# Catalytic Stereoselective Olefin Metathesis for Natural Product Synthesis

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Boston College

The Graduate School of Arts and Sciences

Department of Chemistry

### CATALYTIC STEREOSELECTIVE OLEFIN METATHESIS

FOR

### NATURAL PRODUCT SYNTHESIS

a dissertation

By

### ELSIE C. YU

submitted in partial fulfillment of the requirements

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### CATALYTIC STEREOSELECTIVE OLEFIN METATHESIS

### FOR

### NATURAL PRODUCT SYNTHESIS

### Elsie Yu

### Thesis Advisor: Professor Amir H. Hoveyda

Abstract

# Chapter 1. Efficient Z-Selective Synthesis of Allylic- and Alkenyl Boronates by Catalytic Cross-Metathesis

Efficient Z-selective cross-metathesis reactions to furnish Z-(pinacolato)-allylboron and Z-(pinacolato)alkenylboron compounds through catalytic cross-metathesis are disclosed. Zallylic boron compounds are generated by the use of catalytic amounts of a W-based monoaryloxide monopyrrolide (MAP) complex in up to 91% yield and 96:4 dr after allylation to benzaldehyde. Alkenylboron compounds are prepared in high yields and high Z selectivity in up to 93% yield and 97:3 Z:E. Cross-metathesis reactions with 1,3-dienes and aryl olefins are efficient and highly Z-selective. Combination of cross-metathesis and



cross-coupling to synthesize anticancer agent combretastatin A-4 highlights the utility of this approach.

### Chapter 2. Synthesis of Macrocyclic and Acyclic Z-Enoates and (E,Z) or (Z,E)Dienoates by Catalytic Cross-Metathesis

The first examples of kinetically controlled catalytic olefin metathesis reactions to generate Z- $\alpha$ , $\beta$ -unsaturated macrocyclic and acyclic esters are disclosed. The synthesis of (*E*,*Z*) or (*Z*,*E*)-dienoates are also presented. Reactions promoted by 3.0–10 mol % of Mo-based monoaryloxide monopyrrolide complex proceed to completion to the desired macrocycles within 2–6 h at room temperature. Macrocycles of diverse ring sizes are formed in 79:21 to >98:2 *Z*:*E* selectivity. Pure *Z* isomers can be obtained after purification in up to 75% yield. Acyclic *Z*- $\alpha$ , $\beta$ -unsaturated esters are prepared in the presence of acetonitrile to avoid



using excess amounts of the more valuable cross-partner substrate. Spectroscopic investigations and X-ray analysis rationalize the positive effect of acetonitrile in the reaction system. Linear (*Z*)-enoates are generated in up to 71% yield and up to >98:2 *Z:E*. (*E,Z*)-Dienoates are generated with high *Z* selectivity as well. The utility of the ring-closing metathesis and cross-metathesis is highlighted by the synthesis of an (+)-aspicilin precursor and the C1–C12 fragment of biologically active natural product (–)-laulimalide.

# Chapter 3. Application of *E*-Selective Catalytic Ring-Closing Metathesis in the Total Synthesis of Dolabelides A, B, C and D

Efforts towards the enantioselective synthesis of the dolabelide family of anti-cancer macrolides is presented. Development of a total synthesis incorporating a late-stage kinetically *E*-selective RCM is illustrated. Previous attempts to synthesize the macrolide by ring-closing metathesis (RCM) have demonstrated poor efficiency and low selectivity for the *E* isomer. Methodology developed in our group with acyclic trisubstituted cross-metathesis demonstrates that high selectivity can be achieved with stereodefined 1,2-disubstituted and trisubstituted olefins by the use of the proper catalyst and reaction design. Modern catalytic and stereoselective approaches towards the two main fragments of



dolabelide are presented. More efficient and concise routes will be pursued to highlight the utility of the proposed disconnections and practicality of the total synthesis.

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### Chapter 1

# Efficient Z-Selective Synthesis of Allylic and Alkenyl Boronates by Catalytic Cross-Metathesis

### **1.1 Introduction**

Organoboron reagents, such as allylic boronates and alkenyl boronates, are essential building blocks in the synthesis of new C–C bonds in the synthesis of natural products.<sup>1</sup> Allylic boronates have been frequently used in many stereoselective additions to carbonyls and imines for the synthesis of functionalized homoallylic alcohols and amines,<sup>2</sup> while alkenyl boronates have been quite established as valuable nucleophiles in Suzuki-Miyaura cross-coupling reactions.<sup>3</sup> The stereochemistry of the boron reagents are often reflected in the new bonds that are manifested, making the need for stereodefined *Z*- or *E*-boron compounds quite essential. Because of this, there have been many studies devoted to synthesizing these compounds in a stereoselective fashion. Though there are a number of catalytic methods towards the synthesis of *Z*-allylic and alkenyl boronates, each organoboron is disconnected similarly from one approach to the next. An alternative strategy is olefin metathesis, which offers a unique disconnection from the methods that will be discussed in the next section. Recent advances in olefin metathesis have offered new ways to synthesize functionalized molecules of both cyclic and acyclic nature. One of the shortcomings of

 <sup>(1) (</sup>a) Hall, D. G. In Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine; Wiley-VCH: Weinheim, 2005. (b) Suzuki, A. J. Organomet. Chem. 2002, 653, 83–90. (c) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. Angew. Chem., Int. Ed. 2005, 44, 4442–4489. (d) Negishi, E.-i.; Huang, Z.; Wang, G.; Mohan, S.; Wang, C.; Hattori, H. Acc. Chem. Res. 2008, 41, 1474–1485.

<sup>(2) (</sup>a) Herold, T.; Hofmann, R. W. Angew. Chem., Int. Ed. Engl. 1978, 17, 768–769. (b) Yus, M.; González-Gómez, J. C.; Foubelo, F. Chem. Rev. 2011, 111, 7774–7854 (c) Huo, H.-X.; Duvall, J. R.; Huang, M.-Y.; Hong, R. Org. Chem. Front. 2014, 1, 303–320. (d) Yamamoto, Y.; Asa, N. Chem. Rev. 1993, 93, 2207–2293.

<sup>(3) (</sup>a) Ref. 1 (b) Suzuki, A. Angew. Chem., Int. Ed. 2011, 50, 6722–6737.

metathesis is the development of catalysts that can deliver the desired isomer in a kinetically controlled and efficient manner. Our group has developed stereogenic-at-metal monoaryloxide monopyrrolide (MAP) complexes that have the capability to transform a variety of functionalized terminal olefins into Z 1,2-disubstituted alkenes.<sup>4,5</sup> In this chapter, we will discuss the first examples of Z-selective cross-metathesis (CM) reactions catalyzed by stereogenic-at-Mo and W MAP complexes to deliver Z-(pinacolato)-allylboron [allyl-B(pin)] and Z-(pinacolato)alkenylboron [alkenyl-B(pin)] compounds.<sup>6</sup>

### **1.2 Background**

### **1.2.1. Representative Methods for Synthesis of Allylic Boronates**

Chiral allyl and crotyl reagents are commonly used to form new C–C bonds, especially in a diastereo- and enantioselective manner. Over the years, many groups have worked on synthesizing allylic boronates with different esters as well as developing effective methods for the synthesis of these reagents. Classical methods generally require a cis alkene to generate the desired Z-allylic boranes/boronates, limiting the diversity in crotylating reagents that could be made. Catalytic methods towards the synthesis of these boron-containing reagents have arose. However, few are designed to generate the cis allylic boron.

In the 1980s, Brown reported hydroboration of pinene for the synthesis of diisopinocampheyl allylborane.<sup>7</sup> The synthesis of cis-crotyl boranes starts with cis-2-butene **1.1**.

<sup>(4) (</sup>a) Singh, R.; Schrock, R. R.; Muller, P.; Hoveyda, A. H. *J. Am. Chem. Soc.* 2007, *129*, 12654–12655.
(b) Malcolmson, S. J.; Meek, S. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* 2008, *456*, 933–937. (c) Sattely, E. S.; Meek, S. J.; Malcolmson, S. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* 2009, *131*, 943–953.

<sup>(5) (</sup>a) Meek, S. J.; O'Brien, R. V.; Llaveria, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* 2011, *471*, 461–466.
(b) Mann, T. J.; Speed, A.W. H.; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* 2013, *52*, 8395–8400.

<sup>(6)</sup> Kiesewetter, E. T.; O'Brien, R. V.; Yu, E. C.; Meek, S. J.; Schrock, R. R.; Hoveyda, A. H. J. Am. Chem. Soc. 2013, 135, 6026–6029.

<sup>(7)</sup> Brown, H. C.; Bhat, K. S. J. Am. Chem. Soc. 1986, 108, 293–294.

Metalation of the alkene with Schlosser's base leads to crotyl potassium **1.2** that sits in a  $\eta^3$ -fashion. The anion is added to boronate **1.3** and the methoxy group is removed in the presence of BF<sub>3</sub>·OEt<sub>2</sub> to generate Z-crotyl borane **1.4**. Due to the instability of the reagent, **1.4** is used immediately after generation in the allylation of aldehydes; prolonged storage leads to isomerization of the double bond. While the hydroboration is direct and pinene can be afforded at a reasonable price, the sensitivity of the boron intermediates and product requires rigorous exclusion of water to prevent decomposition.



To address the issue of instability of the reagent, Roush developed tartrate-derived crotyl boronate **1.6**.<sup>8</sup> Synthesis also begins with metalation of **1.1** and is added to triiso-propoxy borate. The borate was hydrolyzed to the boronic acid to allow for esterification with tartrate **1.5** during work-up. Tartrate-derived boronate **1.6** or its antipode (using *ent*-

<sup>(8)</sup> Roush, W. R.; Walts, A. E.; Hoong, L. K.-8190.

**1.5**) can both be isolated in 65–75% yield. Roush and co-workers also investigated the reactivity of (pinacolato)crotylboron.<sup>9</sup> By modifying Brown's procedure,<sup>10</sup> allyl-B(pin) **1.8** is synthesized by addition of **1.2** to fluorodimethoxyborane. Subsequent hydrolysis and esterification with diol **1.7** yields crotyl-B(pin) **1.8** in 68–75% yield. In the same publication, reagent **1.8** was synthesized with chloromethyl-B(pin) and propenyl Grignard with high isomeric ratios (Scheme 1.2).

Scheme 1.2. Synthesis of Crotylboronates through Propenyl Grignard.



Brown's allylating and crotylating boranes (e.g. 1.4) provide high enantioselectivity through reagent control and generally override any facial bias from the electrophile. Roush's ester 1.6 and related derivatives yield high enantioselectivities but are slightly lower. One advantage, however, is that these chiral reagents can be isolated in air and stored for months at -20 °C. These approaches, nonetheless, limit the stereoselectivities to the chiral auxiliaries appended to the boron and the isomeric purity of the synthesized allylating reagent. Additionally, stoichiometric quantities of chirial auxiliaries are required, making these strategies poorly atom economical. Through the use of a pinacol protecting group instead (1.8), chiral catalysts can be implemented to generate the desired product in an enantioselective fashion, in addition to involvement of more atom economically friendly diols. Many groups, including our own, have reported efficient catalytic enantioselective methods utilizing allyl-B(pin) reagents.<sup>2</sup>

<sup>(9)</sup> Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. J. Am. Chem. Soc. 1986, 108, 3422-3434.

<sup>(10)</sup> Brown, H. C.; De Lue, N. R.; Yamamoto, Y.; Maruyama, K.; Kasahara, T.; Murahashi, S.; Sonoda, A. J. Org. Chem. 1977, 42, 4088–4092.

Suzuki and co-workers developed a method for synthesizing (*Z*)-crotyl catecholborane.<sup>11</sup> In the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> in catalytic amounts, 1,3-butadiene **1.10** undergoes 1,4-hydroboration with catecholborane **1.11** to deliver allylic boronate **1.12** as one isomer and is used directly for allylation of benzaldehyde. The reaction effected 2- and 3-subtitued conjugated dienes, but did not present examples of 1-substituted dienes. Substrates such as pentadiene or cyclohexadiene **1.14** are slow to proceed. Suzuki remedied this issue by switching to Rh<sub>4</sub>(CO)<sub>12</sub> and found the reaction was much faster, yielding 92% of the desired homoallylic product **1.15**. Even with the change in the metal, the substrate scope is limited. Additionally, catechol boranes are relatively less stable compared to their pinacolato counterparts.

Scheme 1.3. Suzuki's 1,4-Hydroboration of 1,3-Dienes.



In 2010, Morken and co-workers developed a method for highly selective 1,4-hydroboration of 1,3-dienes (Scheme 1.4).<sup>12</sup> The strategy offers an alternative to classic Pdand Rh-based catalysis for 1,4-hydroboration with only 2.5 mol% of Ni(cod)<sub>2</sub>. Additionally, the reactions works well with terminal dienes, broadening the scope beyond 2-substituted and 2,3-disubstituted dienes. Unhindered alkyl groups (**1.19**) as well as sterically bulky

<sup>(11)</sup> Satoh, M.; Nomoto, Y.; Miyaura, N.; Suzuki, A. Tetrahedron Lett. 1989, 30, 3789-3792.

 <sup>(12)</sup> Examples of 1,4-hydroboration of internal 1,3-dienes are also presented in this report: Ely, R. J.; Morken, J. P. J. Am. Chem. Soc. 2010, 132, 2534–2535.

phenyl groups (1.20) performed similarly well. A variety of different functional groups including phthalimides (1.22), silyl ethers (1.21) as well as free alcohols (1.23) reacted with great efficiency. In all cases, only the Z stereoisomer was detected. A mechanistic study with deuterated pinacolborane ( $d_1$ -1.18) revealed the deuterium sits at the C4 position, with respect to the B(pin) that resides at C1. Together with the observation that the reaction is inefficient with styrene and requires a *S*-cis diene confirmation, the mechanism most likely proceed through  $\eta_4$ -diene III or nickelacycle II to afford the desired product.





1,4-Hydroboration of 1,3-dienes can be facilitated with a copper-based catalyst. In a report disclosure by Tsuji and co-workers, diene **1.24** reacted with Cu(I), sodium *t*-butoxide and bis(pinacolato)diboron to deliver (*Z*)-allylic-B(pin) **1.25** in 85% yield (Scheme 1.5).<sup>13</sup> While this example highlights the use of an inexpensive metal, it was also the only case shown furnishing the *Z* isomer. Compared to the previously mentioned methods,  $B_2(pin)_2$  is used, instead of HB(pin), only to deliver a single pinacolatoboron group to the

<sup>(13)</sup> Semba, K.; Shinomiya, M.; Fujihara, T.; Terao, J.; Tsuji, Y. Chem. Eur. J. 2013, 19, 7125–7132.

molecule. Other studies in his report discussed hydroboration of allenes, but provided different regio- or stereoselectivity, generating 1,1-disubstituted alkenyl-B(pin) reagents or the E isomer of the allylic boron.





Many methods have been reported to synthesize allylic boronates, but most of these reports give rise to the more stable trans isomer. <sup>14</sup> CM with allyl-B(pin) in the presence of commercially available Ru-based catalyst **1.28** gives rise to an inseparable mixture of allylic boron **1.29** (Scheme 1.6).<sup>15</sup> The product was reacted with benzaldehyde in the same vessel to furnish homoallylic alcohol **1.30** in 75% yield as a 18:82 syn:anti mixture, reflecting the *Z*:*E* ratio of **1.29**. More sterically bulky substrates (**1.32–1.34**) produce only the *E*-isomer, but in lower yields, while less sterically encumbered substrates give modest selectivities (**1.31**, 21:79 syn:anti). Selectivity was not the only issue with the less sterically demanding partners. In the examples illustrated, the starting material is a symmetrical 1,2-disubstituted internal olefin to minimize Ru-methylidene formation.<sup>16</sup> A number of internal alkenes like **1.27** are available, but this would be particularly wasteful in more complex scenarios.

<sup>(14)</sup> For representative catalytic methods that generate (*E*)-1,2-disubstituted allylic boronates: (a) S. Sebelius, S.; Olsson, V. J.; Wallner, O. A.; Szabó, K. J. *J. Am. Chem. Soc.* 2006, *128*, 8150–8151. (b) Dutheuil, G.; Selander, N.; Szabó, K. J.; Aggarwal, V. K. *Synthesis* 2008, 2293–2297. (c) Zhang, P.; Roundtree, I. A.; Morken, J. P. Org. Lett. 2012, *14*, 1416–1419. (d) Semba, K.; Shinomiya, M.; Fujihara, T.; Terao, J.; Tsuji, Y. *Chem. Eur. J.* 2013, *19*, 7125–7132.

<sup>(15)</sup> Goldberg, S. D.; Grubbs, R. H. Angew. Chem., Int. Ed. 2002, 41, 807-810.

<sup>(16)</sup> Hong, S. H.; Wenzel, A. G.; Salguero, T. T.; Day, M. W.; Grubbs, R. H. J. Am. Chem. Soc. 2007, 129, 7961–7968.



Scheme 1.6. Grubbs' Ru-Catalyzed CM of Allyl-B(pin).

The only instance, prior to our report, of synthesizing Z-allylic boronates through metathesis was by the Schrock group.<sup>17</sup> W-based complex **1.35** with allyl-B(pin) produces the homocoupled product **1.36** in 96% Z selectivity. There are no examples of cross-metathesis products with **1.26**.





<sup>(17)</sup> Jiang, A. J.; Zhao, Y.; Schrock, R. R.; Hoveyda, A. H. J. Am. Chem. Soc. 2009, 131, 16630–16631.

### 1.2.2. Representative Methods for Synthesis of Alkenyl Boronates

Many groups have worked on developing efficient methods to synthesize alkenyl-B(pin) compounds for their effectiveness of generating new C–C bonds. These compounds are generally sought to be synthesized in pure isomeric form so that the stereochemistry can be carried on in a subsequent cross-coupling reaction. *E*-Alkenyl boronates are readily accessible through hydroboration of alkynes<sup>18</sup> due to *anti*-Markovnikov and cis addition borane reagents. On the other hand, the synthesis of their *Z* counterparts is less direct, leading to many groups working towards efficient *Z*–selective methods.

One of the first instances, which was reported in 1984, involved hydroboration of 1-bromoalkynes by Brown.<sup>19</sup> The initial addition with dibromoborane leads to the alkyl chain being trans to boron (Scheme 1.8). However, by subjecting the alkenyl bromide intermediate to potassium triisopropoxyborohydride, elimination takes place to give *Z*-alkenyl boronate **1.40** (as a mixture of the boronic acid and ester). The product can be easily esterified to alkenyl pinacolatoboron **1.41**. This method provides the desired alkenyl boron compounds in high isomeric purity and high yields, but substrates are limited to 1-bromo-alkynes and also require three steps to arrive at the desired boronic acid esters.

<sup>(18)</sup> For representative catalytic methods for synthesizing (*E*)-1,2-disubstituted alkenylboronates, see: (a) Jang, H.; Zhugralin, A. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* 2011, *133*, 7859–7871. (b) Ho, H. E.; Asao, M.; Yamamoto, Y.; Jin, T. *Org. Lett.* 2014, *16*, 4670–4673. (c) Coombs, J. R.; Zhang, L.; Morken, J. P. *Org. Lett.* 2015, *17*, 1708–1711.

<sup>(19)</sup> Brown, H. C.; Imai, T. Organometallics 1984, 3, 1392-1395.



Scheme 1.8. Brown's Hydroboration of Alkynes.

One of the more commonly used strategies to access alkenyl-B(pin) compounds is through hydrozirconation of alkynes. Srebnik initially developed this method with terminal alkynes, pinacolborane **1.18** and catalytic amounts of Schwartz's reagent (Cp<sub>2</sub>ZrHCl) to prepare compounds such as **1.43** as predominantly the trans isomer (Scheme 1.9a).<sup>20</sup> Aliphatic alkynes (**1.45**, **1.47**) as well as more sterically hindered phenyl (**1.44**) and carbocycles (**1.46**) showed great reactivity as well as selectivity. From here, he and co-workers went on to build a method for *Z*-alkenyl B(pin) reagents (Scheme 1.9b). By starting with the alkynyl boronate, hydrozirconation occurs in a cis fashion to deliver *Z* alkenyl-B(pin) products. A similar set of substrates was explored and all showed good reactivity with excellent *Z* selectivity. While this approach delivers great results in a short amount of time, the Zr-complex is used in a stoichiometric fashion, only to deliver a hydride in the final product. Alkynyl boronate substrates generally need to be synthesized as well, adding another step to the synthesis of these *Z*-alkenyl boronates.

 <sup>(20)</sup> a) Pereira, S.; Srebnik, M. Organometallics 1996, 14, 3127–3128. b) Deloux, L.; Srebnik, M. J. Org. Chem. 1994, 59, 6871-6873.

#### Scheme 1.9. Srebnik's Hydroboration of Alkynes.

a) Hydrozirconation of Terminal Alkynes with Pinacolborane:



 (Z)-1.44
 (Z)-1.45
 (Z)-1.46
 (Z)-1.49

 85% yield
 72% yield
 86% yield
 71% yield

 >98:2 Z:E
 >98:2 Z:E
 >98:2 Z:E
 >98:2 Z:E

In 2008, Molander reported synthesis of potassium trifluoroborate salts through *Z*-alkenyl B(pin) compounds (Scheme 1.10).<sup>21</sup> Hydroboration of the B(pin)-substituted alkyne **1.50** with dicyclohexylborane leads to 1,1-diboryl intermediate **1.51**. Treating the diboryl species with acetic acid cleaves the dicyclohexylboron to yield **1.52** as the pure *Z* isomer. Products derived from unhindered alkynes (**1.52**) and more hindered alkynes (**1.53** and **1.55**) could be accessed. While unhindered, the chloro-containing compound **1.54** was isolated in a 90:10 *Z*:*E* ratio. The method showed limitations with acid-sensitive functionalities such as the *t*-butoxylcarbonyl group in **1.53**. More electron withdrawing compounds,

<sup>(21)</sup> Molander, G. A.; Ellis, N. M. J. Org. Chem. 2008, 73, 6841-6844.

such as those containing nitrile groups, proved to be ineffective in this hydroboration sequence (1.55).



Scheme 1.10. Molander's Synthesis of Z Alkenyl-B(pin)s.

In 2002, Miyaura disclosed a trans-selective hydroboration method of terminal alkynes, catalyzed by [Rh(cod)Cl]<sub>2</sub> (Scheme 1.11).<sup>22</sup> Oxidative addition into the C<sub>sp</sub>-H/D bond leads to the alkynyl-Rh species **X**, which isomerizes to the vinylidene **XI**. From there, oxidative addition into pinacolborane delivers species **XI**. Anti addition of the boron to the vinylidene is favored to deliver thermodynamically favored *E*-**XIII**. The observed  $\beta$ -deuterium atom supports the vinylidene species intermediate mechanism. With the exception of **1.52**, the products disclosed are more sterically hindered, such as phenyl (**1.44**) or contain bulkier  $\alpha$ -substituents (**1.59**, **1.60** and **1.61**). These boronates are obtained in high stereoselectivity only with the addition of triethylamine to suppress the cis-hydroboration pathway.

<sup>(22)</sup> Ohmura, T.; Yamamoto, Y.; Miyaura, N. J. Am. Chem. Soc. 2000, 122, 4990-4991.



Scheme 1.11. Rh-Catalyzed trans-Hydroboration of Terminal Alkynes by Miyaura.

A similar transformation was published by Leitner, but the trans-hydroboration was catalyzed by a Ru-pincer complex (Scheme 1.12).<sup>23</sup> The mechanism proposed is similar to that of Miyaura's (cf. Scheme 1.11) where the reaction goes through a vinylidene intermediate that delivers the trans hydroboration intermediate. The scope of this method includes long aliphatic chains (1.64), carbocycles (1.52), enamines (1.65) and styrenes of different electronics (1.44 and 1.66), all in yields greater than 68% yield. Most of these products are generated with high *Z* selectivities (>90:10 *Z:E*). Though the reaction yields great stereose-lectivities, the reaction must be performed at a low temperature (-15 °C) to furnish such results.

<sup>(23)</sup> Gunanathan, C.; Hölscher, M.; Pan, F.; Leitner, W. J. Am. Chem. Soc. 2012, 134, 14349-14352.



Scheme 1.12. Ru-catalyzed trans-Hydroboration of Terminal Alkynes.

In 2015, Chirik disclosed Co-catalyzed hydroboration of terminal alkynes to generate cis alkenyl-B(pin) compounds (Scheme 1.13).<sup>24</sup> Alkyl-substituted (1.64), allylic phthalimide (1.66) and styrenyl B(pin) compounds (1.44) are generated with high Z selectivities. Electron-rich styrenyl boronates fail to deliver high Z selectivities (1.67, 87:13 Z:E) compared to electron-withdrawing styrenyl boronates. While carbocycle-substituted alkynes exhibit decent reactivity (ca 50% conv), Z selectivities of smaller carbocycles suffer due to slow hydroboration. According to the mechanism proposed, the reaction does not proceed through a metal–vinylidene, which is the intermediate Miyaura claims is responsible for the high selectivities observed. Although this method utilizes an inexpensive metal, the results and scope do not compare favorably to the other methods that take advantage of the reactivity of more costly alternatives.

<sup>(24)</sup> Obligacion, J.; Neely, J. M.; Yazdani, A. N.; Pappas, I.; Chirik, P. J. J. Am. Chem. Soc. 2015, 137, 5855–5858.



Scheme 1.13. Chirik's Co-catalyzed trans-Hydroboration of Terminal Alkynes.

Cross-metathesis offers a different disconnection to generate alkenyl boronates, but the method reported mainly affords the *E* isomer.<sup>25</sup> In 2003, Grubbs reported CM with vinyl-B(pin) and propenyl-B(pin) to synthesize thermodynamically favored *E*-alkenyl boronates.<sup>26</sup> Two examples presented were synthesized by CM with vinyl-B(pin) **1.68** to give 86% yield of **1.71** with 12:88 *Z:E*. When alkene **1.70** was reacted with a mixture of *E*- and *Z*-propenyl-B(pin) **1.69**, the yield increases to 99% and the selectivity also increased to 9:91 *Z:E*.<sup>2616</sup> For alkenyl boronate **1.72**, heightened reactivity and selectivity was also observed when the reaction was performed with **1.69** (versus **1.68**). Because of these results,

<sup>(25)</sup> There is one example of a Z-alkenyl-B(pin) in a report regarding CM of electron-deficient alkenes, see: Quigley, B. L.; Grubbs, R. H. *Chem. Sci.* **2014**, *5*, 501–506.

<sup>(26)</sup> Morrill, C.; Grubbs, R. H. J. Org. Chem. 2003, 68, 6031-6034.

the remainder of the substrate scope was generated with 1,2-disubstituted alkene 1.69.<sup>27</sup> Alkyl-substituted and allylic-substituted alkenyl-B(pin) compounds were synthesized in good yields and good selectivities. More sterically hindered substrates yield purely the trans isomers (1.52 and 1.44). While improved selectivities are observed with 1.69, it is significantly more expensive than monosubstituted 1.68. For these same reasons, we were motivated to develop a highly efficient and stereoselective method based on the CM of vinyl boronate 1.68.





<sup>(27) (</sup>a) Ulman, M.; Grubbs, R. H. J. Org. Chem. 1999, 64, 7202–7207. (b) Sanford, M. S.; Love, J. A.; Grubbs, R. H. J. Am. Chem. Soc. 2001, 123, 6543–6554. (c) Hong, S. H.; Day, M. W.; Grubbs, R. H. J. Am. Chem. Soc. 2004, 126, 7414–7415

# **1.3 Synthesis of** *Z***-(Pinacolato)allylboron Compounds through Stereose**lective Catalytic Cross-Metathesis

## **1.3.1.** Preliminary Studies with Commonly Used Mo- and Ru-Based Complexes, and Stereogenic-at-Mo Complexes

We began our studies by exploring the CM of allyl-B(pin) **1.26** with terminal olefin **1.73** using commercially available catalysts. For ease of isolation during our screening, allylic boron **1.74** was oxidized to allylic alcohol **1.75**. In the presence of 5.0 mol % of Mobased complex **1.76**, allylic alcohol was isolated in 54% yield, but only with 26% *Z*. Rubased complexes failed to perform better. With Ru-complex **1.77**, only 31% of the desired product was obtained with a 15:85 *Z*:*E* ratio. Complex **1.21** yields 16% of **1.75** with mainly *E* product (20:80 *Z*:*E*). The catalysts that are commercially available fail to provide efficient and stereoselective reactions with allyl-B(pin) and terminal olefins.

#### Table 1.1. Catalytic CM with Allylboronate 1.26 and Representative Commercially Available Complexes.

(pin)B + = 1.26 (	$\begin{array}{c} 5.0 \text{ mol } \% \text{ complex} \\ \hline 1.73 \\ (5.0 \text{ equiv}) \end{array} \xrightarrow{5.0 \text{ mol } \% \text{ complex}} 100 \text{ torr, } C_6H_6 \\ 22 \text{ °C, } 2.0 \text{ h} \end{array}$	(pin)B C <sub>8</sub> H <sub>17</sub> H <sub>2</sub> O NaO 1.74 22 °C,	HO H 2 h 1.75
entry	complex	yield (%) <sup>c</sup>	Z:E <sup>b</sup>
1	1.76	54	26:74
2	1.77	31	15:85
3	1.21	16	20:80

<sup>a</sup> Reactions performed in  $C_6H_6$  under  $N_2$  atm. <sup>b</sup> Determined by analysis of <sup>1</sup>H NMR spectra of unpurified mixtures (of **1.74** for conv and of **1.75** for *Z:E*) and refer to consumption of the limiting substrate (±2%). <sup>c</sup> Yield of isolated and purified **1.75** (isomeric mixture).



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We then decided to explore our library of catalysts (Table 1.2). In the presence of adamantyl-based catalyst 1.78, we observed 50% conv to allylic alcohol 1.75 in four hours, but the Z:E ratio is only 87:13 (entry 1). If the reaction is allowed to proceed for 24 h, an equal mixture of the two isomers was detected. The size difference between the adamantyl and bromo-bearing aryloxide group leads to high kinetic selectivity, but olefin isomerization cannot be inhibited. By exchanging the bromide on the aryloxide to a larger iodide, slightly higher conversion was observed after 24 h without significant post-metathesis isomerization (entry 2, 81:19 Z:E). By switching the adamantylimido for arylimido groups (1.80 and 1.81), lower selectivities are observed (entries 3–4). The electron-withdrawing  $CF_3$  group of **1.81** makes the Mo-center more Lewis acidic and thus, more reactive compared to 1.80. Such heightened reactivity may lead to more product, but the products are more prone to post-metathesis isomerization (Table 1.2, entry 4). Because of the orthosubstituents pointing down in the arylimido groups, the kinetic selectivity observed is lower because of a small size difference. In contrast, less post-metathesis isomerization occurs. By switching to a W-based catalyst, 78% of 1.26 was consumed and 1.75 was obtained in 95:5 Z:E (entry 5). While the catalyst is considerably less reactive than its Mo-counterparts, this allows for longer living alkylidene species that can participate in productive CM.<sup>28</sup> The larger steric difference between the imido group and aryloxide helps to furnish high Zselectivity.

<sup>(28)</sup> Yu, M.; Wang, C.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* 2011, *479*, 88–93.

### **1.3.2. MAP–Mo-Catalyzed Z-Selective CM of Allyl-B(pin)**

We discovered a variety of terminal olefins perform well in the CM with allyl-B(pin) **1.26** (Scheme 1.15). Due to the sensitivity of the allylic-B(pin) compounds, the products were treated with benzaldehyde in the same pot to give the functionalized homoallylic alcohols. The diastereoselectivity observed from these reactions is reflective of the *Z* selectivity obtained in the CM reaction. Homoallylic compounds containing long alkyl chains, containing halides or protected ethers, are afforded in high yields and high dr (72–84% yield, 92:8–96:4 dr). Benzyl substituted allylic B(pin) **1.86** is afforded in 91% yield as homoallylic alcohol **1.87** with 95:5 dr. With allylic TBS-ether, only 23% yield of **1.93** is isolated when the reaction is performed in the presence of **1.82**. We required more active

(pin)B 1.26	+C <sub>8</sub> H <sub>17</sub> 100 to 1.73 22 (5.0 equiv)	nplex (pin)l rr, C <sub>6</sub> H <sub>6</sub> .°C	<sup>B</sup> C <sub>8</sub> H <sub>17</sub> 1.74	H <sub>2</sub> O <sub>2</sub> HO− NaOH 22 °C, 2 h	C <sub>8</sub> H <sub>17</sub>
entry	complex; mol %	time (h)	conv (%) <sup>b</sup>	yield (%) <sup>c</sup>	<b>Z:E</b> <sup>b</sup>
1	<b>1.78;</b> 3.0	4.0	50	nd	87:13
2	<b>1.79;</b> 3.0	24	66	nd	81:19
3	<b>1.80;</b> 5.0	5.0	75	nd	78:22
4	<b>1.81;</b> 5.0	4.0	52	nd	69:31
5	<b>1.82;</b> 5.0	2.0	78	65	95:5

Table 1.2. Catalyst Screening of CM with Allylboronate 1.26.

<sup>a</sup> Reactions performed in  $C_6H_6$  under  $N_2$  atm. <sup>b</sup> Determined by analysis of <sup>1</sup>H NMR spectra of unpurified mixtures (of **1.74** for conv and of **1.75** for *Z:E*) and refer to consumption of the limiting substrate (±2%). <sup>c</sup> Yield of isolated and purified **1.75** (isomeric mixture).



complex **1.78** to achieve good reactivity (79% yield) and detected relatively minimal isomerization due to the steric hindrance of the sizeable silyl group (91:9 dr). Esters are tolerated and furnish lactone **1.89** in 68% yield and >98:2 dr after allylation. 1,3-Dienes also behave well in this reaction, delivering **1.95** in 72% yield and 95:5 dr.<sup>29</sup> Dienyl allylic-B(pin) is



Scheme 1.15. Z-Selective CM with Allyl-B(pin) 1.26 with Stereogenic-at-W 1.82.<sup>a</sup>

<sup>&</sup>lt;sup>a</sup> Reactions performed in  $C_6H_6$  under  $N_2$  atm. Yields are of isolated products over two steps. <sup>b</sup> Synthesis of **1.93** involved the use of Mo complex **1.78** under otherwise identical conditions. <sup>c</sup> Formation of **1.89** involved treatment with NaOH.

<sup>(29)</sup> For catalytic Z-selective homocoupling of 1,3-dienes, see: Townsend, E. M.; Schrock, R. R.; Hoveyda, A. H. J. Am. Chem. Soc. 2012, 134, 11334–11337.

noteworthy, not only because CM is not observed with the internal olefin, but also because these products cannot be afforded through 1,4-hydroboration.

# 1.4 Synthesis of Z-(Pinacolato)alkenylboron Compounds through Stereoselective Catalytic Cross-Metathesis

Besides the utility of alkenyl boron compounds, cross-metathesis with vinyl-B(pin) catalyzed by Mo- and W-based complexes were unknown prior to disclosure by our group. One of the challenges with vinyl-B(pin) is the partially empty p orbital of the boron atom (**XXIII**, Figure 1.1). Delocalization of electron density at the alkylidene carbon into the p orbital means a more stable complex, but that also translates to a less reactive complex. Being a more sterically demanding substituent adds another degree of difficulty.

Figure 1.1. Electronics of B(pin)-Alkylidene



## 1.4.1. Preliminary Studies with Commonly Used Mo- and Ru-Based Complexes, and Stereogenic-at-Mo Complexes

Early studies with vinyl-B(pin) **1.68** and allyl benzene **1.96** were performed with commercially available metathesis complexes. With **1.76**, we observed only 68% Z after only 10 minutes. Prolonging the reaction did not provide greater consumption of **1.96**. The highly Lewis acidic bis(hexafluoro)-alkoxide Mo alkylidene is thus more electron-deficient due to the B(pin) substituent and in turn, leads to short catalyst lifetime. With Ru-

based complexes 1.77 and 1.21, similar efficiencies were observed (68-75% yield), but selectivities hovered around 90:10 *E:Z*. Overall, these catalysts are incapable of furnishing the *Z* alkenyl B(pin) compounds with high reactivity.

() ({	<b>1.68</b> 5.0 equiv)	torr, $C_6H_6$ , 22 °C	(pin)BP 1.97	h	
entry	complex	time	conv (%) <sup>b</sup>	yield (%) <sup>b</sup>	<b>Z:E</b> <sup>b</sup>
1	1.76	10 min	33	15	68:32
2	1.77	24 h	98	78	9:91
3	1.21	24 h	86	65	11:89

 Table 1.3. Catalytic CM with Vinylboronate 1.68 and Representative Commercially Available Complexes.

<sup>a</sup> Reactions performed in  $C_6H_6$  under  $N_2$  atm. <sup>b</sup> Determined by analysis of <sup>1</sup>H NMR spectra of unpurified mixtures and refer to consumption of the limiting substrate (±2%). <sup>c</sup> Yield of isolated and purified **1.97** (isomeric mixture).



Our collection of Mo-based complexes provided considerably improved Z selectivities. With adamantyl complexes **1.78** and **1.79**, the CM to **1.97** is highly Z selective even after 18 h, but conversion plateaus around 50%. The smaller adamantyl group (versus aryl groups) can yield higher Z selectivity, but the derived methylidene of these complexes is comparably less stable, leading to shorter catalyst lifetime. In contrast, bulkier arylimidocontaining complexes **1.80** and **1.81** consumes most of the limiting substrate without much loss in selectivity. When the reaction was performed in the presence of W-complex **1.82**, we saw low reactivity as well as poorer selectivity, for reasons that are not clear to us. Due to the relative ease of synthesis of **1.80** compared to **1.81**, we chose to continue our studies with dimethylphenylimido MAP–Mo complex **1.80**.

	(pin)B + Ph - 1.68 1.96 (5.0 equiv)	complex C <sub>6</sub> H <sub>6</sub> , 22 °C, 18 h	(pin)BPh 1.97	
entry	complex; mol %	conv (%) <sup>b</sup>	yield (%) <sup>c</sup>	<b>Z:E</b> <sup>b</sup>
1	<b>1.78;</b> 3.0	56	nd	96:4
2	<b>1.79;</b> 3.0	50	nd	93:7
3	<b>1.80;</b> 5.0	95	68	93:7
4	<b>1.81;</b> 5.0	98	69	93:7
5	<b>1.82;</b> 5.0	66	nd	86:14

Table 1.4. Catalyst Screening of CM with Vinylboronate 1.68.

<sup>a</sup> Reactions performed in  $C_6H_6$  under  $N_2$  atm. <sup>b</sup> Determined by analysis of <sup>1</sup>H NMR spectra of unpurified mixtures and refer to consumption of the limiting substrate (±2%). <sup>c</sup> Yield of isolated and purified **1.97** (isomeric mixture).



### 1.4.2. MAP-Mo-Catalyzed Z-Selective CM of Vinyl-B(pin) with Aliphatic Ole-

### fins

For the reaction of aliphatic olefins with vinyl-B(pin), it was beneficial to perform the reaction with an excess of the boronate. As mentioned previously, B(pin)-substituted alkylidene **XXIII** is favored due to the stabilization of electron density from the alkylidene. Competitive formation of **XXIII** alkylidene effectively reduces the concentration of methylidene in the reaction mixture. From methylidene **XXIV**, there are two pathways to arrive at **XXIII**. Between the product and **1.68**, however, the terminal olefin incurs less steric interactions with **XXIV** through pathway (b). Furthermore, the catalyst is surrounded by
an excess of vinyl-B(pin) making pathway (b) more likely to occur. As a result, post-metathesis isomerization due to methylidene **XXIV** is minimized.



Scheme 1.16. Potential Pathways to Generate B(pin)-Substituted Alkylidene.

The examples shown in Scheme 1.17 illustrate the diverse functional group tolerance of the CM of vinyl B(pin) with Mo-based complex **1.80**. Long alkyl-substituted chains are obtained in good yields and good Z selectivities (**1.45** and **1.98**). Sizeable allylic phthalimide, silyl ether and cyclohexyl substituted alkenyl-B(pin) molecules (**1.58**, **1.100**, **1.57**) are isolated in up to 51-71% yield with 93:7-96:4 Z:E. Pure Z isomer of enol ether **1.99** is isolated in 80% yield. 1,3-dienes are not limited to CM with allyl-B(pin), but also perform well with CM with vinyl-B(pin) (**1.102**, 72% yield, 93:7 Z:E). Diboryl compound **1.101**, generated in 60% yield in 97:3 Z:E, contains two differentiated boryl species that have the potential for two new C–C bond forming reactions.



Scheme 1.17. Z-Selective CM with Vinyl-B(pin) 1.68 with Stereogenic-at-Mo 1.80.<sup>a</sup>

<sup>a</sup> Reactions performed in C<sub>6</sub>H<sub>6</sub> under N<sub>2</sub> atm. Yields are of isomeric mixtures of isolated products, except for **1.99**.

#### **1.4.3. MAP–Mo-Catalyzed Z-Selective CM of Vinyl-B(pin) with Styrenes**

The diverse set of aliphatic olefins metathesized with vinyl-B(pin) encouraged us to explore styrenes as well. The rationale that we had set in place regarding the benefits of excess vinyl-B(pin) does not apply to the styrenyl system (Table 1.5). With complex **1.78**, we observe only 32% conversion to styrenyl-B(pin) **1.44** with moderate selectivity (entry 1). Potential decomposition of the catalyst was suspected and a vacuum of 100 torr was applied. Nonetheless, reactivity is similar with no enhancement in stereoselectivity either (entry 2). Improvement is observed when the stoichiometry is reversed. Under ambient pressure, the conversion almost doubles to 60%, but not without a drop in the *Z*:*E* ratio

(entry 3, 60:40 Z:E). When the reaction is placed under a vacuum of 100 torr, then styrenyl-B(pin) **1.44** is obtained in 66% yield with 95:5 Z:E (entry 4).

	(pin)B	+/ <sup>Ph</sup> 1.103	3.0 mol C <sub>6</sub> H <sub>6</sub> , 22	% 1.78	(pin)B Ph 1.44	in)B Ph 1.44				
entry	1.68:1.103	pressure	time (h)	conv (%) <sup>b</sup>	yield (%) <sup>c</sup>	<b>Z:E</b> <sup>b</sup>				
1	5:1	ambient	24	32	nd	85:15				
2	5:1	100 torr	24	38	nd	85:15				
3	1:5	ambient	24	60	nd	60:40				
4	1:5	100 torr	4.0	87	66	95:5				

 Table 1.5. Catalyst Screening of CM with Vinylboronate 1.68.

<sup>a</sup> Reactions performed in  $C_6H_6$  under  $N_2$  atm. <sup>b</sup> Determined by analysis of <sup>1</sup>H NMR spectra of unpurified mixtures and refer to consumption of the limiting substrate (±2%). <sup>c</sup> Yield of isolated and purified **1.44** (isomeric mixture).

We deduce that B(pin)-substituted alkylidenes are slower to react with styrene and require more styrene to compensate for any stilbenes that are formed from homocoupling.<sup>30</sup> Due to the electronic delocalization, more stable alkylidene complex **XXV** (versus **XXIX**) is postulated to be the resting state in the catalytic cycle. As low quantities of the homocoupled product of vinyl-B(pin) is detected, we can focus on the potential pathways in which **XXV** reacts with styrene. The left pathway in which desired styrenyl-B(pin) products are formed must proceed through metallacyclobutane **XXVI**. However, this process is slow as the incoming olefin must align itself in a way that the two large groups induce steric repulsion with each other. The degenerate pathway that leads to metallacyclobutane **XXVIII** would be faster due to less steric repulsion between the boron and phenyl groups. An excess of styrene drives the reaction to proceed through the slower pathway.

<sup>(30)</sup> Ibrahem, I.; Yu, M.; Schrock, R. R.; Hoveyda, A. H. J. Am. Chem. Soc. 2009, 131, 3844–3845.



Scheme 1.18. Rationale of Excess Styrene in Vinyl-B(pin) CM.

CM of vinyl-B(pin) with styrene demonstrated high efficiency with aryl units of varying electronics (Scheme 1.19). Electron-withdrawing styrenyl-B(pin) compounds with m-OMe 1.104 and p-CF<sub>3</sub> 1.105 are afforded with equally high selectivity (95:5 Z:E, 69–93% yield). A lesser excess of electron-rich styrenes is needed as they are less inclined to



<sup>a</sup> Reactions performed in  $C_6H_6$  under  $N_2$  atm. Yields are of isomeric mixtures of isolated products. <sup>b</sup> Reaction is performed with 1.5 equiv of styrene.

homocouple with each other. With 1.5 equivalents of *p*-OMe styrene, **1.59** was obtained in 69% yield and 93% *Z*. Trimethoxystyrene proceeds to high conversion (80%) to afford **1.106** in 73% yield in a 96:4 *Z*:*E* ratio.

# 1.4.4. Synthesis of Combretastatin A-4 through Suzuki Cross-Coupling of Alkenyl-B(pin)

Combretastatin A-4 was first isolated and studied in 1989 by Pettit and co-workers from the subtropical tree *Combretum caffrum*.<sup>31</sup> The stilbene was found to be one of the strongest inhibitors of colchicine binding to tubulin and also a strong inhibitor of tubulin polymerization with IC<sub>50</sub> values between 2–3  $\mu$ M. The compound was found to exhibit cytotoxicity against multiple colon cancer cell lines and analogues have been synthesized to find treatments for other types of cancer. One of the intriguing details of combretastatin A-4 is that the cis stilbenoid is 10,000 times more active than its trans isomer.

We approached the synthesis of combretastatin A-4 through a Suzuki coupling of the two aryl rings. In our studies of styrene CM with **1.68**, we found styrenyl-B(pin) **1.106** can be synthesized in high yield with a *Z* selectivity of 96:4. We subjected this compound to an excess of aryl bromide **1.107** and catalytic amounts of Pd(PPh<sub>3</sub>)<sub>4</sub> with Cs<sub>2</sub>CO<sub>3</sub>. The boronate was completely consumed and combretastatin was isolated in 74% yield with complete stereoretention (96:4 *Z*:*E*). Overall, our synthesis required three steps<sup>32</sup> and highlights the utility of the efficiency and selectivity of the CM with vinyl-B(pin). With this strategy, we have a shorter route compared to many other syntheses.<sup>33</sup> Compared to syntheses of equal number of steps,<sup>33</sup> our overall yield is significantly higher (45% versus 8.4% overall yield).

<sup>(31)</sup> Pettit, G. R.; Singh, S. B.; Boyd, M. R.; Hamel, E.; Pettit, R. K.; Schmidt, J. M.; Hogan, F. J. Med. Chem. 1995, 38, 1666–1672.

<sup>(32)</sup> For preparation of 3,4,5-trimethoxystyrene, see: Faler, C. A.; Joullié, M. M. Org. Lett. 2007, 9, 1987–1990.

<sup>(33)</sup> For previous syntheses of combretastatin A-4, see: (a) Lawrence, N. J.; Ghani, F. A.; Hepworth, L. A.; Hadfield, J. A.; McGown, A. T.; Pritchard, R. G. Synthesis 1999, 1656–1660. (b) Gaukroger, K.; Hadfield, J. A.; Hepworth, L. A.; Lawrence, N. J.; McGown, A. T. J. Org. Chem. 2001, 66, 8135–8138. (c) Odlo,



Scheme 1.20. Synthesis of Combretastatin A-4 through Cross-coupling of Z-Alkenyl Boronate 1.106.

# **1.5 Conclusions**

We have developed an efficient Mo- and W-catalyzed Z-selective CM for allylic and alkenyl-B(pin) compounds. These transformations highlight the capabilities of high oxidation state alkylidenes to promote efficient CM with allylic and vinyl boronates. The Z-allylic compounds disclosed in this chapter offer a simple disconnection, some of which, such as 1,3-dienes, cannot be accessed through other means. As far as we know, this is the only example of a W-catalyzed cross-metathesis. We found an efficient and Z-selective method to generate alkenyl-B(pin) molecules that not only tolerate aliphatic terminal alkenes, but also styrenes. We discovered that an excess of alkenyl-B(pin) could not only facilitate an efficient CM but also inhibit post-metathesis isomerization due to a B(pin)stabilized alkylidene with aliphatic olefins. Reactions with styrenes are improved with an excess of styrene due to the homodimerization of styrenes compared to the productive CM. We were able to combine two powerful catalytic strategies of CM and cross-coupling to efficiently synthesize combretastatin A-4. Our work has not only been showcased in this report, but also highlighted in cross-coupling for the total synthesis of disorazole C-1<sup>34</sup> and enantioselective allylic substitution for the synthesis of nyasol.<sup>35</sup>

K.; Klaveness, J.; Rongved, P.; Hansen, T. V. *Tetrahedron Lett.* **2006**, *47*, 1101. (d) Lara-Ochoa, F.; Espinoza-Perez, G. *Tetrahedron Lett.* **2007**, *48*, 7007–7010. (e) Pettit, G. R.; Minardi, M. D.; Hogan, F.; Price, P. M. J. Nat. Prod. **2010**, *73*, 399–403. (f) Wardrop, D. J.; Komenda, J. P. Org. Lett. **2012**, *14*, 1548–1551.

<sup>(34)</sup> Speed, A. W. H.; Mann, T. J.; O'Brien, R. V.; Schrock, R. R.; Hoveyda, A. H. J. Am. Chem. Soc. 2014, 136, 16136–16139.

<sup>(35)</sup> Gao, F.; Carr, J. L. Hoveyda, A. H. J. Am. Chem. Soc, 2014, 136, 2149-2161.

# **1.6 Experimental**

• General: <sup>1</sup>H NMR spectra were recorded on a Varian Unity INOVA 400 (400 MHz). Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance resulting from incomplete deuteration as the internal reference (CDCl<sub>3</sub>:  $\delta$  7.26). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, br = broad, m = multiplet, app = apparent), and coupling constants (Hz). <sup>13</sup>C NMR spectra were recorded on Varian Unity INOVA 400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance resulting from incomplete deuteration as the internal reference (CDCl<sub>3</sub>:  $\delta$  77.16). Infrared (IR) spectra were recorded on a Bruker FTIR Alpha (ATR Mode) spectrometer, v<sub>max</sub> in cm<sup>-1</sup>. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). High-resolution mass spectrometry was performed on a JEOL Accu TOF Dart (positive mode) at the Boston College Mass Spectrometry Facility.

**Vacuum Pumps:** KNF Laboport N840.3FTP diaphragm vacuum pump connected to a Welch Labaid vacuum controller generates a vacuum of 100 torr at point of connection to the reaction vessel.

**Materials:** All reactions were carried out in oven-dried (135 °C) or flame-dried glassware under an inert atmosphere of dry  $N_2$  unless otherwise stated. Solvents were purged with argon and purified under a positive pressure of dry argon by a modified Innovative Technologies purification system: diethyl ether (Aldrich), and dichloromethane (Fisher) were passed through activated alumina columns; benzene (Alfa Aesar), and *n*-pentane (Fisher) were passed successively through activated Cu and alumina columns. *n*-Pentane was allowed to stir over concentrated H<sub>2</sub>SO<sub>4</sub> for three days, washed with water, followed by a saturated aqueous solution of NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub>, and filtered before use in a solvent purification system. Tetrahydrofuran (Aldrich) was distilled from sodium benzophenone ketyl. **Metal-based Complexes:** Mo-based bis-alkoxide complex **1.76** was prepared according to a

previously reported procedure.<sup>36</sup> Ruthenium complexes **1.21** and **1.77** were obtained from Materia, Inc. and recrystallized from pentane-dichloromethane prior to use. W complex **1.82** was prepared according to a previously reported procedure.<sup>17</sup> Mo-monopyrrolide-monoaryloxide complexes **1.78**, **1.79** were prepared in situ according to published procedures from Mo-bis(pyrrolide) complex **1.109** with chiral alcohols **1.112** and **1.113**, respectively.<sup>30</sup> Mo-monopyrrolide-monoaryloxide complex **1.80** was prepared in situ according to published procedures from Mo bis(pyrrolide) complex **1.80** was prepared in situ according to published procedures from Mo bis(pyrrolide) complex **1.110** with chiral alcohol **1.113**. Mo-monopyrrolide-monoaryloxide complex **1.81** was prepared in situ according to published procedures from Mo-bis(pyrrolide) complex **1.111** with chiral alcohol **1.112**.<sup>5a</sup> All Mo and W complexes were handled under an atmosphere of N<sub>2</sub> in a dry box.



## Reagents

Allyl alcohol was purchased from Aldrich and used as received.

Allylbenzene was purchased from Aldrich and distilled over CaH<sub>2</sub> prior to use.

112, 3875–3886.

<sup>(36)</sup> Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. J. Am. Chem. Soc. 1990,

(Allyloxy)(tert-butyl)dimethylsilane was prepared according to a literature procedure<sup>37</sup> and distilled from CaH<sub>2</sub> prior to use.

*N*-allylphthalimide was prepared according to a literature procedure<sup>38</sup> and was dried by azeotropic drying with C<sub>6</sub>H<sub>6</sub>.

**Allylboronic acid pinacol ester** was purchased from Frontier Scientific and distilled from CaH<sub>2</sub> prior to use.

Benzaldehyde was purchased from Aldrich and distilled from CaH<sub>2</sub> prior to use.

8-Bromo-1-octene was purchased from Aldrich and distilled from CaH<sub>2</sub> prior to use.

*n*-Butylvinyl ether was purchased from Aldrich and distilled from CaH<sub>2</sub> prior to use.

tert-Butyldimethylsilyl chloride was purchased from Oakwood and used as received.

1-Decene was purchased from Aldrich and distilled over CaH<sub>2</sub> prior to use.

(*E*)-1,3-Decadiene was prepared by the procedure below and purified by distillation from CaH<sub>2</sub> prior to use.

**Hydrogen peroxide** 35 wt % aqueous solution was purchased from Aldrich and used as received.

Imidazole was purchased from Aldrich and used as received.

**1-Methoxy-4-((oct-7-en-1-yloxy)methyl)benzene** was prepared according to a literature procedure.<sup>5a</sup>

*m*-Methoxystyrene was purchased from Aldrich and distilled over CaH<sub>2</sub> prior to use.

*p*-Methoxystyrene was purchased from Aldrich and distilled over CaH<sub>2</sub> prior to use.

Methyltriphenylphosphonium bromide was purchased from Aldrich and was used as received.

trans-2-Nonenal was purchased from Aldrich and used as received.

<sup>(37)</sup> Nielsen, L.; Skrydstrup, T. J. Am. Chem. Soc. 2008, 130, 13145-13151

<sup>(38)</sup> Abulikemu, A.; Halász, G.; Csámpai, A.; Gömöry, A.; Rábai, J. J. Fluorine Chem. 2004, 125, 1143–1146.

**Palladium tetrakis(triphenylphosphine)** was purchased from Strem and used as received. **Phenyl pent-4-enoate** was prepared according to a literature procedure.<sup>5a</sup>

Sodium hexamethyldisilylamide was purchased from Strem and used as received.

Sodium hydroxide was purchased from Fisher and used as received.

Styrene was purchased from Aldrich and distilled over CaH<sub>2</sub> prior to use.

**p-Trifluoromethylstyrene** was purchased from Aldrich and distilled over CaH<sub>2</sub> prior to use.

3,4,5-Trimethoxybenzaldehyde was purchased from Aldrich and used as received.

3,4,5-Trimethoxystyrene was dried by azeotropic drying with anhydrous C<sub>6</sub>H<sub>6</sub>.

Vinylcyclohexane was purchased from Aldrich and distilled over CaH<sub>2</sub> prior to use.

**Vinylboronic acid pinacol ester** was purchased from Aldrich and was purified by silica gel chromatography to remove isopropanol impurity (10 % diethyl ether in hexanes eluent). The boronate was distilled over CaH<sub>2</sub> prior to use.

## • (Pinacolato)allylboron Cross-Metathesis.

(*Z*)-Undec-2-en-1-ol (1.75). In an N<sub>2</sub>-filled glove box, an oven-dried 4 mL vial equipped with a stir bar was charged with allyl(pinacolato)boronate 1.26 (38.3 mg, 0.228 mmol) and 1-decene (216  $\mu$ L, 1.14 mmol). A solution of W-based complex 1.82 in benzene (0.1 M, 114  $\mu$ L, 0.0114 mmol, 5.0 mol %) was then added through a syringe, and a septum, fitted with an outlet needle, was immediately placed on the vial. An adapter was attached to the top of the septum and vacuum (100 torr) was applied. The resulting solution was allowed to stir under vacuum for 2 h. The reaction was quenched by addition of wet CDCl<sub>3</sub> and 1.74 was obtained in 78% conv and 97:3 *Z:E* based on <sup>1</sup>H NMR analysis. The resulting brown solid was dissolved in thf (1 mL) and cooled to 0 °C in an ice bath. A 2.0 M aqueous solution of NaOH solution (320  $\mu$ L, 0.640 mmol) was added, followed by of H<sub>2</sub>O<sub>2</sub> (62  $\mu$ L, 0.64 mmol). The mixture was allowed to warm to 22 °C over 2 h. The solution was neutralized by addition of 1 M HCl and washed with CH<sub>2</sub>Cl<sub>2</sub> (3 x 1 mL). The organic layer was dried over MgSO<sub>4</sub> and filtered. Solvent was removed to reveal yellow oil, which was

purified by silica gel chromatography (10% Et<sub>2</sub>O in hexanes) to obtain **1.75** (24.6 mg, 0.144 mmol, 63% yield) as clear colorless oil. **IR (neat):** 3317 (b), 3015 (w), 2923 (s), 2854 (s), 1465 (m), 1007 (m), 722 (m); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), *Z*-isomer:  $\delta$  5.64 – 5.49 (2H, m), 4.19 (2H, d, *J* = 6.1 Hz), [diagnostic *E* isomer signal 4.08 (2H, d, *J* = 5.5 Hz)], 2.07 (2H, q, *J* = 7.0 Hz), 1.41 – 1.19 (12H, m), 0.92 – 0.82 (3H, m); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  133.4, 128.4, 58.8, 32.0, 29.8, 29.6, 29.4, 29.4, 27.6, 22.8, 14.2; HRMS (ESI<sup>+</sup>) [M+H-H<sub>2</sub>O]<sup>+</sup> calcd for C<sub>11</sub>H<sub>21</sub>: 153.1643, found: 153.1641.

