EFFORTS TOWARDS THE TOTAL SYNTHESIS OF 20-DEOXYAPOPTOLIDINONE
AND “CHIMERIC” ANALOGUES

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by

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_________________________________________________________________________

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Abstract

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Isolated in 1997 from the bacteria, Nocardiopsis sp., apoptolidin was discovered to be remarkably selective in killing cells transformed by the adenovirus E1A oncogene while leaving normal cells unharmed. Apoptolidin’s particularly interesting mode of action has been proposed to involve inhibition of the F1F0-ATP synthase found in the inner-membrane of the mitochondria. Polyketide derived, apoptolidin, consists of a 20-membered macrolide, highly-substituted pyran, and carbohydrate appendages. Because of this structural complexity and cytotoxicity, apoptolidin has garner considerable interest in the scientific community resulting in several total syntheses, SAR work, and further isolations of compounds in the apoptolidin family.
While working towards the total synthesis of apoptolidinone (apoptolidin’s aglycone core), several research groups discovered at physiological pH and temperature, apoptolidin isomerizes to the 21-membered macrolide, isoapoptolidin. Isoapoptolidin was found to be considerably less active than apoptolidin calling into question previous assay data. Attempts were made to block this acyl-migration, but led to a loss in activity.

Our efforts have been focused on synthesizing the 20-deoxy analogue of apoptolidinone eliminating the acyl-migration without adversely affecting the structural conformation of 20-deoxyapoptolidinone. Because of its complexity, 20-deoxyapoptolidinone was partitioned into three smaller fragments.

Fragment A was rapidly synthesized through repetitive thionyl chloride rearrangements demonstrating its utility as an alternative to the classic Wittig and Horner-Wadsworth-Emmons protocol widely used. Fragment B in its various forms was synthesized from commercially available (L)-malic acid utilizing the purchased stereochemistry to influence the addition of several new stereocenters. Fragment C consisting of several propionate units was constructed via repetitive oxazolidinonethione based aldol condensations achieving the fragment in an efficient and timely manner. Once constructed the three fragments are coupled together through a Mukaiyama aldol, Stille coupling and Yamaguchi macrolactonization yielding the desired 20-deoxyapoptolidinone.

Upon completion, the synthesis of 20-deoxyapoptolidinone will provide the framework for future “chimeric” analogues. These “chimeric” analogues will consist of 20-deoxyapoptolidin’s macrolide with the pyran portions of concanamycin and bafilomycin in an effort to achieve cross affinity for F_0F_1- and V-type ATPase.
To my family and friends for all of your love and support
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disappear for at least a moment. Klara, Helen, Nora, and baby you keep me grounded and for that I am truly blessed. To my parents on both sides of the family, your love and support have helped Sara and I get through this endeavor and for that we will always be truly thankful and blessed.

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ABBREVIATIONS

Å ......................................................................................................................... angstrom
α ................................................................. .................................................. alpha
Ac .................................................................................................................. acetate
AcOH ........................................................................................................ acetic acid
ACP ........................................................................................................... acyl carrier protein
AD-Mix ................................................ as asymmetric dihydroxylation catalyst mixture
AT ................................................................................................................. acyl transferase
(b) ............................................................................................................. broad peak in spectra
β .............................................................................................................. beta
Bu ........................................................................................................ butyl
Bz .............................................................................................................. benzoyl
CSA ....................................................................................................... camphor sulfonic acid
d ............................................................................................................. doublet
δ ............................................................................................................... delta
DCM ......................................................................................................... dichloromethane
dd ............................................................................................................ doublet of doublets
dt ............................................................................................................. doublet of triplets
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
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<tbody>
<tr>
<td>DH</td>
<td>dehydratase</td>
</tr>
<tr>
<td>Dibal-H</td>
<td>diisobutyl aluminum hydride</td>
</tr>
<tr>
<td>DIPEA</td>
<td>diisopropyl ethyl amine</td>
</tr>
<tr>
<td>DMAP</td>
<td>dimethylamino pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethyl formamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>E. coli</td>
<td>Escherichia coli</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>ER</td>
<td>enoyl reductase</td>
</tr>
<tr>
<td>FT</td>
<td>Fourier transform</td>
</tr>
<tr>
<td>H/H+</td>
<td>hydrogen/proton</td>
</tr>
<tr>
<td>HPLC</td>
<td>high-pressure liquid chromatography</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
</tr>
<tr>
<td>KR</td>
<td>ketoreductase</td>
</tr>
<tr>
<td>KS</td>
<td>ketosynthase</td>
</tr>
<tr>
<td>L</td>
<td>liter</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>Ln</td>
<td>ligand</td>
</tr>
<tr>
<td>M</td>
<td>module, molar or mass</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
</tbody>
</table>
TBAF .......................................................... tetrabutyl ammonium fluoride
TBDPS ................................................................ tertbutyldiphenylsilyl
TBS .................................................................................. tertbutyldimethylsilyl
TEA ........................................................................................................ triethylamine
Tf ....................................................................................................... trifluormethanesulfonate (triflate)
TFA .................................................................................................... trifluoroacetic acid
THF ........................................................................................... tetrahydrofuran
TLC .......................................................................................... thin layer chromatography
TMS ................................................................................................ trimethylsilyl
UV .............................................................................................. ultraviolet
v ...................................................................................................... wavenumber
Xc .................................................................................................. chiral auxiliary
Z ............................................................................................. (German) opposite, cis
CHAPTER ONE

THE STILLE REACTION AND ITS CONTRIBUTION TO POLYKETIDE NATURAL PRODUCT SYNTHESIS

1.1 Introduction

Polyketide derived natural products provide a vital class of new and exciting therapeutic agents. It is no surprise they have garnered much interest in the synthetic community with their structurally complex nature, novel therapeutic uses and semi-synthetic production through biological organisms such as *E. coli*. But before one can get excited, these natural products must be isolated, characterized and screened for activity. Characterization and activity screens can be further hampered by low natural availability. Chemical synthesis can bridge this gap between isolation and testing by artificially increasing its availability for the necessary screening and structural analysis.

From a synthetic analysis, polyketide natural products such as apoptolidin¹ 1.1 are primarily composed of acetate and propionate units yielding oxygen substitution at odd numbered and hydrogen or alkyl-substitution on even number carbons, Figure 1.1. This repetitive pattern can lead to highly complex structures possessing 1,3-poly-hydroxyl substitution found in the southern half of apoptolidin and poly-olefinic regions similar to the diene and triene portions of apoptolidin’s macrolactone. By understanding the
capabilities and limitations of the polyketide synthase, an enzyme that produces these natural products, one can quickly assemble the necessary organic reactions needed for successful completion of a total synthesis.

![Apoptolidin (1.1)](image)

**Figure 1.1**

The polyketide synthase (PKS) is comprised of modules that are further divided into domains. Each domain performs a particular reaction onto the substrate as it is carried through the enzyme. The PKS modules are comprised of multiple combinations of mostly four domains that perform the necessary reactions for synthesis of the natural product and a fifth domain, the acyltransferase (AT) domain which performs the module to module transfer. The chain is first elongated with the ketosynthase domain choosing between acetyl CoA and methylmalonyl CoA in order to add the proper acetate or propionate unit. The newly formed diketone can be selectively reduced with ketoreductase (KR) yielding alcohol 1.5. The secondary alcohol can be further eliminated with dehydratase (DH) resulting in $\alpha,\beta$ unsaturated thioester 1.6. The unsaturation can be further reduced to saturated 1.7 using an enoylreductase (ER)
domain, Scheme 1.1.\(^3\) In cases where biological means, such as the PKS enzyme, are not viable candidates for yielding sufficient quantities of the natural product for further study, total synthesis can provide a powerful alternative strategy to the desired natural product.

Scheme 1.1

Stereo-controlled aldol and Wittig olefination reactions offer an available knowledge base from which to start constructing such daunting molecules. The poly-olefinic regions can be constructed in a repetitive fashion with reactions such as the Wittig\(^{4a}\), Horner-Wadsworth Emmons\(^{4b,c}\), and thionyl chloride\(^{4d}\) rearrangement. Though serviceable, these reactions, when used in a linear sequence, would require many steps to complete the triene of apoptolidin 1.1, thus consuming large amounts of starting materials and time. Coupling reactions such as the Suzuki\(^5\) and Stille\(^6\) can bring together two \(sp^2\)-hybridized carbons yielding a more convergent approach thus limiting the linearity of one’s synthetic strategy towards concentrated poly-olefinic regions in polyketides.

It is the intention of this introduction to briefly highlight several of the recent developments in the Stille reaction from new mechanistic insights to how these insights
have aided organic chemists in the construction of complex natural products. The introduction will conclude with examples on how the Stille reaction has been utilized in the syntheses of a class of polyketides known as ATPase enzyme inhibitors of which apoptolidin belongs.

1.2 Stille Reaction: History

Brought to the foreground in a 1986 review, the Stille reaction has grown to be one of the most widely used coupling reactions. Similar to other well known cross-coupling reactions like the Suzuki, Hiyama, Sonogashira, Kumada, and Negishi reactions, the Stille reaction has separated itself in its ability to tolerate a wide range of functionality while still providing high selectivity. Historically, the Stille reaction can retrace its roots to attempts to replace tributyltin hydride as a dehalogenation reagent for organic halides.

Kosugi and coworkers were pursuing alternatives to tributyltin hydride because of the high cost associated with only utilization of the hydride in such a large molecule. An effort was put forth to examine larger groups that could be transferred from the tin to the halogenated carbon. In 1973 Kosugi published a free radical allylation of an organohalide yielding one of the first reports of a successful carbon-carbon bond formation via an organotin compound. The reaction had its limitations as it would yield no reaction with acid chlorides and aryl iodide unlike tributyltin hydride. Concurrently, Eaborn published the first use of palladium as a catalyst for the coupling of organohalides and organotins. Quite remarkably, the reaction is still used extensively today as a convenient way to convert organohalides to organostannanes, Scheme 1.2.
\[
\text{ArX} + \text{Bu}_2\text{SnSnBu}_3 \xrightarrow{\text{Pd(PPh}_3)_4} \text{ArSnBu}_3 + \text{Bu}_3\text{SnX}
\]

\(\text{Ar} = \text{NO}_2\text{C}_6\text{H}_4^-, \text{NCC}_4\text{H}_4^-, \text{MeCOC}_6\text{H}_4^-\)

**Scheme 1.2**

In 1978, John K. Stille entered the picture with methodology to convert acid chlorides into unsymmetrical ketones via a palladium catalyst and alkyltin.\(^{14}\) The reaction was a distinct improvement over the use of alkylrhodium complexes for the alkylation of acid chlorides for a number of reasons including: air stability, quantitative yields, and tolerant of a wide variety of substrates.

The Stille reaction was quickly propelled to its lofty status by Farina’s early work on tri(2-furyl)phosphine and triphenylarsine \((\text{AsPh}_3)\).\(^ {15}\) Development of these ligands opened new applications towards the total synthesis of large natural products that because of their complex nature require catalysts capable of reacting under mild conditions. A more in depth look at the rate enhancement of these ligands will be discussed in the following sections on the catalytic cycle of the Stille reaction.

More recently, the scope of the Stille reaction has been broadened by the development of a palladium-free coupling utilizing the copper(I) thiophene carboxylate \((\text{CuTC})\) catalyst developed by Liebskind.\(^ {16}\) Liebskind found the CuTC catalyst to be remarkably reactive even at temperatures below \(0^\circ\text{C}\). Unfortunately, this reactivity is only achieved at very high loadings of stoichimetric or greater. Nevertheless, the CuTC provides a complimentary method to current palladium catalyzed reactions. Examples of
this methodology will be further explored in the following sections through Paterson’s total synthesis of concanamycin\textsuperscript{17} and Elaiophylin\textsuperscript{18}.

In Stille’s 1986 review\textsuperscript{6}, a catalytic cycle was presented entailing an oxidative addition of Pd(0) into a carbon-halogen bond forming trans-product \textit{1.9} followed by transmetallation with the organostannane.\textsuperscript{19} Complex \textit{1.10} isomerizes from the trans to cis-confirmation \textit{1.11} before reductive elimination yields the coupled product and reconstitutes Pd(0), Scheme 1.3. Stille believed the transmetallation step went through a $S_{\text{E2}}$ mechanism \textit{1.8} with electrophilic cleavage of the Sn-C bond and the Pd(II) complex acting as the electrophile. It was not until more recently with the advantageous improvements to NMR and X-Ray spectroscopy have researchers turned their attention back the mechanistic intricacies of the Stille reaction.
The basic fundamental steps, oxidative addition, transmetallation, and reductive elimination are still widely believed to be solid, but a complete picture on how palladium looks at each step in the cycle is still being investigated.\textsuperscript{19} The following will look at each step in the catalytic cycle in more detail with particular emphasis on the mechanistic aspects of the cross coupling of akenyl stannanes and organohalogens, since they pertain to the purpose of this introduction and preceding experimental work.

### 1.2.1 Mechanism: Oxidative Addition

Though not believed to be the rate limiting step, oxidative addition of Pd(0) into the organoelectrophile has proven to be much more complicated than previously interpreted. Because of early spectroscopy and successful isolation of the oxidative addition product, it was widely believed the oxidative addition produced a trans-coordination sphere around palladium.\textsuperscript{6} Most recently, experimentation has proven the trans-product to be thermodynamic in nature after successful isomerization from the kinetically produced cis-complex.\textsuperscript{19} In addition new models have focused on the importance of solvent effects within the coordination sphere of the metal.\textsuperscript{20}

For the most common electrophiles C(sp\textsuperscript{2})-X, the proposed mechanism for oxidative addition is via a concerted 3-centered transition state \textbf{1.12} yielding cis isomer \textbf{1.13}.\textsuperscript{19} In the case of iodouracil and Pd(PPh\textsubscript{3})\textsubscript{4} at room temperature, the kinetic cis-product \textbf{1.14} can be isolated then isomerized to the thermodynamic product \textbf{1.15} upon raising the temperature to 38°C, Scheme 1.4.\textsuperscript{21}
Espinet proposed four concurrent bimolecular pathways could be possible to yield the trans-isomer in his 1998 published work.\textsuperscript{22} They believed two of the pathways are catalyzed by solvent and the other two autocatalyzed by iodide attached to an adjacent palladium complex, Scheme 1.5. Interestingly, the addition of excess ligand (PPh\textsubscript{3}) did not affect the rates of \( k_1 \) and \( k_2 \) but did directly affect the rates of \( k_3 \) and \( k_4 \).
Each of the four pathways is considered to produce differing amounts of the isomerized trans-product **1.16**. When the concentration of the cis-isomer is $10^2$ mol/L with no added PPh$_3$ and the temperature is 322.6 K, the $k_3$ pathway accounts for 67% of the observed isomerization rate while $k_4$ accounts for 21%. Isomerization via Berry pseudo rotations accounts for the remaining isomerized product $k_1(12\%)$ and $k_2(2\%)$. The proposed mechanism of isomerization is further supported with the addition of NaI to the reaction mixture forming the trans-isomer in rapid fashion further supporting an associative mechanism.
The complexity of the Stille reaction has become very apparent over the last decade. Jutand and Amatore have shown the active palladium complex for oxidative addition to be (solvent)Pd(PPh$_3$)$_2$ for triphenylphosphine complexes and similarly for catalysts utilizing dba (trans,trans-dibenzylideneacetone) as a ligand. But because of the high affinity of dba and phosphine ligands for palladium, the active species is only found in very small quantities in comparison to Pd(dba)(PAr$_3$)$_2$. Since Farina had shown significant rate acceleration with AsPh$_3$ and tri-2-furylphosphine during the tranmetallation step, Jutand and Amatore hypothesized there may be similar rate enhancement in the oxidative addition step.

Previous work had shown the presence of the active species (solv)Pd(PAr$_3$)$_2$ in solution through the use of cyclic voltammetry. In analyzing the ligand AsPh$_3$, the active species distinct cyclic voltammogram pattern was not initially recognized. The scan rates were lowered revealing the active species. The data suggests ligand dba is in a fast equilibrium with the solvent forming the active species only in very small observable amounts. With this result, Jutand and Amatore proved AsPh$_3$, tri-2-furylphosphine and triphenylphosphine all go through similar solvent dependent active intermediates.

Further analysis of the oxidative addition with $^1$H NMR yielded three distinct peaks not associated with the oxidative product. Jutand and Amatore established these peaks were coming from a single phenyl group through COSY experiments. Furthermore, addition of excess AsPh$_3$ caused the three peaks to disappear. Jutand and Amatore believe this is the first direct evidence of the T-shaped complex $\text{1.17}$ where a phenyl from another palladium is complexing the palladium performing the oxidative addition, Scheme 1.6. A phenomena first proposed by Farina’s kinetic studies.
Scheme 1.6 demonstrates, addition of excess AsPh₃ will drive the equilibrium to the left thus reducing the quantity of T-shaped complex in solution.

\[
\begin{align*}
\text{[PhPdI(AsPh₃)₂]} & \xrightleftharpoons[K_L]{1.17} \text{PhPd-I} + \text{AsPh₃} \\
& \text{AsPh₃}
\end{align*}
\]

\textbf{Scheme 1.6}

Proton NMR evidence of a T-shaped complex \textbf{1.17} and Farina’s kinetic studies inspired Jutand and Amatore to examine other parts of the reaction that may complex the palladium particularly as vinyl stannanes are used extensively in Stille couplings. In general, only catalytic amounts of the palladium complex are added to the reaction, so one can deduce the concentration of palladium and ligands is much less than that of the vinyl stannane coupling partners. Through UV spectroscopy, Jutand and Amatore were able to show the correlation between absorbance of Pd(dba)(AsPh₃)₂ and a decrease in absorbance when excess vinyl stannane was added.\textsuperscript{20} The effect was reversible with the addition of excess dba ligand. Since in most cases oxidative addition is considered irreversible, the reversibility caused by additional dba ligand suggests the vinylstannane is only complexing the palladium and not oxidatively adding in. Again this poses a problem for the oxidative addition since two ligands, dba and vinyl stannane are competing for complexation to palladium, thus further reducing the amount of the reactive palladium complex, (solv)Pd(AsPh₃)₂. Complexation of this type is of concern when coupling large natural products especially polyketides, because of the propensity of
poly-olefinic stannane coupling partners. Any decrease in the rate of reaction even small in nature can lead to competition from other pathways and possible decomposition.

Though this examination of the oxidative addition step in a Stille coupling is far from complete, it does demonstrate the complexity of this reaction where ligands, solvent, and substrate play a vital role in the rate of addition. Espinet’s analysis of the cis-trans isomerization yielded four potential pathways for this transformation with ligand and solvent participation noted. Jutand and Amatore’s investigation into the rate enhancement of AsPh$_3$ to the oxidative step yielded similar results to PPh$_3$ and tri-2-furylphosphine confirming all three phosphine ligands proceed through a similar solvent dependent pathway. Nucleophilic species such as vinyl stannanes were shown to be competing with the dba ligand for complexation to the palladium species resulting in a reduced concentration of the active (solv)Pd(AsPh$_3$)$_2$ complex.

1.2.2 Mechanism: Transmetallation

One distinct advantage that the Stille reaction has is the convenient use of alkyl stannanes which tend to be readily available, air and moisture stable, and tolerant of the other functional groups.$^{19}$ An explanation for the tolerance is the low polarity of the Sn-C bond rendering it relatively inert. Similar to the oxidative addition, insight into the intricacies of the transmetallation have increased substantially over the last decade with improved instrumentation and better working models. To this end, one must understand all of the variables including the electrophile, nucleophile, ancillary ligands, solvent and additives in order to grasp the complete picture of the coupling.
In a generalized sense, transmetallation of the Pd(II) complex is a ligand-substitution process, which generally proceeds through a tetracoordinated square-planar 16-electron species. Under this model, ligand substitution has been documented to go through two possible pathways associative and dissociative, Scheme 1.17. The dissociative pathway 1.18 proceeds through a 14-electron T-shaped intermediate where substitution occurs opposite of the ligand with greatest $trans$ influence. Destabilization from the trans influence leads to the dissociative equilibrium where the $trans$ influence destabilizes the metal-ligand bond across from it controlling the dissociation equilibrium. The associative pathway 1.19 proceeds through an 18-electron trigonal bipyramidal complex. The ligand with the highest $trans$ effect determines the final position of the substituting ligand through the lowest energy transition state. A demonstration of the complexity of this mechanism is found in the associative pathway where one must also recognize that the substitution may proceed through a direct or solvent-assisted method. For the purpose of most discussions, the electrophilic nature of the palladium complexes lends more to the associative rather than the dissociative pathway.
Alkynyl, aryl and vinyl based stannane coupling partners present an added dimension to the transmetallation dilemma thanks to their π-electron density capable of initial coordination to the metal. Even with the initial coordination, the relatively weak nucleophilic nature of the stannane moiety prevents rapid insertion into the palladium complex. The rate of reaction is further slowed by the necessary cleavage of the strong C-Sn bond. It is because of these two factors that the transmetallation step is considered the rate limiting step. One can take two pathways in solving this problem. The first being attenuating the stannane’s reactivity effectively lowering the energy needed to cleave the C-Sn bond. This approach presents challenges because of the advantages gained by having a strong C-Sn bond. The second approach looks at the palladium itself and designing the proper ligands to promote nucleophilic attack by the vinyl stannane followed by successful cleavage of the C-Sn bond expelling $^+\text{SnR}_3$. Knowing this, Farina
and coworkers set out to look at the transmetallation step to better understand how ligands on palladium were affecting the rate of reaction.

Farina’s 1991 paper on the mechanistic and synthetic implications for tri-2-furylphosphine and triphenylarsine considerably broaden the capabilities of the Stille reaction. Farina points out two key observations, the Stille reaction was virtually compatible with all functional groups and often required temperatures as high as 100°C. This was particularly troublesome for temperature sensitive substrates such as the 3-(triflyoxy)cephems whom initially sparked Farina’s interest.

At the time ligands generally phosphine in nature, were believed to be sterically bulky thus slowing down the overall rate of reaction. To counter this, Beletskaya employed ligandless catalysts or palladium without strong coordinating ligands such as phosphines. This aided in reducing the reaction temperature needed for coupling, but also dramatically affected the stability of the catalyst for the worse. Knowing that too many phosphine ligands was sterically detrimental and a ligandless system was unstable, Farina performed a set of kinetic studies probing the transmetallation mechanism in more detail in order to tailor the necessary ligands for maximum reactivity without sacrificing stability.

The tranmetallation step was considered a substitution process at palladium where organotin would be referred to as the nucleophile and halide or pseudo halide would be considered the leaving group. The organotin would approach the plane of the complex perpendicular to the leaving group thus forming an unstable pentacoordinate system. The leaving group is expelled resulting in retention of configuration. The classic associative pathway would not allow the ligands cis to the leaving group to have very little electronic
impact on the leaving group. To the contrary, Farina observed large kinetic effects when tri-2-furylphosphine was used in two types of Stille couplings.\textsuperscript{26}

The coupling of iodobenzene and vinyltin was examined by a compliment of palladium complexes. Utilizing the weakly coordinated Pd$_2$dba$_3$ species, one can add 4 equivalents of the desired ligand forming the desired palladium complex \textit{in situ}.\textsuperscript{28} Tri-2-furylphosphine and triphenylarsine proved to be very effective in enhancing the reaction rate 100 and 1000x respectively. Their mild nature also proved successful in coupling allylic tin to aryltriflates, thus eliminating olefin migration that plagues couplings with triphenylphosphine.\textsuperscript{15b} What became more apparent and difficult was attempting to correlate the results of Farina's studies into an explanation of why.

Stille believed ligand effects were predominantly steric, but Farina’s results do not correlate with this observation. The ligand tri-o-tolyolphosphine is considerably more sterically encumbering than tris(2,4,6-trimethoxyphenyl)phosphine yet yields a rate 500x faster.\textsuperscript{15b} Triphenylarsine and triphenylphosphine have similar cone angles, but triphenylarsine is able to increase the relative rate by a factor of 10$^3$. Electronic correlations were improved but exceptions still existed. Tri-o-tolyolphosphine and triphenylphosphine are similar electronically though the rate for tri-o-tolyolphosphine is much faster. Based on these results and a NMR study looking at ligand dissociation as a key step for transmetallation, Farina concluded a complete picture of the transmetallation step was still in development.

Though Farina’s development of tri-2-furylphosphine and triphenylarsine has greatly expanded the scope of the Stille reaction, the transmetallation step is still considered the rate limiting step. With a better understanding of the \textit{trans} influence on
the palladium and its ligands one has the ability to attenuate the desired reactivity necessary for synthesizing larger poly-ketide natural products.

1.2.3 Mechanism: Reductive Elimination

Much like the oxidative addition an isomerization event plays a pivotal role in the reductive elimination. Unlike the oxidative addition step where a rapid isomerization from the cis-product to the thermodynamically favored trans-product takes place, the coordination sphere around the palladium must go through a trans to cis configuration in reference to the coupling fragments for reductive elimination to commence. Understanding how this isomerization may be facilitated could lead to rate enhancement under preferred conditions.

Stille envisioned five possible pathways the two organo-coupling partners could isomerize from trans to cis on the palladium.\textsuperscript{29} The first idea was oxidative addition of an organic halide to the palladium complex, while the second involved dissociation of phosphine ligand producing a three-coordinate intermediate. The third possibility was association of a phosphine ligand yielding a five-coordinate complex and the fourth revolved around rearrangement of a phophine ligand after the three- or five-coordinate complexes were already established. The fifth idea looked at distorting the trans complex to a transient tetrahedral geometry.

Stille and Gille first looked at Bis(phosphine)dimethylpalladium(II) complexes particularly because the β-elimination pathway is unavailable, ethane gas is produced when the methyl moieties couple, and pure cis and trans isomers could be easily synthesized, Scheme 1.8. Cis 1.20 was synthesized from the dichloro-precursor and
methyllithium, while the trans palladium complex began with oxidative addition of Pd(0) into methyl iodide followed by transmetallation with methyllithium yielding 1.22.

NMR analysis of the cis and trans complexes yielded substantial differences which could be exploited as a probe into the geometry of palladium complex in real time. For example, the $^{31}$P NMR yields resonances of the cis and trans complex are 11 ppm apart. Previous work on the dianion bis(phosphine)palladium complexes had shown solvent and phosphine concentration to be vital to the outcome of the reaction. Using this precedent, Stille examined $trans$-Bis(diphenylmethylphosphine)dimethylpalladium in perdeuteroiobenzene, which resulted in no detectable amounts of the cis complex. The perdeuteroiobenzene was heated to 50°C, yet no isomerization was observed. The cis complex was placed in a similar environment yielding no trans product or 1,1-reductive elimination. Alternatively, both the cis and trans complexes produce ethane when heated to 50°C in dimethylformamide. Only the cis isomer was observed when both cis and trans were dissolved in DMF separately and heated to 50°C for five minutes at which time the reaction was quenched with pentane crashing out the crystallized complex.
Since no ethane was observed gassing off, Stille concluded the isomerization must happen before the 1,1-reductive elimination.

