# *p*-(Benzyloxy)calix[8]arene: One-Pot Synthesis and Functionalization

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The condensation of hydroquinone monobenzyl ether in the presence of several bases gives a mixture of cyclic oligomers. Using *p*-benzyloxyphenol, paraformaldehyde, and NaOH in 45:82:1 molar ratio in refluxing xylene, *p*-(benzyloxy)calix[8]arene (**2**) was selectively produced in 48% isolated yield. Compound **2** was also functionalized at the lower rim with acetoxy, methyl, pentyl, [(ethyloxy)carbonyl]methyl, and [(*N*,*N*-diethylamino)carbonyl]methyl groups. Replacement of the benzyl groups on these compounds allowed for the first time the high-yield syntheses of calix[8]hydroquinone and its derivatives.

## Introduction

The cyclic phenol−formaldehyde oligomers, called calixarenes,[1] occupy a well-established place in supramolecular chemistry as versatile building blocks for the synthesis of more complex receptors. This is due to their high-yield synthesis from cheap reagents and to the possibility of their functionalization both at the aromatic nuclei (upper rim) and at the phenolic OH groups (lower rim).[2,3] In the case of calix[4]- and calix[6]arenes, well-established procedures for their *selective* functionalization have been developed during the last 20 years.[3,4] In several cases a good control of stereochemical properties of these macrocycles has also been achieved.

For the synthesis of calixarenes two general procedures are available: (i) the one-pot synthesis *via* the base-catalyzed condensation of para-substituted phenols (usually having alkyl or phenyl groups)[2] and (ii) the stepwise procedure from acyclic phenol−formaldehyde precursors.[5] An interesting class of calixarenes is that of calixquinones and calixhydroquinones, obtained so far through indirect procedures from *native* calixarenes.[6,7] These macrocycles have attracted the attention of several research groups because of their redox[6b,e,f] and binding[6f,g] properties and because the quinone or hydroquinone nuclei can be easily functionalized,[7,8] thus allowing the synthesis, *inter alia*, of inherently chiral "meta"-substituted calixarenes. Until now no direct synthesis of calixhydroquinones or calixquinones has been reported. We report here for the first time the one-pot synthesis of *p*-(benzyloxy)calix[8]arene (**2**) and its functionalization at both rims, allowing the obtainment of new host molecules potentially useful in supramolecular chemistry.

## Results and Discussion

**One-pot Synthesis of *p*-(Benzyloxy)calix[8]arene.** The one-pot synthesis of calixarenes *via* the base-catalyzed condensation of phenols and formaldehyde has so far been limited to *p*-alkyl[2a−m] and *p*-phenyl derivatives.[2n] Usually the yields of *p-tert*-butylcalixarenes are higher than with other *p*-alkyl groups.

In order to have a direct access to calixhydroquinone derivatives, we first explored (Scheme 1) the base-catalyzed condensation of hydroquinone **1a** and *p*-methoxyphenol (**1b**) under the classical conditions used to obtain *p*-alkylcalixarenes. In the case of **1a**, a black insoluble material was produced, whereas, with **1b**, a complex mixture of oligomeric compounds, cyclic and acyclic, was obtained.

We then studied more systematically the reaction of *p*-(benzyloxy)phenol (**1c**) and formaldehyde in the presence of a base (Scheme 1). Since the crude reaction product appeared to be insoluble in most organic solvents, it was analyzed after complete acetylation with $CH_3COCl$/

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**Scheme 1**

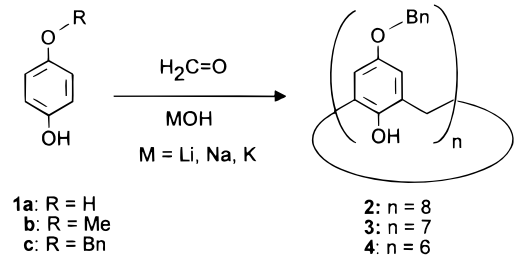



**Table 1. Influence of the Base Used on the Cyclic Product Distribution in the Reaction of 1c and Paraformaldehyde**[a]

| | % relative yield | | |
|---|---|---|---|
| base | calix[6]arene (**4**) | calix[7]arene (**3**) | calix[8]arene (**2**) |
| LiOH | 20 | 17 | 63 |
| NaOH | 10 | 6 | 84 |
| KOH | 7 | 21 | 72 |

[a] Mean values of three runs. Relative yields determined by HPLC (reverse phase C18, methanol/water = 96/4).

pyridine. The compounds were identified by mass spectra and $^1$H NMR after isolation by preparative HPLC (reverse phase $C_{18}$, $CH_3OH/H_2O$ 96/4).

