

Synthesis of Calix[6]arenes Partially Functionalized at the Upper Rim

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Abstract: Several new examples of calix[6]arenes selectively functionalized at the upper rim are reported. Starting from calix[6]arenes 1,3,5-tri-, 1,2,4,5-tetra- and 1,2,3,4,5-pentaalkylated at the lower rim, it is possible to isolate macrocycles 2,4,6-tri-, 3,6-di- and 6-mono functionalized at the upper rim (18-94% yield) with nitro, formyl, bromo, chloromethyl and 2-propenyl groups. Modifications of these moieties allow the synthesis of macrocycles bearing amino, amido, hydroxymethyl, carboxy, cyano and chloromethyl functions which can be used for further transformation and preparation of new molecular receptors, based on calix[6]arenes, which have different geometries. Examples of di- and triquinones on the hexameric macrocycle are also reported.

INTRODUCTION

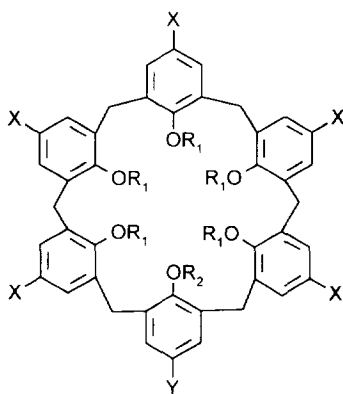
Calixarenes have been widely used in the recent years for the synthesis of receptors for ions and neutral molecules.^{1,2} The increasing interest in these macrocycles is not only due to their easy synthesis through well established and simple methodologies,³ but also to the possibility of shaping their basket through functionalization at the lower (phenolic OH groups) or at the upper rim (aromatic nuclei). Most of the studies on the *selective functionalization* of these compounds have been devoted to calix[4]arenes⁴ and resulted in the synthesis of highly efficient and selective receptors for metal and ammonium ions, or neutral molecules.^{2,5} However the dimensions of the conical apolar cavity of calix[4]arenes is rather small and it is only present when the macrocycle is fixed in the cone conformation, whereas their functionalization at the lower rim can also produce other stereoisomers (partial cone, 1,2-alternate, 1,3-alternate), which have no cavity. Moreover the increasing interest in complexation of larger and polyfunctional guest molecules led us to tackle the problem of selective functionalization of calix[6]arenes. These macrocycles are characterized not only by a larger cavity but also by the presence of six aromatic nuclei suitable for anchoring binding units. When they are functionalized at the proper positions calix[6]arenes may afford a wide variety of receptors with variable flexibility and shapes. However, compared with calix[4]arenes, the regiochemical control of calix[6]arene functionalization is more difficult because of the presence of a larger number of reactive centers and a higher conformational mobility. Although several papers appeared on the complete functionalization of calixarenes at the upper rim with sulfonic,⁶ nitro, amino,⁷ aminomethyl,⁸ phosphonic,⁹ acyl¹⁰ and formyl¹¹ groups, and the synthesis of a large variety of partially functionalized calix[6]arenes at the lower rim are now available,¹² only

few examples of selectively substituted calix[6]arenes at the upper rim are reported. Some of them have been obtained through the stepwise synthesis route¹³ while we recently published methods for the preparation of a monobromo-, a mononitro-, and a 1,4-dinitrocalix[6]arene,¹⁴ together with a partially 1,3,5-de-butylated calix[6]arene derivative¹⁵ which has also been obtained by others.¹⁶

We report in this paper the results of a more systematic work on the selective functionalization of calix[6]arenes at the upper rim.

RESULTS AND DISCUSSION

As a general strategy for the selective functionalization at the upper rim we have exploited the previously reported results on the selective alkylation of the lower rim,¹² which induces a different reactivity between the aromatic positions *para* to the free OH groups compared with those *para* to the OR groups.¹⁷ Most of the partially alkylated compounds used as starting materials in this study are obtained from *p*-*tert*-butylcalix[6]arene **1**, since the corresponding derivatives of *p*-H-calix[6]arene **2** are unknown or very difficult to obtain.^{12a,18} During this work we have found an excellent procedure for the preparation of monobenzylcalix[6]arene **3** in 89% yield, using a weak base (K₂CO₃) and a stoichiometric amount of benzyl bromide in dry acetone. Methylation of compound **3** with NaH/Me₂SO₄ gives the monobenzyloxy-pentamethoxycalix[6]arene **4** in quantitative yield, which is easily converted to the pentamethoxycalix[6]arene **5** by catalytic hydrogenation. No chromatographic separations are required, so compound **5** can be easily obtained in gram quantities.



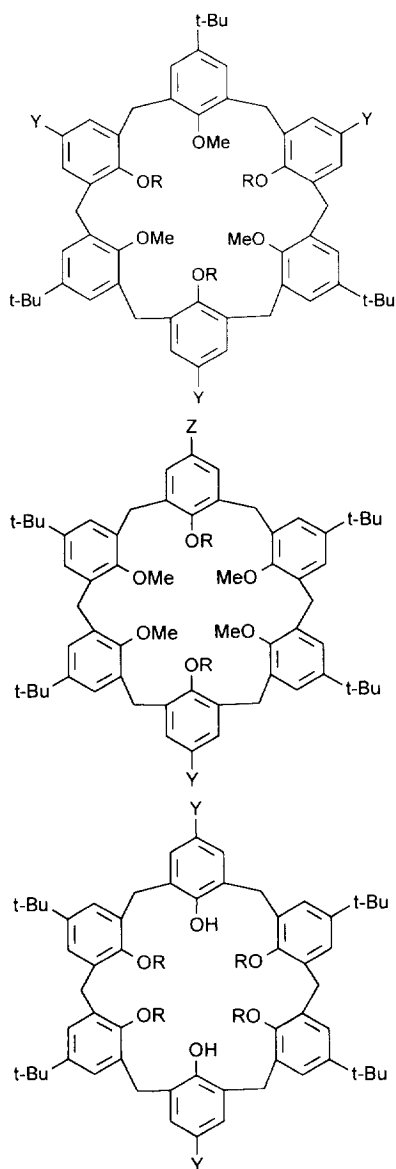
n	R ₁	R ₂	Y	X
1	H	H	<i>t</i> -Bu	<i>t</i> -Bu
2	H	H	H	H
3	H	C ₆ H ₅ CH ₂	H	H
4	Me	C ₆ H ₅ CH ₂	H	H
5	Me	H	H	H
15	Me	H	<i>t</i> -Bu	<i>t</i> -Bu
16	Me	H	NO ₂	<i>t</i> -Bu
17	Me	C(O)Me	NO ₂	<i>t</i> -Bu
18	Me	Me	NO ₂	<i>t</i> -Bu
19	Me	H	NO ₂	H
23	Me	C(O)Me	NH ₂	<i>t</i> -Bu

Selective Nitration.

