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Sequential ring-closing metathesis/Pd-catalyzed, Si-assisted cross-coupling reactions: general synthesis of highly substituted unsaturated alcohols and medium-sized rings containing a 1,3-*cis–cis* diene unit

Scott E. Denmark* and Shyh-Ming Yang

Department of Chemistry, Roger Adams Laboratory, University of Illinois, 600 South Mathews Avenue, Urbana, IL 61801, USA

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Abstract—A sequential ring-closing metathesis/silicon-assisted cross-coupling protocol has been developed. Alkenyldimethylsilyl ethers of allylic, homoallylic and bis(homoallylic) alcohols undergo facile ring closure with Schrock's catalyst to afford 5-, 6-, and 7-membered cycloalkenylsiloxanes, respectively, in some cases with substituents on both alkenyl carbons. These siloxanes are highly effective coupling partners that afford styrenes and dienes (with various aryl and alkenyl halides) in high yield and specificity as well as good functional group compatibility. The siloxanes bearing a *Z*-iodoalkenyl tether undergo an intramolecular coupling process in the presence of $[allylPdCl]_2$ which constitutes a powerful method for the construction of medium-sized rings with an internal 1,3-*cis–cis* diene unit. The formation of 9-, 10-, 11-, and 12-membered carbocyclic dienes is achieved in good yield. Extension to the synthesis of 9-membered ring unsaturated ethers has also been accomplished. Noteworthy features of this process include: (1) highly stereospecific intramolecular coupling, (2) flexible positioning of the revealed hydroxy group, and (3) potential extension to other medium-sized carbocycles and heterocycles.

1. Introduction

The formation of carbon–carbon bonds by transition metal-catalyzed cross-coupling reactions, has evolved into a general and powerful synthetic method over the past three decades.[1] Among the most notable and commonly employed procedures are the Suzuki coupling of organoboranes, the Stille coupling of organostannanes, and the Negishi coupling of organozinc compounds. In recent years, the cross-coupling reactions of organosilicon compounds have been extensively developed and emerged as an extremely viable alternative in view of the high chemical stability, low toxicity, and ease of handling of the precursors.[2,3] A series of reports from these laboratories[4] has demonstrated the ability of organosilicon components (including silacyclobutanes,[4a–d] silanols,[4e,j] silyl hydrides,[4f] cyclic silyl ethers,[4g,k,m,n] and even oligosiloxanes[4h]) to serve as donors in Pd-catalyzed cross-coupling reactions. The practical advantages of this process include: (1) the ease of introduction of the silicon containing moiety, (2) the mildness of reaction conditions, (3) the stereospecificity with respect to both of the addends, and (4) the broad functional group compatibility.

In response to the growing interest in the palladium-catalyzed cross-coupling reactions, a number of methods are now available to introduce silicon-based functionality into molecules.[5] The ability to introduce the silicon donor in a regio- and stereocontrolled fashion is a prerequisite for stereocontrolled construction of alkenes. This feature of the method has been demonstrated in the intramolecular hydrosilylation/cross-coupling[4g] and intramolecular silylformylation/cross-coupling reactions[4m] to efficiently and stereoselectively prepare homoallylic alcohols. In those studies, a temporary silicon tether was employed to set the geometry of an exo alkylidenylsiloxane by hydrosilylation or silylformylation. A recent report by Trost and Ball also describes an intramolecular endo-dig hydrosilylation catalyzed by a cationic ruthenium complex to afford a cycloalkenylsiloxane which contains a geometrically defined alkene in the ring.[6] We envisioned an alternative construction of the cycloalkenylsiloxane that would employ ring-closing metathesis (RCM) of a vinylsilyl ether of an unsaturated alcohol to create the cycloalkenylsiloxane in regio- and stereo-defined form. This cyclic silane could then participate as a coupling partner in Pd-catalyzed cross-coupling reactions.

Keywords: Palladium; Cross-coupling; Organosilicon; RCM; Medium-sized ring.

* Corresponding author. Tel.: +1-217-333-0066; fax: +1-217-333-3984; e-mail: denmark@scs.uiuc.edu

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Ring-closing metathesis of 1,ω-dienes, catalyzed by Mo or Ru complexes, has revolutionized the way in which carbocycles and heterocycles are constructed.[7] There are now several reports of RCM of silicon tethered allylic ethers that employ Grubbs ruthenium alkylidene complexes **1** as the catalyst (Fig. 1).[8] Synthesis of structurally defined and functionalized conjugated dienes via silicon-tethered enyne metathesis with complexes **1** or **2** was also disclosed recently.[9] Moreover, asymmetric RCM of an allylsilyl ether has attracted attention in recent years by the use of a chiral Mo-based complex as the catalyst.[10] Certain vinylsilanes are particularly competent substrates for metathesis reactions. For example, trialkoxyvinylsianes undergo cross metathesis reactions with alkenes upon treatment with catalyst **2**.[11] In addition, a 2-trialkoxysilyl-substituted 1,7-octadiene undergoes ring closure easily to afford the corresponding 1-trialkoxysilylcycloalkene using complex **2**.[5g] However, RCM of sterically more demanding vinylsilyl ethers of unsaturated alcohols requires the sterically less sensitive molybdenum carbene complex **3**, developed by Schrock.[12]

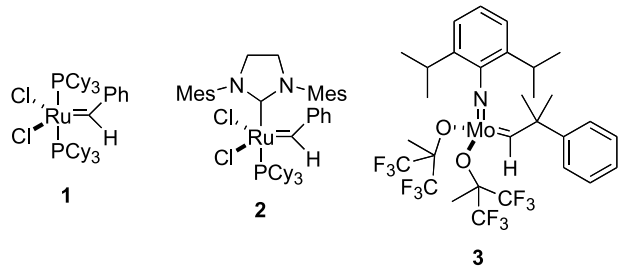
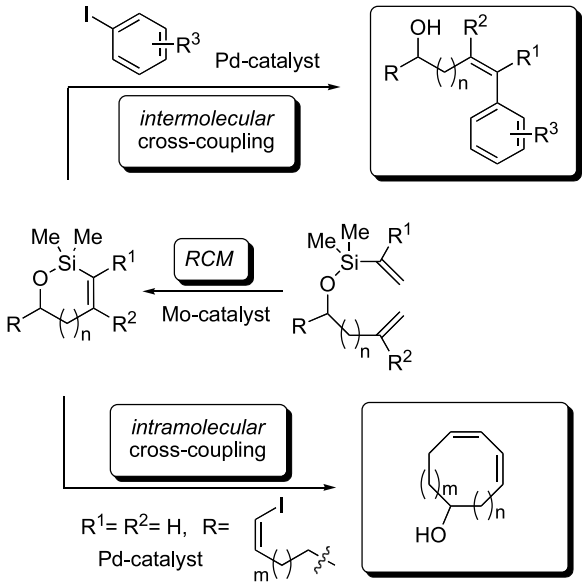


Figure 1. Representative catalysts for RCM.

The main goal of the program described herein was the development of a sequential RCM/Pd-catalyzed, Si-assisted cross-coupling reaction. The precursor cycloalkenylsiloxanes should be easily available by RCM of the vinylsilyl ether of unsaturated alcohols using Mo-complex as catalyst. These cyclosiloxanes would, in turn, be subjected to intermolecular cross-coupling reaction leading to stereocontrolled preparation of highly substituted alkenyl alcohols (Scheme 1). If the siloxane product of RCM contains a suitably disposed electrophile, then the ensuing intramolecular cross-coupling would afford medium-sized rings with an internal, 1,3-*cis*–*cis* diene unit. The synthesis of medium-sized rings,[13] particularly with a conjugated diene unit is well known to be challenging because of unfavorable entropic and enthalpic factors.[14] Indeed palladium-catalyzed intramolecular cross-coupling, especially the Stille coupling of organostannanes, has been widely employed for construction of macrocycles containing an internal diene unit.[15] However, the formation of medium-sized rings with an internal 1,3-diene unit by intramolecular Stille coupling strategies are scarce.[15b] Although significant progress had been recorded in the intermolecular process, the intramolecular cross-coupling reactions of organosilanes have yet to be investigated. We report in full the successful realization of this approach for the stereocontrolled construction of highly substituted unsaturated alcohols as well as 9- to 12-membered carbocycles.[16,17] An extension to the synthesis of medium-sized ring ethers are described as well.

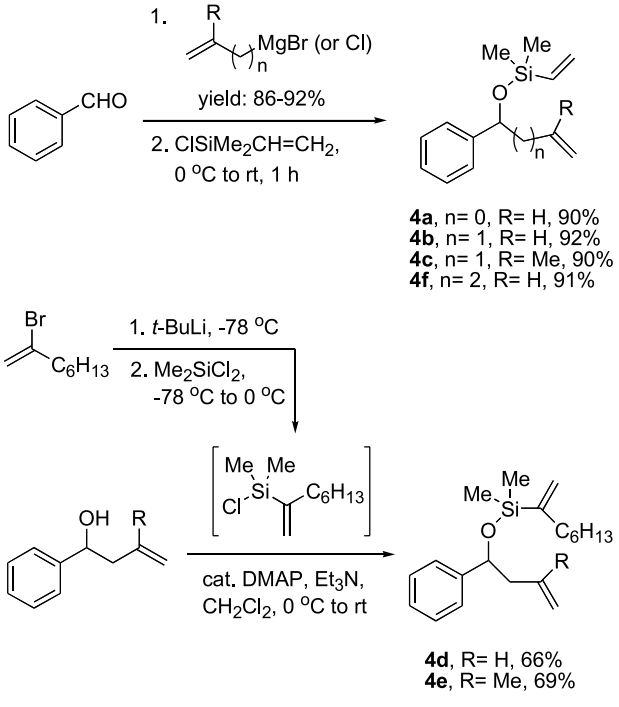


Scheme 1. Sequential RCM/Pd-catalyzed, Si-assisted cross-coupling reactions.

