2014

Exploring a ring-closing metathesis approach to the archazolids

Brianne R. King
Western Washington University

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Exploring a Ring-Closing Metathesis Approach to the Archazolids

By

Brianne R. King

Accepted in Partial Completion
Of the Requirements of the Degree
Master of Science

Kathleen L. Kitto, Dean of the Graduate School

Advisory Committee

Chair, Dr. Gregory W. O’Neil

Dr. James Vyvyan

Dr. Jeff Young
MASTER’S THESIS

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Brianne King
May 7th, 2014
Exploring a Ring-Closing Metathesis Approach to the Archazolids

A Thesis
Presented to
The Faculty of
Western Washington University

In Partial Fulfillment
Of the Requirements for the Degree
Master of Science

By
Brianne R. King
May 2014
Abstract

The archazolids are a complex family of natural products with distinct structural features. Inspired by these unique structural characteristics, our group sought to synthesize an analogue of this family, dihydroarchazolid B. We were encouraged to synthesize this analogue due to its high potential to be a potent cytotoxic agent against the vacuolar-type ATPases (V-ATPases) and because it is a simpler analogue than the parent natural products from a synthetic perspective. Within this work, a ring-closing metathesis (RCM) approach was explored in depth towards the completion of our target. From these efforts, a metathesis deactivating stereotriad was uncovered in a key fragment needed for ring closure. Using the knowledge uncovered in our synthetic endeavors, a possible relay-ring closure event is discussed. The synthetic utility of exploring the effects of contiguous remote functionality on alkene reactivity is also demonstrated as knowledge of this type will better inform our future synthetic challenges.
## Acknowledgements

**Research Advisor:** Dr. Gregory W. O’Neil

**Thesis Committee Members:** Dr. James Vyvyan  
Dr. Jeff Young

**Project Contributors:** Sara Schaefer, Steven Swick, Jamie Welch, Leanne Sebren, Ann Tran, Geoff Melly, Matthew Black

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**Instrument Technicians:** Charles Wandler  
Dr. Hla Win-Piazza

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<tbody>
<tr>
<td>Ac</td>
<td>Acyl</td>
</tr>
<tr>
<td>Aq</td>
<td>Aqueous</td>
</tr>
<tr>
<td>Boc</td>
<td>Di-tert-butyl-carboxylate</td>
</tr>
<tr>
<td>BOP</td>
<td>(Benzotriazol-1-yl oxy)tris(dimethylamino)phosphonium hexafluorophosphate</td>
</tr>
<tr>
<td>Bu</td>
<td>Butyl</td>
</tr>
<tr>
<td>Bz</td>
<td>Benzyl</td>
</tr>
<tr>
<td>CBS</td>
<td>Corey-Bakshi-Shibata</td>
</tr>
<tr>
<td>CDI</td>
<td>Carbonyl diimidazole</td>
</tr>
<tr>
<td>$c$Hex</td>
<td>Cyclo hexane</td>
</tr>
<tr>
<td>CM</td>
<td>Cross metathesis</td>
</tr>
<tr>
<td>COSY</td>
<td>Correlation spectroscopy</td>
</tr>
<tr>
<td>Cp</td>
<td>Cyclopentyl</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DIBAl-H</td>
<td>Diisobutyl aluminum hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMP</td>
<td>Dess-Martin periodinane</td>
</tr>
<tr>
<td>dr</td>
<td>Diastereomeric ratio</td>
</tr>
<tr>
<td>er</td>
<td>Entantiomeric ratio</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>$Et_2O$</td>
<td>Diethyl ether</td>
</tr>
<tr>
<td>EtO</td>
<td>Ethoxy</td>
</tr>
<tr>
<td>EtOAc</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>GH</td>
<td>Grubb’s Hoveyda</td>
</tr>
<tr>
<td>GHII</td>
<td>Grubb’s Hoveyda second generation</td>
</tr>
<tr>
<td>GI</td>
<td>Grubb’s first generation</td>
</tr>
<tr>
<td>GII</td>
<td>Grubb’s second generation</td>
</tr>
<tr>
<td>HMQC</td>
<td>Heteronuclear multiple-quantum correlation</td>
</tr>
<tr>
<td>HWE</td>
<td>Horner-Wadsworth-Emmons</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>IC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>50% inhibitory concentration</td>
</tr>
<tr>
<td>Ipc</td>
<td>isopinocampheylchloro</td>
</tr>
<tr>
<td>'Pr</td>
<td>isopropyl</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>KHMDS</td>
<td>Potassium hexamethyldisilazide</td>
</tr>
<tr>
<td>L-929</td>
<td>Murine leukemia cell line 929</td>
</tr>
<tr>
<td>LiHMD</td>
<td>Lithium hexamethyldisilazide</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>MeLi</td>
<td>Methyl lithium</td>
</tr>
<tr>
<td>MeMgBr</td>
<td>Methyl magnesium bromide</td>
</tr>
<tr>
<td>MHz</td>
<td>Megahertz</td>
</tr>
<tr>
<td>Mmol</td>
<td>Millimole</td>
</tr>
<tr>
<td>MTBE</td>
<td>Methyl-tert-butyl-ether</td>
</tr>
<tr>
<td>n-BuLi</td>
<td>n-Butyllithium</td>
</tr>
<tr>
<td>NEt&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Triethyl amine</td>
</tr>
<tr>
<td>NHC</td>
<td>N-heterocyclic carbine</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>PhCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Toluene</td>
</tr>
<tr>
<td>PMB</td>
<td>p-methoxy benzyl</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>RCM</td>
<td>Ring closing metathesis</td>
</tr>
<tr>
<td>ROM</td>
<td>Ring-opening metathesis</td>
</tr>
<tr>
<td>ROMP</td>
<td>Ring-opening metathesis polymerization</td>
</tr>
<tr>
<td>RRCM</td>
<td>Relay ring-opening metathesis</td>
</tr>
<tr>
<td>rt</td>
<td>Room temperature</td>
</tr>
<tr>
<td>S</td>
<td>Schrock</td>
</tr>
<tr>
<td>SAR</td>
<td>Structure activity relationship</td>
</tr>
<tr>
<td>Sat.</td>
<td>Saturated</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------</td>
</tr>
<tr>
<td>TBACl</td>
<td>Tetrabutylammonium chloride</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-Butyldiphenylsilyl</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-Butyldimethyl silyl</td>
</tr>
<tr>
<td>rBuOH</td>
<td>tert-Butyl alcohol</td>
</tr>
<tr>
<td>TES</td>
<td>Triethylsilyl</td>
</tr>
<tr>
<td>Tf</td>
<td>Triflate</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TIPS</td>
<td>Triisopropylsilyl</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
</tbody>
</table>
Chapter 1. Introduction

1.1 Isolation and Structural Determination of the Archazolid Natural Products

The archazolid family of natural products comprises six members (A-F) sharing distinct structural features (Figure 1-1). The unique architecture of the archazolids is characterized by a 24-membered macrolactone ring with a thiazole side chain, seven alkenes ($2E,5E,9Z,11Z,13E,18E,20E$), and a sequence of eight methyl- and hydroxyl-bearing stereocenters.\(^1\) During a screening for new, biologically active metabolites in from myxobacteria in 1993, Sasse et al. found a strain of *Archangium gephyra* that showed high cytotoxic activity in a screening assay with L929 mouse fibroblasts. This activity was attributed to two new related compounds which they called archazolid A and B.\(^2\) The planar structures of A and B were elucidated by Höfle and Steinmetz on the basis of $^1H$ and $^{13}C$ NMR, COSY, NOE, and HMQC data in 2003. These structures were confirmed by analysis of a $^{13}C$-labeled sample of archazolid A obtained by the feeding of $^{13}C$-enriched acetate and methionine to *Archangium gephyra*.\(^3\) The absolute and relative stereochemistry of archazolid A and B were determined by Menche et al. in 2006 by high field NMR studies in combination with molecular modeling and derivatization.\(^1\) This was followed by synthetic confirmation of archazolid A and B in 2007 by Menche et al. and Trauner et al., respectively.\(^4,5\) Perhaps inspired by interesting structural features and biological properties, the search for novel structural analogues of this interesting family of natural products continued. *A. gephyra* is the source for archazolid A, B and F, while another myxobacterial strain, *Cystobacter violaceus*, produces glycosylated archazolids C, D, and E.\(^6,7,8\) The archazolids are important synthetic targets due to their ability to
inhibit vacuolar-type ATPases (V-ATPases). Inhibition of this molecular target is important in cancer research, which will be discussed in detail in the next section.

1.2 Biological Importance of the Archazolids: V-ATPase Inhibition

V-ATPases are a family of complex multisubunit ATP-dependent proton pumps that regulate pH in endomembrane systems (Figure 1-2). V-ATPases are found in intracellular organelles (lysosomes, endosomes, and secretory vesicles) and the plasma membrane. The V-ATPase plays an important role in the endocytosis pathway and trafficking of receptor-ligand complexes by acidifying intracellular organelles as well as the extracellular space. V-ATPases contain two major domains: the cytoplasmic V₁ domain, and the membrane bound V₀ domain. The V₁ domain is comprised of 8 subunits.
(A-H) and is responsible for ATP-hydrolysis. The $V_o$ domain is comprised of subunits a, d, e, and six c subunits ($c$, $c'$, $c''$). The c subunits, each composed of 4 alpha-helices, form a $H^+$- binding rotor responsible for transporting protons from the cytoplasm to the endosomal/lysosomal lumen or to the extracellular space.$^{11}$

**Figure 1-2.** The V-ATPase.

In recent years, it has been observed that an overexpression of the V-ATPase on the plasma membrane correlates with an invasive phenotype of cancer cells.$^{12}$ This overexpression creates an acidic extracellular pH, which is known to be a key factor in activating proteases involved in tumor cell invasion.$^{13}$ Taken together, these data show that V-ATPase upregulation and overexpression is a well-designed compensatory mechanism that leads to survival and growth advantages in cancer cells.
Consequently, inhibitors of the V-ATPase could be promising and novel anticancer therapeutics and several inhibitors have been developed in order to study the effect of V-ATPase inhibition. Two well-studied inhibitors are concanamycin and bafilomycin, members of the plecomacrolide antibiotic family of natural products (Figure 1-3). The plecomacrolides are a subset of the polyketides, where the term “pleco”

![Bafilomycin A1](image)

L-929 IC$_{50}$ = 3.2 nM

![Concanamycin A](image)

L-929 IC$_{50}$ = 0.23 nM

**Figure 1-3.** Plecomacrolide natural products bafilomycin and concanamycin.

meaning “1 fold” describes their unique secondary structure formed by the polyketide chain that is pendant to the macrolactone core. They are typically found with 16 or 18-membered macrolactone cores. At concentrations in the nanomolar range, bafilomycin and concanamycin are highly specific V-ATPase inhibitors and have been used to study
processes such as endocytosis and exocytosis. However, detailed information on the signaling pathways affected by V-ATPase inhibition is limited for these molecules and others. The archazolids have since emerged as superior V-ATPase inhibitors, in that they are potent and highly selective toward V-ATPases (Table 1-1). Bafilomycin and concanamycin directly impair the function of the mitochondria via interactions with phosphorylation ATPases (P-ATPases) at concentrations in the macromolar range, an effect not observed when treating isolated rat liver cells with archazolid B. These differences can be attributed to the unique molecular mechanism of action of the plecomacrolides and the archazolids. The plecomacrolides bind between two c subunits, whereas the archazolids bind within a single c subunit (Figure 1-4). The archazolids have since emerged over other V-ATPase inhibitors as powerful chemical tools in deciphering the role of the V-ATPase in tumor environments.

Table 1-1. IC$_{50}$ values for the archazolid natural products against murine cell line L-929.

<table>
<thead>
<tr>
<th>Archazolid</th>
<th>IC$_{50}$ [nM]</th>
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<tbody>
<tr>
<td>A</td>
<td>0.81</td>
</tr>
<tr>
<td>B</td>
<td>1.1</td>
</tr>
<tr>
<td>C</td>
<td>1600</td>
</tr>
<tr>
<td>D</td>
<td>330</td>
</tr>
<tr>
<td>E</td>
<td>510</td>
</tr>
<tr>
<td>F</td>
<td>0.11</td>
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</tbody>
</table>
Three studies by Vollmar and et al. have been published in the last two years that highlight the use of the archazolids and seek to define the effects of cancer cell V-ATPase inhibition at the specific cell signaling level. In 2012, it was found that pretreatment of cancer cells with archazolid A effectively decreases metastasis of breast tumors by impairing the trafficking and activation of EGFR and Rho-GTPase Rac1, both of which are pivotal for the movement of cells. In 2013, cell death induction involving archazolid B activating the cellular stress response was demonstrated. Also in 2013, it was shown that V-ATPase inhibition by archazolid leads to apoptosis and growth inhibition of the trastuzumab-resistant cell line JIMT-1 in vitro as well as in vivo. Inhibition of HER2 related signaling and a reduced expression of HER2 on the cell
surface accompany this effect. It was demonstrated that archazolid inhibits growth of 
trastuzumab-resistant tumor cells by targeting HER2 via a mechanism different from 
direct binding to the receptor and that the V-ATPase could thus serve as a promising 
target for the treatment of trastuzumab-resistant tumors.²¹

Clearly, the V-ATPase serves as an important therapeutic target for cancer 
research, and the archazolids are emerging as powerful chemical tools in order to gain a 
clearer understanding of the role of the V-ATPase in tumor environments. The 
archazolids are thus important synthetic targets to this end, and the following section will 
discuss the current routes available towards archazolid A and archazolid B, respectively.
Chapter 2. Previous Syntheses of the Archazolids

2.1 Synthesis of Archazolid A

In 2007, Menche and Hassfeld successfully synthesized archazolid A in 20 steps with a 4% overall yield (longest linear sequence). Their synthetic approach relied on assembly of three main building blocks of similar complexity, as presented in the retrosynthetic plan in Scheme 2-1.22

Scheme 2-1. Menche’s retrosynthetic approach to archazolid A.

The 13E-alkene was envisioned to arise from an aldol condensation between 2 and 3, while the 18E,20E diene was planned to arise from a Heck coupling of 2 with 4. A Horner-Wadsworth-Emmons (HWE) olefination was used to deliver the final macrocyclic ring. This synthesis is flexible in that esterification could also be employed
for ring-closure. This modular total synthesis offers potential for developing large quantities of archazolid A as well as structural analogues for SAR studies.\[^{23}\]

The synthesis of the C\textsubscript{3}-C\textsubscript{11} fragment 3 (Scheme 2-2) began with an anti-selective boron-mediated Paterson aldol reaction with 5 and aldehyde 6 to set the stereocenters at C\textsubscript{7} and C\textsubscript{8} in 7.\[^{24}\] TBS protection followed by reduction and periodate cleavage afforded aldehyde 8 in 85\% over three steps. Aldehyde 8 was subjected to a Still-Gennari modified HWE with phosphonate 9 to give 10 containing the 13E-alkene.\[^{25}\] Following conversion of 10 to enal 11 using DIBAl-H and allylic oxidation with MnO\textsubscript{2}, a second Still-Gennari HWE was employed to install the 11E-alkene with high stereoselectivity. Fragment 3 was completed with a DIBAl-H reduction of the ester followed by oxidation of the resulting primary alcohol using Dess-Martin periodinane.

**Scheme 2-2.** Synthesis of fragment 3.
The synthesis of 2 (Scheme 2-3) began with a LiAlH₄ reduction and allylic oxidation (MnO₂) of vinyl iodide 13²⁶ to give aldehyde 14. An Abiko-Masamune anti-aldol reaction was highlighted as a pivotal step to install the stereocenters at C₁₆ and C₁₇.²⁷ After methylation of the secondary alcohol in 16 with silver oxide and methyl iodide, the ephedrine auxiliary was removed reductively with LiAlH₄ to give 17, which was converted to 2 via DMP oxidation, addition of MeMgBr, and DMP oxidation.

**Scheme 2-3. Synthesis of fragment 2.**

Preparation of 4 began with α-hydroxyacid 18 being converted into thioamide 19 in four steps via amide formation, TBS protection, and treatment with Lawesson reagent (Scheme 2-4). Thiazole 21 was formed via cyclization of thioamide 19 with 20, the free hydroxyl was liberated with TBAF, and the carbamate was installed over two steps. In a subsequent publication regarding the modular total synthesis of archazolids A and B, the authors note that epimerization of the hydroxyl group occurred upon thiazole formation (*).²⁸ This was remedied by re-oxidation with DMP and a selective CBS reduction. This issue, however, was not reported in the initial synthesis of archazolid A. Following formation of 22, a DIBAl-H reduction was performed to give the corresponding
aldehyde. A Brown’s asymmetric crotylation gave alcohol 4 with excellent diastereoselectivity and a moderate yield of 65%.\textsuperscript{29}

**Scheme 2-4.** Synthesis of fragment 4.

The strategy for fragment coupling relied on first joining methyl ketone 2 and aldehyde 3 and was carried out using a boron-mediated aldol condensation (Scheme 2-5). The subsequent Heck reaction of 24 with 4 gave 25 with 6:1 E/Z selectivity after careful optimization of reaction conditions. When performed at elevated temperatures (80°C), some isomerization at the 11Z-alkene was observed. It was reported that this minor stereoisomer could be removed post-macrocyclization. Following addition of phosphonate 26 with use of BOP, PMB removal, and Swern oxidation, 27 was cyclized successfully using NaH. CBS reduction of the ketone at C15 gave the desired stereochemistry in high diastereoselectivity ($ds > 20:1$).\textsuperscript{30} The final step to form 1 was removal of the secondary TBS group using HF/pyridine in THF (80%). This first total synthesis confirmed original
relative and absolute configuration proposals based on spectral data comparison with an authentic sample of archazolid A. \textsuperscript{31}

**Scheme 2-5.** Completion of the archazolid A synthesis.
2.2 Synthesis of Archazolid B

Inspired by remarkable bioactivity and interesting structural features, Trauner, Roethle, and Chen sought to synthesize archazolid B (28) by employing a Hoye relay ring-closing metathesis (RRCM), a Stille coupling, and a Kita esterification as shown in retrosynthetic scheme 2-6. Three main building blocks (29, 30, and 4) lead to a highly convergent synthesis with a 19 step longest linear sequence and highlights the use of several transition metal-mediated transformations.

