Selective Functionalization of Calix[6]arenes at the Upper Rim

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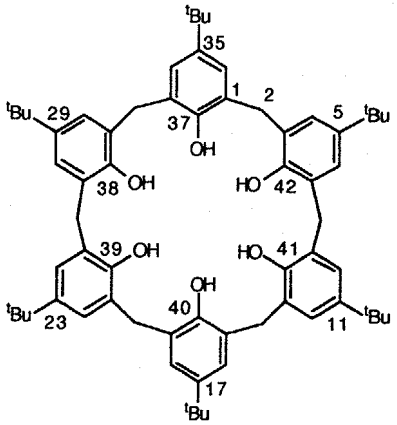
Methylation of partially *O*-benzylated *p-tert*-butylcalix[6]arenes followed by hydrogenolysis constitutes an efficient method for the preparation of partially *O*-alkylated calix[6]arenes in gram amounts, without adhering to column chromatography separations. Selective de-*tert*-butylation followed by halogenation, or *ipso*-nitration of these precursors affords calix[6]arenes containing bromo- or nitro-substituents, respectively, at precise positions of the upper rim.

A large amount of macrocyclic and cleft like structures have been designed for the selective complexation of cationic, anionic or neutral organic substrates. Calix[4]arenes, the cyclic tetramers of phenols, have gained particular attention for this issue, because under certain conformations (cone, partial cone) they contain a cavity.[1,2] However, inclusion of small organic substrates *inside* calix[4]arenes has been reported mainly in the solid state, simply because the cavity is too small to host appropriate substrates in solution. For this reason, calix[4]arenes are now better viewed as molecular platforms, on which functional groups can be oriented in space to define cavities or clefts. Calix[6]arenes, the cyclic hexamers of phenols, are endowed with larger cavities, but these substances are much more flexible and difficult to functionalize than calix[4]arenes. In order to make calix[6]arenes available as molecular building blocks, we have developed procedures for the synthesis and characterization of some partially *O*-alkylated derivatives of *p-tert*-butylcalix[6]arene (**1**) and the parent calix[6]arene.[3] On the other hand, Gutsche has recently described the selective lower rim *O*-benzylation and *O*-aroylation of *p-tert*-butylcalix[6]-arene,[4] and several other examples of functionalized calix[6]arenes exist in the literature.[5-8] In this paper we report on the selective upper rim functionalization exploiting, as for calix[4]arenes,[9] the known differences between anisole and phenol reactivities.



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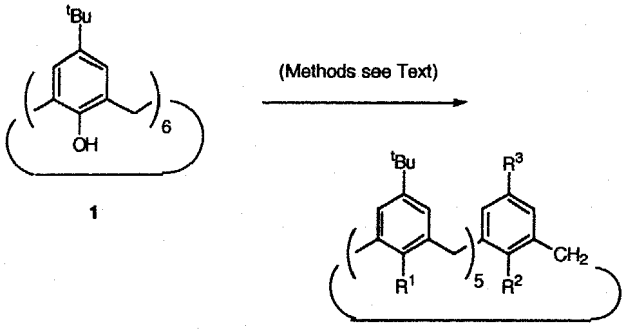
Use of pentamethoxy-*p-tert*-butylcalix[6]arene (**2**) as the starting material illustrates our synthetic strategy. Compound **2** has a phenol ring and five anisole components in its structure. It is the minor component (15%) from direct methylation of *p-tert*-butylcalix[6]arene (**1**), the major one being the 1,2,3-trimethylated[10] isomer (38%).[3] Although **2** can be isolated and purified by column chromatography, a large scale preparation by this procedure can be hardly recommended. Thus, we studied an alternative stepwise route: compound **1** was transformed into the monobenzylated derivative **3**,[3] and this compound was sequentially submitted to exhaustive methylation (to give **4**) and to hydrogenolysis (Scheme 1). Since no chromatographic separations were needed, **2** was accessible in gram amounts by this three-step procedure, in a 76% overall yield.

