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Unexpected regioselective synthesis of 5,17-dibromo-11,23-dihydroxycalix[4]arene hexyl ether

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Using transmetallation, quenching with $B(OCH_3)_3$, and oxidation regioselectively upper-rim functionalized dibromodihydroxycalix[4]arene hexyl ether was synthesized from p-bromocalix[4]arene hexyl ether in good yield.

The interest in calixarenes has been growing continuously as a facet of host-guest chemistry.[1] The diverse chemical reactivity and even the conformational flexibility of calixarenes make them attractive starting materials for organic hosts which may mimic biological processes. Calix[4]arenes can exist as cone, partial cone, 1,2-alternate, and 1,3-alternate conformers, depending mainly on the substituents on the lower rim.[2] A circular array of hydrogen bonds or sterically bulky groups on the lower rim help to maintain the cone conformation which retains a hydrophobic cavity for guest binding. At the lower rim, four hydroxyl groups can be converted to ester or ether functions, giving selective alkali metal binding sites.[3] At the upper rim, four *para*-positions were functionalized by various reactions such as nitration and sulfonation,[4] aminomethylation,[5] *p*-Claisen rearrangement,[6] and chloromethylation.[7] Nevertheless, regioselective functionalization on the upper rim is quite rare compared to that on the lower rim.[8]

Calix[4]arene **2** was alkylated with 1-bromohexane to give a calix[4]arene hexyl ether **3** in 80% yield[9,10] which shows two doublets for $ArCH_2Ar$ protons (4.40 ppm for H_{endo} and 3.00 ppm for H_{exo}, $J = 13.5$ Hz) and a triplet at 3.90 ppm for oxymethylene protons in $CDCl_3$, which imply the cone conformation of **3**.[2a] Subsequent reaction with NBS in MEK afforded the cone structured p-bromocalix[4]arene hexyl ether **4** in 89% yield.[11] The attempt to convert *p*-bromocalix[4]arene hexyl ether **4** to the *p*-hydroxy compound, **5**, by the known procedure[12] was unsuccessful. Treatment of compound **4** with 8 eq. of *n*-BuLi in dry THF at -78 °C followed by quenching with $B(OMe)_3$ and then oxidation with 3N NaOH-28% H_2O_2 gave the unexpected 5,17-dibromo-11,23-dihydroxy-25,26,27,28-tetrahexyloxycalix[4]arene, **6**,[13] in 43% isolated yield. Presumably this result is due to the relative inertness of compound **4** to transmetallation at -78 °C.[14] Raising the temperature and/or a greater excess of *n*-BuLi resulted in a lower yield of diol **6**.

The stereo- and regiochemistry of diol **6** were confirmed from the following data. The splitting patterns of ^1H-NMR spectrum of **6** in $CDCl_3$ were consistent with that of a known cone structure: i.e., two doublets for the bridging methylenes at 3.04 and 4.35 ppm ($J = 13.5$ Hz) and two triplets for oxymethylenes at 3.60 and 3.90 ppm. Conner *et al.* found that distal carboxyl groups at the upper rim form intramolecular hydrogen bonds to give rise to a pinched-cone structure (Figure 1).[15] Steric repulsions between hydroxy and bromo groups enforced **6** to pinched-cone conformation which is evidenced from the high up-field shift of ortho-to-hydroxy protons (A and A') at 5.71 ppm compared to that of ortho-to-bromo protons (B and B') at 7.16 ppm in $CDCl_3$ on ^1H NMR spectrum. The corresponding ortho proton peaks of 4-hexyloxyphenol and 4-bromophenetole are reported to be at 6.76 and 7.34 ppm respectively in the same solvent.[16] The 5,17-Dibromo-11,23-dimethoxy-25,26,27,28-tetrahexyloxycalix[4]arene **7** derived from diol **6** showed arylic A and A' hydrogens at 6.29 and B and B' hydrogens at 7.00 ppm in nitrobenzene-d_5 on ^1H NMR spectrum, but no ν_{OH} band on IR spectrum.[17]

