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Efficient and Selective Formation of Macrocyclic Disubstituted *Z* Alkenes by Ring-Closing Metathesis (RCM) Reactions Catalyzed by Mo- or W-Based Monoaryloxide Pyrrolide (MAP) Complexes: Applications to Total Syntheses of Epilachnene, Yuzu Lactone, Ambrettolide, Epothilone C, and Nakadomarin A

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Abstract: The first broadly applicable set of protocols for efficient *Z*-selective formation of macrocyclic disubstituted alkenes through catalytic ring-closing metathesis (RCM) is described. Cyclizations are performed with 1.2–7.5 mol% of a Mo- or W-based monoaryloxide pyrrolide (MAP) complex at 22°C and proceed to complete conversion typically within two hours. Utility is demonstrated by synthesis of representative macrocyclic alkenes, such as natural products yuzu lactone (13-membered ring: 73% *Z*) epilachnene (15-membered ring: 91% *Z*), ambrettolide (17-membered ring: 91% *Z*), an advanced precursor to epothilones C and A (16-membered ring: up to 97% *Z*), and nakadomarin A (15-membered ring: up to 97% *Z*). We show that catalytic *Z*-selective cyclizations can be performed efficiently on gram-scale with complex molecule starting materials and catalysts that can be handled in air. We elucidate several critical principles of the catalytic protocol: 1) The complementary nature of the Mo catalysts, which deliver high activity but can be more prone towards engendering post-RCM stereoisomerization, versus W variants, which furnish lower activity but are less inclined to cause loss of kinetic *Z* selectivity. 2) Reaction time is critical to retaining kinetic *Z* selectivity not only with MAP species but with the widely used Mo bis(hexafluoro-*tert*-butoxide) complex as well. 3) Polycyclic structures can be accessed without significant isomerization at the existing *Z* alkenes within the molecule.

Keywords: catalysis · macrocyclic *Z* alkenes · molybdenum · olefin metathesis · synthesis · tungsten

Introduction

Few transformations have had as palpable an impact on organic chemistry as catalytic alkene ring-closing metathesis (RCM).[1] During the last two decades, the routes to countless molecules, natural products or otherwise, with one or more cyclic moieties have contained an RCM reaction that generates a small-, medium-, or large-ring olefin.[2] There are several reasons for such a strong predilection. Alkenes are relatively robust and yet can be readily modified in a variety of ways once the cyclization products are in hand; C–C double bonds do not typically require protection and unmasking in the course of a synthesis route; by comparison, and as an example, the alcohol and carboxylic acid (or equivalents thereof) required to bring about a lactonization must often be differentiated from other polar functional groups at the time of the ring closure. Reliability is another factor—an attribute that receives increasing credence with every new total synthesis that utilizes this set of processes.

Catalytic RCM has played a prominent role in connection with the synthesis of macrocyclic alkenes, a structural motif found in an array of biologically active molecules.[3] Since the disclosures by Villemin[4] and Tsuji[5] in 1980, concerning non-stereoselective macrocyclic RCM reactions promoted by (ill-defined) W-based complexes, making evident the potential value of catalytic RCM, a glaring deficiency in catalytic alkene metathesis has persisted: the absence of catalysts that reliably deliver *kinetic control* of stereoselectivity in the formation of large-ring olefins. Dependence on substrate control—attaining stereoselectivity that would originate from the thermodynamic preference for one alkene geometry—does not typically lead to the selective formation of the targeted isomer; *E* and *Z* olefins are frequently gen-

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erated in near equal ratios or, even less favorably, it is the undesired product that is obtained predominantly. A catalyst class that furnishes dependable control of the stereochemical outcome in a macrocyclization would enhance the utility of this important collection of catalytic processes. In spite of such a shortcoming, it is catalytic RCM that is perhaps commonly viewed as the most suitable approach to macrocyclic ring formation; such is true even in the precarious situations where the cyclization must be implemented after a multistep sequence is expended to obtain the requisite precursor—when a non-selective RCM can reduce the yield of the desired alkene isomer and the entire synthesis route by 50% or more (see below for examples).

Development of complexes that preferentially provide the *Z* alkenes constitutes a hard challenge. One principal complication arises from the reversible nature of catalytic olefin metathesis, which threatens the survival of the often energetically less favored *Z* isomer. There are, therefore, two distinct but equally significant requirements for successful design of efficient *Z*-selective catalysts that promote macrocyclic RCM: not only must such species facilitate the formation of the higher energy alkene isomer with exceptional selectivity, they must then refrain from reacting with it to cause adventitious *Z*-to-*E* isomerization. The latter complication regarding chemoselectivity grows increasingly daunting as substrate conversion escalates and the concentration of the product surpasses that of the starting terminal olefins.

Herein, we detail the outcome of our investigations regarding the development of the first class of catalytic olefin metathesis reactions that provide high efficiency and *Z* selectivity in the synthesis of macrocyclic disubstituted alkenes;[6] we show that an assortment of large-ring structures can be accessed stereoselectively through transformations promoted by Mo- or W-based monoaryloxide pyrrolide (MAP) complexes.[7] Syntheses of yuzu lactone, epilachnene, ambrettolide, as well as anticancer and antibacterial agents epothilones A and C[8] and nakadomarin A[9] (Figure 1) have been accomplished through catalytic *Z*-selective RCM. In all cases, reactions with previously available catalysts either afford a near equal mixture of alkene isomers ($\leq$ 65:35) or furnish the undesired *E* alkene predominantly.

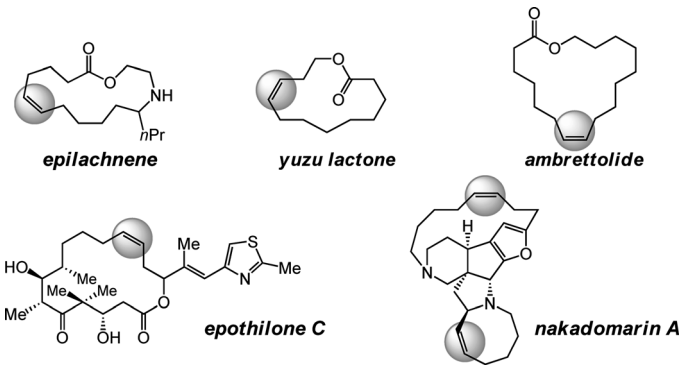


Figure 1. Natural products with a *Z* macrocyclic alkene examined in this study.

Cyclizations of starting materials ranging from sparsely to amply functionalized dienes outline the relationship between optimal catalyst activity and the nuances of substrate structure. Our investigations indicate that the more conformationally mobile substrates might require Mo-based complexes; in contrast, with the relatively preorganized unsaturated chains, use of the less active W catalysts can be preferable. We elucidate the basis of the high chemoselectivity furnished by W-based catalysts; such complexes catalyze RCM but exhibit minimal tendency to react with the resulting and relatively strained macrocyclic *Z* olefin and cause isomerization to the *E* isomer. The latter attribute is highlighted through a total synthesis of nakadomarin A, where the RCM process used to install the cyclooctene moiety proceeds without significant erosion of *Z*:*E* ratio at the sensitive fifteen-membered ring alkene site. We demonstrate that with the relatively robust W-based alkylidenes, which can be handled without rigorous exclusion of air and moisture, gram-scale RCM reaction of a structurally complex diene can be carried out efficiently and with effective kinetic control of stereoselectivity.

Results and Discussion

Mechanistic models for *Z* selectivity in macrocyclic RCM promoted by MAP complexes: We begin by an analysis of the origin of *Z* selectivity in the projected macrocyclic RCM reactions and some of the structural features that lead to effective catalysis by Mo- and W-based MAP complexes. Such an examination helps elucidate the nature of some of the difficulties faced in the course of development of the present class of transformations.

Based on the *Z*-selective ring-opening/cross-metathesis[10] as well as cross-metathesis reactions studied before,[11] we projected that control of olefin stereochemistry originates from sufficient size differential between the imido (Figure 2) and aryloxide ligands of the catalyst. Thus, as shown in Figure 2, the bulky and freely rotating aryloxide can force the alkene, tethered to the metal–alkylidene, to coordinate with the metal center so that the resulting metallacyclobutane substituents are oriented towards the smaller imido unit (cf. **III**, Figure 2). Productive decomposition of **III** would furnish alkene complex **IV** and subsequent release of macrocyclic *Z* olefin produces methylidene complex **V**, which can react with another diene molecule to re-generate **I/II**.