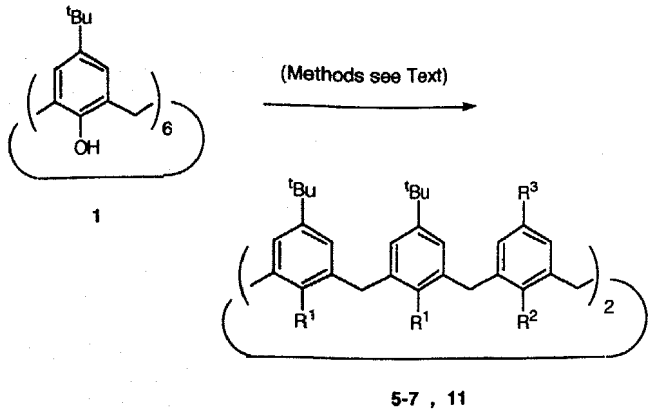


	R^1	R^2	R^3
2	OMe	OH	*t*-Bu
3	OH	OCH_2Ph	*t*-Bu
4	OMe	OCH_2Ph	*t*-Bu
8	OMe	OH	H
9	OMe	OH	Br
10	OMe	OH	NO_2

Scheme 1

Similarly, 1,2,4,5-tetramethoxy-*p-tert*-butylcalix[6]arene (**5**) was obtained in a 75% overall yield via the 1,4-bis-*p*-methylbenzyl derivative **6**[4] (Scheme 2). A direct methylation affords only 35% of this material, and chromatographic purification from the major component (the 1,3,5-trimethylated derivative) is necessary.[3]

As for their calix[4]arene analogues, partially *O*-methylated calix[6]arenes **2** (one free OH) and **5** (two free OH's at opposite rings) are useful starting materials for the selective functionalization of the upper rim. Thus, selective de-*tert*-butylation of **2** with a sixfold excess of aluminum chloride in toluene gave 50% yield of the desired compound **8**, which was subsequently brominated [*N*-bromosuccinimide (NBS), 2-butanone] to the corresponding bromocalix[6]arene **9** (75%). The de-*tert*-butylation



1

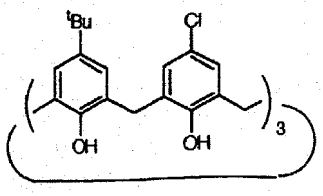
5-7 , 11

	R^1	R^2	R^3
5	OMe	OH	*t*-Bu
6	OH	$OCH_2C_6H_4Me$-4	*t*-Bu
7	OMe	$OCH_2C_6H_4Me$-4	*t*-Bu
11	OMe	OH	NO_2

Scheme 2

reaction was found to be very sensitive to the purity of the Lewis acid and to the stirring efficiency, otherwise considerable amounts of dealkylated compounds at both the phenol and anisole rings were detected. On the other hand, *ipso*-nitration[11] takes place selectively at the free phenolic rings of **2** and **5**, yielding the corresponding nitro and dinitro compounds **10** and **11** (40% and 45%, respectively). Further elaboration (*O*-protection, reduction of the nitro groups, and condensation of the resulting amines) will lead to calix[6]arenes endowed with suitable clefts and other functionalities for the molecular recognition of appropriate organic guests. We will report on these applications in due course.

Preliminary NMR studies on the new calix[6]arenes revealed broad signals for most of the compounds, accounting for a considerable degree of conformational mobility at room temperature. However, resolved peaks were found for **3**, **4**, **6**, and **7** at room temperature. Bidimensional experiments (COSY45, HMQC) showed well resolved AX systems for the methylene protons, indicating a rigid conformation. The number and multiplicities of the rest of the signals were in agreement with the presence of a symmetry element (plane or C_2 axis). From the similarities of the methylene region of **3** and the 1,3,5-tri-*tert*-butyl-2,4,6-trichlorocalix[6]arene (**12**), a fixed winged (out-up-up-out-up-up) conformation, as established previously for **12**,[8] is likely.