Representative experimental procedure for allylboronate CM and subsequent treatment with benzaldehyde: (1S,2R)-1-Phenyl-2-vinyldecan-1-ol (1.83) In an N2-filled glove box, an oven-dried 4 mL vial equipped with a stir bar was charged with allyl(pinacolato)boronate 1.26 (28.1 mg, 0.167 mmol) and 1-decene (158 µL, 0.836 mmol). A benzene solution of W-based complex 1.82 (0.1 M, 84 µL, 0.0084 mmol, 5.0 mol %) was added by a syringe, and a septum, fitted with an outlet needle, was immediately placed on the vial. An adapter was attached to the top of the septum, and vacuum (100 torr) applied. The resulting solution was allowed to stir under vacuum for 2 h. The reaction was guenched by addition of wet CDCl<sub>3</sub>; **1.73** was obtained in 80% conv by <sup>1</sup>H NMR analysis. The resulting brown solid was dissolved in thf (1 mL) and benzaldehyde (34 µL, 0.33 mmol) was added. The resulting mixture was allowed to stir for 2 h. The volatiles were removed in vacuo and the resulting residue was purified by silica gel chromatography (10% Et<sub>2</sub>O in hexanes) to afford 1.83 (32.5 mg, 0.125 mmol, 75% yield, 95:5 syn:anti) as clear yellow oil. IR (neat): 3408 (b), 3065 (w), 3029 (w), 2922 (s), 2853 (s), 1639 (w), 1603 (m), 1454 (w), 1024 (m), 999 (m), 912 (s), 763 (m), 699 (s), 630 (m), 543 (w); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 **MHz**), **Z-isomer:** δ 7.36 – 7.30 (2H, m), 7.26 (3H, s), [diagnostic *E* isomer signal 5.66 (1H, ddd, J = 17.1, 10.3, 9.2 Hz], 5.51 (1H, ddd, J = 17.1, 10.3, 9.1 Hz), 5.12 – 4.94 (2H, m), 4.62 (1H, d, J = 5.8 Hz), 2.41 (tdd, J = 9.4, 5.7, 3.3 Hz, 1H), 2.04 (1H, s), 1.70 - 1.47 (2H), 1.62 Hz = 0.61 Hz = 0.61 Hz = 0.61 Hzm), 1.42 – 1.05 (12H, m), 0.97 – 0.79 (3H, m); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 142.7, 138.8, 128.1, 127.5, 126.9, 117.4, 77.1, 51.6, 32.0, 29.8, 29.8, 29.7, 29.4, 27.4, 22.8, 14.3; **HRMS (ESI<sup>+</sup>)**  $[M+H-H_2O]^+$  calcd for C<sub>18</sub>H<sub>27</sub>: 243.2113, found: 243.2120.

(1*S*,2*R*)-8-Bromo-1-phenyl-2-vinyloctan-1-ol (1.85). Based on the general procedure for CM with allyl(pinacolato)boronate 1.26/addition to benzaldehyde, the reaction affording alcohol 1.85 proceeded to 95% conv. The resulting brown solid was purified by silica gel chromatography (10% Et2O in hexanes) and homoallylic alcohol 1.85 (27.3 mg, 0.0877 mmol, 84% yield, 95:5 *syn:anti*) was obtained as pale yellow oil. IR (neat): 3538 (b), 3402 (b), 3064 (w), 3029 (w), 2928 (m), 1639 (w), 1602 (w), 1493 (w), 1453 (m), 1252 (m), 1027 (m), 914 (m), 764 (m), 700 (s), 643 (m), 631 (m), 560 (m); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), *Z*-isomer:  $\delta$  7.35 – 7.28 (2H, m), 7.27 – 7.22 (3H, m), [diagnostic *E* isomer signal 5.64 (1H, ddd, *J* = 17.2, 10.2, 9.1 Hz)], 5.50 (1H, ddd, *J* = 17.1, 10.2, 9.1 Hz), 5.10 – 4.93 (2H, m), 4.60 (1H, dd, *J* = 5.9, 4.2 Hz), 3.36 (2H, t, *J* = 6.8 Hz), 2.43 – 2.33 (1H, m), 1.99 (1H, d, *J* = 4.3 Hz), 1.80 (2H, m, *J* = 7.0 Hz), 1.63 – 1.49 (1H, m), 1.33 (4H, dddd, *J* = 23.7, 11.2, 6.8, 2.6 Hz), 1.27 – 1.11 (3H, m); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  142.7, 138.7, 128.2, 127.5, 126.8, 117.5, 77.1, 51.5, 34.1, 32.9, 29.6, 28.9, 28.2, 27.2; HRMS (ESI<sup>+</sup>) [M+H-H<sub>2</sub>O]<sup>+</sup> calcd for C<sub>16</sub>H<sub>22</sub>Br: 293.0905, found: 293.0896.

(1*S*,2*R*)-2-Benzyl-1-phenylbut-3-en-1-ol (1.87). Based on the general procedure for CM with allyl(pinacolato)boronate 1.26/addition to benzaldehyde, the reaction affording alcohol 1.87 proceeded to 95% conv. The resulting brown solid was purified by silica gel chromatography (10% Et<sub>2</sub>O in hexanes) and homoallylic alcohol 1.87 (29.9 mg, 0.125 mmol, 88% yield, 95:5 *syn:anti*) was obtained as clear, yellow oil. **IR (neat):** 3570 (b), 3423 (b), 3082 (w), 3062 (w), 3027 (w), 2978 (w), 2918 (w), 2857 (w), 1639 (w), 1603 (w), 1494 (m), 1453 (m), 1420 (w), 1389 (w), 1302 (w), 1029 (m), 996 (m), 914 (m), 745 (m), 697 (s); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), *Z*-isomer:  $\delta$  7.44 – 7.06 (10H, m), [diagnostic *E* isomer 5.80 – 5.67 (1H, m)], 5.59 (1H, dddd, *J* = 17.2, 10.3, 8.7, 1.3 Hz), 4.98 (1H, dt, *J* = 10.4, 1.5 Hz), 4.85 (1H, dq, *J* = 17.1, 1.2 Hz), 4.76 – 4.68 (1H, m), 2.96 (1H, dd, *J* = 13.6, 4.1 Hz), 2.79 (1H, tt, *J* = 9.4, 5.0 Hz), 2.61 (1H, ddd, *J* = 13.7, 9.6, 1.3 Hz), 2.15 (1H, t, *J* = 3.4 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  142.5, 140.2, 137.7, 129.4, 128.3, 128.2, 127.7, 127.0, 126.0, 117.9, 76.6, 52.9, 36.3; HRMS (ESI<sup>+</sup>) [M+H-H<sub>2</sub>O]<sup>+</sup> calcd for C<sub>17</sub>H<sub>17</sub>: 221.1330, found: 221.1334.

(5*S*,6*S*)-6-Phenyl-5-vinyltetrahydro-2H-pyran-2-one (1.89). Based on the general procedure for CM with allyl(pinacolato)boronate 1.26/addition to benzaldehyde, the reaction affording the expected homoallylic alcohol proceeded to 78% conv and >98:2 *syn:anti* (<sup>1</sup>H NMR analysis). The resulting brown solid was treated with a 2 M solution of NaOH (1 mL) to generate lactone 1.89. The mixture was washed with CH<sub>2</sub>Cl<sub>2</sub> (3 x 1 mL). The organic layers were combined and dried over MgSO4 and filtered. Solvent was removed *in vacuo* to afford yellow oil, which was purified by silica gel chromatography (10% Et<sub>2</sub>O in hexanes) to obtain 1.89 (19.1 mg, 0.0944 mmol, 80% yield, >98:2 dr) as white solid (m.p. = 63–66 °C). IR (neat): 3066 (w), 3034 (w), 2928 (w), 1729 (s), 1642 (w), 1456 (m), 1348 (m), 1268 (m), 1197 (s), 1028 (s), 917 (s), 754 (s), 698 (s), 668 (m), 626 (m), 578 (w), 534 (m), 494 (w), 437 (w), 387 (w); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>), Z-isomer:  $\delta$  7.39 – 7.26 (m, 5H), 5.62 – 5.51 (1H, m), 5.07 – 5.02 (1H, m), 4.98 (2H, dt, *J* = 17.2, 1.2 Hz), 2.81 (2H, ddd, *J* = 18.0, 6.9, 4.6 Hz), 2.67 (2H, ddd, *J* = 18.0, 9.7, 7.0 Hz), 2.18 – 2.01 (1H, m), 2.01 – 1.85 (1H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  170.9, 138.3, 136.0, 128.7, 128.554, 127.2, 117.8, 86.0, 44.1, 29.3, 25.1; HRMS (ESI<sup>+</sup>) [M+H]<sup>+</sup> calcd for C<sub>13</sub>H<sub>15</sub>O<sub>2</sub>: 203.1072, found: 203.1076.

(1*S*,2*R*)-8-((4-Methoxybenzyl)oxy)-1-phenyl-2-vinyloctan-1-ol) (1.91). Based on the general procedure for CM with allyl(pinacolato)boronate 1.26/addition to benzaldehyde, the reaction affording alcohol 1.91 proceeded to 95% conv. The resulting brown solid was purified by silica gel chromatography (10% Et<sub>2</sub>O in hexanes) and homoallylic alcohol 1.91 (40.8 mg, 0.111 mmol, 83% yield, 96:4 *syn:anti*) was obtained as pale yellow oil. **IR (neat)**: 3434 (b), 3065 (w), 3030 (w), 3000 (w), 2930 (m), 2855 (m), 1612 (m), 1512 (s), 1454 (m), 1361 (m), 1301 (m), 1246 (s), 1172 (m), 1094 (s), 1035 (s), 913 (m), 820 (m), 764 (m), 702 (s), 631 (w), 582 (w), 516 (w); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), *Z*-isomer:  $\delta$  7.38 – 7.29 (2H, m), 7.26 (3H, s), 6.91 – 6.84 (2H, m), 5.50 (1H, ddd, *J* = 17.1, 10.3, 9.1 Hz), [diagnostic *E* isomer signal 5.28 – 5.14 (2H, m)], 5.10 – 4.95 (2H, m), 4.61 (1H, tt, *J* = 5.1, 2.8 Hz), 4.42 (2H, s), 3.80 (4H, s), 3.41 (2H, t, *J* = 6.7 Hz), 2.40 (1H, dt, *J* = 9.1, 3.4 Hz), 2.02 (1H, s), 1.67 – 1.50 (4H, m), 1.41 – 1.25 (3H, m), 1.19 (3H, ddt, *J* = 10.6, 8.4, 3.8 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  159.2, 142.7, 138.7, 130.9, 129.4, 128.1, 127.5, 126.9,

117.5, 113.9, 77.1, 72.7, 70.3, 55.4, 51.6, 29.9, 29.7, 29.5, 27.4, 26.3; **HRMS (ESI**<sup>+</sup>)  $[M+H-H_2O]^+$  calcd for C<sub>23</sub>H<sub>29</sub>O<sub>2</sub>: 351.2324, found: 351.2318.

(1*S*,2*S*)-2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1-phenylbut-3-en-1-ol (1.93). Based on the general procedure for CM with allyl(pinacolato)boronate 1.26/addition to benzaldehyde but in the presence of Mo-based complex 1.80 (instead of W-based 1.82), the reaction affording homoallylic alcohol 1.93 proceeded to 82% conv. The resulting brown solid was purified by silica gel chromatography (gradient elution, 1–3% Et2O in hexanes) and homoallylic alcohol 1.93 (34.0 mg, 0.116 mmol, 71% yield, 91:9 *syn:anti*) was obtained as clear yellow oil. **IR (neat):** 3454 (b), 3065 (w), 3030 (w), 2928 (m), 2885 (m), 1640 (w), 1603 (w), 1493 (m), 1471 (w), 1421 (w), 1389 (w), 1361 (w), 1254 (m), 1083 (s), 996 (m), 915 (m), 832 (s), 775 (s), 699 (s), 665 (s); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), *Z*-isomer:  $\delta$  7.44 – 7.29 (4H, m), 7.26 (1H, s), [diagnostic *E* isomer 5.85 (1H, ddd, *J* = 17.3, 10.5, 8.7 Hz)], 5.66 (1H, ddd, *J* = 17.1, 10.7, 8.4 Hz), 5.08 – 4.96 (2H, m), 4.84 – 4.80 (1H, m), 4.30 (1H, d, *J* = 3.9 Hz), 3.83 (1H, dd, *J* = 10.1, 4.0 Hz), 3.79 – 3.74 (1H, m), 2.69 – 2.45 (1H, m), 0.94 (8H, s), 0.93 (1H, s), 0.10 (6H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  143.1, 135.9, 128.2, 128.1, 127.4, 126.8, 117.5, 78.0, 66.1, 51.8, 26.0, 26.0, 18.3, -5.4, -5.5; HRMS (ESI<sup>+</sup>) [M+H-H<sub>2</sub>O]<sup>+</sup> calcd for C<sub>17</sub>H<sub>18</sub>OSi: 275.1831, found: 275.1827.

(1*S*,2*S*,*E*)-1-Phenyl-2-vinyldec-3-en-1-ol (1.95). Based on the general procedure for CM with allyl(pinacolato)boronate 1.26/addition to benzaldehyde, the reaction affording alcohol 1.94 proceeded to 78% conv. The resulting brown solid was purified by silica gel chromatography (10% Et<sub>2</sub>O in hexanes) and homoallylic alcohol 1.95 (24.6 mg, 0.0952 mmol, 75% yield, 91:9 *syn:anti*) was obtained as clear yellow oil. IR (neat): 3500 (b), 3064 (w), 3030 (w), 2957 (m), 2925 (s), 2855 (m), 1620 (m), 1494 (m), 1454 (m), 1378 (m), 1326 (m), 1257 (m), 1143 (m), 1046 (m), 1027 (m), 969 (m), 915 (m), 764 (m), 700 (s); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), *Z*-isomer:  $\delta$  7.32 (2H, m), 5.76 – 5.52 (2H, m), 5.42 (1H, ddt, *J* = 15.4, 8.4, 1.4 Hz), 5.07 – 4.90 (2H, m), 4.51 (1H, dd, *J* = 7.3, 2.8 Hz), 3.11 – 2.95 (1H, m), 2.25 (1H, d, *J* = 2.9 Hz), 2.13 – 1.99 (2H, m), 1.44 – 1.18 (8H, m), 0.98 – 0.78 (3H, m); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  142.0, 137.6, 135.5, 128.2, 128.0, 127.7, 127.1,

116.6, 76.5, 55.5, 32.9, 31.8, 29.4, 29.0, 22.8, 14.2; **HRMS (ESI**<sup>+</sup>) [M+H-H<sub>2</sub>O]<sup>+</sup> calcd for C<sub>18</sub>H<sub>25</sub>: 241.1956, found: 241.1959.

## Pinacolato)vinylboron Cross-Metathesis

Representative experimental procedure for vinylboronate CM: (Z)-2-(3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)isoindoline-1,3-dione (1.58). In an N2-filled glove box, an oven-dried 20 mL vial equipped with a stir bar was charged with N-allylphthalimide (21.7 mg, 0.116 mmol) and vinyl(pinacolato)boronate **1.68** (97 µL, 0.579 mmol). A solution of Mo-based complex 1.80 in benzene (0.1 M, 62 µL, 0.0062 mmol, 5 mol %) was added, and then the vial was sealed and the mixture was allowed to stir for 18 h at 22 °C. The reaction was quenched by the addition of wet CDCl<sub>3</sub>. Analysis of the unpurified residue (brown oil) indicated a 95:5 Z:E (<sup>1</sup>H NMR). Silica gel chromatography (gradient elution, 5-10% EtOAc/hexanes) afforded phthalimide 1.58 (31.8 mg, 0.102 mmol, 73% yield) as white crystalline solid (m.p. = 63-66 °C). **IR (neat):** 2978 (w), 2923 (w), 1770 (w), 1709 (s), 1634 (m), 1613 (w), 1468 (w), 1427 (m), 1389 (m), 1371 (m), 1347 (m), 1317 (m), 1295 (m), 1278 (m), 1258 (m), 1212 (w), 1188 (w), 1167 (w), 1141 (m), 1119 (w), 1105 (w), 1089 (w), 1072 (w), 1018 (w), 1000 (w), 967 (m), 943 (m), 877 (m), 844 (w), 832 (m), 797 (w), 759 (m), 723 (s), 696 (w), 673 (w), 600 (w), 578 (w), 530 (m), 464 (w), 425 (w), 411 (w) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), Z-isomer: δ 7.85-7.80 (2H, m), 7.71-7.67 (2H, m), 6.35-6.28 (1H, m), 5.56 (1H, apparent dt, J = 13.6, 2.0 Hz), [diagnostic *E* isomer signal: 4.86 (1H, dt, *J*=, 6.8 Hz)], 4.67 (2H, dd, *J* = 6.4, 2 Hz), 1.31 (12H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 168.2, 146.6, 134.0, 132.4, 123.3, 83.6, 39.2, 25.0; **HRMS (ESI<sup>+</sup>)**  $[M+H]^+$  calcd for C<sub>17</sub>H<sub>21</sub>BNO<sub>4</sub>: 314.1564 found: 314.1558.

(Z)-4,4,5,5-Tetramethyl-2-(3-phenylprop-1-en-yl)-1,3,2- (1.97). Based on the general procedure for CM with vinyl(pinacolato)boronate 1.68, the reaction affording 1.97 proceeded to 95% conv and 93:7 Z:E (<sup>1</sup>H NMR analysis). The resulting brown oil was purified by silica gel chromatography (2% EtOAc in hexanes) and a mixture of 1.97 and phenol 1.112 was obtained. To the resulting mixture, was added a solution of 0.1 M tetra-*n*-butylammonium fluoride in tetrahydrofuran (126  $\mu$ L, 0.00 126 mmol, 7.5 mol %) and the

resulting mixture was allowed to stir for 5 min (to desilylate phenol **1.112**, which has the same Rf as **1.97**).<sup>39</sup> The mixture was diluted with 8 mL hexanes and filtered through Celite. Removal of the volatiles *in vacuo* yielded yellow oil, which was purified by silica gel chromatography (2% EtOAc in hexanes) to afford boronate **1.97** (28.9 mg, 0.118 mmol, 70% yield) as pale yellow oil. **IR (neat):** 3062 (w), 3027 (w), 2978 (w), 2928 (w), 1626 (m), 1601 (w), 1495 (w), 1453 (w), 1434 (w), 1419 (w), 1390 (m), 1371 (w), 1323 (m), 1301 (w), 1279 (w), 1258 (w), 1214 (s), 1164 (w), 1142 (s), 1110 (w), 1075 (w), 1030 (w), 1005 (w), 967 (w), 922 (w), 877 (w), 846 (w), 745 (s), 698 (s), 676 (w), 578 (w), 556 (w), 523 (w), 484 (w), 466 (w), 440 (w); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), *Z* isomer: δ 7.32–7.18 (5H, m), 6.60–6.53 (1H, m), 5.45 (1H, ddd, *J* = 13.2, 1.2, 1.2 Hz), [diagnostic signal for the *E* isomer: 3.50 (2H, d, *J* = 6.3 Hz)], 3.78 (2H, d, *J* = 7.6 Hz), 1.31 (12H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 152.8, 140.8, 128.8, 128.6, 126.1, 83.2, 38.8, 25.0; HRMS (ESI<sup>+</sup>) [M+H]<sup>+</sup> calcd for C15H22BO2: 245.1713; found: 245.1704.

(*Z*)-2-(Dec-1-en-1-yl)-4,4,5,5,-tetramethyl-1,3,2-dioxaborolane (1.45). Based on the general procedure for CM with vinyl(pinacolato)boronate 1.68, the reaction affording 1.45 proceeded to 91% conv and 93:7 *Z*:*E* (<sup>1</sup>H NMR analysis). The resulting brown solid was purified by silica gel chromatography (2% EtOAc in hexanes) and a mixture of 1.45 and phenol 1.112 was obtained. To the resulting mixture was added a solution of 0.1 M of tetra*n*-butylammonium fluoride in tetrahydrofuran (107  $\mu$ L, 0.0107 mmol, 7.5 mol %) after which it was allowed to stir for 5 min (to desilylate the phenol 1.112, which has the same R<sub>f</sub> as 1.97). The mixture was diluted with hexanes (8 mL) and filtered through Celite. Removal of the volatiles *in vacuo* yielded yellow oil, which was purified by silica gel chromatography (2% EtOAc in hexanes) to give alkenylboronate 1.97 (28.0 mg, 0.105 mmol,

<sup>(39)</sup> In certain instances, the CM products from reactions with **1.68** are relatively non-polar (**1.97**, **1.45**, **1.57**, **1.102** and **1.37**) and have the same Rf as aryl alcohol **1.112** and thus cannot be easily and fully separated from the byproduct derived from homocoupling of **1.68** by silica gel chromatography. Once **1.112** is desilylated, the desired *Z*-alkenylboronate can be obtained with exceptional purity. To avoid this complication, a trivial silica gel chromatography (akin to filtration) is performed to remove the aforementioned byproduct prior to desilylation and further purification.

72% yield) as pale yellow oil. **IR (neat):** 2978 (w), 2957 (w), 2924 (m), 2854 (w), 1628 (m), 1436 (m), 1422 (w), 1370 (w), 1318 (w), 1280 (s), 1259 (w), 1215 (w), 1144 (s), 968 (w), 878 (w), 847 (w), 758 (w); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), *Z*-isomer:  $\delta$  6.46-6.39 (1H, m), 5.32 (1H, dd, *J* = 14.8, 6 Hz), [diagnostic *E* isomer signal: 5.42 (1H, d, *J* = 17.9 Hz)], 2.41-2.27 (2H, m), 2.17-2.07 (2H, m), 1.26 (24H, br s), 0.88 (3H, t, *J* = 6.8 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  155.4, 82.9, 32.3, 32.1, 29.6, 29.6, 29.4, 29.2, 25.0, 24.9, 22.8, 14.3; HRMS (ESI<sup>+</sup>) [M+H]<sup>+</sup> calcd for C<sub>16</sub>H<sub>32</sub>BO<sub>2</sub>: 267.2495 found: 267.2486.

#### (Z)-2-(8-((4-Methoxybenzyl)oxy)oct-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaboro-

**lane (1.98).** Based on the general procedure for CM with vinyl(pinacolato)boronate **1.68**, the reaction affording **1.98** proceeded to 95% conv and 97:3 *Z*:*E* (<sup>1</sup>H NMR analysis). The resulting brown solid was purified by silica gel chromatography (gradient elution, 2–5% EtOAc in hexanes) to obtain **1.98** (21.8 mg, 0.0582 mmol, 91% yield) was obtained as pale yellow oil. **IR (neat):** 2977 (m), 2930 (m), 2854 (m), 1626 (m), 1512 (s), 1422 (s), 1370 (m), 1319 (s), 1301 (s), 1246 (s), 1170 (s), 1144 (s), 1097 (s), 968 (m), 878 (m), 846 (m), 821 (m), 758 (m), 676 (w), 579 (w), 514 (w); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) *Z*-isomer: δ 7.68 – 7.58 (2H, m), 7.26 (1H, s), 7.02 (1H, d, J = 1.7 Hz), 6.87 – 6.67 (1H, m), [diagnostic *E* isomer signal 5.80 (1H, d, *J* = 17.7 Hz)], 5.70 (1H, ddt, *J* = 13.5, 2.4, 1.4 Hz), 4.80 (2H, d, *J* = 1.8 Hz), 4.18 (3H, d, *J* = 1.8 Hz), 3.81 (2H, td, *J* = 6.7, 1.8 Hz), 2.82 – 2.70 (2H, m), 2.61 (1H, d, *J* = 1.8 Hz), 2.05 – 1.90 (3H, m), 1.82 – 1.69 (9H, m), 1.69 – 1.59 (17H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 159.2, 155.3, 131.0, 129.3, 113.9, 82.9, 72.7, 70.4, 55.4, 32.3, 29.9, 29.5, 29.0, 26.2, 25.0; HRMS (ESI<sup>+</sup>) [M+H]<sup>+</sup> calcd for C<sub>22</sub>H<sub>36</sub>B<sub>1</sub>O<sub>4</sub>: 375.2707; found: 375.2699.

(Z)-2-(2-Butoxyvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.99). In an N<sub>2</sub>-filled glove box, an oven-dried 20 mL vial equipped with a stir bar was charged with vinyl(pinacolato)boronate 1.68 (22.6 mg, 0.147 mmol) and *n*-butylvinyl ether (191  $\mu$ L, 1.47 mmol). A solution of Mo-based complex 1.80 in benzene (0.1 M, 74  $\mu$ L, 0.0074 mmol, 5 mol %) was added, the vial was sealed and the mixture was allowed to stir for 3 h at 22 °C. Reaction was quenched by addition of wet CDCl<sub>3</sub>; analysis of the unpurified mixture indicated 88:12

*Z:E* (<sup>1</sup>H NMR). Removal of volatiles *in vacuo* afforded brown oil, which was purified by silica gel chromatography (gradient elution, 2–8% EtOAc in hexanes) to afford alkenylboronate **1.99** (27.2 mg, 0.120 mmol, 82% yield) as pale yellow oil. **IR (neat):** 2977 (m), 2933 (m), 2873 (m), 1628 (s), 1434 (m), 1318 (s), 1213 (s), 1144 (s), 1111 (s), 1090 (s), 968 (m), 881 (w), 846 (m), 772 (m), 671 (m), 579 (w); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.70–6.58 (1H, d, *J* = 8.0 Hz), 4.10 (1H, d, *J* = 8.4 Hz), 3.86 (2H, t, *J* = 6.7 Hz), 1.68–1.55 (2H, m), 1.48–1.34 (2H, m), 1.25 (12H, s), 0.93 (3H, t, *J* = 7.9 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  163.0, 82.8, 73.2, 31.9, 24.9, 19.0, 13.9; HRMS (ESI<sup>+</sup>) [M+H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>24</sub>BO<sub>3</sub>: 227.1819; found: 227.1814.

## (Z)-tert-Butyldimethyl((3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)al-

**lyl)oxy)silane (13e)** Based on the general procedure for CM with vinyl(pinacolato)boronate **1.68**, the reaction affording **1.57** proceeded to 94% conv and 94:6 *Z:E* (<sup>1</sup>H NMR analysis). The resulting brown oil was purified by silica gel chromatography (2% Et<sub>2</sub>O in hexanes) to obtain alkenylboronate **1.57** (25.8 mg, 0.0861 mmol, 71% yield) as pale yellow oil. **IR (neat):** 2979 (w), 2956 (w), 2929 (w), 2887 (w), 2857 (w), 1632 (w), 1471 (w), 1434 (w), 1420 (w), 1389 (w), 1371 (w), 1321 (w), 1298 (w), 1258 (m), 1213 (w), 1144 (m), 1083 (s), 1037 (w), 1005 (w), 969 (w), 939 (w), 877 (w), 832 (s), 774 (m), 733 (w), 670 (w); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), *Z* isomer:  $\delta$  6.50 (1H, dt, *J* = 13.0, 6.1 Hz), 5.39 (1H, dt, *J* = 13.6, 1.2 Hz), [diagnostic signal for the *E* isomer: 5.75 (1H, dt, *J* = 18, 1.5 Hz)], 4.51–4.48 (2H, dd, *J* = 6.1, 1.6 Hz), 1.26 (12H, s), 0.91 (9H, s), 0.07 (6H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  154.2, 83.3, 63.4, 26.2, 25.0, 18.5, -4.9; HRMS (ESI<sup>+</sup>) [M+H]<sup>+</sup> calcd for C<sub>15</sub>H<sub>32</sub>BO<sub>3</sub>Si: 299.2214, found: 299.2211.

(Z)-2,2'-(Prop-1-ene-1,3-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (1.101). Based on the general procedure for CM with vinyl(pinacolato)boronate 1.68, the reaction affording 1.101 proceeded to >98% conv and 97:3 Z:E (<sup>1</sup>H NMR analysis). Alkenyl-boronate 1.101 is inseparable from homocoupling of 1.68. Alkenylboronate 1.101 (19 mg, 0.13 mmol, 65% yield) was obtained as pale yellow oil (yield was calculated accounting for the mass of dimer in the product mixture). IR (neat): 3399 (br), 2978 (w), 2931 (w),

1622 (w), 1470 (w), 1371 (m), 1316 (s), 1260 (m), 1215 (w), 1138 (s), 1108 (w), 967 (m), 874 (w), 847 (m), 672 (w), 578 (w); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 6.58 (1H, d, J = 13.4 Hz), [diagnostic signal for the *E* isomer: 5.41 (1H, dt, J = 1.6 Hz)], 5.32 (1H, d, J = 13.4 Hz), 2.19–2.11 (2H, m), 1.28 (12H, s), 1.24 (12H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 150.7, 83.7, 83.5, 83.3, 25.0, 24.9; HRMS (ESI<sup>+</sup>) [M+H]<sup>+</sup> calcd for C<sub>15</sub>H<sub>29</sub>B<sub>2</sub>O<sub>4</sub>: 295.2252, found: 295.2246.

(Z)-2-(2-Cyclohexylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (13d). Based on the general procedure for CM with vinyl(pinacolato)boronate **1.68**, the reaction affording 1.57 proceeded to 72% conv and 93:7 Z:E (<sup>1</sup>H NMR analysis). The resulting brown solid was purified by silica gel chromatography (2% EtOAc in hexanes) and a mixture of 1.57 and phenol 1.112 was obtained. To the resulting mixture was added a solution of 0.1 M tetra-n-butylammonium fluoride in tetrahydrofuran (121 µL, 0.0121 mmol, 7.5 mol %) and the resulting mixture was allowed to stir for 5 min (to desilylate the phenol 1.97, which has the same  $R_f$  as 1.57). The mixture was diluted with hexanes (8 mL) and filtered through Celite. Removal of volatiles *in vacuo* afforded yellow oil, which was purified by silica gel chromatography (2% EtOAc in hexanes) to give alkenylboronate 1.57 (18.4 mg, 0.799 mmol, 50% yield) as colorless oil. IR (neat): 2978 (w), 2922 (m), 2849 (w), 1625 (m), 1438 (w), 1438 (w), 1424 (m), 1389 (m), 1321 (m), 1254 (s), 1214 (w), 1143 (s), 1110 (w), 968 (m), 891 (w), 879 (w), 848 (w), 764 (m), 672 (w); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), Z isomer:  $\delta$  6.25 (1H, m), 5.22 (1H, dd, J = 13.5, 0.9 Hz), [diagnostic signal for the E isomer: 5.34 (1H, d, J = 14.4 Hz)], 2.76–2.66 (1H, m), 1.76–1.57 (6H, m), 1.36–1.27 (2H, m), 1.26 (12H, s), 1.20–1.01 (2H, m); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 160.8, 82.9, 40.8, 33.5, 26.2, 25.9, 25.0; **HRMS (ESI<sup>+</sup>) [M+H]**<sup>+</sup> calcd for C<sub>14</sub>H<sub>26</sub>BO<sub>2</sub>: 237.2026; found: 237.2021.

2-((1*Z*,3*E*)-Deca-1,3-dien-1-yl)-4,4,5,5,-tetramethyl-1,3,2,-dioxaborolane (13g). Based on the general procedure for CM with vinyl(pinacolato)boronate 1.68, the reaction affording 1.102 proceeded to 90% conv and 93:7 *Z*:*E* (<sup>1</sup>H NMR analysis). The resulting brown solid was purified by silica gel chromatography (2% EtOAc in hexanes) and a mixture of 1.102 and phenol 1.112 was obtained. To the resulting mixture was added a solution of 0.1M tetra-*n*-butylammonium fluoride in tetrahydrofuran (111 µL, 0.0111 mmol, 7.5 mol %) and the resulting solution was allowed to stir for 5 min (to desilylate the phenol **1.112**, which has the same R<sub>f</sub> as **1.102**). The mixture was diluted with hexanes (8 mL) and filtered through Celite. Removal of volatiles *in vacuo* gave yellow oil, which was purified by silica gel chromatography (2% EtOAc in hexanes) to afford alkenylboronate **1.102** (28.1 mg, 0.106 mmol, 72% yield) as pale yellow oil. **IR (neat):** 2978 (w), 2958 (w), 2926 (w), 1641 (w), 1589 (w), 1466 (w), 1424 (w), 1389 (w), 1370 (w), 1328 (w), 1299 (w), 1279 (w), 1256 (s), 1215 (w), 1144 (s), 1110 (w), 1007 (w), 965 (m), 880 (w), 847 (w), 766 (w); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), *Z* isomer:  $\delta$  6.89–6.79 (2H, m), 5.87–5.79 (1H, dt, *J* = 14.1, 7.0 Hz), [diagnostic signal for the *E* isomer: 5.42 (1H, d, *J* = 17.7 Hz)], 5.28–5.21 (1H, m), 2.17–2.07 (2H, m), 1.44– 1.23 (20H, m), 0.89 (3H, t, *J* = 6.8 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  151.2, 140.4, 130.8, 83.1, 32.9, 31.9, 29.2, 29.1, 25.0, 22.8, 14.3; HRMS (ESI<sup>+</sup>) [M+H]<sup>+</sup> calcd for C<sub>16</sub>H<sub>30</sub>BO<sub>2</sub>: 265.2339; found: 265.2328.

#### Pinacolato)vinylboron Cross-Metathesis with Styrene

(*Z*)-4,4,5,5-Tetramethyl-2-styryl-1,3,2-dioxaborolane (1.37). In an N<sub>2</sub>-filled glove box, an oven-dried 4 mL vial equipped with a stir bar was charged with vinyl(pinacolato)boronate 1.68 (23.5 mg, 0.153 mmol) and styrene ( $87 \mu$ L, 0.76 mmol). A solution of Mo-based complex 1.78 in benzene (0.06 M, 76  $\mu$ L, 0.0046 mmol, 3 mol %) was added by a syringe, after which a septum, fitted with an outlet needle, was immediately placed on the vial. An adapter was attached to the top of the septum and vacuum (100 torr) was applied. The resulting solution was allowed to stir under vacuum for 4 h. The reaction was quenched by addition of wet CDCl<sub>3</sub> (87% conv to 1.37, 91:9 *Z:E* by <sup>1</sup>H NMR analysis). The resulting brown solid was purified by silica gel chromatography (2% EtOAc in hexanes); a mixture of 1.37 and phenol 1.112 was obtained. To the resulting mixture was added a solution of 0.1 M tetra-*n*-butylammonium fluoride in tetrahydrofuran (127  $\mu$ L, 0.0127 mmol, 7.5 mol %) and the mixture was allowed to stir for 5 min (to desilylate the phenol 1.112, which has the same R<sub>f</sub> as 1.37). The solution was diluted with hexanes (8 mL) and filtered through Celite. The volatiles were removed *in vacuo* to afford yellow oil, which was purified by silica gel chromatography (2% EtOAc in, 0.111

mmol, 66% yield) as clear yellow oil. **IR (neat):** 3059 (w), 2978 (w), 2930 (w), 1618 (m), 1576 (w), 1495 (w), 1452 (w), 1418 (w), 1389 (w), 1371 (w), 1351 (w), 1318 (w), 1255 (s), 1229 (w), 1212 (s), 1140 (w), 1109 (w), 1075 (w), 1029 (w), 1001 (w), 967 (m), 917 (w), 883 (w), 851 (m), 835 (w), 809 (w), 777 (w), 749 (w), 692 (s), 671 (w), 643 (w), 578 (w), 543 (w), 484 (w), 462 (w), 432 (w); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), *Z* isomer:  $\delta$  7.57–7.51 (2H, m), 7.34–7.27 (3H, m), 7.22 (1H, d, *J* = 14.8 Hz), [diagnostic signal for the *E* isomer: 6.20 (1H, d, *J* = 18.4 Hz)], 5.61 (1H, d, *J* = 15.2 Hz), 1.29 (12H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  148.3, 138.6, 128.8, 128.1, 128.1, 83.6, 24.9; HRMS (ESI<sup>+</sup>) [M+H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>20</sub>BO<sub>2</sub>: 231.1556; found: 231.1567.

(Z)-2-(3-Methoxystyryl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.104). In an N2filled glove box, an oven-dried 4 mL vial equipped with a stir bar was charged with vinyl(pinacolato)boronate 1.68 (17.5 mg, 0.114 mmol) and *m*-methoxystyrene (79 µL, 0.57 mmol). A solution of Mo-based complex 1.78 in benzene (0.06 M, 57 µL, 0.0034 mmol, 3 mol %) was added by a syringe, after which a septum, fitted with an outlet needle, was immediately placed on the vial. An adapter was attached to the top of the septum and vacuum (100 torr) was applied. The resulting solution was allowed to stir under vacuum for 4 h. The reaction was guenched by addition of wet CDCl<sub>3</sub> (79% conv to **1.104**, 95:5 Z:E by <sup>1</sup>H NMR analysis). Following purification by silica gel chromatography (gradient elution, 1–3% EtOAc in hexanes), alkenylboronate 1.104 (20.1 mg, 0.077 mmol, 68% yield) was obtained as a clear yellow oil. IR (neat): 2979 (m), 2934 (w), 2835 (w), 1618 (m), 1598 (m), 1581 (m), 1464 (w), 1424 (m), 1372 (m), 1300 (m), 1257 (s), 1143 (s), 1044 (m), 968 (m), 872 (m), 800 (m), 691 (m); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) Z isomer:  $\delta$  7.37–7.30 (1H, m), 7.25–7.14 (2H, m), 7.07 (1H, ddd, J = 7.6, 1.6, 0.9 Hz), 6.87–6.78 (1H, m), [diagnostic signal for the *E* isomer: 6.16 (1H, d, J = 18.4 Hz)], 5.59 (1H, d, J=14.9 Hz), 3.83 (3H, s), 1.30 (12H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 159.6, 148.4, 139.9, 129.0, 121.9, 114.6, 113.4, 83.6, 55.4, 25.0; HRMS (ESI<sup>+</sup>) [M+H]<sup>+</sup> calcd for C<sub>15</sub>H<sub>22</sub>BO<sub>3</sub>: 261.1662; found: 261.1665.

(Z)-4,4,5,5-Tetramethyl-2-(4-(trifluoromethyl)styryl)-1,3,2-dioxaborolane (1.105) In an N<sub>2</sub>-filled glove box an oven-dried 4 mL vial equipped with a stir bar was charged with

vinyl(pinacolato)boronate 1.68 (20.2 mg, 0.131 mmol) and 4-(trifluoromethyl)styrene (97 μL, 0.66 mmol). A solution of Mo-based complex 1.78 in benzene (0.06 M, 66 μL, 0.0039 mmol, 3 mol %) was then added by a syringe, after which a septum, fitted with an outlet needle, was immediately placed on the vial. An adapter was attached to the top of the septum and vacuum (100 torr) was applied. The resulting solution was allowed to stir under vacuum for 4 h. The reaction was quenched by addition of wet CDCl<sub>3</sub> (> 98% conv to **1.105**, 95:5 Z:E). The resulting brown solid was purified by silica gel chromatography (2%) EtOAc in hexanes) and a mixture of 1.105 and phenol 1.102 was obtained. The mixture was distilled in a Kugelrohr apparatus (3 h, 110 °C, 0.75 torr) to afford alkenylboronate 1.104 (36.9 mg, 0.124 mmol, 94 % yield) as white crystalline solid (m.p. = 57-60 °C). IR (neat): 2980 (m), 2931 (w), 1615 (m), 1575 (w), 1391 (w), 1372 (w), 1320 (s), 1258 (s), 1162 (s), 1121 (s), 1066 (s), 1017 (m), 967 (m), 884 (w), 847 (s); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 **MHz**) Z isomer:  $\delta$  7.64 (2H, d, J = 8.8 Hz), 7.56 (2H, d, J = 8.4 Hz), [diagnostic signal for the *E* isomer: 6.26 (1H, d, J = 18.5 Hz)], 5.73 (1H, d, J = 14.9 Hz), 1.29 (12H, s); <sup>13</sup>C **NMR (CDCl<sub>3</sub>, 100 MHz,)**  $\delta$  146.7, 142.0, 129.9 (q, J = 32.1 Hz), 129.0, 125.0 (q, J = 3.8 Hz), 124.4 (q, J = 271 Hz), 83.9, 24.9; <sup>19</sup>F NMR (CDCl<sub>3</sub>, 376 MHz)  $\delta$  +90.4; HRMS (ESI<sup>+</sup>) [M+H]<sup>+</sup> calcd for C<sub>15</sub>H<sub>19</sub>BF<sub>3</sub>O<sub>2</sub>: 299.1430; found: 299.1442.

(*Z*)-2-(4-Methoxystyryl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.59). In an N<sub>2</sub>filled glove box an oven-dried 4 mL vial equipped with a stir bar was charged with vinyl(pinacolato)boronate 1.68 (23.7 mg, 0.154 mmol) and *p*-methoxystyrene (31  $\mu$ L, 0.23 mmol). A solution of Mo-based complex 1.78 in benzene (0.06 M, 77  $\mu$ L, 0.0046 mmol, 3 mol %) was then added by a syringe, after which a septum, fitted with an outlet needle, was immediately placed on the vial. An adapter was attached to the top of the septum and vacuum (100 torr) was applied. The resulting solution was allowed to stir under vacuum for 4 h. The reaction was quenched by addition of wet CDCl<sub>3</sub> (78% conv to 1.59, 97:3 *Z:E* by <sup>1</sup>H NMR analysis). Following purification by silica gel chromatography (gradient elution, 1–3% EtOAc in hexanes), alkenylboronate 1.59 (29.5 mg, 0.113 mmol, 74% yield) was obtained as pale yellow oil. IR (neat): 2979 (m), 2934 (w), 2837 (w), 1606 (s), 1574 (w), 1512 (s), 1442 (m), 1371 (m), 1318 (s), 1250 (s), 1179 (m), 1165 (m), 1143 (s), 1034 (m), 967 (m), 884 (w), 841 (m); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) *Z* isomer: δ 7.59–7.49 (2H, d, *J* = 8.8 Hz), 7.15 (1H, d, *J* = 14.9 Hz), 6.89–6.78 (2H, d, *J* = 8.8 Hz), [diagnostic signal for the *E* isomer: 6.02 (1H, d, *J* = 18.4 Hz)], 5.46 (1H, d, *J* = 15.0 Hz), 3.82 (3H, s), 1.30 (12H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 159.7, 148.2, 131.4, 130.4, 113.5, 83.5, 55.4, 25.0; HRMS (ESI<sup>+</sup>) [M+H]<sup>+</sup> calcd for C<sub>15</sub>H<sub>22</sub>BO<sub>3</sub>: 261.1662; found: 261.1668.

(Z)-4,4,5,5-Tetramethyl-2-(3,4,5-trimethoxystyryl)-1,3,2-dioxaborolane (1.106) In an N<sub>2</sub> filled glovebox, an oven-dried 4 mL vial equipped with a stir bar was charged with vinyl(pinacolato)boronate 1.68 (25.0 mg, 0.160 mmol) and 3,4,5-trimethoxystyrene (46.6 mg, 0.240 mmol). A solution of Mo-catalyst 1.78 in benzene (0.06 M, 80 µL, 0.0048 mmol, 3 mol %) was then added by a syringe, and a septum, fitted with an outlet needle, was quickly attached to the vial. An adapter was attached to the top of the septum, and vacuum (100 torr) was applied. The resulting solution was allowed to stir under vacuum for 4 h. The reaction was quenched by addition of wet CDCl<sub>3</sub> and unpurified boronate **1.106** was obtained in 80% conv and 96:4 Z:E. Following purification by silica gel chromatography (gradient elution, 1–3% EtOAc in hexanes), boronate 1.106 (36.2 mg, 0.113 mmol, 71% yield) was obtained as off-white solid (m.p. = 55-57 °C). IR (neat): 2978 (m), 2938 (m), 2838 (w), 1617 (m), 1579 (s), 1506 (s), 1461 (m), 1413 (m), 1371 (m), 1329 (s), 1246 (s), 1128 (s), 1008 (m), 964 (w), 848 (m), 779 (w), 681 (w); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) Zisomer:  $\delta$  7.10 (1H, d, J = 15.2 Hz), 7.05 (2H, s), [diagnostic signal for the E isomer: 6.06] (1H, d, J = 18.3 Hz), 5.51 (1H, d, J = 15.1 Hz), 3.89 (6H, s), 3.86 (3H, s), 1.30 (12H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz,): δ 152.9, 149.2, 138.4, 134.0, 106.7, 83.6, 61.0, 56.2, 25.0; **HRMS (ESI<sup>+</sup>)**  $[M+H]^+$  calcd for C<sub>17</sub>H<sub>26</sub>BO<sub>5</sub>: 321.1873; found: 321.1875.

**Combretastatin A-4 (1.108).** A 5 mL round bottom flask was charged with alkenylboronate **1.106** (36.2 mg, 0.113 mmol) and 5-bromo-2-methoxyphenol **1.107** (69 mg, 0.34 mmol). The flask was placed in an N<sub>2</sub>-filled glove box, and  $Cs_2CO_3$  (74 mg, 0.23 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (26 mg, 0.023 mmol, 20 mol %) were added. The vessel was then sealed with a septum and removed from the glove box where it was charged with a 10:1 mixture of thf:H<sub>2</sub>O (1.5 mL) and equipped with a reflux condenser. The mixture was allowed to stir at 66 °C for 18 hours until **1.106** was fully consumed (TLC analysis). The solution was then allowed to cool to 22 °C, dried with anhydrous MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to yield yellow oil. Following silica gel chromatography (gradient elution 15%–50 % EtOAc in hexanes), combretastatin A-4 **1.108** (26.7 mg, 0.0844 mmol, 74 % yield, 96:4 *Z:E*) was obtained as white solid (m.p. = 81–85 °C). **IR (neat):** 3419 (br), 3000 (w), 2936 (w), 2836 (w), 1578 (m), 1505 (s), 1454 (m), 1418 (m), 1328 (m), 1271 (s), 1236 (s), 1122 (s), 1026 (w), 1005 (w), 881 (w), 854 (w), 795 (w), 762 (w); <sup>1</sup>**H NMR (CDCl<sub>3</sub>, 400 MHz)** *Z*-isomer: 6.92 (1H, d, J = 2.4), 6.78 (1H, dd, J = 2, 0.8 Hz), 6.73 (1H, d, J = 8.4 Hz), 6.52 (2H, s), 6.46 (1H, d, J = 12 Hz), 6.41(1H, d, J = 12 Hz), 5.51 (1H, s), 3.86 (3H, s), 3.84 (3H, s), 3.69 (6H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 101 MHz)  $\delta$  153.0, 145.9, 145.4, 137.3, 132.8, 130.8, 129.6, 129.2, 115.2, 106.2, 61.1, 56.1; **HRMS (ESI**<sup>+</sup>) [M+H]<sup>+</sup> calcd for C<sub>18</sub>H<sub>21</sub>O<sub>5</sub>: 317.1389; found: 317.1387.





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## Chapter 2

## Synthesis of Macrocyclic and Acyclic Z-Enoates and (E,Z) or (Z,E) Dienoates by Catalytic Cross-Metathesis

## 2.1 Introduction

Conjugated carbonyl units are ubiquitous in macrocyclic and acyclic biologically active molecules.<sup>1</sup> Among these, cladospolide B,<sup>2</sup> neopeltolide,<sup>3</sup> callyspongiolide,<sup>4</sup> laulimalide<sup>5</sup> and phorboxazole A<sup>6</sup> are representative compounds that bear *Z*- $\alpha$ , $\beta$ -unsaturated esters. (Figure 2.1). Access to a single enoate stereoisomer is critical because the stereochemical identity of the alkene unit is often responsible for the biological activity of the natural product. Enoates also serve as valuable precursors to enones, enamides and allyl alcohols and fundamental building blocks for synthesis.  $\alpha$ , $\beta$ - and  $\alpha$ , $\beta$ , $\gamma$ , $\delta$ -Unsaturated esters are commonly used for site-selective functionalizations such as conjugate addition and the isomeric purity of the olefin is critical to the stereochemical outcome of the reaction.<sup>7,8</sup>

- (4) Zhou, J.; Gao, B.; Xu, Z.; Ye, T. J. Am. Chem. Soc. 2016, 138, 6948-6951.
- (5) Crimmins, M. T. Curr. Opin. Drug Discovery Dev. 2002, 5, 944–959.

<sup>(1)</sup> Yu, X.; Sun, D. Molecules 2013, 18, 6230-6268.

<sup>(2)</sup> Chou, C.-Y.; Hou, D. R. J. Org. Chem. 2006, 71, 9887-9890.

<sup>(3)</sup> Ghosh, A. K.; Shurrush, K. A.; Dawson, Z. L. Org. Biomol. Chem. 2013, 11, 7768-7777.

<sup>(6)</sup> Smith, A. B.; Verhoest, P. R.; Minbiole, K. P.; Schelhaas, M. J. Am. Chem. Soc. 2001, 123, 4834-4836.

<sup>(7)</sup> Yamamoto, K.; Ogura, H.; Jukuta, J.-i.; Inoue, H; Hamada, K.; Sugiyama, Y.; Yamada, S. J. Org. Chem. 1998, 63, 4449–4458. Larson, R. T.; Clift, M. D.; Thomson, R. J. Angew. Chem., Int. Ed. 2012, 51, 2481– 2484.

<sup>(8)</sup> For site-selective 1,6-conjugate additions, see: (a) den Hartog, T.; Harutyunyan, S. R.; Font, D.; Minnaard, A. J.; Feringa, B. L. Angew. Chem., Int. Ed. 2008, 47, 398. (b) Uraguchi, D.; Yoshioka, K.; Ueki, Y.; Ooi, T. J. Am. Chem. Soc. 2012, 134, 19370. (c) Lee, K.-s.; Wu, H.; Haeffner, F.; Hoveyda, A. H. Organome-tallics 2012, 31, 7823–7826. (d) Luo, Y.; Roy, I. D.; Madec, A. G. E.; Lam, H. W. Angew. Chem., Int. Ed. 2014, 53, 4186. (e) Meng, F.; Li, X.; Torker, S.; Shi, Y.; Shen, X.; Hoveyda, A. H. Nature 2016, 537, 387–393.


#### **Figure 2.1.** Biologically Active Molecules Containing Z- $\alpha$ , $\beta$ -Unsaturated Esters.

Unsaturated carbonyl compounds have been synthesized through stoichiometric olefination methods that typically generate a mixture of *Z* and *E* isomers and generate significant amounts of waste. Catalytic strategies that afford the corresponding *Z* isomers selectively remain scarce. Olefin metathesis offers an attractive disconnection from conventional methods to be discussed in the next section. Our group has developed stereogenicat-metal monoaryloxide monopyrrolide (MAP) complexes that promote kinetically *Z*-selective cross-metathesis (CM) and ring-closing metathesis (RCM) to transform terminal olefins to a variety of functionalized alkenes, but macrocyclic and acyclic  $\alpha$ , $\beta$ -unsaturated esters to *Z*-enoates are conspicuously missing from this list.<sup>9,10</sup> In this chapter, we will

<sup>(9) (</sup>a) Singh, R.; Schrock, R. R.; Muller, P.; Hoveyda, A. H. J. Am. Chem. Soc. 2007, 129, 12654–12655.
(b) Malcolmson, S. J.; Meek, S. J.; Schrock, R. R.; Hoveyda, A. H. Nature 2008, 456, 933–937. (c) Sattely, E. S.; Meek, S. J.; Malcolmson, S. J.; Schrock, R. R.; Hoveyda, A. H. J. Am. Chem. Soc. 2009, 131, 943–953.

<sup>(10) (</sup>a) Meek, S. J.; O'Brien, R. V.; Llaveria, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* 2011, 471, 461–466.
(b) Mann, T. J.; Speed, A.W. H.; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* 2013, *52*, 8395–

delineate the first examples of kinetically Z-selective ring-closing metathesis and CM reactions to access macrocyclic<sup>11</sup> and acyclic<sup>12</sup> Z-enoates and (E,Z)- or (Z,E)-dienoates catalyzed by Mo-based MAP complexes.

#### 2.2 Background

#### 2.2.1. Representative Methods for Synthesis of Z Enoates

The main challenge of enoate synthesis is preparing these molecules in a stereoselective fashion. The stereochemistry of these olefins are often reflective of the relative stability of the two possible isomeric products. Although there are a number of strategies for accessing the Z isomer, there are no reports of catalytic strategies and moreover, these reactions are have more limitations than just the efficiency and selectivity. Here, we report representative methods with detailed examples to highlight the advantages and drawbacks.

Throughout the years, many people have relied on the Horner-Wadsworth-Emmons (HWE) reaction to synthesize enoates. The HWE reaction utilizes phosphonate-stabilized carbanions, generated through deprotonation of **2.6a** with strong bases such as NaH, to react with aldehydes (**2.6b**) to give the enoate product (**2.6c**). To afford the *Z* isomer, the Still-Gennari variant was developed.<sup>13</sup> Still and Gennari found that in the presence of a strong base to deprotonate trimethylphosphonoacetate (**2.6**) and 18-crown-6 to sequester the counterion, higher ratios of the *Z* product (compared to those used in the HWE reaction) can be obtained with certain substrates. However, in cases where modified conditions with **2.6** do not enhance selectivity, by switching to the more electron-withdrawing bis(trifluoroethyl) phosphonoester, the selectivity can be improved (**2.9**, 89:11 *Z:E* to 92:8 *Z:E*) or completely reversed (**2.10**, 22:78 *Z:E* to >98:2 *Z:E* and **2.11**, >98:2 *E:Z* to >98:2 *Z:E*). The more electron-withdrawing phosphonoacetate allows for faster collapse of the kinetically

<sup>8400. (</sup>c) Kiesewetter, E. T.; O'Brien, R. V.; Yu, E. C.; Meek, S. J.; Schrock, R. R.; Hoveyda, A. H. J. Am. Chem. Soc. 2013, 135, 6026–6029.

<sup>(11)</sup> Zhang, H.; Yu, E. C.; Torker, S. T.; Schrock, R. R.; Hoveyda, A. H. J. Am. Chem. Soc. 2014, 136, 16493-16496.

 <sup>(12)</sup> Yu, E. C.; Johnson, B. M.; Townsend, E. M.; Schrock, R. R.; Hoveyda, A. H. Angew. Chem., Int. Ed. 2016, 55, 13210–13214.

<sup>(13)</sup> Still, W. C.; Gennari, C. Tetrahedron Lett. 1983, 24, 4405-4408.

preferred oxaphosphetane, that delivers the Z isomer, that prevents equilibration of the intermediates. Only in certain cases (e.g., **2.12**) does the more electrophilic phosphonate reagent lead to diminished reactivity. In most instances, efficiency of the reaction does not dramatically change by moving from phosphonate **2.6** to **2.7**.



Panek and co-workers illustrated an application of the Still-Gennari olefination in the synthesis of (+)-neopeltolide.<sup>14</sup> By treating aldehyde **2.14** with phosphonoacetate **2.13** in the presence of KHMDS and 18-crown-6, they were able to isolate the natural product in 62% yield and 87.5:12.5 *Z*:*E*. As observed, the stereoselectivity is moderate for a final step of a total synthesis. Appending the phosphonoacetate requires an additional step and moreover, stoichiometric amounts of phosphate waste is generated from this reaction. Even

<sup>(14)</sup> Youngsaye, W.; Lowe, J. T.; Pohlke, F.; Ralifo, P.; Panek, J. S. Angew. Chem., Int. Ed. 2007, 46, 9211–9214.

though it was not an issue in this instance, use of strong bases such as KHMDS can be detrimental to certain base-sensitive moieties, especially in more functionalized molecules.



Scheme 2.2. Still-Gennari Olefination in Synthesis of (+)-Neopeltolide.

