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TRISUBSTITUTED DOUBLE BOND IN THE CYCLOOCTENE RING. PREPARATION USING THE RCM REACTION

Reiko Mizutani, Takuo Miki, Katsuyuki Nakashima, Masakazu Sono, and Motoo Tori*

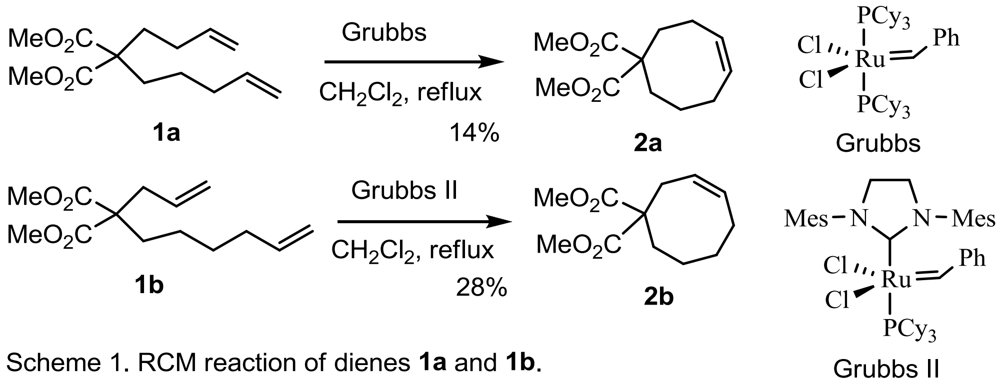
Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima, 770-8514, Japan (tori@ph.bunri-u.ac.jp)

Abstract – Cyclization to eight-membered rings with a trisubstituted double bond was attempted using ring closing metathesis (RCM) reactions. Although simple substrates were not good candidates, the triene with a proper configuration cyclized to the cyclooctene with a tri-cycle (5-8-6 membered) in moderate yield. The formation of one-carbon smaller rings was also observed.

INTRODUCTION

We have prepared the seven-membered carbocycles present in terpenoids using the ring closing metathesis (RCM) reaction.[1,2] This method was applied to the synthesis of tormesol and other liverwort terpenoids with a sphenolobane-type skeleton.[1] At the same time we were also interested in the synthesis of eight-membered carbocycles by applying the RCM reaction. Eight-membered carbocycles are frequently found in terpenoids, especially those with trisubstituted double bonds, for example ophiobolin,[3] fusicoccin,[4] ceroplastrol,[5] serpendione,[6] dactylol,[7] and YW3699.[8,9] It is well known that it can be difficult to cyclize to eight-membered carbocycles.[10] Recently, papers on the synthesis of these molecules have accumulated in the series of carbocycles and heterocycles.[11-25] However, there is no report of systematic work in this area.

We tested simple examples (Scheme 1) to compare the reactivity of the substrates **1a** and **1b** with those for seven-membered carbocycles as a continuation of the systematic studies. Diene **1a** afforded compound **2a** using Grubbs catalyst[26] in CH_2Cl_2 (14% yield), while diene **1b** produced compound **2b**[27] using Grubs II catalyst (28% yield). These simple examples show that the RCM reaction is capable of constructing eight-membered carbocycles, although the double bonds are di-substituted. Therefore, we prepared several substrates and attempted the RCM reaction. The result confirmed the importance of the conformation of the diene substrate. We now describe the details of our results.



Scheme 1. RCM reaction of dienes **1a** and **1b**.

RESULTS AND DISCUSSION

*Cyclization of dienes **4** and **7***

Our work started with simple diene substrates, which cyclize to bicyclic compounds bearing eight- and six-membered carbocycles. The C-6 alkyl chain unit was introduced to enone **3**[28,29] in the presence of a cuprous bromide-dimethyl sulfide complex to afford diene **4** in 93% yield. The RCM cyclization was carried out using the Grubbs second generation catalyst[30] in CH_2Cl_2 under reflux (Table 1). However, the desired product **5** was produced only in a minute quantity, and dimer **6** was formed instead in 68% yield (entry 2).

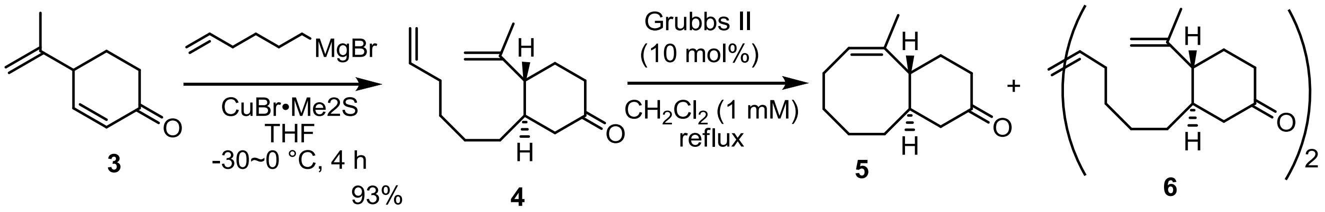


Table 1. RCM reaction of diene **4**.

entry	reaction time (h)	yield (%) **6**
1[a]	1	33
2[b]	2	68

[a] Compound **5** was detected in less than 5% (GC-MS).
[b] Compound **5** was detected in less than 1% (GC-MS).

When the carbonyl group was protected as a ketal, compound **7** did not give an eight-membered carbocycle **9** in CH_2Cl_2, benzene, or toluene. Surprisingly, the seven-membered compound **8** was formed in benzene or toluene as a solvent (Table 2). In entries 2 and 3, microwave was used to get a high temperature. It is known that at higher temperatures the terminal vinyl group is susceptible to rearrangement into di-substituted olefin.[2] It is then cyclized to the one-carbon smaller product **8**.[31] This type of rearrangement has been reported in the literature.[32-38] Simple dienes are not good candidates for construction of trisubstituted cyclooctenes. This is presumably due to the conformational freedom of the vinyl alkyl side chain by free rotation.

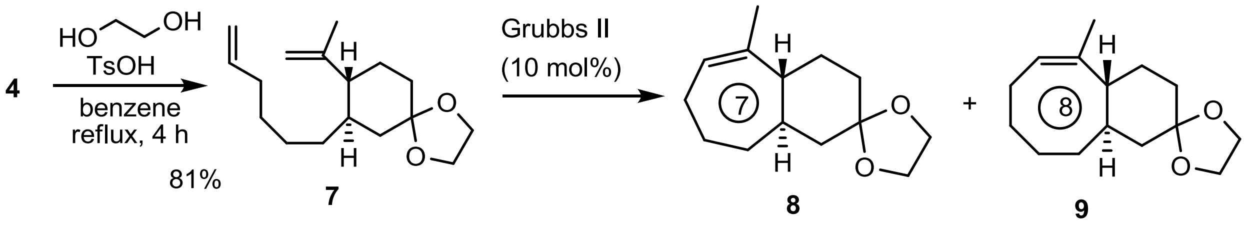


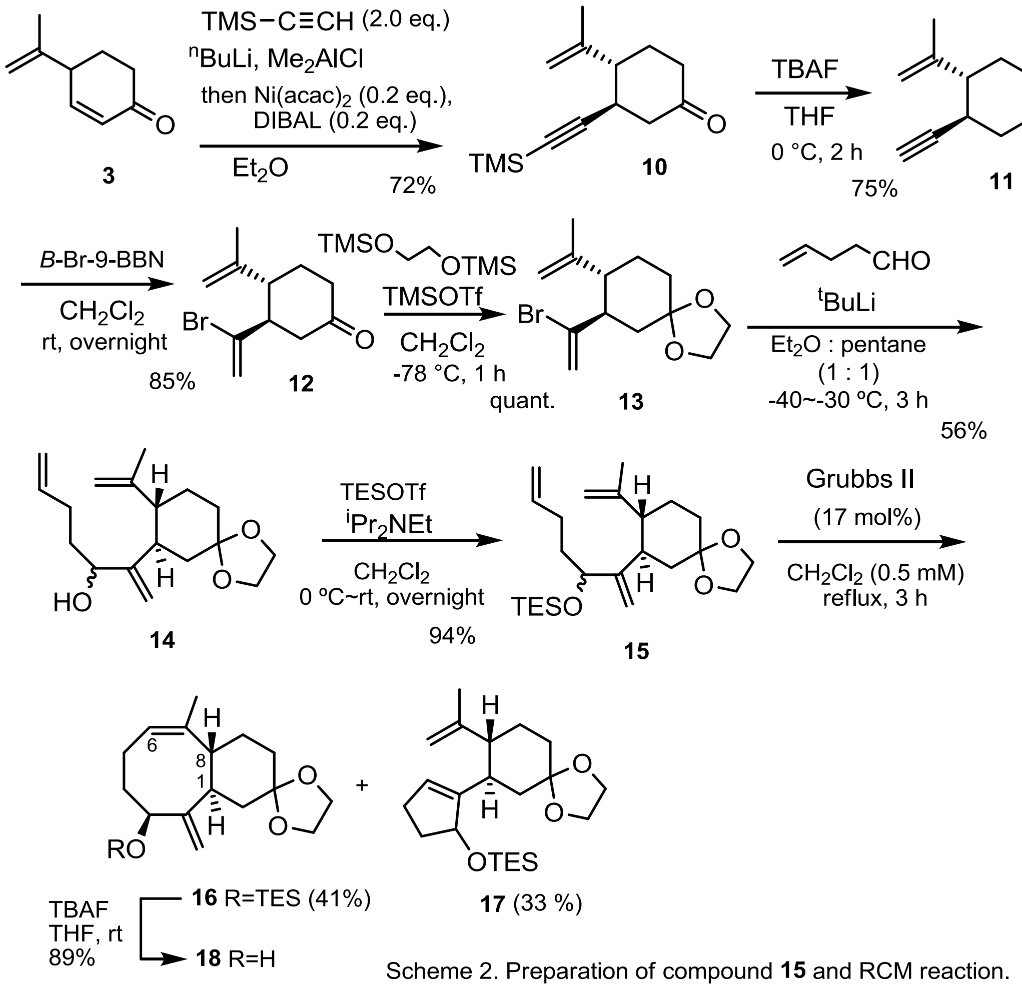
Table 2. RCM reaction of diene **7**.

