VIP Synthetic Methods

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Unusual *E*-Selective Ring-Closing Metathesis To Form Eight-Membered Rings**

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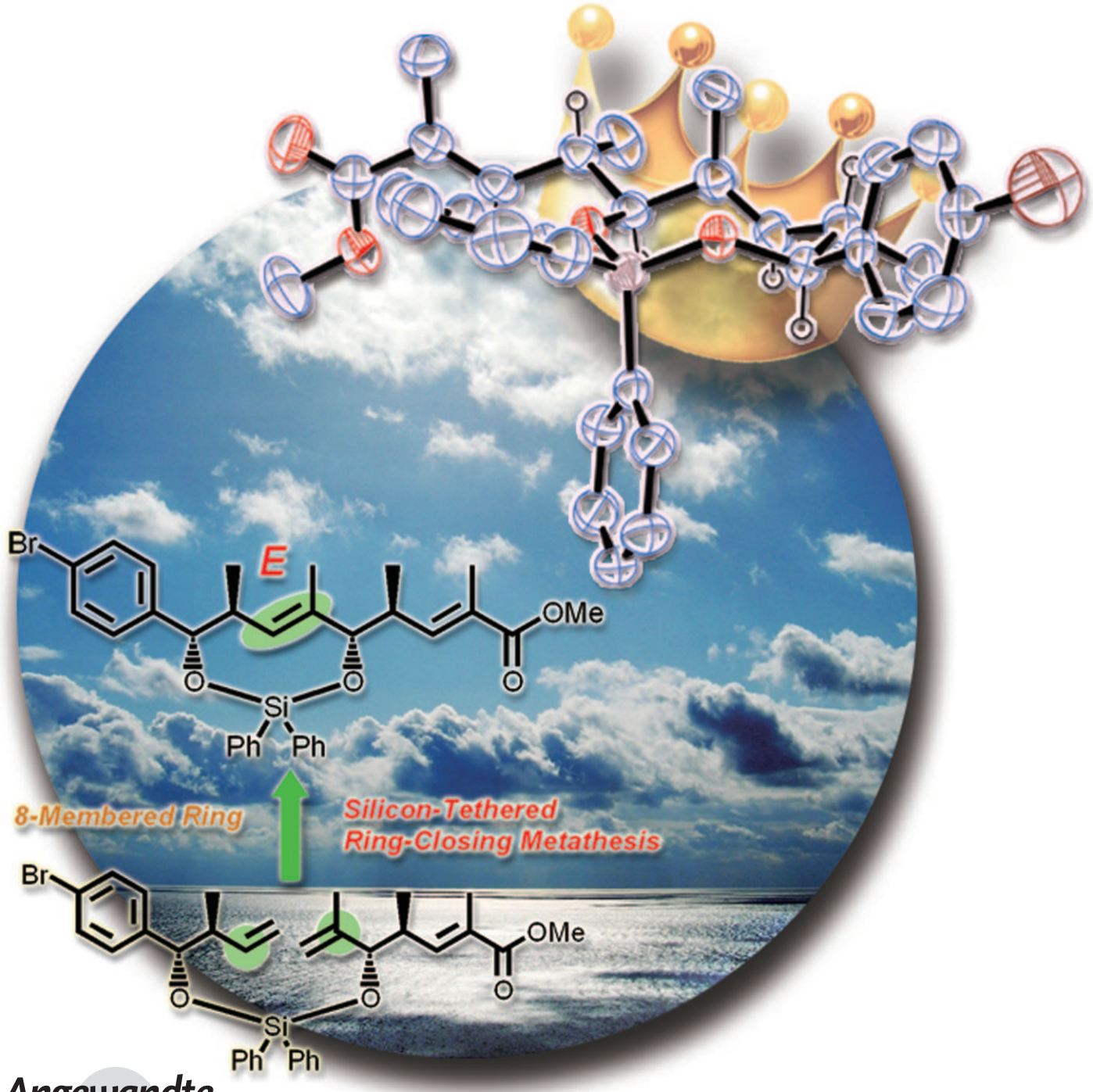
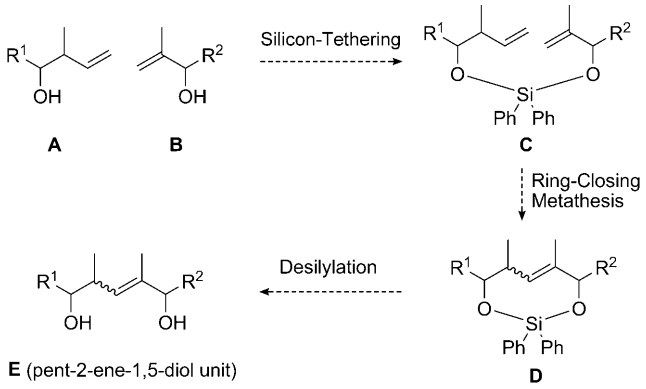