2. Results

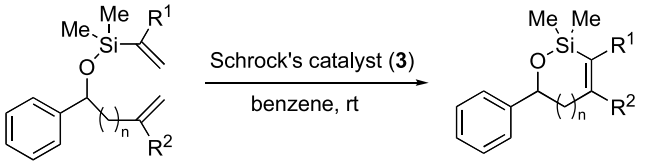
2.1. Sequential RCM/Pd-catalyzed, Si-assisted intermolecular cross-coupling reactions

2.1.1. RCM of olefinic vinylsilyl ethers 4. To test the feasibility of the overall transformation and to further explore the influence of tether length (i.e., ring size) and substituents on the RCM/cross-coupling process, vinylsilyl



Scheme 2. Synthesis of olefinic alkenylsilyl ethers **4**.

Table 1. Molybdenum-catalyzed ring-closing metathesis of **4**[a]



4 **5**

Entry	Substrate, *n*	R^1	R^2	Catalyst, mol%	Time, h	Product	Yield,[b] %
1	**4a**, 0	H	H	7.0	3	**5a**	89
2	**4b**, 1	H	H	5.0	1	**5b**	95
3	**4c**, 1	H	Me	8.0	15	**5c**	91
4	**4d**, 1	C_6H_{13}	H	7.0	12	**5d**	90
5	**4e**, 1	C_6H_{13}	Me	—	—	—	—
6[c]	**4f**, 2	H	H	7.0	12	**5e**	81

[a] Reactions were performed in 0.1 M concentration.
[b] Yields of analytically pure materials.
[c] 91% conversion was observed by ^{1}H NMR analysis.

ethers **4** were prepared (Scheme 2). Vinylsilyl ethers **4a–c** and **4f** could be readily obtained in good yield (90–92%) by the addition of organomagensium bromides (or chlorides) to benzaldehyde followed by silylation of the resulting alcohols with commercially available chlorodimethylvinylsilane. Further, treatment of 1-phenyl-3-buten-1-ol and 1-phenyl-3-methyl-3-buten-1-ol with (1-hexylvinyl)dimethylchlorosilane (generated in situ from 2-bromo-1-octene) gave the corresponding alkenylsilyl ethers **4d–e** in 66–69% yield.

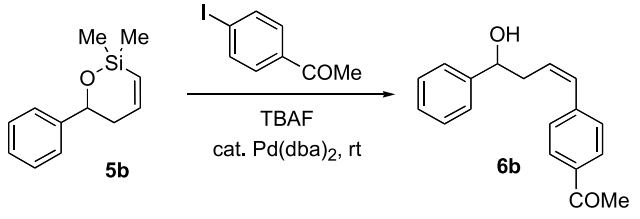
Initial studies on the RCM reaction of **4b** using the Grubbs alkylidene complex **1** failed; none of the desired product, **5b**, was observed by ^{1}H NMR analysis. All variations in conditions, including change of solvent (CH_2Cl_2 or benzene) and/or temperature (rt, 45 or 80 °C) were unsuccessful. Even the more reactive 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene-substituted ruthenium complex **2** ('second generation' Grubbs catalyst) failed to promote the RCM reaction.[18] Gratifyingly, substrate **4b** did undergo the RCM process by the use of the molybdenum complex **3** as the catalyst.[19] After careful optimization, a near quantitative yield of **5b** was obtained with 5 mol% of **3** in benzene (0.1 M) at ambient temperature (Table 1, entry 2).

The allylic ether **4a** (a five-membered ring precursor) suffered RCM under the standard conditions (5 mol% of Mo complex **3** in benzene, 1 h); however, only 75% conversion could be obtained after 1 h. This problem was solved by increasing the catalyst loading; using 7 mol% of catalyst **3**, the complete consumption of **4a** was achieved within 3 h to afford the product **5a** in 89% yield (Table 1, entry 1). However, for the preparation of a seven-membered siloxane **5e**, the reaction only went to 91% completion, giving an 81% yield under these conditions (entry 6). With a monosubstituted alkene or vinylsilane (entries 3 and 4), the RCM process proceeded slowly compared to **4b** albeit ultimately to completion to afford **5c–d** in 91 and 90%, respectively. Unfortunately, substitution on both the alkene and vinylsilane (entry 5) did not lead to a successful closure (even under harsher conditions) presumably due to the significant increase in steric crowding.

2.1.2. Pd-catalyzed intermolecular cross-coupling reactions. Optimization of the Pd(0)-catalyzed coupling of siloxane **5b** with 4-iodoacetophenone employed the conditions developed in these laboratories for alkenylsilanols[4e] (Table 2). Thus, siloxane **5b** was dissolved with a 1.0 M solution of tetrabutylammonium fluoride (TBAF·$3H_2O$) in THF at room temperature, followed by the sequential addition of 4-iodoacetophenone and 5 mol% of $Pd(dba)_2$. The reaction proceeded cleanly to completion in only 10 min (Table 2, entry 1). Decreasing the loading of $Pd(dba)_2$ (3 mol%) only marginally affected the rate of the coupling process (entry 2). However, with a lower catalyst loading (1.0 mol%, entry 3) or less TBAF (1.0 equiv., entry 4), the reaction did not go to completion and a significant amount of 4-iodoacetophenone (5 and 19%, respectively) was recovered.

With suitable conditions for both reactions in hand, we turned our attention to expanding the scope of this process with various aryl iodides. Both the nature and position of substituents on the aromatic ring were studied under the

Table 2. Optimization of the cross-coupling reaction of **5b** with 4-iodoacetophenone[a]

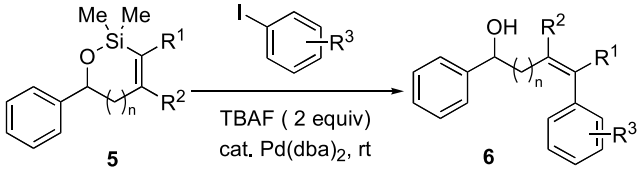


5b **6b**

Entry	$Pd(dba)_2$, mol%	TBAF, equiv.	Time, min	Yield,[b] %
1	5.0	2.0	10	89
2	3.0	2.0	30	86
3	1.0	2.0	180	80[c]
4	5.0	1.0	180	65[d]

[a] All reactions employed 1.1 equiv. of **5b** and 1.0 equiv. of 4-iodoacetophenone at room temperature.
[b] Yield of isolated **6b**.
[c] 5% of 4-iodoacetophenone was recovered.
[d] 19% of 4-iodoacetophenone was recovered.

Table 3. Palladium-catalyzed cross-coupling of **5** with aryl iodides[a]



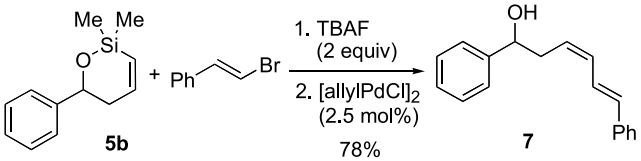
5 **6**

Entry	Substrate, *n*	R^1	R^2	R^3	$Pd(dba)_2$, mol%	Time, min	Product	Yield,[b] %
1	**5a**, 0	H	H	4-CO_2Et	3.0	30	**6a**	85
2	**5b**, 1	H	H	4-COMe	5.0	10	**6b**	90[c]
3	**5b**, 1	H	H	4-OMe	3.0	30	**6c**	92
4	**5b**, 1	H	H	3-CO_2Et	3.0	30	**6d**	93
5	**5b**, 1	H	H	2-Me	3.0	30	**6e**	89
6	**5b**, 1	H	H	2-NO_2	3.0	90	**6f**	86
7	**5b**, 1	H	H	2-CH_2OH	5.0	180	**6g**	90
8	**5b**, 1	H	H	2-CO_2Me	5.0	360	**6h**	84
9	**5c**, 1	H	Me	2-Me	3.0	45	**6i**	83
10[d]	**5d**, 1	C_6H_{13}	H	3-CO_2Et	10.0	24 h	**6j**	81
11	**5e**, 2	H	H	4-OMe	3.0	30	**6k**	85[c]

[a] All reactions employed: **5** (1.1 equiv.), TBAF (2.0 equiv.), aryl iodide (1.0 equiv.) and $Pd(dba)_2$ (3.0 mol%) at room temperature unless otherwise specified.
[b] Yields of analytically pure materials.
[c] Yield of chromatographically homogeneous material.
[d] $Pd(dba)_2$ (2.5 mol%/3 h) and (0.25 mmol/3 h) were added portionwise.