**Scheme 2-6. Retrosynthesis of archazolid B by Trauner et al.**

![Scheme 2-6](image)

The northeastern building block 30 was synthesized beginning with the formation of known ynone 33 from the available (S)-Roche ester (32) (Scheme 2-7). Alkyne 33 underwent a highly diastereoselective reduction with (S)-alpine borane to give a propargylic alcohol, which was protected with triisopropylsilyl ether and then selectively desilylated to give primary alcohol 34. Oxidation to the corresponding aldehyde with Dess-Martin periodinane and the first step in the Corey-Fuchs
transformation (a special example of the Wittig involving formation of a dibromocarbene) was subsequently used to obtain 35. A Tanino and Miyashiti method for installation of a Z vinyl iodide was employed followed by exchange of the secondary silyl protecting group for a tert-butylcarbonate provided 36.34 A highly selective Trost Alder-ene reaction with 3-butenol afforded triene 37.35 Oxidation of allylic alcohol 37 to the corresponding aldehyde with Dess-Martin periodinane followed by Pinnick oxidation gave allylic carboxylic acid 30.

**Scheme 2-7. Synthesis of fragment 30.**

The synthesis of the southwestern thiazole fragment 4 commenced from the known hydroxylalkyl thiazolecarboxylate 38 (available from leucine in 6 steps, the same sequence to form 21).36 Carbamoylation with carbonyldiimidazole/ methyl amine,
followed by selective reduction of the ester to an aldehyde and a Brown crotylation gave multigram quantities of the fragment (Scheme 2-8). \(^8\)

**Scheme 2-8.** Synthesis of fragment 4.

The synthesis of fragment 29 began with obtaining iodide 39 in three steps from propargyl alcohol. Reduction of the ester with DIBAI-H followed by oxidation with Dess-Martin periodinane gave the corresponding aldehyde, which underwent an Evans syn-aldol addition with the boron enolate of benzyl oxazolidinone 40 to give 41. Transformation to the Weinreb amide followed by silyl protection of the secondary alcohol and a phosphonate Claisen reaction gave \(\beta\)-keto phosphonate 42. A HWE olefination with enal 43 afforded dienone 44, which then underwent a diastereoselective NaBH\(_4\) reduction followed by esterification and iodine-tin exchange to give fragment 29 (Scheme 2-9).

**Scheme 2-9.** Synthesis of fragment 29.
Base-mediated esterification between 30 and 4 resulted in migration of the C\textsubscript{2}-C\textsubscript{3} double bond, and so required a Ru-catalyzed activation of 30 as the acyl ketene acetal, as described by Kita\textsuperscript{37}, to give 45. Subsequent thermal deprotection of the Boc group gave iodide 46, which was then subjected to a modified Liebskind coupling with vinyl stannane 29 to give the metathesis precursor 47.\textsuperscript{38} The RRCM (this reaction is discussed in detail in Section 3.3.4) proceeded in a 27% yield followed by deprotection of the secondary alcohol gave archazolid B (28) (Scheme 2-10).\textsuperscript{39}

**Scheme 2-10.** Completion of the synthesis of archazolid B.
2.3 Modular Total Synthesis of Archazolid A and B

In 2009, Menche and Hassfelf presented a modular total synthesis of archazolid A (1) and B (28), developed from the previously reported synthetic strategy. Much of the synthesis of key fragments presented above (2-4) remained the same, but thorough optimization of reaction procedures resulted in revision of key transformations. The retrosynthesis remained the same, with the key difference being use of phosphonate 26 or 48 leading to archazolid A or B, respectively (Scheme 2-11).

**Scheme 2-11.** Revised retrosynthesis for modular approach to archazolids A and B.

For the synthesis of building block 4, it was reported that the previous method for installing the thiazole ring resulted in epimerization of the free hydroxyl stereocenter. This was remedied by oxidation of 21 (mixture of stereoisomers) to the corresponding ketone 49 followed by reduction with (R)-CBS to give enantiopure 21 (Scheme 2-12). The synthesis of 21 to fragment 4 was unchanged.
**Scheme 2-12.** Revised strategy for synthesis of 21.

Synthesis of building block 2 was reevaluated due to the lengthy stepwise procedure previously reported for removal of the Abiki-Masamune auxiliary. It was found that activation of the ester carbonyl by coordination to the free hydroxyl using a Lewis acid allowed promotion of nucleophilic attack of Weinreb amide 50 to give 51 (Scheme 2-13). Best results were obtained with the use of \( \text{t-PrMgCl} \) as the coordinating Lewis acid. With this method, the chiral auxiliary can be recovered, adding to the atom economy of the process. Weinreb amide 51 could be transformed to methyl ketone 2 in two steps (74%).

**Scheme 2-13.** Revised strategy for synthesis of fragment 2.

Unreported in the original synthesis of archazolid A, macrocyclization of 27 to 1 with base resulted in a marked propensity for the anti-configured bonds (C7/C8 and
C\textsubscript{16}/C\textsubscript{17}) to undergo elimination and thus presented a challenge in affording the final ring structure (Figure 2-1). This was overcome serendipitously by use of molecular sieves that were present from the drying of the starting material. It is proposed that the molecular sieves are essential in this process possibly due to the slightly acidic nature of the additive. Completion of the synthesis of 1 after macrocyclization proceeded as previously reported.

![Figure 2-1](image.png)

**Figure 2-1.** Positions C\textsubscript{7}-C\textsubscript{8} and C\textsubscript{16}-C\textsubscript{17} were prone to elimination under mild reaction conditions

To demonstrate the modularity of their synthetic approach, synthesis of 28 was approached using a different order in the fragment coupling processes. This involved an intermolecular HWE of phosphonate 52 (afforded by the addition of phosphonate 48 with BOP to building block 4) and aldehyde 53 (afforded by deprotecting the primary PMB group on 24 followed by Swern oxidation). Following the HWE olefination, an intramolecular Heck macrocyclization was performed, following CBS reduction and HF/pyridine removal of the secondary TBS group to give 28 (Scheme 2-14).
Scheme 2-14. Completion of the synthesis of archazolid B (28).

2.4 Highly stereo- and regioselective approach to the C₉-C₁₂ fragment of the archazolids.

In 2007, Negishi and Huang described an elegant approach to the synthetically challenging C₉-C₁₂ (Z,Z)-1,1,3,4-tetrasubstituted 1,3-diene present in the macrocyclic core of the archazolids. This was accomplished by a 1-halo-1-alkyne hydroboration followed by migratory insertion of 55 and a Zn-promoted transmetalative iodonolysis to give 58. A Pd-catalyzed cross coupling with alkenyl zinc of type 59 and 58 gave the desired
conjugated triene 60 in good yields (83% for 60a; 81% for 60b) (Scheme 2-15). Two protocols described (Zn-II and Zn-III) have provided potential intermediates for the synthesis of the archazolids as isomerically ≥98% pure compounds. To date this group has not published any further synthetic work on the archazolids.

**Scheme 2-15.** Negishi and Huang’s synthesis of the C₉-C₁₂ triene fragment of the archazolids.

![Chemical structure diagram]

2.5 Synthesis of the Eastern fragment of archazolid A

A synthesis of the “Eastern” fragment (C₃-C₁₄) of archazolid A as defined by the retrosynthesis in Scheme 2-16 was described by our group in 2009. The retrosynthetic analysis, including a macrocycle formation by ring-closing metathesis (RCM) at C₁₃-C₁₄ and olefination at C₂-C₃, necessitated the formation of a previously unknown Z,Z-
terminal triene 61. This was envisioned to arise from a tandem allylation/elimination sequence between 63 and aldehyde 62.

**Scheme 2-16.** O’Neil group’s planned retrosynthesis of archazolid A.

The synthesis of 61 began with ester 64, prepared as a separable mixture along with lactone 65 from 4-hydroxy-2-butanone. TBS protection and DIBAI-H reduction to the corresponding primary alcohol 66 was followed by oxidation to the aldehyde (MnO$_2$) and an *anti*-selective brown crotylation to give 68. To set the stage for the allylation/elimination sequence, the free hydroxyl was acylated with methacryloyl chloride followed by RCM with 5 mol % Grubbs’ second-generation catalyst (GII) to form the C$_9$–C$_{10}$ trisubstituted *cis*-alkene embedded in lactone 69 (Scheme 2-17).
Scheme 2-17. Completion of lactone 69 for allylation/elimination sequence.

\[
\begin{align*}
\text{HO-} \rightarrow \overset{\text{ref.}}{\text{65}} & \quad \overset{\text{1. TBSCl, imid.}}{\text{64}} \quad \overset{\text{2. DIBAL-H}}{\text{66}} \\
\text{HO} & \quad \text{TBSO} \\
\text{1. MnO}_2\text{, Et}_2O & \quad \text{TBSO} \\
2. (\text{--})\text{(IPc)}_2B & \quad \text{TBSO}
\end{align*}
\]

Lactone 69 was partially reduced with DIBAL-H to the corresponding lactol 71, in equilibrium with the aldehyde 70. This equilibrium mixture was immediately treated with an \textit{in situ} prepared allylzirconocene 72 and, using basic work-up conditions, the intermediate zirconium alkoxide underwent a \textit{syn} Peterson-type elimination\textsuperscript{42} to give Eastern fragment 61 in 68\% yield with a 4:1 \textit{Z}:\textit{E} selectivity (Scheme 2-18).

Scheme 2-18. Completion of Eastern fragment synthesis.
Chapter 3: Retrosynthetic Plan and Review of Olefin Metathesis

3.1 Retrosynthesis

Structure activity relationship (SAR) studies with natural and synthetic analogues have been limited for the archazolid family of natural products. However, as the six members of this family have been identified, it has become clear which area of the molecule is important for activity. In 2011 Horstmann and Menche published the discovery and isolation archazolids E and F, the most recent additions to the pool of structurally novel analogues of archazolid A and B. In this work, they presented findings regarding the activity of the various members in relation to functional group differences. Looking at the activities in Table 3-1, it is observed that all glucosylated archazolids have a higher L-929 growth inhibition IC\textsubscript{50} value (e.g. are less potent) than

<table>
<thead>
<tr>
<th>Table 3-1. IC\textsubscript{50} values of the archazolids.</th>
</tr>
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| growth inhibition L-929: IC\textsubscript{50} [nM]|%
| archazolid A | 0.81 |
| archazolid B | 1.1 |
| archazolid C | 1600 |
| archazolid D | 330 |
| archazolid E | 510 |
| archazolid F | 0.11 |

A (R\textsuperscript{1} = H, R\textsuperscript{2} = Me, R\textsuperscript{3} = H, R\textsuperscript{4} = Me), Δ\textsuperscript{2,3}
B (R\textsuperscript{1} = H, R\textsuperscript{2} = Me, R\textsuperscript{3} = H, R\textsuperscript{4} = H), Δ\textsuperscript{2,3}
C (R\textsuperscript{1} = H, R\textsuperscript{2} = Me, R\textsuperscript{3} = β-glucoside, R\textsuperscript{4} = Me), Δ\textsuperscript{2,3}
D (R\textsuperscript{1} = H, R\textsuperscript{2} = CH\textsubscript{2}OH, R\textsuperscript{3} = β-glucoside, R\textsuperscript{4} = Me), Δ\textsuperscript{2,3}
E (R\textsuperscript{1} = β-glucoside, R\textsuperscript{2} = Me, R\textsuperscript{3} = H, R\textsuperscript{4} = Me), Δ\textsuperscript{2,3}
F (R\textsuperscript{1} = H, R\textsuperscript{2} = Me, R\textsuperscript{3} = H, R\textsuperscript{4} = H), Δ\textsuperscript{3,4}
the parent archazolids A and B. C_{15}-O-\beta\text{-}glucosylated archazolid E is less potent than A or B, but 3 times more potent than the corresponding C_{7}-O-\beta\text{-}glucosylated archazolid E. This suggests that the C_{15}-OH may not be as important for binding compared with the C_{7}-OH, which is in agreement with previous results obtained for a C_{15}-oxo derivative.\textsuperscript{44} Taken together, these data suggest the fragment between C_{7} and C_{15} to be part of the pharmacophore region of the archazolids that is involved in binding and activity with the V-ATPase. In contrast to this, archazolid F, or iso-archazolid B, is 10 times more potent than archazolid A or B with an IC_{50} in the subnanomolar range. These data indicate a degree of structural flexibility in the C_{1} to C_{4} region is possible while maintaining potency.

SAR studies can be done by simplifying a complex molecule in order to create a more expedient synthetic route.\textsuperscript{45} A logical structural analogue to create is dihydroarchazolid B (archDhB) (Figure 3-1). In removing the double bond in the C_{1} to C_{4} region, it allows us access to a more convergent synthesis by shifting the disconnection point to the lactone moiety as opposed to a HWE disconnection between C_{2} and C_{3}, as previously planned for the synthesis of archazolid A.\textsuperscript{46} This simplification also allows us to avoid instability issues potentially caused by the enone present in archazolid B (the least stable member of the family).
Our retrosynthetic plan presented in Scheme 3-1 relies on two key disconnections to give fragments of similar complexity. Western fragment $W_1$ and Eastern fragment $E_1$ are envisioned to be coupled by esterification adjacent to $C_1$ followed by RCM between $C_{13}$ and $C_{14}$. With our retrosynthetic strategy towards archDhB analogue hinging on macrocycle formation via RCM, a discussion of the details and importance of metathesis in synthesis is important. The purpose of the following sections is to briefly review alkene metathesis beginning with a general overview of catalysts and mechanism, followed by a discussion of the various transformations afforded by employing this technique. Alkene reactivity categorization for the prediction of metathesis outcomes will then be discussed in the context of our synthetic plan.
3.2. Alkene Metathesis

Much progress in the field of organic chemistry is dependent on the ability to construct carbon frameworks through carbon-carbon bond formation. The synthetic chemist has a toolbox of reactions to facilitate this, for example: the Grignard\textsuperscript{47}, Wittig\textsuperscript{48}, and Diels-Alder\textsuperscript{49} reactions. More recently, two additional carbon-carbon bond forming processes have been developed: palladium-catalyzed cross coupling and olefin metathesis reactions (both of which have resulted in two recent Nobel prizes). Metathesis reactions have reshaped the landscape of synthetic organic chemistry, arguably more than any other single process, over the last 15 years\textsuperscript{50}.

Alkenes can be rationalized as two alkylidene (=CHR) groups combined via a double bond and metathesis is defined as any reaction that exchanges these alkylidene groups. Figure 3-2 shows a general schematic for the interchanging of groups in alkene metathesis.
3.3 Metathesis Catalysts

The outcome of olefin metathesis is sensitive to several factors. A very important consideration in performing these reactions is choice of catalyst. The first metathesis process, described in the 1950s, used an aluminum/molybdenum catalyst whose exact structure is unknown. Metathesis catalysts (Figure 3-3) were undefined “black box” entities until 1990, when Schrock and coworkers developed molybdenum catalyst S. The introduction of catalyst S was a groundbreaking advancement in catalyst design because it tolerated a wider range of functional groups than earlier undefined catalysts. In recent years, it has been found to be useful for the formation of sterically crowded systems. The prominent drawback of S is its marked sensitivity to oxygen and moisture as well as to polar or protic functional groups. In 1992, Grubbs and coworkers developed the ruthenium-based catalyst GI (Grubbs 1st-generation catalyst). Catalyst GI tolerates a wider range of functional groups and is less oxygen and moisture sensitive (does not require a glove box, as is the case for S).
Further catalyst re-design involving the specific tuning of auxiliary ligands bound to the ruthenium led to the Grubbs 2nd Generation catalyst GII. The replacement of one of the phosphine ligands with an N-heterocyclic carbene ligand led to an increase in catalytic activity, thermal stability, and functional group tolerance.\textsuperscript{56,57} A valuable alternative to GII that provides further stability and better reactivity is the Grubbs-Hoveyda catalyst GH, where the benzylidene ligand has a chelated ortho-isopropoxy group in place of the phosphine ligand.\textsuperscript{58} The broad utility of alkene metathesis is due largely to the superb selectivity and high functional group compatibility of these ruthenium based catalysts but the search for more efficient and selective catalysts is ongoing.\textsuperscript{59}

\textbf{Figure 3-3.} Commonly used metathesis catalysts.
3.4 Alkene Metathesis Mechanism

The generally accepted mechanism of alkene metathesis was originally proposed and published by Chauvin and Hérisson in 1971. Experimental evidence in the Casey, Katz, and Grubbs groups provided validation for this mechanism. It is important to note that the term “catalyst” refers to a chemical entity in a reaction that is regenerated after each “cycle” of a reaction. In alkene metathesis, the original catalyst is not regenerated. Instead, the metal center serves as an “initiator” for each metathesis event. This “initiator” species serves as the active catalyst. In the case of the Grubbs catalysts, styrene is released upon engagement of one of the alkene substrates. In successive cycles, ethylene is generated after each metathesis event. This is evident in the catalytic cycle of alkene metathesis (Scheme 3-2). Key intermediates in the catalytic cycle are a metal carbene (I, III) and a metallocyclobutane (II, IV). The starting point for the catalytic cycle is metal carbene Ru-I after the initial release of styrene and the first metathesis event to form a new alkene between R\textsuperscript{1} and R\textsuperscript{2}. This metal carbene reacts with the first alkene partner containing R\textsuperscript{1} to generate metallocyclobutane Ru-II. Upon formation of metal carbene Ru-III, ethylene is released and the alkene partner containing R\textsuperscript{2} can interact with Ru-III to form metallocyclobutane Ru-IV. The original metal carbene Ru-I is then regenerated and the new alkene is liberated from the cycle. This cycle continues until either the reaction is quenched (with an excess of an alkene partner resulting in an inactive catalyst, for example) or the lifetime of the catalyst expires.

