PAPERS

# Procedures for the Selective Alkylation of Calix[6]arenes at the Lower Rim

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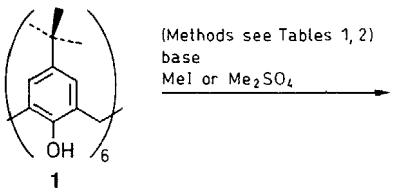
New partially alkylated calix[6]arenes have been synthesized. Depending on the conditions, mono-, 1,2-di-, 1,3-di, 1,2,3-tri-, 1,3,5-tri-, 1,2,4,5-tetra-, and 1,2,3,4,5-pentamethylated derivatives of *p-tert*-butylcalix[6]arene could be obtained in moderate to good yields. Methylation or benzylation of the parent calix[6]arene showed a regioselectivity towards 1,2-di-, and 1,2,3-trisubstitution. The solid state structure of 1,2,4,5-tetrasubstituted *p-tert*-butylcalix[6]arene [R = $O(CH_2CH_2O)_2CH_3$] has been elucidated by X-ray analysis.

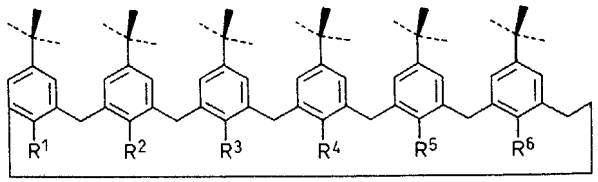
Calix[4]arenes are a versatile class of compounds,[1,2] which after functionalization are capable of complexing neutral molecules and cations in the solid state as well as in solution.[3] The synthetic work has mainly focussed on the synthesis of specific conformations of calix[4]arenes,[4] as well as on the selective introduction of functional groups at both the lower and the upper rim.[5-7] Little is known about the chemistry of calix[6]arenes, which are much more flexible due to the enlargement of the structure with two aryl moieties. The synthesis of several hexafunctionalized derivatives and their complexing abilities towards neutral molecules and cations have been described by Shinkai et al.,[8] Chang and Cho,[9] McKervey et al.,[10] and by some of us.[11] Two very recent papers of Gutsche et al.[12,13] describe the selective benzylation and aroylation of *p-tert*-butylcalix[6]arene, and a few incidental examples of otherwise selectively functionalized calix[6]arenes exist in literature.[14,15] In order to make calix[6]arenes available as molecular building blocks, we have investigated possible synthetic routes towards selectively alkylated calix[6]arenes. In this paper we report procedures for the synthesis and characterization of some partially alkylated derivatives of *p-tert*-butylcalix[6]arene and the parent calix[6]arene.

As a first approach to the selective methylation of *p-tert*-butylcalix[6]arene we have first used the same methodology as in the selective 1,3-dialkylation of *p-tert*-butylcalix[4]arene.[7] The use of a weak base such as potassium carbonate should lead to deprotonation of those phenolic hydrogens, whereby the resulting oxy anion (Chart 1) can be stabilized by two hydrogen bonds of the phenolic hydroxy groups of adjacent aryl moieties.

Consequently, monomethylation will be followed by further methylation at the alternating positions (C-39 or C-41) or at the diametrical position (C-40). The methylation of *p-tert*-butylcalix[6]arene **1** was performed under a number of different reaction conditions (Tables 1 and 2).




**1**




**2-11**

| No. | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | $R^6$ |
|---|---|---|---|---|---|---|
| **2** | OMe | OH | OH | OH | OH | OH |
| **3** | OMe | OMe | OH | OH | OH | OH |
| **4** | OMe | OH | OMe | OH | OH | OH |
| **5** | OMe | OMe | OMe | OH | OH | OH |
| **6** | OMe | OH | OMe | OH | OMe | OH |
| **7** | OMe | OMe | OH | OMe | OMe | OH |
| **8** | OMe | OMe | OMe | OMe | OMe | OH |
| **9** | OMe | OMe | OMe | OMe | OMe | OMe |
| **10** | OBn | OH | OH | OH | OH | OH |
| **11** | [a] | [a] | OH | [a] | [a] | OH |

[a] $O(CH_2CH_2O)_2Me$

**Scheme 1**

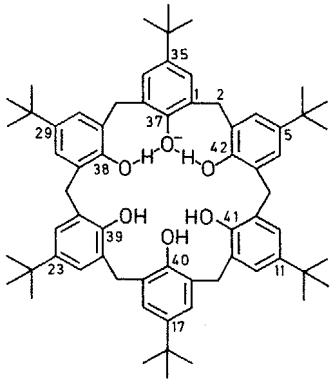



**Chart 1**

In all cases mixtures of alkylated compounds were obtained, which were separated by flash chromatogra-

**Table 1.** Methylation of *p-tert*-Butylcalix[6]arene at Atmospheric Pressure[a]

| Entry | Base | Equiv | Electrophile | Equiv | Solvent | Time (h) | Conditions | Yield (%) 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $K_2CO_3$ | 0.6 | MeI | 10 | acetone | 24 | reflux | 8 | 24 | | | | |
| 2 | $K_2CO_3$ | 3 | MeOTs | 3 | acetone | 20 | reflux | | | 17 | | | 9 |
| 3 | $K_2CO_3$ | 1.5 | MeI | 4 | acetone | 20 | reflux | | | 34 | | | 28 |
| 4 | $K_2CO_3$ | 3 | MeI | 4 | acetone | 18 | reflux | | | 25 | | 6 | 25 |
| 5 | $KHCO_3$ | 3 | MeI | 4 | acetone | 48 | reflux | | 13 | | | | |
| 6 | CsF | 1.2 | MeI | 10 | acetone | 24 | reflux | 62 | 16 | | | | |
| 7 | CsF | 1.2 | MeI | 10 | DMF | 48 | 60°C | 28 | 31 | | | | |
| 8 | CsF | 3.5 | MeI | 10 | DMF | 24 | 60°C | | | | 17 | | 12 |
| 9 | CsF | 3 | MeI | 10 | MeCN | 16 | 60°C | 17 | 9 | | | | |
| 10 | CsF | 6 | MeI | 5 | DMF | 13 | 60°C | | 13 | | 16 | | 19 |
| 11 | CsF | 6 | MeI | 5 | DMF | 90 | 40°C | | 13 | | 14 | | 24 |
| 12 | CsF | 3 | MeI | 10 | DMF | 90 | 40°C | | | | 26 | | |
| 13 | KH | 1.9 | MeI | 15.5 | THF | 16 | r.t. | | 85 | | | | |
| 14 | KH | 3.1 | $Me_2SO_4$ | 20 | THF | 20 | r.t. | | | 81 | | | |

[a] Yields refer to isolated compounds.

