Cone-Structured Deep-Cavity Formation at Upper-Rim of Calix[4]arene Tetrahexyl Ether

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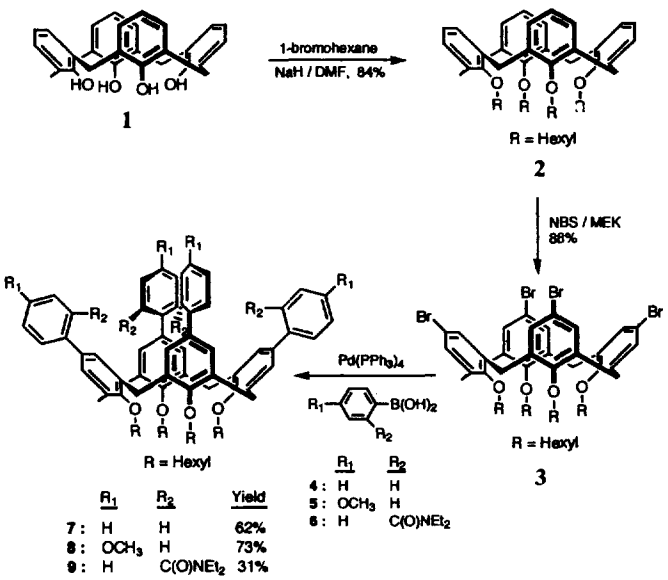
Calixarenes, which are accessible from base-catalyzed condensation of *para*-substituted phenols with formaldehyde, have attracted considerable attention because of their potential as enzyme mimics.[1] Particularly, derivatizations of the calix[4]arene at the "upper-rim" have been extensively studied to varify and elaborate the basket-shaped cavity.[2]

Of special interest, in this regard, has been the chemistry of rigid, hydrophobic deep-cavity calix[4]arene, which is expected to bind large organic guest molecules. But the general synthetic method is not available. The *p*-phenylcalix[4]arene was synthesized by Gutsche and No using stepwise route in extremely low overall yield[3,4] and later the direct substitution route starting from *p*-phenylphenol was in fail.[5] Arduini *et al.* reported the synthesis of *p*-phenylcalix[4]arene derivatives *via* *p*-iodocalix[4]arenes which was obtained in low yield from *p*-mercurated or *p*-thallated calix[4]arenes.[6] At recent, Atwood *et al.* reported a synthetic strategy for *p*-phenylcalix[4]arene tetramethyl ether in high yield by palladium (0)-catalyzed reaction but noted that the partial cone conformation was exhibited predominantly in solution state because the methyl ether of calix[4]arene is rather conformationally mobile.[7] Nicoud *et al.* also used the same reaction for the synthesis of *p*-substituted-phenylcalix[4]arene tetraethyl ether, but the rotation of ethoxy group through the ring resulted in the low yields of cone conformers.[8]

In this communication we report the syntheses of conformationally stable rigid, deep-cavity calix[4]arenes. *p*-Phenyl (**7**), *p*-(*p*-methoxy)phenyl (**8**), and *p*-(*o*-diethylcarbamyl)phenyl (**9**) calix[4]arene tetrahexyl ethers were obtained in high yields in cone conformation by palladium(0)-catalyzed Suzuki reaction between *p*-bromocalix[4]arene tetrahexyl ether **3** and aryl boronic acids.[9,10] The hexyloxy groups on the lower-rim were enough to protect the inversion of benzene units through the 16-membered hole in Suzuki reaction conditions.[11]

Calix[4]arene tetrahexyl ether **2** was obtained in 84% yield by treatment of a DMF solution of calix[4]arene **1** with NaH at 70℃ followed by 1-bromohexane. ^{1}H-NMR spectrum of **2** indicates that it exists in a fixed cone conformation (two doublets at δ 3.15 and δ 4.45 for Ar-CH_2-Ar, J=13.6 Hz).[12] Bromination of **2** with NBS in methyl ethyl ketone at room temperature gave *p*-bromocalix[4]arene tetrahexyl ether **3** in 88% yield. Syntheses of host **7**,[13] **8**,[14] and **9**[15] were performed by the palladium(0)-catalyzed coupling reactions of arylboronic acids **4**, **5**, and **6** with *p*-bromo compound **3** in 62%, 73%, 31% yield, respectively. The low yield of host **9** is due to the unstability against protodeboronation and



Scheme 1.

the large steric hindrance of boronic acid **6**.[10b] Aryl boronic acids were obtained from the corresponding aryl halides by transmetallation with *n*-BuLi, quench with trimethyl borate, and then acidic hydrolysis.

