Cross-Metathesis of Electron-Deficient Polyenes and Studies Toward the Total Synthesis of Arenolide

by

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has been approved for the Department of Chemistry and Biochemistry

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The final copy of this thesis has been examined by the signatories, and we find that both the content and the form meet acceptable presentation standards of scholarly work in the above mentioned discipline.

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Cross-Metathesis of Electron-Deficient Polyenes and Studies Toward the Total Synthesis of Arenolide

Thesis directed by Professor Tarek Sammakia

The selectivity of the cross-metathesis reaction between electron-deficient polyenes and a general terminal alkene by use of different metathesis catalysts is presented. The reaction was found to be the most efficient when applied between a monoene or triene and the terminal alkene, providing the desired product in good to excellent yields. The selectivity is attributed to the reactivity of the terminal alkene of the triene which is furthest removed from the electron-withdrawing aldehyde or ester, rendering it the only alkene capable of reacting with the catalyst. Diene and tetraene substrates were not good partners in this reaction due to a lack of differentiation of the alkenes.

Different approaches toward the total synthesis of arenolide, a 14-membered macrolide with unclear stereochemical assignment and bioactivity, are also discussed. The first approach utilizes a 1,5-*anti* aldol reaction that was found to lack diastereoselectivity when applied to the total synthesis. The second-generation approach focuses on alternative methods to produce the 1,5-*anti* relationship between the alcohols at C9 and C13 with the exo-methylene group at C11. All studies include the use of a key intramolecular vinylogous aldol macrocyclization developed in the Sammakia lab, which was shown to be effective on a model precursor very similar to that of arenolide. Efforts are underway to complete the total synthesis of arenolide.

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Chapter 1

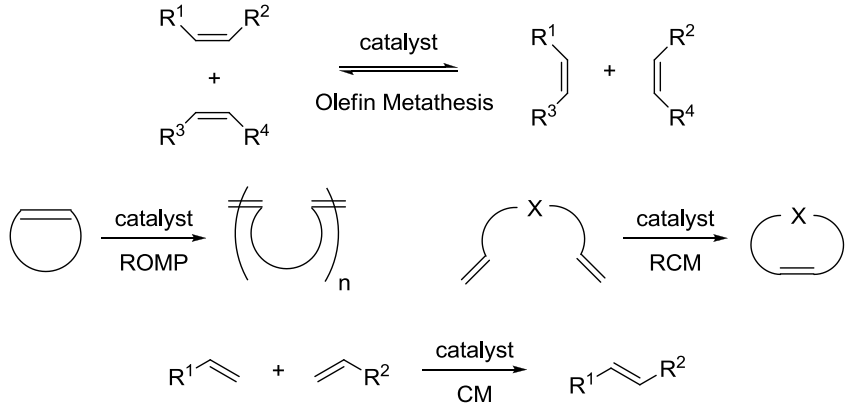
Cross-Metathesis of Electron-Deficient Polyenes

1.1 Olefin Metathesis Background

Olefin metathesis is defined as the exchange of alkylidene moieties between alkenes, and with the advent of catalysts with broad substrate scope and high functional group tolerance, it has become a widely used and powerful technique for the formation of carbon-carbon double-bonds (Scheme 1.1).[1] This method has had broad application in both academic and industrial settings, primarily because of the powerful bond forming opportunity it provides. In addition, its utilization is convenient in that it requires no additional reagents other than the catalytic amount of a metal complex, and in most cases the only by-product of the reaction is a volatile olefin such as ethylene.[2] Olefin metathesis was first introduced in the 1950s primarily as an industrial polymerization technique, the main application of which was in catalytic ring-opening metathesis polymerization reactions (ROMP). These reactions are thermodynamically favored, especially for strained ring systems, and they have seen extensive exploitation in the manufacture of specialty polymers.[3] The next key development in the field was that of catalytic ring-closing metathesis reactions (RCM). In this case, the forward process is entropically driven since the reaction begins with one molecule and provides two molecules as products. The utility of this process lies in its broad substrate scope which the synthesis of small, medium, or large rings from acyclic precursors.[2,4] Finally, olefin cross-metathesis

reactions (CM) were the most recent to be studied and developed. CM reactions are of particular significance because they serve as convenient routes to functionalized and higher olefins from simple alkene precursors. Other synthetically useful reactions involving olefin metathesis include acyclic diene metathesis polymerization,[3] ene-yne metathesis,[5] and many other tandem processes: ring-opening followed by cross-metathesis,[6] ring-opening—ring-closing metathesis reactions,[7] and ene-yne RCM followed by CM reactions are just a few examples.[5]

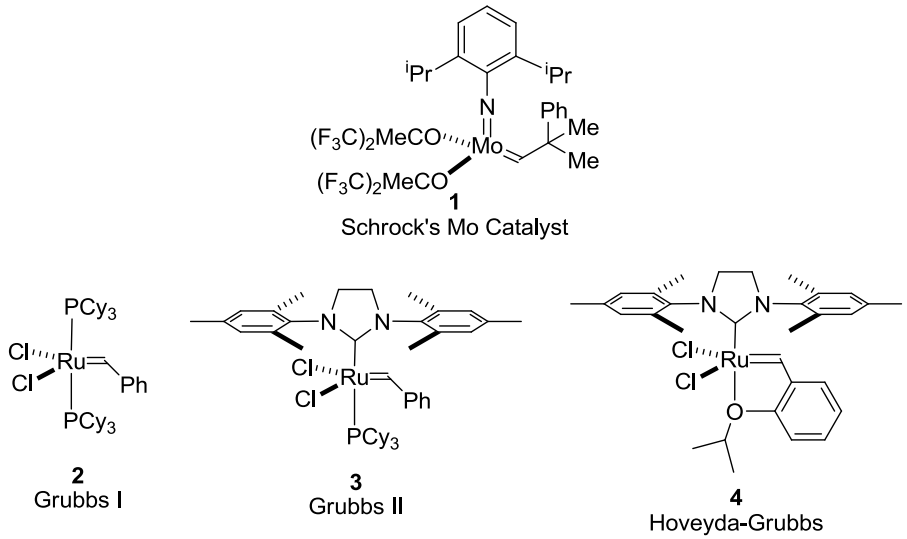
Scheme 1.1. General Metathesis Schematic and Common Metathesis Reactions.



Early olefin metathesis processes were characterized by multi-component catalyst systems; typically transition metal salts in combination with main group alkylating agents.[8] These systems suffered from limited efficacy, however, due to their incompatibility with common functional groups and poorly defined nature which presented difficulties with initiation and control. With the late 1980s and early 1990s came the rapid development of new olefin metathesis catalysts, the most notable of which is the Shrock molybdenum catalyst **1**, shown in Figure 1.1.[9] Unfortunately, this catalyst and others based on the early transition metals are extremely sensitive to oxygen and moisture due to the high oxophilicity of the metal centers.[8] As a result,

catalyst-design began to focus on late transition metals, specifically Ru-derived catalysts, which were known to react preferentially with olefins over alcohols, acids, and other common functional groups. Although their activity is usually lower than **1**, the increased functional group tolerance and ease of handling rendered catalysts **2**, **3** and **4** significantly more practical (Figure 1.1).[4,10-13] With the development of these well-defined ruthenium catalysts, the installation of structural elements within complex natural products, and the synthesis of simpler substrates for further synthetic transformations can be accomplished.

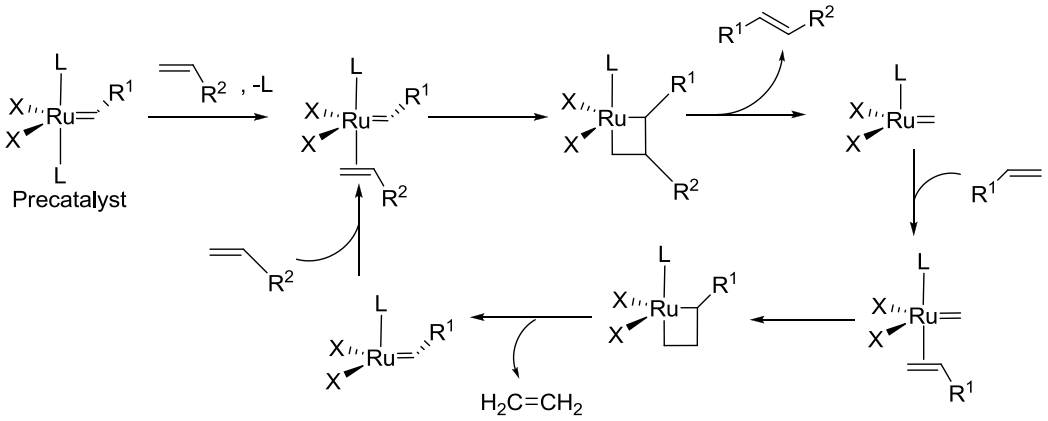
Figure 1.1. Commonly Used Olefin Metathesis Catalysts.



With these new, well-defined catalysts came a dramatic increase in the application of olefin metathesis to complex synthesis, and as a result further detailed experimental and theoretical studies have been carried out to elucidate the mechanism of action of catalysts **2**, **3**, and **4**. The accepted mechanism, first proposed by Chauvin, consists of the formation of a metallacyclobutane intermediate, which is formed by a formal [2+2] reaction between the alkene and the carbenoid, followed by a formal retro-[2+2] to release the product and regenerate a carbene. In the case of

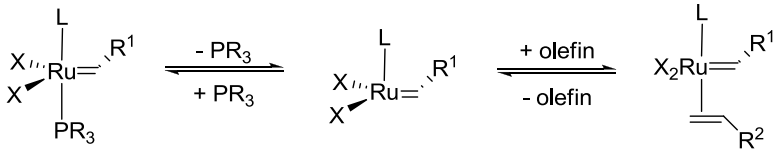
the Grubbs catalysts, dissociation of a phosphine ligand precedes olefin complexation and formation of the metallacyclobutane intermediate. This intermediate then undergoes a formal retro-[2+2] to give the olefin product and a new metallocarbene as shown in Figure 1.2.[14] The resulting metallocarbene then reenters the catalytic cycle by binding to another olefin substrate.

Figure 1.2. Accepted Olefin Metathesis Cycle.



Initial mechanistic studies by Grubbs did not distinguish between an associative and dissociative ligand exchange of the phosphine with olefinic substrate, which is critical since this step forms a coordinatively unsaturated intermediate with greater propensity for binding of the olefin and entry into the catalytic cycle. An associative exchange was originally proposed on the basis of a preference for an 18-electron intermediate over a 14-electron-intermediate. However, most recent investigations have implicated a dissociative ligand exchange followed by the formation of a metallacyclobutane intermediate that collapses to give the olefin product (Scheme 1.2).[10]

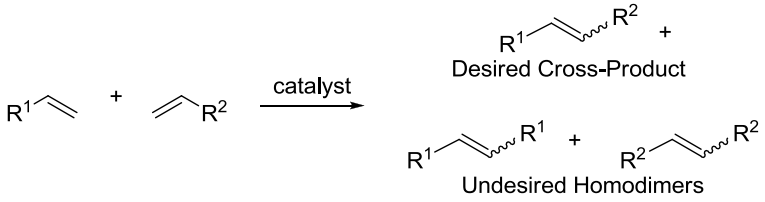
Scheme 1.2. Dissociative Ligand Exchange Mechanism that Allows Entry of Catalyst into the Catalytic Cycle.



1.2 Selectivity in Olefin Cross-Metathesis

Until recently, olefin cross-metathesis (CM) has been an underrepresented area of olefin metathesis when compared to ROMP and RCM reactions. This has primarily been due to several factors: first, in the absence of a strong enthalpic driving force (such as ring-strain release in ROMP) or the entropic advantage of intramolecular reactions (such as RCM), the reaction mixture will be under equilibrium and thermodynamic control, which might or might not favor products. Second, there can be low selectivity for the CM product versus the two possible homodimer products, and third, there can be poor *E* versus *Z* selectivity in the newly formed olefin (Scheme 1.3).[15]

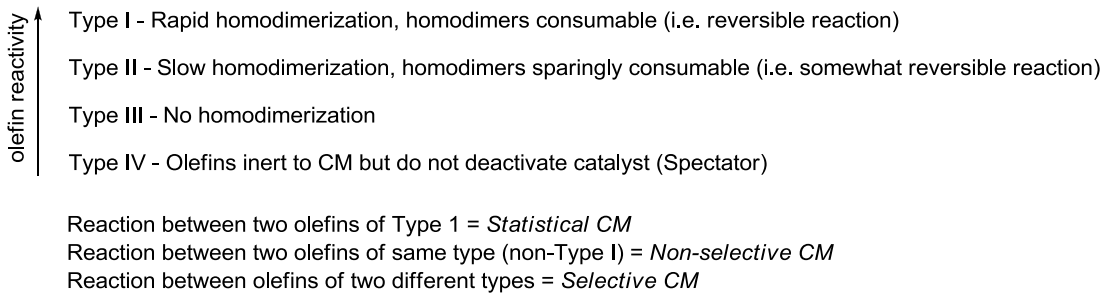
Scheme 1.3. Possible CM Reaction Products.



Recently, however, the rapidly expanding body of CM literature and analyses has provided the foundation for an empirical model for product-selective cross-metathesis. According to Grubbs et al., a straightforward and practical ordering or

categorization of olefin reactivity is first required in order to predict the selectivity for a CM product.[15] The most convenient way to determine this ordering is to rank olefin reactivity as a function of ability to homodimerize relative to other olefins, along with the subsequent reactivity of their homodimers. This analysis leads to a general model that consists of four distinct olefin types and can be used to predict both selective and non-selective CM reactions (Figure 1.3).

Figure 1.3. Olefin Categorization and Rules for Selectivity in CM Reactions.



In general, a reactivity gradient exists from the most active type (Type I olefin) to least active type (Type IV), with sterically unhindered, electron-rich olefins categorized as Type I and increasingly sterically hindered and/or electron-deficient olefins falling into Types II through IV. Note that this activity is catalyst-dependent. What may be classified as a Type I olefin with a more reactive catalyst could be a Type II or III olefin in regards to a less reactive catalyst. The reactivity of an olefin with a given catalyst also determines the role of secondary metathesis events, which can be described as subsequent reactions of a product olefin with the propagating catalyst. Two factors, then, are key to a selective CM reaction, the first being the ability to minimize the number of undesired side products (such as homodimers of the original olefins) by avoiding their initial formation or rendering their formation reversible through secondary metathesis events. The second issue is the prevention of

the desired cross-product from being redistributed into a statistical product mixture of products by secondary metathesis events.[15]

When two Type I olefins are paired in a CM reaction, the rates of homodimerization and cross-product formation are similar, and the reactivities of the homodimers and cross-products toward secondary metathesis events can be high. In these reactions, the desired cross-product will be formed at a rate comparable to the homodimers, and equilibration of the cross-products with the various homodimers through secondary methathesis reactions will result in a statistical product mixture. To avoid statistical product distributions, one can design selective CM reactions by using olefins from two different types whose rates of dimerization are significantly different and/or slower than CM product formation. This improved cross-product selectivity could, however, be accompanied by poor stereoselectivity due to the inability of the cross-product to readily undergo cis/trans isomerization via secondary metathesis processes. Nonetheless, many surveys and investigations have shown that the use of this method as a starting point for the design of potentially selective CM reactions is general and provides reproducible results.[15]

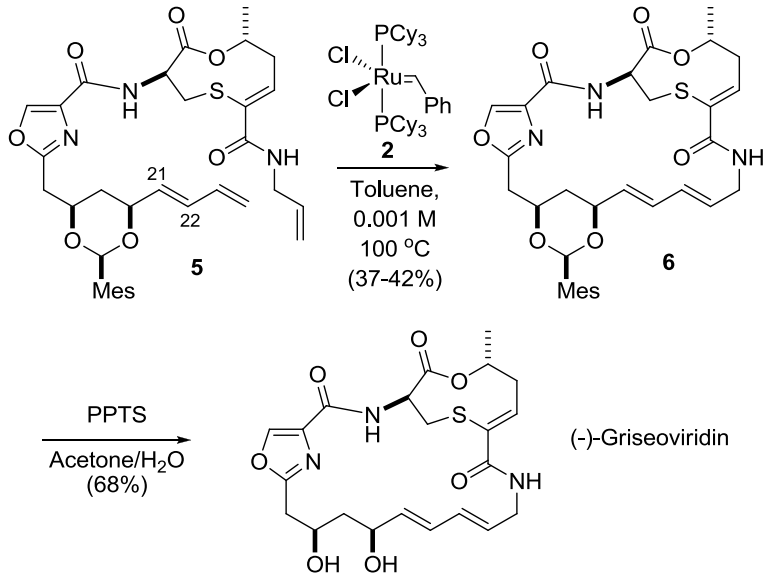
1.3 Polyene Metathesis in Natural Products Synthesis

While olefin metathesis has seen extensive use in the total synthesis of natural products, syntheses involving metathesis reactions with polyenes are more limited. As stated previously, this is due to chemo- and diastereoselectivity issues accompanied by lack of selectivity in regards to the geometry of the newly formed

olefin. Still, there are several daring and successful examples of the use of polyene metathesis reactions in the context of total synthesis.

Meyers and coworker's synthesis of (–)-griseoviridin is one such daring use of metathesis of a polyolefinic substrate.[16] Griseoviridin is part of a family of streptogramin antibiotics, and when combined with certain macrocyclic depsipeptides they exhibit strong synergism with respect to their activity toward Gram-positive bacteria. The group's synthesis utilizes a key late-stage ring-closing metathesis reaction of a seco-triene (**5**, Scheme 1.4). Subsequent deprotection of the cyclized lactam (**6**) provided the target in a total of 24 linear steps from (*S*)-malic acid.

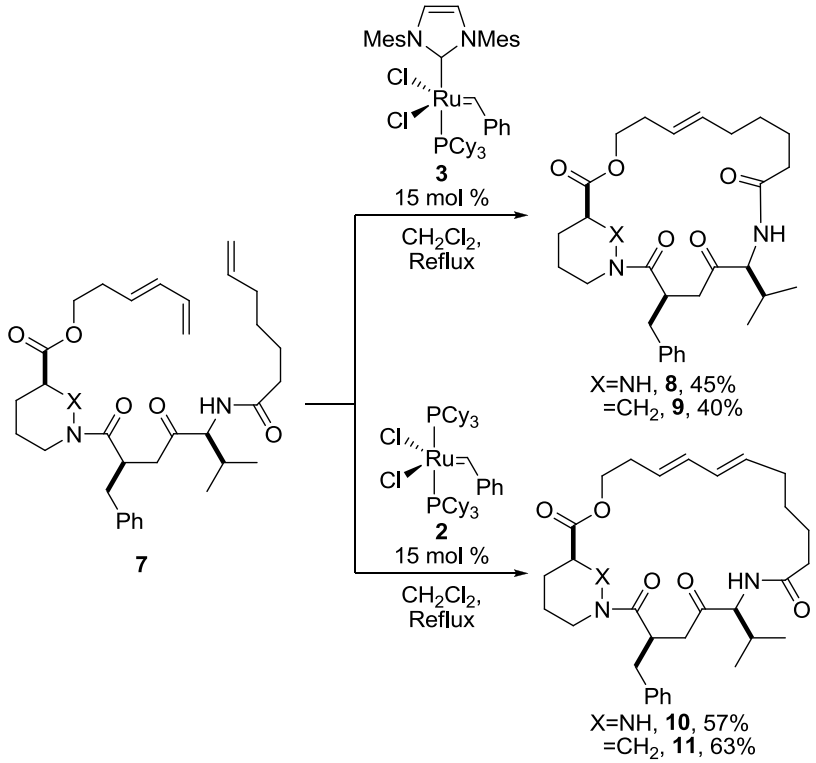
Scheme 1.4. Meyers' Late-Stage RCM in the Total Synthesis of Griseoviridin.



Although the key RCM reaction only occurs in a reproducible 37-43% yield, no other metathesis products were formed in the reaction, and no alkene isomerization was observed. It is somewhat surprising that the reaction is very selective for the terminal olefins when the C21-C22 olefin could also be classified as Type I; steric constraints likely prevented metathesis events at this site.

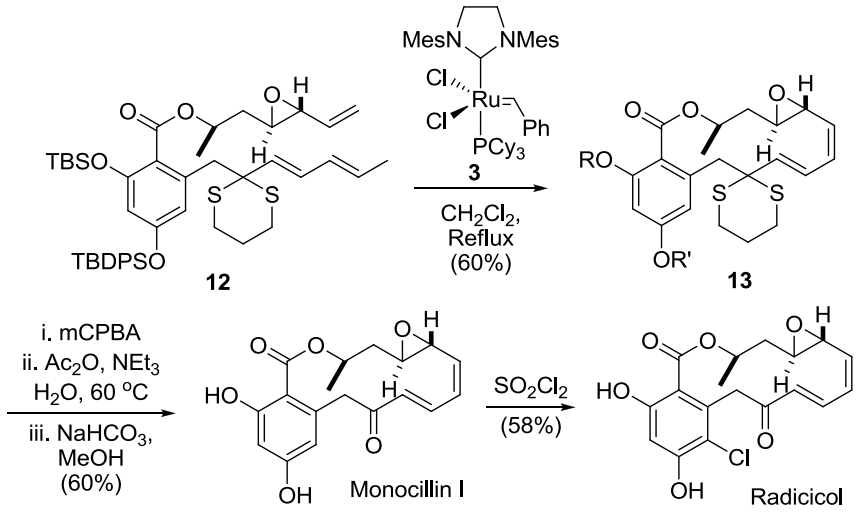
A similar key RCM reaction of an acyclic triene was utilized in Nolan and co-workers' syntheses of sanglifehrin macrolide analogues.[17] Sanglifehrin A is a potent immunosuppressant isolated from *Streptomyces flaveolus* in 1995 by scientists at Novartis. Unlike that in Meyers' synthesis of (–)-griseoviridin, Nolan's key reaction mainly produced the internal metathesis products (**8** and **9**) upon use of catalyst **3** on substrate **7** (Scheme 1.5). Only ~10% of this crude mixture consisted of the desired dienyl macrolide. However, the group was able to obtain solely the desired products **10** and **11**, wherein metathesis takes place between the terminal olefins, by simply switching to catalyst **2**. Also unlike Meyers, Nolan and co-workers isolated some of the *E*,*Z*-diene isomer, although it was in a small amount (<5%) when using either catalyst. The authors propose a plausible explanation for the switch in olefin metathesis selectivity in that the more reactive catalyst **3** offsets the steric limitations and is able to react with the more electron-rich internal olefin of the diene. The less reactive catalyst cannot overcome the steric constraints and is therefore limited to react with the terminal olefin of the diene.

Scheme 1.5. Nolan's RCM Reaction in the Syntheses of Sanglifehrin Analogues.



A final example of yet another selective RCM reaction of an acyclic triene is in Danishefsky's syntheses of radicicol and monocillin I, macrolides isolated from *Monocillin nordinii* that exhibit a variety of antifungal and antibiotic properties.[18] As shown in Scheme 1.6, the macrolide core is formed via selective metathesis at the terminal olefins of **12** with Grubbs' second-generation catalyst (Grubbs II), **3**, although in this instance the selectivity is not so surprising since the olefin proximal to the dithiane is almost certainly too deactivated to participate in the metathesis event.

Scheme 1.6. RCM Reaction and Endgame of Danishefsky's Syntheses of Monocillin I and Radicicol.

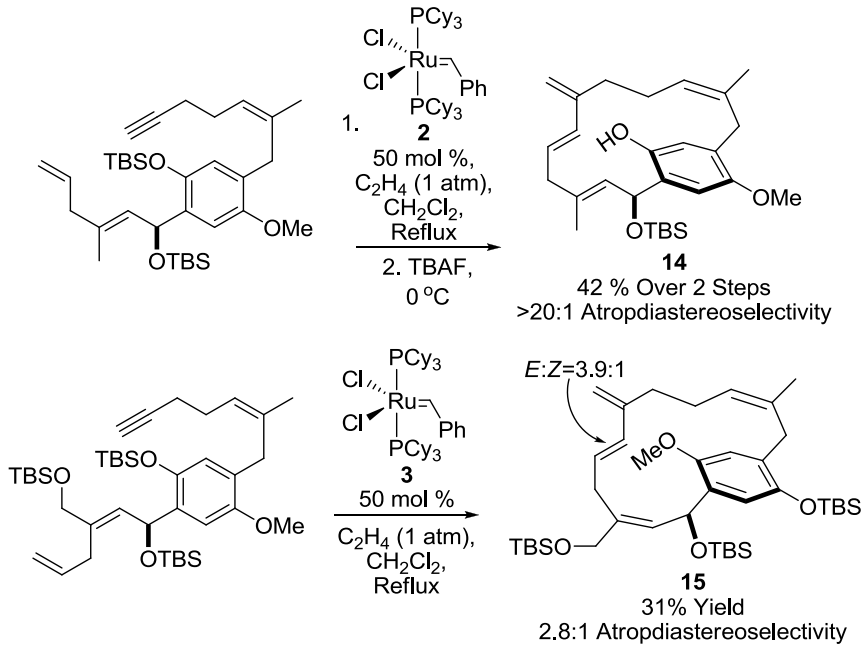


Danishefsky reports that the use of Grubbs' first-generation catalyst (Grubbs I), **2,** resulted in only trace amounts of the desired product, requiring the increased reactivity of Grubbs' second-generation catalyst. After removal of the dithiane and silyl ethers, monocillin I was obtained, and chlorination via SO_2Cl_2 provided radicicol with a longest linear sequence of 14 steps. This efficient synthesis enabled the production of ample amounts of these natural products and their analogues for use in a comprehensive Hsp90-directed drug discovery program.

Shair and co-workers accomplished a very elegant synthesis of (–)-longithorone A, a cytotoxic marine natural product, in 2002 wherein they utilized two difficult ring-closing ene-yne metathesis reactions with two complex polyenes.[19] The key biomimetic transformations of their synthesis consist of an intermolecular Diels-Alder reaction between two fragments, both formed via a similar ring-closing ene-yne metathesis reaction, followed by an intramolecular trans-annular Diels-Alder reaction.

Both ring-closing ene-yne metathesis reactions also produce atropisomers, adding another facet of difficulty to the reactions (Scheme 1.7).

Scheme 1.7. RCM Reactions in Shair's Synthesis of Longithorone A.

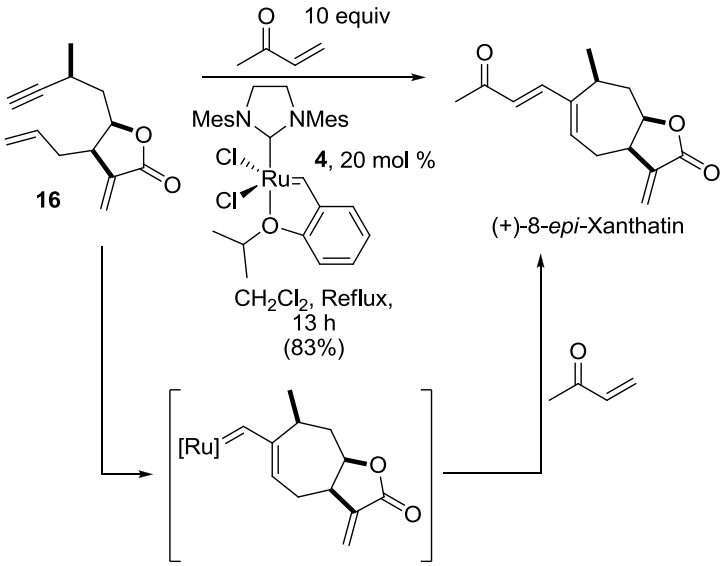


In forming **14**, an atropdiastereoselectivity of >20:1 was determined based on nOe analysis and after deprotection of the silyl ether a 42% yield was obtained over two steps. In the production of **15**, only a 2.8:1 atropdiastereoselectivity was found, along with a 3.9:1 mixture of *E*/*Z* isomers at the newly formed internal olefin. The selectivity in both reactions is impressive given the other olefins in each substrate and also in that only the 1,3-disubstituted diene scaffold was formed in both products. While it is likely that the other trisubstituted olefins in both starting materials are too sterically-hindered to participate in metathesis events, the efficiency in forming both products is still notable.

Another use of an ene-yne RCM reaction with a polyolefinic substrate is that of Martin et al.'s synthesis of (+)-*epi*-8-xanthatin; however, their application also

includes a tandem CM reaction.[20] (+)-*epi*-8-Xanthatin is a sesquiterpene lactone that displays antimalarial activity, and has recently been shown to inhibit the in vitro proliferation of several cultured human tumor cell lines. Their synthesis culminates with a tandem ene-yne RCM/CM reaction with substrate **16** and methyl vinyl ketone (Scheme 1.8) and gives the target compound in a longest linear sequence of 14 steps with an overall yield of 5.5%.

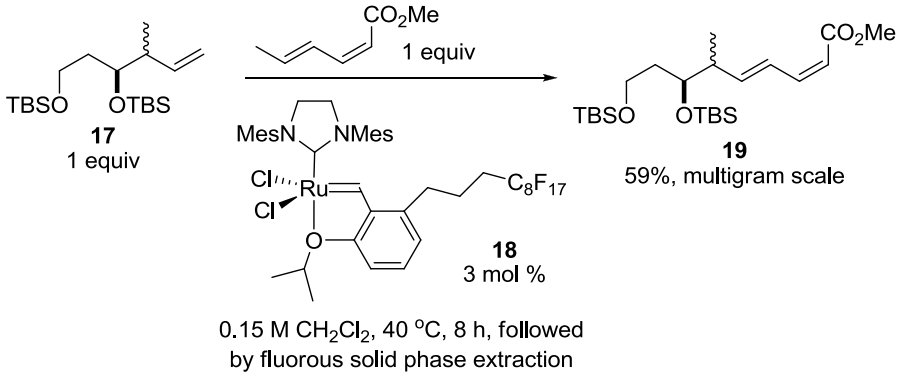
Scheme 1.8. Martin's Tandem RCM/CM Reaction in the Total Synthsis of *epi*-8-Xanthatin.



The selectivity of Martin's reaction is impressive since not only is the starting material a polyene, but methyl vinyl ketone (MVK) is also present in the reaction mixture. Apparently the intramolecular ene-yne RCM reaction is preferred over the possible intermolecular reaction of the terminal olefin in **16** and MVK. All in all, the use of this tandem ene-yne RCM/CM reaction was quite intrepid, and its success is commendable.

While there are several examples of complex ring-closing metathesis reactions involving polyenes in total synthesis, there are even fewer that strictly involve selective cross-metathesis. Only after performing a thorough study (discussed later in this chapter) of the CM between (2*Z*,4*E*)-dienyl esters and other complex terminal olefins were Curran and co-workers able to utilize a metathesis reaction in their synthesis of (–)-dictyostatin and its analogues.[21] Their route allows for the preparation of both epimers of **19**, shown in Scheme 1.9, in only six steps on a multigram scale via CM. This piece was one of three key fragments that enabled the streamlined synthesis of several new dictyostatin analogues.[22]

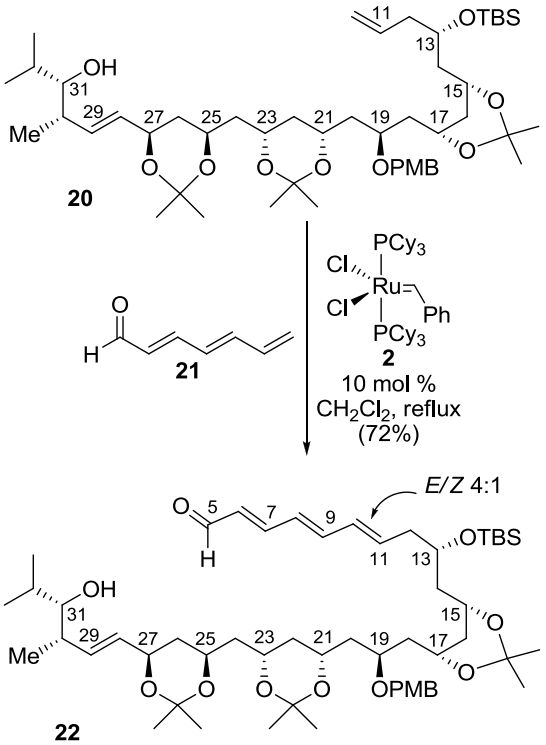
Scheme 1.9. Curran's Polyene CM Reaction in the Synthesis of Dictyostatin.



In the event, Curran and co-workers used **18**, a fluorous derivative of the Hoveyda-Grubbs catalyst, as the metathesis catalyst in order to separate the catalyst upon reaction work-up via fluorous solid-phase extraction (Scheme 1.9). They were then able to reuse the catalyst with little decrease in activity in two subsequent cycles. In total, their initial amount of 1.3 g of catalyst **18** was used to metathesize 33.5 g of **17** into 24.2 g of product **19** as a single stereoisomer (59% overall yield). The reaction strictly provided the product with 2*Z*- and 4*E*-olefin geometries, a characteristic that was necessary to carry on the substrate in their total synthesis.

Another application of polyene CM was demonstrated in one of the key synthetic steps in the total synthesis of the oxopolyene macrolide, RK-397, by previous members of our group, Mark Mitton-Fry and Aaron Cullen.[23] This stereochemically complex natural product was isolated in 1993 from a strain of soil bacteria and was shown to possess antifungal, antitumor, and antibacterial activities.[24] Upon completion of the synthesis of the polyol portion of this target (**20**), a risky CM reaction between the terminal alkene of the polyol fragment and a conjugated triene aldehyde piece (**21**) was studied.

Scheme 1.10. Key Polyene CM Reaction in the Total Synthesis of RK-397.

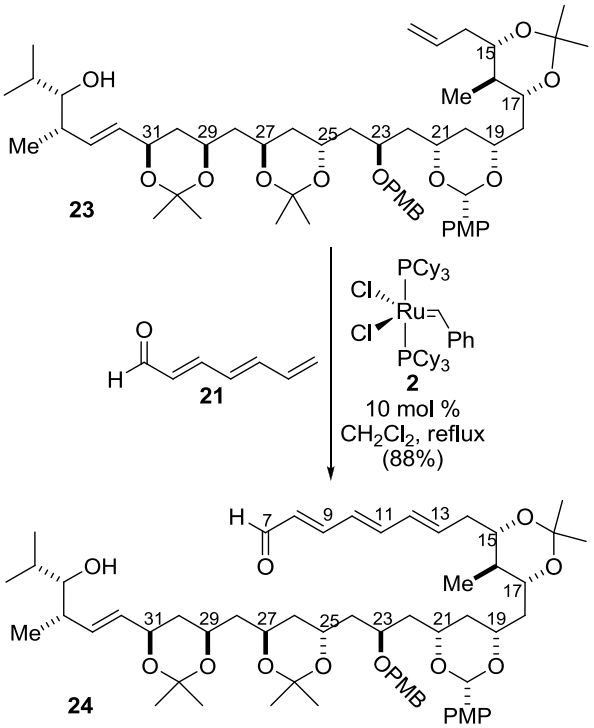


This reaction with catalyst **2** (Grubbs I) was executed to give **22** in an excellent yield of 72% and moderate *E/Z* selectivity of 4:1 (Scheme 1.10). No other metathesis products were isolated from the crude reaction mixture, indicating that only the terminal olefin of the trienal was sufficiently active to react. The two olefins

proximal to the aldehyde were most likely too deactivated to participate in the CM reaction.

Finally, a similarly risky CM reaction was also utilized in our group's synthesis of another oxopolyene macrolide, dermostatin A.[25] Although the success of this reaction in the synthesis of RK-397 provided strong precedence for its application in the dermostatin A synthesis, the compound's polyol portions differed, eliminating any guarantee of success. Gratifyingly, the same trienal piece **21** underwent selective metathesis with the terminal olefin in the polyol portion of dermostatin A, **23** (Scheme 1.11). Again, **24** was the only metathesis product isolated from the reaction mixture, showing the selectivity of the distal olefin towards CM over the two olefins proximal to the aldehyde. Moderate *E*/*Z* selectivity of the newly-formed olefin was again seen in a 4:1 ratio.

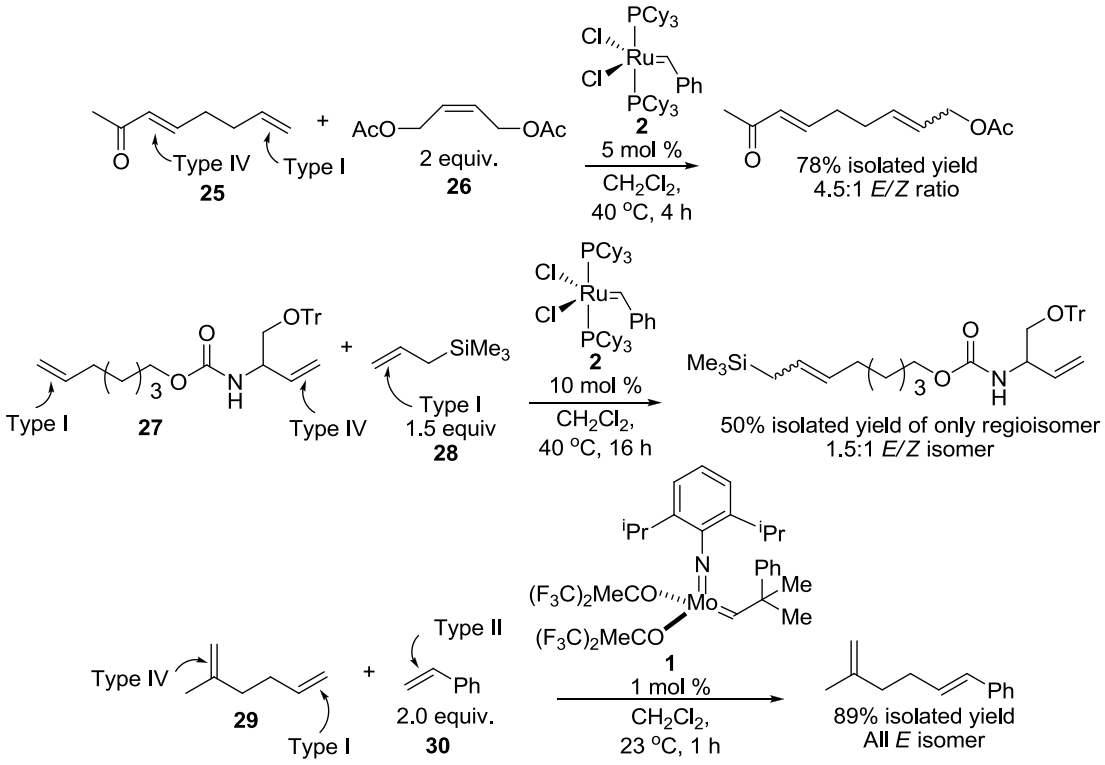
Scheme 1.11. Key CM Reaction in the Total Synthesis of Dermostatin A.