*Ips*o-nitration, i.e. substitution of *tert*-butyl with nitro groups, is a particularly useful reaction in calixarene chemistry because it uses as substrate the most readily available *p*-*tert*-butylcalixarenes and allows substitution of only the *tert*-butyl groups *para* to the free phenolic OH groups.¹⁹

Therefore by treating several partially alkylated calix[6]arenes **6**, **10**, **13** and **15** with 1.1-1.5 equivalents of 63% HNO₃ in a 1:1 (v/v) mixture with 98% H₂SO₄, at room temperature for 40 min - 2 h in dry CH₂Cl₂ it was possible to isolate compounds **7**, **11**, **14**, **16** nitrated in all phenolic nuclei, in 61-80% yield (Table 1). These

conditions appear to give nitrated products in better yield compared with the HNO_3 (60%)/AcOH mixture previously used.¹⁴



n	R	Y	n	R	Y
6	H	<i>t</i> -Bu	32	Me	CHO
7	H	NO ₂	37	C ₆ F ₅ CH ₂	CH ₂ OH
8	CH ₂ COOMe	NO ₂	38	Me	CH(OMe) ₂
9	C(O)Me	NO ₂	40	H	Br
20	C(O)Me	NH ₂	41	Me	Br
27	H	H	42	4-Me-C ₆ H ₄ CH ₂	Br
28	H	CHO	44	Me	CN
29	C ₆ F ₅ CH ₂	H	45	Me	CH ₂ Cl
30	C ₆ F ₅ CH ₂	CHO	46	CH ₂ CH=CH ₂	H
31	Me	H	47	H	CH ₂ CH=CH ₂

n	R	Y	Z
10	H	<i>t</i> -Bu	<i>t</i> -Bu
11	H	NO ₂	NO ₂
12	C(O)Me	NO ₂	NO ₂
21	C(O)Me	NH ₂	NH ₂
22	C(O)Me	NO ₂	NH ₂
24	C(O)Me	NHCO(CH ₂) ₂ COOH	NHCO(CH ₂) ₂ COOH
25	C(O)Me	NHCO(CH ₂) ₃ COOH	NHCO(CH ₂) ₃ COOH
26	C(O)Me	NHCOCH ₂ OCH ₂ COOH	NHCOCH ₂ OCH ₂ COOH

n	R	Y
13	C ₂ H ₄ OC ₂ H ₄ OMe	<i>t</i> -Bu
14	C ₂ H ₄ OC ₂ H ₄ OMe	NO ₂
35	C ₂ H ₄ OC ₂ H ₄ OMe	H
36	C ₂ H ₄ OC ₂ H ₄ OMe	CHO
39	C ₂ H ₄ OC ₂ H ₄ OMe	COOH
43	C ₂ H ₄ OC ₂ H ₄ OMe	Br
49	Bz	<i>t</i> -Bu

Acetylation and/or alkylation with $\text{BrCH}_2\text{COOMe}$ and dimethyl sulfate of compounds **7**, **11**, **16** gave compounds **8-9**, **12**, **17** and **18** completely functionalized at the lower rim and bearing three, two or one nitro groups at the upper rim. The ¹H NMR spectra (see Experimental Section) for all nitro compounds synthesized show only singlets for the methylene bridge protons, indicating a high degree of conformational mobility at room temperature.

Table 1. Nitration of Calix[6]arenes at Room Temperature in Dry CH₂Cl₂.

Starting material	Product	eq HNO ₃ (63%) ^a	Time (min)	Yield (%)
5	19	1.1	5+50 ^b	28
6	7	1.5	50	64
10	11	1.5	120	61 ^c
13	14^d	10.0 ^e	5+50 ^b	66
15	16	1.5	50	80 ^f

^a one equivalent of HNO₃ (63%) for each phenolic nuclei to be nitrated, in 1:1 (v/v) mixture with H₂SO₄ (98%). ^b the nitrating mixture was added over 5 min to the CH₂Cl₂ solution of calixarene kept at -15°C. The reaction mixture was then stirred at room temperature for 50 min. ^c mp > 300°C (Lit.¹⁴ mp > 300°C). ^d Compound **13** was dissolved in glacial AcOH/CH₂Cl₂, 1:6 (v/v). ^e HNO₃ was added neat. ^f mp > 300°C (Lit.¹⁴ mp > 300°C).

Also the direct nitration of compound **5** derived from calix[6]arene **2** give the mononitro-pentamethoxycalix[6]arene **19** in 28% yield.

Reduction of nitrocalixarenes **9**, **12** and **17** was performed with SnCl₂ in dry EtOH or H₂ over PtO₂ or Pd(C) and proceeded without affecting the acetoxy groups present at the lower rim. This complete reduction of **9**, **12** and **17** afforded tri-, di- and monoaminocalix[6]arenes **20**, **21** and **23** in yields of 91%, 80% and 76% respectively. Use of H₂/PtO₂ and milder experimental conditions permitted selective reduction of dinitrocalix[6]arene **12** to its mononitro-monoamino derivative **22** in good yield (62%).

Treatment of diamino-calix[6]arene **21** with a large excess of succinic, glutaric and diglycolic anhydride in THF resulted in the isolation of the corresponding coupling products **24-26** which have two carboxylic functions at the upper rim of the macrocycle in 1,4-position. In this compounds the structure is still highly mobile thus confirming that the presence of the bulky groups such as t-Bu and NHC(O)(CH₂)_nCOOH at the upper rim is not enough to freeze the conformational interconversion when relatively small groups (Me, MeCO) are present at the lower rim.

Selective formylation.

Other than *ipso*-nitration, electrophilic aromatic substitutions need to be performed on *de-tert*-butylated calix[6]arenes. Since, as mentioned before, very few examples of *p*-H-calix[6]arenes selectively *O*-alkylated at the lower rim are known, we have used compounds **27** and **35** obtained through the selective removal of *tert*-butyl groups in partially *O*-alkylated *p-tert*-butylcalix[6]arenes **6** and **13**.