In an effort to necessitate the use of polar solvents, Stille and Gillme dissolved the trans isomer in perdeuteriobenzene and added 4 equivalents of THF per molecule of trans isomer. The complex did not undergo reductive elimination, but rather successfully isomerized to the cis moiety. The addition of diphenylmethylphosphine reversed this process and yielded the trans isomer over the cis counterpart. Unfortunately, reductive elimination was not observed in either case.

Though commonly viewed as an intramolecular reductive elimination, a cross-over experiment with equal molar equivalents of deuterated and non-deuterated bis(diphenylmethylphosphine)dimethylpalladium yielded a small amount of $d_3$-ethane detected as a low intensity 33 m/e peak, Scheme 1.9. Proton NMR analysis of the disappearance of the methyl-palladium signal coincided with the appearance of the coupled ethane product. Reductive elimination and subsequent formation of ethane and $d^6$-ethane for 1.23 and 1.24 along with 1.28 and 1.29 yielded first-order kinetic plots, while reductive elimination of 1.25 and 1.26 showed deviation from the linearity seen in the other two cases.

Further NMR analysis proposed a new $^{31}$P signal not previously seen. The new phosphorous signal proved to be caused by oxidative addition of a coordinatively unsaturated palladium(0) recently formed from reductive elimination of ethane. Fahey and Mahan had seen a similar oxidative addition with triphenylphosphine ligands and Pd(0). This finding though quite interesting would not be beneficial for the overall reaction and needed to be suppressed. Stille employed similar technology used to
stabilize Pt(0) species by adding diphenylacetylene to scavenge any free Pd(0) complexes through direct coordination.\(^{33}\) Once the diphenylacetylene was added the reaction proceeded to completion without any detectable amount of \(d^3\)-ethane present.

\[
\begin{align*}
\text{Ph}_3\text{P} & \quad \text{CH}_3 \\
\text{PPh}_3 & \quad \text{CH}_3 \\
1.23 & \\
\text{Ph}_3\text{P} & \quad \text{CD}_3 \\
\text{PPh}_3 & \quad \text{CD}_3 \\
1.24 & \\
\text{CH}_3 & \quad \text{CH}_3 + \quad \text{CD}_3 & \quad \text{CD}_3
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3\text{Ph}_2\text{P} & \quad \text{CH}_3 \\
\text{PPh}_2\text{CH}_3 & \quad \text{CH}_3 \\
1.25 & \\
\text{CH}_3\text{Ph}_2\text{P} & \quad \text{CD}_3 \\
\text{PPh}_2\text{CH}_3 & \quad \text{CD}_3 \\
1.26 & \\
\text{CH}_3 & \quad \text{CH}_3 + \quad \text{CD}_3 & \quad \text{CD}_3 & \quad \text{CD}_3 & \quad \text{CD}_3
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{P} & \quad \text{CH}_3 \\
\text{P} & \quad \text{Ph} \\
\text{P} & \quad \text{Ph} \\
1.28 & \\
\text{Ph} & \quad \text{Ph} \\
\text{P} & \quad \text{CD}_3 \\
\text{P} & \quad \text{CD}_3 \\
1.29 & \\
\text{CH}_3 & \quad \text{CH}_3 & \quad \text{CD}_3 & \quad \text{CD}_3
\end{align*}
\]

**Scheme 1.9**

Stille’s investigation into the requirements necessary for 1,1-reductive elimination yielded three distinct pathways dependent on the following parameters: organic partners, ability to dissociate ligands, and stability of the palladium complex.\(^{29,34}\) In the case of bis(phosphine)dimethylpalladium(II) 1.30, the complex must first isomerize to the cis moiety 1.31 then undergo ligand dissociation before reductive elimination proceeds, Scheme 1.10.\(^{29}\) The key T- or Y-shaped intermediate 1.32 has been proven through extended Huckel calculations demonstrating the importance of the coupling partners to be positioned adjacent to each other upon coupling.\(^{35}\)
Reductive elimination of vinyl groups proceeds through the same cis complex, but do not require prior dissociation of a ligand for the coupling to occur. Stille believed the stability of the bis(phosphine)olefinpalladium(0) product yielded a low energy alternative to ligand dissociation and thus allowed 1,1-reductive elimination to proceed through the four-coordinate complex 1.33, Scheme 1.11. The three-coordinate T- or Y-shaped complex 1.34 is still present and in competition with the four-coordinate complex, but is not favorable until the end of the reaction when ligand demand is most critical for the Pd(0) product 1.35.

When utilizing a diphosphine ligand 1.35 that bridges trans coordination sites on the palladium, reductive elimination was unachievable at high temperatures in polar solvents. This is due in large part to the coupling partner’s inability to isomerize to the cis conformation. Simple addition of methyl iodide to 1.36 caused rapid reductive
elimination of ethane at 25°C for which cis palladium(II) complexes had been shown to be stable. Similarly, addition of trideuteriomethyl iodide yielded trideutioethane implicating the palladium(IV) complex 1.38 as the source, Scheme 1.12.

Scheme 1.12

Stille and coworkers initial investigations into 1,1-reductive elimination of the Stille reaction have helped to shed light on an otherwise understudied portion of the reaction’s mechanism. Their research demonstrated an isomerization event for the coupling partners to orient themselves cis to one another was crucial and led to their finding on the importance of using polar solvents. They also discovered side reactions free Pd(0) can cause when not sequestered with the addition of dipheylacetylene.

1.2.4 Copper Effects

The “copper effect” was first characterized by Farina and Liebeskind. The conclusion from their investigation was copper scavenged free ligands in solution such as PPh₃. The rate enhancement fit well into the dissociation model for the transmetallation step at the time, but recent investigations in to the transmetallation step suggest a more
associative mechanism is at play. Again, the rate enhancement of CuI can be explained by sequestering of free ligand which may “auto-retard” the associative transmetallation.\textsuperscript{37} The effect is felt the greatest with stronger binding ligands such as PPh\textsubscript{3} and negligible for softer binding ligands like AsPh\textsubscript{3}.

Under very polar solvents, Farina and Liebeskind also reported what they believed to be a Sn/Cu transmetallation.\textsuperscript{38} Piers and Wong have since proved one can use stoichiometric amounts of CuCl and indeed produce coupling between alkenyl iodides and alkenyl stannanes.\textsuperscript{39} Similarly, Liebskind’s copper(I) thiophene carboxylate (CuTC) catalyst has provided a complimentary alternative to palladium catalysts in several total synthesis.\textsuperscript{40} Utilization of the copper(I) thiophene carboxylate catalyst will be further explored in the syntheses of concanamycin and elaiophylin later in this introduction.

### 1.2.5 Synthetic Utility

As detailed above, our understanding of the intricacies of the Stille reaction have grown immensely over the past two decades. With greater understanding of advantages and limitations of the reaction, one can start to explore its full potential in the syntheses of complex natural products.

The total syntheses of rapamycin from Smith and Nicolaou’s group demonstrate the flexibility one has with the Stille reaction. In one approach, the Smith group proposed an intramolecular Stille coupling as the macrolactonic step forming the highly functionalized 29-membered macrolide from vinyl iodide \textbf{1.39}, Scheme 1.13.\textsuperscript{41} The reaction proceeded smoothly in a DMF/THF solvent mixture with rate enhancement
from the addition of tri-2-furylphosphine. Diisopropylethyl amine (DIPEA) base was used in order to scavenge any adventurous H⁺.

![Chemical structure](1.39)

**Scheme 1.13**

Nicolaou and co-workers took a different approach hoping to exploit several of the Stille reactions many perks. Instead of forming one carbon-carbon bond, Nicolaou wanted to form two through a “stitching” strategy.⁴² Using hexabutyl divinyltin 1.42 with a Pd(II) catalyst in a THF/DMF solvent system, the total synthesis of rapamycin was completed, Scheme 1.14. Along with forming two separate carbon-carbon bonds, the
reaction was performed without the aid of protecting groups. The success of this strategy led to a similar route for Danishefsky’s total synthesis of dynemicin.

Structurally, dynemicin contains a highly strained ene-diyne 10-membered ring. Utilizing a similar strategy to Nicolaou’s “stitching” approach; Danishefsky was able to successfully form the 10-membered ring \textbf{1.43} in one step at 81% yield.\textsuperscript{43} As evidence to the importance of conformation in respect to the Stille reaction, when the epoxide was not present \textbf{1.44} zero of the desired enediyne product was obtained, Scheme 1.15.
Nicolaou’s synthesis of rapamycin 1.40 and Danishefsky’s synthesis of dynemicin 1.45 provide equiset examples of retention of stereochemistry about the coupling olefin. An E-vinyl distannane is employed in the synthesis of rapamycin 1.40 while Danishefsky utilizes the Z-isomer of the same molecule to finish the synthesis of dynemicin 1.45.

![Scheme 1.15](image)

In the total synthesis of sanglifehrin, published by Nicolaou\textsuperscript{44} and coworkers, Nicolaou proposes a late stage regio-selective coupling of 1.47 between the less hindered vinyl iodide forming the desired 22-membered macroclide 1.48. To their advantage, the reaction was completely selective for the less hindered vinyl iodide preparing the substrate for the subsequent intermolecular Stille reaction which successfully attached the side chain 1.49 under mild heating, Scheme 1.16.
An achille’s heel of the Stille reaction is $\beta$-hydrogen’s to the reactive carbon. The rate limiting nature of the transmetallation step is in direct competition with the rate of $\beta$-hydride elimination. The use of di- and trisubstituted alkenes as coupling partners has slowed the rate of $\beta$-hydride elimination or prevented it altogether in the case of the trisubstituted olefins, but constrains the synthesis into producing conjugated dienes. The flexibility to use $sp^3$-hybridized carbons would allow the formation of synthetically useful 1,4 “skipped” dienes.

Stille and Hegedus proposed using allylic acetates which contain no $\beta$-hydrogen for elimination. This development was crucial for the construction of 1,4 “skipped” dienes that are found in the natural product amphidinolide A. Much like Nicolaou’s
synthesis of sanglifehrin, Pattenden and Lam were able to selectively form the diene portion of amphidinolide presumably because of the more reactive vinyl iodide versus the allylic acetate 1.52. The total synthesis finishes with an impressive sp²-sp³ Stille macrolactonization cross-coupling 1.53 free of protecting groups, Scheme 1.17.

![Scheme 1.17](image)

With a better understanding of the capabilities and limitations of the Stille reaction, recent endeavors have branched into cascade reaction pathways for natural product construction taking advantage of the Stille reaction’s selectivity and mild reaction conditions. Martin’s total synthesis of manzamine provides a prime example of these principles. Successful addition of the vinyl moiety to the alkyl bromide 1.55 produces the preferred diene 1.57. The diene is then primed for an endo-selective
intramolecular Diels-Alder yielding tricyclic 1.58 as a single diastereomer, Scheme 1.18.\textsuperscript{47}

\begin{center}
\begin{align*}
\text{Br} & \quad \text{CO}_2\text{Me} \\
\text{Pd(PPh}_3\text{)}_4 & (4 \text{ mol\%}) \\
\text{Toluene, 120}^\circ\text{C} \\
\end{align*}
\end{center}

1.56

\begin{center}
\begin{align*}
\text{CO}_2\text{Me} & \quad \text{N} \\
\text{OTBDPS} & \quad \text{OTBDPS} \\
\text{NBOc} & \quad \text{NBOc} \\
\text{OTBDPS} & \quad \text{OTBDPS} \\
\text{1.55} & \quad \text{1.56} \\
\end{align*}
\end{center}

Scheme 1.18

1.2.6 Stille Reaction Summary

The Stille reaction has evolved significantly from its early days of attempting to replace Bu\textsubscript{3}SnH as a dehalogenating reagent. In large part, the reaction’s success can be attributed to several distinct advantages it has over similar reactions such as relatively air and moisture stable palladium catalysts, mild reaction conditions especially with the addition tri-2-furylphophine and triphenylarsine ligands, inert to most functionality, and excellent stereochemical traits like retention of olefin configuration when coupling alkenylstannanes and vinyl iodides.

Mechanistic work over the past decade has increased our understanding of the catalytic cycle for the Stille reaction, but also has developed into a much more
complicated picture than previously envisioned. This mechanistic complexity should allow for further optimization of catalysts and increased tailoring of reaction conditions in the future.

1.3 Stille Reaction in Polyketide derived ATPase inhibitors

The body of this dissertation pertains to the total synthesis of 20-deoxyapoptolidinone an analogue of the naturally occurring apoptolidin. Like many polyketide derived natural products, apoptolidin possesses unsaturation as an $E,E$-diene and $E,E,E$-triene. These islands of unsaturation provide ample targets for utilization of the Stille reaction and understanding of its capabilities outlined above. Apoptolidin itself falls into a category of ATPase enzyme inhibitors that may lead to possible cytotoxic therapeutic agents in the future. As a further demonstration of the power of the Stille reaction, several examples of syntheses of ATPase inhibitors will be examined in the following.

1.3.1 Bafilomycin

![Bafilomycin A1](attachment:figure1.2.png)

Figure 1.2
Isolated in 1984 from the fermentation broth of *Streptomyces griseus*, bafilomycin A proved to be a potent inhibitor of vacuolar ATPase in vitro and in vivo studies. Its vacuolar ATPase inhibition has spiked curiosity, since V-ATPases have been linked to bone resorption, a potential target for the treatment of osteoporosis. Structurally, bafilomycin A consists of a 16-membered macrolide and substituted pyran side-chain, Figure 1.2. SAR work has shown the two dienes to be essential for activity as even partial hydrogenation of the dienes resulted in a significant loss of activity.

The Toshima group saw the carbon-carbon bond at C11-C12 as a prime target for a Stille cross-coupling. Their approach involved reacting a tri-substituted vinyl iodide 1.60 with an interesting vinyl stannane 1.61 adjacent to a methyl-ether, Scheme 1.19. Several palladium catalysts were examined in DMF at 50°C with PdCl₂(dppf) proving to be superior when using one equivalent of both coupling partners and a reaction time of 15 hours, Table 1.1.
TABLE 1.1

BAFILOMYCIN

![Chemical Structure]

**Scheme 1.19**

<table>
<thead>
<tr>
<th>Pd Catalyst (0.2 eq)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd(PPh₃)₄</td>
<td>Trace</td>
</tr>
<tr>
<td>PdCl₂(PPh₃)₂</td>
<td>33</td>
</tr>
<tr>
<td>PdCl₂(MeCN)₂</td>
<td>36</td>
</tr>
<tr>
<td>PdCl₂(dppf)</td>
<td>60</td>
</tr>
</tbody>
</table>

The ¹H NMR spectrum of the product **1.62** yielded a 3:1 inseparable mixture, which was not predicted because of the Stille reaction’s usual ability to retain olefin geometry. The mixture was further carried on through the sequence until formation of the lactone produced no more visible mixture in the ¹H NMR. Toshima and co-workers deduced the mixture consisted of conformational isomers of **1.62** and once the more rigid macrolactone was formed the molecule was unable to adopt more than one isomer. Following the successful coupling of the vinyl iodide and vinyl stannane, Toshima and co-workers were able to complete the total synthesis of Bafilomycin A₁ in 14 remaining steps.

Much like Toshima’s synthesis of bafilomycin A₁⁵¹, Marshall envisioned a cross-coupling at C11-C12 for completion of the bafilomycin V₁.⁵⁰ But unlike Toshima,
Marshall initially looked at palladium-free catalysts in particular Liebeskind’s copper(I) thiophene catalyst. The copper(I) catalyst only yielded recovered starting material when reacted at room temperature for several hours. Similarly, Pd$_2$(dba)$_3$ catalyst and AsPh$_3$ in NMP heated to 55°C only produced small amounts of product. Marshall hypothesized the transmetallation was too sluggish and caused the lack of reactivity. Dried LiCl was added to accelerate this process resulting in reaction completion in five hours at 55°C on a test system, Scheme 1.20.

![Scheme 1.20](image.png)

The desired vinyl stannane 1.66 containing the full side-chain and substituted pyran was prepared and subjected to similar coupling conditions, Scheme 1.21. The combination of Pd$_2$(dba)$_3$ with AsPh$_3$ and LiCl in NMP yielded the coupled product 1.67 in five hours at room temperature.
Upon successful coupling of the vinyl stannane and iodide, Marshall and Adams turned their attention to macrolactonization via Yamaguchi protocol worked out by Evans and Calter. The methyl ester 1.67 was saponified with potassium trimethylsilanolate followed by mixed anhydride formation with 2,4,6-trichlorobenzoyl chloride reagent. Marshall and Adams were disappointed to find the mixed anhydride decomposed upon treatment with DMAP in refluxing toluene. Successful ester formation with (-)-menthol and Calter’s ability to perform a similar macrolactonization, suggested the pyranose side-chain may be playing a role in the instability of the intermediate.

With this hypothesis, Marshall and Adams proposed an intermolecular esterification followed by an intramolecular Stille coupling. In the absence of the vinyl stannane, acid 1.68 was reacted with 2,4,6-trichlorobenzoyl chloride and TEA consuming all of the starting material and presumably forming the mixed anhydride, Scheme 1.22. The mixed anhydride was then added via cannula to stannane 1.68 and a DMAP mixture then stirred for 18 hours at room temperature resulting in no product formation only symmetrical anhydride 1.69. Though discouraged by the aforementioned results,
Marshall and Adams proceeded to deprotect non-lactonized product 1.67 yielding bafilomycin V1 an acyclic analogue of bafilomycin.

Scheme 1.22

In Toshima’s total synthesis of bafilomycin A1, examination of several palladium catalysts proved successful in limiting the number of equivalents necessary for successful coupling. Marshall’s total synthesis of bafilomycin V1 proved too much for the copper(I) thiophene catalyst developed by Liebskind, but successful coupling was achieved with Pd2dba3, AsPh3, and dried LiCl in DMP. As the following examples will continue to demonstrate there is not a specific set of reaction parameters that will work with every system. Instead, careful evaluation of many conditions has shown to be the best approach.

1.3.2 Concanamycin

A member of the vacuolar H+-ATPase inhibitors, concanamycin, has garnered much interest for its ability to disrupt cellular proton transfer leading to many possibilities as an antiviral52a, immunosuppressant52b, and anti-cancer therapeutic.52c Along with the
bafilomycins, concanamycins have shown promise as possible treatments for osteoporosis. Structurally, the concanamycins are very similar to the bafilomycins containing a slightly larger 18-membered ring consisting of two dienes one of which has a methyl enol-ether. In addition, concanamycin 1.70 possesses a substituted pyran side-chain and rhamnose sugar moiety, Figure 1.3.

![Concanamycin A (1.70)](image)

**Figure 1.3**

Do to the complex nature of concanamycin’s macrolide, Toshima and coworkers examined the effectiveness of an inter- versus intramolecular Stille coupling. The intermolecular Stille proceeded smoothly with Pd$_2$(dba)$_3$ in the presence of Ph$_3$As and LiCl in NMP at 40°C after several palladium catalysts were screened, Scheme 1.23.

As Table 1.2 demonstrates, PdCl$_2$(dppf) with LiCl proved inferior to the combination of Pd$_2$(dba)$_3$, LiCl, and Ph$_3$As. Though Toshima gives no reasoning why, it is evident the combination of Pd$_2$(dba)$_3$ and Ph$_3$As produced a significant improvement in the reaction’s overall yield. Taking the lessons learned from the intermolecular Stille coupling, Toshima investigated an intramolecular Stille coupling as the last step in formation of concanamycin’s macrolide.
TABLE 1.2
STILLE CONDITIONS FOR CONCANAMYCIN SYNTHESIS

<table>
<thead>
<tr>
<th>Pd Catalyst (eq.)</th>
<th>Additive(s) (eq.)</th>
<th>Solvent</th>
<th>T(°C)</th>
<th>Time(h)</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PdCl$_2$(dppf) (0.25)</td>
<td>None</td>
<td>DMF</td>
<td>40</td>
<td>15</td>
<td>43</td>
</tr>
<tr>
<td>PdCl$_2$(dppf) (0.2)</td>
<td>LiCl (3.0)</td>
<td>NMP</td>
<td>40</td>
<td>16</td>
<td>49</td>
</tr>
<tr>
<td>Pd$_2$(dba)$_3$ (0.2)</td>
<td>CuI (0.4), Ph$_3$As (0.8)</td>
<td>NMP</td>
<td>40</td>
<td>16</td>
<td>68</td>
</tr>
<tr>
<td>Pd$_2$(dba)$_3$ (0.25)</td>
<td>LiCl (3.0), Ph$_3$As(2.0)</td>
<td>NMP</td>
<td>40</td>
<td>16</td>
<td>72</td>
</tr>
</tbody>
</table>

Upon successful esterification through a modified Yamaguchi method, several palladium and additive combinations were evaluated for their effectiveness in constructing the desired macrolide 1.74, Table 1.3. Drawing from Smith’s work on macrolactin$^{54}$, Toshima evaluated Pd(0) catalysts in conjunction with DIPEA base and polar solvents such as NMP or DMF. Smith had found Pd(II) catalysts to be undesirable since, they predominantly led to slow protodestannylation even with large excesses of DIPEA present.

Optimal results were obtained with Pd$_2$(dba)$_3$, DIPEA, and Ph$_3$As in a DMF-THF solvent mixture heated to 60°C for 18 hours yielding macrolactone 1.74 in 72% yield, Scheme 1.24.$^{53}$ In addition to the successful coupling, Toshima reported high dilution conditions were not needed in contrast to Smith’s work on macrolactin.$^{54}$

Smith
experienced substrate polymerization upon Stille coupling if the system was not properly
diluted. With the macrolactone in hand, Toshima proceeded to perform an aldol condensation using the ethyl ketone of the side-chain thus completing the total synthesis of concanamycin F.

As a demonstration of the versatility of their anti-selective aldol chemistry, Paterson and co-workers proposed a rapid, stereoselective synthesis of concanamycin F. Central to Paterson’s strategy was the late addition of the side-chain via a methyl ketone aldol condensation. Construction of the macrolide followed a similar path to Toshima’s inter- versus intramolecular Stille reaction though Paterson chose to go with Liebeskind’s
copper(I) thiphene-2-carboxylate (CuTC) catalyst in NMP yielding the coupled fragment 1.77 in a remarkable 89% yield, Scheme 1.25. This marked one of the first applications of the copper catalyst for formation of the diene portions of concanamycins and bafilomycins.

![Scheme 1.25](image)

Upon investigation into the intramolecular Stille coupling, Paterson was disappointed to discover the CuTC catalyst only yielding the protodestannylation product. Paterson provides no explanation for the results, but resorts to Toshima’s conditions for the coupling yielding 1.79 in 69% yield, Scheme 1.26. Protecting group manipulation followed by a Mukaiyama aldol coupling completed the total synthesis of concanamycin F.

![Scheme 1.26](image)
Toshima and Paterson’s work demonstrated several new wrinkles into the versatility of the Stille reaction. Because of its functional group tolerance, one is able to examine intramolecular Stille couplings when intermolecular couplings prove to be difficult or transesterification is not feasible as a late stage reaction. Paterson’s utilization of the CuTC catalyst proved to be one of the first successful demonstrations of this new technology on the concanamycins and bafilomycins. The remarkable yield it produced was only slightly dampened by its shortcomings in the intramolecular coupling.

1.3.3 Elaiophylin

A C2-symmetric 16-membered macrolide, elaiophylin was isolated from cultures of *Streptomyces melanosporus* by the Arcamone group\(^{55a}\) and shortly thereafter Arai and co-workers.\(^{55b}\) Elaiophylin displays a wide range of biological activity including antimicrobial activity against Gram-positive bacteria, and inhibitory activity against K+-dependent adenosine triphosphatases.\(^{56a-d}\) Structurally, elaiophylin 1.80 consists of a 16-membered macrolide and two structurally complex pyran side-chains that are terminated with 2-deoxy-\(\alpha\)-L-fucose moieties, Figure 1.4.

\[
\text{Elaiophylin (1.80)}
\]

**Figure 1.4**
Paterson’s total synthesis of Elaiolide, the aglycone of elaiophylin, demonstrate the flexibility of palladium-free Stille cross couplings utilizing Liebeskind’s thiophene-2-carboxylate (CuTC) catalyst. Because of the C₂-symmetry found in Elaiolide, Paterson envisioned a dimerization-type cross-coupling allowing for the construction of a single starting fragment. Promoting much of his anti-aldol chemistry, Paterson and coworkers were able to quickly synthesize vinyl iodide 1.81, Scheme 1.27. Employing 10 equivalents of CuTC in NMP at room temperature yielded the crystalline macrolide 1.83 in a remarkable 15 minutes at 80% yield.

![Scheme 1.27](image-url)

The key element to the success of the reaction was found to be the concentration of the vinyl iodide 1.81. Concentrated reactions (c 0.2M) resulted in multiple macrocycles likely due to similar reaction rates between the inter- and intramolecular cross-coupling. Diluting the system down to 0.01M, based upon the vinyl iodide, resulted in exclusive production of the desired macrolide in high yield. A Felkin-Ahn
controlled methyl ketone aldol condensation was used to further extend the side-chains, which upon deprotection cyclized to form the substituted pyrans revealing Elaiolide.

1.3.4 Amphidinolide

The amphidinolide family of natural products like many natural products has received widespread interest because of exceptional activity against a variety of NCI tumor cell lines. Composed of more than 20 members, the amphidinolides cover a wide range of structural diversity including exo-cyclic alkenes, medium to large (12-29 membered) macrocyclic structures, and synthetically challenging small ring systems (epoxides, tetrahydrofuran rings). Because of their complexity and lack of abundant natural sources, the absolute stereochemistry for many of the members in this family is unknown. Thus, synthetic strategies for these molecules have concentrated on smaller fragments with a controlled number of stereocenters. This approach, along with a convergent process to couple the fragments, allows for multiple stereo-configurations to be examined at a rapid rate. Again, the Stille reaction plays a vital role because of its ability to form sp²-sp² and sp²-sp³ carbon-carbon bonds selectively and efficiently.