optimized conditions: 3.0–5.0 mol% of $Pd(dba)_2$ as the catalyst and 2.0 equiv. of TBAF as the activator at ambient temperature. The results with all aryl iodides examined are complied in Table 3. The coupling of 5-membered siloxane **5a** with ethyl 4-iodobenzoate using a 3.0 mol% catalyst loading, was complete in 30 min to afford **6a** in 85% yield with excellent stereospecificity (Table 3, entry 1). The coupling products showed slight decomposition upon distillation. However, they could be secured in analytically pure form after silica gel chromatography. Although the stereospecificity could not be determined by GC, no other isomer was see by ^{1}H NMR analysis. The 11.6 Hz vicinal coupling constant between the olefinic protons indicated that the *Z*-olefin geometry was maintained. The reaction of the 6-membered siloxane **5b** with 4-iodoacetophenone gave, as expected, **6b** in 90% yield in 10 min with a 5.0 mol% catalyst loading (entry 2). Electrophiles bearing an electron-donation group (entry 3) or an electron-withdrawing group (entry 4), both gave the desired products **6c** and **6d** in 92 and 93% yield, respectively. Sterically hindered substrates, such as in 2-iodotoluene (entry 5) or 2-nitroiodobenzene (entry 6), also gave the expected products **6e** and **6f** in excellent yield (89 and 86%, respectively). The reaction of 2-iodobenzyl alcohol (entry 7) and methyl 2-iodobenzoate (entry 8) proceeded more slowly than the previously mentioned electrophiles to afford **6g** (90%) and **6h** (84%). Even using a 5.0 mol% catalyst loading, reactions of these substrates still required 3–6 h to reach completion. The effect of substitution on the α- and β-positions of the alkenylsilyl group, such as in siloxanes **5c** and **5d**, was also examined with various aryl iodides. Cross-coupling of **5c** with 2-iodotoluene proceeded to completion in 45 min to afford **6i** in 83% yield (entry 9). The α-substituted alkenylsilane **5d** did undergo the coupling process with ethyl 3-iodobenzoate (entry 10), however, at a significantly reduced reaction rate compared to the related silanes. Moreover, the reaction mixture contained a substantial amount of self-coupling of ethyl 3-iodobenzoate. The use of additives[4c] ($AsPh_3$ or *t*-Bu_3P) and/or slightly elevated temperatures (35–45 °C) did not improve the results. Fortunately, the addition of the iodide in portions satisfactorily suppressed the formation of the self-coupling product.[4g] Moreover, increasing the loading and portionwise addition of the Pd(0) complex also provided complete conversion and kept the palladium from precipitating in this slow reaction. By using a 10 mol% catalyst loading, the coupling product **6j** can be obtained in 81% yield after 24 h. Finally, the reaction of 7-membered siloxane **5e** with 4-iodoanisole proceeded similarly to give **6k** in 85% yield (entry 11).

The cross-coupling of **5b** was also successful with (*E*)-2-bromostyrene (Scheme 3). The reaction rate and yield were slightly lower than those obtained with aryl iodides. After 5 h, **7** could be isolated in 78% yield with 2.5 mol% of $[allylPdCl]_2$ as the catalyst.

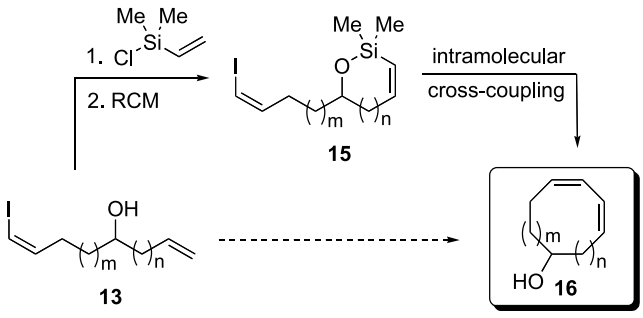


5b **7**

Scheme 3. Cross-coupling of **5b** with (*E*)-2-bromostyrene.

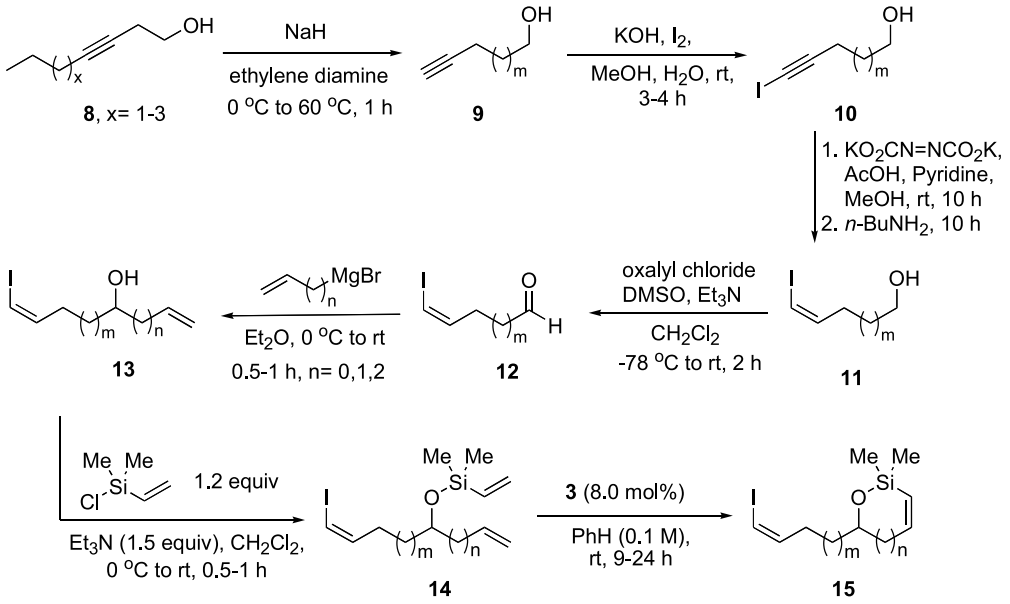
2.2. Sequential RCM/Pd-catalyzed, Si-assisted intramolecular cross-coupling reactions

With the sequential RCM/Pd-catalyzed, silicon-assisted intermolecular cross-coupling reaction successfully demonstrated, we turned our attention toward investigation of the intramolecular coupling process. The strategy, outlined in Scheme 4, involves the generation of cyclic silyl ethers **15**



Scheme 4. Strategy for intramolecular silicon-assisted cross-coupling.

isomerization of internal alkynyl alcohols **8** ($x=1$–3) with sodium 2-aminoethylamide generated in situ from sodium hydride and ethylenediamine.[20] Iodination of **9** with iodine in aqueous KOH gave the iodoalkynyl alcohols **10** in excellent yield (90–95%). Next, *cis*-reduction of **10** with diimide, (generated in situ from potassium azodicarboxylate), afforded the corresponding iodoalkenyl alcohols **11** in moderate yield (56–64%). A small amount of the over-reduction product could be easily removed by treatment of crude material with *n*-$BuNH_2$. Oxidation by the method of Swern was chosen to convert the primary alcohol to the aldehyde in 82–88% yield. The addition of various Grignard reagents to the aldehydes afforded the desired iododienyl



Scheme 5. Synthesis of **15**, precursors for intramolecular cross-coupling.

by Mo-catalyzed RCM and their subsequent participation as nucleophilic partners in Pd-catalyzed intramolecular cross-coupling with an alkenyl iodide appended at a remote position. In these siloxanes, variables, *m* and *n* combine to determine the size of the ring and the location of the hydroxyl group relative to the diene unit.

2.2.1. Synthesis of siloxanes 15. To test the feasibility and generality of the overall transformation, substrates **15** were prepared from terminal alkynyl alcohols **9** as depicted in Scheme 5. The results of the overall transformation are compiled in Tables 4 and 5. Alkynyl alcohols **9a–b** are commercially available materials and substrates **9c–e** were readily available in 82–84% yield by base-promoted alcohols **13** in 85–93% yield. Finally, silylation of **13** with commercially available chlorodimethylvinylsilane gave the targeted vinylsilyl ethers **14** in 86–95% yield. From earlier studies, we already knew that RCM of vinylsilyl ethers required the use of Schrock's molybdenum complex **3**. Gratifyingly, substrates **14** also underwent the RCM process smoothly with **3** without competitive reaction of the vinyl iodide unit. Unfortunately, substrate **14g** (for a five-membered ring precursor) did not lead to a successful closure in the RCM process. Even using 12 mol% of catalyst **3**, only a 21% conversion of **15g** was observed after 60 h at ambient temperature according to ^{1}H NMR analysis. Under slightly harsher conditions (45 °C), no improvement in

Table 4. Preparation of **9**, **10**, **11**, and **12**

m	**9** (yield, %)[a]	**10** (yield, %)[a]	**11** (yield, %)[a]	**12** (yield, %)[a]
1	**9a** (–)	**10a** (91)	**11a** (56)	**12a** (85)
2	**9b** (–)	**10b** (94)	**11b** (61)	**12b** (85)
3	**9c** (83)	**10c** (94)	**11c** (60)	**12c** (86)[b]
4	**9d** (84)	**10d** (95)	**11d** (64)[b]	**12d** (82)[b]
5	**9e** (82)	**10e** (90)	**11e** (61)[b]	**12e** (88)[b]

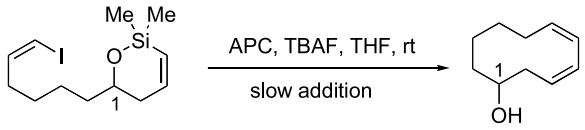
[a] Yields of chromatographically homogeneous material.
[b] Yields of analytically pure material.

