stereoselective HCl elimination using excess LDA, a reaction that had been previously studied in simpler model systems,32 afforded a single alkene product corresponding to 1.2, thus completing the synthesis of the natural product. They completed the synthesis in eleven steps from the ester using chemo-, regio-, diastereo-, and enantioselective steps, each with a high degree of stereocontrol.

1.10. Carreira’s Total Synthesis of Undecachlorosulfolipid A

In 2011, the Carreira group tackled the synthetically challenging synthesis of the most complex CSL isolated thus far, (+)-undecachlorosulfolipid A, which contains 11 chloride substituents and nine contiguous stereocenters. Upon completion of their synthesis they discovered that the structure of the natural product had been assigned incorrectly.60 Their synthesis utilized a Julia-Kocienski coupling reaction between aldehyde 1.98 and sulfone 1.106 as one of their key steps.
Scheme 1.13 Vanderwal’s total synthesis of (+)-Malhamensilipin A

The synthesis of aldehyde 1.98 began with ester 1.94, which was synthesized from commercially available (S)-1,2,4-butanetriol (Scheme 1.14). Dichlorination of the more electron rich alkene with Et$_4$NCl$_3$ occurred with slight preference for the desired diastereomer, dr = 1.8:1. Reduction of the ester with DIBAL, acetylation of the resulting primary alcohol, Sharpless asymmetric dihydroxylation at the remaining alkene followed by cyclodehydration via triflation gave cis-epoxide 1.95 as a single stereoisomer. 1.95 was transformed to 1.97 via a series of protecting group manipulations including acetonide removal, TBS protection, selective deprotection, Dess-Martin oxidation, and a Wittig reaction using phosphonium salt 1.96, synthesized from commercially available (S)-ethyl lactate. Z-olefin 1.97 underwent
stereospecific \textit{anti}-1,2-dichlorination with Et$_4$NCl$^{33}$ (dr = 5:1) followed by deacetylation and Dess-Martin oxidation to provide aldehyde 1.98.

Scheme 1.14 Carreira’s synthesis of aldehyde coupling fragment for Undecachlorosulfolipid A

The synthesis of sulfone 1.106 commenced with commercially available 1,5-pentandiol 1.99 which was then transformed into alcohol 1.100 in only a few steps (Scheme 1.15). Mono-TBDPS protection, TEMPO oxidation, $\alpha,\alpha$-dichlorination via NCS and tBuNH$_2$\textsuperscript{61-62} and enantioselective Zn-acetylide\textsuperscript{63} addition to the $\alpha,\alpha$-dichloroaldehyde provided 1.100 in 92\% ee. Semi-reduction of the alkyne with Red-Al, vanadium-catalyzed epoxidation, and Dess-Martin oxidation of the secondary alcohol to the ketone afforded 1.101. Regioselective epoxide ring opening of 1.101 with ZrCl followed by diastereoselective reduction of the ketone with NaBH$_4$ provided \textit{anti}-chlorohydrin 1.102, setting the desired C7-C9 stereotriad with an \textit{anti-syn} relationship.
Acetonide protection of the 1,3-diol, removal the primary silyl ether with TBAF, Dess-Martin oxidation of the resulting primary alcohol, and a Still-Gennari olefination provided Z-α,β-unsaturated ester 1.103. Cis-epoxide 1.104 was synthesized by reducing ester 1.103 to the primary alcohol with DIBAL followed by Sharpless asymmetric epoxidation with dr = 9:1. Diastereoselective epoxide ring opening with TiCl(OiPr)₃ proceeded via inversion of stereochemistry to give syn-chlorohydrin 1.105, however with low regioselectivity (1,2-diol:1,3-diol = 2:3). The synthesis of this coupling partner was completed by acetonide formation, benzyl
ether cleavage via hydrogenation, Mitsunobu displacement of the primary alcohol with phenyltetrazolylsulfide, followed by oxidation to the sulfone using mCPBA.

With both coupling partners synthesized, the key Julia-Kocienski coupling step was performed between aldehyde 1.98 and sulfone 1.106 in the presence of freshly prepared NaHMDS to give epoxide 1.107 (Z:E = 3:1). Epoxide ring opening with Ph₃PCl₂ proceeded with inversion to afford the desired syn-chlorohydrin 1.108. Subsequent anti-1,2-dichlorination using Et₃NCl₃ produced syn-1,2-dichloride 1.109 with high diastereoselectivity. Deprotection of the benzyl ether with Pd/C and H₂ followed by E-olefin formation with Martin sulfurane and subsequent silyl ether deprotection with HF-pyridine afforded E-olefin 1.110. Regioselective esterification with palmitoyl chloride of the triol, regioselective sulfation of the diol, and removal of the acetonide groups via acidic hydrolysis delivered the completed natural product 1.2.

1.11. Conclusion

Although chlorosulfolipids (CSLs) were first isolated in the 1960s, the first investigations towards their total synthesis did not commence until 2009 mainly due to the lack of synthetic methods to access the polychlorinated motifs and the ambiguity of their absolute configuration. Advancements in NMR technology over the years has allowed for the proper determination of the absolute configuration of CSLs and the development of stereoselective chlorination reactions has made the synthesis of this class of natural products possible. Since Carreira’s inaugural total synthesis of a member of the CSLs in 2009, a number of other groups have also achieved total syntheses of other members of the CSLs including Vanderwal, Matsuda, and Yoshimitsu. Each group employed their own stereoselective chlorination reactions to access the polychlorinated scaffold of the CSLs.
Throughout the syntheses unanticipated stereoselectivities were discovered when attempting to chlorinate frameworks containing neighboring chlorine atoms, as anchimeric assistance of the chloride ions revealed unanticipated outcomes with retention of configuration. Carreira was the first to discover this phenomenon but was also validated by the Vanderwal group. The ability to overcome such disadvantages has allowed for the total syntheses of a number of CSLs, which
should facilitate in biological studies since isolation of significant quantities from natural sources has proven troublesome. This is especially important since many aspects of the biosynthesis of the CSLs remain largely unknown. From the syntheses of CSLs to date, it is evident that the development of chlorination methodologies to access the stereogenic structural motifs of CSLs is imperative. Thus, the development of a chlorination strategy that is readily tolerable by a wide variety of functionalities is an important precursor to constructing a total synthesis of CSLs.

1.12. References


CHAPTER TWO: CHLORINATION OF ALIPHATIC PRIMARY ALCOHOLS VIA TRIPHOSGENE-TRIETHYLAMINE ACTIVATION

2.1. Purpose

The purpose of this chapter is to detail our interest in chloride-containing natural products, specifically the chlorosulfolipids, and our strategy in developing a chlorination method to access the chemical architecture of these natural products. A novel chlorination method is not only important in natural product synthesis but also useful in synthetic organic transformations, as alkyl chlorides are a commonly used and important functionality. This chapter will then introduce our novel methodology, a mild chlorination of primary aliphatic alcohols via a triphosgene-triethylamine activation. This highly useful transformation was readily tolerable by a wide range of sensitive and common functionalities. A detailed description of the reaction mechanism and the scope of the reaction will be presented.

2.2. Classical Chlorination Methods

There are currently over 2000 chlorine-containing natural products that have been identified.\textsuperscript{1-2} Aside from natural products, chlorine-containing small molecules are as equally important to the industrial, agricultural, and pharmaceutical fields.\textsuperscript{3-4} The placement of chlorine atoms on small molecules plays a critical role in determining the biological activity of those molecules.\textsuperscript{4} Alkyl chlorides are also important synthons in synthetic organic chemistry and have been used widely to achieve synthetic transformations to add complexity to molecules.\textsuperscript{5-6} There are a number of classical chlorination methods that have been developed over the years, however, many use harsh reagents or are not adequate for complex molecules with sensitive functionalities. As a result of the widespread use of chlorine-containing molecules in the

synthesis of natural products as well as in industrial, agricultural, and pharmaceutical fields, research in the synthetic development of novel chlorination methods is essential.\textsuperscript{7-12}

2.2.1. Interest in Chlorination Methods

Our research group is interested in a group of chlorine-containing natural products known as the chlorosulfolipids. These natural products consist of a long hydrocarbon backbone with multiple chloride and sulfate substituents. We envisioned developing a method allowing us to chlorinate multiple hydroxy groups via a global chlorination strategy in order to access these natural products, as shown in Scheme 2.1. It would be readily feasible to construct enantio- and diastereoselective polyols using known synthetic protocols. There are currently no literature precedents for the global chlorination of multiple hydroxy groups. However, there are multiple reports in the literature for the conversion of an alcohol to a chloride to introduce a single chloride containing stereogenic center.\textsuperscript{1} Developing a method to be used in a reaction of this magnitude would require mild conditions that complex intermediates with sensitive functionalities could withstand. Another major concern is stereochemical control, as multiple stereogenic centers would be reacting simultaneously, possibly scrambling with one another leading to undesired outcomes.

![Scheme 2.1 Proposed global chlorination strategy](image)

2.3. Preliminary Study

In our initial investigation towards the chlorination of primary alcohols in the presence of nearby ionizable functionalities, we used 1,3-diol \textbf{2.1a} as our model substrate.\textsuperscript{13} We then reacted
2.1a with a variety of classical chlorination methods in addition to our method, in order to prove the effectiveness of our reaction conditions. As shown in Table 2.1, treatment of model substrate 2.1a, using classical chlorinating reagents such as SOCl₂ and PCl₅ (entries 1-2), resulted in complex product mixtures with no primary chloride products being isolated. Treatment of 2.1a under Appel type conditions, using CCl₄ and PPh₃, did in fact produce the primary chloride, but only in 30% isolated yield (entry 3). Further attempts using a PPh₃-triphosgene activation led to an improved isolated yield of the primary chloride at 78%, however, this reaction was hampered by the tedious removal of the triphenylphosphine-derived byproducts. Interestingly, exposure of our model substrate to a triphosgene-triethylamine activation led to the target compound 2.2a in near quantitative yield (entry 5). As a comparative experiment, treatment of 2.1a with a commercially purchased phosgene solution also led to the target alkyl chloride 2.2a in excellent yield (entry 6). In entries 5-6, chlorination was selective for the primary alcohol, leaving the nearby tertiary alcohol intact. In entries 7-8, in an attempt to screen other amine bases as a substitute for triethylamine, such as pyridine or diisopropylethyl amine (Hünig’s base), they did not lead to chlorination at the primary alcohol position but instead produced cyclic carbonate 2.3 as the sole product.¹⁴

<table>
<thead>
<tr>
<th>entry</th>
<th>chlorinating agents</th>
<th>yield in 2.2a</th>
<th>yield in 2.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SOCl₂</td>
<td>complex mixture</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>PCl₅</td>
<td>complex mixture</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>CCl₄, PPh₃</td>
<td>30%</td>
<td>--</td>
</tr>
<tr>
<td>4</td>
<td>Triphosgene, PPh₃</td>
<td>78%</td>
<td>--</td>
</tr>
<tr>
<td>5</td>
<td>Triphosgene, TEA</td>
<td>98%</td>
<td>--</td>
</tr>
<tr>
<td>6</td>
<td>Phosgene, TEA</td>
<td>89%</td>
<td>--</td>
</tr>
<tr>
<td>7</td>
<td>Triphosgene, Py</td>
<td>--</td>
<td>86%</td>
</tr>
<tr>
<td>8</td>
<td>Triphosgene, DIPEA</td>
<td>--</td>
<td>45%</td>
</tr>
</tbody>
</table>

Figure 2.1 Optimization study
2.4. Use of Triphosgene

Triphosgene is a safe alternative for the toxic and dangerous phosgene gas. It exist as a stable nonhygroscopic crystalline material at room temperature making handling and storing more convenient and operational for laboratory experimentation than phosgene gas or diphosgene liquid.\textsuperscript{15-17} A further convenience to using triphosgene is that one mole equates to three moles of phosgene, therefore requiring less material to carry out similar reactions. Triphosgene has been widely used to achieve various functional group interconversions, particularly the insertion of the carbonyl moiety.\textsuperscript{18} There is substantial literature precedent for the conversion of reactive alcohols (i.e. benzylic, allylic, and propargylic) to their corresponding chlorides in pyridine-buffered organic media via triphosgene activation.\textsuperscript{19} However, chlorination of unreactive aliphatic alcohols requires stronger activation, primarily through the use of a nucleophilic promoter, such as triphenylphosphine, which facilitates in triphosgene decomposition, thus leading to chlorination.\textsuperscript{20-22}

2.5. Reaction Conditions

Given the unanticipated effectiveness of a triphosgene and triethylamine mixture to chlorinate model substrate 2.1a, further investigations into the scope and limitations of the reaction were necessary. Our optimized chlorination reaction consisted of 0.5 equivalents of triphosgene and 2.5 equivalents of triethylamine per equivalent of each participating hydroxy group. The activation was performed in dichloromethane at 0°C and allowed to warm to room temperature where it was stirred for three hours to ensure completion of the reaction prior to workup, although the starting material was consumed within minutes by TLC and GC-MS analysis. Reaction work up with 1M HCl followed by extraction in dichloromethane yielded a clean, crude reaction mixture.
2.6. Chlorination of Aliphatic Primary Alcohol vs. Tertiary Alcohol

A number of diols \(2.1a-2.1g\), synthesized by my colleagues, Caitlan Ayala and Alex Nguyen, are shown in Table 2.2, each containing a tertiary and primary alcohol. Upon exposure to our reaction conditions utilizing a triphosgene-triethylamine mixture, the diol substrates underwent chemoselective chlorination at the primary alcohol, leaving the highly ionizable tertiary alcohols intact, to afford chloroalcohols \(2.2a-2.2g\) in excellent yields.

![Chemoselective chlorination of aliphatic primary alcohols](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>starting material</th>
<th>product</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R_1)OH (\xrightarrow{\text{Triphosgene (0.5 equiv)} \xrightarrow{\text{Et}_3\text{N (2.5 equiv)} \xrightarrow{\text{CH}_2\text{Cl}_2, 0 \text{C} \rightarrow \text{rt}} \xrightarrow{\text{OH}} \text{R}_1)Cl</td>
<td>(2.1a)</td>
<td>98%</td>
</tr>
<tr>
<td>2</td>
<td>(R_2)OH (\xrightarrow{\text{Triphosgene (0.5 equiv)} \xrightarrow{\text{Et}_3\text{N (2.5 equiv)} \xrightarrow{\text{CH}_2\text{Cl}_2, 0 \text{C} \rightarrow \text{rt}} \xrightarrow{\text{OH}} \text{R}_1)Cl</td>
<td>(2.1b)</td>
<td>92%</td>
</tr>
<tr>
<td>3</td>
<td>(R_3)OH (\xrightarrow{\text{Triphosgene (0.5 equiv)} \xrightarrow{\text{Et}_3\text{N (2.5 equiv)} \xrightarrow{\text{CH}_2\text{Cl}_2, 0 \text{C} \rightarrow \text{rt}} \xrightarrow{\text{OH}} \text{R}_1)Cl</td>
<td>(2.1c)</td>
<td>89%</td>
</tr>
<tr>
<td>4</td>
<td>(R_4)OH (\xrightarrow{\text{Triphosgene (0.5 equiv)} \xrightarrow{\text{Et}_3\text{N (2.5 equiv)} \xrightarrow{\text{CH}_2\text{Cl}_2, 0 \text{C} \rightarrow \text{rt}} \xrightarrow{\text{OH}} \text{R}_1)Cl</td>
<td>(2.1d)</td>
<td>85%</td>
</tr>
<tr>
<td>5</td>
<td>(R_5)OH (\xrightarrow{\text{Triphosgene (0.5 equiv)} \xrightarrow{\text{Et}_3\text{N (2.5 equiv)} \xrightarrow{\text{CH}_2\text{Cl}_2, 0 \text{C} \rightarrow \text{rt}} \xrightarrow{\text{OH}} \text{R}_1)Cl</td>
<td>(2.1e)</td>
<td>97%</td>
</tr>
<tr>
<td>6</td>
<td>(R_6)OH (\xrightarrow{\text{Triphosgene (0.5 equiv)} \xrightarrow{\text{Et}_3\text{N (2.5 equiv)} \xrightarrow{\text{CH}_2\text{Cl}_2, 0 \text{C} \rightarrow \text{rt}} \xrightarrow{\text{OH}} \text{R}_1)Cl</td>
<td>(2.1f)</td>
<td>93%</td>
</tr>
<tr>
<td>7</td>
<td>(R_7)OH (\xrightarrow{\text{Triphosgene (0.5 equiv)} \xrightarrow{\text{Et}_3\text{N (2.5 equiv)} \xrightarrow{\text{CH}_2\text{Cl}_2, 0 \text{C} \rightarrow \text{rt}} \xrightarrow{\text{OH}} \text{R}_1)Cl</td>
<td>(2.1g)</td>
<td>96%</td>
</tr>
</tbody>
</table>

Figure 2.2 Chemoselective chlorination of aliphatic primary alcohols
The reactions were performed under anhydrous conditions, however, as shown in entry 1, the chlorination was also achieved under nonanhydrous conditions, to afford chloroalcohol 2.2a in similar yield. Entries 2-3 demonstrate that the distance between the two hydroxy groups has no effect on the chlorination of the primary alcohol, and the structural identity of the resulting chloroalcohols, 2.2b and 2.2c were confirmed through X-ray crystallography (Figure 2.1). The highly ionizable tertiary allyl alcohol shown in entry 4 was stable under the reaction conditions, validating the mildness of the reaction. Entries 5-7 with similarly stable ionizable tertiary alcohols (2.1e-2.1g), further established this conclusion, affording chloroalcohols 2.2e-2.2g in excellent yields.

Figure 2.3. X-ray crystallographic data for 2.2b and 2.2c

2.7. Functional Group Compatibility

To further evaluate the compatibility of our chlorination reaction against common functional and protecting groups, my colleagues and I strategically synthesized the primary alcohol substrates in Table 2.3. Simple aliphatic alcohols 2.4a and 2.4b gave their corresponding alkyl chlorides 2.5a and 2.5b in good yields, 82% and 67% respectively. The highly ionizable epoxide 2.4c was also a suitable substrate, remaining intact under the reaction conditions to give the primary chloride 2.5c in 87%. Primary alcohols 2.4d-2.4f (entries 4-6), containing the acid
sensitive protecting groups, THP and TBS ethers readily gave the primary chlorides in excellent yields. Benzyl ether **2.4g** and aryl ester **2.4h** (entries 7-8) were also readily converted to their corresponding alkyl chlorides **2.5g** and **2.5h** in 84% and 98% yield, respectively. The lower isolated yields for entries 2 and 4 are attributed to the high volatility of the alkyl chloride products **2.5b** and **2.5d**. I was responsible for synthesizing primary alcohols **2.4d**, **2.4f**, and **2.4g** and subjecting them to our chlorination conditions to afford their corresponding chloroalcohols **2.5d**, **2.5f**, and **2.5g**.

![Chemical structures and reaction conditions]

<table>
<thead>
<tr>
<th>entry</th>
<th>starting material</th>
<th>product</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;H&lt;/sub&gt;</td>
<td>Ph&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;Cl&lt;/sub&gt;</td>
<td>82%</td>
</tr>
<tr>
<td>2</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;H&lt;/sub&gt;OH</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;H&lt;/sub&gt;Cl</td>
<td>67%</td>
</tr>
<tr>
<td>3</td>
<td>Ph&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;H&lt;/sub&gt;</td>
<td>Ph&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;Cl&lt;/sub&gt;</td>
<td>87%</td>
</tr>
<tr>
<td>4</td>
<td>Ph&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;H&lt;/sub&gt;</td>
<td>Ph&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;Cl&lt;/sub&gt;</td>
<td>87%</td>
</tr>
<tr>
<td>5</td>
<td>TBSO&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;H&lt;/sub&gt;</td>
<td>TBSO&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;Cl&lt;/sub&gt;</td>
<td>78%</td>
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<tr>
<td>6</td>
<td>OTBS&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;H&lt;/sub&gt;</td>
<td>OTBS&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;Cl&lt;/sub&gt;</td>
<td>81%</td>
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<tr>
<td>7</td>
<td>Ph&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;H&lt;/sub&gt;</td>
<td>Ph&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;Cl&lt;/sub&gt;</td>
<td>84%</td>
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<td>8</td>
<td>p-Tol&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;H&lt;/sub&gt;OH</td>
<td>p-Tol&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;H&lt;/sub&gt;Cl</td>
<td>98%</td>
</tr>
</tbody>
</table>

Figure 2.4 Functional group compatibility
2.8. α-Branched Primary Alcohols

Table 2.4 highlights our attempt to chlorinate primary alcohols with branching at the α-carbon in relation to the hydroxy group. My colleagues, Caitlan Ayala and Alex Nguyen, synthesized these substrates, but much to our surprise these alcohols did not undergo chlorination, instead producing their respective diethylcarbamate adducts in moderate yield. 23-26

2-phenyl-propanol 2.6a and 2,2-diphenylethanol 2.6b (entries 1-2) gave diethylcarbamates 2.7a and 2.7b in 62% and 85% yield, respectively. N-Boc-prolinol 2.6c and adamantyl diol 2.6d also provided their corresponding diethylcarbamate products 2.7c and 2.7d in moderate yield, 73% and 62% yield, respectively.

![Figure 2.5 Reactivity of α-Branched primary alcohols](image-url)
2.9. Examining Secondary Alcohol Reactivity

Having established the reactivity patterns of primary and tertiary alcohols, we inevitably turned our attention towards the reactivity of secondary alcohols. Table 2.5 shows our efforts towards the chlorination of various secondary alcohols synthesized by my colleagues and I. In our initial experiment, symmetrical secondary alcohol, 1,3-diphenylpropan-2-ol 2.8a was treated with our standard reaction conditions, resulting in an almost one-to-one mixture of diethylcarbamate 2.9a (40%) and secondary chloride 2.10a (50%) (entry 1). Treatment of diol 2.8b resulted in a mixture of chloro-diethylcarbamate 2.9b (23%) and alkyl dichloride 2.10b (69%), favoring the dichloride in a three-to-one ratio. We attributed the increased dichloride formation to the higher concentration of chloride ions resulting from the doubling of equivalents of triphosgene-triethylamine. Diol 2.8c containing a reactive secondary benzylic alcohol gave dichloride 2.10c exclusively in 91% yield (entry 3). α-Branched secondary alcohols 2.8d and 2.8e (entries 4-5), reacted unexpectedly to produce a mixture of products. We hypothesized that secondary alcohol 2.8d would favor diethylcarbamate formation at the secondary alcohol given the previous reactivity patterns discovered from α-branched alcohols in Table 2.4. Instead, secondary alcohol 2.8d produced a mixture of chloro-diethylcarbamate 2.9d and dichloride 2.10d in 32% and 42% yield, respectively. Chlorination of enantiomerically pure secondary alcohol 2.8e produced a mixture of optically active diethylcarbamate 2.9e (27%) and secondary chloride 2.10e (45%), with complete inversion of the parent stereogenic center. Inversion at the parent stereogenic center of secondary alcohol 2.8e, strongly suggested that our reaction proceeded via an S_N2 type reaction pathway. I was responsible for synthesizing secondary alcohols 2.8a, 2.8d, and 2.8e and subjecting them to our chlorination conditions, affording a mixture of products.
2.10. Reaction Mechanism

An explanation of our proposed mechanism is highlighted in Scheme 2.2. My colleague, Caitlan Ayala, performed a series of GC-MS studies leading to our proposed mechanism. We found that activation of a primary alcohol in the presence of triphosgene and triethylamine quickly led to the formation of chloroformate 2.11. In the absence of $\alpha$-branching, the in situ generated chloride ions rapidly attack at the C1 carbon providing alkyl chloride 2.5 while

![Scheme 2.2](image-url)
releasing CO₂ and another chloride ion equivalent. However, with α-branching, the present steric hindrance greatly affects the rate of substitution by chloride ions. Addition of triethylamine to the acyl carbon outcompetes chloride addition at C1 and produces acylammonium ion intermediate **2.12**. This intermediate was not observable via GC-MS and is presumed to be short lived, if it exists. The acylammonium ion intermediate **2.12** then loses an ethyl group via nucleophilic attack by a chloride ion to produce the observed diethylcarbamate **2.7**. The acylammonium ion intermediate **2.12** showcases the dual role of triethylamine, both as a base and as a carbonyl activator. The use of other amine bases, such as pyridine or diisopropylethyl amine, did not lead to chlorination. This can be used as evidence for the intermediacy of **2.12** as an alternative mechanism for the formation of alkyl chloride **2.5** via C1 substitution of a chloride ion on the acylammonium ion intermediate **2.12**. Diethylcarbamoyl chloride **2.13** is an observable byproduct of this reaction, detectable via GC-MS and NMR, likely produced upon consumption of excess phosgenic species with triethylamine. However, **2.13** was found to have no affect on the direct alcohol carbamoylation leading to diethylcarbamate **2.7**.

Scheme 2.2 Proposed reaction mechanism
2.11. Conclusion

This chapter details a novel chemoselective chlorination of aliphatic primary alcohols using a triphosgene-triethylamine mixture. Simple aliphatic primary alcohols were readily converted to their respective alkyl chlorides in excellent yields. Secondary alcohols as well as \( \alpha \)-branched primary alcohols underwent competitive mechanistic pathways leading to either chlorination or diethylcarbamoylation. We determined that this alternate mechanistic pathway was influenced by steric demands at the carbon adjacent to the reactive center. Further studies were necessary in order to resolve the reactivity of secondary alcohols and \( \alpha \)-branched primary alcohols to favor chlorination over diethylcarbamate formation.

2.12. References


CHAPTER THREE: TRIPHOSGENE-AMINE BASE PROMOTED CHLORINATION OF UNACTIVATED ALIPHATIC ALCOHOLS

3.1. Purpose

The purpose of this chapter is to discuss the improvements of the reactivity of our novel chlorination reaction using triphosgene and triethylamine. While these conditions were excellent for transforming primary aliphatic alcohols to their corresponding alkyl chlorides, this amine based mixture proved problematic when exposed to \( \alpha \)-branched primary alcohols or secondary alcohols. Upon exposure of these substrates to the reaction conditions they either formed the diethylcarbamate exclusively or as a mixture of products with the targeted alkyl chloride. The competitive mechanistic pathway was driven by sterics via the intermediacy of the acylammonium ion, where nucleophilic attack by the chloride ion could occur at one of two carbon centers, leading to the mixture of observed products. After considerable optimization studies, these problems were eradicated by a simple in amine bases to pyridine instead of triethylamine, as shown in Scheme 3.1, resulting in the elimination of the diethylcarbamate adducts.