After several efforts, conditions were found where only the cyclic compounds are produced in the reaction mixture. They were identified as the *p*-(benzyloxy)-calix[8]arene (**2**), and the corresponding calix[7]- (**3**) and calix[6]arene (**4**). The ratio between the three compounds depended on the base used in the condensation, although the cyclic octamer **2** was always the main reaction product (Table 1).

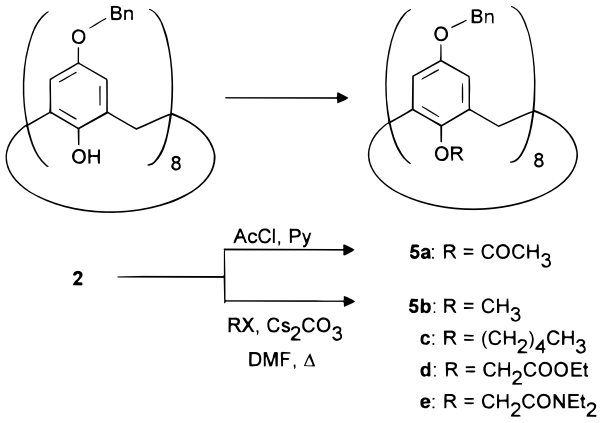
Interestingly, no trace of cyclic tetramer was detected, in sharp contrast with the behavior of *p*-*tert*-butylphenol under similar conditions.[2f]

The highest yield of cyclic octamer **2** was obtained using *p*-(benzyloxy)phenol (**1c**), paraformaldehyde, and NaOH in 45:82:1 molar ratio in refluxing xylene. The pure compound **2** can be isolated in 48% yield by simple filtration from hot $CH_2Cl_2$. This result is interesting because calix[8]hydroquinone derivatives are unknown compounds and have so far not been synthesized even using indirect procedures.

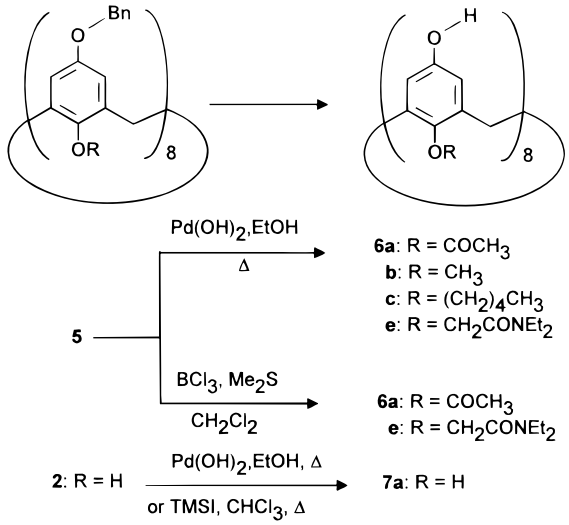
The high insolubility of **2**, which allows its easy purification from the reaction mixture, nevertheless makes its characterization more difficult. NMR spectra can only be taken in a DMSO solution, where, as expected, compound **2** shows a complete conformational freedom, as deduced from the presence of a singlet for the $ArCH_2Ar$ protons at 3.80 ppm. The molecular peak (M) in the mass spectra was only visible using negative CI, easily showing the loss of benzyl groups (M−91). Compound **2** can be almost quantitatively converted to the octacetoxy derivative (**5a**), whereas complete alkylation can be obtained by reaction with the appropriate alkyl halide and $Cs_2CO_3$ in dry DMF at 80 °C to yield compounds **5b**−**e** in 40−60% yield (Scheme 2). All these compounds show a mobile structure in solution, as inferred from the temperature independent (−65/25 °C) $^1$H NMR spectra.

