Cyclization of 1,1-Disubstituted Alkenes to Cyclopentenes

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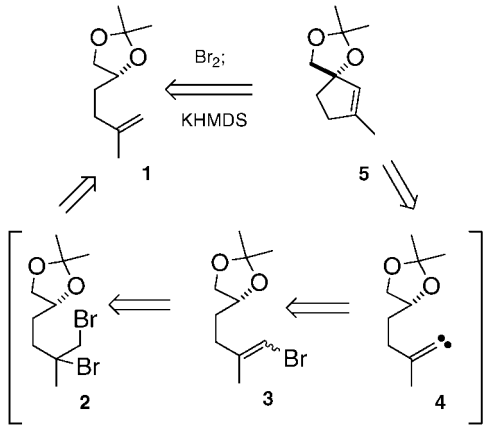
A general method for the cyclization of an unactivated 1,1-disubstituted alkene such as **1** to the corresponding cyclopentene **5** is described. Bromination followed by the addition of strong base in the same pot gave the vinyl bromide **3**, which reacted further in situ to give the alkylidene carbene **4**. This then inserted 1,5 into a C−H bond to give the cyclopentene **5**.

Introduction

Cyclopentene intermediates are important synthons for a variety of natural products.[1] We have been exploring the preparation of cyclopentenes by the 1,5 C−H insertion of intermediate alkylidene carbenes. The alkylidene carbenes can be generated from ketones using diazophosphonates or trimethyl silyldiazomethane.[2,1a] They can also be prepared by converting the ketone to the vinyl halide, followed by exposure of the vinyl halide to potassium bis(trimethylsilyl)amide (KHMDS) to effect α-elimination. [3,1k] We thought that it might be possible to extend this reaction to a simple alkene such as **1** (Scheme 1). Bromination should give **2**, and dehydrobromination would be expected to give **3**, setting the stage for in situ elimination and insertion.[4]

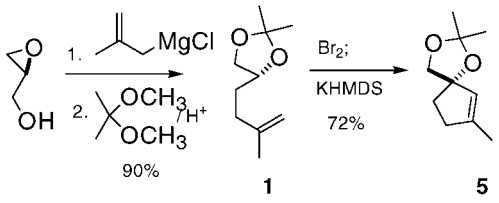
Scheme 1



Results and Discussion

We have prepared **1** (Scheme 2) from (*S*)-glycidol by Grignard opening followed by ketalization.[4] The acetonide **1** was purified on a multigram scale by distillation. As we had hypothesized, bromination followed by exposure to KHMDS nicely cyclized **1** to **5**. This procedure required some optimization. The ketal tended to participate in the bromination, so it was necessary to effect bromination in ether at −78 °C and then immediately add the KHMDS (freshly titrated) before allowing the reaction to come to room temperature. Under these conditions, cyclization proceeded in good yield.

Scheme 2



Our next objective was to explore the general utility of this protocol for the preparation of cyclopentene derivatives, using substrates with unactivated methylene C−H bonds.[1a,j,5] The one-pot protocol for the cyclization gave low yields with alkenes **7**−**9**, so we prepared the long-chain dibromides **10**−**12** (Scheme 3). We were able to effect the desired insertion by treatment of **10**, **11**, and **12** with 2.5 equiv of KHMDS to obtain the cyclopentenes **13**, **14**, and **15a**,**b** (Scheme 3).

We then returned to the one-pot bromination/cyclization protocol. To this end, alkene **16** (Scheme 4) was prepared by reacting 2-methylallylmagnesium chloride with 4-phenoxybutyl bromide. Cyclization of **16** by addition of bromine followed by KHMDS gave a 27% yield of the desired cyclopentene **17**. We prepared and cyclized the dibromide intermediate **18** (Scheme 4) and the vinyl bromide intermediate **19** in an attempt to determine the factor that lowered the yield of the C−H insertion

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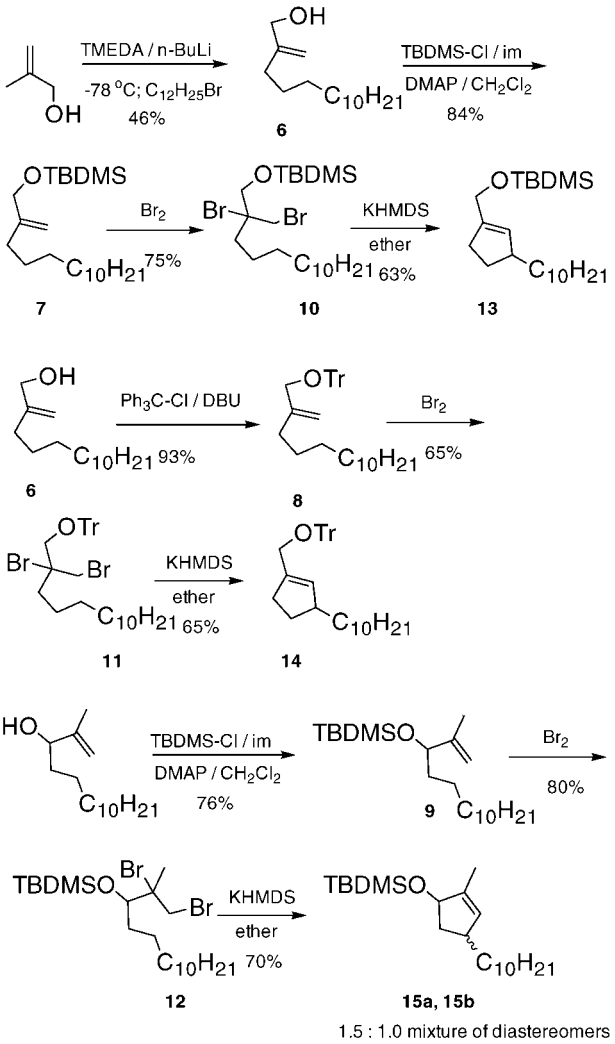
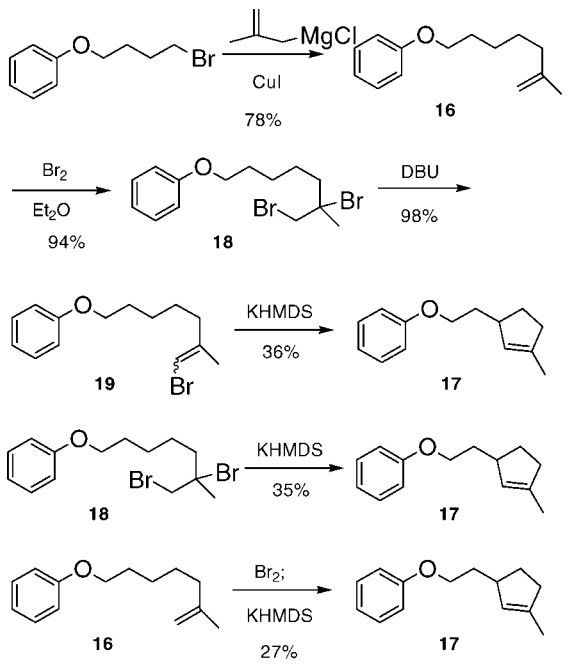
Scheme 3



