A Novel Tandem [1,2]-Brook/Retro-[1,6]-Brook Rearrangement of a 1-(Trimethylsilyl)-2,4-pentadien-1-ol Anion

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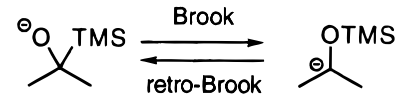
Received July 5, 1996

Introduction and Background

The Brook rearrangement[3] is the migration of a silyl group from a carbon atom to an oxygen anion as illustrated in its simplest [1,2] form (**1** → **2**) in Figure 1. It has been extensively studied mechanistically by Brook and shown to proceed intramolecularly via a mechanism involving a hypervalent pentacoordinate silicon species with retention of configuration at silicon and inversion of configuration at carbon.[4] In accord with that mechanistic hypothesis, substrates having substituents on carbon that help delocalize negative charge, e.g., aryl and vinyl, accelerate the rate of the rearrangement.[4] The counterpart of this rearrangement, the retro-Brook (silyl-Wittig or West) rearrangement[5,6] (e.g., **2** → **1**), namely, the transfer of silicon from oxygen to carbon, has also been observed. Both of these silyl rearrangements are therefore well-established and useful transformations.[6−8] Analogous anionic silyl migrations, including [1,3]-[9,10] and [1,4]-O → C shifts[11−16] and [1,3]-[17] and [1,4]-C → O shifts,[15,16,18] have also been investigated. We report here the first incidence of a [1,6]-O → C (retro-[1,6]-Brook) silyl migration, which, in tandem with a [1,2]-Brook rearrangement, transforms a 1-(trimethylsilyl)-2,4-pentadien-1-ol anion into a 5-(trimethylsilyl)-2-pentenal.

Results and Discussion

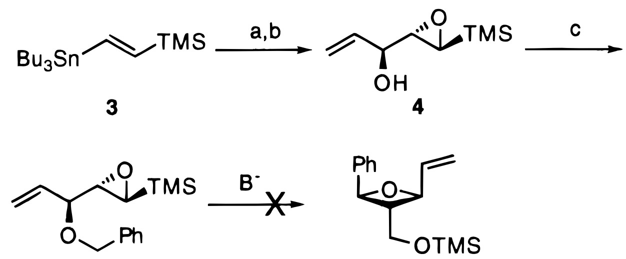
During an attempted synthesis of an analogue of the antiviral compound oxetanocin A[19] in its correct enantiomeric form, the benzyloxy alkenyl silyl epoxide **5** was prepared (Scheme 1) from the known optically active alcohol **4**[20] (which was synthesized in two steps from 1-(trimethylsilyl)-2-(tributylstannyl)ethylene (**3**),[21] the key step being the Sharpless kinetic resolution) by benzylation with sodium hydride and benzyl bromide in 78% yield. In the next step, the intent was to prepare the anion at the benzylic carbon of **5** and have it cyclize on to the epoxide in a 4-*exo*-epoxy mode to form an oxetane[22] with the correct absolute configuration at the allylic and homoallylic centers (the phenyl substituent would be expected to be trans to the adjacent alkoxymethyl substituent due to steric hindrance). This might have then been followed by a [1,2]-silyl shift to give the silyl ether **6**, which has the correct relative and absolute stereochemistry at all three stereocenters for the production of oxetanocin analogues.



1 2

Figure 1.

Scheme 1[a]



3 4 5 6

[a] Reagents and conditions: (a) (i) BuLi, −78 °C, 90 min, (ii) acrolein, −78 °C, 90 min, 73%. (b) L-DIPT, $Ti(O^iPr)_4$, ^tBuOOH, CH_2Cl_2, mol sieves, −25 °C, 18 h, 44%. (c) NaH, THF, Bu_4NI, BnBr, 0 °C, 78%.