**Debenzylation and Further Functionalization.** In order to make the upper rim of the calix available for further functionalization, it was necessary to find an easy and general method for the debenzylation of compounds **5a**−**e**. The removal of benzyl groups from calixarenes has never been simple. Catalytic hydrogenation (Pd/C, $H_2$), even at high temperature and under 3−4 atm pressure, often fails, and therefore, different methods have been used by us and others to cleave the ArO−$CH_2$Ph bond. Among these methods, we have often successfully used bromotrimethylsilane at room temperature in $CHCl_3$, which is very efficient and selective to cleave ArO−$CH_2$Ph bonds over other ethereal bonds ArO−R (R = $CH_2CH_3$, $(CH_2CH_2O)_n$, $CH_2COX$).[9] However, the treatment of compounds **5a**−**e** with a large excess of bromotrimethylsilane, or of the more reactive iodotrimethylsilane also in refluxing $CHCl_3$, gives mixtures of products where the benzyl groups are only partially removed. Complete debenzylation of compounds **5a** and **5e** (76% and 80% yields respectively) was achieved by treating a chloroform solution of these products with dimethyl sulfide and boron trichloride (1 M solution in heptane) at room temperature (Scheme 3).[10]

**Scheme 2**




**Scheme 3**




However, debenzylation of **5b** and **5c** under the same reaction conditions was not complete, and this prompted us to look for a more efficient method. We eventually found the use of $Pd(OH)_2$/C (20%, Pearlsman's catalyst) and cyclohexene in refluxing ethanol[11] to be a very effective and general method to obtain all compounds **6**

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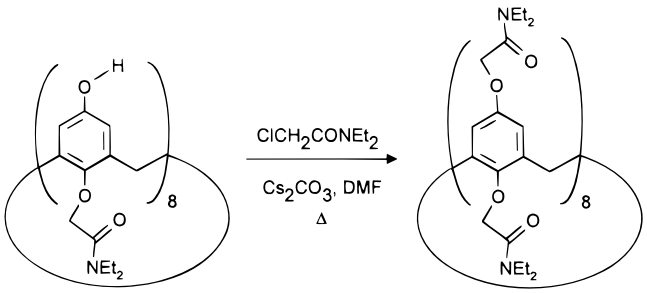
**Scheme 4**




**6e** **7b**

in very good yields (80−90%). These compounds, which bear free OH groups at the upper rim, unlike their benzylated precursor are not very soluble in organic solvents, which indicates that strong intermolecular hydrogen bonds are operating among these molecules. NMR spectra can only be recorded in DMSO-$d_6$ or mixtures $CDCl_3$−$CD_3OD$. Interestingly, compound **6e** is soluble in water solution ($5 \times 10^{-3}$−$10^{-2}$ M) when at least 16 equiv of NaOH are added. NMR spectra in $D_2O$ clearly indicate that the calixarene assumes a rigid conformation in these conditions, since only two doublets at 4.11 and 3.20 ppm appear for the methylene bridge protons. The spectrum results as being very simple and symmetrical; also, the $OCH_2CO$ protons become diasterotopic, originating an AX system (3.94 and 3.20 ppm, $J$ = 14.7 Hz), while the aromatic protons give two doublets with typical *meta* coupling ($J$ = 2.6 Hz). Since the *cone* conformation ($C_8$ symmetry) cannot explain the presence of diastereotopicity for the $OCH_2CO$ and the nonequivalence of the ArH protons, we propose for this salt of **6e** a *1,3,5,7-alternate* conformation (u, d, u, d, u, d, u, d),[1] where the oxygens of both the chelating chains and the phenoxide anions interact with sodium cations.

The octahydroxyoctakis[[[(*N*,*N*-diethylamino)carbonyl])methyl]oxy]calix[8]arene (**6e**) has several noteworthy properties and potentialities: (1) it possesses eight cation binding groups at the lower rim and can be further functionalized at the upper rim with long alkyl chains in order to increase the lipophilicity of the ionophore and (2) binding groups of the same type or different from those present at the lower rim can be introduced on the free OH groups, thus creating ionophores with a channel-like structure or various types of ditopic receptors.

As an example of one of these types of functionalization at the upper rim, we synthesized (Scheme 4) the hexadecamide derivative (**7b**) by reaction of **6e** with $ClCH_2CON(C_2H_5)_2$ in the presence of $Cs_2CO_3$.