Scheme 4



product. However, each of the cyclizations proceeded in only mediocre yield.

We hypothesized that the moderate yield from these

Scheme 5

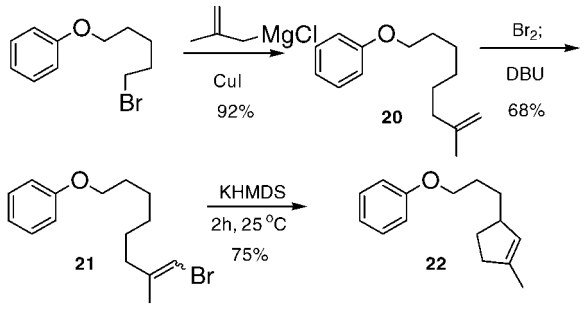


Table 1. Optimization of the Cyclization of Alkenyl Bromide 21 to Cyclopentene 22

entry	solvent	*T* (°C)	base (3 equiv)	time (h)	yield (%)
1	DME	−78 to +25	KHMDS	17	70
2	DME	25	KHMDS	2	70
3	DME	25	LiHMDS	24	0
4	DME	25	NaHMDS	2	69
5	Et_2O	25	KHMDS	2	68
6	toluene	25	KHMDS	2	52
7	benzene	25	KHMDS	2	51
8	DMF	25	KHMDS	2	53
9	CCl_4	25	KHMDS	24	0
10	THF	25	KHMDS	2	67
11	*p*-dioxane	25	KHMDS	2	75

cyclizations was due to the deactivation of the methylene undergoing C−H insertion. The methylene at the cyclization center in substrate **16** is deactivated due to its γ relationship with the phenoxy group.[6] To solve this deactivation problem, we turned to the alkenyl bromide **21** (Scheme 5). Bromide **21** was prepared by coupling 5-phenoxypentyl bromide with 2-methylallylmagnesium chloride to obtain alkene **20**, which was brominated and then treated with DBU.

We first addressed the cyclization of the alkenyl bromide **21**. We found (Table 1) that the best results were obtained using *p*-dioxane/KHMDS (3 equiv)/25 °C. With these results in hand, we tried the bromination of alkene **20**, followed by cyclization of the crude dibromide to **22** using the optimized conditions. This protocol gave a 50% overall yield of the desired cyclopentene.

To address the compatibility of this protocol with other protecting groups, alcohol **23** was prepared (Scheme 6) by coupling 1-bromohexanol with 2-methylallylmagnesium chloride. Alcohol **23** was then alkylated with benzyl bromide to give alkene **24** (Scheme 6). Application of the optimized bromination/cyclization protocol, for the conversion of **20** to **22,** to alkene **24** gave a 50% yield of an 80:20 mixture of **25** and unreacted **24** (Scheme 6). All of the alkene **24** had been consumed in the bromination step, so we concluded that a reduction must have intervened.

The dibromide **26** was prepared from **24** (Scheme 6), and cyclization conditions were optimized to minimize the amount of **24** obtained from the reaction (Table 2). Lower temperature and longer reaction time were found to be the key factors in optimizing this reaction.

We tried the one-pot bromination/cyclization of **24** using the optimized lower temperature conditions for the cyclization. This reaction gave a 57% overall yield of the desired cyclopentene **25**. Under these conditions, less

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Scheme 6

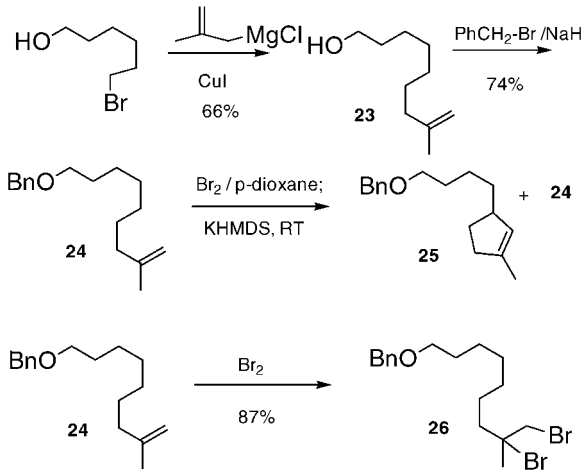
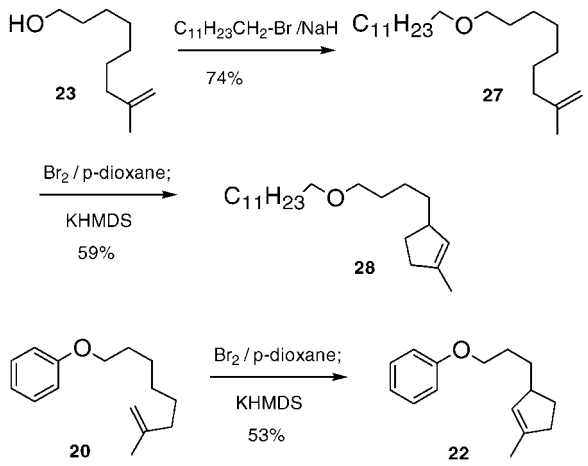