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} & \quad \text{O} & \quad \text{NET}_2 \\
\text{85\%} & \quad & & \\
\text{CH}_2\text{Cl}_2 & \quad 0 \degree \text{C} \rightarrow \text{rt} & \quad & \\
\text{Et}_3\text{N} & \quad & \quad & \\
\text{Ph} & \quad \text{Ph} & \quad \text{O} & \quad \text{Cl} \\
\text{81\%} & \quad & & \\
\end{align*}
\]

Scheme 3.1. Comparing previous work to optimized conditions

3.2. Optimization Study Varying Equivalents of Triethylamine

Our initial studies to improve the reactivity of secondary alcohols began with a comprehensive study in which we varied the equivalents of triethylamine while maintaining 0.5 equivalents of triphosgene and analyzing the crude reaction mixtures via GC-MS. The model substrate used throughout our optimization studies was enantiomerically pure secondary alcohol 3.1. In our previously optimized conditions, we had used 2.5 equivalents of triethylamine to affect the chlorination transformation. As shown in Figure 3.1, our first optimization study varied the equivalents of triethylamine from 1.0 to 2.0 increasing by 0.25 equivalents for each entry. The reactions were all run using the same procedure in either dichloromethane or toluene. The rationale behind lowering the concentration of triethylamine was that a lower concentration might inhibit the formation of the diethylcarbamate functionality 3.4.

In entry 1, using 1.0 equivalent of triethylamine in DCM, the primary product of the reaction was chloroformate 3.2, with minimal formation of alkyl chloride 3.3 or diethylcarbamate 3.4. As expected, as we gradually increased the concentration of triethylamine up to 2.0 equivalents, we observed the disappearance of chloroformate 3.2, however, we also observed a nearly equal appearance of alkyl chloride 3.3 and diethylcarbamate 3.4. Entries 2-5 indicate a near 1:1 ratio of alkyl chloride 3.3 to diethylcarbamate 3.4 production regardless of the concentration of triethylamine. In entries 6-10, in which we ran an identical set of reactions in toluene, we almost exclusively obtained chloroformate 3.2 regardless of triethylamine concentration.
3.3. Optimization Study Using Mixed Amine Base System

From our initial optimization study we concluded that triethylamine alone, as the base and carbonyl activator, was not suitable to complete our intended chlorination. Our ensuing optimization study explored the use of a mixture of amine bases, such as pyridine and triethylamine. Based on our proposed acylammonium ion intermediate 3.5, we hypothesized that our chlorination reaction could take advantage of a stoichiometric amount of pyridine to serve as the base, and a substoichiometric amount of triethylamine to serve as the carbonyl activator, thus promoting chlorination.

As shown in Scheme 3.2, the formation of acylammonium ion intermediate 3.5 would be favored based on the proton transfer equilibrium between protonated pyridine and triethylamine upon chloroformylation 3.2 of the alcohol starting material. This is due to the difference in the pKₐ values of the conjugate acids of pyridine and triethylamine. As shown in Scheme 3.2, a
steady concentration of unprotonated triethylamine will remain in equilibrium as turnover of the reaction continues. As a new alkyl chloride molecule 3.3 is produced, CO₂ and triethylamine are released. Triethylamine can then cycle back and attack another chloroformylation intermediate 3.2, producing acylammonium ion 3.5, thus promoting nucleophilic substitution by free chloride ions.

Figure 3.2 displays our optimization study focusing on utilizing a mixture of amine bases with activation occurring at 0° and then being warmed to room temperature or heated to reflux in dichloromethane. In entries 1-8 we use 1.2 equivalents of pyridine and vary the amount of triethylamine from 0.25 equivalents up to 1.0 equivalent in increments of 0.25. Entries 1-4 were activated at 0° and allowed to warm to room temperature over six hours before being analyzed by GC-MS. Entries 5-8 were ran under identical protocols but allowed to heat to reflux. In entries 1-8, in which we varied the substoichiometric amounts of triethylamine, we were successfully able to suppress the formation of diethylcarbamate 3.4. The reactions conducted at
room temperature (entries 1-4) mostly led to the formation of chloroformate 3.2, but upon heating the reactions to reflux (entries 5-8) we observed an increase in the formation of alkyl chloride 3.3. Entry 7 revealed that using 1.2 equivalents of pyridine and 0.75 equivalents of triethylamine successfully converted secondary alcohol 3.1 to alkyl chloride 3.3 in quantitative yield by GC-MS analysis of the crude reaction mixture.

![Figure 3.2 Optimization study with mixed amine base system](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>amt of Py, equiv</th>
<th>amt of Et₃N, equiv</th>
<th>conditions</th>
<th>3.1</th>
<th>3.2</th>
<th>3.3</th>
<th>3.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2</td>
<td>0.25</td>
<td>0 °C → room temp</td>
<td>0</td>
<td>98</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>1.2</td>
<td>0.50</td>
<td>0 °C → room temp</td>
<td>0</td>
<td>75</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1.2</td>
<td>0.75</td>
<td>0 °C → room temp</td>
<td>0</td>
<td>60</td>
<td>39</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1.2</td>
<td>1.00</td>
<td>0 °C → room temp</td>
<td>0</td>
<td>50</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>1.2</td>
<td>0.25</td>
<td>0 °C → reflux</td>
<td>0</td>
<td>34</td>
<td>66</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>1.2</td>
<td>0.50</td>
<td>0 °C → reflux</td>
<td>0</td>
<td>9</td>
<td>90</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>1.2</td>
<td>0.75</td>
<td>0 °C → reflux</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>1.2</td>
<td>1.00</td>
<td>0 °C → reflux</td>
<td>0</td>
<td>1</td>
<td>90</td>
<td>9</td>
</tr>
<tr>
<td>9</td>
<td>1.0</td>
<td>0</td>
<td>0 °C → room temp</td>
<td>93</td>
<td>0</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>1.2</td>
<td>0</td>
<td>0 °C → room temp</td>
<td>75</td>
<td>0</td>
<td>25</td>
<td>0</td>
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<td>11</td>
<td>1.7</td>
<td>0</td>
<td>0 °C → room temp</td>
<td>35</td>
<td>0</td>
<td>65</td>
<td>0</td>
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<td>12</td>
<td>2.2</td>
<td>0</td>
<td>0 °C → room temp</td>
<td>28</td>
<td>0</td>
<td>72</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>1.0</td>
<td>0</td>
<td>0 °C → reflux</td>
<td>69</td>
<td>0</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>1.2</td>
<td>0</td>
<td>0 °C → reflux</td>
<td>44</td>
<td>0</td>
<td>56</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>1.7</td>
<td>0</td>
<td>0 °C → reflux</td>
<td>2</td>
<td>0</td>
<td>98</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>2.2</td>
<td>0</td>
<td>0 °C → reflux</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

Further investigation into the role of pyridine led to an unexpected result. In entries 9-12, we used pyridine as the lone base and carbonyl activator, varying from 1.0 equivalent up to an
excess of 2.2 equivalents with activation at 0° and allowing the reaction to warm to room temperature over six hours. We discovered that as we increased the amount of pyridine in the reaction we were steadily increasing the formation of alkyl chloride 3.3 with no observable evidence of diethylcarbamate 3.4. When we ran this same set of reactions at reflux (entries 13-16), we observed the complete consumption of starting alcohol 3.1 in the presence of excess pyridine. In entry 13, using 1.0 equivalent of pyridine, there is a 2:1 mixture of starting material 3.1 to alkyl chloride 3.3. However, when we increased to 1.2 equivalents of pyridine there is roughly a 1:1 mixture of chloroformate 3.2 to alkyl chloride 3.3. These experiments suggested that our reaction proceeds via the intermediacy of chloroformate 3.2, as we had suspected. In entry 16, under an excess of 2.2 equivalents of pyridine, we produced the target alkyl chloride 3.3 in quantitative yield and completely eliminated the formation of the diethylcarbamate 3.4 byproduct.

3.4. Optimal Reaction Conditions

There are substantial literature precedents for using a triphosgene-pyridine mixture to chlorinate activated alcohols, such as benzylic, allylic and propargylic systems.\(^5\) There are also literature precedents for the use of a triphosgene-pyridine mixture to convert aliphatic alcohols to their corresponding chloroformates.\(^6-9\) However, the use of this particular system for the chlorination of unactivated aliphatic secondary alcohols remains unexplored. Our typical reaction conditions involved 0.5 equivalents of triphosgene and 2.0 equivalents of pyridine, per each participating hydroxy group, activated at 0° C in dichloromethane. The reaction was then heated to reflux and allowed to stir overnight to ensure the complete consumption of the starting alcohol. Unlike classical chlorination reactions using SOCl\(_2\) or PPh\(_3\) and NCS activation, the use of triphosgene-pyridine did not produce any nuisance byproducts. To evaluate the generality of
these reaction conditions, we screened a variety of secondary alcohols with various common functional and protecting groups.

3.5. Chlorination of Secondary Alcohols

Table 3.1 exhibits various aliphatic secondary alcohols containing common functionalities and protecting groups, all of which were synthesized by my colleagues and I. Enantiomerically pure secondary alcohol 3.6a, under our previous reaction conditions with triphosgene-triethylamine, resulted in a 2:1 product mixture between the targeted alkyl chloride and undesired diethylcarbamate. However, under our new optimized conditions, we successfully isolated alkyl chloride 3.7a in 89% yield, with a complete inversion of stereochemistry, analyzed via optical rotation and compared to its literature value. This substrate confirmed our reaction is stereospecific, and occurs with an inversion of stereochemistry via a presumed S_N2 type reaction mechanism. Simple secondary alcohols 3.6b-3.6c in both acyclic and cyclic forms were readily converted to their corresponding alkyl chlorides 3.7b-3.7c in excellent yields. Our reaction proved to be mild, as highly susceptible β-hydroxy ester 3.6d, synthesized by my colleague Caitlan Ayala, readily afforded the β-chloro ester 3.7d in 82% yield, with only minimal elimination (<10%). Olefins proved a suitable functionality, as secondary alcohols 3.6e-3.6f, containing both internal and external olefins, readily provided their corresponding alkyl chlorides 3.7e-3.7f in 94% and 82% yields, respectively. We also screened a number of protecting groups common in organic synthesis including, tert-butyl dimethylsilyl ether, benzyl ether, p-methoxybenzyl ether, and p-toluoyl ether in substrates 3.6g-3.6j. These protecting groups each reacted cleanly to afford their corresponding secondary alkyl chlorides 3.7g-3.7j in good yields. I was responsible for the synthesis of secondary alcohols 3.6a, 3.6b, 3.6g, 3.6i, and 3.6j and their corresponding alkyl chlorides.
Table 3.1 Chlorination of secondary alcohols with various functional groups

<table>
<thead>
<tr>
<th>entry</th>
<th>starting material</th>
<th>product</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me ( \text{Ph} )</td>
<td>( \text{Ph} )</td>
<td>89%</td>
</tr>
<tr>
<td>2</td>
<td>Ph ( \text{Ph} )</td>
<td>( \text{Ph} )</td>
<td>87%</td>
</tr>
<tr>
<td>3</td>
<td>HO ( \text{N-Boc} )</td>
<td>( \text{N-Boc} )</td>
<td>88%</td>
</tr>
<tr>
<td>4</td>
<td>EtO ( \text{Ph} )</td>
<td>( \text{Ph} )</td>
<td>82%</td>
</tr>
<tr>
<td>5</td>
<td>Ph ( \text{Ph} )</td>
<td>( \text{Ph} )</td>
<td>94%</td>
</tr>
<tr>
<td>6</td>
<td>Ph ( \text{Ph} )</td>
<td>( \text{Ph} )</td>
<td>82%</td>
</tr>
<tr>
<td>7</td>
<td>TBSO ( \text{Ph} )</td>
<td>( \text{Ph} )</td>
<td>90%</td>
</tr>
<tr>
<td>8</td>
<td>BnO ( \text{Ph} )</td>
<td>( \text{Ph} )</td>
<td>84%</td>
</tr>
<tr>
<td>9</td>
<td>PMBO ( \text{Ph} )</td>
<td>( \text{Ph} )</td>
<td>82%</td>
</tr>
<tr>
<td>10</td>
<td>( p\text{-toluoyl} \text{Ph} )</td>
<td>( p\text{-toluoyl} \text{Ph} )</td>
<td>85%</td>
</tr>
</tbody>
</table>
3.6. Reactivity of α-Branched Alcohols

Using a triphosgene-triethylamine mixture to chlorinate α-branched primary alcohols proved unsuccessful, as these conditions exclusively provided the diethylcarbamate products. However, the use of a triphosgene-pyridine mixture resolved these reactivity issues. As shown in Table 3.2, using the same α-branched primary alcohols, we observe a complete reversal in reactivity. Primary alcohols 3.8a-3.8c exclusively afford their corresponding alkyl chlorides 3.9a-3.9c under the optimized conditions, in excellent yields.

Table 3.2 Chlorination of α-branched primary alcohols

<table>
<thead>
<tr>
<th>entry</th>
<th>starting material</th>
<th>product</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R=Ph OH</td>
<td>R=Ph Cl</td>
<td>81%</td>
</tr>
<tr>
<td>2</td>
<td>R=Me OH</td>
<td>R=Me Cl</td>
<td>86%</td>
</tr>
<tr>
<td>3</td>
<td>R=Ome OH</td>
<td>R=Ome Cl</td>
<td>65%</td>
</tr>
</tbody>
</table>

3.7. Extension Towards Diol Chlorination

With optimized reaction conditions that successfully chlorinate both primary and secondary aliphatic alcohols, we shifted our focus towards the chlorination of 1,3- and 1,6-diols. Scheme 3.3 highlights our initial attempts to simultaneously introduce two carbon-chlorine
bonds via global chlorination of multiple hydroxy groups. Treatment of 1,3-diol 3.10, doubling the equivalents of triphosgene (1.0 equivalent) and pyridine (4.0 equivalents) successfully produced alkyl 1,3-dichloride 3.11 in 55% yield. The low isolated yield was attributed to the volatility of the dichloride product. 1,6-diol 3.12 was also subjected to double the equivalents of triphosgene and pyridine and afforded dichloride 3.13 in 73% yield. However, as we had anticipated, when the equivalents of triphosgene and pyridine were not doubled, as shown in the last equation of Scheme 3.3, a mixture of products were produced. There was no observable evidence of dichloride formation, instead, cyclic carbonate 3.15 was produced as the major product in 66% yield and chloro alcohol 3.14 was produced in 14% yield. We concluded that an excess of triphosgene-pyridine must be available to induce simultaneous dichlorination, in order to outcompete the intramolecular carbonate cyclization via the intermediacy of the monochloroformylation.11-12

Scheme 3.3 Reactivity of 1,3- and 1,6-diols
3.8. Reaction Mechanism

The proposed mechanism for the reaction is shown in Scheme 3.4. This reaction mechanism follows a similar reactivity pattern as that utilizing a triphosgene-triethylamine mixture. When triphosgene-pyridine activates the secondary alcohol it leads to the formation of chloroformate 3.16.\textsuperscript{2,6-9} The chloroformate is then activated by an additional equivalent of pyridine, resulting in the intermediacy of N-acylpyridinium species 3.17.\textsuperscript{13-15} The carbonyl activation by pyridine increases the reactivity at the electrophilic secondary carbon center, thus allowing for an S\textsubscript{N}2 nucleophilic attack by chloride ions. This produces the alkyl chloride with inversion of stereochemistry, while releasing CO\textsubscript{2} and pyridine.

![Scheme 3.4 Proposed reaction mechanism](image)

3.9. Conclusion

This chapter details the novel chemoselective chlorination of unactivated secondary alcohols using a triphosgene-pyridine mixture while addressing the reactivity concerns associated with the use of a triphosgene-triethylamine mixture. The use of triphosgene-pyridine in dichloromethane at reflux successfully produced the desired alkyl chlorides in excellent yields while eliminating the formation of the diethylcarbamate byproduct. This reaction is high yielding.
and tolerable by a wide range of common functionalities and protecting groups making it highly useful towards the synthesis of complex molecules. Having established conditions for the chlorination of aliphatic primary and secondary alcohols, it was necessary to focus on the simultaneous global chlorination of multiple hydroxy groups in 1,3-anti and 1,3-syn diols.

3.10. References


4.1. Purpose

The purpose of this chapter is to describe the extension of our chlorination reaction to stereocomplementary acyclic aliphatic 1,3-diols using our mixture of triphosgene-pyridine. Our interest in chlorosulfolipids inspired our research in developing a novel chlorination reaction to access the intriguing molecular structure of these polychloride natural products.\textsuperscript{1-14} While most literature reports focus on developing methods to access vicinal dichloride structural motifs, there are limited reports that focus on the chlorination of the diastereomers of unactivated, acyclic 1,3-diols, as shown in Figure 4.1.\textsuperscript{3, 15} In our previous report,\textsuperscript{16} we had effectively dichlorinated a racemic 1,3 and 1,6-diol. Herein we report the chlorination of 1,3-\textit{anti} diols, which readily afforded their corresponding 1,3-\textit{anti} dichlorides. However, 1,3-\textit{syn} diols needed to be converted into 1,3-\textit{syn} diol monosilyl ethers in order to access their corresponding 1,3-\textit{syn} dichlorides. Furthermore, we report our first attempt at a global chlorination approach by chlorinating a set of 1,3,5-triols in a stereoselective manner.

![Figure 4.1 Comparison of 1,2-diols to 1,3-diols](image)

4.2. Previous Work

We previously reported novel methods to chlorinate primary and secondary aliphatic alcohols using a triphosgene-amine based reaction mixture.\textsuperscript{16-17} Our triphosgene-pyridine based method resolved previous reactivity issues associated with using a triphosgene-triethylamine mixture. As shown in Scheme 4.1, the mechanism of the reaction was proposed to proceed via the intermediacy of pyridinium carbamate 4.2, which was presumably produced upon nucleophilic addition of pyridine to chloroformate 4.1. Pyridinium carbamate 4.2 was susceptible to nucleophilic substitution by chloride ions at the carboxyl position to produce the target alkyl chlorides with inversion of stereochemistry. This process regenerated pyridine as the carbonyl promoter and released CO\textsubscript{2} as the byproduct.

\[\text{Scheme 4.1 Reaction mechanism determined from previous work}\]

4.3. Preliminary Results

Having successfully chlorinated a racemic 1,3-diol,\textsuperscript{16} our chlorination methodology put us in an advantageous position to contribute a viable solution to the synthesis of alkyl 1,3-\textit{anti} and 1,3-\textit{syn} dichlorides in a stereoselective manner. We began our initial study by synthesizing
stereocomplementary 1,3-anti and 1,3-syn diols, 4.3 and 4.6 respectively (Scheme 4.2).\textsuperscript{18} We treated each diol with our reaction conditions of 1.0 equivalent of triphosgene and 4.0 equivalents of pyridine in DCM activating the reaction at 0°C then allowing the reaction to reflux over 12 hours. We were well aware that 1,3-diols readily undergo cyclic carbonate cyclization with triphosgene and amine bases.\textsuperscript{19-23} Treatment of 1,3-anti diol 4.3 resulted in quantitative yield of the target alkyl 1,3-anti dichloride 4.4 (99%), while the cyclic carbonate 4.5 was only detectable in trace amount (1%) via GC-MS analysis of the crude reaction mixture. This result suggested that 1,3-anti diol in the presence of excess triphosgene and pyridine underwent double chloroformylation leading to the dichlorination product. However, when 1,3-syn diol 4.6 was reacted under the same conditions, the major product of the reaction was cyclic carbonate 4.8. Cyclic carbonate 4.8 was produced in 66% yield and 1,3-syn dichloride 4.7 was produced in 34% yield. We hypothesized that upon monochloroformylation, the free hydroxy group trapped the chloroformylation intermediate resulting in the facile 6-membered ring cyclization to form the thermodynamically favorable chair conformation in cyclic carbonate 4.8.

\begin{equation*}
\text{Ph} \begin{array}{c}
\text{OH} \\
\text{OH}
\end{array} \\
\text{4.3}
\end{equation*}

\rightarrow

\begin{equation*}
\text{Ph} \\
\text{Cl} \\
\text{Cl} \\
\text{4.4 (99\%)}
\end{equation*}

+ 

\begin{equation*}
\text{Ph} \begin{array}{c}
\text{O}
\end{array} \\
\text{O} \\
\text{4.5 (1\%)}
\end{equation*}

\begin{equation*}
\text{Ph} \begin{array}{c}
\text{OH} \\
\text{OH}
\end{array} \\
\text{4.6}
\end{equation*}

\rightarrow

\begin{equation*}
\text{Ph} \\
\text{Cl} \\
\text{Cl} \\
\text{4.7 (34\%)}
\end{equation*}

+ 

\begin{equation*}
\text{Ph} \begin{array}{c}
\text{O}
\end{array} \\
\text{O} \\
\text{4.8 (66\%)}
\end{equation*}

\textbf{Conditions:}

triphosgene (1.0 equiv), pyridine (4.0 equiv), CH\textsubscript{2}Cl\textsubscript{2}, 0 °C → reflux, 12 hrs

Scheme 4.2 Reactivity patterns of 1,3-anti and 1,3-syn diols
4.4. Chlorination of 1,3-anti Diols

Stemming from the results of our initial study using 1,3-anti and 1,3-syn diols 4.3 and 4.6, we proceeded to synthesize several 1,3-anti diols to undergo conversion to their respective 1,3-anti dichlorides. As shown in Figure 4.2, substrates 4.9a and 4.9b bearing aromatic, allylic, and aliphatic groups afforded their 1,3-anti dichlorides 4.10a and 4.10b in 90% and 65% yields, respectively. As previously reported,\textsuperscript{16} primary TBS ether found in 4.9c remained intact under our reaction conditions to provide alkyl 1,3-anti dichloride 4.10c in 80% yield.

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>starting material</th>
<th>product</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph OH OH R1 4.9a</td>
<td>Ph Cl Cl R1 4.10a</td>
<td>90%</td>
</tr>
<tr>
<td>2</td>
<td>Ph OH OH R1 4.9b</td>
<td>Ph Cl Cl R1 4.10b</td>
<td>65%</td>
</tr>
<tr>
<td>3</td>
<td>Ph OH OH R1 4.9c</td>
<td>Ph Cl Cl R1 4.10c</td>
<td>80%</td>
</tr>
<tr>
<td>4</td>
<td>Ph OH OH R1 4.9d</td>
<td>Ph Cl Cl R1 4.10d</td>
<td>73%</td>
</tr>
</tbody>
</table>

Figure 4.2 Dichlorination of 1,3-anti diols
Synthetically daunting 1,3-dichloro compounds were also easily accessible via our chlorination procedure. This was especially relevant with the conversion of 1,3-anti β,γ-dihydroxyester 4.9d to its corresponding 1,3-anti β,γ-dichloroester 4.10d in 73% yield. The tolerability of this highly sensitive substrate graciously demonstrates the mildness of our reaction conditions towards structurally complex starting materials. These reactions were carried out very cleanly and analysis of the crude reaction mixtures via GC-MS or NMR revealed quantitative conversion of the 1,3-anti diol starting materials to the target 1,3-anti dichlorides. My colleague Della Saputra was responsible for synthesizing 1,3-anti diol 4.9c and its corresponding dichloride 4.10c. The low percent yields in 4.10b and 4.10d were attributed to the high volatility of the alkyl dichlorides.

4.5. Optimization of 1,3-syn Diol Conversion

The results from our initial screening using 1,3-syn diol 4.6 revealed that the major product from this attempted chlorination was formation of cyclic carbonate 4.8. We envisioned solving this challenge by masking one of the hydroxy groups in the 1,3-syn diol as a monosilylether, therefore inhibiting the competitive formation of the cyclic carbonate. Our rationale behind this hypothesis is illustrated in Scheme 4.3. The free secondary alcohol in modified 1,3-syn diol 4.11 should be readily chlorinated when treated with our triphosgene-pyridine mixture via an intermediacy of pyridinium carbamate 4.12. This process then releases excess chloride ions from the decomposition of triphosgene. The free chloride ions simultaneously attack the pyridinium carbon while gradually cleaving the silyl ether functionality, revealing the second hydroxyl group, thus leading to putative chloroalcohol 4.13. With continued exposure to the triphosgene-pyridine mixture, intermediate 4.13 will undergo
chloroformylation at the exposed secondary hydroxy group, forming pyridinium carbamate 4.14, thus leading to the desired 1,3-syn dichloride.

Scheme 4.3 Chlorination strategy with 1,3-syn monosilylether

To test our hypothesis, we screened a number of silyl ether protecting groups as shown in Figure 4.3. In entries 2-5, we synthesized several monosilylethers 4.15, including trimethylsilyl ether, triethylsilyl ether, dimethylphenylsilyl ether, and diphenylmethyisilyl ether. Each of these substrates were treated with identical reaction conditions, 1.0 equivalent of triphosgene and 4.0 equivalents of pyridine in dichloromethane (25 mM concentration based on starting material) at reflux for 12 hours. From the screening of silyl ethers, we found that dimethylphenylsilyl ether yielded the best results (entry 4). The product ratio between 1,3-syn dichloride 4.7 and cyclic carbonate 4.8 was 80:20, determined via GC-MS analysis of the crude reaction mixtures. Further reaction optimization using the dimethylphenylsilyl ether substrate revealed that the transformation was concentration dependent. Increasing the concentration of the reaction altered
the selectivity between the dichloride and carbonate cyclization. In entries 6-8 we varied the concentration from 5 mM to 500 mM. We determined that increasing the reaction concentration to 500 mM improved the reaction selectivity to 99:1, favoring the 1,3-syn dichloride 4.7.