**Table 2.** Methylation of **1** Under Pressure (T = 70°C, P = 2 atm)[a]

| Entry | Base | Molar Ratio base **1** | Molar Ratio MeI **1** | Time (h) | Yield (%) 2 | 3 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $K_2CO_3$ | 1.1 | 1.1 | 24 | 82 | | | | | |
| 2 | $Cs_2CO_3$ | 1.1 | 1.1 | 40 | 28 | b | | b | | |
| 3 | $KHCO_3$ | 1.1 | 1.1 | 20 | c | | | | | |
| 4 | $K_2CO_3$ | 3.0 | 3.1 | 5 | 43 | | | c | | |
| 5 | $K_2CO_3$ | 3.0 | 3.1 | 20 | | c | | 34 | | |
| 6 | $K_2CO_3$ | 3.0 | 4.0 | 20 | c | 5 | | 72 | 15 | |
| 7 | $K_2CO_3$ | 4.0 | 5.0 | 20 | c | | | 40 | 35 | |
| 8 | $Cs_2CO_3$ | 4.0 | 5.0 | 20 | | | 38 | | | 15 |

[a] Yields refer to isolated compounds.
[b] Significant amounts of **3**, **4**, and **6** were also detected, but these compounds were not isolated.
[c] Traces.

phy. The purified compounds were identified by NMR ($^1H$ and $^{13}C$) spectroscopy and FAB mass spectrometry.

The symmetrical 1,3,5-trimethylated[15,16] compound **6** is the main reaction product when potassium carbonate was used as a base, but the isolated yield depends on the reaction and work up conditions. The reaction at 70°C under pressure (argon, 2 atm) using 3 equivalents of potassium carbonate and 4 equivalents of methyl iodide in acetone (Table 2, entry 6) gave an improved yield of compound **6** (72%). If the reaction is performed under pressure in the presence of only 1.1 equivalents of potassium carbonate and 1.1 equivalents of methyl iodide (Table 2, entry 1), monosubstituted compound **2** was obtained in good yield (82%). Potassium hydrogen carbonate proved not to be a sufficiently strong base; at atmospheric pressure (Table 1, entry 5) or under pressure (Table 2, entry 3) only small amounts of monosubstituted **2** could be isolated. Even when a 10-fold excess of methyl iodide was used under pressure at 120°C only 11% of **2** was isolated. However, when methylation was carried out under sonication with 1.9 equivalents of potassium hydride and 15.5 equivalents of methyl iodide in tetrahydrofuran (THF) (Table 1, entry 13), monosubstituted **2** was obtained in good yield (85%). When the methylation of **1** was carried out with a weaker base, such as cesium fluoride in dimethylformamide (DMF), the control of product distribution was not improved substantially. A moderate yield of 1,3-dimethylated **4** (26%) was obtained with 3 equivalents of cesium fluoride and 10 equivalents of methyl iodide (Table 1, entry 12). 1,2-Dimethylated **3** could be obtained in 34% yield when the reaction was carried out with 1.5 equivalents of potassium carbonate and 4 equivalents of methyl iodide (Table 1, entry 3). A high yield (81%) of 1,2-disubstituted **3** results when **1** was treated with 3.1 equivalents of potassium hydride and 20 equivalents of dimethyl sulfate under sonication in THF (Table 1, entry 14). 1,2,3-Trimethylated **5** and pentamethylated **8** were obtained in 38% and 15% yield, respectively, when **1** was treated with 4 equivalents of cesium carbonate and 5 equivalents of methyl iodide at 70°C under pressure in acetone (Table 2, entry 8). Performing the reaction under the same conditions, but using potassium carbonate as a base, gave 1,2,4,5-tetramethylated **7** in 35% yield (Table 2, entry 7). The formation of dimethylated **3**, trimethylated **5**, and tetramethylated derivative **7** indicates that the difference in $pK_a$ values of the phenolic hydroxy groups of adjacent and alternate aryl moieties of the monomethyl derivative is less pronounced than in the case of *p-tert*-butylcalix[4]arene. This

is in agreement with the weaker H-bonding system in calix[6]arenes compared with calix[4]arenes, observed both in the solid state and in solution.[1,2] Methylation of **1** with 6 equivalents of sodium hydride and 6 equivalents of dimethyl sulfate in THF under sonication gave hexamethylated **9** in nearly quantitative yield. Benzylation of **1**, using conditions which favour monosubstitution (1.1 equivalents of potassium carbonate, 1.1 equivalents of benzyl chloride in acetone), gave monosubstituted **10** in 75–81% yield. A very selective alkylation process was observed when *p-tert*-butylcalix[6]arene **1** was treated with sodium hydride and 2-(2-methoxyethoxy)ethyl *p*-toluenesulfonate in THF. Even with an excess of base and alkylating agent, the 1,2,4,5-tetraalkylated derivative **11** is nearly the sole reaction product (80% yield after recrystallization).

The introduction of methyl groups does not reduce the conformational freedom of the calix[6]arene skeleton, but actually results in a weakening of the intramolecular H-bonding system, which is indicated by the upfield shift of the remaining OH protons[17] in the partially alkylated compounds **2–8**. As a consequence, the macrocycles **2–8** become more flexible and the signals of the methylene protons are sharp at room temperature, whereas those of **1** are broad. The $^1$H NMR spectra of compounds **2–8** are in full agreement with their structures. The substitution pattern of compound **11** has been proven by $^1$H NMR spectroscopy and by solving its X-ray crystal structure.[18] In solution, **11** is conformationally mobile, and the *tert*-butyl absorption region shows two signals in a 1 : 2 ratio, whereas the two methylene signals coincide with the signals of the polyether chains. Interestingly all the signals belonging to the unsubstituted phenolic units are sharper than those of the alkylated residues, suggesting a difference in flexibility. In the solid state (Figure 1) compound **11** adopts a conformation, which is a compromise between steric effects, which tend to orient two adjacent ether chains in the opposite directions, and the intramolecular hydrogen bonds O1B..H1B...O1C [O1B...O1C = 2.78(1) Å], which enforce two adjacent phenolic units to assume the same orientation.