1.4 Previous Polyene Cross-Metathesis Studies

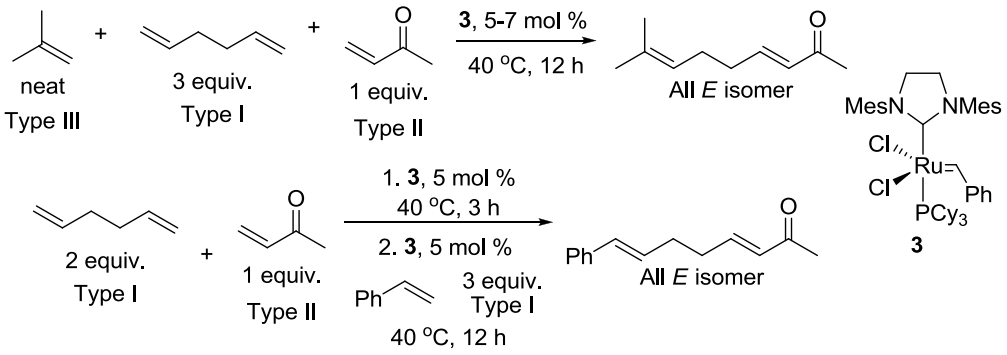
While elucidating an empirical model for product-selective cross-metathesis, Grubbs and co-workers also found that the same model could be applied to chemoselective CM reactions with polyolefinic substrates.[15] In principle, CM would take place with a Type I or Type II olefin in the presence of a Type IV olefin with a given catalyst. And as a proof of concept they showed that the metathesis reaction between substrates **25** and **26** (Scheme 1.12) provided the desired cross-product between the Type I olefin in the diene substrate (with catalyst **2**) and the olefin of substrate **26**. No metathesis took place between the electronically deactivated Type IV olefin of the diene and substrate **26**, exemplifying the chemoselectivity of the CM reaction. Blechert et al. used steric constraints to implement selectivity for a Type I olefin in the presence of a Type IV between substrates **27** and **28** with catalyst **2** as shown in Scheme 1.12.[26] And with catalyst **1**, Crowe and Zhang showed the chemoselective reaction between the Type I olefin in **29** and the Type II olefin in **30** in the presence of a Type IV olefin (Scheme 1.12).[27]

Scheme 1.12. Chemoselective CM Based on Olefin Categorization.



In addition to chemoselective CM reactions, Grubbs' olefin classifications also enable the development of multicomponent processes.[15] In their study, Grubbs et al. demonstrate the execution of a three-component CM reaction. This was done by first taking advantage of the fact that secondary metathesis reactions can be much slower than productive CM reactions. Then by using two olefins which do not react readily with one another, a third diene-containing substrate could be functionalized at both olefins unsymmetrically. A successful example of this concept is the first reaction shown in Scheme 1.13 where olefins of Types I, II and III are all combined to make one product selectively. In this reaction, one of the Type I dienyl-olefins and the Type II olefin readily react and the resulting diene is only reactive at the site distal to the carbonyl, which then reacts with the Type III olefin that remains in solution.

Scheme 1.13. Three-Component CM Reactions.

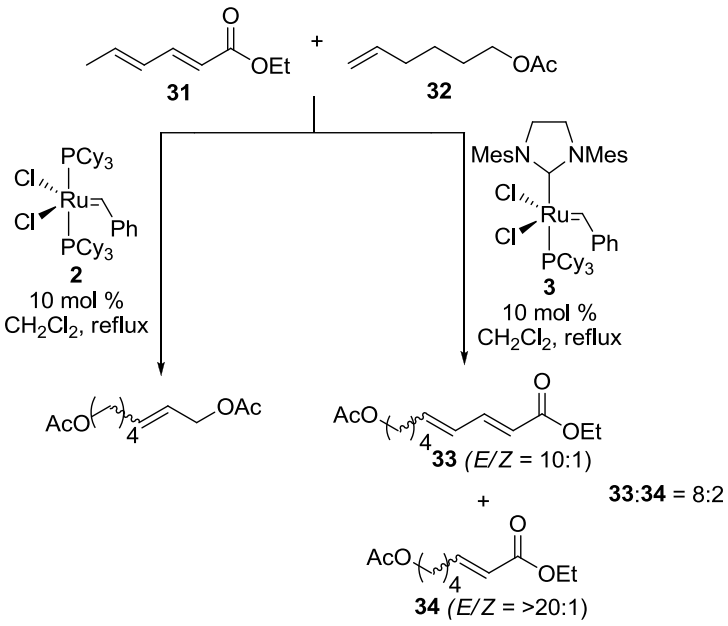


The reaction described at the bottom of Scheme 1.13 shows that two Type I olefins can be utilized in a three-component CM reaction by simply applying a sequential addition strategy.[15] Similarly as before, one of the diene olefins first reacts with the Type II olefin in solution and the resulting diene reacts with styrene upon addition only at the olefin distal to the carbonyl. Had the diene and styrene not been sequentially added, a non-selective mixture of products would have resulted.

Not only do many natural products contain multiple olefins, but conjugated polyene moieties are also abundant. However, few synthetic studies have been undertaken in efforts to build these conjugated scaffolds via olefin metathesis because of potential issues regarding chemo- and diastereoselectivity in the metathesis reactions. Grubbs and co-workers cleverly circumvent these issues, however, in their study involving dienes via deactivation or "protection" of a specific olefin.[28] This is accomplished by attaching an electron-withdrawing or sterically bulky substituent to one of the olefins in the conjugated diene, leaving the remaining olefin more reactive and available to participate in the metathesis reaction. Their initial study consisted of ethyl sorbate (**31**) as the conjugated diene and 5-hexenyl acetate (**32**) as the metathesis partner. With catalyst **2**, however, only homocoupling of **32** occurred

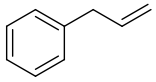
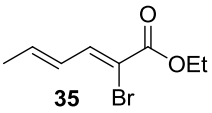
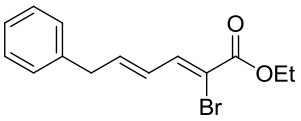
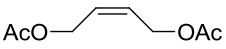
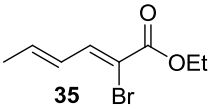
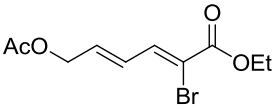
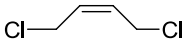
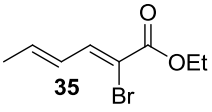
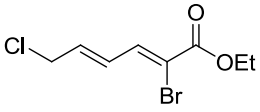
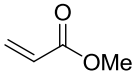
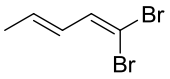
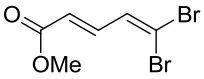
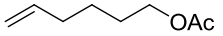
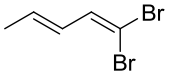
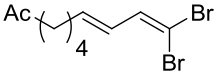
indicating that both of the olefins in **31** were too deactivated (Scheme 1.14). Upon switching to catalyst **3**, a mixture of metathesis proximal and distal to the electron-withdrawing ester took place, in this case indicating that both olefins were rendered too reactive.

Scheme 1.14. Grubbs' Initial Attempts at Achieving Selectivity with Conjugated Dienes.



To increase the deactivation and steric bulk of the α,β-olefin, a vinyl bromide was added to the α-carbon (compound **35** in Table 1.1). When this substrate was paired with reactive monoenes and subjected to the reaction conditions with catalyst **3** (Grubbs II), the desired cross-products were formed with metathesis occurring solely at the γ,δ-olefin. The electron-withdrawing group is now sufficient enough to deactivate the proximal olefin while leaving the distal olefin reactive enough to participate in the metathesis reaction. Representative examples of their study are given in Table 1.1. As shown in entries 4 and 5, the dibromo moiety was also able to sufficiently deactivate the proximal olefin to give the desired cross-products.

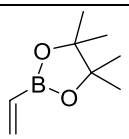
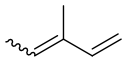
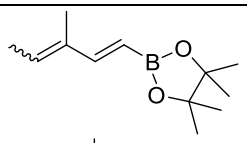
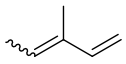
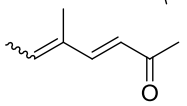
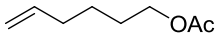
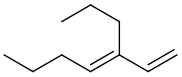
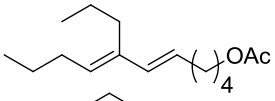
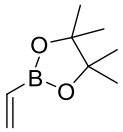
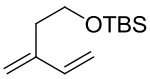
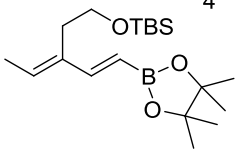
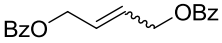
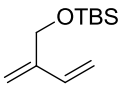
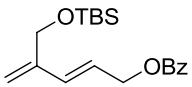
Table 1.1. Olefin CM with Electron-Poor Dienes.[a]

entry	olefin	conjugated diene	product	yield (%)[b] *E*/*Z* ratio
1		 **35**		68 8.5:1
2[c]		 **35**		70 7.5:1
3		 **35**		48 6:1
4				39 >20:1
5				56 5:1

[a]Conditions: olefin (1-3 equiv), conjugated diene (1 equiv), and catalyst **3** (5 mol %) for 12 h in refluxing CH_2Cl_2 (0.2 M). [b]Isolated yields. [c]10 mol % of catalyst **3** was used.

Grubbs et al. were also able to support their hypothesis of the ability to "protect" a particular olefin via steric bulk in the CM reaction.[28] This was carried out by introducing substitution around one of the olefins of the conjugated diene. As shown in Table 1.2, 1,2-disubstituted butadienes and even 2-substituted butadienes were viable metathesis partners with the reaction only taking place at the 3,4-olefin with catalyst **3** (Grubbs II).

Table 1.2. Olefin CM Using 1,2-Disubstituted and 2-Substituted 1,3-Butadienes.[a]

entry	olefin	conjugated diene[b]	product[c]	yield (%)[d]
1				80
2				70
3				77
4[e,f]				69
5[e]				63

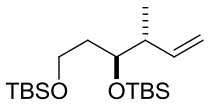
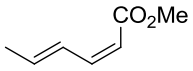
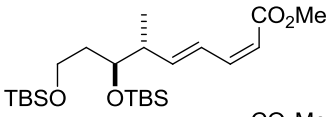
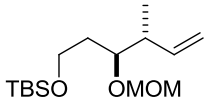
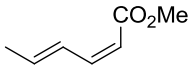
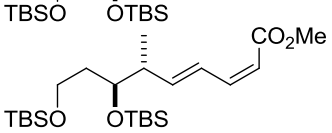
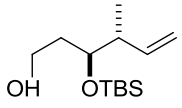
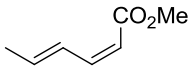
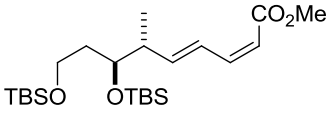
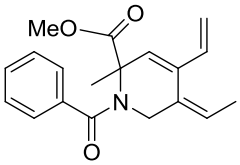
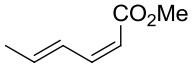
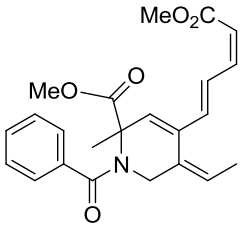
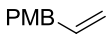
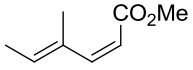
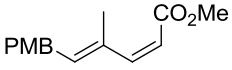
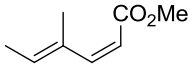
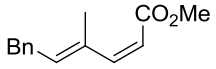
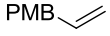
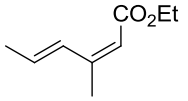
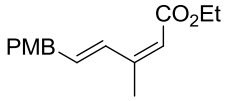
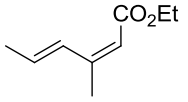
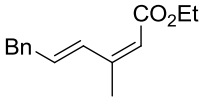
[a]Conditions: olefin (1-4 equiv), diene (1 equiv), and catalyst **3** (5 mol %) in refluxing CH_2Cl_2 (0.2 M) for 12 h. [b]3-Methyl-1,3-pentadiene was purchased as a 70:30 mixture of *E*/*Z* isomers. [c]Only the *E* isomer was observed in all cases; when 3-methyl-1,3-pentadiene was the diene, both *E* and *Z* isomers reacted. [d]Isolated yields. [e]Reaction was run in benzene (0.2 M) at 60 °C for 12 h. [f]Reaction was stopped after 2 h.

Both electron-rich and electron-poor mono-olefins reacted to give good yields and high chemo- and diastereoselectivity. Many of the compounds in Grubbs' study are useful synthetic intermediates and can be easily functionalized further, displaying the utility and viability of achieving selectivity in CM reactions with conjugated dienes via electronic or steric deactivation of a single olefin.

The previously described study by Grubbs et al. served as a departure point for Curran and Moura-Letts in their analysis of synthesizing (2*Z*,4*E*)-dienyl esters via CM for their synthesis of dictyostatin (discussed earlier). They were intrigued by Grubbs' finding that olefins of a conjugated system can be electronically deactivated towards CM, and they hoped the trend would extend to less stable (*Z*)-1,2-disubstituted alkenes.[22] Furthermore, they hoped that selective CM would take place

without Z-alkene isomerization. After solvent, temperature and stoichiometric variables were surveyed, Curran and Moura-Letts were pleased to find conditions that gave high yields of the dienyl fragment of dictyostatin along with many other (2*Z*,4*E*)-dienyl esters. Representative examples of their study are given in Table 1.3.

Table 1.3. CM Reactions with (2*Z*,4*E*)-Dienyl Esters.[a]

entry	Alkene	Diene	Product	Yield[b] (%)
1				58
2				65
3				61
4				76[c]
5				68
6				63
7				71
8				73

[a]Conditions: 1 equiv of alkene, 1 equiv of diene, 5 mol % of **3**, 0.15 M, CH_2Cl_2, 40°C, 8 h. [b]Isolated yields as a single isomer. [c]*E*/*Z* ratio = 8:1.

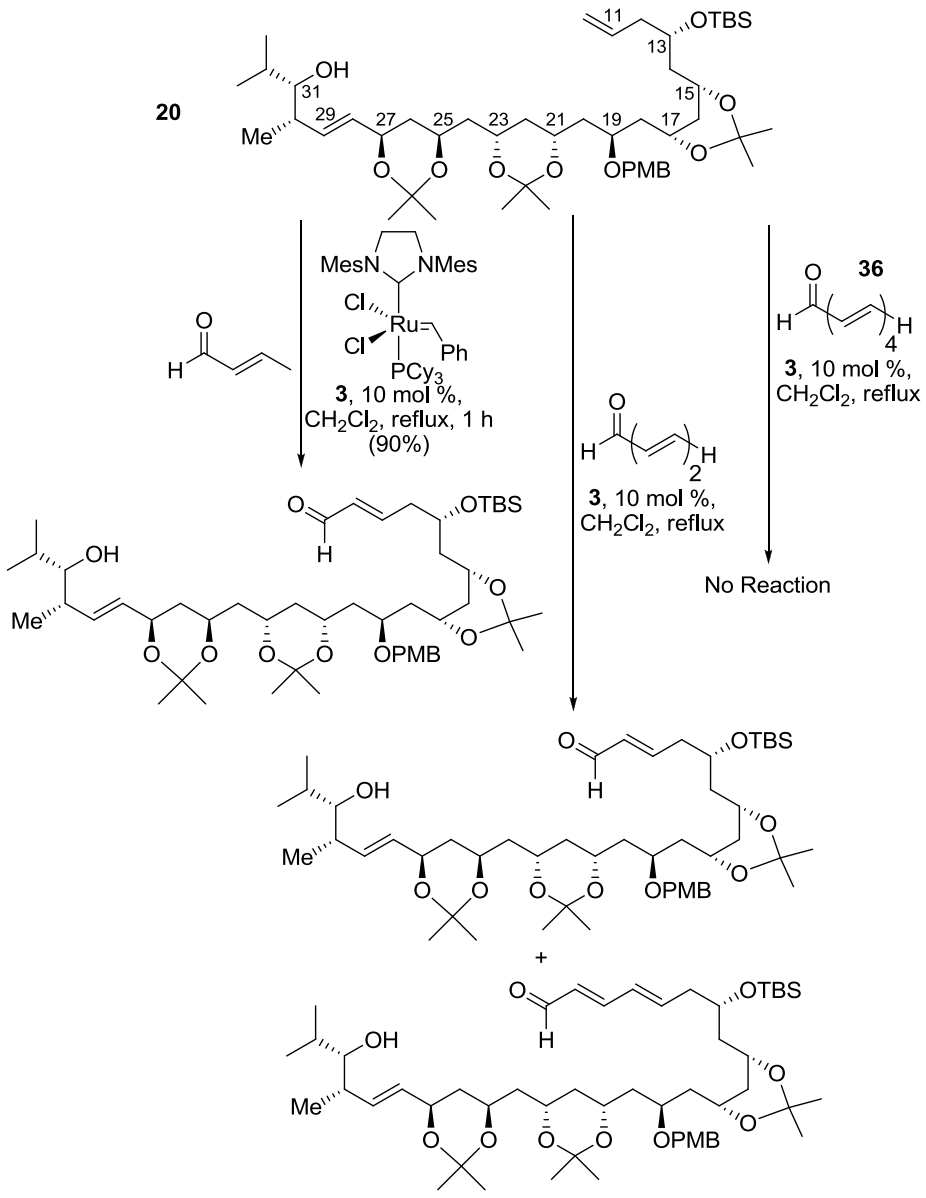
Gratifyingly, all products were exclusively *Z*-isomers at the olefin proximal to the ester, indicating that the olefin was sufficiently deactivated and served as a spectator to CM reactions with catalyst **3** (Grubbs II). Changing the secondary

alcohol protecting group and the use of a free primary alcohol all gave the CM products in comparable yields (Table 1.3, entries 1-3), and metathesis with the complex triene in entry 4 provided a single tetraene isomer in 76% yield. Further proof that the α,β-alkene serves as a spectator olefin in the reaction can be seen in entries 5-8 where the geometry of this olefin in the product does not change. All of the products were single stereoisomers at both the reacting (4*E*) and spectator (2*Z*) sites.

1.5 Cross-Metathesis of Electron-Deficient Polyenes

En route to our group's total syntheses of RK-397 and dermostatin A, the viability of a CM reaction between an electron-deficient polyene and a terminal olefin became a pressing question. Initial effort in answering this question was made by a previous graduate student in the Sammakia group, Dr. Aaron Cullen. Using the completed polyol portion of RK-397 (**20**) as the metathesis partner, he performed a survey of CM reactions with polyenals containing one to four olefins (Scheme 1.15).

Scheme 1.15. Initial Efforts in Completing the Polyene Portion of RK-397.



The preliminary reaction of crotonaldehyde with **20** using catalyst **3** gave a promising result: 90% yield of the desired product after only one hour of reaction time. However, when Dr. Cullen attempted the cross-metathesis with the dienal, he isolated a mixture of distal and proximal metathesis products. As described in Section 1.3, CM between **20** and the trienal proved to be the most efficient route for the total synthesis of RK-397, as it gave the desired product in 72% yield with an *E*/Z

ratio of 4:1 at the newly formed olefin. Dr. Cullen's efforts to complete the polyene portion of the macrolide in an even more efficient fashion extended to CM attempts of **20** with tetraenal **36**, however, this reaction merely returned starting material and did not provide any of the desired product.

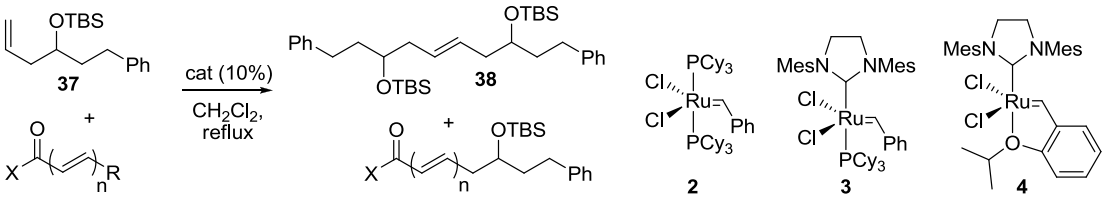
Having determined that the CM reaction involving a trienal was viable in our synthesis of RK-397, the question was then posed as to whether or not CM with electron-deficient polyenes was general. It was also noted that no systematic study of the cross-metathesis of a terminal alkene with polyenes conjugated to an electron-withdrawing group had been reported to our knowledge. Thus, we undertook such a study.

1.5.1 Polyene Study

For our study, we chose as one of the components terminal alkene **37**[29] which falls into the highest reactivity type for all the common Ru metathesis catalysts (Type I, according to Grubbs' nomenclature), and is a representative terminal alkene. We studied the cross-metathesis of **37** with alkenes, dienes, trienes, and tetraenes conjugated to an aldehyde or ester as shown in Scheme 1.16.[15,28,30-38] These compounds are of different reactivity types (we speculated types I - III depending on the choice of catalyst) and as such, we suspected they would require different catalysts and conditions to promote selective cross-metathesis with **37**. The problems we anticipated included the reticence of electron-deficient olefins to participate in metathesis reactions, and in the case of dienes-tetraenes, issues of selectivity with respect to metathesis of the terminal versus internal olefins.[39]

Our results with each aldehyde-derived substrate and catalysts **2 - 4** are shown in Table 1.4. Reactions were run with a 10% catalyst loading in dichloromethane at reflux with **37** as the limiting reagent given that in an application of this method, the terminal alkene would likely be the more valuable component. In addition, preventing homodimerization of **37** was also necessary, resulting in an excess of the electron-deficient alkene. This excess was minimized as much as possible; however, most reactions still necessitated a stoichiometry of 1:2 **37**/polyene substrate. We then studied each substrate pair with each catalyst and noted the following trends. In many cases, we found that the reactions stalled after some time, presumably due to catalyst inactivation or decomposition, and we observed incomplete consumption of **37**. In some reactions, conversion of **37** to the corresponding dimer (**38**) was prominent; thus, while consumption of **37** was high, conversion to the desired product was low. At times, complex mixtures of products were observed, again with consumption of **37**.

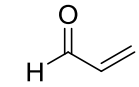
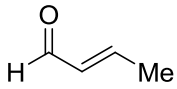
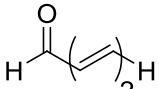
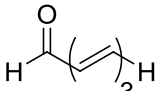
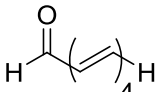
Scheme 1.16. Cross-Metathesis with Electron-Deficient Polyenes.



For the cross-metathesis of acrolein and crotonaldehyde we found that these electron-deficient substrates failed with the less active first-generation Grubbs catalyst (**2**)[40-42]: in the case of acrolein, the reaction stalled at low conversion, and in the case of crotonaldehyde, most of **37** was converted to dimer **38** (36% which consumes 72% of **37**) and provided the desired product in only 16% conversion. This

result reaffirms that α,β-unsaturated carbonyls are spectator olefins (Type IV) to metathesis with catalyst **2** as postulated by Grubbs in his model for CM selectivity.[15] The more active second-generation Grubbs catalyst (**3**),[10,11] or the phosphine-free variant (**4**) described by Hoveyda[12] and by Blechert[13] provided superior results. In regards to crotonaldehyde, catalysts **3** and **4** were essentially equivalent; both provided complete consumption of **37** and cleanly provided the desired product in 91% and 94% yield respectively. Acrolein requires the more active catalyst **4** to proceed to complete conversion, presumably because it is less reactive than crotonaldehyde, and provided the product in a yield of 75%. All of this data is consistent with Grubbs' model for selectivity in CM reactions since the electron-deficient olefin is most certainly of Type II or III for catalysts **3** and **4**, and therefore productive CM with the Type I olefin in **37** was anticipated.

Table 1.4. Cross-Metathesis of **37** with Enal and Polyenal Substrates (Scheme 1.16).

Entry	Substrate (2 equiv)	Cat	Consumption of **37**	Dimer (**38**)	Yield[a]	Comments
1		**2**	7%	3%	ND	
2		**3**	56%	Trace	(54%)	
3	**39**	**4**	92%	Trace	75%	
4[b]		**2**	91%	36%	16%	
5		**3**	>98%	Trace	91%	
6	**40**	**4**	>98%	Trace	94%	
7		**2**	12%	Trace	ND	
8[c]		**3**	46%	ND	ND	1.7:1[d]
9[c]	**41**	**4**	66%	Trace	ND	1.2:1[d]
10		**2**	86%	Trace	72%	4:1 *E*:*Z*[e]
11		**3**	32%	Trace	ND	
12	**42**	**4**	33%	Trace	ND	
13		**2**	37%	Trace	ND	Complex Mixtures by NMR
14		**3**	41%	ND	ND	
15	**43**	**4**	30%	ND	ND	

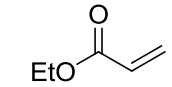
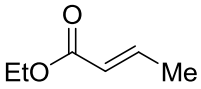
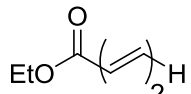
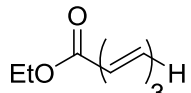
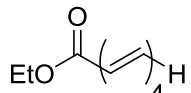
[a]Isolated yield; numbers in parentheses are conversions as determined by NMR. [b]3.0 equiv of 7 were used. [c]Conducted at room temperature. [d]Ratio of terminal to internal metathesis. [e]Isomeric at the alkene distal to the aldehyde.

We were unable to obtain satisfactory results with dienal **41**[23] due to either reactivity or selectivity problems. In the case of the least reactive first-generation Grubbs catalyst (**2**), the reaction cleanly proceeded to the desired product, but consistently stalled at about 12% conversion. The more reactive catalysts (**3** and **4**) provided higher conversion, but suffered from poor selectivity for the terminal alkene (1.7:1 ratio of terminal to internal metathesis with catalyst **3**, and 1.2:1 ratio of terminal to internal metathesis with catalyst **4**). We conclude that dienal **41** is too unreactive for catalyst **2** (as seen with acrolein and crotonaldehyde), yet with catalysts **3** and **4** the substrate is too reactive and metathesis takes place at both olefins. These

results are in accord with Grubbs' findings on the reactivity of conjugated dienes with ethyl sorbate previously discussed.[28]

In contrast, we were pleased to find that trienal **42**[23] is a competent substrate, but only with the least active of the catalysts. In this substrate, the electron-withdrawing aldehyde is sufficiently removed from the terminal alkene that it is reactive enough for the first-generation Grubbs catalyst while the internal alkenes are not. The product is formed as a 4:1 mixture of *E*- to *Z*- olefin isomers at the distal (ε,ζ) alkene. A variety of conditions were studied, however, we were unable to improve this ratio. Surprisingly, reactions with the more reactive catalysts stalled after about 33% consumption of **37** and were not clean, suggesting catalyst decomposition during the reaction. Similarly, reactions with tetraenal substrate **43** also provided complex mixtures by NMR with all catalysts and under all conditions studied, and stalled after low consumption of **37** (30 - 41%).

Table 1.5. Cross-Metathesis of **37** with Enoate and Polyenoate Substrates (Scheme 1.16).

Entry	Substrate (2 equiv)	Cat	Consumption of **37**	Dimer (**38**)	Yield[a]	Comments
1[b]	 **44**	**2**	89%	32%	(26%)	
2[b]		**3**	>98%	Trace	86%	
3[b]		**4**	>98%	2%	92%	
4[b]	 **45**	**2**	86%	36%	(8%)	
5		**3**	>98%	Trace	92%	
6[b]		**4**	>98%	Trace	70%	
7	 **46**	**2**	82%	ND	ND	Several Unidentified Side Products
8		**3**	65%	ND	ND	
9		**4**	98%	ND	ND	2:5[c]
10[d]	 **47**	**2**	96%	2%	84%[e]	5:1 *E*:*Z*[f]
11		**3**	55%	8%	ND	
12		**4**	10%	Trace	ND	
13	 **48**	**2**	67%	2%	(62%)	Complex Mixtures by NMR
14		**3**	17%	Trace	ND	
15		**4**	22%	Trace	ND	

[a]Isolated yield; numbers in parentheses are conversions as determined by NMR. [b]1.3 equiv of substrate were used. [c]Ratio of terminal to internal olefin metathesis. [d]1.5 equiv of substrate were used. [e]Yield is over 2 steps: CM and deprotection. [f]Isomeric at the alkene distal to the ester.

Similar results were obtained with the ester-derived substrates (Table 1.5). In the case of ethyl acrylate or ethyl crotonate, again, the less active first-generation Grubbs catalyst (**2**) provided significant amounts of dimer **38** (32% which consumes 64% of **37**, and 36% which consumes 72% of **37**, respectively). The more reactive catalysts (**3** and **4**) provided the desired product in 70% to 92% yield (Table 1.5, entries 2, 3, 5 and 6).

Dienoate **46**[43] did not provide satisfactory results with any of the catalysts studied. While the consumption of **37** was high in many reactions, several unidentified side products were observed and we were unable to discover conditions

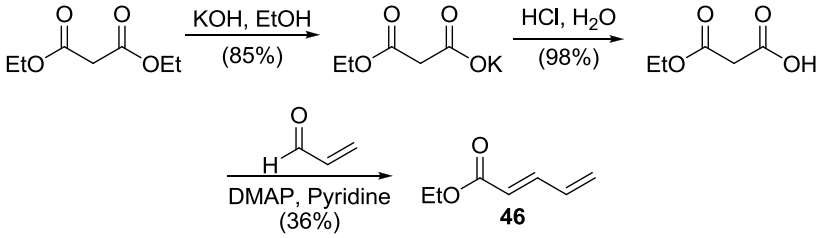
which provided clean reactions. When the most reactive catalyst was used, **4**, the reaction suffered from a lack of selectivity and a 2:5 ratio of terminal to internal metathesis was observed. This result is reminiscent of that obtained with dienal substrate **41**; however, the preference for formation of the internal metathesis product is interesting to note. Assuming metathesis first takes place at the terminal olefin, it is surprising that this initial product is still reactive enough with catalyst **4** to participate in subsequent metathesis events given its bulkiness and electronics.

As in the case of trienal **42**, cross-metathesis with trienoate **47**[23] provided good conversion and high yields with the first-generation Grubbs catalyst (96% consumption of **37**, 84% yield) and a 5:1 ratio of *E*- to *Z*- olefin isomers at the distal (ε,ζ) alkene. The more active catalysts stalled at lower conversion, again presumably due to catalyst inactivation or decomposition.[44] Similar to the trienal, the terminal olefin in **47** differs significantly in reactivity when compared to the internal olefins, therefore promoting selective CM. It should be noted that due to the co-elution of excess starting material and product during purification by flash column chromatography, the isolated yield of the cross-product is over two steps: CM and then deprotection of the silyl ether in the product with HF-acetonitrile. The tetraenoate substrate provided slightly better results than the tetraenal. With the first-generation Grubbs catalyst we observed a 62% conversion to the desired product by NMR; however, we were unable to isolate the product cleanly by flash column chromatography. The more active catalysts stalled at low conversion likely due to catalyst decomposition.

1.5.2 Synthesis of Polyene Substrates

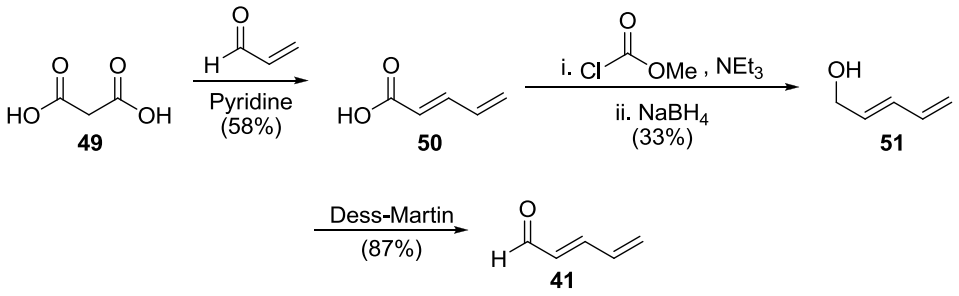
The synthesis of **46** is described in Scheme 1.17 and begins with the formation of a half-acid ester of ethyl malonate which undergoes a Knoevenagel condensation with acrolein to give **46** in a yield of 36%.

Scheme 1.17. Preparation of Substrate **46** (Table 1.4, Entries 4, 5, 6).



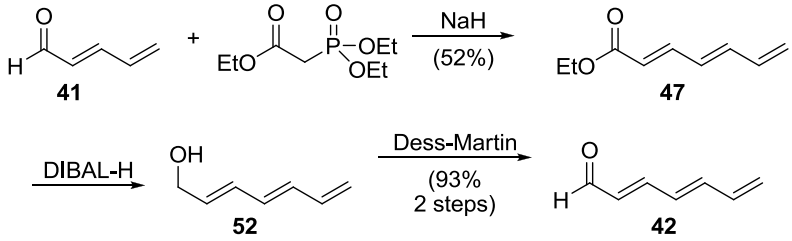
Synthesis of the dienal proved to be a little more difficult. Since the formation of **46** was somewhat low-yielding, a different route to the dienal was explored. Instead of using the three-step process to the dienoate, the one-step formation of the dieneacid (**50**) via a Knoevenagel condensation between **49** and acrolein was utilized. This was followed by a reduction to the dienol (**51**) and subsequent oxidation to the dienal, and it seemed to be a very straightforward route. However, problems were observed in the reduction step and after much experimentation with several different methods, *in-situ* formation of the mixed anyhydride followed by reduction via sodium borohydride proved to be the most reproducible method (albeit low-yielding).[45]

Scheme 1.18. Preparation of Substrate **41** (Table 1.4, Entries 4, 5, 6).



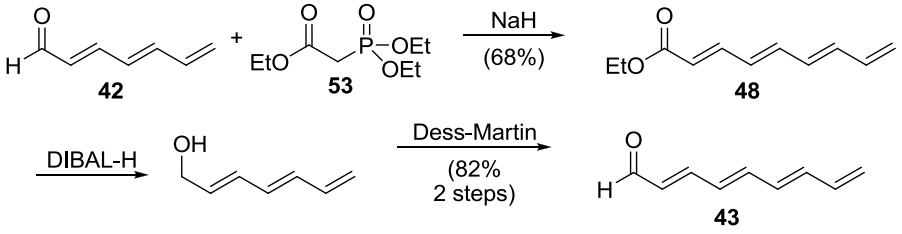
Synthesis of the triene pieces was straightforward and produced modest yields of **42** and **47**. A simple Horner-Wadsworth-Emmons reaction[46] with **41** gave the trienoate, **47**, which was then taken on to trienal **42** via DIBAL-H reduction to the trienol (**52**) followed by oxidation with Dess-Martin periodinane (Scheme 1.19).

Scheme 1.19. Preparation of Substrates **42** and **47** (Tables 1.4 and 1.5, Entries 7, 8, 9).



Finally, as shown in Scheme 1.20, tetraenes were synthesized in a straightforward fashion by the same method used for the synthesis of the triene substrates. Horner-Wadsworth-Emmons reaction of **42** with **53** provided **48**, which was subjected to reduction and oxidation to give **43**.

Scheme 1.20. Preparation of Substrates **43** and **48** (Tables 1.4 and 1.5, Entries 10, 11, 12).



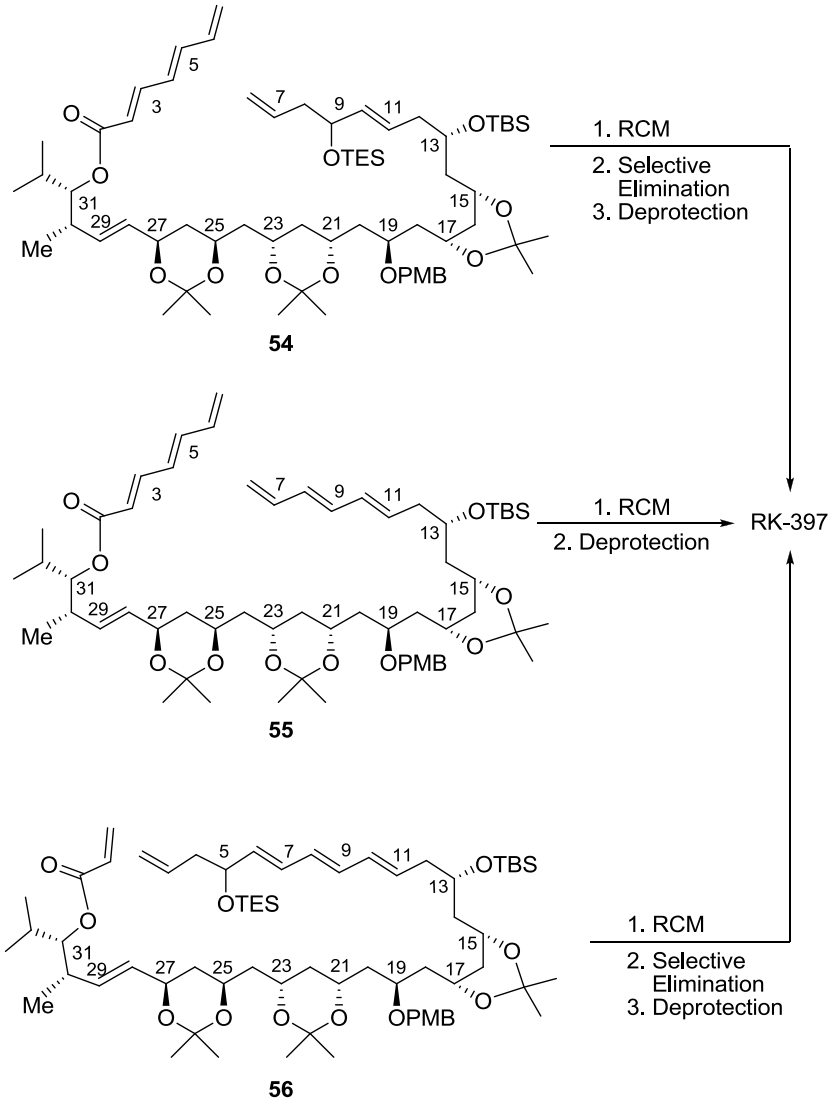
1.6 Conclusion and Future Direction

In conclusion, we have shown that the cross-metathesis of acrolein, ethyl acrylate, crotonaldehyde and ethyl crotonate with terminal alkene **37** proceeds in high yields using the more active ruthenium catalysts (**3** or **4**), while trienal **42** and trienoate **47** require the least active catalyst **2**. We attribute this to the reactivity of the terminal olefin of the triene which is furthest removed from the electron-withdrawing aldehyde or ester, rendering it the only alkene capable of reacting with this catalyst. Diene and tetraene substrates were not good partners in this reaction due to a lack of differentiation of the alkenes. Although one could speculate that polyenes larger than a tetraene would suffer from the same lack of olefin differentiation in cross-metathesis reactions, it would still be interesting to test such a hypothesis in future work. With the development of more reactive or more selective catalysts,[47-49] CM reactions with tetraenes and higher with these new catalysts could be viable.

