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Mono-Functionalization of the tris-(*p-tert*-Butyl)Calix[4]arene.

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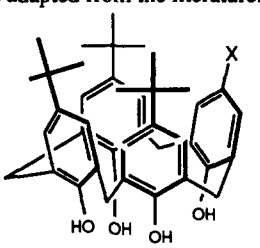
Abstract: Various types of tris-(*p-tert*-butyl)calix[4]arenes displaying an active methylene group at the upper rim have been synthesized in view of developing more elaborated structures.

Introduction of a single functional group at the upper rim of the fully de-*ter*butylated calix[4]arene has been performed by Gutsche and coll.[1] by means of a controlled Mannich reaction, affording the mono-*p*-[dimethylamino)methyl]calix[4]arene. Subsequent transformations involving a "*p*-quinone-methide route" allowed the synthesis of various substituted species. In order to introduce one active site at the upper rim of the more lipophilic (*p-tert*)butylcalix[4]arene platform, we submitted the *tris-p*-tert-butylcalix[4]arene **1**[2] to various functionalizations involving, for some of them, procedures adapted from the literature.

We thought that the chloromethyl group should be a good candidate for the introduction of other functionalities. We thus adapted the procedure developed by Ungaro and coll.[3] to introduce this function by means of soft electrophilic substitution involving the OH-free calixarene platform **1**, tin(VI)chloride and chloromethyl-n-octyl ether. This gave **2** with a yield of 90%. Reaction of **2** with NaN_3 in DMSO gave the azide **3** which was hydrogenated into the amine **4** in a 70% yield process. **2** was also reacted with KCN in DMSO to give the nitrile **5** with 70% yield. In order to develop the Wittig reaction at the upper rim[4], we prepared from **2** the phosphonium salt **6** which unfortunately did not give the expected unsaturated compounds. Introduction of a functional aminomethyl group was performed *via* catalytic reduction of the raw imine (non isolated) obtained by condensation of the previously described mono-formyl calixarene **7**[4] and 2,2-diethoxyethylamine. The resulting unstable aminocalixarene acetal **8** decomposed in deprotection conditions. The Mannich reaction[5] afforded the mono-(dimethylamino) methylcalixarene **9** with a yield of 80 %. All compounds, except **8** which was obtained analytically pure in very low quantities, were fully characterized[6]. Nevertheless, **4** did not give a correct elemental analysis, indicating notably a partial loss of nitrogen correlated with the possible elimination of NH_3 during measurement[7].



1	X =	H
2	=	CH_2Cl
3	=	CH_2N_3
4	=	CH_2NH_2
5	=	CH_2CN
6	=	$CH_2P(C_6H_5)_3, Cl$
7	=	CHO
8	=	$CH_2NHCH_2CH(OEt)_2$
9	=	$CH_2N(CH_3)_2$

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6. **5,11,17-tris(*p-tert*-butyl)-23-chloromethylcalix[4]arene (2):** A soln. of **1** (0.5 g, 0.8 mmol), chloromethyl octyl ether (1.25 ml, 4.8 mmol) and $SnCl_4$ (0.75 ml, 4.8 mmol) in $CHCl_3$ (100 ml) at 0 °C was stirred to r. t. during 2 h. H_2O (50 ml) was added and the aqueous phase was extracted with $CHCl_3$ (50 ml). The organic phases were evaporated and the residue treated with hexane gave **1**. (0.5 g, 90%). Mp: 275°C (dec.). IR: 3150 (OH); 3000 (CH Ar); 1200 (C-OH). UV ($CHCl_3$): 278 (8600); 287 (7480). ^1H NMR: 1.19 (s, 1 Me_3C); 1.22 (s, 2 Me_3C); 3.50, 4.24 (AB, J_{AB} = 12 Hz, 4 ArCH_2

