Cyclization of (4-Methoxy-5-hexenyl)lithium

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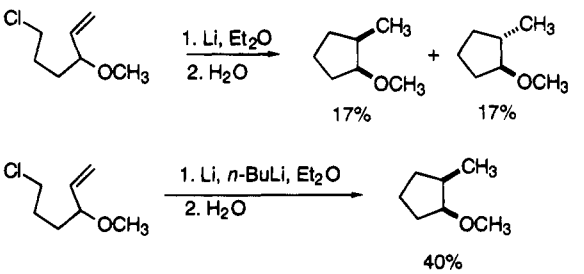
The cyclization of (4-methoxy-5-hexenyl)lithium (**1**), which was prepared by lithium–iodine exchange between 3-methoxy-6-iodo-1-hexene (**2**) and 1.75 molar equiv of *t*-BuLi in diethyl ether–*n*-pentane solution at −78 °C, has been investigated in a variety of solvent systems. The isomeric composition of the *cis*- and *trans*-1-methoxy-2-methylcyclopentane produced upon cyclization of **1** followed by quench with MeOH has been found to be dramatically dependent on the solvent system in which the isomerization is conducted.

The facile cyclization of alkyl-substituted 5-hexenyllithiums provides a convenient and highly diastereoselective route to functionalized cyclopentane-containing products.[1] The stereocontrol inherent in such isomerizations has been attributed to a fairly rigid transition state for the process, shown below for a 4-substituted 5-hexenyllithium, that resembles a chair cyclohexane in which an alkyl substituent preferentially occupies a pseudoequatorial position.[2] Molecular orbital calculations at the 3-21G level suggest that this transition-state geometry is a consequence of energetically favorable coordination of the lithium atom at C(1) with the C(5)–C(6) π-bond.[2] Much less information is available on the cyclization of 5-hexenyllithiums bearing heteroatomic substituents capable of coordination with lithium.[3] Herein we report the results of a study of the isomerization of (4-methoxy-5-hexenyl)lithium (**1**). As shown below, the stereochemical outcome of the ring-closure of **1** is strongly dependent on the solvent system in which the isomerization is conducted.

Some time ago, Smith and Wilson reported that treatment of 6-chloro-3-methoxy-1-hexene with lithium metal in diethyl ether, following quench with water, provided a low yield of *cis*- and *trans*-1-methoxy-2-methylcyclopentane as a 1:1 mixture of isomers.[4] It was further reported that the reaction was totally stereoselective when conducted in the presence of 1 molar equiv of *n*-BuLi giving, as shown below, a 40% yield of *cis*-1-methoxy-2-methylcyclopentane.[4] Since the (4-methoxy-5-hexenyl) radical was a probable intermediate in these reactions,[5] it is not clear whether the observations reported by Smith and Wilson were a result of cyclization of the organolithium or the radical intermediate.[6] In order to assess the stereochemistry of the cyclization of (4-methoxy-5-hexenyl)lithium (**1**), it is desirable to generate the organometallic by a process that does not involve single-electron transfer. To this end, we have prepared **1** from the corresponding iodide by low-temperature lithium–iodine exchange.[7]



Results and Discussion

The requisite substrate, 6-iodo-3-methoxy-1-hexene (**2**), was prepared as summarized in Scheme 1. Treatment of an approximately 0.1 M solution of **2** in *n*-pentane–diethyl ether (or pure diethyl ether) at −78 °C with 1.75 molar equiv of *t*-BuLi gave (4-methoxy-5-hexenyl)lithium (**1**) as demonstrated by the fact that quench of such a reaction mixture delivered 3-methoxy-1-hexene (**3**) in virtually quantitative yield.

It should be noted that, although 2 molar equiv of *t*-BuLi is typically used to accomplish lithium–iodine

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(3) The isomerization of (2-oxa-, (3-oxa-, and (4-oxa-5-hexenyl)-lithiums has been investigated and such systems appear to cyclize via a chair-like transition state. See: (a) Broka, C. A.; Shen, T. *J. Am. Chem. Soc.* **1989**, *111*, 2981. (b) Bailey, W. F.; Zarcone, L. M. J. *Tetrahedron Lett.* **1991**, *32*, 4425. (c) Bailey, W. F.; Punzalan, E. R.; Zarcone, L. M. J. *Heteroat. Chem.* **1992**, *3*, 55.

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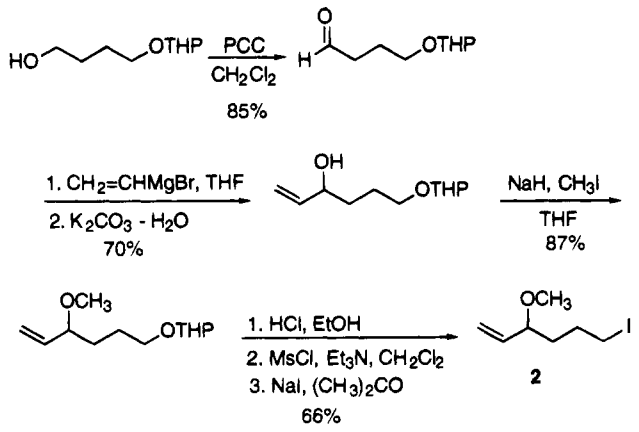
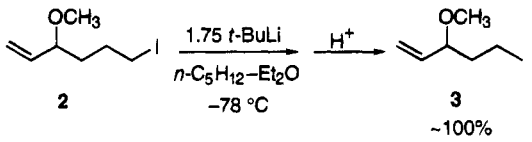
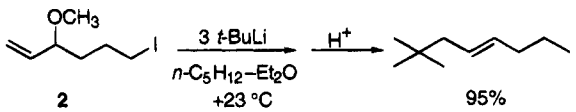
Scheme 1



exchange,[8] it was necessary in the present case to use less than the optimal quantity of the reagent so as to minimize a fairly rapid S_N' addition of excess *t*-BuLi to **1** at elevated temperatures. Indeed, as shown below, (*E*)-