entry	solvent	conc. (mM)	temp. (°C)	time	yield (%) **8**	ratio (GC-MS) **7 : 8 : 9**
1	benzene	10	60	overnight	15	37 : 52 : 0
2[a,b]	toluene	10	150	5 min	-	40 : 27 : 0
3[a,b]	toluene	10	150	15 min	-	33 : 31 : 0
4[b]	benzene	1	reflux	3 h	-	26 : 64 : 1>

[a] under microwave (150 W) irradiation
[b] products were not separated

*Cyclization of triene **15***

We next introduced an sp^2 carbon adjacent to the cyclohexane ring, which might assist the conformation close to the isopropenyl group by keeping the plane around the sp^2 carbon. The 1,4-addition of a vinyl group was accomplished in the presence of a cuprous reagent. However, the stereoselectivity was not as high as expected.[39] Therefore, an ethynyl group was introduced to enone **3** (Scheme 2). The TMS protected acetylene was converted to the ate complex using Me$_2$AlCl, Ni(acac)$_2$, and DIBAL and was reacted with enone **3**.[40,41] The TMS group was removed by TBAF. The bromide was prepared by reductive bromination using *B*-Br-9-BBN in 85% yield.[42] After protection of the carbonyl group as a ketal,[43] the metal exchange of bromine with the lithium atom and addition of 4-pentenal afforded enol **14** as a mixture of the diastereoisomers (the ratio was 5:4 from ^{13}C NMR) in 56% yield.[44] The hydroxy group was protected as a TES ether **15**, which was treated with the Grubbs II catalyst in CH$_2$Cl$_2$ under reflux to give compounds **16** and **17** in 41% and 33% yield, respectively (Scheme 2). Compound **16** was converted to alcohol **18** and its structure was analyzed, because it gave better resolution in its NMR spectra. The eight-membered carbocycle was shown by the HMBC correlations, from the methyl group at the C-7 position to the carbon atoms at the C-6 and 7 positions. The configuration of the hydroxy group was established as β-orientation by the NOESY correlation between H-1 and H-3. Unfortunately, compound **17** proved to be a five-membered carbocycle[45] formed as a result of competitive reaction with the isopropenyl group.

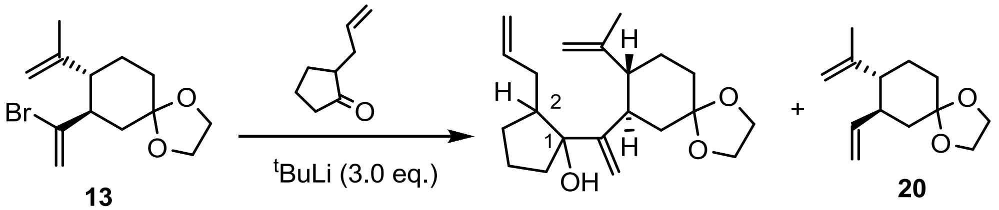


Scheme 2. Preparation of compound **15** and RCM reaction.

These results indicate that the introduction of the sp^2 carbon predominated in the formation of the eight-membered carbocycle as expected. It is very interesting to note that both products **16** and **17** were isolated in a pure form (from ^{13}C NMR). That is to say, a β-OH isomer cyclized to an eight-membered carbocycle, while an α-OH isomer cyclized to a five-membered compound. Unfortunately, we could not verify the configuration of the hydroxy group in compound **17**. Although this is speculation, it is very likely that this is the case, and is presumably attributed to the difference in the conformation of both isomers of substrate **15**.

*Cyclization of trienes **19a** and **19b***

We next planned to construct the tri-cyclic substance which appeared in YW3699.[8,9] The lithio-derivative of bromide **13** was reacted with 2-allylcyclopentanone to afford separable alcohols **19a** and **19b** (Table 3). A better yield was obtained in Et$_2$O at -50˚C for 8 h (entry 2). A low yield was attributed to the rapid formation of debrominated compound **20**. The stereochemistry was later established based on the 2D NMR of the cyclized products.



19a : 1α-OH, 2β-H
19b : 1β-OH, 2α-H

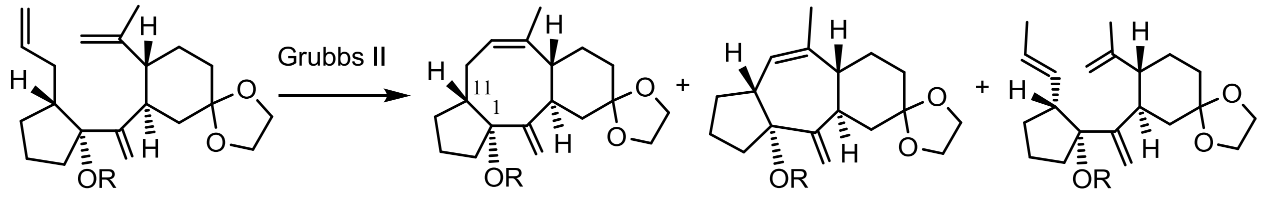
Table 3. Conditions for the coupling reaction of bromide **13** and 2-allylcyclopentanone.

entry	solvent	additive	temp. (°C)	time	yield(%)		
					19a	**19b**	**20**
1	Et_2O	none	-110	3 h	-	-	29
2	Et_2O	none	-50	8 h	25	12	50
3	Et_2O	none	-78 ~ rt	overnight	14	10	55
4	Et_2O	none	-78	3 days	9	5	60
5	Et_2O	$CeCl_3$	-50 ~ rt	overnight	-	-	100
6	THF	$CeCl_3$	-78 ~ rt	overnight	-	-	100

TES-ether **21a**, derived from alcohol **19a** by protection (TESOTf, ^{i}Pr$_2$NEt), was treated with the Grubbs II catalyst under the conditions listed in Table 4. The use of CH_2Cl_2 at rt gave almost full recovery (entry 1), however at higher temperatures the reaction proceeded to afford cyclized compounds. Compounds **22a** and **24** were isolated by chromatographic separation. However, compound **23** was not easy to purify, therefore, was converted to alcohol **26**. Compound **22a** was the desired eight-membered product, while compound **26** was a seven-membered substance, which was presumably produced through a rearranged olefin **24**. As previously discussed, the use of benzene as a solvent resulted in the formation of a large amount of rearranged olefin **24** (entry 4). When 30 mol% of the catalyst was used (entry 5), the yield of compound **22a** was 28%. Therefore, this condition may be used in the cyclization reaction for eight-membered carbocycles.

The structures of these products are shown in Figure 1. The ^{1}H NMR spectrum of compound **22a** showed a broad triplet signal at δ 5.37 as well as a singlet methyl group at δ 1.56, being comparable to those of compound **18**. Since the NMR spectrum of compound **22a** did not give good resolution, it was not easy to see the stereochemistry in detail. This phenomenon was also observed at the stage of alcohol **25a**. Compound **26** gave good resolution in its NMR spectra. Therefore, compound **26** was thoroughly analyzed, because the configurations at C-1 and 11 should be the same in the products. The HMBC correlations between the methyl group at C-9 and the carbons at the C-9 and 10 positions indicated the presence of the cyclized ring. The proton of H-10 appeared at δ 5.40 as a broad doublet with *J*=2.4 Hz. These observations as well as the MS spectrum clearly indicated that compound **26** had a seven-membered carbocycle. The NOE between H-8 and H-11 showed the β-orientation of both protons.

Because the anion attacked the carbonyl group of 2-allylcyclopentanone from the back side of the allyl group, the hydroxy and the allyl groups were always on the same side. Therefore, the structure of compound **26** was established as depicted in the formula. The structure of compound **22a** was thus suggested as 1α-OTES,11β-H following the discussion above. Compound **24** showed the quasi-molecular ion peak at *m/z* 447 $[M+H]^+$ and the formula $C_{27}H_{46}O_3Si$ by HRCIMS, being the isomer of the starting material **21a**. The olefinic proton of H-10[46] was detected at δ 5.43 (dd, *J*=15.6 and 8.6 Hz) showing that the double bond rearranged into the 10,10´-position with the trans stereochemistry ($J_{\mathrm{H10,10'}}$ = 15.6 Hz). This was further confirmed by the NOE between H-10 and H-10´´.