Selective formylation of these macrocycles has been carried out following the methods of Gross²⁰ (Cl₂CHOCH₃/Lewis acid, Table 2) and Duff²¹ (hexamethylene tetramine/CF₃COOH, Table 3) which have already been successfully applied to calixarenes.^{22,23} However the reaction of compound **27** in the presence of Cl₂CHOCH₃/SnCl₄ resulted in the isolation of only small amounts of triformylated compound **28**, while parallel dealkylation reactions seem to be predominant. Better results have been obtained by treating **27** with hexamethylene tetramine (HMTA) and CF₃COOH which allows the isolation of **28** in 18% yield. Much more successful was the formylation of compound **35** which gave the diformylated derivatives **36** in 94% yield *via* the Gross method and in 44% yield under Duff's conditions.

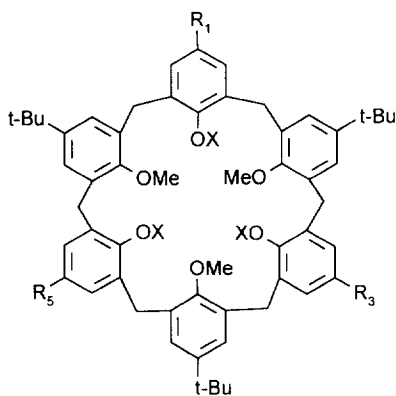
Table 2. Formylation of Calix[6]arenes **29** and **35** with Cl₂CHOCH₃ and TiCl₄ (SnCl₄) at R.T.

Starting material	Product	Molar Ratio of TiCl ₄ ^a to calix	Molar Ratio of Cl ₂ CHOCH ₃ to calix	Time (h)	Yield (%)
29	30	30	30	3	18
29	33	15	15	1	25
29	34	15	15	1	23
35	36	10 ^b	2.5	1	94

^a freshly distilled; ^b SnCl₄ was used.

Table 3. Formylation of Calixarenes **27**, **31** and **35** with HMTA in CF₃COOH at Reflux.

Starting material	Product	Molar Ratio of HMTA to calix	Reaction time (h)	Yield (%)
27	28	27	17	18
31	32	42	36	74
35	36	18	21	44



n	X	R ₁	R ₃	R ₅
33	C ₆ F ₅ CH ₂	CHO	H	H
34	C ₆ F ₅ CH ₂	CHO	CHO	H

Compound **27** has been converted to **31** by methylation with Cs₂CO₃ and MeI in DMF in higher yield (93%) than that reported by Shinkai using NaH in THF.¹⁶ Formylation of **31** under Duff conditions gave triformylated compound **32** in 74% yield. The use of compound **29** and a large amount of TiCl₄ and Cl₂CHOCH₃ (30 eq.) gave compound **30** in 18% yield, while a lower amount of Lewis acid and formylating agent (15 eq.) gave a mixture of the mono- (**33**) (25%) and di- (**34**) (23%) formylated derivatives.

The formyl groups on these derivatives can be easily modified by reduction and oxidation or protected to acetals as exemplified by the synthesis of compound **37** and **39** obtained in quantitative yields and of compound **38** obtained in 81% yield using dry MeOH with a trace of CF₃COOH.

Selective halogenation.

Another interesting functionalization of calixarenes at the upper rim is halogenation (bromination or iodination)^{17,24,25,26} since it allows, by subsequent reactions, the introduction of a large variety of groups such as COOR, CN, NH₂, Ph, etc. which are not easily introduced by direct electrophilic aromatic substitution. We have explored the bromination of trimethoxy-tri-*tert*-butylcalix[6]arene **27** and of tetrakis[2-(2-methoxyethoxy)ethoxy]-tetra-*tert*-butylcalix[6]arene **35** using NBS. Tribromo derivative **40** and dibromo **43**

were obtained in 48 and 34 % yield respectively when reactions were carried out in ethyl acetate as solvent, while the use of 2-butanone increased the amount of isolated **40** to 70%. Alkylation of compound **40** with Cs_2CO_3 in DMF and CH_3I or 4-methylbenzyl bromide gave compound **41** and **42**. The former was reacted under Rosenmund-von Braun conditions (anhydrous CuCN and *N*-methyl pyrrolidinone at 200°C) to give the tricyano compound **44** in 78% yield.

Selective chloromethylation.

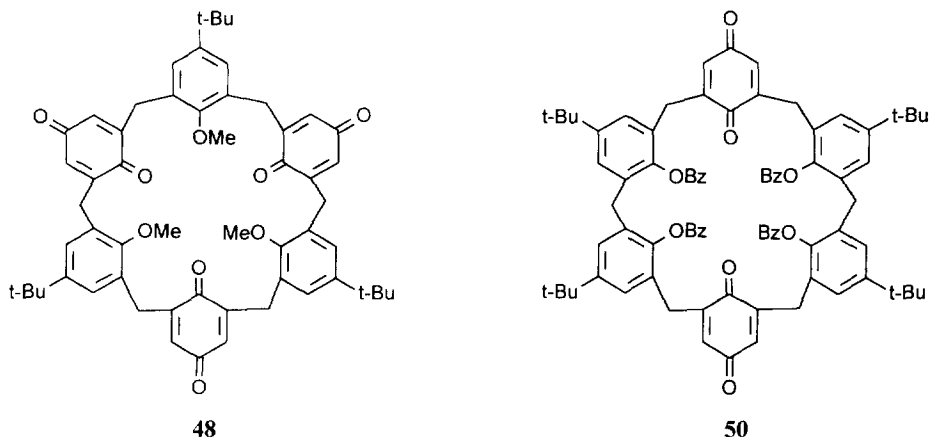
The last electrophilic aromatic substitution which we have carried out is the chloromethylation of compound **31**. As previously reported by some of us²⁷ for tetraalkoxycalix[4]arenes, the use of H_2CO , SnCl_4 and trimethylsilyl chloride is a very efficient and high yield method of chloromethylation of aromatics originally developed in polymer chemistry,²⁸ which avoids the use of carcinogenic $\text{ClCH}_2\text{OCH}_3$. Also for calix[6]arenes, when three positions are protected by *tert*-butyl groups it is possible to introduce three CH_2Cl groups in the 1,3,5 positions to give **45** in 80% yield. This procedure for the preparation of compound **45** is therefore comparable to that recently reported by Shinkai *et al.*, which uses $\text{ClCH}_2\text{OCH}_3/\text{ZnCl}_2$.¹⁶

Claisen rearrangement.

An interesting method of functionalization of the upper rim of calixarenes is the Claisen rearrangement route.²⁹ The 1,3,5-trimethoxy-tri-*tert*-butylcalix[6]arene **27** could be easily alkylated with Cs_2CO_3 in DMF to tris-(2-propenyloxy) derivative **46** in 83% yield.