Olefin metathesis is inherently reversible;[12] as depicted by the general pathway in Figure 3 (box), the kinetically generated *Z* alkene can be catalytically isomerized to the (often) lower energy *E* isomer. Consequently, the same factors that lead to high *Z* selectivity make available a pathway for catalytic post-RCM isomerization. The steric repulsion between the alkylidene substituent and the sizeable aryloxide, shown in complex **VI** (Figure 3), culminates in a strong preference for modes of reaction represented by **I/II** (Figure 2). It follows that re-association of an *E* macrocyclic

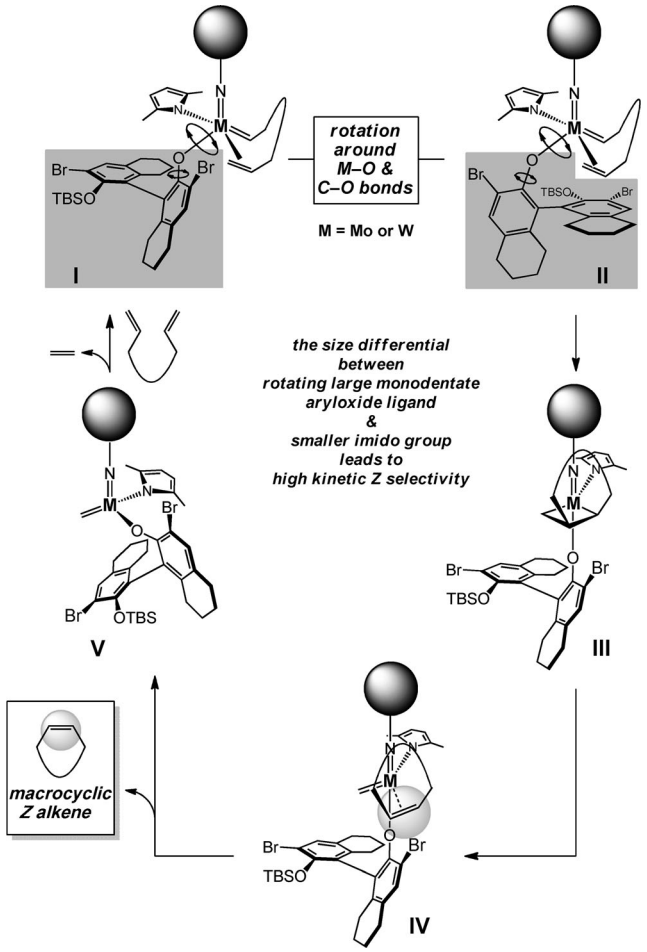


Figure 2. Key structural features of MAP alkylidenes responsible for high *Z* selectivity in macrocyclic RCM reactions.

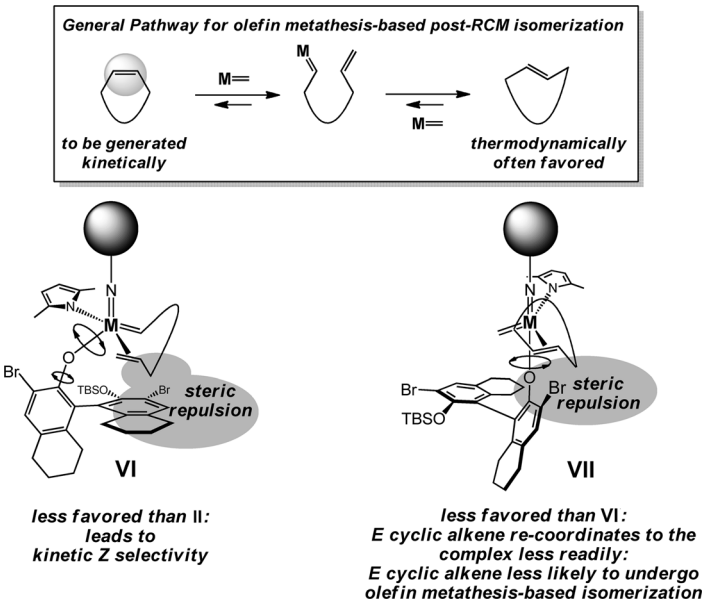


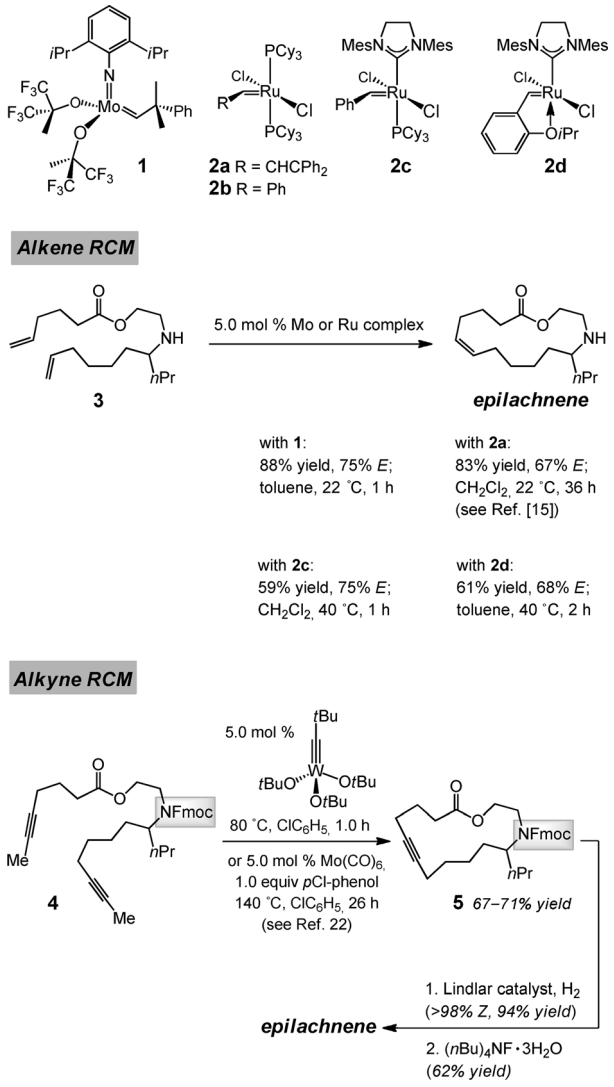
Figure 3. A general scheme for catalytic post-RCM isomerization; structural attributes that result in high *Z* selectivity can also lead to facile post-RCM isomerization.

alkene with the complex, as featured in **VII** (Figure 3), would be similarly unfavorable compared to the corresponding system containing the *Z* isomer (cf. **IV**, Figure 2). That is, the *Z* olefin products are more susceptible towards undergoing ring-opening reactions that lead to *Z*-to-*E* isomerization (cf. Figure 3), whereas any *E* alkene formed is less prone to re-enter the catalytic cycle. The above considerations further emphasize the central challenge in designing olefin metathesis catalysts that efficiently and selectively deliver the less energetically favored stereoisomers: the metal complex must be sufficiently active and discriminating to generate the *Z* alkene with a strong preference but not too potent so that the fragile kinetic selectivity can be preserved.

Z-Selective macrocyclic RCM of less substituted dienes: We began by examining reactions of several relatively unfunctionalized diene precursors as the means to investigate several fundamental aspects of the cyclization process. The influence of ring size and different types of linking units (e.g., carboxylic esters or amides) on the efficiency and stereoselectivity of macrocyclization reactions would hence be probed. We surmised that the requirements rendering a catalyst optimal for a more conformationally mobile substrate, versus one that is more rigid, might be distinct; such studies, together with subsequent investigations involving the more highly functionalized dienes (i.e., precursors to epothilone C and nakadomarin A), would help delineate factors regarding the suitability of different catalyst classes and various substrate types.

Stereoselective synthesis of epilachnene: We chose the fifteen-membered ring macrolactone epilachnene (cf. Scheme 1),[13] secreted by the Mexican bean beetle as part of its pupae defense mechanism,[14] to serve as the initial platform for our investigations. The basis for this selection was partly because the aza-macrolide natural product has been synthesized through catalytic diene RCM as well as alkyne RCM/catalytic hydrogenation strategies; any limitation in the state-of-the-art in connection with either synthesis route could be evaluated and addressed. A catalytic stereoselective RCM furnishing epilachnene would represent a more efficient approach than those formerly outlined,[15] and would likely be applicable to the synthesis of an assortment of other sparingly substituted macrocycles.

Previous syntheses of epilachnene: The results of extant investigations regarding synthesis of epilachene are summarized in Scheme 1. In the presence of Mo-based bis-alkoxide **1**,[16] Ru-based bis-phosphines **2a**[17] and **2b**[18] or those that bear an N-heterocyclic carbene (**2c**,**d**),[19,20] complexes commonly used in olefin metathesis, diene **3** is preferentially converted to the undesired *E* isomer (67–75%). To address this problem, as shown in Scheme 1, an alternative stereoselective route, involving W- or Mo-catalyzed alkyne metathesis,[21] was introduced.[22] Catalytic RCM with the diyne sub-



Scheme 1. Previous approaches to epilachnene involving catalytic ring-closing alkene and alkyne metathesis reactions; unless otherwise noted, findings are from this study. Fmoc = 9-fluorenylmethoxycarbonyl.

strate delivers the macrocyclic alkyne in approximately 70% yield; subsequent partial hydrogenation, promoted by Lindlar's catalyst (i.e., deposited Pd-containing Pb salts) leads to the formation of the *Z* olefin. The latter route delivers exceptional *Z* selectivity (<2% *E*); however, several issues are worthy of note:

1) The basic amine must be masked in order to achieve high catalyst activity, leading to the addition of two steps to the synthesis route (protection and removal of the Fmoc group); the deprotection step was reported to proceed in 62% yield (Scheme 1).[22]

2) Preparation of methyl-substituted internal alkyne, typically involving deprotonation of the corresponding acetylene and alkylation with iodomethane, is needed (vs. terminal C–C triple bonds); otherwise, oligomerization processes dominate.[23]

3) In general, preparation of alkyne-containing substrates tends to be less concise than that of dienes. Synthesis of diyne precursor to **4** (before amine protection) was accomplished in eleven steps (longest linear sequence of eight steps);[22] in contrast, diene **3** is prepared in five steps from inexpensive materials; such discrepancy is due to several factors, among which is the larger number of inexpensive commercially available olefinic compounds.