Other future work in this study includes the completion of the total synthesis of RK-397 via an intramolecular ring closing metathesis reaction instead of a

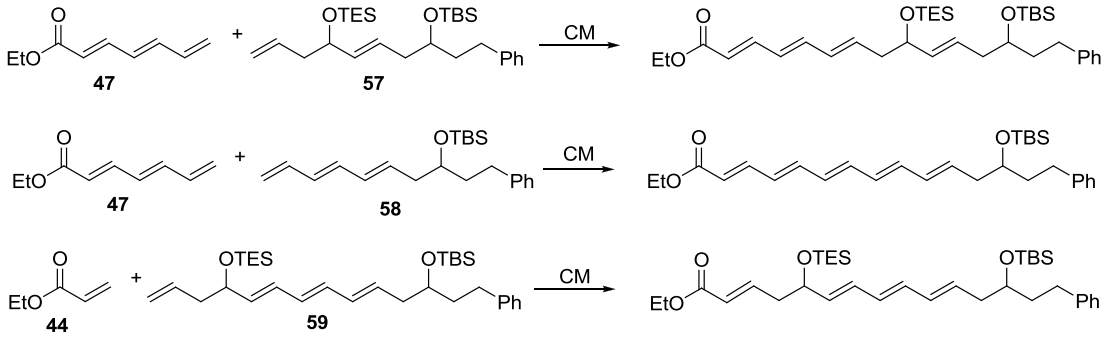
macrolactonization. Having determined that monoenes and trienes are viable cross-metathesis partners, one could imagine this ring closing metathesis reaction in three different scenarios (Scheme 1.21). First, the cyclization could take place between a trieneoate fragment and a monoene bearing a protected homoallylic alcohol, as in substrate **54**. The product would then be subjected to selective elimination to give the desired target. A preliminary study would need to be conducted prior, which would examine the coupling in an intermolecular sense between substrates **47** and **57** (Scheme 1.22).

Scheme 1.21. Ring Closing Metathesis Alternatives in Completing the Total Synthesis of RK-397.



A second option would involve the ring closing metathesis of two conjugated triene moieties as in substrate **55** from Scheme 1.21. Again, an intermolecular model study using similar substrates (**47** and **58**, Scheme 1.22) would confirm the viability of this reaction in a simpler context. This approach would be especially interesting since it would form the macrolide in the most efficient fashion, and it would provide information about the selectivity of a CM reaction involving *two* polyenes.

Scheme 1.22. Preliminary Intermolecular Studies to Assess Viability of Similar Metathesis Reactions in an Intramolecular Setting.



The third and final possibility presented in Scheme 1.21 consists of the intramolecular RCM of two monoene pieces, such as in **56**. The product of which would then be subjected to selective elimination and deprotected to give RK-397. Of course, the study would need to begin with an intermolecular cross-metathesis between similar monoene pieces **44** and **59** to assess whether or not the reaction would be viable (Scheme 1.22). In any and all of the aforementioned studies, it will be interesting to compare the selectivity for the terminal olefin versus internal olefins in the inter- and intramolecular reactions.

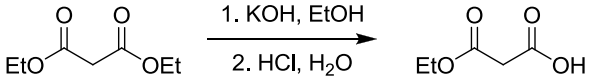
1.7 Experimental Information

General Information:

All reactions were conducted in oven-dried glassware under a dry nitrogen atmosphere. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled over sodium benzophenone ketyl under nitrogen. Dichloromethane (CH_2Cl_2), pyridine, and triethylamine (NEt_3) were distilled over CaH_2 under nitrogen. Acrolein,

crotonaldehyde, ethyl acrylate, and ethyl crotonate were distilled under nitrogen prior to use. Diethyl malonate, 4-dimethylaminopyridine (DMAP), malonic acid, methylchloroformate, sodium borohydride, chloroform, diisobutylaluminum hydride (DIBAL-H, 1.0M in hexanes), sodium hydride (60% in mineral oil), triethyl phosphonoacetate, benzylidenebis(tricyclohexylphosphine)-dichlororuthenium (**2**), (1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro-phenylmethylene) (tricyclohexyl-phosphine) ruthenium (**3**), and (1,3-Bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene) dichloro(*o*-isopropoxyphenyl-ethylene)ruthenium (**4**) were purchased from the Aldrich Chemical Company and used as received. Flash column chromatography was performed using 60 Å silica gel (32-63 μm). ^{1}H NMR spectra were obtained at 500 MHz or 400 MHz and ^{13}C NMR spectra at 125 or 100 MHz in $CDCl_3$ as indicated. Chemical shifts are reported in ppm referenced to $CHCl_3$ (7.24 ppm for ^{1}H) and $CDCl_3$ (77.0 ppm for ^{13}C). IR spectra were recorded as thin films on NaCl plates. Exact mass was obtained using electrospray ionization in positive ion mode (M+H, or M+Na, or M+Li) or in negative ion mode (M+Cl) as indicated.

3-Ethoxy-3-oxopropanoic acid[50]**:**



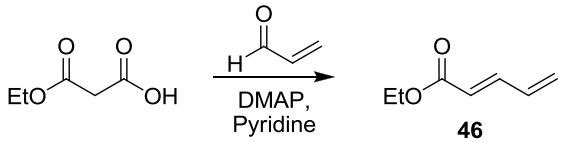
Diethyl malonate (50 g, 312 mmol, 1.0 equiv) was dissolved in absolute ethanol (200 mL) and a solution of potassium hydroxide (17.5 g, 312 mmol, 1.0 equiv) in absolute ethanol (200 mL) was added dropwise over 1 h. The reaction mixture was allowed to stir at room temperature for 2 h, then heated to reflux and allowed to stir for 1 h (during which all solids dissolved), and then left to stand at room temperature overnight. The crude precipitate was recrystallized from the

mother liquors and washed with Et_2O to give the known potassium salt as a colorless crystalline solid (45.4 g, 267 mmol, 85%).

To a cooled (0 °C) solution of the above salt (45.4 g, 267 mmol, 1.0 equiv) in DI H_2O (27 mL) was added concentrated HCl (23.4 mL, 280 mmol, 1.05 equiv) slowly over 30 min. The reaction mixture was allowed to stir at room temperature for 20 min, and was then filtered through cotton, rinsing with Et_2O. The filtrate was then transferred to a separatory funnel and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered through Celite, and concentrated under reduced pressure to give the known half-acid (27.2 g, 206 mmol, 77%) as a colorless oil.

IR (cm^{-1}): 3486, 1743, 1735. NMR (500 MHz, $CDCl_3$): δ 1.29 (3H, t, *J* = 7 Hz), 3.43 (2H, s), 4.23 (2H, q, *J* = 7Hz), 8.21 (1H, br s).

(*E*)-ethyl penta-2,4-dienoate (46)[43]:



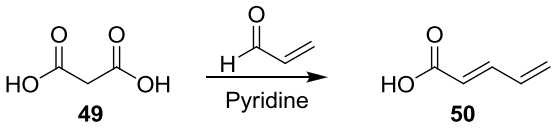
46

To a cooled (0°) solution of the half-acid (27.2 g, 206 mmol, 1.5 equiv) in pyridine (45.7 mL) was added acrolein (9.15 mL, 137 mmol, 1.0 equiv) dropwise via syringe. 4-Dimethylaminopyridine was then quickly added to the reaction flask upon brief exposure to air. The reaction flask was heated to 90 °C and allowed to stir overnight. The deep orange solution was then allowed to cool to room temperature and poured into a separatory funnel already containing DI H_2O (300 mL). Et_2O (40 mL) was added to the separatory funnel, the layers were separated, and then the aqueous layer was extracted with Et_2O (3×40 mL). The combined organic layers

were then washed with 1 M HCl (3×20 mL), dried over $MgSO_4$, filtered through Celite, and concentrated under reduced pressure to give an orange solution. The crude reaction mixture was then purified by distillation under low vacuum (65-67 °C) to give the known dienoate **46** as a colorless oil (6.17 g, 48.9 mmol, 36%).

IR: 1700, 1640, 1560, 1440, 1365, 1175, 1030, 980, 915 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.24 (dd, *J* = 15.5, 11.0, 1H), 6.50 – 6.37 (m, 1H), 5.95 – 5.84 (m, 1H), 5.62 – 5.43 (m, 2H), 4.18 (q, *J* = 7.1, 2H), 1.28 (t, *J* = 7.1, 3H). ^{13}C NMR (25 MHz, $CDCl_3$): δ 166.8, 144.6, 134.8, 125.4, 122.3, 60.3, 14.3.

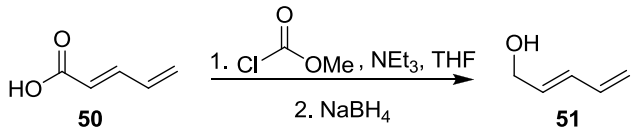
(*E*)-penta-2,4-dienoic acid (50)[51]:



To a heated (40 °C) solution of malonic acid (2.0 g, 19.2 mmol, 1.0 equiv) in pyridine (3 mL) was added acrolein (1.7 mL, 25.0 mmol, 1.3 equiv) dropwise via syringe. The reaction was allowed to stir until the evolution of CO_2 had ceased and then was allowed to cool to room temperature. The reaction mixture was then poured into a flask containing ice (12 g) and was acidified by the dropwise addition of concentrated H_2SO_4 (1.4 mL, 26.9 mmol, 1.4 equiv). The reaction mixture was then transferred to a separatory funnel and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were then dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. The crude yellow-white solid was then recrystallized from hexanes to give the known acid **50** (1.09 g, 11.1 mmol, 58%) as a white crystalline solid.

IR: 3000, 1685, 1640, 1600, 1400, 1220 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 11.83 (br s, 1H), 7.34 (dd, *J* = 15.4, 11.1, 1H), 6.54 – 6.39 (m, 1H), 5.96 – 5.84 (m, 1H), 5.69 – 5.50 (m, 2H).

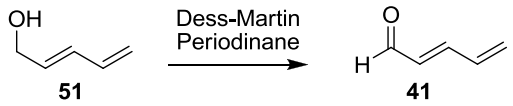
(*E*)-penta-2,4-dien-1-ol (51)[52]:



To a cooled (0 °C) solution of **50** (20 g, 204 mmol, 1.0 equiv) in THF (1 L) was added triethylamine (31.2 mL, 221 mmol, 1.1 equiv) and methylchloroformate (17.3 mL, 221 mmol, 1.1 equiv) both dropwise via syringe. The reaction mixture was allowed to warm to room temperature and stir for 15 mins, and was then cooled to -78 °C. Sodium borohydride (38.6 g, 1020 mmol, 5.0 equiv) was then added to the reaction upon brief exposure to air. The reaction mixture was allowed to warm to room temperature and stir for 7.5 h. The reaction was then quenched by the addition of DI H_2O (100 mL). The volatiles were removed under reduced pressure, and then the crude reaction mixture was acidified by the addition of 1 M HCl. The crude reaction mixture was then transferred to a separatory funnel and the aqueous layer was extracted with CH_2Cl_2 (3×300 mL). The combined organics were then dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (4:1 pentane/Et_2O) provided the known dienol **51** (5.67 g, 67.0 mmol, 33%).

^1H NMR (500 MHz, $CDCl_3$): δ 6.43 – 6.16 (m, 2H), 5.84 (dt, *J* = 15.5, 5.8, 1H), 5.30 – 5.00 (m, 2H), 4.18 (d, *J* = 5.9, 2H), 1.44 (br s, 1H).

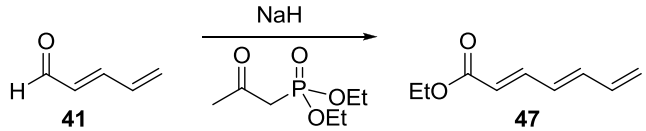
(*E*)-penta-2,4-dienal (41)[23]:



To a cooled (0 °C) solution of **51** (5.12 g, 60.9 mmol, 1.0 equiv) in CH_2Cl_2 (300 mL) was added Dess-Martin Periodinane[53] (32.3 g, 76.1 mmol, 1.25 equiv) upon brief exposure to air. The reaction was allowed to warm to room temperature and stir overnight. Then the reaction mixture was filtered through Celite, rinsing with CH_2Cl_2, and then quenched by the addition of 1:1 $NaHCO_3$:$Na_2S_2O_3$ (300 mL) and allowed to stir for 2 h. The crude mixture was then transferred to a separatory funnel and the organic layer was washed with $NaHCO_3$ (3×100 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (1×100 mL). The combined organics were then dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (CH_2Cl_2) provided the known dienal **41** (4.27 g, 52.0 mmol, 85%).

^{1}H NMR (500 MHz, CDCl3): δ 9.58 (d, *J* = 7.9 Hz, 1H), 7.08 (dd, *J* = 15.4, 10.9 Hz, 1H), 6.58 (dddd, *J* = 16.9, 11.4, 10, 0.7 Hz, 1H), 6.16 (ddd, *J* = 15.4, 7.9, 0.5 Hz, 1H), 5.71-5.75 (m, 1H), 5.60-5.63 (m, 1H). ^{13}C NMR (100 MHz): δ 193.8, 151.9, 134.8, 132.4, 127.6.

(2*E*,4*E*)-Ethyl hepta-2,4,6-trienoate (47)[23]:

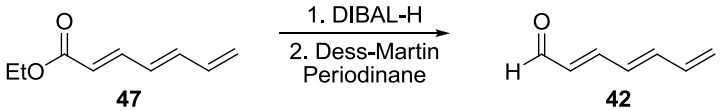


To a cooled (0 °C) suspension of sodium hydride (1.5 g, 60% in mineral oil, 37.5 mmol, 1.4 equiv) in THF (134 mL) was added triethyl phosphonoacetate (8.1

mL, 40.0 mmol, 1.5 equiv) slowly via syringe. Rapid hydrogen gas evolution occurred as the sodium hydride was consumed. After stirring at 0 °C for 30 min, a solution of **41** (2.20 g, 26.8 mmol, 1.0 equiv) in THF (10 mL) was added via cannula and the resulting red solution was set to reflux. The reaction was allowed to stir for 16 h, and was then quenched with saturated $NaHCO_3$ (10 mL). The crude reaction mixture was transferred to a separatory funnel and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were extracted with brine, dried over $MgSO_4$, filtered through Celite, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (20:1 hexanes/ethyl acetate) provided the known trienoate **47** as a colorless oil (2.12 g, 14.0 mmol, 52%).

IR (cm^{-1}): 2924, 2360, 2342, 1718, 1266, 1182, 1031. ^1H NMR (500MHz, $CDCl_3$): δ 7.28 (dd, *J* = 15.3, 11.2 Hz, 1H), 6.53 (dd, *J* = 15, 10.8 Hz, 1H), 6.40 (ddd, *J* = 16.7, 10.4, 10.4 Hz, 1H), 6.30 (dd, *J* = 15, 11.2 Hz, 1H), 5.88 (d, *J* = 15.3 Hz, 1H), 5.40 (d, *J* = 16.7 Hz, 1H), 5.29 (d, *J* = 10 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 144.1, 140.8, 136.2, 130.4, 121.6, 121.6, 60.3, 14.3. HRMS *m*/*z* calcd for C9H12O2 + H^+, 153.0910; found: 153.0906.

(2*E*,4*E*)-Hepta-2,4,6-trienal (42)[23]:



47 **42**

To a cooled (-78 °C) solution of **47** (2.10 g, 14.0 mmol, 1.0 equiv) in CH_2Cl_2 (35 mL) was added DIBAL-H (29.0 mL, 1M in hexanes, 90.0 mmol, 2.1 equiv) slowly via cannula. The ice bath was removed and the reaction was allowed to stir

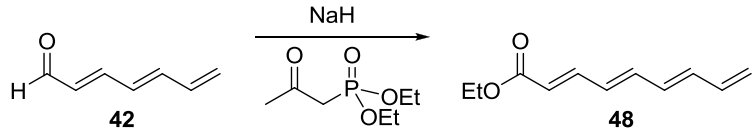
for 4 h at room temperature. The reaction was then diluted with Et_2O (35 mL), and quenched by the sequential addition of DI H_2O (1.5 mL), 1M NaOH (3 mL), and additional DI H_2O (1.5 mL) resulting in the formation of a white precipitate. This suspension was allowed to stir for 30 min then $MgSO_4$ was directly added and the mixture was stirred for an additional 5 min. The solution was filtered through Celite and concentrated under reduced pressure to cleanly provide the desired trienol (1.40 g, 13.0 mmol, 92%) as a white solid. A portion of this material was used directly in the next reaction without further purification.

To a cooled (0 °C) solution of the above trienol (400 mg, 3.60 mmol, 1.0 equiv) in CH_2Cl_2 (18 mL) was added Dess-Martin Periodinane[53] (1.60 g, 3.80 mmol, 1.05 equiv) upon brief exposure to air. The reaction was allowed to warm to room temperature and stir overnight. Then the reaction mixture was filtered through Celite, rinsing with CH_2Cl_2, and then quenched by the addition of 1:1 $NaHCO_3$:$Na_2S_2O_3$ (20 mL) and allowed to stir for 2 h. The crude mixture was then transferred to a separatory funnel and the organic layer was washed with saturated $NaHCO_3$ (3×10 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (1×10 mL). The combined organics were then dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (CH_2Cl_2) provided a 10:1 isomeric mixture of the known trienal **42** (366 mg, 3.40 mmol, 93%) as a translucent yellow oil.

IR (cm^{-1}): 3021, 2817, 2730, 1681, 1615, 1168, 1114, 1017, 979, 918, 887. ^1H NMR (500 MHz, $CDCl_3$): δ 9.56 (d, *J* = 8.0 Hz, 1H), 7.11 (dd, *J* = 15.3, 11.1 Hz, 1H), 6.65 (dd, J = 15.0, 10.1 Hz, 1H), 6.40-6.50 (m, 2H), 6.16 (dd, *J*=15.2, 7.9 Hz,

1H), 5.48 (d, *J* = 17.3 Hz, 1H), 5.40 (d, *J* = 10.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.5, 151.5, 142.7, 135.9, 131.8, 130.4, 123.3.

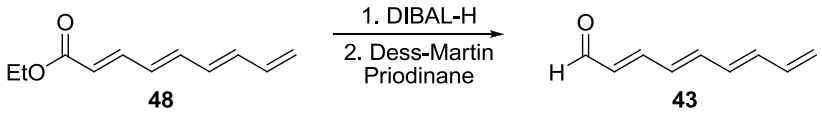
(2*E*,4*E*,6*E*)-Ethyl nona-2,4,6,8-tetraenoate (48):



To a cooled (0 ^{o}C) suspension of sodium hydride (776 mg, 60% in mineral oil, 19.4 mmol, 1.2 equiv) in THF (75 mL) was added triethyl phosphonoacetate (3.85 mL, 19.4 mmol, 1.2 equiv) slowly via syringe. Rapid hydrogen gas evolution occurred as the sodium hydride was consumed. After stirring at 0 ^{o}C for 30 min, a solution of **42** (1.75 g, 16.2 mmol, 1.0 equiv) in THF (6 mL) was added via cannula and the resulting red solution was heated to reflux. After 16 h, the reaction was quenched by the addition of saturated $NaHCO_3$ (10 mL) and the mixture was transferred to a separatory funnel. The aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were washed with brine (1×10 mL), dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (20:1 hexanes/EtOAc) provided the tetraenoate **48** as a white, flaky solid (1.84 g, 10.3 mmol, 64%).

IR (cm^{-1}): 3016, 2991, 1703, 1263, 1156, 1013. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (dd, *J* = 26.5, 11.5 Hz, 1H), 6.55 (dd, *J* = 14.5, 10.5 Hz, 1H), 6.34-6.26 (m, 4H), 5.86 (d, *J* = 15.5 Hz, 1H), 5.32 (d, *J* = 15.0 Hz, 1H), 5.21 (d, *J* = 9.5 Hz, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 1.28 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 144.5, 140.5, 137.6, 136.8, 132.5, 130.7, 121.2, 120.1, 60.6, 14.6. HRMS *m/z* calcd for $C_{11}H_{14}O_2 + Li^+$: 185.1148; found: 185.1159.

(2*E*,4*E*,6*E*)-Nona-2,4,6,8-tetraenal (43):



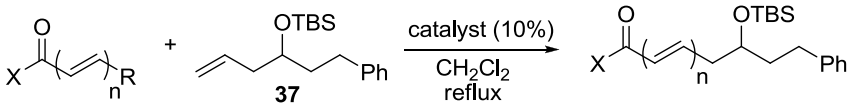
To a cooled (-78 ^{o}C) solution of **48** (500 mg, 2.81 mmol, 1.0 equiv) in CH_2Cl_2 (7 mL) was slowly added DIBAL-H (5.9 mL, 1M in hexanes, 5.9 mmol, 2.1 equiv) via cannula. The ice bath was removed and the reaction was allowed to stir for 4 h at room temperature. The reaction was diluted with Et_2O (7 mL), and quenched by the sequential addition of DI H_2O (0.5 mL), 1M NaOH (1 mL), and additional DI H_2O (0.5 mL) resulting in the formation of a white precipitate. This suspension was stirred for 30 min then $MgSO_4$ was added and the mixture was stirred for an additional 5 min. The solution was filtered through Celite and concentrated under reduced pressure to provide the desired tetraenol (355 mg, 2.61 mmol, 93%) as a white solid. A portion of this material was used directly in the next reaction without further purification.

To a cooled (0 ^{o}C) solution of the tetraenol (28 mg, 0.21 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added Dess-Martin Periodinane[53] (96 mg, 0.23 mmol, 1.1 equiv) in one portion. The suspension was slowly warmed to room temperature and allowed to stir overnight. The mixture was then filtered through a plug of silica over a pad of Celite, rinsing with CH_2Cl_2 (5 mL), and then quenched by the addition of 1:1 $NaHCO_3$/$Na_2S_2O_3$ (10 mL) and allowed to stir for 2 h. The crude mixture was then transferred to a separatory funnel and the organic layer was washed with $NaHCO_3$ (3×3 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (1×3 mL). The combined organics were then dried over $MgSO_4$, filtered through Celite and

concentrated under reduced pressure. Purification by flash column chromatography on silica gel (CH_2Cl_2) provided (CH_2Cl_2) provided tetraenal **43** as a yellow oil (22.5 mg, 0.17 mmol, 82%).

IR (cm^{-1}): 1676, 1591, 1140, 1021. ^1H NMR (500 MHz, $CDCl_3$): δ 9.55 (d, *J* = 8.0 Hz, 1H), 7.12 (dd, *J* = 15.5, 11.0 Hz, 1H), 6.68 (dd, *J* = 14.5, 11.0 Hz, 1H), 6.50-6.30 (m, 4H), 6.14 (dd, *J* = 15.0, 8.0 Hz, 1H), 5.37 (d, *J* = 16.5 Hz, 1H), 5.26 (d, *J* = 10.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8, 151.9, 142.5, 139.2, 136.7, 132.1, 131.5, 130.6, 121.2. HRMS *m/z* calcd for $C_9H_{10}O + Li^+$: 141.0886; found: 141.0879.

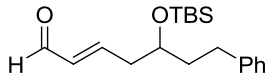
General Metathesis Procedure:



X = H, OEt; n = 1-4; R = H, Me

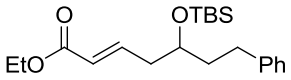
Reactions were carried out in a coldfinger apparatus in which there was no ground glass joint in between the condenser and reaction flask. This was done in order to prevent evaporation of the solvent while carrying out the reaction under nitrogen at reflux overnight. To a solution of alkene **37**[29] (50 mg, 0.17 mmol, 1.0 equiv) and metathesis partner (1-3 equiv) in CH_2Cl_2 (1.72 mL) was quickly added the ruthenium metathesis catalyst (0.1 equiv) upon brief exposure to atmosphere. The reaction was heated and allowed to stir at reflux overnight. The suspension was then cooled to room temperature, filtered through a silica plug over a pad of Celite, washing with CH_2Cl_2, and concentrated under reduced pressure. Purification via flash column chromatography on silica gel (40:1 hexanes/EtOAc) provided the product.

(*E*)-5-(*tert*-Butyldimethylsilyloxy)-7-phenylhept-2-enal (Table 1.4, Entries 3-6):



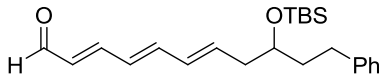
Product was a colorless oil (51.2 mg, 0.16 mmol, 94%). IR (cm^{-1}): 3027, 2929, 2857, 1697, 1471, 1255, 1090, 776. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.47 (d, *J* = 8.0 Hz, 1H), 7.25-7.21 (m, 2H), 7.16-7.11 (m, 3H), 6.84 (dt, *J* = 15.0, 7.5 Hz, 1H), 6.10 (dd, *J* = 15.0, 7.5 Hz, 1H), 3.87 (quintet, *J* = 6.0 Hz, 1H), 2.68-2.62 (m, 1H), 2.60-2.44 (m, 3H), 1.80-1.69 (m, 2H), 0.86 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H) . ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.1, 155.2, 142.1, 135.2, 128.7, 128.5, 126.2, 70.8, 40.7, 39.3, 32.0, 22.3, 18.3, -4.16, -4.24. HRMS *m/z* calcd for $C_{19}H_{30}O_2Si + Na^+$: 341.1907; found: 341.1893.

(*E*)-Ethyl 5-(*tert*-butyldimethylsilyloxy)-7-phenylhept-2-enoate (Table 1.5, Entries 2, 3, 5, 6):



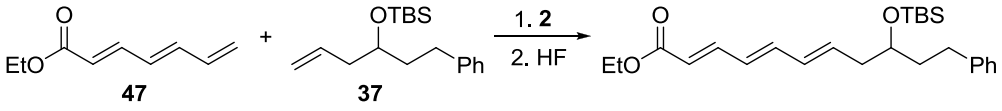
Product was a colorless oil (43.7 mg, 0.12 mmol, 70%). IR (cm^{-1}): 3027, 2930, 2857, 1721, 1257, 1092, 836. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28-7.24 (m, 2H), 7.17-7.15 (m, 3H), 6.95 (dt, *J* = 15.5, 7.5 Hz, 1H), 5.82 (d, *J* = 15.5 Hz, 1H), 4.17 (q, *J* = 7.5 Hz), 3.83 (quintet, *J* = 6.0 Hz, 1H), 2.71-2.65 (m, 1H), 2.61-2.55 (m, 1H), 2.43-2.34 (m, 2H), 1.77-1.73 (m, 2H), 1.27 (t, *J* = 7.5Hz, 3H), 0.89 (s, 9H), 0.5 (s, 3H), 0.4 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 145.9, 142.4, 128.65, 128.56, 126.1, 123.7, 71.1, 60.4, 40.4, 39.3, 32.0, 26.1, 18.3, 14.5, -4.2, -4.3. HRMS *m/z* calcd for $C_{21}H_{34}O_3Si + H^+$: 363.2350; found: 363.2350.

(2*E*,4*E*,6*E*)-9-(*tert*-Butyldimethylsilyloxy)-11-phenylundeca-2,4,6-trienal (Table 1.4, Entry 10):



Product was a colorless oil (46 mg, 0.12 mmol, 70%). IR (cm^{-1}): 3026, 2929, 2856, 1682, 1614, 1255, 1112, 836. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.54 (d, *J* = 8.0 Hz, 1H), 7.28-7.24 (m, 2H), 7.18-7.15 (m, 3H), 7.10 (dd, *J* = 15.0, 11.0 Hz, 1H), 6.63 (dd, *J* = 15.0, 10.5 Hz, 1H), 6.34 (dd, *J* = 15.0, 11.0 Hz, 1H), 6.24-6.10 (m, 2H), 6.02 (dd, *J* = 22.5, 7.5 Hz, 1H), 3.80 (quintet, *J* = 6.0 Hz, 1H), 2.73-2.65 (m, 1H), 2.62-2.54 (m, 1H), 2.41-2.31 (m, 2H), 1.76-1.72 (m, 2H), 0.90 (s, 9H), 0.50 (s, 3H), 0.3 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.9, 152.6, 143.1, 142.5, 138.6, 132.2, 131.1, 128.6, 128.5, 126.0, 71.6, 41.2, 39.3, 32.1, 18.4, -4.1, -4.3. HRMS *m/z* calcd for $C_{23}H_{34}O_2Si + Na^+$: 393.2220; found: 393.2202.

(2*E*,4*E*,6*E*)-Ethyl 9-hydroxy-11-phenylundeca-2,4,6-trienoate (Table 1.5, Entry 10):



To a solution of alkene **37**[29] (100 mg, 0.34 mmol, 1.0 equiv) and trienoate **47** (79 mg, 0.52 mmol, 1.5 equiv) in CH_2Cl_2 (3.44 mL) in a coldfinger was quickly added the ruthenium catalyst **2** (28 mg, 0.03 mmol, 0.1 equiv) upon brief exposure to atmosphere. The reaction was heated and allowed to stir at reflux overnight. The suspension was then cooled to room temperature, filtered through a silica plug over a pad of Celite, rinsing with CH_2Cl_2 (5 mL), and concentrated under reduced pressure. The crude mixture was then taken up in acetonitrile and transferred to a plastic,

conical vial and then concentrated again under reduced pressure. To a cooled (0 °C) solution of this crude mixture (143 mg, 0.34 mmol, 1.0 equiv) and acetonitrile (3.45 mL) was added hydrofluoric acid (48% in water, 0.2 mL, 14 equiv). After stirring at 0 °C for 5 min, the reaction was allowed to come to room temperature and stir overnight. The reaction was then diluted with $CHCl_3$ (5 mL) and transferred to a separatory funnel. The aqueous layer was extracted with $CHCl_3$ (3×3 mL). The combined organic layers were then dried over $MgSO_4$, filtered through Celite, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (5:1 hexanes/EtOAc) yielded the alcohol as a yellow oil (83 mg, 0.28 mmol, 80%).

IR (cm^{-1}): 3454, 3025, 2930, 1708, 1617, 1262, 1136. ^1H NMR (500 MHz, $CDCl_3$): δ 7.29-1.23 (m, 2H), 7.18-7.14 (m, 3H), 6.49 (dd, J =14.5, 11.0 Hz, 1H), 6.23-6.15 (m, 2H), 5.92-5.82 (m, 2H), 4.17 (q, J = 7.5 Hz, 2H), 3.70-3.66 (m, 1H), 2.82-2.75 (m, 1H), 2.69-2.62 (m, 1H), 2.42-2.24 (m, 1H), 1.80-1.73 (m, 2H), 1.91 (br s, 1H), 1.28-1.23 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 144.7, 142.0, 140.6, 135.5, 132.9, 129.0, 128.6, 126.1, 120.9, 70.5, 60.5, 41.4, 38.8, 32.2, 14.5. HRMS *m/z* calcd for $C_{19}H_{24}O_3 + Na^+$: 323.1617; found: 323.1619.

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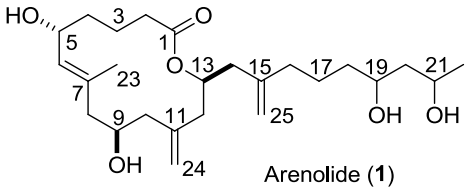
Chapter 2

Studies Toward the Total Synthesis of Arenolide

2.1 Arenolide Isolation, Characterization and Biological Activity

While performing a high throughput cytotoxicity assay in 1998, Faulkner and co-workers screened a number of extracts that had not previously shown activity in earlier bioassays.[1] In doing so they found promising activity in a *Dysidea* sp. extract that had been collected in 1981 in Palau and stored in methanol. From this extract, they isolated three diterpenes of the dolabellane class and a 14-membered macrolide which the group aptly named arenolide (**1**, Figure 2.1) for the sponge's "arena" or sandy feel to the touch.

Figure 2.1. Faulkner's Proposed Structure of Arenolide.



Arenolide (**1**)

Beginning with the high resolution mass measurement, Faulkner et al. were able to deduce arenolide's molecular formula to be $C_{25}H_{42}O_6$. The IR spectrum indicated the presence of a lactone carbonyl, and ^{13}C data required that there be four hydroxyl groups in the compound (C5, C9, C19 and C21). The ^{13}C data also confirmed the presence of the lactone carbonyl along with three other sites of unsaturation: two exocyclic methylene groups (C11 – C24 and C15 – C25), and one endocyclic, trisubstituted olefin (C6 – C7). And since the molecular formula requires

five unsaturations, arenolide had to be monocyclic. ^{1}H NMR and COSY data showed the sequentially coupled signals of arenolide's side chain, and further analysis of the COSY, HMQC and HMBC spectra revealed the substituents around the macrolide's core. Stereochemistry around the macrocycle was determined in a relative sense through interpretation of the NOESY data, and was supported by molecular modeling However, the stereochemistry of the side chain hydroxyl groups at C19 and C21 was not determined and is currently unkonwn.

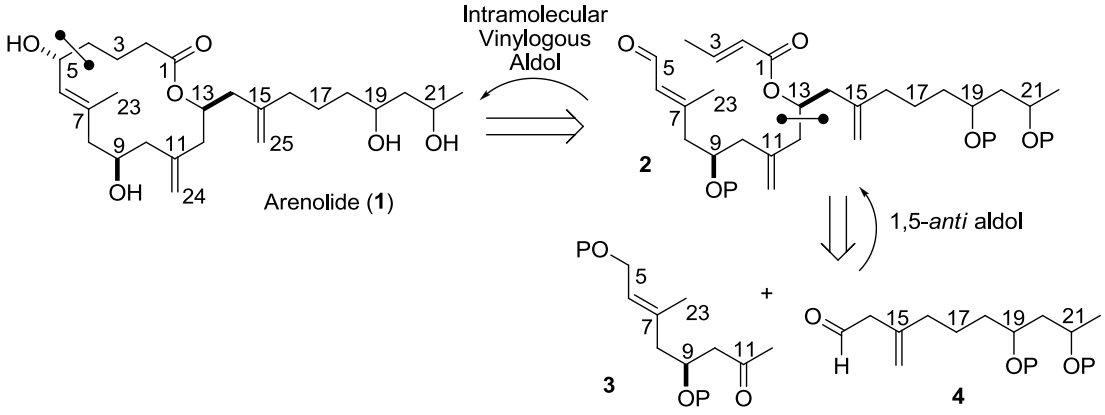
Using a cell proliferation assay, arenolide showed relatively low *in vitro* cytotoxicity against HCT human colon carcinoma cells and A2780 human ovarian carcinoma cells after 72 hours of exposure with IC_{50} values of 21 mM and 9.8 mM respectively. However, Faulkner proposes that much of the isolated macrolide had polymerized before it was assayed, indicating that its bioactivity could potentially be much greater.

Faulkner and co-workers also comment on the fact that neither dolabellanes nor macrolides have previously been reported as being isolated from the *Dysidea* species. After carefully re-analyzing their collection notes from the extracts and finding that no contamination took place across their samples, the group definitively concluded that the source of the isolated compounds was the collected *Dysidea* sp. sample. As an explanation for how the sponge obtained the peculiar compounds, the authors hypothesize that they may have been released by organisms in the vicinity and then absorbed by the sponge.

2.2 Retrosynthetic Analysis of Arenolide

The most obvious first disconnection that could be made for the retrosynthesis of arenolide is the C1 – oxygen bond of the macrolactone. This bond is commonly formed in the forward direction via standard and reliable methods[2] such as the Yamaguchi macrolactonization.[3-5] While these methods are likely to be as reliable in the synthesis of arenolide as they were in their precedented uses, a more novel and original technique of macrocyclization is that developed by our lab using an intramolecular vinylogous aldol reaction.[6] It is this method that Dr. Aaron Cullen, a previous graduate of the Sammakia lab, originally proposed to utilize in his undertaking of the total synthesis of arenolide. In the retrosynthetic direction, this is a disconnection of arenolide's C4 – C5 bond, providing the acyclic precursor, **2**, Figure 2.2.

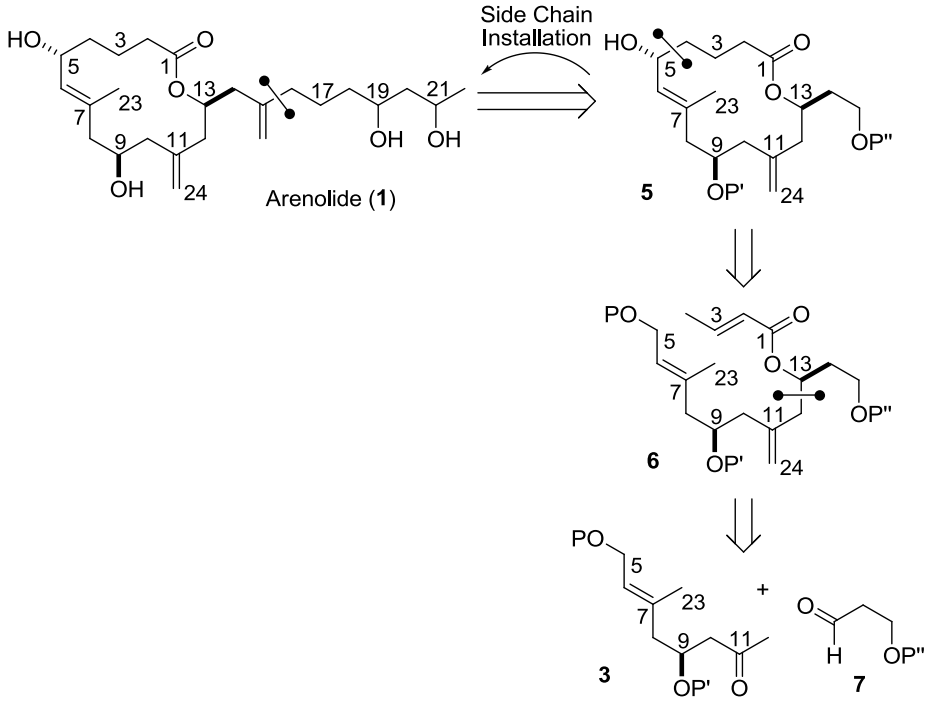
Figure 2.2. Original Retrosynthesis of Arenolide.