Subsequent reaction in refluxing *N,N*-dimethylaniline gave the rearrangement product **47** (42%) which is a useful intermediate for further transformations.

Calix[6]arene-quinones.



Oxidation of trimethoxy-tri-*p-tert*-butylcalix[6]arene **6** with $\text{Ti}(\text{NO}_3)_3 \cdot 3\text{H}_2\text{O}$ gave in 24% yield the triquinone **48** while reaction of tetrabenzoyloxy-*p-tert*-butylcalix[6]arene **49** with $\text{Ti}(\text{CF}_3\text{CO}_2)_3$ in trifluoroacetic acid (TFA) afforded the diquinone **50** in 80% yield.

These calixquinones could not only show interesting redox properties,³⁰ but could also be useful intermediates for further modification at the upper rim³¹ and for the introduction of chromophoric groups.³²

All compounds synthesized in this work are conformationally mobile as demonstrated by their ^1H NMR spectra at room temperature (see Experimental Section) where singlets or broad signals for the protons of the methylene bridges are present. Only the tetraalkoxy-dibromo-tetra-*p*-*tert*-butylcalix[6]arene **43** shows a distinct pattern of sharp signals including the ArCH_2Ar protons which remain unchanged between -50 and $+70^\circ\text{C}$ in CDCl_3 indicating a restricted mobility of the macrocycle over this range of temperature and on the 400 MHz NMR timescale.

Two-dimensional NMR experiments (XHCORR together with COSY and NOESY) allowed assignment of all signals of the NMR spectra and proposal of a preferred conformation for this compound. Two triplets at δ 39.2 and 30.7 ppm are present in the ^{13}C NMR spectrum for the methylene bridge carbons (ArCH_2Ar). The first correlates with a singlet of four protons at 4.06 ppm while the second one correlates with two doublets of four protons each at 4.08 and 3.76 ppm. This indicates³³ that two pairs of aromatic nuclei are each other *anti*-oriented and three sets are *syn*-oriented. The presence, in the molecule, of a symmetry element (plane or C_2 axis) as deduced from ^1H and ^{13}C NMR spectra suggests a 1,2,3-alternate structure (*u,u,d,d,d,u*)³⁴ for this compound (Figure 1).

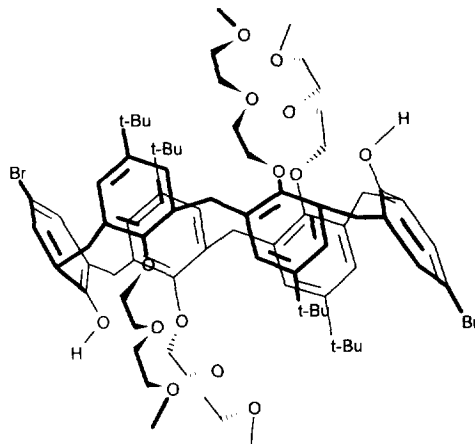


Fig.1. Proposed 1,2,3-alternate structure for compound **43**.

EXPERIMENTAL SECTION

Melting points were determined with an Electrothermal melting point apparatus in a sealed capillary and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded with Bruker spectrometers with Me_4Si as internal standard. Mass spectra were obtained with a Finnigan MAT90, a VG Autospec spectrometer (FAB using 3-nitrobenzyl alcohol as a matrix) or with a Finnigan MAT SSQ710 spectrometer (DCI, CH_4). Analytical thin layer chromatography was performed on precoated silica gel plates (SiO_2 , Merck, 60 F_{254} or Alugram Sil G/UV 254), while silica gel 60 (SiO_2 , Merck, particle size 0.040-0.063 mm, 230-240 mesh) or SDS 60 (particle size 230-400 mesh) was used for preparative column chromatography.

Materials

5,11,17,23,29,35-Hexa-*tert*-butylcalix[6]arene-37,38,39,40,41,42-hexol (**1**),^{35,3} calix[6]arene-37,38,39,40,41,42-hexol (**2**),³⁶ 5,11,17,23,29,35-hexa-*tert*-butyl-38,40,42-trimethoxycalix[6]arene-37,39-41-triol (**6**),³⁷ 5,11,17,23,29,35-hexa-*tert*-butyl-38,39,41,42-tetramethoxycalix[6]arene-37,40-diol (**10**),¹⁴ 5,11,17,23,29,35-hexa-*tert*-butyl-37,38,40,41-tetrakis[2-(2-methoxyethoxy)ethoxy]calix[6]arene-39,42-diol (**13**),^{12a} 5,11,17,23,29,35-hexa-*tert*-butyl-38,39,40,41,42-pentamethoxycalix[6]arene-37-ol (**15**),¹⁴ and 5,17,29-tri-*tert*-butyl-38,40,42-trimethoxycalix[6]arene-37,39,41-triol (**27**),¹⁵ 38,39,41,42-tetrabenzoyloxy-5,11,17,23,29,35-hexa-*tert*-butylcalix[6]arene-37,40-diol (**49**)³⁸ were prepared as described in the literature.

37-Benzylloxycalix[6]arene-38,39,40,41,42-pentol (3)

A mixture of calix[6]arene-37,38,39,40,41,42-hexol **2** (4.0 g, 6.3 mmol) and K₂CO₃ (0.95 g, 6.9 mmol) in dry acetone (400 ml) was refluxed for 1 h. After cooling, benzyl bromide (0.82 ml, 6.9 mmol) was added, and the mixture was refluxed for 66 h. The mixture was quenched with 25% aq NH₄OH (15 ml), stirred for 20 min, acidified with 2N HCl and acetone eliminated under reduced pressure. The residue was extracted with CH₂Cl₂ (3x100 ml) and the organic layer was washed with brine and dried (Na₂SO₄). The solvent was evaporated and the residue was triturated with MeOH. The precipitate obtained was triturated with hexane and filtered to afford pure **3**. Yield 4.05 g (89%); mp 254-260°C. HRMS (FAB): *m/z* = 726.29596 (M⁺, calcd for C₄₉H₄₂O₆ 726.29814). ¹H NMR (200 MHz, CDCl₃): δ = 9.80 (br s, 2 H, OH), 8.90 (br s, 3 H, OH), 7.75 (d, *J* = 8.0 Hz, 2 H, ArH), 7.65 (dd, *J* = 8.0, 10.0 Hz, 2 H, ArH), 7.49 (t, *J* = 10.0 Hz, 1 H, ArH), 7.3-7.1 (m, 13 H, ArH), 6.9-6.7 (m, 5 H, ArH), 5.25 (s, 2 H, OCH₂Ar), 4.5-3.5 (br s, 12 H, ArCH₂Ar); ¹³C NMR (75 MHz, CDCl₃): δ = 151.8, 151.6, 150.5, 149.1, 136.2, 133.3 (s, Ar), 129.6, 129.4, 129.2, 129.1, 129.0, 128.8, 128.7 (d, ArH), 127.82, 127.79, 127.6, 127.5, 127.4 (s, Ar), 127.3, 126.0, 122.1, 121.2, 120.7 (d, ArH), 77.8 (t, OCH₂Ar), 32.2 (t, ArCH₂Ar), 32.0 (t, ArCH₂Ar).