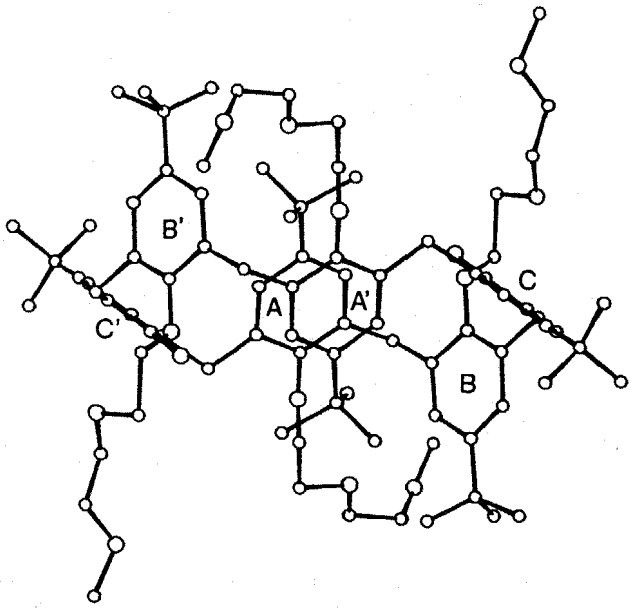
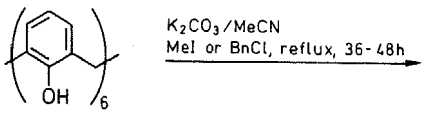
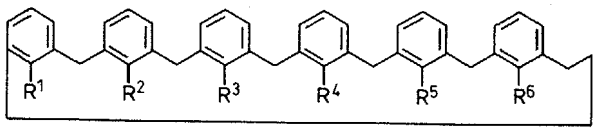



**Figure.** X-ray structure of compound **11**

A rather modest control of the regioselectivity was achieved in the alkylation of the parent calix[6]arene **12** with potassium carbonate as a base. The methylation reaction with 6 equivalents of potassium carbonate and 3 equivalents of methyl iodide gave the monomethylated **13**, 1,2-dimethylated **14**, and 1,2,3-methylated **15** derivatives in 8–32% yield. Benzylation of **12** with 6 equivalents of potassium carbonate and 3 equivalents of benzyl chloride allows the isolation of 1,4-bis(benzyloxy) **16** and 1,2,3-tris(benzyloxy) **17** derivatives in yields of 30% and 35%, respectively. To the best of our knowledge, compounds **13–17** are the first examples of partially alkylated derivatives of the parent calix[6]arene. The 1,2,3-substitution pattern of compound **17** was confirmed by its methylation, followed by debenzylation, which afforded in quantitative yield the 1,2,3-trimethylated **15**. The $^1$H NMR patterns of these compounds are very sharp already at room temperature, and only singlets are present for the methylene protons. This indicates a higher mobility of the partially benzylated calix[6]arene with respect to the analogous derivatives of *p-tert*-butylcalix[6]arene **1**.




**12**




**13-17**

| No. | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | $R^6$ |
|---|---|---|---|---|---|---|
| **13** | OMe | OH | OH | OH | OH | OH |
| **14** | OMe | OMe | OH | OH | OH | OH |
| **15** | OMe | OMe | OMe | OH | OH | OH |
| **16** | OBn | OH | OH | OBn | OH | OH |
| **17** | OBn | OBn | OBn | OH | OH | OH |

**Scheme 2**

We have found procedures for the preparation of the following derivatives of *p-tert*-butylcalix[6]arene; monomethylated **2** (82%), 1,2-dimethylated **3** (81%), 1,3-dimethylated **4** (26%), 1,2,3-trimethylated **5** (38%), 1,3,5-trimethylated **6** (72%), 1,2,4,5-tetramethylated **7** (35%), pentamethylated **8** (15%), monobenzylated **10** (81%) and 1,2,4,5-tetrakis[2-(2-methoxyethoxy)]ethylated **11** (80%). Of the parent calix[6]arene we found procedures for the preparation of 1,2-dimethylated **14** (16%), 1,2,3-trimethylated **15** (32%), 1,4-bisbenzylated **16** (30%) and 1,2,3-trisbenzylated **17** (35%). The partially

alkylated calix[6]arenes can be useful for the construction of more complex host molecules and to investigate the conformational preferences of these macrocycles.

Melting points are uncorrected. $^1$H NMR and $^{13}$C NMR were recorded on Bruker instruments. TMS was used as an internal standard. Preparative column chromatography separations were performed on Merck silica gel 60 (230–400 mesh), while precoated silica gel plates (Merck, 60 $F_{254}$) were used for analytical TLC. FAB mass spectra were performed on a Finnigan MAT 90 spectrometer, with *m*-nitrobenzyl alcohol as a matrix. All solvents were purified by standard procedures. Petroleum ether refers to the fraction with bp 40–60 °C. All other chemicals were analytically pure, and were used without further purification. *p-tert*-Butylcalix[6]arene **1** and calix-[6]arene **12** were prepared as described in literature.[19]

**5,11,17,23,29,35-Hexa-*tert*-butyl-37-methoxycalix[6]arene-38,39,40,41,42-pentol (2):**[20]

Method A: To a stirred slurry of KH (35 % oil dispersion, 168 mg, 1.46 mmol) in THF (20 mL) under Ar was added a solution of *p-tert*-butylcalix[6]arene **1** (750 mg, 0.77 mmol) in THF (80 mL). After 30 min, the stirred solution was sonicated for 1 h. To the pale brown solution was added MeI (1.0 mL, 15.5 mmol). The mixture was first submitted to ultrasound for 1.5 h, and then stirred for 16 h. After quenching with 25 % aq $NH_4OH$ (5 mL), the solvent was evaporated. The residue was extracted with $CH_2Cl_2$ (150 mL). The solution was washed with 10 % HCl (25 mL), $H_2O$ (2 × 50 mL) and dried ($MgSO_4$). Evaporation of the solvent afforded a crude solid that gave **2** upon trituration with hexane in a yield of 85 % (646 mg). The compound was recrystallized from $CHCl_3$/MeOH.