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Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker WP-200-SY (200 MHz) instrument. COSY45 and HMQC experiments were performed on a Bruker AMX 300 (300 MHz). Carbons were assigned by DEPT experiments. TMS was used as an internal standard. IR spectra were recorded on a Philips PU-9761 instrument. Preparative column chromatography separations were performed on SDS silica gel 60A CC (230–400 mesh), while precoated silica gel plates (Aluchrom F_{254}) were used for analytical TLC. FAB mass spectra were performed on a VG AutoSpec instrument, with *m*-nitrobenzyl alcohol as a matrix. All solvents were purified by standard procedures. All other chemicals were analytically pure, and were used without further purification. $AlCl_3$ was purchased from Aldrich. For all new compounds satisfactory microanalyses were obtained: C ± 0.31, H ± 0.47 (Exception: **7**, C + 0.54).

37-Benzyloxy-5,11,17,23,29,35-hexa-*tert*-butyl-38,39,40,41,42-pentamethoxycalix[6]arene (4):

To a stirred slurry of NaH (60% oil dispersion, 215 mg, 5.3 mmol) in THF (80 mL) under Ar was added a solution of calix[6]arene **3**[3] (1.00 g, 0.9 mmol). After 30 min, Me_2SO_4 (0.6 mL, 6.3 mmol) was added. The mixture was stirred at r.t. for 24 h, and quenched with 25% aq ammonia (2 mL). The resulting mixture was stirred for 45 min, acidified with 2N HCl and extracted with Et_2O (2 × 30 mL). The combined extracts were washed with brine (2 × 50 mL), dried ($MgSO_4$) and evaporated. The residue was triturated with MeOH to give pure **4**; yield 920 mg (90%); mp 242 °C.

MS (FAB): m/z = 1132.7 (M^+, calc. 1132.8)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.53 (m, 2H, ArH), 7.36 (m, 3H, ArH), 7.23 (d, J = 2.5 Hz, 2H, ArH), 7.11 (s, 2H, ArH), 7.09 (d, J = 2.5 Hz, 2H, ArH), 6.91 (d, J = 2.5 Hz, 2H, ArH), 6.87 (s, 2H, ArH), 6.84 (d, J = 2.5 Hz, 2H, ArH), 4.87 (s, 2H, $OC\underline{H}_2Ph$), 4.46 (d, J = 14.5 Hz, 2H, $ArC\underline{H}_2Ar$), 4.17 (d, J = 15.4 Hz, 2H, $ArC\underline{H}_2Ar$), 4.04 (d, J = 15.1 Hz, 2H, $ArC\underline{H}_2Ar$), 3.80 (d, J = 15.1 Hz, 2H, $ArC\underline{H}_2Ar$), 3.67 (d, J = 15.4 Hz, 2H, $ArCH_2Ar$), 3.52 (d, J = 14.5 Hz, 2H, $ArC\underline{H}_2Ar$), 3.20 (s, 6H, OCH_3), 2.77 (s, 3H, OCH_3), 2.51 (s, 6H, OCH_3), 1.25 [s, 18H, $C(CH_3)_3$], 1.23 [s, 9H, $C(CH_3)_3$], 1.03 [s, 18H, $C(CH_3)_3$], 0.97 (s, 9H, $C(CH_3)_3$].

^{13}C NMR (50 MHz, $CDCl_3$): δ = 154.3, 154.2, 153.5, 152.0, 145.9, 145.6, 137.8, 133.8, 133.5, 133.3, 133.2 (ArC), 128.4, 127.7, 127.3, 126.7 (ArCH), 125.9 (ArC), 125.1, 125.0, 124.5 (ArCH), 74.5 ($ArCH_2O$), 59.9, 59.8 (OCH_3), 34.0 [$\underline{C}(CH_3)_3$], 31.4, 31.3 [$C(\underline{C}H_3)_3$], 30.8, 30.5 ($ArC\underline{H}_2Ar$).

5,11,17,23,29,35-Hexa-*tert*-butyl-38,39,40,41,42-pentamethoxycalix[6]aren-37-ol (2):

A suspension of calix[6]arene **4** (750 mg, 0.66 mmol) in EtOAc (50 mL) was heated until complete solution and then allowed to cool to r.t. 10% Pd/C (70 mg) was added and the mixture was stirred under H_2 for 1.5 h. The mixture was filtered through Celite and the filtrate was evaporated to dryness. The residue was triturated with MeOH to afford pure **2**; yield: 686 mg (100%); mp 274 °C (dec.) (CH_2Cl_2/MeOH) (Lit.[3] 274 °C, dec).