However, when the rearrangement was carried out, a different reaction course ensued. Addition of 3.6 equiv of *tert*-butyllithium to the silyl epoxide allylic benzyl ether **5** in THF/HMPA, followed by acidic workup, produced the aldehyde **7** in 40% purified yield. In **7** the silyl group and the oxygen atom, which in **5** were on the same carbon, were now at opposite ends of the molecule, indicating that a substantial skeletal rearrangement must have taken place. In the proposed mechanism (Scheme 2), the allylic anion **5a** was formed under the strongly basic conditions (rather than the desired benzylic anion which might lead to **6**) and the epoxide was opened by simple β-elimination to produce the α-silyl alkoxide **8**. A [1,2]-Brook rearrangement then gave the α-silyloxy carbanion **9**, which is a highly resonance-stabilized pentadienyl anion. It has been demonstrated[5] in studies of the anion of benzyl trimethylsilyl ether that this equilibrium lies greatly toward the CSi/OLi species (analogous to **8**), but in this case **9** proved to be only an intermediate and the reaction continued, driven by the stability of the enolate **10** subsequently formed. From this point a retro-[1,6]-Brook migration of the pentadienyl anion **9** gave the dienolate **10**, which was protonated upon workup with aqueous HCl to give the aldehyde **7**.

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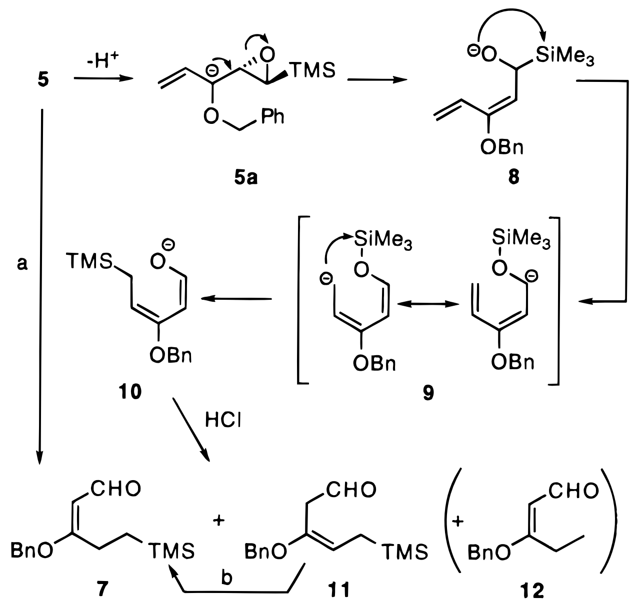
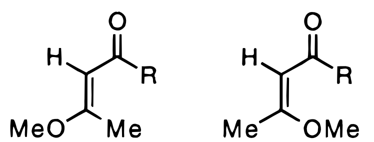
Scheme 2[a]



[a] Reagents and conditions: (a) (i) ^tBuLi, THF/HMPA 25:1, −78 °C 10 min; (ii) aq HCl, 40% **7**. (b) $CDCl_3$, 6 d, quant.



13a,b **14a,b**

a: R = H, **b**: R = Me

Figure 2.

On some occasions, if the acid workup were done too quickly, the isomeric nonconjugated aldehyde **11** was also isolated. However, when the aldehyde **11** was allowed to sit for 6 days in commercial chloroform-*d*, there was presumably enough acid catalyst for it to completely isomerize to the conjugated isomer **7**. In one case, when the reaction was allowed to proceed longer, the desilylated aldehyde **12** was isolated in 12% yield, along with 26% of the silylated aldehyde **7**.

The structure of **7** was assigned as the *E*-isomer based on analogy to the work of Castells,[23] who synthesized both isomers of 3-methoxy-2-butenal (**13a, 14a**). In the ^1H NMR of **7**, the alkene proton appears at δ 5.41, which compares more favorably to **13a** (δ 5.33) than **14a** (δ 5.05). A similar ^1H NMR correlation exists with methyl ketone **13b**.[24] Isomer **13a** is also inherently more stable than **14a**: in methanol, **14a** is completely converted to **13a** in 3 h.[23] Thermodynamic studies of the methyl ketones (**13b, 14b**), the simplest analogues to **7** investigated in the literature, show a K_{eq} of ≥100 in favor of **13b**, or a ΔG of ≥14 kJ mol^{-1}.[25] This data lends strong evidence to the correctness of the assignment of structure **7**.