Table 2. Optimization of the Cyclization of Dibromide 26 to Cyclopentene 25[a]

entry	solvent	*T* (°C)	base	time (h)	% **25**	% **24**
1	Et_2O	−20	KHMDS	48	90	10
2	Et_2O	−30	KHMDS	48	80	20
3	Et_2O	−10	KHMDS	48	84	16
4	DME/dioxane 1/1	−10	KHMDS	48	93	7
5	Et_2O/dioxane 4/1	−10	KHMDS	48	84	16
6	DME	−20	KHMDS	48	93	7
7	THF	−20	KHMDS	48	93	7
8	Et_2O/dioxane 4/1	−20	KHMDS	48	94	6
9	Et_2O	−20	NaHMDS	48	50	50
10	diglyme	−20	KHMDS	48	0	0
11	Et_2O/DMPU	−20	KHMDS	48	0	0
12	DME/dioxane 1/1	−20	KHMDS	48	96	4
13	DME/dioxane 1/2	−20	KHMDS	48	96	4

[a] All reactions assessed by ^{1}H NMR to deteremine the % **24** versus **25**.

Scheme 7



than 1% of **24** was observed in the product. These cyclization conditions were also applied to substrates **27** and **20 (**Scheme 7) to obtain the desired cyclopentenes in 59% and 53% yields respectively, with less than 1% of **27** and of **20** observed in the reaction mixtures.

Conclusion

We have demonstrated that the generation of alkylidene carbenes by the bromination of unactivated 1,1-disubstituted alkenes followed by the treatment of the resulting dibromides with strong base can proceed efficiently. The last procedure illustrated (Scheme 7) appears to be a general one-pot protocol for effecting this transformation.[7]

Experimental Section

General Methods. ^{1}H NMR (at 300 MHz) and ^{13}C NMR (at 75 MHz) spectra were obtained as solutions in deuteriochloroform ($CDCl_3$). The infrared (IR) spectra were determined as neat oils on a Perkin-Elmer model 1650 FTIR spectrometer. Mass spectra (MS) were obtained using FTMS at an ionizing potential of 70 eV. Substances for which C, H analysis are not reported were purified as specified and gave spectroscopic data consistent with being >95% the assigned structure. R_f values indicated refer to thin-layer chromatography (TLC) on 5.0 × 10 cm, 250 mm analytical plates coated with silica gel 60, F_{254}, developed in the solvent system indicated. Materials were visualized using 5% phosphomolybdic acid in ethanol as stain. Elemental analysis was carried out by Quantitative Technologies Inc., Whitehouse, NJ. Column chromatography was carried out on an Isco MPLC using silica gel 60 particle size 0.015−0.040 mm. The solvent mixtures reported are volume/volume mixtures. All glassware was oven dried, and reactions were carried out under a flow of dry nitrogen. Reactions were chilled to the desired temperature using a Neslab CC-100II immersion cooler. Ethylene glycol dimethyl ether (DME), *tert*-butyl methyl ether (MTBE), *p*-dioxane, and 0.5 M potassium bis(trimethylsilyl)amide (KHMDS) in toluene were from Aldrich Sure-Seal bottles kept under dry nitrogen. All reactions were stirred magnetically, unless otherwise noted.

2,2-Dimethyl-4-(3-methyl-but-3-enyl)[1,3]dioxolane (1). To a suspension of magnesium turnings (1.10 g, 45.2 mmol) and 1,2 dibromoethane (0.11 mL, 1.13 mmol) in Et_2O (50 mL) chilled to 0 °C was added methallyl chloride (4.1 g, 45.2 mmol) over 20 min. This was allowed to stir for 2 h at 0 °C and then at room temperature for 1 h. The reaction mixture was then chilled to −78 °C, and (*S*)-glycidol **1** (0.84 g, 11.31 mmol) in 10 mL of ether was added over 10 min. The reaction mixture was allowed to warm to room temperature over 30 min then stirred for an additional 1 h. The mixture was partitioned between aqueous NH_4Cl and, sequentially, CH_2Cl_2 and EtOAc. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude diol (1.20 g, 9.23 mmol) was dissolved in 20 mL of 2,2 dimethoxypropane at room temperature, and TsOH (0.18 g, 0.92 mmol) was added. After 30 min at room temperature, the mixture was partitioned between saturated aqueous $NaHCO_3$ and EtOAc. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was distilled bulb to bulb ($bp_{0.5}$ (pot) = 50−55 °C) to give 1.41 g (90% yield) of **1** as a thin clear oil (TLC R_f = 0.45, 5% EtOAc/hexane): $[\alpha]_D$ −7.0° (*c* 1.00, MeOH); ^{1}H NMR δ 4.72 (d, J = 10.0 Hz, 2H), 4.10 (m, 2H), 3.55 (m, 1H), 2.21−2.01 (m, 2H), 1.85−1.60 (m, 5H), 1.41 (s, 3H), 1.39 (s, 3H); HRMS calcd mass 170.253221, measured mass 170.254782; IR cm^{-1} 2986 (s), 1741 (m), 1650 (m), 1455 (m), 1371 (m); ^{13}C NMR δ C 145.0, CH 75.4, CH_2 110.1, 69.4, 33.8, 31.6, CH_3 75.7, 26.9, 25.7, 22.5.

2,2,7-Trimethyl-1,3-dioxaspiro[4.4]non-6-ene (5). The acetonide **1** (1.6 g, 9.4 mmol) in 200 mL of Et_2O was chilled to −78 °C. Br_2 (1.50 g, 9.4 mmol, neat) was then added over 2 min, and the reaction was allowed to stir for 20 min. A solution of KHMDS (0.5 M in toluene, 75.3 mL, 37.65 mmol) was added over 10 min while the temperature was maintained below −65 °C. After the addition, the reaction was warmed to room temperature over 2 h and then stirred for 24 h. The mixture was partitioned between saturated aqueous $NaHCO_3$ and EtOAc. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was distilled bulb to bulb ($bp_{0.5}$ (pot) = 60 °C − 65 °C) to give 1.13 g (72% yield) of

(7) Although all of the work described here is based on bromides, we have observed that chlorination followed by exposure to KHMDS works equally well.

