3-Methylcalix[4]arene: A New Versatile Precursor to Inherently Chiral Calix[4]arenes

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Introduction

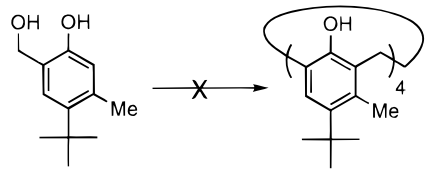
Calix[4]arenes are one of the most extensively developed platforms for the design of synthetic receptors.[1] This interest stems from the synthetic availability of large quantities, the ability to produce rigid well-defined binding sites, and the versatility of these compounds for further functionalization. The utility of calixarenes in materials applications has also been recognized, and these materials have been employed for the formation of porous monolayers,[2] nonlinear optical chromophores,[3] and bowlic liquid crystals.[4]

The importance of receptors with chiral discriminating ability is self-evident and has led to interest in calix[4]-arenes with different forms of chirality.[5] Calix[4]arenes with meta-substituted phenol rings are noncentrosymmetric with C_4 symmetry and are inherently chiral. The opportunity to produce chiral receptors from this substitution pattern has been previously recognized, and a number of meta-substituted calix[4]arenes have been prepared by Böhmer and others.[6] However, these previously investigated compounds have limited utility since the para positions are blocked. This excludes the use of the extensive methodology developed for functionalization of the upper rim which generally requires an unsubstituted para position.[1]

High chirality is also known to manifest important organizational properties in the liquid crystals.[7] Toward this end, we required calix[4]arenes with chiral cores capable of undergoing functionalization on the upper rim by a variety of protocols. In this note, we describe an entry into such a system, 3-methylcalix[4]arene, and demonstrate the utility of this compound for the formation of functionalized chiral calix[4]arenes.

Results and Discussion

We initially endeavored to synthesize 3-methylcalix-[4]arene using the well-known tert-butyl blocking group which can be readily removed by reaction with $AlCl_3$.[8] However, cyclization reactions of **1** (shown below) failed to give **2** under both basic and acidic conditions. Thus,



1 **2**

an alternative blocking group was needed to obtain the targeted calix[4]arene. We considered bromine as a good candidate because it can be easily removed and also provides an entry into other derivatization schemes such as cross-coupling, substitution, and metallation reactions.

The total synthesis of 3-methylcalix[4]arene (**8**) is outlined in Scheme 1. Para-bromination of *m*-cresol (**3**) with NBS in DMF proceeded in high yield (>85%) to give 4-bromo-3-methylphenol (**4**).[14] The most troublesome step in the entire synthesis was the hydroxymethylation of **4** to give 4-bromo-2-(hydroxymethyl)-5-methylphenol (**5**). As determined by TLC, the reaction of **4**, NaOH, and aqueous HCOH (12 h) produced a mixture of products along with the starting material. Column chromatography gave recovered starting material **4** in the first fraction (30%). The desired product **5** (30%) and a small amount of the other possible regioisomer **6** (5%) were collected as the second fraction. A third fraction identified by NMR was the bis-hydroxymethylated byproduct **7** (30%). The purity of **5** was critical to the synthesis since 1 equiv of **6** consumed 3 equiv of **5** when cyclized to form 4-bromo-3-methylcalix[4]arene. Hence, to avoid additional calix[4]arene regioisomers, it was necessary to remove even trace amounts of **6** from **5**. Although purification of **5** by column chromatography was unsuccessful, we were able to obtain **5** in pure form by fractional recrystallization from $CHCl_3$. Cyclization to form 4-bromo-3-methylcalix[4]arene (**8**) was effected by reaction of **5** with $TiCl_4$ in a dilute 1,4-dioxane solution under reflux. Column chromatography and subsequent trituration with diethyl ether gave **8** as white solid in 25% yield. The final step involved reductive debromination of **8** using Pd−C/formic acid in DMF which proceeded in essentially quantitative yields to produce 3-methylcalix[4]arene (**9**). The regioisomeric purity of **9** was confirmed by ^1H and ^{13}C NMR spectroscopy. A