5,11,17,23,29,35-Hexa-*tert*-butyl-38,39,41,42-tetramethoxy-37,40-bis[(4-methylbenzyl)oxy]calix[6]arene (7):

The same procedure as for **4** was followed, starting from calix[6]arene **6**[4] (500 mg, 0.42 mmol), NaH (60% dispersion oil, 101 mg, 2.53 mmol), THF (45 mL) and Me_2SO_4 (0.32 mL, 3.38 mmol); reaction time 40 h. The crude reaction product was recrystallized from CH_2Cl_2/MeOH (1:3) to give pure **7**; yield: 510 mg (100%); mp > 300 °C.

MS (FAB): m/z = 1236.8 (M^+, calc. 1236.8).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.45 (d, J = 8 Hz, 4H, ArH), 7.21 (d, J = 2.4 Hz, 4H, ArH), 7.18 (d, J = 8 Hz, 4H, ArH), 6.98 (s, 4H, ArH), 6.85 (d, J = 2.4 Hz, 4H, ArH), 4.85 (s, 4H, $OC\underline{H}_2Ar$), 4.29 (d, J = 14.0 Hz, 4H, $ArC\underline{H}_2Ar$), 3.82 (br s, 4H, $ArC\underline{H}_2Ar$), 3.60 (d, J = 14.0 Hz, 4H, $ArC\underline{H}_2Ar$), 2.65 (s, 12H, OCH_3), 2.38 (s, 6H, $C\underline{H}_3Ar$), 1.15 [s, 36H, $C(CH_3)_3$], 1.04 [s, 18H, $C(CH_3)_3$].

^{13}C NMR (50 MHz, $CDCl_3$): δ = 154.1, 152.2, 145.5, 137.3, 135.0,

, 133.4, 133.3 (ArC), 129.0, 127.7, 127.0, 125.7, 124.9 (ArH), OCH$_2$Ar), 59.5 (OCH$_3$), 34.0 [C(CH$_3$)$_3$] 31.3 [C(CH$_3$)$_3$], 30.3, ArCH$_2$Ar), 21.2 (CH$_3$Ar).

17,23,29,35-Hexa-*tert*-butyl-38,39,41,42-tetramethoxycalix[6]--37,40-diol (5):

ixture of **7** (1.00 g, 0.8 mmol) and 10% Pd/C (200 mg) in Cl$_2$ (75 mL) was stirred at r.t. under H$_2$ for 24 h. The mixture iltered through Celite and the filtrate was discarded. The residue triturated with MeOH to give **5**; yield: 740 mg (90%); mp C ($CHCl_3$/MeOH) (dec) (Lit.[3] 282 °C, $CHCl_3$/MeOH, dec).

,17,23,29-Penta-*tert*-butyl-38,39,40,41,42-pentamethoxy-[6]aren-37-ol (8):

ixture of calix[6]arene **2** (200 mg, 0.19 mmol), $AlCl_3$ (160 mg, ımol) and anhydr. toluene (3.4 mL) was stirred at 1250 rpm t. for 2 h. The mixture was treated with 1 N HCl (4 mL) and ɔd for 20 min. The organic layer was separated and the aqueous was extracted with CH_2Cl_2 (2 × 25 mL), the combined organic s were washed with brine (2 × 20 mL) and dried (Na_2SO_4). solvent was removed and the residue was purified by column matography (CH_2Cl_2/THF, 100:1) to give **8**; yield 95 mg %); mp 168–172 °C.

(FAB) m/z = 987.1 (M^+, calc. 986.6).