5 as a thick clear oil (TLC R_f = 0.50, 10% ethyl acetate/hexane): $[\alpha]_D$ −13.5 (*c* 1.00, $CHCl_3$); ^{1}H NMR δ 5.35 (s, 1H), 3.82 (s, 2H), 2.41 (m, 1H), 2.21−2.02 (m, 3H), 1.79 (s, 3H), 1.40 (s, 3H), 1.39 (s, 3H); HRMS calcd mass 169.122855, measured mass 169.123422; IR cm^{-1} 3048.0 (b), 2934 (s), 1660 (w), 1368 (s); ^{13}C NMR δ C 146.2, 108.7, 93.0, CH 127.0, CH_2, 73.2, 37.0, 35.0, CH_3 26.8, 16.9.

2-Tridecylprop-2-en-1-ol (6). TMEDA (43.5 mL, 0.288 mol) was added dropwise over 60 min to *n*-BuLi (125 mL of a 2.30 M solution) at −78 °C. After 30 min, methallyl alcohol (14.5 mL, 0.173 mol) was added dropwise over 5 min. The cooling bath was removed, and the reaction was allowed to stir at room temperature for 18 h. The reaction mixture was again cooled to −78 °C, and 1-bromododecane (17.5 mL, 0.072 mol) in petroleum ether (100 mL) was added. The mixture was allowed to stir at room temperature for an additional 18 h and then was chilled to 0 °C and quenched with 50 mL of 10% aqueous HCl. The mixture was partitioned between Et_2O and H_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Bulb-to-bulb distillation of the residue gave a colorless oil (8.0 g, 46% yield) that became a semisolid upon standing: TLC (R_f = 0.5, 20% MTBE/petroleum ether); ^{1}H NMR δ 5.00 (s, 1H), 4.86 (s, 1H), 4.07 (s, 2H), 2.11 (t, *J* = 6.7 Hz, 3H), 1.12−1.63 (m, 22H), 0.85 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR δ C 149.3, CH_2 108.9, 65.9, CH_3 33.0, 31.9, 29.6, 29.5, 29.4, 29.3, 27.8, 22.7, CH_3 14.1. Anal. Calcd for $C_{16}H_{32}O$: C, 79.93; H, 13.42. Found: C, 79.75; H, 13.60.

General Procedure for Alkene Silyl Ethers. *tert*-Butyl-(2-tridecylallyloxy)dimethylsilane (7). To a room-temperature solution of **6** in dry CH_2Cl_2 (0.1 M) were added imidazole (3 equiv) and DMAP (0.15 equiv) followed by (*tert*-butyldimethyl)silyl chloride (2 equiv) in CH_2Cl_2. When the reaction was complete (followed by TLC), the reaction was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2, and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was then chromatographed to give **7** (87% yield) as colorless oil: TLC R_f = 0.35 (100% petroleum ether); ^{1}H NMR δ 5.02 (s, 1H), 4.81 (s, 1 H), 4.07 (s, 2H), 2.01 (t, *J* = 6.6 Hz, 2H), 1.27−1.97 (m, 25H), 0.08 (s, 6H), 0.13−0.94 (s, 9H), 1.27−1.97 (m, 25H); ^{13}C NMR δ C 148.8, CH_2 108.2, 65.9, 32.8, 32.0, 29.7, 29.6, 29.6, 29.4, 27.9, 22.7, 18.4, CH_3 25.9, 14.1; IR cm^{-1} 2926 (s), 2854 (s), 1655 (w), 1463 (m). Anal. Calcd for $C_{22}H_{46}OSi$: C, 74.50; H, 13.07. Found: C, 74.25; H, 13.15.

2-Trityloxymethylpentadec-1-ene (8). To a solution of triphenylmethyl chloride (4.17 g, 15.0 mmol) and DBU (2.66, 17.5 mmol) in 25 mL of CH_2Cl_2 at room temperature was added alcohol **6** (2.59 g, 10.8 mmol). The mixture was stirred at room temperature for 18 h. The reaction mixture was partitioned between CH_2Cl_2 and H_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to give **8** (5.60 g, 11.6 mmol, 93% yield) as a thick colorless oil: TLC R_f = 0.38, 100% petroleum ether; ^{1}H NMR δ 7.40−7.51 (m, 5H), 7.22−7.34 (m, 10H), 5.32 (d, *J* = 1.4 Hz, 1H), 5.02 (s, 1H), 3.63 (s, 2H), 2.02 (t, *J* = 6.8 Hz, 2H), 1.11−1.34 (m, 20H), 0.89−0.94 (m, 5H); ^{13}C NMR δ C 146.9, 144.3, CH_2 128.7, 127.7, 126.9, 109.4, 66.5, 33.6, 31.9, 29.5, 29.4, 27.7, 22.7, CH_3 14.1; IR cm^{-1} 3426 (bw), 2925 (s), 1448 (m). Anal. Calcd for $C_{35}H_{46}O$: C, 87.08; H, 9.60. Found: C, 87.20; H, 9.75.

3-*tert*-Butyldimethylsiloxy-2-methylpentadecene (9). The same procedure was used as for the synthesis of **7** to obtain **9** as a clear oil (76% yield): TLC R_f = 0.85 (100% petroleum ether): ^{1}H NMR δ 4.81 (s, 1H), 4.72 (s, 1H), 4.01 (t, *J* = 6.7 Hz, 1H), 1.73 (s, 3H), 1.34−1.62 (m, 8H), 0.86−0.93 (m, 5H), 0.90 (s, 9H), 0.045 (s, 6H); ^{13}C NMR δ C 148.1, CH 76.9, CH_2 110.4, 36.4, 32.0, 29.7, 29.6, 29.5, 25.6, 22.7, 18.4, CH_3 25.9, 17.2, 14.1; IR cm^{-1} 2923 (s), 2852 (m), 1713 (w), 1447 (w). Anal. Calcd for $C_{22}H_{46}OSi$: C, 74.50; H, 13.22; O. Found: C, 74.32; H, 13.20.