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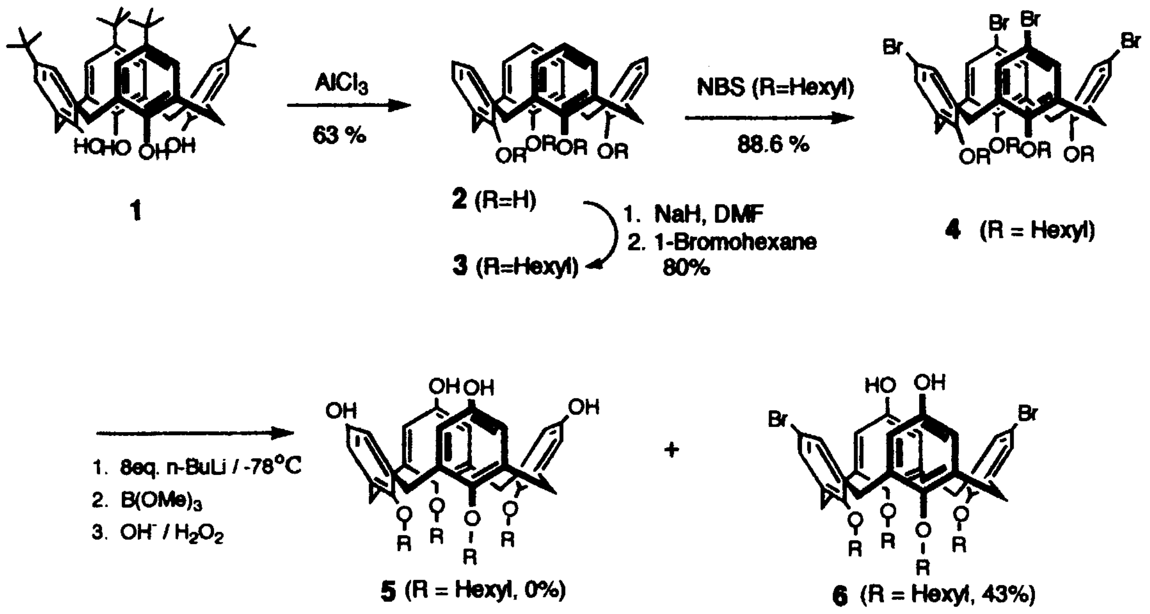

Scheme 1

Boehmer *et al.* have reported the less symmetrical cone-structured calix[4]arenes (the so-called 'arrichoarenes') having two distal *para*-positions connected by an aliphatic chain.[18] In this work, **6** was transformed to **8** whose ^{1}H-NMR spectrum shows similar patterns to the arrichoarene.[19]

In conclusion, a regioselective dibromodihydroxycalix[4]arene hexyl ether was synthesized and characterized. These results show a direct regioselective upper-rim functionalization method from p-bromocalix[4]arene alkyl ether using transmetallation and then quenching with electrophiles.

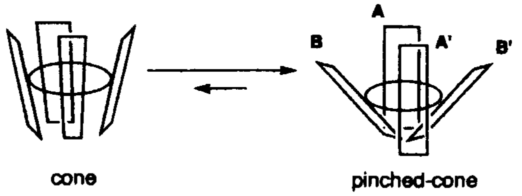

Figure 1 Illustration of Cone and Pinched-cone Conformation.

Scheme 2

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10 3: Mp=94.4~94.8°C; ^{1}H-NMR ($\mathrm{CDCl_3}$) δ 6.60(s,12H,ArH), 4.45(d,J=13.5 Hz, 4H, endo-ArCH),3.90(t,8H,$\mathrm{OCH_2}$), 3.15(d,J=13.5Hz,4H,exo-ArCH), 1.90(m,8H, $\mathrm{OCH_2}\mathit{CH}_2$), 1.30(m,24H,$(\mathit{CH}_2)_3\mathrm{CH_3}$), 0.90(t,12H,$\mathrm{CH_3}$);EIMS m/z 760.5 ($\mathrm{M^+}$,100%).