37-Benzylloxy-38,39,40,41,42-pentamethoxycalix[6]arene (4)

To a stirred slurry of NaH (60% oil dispersion, 0.92 mg, 23 mmol) in THF (160 ml) under argon was added a solution of calix[6]arene **3** (3.0 g, 4.1 mmol). After 30 min at r.t., Me₂SO₄ (2.35 ml, 24.6 mmol) was added. The mixture was stirred for 48 h, and quenched with 25% NH₄OH (10 ml). The resulting mixture was stirred for 15 min, acidified with 2N HCl and extracted with Et₂O (2x50 ml). The combined extracts were washed with brine (2x50 ml), dried (MgSO₄) and evaporated. The residue was triturated with MeOH to give pure **4**. Yield 3.14 g (95%); mp 188-190°C. An analytical sample was obtained by flash chromatography (eluent CH₂Cl₂). Anal. calcd for C₃₄H₅₂O₆: C, 81.37; H 6.58. Found: C, 81.60; H, 6.81. MS (FAB): *m/z* = 797.5 [(M+H)⁺, 797.0]. ¹H NMR (300 MHz, CDCl₃): δ = 7.4-7.3 (m, 5 H, ArH), 7.1-6.8 (m, 18 H, ArH), 4.75 (s, 2 H, OCH₂Ar), 3.99 (s, 4 H, ArCH₂Ar), 3.96 (s, 4 H, ArCH₂Ar), 3.93 (s, 4 H, ArCH₂Ar), 3.22 (s, 6 H, OCH₃), 3.12 (s, 3 H, OCH₃), 2.97 (s, 6 H, OCH₃); ¹³C NMR (75 MHz, CDCl₃): δ = 156.5, 156.4, 156.1, 154.4, 137.7, 134.8, 134.6, 134.5, 134.44, 134.41, 134.3 (s, Ar), 129.7, 129.5, 129.2, 128.7, 128.6, 128.3, 128.2, 127.8, 127.7, 123.7, 123.4, 123.3 (d, ArH), 74.8 (t, OCH₂Ar), 60.2, 60.0 (q, OCH₃), 30.4, 30.3, 30.2 (t, ArCH₂Ar).

38,39,40,41,42-Pentamethoxycalix[6]arene-37-ol (5)

To a solution of calix[6]arene **4** (3.14 g, 3.9 mmol) in EtOAc (300 ml) was added Pd/C 10% (520 mg) and the mixture was stirred under H₂ at r.t. for 18 h. The mixture was filtered through Celite and this was washed with CH₂Cl₂, filtrates was evaporated to dryness. The residue was triturated with MeOH to afford pure **5**. Yield 2.25 g (81%); mp 275-276°C. Anal. calcd for C₄₇H₄₆O₆ 1/3CH₂Cl₂: C, 77.33; H, 6.40. Found: C, 77.36; H, 6.57. HRMS (FAB): *m/z* = 706.33061 (M⁺, 706.32944). ¹H NMR (300 MHz, CDCl₃): δ = 7.34 (s, 1 H, OH), 7.08 (dd, *J* = 2.0, 7.3 Hz, 2 H, ArH), 7.0-6.8 (m, 15 H, ArH), 6.73 (t, *J* = 7.4 Hz, 1 H, ArH), 3.97 (s, 8 H, ArCH₂Ar), 3.83 (s, 4 H, ArCH₂Ar), 3.55 (s, 3 H, OCH₃), 3.32 (s, 6 H, OCH₃), 3.22 (s, 6 H, OCH₃); ¹³C NMR (75 MHz, CDCl₃): δ = 156.6, 156.3, 155.0, 153.8, 134.1, 133.95, 133.93, 133.4, (s, Ar), 129.6, 129.3, 128.7, 128.65, 128.58, 128.54, 124.1, 123.5 (d, ArH), 60.8, 60.4, 60.2 (q, OCH₃), 31.2, 30.9, 30.0 (t, ArCH₂Ar).

General Procedure for Nitration of Calix[6]arenes 5, 6, 10, 13 and 15

To a vigorously stirred solution of calix[6]arene (0.50 mmol) in dry CH_2Cl_2 (10 ml) the nitrating mixture (Table 1) was added under argon at room temperature. The reaction mixture was stirred for 50-120 min, quenched with H_2O (10 ml) and extracted with CH_2Cl_2 (2x25 ml). The organic layer was washed with brine (3x25 ml), dried (Na_2SO_4) and evaporated to dryness.

5,17,29-Tri-tert-butyl-38,40,42-trimethoxy-11,23,35-trinitrocalix[6]arene-37,39,41-triol (7). Purified by column chromatography (AcOEt/hexane, 1:4) and crystallized with Et_2O /hexane. Yield 64%; mp 226°C. Anal. calcd for $\text{C}_{57}\text{H}_{63}\text{N}_3\text{O}_{12}$: C, 69.71; H 6.46; N 4.28. Found: C, 69.97; H, 7.14; N, 3.61. MS (FAB): $m/z = 1041.6$ [$(\text{M}+\text{C}(\text{NH}_2)_3$)]⁺, 1041.5]. ¹H NMR (200 MHz, CDCl_3): $\delta = 8.19$ (s, 3 H, OH), 8.04 (s, 6 H, ArH), 7.02 (s, 6 H, ArH), 3.97 (s, 12 H, ArCH_2Ar), 3.57 (s, 9 H, OCH_3), 1.14 [s, 27 H, $\text{C}(\text{CH}_3)_3$]; ¹³C NMR (50 MHz, CDCl_3): $\delta = 158.4, 151.7, 148.5, 140.7$ (s, Ar), 131.0, 127.5, 126.1, 125.0 (d, ArH), 61.7 (q, OCH_3), 34.3 [s, $\text{C}(\text{CH}_3)_3$], 31.2 [q, $\text{C}(\text{CH}_3)_3$], 30.8 (t, ArCH_2Ar).