In macrocyclic systems, such as phorboxazole A, there may be greater bias for the Z isomer due to ring-strain. In Williams' synthesis of the molecule with trime-thylphosphonoacetate **2.15**, the macrocycle was formed in quantitative yield as a 4:1 Z:E mixture (Scheme 2.3a).<sup>15</sup> Although the reaction delivered the final product in good yield, the reaction was performed at a low temperature over the course of two days. Utilizing the Still-Gennari form of the phosphonoacetate, Forsyth and co-workers obtained precursor **2.18** in 77% yield, but with no improvement in stereoselectivity (4:1 Z:E) (Scheme 2.3b).<sup>16</sup> These examples show that while in certain cases the Still-Gennari olefination can provide decent Z selectivities, the stereochemical outcome is often dependent on the substrate.

<sup>(15)</sup> Williams, D. R.; Kiryanov, A. A.; Emde, U.; Clark, M. P.; Berliner, M. A.; Reeves, J. T. Angew. Chem., Int. Ed. 2003, 42, 1258–1262.

<sup>(16)</sup> Forsyth, C. J.; Ahmed, F.; Cink, R. D.; Lee, C.-S. J. Am. Chem. Soc. 1998, 120, 5597-5598.

Scheme 2.3. Application of Still-Gennari Olefination in Synthesis of Phorboxazole A.

a) Williams' Synthesis of Phorboxazole A.



b) Forsyth's Synthesis of Intermediate towards Phorboxazole A



Ando and co-workers developed a method to address the issue of low selectivities for macrocyclic Z enoates. Previously the group reported diarylphosphonoacetate derivatives in the presence of sodium iodide and 1,8-diazabicyclo[5.4.0]undec-7-ene (dbu) to synthesize Z- $\alpha$ , $\beta$ -unsaturated esters.<sup>17</sup> In 2010, they applied this method to macrocyclic systems.<sup>18</sup> In the presence of the same base and diarylphosphonoacetate **2.19**, macrocycles of different ring sizes (12–18) can be isolated in good yields and high Z selectivities (Scheme 2.5). Ando highlighted that macrocycle **2.21** was obtained in only 54% yield and 83% Z in the presence of K<sub>2</sub>CO<sub>3</sub> and 18-crown-6 in toluene. This reaction suffered from the same issues of extensive waste generation and also long reaction times. The authors noted that dropwise addition of the aldehyde to a solution of the base over the course of the reaction was necessary.

<sup>(17)</sup> Ando, K.; Oishi, T.; Hirama, M.; Ohno, H.; Ibuka, T. J. Org. Chem. 2000, 65, 4745–4749.

<sup>(18)</sup> Ando, K.; Narumiya, K.; Takada, H.; Teruya, T. Org. Lett. 2010, 12, 1460-1463.





Lindlar partial hydrogenation of alkynes is another commonly used approach to generate Z enoates. Wender and co-workers utilized this strategy to synthesize the Z ester in (–)-laulimalide (Scheme 2.5).<sup>19</sup> Alkynyl ester **2.27** was treated with hydrogen in the presence of two portions of 5.0 mol % of Lindlar's catalyst and quinoline. Only a single Z isomer of **2.28** was isolated in exceptional yield (91%). This scenario generated the desired Z alkene with high efficiency, but the potential issue of over reduction to the alkane leading to reliability issues remains a concern. Toxicity of the lead component of Lindlar's catalyst is another factor that should be considered when using this method. In addition, incorporation of the alkyne unit can sometimes increase the step count significantly. In Wender's case, the aldehyde is subjected to a Seyferth-Gilbert homologation, which has similar waste issues as mentioned previously, to incorporate the alkyne and before the ester unit was affixed to the alkyne. One could convert aldehyde **2.24** to the terminal olefin to be used in CM. Integrating alkynes into macrocycles can be problematic as ring strain may prevent the macrocycle to be formed in certain situations.

<sup>(19)</sup> Wender, P. A.; Hegde, S. G.; Hubbard, R. D.; Zhang, I. J. Am. Chem. Soc. 2002, 124, 4956-4957.



Scheme 2.5. Application of Lindlar Hydrogenation in Synthesis of (-)-Laulimalide.

Recently, our group has published a total synthesis of (+)-neopeltolide.<sup>20</sup> In the presence of 10 mol% of Ru-complex **2.31**, 1,4-cis-butene-diol was coupled with terminal olefin **2.29** to deliver allylic alcohol in 55% yield and 97:3 *Z*:*E*. Upon DMP oxidation and Pinnick oxidation, *Z*- $\alpha$ , $\beta$ -unsaturated carboxylic acid **2.33** (precursor to neopeltolide side chain) is afforded in 75% yield in 98:2 *Z*:*E*. Two additional oxidation steps are required to afford the target carboxylic acid **2.33** also adds to the step count, in addition to the waste generation of the synthesis.

Scheme 2.6. Synthesis of Allylic Alcohols through Z-Selective Ru-Catalyzed CM.



(20) Yu, M.; Schrock, R. R.; Hoveyda, A. H. Angew. Chem., Int. Ed. 2015, 54, 215-220.

Vinyl esters and related carbonyl compounds are easily accessible and inexpensive, making them practical substrates for CM. There have been numerous studies on the CM of these substrates, but most of these reports disclose the processes that yield the thermodynamically favored isomer. In 2000, Grubbs and co-workers reported a Ru-catalyzed method to generate  $\alpha,\beta$ -unsaturated carbonyls.<sup>21</sup> Reaction of methyl acrylate **2.34** with terminal olefin 2.35 in the presence of 5.0 mol % of 2.36 gave 91% yield of 2.37 as a 82:18 mixture. Acroleins as well as vinyl ketones can be used as cross partners as well to efficiently generate the corresponding 1,2-disubstituted  $\alpha$ , $\beta$ -unsaturated carbonyl compounds (2.39, 2.40 and 2.41). In all cases, the thermodynamically favored E isomer was obtained predominantly. In 2014, Grubbs studied the Z-selective CM of vinyl acetals.<sup>22</sup> In the presence of 2.0 mol % of Z-selective catalyst 2.44 developed in their group,<sup>23</sup> acetal 2.42 can be coupled with terminal alkene 2.43 to afford alkenyl acetal 2.45 in good yield and high Z selectivity (82% yield, 94% Z). Various olefins containing esters and free alcohols are tolerated under the established conditions. Other acetal compounds such as **2.49** can also be synthesized. The unfunctionalized alkene cross-partners employed in this system are used in large excess, which raises the issue of practicality, particularly in cases where a more valuable olefin cross-partner is involved.

<sup>(21)</sup> Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. J. Am. Chem. Soc. 2000, 122, 3783-3784.

<sup>(22)</sup> Quigley, B. L.; Grubbs, R. H. Chem. Sci. 2014, 5, 501-506.

<sup>(23)</sup> Keitz, B. K.; Endo, K.; Patel, P. R.; Herbert, M. B.; Grubbs, R. H. J. Am. Chem. Soc. 2012, 134, 693-699.

#### Scheme 2.7. Ru-catalyzed CM of Electron-Deficient Olefins.

a) Ru-Catalyzed Cross-Metathesis of  $\alpha,\beta$ -Unsaturated Carbonyls:



2.45 82% yield, 94:6 Z:E



ΟН

2.48

74% vield, >95:5 Z:E

2.49 70% yield, >95:5 Z:E

CO<sub>2</sub>Me

6

2.46

85% vield, >95:5 Z:E

#### 2.2.2. Representative Methods for Synthesis of Dienoates

2.47

88% yield, >95:5 Z:E

The synthesis of dienoates has also been studied due to their prevalence in natural products. Regardless of the olefin stereochemistry, the selectivity of these compounds is generally achieved by conventional methods such as the HWE reaction, the Still-Gennari variant or through the use of stereodefined starting materials. Few of these methods utilize catalyst control to generate the stereochemistry of either olefin of the dienoate.

In Ley's synthesis of (+)-aspicilin, integration of the *cis* olefin is circumvented by utilizing the six-membered ring building block on the right hand side of molecule 2.55.<sup>24</sup> Syn-Dihydroxylation would be a potential option for the incorporation of the syn diol moiety. However, the group constructed their molecules around the readily accessible sixmembered ring starting material to avoid having to synthesize the Z olefin. At the end of

<sup>(24)</sup> Dixon, D. J.; Alison C. Foster, A. C.; Ley, S. V. Org. Lett. 2000, 2, 123-125.

the synthesis, however, cleavage of this protecting group proved to be costly as only 44% yield of **2.56** was obtained. This approach limits the disconnections that can be made, which in turn limits the number of natural products that can be accessed through this strategy.





Suzuki developed a two-step cross-coupling reaction to produce esters.<sup>25</sup> Treatment of boronate **2.57** and alkenyl zinc **2.58** in the presence of 1.0 mol % PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>4</sub> gave Negishi cross-coupling product **2.59**. Alkoxycarbonylation of **2.59** with carbon dioxide and methanol in the presence of palladium dichloride and benzoquinone furnished (*E*,*Z*)-dienoate **2.60**. Using the appropriate alkenyl zinc reagents, the method is amenable to the synthesis of (*Z*,*Z*) and (*E*,*E*)-dienoates as well (**2.61** and **2.62**). The stereochemistry of the resulting dienoate is dependent on the boronate as well as the zinc reagent. Generally, zinc reagents are derived from the corresponding Grignard reagents, which also means limited functional group compatibility, and cannot Thus, preparation of *Z* alkenyl zinc compounds is limited by the availability of the *Z* alkenyl halide precursor.<sup>26</sup> While this method could be utilized for generating *Z* enoates, none were disclosed, most likely, due to the difficulty of synthesizing *Z* boronates at the time.<sup>27</sup> Lastly, this method generates significant amounts of waste from the use of organozinc and halide precursors.

<sup>(25)</sup> Yamashina, N.; Hyuga, S.; Hara, S.; Suzuki, A. Tetrahedron Lett. 1989, 30, 6555-6558.

<sup>(26)</sup> Valente, C.; Belowich, M. E.; Hadei, N.; Organ, M. Eur. J. Org. Chem. 2010, 4343-4354.

<sup>(27)</sup> For representative methods to synthesize Z alkenyl-B(pin) compounds, see chapter 1, section 1.2.2.



Scheme 2.9. Stereoretentive Cross-Coupling and Alkoxycarbonylation.

Relying on the stereochemistry of the boron reagent as well, Jung and co-workers reported an oxidative Pd-catalyzed cross-coupling to generate dienoates.<sup>28</sup> With Z alkenyl-B(pin) **2.63** and *tert*-butyl acrylate **2.64** in the presence of catalytic palladium acetate and oxygen, (E,Z)-dienoate **2.65** can be afforded in high yield (91%). However, there are no other examples of (E,Z)-dienoates reported, most likely due to the issue making Z alkenyl-B(pin) compounds. Protocols for the synthesis of boron-substituted (E,Z)-dienoate compounds have been disclosed.<sup>29</sup> Boronates can participate in Suzuki cross-coupling reactions with alkenyl halides to provide products such as **2.65** or potentially more complex substituents compared to a butyl chain. Regardless, the synthesis of these B(pin)-substituted dienoates still relies on the availability of Z alkenyl halide cross-partners.





Dienoates offer two points of disconnection for cross-metathesis. In Curran's synthesis of dictyostatin, he reported synthesis of the E- $\alpha$ , $\beta$ -unsaturated alkene through an

<sup>(28)</sup> Yoo, K. S.; Yoon, C. H.; Jung, K. W. J. Am. Chem. Soc. 2006, 128, 16384–16393.

<sup>(29)</sup> For the synthesis of B(pin)-substituted dienoates, see: (a) Tseng, N. W.; Lautens, M. *J. Org. Chem.* 2009, 74, 2521–2526. (b) Woerly, E. M.; Struble, J. R.; Palyam, N.; O'Hara, S. P.; Burke, M. D. *Tetrahedron*, 2011, 67, 4333–4343.

HWE reaction and the *Z* olefin through the Still-Gennari modification of the reaction.<sup>30</sup> In another methodology report, Curran and co-workers demonstrated CM of dienoate **2.65** with 1,2-disubstituted **2.66** in the presence of Ru-complex **2.67** to afford (*Z*,*E*)-dienoate **2.68**.<sup>31</sup> A variety of olefins was found to be tolerated including the model system for dictyostatin (**2.69**); In all cases, high *E* selectivity was observed. This reaction is limited to the formation of (*Z*,*E*)-dienoates as the starting material is prepared by the Still-Gennari reaction. Utilizing methyl sorbate [(*E*,*E*)-form of **2.65**]<sup>32</sup> is the starting material leads to undesired reaction with the  $\alpha$ ,β-unsaturated alkene.<sup>33</sup>



In the Schrock lab, Mo-catalyzed Z-selective homocoupling of 1,3-dienes was reported.<sup>34</sup> Terminally substituted 1,3-diene **2.73** in the presence of 5.0 mol % of **2.74** delivered 59% yield of (E,Z,E)-triene **2.75** as a 97:3 Z:E mixture of the newly formed internal olefin. Alkyl as well as aryl substituted alkenes are compatible in this reaction (Scheme

<sup>(30)</sup> Jung, W.-H.; Harrison, C.; Shin, Y. Fournier, J.-H. Balachandran, R.; Raccor, B. S.; Sikorski, R. P.; Vogt, A.; Curran, D. P.; Day, B. W. J. Med. Chem. 2007, 50, 2951–2966.

<sup>(31)</sup> Moura-Letts, G.; Curran, D. P. Org. Lett. 2007, 9, 5-8.

<sup>(32)</sup> For a report regarding synthesis of (*E*,*E*)-dienoates involving CM, see: Murelli, R. P.; Snapper, M. L. Org. Lett. 2007, 9, 1749–1752.

<sup>(33)</sup> Funk, T. W.; Efskind, J.; Grubbs, R. H. Org. Lett. 2005, 7, 187-190.

<sup>(34)</sup> Townsend, E. M.; Schrock, R. R.; Hoveyda, A. H. J. Am. Chem. Soc. 2012, 134, 11334-11337.

2.14), but those carrying more sterically demanding substituents exhibited higher selectivities. Even though this report only examined homocoupling, but it supported the possibility of diene-type compounds serving as effective substrates for our dienoate CM studies.



Scheme 2.12. Z-Selective Mo-Catalyzed Homocoupling of 1,3-Dienes.

### 2.3 Synthesis of Macrocyclic Z Enoates and Dienoates

# 2.3.1. Preliminary Studies with Commonly Used Mo- and Ru-Based Complexes,

#### and Stereogenic-at-Mo Complexes

We were driven to examine the reactivity of enoate RCM with commercially available complexes at the beginning of our studies. In the presence of Ru-complex **2.81**, the reaction was extremely efficient, but delivered the *E* isomer as the major product (87%conv, 95% *E*, Table 2.1, entry 1). With Ru-complex **2.82**, however, no conversion to desired product or oligomers was observed (entry 2). Treatment of diene **2.79** consumed 61% of diene, but only 42% was converted to the 14-membered macrocycle **2.80**. Moreover, the isolated products were a mixture of *Z*:*E* isomers as well as the dimeric macrocycle (entry 3).



Table 2.1. Catalytic RCM with 2.79 with Representative Commercially Available Complexes.

<sup>a</sup> Reactions performed in  $C_6H_6$  under  $N_2$  atm. <sup>b</sup> Reaction performed under a vacuum of 100 torr. <sup>c</sup> Determined by analysis of <sup>1</sup>H NMR spectra of unpurified mixtures (of **2.79** for conv and of **2.80** for *Z*:*E*) and refer to consumption of 2.21 (±2%). <sup>d</sup> Product mixture contained ca. 50% of the dimeric macrocycle.



Given the lack of desirable results from the commercially complexes, we turned to our library of stereogenic-at-metal complexes (Table 2.2). W-complex **2.84** proved to be inefficient over 12 h reaction time (<5% conv, entry 1). Minimal reactivity was observed with Mo-alkylidene **2.85** as well (entry 2). From here, we chose MAP complex with a more electron-deficient arylimido group **2.86** and found 24% conv to the desired product, but with a selectivity of only 72:28 *Z*:*E* (entry 3). In an attempt to increase selectivity, we opted for a more sizeable aryloxide, but reactivity was completely lost with complex **2.87** (entry 4). Generating a more Lewis acidic Mo center with a pentafluorophenylimido group (**2.88**) gave rise to a significant increase in reactivity (60% conv to product, 89:11 *Z*:*E*, entry 5).<sup>35</sup> With more sterically demanding 2,4,6-tri(isopropyl)phenyl substituents (**2.89**), we were unable to enhance stereoselectivity as the reaction did not proceed (entry 6).

<sup>(35)</sup> Wang, C.; Haeffner, F.; Schrock, R. R.; Hoveyda, A. H. Angew. Chem., Int. Ed. 2013, 52, 1939–1943.

 Table 2.2. Catalyst Screening of RCM of 2.79.



entry	complex	time (h)	conv (%) <sup>b</sup>	conv to 2.21 (%) <sup>b</sup>	<b>Z:E</b> <sup>b</sup>	
1	2.84	12	<5	na	nd	
2	2.85	2.0	<10	na	nd	
3	2.86	2.0	30	24	72:28	
4	2.87	2.0	<10	na	nd	
5	2.88	2.0	79	60	89:11	
6	2.89	2.0	<5	na	nd	
4 5 6	2.87 2.88 2.89	2.0 2.0 2.0	<10 79 <5	na 60 na	nd 89:11 nd	

<sup>a</sup> Reactions performed in  $C_6H_6$  under  $N_2$  atm. <sup>b</sup> Determined by analysis of <sup>1</sup>H NMR spectra of unpurified mixtures and refer to consumption of 2.79 (±2%).





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#### 2.3.2. MAP–Mo-Catalyzed Z-Selective RCM of Z Enoates

With further optimization, best results were obtained with only 3.0-5.0 mol % of MAP-Mo complex 2.88 after 2.0 h at a higher concentration of 2.0 mM. With the established conditions at hand, we proceeded to examine a variety of different ring sizes from 14-24 membered rings. Unfunctionalized macrocycles never reached full consumption of the diene, but little to no oligomerization of the diene was observed. Isolated yields ranged from 44-65%, which leads to some discrepancy between the yield and conversion. The reason behind the difference is that we were capable of separating the Z and E isomers through silver nitrate impregnated silica gel chromatography. Even though selectivities peaked at 90:10 Z:E (2.90–2.94), the Z macrocycle can be cleanly isolated. In comparison to the aforementioned unfunctionalized macrocycles, there was a clear impact on the reactivity and selectivity by the different substituents on the ring.<sup>36</sup> With 15-membered rings (2.90 vs. 2.95), reactivity was similar, but inclusion of the Boc protected amine within the macrocycle led to a 10% decrease in Z selectivity. On the other hand, formation of 16- and 17-membered ring systems, bearing amine substituents were more efficient (2.96 and 2.97 versus 2.91 and 2.92, respectively). Macrocycles 2.97-2.99 showed better conversion to the desired Z macrocycle versus oligomerization when compared to 2.92 (60–70% yield vs 50% yield). Unfortunately, stereoselectivities were similar to the unfunctionalized ring system. 24-Membered macrocycle 2.100 was accessible as well as a 83:17 mixture of Z:E isomers. More importantly, the presence of a free indole unit does not affect catalyst activity.

<sup>(36)</sup> Xu, Z.; Johannes, C. W.; Houri, A. F.; La, D. S.; Cogan, D. A.; Hofilena, G. E.; Hoveyda, A. H. J. Am. Chem. Soc. 1997, 119, 10302.



Scheme 2.13. Z-Selective Macrocyclic Enoate RCM of Different Ring Sizes.

Exploration of enamides, both unprotected and protected, led to undesired results. Complete catalyst deactivation was observed with enamides, regardless of the size of the ring that was being formed (**2.101** and **2.102**). Free carbamate only gave 13% conversion to **2.103**, illustrating that even remote nitrogens, though less effectively, can still inhibit

reactivity. The inherently more Lewis basic amide versus ester may lead to stronger chelation to the Mo center when the undesired Mo-alkylidene is generated, rending these species unreactive (Figure 2.2).<sup>37</sup>



Scheme 2.14. Deactivation of Nitrogen-Containing Substrates.

Figure 2.2. Chelation of Enamide-Derived Alkylidene.



Macrocyclic E enoates become more favored with larger ring sizes. In an unfunctionalized system, the thermodynamic preference for the E enoate begins when the ring contains 11 members (Figure 2.3). Thus, our catalytic RCM protocol allows access to the higher energy Z isomers of 14–24 membered macrocycles with good functional group compatibility.

<sup>(37) (</sup>a) Sattely, E. S.; Cortez, G. A.; Moebius, D. C.; Schrock, R. R.; Hoveyda, A. H. J. Am. Chem. Soc. 2005, 127, 8526–8533. (b) Townsend, E. M.; Kilyanek, S. M.; Schrock, R. R.; Müller, P.; Smith, S. J.; Hoveyda, A. H. Organometallics 2013, 32, 4612–4617.



Figure 2.3. Variations in Thermodynamic Preferences of Different Unsaturated Macrocyclic Alkenes.

2.3.3. MAP–Mo-Catalyzed Z-Selective RCM of Dienoates

Applying similar conditions from the enoate system to that of the dienoates, we were able to prepare a variety of (Z,E)- and (E,Z)-dienoates of various ring sizes. With Edienoates as substrates, (E,Z)-macrocycles are synthesized with complete control of stereoselectivity for 15-, 16- and 18-membered rings (2.105, 2.106 and 2.107). Macrocycle 2.105 was isolated in 50% yield, while macrocycles 2.106 and 2.107 were isolated with slightly higher yields (63% and 64% yield). In the formation of 18-membered macrocycle 2.107, no reactivity was observed when the starting triene was treated with 10 mol % of Ru complexes 2.81 or 2.82. In the presence of 10 mol % of Mo-bisalkoxide 2.83, minimal reactivity was observed as well (<10% conv). The RCM proceeds only when 20 mol % of 2.83 was to give macrocycle 2.107 in 47% yield as the pure (E,Z)-isomer in 2 h. With optimal MAP-Mo complex 2.88, 19-membered macrocycle 2.108 was isolated in 71% yield, but only as 91:9 Z: E mixture. Treatment of the starting triene precursor of 2.108 with 20 mol % of Mo-bisalkoxide 2.83 only led to 34% conv of the starting material, but with a slight preference for the (E,E)-isomer over the (E,Z)-isomer (65:35 Z:E). In accord with the observed results, preference for the (E,Z)-isomer was calculated for up to 18-membered rings. Rings containing more than 18 atoms significantly favor the (E,E)-dienoate. Despite

the lower selectivity observed with 19-membered macrocycle **2.108** (compared to **2.105**–**2.107**), we were still able to attain kinetic *Z* selectivity utilizing more Lewis acidic MAP–Mo **2.88**.



Scheme 2.15. Z-Selective Formation of Macrocyclic Dienoates by RCM.

For the synthesis of (Z,E)-dienoates, lower stereoselectivities were detected with this dienoate system. Based on the knowledge that ring sizes containing 18 or more atoms had a low *Z*:*E* thermodynamic preference, we explored the RCM of 18- and 19-membered rings. Though selectivities were found to be <90% *Z*, in both cases we were able to separate the (Z,E) and the (E,E) isomers from each other to obtain yields of the pure (Z,E)-dienoate. 18-Membered ring **2.110** was isolated in 75% yield and 19-membered macrocycle **2.111** was afforded in 57% yield. Examination of the RCM for the formation of **2.111** with catalysts **2.81** and **2.82** revealed a lack of reactivity, underlining the unique reactivity profiles of MAP–Mo complexes.

#### 2.3.4. Application to Formal Synthesis of (+)-Aspicilin

The utility of the reaction was demonstrated through the application of the macrocyclic RCM to the synthesis of a precursor to (+)-aspicilin **2.56**. The 18-membered macrolide was first isolated in 1900 by Hesse from *Aspicilia calcarea* and was later found to be void of any biological activity.<sup>38,39</sup> Although (+)-aspicilin does not contain either an  $\alpha$ , $\beta$ or  $\gamma$ , $\delta$ -*Z* alkene, the *syn* 1,2-diol motif at the  $\gamma$ - and  $\delta$ -position constitutes a masked *Z* alkene. We synthesized the skeleton of our substrate with **2.112** and employed it in a subsequent esterification to afford *E* dienoate **2.113** (Scheme 2.18). Subjection of the triene to 10 mol % of **2.88** under a vacuum of 100 torr in 6 h afforded (*E*,*Z*)-dienoate **2.114** in 69% yield as a single isomer. Deprotection of the PMB group provided the free alcohol in **2.115**, which has been subjected to *syn*-dihydroxylation conditions<sup>40</sup> to afford the final natural product (+)-aspicilin **2.56**.

<sup>(38) (</sup>a) Hesse, O. J. Prakt. Chem. 1900, 62, 430–480. (b) Huneck, S; Schreiber, K.; Steglich, W. *Tetrahedron* 1973, 29, 3687–3693. (c) Quinkert, G.; Heim, N.; Bats, J. W.; Oschkinat, H.; Kessler, H. *Angew. Chem., Int. Ed. Engl.* 1985, 24, 987–988.

<sup>(39) (</sup>a) Enders, D.; Prokopenko, O. F. *Liebigs Ann.* 1995, 1185–1191. (b) Kobayashi, Y.; Nakano, M.; Kumar, G. B.; Kishihara, K. J. Org. Chem. 1998, 63, 7505. (c) Dixon, D. J.; Foster, A. C.; Ley, S. V. Org. *Lett.* 2000, 2, 123. (d) Gandi, V. R. *Tetrahedron* 2013, 69, 6507.

<sup>(40)</sup> Quinkert, G.; Heim, N.; Glenneberg, J.; Billhardt, U.-M.; Autze, V.; Bats, J. W.; Dürner, G. Angew. Chem., Int. Ed. Engl. 1987, 26, 362–364.



Scheme 2.16. Application of Macrocyclic Enoate RCM to Formal Synthesis of (+)-Aspicilin.

## 2.4 Synthesis of Acyclic Z-Enoates and (E,Z)-Dienoates

#### 2.4.1. Preliminary Studies of Enoates with Commonly Used Mo- and Ru-Based

#### **Complexes, and Stereogenic-at-Mo Complexes**

Since the early seminal work of metathesis, new complexes have emerged and displayed proficient in CM. We sought to investigate these complexes in the Z-selective CM of acrylates. Ru-complex **2.82** has been deemed as a Z-selective catalyst. Indeed, when we subjected acrylate **2.117** in the presence of excess decene, the reaction is completely Zselective, but showed poor efficiency. Ru-dithiocatecholate **2.119** showed a complete lack of reactivity, most likely owing to the presence of only terminal olefins in the mixture which leads to decomposition of the catalyst. Mo-bisalkoxide **2.83** shows similar reactivity to **2.82**, but favors the *E* isomer (31:69 *Z:E*).

0	± n oot	~ _	5.0 mol % comple	x n-octy	0
	Bu	yı 🥆 —	100 torr, 22 °C, 4	h 📎	Ot-Bu
2.117				2.1	18
entry	complex	solvent	conv (%) <sup>c</sup>	yield (%) <sup>d</sup>	<i>Z:E</i> <sup>c</sup>
1 <sup>b</sup>	2.82	thf	27	nd	>98:2
2 <sup>b</sup>	2.119	thf	<2	na	na
3	2.83	$C_6H_6$	35	31	31:69

 Table 2.3. Catalytic CM with t-Butyl Acrylate 2.117 and Representative Commercially Available Complexes.

<sup>a</sup> Reactions performed in  $C_6H_6$  under  $N_2$  atm. <sup>b</sup> Reaction performed under ambient pressure. <sup>c</sup> Determined by analysis of <sup>1</sup>H NMR spectra of unpurified mixtures (±2%). <sup>d</sup> Yields of isolated and purified products (±5%).



Turning our attention to our library of catalysts, we observed significantly better reactivity, overall. Catalytic amounts of **2.120** afforded enoate **2.118** in 90% yield in 4 h, but similar to the previously mentioned Mo-complex, the *E* isomer is preferred. The low selectivity is attributed to adventitious post-metathesis isomerization. Incorporating a more sizeable aryloxide (**2.85**) gave the enoate in 92:8 *Z*:*E*, but only with 55% yield.

0 <b>II</b>	+ n cotul	5.0 mol % con	n-octyl C	)
	Bu	100 torr, 22 °C	c, 4 h	Ot-Bu
2.117			2.11	3
entry	complex	conv (%) <sup>b</sup>	yield (%) <sup>b</sup>	<b>Z:E</b> <sup>b</sup>
1	2.120	90	90	6:94
2	2.85	62	55	92:8
3	2.88	96	83	58:42

 Table 2.4. Catalytic Screening of CM with Acrylate 2.117.

<sup>a</sup> Reactions performed in  $C_6H_6$  under  $N_2$  atm. <sup>b</sup> Determined by analysis of <sup>1</sup>H NMR spectra of unpurified mixtures (±2%). <sup>c</sup> Yields of isolated and purified products (±5%).



Determined to acquire a system that would provide us efficiency without the cost of stereoselectivity, we further optimized the reaction conditions with complex **2.88** as no other Mo-based MAP complex yielded better yield and Z selectivity (Table 2.5). By reducing the reaction time from 4 h to just 5 min, the selectivity increases to  $79:21 \ Z:E$  (entry 1). However, by allowing to reaction to proceed for 30 min, the reaction becomes non-selective once again (entry 2). These reaction conditions were not ideal, not only due to the moderate yields and selectivities, but also because of the use of excess amounts of the non-enoate alkene. When the equivalents of decene is decreased to one, there is a dramatic loss in reactivity, though no *E*-enoate is detected (entry 3). An excess of **2.117** with respect to decene leads to a similarly poor reaction (20% conv) that is highly *Z*-selective (entry 4). We hypothesized that the poor reactivity in the presence of more arylate is due to internal chelation of the ester-substituted alkylidene to the Mo alkylidene center. Such chelation would lead to diminished reactivity, productive as well as post-metathesis isomerization.

	0 II + ∩		5.0 mol % <b>2.88</b>	<i>n-</i> octyl	0 	
Ot-Bu			100 torr, 22 °C	Ot-Bu		
2	117			2.11	7	
entry	time (min)	decene:2.117	conv (%) <sup>b</sup>	yield (%) <sup>b</sup>	<b>Z:E</b> <sup>b</sup>	
1	5	3:1	79	62	79:21	
2	30	3:1	82	56	53:47	
3	5	1:1	30	nd	>98:2	
4	5	1:3	20	nd	>98:2	

Table 2.5. Effects of Time and Stoichiometry on the CM with 2.117.

<sup>a</sup> Reactions performed in  $C_6H_6$  under  $N_2$  atm. <sup>b</sup> Determined by analysis of <sup>1</sup>H NMR spectra of unpurified mixtures (±2%). <sup>c</sup> Yields of isolated and purified products (±5%).

Spectroscopic analysis of the reaction between **2.85** and **2.121**, in the absence of any cross-partner, allowed us to gain further insight as to whether internal chelation occurred and was potentially preventing the productive reaction from occurring (Table 2.6). In 15 min, no conversion to **2.122** was observed (entry 1). After 24 h, there was 26% conversion to a new alkylidene that is observed at 11.47 ppm (entry 2). The coupling constant is 160 Hz, which we denote most likely as the *anti* isomer as *anti*-alkylidene species generally reveal coupling constants of greater than 140 Hz.<sup>41</sup> Allowing the reaction to proceed for 72 h did not lead to full conversion (entry 3), showing that the acrylate alkylidene may not be the species responsible for initiating the productive CM.

<sup>(41)</sup> Schrock, R. R.; Hoveyda, A. H. Angew. Chem., Int. Ed. 2003, 42, 4592-4633.



Table 2.6. Preparation of Ester-Substituted Mo-Alkylidene.

<sup>a</sup> Conversion determined by analysis of <sup>1</sup>H NMR spectra of unpurified mixtures (±2%).

A closely related ester-substituted alkylidene was synthesized and isolated (2.123, Figure 2.4).<sup>42</sup> Through NMR analysis, the alkylidene proton resonates at 10.46 ppm and also shows a  $J_{CH}$  value of 182 Hz. Due to the large coupling constant, we were able to confidently designate this resonance as the signal for the *anti* isomer. In addition to spectroscopic evidence (<sup>1</sup>H), single crystal X-ray analysis of compound 2.123 was obtained, confirming the structure of the *anti*-alkylidene. From the X-ray of the crystal, carbonyl association was suggested as the Mo-O (of carbonyl) bond length is 2.33 Å.<sup>43</sup> The distance is considerably long to be a defined covalent bond, but chelation can be implied.

<sup>(42)</sup> Complex **2.123** was synthesized not through the neophylidene precursor, but rather the methylidene precursor in 80 minutes.

<sup>(43)</sup> Mo-O (aryloxide) distance of 2.123 is 1.95 Å.



Figure 2.4. Structural Analysis of Ester-Substituted Mo-Alkylidene.

Since the internal coordination seemed responsible for shutting down the reactivity of critical reaction intermediates, the question became how to interrupt this chelation without diminishing the activity of the alkylidene species. External chelation through a Lewis base could prevent the internal chelation. The Lewis base must be strong enough to coordinate to the Mo center, but at the same time, be readily displaced by an incoming olefin to allow for productive CM. While the addition of a Lewis base could decelerate the reaction by limiting the turnover frequency of the reaction, we postulated that turnover numbers could increase. The catalyst would be longer living as a 16-electron (vs 14-electron) methylidene species by circumventing decomposition and post-metathesis isomerization. Indeed, when the reaction is performed in thf,<sup>44</sup> the yield increased to 70% and selectivity increased to 90:10 Z:E (Table 2.7, entry 1). The reaction was more selective in a less concentrated solution (93:7 Z:E, entry 2). Prolonging this reaction, though, once again only led to increased post-metathesis isomerization without a significant increase in reactivity (64% yield, 69:31 Z:E, entry 3). Exchanging the solvent for acetonitrile was done on the basis that the solvent was mildly Lewis basic, but less sterically demanding compared to thf. In acetonitrile, the reaction was completely selective for Z-2.119, but catalyst activity was significantly diminished (14% conv, entry 4). Reduction of the amount of acetonitrile afforded the product in 67% yield as 91:9 Z:E mixture (entry 5). Performing the reaction with equal amounts of acrylate and cross-partner delivered similar efficiency and selectivity (69% yield, 91:9 Z:E, entry 6). By allowing the reaction to proceed with a 1:2 ratio of decene to acrylate, the desired enoate was isolated in 71% yield and 94:6 Z selectivity.

<sup>(44)</sup> Teng, X.; Cefalo, D. R.; Schrock, R. R.; Hoveyda, A. H. J. Am. Chem. Soc. 2002, 124, 10779-10784.

n-octyl

	U II	<b>н</b> –		5.0 mol % 2.88			
	$\sim$	D <i>t</i> -Bu	-ociyi 🥆 –	100 torr, 22 °C		Ot-Bu	
	2.117	7				2.119	
entry	solvent	2.88 [M]	time (min)	decene:2.117	conv (%) <sup>b</sup>	yield (%) <sup>c</sup>	<b>Z:E</b> <sup>b</sup>
1	thf	0.1	5	3:1	79	70	90:10
2	thf	0.025	5	3:1	71	53	93:7
3	thf	0.025	30	3:1	90	64	69:31
4	CH₃CN	0.025	60	3:1	14	nd	>98:2
5	CH₃CN	0.1	60	2:1	88	67	91:9
6	CH₃CN	0.1	60	1:1	79	69	91:9
7	CH <sub>3</sub> CN	0.1	60	1:2	75	71	94:6

5.0 mol % **2.88** 

Table 2.7. Effects of Coordinating Solvent on CM to 2.119.

Ot-Bu + n-octyl

<sup>a</sup> Reactions performed under N<sub>2</sub> atm. <sup>b</sup> Determined by analysis of <sup>1</sup>H NMR spectra of unpurified mixtures ( $\pm 2\%$ ). <sup>c</sup> Yields of isolated and purified products ( $\pm 5\%$ ). nd = not determined.

#### 2.4.2. MAP–Mo-Catalyzed Z-Selective CM of Z Enoates

We explored the acrylate CM transformations with an array of terminal olefins containing different functionalities. After 1 h, long alkyl chains containing protected ether was synthesized in 71% yield with 93% Z (2.124) and containing benzyl-protected thioether was afforded in 57% yield as the pure Z isomer (2.125). More sterically demanding allylic olefins required 4 h to reach higher conversions. Allylic *p*-methoxybenzylether was crossed with acrylate 2.117 to provide the pure Z-enoate 2.126 in 62% yield. Formation of benzyl enoate 2.K4 was impeded by the homocoupling of allyl benzene and only isolated in 40% yield. As it is relatively sterically encumbering, however, only the cis isomer was detected. β-Branched alkene also exhibited similar efficiency and selectivity as an allylic ether (2.128, 69% yield, 98:2 Z:E). While styrenes did not show any reactivity due to the favored generation of stilbene, sterically demanding vinyl cyclohexane proceeded to afford enoate 2.129 in 64% yield and 94% Z. As vinyl cyclohexane is quite large, the reaction required 24 h. Homocoupling was not an issue in this case, as this side reaction was sluggish compared to the productive CM. We were also capable of facilitating the formation of (Z,E)dienoate **2.130**, though relatively less efficiently, in a highly stereoselective fashion.



Scheme 2.17. (Z)-a,b-Unsaturated Esters through Catalytic Cross-Metathesis.

<sup>a</sup> Reactions performed at 100 torr for 1 h. <sup>b</sup> Reaction performed at 100 torr for 4 h. <sup>c</sup> Reaction performed at ambient pressure for 24 h.

#### 2.4.3. Mechanistic Investigations: The Significance of Acetonitrile

Spectroscopic investigations allowed us to observe the role of acetonitrile in this reaction. The <sup>1</sup>H of Mo-complex **2.88** resonates at 11.09 ppm in deuterated benzene (Figure 2.5). Additional acetonitrile shows a slight downward shift of the singlet with more acetonitrile. In the presence of 5.0 equiv of acetonitrile with respect to the complex, the singlet resides at 11.33 ppm. The observation of a singlet alkylidene peak may lead one to deduce this as a solvent effect. A slightly broadened signal with 1.0 equiv of acetonitrile suggested that there is a fast equilibrium, with respect to the NMR time scale, and the signal moved with different amounts of acetonitrile. Analysis of <sup>13</sup>C NMR of complex **2.88** with varying equivalencies of CH<sub>3</sub><sup>13</sup>CN exhibited shifts in the alkylidene carbon resonance. However, minimal shift differences was observed for the resonance of the C1 of acetonitrile.



Figure 2.5. Spectroscopic Analysis of Effect of Equivalents of Acetonitrile on Mo-MAP 2.88.

(600 MHz, <sup>1</sup>H NMR, 22 °C, C<sub>6</sub>D<sub>6</sub>)

Conducting a variable temperature (VT) spectroscopic study with different equivalencies of acetonitrile with respect to MAP–Mo complex **2.88** allowed us to gain further insight as to the importance of acetonitrile. With 0.5 equiv of CH<sub>3</sub>CN at 20 °C in deuterated toluene, a single peak at 11.05 ppm is observed, in accord with the previous experiment (Figure 2.6). Upon cooling, the peak begins to broaden around -20 °C and separates into two broad singlets around -60 °C. When the sample is analyzed at -80 °C, two sharper peaks are observed, one of which resides at 10.64 ppm and the other which resides at 12.82 ppm. The presence of two resonances confirm that there are two distinct species present in the sample when the complex co-exists with acetonitrile.



Figure 2.6. VT Analysis of 0.5 Equivalents of Acetonitrile on Mo-MAP 2.88.

(600 MHz, <sup>1</sup>H NMR, *d*<sub>8</sub>-toluene)

Further examination with an excess of acetonitrile provided evidence as to assign each peak to different species. In an excess of acetonitrile (5.0 equiv, Figure 2.7), one resonance is detected, though the peak is shifted downfield to 11.24 ppm. Decreasing the temperature in this study showed broadening of the resonance, but never separated into two peaks. The peak moves downfield and sharpens to a singlet at 12.82 ppm at -60 °C, with no appearance of the 10.64 ppm resonance, most likely due to the extremely low concentration of the unbound species. At colder temperatures, only one species is present. Based on the fact that resonances shift downfield in the presence of excess acetonitrile (cf. Figure 2.5), we designate the peak at 12.82 ppm as the acetonitrile-bound species. Though the acetonitrile-bound species is dominant, the VT study with 5.0 equiv of acetonitrile shows that there is still rapid equilibrium between the bound and free species of **2.88**.



Figure 2.7. VT Analysis of 5.0 Equivalents of Acetonitrile on Mo-MAP 2.88.

(600 MHz, <sup>1</sup>H NMR, *d*<sub>8</sub>-toluene)

From these NMR experiments, the acetonitrile-bound species is likely to be the predominant species throughout the reaction course. However, its role in the productive CM cycle remained to be fully elucidated. One possibility is that the acetonitrile chelates to the metal throughout the entire catalytic cycle. The starting 16-electron complex would then go through an 18-electron metallacyclobutane intermediate. Computational evidence calculated energy barriers of greater than 35 kcal/mol, leading us to believe that such a mechanism is not feasible. The studies at low temperature only indicate two alkylidene species, neither of which is an 18-electron species (Integration of the CH<sub>3</sub> protons of acetonitrile indicate mono-CH<sub>3</sub>CN bound species and free acetonitrile molecules). Thus, we speculate that the acetonitrile must dissociate prior to going through the classic 14-electron metallacyclobutane intermediate, in agreement with previous studies discussing the 14-electron species as a well-known intermediate.<sup>35,45</sup>

<sup>(45)</sup> Poater, A.; Solans-Monfort, X.; Clot, E.; Copéret, C.; Eisenstein, O. J. Am. Chem. Soc. 2007, 129, 8207-8216.

# 2.4.4. Preliminary Studies of Dienoates with Commonly Used Mo- and Ru-Based Complexes, and Stereogenic-at-Mo Complexes

After the studies with enoates, we studied whether efficient CM of (E,Z)-dienoates would be possible, with interest in formation of the  $\gamma$ , $\delta$ -alkene. Phenyl dienoate **2.131a** was subjected to a series of commercially available complexes (Table 2.8). Bidentate Ru-complex **2.82** led to no detectable transformation after 4 h. Reaction with Ru-chloride **2.81** was efficient but primarily generated the lower energy *E* isomer. Minimal reaction was observed with Mo-bisalkoxide **2.83**.

Table 2.8. Catalytic CM with Phenyl Dienoate 2.131a and Representative Commercially Available Complexes.

2.131a	+ <i>n</i> -oc OPh (3.	ctyl	5.0 mol % complex C <sub>6</sub> H <sub>6</sub> , 22 °C	noctyl	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
entry	complex	time	conv (%) <sup>a</sup>	yield (%) <sup>b</sup>	Z:E <sup>a</sup>
1	2.82	4	<2	na	na
2	2.81	4	95	87 <sup>c</sup>	2:98
3 <sup>d</sup>	2.83	24	<5	na	na

<sup>a</sup> Determined by analysis of <sup>1</sup>H NMR spectra of unpurified mixtures (±2%). <sup>b</sup> Yields of isolated and purified products (±5%). <sup>c</sup> Yield of product and **2.131a** <sup>d</sup> Reactions performed in  $C_6H_6$  under N<sub>2</sub> atm and under a vacuum of 100 torr.



Studies with MAP complexes led to better reactivity under conditions that allowed for facile reaction (Table 2.9). With Mo-alkylidene **2.85**, 63% conversion of the diene was observed and was selective for the (E,Z)-dienoate (entry 1). Electron-withdrawing pentafluorophenyl imido complex **2.88** was very reactive, not only generating product, but also causing olefin isomerization (56% yield, 87:13 *Z*:*E*, entry 2). With milder and more electron-rich adamantylimido complex **2.133**, 70% yield of dienoate **2.132a** was isolated as the

pure (E,Z)-isomer (entry 3). Subsequent screening with acetonitrile or thf did not lead to enhanced reactivity. Because of the longer chain, the reaction did not suffer from internal chelation of the Lewis basic carbonyl group. Hence, using a Lewis basic solvent only led to lower conversion. Furthermore, it was necessary to use an excess of the cross-partner as the alkenyl-substituted alkylidene is less reactive due to the resonance stabilization.

Table 2.9. Catalytic Screening of CM with Phenyl Dienoate 2.131a.



<sup>a</sup> Determined by analysis of <sup>1</sup>H NMR spectra of unpurified mixtures (±2%). <sup>b</sup> Yields of isolated and purified products (±5%).



2.4.5. MAP–Mo-Catalyzed Z-Selective CM of (E,Z)-Dienoates

Investigation of a variety of different olefins to synthesize (*E*,*Z*)-dienoates allowed us to access both stereoisomers of  $\alpha$ , $\beta$ , $\gamma$ , $\delta$ -unsaturated ester (Scheme 2.18). Our method allowed for access to both *tert*-butyl and phenyl dienoate. CM with dienoate and 1-decene provided (*E*,*Z*)-**2.134b** and **2.134a** in 93:7 *Z*:*E* selectivity. In most cases though, using *tert*butyl dienoate yielded better results. The method tolerated TIPS-protected alkyne to afford desilylated **2.135** in 81% yield and 95% *Z*. Benyl thioether was non-problematic, delivering **2.136** as a 95:5 *Z*:*E* mixture (86% yield). Allylic *p*-methoxybenzyl ether showed lower reactivity, but delivered the product a single stereoisomer (65% yield, >98:2 Z:E). Trisubstituted olefin-containing substrates were tolerated and did not show any detectable signs of isomerization (**2.138**). For optimal reactivity, the reaction required only 1.5 equiv of the alkene, potentially due to competitive binding of the internal olefins that impeded the reaction. Alkene-containing  $\beta$ -branches is also highly efficient and stereoselective (**2.139**, 88% yield, 95:5 Z:E). Alkenyl-B(pin) dienoate can be synthesized in high yield as the pure (*E*,*Z*) isomer.<sup>29</sup> Bromo-containing alkyl chain led to high yields with phenyl dienoate **2.131a** in 87% yield with 98:2 *Z:E*.



**Scheme 2.18.** (*E*,*Z*)- $\alpha$ , $\beta$ , $\gamma$ , $\delta$ -Unsaturated Esters through Catalytic Cross-Metathesis.

<sup>&</sup>lt;sup>a</sup> Overall yield of desilylated product. <sup>b</sup> Reaction was performed in the presence of 1.5 equiv of cross partner. <sup>c</sup> Reaction performed at ambient pressure for 24 h.

#### 2.4.6. Application to Formal Synthesis of (–)-Laulimalide

(–)-Laulimalide was first isolated from marine sponges *Cacospongia mycofijiensis* by Crews and co-workers<sup>46</sup> and from *Hyattella sp* in Indonesia by Moore.<sup>47</sup> Less than a decade later, it was found in Okinawa by Higa's group from *Fasciospongia rimosa*.<sup>48</sup> Laulimalide has been found to have exhibit potent biological activity towards microtubulin stabilization. The naturally occurring macrolide has potent cytotoxicity against KB cell line with IC<sub>50</sub> values of 15 ng/mL and is also rather potent against P388, A549, HT29 and MEL28 cell lines (IC<sub>50</sub> = 10–50 ng/mL). Its mechanism of action is similar to that of paclitaxel, but exhibits activity towards multidrug-resistant cell lines like SKLVLB-1.<sup>49</sup> The potency of this molecule and derivatization has led to many synthetic studies towards laulimalide.<sup>5</sup> We sought to apply our methodology towards the C1–C12 fragment of this molecule at not only the enoate juncture, but also the dihydropyranone.

Our synthesis of the laulimalide fragment began with  $\beta$ -branched olefin **2.142**.<sup>50</sup> In the presence of 5.0 mol % of **2.88** and 2.0 equiv of acrylate **2.117**, 81% of the starting material was converted to *Z*-**2.143** with 91:9 *Z*:*E*. In the same pot, treatment of the CM product with 10 mol % of *p*-toluenesulfonic acid at 40 °C gave the desired dihydropyranone **2.144** in 74% yield over two steps. Only the *Z* enoate is capable of cyclizing and acyclic enoate *E*-**2.143** can be isolated, allowing for separation of the undesired isomer. Subsequent reduction of **2.144** to the mixed acetal allowed for allylation of the oxonium ion to yield substrate **2.145**.<sup>50</sup> The allylic dihydropyran was treated with 10 mol % of **2.88** to yield C1–C12 fragment of (–)-laulimalide with 94:6 *Z*:*E* selectivity.

In both of the CM reactions, the CM proceeds in a 10:1 mixture of acetonitrile and benzonitrile. When CM of **2.142** is performed in pure acetonitrile, only 41% yield of dihydropyranone **2.144** was obtained; the second CM only yields 50% of desired enoate in 100% acetonitrile. While we do not know the reason for the beneficial effect of benzonitrile, it is

<sup>(46)</sup> Quinoa, E.; Kakou, Y.; Crews, P. J. Org. Chem. 1988, 53, 3642-3644.

<sup>(47)</sup> Corley, D. G.; Herb, R.; Moore, R. E.; Scheuer, P. J.; Paul, V. J. J. Org. Chem. 1988, 53, 3644-3646.

<sup>(48)</sup> Jefford, C. W.; Bernardinelli, G.; Tanaka, J.; Higa, T. Tetrahedron Lett. 1996, 37, 159–162.

<sup>(49)</sup> Mooberry, S. L.; Tien, G.; Hernandez, A. H.; Plubrukarn, A., Davidson B. S. *Cancer Res.* 1999, *59*, 653–660.

<sup>(50)</sup> Ghosh, A. K.; Wang, Y.; Kim, J. T. J. Org. Chem. 2001, 66, 8973-8982.
observed that benzonitrile suppressed homocoupling. We speculate that this effect may be related to with the fact that benzonitrile is a stronger donor to the metal center (versus acetonitrile). It is disfavored to perform the reaction in pure benzonitrile because of the low reactivity as well as the high boiling point (191 °C). The presence of a small percentage of benzonitrile provides the benefit of diminishing undesired homocoupling, but still achieving high reactivity to the desired *Z* enoates.



Scheme 2.19. Stereoselective Formal Synthesis of (-)-Laulimalide through Catalytic CM.

Although our synthesis did not provide a shorter route towards the fragment compared to Ghosh's route, this route offered a stereoselective synthesis of the enoate fragment through CM. In Ghosh's RCM of the lactone (disconnected at the  $\alpha$ , $\beta$ -alkene of **2.144**), the dihydropyranone can only be cyclized with 10 mol % of Grubbs' 1<sup>st</sup>-generation complex with 30 mol % of Ti(O*i*-Pr)<sub>4</sub>. The titanium acts as a Lewis acid to prevent coordination of the Lewis basic carbonyl to the metal;<sup>51</sup> without the additive, poor reactivity was observed. The use of acetonitrile as the Lewis base and solvent removed the need for extra additives.

<sup>(51)</sup> Fürstner, A.; Langemann, K. J. Am. Chem. Soc. 1997, 119, 9130-9136.

Formation of the C1–C4 Z-enoate is not Z-selective with the Still-Gennari olefination methods, leading to the use of partial hydrogenation of the ynoate in the synthesis. Other groups have synthesized methyl esters<sup>52</sup> or allylic ethers<sup>53</sup> in high selectivity. However, cleavage of the methyl ester under basic conditions leads to isomerization due to reversible conjugate addition. Thus, similar to allylic ethers, multiple steps are required to adjust the oxidation state to the carboxylic acid. Developing our method around *tert*-butyl acrylate is more practical, not only for ease of handling, but also for subsequent protecting group cleavage under acidic conditions.

# 2.5 Conclusions

In this chapter, we have developed the first catalytic RCM and CM processes that deliver enoates and dienoates in a kinetically *Z*-selective fashion. These transformations demonstrate the powerful capabilities of stereogenic-at-Mo complexes to promote valuable set of reactions in an efficient and stereoselective manner. Utilizing catalytic CM to access macrocyclic and acyclic enoates and dienoates offer a distinct bond disconnection compared to other commonly used methods. The stereochemistry of these conjugated carbonyl functionalities are amenable to further functionalizations that rely on the isomeric purity of enoates. We have detailed the importance of enhancing reactivity of Mo complexes through electron-withdrawing ligands and fine-tuning the catalyst activity through the use of coordinating solvents such as thf and acetonitrile. We have demonstrated the utility of our reaction through the formal synthesis of two naturally occurring macrolides, (+)-aspicilin and (–)-laulimalide.

## 2.6 Experimental

• **General:** <sup>1</sup>H NMR spectra were recorded on a Varian Unity INOVA 400 (400 MHz), Varian Unity INOVA 500 (500 MHz) or Varian 600 (600 MHz) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance resulting from

<sup>(52)</sup> Paterson, I.; De Savi, C.; Tudge, M. Org. Lett. 2001, 3, 3149-3152.

<sup>(53)</sup> Crimmins, M. T.; Stanton, M. G.; Allwein S. P. J. Am. Chem. Soc. 2002, 124, 5958-5959.

incomplete deuteration as the internal reference (CDCl<sub>3</sub>:  $\delta$  7.26, C<sub>6</sub>D<sub>6</sub>:  $\delta$  7.16, toluene-*d*<sub>8</sub>:  $\delta$  2.08). Data are reported as follows chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, br = broad, m = multiplet, sext = sextet), and coupling constants (Hz). <sup>13</sup>C NMR spectra were recorded on Varian Unity INOVA 400 (100 MHz) or Varian 600 (150 MHz) spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance resulting from incomplete deuteration as the internal reference (CDCl<sub>3</sub>:  $\delta$  77.16, C<sub>6</sub>D<sub>6</sub>:  $\delta$  128.06). Infrared (IR) spectra were recorded on a Bruker FTIR Alpha (ATR Mode) spectrometer, v<sub>max</sub> in cm<sup>-1</sup>. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). High-resolution mass spectrometry was performed on a JEOL Accu TOF Dart (positive mode) at the Boston College Mass Spectrometry Facility.

**Vacuum Pumps:** KNF Laboport N840.3FTP diaphragm vacuum pump connected to a Welch Labaid vacuum controller generates a vacuum of 100 torr at point of connection to the reaction vessel.

**Materials:** All reactions were carried out in oven-dried (135 °C) or flame-dried glassware under an inert atmosphere of dry N<sub>2</sub> unless otherwise stated. Solvents were purged with argon and purified under a positive pressure of dry argon by a modified Innovative Technologies purification system: diethyl ether (Aldrich), and dichloromethane (Aldrich) were passed through activated alumina columns; benzene (Aldrich), and *n*-pentane (J. T. Baker) were passed successively through activated Cu and alumina columns. *n*-Pentane was allowed to stir over concentrated H<sub>2</sub>SO<sub>4</sub> for three days, washed with water, followed by a saturated aqueous solution of NaHCO<sub>3</sub>, dried over Na<sub>2</sub>SO<sub>4</sub>, and filtered before distillation from CaH<sub>2</sub>. Tetrahydrofuran (Aldrich) was distilled from sodium benzophenone ketyl.

**Organometallic Complexes.** Mo-based bis(alkoxide) complex **2.83** was prepared according to a previously reported procedure.<sup>54</sup> Mo-monoaryloxide-pyrrolide complexes **2.120**,<sup>9b</sup>

<sup>(54)</sup> Schrock, R.R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. J. Am. Chem. Soc. **1990**, *112*, 3875–3886.

**2.85**,<sup>9b,55</sup> **2.88**<sup>56</sup> and **2.133**<sup>11</sup> were prepared in situ according to published procedures from the corresponding Mo bis(pyrrolide) complexes. Ru-based carbene complex **2.82**<sup>57</sup> was obtained from Aldrich and used as received. **2.119**<sup>58</sup> was synthesized according to a previously reported procedure. Unless otherwise noted, all Mo and Ru complexes were handled under an inert atmosphere of  $N_2$  in a dry box.

# Reagents

Acetonitrile was purchased from Fisher, allowed to sit over activated 4 Å molecular sieves and refluxed and distilled from CaH<sub>2</sub> prior to use.

Acetonitrile-1-<sup>13</sup>C was purchased from Aldrich and used as received.

Acryloyl chloride was purchased from Aldrich and used as received.

Allyl benzene was purchased from Aldrich and distilled from CaH<sub>2</sub> prior to use.

(2*S*,6*R*)-6-Allyl-2-((*R*)-3-(benzyloxy)-2-methylpropyl)-3,6-dihydro-2H-pyran was prepared according to literature procedure from pyran  $9^{50}$  and dried by azeotropic distillation with C<sub>6</sub>H<sub>6</sub> prior to use.

**1-((Allyloxy)methyl)-4-methoxybenzene** was prepared according to literature procedure<sup>59</sup> and distilled from CaH<sub>2</sub> prior to use.

*d*<sub>6</sub>-Benzene was purchased from Cambridge Isotope Laboratories and distilled from Na into

activated 4 Å molecular sieves prior to use.

**Benzonitrile** was purchased from Aldrich, allowed to sit over activated 4 Å molecular sieves and distilled from CaH<sub>2</sub> prior to use

<sup>(55)</sup> Ondi, L.; Varga, J.; Bucsai, A.; Toth, F.; Lorincz, K.; Hegedus, C.; Robbe, E.; Frater, E. G. US Patent **2014**, 309466 A1.

<sup>(56)</sup> Jiang, A. J.; Zhao, Y.; Schrock, R. R.; Hoveyda, A. H. J. Am. Chem. Soc. 2009, 131, 16630–16631.