Dr. Cullen then envisioned setting the *anti* stereochemical relationship between C9 and C13 via a 1,5-*anti* aldol reaction[7] with two fragments: ketone **3** and aldehyde **4** (Figure 2.2). While this method would most likely be reliable, it

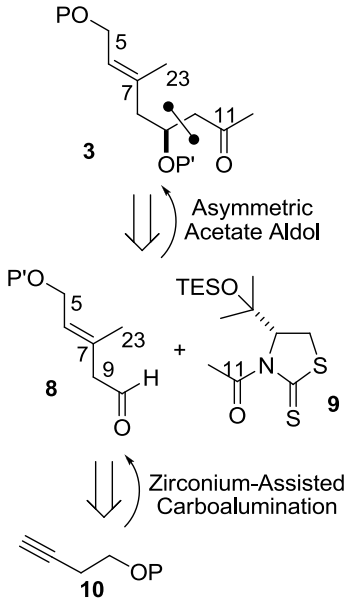
necessitates the use of two very advanced substrates. In efforts to streamline the synthesis and add flexibility, a late-stage installation of the side chain could be exploited, providing a simpler macrocycle, **5**, as our target (Figure 2.3). Retrosynthesis of **5** would still utilize the key intramolecular vinylogous aldol, as well as a 1,5-*anti* aldol to build the acyclic precursor. However, the latter reaction would require the less-advanced aldehyde, **7** (Figure 2.3).

Figure 2.3. Revised Retrosynthesis of Arenolide.



A major benefit of the revised retrosynthesis is the use of ketone **3** which is a common precursor in both retrosyntheses. This substrate could be prepared via the asymmetric acetate aldol reaction developed in our lab, providing compound **8** and the known compound **9** as precursors (Figure 2.4).[8-10] And prior work by Dr. Cullen showed that **8** could be synthesized by using Negishi's zirconium-assisted carboalumination of alkyne **10**.[11,12]

Figure 2.4. Retrosynthesis of Ketone **3**.

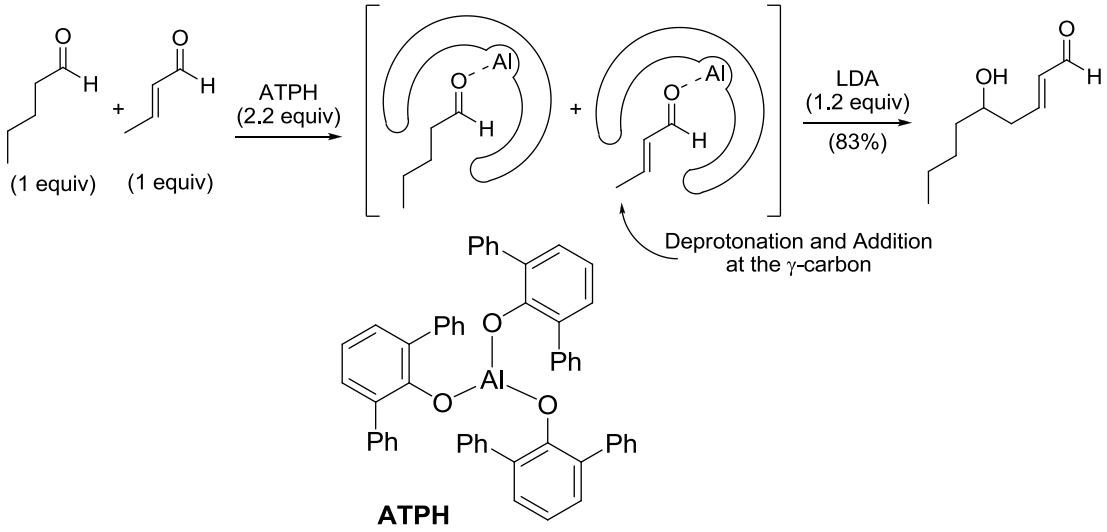


2.3 Intramolecular Vinylogous Aldol

In an effort to expand the scope of the reactivity of Lewis acids and to improve the stereo-, regio- and chemoselectivity of reactions using them, Yamamoto and coworkers pioneered the synthesis and use of "designer Lewis acid catalysts" in the late 1990s.[13,14] Their efforts produced a new class of bulky aluminum-based Lewis acids where sterically hindered phenoxides replaced the classic halogen ligands, resulting in new and unique reactivities. While classical aluminum Lewis acids in solution can exist as dimeric, trimeric, or higher oligomeric structures, Yamamoto's methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD)[15], and aluminum tris(2,6-diphenylphenoxide) (ATPH)[16] Lewis acids are monomeric in organic solvents, leading to high reactivity and selectivity.

One well-developed example of the new and unique reactivity of Yamamoto's designer Lewis acids is that of an intermolecular vinylogous aldol reaction using his bulky Lewis acid, ATPH. In this reaction, ATPH binds to an α,β-unsaturated carbonyl compound and promotes deprotonation at the γ-site, providing a dienolate that can then add to an aldehyde, resulting in the vinylogous aldol product. This is illustrated in the addition of crotonaldehyde to valeraldehyde (Scheme 2.1).[17] This reaction is conducted by first combining the two aldehydes and ATPH, then selectively deprotonating the crotonaldehyde with a bulky base, LDA. Deprotonation is disfavored at the proximal methylene of the valeraldehyde and preferentially occurs at the methyl group of the crotonaldehyde because it is sufficiently removed from the ATPH to be accessible, thereby providing a dienolate. The aldol reaction then occurs at the distal (γ-) carbon of the dienolate due to steric hinderance at the proximal (α-) carbon when the enolate is complexed to ATPH.

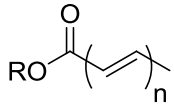
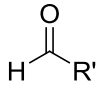
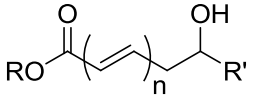
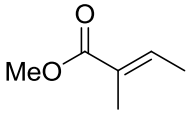
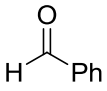
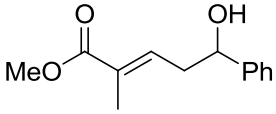
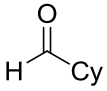
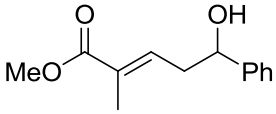
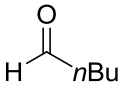
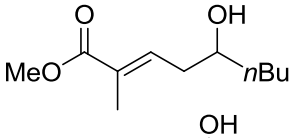
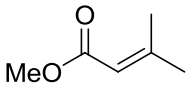
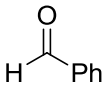
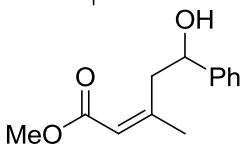
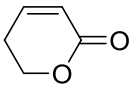
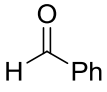
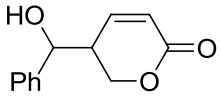
Scheme 2.1. Vinylogous Aldol Reaction of Crotonaldehyde and Valeraldehyde.



Yamamoto and co-workers demonstrated that their newly developed ATPH-mediated intermolecular vinylogous aldol reaction was effective using enolates

derived from conjugated aldehydes,[17] ketones,[17,18] and more significantly, esters.[18-20] Just as with conjugated aldehydes and ketones, reactions with conjugated esters proceed with high selectivity for addition at the sites distal to the ester and give high yields as shown in Table 2.1. Intriguingly, polyenoates add to benzaldehyde at the site most distal to the ester even with extended conjugation in good to high yields (entries 4-7). A piece of data that will prove to be interesting later in this section is that the straight-chain aldehyde, valeraldehyde, is not a practical electrophile using ester-derived enolates. When reacted with methyl crotonate or *E*-methyl 2-methyl crotonate under Yamamoto's conditions, the desired products were only formed in 22% and 42% yields respectively (entries 3 and 10). Yamamoto hypothesizes that valeraldehyde could suffer from competitive deprotonation at the α-carbon under the reaction conditions, and his hypothesis is supported by entries 2 and 9 where branching at the α-carbon to the aldehyde provided improved yields.

Table 2.1. Yamamoto Vinylogous Aldol Reaction with Conjugated Esters.[a]

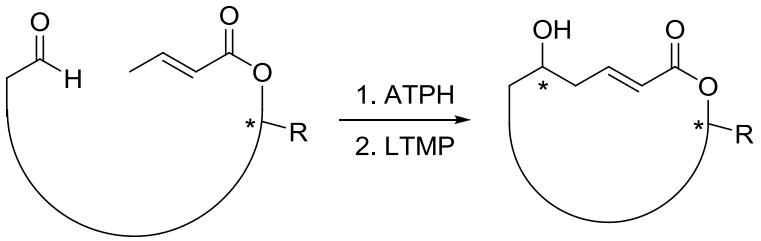
Entry	Conjugated Ester	Aldehyde	Product	Yield
				
1	n=1, R=Me	R'=Ph		97%
2	n=1, R=Me	R'=Cy		90%
3	n=1, R=Me	R'=*n*Bu		22%
4	n=2, R=Me	R'=Ph		97%
5	n=3, R=Et	R'=Ph		88%
6	n=4, R=Et	R'=Ph		80%
7	n=5, R=Et	R'=Ph		40%
8				90%
9				87%
10				42%
11				99% (Exclusively *Z*)
12				70% 2:1 *dr*

[a]Reactions were run with 2 equivs ester, 1 equiv aldehyde, 3.3 equivs ATPH, 2.3 equivs lithium 2,2,6,6-tetramethylpiperidide (LTMP), in toluene/THF (1/1) at -78 ^{o}C for 30 mins.

Of very important note is the fact that both the conjugated ester and aldehyde must be complexed with ATPH in solution before the addition of base in order for the reaction to be successful. Deviation from this protocol results in significantly lower yields and can result in the formation of homo-aldol products.[17,19] This data lends itself to the notion that the ATPH-mediated vinylogous aldol reaction would also be successful in an intramolecular application, and it is from this notion that a project stemmed in our lab. A previous graduate, Dr. Joseph Abramite, set out to

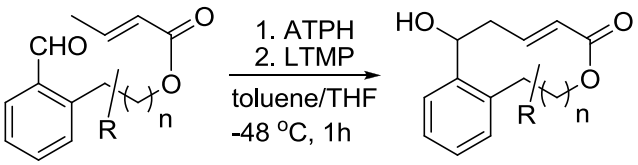
demonstrate that the ATPH-mediated vinylogous aldol reaction could be utilized intramolecularly to cyclize vinylogous ester-aldehydes and form large macrolides in a method that would be practical for the synthesis of natural products (Scheme 2.2). Dr. Abramite also embarked on demonstrating the possibility of remote asymmetric induction with chiral substrates.

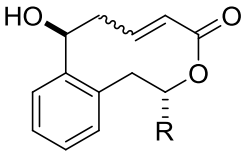
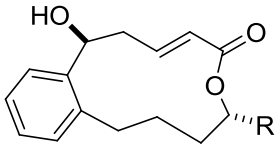
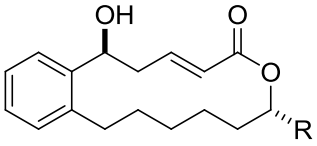
Scheme 2.2. The Intramolecular Vinylogous Aldol Reaction.



Dr. Abramite was successful in forming 10-, 12-, and 14-membered macrolides via the intramolecular vinylogous aldol cyclization, and he found that the process indeed exhibits excellent remote stereocontrol with chiral acyclic substrates (Table 2.2).[6] Ten-membered macrocycles were formed in very good yields (77-82%), with an interesting trend wherein increasing the steric bulk of the ring substituent resulted in greater preference for the *E* alkene in the product (entries 1 and 2). Twelve-membered macrolides were also produced in high yields (81-84%) and the *E*-isomers were exclusively formed. Just as in the case of reactions that formed 10-membered macrolides, the 12-membered ring products are formed with excellent remote asymmetric induction with a >25:1 diastereomeric ratio at the newly formed hydroxyl group. And most importantly for the application of this method to the total synthesis of arenolide, 14-membered macrolides were formed in the highest yields of all (88-90%). Again, excellent remote stereocontrol was observed (~20:1), and only the *E*-alkene isomers were produced.

Table 2.2. ATPH-Mediated Intramolecular Vinylogous Aldol Reaction.



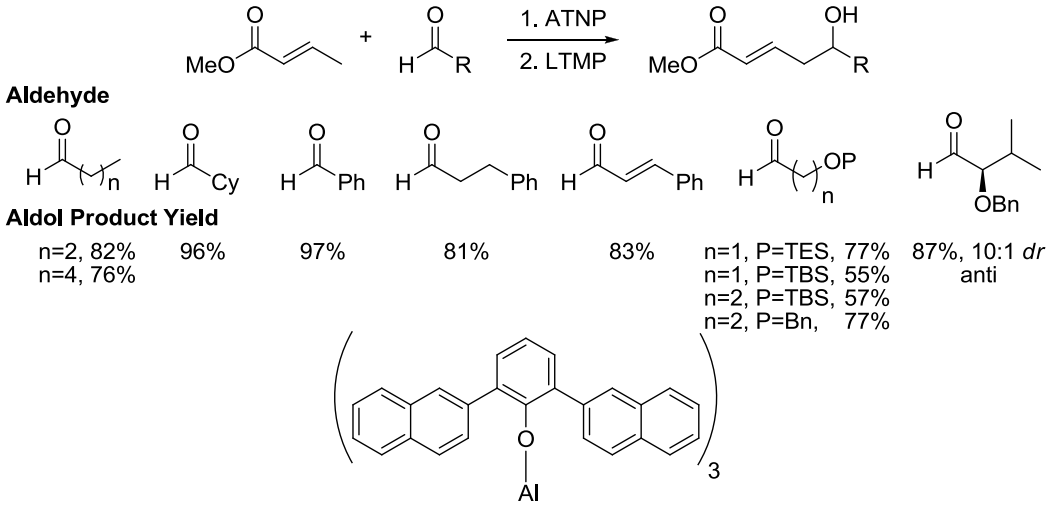
Entry	Product	R	Yield[a]	*Z*/*E*[b]	dr[c]
1		Me	77%	3/1	>25:1[d]
2		*i*-Pr	82%	1/13	>25:1[d]
3		H	81%	*E*	
4		Me	84%	*E*	>25:1[d]
5		*i*-Pr	83%	*E*	>25:1[d]
6		H	90%	*E*	
7		Me	89%	*E*	20:1
8		*i*-Pr	88%	*E*	23:1

[a]Isolated yield after purification. [b]Ratio of alkene stereoisomers produced. [c]Diastereomeric ratios determined by ^{1}H NMR. [d]A single isomer was observed by ^{1}H NMR.

A major drawback of this method is that only non-enolizable aldehydes are effective electrophiles, a finding that is similar to that of Yamamoto in his intermolecular studies wherein enolizable aldehydes required α-branching in order to provide high yields in reactions with ester enolates. Dr. Abramite's studies showed that substrates possessing enolizable aldehydes undergo either competitive enolization or enolate equilibration, and he was unable to find conditions to affect cyclization with ATPH.[21] However, more recent studies by Jeff Gazaille, a current graduate student in the Sammakia lab, have resulted in the development of an even bulkier ATPH-based designer Lewis acid deriving from napthalene (**11**, Scheme 2.3). Initial studies with this new Lewis acid, which has been named ATNP, have shown that the intermolecular vinylogous aldol proceeds in high yields between methyl

crotonate and enolizable aldehydes (Scheme 2.3). As discussed earlier, the ATPH-mediated reaction between methyl crotonate and pentenal provided the desired product in 22% yield (Table 2.1, entry 10)[19], and Yamamoto makes note that this aldehyde is not a viable electrophile. In contrast, Mr. Gazaille has found that the ATNP-mediated reaction provides yields of 82% and 76% with butanal and hexanal respectively. As shown in Scheme 2.3, straight-chain, α-branched, phenyl, and α,β-unsaturated aldehydes all provide high yields of the desired product. Further, the use of aldehydes bearing chirality at the α-carbon provides the product in high yield (87%) and a diastereomeric ratio of 10:1 favoring the *anti* isomer. These results significantly expand the scope of this reaction.

Scheme 2.3. ATNP-Mediated Intermolecular Vinylogous Aldol Reaction.



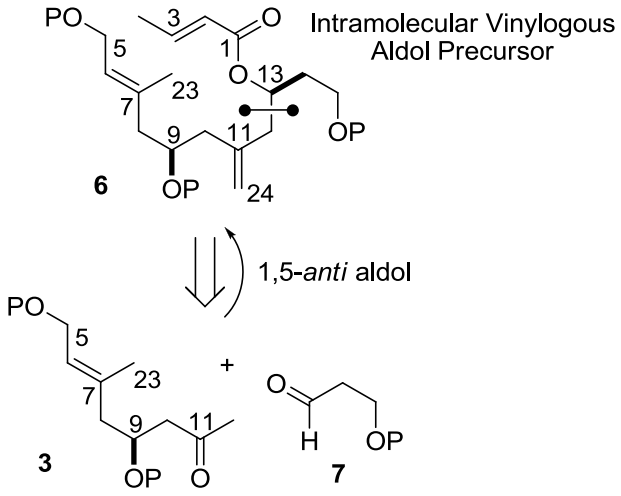
The success of the ATPH-mediated intramolecular vinylogous aldol reaction studies combined with these initial results of the ATNP-mediated intermolecular reaction provides good precedent for the application of this method to the key macrocyclic vinylogous aldol step for our synthesis of arenolide. Our goal is to

demonstrate the utility of the intramolecular vinylogous aldol reaction, whether it be ATPH- or ATNP-mediated, in the complex setting of natural product synthesis. The remainder of this chapter will present our current work towards this goal.

2.4 A 1,5-*Anti* Aldol Approach to Arenolide

As discussed in Section 2.2, we wished to build the main carbon skeleton of arenolide using a 1,5-*anti* aldol reaction between advanced ketone **3** and the simple aldehyde **7**. This reaction is well-precedented and was anticipated to set the stereochemistry at C9 and C13 with high diastereoselectivity. Therefore, the first challenge that had to be met was the synthesis of ketone **3** (Figure 2.5).

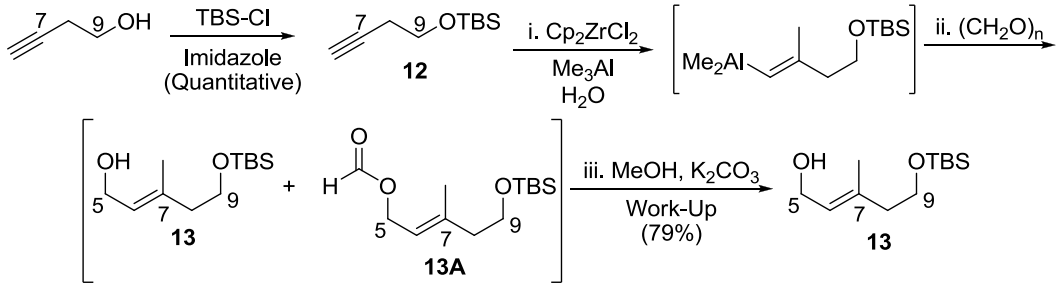
Figure 2.5. Retrosynthesis of Intramolecular Vinylogous Aldol Precursor.



Much of this path was paved previously by Dr. Aaron Cullen and it commenced with the protection of 3-butyn-1-ol to give *tert*-butyldimethylsilyl ether **12** in quantitative yield (Scheme 2.4). The next transformation was the highly efficient zirconium-assisted carboalumination of the terminal alkyne developed by

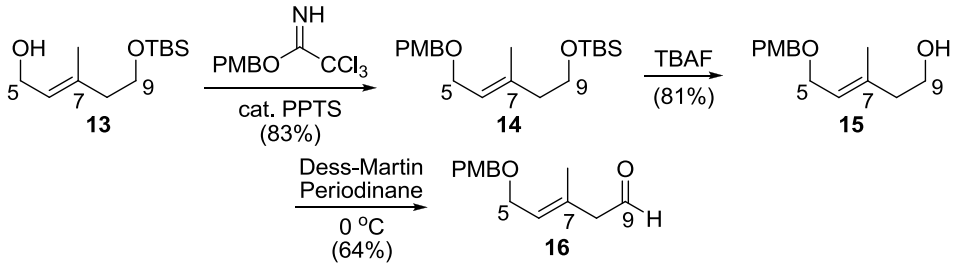
Negishi,[11,22] the carbometallene intermediate of which was then trapped with paraformaldehyde to provide allylic alcohol **13**. No other alkene isomers were formed in this transformation. In his initial investigation of this reaction, Dr. Cullen consistently obtained the desired alcohol along with the undesired formate ester analogue **13A** in an equal mixture. Fortunately, however, cleavage of the formate ester in the work-up via treatment with methanol and potassium carbonate gave the allylic alcohol in 79% yield uncontaminated by the formate.

Scheme 2.4. Synthesis of **13**.



Protection of the primary allylic alcohol with *p*-methoxybenzyl-trichloroacetimidate provided the orthogonally protected diol **14** in 83% yield, at which point the TBS ether was selectively removed with TBAF (81%) and the resulting alcohol was then oxidized with Dess-Martin periodinane (Scheme 2.5). Although Dess-Martin periodinane is a somewhat expensive oxidant to use in large-scale applications, such as at this early point in a total synthesis, other oxidation methods resulted in alkene migration from the C6-C7 position to C8-C9 in conjugation with the produced aldehyde. To some extent, alkene migration even took place at room temperature during the reaction, and as such the reaction was optimally run at 0 °C overnight to provide the desired aldehyde, **16**, in 64% yield.

Scheme 2.5. Preparation of Aldehyde **16**.



2.4.1 Model Study

At this point in the synthesis it was concluded that a model substrate would be utilized to determine the viability of the key intramolecular vinylogous aldol macrocyclization. Therefore, in an effort to obtain a model substrate as quickly as possible, the synthesis was streamlined and continued in a racemic fashion. We had planned to set the stereochemistry at C9 using an asymmetric aldol reaction, but instead opted to build the carbon chain using an aldol reaction between acetone and aldehyde **16** thereby providing ketone **17** in racemic fashion and in 73% yield (Scheme 2.6). This product would then have to undergo a selective 1,5-*anti* aldol reaction via the C12 enolate followed by acylation of the resulting alcohol, conversion of the C11 ketone to the exo-methylene, and finally, the intramolecular vinylogous aldol reaction. We anticipated two potential obstacles to overcome in this route; first the 1,5-*anti* aldol reaction would have to proceed with high levels of stereoselectivity, second the vinylogous aldol reaction could suffer from undesired enolization at C8 to provide an aldehyde enolate. We chose the protecting group at C9 such that we could minimize undesired enolization in the vinyolgous aldol reaction as we felt that this would be the more difficult obstacle. We therefore decided to protect the hydroxyl group at C9 as a *tert*-butyldiphenylsilyl ether in hopes

that its size would prevent enolization proximal to C9 and provide the desired crotonate ester enolate (Figure 2.6). The protecting group was thus installed with imidazole and TBDPSCl and gave **18** in quantitative yield.

Scheme 2.6. Synthesis of 1,5-*Anti* Aldol Ketone **18**.

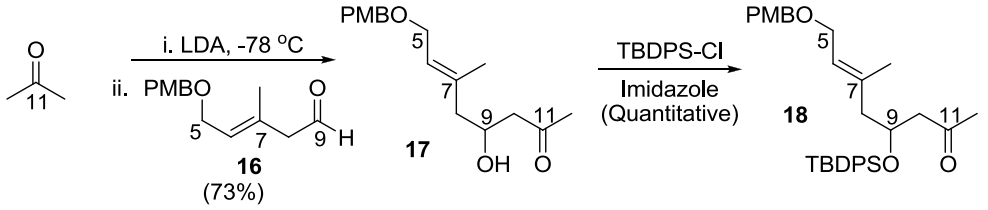
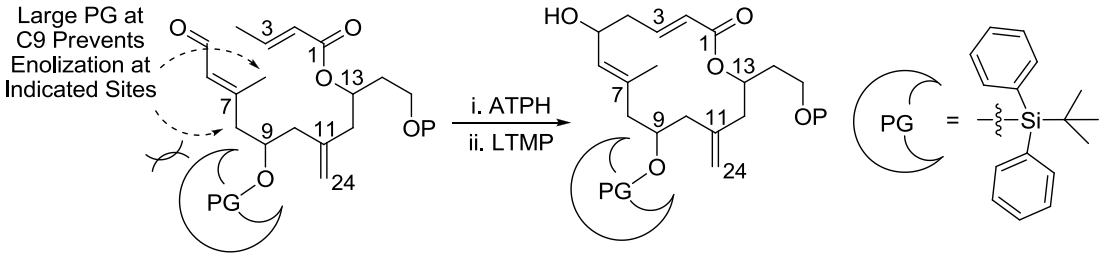


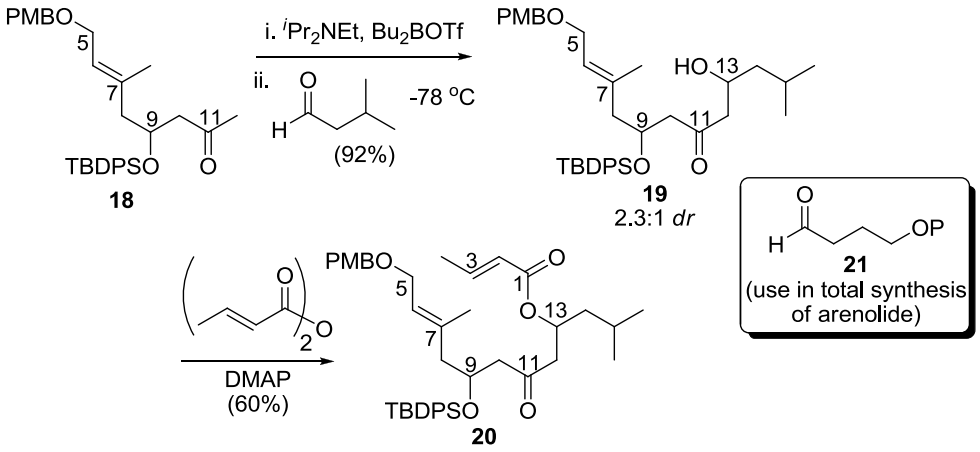
Figure 2.6. Rationale for the Use of a TBDPS Ether at C9.



The 1,5-*anti* aldol reaction was then executed between ketone **18** and isovaleraldehyde by use of dibutylboron triflate and Hunig's base. The reaction proceeded in a very good yield of 92% but with a disappointing diastereomeric ratio of 2.3:1 (Scheme 2.7). We were unable to separate the two diastereomers and deferred stereochemical assignment of the major diastereomer to a later time and both diastereomers were carried on throughout the synthesis. The use of isovaleraldehyde is the only other major difference in the synthesis of our model substrate and the actual compound for the synthesis of arenolide, wherein we planned to use aldehyde **21** in a similar 1,5-*anti* aldol reaction. Silyl groups, such as our TBDPS ether, are known to negatively affect the diastereoselectivity of the 1,5-*anti* aldol reaction;[23-25] however, since our immediate goal was the synthesis of a model substrate, the

diastereomeric ratio was of no consequence at the time. The resulting secondary alcohol was acylated with crotonic anhydride and stoichiometric DMAP to give **20** in a somewhat low yield of only 60%. Other common conditions for this acylation were evaluated in efforts to increase the yield (crotonyl chloride, Hunig's base and catalytic DMAP; crotonic anhydride, NEt_3 and catalytic DMAP), however, these reactions suffered from either poor conversion to product or *E*/*Z* isomerization of the conjugated alkene. Crotonic anhydride and DMAP consistently gave the cleanest acylations.

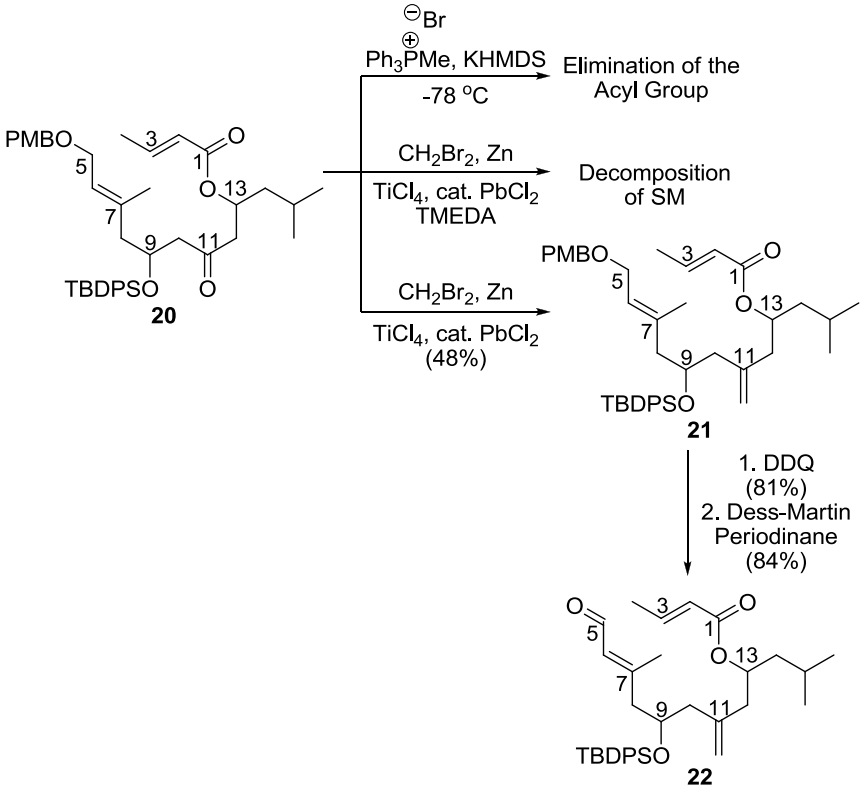
Scheme 2.7. Synthesis of Crotonic Ester **20**.



The remaining steps to complete the model precursor that would be used to test our key intramolecular vinylogous aldol macrocyclization included converting the C11 ketone to a methylene group, deprotection of the primary *p*-methoxybenzyl (PMB) ether, and subsequent oxidation to the aldehyde. Installation of the methylene group proved to be the most difficult transformation of those that remained. Initial investigations began with Wittig olefination by use of methyltriphenylphosphonium bromide and KHMDS[26], but the reaction conditions resulted in the elimination of the acyl group by crude ^{1}H NMR (Scheme 2.8). Modern Takai olefination conditions[27]

with dibromethane, $TiCl_4$, zinc, catalytic lead chloride and TMEDA led to decomposition of starting material. Gratifyingly, the original Takai olefination conditions[28,29] with dibromomethane, $TiCl_4$, zinc and catalytic lead chloride resulted in quantitative conversion to the product, **21**, and an isolated yield of 48%. As we were close to finishing the model substrate, this low yield was tolerated and the synthesis was continued; however, further studies would be necessary before applying this method in the total synthesis of arenolide. Finally, PMB ether deprotection with DDQ (81%) and subsequent oxidation with Dess-Martin periodinane (84%) occurred uneventfully to provide the desired model precursor for our key intramolecular vinylogous aldol reaction.

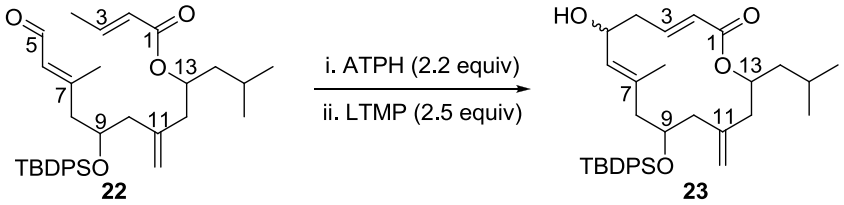
Scheme 2.8. Completion of the Model Precursor **22**.



With macrolide precursor **22** in hand, we were now well poised to examine the viability of our key intramolecular vinylogous aldol reaction in cyclizing to the macrolide. However, only 250 mg of this advanced substrate were obtained and therefore only two key reactions were performed, each on a 125 mg scale. We opted against performing smaller-scale reactions due to difficulties handling the moisture sensitive reagents required in this reaction. The first run was performed at -48 °C with 2.2 equivalents of ATPH and 2.5 equivalents of LTMP as the base (Scheme 2.9). After only 1.5 hours, the reaction appeared to be complete by TLC, and after work-up the crude ^{1}H NMR revealed the presence of a new compound along with several impurities. Flash column chromatography resulted in the isolation of material that appeared as a single spot by TLC; however, the material consisted of multiple compounds and the ^{1}H NMR was too unclear to determine of this material contained the desired macrocycle. The key vinylogous aldol reaction was therefore repeated using the same conditions, but at a lower temperature of -78 °C in hopes of minimizing the formation of by-products. After 4.5 hours the reaction did not look complete by TLC, however, the TLC also did not seem to be changing further and so the reaction was worked-up. The crude ^{1}H NMR looked similar to that belonging to the first run of the reaction, and flash column chromatography again allowed for the isolation of a material that appeared as a single spot but which contained multiple compounds. The components of this mixture were separated and isolated by high performance liquid chromatography (HPLC), which revealed the presence of four major components and several other minor ones. This was not entirely unexpected given the number of possible diastereomers of the product. Two of these four major

compounds were isolated in sufficient amount to analyze by NMR, and both of the compounds had ^{1}H NMR spectra that were consistent with diastereomers of the desired macrolide. High resolution mass spectrometry confirmed the composition of the compounds, providing good evidence that the key intramolecular vinylogous aldol reaction was a success!

Scheme 2.9. Intramolecular Vinylogous Aldol with Model Substrate **22**.



The degree to which our key macrocyclization step was successful, however, was difficult to assess. An accurate yield of all products could not be calculated, and the selectivity of the reaction could not be determined since the stereochemistry of the isolated diastereomers was not ascertained. The crude ^{1}H NMR spectra for both reaction trials were not very clean, and other undesired products were also isolated upon purification. Therefore, while our key reaction required more troubleshooting, a lack of material prohibited further experiments. An attempt at using our recently developed bulky Lewis acid, ATNP, would undoubtedly have been worthwhile; however, our studies surrounding ATNP had not yet begun at the time these trials were performed.

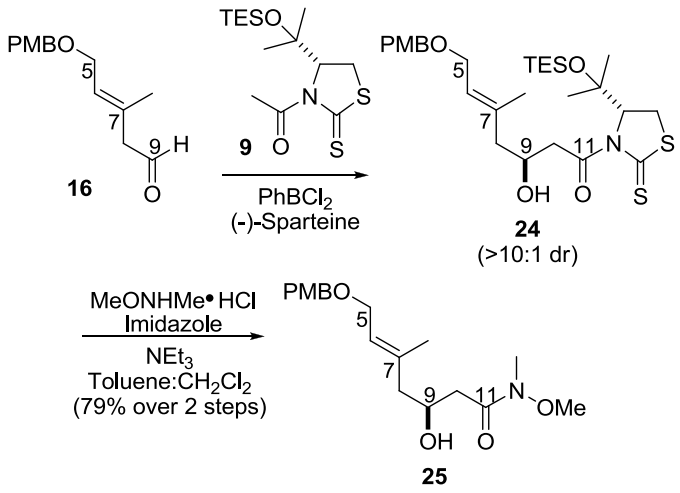
Still, the promising data that these initial trials produced gave us confidence that our desired macrocyclization would succeed in its application to the total synthesis of arenolide. Since the model precursor for which we examined the key intramolecular vinylogous aldol reaction was very similar to that which would be

used en route to arenolide, we felt our results were sufficient precedent to undertake the total synthesis by use of the same key macrocyclization reaction.

2.4.2 Arenolide Study

Our efforts toward the first total synthesis of arenolide began with aldehyde **16**, the same compound that was used en route to our model substrate. Subjection of aldehyde **16** to the asymmetric acetate aldol conditions developed in our lab (dichlorophenylborane, (–)-sparteine and chiral *N*-acetyl thiazolidinethione **9**) gave the desired *S*-isomer with >20:1 diastereoselectivity (Scheme 2.10). The chiral auxiliary was then cleanly converted to the Weinreb amide in 79% over two steps with *N*,*O*-dimethylhydroxylamine hydrochloride, imidazole and triethylamine.

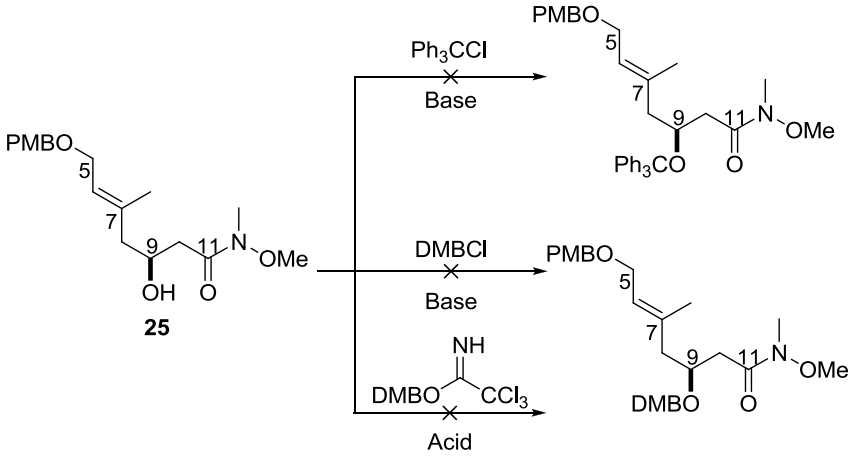
Scheme 2.10. Synthesis of Weinreb Amide **25**.