Angewandte Chemie

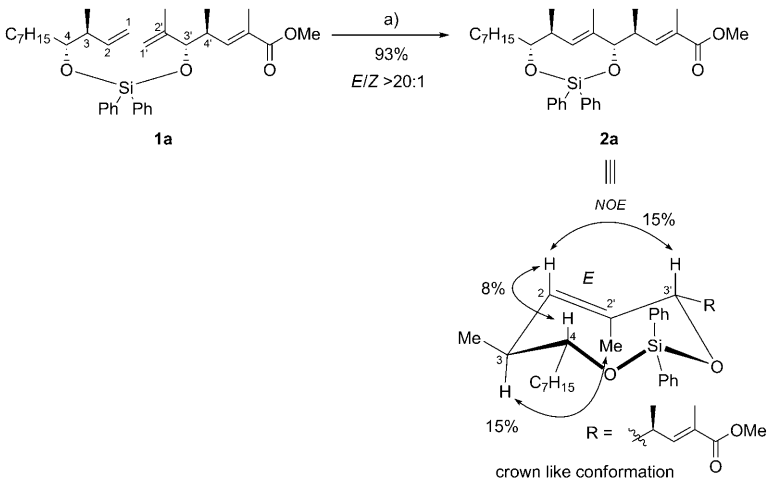
Olefin metathesis has recently emerged as one of the most powerful and convenient methodologies in natural product synthesis. These reactions are particularly attractive because they utilize nonfunctionalized olefins as substrates and thus enable highly convergent strategies.[1] Among the several types of olefin metathesis, ring-closing metathesis (RCM) is considered to be the most useful because of its efficiency and the use of equimolar amounts of the two reacting olefins.

During the course of our synthetic efforts towards polyketide antibiotics, we became interested in the possibility of a novel RCM approach for the construction of a pent-2-ene-1,5-diol unit that is a common motif in many naturally occurring polyketides[2] such as TMC-151C[2a] and migrastatin.[2c] We expected that the requisite pent-2-ene-1,5-diol unit **E** could be constructed from homoallylic alcohol **A** and allylic alcohol **B**, by introducing a silicon tether, RCM, and subsequent desilylation (Scheme 1). Silicon-tethered intramolecular reactions, including Diels–Alder and RCM, have already been utilized in natural product synthesis.[3] In particular,



Scheme 1. Strategy for pent-2-ene-1,5-diol unit by silicon-tethered ring-closing metathesis.

Evans et al. reported a diastereomer-discriminating RCM to form *Z* olefins containing eight-membered rings using silicon-tethered substrates.[4] Harvey et al. also recently applied a similar RCM to the study of natural product synthesis.[5]



Scheme 2. Unusual *E*-selective RCM to form the eight-membered-ring compound **2a**. Reagents and conditions: a) HG-II (20 mol%), *para*-benzoquinone (1.5 equiv)/xylene, reflux, 24 h. The diastereomeric ratio was determined by ^{1}H NMR analysis. HG-II = Hoveyda–Grubbs second-generation catalyst.

Herein we report an unusual *E*-selective RCM to form an eight-membered ring from a silicon-tethered diene, wherein we identified several factors that dictate the preferred formation of the *E* olefin.