Scheme 3-2. Metathesis active catalyst initiation and catalytic cycle.
3.5 Types of Transformations in Alkene Metathesis

3.5.1 Cross Metathesis

Scheme 3-3. General scheme for cross metathesis

\[ \text{catalyst} \]

Alkene cross metathesis (CM) is a convenient route to functionalized and higher olefins from simpler alkene precursors. Di-, tri- and even tetra-substituted alkenes can be accessed via this route.\(^{64,65}\) A general scheme is shown (Scheme 3-3) for CM of two terminal alkenes to create a heterodimer and two homodimers. The major issues with CM are that homodimerization must be controlled to attain useful yields of the heterodimer CM product and \(E/Z\) ratios are difficult to control and predict. These issues have prevented CM from sharing the same spotlight as other metathesis transformations. As a wealth of new data has emerged over the last decade, however, models have been developed that can predict the outcome of these metathesis events.\(^{66}\) Along with the introduction GII, this prediction model (discussed in detail below) has allowed for CM to be highlighted in the synthesis of several complex natural products. As an example, Prunet et al. presented two key CM events in their synthesis of dolabelide C, for example (Figure 3-4).\(^{67}\)
Figure 3-4. Dolabelide C.

Scheme 3-4. CM to form trisubstituted alkenes.

Treatment of the \textit{gem}-disubstituted alkene D1 with boronate B1 in the presence of GII (5 mol \%) afforded the corresponding vinyl iodide D2 with relative ease (Scheme 3-4). The downside to this reaction was the poor 2:1 \textit{E}/\textit{Z} selectivity. After iodination, the
C\textsubscript{1}-C\textsubscript{15} fragment could be isolated in 55% yield. The CM between enone D\textsubscript{3} and \textit{gem}-disubstituted alkene D\textsubscript{4} to form trisubstituted alkene D\textsubscript{5} was more challenging. Optimization experiments finally afforded the transformation that resulted in the C\textsubscript{16}-C\textsubscript{30} fragment in 49% yield as a mixture of 4:1 \textit{E}/\textit{Z} isomers.

### 3.5.2 Ring-Opening Metathesis

**Scheme 3-5.** Ring-opening metathesis polymerization.

Ring-opening metathesis (ROM) (Scheme 3-5) of cyclic olefins has been widely used for the process of “living” polymerization.\textsuperscript{68} ROM polymerization (ROMP) occurs with the use of a metathesis catalyst releasing ring strain to create two terminal alkenes that can then homodimerize with other ring-opened products in order to produce a polymeric chain. The attractiveness of ROM in synthesis is the ability to perform a ROM in tandem with a second transformation. In the presence of a second alkene partner, the opened ring undergoes a CM process (Scheme 3-6). The combination of ring-opening and cross metathesis (ROM-CM) is particularly useful for the selective cross coupling between strained bycyclic olefins and monosubstituted olefins.\textsuperscript{69} An interesting example of the usefulness of ROM taking advantage of ring strain is presented in the synthesis of (+)-asteriscanolide (Scheme 3-7).\textsuperscript{70} Treatment of cyclobutene Ast\textsubscript{1} with G\textsubscript{II} (5 mol \%,
50°C, 10h) in benzene under an ethylene atmosphere produced cylooctadiene Ast2 in 74% yield. The intermediate dialkyl cyclobutane formed initially by ROM proceeds with a facile Cope rearrangement to afford the desired ring structure present in the final target.

**Scheme 3-6.** ROM-CM.

**Scheme 3-7.** ROM in the total synthesis of (+)-asteriscanolide.
3.5.3 Ring-Closing Metathesis

Scheme 3-8. Ring closing metathesis.

One of the most powerful methods for ring closure is the ring closing metathesis reaction (RCM) (Scheme 3-8). RCM is simply a variation of alkene cross metathesis performed intramolecularly. This process has been particularly useful in allowing the closure of difficult to form rings, such as 7- and 8-membered rings. RCM has also found fame in multistep target-oriented synthesis as a seemingly endless collection of ring systems can be created with this method. Common, medium, large, carbocyclic or heterocyclic rings can be formed. Macrocyclizations using RCM are increasingly common in natural product synthesis.71 However, the product distribution of monomer and oligomers is often problematic in the formation of medium to large rings. Careful tuning of concentration, catalyst type, and temperature has been shown to have a significant impact on the outcome of the RCM product:oligomer ratio. This heedful optimization was performed successfully in the synthesis of the 16-membered macrolactone epothilone 490 by Yamamoto et al. (Scheme 3-9).72 During synthesis for SAR studies, it was found that increased steric bulk allylic to one of the terminal alkenes drastically decreased yield of desired product. By increasing the temperature and increasing dilution, this yield
improved greatly. If formation of the monomer is entropically favored over that of the
dimer, the kinetic ratio of the two products should shift toward the monomer at higher
temperature. This was indeed the case, and this methodology was applied to two other
independent and highly functionalized systems in the same study. This work highlights
the utility of RCM: substrate effects (steric bulk) can often be overcome by tuning
reaction conditions. A wide variety of macrocycles can thus be accessed via RCM to
create highly convergent syntheses where olefins are embedded in the ring system.
Chemists are emboldened to commit their molecules for ring closure events over CM,
where one may have to choose precious material to be subjected in excess in order to
favor desired product.

**Scheme 3-9.** Temperature and concentration optimization to achieve successful RCM.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Concentration</th>
<th>Yield of monomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₂Cl₂, 40°C, 6h</td>
<td>2 mM</td>
<td>20%</td>
</tr>
<tr>
<td>PhMe, 110°C, 20 min</td>
<td>0.5 mM</td>
<td>66%</td>
</tr>
</tbody>
</table>

3.5.4 Relay Ring-Closing Metathesis
Although RCM is a generally applicable method for ring closure, this applicability is not universal. Boundaries arise when attempting to apply this efficient technology to increasingly complex synthetic targets. In particular, RCM can fail when the substrate terminal alkenes are sterically hindered or electronically deactivated. The concept of a relay ring-closing metathesis (RRCM) was developed by the Hoye group nearly a decade ago (Scheme 3-10) and can circumvent these issues.73 The RRCM concept allows for directing metal movement throughout the RCM sequence and, in effect, allows the cyclization of otherwise unruly substrates. A relay tether can consist of an alkyl chain, typically 5 or 6 carbons in length, with a non-hindered terminal alkene such that, upon metal initiation with the relay terminal alkene, cyclization occurs quickly due the nature of 5- and 6-membered ring formation being a fast process. The relay tether serves to pass the metal into an otherwise inaccessible (sterically hindered or electronically deactivated) alkene through a sacrificial RCM process. In the example used by Hoye in 2004, diene H1 was unreactive to the GI catalyst and intermolecular incorporation of the ruthenium center was not possible. However, when modified relay substrate H2 was subjected to GI, intermediate H3 was formed, and a smooth cyclization resulted to give intermediate H4. The final cyclopentene H5 was formed quickly. RRCM serves as a nice compliment to traditional RCM, particularly in synthesis of complex macrocycles. Generally, these syntheses employ convergent and modular strategies such that installation of a relay tether becomes a relatively simple task, even when a RRCM strategy is not envisioned when a synthesis is first designed.
**Scheme 3-10.** RRCM approach to sterically hindered and deactivated olefins (E=CO$_2$Et).

This technology was highlighted in the synthesis of archazolid B by Trauner and coworkers in 2007 (Scheme 3-11).$^{74}$ In this example, an RRCM strategy was devised in order to minimize the partial complication of initial activation at C$_{21}$, from which they speculated that undesired cyclization to excise a δ-valerolactone might occur.
Scheme 3-11. RRCM highlighted in the synthesis of archazolid B.

3.6 Categorization of Alkenes for Predictable Reaction Outcomes

Alkene metathesis is an enormously powerful tool to the organic chemist and it is clear that endless synthetic possibilities exist when applying this methodology. As more synthetic challenges are overcome with metathesis, the pool of information regarding reaction optimization, catalyst selection, and substrate selection grows. In order to successfully input lessons from other researchers into individual synthetic goals, it is pertinent that there be some organization to the immense amount of information available. Chaterjee and Grubbs presented a general model for selectivity in cross
metathesis that will briefly be discussed here. This model systematically categorizes olefins in terms of their reactivity, and this can be used to predict both selective and non-selective CM reactions with catalysts having varying activities.

The complex interplay of steric and electronic factors determining the ability of sets of olefins to selectively undergo CM necessitated a direct and empirical ordering of olefin reactivity. The expedient method used for this ranking was inspection of the ability of olefins to homodimerize. Specifically, the ability of olefin homodimerization relative to other olefins was studied. This analysis led to a general model comprising four olefin types, I-IV (Figure 3-5). Type I olefins are those that can undergo rapid homodimerization, and whose homodimers can participate in CM. Type II olefins homodimerize slowly and their homodimers are sparingly consumed. Type III olefins do not homodimerize but are still able to undergo CM with Type I and Type II olefins. Type IV olefins are not able to participate in CM but do not inhibit catalyst activity towards other olefins. In summary, the gradient exists from Type I (most active) to Type IV (least active).

<table>
<thead>
<tr>
<th>Olefin Reactivity</th>
<th>Type I - Rapid Homodimerization, homodimers consumable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Type II - Slow homodimerization, homodimers sparingly consumable</td>
</tr>
<tr>
<td></td>
<td>Type III - No homodimerization</td>
</tr>
<tr>
<td></td>
<td>Type IV - Olefins inert to CM, but do not deactivate catalyst</td>
</tr>
</tbody>
</table>

Reaction between two olefins of Type I = Statistical CM
Reaction between two olefins of same type (non-Type I) = Non-selective
Reaction between olefins of two different types = Selective CM

**Figure 3-5.** Categorization of olefin reactivity and reaction predictions between olefin types.
A second component of this model that allows for outcome predictions in metathesis events is categorization of catalyst activity. While tuning of electronic or steric properties on an olefin (by use of different protecting groups, for example) can be sufficient to change reactivity, simply choosing a catalyst with different activity can elicit the same effect. GII is able to use stilbene, for example, as an efficient CM partner, whereas S and GI are not reactive towards this substrate.\textsuperscript{20}

This model can be applied CM with different combinations of olefins and allows for reaction predictability. In the CM of two Type I olefins, the rates of homodimerization are similar to the reaction rates of the homodimers. In reactions of this type, the desired product is equilibrated with the homodimers through secondary metathesis reactions and this gives a statistical product mixture. In order to provide 90\% of the CM product, one olefin must be in 10 equiv. excess relative to the other partner. To avoid these statistical mixtures, CM reactions can be designed using olefins of two different types. This is effective in selective CM because the rates of dimerization are significantly different/slower than the rate of product formation. In the combination of Type I olefins with Type II or Type III, the Type I olefin homodimerizes and then undergoes secondary metathesis with the Type II/III olefin. In the case of Type II and Type III olefins, where both dimerize at slower rates than product formation, selective CM can be carried out.
3.7 Retrosynthetic approach based on alkene reactivity

Alkene reactivity categorization was considered in our retrosynthetic plan for RCM between C\textsubscript{13} and C\textsubscript{14} due to the higher reactivity of monosubstituted (terminal) alkenes versus di-, tri-, and tetrasubstituted alkenes as noted in Chaterjee’s model. The general pattern that more substitution on a substrate decreases reactivity demonstrates that steric bulk prevents the incorporation of a metal carbenoid in the substrate. Our archazolid target contains only 2 disubstituted alkenes, and 4 trisubstituted alkenes (Figure 3-6). It was demonstrated in Trauner’s synthesis of archazolid B that an RCM to complete the macrocycle between C\textsubscript{20} and C\textsubscript{21} required the use of a relay (RRCM) to prevent unwanted methathesis events and resulted in a low yield (27%, Scheme 3-11). This example further bolstered our decision to make a retrosynthetic disconnection between C\textsubscript{13} and C\textsubscript{14}, along with the fact that our retrosynthetic disconnections result in two fragments of manageable size. It has also been demonstrated that allylic methyl groups can deactivate a substrate towards metathesis (C\textsubscript{22})\textsuperscript{75}, while allylic hydroxyl groups (C\textsubscript{15}) can have metathesis activating effects.\textsuperscript{76}

![Figure 3-6. Types of alkenes present in dihydroarchazolid B.](image)

\textsuperscript{75} Allylic methyl groups can deactivate a substrate towards metathesis. 
\textsuperscript{76} Allylic hydroxyl groups can have metathesis activating effects.
Chapter 4. Work Towards the Total Synthesis of Dihydroarchazolid B

The work presented here is focused on the synthesis of the Western fragment of archDhB towards a completion of the synthesis via esterification with the Eastern fragment E1 and macrocyclization. This chapter begins with the synthesis of the Western fragment as previously reported by the O’Neil group in 2011. While many of the reactions have previously been described, much of the work here has been focused on scaling up and optimizing these reactions. This discussion of reactions is followed by results from initial macrocyclization attempts, a redesign of the western fragment synthesis featuring a different protecting group strategy following these attempts, and subsequent RCM of this new substrate.

4.1 Synthesis of the Western Fragment

The Western fragment (W1) can be further broken down into two fragments, so-called Southwest (SW) and the Northwest (NW) fragments, by an organometallic addition. The fragment NW was envisioned to arise from a HWE olefination between phosphonate W3 and aldehyde W4 (Scheme 4-1).
Scheme 4-1. Retrosynthesis of the Western fragment.

The synthesis of $W_4$ began with a TBS protection of the readily available $(R)$-Roche ester followed by cold DIBAl-H reduction to the corresponding aldehyde $W_5$. Aldehyde $W_5$ underwent a Wittig olefination with the phosphorane $W_6$ to deliver the $E$-alkene geometry with an $E:Z$ ratio greater than 10:1 in $W_7$ (Scheme 4-2). This selectivity is due to the stability of the ylide as a result of electron withdrawing groups adjacent to the negatively charged carbanion formed from deprotonation. Reaction of a stabilized ylide is under thermodynamic control, and thus the thermodynamic trans-oxophosphetane and resulting $E$-alkene is obtained as the major product (for comparison, unstabilized ylides lead to the kinetic product, i.e., the $Z$-alkene, Scheme 4-3). $W_7$ was converted to the corresponding primary alcohol with a DIBAL-H reduction followed by Swern oxidation to give the aldehyde $W_4$ (72% over 3 steps).

\[ \text{(R)-Roche ester} \xrightarrow{1. \text{TBS-Cl, imidazole}} \text{TBSO} \text{W5} + \text{Ph}_3\text{P} = \text{O} \xrightarrow{\text{THF, r.t., 16 h}} \text{MeO} \xrightarrow{\text{DIBAL-H}} \text{W7} \xrightarrow{1. \text{DIBAL-H}} \text{W4} \]

Scheme 4-3. Stabilized ylides lead to the thermodynamic product.

The synthesis of phosphonate W3 began by acylating oxizoldinone W8 with propionyl chloride to give W9 in preparation for a titanium-mediated syn-Evan’s aldol reaction with acrolein (Scheme 4-4). The diastereoselectivity of the two newly formed stereocenters is determined by the transition state shown in Figure 4-1, where a Z-enolate

Scheme 4-4. Syn-Evan’s aldol.

\[ \text{O} \xrightarrow{\text{O}} \text{NH} + \text{Cl} \xrightarrow{n-\text{BuLi}} 80\% \rightarrow \text{O} \xrightarrow{\text{O}} \text{NH} + \text{H} \xrightarrow{\text{TiCl}_4, \text{TEA}, \text{NMP, DCM}} 80\% \rightarrow \text{O} \xrightarrow{\text{O}} \text{OH} \]
is exclusively formed, dipole minimization sets the position of the auxiliary group leading to the facial selectivity of aldehyde approach, and the R-group occupies a preferred equatorial position. Combined, this leads to the syn configuration of the methyl group and secondary alcohol in W10. Following the aldol reaction, the auxiliary group was cleaved by substitution with N,O-dimethylhydroxyl amine and TBS protected to give the Weinreb amide W11.\(^{80}\) From here, W11 was converted into the corresponding ketophosphonate W3 via amide displacement with diethyl ethyl phosphonate (Scheme 4-5).