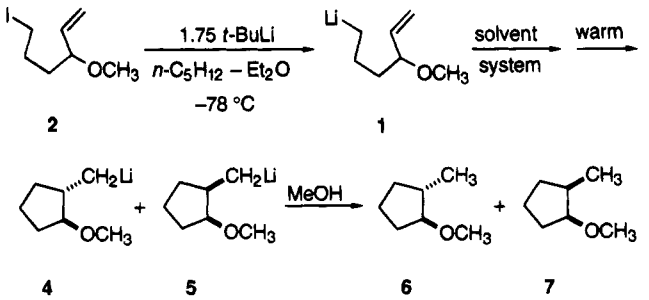


2,2-dimethyl-4-octene is produced in 95% yield when **2** is treated with 3 equiv of *t*-BuLi at −78 °C and the reaction mixture is warmed to room temperature. Fortunately, it proved possible, as noted above, to prepare **1** uncontaminated with the addition product since the exchange is complete well before the S_N' reaction ensues. Unfortunately, some *tert*-butyl iodide, cogenerated with **1** in the exchange reaction, remains in the reaction mixture when less than 2 equiv of *t*-BuLi is used to generate **1** and this proton source results in inadvertent quench of a quantity of the organolithium.[8] Consequently, the yield of **1** from the exchange between **2** and 1.75 equiv of *t*-BuLi is less than quantitative.



The isomerization of **1** was investigated, as illustrated in Scheme 2, by allowing preformed solutions of the olefinic alkyllithium, generated either in *n*-pentane–diethyl ether mixtures or in pure diethyl ether, to warm and stand at various temperatures for 1 h prior to quench with deoxygenated MeOH. The proportions of (*trans*- and (*cis*-(2-methoxycyclopentyl)methyl)lithium (**4** and **5**, respectively) formed upon ring closure of **1** were assayed as *trans*- and *cis*-1-methoxy-2-methylcyclopentane[9] (**6** and **7**, respectively) by capillary GC using *n*-heptane as internal standard. The effect of various Lewis base additives on the stereochemistry of the cyclization of **1** was probed in a separate series of experiments in which

Scheme 2



THF or *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) was added at −78 °C to solutions of **1** prior to warming of the organolithium. The results of these experiments are summarized in Table 1.

Inspection of the data presented in Table 1 reveals that the cyclization of **1** in solutions of *n*-pentane–diethyl ether (Table 1, entries 1–7 and 9) or pure diethyl ether (Table 1, entry 10) leads to a preponderance of (*trans*-(2-methoxycyclopentyl)methyl)lithium (**4**). Not surprisingly, the isomerization is more diastereoselective at lower temperatures (Table 1, *cf.* entries 1 through 6). Contrary to the observation of Smith and Wilson,[4] the presence of 1 molar equiv of *n*-BuLi has little, if any, effect on the stereochemical outcome of the ring-closure of **1** (Table 1, *cf.* entries 3 and 8). In short, the behavior of **1** in these solvent systems is analogous to that of 4-alkyl-substituted 5-hexenyllithiums:[2] the data (Table 1, entries 1–10) provide no evidence for coordination of the Li atom at C(1) with the oxygen atom of the C(4) substituent. Indeed, the trans-selective nature of the cyclization **1** is nicely accommodated by a chair-like transition state in which the 4-methoxy substituent preferentially occupies a pseudoequatorial position.

The stereochemistry of the isomerization of **1** is profoundly affected by the presence of THF or TMEDA in the reaction medium. These lithiophilic Lewis bases, which facilitate the cyclization of 5-hexenyllithiums, have been found to have little effect on the diastereoselectivity of the ring-closure of alkyl-substituted substrates.[2] It is somewhat surprising, therefore, that the cyclization of **1** in the presence of 1.75 molar equiv of TMEDA is cis-selective (Table 1, entries 11–13). THF has a similar, albeit more modest, effect on the stereochemistry of the isomerization of **1** (Table 1, entries 14 and 15). Significantly more THF than TMEDA is required to reverse the trans-selectivity observed for cyclizations in pentane–ether, but as little as 1.75 equiv of THF in the solvent system decreases the trans/cis ratio of the 1-methoxy-2-methylcyclopentane product from 7.7 to 3.0 at 0 °C (Table 1, *cf.* entries 3 and 14). The possibility that the unexpected cis-selectivity observed for the isomerization of **1** in the presence of TMEDA or THF was due to preferential destruction of the trans isomer (**4**) was considered

(8) Normally 2 molar equiv of *t*-BuLi is employed in the lithium–iodine exchange to ensure complete conversion of RCH_2I to RCH_2Li. The exchange equilibrium is rendered operationally irreversible by the use of 2 equiv of *t*-BuLi since an equiv of the reagent rapidly consumes the *t*-BuI generated in the reaction to give isobutane, isobutylene, and lithium iodide.[7] When less than a full 2 molar equiv of *t*-BuLi is used, the residual *t*-BuI remaining in the reaction mixture serves as a proton source and leads to rapid quench of the organolithium product: $RCH_2Li + (CH_3)_3CI \rightarrow RCH_3 + (CH_3)_2C{=}CH_2 + LiI$.