<table>
<thead>
<tr>
<th>entry</th>
<th>-R</th>
<th>concentration (mM)</th>
<th>dichloride 4.7 : carbonate 4.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-H</td>
<td>25</td>
<td>34 : 66</td>
</tr>
<tr>
<td>2</td>
<td>-SiMe₃</td>
<td>25</td>
<td>65 : 35</td>
</tr>
<tr>
<td>3</td>
<td>-SiEt₃</td>
<td>25</td>
<td>32 : 68</td>
</tr>
<tr>
<td>4</td>
<td>-SiMe₂Ph</td>
<td>25</td>
<td>80 : 20</td>
</tr>
<tr>
<td>5</td>
<td>-SiMe₂Ph₂</td>
<td>25</td>
<td>65 : 35</td>
</tr>
<tr>
<td>6</td>
<td>-SiMe₂Ph</td>
<td>5</td>
<td>69 : 31</td>
</tr>
<tr>
<td>7</td>
<td>-SiMe₂Ph</td>
<td>100</td>
<td>80 : 20</td>
</tr>
<tr>
<td>8</td>
<td>-SiMe₂Ph</td>
<td>500</td>
<td>99 : 1</td>
</tr>
</tbody>
</table>

Figure 4.3 Silyl ether screening and optimization study for monosilylether

4.6. Chlorination of Modified 1,3-syn Diols

After optimizing the reaction conditions for the dichlorination of 1,3-syn monosilylethers, we subjected the stereocomplementary diols to our triphosgene-pyridine mixture, as shown in Figure 4.4. The use of monosilylated 1,3-syn diols 4.16a containing a terminal alkene and 4.16b containing a long carbon chain, readily afforded 1,3-syn dichlorides 4.17a and 4.17b in 76% and 82% yields, respectively. Exposure of structurally complex 1,3-syn monosilylether 4.16c, containing primary TBS ether, resulted in 1,3-syn dichloride 4.17c in 94% yield. The successful conversion of monosilylated 1,3-syn β,γ-dihydroxy ester 4.16d to synthetically challenging 1,3-syn β,γ-dichloro ester 4.17d in 92% yield demonstrated the wide scope and mildness of our
methodology. As with the 1,3-\textit{anti} diol substrates, my colleague Della Saputra was responsible for synthesizing substrates 4.16c and 4.17c.

![Dichlorination of 1,3-syn diol monosilyl ethers](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>starting material</th>
<th>product</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph OH OR</td>
<td>Cl Cl</td>
<td>90%</td>
</tr>
<tr>
<td>2</td>
<td>Ph OH OR (_3)Me</td>
<td>Cl Cl (_3)Me</td>
<td>82%</td>
</tr>
<tr>
<td>3</td>
<td>Ph OH OR TBS</td>
<td>Cl Cl TBS</td>
<td>94%</td>
</tr>
<tr>
<td>4</td>
<td>Ph OR OH OtBu</td>
<td>Cl Cl OtBu</td>
<td>92%</td>
</tr>
</tbody>
</table>

Figure 4.4 Dichlorination of 1,3-syn diol monosilyl ethers

### 4.7. Chlorination of 1,3,5-triols

Having successfully chlorinated both 1,3-\textit{anti} and 1,3-syn diol substrates, we opted to push the limits of our reaction towards the construction of stereocomplementary alkyl 1,3,5-trichlorides from their corresponding aliphatic 1,3,5-triols. 1,3,5-\textit{anti} triol 4.18 was treated with 1.5 equivalents of triphosgene and 6.0 equivalents of pyridine in dichloromethane at reflux as shown in Scheme 4.4. GC-MS and NMR analysis of the crude reaction mixture revealed the full conversion of 1,3,5-\textit{anti} triol 4.18 to 1,3,5-\textit{anti} trichloride 4.19, resulting in a 75% yield after
purification via silica gel column chromatography. Treatment of modified 1,3,5-syn triol 4.20 with 1.5 equivalents of triphosgene and 6.0 equivalents of pyridine at the optimal 500 mM reaction concentration resulted in a 55% yield of the 1,3,5-syn trichloride 4.21. These substrates provided promising results to achieving our goal of a global chlorination strategy. Successfully installing three C-Cl bonds in a stereoselective fashion in one reaction in unprecedented. My colleague Della Saputra was responsible for the synthesis of 1,3,5-anti triol 4.18 and its corresponding 1,3,5-anti trichloride 4.19.

Scheme 4.4 Chlorination of stereocomplementary 1,3,5-triols

### 4.8. Determining Relative Stereochemistry

The relative stereochemistry of our acyclic chlorinated compounds was deduced by an analysis developed by Carman and Nouguier. They observed that the \(^{13}\)C chemical shifts of the 1,3-anti dichlorides, especially the C-Cl bonds \(C_\alpha\) and their vicinal carbons \(C_\beta\) and \(C_\beta'\), were roughly 1 ppm more downfield than those signals produced by the corresponding carbons of the 1,3-syn dichlorides. Application of this analysis to our alkyl 1,3-dichlorides, as shown in Figure 4.5, revealed similar
trends. As observed by Carman and Nouguier, the $^{13}$C NMR signals for the chlorinated carbons and their vicinal carbons for 1,3-anti dichlorides 4.9a-4.9d and 4.19 were consistently about 1 ppm more downfield than the corresponding carbons on the stereocomplementary 1,3-syn dichlorides 4.16a-4.16d and 4.21, respectively. Carman and Nouguier’s $^{13}$C NMR chemical shift analysis supported the stereoselectivity in our chlorination reactions. 1,3-anti diols provided 1,3-anti dichlorides whereas 1,3-syn diols lead to their corresponding 1,3-syn dichlorides.

![Figure 4.5 Carman-Nouguier $^{13}$C NMR analysis](image-url)
4.9. Synthesis of 4.9a

Synthesis of allylic 1,3-anti diol 4.9a (Scheme 4.5) commenced with an aldol addition between ethyl acetate and phenylacetaldehyde in the presence of LDA to form a hydroxy ester intermediate. The resulting crude ester was then reduced with LAH to provide diol 4.22. Racemic 1,3-diol 4.22 was then reacted with p-anisaldehyde in the presence of catalytic p-toluenesulfonic acid at reflux using a dean stark apparatus. The crude reaction mixture was then treated with NaBH₄ in methanol in order to create a better chromatographic separation of the desired PMP acetal 4.23 and residual p-anisaldehyde. PMP acetal 4.23 underwent a ring opening reaction with DIBAL, to exclusively afford PMB protected secondary alcohol and free primary alcohol 4.24, which was then oxidized under a TEMPO bleach oxidation resulting in PMB aldehyde 4.25. This aldehyde served as a common intermediate to accessing the majority of our 1,3-anti and 1,3-syn diol substrates. This sequence of reactions was easily carried out in large scale to access PMB aldehyde 4.25.
Anti-PMB alcohol 4.26 was produced upon reacting PMB aldehyde 4.25 with the Lewis acid TiCl$_2$(iPrO)$_2$ in DCM in the presence of molecular sieves, followed by the addition of allyl tributylstannane. Figure 4.6 shows the transition state complex created by the chelation of the titanium metal of the Lewis acid to the carbonyl oxygen and PMB oxygen in aldehyde 4.25. This conformation leads to the anti relationship of the two hydroxy groups after nucleophilic attack of the aldehyde. Attempts to cleave the PMB group directly from 4.26 with DDQ to access 1,3-anti diol 4.9a proved unsuccessful. Cleavage of the PMB group with DDQ would result in a mixture of products, however, the desired 1,3-anti diol 4.9a was never isolated. Protecting the free hydroxy group as an acetate, then DDQ deprotection of the PMB group followed by acetate deprotection using K$_2$CO$_3$ in methanol readily afforded allylic 1,3-anti diol 4.9a.

![Transition state model for nucleophilic attack of aldehyde](image)

**Figure 4.6 Transition state model for nucleophilic attack of aldehyde**

### 4.10. Synthesis of 4.9b and 4.9d

Having established a reliable method for accessing 1,3-anti diols from PMB aldehyde 4.25, the synthesis of the remaining 1,3-anti diol substrates proceeded readily. Long alkyl carbon chain 1,3-anti diol 4.9b was synthesized from anti-PMB alcohol 4.26 (Scheme 4.6). Allylic alcohol 4.26 was subjected to Grubbs II catalyst for an olefin cross metathesis with 6-hexene to yield 4.27. This intermediate was then subjected to Pd/C in MeOH and bubbled with hydrogen
gas until the double bond was hydrogenated and the PMB group cleaved simultaneously to yield the desired long carbon chain 1,3-anti diol 4.9b.

Scheme 4.6 Synthesis of long carbon chain 1,3-anti diol

The synthesis of tert-butyl ester 1,3-anti diol 4.9d commenced with the addition of tert-butyl ketene acetal to PMB aldehyde 4.25 in the presence of Lewis acid TiCl$_2$(iPrO)$_2$ (Scheme 4.7). Once again, this reaction proceeded through the titanium-chelated conformation shown in Figure 4.2 to afford anti-tert-butyl ester PMB alcohol 4.28. The PMB protecting group was then cleaved under hydrogenation conditions, Pd/C in MeOH and bubbled with hydrogen gas, to yield the desired tert-butyl ester 1,3-anti diol 4.9d in excellent yield.

Scheme 4.7 Synthesis of tert-butyl ester 1,3-anti diol
4.11. Synthesis of 1,3-syn Diols 4.16a and 4.16b

To access the 1,3-syn diastereomers we treated precursors of the 1,3-anti substrates to a Mitsunobu reaction in order to invert the stereochemistry of the free hydroxy group. As shown in Scheme 4.8, allylic 1,3-anti PMB alcohol 4.26 was treated with DEAD, PPh₃ and PNBA followed by K₂CO₃ in methanol resulting in the 1,3-syn diol moiety 4.29. Protection of the hydroxy group with Me₂PhSiCl followed by DDQ deprotection of the PMB protecting group resulted in modified allylic 1,3-syn diol 4.16a.

Scheme 4.8 Synthesis of allylic 1,3-syn diol monosilyl ether

Olefin cross metathesis using Grubbs II catalyst and 1-hexene with 4.16a yielded 4.30. The crude coupled compound 4.30 was then hydrogenated with Pd/C and H₂ gas to afford modified long carbon chain 1,3-syn diol 4.16b (Scheme 4.9).

Scheme 4.9 Synthesis of long chain 1,3-syn diol monosilyl ether
4.12. Synthesis of 4.16d

Synthesis of modified tert-butyl ester 1,3-syn diol 4.16d as shown in Scheme 4.10, began with a Grignard reaction between phenylacetaldehyde and allyl magnesium bromide to provide allylic alcohol 4.31. Methyl ester 4.32 was produced via an olefin cross metathesis using Grubbs II catalyst between methyl acrylate and allylic alcohol 4.31. Synthesizing methyl ester benzylidene acetal 4.33 proved troublesome. In my initial attempts at running this reaction following Evans\textsuperscript{27} protocol, the starting material was never fully consumed and although the procedure called for three additions of the reagents, often times five or more additions still did not complete the reaction. After meticulous experimentation, it was found that four additions of freshly distilled benzaldehyde and t-BuOK, at 15-minute intervals successfully produced target compound 4.33. Methyl ester hydrolysis with LiOH, followed by tert-butyl ester formation using Boc-anhydride in tert-butanol with catalytic DMAP provided tert-butyl ester 4.34. Tert-butyl diol 4.35 was produced by the slow cleavage of benzylidene acetal in acetic acid and water at 40°C. At this point, direct silyl ether protection of the diol using Me\textsubscript{2}PhSiCl was unsuccessful, as a mixture of mono-protection and di-protected products formed which were inseparable via column chromatography. However, the use of a bulkier protecting group, using PMB acetimidate provided mono-protected PMB alcohol 4.36. The placement of the PMB group was determined via a series of 2D and 3D NMR studies. However, it is worth noting that the position of the protecting group had no effect on the chlorination reaction, as both mono-protected diols would successfully provide the same 1,3-syn dichloride. The free hydroxy group in 4.36 was protected with Me\textsubscript{2}PhSiCl to provide di-protected intermediate 4.37, which was then treated with DDQ to cleave the PMB protecting group, affording the target tert-butyl ester 1,3-syn diol 4.16d.
4.13. Synthesis of 1,3,5-syn Triol

Synthesis of 1,3,5-syn triol began from intermediate 4.33 (Scheme 4.11), which was subjected to Pd(OH)$_2$ in MeOH and bubbled with hydrogen gas to cleave the benzylidene acetal, thus revealing methyl ester diol 4.38. Treatment of this diol with K$_2$CO$_3$ in MeOH to induce cyclization provided lactone 4.39. The free secondary alcohol was then protected with Me$_2$PhSiCl to provide intermediate 4.40. Subsequent lactone ring opening with LiBH$_4$ provided the modified 1,3,5-syn triol 4.21.
4.14. Conclusion

We were successfully able to implement our chlorination strategy to complex and stereocomplementary 1,3-anti and 1,3-syn diols. The use of triphosgene-pyridine mixture to these structurally intriguing substrates provided their corresponding alkyl dichlorides in excellent yields. Further investigations revealed that triols were readily chlorinated to provide trichloride compounds in excellent yields. There is now substantial evidence to further push the limits of our chlorination reaction towards executing a successful global chlorination strategy in the synthesis of chlorosulfolipid natural products.

4.15. References


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CHAPTER FIVE: EXPERIMENTALS

5.1. General Information

Unless otherwise noted, all materials were used as received from commercial suppliers without further purification. All anhydrous reactions were performed using oven-dried or flame-dried glassware, which were then cooled under vacuum and purged with nitrogen gas. Tetrahydrofuran (THF), dichloromethane (CH$_2$Cl$_2$), acetonitrile, toluene, and diethyl ether (Et$_2$O) were filtered through activated 3Å molecular sieves under nitrogen contained in an M-Braun Solvent Purification System. All reactions were monitored by EMD analytical thin layer chromatography (TLC Silica Gel 60 F$_{254}$, Glass Plates) and analyzed with 254 nm UV light and/or anisaldehyde – sulfuric acid or potassium permanganate treatment. Silica gel for column chromatography was purchased from Dynamic Adsorbents, Inc. (Flash Silica Gel 32-63u). Unless otherwise noted, all $^1$H and $^{13}$C NMR spectra were recorded in CDCl$_3$ using a Bruker DPX-250 spectrometer operating at 250 MHz for $^1$H and 62.5 MHz for $^{13}$C. Chemical shifts (δ) are reported in ppm relative to residual CHCl$_3$ as an internal reference ($^1$H: 7.26 ppm, $^{13}$C: 77.00 ppm). Coupling constants (J) are reported in Hertz (Hz). Peak multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), x (septet), h (heptet), b (broad), and m (multiplet). FT-IR spectra were recorded on Bruker Tensor 27 spectrometer and OPUS 6.5 Data Collection Program, and absorption frequencies were reported in reciprocal centimeters (cm$^{-1}$). High Resolution Mass Spectrometry – Electron Spray Ionization (HRMS-ESI) analyses were performed by the Louisiana State University Mass Spectrometry Facility using an Agilent 6210 Instrument. X-ray structure analyses were performed by the Louisiana State University X-ray Structure Facility using a Bruker APEX-II CCD diffractometer. Gas Chromatography – Mass Spectrometry (GC-MS) studies were conducted on an Agilent Technologies 6890N
Network GC System model number G1530N with 7683B series injector. The column used for this system was an Agilent HP-5MS 5% phenyl methyl siloxane (model number 19091S-433), which was 30 meters in length. The column had an internal diameter of 250 μm and film thickness of 0.25 μm. Solvent delay was set to 3.50 minutes for each trial. Low and high mass readings were set to parameters of 40 to 800 m/z, respectively. Oven, inlet, and detector temperatures were set to 250°C, and helium was used as the inert carrier gas.

5.2. Experimental Procedures for Chapter Two

Unless otherwise noted, into an oven-dried round-bottomed flask, alcohol starting material (2.00 mmol) was dissolved in anhydrous dichloromethane (15 mL), and the solution was then cooled to 0°C. Triethylamine (0.70 mL, 5.00 mmol) was then added via syringe, followed by triphosgene (297 mg, 1.00 mmol) in one portion. The mixture was stirred at 0°C for 3 minutes and then allowed to warm up to room temperature. After stirring for 3 hours, the reaction mixture was poured into a separatory funnel containing a saturated aqueous solution of NaHCO₃ (30 mL), and the biphasic mixture was then shaken vigorously. Upon separation of layers, the aqueous layer was re-extracted with dichloromethane (2 x 30 mL). The organic layers were combined, dried over MgSO₄, filtered, and concentrated under vacuum. The resulting crude material was purified using flash column chromatography using silica gel as the stationary phase and a mixture of either hexanes/ethyl acetate, pentane/diethyl ether or pentane/dichloromethane as the mobile phase.

\((\pm)\)-4-chloro-2-phenylbutan-2-ol 2.2a

\[
\begin{align*}
\text{Ph} & \quad \text{Me} \\
\text{OH} & \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{Me} \\
\text{OH} & \quad \text{Cl}
\end{align*}
\]
Diol 2.1a (332 mg, 2.00 mmol, CAS #7133-68-8) was utilized along with the requisite amounts of triethylamine and triphosgene, producing 2.2a in 98% yield as a colorless oil (361 mg, 1.96 mmol). Purified product was eluted with 90:10 hexanes : EtOAc. \(^1\)H NMR (250 MHz, CDCl\(_3\)); \(\delta\) (ppm) = 7.46-7.24 (5H, m), 3.56 (1H, ddd, \(J = 10.8, 8.4, 7.8\) Hz), 3.35 (1H, ddd, \(J = 10.7, 8.9, 6.4\) Hz), 2.35-2.29 (2H, m), 2.04 (1H, s), 1.62 (3H, s). \(^{13}\)C NMR (62.5 MHz, CDCl\(_3\)); \(\delta\) (ppm) = 146.30, 128.36, 126.94, 124.48, 74.24, 46.54, 40.42, 30.70. IR (cm\(^{-1}\)):\(f = 3553, 3421, 3028, 2931, 1375, 1099, 699.\) HRMS-ESI: (M-OH)^+ = 167.0622 calculated for C\(_{10}\)H\(_{12}\)Cl, experimental = 167.0626.

\(3\)-chloro-1,1-diphenylpropan-1-ol 2.2b

Diol 2.1b (200 mg, 1.20 mmol, CAS #13961-05-2) was utilized along with the requisite amounts of triethylamine (0.42 mL, 3.00 mmol) and triphosgene (178 mg, 0.600 mmol), producing 2.2b in 92% yield as colorless crystals (271 mg, 1.10 mmol). Purified product was eluted with 90:10 hexanes : EtOAc. \(^1\)H NMR (250 MHz, CDCl\(_3\)); \(\delta\) (ppm) = 7.33-7.14 (10H, m), 3.44-3.38 (2H, m), 2.75-2.68 (2H, m), 2.21 (1H, m). \(^{13}\)C NMR (62.5 MHz, CDCl\(_3\)); \(\delta\) (ppm) = 145.71, 128.34, 127.25, 125.73, 77.65, 44.78, 40.45. IR (cm\(^{-1}\)):\(f = 3553, 3456, 3059, 2968, 1054, 696.\) HRMS-ESI: (M-OH)^+ = 229.0779 calculated for C\(_{15}\)H\(_{14}\)Cl, experimental = 229.0786.

\(5\)-chloro-1,1-diphenylpentan-1-ol 2.2c
Diol 2.1c (512 mg, 2.00 mmol, CAS #60344-50-5) was utilized along with the requisite amounts of triethylamine and triphosgene, producing 2.2c in 89% yield as colorless crystals (491 mg, 1.79 mmol). Purified product was eluted with 95:5 → 90:10 hexanes : EtOAc. $^1$H NMR (250 MHz, CDCl$_3$); δ (ppm) = 7.44-7.20 (10H, m), 3.50 (2H, t, J = 6.8 Hz), 2.34-2.27 (2H, m), 2.15 (1H, s), 1.81 (2H, p, J = 7.0 Hz), 1.51-1.38 (2H, m). $^{13}$C NMR (62.5 MHz, CDCl$_3$); δ (ppm) = 146.73, 128.10, 126.81, 125.88, 78.02, 44.66, 41.07, 32.81, 21.22. IR (cm$^{-1}$): $f$ = 3562, 3465, 3059, 2953, 1447, 699. HRMS-ESI: (M-OH)$^+$ = 257.1092 calculated for C$_{17}$H$_{18}$Cl, experimental = 257.1099.

$^{\pm}$-(E)-5-chloro-3-methyl-1-phenylpent-1-en-3-ol 2.2d

Diol 2.1d$^1$ (385 mg, 2.00 mmol) was utilized along with the requisite amounts of triethylamine and triphosgene, producing 2.2d in 85% yield as a yellow oil (356 mg, 1.67 mmol). Product was eluted with 90:10 hexanes : EtOAc. $^1$H NMR (250 MHz, CDCl$_3$); δ (ppm) = 7.42-7.23 (5H, m), 6.64 (1H, d, J = 16.1 Hz), 6.25 (1H, d, J = 16.1 Hz), 3.74-3.56 (2H, m), 2.25-2.06 (2H, m), 1.79 (1H, s), 1.45 (3H, s). $^{13}$C NMR (62.5 MHz, CDCl$_3$); δ (ppm) = 136.40, 134.92, 128.55, 127.87, 127.61, 126.40, 72.75, 44.94, 40.33, 28.86. IR (cm$^{-1}$): $f$ = 3553, 3399, 3026, 2928, 1272, 969, 692. HRMS-ESI: (M-OH)$^+$ = 193.0779 calculated for C$_{12}$H$_{14}$Cl, experimental = 193.0787.

$^1$ Diol 2.1d was prepared via addition of lithium enolate of ethyl acetate to (E)-4-phenylbut-3-en-2-one (CAS #122-57-6), which is then followed by reduction of the resulting aldol product with LiAlH$_4$. 

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2-benzyl-4-chloro-1-phenylbutan-2-ol 2.2e

Diol 2.1e (550 mg, 2.00 mmol, CAS #497845-92-8) was utilized along with the requisite amounts of triethylamine and triphosgene, producing 2.2e in 97% yield as a colorless oil (532 mg, 1.94 mmol). Product was eluted with 90:10 hexanes : EtOAc. $^1$H NMR (250 MHz, CDCl$_3$); $\delta$ (ppm) = 7.40-7.22 (10H, m), 3.72-3.66 (2H, m), 2.83 (4H, s), 1.99-1.92 (2H, m), 1.55 (1H, s). $^{13}$C NMR (62.5 MHz, CDCl$_3$); $\delta$ (ppm) = 136.36, 130.59, 128.41, 126.80, 73.74, 45.81, 41.39, 40.25. IR (cm$^{-1}$): $f$ = 3561, 3468, 3028, 2923, 1453, 1089, 700. HRMS-ESI: (M+Na)$^+$ = 297.1022 calculated for C$_{17}$H$_{19}$ClNaO, experimental = 297.1000.

1-(2-chloroethyl)cyclohexanol 2.2f

Diol 2.1f (288 mg, 2.00 mmol, CAS #40894-17-5) was utilized along with the requisite amounts of triethylamine and triphosgene, producing 2.2f in 93% yield as a colorless oil (304 mg, 1.86 mmol). Product was eluted with 90:10 hexanes : EtOAc. $^1$H NMR (250 MHz, CDCl$_3$); $\delta$ (ppm) = 3.67 (2H, m), 1.97 (2H, m), 1.65-1.45 (9H, m), 1.42 (1H m), 1.30 (1H, m). $^{13}$C NMR (62.5 MHz, CDCl$_3$); $\delta$ (ppm) = 71.19, 44.66, 40.09, 38.00, 25.45, 21.94. IR (cm$^{-1}$): $f$ = 3387, 2931, 1448, 1171. HRMS-ESI: (M-OH)$^+$ = 145.0779 calculated for C$_8$H$_{14}$Cl, experimental = 145.0774.
1-(2-chloroethyl)cyclopentanol 2.2g

![Chemical structure of 1-(2-chloroethyl)cyclopentanol](image)

Diol 2.1g (260 mg, 2.00 mmol, CAS #73089-93-7) was utilized along with the requisite amounts of triethylamine and triphosgene, producing 2.2g in 96% yield as a colorless oil (285 mg, 1.92 mmol). Product was eluted with 70:30 pentane : Et₂O. ¹H NMR (250 MHz, CDCl₃); δ (ppm) = 3.72-3.66 (2H, m), 2.12-2.01 (2H, m), 1.83-1.55 (8H, m), 1.41 (1H, s). ¹³C NMR (62.5 MHz, CDCl₃); δ (ppm) = 81.47, 44.05, 41.07, 39.70, 23.32. IR (cm⁻¹): f = 3393, 2961, 2874, 1452, 1211, 731. HRMS-ESI: (M-OH)⁺ = 131.0622 calculated for C₇H₁₂Cl, experimental =131.0634.

(±)-4-methyl-4-phenyl-1,3-dioxan-2-one 2.3

![Chemical structure of (±)-4-methyl-4-phenyl-1,3-dioxan-2-one](image)

Diol 2.1a (332 mg, 2.00 mmol) was utilized along with the requisite amounts of pyridine (0.40 mL, 5.00 mmol) and triphosgene (297 mg, 0.500 mmol), producing 2.3 in 86% yield as a colorless oil (329 mg, 1.71 mmol). Purified product was eluted with 60:40 hexanes: EtOAc. ¹H NMR (250 MHz, CDCl₃); δ (ppm) = 7.40-7.25 (5H, m), 4.31 (1H, ddd, J = 11.2, 4.7, 4.2 Hz), 4.03 (1H, ddd, J = 11.2, 10.0, 4.5 Hz), 2.46-2.26 (2H, m), 1.70 (3H, s). ¹³C NMR (62.5 MHz, CDCl₃); δ (ppm) = 148.62, 142.24, 128.76, 127.83, 123.80, 84.26, 64.99, 33.16, 29.99. IR (cm⁻¹)
HRMS-ESI: (M+Na)$^+$ = 215.0684 calculated for C$_{11}$H$_{12}$NaO$_3$, experimental = 215.0698.

(3-chloropropyl)benzene 2.5a

Alcohol 2.4a (0.27 mL, 2.00 mmol, CAS #122-97-4) was utilized along with the requisite amounts of triethylamine and triphosgene, producing 2.5a in 82% yield as a colorless oil (252 mg, 1.63 mmol). Product was eluted with 100% hexanes. $^1$H NMR (250 MHz, CDCl$_3$); $\delta$ (ppm) = 7.38-7.22 (5H, m), 3.56 (2H, t, J = 6.5 Hz), 2.82 (2H, t, J = 7.1 Hz), 2.14 (1H, dt, J = 7.4, 6.7 Hz), 2.11 (1H, ddd, J = 7.3, 6.6, 6.6 Hz). $^{13}$C NMR (62.5 MHz, CDCl$_3$); $\delta$ (ppm) = 140.61, 128.46, 128.41, 126.05, 44.14, 33.95, 32.68. Compound 2.5a is known (CAS #104-52-9).

(±)-8-chloro-2,6-dimethyloct-2-ene 2.5b

Alcohol 2.4b (0.36 mL, 2.00 mmol, CAS #106-22-9) was utilized along with the requisite amounts of triethylamine and triphosgene, producing 2.5b in 67% yield as a colorless oil (233 mg, 1.34 mmol). Product was eluted with 100% pentane. $^1$H NMR (250 MHz, CDCl$_3$); $\delta$ (ppm) = 5.09 (1H, m), 3.64-3.48 (2H, m), 1.99 (1H, p, J = 6.35 Hz), 1.82-1.51 (10H, m), 1.35 (1H, m), 1.19 (1H, m) 0.91 (3H, d, J = 6.4 Hz). $^{13}$C NMR (62.5 MHz, CDCl$_3$); $\delta$ (ppm) = 131.32, 124.33, 43.16, 39.60, 36.57, 29.97, 25.58, 25.22, 18.84, 17.53. IR (cm$^{-1}$): $f$ = 2963, 2916, 1451, 1378,
GC-MS: $M^+ = 174.7$ calculated for $C_{10}H_{19}Cl$, experimental $= 174.0$ (material was not ionizable under ESI).