**Scheme 4-5.** Synthesis of phosphonate W3.

To complete the NW fragment, a HWE\(^{81}\) olefination as described by Paterson was carried out between phosphonate W3 and aldehyde W4\(^{82}\) with Ba(OH)\(_2\).\(^{83}\) The cis
selectivity of this process is said to be enhanced by the microcrystalline structure of the barium hydroxide as well as the bulkiness of the phosphonate. Following the formation of \textbf{W12} from the HWE, a previously described selective NaBH$_4$ reduction$^{84}$ to give alcohol \textbf{W13} was followed by methylation with methyl triflate to afford methyl ether \textbf{NW} (Scheme 4-6).

**Scheme 4-6.** Synthesis of the NW fragment.

Fragment \textbf{SW} was synthesized beginning with selective lithium-halogen exchange of 2,4-dibromothiazole and subsequent organometallic addition into ethyl isovalerate derived Weinreb amide \textbf{W14}.$^{85}$ The resulting ketone \textbf{W15} was selectively reduced to the corresponding alcohol with (R)-(+)\text{-}CBS (ee >95%)$^{86}$ followed by TES protection to afford thiazole \textbf{SW} (Scheme 4-7).
Scheme 4-7. Synthesis of the SW fragment.

Selective primary TBS removal\textsuperscript{87} followed by mild Dess-Martin periodinane\textsuperscript{88} oxidation of fragment NW gave aldehyde W16, setting the stage for coupling with a fragment SW-derived organometallic reagent (Scheme 4-8).

Scheme 4-8. Selective deprotection of a primary TBS group.

Aldehyde W16 and fragment SW were coupled via organometallic addition after lithium halogen exchange on the bromothiazole. The resulting alcohol W17 was found to be a 2.5:1 (W17a:W17b) mixture of products in excess of the undesired diastereomer as a result of Felkin-control.\textsuperscript{89} Oxidation with Dess-Martin periodinane to the corresponding ketone followed by selective reduction to the desired diastereomer with L-Selectride remedied this.\textsuperscript{90} L-Selectride, in contrast to other reducing agents, was found to give the
best balance of yield to selectivity, with a 73% yield and a greater than 10:1 mixture of diastereomers (Scheme 4-9).

**Scheme 4-9.** Thiazole coupling and L-Selectride reduction.

Following acylation of alcohol **W17b**, the secondary TES protecting group was removed in the presence of the secondary TBS group to give alcohol **W19**. The carbamate was then added with methyl amine and carbonyldiimidazole and DIBAI-H was then used to deacylate the hydroxyl group at C23 and give **W1** (Scheme 4-10).
Scheme 4-10. Completion of the synthesis of W1

4.2 Fragment Coupling and RCM Results.

W1 was coupled with W2 via a Yamaguchi style esterification to give WE with a yield of 70% (Scheme 4-11).

Scheme 4-11. Yamaguchi esterification.

With the TBS protected WE in hand, RCM was attempted with a variety of conditions (Table 4-1). In all cases, we were not graced with the presence of the RCM product and observed either starting material or decomposition. Higher temperatures (80°C and 110°C in PhMe) led to more complex mixtures of products compared to
reactions performed at room temperature or 50°C. We attributed this result to the bulky TBS group flanking the C_{14} terminal olefin preventing catalyst engagement at that position (Scheme 4-12). To remedy this, we envisioned removing the TBS group at C_{15}, but all conditions tried for deprotection proved unsuccessful (Scheme 4-13).

Table 4-1. RCM conditions and results.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temp</th>
<th>Time</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>GII</td>
<td>DCM</td>
<td>rt</td>
<td>24 h</td>
<td>SM</td>
</tr>
<tr>
<td>GII</td>
<td>DCM</td>
<td>45 ℃</td>
<td>24 h</td>
<td>mostly SM</td>
</tr>
<tr>
<td>GII</td>
<td>PhMe</td>
<td>50 ℃</td>
<td>24 h</td>
<td>mostly SM</td>
</tr>
<tr>
<td>GI</td>
<td>DCM</td>
<td>rt</td>
<td>24 h</td>
<td>SM</td>
</tr>
<tr>
<td>GI</td>
<td>PhMe</td>
<td>50 ℃</td>
<td>24 h</td>
<td>mostly SM</td>
</tr>
<tr>
<td>GI</td>
<td>PhMe</td>
<td>80 ℃</td>
<td>24 h</td>
<td>complex mix</td>
</tr>
<tr>
<td>GI</td>
<td>PhMe</td>
<td>110 ℃</td>
<td>24 h</td>
<td>complex mix</td>
</tr>
<tr>
<td>GH</td>
<td>DCM</td>
<td>rt</td>
<td>24 h</td>
<td>SM</td>
</tr>
<tr>
<td>GH</td>
<td>PhMe</td>
<td>50 ℃</td>
<td>24 h</td>
<td>mostly SM</td>
</tr>
<tr>
<td>GH</td>
<td>PhMe</td>
<td>80 ℃</td>
<td>24 h</td>
<td>complex mix</td>
</tr>
<tr>
<td>GH</td>
<td>PhMe</td>
<td>110 ℃</td>
<td>24 h</td>
<td>complex mix</td>
</tr>
</tbody>
</table>

Reactions from room temperature (rt) to 50 ℃ were performed using 10 mol% catalyst (added in two 5% batches, with the second at roughly half of the time indicated). Those performed at 80 and 110 ℃ used a single lot of 5% catalyst added once the reaction mixture had reached the desired temperature. All reactions were performed in degassed solvent (0.005 M) under a steady stream of N\textsubscript{2}. \textsuperscript{b)No RCM product was detected by MS.

Scheme 4-12. Large group prevents catalyst engagement with terminal alkene.
**Scheme 4-13.** Failure to remove the secondary TBS group.

A protection group swap was then envisioned in order to introduce a more labile TES group that could be removed without decomposition of the somewhat sensitive terminal triene.

### 4.3 Synthesis of the Second Generation Western Fragment (W2).

**Figure 4-2.** Second generation Western fragment (W2).

Due to our need to selectively remove both a primary TBS group at C$_{23}$ as well as a secondary TES group on the thiazole moiety, the TES group at C$_{15}$ could not be
installed early in the synthesis of the second-generation Western fragment W2 (Figure 4-2).

The synthesis of W2 diverges from the synthesis of W1 following the Dess-Martin oxidation to give ketone W18. To accomplish this, the ketone was not reduced and protected at this stage (as is done for the synthesis of W1) but instead was left in its oxidized form until the final step to form W2. As shown in Scheme 4-14, a TES deprotection of the secondary alcohol on the thiazole moiety of W18 followed by carbamate addition afforded W20. The protection group swap was carried out by removing the secondary TBS group with HF/pyridine at C15 and subsequently adding a TES group with TES triflate to give TES compound W21. Completion of the synthesis of W2 was done with a high-yielding L-Selectride reduction. This gave fragment W2 in 16-steps and 8.5% yield (longest linear sequence) from W18 as opposed to 16-steps and 4.7% from our previous synthesis (Ref. Schemes 4-9 and 4-10).

**Scheme 4-14. Synthesis of W2.**
With W2 in hand, esterification with E1 gave desired product WE2 in 60% yield (Scheme 4-15).

**Scheme 4-15.** Yamaguchi esterification with W2.

Deprotection at C15 was then achieved with HF/pyr at 4 °C for 20h. This gave the free-hydroxyl WE3 with which the RCM was investigated.

**Scheme 4-16.** TES deprotection and RCM.
Table 4-2. RCM conditions and results with free C_{15}-OH.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Solvent</th>
<th>Temp</th>
<th>Time</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMe</td>
<td>50 °C</td>
<td>17 h</td>
<td>complex mix$^c$</td>
</tr>
<tr>
<td>2</td>
<td>PhMe</td>
<td>80 °C</td>
<td>17 h</td>
<td>complex mix$^c$</td>
</tr>
<tr>
<td>3</td>
<td>PhMe$^a$</td>
<td>50 °C</td>
<td>17 h</td>
<td>complex mix$^c$</td>
</tr>
<tr>
<td>4</td>
<td>DCM$^a$</td>
<td>45 °C</td>
<td>17 h</td>
<td>complex mix$^c$</td>
</tr>
<tr>
<td>5</td>
<td>DCM$^{a,b}$</td>
<td>rt</td>
<td>48 h</td>
<td>complex mix$^c$</td>
</tr>
</tbody>
</table>

Reactions were performed using 10-30 mol% catalyst GII added as a single lot with 30-90 mol% p-benzoquinone (unless otherwise indicated). All reactions were performed in degassed solvent (0.0005 M).

$^a$ Ran under a steady stream of N$_2$. $^b$ No p-benzoquinone added. $^c$ No RCM product detected by NMR. Reactions 1 and 5 showed small amounts of starting material. Reactions 2-4 showed no starting material. In all reactions, new peaks may be attributed to oligomer formation and unproductive metathesis with styrene/etc.

As shown in Scheme 4-16 and Table 4-2, none of the conditions employed for the RCM of WE3 afforded the desired product. After reaction 5 showed no difference in the $^1$H NMR peak distribution in comparison to reactions 1-4 (see Supporting Information), isolation of the likely major product was carried out by preparative TLC on silica. The most striking feature observed in the $^1$H NMR spectrum of the clean major spot obtained was the absence of methoxy protons H$_a$ and H$_b$ that have very distinct chemical shifts in the starting material spectrum and are not expected to change dramatically upon macrocyclization (Figure 4-3).

**Figure 4-3.** Protons with distinct chemical shifts in $^1$H NMR spectra.
In order for protons $H_a$ and $H_b$, and thus the Northwest portion of the molecule, to be absent from the major RCM product, it was hypothesized that after the catalyst $\text{GII}$ engages the terminal double bond adjacent to the free hydroxyl, it might “bite down” onto one of the two alkenes between $C_{18}$ to $C_{21}$ (Scheme 4-17). It was envisioned that the terminal alkene at $C_{14}$ forms a metallocyclcobutane intermediate with either the

**Scheme 4-17.** Formation of either a 5- or 7-membered ring.

![Scheme 4-17](image)

trisubstituted $C_{18}$-$C_{19}$ alkene (red arrow) or disubstituted $C_{20}$-$C_{21}$ (blue arrow) and goes on to form cyclopentene ring $\text{R1}$ or cycloheptene ring $\text{R2}$, respectively. The remainder of the molecule (after ring excision) would then participate in further metathesis events, leading to the complex mixtures observed in the $^1$H NMR spectra for the full-system RCM reactions 1-5 (Table 4-2).

To test this ring excision hypothesis and to confirm formation of $\text{R1}$ or $\text{R2}$, compound $\text{W21}$ was subjected to the same dilute RCM conditions used for reaction 1 and 5 with $\text{WE3}$ (Scheme 4-18).
Scheme 4-18. Formation of R1 from W21 under RCM conditions.

After GC-MS analysis of the crude mixtures resulting from both reactions, parent ion peaks for R1 and trace R3, but not for R2, were found. Although 5-membered ring formation is energetically favorable over 7-membered ring formation, this result was surprising because the RCM reaction occurred on a trisubstituted alkene. There are only a few reports of RCM reactions involving trisubstituted double bonds, even when forming 5- and 6-membered rings, and \(^\text{92}\) (as discussed in Chapter 3) a disubstituted alkene should be more reactive and more likely to participate in metathesis than a trisubstituted alkene. Clearly, the lower in energy 5-membered ring formation trumps this difference in alkene reactivity. To confirm that the cyclopentene ring excision was occurring in the RCM attempts, R1 was purposefully synthesized as outlined in Scheme 4-19. This began with a HWE olefination between the previously synthesized phosphonate W3 and acetyl aldehyde followed by selective reduction (NaBH\(_4\)), methylation and TBS deprotection to give W22. Cyclization occurred efficiently to give R1 with no observable starting material by \(^1\)H NMR.
Scheme 4-19. Independently synthesized cyclopentene ring R1.

With R1 successfully synthesized, the presence of the cyclopentene ring R1 in crude $^1$H NMR spectra of the RCM reactions (for WE3 and W21) was confirmed by spectral comparison (Figure 4-4). COSY NMR analysis of R1 allowed identification of peaks representative of protons Ha-Hc in the clean R1 $^1$H NMR, which are clearly identifiable in the crude RCM reaction 5 $^1$H NMR.
Figure 4-4. $^1$H NMR (CDCl$_3$, 500 MHz) spectral comparison of clean R1 and crude RCM reaction 5 (Table 4-2).

In contrast to the propensity of W21 to undergo a ring excision under RCM conditions, the TBS protected compound W20 does not display this effect (Scheme 4-20). This indicates one of two events occurring: either the TBS is too bulky for the catalyst to engage the C$_{14}$ terminal alkene, or the catalyst engages with the alkene at this position, but the TBS group hinders 5-membered ring formation. One way to confirm which situation is determining the reactivity of the C$_{14}$ terminal olefin is to install a relay tether for directed metal movement to the alkene in question.
**Scheme 4-20.** Unreactivity towards metathesis due to the bulky TBS group.

In the next chapter, design and application of a relay model for probing the reactivity of the $C_{14}$ terminal olefin will be discussed as a means to overcome the ring-excision process in a RCM approach to archDhB.
Chapter 5. Synthetic Studies Towards a RRCM Approach to Dihydroarchazolid B

In order to validate a RRCM approach (Section 3.5.4) to archDhB, a model compound was designed to initially test the relay concept at an olefin bearing an allylic TBS group. A straight chain relay tether six carbons in length was desired for efficient triggering and release of cyclopentene, leading to directed metal movement for installation of the catalyst at the desired alkene (Scheme 5-1).

**Scheme 5-1.** Design of a relay substrate.

The synthesis of M1 was then envisioned and arose from a cross metathesis between compound M2 and M3 and use of our group’s acyloxysulfone “masked alkene” chemistry to easily convert a relay tether precursor into the corresponding terminal alkene with a sodium mercury amalgam-mediated elimination (Scheme 5-2).

**Scheme 5-2.** Simplified allylic TBS relay model retrosynthesis.
5.1 Synthesis and Evaluation of M1

Compound M2 was easily accessed from hexanal via addition of vinyl magnesium bromide and TBS protection (Scheme 5-3).

**Scheme 5-3. Synthesis of M2.**

M2 was easily accessed from hexanal via addition of vinyl magnesium bromide and TBS protection (Scheme 5-3).

Synthesis of M3 commenced by oxidizing readily available hex-5-en-1-ol to the corresponding aldehyde with the Swern method followed by nucleophilic addition of methyl phenyl sulfone and trapping of the resulting anion with acetyl chloride in situ (Scheme 5-4).

**Scheme 5-4. Synthesis of M3.**

CM between M2 and an excess of M3 was attempted at this stage. However, even with moderate catalyst loading (20 mol% GII), only trace amounts of the desired cross product were obtained. The major product from this reaction was the dimer M4 of the β-acyloxy sulfone relay tether M3 (Scheme 5-5).
Scheme 5-5. Unproductive metathesis.

To test the reactivity of the dimer M4, a CM reaction was performed with M2 and CM M5 product was obtained in good yield with no observable starting material (Scheme 5-6). In the initial CM attempt with the monomer M3, the catalyst was likely tied up in formation of the dimer, which was shown to be a slow process (starting material M3 observable after 20 h). By subjecting the dimer M4 in excess in a CM with M2, this unproductive metathesis event was avoided and product could be afforded in an efficient manner.

Scheme 5-6. Successful CM with acyloxysulfone dimer M4.
With M5 in hand, a facile sodium mercury amalgam mediated elimination afforded desired relay product M1. Mild RCM conditions allowed the relay to trigger and gave back substrate M2 with no starting M5 observable (Scheme 5-7).

**Scheme 5-7.** Allylic TBS relay model proof-of-concept study.

**5.2 Synthesis of a Functionalized Relay Model**

Encouraged by the success of the M1 relay model study, a more accurate model was desired. Initially, CM was attempted between M4 and fully functionalized W1 (Scheme 5-8).

**Scheme 5-8.** Efforts towards synthesizing M6 using fully functionalized W1.
With multiple attempts resulting in complex mixtures and only small amounts of desired CM product, this approach was deemed inefficient. To conserve precious \textbf{W1}, a simplified model \textbf{M6} was designed (Figure 5-1) that contains the same stereotriad as \textbf{W1}.

![stereotriad]

**Figure 5-1.** Model compound \textbf{M6}.

Prior to synthetic efforts towards \textbf{M6}, model consistency was tested by synthesizing \textbf{M7} and \textbf{M8} (Scheme 5-9) for subjection under the same RCM conditions as for \textbf{W20} and \textbf{W21}, respectively. \textbf{M7} and \textbf{M8} were easily synthesized with a Paterson-type HWE olefination between previously made phosphonate \textbf{W3} and cyanamic aldehyde followed by selective NaBH$_4$ reduction and methylation with methyl triflate. Synthesis of \textbf{M8} diverged from \textbf{M7} with a TBS deprotection.

**Scheme 5-9.** Synthesis of \textbf{M7} and \textbf{M8} for proof-of-concept study.
Subjecting M7 and M8 to RCM conditions used to explore the ring excision process with W20 and W21 gave us the expected results. Under RCM conditions, M7 did not undergo any reaction, whereas M8 was transformed into the cyclopentene ring R2 and further metathesis products (Scheme 5-10).