4) Catalytic alkyne RCM may need elevated temperatures (Scheme 1). However, more recent advances have led to the development of catalysts that do not call for the use of chlorinated solvents and/or an additive and operate at ambient temperature.[24]

Z-Selective diene RCM with MAP complexes: Treatment of unsaturated amine **3** with 1.2 mol%[25] Mo-based adamantylimido alkylidene **6** or 5.0 mol% W-based metallacyclobutane arylimido complex **7** (Scheme 2) delivers epilachnene in 70% and 82% yield and 91% *Z* selectivity. The suitability of the aforementioned complexes was established through an initial screening of a simpler model system, details of which were disclosed in the preliminary account of this investigation.[6] Several additional aspects of the above findings are noteworthy:

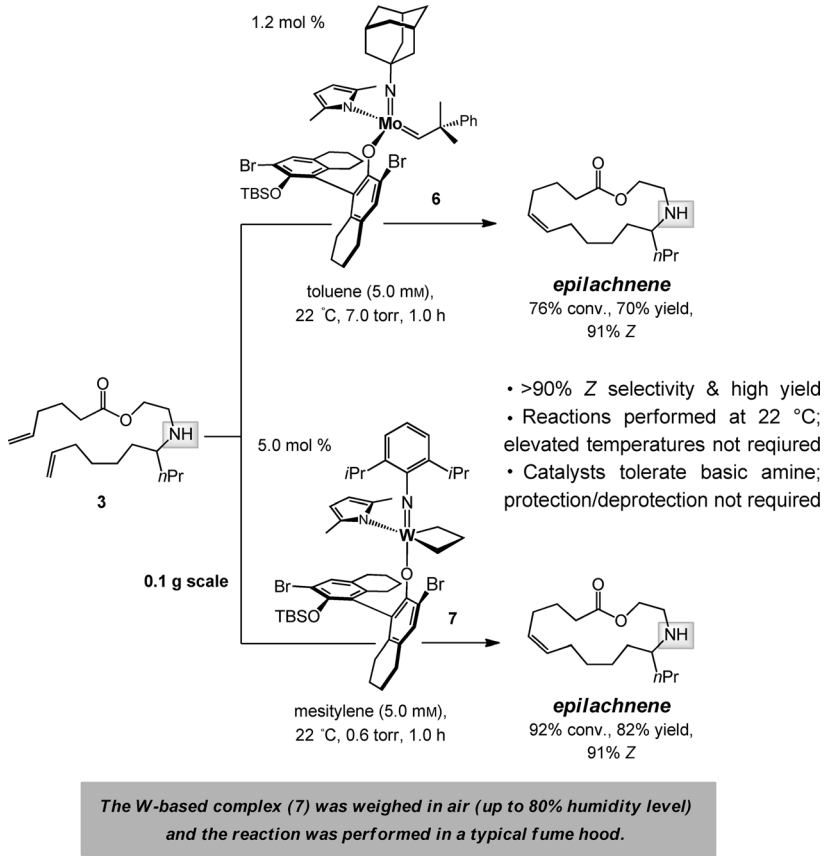
1) Metallacyclobutane **7**[26] is sufficiently robust that it can be weighed in air and various manipulations can be performed in a fume hood with standard glassware. The W-catalyzed cyclization, performed at 0.1 gram-scale, entailed handling of the W-based complex in air at nearly 80% humidity level.

2) Metallacyclobutane **7** is prepared by subjection of a solution of the corresponding neophylidene complex to an atmosphere of ethylene; this complex can be viewed as a more attractive option for catalyzing olefin metathesis reactions, compared to its more sterically congested alkylidene precursor, perhaps due to a faster rate of initiation [i.e., release of ethylene in solution affords the active methylidene (cf. **V**, Figure 2)].

3) The *Z*-selective synthesis of epilachnene by catalytic diene RCM does not demand protection and deprotection of the amine unit, underscoring the stability of the Mo- and W-based alkylidenes towards this commonly occurring class of functional groups (in contrast to the corresponding alkylidynes; cf. Scheme 1).

Stereoselective synthesis of yuzu lactone, ambrettolide and other relatively unfunctionalized Z-macrocyclic olefins: Macrocyclic esters or amides of different ring sizes can be synthesized by the use of Mo or W alkylidenes **6** and **7** with unprecedented *Z* selectivity and with efficiency levels that should render the method of notable utility; relevant results are summarized in Table 1. The disparity between the percent conversion and yield is largely due to adventitious oligomerization (as judged by ^{1}H NMR analysis).

Two of the macrocycles are natural products: the thirteen-membered camphor- and minty-smelling yuzu lactone (entries 1–4, Table 1), and seventeen-membered musk-odored ambrettolide (entries 17–20). For comparison, and to underline the uniqueness of the MAP complexes, the data regard-



Scheme 2. Practical and *Z*-selective synthesis of epilachnene.

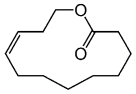
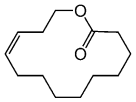
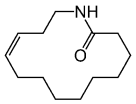
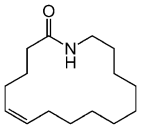
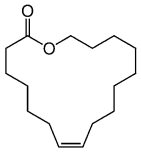
ing the RCM promoted by Mo alkylidene **1** and Ru-based carbene **2c** are presented in Table 1; with the latter two complexes, in all cases, substantial amounts of the *E* alkenes are formed and at times with a significant preference (93% *E* in entries 5 and 6, Table 1). With Mo- and W-based alkylidenes **6** and **7**, there is 69–73% *Z* selectivity in the formation of thirteen-membered yuzu lactone, whereas a higher 93:7 *Z*:*E* ratio can be obtained with sixteen-membered ring **10** (entry 15, Table 1), the identity of which was further confirmed through X-ray crystallography.[27] The above-mentioned *Z* selectivity variations as a function of ring size suggest that a comparatively strained ring (e.g., yuzu lactone) undergoes ring-opening more readily (cf. Figure 2 and 3) and alkene isomerization proceeds at a faster rate. In this vein, when the RCM with complex **6** leading to yuzu lactone is analyzed after 10 min (20% conv.), 82% of the *Z* alkene is found in the mixture (vs. 69:31 *Z*:*E* after one hour). It can be concluded that, at least in certain cases involving relatively strained products, post-RCM isomerization is more competitive, giving rise to relatively high *E*:*Z* selectivity when the highly active bis-alkoxide **1** is used (e.g., 83% *E*, entry 1 vs. 44% *E*, entry 13, Table 1).[28] Calculations indicate that the *E*-**8** isomer is 1.9 kcal mol^{-1} lower in energy than its corresponding *Z* isomer,[27] thus predicting approximately 96% *E* selectivity in a cyclization that is under thermodynamic control; such findings compare favorably with 93:7 *E*:*Z* ratio in entries 5 and 6 in Table 1. Yet, catalytic RCM reactions with **6** or **7** provide 80–82% of the *Z* macrocyclic alkene, pointing to a substantial degree of catalyst control with the MAP complexes (entries 7 and 8, Table 1).

***Z*-Selective macrocyclic RCM en route to epothilone C**: The next phase of our studies relates to examining the catalytic RCM reaction that have served as precursors to epothilones C and A.[29] In such instances, lack of stereoselectivity in the RCM reactions is costly since cyclization takes place at the end of a multistep route to the requisite diene;[30] further complicating the matter, as reported previously[29c] and in our experience, the desired macrolactone is virtually inseparable from the *E* isomer. Moreover, it has been demonstrated that olefin stereochemistry impacts the level of biological activity.[31] Finally, access to the appropriate macrocyclic alkene precursors are required if the subsequent functionalizations are to proceed with the desired sense of stereochemical control (e.g., epoxidation[29] or cyclopropanation[32]).

One goal of this segment of our studies was to showcase the practical utility of the catalytic RCM approach. A highly *Z*-selective RCM leading to epothilone A—particularly if performed on gram-scale and in a practical manner—would bear notable implications regarding the efficiency with which macrocyclic natural products and their corresponding analogues, including those that are not accessible through fermentation procedures, can be accessed in meaningful quantities. Additionally, the substrate is significantly more functionalized and thus its conformational mobility more restricted than those probed earlier. Accordingly, we set out to establish whether the requirements for optimal *Z*-selective macrocyclic RCM are distinct from those that effect cyclizations furnishing the less substituted macrocycles.

Effect of catalyst structure on Z selectivity: The RCM-based approach towards the sixteen-membered ring moiety of epothilone C has been investigated by several research groups;[29] the desired *Z* olefin was formed as the minor isomer in most cases and in equal amounts to the undesired *E* alkene in others;[30] the examples in entries 1–3 of Table 2 are representative (see below for a more detailed analysis of these earlier findings). As with epilachnene (cf. Scheme 1),

Table 1. Synthesis of macrocyclic esters and amides through catalytic *Z*-selective RCM.[a]

Entry	Macrocyclic *Z* alkene	Complex[b]	Loading [mol%]	Conditions	Conv. [%][c]	Yield [%][d]	*Z*:*E*[e]
1		**1**	5.0	ambient	92	30	17:83
2		**2c**	5.0	ambient	93	46	15:85
3		**6**	***3.0***	7.0 torr	***63***	***49***	***69:31***
4	***yuzu lactone***	**7**	***5.0***	7.0 torr	***74***	***46***	***73:27***
5		**1**	5.0	ambient	97	67	7:93
6		**2c**	5.0	ambient	98	74	7:93
7		**6**	***3.0***	7.0 torr	***74***	***50***	***80:20***
8	**8**	**7**	***5.0***	7.0 torr	***82***	***54***	***82:18***
9		**1**	5.0	ambient	96	56	21:79
10		**2c**	5.0	ambient	98	68	15:85
11		**6**	***3.0***	7.0 torr	***72***	***50***	***95:5***
12	**9**	**7**	5.0	7.0 torr	<20	nd	nd
13		**1**	5.0	ambient	93	53	56:44
14		**2c**	5.0	ambient	98	60	66:34
15		**6**	***3.0***	7.0 torr	***81***	***69***	***93:7***
16	**10**	**7**	5.0	7.0 torr	<20	nd	nd
17		**1**	5.0	ambient	95	65	23:77
18		**2c**	5.0	ambient	95	61	24:76
19		**6**	***3.0***	7.0 torr	***85***	***77***	***91:9***
20	***ambrettolide***	**7**	***5.0***	7.0 torr	***90***	***78***	***88:12***