General Preparation of Dibromides 10−12. Bromine (1.0 equiv) was added to the substrate in dry ether (0.1 M) at −78 °C under nitrogen. When bromination was complete (followed by TLC), the reaction mixture was quenched with 10% $Na_2S_2O_3$ and then extracted with EtOAc. The organic extract was combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was then chromatographed to give the corresponding dibromide (**13**, 75% yield; **14**, 65% yield; **15**, 80% yield). The dibromide was dried by azeotroping with toluene under reduced pressure.

General Preparation of Cyclopentenes 13, 14, and 15a,b. The dibromide in ether (0.1 M) was cooled to −78 °C under nitrogen, and KHMDS (2.5 equiv) was added dropwise. The reaction was allowed to warm to room temperature and then allowed to stir for 18 h. The reaction mixture was then partitioned between saturated aqueous $NaHCO_3$ and EtOAc, and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to give the cyclopentene products as colorless oils.

1-*tert*-Butyldimethylsilyloxymethyl-3-decylcyclopentene (13): TLC R_f = 0.43 (100% petroleum ether); ^{1}H NMR δ 5.49 (bs, 1H), 4.23 (s, 2H), 2.64 (s, 1H), 2.01−2.10 (m, 3H), 1.10−1.54 (m, 19H), 0.89 (s, 9H), 0.83−0.89 (m, 3H), 0.04 (s, 6H); ^{13}C NMR δ 129.2, 62.6, 45.4, 36.1, 31.9, 30.4, 29.9, 29.7, 29.4, 28.0, 22.7, 18.4, 14.1, −5.3; IR cm^{-1} 2924 (s), 2853 (m), 1077 (w). Anal. Calcd for $C_{22}H_{44}OSi$: C, 74.92; H, 12.58. Found: C, 74.83; H, 12.45.

1-Trityloxymethyl-3-decylcyclopentene (14): TLC R_f = 0.38 (100% petroleum ether); ^{1}H NMR δ 7.41−7.52 (m, 6H), 7.21−7.34 (m, 9H), 5.73 (bs, 1H), 3.61 (s, 2H), 2.74 (s, 1H), 2.20−2.32 (m, 1H), 2.01−2.20 (m, 1H), 1.34−1.55 (m, 20H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR δ 144.3, 141.1, 129.9, 128.6, 127.7, 126.9, 63.5, 45.5, 36.2, 32.6, 31.9, 30.2, 29.9, 29.7, 29.7, 29.4, 28.0, 22.7; IR cm^{-1} 2927 (s), 2855 (m), 1650 (w). Anal. Calcd for $C_{35}H_{44}O$: C, 87.45; H, 9.23. Found: C, 87.38; H, 9.15.

3-Decyl-5-*tert*-butyldimethylsilyloxy-1-methylcyclopentene (15a): TLC R_f = 0.45 (100% petroleum ether); ^{1}H NMR δ 5.39 (d, *J* = 1.4 Hz, 1H), 4.51−4.62 (m, 1H), 2.40−2.54 (m, 1H), 1.74 (s, 3H), 1.21−1.64 (15H), 0.90−1.01 (m, 6H), 0.93 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), ^{13}C NMR δ 141.92, 130.78, 79.30, 42.43, 41.85, 36.69, 31.95, 29.86, 29.69, 29.37, 29.06, 27.86, 25.92, 22.72, 18.23, 14.12, 13.73; IR cm^{-1} 3390 (bw), 2926 (s), 2854 (s), 1712 (bs), 1463 (m). Anal. Calcd for $C_{22}H_{44}OSi$: C, 74.92; H, 12.58. Found: C, 74.80; H, 12.65.

3-Decyl-5-*tert*-butyldimethylsilyloxy-1-methylcyclopentene (15b): TLC R_f = 0.30 (100% petroleum ether); ^{1}H NMR δ 5.41 (d, *J* = 0.81 Hz, 1H), 4.62−4.75 (m, 1H), 2.73 (s, 1H), 1.72 (s, 3H), 1.64−1.93 (m, 2H), 1.26−1.37 (m, 18H), 0.83−0.94 (m, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR δ 141.16, 132.25, 79.66, 43.04, 41.37, 36.65, 31.91, 29.86, 29.66, 29.33, 28.03, 25.94, 22.68, 18.31, 14.10, 13.92; IR cm^{-1} 3366 (bw), 2925 (s), 2854 (s), 1712 (m), 1376 (m). Anal. Calcd for $C_{22}H_{44}OSi$: C, 74.92; H, 12.58. Found: C, 74.72; H, 12.40.

General Procedure for Coupling Bromides with 2-Methylallylmagnesium Chloride. 2-Methyl-7-phenoxyhept-1-ene (16). To a flask containing 4-phenoxybutyl bromide (10.4 g, 45.0 mmol), CuI (857 mg, 50.0 mmol), and anhydrous Et_2O (220 mL) at 0 °C was added 2-methylallylmagnesium chloride (100 mL, 50.0 mmol, 0.5 M in THF) dropwise over 10 min. The mixture was stirred at ambient temperature for 2 h. The mixture was poured into saturated aqueous NH_4Cl (400 mL) followed by the addition of Et_2O (200 mL). The mixture was filtered through a bed of Celite using Et_2O (100 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure. The residual oil was chromatographed to obtain **16** (7.2 g, 35.3 mmol, 78% yield) as a clear oil: TLC R_f (5% EtOAc/hexane) = 0.73; ^{1}H NMR δ 1.39−1.57 (m, 4H), 1.72 (s, 1H), 1.80 (t, *J* = 7.0 Hz, 2H), 2.04 (t, *J* = 6.6 Hz, 2H), 3.95 (t, *J* = 6.5 Hz, 2H), 4.69 (dd, *J* = 7.2 Hz, *J* = 0.8 Hz, 2H), 6.83−6.96 (m, 3H), 7.21−7.32 (m, 2H); ^{13}C NMR δ CH_3: 20.92 CH_2: 24.3, 25.9, 27.8, 36.3, 66.3, 108.5 CH: 113.1, 119.0, 127.9 C: 144.3, 157.7; IR 3072, 2936, 2860, 1649, 1601, 1587 cm^{-1}; MS *m*/*z* 204 (25), 148 (5), 133 (10), 120 (13), 110 (100); calcd for $C_{14}H_{20}O$ 204.151 415, found 204.150 699.