Finally, we prepared (Scheme 3) calix[8]hydroquinone (**7a**) following two different debenzylation procedures (iodotrimethylsilane in chloroform or $Pd(OH)_2$/C and cyclohexene in ethanol and DMF).

## Experimental Section

**General Procedures.** Most of the solvents and all reagents were obtained from commercial supplies and used without further purification. DMF was freshly distilled and stored over 4 Å molecular sieves. Proton and carbon nuclear magnetic resonance spectra ($^1$H NMR and $^{13}$C NMR) were recorded on a Bruker AC100, Bruker AC300 and Bruker AMX400 spectrometers. Chemical shifts are reported as $\delta$ values in ppm from tetramethylsilane ($\delta$ 0.0) as internal standard. Analytical thin-layer chromatography was carried out on silica gel plates ($SiO_2$, Merk 60 $F_{254}$). Mass spectra were performed with Finnigan MAT SSQ 710 (CI, $CH_4$) and FinniganMAT 90 (FAB, NBA). Infrared spectra were recorded with a Perkin-Elmer model 298 spectrometer. Melting points were obtained in a nitrogen-sealed capillary on Electrothermal Apparatus. All compounds gave satisfactory elemental analyses. All reactions were performed with efficient stirring in a nitrogen atmosphere. Petroleum ether refers to the fraction boiling at 40−60 °C.

**5,11,17,23,29,35,41,47-Octakis(benzyloxy)-49,50,51,52,53,54,55,56-octahydroxycalix[8]arene (2).** A 20.0 g (0.1 mol) sample of *p*-(benzyloxy)phenol (**1c**) (purchased from Fluka, purum, >99%) was dissolved in 400 mL of xylene in a 1 L round-bottomed flask equipped with a Dean & Stark water collector. The solution was heated to 100 °C, then 1.1 mL (2 mmol) of 2 N NaOH aqueous solution and 5.4 g (179.8 mmol) of paraformaldehyde were added. After 2 h the temperature was increased to 150 °C and a precipitate began to form. The reaction mixture was refluxed for 48 h and then cooled and filtered on a Buchner funnel. The resulting solid was washed with diethyl ether and then transferred to a 250 mL round-bottomed flask and suspended in 200 mL of methylene cloride. This heterogeneous solution was refluxed for 3 h and then hot filtered on a Buchner funnel to yield 10.2 g (48%) of white compound **2**: mp >300 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.63 (s, 8H), 7.29 (s, 40H), 6.60 (s, 16H), 4.80 (s, 16H), 3.80 (s, 16H); MS (CI−) $m/z$ 1697 ($M^-$); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 151.0, 146.6, 137.6, 128.9, 128.1, 127.6, 69.7, 32.0; MS (CI−) 1696 ($M^+$); Anal. Calcd for $C_{112}H_{96}O_{16}$: C, 79.23; H, 5.69. Found: C, 79.11; H, 5.80.

**Analysis of Products Distribution in the One-Pot Condensation of *p*-(Benzyloxy)phenol and Formaldehyde.** The crude solid resulting from condensation reaction in xylene, once filtered on a Buchner and washed with diethyl ether, was submitted to acetylation reaction. A 0.2 g sample of this solid (mixture of calix[8]-, -[7]- and -[6]arenes) was dissolved in hot pyridine (5 mL) and 0.4 mL of acetyl chloride was slowly added. After stirring at room temperature for 24 h, 50 mL of 1 N HCl was added and the precipitate filtered under suction. A sample of this solid was dissolved in the minimum amount of chloroform and then an excess of methanol was added. This solution was analyzed by HPLC (reverse phase C18, eluent methanol/water = 96/4, flux 1.5 mL/min). Samples of the eluate were collected in correspondence of the single peaks and analyzed by mass spectrometry: hexamer, $t_R$ = 7.31 min, MS ($CI^+$) $m/z$ 1526.1 $[(M + 1)]^+$; heptamer, $t_R$ =10.66 min, MS ($CI^+$) $m/z$ 1779.6 $[(M + 1)]^+$; octamer, $t_R$ = 17.21 min, MS ($CI^-$) $m/z$ 2033.0 $(M)^-$.