When silicon-tethered diene **1a**, prepared from the corresponding homoallylic alcohol and allylic alcohol, was treated with the Hoveyda–Grubbs second-generation catalyst[6] (HG-II) in the presence of *para*-benzoquinone[7] in refluxing xylene for 24 hours, an eight-membered ring containing an *E* olefin (**2a**; $E/Z > 20{:}1$) was obtained in 93% yield almost as a single isomer (Scheme 2).

The stereochemistry of the newly formed carbon–carbon double bond in **2a** was assigned *E* by using NOE experiments. This result was surprising because we had expected the exclusive formation of the *Z* olefin by analogy to the results of Evans[4] and Harvey.[5] To the best of our knowledge, there is only one reported example of a RCM giving an eight-membered ring that selectively generates an *E* olefin (Prunet et al.).[8]

(*E*)-Dioxasilacyclooctene **2a** was obtained as a single atrope isomer, and NOE analysis of **2a** also indicated a crownlike conformation wherein all substituents except one phenyl group of the diphenylsilyl group occupied pseudoequatorial positions.[9] We reasoned that the present selective *E*-olefin formation could be attributed to these conformational characteristics.

To clarify the structural requirements of this unusual *E*-olefin-forming reaction, in addition to its scope and limitations, we examined the RCM in detail using a series of systematically designed silylene acetals.

Prior to RCM experiments, we tried to develop an efficient method for preparing the silylene acetal (RCM precursor) from two different alcohols (Scheme 3). Generally, silicon tethering is not always high-yielding because of the competitive formation of symmetrical silylene acetals. Ph_2SiCl_2, a well-known silylating reagent, was first employed for preparing **1a**. Although a relatively high chemical yield (74%) of **1a** was achieved, use of excess homoallylic alcohol **3**

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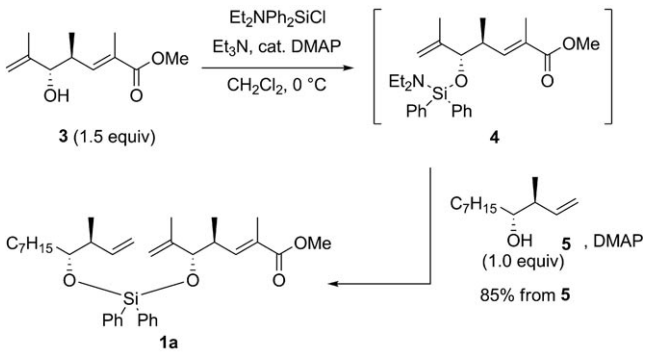


Scheme 3. The development of silicon-tethering by using the Et_2NPh_2SiCl/Et_3N/DMAP method. DMAP = *N*,*N*-4-dimethylaminopyridine.

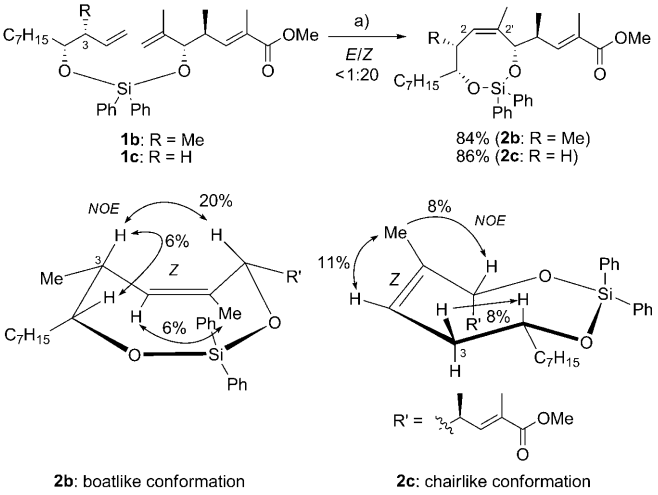
(3.2 equiv) was necessary to realize a high yield. After extensive experiments, we were able to develop the Et_2NPh_2SiCl/Et_3N/DMAP method. The improved method consists of the initial treatment of **3** (1.5 equiv) with Et_2NPh_2SiCl[10] (1.5 equiv) in the presence of Et_3N and a catalytic amount of DMAP to form intermediate **4**, and subsequent addition of alcohol **5** and DMAP to obtain heterodimer **1a** in 85% yield.[11]