Method B: A mixture of *p-tert*-butylcalix[6]arene **1** (500 mg, 0.51 mmol), $K_2CO_3$ (80 mg, 0.56 mmol), and MeI (0.36 mL, 4.13 mmol) in dry acetone (50 mL) was heated at 70 °C under Ar in an autoclave for 20 h. After cooling, the solvent was evaporated, $CH_2Cl_2$ (100 mL) was added and the solution was washed with 10 % HCl (25 mL). The aqueous layer was extracted again with $CH_2Cl_2$ (2 × 50 mL), and the combined extracts were washed with $H_2O$ (3 × 50 mL), dried ($MgSO_4$) and evaporated to give crude **2**. Purification was achieved by column chromatography (silica gel, $CH_2Cl_2$/hexane, 2 : 1), followed by recrystallization from $CHCl_3$/MeOH; yield 413 mg (82 %); mp > 320 °C.

| | | | |
|---|---|---|---|
| $C_{67}H_{86}O_6$ | calc. | C 81.43 | H 8.70 |
| (987.4) | found | 81.08 | 8.75 |

MS (FAB): $m/z$ = 986.4 ($M^+$, calc. 986.6).

$^1$H NMR (250 MHz, $CDCl_3$): $\delta$ = 9.79 (s, 2 H, ArOH), 9.60–9.50 (br s, 1 H, ArOH), 8.78 (s, 2 H, ArOH), 7.13–7.10 (br m, 10 H, ArH), 7.00 (s, 2 H, ArH), 4.00 (s, 3 H, $OCH_3$), 4.00–3.85 (br m, 8 H, $ArCH_2Ar$), 3.73 (br s, 4 H, $ArCH_2Ar$), 1.28, 1.26 [s, 18 H, $C(CH_3)_3$], 1.22, 1.15 [s, 9 H, $C(CH_3)_3$].

$^{13}$C NMR (250 MHz, $CDCl_3$): $\delta$ = 151.0, 149.3, 148.1, 147.5, 146.7, 144.3, 143.6, 143.0, 132.3, 127.5, 127.3, 126.9, 126.8 (s, ArC), 126.2, 126.0, 125.9, 125.5 (d, ArCH), 63.4 (q, $OCH_3$), 34.3, 34.0, 33.99, 33.95 [s, $\underline{C}(CH_3)_3$], 33.5, 32.6, 32.3 (t, $ArCH_2Ar$), 31.61, 31.57, 31.5, 31.3 [q, $C(\underline{C}H_3)_3$].

**5,11,17,23,29,35-Hexa-*tert*-butyl-37,38-dimethoxycalix[6]arene-39,40,41,42-tetrol (3):**

A solution of *p-tert*-butylcalix[6]arene (**1**) (1.00 g, 1.03 mmol) in THF (80 mL) was added under Ar to KH (35 % oil dispersion, 370 mg, 3.23 mmol). After sonication for 45 min, $Me_2SO_4$ (2.0 mL, 20 mmol) was added to the pale brown solution. The mixture was submitted to ultrasound for 2 h, and then stirred at r. t. for 20 h. The reaction was quenched with 25 % aq $NH_4OH$ (5 mL) and extracted with $Et_2O$ (3 × 75 mL). The extract was washed with 10 % HCl (25 mL), brine (2 × 50 mL), dried ($MgSO_4$) and evaporated. The residue was triturated with hexane to give almost pure **3**. Additional compound could be obtained from the hexane solution by evaporation and treatment with some EtOH. The combined solids were recrystallized from $CHCl_3$/hexane, yield: 835 mg (81 %); mp 270 °C ($CHCl_3$/hexane).

| | | | |
|---|---|---|---|
| $C_{68}H_{88}O_6 \cdot 0.25\,H_2O$ | calc. | C 81.19 | H 8.87 |
| (1005.9) | found | 80.84 | 8.77 |

Karl Fischer: $H_2O$, 0.45. $C_{68}H_{88}O_6 \cdot 0.25\,H_2O$ requires $H_2O$, 0.45 %.

MS (FAB): $m/z$ = 1000.6 ($M^+$, calc. 1000.7).

$^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.60–8.50, 8.25–8.15 (br s, 2 H, ArOH), 7.12 (d, 2 H, $J$ = 2.5 Hz, ArH), 7.11 (d, 2 H, $J$ = 2.5 Hz, ArH), 7.07 (m, 4 H, ArH), 7.01 (d, 2 H, $J$ = 2.5 Hz, ArH), 6.92 (d, 2 H, $J$ = 2.5 Hz, ArH), 4.11 (br s, 2 H, $ArCH_2Ar$), 3.91 (br s, 4 H, $ArCH_2Ar$), 3.80 (s, 6 H, $OCH_3$), 3.75 (br s, 2 H, $ArCH_2Ar$), 3.72 (br s, 4 H, $ArCH_2Ar$), 1.28, 1.23, 1.13 [s, 18 H, $C(CH_3)_3$].

$^{13}$C NMR (250 MHz, $CDCl_3$): $\delta$ = 152.4, 148.8, 148.1, 147.1, 143.6, 143.0, 132.8, 132.6, 127.4, 127.2, 126.83, 126.77 (s, ArC), 126.4, 125.9, 125.7, 125.5, 124.9 (d, ArCH), 61.5 (q, $OCH_3$), 34.2, 34.1, 33.9 [s, $\underline{C}(CH_3)_3$], 32.4 (t, $ArCH_2Ar$), 31.6, 31.5, 31.4 [q, $C(\underline{C}H_3)_3$].[21]

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

To a stirred slurry of *p-tert*-butylcalix[6]arene (**1**) (1.0 g, 1.03 mmol) and CsF (468 mg, 3.0 mmol) in DMF (30 mL) was added MeI (0.64 mL, 10 mmol) at 40 °C. After stirring for 90 h, the solvent was evaporated and the residue was taken up in $CH_2Cl_2$ (150 mL). The organic layer was successively washed with 1 N HCl (2 × 50 mL), $H_2O$ (2 × 50 mL), and dried ($MgSO_4$). After filtration and evaporation of the solvent, a crude white solid was obtained, from which **4** could be isolated by column chromatography (silica gel, $CH_2Cl_2$ petroleum ether, 9 : 1). The crude compound was dissolved in $CHCl_3$, triturated with a minimal amount of MeOH. The solution was cooled for 24 h at −30 °C and filtered. The filtrate was evaporated, and the remaining solid was triturated with MeOH to afford pure **4**. An analytical sample was recrystallized from $CHCl_3$/MeOH; yield: 268 mg (26 %); mp 257 °C ($CHCl_3$/MeOH).

| | | | |
|---|---|---|---|
| $C_{68}H_{88}O_6 \cdot 0.30\,H_2O$ | calc. | C 81.12 | H 8.87 |
| (1006.8) | found | 80.85 | 9.05 |

Karl Fischer: $H_2O$, 0.54. $C_{68}H_{88}O_6 \cdot 0.30\,H_2O$ requires $H_2O$, 0.54 %.