Table 5. Preparation of alcohols **13**, silyl ethers **14**, and siloxanes **15**

m, *n*	Alcohol **13** (yield, %)[a]	Silyl ether **14** (yield, %)[a]	Siloxane **15** (yield, %)[a]
1, 1	**13a** (93)	**14a** (86)	**15a** (83)
2, 1	**13b** (91)	**14b** (95)	**15b** (81)
3, 1	**13c** (88)	**14c** (94)	**15c** (82)
4, 1	**13d** (92)	**14d** (93)	**15d** (81)
5, 1	**13e** (91)	**14e** (93)	**15e** (83)
2, 2	**13f** (91)	**14f** (95)	**15f** (80)
4, 0	**13g** (85)	**14g** (87)	**15g** (–)

[a] Yields of analytically pure materials.

Table 6. Optimization of the intramolecular cross-coupling reaction of **15c**[a]



15c **16c**

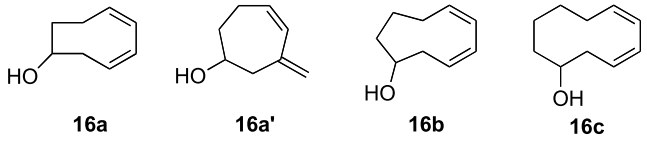
Entry	**15c** (M, in THF)	APC, mol%	TBAF, equiv.	Time, h	**16c** (%)[b]
1[c]	—	3.0	2.0	30	<10
2[d]	0.5	3.0	2.0	20	14
3	0.1	3.0	10.0	32	45
4	0.1	3.0	20.0	34	32
5	0.05	3.0	10.0	50	46
6	0.1	5.0	10.0	40	62
7	0.1	5.0	5.0	40	44
8	0.1	7.5	10.0	40	74
9	0.1	10.0	10.0	40	75
10[d]	0.1	7.5	10.0	43	75

[a] All reactions were performed on a 0.1 mmol scale by slow addition a solution of **15c** to a mixture of APC and TBAF solution unless otherwise specified.
[b] The percentage of product was determined by ^{1}H NMR analysis comparing the integrated area of the diene to the total integrated area of H(C1).
[c] The reaction was run in THF (0.01 M, dilute condition).
[d] 0.5 mmol scale.

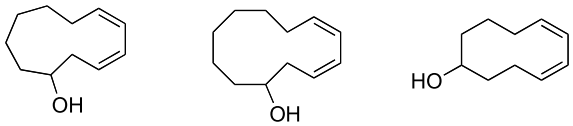
conversion was observed. Not surprisingly, the yields of these reactions are not influenced by chain length.

2.2.2. Optimization of intramolecular cross-coupling reaction. Optimization of the Pd-catalyzed, intramolecular cross-coupling reaction of **15c** (to form a 10-membered ring) employed allylpalladium chloride dimer (APC) as the catalyst and a 1.0 M solution of tetrabutylammonium fluoride (TBAF) in THF as the activator. We chose this substrate because in cycloalkenes, the maximum strain is found in the 10-membered ring.[14] The results from studies of the catalyst loading and the amount of activator are collected in Table 6. Typical conditions, which would favor intra- vs intermolecular coupling (high dilution, entry 1, or slow addition of substrate, entry 2) did not promote this intramolecular process well. Under these conditions, unreacted vinylsilanes and oligomers were observed by ^{1}H NMR analysis. Therefore, to maintain efficient fluoride activation, promote transmetalation and maintain a low concentration of **15c** (to prevent oligomerization), the amount of TBAF solution was increased. To our delight, the percentage of the desired product, **16c**, increased dramatically to 45% (entry 3). Neither increasing the amount of TBAF solution nor adding more dilute solutions of **15c** had a beneficial effect (entries 4–5). However, we found that the catalyst loading did have a significant effect on the success of this intramolecular process (entries 3, 6, 8, and 10). A great improvement in the production of **16c** to

Table 7. Pd-catalyzed intramolecular cross-coupling reactions of **15**[a]



16a **16a'** **16b** **16c**



16d **16e** **16f**

Entry	Substrate **15**	APC, mol%	Time, h	Product **16**, yield/%[b]
1	**15a**	7.5	60	**16a**+**16a′** (60%,1:1)[c,d]
2	**15b**	7.5	45	**16b** (70%)
3	**15c**	7.5	45	**16c** (63%)
4	**15d**	10.0	75	**16d** (55%)
5	**15e**	10.0	75	**16e** (72%)
6	**15f**	10.0	60	**16f** (71%)

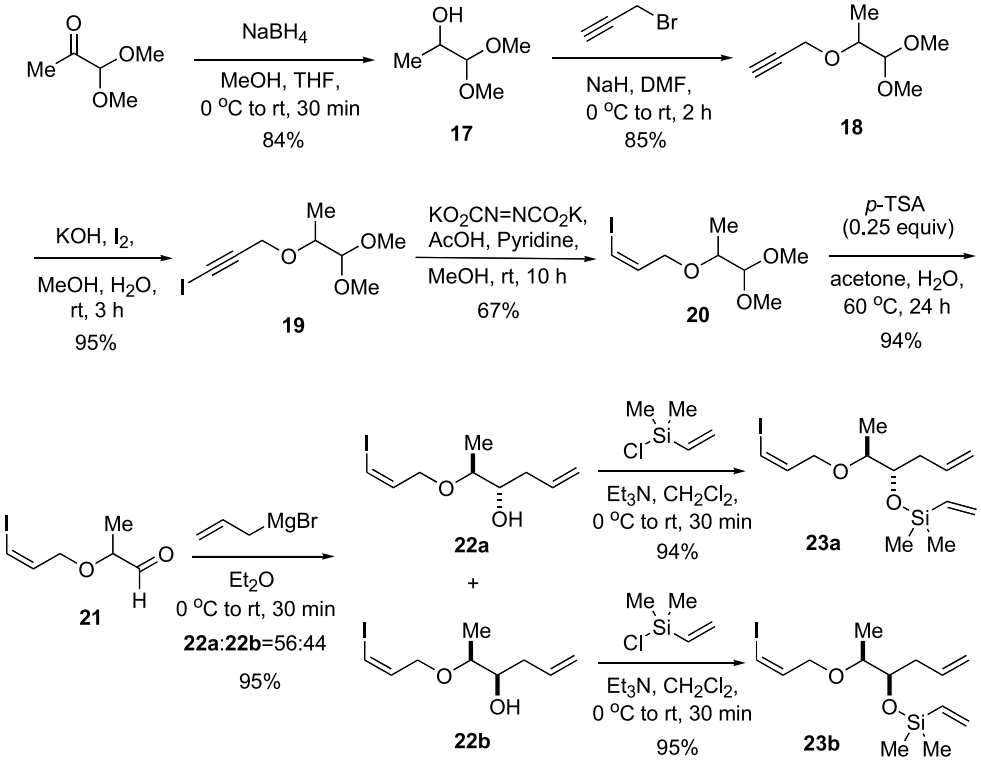
[a] All reactions were performed on a 1.0 mmol scale (0.1 M in THF), with TBAF (10.0 equiv.), and slow addition condition at room temperature.
[b] Yield of analytically pure materials.
[c] Yield of chromatographically homogeneous material.
[d] The ratio was determined by ^{1}H NMR analysis.

62% was obtained by using 5.0 mol% of APC (entry 6). Decreasing the amount of TBAF solution, decreased the percentage of **16c** to 44% (entry 7). Finally, by employing 7.5 mol% of APC, the percentage of **16c** in the coupling products jumped to 75% (entries 8 and 10). No further improvement was observed using even with 10 mol% of APC (entry 9).

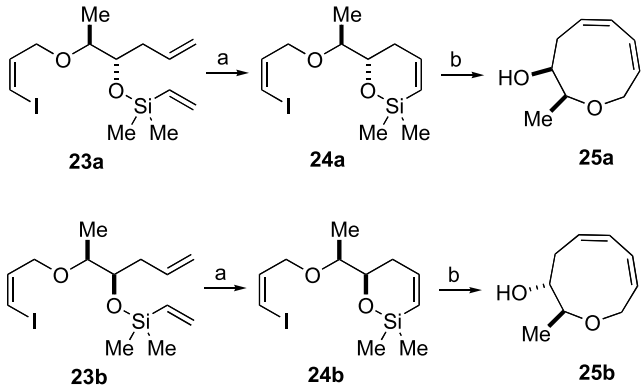
2.2.3. Scope and limitations of Si-assisted intramolecular cross-coupling reactions. The scope of this silicon-assisted, intramolecular cross-coupling process with regard to ring size was examined under the following conditions: 7.5–10.0 mol% of APC and 10.0 equiv. of TBAF solution at room temperature. The results with all substrates examined are compiled in Table 7. Under the optimal conditions, the 9-membered carbocycle **16b** containing a 1,3-*cis*–*cis* diene unit was obtained in 70% yield from siloxane **15b** after 45 h addition time (entry 2). Moreover, intramolecular coupling of **15c** gave the corresponding 10-membered cyclic product **16c** in 63% yield (entry 3). In the coupling of **15d**, the amount of **16d** observed was only 42% by ^{1}H NMR analysis under these conditions. Increasing the catalyst loading to 10 mol%, increased the yield of **16d** to 59% after a 42 h addition. Finally, by using 10 mol% of APC and increasing the addition time to 75 h, we were able to produce **16d** in 55% yield (67% by ^{1}H NMR). Similarly, only 49% of **16e** and 55% of **16f** were observed by ^{1}H NMR analysis under the standard conditions. By employing similar conditions used for **15d**, the desired coupling products **16e** and **16f** were obtained in 72 and 71% yield, respectively (entries 5–6). Unfortunately, substrate **15a** afforded a mixture of desired product **16a** and cine rearrangement product **16a′** in 60% yield in a 1:1 ratio, presumably due to the more difficult construction of a cyclooctadiene.