(±)-2-(2-chloroethyl)-3-phenyloxirane 2.5c

Alcohol 2.4c (328 mg, 2.00 mmol, CAS #199534-08-2) was utilized along with the requisite amounts of triethylamine and triphosgene, producing 2.5c in 87% yield as a colorless oil (321 mg, 1.74 mmol). Product was eluted with 60:40 hexanes : CH$_2$Cl$_2$. $^1$H NMR (250 MHz, CDCl$_3$); δ (ppm) = 7.40-7.25 (5H, m), 3.74 (1H, d, J = 1.7 Hz), 3.71 (2H, t, J = 6.4 Hz), 3.14 (1H, dddd, J = 6.4, 4.9, 2.1 Hz), 2.28-2.05 (2H, m). $^{13}$C NMR (62.5 MHz, CDCl$_3$); δ (ppm) = 136.93, 128.39, 128.15, 125.45, 60.08, 58.55, 40.98, 35.24. IR (cm$^{-1}$): $f = 3065, 2988, 1461, 885, 698$. HRMS-ESI: (M+H)$^+$ = 183.0577 calculated for $C_{10}H_{12}ClO$, experimental = 183.0582

(±)-2-(3-chloropropoxy)tetrahydro-2H-pyran 2.5d

Alcohol 2.4d (320 mg, 2.00 mmol, CAS #2162-33-6) was utilized along with the requisite amounts of triethylamine and triphosgene, producing 2.5d in 63% yield as a colorless oil (233 mg, 1.30 mmol). Purified product was eluted with 98:2 → 95:5 hexanes : EtOAc. $^1$H NMR (250 MHz, CDCl$_3$); δ (ppm) = 4.59 (1H, t, J = 3.1 Hz), 3.92-3.81 (2H, m), 3.66 (2H, t, J = 6.5 Hz), 3.56-3.48 (2H, m), 2.04 (2H, p, J = 6.3 Hz), 1.88-1.51 (6H, m). $^{13}$C NMR (62.5 MHz,
CDCl$_3$; $\delta$ (ppm) = 98.73, 63.70, 62.09, 41.85, 32.62, 30.46, 25.27, 19.35. IR (cm$^{-1}$): $f$ = 2942, 2872, 1260, 1033, 653. HRMS-ESI: (M+Na)$^+$ = 201.0658 calculated for C$_8$H$_{15}$ClNaO$_2$, experimental = 201.0645

tert-butyl(3-chloropropoxy)dimethylsilane 2.5e

Alcohol 2.4e (550 mg, 2.00 mmol, CAS #73842-99-6) was utilized along with the requisite amounts of triethylamine and triphosgene, producing 2.5e in 78% yield as a colorless oil (327 mg, 1.57 mmol). Product was eluted with 95:5 hexanes : EtOAc. $^1$H NMR (250 MHz, CDCl$_3$); $\delta$ (ppm) = 3.75 (2H, t, J = 5.7 Hz), 3.65 (2H, t, J = 6.4 Hz), 1.95 (2H, p, J = 6.2 Hz), 0.89 (9H, s), 0.06 (6H, s). $^{13}$C NMR (62.5 MHz, CDCl$_3$); $\delta$ (ppm) = 59.27, 41.66, 35.28, 25.76, 18.16, -5.55. IR (cm$^{-1}$): $f$ = 2956, 2930, 2858, 1255, 774. GC-MS: (M-tBu)$^+$ = 151.7 calculated for C$_5$H$_{12}$ClOSi, experimental = 151.0 (material was not ionizable under ESI).

(±)-tert-butyl((4-chloro-1-phenylbutan-2-yl)oxy)dimethylsilane 2.5f

Alcohol 2.4f (560 mg, 2.00 mmol, CAS #146877-29-4 for (S)-2.4f) was utilized along with the requisite amounts of triethylamine and triphosgene, producing 2.5f in 81% yield as a colorless oil (481 mg, 1.62 mmol). Purified product was eluted with 100:0 → 98:2 hexanes : EtOAc. $^1$H NMR (250 MHz, CDCl$_3$); $\delta$ (ppm) = 7.38-7.23 (5H, m), 4.15 (1H, p, J = 6.2 Hz),
3.67 (1H, t, J = 6.7 Hz), 2.91 (1H, dd, J = 13.3, 6.0 Hz), 2.79 (1H, dd, J = 13.4, 6.9 Hz), 1.92 (2H, q, J = 6.7 Hz), 0.96 (9H, s), 0.13, (3H, s), 0.00 (3H, s). $^{13}$C NMR (62.5 MHz, CDCl$_3$); δ (ppm) = 138.14, 129.53, 128.19, 126.21, 70.42, 44.02, 41.56, 39.33, 25.75, 17.92, -4.78, -4.93. IR (cm$^{-1}$): $f =$ 3029, 2955, 1082, 775, 699. HRMS-ESI: (M+Na)$^+$ = 321.1417 calculated for C$_{16}$H$_{27}$ClNaOSi, experimental = 321.1422.

$((3$-chloropropoxy)methyl)benzene 2.5g

Alcohol 2.4g (0.32 mL, 2.0 mmol, CAS #4799-68-2) was utilized along with the requisite amounts of triethylamine and triphosgene, producing 2.5g in 84% yield as a colorless oil (310 mg, 1.68 mmol). Product was eluted with 95:5 hexanes : EtOAc. $^1$H NMR (250 MHz, CDCl$_3$); δ (ppm) = 7.31-7.18 (5H, m), 4.44 (2H, s), 3.60 (2H, t, J = 6.5 Hz), 3.54 (2H, t, J = 5.9 Hz), 1.98 (2H, p, J = 6.3 Hz). $^{13}$C NMR (62.5 MHz, CDCl$_3$); δ (ppm) = 138.15, 128.30, 127.54, 127.51, 73.01, 66.60, 41.88, 32.68. Compound 2.5g is known (CAS #26420-79-1).

3-chloropropyl 4-methylbenzoate 2.5h

Alcohol 2.4h (388 mg, 2.00 mmol, CAS #508195-77-5) was utilized along with the requisite amounts of triethylamine and triphosgene, producing 2.5h in 98% yield as a colorless oil (415 mg, 1.96 mmol). Product was eluted with 95:5 hexanes : EtOAc. $^1$H NMR (250 MHz,
CDCl$_3$; $\delta$ (ppm) = 7.92 (2H, d, J = 8.2 Hz), 7.24 (2H, d, J = 8.0 Hz), 4.46 (2H, t, J = 6.1 Hz), 3.70 (2H, t, J = 6.5 Hz), 2.41 (3H, s), 2.23 (2H, p, J = 6.3 Hz). $^{13}$C NMR (62.5 MHz, CDCl$_3$); $\delta$ (ppm) = 166.12, 143.47, 129.33, 128.86, 127.06, 61.22, 41.12, 31.52, 21.36. IR (cm$^{-1}$): $f$ = 2966, 2874, 1715, 1178, 841, 753. HRMS-ESI: (M+H)$^+$ = 213.0682 calculated for C$_{11}$H$_{14}$ClO$_2$, experimental = 213.0686.

$\pm$-2-phenylpropyl diethylcarbamate 2.7a

![Diagram of the reaction between 2.6a and triphosgene to form 2.7a]

Alcohol 2.6a (0.28 mL, 2.00 mmol, CAS #1123-85-9) was utilized along with the requisite amounts of triethylamine and triphosgene, producing 2.7a in 62% yield as a colorless oil (290 mg, 1.24 mmol). Product was eluted with 90:10 hexanes : EtOAc. $^1$H NMR (250 MHz, CDCl$_3$); $\delta$ (ppm) = 7.33-7.16 (5H, m), 4.16 (2H, d, J = 7.2 Hz), 3.22 (4H, b), 3.13 (1H, h, J = 7.0 Hz), 1.31 (3H, d, J = 7.0 Hz), 1.05 (6H, b). $^{13}$C NMR (62.5 MHz, CDCl$_3$); $\delta$ (ppm) = 155.65, 143.45, 128.16, 127.14, 126.28, 69.88, 41.49 (b), 41.05 (b), 39.11, 17.75, 13.58 (b). IR (cm$^{-1}$): $f$ = 3029, 2972, 1694, 1270, 699. HRMS-ESI: (M+H)$^+$ = 236.1651 calculated for C$_{14}$H$_{22}$NO$_2$, experimental = 236.1653.

2,2-diphenylethyl diethylcarbamate 2.7b

![Diagram of the reaction between 2.6b and triphosgene to form 2.7b]
Alcohol 2.6b (484 mg, 2.00 mmol, CAS #1883-32-5) was utilized along with the requisite amounts of triethylamine and triphosgene, producing 2.7b in 85% yield as a colorless oil (321 mg, 1.74 mmol). Product was eluted with 90:10 hexanes : EtOAc. \(^1\)H NMR (250 MHz, CDCl\(_3\)); \(\delta\) (ppm) = 7.34-7.18 (10H, m), 4.63 (2H, d, 7.6 Hz), 4.40 (1H, t, 7.6 Hz), 3.24 (2H, b), 3.05 (2H, b), 1.08 (3H, b), 0.83 (3H, b). \(^{13}\)C NMR (62.5 MHz, CDCl\(_3\)); \(\delta\) (ppm) = 155.57, 141.39, 128.37, 128.22, 126.54, 67.31, 50.18, 41.70 (b), 41.12 (b), 13.49. IR (cm\(^{-1}\)): \(f = 2974, 1693, 1454, 1270, 698\). HRMS-ESI: (M+H)\(^+\) = 298.1807 calculated for C\(_{19}\)H\(_{24}\)NO\(_2\), experimental = 298.1797.

\((S)-\text{tert-butyl 2-}((\text{diethylcarbamoyl})\text{oxy})\text{methyl}\text{pyrrolidine-1-carboxylate 2.7c}\)

Alcohol 2.6c (402 mg, 2.00 mmol, CAS #170491-63-1) was utilized along with the requisite amounts of triethylamine and triphosgene, producing 2.7c in 73% yield as a colorless oil (438 mg, 1.46 mmol). Product was eluted with 80:20 hexanes : EtOAc. \(^1\)H NMR (250 MHz, CDCl\(_3\)); \(\delta\) (ppm) = 4.15-3.95 (3H, m), 3.50-3.15 (6H, m), 2.00-1.77 (4H, m), 1.44 (9H, s), 1.09 (6H, t, \(J = 7.1\) Hz). \(^{13}\)C NMR (62.5 MHz, CDCl\(_3\)); \(\delta\) (ppm) = 155.38, 154.08, 79.15 (b), 78.78 (b), 65.04 (b), 64.59 (b), 55.55, 46.18, 41.39 (b), 41.01 (b), 28.09, 23.01, 13.66 (b), 13.18 (b). IR (cm\(^{-1}\)): \(f = 2973, 1690, 1424, 1365, 1227, 767\). HRMS-ESI: (M+Na\(^+\)) = 323.1947 calculated for C\(_{15}\)H\(_{28}\)N\(_2\)NaO\(_4\), experimental = 323.1949.
Alcohol 2.6d (364 mg, 2.00 mmol, CAS #38584-37-1) was utilized along with the requisite amounts of triethylamine and triphosgene, producing 2.7d in 62% yield as a colorless oil (351 mg, 1.24 mmol). Product was eluted with 50:50 hexanes : EtOAc. ^1H NMR (250 MHz, CDCl_3); δ (ppm) = 3.78 (2H, s), 3.30 (4H, q, J = 3.2 Hz), 1.77-1.65 (2H, m), 1.62-1.58 (2H, m), 1.50-1.48 (4H, m), 1.56 (2H, b), 1.15 (6H, t, J = 7.1 Hz). ^13C NMR (62.5 MHz, CDCl_3); δ (ppm) = 155.91, 73.54, 68.20, 46.82, 44.53, 41.60 (b), 41.11 (b), 38.01, 36.96, 35.37, 30.08, 13.98 (b), 13.36 (b). IR (cm\(^{-1}\)): f = 3431, 2904, 1679, 1427, 1272, 1172, 768. HRMS-ESI: (M+H)^+ = 282.2069 calculated for C\(_{16}\)H\(_{28}\)NO\(_3\), experimental = 282.2077.

1,3-diphenylpropan-2-yl diethylcarbamate 2.9a and

(2-chloropropane-1,3-diyl)dibenzene 2.10a

Alcohol 2.8a (420 mg, 2.00 mmol, CAS #5381-92-0) was utilized along with the requisite amounts of triethylamine and triphosgene, producing 2.9a in 40% yield as a colorless oil (251 mg, 0.80 mmol) and 2.10a in 50% yield as a colorless oil (231 mg, 1.00 mmol). Purified products were eluted with 100:0 → 98:2 → 95:5 → 90:10 hexanes : EtOAc.
The more polar product (2.9a): $^1$H NMR (250 MHz, CDCl$_3$); $\delta$ (ppm) = 7.35-7.23 (10H, m), 5.26 (1H, p, $J$ = 6.4 Hz), 3.23 (4H, b), 2.97 (2H, dd, $J$ = 13.7, 6.7 Hz), 2.90 (2H, dd, $J$ = 13.9, 5.9 Hz), 1.04 (6H, b). $^{13}$C NMR (62.5 MHz, CDCl$_3$); $\delta$ (ppm) = 155.25, 137.77, 129.46, 126.19, 75.78, 40.92 (b), 39.91 (b), 13.73 (b). IR (cm$^{-1}$): $f$ = 3028, 2931, 1690, 1270, 1069. HRMS-ESI: (M+Na)$^+$ = 334.1783 calculated for C$_{20}$H$_{25}$NNaO$_2$, experimental = 334.1795.

The less polar product (2.10a): $^1$H NMR (250 MHz, CDCl$_3$); $\delta$ (ppm) = 7.39-7.24 (10H, m), 4.34 (1H, dddd, $J$ = 8.0, 8.0, 5.6, 5.6 Hz), 3.16 (2H, dd, $J$ = 14.1, 5.6 Hz), 3.05 (2H, dd, $J$ = 14.2, 8.1 Hz). $^{13}$C NMR (62.5 MHz, CDCl$_3$); $\delta$ (ppm) = 137.78, 129.27, 128.35, 126.74, 63.89, 44.23. IR (cm$^{-1}$): $f$ = 3064, 2917, 1734, 1603. Compound 2.10a is known (CAS #50434-32-7).

(±)-4-chloro-1-phenylbutan-2-yl diethylcarbamate 2.9b and (±)-(2,4-dichlorobutyl)benzene 2.10b

Alcohol 2.8b (420 mg, 2.00 mmol, CAS #74578-77-1) was utilized along with triethylamine (1.39 mL, 10.0 mmol), triphosgene (539 mg, 2.00 mmol), and 30 mL of CH$_2$Cl$_2$ producing 2.9b in 23% yield as a colorless oil (131mg, 0.46 mmol) and 2.10b in 69% yield as a colorless oil (282 mg, 1.39 mmol). Purified products were eluted with 100:0 $\rightarrow$ 90:10 hexanes : EtOAc.

The more polar product (2.9b): $^1$H NMR (250 MHz, CDCl$_3$); $\delta$ (ppm) = 7.33-7.19 (5H, m), 5.12 (1H, m), 3.62-3.46 (2H, m), 3.24 (4H, b), 3.00 (1H, dd, $J$ = 13.7, 5.9 Hz), 2.86 (1H, dd,
J = 13.7, 7.0 Hz), 2.07-1.98 (2H, m), 1.08 (6H, t, J = 6.7 Hz). $^{13}$C NMR (62.5 MHz, CDCl$_3$); $\delta$ (ppm) = 155.17, 136.99, 129.47, 128.32, 126.48, 72.74, 41.62 (b), 41.02 (b), 40.75, 36.78, 14.04 (b), 13.46 (b). IR (cm$^{-1}$): $f$ = 3029, 2972, 2933, 1693, 1168, 701. HRMS-ESI: (M+H)$^+$ = 284.1417 calculated for C$_{15}$H$_{23}$ClNO$_2$, experimental = 284.1415.

**The less polar product (2.10b):** $^1$H NMR (250 MHz, CDCl$_3$); $\delta$ (ppm) = 7.38-7.20 (5H, m), 4.35 (1H, dddd, J = 10.0, 6.9, 6.9, 3.3 Hz), 3.82-3.66 (2H, m), 3.13 (1H, dd, J = 14.1, 7.2 Hz), 3.06 (1H, dd, J = 14.0, 6.6 Hz), 2.27-2.01 (2H, m). $^{13}$C NMR (62.5 MHz, CDCl$_3$); $\delta$ (ppm) = 137.08, 129.31, 128.47, 126.95, 59.92, 44.72, 41.68, 39.99. IR (cm$^{-1}$): $f$ = 3030, 2964, 1454, 699. GC-MS: M$^+$ = 203.1 calculated for C$_{10}$H$_{12}$Cl$_2$, experimental = 203.3 (material was not ionizable under ESI).

(±)-(1,3-dichloropropyl)benzene 2.10c

Alcohol 2.8c (304mg, 2.00 mmol, CAS #4850-49-1) was utilized along with triethylamine (1.39 mL, 10.0 mmol), triphosgene (593 mg, 2.00 mmol), and 30 mL of CH$_2$Cl$_2$, producing 2.10c in 91% yield as a colorless oil (354 mg, 1.82 mmol). Purified products were eluted with 100% hexanes. $^1$H NMR (250 MHz, CDCl$_3$); $\delta$ (ppm) = 7.43-7.29 (5H, m), 5.12 (1H, dd, J = 8.9, 5.4 Hz), 3.76 (2H, ddd, J = 11.1, 8.1, 5.2 Hz), 3.57 (2H, ddd, J = 11.1, 5.7, 5.7 Hz), 2.56 (1H, dddd, J = 14.6, 9.0, 5.5, 5.5 Hz), 2.40 (1H, dddd, J = 14.6, 8.1, 5.5, 5.5 Hz). $^{13}$C NMR (62.5 MHz, CDCl$_3$); $\delta$ (ppm) = 140.46, 128.73, 128.54, 126.89, 59.95, 42.16, 41.74. IR (cm$^{-1}$): $f$ = 3064, 2966, 1310, 695. GC-MS: M$^+$ = 189.1 calculated for C$_9$H$_{10}$Cl$_2$, experimental = 189.8 (material was not ionizable under ESI).
(+)-3-chloro-1-cyclohexylpropyl diethylcarbamate 2.9d and
(+)-1,3-dichloropropyl)cyclohexane 2.10d

Alcohol 2.8d (316 mg, 2.00 mmol, CAS #79388-47-9) was utilized along with triethylamine (1.39 mL, 10.0 mmol), triphosgene (593 mg, 2.00 mmol), and 30 mL of CH2Cl2, producing 2.9d in 42% yield as a colorless oil (164 mg, 0.85 mmol) and 2.10d in 32% yield as a colorless oil (177 mg, 0.64 mmol). Purified products were eluted with 100:0 → 90:10 hexanes : EtOAc.

The more polar product (2.9d): ¹H NMR (250 MHz, CDCl₃); δ (ppm) = 4.74 (1H, ddd, J = 7.4, 5.1, 4.7 Hz), 3.5 (2H, t, J = 7.6 Hz), 3.24 (4H, b), 2.04-1.95 (2H, m), 1.68 (6H, b), 1.57-0.93 (11H, m). ¹³C NMR (62.5 MHz, CDCl₃); δ (ppm) = 155.57, 75.79, 41.60, 41.43, 40.97 (b), 35.02, 28.62, 27.95, 26.26, 25.94, 14.10 (b), 13.37 (b). IR (cm⁻¹): f = 2973, 2929, 2855, 1693, 1273, 1171, 766. HRMS-ESI: (M+H)⁺ = 276.1730 calculated for C₁₄H₂₇ClNO₂, experimental = 276.1732.

The less polar product (2.10d): ¹H NMR (250 MHz, CDCl₃); δ (ppm) = 4.02 (1H, dt, J = 6.4, 4.7 Hz), 3.73 (2H, t, J = 6.4 Hz), 2.12 (2H, q, J = 6.5 Hz), 1.80-156 (6H, m), 1.10-1.30 (5H, m). ¹³C NMR (62.5 MHz, CDCl₃); δ (ppm) = 65.51, 44.09, 42.23, 37.96, 29.78, 28.16, 25.98. IR (cm⁻¹): f = 2928, 2854, 1449, 735. GC-MS: (M-Cl)⁺ = 159.7 calculated for C₉H₁₆Cl, experimental = 159.8 (material was not ionizable under ESI).
Alcohol 2.8e (545 mg, 4.00 mmol, CAS #1572-95-8) was utilized along with triethylamine (1.39 mL, 10.0 mmol), triphosgene (539 mg, 2.00 mmol), and 30 mL of CH₂Cl₂ producing 2.9e in 27% yield as a colorless oil (256 mg, 1.09 mmol) and 2.10e in 45% yield as a colorless oil (276 mg, 1.79 mmol). Purified products were eluted with 100% pentane followed by 90:10 hexanes : EtOAc.

**The more polar product (2.9e):** ¹H NMR (250 MHz, CDCl₃); δ (ppm) = 7.32-7.16 (5H, m), 5.04 (1H, x, J = 6.4 Hz), 3.23 (4H, q, b, J = 6.4 Hz), 2.95 (1H, dd, J = 13.6, 6.4 Hz), 2.78 (1H, dd, J = 13.5, 6.6 Hz), 1.22 (3H, d, J = 6.2 Hz), 1.06 (6H, t, b, J = 6.8 Hz). ¹³C NMR (62.5 MHz, CDCl₃); δ (ppm) = 155.37, 137.84, 129.39, 128.08, 126.13, 71.73, 42.50, 41.28, 19.65, 13.64. IR (cm⁻¹): f = 3029, 2976, 2933, 1694, 1317, 1173. HRMS-ESI: (M+Na)⁺ = 258.1470 calculated for C₁₄H₂₁NNaO₂, experimental = 258.1464.

**The less polar product (2.10e):** ¹H NMR (250 MHz, CDCl₃); δ (ppm) = 7.39-7.23 (5H, m), 4.26 (1H, x, J = 6.7 Hz), 3.13 (1H, dd, J = 14.0, 7.0 Hz), 2.99 (1H, dd, J = 13.8, 6.8 Hz), 1.54 (3H, d, J = 6.6 Hz). ¹³C NMR (62.5 MHz, CDCl₃); δ (ppm) = 137.85, 129.23, 128.30, 126.68, 58.41, 46.57, 24.55. [α]₂₅^D = +23.05 (c = 8.5 in CHCl₃). Compound 2.10e is known (CAS #16583-73-6).
5.3. Experimental Procedures for Chapter Three

Unless otherwise noted, alcohol (2.0 mmol) was placed in an oven-dried round-bottomed flask and dissolved in anhydrous dichloromethane (15 mL). The solution was then cooled to 0°C. Pyridine (0.32 mL, 4.0 mmol) was then added via syringe, followed by triphosgene (297 mg, 1.0 mmol) in one portion. The solution was allowed to stir for 5 minutes, and then warmed to gentle reflux overnight. The reaction was then poured into a separatory funnel containing 1 M HCl aqueous solution (30 mL), and the biphasic mixture was shaken vigorously. Upon separation of layers, the aqueous layer was re-extracted with dichloromethane (2 x 30 mL). Organic extracts were collected, dried over MgSO₄, filtered, and concentrated under vacuum. The resulting crude material was purified using flash column chromatography using silica gel as the stationary phase and a mixture of either hexanes/ethyl acetate, pentane/diethyl ether or pentane/dichloromethane as the mobile phase.

(+)-(S)-(2-chloropropyl)benzene 3.6a

![Diagram](image.png)

Alcohol 3.6a (272 mg, 2.00 mmol, CAS #1572-95-8) was utilized along with pyridine (0.32 mL, 4.00 mmol) and triphosgene (297 mg, 1.00 mmol) to produce 3.7a in 89% yield as a colorless oil (273 mg, 1.77 mmol). Purified product was eluted with 100% hexanes. ¹H NMR (250 MHz, CDCl₃); δ (ppm) = 7.37-7.21 (5H, m), 4.24 (1H, x, J = 6.8 Hz), 3.11 (1H, dd, J = 13.8, 7.0 Hz), 2.98 (1H, dd, J = 13.9, 7.0 Hz), 1.53 (3H, d, J = 6.5 Hz). ¹³C NMR (62.5 MHz, CDCl₃); δ (ppm) = 137.9, 129.2, 128.3, 126.7, 58.4, 46.6, 24.6. [α]²⁵D = +23.12 (c = 2.2 in CDCl₃). Compound 3.7a is known (CAS #16583-73-6).
(2-chloropropane-1,3-diyl)dibenzene 3.7b

\[
\begin{array}{c}
\text{Ph} \quad \text{OH} \\
3.6b \\
\text{Ph} \\
\end{array} \quad \text{Triphosgene} \\
\text{(0.5 equiv)} \\
\begin{array}{c}
\text{Py} \quad \text{(2.0 equiv)} \\
\text{CH}_2\text{Cl}_2, \text{0 °C} \rightarrow \text{reflux} \\
\end{array} \quad \begin{array}{c}
\text{Cl} \\
3.7b \\
\text{Ph} \\
\end{array}
\]

Alcohol 3.6b (420 mg, 2.00 mmol, CAS #5381-92-0) was utilized along with pyridine (0.32 mL, 4.00 mmol) and triphosgene (297 mg, 1.00 mmol) to produce 3.7b in 87% yield as a colorless oil (397 mg, 1.73 mmol). Purified product was eluted with 100:0 → 90:10 hexanes : EtOAc. $^1$H NMR (250 MHz, CDCl$_3$); δ (ppm) = 7.38-7.23 (10H, m), 4.34 (1H, dddd, $J$ = 8.0, 8.0, 5.6, 5.2 Hz), 3.16 (2H, dd, $J$ = 14.1, 5.6 Hz), 3.04 (2H, dd, $J$ = 14.2, 8.0 Hz). $^{13}$C NMR (62.5 MHz, CDCl$_3$); δ (ppm) = 137.8, 129.3, 128.3, 126.7, 63.9, 44.2. IR (cm$^{-1}$): $f$ = 3088, 3064, 3029, 1603, 1498, 1455, 911, 741, 700, 670. Compound 3.7b is known (CAS #50434-32-7).