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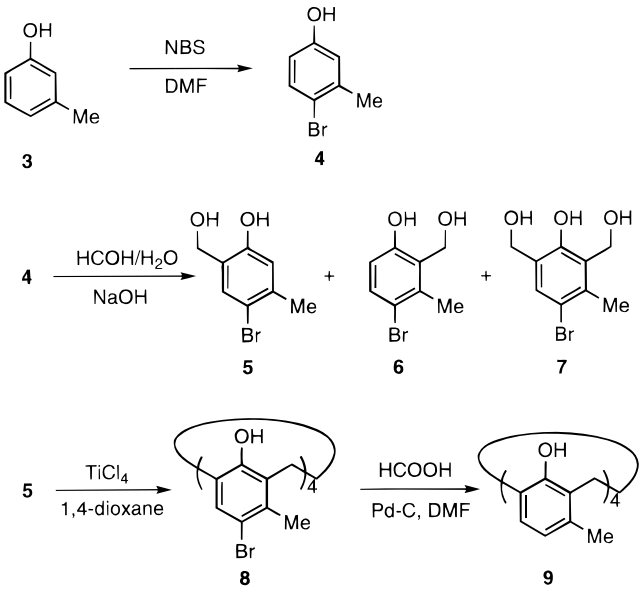
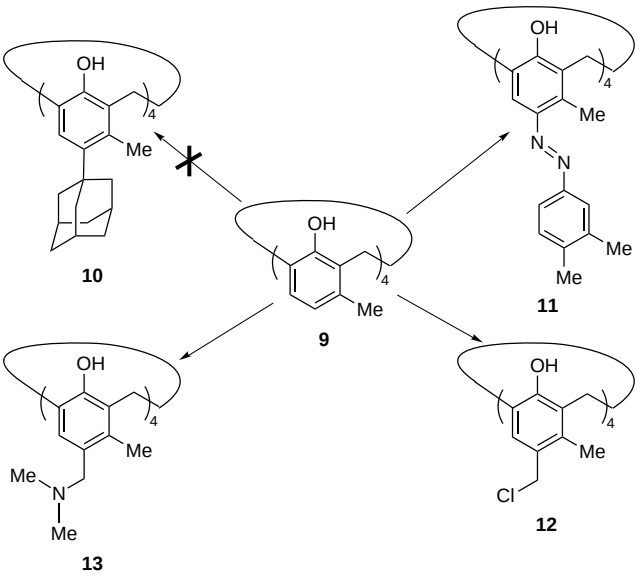
Scheme 1



Scheme 2



singlet at 3.92 ppm for the $ArCH_2Ar$ group shows that **9** is conformationally averaged on the NMR time scale. Similar to 3,4-dimethylcalix[4]arene,[6a] **9** is frozen in a cone conformation at lower temperature and the typical doublet pattern is observed for the $ArCH_2Ar$ groups. We have determined the coalescence temperature to be −6 °C (200 MHz), and from a $\Delta\nu = 55$ Hz and $^2J = 14.6$ Hz, we calculate an energy barrier for ring interconversion of $\Delta G = 13.03$ kcal/mol. The chemical shift at 10.61 ppm for ArOH indicates a intramolecular hydrogen bonding similar to that observed for 3,4-dimethylcalix[4]arene.

To ascertain the versatility of **9**, we subjected it to a number of upper rim functionalization reactions (Scheme 2) which are known to proceed in good yields for the parent calix[4]arene system. In general, the electronic influence of the methyl group in **9** should enhance reactivity with electrophiles; however the methyl group may also limit reactions with sterically bulky electrophiles. Among the many functionalization reactions of calix[4]arenes, we are particularly interested in diazo addition reactions because we have found them to be useful for the construction of bowlic liquid crystals.[4] Diazo addition reactions, first observed by Shinkai, are know to be autoaccelerative[9] and can proceed to the tetrasubstituted product in high yields.[4a] Subjecting **9** to these procedures gave **11** as a yellow solid in 45% yield. We believe that the lower yield than we have previously attained in the parent system[4a] is due to poor solubility of the di- or triazo-substituted 3-methylcalix[4]arenes.