The ^{1}H-NMR spectrum of host **7** shows a singlet at δ 7.10 (20H) for *p*-phenyl hydrogens, a sharp singlet at δ 6.94 (8H) for aryl protons of the calix[4]arene, and a triplet at δ 4.0 for oxymethylene protons. The typical two doublet pattern of the methylene bridge protons at δ 4.57 (4H, H_{endo}, J=13.1 Hz) and δ 3.29 (4H, H_{exo}, J=13.1 Hz) indicates that host **7** exists in the cone conformation in solution. The ^{1}H-NMR spectrum of host **8** shows similar patterns to that of host **7** except a sharp singlet at δ 3.72 for methoxy protons and one pair of doublets at δ 7.03 and δ 6.65 (J=8.3 Hz) for the aryl protons of *p*-methoxyphenyl group. The peaks of the ^{1}H-NMR spectrum of host **9** are rather broad presumably due to the slow rotation of bulky ortho diethylcarbamyl groups and the consequent slow rotation of *p*-aryl groups on ^{1}H-NMR time scale. However the distinctive two doublets of cone conformation at δ 4.43 and δ 3.17 (J=12.6 Hz) were observed, which indicates that large aryl groups having bulky ortho substituent can be introduced without changing the cone conformation when the lower-rim of calix[4]arene was protected with hexyloxy groups.

The representative procedure for the synthesis of host **8** is as follows; *p*-bromo compound **3** (100 mg, 0.09 mmol) and tetrakis(triphenylphosphine)-palladium(0) (9.4 mg, 0.09 mol%) were dissolved in 10 mL of benzene. Aqueous 2 M Na_2CO_3 (5 mL) and *p*-methoxyphenyl boronic acid (85 mg, 0.56 mmol) in 5 mL of EtOH were then added. The mixture was refluxed for 24 hrs and cooled to room temperature. The organic phase was separated and the aqueous phase was extracted with 20 mL of ether. The combined organic phases were dried with brine and then with anhydrous $MgSO_4$. The solvent was evaporated, and the crude mixture was purified by column chromatography (silica gel, 1×25 cm, hexane/CH_2Cl_2=1/1). Product **8** was obtained in 73% yield (80 mg) after recrystallization from a mixture of CH_2Cl_2 and methanol.

Conclusively we observed that the Pd(0)-catalyzed coupling reaction of *p*-bromocalix[4]arene tetrahexyl ether **3** with arylboronic acids having various functional groups, *e.g.*, even a sterically hindered ortho substituent can be used as a general method to get a calix[4]arene derivative having cone-structured rigid deep-cavity. Molecular recognition studies and further functionalizations of obtained hosts are in progress.

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13. **7**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.10 (s, 20H, -ArH), 6.94 (s, 8H, OAr-), 4.57 (d, 4H, J=13.1 Hz, *endo*-ArC*H*), 4.0 (t, 8H, J=7.4 Hz, OCH_2), 3.29 (d, 4H, J=13.1 Hz, *exo*-ArCH), 2.02 (m, 8H, OCH_2CH_2), 1.57-1.27 (m, 24H, $(CH_2)_3CH_3$), 0.95 (m, 12H, CH_3); MS (FAB(+)), m/z 1065 (M^+, 7%).
14. **8**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.03 (d, 8H, J=8.3 Hz, -*Ar*OCH_3), 6.88 (s, 8H, O*Ar*Ar), 6.65 (d, 8H, J=8.3 Hz, -*Ar*OCH_3), 4.55 (d, 4H, J=13.3 Hz, *endo*-ArC*H*), 3.98 (t, 8H, J=7.3 Hz, OCH_2), 3.72 (s, 12H, OCH_3), 3.25 (d, 4H, J=13.3 Hz, *exo*-ArCH), 1.98 (m, 8H, OCH_2CH_2), 1.45-1.28 (m, 24H, $(CH_2)_3CH_3$), 0.95 (m, 12H, CH_3).
15. **9**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.2-6.9 (m, 16H, -ArH), 6.8 (d, 8H, OAr-), 4.43 (d, 4H, J=12.6 Hz, *endo*-ArC*H*), 3.8 (br s, 8H, OCH_2), 3.17 (d, 4H, J=12.6 Hz, *exo*-ArC*H*), 2.9 (br s, 8H, NCH_2), 2.6 (br s, 8H, NCH_2), 1.94 (br s, 8H, OCH_2CH_2), 1.39-1.25 (m, 24H, $(CH_2)_3CH_3$), 0.94-0.70 (m, 36H, CH_3); MS (FAB(+)), m/z 1462 (M^+, 20%), 1390 (M^+-NEt_2, 5%); FT-IR (KBr), 1633 cm^{-1} ($\nu_{C=O}$).