$N$-Boc-4-chloropiperidine 3.7c

\[
\begin{array}{c}
\text{HO} \\
3.6c \\
\text{N-Boc} \\
\end{array} \quad \text{Triphosgene} \\
\text{(0.5 equiv)} \\
\begin{array}{c}
\text{Py} \quad \text{(2.0 equiv)} \\
\text{CH}_2\text{Cl}_2, \text{0 °C} \rightarrow \text{reflux} \\
\end{array} \quad \begin{array}{c}
\text{Cl} \\
3.7c \\
\text{N-Boc} \\
\end{array}
\]

Alcohol 3.6c (403 mg, 2.00 mmol) was utilized along with pyridine (0.32 mL, 4.00 mmol) and triphosgene (297 mg, 1.00 mmol) to produce 3.7c in 88% yield as a pale yellow oil (387 mg, 1.76 mmol). Purified product was eluted with 90:10 → 80:20 pentane : diethyl ether. $^1$H NMR (400 MHz, CDCl$_3$); δ (ppm) = 4.20 (1H, m), 3.73-3.68 (2H, m), 3.32-3.26 (2H, m) 2.06-1.99 (2H, m), 1.86-1.76 (2H, m), 1.46 (9H, s). $^{13}$C NMR (100 MHz, CDCl$_3$); δ (ppm) = 154.5, 79.6, 56.8, 41.3 (b), 34.9, 28.3. IR (cm$^{-1}$): $f$ = 2977, 2870, 2839, 1692, 1478, 1419, 1366,
1264, 1218, 1165, 1110, 1001, 895, 767, 719. HRMS-ESI: (M+Na)$^+$ = 242.0918 calculated for C$_{10}$H$_{18}$ClNO$_2$, experimental = 242.0918.

(±)-(R/S)-3-chloro-4-phenyl-buty lethylesterate 3.7d

Alcohol 3.6d (417 mg, 2.00 mmol) was utilized along with pyridine (0.32 mL, 4.00 mmol) and triphosgene (297 mg, 1.00 mmol) to produce 3.7d in 82% yield as a pale yellow oil (372 mg, 1.64 mmol). Purified product was eluted with 100% pentane. $^1$H NMR (400 MHz, CDCl$_3$); δ (ppm) = 7.34-7.22 (5H, m), 4.51 (1H, dt, J = 13.4, 7.3 Hz), 4.16 ppm (2H, q, J = 6.8 Hz), 3.09 (2H, dd, J = 6.7, 4.6 Hz), 2.75-2.71 (2H, m), 1.27 (3H, t, J = 7.1 Hz). $^{13}$C NMR (100 MHz, CDCl$_3$); δ (ppm) = 170.1, 137.0, 129.5, 128.6, 127.1, 60.9, 57.7, 44.3, 42.6, 14.2. IR (cm$^{-1}$): f = 3065, 3030, 2983, 2905, 1737, 1654, 1304, 1150, 1096, 910, 747, 650. HRMS-ESI: (M+H)$^+$ = 227.0833 calculated for C$_{12}$H$_{15}$ClO$_2$, experimental = 227.0835.

(±)-(R/S)-2-chloro-1-phenyl-4-pentene 3.6e

Alcohol 3.6e (324 mg, 2.00 mmol) was utilized along with pyridine (0.32 mL, 4.00 mmol) and triphosgene (297 mg, 1.00 mmol) to produce 3.7e in 94% yield as a colorless oil (340 mg, 1.88 mmol). Purified product was eluted with 100% pentane. $^1$H NMR (400 MHz, CDCl$_3$); δ (ppm) = 7.36-7.24 (5H, m), 5.93 (1H, m), 5.20-5.15 (2H, m), 4.17 (1H, m), 3.10 (1H, dd, J =
14.1, 6.2 Hz), 3.04 (1H, dd, J = 14.1, 6.4 Hz), 2.59 (1H, m), 2.48 (1H, m). ¹³C NMR (100 MHz, CDCl₃); δ (ppm) = 137.8, 134.0, 129.4, 128.5, 126.8, 118.3, 62.5, 44.2, 41.8. IR (cm⁻¹): f = 3080, 3030, 2981, 2952, 1643, 1604, 1543, 1433, 1284, 1031, 993, 920, 700, 618. GC-MS: M⁺ = 180.1 calculated for C₁₁H₁₃Cl, experimental = 180.0 (material was not ionizable under ESI).

(±)-(R/S)-trans-styryl-2-chloro-pentene 3.7f

Alcohol 3.6f (377 mg, 2.00 mmol) was utilized along with pyridine (0.32 mL, 4.00 mmol) and triphosgene (297 mg, 1.00 mmol) to produce 3.7f in 82% yield as a yellow oil (339 mg, 1.64 mmol). Purified product was eluted with 100% pentane. ¹H NMR (400 MHz, CDCl₃); δ (ppm) = 7.38-7.17 (5H, m), 6.48 (1H, d, J = 15.8 Hz), 6.25 (1H, m), 5.94-5.83 (1H, m), 5.18-5.10 (2H, m), 4.03 (1H, m), 2.72-2.61 (2H, m), 2.59-2.50 (2H, m). ¹³C NMR (100 MHz, CDCl₃); δ (ppm) = 137.1, 134.0, 133.2, 128.6, 127.4, 126.2, 125.5, 118.2, 61.5, 42.0, 41.2. IR (cm⁻¹): f = 3081, 3061, 3028, 2980, 2946, 1644, 1495, 1449, 1289, 967, 918, 744, 694. HRMS-ESI: (M + H)⁺ theoretical = 207.0935 calculated for C₁₃H₁₆Cl, experimental = 207.0936.

(±)-(R/S)-3-chloro-4-phenyl-tert-butyldimethylsilylboutanol 3.7g

Alcohol 3.6g (560 mg, 2.00 mmol) was utilized along with pyridine (0.32 mL, 4.00 mmol) and triphosgene (297 mg, 1.00 mmol) to produce 3.7g in 90% yield as a colorless oil (536
mg, 1.80 mmol). Purified product was eluted with 100:0 90:10 hexanes : EtOAc. $^1$H NMR (400 MHz, CDCl$_3$); δ (ppm) = 7.36-7.22 (5H, m), 4.33 (1H, ddt, $J = 10.1, 9.8, 3.4$ Hz), 3.85-3.73 (2H, m), 3.08 (2H, d, $J = 6.8$ Hz), 2.03 (1H, m), 1.81 (1H, ddt, $J = 14.3, 9.8, 4.4$ Hz), 0.89 (9H, s), 0.05 (6H, d, $J = 7.1$ Hz). $^{13}$C NMR (100 MHz, CDCl$_3$); δ (ppm) = 137.9, 129.4, 128.4, 126.7, 60.3, 59.8, 45.1, 40.6, 25.9, 18.3, -5.4. IR (cm$^{-1}$): $f = 3030, 2954, 2930, 2857, 1472, 1472, 1256, 1110, 910, 837, 778$. HRMS-ESI: (M+H)$^+$ = 299.1592 calculated for C$_{16}$H$_{28}$ClOSi, experimental = 299.1599.

(±)-(R/S)-3-chloro-4-phenyl-benzyloxybutanol 3.7h

Alcohol 3.6h (256 mg, 2.00 mmol) was utilized along with pyridine (0.32 mL, 4.00 mmol) and triphosgene (297 mg, 1.00 mmol) to produce 3.7h in 84% yield as a colorless oil (462 mg, 1.69 mmol). Purified product was eluted with 98:2 hexanes : EtOAc. $^1$H NMR (400 MHz, CDCl$_3$); δ (ppm) = 7.34-7.21 (10H, m), 4.54-4.45 (2H, m), 3.88 (1H, m), 3.69-3.60 (2H, m), 2.97 (1H, dd, $J = 13.5, 6.0$ Hz), 2.80 (1H, dd, $J = 13.6, 6.4$ Hz), 1.96-1.90 (2H, m). $^{13}$C NMR (100, CDCl$_3$); δ (ppm) = 138.3, 138.1, 129.5, 128.4, 128.0, 127.8, 126.4, 77.1, 72.1, 41.7, 40.6, 37.4. IR (cm$^{-1}$): $f = 3063, 3023, 2925, 2866, 1496, 1456, 1350, 1289, 1073, 1029, 910, 737, 699, 651$. HRMS-ESI: (M+Na)$^+$ = 297.1017 calculated for C$_{17}$H$_{19}$ClO, experimental = 297.1019.
(±)-(R/S)-3-chloro-4-phenyl-p-methoxybenzylxybutanol 3.7i

Alcohol 3.6i (572 mg, 2.00 mmol) was utilized along with pyridine (0.32 mL, 4.00 mmol), and triphosgene (297 mg, 1.00 mmol) to produce 3.7i in 82% yield as a colorless oil (498 mg, 1.64 mmol). Purified product was eluted with 90:10 hexanes : EtOAc. $^1$H NMR (400 MHz, CDCl$_3$); δ (ppm) = 7.33-7.19 (5H, m), 6.87 (2H, d, $J = 8.6$ Hz), 4.42 (2H, q, $J = 10.9$ Hz), 3.86 (1H, m), 3.81 (3H, s), 3.67-3.57 (2H, m), 2.95 (1H, dd, $J = 13.6, 6.1$ Hz), 2.78 (1H, dd, $J = 13.7, 6.4$ Hz), 1.96-1.86 (2H, m). $^{13}$C NMR (100 MHz, CDCl$_3$); δ (ppm) = 159.3, 138.2, 130.4, 129.5, 128.4, 126.4, 113.9, 76.8, 71.8, 55.3, 41.7, 40.7, 37.4. IR (cm$^{-1}$): $f$ = 3063, 3030, 2936, 2870, 1612, 1513, 1248, 1076, 1034, 822, 740, 701. HRMS-ESI: (M+Na)$^+$ = 327.1122 calculated for C$_{18}$H$_{21}$ClNaO$_2$, experimental = 327.1133.

(±)-(R/S)-3-chloro-4-phenyl-p-toluoylbutanol 3.7j

Alcohol 3.6j (568 mg, 2.00 mmol) was utilized along with pyridine (0.32 mL, 4.00 mmol) and triphosgene (297 mg, 1.00 mmol) to produce 3.7j in 85% yield as a colorless oil (514 mg, 1.70 mmol). Purified product was eluted with 90:10 hexanes : EtOAc. $^1$H NMR (400 MHz, CDCl$_3$); δ (ppm) = 7.91 (2H, d, $J = 8.2$ Hz), 7.35-7.24 (5H, m), 4.55 (1H, ddd, $J = 11.2, 6.2, 4.7$ Hz), 4.47 (1H, m), 4.32 (1H, m), 3.13 (2H, d, $J = 6.8$ Hz), 2.42 (3H, s), 2.31 (1H, m), 2.09 (1H, m). $^{13}$C NMR (100 MHz, CDCl$_3$); δ (ppm) = 166.5, 143.8, 137.4, 129.6, 129.4, 129.1, 128.5,
127.4, 127.0, 61.8, 59.9, 45.0, 36.7, 21.7. IR (cm\(^{-1}\)): \( f = 3087, 3062, 2964, 2861, 1715, 1270, 1177, 1109, 1021, 752, 700 \). HRMS-ESI: \((M+H)^+ = 303.1152 \) calculated for \( \text{C}_{18}\text{H}_{20}\text{ClO}_2 \), experimental = 303.1145.

\textit{1-chloro-2,2'-diphenylethane 3.9a}

\begin{center}
\text{Ph} \quad \text{Ph} \\
\text{OH} \quad \text{Cl} \\
\text{3.8a} \quad \text{3.9a}
\end{center}

Alcohol \textbf{3.8a} (397 mg, 2.00 mmol, CAS #1883-32-5) was utilized along with pyridine (0.32 mL, 4.00 mmol) and triphosgene (297 mg, 1.00 mmol) to produce \textbf{3.9a} in 81% yield as a light yellow oil (350 mg, 1.62 mmol). Purified product was eluted with 100% hexanes. \(^1\)H NMR (250 MHz, CDCl\(_3\)); \( \delta \) (ppm) = 7.35-7.21 (10H, m), 4.34 (1H, t, \( J = 7.8 \) Hz), 4.07 (2H, d, \( J = 7.8 \) Hz). \(^{13}\)C NMR (62.5 MHz, CDCl\(_3\)); \( \delta \) (ppm) = 141.2, 128.5, 127.9, 126.9, 53.5, 47.1. IR (cm\(^{-1}\)): \( f = 3062, 3029, 1494, 1452, 910, 737, 699 \). GC-MS: \( M^+ = 216.1 \) calculated for \( \text{C}_{14}\text{H}_{13}\text{Cl} \), experimental = 216.0 (material was not ionizable under ESI).

\textit{1-chloro-2-phenylpropane 3.9b}

\begin{center}
\text{Me} \quad \text{Ph} \\
\text{OH} \quad \text{Cl} \\
\text{3.8b} \quad \text{3.9b}
\end{center}

Alcohol \textbf{3.8b} (0.28 mL, 2.00 mmol, CAS #1123-85-9) was utilized along with pyridine (0.32 mL, 4.00 mmol) and triphosgene (297 mg, 1.00 mmol) to produce \textbf{3.9b} in 86% yield as a colorless oil (266 mg, 1.73 mmol). Purified product was eluted with 100% hexanes. \(^1\)H NMR (250 MHz, CDCl\(_3\)); \( \delta \) (ppm) = 7.39-7.19 (5H, m), 3.72 (1H, dd, \( J = 10.7, 6.2 \) Hz), 3.61 (1H, dd, \( J = 10.7, 6.2 \) Hz).
= 10.7, 7.8 Hz), 3.12 (1H, x, J = 7.0 Hz), 1.42 (3H, d, J = 7.0 Hz). $^{13}$C NMR (62.5 MHz, CDCl$_3$); δ (ppm) = 143.2, 128.5, 127.1, 126.8, 50.7, 42.2, 18.9. IR (cm$^{-1}$): $f$ = 3030, 2970, 2875, 1494, 1454, 1015, 910, 762, 720, 699. GC-MS: (M)$^+$ = 154.1 calculated for C$_9$H$_{11}$Cl, experimental = 154.0 (material was not ionizable under ESI).

**N-Boc-2-chloromethylproline 3.9c**

Alcohol 3.8c (345 mg, 2.00 mmol, CAS #170491-63-1) was utilized along with pyridine (0.32 mL, 4.00 mmol) and triphosgene (297 mg, 1.00 mmol) to produce 3.9c in 65% yield as a colorless oil (244 mg, 1.11 mmol). Purified product was eluted with 90:10 hexanes : EtOAc. $^1$H NMR (400 MHz, CDCl$_3$); δ (ppm) = 4.04 (0.5H, b), 3.95 (0.5H, b), 3.75 (0.5H, b, d, J = 9.9 Hz), 3.66 (0.5H, b, d, J = 9.9 Hz), 3.54 (0.5H, t, J = 9.0 Hz), 3.46-3.33 (2.5H, m), 2.00 (2H, t, J = 6.4 Hz), 1.88-1.78 (2H, m). $^{13}$C NMR (100, MHz, CDCl$_3$); δ (ppm) = 154.5, 154.2, 79.8, 79.5, 58.1, 58.0, 47.3, 46.8, 45.5, 45.3, 29.2, 28.4, 23.6, 22.8. IR (cm$^{-1}$): $f$ = 2977, 2879, 1695, 1392, 1118, 910, 733. HRMS-ESI: (M+Na)$^+$ = 242.0924 calculated for C$_{10}$H$_{18}$ClNNaO$_2$, experimental = 242.0917.

(±)-(2,4-dichlorobutyl)benzene) 3.11
Alcohol 3.10 (332 mg, 2.00 mmol, CAS #74578-77-1) was utilized along with pyridine (0.65 mL, 8.00 mmol) and triphosgene (593 mg, 2.00 mmol) in 30 mL of CH₂Cl₂ to produce 3.11 in 55% yield as a colorless oil (223 mg, 1.10 mmol). Purified product was eluted with 100:0 □ 90:10 hexanes : EtOAc. ¹H NMR (400 MHz, CDCl₃); δ (ppm) = 7.36-7.22 (5H, m), 4.35 (1H, m), 3.78-3.69 (2H, m), 3.13 (1H, dd, J = 14.1, 7.3 Hz), 3.06 (1H, dd, J = 14.0, 6.6 Hz), 2.20 (1H, m), 2.08 (1H, m). ¹³C NMR (100 MHz, CDCl₃); δ (ppm) = 137.1, 129.4, 128.5, 127.0, 60.0, 44.8, 41.7, 40.1. IR (cm⁻¹): f = 3031, 2965, 1496, 1454, 1318, 1285, 910, 735, 701. GC-MS: M⁺ = 202.0 calculated for C₁₀H₁₂Cl₂, experimental = 202.0 (material was not ionizable under ESI).

4,8-dichlorooct-1-ene 3.13

Alcohol 3.12 (288 mg, 2.00 mmol, CAS #7310-51-2) was utilized along with pyridine (0.64 mL, 8.00 mmol) and triphosgene (593 mg, 2.00 mmol) in 30 mL of CH₂Cl₂ to produce 3.13 in 73% yield as a colorless oil (264 mg, 1.47 mmol). Purified product was eluted with 100:0 □ 90:10 hexanes : EtOAc. ¹H NMR (400 MHz, CDCl₃); δ (ppm) = 5.85 (1H, m), 5.16-5.12 (2H, m), 3.93 (1H, m), 3.55 ( 2H, t, J = 6.4 Hz), 2.53-2.49 (2H, m), 1.87-1.66 (6H, m). ¹³C NMR (100 MHz, CDCl₃); δ (ppm) = 134.0, 118.1, 62.2, 44.7, 42.7, 37.0, 32.1, 23.8. IR (cm⁻¹): f = 3081, 2950, 2868, 1643, 995, 911, 735, 650. GC-MS: (M)⁺ = 180.0 calculated for C₈H₁₄Cl₂, experimental = 179.9 (material not ionizable under ESI).
4-chloro-1-phenylbutan-2-ol 3.14 and 4-benzyl-1,3-dioxan-2-one 3.15

Alcohol 3.10 (332 mg, 2.00 mmol, CAS #74578-77-1) was utilized along with pyridine (0.32 mL, 4.00 mmol) and triphosgene (297 mg, 1.00 mmol) to produce 3.15 in 66% yield as a colorless oil (254 mg, 1.32 mmol) and 3.14 in 14% yield as a colorless oil (50 mg, 0.27 mmol). Purified products were eluted with 90:10 ☐ 80:20 ☐ 70:30 hexanes : EtOAc.

The less polar product (3.14): $^1$H NMR (400 MHz, CDCl$_3$); $\delta$ (ppm) = 7.38-7.22 (5H, m), 4.08 (1H, ddd, $J$ = 15.8, 7.9, 4.7 Hz), 3.80-3.65 (2H, m), 2.86 (1H, dd, $J$ = 13.5, 4.2 Hz), 2.71 (1H, dd, $J$ = 13.5, 8.6 Hz), 2.01-1.93 (2H, m), 1.66 (1H, d, $J$ = 3.0 Hz). $^{13}$C NMR (100 MHz, CDCl$_3$); $\delta$ (ppm) = 137.7, 129.3, 129.6, 126.6, 69.4, 43.9, 41.7, 39.1. IR (cm$^{-1}$): $f$ = 3425, 3378, 3063, 3029, 2943, 2920, 1946, 1454, 1081, 742, 701. HRMS-ESI: 207.0553 calculated for C$_{10}$H$_{13}$ClNaO, experimental = 207.0543.

The more polar product (3.15): $^1$H NMR (400 MHz, CDCl$_3$); $\delta$ (ppm) = 7.37-7.22 (5H, m), 4.67 (1H, m), 4.45-4.27 (2H, m), 3.15 (1H, dd, $J$ = 13.8, 5.7 Hz), 2.92 (1H, dd, $J$ = 13.8, 7.3 Hz), 2.03-1.83 (2H, m). $^{13}$C NMR (100 MHz, CDCl$_3$); $\delta$ (ppm) = 148.6, 135.0, 129.4, 128.7, 127.1, 79.5, 66.8, 41.3, 26.2. IR (cm$^{-1}$): $f$ = 3352, 3028, 2973, 2932, 2875, 1753, 1409, 1250, 1188, 1124, 911, 738, 703. HRMS-ESI: (M-CO+H)$^+$ = 167.1072 calculated for C$_{10}$H$_{15}$O$_2$, experimental = 167.1055.
5.3.1. Experimental Procedures for Secondary Alcohols

(E)-1-phenylhepta-1,6-dien-4-ol 3.6f

Trans-styryl acetic acid 3.18 (3.30 g, 20.35 mmol) was dissolved in THF (50mL), and carbonyldiimidazole (4.30 g, 26.45 mmol) was then added in one portion. The reaction was then allowed to stir overnight. The crude reaction mixture was concentrated in vacuo, diluted with Et₂O (50mL), and then washed with saturated brine solution (3 x 50mL). Collected aqueous layers were extracted with Et₂O (3 x 50mL) and combined to the organic layer. The organic fractions were then dried over MgSO₄, concentrated under vacuum, and taken to the next step without further purification. This crude material was then dissolved in THF (50 mL), and MeONHMe•HCl (1.85 g, 18.99 mmol) was added. A catalytic amount of sodium hydride (~5 mg) was then added to the solution, and the reaction mixture was allowed to stir for 3 hours. The reaction was quenched with a half-saturated NH₄Cl solution (50 mL). Upon separation of layers, the organic layer was washed with a saturated NaHCO₃ solution (50 mL), which was then back extracted with EtOAc (3 x 50 mL). The organic layers were combined, dried over MgSO₄, filtered, and concentrated in vacuo. The resulting crude material was purified with 80:20 hexanes : EtOAc to yield Weinreb amide 3.19 in 57% yield (2.39 g, 11.66 mmol) as a yellow oil.

¹H NMR (400 MHz, CDCl₃); δ (ppm) = 7.38-7.20 (5H, m), 6.51 (1H, d, J = 15.9 Hz), 6.37 (1H, ddd, J = 15.8, 6.9, 6.8 Hz), 3.72 (3H, s), 3.39 (2H, d, J = 6.4 Hz), 3.21 (3H, s). ¹³C NMR (100
MHz, CDCl$_3$); $\delta$ (ppm) = 137.1, 133.1, 128.5, 127.4, 126.3, 122.8, 61.2, 36.5, 32.3 (b), 29.7.

**FT-IR (cm$^{-1}$):** $f = 2936, 1749, 1722, 1448, 1419, 1177, 999, 968, 910, 735$.  
**HRMS-ESI (M+H$^+$):** theoretical = 206.1176 calculated for C$_{12}$H$_{16}$NO$_2$, experimental = 206.1170.

Weinreb amide 3.19 (1.16g, 5.65 mmol) was dissolved in dry THF (50 mL), and the solution was cooled to 0°C. Allylmagnesium bromide (11.3 mL, 11.3 mmol, 1.0M in Et$_2$O) was then added slowly over 20 minutes. The reaction was stirred for an hour and then quenched with a half-saturated NH$_4$Cl (50 mL) solution. Upon separation of layers, the aqueous layer was extracted with EtOAc (3 x 50mL). Organic layers were combined and dried over MgSO$_4$. The crude material was concentrated in vacuo and purified with 90:10 hexanes : EtOAc to afford ketone 3.20 in 82% yield (855 mg, 4.59 mmol) as a yellow oil.  

**$^1$H NMR (400 MHz, CDCl$_3$);** $\delta$ (ppm) = 7.38-7.22 (5H, m), 6.48 (1H, d, $J = 15.9$ Hz), 6.31 (1H, ddd, $J = 16.0, 7.1, 6.9$ Hz), 6.00-5.89 (2H, m), 5.23-5.15 (2H, m), 3.36 (2H, d, $J = 7.0$ Hz), 3.27 (2H, d, $J = 6.9$ Hz).  

**$^{13}$C NMR (100 MHz, CDCl$_3$);** $\delta$ (ppm) = 206.4, 136.8, 133.9, 130.3, 128.6, 127.6, 126.3, 121.7, 119.2, 47.3, 46.4.  

**FT-IR (cm$^{-1}$):** $f = 3082, 3061, 3027, 2981, 1717, 1639, 1578, 1449, 1424, 1323, 1071, 993, 967, 912, 741, 695, 650$.  
**HRMS-ESI (M + H$^+$):** theoretical = 187.1117 calculated for C$_{13}$H$_{15}$O, experimental = 187.1117.

Ketone 3.20 (855 mg, 4.60 mmol) as a solution in Et$_2$O (20 mL) was added via cannula into a cooled (0°C) suspension of lithium aluminum hydride (209 mg, 5.50 mmol). The reaction mixture was then allowed to warm to room temperature and set to reflux for 30 minutes. After cooling the reaction mixture to 0°C, deionized water (0.21 mL) was slowly added, which was followed by 15% aqueous sodium hydroxide solution (0.21 mL), and then deionized water (0.63 mL). This workup sequence resulted in formation of white precipitates. The solution was then allowed to stir for an hour. The filtrate was collected using vacuum filtration and concentrated in
vacuo. The crude material was then purified with 90:10 → 80:20 hexanes : EtOAc to give **3.6f** with a yield of 94% (811 mg, 4.31 mmol) as a colorless oil. ^1^H NMR (400 MHz, CDCl$_3$); δ (ppm) = 7.37-7.20 (5H, m), 6.49 (1H, d, J = 16.1 Hz), 6.25 (1H, ddd, J = 15.9, 7.1, 6.9 Hz), 5.87 (1H, m), 5.19-5.14 (2H, m), 3.78 (1H, m), 2.48-2.33 (3H, m), 2.24 (1H, m), 1.76 (1H, m). ^13^C NMR (100 MHz, CDCl$_3$); δ (ppm) = 137.2, 134.6, 133.1, 128.5, 127.3, 126.1, 118.2, 70.2, 41.4, 40.5, 29.7. FT-IR (cm$^{-1}$): f = 3416, 3079, 3027, 2930, 1641, 1599, 1495, 1449, 1073, 997, 967, 912, 742. HRMS-ESI (M + H$^+$): theoretical = 189.1274 calculated for C$_{13}$H$_{17}$O, experimental = 189.1275.