<sup>(57)</sup> Endo, K.; Grubbs, R. H. J. Am. Chem. Soc., 2011, 133, 8525-8527.

<sup>(58)</sup> Koh, M. J.; Khan, R. K. M.; Torker, S.; Yu, M.; Mikus, M. S.; Hoveyda, A. H. Nature 2015, 517, 181– 186.

<sup>(59)</sup> Harada, N.-a.; Nishikata, T.; Nagashima, H. Tetrahedron 2012, 68, 3243-3252.

**Benzyl(hex-5-en-1-yl)sulfane** was prepared according to literature procedure<sup>60</sup> and dried by azeotropic distillation with C<sub>6</sub>H<sub>6</sub> prior to use.

(4*S*,6*R*)-7-(Benzyloxy)-6-methylhept-1-en-4-ol was prepared according to literature procedure<sup>50,61</sup> and dried by azeotropic distillation with C<sub>6</sub>H<sub>6</sub> prior to use.

**Bis(cyclopentadienyl)zirconium(IV) dichloride** was purchased from Aldrich and used as received.

6-Bromo-1-hexanol was purchased from Aldrich and used as received.

8-Bromo-1-octene was purchased from Oakwood and distilled from CaH<sub>2</sub> prior to use.

5-Bromo-1-pentene was purchased from Aldrich and used as received.

11-Bromo-1-undecanol was purchased from TCI and used as received.

*cis*-2-Buten-1,4-diol was purchased from Aldrich and used as received.

*n*-Butyl acrylate was purchased from Aldrich, washed with 2 M NaOH solution and distilled from CaH<sub>2</sub> prior to use.

*tert*-Butyl acrylate was purchased from Aldrich, washed with 2 M NaOH solution and distilled from CaH<sub>2</sub> prior to use.

*tert*-Butyldimethyl(oct-7-en-1-yloxy)silane was prepared according to literature procedure<sup>62</sup> and dried by azeotropic distillation with C<sub>6</sub>H<sub>6</sub> prior to use.

tert-Butyldimethylsilyl chloride was purchased from Aldrich and used as received.

*tert*-Butyl hydroperoxide was purchased from Aldrich and used as a 5.5 M solution in decane.

*n*-Butyllithium (1.6 M solution in hexanes) was purchased from Strem and used as received.

Calcium hydride was purchased from Strem and used as received.

<sup>(60)</sup> Lin, Y. A.; Chalker, J. M.; Floyd, N.; Bernardes, G. J. L.; Davis, B. G. J. Am Chem. Soc. 2008, 130, 9642–9643.

<sup>(61)</sup> The diastereoselectivity of the compound is dependent on the batch of Brown's reagent and the consistency in temperature throughout the allyl addition reaction. Synthesis of 2.143 afforded the product in 85:15 diastereomeric ratio and was found constant throughout the synthesis to 2.146.

<sup>(62)</sup> Nielsen, L.; Skrydstrup, T. J. Am. Chem. Soc. 2008, 130, 13145-13151.

*d*-Chloroform was purchased from Cambridge Isotope Laboratories and passed through basic

alumina then stored in activated 4 Å molecular sieves prior to use.

Chlorotriethylsilane was purchased from Fisher and used as received.

Crotonaldehyde was purchased from Aldrich and used as received.

**Dec-9-en-1-yn-1-yltriisopropylsilane** was prepared according to literature procedure<sup>63</sup> and dried by azeotropic distillation with C<sub>6</sub>H<sub>6</sub> prior to use.

(*E*)-1,3-Decadiene was synthesized according to literature procedure<sup>34</sup> and purified by distillation from  $CaH_2$  prior to use.

1-Decene was purchased from Aldrich and distilled over CaH<sub>2</sub> prior to use.

Di-tert-butyl dicarbonate was purchased Aldrich and used as received.

**2,3-Dichloro-5,6-dicyano-***p***-benzoquinone** was purchased from Aldrich and used as received.

(-)-Diethyl tartrate was purchased from Aldrich and used as received.

**4-Dimethylaminopyridine (dmap)** was purchased from Advanced ChemTech and used as received.

Dimethylformamide was purchased from Aldrich and used as received.

Dodec-11-enal was prepared according to literature procedure.<sup>64</sup>

Dodec-11-en-1-ol was prepared according to literature procedure.<sup>65</sup>

**Ethyl acrylate** was purchased from Aldrich, washed with 2 M NaOH solution, dried over Na<sub>2</sub>SO<sub>4</sub> and distilled from CaH<sub>2</sub> prior to use.

**2-Ethylhexyl acrylate** was purchased from Aldrich, washed with 2 M NaOH solution, dried over Na<sub>2</sub>SO<sub>4</sub> and distilled from CaH<sub>2</sub> prior to use.

Geraniol was purchased from Aldrich as used as received.

<sup>(63)</sup> Koh, M. J.; Nguyen, T. T.; Zhang, H.; Schrock, R. R.; Hoveyda, A. H. Nature 2016, 531, 459–465.

<sup>(64)</sup> Chung, W.-J.; Carlson, J. S.; Vanderwal, C. D. J. Org. Chem. 2014, 79, 2226–2241.

<sup>(65)</sup> Kumaraswamy, G.; Sadaiah, K.; Raghu, N. Tetrahedron: Asymm. 2012, 23, 587–593.

Hexadec-15-en-1-amine was prepared according to literature procedure.<sup>66</sup>

Hexadec-15-en-1-ol was prepared according to literature procedure.<sup>69</sup>

Heptadec-16-en-1-ol was prepared according to literature procedure.<sup>67</sup>

Imidazole was purchased from Oakwood and used as received.

**3-Indoleacetic acid** was purchased Aldrich and used as received.

Magnesium purum was purchased from Aldrich and used as received.

**4-Methoxybenzyl-2,2,2-trichloroacetimidate** was purchased from Aldrich and used as received.

8-Nonenal was prepared according to literature procedure.<sup>68</sup>

Pentadec-14-en-1-ol was prepared according to literature procedure.<sup>69</sup>

(E)-Penta-2,4-dienoic acid was purchased from Aldrich and used as received.

Pent-4-en-2-ol was purchased from Aldrich and used as received.

Pivaloyl chloride was purchased from Alfa Aesar and used as received.

Sodium *tert*-butoxide was purchased from Fisher and used as received.

Sodium hydride was purchased from Aldrich and used as received.

Sodium phenoxide was purchased from Fisher and used as received.

Styrene was purchased from Aldrich and distilled over CaH<sub>2</sub> prior to use.

**Tetrabutylammonium fluoride solution** was purchased from Aldrich as a 1.0 M solution in thf and used as received.

Tetradec-13-en-1-ol was prepared according to literature procedure.<sup>70</sup>

<sup>(66)</sup> Hong, S.; Kawaoka, A. M.; Marks, T. J. J. Am. Chem. Soc. 2003, 125, 15878–15892.

<sup>(67)</sup> Zubkov, T.; Lucassen, A. C. B.; Freeman, D.; Feldman, Y.; Cohen, S. R.; Evmenenko, G.; Dutta, P.; van der Boom, M. E. J. Phys. Chem. B. 2005, 109, 14144–14153.

<sup>(68)</sup> Chung, W.-J.; Carlson, J. S.; Bedke, D. K.; Vanderwal, C. D. Angew. Chem., Int. Ed. 2013, 52, 10052– 10055.

<sup>(69)</sup> Hon, Y.-S.; Wong, Y.-C.; Chang, C.-P.; Hsieh, C.-H. Tetrahedron 2007, 63, 11325–11340.

<sup>(70)</sup> Gao, Y.; Shan, Q.; Liu, J.; Wang, L.; Du, Y. Org. Biomol. Chem. 2014, 12, 2071–2079.

(S)-Tetradec-13-en-2-ol was prepared according to literature procedure.<sup>71</sup>

Titanium(IV) isopropoxide was purchased from Aldrich and used as received.

Tridec-12-en-1-ol was prepared according to literature procedure.<sup>72</sup>

*d*<sub>8</sub>-Toluene was purchased from Cambridge Isotope Laboratories and distilled from CaH<sub>2</sub> then stored in activated 4 Å molecular sieves prior to use.

*p*-Toluenesulfonic acid monohydrate was purchased from Aldrich and used as received.

Trichloroacetyl isocyanate was purchased from Aldrich and used as received.

Triethylamine was purchased from Aldrich and used as received.

Trimethylacetyl chloride was purchased from Fisher and used as received.

10-Undecenal was purchased from Aldrich and used as received.

Vinylcyclohexane was purchased from Aldrich and distilled over CaH<sub>2</sub> prior to use.

Zinc powder was purchased from Aldrich and used as received.

Zinc(II) chloride was purchased from Aldrich and used as received.

#### Preparation of Mo MAP complexes

In an N<sub>2</sub>-filled glove box, a 4 mL vial with a magnetic stir bar was charged with Mo bispyrrolide complex **2.170** (17.0 mg, 0.0279 mmol), alcohol **2.171** (10.0 mg, 0.0279 mmol), and C<sub>6</sub>D<sub>6</sub> (1 mL). The vial was tightly capped and the mixture was allowed to stir at 22 °C for 1 h (65 °C for 48 h with alcohol **2.171**), at which time it was transferred to an NMR tube (with a screw cap) by a pipette. The tube was capped and sealed with Teflon tape. NOTE: For in situ-generated complexes, the diagnostic signals of the C<sub> $\alpha$ </sub>-H of the *syn* alkylidenes are as follows:

Diagnostic NMR data of Mo complex 2.87: <sup>1</sup>H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>): δ 11.20 (1H, s); <sup>19</sup>F NMR (376 MHz, C<sub>6</sub>D<sub>6</sub>): δ –60.17 (3F, s).

<sup>(71)</sup> Kobayashi, Y.; Nakano, M.; Kumar, G. B.; Kishihara, K. J. Org. Chem. 1998, 63, 7505–7515.

<sup>(72)</sup> Berube, M.; Poirier, D. Can. J. Chem. 2009, 87, 1180-1199.

Diagnostic NMR data of Mo-complex **2.88**: <sup>1</sup>**H** NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>):  $\delta$  11.10 (1H, s); <sup>19</sup>F NMR (470 MHz, C<sub>6</sub>D<sub>6</sub>):  $\delta$  –145.34 (2F, d, J = 23.5 Hz), –159.03 (1F, t, J = 20.4 Hz), –164.69 (2F, dt, J = 18.8, 6.1 Hz).

Diagnostic data of Mo complex **2.89**: <sup>1</sup>**H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>)**:  $\delta$  12.34 (1H, s); <sup>19</sup>**F NMR (376 MHz, C<sub>6</sub>D<sub>6</sub>)**:  $\delta$  –144.34 (2F, dd, J = 22.9 Hz, J = 5.6 Hz), –157.02 (1F, t, J = 15.8 Hz), –163.94 (2F, dt, J = 21.8, 6.0 Hz).



#### Synthesis of RCM Substrates for Macrocyclic Z Enoates

General Procedure A: Preparation of ene-acrylate and ene-acrylamide substrates from alcohols or amines. A solution of an alcohol or an amine (0.5 mmol) in  $CH_2Cl_2$  (5 mL) was treated with  $Et_3N$  (1.5 mmol) and acryloyl chloride (0.75 mmol) at 0 °C. The mixture was allowed to warm to 22 °C and stir for 1 h, before it was diluted with  $CH_2Cl_2$ (10 mL) and washed with a saturated solution of aqueous  $NH_4Cl$ . The aqueous layer was washed with  $CH_2Cl_2$  (3x10 mL), and the combined organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (5–15% EtOAc in hexanes) to provide the target ene-acrylate or ene-acrylamide product.

**Dodec-11-en-1-yl acrylate (2.79).** Following General Procedure A, acylation of dodec-11-en-1-ol (100 mg, 0.543 mmol) to afford **2.79** as colorless oil (113 mg, 0.472 mmol, 87% yield). **IR (neat)**: 2924 (m), 2854 (w), 1726 (s), 1638 (w), 1465 (w), 1407 (m), 1295 (w), 1270 (m), 1186 (s), 1059 (w), 984 (w), 964 (w), 908 (w), 809 (w); <sup>1</sup>H NMR (400 MHz, **CDCl**<sub>3</sub>): δ 6.39 (1H, dd, *J* = 17.6 Hz, 1.2 Hz), 6.11 (1H, dd, *J* = 17.6 Hz, 10.4 Hz), 5.80 (2H, m), 4.98 (1H, dq, *J* = 17.2 Hz, 1.6 Hz), 4.92 (1H, dq, *J* = 10.4 Hz, 1.6 Hz), 4.14 (2H, t, *J* = 6.8 Hz), 2.03 (2H, q, *J* = 6.8 Hz), 1.66 (2H, tt, *J* = 7.2 Hz, 6.4 Hz), 1.37–1.27 (14H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 166.3, 139.2, 130.4, 128.6, 114.1, 64.7, 33.8, 29.5, 29.4, 29.2, 29.1, 28.9, 28.6, 25.9; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>15</sub>H<sub>27</sub>O<sub>2</sub>: 239.2011, found: 239.2013.

**Tridec-12-en-1-yl acrylate (2.147).** Following General Procedure A, acylation of tridec-12-en-1-ol (80 mg, 0.40 mmol) afforded **2.147** as colorless oil (85 mg, 0.34 mmol, 83% yield). **IR (neat)**: 2924 (m), 2854 (w), 1726 (s), 1638 (w), 1465 (w), 1407 (w), 1295 (w), 1270 (w), 1186 (s), 1059 (w), 984 (w), 965 (w), 909 (w), 809 (w); <sup>1</sup>H NMR (400 MHz, **CDCl**<sub>3</sub>):  $\delta$  6.39 (1H, dd, J = 17.2 Hz, 1.2 Hz), 6.12 (2H, dd, J = 17.2 Hz, 10.4 Hz), 5.81 (2H, m), 4.99 (1H, dq, J = 17.2 Hz, 1.6 Hz), 4.92 (1H, dq, J = 10.4 Hz, 1.2 Hz), 4.14 (2H, t, J = 6.8 Hz), 2.03 (2H, q, J = 6.8 Hz), 1.66 (2H, m), 1.37–1.27 (16H, m); <sup>13</sup>C NMR (100 MHz, **CDCl**<sub>3</sub>):  $\delta$  166.3, 139.2, 130.4, 128.6, 114.1, 64.7, 33.8, 29.53, 29.51, 29.47, 29.45, 29.2, 29.1, 28.9, 28.6, 25.9; **HRMS (DART)** [M+H]<sup>+</sup> calcd for C<sub>16</sub>H<sub>29</sub>O<sub>2</sub>: 253.2168, found: 253.2176.

**2-((***tert***-Butoxycarbonyl)(dec-9-en-1-yl)amino)ethyl acrylate (2.152).** Following General Procedure A, acylation of *tert*-butyl dec-9-en-1-yl(2-hydroxyethyl)carbamate<sup>73</sup> (100 mg, 0.334 mmol) afforded **2.152** (101 mg, 0.287 mmol, 86% yield) as colorless oil (in a ~1:1 mixture of carbamate rotamers). **IR (neat)**: 2975 (w), 2927 (m), 2855 (w), 1729 (m), 1695 (s), 1638 (w), 1466 (w), 1407 (m), 1366 (w), 1293 (w), 1267 (w), 1158 (s), 1060 (w), 985 (w), 910 (w), 810 (w); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  6.37 (1H, d, *J* = 17.2 Hz), 6.08 (1H, dd, *J* = 17.2 Hz, 10.4 Hz), 5.81–5.71 (2H, m), 4.95 (1H, d, *J* = 17.2 Hz), 4.88 (1H, d, *J* = 10.4 Hz), 4.22 (2H, m), 3.46–3.41 (2H, m), 3.17 (2H, m), 1.99 (2H, q, *J* = 7.2 Hz), 1.47 (2H, m), 1.41 (9H, s), 1.36-1.24 (10H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  165.9, 155.5, 155.2, 139.0, 131.0, 130.8, 128.2, 114.1, 79.6, 62.6, 48.1, 47.9, 45.9, 33.7, 29.4, 29.3, 29.0, 28.8, 28.6, 28.3, 28.2, 26.7; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>20</sub>H<sub>36</sub>NO4: 354.2644, found: 354.2654.

<sup>(73)</sup> Wood, M. E.; Bissiriou, S.; Lowe, C.; Windeatt, K. M. Org. Biomol. Chem. 2013, 11, 2712-2723.

**Tetradec-13-en-1-yl acrylate (2.148).** Following General Procedure A, acylation of tetradec-13-en-1-ol (100 mg, 0.472 mmol) afforded **2.148** as colorless oil (106 mg, 0.396 mmol, 84% yield). **IR (neat)**: 2924 (m), 2853 (m), 1727 (s), 1638 (w), 1465 (w), 1407 (m), 1295 (w), 1270 (w), 1187 (s), 1059 (w), 985 (w), 964 (w), 909 (w), 810 (w); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  6.40 (1H, dd, J = 17.2 Hz, 1.2 Hz), 6.12 (1H, dd, J = 17.2 Hz, 10.4 Hz), 5.81 (2H, m), 4.99 (1H, dq, J = 17.2 Hz, 1.6 Hz), 4.93 (1H, ddt, J = 10.4 Hz, 2.0 Hz, 1.2 Hz), 4.15 (2H, t, J = 6.8 Hz), 2.04 (2H, q, J = 7.2 Hz), 1.67 (2H, tt, J = 8.0 Hz, 6.8 Hz), 1.37–1.27 (18H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  166.5, 139.4, 130.6, 128.8, 114.2, 64.9, 34.0, 29.75, 29.74, 29.70, 29.65, 29.4, 29.3, 29.1, 28.8, 26.1; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>17</sub>H<sub>31</sub>O<sub>2</sub>: 267.2324, found: 267.2318.

**2-((***tert***-Butoxycarbonyl)(undec-10-en-1-yl)amino)ethyl acrylate (2.153).** Following General Procedure A, acylation of *tert*-butyl (2-hydroxyethyl)(undec-10-en-1-yl)carbamate (100 mg, 0.322 mmol) afforded **2.153** as colorless oil (92 mg, 0.251 mmol, 78% yield). **IR (neat)**: 2975 (w), 2927 (m), 2855 (w), 1730 (w), 1697 (s), 1466 (w), 1408 (m), 1366 (w), 1294 (w), 1268 (w), 1184 (m), 1159 (m), 1060 (w), 985 (w), 910 (w); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  6.49 (1H, d, J = 17.2 Hz), 6.09 (1H, dd, J = 17.2 Hz, 10.4 Hz), 5.83–5.73 (2H, m), 4.96 (1H, d, J = 17.2 Hz), 4.90 (1H, d, J = 10.4 Hz), 4.23 (2H, m), 3.43 (2H, m), 3.18 (2H, m), 2.01 (2H, q, J = 6.8 Hz), 1.48 (2H, m), 1.43 (9H, s), 1.36–1.22 (12H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  165.9, 155.5, 155.2, 139.1, 131.0, 130.8, 128.2, 114.1, 79.6, 79.5, 62.6, 48.1, 47.9, 45.9, 33.7, 29.5, 29.33, 29.30, 29.0, 28.5, 26.7; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>21</sub>H<sub>38</sub>NO<sub>4</sub>: 368.2800, found: 368.2798.

**Pentadec-14-en-1-yl acrylate (2.149).** Following General Procedure A, acylation of pentadec-14-en-1-ol (30 mg, 0.13 mmol) afforded **2.149** as colorless oil (35 mg, 0.12 mmol, 94% yield). **IR (neat)**: 2924 (s), 2854 (m), 1728 (s), 1638 (w), 1465 (w), 1407 (w), 1295 (w), 1271 (w), 1189 (s), 1060 (w), 985 (w), 965 (w), 909 (w), 810 (w); <sup>1</sup>H NMR (400 **MHz, CDCl3**): δ 6.39 (1H, d, *J* = 17.2 Hz), 6.11 (1H, dd, *J* = 17.2 Hz, 10.6 Hz), 5.86–5.76 (2H, m), 4.98 (1H, d, *J* = 17.2 Hz), 4.92 (1H, d, *J* = 10.4 Hz), 4.14 (2H, t, *J* = 6.8 Hz), 2.03 (2H, q, *J* = 6.8 Hz), 1.66 (2H, quint, *J* = 6.8 Hz), 1.37–1.26 (20H, m); <sup>13</sup>C NMR (100 MHz, **CDCl3**): δ 166.3, 139.2, 130.4, 128.6, 114.0, 64.7, 33.8, 29.60, 29.59, 29.57, 29.53, 29.48, 29.2, 29.1, 28.9, 28.6, 25.9; **HRMS (DART)** [**M**+**H**]<sup>+</sup> calcd for C<sub>18</sub>H<sub>33</sub>O<sub>2</sub>: 281.2481, found: 281.2480.

**3-((***tert***-Butoxycarbonyl)(undec-10-en-1-yl)amino)propyl acrylate (2.154).** Following General Procedure A, acylation of *tert*-butyl (3-hydroxypropyl)(undec-10-en-1-yl)carbamate (100 mg, 0.306 mmol) afforded **2.154** as colorless oil (66 mg, 0.174 mmol, 57% yield). **IR (neat)**: 2974 (w), 2926 (m), 2855 (w), 1728 (m), 1694 (s), 1468 (w), 1410 (s), 1389 (w), 1366 (w), 1295 (w), 1270 (w), 1224 (w), 1184 (m), 1058 (w), 986 (w), 908 (w), 810 (w); <sup>1</sup>**H NMR (400 MHz, CDCl3**):  $\delta$  6.40 (1H, dd, *J* = 17.2 Hz, 1.2 Hz), 6.11 (1H, dd, *J* = 17.2 Hz, 10.4 Hz), 5.82 (1H, d, *J* = 10.4 Hz), 5.80 (1H, m), 4.98 (1H, dq, *J* = 17.2 Hz, 1.6 Hz), 4.92 (1H, d, *J* = 10.4 Hz), 4.17 (2H, t, *J* = 6.4 Hz), 3.26 (2H, br s), 3.14 (2H, br s), 2.02 (2H, q, *J* = 7.2 Hz), 1.89 (2H, br s), 1.49 (2H, m), 1.44 (9H, s), 1.39–1.26 (14H, m); <sup>13</sup>**C NMR (100 MHz, CDCl3**):  $\delta$  166.1, 155.4, 139.2, 130.7, 128.4, 114.1, 79.2, 62.4, 47.4, 47.3, 44.1, 33.8, 29.5, 29.4, 29.3, 29.1, 28.9, 28.4, 26.8; **HRMS (DART) [M+H]**<sup>+</sup> calcd for C<sub>22</sub>H<sub>40</sub>NO<sub>4</sub>: 382.2957, found: 382.2965.

**7-((4-Methoxybenzyl)oxy)pentadec-14-en-1-yl acrylate (2.156).** Following General Procedure A, acylation of 7-((4-methoxybenzyl)oxy)pentadec-14-en-1-ol (114 mg, 0.315 mmol) afforded **2.156** as colorless oil (103 mg, 0.249 mmol, 79% yield). **IR (neat)**: 2930 (s), 2856 (m), 1725 (s), 1613 (w), 1513 (m), 1464 (w), 1407 (w), 1297 (w), 1271 (w), 1247 (s), 1192 (s), 1062 (w), 1038 (w), 986 (w), 811 (w); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.26 (2H, d, *J* = 8.4 Hz), 6.87 (2H, d, *J* = 8.4 Hz), 6.40 (1H, d, *J* = 17.2 Hz), 6.12 (1H, dd, *J* = 17.2 Hz, 10.4 Hz), 5.86–5.76 (2H, m), 4.99 (1H, dq, *J* = 17.2 Hz, 1.6 Hz), 4.93 (1H, d, *J* = 10.4 Hz), 4.42 (2H, s), 4.15 (2H, t, *J* = 6.8 Hz), 3.80 (3H, s), 3.33 (1H, quint, *J* = 5.6 Hz), 2.04 (2H, q, *J* = 6.8 Hz), 1.64 (2H, quint, *J* = 6.8 Hz), 1.54–1.29 (18H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  166.3, 159.0, 139.2, 131.2, 130.4, 129.3, 128.6, 114.1, 113.7, 78.5, 70.4, 64.6, 55.3, 33.8, 33.7, 29.7, 29.4, 29.1, 28.9, 28.6, 25.9, 25.3, 25.2; HRMS (DART) [M-H]<sup>+</sup> calcd for C<sub>26</sub>H<sub>39</sub>O<sub>4</sub>: 415.2848, found: 415.2834.

**7-(2-(1***H***-Indol-3-yl)acetoxy)pentadec-14-en-1-yl acrylate (2.155).** Following General Procedure A, acylation of 1-hydroxypentadec-14-en-7-yl 2-(1*H*-indol-3-yl) acetate (78 mg, 0.195 mmol) afforded **2.155** as colorless oil (63 mg, 71% yield). **IR (neat)**: 3380 (br), 2928 (m), 2856 (w), 1723 (s), 1638 (w), 1458 (w), 1431 (w), 1408 (w), 1354 (w), 1338 (w), 1296 (w), 1270 (w), 1194 (m), 1122 (w), 1096 (w), 1061 (w), 1010 (w), 985 (w), 909 (w), 811 (w), 741 (w); <sup>1</sup>**H NMR (400 MHz, CDCl3**):  $\delta$  8.17 (1H, br s), 7.63 (1H, d, *J* = 7.6 Hz), 7.34 (1H, d, *J* = 8.0 Hz), 7.21–7.10 (3H, m), 6.41 (1H, d, *J* = 17.2 Hz), 6.13 (1H, dd, *J* = 17.2 Hz, 10.4 Hz), 5.85-5.75 (2H, m), 4.99 (1H, dq, *J* = 17.2 Hz, 1.6 Hz), 4.94 (1H, dq, *J* = 10.6 Hz, 1.2 Hz), 4.89 (1H, quint, *J* = 7.2 Hz), 4.11 (2H, t, *J* = 6.8 Hz), 3.76 (2H, s), 2.02 (2H, q, *J* = 6.8 Hz), 1.63-1.49 (6H, m), 1.34–1.21 (14H, m); <sup>13</sup>C NMR (100 MHz, CDCl3):  $\delta$  171.9, 166.4, 139.2, 136.1, 130.5, 128.6, 127.3, 122.9, 122.1, 119.5, 118.9, 114.2, 111.1, 108.9, 74.6, 64.7, 34.2, 34.0, 33.7, 31.8, 29.3, 29.0, 28.9, 28.8, 28.4, 25.7, 25.2, 25.0; **HRMS (DART) [M+H]<sup>+</sup>** calcd for C<sub>28</sub>H<sub>39</sub>NO<sub>4</sub>: 454.2957, found: 454.2955.

Hexadec-15-en-1-yl acrylate (2.150). Following General Procedure A, esterification of hexadec-15-en-1-ol (100 mg, 0.427 mmol) afforded 2.150 as colorless oil (87 mg, 0.295 mmol, 69% yield). IR (neat): 2923 (m), 2853 (w), 1727 (s), 1638 (w), 1465 (w), 1407 (w), 1295 (w), 1270 (w), 1186 (s), 1059 (w), 985 (w), 964 (w), 908 (w), 809 (w), 721 (w); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  6.39 (1H, dd, J = 17.6 Hz, 1.6 Hz), 6.12 (1H, dd, J = 17.6 Hz, 10.4 Hz), 5.86–5.76 (2H, m), 4.99 (1H, dq, J = 17.2 Hz, 1.6 Hz), 4.92 (1H, dq, J = 10.4 Hz, 1.2 Hz), 4.15 (2H, t, J = 6.8 Hz), 2.04 (2H, q, J = 6.8 Hz), 1.66 (2H, quint, J = 6.8 Hz), 1.37–1.26 (22H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  166.3, 139.2, 130.4, 128.6, 114.0, 64.7, 33.8, 29.62, 29.60, 29.58, 29.54, 29.48, 29.2, 29.1, 28.9, 28.6, 25.9; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>35</sub>O<sub>2</sub>: 295.2637, found: 295.2652.

**Heptadec-16-en-1-yl acrylate (2.151).** Following General Procedure A, esterification of heptadec-16-en-1-ol (100 mg, 0.394 mmol) afforded **2.151** as colorless oil (85 mg, 0.276 mmol, 70% yield). **IR (neat)**: 2924 (s), 2854 (s), 1728 (s), 1466 (w), 1407 (w), 1295 (w), 1271 (w), 1189 (m), 1060 (w), 985 (w), 909 (w), 810 (w); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 6.40 (1H, dd, *J* = 17.6 Hz, 1.6 Hz), 6.12 (1H, dd, *J* = 17.6 Hz, 10.4 Hz), 5.87–5.76 (2H, m), 4.99 (2H, d, *J* = 17.2 Hz), 4.15 (2H, t, *J* = 6.8 Hz), 2.04 (2H, q, *J* = 6.8 Hz), 1.67 (2H,

q, J = 6.8 Hz), 1.37–1.26 (24H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  166.3, 139.3, 130.4, 128.6, 114.0, 64.7, 33.8, 29.63, 29.61, 29.59, 29.54, 29.48, 29.2, 29.1, 28.9, 28.6, 25.9; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>20</sub>H<sub>37</sub>O<sub>2</sub>: 309.2794, found: 309.2800.

**11-(2-(1***H***-Indol-3-yl)acetoxy)docos-21-en-1-yl acrylate (2.157).** Following General Procedure A, acylation of 22-hydroxydocos-1-en-11-yl 2-(1*H*-indol-3-yl)acetate (122 mg, 0.245 mmol) afforded **2.157** as colorless oil (94 mg, 0.172 mmol, 70% yield). **IR (neat)**: 3387 (br), 2926 (s), 2854 (m), 1726 (s), 1458 (w), 1434 (w), 1408 (w), 1354 (w), 1336 (w), 1296 (w), 1271 (w), 1247 (w), 1192 (m), 1122 (w), 1095 (w), 1061 (w), 1010 (w), 985 (w), 909 (w), 810 (w), 740 (w); **<sup>1</sup>H NMR (400 MHz, CDCl3**):  $\delta$  8.111 (1H, br s), 7.62 (1H, d, *J* = 8.0 Hz), 7.35 (1H, d, *J* = 8.4 Hz), 7.21–7.17 (2H, m), 7.12 (1H, t, *J* = 8.0 Hz), 6.40 (1H, dd, *J* = 17.2 Hz, 1.6 Hz), 6.13 (1H, dd, *J* = 17.2 Hz, 10.4 Hz), 5.87–5.77 (2H, m), 4.99 (1H, dq, *J* = 17.2 Hz, 1.6 Hz), 4.95 (1H, d, *J* = 6.8 Hz), 1.67 (2H, quint, *J* = 6.4 Hz), 1.50 (4H, m), 1.38–1.20 (28H, m); <sup>13</sup>C NMR (100 MHz, CDCl3):  $\delta$  171.9, 166.4, 139.2, 136.1, 130.4, 128.6, 127.3, 122.9, 122.1, 119.5, 118.9, 114.1, 111.0, 108.9, 74.8, 64.7, 34.1, 33.8, 31.7, 29.50, 29.47, 29.41, 29.3, 29.2, 29.1, 28.9, 28.6, 25.9, 25.2; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>35</sub>H<sub>54</sub>NO<sub>4</sub>: 552.4053, found: 552.4054.

**11-(Carbamoyloxy)docos-21-en-1-yl acrylate (2.161).** Following General Procedure A, acylation of 22-hydroxydocos-1-en-11-yl carbamate (93 mg, 0.24 mmol) to afforded **2.161** as colorless oil (83 mg, 0.187 mmol, 78% yield). **IR (neat)**: 3428 (w), 3333 (w), 3268 (w), 3211 (w), 2921 (s), 2850 (m), 1726 (m), 1687 (s), 1639 (w), 1611 (w), 1468 (w), 1407 (m), 1332 (w), 1296 (w), 1271 (w), 1192 (m), 1121 (w), 1071 (w), 1054 (w), 986 (w), 912 (w), 810 (w); <sup>1</sup>**H NMR (400 MHz, CDCl3**):  $\delta$  6.38 (1H, dd, J = 17.2 Hz, 1.2 Hz), 6.11 (1H, dd, J = 17.2 Hz, 10.4 Hz), 5.80 (2H, m), 4.98 (1H, d, J = 17.2 Hz), 4.91 (1H, d, J = 10.4 Hz), 4.70 (1H, quint, J = 6.4 Hz), 4.66 (2H, s), 4.14 (2H, t, J = 6.8 Hz), 2.02 (2H, q, J = 6.8 Hz), 1.65 (2H, quint, J = 6.8 Hz), 1.49 (4H, m), 1.35–1.26 (28H, m); <sup>13</sup>C NMR (100 MHz, CDCl3):  $\delta$  166.3, 157.1, 139.2, 130.4, 128.6, 114.1, 75.3, 64.7, 34.3, 33.8, 29.55, 29.54, 29.49, 29.45, 29.37, 29.2, 29.1, 28.9, 28.6, 25.9, 25.2; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>26</sub>H<sub>48</sub>NO<sub>4</sub>: 438.3583, found: 438.3600.

N-Benzyl-N-(dodec-11-en-1-yl)acrylamide (2.158). BnNH<sub>2</sub> (39 µL, 0.36 mmol) was added to a solution of dodec-11-enal (65 mg, 0.36 mmol) in EtOH (4 mL). The solution was allowed to stir at 22 °C for 2 h. NaBH<sub>4</sub> (27 mg, 0.71 mmol) was added, and the mixture was allowed to stir at 22 °C for 12 h. At this point, the reaction was quenched through addition of an aqueous solution of NaOH (1 M) and washed with Et<sub>2</sub>O (3 x). The combined organic layer was dried over MgSO<sub>4</sub> and concentrated *in vacuo* to provide the unpurified residue as colorless oil, which was directly subjected to the esterification conditions (without purification). Following General Procedure A, esterification of the unpurified amine afforded 2.158 as colorless oil (57 mg, 0.18 mmol, 49% vield), in a mixture of amide rotamers. IR (neat): 2924 (s), 2853 (m), 1650 (s), 1614 (m), 1427 (m), 1357 (w), 1215 (w), 977 (w), 908 (w), 791 (w), 729 (w), 698 (w); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.37–7.17 (5H, m), 6.62 (1H, dd, J = 16.8 Hz, 10.4 Hz, rotamer), 6.51 (1H, dd, J = 16.8 Hz, 10.4 Hz, rotamer), 4.43 (1H, dd, J = 16.8 Hz, 1.6 Hz, rotamer), 4.39 (1H, dd, J = 16.8 Hz, 1.6 Hz, rotamer), 5.81 (1H, ddt, J = 16.8 Hz, 10.4 Hz, 6.8 Hz), 5.73 (1H, d, J = 10.4 Hz, rotamer), 5.64 (1H, d, J = 10.0 Hz, rotamer), 5.00 (1H, d, J = 17.6 Hz), 4.93 (1H, d, J = 10.0 Hz), 4.66 (2H, s, rotamer), 4.60 (2H, s, rotamer), 3.41 (2H, t, J = 7.6 Hz, rotamer), 3.25 (2H, t, J = 7.6 Hz), 1.55 (2H, m), 1.38–1.25 (14H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  166.8, 166.5, 139.4, 139.3, 137.9, 137.3, 129.0, 128.7, 128.5, 128.4, 128.2, 128.1, 127.72, 127.69, 127.4, 126.4, 114.3, 114.2, 51.2, 49.1, 47.4, 46.9, 33.9, 32.0, 29.7, 29.64, 29.58, 29.51, 29.47, 29.4, 29.22, 29.21, 29.0, 27.7, 27.2, 26.9, 22.8, 14.2; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>22</sub>H<sub>34</sub>NO: 328.2635, found: 368.2687.

*N*-(Hexadec-15-en-1-yl)acrylamide (2.159). Following General Procedure A, esterification of hexadec-15-en-1-amine (92 mg, 0.39 mmol) afforded 2.159 as a white waxy solid (60 mg, 0.21 mmol, 53% yield). IR (neat): 3303 (m), 2917 (s), 2849 (m), 1652 (m), 1620 (m), 1541 (m), 1471 (m), 1410 (w), 1241 (w), 1232 (w), 999 (w), 915 (w), 719 (w), 676 (w); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  6.27 (1H, dd, J = 17.2 Hz, 1.2 Hz), 6.07 (1H, dd, J = 16.8 Hz, 10.0 Hz), 5.81 (1H, ddt, J = 16.8 Hz, 10.0 Hz, 6.8 Hz), 5.63 (1H, dd, J = 10.0 Hz, 1.6 Hz), 5.51 (1H, br), 4.99 (1H, d, J = 17.2 Hz), 4.93 (1H, d, J = 10.4 Hz), 3.33 (2H, q, J = 6.8 Hz), 2.04 (2H, q, J = 6.8 Hz), 1.53 (2H, quint, J = 7.2 Hz), 1.39–1.25 (22H, m); <sup>13</sup>C

NMR (100 MHz, CDCl<sub>3</sub>): δ 165.5, 139.2, 131.0, 126.0, 114.0, 39.6, 33.8, 29.61, 29.60, 29.57, 29.54, 29.50, 29.47, 29.3, 29.1, 28.9, 26.9; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>36</sub>NO: 294.2791, found: 294.2843.

*tert*-Butyl acryloyl(hexadec-15-en-1-yl)carbamate (2.160). A solution of amide 2.159 (50 mg, 0.171 mmol) in thf (2 mL) was treated with 4-dimethylamino pyridine (27 mg, 0.188 mmol) and Boc<sub>2</sub>O (41 mg, 0.188 mmol), and the mixture was allowed to stir at 22 °C for 24 h. The solvent was removed *in vacuo*, and the resulting light yellow oil was purified by silica gel chromatography (5% EtOAc in hexanes) to afford 2.160 (41 mg, 62% yield) as colorless oil. **IR (neat)**: 2924 (s), 2854 (m), 1730 (s), 1686 (m), 1458 (w), 1404 (w), 1384 (w), 1367 (m), 1355 (m), 1301 (w), 1257 (w), 1206 (w), 1146 (s), 1106 (w); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  6.98 (1H, dd, *J* = 16.8 Hz, 10.4 Hz), 6.29 (1H, dd, *J* = 16.8 Hz, 10.0 Hz), 5.81 (1H, ddt, *J* = 16.8 Hz, 10.4 Hz), 3.67 (2H, t, *J* = 7.6 Hz), 2.04 (2H, q, *J* = 6.8 Hz), 1.57–1.53 (11H, m), 1.39–1.25 (22H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  168.6, 153.3, 139.3, 131.7, 127.2, 114.0, 83.0, 44.8, 33.8, 29.63, 29.58, 29.54, 29.53, 29.48, 29.3, 29.1, 28.9, 28.7, 28.0, 27.9, 26.9; HRMS (DART) [M+H–C4H<sub>8</sub>]<sup>+</sup> calcd for C<sub>20</sub>H<sub>36</sub>NO<sub>3</sub>: 338.2690, found: 338.2766.

#### Synthesis of Macrocyclic Z Enoates

General Procedure B: Synthesis of macrocyclic Z-enoates through catalytic ring-closing metathesis (RCM) reactions with MAP–Mo complex **2.88**. In a N<sub>2</sub>-filled glove-box, an oven-dried 50 mL round-bottom flask equipped with a magnetic stir bar was charged with a solution of ene-acrylate substrate (1.0 equiv) in benzene (1.0 or 2.0 mM). A stock solution of complex **2.88** (0.1 M in benzene, 3.0 or 5.0 mol %) was added the substrate solution by syringe. The flask was then connected to a 100-torr vacuum generated from a diaphragm vacuum pump. The resulting solution was allowed to stir for 2 h, before the reaction was quenched with wet diethyl ether. The mixture was concentrated *in vacuo*, and the resulting oily residue was passed through a short pad of silica gel (20% Et<sub>2</sub>O in hexane) and the volatiles were removed. The per cent conversion and *Z*:*E* ratio of the resulting mixture was determined by <sup>1</sup>H NMR analysis. Purification of the mixture by silica gel chromatography

(impregnated with 15% AgNO<sub>3</sub>) or preparative TLC provided the target Z-alkene macrocycle.

(*Z*)-Oxacyclotetradec-3-en-2-one (2.80). Following General Procedure B, in the presence of 5.0 mol % complex 2.88 (0.1 M in benzene, 0.0026 mmol, 26 µL), cyclization of eneacrylate 2.79 (12 mg, 0.050 mmol; in 50 mL of benzene) to the desired macrocycles proceeded to 68% conv in 2 h. The *Z*:*E* ratio of the unpurified product was 89:11. The residue was purified by silica gel chromatography (15% silver nitrate impregnated; 100% hexanes) afforded 2.80 as colorless oil (6.4 mg, 0.030 mmol, 60% yield; >98:2 *Z*:*E*). **IR (neat)**: 2925 (s), 2858 (m), 1719 (s), 1640 (w), 1461 (w), 1410 (w), 1291 (w), 1240 (w), 1223 (w), 1190 (m), 1167 (m), 814 (w); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  6.10 (1H, dt, *J* = 11.6 Hz, 8.0 Hz), 5.80 (1H, dt, *J* = 11.6 Hz, 1.2 Hz), 4.28 (2H, t, *J* = 5.6 Hz), 2.62 (2H, qd, *J* = 7.2 Hz, 1.2 Hz), 1.71 (2H, m), 1.51 (2H, m), 1.43–1.19 (12H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$ 167.3, 147.5, 121.0, 62.6, 27.34, 27.28, 26.9, 26.3, 25.8, 24.6, 24.2, 24.1, 22.2; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>13</sub>H<sub>23</sub>O<sub>2</sub>: 211.1698, found: 211.1700.

(*Z*)-Oxacyclopentadec-3-en-2-one (2.90). Following General Procedure B, in the presence of 5.0 mol % of complex 2.88 (0.1 M in benzene, 0.002 mmol, 20 µL), cyclization of ene-acrylate 2.147 (10 mg, 0.040 mmol; in 40 mL of benzene) to the desired macrocyclic products proceeded to 64% conv in 2 h. The *Z*:*E* ratio of the unpurified residue was 87:13. The residue was purified by silica gel chromatography (15% silver nitrate impregnated; 100% hexanes) to afford 2.90 as colorless oil (3.9 mg, 0.018 mmol, 44% yield; >98:2 *Z*:*E*). **IR (neat)**: 2926 (s), 2857 (m), 1717 (s), 1458 (w), 1287 (w), 1225 (w), 1192 (m), 1173 (m), 1156 (m), 817 (w); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  6.13 (1H, dt, *J* = 11.6 Hz, 8.0 Hz), 5.78 (1H, dt, *J* = 11.6 Hz, 1.6 Hz), 4.25 (2H, t, *J* = 5.6 Hz), 2.59 (2H, qd, *J* = 7.6 Hz, 1.6 Hz), 1.68 (2H, m), 1.48–1.26 (16H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  167.3, 148.0, 120.9, 64.4, 28.4, 28.2, 27.3, 26.8, 26.6, 26.42, 26.36, 26.0, 25.9, 25.0; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>25</sub>O<sub>2</sub>: 225.1855, found: 225.1858. The above spectral data match the reported ones.<sup>20</sup>

(*Z*)-*tert*-**Butyl 15-oxo-1-oxa-4-azacyclopentadec-13-ene-4-carboxylate (2.95).** Following General Procedure B, in the presence of 5.0 mol % of complex **2.88** (0.1 M in benzene, 0.002 mmol, 20 µL), cyclization of ene-acrylate **2.152** (10 mg, 0.029 mmol; in 14 mL of benzene) to the desired products proceeded to 55% conv in 2 h. The *Z*:*E* ratio of the unpurified product was 79:21. The residue was purified by silica gel chromatography (15% silver nitrate impregnated; 10% Et<sub>2</sub>O/hexane) to afford **2.95** as colorless oil, in ~1:1 mixture of carbamate rotamers (4.0 mg, 0.013 mmol, 43% yield; >98:2 *Z*:*E*). **IR (neat)**: 2927 (m), 2856 (w), 1720 (s), 1695 (s), 1639 (w), 1459 (w), 1411 (m), 1365 (m), 1281 (w), 1247 (w), 1151 (s), 1105 (m), 818 (w); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  6.15–6.08 (1H, m), 5.86 (1H, d, *J* = 11.6 Hz), 4.29 (2H, m), 3.59–3.53 (H, m), 3.20–3.14 (2H, m), 2.73 (2H, q, *J* = 7.2 Hz), 1.54-1.22 (21H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  166.9, 155.6, 155.2, 150.3, 149.9, 120.6, 120.4, 79.6, 79.4, 65.1, 48.4, 47.8, 46.3, 30.3, 29.7, 28.4, 26.7, 28.5, 26.3, 26.1, 25.2, 24.0; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>18</sub>H<sub>32</sub>NO4: 326.2331, found: 326.2344.

(*Z*)-Oxacyclohexadec-3-en-2-one (2.91). Following General Procedure B, in the presence of 3.0 mol % complex 2.88 (0.1 M in benzene, 0.0017 mmol, 17 µL), cyclization of eneacrylate 2.148 (15 mg, 0.056 mmol) to the target macrocycle proceeded to 70% conv in 2 h. The *Z*:*E* ratio of the unpurified product was 83:17. The residue was purified by silica gel chromatography (15% silver nitrate impregnated; 100% hexanes) to afford 2.91 as color-less oil (6.6 mg, 0.028 mmol, 51% yield; >98:2 *Z*:*E*). **IR (neat)**: 2926 (s), 2856 (m), 1719 (s), 1459 (w), 1413 (w), 1287 (w), 1169 (m), 819 (s); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  6.17 (1H, dt, *J* = 11.6 Hz, 7.6 Hz), 5.76 (1H, dt, *J* = 11.6 Hz, 1.6 Hz), 4.22 (2H, t, *J* = 5.6 Hz), 2.65 (2H, qd, *J* = 7.6 Hz, 1.6Hz), 1.66 (2H, m), 1.48–1.26 (20H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  167.1, 149.1, 120.5, 63.8, 28.7, 28.4, 27.9, 27.1, 26.7, 26.5, 26.2, 25.5, 24.6; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>15</sub>H<sub>27</sub>O<sub>2</sub>: 239.2011, found: 239.2023. The above spectral data match the reported ones.<sup>18</sup>

(Z)-tert-Butyl 16-oxo-1-oxa-4-azacyclohexadec-14-ene-4-carboxylate (2.96). Following General Procedure B, in the presence of 5.0 mol % of complex 2.88 (0.1 M in benzene,

0.0014 mmol, 14  $\mu$ L), cyclization of ene-acrylate **2.153** (10 mg, 0.027 mmol) to the expected macrocycle proceeded to 90% conv in 2 h. The *Z*:*E* ratio of the unpurified product was 83:17. The residue was purified by silica gel chromatography (15% silver nitrate impregnated; 10% Et<sub>2</sub>O in hexanes) to afford **2.96** as colorless oil, in a ~1:1 mixture of amide rotamers (5.9 mg, 0.018 mmol, 64% yield; >98:2 *Z*:*E*). **IR (neat)**: 2927 (m), 2856 (w), 1720 (s), 1695 (s), 1639 (w), 1459 (w), 1411 (m), 1365 (m), 1281 (w), 1247 (w), 1151 (s), 818 (w); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  6.26 (1H, m), 5.83 (2H, d, *J* = 12.0 Hz), 4.29 (2H, br s), 3.46 (2H, m), 3.21 (2H, br s), 2.71 (2H, q, *J* = 6.8Hz), 1.58–1.48 (4H, m), 1.46 (9H, s), 1.28 (10H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  166.5, 155.8, 155.3, 151.0, 120.1, 79.5, 63.5, 48.0, 46.8, 30.3, 29.7, 28.4, 27.5, 27.4, 27.0, 26.9, 26.6, 26.3, 25.1; **HRMS (DART) [M+H]**<sup>+</sup> calcd for C<sub>19</sub>H<sub>34</sub>NO<sub>4</sub>: 340.2487, found: 340.2494.

(*Z*)-Oxacycloheptadec-3-en-2-one (2.92). Following General Procedure B, in the presence of 5.0 mol % of complex 2.88 (0.1 M in benzene, 0.0018 mmol, 18 µL), cyclization of ene-acrylate 2.149 (10 mg, 0.036 mmol) to the target macrocycle proceeded with 78% conversion in 2 h. The *Z*:*E* ratio of the unpurified product was 90:10. The residue was purified by preparative TLC (15% EtOAc in hexanes) delivered 2.92 as colorless oil (4.8 mg, 0.018 mmol, 50% yield; >98:2 *Z*:*E*). **IR (neat)**: 2925 (s), 2855 (m), 1719 (s), 1459 (w), 1413 (w), 1284 (w), 1190 (m), 1169 (s), 819 (w); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  6.14 (1H, dt, *J* = 11.6 Hz, 7.2 Hz), 5.77 (1H, dt, *J* = 12.0 Hz, 1.6 Hz), 4.22 (2H, t, *J* = 5.6 Hz), 2.64 (2H, qd, *J* = 7.6 Hz, 1.6Hz), 1.66 (2H, tt, *J* = *J* = 7.2 Hz, 6.0 Hz), 1.52–1.26 (22H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  167.0, 149.4, 120.5, 63.8, 28.8, 28.2, 28.1, 27.9, 27.6, 27.4, 27.12, 27.08, 26.7, 26.6, 26.3, 25.1; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>16</sub>H<sub>29</sub>O<sub>2</sub>: 253.2168, found: 253.2176.

(Z)-tert-Butyl 17-oxo-1-oxa-5-azacycloheptadec-15-ene-5-carboxylate (2.97). Following General Procedure B, in the presence of 3.0 mol % of complex 2.88 (0.1 M in benzene, 0.0026 mmol, 26  $\mu$ L), cyclization of ene-acrylate 2.154 (15 mg, 0.039 mmol) to the desired macrocycles proceeded with 88% conv in 2 h. The Z:E ratio of unpurified macrocycle was 90:10. The residue was purified by silica gel chromatography (impregnated with 15% silver nitrate; 10% Et<sub>2</sub>O/hexanes) to afford 2.97 as colorless oil (9.3 mg, 0.023 mmol, 60% yield; >98:2 *Z*:*E*). **IR (neat)**: 2927 (m), 2856 (w), 1718 (s), 1693 (s), 1459 (w), 1413 (m), 1365 (w), 1249 (w), 1224 (w), 1157 (s); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  6.19 (1H, dt, *J* = 11.2 Hz, 7.6 Hz), 5.79 (1H, dt, *J* = 12.0 Hz, 1.2 Hz), 4.21 (2H, t, *J* = 6.0 Hz), 3.25–3.16 (4H, m), 2.64 (2H, qd, *J* = 7.2 Hz, 1.2 Hz), 1.93 (2H, m), 1.55–1.25 (23H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  166.7, 155.6, 149.7, 120.3, 79.2, 61.9, 47.8, 44.8, 30.3, 29.7, 28.8, 28.5, 28.0, 27.7, 27.5, 27.4, 27.1, 26.9, 25.2; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>20</sub>H<sub>36</sub>NO<sub>4</sub>: 354.2644, found: 354.2655.

(Z)-11-((4-Methoxybenzyl)oxy)oxacycloheptadec-3-en-2-one (2.99). Following General Procedure B, in the presence of 5.0 mol % complex 2.88 (0.1 M in benzene, 0.0012 mmol, 12  $\mu$ L), cyclization of ene-acrylate **2.156** (10 mg, 0.024 mmol) to the desired macrocycles proceeded to 79% conv in 2 h. The Z:E ratio of the unpurified product was 87:13. The residue was purified by silica gel chromatography (15% silver nitrate impregnated; 10% Et<sub>2</sub>O in hexanes) to afford **2.99** as colorless oil (6.4 mg, 69% yield; >98:2 Z:E). **IR (neat)**: 2928 (s), 2855 (m), 1717 (s), 1612 (w), 1512 (m), 1459 (w), 1300 (w), 1246 (s), 1172 (s), 1109 (w), 1078 (w), 1037 (m), 820 (m); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.26 (2H, m), 6.86 (2H, dt, J = 8.4 Hz, 1.5 Hz), 6.16 (1H, dt, J = 11.6 Hz, 7.2 Hz), 5.76 (1H, dt, J = 7.2Hz, 1.6 Hz), 4.45 (1H, d, J = 11.2 Hz), 4.40 (1H, d, J = 11.2 Hz), 4.28 (1H, ddd, J = 10.8Hz, 6.4 Hz, 4.4 Hz), 4.14 (1H, ddd, *J* = 6.0 Hz, 4.8 Hz), 3.80 (3H, s), 3.37 (1H, tt, *J* = 6.4 Hz, 5.6 Hz), 2.67 (1H, dqd, J = 15.2 Hz, 8.0 Hz, 1.6 Hz), 2.54 (1H, dqd, J = 15.2 Hz, 8.0 Hz, 1.6 Hz), 1.67–1.26 (20H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 166.9, 159.0, 149.1, 131.3, 129.2, 120.5, 113.7, 70.0, 63.7, 55.3, 32.0, 31.6, 28.7, 28.2, 28.00, 27.96, 27.55, 27.53, 25.2, 24.1, 23.9; HRMS (DART) [M-H]<sup>+</sup> calcd for C<sub>24</sub>H<sub>35</sub>O<sub>4</sub>: 387.2535, found: 387.2531.

(Z)-17-Oxooxacycloheptadec-15-en-8-yl 2-(1*H*-indol-3-yl)acetate (2.98). Following General Procedure B, with 5.0 mol % complex 2.88 (0.1 M in benzene, 0.0016 mmol, 16  $\mu$ L), cyclization of ene-acrylate 2.155 (15 mg, 0.033 mmol) to the desired product proceeded to 80% conv in 2 h. The *Z*:*E* ratio of the unpurified product was 88:12. The residue was purified by preparative TLC (30% EtOAc in hexanes) afforded 2.98 as colorless oil (9.0 mg, 0.023 mmol, 71% yield; >98:2 *Z*:*E*). **IR (neat)**: 3380 (b), 2928 (m), 2857 (w),

1715 (s), 1642 (w), 1458 (w), 1413 (w), 1354 (w), 1338 (w), 1294 (w), 1267 (w), 1247 (w), 1161 (m), 1123 (w), 1098 (w), 1010 (w), 970 (w), 821 (w), 741 (m); <sup>1</sup>**H NMR (400 MHz, CDCl3**):  $\delta$  8.08 (1H, br s), 7.62 (1H, d, *J* = 8.0 Hz), 7.36 (1H, d, *J* = 8.0 Hz), 7.26–7.17 (2H, m), 7.12 (1H, td, *J* = 8.0 Hz, 1.2 Hz), 6.16 (1H, dt, *J* = 11.6 Hz, 7.6 Hz), 5.77 (1H, dt, *J* = 11.6 Hz, 1.6 Hz), 4.89 (1H, quint, *J* = 6.0 Hz), 3.76 (3H, s), 2.60 (2H, m), 1.64–1.30 (20H, m); <sup>13</sup>**C NMR (100 MHz, CDCl3**):  $\delta$  171.7, 166.9, 149.2, 136.1, 127.3, 122.9, 122.1, 120.5, 119.5, 118.9, 111.0, 108.9, 73.7, 63.7, 32.1, 31.7, 31.2, 28.6, 28.2, 27.94, 27.88, 27.1, 25.1, 23.9, 23.6; **HRMS (DART) [M+H]**<sup>+</sup> calcd for C<sub>24</sub>H<sub>35</sub>O<sub>4</sub>: 426.2644, found: 426.2648.

(*Z*)-Oxacyclooctadec-3-en-2-one (2.93). Following General Procedure B, in the presence of 3.0 mol % complex 2.88 (0.1 M in benzene, 0.0015 mmol, 15 µL), cyclization of eneacrylate 2.150 (15 mg, 0.051 mmol) to the expected product proceeded to 83% conv in 2 h. The *Z*:*E* ratio of the unpurified product was 83:17. The residue was purified by silica gel chromatography (15% silver nitrate impregnated; 100% hexanes) delivered 2.93 as colorless oil (7.0 mg, 0.026 mmol, 51% yield; >98:2 *Z/E*). **IR (neat)**: 2925 (s), 2855 (m), 1721 (s), 1642 (w), 1461 (w), 1410 (m), 1290 (m), 1168 (m), 819 (w); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  6.17 (1H, dt, *J* = 11.6 Hz, 8.0 Hz), 5.76 (1H, dt, *J* = 11.6 Hz, 1.2 Hz), 4.20 (2H, t, *J* = 6.0 Hz), 2.64 (2H, q, *J* = 7.2 Hz), 1.66 (2H, tt, *J* = 7.2 Hz, 6.0 Hz), 1.47–1.31 (24H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  166.9, 149.3, 120.4, 63.8, 28.8, 28.6, 28.5, 28.0, 27.8, 27.7, 27.6, 27.1, 26.8, 26.4, 26.3, 25.1; **HRMS (ESI**<sup>+</sup>) [M+H]<sup>+</sup> calcd for C<sub>17</sub>H<sub>31</sub>O<sub>2</sub>: 267.2324, found: 263.2335. The above spectral data match the reported ones.<sup>18</sup>

(Z)-Oxacyclononadec-3-en-2-one (2.94). Following General Procedure B, in the presence of 5.0 mol % of complex 2.88 (0.1 M in benzene, 0.0024 mmol, 24  $\mu$ L), cyclization of eneacrylate 2.151 (15 mg, 0.047 mmol) to the expected macrocycle to 85% conv in 2 h. The *Z:E* ratio of the unpurified product was 89:11. The residue was purified by preparative TLC (15% EtOAc in hexanes) to afford 2.151 as colorless oil (9.5 mg, 0.031 mmol, 65% yield; >98:2 *Z:E*). **IR (neat)**: 2925 (s), 2855 (s), 1720 (s), 1643 (w), 1460 (w), 1413 (w), 1284 (w), 1168 (m), 820 (w); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  6.17 (1H, dt, *J* = 11.6 Hz, 7.6 Hz), 5.76 (1H, dt, *J* = 11.6 Hz, 1.6 Hz), 4.18 (2H, t, *J* = 6.4 Hz), 2.60 (2H, qd, *J* = 7.6 Hz, 1.6 Hz), 1.66 (2H, tt, J = 7.6 Hz, 6.4 Hz), 1.48–1.26 (26H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  166.9, 149.3, 120.4, 64.0, 28.7, 28.6, 28.5, 28.4, 28.1, 28.0, 27.9, 27.6, 27.5, 27.4, 27.2, 27.0, 25.3; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>18</sub>H<sub>33</sub>O<sub>2</sub>: 281.2481, found: 281.2488.