In the total synthesis of Amphidinolide A published by Pattenden and coworkers, a novel combination of sp²-sp² and less common sp²-sp³ Stille reactions were proposed. Utilizing the palladium(0) catalysis Pd₂(dba)₃ in conjunction with Ph₃As, distannane 1.51 was successfully coupled to vinyl iodide 1.52 in 51% yield, Scheme 1.28. As expected, the more reactive vinyl iodide reacted with the less sterically bulky vinyl tin yielding the silyl-protected version of allylic acetate 1.53.
After global removal of the TES-ethers, successful intramolecular Stille coupling of the allylic acetate and vinyl stannane was accomplished with Pd\textsubscript{2}(dba)$_3$ and LiCl in cyclohexane constructing the desired macrolide 1.54 in 42% yield. This macrolactonization further reinforces the remarkable tolerance the Stille reaction has for various functional groups including four unprotected hydroxyl groups present during the coupling reaction. Pattenden reported removal of the TES-ethers improved the reactivity of the vinyl stannane presumably through steric and electronic effects on the Sn-C bond. As demonstrated by this novel approach, use of allylic acetates and vinyl stannanes yields “1,4-skipped” dienes an important structural feature of the amphidinolide family and one of the first examples of this type of coupling.$^{45}$

Williams and Meyer’s total synthesis of amphidinolide K presented several challenges in large part due to the undetermined stereogenicity of several carbons within
the structure.\textsuperscript{57} Because of this, a convergent route was devised to allow for post synthesis modifications in order to probe the absolute configuration of amphidinolide K. Williams and Meyer preferred a late stage Stille coupling of the free acid to the vinyl tin moiety containing rest of the carbon backbone of amphidinolide K. This strategy could be deemed risky because of the propensity of similar vinylstannane fragments to undergo \textit{cine} addition rather than the preferred \textit{ipso} substitution.\textsuperscript{61} Upon successful coupling, a Mitsunobu would be employed to complete the macrocycle and lead to global deprotection finishing the natural product.

In addition to the risk involved with \textit{cine} versus \textit{ipso} addition, the Stille coupling posed several more challenges. The first hurdle involved the steric constraints of coupling two tri-substituted alkene. The second was the thermal stability of the vinyl iodide which proved unstable to temperatures above 60°C and finally, the coupling would be performed on the seco-acid of the vinyl iodide.\textsuperscript{57} Ultimately, Williams and Meyer found coupling alkenyl stannane \textbf{1.84} and vinyl iodide \textbf{1.85} could be achieved with the combination of Pd\textsubscript{2}(dba)\textsubscript{3}, Ph\textsubscript{3}As and CuTC. The reaction proceeded smoothly under mild heating to yield 50% of seco-acid \textbf{1.86}, Scheme 1.29. Interestingly, Williams and Meyer observed no reaction without a copper cocatalyst.\textsuperscript{57} Copper(I) iodide was used, but did not form the desired product. CuTC improved the reaction dramatically, though attempts to use it solely as the only coupling agent resulted in exclusive homocoupling of the stannane.
The total synthesis of Amphidinolide K was finished with a Mitsunobu macrolactonization followed by global deprotection. The optical rotation of Williams and Meyer’s amphidinolide proved to be the antipode of the natural product allowing for unambiguous assignment of the stereogenicity of the molecule with help from the X-ray diffraction study obtained from a crystal of the synthetic product. The utilization of a copper cocatalyst, more specifically CuTC, demonstrated yet another weapon in the Stille coupling arsenal for bringing together weakly reactive or sterically encumbered coupling partners.

1.3.5 Apoptolidin

Isolated in 1997 by Hayakawa and co-workers from *Nocardiopsis* sp\(^{62a}\), apoptolidin has garnered much synthetic interest due to its exceptionally selective cytotoxicity and unclear mode of action.\(^{62}\) Structurally apoptolidin exhibits all of the distinct features of a polyketide: acetate and propionate subunits, along with 1,3-diols and poly-olefinic regions. These olefinic regions more specifically the *E,E* diene and *E,E,E*-triene portions of the macrolide have presented a unique challenge due to their repetitive
anti-olefin geometry. As one would expect, classic Wittig technology\textsuperscript{63} along with the Horner-Wadsworth-Emmons olefination\textsuperscript{62a} and Thionyl-chloride rearrangement\textsuperscript{64} reactions have been the work-horses for formation of the triene portion. The C10-C13 diene has been a key disconnection in the retro-synthesis of apoptolidin. Construction of the desired diene has revolved around two strategies involving a Stille or Suzuki coupling for their function group tolerance during this crucial late stage reaction.

Nicolaou’s 2000 communication on apoptolidin provided the first successful synthesis of apoptolidin’s macrocyclic core.\textsuperscript{62a} Retrosynthetically Nicolaou envisioned a Yamaguchi macrolactonization and C11-C12 Stille coupling for the key disconnections yielding fragment 1.88 with extensive oxygen substitution and a highly unsaturated fragment 1.89, Scheme 1.30.
Upon successful synthesis of vinyl iodide 1.89 and alkenyl stannane 1.88, Nicolaou and coworkers were able to readily couple the fragments with Pd(CH$_3$CN)$_2$Cl$_2$ in DMF affording ester 1.90 in 60% yield, Scheme 1.31. Global deprotection under fluoride ion was followed by Yamaguchi macrolactonization producing the desired 20-membered macrolide 1.87 in high yield. The lactonization selectivity was a pleasant surprise and demonstrated the propensity of the rigid backbone of the macrolide to prefer the 20-membered ring over the possible 21-membered. With a direct route to the macrolide, Nicolaou’s group set their sights on the first total synthesis of apoptolidin utilizing the above aforementioned intermolecular Stille coupling followed by Yamaguchi macrolactonization.

![Scheme 1.31](image-url)
Following the lessons learned from the macrolactone synthesis, Nicolaou successfully coupled alkenyl stannane 1.91 with vinyl iodide 1.92 in 86% yield, Scheme 1.32. The coupling works remarkably well considering the C9-hydroxyl is unprotected and sensitive functionality like the mixed acetal is unaffected. Nicolaou reported protection of the C9-hydroxyl as a TBS- or TMS-ether resulted in no cross-coupling. Even C9 conversion to the acetate proved futile. Ideally, conversion of the TBS to the TMS-ether should have alleviated some of the steric constraints of the reaction, but since the reaction still did not proceed, one must also consider electronic and conformational effects of the allylic alcohol in conjunction with the vinyl stannane moiety.

Nicolaou further explored the cytotoxicity of apoptolidin through SAR work on truncated analogues utilizing the Stille reaction in their construction. The cross-coupling of alkenyl stannane 1.91 with vinyl iodide 1.94 demonstrates the necessity of four equivalents of the alkenyl stannane in relationship to the vinyl iodide, Scheme 1.33. Only 1.5 equivalents of the vinyl stannane were utilized resulting in a yield reduction of
86% to 66%. From these results, it is clear the desired cross-coupling is competing with the homo-coupling of the vinyl stannane. Excess of the alkenyl stannane guarantees enough of the tin moiety will be present for successful coupling to the vinyl iodide before complete homo-coupling can take place.

![Scheme 1.33](image)

Nicolaou’s work on apoptolidin demonstrated the influence functionality like a hydroxyl group can have on the necessary electronics of the Stille coupling. This influential work also highlighted the difficulty in overcoming side-reactions most notably Nicolaou’s use of multiple equivalents of alkenyl stannane to drive the reaction to completion. Soon after Nicolaou’s published synthesis of apoptolidin’s macrocycle, Toshima and coworkers presented their strategy for completion of this important macrolide.

Toshima’s work on the synthesis of the macrocyclic core of apoptolidin centered on an intramolecular Stille coupling as the last step or just before global deprotection. Toshima, like Nicolaou, thought a carbon-carbon disconnection at C11-C12 was the likeliest candidate for the Stille coupling. The initial strategy was to perform the Stille
coupling while the hydroxyls at C16 and more importantly C9 were protected as TBS-ethers. As presented above, Nicolaou saw no reactivity while the C9 hydroxyl was protected as an ether or ester. Toshima hoped to get around this dilemma by employing an intramolecular strategy. Much to their dismay, the Stille reaction was still unsuccessful with the C9-hydroxyl protected as a TBS-ether. TBAF deprotection of the C9 and C16 TBS-ethers led to product with PdCl\(_2\)(MeCN)\(_2\) catalyst in the presence of Ph\(_2\)PO\(_2\)NBu\(_4\) and LiCl additives in DMF solvent. The only isolatable product was macrolactone 1.98, albeit in modest yields of 30%, Scheme 1.34. Unlike Nicolaou and Toshima, Koert and coworkers found palladium catalyzed couplings less than desirable preferring to explore palladium-free systems utilizing Liebskinds copper(I) thiophene carboxylate catalyst (CuTC).\(^{16}\)

Scheme 1.34
Repeated attempts to couple vinyl iodide 1.99 and alkenyl stannane 1.100 led to undesirable yields of less than 30% even with extended reaction times and additional heating.\textsuperscript{67} In contrast, the CuTC complex in two equivalents achieved an 80% yield in one hour at -10°C, Scheme 1.35. The resulting ester was treated with LiOH yielding acid 1.101 in 87% yield. Surprisingly, modified Yamaguchi protocol led to the desired 20-membered macrolide as the only isolated product.\textsuperscript{68} Global deprotection with HF/pyridine led to one of the first total syntheses of apoptolidinone 1.102.

\begin{center}
\includegraphics[width=\textwidth]{Scheme1.35.png}
\end{center}

\textbf{Scheme 1.35}
1.4 Conclusion

The Stille reaction\textsuperscript{42} has played a vital role in the successful synthesis of countless natural products including apoptolidin and its family of analogues. Though composed of three basic mechanistic aspects oxidation, transmetallation, and reductive elimination, understanding the intricacies that make up each component can be the difference between no reaction and a successful coupling. Advances in catalyst design and additive ligands such as AsPh\textsubscript{3} have vastly expanded the capabilities of the Stille reaction yielding inroads into complex cross-couplings as final steps to the total synthesis of structurally and therapeutically interesting polyketide natural products.
CHAPTER TWO

SYNTHESIS OF FRAGMENT “B” A C12-C23 SYNTHON OF 20-DEOXYAPOPTOLIDONONE AND DERIVATIVES THEREIN

2.1 Purpose

This chapter will focus on the synthesis of “fragment B” a key component in our strategy towards the total synthesis of 20-deoxyapoptolidinone, its parent molecule apoptolidinone and future “chimeric” analogues. To this end, a route to fragment B (C12-C23) has evolved through the contribution of several key factors: cost, robust chemistry, and flexibility for modifications. Through this evolution, a common precursor was developed for the successful completion of fragment B synthons necessary for the completion of 20-deoxyapoptolidionone, apoptolidinone, and future analogues.

2.2 Initial Apoptolidin Syntheses

Upon entering the project in early 2001, only three synthesis papers on apoptolidin had been published. From these papers, one can quickly discern the difficulties in construction of such a large and complex natural product. Soon after apoptolidin’s discovery, the Nicolaou group published a synthetic route to its
macrocyclic core. Koert\textsuperscript{69a} and Sulikowski\textsuperscript{69b} quickly followed with differing approaches to the synthesis of the “southern half” or pyran portion of apoptolidin.

Nicolaou and coworkers devised cutting apoptolidin’s macrolide \textit{2.1} in half yielding the poly-oxygenated C12-C20 fragment \textit{2.2} and unsaturated triene \textit{2.3}, Scheme 2.1. A Stille coupling would be employed to form the necessary C11-C12 bond, while a Yamaguchi macrolactonization would complete the synthesis.

![Scheme 2.1 Nicolaou’s Retrosynthetic Analysis](image)

Synthesis of triene \textit{2.3} began with Brown crotylation of known aldehyde \textit{2.4}\textsuperscript{70} producing the desired \textit{syn}-stereochemistry in 82\% yield, Scheme 2.2.\textsuperscript{71} TBS-protection followed by oxidative cleavage via ozone prepared aldehyde \textit{2.5} for Wittig olefination. A reduction-oxidation strategy coupled with a Horner-Wadsworth-Emmons (HWE) reaction installed the second level of unsaturation in excellent overall yield.\textsuperscript{72} The resulting ester was again reduced and oxidized setting up the crucial second HWE
reaction to install the last level of unsaturation. In an attempt to avoid harsh basic conditions necessary for converting methyl and ethyl esters to the corresponding acid, Nicolaou proposed using a TMS-masked ester which is easily converted to the acid via a fluoride source such as TBAF. Conversion of the alkyne to vinyl stannane 2.3 was carried out under tributyltin hydride and Pd(II) catalyst yielding a 4:1 mixture of regioisomers. Much to the delight of Nicolaou, the desired β-(E) vinylstannane 2.3 could be chromatographically separated in 69% yield. Removal of the C9-TBS ether was crucial in achieving high yields of the preferred vinyl stannane. This subtle observation foreshadowed the necessity to have the C9-hydroxyl deprotected when attempting to form the C11-C12 bond.

Scheme 2.2
Nicolaou began the synthesis of vinyl iodide 2.2 with PMB-protection of commercially available (S)-glycidol 2.8 under basic conditions, Scheme 2.3. Selective opening of the epoxide with allenylmagnesium bromide yielded terminal alkyne 2.9 and set the desired stereochemistry at C16. The newly revealed secondary alcohol was then protected as the TBS-ether allowing for methylation of the terminal alkyne and subsequent deprotection-oxidation of the PMB-ether to aldehyde 2.10 in 89% yield for the 3 steps. Brown allylation of aldehyde 2.10 produced the necessary syn-stereochemistry between C16-C17 in 85% yield. Upon conversion of the secondary alcohol to the methyl-ether, Nicolaou successfully installed the desired C19-hydroxyl through an asymmetric dihydroxylation using Sharpless’s AD-mix α. A 6:1 diasteromeric ratio was formed in favor of the desired isomer. Difficulty in separating the diastereomers led to selective protection of the primary alcohol with Bu₂SnO and BnBr. TBS-ether protection of the remaining alcohol preceded hydrozirconation of the disubstituted alkyne yielding the desired regioisomer 2.2 in 65% overall yield.
With the vinyl iodide 2.2 and triene 2.3 fragments in hand, Nicolaou successfully performed a Stille coupling utilizing Pd(II) catalyst Pd(CH₃CN)₂Cl₂ in DMF to afford 60% of the desired product over a 48 hour period, Scheme 2.4. Global deprotection with TBAF and Yamaguchi macrolactonization led to the formation of apoptolidin’s macrolactone 2.1 in 48% yield for the 2 steps.
An examination of Nicolaou’s work provides several clues in preparing an efficient strategy for the synthesis of apoptolidinone and 20-deoxyapoptolidinone. First, one does not necessarily need to have the C16-hydroxyl protected upon macrolactonization, since based upon Nicolaou’s work, Scheme 2.4, the 20-membered macrolide appears to be thermodynamically favored over the smaller 16-membered macrolide. Second, a Stille coupling of C11-C12 is a feasible disconnection for late stage coupling of the fragments.

Koert and coworkers$^{69a}$ published a fragment synthesis of apoptolidin about the same time Nicolaou had done the same. Ironically, Koert’s work focused on the “southern-half” of apoptolidin yielding in conjunction with Nicololau’s work on apoptolidin’s macrolactone a complete picture on how one could go about synthesizing this structurally and biologically relevant natural product. Koert’s synthesis of fragment C18-C28 is quite remarkable, because eight stereocenters are installed in only 10 steps starting from an achiral β-ketoester.

Koert’s synthesis began with a stereospecific reduction of β-ketoester 2.12 leading to secondary alcohol 2.13 in 86% yield with excellent enantiomeric excess, Scheme 2.5.$^{79}$ Protection of 2.13 as the TBS-ether allows for successful DIBAL-H reduction of the methyl ester to aldehyde 2.14 in 86% yield for the two steps. A stannous triflate mediated aldol reaction$^{80}$ with β-keto imide dipropionyl auxiliary$^{81}$ produced the desired syn-stereochemistry 2.16 in 97% yield with a 96:4 diastereomeric ratio. Stereoselective reduction of hydroxyketone 2.16 with Me₄NBH(OAc)$_3$ yielded the necessary 1,3-anti diol in high selectivity (>95:5).$^{82}$ Conversion of the chiral auxiliary to the corresponding Weinreb amide was preformed under standard conditions synthesizing
amide 2.17 in 81% yield. Upon removal of the auxiliary, diol 2.17 was protected as the bisTMS-ether. Vinyllithium addition of the lithiated moiety of E-1-bromopropene yielded ketone 2.18 in 75% yield for the two steps. With the successful synthesis of enone 2.18, Koert and coworkers turned their attention to installation of the C19-C20 diol.

Koert envisioned introducing the stereochemistry of the C19-C20 diol through a Sharpless dihydroxylation via the commercially available AD-mix. Due to the electron deficient nature of the alkene targeted for dihydroxylation, Koert proposed doping the reaction with additional osmium. Upon utilizing the AD-mix α with the additional osmium α,β-unsaturated ketone 2.18 was successfully converted to the desired diol 2.19 in 98% yield but a disappointing 3:1 diastereomeric ratio, Scheme 2.6. In an effort to
improve the selectivity of the dihydroxylation, alkene 2.18 was cyclized under acid conditions to pyran 2.20, and then subjected to dihydroxylation. Diol 2.21 was produced in good yields, but to their disappointment, in poor diastereoselectivity. In both cases the diastereomeric mixture could be chromatographically separated and taken on to the next step. 1,2-acetonide protection of triol 2.21 yielded crystalline product 2.22, which X-ray crystallography allowed unambiguous assignment of the stereochemistry in the product.

Scheme 2.6

Koert’s initial paper, much like Nicolaou’s, provides clues to the pitfalls in synthesizing apoptolidin. Most importantly, a dihydroxylation at C19-C20 would need to
be asymmetric in nature requiring an additional chiral source. The α,β unsaturated alkene proved difficult to activate with electropositive osmium catalysts, so additional osmium was necessary. Koert’s elegant use of the Ruthenium-BINAP reduction and β-keto imide diproponyl auxiliary provided a rapid and efficient strategy for installation of several chiral elements found in the fragment and its eventual complete synthesis.

Along the same lines of Koert, Sulkowski’s group⁶⁹b began their quest for the total synthesis of apoptolidin examining the synthesis of the “southern-half” of this complex polyketide. But unlike Koert, Sulikowski utilized a stereoselective Mukaiyama aldol condensation to install the syn-stereochemistry found at C19-C20 bypassing the challenges associated with dihydroxylating an electron deficient alkene, Scheme 2.7.

Synthesis of aldehyde 2.24 began with readily available tris-trimethylsilyl ether 2.26 derived from L-malic acid, Scheme 2.8.⁸⁵ In situ removal of the TMS-ethers and subsequent formation of the preferred 6-membered acetal ring developed by Noyori⁸⁶
preceded protection of the primary alcohol with benzyl bromide under basic conditions producing acetal 2.27 in 90-95% yield. Chelation controlled opening of the acetal with Na(CN)BH₃ in TFA yielded the desired unprotected secondary alcohol 2.28 in a 5:1 mixture. Methyl ether formation under basic conditions yielded the necessary C17 functionality found in apoptolidin. Oxidative removal of the p-methoxybenzyl protecting group is followed by Swern oxidation to aldehyde 2.24 in 60% yield for the three steps.

Scheme 2.8

Sulikowski’s effort towards desired ketone 2.25 would require the formation of several hydroxyl and alkyl stereocenters for which multiple oxazolidinonethione mediated aldol condensations were envisioned utilizing Crimmin’s TiCl₄ / (-)-sparteine protocol. The strategy commences with the synthesis of acetonide 2.29 from L-ascorbic acid in six scaleable steps. With sizeable quantities of acetonide 2.29 in hand a number of protection/deprotection and reduction-oxidation steps were performed yielding aldehyde 2.30 in 9 steps from acetonide 2.29, Scheme 2.9. Aldehyde 2.30 is readily reacted with acyloxazolidinonethione auxiliary 2.31 under Lewis acidic conditions forming the desired syn-stereochemistry at C24-C25 and anti-stereochemistry between
C24-C25 and C27. The newly formed secondary alcohol was protected as the TBS-ether followed by quick reductive removal of the auxiliary with sodium borohydride in ethanol. The resulting alcohol was successfully oxidized to aldehyde 2.33 in 69-80% yield for the three steps. A second aldol condensation was performed utilizing the same auxiliary as the first aldol, but instead produced the non-Evans product because of an increase in the number of equivalents of TiCl₄ and (-)-sparteine base. With the stereochemistry set for C22-C27, Sulikowski’s group turned their attention to removal of the auxiliary and installation of the desired enol silane 2.36 necessary to couple to aldehyde 2.24.

Removal of the auxiliary through a transamidation with Weinreb’s salt was quickly followed by TES-ether formation yielding amide 2.35 in 82% yield for the two steps, Scheme 2.10. The recently formed amide is subsequently attacked by lithiated (methyloxymethoxy)methyl generated from (methyloxymethoxy)methyltributylstannane.
yielding the desired ketone.\textsuperscript{91} Enol silane formation with Masamune’s base produced the necessary (Z)-enol silane \textbf{2.36} in 85% yield for the two steps.\textsuperscript{92} Under Lewis acidic conditions enol silane \textbf{2.36} was readily reacted with aldehyde \textbf{2.24} yielding ketone \textbf{2.23} in good overall yields and selectivity. Reduction of ketone \textbf{2.23} and subsequent acetonide formation permitted determination of the newly formed stereocenters through Rychnovský’s acetonide method.\textsuperscript{93}

On first examination, the routes to aldehyde \textbf{2.24} and ketone \textbf{2.25} were very linear and lengthy. Aldehyde \textbf{2.24} required 8 steps to produce a four carbon fragment while ketone \textbf{2.25} required 15 steps before the first aldol reaction. Though lengthy, one distinct advantage of Sulikowski’s strategy was the utilization of low cost chiral starting materials such as L-malic acid. This approach yields large amounts of early intermediates in a cost
effective manner. Sulkowski’s use of the oxazolidinonethione chemistry was also noted and later utilized in a similar fashion to construct the “southern-half” of 20-deoxyapoptolidinone.

2.3 Synthesis of the C19-C20 Syn -diol Through an Asymmetric Dihydroxylation

Our initial target for the project was the aglycone of apoptolidin or apoptolidinone, since no total syntheses of apoptolidin had been published prior to the start of this project. With this in mind our synthetic strategy began with splitting this large natural product into three smaller fragments of similar complexity. Such a convergent approach would reduce the linearity of the reaction sequence thus improving the overall yield and chances for success.

Key disconnections at C11-C12, C22-C23, and the macrolide ester moiety yields fragments A, B, and C each possessing interesting structural elements, Figure 2.1. Our strategy hinged on two novel approaches: the triene portion of fragment A would be installed via repetitive thionyl chloride rearrangements and fragments B and C would be coupled through an anti-Felkin aldol condensation. The bulk of this chapter will focus on the successful construction of fragment B synthons for apoptolidinone and analogue 20-deoxyapoptolidonone.
At first glance, fragment B appears to have C$_2$-symmetry about the C18-carbon. With this in mind, a bi-directional approach was proposed. The stereochemistry at C17 could be inexpensively purchased as L-malic acid, Scheme 2.11. The C19-C20 diol would be installed via an asymmetric dihydroxylation and the stereochemistry at C16 would be constructed via a Keck chelation controlled allylation.
Initial work on fragment B focused on completion of the right-side of the molecule for two reasons with the first being literature precedent. Koert and coworkers had already shown the stereochemistry at C19-C20 could be installed through an asymmetric dihydroxylation.\textsuperscript{69a} Second by completing the right-hand side of the fragment, studies into the anti-Felkin aldol proposed to couple fragments B and C could be started.

The synthesis of ketone 2.38 began with borane reduction of L-malic acid yielding a viscous crude triol, which was subsequently protected as the 1,2-acetonide 2.39, Scheme 2.12.\textsuperscript{94} Benzyl protection of the primary alcohol followed by unmasking of the acetonide under acidic hydrolysis proceeded in good overall yield diol 2.40. Selective primary alcohol protection with TBDPSCI leads to methyl ether 2.41 formation with silver(I) oxide and methyl iodide.\textsuperscript{95} Removal of the primary benzyl group proved more difficult than initially thought, repeatedly yielding less than 100% conversion. Interestingly if the methyl ether at C17 was instead a TBS-ether, debenzylation of 2.41
proceeded smoothly to the unprotected alcohol in 100% conversion. Unfortunately, such a change would warrant subsequent conversion to the preferred methyl ether later in the synthesis adding additional unnecessary steps. Swern oxidation of the primary alcohol was immediately followed by Wittig olefination in a one-pot sequence producing ethyl ester 2.42 in 82% over two steps. Unfortunately, installation of the C19-C20 syn-diol with Sharpless’s AD-mix α reagent yielded low yields even with prolonged reaction times of 48-72 hours.