(9) Authentic samples of *trans*-1-methoxy-2-methylcyclopentane (**6**) and *cis*-1-methoxy-2-methylcyclopentane (**7**) were independently prepared from the corresponding alcohols (NaH, CH_3I, THF). Pure *trans*-2-methylcyclopentanol was prepared by hydroboration–oxidation of 1-methylcyclopentene using 9-BBN as described by Brown and coworkers [Brown, H. C.; Liotta, R.; Brener, L. *J. Am. Chem. Soc.* **1977**, *99*, 3427]. Pure *cis*-2-methylcyclopentanol was prepared by reduction of 2-methylcyclopentanone using L-Selectride as previously described [Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159].

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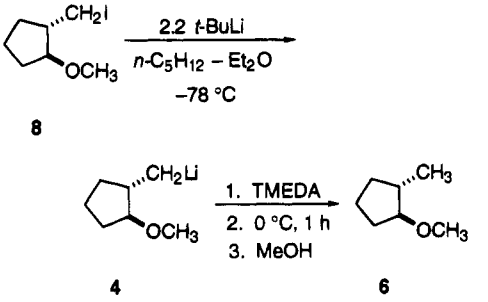
Table 1. Cyclization of (4-Methoxy-5-hexenyl)lithium (1)[a]

entry	solvent system	temp, °C	products, % yield[b] 3	6 + 7	trans/cis[c]
1	n-C_5H_{12}–Et_2O 3:2 by vol	22	7.3	88.6	3.9
2		10	20.9	67.2	6.9
3		0	12.1	88.1	7.7
4		−10	44.7	55.5	11.3
5		−20	49.0	47.8	19.8
6		−30	73.9	22.0	21.9
7		−78	~100		
8	1 equiv of n-BuLi[d]	0	18.6	75.5	7.3
9	n-C_5H_{12}–Et_2O 9:1 by vol	0	25.1[e]	63.7	4.6
10	Et_2O	0	36.0	65.4	11.1
11	TMEDA[f]	20	18.3[g]	73.6	0.34
12		0	22.2	74.5	0.25
13		−20	10.0[h]	74.4	0.25
14	THF[i]	0	49.6	49.0	3.0
15	THF[j]	0	9.7[k]	77.1	0.66

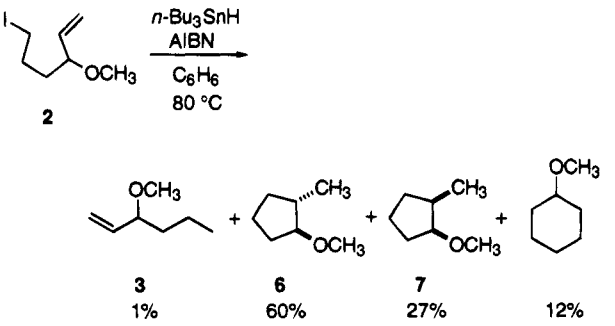
[a] (4-Methoxy-5-hexenyl)lithium (**1**) was generated at −78 °C by addition of 1.75 equiv of *t*-BuLi to a solution of iodide **2** in either *n*-pentane–diethyl ether or pure diethyl ether. Where indicated, TMEDA or THF was added at −78 °C. The cooling bath was then removed, and the mixture was allowed to stand at the specified temperature for 1 h before the addition of an excess of oxygen-free methanol. [b] Yields were determined by capillary GC using *n*-heptane as internal standard and correction for detector response. [c] Ratio of *trans*- (**6**) and *cis*-2-methoxy-1-methylcyclopentane (**7**) with an assumed error of ~±10%. [d] *n*-BuLi in hexane (1 molar equiv) was added at −78 °C to a solution of **1** in n-C_5H_{12}–Et_2O (3:2 by vol), and the mixture was allowed to warm and stand at 0 °C for 1 h. [e] Product mixture contained 8% of 2,2-dimethyl-4-octene. [f] TMEDA (1.75 molar equiv) was added to a solution of **1** in n-C_5H_{12}–Et_2O (3:2 by vol), and the mixture was allowed to warm and stand at the specified temperature for 1 h. [g] Product mixture contained 4% of 2,2-dimethyl-4-octene. [h] Product mixture contained 6% of 2,2-dimethyl-4-octene. [i] THF (1.75 molar equiv) was added to a solution of **1** in n-C_5H_{12}–Et_2O (3:2 by vol), and the mixture was allowed to warm and stand at 0 °C for 1 h. [j] THF (72.5 molar equiv) was added. [k] Product mixture contained 10% of 2,2-dimethyl-4-octene.

but excluded on the basis of the high material balance (Table 1, entries 11–15) and the fact that no products other than those reported in Table 1 were detected in reaction mixtures.