MS (FAB): $m/z$ = 1000.4 ($M^+$, calc. 1000.7).

$^1$H NMR (250 MHz, $CDCl_3$): $\delta$ = 8.70–8.60 (br s, 1 H, ArOH), 8.10–8.00 (br s, 2 H, ArOH), 7.11 (s, 4 H, Ar), 7.06 (s, 2 H, ArH), 7.01 (s, 2 H, ArH), 7.0–6.95 (m, 4 H, ArH), 6.90 (s, 1 H, ArOH), 3.91, 3.87, 3.80 (s, 4 H, $ArCH_2Ar$), 3.73 (s, 6 H, $OCH_3$), 1.27 [s, 18 H, $C(CH_3)_3$], 1.25, 1.22 [s, 9 H, $C(CH_3)_3$], 1.12 [s, 18 H, $C(CH_3)_3$].

$^{13}$C NMR (250 MHz, $CDCl_3$): $\delta$ = 151.8, 150.7, 149.6, 149.4, 148.0, 143.3, 143.0, 142.6, 132.9, 132.5, 127.4, 127.3 (s, ArC), 126.7, 126.5, 126.4, 126.3 (d, ArCH), 126.2 (s, ArC), 125.6, 125.4 (d, ArCH), 62.3 (q, $OCH_3$), 34.6, 34.3 [s, $\underline{C}(CH_3)_3$], 32.8, 32.2 (t, $ArCH_2Ar$), 32.0, 31.6 [q, $C(\underline{C}H_3)_3$].

**5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39-trimethoxycalix[6]arene-40,41,42-triol (5):**

A mixture of *p-tert*-butylcalix[6]arene (**1**) (500 mg, 0.5 mmol), $Cs_2CO_3$ (683 mg, 2.1 mmol), and MeI (162 µL, 2.61 mmol) in dry acetone (50 mL) was heated for 20 h under Ar at 70 °C in an autoclave. After evaporation of the solvent, the crude residue was taken up in $CH_2Cl_2$ (100 mL), and washed with 1 N HCl (25 mL). The aqueous layer was extracted again with $CH_2Cl_2$ (2 × 25 mL), dried ($Na_2SO_4$), and evaporated to dryness. The crude product was separated by column chromatography (silica gel, $CH_2Cl_2$/MeOH, 99.8 : 0.2) to give pure **5** and **8**, which were further purified by recrystallization from $CH_2Cl_2$/MeOH: **5**: yield: 198 mg (38 %); mp > 300 °C.

| | | | |
|---|---|---|---|
| $C_{69}H_{90}O_6 \cdot 0.17\,H_2O$ | calc. | C 81.37 | H 8.94 |
| (1018.5) | found | 81.10 | 9.01 |

Karl Fischer: $H_2O$, 0.30. $C_{69}H_{90}O_6 \cdot 0.17\,H_2O$ requires $H_2O$, 0.30 %.

MS (FAB): $m/z$ = 1014.7 ($M^+$, calc. 1014.7).

$^1$H NMR (250 MHz, $CDCl_3$): $\delta$ = 8.29 (s, 2 H, ArOH), 7.56 (s, H, ArOH), 7.12, 7.10 (s, 4 H, ArH), 7.07 (d, 2 H, $J$ = 2.3 Hz, ArH), 7.02 (d, 2 H, $J$ = 2.4 Hz, ArH), 6.95–6.90 (m, 4 H, ArH), 4.12–4.00 (br s,

4H, $ArCH_2Ar$), 3.90 (s, 6H, $OCH_3$), 3.84, 3.79 (s, 4H, $ArCH_2Ar$), 2.91 (s, 3H, $OCH_3$), 1.29, 1.25 [s, 9H, $C(CH_3)_3$], 1.17, 1.10 [s, 18H, $C(CH_3)_3$].

$^{13}C$ NMR (250 MHz, $CDCl_3$): $\delta$ = 154.7, 151.7, 150.0, 148.8, 147.3, 146.2, 142.6, 142.0 (s, ArC), 133.7, 132.6, 132.1, 126.6, 126.1, (s, ArC), 126.4, 126.3, 126.0, 125.5, 125.2, 125.0 (d, ArCH), 61.8, 60.7 (q, $OCH_3$), 34.2, 33.9 [s, $\underline{C}(CH_3)_3$], 32.0 (t, $ArCH_2Ar$), 31.6, 31.54, 31.49, 31.3 [q, $C(\underline{C}H_3)_3$].

**5,11,17,23,29,35-Hexa-*tert*-butyl-37,39,41-trimethoxycalix[6]arene-38,40,42-triol (6):**

A mixture of *p-tert*-butylcalix[6]arene (**1**) (1.00 g, 1.03 mmol), $K_2CO_3$ (426 mg, 3.1 mmol), MeI (260 µL, 4.13 mmol) in dry acetone (75 mL) was heated at 70 °C under Ar in an autoclave for 20 h. The solvent was removed and the crude residue was taken up in $CH_2Cl_2$ (100 mL) and washed with 10% HCl (25 mL). The aqueous layer was extracted again with $CH_2Cl_2$ (2 × 50 mL), and the combined solutions were washed with $H_2O$ (2 × 50 mL), dried ($MgSO_4$) and evaporated to almost dryness. Hot hexane was added and the insoluble material was filtered. The hexane filtrate was evaporated and the residue was successively crystallized from $Et_2O$/EtOH to give **7** (15%) and $CHCl_3$/hexane to give some **3** (5%). The remaining materials were combined, absorbed on silica gel, and separated by column chromatography (silica gel, hexane/THF, 9 : 1) to give **6**, which was further purified by recrystallization from $CHCl_3$/MeOH (753 mg, 72%), for spectral data see Ref. 15.