Scheme 2.12

The electronic consequences of attempting to dihydroxylate a α,β unsaturated esters were understood, but the complete lack of reactivity was puzzling. Some reactivity was expected albeit at a decreased rate. Further examination of Koert’s first apoptolidin paper, revealed the dihydroxylation was performed without the C17-methoxy group as found in 2.42. Because of this difference, steric elements brought forth by this methoxy group had to be considered. Interestingly almost a year later, Koert and
coworkers published the total synthesis of apoptolidin utilizing a similar dihydroxylation which took 9 days at 0°C.\textsuperscript{67}

Assuming the methoxy at C17 is playing a negative role in the dihydroxylation of C19-C20, a new strategy of tying the hydroxyl at C17 to the C18-hydroxyl was proposed through an 1,2-acetonide. Starting with acetonide 2.39, readily synthesized from L-malic acid in two steps, a one-pot Swern oxidation-Wittig olefination sequence produces α,β unsaturated ester 2.44 in 80% yield, Scheme 2.13. Asymmetric dihydroxylation under Sharpless AD-mix α conditions synthesized the preferred diol 2.45 in 77% (11:1 dr) yield.\textsuperscript{97} Surprisingly, the reaction was complete in less than 24 hours without the use of additional OsO\textsubscript{4}. The C19-C20 diol was subsequently protected as bis-acetonide 2.46 with 2,2-DMP and CSA. Selective removal of the terminal acetonide with acidic THF was followed with TBDPSCl protection of the primary alcohol producing alcohol 2.48 in 81% yield over two steps. Much to our disappointment, methyl ether formation with silver(I) oxide and methyl iodide led to decomposition rather than the desired product 2.49. Attempts with hindered amine bases such as 2,6-di-\textit{tert}-butylpyridine and methyl triflate yielded no reaction even at elevated temperatures. Non-hindered bases were avoided because of possible epimerization at C20. Unfortunately, the linearity of this sequence was increasing and methyl ether formation at C17 upon acetonide removal and primary protections proved to be difficult. A new strategy to the C19-C20 diol was necessary.
Glycolate auxiliaries utilizing Evans’ aldol protocol proved to be a suitable alternative to the asymmetric dihydroxylation. After successfully acylating (R)-oxazolidione with acetylbenzoxy chloride, auxiliary 2.51 was enolized with dibutylboron triflate and triethylamine. Aldehyde 2.50 was subsequently added to the reaction producing alcohol 2.52 in 40% yield as a single diastereomer, Scheme 2.14. Protection of the secondary alcohol as TBS-ether 2.54 aided with further purification. Selective removal of the primary TBDPS-ether proved difficult as complete deprotection of the molecule always resulted. A reexamination of the protecting group strategy was in order, but before that could come to fruition Wender and Sulikowski published several papers on the stability of apoptolidin during biological testing.
In their attempts to isolate apoptolidin from crude cell extracts, the Wender group noticed the presence of a separate isomer of apoptolidin which they named isoapoptolidin, Figure 2.2. Further characterization found isoapoptolidin to be the 21-membered acyl-migration product of apoptolidin. Acyl-migration studies on apoptolidin yielded no isoapoptolidin at low temperature (-20°C) storage conditions, while rapid isomerization was observed when the sample was warmed to ambient temperature. Further analysis of this isomerization yields an equilibrium of 1.4:1 for apoptolidin to isoapoptolidin. This proved increasingly important when Wender found isoapoptolidin to be significantly less active than apoptolidin calling into question previous assay results.
Curious to see if eliminating the acyl migration would prevent the formation of isoapoptolidin, Wender converted the C20-hydroxyl to a methyl ether resulting in a significant loss of activity.\textsuperscript{99c} Believing the protection of the hydroxyl group may have adversely affected hydrogen bonding and conformation of the macrolide, we put forth an effort to synthesize 20-deoxyapoptolidinone, Figure 2.3.

\textbf{Figure 2.2}

\textbf{Figure 2.3}
Even with apoptolidin available in sizeable amounts (109 mg/L) from fermentation, degradative synthesis to remove the C20-hydroxyl group would have been extremely difficult. A modification to the synthesis of fragment B was proposed to synthesize a common precursor for apoptolidinone and 20-deoxyapoptolidinone in order to quickly access both molecules.

2.4 A Common Precursor for the Synthesis of Apoptolidinone and 20-deoxyapoptolidinone

Since the difference between apoptolidinone and 20-deoxyapoptolidinone is a C20-hydroxyl group, a common precursor was sought to enable quick synthesis of both targets. A strategy starting with (L)-Malic acid was preferred, because of its availability and previous experimental experience (See Scheme 2.12). A retrosynthetic analysis of fragment B, without the C20-hydroxyl, divided the molecule into three components, Scheme 2.15. The central C17-hydroxyl group would be garnered from (L)-malic acid while synthesis of the syn C16-C17 diol would be facilitated by a Keck chelation-controlled allylation and allyl tributylstannane. The C19-hydroxyl would be installed through a Mukaiyama aldol utilizing ketene acetal resulting in the desired 1,3-anti stereochemistry based upon literature precedent from Evans.
A diesterification of (L)-malic acid under acidic conditions and THF reflux for 48 hours produced the desired diethyl malate 2.60 in good yields, Scheme 2.16. Use of a microwave synthesizer shortened the reaction time to five minutes while maintaining excellent yields. The only drawback was scalability; as the microwave’s reaction vessel was limited to one gram reactions. Controlled reduction of the ethyl ester α to the C17-hydroxyl with borane dimethylsulfide complex and catalytic sodium borohydride resulted in the preferred primary alcohol which was subsequently protected as TBDPS-ether 2.61 in 81% yield over two steps. Methyl ether formation with Merwein’s reagent and Proton Sponge was successful in 85% yield. Optimum results were obtained when the Proton Sponge was recrystallized and Merwein’s reagent was of good quality. The ethyl ester is subsequently reduced directly to aldehyde 2.50 with DIBAL-H in 76% yield.
With aldehyde 2.50 in hand, installation of the C19-stereochemistry through a Lewis acid promoted Mukaiyama aldol condensation became the next directive. Utilizing ketene acetal 2.59 derived from methyl acetate\textsuperscript{105} and Lewis acids BF$_3$•OEt$_2$ and TiCl$_4$, synthesis of methyl ester 2.63 was successful albeit in unimpressive selectivity’s of 4:1 and 2:1 for TiCl$_4$ and BF$_3$•OEt$_2$ respectively, Scheme 2.17.\textsuperscript{101} Changing the ketene acetal to the TBS-trapped version or using the TMS-enol derived from acetone proved insufficient in improving the yields or selectivities. While a literature search commenced, synthesis of the left side of fragment B was investigated.
With the allylation occurring before the Mukaiyama aldol, a slightly different approach was necessary in preparing (L)-malic acid to yield the desired aldehyde at C16 instead of C19 as demonstrated above. Selective esterification of the α-acid to the hydroxyl was achieved with mixed anhydride formation via trifluoroacetic anhydride followed by methanol workup, Scheme 2.18. Reduction of crystalline acid 2.64 at the acid moiety with borane dimethyl sulfide complex prepared the substrate for subsequent TBS-protection yielding 60% of methyl ester 2.65 over two steps. Merwein’s reagent with Proton Sponge was used to successfully prepare methyl ether 2.66 in high yields. Strong basic conditions such as sodium hydride and dimethyl sulfate produce lower yields presumably from TBS-migration. Reduction of the methyl ester with 1.5 equivalents of DIBAL-H proceeded smoothly to aldehyde 2.67 in lieu of allylation via Keck’s Lewis acid protocol.

Scheme 2.18
Through a series of published Lewis acid evaluations, Keck had found magnesium bromide diethyl etherate to provide the highest syn-bias in obtaining 1,2-syn diols upon chelation controlled allylation.\textsuperscript{107} Utilizing this precedent, aldehyde 2.67 was readily reacted with magnesium bromide diethyl etherate and allyl tributylstannane at low temperatures, Scheme 2.19. Dilution was found to play a critical role in this reaction as proper dilution of the allyl tributylstannane led to increased selectivities. Homo-allylic alcohol 2.68 was produced in 98\% yield as a single diastereomer based upon $^1\text{H}$ NMR analysis. The reaction is spot-to-spot and incredibly clean even when examining the crude $^1\text{H}$ NMR. The resulting secondary alcohol was protected as the desired TBS-ether under standard conditions thus completing the left-side of the fragment. Upon this development, my attention turned to completion of the right-hand side of fragment B.

![Scheme 2.19](image)

Selective removal of primary TBS-ether 2.69 was achieved with acidic methanol in 15 minutes at room temperature, Scheme 2.20. The reaction was then quenched with a small amount of triethylamine followed by solvent removal under reduced pressure. The
crude oil was diluted in methylene chloride and cooled to 0°C prior to addition of oxidant PCC. The desired aldehyde **2.71** was formed in 78% yield over the two steps.

During the synthesis of the left-hand side of the molecule, a literature search uncovered an Evans paper\(^{108}\) which revealed changing the solvent from methylene chloride to toluene dramatically improved the selectivities of their Mukaiyama aldol reactions. In addition to the toluene switch, \textit{in situ} generation of TiCl\(_2\)(OiPr)\(_2\) was also shown to improve selectivities.

With Evans’s work as a backdrop, a solution of TiCl\(_4\) and Ti(OiPr)\(_4\) in toluene was prepared before dropwise addition of aldehyde **2.71** in toluene, Scheme 2.20. Upon reacting with the Lewis acid combination for 15 minutes, ketene acetal **2.59** was added and the reaction monitored by TLC. Once the reaction was quenched and purified, ester **2.72** was found in 76% yield as a single diastereomer by \(^1\)H NMR analysis.

An effort to validate the newly generated stereocenter at C19 began with silyl ether formation with hexamethyldisilazane in pyridine. The crude product was quickly reduced to aldehyde **2.73** in 50% over two steps, Scheme 2.21. The protection worked
well, but the Rf of the protected ester and the newly generated aldehyde proved to be very similar making it difficult to determine if the reaction was completed. This resulted in a substantial amount of recovered starting material leading to a reduced overall yield. Aldehyde 2.73 was then reacted with oxzolidinithione 2.31 derived from (L)-phenylalanine under Crimmin’s aldol conditions.\textsuperscript{89} Again, it was discovered the yield was very poor though the selectivity was excellent as expected. The loss in yield can be attributed to the labiality of the TMS-ether which was not robust enough to handle the strong Lewis acidic conditions. Nevertheless, ample material was available to proceed with the final deprotection / protection step. Alcohol 2.74 was dissolved in a small amount of 2,2-dimethoxypropane and cooled to 0°C. A catalytic amount of CSA was added leading to rapid deprotection of the TMS-ether and acetonide formation. The freshly generated acetonide was analyzed via \textsuperscript{13}C NMR yielding the acetonide’s two methyl groups at 24.5ppm and the quaternary carbon at 100.4 ppm. These shifts are indicative of a 1,3-\textit{anti} relationship based upon Rychnovshy’s 1,3-diol work\textsuperscript{93} and confirming the C19 hydroxyl is also positioned in an 1,3-\textit{anti} relationship with C17 as desired.
Aldol adduct 2.72 was converted to the Weinreb amide 2.76 under standard conditions leading to secondary alcohol protection with PMB-imidate and triflic acid, Scheme 2.22. Amide conversion to preferred ketone 2.57 proceeded in disappointingly moderate to low yields. The reaction always seemed to require a large excess of ethyl Grignard before product was observed. This led to multiple Grignard additions to amide 2.77 resulting in a mixture of ethyl ketone 2.57 and tertiary alcohol. With the ethyl ketone successfully synthesized, our attention turned to the aldol condensation of fragments B and C.

Scheme 2.22
In a demonstration of the flexibility of the synthesis route, aldehyde 2.71 was reacted with acylated oxazolidinone 2.51 to form C19-C20 syn-diol 2.78 present in the parent compound apoptolidinone, Scheme 2.23. The reaction proceeded in good yields as a single diastereomer. Auxiliary displacement with trimethyl aluminum and Weinreb’s salt yielded the desired amide in moderate yields of 44%. PMB-protection followed by ethyl Grignard addition should yield ethyl ketone 2.79.

![Scheme 2.23](image)

With successful completion of ethyl ketone 2.57, a two pronged approach to the anti-Felkin coupling of fragments A and B was developed and initiated by a fellow colleague on the project Dr. William “Bill” Paquette, Scheme 2.24. The first strategy involved lithium enolate formation with Masamune’s base or LiHMDS. Masamune’s base was examined first due to literature precedent on similar substrates, yet repeated attempts yielded nothing more than starting material 2.57 and 2.80, Table 2.1. With Masamune’s base yielding no reaction, Bill proceeded to investigate the reaction with
commercially and in situ prepared LiHMDS solutions. Again, to our disappointment no reaction was detected. Examination of reaction procedures and our technique led us to believe water contamination was quenching the reaction before it could take place. An effort was put forth to ensure dryness among the utilized reagents and solvent, but yet again only starting material was the result.

The second approach to the coupling of fragments B and C involved Lewis acid catalyzation. Evans and others\textsuperscript{113} had demonstrated boron derived Lewis acids to be particularly effective in anti-Felkin aldol condensations. With this knowledge, a commercial sample of PhBCl\textsubscript{2} was obtained because of its effectiveness in the total synthesis of bafilomycin A\textsubscript{1}.\textsuperscript{113c} Following Evans’s protocol ethyl ketone 2.57 was subjected to PhBCl\textsubscript{2} and DIPEA at low temperatures prior to dropwise addition of aldehyde 2.77, Scheme 2.24. A TLC of the reaction displayed a myriad of spots causing the reaction to be quenched and worked up. Upon workup the crude \textsuperscript{1}H NMR was investigated and found to be a complex mixture.

Thoroughly frustrated at this point, Bill and I proceeded to use the strong Lewis acid TiCl\textsubscript{4} in an attempt to yield some of aldol adduct 2.81 and prove the coupling viable.\textsuperscript{114} The reaction proceeded forward from the lack of starting material on TLC, so it was quenched and the crude \textsuperscript{1}H NMR analyzed. Several peaks from the aldehyde and ethyl ketone were identified, but taken in conjunction with the TLC it was quite evident several products had been formed. Column chromatography of the crude material yielded no further clues as isolation of the individual spots became very difficult due to the scale of the reaction and number of individual compounds present.
TABLE 2.1

ANTI-FELKIN ALDOL CONDENSATION

![Chemical structure]

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Aldehyde</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 eq.</td>
<td>2 eq.</td>
<td>(Me₂PhSi)₂NLi (1.5 eq), -78°C</td>
<td>SM</td>
</tr>
<tr>
<td>1 eq.</td>
<td>2 eq.</td>
<td>LiHMDS, (1.3 eq), -78°C</td>
<td>SM</td>
</tr>
<tr>
<td>1 eq.</td>
<td>4 eq.</td>
<td>PhBCl₂ (1.2 eq.), iPr₂NEt, -78°C</td>
<td>Complex Mixture</td>
</tr>
<tr>
<td>1 eq.</td>
<td>1.1 eq.</td>
<td>TiCl₄ (1.2 eq.), iPr₂NEt, -78°C</td>
<td>Product?</td>
</tr>
</tbody>
</table>

Since developments in the anti-Felkin aldol coupling of fragments B and C were proceeding at a less than desirable pace, a decision was made to fall back to our alternative approach and install the C22-C23 stereochemistry through an Evans aldol type reaction similar to what Sulikowski₆⁹ and Evans¹¹⁵ had used in their syntheses. Upon completion of the aldol, the auxiliary would have to be converted to the necessary methyl ketone for proper coupling to a truncated version of fragment B. One advantage to this strategy was the newly formed methyl ketone should behave very similar to the Mukaiyama aldol demonstrated in construction of ethyl ketone 2.57. With truncation of the right-side of fragment B, elongation of the left-side became more important for immediate coupling to fragment A upon successful aldol coupling to fragment C.

Hydroboration of allyl fragment 2.69 with borane-THF complex yielded the desired primary alcohol in 81% yield, Scheme 2.25. The Markonikov product was also
produced in 10-12% yield, but was easily separated through column chromatography. Oxidation of alcohol 2.82 to aldehyde 2.83 proceeded smoothly even on multiple gram scale with TPAP/NMO in 92% yield. Conversion of aldehyde 2.83 with Colvin’s reagent\textsuperscript{116} produced a wide range of yields from 30-90%. The inconsistencies in the reaction’s yield led to further optimization examining the consequences of the starting material’s purity and length of the reaction. Ultimately, the purity of the starting materials was important, but the length of the reaction was the key too higher, more consistent yields. Originally, the reaction was allowed one hour at -78°C then warmed to 0°C for 90 minutes upon aldehyde addition to the deprotonated TMS-diazomethane. Eventually, it was found extending the time period at 0°C to two hours and allowing the reaction to slowly warm to room temperature over the last 30 minutes significantly cleans up the reaction and leads to higher yields. The newly formed crude alkyne was deprotonated with nBuLi and reacted with MeI to synthesize di-substitued alkyne 2.84 in 74% yield for the one-pot synthesis.

\begin{center}
\begin{tikzpicture}
\node (a) at (-3,0) {\text{OMe}}; \node (b) at (0,0) {\text{OTBS}}; \node (c) at (3,0) {\text{HO}}; \node (d) at (6,0) {\text{OMe}}; \node (e) at (9,0) {\text{OTBS}}; \node (f) at (-3,-3) {\text{O}}; \node (g) at (0,-3) {\text{OTBS}}; \node (h) at (3,-3) {\text{OTBS}}; \node (i) at (6,-3) {\text{OTBS}}; \node (j) at (-3,-6) {\text{OME}}; \node (k) at (0,-6) {\text{OTBS}}; \node (l) at (3,-6) {\text{OTBS}}; \node (m) at (6,-6) {\text{OTBS}}; \node (n) at (9,-6) {\text{OTBS}}; \node (o) at (0,-9) {\text{MeI}}; \node (p) at (3,-9) {\text{2.84}}; \node (q) at (6,-9) {\text{2.83}}; \node (r) at (9,-9) {\text{2.82}}; \node (s) at (12,0) {\text{TPAP, NMO, 92%}}; \node (t) at (12,-3) {1. n-BuLi, TMS-diazomethane, 81%}; \node (u) at (12,-6) {2. n-BuLi, MeI, 74%};
\draw[->] (a) -- (b) node[midway, above] {\text{BH}_3\text{-THF, 81%}}; \draw[->] (b) -- (c) node[midway, above] {TPAP, NMO, 92%}; \draw[->] (c) -- (d) node[midway, above] {1. n-BuLi, TMS-diazomethane, 2. n-BuLi, MeI, 74%}; \draw[->] (d) -- (e) node[midway, above] {2.84}; \draw[->] (e) -- (f) node[midway, above] {2.83}; \draw[->] (f) -- (g) node[midway, above] {2.82}; \draw[->] (g) -- (h) node[midway, above] {2.69}; \draw[->] (h) -- (i) node[midway, above] {2.84}; \draw[->] (i) -- (j) node[midway, above] {2.83}; \draw[->] (j) -- (k) node[midway, above] {2.82}; \draw[->] (k) -- (l) node[midway, above] {2.69}; \draw[->] (l) -- (m) node[midway, above] {2.84}; \draw[->] (m) -- (n) node[midway, above] {2.83}; \draw[->] (n) -- (o) node[midway, above] {2.82}; \draw[->] (o) -- (p) node[midway, above] {2.69}; \draw[->] (p) -- (q) node[midway, above] {2.83}; \draw[->] (q) -- (r) node[midway, above] {2.82}; \draw[->] (r) -- (s) node[midway, above] {2.84}; \draw[->] (s) -- (t) node[midway, above] {2.83}; \draw[->] (t) -- (u) node[midway, above] {2.82}; \draw[->] (u) -- (v) node[midway, above] {2.84}; \draw[->] (v) -- (w) node[midway, above] {2.83}; \draw[->] (w) -- (x) node[midway, above] {2.82}; \draw[->] (x) -- (y) node[midway, above] {2.84}; \draw[->] (y) -- (z) node[midway, above] {2.83}; \draw[->] (z) -- (a) node[midway, above] {2.82};
\end{tikzpicture}
\end{center}

\textbf{Scheme 2.25}
Final preparation of the fragment for coupling to fragment C involved selective removal of the primary TBS-ether 2.84 with catalytic CSA in methanol, Scheme 2.26. Oxidation of the primary alcohol produced aldehyde 2.85 in 75% yield for the two steps. Upon completion of aldehyde 2.85 in 13 steps, our attention turned to successful coupling of fragments B and C for the eventual completion of 20-deoxyapoptolidinone.

\[ \text{Scheme 2.26} \]

2.5 Conclusion

The preceding chapter has demonstrated the evolution of fragment “B” which has been influenced by several factors including synthetic difficulties through poor reactivity (asymmetric dihydroxylation) and selectivity (initial attempts at Mukaiyama aldol), to published reports (Wender and Sulikowski’s report of isoapoptolidin), and finally our inability to proceed further on the anti-Felkin aldol condensation. These developments have shaped the fragment’s structure and synthetic pathway yielding aldehyde 2.85 in 13 robust steps. With viable routes to all three fragments, the next step in the journey to 20-deoxyapoptolidinone was to successfully fit all of the puzzle pieces (fragments A,B,C) together.
CHAPTER THREE

WORK TOWARDS THE TOTAL SYNTHESIS OF 20-DEOXYAPOPTOLIDINONE: THROUGH STEREOSELECTIVE ALDOL AND STILLE COUPLING REACTIONS

3.1 Purpose

This chapter will center on the three crucial coupling reactions, stereoselective aldol, Stille coupling and marcolactonization via Yamaguchi protocol, necessary to complete the total synthesis of 20-deoxyapoptolidinone. It will be shown; investigations into the C19-C20 aldol coupling have come full circle eventually settling on a Mukaiyama type coupling similar to the one demonstrated in Chapter Two. An alternative to Nicolaou’s Stille coupling of C11-C12 will be discussed illustrating the difficulties in coupling such fragments. Finally, an end game strategy involving a Yamaguchi macrolactonization and global deprotection for the synthesis of 20-deoxyapoptolidinone will be discussed to assess current progress and future work ahead.

3.2 Coupling of Fragments B and C via a Methyl Ketone Aldol Condensation

Methyl ketone 3.4 (Fragment C) was successfully synthesized by an efficient oxazolidinonethione controlled aldol condensation utilizing Crimmin’s TiCl₄ conditions, Scheme 3.1.⁶⁹b Aldehyde 3.1 was constructed using the procedures optimized in Dr. Bill
Paquette’s thesis.\textsuperscript{117} Oxazolidinonethione 3.2 was enolized with TiCl\(_4\) and (-)-sparteine prior to aldehyde addition leading to the synthesis of alcohol 3.3 in 92\% yield as a single diastereomer. Transamidation with Weinreb’s salt and AlMe\(_3\) under standard conditions were quickly followed by secondary alcohol protection with TESOTf. Methyl ketone 3.4 was completed by MeLi addition thus converting the Weinreb amide to the preferred methyl ketone is 76\% yield over the last three steps.

![Scheme 3.1](image)

Scheme 3.1

With methyl ketone 3.4 and aldehyde 3.12 (fragment B see Chapter Two) synthesized, my efforts focused on their successful coupling to reveal the desired C19-hydroxyl. A 1,3-\textit{anti} relationship between C19 and C17 was preferred as it represented the structural composition of the parent molecule apoptolidin. To this end, a literature search presented four working models from Reetz\textsuperscript{118} 3.7, Evans\textsuperscript{101,119} 3.8, Keck\textsuperscript{120} and Reetz\textsuperscript{118} 3.9, and Roush\textsuperscript{121} 3.10 (Figure 3.1) for the synthesis of alcohol 3.13, Scheme 3.2.
The Reetz 3.7 and Evans 3.8 transition states signify polar models that demonstrate the 1,3-anti stereoisduction through electrostatic repulsion and the monodentate nature of the metal. Evans proposed transition state 3.8 as an improvement over Reetz’s 3.7 transition state which is largely based upon Cram’s rules. Evans felt Reetz’s
transition state failed to take into account the torsional interactions along with the primary electrostatic consequences.\textsuperscript{101} Their experimental work led to a tweak of Reetz’s transition state minimizing both electrostatic and steric repulsions through a staggered rather than \textit{anti} configuration. A definite benefit to this strategy was the high propensity of the 1,3-\textit{anti} stereochemistry found upon isolation.

Keck and Roush proposed cyclic transition states \textbf{3.9} and \textbf{3.10} yielding rigid platforms for aldehyde \(\pi\)-facial selectivity resulting in high degrees of stereoselectivity. Keck and Reetz’s metal based chelation between the aldehyde and \(\beta\)-alkoxy group is largely affected by the metal’s ability to chelate two electronegative elements and the nature of the protecting group on the \(\beta\)-hydroxy group.\textsuperscript{118b-d, 120a} The protecting group can affect the selectivity of the reaction in two ways. First, formation of a strong six-membered chelate is necessary for rigidifying the transition state and yielding only one acceptable face of the aldehyde for attack. This process is dependent on metals with high affinities for oxygen and protecting groups that do not inactivate the \(\beta\)-alkoxy group such as silyl ethers. The second factor determining selectivity is the steric bulk of the \(\beta\)-alkoxy protecting group.\textsuperscript{120a} A bulky protecting group is necessary to force the (R)-group in Keck’s transition state \textbf{3.9} into a pseudo axial position effectively blocking one-side of the aldehyde. In the case of 20-deoxyapoptolidinone, the C17-methyl ether lacks steric bulk allowing the (R)-group to adopt a psuedoequitorial confirmation thus increasing the opportunity for the nucleophile to attack either side of the aldehyde. Keck documented a 32:1 selectivity with TiCl\(_4\) and a benzyl protecting group compared to 4:1 with TiCl\(_4\) and methyl-ether functionality. Though discouraged by these results, the 4:1 preference for the 1,3-\textit{anti} product was sufficient to warrant further investigations.
Roush’s metal enolate model 3.10 rounds out the group and much like Keck’s model, it is largely dependent on the metal’s ability to facilitate multiple coordination sites, yet differs in the role the enolate plays in the overall selectivity.\textsuperscript{121} It is for this reason, the aldehyde will approach the enolate from the least hindered side away from the (L)- or large group. Since the transition state is enolate centric, protecting groups on the \(\beta\)-alkoxy group are less important allowing a multitude of protecting group strategies not afforded by Keck’s chelation controlled addition. In reviewing these model systems, a decision was made to initially explore metal enolates derived from titanium, tin, and lithium as Keck’s chelation controlled aldehyde model would be less effective with the methyl ether at C17.

Still possessing some SnOTf\(_2\) from work on the \textit{anti}-Felkin aldol (Chapter Two, p. 102), ketone 3.11 was diluted in methylene chloride and cooled to -78°C, Scheme 3.3. It should be noted the MOM-ether at C25 was part of an orthogonal protecting group scheme, which was later dropped in favor of the TBS-ether for rapid global deprotection at the end of the synthesis. Excess DIPEA was added and the reaction stirred for one hour prior to addition of a solution of aldehyde 3.12 in methylene chloride. The reaction was continuously monitored by TLC for several hours. When no reaction was observed the dry ice acetone bath was removed and the reaction was allowed to warm to 0°C. The reaction was allowed to stir for several more hours leading to no observable reaction, Table 3.1. Believing the SnOTf\(_2\) may have been unreactive, the reaction was quenched and the starting material reisolated.

A second attempt with recently purchased TiCl\(_4\) was explored and quickly abandoned because of rapid decomposition observed through color change and TLC
analysis when it was added to ketone 3.11. A third attempt with \textit{in situ} generated LDA led to what appeared to be possible coupling as a new spot was visible on TLC, but its polarity revealed it to be less polar than the ketone. This led to the suspicion that the aldol may have commenced but was rapidly followed by elimination yielding the stable \(\alpha,\beta\)-unsaturated ketone. Support of this hypothesis is based on TLC observations that showed the Rf of the product spot was higher than that of the aldehyde and ketone. The desired secondary alcohol from this reaction would be predicted to have a Rf below the starting aldehyde and ketone.

