Stereochemistry of the cyclization of 4-(*t*-butyldimethyl)siloxy-5-hexenyllithium: *cis*-selective ring-closure accompanied by retro-[1,4]-Brook rearrangement

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Dedicated to Professor Eusebio Juaristi on the occasion of his 55th birthday

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Abstract

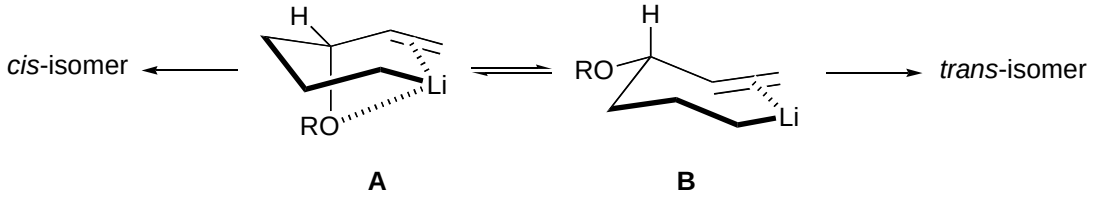
The stereochemistry of the cyclization of 4-(*t*-butyldimethyl)siloxy-5-hexenyllithium, generated from the corresponding iodide by low - temperature lithium – iodine exchange, has been studied. The results of these studies demonstrate that the ring closure, which is *cis*-selective in all of the solvent systems investigated, is accompanied by a facile [1,4]-C→O migration of the silyl group in *cis*-[2-(*t*-butyldimethylsiloxy)cyclopentylmethyl]lithium (a retro-[1,4]-Brook rearrangement). The factors responsible for the *cis*-selectivity observed in these cyclizations are discussed.

Keywords: Organolithiums, cyclization, stereochemistry, retro-[1,4]-Brook rearrangement

Introduction

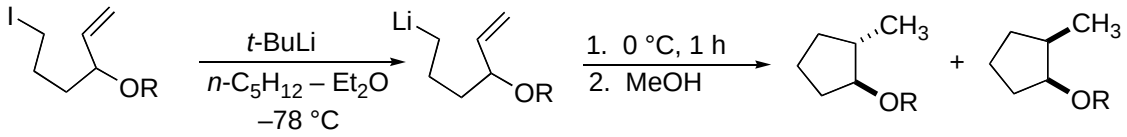
The well-studied 5-exo cyclization of 5-hexenyllithiums, which involves a chair-like transition state in which the Li-atom is intramolecularly coordinated to the C(5)-C(6) π-bond,[1] has been used to prepare a variety of carbocyclic[2] and heterocyclic[3] ring systems. The cyclization of 5-hexenyllithiums bearing heteroatomic substituents capable of intramolecular coordination to the Li-atom has received less attention.[4] In this connection, we recently reported the results of a detailed investigation of the stereochemical outcome of cyclization of 5-hexenyllithiums bearing an alkoxy substituent at the C(4) position.[5] This study demonstrated that the diastereoselectivity of the ring-closure of 4-alkoxy substituted 5-hexenyllithiums may be affected by the medium in which the cyclization is conducted. The origin of these often dramatic solvent effects was attributed to the ability of certain lithiophilic Lewis bases, such as TMEDA and 1,4-dioxane, to competitively complex the lithium iodide salt, generated as a co-product of the lithium–iodine exchange used to generate the 5-hexenyllithium, and remove this impediment to otherwise favorable intramolecular coordination of the C(1)-Li atom with both the π-bond and a

pseudoaxial 4-OR group, as illustrated in Scheme 1, leading to a *cis*-selective ring-closure.[5,6] In short, intraaggregate association of the 4-OR group with LiI disrupts intramolecular the Li–O coordination depicted in **A** and leads to *trans*-selective closure via activated complex **B**.



Scheme 1

An unexpected but apparently related feature of the cyclization of 4-alkoxy-5-hexenyllithiums uncovered in these studies is illustrated in Scheme 2: the ring closure of 4-*tert*-butoxy-5-hexenyllithium (**2**) is more highly *cis*-selective in all solvent systems studied than is the cyclization of the 4-methoxy analog (**1**).[5]