2-(2-Phenoxyethyl)-1-methylcyclopentene (17). To **16** (2.29 mmol) and Et_2O (50 mL) in a 200 mL flask chilled to −78 °C was added bromine (780 mg, 4.90 mmol) dropwise over 5 min with stirring. After 30 min at −78 °C, KHMDS (39.2 mL, 19.6 mmol, 0.5 M in toluene) was added dropwise over 5 min, with stirring, at −78 °C. The mixture was stirred for 17

h at ambient temperature. The reaction mixture was partitioned between Et_2O and, sequentially, saturated aqueous $NaHCO_3$ and H_2O. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil was chromatographed to afford the cyclopentene **17** (0.27 g, 1.32 mmol, 27% yield) as a clear oil: TLC R_f (5% EtOAc/hexane) = 0.73; ^{1}H NMR δ 1.42−1.56 (m, 1H), 1.72 (s, 3H), 1.74−1.92 (m, 2H), 2.15−2.19 (m, 1H), 2.19−2.25 (m, 2H), 2.76−2.89 (m, 1H), 3.98 (t, J = 6.8 Hz, 2H), 5.31 (t, J = 1.7 Hz, 1H), 6.83−6.96 (m, 3H), 7.21−7.28 (m, 2H); ^{13}C NMR δ CH_3: 15.7 CH_2: 29.2, 34.1, 34.3, 65.1 CH: 41.1, 112.9, 118.3, 126.3, 126.9 C: 139.0, 157.6; IR 3039, 2934, 1600, 1497, 1245 cm^{-1}; MS *m*/*z* 202 (18), 109 (50), 108 (100), 107 (15); calcd for $C_{14}H_{18}O$ 202.135 765, found 202.136 123.

General Procedure for the Bromination of Alkenes. 1,2-Dibromo-2-methyl-7-phenoxyheptane (18). To a 100 mL flask containing **16** (1.5 g, 7.35 mmol) and Et_2O (50 mL) at −50 °C was added bromine (1.18 g, 7.35 mmol) dropwise over 5 min. The solution was stirred at −50 °C for 30 min. The reaction mixture was partitioned between Et_2O and, sequentially, saturated aqueous $NaHCO_3$ and H_2O. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil was chromatographed to afford **18** (2.5 g, 6.87 mmol, 93%) as a clear oil: TLC R_f (5% EtOAc/hexane) = 0.62; ^{1}H NMR δ 1.42−1.63 (m, 4H), 1.78−1.97 (m, 7H), 3.83 (q, J = 10.5, 2H), 3.97 (t, J = 6.6, 2H), 6.83−6.97 (m, 3H), 7.22−7.31 (m, 2H); ^{13}C NMR δ CH_3: 29.2 CH_2: 24.2, 24.4, 27.6, 40.6, 40.9, 66.2 CH: 113.0, 119.1, 127.9 C: 66.4, 157.6; IR 2940, 2864, 1600, 1586, 1497, 1471 cm^{-1}. MS *m*/*z* 366 (4), 364 (8), 362 (4), 135 (4), 133 (5), 119 (9), 117 (10), 109 (100); calcd for $C_{14}H_{20}Br_2O$ 361.988 088, found 361.987 000.

(*E*/*Z*)-1-Bromo-2-methyl-7-phenoxyhept-1-ene (19). A flask containing a stirring solution of **18** (3.0 g, 8.3 mmol), DBU (3.1 g, 20.2 mmol), and benzene (30 mL) was heated to reflux for 7 h. The cooled solution was acidified to pH = 2 using 1 N aqueous HCl. The reaction mixture was partitioned between Et_2O and H_2O. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil was chromatographed to afford **21** (2.3 g, 8.1 mmol, 98% yield) as a clear oil: TLC R_f (5% EtOAc/hexane) = 0.62; ^{1}H NMR δ 1.39−58 (m, 4H), 1.71−1.86 (m, 5H), 2.09−2.29 (m, 2H), 3.91−4.02 (m, 2H), 5.89 (d, J = 1.2 Hz, 1H), 6.82−7.01 (m, 3H), 7.21−7.34 (m, 2H); ^{13}C NMR δ (major isomer) CH_3 17.5, OCH_2 66.1, =CHBr 99.7, (minor isomer) CH_3 20.6, OCH_2 66.2, =CHBr 99.2; IR 2938, 2860, 1600, 1497, 1472 cm^{-1}; MS *m*/*z* 384 (10), 282 (10), 135 (16), 133 (16), 109 (100); calcd for $C_{14}H_{19}BrO$ 282.061 926, found 282.061 290.

2-Methyl-8-phenoxy-1-octene (20). The same procedure was used as in the synthesis of **16** (3.3 g, 15.1 mmol, 92% yield) to yield **20** as a clear oil: TLC R_f (5% EtOAc/hexane) = 0.75; ^{1}H NMR δ 1.29−1.53 (m, 6H), 1.71 (s, 3H), 1.79 (m, 2H), 2.01 (m, 2H), 3.95 (t, J = 6.6 Hz, 2H), 6.88−6.92 (m, 3H), 7.24−7.30 (m, 2H); ^{13}C NMR δ CH_3 20.9, CH_2 24.5, 26.1, 27.6, 27.8, 28.8, 36.3, 108.3, CH 113.0, 119.0, 127.9, C 144.5, 157.7; IR 3071, 2932, 2857, 1648, 1601, 1586 cm^{-1}; MS R_f 218 (10), 162 (2), 124 (22), 109 (13), 95 (28), 91 (100); calcd for $C_{15}H_{22}O$ 218.167 066, found 218.166 603.