A potential complication that must be considered in reviewing these results is the possibility that the isomerization of **1** to give **4** and **5** is a reversible process in the presence of a Lewis base. Were this the case, the distribution of **6** and **7** observed for isomerizations of **1** in the presence of TMEDA (or THF) might reflect the relative stability of **4** and **5** rather than differences in activation energy for the ring-closures. Although a preponderance of evidence indicates that cyclization of 5-hexenyllithiums is an operationally irreversible process,[2] it was deemed imprudent to rely on precedent to exclude the possibility that an initially trans-rich mixture of **4** and **5** had isomerized via reversible ring-opening to give the final cis-rich product composition. In order to address this question, **1** was isomerized at 0 °C in a mixture of *n*-pentane–diethyl ether, the resulting trans-rich ((2-methoxycyclopentyl)methyl)lithium products (Table 1, entry 3) were trapped with iodine, and isomerically pure *trans*-1-methoxy-2-(iodomethyl)cyclopentane (**8**) was isolated in 76% yield from the reaction mixture by preparative GC. Treatment of **8** with *t*-BuLi at −78 °C returned isomerically pure **4**. As shown below, **4** is not isomerized upon standing for 1 h at 0 °C in the presence of TMEDA: quench of the reaction mixture with MeOH delivered isomerically pure **6** in quantitative yield. Thus, the product ratios observed for isomerization of **1** reflect the stereoselectivities of a cyclization process that is kinetically controlled.



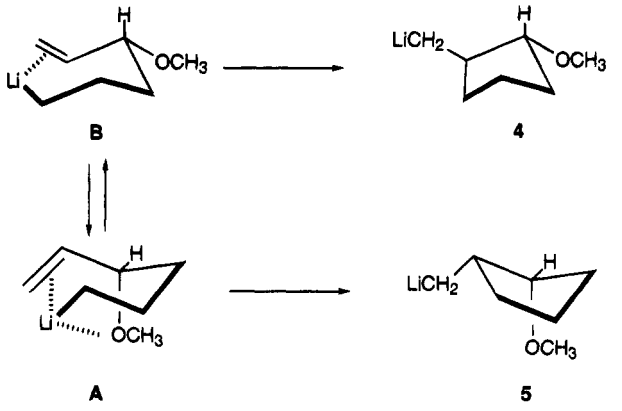
For comparison purposes, the radical-mediated cyclization of **2** was investigated in benzene solution at 80 °C. As expected,[2,6] isomerization of the 4-methoxy-5-hexenyl radical, generated from **2** as shown below, is less selective than is ring-closure of **1**: while both 5-exo (**6**/**7** = 2.2) and 5-endo products are formed in the radical-mediated process, no trace of methoxycyclohexane was observed in any of the experiments involving **1**.



The effect of THF and TMEDA on the stereochemistry of the cyclization of **1** is intriguing. On the reasonable assumption that the ring-closure of **1** involves a chair-like transition state in which the lithium atom is coordinated with the π-bond,[2] the formation of cis product **5** requires the CH_3O group at C(4) to preferentially occupy a pseudoaxial position. It is tempting to speculate, as illustrated in Scheme 3, that cis-selective cyclization of **1** is a consequence of stabilization of the transition state leading to **5** (Scheme 3, **A**) via intramolecular coordination of the lithium atom with the proximal oxygen atom of the ether moiety. However, it is difficult to reconcile this rationale with the effect of variation in the reaction medium on the stereochemistry of the cyclization.

The results summarized in Table 1 demonstrate that solvent systems containing TMEDA or THF, which should coordinate lithium more strongly than do *n*-pentane–diethyl ether mixtures and lessen the relative importance of the putative intramolecular Li–O interaction in transition state **A**, give cis-rich product mixtures. A tentative and highly speculative solution to this apparent dilemma would posit that the Lewis base additives affect the stereochemistry of the cyclization of **1** by sequestering the LiI generated in the exchange reaction used to prepare **1**. It is well known that organolithium compounds co-associate with lithium halides,[13] and it is likely that **1**, whose degree of association under the reaction conditions is unknown, exists as an

Scheme 3



aggregate containing LiI. Intraaggregate coordination of the 4-OCH_3 substituent with LiI might be expected to disrupt the intramolecular Li–O interaction depicted in Scheme 3 for activated complex **A** and result in a trans-selective ring-closure. Preferential complexation of LiI with Lewis base additives[14] may simply serve to remove this impediment to intramolecular stabilization of transition state **A** and result in cis-selective cyclization. This possibility is being investigated.

Although the etiology of the effect of solvent on the stereochemistry of the ring-closure of **1** remains obscure, the results presented above suggest that the diastereoselectivity of the isomerization of 5-hexenyllithiums bearing heteroatomic substituents may be dramatically affected by choice of reaction medium.

Experimental Section

General. General spectroscopic and chromatographic procedures, methods used for the purification of reagents and solvents, and precautions regarding the manipulation of organolithiums have been previously described.[2] NMR spectra were recorded using solutions in $CDCl_3$ unless otherwise noted.