1, R = Me
2, R = *t*-Bu

3 **4**

R	**3** / **4**
Me	8 : 1
t-Bu	1 : 4

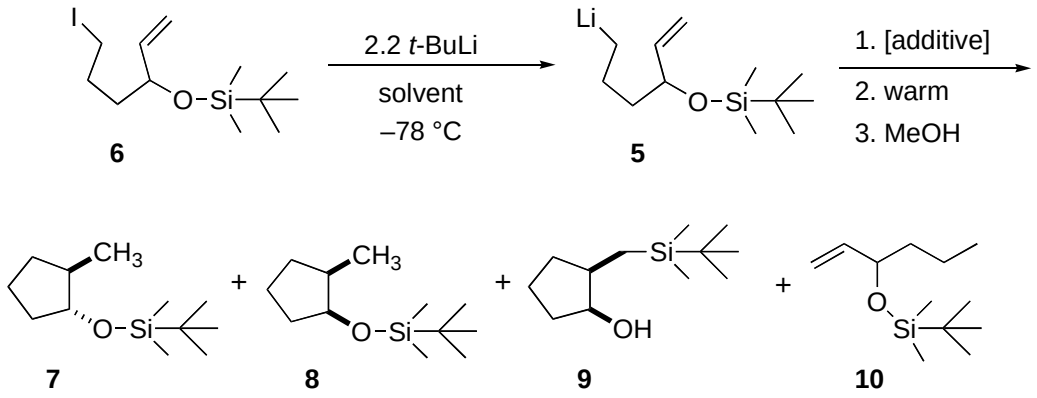
Scheme 2

The disparate stereochemical behavior of **1** and **2** was credited to the steric interactions between the alkoxy substituent and the LiI present in the reaction mixtures: co-association of LiI with the *tert*-butoxy group in **2** may be less favorable for this large group than it is for the smaller 4-OMe group in **1**.[5] Consequently, the more sterically demanding 4-*tert*-butoxy group inhibits association with LiI while having little effect on the favorable intramolecular Li-O association that stabilizes the pseudoaxial conformation (Scheme 1; **A**, R = *t*-Bu) of **2**.

It was of interest to determine whether the ring closure of other 5-hexenyllithiums bearing a bulky 4-substituent capable of coordination with lithium would display similar stereochemical behavior. To this end, we have investigated the cyclization of 4-(*t*-butyldimethyl)siloxy-5-hexenyllithium (**5**) generated from 3-[(*t*-butyldimethyl)siloxy]-6-iodo-1-hexene (**6**) by low-temperature lithium–iodine exchange with *t*-BuLi.

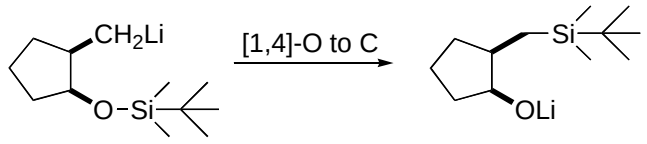
Results and Discussion

The preparation of 3-[(*t*-butyldimethyl)siloxy]-6-iodo-1-hexene (**6**) from 6-chloro-1-hexen-3-ol has been previously described.[7] As illustrated in Scheme 3, 4-(*t*-butyldimethyl)siloxy-5-hexenyllithium (**5**) was generated at –78 °C, in diethyl ether, *n*-pentane – diethyl ether mixtures, or pure *n*-pentane, by treatment of **6** with 2.2 molar equiv of *t*-BuLi in pentane following our usual protocol.[8] The ring closure of **5** was investigated by allowing solutions of the organolithium to warm and stand for 1 h before quench with an excess of deoxygenated MeOH. The products (**7**, **8** and **9**) of the kinetically controlled ring closure of **5** were assayed by capillary GC using *n*-heptane as internal standard. The effect of TMEDA and HMPA on the stereochemistry of the cyclization of **5** was investigated in a separate series of experiments in which these Lewis bases were added at –78 °C to solutions of **5** prior to warming of the organolithium. The results of these experiments are summarized in Table 1.

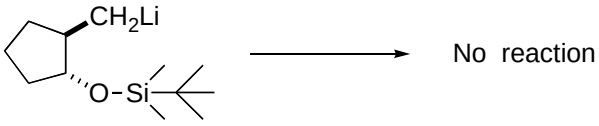


Scheme 3

Before reviewing the data presented in Table 1, it is worth noting that the formation of alcohol **9** from the cyclization of **5** (Scheme 3) is not unexpected. Some time ago we reported[7] that *cis*-[2-(*t*-butyldimethylsiloxy)cyclopentylmethyl]lithium (**11**), which gives **8** upon quench with MeOH, is prone to a facile, intramolecular [1,4]-C→O migration of the silyl group (a retro-[1,4]-Brook rearrangement).[9] As illustrated below, this rearrangement is confined exclusively to **11**; the *trans*-isomer (**12**) is completely stable with respect to silyl migration.[7] The retro-Brook rearrangement of **11**, which delivers **9** upon quench with a proton source, is a high-yield process at room temperature in hydrocarbon and ether solvents as well as at lower temperatures in the presence of TMEDA or HMPA.[7]



11



12

Cursory inspection of the data presented in Table 1 reveals that the cyclization of 4-(*t*-butyldimethyl)siloxy-5-hexenyllithium (**5**) is *cis*-selective in all of the solvent systems investigated. Moreover, this *cis*-selectivity is quite substantial at 0 °C in a pentane medium (Table 1, entry 1) and in the presence of 2.2 molar equiv of HMPA (Table 1, entry 10). As noted above, retro-[1,4]-Brook rearrangement of **11** is significant at room temperature (Table 1, entries 2 and 8) and at lower temperatures in the presence of TMEDA or HMPA (Table 1, entries 9 and 10). Consequently, the stereochemical outcome of these cyclizations is best appreciated by summing the yields of **8** and **9**, as shown in the last column of Table 1, to give the total *cis*-[2-(*t*-butyldimethylsiloxy)cyclopentylmethyl]lithium (**11**) produced upon ring closure of **5**.