-Ar); 4.40 (s, CH_2Cl); 7.02-7.08 (m, 8 Ar*H*); 10.28 (s, 4 O*H*). ^{13}C NMR: 31.53 (*Me*$_3$C); 32.31, 32.56 (Ar*C*H$_2$Ar); 34.16 (Me$_3$*C*); 46.26 (*C*H$_2$Cl); 125.78, 125.99, 126.3, 129.46 (*C*H of Ar); 127.05, 127.64, 128.13, 129.00, 130.92, 144.76, 146.36, 146.67, 149.44 ($C_{(o)}$,$C_{(p)}$ and $C_{(i)}$ of Ar). ES-MS (neg. mode): 639.4, 641.5 [2-H]$^-$. Anal. calc for $C_{41}H_{49}O_4Cl$, 0.5 $CHCl_3$ (700.98): C 71.11, H 7.11, O 9.12; found: C 71.09, H 7.27, O 8.61. **5,11,17-tris(*p-tert*-butyl)-23-azido methylcalix[4]arene (3):** A soln. of **2** (0.5 g, 0.8 mmol) and NaN_3 (0.5 g, 8 mmol) in DMSO (5 ml) was stirred at 80° C under N_2 during 3 h. After cooling, H_2O (10 ml) was added. The resulting precipitate was chromatographed (SiO_2, CH_2Cl_2) to give **3**. (0.43 g, 80%). Mp: 272-273°C. IR: 2100 (N_3). UV: (CH_2Cl_2): 279.50 (10700); 288.50 (8200). ^1H NMR: 1.19 (s, 1 *Me*$_3$C); 1.22 (s, 2 *Me*$_3$C); 3.53, 4.22 (AB, J_{AB} = 13 Hz, 4 Ar*C*H$_2$Ar); 4.12 (s, *C*H$_2$N$_3$); 6.99-7.09 (m, 8 Ar*H*); 10.29 (s, 4 O*H*). ^{13}C NMR: 31.61 (*Me*$_3$C); 32.46, 32.67 (Ar*C*H$_2$Ar); 34.25 (*C*H$_2$N$_3$); 54.53 (Me3*C*); 125.87, 126. 08, 126.43, 129.07 (*C*H of Ar); 127.17, 127.74, 128.22, 129.14, 144.75, 144.85, 146.49, 146.76, 149.39 ($C_{(o)}$, $C_{(p)}$ and $C_{(i)}$ of Ar). ES-MS (neg. mode): 646.6 [3-H]$^-$. Anal. calc. for $C_{41}H_{49}N_3O_4$, CH_2Cl_2 (732.79): C 68 .94, H 7.02, N 5.74; found: C 69.34, H 6.85, N 5.78. **5,11,17-tris(*p-tert*-butyl)-23-aminomethylcalix[4] are-ne (4):** 5% Pd/C and **3** (0.34 g, 0.5 mmol) in EtOH:CH_2Cl_2 (40:10) were stirred at r. t. under H_2 during 4 h. After filtration and removal of solvant, the residue was dissolved in MeOH then precipitated by addition of Et_2O and hexane, to give **4**. (0.22 g, 70%). Mp: 256-257°C. IR (KBr): 3380 (NH), 1600 (NH). UV (CH_2Cl_2): 279.5(9100); 285.5 (7400). ^1H NMR: 1.20 (s, 1 *Me*$_3$C); 1.23 (s, 2 *Me*$_3$C); 3.51, 4.23 (AB, J_{AB} = 11.4 Hz, 4 Ar*C*H$_2$Ar); 3.85 (s, *C*H$_2$NH$_2$); 7.04-7.19 (m, 8 ArH); 9.27 (s, 4 OH). ^{13}C NMR: 31.56, 31.47 (*Me*$_3$C); 32.13, 32.55 (Ar*C*H$_2$Ar); 32.13, 32.55 (Me$_3$*C*); 43.39 (*C*H$_2$NH$_2$); 125.84, 125.92, 126.34, 129.99 (*C*H of Ar); 126.99, 127.60, 128.11, 129.47, 144.63, 144.86, 146.36, 146.58, 150.09 ($C_{(o)}$, $C_{(p)}$ and $C_{(i)}$ of Ar). ES-MS (pos. mode): 622.5 [4+H]$^+$. **5,11,17-tris(*p-tert*-butyl)-23-cyanomethylcalix[4]arene (5):** A mixture of **2** (0.3 g, 0.47 mmol) and KCN (0.2 g, 