11 **4**:Mp=109.7-111.2°C; ^{1}H-NMR ($\mathrm{CDCl_3}$) δ 6.85(s,8H,ArH),4.45(d,J=13.5 Hz, 4H,endo-ArCH), 3.90(t,J=14.4Hz,8H,$\mathrm{OCH_2}$), 3.15(d,J=13.5Hz,4H,exo-ArCH), 1.9(m,8H,$\mathrm{OCH_2}\mathit{CH}_2$), 1.30(m,24H,$(\mathit{CH}_2)_3\mathrm{CH_3}$), 0.90(t,12H,$\mathrm{CH_3}$); EIMS m/z 1076 ($\mathrm{M^+}$, 100%).

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13 **6**: Mp=168.0~170.0°C; ^{1}H-NMR($\mathrm{CDCl_3}$) δ 7.16(s,4H,ArH), 5.71(s,4H,ArH),4.30(d,J=13.5Hz,4H, endo-ArCH), 3.90(t,4H,$\mathrm{OCH_2}$),3.60(t,4H,$\mathrm{OCH_2}$), 3.00(d,J=13.5Hz,4H,exo-ArCH),1.90(m,8H,$\mathrm{OCH_2}\mathit{CH}_2$), 1.30(m,24H,$(\mathit{CH}_2)_3\mathrm{CH_3}$),0.90(t,12H,$\mathrm{CH_3}$);(nitrobenzene-$d_5$) δ 7.00 (s,4H,ArH),6.45(s,4H,ArH),5.90(bs,2H,OH),4.50(d, J=13.3 Hz, 4H, endo-ArCH),3.90(t,4H,$\mathrm{CH_2O}$),3.80(t, 4H,$\mathrm{OCH_2}$), 3.20(d, J=13.3 Hz, 4H,exo-ArCH), 1.80(m,8H,$\mathrm{OCH_2}\mathit{CH}_2$), 1.30(m,24H,$(\mathit{CH}_2)_3\mathrm{CH_3}$), 0.90(t,12H,$\mathrm{CH_3}$); IR ($\mathrm{CCl_4}$) 3300 $\mathrm{cm^{-1}}$; EIMS m/z 870($\mathrm{M^+}$-Br,100%); $\mathrm{FAB^+}$ (NOBA) m/z 950($\mathrm{M^+}$,15%).

14 Recently we confirmed that tetralithiation can be achieved by t-butyllithium instead of n-butyllithium at -78 °C. Even the lithiation by n-butyllithium at higher temperature resulted in tetralithiation, the former method gave better results.

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17 **7**: ^{1}H-NMR (nitrobenzene-d_5) δ 7.00 (s,4H,ArH), 6.29(s,4H,ArH), 4.40 (d, J=13.3Hz,4H,endo-ArCH), 3.90(t,4H,$\mathrm{OCH_2}$), 3.70(t,4H,$\mathrm{OCH_2}$), 3.40(s,6H,$\mathrm{OCH_3}$), 3.10(d,J=13.3Hz,4H,exo-ArCH), 1.90(m,8H,$\mathrm{OCH_2}\mathit{CH}_2$), 1.40 (m,24H,$\mathrm{(CH_2)_3CH_3}$), 0.90(t,12H,$\mathrm{CH_3}$).

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19 **8**: ^{1}H-NMR ($\mathrm{CDCl_3}$) δ 7.26(s,4H,ArH), 5.80(s,4H,ArH), 4.40(d,J=13.5Hz,4H,endo ArCH),4.20(t,4H,$\mathrm{CH_2O}$), 3.60(t,4H,$\mathrm{OCH_2}$),3.20(t,4H,$\mathrm{OCH_2}$),3.00(d, J=13.5 Hz, 4H, exo-ArCH), 1.90(m, 8H, $\mathrm{OCH_2}\mathit{CH}_2$), 1.30(m, 24H, $(\mathit{CH}_2)_3\mathrm{CH_3}$), 0.90(t,12H,$\mathrm{CH_3}$).