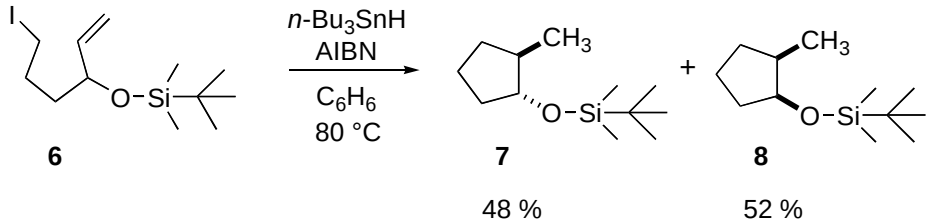
The *cis*-selective stereochemistry that characterizes the cyclization of **5** is reminiscent of that found in the cyclization of 4-*tert*-butoxy-5-hexenyllithium (**2**) depicted in Scheme 2 and it likely has a similar etiology.[5] Formation of the *cis*-isomer (**11**) upon ring closure of **5** requires that the allylic siloxy group occupy a pseudoaxial position and, as noted elsewhere,[5,6] intramolecular coordination of the lithium atom with the proximal oxygen might be expected to stabilize such an arrangement (Scheme 1, **A**). The trans-isomer arises from cyclization of a species bearing a pseudoequatorial siloxy group (Scheme 1, **B**). It is well known that organolithiums co-associate with lithium halides and it is likely, given the method used to prepare **5**, that it exists as an aggregate containing the co-generated LiI.[10] Intraaggregate coordination of the 4-OTBDMS group with LiI may disrupt the intramolecular Li–O coordination depicted in structure **A** (Scheme 1) and we have suggested that Lewis base additives, such as TMEDA which form stable complexes with lithium halides,[11] affect the stereochemistry of such cyclizations by sequestering the LiI generated in the exchange reaction. Moreover, although LiI has a reasonable solubility in diethyl ether, it is essentially insoluble in *n*-pentane. Thus, an increase in the proportion of pentane solvent in the reaction medium, or the addition of a lithiophilic Lewis base, should lead to an increase in the cis/trans product ratio because the lithium iodide will be less soluble in such a solvent system. These expectations are fully in accord with the data (Table 1).

Table 1. Cyclization (Scheme 3) of 4-(*t*-butyldimethyl)siloxy-5-hexenyllithium (**5**)[a]

			products, % yield [b]				
entry	solvent system	temp, °C	**10**	**7**	**8**	**9**	cis/ trans [c]
1	*n*-C_5H_{12}	0	28.4	4.7	6.8		14.2
2	*n*-C_5H_{12}–Et_2O 3:2 by vol	24	11.6	17.4	37.5	33.4	4.1
3	3:2 by vol	10	11.3	18.2	44.9	25.6	3.9
4	3:2 by vol	0	8.4	17.0	64.4	6.2	4.2
5	3:2 by vol	–10	18.0	16.6	61.3	4.2	3.9
6	3:2 by vol	–20	30.9	13.8	52.4	3.0	4.0
7	3:2 by vol	–30	59.1	6.1	29.9	2.5	5.3
8	Et_2O	24	31.5	20.2	9.5	38.7	2.4
9	TMEDA [d]	0	21.1	14.1	6.7	58.1	4.6
10	HMPA [e]	0	38.4	8.6	10.1	43.0	6.2

[a] 4-(*t*-Butyldimethyl)siloxy-5-hexenyllithium (**5**) was generated at –78 °C by addition of 2.2 equiv of *t*-BuLi to a solution of iodide **6** in either *n*-pentane – diethyl ether, pure diethyl ether, or pure *n*-pentane. Where indicated, dry TMEDA or HMPA 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 *cis* (**8** + **9**) / *trans* (**7**). [d] TMEDA (2.2 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. [e] HMPA (2.2 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.

For comparison purposes, the radical-mediated cyclization of **6** was investigated in benzene solution at 80 °C (Scheme 4). In contrast to the *cis*-selective cyclization of the organolithium **5** (Table 1), ring-closure of the radical derived from iodide **6** gave essentially equal amounts of *trans*-(**7**) and *cis*-2-methyl-1-(*t*-butyldimethylsiloxy)cyclopentane (**8**).