**TABLE 3.1**

**METAL ENOLATE ALDOL REACTIONS**

![Scheme 3.3](image)

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Aldehyde</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2 eq.</td>
<td>1 eq.</td>
<td>SnOTf(_2) (2.6 eq), DIPEA (3.0 eq), -78°C</td>
<td>SM</td>
</tr>
<tr>
<td>1.2 eq.</td>
<td>1 eq.</td>
<td>TiCl(_4) (2.0 eq), DIPEA (3.0 eq), -78°C</td>
<td>Decomposition</td>
</tr>
<tr>
<td>1.1 eq.</td>
<td>1 eq.</td>
<td>LDA (1.2 eq), -78°C</td>
<td>Elimination</td>
</tr>
</tbody>
</table>

Following multiple failed attempts with metal enolates, a decision was made to step back and explore the possibility of a Mukaiyama aldol coupling similar to the one
used in the construction of the ethyl ketone version of fragment B (Chapter Two). The reaction had not been explored initially because of concerns for epimerization of the ketone when attempting to form the necessary enol silane. But with no observed epimerization from the use of LDA and past positive results with the Mukaiyama, a strategy using such a coupling appeared to be a viable alternative.

3.3 Generation of C19 Stereocenter via Mukaiyama Aldol Condensation

In an approach to prove the Mukaiyama viable and additionally conserve key starting materials, enol silane 3.15 was constructed from enolization of 3-methyl-2-butanoine 3.14 with LDA followed by subsequent trapping with TMSCl, Scheme 3.4. The resulting enol silane 3.15 was diluted in toluene and added to a solution of aldehyde 3.16 and toluene. The aldol was commenced with the dropwise addition of freshly prepared TiCl$_2$(OiPr)$_2$ leading to complete consumption of the aldehyde in approximately 30 minutes. Subsequently, the same reaction was run with BF$_3$•OEt$_2$ yielding similar reaction times. In both reactions, the crude $^1$H NMR looked spectacular thanks in large part to the completeness of the reaction and the ability to pump off any excess ketone or enol silane. Based upon the crude $^1$H NMR and the mass of the crude product, the yield was well above 90% with diastereomeric ratios of 5:1 and 6:1 for BF$_3$•OEt$_2$ and TiCl$_2$(OiPr)$_2$ respectively. Encouraged by the results, an effort to duplicate them was put forth on the desired system of aldehyde 3.12 and methyl ketone 3.4.
Scheme 3.4

The first step was the crucial production of enol silane 3.18 from ketone 3.4. Scheme 3.5. Initial attempts with freshly prepared LDA and TMSCl yielded no observable formation of enol silane 3.18.\(^\text{105}\) A conscious effort was made to keep the equivalents of base and TMSCl at a minimum in fear of degrading the ketone starting material. A literature search\(^\text{122}\) proved this approach was much too conservative and in reality demanded large excesses of base and TMSCl.

Scheme 3.5

The literature search led to Miyashita’s work on scytophycin C.\(^\text{122b}\) Further investigation into Miyashita’s total synthesis finds the methyl ketone aldol coupling was modeled after Paterson’s earlier work also on scytophycin C.\(^\text{122a}\) Following Paterson’s
precident, Miyashita was able to successfully trap the lithium enolate as the TMS-enol silane 3.20, Scheme 3.6. Contrary to our strategy, Miyashita and Paterson used nearly seven equivalents of LiHMDS and 17 equivalent of a 1:1 mixture of TMSCl and Et₃N. Half of the base and silyl trapping complex was added initially and after 30-45 minutes of reaction time to insure methyl ketone 3.19 was driven to product. Following successful synthesis of enol silane 3.20, Miyashita proceeded with a BF₃•OEt₂ mediated Mukaiyama aldol condensation synthesizing ester 3.22 in 82% yield. With no reference to possible epimerization of the α-stereocenter, an effort was quickly put forth to mimic this procedure on our own methyl ketone (fragment C).

![Scheme 3.6](image-url)
With a viable procedure in hand, multiple equivalents of base and TMS:TEA complex were synthesized. To insure dryness, the ketone was stored over molecular sieves prior to enol silane formation. Additions of the freshly prepared LiHMDS and TMS:TEA solution proceeded smoothly yielding a slightly yellow reaction solution upon completion. The reaction was then diluted with pentane and added to a mixture of additional pentane and pH 7.0 buffer. The crude enol silane 3.18 was quickly extracted to limit any quenching that may have occurred while in contact with the buffer solution. Surprisingly, the enol silane was quiet robust for being TMS-based even being observed on non-neutralized TLC plates. In most cases the crude material was not further purified, but rather used crude in the Mukaiyama aldol condensation between fragments B and C. Overall the reaction was remarkably consistent producing enol silane 3.18 in 65-75% crude yield.

![Scheme 3.7](image)

With a reproducible pathway to enol silane 3.18, our attention turned to successfully coupling fragments B and C through a Mukaiyama aldol condensation similar to what was described in Chapter Two. Since the combination of freshly prepared TiCl₂(OiPr)₂ and toluene had worked well in the past their use constituted the most logical starting point. Upon addition of the enol silane 3.18, a new spot became visible via TLC, Scheme 3.8. After stirring for one hour, the reaction was quenched as it did not
seem to be progressing towards completion. Column chromatography yielded recovered starting material (enol silane 3.18 and aldehyde 3.16), ketone 3.23, and a new purple colored spot on TLC via anisaldehyde stain. Further analysis revealed it contained many of the same $^1$H NMR characteristics as ketone 3.23, but did not contain the indicative methyl ketone singlet found in the $^1$H NMR of ketone 3.4. Integration of the TBS-ether portion of the $^1$H NMR suggested only one TBS-ether was still present in the molecule. The lack of a methyl ketone and second TBS-ether led to the hypothesis the enol silane had been quenched and reverted back to its ketone form. Once it was ketone 3.4, the Lewis acidic conditions of the Mukaiyama aldol may have been sufficient enough to promote closure to hemiketal 3.24. Several more attempts with TiCl$_2$(OiPr)$_2$ and toluene led to similar disappointing results. More reactive titaniums were not explored because of possible decomposition observed in previous aldol couplings of methyl ketone 3.11 and aldehyde 3.12.

\[ \text{Scheme 3.8} \]
In conjunction with exploration of titanium based Lewis acids, an examination of \( \text{BF}_3\cdot\text{OEt}_2 \) was begun. There were distinct advantages to using \( \text{BF}_3\cdot\text{OEt}_2 \) as Sulikowski had already demonstrated its effectiveness in their synthesis of apoptolidinone.\(^{69b,123}\) Being monodentate in nature, the selectivity of the aldol should follow Evans’s polar model \( \text{3.8} \) leading to the desired \( 1,3\text{-anti} \) diol in respect to C17 and C19.\(^{101}\) A new addition to the reaction conditions, discovered in Sulikowski’s work,\(^{123}\) was the addition of CaH\(_2\) presumably to insure the reaction was dry, Scheme 3.9. Upon addition of enol silane \( \text{3.18} \) to the solution of aldehyde \( \text{3.16} \) and \( \text{BF}_3\cdot\text{OEt}_2 \), no reaction was detected after several hours. To promote aldol condensation, the reaction was warmed from -100°C to -78°C, while being monitored by TLC. A new brown colored spot was observed along with the less than desirable purple spot. As the reaction was monitored, it became apparent the purple spot was growing in intensity while the brown spot had presumably formed earlier and was not growing larger. With the purple spot becoming more prominent the reaction was quenched early, so that the brown spot could be isolated via column chromatography and analyzed further to determined if the desired \( \text{3.23} \) alcohol had been formed.
With similar Rf values, the newly formed brown spot and aldehyde 3.16 starting material were difficult to separate though after several column a sufficient amount of the unknown brown spot was collected. Much to our delight, $^1$H NMR confirmed that the brown spot was ketone 3.23. This was concluded by the retention of nearly all of the structural features found in the aldehyde and ketone, while observing no methyl ketone or aldehyde peaks, but instead finding a new CHOH peak at 4.1ppm. The disappointing part of the reaction was the low yield of approximately 10-15% and less than 100% conversion. One benefit of this coupling strategy was the ability to recover nearly all of the unreacted starting material, though that did not yield much comfort when similar yields were repeatedly obtained. Even with the addition of CaH$_2$ and repeated isolation of the presumed hemiketal (purple spot), trace water was believed to be the hindering factor in obtaining higher conversions and thus increased yields.

To combat any water introduction to the reaction, all starting materials were rigorously dried over four angstrom molecular sieves for several hours prior to the aldol
condensation. Overnight was preferred though not always feasible with time constraints. The reaction vessel also contained molecular sieves in attempt to further promote dryness as the reaction proceeded. All glassware was meticulously flame dried and flushed with nitrogen before the reaction commenced. The methylene chloride was checked for water content and found to be consistently below 10 ppm. As for the reaction, the yield was improved to 40-45% of coupled product 3.25, Scheme 3.10. These numbers, though encouraging, left much to be desired in such a crucial coupling sequence. Nevertheless, with alcohol 3.25 in hand hydrozirconization of the alkyne was examined, while efforts continued on optimizing the aldol coupling.

![Scheme 3.10](image)

Experience in making test fragments to explore the Stille coupling of fragments A and B showed us commercially available Schwartz reagent to be unreactive. Personal communications through Bill’s visit with Prof. Wipf’s group led us to synthesize the reagent in house according to Lipshutz’s method. A quick halogen-hydride exchange between LiAlH₄ and bis(cyclopentadienyl)zirconium(IV) dichloride 3.26 is followed by
several solvent washes to yield highly reactive and pure Schwartz reagent, Scheme 3.11. The newly synthesized reagent is adequately reactive for 2-3 weeks when stored in a foil covered, plastic vial at room temperature.

![Scheme 3.11](image)

Before the hydrozirconization was attempted the C19-hydroxyl was orthogonally protected as acetate 3.27 with acetic anhydride and triethylamine, Scheme 3.12. Following successful conversion to the protected acetate, ketone 3.27 was diluted in THF and cooled to 0°C. Freshly prepared Schwartz reagent was added and the reaction was covered with aluminum foil to avoid possible light degradation. Upon addition of the Schwartz reagent a large amount of gas evolution is present followed by the reaction solution turning a bright yellow color. The reaction was then heated to reflux and left to stir for 3 hours. Upon removal of the foil after 3 hours, it was discovered the reaction had run dry. Since the contents of the flask did not appear to be degraded (burnt or black in color), the reaction was diluted with additional THF. A TLC revealed complete consumption of the starting ketone with several other new spots present. Believing the reaction may have worked, a solution of iodine in THF was added to the reaction at -20°C then quenched and isolated. Upon isolation, the desired vinyl iodide was not observed in the crude \(^1\)H NMR, but rather the \(^1\)H NMR appeared to show proto-dezirconization yielding alkene 3.28.
Even though the reaction went to dryness, it served as a valuable lesson on what must be considered when working on such a small scale. A sealed tube was thought of as an alternative if a similar reaction of scale and delicacy was necessary. Ultimately, if the vinyl iodide could be established earlier in the reaction sequence there would be a greater opportunity of performing the transformation on a much larger sample size decreasing the sensitivity of the reaction to internal and external conditions. For this reason an investigation into further optimization of the vinyl iodide formation was put forth with the final goal of performing the aldol condensation on an aldehyde with the vinyl iodide already installed.
3.4 Optimization of Vinyl Iodide Formation

As briefly explained above, the commercial supply of Schwartz reagent was ineffective in converting our alkyne fragment to the desired vinyl iodide. It was by chance that Bill happened to visit the Wipf group during a post-doctoral interview that he was able to find out that they synthesize their own reagent and were having similar reactivities or lack thereof with the commercially available products. Following their advice and Lipshutz’s procedure, we were able to synthesize viable Schwartz reagent on a consistent manner from bis(cyclopentadienyl)zirconium(IV) dichloride.

Initially we investigated Nicolaou’s procedure in which a similar alkyne 3.29 from the southern half of apoptolidin was converted to the vinyl iodide 3.30 in good yields and selectivities, Scheme 3.13. This procedure required multiple equivalents of the Schwartz reagent in refluxing THF for three hours. One benefit to the reaction was the color change from yellow-orange to a deep purple color over the three hour period.

Following Nicolaou’s procedure, alkyne 3.31 was dissolved in THF and cooled to 0°C, Scheme 3.14. Recently prepared Schwartz reagent was added and the reaction covered in aluminum foil. The reaction was heated to reflux and stirred for three hours.
when it was observed the reaction turned from a yellow-orange color to a deep purple as expressed by Nicolaou. After three hours of refluxing, the reaction was allowed to cool before further cooling it to -20°C prior to addition of the iodine-THF solution. The iodide-zirconocene exchange was visually evident as the deep purple color of the reaction mixture would disappear as the exchange would take place then revert to a dark purple color as excess iodine solution was added. An unfortunate drawback to this procedure was the inconsistent yields of vinyl iodide 3.32 ranging from 30-60% along with the respectable 6:1 regioselectivity. In the worst cases, the alkyne would be reduced to the alkene like Scheme 3.11 yielding no observable vinyl iodide.

![Scheme 3.14](image)

Upon further literature review, it was found excessive Schwartz reagent, heating and reaction times could all be detrimental to the yield. With this knowledge subsequent hydrozirconization reactions were closely monitored via TLC to discover the necessary equivalents of Schwartz reagent along with proper temperature and time. The first objective was reducing the equivalents of Schwartz reagent and iodine to two equivalents versus three equivalents used exclusively with Nicolaou’s procedure. Upon addition of the Schwartz reagent, the reaction was quickly warmed to 50°C while monitoring with TLC, Scheme 3.15. After 35-40 minutes at 50°C, the reaction turned from yellowish-orange to the deep purple similar to Nicolaou’s procedure. A TLC at this
point revealed all of the starting alkyne was consumed leaving a dark grayish green spot on TLC when stained with anisaldehyde. Directly above the product spot and partially underneath it was another spot which seemed to dissipate as the reaction was allowed to stir at 50°C. Since the second spot was dissipating as the reaction commenced, the spot in question was believed to be the internal zirconcene addition which will slowly convert to the external product with additional heating. Unfortunately, as the reaction proceeds further another spot directly below the product spot begins to appear and increases in intensity as the reaction is heated. This left me with a dilemma on whether to heat the reaction longer leading to higher selectivities or shorter to insure fewer impurities. In the end, it was found a slight excess (two equivalents) of Schwartz reagent heated to 50°C for 45-50 minutes proved to give the highest yields 70-80% with good selectivities 9:1 and minimal by-products.

![Scheme 3.15](image)

With the hydrozirconization optimized, efforts again turned back to improving the yield of the aldol condensation between enol silane 3.18 and the vinyl iodide version of aldehyde 3.12. Clean removal of the primary TBS-ether 3.32 with acidic methanol was followed by oxidation to the desired aldehyde 3.34 in good yields for the two steps, Scheme 3.16. Aldehyde 3.34 and enol silane 3.18 were dried overnight over molecular sieves prior to the aldol condensation.
Once dried the solution of aldehyde 3.34 and enol silane (freshly prepared) were combined at -78°C, Scheme 3.17. Dropwise addition of BF$_3$•OEt$_2$ soon followed. Alcohol 3.35 was produced in a 38% yield for the reaction. Unfortunately, repeated attempts yielded similar results or worse in some cases.
A literature search revealed Roush’s synthesis of bafilomycin A₁ where a similarly complex enol silane 3.36 was formed and subsequently put under high vacuum for two hours prior to reacting with aldehyde 3.37, Scheme 3.18. Following Roush’s precedent, enol silane 3.18 was put under high vacuum for two hours immediately after it had been synthesized. After two hours, it was diluted in methylene chloride and added dropwise to a methylene chloride solution of aldehyde 3.34 which had been cooled to -78°C, Scheme 3.16. Dropwise addition of BF₃•OEt₂ led to nearly 100% conversion based upon TLC analysis. Upon workup and column chromatography the yield had been improved from 35-40% to 74% of alcohol 3.35. It was also clear the selectivity of the reaction had improved as attempts to detect a minor diastereomer beyond the regioisomer of the vinyl iodide were difficult. To date the reaction has been performed on nearly a gram scale with consistent yields and selectivities.

![Scheme 3.18](image)

3.5 Stille Reaction

With the aldol coupling providing adequate yields and substantial product, our focus shifted to the second of three crucial coupling steps, the Stille reaction. A literature search of Nicolaou⁶⁵,¹²⁷ and Koert’s⁶⁷,¹²⁸ total syntheses of apoptolidin revealed two diverging Stille procedures. Nicolaou relied on a palladium(II) catalyst approach
consuming multiple equivalents of the triene 3.39 versus one equivalent of the vinyl iodide 3.40, Scheme 3.19. This approach though advantageous in excellent yields posed a problem if quantities of the triene were limited.

Scheme 3.19

Koert and coworkers focused on Liebskind’s palladium-less coupling, Scheme 3.20. The coupling yielded similar results to Nicolaou’s strategy, but did not rely on the deprotection of the C9-hydroxyl, multiple equivalents of the triene, and heating the reaction. A disadvantage was the stoichiometric requirement of the copper(I) thiophene carboxylate catalyst. In either case, the outcome was the desired coupled product 3.44 in high yields.
With the knowledge of Nicolaou’s Stille procedure requiring multiple equivalents of triene, my colleague on this project Dr. Bill Paquette decided to pursue Koert’s palladium-less pathway initially. Commercially available copper(I) thiophene carboxylate (CuTC) catalyst was purchased, but did not demonstrate the reactivity reported by Koert and coworkers. Believing the commercially available product may not be as active as freshly prepared CuTC, Bill proceeded to synthesize the reagent in house. The freshly prepared reagent offered no improvement over the commercially available version, so reluctantly Bill reverted back to Nicoaloau’s palladium procedure.

After exploratory work utilizing test systems, Bill was able to couple vinyl iodide 3.32 and triene 3.45 in respectable yields, Scheme 3.21. From this work and Nicolaou’s work on apoptolidin it became very clear this particular Stille reaction was sensitive to the number of equivalents of vinyl stannane and the necessity of deprotecting the C9-hydroxyl.
Taking these observations into consideration, I first set out to repeat the work Bill had accomplished on a very similar substrate. This approach served two purposes. The first was becoming familiar with the reaction, while the second investigated the possibility of performing the Stille coupling prior to the aldol condensation (See section 3.3). Alcohol 3.33 was dissolved in dry DMF and quickly followed by vinyl stannane 3.45, Scheme 3.22. To the reaction mixture was added a catalytic amount of PdCl₂(CH₃CN)₂ subsequently turning the reaction to a dark greenish-black color. The reaction was allowed to stir overnight yielding after column chromatography diol 3.46 in 33% yield. The low yield was a consequence of using a slight excess of the vinyl stannane 3.45 due to the limited availability of the triene at the time. Believing the availability of the triene could be a continuing concern; investigations into more efficient means of producing the Stille coupling were explored.
A literature search revealed Pattenden’s\textsuperscript{46} total synthesis of amphi
dinolide A and Williams’s\textsuperscript{57} total synthesis of (+)-amphidinolide K. In each case the principle author
expresses the difficulties in successfully coupling hindered vinyl stannanes to substituted
vinyl iodides. To combat the steric encumbrance, additives were examined to increase
the rate of coupling versus side reactions such as homo-coupling of vinyl stannane
fragments. In the case of Pattenden’s total synthesis of amphi
dinolide A, triphenylarsine
was added based upon work by Farina\textsuperscript{15b} to attenuate the reactivity of the palladium
facilitating an increased rate of transmetallation and overall reaction leading to allylic
acetate 3.49, Scheme 3.23.
Williams’s total synthesis of amphidinolide K employed a Cu(I) cocatalyst specifically copper(I) thiophene carboxylate (CuTC) in conjunction with the palladium catalyst, Pd$_2$(dba)$_3$, Scheme 3.24.$^{57}$ Williams found utilizing the copper catalyst alone led to homo-coupling of the vinyl stannanes, in contrast no reaction was observed with only the palladium catalyst. Remarkably the reaction is successful in coupling fragments 3.50 and 3.51 while epoxide and acid functionality are present in the molecule. The use of the CuTC catalyst in combination with a palladium source was particularly intriguing and ironic to a certain extent as Bill and I continued to have problems with palladium and CuTC by themselves, but combining them may have been the “magic bullet” that was eluding us.
The combination of palladium and copper catalysts intrigued me enough to explore Williams’s conditions on a test coupling between truncated 3.53 and protected triene 3.54, Scheme 3.25. The vinyl tin and iodide were dissolved in dry NMP at room temperature. To the solution was added Pd$_2$(dba)$_3$, Ph$_3$As, and CuTC in that order. The reaction was then heated at 40°C for one hour under a veil of aluminum foil. The TLC after one hour of heating revealed no starting vinyl iodide 3.53 so the reaction was quenched and worked up. The polarity of the new product made purification rather difficult leading to a semi-pure isolation that appeared to show the coupling was a success, but with the price of a TBS-ether deprotection. Bill had observed the TBS-deprotection on several occasions when using reactive palladium sources.\textsuperscript{117}
Encouraged by the possible opportunity to perform the Stille coupling without C9-deprotection, the coupling reaction was repeated with triene 3.54 still TBS-protected and vinyl iodide 3.32, Scheme 3.26. After heating the mixture for one hour, the TLC showed considerable vinyl iodide still present along with unreacted vinyl tin. The heat was removed and the reaction stirred overnight to no avail. The reaction was quenched and the vinyl iodide reisolated. Unfortunately, during the reaction, vinyl tin 3.54 was consumed presumably as the homo-coupled product. Based upon literature precedent\textsuperscript{65,115} and our experimental observations, it had become clear the C9-hydroxyl must be deprotected even with the addition of cocatalysts such as CuTC.

![Scheme 3.26](image)

The C9-TBS ether was removed under protocol worked out by Bill utilizing the fluoride source TBAF\textsuperscript{117}. Because of the steric environment around the C9-TBS ether, TBAF deprotection was sluggish and never reached completion even after several days of stirring. Nevertheless, a conversion rate of approximately 65-70\% could be attained in 24 hours. Longer reaction times were avoided because of the sensitivity of the substrate.
The newly deprotected triene 3.45 was diluted with aldehyde 3.34 in dry NMP prior to Pd$_2$(dba)$_3$, Ph$_3$As and CuTC addition, Scheme 3.27. The reaction was stirred overnight yielding 41% of coupled product 3.57 with the aldehyde still intact.

![Scheme 3.27]

The C9-hydroxyl of aldehyde 3.57 was quickly reprotected as the TBS-ether under standard conditions to insure it would not interfere with the Mukaiyama aldol, Scheme 3.28. Following the TBS-protection, aldehyde 3.58 was dissolved in methylene chloride and dried via molecular sieves overnight. The solution was then cooled to -78°C prior to enol silane 3.18 addition. Dropwise addition of BF$_3$•OEt$_2$ yielded a new TLC spot that was isolated and analyzed through $^1$H NMR. For the most part the spectrum looked favorable for formation of ester 3.59, but several of the olefin peaks between 6-7ppm were non-existent. Because of the lack of olefin peaks and the use of a Lewis acid, one may hypothesize a Diels-Alder may have taken place. With a viable route to the Mukaiyama aldol already proven (Scheme 3.17) and a Stille procedure tested on a complex system (Scheme 3.27), the decision was made to continue to pursue the synthesis with the aldol condensation prior to the Stille reaction.
With the successful synthesis of coupled fragment 3.57 (Scheme 3.27), the next logical step was to investigate the Stille reaction on the full carbon backbone of the southern-half of 20-deoxyapoptolidinone. Utilizing the reaction procedure described in Scheme 3.9, the newly formed secondary alcohol was subsequently protected as the TMS-ether under standard conditions to yield 31% of vinyl iodide 3.60 over the two steps, Scheme 3.29. The secondary alcohol was protected to aid in further purification and as a precaution for the Stille reaction. Following the conditions set forth in Scheme 3.27, ester 3.61 was successfully produced in 30% yield finalizing the carbon backbone of 20-deoxyapoptolidinone.
Continuing to investigate the Stille coupling utilizing Williams’s\textsuperscript{57} palladium and copper catalyst mixture, the next step in the progression was coupling the unprotected alcohol thus eliminating the need to deprotect it prior to macrolactonization. As seen with the protected version 3.61, the reaction yielded the coupled fragment in 30-35\% yield. A large portion of the unreacted alcohol continued to be recoverable, but as seen in the past the triene was consumed. The lower yield was attributed to only using a slight excess of the triene with respect to the alcohol. As Nicolaou\textsuperscript{115} had observed several equivalents of the triene were necessary to push for higher yields as side reactions such as the homo-coupling was in direct competition. Even though an improvement to Nicolaou’s procedure had not been accomplished, substantial amount of material had
been successfully synthesized necessitating the saponification of the ester to prepare the substrate for the final key coupling step the macrolactonization.

### 3.6 Saponification

Our synthetic strategy hinged on our ability to close the macrolide via a Yamaguchi macrolactonization or similar acylation. In order to accomplish this goal, the ethyl ester in 3.62 needed to be efficiently converted to the acid without disrupting any of the other functionality in the molecule, Scheme 3.30. In reviewing the saponification conditions used by Koert\(^67,128\) in his total syntheses of apoptolidin and Dr. Bill Paquette’s\(^117\) work on the macrolide portion of 20-deoxyapoptolidinone, in both cases LiOH was used to successfully convert ethyl esters to the free acid.

At room temperature, ethyl ester 3.62 was dissolved in THF followed by further dilution with methanol to a 2:1 ratio of THF and methanol, Scheme 3.29. Multiple equivalents of a LiOH solution (1M in water) was added to the reaction prior to the vial being sealed due to the small scale. The reaction was left to stir overnight at room temperature. A TLC of the reaction still showed ester 3.62 present after 18 hours along with a promising more polar spot. The reaction was stirred for an additional 24 hours then analyzed by TLC. At that point, the starting material had been consumed, but along with the more polar spot was a new spot with a similar Rf as the starting ester. The reaction was quenched and purified with the spot of similar polarity being the only isolatable one.
The new product was analyzed with $^1$H NMR clearly demonstrating ester 3.62 had been consumed in the reaction. The TES-ether at C23 was also no longer present. Unfortunately, the $^1$H NMR also showed several distinct new peaks in the olefin and vinyl methyl region. Through further examination, it was determined the C9-hydroxyl had most likely been eliminated during the saponification step yielding acid 3.63. This led to five distinct methyl peaks between 1.5-2ppm and a new proton peak in the olefin region 6-6.5ppm. With this discovery, a look back at the apoptolidin syntheses of Koert$^{67,128}$, Toshima$^{66}$, and Nicolaou$^{65,115}$ revealed all C9-hydroxyls were either protected as silyl-ethers or a glycosylation had been performed to attach the carbohydrate prior to saponification.