**4-((tert-butyldimethylsilyl)oxy)-1-phenylbutan-2-ol 3.6g**

Diol **3.10** (479 mg, 2.88 mmol, CAS #74578-77-1) was dissolved in CH$_2$Cl$_2$ (75 mL). Imidazole (432 mg, 6.34 mmol) was then added, and the reaction mixture was cooled to -42°C. TBSCI (478 mg, 3.17 mmol) was then added in one portion. The reaction mixture was stirred overnight while slowly warming up to room temperature and then quenched with a half-saturated NH$_4$Cl solution (50 mL). Upon separation of layers, the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 30mL), washed with brine, dried over MgSO$_4$, filtered, and concentrated under vacuum. The crude material was purified with 90:10 hexanes : EtOAc to give **3.6g** in 56% yield as a colorless oil (452 mg, 1.61 mmol). ^1^H NMR (400 MHz, CDCl$_3$); δ (ppm) = 7.32-7.20 (5H, m), 4.08 (1H, m), 3.90 (1H, p, J = 4.8 Hz), 3.79 (1H, ddd, J = 10.4, 6.5, 6.3 Hz), 3.35 (1H, d, J = 2.0 Hz), 2.85 (1H, dd, J = 13.5, 7.0 Hz), 2.74 (1H, dd, J = 13.5, 6.2 Hz), 1.71-1.66 (2H, m), 0.91 (9H, s), 0.08 (6H, s). ^13^C NMR (100 MHz, CDCl$_3$); δ (ppm) = 138.8, 129.4, 128.4, 126.3, 73.0,
62.6, 44.0, 37.6, 25.9, 18.2, -5.5. IR (cm\(^{-1}\)): \(f = 3455, 2954, 2930, 2857, 1472, 1255, 1085, 909, 836, 777, 740, 700\). HRMS-ESI: \((\text{M}+\text{H})^+ = 281.1931\) calculated for \(\text{C}_{16}\text{H}_{29}\text{O}_2\text{Si}\), experimental = 281.1922.

3-methylphenyl-benzzyloxypropanol 3.6h

![](diagram.png)

Diol 3.10 (2.78g, 16.8 mmol, CAS #74578-77-1) in a solution of DMF (20 mL) was slowly added via cannula to a cooled suspension (0°C) of NaH (0.426 g, 18.42 mmol) in DMF (20 mL). After stirring for 30 minutes, benzyl bromide (1.99 mL, 16.8 mmol) was added. The reaction was then warmed to room temperature and stirred overnight. After quenching the reaction with a half-saturated \(\text{NH}_4\text{Cl}\) solution, the mixture was then extracted with EtOAc (3 x 30 mL), and the collected organic layers were washed with water and dried over \(\text{MgSO}_4\). The crude material was purified with 90:10 \(\rightarrow\) 80:20 \(\rightarrow\) 70:30 hexanes : EtOAc, and alcohol 3.6h was isolated in 24% yield (1.08 g, 3.95 mmol) as a yellow oil. \(^1\text{H}\) NMR (400 MHz, CDCl\(_3\)); \(\delta\) (ppm) = 7.36-7.19 (10H, m), 4.59 (1H, d, \(J = 11.4\) Hz), 4.48 (1H, d, \(J = 11.4\) Hz), 3.86 (1H, m), 3.81-3.70 (2H, m), 3.04 (1H, dd, \(J = 13.4, 5.8\) Hz), 2.79 (1H, dd, \(J = 13.6, 7.0\) Hz), 2.22 (1H, t, \(J = 5.0\) Hz), 1.67-1.81 (2H, m). \(^{13}\text{C}\) NMR (100 MHz, CDCl\(_3\)); \(\delta\) (ppm) = 138.4, 138.1, 129.5, 128.5, 128.4, 128.0, 127.8, 126.3, 79.6, 71.6, 60.7, 40.5, 30.1. IR (cm\(^{-1}\)): \(f = 3410, 3086, 3063, 3029, 2493, 2875, 1604, 1496, 1454, 1056, 1029, 910, 738, 699\). HRMS-ESI (\(\text{M} + \text{H}^+\)): theoretical = 257.1536 calculated for \(\text{C}_{17}\text{H}_{21}\text{O}_2\), experimental = 257.1529.
Alcohol 23 (2.88 g, 10.3 mmol, CAS #146877-29-4) was dissolved in THF (150 mL) and cooled to 0°C. NaH (1.12 g, 46.8 mmol) was then added slowly, and the suspension was stirred for 30 minutes. PMBCl (2.31 g, 14.8 mmol) was then added, and the reaction mixture was brought to room temperature and stirred overnight. The reaction was then slowly quenched with methanol (60 mL), followed by addition of a half-saturated brine solution (50 mL). Upon separation of layers, the aqueous solution was extracted with EtOAc (3 x 50 mL). The organic layers were combined and washed with saturated NaCl, dried over MgSO₄, filtered, and concentrated under vacuum. The resulting crude material was dissolved in THF (50 mL) and treated with 1.0 M TBAF solution in THF (20.5 mL, 20.56 mmol). After stirring overnight, EtOAc (100 mL) was then added. This organic solution was washed sequentially with deionized H₂O and brine, and it was then dried over MgSO₄, filtered, and concentrated under vacuum. Purification of the resulting crude material with 80:20 □ 70:30 □ 60:40 hexanes : EtOAc to yield alcohol 8i in 23% yield as a colorless oil (664 mg, 2.32 mmol). ¹H NMR (400 MHz, CDCl₃); δ (ppm) = 7.32-7.20 (5H, m), 6.91-6.83 (2H, m), 4.52 (1H, d, J = 11.1 Hz), 4.41 (1H, d, J = 11.0 Hz), 3.85 (1H, m), 3.81 (3H, t, J = 4.2 Hz), 3.78-3.66 (2H, m), 3.03 (1H, dd, J = 13.5, 5.8 Hz), 2.77 (1H, dd, J = 13.5, 5.8 Hz), 1.81-1.62 (2H, m). ¹³C NMR (100 MHz, CDCl₃); δ (ppm) = 159.3, 138.4, 130.2, 129.6, 128.7, 128.4, 126.3, 113.9, 79.4, 71.2, 60.7, 55.3, 40.5, 36.1. IR (cm⁻¹): ν = 3417, 2941, 1613, 1514, 1249, 1035, 822, 741, 703. HRMS-ESI: (M+Na)⁺ = 309.1467 calculated for C₁₈H₂₂NaO₃, experimental = 309.1465.
3-hydroxy-4-phenylbutyl 4-methylbenzoate 3.6j

Alcohol 3.21 (1.12g, 4.00 mmol, CAS #146877-29-4) was dissolved in CH$_2$Cl$_2$ (40 mL) and cooled to 0°C. DIPEA (3.56 mL, 20.0 mmol), DMAP (0.24 g, 2.00 mmol), p-Toluoyl chloride (0.63 mL, 4.80 mmol) was sequentially added. After stirring for 3 hours, the reaction mixture was quenched with 2M HCl solution (40 mL). Upon separation of layers, the aqueous solution was extracted with CH$_2$Cl$_2$ (3 x 30 mL), dried over MgSO$_4$, filtered, and concentrated under vacuum. The resulting crude material was then dissolved in THF (25 mL) and treated with 1.0 M TBAF solution in THF (8.0 mL, 8.00 mmol). After stirring overnight, EtOAc (100 mL) was then added. This organic solution was washed sequentially with deionized H$_2$O and brine, and it was then dried over MgSO$_4$, filtered, and concentrated under vacuum. Purification of the resulting crude material with 80:20 hexanes : EtOAc to yield 3.6j in 65% yield as a colorless oil (744 mg, 2.62 mmol). $^1$H NMR (400 MHz, CDCl$_3$); $\delta$ (ppm) = 8.00 (1H, d, $J = 8.1$ Hz), 7.92 (1H, d, $J = 8.1$ Hz), 7.34-7.23 (5H, m), 4.59 (1H, ddd, $J = 11.1$, 8.6, 5.2 Hz), 4.43 (1H, p, $J = 5.6$ Hz), 4.01 (1H, ddt, $J = 8.6$, 8.6, 4.3 Hz), 2.88 (1H, dd, $J = 13.6$, 4.6 Hz), 2.78 (1H, dd, $J = 13.6$, 8.2 Hz), 2.43 (3H, d, $J = 8.2$ Hz), 2.03 (1H, m), 1.89 (1H, m). $^{13}$C NMR (400 MHz, CDCl$_3$); $\delta$ (ppm) = 167.0, 143.7, 138.1, 130.2, 129.7, 129.5, 129.1, 128.6, 127.4, 126.6, 69.6, 62.0, 44.0, 36.0, 21.7. IR (cm$^{-1}$): $f$ = 3482, 3029, 2957, 2919, 1712, 1612, 1455, 1274, 1178, 1111, 1021, 972, 842, 753, 701. HRMS-ESI: (M+H)$^+$ = 285.1491 calculated for C$_{18}$H$_{21}$O$_3$, experimental = 285.1494.
5.4. Experimental Procedures for Chapter Four

5.4.1. Experimental Procedures for 1,3-anti Dichlorides

Unless otherwise noted, 1,3-anti diol starting material was dissolved in anhydrous dichloromethane (~60-100 mM concentration). The solution was then cooled to 0°C. Triphosgene was added in one portion, followed by pyridine via syringe. The solution was stirred for 5 min and then warmed to gentle reflux for 3-6 hours. After cooling to room temperature, the reaction mixture was then poured into a separatory funnel containing aqueous HCl solution (1M, 10 mL), and the biphasic mixture was shaken vigorously. Upon separation of layers, the aqueous layer was re-extracted with dichloromethane (2 × 15 mL). Organic extracts were collected, dried over Na$_2$SO$_4$, filtered, and concentrated under vacuum. The resulting crude material was purified using flash column chromatography with silica gel as the stationary phase and a mixture of hexanes/ethyl acetate, pentane/diethyl ether, or pentane/dichloromethane as the mobile phase.

$((2S,4S)-2,4$-dichlorohept-6-en-1-yl)benzene 4.10a

1,3-anti diol 4.9a (50 mg, 0.24 mmol) was dissolved in CH$_2$Cl$_2$ (4.0 mL) and treated with triphosgene (71 mg, 0.24 mmol) and pyridine (78 µL, 0.96 mmol) to produce 1,3-anti dichloride 4.10a in 90% yield as colorless oil (52 mg, 0.21 mmol). The purified product was eluted with 100% hexanes. $^1$H NMR (400 MHz, CDCl$_3$); δ (ppm) = 7.41-7.23 (5H, m), 5.86 (1H, m), 5.19-5.14 (2H, m), 4.50 (1H, p, J = 6.6 Hz), 4.32 (1H, p, J = 6.5 Hz), 3.15 (1H, dd, J = 14.1, 7.4 Hz), 3.07 (1H, dd, J = 14.1, 6.4 Hz), 2.54 (2H, t, J = 6.6 Hz), 2.05-2.02 (2H, m). $^{13}$C NMR (100 MHz, CDCl$_3$); δ (ppm) = 137.16, 133.53, 129.34, 128.47, 126.93, 118.39, 60.50, 59.24, 45.57, 44.98,
42.84. IR (cm⁻¹): \( f = 3081, 3065, 3029, 2961, 2854, 1698, 1643, 1604, 1496, 1454, 1277, 1239, 922, 700 \). HRMS-ESI: \((M-H_2Cl)^{+} = 205.0779\) calculated for \(C_{13}H_{14}Cl\), experimental = 205.0789. GC-MS: \(Rt = 18.72\) min; \(M^+ = 242.1\) calculated for \(C_{13}H_{16}Cl_2\), experimental = 242.1.

\((\pm)-(2S,4S)-2,4\text{-dichlorotridecyl})\text{benzene} \ 4.10b\)

1,3-anti diol \(4.9b\) (97 mg, 0.37 mmol) was dissolved in \(CH_2Cl_2\) (6.0 mL) and treated with triphosgene (110 mg, 0.37 mmol) and pyridine (119 µL, 1.47 mmol) to produce 1,3-anti dichloride \(4.10b\) in 65% yield as a colorless oil (72 mg, 0.24 mmol). The purified product was eluted with 100% hexanes. \(^1H \text{NMR} \ (400 \text{ MHz, CDCl}_3); \ \delta \ (ppm) = 7.37-7.24 \ (5H, m), 4.52 \ (1H, m), 4.26 \ (1H, m), 3.14 \ (1H, dd, \ J = 13.8, 7.5 \text{ Hz}), 3.06 \ (1H, dd, \ J = 14.0, 6.3 \text{ Hz}), 2.08-1.94 \ (2H, m), 1.74 \ (1H, m), 1.54-1.42 \ (3H, m) 1.31 \ (3H, s), 0.91 \ (3H, t, \ J = 6.3 \text{ Hz}). \ ^{13}C \text{NMR} \ (100 \text{ MHz, CDCl}_3); \ \delta \ (ppm) = 137.21, 129.35, 128.44, 126.89, 60.82, 60.66, 46.33, 45.01, 38.74, 31.73, 29.10, 29.01, 26.38, 22.61, 14.07 \text{ IR (cm}^{-1}): \ f = 2958, 2929, 2854, 1496, 1456, 750, 699, 612. \) HRMS-ESI: \((M-HCl)_2^{+} = 229.1951\) calculated for \(C_{17}H_{25}\), experimental = 229.1948. GC-MS: \(Rt = 21.92\) min; \(M^+ = 300.1\) calculated for \(C_{17}H_{26}Cl_2\), experimental = 300.1.

\((\pm)-\text{tert-butyl}((5S,7S,E)-5,7\text{-dichloro-2-methyl-8-phenyloct-2-en-1yl})\text{oxy})\text{dimethylsilane} \ 4.10c\)
1,3-anti diol 4.9c (55 mg, 0.15 mmol) was dissolved in CH₂Cl₂ (1.5 mL) and treated with triphosgene (45 mg, 0.15 mmol) and pyridine (49 µL, 0.60 mmol) to produce 1,3-anti dichloride 4.10c in 80% yield as a colorless oil (48 mg, 0.12 mmol). The purified product was eluted with 100% hexanes. ¹H NMR (400 MHz, CDCl₃); δ (ppm) = 7.36-7.21 (5H, m), 5.47 (1H, t, J = 8.0 Hz), 4.47 (1H, p, J = 8.0 Hz), 4.27 (1H, p, J = 8.0 Hz), 4.03 (2H, s), 3.12 (1H, dd, J = 16.0, 8.0 Hz), 3.03 (1H, dd, J = 16.0, 8.0 Hz), 2.55-2.46 (2H, m), 2.02-1.98 (2H, m), 1.60 (3H, s), 0.92 (9H, s), 0.06 (6H, s). ¹³C NMR (100 MHz, CDCl₃); δ (ppm) = 137.87, 137.20, 129.36, 128.47, 126.93, 118.85, 68.04, 60.55, 60.04, 45.59, 45.04, 36.73, 25.94, 18.41, 13.78, -5.27. IR (cm⁻¹): f = 2954, 2928, 2855, 1252, 1109, 1072, 835, 775, 699. HRMS-ESI: (M-2Cl+H)⁺ = 329.2295 calculated for C₂₁H₃₃OSi, experimental = 329.2289. Rt = 23.58 min; (M-C₄H₉)⁺ = 343.1 calculated for C₁₇H₂₅Cl₂OSi, experimental = 343.1.

(±)-(3S,5S)-tert-butyl 3,5-dichloro-6-phenylhexanoate 4.10d

1,3-anti diol 4.9d (150 mg, 0.54 mmol) was dissolved in CH₂Cl₂ (8.0 mL) and treated with triphosgene (160 mg, 0.54 mmol) and pyridine (175 µL, 2.16 mmol) to produce 1,3-anti dichloride 4.10d in 73% yield as a colorless oil (125 mg, 0.40 mmol). The purified product was eluted with 90:10 hexanes:EtOAc. ¹H NMR (400 MHz, CDCl₃); δ (ppm) = 7.37-7.24 (5H, m), 4.62 (1H, m), 4.48 (1H, dtd, J = 10.0, 6.9, 2.9 Hz), 3.16 (1H, dd, J = 14.2, 7.2 Hz), 3.07 (1H, dd, J = 14.1, 6.5 Hz), 2.74 (1H, dd, J = 15.5, 7.7 Hz), 2.65 (1H, dd, J = 15.6, 6.2 Hz), 2.13-2.01 (2H, m), 1.49, (9H, s). ¹³C NMR (100 MHz, CDCl₃); δ (ppm) = 168.58, 136.95, 129.30, 128.43,
126.91, 81.44, 59.93, 55.32, 45.41, 44.81, 44.78, 27.95. IR (cm\(^{-1}\)): \( f = 2978, 2931, 1728, 1367, 1145, 751, 699 \). HRMS-ESI: (M-H\(_2\)Cl\(_2\))^+ = 244.1463 calculated for C\(_{16}\)H\(_{20}\)O\(_2\), experimental = 244.1957.

\((\pm)-(2S,4S)-2,4,6\text{-trichlorohexyl})\text{benzene 4.19}\)

1,3,5-\(\text{anti}\) triol 4.18 (37 mg, 0.175 mmol) was dissolved in CH\(_2\)Cl\(_2\) (2.5 mL) and treated with triphosgene (78 mg, 0.27 mmol) and pyridine (85 \(\mu\)L, 1.05 mmol) to produce 1,3,5-\(\text{anti}\) trichloride 4.19 in 75% yield as a colorless oil (35 mg, 0.13 mmol). The purified product was eluted with 100% hexanes. \(^1\)H NMR (400 MHz, CDCl\(_3\)); \( \delta \) (ppm) = 7.38-7.24 (5H, m), 4.49 (2H, p, J = 8.0 Hz), 3.79-3.70 (2H, m), 3.18 (1H, dd, J = 12.0, 8.0 Hz), 3.07 (1H, dd, J = 12.0, 8.0 Hz), 2.18-1.96 (4H, m). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)); \( \delta \) (ppm) = 136.99, 129.36, 128.53, 127.01, 60.02, 57.27, 46.02, 44.93, 41.26, 41.11. IR (cm\(^{-1}\)): \( f = 2964, 2925, 1454, 906, 701 \). HRMS-ESI: (M+H)^+ = 229.0545 calculated for C\(_{12}\)H\(_{15}\)Cl\(_2\), experimental = 229.0527. GC-MS: Rt = 20.29 min; M^+ = 264.0 calculated for C\(_{12}\)H\(_{15}\)Cl\(_3\), experimental = 264.0.

**5.4.2. Experimental Procedures for 1,3-\(\text{syn}\) Dichlorides**

Unless otherwise noted, 1,3-\(\text{syn}\) diol monosilylether starting material was dissolved in anhydrous dichloromethane (∼500 mM concentration). The solution was then cooled to 0°C. Triphosgene was added in one portion, followed by pyridine via syringe. The solution was stirred for 5 min and then warmed to gentle reflux for 3-6 hours. After cooling to room temperature, the reaction mixture was then poured into a separatory funnel containing aqueous HCl solution (1M, 10 mL), and the biphasic mixture was shaken vigorously. Upon separation of layers, the aqueous
layer was re-extracted with dichloromethane (2 × 15 mL). Organic extracts were collected, dried over Na₂SO₄, filtered, and concentrated under vacuum. The resulting crude material was purified using flash column chromatography with silica gel as the stationary phase and a mixture of hexanes/ethyl acetate, pentane/diethyl ether, or pentane/dichloromethane as the mobile phase.

\((\pm)-((2S,4R)-2,4\text{-dichlorohept-6-en-1-yl})\text{benzene 4.17a}\)

\[
\begin{array}{c}
\text{Ph} \quad \text{OH} \quad \text{OSiMe}_2\text{Ph} \\
4.16a
\end{array}
\xrightarrow{\text{triphosgene (1.0 equiv) pyridine (4.0 equiv)}}
\begin{array}{c}
\text{Ph} \quad \text{Cl} \quad \text{Cl} \\
4.17a
\end{array}
\]

\(\text{CH}_2\text{Cl}_2, 0°C → \text{reflux}\)

1,3-syn diol monosilylether 4.16a (114 mg, 0.34 mmol) was dissolved in \(\text{CH}_2\text{Cl}_2\) (0.68 mL) and treated with triphosgene (101 mg, 0.34 mmol) and pyridine (108 μL, 1.34 mmol) to produce 1,3-syn dichloride 4.17a in 76% yield as a colorless oil (62 mg, 0.26 mmol). The purified product was eluted with 100% hexanes. \(^1\text{H NMR (400 MHz, CDCl}_3); \delta (ppm) = 7.38-7.24 (5H, m), 5.85 (1H, m), 5.17-5.13 (2H, m), 4.31-4.18 (2H, m), 3.14 (1H, dd, \(J = 14.1, 5.5\) Hz), 3.02 (1H, dd, \(J = 14.1, 7.9\) Hz), 2.61 (1H, dt, \(J = 14.9, 5.7\) Hz), 2.47 (1H, dt, \(J = 14.6, 7.3\) Hz), 2.33-2.20 (2H, m). \(^{13}\text{C NMR (100 MHz, CDCl}_3); \delta (ppm) = 137.14, 133.04, 129.37, 128.47, 126.98, 118.65, 59.82, 58.30, 45.37, 44.10, 41.13. \text{IR (cm}^{-1}); f = 3065, 3029, 2963, 2918, 1434, 923, 749, 699. \text{HRMS-ESI: (M-HCl}_2)^+ = 171.1168 \text{ calculated for C}_{13}\text{H}_{15}, \text{experimental} = 171.1172. \text{GC-MS: Rt = 18.70 min; M}^+ = 242.1 \text{ calculated for C}_{13}\text{H}_{16}\text{Cl}_2, \text{experimental} = 242.0.

\((\pm)-((2S,4R)-2,4\text{-dichlorotridecyl})\text{benzene 4.17b}\)

\[
\begin{array}{c}
\text{Ph} \quad \text{OH} \quad \text{OSiMe}_2\text{Ph} \\
4.16b
\end{array}
\xrightarrow{\text{triphosgene (1.0 equiv) pyridine (4.0 equiv)}}
\begin{array}{c}
\text{Ph} \quad \text{Cl} \quad \text{Cl} \\
4.17b
\end{array}
\]

\(\text{CH}_2\text{Cl}_2, 0°C → \text{reflux}\)
1,3-syn diol monosilylether 4.16b (110 mg, 0.28 mmol) was dissolved in CH₂Cl₂ (0.56 mL) and treated with triphosgene (83 mg, 0.28 mmol) and pyridine (89 µL, 1.10 mmol) to produce 1,3-syn dichloride 4.17b in 82% yield as a colorless oil (68.5 mg, 0.23 mmol). The purified product was eluted with 100% hexanes. ¹H NMR (400 MHz, CDCl₃); δ (ppm) = 7.41-7.26 (5H, m), 4.29 (1H, tdd, J = 8.0, 5.8, 5.8 Hz), 4.26 (1H, m), 3.16 (1H, dd, J = 14.0, 5.4 Hz), 3.02 (1H, dd, J = 14.1, 8.1 Hz), 2.32 (1H, dt, J = 14.7, 7.5 Hz), 2.20 (1H, dt, J = 13.7, 6.4 Hz), 1.79 (1H, m), 1.66 (1H, ddt, J = 14.0, 14.0, 4.7 Hz), 1.56-1.40 (2H, m), 1.37-1.28 (8H, m), 0.93 (3H, t, J = 6.5 Hz). ¹³C NMR (100 MHz, CDCl₃); δ (ppm) = 137.24, 129.38, 128.45, 126.95, 59.96, 59.94, 46.28, 44.06, 37.08, 31.73, 29.10, 28.96, 25.94, 22.61, 14.08. IR (cm⁻¹): f = 3028, 2956, 2926, 2855, 1497, 1455, 1254, 1119, 1059, 831, 791, 699. HRMS-ESI: (M-HCl₂)⁺ = 229.1951 calculated for C₁₇H₂₅, experimental = 229.1955. GC-MS: Rt = 21.88 min; M⁺ = 300.1 calculated for C₁₇H₂₆Cl₂, experimental = 300.1.

(±)-tert-butyl(((5R,7S,E)-5,7-dichloro-2-methyl-8-phenyloct-2-en-1-yl)oxy)dimethylsilane 4.17c

1,3-syn diol monosilylether 4.16c (38 mg, 0.076 mmol) was dissolved in CH₂Cl₂ (0.15 mL) and treated with triphosgene (23 mg, 0.076 mmol) and pyridine (25 µL, 0.31 mmol). The crude was eluted with 100% hexanes → 98:2 hexanes:EtOAc to produce 1,3-syn dichloride 4.17c in 93% yield as a colorless oil (29 mg, 0.071 mmol). ¹H NMR (400 MHz, CDCl₃); δ (ppm) = 7.39-7.24 (5H, m), 5.50 (1H, t, J = 8.0 Hz), 4.28 (1H, p, J = 8.0 Hz), 4.20 (1H, p, J = 8.0 Hz), 4.04 (2H, s), 3.15 (1H, dd, J = 16.0, 8.0 Hz), 2.99 (1H, dd, J = 16.0, 8.0 Hz), 2.62-2.47 (2H, m),
2.32-2.22 (2H, m), 1.63 (3H, s), 0.95 (9H, s), 0.10 (6H, s). $^{13}$C NMR (100 MHz, CDCl$_3$); δ (ppm) = 138.00, 137.24, 129.40, 128.46, 126.96, 118.47, 68.06, 60.02, 59.20, 45.67, 44.05, 35.19, 25.94, 18.41, 13.79, -5.28. IR (cm$^{-1}$): $f =$ 2954, 2928, 2856, 1253, 1111, 1072, 836, 776, 699. HRMS-ESI: (M+Na)$^+$ = 423.1648 calculated for C$_{21}$H$_{34}$Cl$_2$NaOSi, experimental = 423.1676. Rt = 23.58 min; (M-C$_4$H$_9$)$^+$ = 343.1 calculated for C$_{17}$H$_{25}$Cl$_2$OSi, experimental = 343.1.