5,11,23,29-Tetra-tert-butyl-38,39,41,42-tetramethoxy-17,35-dinitrocalix[6]arene-37,40-diol (11). Pure compound 11 was obtained by trituration with CH_3CN . Yield 61%; mp >300°C (Lit.¹⁴ >300°C).

11,17,29,35-Tetra-tert-butyl-37,38,40,41-tetrakis[2-(2-methoxyethoxy)ethoxy]-5,23-dinitrocalix[6]arene-39,42-diol (14). The crude product was purified by preparative plate chromatography (silica gel, hexane/THF, 1.4:1). Yield 66%; mp 190-192°C (EtOH). Anal. calcd for $\text{C}_{78}\text{H}_{106}\text{N}_2\text{O}_{18}$: C, 68.91; H, 7.85; N, 2.06. Found: C, 68.83; H, 7.94; N, 2.13. MS (CI): $m/z = 1359.9$ [$(\text{M}+\text{H})^+$], 1359.8]. ¹H NMR (400 MHz, CDCl_3): $\delta = 8.80$ (br s, 2 H, OH), 7.90 (br s, 4 H, ArH), 7.1-6.9 (br s, 8 H, ArH), 4.20-3.35 (br s, 44 H, OCH_2 , ArCH_2Ar), 3.28 (s, 12 H, OCH_3), 1.07 [s, 36 H, $\text{C}(\text{CH}_3)_3$]; ¹³C NMR (25 MHz, CDCl_3): $\delta = 159.0, 152.2, 147.1, 140.3, 133.3, 131.5$ (s, Ar), 128.4, 126.8, 126.1, 124.2 (d, ArH), 72.8, 71.8, 70.3, 69.7 (t, OCH_2), 58.8 (q, OCH_3), 34.0 [s, $\text{C}(\text{CH}_3)_3$], 31.2 [q, $\text{C}(\text{CH}_3)_3$], 29.8 (t, ArCH_2Ar).

5,11,17,23,29-Penta-tert-butyl-38,39,40,41,42-pentamethoxy-35-nitrocalix[6]arene-37-ol (16). The residue was triturated with hexane (45 ml) and filtered; yield 80%; mp 201-202°C (Lit.¹⁴ 201-202°C).

38,39,40,41,42-Pentamethoxy-35-nitrocalix[6]arene-37-ol (19). The residue was purified by column chromatography (AcOEt/ hexane 1:5) and then crystallized with CHCl_3 /hexane. Yield 28%; mp 258-260°C. Anal. calcd for $\text{C}_{47}\text{H}_{45}\text{NO}_8\text{H}_2\text{O}$: C, 73.32; H, 6.15; N, 1.82. Found: C, 73.53; H, 6.06; N, 1.86. HRMS (FAB): $m/z = 751.31097$ (M^+ , 751.310495). ¹H NMR (300 MHz, CDCl_3): $\delta = 8.69$ (s, 1 H, OH), 7.87 (s, 2 H, ArH), 7.1-6.8 (m, 15 H, ArH), 3.98 (s, 4 H, ArCH_2Ar), 3.96 (s, 4 H, ArCH_2Ar), 3.84 (s, 4 H, ArCH_2Ar), 3.58 (s, 3 H, OCH_3), 3.29 (s, 6 H, OCH_3), 3.27 (s, 6 H, OCH_3); ¹³C NMR (75 MHz, CDCl_3): $\delta = 158.4, 156.7, 156.5, 154.8, 140.3, 134.7, 134.1, 134.0, 133.9, 131.6$ (s, Ar), 129.7, 129.6, 129.2, 128.8, 128.7 (d, ArH), 127.9 (s, Ar), 124.7, 124.5, 123.6, 123.3 (d, ArH), 61.1, 60.5, 60.2 (q, OCH_3), 31.4, 31.1, 30.0 (t, ArCH_2Ar).

5,17,29-Tri-tert-butyl-38,40,42-trimethoxy-37,39,41-tris[(methoxycarbonyl)methoxy]-11,23,35-trinitrocalix[6]arene (8)

To a solution of 7 (200 mg, 0.2 mmol) in dry DMF (30 ml), Cs_2CO_3 (400 mg, 1.23 mmol) and methyl bromoacetate (120 μl , 1.14 mmol) were added, whereupon the mixture was stirred at 70°C for 18 h. After cooling the mixture was extracted with Et_2O (2x50 ml) and the organic layer was washed with HCl 5% (2x25 ml), brine (3x25 ml), dried (MgSO_4) and the solvent was evaporated. The residue was purified by chromatography (CH_2Cl_2) and triturated with MeOH to afford 8. Yield 72%; mp 158-160°C. Anal. calcd for $\text{C}_{66}\text{H}_{75}\text{N}_3\text{O}_{18}$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.54; H, 6.68; N, 2.73. MS (FAB): $m/z = 1198.7$

[(M+H)⁺, 1198.5]. ¹H NMR (200 MHz, CDCl₃): δ = 7.69 (s, 6 H, ArH), 7.19 (s, 6 H, ArH), 4.32 (s, 6 H, OCH₂CO₂Me), 4.00 (bs, 12 H, ArCH₂Ar), 3.69 (s, 9 H, CH₃OCO), 3.02 (s, 9 H, OCH₃), 1.29 [s, 27 H, C(CH₃)₃]; ¹³C NMR (50 MHz, CDCl₃): δ = 168.5(s, CO), 158.9, 154.3, 147.2, 144.1, 135.8, 133.1 (s, Ar), 127.5, 123.4 (t, ArH), 69.5 (t, OCH₂CO₂CH₃), 60.2 (q, OCH₃), 52.1 (q, OCH₂CO₂CH₃), 34.3 [s, C(CH₃)₃], 31.4 [q, C(CH₃)₃], 31.3 (t, ArCH₂Ar).