3.2 mmol) in dry DMSO was stirred at 80°C under N_2 during 3 h then cooled. Addition of H_2O (10 ml), extraction with CH_2Cl_2, evaporation of the organic phase then addition of MeOH gave **5**. (0.2 g, 70%). Mp: 238-239°C. UV (CH_2Cl_2): 279.50 (12900); 282 (11700). IR (KBr): 2260 (CN). ^1H NMR: 1.20 (s,1 *Me*$_3$C); 1.21 (s, 2 *Me*$_3$C); 3.52 (s, *C*H$_2$CN); 3.43, 4.24 (AB, J_{AB}= 10 Hz, 4 Ar*C*H$_2$Ar); 6.77 (s, 2 Ar*H*); 6.96-7.06 (m, 6 Ar*H*); 10.28 (s, 4 O*H*). ^{13}C NMR: 31.43, 31.49 (*Me*$_3$C); 32.32, 32.57 (Ar*C*H$_2$Ar); 34.08 (Me$_3$*C*); 29.76 (Ar*C*H$_2$CN); 125.76, 125.93, 126.05, 129.35 (Ar*C*H); 134.47 (CH$_2$*C*N); 127.44, 127.76, 127.89, 128.44, 144.47, 144.54, 146.41, 146.73, 147.25 ($C_{(o)}$, $C_{(p)}$ and $C_{(i)}$ of Ar). ES-MS (neg. mode): 630.4 [5-H]$^-$. Anal. calc. for $C_{42}H_{49}NO_4$, 0.4 CH_2Cl_2, H_2O (683.84): C 74.47, H 7.63, O 11.70, N 2.05; found: C 74.25, H 7.93, O 11.96, N 1.82. **(23-[5,11,17-tris(*p-tert*-butyl)calix[4]arene]methylene)-yl) triphenylphosphonium chloride (6):** A soln. of **2** (0.62 g, 0.9 mmol) and triphenylphosphine (0.245 g, 0.9 mmol) in benzene was refluxed during 2 h. The resulting precipitate was filtered, rinsed with benzene then dried under vacuum. **6** (0.7 g, 95%). Mp: >250° (dec). IR (KBr): 1440, 1110, 1000 (strong, R_4P^+). ^1H-NMR($CDCl_3$): 1.16 (s, 3 *Me*$_3$C); 3.00-4.50 (*br.* AB, 4 Ar-C*H*2-Ar); 5.26 (d, J_{P-H}= 13.6, Ar-*C*H$_2$-P); 6.77 (d, J= 2.5, 2 H of Ar); 6.86 (d, J= 2.3, 2 H of Ar); 7.10-7.12 (s+d, 4 H of Ar); 7.22-7.23 (m, 9 H of C_6H_5); 7.36 (10 H of C_6H_6); 7.61-7.72 (m, 6 H of C_6H_5); 10.19 (4 O*H*). ^{13}C NMR: 31.42 (Ar*C*H$_2$Ar); 31.60 (*Me*$_3$C); 32.23 (d, J_{PC}= 46 Hz, *C*H$_2$P); 34.06, 34.08 (Me$_3$*C*); 118.45 (d, J_{PC}= 84 Hz, $C_{(i)}$, C_6H_5); 129.87 (d, J_{PC}= 12 Hz, $C_{(o)}$, C_6H_5); 134.0 (d, J_{PC}= 10 Hz, $C_{(m)}$, C_6H_5); 134.45 (d, J_{PC}= 3 Hz, $C_{(p)}$, C_6H_5); 121.49, 125.85, 125.91, 126.03, 126.62, 127.91, 128.24, 128.37, 128.89, 128.92, 131.71, 131.79, 144.58, 144.81, 146.30, 146.79, 148.74, 148.79, (C of phenol). ES-MS (pos. mode): 867.6 [6+ H]$^+$. Anal. calc. for $C_{59}H_{64}O_4PCl$ (903.59): C 78.42, H 7.14, O 7.08; found: C 78.66, H 7.28, O 7.13. **5,11,17-tris(*p-tert*-butyl)-23-[(2,2-diethoxyethyl) amino]methylcalix[4]arene (8):** A mixture of aldehyde **7** (0.1 g, 0.16 mmoles), aminoacetaldehyde-diethylacetal (0.05 ml, 0.34 mmoles) and neutral Al_2O_3 (0.5 g) in 10 ml of EtOH was heated overnight at 