At this point in our synthesis it was necessary to make a decision in regards to which protecting group would be installed on the newly-formed hydroxyl at C9. As mentioned earlier, silyl ethers are known to decrease the diastereoselectivity of the 1,5-*anti* aldol reaction, and this was evidenced in the synthesis of our model substrate. Also discussed earlier, we hypothesized that a bulky protecting group would be best

in order to minimize aldehyde enolization in our key intramolecular vinylogous aldol reaction. Finally, the group has to be orthogonal to the primary PMB ether at C5. Alkyl ethers such as PMB, benzyl, and methoxy methyl (MOM) groups are known to aid in the selectivity of the 1,5-*anti* aldol,[23-25] and therefore our efforts first turned towards the installation of a bulky alkyl group, a triphenylmethyl (trityl) ether. Unfortunately, despite numerous attempts with many different conditions, the desired group could not be installed in good conversion or yield (Scheme 2.11). Next, the introduction of a dimethoxybenzyl (DMB) ether was attempted, but just like the trityl group, the DMB group was also reluctant to go on.

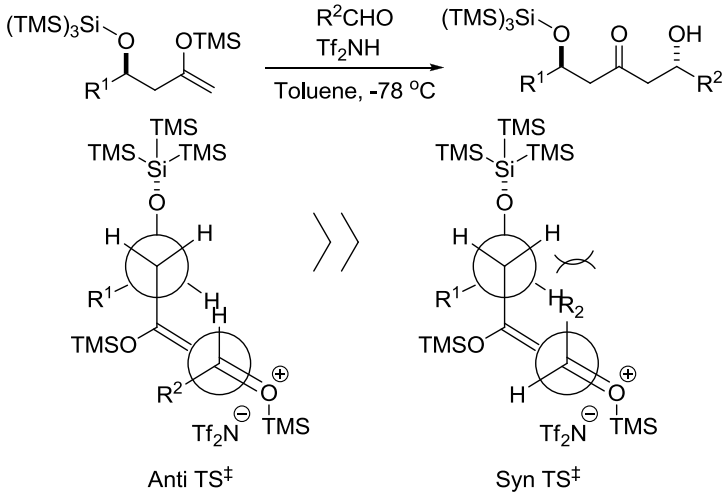
Scheme 2.11. Failed Protecting Group Installations.



Recently, Yamamoto and Yamaoka demonstrated the use of a very large tris(trimethylsilyl) ether in a highly selective 1,5-*anti* aldol reaction.[30] As shown in Figure 2.7, the method involves the Lewis-acid-catalyzed attack of the TMS-enol ether of the β-alkoxy-protected ketone on the aldehyde. The reaction is effective for straight-chain and branched ketones paired with various aldehydes, and provides the desired *anti*-aldol products in good yields and very high selectivities. Yamamoto attributes the *anti* selectivity to a model wherein the alkyl group of the aldehyde

prefers to minimize its steric interaction with the methylene group of the enol ether and therefore adopts the transition-state leading to the 1,5-*anti* product (Figure 2.7). The steric bulk of the tris(TMS) protecting group along with the 1,5-*anti* selectivity that it imparts in the aldol reaction looked to be the perfect solution to our protecting group scheme. Therefore, our efforts turned towards installation of the tris(TMS) group onto the hydroxyl group at C9.

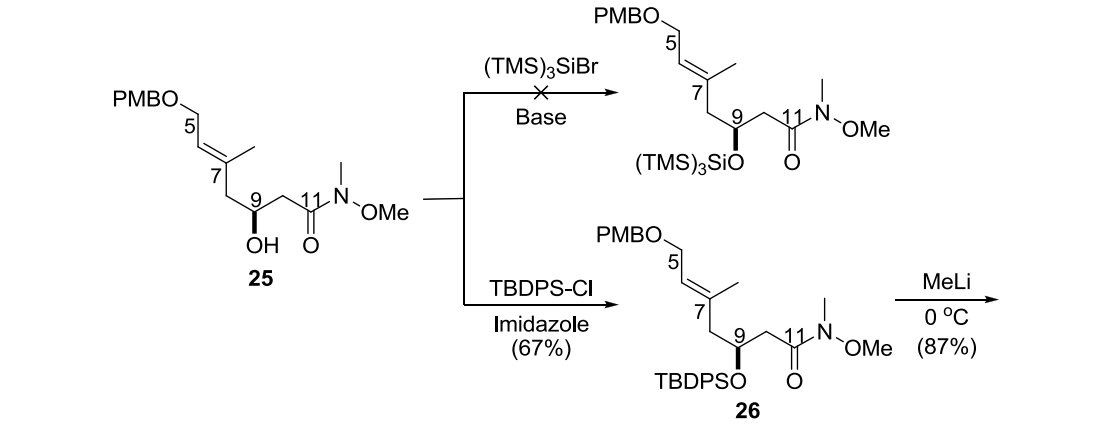
Figure 2.7. Yamamoto's Supersilyl-Directed 1,5-*Anti* Aldol Reaction and Its Plausible Transition States.



Much to our dismay, the tris(TMS) ether could not be installed. Various bases and conditions were evaluated; however, none provided the desired product in significant yield. After many failed attempts, it was reasoned that since Yamamoto proposes a simple steric argument for the 1,5-*anti* stereoinduction outcome, a TBDPS ether may sufficiently mimic the steric bulk of the tris(TMS) to be successful under the same reaction conditions. Therefore, Weinreb amide **25** was protected as a TBDPS ether, converted to the methyl ketone by subjection to methyllithium, and then the Lewis-acid-catalyzed 1,5-*anti* aldol reaction was attempted (Scheme 2.12).

Conversion to the TMS-enol ether was smooth; however, upon addition to the aldehyde followed by subjection to catalytic trifluoromethanesulfonimide (Tf_2NH), the enol ether merely converted back to starting material ketone and none of the desired aldol adduct was isolated.

Scheme 2.12. Attempts at Yamamoto's Lewis-Acid-Catalyzed 1,5-*Anti* Aldol Reaction.

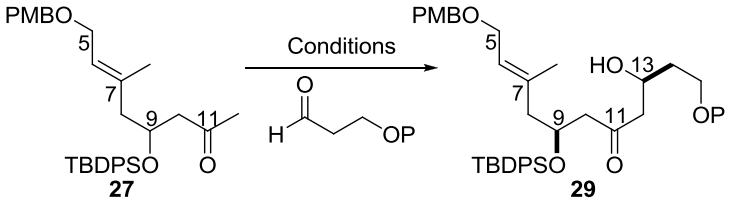


P	Additive	Result
P=TBS	None	Conversion Back To Ketone
P=TBS	2,6-lutidine	Decomposition
P=MOM	None	Conversion Back to Ketone

Once again we had returned to the same protecting group question as before: what group at C9 would promote diastereoselectivity for the 1,5-*anti* aldol reaction, but also prevent enolization of the aldehyde in the key intramolecular vinylogous aldol reaction? After failing to install a group that would meet both criteria, the next plan of action became testing each criteria individually. First, in efforts to meet steric bulk requirements, the 1,5-*anti* aldol reaction was examined with a TBDPS-protected

ether at C9 using the traditional boron-mediated conditions (Table 2.3).[7,31] Although this reaction was utilized in the synthesis of our model substrate in which we observed poor diastereoselectivity, it was plausible that the reaction could be optimized. Disappointingly, however, our examination with the TBDPS ether failed. Despite attempts with different borane sources, including the chiral chlorodiisopinocampheylborane, along with different aldehydes, the best observed diastereoselectivity was a mere 2:1.

Table 2.3. 1,5-*Anti* Aldol Attempts With a TBDPS Ether at C9.



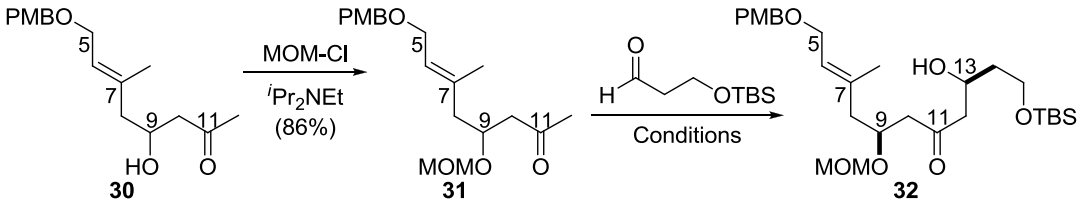
Entry	Conditions	Aldehyde	Result
1	Bu_2BOTf, $^iPr_2NEt$	P=TBS	~1:1 Diastereoselectivity
2	Bu_2BOTf, $^iPr_2NEt$	P=MOM	~2:1 Diastereoselectivity[a]
3	(-)-DIP-Cl, NEt_3	P=TBS	~1:1 Diastereoselectivity
4	(-)-DIP-Cl, NEt_3	P=MOM	~2:1 Diastereoselectivity[a]

[a] Major diastereomer not determined.

Efforts were then exerted to individually test the remaining requirement: a protecting group that would promote selectivity in the 1,5-*anti* aldol reaction. The alkyl protecting group, methoxy methyl (MOM) ether has significant precedence for promoting good 1,5-*anti* stereoinduction, and therefore it was installed and examined (Scheme 2.13). Although this protecting group would most likely not be bulky enough to prohibit enolization of the aldehyde in the intramolecular vinylogous aldol reaction, it was at least orthogonal to the other protecting groups on the substrate and, in theory, it could be altered later in the synthesis, if need be. Surprisingly, however, the MOM-protected *β*-alkoxy ketone **31** was reluctant to participate in the reaction.

Despite attempts with different boranes and amine bases, and even upon allowing reactions to warm to room temperature, still none of the desired aldol adduct was observed.

Scheme 2.13. 1,5-*Anti* Aldol Attempts With a MOM Ether at C9.



Conditions	Result
Bu_2BOTf, $^{i}Pr_2NEt$	No Conversion to Product
(-)-DIP-Cl, NEt_3	No Conversion to Product
Cy_2BCl, NEt_3	No Rxn

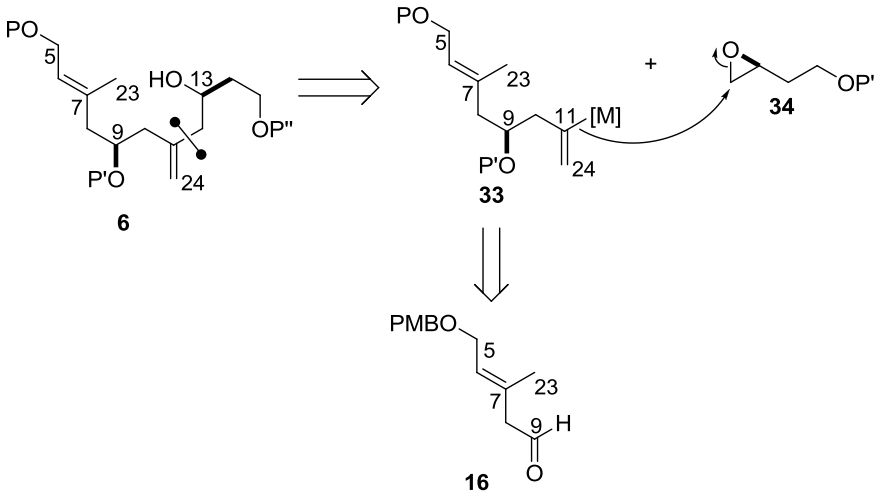
At this point, we decided to re-evaluate our approach to the total synthesis of arenolide. A different route that did not include the 1,5-*anti* aldol reaction to build the macrocycle precursor was necessary. The design of such a route and our efforts towards its implementation in the synthesis of arenolide will be discussed in the following section.

2.5 Second-Generation Approach to Arenolide

In order to avoid a complete reworking of our synthetic strategy towards arenolide, focus was placed on a simple alternative to the 1,5-*anti* aldol reaction. A straightforward solution was proposed involving a vinyl metal nucleophilic attack upon an enantiopure epoxide (Figure 2.8). This is a very attractive route since circumventing the 1,5-*anti* aldol reaction evades the requirement of confirming the 1,5-*anti* stereochemistry of the aldol product, and it avoids the late-stage

methylenation of the ketone at C11 which only proceeded in 48% yield on the model substrate (Scheme 2.8). And as previously mentioned this route also prevented a complete revision of our strategy since it involves the same retrosynthetic precursors as our first-generation approach. Aldehyde **16** from our original route would simply need to be converted to the vinyl halide, and then metal-mediated coupling with epoxide **34** would provide advanced precursor **6**.

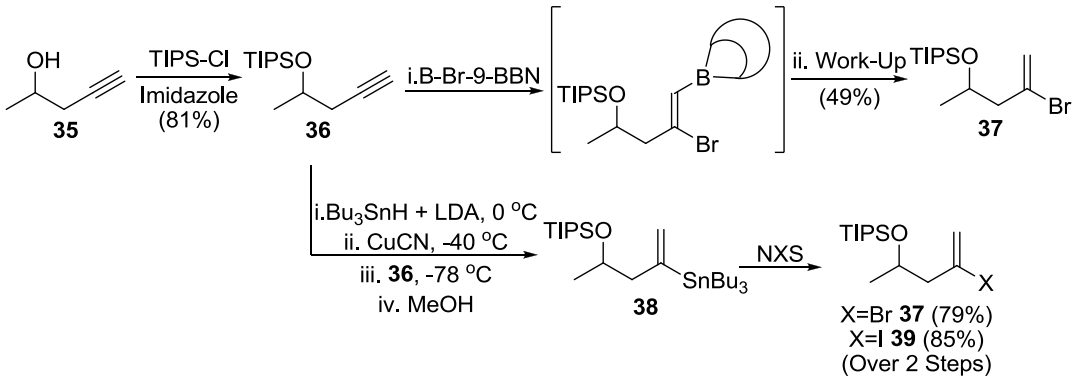
Figure 2.8. Second-Generation Retrosynthesis.



Model substrates **37** and **39** were used to assess the newly proposed route and were prepared beginning with protection of commercially available 3-pentyn-2-ol as the triisopropylsilyl (TIPS) ether with TIPS-Cl and imidazole (Scheme 2.14). Conversion of the terminal alkyne to the vinyl halide was first attempted by subjection of **36** to B-bromo-9-BBN. Although the reaction conditions resulted in the clean addition of the bromine and BBN group across the alkyne, hydrolysis of the borane during the reaction work-up often resulted in decomposition of the product. After numerous attempts at troubleshooting failed to improve the reaction yield, conversion of the alkyne to the vinyl tin species **38** via the stannylcuprate was found

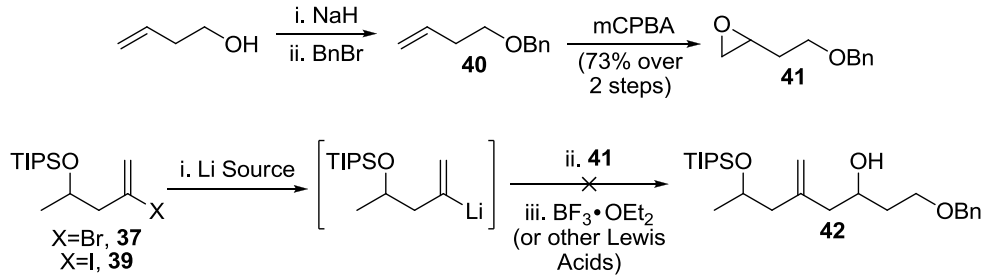
to be much more effective.[32-34] Subsequent treatment of **38** with *N*-bromosuccinimide or *N*-iodosuccinimide gave the desired vinyl halide in 79% and 85% yield respectively over two steps.

Scheme 2.14. Preparation of Vinyl Halides **37** and **39**.



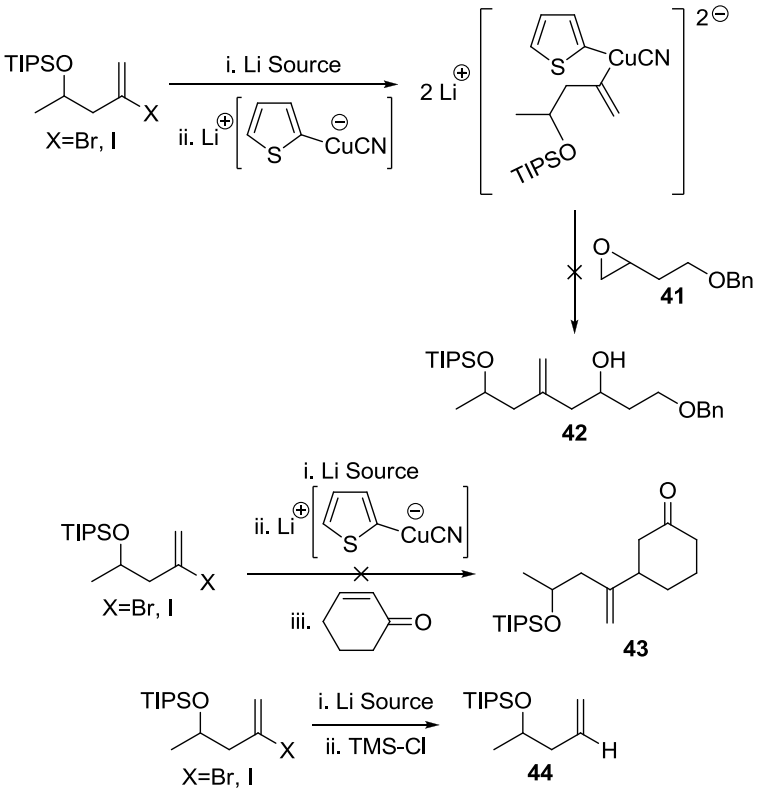
Racemic epoxide **41** was then synthesized in 73% yield over two steps via benzyl protection of 3-buten-1-ol with sodium hydride and benzyl bromide, followed by epoxidation with mCPBA, and we were well poised to investigate our newly devised route (Scheme 2.15). Initial epoxide-opening attempts with compounds **37** and **39** were executed via lithium-halogen exchange with *n*-butyllithium followed by addition of epoxide **41** and BF_3•etherate (Scheme 2.15).[35-37] We were pleased to find that the reaction gave the desired product in good conversion in our initial runs, however, the reaction was eventually found to be irreproducible. In many instances a nucleophilic halogen would open the epoxide to form the halohydrin, and often times a THF-derived polymer involving the epoxide could be isolated. Various Lewis acids were screened including $Ti(O^iPr)_4$, $B(C_6F_5)_3$ and $Cu(OTf)_2$, along with several different lithium sources and additives, however, conditions were not found to effect the desired transformation in sufficient yield.

Scheme 2.15. Synthesis of Epoxide 41 and Failed Epoxide-Opening via Lithium-Halogen Exchange of **37** and **39**.



Cuprate addition of the vinyl halide to the epoxide was attempted next; lithium-halogen exchange via a lithium source followed by subjection to lithium-2-thienylcyanocuprate formed the desired cuprate *in situ*, to which the epoxide was then added (Scheme 2.16).[38-40] Unfortunately, however, this method also proved to be unsuccessful. A test reaction involving reliable cuprate reaction partner, 2-cyclohexen-1-one, was performed; however, no addition of the vinyl group to the *β*-position (**43**) was observed, indicating that perhaps the desired cuprate was not forming. This led to other reactions to test whether or not the lithium-halogen exchange was taking place. Subjection of vinyl halides **37** and **39** to various lithium sources followed by trapping with TMS-Cl did not form the desired vinyl-TMS but instead merely resulted in the reduced vinyl halide, compound **44**. Conversion to compound **44** suggests that lithium-halogen exchange does take place; however, it is clear that the vinyl-metal species does not behave as desired, either because it gets protonated too quickly or for some other unknown reason.

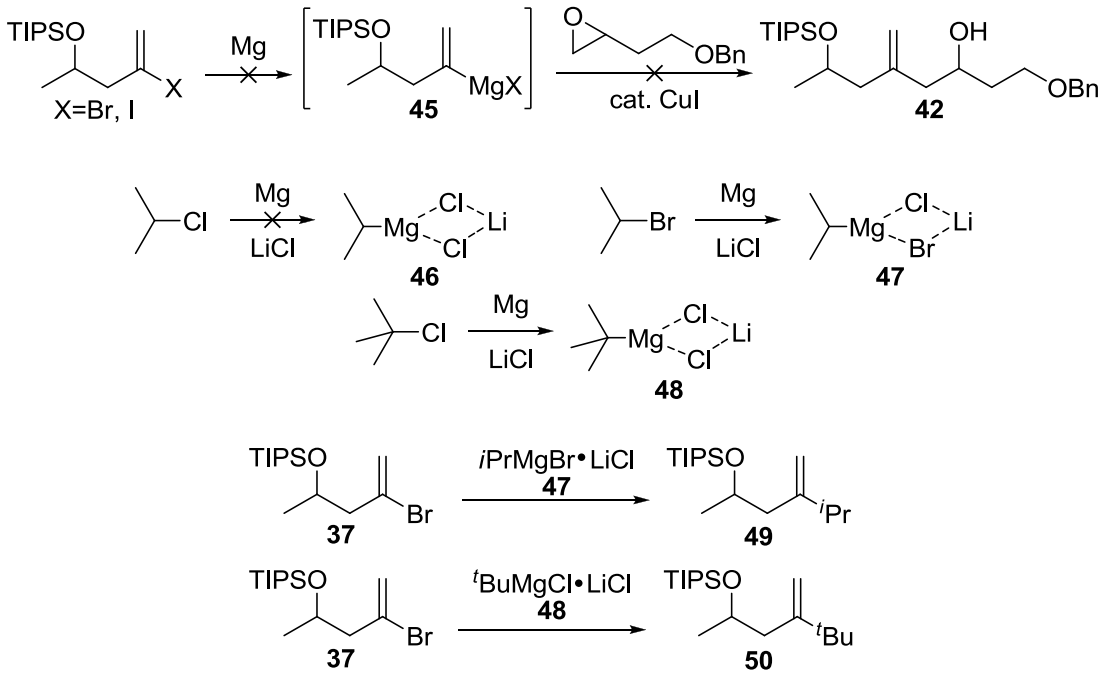
Scheme 2.16. Cuprate Addition and Lithium-Halogen Exchange Studies.



Copper-mediated addition of the vinyl Grignard **45** to the epoxide was also examined (Scheme 2.17). Somewhat discouragingly, the large amount of precedence for this approach strictly involves the formation of the Grignard on large scale, and therefore was anticipated to be difficult to apply to our synthesis. Indeed, after much experimentation, formation of the vinyl Grignard reagent on small scale was unsuccessful. Knochel's highly reactive magnesium-insertion reagent, **46**,[41-43] was also investigated, however, this reagent was found to be very difficult to prepare and not useful for our purposes. Variations of the reagent, compounds **47** and **48**, were more readily prepared via formation of the Grignard reagent in the presence of LiCl. Disappointingly, both of these reagents led to the formation of their respective alkyl-substituted vinyl compounds, **48** and **50**, when added to vinyl bromide **37**, prohibiting

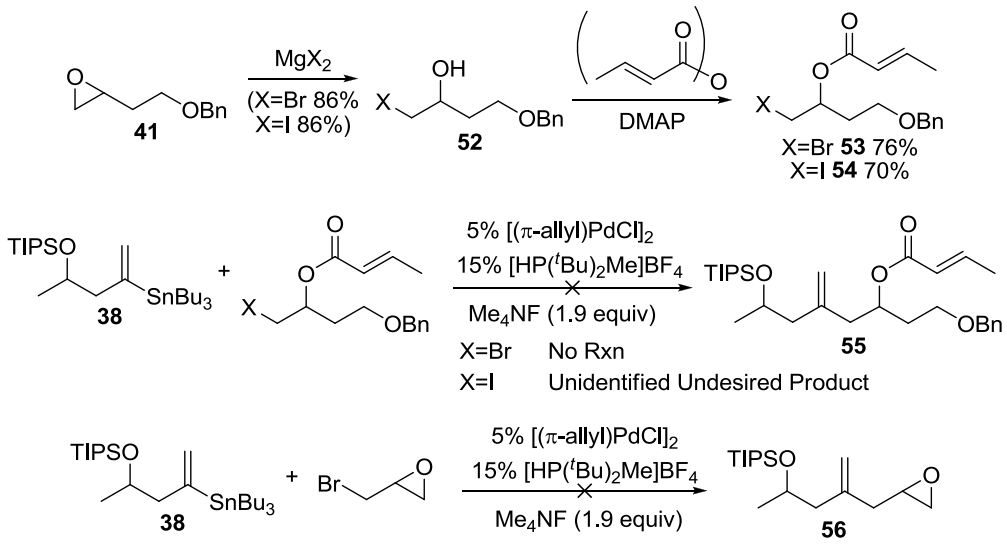
any reaction with another electrophile. Much to our dismay, it had become apparent that the vinyl nucleophilic attack upon an enantiopure epoxide would not be an effective method to prepare our desired product.

Scheme 2.17. Vinyl Grignard Studies.



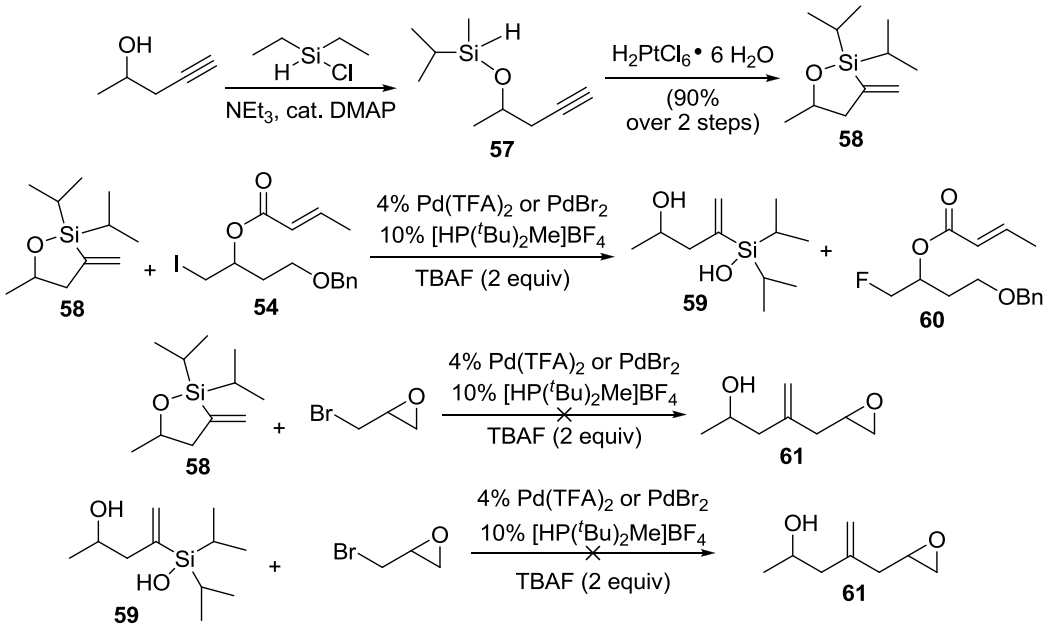
Other metal-mediated couplings were then studied, beginning with a Stille coupling between the vinyl tin **38** and alkyl halides **53** and **54** (Scheme 2.18). The alkyl halides were easily prepared via magnesium halide addition to the epoxide and then crotylation of the resulting halohydrin. Unfortunately, when the coupling substrates were subjected to room temperature Stille conditions developed by Fu[44] ([π-allylPdCl]$_2$, [HP(^{t}Bu)$_2$Me]BF$_4$ and Me$_4$NF), no reaction took place with alkyl bromide **53** and an unidentified undesired product was formed with alkyl iodide **54**. The same Stille conditions were used to attempt the coupling of **38** and commercially available epi-bromohydrin, however, the same unidentified undesired product as before was isolated.

Scheme 2.18. Stille Coupling Reaction Studies.



Next, Hiyama couplings were investigated between cyclic silane **58** and alkyl iodide **54** along with epi-bromohydrin, as shown in Scheme 2.19. Cyclic silane **58** was synthesized in an unoptimized 31% yield over two steps from 4-pentyn-2-ol; the silyl group was added to the alcohol via triethylamine and catalytic DMAP and then a platinum-catalyzed intramolecular hydrosilylation reaction was utilized with H_2PtCl_6.[45-47] This transformation was especially effective since the 5-exo product was formed exclusively with none of the undesired 6-endo product detected. Again, room temperature Hiyama conditions pioneered by Fu[48,49] were utilized ($Pd(TFA)_2$ or $PdBr_2$, $[HP(^tBu)_2Me]BF_4$ and TBAF), however, the reaction between **58** and vinyl iodide **54** gave no desired product. Instead, the cyclic silane merely converted to the vinyl silane **59** and the iodide was substituted with a fluoride. Similar results were seen in the attempted coupling of **58** and epibromohydrin; only the vinyl silane was present in the crude reaction mixture. The vinyl silane was thought to be a possible Hiyama coupling partner, and so it was also subjected to Fu's conditions with epibromohydrin. Unfortunately, no reaction took place.

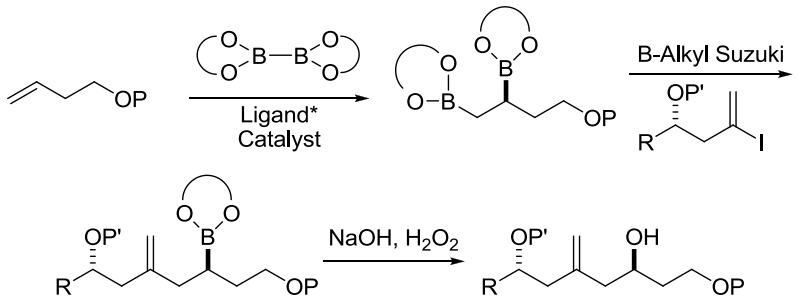
Scheme 2.19. Hiyama Coupling Reaction Studies.



Many other similar sp^2-sp^3 couplings have been accomplished in the context of total synthesis, most of which are executed via the metal-mediated opening of an epoxide which failed with our system.[36,37,50] The alkoxy group α- to the halide on the electrophile made our system more difficult to attempt other precedented sp^2-sp^3 couplings, specifically because our substrates were strictly defined, and therefore limited, in their reactivities. We could not invert their reactivities, e.g., make the vinyl halide the electrophile and the α-alkoxy substrate the nucleophile, since any metal intermediates of the α-alkoxy moiety would quickly eliminate to give the unreactive terminal alkene. Fortunately, a clever idea surfaced wherein the α-alkoxy group is circumvented, expanding the substrates' possible reactivities once again. The suggestion involved the utilization of a diboration reaction[51-57] of the terminal alkene from which our epoxide was originally synthesized (Scheme 2.20). After selectively functionalizing the diborane product at the terminal position via a B-alkyl

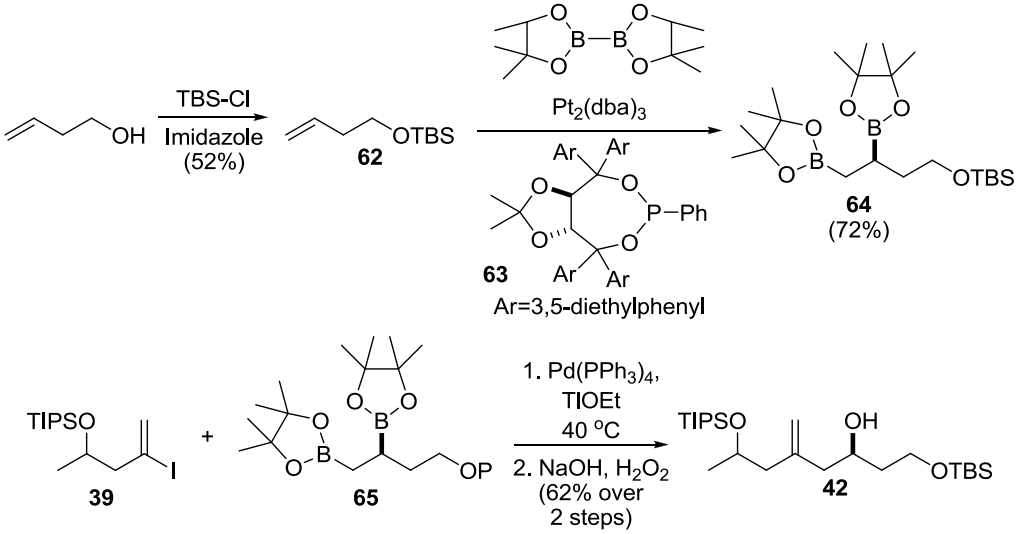
Suzuki coupling with the vinyl halide, the remaining secondary borane could then easily be oxidized to an alcohol. In addition, the desired stereochemistry of the eventual alcohol would be set in the diboration step.[51,57] The idea enabled the inversion of reactivities between the desired substrates and was deemed a promising and even more efficient alternative to the 1,5-*anti* aldol reaction, therefore, it was immediately investigated.

Scheme 2.20. Proposed Diboration, B-Alkyl Suzuki Coupling, then Oxidation.



Just as with the previously prepared epoxide, synthesis of the diboronic ester began with the protection of 3-buten-1-ol as the TBS ether. Asymmetric diboration of the terminal alkene by use of bis(pinacolato)diboron, a novel TADDOL ligand and $Pt_2(dba)_3$ cleanly gave the desired bis(boronic ester) **64** in 71% yield.[57] Gratifyingly, our initial B-alkyl Suzuki coupling attempt between **64** and model vinyl iodide **39** with $Pd(PPh_3)_4$ and thallium ethoxide[58-61] provided the desired product and after oxidizing the remaining secondary boronic ester to the alcohol could be isolated in 62% yield.

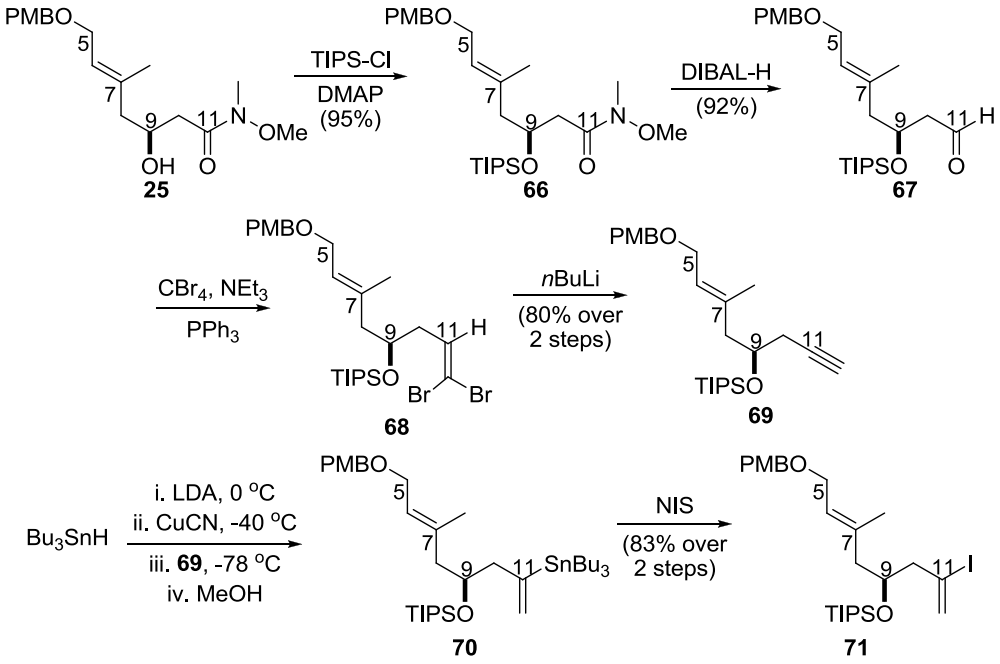
Scheme 2.21. Successful Implementation of the Diboration, B-Alkyl Suzuki Coupling and Oxidation Sequence.



After the lengthy amount of failure we had endured beginning with the lack of diastereoselectivity in the 1,5-*anti* aldol reaction and continuing into the failed metal-mediated couplings, we had finally devised a very promising route to the key intramolecular vinylogous aldol precursor and immediately set upon applying that route to the synthesis of arenolide. Beginning with an intermediate from our 1,5-*anti* aldol route, Weinreb amide **25** was protected as the TIPS ether in 95% yield (Scheme 2.22). Next, conversion of the Weinreb amide to the aldehyde, **67**, via DIBAL-H reduction was smooth and gave the desired product in 92% yield. Initial attempts at installing the alkyne were performed by use of the Ohira-Bestmann reagent[62]; however, this method consistently gave only 40% yield of the desired product, **69**. Application of the Corey-Fuchs protocol,[63,64] which called for conversion of the aldehyde to the dibromo-alkene (**68**) followed by elimination to the alkyne, gave superior results and provided the terminal alkyne in 80% yield over two steps. And gratifyingly, formation of the vinyl iodide was smooth via the method developed

earlier with our model alkyne **36** (Scheme 2.14). Copper-mediated addition of tributyltin hydride across the alkyne followed by conversion of the crude vinyl tin **70** to the iodide with *N*-iodosuccinimide cleanly afforded the desired product **71** over two steps in 83% yield.

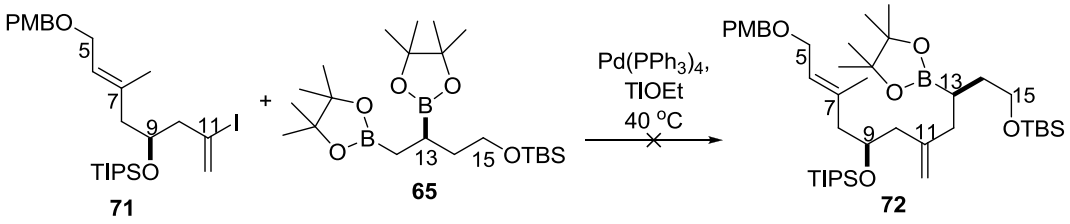
Scheme 2.22. Preparation of Vinyl Iodide **71**.