(*Z*)-1*H*-Indol-3-yl 2-(24-oxooxacyclotetracos-22-en-12-yl)acetate (2.100). Following General Procedure B, in the presence of 5.0 mol % complex 2.88 (0.1 M in benzene, 0.0018 mmol, 18 µL), cyclization of ene-acrylate 2.157 (20 mg, 0.036 mmol) to the desired macrocycle to 76% conv in 2 h. The *Z*:*E* ratio of the unpurified product was 83:17. The residue was purified by preparative TLC (15% EtOAc in henxaes) gave 2.100 as colorless oil (12.0 mg, 0.023 mmol, 63% yield; >98:2 *Z*:*E*). IR (CDCl<sub>3</sub>): 3376 (b), 2924 (s), 2854 (m), 1715 (s), 1458 (w), 1415 (w), 1353 (w), 1339 (w), 1292 (w), 1247 (w), 1168 (m), 1122 (w), 1095 (w), 1010 (w), 981 (w), 822 (w), 740 (w); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.07 (1H, br s), 7.62 (1H, d, *J* = 8.0 Hz), 7.36 (1H, d, *J* = 8.4 Hz), 7.21–7.17 (2H, m), 7.12 (1H, td, *J* = 8.0 Hz), 4.89 (1H, quint, *J* = 6.4 Hz), 4.21–4.10 (2H, m), 3.75 (2H, s), 2.59 (2H, quint, *J* = 6.8 Hz), 1.70–1.24 (34H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  171.7, 166.9, 149.1, 136.0, 127.3, 122.8, 122.1, 120.3, 119.5, 118.9, 111.0, 108.9, 74.2, 64.1, 32.4, 32.1, 31.7, 29.2, 29.1, 29.01, 29.00, 28.98, 28.93, 28.89, 28.85, 28.70, 28.63, 28.3, 28.0, 26.0, 24.4, 23.5; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>33</sub>H<sub>50</sub>NO4: 524.3740, found: 524.3763.

#### Synthesis of RCM Substrates for Macrocyclic (E,Z)-Dienoates

General Procedure C: Preparation of ene-dienoate substrates from the alcohols. Pivaloyl chloride (2 mmol, 2.0 equiv) and Et<sub>3</sub>N (2 mmol, 2.0 equiv) were sequentially added to a solution of 2,4-pentadienoic acid (2 mmol, 2.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) at 0 °C. The mixture was allowed to warm to 22 °C and stir for 2 h. This in situ-generated solution of the mixed anhydride was transferred drop-wise to a solution of alcohol (1 mmol, 1.0 equiv), 4-dimethylamino pyridine (0.25 mmol, 0.25 equiv), and Et<sub>3</sub>N (4 mmol, 4.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) at 0 °C. The mixture was then allowed to warm to 22 °C and stir for 12 h, before it was diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with a saturated solution of aqueous Na-HCO<sub>3</sub>. The aqueous layer was washed with CH<sub>2</sub>Cl<sub>2</sub>, and the combined organic layers were

dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting light yellow oil was purified by silica gel chromatography to afford the desired ene-dienoate compound.

(*E*)-Undec-10-en-1-yl penta-2,4-dienoate (2.104). Following General Procedure C, esterification of undec-10-en-1-ol (170 mg, 1.00 mmol) with the in situ-generated mixed anhydride solution (1 M in CH<sub>2</sub>Cl<sub>2</sub>, 2 mL) to afford **2.104** as colorless oil (190 mg, 0.760 mmol, 76% yield). **IR (neat)**: 2924 (m), 2854 (w), 1716 (s), 1642 (w), 1600 (w), 1465 (w), 1304 (w), 1264 (s), 1199 (s), 1141 (s), 1006 (m), 962 (w), 909 (m), 867 (w); <sup>1</sup>H NMR (400 MHz, **CDCl**<sub>3</sub>):  $\delta$  7.25 (1H, dd, *J* = 15.6 Hz, 10.4 Hz), 6.45 (1H, dt, *J* = 16.4 Hz, 10.4 Hz), 5.91 (1H, d, *J* = 15.2 Hz), 5.82 (1H, dddd, *J* = 16.4 Hz, 10.4 Hz, 6.4 Hz, 6.4 Hz), 5.60 (1H, d, *J* = 17.2 Hz), 5.48 (1H, d, *J* = 10.4 Hz), 4.97 (2H, m), 4.14 (2H, t, *J* = 6.4 Hz), 2.03 (2H, q, *J* = 6.8 Hz), 1.66 (2H, quint, *J* = 6.8 Hz), 1.41–1.28 (12H, m); <sup>13</sup>C NMR (100 MHz, **CDCl**<sub>3</sub>):  $\delta$  166.9, 144.5, 139.1, 134.7, 125.4, 122.2, 114.1, 64.6, 33.8, 29.4, 29.3, 29.2, 29.1, 28.9, 28.6, 25.9; **HRMS (DART) [M+H]**<sup>+</sup> calcd for C<sub>16</sub>H<sub>27</sub>O<sub>2</sub>: 251.2011, found: 251.2008.

(*E*)-Dodec-11-en-1-yl penta-2,4-dienoate (2.162). Following General Procedure C, esterification of dodec-11-en-1-ol (184 mg, 1.00 mmol) with the in situ-generated mixed anhydride solution (1 M in CH<sub>2</sub>Cl<sub>2</sub>, 2 mL) afforded 2.162 as colorless oil (158 mg, 0.600 mmol, 60% yield). IR (neat): 2924 (m), 2854 (w), 1715 (s), 1641 (w), 1600 (w), 1465 (w), 1304 (w), 1263 (s), 1199 (s), 1141 (s), 1006 (m), 962 (w), 909 (m), 867 (w); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.25 (1H, dd, J = 15.6 Hz, 11.2 Hz), 6.45 (1H, dt, J = 16.8 Hz, 10.8 Hz), 5.91 (1H, d, J = 15.6 Hz), 5.82 (1H, dddd, J = 16.8 Hz, 10.4 Hz, 6.4 Hz, 6.4 Hz), 5.60 (1H, d, J = 17.2 Hz), 5.48 (1H, d, J = 10.4 Hz), 4.97 (2H, m), 4.14 (2H, t, J = 6.4 Hz), 2.03 (2H, q, J = 6.8 Hz), 1.66 (2H, tt, J = 7.2 Hz, 6.8 Hz), 1.41–1.28 (14H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  166.9, 144.5, 139.2, 134.8, 125.4, 122.3, 114.1, 64.6, 33.8, 29.47, 29.45, 29.42, 29.2, 29.1, 28.9, 28.6, 25.9; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>17</sub>H<sub>29</sub>O<sub>2</sub>: 265.2168, found: 265.2166.

(*E*)-Tetradec-13-en-1-yl penta-2,4-dienoate (2.163). Following General Procedure C, esterification of tetradec-13-en-1-ol (150 mg, 0.71 mmol) with the in situ-generated mixed

anhydride solution (1 M in CH<sub>2</sub>Cl<sub>2</sub>, 1.4 mL) afforded **2.163** as colorless oil (86 mg, 0.30 mmol, 46% yield). **IR (neat)**: 2923 (m), 2853 (w), 1716 (s), 1642 (w), 1600 (w), 1465 (w), 1304 (w), 1264 (s), 1199 (m), 1142 (s), 1006 (m), 908 (m), 867 (w); <sup>1</sup>H NMR (400 MHz, **CDCl<sub>3</sub>**):  $\delta$  7.26 (1H, dd, J = 15.6 Hz, 10.8 Hz), 6.46 (1H, dtd, J = 16.8 Hz, 10.8 Hz, 1.2 Hz), 5.91 (1H, d, J = 15.6 Hz), 5.81 (1H, dddd, J = 16.8 Hz, 10.4 Hz, 6.4 Hz, 6.4 Hz), 5.61 (1H, d, J = 16.8 Hz), 5.49 (1H, d, J = 10.4 Hz), 4.99 (1H, dq, J = 16.8 Hz, 1.6 Hz), 4.93 (1H, dt, J = 10.4 Hz, 1.2 Hz), 4.14 (2H, t, J = 6.4 Hz), 2.04 (2H, q, J = 6.8 Hz), 1.66 (2H, quint, J = 6.8 Hz), 1.37–1.27 (18H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  166.9, 144.5, 139.2, 134.8, 125.4, 122.3, 114.1, 64.6, 33.8, 29.58, 29.56, 29.53, 29.5, 29.2, 29.1, 28.9, 28.6, 25.9; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>33</sub>O<sub>2</sub>: 293.2481, found: 293.2482.

(*E*)-Henicosa-1,3,20-trien-5-one (2.164). Following General Procedure C, esterification of pentadec-14-en-1-ol (79 mg, 0.35 mmol) with the in situ-generated mixed anhydride solution (0.35 M in CH<sub>2</sub>Cl<sub>2</sub>, 2 mL) afforded 2.164 as colorless oil (78 mg, 0.23 mmol, 67% yield). **IR (neat)**: 2923 (m), 2853 (w), 1716 (s), 1642 (w), 1600 (w), 1465 (w), 1304 (w), 1264 (s), 1199 (m), 1141 (s), 1006 (m), 909 (m), 867 (w); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.25 (dd, *J* = 15.6 Hz, 11.2 Hz, 1H), 6.45 (dtd, *J* = 16.8 Hz, 10.4 Hz, 1.2 Hz, 1H), 5.91 (d, *J* = 15.2 Hz, 1H), 5.81 (dddd, *J* = 16.8 Hz, 10.4 Hz, 6.4 Hz, 6.4 Hz, 1H), 5.60 (d, *J* = 17.2 Hz, 1H), 5.48 (d, *J* = 10.0 Hz, 1H), 4.99 (dq, *J* = 17.2 Hz, 1.6 Hz, 1H), 4.92 (dt, *J* = 10.4 Hz, 1.2 Hz, 1H), 4.14 (t, *J* = 6.8 Hz, 2H), 2.04 (q, *J* = 6.8 Hz, 2H), 1.66 (quint, *J* = 6.8 Hz, 2H), 1.37–1.26 (m, 20H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  166.9, 144.5, 139.2, 134.8, 125.4, 122.3, 114.0, 64.6, 33.8, 29.60, 29.58, 29.54, 29.48, 29.2, 29.1, 28.9, 28.7, 25.9; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>20</sub>H<sub>35</sub>O<sub>2</sub>: 307.2637, found: 307.2645.

#### Synthesis of Macrocyclic (*E*,*Z*)-Dienoates

General Procedure D: Preparation of macrocyclic (E,Z)-dienoates through catalytic RCM with Mo MAP complex **2.88**. In a N<sub>2</sub>-filled glove-box, an oven-dried round-bottom flask equipped with a magnetic stir bar was charged with a solution of ene-dienoate substrate (1.0 equiv) in benzene (2 mM). A stock solution of complex **2.88** (0.1 M in benzene, 5.0 mol %) was added by syringe. The flask was then connected to a 100 torr vacuum generated from a diaphragm vacuum pump. The resulting solution was allowed to stir for 2 h, before

the reaction was quenched with wet diethyl ether. The mixture was concentrated *in vacuo*, and the residue was passed through a short pad of silica gel (20% Et<sub>2</sub>O in hexanes) and concentrated *in vacuo*. The percent conversion and *Z*:*E* ratio of the unpurified mixture was determined by <sup>1</sup>H NMR analysis. Purification through silica gel chromatography (15% silver nitrate impregnated) provided the desired (*E*,*Z*)-macrocyclic compound.

(*3E*,5*Z*)-Oxacyclopentadeca-3,5-dien-2-one (2.105). Following General Procedure D, in the presence of 5.0 mol % of Mo-complex 2.88 (0.1 M in benzene, 0.0024 mmol, 24 µL), cyclization of ene-dienoate 2.104 (12 mg, 0.048 mmol) to the desired macrocycle proceeded to 57% conv in 2 h. The *Z*:*E* ratio of the unpurified product was >98:2. The residue was purified by silica gel chromatography (silver nitrate impregnated; 5% Et<sub>2</sub>O in hexanes) to afford 2.105 (5.4 mg, 0.024 mmol, 50% yield) as colorless oil. IR (neat): 2926 (m), 2855 (w), 1712 (s), 1635 (w), 1463 (w), 1248 (m), 1043 (w), 993 (w), 961 (w), 872 (w), 707 (w); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.59 (1H, dd, *J* = 15.2 Hz, 11.6 Hz), 6.20 (1H, t, *J* = 11.2 Hz), 5.97 (1H, q, *J* = 9.6 Hz), 5.81 (1H, d, *J* = 15.6 Hz), 4.23 (2H, t, *J* = 5.2 Hz), 2.27 (2H, dt, *J* = 8.4 Hz, 6.8 Hz), 1.68–1.62 (2H, m), 1.59–1.53 (2H, m), 1.50–1.25 (10H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  166.7, 140.9, 139.8, 127.6, 121.3, 64.5, 28.6, 27.9, 27.8, 27.3, 27.3, 26.3, 25.8, 25.5; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>23</sub>O<sub>2</sub>: 223.1698, found: 223.1707.

(*3E*,5*Z*)-Oxacyclohexadeca-3,5-dien-2-one (2.106). Following General Procedure D, in the presence of 5.0 mol % of Mo-complex 2.88 (0.1 M in benzene, 0.0019 mmol, 19 µL), cyclization of ene-dienoate 2.162 (10 mg, 0.038 mmol) to the desired macrocycle proceeded to 83% conv in 2 h. The *Z*:*E* ratio of the unpurified product was >98:2. The residue was purified by silica gel chromatography (silver nitrate impregnated; 5% Et<sub>2</sub>O in hexanes) to afford 2.106 (5.7 mg, 0.024 mmol, 64% yield) as colorless oil. IR (neat): 2925 (m), 2854 (w), 1710 (s), 1634 (w), 1460 (w), 1379 (w), 1252 (m), 1165 (w), 1054 (w), 1041 (w), 1019 (w), 993 (w), 961 (w), 872 (w), 704 (w); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.66 (1H, dd, *J* = 14.8 Hz, 11.6 Hz), 6.17 (1H, t, *J* = 11.2 Hz), 5.93 (1H, q, *J* = 8.8 Hz), 5.81 (1H, d, *J* = 15.2 Hz), 4.18 (2H, t, *J* = 6.0 Hz), 2.28 (2H, q, *J* = 8.0 Hz), 1.71 (2H, m), 1.47–1.25 (14H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  166.7, 141.1, 139.2, 126.9, 121.2, 64.6, 27.9,

27.6, 27.5, 27.1, 27.0, 26.9, 26.4, 26.2, 26.0; **HRMS (DART)** [**M**+**H**]<sup>+</sup> calcd for C<sub>15</sub>H<sub>25</sub>O<sub>2</sub>: 237.1855, found: 237.1849.

(*3E*,5*Z*)-Oxacyclooctadeca-3,5-dien-2-one (2.107). Following the General Procedure D, in the presence of 5.0 mol % of Mo-complex **2.88** (0.1 M in benzene, 0.0017 mmol, 17  $\mu$ L), cyclization of ene-dienoate **2.163** (10 mg, 0.034 mmol) to the desired macrocycle proceeded to 78% conv in 2 h. The *Z*:*E* ratio of the unpurified product was >98:2. The residue was purified by silica gel chromatography (silver nitrate impregnated; 5% Et<sub>2</sub>O in hexanes) to afford **2.107** (5.6 mg, 0.021 mmol, 63% yield) as colorless oil. **IR (neat)**: 2925 (m), 2855 (w), 1713 (s), 1636 (w), 1459 (w), 1259 (m), 1157 (w), 994 (w), 872 (w); <sup>1</sup>**H NMR (400 MHz, CDCl3**):  $\delta$  7.58 (1H, ddd, *J* = 15.2 Hz, 11.2 Hz, 1.2 Hz), 6.15 (1H, t, *J* = 11.2 Hz), 5.85 (1H, m), 5.84 (1H, d, *J* = 15.2 Hz), 4.21 (2H, t, *J* = 5.2 Hz), 2.30 (2H, q, *J* = 7.6 Hz), 1.71–1.65 (2H, m), 1.47–1.27 (18H, m); <sup>13</sup>C NMR (100 MHz, CDCl3):  $\delta$  167.0, 141.0, 138.7, 126.9, 121.7, 64.1, 28.3, 28.0, 27.7, 27.6, 27.5, 27.3, 27.0, 26.9, 26.8, 26.7, 24.7; **HRMS (DART) [M+H]**<sup>+</sup> calcd for C<sub>17</sub>H<sub>29</sub>O<sub>2</sub>: 265.2168, found: 265.2169.

(*3E*,5*Z*)-Oxacyclononadeca-3,5-dien-2-one (2.108). Following the General Procedure D, in the presence of 5.0 mol % of Mo-complex 2.88 (0.1 M in benzene, 0.0009 mmol, 9 µL), cyclization of ene-dienoate 2.164 (6 mg, 0.018 mmol) to the desired macrocycle proceeded to 72% conv in 2 h. The *Z*:*E* ratio of the unpurified product was 91:9. The residue was purified by silica gel chromatography (silver nitrate impregnated; 5% Et<sub>2</sub>O/hexanes) to afford 2.108 (3.6 mg, 0.013 mmol, 71% yield; 91:9 *Z*:*E*) as colorless oil. IR (neat): 2924 (m), 2854 (w), 1713 (s), 1637 (w), 1459 (w), 1258 (m), 1154 (w), 1053 (w), 993 (w), 962 (w), 871 (w), 707 (w); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.54 (1H, ddd, *J* = 15.6 Hz, 11.6 Hz, 1.2 Hz), 6.14 (1H, t, *J* = 7.2 Hz), 5.85 (1H, d, *J* = 11.6 Hz), 5.84 (1H, m), 4.22 (2H, t, *J* = 5.2 Hz), 2.29 (2H, q, *J* = 7.6 Hz), 1.70–1.64 (2H, m), 1.47–1.26 (20H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  167.0, 141.2, 138.7, 126.9, 121.8, 64.3, 28.7, 28.5, 28.4, 28.2, 28.1, 27.94, 27.90, 27.75, 27.51, 27.50, 25.9; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>18</sub>H<sub>31</sub>O<sub>2</sub>: 279.2324, found: 279.2319.

#### Synthesis of RCM Substrates for Macrocyclic (Z,E)-Dienoates

(*E*)-Hexadeca-13,15-dien-1-yl acrylate (2.109). Acylation of (*E*)-hexadeca-13,15-dien-1-ol<sup>21</sup> (91 mg, 0.38 mmol) according to General Procedure A afforded 2.109 as colorless oil (76 mg, 0.76 mmol, 68% yield). **IR (neat)**: 2924 (s), 2854 (m), 1728 (s), 1465 (w), 1407 (w), 1295 (w), 1271 (w), 1189 (m), 1059 (m), 1003 (w), 985 (w), 965 (w), 896 (w), 810 (w); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  6.40 (1H, dd, J = 17.2 Hz, 1.2 Hz), 6.31 (1H, dt, J = 16.8 Hz, 10.4 Hz), 6.12 (1H, dd, J = 17.2 Hz, 10.4 Hz), 6.04 (1H, dd, J = 14.8 Hz, 10.4 Hz), 5.81 (1H, dd, J = 10.8 Hz, 1.2 Hz), 5.71 (1H, dt, J = 14.8 Hz, 7.2 Hz), 5.08 (1H, d, J = 16.8 Hz), 4.95 (1H, d, J = 10.4 Hz), 4.15 (2H, t, J = 6.8 Hz), 2.07 (2H, q, J = 7.2 Hz), 1.66 (2H, quint, J = 6.8 Hz), 1.43–1.26 (18H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  166.3, 137.3, 135.6, 130.8, 130.4, 128.6, 114.5, 64.7, 32.5, 29.57, 29.54, 29.52, 29.48, 29.46, 29.22, 29.18, 29.17, 28.6, 25.9; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>33</sub>O<sub>2</sub>: 293.2481, found: 293.2482.

(*E*)-Heptadeca-14,16-dien-1-yl acrylate (2.166). Esterification of (*E*)-heptadeca-14,16dien-1-ol (52 mg, 0.23 mmol) according to General Procedure A to afford 2.166 as colorless oil (53 mg, 0.19 mmol, 82% yield). IR (neat): 2923 (s), 2853 (m), 1727 (s), 1466 (w), 1407 (w), 1295 (w), 1271 (w), 1188 (s), 1059 (m), 1002 (w), 985 (w), 965 (w), 896 (w), 810 (w); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  6.39 (1H, dd, J = 17.2 Hz, 1.2 Hz), 6.31 (1H, dt, J = 17.2 Hz, 10.4 Hz), 6.12 (1H, dd, J = 17.2 Hz, 10.4 Hz), 6.04 (1H, dd, J = 14.4 Hz, 10.4 Hz), 5.81 (1H, dd, J = 10.0 Hz, 1.6 Hz), 5.70 (1H, dt, J = 14.4 Hz, 7.2 Hz), 5.08 (1H, d, J = 16.8 Hz), 4.94 (1H, d, J = 10.0 Hz), 4.15 (2H, t, J = 6.8 Hz), 2.07 (2H, q, J = 7.2 Hz), 1.66 (2H, quint, J = 7.2 Hz), 1.43–1.26 (20H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  166.3, 137.3, 135.6, 130.8, 130.4, 128.6, 114.5, 64.7, 32.5, 29.61, 29.59, 29.56, 29.53, 29.48, 29.47, 29.23, 29.19, 29.17, 28.6, 25.9; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>20</sub>H<sub>35</sub>O<sub>2</sub>: 307.2637, found: 307.2643.

Synthesis of Macrocyclic (*Z*,*E*)-Dienoates

General Procedure E: Preparation of macrocyclic (*Z*,*E*)-dienoates through catalytic RCM with Mo-complex 2.88: Substrates were subjected to azeotropic drying with benzene prior to the RCM reaction. In a N<sub>2</sub>-filled glove-box, an oven-dried round-bottom flask equipped with a magnetic stir bar was charged with a solution of diene-acrylate substrate (1.0 equiv) in benzene (2 mM). A stock solution of complex 2.88 (0.1 M in benzene, 10 mol %) was added by syringe. The vessel was then connected to a 100 torr vacuum generated from a diaphragm vacuum pump. The resulting solution was allowed to stir for 6 h, before the reaction was quenched through addition of wet diethyl ether. The resulting mixture was concentrated *in vacuo*, and the residue was passed through a short pad of silica gel (20% Et<sub>2</sub>O in hexanes) and concentrated *in vacuo*. Percent conversion and *Z*:*E* ratio of the unpurified mixture was determined by <sup>1</sup>H NMR analysis. Purification of this mixture through silica-gel chromatography (15% silver nitrate impregnated) provided the desired (*Z*,*E*)-macrocycle.

(*3Z*,5*E*)-Oxacyclooctadeca-3,5-dien-2-one (2.110). Following General Procedure E, in the presence of 10 mol % of Mo complex 2.88 (0.1 M in benzene, 0.004 mmol, 40 µL), cyclization of diene-acrylate 2.109 (12 mg, 0.040 mmol) to the desired macrocycle proceeded to 91% conv in 2 h. The *Z*:*E* ratio of the unpurified product was 87:13. The residue was purified by silica gel chromatography (15% silver nitrate impregnated; 5% Et<sub>2</sub>O/hexanes) to afford 2.110 (8.0 mg, 0.048 mmol, 75% yield; >98:2 *Z*:*E*) as colorless oil. **IR** (neat): 2926 (s), 2855 (w), 1705 (s), 1638 (w), 1460 (w), 1276 (w), 1216 (w), 1167 (m), 999 (w), 961 (w); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.18 (1H, dd, *J* = 15.2 Hz, 11.2 Hz), 6.54 (1H, t, *J* = 11.6 Hz), 6.04 (1H, dt, *J* = 15.2 Hz, 7.2 Hz), 5.53 (1H, d, *J* = 11.2 Hz), 4.24 (2H, t, *J* = 5.6 Hz), 2.19 (2H, q, *J* = 7.2 Hz), 1.73–1.67 (2H, m), 1.52–1.24 (18H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  167.0, 144.6, 143.5, 127.5, 116.6, 63.9, 31.8, 28.7, 27.7, 27.5, 27.1, 27.0, 26.7, 26.4, 26.3, 26.2, 25.7; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>17</sub>H<sub>29</sub>O<sub>2</sub>: 265.2168, found: 265.2158.

(3*Z*,5*E*)-Oxacyclooctadeca-3,5-dien-2-one (2.111). Following the General Procedure E, in the presence of 10 mol % of Mo complex 2.88 (0.1 M in benzene, 0.005 mmol, 50  $\mu$ L), cyclization of ene-dienoate 2.166 (15 mg, 0.050 mmol) to macrocycle 2.111 proceeded

with 74% conversion in 2 h. The *Z*:*E* ratio of the unpurified product was 83:17. The residue was purified by silica gel chromatography (15% silver nitrate impregnated; 5% Et<sub>2</sub>O in hexanes) to afford **2.111** (8.0 mg, 0.029 mmol, 57% yield; >98:2 *Z*:*E*) as colorless oil. **IR** (neat): 2926 (s), 2855 (w), 1706 (s), 1638 (w), 1599 (w), 1459 (w), 1417 (w), 1275 (w), 1215 (w), 1170 (m), 998 (w), 961 (w), 822 (w); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.13 (1H, ddq, *J* = 15.2 Hz, 11.6 Hz, 1.6 Hz), 6.52 (1H, t, *J* = 11.2 Hz), 6.05 (1H, dt, *J* = 15.6 Hz, 11.2 Hz), 5.53 (1H, d, *J* = 11.6 Hz), 4.23 (2H, t, *J* = 5.6 Hz), 2.18 (2H, q, *J* = 7.2 Hz), 1.71–1.64 (2H, m), 1.48–1.24 (20H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  167.0, 145.0, 143.6, 127.3, 116.5, 64.3, 32.0, 28.8, 28.5, 28.2, 27.6, 27.5, 27.4, 27.3, 27.2, 26.9, 25.7; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>18</sub>H<sub>31</sub>O<sub>2</sub>: 279.2324, found: 279.2329.

### Stereoselective Formal Synthesis of (+)-Aspicilin



Scheme 2.20. Synthesis of Diene Precursor 2.112.

(2*S*,13*R*)-13-((4-Methoxybenzyl)oxy)pentadec-14-en-2-ol (2.112). Alcohol 2.112 was prepared from known (*S*)-tetradec-13-en-2-ol by means of the sequence described in Scheme 2.20. **IR (neat)**: 3380 (br), 2924 (s), 2853 (m), 1613 (w), 1586 (w), 1513 (m), 1464 (w), 1421 (w), 1371 (w), 1301 (w), 1247 (s), 1172 (w), 1109 (w), 1074 (w), 1037 (m), 993 (w), 925 (w), 821 (w); <sup>1</sup>H NMR (400 MHz, CDCI<sub>3</sub>): δ 7.25 (2H, d, *J* = 8.0 Hz), 6.87 (2H, d, *J* = 7.6 Hz), 5.72 (1H, ddd, *J* = 17.2 Hz, 10.4 Hz, 8.0 Hz), 5.22–5.16 (2H, m), 4.52 (1H,

d, J = 11.6 Hz), 4.28 (1H, d, J = 11.6 Hz), 3.80 (3H, s), 3.78 (1H, m), 3.69 (1H, q, J = 6.8 Hz), 1.65–1.25 (20H, m), 1.18 (3H, d, J = 6.4 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  159.0, 139.3, 130.9, 129.3, 116.8, 113.7, 80.2, 69.6, 68.1, 55.2, 39.3, 35.5, 29.61, 29.57, 29.54, 29.51, 25.7, 25.3, 23.5; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>23</sub>H<sub>37</sub>O<sub>3</sub>: 361.2743, found: 361.2741; [ $\alpha$ ] $p^{22}$  +13.1 (c=1.33, CHCl<sub>3</sub>).

(E)-(2S,13R)-13-((4-Methoxybenzyl)oxy)pentadec-14-en-2-yl penta-2,4-dienoate (2.113). Pivaloyl chloride (122  $\mu$ L, 1.0 mmol) and Et<sub>3</sub>N (139  $\mu$ L, 1.0 mmol) were successively added to a stirred suspension of 2,4-pentadienoic acid (100 mg, 1.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) at 22 °C. The mixture was allowed to stir for 2 h. At 0 °C, the solution containing the acid chloride was added drop-wise to a solution of alcohol **2.112** (100 mg, 0.276 mmol), 4-dimethylamino pyridine (18 mg, 0.14 mmol), and Et<sub>3</sub>N (192 µL, 1.38 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL). The mixture was allowed to warm to 22 °C and stir for 12 h, and was then diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with a saturated aqueous solution of NaHCO<sub>3</sub>. The aqueous layer was washed with  $CH_2Cl_2$  (3 x), and the combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting light yellow oil was purified by silica gel chromatography (5% EtOAc in hexanes) to afford 2.113 (98 mg, 0.22 mmol, 80% yield) as light vellow oil. **IR (neat)**: 2924 (m), 2853 (w), 1712 (s), 1613 (w), 1512 (s), 1464 (w), 1302 (w), 1264 (s), 1246 (s), 1172 (w), 1144 (w), 1123 (w), 1109 (w), 1009 (w), 992 (w), 923 (m), 819 (m); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.27 (2H, d, J = 8.4 Hz), 6.89 (2H, d, J= 8.4 Hz), 5.74 (1H, ddd, *J* = 17.2 Hz, 10.4 Hz, 7.6 Hz), 5.21 (2H, m), 4.54 (1H, d, *J* = 11.2 Hz), 4.30 (1H, d, *J* = 11.2 Hz), 3.82 (3H, s), 3.81 (1H, q, *J* = 6.4 Hz), 3.71 (1H, q, *J* = 6.8 Hz), 1.65–1.60 (1H, m), 1.50–1.27 (19H, m), 1.20 (3H, d, J = 6.4 Hz); <sup>13</sup>C NMR (100 **MHz**, **CDCl**<sub>3</sub>): δ 166.5, 159.0, 144.3, 139.3, 134.8, 130.9, 129.3, 125.2, 122.8, 116.8, 113.7, 80.2, 71.1, 69.6, 55.2, 36.0, 35.5, 29.54, 29.52, 29.49, 29.44, 25.4, 25.3, 20.0; HRMS (DART)  $[M+H]^+$  calcd for C<sub>28</sub>H<sub>43</sub>O<sub>4</sub>: 443.3161, found: 443.3168;  $[\alpha]_D^{22}$  +6.0 (c=0.40, CHCl<sub>3</sub>).

### (3E,5Z,7R,18S)-7-((4-Methoxybenzyl)oxy)-18-methyloxacyclooctadeca-3,5-dien-2-

**one (2.114).** In a N<sub>2</sub>-filled glove box, an oven-dried 200-mL round bottom flask equipped with a magnetic stir bar was charged with the ene-dienoate **2.113** (59 mg, 0.13 mmol) and

benzene (67 mL). Complex 2.88 (0.1 M in benzene, 0.013 mmol, 133 µL) was added by syringe, after which the flask was then connected to a 100 torr vacuum generated from a diaphragm vacuum pump. The resulting solution was allowed to stir for 6 h. The reaction was then quenched through addition of wet diethyl ether. The mixture was concentrated in *vacuo*, and the residue was passed through a short pad of silica gel (20% Et<sub>2</sub>O/hexanes) and concentrated in vacuo. Based on the <sup>1</sup>H NMR analysis of the unpurified mixture, cyclization of 2.113 to the target macrocycle 2.114 proceeded to 89% conv and in >98% Z selectivity. The mixture was purified by silica gel chromatography (5% EtOAc in hexanes) to afford **2.114** (38 mg, 0.090 mmol, 69% yield) as colorless oil. **IR (neat)**: 2927 (s), 2855 (m), 1709 (s), 1639 (w), 1612 (w), 1513 (m), 1460 (w), 1352 (w), 1301 (m), 1268 (s), 1248 (s), 1204 (w), 1174 (m), 1150 (w), 1123 (w), 1070 (w), 1037 (w), 994 (w), 870 (w), 821 (w), 714 (w); <sup>1</sup>**H** NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.52 (2H, ddd, J = 15.2 Hz, 11.6 Hz, 1.2 Hz), 7.24 (2H, m), 6.87 (2H, m), 6.35 (1H, t, *J* = 11.6 Hz), 5.93 (1H, d, *J* = 15.2 Hz), 5.70 (1H, t, J = 10.4 Hz), 5.17 (1H, m), 4.50 (1H, d, J = 15.6 Hz), 4.44 (1H, td, J = 8.4 Hz, 6.4 Hz), 4.30 (1H, d, J = 11.6 Hz), 3.80 (3H, s), 1.79 (1H, m), 1.64–1.09 (22H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ166.7, 159.2, 141.0, 138.7, 130.4, 129.4, 128.8, 123.2, 113.8, 73.4, 70.3, 60.7, 55.2, 35.7, 34.3, 29.6, 28.2, 27.9, 27.4, 26.8, 24.8, 23.8, 20.7; HRMS (DART)  $[M]^+$  calcd for C<sub>26</sub>H<sub>38</sub>O<sub>4</sub>: 414.2770, found: 414.2776;  $[\alpha]_D^{22}$  –162.1 (c=0.27, CHCl<sub>3</sub>).

(*3E*,5*Z*,7*R*,18*S*)-7-hydroxy-18-methyloxacyclooctadeca-3,5-dien-2-one (2.115). A solution of macrocyclic PMB-ether 2.114 (39 mg, 0.094 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was treated successively with H<sub>2</sub>O (0.5 mL) and ddq (43 mg, 0.19 mmol) at 0 °C. The mixture was allowed to stir at 0 °C for 1 h and then allowed to warm to 22 °C. A saturated aqueous solution of NaHCO<sub>3</sub> was added, and the aqueous fraction was washed with EtOAc (3 x). The combined organic layer was dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The resulting light yellow oil was purified by silica gel chromatography (30% EtOAc in hexanes) to afford 2.115 (22 mg, 91% yield) as off-white waxy solid: m.p.: 82–84 °C; **IR (neat)**: 3415 (br), 2976 (w), 2926 (s), 2855 (m), 1711 (s), 1639 (w), 1606 (w), 1461 (w), 1378 (w), 1353 (w), 1300 (w), 1270 (s), 1178 (w), 1151 (w), 1127 (w), 1020 (w), 963 (w), 869 (w), 716 (w); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ 7.56 (1H, dd, *J* = 15.6 Hz, 11.6 Hz), 6.21 (1H, t, *J* = 11.2 Hz), 5.92 (1H, d, *J* = 15.2 Hz), 5.70 (1H, t, *J* = 10.0 Hz), 5.20 (1H, m), 4.82 (1H, td,

J = 9.2 Hz, 6.0 Hz), 1.76 (2H, m), 1.61–1.08 (21H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$ 166.8, 141.5, 138.7, 127.0, 123.0, 69.5, 67.2, 36.4, 35.8, 29.8, 28.4, 28.0, 27.9, 27.6, 26.7, 25.1, 24.0, 20.8; **HRMS (DART)** [M+H-H<sub>2</sub>O]<sup>+</sup> calcd for C<sub>18</sub>H<sub>29</sub>O<sub>2</sub>: 277.2168, found: 277.2177; [ $\alpha$ ] $p^{22}$  –71.4 (c=0.40, CHCl<sub>3</sub>). The above spectral data match the reported ones.<sup>40</sup>

#### Preparation of Substrates for Cross Metathesis

Representative procedure for dienoate synthesis. tert-Butyl (E)-penta-2,4-dienoate (2.131b). To a flame-dried round bottom flask charged with a magnetic stir bar was added (E)-penta-2,4-dienoic acid (1.00 g, 10.2 mmol) in thf (20 mL) and triethylamine (1.50 mL, 11.2 mmol). The mixture was allowed to cool 0 °C after which it was charged with trimethylacetyl chloride (1.20 mL, 9.74 mmol) dropwise. The solution was allowed to warm to 22 °C and stir for 2 h. The viscous solution was then filtered through a pad of Celite and the supernatant was concentrated in vacuo. The resulting brown oil was dissolved in thf and cooled to -78 °C. A suspension of sodium *tert*-butoxide (1.07 g, 11.2 mmol) in thf was added through cannula into the clear brown solution and the mixture was allowed to warm to 22 °C and stir for 12 h. Water was then added and the aqueous solution was washed with diethyl ether (3 x). The combined organics were washed with brine, dried over MgSO<sub>4</sub> and concentrated under reduced pressure (Note: Product is volatile). The brown oil residue was immediately purified by silica gel chromatography (100% hexanes and then 3% Et<sub>2</sub>O in hexanes) to afford 2.131b as colorless oil (793 mg, 5.14 mmol, 50% yield). IR (neat): 3005 (m), 2978 (s), 2932 (m), 1707 (s), 1642 (s), 1600 (s), 1478 (m), 1455 (m), 1417 (m), 1393 (s), 1368 (s), 1308 (s), 1271 (s), 1212 (s), 1173 (s), 1139 (s), 1008 (s), 979 (s), 949 (m), 907 (s), 870 (s), 849 (s), 766 (m), 729 (s), 649 (m), 616 (w) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, **400 MHz**):  $\delta$  7.16 (1H, ddt, J = 15.4, 11.0, 0.8 Hz), 6.43 (1H, dddd, J = 16.9, 10.9, 10.0, 0.7 Hz), 5.84 (1H, dq, J = 15.4, 0.7 Hz), 5.57 (1H, ddt, J = 17.0, 1.5, 0.8 Hz), 5.44 (1H, ddt, J = 10.0, 1.4, 0.7 Hz), 1.49 (9H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  166.3, 143.7, 135.0, 124.9, 124.3, 80.5, 28.3; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>9</sub>H<sub>15</sub>O<sub>2</sub>: 155.1072; found: 155.1073.

**Phenyl (***E***)-penta-2,4-dienoate (2.131a).** Following the general procedure for dienoates synthesis, the resulting brown oil was immediately purified by silica gel chromatography (100% hexanes to 1% Et<sub>2</sub>O in hexanes) to afford **2.131a** (1.00 g, 5.74 mmol, 68% yield) as colorless oil. **IR (neat):** 3043 (w), 1728 (s), 1638 (m), 1589 (m), 1487 (m), 1415 (w), 1304 (m), 1186 (s), 1120 (s), 1006 (s) cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$  7.50–7.42 (1H, m), 7.41–7.36 (2H, m), 7.25–7.22 (1H, m), 7.15–7.11 (2H, m), 6.55 (1H, dddd, *J* = 17.0, 10.8, 10.0, 0.7 Hz), 6.11 (1H, dd, *J* = 15.4, 0.8 Hz), 5.70 (1H, ddt, *J* = 17.1, 1.3, 0.8 Hz), 5.58 (1H, ddt, *J* = 10.1, 1.4, 0.7 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  165.3, 150.9, 146.7, 134.7, 129.5, 126.8, 125.9, 121.7, 121.4; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>11</sub>H<sub>11</sub>O<sub>2</sub>: 175.0759, found: 175.0765.

**Triethyl(pent-4-en-2-yloxy)silane (2.167).** To a flask charged containing a stir bar was added 4-penten-2-ol (711 mg, 8.30 mmol) in dichloromethane (28 mL) and imidazole (674 mg, 9.90 mmol). To the mixture was added chlorotriethylsilane (1.70 mL, 9.90 mL) and the reaction was allowed to stir at 22° C for 12 h. The solution was concentrated under reduced pressure. The suspension was diluted with hexanes and filtered through a pad of Celite. The supernatant was concentrated in vacuo and the resulting residue was purified by chromatography on basic alumina (100% hexanes) to afford **2.167** (976 mg, 4.87 mmol, 60% yield) as colorless oil. **IR (neat):** 2954 (s), 2938 (w), 2911 (m), 2876 (s), 1414 (w), 1237 (m), 1128 (m), 1128 (br), 1003 (s), 739 (s) cm<sup>-1</sup>; <sup>1</sup>**H NMR (400 MHz, CDCl3):**  $\delta$  5.81 (1H, ddt, *J* = 17.3, 10.2, 7.2 Hz), 5.09–5.00 (2H, m), 3.84 (1H, sext, *J* = 6.1 Hz), 2.24 (1H, dddt, *J* = 14.2, 7.1, 5.9, 1.3 Hz), 2.15 (1H, dddt, *J* = 13.7, 7.4, 6.3, 1.2 Hz), 1.14 (3H, d, *J* = 6.1 Hz), 0.96 (9H, t, *J* = 7.9 Hz), 0.59 (6H, q, *J* = 7.9 Hz); <sup>13</sup>C **NMR (150 MHz, CDCl3):**  $\delta$  135.7, 116.7, 68.4, 44.5, 23.6, 7.0, 5.1; **HRMS (DART) [M+H]**<sup>+</sup> calcd for C<sub>11</sub>H<sub>25</sub>OSi: 201.1675, found: 201.1677.

(*E*)-3,7-Dimethyl-1-(pent-4-en-1-yloxy)octa-2,6-diene (2.168): In an N<sub>2</sub>-filled glove box, an oven-dried flask with a magnetic stir bar was charged with sodium hydride (324 mg, 13.5 mmol). The flask was sealed with a septum, taped and removed from the glove box. To the flask was added dmf (11 mL) and the mixture was cooled to 4 °C. A cooled solution of geraniol (2.08 g, 13.5 mmol) in dmf (4 mL) was added by cannula. The resulting mixture

was allowed to warm to 22 °C and stir for 1 h. To the mixture was then added, 5-bromo-1pentene (0.800 mL, 6.75 mmol). The mixture was heated to 60 °C and allowed to stir for 12 h. At this time the reaction was quenched by addition of H<sub>2</sub>O. The aqueous layer was washed with Et<sub>2</sub>O (3 x 30 mL). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The resulting yellow oil was purified by silica gel chromatography (100% pentane to 1% Et<sub>2</sub>O in pentane) to afford **2.168** (675 mg, 3.03 mmol, 45% yield) as pale yellow oil. **IR (neat):** 2967 (m), 2917 (m), 2853 (m), 1641 (w), 1443 (m), 1376 (m), 1104 (s), 1040 (w), 991 (m), 910 (s) cm<sup>-1</sup>; <sup>1</sup>**H NMR (600 MHz, CDCl<sub>3</sub>):**  $\delta$  5.81 (1H, ddt, *J* = 17.1, 10.2, 6.7 Hz), 5.35 (1H, ddq, *J* = 6.7, 5.4, 1.3 Hz), 5.09 (1H, dddd, *J* = 7.0, 5.6, 2.8, 1.4 Hz), 5.02 (1H, ddt, *J* = 17.1, 1.7 Hz), 4.95 (1H, ddt, *J* = 10.2, 2.1, 1.2 Hz), 3.97 (2H, ddq, *J* = 6.7, 5.3, 0.8 Hz), 3.41 (2H, t, *J* = 6.6 Hz), 2.14–2.08 (2H, m), 2.05–2.00 (2H, m), 1.71–1.64 (10H, m), 1.61–1.58 (3H, m); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$  140.0, 138.5, 131.7, 124.2, 121.2, 114.8, 69.6, 67.4, 39.7, 30.5, 29.1, 26.5, 25.8, 17.8, 16.6; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>15</sub>H<sub>27</sub>O: 223.2062, found: 223.2062.

#### Enoate Cross-Metathesis

Representative procedure for cross-metathesis of *tert*-butyl acrylate with 1-decene. *tert*-Butyl (*Z*)-undec-2-enoate (2.119). In an N<sub>2</sub>-filled glove box, a 4 mL vial with a magnetic stir bar was charged with 1-decene (15.6 mg, 0.111 mmol) and *tert*-butyl acrylate 2.117 (28.5 mg, 0.222 mmol). A septum fitted with an outlet needle was placed on the vial. To the mixture was added a catalyst solution of 2.88 (0.1 M in acetonitrile, 56 µL, 0.0056 mmol, 5.0 mol %) through a syringe and the mixture was allowed to stir at 22 °C for 1 h under a vacuum of 100 torr. The mixture was then exposed to air out of the glove box, and concentrated in vacuo. The resulting residue was purified by silica gel chromatography (1% Et<sub>2</sub>O in hexanes) to afford 2.119 (16.8 mg, 0.0699 mmol, 63% yield, 96:4 *Z:E*) as pale yellow oil. IR (neat): 2958 (m), 2924 (s), 2855 (s), 1717 (s), 1640 (m), 1457 (m), 1411 (m), 1391 (w), 1367 (m), 1293 (w), 1255 (w), 1214 (m), 1149 (s), 1124 (m), 981 (w), 854 (w), 820 (s), 746 (m), 723 (w) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), *Z*-isomer:  $\delta$  [diagnostic *E* isomer signal: 6.86 (1H, dt, *J* = 15.6, 6.9, 6.9 Hz)], 6.11 (1H, dt, *J* = 11.5, 7.5, 7.5 Hz), 5.66 (1H, dt, *J* = 11.6, 1.8, 1.8 Hz), 2.60 (2H, qd, *J* = 7.5, 7.5, 7.4, 1.8 Hz), 1.48 (9H, s, *J*  = 0.9 Hz), 1.37–1.19 (12H, m), 0.88 (3H, m); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  166.2, 149.2, 121.6, 80.1, 32.0, 29.6, 29.5, 29.4, 29.3, 29.0, 28.4, 22.8, 14.3; HRMS (DART) [M+H–C4H8]<sup>+</sup> calcd for C<sub>11</sub>H<sub>20</sub>O<sub>2</sub>: 185.1542; found: 185.1539.

*tert*-Butyl (*Z*)-9-((*tert*-butyldimethylsilyl)oxy)non-2-enoate (2.124). Following the general enoate cross-metathesis procedure, the resulting brown oil was purified by silica gel chromatography (1.5% Et<sub>2</sub>O in hexanes) to afford 2.124 (23.5 mg, 0.0686 mmol, 71% yield, 96:4 *Z*:*E*) as colorless oil. **IR (neat):** 2929 (m), 2856 (m), 1717 (s), 1640 (w), 1472 (m), 1462 (m), 1411 (w), 1390 (w), 1366 (m), 1253 (m), 1214 (m), 1148 (s), 1098 (s), 1041 (w), 1006 (w), 937 (w), 833 (s), 733 (s), 661 (w) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), Z-isomer:  $\delta$  6.10 (1H, dt, *J* = 11.6, 7.5 Hz), 5.66 (1H, dt, *J* = 11.6, 1.8 Hz), 3.59 (2H, t, *J* = 6.6 Hz), 2.60 (2H, qd, *J* = 7.4, 1.8 Hz), 1.53–1.38 (4H, m), 1.48 (9H, s), 1.33 (4H, m), 0.89 (9H, s), 0.04 (6H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  166.2, 149.0, 121.6, 80.1, 63.4, 32.9, 29.3, 29.3, 28.9, 28.4, 26.1, 25.8, 18.5, -5.1; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>39</sub>O<sub>3</sub>Si: 343.2669, found: 343.2683.

*tert*-Butyl (*Z*)-7-(benzylthio)hept-2-enoate (2.125). Following the general enoate crossmetathesis procedure, the resulting brown oil was purified by silica gel chromatography (1% Et<sub>2</sub>O in hexanes) to afford 2.125 (17.2 mg, 0.0561 mmol, 63% yield, >98:2 *Z:E*) as colorless oil. **IR (neat):** 3029 (w), 2976 (m), 2924 (w), 2855 (w), 1712 (s), 1639 (m), 1494 (w), 1453 (m), 1411 (m), 1296 (w), 1236 (s), 1214 (s), 1148 (s), 1071 (w), 853 (w), 821 (m), 768 (w), 742 (m), 700 (s), 564 (w), 471 (w) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), *Z*isomer:  $\delta$  7.27 (4H, d, *J* = 4.3 Hz), 7.22–7.16 (1H, m), 6.02 (1H, dt, *J* = 11.5, 7.5, 7.5 Hz), 5.63 (1H, dt, *J* = 11.6, 1.7, 1.7 Hz), 3.66 (2H, s), 2.56 (2H, qd, *J* = 7.5, 1.8 Hz), 2.38 (2H, q, *J* = 8.0, 7.6 Hz), 1.63–1.50 (4H, m), 1.44 (9H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  166.1, 148.3, 138.7, 128.9, 128.6, 127.0, 122.0, 80.2, 36.4, 31.3, 28.9, 28.4, 28.4; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>18</sub>H<sub>27</sub>O<sub>2</sub>S: 307.1732, found: 307.1742.

*tert*-Butyl (*Z*)-4-((4-methoxybenzyl)oxy)but-2-enoate (2.126). Following the general enoate cross-metathesis procedure for 4 h, the resulting brown oil was purified by silica gel

chromatography (5% Et<sub>2</sub>O in hexanes) to afford **2.126** (19.7 mg, 0.0708 mmol, 62% yield, >98:2 *Z*:*E*) as colorless oil. **IR (neat):** 3000 (w), 2977 (w), 2932 (w), 2852 (w), 2837 (w), 1709 (s), 1612 (m), 1512 (s), 1456 (m), 1410 (m), 1387 (m), 1367 (m), 1301 (s), 1245 (s), 1233 (s), 1152 (s), 1087 (s), 849 (m), 814 (s), 757 (w), 748 (w), 637 (w) cm<sup>-1</sup>; <sup>1</sup>H NMR (**CDCl3, 400 MHz**), *Z*-isomer:  $\delta$  7.32–7.19 (2H, m), 6.92–6.83 (2H, m), 6.31 (1H, dtd, *J* = 11.8, 4.9, 4.9, 0.9 Hz), 5.76–5.67 (1H, m), 4.58 (2H, ddd, *J* = 4.9, 2.4, 0.9 Hz), 4.47 (2H, s), 3.80 (3H, d, *J* = 0.9 Hz), 1.47 (9H, s); <sup>13</sup>C NMR (**CDCl3, 100 MHz**):  $\delta$  165.7, 159.4, 147.1, 130.2, 129.6, 121.5, 114.0, 80.7, 72.6, 68.3, 55.4, 28.3; **HRMS (DART) [M+H]**<sup>+</sup> calcd for C<sub>16</sub>H<sub>23</sub>O<sub>4</sub>: 279.1596, found: 279.1608.

(*Z*)-*tert*-**Butyl 4-phenylbut-2-enoate (2.127).** Following the general enoate cross-metathesis procedure for 4 h, the resulting brown oil was purified by silica gel chromatography (1% Et<sub>2</sub>O in hexanes) to afford **2.127** (8.8 mg, 0.040 mmol, 40% yield, >98:2 *Z*:*E*) as colorless oil. **IR (neat):** 3538 (b), 3402 (b), 3064 (w), 3029 (w), 2928 (m), 1639 (w), 1602 (w), 1493 (w), 1453 (m), 1252 (m), 1027 (m), 914 (m), 764 (m), 700 (s), 643 (m), 631 (m), 560 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), *Z*-isomer:  $\delta$  7.35–7.27 (2H, m), 7.23 (3H, dddd, *J* = 7.4, 2.9, 1.8, 1.1 Hz), 6.25 (1H, dtd, *J* = 11.5, 7.5, 7.4, 0.5 Hz), 5.77 (1H, dtd, *J* = 11.5, 1.8, 1.8, 0.6 Hz), 3.99 (2H, dd, *J* = 7.5, 1.8 Hz), [diagnostic *E* isomer signal: 3.53 (1H, d, *J* = 5.2 Hz)], 1.52 (9H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  166.0, 146.4, 139.9, 128.7, 126.4, 121.9, 80.5, 35.1, 28.4; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>19</sub>O<sub>2</sub>: 219.1385, found: 219.1395.

*tert*-Butyl (*Z*)-5-((triethylsilyl)oxy)hex-2-enoate (2.128). Following the general enoate cross-metathesis procedure for 4 h, the resulting brown oil was purified by silica gel chromatography (1.5% Et<sub>2</sub>O in hexanes) to afford 2.128 (17.5 mg, 0.0582 mmol, 70% yield, >98:2 *Z*:*E*) as colorless oil. **IR (neat):** 2956 (m), 2934 (w), 2912 (w), 2877 (m), 1716 (s), 1640 (w), 1458 (m), 1412 (m), 1392 (s), 1367 (w), 1301 (w), 1226 (m), 1205 (m), 1152 (s), 1130 (s), 1093 (s), 1005 (s), 880 (w), 858 (m), 818 (m), 776 (m), 724 (s), 671 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), *Z*-isomer: δ [diagnostic *E* isomer signal: 6.83 (1H, dt, *J* = 15.2, 7.5, 7.5 Hz)], 6.25 (1H, dt, *J* = 11.7, 7.2, 7.2 Hz), 5.74 (1H, dt, *J* = 11.7, 1.8, 1.8 Hz), 3.95 (1H, pd, *J* = 6.2, 6.2, 6.2, 6.2, 4.9 Hz), 2.81 (1H, dddd, *J* = 15.5, 7.1, 5.0, 1.9
Hz), 2.76–2.64 (1H, m), 1.47 (9H, s), 1.17 (3H, d, J = 6.1 Hz), 1.00–0.89 (9H, m), 0.65– 0.51 (6H, m); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  166.1, 145.3, 122.7, 80.1, 67.9, 38.7, 28.4, 24.0, 7.0, 5.1; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>16</sub>H<sub>33</sub>O<sub>3</sub>Si: 301.2199, found: 301.2187.

*tert*-Butyl (*Z*)-3-cyclohexylacrylate (2.129). Following the general enoate cross-metathesis procedure under ambient pressure with acrylate 2.117 (10.6 mg, 0.0827 mmol) and vinyl cyclohexane (18.2 mg, 0.165 mmol) for 24 h in a sealed vial, the resulting brown oil was purified by basic alumina chromatography (100% hexanes) to afford 2.129 (11.1 mg, 0.0528 mmol, 64% yield, 94:6 *Z*:*E*) as colorless oil. **IR (neat):** 2956 (m), 2923 (s), 2853 (s), 1716 (s), 1640 (m), 1457 (m), 1411 (m), 1390 (w), 1366 (m), 1295 (m), 1214 (s), 1148 (m), 1124 (w), 980 (w), 855 (w), 820 (m), 746 (w), 722 (w) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), *Z*-isomer:  $\delta$  [diagnostic *E* isomer signal: 6.81 (1H, dd, *J* = 15.7, 6.7 Hz)], 5.91 (1H, dd, *J* = 11.6, 9.7 Hz), 5.56 (1H, dd, *J* = 11.6, 1.1 Hz), 3.30–3.12 (1H, m), 1.81–1.60 (6H, m), 1.49 (9H, s), 1.34–0.99 (4H, m); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  166.1, 154.0, 119.8, 80.1, 37.3, 32.6, 28.4, 26.1, 25.7; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>13</sub>H<sub>23</sub>O<sub>2</sub>: 211.1698, found: 211.1703.

*tert*-Butyl (2*Z*,4*E*)-undeca-2,4-dienoate (2.130). Following the general enoate cross-metathesis procedure under ambient pressure for 24 h in a sealed vial, the resulting brown oil was purified by basic alumina chromatography (100% hexanes) to afford 2.130 (7.3 mg, 0.031 mmol, 64% yield, 93:7 *Z*:*E*) as colorless oil. **IR (neat):** 2957 (m), 2923 (m), 2854 (m), 1711 (m), 1638 (m), 1600 (w), 1458 (w), 1417 (w), 1391 (w), 1366 (m), 1258 (w), 1214 (m), 1150 (m), 998 (m), 962 (m), 865 (w), 844 (w), 817 (m), 751 (w), 723 (w) cm<sup>-1</sup>; <sup>1</sup>**H NMR (CDCl3, 600 MHz)**, *Z*-isomer:  $\delta$  7.34 (1H, ddq, *J* = 15.3, 11.3, 1.4 Hz), [diagnostic *E* isomer signal: 7.15 (1H, dd, *J* = 15.3, 10.5 Hz)], 6.47 (1H, td, *J* = 11.3, 0.8 Hz), 6.02 (1H, dtt, *J* = 14.9, 7.0, 0.8 Hz), 5.48 (1H, dq, *J* = 11.4, 0.8 Hz), 2.21–2.16 (2H, m), 1.50 (9H, s), 1.47–1.35 (2H, m), 1.34–1.26 (6H, m), 0.90–0.86 (3H, t, *J* = 7.2 Hz); <sup>13</sup>**C NMR (CDCl3, 150 MHz**):  $\delta$  166.3, 145.2, 144.4, 127.0, 117.6, 80.1, 33.2, 31.8, 29.1, 29.0, 28.4, 22.7, 14.2; **HRMS (DART) [M+H]**<sup>+</sup> calcd for C<sub>15</sub>H<sub>27</sub>O<sub>2</sub>: 239.2011, found: 239.2014.