6 **7** **8**

48 % 52 %

Scheme 4

Experimental Section

General Procedures. 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.[1,5,12] The concentration of commercial solutions of *t*-BuLi in pentane was determined immediately prior to use by the method of Watson and Eastham.[13] The preparations of 3-[(*t*-butyldimethyl)siloxy]-6-iodo-1-hexene (**6**), *trans*-2-methyl-1-(*t*-butyldimethylsiloxy)cyclopentane (**7**), *cis*-2-methyl-1-(*t*-butyldimethylsiloxy)cyclopentane (**8**), and *cis*-2-[(*t*-butyldimethylsilyl)methyl]cyclopentanol (**9**) have been previously described.[7]

3-(*t*-Butyldimethyl)siloxy-1-hexene (10). A solution of 1.00 g (10.0 mmol) of 1-hexen-3-ol, 1.81 g (12.0 mmol) of *tert*-butyldimethylsilyl chloride, and 1.70 g (25.0 mmol) of imidazole in 2.5 mL of dry DMF was heated at 35 °C for 24 h. The cooled reaction mixture was diluted with 25 mL of water and 30 mL of diethyl ether, the layers were separated, and the aqueous layer was extracted with two 20-mL portions of diethyl ether. The combined extract and washings were washed successively with 20 mL of aqueous ammonium chloride, 20 mL of water and 20 mL of brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by preparative GC on a 10–ft, 10% FFAP on Chromosorb W NAW (80/100 mesh) column at 150 °C to afford 1.85 g (86%) of the title compound: ^{1}H NMR ™ 0.024 (s, 3 H), 0.04 (s, 3 H), 0.89 (s, 9 H), 1.37–1.45 (m, 4 H), 0.88 (t, J = 6.72 Hz, 3 H), 4.06–4.09 (m, 1 H), 4.99 (apparent d of t, J_{cis} = 10.3 Hz, J_{gem} = 1.59 Hz, ^4J = 1.22 Hz, 1 H), 5.12 (apparent d of t, J_{trans} = 17.1 Hz, J_{gem} = 1.59 Hz, 4J = 1.43 Hz, 1 H), 5.79 (ddd, J_{trans} = 17.1 Hz, J_{cis} = 10.3 Hz, ^3J = 6.10 Hz, 1 H); ^{13}C NMR δ –4.84, –4.37, 14.10, 18.43, 25.65, 25.77, 40.40, 73.70, 113.30, 141.99. Anal. Calcd for $C_{12}H_{26}SiO$: C, 67.22; H, 12.22. Found: C, 66.82; H, 11.86.

General procedure for the preparation and cyclization of 4-(*t*-butyldimethyl)siloxy-5-hexenyllithium (5)

Organolithium **5** was prepared from 3-[(*t*-butyldimethyl)siloxy]-6-iodo-1-hexene (**6**) following our general protocol. Typically, a 0.1 M solution of **6** the iodide in either *n*-pentane, diethyl ether, or an *n*-pentane – diethyl ether mixture containing an accurately weighed quantity of *n*-heptane as internal standard was cooled under an argon atmosphere to –78 °C (acetone – dry ice bath) and 2.20 molar equivalents of *t*-BuLi in *n*-pentane was added dropwise via syringe over a period of 5 min. The mixture was stirred at –78 °C for 5 min, and the organolithium was treated in one of the following ways. *(A) Cyclization at Elevated Temperatures.* The cooling bath was removed, and the solution of **5** was allowed to warm and stand at the appropriate temperature for 1 h under a blanket of argon before the addition of 1.0 mL of dry, deoxygenated MeOH. *(B) Cyclization in the Presence of Additives.* The organolithium solution was maintained at –78 °C under a blanket of argon and the dry, deoxygenated additive (typically 2.20 molar equivalents of TMEDA or HMPA) 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 1 h under

a blanket of argon 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 x 0.20-mm HP-1 cross-linked methyl silicone fused-silica capillary column using temperature programming (35 °C for 5 min, 20 °C/min to 250 °C) and by GC-MS on a 25-m x 0.20-mm HP-5 methyl phenyl (20%) silicone fused-silica capillary column using temperature programming (35 °C for 5 min, 20 °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.

Radical cyclization of 3-[(*t*-butyldimethyl)siloxy]-6-iodo-1-hexene

A solution of 134 mg (0.38 mmol) of iodide **6** in 16 mL of freshly distilled, dry benzene under an atmosphere of nitrogen. The solution was heated at reflux and a solution of 123 mg (0.42 mmol) of tributyltin hydride and 5.0 mg of AIBN in 5.0 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 consisted of 48% of **7** and 52% of **8**.

Acknowledgements

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