We were now poised to attempt the B-alkyl Suzuki coupling between the enantiopure substrates **71** and bis(boronic ester) **65** with hopes of finally overcoming all of the obstacles associated with developing a route alternative to that which includes the 1,5-*anti* aldol reaction. In the event, conditions that had previously been successfully optimized for the coupling of model substrate **39** and the same bis(boronic ester) **65** were utilized; however, none of the desired product was formed (Scheme 2.23). Instead, the reaction produced a complex mixture of alkene-containing products which could not be identified. Alternative conditions were studied, including different palladium catalysts, bases and solvents, but unfortunately

none of the coupling product could be isolated. However, time constraints limited an exhaustive survey of the many different combination of Suzuki coupling reagents, and therefore this route to the key vinylogous aldol precursor, and ultimately the arenolide core, still holds a great deal of potential. Nonetheless, for that potential to be realized, conditions which successfully promote this B-alkyl Suzuki coupling between **71** and **65** would first need to be identified.

Scheme 2.23. Failed B-Alkyl Suzuki Coupling Between **71** and **65**.



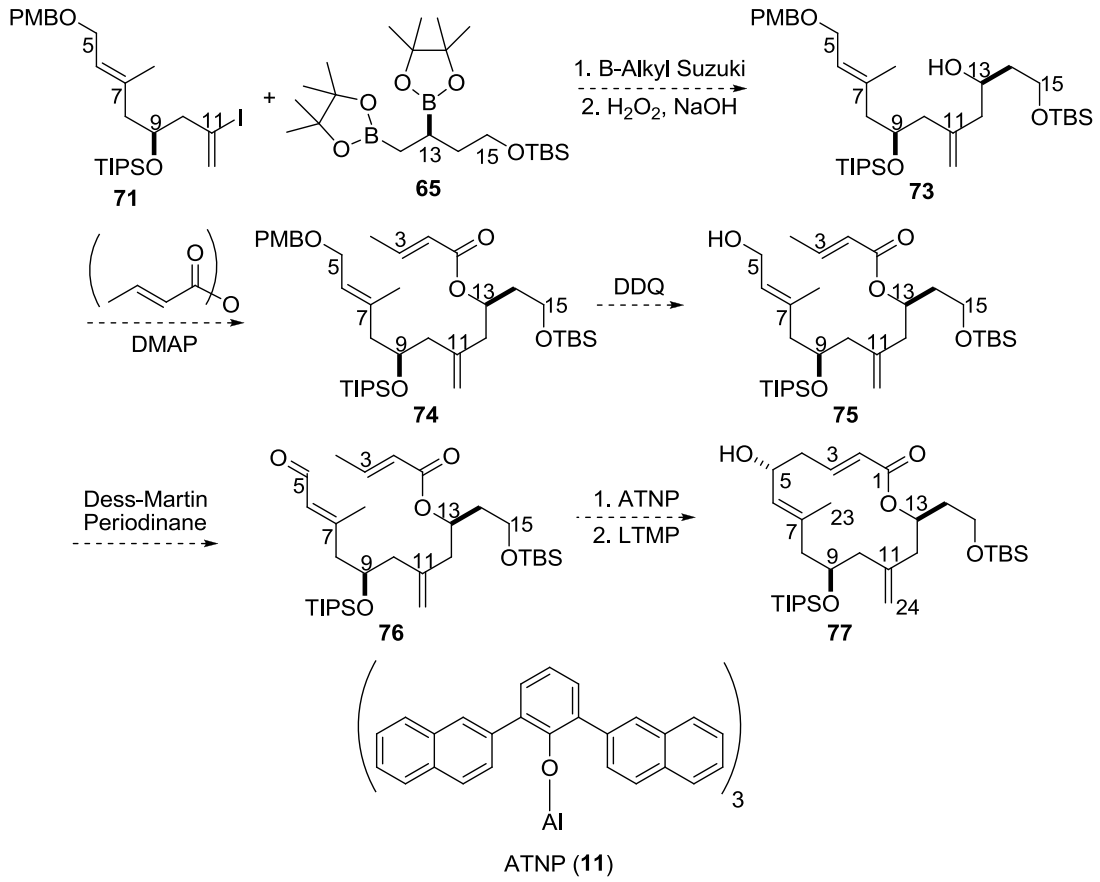
2.6 Conclusion and Future Direction

In conclusion, two main approaches toward the macrocyclic core of arenolide have been thoroughly studied. The first approach culminated with the completion of a model substrate upon which our key intramolecular vinylogous aldol reaction was attempted. Gratifyingly, the desired macrocycle was formed and isolated; however, the yield and diastereoselectivity of the reaction was not determined. Nonetheless, it is apparent that this key reaction holds a significant amount of potential and now some precedent for its success in the total synthesis of arenolide, especially considering our lab's recent development of the bulkier and more versatile Lewis Acid, ATNP. Its use should undoubtedly provide the macrocycle in good yield and stereoselectivity.

This original approach to the core of arenolide utilized a 1,5-*anti* aldol reaction which was found to lack diastereoselectivity when applied to the total synthesis. Therefore, a re-working of our synthetic plan was required and a second-generation approach was developed with a focus on alternative methods to produce the 1,5-*anti* relationship between the alkoxy groups at C9 and C13 with the exo-methylene group at C11. Extensive studies on metal-mediated couplings to produce the desired moiety were performed, and success was initially found via use of a B-alkyl Suzuki reaction using a model alkene and a diboronate substrate. However, this coupling failed when applied to the substrate required for the total synthesis.

Future work in this project must clearly focus on the completion of the total synthesis of arenolide. Upon identification of conditions that will successfully couple vinyl halide **71** and diboronate **65**, mere acylation, PMB deprotection and subsequent oxidation reactions remain to arrive at the intramolecular vinylogous aldol precursor, **76** (Scheme 2.24). The key macrocyclic reaction was shown to be effective on a model substrate described in this chapter (**22**, Scheme 2.9), and with our lab's newly developed and bulkier Lewis acid, ATNP, this key transformation is highly anticipated to be successful.

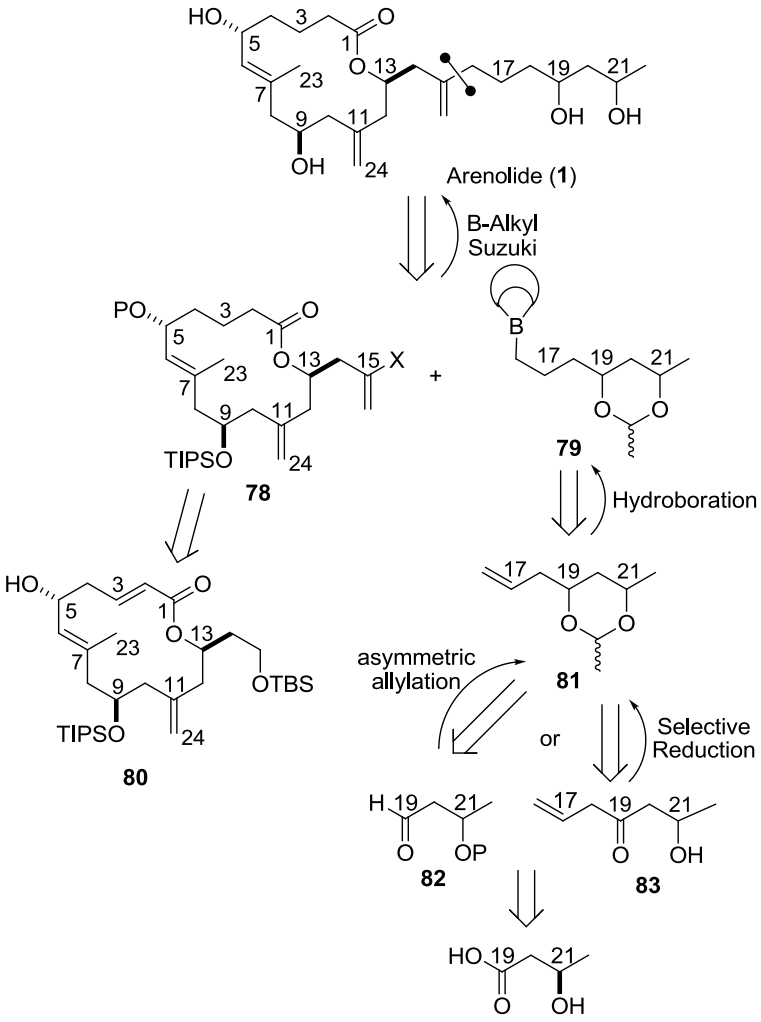
Scheme 2.24. Key Vinylogous Aldol Macrocyclization En Route to the Total Synthesis of Arenolide.



With a direct and well-studied route which holds a significant potential in completing the macrocyclic core of arenolide, as that described in this chapter, attention must now be refocused on the synthesis of the diastereomeric side chains and their coupling to the natural product's core. The absolute and relative stereochemistries of the hydroxyl groups at C19 and C21 remain undetermined; therefore, all four diastereomers of the side chain must be synthesized and then coupled to the macrocyclic core in order for comparison of known spectral data and determination of arenolide's absolute stereochemistry to take place (Figure 2.9). Thus, the side chain synthesis requires flexibility in order to construct all of the

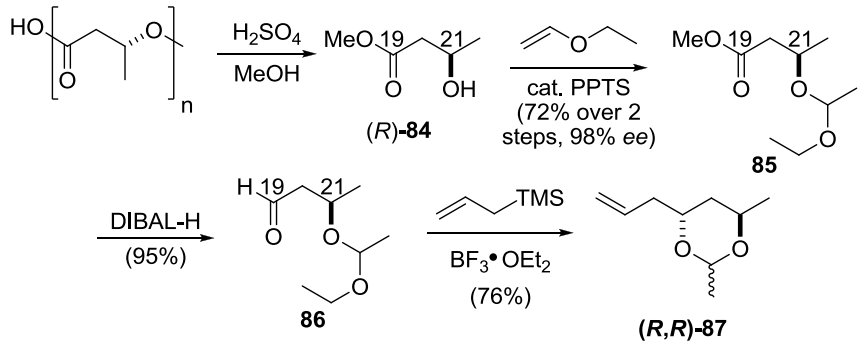
diastereomers, and all of the side chains should ideally intercept at a common intermediate in order to be efficiently incorporated into the total synthesis. Retrosynthetically, the access point for each side chain stereoisomer could be through a B-alkyl Suzuki coupling reaction between the exo-macrocyclic vinyl halide of **78** and respective side chain borane **79**. Each borane side chain could be built via a 9-BBN hydroboration reaction of ethylidene acetal **81**. Gratifyingly, Dr. Aaron Cullen has studied the synthesis of each possible side chain diastereomer.[65] In his work he determined that all four stereoisomers could be prepared either via an asymmetric allylation of a *β*-alkoxy aldehyde **82** or a selective reduction of allylic ketone **83**, and he found that both **82** and **83** can be synthesized from poly[(*R*)-3-hydroxybutyric acid].

Figure 2.9. Endgame for the Total Synthesis of Arenolide.



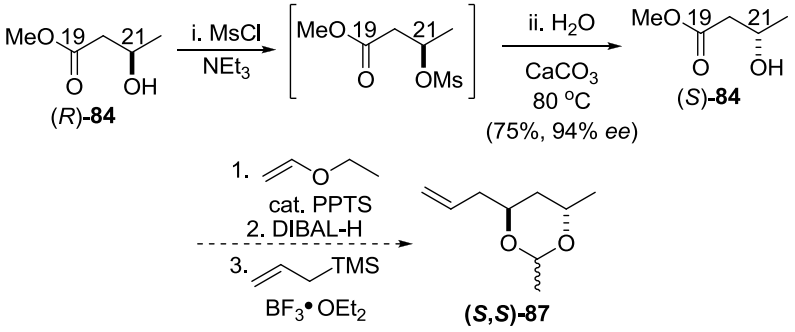
Dr. Cullen efficiently built both the (*R*,*R*)- and (*S*,*S*)-isomers of **87** via similar routes commencing with the depolymerization and esterification of poly[(*R*)-3-hydroxybutyric acid] (Scheme 2.25).[66] The C21 hydroxyl group of the (*R*,*R*)-isomer was then protected as an acetal in 72% yield over the two steps and with 98% *ee*, followed by DIBAL-H reduction of the C19 ester to the aldehyde gave **86** in 95% yield. An asymmetric allylation method developed by our lab[65] was then utilized to give exclusively the *anti* side chain isomer, **(*R*,*R*)-87**, in 76% yield.

Scheme 2.25. Preparation of **(*R*,*R*)-87.**



The (*S*,*S*)-isomer was prepared in the same method as its enantiomer, however, after depolymerization and esterification of poly[(*R*)-3-hydroxybutyric acid], the C21 stereocenter was inverted by conversion of the hydroxyl group to a mesylate followed by the S_N2 addition of water which, upon work-up, gave (*S*)-3-hydroxybutyrate **84** in 75% yield and 94% *ee* (Scheme 2.26). While the formation of methyl crotonate may be expected under these reaction conditions via elimination of the secondary mesyl group, gratifyingly, none of this undesired product was formed.

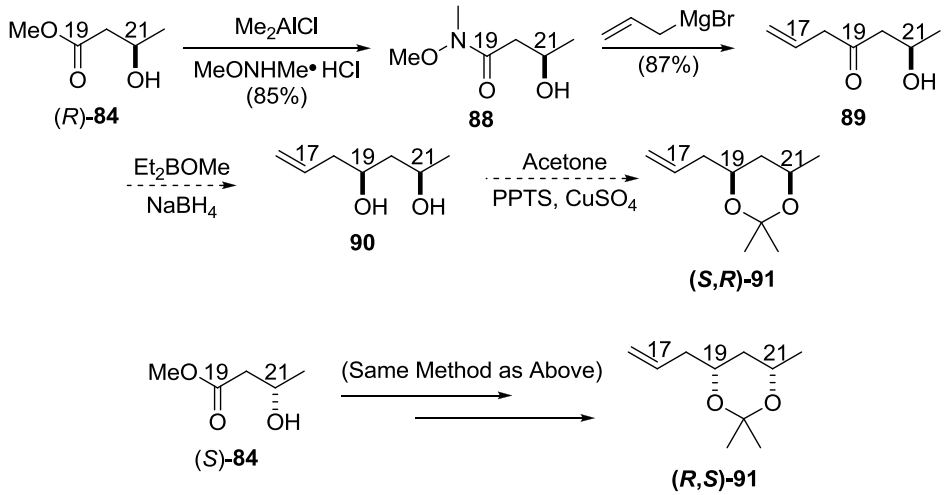
Scheme 2.26. Preparation of (*S*,*S*)-**87**.



With completion of the synthesis of the *anti*-stereoisomers, Dr. Cullen's focus was then direction towards the synthesis of the *syn*-enantiomers. Conversion of **(*R*)-84** to the Weinreb amide in 85% followed by subsequent addition of allylmagnesium bromide gave *α*-alkoxy ketone **89** in 87% yield. A stereoselective reduction of the

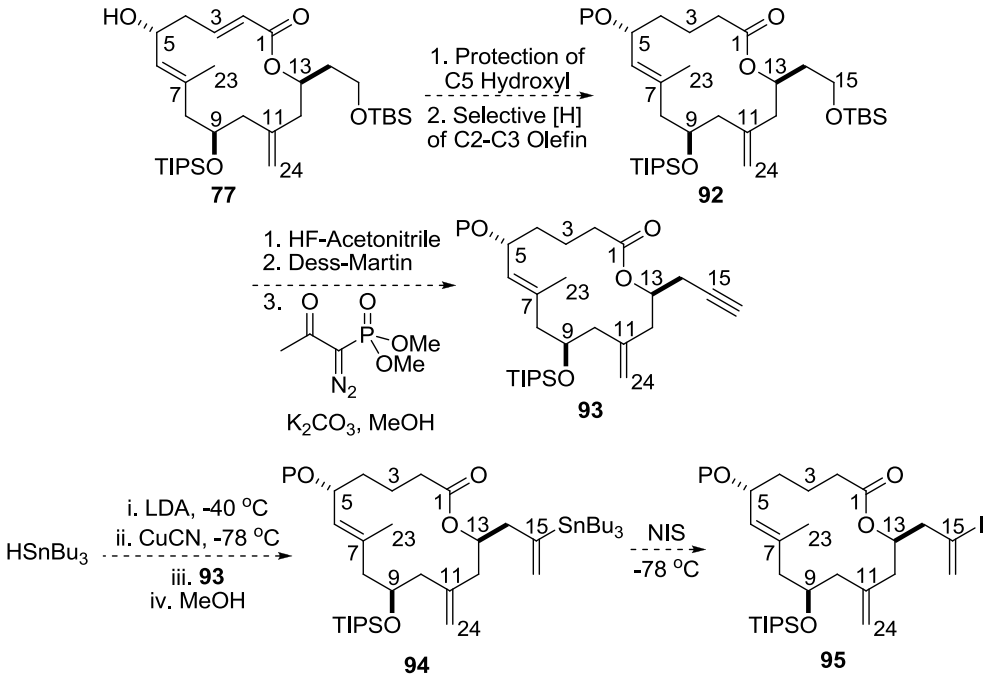
ketone, e.g., the Narasaka-Prasad reduction protocol,[67] would then provide the requisite (*S*,*R*)-*syn*-diol in a precedented fashion. And if this sequence is successful, the same method would be utilized to build the (*R*,*S*)-isomer.

Scheme 2.27. Preparation of **(*S*,*R*)-91** and **(*R*,*S*)-91.**



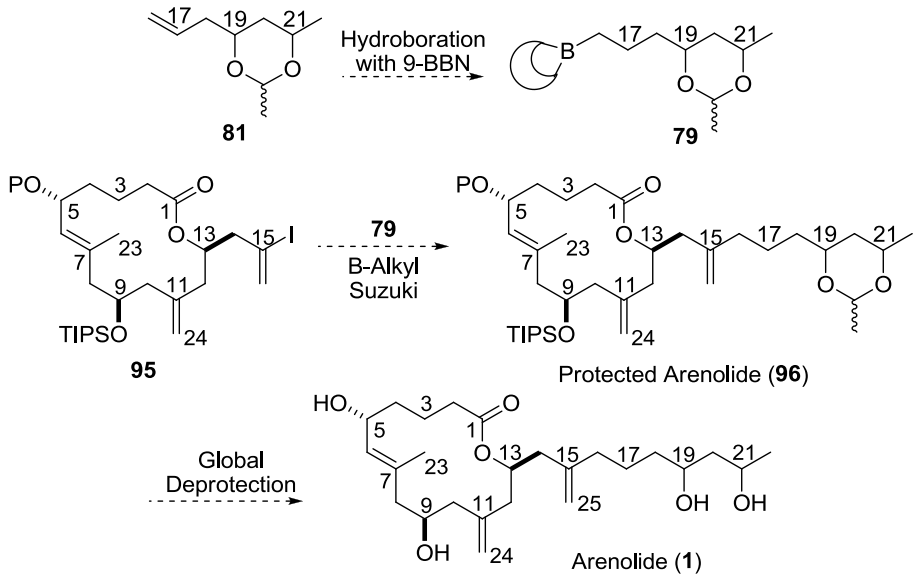
As discussed earlier, endgame of the total synthesis of arenolide would consist of conversion of the cyclized macrolide to exocyclic vinyl halide **95** via protection of the secondary alcohol and selective reduction of the *α*,*β*-unsaturated ester olefin (Scheme 2.28). Installation of the vinyl halide would proceed via the corresponding alkyne (**93**). This would be prepared by the selective deprotection of the TBS-ether of **77**, oxidation of the subsequent alcohol to the aldehyde, and then conversion to the alkyne using the Ohira-Bestmann reagent[62] or the Corey-Fuchs method.[64] The alkyne could then be converted to the vinyl halide by the sequence already used in our synthesis of the macrocyclic precursor: copper-mediated tributyltin hydride addition across the alkyne and then installation of the iodide by subjection to *N*-iodosuccinimide.

Scheme 2.28. Completion of the Macrocyclic Core.



After hydroboration of all four of the diastereomeric ethylidene acetal side chain alkenes, coupling to the macrocyclic core by use of a B-alkyl Suzuki reaction would be studied (Scheme 2.29). After coupling, global deprotection would provide all of the stereoisomers of arenolide which are to be analyzed in order to determine the natural product's absolute stereochemistry and better assess its bioactivity. It is possible that in assaying all four of the stereoisomers, one may display more potent activity than the natural product and possibly provide significant structure-activity relationship data. Current efforts are underway to complete the total synthesis of arenolide, determine its absolute stereochemistry, and assess its bioactivity as well as that of its stereoisomers.

Scheme 2.29. Completion of Arenolide.



2.7 Experimental Information

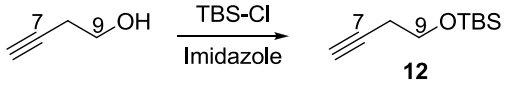
General Information:

All reactions were conducted in oven-dried glassware under a dry nitrogen atmosphere. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled over sodium benzophenone ketyl under N_2. Dichloromethane (CH_2Cl_2), diisopropylethylamine ($^iPr_2NEt$), triethylamine (NEt_3), isovaleraldehyde, dibromomethane, and toluene were distilled over CaH_2 and under N_2. Diisopropylamine ($^iPr_2NH$) was distilled over sodium and under N_2. Titatinium(IV) chloride was distilled over copper turnings and under N_2. *N*,*N*-dimethylformamide (DMF) was distilled over CaH_2 and under reduced pressure (~2 torr). Acetone was distilled over ground $CaSO_4$ and under N_2. 3-Butyn-1-ol, imidazole, *tert*-butyldimethylsilylchloride (TBS-Cl), cyclohexane, trimethylaluminum (2.0 M in

hexanes), prilled paraformaldehyde (methanol-free), pyridinium *p*-toluene sulfonate (PPTS), tetrabutylammonium fluoride (TBAF; 1.0 M in tetrahydrofuran), *n*-butyllithium (solution in hexanes), methyllithium (solution in Et_2O), *tert*-butyldiphenylsilylchloride (TBDPS-Cl), dibutylboron triflate, crotonic anhydride, 4-(dimethylamino)pyridine (DMAP), lead(II) chloride, 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ), 2,6-diphenylphenol, 2,2,6,6-tetramethylpiperidine, dichlorophenyl borane (97%), (–)-sparteine, *N*,*O*-dimethyl hydroxylamine, chlorotrimethylsilane, chloromethyl methyl ether, sodium hydride (60% in mineral oil), benzyl bromide, triisopropylchlorosilane (TIPS-Cl), tributyltin hydride, copper(I) cyanide, *N*-bromosuccinimide (NBS), *N*-iodosuccinimide (NIS), magnesium, iodine, 4-pentyn-2-ol, chlorodiisopropylsilane, chloroplatinic acid hexahydrate, isopropanol, 3-buten-1-ol, bis(pinacolato)diboron, dioxane, tetrakis(triphenylphosphine)palladium, thallium ethoxide, diisobutylaluminum hydride (DIBAL-H, 1.0 M solution in hexanes), carbon tetrabromide, and triphenylphosphine were purchased from Aldrich and used without further purification. Zirconocene dichloride was purchased from Aldrich and heated to 80 °C under reduced pressure for 2 h prior to use. Zinc dust was activated prior to use by being placed on a Buchner funnel and then washed with 5% HCl several times, followed by thorough washings with DI H_2O, methanol, and Et_2O. 3-Chloroperbenzoic acid (mCPBA) was purified prior to use by dissolving in CH_2Cl_2 (~1g/30mL), washing with pH=7.5 1M phosphate buffer (3x100 mL) and brine, drying over $MgSO_4$, filtering through Celite and concentrating under reduced pressure. Flash column chromatography was performed using 60 Å silica gel (32-63 μm). ^{1}H NMR spectra were obtained at 500 MHz or 400 MHz and ^{13}C NMR spectra

at 125 or 100 MHz in $CDCl_3$ as indicated. Chemical shifts are reported in ppm referenced to $CHCl_3$ (7.24 ppm for ^1H) and $CDCl_3$ (77.0 ppm for ^{13}C). IR spectra were recorded as thin films on NaCl plates. Exact mass was obtained using electrospray ionization in positive ion mode (M+H, or M+Na, or M+Li) or in negative ion mode (M+Cl) as indicated.

(But-3-ynyloxy)(*tert*-butyl)dimethylsilane (12):

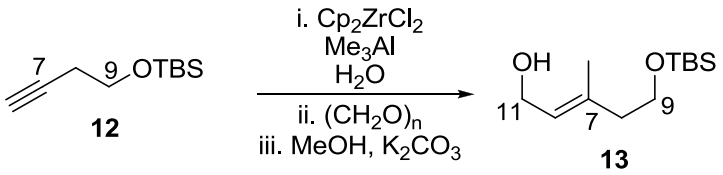


12

To a solution of 3-butyn-1-ol (10.0 g, 140. mmol, 1.0 equiv) in CH_2Cl_2 (180 mL) was added imidazole (12.0 g, 170 mmol, 1.2 equiv) followed by *tert*-butyldimethylsilylchloride (26.0 g, 160 mmol, 1.1 equiv) both upon brief exposure to air, at which point a white precipitate formed. After being allowed to stir overnight, the suspension was quenched with saturated $NaHCO_3$ (20 mL). The mixture was then diluted with DI H_2O and transferred to a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (2×15 mL) and the combined organics were dried over $MgSO_4$, filtered through Celite, and concentrated under reduced pressure to give the known ether **12** as a pale yellow oil (26.0 g, 140 mmol, ~99%).

IR (cm^{-1}): 3315, 2956, 2930, 2885, 2858, 1472, 1464. ^1H NMR (500 MHz, $CDCl_3$): δ 3.72 (t, *J* = 7.1, 2H), 2.38 (td, *J* = 7.1, 2.7, 2H), 1.94 (t, *J* = 2.7, 1H), 0.88 (s, 9H), 0.08 (s, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ 81.53, 69.26, 61.73, 25.88, 22.84, 18.33, -5.30.

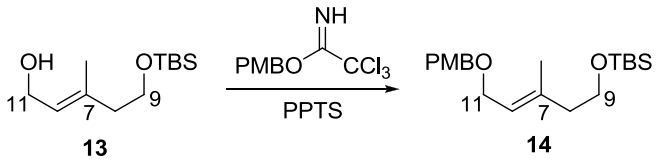
(*E*)-5-(*tert*-Butyldimethylsilyloxy)-3-methylpent-2-en-1-ol (13):



To a solution of pre-dried zirconocene dichloride (22.0 g, 76.0 mmol, 2.0 equiv) in CH_2Cl_2 (191 mL) was added trimethylaluminum (115 mL, 2.0 M solution in hexanes, 229 mmol, 6.0 equiv). The solution was stirred for 15 min, and then cooled (0 °C) and DI H_2O (0.690 mL, 38.0 mmol, 1.0 equiv) was carefully added by syringe. *Caution: Water must be added slowly as rapid gas evolution occurs!* The pale-yellow solution was allowed to stir for 0.5 h at 0 °C, then alkyne **12** (7.00 g, 38.0 mmol, 1.0 equiv) was added via cannula. The solution was allowed to warm to room temperature and stirred for 24 h, then re-cooled to 0 °C at which time prilled paraformaldehyde (5.70 g, 191 mmol, 5.0 equiv) was added by a powder addition funnel. The resulting suspension was allowed to stir at room temperature for 2 days and then was quenched with methanol. The addition of methanol resulted in the formation of a gel, which can be homogenized by the addition of Et_2O and saturated K_2CO_3 followed by rapid stirring for 1.5 h. The milky-white solution was then filtered through Celite, diluted with CH_2Cl_2, and then transferred to a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (4×20 mL), and the combined organics were dried over $MgSO_4$, filtered through Celite, and concentrated under reduced pressure to give a yellow oil. Purification by flash column chromatography on silica gel (5:1 hexanes/ethyl acetate) gave the known alcohol **13** as a clear, pale-yellow oil (6.90 g, 30 mmol, 79%).

IR (cm^{-1}): 3343, 2955, 2929, 2857, 1412. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.43 – 5.40 (m, 1H), 4.13 (d, *J* = 6.9, 2H), 3.67 (t, *J* = 7.0, 2H), 2.22 (t, *J* = 7.0, 2H), 2.15 (br s, 1H), 1.67 (s, 3H), 0.86 (s, 9H), 0.02 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.92, 125.17, 62.04, 59.33, 42.77, 25.92, 18.32, 16.68, -5.30.

(*E*)-*tert*-Butyl(5-(4-methoxybenzyloxy)-3-methylpent-3-enyloxy)dimethylsilane (14):



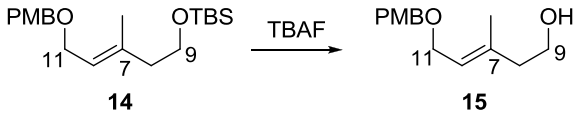
13 **14**

To a cooled (0 °C) solution of alcohol **13** (2.60 g, 11.0 mmol, 1.0 equiv) in 2:1 cyclohexane/CH_2Cl_2 (18 mL/9 mL) was added *p*-methoxybenzyl trichloroacetimidate[68] (4.70 g, 17.0 mmol, 1.5 equiv), followed by pyridinium *p*-toluene sulfonate (0.284 g, 1.1 mmol, 0.1 equiv). The solution was stirred at 0 °C for 15 min, and then allowed to warm to room temperature. After 20 h, the reaction was quenched with half-saturated $NaHCO_3$ (10 mL) and transferred to a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL) and the combined organics were dried over $MgSO_4$, filtered through Celite, and concentrated under reduced pressure. The crude material was then diluted with hexanes and a white precipitate crashed out of solution. This suspension was filtered through Celite and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (12:1 hexanes/ethyl acetate) gave the bis-protected ether **14** as a yellow oil (3.30 g, 9.4 mmol, 83%).

IR (cm^{-1}): 2954, 2929, 2856, 1613, 1513. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 – 7.23 (m, 2H), 6.89 – 6.82 (m, 2H), 5.38 – 5.34 (m, 1H), 4.41 (s, 2H), 3.97 (d, *J* =

6.7, 2H), 3.78 (s, 3H), 3.67 (t, *J* = 7.1, 2H), 2.23 (t, *J* = 7.1, 2H), 1.64 (s, 3H), 0.86 (s, 9H), 0.02 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.12, 137.37, 130.63, 129.39, 122.75, 113.73, 71.67, 66.23, 62.17, 55.27, 42.87, 25.94, 18.33, 16.94, -5.28.

(*E*)-5-(4-Methoxybenzyloxy)-3-methylpent-3-en-1-ol (15):

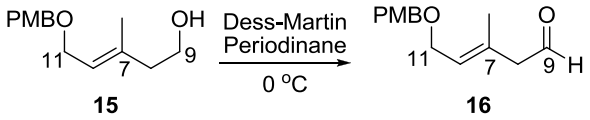


14 **15**

To a cooled (0 °C) solution of bis-protected ether **14** (3.30 g, 9.4 mmol, 1.0 equiv) in THF (47 mL) was added TBAF (14.0 mL, 1 M solution in THF, 14 mmol, 1.5 equiv) slowly via syringe. The reaction was allowed to slowly warm to room temperature and after 1.5 h was quenched with DI H_2O (10 mL) and saturated NH_4Cl (10 mL). After stirring for 5 min, the mixture was transferred to a separatory funnel and the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organics were washed with brine (1×15 mL), dried over $MgSO_4$, filtered through Celite, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (1:1 hexanes/ethyl acetate) provided the desired alcohol **15** (1.80 g, 7.50 mmol, 81%) as a colorless oil.

IR (cm^{-1}): 3405, 2935, 1612, 1586. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 – 7.21 (m, *J* = 9.1, 2H), 6.89 – 6.81 (m, 2H), 5.46 (t, *J* = 6.7, 1H), 4.42 (s, 2H), 3.99 (d, *J* = 6.7, 2H), 3.78 (s, 3H), 3.72 – 3.65 (m, 2H), 2.28 (t, *J* = 6.3, 1H), 1.65 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.19, 136.59, 130.43, 129.44, 123.82, 113.78, 71.95, 66.15, 60.24, 55.27, 42.57, 16.37.

(*E*)-5-(4-Methoxybenzyloxy)-3-methylpent-3-enal (16):

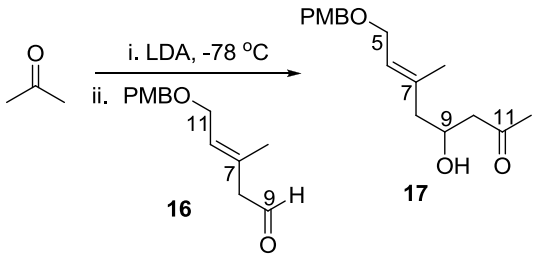


15 **16**

To a cooled (0 °C) solution of alcohol **15** (0.23 g, 0.952 mmol, 1.0 equiv) in CH_2Cl_2 (9.5 mL) was added Dess-Martin periodinane[69] (0.61 g, 1.43 mmol, 1.5 equiv) in one portion. The resulting white suspension was kept at 0 °C and allowed to stir overnight. Then the mixture was filtered through Celite, quenched with saturated 1:1 $Na_2S_2O_3$/$NaHCO_3$ (10 mL), and allowed to stir for at least 2 h at room temperature. The crude mixture was then transferred to a separatory funnel and the organic layer was washed with saturated $NaHCO_3$ (2×7 mL). The combined aqueous layers were then extracted with CH_2Cl_2 (3×7 mL) and the combined organics were then dried over $MgSO_4$, filtered through Celite, and concentrated under reduced pressure. Alkene migration was found to take place during purification by flash column chromatography on silica gel (CH_2Cl_2), therefore, the crude material was used directly in the next reaction without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.63 (t, *J* = 2.3, 1H), 7.28 – 7.24 (m, 2H), 6.88 – 6.84 (m, 2H), 5.56 – 5.52 (m, 1H), 4.43 (s, 2H), 4.03 (d, *J* = 6.6, 2H), 3.78 (s, 3H), 3.09 (d, *J* = 1.4, 2H), 1.68 (s, 3H).

(*E*)-4-Hydroxy-8-(4-methoxybenzyloxy)-6-methyloct-6-en-2-one (17):

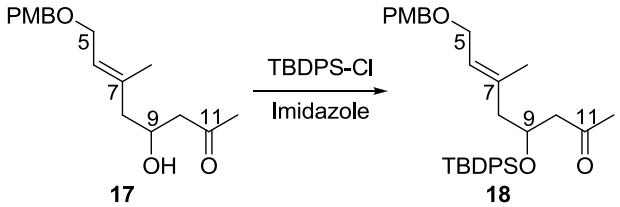


16 **17**

To a cooled (-78 °C) solution of diisopropylamine (1.64 mL, 11.5 mmol, 1.4 equiv) in THF (25 mL) was added *n*-butyllithium (7.9 mL, 1.46 M solution in hexanes, 1.4 equiv) dropwise via syringe. The reaction was allowed to stir for 15 mins, and then acetone (0.785 mL, 10.7 mmol, 1.3 equiv) was added via syringe. After stirring for another 30 mins at -78 °C, aldehyde **16** (1.93 g, 8.22 mmol, 1.0 equiv) in a small amount of THF was added to the reaction mixture via cannula. The reaction was allowed to stir for 40 mins and then was quenched by the addition of saturated NH_4Cl (20 mL). The solution was allowed to warm to room temperature and was then transferred to a separatory funnel. The aqueous phase was extracted with ethyl acetate (3×10 mL) and then the combined organics were dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. Purification by flash column chromatography (1:1 hexanes/ethyl acetate) provided the desired aldol adduct **17** (1.75 g, 6.0 mmol, 73%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 – 7.22 (m, 3H), 6.88 – 6.83 (m, 2H), 5.45 (t, *J* = 6.6, 1H), 4.42 (s, 2H), 4.23 – 4.13 (m, 1H), 4.04 – 3.95 (m, 2H), 3.78 (s, 3H), 2.80 (d, *J* = 3.1, 1H), 2.64 – 2.47 (m, 2H), 2.22 (dd, *J* = 13.6, 7.7, 1H), 2.18 – 2.09 (m, 4H), 1.66 (s, 3H).

(*E*)-4-(*tert*-Butyldiphenylsilyloxy)-8-(4-methoxybenzyloxy)-6-methyloct-6-en-2-one (18):

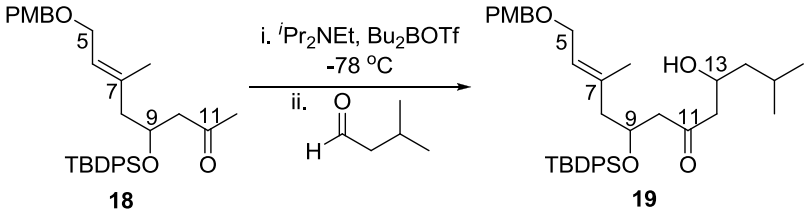


17 **18**

To a solution of **17** (1.35 g, 4.62 mmol, 1.0 equiv) in DMF (15.4 mL) was added imidazole (1.57 g, 23.1 mmol, 5.0 equiv) upon brief exposure to air. Then *tert*-butydiphenylsilylchloride (3.0 mL, 11.5 mmol, 2.5 equiv) was added dropwise via syringe, upon which a white precipitate formed. The reaction was allowed to stir overnight and was then quenched by the addition of saturated $NaHCO_3$ (15 mL). The crude mixture was transferred to a separatory funnel and the aqueous phase was extracted with ethyl acetate (3×10 mL). The combined organics were dried over $MgSO_4$, filtered through Celite and then concentrated under reduced pressure. Purification by flash column chromatography (6:1 hexanes/ethyl acetate) gave the protected product **18** (2.40 g, 4.52 mmol, 98%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 – 7.61 (m, *J* = 6.8, 0.9, 4H), 7.45 – 7.31 (m, 6H), 7.23 – 7.17 (m, 2H), 6.88 – 6.80 (m, 2H), 5.28 (t, *J* = 6.6, 1H), 4.34 (s, 2H), 4.34 – 4.28 (m, 1H), 3.85 (d, *J* = 6.6, 2H), 3.78 (s, 3H), 2.59 – 2.42 (m, 2H), 2.20 – 2.05 (m, 2H), 2.01 (s, 3H), 1.25 (s, 3H), 1.00 (s, 9H).