19a R=H
21a R=TES

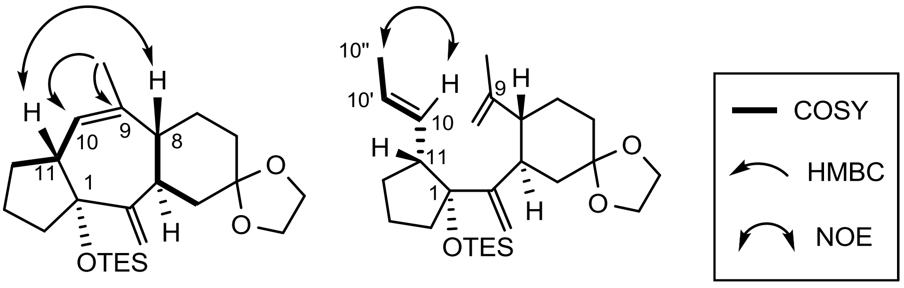
22a R=TES
25a R=H

23 R=TES
26 R=H

24 R=TES
27 R=H

Table 4. Conditions for the RCM reaction of **21a**.

entry	Grubbs II (mol%)	solvent	conc. (mM)	temp.	time (h)	yield (%)	ratio (GC-MS)			
							21a	**22a**	**23**	**24**
1	15	CH_2Cl_2	1	rt	5	88	86	0	2	12
2	15+15	CH_2Cl_2	1	rt~reflux	12	21	0	22	23	55
3	20	CH_2Cl_2	1	reflux	17	53	17	29	3	51
4	20	benzene	1	reflux	10	49	0	19	6	75
5	30	CH_2Cl_2	1	reflux	25	55	0	51	24	25
6	15+15	CH_2Cl_2	0.5	reflux	12	49	0	38	-	62

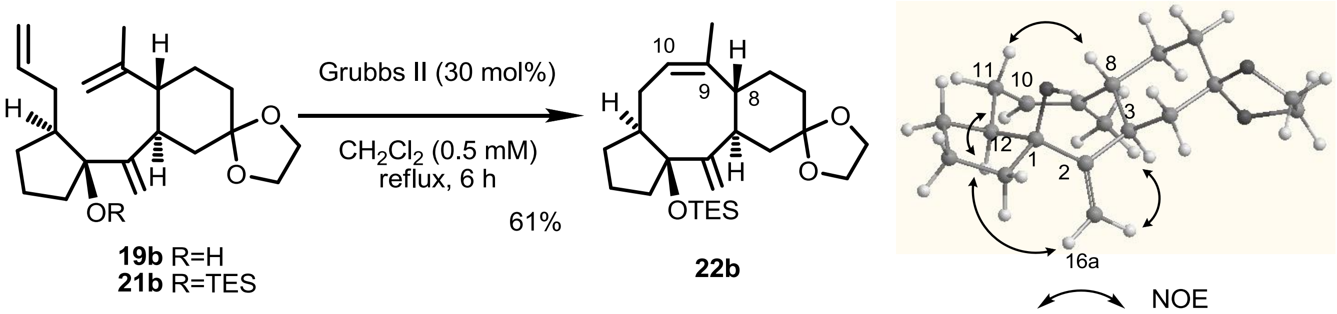


26

24

Figure 1. 2D NMR correlations detected for compounds **24** and **26**.

TES-ether **21b**, prepared by protection of alcohol **19b**, was subjected to the reaction with Grubbs II catalyst (30 mol%) in CH_2Cl_2 (0.5 mM), and the desired eight-membered compound **22b** was isolated in 61% yield (Scheme 3). Compound **22b** exhibited a molecular ion peak at *m/z* 418 and the molecular formula was determined to be $C_{25}H_{42}O_3Si$ by HRMS. It was obvious that this compound had the eight-membered ring, because the HMBC spectrum indicated the correlations between the methyl group at C-9 and C-9 and 10, and the proton at C-10 appeared at δ 5.39 as a triplet (J = 8.4 Hz). The stereochemistry was deduced by the NOESY correlations between H-8 and H-11β, H-10 and H-12, and H-12 and H-16a. Therefore, the structure of **22b** was established as depicted in the formula (Scheme 3).



Scheme 3. RCM reaction of **21b** and NOE correlations for **22b** (TES group was substituted with H for clarity).

CONCLUSION

In summary, we have demonstrated some examples of synthesizing eight-membered carbocycles with a trisubstituted double bond present in the terpenoids. Although simple examples such as compounds **4**, **7** and **15** did not necessarily give satisfactory results, more complex examples such as compounds **21a** and **21b** afforded the cyclized products in low or moderate yield under the correct conditions. Compound **21b** gave a higher yield of the eight-membered carbocycle than compound **21a**. This result confirmed the importance of the conformation of the diene substrate, although the relative stability of the transition states is not clear at this stage.

EXPERIMENTAL

General. All reactions were carried out under an argon (Ar) atmosphere. Anhydrous solvents were purchased from Kanto Chemical Co., Inc. Reagents were purchased at the highest commercial quality and were used without further purification. The IR spectra were measured on a JASCO FT/IR 500 spectrophotometer. Mass spectra, including high-resolution spectra, were recorded on a JEOL JMS-700 MStation. ^{1}H and ^{13}C NMR spectra were measured on a Varian Unity 600 (600 MHz and 150 MHz, respectively) and a Varian Unity 200 (200 MHz and 50 MHz, respectively) spectrometer. Silica gel 60 (70-230 mesh, Fuji Silysia) was used for column chromatography. Silica gel BW-300 (200-400 mesh, Fuji Silysia) was used for column chromatography and a silica-gel 60F_{254} plate (0.25mm, Merck) was used for TLC.

*Preparation of dimethyl 2-allyl-2-(hex-5-enyl)malonate (**1a**)*

Dimethyl allylmalonate (263 mg, 1.23 mmol) in DMF (5 mL) was treated with NaH (26.0 mg, 0.65 mmol) for 30 min at rt. 6-Bromohexene (0.14 mL 1.35 mmol) was added and the mixture was stirred overnight at rt. 1M HCl (5 mL) was added and the mixture was extracted with Et_2O. The organic layer was washed with brine, dried ($MgSO_4$) and then evaporated to give a residue. The residue was purified by silica-gel column chromatography (hexane-EtOAc, 0-100%) to afford **1a** (285 mg, 73%). FTIR 1740 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.5-5.9 (2H, m), 4.8-5.2 (4H, m), 3.71 (6H, s), 2.64 (2H, d, *J*=7.6 Hz), 2.05 (2H, m), 1.8-1.9 (2H, m), 1.39 (2H, m), 1.1-1.3 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.8 (C × 2), 138.6 (CH), 132.5 (CH), 118.9 (CH_2), 114.6 (C), 57.6 (C), 52.3 (CH_3 × 2), 37.0 (CH_2), 33.4 (CH_2), 32.1 (CH_2), 28.9 (CH_2), 23.3 (CH_2); MS (CI) *m/z* 255 $[M+H]^+$, 229, 191, 165, 123, 111, 87 (base); HRCIMS Found *m/z* 255.1596 $[M+H]^+$ $C_{14}H_{23}O_4$ requires 255.1596.

*Preparation of dimethyl 2-(but-3-enyl)-2-(pent-4-enyl)malonate (**1b**)*

A mixture of dimethyl 3-butenylmalonate (1 g, 5.37 mmol), NaH (240 mg, 5.9 mmol), and 5-bromopentene (0.73 mL 5.9 mmol) in DMF (20 mL) was stirred at rt overnight. 6M HCl was added and the mixture was extracted with Et_2O. The organic layer was washed with brine, dried ($MgSO_4$) and then evaporated to give a residue. The residue was purified by silica-gel column chromatography (hexane-EtOAc, 0-2%) to afford **1b** (653.7 mg, 48%). FTIR 1740, 1640 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.77 (2H, ddt, *J* = 15, 11, 6.8 Hz), 5.03 (2H, br d, *J* = 15 Hz), 4.96 (2H, br d, *J* = 11 Hz), 3.71 (5H, s), 2.15-1.85 (5H, m), 1.33-1.18 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.0 (C × 2), 137.9 (CH), 137.4 (CH), 114.9 (CH_2 × 2), 57.1 (C), 52.2 (CH_3 × 2), 33.6 (CH_2), 31.9 (CH_2), 31.6 (CH_2), 28.3 (CH_2), 23.2 (CH_2); MS (CI) *m/z* 255 $[M+H]^+$, 223, 213, 191, 163, 145 (base), 132, 113, 93, 81; HRMS (CI) Found *m/z* 255.1577 $[M+H]^+$, $C_{14}H_{23}O_4$ requires 255.1596.

*Preparation of dimethyl cyclooct-3-ene-1,1-dicarboxylate (**2a**)*

To a stirred solution of ester **1a** (45.5 mg, 0.18 mmol) in CH_2Cl_2 (12 mL) Grubbs II was added (7.6 mg, 5 mol%) in CH_2Cl_2 (5 mL) and the solution was refluxed for 15 h under Ar atmosphere. The reaction was quenched by bubbling air and the solvent was evaporated. The residue was purified by silica-gel column chromatography (hexane-EtOAc, 0-25%) to afford **2a** (11.4 mg, 28%). FTIR 1730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.8-5.9 (1H, m), 5.4-5.5 (1H, m), 3.72 (6H, s), 2.73 (2H, d, *J* = 8 Hz), 2.0-2.2 (4H, m), 1.5-1.6 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.3 (C × 2), 134.0 (CH), 125.7 (CH), 52.5 (CH_3 × 2), 59.0 (C), 30.9 (CH_2), 29.8 (CH_2), 29.4 (CH_2), 26.7 (CH_2), 23.5 (CH_2); MS (CI) *m/z* 227 $[M+H]^+$, 195, 166, 127, 89 (base), 61; HRCIMS Found *m/z* 227.1267 $[M+H]^+$ $C_{12}H_{19}O_4$ requires 227.1283.