2.2.4. Formation of medium-sized ring ethers. To demonstrate the versatility and effectiveness of this process, we next investigated extension to medium-sized heterocycles. Medium ring ethers have attracted a great deal of attention as synthesis targets in view of their occurrence in several classes of marine natural product structures.[21] Thus, the diastereomeric silyl ethers **23a–b** were selected to test this application by generation of the corresponding 9-membered oxacyclic dienes[22] (Scheme 6). The preparation of **23a–b** began with the reduction of pyruvic aldehyde dimethoxy acetal with $NaBH_4$ in MeOH/THF to afford hydroxyl acetal **17** in 84% yield. Alkylation of the sodium alkoxide of **17** (from sodium hydride in DMF) with propargyl bromide afforded **18** in 85% yield. Conversion of **18** to **20** was achieved by iodination followed by a *cis*-reduction of iodoalkyne **19** to iodoalkene **20** employing the condition established above. Hydrolysis of dimethoxy acetal was effected by treatment of **20** with *p*-toluenesulfonic acid in an acetone/H_2O mixture to give aldehyde **21** in 94% yield. Treatment of aldehyde **21** with allylmagnesium bromide for 0.5 h afforded hydroxyl dienyliodide **22a–b** in 95% yield as a 56:44 mixture of diastereomers, which were easily separated by silica gel chromatography. Finally, silylation of the alcohols with chlorodimethylvinylsilane in CH_2Cl_2 for 30 min furnished **23a–b** in 94 and 95% yield, respectively.

With these materials in hand, the ring closing metathesis of **23a** was carried out using 10 mol% of the Mo complex **3** to afford the target siloxane **24a** in 81% yield. Similarly, RCM of **23b** proceeded smoothly to afford cyclic silyl ethers **24b** in 80% yield under the same conditions (Scheme 7). Gratifyingly, exposure of the siloxanes to the optimal conditions established above promoted the intramolecular



Scheme 6. Synthesis of **23a–b**.



Scheme 7. Formation of medium-sized ring ethers **25**. Reagents and conditions: (a) **3** (10.0 mol%), benzene (0.1 M), rt, 36 h, **24a** (81%); **24b** (80%). (b) APC (7.5 mol%), TBAF (10.0 equiv.), rt, 45 h, **25a** (72%); **25b** (77%).

cross-coupling effectively. Both diastereomers reacted with equal facility to afford the oxonane dienes **25a** and **25b**, in 72 and 77% yield, respectively with no difference in rate or efficiency.

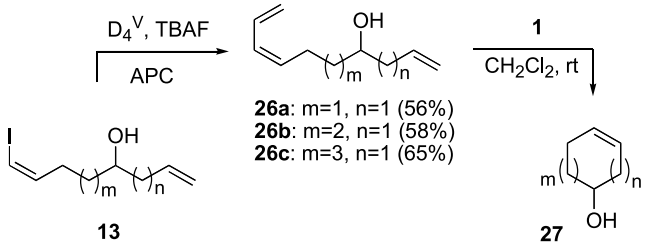
3. Discussion

3.1. Ring-closing metathesis of olefinic alkenylsilyl ethers

The RCM of alkenylsilyl ethers **4** proceeded smoothly as expected from the literature reports.[12] The more reactive Mo complex **3** is the catalyst of choice for all of the variants examined as the Ru-based complexes were ineffective. The formation of 5- or 7-membered siloxanes **5a** and **5e** (Table 1, entries 1 and 6) as well as substitution on the double bond (Table 1, entries 3–4) were associated with lower RCM reaction rates. This behavior was particularly apparent in the case of **4e**; all attempts to effect ring closure led to failure presumably due to the significant steric hindrance at both ends of the alkene. Interestingly, in the cases of **14a–f**, the RCM proceeded smoothly in the presence of an alkenyl iodide function. In fact, alkylidene **1** has been shown to react with acetylenic halides through halide exchange. Moreover, some dienes or dienynes containing a vinyl halide (Br or I) also failed to cyclize using either **1** or Mo-complex **3**.[12e,23] It has been hypothesized that formation of more stable and unreactive Fischer-type carbene complexes from vinyl bromides or vinyl ethers and Ru-alkylidene complexes might prevent the initiation step at the terminal alkene.[11c,23b,24] Although the reason for the failure of RCM with vinyl bromide containing dienes using catalyst **3** has not been determined, the successful ring closure of **14** indicated that the initiation step at the terminal alkene did occur, and that subsequent combination with the alkenylsilyl species proceeded without interference of the iodoalkenyl group. RCM of **14g** (a five-membered siloxane precursor) was not successful; only 21% conversion was observed. This was surprising in light of the successful RCM of **4a** to oxasilacyclopentene **5a** (Table 1). Perhaps, the smaller substituent at the allylic position of the oxasilacyclopentene ring permits the strained RCM product to compete with the starting material in this reversible process. Thus, **5a** with a sterically more demanding phenyl group deters RCM of the product.

3.2. Ring-closing metathesis of trienes

In formulating the intramolecular cross-coupling reaction, it was not lost upon us that the iodo alcohols **13** could also be converted to cycloalkadienes **16** by an inverted sequence of cross-coupling (vinylation) followed by RCM of the triene. Indeed, RCM of trienes have been reported recently for construction of macrolides containing a 1,3-diene system. Moreover, the more sterically sensitive Ru-complex **1** has been shown to react preferentially with the terminal double bond of a diene preferably to afford macrocycles with a internal diene unit.[25] To the best of our knowledge, formation of medium-sized ring with a diene unit by RCM is still rare.[26] Thus, to determine whether the intramolecular cross-coupling was of any tactical advantage, we undertook the preparation of the requisite trienes **26** and assayed their potential for RCM to dienes (Scheme 8). Vinylation of **13** was readily accomplished by our recently described method using 1,3,5,7-tetramethyl-1,3,5,7-tetravinylcyclotetrasiloxane (D_4^V) to afford the desired trienes **26a–c** in 56–65% yield.[4h] Initial studies on the RCM of trienes, **26a**, using Grubbs alkylidene complex **1** (5.0 mol%) produced only the six-membered ring compound **27a** in greater than 95% conversion in 6 h at room temperature. However, only 22% of the seven-membered ring product **27b** was obtained along with 58% of **26b** recovered under the same conditions. Furthermore, none of closure products of **27c** were observed under these conditions and complex mixtures were obtained in refluxing CH_2Cl_2. Clearly, closure on the internal double bond of the diene to afford smaller rings predominated.[27,28] We thus demonstrated the utility and further substantiated the advantages of the intramolecular cross-coupling method.



Scheme 8. RCM of trienes **26**.

3.3. Si-assisted cross-coupling reactions

The intermolecular cross-coupling of cycloalkenylsiloxanes **5** with various aryl iodides proceeded rapidly and efficiently. For all aryl iodides examined, the reaction conditions were mild and gave uniformly high yields. Noteworthy features of this process include: (1) electron-withdrawing or donating groups exhibit similar reactivity (Table 3, entries 2–4), (2) the steric effect of ortho substituents is minimal (Table 3, entry 5) except in the cases where possible coordination of the palladium may slow the reductive elimination step (Table 3, entries 6–8), (3) the reaction tolerates diverse functional groups such as

ester, ether, nitro and even a free hydroxyl group, and (4) the reactions of all iodides were stereospecific. The influence of the siloxane ring size as well as the substitution on the double bond in coupling reactions was systematically investigated. The results in Table 3 reveal that: (1) different cyclic alkenyl silanes exhibit similar reactivity in the coupling reaction (Table 3, entries 1, 3 and 11) and (2) substitution on the β-*trans*-position of the silyl group did not affect the reactivity significantly (Table 3, entry 9).

A comparison between these results and those described previously reveals that mono-substitution of alkenyl silanes (silacyclobutanes[4a–d] and silanols[4e]) in either the α- or the β-position does not affect the rate of the cross-coupling process significantly. The disubstituted alkenylsilanes including cyclic siloxanes[4g] and silyl hydrides[4f] are also very reactive in the coupling process except in the case of substitution on both of α- and β-*cis*-positions, as in **5d**. The steric influence may slow the coupling reaction and allow a competitive homocoupling of the aryl iodides to intervene.