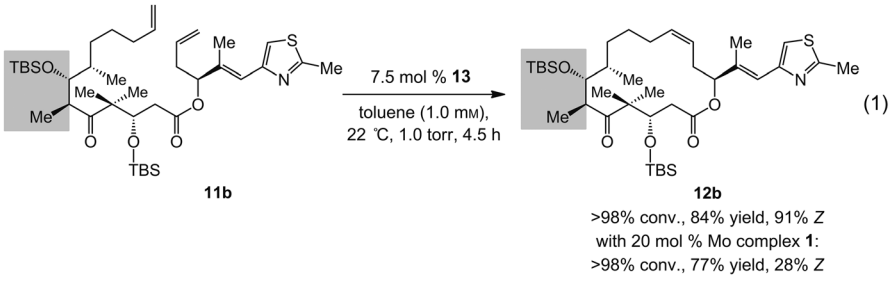
[a] Reactions were carried out in purified toluene (5.0 mM) at 22 °C for one h under an atmosphere of N_2 or under vacuum, as noted; see the Supporting Information for details. [b] Complexes **1**, **2c** and **7** were prepared prior to use, whereas alkylidene **6** was synthesized in situ from the corresponding bispyrrolide and aryl alcohol, proceeding in approximately 60% yield (3.0 mol% effective catalyst loading). See the Supporting Information for details. [c] Conversion and *Z*:*E* ratios measured by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures; *Z*:*E* ratios for **10** and ambrettolide was established by analysis of ^{13}C NMR spectra; the variance of values are estimated to be ±2%. [d] Yield of isolated products (isomeric mixtures) after purification; the variance of values are estimated to be ±5%. nd = not determined.

the indirect route of utilizing catalytic alkyne RCM/partial hydrogenation strategy has been applied to this problem;[33] similar analysis regarding the two strategies applies here as well.

Use of Mo-based adamantylimido alkylidene **6** and W-based di(*i*Pr)imido complex **7** (entries 4 and 5 of Table 2) gives rise to a significant reversal of selectivity in favor of the desired *Z*-**12a**, delivering 85:15 and 79:21 *Z*:*E* selectivity, respectively. We attribute the improved stereochemical control with the Mo complex (**6** vs. **7**) to the larger size difference between an adamantylimido and the aryloxide ligands (vs. a 2,6-(*i*Pr)$_2$phenylimido in **7**; cf. Figure 2). Support for the above proposal is found in the exceptional *Z* selectivity observed with W-based alkylidene **13** (structure shown in Scheme 3) even at a relatively high concentration for a macrocyclization (0.05 M),[34] when reaction of the active complex with the *Z* macrocycle is more likely to occur; under the latter conditions, macrolactone **12a** is isolated in up to 86% yield and with only 4% contamination with the undesired *E* isomer (entry 8, Table 2). The positive influence of reduced pressure (entries 6 and 7, Table 2),[35] as detailed previously,[11] is tied to enhancing catalyst longevity by minimization of the concentration of the exceptionally reactive and relatively unstable methylidene complexes (cf. **V**, Figure 2), which can be generated by reaction of an alkylidene intermediate with the volatile ethylene (formed as byproduct). When the W-catalyzed RCM is performed with 3.0 mol% **13** at 0.05 M concentration, **12a** is formed in 63% yield and 97% *Z* selectivity (entry 9, Table 2).

In a similar fashion, diene **11b**, a diastereoisomer of **11a**, can be converted to macrocyclic olefin **12b** in 84% yield and with 91% *Z* selectivity [Eq. (1)]. The relatively lower degree of stereochemical control, versus RCM of **11a** (96:4 *Z*:*E*), might be because there is a stronger inherent preference for the formation of the undesired *E* alkene in the case of **11b** (i.e., substrate- vs. catalyst-control are in stronger opposition); this is reflected in the slightly higher percentage of *E* isomer generated when the reaction is carried out with Mo bis-alkoxide **1** (28% *Z* vs. 33% *Z* with **11a**). The finding in Equation (1) bodes well for the utility of MAP complexes in the preparation of analogues of this class of naturally occurring molecules.[36]

The above findings, collectively, reaffirm the notion that it is the capacity to generate high kinetic *Z* selectivity together



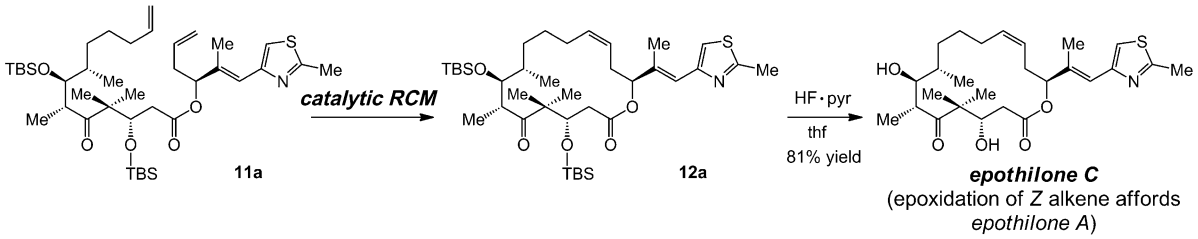
(1)

with possessing the appropriate balance of sufficient (but not too high) reactivity levels that render W complex **13** the most attractive choice for macrocyclic RCM of the heavily functionalized dienes such as **11a** (another relevant case will be presented below). The validity of such reactivity/*Z* selectivity relationships finds additional support in the variations in the conversion and *Z* selectivity values obtained for RCM of dienes leading to sparsely functionalized macrocyclic lactones **8**, **14**, and ambrettolide, respectively (Scheme 3). Compared to the transformations with complexes **6** and **7**, W-based alkylidene **13** provides generally lower conversion as a result of its subordinate activity (vs. Mo- based MAP complexes). On the other hand, higher *Z*:*E* values are observed in reactions with the corresponding conformationally more flexible dienes when **13** is employed (e.g., vs. **11a**): the less effective complex does not promote post-RCM isomerization or no more than to a minimal degree.

Study of olefin metathesis-based post-RCM isomerization in reactions with 12a: Considering the significant role that stereoisomeric interconversion can play in determining the stereoisomeric purity with which a macrocyclic product is isolated, we chose to examine the extent of the influence of such processes, vis-à-vis the formation of macrolactone **12a** in greater detail.

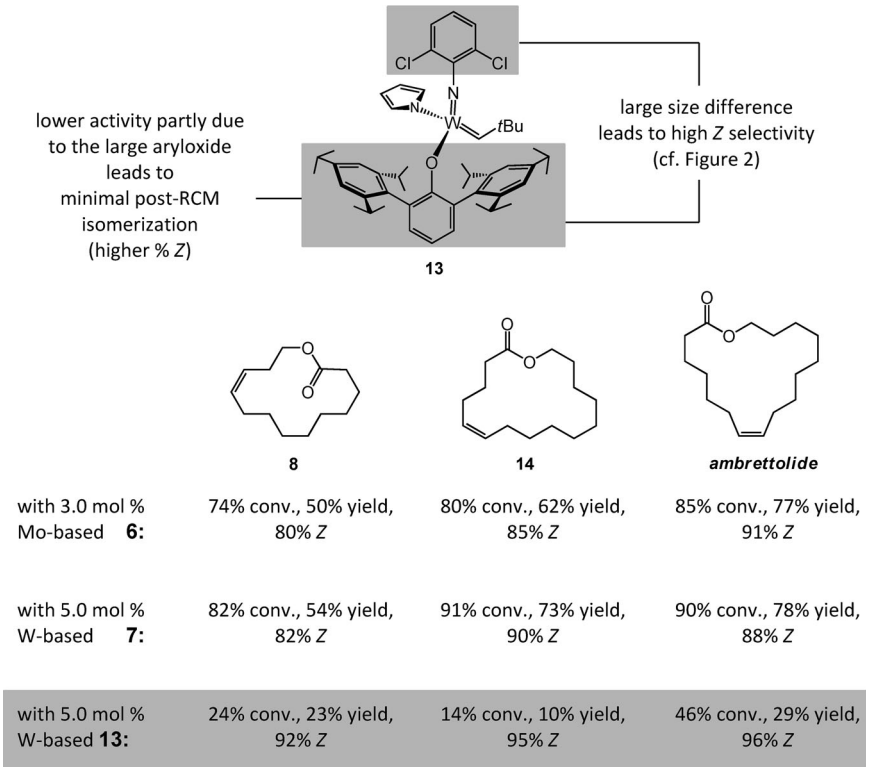
*Studies with Mo-based bis-alkoxide **1***: We first probed the ring closure performed in the presence of Mo complex **1**, a transformation originally disclosed in 1997 (entry 1, Table 2).[29b] The highly reactive complex (**1**) generates 67:33 *Z*:*E* ratio; based on our investigations described above, we suspected that post-RCM isomerization might be partly responsible for such preference. To probe this possibility, we investigated the degree of stereochemical control in the RCM of **11a** promoted with bis-alkoxide **1** as a function of time. These studies led us to determine that, remarkably, as illustrated in Scheme 4, within only ten minutes, there is 92% conversion to **12a**, which is isolated in 89% yield (inseparable isomeric mixture) and 72:28 *Z*:*E* selectivity. When the RCM reaction is performed at 7.0 torr, *Z* selectivity is not improved, indicating that the selectivity largely represents the degree of kinetic control. The latter finding is significantly superior to 33% *Z* reported previously for the same reaction being performed with 20 mol% **1** for the duration of one hour (86% yield).[29b] The same considerations likely apply to the RCM process shown in Equation (1) (with diastereomer **11b**). These findings point to the importance of the need for careful determination of the optimal catalyst loading and/or reaction time