*Preparation of dimethyl cyclooct-4-ene-1,1-dicarboxylate (**2b**)*[27]

To a stirred solution of ester **1b** (127.0 mg, 0.5 mmol) in CH_2Cl_2 (40 mL) Grubbs catalyst was added (12 mg, 3 mol%) in CH_2Cl_2 (10 mL) and the solution was refluxed overnight under Ar atmosphere. The reaction was quenched by bubbling air and the solvent was evaporated. The residue was purified by silica-gel column chromatography (hexane-EtOAc, 0-5%) to afford **2b** (16.0 mg, 14%). FTIR 1730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.73-5.20 (2H, m), 3.72 (6H, s), 2.39-2.11 (6H, m), 1.63-1.51 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.0 (C × 2), 131.5 (CH), 126.3 (CH), 58.3 (C), 52.4 (CH_3 × 2), 31.2 (CH_2), 28.0 (CH_2), 25.7 (CH2), 24.3 (CH_2), 24.2 (CH_2); MS (CI) *m/z* 227 $[M+H]^+$, 195, 163 (base), 139, 119, 107, 99, 79; HRMS (CI) Found *m/z* 227.1282 $[M+H]^+$, $C_{12}H_{19}O_4$ requires 227.1283.

Preparation of (3R,4R*)-3-(hex-5-enyl)-4-(prop-1-en-2-yl)cyclohexanone (**4**)*

To a Grignard reagent prepared from 6-bromo-1-hexene (1.84 g, 11.3 mmol) and Mg (271.2 mg, 11.3 mmol) in THF (2 mL) a suspension of $CuBr{\bullet}Me_2S$ was added (348 mg, 1.70 mmol) in THF (15 mL). Compound **3** (768.7 mg, 5.65 mmol) in THF (5.0 mL) was slowly added to this solution at -30 °C. The mixture was kept at -30~0 °C for 1 h. Sat. NH_4Cl soln. and aq. ammonia were added and the mixture was stirred for 30 min. The solvent was evaporated and the mixture was extracted with Et_2O. The organic layer was washed with water and brine, dried ($MgSO_4$), and was then evaporated to afford a residue. The residue was purified by silica-gel column chromatography (hexane-EtOAc, 0-30%) to afford **4** (1.21 g, 93%). FTIR 1720, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.79 (1H, ddt, *J* = 17.1, 10.3, 6.3 Hz), 4.99 (1H, br d, *J* = 17.1 Hz), 4.93 (1H, br d, *J* = 10.3 Hz), 4.82 (2H, m), 2.52 (1H, dd, *J* = 13.8, 4.2 Hz), 2.39 (2H, m), 2.18 (1H, ddd, *J* = 11.7, 10.3, 3.3 Hz), 2.02-1.90 (4H, m), 1.81-1.68 (2H, m), 1.62 (3H, s), 1.54-1.28 (4H, m), 1.32-1.04 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.1 (C), 146.7 (C), 138.8 (CH), 114.4 (CH_2), 112.4 (CH_2), 50.4 (CH), 46.2 (CH_2), 41.2 (CH_2), 40.2 (CH), 33.9 (CH_2), 33.6 (CH_2), 31.6 (CH_2), 29.0 (CH_2), 25.3 (CH_2), 18.8 (CH_3); MS (Cl) *m/z* 221 $[M+H]^+$ (base), 203, 165, 137, 111, 97, 68; HRMS (CI) Found *m/z* 221.1889 $[M+H]^+$, $C_{15}H_{25}O$ requires 221.1906.

Attempted RCM reaction of (3R,4R*)-3-(hex-5-enyl)-4-(prop-1-en-2-yl)cyclohexanone (**4**)*

To a stirred solution of **4** (61.4 mg, 0.28 mmol) in CH_2Cl_2 (270 mL) Grubbs II was added (25.0 mg, 0.028 mmol) in CH_2Cl_2 (10 mL). The mixture was heated under reflux for 1 h. The reaction mixture was quenched by bubbling air and was then evaporated. The residue was purified by silica-gel column chromatography (hexane-AcOEt 0-50%) to give dimer **6** (19.2 mg, 33%). FTIR 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.34 (2H, dd, *J* = 3.9, 1.8 Hz), 4.81 (2H, d, *J* = 1.5 Hz), 4.80 (2H, s), 2.51 (2H, dd, *J* = 13.8, 3.6 Hz), 2.41-2.36 (4H, m), 2.17 (2H, dt, *J* = 10.8, 3.0 Hz), 2.06-1.89 (8H, m), 1.81-1.70 (4H, m), 1.55 (6H, s), 1.45-1.06 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.6 (C), 146.8 (C), 130.3 (CH), 112.4 (CH_2), 50.5 (CH), 46.2 (CH_2), 41.2 (CH_2), 40.2 (CH), 34.0 (CH_2), 32.5 (CH_2), 31.6 (CH_2), 29.7 (CH_2), 25.3 (CH_2), 18.8 (CH_3); MS (Cl) *m/z* 413 $[M+H]^+$ (base), 395, 137, 58; HRMS (CI) Found *m/z* 413.3392 $[M+H]^+$, $C_{28}H_{45}O_2$ requires 413.3420.

Preparation of (7R,8R*)-7-(hex-5-enyl)-8-(prop-1-en-2-yl)-1,4-dioxaspiro[4.5]decane (**7**)*

Ketone **4** (263 mg, 1.19 mmol) was treated with ethylene glycol (0.1 mL, 1.79 mmol) and TsOH (26 mg) in PhH (40 mL) under reflux with the aid of the Dean-Stark water separator for 12 h. The mixture was washed with sat. aq. $NaHCO_3$ soln. and brine and then evaporated. The residue was purified by silica-gel column chromatography (hexane-EtOAc, 0-20%) to afford **7** (193.7 mg, 73%). FTIR 1640 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (1H, m), 4.99 (1H, d, *J* = 16.7 Hz), 4.95 (1H, d, *J* = 10.0 Hz), 4.75 (2H, m), 3.96 (4H, m), 2.10-1.80 (4H, m), 1.80-1.50 (8H, m), 1.61 (3H, s), 1.40-1.10 (4H, m); MS (CI) *m/z* 265 $[M+H]^+$, 181 (base), 99; HRMS (CI) Found *m/z* 265.2157 $[M+H]^+$, $C_{17}H_{29}O_2$ requires 265.2168.

Attempted RCM reaction of (7R,8R*)-7-(hex-5-enyl)-8-(prop-1-en-2-yl)-1,4-dioxaspiro[4.5]decane (**7**)*

To a stirred solution of ketal **7** (32.7 mg, 0.12 mmol) in PhH (10 mL) Grubbs II was added (11.8 mg, 0.012 mmol) in PhH (2 mL). The mixture was heated at 60 overnight. The mixture was quenched by bubbling air and was then evaporated. The residue was purified by silica-gel column chromatography (hexane-AcOEt 0-50%) to give **7** (9.5 mg) and **8** (4.2 mg, 15%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.46 (1H, t, *J* = 9.9 Hz), 3.96 (4H, s), 1.85-1.62 (5H, m), 1.67 (3H, s), 1.64-1.36 (9H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5 (C), 124.0 (CH), 109.3 (C), 64.3 (CH_2), 64.2 (CH_2), 48.7 (CH), 43.5 (CH_2), 35.3 (CH), 35.0 (CH_2), 33.4 (CH_2), 27.8 (CH_2), 24.5 (CH_2), 24.2 (CH_2), 23.1 (CH_3); MS (Cl) *m/z* 223 $[M+H]^+$ (base), 222, 203, 160, 121, 89, 44; HRMS (CI) Found *m/z* 223.1690 $[M+H]^+$, $C_{14}H_{23}O_2$ requires 223.1698.

Preparation of (3R,4R*)-4-(prop-1-en-2-yl)-3-((trimethylsilyl)ethynyl)cyclohexanone (**10**)*

A solution of trimethylsilylacetylene (136.5 mg, 1.39 mmol) in Et_2O (2 mL) was treated with ^{n}BuLi (in hexane, 1.59 M, 0.87 mL, 1.39 mmol) at 0 °C for 1.5 h. Me_2AlCl (in hexane, 1 M, 1.33 mL, 1.33 mmol) was added to this solution at -40 °C and the mixture (A) was stirred for 4 h. In another flask (B), a solution of $Ni(acac)_2$ (35.5mg, 0.14 mmol) in Et_2O (1.5 mL) was treated with DIBAL (in toluene, 1 M 0.14 mL, 0.14 mmol) at 0 °C for 10 min. The mixture (A) was added to the flask (B) at -25 °C followed by the addition of a solution of **3** (94.2 mg, 0.67 mmol) in Et_2O (4 mL) over 1 h at -30 °C and then the mixture was stirred for 3 h. Saturated aq. KH_2PO_4 soln. was added at rt and the mixture was stirred for 15 min. Sulfuric acid (10%) was added and the mixture was extracted with Et_2O. The organic layer was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and was then evaporated to afford a residue.