With the efficient methodology established, we next prepared the C3-epimer **1b** and the C3-demethyl derivative **1c**. These compounds were then subjected to a RCM using HG-II (Scheme 4). In both cases, RCM products were obtained in high yields. The stereochemistry of the C2–C2′ double bond was determined to be *Z* for the two products. Furthermore, NOE experiments revealed that the C3-epimer **2b** had a boatlike conformation wherein the C3-methyl group occupied a pseudoequatorial position, and the C3-demethyl derivative adopted a chairlike conformation as depicted in Scheme 4.[12]

We then prepared several related silicon-tethered substrates and subjected them to RCM. The results are summarized in Table 1. The stereochemistry of the newly formed carbon–carbon double bonds was determined by NOE experiments of either the RCM products or the products obtained after desilylation.[13] The conformation of the RCM products are also indicated in Table 1. Because we had already observed the selective *Z*-olefin formation with the *syn* isomer **1b** and demethyl derivative **1c**, the relative stereochemistry of the homoallylic alcohol moiety was fixed as *anti*. The silylene acetals **6a** and **6b**, which are closely related to **1a**, afforded the *E* olefins **7a** and **7b**, respectively (entries 1 and 2). Replacement of a relatively bulky side chain at C3′ with isopropyl was next examined. The silylene acetal **6c**, which has the same stereochemistry as **1a**, afforded the *E* olefin **7c** selectively, whereas the *Z* olefin **7d** was selectively formed from the C3′-epimer **6d** (entries 3 and 4). The RCM product **7d** was found to possess the chairlike conformation by NOE experiments. The silylene acetal **6e** lacking an isopropyl group also completely reversed the stereochemistry, thereby affording the *Z* olefin **7e** exclusively (entry 5). It was also found that the RCM of the silylene acetal **6f**, which has a less bulky *n*-butyl substituent, was nonselective and afforded the *E* olefin **7f** and *Z* olefin **8f** in a low combined yield (entry 6).[14] In contrast, its epimer **6g** afforded the *Z* olefin **7g** as a single isomer. These results indicate that a sterically demanding substituent at the allylic C3′ position with an appropriate relative stereochemistry is necessary for selective *E*-olefin formation. Moreover, the formation of the *Z* olefin **7h** with the C2′-demethyl derivative **6h** revealed an additional structural requirement for *E*-olefin formation.

The *para*-bromophenyl derivative **7i**, obtained by the RCM of **6i**, was a crystalline compound. The stereochemistry of **7i** was unambiguously confirmed by X-ray crystallographic analysis (Figure 1).[15] For the cyclization product **7i**, all substituents, except one of the phenyl groups, occupied pseudoequatorial positions in its crownlike conformation as expected. Moreover, a torsion angle of 144.6° for C3-C2-C2′-C3′ bonds in the solid-state structure indicates a significant loss of π character in the newly formed double bond.

From these results, we can conclude that the *E* olefin is produced selectively when the substrate satisfies the following requirements: 1) *anti* stereochemistry for homoallylic part **A**,



Scheme 4. RCM of the *syn* isomer **1b** and C3-demethyl derivative **1c**. Reagents and conditions: a) HG-II (10 mol%), *para*-benzoquinone (1.5 equiv)/xylene, reflux, 24 h. Diastereomeric ratio was determined by ^{1}H NMR analysis.