Literature procedures, incorporating some minor modifications, were followed for the preparation of 4-[(tetrahydropyran-2-yl)oxy]-1-butanol,[15] 4-[(tetrahydropyran-2-yl)oxy]butanal,[15] and 1-methylcyclopentene.[16]

6-[Tetrahydropyran-2-yl)oxy]-1-hexen-3-ol. An addition funnel was charged with 100 mL of a 1.0 M solution of vinylmagnesium bromide (0.100 mol) in THF, and the Grignard reagent was added dropwise at room temperature under an atmosphere of nitrogen to a solution of 18.0 g (0.105 mol) of 4-(tetrahydropyranyloxy)butanal[15] in 90 mL of dry THF. The resulting mixture was heated at gentle reflux for 1 h, then cooled in an ice bath, and cautiously hydrolyzed by dropwise addition of 10.0 mL of water followed by 10.0 mL of saturated, aqueous potassium carbonate solution. The mixture was extracted with three 30-mL portions of diethyl ether, the combined ethereal extracts were dried ($MgSO_4$) and concentrated at reduced pressure, and the residue was purified by flash chromatography on silica gel (20% ethyl acetate–hexanes) to give 14.60 g (70%) the title compound: R_f 0.24 (20% ethyl acetate–hexanes); ^1H NMR (two diastereomers) δ 1.49–1.70 (m, 10 H), 2.26 (brs, 1 H), 3.36–3.52 (m, 2 H), 3.73–3.87 (m, 2 H), 4.11–4.15 (m, 1 H), 4.58 (t, J = 3.42 Hz, 1 H), 5.08 (apparent dt, J_{cis} = 10.39 Hz, ^4J = 1.38 Hz, J_{gem} = 1.40 Hz, 1H), 5.22 (apparent dt, J_{trans} = 17.24 Hz, ^4J = 1.47 Hz, J_{gem} = 1.40 Hz, 1 H), 5.85 (ddd, J_{trans} = 17.24 Hz, J_{cis} = 10.39 Hz, ^3J = 5.20 Hz, 1H); ^{13}C NMR (two diastereomers) δ 19.49, 19.53, 25.39, 25.68, 25.81, 30.61, 34.32, 62.24, 62.28, 67.50, 67.54, 72.66, 98.79, 98.84, 114.40, 141.10; IR (neat) 3441, 2938, 1719, 1359, 1029 cm^{-1}; HRMS calcd for $C_{11}H_{18}O_2$ ($M^+ - H_2O$) m/z 182.1307, found m/z 182.1307.

3-Methoxy-6-[(tetrahydropyran-2-yl)oxy]-1-hexene. Following the general procedure of Brown and Barton,[17] a stirred suspension of 1.20 g (50.0 mmol) of oil-free sodium hydride in 25.0 mL of dry THF was heated at 45–50 °C and a solution of 2.54 g (12.7 mmol) of 6-[(tetrahydropyran-2-yl)oxy]-1-hexene-3-ol and 1.60 mL (25.5 mmol) of methyl iodide in 15.0 mL of dry THF was added dropwise over a 30-min period. The resulting mixture was heated at 45–50 °C for an additional 1 h and then cooled in an ice bath, and 8.0 mL of water was cautiously added. The resulting mixture was extracted several times with diethyl ether, and the combined extracts were washed with brine, dried ($MgSO_4$), and concentrated to give an oil which was purified by flash chromatography on silica gel (10% ethyl acetate–hexenes) to afford 2.35 g (87%) of product: ^1H NMR δ 1.48–1.79 (m,10 H), 3.25 (s, 3 H), 3.35–3.39 (m,1 H), 3.45–3.52 (m, 2 H), 3.69–3.83 (m, 2 H), 4.56 (t, J = 3.40 Hz, 1 H), 5.13–5.19 (m, 2 H), 5.59–5.69 (m,1 H); ^{13}C NMR δ 19.52, 25.47, 25.39, 30.69, 32.01, 56.10, 62.14, 67.32, 82.79, 98.68, 117.10, 138.70; IR (neat) 2939, 1451, 1352, 1119, 1033 cm^{-1}; HRMS calcd for $C_7H_{13}O_2$ ($M^+ - C_5H_9O$) m/z 129.0916, found m/z 129.0912.

4-Methoxy-5-hexen-1-ol. The pH of a solution of 2.05 g (10.2 mmol) of 3-methoxy-6-[(tetrahydropyran-2-yl)oxy]-1-hexene in 80.0 mL of ethyl alcohol was adjusted to ~3 by the dropwise addition of 0.1 M aqueous hydrochloric acid. The resulting solution was heated at reflux for 30 min, allowed to cool to room temperature, and then poured into 25 mL of water and extracted with diethyl ether. The ethereal extract was dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (20% ethyl acetate–hexanes) to give 1.01 g (81%) of the title compound: ^1H NMR δ 1.60–1.66 (m, 4 H), 2.25 (br s,1 H), 3.26 (s, 3 H), 3.50 –3.55 (m,1 H), 3.61 (t, J = 6.00 Hz, 2 H), 5.14–5.21 (m, 2 H), 5.58–5.71 (m,1 H); ^{13}C NMR δ 28.68, 32.11, 56.08, 62.65, 82.84, 117.20, 138.30; IR (neat) 3402, 2935, 1422, 928 cm^{-1}. Anal. Calcd for $C_7H_{14}O_2$: C, 64.58 ; H, 10.84. Found: C, 64.21; H, 11.01.