This is the first example of a Brook or retro-Brook rearrangement of this type. Indeed, no other retro-[1,*n*]-Brook rearrangements for $n \geq 5$ have been reported, although in one case[26] 4-lithio-1-[(trimethylsilyl)oxy]-benzene rearranged to 4-(trimethylsilyl)phenol at room temperature. However, crossover studies showed that reaction to be intermolecular and therefore not a true Brook rearrangement. It has not been shown conclusively that the transformation of **5** into **7** is intramolecular and not intermolecular (as the presence of **12** may even suggest). However, since the conditions of the reaction are quite dilute (0.02 M) and cold (−78 °C), and the reaction is geometrically feasible (unlike the phenol case), it seems reasonable to assume that it proceeded via an intramolecular reaction. Also, the reaction was presumably aided by the use of a lithium base, since it has been shown[15] that, for a 1,4-silyl shift to occur, a lithium base favors the alkoxide product, whereas a sodium base favors the carbanion product.

Conclusion

The first retro-[1,6]-Brook rearrangement has been carried out as one step of the unexpected transformation of the silyl allyl epoxide **5** to the unsaturated aldehyde **7**, thereby adding dimension and depth to the continuing investigation of silyl migrations.

Experimental Section

All solvents were distilled prior to use: tetrahydrofuran (THF) and diethyl ether from Na/benzophenone and hexamethylphosphoramide (HMPA) from calcium hydride. Other reagents were used as provided except for benzyl bromide, which was also distilled. All reactions were carried out under an atmosphere of Ar. (α*S*,2*S*,3*S*)-α-ethenyl-3-(trimethylsilyl)oxiranemethanol (**4**) was prepared in ≥98% ee according to the method of Baldwin *et al.*[20] Purity of the new materials **5** and **7** was established by a combination of high-resolution mass spectrometry and high-field ^1H and ^{13}C NMR data while the structures of **11** and **12** were assigned solely on the basis of high field ^1H NMR data (see Supporting Information).

(2*S*,3*S*)-2-[(1*S*)-(phenylmethoxy)-2-propenyl]-3-(trimethylsilyl)oxirane (5). To a suspension of sodium hydride (41.9 mg, 1.05 mmol) in THF (1.25 mL) at 0 °C was slowly added a solution of (α*S*,2*S*,3*S*)-α-ethenyl-3-(trimethylsilyl)oxiranemethanol (**4**; 113.1 mg, 0.656 mmol). The mixture was allowed to warm to room temperature over 20 min, after which tetrabutylammonium iodide (22 mg, 0.060 mmol) and benzyl bromide (117 μL, 0.984 mmol) were added. Stirring continued until TLC control (SiO_2, 13% ethyl acetate/87% hexane or 50% methylene chloride/50% hexane) indicated no further starting material. Diethyl ether was then added, the solution washed with water, and the aqueous layer extracted with diethyl ether. The organic fractions were combined, washed with water and brine, and dried over $MgSO_4$, and the solvent was removed *in vacuo*. Column chromatography (SiO_2, 13% methylene chloride/87% hexane → 50% methylene chloride/50% hexane) afforded 134 mg of **5** (0.510 mmol, 78%) as a colorless oil: $[\alpha]^{22}_D = -5.7°$ (c = 0.92, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35−7.26 (5H, m), 5.85 (1H, ddd, J = 17.7, 10.0, 7.2 Hz), 5.339 (1H, ddd, J = 17.7, 1.6, 1.1 Hz), 5.334 (1H, ddd, J = 10.0, 1.6, 0.9 Hz), 4.63 (1H, d, J = 12.0 Hz), 4.49 (1H, d, J = 12.1 Hz), 3.75 (1H, dd, J = 7.2, 4.6 Hz), 2.92 (1H, dd, J = 4.6, 3.5 Hz), 2.20 (1H, dd, J = 3.5, 0.3 Hz), 0.07 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.2, 134.9, 128.4, 127.7, 127.6, 119.1, 80.7, 70.6, 56.9, 49.5, −3.7; IR (thin film) 1250, 1071, 870, 843, 698 cm^{-1}; HRMS (EI) *m/z* 262.1388, calcd for $C_{15}H_{22}O_2Si$ 262.1389.