**5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,40,41-tetramethoxycalix[6]-arene-39,42-diol (7):**

A mixture of *p-tert*-butylcalix[6]arene (**1**) (1.00 g, 1.03 mmol), $K_2CO_3$ (570 mg, 4.06 mmol), and MeI (320 µL, 5.09 mmol) in dry acetone (70 mL), was heated at 70 °C under Ar in an autoclave for 20 h. The mixture was poured into 10% HCl (100 mL), and the aqueous layer was extracted with $CH_2Cl_2$ (2 × 50 mL), washed with brine (2 × 50 mL), dried over $Na_2SO_4$, and evaporated to dryness. Hot hexane was added, and the insoluble material was filtered. The filtrate was evaporated, and the residue was triturated with cold MeOH to give **7**, which was further purified by recrystallization from $CHCl_3$/MeOH; yield: 390 mg (35%); mp 282 °C (dec) ($CHCl_3$/MeOH).

| | | | |
|---|---|---|---|
| $C_{70}H_{92}O_6$ | calc. | C 81.66 | H 9.01 |
| (1029.5) | found | 81.37 | 9.38 |

MS (FAB): $m/z$ = 1028.4 ($M^+$, calc. 1028.7).

$^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 8.03 (s, 4H, ArH), 7.06 (m, 8H, ArH), 6.70 (s, 4H, ArH), 3.97 (br s, 4H, $ArCH_2Ar$), 3.87 (br s, 8H, $ArCH_2Ar$), 3.14 (s, 6H, $OCH_3$), 1.18 [s, 36H, $C(CH_3)_3$], 0.94 [s, 18H, $C(CH_3)_3$].

$^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ = 153.2, 149.4, 146.6, 141.8, 133.9, 132.3, 127.3 (s, ArC), 126.4, 126.1, 123.9 (d, ArCH), 61.4 (q, $OCH_3$), 34.1, 33.7 [s, $\underline{C}(CH_3)_3$], 31.4, 31.2 [q, $C(\underline{C}H_3)_3$], 30.9, 30.8 (t, $ArCH_2Ar$).

**5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41-pentamethoxy-calix[6]aren-42-ol (8):**

For preparation see compound **5**. Yield: 80 mg (15%); mp 274 °C (dec) ($CH_2Cl_2$/MeOH).

| | | | |
|---|---|---|---|
| $C_{71}H_{94}O_6 \cdot H_2O$ | calc. | C 80.39 | H 9.12 |
| (1061.5) | found | 80.45 | 9.08 |

MS (FAB): $m/z$ = 1043.7 [$(M+H)^+$, calc. 1043.7].

$^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ = 7.34 (s, 1H, ArOH), 7.10 (d, 2H, $J$ = 2.3 Hz, ArH), 7.02 (s, 4H, ArH), 7.01 (d, 2H, $J$ = 2.3 Hz, ArH), 6.88, 6.79 (s, 2H, ArH), 3.95, 3.92, 3.80 (s, 4H, $ArCH_2Ar$), 3.50 (s, 3H, $OCH_3$), 3.06, 3.05 (s, 6H, $OCH_3$), 1.18, 1.15 [s, 18H, $C(CH_3)_3$], 1.11, 0.89 [s, 9H, $C(CH_3)_3$].

$^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ = 154.3, 153.0, 149.4, 146.4, 145.7, 133.6, 133.4, 132.5 (s, ArC), 127.0, 126.3, 126.1 (d, ArCH), 125.9 (s, ArC), 125.7, 125.4, 124.7 (d, ArCH), 60.7, 60.5, 59.9 (q, $OCH_3$), 34.1, 33.9 [s, $\underline{C}(CH_3)_3$], 31.4, 31.3, 31.2 [q, $C(\underline{C}H_3)_3$], 30.3 (t, $ArCH_2Ar$).

**5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexamethoxy-calix[6]arene (9):**

A suspension of *p-tert*-butylcalix[6]arene (**1**) (0.50 g, 0.5 mmol) in THF (30 mL) was sonicated in an ultrasound bath under Ar for 15 min and was added, via a syringe, to a suspension of NaH (0.14 g, 3.0 mmol) in THF (20 mL). The mixture was stirred at r.t. for 5 min, and sonicated for 15 min. After addition of $Me_2SO_4$ (0.30 mL, 3.0 mmol), an additional cycle of stirring and sonication was started, and the mixture was stirred for 15 h. The reaction was quenched with 25% aq $NH_4OH$ (2 mL), acidified with 5% HCl, and extracted with $CH_2Cl_2$ (3 × 25 mL). The organic layer was dried ($MgSO_4$). After evaporation of the solvent, the residue was triturated with $Et_2O$ to give pure **9** in 94–99% yield. For spectral data see Ref. 9.

**37-Benzyloxy-5,11,17,23,29,35-hexa-*tert*-butylcalix[6]arene-38,39,40,41,42-pentol (10):**

A mixture of *p-tert*-butylcalix[6]arene (**1**) (0.50 g, 0.5 mmol) and $K_2CO_3$ (80 mg, 0.56 mmol) in acetone (50 mL) was refluxed for 2 h. After cooling, benzyl chloride (65 µL, 0.65 mmol) was added, and the mixture was refluxed for 20 h. The mixture was quenched with 25% aq $NH_4OH$ (2 mL), acidified with 5% HCl, and extracted with $CH_2Cl_2$ (3 × 25 mL). The organic layer was dried ($Na_2SO_4$), filtered, and evaporated. The residue was triturated with hexane. The precipitate was unreacted **1** (64 mg, 0.06 mmol). The filtrate was evaporated, and the remaining solid was triturated with cold MeOH to afford pure **10**; yield: 415 mg (78%); mp 228–231 °C ($CHCl_3$/MeOH).

| | | | |
|---|---|---|---|
| $C_{73}H_{90}O_6$ | calc. | C 82.44 | H 8.52 |
| (1063.5) | found | 82.45 | 8.30 |

MS (FAB): $m/z$ = 1062.6 ($M^+$, calc. 1062.7).

$^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ = 9.98 (s, 2H, ArOH), 9.79 (br s, 1H, ArOH), 9.09 (s, 2H, ArOH), 7.76 (d, 2H, $J$ = 7.6 Hz, ArH), 7.62 (t, 2H, $J$ = 7.5 Hz, ArH), 7.43 (t, 1H, $J$ = 7.5 Hz, ArH), 7.14 (s, 12H, ArH), 7.11 (s, 6H, ArH), 7.09, 7.06 (s, 2H, ArH), 5.19 (s, 2H, $PhCH_2OAr$), 4.43 (d, 2H, $J$ = 13.4 Hz, $ArCH_2Ar$), 4.24 (d, 2H, $J$ = 15.0 Hz, $ArCH_2Ar$), 4.00 (d, 2H, $J$ = 13.9 Hz, $ArCH_2Ar$), 3.55 (d, 2H, $J$ = 14.9 Hz, $ArCH_2Ar$), 3.53 (d, 2H, $J$ = 13.4 Hz, $ArCH_2Ar$), 3.38 (d, 2H, $J$ = 13.9 Hz, $ArCH_2Ar$), 1.27, 1.25 [s, 18H, $C(CH_3)_3$], 1.21, 1.17 [s, 9H, $C(CH_3)_3$].