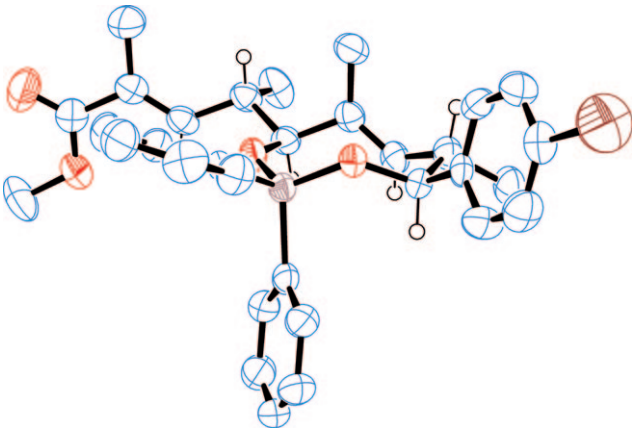
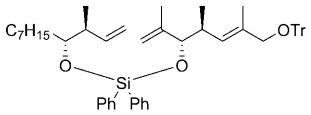
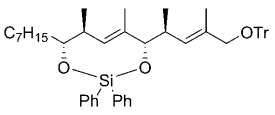
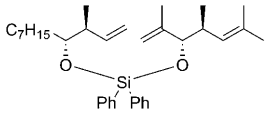
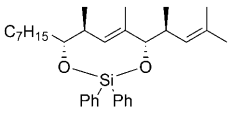
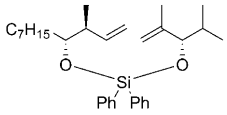
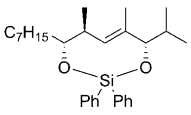
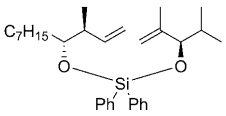
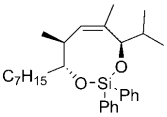
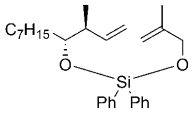
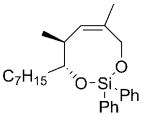
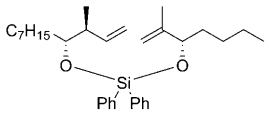
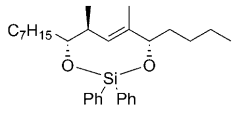
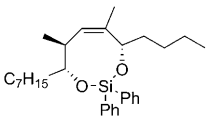
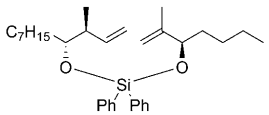
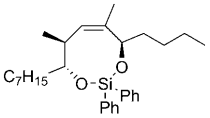
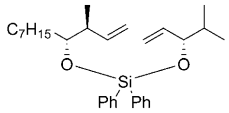
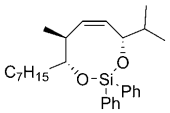
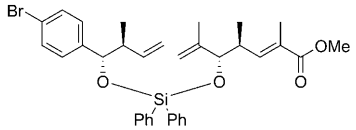
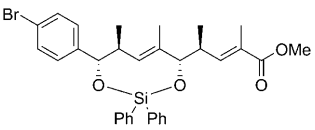


Figure 1. An X-ray derived ORTEP drawing of *E* eight-membered ring **7i**. Ellipsoids are drawn at 50% probability.

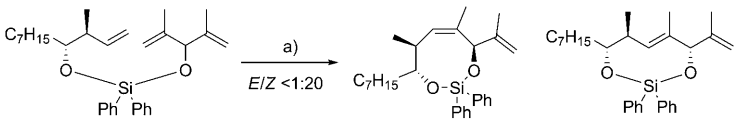
Table 1: RCM of various silylene acetals.[a]

Entry	Substrate	Product		Yield [%]	*E*/*Z*[c]	Conformation
1		**6a** 	**7a**	75	>20:1	crownlike
2		**6b** 	**7b**	61	>20:1	crownlike
3		**6c** 	**7c**	65	>20:1	crownlike
4[b]		**6d** 	**7d**	84	<1:20	chairlike
5[b]		**6e** 	**7e**	82	<1:20	chairlike
6		**6f**  	**7f** **8f**	23 13	1.8:1	crownlike chairlike
7		**6g** 	**7g**	92	<1:20	chairlike
8[b]		**6h** 	**7h**	83	<1:20	chairlike
9		**6i** 	**7i**	57 (brsm 68%)	>20:1	crownlike

[a] Reagents and conditions: HG-II (20 mol%), *para*-benzoquinone (1.5 equiv)/xylene, reflux, 24 h. [b] Reagents and conditions: HG-II (10 mol%), *para*-benzoquinone (1.5 equiv)/xylene, reflux, 24 h. [c] Diastereomeric ratio was determined by ^{1}H NMR analysis. brsm = based on recovered starting material.