(±)-(3R,5S)-tert-butyl 3,5-dichloro-6-phenylhexanoate 4.17d

![](image)

1,3-syn diol monosilylether 4.16d (29 mg, 0.070 mmol) was dissolved in CH$_2$Cl$_2$ (0.14 mL) and treated with triphosgene (21 mg, 0.070 mmol) and pyridine (23 μL, 0.28 mmol) to produce 1,3-syn dichloride 4.17d in 92% yield as a colorless oil (20 mg, 0.065 mmol). The purified product was eluted with 100% hexanes, buffered with 1% Et$_3$N. $^1$H NMR (500 MHz, CDCl$_3$); δ (ppm) = 7.38-7.20 (5H, m), 4.47 (1H, m), 4.29-4.23 (1H, m), 3.16 (1H, dd, $J =$ 14.2, 5.2 Hz), 2.98 (1H, dd, $J =$ 14.2, 8.3 Hz), 2.72 (1H, dd, $J =$ 15.8, 5.1 Hz), 2.63 (1H, dd, $J =$ 15.8, 8.4 Hz), 2.34-2.24 (2H, m), 1.46 (9H, s). $^{13}$C NMR (125 MHz, CDCl$_3$); δ (ppm) = 168.86, 137.08, 129.40, 128.48, 127.00, 81.60, 59.46, 54.65, 45.58, 43.87, 43.61, 28.05. IR (cm$^{-1}$): $f =$ 2977, 2927, 2854, 1715, 1368, 1296, 1255, 1148, 700. HRMS-ESI: (M+Na)$^+$ = 339.0889 calculated for C$_{16}$H$_{22}$Cl$_2$NaO$_2$, experimental = 339.0891.
(±)-(2S,4R)-2,4,6-trichlorohexyl benzene 4.21

1,3,5-syn triol monosilylether 4.20 (60 mg, 0.17 mmol) was dissolved in CH₂Cl₂ (0.34 mL) and treated with triphosgene (77 mg, 0.26 mmol) and pyridine (82 µL, 1.02 mmol) to produce 1,3,5-syn trichloride 4.21 in 55% yield as a colorless oil (25 mg, 0.09 mmol). The purified product was eluted with 100% hexanes, buffered with 1% Et₃N. ¹H NMR (400 MHz, CDCl₃); δ (ppm) = 7.37-7.24 (5H, m), 4.37 (1H, dtd, J = 10.0, 7.0, 3.0 Hz), 4.30 (1H, ddd, J = 13.8, 7.8, 6.0 Hz), 3.78-3.68 (2H, m), 3.15 (1H, dd, J = 14.1, 5.5 Hz), 3.03 (1H, dd, J = 14.2, 7.9 Hz), 2.34 (1H, dt, J = 14.5, 7.6 Hz), 2.26-2.18 (2H, m), 2.07 (1H, ddt, J = 10.7, 9.8, 5.0 Hz). ¹³C NMR (100 MHz, CDCl₃); δ (ppm) = 136.94, 129.40, 128.52, 127.06, 59.29, 56.38, 45.95, 43.98, 41.26, 39.77. IR (cm⁻¹): f = 3029, 2964, 2923, 2852, 1497, 1454, 1438, 1311, 1247, 749, 700. HRMS-ESI: (M-Cl)⁺ = 229.0545 calculated for C₁₂H₁₅Cl₂, experimental = 229.0543. GC-MS: Rt = 20.25 min; M⁺ = 264.0 calculated for C₁₂H₁₅Cl₃, experimental = 264.0.
5.4.3. Experimental Procedures for 1,3-anti Diols

Preparation of 1,3-anti Diol 4.9a

A solution of LDA in THF (300 mL) was prepared by dissolving diisopropylamine (37.6 mL, 266.00 mmol) in THF while cooling to -78°C. n-BuLi (106.5 mL, 266.00 mmol) was slowly added. The mixture was allowed to stir for 15 minutes before ethyl acetate (26 mL, 266.00 mmol) was added dropwise. After stirring the resulting mixture for 20 minutes, phenylacetaldehyde (18.6 mL, 166.40 mmol) was added. The mixture was allowed to stir until complete consumption of aldehyde and then quenched with a half-saturated NH₄Cl (150 mL) solution. Upon separation of layers, the aqueous layer was extracted with EtOAc (3 x 50 mL). Organic layers were combined and dried over MgSO₄ and concentrated in vacuo.

The resulting crude material was then dissolved in Et₂O (20 mL). The solution was then added dropwise via cannula to a cooled (0°C) suspension of lithium aluminum hydride (7.0 g, 183.00 mmol) in Et₂O (500 mL). After stirring for one hour, the reaction was quenched by the
slow addition of deionized water (7.0 mL), which was followed by addition of a 15% aqueous sodium hydroxide solution (7.0 mL), and then deionized water (21.0 mL). This workup sequence resulted in the formation of white precipitates. After further stirring for one hour, the filtrate was collected using vacuum filtration and concentrated in vacuo. The crude material was then purified in 30:70 → 20:80 hexanes:EtOAc to give 1,3-diol 4.22 with a yield of 56% (15.49 g, 93.26 mmol) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$); δ (ppm) = 7.36-7.23 (5H, m), 3.91-3.84 (2H, m), 2.87-2.76 (2H, m), 2.42-2.37 (2H, bs), 1.82-1.75 (2H, m). $^{13}$C NMR (100 MHz, CDCl$_3$); δ (ppm) = 138.08, 129.36, 128.51, 126.47, 72.77, 61.43, 44.26, 37.70. Compound 4.22 is known (CAS #74578-77-1).

$^{(+)}$-4-benzyl-2-(4-methoxyphenyl)-1,3-dioxane 4.23

1,3-Diol 4.22 (15.49 g, 93.26 mmol) was dissolved in toluene (300 mL) and $p$-anisaldehyde (17.0 mL, 136.20 mmol) and TsOH (177 mg, 0.93 mmol) were added. The resulting mixture was heated to reflux using a dean stark apparatus. After stirring overnight, the reaction was quenched by the addition of solid NaHCO$_3$ (300 mg), and the mixture was then concentrated in vacuo. In order to create better chromatographic separation between the product and residual $p$-anisaldehyde, the crude material was dissolved in MeOH (200 mL) and carefully treated with NaBH$_4$ (5.29 g, 139.90 mmol). The mixture was stirred until $p$-anisaldehyde was fully consumed. After removing the organic solvent under vacuum, the crude material was then quenched with a half-saturated NH$_4$Cl solution (100 mL) and then extracted with EtOAc (3 x 100 mL). The organic layer was dried over MgSO$_4$ and concentrated in vacuo. The crude material was purified with 80:20 hexanes:EtOAc to give acetal 4.23 with a yield of 97% (25.59 g, 90.10 mmol) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$); δ (ppm) = 7.43 (2H, d, $J = 8.2$
Hz), 7.35-7.24 (5H, m), 6.90 (2H, d, \( J = 8.4 \) Hz), 5.48 (1H, s), 4.24 (1H, m), 3.95 (1H, m), 3.81 (3H, s), 3.09 (1H, dd, \( J = 13.5, 6.3 \) Hz), 2.80 (1H, dd, \( J = 13.6, 6.9 \) Hz), 1.84 (1H, m), 1.49 (1H, m). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)); \( \delta \) (ppm) = 159.85, 137.74, 131.35, 129.54, 128.29, 127.32, 126.35, 113.58, 101.06, 77.99, 66.95, 55.28, 42.60, 30.77. IR (cm\(^{-1}\)): \( f = 2953, 2840, 1614, 1516, 1247, 1171, 1103, 1031, 907, 825, 726, 699, 532. \) HRMS-ESI: (M+)\(^+\) = 285.1485 calculated for C\(_{18}\)H\(_{21}\)O\(_3\), experimental = 285.1484.

\((-\cdots)-3-((4\text{-methoxybenzyl})oxy)-4\text{-phenylbutan-1}\text{-ol} \textbf{4.24}\)

Acetal \textbf{4.23} (9.46 g, 33.30 mmol) was dissolved in CH\(_2\)Cl\(_2\) (200 mL) and cooled to -78°C. DIBAL (48.3 mL, 48.30 mmol, 1M solution in toluene) was added dropwise. The reaction was allowed to stir at -78°C for two hours before being allowed to slowly warm to room temperature overnight. After cooling back to 0°C, the reaction mixture was slowly quenched with a saturated aqueous solution of Rochelle’s salt (150 mL) and vigorously stirred for two hours. Upon separation of layers, the aqueous layer was then extracted with CH\(_2\)Cl\(_2\) (3 x 100 mL). The organic layers were collected, dried over Na\(_2\)SO\(_4\), and concentrated in vacuo. The crude mixture was purified in 70:30 → 60:40 hexanes:EtOAc to give alcohol \textbf{4.24} with a yield of 80% (7.29 g, 25.48 mmol) as a yellow oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)); \( \delta \) (ppm) = 7.35-7.20 (7H, m), 6.89 (2H, d, \( J = 8.6 \) Hz), 4.54 (1H, d, \( J = 11.0 \) Hz), 4.43 (1H, d, \( J = 11.0 \) Hz), 3.89-3.68 (3H, m), 3.83 (3H, s), 3.05 (1H, dd, \( J = 13.5, 5.8 \) Hz), 2.80 (1H, d, \( J = 13.6, 7.0 \) Hz), 2.43 (1H, bs), 1.83-1.67 (2H, m). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)); \( \delta \) (ppm) = 159.25, 138.38, 130.13, 129.52, 129.45, 128.34, 126.23, 113.84, 79.23, 71.15, 60.62, 55.22, 40.46, 36.02. IR (cm\(^{-1}\)): \( f = 3409, 3029, 2936, 2866, 1612, 1513, 1247, 1173, 1033, 906, 822, 725, 700, 647, 513. \) HRMS-ESI: (M+Na)\(^+\) = 309.1461 calculated for C\(_{18}\)H\(_{22}\)NaO\(_3\), experimental = 309.1471.
(±)-3-((4-methoxybenzyl)oxy)-4-phenylbutanal **4.25**

Alcohol **4.24** (7.29 g, 25.48 mmol) was dissolved in CH₂Cl₂ (250 mL) and cooled to 0°C. TEMPO (399 mg, 2.55 mmol) and KBr (1.3 mL, 2.55 mmol, 2M solution) were then added to the solution. A bleach solution containing NaOCl (35 mL, 28.03 mmol, Clorox brand) and NaHCO₃ (519 mg, 15 mg per 1 mL of bleach) was added slowly to maintain the internal reaction temperature near 0°C. Upon completion, the biphasic layers were separated. The aqueous layer reaction was then extracted with CH₂Cl₂ (3 x 100 mL). The combined organic layers were then washed with Na₂S₂O₃, followed by a saturated NaHCO₃ solution, and then dried over Na₂SO₄ and concentrated in vacuo. The crude mixture was purified in 80:20 → 70:30 hexane:EtOAc to give aldehyde **4.25** with a yield of 69% (5.00 g, 17.60 mmol) as a colorless solid. ¹H NMR (400 MHz, CDCl₃); δ (ppm) = 9.71 (1H, t, J = 2.1 Hz), 7.33-7.17 (7H, m), 6.86 (2H, d, J = 8.6 Hz), 4.47 (2H, q, J = 11.1, 4.4 Hz), 4.19-4.13 (1H, m), 3.81 (3H, s), 3.03 (1H, dd, J = 13.6, 6.0 Hz), 2.81 (1H, dd, J = 13.6, 6.8 Hz), 2.63 (1H, ddd, J = 16.6, 7.7, 2.5 Hz), 2.51 (1H, ddd, J = 16.5, 4.4, 1.7 Hz). ¹³C NMR (100 MHz, CDCl₃); δ (ppm) = 201.31, 159.27, 137.60, 130.01, 129.53, 129.46, 128.48, 126.56, 113.81, 75.07, 71.33, 55.26, 48.04, 40.59. IR (cm⁻¹): f = 2975, 2850, 1719, 1612, 1513, 1248, 1087, 1033, 702. HRMS-ESI: (M+Na)⁺ = 307.1310 calculated for C₁₈H₂₀O₃Na, experimental = 307.1308.

(±)-(4R,6R)-6-((4-methoxybenzyl)oxy)-7-phenylhept-1-en-4-ol **4.26**

PMB aldehyde **4.25** (1.50 g, 5.28 mmol) was dissolved in CH₂Cl₂ (25 mL) in a round bottom flask containing 4Å molecular sieves. After cooling the mixture to -78°C, freshly prepared TiCl₄(OiPr)₂ (10.3 mL, 7.92 mmol, 0.77M in CH₂Cl₂) was then added and allowed to stir for 10 minutes. Tributylallylstannane (2.50 mL, 7.92 mmol) was added dropwise. The
reaction was stirred until completion and then quenched with a saturated NaHCO$_3$ solution (25 mL) and allowed to warm to room temperature. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 20 mL). The combined organic layers were then dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude mixture was purified in 80:20 → 70:30 hexanes:EtOAc to give alcohol 4.26 in 95% yield (1.63 g, 5.00 mmol) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$); δ (ppm) = 7.35-7.20 (7H, m), 6.88 (2H, d, J = 8.2 Hz), 5.81 (1H, m), 5.09 (2H, d, J = 13.2 Hz), 4.45 (2H, dd, J = 15.8, 10.8 Hz), 4.03-3.93 (2H, m), 3.81 (3H, s), 3.03 (1H, dd, J = 13.8, 6.4 Hz), 2.80 (1H, dd, J = 13.7, 6.7 Hz), 2.66 (1H, d, J = 3.3 Hz), 2.20 (2H, t, J = 6.7 Hz), 1.68-1.59 (2H, m). $^{13}$C NMR (100 MHz, CDCl$_3$); δ (ppm) = 159.16, 138.50, 134.80, 130.15, 129.49, 129.39, 128.25, 126.13, 117.43, 113.73, 77.53, 71.38, 67.51, 55.14, 42.08, 40.41, 39.73. IR (cm$^{-1}$): $f$ = 3359, 3064, 3027, 2917, 2859, 1496, 1434, 1247, 1081, 1032, 909, 730, 699. HRMS-ESI: (M+Na)$^+$ = 349.1774 calculated for C$_{21}$H$_{26}$NaO$_3$, experimental = 349.1768.

$(\pm$)-(2$R$,4$R$)-1-phenylhept-6-ene-2,4-diol 4.9a

Alcohol 4.26 (150 mg, 0.46 mmol) was dissolved in CH$_2$Cl$_2$ (10 mL). DMAP (56 mg, 0.46 mmol) was added to the reaction mixture, followed by addition of acetic anhydride (0.22 mL, 2.30 mmol) and pyridine (0.40 mL, 4.60 mmol). Upon completion, the reaction was quenched with a 2M HCl solution (15 mL) and extracted with CH$_2$Cl$_2$ (3 x 15 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated under vacuum to give the crude acetate protected alcohol.

The resulting crude product was then dissolved in a mixture of CH$_2$Cl$_2$:H$_2$O (8 mL:few drops) and treated with DDQ (157 mg, 0.69 mmol). Upon completion, the reaction was quenched with a saturated NaHCO$_3$ solution (15 mL) and extracted with CH$_2$Cl$_2$ (3 x 15 mL).
The combined organic layers were dried over Na₂SO₄ and concentrated under vacuum. The crude monoprotected alcohol was then dissolved in MeOH (5 mL) and treated with K₂CO₃ (127 mg, 0.92 mmol). Upon completion, the reaction was quenched with a half saturated NH₄Cl solution (15 mL) and extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under vacuum. The crude mixture was purified in 70:30 → 60:40 hexanes:EtOAc to give 1,3-anti diol 4.9a in 62% yield (59 mg, 0.28 mmol) over three steps, as a clear oil. ¹H NMR (400 MHz, CDCl₃); δ (ppm) = 7.35-7.21 (5H, m), 5.81 (1H, m), 5.16-5.10 (2H, m), 4.19 (1H, p, J = 6.1 Hz), 4.03 (1H, p, J = 5.9 Hz), 2.84-2.75 (2H, m), 2.35 (1H, bs), 2.29-2.24 (3H, m), 1.69 (2H, dd, J = 6.0, 5.5 Hz). ¹³C NMR (100 MHz, CDCl₃); δ (ppm) = 138.26, 134.60, 129.35, 128.59, 126.54, 70.04, 68.08, 44.04, 41.99, 41.52. IR (cm⁻¹): f = 3335, 3076, 3028, 2914, 1496, 1433, 1327, 1080, 995, 914, 743, 698, 489. HRMS-ESI: (M+H)⁺ = 207.1380 calculated for C₁₃H₁₉O₂, experimental = 207.1381.

Preparation of 1,3-anti Diol 4.9b

Grubbs II catalyst (24 mg, 0.028 mmol) was dissolved in CH₂Cl₂ (8 mL). Allylic alcohol 4.26 (178 mg, 0.55 mmol) and 1-hexene (0.70 mL, 5.50 mmol) were then added, and the reaction mixture was heated to reflux. Upon completion, the reaction mixture was cooled to room temperature and concentrated in vacuo to afford alkene 4.27. The crude mixture was then
introduced into a round bottom flask under vacuum. 10% Pd/C (300 mg, 0.28 mmol) was added carefully, followed by the addition of MeOH (5 mL). The black suspension was then purged and bubbled with a balloon of H₂ gas overnight. Upon completion, the reaction mixture was filtered through a pad of celite via vacuum filtration. The solid residue was rinsed with EtOAc (3 x 10 mL), and the filtrate was concentrated in vacuo. The crude mixture was purified in 60:40 hexanes:EtOAc to give aliphatic chain 4.9b in 67% yield (97 mg, 0.37 mmol) over two steps, as a colorless oil. ¹H NMR (400 MHz, CDCl₃); δ (ppm) = 7.37-7.24 (5H, m), 4.20 (1H, t, J = 5.8 Hz), 3.97 (1H, t, J = 5.5 Hz), 2.82 (2H, d, J = 6.6 Hz), 2.67 (2H, s), 1.67 (2H, t, J = 5.7 Hz), 1.59-1.43 (2H, m), 1.32 (10H, bs), 0.93 (3H, t, J = 6.2 Hz). ¹³C NMR (100 MHz, CDCl₃); δ (ppm) = 138.43, 129.40, 128.57, 126.50, 70.13, 69.22, 44.06, 41.91, 37.46, 31.83, 29.61, 29.28, 25.78, 22.67, 14.11. IR (cm⁻¹): f = 3434, 3325, 2925, 2854, 1496, 1454, 1130, 1081, 836, 746, 699, 606, 504. HRMS-ESI: (M+H)⁺ = 265.2162 calculated for C₁₇H₂₉O₂, experimental = 265.2162.

Preparation of 1,3-anti Diol 4.9d

(±)-(3S,5R)-tert-butyl 3-hydroxy-5-((4-methoxybenzyl)oxy)-6-phenylhexanoate 4.9d

Aldehyde 4.25 (1.46 g, 5.12 mmol) was dissolved in CH₂Cl₂ (40 mL) and cooled to -78°C. TiCl₂(OiPr)₂ was added dropwise and the reaction mixture was stirred for 20 minutes. A
solution of ketene acetal (1.54 g, 7.69 mmol) was then added slowly in 3 portions with 3 mL of CH₂Cl₂. The reaction was quenched with a solution of pH 7 phosphate buffer (30 mL) and Rochelle’s salt (25 mL). The mixture was allowed to stir to room temperature and extracted with CH₂Cl₂ (3 x 50 mL). The organic layers were then dried over Na₂SO₄ and concentrated under vacuum. The crude mixture was purified in 80:20 → 70:30 hexane:EtOAc to give 4.28 with a yield of 58% (1.22 g, 2.96 mmol) as a yellow oil. ¹H NMR (400 MHz, CDCl₃); δ (ppm) = 7.30-7.18 (8H, m), 6.87-6.83 (2H, m), 4.41 (2H, d, J = 2.2 Hz), 4.24 (1H, m), 3.95 (1H, ddd, J = 9.0, 6.2, 3.1 Hz), 3.79 (3H, s), 3.25 (1H, d, J = 3.8 Hz), 2.96 (1H, dd, J = 13.6, 6.2 Hz), 2.78 (1H, dd, J = 13.6, 6.5 Hz), 2.34-2.31 (2H, m), 1.62 (1H, m), 1.52 (1H, ddd, J = 14.4, 8.9, 3.0 Hz), 1.43 (9H, s). ¹³C NMR (100 MHz, CDCl₃); δ (ppm) = 172.05, 159.21, 138.55, 130.44, 129.62, 129.54, 128.40, 128.32, 126.20, 113.80, 81.02, 71.79, 65.11, 55.26, 42.84, 40.84, 40.59, 28.08. IR (cm⁻¹): f = 3491, 2976, 2934, 1724, 1514, 1248, 1150, 822, 701. HRMS-ESI: (M+Na)⁺ = 423.2142 calculated for C₂₄H₃₂NaO₅, experimental = 423.2125.

(±)-(3S,5R)-tert-butyl 3,5-dihydroxy-6-phenylhexanoate 4.9d

PMB alcohol 4.28 (300 mg, 0.75 mmol) was placed under vacuum and treated with Pd/C (80 mg, 0.075 mmol) then dissolved in MeOH (10 mL) while being bubbled with H₂ gas via balloon. Upon completion, the reaction mixture was filtered thru a celite cake and rinsed with EtOAc (3x10 mL). The crude mixture was purified in 80:20 → 65:35 hexanes:EtOAc to give tert-butyl ester diol 4.9d in 88% yield (185 mg, 0.66 mmol) as a clear oil. ¹H NMR (400 MHz, CDCl₃); δ (ppm) = 7.33-7.22 (5H, m), 4.34 (1H, ddd, J = 15.8, 7.9, 4.0 Hz), 4.17 (1H, dd, J = 14.2, 7.4 Hz), 3.65 (1H, d, J = 3.8 Hz), 2.80 (2H, d, J = 6.7 Hz), 2.74 (1H, bs), 2.48-2.36 (2H, m), 1.65 ( 2H, dddd, J = 32.3, 14.4, 8.3, 2.8 Hz), 1.47 (9H, s). ¹³C NMR (100 MHz, CDCl₃); δ
(ppm) = 172.24, 138.33, 129.32, 128.45, 126.36, 81.28, 69.52, 68.96, 65.61, 44.01, 42.23, 41.48, 28.03. IR (cm\(^{-1}\)): \(f = 3041, 2977, 2933, 1707, 1454, 1367, 1254, 1146, 1080, 954, 843, 747, 700\).

HRMS-ESI: \((M+Na)^+ = 303.1567\) calculated for \(C_{16}H_{24}NaO_4\), experimental = 303.1556.

5.4.4. Experimental Procedures for 1,3-syn Diol Monosilylethers

Preparation of 1,3-syn Diol Monosilylether 4.16a

\[
\begin{align*}
&\text{PMB} & \text{O} & \text{OH} & \text{PMB} & \text{O} & \text{OH} \\
&\text{Ph} & \text{4.26} & \text{DEAD, PPh}_3, \text{PNBA; K}_2\text{CO}_3, \text{MeOH} & \text{Ph} & \text{4.29} \\
1. & \text{Me}_3\text{PhSiCl, Et}_3\text{N, DMAP} & & & 2. \text{DDQ} & \text{Ph} & \text{OSiMe}_2\text{Ph} & \text{4.16a}
\end{align*}
\]

\((\pm)-(4S,6R)-6-((4\text{-methoxybenzyl})\text{oxy})-7\text{-phenylhept-1-en-4-ol 4.29}\)

Alcohol 4.26 (1.14 g, 3.49 mmol) was dissolved in toluene (125 mL). PPh\(_3\) (2.56 g, 9.77 mmol) and \(p\)-nitrobenzoic acid (1.63 g, 9.77 mmol) were added and the reaction was stirred for 5 minutes before the dropwise addition of diethylazodicarboxylate (1.53 mL, 9.77 mmol). The reaction mixture was stirred at room temperature overnight then concentrated in vacuo. The crude mixture was then dissolved in MeOH (100 mL) and K\(_2\)CO\(_3\) (2.70 g, 19.54 mmol) was added and stirred for two hours. The reaction was quenched with deionized water (100 mL) and extracted with CH\(_2\)Cl\(_2\) (3 x 50 mL). The organic layers were dried over Na\(_2\)SO\(_4\) and concentrated in vacuo. The crude mixture was purified in 80:20 \(\rightarrow\) 70:30 hexanes:EtOAc to give alcohol 4.29 in 67\% yield (767 mg, 2.35 mmol) as a colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)); \(\delta\) (ppm) = 7.35-7.20 (7H, m), 6.91-6.87 (2H, m), 4.29 (1H, m), 5.11-5.04 (2H, m), 4.58 (1H, d, \(J = 10.8\) Hz), 4.43 (1H, d, \(J = 10.8\) Hz), 3.88 (1H, ddt, \(J = 7.6, 7.5, 5.2\) Hz), 3.82 (3H, s), 3.78 (1H, dd, \(J = 12.2, 6.5\) Hz), 3.53 (1H, bs), 3.04 (1H, dd, \(J = 13.6, 5.1\) Hz), 2.79 (1H, dd, \(J = 13.6, 7.2\) Hz),
2.22-2.11 (2H, m), 1.64-1.61 (2H, m). $^{13}$C NMR (100 MHz, CDCl$_3$); $\delta$ (ppm) = 159.28, 138.02, 134.79, 129.68, 129.59, 129.44, 128.34, 126.27, 117.14, 113.87, 80.50, 70.90, 70.57, 55.17, 41.89, 40.55, 40.27. IR (cm$^{-1}$): $f$ = 3464, 3027, 2935, 2912, 2865, 1709, 1612, 1513, 1247, 1079, 1033, 821, 746, 701. HRMS-ESI: (M+Na)$^+$ =349.1774 calculated for C$_{21}$H$_{26}$NaO$_3$, experimental = 349.1768.

($\pm$)-(2R,4S)-4-((dimethyl(phenyl)silyl)oxy)-1-phenylhept-6-en-2-ol 4.16a

Allylic alcohol 4.29 (1.12 g, 3.43 mmol) was dissolved in CH$_2$Cl$_2$ (40 mL). Et$_3$N (0.86 mL, 6.17 mmol) was added along with DMAP (18 mg, 0.27 mmol) and stirred for five minutes. Me$_2$PhSiCl (0.7 mL, 4.12 mmol) was then added and the reaction was stirred overnight. The reaction was quenched with a half saturated NH$_4$Cl solution (40 mL) and extracted with CH$_2$Cl$_2$ (3 x 30 mL). The organic layers were collected and concentrated in vacuo. The crude mixture was then dissolved in a mixture of CH$_2$Cl$_2$:H$_2$O (30 mL:few drops) and DDQ (1.2 g, 5.15 mmol) was added. Upon completion, the reaction was diluted with CH$_2$Cl$_2$ (40 mL) and vacuum filtered. The mixture was then washed with a saturated NaHCO$_3$ solution (50 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude mixture was purified in 90:10 $\rightarrow$ 80:20 hexanes:EtOAc to give monoprotected alcohol 4.16a in 80% yield over two steps (936 mg, 2.75 mmol) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$); $\delta$ (ppm) = 7.60-7.56 (2H, m), 7.39-7.10 (8H, m), 5.66 (1H, ddt, $J$ = 17.2, 10.4, 6.8 Hz), 4.99-4.92 (2H, m), 4.05-3.89 (2H, m), 2.98 (1H, s), 2.75-2.62 (2H, m), 2.24-2.11 (2H, m), 1.65-1.53 (2H, m), 0.41 (6H, q, $J$ = 4.2 Hz). $^{13}$C NMR (100 MHz, CDCl$_3$); $\delta$ (ppm) = 138.45, 137.33, 133.98, 133.51, 129.82, 129.44, 128.36, 127.92, 126.25, 117.55, 72.63, 71.69, 44.09, 42.17, 42.07, -1.00, -1.14. IR (cm$^{-1}$): $f$ = 3443, 3069, 3026,
2941, 1428, 1251, 1116, 1065, 913, 823, 783, 738, 697. HRMS-ESI: (M+H)$^+$ = 341.1931 calculated for C$_{21}$H$_{29}$O$_2$Si, experimental = 341.1925.