6-Iodo-3-methoxy-1-hexene (2). Following the general procedure of Crossland and Servis,[18] 1.00 g (7.69 mmol) of 4-methoxy-5-hexene-1-ol was converted to its mesylate. The crude mesylate was added to a solution of 2.75 g (18.3 mmol) of dry sodium iodide in 30.0 mL of freshly distilled acetone, and the mixture was stirred at room temperature under and atmosphere of nitrogen for 10 h and then heated at gentle reflux for 45 min. Inorganic salts were then removed by filtration, the solid was washed well with acetone, and the combined filtrate and washings were concentrated by rotary evaporation. The residue was taken up in diethyl ether, and the solution was washed with 5% aqueous sodium thiosuflate solution and dried ($MgSO_4$). The solution was concentrated under reduced pressure, and the residue was purified by passage through a short column of activated alumina using pentane as the eluent to give 1.51 g (82%) of the title iodide as an oil: ^1H NMR δ 1.58–1.67 (m, 2 H), 1.84–1.91 (m, 2 H), 3.18 (t, J = 6.97 Hz, 2 H), 3.25 (s, 3 H), 3.50–3.53 (m,1 H), 5.16–5.22 (m, 2 H), 5.57 –5.64 (m,1 H); ^{13}H NMR δ 6.72, 29.45, 36.17, 56.20, 81.67, 117.40, 138.30; IR (neat) 2923, 1460, 1377, 1118 cm^{-1}; HRMS calcd for $C_5H_{10}OI$ ($M^+ - C_2H_3$) m/z 212.9776, found m/z 212.9775.

***trans*-2-Methylcyclopentanol.** Following the general procedure described by Brown and co-workers,[19] 2.46 g (0.030 mol) of 1-methylcyclopentene was added to 60.0 mL of a 0.50

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M solution of 9-BBN (0.030 mol) in THF, and the resulting solution was heated at reflux for 1 h under an atmosphere of nitrogen. The reaction mixture was then cooled in an ice bath and treated successively with 11.0 mL of 3.0 M aqueous sodium hydroxide solution and 11.0 mL of 30% hydrogen peroxide solution. The mixture was then allowed to stir at room temperature for 1 h. Solid, anhydrous potassium carbonate was added, the organic phase was separated, and solvent was removed at reduced pressure. Distillation of the residue gave 2.60 g (87%) of the title alcohol: bp 54–57 °C (9.5 mm) [lit.[20] bp 150–151 °C (740 mm)]; ^{1}H NMR δ 0.96 (d, J = 6.70 Hz, 3 H), 1.14–1.16 (m, 1 H), 1.49–1.62 (m, 2 H), 1.63 (s, 1 H), 1.68–1.94 (m, 4 H), 3.70–3.74 (m, 1 H); ^{13}C NMR δ 18.15, 21.39, 31.57, 34.08, 42.67, 80.50 [lit.[21] ^{13}C NMR δ 19.5, 22.7, 33.0, 35.1, 43.4, 81.0].

***trans*-1-Methoxy-2-methylcyclopentane (6).** A stirred suspension of 1.34 g (55.8 mmol) of oil-free sodium hydride in 30 mL of dry THF was heated at 45–50 °C under an atmosphere of nitrogen, and a solution of 2.00 g (20.0 mmol) of *trans*-2-methylcyclopentanol and 1.88 mL (30.0 mmol) of methyl iodide in 15 mL of dry THF was added dropwise over a 30-min period. The resulting mixture was heated at 45–50 °C for an additional 1 h. The reaction mixture was then cooled in an ice bath and hydrolyzed by cautious addition of 3.0 mL of water. The resulting solution was extracted several times with diethyl ether, the combined extracts were dried ($MgSO_4$), and solvent was removed by rotary evaporation. Preparative GC on a 10-ft, 10% FFAP on Chromosorb W NAW (80/100 mesh) column at 100 °C afforded 2.00 g (89%) of the ether: ^{1}H NMR δ 0.96 (d, J = 6.70 Hz, 3 H), 1.11–1.15 (m, 1 H), 1.56–1.65 (m,2 H), 1.81–1.90 (m, 2 H), 3.28 (s, 3 H), 3.25–3.30 (m, 1 H); ^{13}C NMR δ 19.03, 22.27, 30.57, 32.14, 39.71, 56.76, 89.60. Anal. Calcd for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.54; H, 12.33.

***cis*-2-Methylcyclopentanol.** Following the procedure described by Brown,[22] 3.00 g (30.6 mmol) of 2-methylcyclopentanone in 12 mL of dry THF was added at −78 °C to 61.0 mL of a 1.0 M solution of L-Selectride (61.0 mmol) in THF and the mixture was stirred at −78 °C for 1 h. After warming to room temperature, the product mixture was quenched by sequential addition of 30.0 mL of 3.0 M sodium hydroxide and 30.0 mL of 30% hydrogen peroxide and the reaction mixture was allowed to stir at room temperature for 1 h. Solid, anhydrous potassium carbonate was added, the organic phase was separated, and solvent was removed at reduced pressure. Distillation of the residue yielded 2.80 g (91%) of the alcohol: bp 56–57 °C (24 mm) [lit.[23] bp 55–65 °C (12 mm)]; ^{1}H NMR δ 0.99 (d, J = 6.79 Hz, 3 H), 1.28–1.35 (m, 1 H), 1.49–1.88 (m, 6 H), 2.36 (br s, 1 H), 4.01–4.05 (m, 1 H); ^{13}C NMR δ 13.49, 21.95, 30.57, 34.47, 39.59, 76.07 [lit.[21] ^{13}C NMR δ 14.9, 23.3, 32.2, 35.7, 41.0, 76.4].