**Scheme 5-10. M6 proof-of-concept study.**

![Scheme 5-10](image)

The model was validated by these results and synthesis of M6 commenced. Initial attempts at installing the β-acyloxsulfone tether involved a CM between previously reported Weinreb amide W11 and the dimer M4 as well as CM between phosphonate W3 and monomer M3 (Scheme 5-11).

**Scheme 5-11. Efforts towards synthesizing M6.**

![Scheme 5-11](image)
As shown in Scheme 5-11, neither route was feasible as the reaction with W11 and M4 produced no desired product and the CM product of W3 and M3 proved to be very polar and difficult to isolate. Taking these difficulties with the β-acyloxsulfone relay tether installation into account, focus was directed towards a different ether containing relay tether shown to be effective in RRCM of complex natural products.94 Scheme 5-12 shows compound M9 arising from a HWE olefination between phosphonate M10 and cinnamic aldehyde.

**Scheme 5-12.** Retrosynthesis of an ether containing relay model.

![Scheme 5-12](image)

The synthesis of M10 proceeded smoothly with ozonolysis of phosphonate W3 followed by Wittig olefination. Subsequent HWE olefination with cinnamic aldehyde gave ketone M11. The ketone was reduced with NaBH₄ to give alcohol M12 and methylation was then attempted, however the methyl ether was not obtained under any of the reaction conditions shown in Scheme 5-13.
Scheme 5-13. Efforts towards synthesizing an ether containing relay compound.

This route was abandoned and an alternative synthesis of M6 was then designed based on an Evan’s syn-selective aldol reaction between thiazolidine thione M14 and the cross product (M13) of relay tether M3 with crotonaldehyde. From here, the auxiliary was cleaved with methanol to give methyl ester M15 followed by sodium mercury amalgam mediated elimination of the β-acyloxy sulfone and TBS protection to give compound M16. Conversion of M16 into the phosphonate M17 and subsequent HWE olefination, reduction and methylation afforded desired model compound M6 (Scheme 5-14).

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Scheme 5-14. Completion of the synthesis of M6.

5.3 Evaluation of Functionalized Relay Model M6

With compound M6 finally in hand, reactions were carried out to assess the reactivity of the relay tether and to deduce whether or not the allylic TBS group prevents ring excision or simply prevents the catalyst GII from reacting with the terminal alkene in W1. Results are shown in Scheme 5-15 and Table 5-1.
Scheme 5-15. Results of relay studies.

Table 5-1. Results of relay studies.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Solvent</th>
<th>Temp</th>
<th>Time</th>
<th>Result(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMe</td>
<td>rt</td>
<td>17 h</td>
<td>Primarily M6 (trace M18)</td>
</tr>
<tr>
<td>2</td>
<td>PhMe</td>
<td>50 °C</td>
<td>17 h</td>
<td>Mix of all 4 products</td>
</tr>
<tr>
<td>3</td>
<td>PhMe</td>
<td>80 °C</td>
<td>17 h</td>
<td>Mix of W7, R3 (trace M18)</td>
</tr>
<tr>
<td>4</td>
<td>PhMe</td>
<td>110 °C</td>
<td>17 h</td>
<td>Primarily R3 (trace W7)</td>
</tr>
<tr>
<td>5</td>
<td>DCM</td>
<td>45 °C</td>
<td>17 h</td>
<td>Mix of all 4 products</td>
</tr>
</tbody>
</table>

Reactions performed using 5 mol% catalyst in degassed solvent (0.001 M). \(^b\)No RCM product was detected by MS. \(^c\)Confirmed by crude \(^1\)H NMR and LC-MS of crude mixtures.
Unlike the results for the **M1** model study, the relay does not trigger at room temperature. Elevated temperatures (80 and 110 °C) are needed for relay triggering, a surprising result due to the fast nature of cyclopentene formation after catalyst activation. Overall, it was found that the TBS group does not hinder 5-membered ring formation. The likely scenario for the inability of the terminal alkene with the allylic TBS to undergo metathesis reactions is that the catalyst is prevented from accessing the alkene. Once the alkene is accessed by the catalyst upon relay triggering, the 5-membered ring formation occurs, albeit only at elevated temperatures. A key result of this study was the presence of **W7** in the reaction mixtures for reactions 2-5 in Table 5-1. These data suggest that there is a lifetime of the intermediate **M6-1**: due to the high dilution, **M6-1** has to go “find” a terminal alkene, such as **M6**, in order for the formation of **W7** to occur and it must do this before the formation of **R3** (Scheme 5-16). This is a promising result and indicates a potential for successful ring closure using a RRCM approach for the full system to form **archDhB** using the 80 °C reaction conditions due to the favorable **W7:R3** ratio (Scheme 5-17).
Scheme 5-16. Lifetime of intermediate M6-1.

Scheme 5-17. Potential reaction conditions for successful RRCM.
Chapter 6. Conclusion

6.1 Serendipity Leads to Discovery of a Metathesis Deactivating Stereotriad

From the work presented in the model studies with M6, a surprising finding was the unreactivity of our relay compound. Typically, 5- and 6-membered ring formation from a relay tether is fast and occurs with little energetic input (i.e. heat). Comparing the behavior of our simplified allylic TBS compound with M6 at room temperature, we were able to demonstrate that it is not just the allylic TBS group driving the reactivity of the nearby alkene as previously hypothesized for the observed unreactivity of WE1 towards metathesis (ref. Section 4.2, Scheme 4-12) (Figure 6-1).

![Diagram showing comparison of M4-1 and M6](image)

**Figure 6-1.** Comparison of the simplified allylic TBS substrate M4-1 to model compound M6 with the stereotriad present in the Western fragment.

Due to the interesting nature of this unexpected differential reactivity and coupled by our finding that few examples exploring remote functionality additional to the allylic
position are present in the literature, we were encouraged to explore our results further in order to probe the role of contiguous remote functionality in alkene reactivity.

In order to examine the role of remote functionality, a series of compounds were synthesized that differed from the stereotriad in the Western fragment and M6 by either lacking a particular stereochemical configuration or by having groups absent from the stereotriad altogether. As demonstrated in Scheme 6-1, eliminating the methoxy group as a stereocenter in M12 by retaining the planar methyl ester allows relay loss to occur at room temperature to give M16. Methyl ester M12 was reduced to the corresponding alcohol with DIBAl-H and methylated using methyl triflate and LiHMDS to produce M15. With the methoxy group as a free-rotating bond, relay loss occurred under the same metathesis conditions as M12 at room temperature to give M17 and orientationally divergent CM product M18 in a 1:1 mixture.

Scheme 6-1. Effects of eliminating the β-methoxy group as a stereocenter.
These results clearly indicate that it is not just the allylic OTBS even when combined with a homoallylic methyl group that is responsible for the relay inactivity seen in compound M6.\textsuperscript{95} When the $\beta$-group is the free alcohol M19 ($R = H$), it remains similarly inert to metathesis, demonstrating that additional functionality on the oxygen need not be necessary to prevent relay loss (Scheme 6-2).

**Scheme 6-2.** Removed functionality at $\beta$-position and reactivity effects.

Compound M21 was also produced in order to investigate if the $\alpha$-methyl group was playing a key role in this relay loss inhibition (Scheme 6-3).\textsuperscript{96} This was accomplished by metathesis with the acyloxy sulfone dimer M4 and M20, followed by sodium mercury amalgam mediated elimination of cross product to produce M21. By subjecting M21 to the same room temperature metathesis conditions, clean relay loss

**Scheme 6-3.** $\alpha$-Methyl group important for deactivating effect
was observed by NMR analysis to give back M20.

The results in Schemes 6-2 and 6-3 suggest a collective metathesis deactivating ability for the three sequential stereocenters flanking the relay tether in compound M6. As discussed in Chapter 3, Chaterjee and Grubbs came up with a generalized model to categorize alkene reactivity towards metathesis, focusing on the rates of homodimerization and secondary metathesis of individual substrates as a guide. These categorization rules generally focus on olefin substitution patterns and functional groups at the allylic position.

Looking at the results from our series of relay-containing compounds, our data suggests the focus on the allylic position to be an oversimplification. In order to accurately categorize olefin reactivity, it may be necessary to look at the collective metathesis deactivating effects of contiguous functionality.

### 6.2 Future Work

In conclusion, we were able to explore the use of a relay tether to potentially overcome difficulties associated the ring-closing step towards archDhB. Through this exploration, we found conditions that may allow us to perform a RRCM to achieve ring closure and subsequently complete the synthesis of this novel archazolid analogue (Scheme 6-4). Coming out of this relay work, we also happened upon a synergistic deactivating effect of contiguous functionality contained in the C_{15}-C_{17} stereotriad of the Western fragment.
**Scheme 6-4.** Conditions for a potential successful RRCM towards archDhB.

The three stereocenters together are responsible for collectively inhibiting what is typically a rapid 5-membered ring forming RCM (Figure 6-2). These results are pushing our group to further categorize olefins by their metathesis reactivity by investigating additional extended functionality systems. Ultimately, these efforts will give us a better understanding of the alkene functionality present in the archazolid family and allow us to proceed informed in our endeavors towards a completion of a synthesis of dihydroarchazolid B (archDhB).

**Figure 6-2.** Metathesis deactivating stereotriads present in the Western fragment and M6.
7. Experimental

All reactions were carried out under N\textsubscript{2} in flame-dried glassware. The solvents used were dried by passing the solvent through a column of activated alumina under nitrogen immediately prior to use. All other reagents were purchased and used as received. All TLC analysis used 0.25 mm silica layer fluorescence UV254 plates. Flash chromatography: SilaCycle silica gel P60 (230-400 mesh). IR: Nicolet iS10 spectrometer, wavenumbers (\textit{\nu}) in cm\textsuperscript{-1}. NMR: Spectra were recorded on a Varian Mercury 300, or Inova 500 spectrometer in the solvents indicated; chemical shifts (\delta) are given in ppm, coupling constants (\textit{J}) in Hz. The solvent signals were used as references (CDCl\textsubscript{3}: \delta C = 77.0 ppm; residual CHCl\textsubscript{3} in CDCl\textsubscript{3}: \delta H = 7.26 ppm). MS(ESI): Waters LCT Premier mass spectrometer.
Alcohol W17b

To a solution of ketone W18 (300 mg, 0.445 mmol) in THF (5 ml) at 0 °C, HF-pyr (70%, 185 µl) was added. The resulting solution was kept at 4°C for 20h. The reaction was quenched with aq. NaHCO₃ (10 ml) and extracted with MTBE (2 x 10 ml). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) afforded the intermediate secondary alcohol W17b (211 mg, 82%) as an oil.

IR (ATR) 3405, 2955, 2928, 2855, 2323, 1687, 1384, 1321, 1250, 1084, 1024, 920, 834, 775, 671. ¹H NMR (500 MHz, CDCl₃): δ 8.12 (s, 1H), 6.45 (ddd, J = 2.3, 10.7, 17.2 Hz, 1H), 5.83 (m, 3H), 5.16 (dt, J = 1.5, 17.1 Hz, 1H), 5.08 (m, 1H), 5.03 (dt, J = 5, 10.7 Hz, 1H), 4.61 (d, J = 5.4 Hz, 1H), 4.43 (m, 1H), 3.34 (d, J = 9.9 Hz, 1H), 3.09 (d, J = 1.4 Hz, 3H), 2.68 (bs, H-OTBS, 1H), 1.91 (m, 1H), 1.79 (t, J = 6.4 Hz, 2H), 1.58 (m, 1H), 1.35 (dd, J = 2.8, 6.9 Hz, 3H), 1.25 (s, 3H), 1.01 (m, 6H), 0.91 (s, 9H), 0.59 (d, J = 6.9 Hz, 3H), 0.035 (s, 3H), -0.005 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 195.95, 175.69, 153.99, 141.72, 135.77, 132.67, 129.64, 127.68, 126.38, 113.99, 88.34, 71.42, 70.62, 55.86, 47.46, 47.43, 46.52, 41.94, 29.90, 26.28,
24.80, 23.44, 22.07, 18.45, 16.96, 8.85, -3.73, -5.04. HRMS (TOF ES+): Calcd for C_{29}H_{49}NO_{4}SSiNa^+ (M+Na)^+: 558.3049. Found: 558.3052.

Ketone **W20**

To a solution of **W17b** (211 mg, 0.364 mmol) in DCM (7.3 ml), carbonyldiimidazole (240 mg, 1.46 mmol) was added portion-wise over 1h. The solution was then cooled to 0°C and methyl amine was added (2.0 M, 1.1 ml). The resulting mixture was allowed to warm to r.t. over 4 h. The reaction was quenched with aq. NaHCO$_3$ (15 ml) and extracted with DCM (2 x 10 ml). The combined organic extracts were dried over MgSO$_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) afforded ketone **W20** (212 mg, 91%) as an oil.

IR (ATR) 3350, 2956, 2929, 1721, 1687, 1527, 1472, 1386, 1249, 1126, 1085, 919, 833, 774, 647. $^1$H NMR (500 MHz, CDCl$_3$): δ 8.11 (d, $J = 2.4$ Hz, 1H), 6.46 (m, 1H), 6.08 (m, 1H), 5.85 (m, 3H), 5.16 (dd, $J = 1.7$, 17.2 Hz, 1H), 5.03 (dd, $J = 1.7$, 10.6 Hz, 1H), 4.78 (s, 1H), 4.61 (m,
1H), 4.47 (m, 1H), 3.34 (d, \( J = 9.9 \) Hz, 1H), 3.11 (m, 3H), 2.83 (d, \( J = 4.7 \) Hz, 3H), 1.89 (m, 2H), 1.76 (m, 1H), 1.59 (m, 4H), 1.35 (m, 3H), 0.99 (m, 6H), 0.91 (s, 9H), 0.58 (m, 3H), 0.036 (s, 3H), -0.007 (s, 3H). \( ^{13} \)C NMR (125 MHz, CDCl3): \( \delta \) 195.90, 171.48, 156.06, 154.24, 141.72, 135.71, 132.65, 129.76, 127.72, 126.22, 113.99, 88.35, 72.45, 71.37, 55.88, 46.44, 44.28, 41.91, 27.91, 26.19, 24.80, 23.15, 22.36, 18.46, 16.62, 10.86, 8.87, -3.72, -5.04. HRMS (TOF ES+): Calcd for C\textsubscript{31}H\textsubscript{52}N\textsubscript{2}O\textsubscript{5}SSiNa\textsuperscript{+} (M+Na)\textsuperscript{+}: 615.3264. Found: 615.3256.

Alcohol **W20-1**

To a solution of ketone **W20** (42 mg, 0.066 mmol) in THF (1.5 ml) at 0 °C, HF-pyr (70%, 390 µl) was added. The resulting solution was kept at r.t. for 20 h. The reaction was quenched withaq. NaHCO\textsubscript{3} (5 ml) and extracted with MTBE (2 x 10 ml). The combined organic extracts were dried over MgSO\textsubscript{4}, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) afforded the intermediate secondary alcohol **W20-1** (27 mg, 86%) as an oil.
IR (ATR) 3350, 2959, 2929, 2871, 1715, 1687, 1532, 1472, 1368, 1252, 1125, 1082, 964, 920, 813, 750. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.11 (s, 1H), 6.44 (ddd, $J = 6.1, 10.7, 17.2$ Hz, 1H), 6.08 (dq, $J = 2.7, 8.3$ Hz, 1H), 5.94-5.79 (m, 3H), 5.29 (dq, $J = 1.7, 17.2$ Hz, 1H), 5.19 (d, $J = 10.6$ Hz, 1H), 4.79 (m, H$_{N-H}$), 4.47 (m, 1H), 4.19 (s, 1H), 3.41 (d, $J = 9.7$ Hz, 1H), 3.13 (d, $J = 8.7$ Hz, 3H), 2.10-2.01 (m, 2H), 1.96-1.83 (m, 4H), 1.77 (m, 1H), 1.65 (s, 3H), 1.35 (dd, $J = 1.8, 6.9$ Hz, 3H), 0.98 (m, 6H), 0.67 (dd, $J = 7.2, 12.2$ Hz, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 195.86, 171.59, 156.11, 154.38, 138.42, 134.36, 133.61, 129.61, 127.58, 126.28, 115.39, 90.82, 75.72, 56.01, 46.50, 44.38, 40.07, 29.93, 27.92, 24.84, 23.19, 22.36, 16.76, 13.12, 11.28. HRMS (TOF ES+): Calcd for C$_{25}$H$_{38}$N$_2$O$_5$SNa$^+$ (M+Na)$^+$: 501.2399. Found: 501.2388.

**Ketone W20-2**

To a solution of alcohol **W20-1** (27 mg, 0.057 mmol) in DCM (1.0 ml) at -78°C was added 2,6-lutidine (10 µl, 0.0855 mmol) followed by addition of TES-OTf (15 µl, 0.068 mmol). The resulting mixture was stirred at -78°C for 2.5h. The reaction was quenched with aq. NaHCO$_3$ (5 ml) and extracted with
DCM (2 x 2 ml). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography (4:1 to 1:1 hexanes:ethyl acetate) afforded the ketone W20-2 (27 mg, 81%) as an oil.