## Dienoate Cross-Metathesis

Representative procedure for dienoate cross-metathesis. *tert*-Butyl (2*E*,4*Z*)-trideca-2,4-dienoate (2.134b). In an N<sub>2</sub>-filled glove box, a 4 mL vial with a magnetic stir bar was charged with dienoate 2.131b (11.0 mg, 0.0713 mmol) and 1-decene (30.0 mg, 0.214 mmol). A septum fitted with an outlet needle was placed on the vial. A solution containing complex 2.133 (0.1 M in C<sub>6</sub>H<sub>6</sub>, 36  $\mu$ L, 0.0036 mmol, 5.0 mol %) was then added by syringe and the mixture was allowed to stir at 22 °C for 15 min under a vacuum of 100 torr. The solution was then exposed to air out of the glove box, and concentrated in vacuo.

For facile separation of the ligand, the brown oil residue was added thf (1.0 mL) and tbaf (1.0 M in thf, 5.3 µL 0.0053 mmol). The mixture was allowed to stir at 22 °C for 10 min after which it was diluted with hexanes and filtered through a pad of Celite. Purification by silica gel chromatography (100% hexanes to 1% Et<sub>2</sub>O in hexanes) afforded **2.134b** (14.4 mg, 0.0540 mmol, 76% yield, 93:7 *Z:E*) as colorless oil. **IR (neat):** 3006 (w), 2957 (m), 2924 (s), 2854 (m), 1708 (s), 1636 (m), 1605 (m), 1457 (m), 1410 (m), 1391 (m), 1367 (s), 1308 (s), 1256 (s), 1153 (s), 1132 (s), 994 (m), 979 (m), 962 (m), 912 (w), 870 (s), 853 (m), 766 (w), 733 (s), 705 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), *Z*-isomer:  $\delta$  7.52 (1H, ddd, *J* = 15.3, 11.6, 1.1 Hz), [diagnostic (*E,E*) isomer signal: 7.15 (1H, dd, *J* = 15.3, 9.9 Hz)], 6.09 (1H, dddd, *J* = 12.2, 10.6, 1.9, 0.8 Hz), 5.85–5.76 (2H, m), 2.28 (2H, qd, *J* = 7.4, 1.5 Hz), 1.49 (9H, s), 1.39 (2H, m), 1.34–1.20 (10H, m), 0.93–0.83 (3H, m); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 28.8, 14.2; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>17</sub>H<sub>31</sub>O<sub>2</sub>: 267.2324; found: 267.2337.

*tert*-Butyl (2*E*,4*Z*)-trideca-2,4-dien-12-ynoate (desilylated-2.135). Following the general dienoate cross-metathesis procedure, to the brown oil residue was added thf (1 mL) and tbaf (1.0 M in thf, 200  $\mu$ L 0.00200 mmol). The resulting mixture was allowed to stir at 22 °C for 20 min. The mixture was then diluted with hexanes and filtered through a pad of Celite. The supernatant was concentrated and the resulting residue was purified by silica gel chromatography (100% hexanes to 1% Et<sub>2</sub>O in hexanes) to obtain desilylated-2.135 (15.3 mg, 0.0583 mmol, 87% yield, 95:5 *Z*:*E*) as pale yellow oil. **IR (neat):** 3312 (b), 3006 (w), 2927 (m), 2856 (m), 1707 (s), 1636 (m), 1604 (w), 1458 (w), 1411 (w), 1391 (w), 1367 (m), 1309 (m), 1273 (m), 1257 (m), 1141 (s), 1118 (m), 995 (w), 979 (w), 870 (w),

852 (w), 767 (w), 704 (w), 629 (w) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), *Z*-isomer: δ 7.51 (1H, ddt, J = 15.3, 11.6, 1.1 Hz), [diagnostic (*E*,*E*) isomer signal: 7.15 (1H, dd, J = 15.3, 10.1 Hz)], 6.09 (1H, ddtd, J = 11.5, 10.7, 1.6, 0.7 Hz), 5.86–5.75 (2H, m), 2.29 (2H, qd, J = 7.6, 1.7 Hz), 2.18 (2H, td, J = 7.0, 2.6 Hz), 1.94 (1H, t, J = 2.7 Hz), 1.60–1.22 (17H, m); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 166.9, 140.9, 138.6, 126.7, 123.3, 84.8, 80.4, 68.3, 29.4, 28.8, 28.7, 28.5, 28.3, 28.3, 18.5; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>17</sub>H<sub>27</sub>O<sub>2</sub>: 263.2011; found: 263.2011.

*tert*-Butyl (2*E*,4*Z*)-9-(benzylthio)nona-2,4-dienoate (2.136). Following the general dienoate cross-metathesis procedure, the resulting residue was purified by silica gel chromatography (100% hexanes to 5% Et<sub>2</sub>O in hexanes) to afford 2.136 (24.8 mg, 0.0746 mmol, 86% yield, 94:6 *Z*:*E*) was obtained as colorless oil. **IR (neat)**: 3005 (w), 2976 (m), 2929 (s), 2855 (w), 1704 (s), 1634 (m), 1603 (m), 1494 (w), 1477 (w), 1454 (m), 1411 (w), 1391 (w), 1391 (m), 1366 (s), 1308 (s), 1274 (s), 1138 (s), 1071 (w), 1029 (w), 995 (m), 979 (m), 962 (m), 916 (w), 870 (m), 851 (m), 767 (m), 700 (s), 617 (w), 565 (w), 470 (w) cm<sup>-1</sup>; <sup>1</sup>H **NMR (CDCl<sub>3</sub>, 400 MHz**), *Z*-isomer:  $\delta$  7.45 (1H, ddd, *J* = 15.2, 11.5, 1.1 Hz), 7.29–7.15 (5H, m), [diagnostic (*E*,*E*) isomer signal: 7.10 (1H, dd, *J* = 15.4, 10.5 Hz)], 6.10–6.00 (1H, m), 5.77 (1H, d, *J* = 15.2 Hz), 5.74–5.67 (1H, m), 3.66 (2H, s), 2.37 (2H, t, *J* = 7.2 Hz), 2.23 (2H, qd, *J* = 7.5, 1.5 Hz), 1.53 (4H, m), 1.46 (9H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  166.8, 140.2, 138.7, 138.4, 128.9, 128.6, 127.0, 126.9, 123.5, 80.4, 36.4, 31.3, 28.8, 28.6, 28.3, 27.9; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>20</sub>H<sub>29</sub>O<sub>2</sub>S: 333.1888; found: 333.1893.

*tert*-Butyl (2*E*,4*Z*)-6-((4-methoxybenzyl)oxy)hexa-2,4-dienoate (2.137). Following the general dienoate cross-metathesis procedure, the resulting brown oil was purified by silica gel chromatography (100% hexanes to 10% Et<sub>2</sub>O in hexanes) to afford 2.137 as colorless oil (16.7 mg, 0.0798 mmol, 69% yield, >98:2 *Z*:*E*). IR (neat): 3002 (w), 2976 (w), 2934 (w), 2854 (w), 2837 (w), 1706 (s), 1640 (w), 1611 (m), 1513 (m), 1457 (w), 1391 (w), 1367 (m), 1310 (m), 1277 (m), 1248 (s), 1156 (s), 1127 (m), 1085 (m), 1036 (m), 983 (w), 871 (w), 849 (w), 820 (w), 765 (w), 702 (w) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), *Z*-isomer: δ 7.43 (1H, ddd, *J* = 15.2, 11.7, 1.1 Hz), 7.30–7.24 (2H, m), 6.91–6.86 (2H, m), 6.26–6.17 (1H, m), 5.93 (1H, dtt, *J* = 11.0, 6.5, 0.9 Hz), 5.85 (1H, dt, *J* = 15.3, 0.7 Hz), 4.46 (2H, s),

4.28–4.22 (2H, dd, J = 6.8, 1.6 Hz), 3.81 (3H, s), 1.49 (9H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 166.4, 159.5, 137.7, 135.7, 130.1, 129.7, 128.6, 125.2, 114.0, 80.6, 72.4, 65.8, 55.4, 28.3; HRMS (DART) [M+NH4]<sup>+</sup> calcd for C<sub>18</sub>H<sub>28</sub>NO<sub>4</sub>: 322.2018; found: 322.2008.

*tert*-Butyl (2*E*,4*Z*)-11-(((*E*)-3,7-dimethylocta-2,6-dien-1-yl)oxy)undeca-2,4-dienoate (2.138). Following the general dienoate cross-metathesis procedure, the brown oil residue was purified by silica gel chromatography (15% impregnanted with silver nitrate, 10% Et<sub>2</sub>O in hexanes) to afford 2.138 as colorless oil (21.5 mg, 0.0617 mmol, 73% yield, 97:3 *Z*:*E*). **IR (neat)**: 2923 (s), 2853 (m), 1710 (s), 1672 (w), 1636 (m), 1605 (w), 1455 (m), 1410 (w), 1367 (m), 1308 (m), 1273 (m), 1257 (m), 1154 (s), 1130 (m), 1069 (w), 1030 (w), 994 (m), 980 (w), 871 (w), 853 (w), 776 (w), 706 (w) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), *Z*-isomer:  $\delta$  7.58–7.45 (1H, m), [diagnostic (*E*,*E*) isomer signal: 7.15 (1H, dd, *J* = 15.4, 10.3 Hz)], 6.11 (1H, t, *J* = 11.1 Hz), 5.84–5.75 (2H, m), 5.40–5.30 (1H, t, *J* = 6.6 Hz), 5.09 (1H, t, *J* = 6.8 Hz), 3.96 (2H, d, *J* = 6.8 Hz), 3.41 (2H, t, *J* = 6.5 Hz), 2.44–2.31 (2H, m), 2.15–2.06 (2H, m), 2.06–1.99 (2H, m), 1.77–1.67 (5H, m), 1.65 (3H, s), 1.60 (3H, s), 1.49 (9H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  166.8, 140.1, 138.5, 131.7, 127.1, 124.2, 123.5, 121.1, 80.3, 69.3, 67.5, 39.7, 29.6, 28.3, 26.5, 25.8, 25.1, 17.8, 16.6; HRMS (DART) [M+NH4]<sup>+</sup> calcd for C<sub>22</sub>H<sub>40</sub>NO<sub>3</sub>: 366.3008; found: 366.3014.

*tert*-Butyl (2*E*,4*Z*)-7-((triethylsilyl)oxy)octa-2,4-dienoate (2.139). Following the general dienoate cross-metathesis procedure, the resulting brown oil was purified by silica gel chromatography (100% hexanes to 3% Et<sub>2</sub>O in hexanes) to afford 2.139 as colorless oil (24.6 mg, 0.0753 mmol, 89% yield, 95:5 *Z*:*E*). IR (neat): 2956 (m), 2934 (w), 2912 (w), 2877 (m), 1709 (s), 1637 (m), 1605 (w), 1457 (w), 1411 (w), 1391 (w), 1367 (m) 1311 (m), 1281 (s), 1257 (m), 1156 (s), 1125 (s), 1087 (m), 1065 (m), 1004 (s), 982 (m), 963 (m), 871 (m), 854 (m), 740 (s), 725 (s), 672 (w), 610 (w) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), *Z*-isomer:  $\delta$  7.48 (1H, ddd, *J* = 15.2, 11.6, 1.2 Hz), [diagnostic (*E*,*E*) isomer signal: 7.15 (1H, dd, *J* = 15.3, 10.4 Hz)], 6.17 (1H, t, *J* = 11.1 Hz), 5.94–5.83 (1H, m), 5.80 (1H, d, *J* = 15.2 Hz), 3.89 (1H, sext, *J* = 6.0 Hz), 2.42 (2H, ddd, *J* = 7.7, 6.0, 1.5 Hz), 1.49 (9H, s), 1.15 (3H, d, *J* = 6.1 Hz), 0.95 (9H, t, *J* = 7.9 Hz), 0.58 (6H, q, *J* = 7.7 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100

**MHz**): δ 166.7, 138.6, 136.9, 128.1, 123.7, 80.3, 68.1, 38.3, 28.3, 23.8, 7.0, 5.0.; **HRMS** (**DART**) [**M+NH**<sub>4</sub>]<sup>+</sup> calcd for C<sub>18</sub>H<sub>38</sub>NO<sub>3</sub>Si: 344.2621; found: 344.2635.

*tert*-Butyl (2*E*,4*Z*)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)penta-2,4-dienoate (2.140). Following the general dienoate cross-metathesis procedure, the brown oil residue was purified by silica gel chromatography (100% hexanes to 1% Et<sub>2</sub>O in hexanes) to afford 2.140 as colorless oil (13.2 mg, 0.0541 mmol, 64% yield, >98:2 *Z*:*E*). IR (neat): 2978 (m), 2931 (w), 1709 (m), 1631 (w), 1586 (m), 1424 (w), 1391 (w), 1368 (m), 1356 (m), 1303 (m), 1258 (s), 1232 (m), 1137 (s), 1072 (w), 1015 (w), 980 (m), 967 (m), 877 (m), 846 (m), 793 (w), 768 (w), 723 (m), 672 (w) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), *Z*-isomer:  $\delta$  7.96 (1H, ddd, *J* = 15.4, 11.5, 1.0 Hz), 6.89 (1H, t, *J* = 12.4 Hz), [diagnostic (*E*,*E*) isomer signal: 6.70 (1H, dd, *J* = 15.4, 10.6 Hz)], 5.88 (1H, dt, *J* = 15.4, 0.7 Hz), 5.76 (1H, dt, *J* = 13.3, 0.8 Hz), 1.50 (9H, s), 1.30 (12H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  166.3, 147.1, 142.8, 127.2, 83.7, 80.4, 28.3, 25.0.; HRMS (DART) [M+NH4]<sup>+</sup> calcd for C<sub>15</sub>H<sub>29</sub>BNO4: 298.2190; found: 298.2193.

Phenyl (2*E*,4*Z*)-trideca-2,4-dienoate (2.134a). Following the general dienoate cross-metathesis procedure with dienoate 2.131a, the resulting residue was purified by silica gel chromatography (1% Et<sub>2</sub>O in hexanes) to obtain 2.134a as pale yellow oil (18.6 mg, 0.0649 mmol, 84% yield, 96:4 *Z*:*E*). **IR (neat):** 2923 (s), 2853 (m), 1730 (s), 1633 (m), 1592 (w), 1492 (m), 1457 (w), 1411 (w), 1194 (s), 1071 (s); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>), *Z* isomer:  $\delta$  7.79 (1H, ddd, *J* = 15.3, 11.7, 1.1 Hz), 7.41–7.37 (2H, m), 7.25–7.22 (1H, m), 7.15–7.12 (2H, m), 6.21 (1H, dd, *J* = 12.2 10.4 Hz), 6.06 (1H, d, *J* = 15.3 Hz), 5.95 (1H, dtt, *J* = 9.7, 7.8, 1.1 Hz), 2.34 (2H, qd, *J* = 7.6, 1.5 Hz), [diagnostic (*E*,*E*) isomer signal: 2.21 (2H, q, *J* = 6.9 Hz)], 1.43 (2H, m), 1.35–1.24 (10H, m), 0.91–0.86 (3H, m); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 165.8, 151.0, 143.1, 141.6, 129.5, 126.5, 125.8, 121.8, 120.3, 32.0, 29.6, 29.5, 29.4, 29.4, 28.6, 22.8, 14.2; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>27</sub>O<sub>2</sub>: 287.2011, found: 287.2025.

**Phenyl (2***E***,4***Z***)-11-bromoundeca-2,4-dienoate (2.141).** Following the general dienoate cross-metathesis procedure with dienoate **2.131b**, the resulting brown oil was purified by silica gel chromatography (2% Et<sub>2</sub>O in hexanes) to afford **2.141** (19.3 mg, 0.0572 mmol, 87% yield, 94:6 *Z*:*E*)as colorless oil. **IR (neat):** 2929 (m), 2855 (m), 1728 (s), 1633 (m), 1591 (w), 1492 (m), 1456 (w), 1259 (br), 1195 (s), 1128 (s), 1128 (s); <sup>1</sup>H NMR (400 MHz, **CDCI<sub>3</sub>)**, *Z* **isomer:**  $\delta$  7.78 (1H, ddd, *J* = 15.2, 11.7, 0.9 Hz), 7.42–7.36 (2H, m), 7.26–7.21 (1H, m), 7.16–7.11 (2H, m), 6.22 (1H, ddtd, *J* = 11.6, 10.8, 1.5, 0.7 Hz), 6.07 (1H, d, *J* = 15.2), 5.93 (1H, ddt, *J* = 10.8, 7.8, 1.0 Hz), 3.41 (2H, t, *J* = 6.8 Hz), 2.35 (2H, qd, *J* = 7.3, 1.5 Hz), [diagnostic (*E*,*E*) isomer signal: 2.22 (2H, q, *J* = 6.8 Hz)], 1.86 (2H, dq, *J* = 8.7, 6.8 Hz), 1.51–1.41 (4H, m), 1.41–1.32 (2H, m); <sup>13</sup>C NMR (100 MHz, CDCI<sub>3</sub>):  $\delta$  165.8, 150.9, 142.6, 141.4, 129.5, 126.7, 125.8, 121.8, 120.5, 34.0, 32.8, 29.3, 28.5, 28.4, 28.1; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>17</sub>H<sub>22</sub>O<sub>2</sub>Br: 337.0803, found: 337.0813.

## • Synthesis of C1–C12 Fragment of (–)-Laulimalide

(((4S,6R)-7-(Benzyloxy)-6-methylhept-1-en-4-yl)oxy)triethylsilane (2.142). To a flask containing (4S,6R)-7-(benzyloxy)-6-methylhept-1-en-4-ol (218 mg, 0.930 mmol) in CH<sub>2</sub>Cl<sub>2</sub>, stirring at 22 °C, was added imidazole (127 mg, 1.86 mmol) and chlorotriethylsilane (234 µL, 1.39 mmol). The mixture was allowed to stir for 2 h. The mixture was then concentrated and dissolved in pentane. After filtration through a pad of Celite the resulting residue was washed with pentane and filtered again. The supernatant was concentrated in vacuo and the resulting pale yellow oil was purified by silica gel chromatography  $(10\% \text{ Et}_2\text{O in hexanes})$  to afford **2.142** (296 mg, 0.849 mmol, 91% yield) as pale yellow oil. IR (neat): 2954 (m), 2935 (m), 2909 (m), 2876 (m), 1639 (m), 1496 (w), 1455 (m), 1414 (w), 1362 (w), 1238 (w), 1205 (w), 1096 (s), 1073 (m), 1004 (m), 908 (s), 732 (s), 698 (s), 651 (w) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.27 (5H, m), 5.83–5.66 (1H, m), 5.03–4.97 (1H, m), 4.95 (1H, q, J = 1.3 Hz), 4.43 (2H, s), 3.77 (1H, dtd, J = 8.4, 5.8, 4.3 Hz), 3.34–3.22 (1H, m), 3.16 (1H, dt, *J* = 9.0, 6.4 Hz), 2.18 (2H, ddt, *J* = 7.1, 5.8, 1.3 Hz), 1.99-1.84 (1H, m), 1.44 (1H, ddd, J = 13.4, 8.4, 4.6 Hz), 1.19-1.12 (1H, m), 0.94-0.86(12H, m), 0.54 (6H, q, J = 8.1 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  139.0, 135.2, 128.4, 127.6, 127.5, 117.0, 76.5, 73.0, 70.0, 43.0, 41.2, 29.9, 17.4, 7.1, 5.3; HRMS (DART)  $[M+H]^+$  calcd for C<sub>21</sub>H<sub>37</sub>O<sub>2</sub>Si: 349.2563, found: 349.2548.

(*S*)-6-((*R*)-3-(Benzyloxy)-2-methylpropyl)-5,6-dihydro-2H-pyran-2-one (2.144). In an N<sub>2</sub>-filled glove box, a 4 mL vial with a magnetic stir bar was charged with alkene 2.142 (31.5 mg, 0.0904 mmol) and acrylate 2.117 (23.2 mg, 0.181 mmol). A catalyst solution of 2.88 (0.1 M in 10:1 CH<sub>3</sub>CN:PhCN, 22  $\mu$ L, 0.0022 mmol, 2.5 mol %) was added to the mixture. The mixture was allowed to stir at 22 °C for 2 h under a vacuum of 100 torr. The vacuum was then released and to the mixture was added a second catalyst solution of 2.88 (0.1 M in CH<sub>3</sub>CN:PhCN, 22  $\mu$ L, 0.0022 mmol, 2.5 mol %). The solution was allowed to stir at 22 °C for an additional 2 h under a vacuum of 100 torr. The mixture was then exposed to air out of the glove box and concentrated under reduced pressure (81% conv, 91:9 *Z:E*). The brown oil residue containing *tert*-butyl (5*S*,7*R*,*Z*)-8-(benzyloxy)-7-methyl-5-((triethylsilyl)oxy)oct-2-enoate (2.142) was used for the following step without further purification.

To the unpurified mixture containing **2.143** was added toluene (0.1 mL) and *p*-toluenesulfonic acid (1.7 mg, 0.0090 mmol). The vial was then capped and sealed with electrical tape and allowed to stir at 40 °C for 1 h. The mixture was allowed to cool to 22 °C and concentrated under reduced pressure. The resulting dark green oil was then purified by silica gel chromatography (100% hexanes to 10% Et<sub>2</sub>O in hexanes) to afford **2.144** (17.4 mg, 0.0668 mmol, 74% yield) as colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.38–7.26 (5H, m), 6.91–6.81 (1H, m), 6.04–5.98 (1H, m), [diagnostic *E* isomer signal of acyclic enoate **7**: 5.81 (1H, d, *J* = 15.6 Hz)], 4.56 (1H, ddt, *J* = 10.9, 9.2, 4.5 Hz), 4.49 (2H, s), 3.35 (2H, dd, *J* = 6.0, 0.9 Hz), 2.37–2.29 (2H, m), 2.21–2.11 (1H, m), 1.98 (1H, ddd, *J* = 14.2, 9.1, 5.1 Hz), 1.51–1.41 (1H, m), 0.99 (3H, d, *J* = 6.8 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  164.6, 145.2, 138.7, 128.5, 127.6, 121.6, 76.0, 75.9, 73.1, 39.4, 30.1, 29.4, 16.9. The above spectral data match the reported ones.<sup>50</sup>

*tert*-Butyl (Z)-4-((2R,6S)-6-((R)-3-(benzyloxy)-2-methylpropyl)-5,6-dihydro-2H-pyran-2-yl)but-2-enoate (2.146). In an N<sub>2</sub>-filled glove box, a 4 mL vial with a magnetic stir bar was charged with alkene 2.145 (17.2 mg, 0.0601 mmol) and acrylate 2.117 (15.4 mg, 0.120 mmol). A solution of complex 2.88 (0.1 M in 10:1 CH<sub>3</sub>CN:PhCN, 30  $\mu$ L, 0.0030 mmol, 5.0 mol %) was added to the mixture. The solution was allowed to stir at 22 °C for

2 h under a vacuum of 100 torr. The mixture was then removed from the vacuum and a second catalyst solution of 2.88 was added (0.1 M in 10:1 CH<sub>3</sub>CN:PhCN), 30 µL, 0.0030 mmol, 5.0 mol %). The mixture was allowed to stir at 22 °C for 2 h under a vacuum of 100 torr after which it was exposed to air and then the volatiles were removed in vacuo. The resulting brown oil was purified by silica gel chromatography (100% hexanes to 5% EtOAc in hexanes) to afford **2.146** (14.6 mg, 0.0378 mmol, 63% yield, 94:6 Z:E) as colorless oil. IR (neat): 3031 (w), 2975 (m), 2958 (m), 2925 (m), 2854 (m), 1713 (s), 1642 (w), 1454 (m), 1412 (m), 1392 (w), 1366 (m), 1297 (w), 1223 (m), 1150 (s), 1091 (m), 1029 (m), 951 (w), 853 (w), 820 (m), 737 (m), 698 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.38–7.26 (5H, m), [diagnostic signal for E isomer: 6.95–6.81 (1H, m)], 6.28 (1H, dt, J = 11.6, 7.0Hz), 5.86–5.80 (1H, m), 5.77 (1H, d, J = 11.6 Hz), 5.70 (1H, dtd, J = 10.2, 2.6, 1.5 Hz), 4.50 (2H, s), 4.28 (1H, d, J = 9.1 Hz), 3.80 (1H, ddt, J = 12.4, 7.3, 3.6 Hz), 3.36 (1H, dd, J = 9.1, 5.7 Hz), 3.25 (1H, dd, J = 9.1, 6.7 Hz), 3.03–2.81 (2H, m), 2.13–2.00 (1H, m), 2.00-1.87 (2H, m), 1.68 (1H, ddd, J = 14.0, 9.9, 4.1 Hz), 1.48 (9H, s), 1.20 (1H, ddd, J = 14.0, 9.9, 4.1 Hz) 13.5, 9.7, 3.3 Hz), 0.94 (3H, d, J = 6.7 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  166.1, 145.5, 139.0, 129.2, 128.4, 127.7, 127.5, 124.9, 122.8, 80.2, 76.4, 73.1, 72.3, 65.2, 39.6, 33.5, 31.5, 29.8, 28.4, 16.9; **HRMS (DART)** [M+NH4]<sup>+</sup> calcd for C<sub>24</sub>H<sub>38</sub>NO<sub>4</sub>: 404.2801, found: 404.2801; **[α]D**<sup>22</sup> –42.7 (c=1.33, CHCl<sub>3</sub>).



































100 90 f1 (ppm) 




































100 90 f1 (ppm) 





















































-\*



100 90 f1 (ppm) 


















































100 90 f1 (ppm)











































10 -155 f1 (ppm) -20 -115 -120 -125 -130 -135 -140 -145 -150 -160 -165 -170 -175 -180 -185 -190 -195





-150 f1 (ppm) 00 -105 -110 -115 -120 -125 -130 -135 -140 -145 -155 -160 -165 -170 -175 -180 -185 -190 -195 -2

## • NMR Studies with Lewis base-bound Mo-MAP Complexes







## Figure 2.9. <sup>13</sup>C NMR Spectra of Complex 2.88 with Different Additives (600 MHz, 22 °C, C<sub>6</sub>D<sub>6</sub>)



## Figure 2.10. <sup>1</sup>H NMR Spectra of Complex 2.88 with Varying Quantities of CH<sub>3</sub><sup>13</sup>CN (600 MHz, 22 °C, C<sub>6</sub>D<sub>6</sub>)



## Figure 2.11. <sup>13</sup>C NMR Spectra of Complex 2.88 with Varying Quantities of CH<sub>3</sub><sup>13</sup>CN (600 MHz, 22 °C, C<sub>6</sub>D<sub>6</sub>)



Figure 2.12. VT NMR Spectra of Complex 2.88 with 0.5 equiv of CH<sub>3</sub><sup>13</sup>CN (600 MHz, <sup>1</sup>H NMR, *d*<sub>8</sub>-toluene)



Figure 2.13. VT NMR Spectra of Complex 2.88 with 5.0 equiv of CH<sub>3</sub><sup>13</sup>CN (600 MHz, <sup>1</sup>H NMR, *d*<sub>8</sub>-toluene)
## • X-Ray Structure for Complex 2.123

## Table 2.10. Crystal data and structure refinement for 2.123.

Identification code	x13096	
Empirical formula	C54 H56 Mo N2 O3	
Formula weight	876.94	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 10.9333(11) Å	a= 90°.
	b = 18.1477(17) Å	b=99.289(2)°.
	c = 23.563(2) Å	$g = 90^{\circ}$ .
Volume	4614.0(8) Å <sup>3</sup>	
Z	4	
Density (calculated)	1.262 Mg/m <sup>3</sup>	
Absorption coefficient	0.329 mm <sup>-1</sup>	
F(000)	1840	
Crystal size	0.360 x 0.320 x 0.220 mm <sup>3</sup>	
Theta range for data collection	1.423 to 31.506°.	
Index ranges	-16<=h<=16, -24<=k<=26, -34<=l<=34	
Reflections collected	160639	
Independent reflections	15342 [R(int) = 0.0382]	
Completeness to theta = $25.242^{\circ}$	100.0 %	

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7462 and 0.6507
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	15342 / 1 / 553
Goodness-of-fit on F <sup>2</sup>	1.030
Final R indices [I>2sigma(I)]	R1 = 0.0268, wR2 = 0.0671
R indices (all data)	R1 = 0.0318, wR2 = 0.0702
Extinction coefficient	n/a
Largest diff. peak and hole	0.751 and -0.714 e.Å <sup>-3</sup>

	х	у	Z	U(eq)	
Mo(1)	7616(1)	6263(1)	8208(1)	10(1)	
C(1)	6038(1)	6668(1)	8274(1)	14(1)	
C(2)	6431(1)	7436(1)	8305(1)	14(1)	
O(1)	7545(1)	7547(1)	8268(1)	16(1)	
O(2)	5616(1)	7950(1)	8368(1)	16(1)	
C(3)	5961(1)	8749(1)	8397(1)	18(1)	
C(4)	4730(1)	9111(1)	8450(1)	30(1)	
C(5)	6396(1)	8971(1)	7842(1)	23(1)	
C(6)	6922(1)	8895(1)	8926(1)	28(1)	
N(1)	7667(1)	6383(1)	7346(1)	13(1)	
C(11)	5585(1)	6924(1)	6902(1)	22(1)	
C(12)	6799(1)	6565(1)	6865(1)	15(1)	
C(13)	7274(1)	6379(1)	6380(1)	18(1)	
C(14)	8472(1)	6073(1)	6554(1)	17(1)	
C(15)	8688(1)	6079(1)	7144(1)	14(1)	
C(16)	9812(1)	5860(1)	7556(1)	18(1)	
N(2)	7247(1)	5335(1)	8232(1)	12(1)	
C(21)	6927(1)	4597(1)	8234(1)	13(1)	

Table 2.11. Atomic coordinates (  $x \ 10^4$ ) and equivalent isotropic displacement parameters (Å<sup>2</sup>x 10<sup>3</sup>) for 2.123. U(eq) is defined as one third of the trace of the orthogonalized U<sup>ij</sup> tensor.

C(22)	7701(1)	4112(1)	8601(1)	14(1)
C(23)	7410(1)	3364(1)	8572(1)	19(1)
C(24)	6388(1)	3103(1)	8199(1)	21(1)
C(25)	5624(1)	3590(1)	7850(1)	21(1)
C(26)	5866(1)	4343(1)	7859(1)	16(1)
C(27)	5040(1)	4868(1)	7467(1)	22(1)
C(28)	3658(1)	4717(1)	7468(1)	34(1)
C(29)	5333(1)	4837(1)	6856(1)	33(1)
C(17)	8830(1)	4389(1)	9006(1)	17(1)
C(18)	8854(1)	4098(1)	9618(1)	24(1)
C(19)	10036(1)	4181(1)	8792(1)	25(1)
O(3)	8899(1)	6396(1)	8881(1)	13(1)
C(31)	9181(1)	6923(1)	9289(1)	11(1)
C(32)	10300(1)	7313(1)	9304(1)	12(1)
C(33)	10588(1)	7876(1)	9711(1)	13(1)
C(34)	9769(1)	8034(1)	10091(1)	15(1)
C(35)	8683(1)	7631(1)	10096(1)	14(1)
C(36)	8375(1)	7064(1)	9689(1)	12(1)
C(41)	11142(1)	7122(1)	8886(1)	14(1)
C(42)	11621(1)	6411(1)	8867(1)	18(1)
C(43)	12393(1)	6234(1)	8469(1)	26(1)
C(44)	12684(1)	6761(1)	8087(1)	28(1)
C(45)	12224(1)	7467(1)	8106(1)	28(1)

C(46)	11459(1)	7649(1)	8503(1)	22(1)
C(51)	11794(1)	8280(1)	9791(1)	15(1)
C(52)	12888(1)	7906(1)	10006(1)	17(1)
C(53)	14008(1)	8284(1)	10135(1)	21(1)
C(54)	14047(1)	9036(1)	10043(1)	24(1)
C(55)	12970(1)	9411(1)	9828(1)	27(1)
C(56)	11842(1)	9037(1)	9704(1)	23(1)
C(61)	7931(1)	7804(1)	10554(1)	16(1)
C(62)	7710(1)	8538(1)	10686(1)	21(1)
C(63)	7065(1)	8715(1)	11134(1)	27(1)
C(64)	6632(1)	8160(1)	11454(1)	30(1)
C(65)	6846(1)	7430(1)	11327(1)	26(1)
C(66)	7488(1)	7250(1)	10882(1)	20(1)
C(71)	7209(1)	6633(1)	9652(1)	13(1)
C(72)	6063(1)	6991(1)	9590(1)	16(1)
C(73)	4964(1)	6588(1)	9516(1)	20(1)
C(74)	4998(1)	5824(1)	9509(1)	21(1)
C(75)	6133(1)	5461(1)	9584(1)	20(1)
C(76)	7231(1)	5864(1)	9657(1)	16(1)

Mo(1)-N(2)	1.7340(9)
Mo(1)-C(1)	1.9045(11)
Mo(1)-O(3)	1.9543(7)
Mo(1)-N(1)	2.0536(9)
Mo(1)-O(1)	2.3368(8)
Mo(1)-C(2)	2.5218(11)
C(1)-C(2)	1.4563(15)
C(1)-H(1)	0.939(12)
C(2)-O(1)	1.2516(13)
C(2)-O(2)	1.3146(13)
O(2)-C(3)	1.4972(14)
C(3)-C(5)	1.5170(16)
C(3)-C(6)	1.5186(18)
C(3)-C(4)	1.5214(17)
C(4)-H(4A)	0.9800
C(4)-H(4B)	0.9800
C(4)-H(4C)	0.9800
C(5)-H(5A)	0.9800
C(5)-H(5B)	0.9800
C(5)-H(5C)	0.9800
C(6)-H(6A)	0.9800

Table 2.12. Bond lengths [Å] and angles [°] for 2.123.

C(6)-H(6B)	0.9800
C(6)-H(6C)	0.9800
N(1)-C(12)	1.3950(13)
N(1)-C(15)	1.3962(13)
C(11)-C(12)	1.4942(16)
С(11)-Н(11А)	0.9800
C(11)-H(11B)	0.9800
С(11)-Н(11С)	0.9800
C(12)-C(13)	1.3710(15)
C(13)-C(14)	1.4210(16)
С(13)-Н(13)	0.9500
C(14)-C(15)	1.3710(14)
С(14)-Н(14)	0.9500
C(15)-C(16)	1.4919(15)
С(16)-Н(16А)	0.9800
С(16)-Н(16В)	0.9800
С(16)-Н(16С)	0.9800
N(2)-C(21)	1.3856(13)
C(21)-C(22)	1.4152(14)
C(21)-C(26)	1.4164(15)
C(22)-C(23)	1.3930(15)
C(22)-C(17)	1.5192(15)
C(23)-C(24)	1.3882(17)

C(23)-H(23)	0.9500
C(24)-C(25)	1.3909(17)
C(24)-H(24)	0.9500
C(25)-C(26)	1.3922(16)
C(25)-H(25)	0.9500
C(26)-C(27)	1.5178(16)
C(27)-C(29)	1.528(2)
C(27)-C(28)	1.5350(19)
С(27)-Н(27)	1.0000
C(28)-H(28A)	0.9800
C(28)-H(28B)	0.9800
C(28)-H(28C)	0.9800
C(29)-H(29A)	0.9800
C(29)-H(29B)	0.9800
С(29)-Н(29С)	0.9800
C(17)-C(19)	1.5333(17)
C(17)-C(18)	1.5340(16)
С(17)-Н(17)	1.0000
C(18)-H(18A)	0.9800
C(18)-H(18B)	0.9800
C(18)-H(18C)	0.9800
C(19)-H(19A)	0.9800
C(19)-H(19B)	0.9800

C(19)-H(19C)	0.9800
O(3)-C(31)	1.3564(12)
C(31)-C(32)	1.4084(14)
C(31)-C(36)	1.4145(13)
C(32)-C(33)	1.4026(14)
C(32)-C(41)	1.4920(14)
C(33)-C(34)	1.3945(14)
C(33)-C(51)	1.4940(15)
C(34)-C(35)	1.3969(15)
C(34)-H(34)	0.9500
C(35)-C(36)	1.4095(14)
C(35)-C(61)	1.4918(14)
C(36)-C(71)	1.4861(14)
C(41)-C(42)	1.3961(16)
C(41)-C(46)	1.3965(16)
C(42)-C(43)	1.3964(16)
C(42)-H(42)	0.9500
C(43)-C(44)	1.386(2)
C(43)-H(43)	0.9500
C(44)-C(45)	1.380(2)
C(44)-H(44)	0.9500
C(45)-C(46)	1.3926(16)
C(45)-H(45)	0.9500

C(46)-H(46)	0.9500
C(51)-C(56)	1.3911(17)
C(51)-C(52)	1.3972(15)
C(52)-C(53)	1.3935(15)
C(52)-H(52)	0.9500
C(53)-C(54)	1.3825(19)
C(53)-H(53)	0.9500
C(54)-C(55)	1.3843(19)
C(54)-H(54)	0.9500
C(55)-C(56)	1.3960(17)
C(55)-H(55)	0.9500
C(56)-H(56)	0.9500
C(61)-C(62)	1.3983(17)
C(61)-C(66)	1.3996(17)
C(62)-C(63)	1.3980(16)
C(62)-H(62)	0.9500
C(63)-C(64)	1.386(2)
C(63)-H(63)	0.9500
C(64)-C(65)	1.386(2)
C(64)-H(64)	0.9500
C(65)-C(66)	1.3932(15)
C(65)-H(65)	0.9500
C(66)-H(66)	0.9500

- C(71)-C(76) 1.3964(16)
- C(71)-C(72) 1.3982(15)
- C(72)-C(73) 1.3931(15)
- С(72)-Н(72) 0.9500
- C(73)-C(74) 1.3871(19)
- С(73)-Н(73) 0.9500
- C(74)-C(75) 1.3910(17)
- C(74)-H(74) 0.9500
- C(75)-C(76) 1.3934(16)
- C(75)-H(75) 0.9500
- C(76)-H(76) 0.9500
- N(2)-Mo(1)-C(1) 98.85(4)
- N(2)-Mo(1)-O(3) 103.56(4)
- C(1)-Mo(1)-O(3) 115.28(4)
- N(2)-Mo(1)-N(1) 100.26(4)
- C(1)-Mo(1)-N(1) 102.06(4)
- O(3)-Mo(1)-N(1) 131.23(3)
- N(2)-Mo(1)-O(1) 162.95(4)
- C(1)-Mo(1)-O(1) 64.56(4)
- O(3)-Mo(1)-O(1) 81.64(3)
- N(1)-Mo(1)-O(1) 87.71(3)
- N(2)-Mo(1)-C(2) 133.71(4)

- C(1)-Mo(1)-C(2) 35.03(4)
- O(3)-Mo(1)-C(2) 97.70(3)
- N(1)-Mo(1)-C(2) 95.54(3)
- O(1)-Mo(1)-C(2) 29.54(3)
- C(2)-C(1)-Mo(1) 96.33(7)
- C(2)-C(1)-H(1) 123.2(9)
- Mo(1)-C(1)-H(1) 139.9(10)
- O(1)-C(2)-O(2) 125.36(10)
- O(1)-C(2)-C(1) 115.64(9)
- O(2)-C(2)-C(1) 118.99(9)
- O(1)-C(2)-Mo(1) 67.01(6)
- O(2)-C(2)-Mo(1) 167.58(8)
- C(1)-C(2)-Mo(1) 48.64(5)
- C(2)-O(1)-Mo(1) 83.44(6)
- C(2)-O(2)-C(3) 121.44(9)
- O(2)-C(3)-C(5) 109.34(9)
- O(2)-C(3)-C(6) 109.96(9)
- C(5)-C(3)-C(6) 112.94(11)
- O(2)-C(3)-C(4) 101.70(10)
- C(5)-C(3)-C(4) 111.12(10)
- C(6)-C(3)-C(4) 111.19(11)
- C(3)-C(4)-H(4A) 109.5
- C(3)-C(4)-H(4B) 109.5

- H(4A)-C(4)-H(4B) 109.5
- C(3)-C(4)-H(4C) 109.5
- H(4A)-C(4)-H(4C) 109.5
- H(4B)-C(4)-H(4C) 109.5
- C(3)-C(5)-H(5A) 109.5
- C(3)-C(5)-H(5B) 109.5
- H(5A)-C(5)-H(5B) 109.5
- C(3)-C(5)-H(5C) 109.5
- H(5A)-C(5)-H(5C) 109.5
- H(5B)-C(5)-H(5C) 109.5
- C(3)-C(6)-H(6A) 109.5
- C(3)-C(6)-H(6B) 109.5
- H(6A)-C(6)-H(6B) 109.5
- C(3)-C(6)-H(6C) 109.5
- H(6A)-C(6)-H(6C) 109.5
- H(6B)-C(6)-H(6C) 109.5
- C(12)-N(1)-C(15) 107.05(8)
- C(12)-N(1)-Mo(1) 134.89(7)
- C(15)-N(1)-Mo(1) 116.48(7)
- С(12)-С(11)-Н(11А) 109.5
- С(12)-С(11)-Н(11В) 109.5
- H(11A)-C(11)-H(11B) 109.5
- C(12)-C(11)-H(11C) 109.5

- H(11A)-C(11)-H(11C) 109.5
- H(11B)-C(11)-H(11C) 109.5
- C(13)-C(12)-N(1) 108.64(10)
- C(13)-C(12)-C(11) 128.05(10)
- N(1)-C(12)-C(11) 123.28(9)
- C(12)-C(13)-C(14) 108.07(9)
- С(12)-С(13)-Н(13) 126.0
- С(14)-С(13)-Н(13) 126.0
- C(15)-C(14)-C(13) 106.88(10)
- С(15)-С(14)-Н(14) 126.6
- С(13)-С(14)-Н(14) 126.6
- C(14)-C(15)-N(1) 109.35(9)
- C(14)-C(15)-C(16) 130.28(10)
- N(1)-C(15)-C(16) 120.27(9)
- C(15)-C(16)-H(16A) 109.5
- C(15)-C(16)-H(16B) 109.5
- H(16A)-C(16)-H(16B) 109.5
- С(15)-С(16)-Н(16С) 109.5
- H(16A)-C(16)-H(16C) 109.5
- H(16B)-C(16)-H(16C) 109.5
- C(21)-N(2)-Mo(1) 178.17(8)
- N(2)-C(21)-C(22) 118.53(9)
- N(2)-C(21)-C(26) 119.57(9)

- C(22)-C(21)-C(26) 121.86(10)
- C(23)-C(22)-C(21) 117.82(10)
- C(23)-C(22)-C(17) 120.67(10)
- C(21)-C(22)-C(17) 121.50(9)
- C(24)-C(23)-C(22) 121.17(11)
- С(24)-С(23)-Н(23) 119.4
- С(22)-С(23)-Н(23) 119.4
- C(23)-C(24)-C(25) 120.19(11)
- C(23)-C(24)-H(24) 119.9
- C(25)-C(24)-H(24) 119.9
- C(24)-C(25)-C(26) 121.35(11)
- С(24)-С(25)-Н(25) 119.3
- С(26)-С(25)-Н(25) 119.3
- C(25)-C(26)-C(21) 117.58(10)
- C(25)-C(26)-C(27) 120.89(10)
- C(21)-C(26)-C(27) 121.51(10)
- C(26)-C(27)-C(29) 110.82(11)
- C(26)-C(27)-C(28) 112.16(11)
- C(29)-C(27)-C(28) 110.50(11)
- С(26)-С(27)-Н(27) 107.7
- С(29)-С(27)-Н(27) 107.7
- С(28)-С(27)-Н(27) 107.7
- C(27)-C(28)-H(28A) 109.5

- C(27)-C(28)-H(28B) 109.5
- H(28A)-C(28)-H(28B) 109.5
- С(27)-С(28)-Н(28С) 109.5
- H(28A)-C(28)-H(28C) 109.5
- H(28B)-C(28)-H(28C) 109.5
- С(27)-С(29)-Н(29А) 109.5
- С(27)-С(29)-Н(29В) 109.5
- H(29A)-C(29)-H(29B) 109.5
- С(27)-С(29)-Н(29С) 109.5
- H(29A)-C(29)-H(29C) 109.5
- H(29B)-C(29)-H(29C) 109.5
- C(22)-C(17)-C(19) 111.50(9)
- C(22)-C(17)-C(18) 111.44(10)
- C(19)-C(17)-C(18) 109.81(10)
- С(22)-С(17)-Н(17) 108.0
- С(19)-С(17)-Н(17) 108.0
- С(18)-С(17)-Н(17) 108.0
- С(17)-С(18)-Н(18А) 109.5
- С(17)-С(18)-Н(18В) 109.5
- H(18A)-C(18)-H(18B) 109.5
- С(17)-С(18)-Н(18С) 109.5
- H(18A)-C(18)-H(18C) 109.5
- H(18B)-C(18)-H(18C) 109.5

- С(17)-С(19)-Н(19А) 109.5
- С(17)-С(19)-Н(19В) 109.5
- H(19A)-C(19)-H(19B) 109.5
- С(17)-С(19)-Н(19С) 109.5
- H(19A)-C(19)-H(19C) 109.5
- H(19B)-C(19)-H(19C) 109.5
- C(31)-O(3)-Mo(1) 135.52(7)
- O(3)-C(31)-C(32) 118.01(9)
- O(3)-C(31)-C(36) 120.34(9)
- C(32)-C(31)-C(36) 121.65(9)
- C(33)-C(32)-C(31) 118.72(9)
- C(33)-C(32)-C(41) 121.77(9)
- C(31)-C(32)-C(41) 119.51(9)
- C(34)-C(33)-C(32) 119.60(10)
- C(34)-C(33)-C(51) 117.54(9)
- C(32)-C(33)-C(51) 122.66(9)
- C(33)-C(34)-C(35) 122.11(10)
- C(33)-C(34)-H(34) 118.9
- C(35)-C(34)-H(34) 118.9
- C(34)-C(35)-C(36) 119.14(9)
- C(34)-C(35)-C(61) 117.65(9)
- C(36)-C(35)-C(61) 123.15(10)
- C(35)-C(36)-C(31) 118.67(9)

- C(35)-C(36)-C(71) 122.16(9)
- C(31)-C(36)-C(71) 119.12(9)
- C(42)-C(41)-C(46) 118.58(10)
- C(42)-C(41)-C(32) 120.66(10)
- C(46)-C(41)-C(32) 120.76(10)
- C(41)-C(42)-C(43) 120.37(12)
- C(41)-C(42)-H(42) 119.8
- C(43)-C(42)-H(42) 119.8
- C(44)-C(43)-C(42) 120.28(12)
- C(44)-C(43)-H(43) 119.9
- С(42)-С(43)-Н(43) 119.9
- C(45)-C(44)-C(43) 119.78(11)
- C(45)-C(44)-H(44) 120.1
- C(43)-C(44)-H(44) 120.1
- C(44)-C(45)-C(46) 120.28(13)
- C(44)-C(45)-H(45) 119.9
- С(46)-С(45)-Н(45) 119.9
- C(45)-C(46)-C(41) 120.69(12)
- C(45)-C(46)-H(46) 119.7
- С(41)-С(46)-Н(46) 119.7
- C(56)-C(51)-C(52) 118.80(10)
- C(56)-C(51)-C(33) 121.35(10)
- C(52)-C(51)-C(33) 119.60(10)

- C(53)-C(52)-C(51) 120.72(11)
- С(53)-С(52)-Н(52) 119.6
- С(51)-С(52)-Н(52) 119.6
- C(54)-C(53)-C(52) 119.97(11)
- С(54)-С(53)-Н(53) 120.0
- С(52)-С(53)-Н(53) 120.0
- C(53)-C(54)-C(55) 119.81(11)
- C(53)-C(54)-H(54) 120.1
- C(55)-C(54)-H(54) 120.1
- C(54)-C(55)-C(56) 120.48(12)
- С(54)-С(55)-Н(55) 119.8
- С(56)-С(55)-Н(55) 119.8
- C(51)-C(56)-C(55) 120.21(12)
- С(51)-С(56)-Н(56) 119.9
- С(55)-С(56)-Н(56) 119.9
- C(62)-C(61)-C(66) 118.31(10)
- C(62)-C(61)-C(35) 119.74(10)
- C(66)-C(61)-C(35) 121.86(10)
- C(63)-C(62)-C(61) 120.81(12)
- С(63)-С(62)-Н(62) 119.6
- C(61)-C(62)-H(62) 119.6
- C(64)-C(63)-C(62) 120.18(12)
- С(64)-С(63)-Н(63) 119.9

C(62)-C(63)-H(63) 119.9	C(62)-C(63)-H(63)	119.9
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- C(65)-C(64)-C(63) 119.52(11)
- C(65)-C(64)-H(64) 120.2
- C(63)-C(64)-H(64) 120.2
- C(64)-C(65)-C(66) 120.61(13)
- C(64)-C(65)-H(65) 119.7
- С(66)-С(65)-Н(65) 119.7
- C(65)-C(66)-C(61) 120.58(12)
- С(65)-С(66)-Н(66) 119.7
- С(61)-С(66)-Н(66) 119.7
- C(76)-C(71)-C(72) 118.65(10)
- C(76)-C(71)-C(36) 120.81(9)
- C(72)-C(71)-C(36) 120.50(10)
- C(73)-C(72)-C(71) 120.60(11)
- С(73)-С(72)-Н(72) 119.7
- С(71)-С(72)-Н(72) 119.7
- C(74)-C(73)-C(72) 120.18(11)
- С(74)-С(73)-Н(73) 119.9
- С(72)-С(73)-Н(73) 119.9
- C(73)-C(74)-C(75) 119.83(11)
- C(73)-C(74)-H(74) 120.1
- С(75)-С(74)-Н(74) 120.1
- C(74)-C(75)-C(76) 119.99(11)

C(74)-C(75)-H(75)	120.0
C(76)-C(75)-H(75)	120.0
C(75)-C(76)-C(71)	120.73(10)
С(75)-С(76)-Н(76)	119.6
С(71)-С(76)-Н(76)	119.6

Symmetry transformations used to generate equivalent atoms:

Table 2.13. Anisotropic displacement parameters ( $Å^2x \ 10^3$ ) for 2.123. The anisotropicdisplacement factor exponent takes the form:  $-2p^2[h^2 a^{*2}U^{11} + ... + 2hk a^* b^* U^{12}]$ 

	U11	U22	U33	U23	U13	U12	
Mo(1)	12(1)	9(1)	8(1)	0(1)	0(1)	0(1)	
C(1)	16(1)	14(1)	12(1)	1(1)	2(1)	0(1)	
C(2)	18(1)	13(1)	9(1)	1(1)	1(1)	2(1)	
O(1)	16(1)	12(1)	18(1)	0(1)	2(1)	0(1)	
O(2)	20(1)	12(1)	18(1)	1(1)	5(1)	3(1)	
C(3)	26(1)	11(1)	20(1)	1(1)	7(1)	2(1)	
C(4)	34(1)	18(1)	42(1)	2(1)	16(1)	9(1)	
C(5)	34(1)	16(1)	21(1)	5(1)	9(1)	3(1)	
C(6)	44(1)	17(1)	21(1)	-3(1)	0(1)	-2(1)	
N(1)	16(1)	14(1)	9(1)	1(1)	1(1)	0(1)	
C(11)	21(1)	29(1)	15(1)	4(1)	-1(1)	6(1)	
C(12)	18(1)	15(1)	11(1)	3(1)	-1(1)	-1(1)	
C(13)	22(1)	21(1)	10(1)	1(1)	0(1)	-2(1)	
C(14)	22(1)	18(1)	11(1)	0(1)	4(1)	-1(1)	
C(15)	17(1)	13(1)	12(1)	0(1)	2(1)	-1(1)	
C(16)	17(1)	22(1)	15(1)	0(1)	1(1)	2(1)	
N(2)	15(1)	11(1)	10(1)	0(1)	0(1)	0(1)	
C(21)	16(1)	10(1)	12(1)	-1(1)	2(1)	-1(1)	

C(22)	19(1)	12(1)	12(1)	0(1)	2(1)	1(1)
C(23)	26(1)	11(1)	19(1)	2(1)	2(1)	1(1)
C(24)	26(1)	12(1)	25(1)	-1(1)	4(1)	-3(1)
C(25)	20(1)	15(1)	25(1)	-4(1)	0(1)	-3(1)
C(26)	17(1)	14(1)	18(1)	-2(1)	0(1)	0(1)
C(27)	21(1)	16(1)	26(1)	-2(1)	-8(1)	0(1)
C(28)	22(1)	35(1)	43(1)	-3(1)	-2(1)	6(1)
C(29)	36(1)	32(1)	28(1)	10(1)	-2(1)	0(1)
C(17)	22(1)	13(1)	14(1)	1(1)	-2(1)	2(1)
C(18)	33(1)	22(1)	15(1)	4(1)	-4(1)	2(1)
C(19)	21(1)	28(1)	26(1)	-2(1)	0(1)	1(1)
O(3)	14(1)	14(1)	9(1)	-2(1)	0(1)	0(1)
C(31)	13(1)	12(1)	8(1)	-1(1)	0(1)	1(1)
C(32)	13(1)	14(1)	9(1)	0(1)	1(1)	1(1)
C(33)	14(1)	14(1)	11(1)	-1(1)	1(1)	0(1)
C(34)	16(1)	16(1)	12(1)	-4(1)	1(1)	0(1)
C(35)	14(1)	16(1)	10(1)	-2(1)	2(1)	2(1)
C(36)	12(1)	14(1)	9(1)	0(1)	1(1)	1(1)
C(41)	12(1)	20(1)	10(1)	-3(1)	1(1)	-1(1)
C(42)	18(1)	24(1)	13(1)	-3(1)	0(1)	5(1)
C(43)	18(1)	40(1)	18(1)	-9(1)	-1(1)	11(1)
C(44)	14(1)	56(1)	16(1)	-10(1)	3(1)	0(1)
C(45)	26(1)	44(1)	17(1)	-3(1)	9(1)	-11(1)

C(46)	25(1)	25(1)	16(1)	-1(1)	7(1)	-5(1)
C(51)	16(1)	18(1)	11(1)	-3(1)	2(1)	-3(1)
C(52)	17(1)	18(1)	17(1)	-4(1)	3(1)	-1(1)
C(53)	15(1)	27(1)	20(1)	-5(1)	3(1)	-2(1)
C(54)	20(1)	28(1)	24(1)	-5(1)	4(1)	-9(1)
C(55)	28(1)	19(1)	35(1)	2(1)	3(1)	-8(1)
C(56)	22(1)	19(1)	27(1)	2(1)	0(1)	-2(1)
C(61)	14(1)	22(1)	11(1)	-4(1)	1(1)	2(1)
C(62)	21(1)	24(1)	18(1)	-7(1)	2(1)	4(1)
C(63)	25(1)	34(1)	21(1)	-11(1)	3(1)	9(1)
C(64)	24(1)	50(1)	15(1)	-7(1)	6(1)	10(1)
C(65)	24(1)	41(1)	14(1)	1(1)	7(1)	4(1)
C(66)	19(1)	27(1)	12(1)	-1(1)	3(1)	3(1)
C(71)	14(1)	17(1)	9(1)	0(1)	2(1)	-1(1)
C(72)	15(1)	19(1)	13(1)	-1(1)	3(1)	1(1)
C(73)	15(1)	28(1)	16(1)	0(1)	4(1)	-1(1)
C(74)	19(1)	27(1)	18(1)	2(1)	5(1)	-8(1)
C(75)	24(1)	18(1)	18(1)	2(1)	5(1)	-5(1)
C(76)	18(1)	17(1)	13(1)	1(1)	4(1)	0(1)

	Х	у	Z	U(eq)	
H(1)	5245(12)	6515(8)	8328(6)	17	
H(4A)	4130	9013	8102	45	
H(4B)	4849	9644	8497	45	
H(4C)	4418	8911	8785	45	
H(5A)	7188	8730	7818	35	
H(5B)	6502	9507	7835	35	
H(5C)	5777	8820	7514	35	
H(6A)	6603	8729	9270	42	
H(6B)	7099	9424	8956	42	
H(6C)	7685	8626	8893	42	
H(11A)	5130	7006	6514	33	
H(11B)	5732	7398	7102	33	
H(11C)	5098	6604	7116	33	
H(13)	6872	6443	5994	22	
H(14)	9019	5898	6309	20	
H(16A)	10429	5650	7343	27	
H(16B)	9585	5492	7825	27	

Table 2.14. Hydrogen coordinates (x  $10^4$ ) and isotropic displacement parameters (Å<sup>2</sup>x  $10^3$ ) for 2.123.