The residue was purified by silica-gel chromatography (hexane-EtOAc, 0-5%) to give (**10**) (112.9 mg, 72%). FTIR 2160, 1720, 1640 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.89 (1H, s), 4.86 (1H, s), 2.70 (1H, m), 2.50-2.36 (4H, m), 2.01 (1H, m), 1.75 (3H, s), 1.72 (2H, m), 0.12 (9H, s); MS (Cl) *m/z* 235 [M+H]$^+$, 211 (base), 89, 73; HRMS (CI) Found *m/z* 235.1523 [M+H]$^+$, $C_{14}H_{23}OSi$ requires 235.1518.

Preparation of (3R,4R*)-3-ethynyl-4-(prop-1-en-2-yl)cyclohexanone (**11**)*

To a stirred solution of **10** (145.0 mg, 0.62 mmol) in THF (2 mL) TBAF was added (in THF, 1 M, 1.24 mL, 1.24 mmol) at 0 °C and the mixture was stirred for 3 h. Water was added and the mixture was extracted with Et_2O. The organic layer was washed with brine, dried ($MgSO_4$), and was then evaporated to afford a residue. The residue was purified by silica-gel column chromatography (hexane-EtOAc, 0-10%) to give **11** (75.3 mg, 75%). FTIR 3300, 2120, 1720, 1640 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.95 (1H, s), 4.93 (1H, s), 2.72 (2H, m), 2.55-2.39 (4H, m), 2.17 (1H, d, *J* = 2.1 Hz), 2.03 (1H, m), 1.77 (3H, s), 1.72 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.3 (C), 145.5 (C), 112.6 (CH_2), 84.6 (C), 70.7 (CH), 49.6 (CH), 46.3 (CH_2), 40.6 (CH_2), 33.6 (CH), 30.4 (CH_2), 19.7 (CH_3); MS (Cl) *m/z* 163 [M+H]$^+$ (base), 145, 121, 89; HRMS (CI) Found *m/z* 163.1078 [M+H]$^+$, $C_{11}H_{15}O$ requires 163.1081.

Preparation of (3R,4R*)-3-(1-bromovinyl)-4-(prop-1-en-2-yl)cyclohexanone (**12**)*

To a stirred solution of **11** (147.0 mg, 0.91 mmol) in CH_2Cl_2 (2.7 mL) and hexane (2.7 mL), *B*-Br-9-BBN was added (in hexane, 1 M, 1.82 mL, 1.82 mmol) at -25 °C over 1 h and the mixture was stirred at 0 °C for 6 h. AcOH was added and the mixture was stirred for 1 h at 0 °C. H_2O_2 (30%) was added and the mixture was then extracted with Et_2O. The organic layer was washed with saturated aq. Na_2SO_3 soln. and brine, dried ($MgSO_4$), and was then evaporated to afford a residue. The residue was purified by silica-gel column chromatography (hexane-EtOAc, 0-5%) to give **12** (187.2 mg, 85%). FTIR 1720, 1640 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.61 (1H, d, *J* = 1.5 Hz), 5.42 (1H, d, *J* = 1.5 Hz), 4.88 (1H, s), 4.86 (1H, s), 2.73-2.60 (2H, m), 2.47-2.38 (2H, m), 1.92-1.84 (2H, m), 1.68 (3H, s), 1.58-1.52 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.2 (C), 144.6 (C), 136.7 (C), 117.9 (CH_2), 113.3 (CH_2), 51.0 (CH), 47.6 (CH_2), 41.8 (CH_2), 40.7 (CH_2), 30.0 (CH_2), 27.1 (CH_3) MS (Cl) *m/z* 245, 243 [M+H]$^+$, 189, 187, 163 (base), 121; HRMS (CI) Found *m/z* 243.1402 [M+H]$^+$, $C_{11}H_{16}OBr$ requires 243.1410.

Preparation of (7R,8R*)-7-(1-bromovinyl)-8-(prop-1-en-2-yl)-1,4-dioxaspiro[4.5]decane (**13**)*

To a stirred solution of **12** (664 mg, 2.66 mmol) in CH_2Cl_2 (26 mL), TMSOTf (0.02 mL, 0.08 mmol) and 1,2-bis(trimethylsilyloxy)ethane (0.65 mL, 2.26 mmol) were added at -78 °C. The mixture was stirred for 2 h before quenching by the addition of pyridine (3 drops) at rt. The mixture was extracted with Et_2O. The organic layer was washed with saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$) and then evaporated to afford a residue. The residue was purified by silica-gel column chromatography (hexane-EtOAc, 0-2%) to give **13** (605 mg, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.59 (1H, d, J = 1.5 Hz), 5.38 (1H, d, J = 1.5 Hz), 4.80 (1H, s), 4.78 (1H, s), 3.96 (4H, s), 2.54 (1H, td, J = 9.9, 4.8 Hz), 2.21 (1H, td, J = 9.9, 6.0 Hz), 1.82-1.74 (4H, m), 1.70-1.57 (2H, m), 1.66 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.3 (C), 138.5 (C), 117.0 (CH_2), 112.4 (CH_2), 108.3 (C), 64.4 (CH_2), 64.3 (CH_2), 48.6 (CH_2), 48.1 (CH), 40.1 (CH_2), 34.5 (CH_2), 28.4 (CH_2), 22.2 (CH_3); MS (Cl) m/z 289, 287 $[M+H]^+$, 207, 205, 203, 99 (base), 86; HRMS (CI) Found m/z 287.0631 $[M+H]^+$, $C_{13}H_{20}O_2Br$ requires 287.0646.

Preparation of 2-((7R,8R*)-8-(prop-1-en-2-yl)-1,4-dioxaspiro[4.5]decan-7-yl)hepta-1,6-dien-3-ol (**14**)*

A solution of **13** (150 mg, 0.52 mmol) in Et_2O (6 mL) was treated with ^{t}BuLi (in hexane, 1.59 M, 0.98 mL, 1.58 mmol) at -78 °C. The mixture was stirred for 15 min and 4-pentenal (66 mg, 0.79 mmol) was added. The reaction temperature was raised to -30 °C for 3 h with stirring. Saturated aq. $NaHCO_3$ soln. was added and the mixture was extracted with Et_2O. The organic layer was washed with brine, dried ($MgSO_4$), and then evaporated to afford a residue. The residue was purified by silica-gel column chromatography (hexane-EtOAc, 0-30%) to give **14** (13 mg, 56%). FTIR 3450, 1640 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (m), 5.18 (m), 5.14 (m), 5.08-4.92 (m), 4.97 (m), 4.92 (m), 4.74 (m), 4.66 (s), 4.03 (dd, J = 5.1, 2.7 Hz), 3.96 (s), 2.48 (m), 2.30-2.01 (m), 1.88-1.69 (m), 1.67 (s), 1.65-1.45 (m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5 (C), 154.4 (C), 149.4 (C), 147.9 (C), 138.5 (CH), 138.4 (CH), 114.7 (CH × 2), 111.9 (CH_2), 111.7 (CH_2), 109.1 (CH_2), 108.6 (C), 74.0 (CH), 72.7 (CH), 64.3 (CH_2), 64.2 (CH_2), 50.7 (CH), 49.2 (CH), 42.5 (CH_2), 42.2 (CH_2), 42.2 (CH). 41.9 (CH), 35.4 (CH_2), 34.9 (CH_2), 34.7 (CH_2), 34.6 (CH_2), 30.2 (CH_2), 30.1 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 20.3 (CH_3), 20.0 (CH_3) [signals overlapped due to the presence of the diastereoisomers]; MS (Cl) m/z 293 $[M+H]^+$, 275, 231, 213, 181, 147, 99 (base), 86; HRMS (CI) Found m/z 293.2133 $[M+H]^+$, $C_{18}H_{29}O_3$ requires 293.2117.

Preparation of 2-((7R,8R*)-8-(prop-1-en-2-yl)-1,4-dioxaspiro[4.5]decan-7-yl)-3-triethylsilyloxy-hepta-1,6-diene (**15**)*

To a stirred solution of **14** (31.5 mg, 0.11 mmol) in CH_2Cl_2 (5.0 mL) *i*Pr_2NEt was added (71.1 mg, 0.55 mmol) followed by TESOTf (87.2 mg, 0.33 mmol) at 0 °C. The temperature was gradually raised to rt with stirring overnight. Saturated aq. $NaHCO_3$ soln. was added and the mixture was extracted with Et_2O. The organic layer was washed with brine, dried ($MgSO_4$), and then evaporated to afford a residue. The residue was purified by silica-gel column chromatography (hexane-EtOAc, 0-5%) to give **15** (41.6 mg, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.82 (m), 5.17 (m), 5.14 (m), 5.03 (m), 4.95 (m), 4.90 (m), 4.87 (m), 4.71 (m), 4.68 (m), 4.03 (dd, J = 5.7, 5.4 Hz), 3.98-3.93 (m), 2.25-2.14 (m), 2.11-1.98 (m), 1.98-1.86 (m), 1.82-1.77 (m), 1.74-1.67 (m), 1.65 (s), 1.51-1.34 (m), 0.94 (t, J = 7.8 Hz), 0.57 (q, J = 7.8 Hz); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 153.6 (C), 153.0 (C), 147.8 (C), 147.7 (C), 139.0 (CH), 144.1 (CH_2), 109.8 (CH_2), 109.4 (CH_2), 108.8 (C), 108.6 (C), 75.7 (CH), 73.4 (CH), 64.4 (CH_2), 64.2 (CH_2), 50.3 (CH), 48.2 (CH), 43.6 (CH_2), 43.2 (CH_2), 40.9 (CH), 40.4 (CH), 35.5 (CH_2), 35.0 (CH_2), 34.9 (CH_2), 34.7 (CH_2), 30.2 (CH_2), 29.0 (CH_2), 21.4 (CH_3), 20.5 (CH_3), 7.0 (CH_3 × 3), 4.9 (CH_2 × 3) [signals overlapped due to the presence of the diastereoisomers]; MS (Cl) *m/z* 406 $[M]^+$, 377, 351, 275 (base), 199, 155, 99, 87; HRMS (CI) Found *m/z* 406.2913 $[M]^+$, $C_{24}H_{42}O_3Si$ requires 406.2904.