IR (ATR) 3350, 3955, 2927, 2872, 1716, 1688, 1525, 1471, 1418, 1369, 1244, 1126, 1084, 1008, 963, 919, 828, 730. ¹H NMR (300 MHz, CDCl₃): δ 8.10 (s, 1H), 6.46 (m, 1H), 6.28 (t, J = 5.6 Hz, 1H), 5.94-5.76 (m, 3H), 5.17 (d, J = 17.2 Hz, 1H), 5.03 (dd, J = 1.2, 10.4 Hz, 1H), 4.78 (d, J = 4.1 Hz, 1H), 4.64 (d, J = 5.7 Hz, 1H), 4.46 (q, J = 6.9 Hz, 1H), 3.35 (d, J = 10 Hz, 1H), 3.12 (d, J = 5.4 Hz, 3H), 2.83 (d, J = 4.8 Hz, 3H), 1.89 (m, 2H), 1.77 (m, 1H), 1.60 (m, 1H), 1.59 (s, 3H), 1.35 (dd, J = 2.2., 6.8 Hz, 3H), 0.96 (m, 15H), 0.58 (m, 9H). ¹³C NMR (75 MHz, CDCl₃): δ 195.90, 171.48, 171.16, 156.07, 154.27, 141.87, 135.73, 132.83, 129.77, 127.74, 126.20, 113.81, 88.39, 72.46, 71.78, 55.85, 46.46, 44.30, 41.97, 27.90, 24.82, 23.15, 22.37, 16.63, 10.88, 8.91, 7.19, 5.27. HRMS (TOF ES+): Calcd for C₃₁H₅₉N₂O₅SSiNa⁺ (M+Na)⁺: 615.3264. Found: 615.3259.

Alcohol W2

To a solution of ketone W20-2 (27 mg, 0.046 mmol) in THF (0.5 ml) at -78 °C was added L-Selectride (1.0 M, 70 µl) and the mixture was stirred for 30 min. The reaction was quenched with
aq. NH₄Cl (15 ml) and extracted with MTBE (2 x 15 ml). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) afforded W₂ (28 mg, 98%) as a 10:1 (NMR) mixture of stereoisomers.

IR (ATR) 3212, 3996, 2875, 1713, 1455, 1242, 1196, 1127, 1085, 1005, 964, 739. 

¹H NMR (500 MHz, CDCl₃): δ 7.07 (s, 1H), 6.34 (m, 1H), 6.04 (m, 1H), 5.86 (m, 3H), 5.61 (q, J = 7.8 Hz, 1H), 5.18 (dt, J = 1.5, 10.4 Hz, 1H), 4.75 (bs, 1H), 4.65 (m, 1H), 4.61 (bs, 1H), 3.36 (d, J = 9.8 Hz, 1H), 3.14 (d, J = 2.9 Hz, 3H), 2.81 (d, J = 4.7 Hz, 3H), 2.44 (bs, H OH), 1.96-1.40 (m, 4H), 1.59 (s, 3H), 1.24 (s, 3H), 0.96 (m, 15H), 0.59 (m, 6H).

¹³C NMR (125 MHz, CDCl₃): δ 171.33, 156.20, 141.89, 134.90, 129.67, 129.66, 127.87, 114.64, 113.84, 88.41, 71.73, 55.85, 49.67, 44.72, 44.01, 41.93, 29.91, 27.84, 27.19, 24.81, 23.24, 22.22, 16.83, 14.34, 10.87, 8.93, 7.21, 5.27. HRMS (TOF ES+): Calcd for C₃₁H₅₄N₂O₅SSiNa⁺ (M+Na)⁺: 617.3420. Found: 617.3426.

Ester WE2

Method 1. Acid E₁ (20 mg, 0.049 mmol) and alcohol W₂ (16 mg, 0.027 mmol) were added to a dry reaction tube with Et₂O (2-3 mL) The Et₂O was then evaporated off using a steady stream of
nitrogen. To this mixture was added toluene (2.7 mL) and the reaction was cooled to -78°C. Et₃N (45 µl, 0.324 mmol) was then added, followed by addition of DMAP (82 mg, 0.675 mmol). 2,4,6-TCBC (48 µl, 0.305 mmol) was then added, and the reaction was warmed to r.t. and stirred overnight. The reaction was quenched with aq. NaHCO₃ (5 ml) and extracted with EtOAc (2 x 3 ml). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (4:1 to 1:2 hexanes:ethyl acetate) afforded ester WE2 (16 mg, 60%) as an oil.

**Method 2.** 4Å molecular sieves were flame dried under vacuum and alcohol # (17.5 mg, 0.0295 mmol) was added to this same reaction tube in DCM (0.5 ml) and the mixture was stirred for 15 min at rt. BOP (39 mg, 0.0885 mmol), DMAP (11 mg, 0.0885 mmol) and acid # (13.2 mg, 0.0325 mmol) (added with 0.6 ml DCM) were then added sequentially. The resulting mixture was stirred at r.t. overnight. The reaction was quenched with brine (5 ml) and extracted with DCM (2 x 3 ml). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (4:1 to 1:2 hexanes:ethyl acetate) afforded ester # (10 mg, 34%) as an oil.

¹H NMR (500 MHz, CDCl₃): δ 7.06 (s, 1H), 6.67 (dd, J = 11, 17.6 Hz, 1H), 6.23 (m, 2H), 6.05 (m, 1H), 5.84 (m, 3H), 5.55 (dd, J = 8.6, 14.8 Hz, 1H), 5.17 (dd, J = 6.5, 17.3 Hz, 1H), 5.10-5.00 (m,3H), 4.75 (bs, 1H), 4.65 (d, J = 5.4 Hz, 1H), 4.08 (m, 1H), 3.34 (dd, J = 2.9, 10.2 Hz, 1H), 3.13 (d, J = 12.2 Hz, 1H), 3.01 (m, 1H), 2.82 (d, J = 4.6 Hz, 3H), 2.31 (m, 2H), 2.01-1.51 (m, 11H), 1.84 (d, J = 1.1 Hz, 3H), 1.74 (s, 3H), 1.55 (s, 6H), 1.52 (s, 6H), 0.99-0.81 (m, 27H), 0.59 (m, 6H), -0.029 (s, 3H), -0.0613 (s,3H). ¹³C NMR (75 MHz, CDCl₃): δ 173.05, 171.53, 156.27,
156.26, 154.55, 142.02, 136.03, 134.81, 134.34, 133.38, 132.41, 132.34, 130.72, 129.83, 128.59,
127.28, 113.95, 113.76, 88.54, 73.14, 71.90, 71.88, 55.93, 55.82, 44.81, 42.07, 41.82, 40.75,
39.27, 34.18, 30.04, 27.99, 26.17, 24.97, 24.86, 23.35, 22.46, 19.70, 18.49, 17.21, 17.18, 15.96,
10.90, 9.03, 7.33, 5.41, -3.98, -4.55.

Alcohol WE3

To a solution of WE2 (15 mg, 0.0153 mmol) in THF (2 ml) at 0 °C, HF-pyr (70%, 50 µl) was added. The resulting solution was kept at 4 °C for 20 h. The reaction was quenched with aq. NaHCO₃ (5 ml) and extracted with EtOAc (2 x 5 ml). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) afforded the intermediate secondary alcohol WE3 (8.7 mg, 65%) as an oil.

¹H NMR (300 MHz, CDCl₃): δ 7.05 (s, 1H), 6.67 (dd, J = 10.7, 17.2 Hz, 1H), 6.22 (m, 1H),
6.05 (m, 1H), 5.97-5.77 (m, 3H), 5.59 (dd, J = 1.9, 5.8 Hz, 1H), 5.54 (d, J = 8.4 Hz, 1H), 5.35-
4.99 (m, 4H), 4.76 (bs, 1H), 4.19 (bs, 1H), 3.95 (m, 2H), 3.39 (d, J = 9.9 Hz, 1H), 3.12 (d, J = 6.4
Hz, 3H), 3.02 (m, 1H), 2.81 (d, J = 4.8 Hz, 3H), 2.29 (m, 2H), 2.09-1.51 (m, 23H), 1.24 (s, 3H),
0.99-0.79 (m, 18H), 0.67 (t, J = 7.6 Hz, 3H), -0.031 (s, 3H), -0.064 (s, 3H).

β-acyloxysulfone M3

To a solution of methyl phenyl sulfone (3.75 g, 24 mmol) in THF (100 mL) at -78°C was added
lithium bis(trimethylsilyl)amide (1.0M in THF, 24 mL) and resulting mixture was stirred at for 15
min. The solution was warmed to 0°C for 10 min, and then cooled back to -78°C before adding 5-
hexanal (1.96 g, 20 mmol). The resulting mixture was warmed to r.t. for 5h followed by cooling
to -78°C and addition of acetyl chloride (1.43 ml, 20 mmol). The mixture was allowed to warm to
r.t. and stirred overnight. The reaction was quenched with aqueous NH₄Cl (150 ml) and extracted
with MTBE (2 x 50 ml). The combined organic extracts were dried over MgSO₄, filtered, and
concentrated in vacuo. Purification by flash column chromatography on silica (4:1 hexanes:ethyl
acetate) afforded β-acyloxysulfone M3 (5.4 g, 97%) as a clear orange oil.

IR (ATR) 2928, 1739, 1640, 1585, 1447, 1305, 1232, 1146, 1085, 1025, 916, 744, 688, 537. ¹H
NMR (500 MHz, CDCl₃): δ 7.90 (dd, J = 1.2, 8.4 Hz, 2H), 7.68 (tt, J = 1.3, 6.7, 14.8 Hz, 1H),
7.58 (m, 2H), 5.72 (ddd, J = 6.75, 10.2, 17.0 Hz, 1H), 5.25 (m, 1H), 4.96 (m, 2H), 3.46 (dd, J =
8.1, 14.8 Hz, 1H), 3.26 (dd, J = 3.4, 14.8 Hz, 1H), 2.02 (m, 2H), 1.79 (s, 3H), 1.65 (m, 2H), 1.36
(m, 2H). ¹³C NMR (125 MHz, CDCl3): δ 170.09, 137.94, 134.05, 129.53, 128.43, 115.49, 68.12,
\(\beta\)-acyloxsulfone dimer M4

\[
\begin{align*}
\text{PhO}_2\text{S} & \quad \text{OAc} \\
\text{OAc} & \quad \text{SO}_2\text{Ph}
\end{align*}
\]

A solution of \(\beta\)-acyloxsulfone M3 (1.0 g, 3.37 mmol) was added in toluene (60 mL) at r.t.. The mixture degassed and then warmed to 60\(^\circ\)C, Grubbs 2\(^{\text{nd}}\) Generation catalyst (143 mg, 5 mol \%) was added, and the reaction mixture was stirred for 20h before concentrating \textit{in vacuo}. Purification by flash column chromatography on silica (1:1 hexanes:ethyl acetate to 100\% ethyl acetate) afforded \(\beta\)-acyloxsulfone M4 (660 mg, 70\%) as an oil.

IR (ATR) 2928, 1739, 1640, 1447, 1373, 1305, 1231, 1145, 1086, 1025, 999, 915, 744, 688. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.92 (m, 4H), 7.66 (tt, \(J = 1.2, 6.1\) Hz, 2H), 7.57 (m, 4H), 5.32-5.17 (m, 4H), 3.47 (d, \(J = 7.9\) Hz, 1H), 3.42 (d, \(J = 7.9\) Hz, 1H), 3.28 (d, \(J = 3.4\) Hz, 1H), 3.23 (d, \(J = 3.4\) Hz, 1H), 1.92 (m, 4H), 1.77 (s, 6H), 1.61 (m, 4H), 1.28 (m, 4H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 169.85, 139.51, 133.80, 133.68, 130.09, 129.36, 129.29, 128.16, 127.34, 67.97, 59.22, 59.11, 44.48, 33.75, 33.52, 33.48, 31.84, 31.78, 24.74, 20.71. HRMS (TOF ES+) Calcd for for \(\text{C}_{28}\text{H}_{36}\text{O}_8\text{S}_2\text{Na}^+\) (M+Na\(^+\)): 587.1749. Found: 587.1747.
\(\beta\)-acyloxsulfone \textbf{M5}

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\text{OTBS}}; \node at (1,0) {\text{\text{OAc}}}; \node at (2,0) {\text{\text{SO}_2\text{Ph}}};
\end{tikzpicture}
\end{center}

A solution of \(\beta\)-acyloxsulfone \textbf{M4} (73 mg, 0.129 mmol) and known tert-butyldimethyl(oct-1-en-3-yloxy)silane (6 mg, 0.026 mmol) were added in toluene (1 mL) at rt. The mixture was degassed and then warmed to 60\(^\circ\)C, Grubbs 2\textsuperscript{nd} Generation catalyst (5 mg, 20 mol %) was added, and the reaction mixture was stirred for 20h before concentrating \textit{in vacuo}. Purification by flash column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate to 100% ethyl acetate) afforded \(\beta\)-acyloxsulfone \textbf{M5} (11 mg, 85\%) as an oil.

\textbf{Compound M1}

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\text{OTBS}}; \node at (1,0) {\text{});
\end{tikzpicture}
\end{center}

MeOH (784 \(\mu\)l) was added to a dry mixture of sodium mercury amalgam (115 mg, 0.250 mmol) and NaH\textsubscript{2}PO\textsubscript{4} (41 mg, 0.292 mmol), followed by the addition of \(\beta\)-acyloxsulfone \textbf{M5} (20 mg, 0.0392 mmol) in THF (196 \(\mu\)l). The resulting mixture was stirred for 30 min at r.t. before filtering through cotton into aqueous brine (10 ml) and extracting with MTBE (2 x 5 ml). The combined organic extracts were dried over MgSO\textsubscript{4}, filtered, and concentrated \textit{in vacuo}. Purification by flash column chromatography on silica (10:1 hexanes:ethyl acetate) afforded compound \textbf{M1} (7 mg, 58 \%) as an oil.
IR (ATR): 2926, 2855, 1252, 1077, 965, 834, 809, 773. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 5.81 (ddd, 
\(J = 6.5, 10.1, 16.9\) Hz, 1H), 5.43 (m, 2H), 4.98 (m, 2H), 4.01 (q, 
\(J = 6.2\) Hz, 1H), 2.04 (m, 4H), 1.53-1.16 (m, 10H), 0.89 (m, 12H), 0.035 (s, 3H), 0.017 (s, 3H). \(^{13}\)C NMR (75 MHz, CDCl3): \(\delta\) 138.78, 134.16, 129.72, 114.45, 73.78, 38.46, 33.21, 31.79, 31.52, 29.69, 25.92, 25.07, 22.64, 18.27, 14.03, -4.18, -4.74.

Aldehyde M13

\[
\begin{align*}
&\text{OAc} & & \text{O} \\
\text{M4} & & \text{SO}_2\text{Ph} & & \text{GII, PhMe, 60°C} & & \text{OAc} & & \text{SO}_2\text{Ph} \\
& & & & & & & & \\
\end{align*}
\]

To a degassed solution of \(\beta\)-acyloxsulfone M4 (500 mg, 1.79 mmol) and crotonaldehyde (1.5 ml, 17.9 mmol) in toluene (18 ml) at 60°C was added Grubbs’ Second Generation catalyst (38 mg, 0.045 mmol) and the resulting mixture was stirred for 6h before concentrating \textit{in vacuo}. Purification on silica gel (Teledyne Isco CombiFlashRf1000 with a gradient elution of 1:1 to 1:2 to 100% hexanes:ethyl acetate, 10 ml fractions, 18 ml/min flow rate, solid sample loading) afforded aldehyde M13 (548 mg, 94%) as a clear orange oil.

\(^1\)H NMR (300 MHz, CDCl3): \(\delta\) 9.47 (d, \(J = 7.8\) Hz, 1H), 7.89 (d, \(J = 7.8\) Hz, 2H), 7.65 (m, 1H), 7.57 (m, 2H), 6.76 (dt, \(J = 6.6, 15.6\) Hz, 1H), 6.06 (m, 1H), 5.25 (m, 1H), 3.45 (dd, \(J = 7.7, 14.8\) Hz, 1H), 3.25 (dd, \(J = 3.9, 14.8\) Hz, 1H), 2.31 (m, 2H), 1.79 (s, 3H), 1.69 (m, 2H), 1.49 (m, 2H).
Methyl ester M15

To a solution of thiazolidine thione M14 (404 mg, 1.52 mmol) in DCM (6.5 ml) at 0°C was added titanium tetrachloride (1.0 M, 1.6 ml) and the resulting orange solution was stirred at 0°C for 5 min before adding triethyl amine (214 µl, 1.52 mmol) to give a wine red solution. The mixture was stirred for 10 min before cooling to -78°C and adding of N-methylpyrrolidine (147 µl, 1.52 mmol). The mixture was stirred for 20 min and then aldehyde M13 (542 mg, 1.67 mmol) was added as a solution in DCM (3 ml). The mixture was stirred at -78°C for 1 hr followed by warming to 0°C for 1 hr. The reaction was quenched with aqueous half-saturated NH₄Cl (20 ml) and extracted with DCM (2 x 10 ml). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo to give crude oil. The crude product was used without further purification.
To a solution of the crude alcohol obtained above in a DCM:MeOH solution (10:1, 15 ml) at 0°C was added imidazole (1.53 g, 22.5 mmol) and resulting mixture was allowed to slowly warm to r.t. while stirring for 15h. The reaction was quenched with aqueous half-saturated NH₄Cl (30 ml) and extracted with DCM (2 x 15 ml). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (1:2 hexanes:ethyl acetate to 100% ethyl acetate) afforded methyl ester M15 (297 mg, 93%) as an oil.