In the cases of intramolecular cross-coupling, the results, compiled in Table 7, reveal good generality for the construction of 9-, 10-, 11-, and 12-membered cycloalkadienes, (Table 7, entries 2–6). With the exception of **15a**, all of the substrates examined gave the corresponding medium-sized rings bearing the 1,3-*cis*–*cis* diene unit stereospecifically in respectable yield from highly flexible starting materials without significant conformational constraints.[29] Notably, modulation of the location of the hydroxy group was successfully achieved by adjustment of chain length and ring size of the silyl ether (cf. Table 7, entries 3 and 6). An extension of the intramolecular coupling process for construction medium-sized ether rings, such as **25a** and **25b**, was examined under the standard reaction conditions. Interestingly, both diastereomers reacted similarly without significant difference in reaction rate and yield. This observation bodes well for the application of the process in the synthesis of complex, medium-ring ether natural products.[30]

4. Conclusion

The sequential RCM/cross-coupling reactions of olefinic alkenylsilyl ethers has been demonstrated. The cycloalkenylsiloxanes serve as competent donors in rapid and high-yielding cross-coupling reactions with various aryl and alkenyl halides. The intermolecular cross-coupling reactions proceeded with high stereospecificity and good functional group compatibility. In addition, the influences of siloxane ring size and olefin substitution are similar to those observed in the acyclic coupling processes. The Pd-catalyzed, silicon-assisted intramolecular cross-coupling reaction provides an effective and potentially powerful method for construction of medium-sized rings with an internal 1,3-*cis*–*cis* diene unit. Noteworthy features of this intramolecular process include: (1) a highly stereospecific intramolecular coupling process, (2) the flexible positioning of hydroxy group, and (3) the potential extension to other medium-sized carbocycles and heterocycles.

5. Experimental

5.1. General

All reactions were performed in oven-dried (140 °C) or flame-dried glassware under an inert atmosphere of dry Ar or N_2. The following reaction solvents were distilled from the indicated drying agents: diethyl ether (Na, benzophenone), THF (Na, benzophenone), CH_2Cl_2 (P_2O_5), benzene (Na), toluene (Na), methanol ($Mg(OMe)_2$), triethylamine (CaH_2). *n*-Butyllithium solutions were titrated following the method of Gilman.[31] Brine refers to a saturated aqueous solution of NaCl. Grignard solutions were titrated using 2,2′ -phenanthroline as an indicator. Kugelrohr distillations were performed on a Büchi GKR-50 Kugelrohr; boiling points (bp) corresponding to uncorrected air-bath temperatures (ABT). All reaction temperatures correspond to internal temperatures measured by Teflon-coated thermocouples unless otherwise noted.

^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Varian Unity 400 (400 MHz, ^{1}H; 100 MHz, ^{13}C), Unity 500 (500 MHz, ^{1}H; 126 MHz, ^{13}C). Spectra are referenced to residual chloroform (δ 7.26 ppm, ^{1}H; δ 77.0 ppm, ^{13}C) and residual acetone (δ 2.04 ppm, ^{1}H; δ 29.8 ppm, ^{13}C). Chemical shifts are reported in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Coupling constants, *J*, are reported in Hertz. Mass spectroscopy was performed by the University of Illinois Mass Spectrometer Center. Electron impact (EI) spectra were performed on a Finnigan-MAT CH-5 spectrometer. Data are reported in the form of *m*/*z* (intensity relative to base peak = 100). Infrared spectra (IR) were recorded on a Mattson Galaxy 5020 spectrophotometer. Peaks are reported in cm^{-1} with indicated relative intensities: s (strong, 67–100%); m (medium, 34–66%); w (weak, 0–33%). Elemental analyses were performed by the University of Illinois Microanalytical Service Laboratory.

Analytical thin-layer chromatography was performed on Merck silica or aluminum oxide, basic gel plates with QF-254 indicator. Visualization was accomplished with UV light and/or Iodide. Diethyl ether was of reagent grade and used as received; other solvents for chromatography and filtration were technical grade and distilled from the indicated drying agents: hexane and pentane ($CaCl_2$); CH_2Cl_2 ($CaCl_2$); ethyl acetate (K_2CO_3). Column chromatography was performed using EM Science 230–400-mesh silica gel or Aldrich 150-mesh aluminum oxide, activated, basic, Brockmann I.

Analytical capillary gas chromatography (GC) was performed using the following gas chromatography fitted with a flame ionization detector (H_2 carrier gas, 1 mL/min): Hewlett Packard 5890 Series II. The following column was used: HP-5 50-m cross-linked 5%-Phenyl methyl silicone gum phase or Ultra-2 50-m cross-linked 5%-Phenyl methyl silicone gum phase. The detector temperature was 300 °C. Retention times (t_R) and integrated ratios were obtained from Hewlett Packard 3393A integrators.

All commercial reagents were purified by distillation or

recrystallization prior to use. A 1.0 M solution of tetrabutylammonium fluoride in THF was prepared from solid tetrabutylammonium fluoride trihydrate ($TBAF\cdot 3H_2O$, Fluka) and distilled THF in a volumetric flask and was stored in a Schlenk bottle. Palladium bis(dibenzylideneacetone) ($Pd(dba)_2$) was purchased from Jansen and used without purification. π-Allylpalladium chloride dimer $[allylPdCl]_2$ (APC) was purchased from ACROS and was recrystallized from benzene prior to use.

5.2. Representative experiments

5.2.1. General procedure I: silylation with chlorodimethylvinylsilane. To a solution of the requisite unsaturated alcohol in CH_2Cl_2 was added Et_3N (1.5 equiv.) and dimethylvinylchlorosilane (1.2 equiv.) sequentially under N_2 atmosphere at 0 °C. The white suspension was allowed to warm to room temperature and was stirred for 0.5–1.0 h. The mixture was poured into ice water and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, then were dried (Na_2SO_4), and filtered. After removal of solvent, the residue was purified by silica gel chromatography followed by Kugelrohr distillation to afford the corresponding silyl ether.

5.2.1.1. Preparation of dimethyl[(1-phenyl-3-butenyl)oxy]vinylsilane (4b). Following General procedure I, a solution of 1-phenyl-3-buten-1-ol (3.19 g, 21.5 mmol) in CH_2Cl_2 (30 mL), chlorodimethylvinylsilane (3.86 mL, 28.0 mmol, 1.2 equiv.), and Et_3N (4.48 mL, 32.3 mmol, 1.5 equiv.) were combined. After being stirred at room temperature for 2 h, the mixture was then poured to ice water (30 mL) and the aqueous layer was extracted with CH_2Cl_2 (2×30 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed by rotary evaporation. The residue was distilled under reduced pressure to afford 4.59 g (92%) of **4b** as a colorless liquid. Bp 74–75 °C (0.1 mm Hg); R_f 0.13 (silica gel, hexane, PMA); IR (neat) ν 2960 (s), 1641 (m), 1407 (m), 1253 (s), 1087 (s), 1068 (s), 1009 (s), 916 (s), 836 (s), 785 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.26 (m, 5H), 6.11 (dd, J=19.8, 14.9 Hz, 1H), 6.00 (dd, J=14.9, 4.4 Hz, 1H), 5.80–5.78 (m, 1H), 5.77 (dd, J=20.0, 4.4 Hz, 1H), 5.11–5.05 (m, 2H), 4.74 (dd, J=7.6, 5.5 Hz, 1H), 2.59–2.43 (m, 2H), 0.18 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.6, 137.7, 135.1, 133.0, 128.0 (2 C), 127.0, 126.0 (2 C), 116.9, 75.0, 45.0, −1.5, −1.7; MS (CI, 130 eV) 233 (4, $M^+ + 1$), 217 (34), 205 (35), 191 (100), 155 (23), 131 (37), 85 (19). Anal. Calcd for $C_{14}H_{20}OSi$: C: 72.36; H: 8.67. Found: C: 72.22; H: 8.56.

5.2.1.2. Preparation of dimethyl{[(*Z*)-9-iodo-1,8-nonadienyl]-4-oxy}vinylsilane (14b). Following General procedure I, a solution of **13b** (3.99 g, 15 mmol) in CH_2Cl_2 (25 mL), chlorodimethylvinylslane (2.49 mL, 18.0 mmol, 1.2 equiv.), and Et_3N (3.13 mL, 22.5 mmol, 1.5 equiv.) were combined. After being stirred at room temperature for 1 h, the mixture was poured into ice water (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with brine (50 mL), then were dried (Na_2SO_4), and filtered. After removal of solvent, the residue was purified by chromatography (silica gel, hexane/EtOAc, 49/1) followed by Kugelrohr distillation to afford 5.0 g (95%) of **14b** as a colorless liquid. Bp 120–125 °C (0.05 mm Hg, ABT); R_f 0.39 (silica gel, hexane/EtOAc, 49/1, PMA); IR (neat) ν 3073 (m), 2942 (s), 2861 (m), 1641 (m), 1407 (m), 1276 (m), 1251 (s), 1089 (s), 914 (s), 835 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.20–6.12 (m, 3H), 6.00 (dd, J=15.0, 4.0 Hz, 1H), 5.83–5.76 (m, 1H), 5.77 (dd, J=20.5, 4.0 Hz, 1H), 5.06–5.03 (m, 2H), 3.71 (quint, J=6.0 Hz, 1H), 2.21 (dd, J=7.5, 6.0 Hz, 2H), 2.13 (q, J=7.0 Hz, 2H), 1.57–1.39 (m, 4H), 0.19 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.2, 138.1, 135.1, 133.0, 117.0, 82.5, 72.1, 42.1, 36.1, 34.6, 23.9, −1.37, −1.39; MS (EI, 70 eV) 349 (1, $M^+ - 1$), 335 (10), 323 (8), 309 (73), 207 (13), 180 (8), 155 (14), 121 (15), 97 (38), 85 (100). Anal. Calcd for $C_{13}H_{23}IOSi$: C, 44.57; H, 6.62; I, 36.23. Found: C, 44.66; H, 6.56; I, 35.92.