NMR (200 MHz, $CDCl_3$): δ = 7.52 (s, 1 H, OH), 7.08 (d, 2.5 Hz, 2 H, ArH), 7.03 (d, J = 2.5 Hz, 2 H, ArH), 6.99 (d, 2.5 Hz, 2 H, ArH), 6.94 (d, J = 2.5 Hz, 2 H, ArH), 6.90 (s, 2 H,), 6.86 (d, J = 7.4 Hz, 2 H, ArH), 6.63 (m, 1 H, ArH), 3.93 (br H, ArCH$_2$Ar), 3.82 (br s, 4 H, ArCH$_2$Ar), 3.43 (s, 3 H, OCH$_3$), (s, 6 H, OCH$_3$), 3.00 (s, 6 H, OCH$_3$), 1.16 [s, 18 H, C(CH$_3$)$_3$], [s, 18 H, C(CH$_3$)$_3$], 1.02 [s, 9 H, C(CH$_3$)$_3$].

NMR (50 MHz, $CDCl_3$): δ = 154.3, 152.9, 151.9, 146.5, 145.6, 2, 133.5, 133.2, 133.1, 132.4 (ArC), 128.0 (ArCH), 127.8 (ArC), 4, 126.0, 125.5, 119.7 (ArCH), 60.6, 60.3 (OCH$_3$), 34.1 CH$_3$)$_3$], 31.5 (ArCH$_2$Ar), 31.3 [C(CH$_3$)$_3$], 31.2 [C(CH$_3$)$_3$], 30.3 CH$_2$Ar).

3romo-5,11,17,23,29-penta-*tert*-butyl-38,39,40,41,42-pentameth-calix[6]aren-37-ol (9):

ı solution of calix[6]arene **8** (100 mg, 0.10 mmol) in 2-butanone ıL) was added NBS (23 mg, 0.13 mmol). The mixture was stirred t. for 5.5 h, 10% $NaHSO_3$ (1.5 mL) was added and the mixture stirred for 1 h and extracted with CH_2Cl_2 (2 × 15 mL). The ınic layer was washed with brine (2 × 30 mL) and dried $_2SO_4$). The solvent was eliminated and the residue was triturated ı MeOH (2 mL) and filtered to give **9**; yield: 80 mg (75%); mp –194 °C.

AB) m/z = 1064.6 (M, calc. 1064.5)

NMR (200 MHz, $CDCl_3$): δ = 7.73 (s, 1 H, OH), 6.99 (d, 2.4 Hz, 2 H, ArH), 6.94 (s, 4 H, ArH), 6.91 (s, 2 H, ArH), 6.86 J = 2.4 Hz, 2 H, ArH), 6.83 (s, 2 H, ArH), 3.85 (br s, 8 H, CH$_2$Ar), 3.69 (br s, 4 H, ArCH$_2$Ar), 3.41 (s, 3 H, OCH$_3$), 3.14 5 H, OCH$_3$), 2.93 (s, 6 H, OCH$_3$), 1.11 [s, 18 H, C(CH$_3$)$_3$], 1.07 18 H, C(CH$_3$)$_3$], 0.95 [s, 9 H, C(CH$_3$)$_3$].

NMR (50 MHz, $CDCl_3$): δ = 154.2, 152.8, 151.1, 146.7, 145.6, .3, 133.7, 133.5, 133.2, 132.8, 131.6 (ArC), 130.5 (ArCH), 130.0 C), 126.3, 126.1, 125.9, 125.4 (ArCH), 111.6 (ArC), 60.7, 60.3 CH$_3$), 34.1, 34.0 [C(CH$_3$)$_3$], 31.3 [C(CH$_3$)$_3$], 30.3 (ArCH$_2$Ar).

1,17,23,29-Penta-*tert*-butyl-38,39,40,41,42-pentamethoxy-35-ocalix[6]aren-37-ol (10):

a stirred mixture of calix[6]arene **2** (200 mg, 0.19 mmol) in an-lr. CH_2Cl_2 (1.2 mL) and glacial AcOH (1.2 mL) was added 65% NO$_3$ (64 μL, 0.92 mmol), at 0 °C. The mixture was rapidly allowed warm to r.t. and stirred for 30 min. H_2O was added (6 mL) and mixture was extracted with CH_2Cl_2 (2 × 25 mL). The organic er was washed with brine (2 × 20 mL), dried (Na_2SO_4) and eva-ated. The residue was triturated with hexane (14 mL) and fil-ed. The filtrate was reduced to 50% and cooled to 0 °C. The ulting solid was filtered to give **10**; yield: 78 mg (40%); mp 1–202 °C.