¹H NMR (300 MHz, CDCl₃): δ 7.89 (m, 4H), 7.65 (m, 2H), 7.56 (m, 4H), 5.58 (M, 2H), 5.42 (dq, J = 1.1, 6.3 Hz, 1H), 5.36 (dq, J = 1.3, 6.4 Hz, 1H) 5.23 (m, 2H), 4.27 (s, 2H), 3.64 (s, 6H), 3.44 (J = 8.0 Hz, 1H), 3.38 (d, J = 8.0 Hz, 1H), 3.26 (d, J = 3.6 Hz, 1H), 3.19 (d, J = 3.6 Hz, 1H), 2.68 (m, 2H), 2.55 (m, 2H), 1.97 (q, J = 7.5 Hz, 4H), 1.74 (s, 3H), 1.73 (s, 3H), 1.56 (m, 4H), 1.29 (p, J = 7.6 Hz, 4H), 1.11 (m, 6H). ¹³C NMR (75 MHz, CDCl₃): δ 175.58, 169.85, 139.41, 133.84, 133.68, 131.99, 130.27, 130.23, 129.30, 128.12, 127.29, 73.04, 73.02, 67.78, 67.76, 59.13, 59.07, 51.72, 45.01, 44.99, 44.43, 33.42, 33.36, 31.49, 31.43, 26.94, 24.07, 24.05, 20.66, 11.64, 11.62. HRMS (TOF ES+) Calcld for C₂₉H₅₈O₇SNa⁺ (M+Na)⁺: 435.1454. Found: 435.1449.

Methyl ester M15-1

MeOH (9 ml) was added to a dry mixture of sodium mercury amalgam (1.9 g, 4.14 mmol) and NaH₂PO₄ (685 mg, 4.82 mmol), followed by the addition of methyl ester M15 (247 mg, 0.599
mmol) in THF (3 ml). The resulting mixture was stirred for 30 min at r.t. before filtering through cotton into aqueous brine (20 ml) and extracting with MTBE (2 x 10 ml). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (1:1 hexanes:ethyl acetate) afforded methyl ester **M15-1** (87 mg, 72 %) as an oil.

**1H NMR (300 MHz, CDCl₃):** \( \delta 5.77\ (\text{ddd}, J = 6.7, 10.1, 17.0\ \text{Hz}, 1\text{H}), 5.66\ (\text{m}, 1\text{H}), 4.43\ (\text{ddt}, J = 1.3, 6.6, 15.4\ \text{Hz}, 1\text{H}), 4.94\ (\text{m}, 2\text{H}), 4.29\ (t, J = 5.6\ \text{Hz}, 1\text{H}), 3.67\ (s, 3\text{H}), 2.58\ (\text{m}, 1\text{H}), 2.01\ (\text{m}, 4\text{H}), 1.45\ (p, J = 7.7\ \text{Hz}, 2\text{H}), 1.15\ (\text{dd}, J = 0.8, 7.5\ \text{Hz}, 3\text{H}).

**13C NMR (75 MHz, CDCl₃):** \( \delta 175.68, 138.52, 133.17, 129.41, 144.06, 73.24, 51.71, 45.06, 33.09, 31.58, 28.28, 11.61.

**Methyl ester M16**

To a solution of methyl ester **M15-1** (87 mg, 0.41 mmol) in DCM (4.1 ml) at 0°C was added imidazole (70 mg, 1.03 mmol) and tertbutyldimethylsilyl chloride (80.3 mg, 0.533 mmol) and the resulting mixture was allowed to warm to r.t. while stirring overnight. The reaction was quenched with water (10 ml) and extracted with DCM (2 x 5 ml). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (4:1 hexanes:ethyl acetate) afforded methyl ester **M16** (110 mg, 66%) as an oil.

\([\alpha]_D^{20} = +2.08\ (c 0.026, \text{CH}_2\text{Cl}_2). \text{IR (ATR):} 2954, 2926, 2855, 1640, 1595, 1360, 1249, 1085, 1035, 961, 909, 833, 774, 747, 690.\) **1H NMR (300 MHz, CDCl₃):** \( \delta 5.79\ (\text{ddd}, J = 6.3, 10.1, 17.1\ \text{Hz}, 1\text{H})

94
Hz, 1H), 5.57 (dt, \( J = 6.7, 15.4 \text{ Hz}, 1H \)), 5.41 (ddt, \( J = 1.0, 6.8, 15.4 \text{ Hz}, 1H \)), 4.98 (m, 2H), 4.31 (t, \( J = 6.3 \text{ Hz}, 1H \)), 3.63 (s, 3H), 2.49 (dt, \( J = 6.9, 13 \text{ Hz}, 1H \)), 2.03 (m, 4H), 1.44 (p, \( J = 7.7 \text{ Hz}, 2H \)), 1.14 (d, \( J = 6.9 \text{ Hz}, 3H \)), 0.86 (s, 9H), 0.013 (d, \( J = 0.8 \text{ Hz}, 3H \)), -0.006 (d, \( J = 1.0 \text{ Hz}, 3H \)).

\(^{13}\text{C} \text{ NMR (75 MHz, CDCl}_3\)): \( \delta \ 174.96, 138.61, 131.85, 131.54, 114.57, 74.93, 51.35, 47.14, 33.16, 31.47, 28.41, 25.74, 18.07, 11.89, -2.96, -4.05, -5.05 \).

Phosphonate M17

To a solution of diethyl phosponate (137 \( \mu \text{l}, 0.842 \text{ mmol} \)) in THF (2 ml) at -78°C was added \( n \)-butyl lithium (1.6 M in hexanes, 484 \( \mu \text{l}, 0.775 \text{ mmol} \)) dropwise. The resulting mixture was stirred for 30 min before addition of methyl ester M16 (110 mg, 0.337 mmol) with THF (2 ml). The reaction was stirred for 30 min and subsequently quenched with half sat. aqueous NH\(_2\)Cl (10 ml) and extracted with MTBE (2 x 5 ml). The combined organic extracts were dried over MgSO\(_4\), filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (1:1 hexanes:ethyl acetate) afforded phosphonate M17 (121 mg, 78\%) as an oil.

\(^1\text{H} \text{ NMR (500 MHz, CDCl}_3\)): \( \delta \ 5.75 \ (\text{ddd}, \( J = 1.2, 6.6, 17 \text{ Hz}, 1H \)), 5.46 (m, 1H), 5.25 (ddd, \( J = 1.3, 7.8, 15.4 \text{ Hz}, 1H \)), 4.96 (dp, \( J = 2, 17 \text{ Hz}, 1H \)), 4.91 (dq, \( J = 1, 10.2 \text{ Hz} \)), 4.12-3.98 (m, 5H), 3.56 (m, 1H), 3.27 (p, \( J = 6.7 \text{ Hz}, 1H \)), 1.99 (m, 4H), 1.41 (p, \( J = 7.3 \text{ Hz}, 2H \)), 1.28 (m, 6H), 1.21 (dd, \( J = 7, 17 \text{ Hz}, 3H \)), 0.98 (dd, \( J = 1.2, 6.7, 3H \)), 0.85 (s, 9H), 0.029 (s, 3H), -0.029 (s, 3H). \(^{13}\text{C} \text{ NMR (75 MHz, CDCl}_3\)): \( \delta \ 174.96, 138.61, 131.85, 131.54, 114.57, 74.93, 51.35, 47.14, 33.16, 31.47, 28.41, 25.74, 18.07, 11.89, -2.96, -4.05, -5.05 \).
NMR (125 MHz, CDCl₃): δ 208.69, 138.63, 132.85, 132.15, 131.67, 130.18, 114.80, 74.64, 62.58, 53.77, 52.89, 49.01, 48.02, 46.29, 45.25, 33.37, 31.63, 29.35, 25.95, 24.06, 18.24, 16.56, 13.94, 13.31, 11.66, 11.61, 10.47, 10.42, -3.79, -3.98, -4.66, -4.78. HRMS (TOF ES+) Calcd for C₂₃H₄₅O₅PSiNa⁺ (M+Na)⁺: 483.2672. Found: 483.2665.

Ketone M17-1

![Ketone M17-1](image)

Ba(OH)₂·8H₂O (83 mg, 0.263 mmol) was dried at 130°C for 3 hours under vacuum prior to the addition of phosphonate M17 (121 mg, 0.263 mmol) in THF (1.55 ml). The resulting mixture was stirred at r.t. for 1.25h. Cinnamic aldehyde (100 µl, 0.789 mmol) was then added in 40:1 THF:H₂O (1.32 ml) and the reaction mixture stirred overnight. The reaction was quenched with aq. NaHCO₃ (10 ml) and extracted with MTBE (2 x 5 ml). The combined organic extracts were washed with 1M HCl (15 ml) and extracted with MTBE (2 x 5 ml), dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (20:1 hexanes:ethyl acetate) afforded ketone M17-1 (100 mg, 87%) as an oil.

¹H NMR (300 MHz, CDCl₃): δ 7.49 (d, J = 7.3 Hz, 2H), 7.37 (t, J = 7.2 Hz, 2H), 7.31 (t, J = 7.2 Hz, 1H), 7.22-7.11 (m, 2H), 6.91 (d, J = 14.8 Hz, 1H), 5.75 (ddd, J = 6.6, 10, 16.9 Hz, 1H), 5.49 (dt, J = 6.9, 15.4 Hz, 1H), 5.34 (ddt, J = 1.1, 8.5, 15.4 Hz, 1H), 4.95 (dq, J = 1.2, 10.1 Hz, 1H),...
4.90 (dq, $J = 1.2, 10.1$ Hz, 1H), 4.19 (t, $J = 7.7$ Hz, 1H), 3.43 (p, $J = 6.8$ Hz, 1H), 1.97 (m, 7H), 1.39 (m, 2H), 1.16 (d, $J = 6.8$ Hz, 3H), 0.89 (s, 9H), 0.063 (s, 3H), 0.019 (s, 3H). \(^{13}\)C NMR (75 MHz, CDCl\textsubscript{3}): $\delta$ 204.36, 139.45, 138.66, 138.31, 136.73, 136.53, 131.94, 131.67, 128.85, 128.81, 127.11, 124.69, 114.46, 76.38, 46.64, 33.10, 31.47, 28.33, 25.88, 18.19, 15.12, 12.04, -3.98, -4.76. HRMS (TOF ES\textsuperscript{+}) Calcd for C\textsubscript{28}H\textsubscript{42}O\textsubscript{2}SiNa\textsuperscript{+} (M+Na): 461.2852. Found: 461.2860.

Alcohol M\textsubscript{17-2}

To a solution of ketone M\textsubscript{17-1} (50 mg, 0.114 mmol) in MeOH (1.5 ml) at 0°C under air was added NaBH\textsubscript{4} (17 mg, 0.456 mmol). The resulting mixture was stirred for 1h. The reaction was quenched with aq. NaHCO\textsubscript{3} (5 ml) and extracted with MTBE (2 x 5 ml). The combined organic extracts were dried over MgSO\textsubscript{4}, filtered, and concentrated \textit{in vacuo}. Purification by flash column chromatography on silica (20:1 hexanes:ethyl acetate) afforded alcohol M\textsubscript{17-2} (40 mg, 79%) as an oil.

$[\alpha]_D^{20} = +36$ (c 0.03, CH\textsubscript{2}Cl\textsubscript{2}). IR (ATR): 2926, 2584, 1741, 1381, 1249, 1085, 1035, 962, 834, 774, 690. \(^{1}\)H NMR (300 MHz, CDCl\textsubscript{3}): $\delta$ 7.41 (d, 7.7 Hz, 2H), 7.30 (t, $J = 7.2$ Hz, 2H), 7.19 (m, 1H), 7.02 (dd, $J = 10.9, 15.5$ Hz, 1H), 6.51 (d, $J = 15.5$ Hz, 1H), 6.14 (d, $J = 11$ Hz, 1H), 5.82 (ddd, $J = 6.6, 10.2, 16.8$ Hz, 1H), 5.61 (m, 2H), 5.01 (m, 2H), 4.31 (m, 2H), 4.01 (d, $J = 9.4$ Hz, 1H), 2.09 (m, 4H), 1.92 (m, 1H), 1.85 (s, 3H), 1.50 (p, $J = 7.5$ Hz, 2H), 0.92 (s, 9H), 0.67 (d, $J = 97$
7.1 Hz, 3H), 0.103 (s, 3H), 0.059 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 139.57, 138.61, 137.76, 132.93, 131.95, 129.08, 128.55, 127.47, 127.23, 126.24, 124.96, 114.67, 80.70, 78.00, 41.37, 33.24, 31.67, 28.48, 25.79, 18.05, 13.10, 11.75, -0.0097, -4.18, -5.11.

Methyl ester M6

\[
\begin{align*}
\text{OTBS} & \quad \text{LiHMDS, MeI} \\
\text{HO} & \quad \text{M17-2} \\
\text{Methyl ester M6} & \quad \text{MeO} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]

To a solution of alcohol M17-2 (60 mg, 0.136 mmol) in THF (2 ml) at -78°C was added lithium bis(trimethylsilyl)amide (1.0 M in THF, 204 µl). The mixture was stirred for 30 min. Methyl iodide (42 µl, 0.68 mmol) was then added and the reaction mixture was warmed to r.t. while stirred overnight. The reaction was quenched with aq. NaHCO$_3$ (5 ml) and extracted with MTBE (2 x 3 ml). The combined organic extracts were dried over MgSO$_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (20:1 hexanes:ethyl acetate) afforded M6 (51 mg, 68%) as an oil.

$[\alpha]_D^{20} = +1.25$ (c 0.024, CH$_2$Cl$_2$). IR (ATR): 2926, 2855, 1641, 1496, 1461, 1381, 1321, 1249, 1085, 1035, 963, 834, 773, 690. $^1$H NMR (300 MHz, CDCl$_3$): δ 7.42 (d, $J = 7.5$ Hz, 2H), 7.32 (t, $J = 7.4$ Hz, 2H), 7.21 (t, $J = 7$ Hz, 1H), 7.04 (dd, $J = 10.9$, 15.5 Hz, 1H), 6.56 (d, $J = 15.5$ Hz, 1H), 6.12 (d, $J = 11.2$ Hz, 1H), 5.81 (ddd, $J = 6.7$, 10.2, 16.9 Hz, 1H), 5.53 (m, 2H), 4.97 (m, 2H), 4.60 (d, $J = 6.2$ Hz, 1H), 3.45 (d, $J = 9.9$ Hz, 1H), 3.17 (s, 3H), 2.05 (m, 4H), 1.73 (s, 3H), 98
1.62 (m, 1H), 1.47 (m, 2H), 0.94 (s, 9H), 0.66 (d, $J = 6.9$ Hz, 3H), 0.069 (s, 3H), 0.015 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 138.81, 137.64, 137.36, 133.25, 132.09, 130.02, 128.59, 127.36, 127.25, 126.26, 124.53, 114.45, 88.39, 71.07, 55.75, 42.37, 33.28, 31.67, 28.59, 26.02, 18.25, 11.00, 8.81, 0.49, -3.72, -5.11. HRMS (TOF ES+) Calcd for C$_{29}$H$_{46}$O$_2$SiNa$^+$ (M+Na)$^+$: 477.3165. Found: 477.3150.

Alcohol M19

To a solution of methyl ester M16 (50 mg, 0.153 mmol) in DCM (2 ml) at -78°C was added DIBAl-H (70 µl, 0.337 mmol). The resulting mixture was warmed to 0°C and stirred for 45 min. The reaction was quenched by diluting with ethyl acetate (2 ml) into Rochelle’s salt (2M, 4 ml). The mixture was stirred for 45 min before being transferred to a separatory funnel and extracted with ethyl acetate (2 x 5 ml). The combined organic extracts were dried over MgSO$_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (10:1 to 4:1 hexanes:ethyl acetate) afforded # (30 mg, 66%) as an oil.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 5.80 (ddd, $J = 6.8, 10.1, 17.0$ Hz, 1H), 5.54 (m, 2H), 4.98 (m, 2H), 4.18 (dd, $J = 4.2, 6.5$ Hz, 1H), 3.65 (td, $J = 1.4, 10.3$ Hz, 1H), 3.47 (m, 1H), 2.96 (d, $J = 4.6$ Hz, 1H), 2.03 (m, 5H), 1.47 (p, $J = 7.8$ Hz, 1H), 0.87 (s, 9H), 0.77 (d, $J = 7.1$ Hz, 3H), 0.063 (s, 3H), 0.028 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 138.58, 132.45, 129.49, 114.61, 65.90, 40.92,
33.20, 31.63, 28.50, 25.79, 18.06, 12.55, -1.61, -4.26, -5.11. HRMS (TOF ES+) Calcd for C\textsubscript{17}H\textsubscript{34}O\textsubscript{2}SiNa\textsuperscript{+} (M+Na): 321.2226. Found: 321.2222.

Methyl ether M\textsubscript{20}

![Methyl ether M20 reaction scheme]

To a solution of alcohol \# (21 mg, 0.0704 mmol) in THF (1.5 ml) at -78°C was added lithium bis(trimethylsilyl)amide (1.0 M in THF, 106 µl). The mixture was stirred for 30 min. Methyl triflate (12 µl, 0.106 mmol) was then added and the reaction mixture was stirred for 1h. The reaction was quenched with aq. NaHCO\textsubscript{3} (5 ml) and extracted with MTBE (2 x 3 ml). The combined organic extracts were dried over MgSO\textsubscript{4}, filtered, and concentrated \textit{in vacuo}. Purification by flash column chromatography on silica (20:1 hexanes:ethyl acetate) afforded \# (15 mg, 68%) as an oil.