(*E*/*Z*)-1-Bromo-2-methyl-8-phenoxy-oct-1-ene (21). A flask containing a stirring solution of **29** (15.0 g, 39.6 mmol), DBU (14.7 g, 96.4 mmol), and benzene (150 mL) was heated to reflux for 7 h. The cooled solution was acidified to pH = 2 using 1 N aqueous HCl. The reaction mixture was partitioned between Et_2O and H_2O. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil was chromatographed to afford **21** (8.5 g, 28.6 mmol, 72% yield) as a clear oil: TLC R_f (5% EtOAc/hexane) = 0.69; ^{1}H NMR δ 1.27−1.52 (m, 6H), 1.71−1.82 (m, 5H), 2.11−2.28 (m, 2H), 3,82−3.96 (m, 2H), 5.88 (d, J = 1.1 Hz, 1H), 6.82−6.92 (m, 3H), 7.23−7.29 (m, 2H); ^{13}C NMR δ (major isomer) CH_3 17.5, OCH_2 66.3, =CHBr 99.5, (minor isomer) CH_3 20.6, OCH_2 66.2, =CHBr 99.0; IR 2935, 2857, 1600, 1496, 1470, 753 cm^{-1}; MS *m*/*z* 298 (8), 296 (8), 123 (23), 122 (13), 94 (100); calcd for $C_{15}H_{21}BrO$ 296.077 58, found 296.076 303.

General Procedure for Cyclization of 1,1-Disubstituted Alkenes. 3-(3-Phenoxypropyl)-1-methylcyclopentene (22). To 1,1-disubstituted alkene **20** (2.29 mmol) and 3/1 *p*-dioxane/DME (50 mL) in a 200 mL flask chilled to −20 °C was added bromine (366 mg, 2.29 mmol) dropwise over 5 min with stirring. After 30 min at −20 °C, KHMDS (13.8 mL, 6.90 mmol, 0.5 M in toluene) was added dropwise over 5 min, with stirring, at −20 °C. The mixture was stirred for 48 h at −20 °C. The reaction mixture was partitioned between Et_2O and, sequentially, saturated aqueous $NaHCO_3$ and H_2O. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil was chromatographed to afford the cyclopentene **22** (0.26 g, 1.21 mmol, 53% yield) as a clear oil: TLC R_f (5% EtOAc/hexane) = 0.75; ^{1}H NMR δ 1.34−1.57 (m, 3H), 1.72 (s, 3H), 1.75−1.83 (m, 2H), 2.01−2.18 (m, 1H), 2.19−2.25 (m, 2H), 2.66 (bs, 1H), 3.95 (t, J = 6.6 Hz, 2H), 5.29 (s, 1H), 6.82−2.96 (m, 3H), 7.21−7.31 (m, 2H); ^{13}C NMR δ CH_3 15.2, CH_2 26.1, 29.3, 31.2, 34.9, 66.5, CH 44.1, 113.0, 118.9, 127.1, 127.9, C 138.9, 157.6; IR 3037, 2937, 1609, 1586, 1497, 880 cm^{-1}; MS *m*/*z* 216 (53), 123 (70), 122 (100), 120 (75), 107 (66); calcd for $C_{15}H_{20}O$ 216.151 415, found 216.149 759.

8-Methylnon-8-en-1-ol (23). The same procedure was used as in the synthesis of **16** (5.7 g, 36.5 mmol, 66% yield) to yield **23** as a clear oil: TLC R_f (30% EtOAc/hexane) = 0.45; ^{1}H NMR δ 1.21−1.41 (m, 9H), 1.50−1.61 (m, 2H), 1.71 (s, 3H), 2.00 (t, J = 7.2 Hz, 2H), 3.64 (t, J = 6.6 Hz, 2H), 4.67 (d, J = 7.7 Hz, 2H); ^{13}C NMR δ CH_3 20.7, CH_2 23.8, 24.1, 25.8, 25.9, 27.7, 31.0, 36.2, 108.1, C 144.3; IR 3334, 3073, 2930, 2856, 1649, 885 cm^{-1}; MS *m*/*z* 156 (3), 141 (3), 138 (13), 123 (100), 110 (58), 109 (61); calcd for $C_{10}H_{20}O$ 156.151 415, found 156.150 419.

9-Benzyloxy-2-methyl-1-nonene (24). To a flask containing **23** (3.0 g, 19.2 mmol) and DMF (5 mL) was added sodium hydride (770 mg, 19.2 mmol, 60% in mineral oil) portionwise. After the white suspension was stirred for 30 min at 25 °C, benzyl bromide (3.3 g, 19.2 mmol) was added dropwise over 10 min. The mixture was stirred at 25 °C for 17 h. The reaction mixture was partitioned between Et_2O and, sequentially, H_2O and brine. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil was chromatographed to obtain **24** (3.5 g, 14.2 mmol, 74% yield) as a clear oil: TLC R_f (5% EtOAc/hexane) = 0.73; ^{1}H NMR δ 1.22−1.48 (m, 8H), 1.54−1.63 (m, 2H), 1.70 (s, 3H), 1.99 (t, J = 7.1 Hz, 2H), 3.46 (t, J = 6.6 Hz, 2H), 4.50 (s, 2H), 4.67 (d, J = 7.5 Hz, 2H), 7.24−7.34 (m, 5H); ^{13}C NMR δ CH_3 20.9, CH_2 24.7, 26.1, 27.8, 27.9, 28.1, 36.3, 70.1, 71.4, 108.1, CH 125.9, 126.1, 126.8, 127.3, 127.5, C 137.2, 144.6; IR 3068, 3029, 2930, 2855, 1648, 1454 cm^{-1}; MS *m*/*z* 246 (2), 137 (49), 131 (20), 108 (22), 107 (100), 106 (24); calcd for $C_{17}H_{26}O$ 246.198 366, found 246.197 659.