Chloromethylated calix[4]arenes are very useful intermediates for the preparation of more complex host molecules,[10] and 4-(chloromethyl)-3-methylcalix[4]arene (**12**) was prepared by adaptation of Ungaro's procedure in over 88% yield.[11] This reaction proceeds in higher yield than observed for the parent calix[4]arene system, indicating that the electrophilic addition is accelerated by the *m*-methyl group. Another versatile functionalization procedure is the quinonemethide methodology reported by Gutsche and Nam.[12] This scheme first involves aminomethylation followed by quaternization to allow for nucleophilic substitution reactions. We find that **9** can be easily converted to 4-((dimethyamino)-methyl)-3-methylcalix[4]arene (**13**), and this system also displays a higher yield (75%) than the parent calix[4]-arene system. The greater steric demands of **9** are apparent from the lack of reactivity with adamantyl-based carbocations which were recently reported to react with the parent system in good yield.[13]

The chiral calix[4]arenes reported here are conformationally dynamic and, hence, have little utility as chiral receptors. We are presently investigating conformational locking to produce resolvable materials by functionalization of the lower rim with sterically bulky groups and $W{=}O^{4+}$ complexation.

Experimental Section

4-Bromo-2-(hydroxymethyl)-5-methylphenol (5). A mixture of **4**[14] (56 g, 0.30 mol), a solution of NaOH (12 g, 0.30 mol) in 120 mL of H_2O, and aqueous formaldehyde (22.5 mL, 0.30 mol) was stirred at rt under argon for 12 h. The resulting yellow solution was then neutralized with AcOH and extracted with EtOAc (2 × 200 mL). The organic phase was separated and dried over $MgSO_4$, and after removal of the solvent in vacuum, the resultant yellow oil was purified by column chromatography (gradient silica column starting with EtOAc:hexane (1:10) and ending with EtOAc) to give three fractions of white solids. The second fraction contained a 30% yield of **5** along with 5% of **6**. Recrystallization of this fraction from $CHCl_3$ gave 13.0 g (20%) of **5** as white crystals: mp 116.5−118 °C; ^{1}H NMR (acetone-d_6) δ 8.61 (s, 1H), 7.40 (s, 1H), 6.76 (s, 1H), 4.66 (s, 2H), 2.24 (s, 3H); ^{13}C NMR δ 154.3, 136.7, 130.8, 127.7, 117.6, 113.3, 59.6, 21.8. Anal. Calcd for $C_8H_9BrO_2$: C, 44.27; H, 4.18. Found: C, 44.21; H, 4.18.

4-Bromo-2-(hydroxymethyl)-3-methylphenol (6). Isolated as a byproduct from **4** in 5% yield (see text): ^{1}H NMR (acetone-d_6) δ 8.92 (b, 1H), 7.27 (d, $J = 8.66$ Hz, 1H), 6.63 (d, 1H), 4.83 (s, 2H), 2.37 (s, 3H); ^{13}C NMR δ 155.0, 136.4, 131.3, 126.3, 114.6, 114.2, 57.3, 17.9. Anal. Calcd for $C_8H_9BrO_2$: C, 44.27; H, 4.18. Found: C, 44.21; H, 4.18.

4-Bromo-2,6-bis(hydroxymethyl)-3-methylphenol (7). Isolated as a byproduct from the preparation of **5**. This material was in the third fraction off the column and was obtained in 30% yield: mp 121−122 °C; ^{1}H NMR (acetone-d_6) δ 7.35 (s, 1H), 4.87 (s, 2H), 4.68 (s, 2H), 2.31 (s, 3H); ^{13}C NMR δ 154.0, 134.6, 129.7, 127.7, 126.1, 114.6, 60.4, 59.1, 18.2. Anal. Calcd for $C_9H_{11}BrO_3$: C, 43.75; H, 4.49. Found: C, 44.07; H, 4.46.