**5,11,17,23,29,35,41,47-Octakis(benzyloxy)-49,50,51,52,53,54,55,56-octaacetoxycalix[8]arene (5a).** A 0.2 g (0.12 mmol) sample of **2** was dissolved in the minimum amount (~5 mL) of hot pyridine, then 0.4 mL of acetyl chloride was slowly added. The solution was stirred at room temperature for 24 h, then 50 mL of 1 N HCl was added to the reaction mixture, causing the precipitation of a white solid which was filtered, dissolved in $CH_2Cl_2$, and precipitated with hexane (95% yield): mp 137−138 °C; IR (KBr) 1760 $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 7.26 (s, 40H), 6.55 (s, 16H), 4.80 (s, 16H), 3.56 (s, 16H), 1.95 (s, 24H); $^{13}$C NMR $\delta$ 169.0, 156.3, 140.9, 136.6, 132.8, 128.3, 127.8, 127.5, 115.0, 69.9, 31.5, 20.0; MS ($CI^-$) $m/z$ 2033 ($M^-$). Anal. Calcd for $C_{128}H_{112}O_{24}$: C, 75.58; H, 5.54. Found: C, 75.43; H, 5.62.

**General Procedure for the Alkylation of Compound 2.** A solution of 0.65 g (0.38 mmol) of compound **2** was dissolved in 20 mL of dry DMF and stirred with 13.3 mmol of $Cs_2CO_3$ and 22.8 mmol of alkyl halide at 90 °C. After 10−20 h, the cooled reaction mixture was quenched with 1 N HCl (75 mL) and the crude product was filtered on a Buchner funnel and washed with water. After drying, pure products **5b**−**e** were purified as reported below.

**5b.** Methyl iodide was used as alkylating agent. The crude product was dissolved in $CH_2Cl_2$ and precipitated with $CH_3OH$ to give 0.28 g (yield 40%) of pure product: mp = 104−5 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.19 (m, 40H), 6.51 (s, 16H), 4.72 (s, 16H), 3.92 (s, 16H), 3.41 (s, 24H); $^{13}$C NMR ($CDCl_3$) $\delta$ 154.6, 150.5, 137.1, 134.8, 128.4, 127.7, 127.5, 115.0, 70.0, 60.8, 33.1; MS (FAB) $m/z$ 1809 ($M^+$). Anal. Calcd for $C_{120}H_{112}O_{16}$: C, 79.63; H, 6.23. Found: C, 79.81; H, 6.34.

**5c.** In this reaction pentyl iodide was the alkylating agent. The crude product was dissolved in $CH_2Cl_2$ and purified by column chromatography ($SiO_2$) using petroleum ether/THF (7/3) as eluent: yield = 60%; mp 98−100 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.11 (s, 40H), 6.50 (s, 16H), 4.61 (s, 16H), 3.97 (s, 16H), 3.58 (t, 16H), 1.55 (m, 16H), 1.31 (m, 32H), 0.84 (m, 24H); $^{13}$C NMR ($CDCl_3$) $\delta$ 154.6, 149.4, 137.3, 135.0, 128.2, 127.5, 127.4, 115.0, 73.6, 69.7, 30.5, 30.0, 28.4, 22.6, 14.0; MS ($CI^+$) *m*/*z* 2257 ($M^+$). Anal. Calcd for $C_{152}H_{176}O_{16}$: C, 80.82; H, 7.85. Found: C, 80.87; H, 7.92.

**5d.** The alkylating agent was 2-bromoethyl acetate. The crude product was dissolved in $CH_2Cl_2$ and precipitated with $CH_3OH$ (50% yield): mp >300 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.20 (m, 40H), 6.53 (s, 16H), 4.68 (s, 16H), 4.21 (s, 16H), 4.01 (m, 32H), 1.05 (t, *J* = 7.1 Hz, 24H); $^{13}$C NMR ($CDCl_3$) $\delta$ 168.7, 155.1, 148.7, 136.9, 134.3, 128.2, 127.5, 127.4, 115.0, 70.2, 69.6, 60.8, 30.6, 13.8; MS (FAB) *m*/*z* 2385 ($M^+$). Anal. Calcd for $C_{144}H_{144}O_{32}$: C, 72.47; H, 6.07. Found: C, 72.39; H, 6.26.