5.2.1.3. Preparation of dimethyl{(2*S,3*S**)-{2-{[(*Z*)-3-iodo-2-propenyl]oxy}-5-hexenyl}-3-oxy}vinylsilane (23a).** Following General procedure I, a solution of **22a** (4.23 g, 15 mmol) in CH_2Cl_2 (15 mL), chlorodimethylvinylslane (2.48 mL, 18.0 mmol, 1.2 equiv.), and Et_3N (3.13 mL, 22.5 mmol, 1.5 equiv.) were combined. After being stirred at room temperature for 30 min, the mixture was poured into ice water (30 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with brine (50 mL), then were dried (Na_2SO_4), and filtered. After removal of solvent, the residue was purified by chromatography (silica gel, hexane/EtOAc, 100/0 to 19/1) followed by Kugelrohr distillation to afford 5.16 g (94%) of **23a** as a colorless liquid. Bp 145–150 °C (0.3 mm Hg, ABT); R_f 0.16 (silica gel, hexane/EtOAc, 49/1, PMA); IR (neat) ν 3075 (m), 2971 (s), 2900 (m), 1691 (m), 1639 (m), 1616 (m), 1407 (m), 1276 (s), 1253 (s), 1093 (s), 1006 (s), 956 (m), 914 (s), 836 (s) cm^{-1}; ^1H NMR: (500 MHz, $CDCl_3$) δ 6.43 (dt, J=7.5, 5.5 Hz, 1H), 6.33 (dt, J=7.5, 1.5 Hz, 1H), 6.15 (dd, J=20.5, 15.0 Hz, 1H), 5.99 (dd, J=15.0, 4.0 Hz, 1H), 5.80 (ddt, J=17.5, 10.5, 7.5 Hz, 1H), 5.76 (dd, J=20.5, 4.0 Hz, 1H), 5.09–5.02 (m, 2H), 4.14 (ddd, J=13.5, 5.0, 1.5 Hz, 1H), 4.05 (ddd, J=13.5, 5.5, 1.5 Hz, 1H), 3.65 (dt, J=8.0, 4.5 Hz, 1H), 3.38 (qd, J=6.5, 4.5 Hz, 1H), 2.32 (dddt, J=14.0, 7.0, 6.0, 1.5 Hz, 1H), 2.15 (dtt, J=14.0, 7.5, 1.5 Hz, 1H), 1.12 (d, J=6.5 Hz, 3H), 0.19 (s, 6H); ^{13}C NMR: (126 MHz, $CDCl_3$) δ 139.0, 138.1, 135.5, 132.9, 116.9, 82.2, 77.5, 74.9, 72.0, 37.1, 15.0, −1.32, −1.33; MS (EI, 70 eV) 366 (0.3, M^+), 351 (0.5), 325 (4), 241 (7), 211 (12), 167 (78), 155 (100), 131 (35), 85 (74); GC: t_R **23a**, 9.57 min (HP-5, 200 °C, 15 psi). Anal. Calcd for $C_{13}H_{23}O_2ISi$: C, 42.63; H, 6.33; I, 34.64. Found: C, 42.79; H, 6.43; I, 34.81.

5.2.2. General procedure II: molybdenum-catalyzed ring-closing metathesis of 4, 14, or 23. In a flame-dried, 25-mL flask was placed freshly distilled benzene which was then moved into a dry box. Schrock's catalyst (0.05–0.1 equiv.) and compound **4**, **14**, or **23** (1.0 equiv.) were added sequentially to the flask. The yellow-brown solution was stirred at room temperature in the dry box and the reaction was monitored by ^1H NMR analysis. When the reaction was complete, the solvent was removed by rotary evaporation to give a brown residue, which was filtered through a short column of silica gel and was further eluted with hexane/EtOAc, 49/1. The filtrate was concentrated in

vacuo followed by Kugelrohr distillation to afford the product **5**, **15**, or **24**.

5.2.2.1. Preparation of 2,2-Dimethyl-6-phenyl-1-oxa-2-silacyclohex-3-ene (5b). Following General procedure II, benzene (10 mL), Schrock's catalyst (38 mg, 0.05 mmol, 0.05 equiv.), and **4b** (232 mg, 1.0 mmol) were combined and the mixture was stirred at room temperature for 1 h in the dry box. After removal of the solvent by rotary evaporation, the residue was filtered through a short column of silica gel which was eluted with 100 mL of hexane/EtOAc, 49/1. The filtrate was concentrated followed by Kugelrohr distillation to afford 193 mg (95%) of **5b** as a colorless liquid. Bp 95–100 °C (0.4 mm Hg ABT); R_f 0.15 (silica gel, hexane/EtOAc, 49/1, PMA); IR (neat) ν 1587 (s), 1521 (s), 1064 (s), 957 (s), 837 (s), 789 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, $J=8.8$, 1.6 Hz, 2H), 7.37 (td, $J=8.8$, 1.6 Hz, 2H), 7.28 (tt, $J=8.8$, 1.6 Hz, 1H), 6.86 (ddd, $J=14.0$, 6.0, 2.4 Hz, 1H), 5.88 (ddd, $J=14.0$, 2.8, 0.8 Hz, 1H), 5.01 (dd, $J=10.0$, 3.6 Hz, 1H), 2.43–2.38 (m, 2H), 0.3 (s, 3H), 0.28 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 147.0, 144.4, 128.3 (2 C), 127.4, 127.2, 125.6 (2 C), 73.3, 39.0, −0.2, −0.6; MS (EI, 70 eV) 204 (37, M^+), 189 (7), 130 (100), 98 (35), 83 (22). Anal. Calcd for $C_{12}H_{16}OSi$: C, 70.53; H, 7.89. Found: C, 70.34; H, 7.96.

5.2.2.2. Preparation of 2,2-dimethyl-6-[(*Z*)-5-iodo-4-pentenyl]-1-oxa-2-silacyclohex-3-ene (15b). Following General procedure II, benzene (10 mL), **14b** (350 mg, 1.0 mmol), and Schrock's catalyst (61.2 mg, 0.08 mmol, 0.08 equiv.) were combined and the mixture was stirred at room temperature for 24 h in the dry box. After removal of solvent by rotary evaporation, the residue was purified by chromatography (silica gel, hexane/CH_2Cl_2, 19/1 to 4/1) followed by Kugelrohr distillation to afford 261 mg (81%) of **15b** as a colorless liquid. Bp 85–90 °C (0.02 mm Hg, ABT); R_f 0.30 (silica gel, hexane/EtOAc, 49/1, PMA); IR (neat) ν 2985 (m), 2926 (s), 1608 (m), 1587 (m), 1352 (m), 1275 (m), 1249 (s), 1163 (m), 1087 (m), 953 (s), 901 (m), 842 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.75 (ddd, $J=$ 14.5, 4.5, 3.5 Hz, 1H), 6.19–6.15 (m, 2H), 5.73 (dt, $J=14.5$, 1.5 Hz, 1H), 3.93–3.88 (m, 1H), 2.20–2.09 (m, 4H), 1.65–1.45 (m, 4H), 0.178 (s, 3H), 0.176 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.1, 141.3, 127.1, 82.4, 71.0, 37.1, 36.4, 34.5, 23.9, −0.4, −0.6; MS (EI, 70 eV) 322 (12, M^+), 307 (5), 195 (60), 180 (18), 153 (35), 127 (93), 98 (100), 75 (90). Anal. Calcd for $C_{11}H_{19}IOSi$: C, 41.00; H, 5.94; I, 39.38. Found: C, 41.03; H, 5.97; I, 38.97.

5.2.2.3. Preparation of ($6S^*$)-2,2-dimethyl-6-{($1S^*$)-1-{[(*Z*)-3-iodo-2-propenyl]oxy}ethyl}-1-oxa-2-silacyclohex-3-ene (24a). Following General procedure II, benzene (10 mL), **23a** (366 mg, 1.0 mmol), and Schrock's catalyst (61.2 mg, 0.08 mmol, 0.08 equiv.) were combined and the mixture was stirred at room temperature for 24 h in the dry box. Additional Schrock's catalyst (15.3 mg, 0.02 mmol, 0.02 equiv.) was added and then was stirred for 12 h. After removal of solvent by rotary evaporation, the residue was purified by chromatography (silica gel, hexane/Et_2O, 49/1 to 97/3) followed by Kugelrohr distillation to afford 273 mg (81%) of **24a** as a colorless liquid. Bp 125–130 °C (0.2 mm Hg, ABT); R_f 0.17 (silica gel, hexane/EtOAc, 97/3, PMA); IR (neat) ν 3070 (m), 2985 (s), 2896 (m), 1608 (m), 1587 (s), 1382 (m), 1276 (s), 1249 (s), 1157 (m), 1101 (s), 1062 (s), 952 (s), 902 (s), 842 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.79 (ddd, $J=14.0$, 6.0, 2.0 Hz, 1H), 6.44 (dt, $J=7.5$, 5.5 Hz, 1H), 6.34 (dt, $J=7.5$, 1.5 Hz, 1H), 5.73 (ddd, $J=14.0$, 3.0, 1.0 Hz, 1H), 4.19 (ddd, $J=13.5$, 5.5, 1.5 Hz, 1H), 4.13 (ddd, $J=13.5$, 6.0, 1.5 Hz, 1H), 3.94 (ddd, $J=11.0$, 4.5, 2.5 Hz, 1H), 3.49 (qd, $J=6.5$, 4.5 Hz, 1H), 2.29 (dddd, $J=17.5$, 11.0, 3.0, 2.5 Hz, 1H), 2.07 (dddd, $J=17.5$, 6.0, 2.5, 1.0 Hz, 1H), 1.17 (d, $J=6.5$ Hz, 3H), 0.19 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.2, 139.0, 127.0, 82.4, 77.9, 73.4, 72.1, 31.0, 15.0, −0.4, −0.6; MS (EI, 70 eV) 338 (0.2, M^+), 323 (1), 211 (2), 167 (22), 155 (14), 138 (9), 127 (100), 111 (13), 75 (15). Anal. Calcd for $C_{11}H_{19}O_2ISi$: C, 39.06; H, 5.66; I, 37.52. Found: C, 39.06; H, 5.66; I, 37.47.