RCM reaction of 2-((7R,8R*)-8-(prop-1-en-2-yl)-1,4-dioxaspiro[4.5]decan-7-yl)-3-triethylsilyloxy-hepta-1,6-diene (**15**)*

A solution of **15** (32.9 mg, 0.082 mmol) in CH_2Cl_2 (160 mL) was treated with Grubbs II (14.7 mg, 0.016 mmol) in CH_2Cl_2 (4 mL) under reflux for 1 h. The solvent was evaporated and the residue was purified by silica-gel column chromatography (hexane-toluene, 0-90%) to give **16** (12.6 mg, 41%), **17** (10 mg, 32%).

16; ^1H NMR (300 MHz, $CDCl_3$) δ 5.32 (1H, br t, *J* = 7.2 Hz), 5.13 (1H, s), 4.82 (1H, d, *J* = 1.8 Hz), 4.03-4.00 (1H, m), 3.97 (4H, s), 2.50-2.37 (2H, m), 2.19-2.16 (2H, m), 1.93-1.90 (1H, m), 1.85-1.77 (3H, m), 1.72-1.63 (2H, m), 1.55 (3H, s), 1.52-1.34 (2H, m), 0.93 (9H, t, *J* = 8.1 Hz), 0.55 (6H, q, *J* = 8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3 (C), 138.9 (C), 124.5 (CH), 112.7 (C), 108.8 (C), 70.9 (CH), 64.4 (CH_2), 64.2 (CH_2), 47.5 (CH), 42.6 (CH_2), 40.7 (CH_2), 40.0 (CH_2), 34.7 (CH_2), 26.5 (CH_2), 23.5 (CH_2), 18.9 (CH_3), 6.9 (CH_3 × 3), 5.0 (CH_2 × 3); MS (Cl) *m/z* 379 $[M+H]^+$, 349, 247, 210 (base), 99, 87, 59; HRMS (CI) Found *m/z* 379.2668 $[M+H]^+$, $C_{22}H_{39}O_3Si$ requires 379.2668.

17; ^1H NMR (300 MHz, $CDCl_3$) δ 5.48 (1H, br s), 4.67 (1H, d, *J* = 1.5 Hz), 4.63 (1H, s), 3.94 (1H, m), 3.93 (4H, s), 2.46 (1H, td, *J* = 8.7, 3.3 Hz), 2.39-2.31 (1H, m), 2.21-2.08 (3H, m), 2.01 (1H, dt, *J* = 8.7, 3.3 Hz), 1.77 (1H, m), 1.71-1.62 (4H, m), 1.57 (3H, s), 1.55-1.46 (1H, m), 0.99 (9H, t, *J* = 7.8 Hz), 0.63 (6H, q, *J* = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7 (C), 148.6 (C), 126.4 (CH), 110.8 (CH_2), 108.6 (C), 80.5 (CH), 64.3 (CH_2 × 2), 50.4 (CH), 41.9 (CH_2), 38.0 (CH_2). 35.1 (CH_2), 34.3 (CH_2), 30.1 (CH), 29.7 (CH_3), 20.4 (CH_2), 6.9 (CH_3 × 3), 5.0 (CH_2 × 3); MS (Cl) *m/z* 378 $[M]^+$, 349, 289, 247 (base), 210, 155, 99, 89, 75, 61; HRMS (CI) Found *m/z* 378.2590 $[M]^+$, $C_{22}H_{38}O_3Si$ requires 378.2590.

Preparation of (1R,3S*,8R*)-11-ethylenedioxy-2-exomethylene-7-methylbicyclo[6.4.0]-6-dodecen-3-ol (**18**)*

A solution of **16** (7.8 mg, 0.021 mmol) in THF (1 mL) was treated with TBAF (in THF, 1 M, 0.06 mL, 0.06 mmol) at 0 °C for 6 h. Water was added and the mixture was extracted with Et_2O. The organic layer was washed with brine, dried ($MgSO_4$), and then evaporated to afford a residue. The residue was purified by silica-gel column chromatography (hexane-EtOAc, 0-50%) to give **18** (4.7 mg, 89%). FTIR 3440, 1640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.33 (1H, br t, *J* = 7.8 Hz), 5.15 (1H, s), 4.90 (1H, s), 4.14 (1H, dd, *J* = 10.8, 7.8 Hz), 3.99-3.97 (4H, m), 2.48-2.35 (2H, m), 2.27-2.18 (1H, m), 2.06-1.97 (2H, m), 1.86-1.76 (3H, m), 1.72-1.58 (4H, m), 1.56 (3H, s), 1.49-1.40 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3 (C), 139.2 (C), 124.4 (CH), 111.8 (CH_2), 108.6 (CH), 70.9 (CH), 64.5 (CH_2), 64.3 (CH_2), 47.3 (CH), 40.5 (CH_2), 40.2 (CH_2), 39.9 (CH), 34.7 (CH_2), 26.3 (CH_2), 23.6 (CH_2), 18.9 (CH_3); MS (Cl) *m/z* 264 $[M+H]^+$, 247 (base), 202, 169, 99, 86, 56; HRMS (CI) Found *m/z* 265.1804 $[M+H]^+$, $C_{16}H_{25}O_3$ requires 265.1804.

Preparation of (1R,2R*)-2-allyl-1-(1-((7R*,8R*)-8-(prop-1-en-2-yl)-1,4-dioxaspiro[4.5]decan-7-yl)vinyl)cyclopentanol (**19a**) and (1S*,2S*)-2-allyl-1-(1-((7R*,8R*)-8-(prop-1-en-2-yl)-1,4-dioxaspiro[4.5]decan-7-yl)vinyl)cyclopentanol (**19b**)*

A solution of **13** (150 mg, 0.52 mmol) in Et_2O (5 mL) was treated with ^{t}BuLi (in pentane, 1.59 M, 0.98 mL, 1.56 mmol) at -50 °C for 20 min. A solution of 2-allylcyclopentanone (96.7 mg, 0.78 mmol) in Et_2O (2 mL) was added and the mixture was stirred for 8 h. Saturated aq. $NaHCO_3$ soln. was added and the mixture was extracted with Et_2O. The organic layer was washed with brine, dried ($MgSO_4$), and then evaporated to afford a residue. The residue was purified by silica-gel column chromatography (hexane-EtOAc, 0-40%) to give **19a** (42.2 mg, 25%) and **19b** (21.3 mg, 12%).

19a: FTIR 3490, 1640 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (1H, m), 5.24 (1H, s), 5.02 (1H, s), 5.01 (1H, d, *J* = 17.1 Hz), 4.95 (1H, d, *J* = 10.2 Hz), 4.77 (1H, s), 4.70 (1H, s), 3.96-3.91 (4H, m), 2.44 (1H, td, *J* = 12.0, 4.2 Hz), 2.24-2.02 (4H, m), 2.00-1.69 (7H, m), 1.69 (3H, s), 1.66-1.38 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9 (C), 148.6 (C), 138.1 (CH), 114.8 (CH_2), 112.3 (CH_2), 109.8 (CH_2), 108.6 (C), 84.8 (C), 64.4 (CH_2), 64.2 (CH_2), 50.0 (CH), 45.5 (CH), 44.2 (CH_2), 40.1 (CH), 39.5 (CH_2), 34.8 (CH_2), 33.5 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 21.9 (CH_3), 23.1 (CH_2); MS (Cl) *m/z* 332 $[M]^+$, 315 (base), 270, 253, 229, 213, 181, 99, 56; HRMS (CI) Found *m/z* 332.2343 $[M]^+$, $C_{21}H_{33}O_3$ requires 332.2352.