**5e.** 2-Chloro-*N*,*N*-diethylacetamide was the alkylating agent. The crude product was dissolved in $CH_2Cl_2$, then $CH_3OH$ was added to the solution which was left for 10 h at −10 °C. The filtration gave 0.61 g (61% yield) of pure product: mp >300 °C; IR (KBr) 1645 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 7.13 (m, 40H), 6.54 (s, 16H), 4.54 (s, 16H), 4.42 (s, 16H), 4.04 (s, 16H), 3.25 (q, *J* = 7 Hz, 16H), 3.12 (q, *J* = 7 Hz, 16H), 0.99 (t, *J* = 7 Hz, 24H), 0.93 (t, *J* = 7 Hz, 24H); $^{13}$C NMR ($CDCl_3$) $\delta$ 166.9, 155.0, 149.2, 137.0, 134.5, 128.0, 127.5, 127.4, 115.0, 72.1, 69.4, 41.1, 39.9, 30.5, 14.1, 12.7; MS (FAB) *m*/*z* 2601 ($M^+$). Anal. Calcd for $C_{160}H_{184}O_{24}N_8$: C, 73.83; H, 7.12; N, 4.30. Found: C, 73.71; H, 7.19; N, 4.48.

**General Procedure for the Debenzylation of Calix[8]arenes 5 and 2.** A sample (0.1 mmol) of compound **5a**−**c**,**e** or **2** was dissolved in hot ethanol (50 mL) and stirred in an inert atmosphere at 90 °C with 18 mL of cyclohexene and 0.7 g of $Pd(OH)_2$/C (20%, Pearlman's catalyst) per gram of compound. After 15−18 h, the carbon was removed by filtration and the liquid was evaporated under vacuum, leaving the crude product in nearly quantitative yields (>90%). The product was purified by crystallization.

**6a.** Yield = 76%, mp 235 °C (dec); $^1$H NMR (DMSO-$d_6$) $\delta$ 9.25 (s, 8H), 6.39 (s, 16H), 3.34 (s, 16H), 1.97 (s, 24H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 173.9, 159.6, 144.5, 137.9, 120.2, 24.8, 18.7; MS (FAB) *m*/*z* 1312 ($M^+$). Anal. Calcd for $C_{72}H_{64}O_{24}$: C, 65.85; H, 4.91. Found C, 65.77; H, 4.98.

**6b.** Yield = 90%; mp >300 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.93 (s, 8H), 6.31 (s, 16H), 3.79 (s, 16H), 3.58 (s, 24H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 152.8, 148.6, 134.2, 115.0, 60.3, 29.4; MS ($CI^+$) *m*/*z* 1088 ($M^+$). Anal. Calcd for $C_{64}H_{64}O_{16}$: C, 70.58; H, 5.92. Found: C, 70.49; H, 6.00.

**6c.** Yield = 90%; mp 347−9 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.75 (s, 8H), 6.27 (s, 16H), 3.79 (s, 16H), 3.50 (t, 16H), 1.56 (t, 16H), 1.30 (t, 16H), 1.24 (t, 16H), 0.77 (q, 24H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 152.6, 147.6, 134.1, 115.0, 72.8, 29.4, 27.8, 22.0, 13.7; MS ($CI^+$) *m*/*z* 1537 ($M^+$). Anal. Calcd for $C_{96}H_{128}O_{16}$: C, 74.97; H, 8.38. Found: C, 75.06; H, 8.47.

**6e.** Yield = 80%: mp >300 °C; $^1$H NMR ($CDCl_3$/$CD_3OD$ = 3/1) $\delta$ 6.38 (s, 16H), 4.41 (s, 16H), 3.93 (s, 16H), 3.16 (d, *J* = 7 Hz, 16H), 3.13 (d, *J* = 7 Hz, 16H), 1.04 (t, *J* = 7 Hz, 24H), 0.94 (t, *J* = 7 Hz, 24H); $^{13}$C NMR ($CDCl_3$/$CD_3OD$ = 3/1) $\delta$ 168.7, 153.9, 148.6, 135.3, 116.1, 72.0, 42.1, 41.0, 30.9, 14.2, 12.9; MS ($FAB^+$) *m*/*z* 1880.7 ($M^+$). Anal. Calcd for $C_{104}H_{136}O_{24}N_8$: C, 66.37; H, 7.27; N, 5.95. Found: C, 66.45; H, 7.39; N, 6.07.