37,39,41-Triacetoxy-5,17,29-Tri-tert-butyl-38,40,42-trimethoxy-11,23,35-trinitrocalix[6]arene (9)

Method A: To NaH (60% mineral oil, 40 mg, 1.0 mmol) was added a solution of calixarene **7** (200 mg, 0.2 mmol) in THF (10 ml). After 30 min an excess of acetyl chloride (200 μl) was dropped and the mixture stirred overnight at r.t. The solvent was eliminated and the residue was taken off with CH₂Cl₂ (75 ml), washed with 10% HCl (2x25 ml), brine (2x25 ml), dried (Na₂SO₄) and the solvent eliminated. The residue was purified by column chromatography (CH₂Cl₂) and crystallized (MeOH) to give **9**. Yield 70 mg (31%);

Method B: A solution of calixarene **7** (240 mg, 0.24 mmol), Ac₂O (10 μl) and H₂SO₄ (2 drops) was heated at 80°C under argon for 18 h. The mixture was poured into cold MeOH and the solvent was evaporated. The residue was dissolved in Et₂O (100 ml) and washed with saturated solution of Na₂CO₃, brine, dried (MgSO₄) and the solvent was evaporated. The residue was dissolved in THF-hexane (1:1) and filtered through silica gel to afford **9**. Yield 140 mg (63%); mp 168-172°C (dec.). Anal. calcd for C₆₃H₆₉N₃O₁₅: C, 68.27; H, 6.27; N, 3.79. Found: C, 68.73; H, 6.62; N, 3.43. MS (FAB): *m/z* = 1240.4 [(M+Cs)⁺, 1240.4]. ¹H NMR (200 MHz, CDCl₃): δ = 7.92 (s, 6 H, ArH), 6.90 (s, 6 H, ArH), 3.85 (br s, 12 H, ArCH₂Ar), 3.43 (s, 9 H, OCH₃), 1.60 (s, 9 H, OCOCH₃), 1.15 [s, 27 H, C(CH₃)₃]; ¹³C NMR (75 MHz, CDCl₃): δ = 167.8 (s, OCOCH₃), 153.6, 152.2, 147.2, 145.2, 135.5, 130.8 (s, Ar), 126.3, 123.8 (d, ArH), 60.2 (q, OCH₃), 34.2 [s, C(CH₃)₃], 31.3 (t, ArCH₂Ar), 31.2 [q, C(CH₃)₃], 19.9 (q, OCOCH₃).

37,40-Diacetoxy-5,11,23,29-tetra-tert-butyl-38,39,41,42-tetramethoxy-17,35-dinitrocalix[6]arene (12)

To a stirred slurry of NaH (60% oil dispersion, 865 mg, 19.8 mmol) in THF (50 ml) under argon was added a solution of calix[6]arene **11** (2.0 g, 1.98 mmol) in THF (50 ml), at room temperature. After 15 min, an excess of acetyl chloride (2 ml) was slowly added. The mixture was stirred at r.t. for 24 h, the solvent was evaporated, the residue was acidified with 1N HCl and extracted with CH₂Cl₂. The combined extracts were washed with H₂O, dried (Na₂SO₄) and evaporated. The residue was triturated with EtOH to give pure **12**. Yield 100%; mp > 300°C. Anal. calcd for C₆₆H₇₈N₂O₁₂·H₂O: C, 71.46; H, 7.27; N, 2.52. Found: C, 71.51; H, 7.41; N, 2.40. MS (FAB): *m/z* = 1113.9 [(M+Na)⁺, 1113.5]. ¹H NMR (200 MHz, CDCl₃): δ = 8.02 (s, 4 H, ArH), 6.91 (d, *J* = 2.4 Hz, 4 H, ArH), 6.86 (d, *J* = 2.4 Hz, 4 H, ArH), 3.89 and 3.82 (br s, 12 H, ArCH₂Ar), 3.26 (s, 12 H, OCH₃), 1.79 (br s, 6 H, COCH₃), 1.15 [s, 36 H, C(CH₃)₃]; ¹³C NMR (75 MHz, CDCl₃): δ = 153.6, 146.4, 145.1, 136.3, 133.0, 130.6 (s, Ar), 127.0, 125.3, 124.1 (d, ArH), 60.4 (q, OCH₃), 34.1 [s, C(CH₃)₃], 31.7 (t, ArCH₂Ar), 31.2 [q, C(CH₃)₃], 30.3 (t, ArCH₂Ar), 20.0 (q, ArCH₃).

37-Acetoxy-5,11,17,23,29-penta-tert-butyl-38,39,40,41,42-pentamethoxy-35-nitrocalix[6]arene (17)

A solution of 5,11,17,23,29-penta-tert-butyl-38,39,40,41,42-pentamethoxy-35-nitrocalix[6]aren-37-ol (**16**) (1.0 g, 1 mmol) in acetic anhydride (25 ml) and a catalytic amount (4 drops) of conc. H₂SO₄ was stirred at room temperature for 24 h. The crude reaction was poured into methanol and the solvent was evaporated, the acetic acid was neutralized with a solution of saturated NaHCO₃ (200 ml) and then was extracted with CHCl₃

(3x75 ml). The organic layer was washed with brine, dried (Na₂SO₄) and the solvent evaporated. The residue was triturated with cold MeOH and filtered to give **17**. Yield 83%; mp 185-190°C. Anal. calcd for C₆₉H₈₇NO₉ MeOH: C, 75.98; H, 8.29; N, 1.27. Found: C, 75.80; H, 8.28; N, 1.20. MS (FAB): *m/z* = 1073.4 (M⁺, 1073.6). ¹H NMR (300 MHz, CDCl₃): δ = 7.87 (s, 2 H, ArH), 7.15 (d, *J* = 2.4 Hz, 2 H, ArH), 7.10 (s, 2 H, ArH), 6.96 (d, *J* = 2.4 Hz, 2 H, ArH), 6.93 (d, *J* = 2.3 Hz, 2 H, ArH), 6.77 (d, *J* = 2.3 Hz, 2 H, ArH), 3.95 (br s, 12 H, ArCH₂Ar), 3.34 (s, 6 H, OCH₃), 2.97 (s, 3 H, OCH₃), 2.94 (s, 6H, OCH₃), 1.71 (s, 3H, COCH₃), 1.23 [s, 18H, C(CH₃)₃], 1.22 [s, 9H, C(CH₃)₃], 1.05 [s, 18 H, C(CH₃)₃]; ¹³C NMR (75 MHz, CDCl₃): δ = 167.7 (s, CO), 154.2, 153.8, 153.6, 152.2, 146.4, 145.8, 145.6, 145.2, 136.2, 133.5, 133.4, 133.0, 130.6 (s, Ar), 127.8, 126.5, 125.7, 125.4, 125.1, 123.4 (d, ArH), 60.2, 60.1, 60.0 (q, OCH₃), 34.2, 34.1, 34.0 [s, C(CH₃)₃], 31.4, 31.3, 31.0 [q, C(CH₃)₃], 31.1, 31.0, 29.4, (t, ArCH₂Ar), 19.9 (q, COCH₃).