Table 2. Catalytic RCM for stereoselective total syntheses of epothilones C and A.[a]

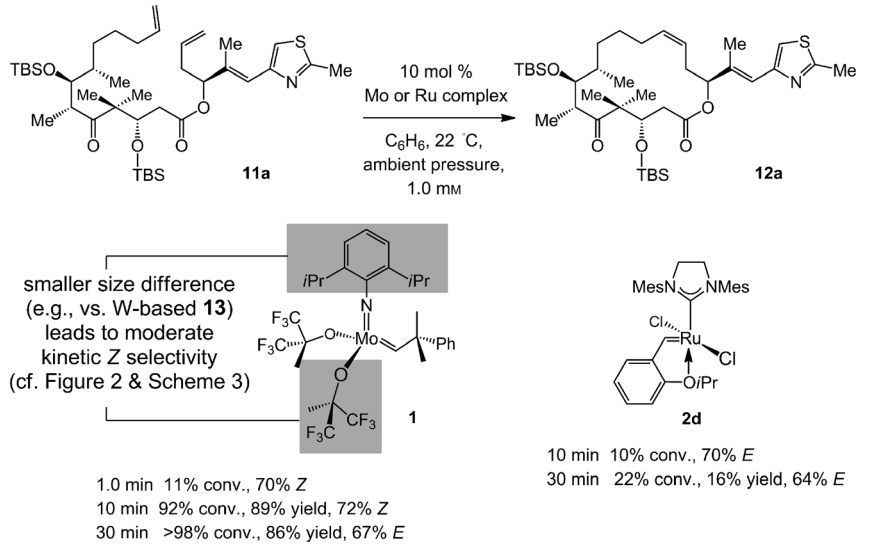


Entry	Complex[b]	Loading [mol%]	Conditions	*t* [h]	Temp. [°C]	Conv. [%][c]	Yield [%][d]	*Z*:*E*[c]
1[e]	**1**	20	ambient; 1.0 mM (C_6H_6)	1.0	22	>98	86	33:67
2[e]	**2b**	10	ambient; 1.5 mM (CH_2Cl_2)	20	25	>98	85	54:46
3	**2d**	5.0	ambient; 1.0 mM (C_7H_8)	16	40	96	nd	34:66
4	**6**	10	ambient; 1.0 mM (C_6H_6)	1.5	22	87	nd	85:15
5	**7**	10	ambient; 1.0 mM (C_6H_6)	2.5	22	72	nd	79:21
6	**13**	10	ambient; 1.0 mM (C_6H_6)	2.5	22	77	nd	96:4
7	**13**	10	***1.0 torr; 1.0 mM (toluene)***	***2.5***	***22***	***98***	***86***	***96:4***
8	**13**	***5.0***	***1.0 torr; 0.01 M (toluene)***	***2.0***	***22***	***98***	***86***	***96:4***
9	**13**	***3.0***	***1.0 torr; 0.05 M (toluene)***	***3.0***	***22***	***97***	***63***	***97:3***

[a] Reactions were carried out under an atmosphere of N_2 or vacuum; see the Supporting Information for details. [b] Complex **2d**, **7** and **13** were prepared prior to use, whereas alkylidene **6** was synthesized in situ from the corresponding bis-pyrrolide and aryl alcohol, proceeding in approximately 60% yield of the MAP complex (ca. 3.0 mol% effective catalyst loading). See the Supporting Information for details. [c] Conversion and *Z*:*E* ratios measured by analysis of 500 MHz ^{1}H NMR spectra of unpurified mixtures; the variance of values are estimated to be ±2%. [d] Yield of isolated products after purification (isomeric mixture); the variance of values are estimated to be ±5%. nd = not determined. [e] See Ref. [29b]. [f] See Ref. [29a].



Scheme 3. Reactivity versus *Z* selectivity furnished by W-based complex **13**.



Scheme 4. *Z* Selectivity as a function of time in RCM promoted by complex **1**.

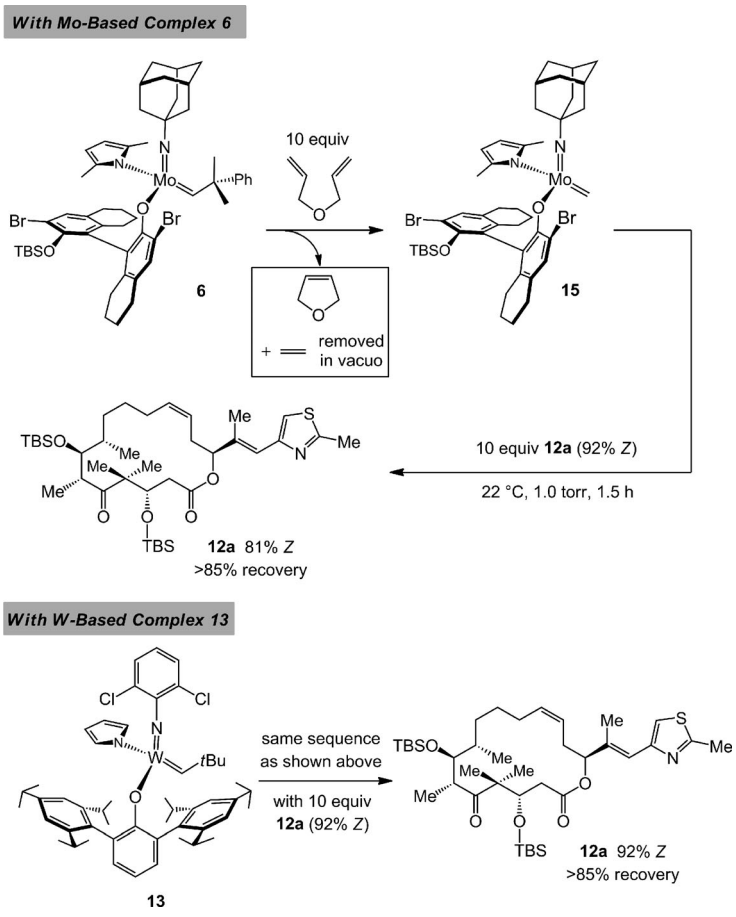
when carrying out catalytic RCMs that generate disubstituted macrocyclic alkenes; vigilant analysis of changes in the olefin stereochemistry as the cyclization progresses, regardless of which class of catalysts is being employed, might be necessary for achieving the best results.

Two additional points regarding this aspect of our studies are worthy of note:

1) The reduced size differential between the arylimido and hexa-fluoro-*tert*-butoxide ligands within Mo complex **1** conspire to furnish relatively moderate *Z* selectivity compared to that delivered with W-based alkylidene **13** (cf. Table 2). Further, the higher activity of the Mo bis-alkoxide, versus a MAP complex such as **13**, manifested by a more efficient post-RCM isomerization, leads to a more facile erosion of kinetic selectivity.

2) Although there is no detectable difference in selectivity during the first ten minutes of the Mo-catalyzed transformation (Scheme 4), substantial *Z*-to-*E* isomerization occurs within 30 min (72:28→33:67 *Z*:*E*). In stark contrast, in the cyclization with Ru-based carbene **2d**, the *E* isomer is favored early on (Scheme 4), suggesting that the cyclization process might be kinetically *E*-selective. The relatively low activity of the Ru complex makes it unlikely that olefin isomerization is occurring.

Studies with MAP complexes: We then turned to a more detailed analysis of the possible impact of post-RCM isomerization in reactions with Mo- and W-based complexes **6** and **13**. Due to the relatively high *Z* selectivities observed with the latter two alkylidenes (≥85:15), we chose to investigate the extent of loss of stereoselectivity which could occur upon resubjection of a sample of 92:8 mixture *Z*- and *E*-**12a** to a solution containing the activated forms of alkylidenes **6** and **13**, respectively. Thus, as depicted in Scheme 5, a sample of Mo complex **6** was pre-treated with diallylether to generate methylidene **15**, the species released upon RCM and responsible for initiation of a new catalytic cycle (cf. **V**, Figure 2). Subsequent in vacuo removal of residual diallylether and the ethylene generated was followed by the addition of ten equivalents of **12a** (corresponding to 10 mol% catalyst loading). After 90 min, the macrolactone was recovered as an 81:19 mixture of *Z* and *E* isomers (vs. the initial 92:8 ratio). In contrast, when an identical procedure is performed with W alkylidene **13**, there is no detecta-



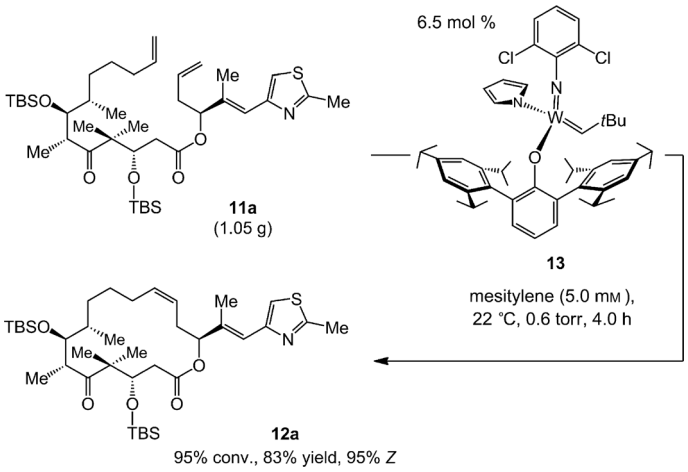
Scheme 5. Olefin metathesis-based post-RCM isomerization of macrocyclic epothilone C precursor **12a** with a Mo- and a W-based complex. TBS = *tert*-butyldimethylsilyl.

ble loss of stereoselectivity (Scheme 5). The above experiments demonstrate that, whereas some loss of *Z* selectivity can take place in the course of RCM when Mo complex **6** is used, the methylidene derived W-based alkylidene **13** reacts with exceptional chemoselectivity with the terminal alkenes of **11a** in preference to the cyclic disubstituted olefin in **12a**. The small amount of *E*-**12a**, formed in the reactions with **13**, is probably due to a lack of perfection in kinetic selectivity (i.e., reaction via complex related to **VI**, Figure 3).