### 3.8 New End Game Strategy

With reprotecting the C9-hydroxyl as a silyl-ether viewed as counter-productive, an investigation was begun into saponification of the ester prior to Stille cross-coupling. Williams$^{57}$ work on (+)-amphidinolide demonstrated a Stille coupling with the free acid (See Scheme 3.23) to be very plausible only limited by the possibility of lower yields. Triene 3.54 was successfully converted to the free acid using LiOH in a
THF:methanol:water mixture over several days, Scheme 3.31. As expected the TBS-ether at C9 was still intact and prepared for deprotection with TBAF in THF. The deprotection is painfully slow probably in large part to the sterically crowded nature of the C9-hydroxyl. Vince Lombardo, a colleague on the apoptolidin project, has since optimized the saponification and deprotection procedure cutting the time for each in half. He has also shown the Stille coupling to be more than adequate in successfully coupling the triene acid to the southern-half of 20-deoxyapoptolidin. Since at this point, Vince has taken over the synthesis and is progressing towards finishing 20-deoxyapoptolidin. The strategy to finish this complex molecule will be pursued at a later date.

With the Stille coupling completed, the entire carbon backbone of 20-deoxyapoptolidinone is present. The third crucial coupling step, macrolactonization, will involve Yamaguchi’s conditions of mixed anhydride formation with 2,4,6-

Scheme 3.31
trichlorobenzoyl chloride and triethylamine followed by DMAP addition, Scheme 3.32. Once macrolide 3.67 has been synthesized, global deprotection with a fluoride source possibly HF/pyr. will remove all of the silyl-ethers permitting hemi-ketal formation at C21 yielding the desired poly-substituted hydro-pyran of 20-deoxyapoptolidinone 3.68.

![Scheme 3.32](image)

**Scheme 3.32**

3.9 Conclusion

The above chapter has demonstrated efficient and stereoselective means to achieve the three crucial coupling steps required to yield apoptolidinone. Literature and past experience proved invaluable in discovering a successful strategy for the coupling of fragments B and C through a Mukaiyama aldol condensation. The difficulties with
Nicolaou’s palladium based Stille coupling and Koerts copper(I) thiophene carboxylate (CuTC) catalyst led to a synergist approach utilizing both in the eventual coupling of the triene acid and the southern-half of the molecule. The final coupling event, the macrolactionization, is currently in the experimental stage utilizing classic Yamaguchi methods, which based on Dr. Bill Paquette’s preliminary work on the macrolide should be very successful in getting us one step closer.
CHAPTER FOUR

FUTURE WORK TOWARDS “CHIMERIC” ANALOGUES

4.1 Purpose

This chapter will lay the ground work for one possible direction the apoptolidin project may lead into with the completion of the total synthesis of 20-deoxyapoptolidin. Apoptolidin shares many structural characteristics with bafilomycin and concanamycin yet their biological target is very specific. Exploration into this structural specificity may lend insight into the evolutionary pathway by which each molecule came to be and provide vital clues into structural features recognized by the active site such as the pyran rings. To probe this specificity, a strategy of constructing “chimeric” analogues containing the substituted pyrans of concanamycin and bafilomycin with various forms of apoptolidin’s macrolide will be explored. Once synthesized these unique analogues will be assayed for cross activity.

4.2 Background

Apoptolidin has been shown to act on the F₀F₁-ATPase enzyme found in the inner membrane of the mitochondria. The F₀F₁-ATPase is thought to regulate the proton gradient between the inside of the mitochondria and the inter-membrane allowing the cell
to phosphorylate ADP to ATP. Apoptolidin affects this gradient closing off the cell’s ability to generate ATP. With its ability to synthesize ATP compromised the cell proceeds down the path of cell death, apoptosis. Apoptolidin has been shown to be particularly effective against transformed (cancerous) cells when compared to non-transformed (normal) cells by several orders of magnitude.\textsuperscript{130a}

In contrast, bafilomycin and concanamycin act on the vacuolar or V-type ATPase.\textsuperscript{131} Interestingly neither apoptolidin, bafilomycin, nor concanamycin are significant cross inhibitors of other types of ATPase enzymes even though they share similar structural features, Figure 4.1. For example, each of the three polyketide natural products possesses a macrolide core with a substituted pyran side chain. Structurally within these macrolides is a high degree of unsaturation lending to remarkably rigid large macrocycles. Apoptolidin is a 20-membered macrolide while concanamycin is 18 and bafilomycin is a 16-membered macrolactone. When you look at concanamycin and bafilomycin the first question that comes to my mind is why the polyketide synthase chose the C17-hydroxyl over the C19-hydroxyl in concanamycin and performed a similar macrolactonization on the C15-hydroxyl instead of the C17-hydroxyl in bafilomycin.

Like the macrolides the pyran appendages have a similar substitution pattern differing in no methyl substitution at C20 and C22 for bafilomycin and concanamycin respectively. Bafilomycin and concanamycin also contain an \textit{anti}-proponate unit while apoptolidin only contains \textit{syn}-proponate units. In addition to the similarities and differences already expressed apoptolidin and concanamycin contain carbohydrate appendages (not shown in Figure 4.1) which will not be probed in this initial work.
It is our goal to probe this specificity by initially attaching the pyran rings of bafilomycin and concanamycin to the macrolide core of 20-deoxyapoptolidinone, Figure 4.2. We intend to use the macrocycle of 20-deoxyapoptolidinone, because of its presumed increase in stability over its parent apoptolidinone. The hope is to find some limited cross activity that may be amplified by further analogue development such as ring contraction of the 20-membered apoptolidin macrocycle to a 16 or 18-membered macrolactone similar to bafilomycin and concanamycin. The “chimeric” analogues 4.5 (cocanamycin pyran) and 4.6 (bafilomycin pyran) will require new synthetic strategies, since they possess an anti-proponate unit, but beyond constructing a new fragment C, the rest of the synthesis will rely on chemistry from the total synthesis of 20-deoxyapoptolidinone.
4.3 Paterson’s Anti-Aldol Chemistry

The most striking difference between the pyrans of bafilomycin, concanamycin and apoptolidin is the anti-stereochemistry found at C24-C25 for concanamycin and C22-C23 for bafilomycin. Since the stereochemical pattern is different from apoptolidin’s, a new strategy would need to be developed in order to properly synthesize the fragment C analogues to resemble those of bafilomycin and concanamycin. A literature search revealed Paterson’s anti-aldol chemistry\(^\text{132}\) which he exploited in the total synthesis of (-)-ACRL Toxin IIIB\(^\text{132a}\).

The first step in the utilization of Paterson’s protocol was the construction of his chiral auxiliary from ethyl (S)-(−)-lactate much like the preparation of oxazolidinone auxiliaries from phenylalanine for Evans aldol chemistry. Inexpensive and commercially available ethyl (S)-(−)-lactate 4.7 was converted into the Weinreb amide 4.8 using Weinreb’s salt and isopropyl Grignard reagent in 87% yield, Scheme 4.1.\(^\text{109b,132a}\) The amide is quickly converted to the ethyl ketone then followed by protection of the primary alcohol as the benzyl ester as a two part conversion with no purification between steps. Protected ethyl ketone 4.9 was produced in 40% yield for the two steps. A substantial
amount (11%) of protected amide \textbf{4.10} was also isolated demonstrating the ethyl ketone formation was not proceeding as well as the TLC had shown. Nevertheless, an adequate quantity of Paterson’s auxiliary had been synthesized and was carried on to the first aldol condensation.

\[
\begin{align*}
\text{HO} & \quad \text{OEt} \\
\text{O} & \quad \text{H} \\
\text{O} & \quad \text{N} \\
\text{OCH}_3 & \quad \text{BzO} \\
\text{BzO} & \quad \text{N} \\
\text{OCH}_3 & \quad \text{BzO}
\end{align*}
\]

\[
\text{OCH}_3
\]

\[4.10 \text{ (11%)}
\]

\begin{align*}
& \text{4.7} \quad \text{(CH}_3\text{O})\text{NH(CH}_3\text{)}^+\text{HCl} \\
& \quad \text{iPrMgCl, THF, 87%} \\
& \quad 1. \text{EtMgBr} \\
& \quad 2. \text{Bz}_2\text{O, DMAP DIPEA}
\end{align*}

\[
\begin{align*}
\text{HO} & \quad \text{NOCOOCH}_3 \\
\text{BzO} & \quad \text{I}
\end{align*}
\]

\[
\text{4.9 \text{ (40%)}}
\]

\[
\text{BzO} \quad \text{NOCOOCH}_3
\]

\[4.10 \text{ (11%)}
\]

\section*{Scheme 4.1}

Paterson’s \textit{anti}-aldol chemistry relies on steric and electronic contributions from the auxiliary allowing facial selectivity at the aldehyde.\textsuperscript{132a} A demonstration of the steric and electronic factors are shown in the aldol coupling of enolate \textbf{4.11} and RCHO yielding two proposed transition states, Scheme 4.2. Hydrogen bonding between the aldehyde proton and the benzoate protecting group is thought to further stabilize \textbf{TS-1} in favor of \textit{si}-facial attack leading to \textit{anti}-product \textbf{4.12}. In \textbf{TS-2}, the benzoate group is positioned outside of the chair arrangement reducing steric requirements for the protecting group, but leading to an unfavorable electronic repulsion between the benzoate and enolate oxygens. Since alcohol \textbf{4.13} is not readily produced in the aldol reaction, the electronic repulsion is believed to trump the steric benefits of positioning the benzoate group outside of the chair arrangement. In both transition states, the electronic effects outweigh their steric counterparts when determining the favored and unfavorable pathway.
In much of Paterson’s work Lewis acid \( c\)-Hex\(_2\)BCl is preferred along with dimethylethylamine base. Knowing this, ethyl ester 4.9 was slowly added to a mixture of \( c\)-Hex\(_2\)BCl and dimethylethylamine and allowed to stir for several hours, Scheme 4.3. For the construction of the bafilomycin pyran, isobutyraldehyde was added and the reaction stirred overnight. Upon workup and purification 77% of a single diastereomer of alcohol 4.14 was isolated. The sequence was repeated with crotonaldehyde yielding 72% of the desired alcohol 4.15. The newly formed alcohol 4.14 was efficiently protected as the TBS-ether under standard conditions followed by LiBH\(_4\) reduction of the ketone and removal of the benzyl ester yielding the preferred diol. Oxidative cleavage with NaIO\(_4\)
proceeded smoothly yielding aldehyde 4.16 in 85% yield for the three steps. The auxiliary was removed from alcohol 4.15 in a similar fashion, but because of the allylic alcohol milder reductive conditions were employed. Sodium borohydride reduction converted the ketone to the corresponding alcohol, while potassium carbonate yielded a milder sequence for removal of the benzyl ester. Oxidative cleavage yielded 77% of aldehyde 4.17 for the 4 steps. Since both concanamycin and bafilomycin do not possess substitution at C22 and C20 respectively, a methyl ketone aldol would be necessary to further elongate these analogue fragments.

**Scheme 4.3**

4.4 Felkin Controlled Mukaiyama Aldol Condensation

Reverting back to previous experience with the Mukaiyama aldol reaction (See Chapters Two and Three), ketene acetal 4.18 was synthesized from methyl acetate\(^{105}\) and prepared to couple to aldehydes 4.16 and 4.17. Aldehyde 4.16 was diluted in methylene chloride and cooled to -78°C, Scheme 4.4. An excess of ketene acetal 4.18 was added followed by dropwise addition of \(\text{BF}_3\cdot\text{OEt}_2\).\(^{134}\) The reaction was monitored by TLC then worked up and purified via column chromatography. Alcohol 4.19 was isolated in 60%
yield as a single diastereomer determined by $^1$H NMR. The high selectivity is predicted by Dias’s$^{134}$ proposed transition state model 4.20 based upon similar work performed by Evans.$^{101}$ Aldehyde 4.17 was subjected to similar conditions yielding 64% of isolated product 4.21 which appears to be a 4:1 mixture of diastereomers via $^1$H NMR. To date, further investigation into this mixture of diastereomers has not taken place.

As with the synthesis of 20-deoxyapoptolidinone the ultimate goal is the construction of methyl ketones 4.24 and 4.25. To do this, esters 4.19 and 4.21 will be converted to the Weinreb amide under standard conditions followed by TBS-ether formation with TBSOTf and 2,6-lutidine, Scheme 4.5.$^{109}$ The synthesis is completed with MeLi substitution converting the Weinreb amide to the corresponding methyl ketone in a fast and efficient manner. In addition to the construction of the methyl ketones, a
small amount of esters 4.19 and 4.21 was dissolved in THF and subjected to TBAF deprotection. The TLC showed two polar spots presumably from lactones 4.22 and 4.23 and the open form ester. The scale of the reactions did not allow for isolation, so the reaction will be repeated on the necessary scale to facilitate isolation and characterization. We would like to assay the concanamycin, bafilomycin and apoptolidin lactones to see if they possess any activity by themselves.

Scheme 4.5

With methyl ketones 4.24 and 4.25 constructed, the next step would be a similar Mukaiyama aldol as was used in the synthesis of the southern-half of 20-deoxyapoptolidinone (See Chapter Three). Methyl ketone 4.24 would be converted to enol silane 4.26 with LiHMDS and a mixture of TMSCl and Et$_3$N, Scheme 4.6. The
enol silane would be most likely reacted with aldehyde 4.27 following protocol used in the synthesis of 20-deoxyapoptolidinone. The resulting vinyl iodide 4.28 would be primed for Still coupling and eventual completion of the bafilomycin based “chimeric” analogue.

![Scheme 4.6](image)

**Scheme 4.6**

### 4.5 Elongation of Fragment B to Methyl Ketone

A separate strategy for completion of vinyl iodide 4.28 would require elongation of aldehyde 4.29, Scheme 4.7. A stereoselective Mukaiyama aldol condensation with aldehyde 4.29 and ketene acetal 4.18 yielded ester 4.30 in 77% yield as a single diastereomer. The resulting ester was quickly converted to the Weinreb amide in 59% yield. Then subjected to PMB-imidate under acidic conditions and finally converted to the methyl ketone with MeLi in 39% yield for the two steps. Conversion of methyl ketone 4.31 to the desired enol silane 4.32 would be accomplished using the same protocol as reported in Chapter Three (LiHMDS with TMSCI:Et$_3$N).
Using the procedure demonstrated in Scheme 4.4, enol silane **4.32** and aldehyde **4.16** would be subjected to BF$_3$•OEt$_2$ at low temperatures yielding aldol product **4.33**, Scheme 4.8. The aldol condensation should follow Dias$^{134}$ and Evans’s$^{101}$ working model predicting excellent selectivity for this reaction. The secondary alcohol would be protected as the TBS-ether before hydrozirconization could commence. Ideally the vinyl iodide would be installed sooner in the reaction sequence but the formation of the enol silane under basic conditions may lead to some elimination resulting in the unsatisfactory possibility of multiple products. With vinyl iodide **4.34** synthesized the “chimeric” analogue fragment would be subjected to Stille coupling and our end game strategy used in the synthesis of 20-deoxyapoptoldidinone (See Chapter Three).
4.6 End Game Strategy for “Chimeric” Analogues

Continuing the precedent set in the construction of 20-deoxyapoptolidinone, vinyl iodide 4.34 and stannane 4.35 would be dissolved in NMP solvent and subjected to a palladium and copper(I) thiophene carboxylate (CuTC) catalyst cocktail. The resulting acid 4.36 would possess the entire carbon backbone of the analogue and should be successfully closed under Yamaguchi macrolactonization conditions. The synthesis would conclude with global deprotection revealing the C25-hydroxyl which would rapidly close down and form the bafilomycin pyran ring leading to the completion of the bafilomycin - 20-deoxyapoptolidinone “chimeric” analogue. Macrolide 4.6 and 4.5 will be screened in conjunction with 20-deoxyapoptolidinone as we investigate cross inhibitory activity against several types of ATPase enzymes (V- and F_{1}F_{0}-type).
4.7 Conclusion

A foundation for one possible direction the apoptolidin project has been laid through the successful utilization of Paterson’s anti-aldol chemistry. Exploration into the uniqueness of apoptolidin, concanamycin, and bafilomycin pyran rings may lead to a better understanding on the importance of the pyran ring for active site recognition. These insights may prove invaluable in the construction of site specific analogues for further increases in activity.
CHAPTER FIVE

EXPERIMENTAL METHODS

5.1 General Methods

All commercial materials were used without further purification unless otherwise noted. Anhydrous reactions were run under nitrogen or argon atmosphere in flame or oven-dried glassware. Tetrahydrofuran (THF), dichloromethane (CH$_2$Cl$_2$), diethyl ether (Et$_2$O), and toluene (PhCH$_3$), were further purified with activated alumina under nitrogen atmosphere.

All reactions were monitored by E. Merck analytical thin layer chromatography (TLC) plates (silica gel 60 GF, aluminum backed) and analyzed with 254 nm UV light and/or anisaldehyde/sulfuric acid treatment. Column chromatography was performed using E. Merck (Silica Gel 60, 230-400 mesh). Biotage chromatography utilized Flash 12+M, 25+S, 25+M, and 40+M KP-Sil™ Silica (32-63 μM, 60 Å, nominally 500 m$^2$/g silica) cartridges.

All $^1$H and $^{13}$C spectra were obtained on Varian Unity Plus 300 and 500 spectrometers (operating at 299.701 and 499.864 MHz for $^1$H and 75.368 and 125.706 for $^{13}$C respectively). Chemical shifts (δ) are reported in parts per million (ppm) relative to an internal standard of CHCl$_3$ reference ($^1$H: 7.26 ppm, $^{13}$C: 77.00 ppm) and coupling
constants ($J$) were reported in hertz (Hz). Peak multiplicity is shown as follows: s (singlet), d (doublet), t (triplet), and q (quartet). FTIR spectra were obtained from a Perkin-Elmer Paragon 1000 spectrometer. Mass spectra (FAB) were obtained using 3-nitrobenzyl alcohol (NBA) as a matrix with either a JEOL AX505HA or JEOL JMS-GCmate mass spectrometer.

5.2 Experimental Methods

![Chemical Structure]

4-(tert-Butyl-dimethyl-silanyloxy)-2-methoxy-butyric acid methyl ester, 2.66.

To a solution of 2.65 (10.2g, 40.1 mmol) in CH$_2$Cl$_2$ (200 mL) at room temperature was added Me$_3$O•BF$_4$ (8.6g, 56.2 mmol) followed by Proton Sponge (11.27g, 56.2 mmol). The reaction was stirred for 18 hrs where upon the solvent was removed under reduced pressure. The residue was redissolved in a 50/50 solution of ether/hexanes (200 mL) and the resulting suspension was filtered. The filtrate was washed with diluted acetic acid (0.5M, 2 x 50 mL), brine solution (50 mL), dried over MgSO$_4$, filtered, and concentrated. The crude material was purified via column chromatography (hexanes:EtOAc, 5:1) to afford ester 2.66 (7.0g, 26.7 mmol, 67%) as a colorless oil. Recovered starting material (1.36g, 5.35 mmol) was recycled and subjected to the above for mentioned conditions.