$^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ = 149.6, 148.4, 148.3, 146.8, 144.6, 143.8, 141.9, 136.6, 132.7 (s, ArC), 129.2, 128.7 (d, ArCH), 127.5 (s, ArC), 127.4 (d, ArCH), 127.1, 127.0, 126.3 (s, ArC), 126.2, 126.1, 126.0, 125.6 (d, ArCH), 78.0 (d, $CH_2$), 34.5, 34.1 [s, $\underline{C}(CH_3)_3$], 33.4, 32.8 (t, $ArCH_2Ar$), 31.8, 31.6, 31.4 [q, $C(\underline{C}H_3)_3$].

**5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,40,41-tetrakis[2-(2-methoxyethoxy)ethoxy]calix[6]arene-39,42-diol (11):**

To a solution of *p-tert*-butylcalix[6]arene (**1**) (3.0 g, 3.1 mmol) in dry THF (100 mL) was added NaH (50% in oil, 1.15 g, 24 mmol) and 2-(2-methoxyethoxy)ethyl toluenesulfonate[22] (5.9 g, 21.6 mmol), whereupon the mixture was refluxed for 24 h. After evaporation of the solvent, the residue was quenched with 2 N HCl (150 mL) and extracted with $CH_2Cl_2$ (2 × 100 mL). The organic phase was washed with distilled $H_2O$ (2 × 100 mL), dried ($MgSO_4$) and evaporated to dryness. The residue was recrystallized from $CHCl_3$/EtOH to afford pure **11**; yield: 3.4 g (80%); mp 214–216 °C ($CHCl_3$/EtOH).

| | | | |
|---|---|---|---|
| $C_{86}H_{124}O_{14}$ | calc. | C 74.75 | H 9.04 |
| (1381.9) | found | 74.53 | 9.10 |

MS (CI): $m/z$ = 1380.5 ($M^+$, calc. 1380.9).

$^1H$ NMR (100 MHz, $CDCl_3$): $\delta$ = 7.11 (br s, 4H, ArH), 6.97 (s, 4H, ArH), 6.63 (br s, 4H, ArH), 3.89, 3.51 (br s, 20H, and br s, 24H, $ArCH_2Ar$ and $OCH_2$), 3.31 (s, 12H, $OCH_3$), 1.19 [s, 18H, $C(CH_3)_3$], 0.93 [s, 36H, $C(CH_3)_3$].

$^{13}C$ NMR (25 MHz, $CDCl_3$): $\delta$ = 151.6, 150.6 (s, ArC-*i*), 146.5, 142.0 (s, ArC-*p*), 133.2, 133.0 (s, ArC-*o*), 126.6, 126.1, 125.9, 125.4 (d, ArCH), 72.7, 72.1, 70.6, 70.4 (t, $OCH_2$), 59.0 (q, $OCH_3$), 34.0, 33.9 [s, $\underline{C}(CH_3)_3$)$_3$], 31.6, 31.3 [q, $C(\underline{C}H_3)_3$], 31.0 (t, $ArCH_2Ar$).

**Methylation of Calix[6]arene (12):**
A suspension of calix[6]arene (**12**) (600 mg, 0.95 mmol), $K_2CO_3$ (0.39 g, 2.85 mmol) and MeI (0.41 g, 2.85 mmol) in dry MeCN (60 mL) was refluxed for 48 h. The solvent was removed and the residue was quenched with 10% HCl (75 mL). The water layer was extracted with $CH_2Cl_2$ (2 × 50 mL) and the combined organic layers were washed with $H_2O$ (2 × 100 mL). The solvent was removed under reduced pressure and the residue was chromatographed (silica gel, $CHCl_3$/hexane, 2:1) to give compounds **13**, **14**, and **15**.

*37-Methoxycalix[6]arene-38,39,40,41,42-pentol* (**13**): Yield: 49 mg (8%); mp 239–240 °C (dec) ($CHCl_3$/hexane).

$C_{43}H_{38}O_6$ (650.8) calc. C 79.36 H 5.89; found 79.11 6.01

MS (CI): $m/z$ = 650.6 ($M^+$, calc. 650.3).

$^1$H NMR (100 MHz, $CDCl_3$): $\delta$ = 9.60 (s, 3 H, ArOH), 8.52 (s, 2 H, ArOH), 7.20–6.70 (m, 18 H, ArH), 4.02 (s, 4 H, $ArCH_2Ar$), 3.97 (s, 3 H, $OCH_3$), 3.92, 3.75 (s, 4 H, $ArCH_2Ar$).

$^{13}$C NMR (25 MHz, $CDCl_3$): $\delta$ = 151.5, 150.4 (s, Ar*C-i*), 133.0, 127.9, 127.6, 127.4 (s, ArC), 129.5, 129.3, 129.1, 129.0, 128.8, 125.7, 122.1, 121.2, 120.7 (d, ArCH), 63.4 (q, $OCH_3$), 32.1, 31.9, 31.5 (t, $ArCH_2Ar$).

*37,38-Dimethoxycalix[6]arene-39,40,41,42-tetrol* (**14**): Yield: 101 mg (16%): mp 270–271 °C (dec) ($CHCl_3$/hexane).

$C_{44}H_{40}O_6$ (664.8) calc. C 79.49 H 6.06; found 79.23 6.12

MS (CI): $m/z$ = 664.4 ($M^+$, calc. 664.25).

$^1$H NMR (100 MHz, $CDCl_3$): $\delta$ = 8.75, 8.28 (s, 2 H, ArOH), 7.20–6.70 (m, 18 H, ArH), 4.15 (s, 2 H, $ArCH_2Ar$), 3.97, 3.79 (s, 6 H and s, 10 H, $ArCH_2Ar$, $OCH_3$).