Practical aspects of W-catalyzed macrocyclic RCM: Dichlorophenylimido MAP alkylidine **13** is sufficiently stable such that it can be handled and weighed in open air; the requisite apparatus can be set up and reactions performed in a typical fume hood without the need for strict exclusion of air and moisture.[27] When complex **13**, which must be stored under inert atmosphere (e.g., N_2) for long-term storage, is exposed to air, there is $\leq 10\%$ decomposition within ten minutes (as judged by spectroscopic analysis), more than sufficient time to set up a reaction.

To challenge further the practical aspects of the W-catalyzed protocol, we chose to establish whether the W-catalyzed RCM of the relatively complex diene **11a** can be performed on gram-scale with MAP alkylidene **13** in an efficient and stereoselective fashion. We surmised that the reliability of the catalytic protocol would be more convincingly illustrated if the *Z*-selective RCM were to be carried out with a starting material prepared by a relatively protracted sequence (i.e., 16 steps for **11a**).[30,29a] To accomplish this task, however, first, a significant revision of the originally reported route to **11a** had to be implemented; otherwise, access to sufficient quantities of the diene proved to be too costly and labor intensive. A modified synthesis Scheme was accordingly developed,[37] allowing us to secure nearly 12 grams of **11a**. Some of the notable attributes of the revised route for preparation of enantiomerically pure **11a** include a highly diastereoselective aldol addition (96:4 vs. 60:40 d.r. reported previously), the need for fewer equivalents of enantiomerically pure intermediates and smaller number of purifications through silica gel chromatography.[27]

We subsequently determined that in the presence of 6.5 mol% W complex **13**, RCM can be effected with gram quantities of **11a** to afford macrocycle **12a**, precursor to epothilones C and A, in 83% yield and with 95% *Z* selectivity (Scheme 6). The transformation reaches 95% conversion within four hours at 22°C and proceeds readily when performed in a typical laboratory fume hood with humidity levels reaching approximately the 80% level.



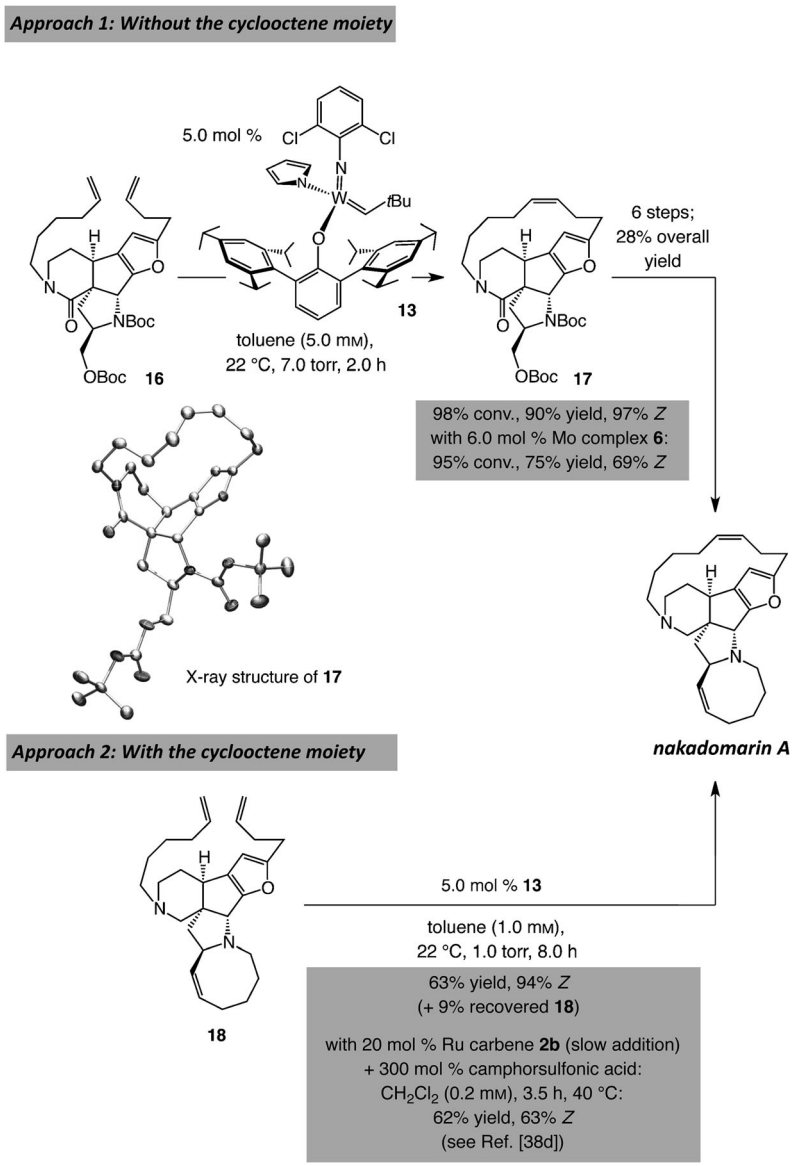
Scheme 6. A practical catalytic method for *Z*-selective macrocyclic RCM.

***Z*-Selective RCM reactions en route to nakadomarin A**: The final stage of our investigations corresponds to the formation of two ring structures, one macrocyclic and the other a cyclooctenyl moiety, en route to stereoselective total synthesis of nakadomarin A. The earlier approaches utilized olefin metathesis to prepare the larger ring structure of nakadomarin A, albeit with relatively low efficiency (15–30 mol% Ru complex) and minimal or stereoselectivity in favor of the undesired isomer (~2:1–1:2 *E*:*Z*).[38] Due to the

ineffective stereochemical control in the macrocyclic ring formation, as with epilachnene and epothilone C, strategies involving alkyne RCM/partial hydrogenation sequence have been introduced.[22,39] We demonstrated in our initial disclosure[6] that in the presence of W alkylidene **13**, macrocyclic RCM reactions with tetracyclic substrate **16** as well as the more strained pentacyclic **18** proceed efficiently and with exceptional *Z* selectivity (90% yield and 97:3 *Z*:*E* and 63% yield and 94:6 *Z*:*E*, respectively); these advances are summarized in Scheme 7.

Attempts to effect alkyne RCM of the Me-substituted diyne corresponding to **18** and bearing the two Lewis basic tertiary amines, with either Mo- or W-based alkylidynes, including the more recently developed variations,[24] has been reported to lead to <5% conversion even with 30–50 mol% of a metal complex and at 80°C (up to 18 h). Use of a less strained tetracyclic diyne-diamide was thus required (100 mol% $Mo(CO)_6$, 500 mol% 2-fluorophenol, 0.26 mM, C_6H_5Cl, reflux, 2.5 h; 39% yield).[39c] The relative facility of catalytic RCM with diene **18** (Scheme 7) and the strong resistance of the aforementioned diyne in regards to cyclization point to the sensitivity of the alkyne metathesis catalysts towards basic amines as well as the comparative ease with which a less strained macrocyclic alkene can be synthesized (vs. a large ring alkyne).

Study of olefin metathesis-based strategies en route to towards nakadomarin A offers a distinct framework for outlining some of the advantages offered by high-oxidation metal complexes (Mo- and W-based) versus Ru carbenes. The role of adventitious olefin-metathesis-based isomerization on the observed stereoselectivity can be further probed in the context of another relatively complex but structurally distinct polycyclic molecule (vs. epothilone C precursor **11a**). What is more, the polycyclic constitution of nakadomarin A provides the opportunity for investigation of whether the alkene within the eight-membered ring can be formed through Mo- or W-catalyzed RCM after the relatively sensitive macrocyclic olefin has been generated and without significant diminution in the stereochemical purity of the latter. Such studies would illustrate whether the RCM catalysts can be used for stereoselective preparation of polycyclic structures where the stereochemical integrity of one or more *Z* alkene units must be preserved while additional rings are being generated.

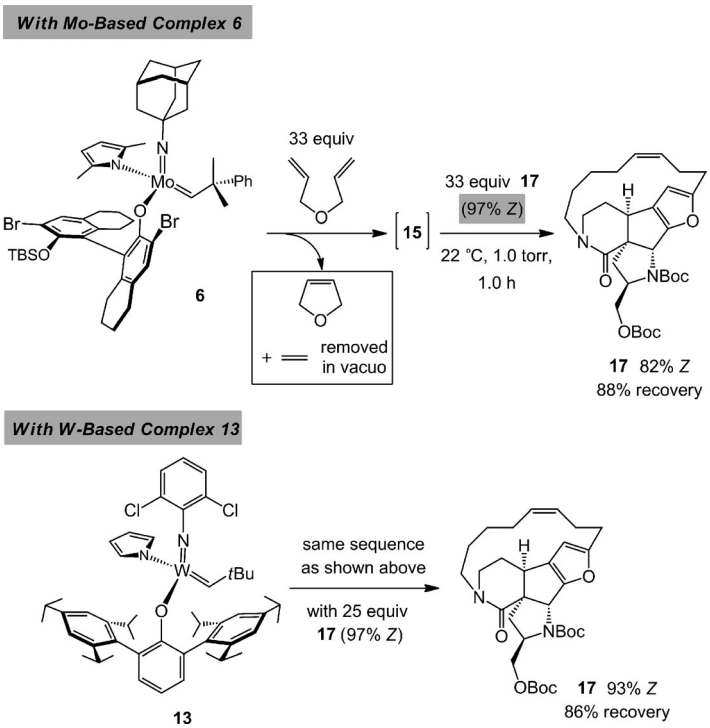


Scheme 7. W-Catalyzed *Z*-selective RCM en route to nakadomarin A. BOC = *tert*-butyloxycarbonyl.