4-Bromo-3-methylcalix[4]arene (8). This compound was prepared from **5** in 25% yield according to the literature procedure reported for 3,4-dimethylcalix[4]arene:[6a] mp >295 °C dec; MS 852 (M^+, FAB); ^{1}H NMR ($CDCl_3$) δ 10.13 (s, 4H), 7.34 (s, 4H), 3.93 (s, 8H), 3.69 (s, CH_2Cl_2), 2.52 (s, 12H); ^{13}C NMR δ 149.0, 132.6, 132.5, 125.5, 122.3, 117.3, 27.6, 20.8. Anal. Calcd for $C_{32}H_{28}Br_4O_4 \cdot 1.3CH_2Cl_2$: C, 46.92; H, 3.23. Found: C, 46.61; H, 3.54.

3-Methylcalix[4]arene (9). A mixture of **7** (1.0 g, 1.26 mmol) in formic acid (85%, 5 mL), 10% Pd−C (0.5 g, 0.47 mmol), and DMF (25 mL) was refluxed under argon for 12 h. The resulting solution was poured into H_2O and extracted with CH_2Cl_2 (2 × 50 mL). The organic phase was then separated , dried over $MgSO_4$, and evaporated in vacuum. The yellow residue was redissolved in CH_2Cl_2, evaporated onto silica gel, and then purified by column chromatography (silica gel, CH_2Cl_2) to give 0.59 g (98%) of **8** as a white solid: mp >375 °C dec; MS 480 (M^+, EI); ^{1}H NMR ($CDCl_3$) δ 10.61 (s, 4H), 7.04 (d, 4H), 6.61 (d, 4H), 3.91 (s, 8H), 2.41 (s, 12H); ^{13}C NMR δ 149.9, 136.0, 128.7, 126.6, 124.8, 123.5, 27.2, 20.6. Anal. Calcd for $C_{32}H_{32}O_4 \cdot 2H_2O$: C, 74.4; H, 7.01. Found: C, 73.95; H, 6.89.

Calix[4]arene 11. Prepared from **9** in 45% yield according to the published procedure for the diazo coupling of calix[4]arene:[9] mp >375 °C; MS 1009 ($(M + 1)^+$, FAB); ^{1}H NMR (DMSO-d_6) δ 7.59 (s, 4H), 7.54 (s, 4H), 7.48 (d, J = 8.07 Hz, 4H), 3.93 (s, 8H), 7.22 (s, J = 8.07 Hz, 8H), 4.08 (s, 8H), 2.77 (s, 12H), 2.26 (s, 12H), 2.24 (s, 12H). Anal. Calcd for $C_{64}H_{64}N_8O_4 \cdot 1.3CH_2Cl_2$: C, 69.97; H, 5.95; N, 10.01. Found: C, 69.90; H, 5.94; N, 10.16.

Calix[4]arene 12. Prepared from **9** in 88% yield according to the published procedure for the chloromethylation of calix[4]arene:[11] mp >255 °C dec; MS 675 ($(M + 1)^+$, FAB); ^{1}H NMR ($CDCl_3$) δ 10.44 (s, 4H), 7.12 (s, 4H), 4.46 (s, 8H), 3.95 (s, 8H), 2.50 (s, 12H); ^{13}C NMR δ 150.4, 135.6, 131.1, 129.1, 127.3, 124.3, 46.0, 26.7, 16.0. Anal. Calcd for $C_{36}H_{40}Cl_4O_4 \cdot CH_2Cl_2$: C, 58.19; H, 5.50. Found: C, 58.43; H, 5.05.

Calix[4]arene 13. Prepared from **9** in 75% yield according to the published procedure for aminomethylation of calix[4]arene:[12a] mp >280 °C dec; MS 709 ($(M + 1)^+$, FAB); ^{1}H NMR ($CDCl_3$) δ 7.01 (s, 4H), 3.96 (s, 8H), 3.17 (s, 8H), 2.46 (s, 12H), 2.16 (s, 24H); ^{13}C NMR δ 149.1, 131.3, 130.1, 127.1, 123.8, 63.1, 45.4, 26.9, 16.0. Anal. Calcd for $C_{44}H_{66}N_4O_4 \cdot H_2O$: C, 72.72; H, 8.53; N, 7.70. Found: C, 72.93; H, 8.42; N, 7.39.

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