***cis*-1-Methoxy-2-methylcyclopentane (7).** A stirred suspension of 2.20 g (91.6 mmol) of oil-free sodium hydride in 50 mL of dry THF was heated at 45–50 °C under an atmosphere of nitrogen, and a solution of 3.23 g (32.3 mmol) of *cis*-2-methylcyclopentanol and 6.93 g (48.8 mmol) of methyl iodide in 20 mL of dry THF was added dropwise over a 30-min period. The resulting mixture was heated at 45–50 °C for an additional 1 h. The reaction mixture was then cooled in an ice bath and hydrolyzed by cautious addition of 6.0 mL of water. The resulting solution was extracted several times with diethyl ether, the combined extracts were dried ($MgSO_4$), and solvent was removed by rotary evaporation. Preparative GC on a 10-ft, 10% FFAP on Chromosorb W NAW (80/100 mesh) column at 100 °C afforded 3.20 g (87%) of the ether: ^{1}H NMR δ 0.95 (d, J = 6.91 Hz, 3 H), 1.32–1.35 (m, 1 H), 1.47–1.52 (m,1 H), 1.62–1.74 (m, 4 H), 1.88–1.95 (m, 1 H), 3.275 (s, 3 H), 3.51–3.56 (m, 1 H); ^{13}C NMR δ 13.60, 21.42, 29.74, 31.07, 37.90, 56.82, 85.05. Anal. Calcd for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C,73.38; H, 11.94.

1-Hexen-3-ol. A solution of 20.0 mL (0.299 mol) of freshly distilled acrolein in 30 mL of dry diethyl ether was slowly added under nitrogen to propylmagnesium bromide, prepared from 36.9 g (0.300 mol) of 1-bromopropane and 8.20 g (0.34 mol) of magnesium metal turnings in 20 mL of dry diethyl ether. The reaction mixture was stirred at room temperature for an additional hour and then poured into 170 mL of ice-cold 10% aqueous sulfuric acid solution. The mixture was extracted several times with diethyl ether, the ethereal extract was dried ($MgSO_4$), and solvent was removed. Distillation of the residue gave 21.5 g (85%) of the alcohol: bp 49–51 °C (26 mm) [lit.[24] bp 90–94 °C (150 mm)]; ^{1}H NMR δ 0.89 (t, J = 7.14 Hz, 3 H), 1.32–1.50 (m, 4 H), 2.01 (s, 1 H), 4.02–4.09 (m, 1 H), 5.05 (apparent d of t, J_{cis} = 10.34 Hz, J_{gem} = 1.43 Hz, ^4J = 1.33 Hz, 1H), 5.17 (apparent dt, J_{trans} = 17.23 Hz, ^4J = 1.42 Hz, J_{gem} = 1.43 Hz, 1H), 5.82 (ddd, J_{trans} = 17.23 Hz, J_{cis} = 10.34 Hz, ^3J = 6.27 Hz, 1H); ^{13}C NMR δ 13.89, 18.48, 39.10, 72.89, 114.4, 141.3.

3-Methoxy-1-hexene (3). A stirred suspension of 5.40 g (225 mmol) of oil-free sodium hydride in 50 mL of dry THF was heated at 45–50 °C under an atmosphere of nitrogen, and a solution of 8.00 g (80 mmol) of 1-hexene-3-ol and 17.1 g (119.4 mmol) of methyl iodide in 15 mL of dry THF was added dropwise over a 30-min period. The resulting mixture was heated at 45–50 °C for an additional 1 h. The reaction mixture was then cooled in an ice bath and hydrolyzed by cautious addition of 10 mL of water. The resulting solution was extracted several times with diethyl ether, the combined extracts were dried ($MgSO_4$), and solvent was removed by rotary evaporation. Distillation of the residue yielded 8.20 g (89%) of the ether: bp 88–91 °C (760 mm) [lit.[25] bp 113–115 °C (760 mm)]; ^{1}H NMR δ 0.89 (t, J = 7.25 Hz, 3 H), 1.31–1.58 (m, 4 H), 3.26 (s, 3 H), 3.45–3.52 (m, 1 H), 5.12–5.20 (m, 2 H), 5.56–5.69 (m, 1 H); ^{13}C NMR δ 13.99, 18.49, 37.47, 56.09, 82.83, 116.9, 138.9. Anal. Calcd for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.29; H, 11.96.

2,2-Dimethyl-4-octene. A solution of 0.1685 g (0.7021 mmol) of 6-iodo-3-methoxy-1-hexene (**2**) and 0.1257 g (1.257 mmol) of dry heptane as internal standard in 7.0 mL of dry *n*-pentane–diethyl ether (3:2 by volume) was cooled to −78 °C, and 1.20 mL of a 1.70 M solution of *t*-BuLi (2.03 mmol) in pentane was slowly added to the solution over a 2-min period. The resulting mixture was allowed to stir for an additional 5 min at −78 °C, the cooling bath was then removed, and the mixture was allowed to warm and stand at room temperature for 1 h. The mixture was quenched with 1.0 mL of deoxygenated methanol, washed with distilled water, and dried ($MgSO_4$). GC analysis of the reaction mixture indicated that the title compound had been produced in 95% yield as an approximately 99/1 ratio of trans/cis isomers. An analytical sample of the trans-isomer of the known[26] alkene was obtained by preparative GC on a 10-ft, 10% FFAP on Chromosorb W NAW (80/100 mesh) column at 100 °C: ^{1}H NMR δ 0.85 (s, 9 H), 0.88 (t, J = 7.29 Hz, 3 H), 1.30–1.43 (m, 2 H), 1.84 (d, J = 6.14 Hz, 2 H), 1.93–2.01 (m, 2 H), 5.30–5.48 (m, 2 H); ^{13}C δ 13.63, 22.77, 29.25, 30.81, 34.79, 47.16, 127.4, 132.5.