(*E*)-8-(*tert*-Butyldiphenylsilyloxy)-4-hydroxy-12-(4-methoxybenzyloxy)-2,10-dimethyldodec-10-en-6-one (19):

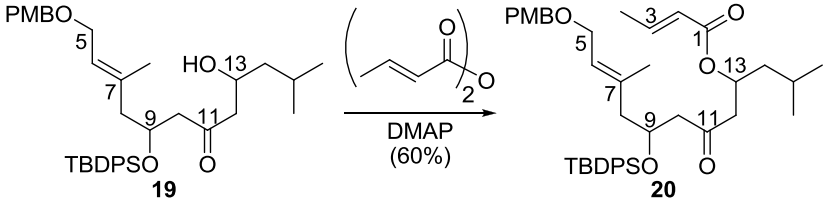


To a cooled (-78 °C) solution of **18** (2.40 g, 4.52 mmol, 1.0 equiv) and diisopropylethylamine (1.2 mL, 7.01 mmol, 1.55 equiv) in Et_2O (45 mL) was added dibutylboron triflate (6.33 mL, 1.0 M solution in toluene, 6.33 mmol, 1.4 equiv) dropwise via syringe. The reaction was allowed to stir for 30 mins and then a 1.0 M

solution of isovaleraldehyde (6.33 mL, 6.33 mmol, 1.4 equiv) in THF was added slowly via syringe pump over 1 h. After being allowed to stir for 2 h at -78 °C, the reaction was allowed to warm to 0 °C and then 32 mL of a 1:6 pH=7 buffer/MeOH solution was added via syringe. Next, 13.7 mL of a 1:2 30% H_2O_2/MeOH solution was added to the reaction via syringe. Finally, the reaction was then allowed to warm to room temperature and stir for 1 h, at which point it was transferred to a separatory funnel. The aqueous phase was extracted with Et_2O (2×10 mL) and then the combined organics were washed with saturated $NaHCO_3$ (1×10 mL) and brine (1×10 mL). The organics were then dried over $MgSO_4$, filtered through Celite and then concentrated under reduced pressure. Purification by flash column chromatography (5:1 hexanes/ethyl acetate) gave the desired aldol product **19** (2.56 g, 4.14 mmol, 92%).

Unless otherwise indicated, signals correspond to both diastereomers of the product. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 – 7.57 (m, 4H), 7.44 – 7.32 (m, 6H), 7.22 – 7.16 (m, 2H), 6.88 – 6.77 (m, 2H), 5.33 – 5.22 (m, 1H), 4.39 – 4.24 (m, 3H), 4.03 – 3.93 (m, 1H), 3.84 (d, *J* = 6.6, 2H), 3.77 (s, 3H), 2.98 (d, *J* = 3.5, 0.2H, minor diastereomer), 2.93 (d, *J* = 3.3, 0.6H, major diastereomer), 2.59 – 2.23 (m, 4H), 2.23 – 2.06 (m, 2H), 1.79 – 1.64 (m, 1H), 1.43 – 1.31 (m, 1H), 1.26 – 1.21 (m, 3H), 1.03 – 0.96 (m, 10H), 0.86 (d, *J* = 6.6, 6H).

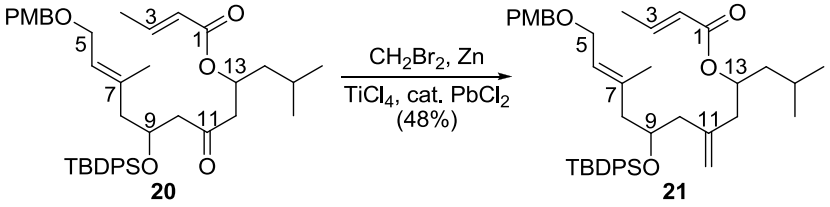
(*E*)-((*E*)-8-(*tert*-Butyldiphenylsilyloxy)-12-(4-methoxybenzyloxy)-2,10-dimethyl-6-oxododec-10-en-4-yl) but-2-enoate (20):



To a cooled (0 °C) solution of **19** (2.42 g, 3.93 mmol, 1.0 equiv) and CH_2Cl_2 (39 mL) was added crotonic anhydride (1.2 mL, 7.86 mmol, 2.0 equiv), followed by DMAP (0.720 g, 5.89 mmol, 1.5 equiv) upon brief exposure to air. The reaction was allowed to stir at 0 °C for 3 h and was then quenched the addition of saturated $NaHCO_3$ (30 mL). The crude mixture was then transferred to a separatory funnel and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL) and the combined organics were washed with DI H_2O (1×10 mL), dried over $MgSO_4$, filtered through Celite and then concentrated under reduced pressure. Purification by flash column chromatography (9:1 hexanes/ethyl acetate) provided the acylated product **20** (1.61 g, 2.36 mmol, 60%).

Unless otherwise indicated, signals correspond to both diastereomers of the product. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 – 7.64 (m, 4H), 7.46 – 7.32 (m, 6H), 7.25 – 7.19 (m, 2H), 6.97 – 6.89 (m, 1H), 6.89 – 6.83 (m, 2H), 5.82 – 5.72 (m, 1H), 5.37 – 5.24 (m, 2H), 4.40 – 4.28 (m, 4H), 3.87 (d, *J* = 6.6, 2H), 3.80 (s, 3H), 2.73 – 2.41 (m, 4H), 2.20 – 2.08 (m, 2H), 1.90 – 1.80 (m, 3H), 1.63 – 1.46 (m, 2H), 1.34 – 1.21 (m, 4H), 1.00 (s, *J* = 8.6, 9H), 0.93 – 0.85 (m, 6H).

(*E*)-((*E*)-8-(*tert*-Butyldiphenylsilyloxy)-12-(4-methoxybenzyloxy)-2,10-dimethyl-6-methylenedodec-10-en-4-yl) but-2-enoate (21):

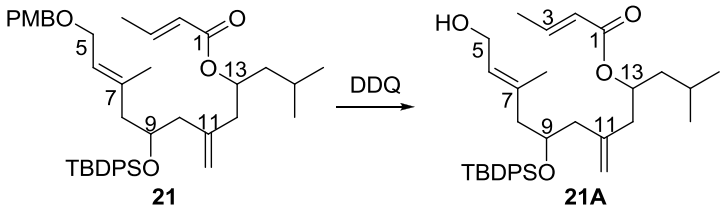


To a solution of zinc dust (0.086 g, 1.31 mmol, 9.0 equiv) in THF (1.5 mL) was added lead (II) chloride (4.06 mg, 0.015 mmol, 0.10 equiv) upon brief exposure to air, followed by dibromomethane (0.051 mL, 0.730 mmol, 5.0 equiv) dropwise via syringe. After being allowed the stir for 30 mins, the reaction was then cooled (0 °C) and a 1.0 M solution of titanium (IV) chloride (0.22 mL, 0.22 mmol, 1.5 equiv) in THF was added dropwise via a *glass-syringe*. Then the reaction was allowed to warm to room temperature and stir for 30 mins at which time a solution of **20** (0.100 g, 0.146 mmol, 1.0 equiv) in THF was added via cannula. The reaction was allowed to stir overnight, and then was diluted with Et_2O and DI H_2O and transferred to a separatory funnel containing saturated NH_4Cl (3 mL). The aqueous phase was extracted with Et_2O (2×5 mL), and the combined organics were washed with DI H_2O (1×5 mL), dried over $MgSO_4$, filtered through Celite and then concentrated under reduced pressured. Purification by flash column chromatography (10:1 hexanes/ethyl acetate) gave **21** (0.048 g, 0.070 mmol, 48%).

Unless otherwise indicated, signals correspond to both diastereomers of the product. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 – 7.62 (m, 4H), 7.44 – 7.30 (m, 6H), 7.23 – 7.18 (m, 3H), 6.94 – 6.80 (m, 3H), 5.78 – 5.68 (m, 1H), 5.32 (t, *J* = 6.1, 1H), 5.01 – 4.91 (m, 1H), 4.74 (d, *J* = 5.3, 3H), 4.35 (s, 2H), 3.99 – 3.90 (m, 1H), 3.88 (d,

J = 6.7, 2H), 3.78 (s, 3H), 2.20 – 1.99 (m, 5H), 1.96 – 1.86 (m, 1H), 1.83 (dd, *J* = 6.9, 1.7, 3H), 1.54 – 1.45 (m, 1H), 1.45 – 1.32 (m, 1H), 1.29 (s, 3H), 1.22 – 1.12 (m, 1H), 0.99 (s, 9H), 0.82 (dd, 6H).

(*E*)-((*E*)-8-(*tert*-Butyldiphenylsilyloxy)-12-hydroxy-2,10-dimethyl-6-oxododec-10-en-4-yl) but-2-enoate (21A):

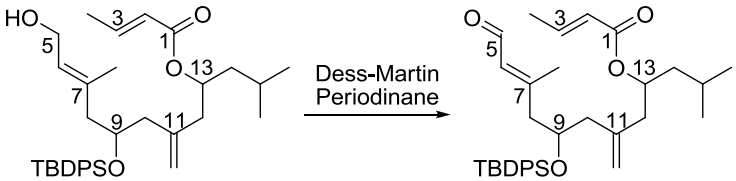


To a cooled (0 °C) solution of **21** (0.530 g, 0.78 mmol, 1.0 equiv) in 19:1 CH_2Cl_2/DI H_20 (18.4 mL/0.97 mL) was added DDQ (0.352 g, 1.55 mmol, 2.0 equiv) upon brief exposure to air. After being allowed to stir for 1.5 h at 0 °C, the reaction was quenched with the addition of saturated $NaHCO_3$ (10 mL) and then transferred to a separatory funnel. The aqueous phase was extracted with CH_2Cl_2 (3×7 mL) and then the combined organics were dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. Purification by flash column chromatography (7:1 hexanes/ethyl acetate) provided the free alcohol **21A** (0.348 g, 0.618 mmol, 80%).

Unless otherwise indicated, signals correspond to both diastereomers of the product. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.61 (m, 4H), 7.44 – 7.28 (m, 6H), 6.88 (dq, *J* = 13.8, 6.9, 1H), 5.74 (dd, *J* = 15.5, 1.7, 1H), 5.28 (t, *J* = 6.4, 1H), 4.98 – 4.89 (m, 1H), 4.76 (d, *J* = 4.6, 2H), 4.07 – 3.86 (m, 3H), 2.26 (dd, *J* = 14.2, 4.9, 1H), 2.16 – 2.00 (m, *J* = 29.1, 14.0, 7.1, 4H), 1.92 (dd, *J* = 13.8, 7.0, 1H), 1.83 (dt, *J* = 5.0,

2.5, 3H), 1.57 – 1.47 (m, 1H), 1.47 – 1.35 (m, 1H), 1.30 (s, 3H), 1.27 – 1.19 (m, 1H), 0.98 (s, *J* = 9.4, 9H), 0.82 (dd, *J* = 17.9, 6.6, 6H).

(*E*)-((*E*)-8-(*tert*-Butyldiphenylsilyloxy)-2,10-dimethyl-6,12-dioxododec-10-en-4-yl) but-2-enoate (22):

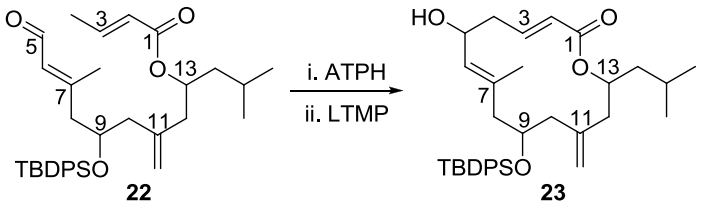


21A **22**

To a cooled (0 °C) solution of **21A** (0.348 g, 0.62 mmol, 1.0 equiv) in CH_2Cl_2 (6.2 mL) was added Dess-Martin periodinane[69] (0.315 g, 0.74 mmol, 1.2 equiv) upon brief exposure to air. After being allowed to stir for 2 h at 0 °C, the reaction was filtered through Celite and then quenched by the addition of saturated 1:1 $Na_2S_2O_3$/$NaHCO_3$ (7 mL) and allowed to stir for another 2 h. The crude mixture was then transferred to a separatory funnel and the aqueous phase was extracted with CH_2Cl_2 (3×5 mL). The combined organics were dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. Purification by flash column chromatography (10:1 hexanes/ethyl acetate) provided the desired aldehyde **22** (0.290 g, 0.52 mmol, 84%)

Unless otherwise indicated, signals correspond to both diastereomers of the product. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.84 (d, *J* = 8.1, 1H), 7.68 – 7.60 (m, 4H), 7.44 – 7.32 (m, 6H), 6.92 – 6.83 (m, 1H), 5.79 (d, *J* = 8.1, 1H), 5.72 (dd, *J* = 15.5, 1.7, 1H), 4.98-4.89 (m, 1H), 4.74 (d, *J* = 26.0, 2H), 4.06 – 3.95 (m, 1H), 2.36 – 2.10 (m, 4H), 2.00 (dd, *J* = 14.4, 7.3, 1H), 1.85 – 1.82 (m, 4H), 1.56 – 1.43 (m, 4H), 1.43 – 1.33 (m, 1H), 1.20 – 1.09 (m, 1H), 0.99 (s, 9H), 0.82 (dd, *J* = 15.0, 6.6, 6H).

(3*E*,7*E*)-10-(*tert*-Butyldiphenylsilyloxy)-6-hydroxy-14-isobutyl-8-methyl-12-methyleneoxacyclotetradeca-3,7-dien-2-one (23):

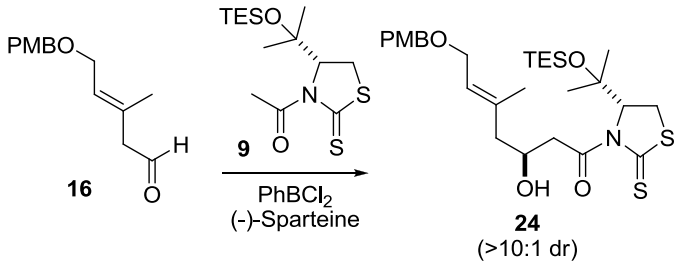


To a flask containing 2,6-diphenylphenol (0.290 g, 1.18 mmol, 6.6 equiv) was added toluene (2 mL) via cannula and then N_2 was bubbled through the solution for 15 mins. Trimethylaluminum (0.20 mL, 2.0 M solution in hexanes, 0.39 mmol, 2.2 equiv) was then added to the reaction solution dropwise via syringe. The pale yellow solution was allowed to stir for 30 mins at room temperature and then it was cooled (-78 °C), at which point a solution of **22** (0.100 g, 0.178 mmol, 1.0 equiv) in toluene (1.8 mL) was added to the reaction via cannula. This **22**/ATPH solution was then allowed to stir at -78 °C for 45 min. Meanwhile, to a separate cooled (-78 °C) solution of 2,2,6,6-tetramethylpiperidine (0.08 mL, 0.46 mmol, 2.6 equiv) in THF (1.2 mL) was added *n*-butyllithium (0.295 mL, 1.51 M solution in hexanes, 0.45 mmol, 2.5 equiv) dropwise via syringe. This LTMP solution was allowed to stir for 30 mins at -78 °C (during which the solution changed from clear to cloudy pale yellow), at which point more toluene (9 mL) was added to the solution via cannula. Then the **22**/ATPH solution was added to the LTMP solution slowly via cannula over 45 mins. The reaction was allowed to stir for 4.5 h and was then quenched by the addition of isopropanol (1 mL), and then saturated NH_4Cl (10 mL) was added quickly thereafter. The biphasic mixture was allowed to warm to room temperature, then filtered through Celite and transferred to a separatory funnel. The aqueous phase was

extracted with Et_2O (3×5 mL), and then the combined organics were washed with brine (1×5 mL), dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. Purification by flash column chromatography (6:1 hexanes/ethyl acetate) provided a mixture of products which needed to be separated via HPLC. HPLC runs were executed with a micro-porasil column, injecting 100 μL of a 1 mg/100 μL solution per run, flow rate of 1.5 mL/min and with 5:1 hexanes/ethyl acetate as the eluent.

One isolated product's ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 – 7.65 (m, 4H), 7.46 – 7.33 (m, 6H), 6.48 (dt, *J* = 16.2, 8.2, 1H), 5.51 (d, *J* = 15.8, 1H), 5.01 – 4.83 (m, *J* = 17.2, 2H), 4.73 (s, 3H), 4.61 (d, *J* = 9.7, 1H), 4.40 – 4.27 (m, *J* = 9.4, 1H), 3.94 – 3.78 (m, 1H), 2.69 – 2.55 (m, 1H), 2.29 – 2.20 (m, 3H), 2.12 – 1.95 (m, 7H), 1.56 (s, *J* = 1.2, 3H), 0.99 (s, 9H), 0.87 (dd, *J* = 6.6, 3.1, 6H).

(*S*,*E*)-3-Hydroxy-7-(4-methoxybenzyloxy)-5-methyl-1-((*R*)-2-thioxo-4-(2-(tri-ethylsilyloxy)propan-2-yl)thiazolidin-3-yl)hept-5-en-1-one (24):

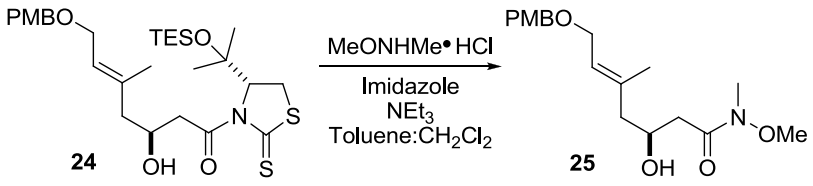


To a cooled (0 °C) solution of thiazolidinethione **9**[8-10] (0.840 g, 2.52 mmol, 1.3 equiv) in CH_2Cl_2 (11 mL) was added dichlorophenyl borane (0.33 mL, 2.52 mmol, 1.3 equiv) dropwise via syringe. The resulting yellow-orange solution was allowed to stir at 0 °C for 10 min, then (–)-sparteine (1.2 mL, 5.04 mmol, 2.6 equiv) was slowly added via syringe. The reaction was allowed to warm to room

temperature and stir for a total of 45 min, at which time the solution was then cooled to -78 °C and aldehyde **16** (0.455 g, 1.94 mmol, 1.0 equiv) was added. After stirring for 2 h at -78 °C, the solution was allowed to warm to 0 °C slowly over 18 h. The reaction was then diluted with an equal volume of hexanes and quenched at 0 °C with 30% H_2O_2 (6 mL). Vigorous stirring at 0 °C was continued for 20 min. The solution was diluted further with 4:1 hexanes/CH_2Cl_2, and then transferred to a separatory funnel. The organic phase was extracted with DI H_2O (1×5 mL) and brine (1×5 mL), dried over $MgSO_4$, filtered through Celite, and concentrated under reduced pressure to give **24** as a bright-yellow oil. Due to decomposition during flash column chromatography, the crude material was used directly in the next reaction. However, a portion of this material was purified by flash column chromatography (4:1 hexanes:ethyl acetate) using neutral silica gel.

^{1}H NMR (500 MHz): δ 7.26 – 7.22 (m, 2H), 6.88 – 6.84 (m, 2H), 5.50 – 5.44 (m, 1H), 5.30 (dd, *J* = 1.0, 8.1, 1H), 4.42 (s, 2H), 4.22 – 4.16 (m, 1H), 3.98 (d, *J* = 6.6, 2H), 3.78 (s, 3H), 3.48 (dd, , *J* = 9.3, 17.6, 1H), 3.45 (dd, 1H, *J* = 8.1, 11.4 Hz), 3.38 (dd, 1H, *J*=1.0, 11.5 Hz), 3.29 (dd, *J* = 2.9, 17.3, 1H), 3.14 (d, *J* = 4.3, 1H), 2.26 (dd, *J* = 7.5, 13.6, 2H), 1.66 (s, 3H), 1.28 (s, 3H), 1.24 (s, 3H), 0.96 – 0.90 (m, 9H), 0.62 – 0.56 (m, 6H).

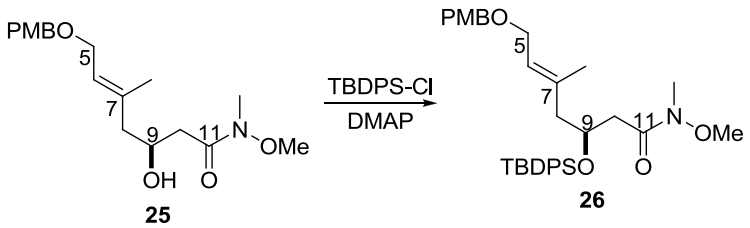
(*S*,*E*)-3-Hydroxy-N-methoxy-7-(4-methoxybenzyloxy)-N,5-dimethylhept-5-enamide (25):



To a solution of crude **24** (1.10 g, 1.94 mmol, 1.0 equiv) in 1:1 toluene/ CH_2Cl_2 (9.7 mL/9.7 mL) was added imidazole (0.791 g, 11.6 mmol, 6.0 equiv), triethylamine (0.82 mL, 5.81 mmol, 3.0 equiv), and *N*,*O*-dimethyl hydroxylamine (0.567 g, 5.81 mmol, 3.0 equiv). The reaction was allowed to stir at room temperature for 4 h. The reaction was then diluted with CH_2Cl_2 and quenched with saturated $NaHCO_3$, and transferred to a separatory funnel. The aqueous phase was extracted with CH_2Cl_2 (3×10 mL), and the combined organic phases were dried over $MgSO_4$, filtered through Celite, and concentrated under reduced pressure. Purification by flash column chromatography (2:3 hexanes/ethyl acetate) gave **25** (0.516 g, 1.53 mmol, 79% over two steps) as a yellow oil.

IR (cm^{-1}): 3442, 2934, 2855, 1648, 1613, 1514. ^{1}H NMR (500 MHz): δ 7.28 – 7.24 (m, *J* = 4.2, 2H), 6.91 – 6.84 (m, 2H), 5.50 (t, *J* = 6.2, 1H), 4.44 (s, 2H), 4.28 – 4.18 (m, 1H), 4.07 – 3.97 (m, 2H), 3.81 (s, 3H), 3.67 (s, 3H), 3.64 (br d, *J* = 1.7, 1H), 3.20 (s, 3H), 2.67 (d, *J* = 16.5, 1H), 2.48 (dd, *J* = 16.7, 9.3, 1H), 2.33 (dd, *J* = 13.6, 7.6, 1H), 2.21 (dd, *J* = 13.6, 5.9, 1H), 1.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.53, 159.08, 136.66, 130.44, 129.37, 124.24, 113.68, 77.32, 77.00, 76.68, 71.74, 66.08, 65.99, 61.20, 55.22, 46.68, 37.74, 31.80, 16.66. $[\alpha]^{27}_D$ = +16.0 (*c* 1.13, CH_2Cl_2).

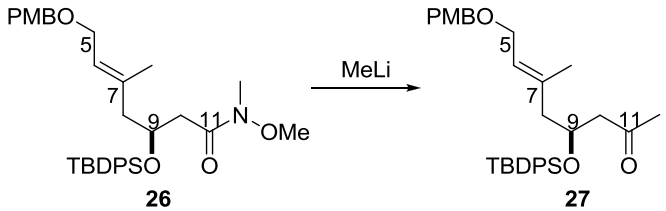
(*S*,*E*)-*N*-Methoxy-7-(4-methoxybenzyloxy)-N,5-dimethyl-3-(triisopropylsilyloxy) hept-5-enamide (26):



To a solution of **25** (0.050 g, 0.17 mmol, 1.0 equiv) in DMF (0.9 mL) was added imidazole (0.023 g, 0.34 mmol, 2.0 equiv) upon brief exposure to air. Then TBDPS-Cl (0.06 mL, 0.22 mmol, 1.3 equiv) was added dropwise via syringe, upon which a white precipitate formed. The reaction was allowed to stir overnight and was then quenched by the addition of saturated $NaHCO_3$ (3 mL). The crude mixture was transferred to a separatory funnel and the aqueous phase was extracted with CH_2Cl_2 (3×3 mL). The combined organics were dried over $MgSO_4$, filtered through Celite and then concentrated under reduced pressure. Purification by flash column chromatography (6:1 hexanes/ethyl acetate) gave the protected product **26** (0.089 g, 0.168 mmol, 98%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 – 7.65 (m, 6H), 7.43 – 7.29 (m, 4H), 7.23 – 7.16 (m, 2H), 6.87 – 6.79 (m, 2H), 5.30 (t, *J* = 6.1, 1H), 4.47 – 4.37 (m, 1H), 4.33 (s, 3H), 3.84 (d, *J* = 6.6, 2H), 3.77 (s, 3H), 3.58 (s, 3H), 3.09 (s, 3H), 2.74 – 2.62 (m, 1H), 2.42 (dd, *J* = 15.2, 4.9, 1H), 2.16 (d, *J* = 6.6, 2H), 1.20 (s, 3H), 0.99 (d, *J* = 6.3, 9H).

(*S*,*E*)-4-(*tert*-Butyldiphenylsilyloxy)-8-(4-methoxybenzyloxy)-6-methyloct-6-en-2-one (27):



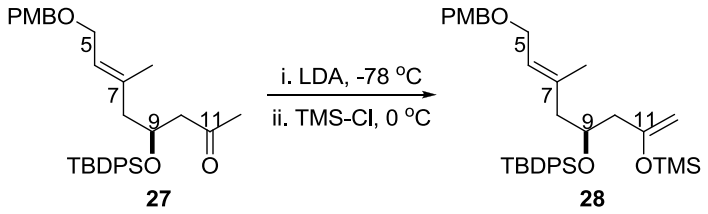
26 **27**

To a cooled (0 °C) solution of **26** (0.168 g, 0.29 mol, 1.0 equiv) in Et_2O (2.9 mL) was added methyllithium (0.37 mL, 1.6 M solution in Et_2O, 0.58 mmol, 2.0 equiv) dropwise via syringe. The reaction was allowed to stir for 45 mins at 0 °C and

was then quenched by the addition of saturated NH_4Cl (4 mL) and allowed to warm to room temperature. The crude mixture was transferred to a separatory funnel and the aqueous phase was extracted with CH_2Cl_2 (3×3 mL). The combined organics were dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. Purification by flash column chromatography (6:1 hexanes/ethyl acetate) gave the desired ketone **27** (0.135 g, 0.25 mmol, 87%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 – 7.61 (m, *J* = 6.8, 0.9, 4H), 7.45 – 7.31 (m, 6H), 7.23 – 7.17 (m, 2H), 6.88 – 6.80 (m, 2H), 5.28 (t, *J* = 6.6, 1H), 4.34 (s, 2H), 4.34 – 4.28 (m, 1H), 3.85 (d, *J* = 6.6, 2H), 3.78 (s, 3H), 2.59 – 2.42 (m, 2H), 2.20 – 2.05 (m, 2H), 2.01 (s, 3H), 1.25 (s, 3H), 1.00 (s, 9H).

(*S*,*E*)-6-(4-(4-Methoxybenzyloxy)-2-methylbut-2-enyl)-2,2,9,9-tetramethyl-4-methylene-8,8-diphenyl-3,7-dioxa-2,8-disiladecane (28):



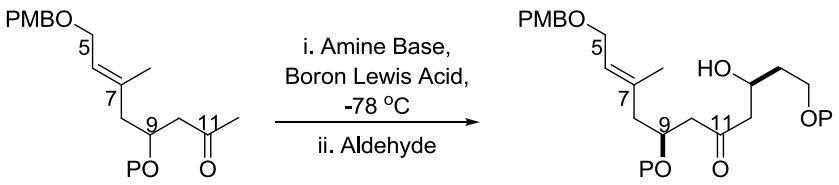
27 **28**

To a cooled (0 °C) solution of diisopropylamine (0.04 mL, 0.258 mmol, 1.6 equiv) in THF (0.8 mL) was added *n*-butyllithium (0.16 mL, 1.47 M solution in hexanes, 0.242 mmol, 1.5 equiv) dropwise via syringe. The solution of LDA was allowed to stir at 0 °C for 30 mins and was then cooled (-78 °C), at which time a solution of **27** (0.086 g, 0.161 mmol, 1.0 equiv) and chlorotrimethylsilane (0.03 mL, 0.242 mmol, 1.5 equiv) in THF (0.5 mL) was added via cannula. The reaction was allowed to stir at -78 °C for 45 mins, then allowed to warm to 0 °C and was then quenched by the addition of saturated $NaHCO_3$ (3 mL). The crude mixture was

transferred to a separatory funnel and the organic phase was washed with $NaHCO_3$ (3×3 mL), and then the combined aqueous was extracted with hexanes (3×3 mL). The combined organics were dried over $MgSO_4$, filtered through Celite and then concentrated under reduced pressure to give the enol ether **28** (0.087 g, 0.144 mmol, 90%). Upon purification, the enol ether was found to revert back to starting material and therefore, flash column chromatography was avoided.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 – 7.62 (m, 4H), 7.42 – 7.29 (m, 6H), 7.23 – 7.20 (m, 2H), 6.87 – 6.80 (m, 2H), 5.34 (t, *J* = 6.2, 1H), 4.36 (s, 2H), 4.10 – 4.02 (m, 1H), 3.96 (d, *J* = 1.5, 2H), 3.88 (qd, *J* = 11.9, 6.7, 2H), 3.78 (s, 3H), 2.25 – 2.04 (m, 4H), 1.26 (s, 3H), 1.00 (s, 9H), 0.09 – 0.05 (m, 9H).

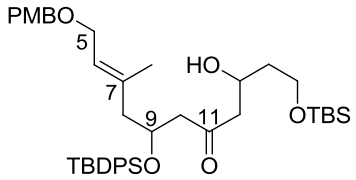
General 1,5-*Anti* Aldol Reaction Procedure:



To a cooled (-78 °C) solution of the ketone (0.160 mmol, 1.0 equiv) and the amine base (0.045 mL, 0.256 mmol, 1.6 equiv) in Et_2O (1.6 mL) was added the boron Lewis acid (0.24 mL, 1.0 M solution in toluene, 0.24 mmol, 1.5 equiv) dropwise via syringe. The reaction was allowed to stir for 30 mins and then a solution of the aldehyde (0.24 mL, 1.0 M in THF, 0.24 mmol, 1.5 equiv) in THF was added slowly via syringe pump over 1 h. After being allowed to stir for 2 h at -78 °C, the reaction was allowed to warm to 0 °C and then 1.2 mL of a 1:6 pH=7 buffer/MeOH solution was added via syringe. Next, 0.5 mL of a 1:2 30% H_2O_2/MeOH solution was added to the reaction via syringe. Finally, the reaction was then allowed to warm to room temperature and stir for 1 h, at which point it was transferred to a separatory funnel.

The aqueous phase was extracted with Et_2O (2×5 mL) and then the combined organics were washed with saturated $NaHCO_3$ (1×5 mL) and brine (1×5 mL). The organics were then dried over $MgSO_4$, filtered through Celite and then concentrated under reduced pressure. Purification by flash column chromatography gave the desired aldol product.

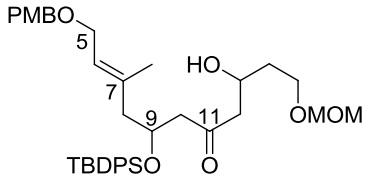
(*E*)-9-Hydroxy-5-(4-(4-methoxybenzyloxy)-2-methylbut-2-enyl)-2,2,13,13,14,14-hexamethyl-3,3-diphenyl-4,12-dioxa-3,13-disilapentadecan-7-one:



Purification by flash column chromatography using 1:1 hexanes/ethyl acetate gave a mixture of aldol product diastereomers.

Unless otherwise indicated, ^{1}H NMR signals correspond to both diastereomers of the product. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.61 (m, 4H), 7.43 – 7.32 (m, 6H), 7.22 – 7.16 (m, 2H), 6.87 – 6.80 (m, 2H), 5.28 (t, *J* = 6.6, 1H), 4.38 – 4.27 (m, 3H), 4.18 – 4.08 (m, 1H), 3.84 (d, *J* = 6.6, 2H), 3.82 – 3.69 (m, 5H), 3.47 (d, *J* = 2.6, 1H), 2.61 – 2.37 (m, 4H), 2.22 – 2.02 (m, 2H), 1.65 – 1.47 (m, 2H), 1.22 (s, 3H), 0.99 (s, 9H), 0.91 – 0.83 (m, 9H), 0.09 – -0.01 (m, *J* = 1.3, 6H).

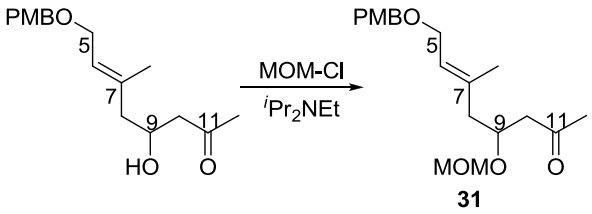
(*E*)-7-Hydroxy-11-(4-(4-methoxybenzyloxy)-2-methylbut-2-enyl)-14,14-dimethyl-13,13-diphenyl-2,4,12-trioxa-13-silapentadecan-9-one:



Purification by flash column chromatography using 2:1 hexanes/ethyl acetate gave a mixture of aldol product diastereomers.

Unless otherwise indicated, ^{1}H NMR signals correspond to both diastereomers of the product. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 – 7.61 (m, 4H), 7.44 – 7.32 (m, 6H), 7.23 – 7.17 (m, 2H), 6.87 – 6.79 (m, 2H), 5.28 (t, *J* = 6.5, 1H), 4.58 (s, 0.6H, minor diastereomer), 4.58 (s, 1.4H, major diastereomer), 4.38 – 4.26 (m, 3H), 4.17 – 4.05 (m, 1H), 3.84 (d, *J* = 6.6, 2H), 3.77 (s, 3H), 3.68 – 3.54 (m, 2H), 3.33 (s, 3H), 3.21 (d, *J* = 3.3, 0.3H, minor diastereomer), 3.17 (d, *J* = 3.1, 0.7H, major diasteromer), 2.57 – 2.35 (m, 4H), 2.21 – 2.06 (m, 2H), 1.70 – 1.55 (m, 2H), 1.23 (s, 3H), 1.02 – 0.96 (m, 9H).

(*E*)-8-(4-Methoxybenzyloxy)-4-(methoxymethoxy)-6-methyloct-6-en-2-one (31):



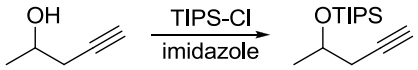
31

To a cooled (0 °C) solution of alcohol (0.41 g, 1.41 mmol, 1.0 equiv) in CH_2Cl_2 (2.8 mL) was added diisopropylethylamine (0.61 mL, 3.53 mmol, 2.5 equiv) and chloromethyl methyl ether (0.21 mL, 2.82 mmol, 2.0 equiv) both dropwise via syringe. The reaction was allowed to warm to room temperature and stir overnight, at which time the dark orange solution was then diluted with CH_2Cl_2 (3 mL) and transferred to a separatory funnel. The organic phase was washed with 5% aqueous HCl (3×5 mL), and then the combined organics were dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. Purification by flash column

chromatography (2:1 hexanes/ethyl acetate) gave the desired protected alcohol **31** (0.41 g, 1.21 mmol, 86%).

^{1}H NMR (500 MHz, $CDCl_3$): δ7.28 – 7.17 (m, 2H), 6.91 – 6.81 (m, 2H), 5.42 (t, *J* = 7.5, 1H), 4.61 (q, *J* = 6.9, 2H), 4.40 (s, 2H), 4.24 – 4.16 (m, 1H), 3.96 (d, *J* = 6.6, 2H), 3.78 (s, 3H), 3.30 (s, 3H), 2.65 (dd, *J* = 16.5, 7.8, 1H), 2.50 (dd, *J* = 16.5, 4.4, 1H), 2.37 (dd, *J* = 13.4, 5.9, 1H), 2.23 – 2.07 (m, 4H), 1.65 (s, 3H).

Triisopropyl(pent-4-yn-2-yloxy)silane (36):

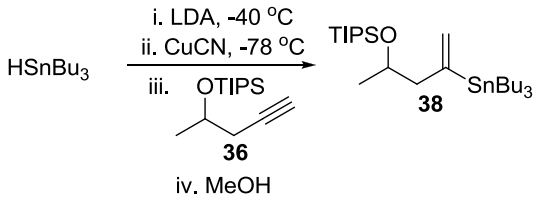


36

To a solution of 4-pentyn-2-ol (1.0 mL, 10.6 mmol, 1.0 equiv) in CH_2Cl_2 (13.3 mL) was added triisopropylchlorosilane (2.9 mL, 13.8 mmol, 1.3 equiv) dropwise via syringe. Imidazole (1.08 g, 15.9 mmol, 1.5 equiv) was then added upon brief exposure to air, upon which a white precipitate formed. The reaction was allowed to stir overnight, at which time it was quenched by the addition of saturated $NaHCO_3$ (10 mL). The crude mixture was then transferred to a separatory funnel, and the aqueous phase was extracted with CH_2Cl_2 (3×5 mL), and then combined organics were dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. Purification by flash column chromatography (hexanes) provided the alkyne **36** (2.08 g, 8.63 mmol, 81%) as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.12 – 3.98 (m, 1H), 2.47 – 2.35 (m, 1H), 2.25 (ddd, *J* = 16.5, 8.1, 2.7, 1H), 1.96 (t, *J* = 2.7, 1H), 1.28 (d, *J* = 6.0, 3H), 1.12 – 0.97 (m, 21H).

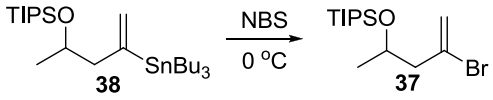
Triisopropyl(4-(tributylstannyl)pent-4-en-2-yloxy)silane (38):



To a cooled (0 °C) solution of diisopropylamine (0.74 mL, 5.20 mmol, 2.5 equiv) in THF (21 mL) was added *n*-butyllithium (3.4 mL, 1.52 M solution in hexanes, 5.20 mmol, 2.5 equiv) dropwise via syringe. The solution of LDA was allowed to stir at 0 °C for 20 mins, and then tributyltin hydride (1.3 mL, 4.78 mmol, 2.3 equiv) was added dropwise via syringe. The pale yellow solution was allowed to stir for 1 h, at which point it was then cooled (-40 °C) via an acetonitrile/dry ice bath. The dark orange/brown solution was allowed to stir at -40 °C for 30 mins at which point it was cooled (-78 °C) and then methanol (0.14 mL, 3.33 mmol, 1.6 equiv) was added via syringe, followed by a solution of **36** (0.500 g, 2.1 mmol, 1.0 equiv) in THF (2 mL) was added to the reaction via cannula. The solution was allowed to stir for 2 h, and then methanol (3.9 mL, 96.0 mmol, 46 equiv) was added via syringe, and the reaction was allowed to warm to 0 °C and stir for another 30 mins. The reaction was then quenched by the addition of 9:1 saturated NH_4Cl/NH_4OH (10 mL), and the black crude mixture was transferred to a separatory funnel. The aqueous phase was extracted with Et_2O (3×10 mL), and then the combined organics were dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure to give the vinyl tin species **38**. Purification by flash column chromatography was found to reduce the tin to give the undesired terminal alkene, and therefore the crude material

(1.81 g, 164% - excess yield due to by-products) was used directly in the next reaction.