19b: FTIR 3480, 1640 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75 (1H, m), 5.27 (1H, s), 5.02 (1H, s), 4.98 (1H, d, *J* = 17.0 Hz), 4.92 (1H, d, *J* = 9.9 Hz), 4.74 (1H, s), 4.69 (1H, s), 3.95 (4H, s), 2.36-2.09 (4H, m), 1.99-1.60 (11H, m), 1.67 (3H, s), 1.50-1.37 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9 (C), 147.9 (C), 138.2 (CH), 114.8 (CH_2), 112.2 (CH_2), 110.0 (CH_2), 108.7 (C), 85.1 (C), 64.4 (CH_2), 64.2 (CH_2), 49.1 (CH), 45.7 (CH), 45.2 (CH_2), 41.0 (CH), 39.8 (CH_2), 34.8 (CH_2), 33.0 (CH_2), 30.1 (CH_2), 28.9 (CH_2), 21.8 (CH_3), 21.3 (CH_2); MS (Cl) *m/z* 333, $[M+H]^+$, 315 (base), 271, 253, 181, 99, 69, 51; HRMS (CI) Found *m/z* 333.2430 $[M+H]^+$, $C_{21}H_{33}O_3$ requires 333.2429.

Preparation of (1R,2R*)-2-allyl-1-(1-((7R*,8R*)-8-(prop-1-en-2-yl)-1,4-dioxaspiro[4.5]decan-7-yl)vinyl)cyclopentanol triethylsilyl ether (**21a**)*

A solution of **19a** (20 mg, 0.06 mmol) in CH_2Cl_2 (1.0 mL) was treated with *i*Pr_2NEt (46.5 mg, 0.36 mmol) at 0 °C for 5 min followed by the addition of TESOTf (47.6 mg, 0.18 mmol). The temperature of the mixture was gradually raised to rt overnight. Saturated aq. $NaHCO_3$ was added and the mixture was extracted with Et_2O. The organic layer was washed with brine, dried ($MgSO_4$), and then evaporated to afford a residue. The residue was purified by silica-gel column chromatography (hexane-toluene, 0-90%) to give **21a** (25.6 mg, 97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (1H, ddt, *J* = 17.0, 10.0, 6.9 Hz), 5.33 (1H, s), 5.04 (1H, d, *J* = 1.2 Hz), 4.95 (1H, dq, *J* = 17.0, 2.4 Hz), 4.88 (1H, dq, *J* = 10.0, 1.2 Hz), 4.74 (1H, s), 4.67 (1H, s), 3.90 (4H, m), 2.18-2.00 (4H, m), 1.90-1.68 (8H, m), 1.66 (3H, s), 1.64-4.36 (5H, m), 0.94 (9H, t, *J* = 8.1 Hz), 0.61 (6H, q, *J* = 8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0 (C), 147.0 (C), 139.2 (CH), 114.0 (CH_2), 112.7 (CH_2), 111.4 (CH_2), 109.3 (C), 67.9 (C), 64.4 (CH_2), 64.1 (CH_2), 50.1 (CH), 48.4 (CH), 44.8 (CH_2), 40.5 (CH), 36.7 (CH_2), 35.0 (CH_2), 32.9 (CH_2), 29.8 (CH_2), 29.4 (CH_2), 22.2 (CH_3), 21.9 (CH_2), 7.36 (CH_3 × 3), 6.73 (CH_2 × 3); MS (Cl) *m/z* 446 $[M]^+$, 417, 363, 315, 279, 154 (base); HRMS (CI) Found *m/z* 446.3208 $[M]^+$, $C_{27}H_{46}O_3Si$ requires 446.3217.

Preparation of (1S,2S*)-2-allyl-1-(1-((7R*,8R*)-8-(prop-1-en-2-yl)-1,4-dioxaspiro[4.5]decan-7-yl)vinyl)cyclopentanol triethylsilyl ether (**21b**)*

A solution of **19b** (9.2 mg, 0.028 mmol) in CH_2Cl_2 (1.0 mL) was similarly treated with *i*Pr_2NEt (10.7 mg, 0.083 mmol) and TESOTf (14.8 mg, 0.056 mmol) to afford (**21b**) (9.2 mg, 74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (1H, ddt, *J* = 17.1, 11.1, 7.5 Hz), 5.31 (1H, s), 5.03 (1H, s), 4.89 (1H, d, *J* = 17.1 Hz), 4.83 (1H, d, *J* = 11.1 Hz), 4.73 (1H, s), 4.66 (1H, s), 3.95 (4H, s), 2.23 (1H, t, *J* = 11.1 Hz), 2.13-2.03 (3H, m), 1.93 (1H, dt, *J* = 13.8, 2.4 Hz), 1.82-1.71 (6H, m), 1.65 (3H, s), 1.63-1.56 (2H, m), 1.45-1.26 (4H, m), 0.94 (9H, t, *J* = 7.5 Hz), 0.58 (6H, q, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3 (C), 147.5 (C), 139.2 (CH), 114.1 (CH_2), 112.2 (CH_2), 111.5 (CH_2), 108.7 (C), 87.7 (C), 64.4 (CH_2), 64.3 (CH_2), 48.6 (CH), 47.7 (CH), 45.1 (CH_2), 41.1 (CH), 36.8 (CH_2), 34.8 (CH_2), 32.5 (CH_2), 30.3 (CH_2), 28.9 (CH_2), 21.8 (CH_2), 21.6 (CH_2), 7.4 (CH_3 × 3), 6.7 (CH_2 × 3); MS (Cl) *m/z* 447 $[M+H]^+$, 446, 417, 371, 315 (base), 253, 239, 207, 154, 99, 89, 53; HRMS (CI) Found *m/z* 447.3284 $[M+H]^+$, $C_{27}H_{47}O_3Si$ requires 447.3294.

RCM reaction of (1R,2R*)-2-allyl-1-(1-((7R*,8R*)-8-(prop-1-en-2-yl)-1,4-dioxaspiro[4.5]decan-7-yl)vinyl)cyclopentanol triethylsilyl ether (**21a**)*

A solution of **21a** (7.3 mg, 0.016 mmol) in CH_2Cl_2 (16 mL) was heated under reflux with Grubbs II (5.4 mg, 0.0048 mmol) for 25 h. The solvent was evaporated and the residue was separated by silica-gel column chromatography (hexane-AcOEt, 5%) to give a mixture of **22a** and **24** (3.5 mg), which was further purified by HPLC (hexane-AcOEt, 2%) to give **22a** and **24**.

22a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.37 (1H, br t, *J* = 7.8 Hz), 5.00 (1H, s), 4.74 (1H, s), 4.00-3.89 (4H, m), 2.51 (1H, br s), 2.18 (1H, br s), 1.96 (1H, br d, *J* = 11.1 Hz), 1.85-1.79 (2H, m), 1.56 (3H, s), 0.97 (9H, t, *J* = 7.8 Hz), 0.68 (6H, q, *J* = 7.8 Hz) [protons could not be assigned due to slow rotation]; MS (Cl) *m/z* 419 $[M+H]^+$ (base), 418, 389, 287, 249, 89; HRMS (CI) Found *m/z* 419.2985 $[M+H]^+$, $C_{25}H_{43}O_3Si$ requires 419.2982.

24: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.43 (1H, ddd, *J* = 15.6, 7.4, 1.1 Hz), 5.28 (1H, dqd, *J* = 15.6, 6.6, 0.8 Hz), 5.27 (1H, s), 4.96 (1H, s), 4.72 (1H, s), 4.66 (1H, s), 3.95-3.92 (4H, m), 2.22 (1H, m), 2.16 (1H, m), 2.14 (1H, m), 2.07 (1H, m), 1.94 (1H, dt, *J* = 13.2, 3.0 Hz), 1.78 (1H, m), 1.76 (2H, m), 1.70 (2H, m), 1.66 (3H, m), 1.65 (3H, s), 1.62 (3H, d, *J* = 6.6 Hz), 1.52 (1H, m), 1.37 (1H, m), 0.94 (9H, q, *J* = 7.5 Hz), 0.61 (6H, t, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1 (C), 147.1 (C), 130.9 (CH), 125.0 (CH), 112.6 (CH_2), 111.0 (CH_2), 108.8 (CH_2), 88.4 (C), 64.4 (CH_2), 64.2 (CH_2), 52.1 (CH), 50.1 (CH), 44.6 (CH_2), 40.4 (CH), 36.9 (CH_2), 34.8 (CH_2), 30.3 (CH_2), 29.8 (CH_2), 22.1 (CH_3), 22.0 (CH_2), 18.3 (CH_3), 7.3 (CH_3 × 3), 6.7 (CH_2 × 3); MS (Cl) *m/z* 447 $[M+H]^+$, 446, 417, 363, 315 (base), 253, 154, 99, 86; HRMS (CI) Found *m/z* 447.3271 $[M+H]^+$, $C_{27}H_{47}O_3Si$ requires 447.3295.

Preparation of (1R,3R*,8R*,12R*)-5-ethylenedioxy-2-exomethylene-9-methyltricyclo[10.3.0.0^{3,8}]-9-pentadecen-1-ol (**25a**) and (1R*,3R*,8R*,11R*)-5-ethylenedioxy-2-exomethylene-9-methyltricyclo-[9.3.0.0^{3,8}]-9-tetradecen-1-ol (**26**)*

A partially separated fraction (22.1 mg, 0.05 mmol) of the RCM reaction products from **21a** was dissolved in THF (1 mL) and TBAF (in THF, 1 M, 0.1 mL, 0.1 mmol) was added at 0 °C. The mixture was stirred overnight. Water was added and the mixture was extracted with Et_2O. The organic layer was washed with brine, dried ($MgSO_4$), and was then evaporated to afford a residue. The residue was separated by silica-gel column chromatography (hexane-EtOAc, 0-50%) to give **25a** (2.1 mg, 14%) and **26** (1.0 mg, 7%).