70°C. After cooling, 5% Pd/C (0.03 g) was added and the mixture was stirred under H_2 during 2 h. Solid material was filtered then rinsed with warm EtOH and CH_2Cl_2. The filtrates were evaporated and the residue chromatographed (SiO_2; CH_2Cl_2) to give **9** (0.08 g, 70%). A second chromatography gave an analytical sample (0.01g). Mp: 128°C (dec.). IR (KBr): 3180 (OH), 2960 (CH), 1200 (C-OH ArOH). UV (CH_2Cl_2): 285.5 nm (sh, 8800); 279.5 nm (10800). ^1H NMR ($CDCl_3$): 1.15-1.25 (m, 3 *Me*$_3$C + 2 OCH$_2$*C*H$_3$); 2.71 (d, J= 5.5 Hz, *C*H$_2$CH); 3.40-3.70 (m, 10H, 2 Ar*C*H$_2$Ar + 2 *C*H$_2$O+ *C*H$_2$NH); 4.25 (1/2 AB, J_{AB}= 13.4, 2 Ar*C*H$_2$Ar); 4.58 (t, J= 5.5, *C*H(OEt)$_2$); 6.98-7.08 (m, 10 H, 8 Ar*H*). ^{13}C NMR ($CDCl_3$): 15.45 (OCH$_2$*C*H$_3$); 31.48, 31.59 (*Me*$_3$C); 32.36, 32.59 (Ar*C*H$_2$Ar); 34.08, 34.15 (Me$_3$*C*); 51.81 (Ar*C*H$_2$NH); 53.56 (*C*H$_2$CH); 62.42 (O*C*H$_2$CH$_3$); 102.14 (*C*H(OEt)$_2$); 125.79, 125.96, 126.17, 128.96 (*C*H of Ar);127.41, 127.77, 128.05, 128.54, 133.69, 144.60, 146.40, 146.78, 148,10 ($C_{(o)}$, $C_{(p)}$ and $C_{(i)}$ of Ar). ES-MS (pos. mode): 738.8 [8+ H]$^+$. **5,11,17-tris(*p-tert*-butyl)-23-(dimethyl amino)methylcalix[4]arene (9):** A soln. of **1** (1.3 g, 2.2 mmol), formalin (0.7 ml, 9.3 mmol) and 40% aqueous dimethylamine (1.3 ml, 10 mmol) in 25 ml of THF was stirred at r. t. during 2 days then evaporated. The residue was extracted with CH_2Cl_2 (25 ml) and H_2O (25 ml). The aqueous phase was washed with $CHCl_3$ (2x25 ml) and the organic phases were evaporated. The residue was recrystallized in CH_2Cl_2-CH_3OH to give **9**. (1.15 g, 80%). Mp: 345-347°C. UV (CH_2Cl_2): 279.50 (11100); 286.50 (9000). IR (KBr): 3150 (OH), 2970 (CH), 1480 (C-N), 1200 (C-OH). ^1H NMR: 1.19 (s,1 *Me*$_3$C); 1.21 (s, 2 *Me*$_3$C); 2.20 (s, *Me*$_2$N); 3.20 (s, *C*H$_2$NMe$_2$); 3.49, 4.24 (AB, J_{AB}= 13 Hz, 4 Ar*C*H$_2$Ar); 6.95 (s, 2 Ar*H*); 7.00-7.03 (m, 6 Ar*H*); 9.53 (br.s, 4 O*H*). ^{13}C NMR: 31.42, 31.48 (*Me*$_3$C); 32.21, 32.57 (Ar*C*H$_2$Ar); 34.01, 34.08 (Me$_3$*C*); 45.35 (*C*H$_2$NMe$_2$); 63.86 (*Me*$_2$N); 125.78, 125.90, 126.07, 129.54 (Ar*C*H); 127.44, 127.70, 127.89, 128.36, 132.18, 144.44, 144.47, 146.44, 146.72, 148,06 ($C_{(o)}$, $C_{(p)}$ and $C_{(i)}$ of Ar). ES-MS (pos. mode): 651.2 [9+ H]$^+$. Anal. calc. for $C_{43}H_{55}NO_4$ (649.92): C 79.47, H 8.53, O 9.85, N 2.15; found: C 79.24, H 8.66, O 10.05, N 1.99.

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