5.2.3. General procedure III: palladium-catalyzed intermolecular cross-coupling of 5 with aryl or alkenyl halides. Substrate **5** (1.1 equiv.) was dissolved in a solution of TBAF (1.0 M in THF, 2.0 equiv.) under an Ar atmosphere at ambient temperature. After 2 min, aryl or alkenyl halide (1.0 equiv.) and the palladium catalyst (0.03–0.1 equiv.) were then added sequentially. The reaction was monitored by TLC analysis. When the halide was consumed, 2 mL of EtOAc/hexane, 7/3 were added. The mixture was filtered through a short column of silica gel, which was then eluted with EtOAc/hexane, 7/3 (150–200 mL). The filtrate was concentrated by rotary evaporation to give a crude product which was purified by silica gel chromatography.

5.2.3.1. Coupling reaction of 5b with ethyl 3-iodobenzoate. Preparation of ethyl 3-[(*Z*)-4-hydroxy-4-phenyl-1-butenyl]benzoate (6d). Following General procedure III, **5b** (225 mg, 1.1 mmol, 1.1 equiv.), a solution of TBAF in THF (1.0 M, 2.0 mL, 2.0 mmol, 2.0 equiv.), ethyl 3-iodobenzoate (276 mg, 1.0 mmol) and $Pd(dba)_2$ (17.2 mg, 0.03 mmol, 0.03 equiv.) were combined. The mixture was stirred at room temperature for 30 min and then 2 mL of EtOAc/hexane, 7/3 were added. The mixture was filtered through a short column of silica gel which was eluted with 150 mL of EtOAc/hexane, 7/3. The filtrate was concentrated to give a crude product which was purified by chromatography (silica gel, hexane/EtOAc, 9/1 to 4/1) to afford 276 mg (93%) of **6d** as a pale yellow (non-distillable) oil. R_f 0.34 (silica gel, hexane/EtOAc, 3/1, PMA); IR (neat) ν 3465 (s), 1718 (s), 1602 (m), 1280 (s), 1188 (s), 1106 (s), 759 (s), 701 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.90 (dd, $J=7.6$, 1.2 Hz, 1H), 7.43 (d, $J=7.6$ Hz, 1H), 7.39–7.26 (m, 6H), 6.58 (d, $J=11.6$ Hz, 1H), 5.80 (dt, $J=$ 11.6, 7.2 Hz, 1H), 4.82 (dd, $J=7.6$, 5.6 Hz, 1H), 4.37 (q, $J=7.2$ Hz, 2H), 2.83 (dtd, $J=15.2$, 7.6, 1.6 Hz, 1H), 2.76–2.69 (m, 1H), 2.26 (br s, 1H, HO), 1.39 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.6, 143.8, 137.3, 132.9, 130.6, 130.3, 129.8, 129.0, 128.4 (2 C), 128.2, 127.8, 127.6, 125.8 (2 C), 74.0, 61.0, 38.0, 14.3; MS (EI, 70 eV) 296 (0.2, M^+), 278 (2), 251 (5), 205 (3), 191 (100), 117 (54), 107 (39). Anal. Calcd for $C_{19}H_{20}O_3$: C: 76.99; H: 6.81. Found: C: 76.85; H: 6.75.

5.2.4. General procedure IV: Pd-catalyzed intramolecular cross-coupling of 15 or 24. Catalyst $[allylPdCl]_2$ (0.075–0.10 equiv.) was dissolved in a solution of TBAF in

THF (1.0 M, 10.0 equiv.) under an N_2 atmosphere at ambient temperature. To the mixture was added slowly a solution of **15** or **24** in THF (0.1 M) by syringe pump. After complete addition of **15** or **24**, the deep brown solution was stirred for additional 2 h. The solvent was removed by rotary evaporation and 5 mL of EtOAc/hexane, 7/3, were then added. The mixture was filtered through a short column of silica gel, which was then eluted with EtOAc/hexane, 7/3 (300–400 mL). The eluate was concentrated by rotary evaporation to give a crude product, which was purified by silica gel chromatography followed by Kugelrohr distillation to afford **16** or **25**.

5.2.4.1. Preparation of (3*Z*,5*Z*)-cyclononadienol (16b). Following General procedure IV, $[allylPdCl]_2$ (27.5 mg, 0.075 mmol, 0.075 equiv.) and a solution of TBAF in THF (1.0 M, 10.0 mL, 10.0 mmol, 10.0 equiv.) were combined. The solution of **15b** in THF (0.1 M, 322 mg, 1.0 mmol) was added slowly by syringe pump for 43 h. The solvent was removed by rotary evaporation and 5 mL of EtOAc/hexane, 7/3, were then added. The mixture was filtered through a short column of silica gel, which was then eluted with EtOAc/hexane, 7/3 (350 mL). The eluate was concentrated by rotary evaporation to give a crude product, which was purified by chromatography (silica gel, hexane/EtOAc, 9/1 to 4/1) followed by Kugelrohr distillation to afford 97 mg (70%) of **16b** as a colorless oil. Bp 75–80 °C (0.2 mm Hg, ABT); R_f 0.17 (silica gel, hexane/EtOAc, 4/1, PMA); IR (neat) ν 3350 (s), 3002 (s), 2929 (s), 2858 (s), 1637 (m), 1454 (s), 1356 (m), 1258 (m), 1064 (s), 996 (s), 903 (m), 803 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.96 (ddd, J= 11.0, 2.0, 1.0 Hz, 1H), 5.81 (d, J=11.0 Hz, 1H), 5.76–5.66 (m), 3.90 (quint, J=5.5 Hz, 1H), 2.39 (t, J=7.3 Hz, 2H), 2.15–2.00 (m, 2H), 1.84–1.78 (m, 2H), 1.60–1.52 (m, 2H), 1.40–1.33 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.1, 129.9, 128.5, 127.3, 71.2, 38.3, 36.2, 30.9, 19.7; MS (EI, 70 eV) 138 (12, M^+), 120 (5), 109 (27), 94 (47), 79(100), 67 (42). Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.16; H, 10.29.

5.2.4.2. Preparation of (8*S,9*S**)-8-hydroxy-9-methyl-1-oxa-3*Z*,5*Z*-cyclononadiene (25a).** Following General procedure IV, $[allylPdCl]_2$ (27.5 mg, 0.075 mmol, 0.075 equiv.) and a solution of TBAF in THF (1.0 M, 10.0 mL, 10.0 mmol, 10.0 equiv.) were combined. The solution of **24a** in THF (0.1 M, 338 mg, 1.0 mmol) was added slowly by syringe pump for 43 h. The solvent was removed by rotary evaporation and 5 mL of EtOAc/hexane, 7/3, were then added. The mixture was filtered through a short column of silica gel, which was then eluted with EtOAc/hexane, 7/3 (300 mL). The eluate was concentrated by rotary evaporation to give a crude product, which was purified by chromatography (silica gel, hexane/EtOAc, 19/1 to 17/3) followed by Kugelrohr distillation to afford 111 mg (72%) of **25a** as a colorless oil. Bp 80–85 °C (0.3 mm Hg, ABT); R_f 0.08 (silica gel, hexane/EtOAc, 4/1, PMA); IR (neat) ν 3407 (s), 3002 (s), 2969 (s), 2919 (s), 1625 (m), 1448 (m), 1415 (m), 1274 (m), 1245 (m), 1143 (s), 1124 (s), 1081 (s), 1052 (s), 1016 (s), 989 (s), 863 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.07 (ddq, J=11.5, 3.0, 1.5 Hz, 1H), 6.00 (dd, J=11.0, 1.0 Hz, 1H), 5.84 (dddd, J=11.5, 7.5, 6.5, 1,0 Hz, 1H), 5.68 (tdd, J=11.0, 5.5, 1.0 Hz, 1H), 4.35 (dd, J=12.5, 6.5 Hz, 1H), 3.74 (qd, J=6.5, 1.5 Hz, 1H), 3.65 (dd, J=12.5, 7.5 Hz, 1H), 3.55 (td, J=9.5, 4.5 Hz, 1H), 2.63 (dt, J=12.5, 11.0 Hz, 1H), 2.28 (dddt, J= 12.5, 5.5, 4.5, 1.5 Hz, 1H), 1.79 (br s, 1H, HO), 1.22 (d, J= 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 132.5, 129.61, 129.55, 129.45, 81.6, 73.5, 70.3, 35.7, 17.9; MS (EI, 70 eV) 154 (3, M^+), 139 (34), 128 (32), 115 (53), 92 (17), 77 (100), 64 (28). Anal. Calcd for $C_9H_{14}O_2$: C, 70.08; H, 9.16. Found: C, 69.98; H, 9.31.

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Supplementary data

Complete experimental details for all preparative procedures along with full characterization of all starting materials and products (94 pages) are provided.

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.06.149

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