H(16C)	10162	6294	7770	27
H(23)	7919	3026	8812	23
H(24)	6211	2590	8182	25
H(25)	4922	3405	7600	25
H(27)	5221	5379	7616	27
H(28A)	3427	4249	7271	51
H(28B)	3164	5117	7267	51
H(28C)	3502	4688	7865	51
H(29A)	6199	4978	6858	49
H(29B)	4789	5178	6610	49
H(29C)	5200	4335	6705	49
H(17)	8781	4939	9019	20
H(18A)	8062	4208	9745	36
H(18B)	9529	4336	9879	36
H(18C)	8986	3563	9624	36
H(19A)	10094	3643	8767	38
H(19B)	10745	4368	9062	38
H(19C)	10041	4397	8412	38
H(34)	9956	8430	10356	18
H(42)	11420	6046	9126	22
H(43)	12721	5750	8461	31
H(44)	13198	6637	7812	34
H(45)	12431	7830	7847	34

H(46)	11149	8138	8514	26	
H(52)	12868	7389	10064	20	
H(53)	14744	8025	10286	25	
H(54)	14811	9293	10127	29	
H(55)	12998	9927	9764	33	
H(56)	11106	9300	9561	27	
H(62)	8003	8922	10468	25	
H(63)	6922	9216	11219	32	
H(64)	6193	8279	11758	35	
H(65)	6551	7049	11546	31	
H(66)	7627	6748	10799	23	
H(72)	6032	7514	9598	19	
H(73)	4190	6837	9470	23	
H(74)	4248	5550	9454	25	
H(75)	6159	4937	9584	24	
H(76)	8004	5613	9711	19	

• <sup>1</sup>H and <sup>13</sup>C NMR Spectra of Acyclic Enoate CM Studies

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## **Chapter 3**

## Application of *E*-Selective Catalytic Ring-Closing Metathesis in the Total Synthesis of Dolabelides A, B, C and D

## 3.1 Introduction

Within the realm of natural products, many of these molecules possess trisubstituted olefins and in particular, within a macrocycle. These alkene functionalities often prove to be critical to the biological activity of the compound. Over the last two decades, catalytic ring-closing metathesis (RCM) has been one of the most commonly used strategies for closure of these macrocycles, allowing for easy access to the alkene. In other cases, the olefin handle allows for further transformations post-cyclization. In cases with lactone macrocycles, RCM allows for an alternative strategy to macrolactonization that eliminates the need for additional protection/deprotection steps for the requisite alcohol and carboxylic acid.

Catalytic RCM has been viewed by many groups as the most direct strategy to synthesize macrocyclic rings and even a key step in many natural product syntheses.<sup>1</sup> However, the stereochemical outcome of the reaction is often unpredictable due to the low degree of kinetic control of the stereoselectivity during the formation of the macrocyclic alkene. <sup>2</sup> Though altering reaction conditions can sometimes render improved stereoselectivities, the ratio of the *Z* and *E* isomers are determined by the thermodynamics of the substrate conformation. These thermodynamics generally lead to mixtures of the two isomers. In the case of disubstituted olefins, there is almost a 1.0 kcal/mol preference for the *E* isomer. On the other hand, there can be essentially no energetic difference between

For reviews regarding applications of catalytic olefin metathesis in natural product synthesis, see: (a) Love, J. A. *Handbook of Metathesis Vol. 2* (Ed.: R. H. Grubbs), Wiley-VCH, Weinheim, Germany, 2003, 296–322. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* 2005, 44, 4490–4527. (c) *Metathesis in Natural Product Synthesis* (Eds.: Cossy, J.; Arsenyadis, S.; Meyers C.) Wiley-VCH, Weinheim, Germany, 2010, 149–182. (d) Fürstner, A. *Chem. Commun.* 2011, 47, 6505–6511.

<sup>(2) (</sup>a) Gradillas, A.; Perez-Castells, J. Angew. Chem., Int. Ed. 2006, 45, 6086–6101. (b) See Ref. 1c.
the two stereoisomers in trisubstituted olefins, making this a comparably more challenging transformation.<sup>3</sup> As catalytic RCM is often a key late-stage step in a total synthesis, having poor chemoselectivity is quite detrimental to the yield of the metathesis step as well as the overall yield of the synthesis.

Over many years, our group has worked on development of new Mo- and W-based catalysts to achieve high selectivity to generate both Z and E alkenes through metathesis reactions.<sup>4</sup> This class of catalysts has been able to deliver the desired isomer kinetically as well as prevent adventitious post-metathesis isomerization of the cross-metathesis (CM) product. More recently, methods towards synthesizing both E and Z trisubstituted acyclic olefins by catalytic CM have been established by a stereoretentive reaction that generates high value trisubstituted alkenes from easily accessible stereodefined alkenes.<sup>5</sup> Here in this chapter, we will illustrate a new route towards the synthesis of dolabelide and additionally, an application of this stereoretentive metathesis to a macrocyclic system.

#### 3.2 Background

In 1995, the isolation and characterization of two 22-membered macrolides dolabelides A (**3.1**) and B (**3.2**) were reported by Ojika and Yamada (Figure 1).<sup>6</sup> These molecules were isolated from the Japanese sea hare Dolabella auricularia and were found to exhibit cytotoxicity towards HeLa-S<sub>3</sub> cells with IC<sub>50</sub> values of 6.3 and 1.3  $\mu$ g/mL, respectively. Yamada isolated and characterized two new family members dolabelides C (**3.3**) and D (**3.4**) two years later.<sup>6</sup> The two new marine macrolides also exhibit cytotoxicity towards the same cervical cancer cells of IC<sub>50</sub> values of 1.9 and 1.5  $\mu$ g/mL, respectively. At this point and time, the mechanism of action is unknown.

<sup>(3)</sup> Cuvigny, T.; Hervé du Penhoat, C.; Julia, M. Tetrahedron Lett. 1980, 21, 1331–1334.

<sup>(4) (</sup>a) Singh, R.; Schrock, R. R.; Muller, P.; Hoveyda, A. H. J. Am. Chem. Soc. 2007, 129, 12654–12655.
(b) Malcolmson, S. J.; Meek, S. J.; Schrock, R. R.; Hoveyda, A. H. Nature 2008, 456, 933–937. (c) Sattely, E. S.; Meek, S. J.; Malcolmson, S. J.; Schrock, R. R.; Hoveyda, A. H. J. Am. Chem. Soc. 2009, 131, 943–953.

<sup>(5)</sup> Nguyen, T. T.; Koh, M. J.; Mann, T. J.; Schrock, R. R.; Hoveyda, A. H. Nature 2017, 552, 347-354.

<sup>(6) (</sup>a) Ojika, M.; Nagoya, T.; Yamada, K. *Tetrahedron Lctt.* 1995, *36*, 7491–7494. (b) Suenaga, K.; Nagoya, T.; Shibata, T.; Kigoshi, H.; Yamada, K. *J. Nat. Prod.* 1997, *60*, 155–157.



Figure 3.1. Structures of the family members of dolabelides.

The precise structure of these molecules were determined mainly by 2D NMR and mass spectrometry. All four molecules of the dolabelide family share 11 stereogenic centers. Of the eleven, eight are oxygen-bearing stereogenic centers, containing both 1,3-*anti* and 1,3-*syn*-diols. Two *E* trisubstituted olefins are also present, one of which is within the macrocycle and the other which is exocyclic. Because of the structural complexity of this family of molecules, they have garnered much attention by a number of synthetic groups.

While endocyclic trisubstituted alkenes have been integrated through commercially available starting materials in certain cases, RCM still remains as one of the most common ways to make this functionality when these olefins cannot be incorporated in more functionalized molecules, such as dolabelide. A number of other studies<sup>7</sup> have been

<sup>(7) (</sup>a) Grimaud, L.; de Mesmay, R.; Prunet, J. Org. Lett. 2002, 4, 419. (b) Schmidt, D. R.; Park, P. K.; Leighton, J. L. Org. Lett. 2003, 5, 3535–3537. (c) Desroy, N.; Le Roux, R.; Phansavath, P.; Chiummiento, L.; Boninib, C.; Genêt, J.-P. Tetrahedron Lett. 2003, 44, 1763–1766. (d) Le Roux, R.; Desroy, N.; Phansavath, P.; Genêt, J.-P. Synlett 2005, 429–431. (e) Keck, G. E.; McLaws, M. D. Tetrahedron Lett. 2005, 46, 4911–4914. (f) Vincent, A.; Prunet, J. Synlett, 2006, 2269–2271. (g) Roche, C.; Desroy, N.; Haddad, M.; Phansavath, P., Genêt, J.-P. Org. Lett. 2008, 10, 3911–3914. (h) Whitehead, A. Waetzig, J. D.; Thomas, C. D.; Hanson, P. R. Org. Lett. 2008, 10, 1421–1424. (i) Waetzig, J. D.; Hanson, P. R. Org.

reported on synthesizing smaller fragments, but only two total syntheses<sup>8,9</sup> have been accomplished, both of which incorporate RCM to generate the macrocyclic trisubstituted olefin (Figure 3.2). Leighton disclosed the first total synthesis of dolabelide D in 2006, and then, in 2011, Hanson reported his total synthesis of dolabelide C. In both of these syntheses, the endgame includes utilizing an esterification/late-stage RCM sequence to complete the macrolide skeleton. These disconnections lead to two fragments of similar complexity, the C1–C14 and C15–C30 segments.





#### 3.2.1. Leighton: Silyl-based Allylations and Rhodium-catalyzed Formylations

Leighton's strategy was to connect the C1–C14 and C15–C30 pieces through a Yamaguchi esterification and complete the molecule through RCM as his final step. His approach to arrive at the C1–C14 carboxylic acid was to dissect it at the C7–C8 bond through a boron aldol reaction. Starting with methacrolein **3.5**, diene **3.7** is obtained to through an enantio- and diastereoselective Leighton allylation with *ent*-**3.6** (61% yield, 94:6 er, >20:1 dr).<sup>10</sup> The diene sets the stage for a chemoselective Rh-catalyzed hydroformylation<sup>11</sup> of the monosubstituted olefin and then a subsequent diastereoselective

*Lett.* **2008**, *10*, 109–112. (j) Braun, M. G.; Vincent, A.; Boumediene, M.; Prunet, J. J. Org. Chem. **2011**, *76*, 4921–4929. (k) Yadav, J. S.; Nayak, S.; Sabitha, G. RSC Adv. **2013**, *3*, 21007–21015.

<sup>(8)</sup> Park, P. K.; O'Malley, S. J.; Schmidt, D. R.; Leighton, J. L. J. Am. Chem. Soc. 2006, 128, 2796–2797.

<sup>(9)</sup> Hanson, P. R.; Chegondi, R.; Nguyen, J.; Thomas, C. D.; Waetzig, J. D.; Whitehead, A. J. Org. Chem. **2011**, *76*, 4358–4370.

<sup>(10)</sup> Kubota, K.; Leighton, J. L. Angew. Chem., Int. Ed. 2003, 42, 946-948.

<sup>(11)</sup> Breit, B.; Seiche, W. Synthesis 2001, 1-36.

hydroboration<sup>12</sup> to afford 1,1-disubstituted olefin **3.8** in 13:1 dr. Aldehyde **3.9** can then be attained in four steps of protecting group and oxidation state manipulations. The other half of the fragment begins with enantioselective Leighton crotylation of **3.10** with silyl-based allylating reagent **3.11** in 80% yield and 95:5 er.<sup>13</sup> The subsequently protected alcohol was subjected to a Wacker oxidation to arrive at methyl ketone **3.13**. Aldehyde **3.9** and ketone

Scheme 3.1. Leighton's synthesis of acid fragment C1–C14.



(12) Still, W. C.; Barrish, J. C. J. Am. Chem. Soc. 1983, 105, 2487-2489.

(13) Hackman, B. M.; Lombardi, P. J.; Leighton, J. L. Org. Lett. 2004, 6, 4375-4377.

**3.13** were coupled through a boron aldol reaction that resulted in 10:1 dr of **3.14**, based on the 1,5-*anti* relationship with a para-methoxybenzyl (PMB) protecting group.<sup>14</sup> The ketone was reduced in the presence of L-Selectride to obtain alcohol **3.15** with 5:1 dr. Three subsequent steps from alcohol **3.15** provides the carbon skeleton of the northern fragment as acid **3.16**.

With chiral silane  $3.17^{15}$  at hand, Leighton and co-workers applied their Rhcatalyzed tandem silylformylation-crotylsilylation<sup>16</sup> and silyl protection to arrive at 1,5-*syn* diol **3.18** as a 4:1 mixture of diastereomers. The ensuing Brook-type rearrangement of the protected alcohol followed by trapping with methyl iodide leads to protected ether **3.19**. The terminal alkene is oxidized to the methyl ketone through a Wacker oxidation that also allowed for cleavage of a silyl ether and the resulting alcohol was protected as acetate **3.20**. The long chain was appended through an aldol reaction with (+)-(ipc)<sub>2</sub>BCl and 5-hexenal to deliver **3.21**. An *anti*-diastereoselective reduction inputs the final desired stereogenic center (**3.22**). Two protection/deprotection steps complete the southern alcohol fragment **3.23**.

<sup>(14) (</sup>a) Vulpetti, A.; Bemardi, A.; Gennari, C.; Goodman, J. M.; Paterson, I. *Tetrahedron* 1993, 49, 685–696. (b) Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. J. Am. Chem. Soc. 1994, 116, 11287–11314. (c) Paton, R. S.; Goodman, J. M. J. Org. Chem. 2008, 73, 1253–1263.

<sup>(15)</sup> Schmidt, D. R.; O'Malley, S. J.; Leighton, J. L. J. Am. Chem. Soc. 2003, 125, 1190-1191.

 <sup>(16) (</sup>a) Zacuto, M. J.; O'Malley, S. J.; Leighton, J. L. J. Am. Chem. Soc. 2002, 124, 7890. (b) Zacuto, M. J.;
 O'Malley, S. J.; Leighton, J. L. Tetrahedron 2003, 59, 8889.



Scheme 3.2. Leighton's synthesis of alcohol fragment C15–C30.

The two fragments **3.16** and **3.23** were brought together through a Yamaguchi esterification in high yield (74%). Protecting group removals led to the diene substrate **3.25** for RCM. Upon subjection to 25 mol % of Grubbs second-generation complex **3.26**, all of **3.25** was consumed and a mixture of 55:45 *E:Z* of **3.4** was observed in the unpurified mixture. Unfortunately, only 31% of the *E* isomer was isolated in the last step. The RCM presented here is a classic example of substrate-controlled selectivity, highlighting the necessity of a better design of an RCM system to help favor the formation of the *E* macrocycle.



Scheme 3.3. Leighton's RCM attempt to dolabelide D.

# 3.2.2. Hanson: Phosphate-tether-mediated Strategy

Five years later, Hanson tackled dolabelide C through a similar approach by bringing two fragments together through an esterification and closing the ring through a late-stage RCM. The stereochemistry is set through diol **3.27**. Triene **3.29** is formed by reacting diol **3.27** with phosphanediamine **3.28**. The triene was cyclized in the presence of Grubbs' 2<sup>nd</sup>-generation complex **3.30** in good yield (85–90% yield). The two enantiomers of bicyclic phosphate **3.31** were used as starting points for the two halves of the molecule.

Scheme 3.4. Hanson's synthesis of chiral phosphate-tethers.



The exocyclic olefin of **3.31** was coupled with **3.32** with Ru-complex **3.30** to arrive at **3.33**. The newly generated alkene was subjected to a diimide reduction with 2-nitrobenzenesulfonylhydrazide to furnish **3.34** with high chemoselectivity and high yield. Subsequent Pd-catalyzed formate reduction and methylation led to selective opening of the

ring to arrive at terminal olefin **3.35** in 87% yield. Aldehyde **3.36** was synthesized in three steps from **3.35**, setting the stage to complete the carbon skeleton. Addition of the Grignard reagent, derived from iodide **3.37**, to the aldehyde and oxidation of the proceeding alcohol garnered **3.38** in 95% and 90% yield, respectively. The acetonide was cleaved by the treatment of CeCl<sub>3</sub>·7H<sub>2</sub>O, without interference with the TBS ether. Evans' conditions for the Narasaka-Prasad *syn*-reduction of the ketone furnished triol **3.39** with the proper

Scheme 3.5. Hanson's approach to C1–C14 fragment.



stereochemistry with complete diastereoselectivity.<sup>17</sup> Final functional group manipulations over four steps yielded target acid **3.40**.

With the other enantiomer of **3.31**, terminal olefin **3.41** was appended through aforementioned CM/reduction strategy (cf. Scheme 3.5) for the previous fragment to furnish **3.42**. Methyl cuprate addition yielded the propionate unit in 91% yield. The phosphate group was easily removed through LiAlH<sub>4</sub> reduction to diol **3.43**. Terminal olefin and aldehyde were installed over a series of steps to arrive at fragment **3.44**. The remainder of the chain was appended through addition of the organolithium species derived from iodide **3.45**, but with poor stereoselectivity of 1:1 dr of **3.46**. By oxidizing the alcohol and reducing the ketone again, the selectivity could be improved to 2.7:1 dr.

Scheme 3.6. Hanson's approach to C15–C30 fragment.



(17) (a) Chen, K. M.; Hardtmann, G. E.; Prasad, K.; Repič, O.; Shapiro, M. J. *Tetrahedron Lett.* 1987, 28, 155–158. (b) Evans, D. A.; Chapman, K. T.; Carreira, E. M. J. Am. Chem. Soc. 1988, 110, 3560–3578.

The two fragments **3.38** and **3.46** were strung together through Yamaguchi esterification to obtain diene **3.47** (Scheme 3.7). Four more steps led to RCM substrate **3.48** free of protecting groups. Upon subjection to 20 mol % of Grubbs second-generation complex **3.26**, Hanson and co-workers observed complete consumption of **3.46**. However, they observed similar results to that of Leighton and co-workers, where most of the material had been converted to byproducts and only 21% yield of the *E* isomer of dolabelide C was isolated. Attempts with catalysts with different aryl groups on the N-heterocyclic carbene (NHC) (**3.50** and **3.51**) or phosphine initiators (**3.49**) only led to similarly non-selective results (Table 1). The set of inferior results with the commercially available Ru-based complexes, once again, underlines the need for an enhanced system for RCM for macrocycles favoring the *E* isomer.







Table 1. Screening of Catalysts for 3.48 to dolabelide C.

#### 3.2.3. Representative Methods for Synthesis of Trisubstituted Alkenes

Due to the prevalence of trisubstituted alkenes, particularly 2-methyl-2-butenyl type moieties, in biologically active molecules, there has been progress towards new strategies to effectively synthesize this class of olefins. Fürstner and co-workers developed a trans-hydrostannation strategy of propargylic alkynols to afford *E*-trisubstituted olefins.<sup>18</sup> The method highlights the high regioselectivity as well as the high efficiency of the trans-hydrostannation of internal alkynes. However, the high selectivity is afforded only if there is a proximal alcohol to assist in directing the hydrostannation (Figure 3.3). The scope of the method indicates that the farther away the alcohol or directing group sits, the lower the proximal-to-distal hydrostannation ratio.

Figure 3.3. Proposed Intermediate Complex for trans-Hydrostannation.



<sup>(18) (</sup>a) Rummelt, S. M.; Radkowski, K.; Roşca, D.-A.; Fürstner, A. J. Am. Chem. Soc. 2015, 137, 5506-5519.
(b) Lehr, K.; Mariz, R.; Leseurre, L.; Gabor, B.; Fürstner, A. Angew. Chem., Int. Ed. 2011, 50, 11373-11377. (c) Roşca, D.-A.; Radkowski, K.; Wolf, L. M.; Wagh, M.; Goddard, R.; Thiel, W. Fürstner, A. J. Am. Chem. Soc. 2017, 139, 2443-2455.

In the synthesis of macrocycle 5,6-dihydrocineromycin B, a relative of antibiotic compounds ingramycin and cineromycin B, Fürstner generates the macrocycle through alkyne RCM and applies the trans-hydrostannation strategy to arrive at compound **3.56** as a single isomer (Scheme 3.8).<sup>19</sup> Absolute chemoselectivity for the alkyne over the alkene, as well as complete regioselectivity with respect to the alkyne is observed. While the selectivities were not always perfect in the acyclic systems reported in the substrate scope, a more complex macrocyclic system shows better regioselectivity between the proximal and distal positions of the alkyne (with respect to the propargylic alcohol). Although the trans-hydrostannation works well, the final product must include the methyl unit. To afford the methyl substituent, a subsequent Stille coupling is performed to arrive at the final compound **3.57**. The authors noted that Stille coupling with methyl iodide was not very common, but were able to find reaction conditions that promoted the cross-coupling.<sup>20</sup> Fast addition of the reagents allowed for stannane **3.56** was converted to methyl alkene **3.57** in 92% yield.

<sup>(19)</sup> Rummelt, S. M.; Preindl, J.; Sommer, H.; Fürstner, A. Angew. Chem., Int. Ed. 2015, 54, 6241 –6245.

<sup>(20)</sup> Fürstner, A.; Funel, J.-A.; Tremblay, M.; Bouchez, L. C.; Nevado, C.; Waser, M.; Ackerstaff, J.; Stimson, C. C. *Chem. Commun.* **2008**, 2873–2875.



Scheme 3.8. Macrocyclic Trisubstituted Alkene Synthesis through trans-Hydrostannation/Cross-Coupling.

Young and co-workers developed a strategy to access trisubstituted macrocyclic *E*alkenyl siloxanes in 2011.<sup>21</sup> Two years later, they found that they were capable of accessing *E* trisubstituted macrocycles by exchanging the silyl group for a bromide and subjecting the halide to cross-coupling reaction conditions. By utilizing the sterics of the siloxy group for the RCM, Young *et al.* were able to access the *E* macrocycle (**I** to **II**, Scheme 3.9). The bromonium ion is formed in the presence of bromine and the silyl group is removed to eliminate the bromine (**VI** or **VII**) to yield the alkenyl bromide **VIII** with stereoinversion. While the reaction may seem to work well at first glance, the *E* geometry of the siloxane alkene is not always generated preferentially as it is determined by the size of the ring. Additionally, treating more precious compounds in the presence of bromine and tetrabutylammonium fluoride may lead to undesired reactions with other functionalities.

<sup>(21) (</sup>a) Wang, Y.; Jimenez, M.; Hansen, A. S.; Raiber, E.-A.; Schreiber, S. L.; Young, D. W. J. Am. Chem. Soc. 2011, 133, 9196–9199. (b) Wang, Y.; Jimenez, M.; Sheehan, P.; Zhong, C.; Hung, A. W.; Tam, C. P.; Young, D. W. Org. Lett. 2013, 15, 1218–1221.

Even so, the reaction requires the synthesis of the hydrosilylated alkenyl siloxane from an alkyne by hydrosilylation in addition to the RCM and bromination step to arrive at the *E*-alkenyl bromide. These steps also do not include the final cross-coupling that is required to afford the methyl substituent in the alkenyl position.

Scheme 3.9. Macrocyclic Trisubstituted Alkene RCM and Bromide Exchange.



Our group has developed a Mo-catalyzed stereoretentive method for synthesizing trisubstituted alkenyl halides (Scheme 3.10).<sup>5</sup> Initial studies found that with terminal olefins, the reactivity was poor and also provided low selectivity. Nonetheless, when stereodefined trisubstituted alkenes were utilized (**3.62**), the stereochemistry relayed to the final product (**3.65**, 95:5 *E:Z* or 91:9 *Z:E*) and good reactivity was observed. *Z* and *E* trisubstituted alkenes can be synthesized, but for our purposes, we are interested in the synthesis and the stereochemical model to the *E* isomer.



Scheme 3.10. Mo-Catalyzed Stereoretentive CM to Generate Trisubstituted Alkenes.

In cases involving a stereodefined trisubstituted alkene (such as **3.62**), there is a greater energetic difference between the two metallacyclobutane intermediates. Intermediates **IX** and **X** each lead to the *E* and *Z* isomer of the desired trisubstituted product, respectively. Still, there are two steric interactions that make **X** less favored: 1) There is a greater penalizing interaction between the larger R group (R<sub>L</sub>) with the chloride than with the smaller R group (R<sub>S</sub>). 2) Because we have introduced a methyl group (versus a proton with a terminal olefin), a disfavored steric interaction between the methyl group and the large rotating aryloxide now exists. Because Ca is in closer proximity to the sizeable ligands than C $\beta$ ,<sup>22</sup> having any substituents pointing towards the large ligand Ca is more penalizing than that C $\beta$ .





<sup>(22)</sup> Marinescu, S. C.; Schrock, R. R.; Müller, P.; Hoveyda, A. H. J. Am. Chem. Soc. 2009, 131, 10840-10841.

# **3.3 Synthesis Strategy**

With the many studies on synthesizing the fragments of dolabelide, we were interested in designing a new route that would incorporate modern methods to synthesize the linear precursors in an efficient manner. Like the previously discussed total syntheses,<sup>8,9</sup> we split the molecule into two similarly sized fragments: the C1–C14 (**3.66** or **3.67**) and C15–C30 (**3.74** or **3.75**) carbon chains (cf. Scheme 2). The top fragment would be disconnected at the C7–C8 bond through a boron aldol between **3.68** and **3.71** (Scheme 3.8). The C7-aldehyde would be incorporated through a homologation and the acid portion would be introduced through oxidation of terminal olefin **3.69**, which can be obtained through crotylation of the enantiomerically pure commercially available diol **3.70**. The hydroxyl precursor of ketone **3.71** would be installed through a boron conjugate addition to enone **3.72** that would be derived from ester **3.73**.

Scheme 3.12. Retrosynthesis of Fragment C1–C14.



Similar strategies would be applied to synthesize the latter half of dolabelide (Scheme 3.9). The alkene of **3.74** and **3.75** would originate from protoboration/cross-coupling. The hydroxyl group of ethyl ketone **3.76** would be installed through a boron conjugate addition to enone **3.77** that would be derived from a higher oxidation state of commercially available alcohol **3.78**. The bottom fragment would be built through a boron aldol between aldehyde **3.76** and ketone **3.79**. The aldehyde would be installed through an allylic oxidation. The carbon skeleton would be built through a diboration/cross-coupling sequence from pentene and alkenyl bromide **3.81**.



Scheme 3.13. Retrosynthesis of Fragment C15-C30.

Post-esterification, the diene substrate would be ready to be subjected towards RCM conditions. We designed the substrate based on the stereochemical model of the acyclic system (cf. Scheme 3.10). Using the rationale as the basis of our RCM model, we designed two models that would facilitate the formation of the *E* macrocycle. The first model would consist of using a stereodefined trisubstituted alkene and either a terminal olefin or a 1,2-disubstituted olefin, *cis* or *trans*. Due to the sterics of the large neophylidene group of **XI**, initiation would occur on the mono- or disubstituted olefin (alkenyl-G of substrate). Reaction with the trisubstituted would occur in the aligned fashion shown in **XII**, based on the same rationale noted earlier of minimizing steric interactions that would take place at C $\alpha$ . This then leads to metallacyclobutane intermediate **X**, which can release the desired trisubstituted *E* macrocycle. A more stable ethylidene **XIV** (versus methylidene) is then generated and can reenter the catalytic cycle by reacting with the starting diene in the same manner as before, with the least sterically encumbered alkene to arrive at **XV**. Propene or butene would be released along with the propagating alkylidene species.



Scheme 3.14. Stereochemical Model for Trisubstituted RCM with Stereodefined Trisubstituted Alkene.

The second model would take advantage of the electronics and stability of an alkenyl-B(pin).<sup>23</sup> Between a 1,1-disubstituted olefin and a 1,2-disubstituted alkenyl-B(pin), neophylidene **XI** would prefer to react with the terminal olefin since the two protons will incur the less disfavored interactions [versus B(pin)] with the neophylidene. Polarization of both the alkylidene and the alkenyl-B(pin), illustrated in **XVI**, leads to the necessary metallacyclobutane **XVII** to yield the *E* trisubstituted ring. The longevity of **XVIII** allows for longer catalyst lifetime and slower, but proper reinitiation with the terminal olefin to reach intermediate **XIX**. From there, vinyl-B(pin) is released and the propagating alkylidene species **XVI** is regenerated.

<sup>(23) (</sup>a) Kiesewetter, E. T.; O'Brien, R. V.; Yu, E. C.; Meek, S. J.; Schrock, R. R.; Hoveyda, A. H. J. Am. Chem. Soc. 2013, 135, 6026–6029. (b) Shen, X.; Nguyen, T. T.; Koh, M. J.; Xu, D.; Speed, A. W. H.; Schrock, R. R.; Hoveyda, A. H.



Scheme 3.15. Stereochemical Model for Trisubstituted RCM with Alkenyl-B(pin).

# 3.4 Synthesis of C1-C14 Acid Fragment

#### **3.4.1.** C1–C7 Aldehyde and Diastereoselective Crotylation

Disconnecting the molecule, the carboxylic acid was noted as a disguised terminal alkene. To install this alkene, we were interested in performing an enantio- and diastereoselective crotylation. We hypothesized that Krische's diastereo- and enatioselective crotylation would be an appropriate approach towards terminal alkene **3.85**.<sup>24</sup> When monoprotected diol **3.83**<sup>25</sup> was subjected to 2.5 mol% of [Ir(cod)Cl<sub>2</sub>] and 5.0 mol % of (*R*)-SEGPhos with reagent **3.84**, high diastereoselectivity is observed between the two new stereogenic centers set. However, what was not expected was epimerization of the  $\alpha$ -stereogenic center. While the oxidation and crotylation can all be performed in one

<sup>(24)</sup> Kim, I. S.; Han, S. B.; Krische, M. J. J. Am. Chem. Soc. 2009, 131, 2514-2520.

<sup>(25)</sup> Clark, S. J.; Romiti, F.; Sieng, B.; Paterson, L. C.; Stewart, A.; Chaudhury, S.; Thomas, L. H. Org. Lett. 2015, 17, 4694–4697.

pot, the  $\alpha$ -stereogenic center is incapable of tolerating the high pressure conditions, even in the presence of a considerably mild base, leading to the observed 1:1 mixture of epimers, generating four different diastereomers (Scheme 3.16). Upon further examination, we found no examples of electrophiles in reports by Krische that contain epimerizable  $\alpha$ stereogenic centers; only a few substrates containing  $\beta$ -stereogenic centers have been reported.<sup>26</sup>





With this setback, we reverted to the well-established allylation method developed by Roush.<sup>27</sup> From alcohol **3.83**, we were able to furnish the crotylated product **3.85** in two steps with 80% yield with 10:1 dr (Scheme 3.14). While this method can provide high dr and high yield, avoiding the usage of stoichiometric amounts of chiral auxiliaries would be preferred. The reaction also requires steady control of lower temperatures over a long period of time, making it a less desirable approach.





- (26) (a) Gao, X.; Zhang, Y. J.; Krische, M. J. Angew. Chem., Int. Ed. 2011, 50, 4173–4175. (b) Feng, J.; Kasun, Z. A.; Krische, M. J. J. Am. Chem. Soc. 2016, 138, 5467–5478. (c) Kim, S. W.; Lee, W.; Krische, M. J. Org. Lett. 2017, 19, 1252–1254. (d) Kim, S. W.; Zhang, W.; Krische, M. J. Acc. Chem. Res. 2017, 50, 2371–2380.
- (27) Roush, W. R.; Walts, A. E.; Hoong, L. K. J. Am. Chem. Soc. 1985, 107, 8186-8190.

Secondary alcohol **3.85** was protected with a TBS group to attain silyl ether **3.86**. Treatment of the terminal alkene to 5.0 mol % of RuCl<sub>4</sub> with NaIO<sub>4</sub> provided acid **3.87**. For the remainder of the synthesis, the acid was capped as methyl ester **3.88a** using (trimethylsilyl)diazomethane or allyl ester **3.88b** in the presence of allylbromide. Deprotection of the primary TBDPS silyl ether led to alcohol **3.89a-b** in 52–54% yield over four steps. DMP oxidation of the alcohol to aldehyde **3.90a-b** set the stage for a homologation with phosphonium salt to arrive at the C7-aldehyde **3.92a-b**.





Due to the lengthy synthesis of aldehyde **3.92**, we sought to improve this route. One of the main challenges was to set the stereochemistry of the C2–C4 portion. Epimerization of the C4 stereogenic center is an issue. Precedence for enantioselectively generating the C2 and C3 stereogenic centers in an *anti* fashion is limited. In 2013, Roush disclosed an enantioselective borane-mediated reductive *anti* aldol reaction of acrylate esters. The revised route was designed to incorporate this method.

The synthesis would begin with valerolactone **3.94** derived from the oxidative degradation of diosgenin (**3.93**) that incorporates the desired C4 stereochemistry.

Affording the lactone through a Baeyer-Villiger oxidation is significantly more atomeconomical. However, (*R*)-3-methylcyclopentan-1-one, for the ring expansion, is more expensive (9.10/mmol) compared to diosgenin (0.22/mmol). Ring-opening of **3.94** with methanolic sodium methoxide yields **3.95**.<sup>28</sup> After oxidation of the alcohol to aldehyde **3.96**, *anti* reductive aldol reaction of *tert*-butyl acrylate with the enantiomerically enriched aldehyde provides alcohol **3.97**.<sup>29</sup> Protection of the alcohol as TBS ether **3.98** and chemoselective reduction of the methyl ester<sup>30</sup> would afford aldehyde **3.99**. With this route, the synthesis of the C1–C14 fragment would be reduced by five steps.

Scheme 3.19. Alternative Approach to C1–C14 Aldeyde.



# **3.4.2.** Synthesis of C8–C14 Ketone through Enantioselective C–B Bond Formation by (Pinacolato)boron Conjugate Addition to a Methyl Ketone

To connect pieces **3.92** and **3.109** by an aldol reaction through a boron enolate, the synthesis required a methyl ketone with a  $\beta$ -stereogenic PMB ether. Chiral  $\beta$ -hydroxy compounds are usually derived through Noyori hydrogenations of  $\beta$ -ketoesters<sup>31</sup> or through an acetate aldol reaction with a chiral auxiliary.<sup>32</sup> Over the past decade,

<sup>(28)</sup> Yu, S.; Pan, X.; Lin, X.; Ma, D. Angew. Chem., Int. Ed. 2005, 44, 135-138.

<sup>(29)</sup> Allais, C.; Nuhant, P.; Roush, W. R. Org. Lett. 2013, 15, 3922-3925.

<sup>(30) (</sup>a) Usuki, T.; Sugimura, T.; Komatsu, A.; Koseki, Y. *Org. Lett.* 2014, 16, 1672–1675. (b) Shirokane, K.; Wada, T.; Yoritate, M.; Minamikawa, R.; Takayama, N.; Sato, T.; Chida, N. *Angew. Chem., Int. Ed.* 2014, *53*, 512–516.

<sup>(31) (</sup>a) Custar, D. W.; Zabawa, T. P.; Scheidt, K. A. J. Am. Chem. Soc. 2008, 130, 804–805. (b) Custar, D.
W.; Zabawa, T. P.; Hines, J.; Crews, C. M.; Scheidt, K. A. J. Am. Chem. Soc. 2009, 131, 12406–12414.

<sup>(32)</sup> Guinchard, X.; Roulland, E. Org. Lett. 2009, 11, 4700-4703.

enantioselective C–B bond forming processes have been developed.<sup>33</sup> In 2012, our group reported an NHC-catalyzed enantioselective (pinacolato)boron conjugate addition (BCA) process that was applicable to a variety of different  $\alpha$ , $\beta$ -unsaturated carbonyls, including alkyl-substituted ketones.<sup>34</sup> With enone **3.105**, the reaction with NHC, derived from 5.0 mol % of imidazolinium salt **3.106** and dbu, and B<sub>2</sub>(pin)<sub>2</sub> and subsequent mild oxidation with NaBO<sub>3</sub>·4H<sub>2</sub>O gave desired  $\beta$ -hydroxy ketone **3.107** in 90% yield and 95:5 er. The fragment was completed after protecting the alcohol as PMB ether **3.109** with reagent **3.108** in the presence of 10 mol % of camphorsulfonic acid in 73% yield.



Scheme 3.20. NHC-Catalyzed Enantioselective Boron Conjugate Addition of 3.105.

<sup>(33)</sup> Lee, J.-E.; Yun, J.; *Angew. Chem., Int. Ed.* **2008**, *47*, 145–147. (b) Bonet, A.; Gulyás, H.; Fernández, E. *Angew. Chem., Int. Ed.* **2010**, *49*, 5130–5134.

<sup>(34)</sup> Wu. H.; Radomkit, S.; O'Brien, J. M.; Hoveyda, A. H. J. Am. Chem. Soc. 2012, 134, 8277-8285.

#### 3.4.3. Completion of C1–C14 Carboxylic Acid Fragment

Methyl ketone **3.109** was coupled with aldehyde **3.92** using *n*-Bu<sub>2</sub>BOTf to yield aldol product **3.110** in 70–78% yield. Due to the 1,5-stereoinduction from the stereogenic PMB ether,<sup>14</sup> we were able to achieve >20:1 dr with the boron aldol addition. Subjection of ketone **3.110** to an Evans-Saksena reduction generated diol **3.111**.<sup>17b</sup> The unpurified mixture was treated with DDQ to arrive at triol **3.112**, which was fully protected with acetic anhydride to deliver trisacetate **3.113** in 70% yield over two steps. Treatment of methyl ester **3.113a** with potassium trimethylsilanolate, however, did not yield the desired carboxylic acid and rather cleaved one of the acetate groups. Cleavage of allyl ester **3.113b**, on the other hand, with 10 mol % Pd(PPh<sub>3</sub>)<sub>4</sub> was successful,<sup>8</sup> producing acid **3.114** in 78% yield over 3 steps.





<sup>78%</sup> yield over 3 steps (with 3.111b)

# 3.5 Synthesis of C15-C30 Alcohol Fragment

# **3.5.1.** Synthesis of C15–C22 Ketone through Enantioselective C–B Bond Formation by (Pinacolato)boron Conjugate Addition to an Ethyl Ketone

The synthesis a chiral  $\beta$ -hydroxy ketone was required to form the propionate moiety in the southern fragment. Encouraged by the success of the C8–C14 segment synthesis, we applied the same NHC-catalyzed BCA conditions to ethyl ketone **3.117** with imidazolinium salt **3.106**. The unpurified mixture shows 42% conversion of the starting material to the desired product **3.118** with only 87:13 er. These results were unexpected as the BCA method from our group shows compatibility with bulkier alkyl-substituted ketones such as *n*-pentyl and isopropyl groups.



Control studies with ethyl ketones **3.119** and **3.121** lead to high conversion (85% and 98% conv, respectively), confirming the compatibility of the BCA with ethyl ketones (Scheme 3.19).



Scheme 3.23. Control NHC-Catalyzed BCA Experiments with Ethyl Ketones.

The metal-free BCA report presents an efficient reaction of alkyne-containing alkyl chain  $(80\% \text{ yield}, 94:6 \text{ er}).^{35}$  A control with TMS-protected alkyne **3.123** as the substrate strikingly improves reactivity (>98% conv, 74% yield), but there is still much to be desired in terms of enantioselectivity (86:14 er). With Co-protected alkyne **3.126**, no desired product was observed. However, these results did not align with those reported. Based on the transition state **3.127**,<sup>35</sup> the longer side chain, especially when the protecting group is larger, could lead to undesired steric interactions between the N-aryl rings and the alkyne moiety (Figure 3.5).



Scheme 3.24. Control NHC-Catalyzed BCA Experiments with Protected Alkynes.

<sup>(35)</sup> Wu. H.; Garcia, J. M.; Haeffner, F.; Radomkit, S.; Zhugralin, A. Z.; Hoveyda, A. H. J. Am. Chem. Soc. **2015**, *137*, 10585–10602.



Figure 3.4. Transition State of BCA to (*E*)-4-Phenylbut-3-en-2-one.

With these results in hand, we explored different imidazolinium salts in search for improved reactivity as well as higher enantioselectivity (Table 3.2). Performing the reaction at 60 °C with **3.106** leads to full consumption of **3.117**, but the enantioselectivity drops to 74:26 er (entry 2). Decreasing the size of the ortho-group from a mesityl to a phenyl group in the N-aryl group of the imidazolinium salt (**3.120**) leads to a non-selective reaction (49:51 er) with similar reactivity (41% conv) (entry 3). Without a meta-group on the N-aryl ring (**3.124**), 47% of the enone is converted to **3.118** and a slight increase to 8.5:91.5 er (entry 4). Increasing the catalyst loading or temperature delivers more product (52%, entry 5 and 74% conv, entry 6, respectively), but enantioselectivity drops back to about 15:85 er. By performing the reaction in the presence twice the amount of dbu, >98% conversion of the starting material is detected and the product is afforded with 9:91 er (entry 7). Other imidazolinium salts with different substituents on the N-aryl ring (**3.127**,

**3.128** and **3.129**), while still bearing an N-mesityl group, leads to lower reactivity (<35% conv) and also lower er (50:50–35:65 er) (entry 8–10). With imidazolinium salt **3.130** that

1		imidazolinium O dbu (10 ↓	imidazolinium salt (5.0 mol %) dbu (100 mol %) B₂(pin)₂ (1.1 eq), MeOH (60 eq) thf, 22 °C, 14 h	
	3.117	B <sub>2</sub> (pin) <sub>2</sub> (1.1 eq thf, 22		
	entry	imidazolinium salt	conv (%) <sup>b</sup>	er <sup>c</sup>
	1	3.106	42	87:13
	2 <sup>d</sup>	3.106	>98	74:26
	3	3.120	41	49:51
	4	3.124	47	8.5:91.5
	5 <sup>e</sup>	3.124	52	15:85
	6 <sup>f</sup>	3.124	74	13:87
	7 <sup>g</sup>	3.124	>98	9:91
	8	3.127	26	54:46
	9	3.128	32	35:65
	10	3.129	30	50:50
	11	3.130	40	11:89
	12	3.131	15	nd
	13	3.132	30	26:74

 Table 3.2. Imidazolinium Salt Screen for NHC-Catalyzed Boron Conjugate Addition to 3.117.

<sup>a</sup> Reactions carried out under N<sub>2</sub>. <sup>b</sup> Determined by analysis of 400 MHz <sup>1</sup>H NMR spectra of unpurified mixtures. <sup>c</sup> Determined by chiral HPLC analysis. <sup>d</sup> Reaction performed at 60 °C. <sup>e</sup> Reaction performed with 10 mol % of **3.113**. <sup>f</sup> Reaction performed at 40 °C. <sup>g</sup> Reaction performed with 200 mol % of dbu. nd = not determined

 $BF_4$ 

Θ

BF<sub>4</sub>



(*R*,*R*)-**3.106** 















(S,S)-**3.124** 





bears a bulkier group (versus mesityl), the BCA leads to similar results compared to **3.106** (40% conv, 11:89 er, entry 11). Adding sterics to both ortho-positions leads to only 15% conv (entry 12). In the presence of 5.0 mol % of **3.132**, 30% of product is observed in the unpurified mixture as a 1:3 mixture of the two enantiomers.

Hence, we decided to proceed with imidazolinium salt **3.124** for the BCA in the presence of 2.0 equiv of dbu as these conditions gave the best conversion and er of the many imidazolinium salts screened. Synthesis of the fragment was completed by protecting the alcohol with **3.108** in the presence of 1.0 mol % of triflic acid to afford PMB ether **3.133** in 87% yield.



Scheme 3.25. Enantioselective NHC-Catalyzed Boron Conjugate Addition to 3.117.

#### 3.5.2. Synthesis of C23–C30 Aldehyde Fragment

We envisioned setting the stereogenic center and building the carbon scaffold of aldehyde **3.146** through Morken's one-pot diboration/cross-coupling strategy (Scheme 3.22).<sup>36</sup> In the presence of 1.0 mol % of Pt(dba)<sub>3</sub> and 1.2 mol % of TADDOL-PPh ligand, B<sub>2</sub>(pin)<sub>2</sub> and pentene could be converted to 1,2-diboryl species **3.135**. The unpurified reaction mixture was treated with a solution of Pd(OAc)<sub>2</sub>, complexated with RuPhos, bromide **3.136a** and potassium hydroide. After 12 h, none of the desired product was observed. Several conditions for the cross-coupling were screened through the use of the bromide and the chloride version of alkene **3.136**. Unfortunately, the desired product was not observed. We propose that another possibility would be to utilize catalytic conjunctive

<sup>(36)</sup> Mlynarski, S. N.; Schuster, C. H.; Morken, J. P. Nature 2014, 505, 386-390.

cross-coupling (Scheme 3.27).<sup>37</sup> Oxidative addition may be faster with an alkenyl triflate (versus alkenyl halide). The cationic Pd species generated would facilitate 1,2-kmetallate shift to afford the desired product **3.137**. We propose utilizing a lithium-based nucleophile as the reaction promoted mainly Suzuki-Miyaura transmetallated product in the presence of propyl Grignard<sup>38</sup> (36% conv to Suzuki cross-coupling product, 26% conv to **3.137**). Studies are ongoing in our group to amend the issues related with the cross-coupling reaction.

Scheme 3.26. Diboration/Cross-Coupling Strategy towards Fragment 3.146.



Scheme 3.27. Conjunctive Cross Strategy towards Fragment C23-C30 Fragment.



Returning to classical chemistry, synthesis of aldehyde **3.151** begins with ringopening of kinetically resolved epoxide **3.143**<sup>39</sup> with alkynyl lithiate **3.144** (Scheme 3.23). Removal of the TMS group and protection of the alcohol furnishes alkyne fragment **3.146** 

<sup>(37)</sup> Zhang, L.; Lovinger, G. J.; Edelstein, E. K.; Szymaniak, A. A.; Chierchia M. P. Morken, J. P. Science, **2016**, *351*, 70–74.

<sup>(38)</sup> Lovinger, G. J.; Aparece, M. D.; Morken, J. P. J. Am. Chem. Soc. 2017, 139, 3153-3160.

<sup>(39) (</sup>a) Jacobsen, E. N. Acc. Chem. Res. 2000, 33, 421-431. (b) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. J. Am. Chem. Soc., 2002, 124, 1307–1315.

in 67% yield over 3 steps. Cu-catalyzed silylcupration/methylation yields the trisubstituted olefin **3.147** with the necessary *E* geometry in high yield. Exchange of the silyl group with NIS delivers iodide **3.148** in 67% yield. Homologation of the alkene leads to aldehyde **3.149** containing TES ether. Upon subjection of ketone **3.133** with aldehyde **3.149** in a boron aldol reaction, low reactivity is observed (28% conv) and the isolated product is desilylated. Thus, the silyl group is then cleaved<sup>40</sup> and the resulting protected as acetate **3.151** (87% yield over 3 steps) at this stage.





#### **3.5.3.** Completion of C15–C30 Alcohol Fragment and Hydroboration Studies

To synthesize alcohol fragment **3.152**, we coupled ethyl ketone **3.133** and enal **3.151** by chlorodicyclohexylboron-promoted aldol reaction and isolated the desired product with high diastereoselectivity. The alcohol was protected, affording TBS ether **3.153**, which would be a common intermediate for dolabelide A, B, C and D. PMB ether was cleaved to afford alcohol **3.154** to perform a directed *anti*-reduction<sup>17b</sup> of the ketone in high yield (**3.155**). The diol was protected as the acetal and the silyl ether was cleaved for later use to attain alkyne **3.157** in 95% yield. The alkyne was subjected to hydroboration

<sup>(40)</sup> Nakajima, N.; Ubukata, M. Heterocycles 2004, 64, 333-345.

conditions. What was observed, however, was a second hydroboration to **3.158**, leading to no alkenyl-B(pin) to be detected in the unpurified mixture. We hypothesize that milder hydroboration conditions could suffice, but that protoboration of the alkyne developed by our group may be applicable here.<sup>41</sup>





# **3.6 Conclusions**

We have developed routes that may be applicable to the synthesis of dolabelide. By applying modern methods to these pieces, the syntheses can be rendered more convergent and stereoselective through catalytic processes rather than chiral auxiliaries. At this point, we have been able to apply our own boron conjugate addition method to synthesize two key ketone fragments in the route with high enantioselectivity. While some pieces demonstrated little success with novel catalytic methods, we plan to challenge the limits of modern methods and develop new and shorter paths for these fragments. Improvement on

<sup>(41)</sup> Jang, H.; Zhugralin, A. R.; Lee, Y.; Hoveyda, A. H. J. Am. Chem. Soc. 2011, 133, 7859–7871.

the final RCM step can be accomplished through the use of a kinetically *E*-selective catalyst and proper substrate design.<sup>42</sup> With our synthesis plan and stereochemical models for the RCM, we hope to establish new and more efficient routes for the preparation of dolabelide. Importantly, this would be the first example of a kinetically *E*-selective RCM of a trisubstituted alkene.

### **3.7 Experimental**

• General. <sup>1</sup>H NMR spectra were recorded on a Varian Unity INOVA 400 (400 MHz), Varian Unity INOVA 500 (500 MHz) or Varian 600 (600 MHz) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance resulting from incomplete deuteration as the internal reference (CDCl<sub>3</sub>:  $\delta$  7.26, C<sub>6</sub>D<sub>6</sub>:  $\delta$  7.16). Data are reported as follows chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, br = broad, m = multiplet, sext = sextet), and coupling constants (Hz). <sup>13</sup>C NMR spectra were recorded on Varian Unity INOVA 400 (100 MHz) or Varian 600 (150 MHz) spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance resulting from incomplete deuteration as the internal reference (CDCl<sub>3</sub>:  $\delta$  77.16, C<sub>6</sub>D<sub>6</sub>:  $\delta$  128.06). Infrared (IR) spectra were recorded on a Bruker FTIR Alpha (ATR Mode) spectrometer, v<sub>max</sub> in cm<sup>-1</sup>. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). High-resolution mass spectrometry was performed on a JEOL Accu TOF Dart (positive mode) at the Boston College Mass Spectrometery Facility.

<sup>(42)</sup> For representative examples where a Z-selective catalyst for macrocyclic RCM would significantly improve the overall efficiency of the total synthesis, see: (a) Humphrey, J. M.; Liao, Y.; Ali, A.; Rein, T.; Wong, Y.; Chen, H.; Courtney, H. K.; Martin, S. F. J. Am. Chem. Soc. 2002, 124, 8584–8592. (b) Fürstner, A.; Stelzer, F.; Rumbo, A.; Krause, H. Chem. Eur. J. 2002, 8, 1856–1871. (c) She, J.; Lampe, J. W.; Polianski, A. B.; Watson, P. S. Tetrahedron Lett. 2009, 50, 298–301. (d) Smith, B. J.; Sulikowski, G. A. Angew. Chem., Int. Ed. 2010, 49, 1599–1602.

**Vacuum Pumps.** KNF Laboport N840.3FTP diaphragm vacuum pump connected to a Welch Labaid vacuum controller generates a vacuum of 100 torr at point of connection to the reaction vessel.

**Materials.** All reactions were carried out in oven-dried (135 °C) or flame-dried glassware under an inert atmosphere of dry  $N_2$  unless otherwise stated. Solvents were purged with argon and purified under a positive pressure of dry argon by a modified Innovative Technologies purification system: diethyl ether (Aldrich), and dichloromethane (Aldrich) were passed through activated alumina columns; benzene (Aldrich). Tetrahydrofuran (Aldrich) was distilled from sodium benzophenone ketyl.

### Reagents

Acetic acid was purchased from Fisher and used as received.

Acetic anhydride was purchased from Acros and used as received.

Allyl bromide was purchased from Aldrich and used as received.

**Bis(pinacolato)diboron** was purchased from Advanced Chem Tech and recrystallized from pentane prior to use.

Boron trifluoride etherate was purchased from Aldrich and used as received.

*n*-Butyl lithium was purchased from Aldrich and titrated prior to use.

tert-Butyl(chloro)diphenylsilane was purchased from Oakwood and used as received.

*tert*-Butyldimethylsilyl trifluoromethanesulfonate was purchased from TCI and used as received.

Camphorsulfonic acid was purchased from Aldrich and used as received.

Chloro(dimethyl)phenylsilane was purchased from Oakwood and used as received.

Chlorodicyclohexylborane was prepared according to literature procedure.<sup>43</sup>

Chlorotriethylsilane was purchased from Oakwood and used as received.

Copper(I) cyanide was purchased from Strem and used as received.

<sup>(43)</sup> Brown, H. C.; Dhar, R. K.; Ganesan, K. Singaram, B. J. Org. Chem. 1992, 57, 499–504.

*E*-Crotyl boronate was prepared according to literature procedure.<sup>44</sup>

Dess-Martin periodinane was purchased from Oakwood and used as received.

**1,8-Diazabicyclo(5.4.0)undec-7-ene** was purchased from Aldrich and distilled over CaH<sub>2</sub> prior to use.

Dibutylboron triflate was purchased from Aldrich and used as received.

**2,3-Dichloro-5,6-dicyano-1,4-benzoquinone** was purchased from Aldrich and used as received.

Diisobutylaluminium hydride was purchased from Aldrich and used as received.

*N*,*N*-Diisopropylethylamine was purchased from Aldrich and used as received.

2,2-Dimethoxypropane was purchased from Aldrich and used as received.

4-Dimethylaminopyridine was purchased from Oakwood and used as received.

*N*,*N*-Dimethylformamide was purchased from Aldrich and used as received.

**Hydrogen peroxide** was purchased from Aldrich as a 30% wt solution in H<sub>2</sub>O and used as received.

Imidazole was purchased from Oakwood and used as received.

Iodomethane was purchased from Alfa Aesar and used as received.

*N***-Iodosuccinimide** was purchased from Oakwood and recrystallized from CCl<sub>4</sub> and 1,4dioxane prior to use.

Lithium was purchased from Strem and used as received.

Lithium chloride was purchased from Aldrich and used as received.

**2,6-Lutidine** was purchased from Aldrich and used as received.

Methacrolein was purchased from Aldrich and used as received.

Methanol was purchased from Acros and used as received.

**4-Methoxybenzyl-2,2,2-trichloroacetimidate** was prepared according to literature procedure.<sup>45</sup>

(Methoxymethyl)triphenylphosphonium chloride was purchased from Aldrich and used as received.

<sup>(44)</sup> Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. J. Am. Chem. Soc. 1990, 112, 6339-6348.

<sup>(45)</sup> Joly, G. D.; Jacobsen, E. N. Org. Lett. 2002, 4, 1795–1798.

**Methylmagnesium bromide** was purchased from Aldrich as a 3.0 M solution in Et<sub>2</sub>O and used as received.

Morpholine was purchased from Aldrich and used as received.
Oxalyl chloride was purchased from Oakwood and used as received.
Potassium carbonate was purchased from Fisher and used as received.
Propionic acid was purchased from Acros and used as received.

(*R*)-2-propyloxirane was prepared according to literature procedure.<sup>46</sup>

Pyridinium *p*-toluenesulfonate was purchased from Aldrich and used as received.

Ruthenium(III) chloride hydrate was purchased from Aldrich and used as received.

Sodium metaperiodate was purchased from Aldrich and used as received.

Sodium perborate was purchased from Aldrich and used as received.

Sodium triacetoxyborohydride was purchased from Aldrich and used as received.

Tetrakis[triphenylphosphine]palladium(0) was purchased from

Tetra-*n*-butylammonium fluoride was purchased from Aldrich as a 1.0 M solution in thf and used as received.

Triethyl orthoacetate was purchased from

Triethylamine was purchased from Aldrich and used as received.

Trifluoromethanesulfonic acid was purchased from TCI and used as received.

Trimethyl phosphonoacetate was purchased from Aldrich and used as received.

Trimethylsilylacetylene was purchased from Oakwood and used as received.

**1-(Triphenyl-\lambda^5-phosphaneylidene)butan-2-one** was prepared according to literature procedure.<sup>47</sup>

<sup>(46) (</sup>a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. Science 1997, 277, 936–938; (b) Schaus,

S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. J. Am. Chem. Soc. 2002, 124, 1307–1315.