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ 5.80 (m, 1H), 5.53 (m, 1H), 4.97 (m, 2H), 4.13 (m, 1H), 3.38-3.08 (m, 5H), 2.03 (m, 4H), 1.74 (m, 1H), 1.55 (m, 2H), 1.25 (m, 3H), 0.87 (m, 9H), 0.017 (m, 3H), -0.013 (m, 3H). \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): δ 138.97, 132.59, 130.75, 114.69, 75.31, 73.37, 58.83, 40.45, 33.45, 31.82, 28.81, 26.10, 18.40, 11.55, 0.19, -3.84, -4.86.
Ketone W22-1

\[
\begin{align*}
\text{(OEt)\textsubscript{2}P(O)} & \quad \text{OTBS} & \quad \text{W3} & \quad + & \quad \text{W22-1} \\
\text{Ba(OH)}\textsubscript{2} & \quad \text{THF:H\textsubscript{2}O}
\end{align*}
\]

Ba(OH)\textsubscript{2}·8H\textsubscript{2}O (178 mg, 0.56 mmol) was dried at 130°C for 3 hours under vacuum prior to the addition of phosphonate W3 (174 mg, 0.47 mmol) in THF (2.8 ml). The resulting mixture was stirred at r.t. for 1.25h. Aldehyde # (300 mg, 2.6 mmol) was then added in 40:1 THF:H\textsubscript{2}O (2.4 ml) and the reaction mixture stirred overnight. The reaction was quenched with aq. NaHCO\textsubscript{3} (10 ml) and extracted with MTBE (2 x 5 ml). The combined organic extracts were washed with 1M HCl (15 ml) and extracted with MTBE (2 x 5 ml), dried over MgSO\textsubscript{4}, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (20:1 to 10:1 hexanes:ethyl acetate) afforded ketone W22-1 (206 mg, 92%) as an oil.

Alcohol W22-2

\[
\begin{align*}
\text{W22-1} & \quad \xrightarrow{\text{NaBH}_{4}, \text{MeOH}} & \quad \text{W22-2}
\end{align*}
\]

To a solution of ketone W22-1 (70 mg, 0.248 mmol) in MeOH (1.3 ml) at 0°C under air was added NaBH\textsubscript{4} (37 mg, 0.992 mmol). The resulting mixture was stirred for 1h. The reaction was quenched with aq. NaHCO\textsubscript{3} (5 ml) and extracted with MTBE (2 x 5 ml). The combined organic
extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (10:1 hexanes:ethyl acetate) afforded alcohol **W22-2** (65 mg, 92%) as an oil.

Methyl ether **W22-3**

To a solution of alcohol **W22-1** (65 mg, 0.228 mmol) in THF (1 ml) at -78°C was added lithium bis(trimethylsilyl)amide (1.0 M in THF, 343 µl). The mixture was stirred for 30 min. Methyl triflate (40 µl, 0.343 mmol) was then added and the reaction mixture was stirred for 1h. The reaction was quenched with aq. NaHCO₃ (5 ml) and extracted with MTBE (2 x 3 ml). The combined organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (20:1 hexanes:ethyl acetate) afforded methyl ether **W22-3** (45 mg, 66%) as an oil.

1H NMR (500 MHz, CDCl₃): δ 5.23 (ddd, J = 5.6, 10.5, 17.2 Hz, 1H), 5.39 (qd, J = 1.3, 6.5, 13.3 Hz, 1H), 5.17 (dt, J = 1.7, 17.2 Hz, 1H), 5.03 (dt, J = 1.6, 10.5 Hz, 1H), 4.63 (dq, J = 1.5, 5.6 Hz, 1H), 3.32 (d, J = 10 Hz, 1H), 3.12 (s, 3H), 1.64 (dd, J = 1.0, 6.7 Hz, 3H), 1.56 (m, 1H), 1.46 (t, J = 1.1 Hz, 3H), 0.92 (s, 9H), 0.60 (d, J = 6.9 Hz, 3H), 0.048 (s, 3H), 0.0029 (s, 3H).

13C NMR (125 MHz, CDCl₃): δ 141.73, 141.28, 133.69, 124.74, 122.89, 114.04, 113.61, 88.35, 87.81, 75.41, 71.24, 56.15, 55.35, 55.34, 42.71, 41.48, 25.99, 18.27, 12.99, 11.52, 9.69, 9.51, 8.69, -
3.61, -3.92, -4.97, -5.24. HRMS (TOF CI+) Calcd for $C_{16}H_{35}O_2Si^+$ (M+H)$^+$: 299.2406. Found: 299.2377.

Alcohol **W22**

![Diagram of reaction](image)

To a solution of methyl ether **W22-3** (45 mg, 0.113 mmol) in THF (0.75 ml) at 0 °C, HF-pyr (70%, 195 µl) was added. The resulting solution was kept at r.t. for 20h. The reaction was quenched with aq. NaHCO$_3$ (5 ml) and extracted with MTBE (2 x 10 ml). The combined organic extracts were dried over MgSO$_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (10:1 to 4:1 hexanes:ethyl acetate) afforded the secondary alcohol **W22** (22 mg, 98%) as an oil.

$^1$H NMR (500 MHz, CDCl$_3$): δ 5.92 (dq, $J = 1.2, 5.2, 5.4$ Hz, 1H), 5.41 (qd, $J = 1.3, 5.3$ Hz, 1H), 5.29 (dt, $J = 1.8, 17.2$ Hz, 1H), 5.20 (dt, $J = 1.8, 10.6$ Hz, 1H), 4.19 (m, 1H), 3.82 (d, $J = 8.5$ Hz, 1H), 3.38 (d, $J = 939$ Hz, 1H), 3.13 (s, 3H), 2.06 (m, 1H), 1.64 (dd, $J = 1.07, 6.9$ Hz, 3H), 1.63 (s, 3H), 1.52 (m, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): δ 138.46, 133.03, 125.09, 115.31, 91.09, 76.07, 55.51, 39.73, 13.33, 13.22, 10.26. HRMS (TOF CI+) Calcd for $C_{11}H_{20}O_2SiNa^+$ (M+Na)$^+$: 207.1361. Found: 207.1361.
Cyclopentene R2

W22 (11 mg, 0.0596 mmol) was added in DCM (6 ml). The mixture underwent two freeze-pump-thaw cycles. Once r.t. was reached, Grubbs’ Second Generation catalyst (2.5 mg, 0.003 mmol) was added and the resulting mixture was stirred at r.t. overnight. The reaction mixture was transferred to a round bottom flask and concentrated *in vacuo*. Purification on silica gel (1:1 to 1:2 hexanes:ethyl acetate to 100% ethyl acetate) afforded cyclopentene R2 (10 mg, 91%) as an oil.

IR (ATR) 3360, 2925, 1653, 1558, 1456, 1375, 1192, 1090, 1019, 968, 897. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 5.57 (s, 1H), 4.41 (d, $J = 1.6$ Hz, 1H), 4.17 (d, $J = 6.1$ Hz, 1H), 3.38 (s, 3H), 2.16 (m, 1H), 1.78 (s, 3H), 1.59 (s, 1H) 1.06 (d, $J = 7.2$ Hz, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 144.79, 130.81, 88.51, 82.72, 58.81, 46.93, 14.98, 12.28. HRMS (TOF Cl+) Calcd for C$_8$H$_{13}$O$_2^-$(M-H)$^-$: 141.0916. Found: 141.0916.
Ketone M7-1

\[
\begin{align*}
\text{Ba(OH)}_2 \cdot 8\text{H}_2\text{O} \ (139 \text{ mg}, 0.441 \text{ mmol}) \text{ was dried at 130°C for 3 hours under vacuum prior to the}  \\
\text{addition of phosphonate W3 (173 mg, 0.441 mmol) in THF (2.5 ml). The resulting mixture was}  \\
\text{stirred at r.t. for 1.25h. Cinnamic aldehyde (166 µl, 1.322 mmol) was then added in 40:1}  \\
\text{THF:H}_2\text{O (2.2 ml) and the reaction mixture stirred overnight. The reaction was quenched with aq.}  \\
\text{NaHCO}_3 (10 ml) \text{ and extracted with MTBE (2 x 5 ml). The combined organic extracts were}  \\
\text{washed with 1M HCl (15 ml) and extracted with MTBE (2 x 5 ml), dried over MgSO}_4, \text{ filtered,}  \\
\text{and concentrated } \textit{in vacuo}. \text{ Purification by flash column chromatography on silica (4:1}  \\
\text{hexanes:ethyl acetate) afforded ketone M7-1 (155mg, 95%) as an oil.}  \\
\end{align*}
\]

IR (ATR) 2955, 2928, 2855, 1652, 1617, 1472, 1362, 1251, 1203, 1073, 1025, 965, 835, 776, 750, 689. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 7.49 (d, J = 8.1 \text{ Hz}, 2\text{H}), 7.35 (m, 3\text{H}), 7.18 (s, 1\text{H}), 7.11 (dd, J = 1.7, 10.2 \text{ Hz}, 1\text{H}), 6.91 (d, J = 13.6 \text{ Hz}, 1\text{H}), 5.76 (ddd, J = 1.8, 6.6, 17.2 \text{ Hz}, 1\text{H}), 5.14 (dt, J = 1.8, 17.2 \text{ Hz}, 1\text{H}), 5.01 (dt, J = 1.9, 10.5 \text{ Hz}, 1\text{H}), 4.23 (t, J = 6.8 \text{ Hz}, 1\text{H}), 3.43 (p, J = 6.8 \text{ Hz}, 1\text{H}), 1.97 (s, 3\text{H}), 1.17 (dd, J = 1.6, 6.8 \text{ Hz}, 3\text{H}), 0.91 (d, J = 1.9 \text{ Hz}, 3\text{H}), 0.05 (s, 3\text{H}), 0.01 (s, 3\text{H}). \(^1\)C NMR (75 MHz, CDCl\(_3\)): \(\delta 204.09, 139.74, 139.71, 138.37, 136.53, 136.50, 128.88, 128.82, 127.12, 124.63, 76.31, 46.48, 25.87, 18.20, 15.06, 12.05, -4.19, -4.83.\)
Alcohol M7-2

To a solution of ketone M7-1 (155 mg, 0.4182 mmol) in MeOH (2.1 ml) at 0°C under air was added NaBH₄ (64 mg, 1.6729 mmol). The resulting mixture was stirred for 1h. The reaction was quenched with aq. NaHCO₃ (5 ml) and extracted with MTBE (2 x 5 ml). The combined organic 
extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash column 
chromatography on silica (4:1 hexanes:ethyl acetate) afforded alcohol M7-2 (116 mg, 75%) as an oil.

IR (ATR) 3420, 3955, 1462, 1404, 1252, 1142, 1081, 960, 890, 775, 690. ¹H NMR (500 MHz, CDCl₃): δ 7.42 (d, J = 7.8 Hz, 2H), 7.31 (t, J = 7.9 Hz, 2H), 7.21 (tt, J = 1.7, 7.4 Hz, 1H), 7.05 (dd, J = 11, 15 Hz, 1H), 6.53 (d, J = 15.6 Hz, 1H), 6.15 (d, J = 11 Hz, 1H), 5.97 (ddd, J = 6.4, 10.5, 17 Hz, 1H), 5.24 (m, 2H), 4.39 (m, 1H), 4.07 (d, J = 1.7, 1H), 4.01 (d, J = 1.3, 9.4 Hz, 1H), 1.86 (d, J = 1.0 Hz, 3H), 0.95 (s, 9H), 0.70 (d, J = 7.1 Hz, 3H), 0.13 (s, 3H), 0.09 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 139.51, 137.82, 137.40, 137.39, 132.19, 128.68, 127.75, 126.37, 124.99, 116.37, 80.61, 41.42, 25.92, 18.22, 12.79, 11.79, -4.29, -5.07.
Methyl ether M7

To a solution of alcohol M7-2 (45 mg, 0.1208 mmol) in THF (1.2 ml) at -78°C was added lithium bis(trimethylsilyl)amide (1.0 M in THF, 181 µl). The mixture was stirred for 30 min. Methyl triflate (20 µl, 0.181 mmol) was then added and the reaction mixture was stirred for 1h. The reaction was quenched with aq. NaHCO₃ (5 ml) and extracted with MTBE (2 x 3 ml). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo.

Purification by flash column chromatography on silica (20:1 to 10:1 hexanes:ethyl acetate) afforded M7 (44 mg, 95%) as an oil.

[α]D²⁰ = +204 (c 0.025, CH₂Cl₂). IR (ATR) 2954, 2927, 2855, 1596, 1471, 1250, 108 3, 876, 774, 690, 746. ¹H NMR (500 MHz, CDCl₃): δ 7.43 (d, J = 8.1 Hz, 2H) 7.32 (m, 2H), 7.22 (tt, J = 1.2, 6.8 Hz, 1H), 7.04 (dd, J = 4.7, 11, 15.4 Hz, 1H), 6.57 (d, J = 15.3 Hz, 1H), 6.12 (d, J = 11 Hz, 1H), 5.84 (ddd, J = 5.6, 10.4, 17.2 Hz, 1H), 5.19 (dt, J = 1.7, 17.2 Hz, 1H), 5.06 (dt, J = 1.5, 10.6 Hz, 1H), 4.66 (dq, J = 1.5, 5.7 Hz, 1H), 3.45 (d, J = 9.9 Hz, 1H), 3.18 (s, 3H), 1.74 (d, J = 1.2, 3H), 1.63 (m, 1H), 0.95 (s, 9H), 0.64 (d, J = 7.0 Hz, 3H), 0.08 (s, 3H), 0.03 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 141.67, 137.78, 137.38, 132.38, 130.07, 128.79, 127.56, 126.45, 124.65, 114.02, 88.42, 71.41, 55.89, 41.99, 26.19, 18.46, 11.14, 8.86, -3.74, -5.02. HRMS (TOF ES+) Calcd for C₂₄H₃₈O₂SiNa⁺ (M+Na)⁺: 409.2539. Found: 409.2529.
Alcohol M8

To a solution of methyl ether M7 (20 mg, 0.052 mmol) in THF (1.5 ml) at 0 °C, HF-pyr (70%, 390 μl) was added. The resulting solution was kept at r.t. for 20h. The reaction was quenched with aq. NaHCO₃ (10 ml) and extracted with MTBE (2 x 5 ml). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (4:1 hexanes:ethyl acetate) afforded the secondary alcohol M8 (6 mg, 43%) as an oil.

¹H NMR (300 MHz, CDCl₃): δ 7.42 (d, J = 2 Hz, 2H), 7.32 (t, J = 7.2 Hz, 2H), 7.22 (tt, J = 2.3, 8.2 Hz, 1H), 7.02 (dd, J = 10.95, 15.6 Hz, 1H), 6.55 (d, J = 15.6 Hz, 1H), 6.14 (dt, J = 0.5, 11 Hz, 1H), 5.94 (ddd, J = 5.1, 10.4, 17.1 Hz, 1H), 5.33 (dt, J = 1.8, 17.2 Hz, 1H), 5.23 (dt, J = 1.7, 10.5 Hz, 1H), 4.25 (m, 1H), 3.52 (d, J = 9.6 Hz, 1H), 3.12 (s, 3H), 2.10 (m, 1H), 1.78 (d, J = 1.2 Hz, 3H), 0.74 (d, J = 7.1 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 138.40, 135.90, 133.01, 129.89, 128.80, 127.73, 126.49, 124.40, 115.35, 90.81, 75.63, 55.98, 40.09, 13.01, 11.54
As an alternative to the previously reported methylation of alcohol W13, Meerwien’s salt can be used as a methylating agent. A solution of alcohol W13 (100 mg, 0.203 mmol) in DCM (4 ml) was transferred via cannula to a reaction tube containing Meerwein’s salt (90 mg, 0.611 mmol) and proton sponge (175 mg, 0.815 mmol). The resulting mixture was stirred at r.t. for 2h. The reaction was quenched with ice cold water (5 ml), then transferred to a separatory funnel containing aq. NaHCO$_3$ (10 ml) and was extracted with MTBE (2 x 5 ml). The combined organic extracts were washed with brine, and extracted again with MTBE (2 x 5 ml). The combined organic extracts were dried over MgSO$_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (20:1 hexanes:ethyl acetate) afforded methyl ether NW (56 mg, 55%) as an oil.

crude NMR of:

M6

GII (5 mol%)
0.001 M PhMe
50°C

mixture
crude NMR of:

M6

GII (5 mol%)
0.001 M PhMe
80°C

No starting material, some ring closed product
crude NMR of:

M6

GII (5 mol\%)  
0.001 M PhMe  
110°C

predominantly ring-closed product
crude NMR of:

\[
\text{MeO} - \text{OTBS} - \text{M12} + \text{GII (5 mol\%)} \rightarrow \text{0.001 M PhMe} \quad \text{rt} \quad \text{MeO} - \text{OTBS} - \text{M16} + \text{some SM}
\]
crude NMR of:

GII (5 mol%) 0.001 M PhMe  
rt

Mixture of CM products
9. References

20. It was not specified which archazolid molecule was used (A or B).


45. For an example of how simplification from a synthesis standpoint leads to valuable SAR information, see the following article about devazepide, simplified from asperlicin: J. Carillo, N Agra, *Anticancer Drugs*, **2009**, *7*, 527-533.


97. *No reports of metathesis deactivating stereotriads are present in the literature to date.*