Comparison of macrocyclic RCM reactions with Ru- versus W-based complexes: In contrast to the findings in Scheme 7, the most selective formerly reported procedure for conversion of **18** to nakadomarin A involved the use of 20 mol% Ru carbene **2b**; three equivalents of a strong Brønsted acid was also required so that 63% *Z* selectivity could be achieved.[38d] The difficult nature of the latter RCM process originates largely from the relatively high ring strain associated with the *Z* alkene-containing macrocycle. Hence, it is the less active first-

generation Ru carbene (vs. **2c** and **2d**), which must be added at a slow rate to the reaction mixture, that preserves the small kinetic preference for the *Z* alkene isomer.

Study of olefin metathesis-based post-RCM isomerization in catalytic RCM of diene 16: We subjected samples of fifteen-membered ring structure **17**, consisting of 97% of the *Z* alkene to solutions of Mo-based methylidene **15** and that derived from W-based complex **13** (Scheme 8). As in the case of **12a**, substantial loss of *Z* selectivity is detected within one hour in the case of Mo complex **6** (from 3% to 18% *E*). In contrast to the macrocycle precursor to epothilone C where alkene isomerization is undetected (cf. Scheme 5), however, the presence of the less reactive methylidene derived from **13** leads to recovery of a sample of **17** that is of slightly lower *Z*:*E* ratio (93:7 vs. 97:3; Scheme 8). It is likely that, as a result of diminished steric hindrance and a higher degree of angle strain within the macrocyclic unit of **17**, in contrast to **12a**, there is a stronger sensitivity towards ring-opening/ring-closing sequence (cf. Figure 3), culminating in lowering of stereochemical purity at the olefinic site. Considering that the reaction time for the conversion of **16** to **17** is two hours (cf. Scheme 7; vs. 1.0 h in Scheme 8), it is probably that at least part of the 3% *E*-**17** obtained is the result of some post-RCM isomerization, rather than any imperfection in kinetic selectivity delivered by W complex **13**. The above findings emphasize the difficulty posed by an efficient and highly *Z*-selective macrocyclic RCM route to the polycyclic natural product.

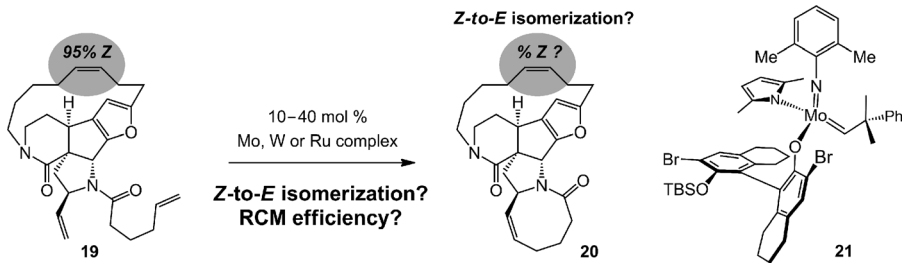


Scheme 8. Examination of catalyst-induced post-RCM isomerization of nakadomarin A precursor **17** with a Mo- and a W-based complex.

Synthesis of the cyclooctene ring through catalytic RCM; impact on macrocyclic alkene stereochemistry: *Studies with diamide **19***: As mentioned earlier, an intricate RCM reaction leading to nakadomarin A involves conversion of pentacyclic diamide **19** to hexacyclic **20** (Table 3), which can be synthesized from **17** in four steps and 66% overall yield. The resulting hexacyclic product would subsequently be converted to the target molecule through reduction of the amide functional groups (e.g., dibal–H). Can the strained hexacyclic natural product be synthesized without significant isomerization of the macrocyclic *Z* alkene?

Conversion of bis-amide diene **19** to eight-membered ring lactam **20** proceeds to 60% conversion in the presence of 30 mol% Mo complex **1** after six hours at 22°C (entry 1, Table 3); the desired product is obtained with minor loss of macrocyclic alkene stereoisomeric purity. With the less active Ru carbene **2b** (entry 2, Table 3), 100 mol% loading, heating to 40°C and 24 h of reaction time are required for achieving >98% conversion, but formation of the cyclooctene ring proves costly: there is substantial reduction in the macrocyclic *Z*:*E* ratio (72% vs. 95% *Z*).[40] There is no detectable conversion to **20** with W-based alkylidene **13**, even when 30 mol% of the starting complex is utilized (entry 3, Table 3). When 10 mol% of Mo-based MAP alkylidene **21**

Table 3. Synthesis of nakadomarin A cyclooctene ring through catalytic RCM of a diamide precursor. Efficiency and competitive *Z*-to-*E* isomerization of the macrocyclic alkene.[a]



Entry	Complex[b]	Loading [mol%]	Solvent	*t* [h];	Temp. [°C]	Conv. [%][c]	Yield [%][d]	*Z*:*E*[c] (macrocycle)
1	**1**	30	toluene	6.0	22	60	39	90:10
2	**2b**	100	CH_2Cl_2	24	40	>98	90	72:28
3	**13**	30	toluene	24	22	<5	na	na
4	**21**	10	toluene	24	80	72	32	95:5

[a] Reactions were carried out in purified toluene (5.0 mM) at 22°C an atmosphere of N_2 or under vacuum; see the Supporting Information for details. [b] Complex **1**, **2b**, and **13** were prepared prior to use, whereas alkylidene **21** was synthesized in situ from the corresponding bis-pyrrolide and aryl alcohol. See the Supporting Information for details. [c] Conversion and *Z*:*E* ratios measured by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures. [d] Yield of isolated and purified product. na = not applicable.

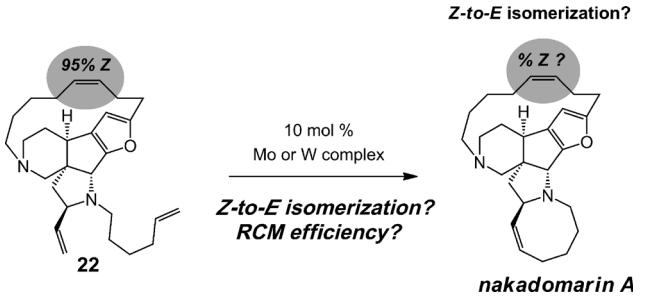
is employed (entry 4), ring closure occurs without loss of stereochemistry in spite of the elevated temperature and extended reaction time (80 °C, 24 h); nevertheless, a large portion of **19** remains unreacted (28 %) and there is significant amount of hompocoupling product under the somewhat severe conditions (hence, 32 % yield of **20** in entry 4, Table 3).[41]

There are several possible reasons for the comparative lack of efficiency in catalytic RCM reactions for converting **19** to **20**. The angle strain associated with the formation of the desired hexacyclic diene is compounded by the presence of the two rigidifying amide groups; a related rationale has been put forth vis-à-vis cyclooctene formation through RCM with a macrocyclic diyne substrate.[39b] The sterically hindered vinyl group bearing a substitution at its allylic site can discourage facile ring closure. Finally, there is the possibility that the alkylidenes and carbenes derived from initial reaction at the either of the terminal alkenes might be partially deactivated due to intramolecular chelation with a neighboring Lewis basic amide carbonyl.[42]

*Studies with diamine **22***: Based on the above-mentioned impediments we synthesized diamine **22** (dibal–H, 75 % yield) and examined the possibility of converting it to nakadomarin through catalytic RCM. As shown in entry 1 of Table 4, the presence of 10 mol % bis-alkoxide **1** gives rise to complete erosion of *Z* selectivity within one hour (95:5→55:45 *Z*:*E*). With the sterically more demanding Mo alkylidene **6** or tungstacyclobutane **7**, substrate **22** is consumed at the same rate, but formation of the eight-membered ring amine is accompanied by significantly less diminution in *Z*:*E* ratio (entries 2 and 3, Table 4: 95:5→85:15 and 82:18 *Z*:*E*, respectively); it is noteworthy that W complex **7** delivers similar degrees of *Z*-to-*E* olefin isomerization as is observed with Mo species **6** (see Scheme 2 for another example). There is minimal RCM when Mo-based MAP complex **21** is used (entry 4, Table 4). The higher activity obtained with alkylidene **6** as opposed to **21** can be attributed to the smaller size of the adamantylimido ligand (vs. the 2,6-dialkylphenylimido). In all instances, where complete disappearance of triene **22** is observed (entries 1–3, Table 4), a relatively wide gap exists between the conversion and isolated yield values (>98 % conv vs. 32–43 % yield). The origin of the latter discrepancy is the formation of a considerable amount of unidentifiable byproducts that likely arise from oligomerization reactions involving the two terminal olefins in **22** or those generated through ring-opening of the macrocyclic moiety (determined by spectroscopic analysis). It is similarly feasible that the terminal alkenes that serve as precursors to either the large or medium rings, some generated through a ring-opening process, can participate in RCM reactions with one another, leading to the formation of the alternative polycyclic products. Parallel issues regarding byproduct formation were observed in Mo-catalyzed reactions with diamide **19** (Table 3, entries 1 and 4).