(*E*)-3-(Phenylmethoxy)-5-(trimethylsilyl)-2-pentenal (7). To a solution of the epoxide **5** (5.8 mg, 0.022 mmol) in THF/HMPA (1 mL/0.04 mL) at −78 °C was added over 15 min *tert*-butyllithium (1.14 M, 70 μL, 0.080 mmol). The solution turned yellow and remained yellow after all the *tert*-butyllithium had been added. Stirring was continued for 10 min at −78 °C, and

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the reaction was quenched with 1 mL of aqueous HCl (1 M) and diluted with diethyl ether. The layers were separated, the aqueous layer was extracted with diethyl ether, and the combined organic extracts were washed with water and brine and dried over $MgSO_4$. The solvent was removed and the crude mixture allowed to sit in commercial $CDCl_3$ overnight. Column chromatography (SiO_2, 8% ethyl acetate/92% hexane) afforded 2.3 mg of **7** (0.009 mmol, 40%) as a colorless oil. **7**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.84 (1H, d, $J = 7.8$ Hz), 7.41−7.35 (5H, m), 5.41 (1H, d, $J = 7.8$ Hz), 4.87 (2H, s), 2.63 (2H, m), 0.90 (2H, m), 0.04 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.0, 181.9, 135.0, 128.7, 128.5, 127.7, 104.1, 70.6, 26.1, 16.0, −1.9; IR (thin film) 2953, 1659, 1603, 860, 835 cm^{-1}; HRMS (EI) *m/z* 263.1464 calcd for $C_{15}H_{23}O_2Si$ 263.1467 $(M + H)^+$, 262.1391 calcd for $C_{15}H_{22}O_2Si$ 262.1389.

(*E*)-3-(Phenylmethoxy)-5-(trimethylsilyl)-3-pentenal (11). Another experiment conducted exactly as described above but omitting the step of dissolving the crude material in $CDCl_3$ gave a mixture of 10% **7** and 13% of the isomeric product (*E*)-3-(phenylmethoxy)-5-(trimethylsilyl)-3-pentenal (**11**), which isomerized to **7** upon standing in $CDCl_3$. **11**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.63 (1H, t, $J = 2.7$ Hz), 7.36−7.39 (5H, m), 4.79 (1H, t, $J = 8.5$ Hz), 4.72 (2H, s), 3.19 (2H, dd, $J = 2.7$, 0.6 Hz), 1.56 (2H, d, $J = 8.2$ Hz), 0.02 (9H, s).

(*E*)-3-(Phenylmethoxy)-2-pentenal (12). Another experiment conducted as described above but involving a longer reaction time (3.5 h), gave 26% of **7**, along with 40% of recovered **5**, and 12% of the desilylated product (*E*)-3-(phenylmethoxy)-2-pentenal (**12**). **12**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.84 (1H, d, $J = 7.7$ Hz), 7.38−7.34 (5H, m), 5.45 (1H, d, $J = 7.8$ Hz), 4.88 (2H, s), 2.70 (2H, q, $J = 7.6$ Hz), 1.25 (3H, t).

Acknowledgment. We thank the National Institutes of Health (Grant GM 47228) and the Agricultural Research Division of American Cyanamid Co. for generous financial support. C.J.N. thanks the Natural Sciences and Engineering Research Council (NSERC) of Canada for a fellowship.

Supporting Information Available: High-field ^{1}H and ^{13}C NMR spectra (recorded on a Bruker ARX400 spectrometer) of the new compounds **5** and **7** and ^{1}H NMR data for **11** and **12** (6 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.

JO961265S