MS (FAB): m/z = 1031.7 (M^+, calc. 1031.6).

IR ($CHCl_3$): ν = 1490, 1330 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.04 (s, 1 H, OH), 7.85 (s, 2 H, ArH), 7.06 (d, J = 2.4 Hz, 2 H, ArH), 7.04 (s, 4 H, ArH), 6.94 (d, J = 2.4 Hz, 2 H, ArH), 6.89 (s, 2 H, ArH), 3.93 (br s, 4 H, ArCH$_2$Ar), 3.92 (br s, 4 H, ArCH$_2$Ar), 3.84 (br s, 4 H, ArCH$_2$Ar), 3.53 (s, 3 H, OCH$_3$), 3.31 (s, 6 H, OCH$_3$), 2.98 (s, 6 H, OCH$_3$), 1.18 [s, 18 H, C(CH$_3$)$_3$], 1.11 [s, 18 H, C(CH$_3$)$_3$], 1.01 [s, 9 H, C(CH$_3$)$_3$].

^{13}C NMR (50 MHz, $CDCl_3$): δ = 158.4, 154.2, 153.9, 152.5, 147.2, 145.7, 145.3, 140.3, 133.9, 133.5, 133.2, 132.7, 130.7, 128.5 (ArC), 126.7, 126.4, 126.1, 125.8, 125.3, 124.1 (ArCH), 60.9, 60.4, 60.2 (OCH$_3$), 34.2, 34.0 [C(CH$_3$)$_3$], 31.4 (ArCH$_2$Ar), 31.2 [C(CH$_3$)$_3$], 30.3 (ArCH$_2$Ar).

5,11,23,29-Tetra-*tert*-butyl-38,39,41,42-tetramethoxy-17,35-dinitro-calix[6]aren-37,40-diol (11):

To a well stirred mixture of calix[6]arene **5** (1.000 g, 0.10 mmol) in anhydr. CH_2Cl_2 (16 mL), and glacial AcOH (3.5 mL) was added 65% HNO_3 (680 μL, 9.77 mmol), at –15 °C. After 5 min, the mixture was rapidly allowed to warm to r.t. and stirred for 40 min. H_2O was added (20 mL) and the mixture was extracted with CH_2Cl_2 (2 × 25 mL). The organic layer was washed with brine (2 × 20 mL), dried (Na_2SO_4) and evaporated. The residue was triturated with MeCN (10 mL) and filtered to give **11**; yield: 434 mg (45%); mp > 300 °C.

MS (FAB) m/z = 1028.2 ($M^+ + Na^+$, calc. 1029.5).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.39 (s, 2 H, OH), 7.66 (s, 4 H, ArH), 6.98 (d, 4 H, J = 2.2 Hz, ArH), 6.93 (d, 4 H, J = 2.2 Hz, ArH), 3.91 (br s, 4 H, ArCH$_2$Ar), 3.81 (br s, 8 H, ArCH$_2$Ar), 3.24 (br s, 12 H, OCH$_3$), 1.09 [s, 36 H, C(CH$_3$)$_3$].

^{13}C NMR (50 MHz, $CDCl_3$): δ = 158.1, 152.6, 147.6, 140.5, 133.8, 130.4, 128.5 (ArC), 127.2, 126.2, 123.4 (ArCH), 61.3 (OCH$_3$), 34.2 [C(CH$_3$)$_3$], 31.2 [C(CH$_3$)$_3$], 31.0 (ArCH$_2$Ar).

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(10) The phenolic hydroxy groups, which are attached to carbon atoms 37–42 (compound **12**) are numerated from 1–6 to give a better insight on the substitution pattern of the different derivatives. Of course, the name calix[6]arene is used instead of the official CA name: heptacyclo[31.3.1.1.^{3,7}1.^{15,19}1.^{21,25}1.^{27,31}]dotetraconta-1(37),3,5,7(42),9,11,13(41),15,17,19(40),21,23,25(39),27,29,31(38),33,35-octadecaene-5,11,17,23,29,35-hexol.

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