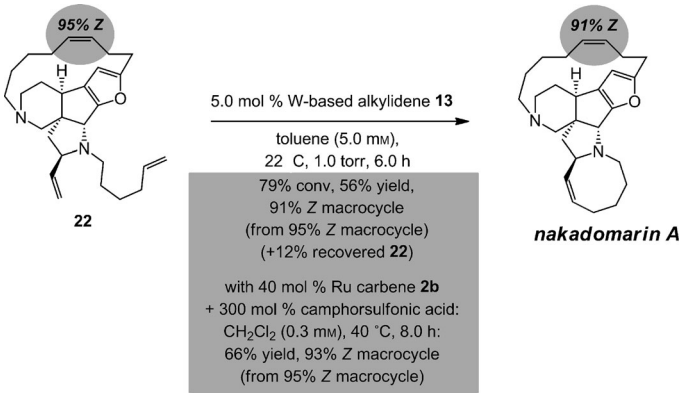
Considering the outcome of the experiments summarized in Scheme 5 and 8 in connection with post-RCM isomerization, it follows that with W-based MAP complex **13** formation of the cyclooctene ring occurs with the least degree of loss in the stereoselectivity at the macrocyclic alkene site. Specifically, as shown in Scheme 9, with 5.0 mol % of W complex **13**, hexacyclic diamine **22** can be transformed to nakadomarin A in 56 % yield (64 % based on recovered substrate) with 91:9 *Z*:*E* ratio for the larger ring olefin. With 10 mol % **13**, under otherwise identical conditions, the natural product is obtained in 48 % yield and 88:12 *Z*:*E* ratio (>98 % conversion); thus, with lower catalyst loading, a better balance between efficiency and preservation of kinetic selectivity can be achieved, resulting in 12 % of recovered

Table 4. Synthesis of nakadomarin A cyclooctene through catalytic RCM of a diamine precursor. Efficiency and competitive *Z*-to-*E* isomerization of the macrocyclic alkene.[a]



Entry	Complex[b]	Conv. [%][c]	Yield [%][d]	*Z*:*E*[c] (macrocycle)
1	**1**	>98	32	55:45
2	**6**	>98	38	85:15
3	**7**	>98	43	82:18
4	**21**	17	nd	nd

[a] Reactions were carried out in purified toluene at 22 °C for 6.0 h under 1.0 torr of under vacuum; see the Supporting Information for details. [b] Complexes **1**, **6**, and **7** were prepared prior to use; alkylidene **21** was synthesized in situ from the corresponding bis-pyrrolide and aryl alcohol. See the Supporting Information for details. [c] Conversion and *Z*:*E* ratios measured by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures. [d] Yield of isolated products after purification; the variance of values are estimated to be $< \pm 5$ %. nd = not determined.



Scheme 9. Synthesis of nakadomarin A through cyclooctene formation by W-catalyzed RCM. Minimal isomerization at macrocyclic alkene site.

22 and less product decomposition and post-RCM isomerization.

Comparison with the previous approaches: Conversion of pentacyclic diamine **22** to nakadomarin A demands 40 mol% of Ru carbene **2b** and eight hours of reaction time, as shown in Scheme 9. Moreover, significantly more dilute conditions (0.3 vs. 5.0 mM) and 300 mol% of camphorsulfonic acid are needed (60–70% conv., 27% yield and 60% *E*, otherwise). It is worthy of note that, in spite of the fact that formation of the cyclooctene moiety in the majority of the formerly reported total syntheses of nakadomarin A was implemented in the absence of the rigidifying macrocyclic alkene,[38,39c] 20–100 mol% of a Ru-based carbene proved necessary for achieving a reasonably efficient cyclization.[38a–c,e]

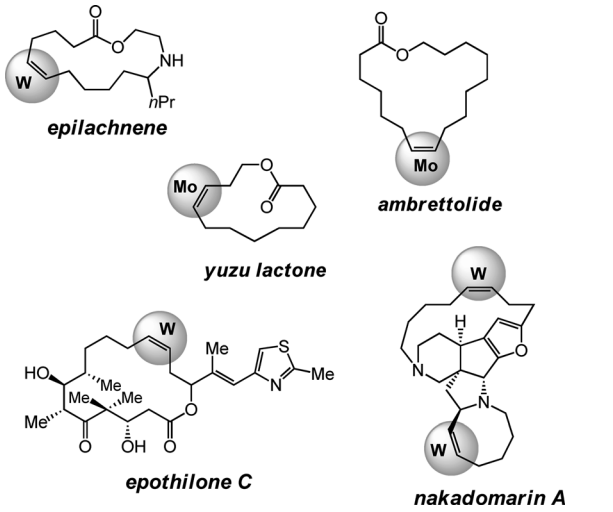


Figure 4. Efficient and *Z*-selective and complementary Mo- and W-catalyzed macrocyclic RCM.)

Conclusion

The ability of Mo- and W-based MAP species to promote *Z*-selective macrocyclic ring formation substantially enhances the effectiveness of one of the most critical and commonly employed transformations in chemistry. Successful applications to total syntheses of epilachene, epothilone C, and nakadomarin A leads to a near doubling of the overall efficiency with which these notable biologically active natural products can be accessed through an RCM-containing route. Our findings confirm that in planning a multistep pathway for the preparation of a complex molecule, the Mo as well as the W complexes can be relied upon to deliver the desired outcome at the late stages of an extended synthesis scheme. As the result of the appropriate reactivity exhibited by the Mo or W catalysts, which are tolerant of basic amines, RCM reactions can be carried out often with minimal or no alkene isomerization.

An outcome of the present studies is the complementarity of the Mo- and W-based catalysts. In situations where the substrate dienes do not enjoy a higher degree of preorganization, the high activity of Mo-based alkylidenes might be needed; in cases where the relatively rigid starting materials are involved, and in particular where post-RCM isomerization can be detrimental, the relatively less active W alkylidenes might emerge as the catalysts of choice (Figure 4). The elucidation of the finely balanced activity profile furnished by the Mo and W monopyrrolide complexes and the significance of reaction time to the preservation of kinetic selectivity in catalytic olefin metathesis reactions are two of the noteworthy lessons learned in the course of these inquiries. Equally noteworthy is the possibility of accessing polycyclic ring structure through W-catalyzed RCM reactions that are efficient and do not cause significant *Z*-to-*E* isomerization of an alkene site within the same molecule.

The impact of catalytic *Z*-selective macrocyclic RCM is not limited to the target molecules examined here; routes leading to a number of other complex and biologically active molecules[43] can be made more efficient by the catalysts and strategies detailed above. The advances put forth in this report are expected to exert a wide-ranging and immediate impact on the synthesis of an assortment of organic molecules.

Experimental Section

Procedure for gram-scale *Z*-selective macrocyclic ring-closing metathesis: A 500 mL Schlenk flask was fitted with an Airfree® connecting adapter. The connecting adapter was fitted with a rubber septum; the flask was then connected to an N_2-filled manifold. The apparatus was flame-dried and charged with diene **11a** (1.05 g, 1.43 mmol, used without azeotropic removal of water through distillation with benzene). W-based complex **13**·toluene (99.0 mg, 0.0926 mmol) was weighed on a balance (in air) and added to the reaction vessel. (The remaining W complex was transferred back to an N_2-filled dry box.) The resulting mixture was subjected to vacuum, back-filled with N_2 three times and charged with mesitylene (285 mL, freshly distilled); the valve on the connecting adapter was closed to isolate the septum from the vessel. The resulting solution was exposed to vacuum (0.60 torr) and allowed to stir for four hours at 22 °C, after which the reaction was quenched through the addition of diethyl ether (ca. 1 mL; undistilled). Purification by silica gel chromatography (hexanes/Et_2O, 20:1) afforded **12a** (0.833 g, 1.18 mmol, 83% yield, 95:5 *Z*/*E*) as a white foam along with recovered starting material (55.5 mg, 0.0756 mmol, 5.3%).

Compound 12a: IR (neat): $\tilde{\nu}$ = 2955 (m), 2924 (s), 2854 (m), 1743 (m), 1697 (w), 1462 (m), 1378 (w), 1254 (m), 1182 (w), 1158 (w), 1097 (w), 1066 (w), 1019 (w) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 6.96 (1H, s), 6.57 (1H, s), 5.53 (1H, dt, J = 11.2, 4.2 Hz), 5.42–5.23 (1H, m), 5.02 (1H, d, J = 10.2 Hz), 4.03 (1H, dd, J = 10.2, 1.2 Hz), 3.89 (1H, d, J = 8.4 Hz), 3.05–2.96 (1H, m), 2.82 (1H, dd, J = 16.2, 1.2 Hz), 2.79–2.70 (2H, m), 2.70 (3H, s), 2.67 (1H, dd, J = 16.2, 10.2 Hz), 2.40–2.33 (1H, m), 2.11 (3H, d, J = 1.2 Hz), 2.10–2.06 (1H, m), 1.90–1.82 (1H, m), 1.62–1.46 (3H, m), 1.30–1.00 (1H, m), 1.19 (3H, s), 1.14 (3H, s), 1.09 (3H, d, J = 6.6 Hz), 0.95 (3H, d, J = 6.6 Hz), 0.94 (9H, s), 0.84 (9H, s), 0.12 (3H, s), 0.10 (3H, s), 0.07 (3H, s), −0.10 ppm (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 215.2, 171.5, 164.8, 152.7, 138.8, 135.3, 123.0, 119.7, 116.3, 79.8, 79.5, 76.6, 53.6, 48.2, 39.1, 38.0, 32.0, 31.6, 29.4, 28.6, 26.6, 26.4, 25.2, 24.4, 19.4, 19.3, 18.9, 18.8, 17.9, 15.5, −3.0, −3.1, −3.5, −5.5 ppm. HRMS (ESI$^+$) $[M+H]^+$ calcd for $C_{38}H_{67}NO_5SSi_2$: 706.4357, found: 706.4348.

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