<sup>(47)</sup> Marqués-López, E.; Herrera, R. P.; Marks, T.; Jacobs, W. C.; Christmann, M. Synthesis **2013**; 45, 1016–1028
# Synthesis of Fragment C1-C7

(*R*)-4-((*tert*-Butyldiphenylsilyl)oxy)-2-methylbutan-1-ol (3.83).<sup>48</sup> To a solution of diol 3.82 (1.20 g, 11.5 mmol) in DMF (45 mL) at -50 °C were added sequentially TBDPSCl (3.0 mL, 12 mmol) and dbu (2.40 mL, 16.1 mmol). The resulting mixture was allowed to stir at -50 °C for 30 min then diluted with EtOAc (80 mL). The reaction mixture was sequentially washed with saturated solution of aqueous NH<sub>4</sub>Cl (100 mL), saturated solution of aqueous NH<sub>4</sub>Cl (100 mL), saturated solution of aqueous NaHCO<sub>3</sub> (100 mL) and brine (100 mL). The organic phase was dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The product was purified by silica get chromatography (10% to 20% EtOAc in hexanes) to afford alcohol **3.83** (2.76 g, 8.06 mmol, 70% yield) as clear, colorless oil. IR (neat) 3360 (w), 2956 (w), 2929 (w), 2857 (w), 1427 (w), 1106 (m), 1085 (m), 822 (m), 736 (s); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.72–7.74 (4H, m), 7.49–7.35 (6H, m), 3.82–3.66 (2H, m), 3.57–3.45 (2H, m), 2.46 (1H, t, *J* = 6.0 Hz), 1.87 (1H, app sextet, *J* = 6.8 Hz), 1.66 (1H, dddd, *J* = 14.1, 7.7, 6.8, 5.2 Hz), 1.57–1.43 (1H, m, CH<sub>2</sub>-C5), 1.06 (9H, s), 0.91 (3H, d, *J* = 6.8 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  135.7, 133.6, 129.8, 127.8, 68.4, 62.6, 36.9, 34.0, 26.9, 19.3, 17.3; HRMS (DART) calcd for C<sub>21</sub>H<sub>31</sub>O<sub>2</sub>Si [M+H]<sup>+</sup> 343.2093, found 343.2082; [ $\alpha$ ]p<sup>20</sup> = +6.0 (c = 1.0, CHCl<sub>3</sub>).

(3R,4S,5R)-7-((*tert*-Butyldiphenylsilyl)oxy)-3,5-dimethylhept-1-en-4-ol (3.85). To a solution of alcohol 3.83 (2.00 g, 5.84 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (12 mL) was added DMP (3.72 g, 8.76 mmol). The resulting mixture was allowed to stir at 22 °C for 2 h before addition of saturated solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and saturated solution of NaHCO<sub>3</sub>. The resulting mixture was allowed to vigorously stir at 22 °C until two clear phases were obtained (*ca.* 10 min). The reaction mixture was washed with Et<sub>2</sub>O (3 x) and the combined organic extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The resulting solution was concentrated under reduced pressure to afford the unpurified aldehyde **3.86**, which was used without purification in the next step.

<sup>(48) (</sup>a) Francais, A.; Leyva, A.; Etxebarria-Jardi, G.; Ley, S. V. Org. Lett. 2010, 12, 340-343. (b) Clark, J. S.; Romiti, F.; Sieng, B.; Paterson, L. C.; Stewart, A.; Chaudhury, S.; Thomas, L. H. Org. Lett. 2015, 17, 4694-4697.

The unpurified aldehyde **3.86** was dried prior to use by azeotropic removal of H<sub>2</sub>O by dissolution in toluene, concentration under reduced pressure and drying under high vacuum. A solution of aldehyde 3.86 in toluene (8.00 mL) precooled to -78 °C was added to a mixture of E-crotyl boronate 3.87 (23.4 mL of a 0.5 M solution in toluene, 11.7 mmol) and 4 Å molecular sieves (1.00 g) at -78 °C. The mixture was allowed to stir at -78 °C for 16 h, then the reaction was quenched by addition of 1 M aqueous NaOH (40 mL). The mixture was allowed to warm to 22 °C and allowed to vigorously stir at this temperature for 1 h before filtration through Celite using Et<sub>2</sub>O for washing. The mixture was washed with Et<sub>2</sub>O  $(3 \times)$  and the combined organic extracts were washed with brine (100 mL), dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The product was purified by silica gel chromatography (5% to 10% Et<sub>2</sub>O in hexanes) to afford alcohol **3.85** (1.9 g, 4.7 mmol, 80% yield, dr = 10.1) as clear, colorless oil. **IR (neat):** 3481 (b), 2960 (w), 2930 (w), 2857 (w), 1427 (w), 1106 (m), 1085 (m), 997 (m), 822 (w), 737 (s); <sup>1</sup>H NMR (400 **MHz**, **CDCl**<sub>3</sub>): δ 7.73–7.67 (4H, m), 7.47–7.37 (6H, m), 5.78 (1H, ddd, *J* = 17.0, 10.3, 8.4) Hz), 5.18–5.10 (2H, m), 3.81 (1H, dt, J = 10.3, 6.0 Hz), 3.73 (1H, ddd, J = 10.3, 7.4, 5.6 Hz), 3.26 (1H, dt, J = 7.7, 3.5 Hz), 2.35–2.26 (1H, m), 2.00–1.92 (1H, m), 1.78 (1H, dtd, J = 13.7, 7.4, 6.0 Hz), 1.74 (1H, d, J = 3.5 Hz), 1.57 (1H, dddd, J = 13.7, 7.4, 6.0, 5.6 Hz), 1.08 (9H, s), 1.01 (3H, d, J = 6.8 Hz), 0.88 (3H, d, J = 6.8 Hz); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 141.8 (CH-C1), 135.7, 135.7, 134.0, 129.7, 127.8, 116.2, 77.0, 62.0, 42.1, 37.2, 31.2, 27.0, 19.3, 16.8, 12.5; **HRMS (DART)** calcd for C<sub>25</sub>H<sub>37</sub>O<sub>2</sub>Si [M+H]<sup>+</sup> 397.2563, found 397.2577;  $[\alpha]_{D^{20}}$  +3.8 (c = 1.0, CHCl<sub>3</sub>).

Allyl (2*S*,3*S*,4*R*)-3-((*tert*-butyldimethylsilyl)oxy)-6-hydroxy-2,4-dimethylhexanoate (3.86). 2,6-Lutidine (2.20 mL, 18.9 mmol) and TBSOTf (2.17 mL, 9.45 mmol) were sequentially added to a solution of alcohol 3.85 (2.50 g, 6.30 mmol) in  $CH_2Cl_2$  (30 mL) at 0 °C. The resulting mixture was allowed to stir at 0 °C for 3 h before addition of saturated solution of aqueous NaHCO<sub>3</sub> (50 mL). The resulting mixture was washed with  $Et_2O$  (3 x) and the combined organic extracts were sequentially washed with 10% aqueous  $CuSO_4$  (80 mL), 1 M aqueous HCl (80 mL), brine (80 mL). The organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to obtain the unpurified alkene **3.86**, which was used in the next step without purification. Alkene **3.86** was dissolved in a 2:2:3 mixture of CCl<sub>4</sub>:MeCN:H<sub>2</sub>O (56.0 mL) at 22 °C. NaIO<sub>4</sub> (5.40 g, 25.2 mmol) was added and the mixture was allowed to stir at 22 °C until all the NaIO<sub>4</sub> has dissolved. RuCl<sub>3</sub>·xH<sub>2</sub>O (*ca.* 40% Ru, 163 mg, 0.32 mmol) was added and the mixture was allowed to vigorously stir at 22 °C for 18 h. The reaction mixture was diluted with 1 M aqueous HCl (60.0 mL) and washed with EtOAc (3 ×). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The resulting residue was diluted with EtOAc (5 mL) and filtered through celite using EtOAc for washing. The filtrate was concentrated under reduced pressure to afford the unpurified carboxylic acid **3.87**, which was used without purification in the next step.

To a solution of the unpurified carboxylic acid **3.87** in dry acetone (60.0 mL) was added  $K_2CO_3$  (1.74 g, 12.6 mmol) and allyl bromide (2.73 mL, 31.5 mmol). The reaction mixture was heated at reflux for 2 h, then cooled to 22 °C and concentrated under reduced pressure. The residue was dissolved in Et<sub>2</sub>O (100 mL), washed with saturated solution of aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (60.0 mL) and brine (30.0 mL), dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to give the unpurified allyl ester 3.88b, which was used in the next step without purification.

To a solution of unpurified allyl ester **3.88b** in thf (30 mL) was added tbaf (30 mL, 30.0 mmol, 1.0 M in thf) and acetic acid (1.7 mL, 30.0 mL). The reaction was allowed to stir at 22 °C for 20 h. The reaction was quenched by the addition of saturated solution of aqueous NaHCO<sub>3</sub>. The mixture was washed with Et<sub>2</sub>O (3 x). The combined organic layers were washed with saturated solution of aqueous NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography (100% hexanes to 3% Et<sub>2</sub>O in hexanes) to afford **3.89b** as colorless oil (515 mg, 1.59 mmol, 52% yield over 4 steps). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  5.90 (1H, ddt, *J* = 17.2, 10.5, 5.8 Hz), 5.31 (1H, dq, *J* = 17.2, 1.6 Hz), 5.22 (1H, dq, *J* = 10.4, 1.3 Hz), 4.58 (1H, ddt, *J* = 13.3, 5.8, 1.4 Hz), 4.51 (1H, ddt, *J* = 13.3, 5.7, 1.4 Hz), 3.89 (1H, dd, *J* = 7.5, 2.7 Hz), 3.70 (1H, dt, *J* = 11.9, 5.7 Hz), 3.62 (1H, dt, *J* = 10.9, 6.9 Hz), 2.70 (1H, p, *J* = 7.2 Hz), 1.89–1.75 (2H, m), 1.69–1.59 (2H, m), 1.48–1.39 (1H, m), 1.10 (4H, d, *J* = 7.2 Hz), 0.89 (3H, d, *J* = 6.9 Hz), 0.85 (9H, s), 0.05 (3H, s), -0.01 (3H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): 175.4, 132.2, 118.4, 77.0, 65.2, 61.2, 45.3, 37.1, 32.9, 26.1, 18.4, 14.4, 14.0, -4.0, -4.3; [ $\alpha$ ] $p^{20}$  +24.2 (c = 1.0, CHCl<sub>3</sub>).

Allyl (2*S*,3*S*,4*R*)-3-((*tert*-butyldimethylsilyl)oxy)-2,4-dimethyl-7-oxoheptanoate (3.92b). To a solution of alcohol 3.89b (130 mg, 0.39 mmol) in  $CH_2Cl_2$  (2 mL) was added DMP (250 mg, 0.59 mmol). The reaction was allowed to stir at 22 °C for 1 h. The reaction was quenched by the addition of saturated solution of aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and NaHCO<sub>3</sub>. The mixture was washed with Et<sub>2</sub>O (3 x). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The resulting residue was triturated with hexanes and the white precipitate removed by filtrattion. The filtrate was concentrated under reduced pressure. The unpurified aldehyde 3.90b was used without purification.

To a solution of methoxymethyl)triphenylphosphonium chloride in thf (1 mL), stirring at 0 °C, was added *n*-BuLi (520  $\mu$ L, 0.79 mmol, 1.5 M in hexanes). The reaction was allowed to warm to 22 °C and stir for 1 h. Upon which time, the mixture was cooled to 0 °C and was added a solution of unpurified aldehyde **3.90b** in thf (0.5 mL). The reaction was allowed to stir at 22 °C for 1 h. The reaction was quenched upon the addition of H<sub>2</sub>O (2 mL) and washed with EtOAc (3 x). The combined organic extracts were washed with hexanes, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to afford unpurified enol ether 3.91b, which was used without purification in the next step.

To a solution of the unpurified enol ether **3.91b** in thf (0.3 mL) was added HCl (2.0 M in H<sub>2</sub>O). The mixture was allowed to stir at 22 °C for 16 h. The reaction was diluted with Et<sub>2</sub>O (3 mL) and brine (3 mL). The reaction mixture was washed with Et<sub>2</sub>O (3 x). The combined organic extracts were washed with saturated solution of aqueous NaHCO<sub>3</sub> and brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography (5% EtOAc in hexanes) to afford 3.92b (80 mg, 0.23 mmol, 60% yield) as clear, colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  9.75 (1H, t, *J* = 1.7 Hz), 5.91 (1H, ddt, *J* = 17.3, 10.5, 5.8 Hz), 5.32 (1H, dq, *J* = 17.3, 1.6 Hz), 5.23 (1H, dq, *J* = 10.4, 1.3 Hz), 4.56 (2H, qdt, *J* = 13.3, 5.8, 1.4 Hz), 3.90 (1H, dd, *J* = 7.4, 2.8 Hz), 2.67 (1H, p, *J* = 7.2 Hz), 2.44 (2H, tdd, *J* = 8.5, 6.3, 1.8 Hz), 1.76–1.65 (1H, m), 1.59 (1H, dddd, *J* = 11.4, 7.6, 3.8, 2.2 Hz), 1.50 (1H, dtd, *J* = 13.3, 8.5, 6.2 Hz), 1.09 (3H, d, *J* = 7.2 Hz), 0.93–0.88 (3H, m), 0.86 (12H, s), 0.06 (4H, s), 0.00 (3H, s); <sup>13</sup>C NMR

(CDCl<sub>3</sub>, 100 MHz):  $\delta$  202.4, 175.0, 132.2, 118.5, 76.6, 65.2, 45.3, 42.2, 35.6, 26.4, 26.1, 18.5, 13.9, 13.7, -4.1, -4.2;  $[\alpha]_D^{20} = +12.1$  (c = 1.0, CHCl<sub>3</sub>).

## Synthesis of Fragment C8-C14

Ethyl (*E*)-4-methylhex-4-enoate (3.102). To a solution of methacrolein (5.0 mL, 60 mmol) in Et<sub>2</sub>O (120 mL), stirring at 0 °C, was added methylmagnesium bromide (22 mL, 66 mmol, 3.0 M in Et<sub>2</sub>O). The reaction was allowed to stir at 0 °C for 30 min, at which time was quenched by the addition of saturated solution of aqueous NH<sub>4</sub>Cl and washed with Et<sub>2</sub>O (3 x). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The unpurified alcohol **3.101**, triethyl orthoacetate (50 mL, 270 mmol) and propionic acid (450  $\mu$ L, 6.0 mmol) and was affixed a Dean-Stark trap. The reaction was heated to 160 °C and allowed to stir for 16 h. The reaction was allowed to cool to 22 °C and then diluted with Et<sub>2</sub>O and 3 M HCl. The layers were separated and the mixture was washed with Et<sub>2</sub>O (3 x). The combined organic extracts were washed with saturated solution of aqueous NaHCO<sub>3</sub> and brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography (1% to 2% Et<sub>2</sub>O in hexanes) to afford **3.102** (8.4 mL, 54 mmol, 89% yield).

(3*E*,7*E*)-7-Methylnona-3,7-dien-2-one (3.105). To a solution of ester (2.0 g, 13 mmol) in  $CH_2Cl_2$  (40 mL), stirring at -78 °C, was added DIBAL-H (13 mL, 13 mmol, 10 M in  $CH_2Cl_2$ ). The reaction was allowed to stir at -78 °C for 1 h. The mixture was allowed to warm to 22 °C and quenched by the addition of 1 M aqueous HCl. The layers were separated and the aqueous layer was back washed with  $CH_2Cl_2$  (3 x). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The unpurified oil was used without purification in the next step.

A solution of phosphonoacetate **3.104** (2.7 mL, 19 mmol), LiCl (970 mg, 23 mmol) and dbu (2.9 mL, 19 mmol) in CH<sub>3</sub>CN (40 mL) was allowed to stir at 22 °C for 30 min. To the mixture was added a solution of aldehyde in CH<sub>3</sub>CN (10 mL) and allowed to stir at 22 °C for 16 h. The reaction was quenched by the addition of saturated solution of aqueous NH<sub>4</sub>Cl

and washed with  $Et_2O$  (3 x). THe combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography (5%  $Et_2O$  in pentane) to afford **3.105** (1.6 g, 15 mmol, 80% yield over 2 steps).

(S,E)-4-hydroxy-7-methylnon-7-en-2-one (3.107). In an N<sub>2</sub>-filled glove box, a 4 mL vial with a magnetic stir bar was charged with a solution of NHC, which was prepared from **3.106** (109 mg, 0.16 mmol, 5.0 mol %), dbu (99 µL, 0.66 mmol, 20 mol %), and thf (7.9 mL, 0.036 M solution of catalyst) for 30 min at 22 °C. Bis(pinacolato)diboron (918 mg, 3.60 mmol), enone 3.105 (500 mg, 3.28 mmol) and methanol (11.9 mL) were added to the vial (0.26 M solution of substrate), which was sealed with a cap before removal from the glovebox. The mixture was allowed to stir at 22 °C for 14 h, after which the reaction was quenched by the addition of an aqueous solution of NH<sub>4</sub>Cl (0.7 M) and the mixture was allowed to stir for an additional 20 min. The aqueous layer was washed with diethyl ether (3 x). The combined organic layers were dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under vacuum. To a solution of the resulting yellow oil in thf (1.5 mL) was added NaBO<sub>3</sub>·4H<sub>2</sub>O (2.02 g, 13.1 mmol) and H<sub>2</sub>O (1.5 mL). The mixture was allowed to stir at 22 °C for 4 h at which time the reaction was quenched with the addition of H<sub>2</sub>O and washed with EtOAc (3 x). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography (20% EtOAc in hexanes) to afford **3.107** (450 mg, 2.64 mmol, 80% yield) as clear, colorless oil. IR (neat): 3466 (br), 29221 (m), 2861 (w), 1709 (s), 1418 (m), 1360 (m), 1243 (w), 1089 (m), 1013 (m), 976 (m), 907 (m), 821 (w), 570 (w) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  5.31–5.12 (1H, m), 4.01 (1H, d, J = 8.3 Hz), 2.92 (1H, d, J = 3.5Hz), 2.62 (1H, dd, *J* = 17.6, 3.2 Hz), 2.54 (1H, dd, *J* = 17.6, 8.7 Hz), 2.18 (3H, d, *J* = 2.5 Hz), 2.06 (1H, ddt, J = 22.0, 14.2, 7.2 Hz), 1.62–1.60 (5H, m), 1.60–1.54 (2H, m), 1.48 (1H, dddd, J = 13.9, 9.4, 6.4, 4.8 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 214.5, 135.4, 119.1, 80.7, 67.5, 50.1, 35.7, 34.7, 30.9, 15.7, 13.5, 9.0; HRMS (DART)  $[M+H]^+$  calcd for C<sub>10</sub>H<sub>19</sub>O<sub>2</sub>: 171.1380; found: 171.1382.

(S,E)-4-((4-methoxybenzyl)oxy)-7-methylnon-7-en-2-one (3.109). To a solution of alcohol x (450 mg, 2.64 mmol) in CH<sub>2</sub>Cl<sub>2</sub> was added PMBTCA **3.108** (897 µL, 4.32 mmol) and CSA (33 mg, 0.14 mmol). The reaction was allowed to stir at 22 °C for 18 h. The reaction was diluted with hexanes (40 mL) and allowed to stir vigorously for 10 min. The mixture was filtered through Celite. The filtrate was washed with saturated solution of aqueous NaHCO<sub>3</sub> and brine. The organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography (10% to 20% Et<sub>2</sub>O in hexanes) to afford **3.109** (527 mg, 1.81 mmol, 63% yield) as clear, colorless oil. **IR (neat):** 2931 (m), 2912 (m), 2862 (m), 1712 (s), 1612 (m), 1512 (s), 1357 (s), 1245 (s), 1173 (s), 1078 (s), 1034 (s), 820 (s), 513 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.23 (1H, d, J = 8.8 Hz), 6.86 (1H, d, J = 8.7 Hz), 5.21 (1H, dtdd, *J* = 7.7, 6.4, 2.5, 1.2 Hz), 4.45 (1H, d, *J* = 10.9 Hz), 4.41 (1H, d, *J* = 10.9 Hz), 3.92–3.85 (1H, m), 3.80 (2H, s), 2.74 (1H, dd, J = 15.8, 7.4 Hz), 2.51 (1H, dd, J = 15.8, 4.9 Hz), 2.15 (2H, s), 2.08-2.00 (2H, m), 1.72-1.60 (2H, m), 1.59 (4H, dt, J = 2.1, 1.2 Hz), 1.57 (6H, J = 2.1, 1.2 Hz), 1.57dq, J = 6.7, 1.0 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  207.9, 171.1, 130.8, 129.6, 118.9, 113.9, 75.1, 71.3, 55.4, 48.7, 35.3, 32.8, 31.3, 15.8, 13.5; HRMS (DART) [M+H]<sup>+</sup> calcd for  $C_{18}H_{27}O_3$ : 291.1955; found: 291.1974;  $[\alpha]_D^{20} + 3.2$  (c = 1.0, CHCl<sub>3</sub>).

# Synthesis of Fragment C1-C14

Allyl (2*S*,3*S*,4*R*,7*S*,11*S*,*E*)-3-((*tert*-butyldimethylsilyl)oxy)-7-hydroxy-11-((4methoxybenzyl)oxy)-2,4,14-trimethyl-9-oxohexadec-14-enoate (3.110b). To a solution of ketone 3.109 (30.5 mg 0.105 mmol) in Et<sub>2</sub>O (0.7 mL), stirring at -78 °C was added DIPEA (21 µL, 0.12 mmol) and then Bu<sub>2</sub>BOTf (34 µL, 0.14 mmol) dropwise. The resulting mixture was allowed to stir at -78 °C for 30 min. The mixture was cooled to -100 °C and a solution of aldehyde 3.92b (30 mg, 0.088 mmol) in Et<sub>2</sub>O (0.2 mL) was added. The reaction was allowed to stir at -100 °C for 2 h, at which time the reaction was quenched by the addition of pH 7 buffer/MeOH (1.4 mL, 1:6 v/v) solution. The reaction was allowed to warm to 0 °C and H<sub>2</sub>O<sub>2</sub> (300 µL, 30 % wt in H<sub>2</sub>O) was added. The reaction was allowed to warmed to 22 °C and stir for 1 h. The mixture was diluted with Et<sub>2</sub>O (3 x). The combined organic layers were washed with NaHCO<sub>3</sub>. The aqueous layer was washed with EtOAc (3 x). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography (100% CH<sub>2</sub>Cl<sub>2</sub> to 10% Et<sub>2</sub>O in CH<sub>2</sub>Cl<sub>2</sub>) to afford **3.110b** (41 mg, 0.065 mmol, 74% yield) as clear, colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.25–7.18 (2H, m), 6.88–6.81 (2H, m), 5.91 (1H, ddtd, *J* = 17.3, 10.4, 5.7, 1.4 Hz), 5.32 (1H, dq, *J* = 17.2, 1.6 Hz), 5.22 (2H, ddq, *J* = 9.2, 6.6, 1.3 Hz), 4.62–4.48 (2H, m), 4.48–4.36 (2H, m), 4.04–3.94 (1H, m), 3.88 (2H, dt, *J* = 7.5, 2.7 Hz), 3.79 (3H, s), 3.01 (1H, s), 2.78–2.70 (1H, m), 2.70–2.63 (1H, m), 2.63 (1H, s), 2.56–2.45 (2H, m), 1.60–1.54 (6H, m), 1.09 (3H, dd, *J* = 7.2, 3.2 Hz), 0.86 (14H, s), 0.05 (3H, d, *J* = 4.0 Hz), 0.00 (3H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  211.1, 175.3, 159.4, 135.2, 132.3, 130.5, 129.6, 119.0, 118.3, 113.9, 77.0, 75.1, 71.4, 67.9, 65.1, 55.4, 50.6, 48.5, 45.4, 36.1, 35.2, 34.7, 32.6, 30.1, 26.2, 18.5, 15.8, 14.1, 13.8, 13.5, -3.9, -4.2.

(2S,3S,4R,7S,9R,11S,E)-3-((tert-butyldimethylsilyl)oxy)-7,9-dihydroxy-11-((4-Allyl methoxybenzyl)oxy)-2,4,14-trimethylhexadec-14-enoate (3.111b). Me<sub>4</sub>NHB(OAc)<sub>3</sub> (170 mg, 0.57 mmol, 90%) was stirred in a 1:1 mixture of AcOH (0.3 mL) and CH<sub>3</sub>CN (0.3 mL) at 22 °C for 30 min. The mixture was cooled to -40 °C and to the mixture was added a solution of ketone 3.110b in a 1:1 mixture of AcOH and CH<sub>3</sub>CN (0.6 mL). The reaction was allowed to stir at -40 °C for 1 h and then allowed to warm to 0 °C and stir for an additional 1 h. The reaction was quenched by the addition of saturated solution of aqueous potassium sodium tartrate and vigorously stirred for 5 min at which time was poured into a flask containing CH<sub>2</sub>Cl<sub>2</sub>. To the mixture was carefully added saturated solution of aqueous NaHCO<sub>3</sub>. The layers were separated and the aqueous layer was back washed with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were washed with saturated solution of aqueous NaHCO<sub>3</sub> and brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The resulting oil was purified by silica get chromatography (20% to 33% EtOAc in hexanes) to afford **3.111b** (31 mg, 0.049 mmol,  $dr = \ge 20.1$ , 86% yield). <sup>1</sup>H NMR (400 **MHz, CDCl<sub>3</sub>**):  $\delta$  7.24 (2H, m), 6.95–6.83 (2H, m), 5.91 (1H, ddt, J = 16.3, 10.7, 5.8 Hz), 5.32 (1H, dt, J = 17.0, 1.7 Hz), 5.26–5.17 (2H, m), 4.63–4.42 (3H, m), 4.35 (1H, d, J =10.7 Hz), 4.10 (1H, dd, J = 10.9, 5.7 Hz), 3.87 (2H, tt, J = 9.9, 4.3 Hz), 3.79 (3H, s), 3.69 (1H, m), 2.67 (1H, dd, J = 9.5, 4.6 Hz), 1.98 (2H, m), 1.87–1.70 (2H, m), 1.61 (2H, m),

1.58 (9H, m), 1.46 (3H, m), 1.25 (3H, m), 1.13–1.05 (3H, m), 0.86 (12H, s), 0.05 (3H, s), 0.01 (3H, s)

### (2S,3S,4R,7S,9R,11S,E)-7,9,11-Triacetoxy-3-((tert-butyldimethylsilyl)oxy)-2,4,14-

trimethylhexadec-14-enoic acid (3.114). To a solution of ether 3.111b (31 mg, 0.049 mmol) in a 1:1 mixture of pH 7 buffer (2 mL) and  $CH_2Cl_2$  (2 mL) was added DDQ (45 mg, 0.20 mmol). The reaction was allowed to stir at 22 °C for 90 min. The mixture was diluted with  $CH_2Cl_2$  and NaHCO<sub>3</sub>. The layers were separated and the aqueous layer was back washed with  $CH_2Cl_2$ . The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The unpurified alcohol 3.112b was used without purification in the next step.

To a solution of unpurified alcohol **3.112b** in CH<sub>2</sub>Cl<sub>2</sub> (0.2 mL) was added DMAP (1.8 mg, 0.015 mmol), pyridine (150  $\mu$ L, 2.0 mmol) and acetic anhydride (93  $\mu$ L, 0.98 mmol). The reaction was allowed to stir at 22 °C for 1 h, at which time the reaction was quenched by the addition of saturated NH<sub>4</sub>Cl and washed with Et<sub>2</sub>O. The combined organic extracts were washed with 10% aqueous CuSO<sub>4</sub>, 1 M HCl and saturated solution of aqueous NaHCO<sub>3</sub>. The organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The unpurified acetate **3.113b** was used without purification in the next step.

To a solution of the unpurified allyl ester **3.113b** in thf was added Pd(PPh<sub>3</sub>)<sub>4</sub> (5.7 mg, 4.9  $\mu$ mol) and morpholine (53  $\mu$ L, 0.59 mmol). The reaction was allowed to stir at 22 °C for 2 h, at which time the reaction was concentrated under reduced pressure. The residue was dissolved in EtOAc (6 mL) and washed with 1 M HCl and brine. The organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography (10% to 20% acetone in hexanes) to afford **3.114** (23 mg, 0.038 mmol, 79% yield over 3 steps) as clear, colorless oil.

# Synthesis of Fragment C15-C22

(*E*)-Dec-4-en-9-yn-3-one (3.117). To a solution of oxalyl chloride (877  $\mu$ L, 6.91 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (14 mL), stirring at -78 °C, was added a solution of dmso (1.47 mL, 13.8 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (14 mL). The reaction was allowed to stir at -78 °C for 15 min. To the mixture

was added alcohol **3.115** (508  $\mu$ L, 4.60 mmol) at -78 °C and allowed to stir for 15 min. To the mixture was then added, triethylamine (1.90 mL, 13.8 mmol) at -78 °C and allowed to stir at -78 °C for 5 min before allowing the reaction to be warmed to 22 °C. The mixture was filtered through a pad of Celite and washed with CH<sub>2</sub>Cl<sub>2</sub>. The filtrate was concentrated under reduce pressure to afford the unpurified aldehyde as a yellow oil. The residue was used without purification for the next step.

To a solution of unpurified aldehyde in chloroform (14 mL) was added ylide **3.116** (2.29 g, 6.91 mmol). The mixture heated to reflux and allowed to stir for 16 h, in which the reaction became homogeneous. The reaction was concentrated under reduced pressure. The unpurified material was triturated with hexanes and filtered. The filtrated was concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography (3% to 10% Et<sub>2</sub>O in hexanes) to afford **3.117** (384 mg, 2.56 mmol, 56% yield) as pale yellow oil. **IR (neat):** 3296 (m), 2976 (m), 2938 (s), 2910 (m), 1697 (s), 1671 (s), 1630 (s), 1458 (m), 1434 (m), 1415 (m), 1358 (m), 1277 (m), 1203 (w), 1125 (m), 1038 (w), 977 (s), 633 (s) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCI<sub>3</sub>):  $\delta$  6.81 (1H, dt, *J* = 15.9, 6.9 Hz), 6.14 (1H, dtd, *J* = 16.0, 1.5, 0.4 Hz), 2.56 (2H, q, *J* = 7.3 Hz), 2.23 (2H, td, *J* = 7.0, 2.6 Hz), 1.98 (1H, td, *J* = 2.7, 0.4 Hz), 1.75–1.64 (2H, m), 1.10 (3H, td, *J* = 7.3, 0.4 Hz); <sup>13</sup>C NMR (100 MHz, CDCI<sub>3</sub>):  $\delta$  201.1, 145.6, 130.8, 83.7, 69.2, 33.5, 31.3, 27.0, 18.1, 8.2; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>10</sub>H<sub>15</sub>O: 151.1123, found: 151.1130.

(*R*)-5-Hydroxydec-9-yn-3-one (3.118). In an N<sub>2</sub>-filled glove box, a 4 mL vial with a magnetic stir bar was charged with a solution of NHC, which was prepared from 3.108 (44.8 mg, 0.0719 mmol, 5.0 mol %), dbu (438 mg, 2.88 mmol, 200 mol %), and thf (2.0 mL, 0.036 M solution of catalyst) for 30 min at 22 °C. Bis(pinacolato)diboron (402 mg, 1.58 mmol), enone 3.117 (216 mg, 1.44 mmol) and methanol (3.5 mL) were added to the vial (0.26 M solution of substrate), which was sealed with a cap before removal from the glove box. The mixture was allowed to stir at 22 °C for 16 h, after which the reaction was quenched by the addition of an aqueous solution of NH<sub>4</sub>Cl (0.7 M) and the mixture was allowed to stir for an additional 20 min. The aqueous layer was washed with diethyl ether (3 x). The combined organic layers were dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under vacuum. To a solution of the resulting yellow oil in thf (2.5 mL) was

added NaBO<sub>3</sub>·4H<sub>2</sub>O (1.10 g, 7.19 mmol) and H<sub>2</sub>O (2.5 mL). The mixture was allowed to stir at 22 °C for 4 h at which time the reaction was quenched with the addition of H<sub>2</sub>O and washed with Et<sub>2</sub>O (3 x). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography (10% to 50% Et<sub>2</sub>O in hexanes) to afford **3.118** (139 mg, 0.829 mmol, 58% yield) as clear, colorless oil. **IR (neat):** 3455 (b), 3293 (m), 2976 (m), 2938 (m), 1706 (s), 1455 (m), 1411 (m), 1375 (m), 1327 (m), 1274 (m), 1217 (w), 1149 (m), 1116 (m), 1098 (m), 1007 (m), 852 (w), 635 (s), 549 (w), 521 (w) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  4.06 (1H, s), 3.10 (1H, s), 2.62 (1H, dd, *J* = 17.6, 2.9 Hz), 2.52 (1H, dd, *J* = 17.6, 9.1 Hz), 2.45 (2H, q, *J* = 7.4 Hz), 2.27–2.19 (2H, m), 1.94 (1H, t, *J* = 2.7 Hz), 1.79–1.46 (4H, m), 1.28–1.21 (2H, m), 1.06 (3H, t, *J* = 7.3 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  212.8, 84.3, 68.7, 67.3, 48.7, 36.9, 35.4, 24.5, 18.4, 7.7; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>10</sub>H<sub>17</sub>O<sub>2</sub>: 169.1229, found: 169.1221.

(R)-5-((4-Methoxybenzyl)oxy)dec-9-yn-3-one (3.133). To a solution of alcohol 3.118 (139 mg, 0.826 mmol) in Et<sub>2</sub>O (8.3 mL) was added PMBTCA **3.108** (280 mg, 0.991 mmol) and TfOH (826 µL, 8.26 µmol, 0.01 M in Et<sub>2</sub>O). The reaction was allowed to stir at 22 °C for 1 h. The reaction was quenched upon the addition of saturated solution of aqueous NaHCO<sub>3</sub>. The aqueous and organic layers were separated and the aqueous layer was washed with diethyl ether (3 x). The combined organic layers were dried over MgSO4, filtered and concentrated under reduced pressure. The resulting residue was purified by chromatography on basic alumina (10% Et<sub>2</sub>O in hexanes) to afford **3.133** as colorless oil (208 mg, 0.722 mmol, 87% yield). IR (neat): 3289 (w), 2937 (m), 2872 (s), 2837 (w), 1710 (s), 1612 (s), 1586 (w), 1513 (s), 1459 (m), 1411 (m), 1358 (m), 1301 (m), 1246 (s), 1174 (s), 1111 (s), 1090 (s), 1058 (s), 1033 (s), 821 (s), 756 (w), 637 (s), 572 (w), 517 (w) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.24–7.19 (2H, m), 6.88–6.83 (2H, m), 4.43 (2H, d, J = 2.4 Hz), 3.95 (1H, dd, J = 7.0, 5.4 Hz), 3.79 (3H, d, J = 0.8 Hz), 2.75 (1H, dd, J = 0.4 Hz) 15.8, 7.3 Hz), 2.50–2.40 (3H, m), 2.19 (2H, tt, J = 4.4, 2.8 Hz), 1.95 (1H, td, J = 2.7, 0.8 Hz), 1.71–1.56 (3H, m), 1.04 (3H, td, J = 7.3, 0.7 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$ 210.3, 159.3, 130.7, 129.5, 113.9, 84.3, 75.0, 71.5, 68.7, 55.4, 47.5, 37.4, 33.6, 24.3, 18.6, 7.8; **HRMS (DART)**  $[M+Na]^+$  calcd for C<sub>18</sub>H<sub>24</sub>O<sub>3</sub>Na: 311.1623, found: 311.1626.

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Retention Time	Area	Area %	Retention Time Area	Area %
12.512	8585301	50.435	14.652 205811	8.655
13.729	8437167	49.565	16.187 2172220	91.345

Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material; Chiralpak AZ-H column, 97.0:3.0 hexanes/iPrOH, 1.0 mL/min, 220 nm.

### Synthesis of C23-C30 Fragment

(*R*)-Triethyl(hept-1-yn-4-yloxy)silane (3.146). To a solution of TMS-acetylene (4.0 mL, 28 mmol) in thf (40 mL), stirring at -78 °C, was added *n*-BuLi (18 mL, 28.8 mmol, 1.6 M in hexanes). The reaction was allowed to stir at -78 °C for 15 min. o the solution was added epoxide 3.143 (2.0 mL, 19.2 mmol) and immediately followed by BF<sub>3</sub>·OEt<sub>2</sub> (3.6 mL, 28.8 mmol). The reaction was allowed to stir at -78 °C for 1 h. The reaction was quenched by the addition of NH<sub>4</sub>Cl and washed with Et<sub>2</sub>O (3 x). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The unpurified alcohol was dissolved in MeOH (20 mL) and was added K<sub>2</sub>CO<sub>3</sub> (10.6 g, 77.1 mmol). The mixture was allowed to stir at 22 °C for 16 h, at which time was diluted with brine/NH<sub>4</sub>Cl (4:1) and washed with Et<sub>2</sub>O (3 x). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered not combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The unpurified alcohol was allowed to stir at 22 °C for 16 h, at which time was diluted with brine/NH<sub>4</sub>Cl (4:1) and washed with Et<sub>2</sub>O (3 x). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered not concentrated pressure. The unpurified alcohol **3.145** was used without purification in the next step.

To a solution of unpurified alcohol **3.145** in  $CH_2Cl_2$  (100 mL) was added imidazole (3.92 g, 57.7 mmol) and TESCl (7.25 mL, 43.2 mmol). The reaction was allowed to stir at 22 °C for 2 h, at which time the volatiles were removed under reduced pressure. To the mixture was added hexanes and filtered. The filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (1% Et<sub>2</sub>O in hexanes) to afford **3.146** (2.9 g, 12.9 mmol, 67% yield) as clear, colorless oil. **IR (neat):** 3314 (m), 2957 (s),

2936 (s), 2912 (s), 2876 (s), 1459 (m), 1415 (m), 1377 (m), 1364 (m), 1239 (m), 1128 (s), 1111 (s), 1092 (s), 1042 (s), 1007 (s), 931 (w), 888 (w), 838 (w), 783 (m), 728 (s), 635 (s) cm<sup>-1</sup>; <sup>1</sup>**H NMR (CDCl<sub>3</sub>, 400 MHz):**  $\delta$  3.88–3.73 (1H, m), 2.34–2.30 (2H, m), 1.98 (1H, td, *J* = 2.7, 0.5 Hz), 1.69–1.26 (4H, m), 0.97 (9H, td, *J* = 7.9, 0.5 Hz), 0.94–0.90 (3H, m), 0.66–0.58 (6H, m); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  81.9, 70.8, 70.0, 39.1, 27.7, 18.6, 14.3, 7.0, 5.1; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>13</sub>H<sub>27</sub>OSi: 227.1831; found: 227.1827.

(*R*,*E*)-((1-(Dimethyl(phenyl)silyl)-2-methylhept-1-en-4-yl)oxy)triethylsilane (3.147). Lithium metal (312 mg, 45.0 mmol) was added to a flame dried round-bottomed flask. The flask was evacuated and refilled with argon before thf (20 mL) was added. The mixture was cooled to 0 °C and PhMe<sub>2</sub>SiCl (1.66 mL, 10.00 mmol) was added. The resulting mixture was stirred at 0 °C for 6 h to afford PhMe<sub>2</sub>SiLi (0.5 M) as a dark red solution. The solution was used immediately for the reaction.

To a mixture of CuCN (653 mg) in thf (16 mL), stirring at 0 °C, was added PhMe<sub>2</sub>SiLi (28.2 mL, 0.5 M in thf). The reaction was allowed to stir at 0 °C for 30 min. The solution was added a solution of alkyne **3.146** (1.1 g, 4.86 mmol) in thf (40 mL). The reaction was allowed to stir at 0 °C for 1 h. To the reaction was added MeI (3.0 mL, 48.6 mmol) at 0 °C. The reaction was allowed to stir at 0 °C for 1 h, at which time was quenched by the addition of NH<sub>4</sub>OH and Et<sub>2</sub>O. The mixture was allowed to stir vigorously for 5 min and washed with Et<sub>2</sub>O (3 x). The combined organic extracts were washed with H<sub>2</sub>O and brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography (100% hexanes to 0.25% Et<sub>2</sub>O in hexanes) to afford **3.147** (1.7 g, 4.51 mmol, 92% yield) as clear, colorless oil. **IR (neat):** 2955 (m), 2910 (m), 2875 (m), 1614 (w), 1458 (w), 1427 (m), 1413 (w), 1377 (w), 1247 (s), 1110 (s), 1089 (s), 1039 (s), 1010 (s), 940 (w), 806 (s), 80 (s), 725 (s), 698 (s), 645 (m), 580 (m) cm<sup>-1</sup>; <sup>1</sup>H **NMR (CDCl<sub>3</sub>, 400 MHz):** δ 7.59–7.49 (2H, m), 7.37–7.30 (3H, m), 5.38 (1H, q, J = 1.0 Hz), 3.82 (1H, q, J = 5.9 Hz), 2.27 (2H, ddd, J = 16.4, 6.5, 1.0 Hz), 1.71 (3H, d, J = 0.9 Hz), 1.49-1.29 (1H, m), 0.99-0.93 (10H, m), 0.92-0.88 (3H, m), 0.59 (7H, q, J = 7.9 Hz), 0.36 (3H, s), 0.34 (3H, s), 0.07 (4H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 154.7, 133.9,

128.8, 127.8, 124.1, 71.2, 51.4, 39.6, 22.9, 18.7, 14.4, 7.1, 5.3, 1.2, -0.8, -0.9; **HRMS** (DART) [M+H]<sup>+</sup> calcd for C<sub>22</sub>H<sub>41</sub>OSi<sub>2</sub>: 377.2696, found: 377.2709.

(*R*,*E*)-Triethyl((1-iodo-2-methylhept-1-en-4-yl)oxy)silane (3.148). To a solution of alkenyl silane 3.147 (349.9 mg, 0.929 mmol) in CH<sub>3</sub>CN (4.5 mL) and benzene (2 mL), stirring at 0 °C, was added a solution of NIS (1.045 g, 4.644 mmol) in CH<sub>3</sub>CN (4.5 mL). The reaction was allowed to stir at 0 °C for 4 h. The reaction was quenched by the addition of saturated solution of aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and washed with Et<sub>2</sub>O (3 x). The combined organic extracts were washed with H<sub>2</sub>O and brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography (100% hexanes) to afford 3.148 (277.5 mg, 0.7528 mmol, 81% yield) as pale yellow oil. IR (neat): 2956 (s), 2936 (s), 2912 (w), 2875 (m), 1458 (w), 1427 (w), 1414 (w), 1377 (w), 1259 (m), 1088 (s), 1039 (s), 1011 (s), 978 (w), 932 (w), 801 (s), 774 (s), 726 (s), 700 (s), 670 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  5.91 (1H, d, *J* = 1.6 Hz), 3.78 (1H, p, *J* = 6.0 Hz), 2.36–2.28 (2H, m), 1.84 (3H, d, *J* = 1.0 Hz), 1.43–1.22 (4H, m), 0.95 (9H, t, *J* = 7.9 Hz), 0.93–0.86 (3H, m), 0.58 (7H, q, *J* = 8.0 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  145.3, 70.4, 47.7, 39.7, 24.6, 18.7, 14.4, 7.1, 5.2, 1.2; HRMS (DART) [M+H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>30</sub>IOSi: 369.1111, found: 369.1148.

(*R*,*E*)-6-Methyl-8-oxooct-6-en-4-yl acetate (3.151). To a solution of iodide 3.148 (278 mg, 0.753 mmol) in Et<sub>2</sub>O (8 mL), stirring at -78 °C, was added *n*-BuLi (641 µL, 1.50 mmol, 2.35 M in hexanes). The reaction was allowed to stir at -78 °C for 30 min. To the reaction was then added DMF (292 µL, 3.77 mmol) at -78 °C and was allowed to stir at -78 °C for 30 min. The reaction was quenched by the addition of saturated solution of aqueous NH<sub>4</sub>Cl and washed with Et<sub>2</sub>O (3 x). The combined organic extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The unpurified aldehyde 3.150 was used without purification in the next step.

To the unpurified aldehyde **3.150** in EtOH (1.5 mL) was added AcOH (140  $\mu$ L, 2.45 mmol) and tbaf (1.51 mL, 1.51 mmol, 1.0 M in thf). The reaction was allowed to stir at 22 °C for 1 h. The reaction was diluted with Et<sub>2</sub>O and quenched by the addition of saturated solution of aqueous NH<sub>4</sub>Cl. The layers were separated and the aqueous layer was washed with Et<sub>2</sub>O.

The combined organic extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The unpurified alcohol **3.150** was used without purification in the next step.

To the unpurified alcohol **3.150** in CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL) was added triethylamine (157 µL, 1.13 mmol), DMAP (9.2 mg, 0.0753 mmol) and acetic anhydride (85 µL, 0.904 mmol). The mixture was allowed to stir at 22 °C for 2 h, at which time the reaction was quenched by the addition of saturated solution of aqueous NH<sub>4</sub>Cl and washed with CH<sub>2</sub>Cl<sub>2</sub>. The organics were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The resulting oil was purified immediately by silica gel chromatography (5% to 15% Et<sub>2</sub>O in hexanes) to afford **3.151** (128 mg, 0.647 mmol, 45% yield) as clear, colorless oil. **IR (neat):** 2960 (m), 2935 (m), 2874 (m), 1736 (s) , 1675 (s), 1633 (w), 1440 (w), 1374 (w), 1236 (m), 1196 (s), 1126 (m), 1113 (w), 1069 (w), 1046 (m), 1022 (s) cm<sup>-1</sup>; <sup>1</sup>**H NMR (CDCl<sub>3</sub>, 400 MHz):**  $\delta$  9.94 (1H, d, *J* = 8.0 Hz), 5.83 (1H, dq, *J* = 8.0, 1.2 Hz), 5.09 (1H, tt, *J* = 8.1, 4.8 Hz), 2.43 (1H, ddd, *J* = 13.6, 8.3, 0.9 Hz), 2.34 (1H, ddd, *J* = 13.6, 4.8, 1.0 Hz), 2.18 (3H, d, *J* = 1.4 Hz), 1.98 (3H, s), 1.64–1.43 (2H, m), 1.43–1.23 (1H, m), 0.89 (4H, t, *J* = 7.3 Hz); <sup>13</sup>**C NMR (CDCl<sub>3</sub>, 100 MHz):**  $\delta$  191.0, 170.7, 159.3, 129.8, 71.1, 45.9, 36.6, 21.1, 18.7, 17.7, 13.9; **HRMS (DART) [M+H]**<sup>+</sup> calcd for C<sub>14</sub>H<sub>19</sub>O<sub>2</sub>: 199.1334, found: 199.1334.

### Synthesis of C15-C30 Fragment

#### (4R,8R,9R,12R,E)-8-Hydroxy-12-((4-methoxybenzyl)oxy)-6,9-dimethyl-10-

**oxoheptadec-6-en-16-yn-4-yl acetate (3.153).** To a solution of ketone **3.133**<sup>49</sup> (187 mg, 0.647 mmol) in Et<sub>2</sub>O (3.2 mL), stirring at 0 °C, was added triethylamine (135  $\mu$ L, 0.971 mmol) and chlorodicyclohexylborane (170  $\mu$ L, 0.777 mmol). The reaction was allowed to stir for 2 h. The mixture was cooled to -78 °C and a solution of aldehyde **3.151** (128 mg, 0.647 mmol) in Et<sub>2</sub>O (3.2 mL) was added. The reaction was allowed to stir at -78 °C for 30 min. The reaction was allowed to warm to -20 °C and allowed to proceed at -20 °C for 14 h. The reaction was allowed to warm to 0 °C and was quenched with a solution of pH 7 buffer/MeOH (3.0 mL, 2:1 v/v). To the mixture was added H<sub>2</sub>O<sub>2</sub> (0.5 mL, 30 % wt in H<sub>2</sub>O)

<sup>(49)</sup> Compound was dried under azeotropic conditions with C<sub>6</sub>H<sub>6</sub>.

was added. The reaction was allowed to warm to 22 °C and stir for 1 h. The mixture was diluted with Et<sub>2</sub>O and layers were separated. The aqueous phase was back washed with Et<sub>2</sub>O (3 x). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography (10% to 50% Et<sub>2</sub>O in CH<sub>2</sub>Cl<sub>2</sub>) to afford **3.152** (141 mg, 0.290 mmol, 45% yield) as clear, colorless oil. **IR (neat)**: 3476 (br), 3294 (w), 2958 (m), 2933 (m), 2873(w), 1732 (s), 1711 (s), 1613 (m), 1514 (s), 1456 (s), 1373 (s), 1302 (m), 1243 (s), 1174 (m), 1109 (m), 1024 (s), 820 (m), 757 (w), 635 (m) cm<sup>-1</sup>; <sup>1</sup>**H NMR (CDCl<sub>3</sub>, 400 MHz)**: 7.22 (2H, d, *J* = 8.6 Hz), 6.85 (2H, d, *J* = 8.6 Hz), 5.17–5.11 (1H, m), 5.02 (1H, tt, *J* = 7.7, 5.2 Hz), 4.44 (2H, s), 4.05–3.95 (1H, m), 3.79 (4H, s), 2.93–2.84 (1H, m), 2.65–2.49 (2H, m), 2.18 (2H, t, *J* = 1.5 Hz), 2.01 (3H, s), 1.69–1.24 (7H, m), 0.94–0.86 (7H, m); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  213.5, 171.1, 169.4, 159.3, 136.7, 130.6, 129.6, 128.4, 113.9, 84.3, 74.5, 72.0, 71.5, 70.4, 68.7, 55.4, 55.4, 53.2, 47.9, 45.0, 36.4, 33.4, 24.2, 21.3, 18.7, 18.6, 17.3, 14.0, 13.3; HRMS (DART) [M+NH4]<sup>+</sup> calcd for C<sub>16</sub>H<sub>33</sub>O<sub>3</sub>Si: 504.3325, found: 504.3340.

(4*R*,8*R*,9*R*,12*R*,*E*)-8-((*tert*-Butyldimethylsilyl)oxy)-12-((4-methoxybenzyl)oxy)-6,9dimethyl-10-oxoheptadec-6-en-16-yn-4-yl acetate (3.153). To a solution of alcohol 3.152 (54.4 mg, 0.112 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (200 µL), stirring at -20 °C, was added 2,6-lutidine (103 µL, 0.445 mmol) and TBSOTf (26 µL, 0.224 mmol). The reaction was allowed to warm to 22 °C and stir for 1 h. The reaction was diluted CH<sub>2</sub>Cl<sub>2</sub> and quenched by the addition of saturated solution of aqueous NaHCO<sub>3</sub>. The layers were separated and the aqueous layer was washed with EtOAc (3 x). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography (15% Et<sub>2</sub>O in hexanes) to afford **3.153** (35.6 mg, 0.0592 mmol, 53% yield) as colorless oil. **IR (neat):** 3310 (w), 2956 (m), 2931 (m), 2857 (m), 1735 (s), 1716 (m), 1613 (m), 1514 (s), 1461 (m), 1372 (m), 1302 (w), 1244 (s), 1173 (m), 1056 (s), 1037 (s), 938 (w), 911 (w), 835 (s), 776 (s), 733 (m), 669 (m), 628 (m), 572 (w), 517 (w) cm<sup>-1</sup>; <sup>1</sup>**H NMR (CDCl<sub>3</sub>, 400 MHz**): 7.24–7.19 (2H, m), 6.86– 6.81 (2H, m), 5.08 (1H, dq, J = 9.3, 1.2 Hz), 5.06–4.97 (2H, m), 4.45 (2H, d, J = 4.1 Hz), 3.97 (1H, dq, J = 7.8, 4.8, 4.2 Hz), 3.78 (3H, s), 2.90 (1H, dd, J = 17.2, 7.3 Hz), 2.66–2.60 (1H, m), 2.58–2.49 (1H, m), 2.33–2.11 (5H, m), 2.01 (3H, s), 1.94 (1H, q, J = 2.6 Hz), 1.69 (4H, dd, J = 4.5, 1.4 Hz), 1.66–1.53 (4H, m), 1.53–1.45 (2H, m), 1.41–1.27 (1H, m), 0.90 (4H, td, J = 7.3, 3.6 Hz), 0.85 (3H, d, J = 7.0 Hz), 0.81 (9H, s), -0.04 (7H, d, J = 1.7Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  212.7, 170.8, 159.3, 134.0, 131.0, 130.0, 129.5, 129.5, 113.9, 84.4, 74.3, 72.5, 72.4, 71.7, 68.6, 55.4, 53.6, 50.3, 44.3, 36.2, 33.8, 26.0, 24.4, 21.5, 18.6, 18.6, 18.1, 17.5, 14.1, 13.0, -4.0, -5.0; HRMS (DART) [M+NH4]<sup>+</sup> calcd for C<sub>13</sub>H<sub>23</sub>O<sub>2</sub>: 618.4190, found: 618.4168.

#### (4R,8R,9S,10S,12R,E)-8-((tert-Butyldimethylsilyl)oxy)-10,12-dihydroxy-6,9-

dimethylheptadec-6-en-16-yn-4-yl acetate (3.155). To a solution of 3.153 (35.6 mg, 0.0592 mmol) in  $CH_2Cl_2(2 mL)$  and pH 7 buffer (2 mL) was added DDQ (53.8 mg, 0.237 mmol). The biphasic mixture was allowed to stir at 22 °C for 90 min, at which time the reaction was diluted with  $CH_2Cl_2$  and quenched by the addition of saturated solution of aqueous NaHCO<sub>3</sub>. The layers were separated and the aqueous layer was back washed with  $CH_2Cl_2$ . The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated. The unpurified alcohol 3.154 was used without purification in the next step.

Me<sub>4</sub>NHB(OAc)<sub>3</sub> (17.3 mg, 0.592 mmol, 90%) was stirred in a 1:1 mixture of AcOH and CH<sub>3</sub>CN (0.5 mL) at 22 °C for 30 min. The mixture was cooled to -40 °C and to the mixture was added a solution of alcohol **3.154** in a 1:1 mixture of AcOH and CH<sub>3</sub>CN (1.0 mL). The reaction was allowed to stir at -40 °C for 1 h and then allowed to warm to 0 °C and stir for an additional 2 h. The reaction was quenched by the addition of saturated solution of aqueous potassium sodium tartrate and vigorously stirred for 5 min at which time was poured into a flask containing CH<sub>2</sub>Cl<sub>2</sub>. To the mixture was carefully added saturated solution of aqueous NaHCO<sub>3</sub>. The layers were separated and the aqueous layer was back washed with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were washed with saturated solution of aqueous NaHCO<sub>3</sub> and brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The resulting oil was purified by silica get chromatography (50% Et<sub>2</sub>O in hexanes) to afford **3.155** (25.1 mg, 0.0519 mmol, 88% yield) as clear, colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, **400 MHz**): 5.18 (1H, dq, *J* = 9.3, 1.3 Hz), 5.02 (1H, qd, *J* = 6.7, 5.1 Hz), 4.30 (1H, dt, *J* = 9.0, 7.5 Hz), 3.98–3.85 (2H, m), 2.35–2.10 (6H, m), 2.01 (3H, d, *J* = 2.1 Hz), 1.93 (1H,

t, *J* = 2.6 Hz), 1.81–1.17 (21H, m), 0.87 (12H, s), 0.06 (4H, s), 0.02 (4H, d, *J* = 4.4 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 170.9, 133.5, 130.7, 84.6, 76.1, 73.9, 72.6, 68.5, 44.4, 39.6, 36.6, 36.3, 31.7, 25.9, 24.9, 22.8, 21.5, 18.6, 18.1, 17.5, 14.2, 14.1, 12.7, -3.6, -4.9.

(4*R*,8*R*,9*R*,*E*)-9-((4*S*,6*R*)-2,2-dimethyl-6-(pent-4-yn-1-yl)-1,3-dioxan-4-yl)-8-hydroxy-6-methyldec-6-en-4-yl acetate (3.157). To a solution of diol 3.155 (30.8 mg) in CH<sub>2</sub>Cl<sub>2</sub> (160  $\mu$ L) was added 2,2-dimethoxypropane (237  $\mu$ L) and PPTS (1.6 mg, 0.0064 mmol). The reaction was allowed to stir at 22 °C for 16 h. The reaction was concentrated under reduced pressure. The unpurified acetal 3.156 was used without purification in the next step.

To a solution of unpurified acetal **3.156** in thf was added tbaf (638 µL, 0.638 mmol, 1.0 M in thf). The reaction was allowed to stir at 22 °C for 16 h, at which time the reaction was diluted with Et<sub>2</sub>O and quenched by the addition of saturated solution of aqueous NH<sub>4</sub>Cl. The layers were separated and the organic layer was washed with brine. The aqueous layer was back washed with EtOAc. The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography (50% Et<sub>2</sub>O in hexanes) to afford **3.157** (24.8 mg, 0.0606 mmol, 95% yield) as clear, colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): 5.19–5.13 (1H, m), 5.03 (1H, tt, *J* = 7.3, 5.7 Hz), 4.27 (1H, dd, *J* = 9.2, 8.3 Hz), 3.76 (3H, tt, *J* = 9.2, 5.1 Hz), 2.30–2.13 (4H, m), 2.02 (2H, s), 1.94 (1H, t, *J* = 2.6 Hz), 1.71 (3H, d, *J* = 1.4 Hz), 1.70–1.61 (2H, m), 1.61–1.45 (4H, m), 1.39–1.37 (3H, m), 1.36–1.32 (4H, m), 0.93–0.86 (3H, m), 0.70 (3H, d, *J* = 7.0 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  171.0, 150.1, 135.1, 129.3, 100.8, 84.4, 72.7, 72.3, 72.2, 68.6, 66.4, 44.9, 44.2, 38.0, 36.3, 34.9, 24.7, 24.6, 21.4, 18.7, 18.4, 17.3, 14.1, 11.5.







































![](_page_431_Figure_1.jpeg)










