$^{13}$C NMR (25 MHz, $CDCl_3$): $\delta$ = 154.5, 151.4, 150.1 (s, ArC-*i*), 133.7, 133.6 127.9,127.8, 127.7, 127.1 (s, ArC-*o*), 129.5, 129.4, 129.1, 128.9, 128.7, 128.2, 125.0, 121.4, 120.7 (d, ArCH), 61.6 (q, $OCH_3$), 31.7, 31.4, 31.2 (t, $ArCH_2Ar$).

*37,38,39-Trimethoxycalix[6]arene-40,41,42-triol* (**15**): Yield 206 mg (32%); mp 283–285 °C ($CHCl_3$/hexane).

$C_{45}H_{42}O_6$ (678.8) calc. C 79.62 H 6.24; found 79.41 6.31

MS (CI): $m/z$ = 678.6 ($M^+$, calc. 678.3).

$^1$H NMR (100 MHz, $CDCl_3$): $\delta$ = 8.45 (s, 2 H, ArOH), 7.65 (s, 1 H, ArOH), 7.20–6.60 (m, 18 H, ArH), 4.08 (s, 4 H, $ArCH_2Ar$), 3.90 (s, 6 H, $OCH_3$), 3.88, 3.79 (s, 4 H, $ArCH_2Ar$), 3.33 (s, 3 H, $OCH_3$).

$^{13}$C NMR (25 MHz, $CDCl_3$): $\delta$ = 151.3, 134.4, 133.3, 132.9, 129.0, 128.8, 127.7, 126.9, 126.6 (s, ArC), 129.4, 129.2, 128.7, 125.2, 123.6, 120.4, 120.1 (d, ArCH), 61.9, 60.5 (q, $OCH_3$), 31.6, 31.1, 30.6 (t, $ArCH_2Ar$).

**Benzylation of Calix[6]arene (12):**
To a solution of calix[6]arene (**12**) (0.60 g, 0.95 mmol) in MeCN (60 mL) was added $K_2CO_3$ (0.39 g, 2.85 mmol) and BnCl (0.36 g, 2.85 mmol). After refluxing the mixture for 36 h, the solvent was removed under reduced pressure and the residue was quenched with 10% HCl (50 mL). The water layer was extracted with $CH_2Cl_2$ (2 × 50 mL), and the combined organic layers were washed with $H_2O$ (3 × 80 mL). The organic phase was dried ($MgSO_4$) and evaporated to dryness. The residue was chromatographed (silica gel, $CHCl_3$/hexane, 2:1) to give compounds **16** and **17**.

*37,40-Bis(benzyloxy)calix[6]arene-38,39,41,42-tetrol* (**16**): Yield: 233 mg (30%); mp 210–212 °C ($CH_2Cl_2$/hexane).

$C_{56}H_{48}O_6$ (817.0) calc. C 82.33 H 5.92; found 82.08 5.99

MS (CI): $m/z$ = 816.3 ($M^+$, calc. 816.4).

$^1$H NMR (100 MHz, $CDCl_3$): $\delta$ = 7.93 (s, 4 H, ArOH), 7.4–6.6 (m, 28 H, ArH, PhH), 5.01 (s, 4 H, $OCH_2Ph$), 3.90 (s, 8 H, $ArCH_2Ar$), 3.73 (s, 4 H, $ArCH_2Ar$).

$^{13}$C NMR (25 MHz, DMSO-$d_6$): $\delta$ = 154.1, 151.4 (s, ArC-*i*), 137.8, 133.5, 130.2, 128.7, 126.5 (s, ArC, PhC), 129.1, 128.4, 127.8, 125.5, 123.8, 120.5 (d, ArCH, PhCH), 72.9 (t, $OCH_2Ph$), 31.1, 30.3 (t, $ArCH_2Ar$).

*37,38,39-Tris(benzyloxy)calix[6]arene-40,41,42-triol* (**17**): Yield: 302 mg (35%); mp 232–234 °C ($CH_2Cl_2$/hexane).

$C_{63}H_{54}O_6$ (907.1) calc. C 83.42 H 6.00; found 83.24 6.08

MS (CI): $m/z$ = 906.0 ($M^+$, calc. 906.4).

$^1$H NMR (100 MHz, $CDCl_3$): $\delta$ = 8.19 (s, 3 H, ArOH), 7.5–6.7 (m, 33 H, ArH, PhH), 4.92 (s, 6 H, $OCH_2Ph$), 4.15, 3.78, 3.67 (s, 4 H, $ArCH_2Ar$).

$^{13}$C NMR (25 MHz, $CDCl_3$): $\delta$ = 154.0, 153.5, 151.6, 150.7 (s, ArC-*i*), 137.7, 136.0, 134.1, 133.7, 133.6 (s, ArC, PhC), 130.1, 129.2, 129.0, 128.7, 128.5, 128.2, 127.9, 127.8, 125.2, 124.3, 120.6, 120.1 (d, ArCH, PhCH), 76.6, 74.7 (t, $OCH_2Ph$), 31.8, 31.5, 31.1 (t, $ArCH_2Ar$).

**Crystal Structure Analysis of Compound 11:**
Crystal data: $C_{88}H_{112}O_{14}$, M = 1393.844 a.m.u. Triclinic a = 15.335 (2), b = 14.218 (3), c = 10.501 (2) Å, $\alpha$ = 107.53(2), $\beta$ = 105.27 (2), $\gamma$ = 95.50 (s)°, V = 2067.7 (8) Å$^3$ (The cell parameters were obtained by least-squares fit of 32 $(\Theta,\chi,\phi)_{hkl}$ carefully centered reflections found in a random exploration of reciprocal lattice in the range 25° ≤ $\Theta$ ≤ 40°, $\lambda$ = 1.54178 Å), space group P$\bar{1}$, Z = 1, F (000) = 752, $D_x$ = 1.119 gr cm$^{-3}$. Colorless, triclinic crystals, grown from $CHCl_3$/EtOH, $\mu$ (Cu-$K_\alpha$) = 5.6 cm$^{-1}$.

Data Collection and Processing were carried out according standard procedures.

Structure Analysis and Refinement: the structure was solved by Direct Methods using the SIR88 computer program[23] and completed and refined with the SHELX76 package of crystallographic computer programs.[24] The geometrical calculations were performed by PARST.[25] The atomic scattering factors were obtained by analytical approximation according to the literature.[26] Perspective plots of the molecule have been obtained by PLUTO.[27] All calculations were carried out on the Gould Encore 91 of the Centro di Studio per la Strutturistica Diffrattometrica del CNR, Parma, Italy. Supplementary material is available from the authors or the editorial office.

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