25a: FTIR 3480, 1640 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.42-5.23 (2H, m), 4.86 (1H, s), 3.96 (4H, s), 2.74-1.62 (15H, m), 1.57 (3H, s), 1.25-0.94 (4H, m); MS (Cl) *m/z* 305 [M+H]$^+$, 287 (base), 242, 205, 161, 99, 89; HRMS (CI) Found *m/z* 305.2116 [M+H]$^+$, $C_{19}H_{29}O_3$ requires 305.2116.

26: FTIR 3380 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.40 (1H, s), 5.07 (1H, s), 4.81 (1H, d, *J* = 1.6 Hz), 4.01-3.88 (4H, m), 2.54 (1H, ddd, *J* = 14.6, 10.2, 3.8 Hz), 2.48 (1H, br t, *J* = 10.0 Hz), 2.16 (1H, m), 2.13 (1H, m), 2.08 (1H, m), 1.92 (1H, m), 1.89 (3H, s), 1.86 (1H, m), 1.85 (1H, m), 1.84 (1H, m), 1.80 (2H, m), 1.70 (1H, m), 1.69 (1H, m), 1.68 (1H, m), 1.64 (1H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.6 (C), 143.6 (C), 128.4 (C), 109.3 (C), 106.8 (CH_2), 81.9 (C), 64.3 (CH_2), 64.1 (CH_2), 49.5 (CH), 43.1 (CH), 38.9 (CH_2), 37.8 (CH_2), 36.9 (CH), 33.8 (CH_2), 31.8 (CH_2), 26.5 (CH_2), 23.4 (CH_3), 22.0 (CH_2); MS (Cl) *m/z* 291 [M+H]$^+$, 273, 89 (base); HRMS (CI) Found *m/z* 291.1966 [M+H]$^+$, $C_{18}H_{27}O_3$ requires 291.1961.

RCM reaction of (1S,2S*)-2-allyl-1-(1-((7R*,8R*)-8-(prop-1-en-2-yl)-1,4-dioxaspiro[4.5]decan-7-yl)vinyl)cyclopentanol triethylsilyl ether (**21b**)*

A solution of **21b** (16.2 mg, 0.036 mmol) in CH_2Cl_2 (72 mL) was treated with Grubbs II (9.7 mg, 0.011 mmol) under reflux for 6 h. The solvent was evaporated and the residue was separated by silica-gel column chromatography (hexane-AcOEt, 2%) to give **22b** (6.2mg, 61%). FTIR 1610, 1000 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.39 (1H, t, *J* = 8.0 Hz), 4.72 (1H, s), 4.70 (1H, s), 3.95 (4H, s), 3.17 (1H, td, *J* = 11.4, 3.6 Hz), 2.56 (1H, td, *J* = 10.2, 3.0 Hz), 2.47 (1H, td, *J* = 13.2, 1.8 Hz), 2.40 (1H, t, *J* = 13.2 Hz), 2.30 (1H, m), 1.93 (1H, m), 1.76 (1H, m), 1.69-1.60 (8H, m), 1.56 (3H, s), 1.49-1.38 (1H, m), 1.42 (1H, m), 1.02 (9H, t, *J* = 7.8 Hz), 0.73 (6H, q, *J* = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2 (C), 139.3 (C), 125.6 (C), 111.1 (C), 109.0 (C), 89.4 (C), 64.2 (CH_2), 64.0 (CH_2), 59.0 (CH), 50.9 (CH), 42.4 (CH_2), 41.1 (CH_2), 38.3 (CH), 34.1 (CH_2), 32.2 (CH_2), 26.9 (CH_2), 25.0 (CH_2), 21.3 (CH_2), 19.3 (CH_3), 7.6 (CH_3 × 3), 6.9 (CH_2 × 3); MS (Cl) *m/z* 418 [M]$^+$, 389, 375, 343, 329, 287 (base), 243; HRMS (CI) Found *m/z* 418.2910 [M]$^+$, $C_{25}H_{42}O_3$ Si requires 418.2903.

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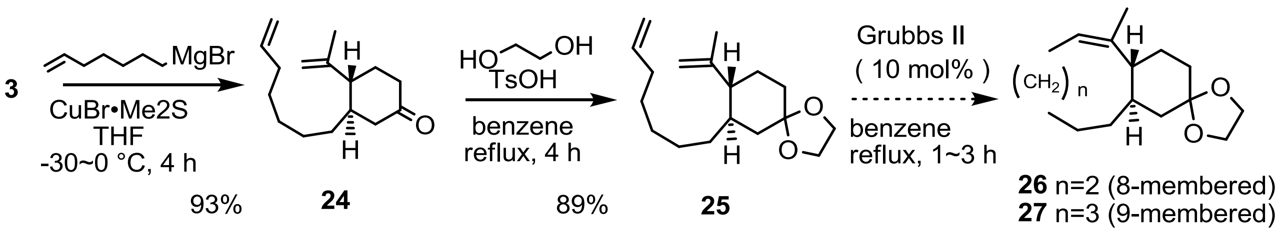
31. One-carbon longer substance **25** was prepared and the RCM reaction was attempted. However, the starting material was recovered.



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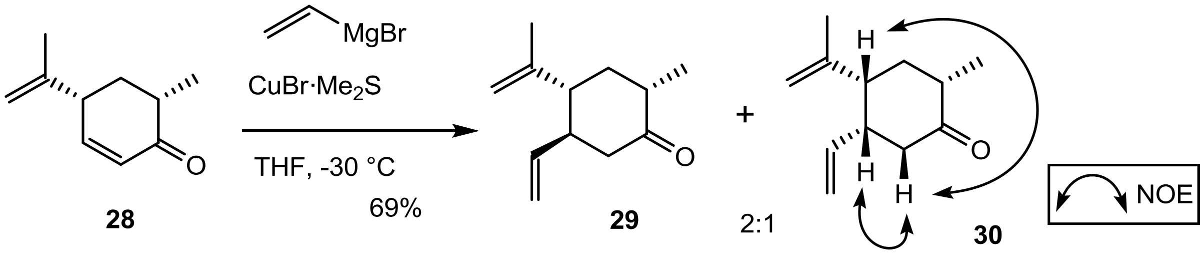
39. The selectivity of the conjugate addition of a vinyl group was not as high as expected. The desired trans adduct **29** was produced in a ratio of 2:1 at the highest.



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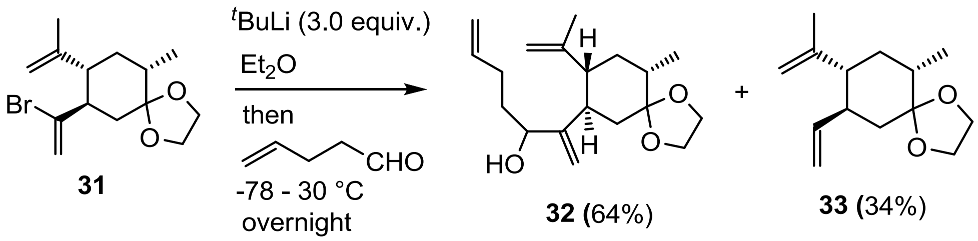
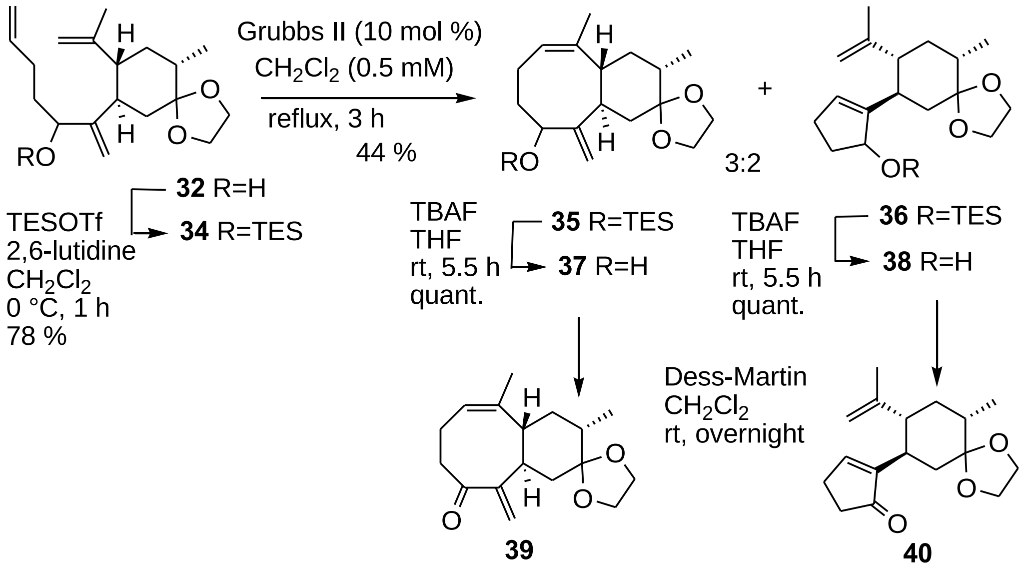
44. This coupling was also accomplished with compound **31**. However, the highest yield was 64%.



45. Similar reaction and derivatization to enones **39** and **40** were also carried out. The spectral data for these compounds supported the assigned structure.



46. The numbering of compound **24** was based on compound **26**.