$[\alpha]_D^{20}$ -35.3° (c 3.4, CHCl$_3$); IR (film cm$^{-1}$) 2955.1, 2858, 1755.6, 1255.8, 1108.7, 837.1; $^1$H NMR (300 MHz, CDCl$_3$) δ(ppm) 3.92 (dd, 1H, $J = 4.2, 8.7$ Hz, CH(OCH$_3$), 3.73 (s, 3H, CH$_3$OC(O)), 3.65-3.73 (m, 2H, CH$_2$OTBS), 3.37 (s, 3H, CH$_3$OCH), 1.94 (dddd, 1H, $J = 4.2, 6.0, 8.5, 14.5$ Hz, CH$_2$CH$_2$OTBS), 1.81 (tdd, 1H, $J = 4.8, 8.7, 13.8$ Hz,
$\text{CH}_2\text{CH}_2\text{OTBS}$), 0.87 (s, 9H, SiC(CH$_3$)$_3$), 0.027 (s, 6H, Si(CH$_3$)$_2$); $^{13}$C NMR (75 MHz, CDCl$_3$) δ(ppm) 173.4, 77.0, 58.5, 58.2, 51.8, 35.8, 25.8, 18.2, -5.4, -5.5; HRMS (FAB) m/z (M+H)$^+$ calcd for C$_{20}$H$_{44}$O$_4$Si$_2$, 263.1679; obsd 263.1656. (Reference DG-V-209)
4-(tert-Butyl-dimethyl-silyloxy)-2-methoxy-butyraldehyde, 2.67. To a solution of 2.66 (750 mg, 2.86 mmol) in CH$_2$Cl$_2$ (25 mL) at -78°C was added DIBAL (1.0M in CH$_2$Cl$_2$, 3.33 mL, 4.00 mmol) dropwise over 15 minutes. The reaction was stirred for one hour then quenched with methanol (2.5 mL). A saturated solution of potassium sodium tartrate (Rochelle’s Salt, 25 mL) was added and stirred for one hour at room temperature. The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 20 mL). The organics were then combined and washed with brine solution, dried over MgSO$_4$, filtered, and concentrated. The crude material was purified via column chromatography (hexanes:EtOAc, 10:1) to afford aldehyde 2.67 (550 mg, 2.37 mmol, 83%) as a colorless oil. [α]$_D^{20}$ -38.6° (c 7.0, CHCl$_3$); IR (film cm$^{-1}$) 2931.3, 2857.9, 1728.3, 1255.6, 1096.8, 836.9; $^1$H NMR (500 MHz, CDCl$_3$) δ (ppm) 9.68 (d, 1H, J = 1.2 Hz, CH(O), 3.68-3.79 (m, 1H, CHOCH$_3$), 3.68-3.79 (m, 2H, CH$_2$OTBS), 3.46 (s, 3H, CH$_3$OCH), 1.94 (tdd, 1H, J = 4.9, 7.0, 14.2 Hz, CH$_2$CH$_2$OTBS), 1.82 (dtd, 1H, J = 4.9, 6.7, 11.5 Hz, CH$_2$CH$_2$OTBS), 0.89 (s, 9H, Si(CH$_3$)$_3$), 0.049 (s, 6H, Si(CH$_3$)$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$) δ (ppm) 203.5, 82.8, 58.3, 57.9, 33.5, 25.8, 18.2, -5.4, -5.5; HRMS (FAB) m/z (M+H)$^+$ calcd for C$_{20}$H$_{44}$O$_4$Si$_2$, 233.1573; obsd 233.1569. (Reference DG-V-130)
7-(tert-Butyl-dimethyl-silanyloxy)-5-methoxy-hept-1-en-4-ol, 2.68. To a solution of aldehyde 2.67 (95mg, 0.409 mmol) in CH$_2$Cl$_2$ (5 mL) at 0°C was added MgBr$_2$•OEt$_2$ (127mg, 0.491 mmol). The suspension was stirred for 30 minutes before cooling to -78°C. A solution of allyltributyltin (165 µL, 0.532 mmol) in CH$_2$Cl$_2$ (5 mL) at room temperature was added via cannula over 15 minutes. The reaction was monitored via TLC before quenching with Sat. NaHCO$_3$ solution (2 mL). The layers were separated and the aqueous layer extracted with CH$_2$Cl$_2$ (2 x 5 mL). The organics were washed with Brine solution, dried over MgSO$_4$, filtered and concentrated. The crude material was purified via column chromatography (hexanes:EtOAc, 5:1) to afford alcohol 2.68 (110mg, 0.401 mmol, 98%, dr: >20:1) as a colorless oil. $[\alpha]_D^{20}$ -5.6° (c 1.9, CHCl$_3$); IR (film cm$^{-1}$) 3445.7, 2929.8, 2857.9, 1642, 1256.5, 1094.1, 835.9; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ (ppm) 5.9 (tdd, 1H, $J$ = 7.1, 10.2, 17.2 Hz, CH$_2$=CH), 5.1-5.18 (m, 2H, CH$_2$=CH), 3.70-3.79 (m, 2H, CH$_2$OTBS), 3.6 (qd, 1H, $J$ = 4.8, 8.0 Hz, CHOCH$_3$), 3.45 (s, 3H, CHOCH$_3$), 3.29-3.34 (m, 1H, CHO), 2.68 (d, 1H, $J$ = 5.2 Hz, CHO), 2.39 (tddd, 1H, $J$ = 1.3, 4.8, 6.2, 8.0 Hz, CH$_2$CH=CH$_2$), 2.25-2.32 (m, 1H, CH$_2$CH=CH$_2$), 1.85 (tdd, 1H, $J$ = 5.6, 7.3, 14.4 Hz, CH$_2$CH$_2$OTBS), 0.92 (s, 9H, SiC(CH$_3$)$_3$), 0.091 (s, 3H, Si(CH$_3$)$_2$), 0.088 (s, 3H, Si(CH$_3$)$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ (ppm) 135.4, 117.5, 80.7, 77.5, 77.3, 77.0, 72.5, 59.5, 58.7, 38.1, 33.5, 26.1, 18.5, -5.1, -5.2; HRMS (FAB) m/z (M+H)$^+$ calcd for C$_{29}$H$_{44}$O$_4$Si$_2$, 275.2042; obsd 275.2052. (Reference DG-IV-268)
4,7-Bis-(tert-butyl-dimethyl-silanyloxy)-5-methoxy-hept-1-ene, 2.69. To a solution of 2.68 (5.0 g, 18.2 mmol) in DMF (90 mL) at 0°C was added TBSCl (3.57 g, 23.7 mmol) followed by Imidazole (1.49 g, 21.8 mmol). The reaction was allowed to warm to room temperature then stirred for 12 hours before recooling to 0°C. The reaction was quenched with dropwise addition of Sat. NaHCO₃ solution (20 mL). The mixture was diluted with diethyl ether (100 mL) and the layers separated. The aqueous layer was extracted with ether (2 x 50 mL). The organics were combined and washed with H₂O (25 mL), brine (25 mL), dried over MgSO₄, filtered and concentrated. The crude product was purified via column chromatography (hexanes:EtOAc, 10:1) to afford 2.69 (6.95 g, 17.9 mmol, 98%) as a colorless oil. [α]D²⁰ -23.4° (c 3.5, CHCl₃); IR (film cm⁻¹) 3082.1, 2949.8, 2847.3, 1470, 1249.6, 1095.8, 834.3, 772.8; ¹H NMR (300 MHz, CDCl₃) δ (ppm) 5.8 (tdd, 1H, J = 7.2, 10.0, 17.2 Hz, CH₂=CH), 4.97-5.1 (m, 2H, CH₂=CH), 3.81 (td, 1H, J = 4.2, 8.3 Hz, CHOTBS), 3.70 (dd, 2H, J = 4.8, 7.9 Hz, CH₂OTBS), 3.39 (s, 3H, CHOCH₃), 3.32 (ddd, 1H, J = 2.9, 4.7, 9.5, CHOMe), 2.27-3.38 (m, 1H, CH₂CH=CH₂), 2.03-2.15 (m, 1H, CH₂CH=CH₂), 1.83 (dtd, 1H, J = 2.9, 7.9, 8.0, 14.0 Hz, CH₂CH₂OTBS), 1.43-1.56 (m, 1H, CH₂CH₂OTBS), 0.894 (s, 9H, SiC(CH₃)₃), 0.888 (s, 9H, SiC(CH₃)₃), 0.064 (s, 3H, Si(CH₃)₂), 0.051, (s, 6H, Si(CH₃)₂), 0.045, (s, 3H, Si(CH₃)₂); ¹³C NMR (MHz, CDCl₃) δ (ppm) 136.1, 116.5, 80.1, 72.1, 59.6, 58.4, 36.6, 32.2, 26.0, 25.9, 18.3, 18.1, -4.5, -5.3, -5.4; HRMS (FAB) m/z (M+H)+ calcd for C₂₀H₄₄O₃Si₂, 389.2907; obsd 389.2916. (Reference DG-IV-268)
4-(tert-Butyl-dimethyl-silanyloxy)-3-methoxy-hept-6-en-1-ol, 2.70. To a solution of 2.69 (2.1 g, 5.41 mmol) in methanol (50 mL) was added camphorsulfonic acid (126 mg, 0.541 mmol) at room temperature. The reaction was quickly monitored by TLC showing consumption of starting material after 20 minutes. The reaction was quenched with Et$_3$N (5 mL) and the solvent removed under reduced pressure. The crude product was purified via column chromatography (hexanes:EtOAc, 3:1) to afford 2.70 (1.16 g, 4.23 mmol, 78%) as a colorless oil. \([\alpha]_D^{20} -29.6^\circ (c 1.7, \text{CHCl}_3); \text{IR (film cm}^{-1}\text{)} 3077.3, 2929.6, 2857.8, 1642.2, 1472.1, 1101.9, 775.4; \text{^1H NMR (300 MHz, CDCl}_3\text{) \[\delta (\text{ppm}) 5.83 (tdd, 1H, } J = 7.2, 10.1, 17.2 \text{ Hz, } \text{CH}_2=\text{CH}), 5.00-5.11 (m, 2H, } \text{CH}_2=\text{CH}), 3.81 (td, 1H, } J = 4.2, 8.3 \text{ Hz, CHOTBS), 3.7 (dd, 2H, } J = 4.8, 7.9 \text{ Hz, CH}_2\text{OTBS), 3.39 (s, 3H, CHOCH}_3\text{), 3.32 (ddd, 1H, } J = 2.9, 4.7, 9.5, \text{ CHOMe), 2.68 (d, 1H, } J = 5.2 \text{ Hz, CHO}_2\text{OH), 2.39 (tddd, 1H, } J = 1.3, 4.8, 6.2, 8.0 \text{ Hz, } \text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2\text{), 2.25-2.32 (m, 1H, } \text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2\text{), 1.85 (tdd, 1H, } J = 5.6, 7.3, 14.4 \text{ Hz, CH}_2\text{CH}_2\text{OTBS), 1.75 (dtd, 1H, } J = 5.2, 6.1, 14.4 \text{ Hz, CH}_2\text{CH}_2\text{OTBS), 0.92 (s, 9H, SiC(CH}_3)_3\text{), 0.091 (s, 3H, Si(CH}_3)_2\text{), 0.088, (s, 3H, Si(CH}_3)_2\text{); ^13C NMR (75 MHz, CDCl}_3\text{) \[\delta (\text{ppm}) 135.7, 116.9, 83.9, 71.9, 61.3, 58.0, 36.4, 31.4, 25.8, 18.0, -4.4, -4.5; \text{HRMS (FAB) m/z (M+H)}^+ \text{calcd for C}_{14}\text{H}_{30}\text{O}_3\text{Si, 275.2042; obsd 275.2062. (Reference DG-VII-101)\]}}
**4-(tert-Butyl-dimethyl-silanyloxy)-3-methoxy-hept-6-enal, 2.71.** To a solution of oxalyl chloride (0.400 ml, 4.65 mmol) in CH$_2$Cl$_2$ (20 mL) at -78°C was added DMSO (0.616 ml, 8.67 mmol) dissolved in CH$_2$Cl$_2$ (5 mL). After 15 minutes, alcohol 2.70 (1.16g, 4.23 mmol) dissolved in CH$_2$Cl$_2$ (25 mL) was added dropwise then stirred for 45 minutes before adding DIPEA (3.49ml, 21.2 mmol). Upon addition of the base, the reaction was allowed to warm to room temperature and monitored by TLC. The oxidation was quenched with H$_2$O (10 mL) and diluted with ether (50 mL) when starting material was no longer observed. The organics were extracted, combined and further washed with Sat. NaHSO$_4$ Solution (20 mL), Brine (20 mL), dried over MgSO$_4$, filtered and concentrated. The crude product was purified via column chromatography (hexanes:EtOAc, 10:1) to afford 2.71 (722mg, 2.65 mmol, 63%) as a colorless oil [α]$_D^{20}$ -16.6$^\circ$ (c 8.3, CHCl$_3$); IR (film cm$^{-1}$) 3078.1, 2930.8, 2858.3, 2719.8, 1729.6, 1472.3, 1257.4, 1103.2, 837.3, 776.9; $^1$H NMR (500 MHz, CDCl$_3$) δ(ppm) 9.82 (t, 1H, =CH), 5.03-5.11 (m, 2H, =CH), 3.88 (td, 1H, J = 4.2, 8.2 Hz, CHOTBS), 3.88 (td, 1H, J = 4.1, 8.3 Hz, CHOCH$_3$), 3.38 (s, 3H, CHOCH$_3$), 2.69 (ddd, 1H, J = 1.5, 3.8, 16.7 Hz, CH$_2$CHO), 2.54 (ddd, 1H, J = 2.4, 8.4, 16.6 Hz, CH$_2$CHO), 2.34-2.40 (m, 1H, CH$_2$CH=CH$_2$), 0.87 (s, 9H, SiC(CH$_3$)$_3$), 0.059 (s, 6H, Si(CH$_3$)$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$) δ(ppm) 201.5, 135.6, 117.4, 78.8, 71.8, 58.3, 44.0, 36.6, 26.1, 18.3, -4.2, -4.3; HRMS (FAB) m/z (M+H)$^+$ calcd for C$_{20}$H$_{44}$O$_4$Si$_2$, 273.1886; obsd 273.1892. (Reference DG-VII-103)
6-(tert-Butyl-dimethyl-silanyloxy)-3-hydroxy-5-methoxy-non-8-enoic acid methyl ester, 2.72. In a flame dried 50 mL round bottom flask at room temperature, Ti(OiPr)$_4$ (0.353ml, 1.18 mmol) is dissolved in toluene (10 mL) followed by dropwise addition of TiCl$_4$ (0.119ml, 1.08 mmol). The resulting slightly yellow solution is stirred for 10 minutes before cooling to -78°C producing a white slurry. Aldehyde 2.71 (536mg, 1.97 mmol) was dissolved in toluene (5ml) before dropwise addition to the reaction. After 15 minutes, ketene acetal 2.59 (575mg, 3.93 mmol) dissolved in toluene (5 mL) was added to the reaction. The reaction was quenched with Sat. NaHCO$_3$ Solution (10 mL) and warmed to room temperature after one hour to prevent side reactions and decomposition. The organics were extracted with CH$_2$Cl$_2$ (2 x 25 mL) combined and washed with Brine solution (15 mL), dried over MgSO$_4$, filtered and concentrated. The crude product was purified via column chromatography (hexanes:EtOAc, 5:1) to afford 2.72 (510mg, 1.48 mmol, 75%, >20:1 dr) as a colorless oil. $[\alpha]_D^{20} -16.2^\circ$ (c 3.1, CHCl$_3$); IR (film cm$^{-1}$) 3450.8, 2956.6, 2847.8, 1732.8, 1255.4, 1092.1, 836.6; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$(ppm) 5.77-5.92 (m, 1H, CH=CH$_2$), 5.01-5.12 (m, 2H, CH=CH$_2$), 4.16-4.26 (m, 1H, CHOH), 3.87 (ddd, 1H, $J = 3.7$, 4.7, 8.3 Hz, CHOTBS), 3.72 (s, 3H, C(O)OCH$_3$), 3.43 (s, 3H, CHOCH$_3$), 3.40-3.48 (m, 1H, CHOMe), 2.51 (d, 2H, $J = 6.4$, CH$_2$C(O)OMe), 2.34 (tddd, 1H, $J = 1.4$, 3.6, 6.5, 13.2 Hz, CH$_2$CH=CH$_2$), 2.05-2.18 (m, 1H, CH$_2$CH=CH$_2$), 1.77 (ddd, 1H, $J = 3.6$, 9.5, 14.3 Hz, CH$_2$CHOH), 1.55 (ddd, 1H, $J = 2.8$, 8.7, 14.4 Hz, CH$_2$CHOH), 0.90 (s, 9H, SiC(CH$_3$)$_3$), 0.096 (s, 3H, Si(CH$_3$)$_2$), 0.077,
(s, 3H, Si(CH$_3$)$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$) δ(ppm) 173.0, 135.7, 116.9, 81.0, 72.0, 65.5, 58.4, 51.7, 41.7, 36.5, 35.8, 25.8, 18.0, -4.5; HRMS (FAB) m/z (M+H)$^+$ calcd for C$_{20}$H$_{44}$O$_4$Si$_2$, 347.2254; obsd 347.2246. (Reference DG-V-13 & 65)
(3S,5S,6S)-6-(tert-butyldimethylsilyloxy)-5-methoxy-3-(trimethylsilyloxy)non-8-enal, **2.73**. In a 25 mL round bottom flask, methyl ester **2.72** was dissolved in pyridine (5.0 mL) at room temperature. To the reaction was added hexamethyldisilazane (0.705 ml, 3.32 mmol) and two drops of TMSCl. The reaction was allowed to stir at room temperature while being monitored by TLC. Upon complete consumption of the starting material, the reaction was diluted with diethyl ether (15 mL) and quenched with Sat. NaHCO₃ solution (10 mL). The organics were separated and washed with H₂O (2 x 10 mL), brine solution (5.0 mL) then dried with MgSO₄ and silica gel (10g). The solids were filtered off and the solvent removed under reduced pressure. The crude product was then carried on to the DIBAL reduction without further purification.

In a flame dried 50 mL rbf, TMS-ether **2.73** was dissolved in CH₂Cl₂ (7.0 mL) and cooled to -78°C. Dropwise addition of DIBAL (0.996 mL, 1.0M in CH₂Cl₂) was followed by careful monitoring via TLC. After observing complete consumption of starting material, the reaction was quenched with careful addition of MeOH (2.0 mL). The reaction was then diluted with CH₂Cl₂ (20 mL) and a saturated solution of potassium sodium tartrate (Rochelle’s Salt, 10 mL). The mixture was stirred for one hour prior to extraction with CH₂Cl₂ (2 x 15 mL). The organic layers were combined and washed with brine solution (15 mL), dried with MgSO₄, filtered and concentrated. The crude product was purified via column chromatography (hexanes:EtOAc, 20:1) to afford **2.73** (131mg, 0.337 mmol, 51%) as a colorless oil. [α]D⁰ ²⁰ -37.5° (c 0.9, CHCl₃); IR (film cm⁻¹) 2956.6,
2931.5, 2856.1, 1728.7, 1251.2, 1096.3, 1071.1, 836.6; $^1$H NMR (500 MHz, CDCl$_3$) δ(ppm) 9.81 (t, 1H, $J = 2.4$ Hz, CHO), 5.83 (tdd, 1H, $J = 7.2$, 10.1, 17.2 Hz, CH=CH$_2$), 5.01-5.09 (m, 2H, CH=CH$_2$), 4.35 (dtd, 1H, $J = 4.0$, 5.4, 9.3 Hz, CHOTMS), 3.90 (td, 1H, $J = 3.7$, 8.7 Hz, CHOTBS), 3.37 (s, 3H, CHOCH$_3$), 3.33 (ddd, 1H, $J = 1.7$, 4.3, 10.4 Hz, CHOMe) 2.57 (dd, 2H, $J = 5.5$, 16.0 Hz, CH$_2$CHO), 2.26-2.32 (m, 1H, CH$_2$CH=CH$_2$), 1.99-2.06 (m, 1H, CH$_2$CH=CH$_2$), 1.86 (ddd, 1H, $J = 1.7$, 9.0, 14.1 Hz, CH$_2$CHOMe), 1.46 (ddd, 1H, $J = 4.0$, 10.5, 14.3 Hz, CH$_2$CHOMe), 0.89 (s, 9H, SiC(CH$_3$)$_3$), 0.13 (s, 9H, Si(CH$_3$)$_3$), 0.066 (s, 3H, Si(CH$_3$)$_2$), 0.053, (s, 3H, Si(CH$_3$)$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$) δ(ppm) 202.3, 136.4, 116.9, 80.1, 70.9, 65.7, 57.5, 52.3, 37.1, 36.1, 26.1, 18.2, 0.59, -4.19, -4.24; HRMS (FAB) m/z (M+OTMS)$^+$ calcd for C$_{16}$H$_{31}$O$_3$Si, 299.2042; obsd 299.2039. (Reference DG-VII-288)
(2S,3R,5R,7S,8S)-1-((S)-4-benzyl-2-thioxooxazolidin-3-yl)-8-(tert-butyldimethylsilyloxy)-3-hydroxy-7-methoxy-2-methyl-5-(trimethylsilyloxy)undec-10-en-1-one, 2.74. Oxazolidinethione 2.31 (67.6mg, 0.271 mmol) was dissolved in CH$_2$Cl$_2$ (4.0 mL) and cooled to 0°C. TiCl$_4$ (29.7µL, 0.271 mmol) was added to the solution, which was stirred for 5 minutes. (-)-Sparteine (80µL, 0.348 mmol) was then added and the reaction was allowed to stir for 20 minutes forming the titanium enolate as evidenced by the deep red color. In a separate flask, aldehyde 2.73 was dissolved in CH$_2$Cl$_2$ (1.0 mL) and dried over 4Å molecular sieves prior to addition. The aldehyde solution was added to the enolate via cannula slowly at -78°C. The reaction was monitored by TLC and quenched with Sat. NH$_4$Cl solution (5.0 mL) after 1 hour and stirred vigorously for 15 seconds. The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 10 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated to afford a crude oil. The crude product was then purified via column chromatography (hexanes:EtOAc, 3:1) to yield alcohol 2.74 (45mg, 0.0706 mmol, 27%) as a colorless oil. [$\alpha$]$_D^{20}$ -22.5º (c 0.52, CHCl$_3$); IR (film cm$^{-1}$) 3417.3, 2956.6, 2847.0, 1741.2, 1259.6, 1096.3, 1016.7, 840.8, 807.3; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$(ppm) 7.21-7.36 (m, 5H, Ph), 5.84 (tdd, 1H, $J = 7.2, 10.1, 17.2$ Hz, CH=CH$_2$), 5.07 (ddd, 1H, $J = 1.3, 3.4, 17.1$ Hz, CH=CH$_2$), 5.03 (d, 1H, $J = 10.1$ Hz, CH=CH$_2$), 4.90-4.95 (m, 1H, CHN), 4.66-4.71 (m, 1H, CHOH), 4.33-4.37 (m, 1H, CH$_2$), 4.26-4.33 (m, 2H, CH$_2$O), 4.18 (dd, 1H, $J = 4.3, 8.6$ Hz, CHOTMS), 3.90 (td, 1H, $J = 3.7, 7.8$ Hz, CHOTBS), 3.60 (d, 1H, $J = 1.6$ Hz, CHOH), 3.38 (s, 3H,
CHOCH₃), 3.27-3.32 (m, 2H, CHOMe, CH₂Ph), 2.75 (dd, 1H, J = 10.2, 13.3 Hz, CH₂Ph), 2.30 (ddd, 1H, J = 3.4, 7.1, 14.0 Hz, CH₂CH=CH₂), 2.04-2.11 (m, 1H, CH₂CH=CH₂), 1.91 (ddd, 1H, J = 1.8, 8.9, 14.2 Hz, CH₂CHOMe), 1.85 (ddd, 1H, J = 4.2, 10.6, 14.5 Hz, CH₂CHOH), 1.44-1.55 (m, 2H, CH₂CHOMe, CH₂CHOH), 1.31 (d, 3H, J = 6.9 Hz, CH₂CH(O)), 0.89 (s, 9H, SiC(CH₃)₃), 0.13 (s, 9H, Si(CH₃)₃), 0.066 (s, 3H, Si(CH₃)₂), 0.053, (s, 3H, Si(CH₃)₂); ¹³C NMR (125 MHz, CDCl₃) δ(ppm) 185.2, 177.2, 136.3, 135.3, 129.4, 129.0, 127.4, 116.7, 80.1, 71.0, 70.1, 69.0, 68.6, 60.3, 57.3, 43.1, 40.5, 37.5, 36.0, 35.7, 25.9, 18.1, 10.9, 0.4, -4.4; HRMS (FAB) m/z (M+OTMS+OH)+ calcd for C₂₉H₄₅NO₄Si, 531.2839; obsd 531.2840. (Reference DG-VII-289)
(S)-1-((S)-4-benzyl-2-thioxooxazolidin-3-yl)-2-((4R,6R)-6-((2S,3S)-3-(tert-butyldimethylsilyloxy)-2-methoxyhex-5-enyl)-2,2-dimethyl-1,3-dioxan-4-yl)propan-1-one, 2.75. In a 25 mL round bottom flask, alcohol 2.74 (45mg, 0.0706 mmol) was dissolved in dimethoxypropane (1.5 mL) and cooled to 0°C. A catalytic amount of CSA (2 mg) was added to the reaction then monitored via TLC. Upon completion, the reaction was quenched with Et$_3$N (1.0 mL) and concentrated under reduce pressure. The crude product was purified via column chromatography (hexanes:EtOAc, 10:1) to afford 2.75 (33mg, 0.055 mmol, 78%) as a colorless oil $[\alpha]_{D}^{20} +47.9^\circ$ (c 5.0, CHCl$_3$); IR (film cm$^{-1}$) 2924.5, 2849.0, 1695.1, 1366.3, 1224.6, 1190.5, 1105.5; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$(ppm) 7.21-7.36 (m, 5H, Ph), 5.83 (tdd, 1H, $J = 7.2, 10.1, 17.2$ Hz, CH=C=CH$_2$), 5.00-5.08 (m, 2H, CH=CH$_2$), 4.83-4.89 (m, 1H, CHN), 4.72-4.79 (m, 1H, CHOC), 4.32 (dd, 1H, CH$_2$O), 4.24 (ddd, 1H, $J = 0.60, 7.3, 9.1$ Hz, CH$_2$O), 4.09-4.14 (m, 1H, CHCH$_3$), 3.93 (dd, 1H, $J = 2.5, 6.4$ Hz, CH(OTBS)CHOC), 3.80 (m, 1H, CHOTBS), 3.39 (s, 3H, CHOCH$_3$), 3.35 (ddd, 1H, $J = 1.7, 4.4, 10.2$ Hz, CHOME), 3.29 (dd, 1H, $J = 3.3, 13.3$ Hz, CH$_2$Ph), 2.75 (dd, 1H, $J = 6.8$ Hz, CH$_2$CH=CH$_2$), 2.00-2.07 (m, 1H, CH$_2$CH=CH$_2$), 1.61-1.74 (m, 2H, CH$_2$CHOME, CH$_2$CHOCH), 1.25-1.39 (m, 2H, CH$_2$CHOME, CH$_2$CHOCH), 1.33 (s, 3H, CCH$_3$), 1.32 (d, 3H, $J = 6.8$ Hz, CH$_3$CHC(O)), 1.29 (s, 3H, CCH$_3$), 0.89 (s, 9H, SiC(CH$_3$)$_3$), 0.067 (s, 3H, Si(CH$_3$)$_2$), 0.048, (s, 3H, Si(CH$_3$)$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$(ppm) 185.1, 176.0, 136.2, 135.3, 129.5, 129.0, 127.4, 116.6, 100.4, 80.1, 71.7, 70.1, 68.2, 63.3, 60.5, 58.6,
42.7, 37.6, 36.5, 36.3, 35.7, 25.9, 24.5, 18.2, 13.3, -4.4, -4.5; HRMS (FAB) m/z (M+H)^+
calcd for C_{32}H_{51}NO_{6}Si, 605.3206; obsd 605.3230. (Reference DG-VII-290)
6-(tert-Butyl-dimethyl-silanyloxy)-3-hydroxy-5-methoxy-non-8-enoic acid methoxy-methyl-amide, 2.73. In a solution of THF (20 mL) were dissolved alcohol 2.72 (305mg, 0.88 mmol) and Weinreb’s salt (215mg, 2.20 mmol). The mixture was then cooled to -30°C prior to dropwise addition of iPrMgCl (2.20 mL, 2.0M in THF) over a 45 minute period. Following the addition of the iPrMgCl, the reaction was warmed to 0°C and monitored by TLC. Once completed, the reaction was quenched with Sat. NH₄Cl solution (10 mL). The organics were extracted with ethyl acetate (3 x 15ml) combined and dried over MgSO₄, filtered and concentrated. The crude product was purified via column chromatography (hexanes:EtOAc, 2:1) to afford 2.73 (270mg, 0.719 mmol, 82%) as a colorless oil. [α]D<sup>20</sup> -5.7° (c 4.7, CHCl₃); <sup>1</sup>H NMR (500 MHz, CDCl₃) δ(ppm) 5.84 (tdd, 1H, J = 7.2, 10.0, 17.4 Hz, CH=CH₂), 5.00-5.08 (m, 2H, CH=CH₂), 4.20 (tt, 1H, J = 2.9, 9.1 Hz, CHOH), 3.82 (td, 1H, J = 4.2, 8.4 Hz, CHOTBS), 3.67 (s, 3H, NOCH₃), 3.47 (ddd, 1H, J = 2.7, 4.5, 9.4 Hz, CHOMe), 3.43 (s, 3H, CHOCH₃), 3.18 (s, 3H, NCH₃), 2.49-2.67 (m, 2H, CH₂C(O)N), 2.29-2.36 (m, 1H, CH₂CH=CH₂), 2.10 (ddd, 1H, J = 0.9, 8.1, 14.2 Hz, CH₂CH=CH₂), 1.76 (ddd, 1H, J = 2.6, 9.7, 13.6 Hz, CH₂CHOMe), 1.44-1.50 (m, 1H, CH₂CHOMe), 0.88 (s, 9H, Si(CH₃)₃), 0.076 (s, 3H, Si(CH₃)₂), 0.052, (s, 3H, Si(CH₃)₂); <sup>13</sup>C NMR (125 MHz, CDCl₃) δ(ppm) 173.7, 135.9, 116.7, 80.5, 72.2, 65.1, 61.2, 58.7, 38.8, 36.6, 36.3, 31.8, 25.8, 18.1, -4.4, -4.5; HRMS (FAB) m/z (M+H)<sup>+</sup> calcd for C<sub>18</sub>H<sub>37</sub>NO₅Si, 376.2519; obsd 376.2541. (Reference DG-V-66 & 85)
6-(tert-Butyl-dimethyl-silanyloxy)-5-methoxy-3-(4-methoxy-benzyloxy)-non-8-enoic acid methoxy-methyl-amide, **2.74**. To a solution of alcohol 2.73 (270mg, 0.719 mmol) in dry ether (10 mL) was added p-methoxybenzyl imidate (305mg, 1.08 mmol). The imidate was quickly followed by dropwise addition of triflic acid (54 µL, 0.04M in Ether). The reaction was monitored by TLC over a 90 minute period. Upon consumption of the starting material, the reaction was quenched with Et₃N (1 mL) then concentrated under reduced pressure. The resulting crude oil was purified via column chromatography (hexanes:EtOAc, 2:1) to afford 2.74 (317mg, 0.639 mmol, 89%) as a colorless oil. [α]_D^{20} -15.9° (c 4.1, CHCl₃); ^1H NMR (500 MHz, CDCl₃) δ (ppm) 7.25 (d, 2H, J = 7.7 Hz, OPMB), 6.85 (d, 2H, J = 8.7 Hz, OPMB), 5.82 (dtdd, 1H, J = 1.6, 7.2, 10.0, 17.2 Hz, CH=CH₂), 4.90-5.07 (m, 2H, CH=CH₂), 4.54 (d, 1H, J = 11.1 Hz, OPMB), 4.44 (dd, 1H, J = 2.1, 11.0 Hz, OPMB), 4.07-4.13 (m, 1H, CHOPMB), 3.77-3.84 (m, 1H, CHOTBS), 3.79 (s, 3H, OPMB), 3.66 (s, 3H, NOCH₃), 3.33-3.38 (m, 1H, CHOMe), 3.29 (s, 3H, CHOCH₃), 3.19 (s, 3H, NCH₃), 2.89 (dd, 1H, J = 5.6, 14.8 Hz, CH₂C(O)N), 2.54 (dd, 1H, J = 5.8, 15.0 Hz, CH₂C(O)N), 2.31 (dddd, 1H, J = 1.4, 3.6, 6.7, 12.1 Hz, CH₂CH=CH₂), 2.01-2.08 (m, 1H, CH₂CH=CH₂), 1.82-1.89 (m, 1H, CH₂CHOMe), 1.52 (ddd, 1H, J = 3.7, 10.4, 14.4 Hz, CH₂CHOMe), 0.87 (s, 9H, SiC(CH₃)₃), 0.045 (s, 3H, Si(CH₃)₂), 0.038 (s, 3H, Si(CH₃)₂); ^13C NMR (125 MHz, CDCl₃) δ (ppm) 172.5, 159.0, 136.2, 130.9, 129.3, 116.6, 113.6, 80.3, 73.6, 71.6, 71.4,
61.2, 57.8, 55.3, 38.0, 36.3, 35.0, 32.0, 25.8, 25.8, 18.1, -4.4, -4.5; HRMS (FAB) m/z 

(M+H)^+ calcd for C_{26}H_{46}O_6NSi, 496.3094; obsd 496.3142. (Reference DG-V-86)
8-(tert-Butyl-dimethyl-silanyloxy)-7-methoxy-5-(4-methoxy-benzyloxy)-undec-10-en-3-one, 2.57. A solution of amide 2.74 (37mg, 0.075mmol) in THF (2 mL) was prepared and cooled to 0°C. Ethyl magnesium bromide (26 mL, 3.0M in Et₂O) was added via dropwise addition over five minutes. The reaction was allowed to warm to room temperature while monitoring with TLC. Depending on the quality of the EtMgBr, a second addition may be necessary. Once completed, the reaction was quenched with Sat. NH₄Cl solution (1 mL). The organics were extracted with Et₂O (3 x 5 mL), combined and washed with Brine solution (5ml), dried over MgSO₄, filtered and concentrated. The crude product was purified via column chromatography (hexanes:EtOAc, 3:1) to afford 2.57 (18mg, 0.038 mmol, 52%) as a colorless oil.