Preparation of 1,3-syn Diol Monosilylether 4.16b

(±)-(2R,4S)-4-((dimethyl(phenyl)silyl)oxy)-1-phenylundecan-2-ol 4.16b

Alcohol 4.16a (145 mg, 0.43 mmol) along with 1-hexene (0.53 mL, 4.30 mmol) were added simultaneously to a round bottom flask containing Grubb’s 2$^{nd}$ generation catalyst (74 mg, 0.0086 mmol) dissolved in CH$_2$Cl$_2$ (6 mL). The reaction mixture was then heated to reflux overnight. Upon completion, the reaction was concentrated in vacuo to give crude intermediate 4.30, which was then placed under vacuum and treated with Pd/C (46 mg, 0.043 mmol) and dissolved in EtOAc (5 mL). The reaction was then bubbled with H$_2$ gas until completion. It was then filtered through celite via vacuum filtration, rinsed with EtOAc (3 x 10 mL) and concentrated in vacuo. The crude mixture was purified with 90:10 → 80:20 hexanes:EtOAc to give 4.16b in 66% yield over two steps (113 mg, 0.28 mmol) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$); $\delta$ (ppm) = 7.66 (2H, d, J = 6.2 Hz), 7.47-7.24 (8H, m), 4.05-3.94 (2H, m), 3.18 (1H, s), 2.82 (1H, dd, J = 13.6, 6.6 Hz), 2.75 (1H, dd, J = 13.7, 5.8 Hz), 1.71-1.61 (2H, m), 1.48 (2H, q, J = 7.0 Hz), 1.37-1.22 (10H, m), 0.95 (3H, t, J = 6.9 Hz), 0.50 (6H, d, J = 2.6 Hz). $^{13}$C NMR (100 MHz, CDCl$_3$); $\delta$ (ppm) = 138.50, 137.54, 133.45, 129.68, 129.41, 128.30, 127.83, 126.18, 72.32, 71.85, 44.13, 42.21, 37.60, 31.71, 29.55, 29.12, 24.61, 22.58, 14.05, -1.00, -1.20.
IR (cm$^{-1}$): $f = 3383, 3068, 3027, 2927, 2856, 1455, 1428, 1252, 1118, 1084, 829, 785, 742, 700.$

HRMS-ESI: (M+H)$^+$ = 399.2714 calculated for C$_{25}$H$_{39}$O$_2$Si, experimental = 399.2709.

**Preparation of 1,3-syn Diol Monosilylether 4.16d**

1-phenylpent-4-en-2-ol 4.31

Phenylacetaldehyde (5.6 mL, 49.92 mmol) was dissolved in THF (200 mL) and cooled to -78°C. Allyl magnesium bromide (55 mL, 54.91 mmol, 1M in diethyl ether) was added to the reaction mixture dropwise using an addition funnel. Upon completion, the reaction mixture was quenched with a half saturated NH$_4$Cl solution (100 mL), extracted with ethyl acetate (3 x 50 mL). The organic layers were combined and dried over Na$_2$SO$_4$, and concentrated under vacuum. The crude mixture was purified in 100% CH$_2$Cl$_2$ $\rightarrow$ 90:10 CH$_2$Cl$_2$:EtOAc to give allylic alcohol 4.31 in 62% yield (5.03 g, 31.03 mmol) as a clear oil. $^1$H NMR (400 MHz, CDCl$_3$); $\delta$ (ppm) = 7.37-7.24 (5H, m), 5.90 (1H, m), 5.20 (1H, m), 5.17 (1H t, $J = 1.2$ Hz), 3.92 (1H, dddd, $J = 12.6,$
7.9, 4.7, 3.1 Hz), 2.86 (1H, dd, J = 13.6, 4.9 Hz), 2.76 (1H, dd, J = 13.6, 8.0 Hz), 2.37 (1H, dddt, J = 14.0, 6.4, 4.9, 1.1 Hz), 2.26 (1H, m), 1.73 (1H, t, J = 3.1 Hz). $^{13}$C NMR (100 MHz, CDCl$_3$); δ (ppm) = 138.36, 134.66, 129.40, 128.52, 126.47, 118.13, 71.66, 43.28, 41.18. IR (cm$^{-1}$): $f$ = 3395, 3076, 3028, 2918, 1640, 1495, 1454, 1078, 1031, 997, 914, 744, 699. Compound 4.31 is known (CAS #61077-65-4).

(±)-(E)-methyl 5-hydroxy-6-phenylhex-2-enoate 4.32

Grubb’s 2$^{nd}$ generation catalyst (263 mg, 0.31 mmol) was dissolved in CH$_2$Cl$_2$ (60 mL). Allylic alcohol 4.31 (4.96 g, 30.60 mmol) and methyl acrylate (14.0 mL, 153.00 mmol) were added simultaneously to the reaction mixture and brought to reflux overnight. Upon completion, the reaction was cooled then concentrated under vacuum. The crude mixture was purified in 80:20 → 70:30 hexanes:EtOAc to give methyl ester alcohol 4.32 in 43% yield (2.90 g, 13.16 mmol) as a dark oil. $^1$H NMR (400 MHz, CDCl$_3$); δ (ppm) = 7.34-7.20 (5H, m), 7.03 (1H, dt, J = 15.7, 7.3 Hz), 5.93 (1H, dt, J = 15.6, 1.4 Hz), 3.98 (1H, tq, J = 8.0, 4.1 Hz), 3.73 (3H, s), 2.84 (1H, dd, J = 13.6, 4.7 Hz), 2.72 (1H, dd, J = 13.6, 8.2 Hz), 2.50-2.35 (2H, m), 1.74 (1H, d, J = 2.4 Hz). $^{13}$C NMR (100 MHz, CDCl$_3$); δ (ppm) = 166.70, 145.25, 137.69, 129.36, 128.67, 126.72, 123.52, 71.29, 51.48, 43.59, 39.33. IR (cm$^{-1}$): $f$ = 3436, 3027, 2949, 2848, 1704, 1656, 1436, 1321, 1271, 1212, 1160, 1033, 746, 699. HRMS-ESI: (M+H)$^+$ = 221.1172 calculated for C$_{13}$H$_{17}$O$_3$, experimental = 221.1178.

(±)-methyl 2-((2S,4R,6R)-6-benzyl-2-phenyl-1,3-dioxane-4-yl)acetate 4.33

Methyl ester alcohol 4.32 (1.7 g, 7.72 mmol) was dissolved in THF (40 mL) and cooled to 0°C. Freshly distilled benzaldehyde (0.9 mL, 8.50 mmol) followed by t-BuOK (86 mg, 0.77
mmol) was added to the reaction mixture and the resulting yellow solution was stirred for 15 minutes at 0°C. This sequence of addition and stirring was repeated three times and the reaction mixture was quenched with a solution of pH 7 phosphate buffer (40 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The crude mixture was purified in 80:20 hexanes:EtOAc to afford methyl ester benzylidene acetal 4.33 in 67% yield (1.68 g, 5.15 mmol) as a clear oil. ¹H NMR (400 MHz, CDCl₃); δ (ppm) = 7.51-7.49 (2H, m), 7.36-7.20 (8H, m), 5.53 (1H, s), 4.24 (1H, m), 4.02 (1H, dtd, J = 11.0, 6.4, 2.3 Hz), 3.63 (3H, s), 3.05 (1H, dd, J = 13.7, 6.6 Hz), 2.77 (1H, dd, J = 13.7, 6.4 Hz), 2.69 (1H, dd, J = 15.7, 7.3 Hz), 2.45 (1H, dd, J = 15.7, 5.7 Hz), 1.62 (1H, dt, J = 13.0, 2.5 Hz), 1.45 (1H, dt, J = 13.1, 11.2 Hz). ¹³C NMR (100 MHz, CDCl₃); δ (ppm) = 170.68, 138.20, 137.28, 129.25, 128.30, 128.04, 127.81, 126.15, 125.80, 100.17, 77.02, 72.82, 51.33, 42.04, 40.36, 35.60. IR (cm⁻¹): f = 3063, 3030, 2950, 2915, 2850, 1735, 1437, 1403, 1346, 1200, 1109, 1056, 1043, 1009, 751, 698. HRMS-ESI: (M+H)⁺ = 327.1591 calculated for C₂₀H₂₃O₄, experimental = 327.1585.

(±)-tert-butyl 2-((2S,4R,6R)-6-benzyl-2-phenyl-1,3-dioxan-4-yl)acetate 4.34

Methyl ester benzylidene acetal 4.33 (1.5 g, 4.60 mmol) was dissolved in a 1:1 mixture THF:H₂O (20 mL) and LiOH (965 mg, 23.00 mmol) was subsequently added and stirred. Upon completion the reaction mixture was quenched with 1M HCl (20 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated under vacuum to give the carboxylic acid.

The crude carboxylic acid was then dissolved in tert-butanol (20 mL). Di-tert-butyl dicarbonate (2.0 g, 9.20 mmol) and DMAP (169 mg, 1.38 mmol) were then added to the reaction
mixture. Through TLC monitoring, the completed reaction was concentrated under vacuum and the crude reaction mixture was purified in 95:5 → 90:10 hexanes:EtOAc to give the tert-butyl ester benzylidene acetal 4.34 in 69% yield (1.17 g, 3.17 mmol) as a clear oil over two steps. $^1$H NMR (400 MHz, CDCl$_3$); δ (ppm) = 7.49-7.47 (2H, m), 7.36-7.19 (8H, m), 5.54 (1H, s), 4.20 (1H, dddd, $J$ = 11.3, 7.4, 6.0, 2.5 Hz), 4.04 (1H, ddd, $J$ = 11.1, 6.5, 2.4 Hz), 3.07 (1H, dd, $J$ = 13.7, 6.5 Hz), 2.78 (1H, dd, $J$ = 13.7, 6.5 Hz), 2.60 (1H, dd, $J$ = 15.2, 7.2 Hz), 2.39 (1H, dd, $J$ = 15.2, 6.0 Hz), 1.64 (1H, dt, $J$ = 13.0, 2.3 Hz), 1.42 (9H, s). $^{13}$C NMR (100 MHz, CDCl$_3$); δ (ppm) = 169.89, 138.42, 137.53, 129.44, 128.43, 128.21, 127.99, 126.32, 125.91, 100.30, 80.63, 77.34, 73.49, 42.27, 42.12, 35.83, 27.98. IR (cm$^{-1}$): $f$ = 3064, 3031, 2977, 2927, 2868, 1727, 1454, 1367, 1345, 1145, 1110, 1018, 750, 698. HRMS-ESI: (M+H)$^+$ = 369.2060 calculated for C$_{23}$H$_{29}$O$_4$, experimental = 369.2062.

(±)-(3R,5R)-tert-butyl 3,5-dihydroxy-6-phenylhexanoate 4.35

_Tert_-butyl ester benzylidene acetal 4.34 (180 mg, 0.49 mmol) was dissolved in a 1:1 mixture of AcOH:H$_2$O (5 mL) and heated to 40°C on a sand bath for 48 hours. Upon completion, the reaction was cooled and concentrated under vacuum and purified in 90:10 → 80:20 hexanes:EtOAc to afford tert-butyl ester diol 4.35 in 61% yield (84 mg, 0.30 mmol) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$); δ (ppm) = 7.30-7.18 (5H, m), 4.17 (1H, tt, $J$ = 8.2, 4.4 Hz), 4.08 (1H, m), 2.82 (1H, dd, $J$ = 13.5, 6.8 Hz), 2.70 (1H, dd, $J$ = 13.5, 6.3 Hz), 2.41-2.30 (2H, m) 1.61-1.53 (2H, m), 1.42 (9H, s). $^{13}$C NMR (100 MHz, CDCl$_3$); δ (ppm) = 171.67, 138.06, 129.30, 128.29, 126.22, 81.12, 72.91, 68.82, 44.05, 42.63, 41.17, 27.91. IR (cm$^{-1}$): $f$ = 3403, 3028, 2878, 2934, 1720, 1367, 1257, 1146, 1087, 843, 733, 700. HRMS-ESI: (M+Na)$^+$ = 303.1567 calculated for C$_{16}$H$_{24}$NaO$_4$, experimental = 303.1575.
(±)-(3R,5R)-tert-butyl 5-hydroxy-3-((4-methoxybenzyl)oxy)-6-phenylhexanoate 4.36

Tert-butyl ester diol 4.35 (118 mg, 0.42 mmol) was dissolved in CH₂Cl₂ (2.5 mL) and cooled to 0°C. PMB acetimidate (95 μL, 0.46 mmol) and PTSA (10 mg, 0.053 mmol) were added to the reaction mixture and stirred to completion. The reaction was quenched with H₂O (5 mL) and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The crude mixture was purified 90:10 → 86:14 → 82:18 hexanes:diethyl ether to give monobenzyl ether protected tert-butyl ester diol 4.36 in 45% yield (75 mg, 0.19 mmol) as a colorless oil. ¹H NMR (400 MHz, CDCl₃); δ (ppm) = 7.34-7.21 (7H, m), 6.90-6.87 (2H, m), 4.55 (1H, d, J = 11.0 Hz), 4.44 (1H, d, J = 11.0 Hz), 4.13 (1H, m), 3.88 (1H, m), 3.82 (3H, s), 3.72 (1H, d, J = 2.2 Hz), 3.02 (1H, dd, J = 13.6, 5.6 Hz), 2.81 (1H, dd, J = 13.6, 6.8 Hz), 2.35 (1H, dd, J = 15.7, 7.6 Hz), 2.27 (1H, dd, J = 15.7, 5.1 Hz), 1.77-1.58 (2H, m), 1.42 (9H, s). ¹³C NMR (100 MHz, CDCl₃); δ (ppm) = 171.46, 159.27, 138.14, 129.92, 129.56, 129.49, 128.39, 126.30, 113.87, 80.82, 79.40, 70.86, 67.43, 55.24, 42.83, 40.46, 40.26, 28.02. IR (cm⁻¹): ν = 3467, 3029, 2978, 2934, 1721, 1612, 1513, 1367, 1247, 1079, 1032, 909, 729, 700. HRMS-ESI: (M+Na)⁺ = 423.2142 calculated for C₂₄H₃₂NaO₅, experimental = 423.2153.

(±)-(3R,5R)-tert-butyl-5-((dimethyl(phenyl)silyl)oxy)-3-((4-methoxybenzyl)oxy)-6-phenylhexanoate 4.37

Monobenzyl ether protected tert-butyl ester diol 4.36 (162 mg, 0.40 mmol) was dissolved in CH₂Cl₂ (4 mL). Et₃N (0.1 mL, 0.72 mmol) and DMAP (2 mg, 0.032 mmol) were added, followed by addition of dimethylphenylsilyl chloride (0.1 mL, 0.60 mmol). Upon completion, the reaction was quenched with a half saturated NH₄Cl solution (5 mL), and extracted with CH₂Cl₂ (3 x 10 mL). The organic layers were combined and washed with a saturated NaHCO₃
solution, dried over Na$_2$SO$_4$, and concentrated under vacuum to afford diprotected tert-butyl ester diol 4.37 in 83% yield (178 mg, 0.33 mmol) as a colorless oil. HRMS-ESI: (M+H)$^+$ = 535.2874 calculated for C$_{32}$H$_{43}$O$_5$Si, experimental = 535.2895.

($\pm$)-(3R,5R)-tert-butyl-5-((dimethyl(phenyl)silyl)oxy)-3-hydroxy-6-phenylhexanoate 4.16d

Diprotected tert-butyl diol 4.37 (40 mg, 0.070 mmol) was dissolved in a mixture of CH$_2$Cl$_2$ (2 mL) and a few droplets of H$_2$O. To this solution was added DDQ (25 mg, 0.11 mmol) and the reaction was stirred vigorously. Upon completion, the reaction was quenched with a saturated NaHCO$_3$ solution (5 mL) and extracted with CH$_2$Cl$_2$ (3 x 5 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated under vacuum. The crude mixture was purified in 100% CH$_2$Cl$_2$ to afford the monosilylated tert-butyl ester diol 4.16d in 66% yield (19 mg, 0.046 mmol) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$); $\delta$ (ppm) = 7.60-7.57 (10H, m), 4.29 (1H, p, $J$ = 6.4 Hz), 3.94 (1H, dt, $J$ = 11.2, 7.1 Hz), 2.78 (1H, s), 2.73 (1H, dd, $J$ = 13.0, 6.6 Hz), 2.66 (1H, dd, $J$ = 13.5, 5.9 Hz), 2.42 (1H, dd, $J$ = 14.9, 5.4 Hz), 2.35 (1H, dd, $J$ = 15.1, 7.0 Hz), 1.68-1.64 (2H, m), 1.36 (9H, s), 0.43 (6H, d, $J$ = 3.1 Hz). $^{13}$C NMR (100 MHz, CDCl$_3$); $\delta$ (ppm) = 170.40, 138.28, 137.37, 133.46, 129.81, 129.41, 128.40, 127.92, 126.31, 80.66, 71.03, 69.51, 44.04, 44.00, 42.87, 28.00, -1.21, -1.31. IR (cm$^{-1}$): $f$ = 3437, 3069, 3027, 2932, 1724, 1368, 1152, 905, 730, 702. HRMS-ESI: (M+Na)$^+$ = 437.2119 calculated for C$_{24}$H$_{34}$NaO$_4$Si, experimental = 437.2129.
5.4.5. Experimental Procedures for 1,3,5-syn Triol

Preparation of 1,3,5-syn Triol 4.21

\[
\text{Ph} \quad \text{4.33} \quad \overset{\text{Pd(OH)}_2}{\xrightarrow{\text{MeOH}}} \quad \text{Ph} \quad \text{4.38} \quad \overset{\text{K}_2\text{CO}_3, \text{MeOH}}{} \quad \text{4.21}
\]

\((\pm)-\text{methyl (3R,5R)-3,5-dihydroxy-6-phenylhexanoate 4.38}\)

Methyl ester 4.33 (2.20 g, 6.75 mmol) was dissolved in MeOH (60 mL) and then Pd(OH)$_2$ (1.90 g, 13.49 mmol) was added. The reaction was then purged and bubbled with H$_2$ gas via balloon and stirred to completion. The mixture was then filtered through celite via vacuum filtration, rinsed with EtOAc (3 x 20 mL) and concentrated in vacuo. The crude mixture was purified in 60:40 → 50:50 hexanes:EtOAc to give 1,3-syn diol 4.38 in 58% yield (0.93 g, 3.92 mmol) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$); δ (ppm) = 7.30-7.18 (5H, m), 4.21 (1H, bs), 4.16 (1H, d, $J = 2.7$ Hz), 4.05 (1H, m), 3.71 (1H, d, $J = 2.7$ Hz), 3.65 (3H, s), 2.78 (1H, dd, $J = 13.6, 7.0$ Hz), 2.71 (1H, dd, $J = 13.5, 6.0$ Hz), 2.49-2.37 (2H, m), 1.63-1.53 (2H, m). $^{13}$C NMR (100 MHz, CDCl$_3$); δ (ppm) = 172.34, 137.85, 129.19, 128.17, 126.13, 72.60, 68.34, 51.45, 43.98, 41.46, 41.23. IR (cm$^{-1}$): $f = 3428, 3060, 3028, 2951, 2917, 1729, 1438, 1266, 1198, 1081, 910, 731, 700$. HRMS-ESI: (M+H)$^+ = 239.1278$ calculated for C$_{13}$H$_{19}$O$_4$, experimental 239.1279.
(±)-(4R,6R)-6-Benzyl-4-hydroxytetrahydro-2H-pyran-2-one 4.39

Diol 4.38 (877 mg, 3.68 mmol) was dissolved in MeOH: H2O (10:1, 33 mL) and K2CO3 (1.00 g, 7.37 mmol) was added and stirred at room temperature. Upon consumption of starting material, the reaction was quenched with a 1M HCl solution (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na2SO4 and concentrated in vacuo. The crude mixture was purified in 50:50 → 40:60 hexanes:EtOAc to give 4.39 in 75% yield (567 mg, 2.75 mmol) as a colorless oil. 1H NMR (400 MHz, CDCl3); δ (ppm) = 7.30-7.19 (5H, m), 4.91 (1H, dtd, J = 11.5, 6.3, 2.9 Hz), 4.17 (1H, p, J = 3.8 Hz), 3.71 (1H, bs), 2.99 (1H, dd, J = 14.0, 6.3 Hz), 2.88 (1H, dd, J = 14.0, 6.3 Hz), 2.51 (2H, d, J = 4.1 Hz), 1.87 (1H, dt, J = 14.5, 3.5 Hz), 1.59 (1H, ddd, J = 14.5, 11.5, 3.0 Hz). 13C NMR (100 MHz, CDCl3); δ (ppm) = 171.29, 135.99, 129.31, 128.22, 126.53, 76.39, 61.72, 41.26, 38.08, 34.46. IR (cm⁻¹): f = 3420, 3029, 2923, 1705, 1496, 1389, 1252, 1066, 1041, 755, 702. HRMS-ESI: (M+H)⁺ = 207.1016 calculated for C12H15O3, experimental = 207.1014.

(±)-(4R,6R)-6-benzyl-4-(((dimethyl(phenyl)silyl)oxy)tetrahydro-2H-pyran-2-one 4.40

Alcohol 4.39 (390 mg, 1.89 mmol) was dissolved in CH2Cl2 (8 mL). Et3N (0.50 mL, 3.40 mmol) and DMAP (10 mg, 0.08 mmol) were added and stirred for 5 minutes. Me2PhSiCl (0.50 mL, 2.84 mmol) was then added and stirred at room temperature. Upon completion, the reaction was quenched with a half saturated NH4Cl solution (15 mL) and extracted with CH2Cl2 (3 x 15 mL). The combined organic layers were washed with NaHCO3, dried over Na2SO4 and concentrated in vacuo. The crude mixture was purified in 80:20 → 70:30 hexanes:EtOAc to give 4.40 in 83% yield (537 mg, 1.58 mmol) as a colorless oil. 1H NMR (400 MHz, CDCl3); δ (ppm) = 7.52-7.21 (10H, m), 4.97 (1H, dtd, J = 11.3, 6.3, 3.0 Hz) 4.24 (1H, p, J = 3.8 Hz), 3.06 (1H,
dd, $J = 13.9, 5.9$ Hz), 2.91 (1H, dd, $J = 13.9, 6.6$ Hz), 2.57 (1H, dq, $J = 17.5, 1.6$ Hz), 2.51 (1H, dd, $J = 17.5, 4.4$ Hz), 1.78 (1H, m), 1.58 (1H, ddd, $J = 14.2, 11.3, 2.9$ Hz), 0.37 (6H, d, $J = 10.4$ Hz). $^{13}$C NMR (100 MHz, CDCl$_3$);δ (ppm) = 170.16, 136.89, 136.23, 133.27, 129.92, 129.55, 128.46, 127.99, 126.75, 76.24, 63.48, 41.52, 39.02, 35.24, -1.47, -1.65. IR (cm$^{-1}$): $f = 3395, 3067, 3028, 2956, 2923, 1706, 1496, 1427, 1389, 1252, 1118, 1064, 1040, 830, 790, 699$. HRMS-ESI: (M+H)$^+$ = 341.1567 calculated for C$_{20}$H$_{25}$O$_3$Si, experimental = 341.1569.

($\pm$)-(3S,5R)-3-(((dimethyl(phenyl)silyl)oxy)-6-phenylhexane-1,5-diol 4.21

Lactone 4.40 (200 mg, 0.59 mmol) was dissolved in THF (5 mL) and cooled to -78°C. LiBH$_4$ (26 mg, 1.18 mmol) was then added and the reaction was stirred to completion. The reaction was quenched with deionized H$_2$O (10 mL) and extracted with ether (3 x 20 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude mixture was purified in 70:30 $\rightarrow$ 60:40 $\rightarrow$ 50:50 hexanes:EtOAc to give 4.21 in 34% yield (70 mg, 0.20 mmol) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$); δ (ppm) = 7.63-7.17 (10H, m), 4.16 (1H, p, $J = 6.4$ Hz), 3.92 (1H, p, $J = 6.7$ Hz), 3.71-3.60 (2H, m), 2.71 (2H, d, $J = 6.4$ Hz), 1.79 (1H, dt, $J = 13.3, 7.3$ Hz), 1.71-1.65 (4H, m), 1.28 (1H, m). $^{13}$C NMR (100 MHz, CDCl$_3$);δ (ppm) = 138.12, 137.31, 133.49, 129.90, 129.40, 128.48, 127.97, 126.44, 70.62, 70.44, 59.63, 44.38, 42.97, 38.76, -1.26, -1.36. IR (cm$^{-1}$): $f = 3372, 3337, 3026, 2923, 2852, 1454, 1081, 700$. HRMS-ESI: (M+H)$^+$ = 345.1886 calculated for C$_{20}$H$_{29}$O$_3$Si, experimental = 345.1871.
APPENDIX A: COPYRIGHT RELEASES

Title: Chlorination of Aliphatic Primary Alcohols via Triphosgene-Triethylamine Activation

Author: Caitlan E. Ayala, Andres Villalpando, Alex L. Nguyen, et al.

Publication: Organic Letters

Publisher: American Chemical Society

Date: Jul 1, 2012

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Triphosgene–pyridine mediated stereoselective chlorination of acyclic aliphatic 1,3-diols


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APPENDIX B: $^1$H AND $^{13}$C NMR DATA
Ph
\[\text{OH}\]
3.6f
VITA

Andres “Andy” Villalpando was born in Santa Cruz, California to Francisco Villalpando and Martha Villalpando in 1989. He attended primary school in Poway, California and graduated from Poway High School in 2007. The following summer, he enrolled at Whittier College where he received a Bachelor of Arts degree in Chemistry with a minor in Spanish in May 2011. With a growing interest in Organic Chemistry, he enrolled in the graduate school at Louisiana State University in August 2011 to pursue his doctorate degree in the Department of Chemistry. He joined the research group of Dr. Rendy Kartika in January 2012 and is currently a candidate for the degree of Doctor of Philosophy in Chemistry, to be awarded May 2016.