3-(4-Benzyloxybutyl)-1-methylcyclopentene (25). The same procedure was used as in the synthesis of **22** (0.28 g, 1.16 mmol, 57% yield) to yield **25** as a clear oil: TLC R_f (5% EtOAc/hexane) = 0.73; ^{1}H NMR δ 1.19−1.29 (m, 1H), 1.30−1.43 (m, 4H), 1.57−1.63 (m, 2H), 1.70 (s, 3H), 1.99−2.09 (m, 1H), 2.19 (bs, 2H), 2.59 (bs, 1H), 3.46 (t, J = 6.6 Hz, 2H), 4.49 (s, 2H), 5.26 (s, 1H), 7.21−7.33 (m, 5H); ^{13}C NMR δ CH_3 15.2, CH_2 23.1, 28.5, 28.6, 29.3, 34.8, 69.0, 71.4, CH 44.3, 125.9, 126.1, 126.3, 126.6, 126.8, 127.5, C 137.2, 138.4; IR 3031, 2930, 2855, 1453, 820 cm^{-1}; MS *m*/*z* 244 (0.1), 161 (0.5), 153 (100), 135 (61), 107 (57); calcd for $C_{17}H_{24}O$ 244.182 716, found 244.182 412.

9-Benzyloxy-1,2-dibromo-2-methylnonane (26). The same procedure was used as in the synthesis of **18** (7.1 g, 17.4 mmol, 87% yield) to yield **26** as a clear oil: TLC R_f (5% EtOAc/hexane) = 0.67; ^{1}H NMR δ 1.28−1.41 (m, 7H), 1.41−1.52 (m, 2H), 1.52−1.65 (m, 2H), 1.84 (s, 3H), 1.85−1.89 (m, 1H), 3.47 (t, J = 6.5, 2H), 3.84 (q, J = 10.2 Hz, 2H), 4.50 (s, 2H), 7.25−7.35 (m, 5H); ^{13}C NMR δ CH_3 29.2, CH_2 23.9, 24.6, 27.8, 28.2, 40.7, 41.0, 69.0, 71.4, CH 125.9, 126.1, 126.8, C 66.7, 137.2; IR 2933, 2855, 1453, 1378, 1101 cm^{-1}; MS *m*/*z* 298 (8), 296 (8), 123 (23), 122 (130, 94 (100); calcd for $C_{15}H_{21}BrO$ 296.077 58, found 296.076 303.

1-(8-Methylnon-8-en-1-oxy)dodecane (27). To a flask containing **23** (3.0 g, 19.2 mmol) and DMF (5 mL) was added sodium hydride (770 mg, 19.2 mmol, 60% in mineral oil) portionwise. After the white suspension was stirred for 30 min

at 25 °C, 1-bromododecane (4.7 g, 19.2 mmol) was added dropwise over 10 min. The mixture was stirred at 25 °C for 17 h. The reaction mixture was partitioned between Et_2O and, sequentially, H_2O and brine. The combined organic extract was dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil was chromatographed to obtain **27** (5.2 g, 14.1 mmol, 73% yield) as a clear oil: TLC R_f (5% EtOAc/hexane) = 0.77; ^{1}H NMR δ 0.88 (t, J = 6.9 Hz, 3H), 1.26−1.44 (m, 26H), 1.52−1.59 (m, 4H), 1.71 (s, 3H), 2.00 (t, J = 7.1 Hz, 2H), 3.39 (t, J = 6.7 Hz, 4H), 4.66 (d, J = 6.7 Hz, 2H); ^{13}C NMR δ CH_3 12.54, 20.79, CH_2 21.14, 24.63, 24.68, 26.02, 26.65, 27.24, 27.41, 27.68, 27.72, 27.82, 27.84, 27.91, 28.09, 28.11, 28.14, 28.26, 32.26, 69.37, 108.01, C 144.52; IR 3074, 2925, 2854, 1649, 1466 cm^{-1}; MS m/z 324 (10), 169 (39), 166 (11), 139 (27), 138 (100); calcd for $C_{22}H_{44}O$ 324.339 26, found 324.338 875.

3-(4-Dodecanoxybutyl)methyl-1-cyclopentene (28). The same procedure was used as in the synthesis of **22**: (0.29 g, 0.80 mmol, 59% yield), clear oil: TLC R_f (5% EtOAc/hexane) = 0.77; ^{1}H NMR δ 0.88 (t, J = 6.3 Hz, 3H), 1.19−1.42 (m, 23H), 1.54−1.62 (m, 4H), 1.71 (s, 3H), 2.01−2.12 (m, 1H), 2.17−2.22 (m, 2H), 2.6 (bs, 1H), 3.39 (t, J = 6.8 Hz, 2H), 3.40 (t, J = 6.7 Hz, 2H), 5.26 (t, J = 1.7 Hz, 1H); ^{13}C NMR δ CH_3 12.6, 15.2, CH_2 21.2, 23.0, 24.7, 26.4, 27.8, 28.0, 28.11, 28.12, 28.16, 28.27, 28.5, 29.3, 30.4, 34.8, 34.9, 69.40, 69.44, CH 44.3, 127.5, C 138.4; IR 2925, 2854, 1458, 1376, 1117 cm^{-1}; MS m/z 322 (0.2), 279 (0.2), 153 (1.4), 136 (41), 107 (100); calcd for $C_{22}H_{42}O$ 322.323 566, found 322.322 845.

1,2-Dibromo-2-methyl-8-phenoxyoctane (29). The same procedure was used as in the synthesis of **20** (28.0 g, 74.0 mmol, 82% yield) to yield **29** as a clear oil: TLC R_f (5% EtOAc/hexane) = 0.69; ^{1}H NMR δ 1.37−1.59 (m, 6H), 1.76−1.94 (m, 7H), 3.85 (q, J = 10.3 Hz, 2H), 3.96 (t, J = 6.5 Hz, 2H), 6.75−6.95 (m, 3H), 7.25−7.37 (m, 2H); ^{13}C NMR δ CH_3 29.15, CH_2 23.9, 24.4, 27.3, 27.7, 40.6, 40.9, 66.1, CH 112.9, 119.0, 127.9, C 66.5, 157.5; IR 2938, 1600, 1585, 1472, 1247, 813 cm^{-1}. This material decomposed on attempted mass spectrometric analysis.

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Supporting Information Available: ^{1}H and ^{13}C spectra for compounds **16**−**28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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