[α]D²⁰ -20.5° (c 1.1, CHCl₃); IR (film cm⁻¹) 3071.7, 2955.6, 2929.7, 2856.8, 1715.0, 1513.9, 1249.3, 1100.8, 1037.2, 835.6, 808.6, 776.0; ¹H NMR (500 MHz, CDCl₃) δ(ppm) 7.23 (d, 2H, J = 8.3 Hz, OPMB), 6.85 (d, 2H, J = 8.3 Hz, OPMB), 5.78-5.87 (m, 1H, CH=CH₂), 5.00-5.08 (m, 2H, CH=CH₂), 4.45 (ab quartet, 2H, J = 10.9 Hz, OPMB), 4.08 (ddd, 1H, J = 4.9, 7.7, 12.6 Hz, CHOPMB), 3.80-3.84 (m, 1H, C₃H₃OTBS), 3.32 (ddd, 1H, J = 1.4, 4.4, 10.1 Hz, CHOMe), 3.29 (s, 3H, CHOCH₃), 2.75 (dd, 1H, J = 6.9, 15.8 Hz, CH₂C(O)CH₂CH₃), 2.58 (dd, 1H, J = 5.1, 15.6 Hz, CH₂C(O)CH₂CH₃), 2.44 (q, 2H, J = 7.2, 7.4 Hz, C(O)CH₂CH₃), 2.26-2.33 (m, 1H, CH₂CH=CH₂), 2.01-2.08 (m, 1H, CH₂CH=CH₂), 1.87 (ddd, 1H, J = 1.4, 8.3, 14.3 Hz, CH₃CHOMe), 1.39-1.46 (m, 1H, CH₂CHOMe), 1.04 (dt, 3H, J = 0.70, 7.3 Hz, C(O)CH₂CH₃), 0.88 (s, 9H, SiC(CH₃)₃), 0.046 (s, 3H, Si(CH₃)₂), 0.042, (s, 3H,
Si(CH$_3$)$_2$; $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ (ppm) 210.1, 159.1, 136.1, 130.8, 129.3, 116.6, 113.7, 80.4, 73.3, 71.4, 71.3, 57.8, 55.2, 48.4, 37.1, 36.2, 34.6, 25.8, 18.1, 7.6, -4.4, -4.5; HRMS (FAB) m/z (M+H)$^+$ calcld for C$_{26}$H$_{44}$O$_3$Si, 465.3036; obsd 465.2752.
Compound **2.69** (5.7g, 14.7 mmol) was dissolved in THF (200 mL) and cooled to -10° C. A solution of Borane-THF Complex (36.7 mL, 1M in THF) was added dropwise over 30 minutes. Upon consumption of the starting material as observed by TLC the reaction was quenched with methanol addition until gas evolution ceased. A solution of NaOH (90 mL, 3.0M in H₂O) was added followed by H₂O₂ (60 mL, 30% solution in H₂O). The reaction was allowed to warm to 0°C for 30 minutes then room temperature for 45 minutes. Brine (50 mL) was added to the reaction then extracted with ethyl acetate (3 x 75 mL). The organics were combined, dried over MgSO₄, filtered, and concentrated. The crude product was purified via column chromatography (hexanes:EtOAc, 5:1) to afford **2.79** (4.73g, 11.6 mmol, 79%) as a colorless oil. [α]D²⁰ -25.1° (c 10.8, CHCl₃); IR (film cm⁻¹) 3368.6, 2954.8, 2929.3, 2857.9, 1472.2, 1255.9, 1099.0, 835.2, 774.3; ¹H NMR (500 MHz, CDCl₃) δ(ppm) 3.80 (ddd, 1H, J = 3.0, 4.8, 8.2 Hz, CHOTBS), 3.70 (dd, 2H, J = 4.7, 7.8 Hz, CH₂OTBS), 3.64 (dt, 2H, J = 2.1, 6.3 Hz, CH₂OH), 3.38 (s, 3H, OCH₃), 3.35 (ddd, 1H, J = 2.7, 5.0, 9.6 Hz, CHOMe), 1.78-1.86 (m, 1H, CH₂CH₂OTBS), 1.52-1.76 (m, 3H, CH₂CH₂OTBS & CH₂CHOTBS), 1.38-1.51 (m, 2H, CH₂CH₂OH), 0.89 (s, 18H, SiC(CH₃)₃), 0.086 (s, 3H, Si(CH₃)₂), 0.077, (s, 3H, Si(CH₃)₂), 0.049 (s, 3H, Si(CH₃)₂), 0.044, (s, 3H, Si(CH₃)₂); ¹³C NMR (125 MHz, CDCl₃) δ(ppm) 80.2, 72.1, 63.2, 59.6, 58.5, 32.1, 29.3, 28.0, 26.0, 25.9, 18.3, 18.1, -4.4, -4.6, -5.3, -5.4; HRMS (FAB) m/z (M+H)⁺ calcd for C₂₀H₄₆O₄Si₂, 407.3013; obsd 407.3026. (Reference DG-VI-110 & 193)
4,7-Bis-(tert-butyl-dimethyl-silanyloxy)-5-methoxy-heptanal, 2.80. To a solution of CH$_2$Cl$_2$ (60 mL) at -78°C was added oxalyl chloride (1.09 ml, 12.7 mmol) followed by DMSO (1.69 mL, 23.8 mmol) dissolved in CH$_2$Cl$_2$ (10 mL). After 15 minutes, dropwise addition of alcohol 2.79 (4.7g, 11.6 mmol) dissolved in CH$_2$Cl$_2$ (30ml). The reaction was stirred for 45 minutes then DIPEA (9.62 mL, 58 mmol) was added. The reaction was allowed to warm to room temperature and monitored by TLC. H$_2$O (20 mL) quench followed by ether dilution (50 mL). The layers were separated and the aqueous layer was extracted with ether (3 x 20 mL). The organics were combined then washed with H$_2$O (25ml), Sat. NaHSO$_4$ solution (25 mL), Brine (25 mL), dried over MgSO$_4$, filtered, and concentrated. The crude product was purified via column chromatography (hexanes:EtOAc, 10:1) to afford 2.80 (4.15g, 10.3 mmol, 88%) as a colorless oil. [α]$_D^{20}$ -29.3° (c 4.3, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) δ(ppm) 9.78 (t, 1H, J = 1.6 Hz, CH$_2$CHO), 3.84 (ddd, 1H, J = 3.6, 4.6, 8.4 Hz, CHOTBS), 3.71 (dd, 2H, J = 4.5, 8.0 Hz, CH$_2$OTBS), 3.38 (s, 3H, CHOCH$_3$), 3.34 (ddd, 1H, J = 2.7, 4.8, 9.9 Hz, CHOMe), 2.43-2.58 (m, 2H, CH$_2$CHO), 1.91 (ddddd, 1H, J = 3.5, 6.6, 8.8, 14.1 Hz, CH$_2$CHOTBS), 1.79-1.86 (m, 1H, CH$_2$CHOTBS), 1.64 (ddt, 1H, J = 6.0, 8.6, 14.5 Hz, CH$_2$CH$_2$OTBS), 1.47 (tdd, 1H, J = 4.5, 9.8, 14.3 Hz, CH$_2$CH$_2$OTBS), 0.89 (s, 18H, SiC(CH$_3$)$_3$), 0.080 (s, 3H, Si(CH$_3$)$_2$), 0.060, (s, 3H, Si(CH$_3$)$_2$), 0.048 (s, 3H, Si(CH$_3$)$_2$), 0.043, (s, 3H, Si(CH$_3$)$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$) δ(ppm) 202.5, 80.0, 70.7, 59.5, 58.3, 40.5, 31.8, 25.9, 25.8, 23.8, 18.3, 17.9, -4.3, -4.6, -5.4, -5.5; HRMS (FAB) m/z
(M+H)$^+$ calcd for $\text{C}_{20}\text{H}_{44}\text{O}_4\text{Si}_2$, 405.2856; obsd 405.2832. (Reference DG-VI-112 & 157)
6,9-Bis-(tert-butyl-dimethyl-silanyloxy)-7-methoxy-non-2-yne, 2.81. To a solution of (trimethylsilyl)diazomethane (0.520 mL, 2.0 M in Hexanes) in THF (5 mL) at -78°C was added n-BuLi (0.515 mL, 2.1 M in Hexanes) dropwise over 5 minutes. The solution was stirred at the same temperature for 30 minutes before slow addition of aldehyde 2.80 (350 mg, 0.866 mmol) in THF (5 mL). The reaction was then stirred for one hour at -78°C, then 1.5 hours at 0°C before quenching with H2O (5 mL). The layers were separated and the aqueous layer extracted with ether (2 x 5 mL). The organics were then washed with brine (5 mL), dried over MgSO4, filtered, and concentrated. The crude product was carried onto the next step without further purification. [α]D20  -33.9° (c 2.5, CHCl3); IR (film cm⁻¹) 3315.0, 2956.9, 2930.0, 2858.1, 1472.2, 1257.4, 1100.2, 836.0, 775.2; ¹H NMR (300 MHz, CDCl3) δ (ppm) 4.0, (ddd, 1H, J = 3.0, 4.4, 9.1 Hz, CHOTBS), 3.71 (dd, 2H, J = 4.6, 8.0 Hz, CH2OTBS), 3.40 (s, 3H, CHOCH3), 3.35 (ddd, 1H, J = 2.2, 4.4, 7.1 Hz, CHOMe), 2.15-2.40 (m, 2H, CH2CCH), 1.96 (t, 1H, J = 2.6 Hz, CH2CCH), 1.72-1.91 (m, 2H, CH2CHOMe), 1.39-1.60 (m, 2H, CH2CHOTBS), 0.91 (s, 18H, SiC(CH3)3), 0.11 (s, 6H, Si(CH3)2), 0.060 (s, 3H, Si(CH3)2), 0.055 (s, 3H, Si(CH3)2); ¹³C NMR (125 MHz, CDCl3) δ (ppm) 84.7, 80.1, 69.9, 68.7, 59.9, 58.3, 32.0, 30.2, 26.2, 26.1, 18.6, 18.3, 15.4, -4.1, -4.5, -5.1, -5.2; HRMS (FAB) m/z (M-CH3OH)+ calcd for C20H40O3Si2, 367.2489; obsd 367.2502. (Reference DG-VI-11)

The crude alkyne was diluted with THF (10 mL) and cooled to -78°C. Dropwise addition of n-BuLi (0.910 mL, 2.1 M in Hexanes) produced a dark orange solution. After 40 minutes at -78°C, MeI (0.270 mL, 4.33 mmol) was added and the reaction was
allowed to warm to room temperature. After two hours, the reaction was recooled to 0°C and quenched with distilled H$_2$O (5 mL). The layers were separated and the aqueous layer extracted with ether (2 x 5 mL). The organics were combined and washed with brine (5 mL), dried over MgSO$_4$, filtered, and concentrated. The crude product was purified via column chromatography (hexanes:EtOAc, 15:1) to afford **2.81** (265 mg, 0.641 mmol, 74%) as a colorless oil. [α]$_D^{20}$ -39.7° (c 1.31, CHDCl$_3$); IR (film cm$^{-1}$) 2956.5, 2929.6, 2857.9, 1256.4, 1101.6, 1079.4, 836.0, 774.9; $^1$H NMR (500 MHz, CDCl$_3$) δ (ppm) 3.96 (ddd, 1H, $J$ = 3.0, 4.5, 9.1 Hz, CHOTBS), 3.70 (dd, 2H, $J$ = 4.6, 8.0 Hz, CH$_2$OTBS), 3.38 (s, 3H, CHOCH$_3$), 3.32 (ddd, 1H, $J$ = 2.5, 4.5, 9.9 Hz, CHOME), 3.18-3.19 (m, 1H, CH$_2$CCCH$_3$), 2.09-2.18 (m, 1H, CH$_2$CCCH$_3$), 1.83 (dt, 1H, $J$ = 2.5, 8.1, 14.0 Hz, CH$_2$CHOME), 1.77 (t, 3H, $J$ = 2.6 Hz, CH$_2$CCCH$_3$), 1.71 (dt, 1H, $J$ = 2.9, 8.2, 13.5 Hz, CH$_2$CHOME), 1.41-1.51 (m, 2H, CH$_2$CHOTBS), 0.893 (s, 9H, SiC(CH$_3$)$_3$), 0.887 (s, 9H, SiC(CH$_3$)$_3$), 0.087 (s, 3H, Si(CH$_3$)$_2$), 0.085, (s, 3H, Si(CH$_3$)$_2$), 0.046 (s, 3H, Si(CH$_3$)$_2$), 0.041 (s, 3H, Si(CH$_3$)$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$) δ (ppm) 80.1, 79.3, 75.9, 70.2, 59.9, 58.3, 32.1, 30.8, 26.2, 26.1, 18.6, 18.3, 15.7, 3.7, -4.1, -4.5, -5.1, -5.2; HRMS (FAB) m/z (M+H)$^+$ calcd for C$_{22}$H$_{46}$O$_3$Si$_2$, 415.3064; obsd 415.3076. (Reference DG-VI-11 & 12)
6,9-Bis-(tert-butyl-dimethyl-silylxyloxy)-2-iodo-7-methoxy-non-2-ene, 3.32.

Alkyne 3.31 (109mg, 0.263 mmol) was dissolved in dry THF (1.5 mL) at room temperature. Freshly prepared Schwartz reagent (135mg, 0.526 mmol) was added in one portion leading to observed gas evolution. The reaction flask was covered with foil and heated to 50°C over 15 minutes. The reaction was then maintained at 50-55°C for 45 minutes and monitored by TLC. After 45 minutes, the reaction was cooled to room temperature for 5 minutes before cooling to -35°C. N-iodosuccimide (118mg, 0.526 mmol) dissolved in THF (0.5 mL) was added dropwise to the reaction changing the color from orange to dark red. After 30 minutes, the reaction was warmed to room temperature diluted with ethyl acetate (20 mL) washed with sat. NaHSO₃ solution (15 mL), sat. NaHCO₃ solution (15 mL), brine solution (10 mL), dried over MgSO₄, filtered, and concentrated. The crude product was purified via column chromatography (hexanes:EtOAc, 20:1) to afford 3.32 (104mg, 0.192 mmol, 73%, 9:1 mixture of isomers) as a colorless oil. \[^{20}\alpha\]D \(\ ^{20}\) -24.1° (c 1.8, CHCl₃); IR (film cm\(^{-1}\)) 2954.7, 2927.9, 2856.4, 1472.0, 1256.7, 1100.7, 835.5, 774.3; \(^1\)H NMR (500 MHz, CDCl₃) δ (ppm) 6.19 (dt, 1H, \( J = 1.4, 7.4 \) Hz, \( \text{CH} = \text{C(I)CH}_3 \)), 3.77-3.80 (m, 1H, CHOTBS), 3.72 (dd, 2H, \( J = 4.6 \), 8.0 Hz, \( \text{CH}_2\text{OTBS} \)), 3.40 (s, 3H, CHOCH₃), 3.34 (ddd, 1H, \( J = 2.7 \), 4.6, 9.8 Hz, CHOMe), 2.93 (bs, 3H, CH=C(C(I)CH₃)), 2.17-2.26 (m, 1H, CH₂CH=C(C(I)CH₃)), 1.96-2.05 (m, 1H, CH₂CH=C(C(I)CH₃)), 1.79-1.87 (m, 1H, CH₂CHOMe), 1.59-1.66 (m, 1H, CH₂CHOMe), 1.35-1.55 (m, 2H, CH₂CHOTBS), 0.923 (s, 9H, SiC(CH₃)₃), 0.919 (s, 9H, SiC(CH₃)₃), 0.106 (s, 3H, Si(CH₃)₂), 0.092, (s, 3H, Si(CH₃)₂), 0.077 (s, 3H, Si(CH₃)₂), 0.072 (s, 3H,
Si(CH₃)₂; \(^{13}\)C NMR (125 MHz, CDCl₃) \(^{\delta}\) (ppm) 141.2, 93.6, 80.0, 71.3, 59.6, 58.4, 32.0, 30.7, 27.5, 27.3, 26.0, 25.9, 18.3, 18.0, -4.3, -4.7, -5.3, -5.4; HRMS (FAB) m/z (M+H)^+ calcd for C\(_{22}\)H\(_{47}\)IO\(_3\)Si\(_2\), 543.2187; obsd 543.2175. (Reference DG-VII-170)
4-(tert-Butyl-dimethyl-silanyloxy)-8-iodo-3-methoxy-non-7-en-1-ol, 3.33. To a solution of 3.32 (265mg, 0.489mmol) dissolved in methanol (5 mL) was added camphorsulfonic acid (11.4mg, 0.0489 mmol) at room temperature. The reaction was stirred and closely monitored by TLC. After 15 minutes, the reaction was quenched with Et$_3$N (1.5 mL). Solvent was removed under reduced pressure resulting in a crude oil which was further purified via column chromatography (hexanes:EtOAc, 3:1) to afford 3.33 (160mg, 0.374 mmol, 76%) as a colorless oil. [α]$_D^{20}$ -28.8° (c 3.9, CHCl$_3$); IR (film cm$^{-1}$) 3400.6, 2929.0, 2856.9, 1471.1, 1255.9, 1103.7, 1055.8, 836.2, 775.0; $^1$H NMR (500 MHz, CDCl$_3$) δ(ppm) 6.19 (qt, 1H, $J$ = 1.4, 1.39, 7.37 Hz, CH=C(I)CH$_3$), 3.84 (ddd, 1H, $J$ = 3.2, 4.3, 8.7 Hz, CHOTBS), 3.77 (ddd, 2H, $J$ = 1.3, 4.7, 6.4 Hz, CH$_2$OH), 3.43 (s, 3H, CHOCH$_3$), 3.34 (td, 1H, $J$ = 4.4, 8.7 Hz, CHOCH$_3$), 2.40 (bs, 3H, CH=C(I)CH$_3$), 2.18-2.27 (m, 1H, CH$_2$CH=C(I)CH$_3$), 1.97-2.05 (m, 1H, CH$_2$CH=C(I)CH$_3$), 1.83-1.89 (m, 1H, CH$_2$CHOH), 1.62-1.72 (m, 2H, CH$_2$CHOH & CH$_2$CHOTBS), 1.47 (dddd, 1H, $J$ = 5.2, 8.8, 10.2, 13.9 Hz, CH$_2$CHOTBS), 0.93 (s, 9H, Si(CH$_3$)$_3$), 0.012 (s, 3H, Si(CH$_3$)$_2$), 0.011, (s, 3H, Si(CH$_3$)$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$) δ(ppm) 140.8, 83.9, 71.0, 61.3, 57.9, 31.1, 30.5, 27.5, 27.3, 25.8, 25.7, 18.0, -4.3, -4.6; HRMS (FAB) m/z (M+H)$^+$ calcd for C$_{16}$H$_{33}$IO$_3$Si, 429.1322; obsd 429.1336. (Reference DG-VII-181)
4-(tert-Butyl-dimethyl-silanyloxy)-8-iodo-3-methoxy-non-7-enal, 3.34. To a solution of alcohol 3.33 (160mg, 0.374 mmol) in CH$_2$Cl$_2$ (5 mL) was added 4Å molecular sieves. The sieves and alcohol 3.33 were stirred for five minutes before NMO (175mg, 1.50 mmol) and TPAP (6.6mg, 0.0187 mmol) were added. The reaction was then monitored by TLC. Upon completion after 20 minutes, nearly all of the solvent was removed under reduced pressure followed by column chromatography yielding aldehyde 3.34 (109mg, 0.256mmol, 68%) as a colorless oil. $[\alpha]_D^{20}$ -17.1° (c 2.4, CHCl$_3$); IR (film cm$^{-1}$) 2929.3, 2856.9, 1728.4, 1694.1, 1462.5, 1255.6, 1105.1, 836.4, 775.8; $^1$H NMR (500 MHz, CDCl$_3$) δ (ppm) 9.82 (dd, 1H, $J$ = 1.5, 2.3 Hz, CH$_2$CHO), 6.16 (qt, 1H, $J$ = 1.5, 7.4 Hz, CH=C(I)CH$_3$), 3.38 (s, 3H, OMe), 2.67 (ddd, 1H, $J$ = 1.5, 3.6, 4.4, 8.3 Hz, CH$_2$CHO), 2.16-2.25 (m, 1H, CH$_2$CH=C(I)CH$_3$), 1.93-2.02 (m, 1H, CH$_2$CH=C(I)CH$_3$), 1.61-1.69 (m, 1H, CH$_2$CHOTBS), 0.88 (s, 9H, SiC(CH$_3$)$_3$), 0.083 (s, 6H, Si(CH$_3$)$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$) δ (ppm) 201.0, 140.6, 78.5, 70.7, 58.0, 43.5, 30.4, 27.5, 27.3, 25.8, 25.7, 17.9, -4.3, -4.7; HRMS (FAB) m/z (M+H)$^+$ calcd for C$_{16}$H$_{31}$IO$_3$Si, 427.1166; obsd 427.1147. (Reference DG-VII-182)
2,4,13-Tris-(tert-butyl-dimethyl-silylamoxy)-10-hydroxy-17-iodo-1,12-dimethoxy-5,7-dimethyl-6-triethylsilylamoxy-octadec-16-en-8-one, 3.35. To a solution of THF (2.0 mL) at 0°C was added hexamethyldisilazane (0.510 mL, 2.40 mmol) followed by dropwise addition of n-BuLi (1.15 mL, 2.1M in Hexanes). The resulting mixture was stirred for 30 minutes at 0°C. TMSCl (0.865, 6.77 mmol) was added to a separate flame dried flask and was quickly followed by slow addition of Et$_3$N (0.951 mL, 6.77 mmol) resulting in gas evolution and a white slurry. In a third flame dried flask, ketone 3.4 (235 mg, 0.398 mmol) was dissolved in THF (3.0 mL) and cooled to -78°C. Approximately half of the Et$_3$N-TMSCl slurry was added to the ketone followed by half of the LiHMDS solution. After 30 minutes at -78°C, the balance of the Et$_3$N-TMC1 and LiHMDS solution were added consecutively. The reaction was stirred for an additional hour before being quenched with pH 7.0 buffer (5 mL). The reaction was further diluted with Et$_2$O (10 mL). The layers were separated and the aqueous layer extracted with ether (3 x 5 mL). The organics were then dried over MgSO$_4$, filtered, and concentrated. The crude oil can be further purified on a neutralized silica column if desired. The crude enol silane 3.18 was placed under the high vacuum pump for two hours prior to use in the Mukaiyama aldol condensation.
In a flame dried, nitrogen flushed flask, aldehyde **3.34** (260mg, 0.610 mmol) was dissolved in CH$_2$Cl$_2$ (5 mL) containing 4Å molecular sieves. The flask was cooled to 0°C before enol silane **3.18** (894mg, 1.35 mmol) dissolved in CH$_2$Cl$_2$ (5 mL) was added. The mixture was stirred for one hour over the molecular sieves prior to cooling further to -78°C. Dropwise addition of BF$_3$•OEt$_2$ (77µL, 0.610 mmol) was followed by careful monitoring via TLC. Upon consumption of the aldehyde, the reaction was quenched by pouring the contents into a separatory funnel containing Sat. NaHCO$_3$ solution (25 mL). The organics were extracted with CH$_2$Cl$_2$ (3 x 15 mL) then combined, washed with Brine solution (15 mL), dried over MgSO$_4$, and condensed under reduced pressure. The resulting crude oil was further purified via column chromatography (hexanes:EtOAc, 10:1) to afford **3.35** (459mg, 0.451 mmol, 74%) as a colorless oil. 

$[\alpha]_{D}^{20}$ -18.6° (c 2.3, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ (ppm) 6.17 (dt, 1H, $J = 1.5, 7.5$ Hz), 4.24 (dd, 1H, $J = 1.7, 7.4$ Hz), 4.14-4.21 (m, 1H), 3.93 (ddd, 1H, $J = 1.6, 4.5, 9.3$ Hz), 3.77-3.81 (m, 1H), 3.67-3.73 (m, 1H), 3.44-3.49 (m, 1H), 3.42 (s, 3H), 3.35 (s, 3H), 3.30 (d, 2H, $J = 4.8, 9.7$ Hz), 2.60-2.70 (m, 3H), 2.38 (bs, 3H), 2.16-2.25 (m, 1H), 1.95-2.04 (m, 1H), 1.60-1.86 (m, 5H), 1.35-1.44 (m, 2H), 1.10 (d, 3H, $J = 7.0$ Hz), 0.94 (t, 9H, $J = 7.9$ Hz), 0.91 (s, 9H), 0.892 (s, 9H), 0.888 (s, 9H), 0.84 (d, 3H, $J = 7.0$ Hz), 0.56-0.62 (m, 6H), 0.111 (s, 3H), 0.104 (s, 3H), 0.086 (s, 3H), 0.079 (s, 3H), 0.076 (s, 3H), 0.072 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ (ppm) 213.9, 141.0, 93.8, 80.5, 76.8, 72.9, 71.5, 70.0, 69.4, 64.8, 58.9, 58.6, 50.1, 48.1, 43.1, 40.8, 36.0, 31.6, 30.8, 27.5, 27.3, 26.1, 25.9, 25.86, 22.7, s 18.3, 18.2, 18.0, 14.1, 9.7, 9.6, 7.1, 5.6, -2.8, -4.0, -4.3; HRMS (FAB) m/z (M-OTBS)$^+$ calcd for C$_{40}$H$_{82}$O$_7$Si$_3$, 885.4413; obsd 885.4387.
REFERENCES