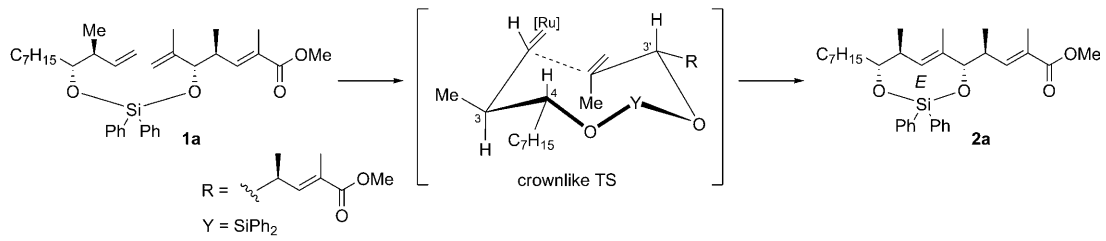
2) a *cis* relationship between R^1 and R^2 in the eight-membered dioxasilacyclooctene **D** in Scheme 1, 3) the presence of C2′–Me, and 4) the presence of a sterically demanding substituent at the C4′-position.

We also carried out the RCM of **9** which has two prochiral isopropenyl groups (Scheme 5). The silylene acetal **9** satisfies the structural requirement for *E*-olefin formation, and this experiment was conducted to establish the feasibility of *E*-olefin formation. RCM of **9** gave the *Z* olefin **10** in 83% yield



9 → **10** (83%) *Z* chairlike + **11** (trace) *E*

Scheme 5. *E*-olefin formation versus *Z* olefin formation. Reagents and conditions: a) HG-II (20 mol%), *para*-benzoquinone (1.5 equiv)/xylene, reflux, 24 h. The diastereomeric ratio was determined by ^{1}H NMR analysis.



Scheme 6. Proposed transition state for the RCM of **1a**.

and the *E* olefin **11** was isolated in only a trace amount. This result shows that the RCM strongly favors *Z*-olefin formation, and thus the present *E*-olefin-forming RCM is quite unusual.

With these results, we propose a plausible transition state (TS) for the cyclization of **1a**, **6a**, **6b**, **6c**, and **6i** to give the corresponding *E* olefins. As an example, the transition state for the cyclization of **1a** into **2a** is shown in Scheme 6. Thus, on the basis of conformational analysis of **2a**, its formation may proceed via a crownlike TS wherein all substituents occupy pseudoequatorial positions. Other possible chair- or boatlike transition states leading to a *Z* olefin might be less stable either because of the transannular strain between C3-H and C3′-R or a steric repulsion between C3-Me and C3′-H. In the case of other isomers, either the chairlike or boatlike transition states might be free from a nonbonding interaction to produce *Z* olefins, given the conformational analyses of **2b** and **2c**.

In conclusion, we have observed a unique RCM of silylene acetals that generate an *E* olefin in an eight-membered ring. We propose a plausible transition state for this reaction as well as clarify the structural requirements for *E*-olefin-forming RCM. Although the *E* olefin was produced only in a limited number of cases, our methodology will be useful for the construction of a pent-2-ene-1,5-diol unit, which is common to many naturally occurring polyketide antibiotics. Applications along these lines are underway and will be reported in due course.

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Keywords: cyclization · metathesis · polyketides · silicon · stereoselectivity

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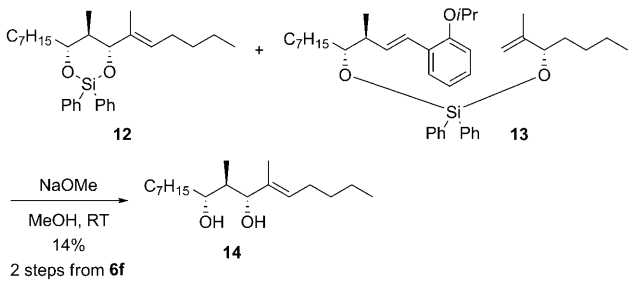
[14] We also observed the formation of the six-membered silylene acetal **12**, which was probably derived from **7f** through rearrangement. The structure of **12** was confirmed by correlating to the diol **14** (14% yield from **6f**). For details, see the Supporting Information.



[15] CCDC 784810 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