Radical Cyclization of 6-Iodo-3-methoxy-1-hexene. A three-necked, round-bottomed flask, equipped with a stirring bar, condenser, and nitrogen inlet, was charged with 135 mg (0.560 mmol) of 6-iodo-3-methoxy-1-hexene (**2**) in 26 mL of freshly distilled, dry benzene. The solution was heated at reflux, and a solution of 180.7 mg (0.621 mmol) of tributyltin hydride and 5.00 mg of AIBN in 6.0 mL of dry benzene was added dropwise over a 1 h period by syringe. The resulting mixture was heated at gentle reflux for an additional hour and then cooled to room temperature and concentrated. GC analysis of the concentrate indicated that the reaction mixture

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consisted of 60% *trans*-1-methoxy-2-methylcyclopentane (**6**), 27% *cis*-1-methoxy-2-methylcyclopentane (**7**), 12% methoxycyclohexane, and *ca.* 0.7% 3-methoxy-1-hexene (**3**).

Cyclization of (4-Methoxy-1-hexenyl)lithium (1). A 0.1 M solution of 6-iodo-3-methoxy-1-hexene (**2**) in *n*-pentane–diethyl ether (3:2 by volume) containing an accurately weighed quantity of *n*-heptane as internal standard was cooled to −78 °C (acetone–dry ice bath) and 1.75 molar equiv (relative to alkenyl iodide) of *t*-BuLi in pentane was added dropwise via syringe over a period of 5 min. The mixture was stirred at −78 °C for 5 min before treatment in one of the following ways. **(A) Quench at −78 °C.** Dry, deoxygenated MeOH (1.0 mL) was added to the cold reaction mixture, and the cooling bath was removed. **(B) Cyclization at Elevated Temperatures.** The cooling bath was removed, and the solution was allowed to warm and stand at the appropriate temperature under a blanket of argon for 1 h before the addition of 1.0 mL of dry, deoxygenated MeOH. **(C) Cyclization in the Presence of Additives.** The organolithium solution was maintained at −78 °C under a blanket of argon, and the dry, deoxygenated additive was added by syringe. The resulting mixture was stirred for an additional 5 min at −78 °C and then allowed to warm and stand at the appropriate temperature for a period of 1 h prior to the addition of 1.0 mL of dry, deoxygenated MeOH. Reaction mixtures were washed with water, dried ($MgSO_4$), and analyzed by GC on a 25-m × 0.20-mm HP-1 cross-linked methyl silicone fused-silica capillary column using temperature programming (35 °C for 20 min, 30 °C/min to 250 °C) and by GC-MS on a 25-m × 0.20-mm HP-5 methyl phenyl (20%) silicone fused-silica capillary column using temperature programming (35 °C for 20 min, 30 °C/min to 250 °C). Reaction products were identified by comparison of their GC retention times and mass spectra with those of authentic samples. All yields reported in Table 1 were corrected for detector response under the conditions of the analysis using accurately weighed samples of pure product and standard.

***trans*-1-Methoxy-2-(iodomethyl)cyclopentane (8).** A solution of **1**, prepared from 0.538 g (2.24 mmol) of 6-iodo-3-methoxy-1-hexene (**2**) in *n*-pentane–diethyl ether as described above, was allowed to warm and stand at 0 °C for 1 h to effect cyclization to (*trans*- and (*cis*-(2-methoxycyclopentyl)methyl)-lithium (**4** and **5**, respectively). In another flask, a solution of 1.12 g (4.41 mmol) of iodine in 15 mL of dry diethyl ether was cooled to −78 °C under an atmosphere of argon. The solution of **4** and **5** was then added dropwise to the iodine solution via a Teflon cannula. The reaction mixture was stirred at −78 °C for 0.5 h and then warmed to room temperature and washed with two 20-mL portions of 5% aqueous sodium thiosulfate. The organic phase was separated, washed with water, dried ($MgSO_4$), and concentrated by rotary evaporation to give 0.460 g (85%) of 1-methoxy-2-(iodomethyl)cyclopentane as a mixture of isomers (trans/cis = 7.8). Preparative GC on a 10-ft, 10% FFAP on Chromosorb W NAW (80/100 mesh) column at 150 °C afforded 0.410 g (76%) of pure *trans*-1-methoxy-2-(iodomethyl)cyclopentane: ^1H NMR δ 1.29–1.32 (m, 1 H), 1.62–2.05 (m, 6 H), 3.16–3.29 (m, 2 H), 3.30 (s, 1 H), 3.40–3.46 (m, 1 H); ^{13}C NMR δ 11.83, 22.09, 31.15, 31.26, 47.55, 56.87, 87.05; HRMS calcd for $C_7H_{13}OI$ *m/z* 240.0011, found *m/z* 240.0009.

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Supplementary Material Available: Copies of the ^1H and ^{13}C NMR spectra for all new compounds for which combustion analytical data are not available (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.