**7a.** In the workup of the reaction, solutions containing the product may easily darken, owing to the oxidation of some hydroquinone nuclei of the macrocycle. The crude product was therefore dissolved in $CHCl_3$ and stirred under a nitrogen atmosphere with a 1% solution of $Na_2S_2O_4$ for 2 h. Then the yellow solid was filtered under nitrogen and collected: mp >300 °C; IR (KBr) 1660 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.59 (s, 8H), 8.36 (s, 8H), 6.36 (s, 16H), 3.70 (s, 16H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 150.4, 143.6, 128.8, 114.6, 31.0; MS ($CI^+$) *m*/*z* 920 [(M − 2CO)]$^+$. Anal. Calcd for $C_{56}H_{48}O_{16}$: C, 68.85; H, 4.95. Found: C, 68.98; H, 5.02.

Compounds **5a** and **5e** were also debenzylated in good yields to **6a** (76%) and **6e** (80%) also using the following procedure.

A sample of 0.33 mmol of compound **5a** or **5e** was dissolved in 10 mL of $CHCl_3$ and treated with 3.4 mL of dimethyl sulfide (46.2 mmol) and 23.1 mL (23.1 mmol) of a $BCl_3$ solution (1 M in $CH_2Cl_2$) at room temperature. After 4 h, the solvent and the excess of dimethyl sulfide were removed by evaporation under vacuum and the remaining solid was treated with water. The resulting solid was separated by filtration and slowly crystallized from $CHCl_3$/$CH_3OH$ = 3/1.

**5,11,17,23,29,35,41,47,49,50,51,52,53,54,55,56-Hexadecahydroxycalix[8]arene (7a). Method A:** a suspension of 0.14 g (0.08 mmol) of **2** in 5 mL of $CHCl_3$ was treated with 0.5 mL (3.51 mmol) of iodotrimethylsilane and stirred at 60 °C. After 12 h, 5 mL of $CH_3OH$ was added and then the solvent removed, giving 0.07 g (0.07 mmol) (87.5%) of a dark solid which became ink-blue when treated with water. This product was suspended in 5 mL of $CHCl_3$ and treated with 5 mL of a 1% solution of $Na_2S_2O_4$. The mixture was stirred under an argon atmosphere at room temperature for 2 h and then the product was isolated by filtration under flushing nitrogen (yield 80%).

**Method B:** see above, General Procedure for the Debenzylation of Calix[8]arenes **5** and **2**.

**5,11,17,23,29,35,41,47,49,50,51,52,53,54,55,56-Hexadecakis[[[(*N*,*N*-diethylamino)carbonyl]methyl]oxy]-calix[8]arene (7b).** A 0.23 g (0.12 mmol) sample of **6e** was dissolved in 10 mL of dry DMF and to this solution were added 3.2 g (9.8 mmol) of $Cs_2CO_3$ and 1.1 mL (10.4 mmol) of 2-chloro-*N*,*N*-diethylacetamide. After 10 h of stirring at 80 °C, the reaction was quenched with 50 mL of 1 N HCl. $CH_2Cl_2$ (30 mL) was added and the organic layer was separated and extracted several times with 1 N HCl. The final organic layer was evaporated under reduced pressure till a volume of 5 mL was reached and the product precipitated with petroleum ether: $^1$H NMR ($CDCl_3$) $\delta$ 6.42 (s, 16H), 4.37 (s, 16H), 4.23 (s, 16H), 3.82 (s, 16H), 3.32−3.26 (m, 64H), 1.0−0.85 (m, 96H); $^{13}$C NMR ($CDCl_3$) $\delta$ 166.9, 154.6, 134.6, 115.1, 71.5, 66.8, 41.4, 40.2, 31.1, 14.3, 12.9; MS ($FAB^+$) *m*/*z* 2809 [(M + Na)]$^+$, 2825 [(M + K)]$^+$. Anal. Calcd for $C_{152}H_{224}O_{32}N_{16}$: C, 65.49; H, 8.09; N, 8.04. Found: C, 65.37; H, 8.17; N, 8.15.

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