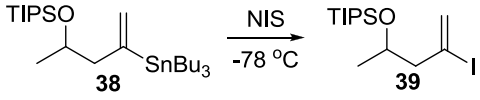
(4-Bromopent-4-en-2-yloxy)triisopropylsilane (37):



To a cooled (0 °C) solution of crude **38** (1.81 g, 3.41 mmol, 1.0 equiv – note: a portion of this crude material was by-products from the previous reaction) in CH_2Cl_2 (34 mL) was added *N*-bromosuccinimide (0.758 g, 4.26 mmol, 1.25 equiv) in one portion upon brief exposure to air. The orange solution was allowed to stir for 1 h at 0 °C, at which point the reaction was quenched by the addition of saturated Na_2SO_3 (10 mL) and allowed to warm to room temperature. The crude solution was then transferred to a separatory funnel, and the organic phase was washed with Na_2SO_3 (2×7 mL), and 1M NaOH (3×7 mL). The combined aqueous phases were then extracted with Et_2O (3×7 mL), and then the combined organics were dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. Purification by flash column chromatography (hexanes) provided the desired vinyl bromide **37** (0.53 g, 1.64 mmol, 79% - based on theoretical yield of the previous reaction).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.60 (s, 1H), 5.41 (s, 1H), 4.27 – 4.17 (m, 1H), 2.68 (dd, *J* = 14.0, 5.4, 1H), 2.42 (dd, *J* = 13.9, 7.4, 1H), 1.18 (d, *J* = 6.0, 4H), 1.07 – 1.04 (m, 21H).

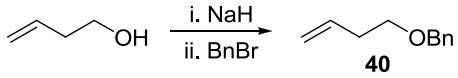
(4-Iodopent-4-en-2-yloxy)triisopropylsilane (39):



Vinyl iodide **39** was prepared in the same method as vinyl bromide **37**, except that *N*-iodosuccinimide (1.5 equiv) was used and the reaction was allowed to take place at -78 °C (warmer temperatures produced the trans-substituted alkenyliodide). Vinyl tributyltin **38** (1.85 g, 3.48 mmol – note: a significant portion of crude material was by-products from the previous reaction, at most only 0.360 g, 0.678 mmol, of this material is **38**) gave the vinyl iodide (0.212 g, 0.576 mmol, 85% - based on theoretical yield of the previous reaction).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.06 (s, 1H), 5.74 (s, 1H), 4.24 – 4.09 (m, 1H), 2.67 (dd, *J* = 13.8, 5.1, 1H), 2.36 (ddd, *J* = 13.9, 7.5 1H), 1.16 (d, *J* = 6.0, 3H), 1.07 – 1.05 (m, 21H).

((But-3-enyloxy)methyl)benzene (40)[70]**:**

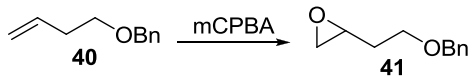


40

To a cooled (0 °C) solution of washed sodium hydride (hexanes, 3×10 mL) (1.85 g, 60% in mineral oil, 46.3 mmol, 1.7 equiv) in THF (62 mL) was added 3-buten-1-ol (2.4 mL, 27.7 mmol, 1.0 equiv) dropwise via syringe. The reaction was allowed to warm to room temperature and stir for 1 h, and then benzyl bromide (4.0 mL, 33.3 mmol, 1.2 equiv) was added dropwise via syringe. The mixture was allowed to stir overnight, at which time it was then quenched by the addition of brine (30 mL). The crude mixture was transferred to a separatory funnel and the aqueous phase was extracted with Et_2O (3×10 mL), and then the combined organics were dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. Distillation under high vac (bp ~95 °C) provided the known benzyl alcohol **40** (4.25 g, 26.2 mmol, 94%) as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 – 7.20 (m, 5H), 5.91 – 5.74 (m, 1H), 5.16 – 4.95 (m, 2H), 4.51 (s, 2H), 3.51 (t, *J* = 6.8, 2H), 2.49 – 2.22 (m, 2H).

2-(2-(benzyloxy)ethyl)oxirane (41)[70]:

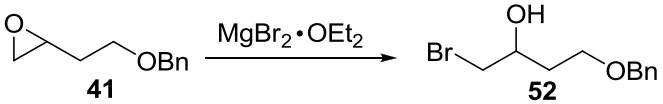


40 **41**

To a cooled (0 °C) solution of **41** (4.50 g, 27.7 mmol, 1.0 equiv) in CH_2Cl_2 (92 mL) was added mCPBA (9.57 g, 55.5 mmol, 2.0 equiv) upon brief exposure to air. The reaction was allowed to warm to room temperature and then stir overnight, at which time it was quenched by the addition of saturated $NaHCO_3$ (50 mL). The crude mixture was transferred to a separatory funnel and the organic phase was washed with saturated $NaHCO_3$ (2×10 mL) and then the combined aqueous phases were extracted with CH_2Cl_2 (1×10 mL). The combined organics were dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. Flash column chromatography (5:1 hexanes/ethyl acetate provided the known epoxide **41** (3.59 g, 20.14 mmol, 73%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 – 7.21 (m, 5H), 4.52 (s, 2H), 3.69 – 3.52 (m, 2H), 3.13 – 2.99 (m, 1H), 2.82 – 2.72 (m, 1H), 2.51 (dd, *J* = 5.0, 2.7, 1H), 1.90 (dddd, *J* = 14.3, 7.2, 6.2, 4.7, 1H), 1.76 (ddd, *J* = 14.4, 12.0, 6.0, 1H).

4-(Benzyloxy)-1-bromobutan-2-ol (52):



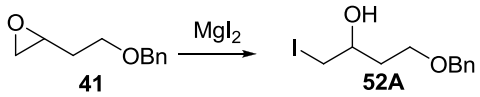
41 **52**

To a solution of **41** (0.100 mg, 0.56 mmol, 1.0 equiv) in Et_2O (5.6 mL), was added magnesium bromide ethyl etherate (0.362 g, 1.40 mmol, 2.5 equiv) upon brief exposure to air. After 10 mins the reaction was quenched by the addition of saturated

$NaHCO_3$ (5 mL), upon which a white precipitate formed. The crude mixture was transferred to a separatory funnel and then the aqueous phase was extracted with ethyl acetate (3×3 mL). The combined organics were washed with DI H_2O (1×3 mL), dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. Purification by flash column chromatography (5:1 hexanes/ethyl acetate) gave the desired bromo-halohydrin **52** (0.125 g, 0.48 mmol, 86%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 – 7.25 (m, 5H), 4.51 (s, 2H), 4.06 – 3.96 (m, 4.1, 1H), 3.67 (dddd, *J* = 33.2, 9.4, 6.8, 4.6, 2H), 3.43 (ddd, *J* = 16.5, 10.3, 5.5, 2H), 3.10 (d, *J* = 4.0, 1H), 1.97 – 1.78 (m, 2H).

4-(Benzyloxy)-1-iodobutan-2-ol (52A):

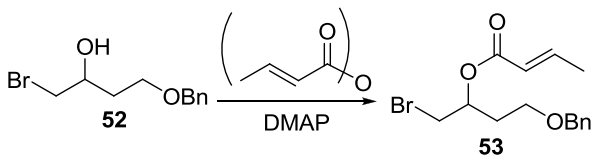


41 **52A**

To a suspension of magnesium (0.341 g, 14.0 mmol, 5.0 equiv) in Et_2O (14 mL) was added iodine (1.78 g, 7.01 mmol, 2.5 equiv) upon brief exposure to air. The flask was then placed in a sonicator until the suspension decolored. Then a solution of epoxide **41** (0.500 g, 2.81 mmol, 1.0 equiv) in Et_2O (14 mL) was added to the reaction suspension via cannula. After 5 mins the reaction was quenched by the addition of saturated $NaHCO_3$ (20 mL), upon which a white precipitate formed. The crude mixture was transferred to a separatory funnel (leaving remaining magnesium behind), and the aqueous phase was extracted with ethyl acetate (3×10 mL). The combined organics were washed with DI H_2O (1×10 mL), dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. Purification by flash column chromatography (5:1 hexanes/ethyl acetate) provided the iodo-halohydrin **52A** (0.739 g, 2.41 mmol, 86%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 – 7.26 (m, 5H), 4.50 (s, 2H), 3.86 – 3.74 (m, 1H), 3.67 (dddd, *J* = 11.8, 9.5, 6.9, 4.4, 2H), 3.26 (ddd, *J* = 16.2, 10.1, 5.5, 2H), 3.14 (d, *J* = 3.9, 1H), 2.00 – 1.77 (m, 2H).

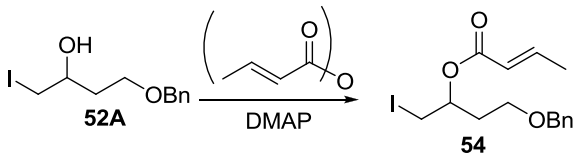
(*E*)-4-(Benzyloxy)-1-bromobutan-2-yl but-2-enoate (53):



To a cooled (0 °C) solution of **52** (0.040 g, 0.15 mmol, 1.0 equiv) in CH_2Cl_2 (1.5 mL) was added crotonic anhydride (0.045 mL, 0.305 mmol, 2.0 equiv) dropwise via syringe. DMAP (0.047 g, 0.038 mmol, 2.5 equiv) was then added upon brief exposure to air. The reaction was then allowed to stir at 0 °C overnight, at which time it was quenched by the addition of saturated $NaHCO_3$ and transferred to a separatory funnel. The aqueous phase was extracted with CH_2Cl_2 (3×3 mL), and then the combined organics were dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. Purification by flash column chromatography (15:1 hexanes/ethyl acetate) provided the alkyl bromide **53** (0.038 g, 0.12 mmol, 76%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 – 7.25 (m, 5H), 6.99 (dq, *J* = 15.5, 6.9, 1H), 5.82 (dq, *J* = 15.5, 1.7, 1H), 4.97 – 4.82 (m, 1H), 4.46 (s, 2H), 3.54 – 3.47 (m, 2H), 3.45 (dd, *J* = 10.7, 4.8, 1H), 3.31 (dd, *J* = 10.7, 4.9, 1H), 2.01 – 1.94 (m, 6.1, 2H), 1.87 (dd, *J* = 6.9, 1.7, 3H).

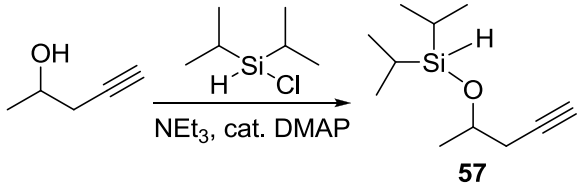
(E)-4-(benzyloxy)-1-iodobutan-2-yl but-2-enoate (53):



Alkyl iodide **54** was prepared in the same method as alkyl bromide **53**. Iodohalohydrin **52A** (0.148 g, 0.48 mmol) gave the alkyl iodide (0.125 g, 0.33 mmol, 69%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 – 7.25 (m, 5H), 6.99 (dq, *J* = 15.5, 6.9, 1H), 5.83 (dq, *J* = 15.5, 1.7, 1H), 5.26 – 5.18 (m, 1H), 4.46 (s, 2H), 3.61 (dd, *J* = 11.0, 4.4, 1H), 3.57 – 3.39 (m, 3H), 2.08 – 1.93 (m, 2H), 1.87 (dd, *J* = 6.9, 1.7, 3H).

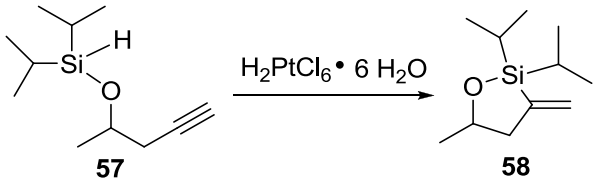
Diisopropyl(pent-4-yn-2-yloxy)silane (57):



To a cooled (0 °C) solution of 4-pentyn-2-ol (0.56 mL, 5.94 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) was added DMAP (0.073 g, 0.59 mmol, 0.10 mmol) upon brief exposure to air. To the reaction was then added triethylamine (0.84 mL, 6.00 mmol, 1.01 equiv) followed by chlorodiisopropylsilane (1.03 mL, 6.00 mmol, 1.01 equiv) both dropwise via syringe. The reaction was allowed to stir for 30 mins at 0 °C and then transferred to a separatory funnel. The organic phase was then washed with 1 M HCl (1×30 mL), saturated $NaHCO_3$ (1×30 mL) and brine (1×30 mL), dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. The crude material was used directly in the following reaction.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.16 (t, *J* = 1.6, 1H), 4.03 – 3.88 (m, 1H), 2.40 (ddd, *J* = 16.5, 5.2, 2.7, 1H), 2.27 (ddd, *J* = 16.5, 7.2, 2.7, 1H), 1.97 (t, *J* = 2.7, 1H), 1.27 (d, *J* = 6.1, 3H), 1.08 – 0.97 (m, 14H).

2,2-Diisopropyl-5-methyl-3-methylene-1,2-oxasilolane (58):

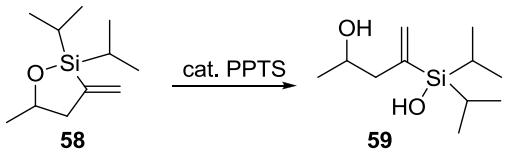


57 **58**

To a crude solution of **57** (1.18 g, 5.94 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) was added a solution of chloroplatinic acid hexahydrate (0.031 g, 0.059 mmol, 0.01 equiv) in isopropanol (0.1 mL) via cannula. The yellow/orange solution was then allowed to stir for 10 mins, at which point the solution had become dark red. The crude mixture was concentrated under reduced pressure. Purification by flash column chromatography (35:1 hexanes/ethyl acetate) gave the siloxane **58** (0.377 g, 1.90 mmol, 32%). It was found that **58** converted to vinyl silanol **59** during purification, and therefore, flash column chromatography should be avoided.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.76 (td, *J* = 2.8, 1.5, 1H), 5.36 (td, *J* = 2.9, 1.8, 1H), 4.16 – 4.03 (m, 1H), 2.57 (ddt, *J* = 15.3, 5.1, 1.6, 1H), 2.12 (ddt, *J* = 15.2, 9.0, 2.9, 1H), 1.25 (d, *J* = 6.0, 3H), 1.08 – 0.93 (m, 14H).

(4-hydroxypent-1-en-2-yl)diisopropylsilanol (59):

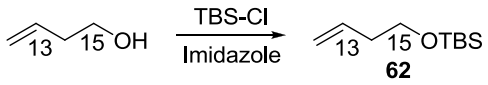


58 **59**

To a solution of **58** (0.02 g, 0.101 mmol, 1.0 equiv) in 1:1 acetonitrile/DI H_2O (0.5 mL/0.5 mL) was added pyridinium *p*-toluene sulfonate (5 mg, 0.020 mmol, 0.20 equiv) upon brief exposure to air. The reaction was allowed to stir overnight, and was then transferred to a separatory funnel. The organic phase was washed with saturated $NaHCO_3$ (2×3 mL) and the combined aqueous phases were extracted with ethyl acetate (3×3 mL). The combined organics were dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. Purification by flash column chromatography (5:1 hexanes/ethyl acetate) gave the vinyl silanol **59**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.75 – 5.67 (m, 1H), 5.45 – 5.39 (m, 1H), 3.94 – 3.85 (m, 1H), 2.39 (dd, *J* = 13.6, 2.9, 1H), 2.26 (dd, *J* = 13.7, 8.1, 1H), 1.18 (d, *J* = 6.2, 3H), 1.05 – 0.92 (m, 14H).

(But-3-enyloxy)(*tert*-butyl)dimethylsilane (62):

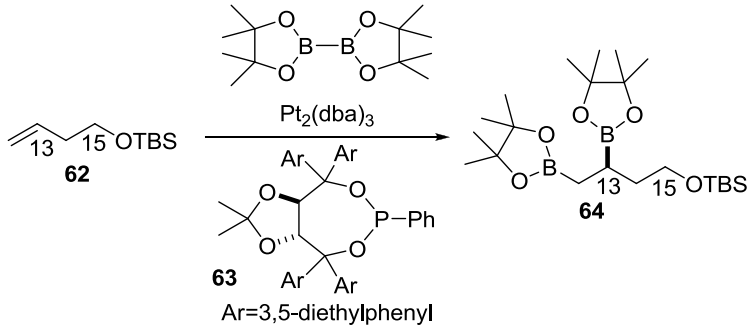


62

To a solution of 3-buten-1-ol (0.30 mL, 3.47 mmol, 1.0 equiv) in CH_2Cl_2 (4.3 mL) was added *tert*-butyldimethylsilylchloride (0.523 g, 3.47 mmol, 1.0 equiv) and imidazole (0.354 g, 5.20 mmol, 1.5 equiv) both upon brief exposure to air, at which point a white, chunky precipitate formed. The reaction was allowed to stir overnight, and was then quenched by the addition of saturated $NaHCO_3$, transferred to a separatory funnel and the aqueous phase was extracted with CH_2Cl_2 (3×5 mL). Combined organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. A white precipitate remained, and was removed from the desired oil by filtering through Celite and rinsing with hexanes to give the protected alcohol **62** (0.339 g, 1.82 mmol, 52%).

IR (cm^{-1}): 2923, 2852. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.85 – 5.74 (m, *J* = 17.1, 10.2, 6.9, 1H), 5.09 – 4.96 (m, 2H), 3.64 (t, *J* = 6.8, 2H), 2.25 (qt, *J* = 6.8, 1.3, 2H), 0.87 (s, 9H), 0.03 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.42, 116.28, 62.80, 37.46, 25.93, 18.36, -5.27.

(*R*)-(3,4-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butoxy)(*tert*-butyl)dimethylsilane (64):

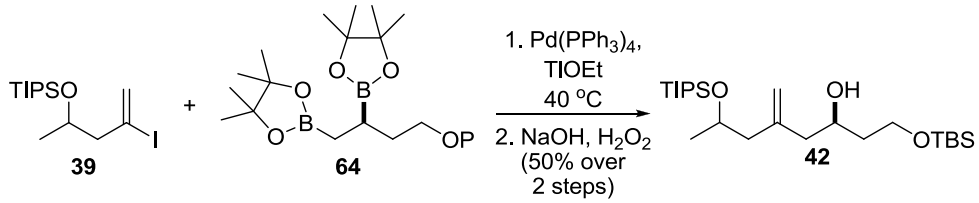


To a Schlenk tube with a side-arm was added bis(pinacolato)diboron (0.358 g, 1.41 mmol, 1.05 equiv), $Pt_2(dba)_3$[57,71] (0.037 g, 0.034 mmol, 0.025 equiv), and ligand **63**[57] (0.064 g, 0.080 mmol, 0.06 equiv) followed by THF (13 mL). The flask was sealed and then the violet solution was heated to 80 °C and allowed to stir for 0.5 h. The resulting brown solution was then allowed to cool to room temperature and then a solution of TBS ether **62** (0.250 g, 1.34 mmol, 1.0 equiv) in THF (2 mL) was added to the solution via cannula. The flask was sealed again and then heated to 60 °C and allowed to stir overnight. The reaction solution was then cooled to room temperature, transferred to a round bottom flask and then concentrated under reduced pressure. Purification by flash column chromatography (20:1 hexanes/ethyl acetate) provided the desired bis-boronic ester **64** (0.423 g, 0.961 mmol, 72%).

IR (cm^{-1}): 2978, 2929, 2857, 1471. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.67 – 3.51 (m, *J* = 10.0, 6.1, 2H), 1.79 – 1.65 (m, 1H), 1.59 – 1.44 (m, 1H), 1.34 – 1.06 (m,

J = 1.7, 22H), 0.91 – 0.74 (m, 13H), 0.01 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 82.84, 82.81, 62.86, 36.56, 26.05, 24.88, 24.84, 24.80, 24.74, 18.42, -5.19. $[\alpha]^{26}_D$ = -2.1 (*c* 1.0, CH_2Cl_2).

(7*R*)-13,13-diisopropyl-2,2,3,3,11,14-hexamethyl-9-methylene-4,12-dioxa-3,13-disilapentadecan-7-ol (42):

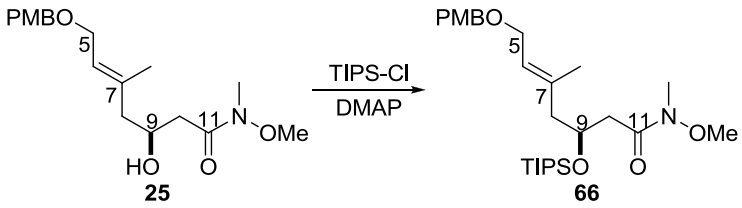


To a flask containing vinyl iodide **39** (0.048 g, 0.129 mmol, 1.0 equiv) was added a solution of bis(boronic ester) **64** (0.114 g, 0.259 mmol, 2.0 equiv) in 5:1 dioxane/DI H_2O (2.1 mL/0.4 mL) via cannula and then N_2 was bubbled through the solution for 15 mins. Tetrakis(triphenylphosphine)palladium (0.015 g, 0.013 mmol, 0.20 equiv) was added to the solution upon brief exposure to air and then thallium ethoxide (0.018 mL, 0.259 mmol, 2.0 equiv) was added to the reaction via glass syringe, upon which bright yellow precipitate formed. (*Note: thallium salts are generally quite toxic and should be handled with extreme care*.) The solution was then heated (40 °C) and allowed to stir overnight, at which time the brown suspension was cooled to room temperature and quenched by the addition of 1M aqueous $KHSO_4$ and allowed to stir for 20 mins. The crude suspension was then filtered through Celite and the filtrate was transferred to a separatory funnel. The organic phase was washed with brine, dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. To a cooled (0 °C) solution of this crude oil in THF (1.3 mL) was added 3M NaOH (0.4 mL, 1.17 mmol, 9.0 equiv) and 30% aqueous H_2O_2 (0.2 mL,

6.23 mmol, 48 equiv) both dropwise via syringe. The reaction was allowed to warm to room temperature and stir for 4 h, at which time it was quenched by the addition of saturated $Na_2S_2O_3$ and transferred to a separatory funnel. The aqueous phase was extracted with ethyl acetate (3×3 mL), and then the combined organics were dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. Purification by flash column chromatography (35:1 hexanes/ethyl acetate) gave the desired alcohol (0.029 g, 0.065 mmol, 50%).

Unless otherwise indicated, signals correspond to both diastereomers of the product. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.90 – 4.80 (m, 2H), 4.14 – 4.01 (m, 1H), 4.01 – 3.91 (m, 1H), 3.91 – 3.83 (m, 1H), 3.83 – 3.72 (m, 1H), 3.21 (br s, 1H), 2.45 – 2.29 (m, 1H), 2.29 – 2.04 (m, 3H), 1.72 – 1.52 (m, 2H), 1.14 (d, *J* = 6.0, 3H), 1.10 – 0.97 (m, 21H), 0.88 (s, 9H), 0.05 (s, 6H).

(*S*,*E*)-*N*-Methoxy-7-(4-methoxybenzyloxy)-*N*,5-dimethyl-3-(triisopropylsilyloxy)-hept-5-enamide (66):

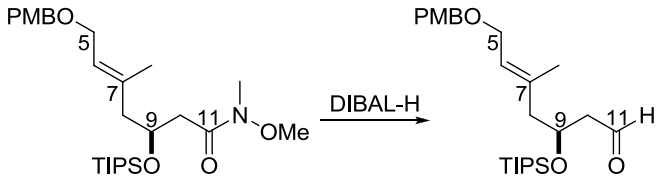


To a solution of **25** (0.781 g, 2.32 mmol, 1.0 equiv) in DMF (11.6 mL) was added triisopropylchlorosilane (2.5 mL, 11.57 mmol, 5.0 equiv) via syringe and DMAP (1.56 g, 12.73 mmol, 5.5 equiv) upon brief exposure to air, at which point reaction formed a white precipitate. The reaction was allowed to stir for 2d and was then quenched by the addition of saturated $NaHCO_3$. The reaction was then diluted with CH_2Cl_2 and DI H_2O and was transferred to a separatory funnel. The aqueous

was extracted with CH_2Cl_2 (3×10 mL) and the combined organics were dried over $MgSO_4$, filtered through Celite, and concentrated under reduced pressure. Purification by flash column chromatography (3:1 hexanes/ethyl acetate) provided **66** as a yellow oil (1.081 g, 2.19 mmol, 95%).

IR (cm^{-1}): 2940, 2865, 16640, 1514, 1464. ^1H NMR (500 MHz, $CDCl_3$): δ 7.26 – 7.21 (m, 4H), 6.88 – 6.82 (m, 3H), 5.41 (t, *J* = 6.3, 1H), 4.54 (s, 1H), 4.39 (s, 3H), 3.99 – 3.91 (m, 3H), 3.78 (s, 4H), 3.63 (s, 4H), 3.11 (s, 4H), 2.60 (dd, *J* = 15, 6.2, 1H), 2.51 (dd, *J* = 15.5, 4.9, 1H), 2.40 (dd, *J* = 13.1, 4.6, 1H), 2.22 (dd, *J* = 13.2, 8.2, 1H), 1.66 (s, 4H), 1.12 – 0.9 (m, 21H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.11, 136.78, 130.57, 129.35, 124.59, 113.72, 71.72, 67.92, 66.20, 61.22, 55.26, 48.62, 39.17, 29.69, 18.13, 18.11, 17.04, 12.52. $[\alpha]^{27}_D$ = +22.8 (*c* 0.5, CH_2Cl_2).

(*S*,*E*)-7-(4-Methoxybenzyloxy)-5-methyl-3-(triisopropylsilyloxy)hept-5-enal (67):



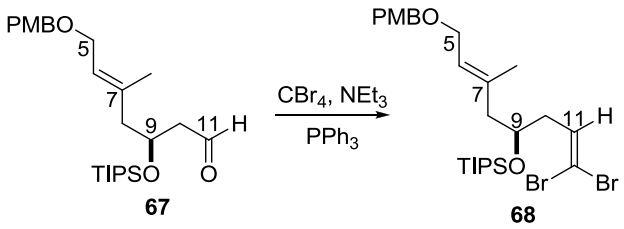
66 **67**

To a cooled (-78 °C) solution of **66** (1.081 g, 2.19 mmol, 1.0 equiv) and THF (22 mL) was added DIBAL-H (3.28 mL, 1.0 M solution in hexanes, 3.28 mmol, 1.5 equiv) via syringe. The reaction was allowed to stir for 1.5 h at -78 °C, and then excess DIBAL-H was quenched by the addition of ethyl acetate. The solution was allowed warm to room temperature and was then transferred to a separatory funnel that already contained half-saturated Rochelle's salt (20 mL). The aqueous phase was extracted with ethyl acetate (3×10 mL), and the combined organics were dried over $MgSO_4$, filtered through Celite, and concentrated under reduced pressure.

Purification by flash column chromatography (10:1 hexanes/ethyl acetate) gave the desired aldehyde **67** (0.876 g, 2.02 mmol, 92%) as a colorless oil.

IR (cm^{-1}): 2942, 2866, 1724, 1613, 1514, 1464. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.81 (t, *J* = 2.3, 1H), 7.26 – 7.20 (m, 2H), 6.88 – 6.82 (m, 2H), 5.41 (t, *J* = 6.5, 1H), 4.52 – 4.43 (m, 1H), 4.40 (s, 2H), 4.01 – 3.88 (m, 2H), 3.78 (s, 3H), 2.58 (ddd, *J* = 16.0, 5.3, 2.0, 1H), 2.51 – 2.40 (m, 2H), 2.24 (dd, *J* = 13.3, 9.2, 1H), 1.63 (s, 3H), 1.11 – 0.99 (m, 21H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.89, 159.17, 135.82, 130.43, 129.37, 125.38, 113.77, 71.91, 67.39, 66.09, 55.27, 50.17, 48.33, 18.09, 18.08, 17.13, 12.45. $[\alpha]^{27}_D$ = +4.5 (*c* 0.55, CH_2Cl_2).

(*R*,*E*)-(1,1-Dibromo-8-(4-Methoxybenzyloxy)-6-methylocta-1,6-dien-4-yloxy)tri-isopropylsilane (68):

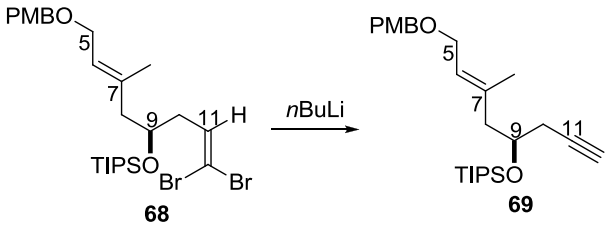


To a cooled (0 °C) solution of carbon tetrabromide (1.54 g, 4.64 mmol, 2.3 equiv) in CH_2Cl_2 (20.2 mL), was added triphenylphosphine (2.43 g, 9.27 mmol, 4.6 equiv) upon brief exposure to air. The yellow-orange solution was allowed stir for 30 min at 0 °C, and then triethylamine (1.76 mL, 12.49 mmol, 6.2 equiv) was added via syringe. Then a solution of **67** (0.876 g, 2.02 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added to the reaction via cannula. After stirring for 1.5 h at 0 °C, the maroon solution was quenched by the addition of saturated NH_4Cl (20 mL), upon which the solution turned orange, and was allowed to warm to room temperature. The crude solution was transferred to a separatory funnel and the organic phase was washed

with saturated $NaHCO_3$ (7 mL), and then the aqueous phase was extracted with ethyl acetate (2×7 mL). The combined organics were then dried over $MgSO_4$, filtered through Celite, and concentrated under reduced pressure. Purification by flash column chromatography (35:1 hexanes/ethyl acetate) provided **68** (1.19 g, 2.02 mmol, quantitative) as a translucent, colorless oil.

IR (cm^{-1}): 2942, 2865, 1613, 1513, 1463. ^1H NMR (500 MHz, $CDCl_3$): δ7.28 – 7.20 (m, 2H), 6.90 – 6.82 (m, 2H), 6.53 (dd, *J* = 7.5, 6.4, 1H), 5.42 (t, *J* = 6.3, 1H), 4.41 (s, 2H), 4.12 – 4.05 (m, 1H), 4.03 – 3.93 (m, 2H), 3.79 (s, 3H), 2.37 – 2.09 (m, 4H), 1.64 (s, 3H), 1.04 (s, 21H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.13, 136.10, 135.47, 130.55, 129.34, 124.80, 113.75, 89.53, 71.74, 69.26, 66.16, 55.27, 47.68, 39.84, 18.13, 17.06, 12.52. $[\alpha]^{27}_D$ = -9.5 (*c* 0.5, CH_2Cl_2).

(*R*,*E*)-Triisopropyl(8-(4-Methoxybenzyloxy)-6-methyloct-6-en-1-yn-4-yloxy)silane (69):

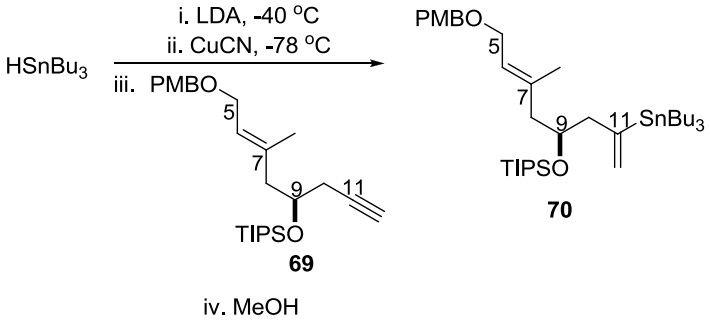


To a cooled (-78 °C) solution of **68** (1.19 g, 2.02 mmol, 1.0 equiv) in THF (20.2 mL) was added *n*-butyllithium (3.43 mL, 1.47 M in hexanes, 5.04 mmol, 2.5 equiv) via syringe. After stirring at -78 °C for 4 h, the dark-brown solution was allowed to warm to -40 °C via an acetonitrile/dry ice bath. After stirring for another 40 min at -40 °C, the reaction was quenched by the addition of saturated NH_4Cl (20 mL) and then allowed to warm to room temperature, upon which the solution turned orange. The crude mixture was transferred to a separatory funnel and the aqueous

phase was extracted (3×7 mL). The combined organics were dried over $MgSO_4$, filtered through Celite, and concentrated under reduced pressure. Purification by flash column chromatography (20:1 hexanes/ethyl acetate) gave the desired alkyne **69** (0.698 g, 1.62 mmol, 80%) as a colorless translucent oil.

IR (cm^{-1}): 3311, 2942, 2866, 1612, 113, 1464. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 – 7.22 (m, 2H), 6.89 – 6.83 (m, 2H), 5.49 (t, *J* = 6.1, 1H), 4.41 (s, 2H), 4.11 – 4.03 (m, 1H), 4.03 – 3.93 (m, 2H), 3.78 (s, 3H), 2.46 – 2.23 (m, 4H), 1.96 (t, *J* = 2.6, 1H), 1.66 (s, 3H), 1.10 – 1.00 (m, 21H). ^{13}C NMR (75 MHz, CDCl3) δ 159.12, 136.34, 130.61, 129.37, 124.77, 113.74, 81.45, 71.69, 70.24, 69.68, 66.24, 55.27, 46.68, 26.72, 18.12, 17.35, 12.53. $[\alpha]^{26}_D$ = -3.1 (*c* 1.1, CH_2Cl_2).

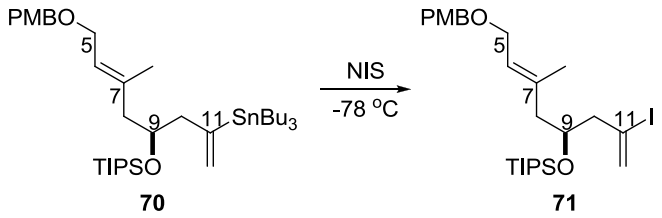
(*S*,*E*)-Triisopropyl(8-(4-Methoxybenzyloxy)-6-methyl-2-(tributylstannyl)octa-1,6-dien-4-yloxy)silane (70):



To a cooled (0 °C) solution of diisopropylamine (0.25 mL, 1.77 mmol, 2.5 equiv) in THF (7.1 mL) was added *n*-butyllithium (1.2 mL, 1.52 M solution in hexanes, 1.77 mmol, 2.5 equiv) dropwise via syringe. The solution of LDA was allowed to stir at 0 °C for 20 mins, and then tributyltin hydride (0.4 mL, 1.62 mmol, 2.3 equiv) was added dropwise via syringe. The pale yellow solution was allowed to stir for 1 h, at which point it was then cooled (-40 °C) via an acetonitrile/dry ice bath and. The dark orange/brown solution was allowed to stir at -40 °C for 30 mins at

which point it was cooled (-78 °C) and then methanol (0.046 mL, 1.13 mmol, 1.6 equiv) was added via syringe, followed by a solution of **69** (0.304 g, 0.706 mmol, 1.0 equiv) in THF (2 mL) was added to the reaction via cannula. The solution was allowed to stir for 2 h, and then methanol (1.3 mL, 32.5 mmol, 46 equiv) was added via syringe, and the reaction was allowed to warm to 0 °C and stir for another 30 mins. The reaction was then quenched by the addition of 9:1 saturated NH_4Cl/NH_4OH (10 mL), and the black crude mixture was transferred to a separatory funnel. The aqueous phase was extracted with Et_2O (3×10 mL), and then the combined organics were dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure to give the vinyl tin species **70**. Purification by flash column chromatography was found to reduce the tin to give the undesired terminal alkene, and therefore the crude material (0.837 g, 164% - excess yield due to by-products) was used directly in the next reaction.

(*S*,*E*)-(2-Iodo-8-(4-methoxybenzyloxy)-6-methylocta-1,6-dien-4-yloxy)triiso-propylsilane (71):



70 **71**

To a cooled (-78 °C) solution of crude **70** (0.837 g, 1.16 mmol, 1.0 equiv – note: a portion of this crude material was byproducts from the previous reaction) in CH_2Cl_2 (11.6 mL) was added *N*-iodoosuccinimide (0.391 g, 1.74 mmol, 1.5 equiv) in one portion upon brief exposure to air. The reaction was allowed to stir for 1 h at -78 °C, at which point the dark brown solution was then quenched by the addition of

saturated Na_2SO_3 (7 mL) and allowed to warm to room temperature. The crude solution was then transferred to a separatory funnel, and the organic phase was washed with Na_2SO_3 (2×5 mL), and 1M NaOH (3×5 mL). The combined aqueous phases were then extracted with Et_2O (3×5 mL), and then the combined organics were dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. Purification by flash column chromatography (35:1 hexanes/ethyl acetate) provided the desired vinyl iodide **71** (0.326 g, 0.584 mmol, 83% - based on theoretical yield of previous reaction) as a colorless, translucent oil.

IR (cm^{-1}): 2941, 2865, 1729, 1614, 1586, 1513, 1464. ^1H NMR (500 MHz, $CDCl_3$): δ 7.28 – 7.22 (m, 2H), 6.89 – 6.81 (m, 2H), 6.10 – 6.08 (m, 1H), 5.75 – 5.71 (m, 1H), 5.42 (t, *J* = 6.1, 1H), 4.41 (s, 2H), 4.25 – 4.17 (m, 1H), 4.01 – 3.95 (m, 2H), 3.79 (s, 3H), 2.56 – 2.42 (m, 2H), 2.33 – 2.19 (m, 2H), 1.67 (s, 3H), 1.05 (s, 21H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.09, 136.52, 130.56, 129.34, 128.12, 124.75, 113.72, 108.68, 71.67, 69.75, 66.15, 55.26, 52.42, 47.14, 18.24, 17.13, 12.75. $[\alpha]^{26}_D$ = +5.5 (*c* 0.55, CH_2Cl_2).

2.8. References

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