5,11,17,23,29-Penta-tert-butyl-37,38,39,40,41,42-hexamethoxy-35-nitrocalix[6]arene (18)

To a stirred slurry of NaH (60% oil dispersion, 187 mg, 4.7 mmol) in THF (80 ml) under argon was added a solution of calix[6]arene **16** (800 mg, 0.78 mmol). After 30 min at r.t., Me₂SO₄ (0.5 ml, 5.5 mmol) was added. The mixture was stirred at r.t. for 41 h, and quenched with 25% aq NH₄OH (3 ml). The resulting mixture was stirred for 15 min, acidified with 2N HCl and the solvent was evaporated. The residue was extracted with CH₂Cl₂ (2x50 ml). The combined extracts were washed with brine (2x20 ml), dried (Na₂SO₄) and evaporated. The residue was triturated with MeOH to give pure **18**: yield 72%; mp 252-254°C. Anal. calcd for C₆₈H₈₇NO₈ MeOH: C, 76.84; H, 8.50; N, 1.30. Found: C, 76.99; H, 8.58; N, 1.39. MS (FAB): *m/z* = 1045.6 (M⁺, 1045.6). ¹H NMR (300 MHz, CDCl₃): δ = 7.73 (s, 2 H, ArH), 7.14 (d, *J* = 2.5 Hz, 2 H, ArH), 7.07 (d, *J* = 2.5 Hz, 2 H, ArH), 7.06 (s, 2 H, ArH), 6.89 (d, *J* = 2.5 Hz, 2 H, ArH), 6.77 (d, *J* = 2.5 Hz, 2 H, ArH), 3.99 (br s, 4 H, ArCH₂Ar), 3.95 (br s, 8 H, ArCH₂Ar), 3.44 (s, 3 H, OCH₃), 3.32 (s, 6 H, OCH₃), 2.81 (s, 9 H, OCH₃), 1.25 [s, 18 H, C(CH₃)₃], 1.19 [s, 9 H, C(CH₃)₃], 0.99 [s, 18 H, C(CH₃)₃]; ¹³C NMR (75 MHz, CDCl₃): δ = 161.2, 154.0, 153.4, 146.4, 145.8, 145.6, 143.5, 136.5, 133.6, 133.5, 133.48, 133.2, 131.7 (s, Ar), 127.5, 126.4, 126.1, 125.2, 125.1, 123.4 (d, ArH), 60.4, 60.0, 59.9 (q, OCH₃), 34.2, 34.1, 34.0 [s, C(CH₃)₃], 31.4, 31.1 [q, C(CH₃)₃], 30.8, 30.3, 30.1 (t, ArCH₂Ar).

37,39,41-Triacetoxy-11,23,35-triamino-5,17,29-tri-tert-butyl-38,40,42-trimethoxycalix[6]arene (20)

Method A: A suspension of SnCl₂·2H₂O (153 mg, 0.68 mmol), calix[6]arene **9** (50 mg, 0.045 mmol) in dry EtOH (3 ml) was heated at reflux for 20 h. The solvent was evaporated and the residue was treated with H₂O (15 ml) and filtered. The filtrate was treated with aqueous solution of sodium tartrate (10 ml) and filtered. The solid was dissolved in CH₂Cl₂, dried (Na₂SO₄) and the solvent eliminated to give **20**. Yield 62%.

Method B: A suspension of calix[6]arene **9** (50 mg, 0.045 mmol) and PtO₂ in THF (12 ml) was bubbled with an hydrogen stream at r.t. for 15 min. The mixture was stirred under H₂ in the dark for 20 h. Then it was filtered and the filtrate was evaporated to dryness in the dark. The residue was dried under vacuum to afford pure compound **20** that was stored under argon. Yield 91%; mp 187-189°C. MS (FAB): *m/z* = 1018.6 [(M+H)⁺, 1018.7]. ¹H NMR (200 MHz, CDCl₃): δ = 7.00 (br s, 12 H, ArH), 4.20-3.20 (br s, 12 H, ArCH₂Ar), 3.49 (s, 9 H, OCH₃), 2.21 (br s, 9 H, OCOCH₃), 1.20 [s, 27 H, C(CH₃)₃]; ¹³C NMR (50 MHz, CDCl₃): δ = 169.8 (s, OCOCH₃), 154.0, 146.5, 143.9, 133.8, 132.2, 126.7 (s, Ar), 126.0, 115.3 (d, ArH), 60.3 (q, OCH₃), 34.1 [s, C(CH₃)₃], 31.4 [s, C(CH₃)₃], 29.7 (t, ArCH₂Ar), 20.3 (q, OCOCH₃).

37,40-Diacetoxy-17,35-diamino-5,11,23,29-tetra-tert-butyl-38,39,41,42-tetramethoxycalix[6]arene (21)

A suspension of calix[6]arene **12** (1.2 g, 1.0 mmol) and PtO₂ (0.48 g, 2 mmol) in THF (90 ml) was bubbled with an hydrogen stream at r.t. for 30 min. The mixture was heated at reflux under H₂ for 2 h. After cooling the mixture was filtered through a short column of Celite and the filtrate evaporated to dryness. The residue was triturated with hexane to afford pure **21**. Yield 80%; mp 243°C. Anal. calcd for C₆₆H₈₂N₂O₈·2H₂O: C, 74.27; H, 8.12; N, 2.62. Found: C, 74.03; H, 8.06; N, 2.41. MS (FAB): *m/z* = 1031.8 [(M+H)⁺, 1031.6]. ¹H NMR (200 MHz, CDCl₃): δ = 6.75 (br s, 4 H, ArH), 6.6-6.5 (m, 8 H, ArH), 5.57 (br s, 4 H, NH₂), 3.66 (br s, 4 H, ArCH₂Ar), 3.29 (br s, 8 H, ArCH₂Ar), 3.17 (br s, 12 H, OCH₃), 1.87 (br s, 6 H, COCH₃), 0.89 [s, 36 H, C(CH₃)₃]; ¹³C NMR (50 MHz, CDCl₃): δ = 169.8 (s, CO), 154.6, 146.4, 145.8, 138.1, 133.7, 131.9, 126.7, 125.7, 114.5 (Ar), 60.4 (q, OCH₃), 34.1 [s, C(CH₃)₃], 31.6 (t, ArCH₂Ar), 31.3 [q, C(CH₃)₃], 30.7 (t, ArCH₂Ar), 20.5 (q, COCH₃).

37,40-Diacetoxy-17-amino-5,11,23,29-tetra-tert-butyl-38,39,41,42-tetramethoxy-35-nitrocalix[6]arene (22)

A suspension of calix[6]arene **12** (50 mg, 0.045 mmol) and PtO₂ (20 mg, 0.09 mmol) in THF (4 ml) was bubbled with an hydrogen stream at r.t. for 5 min. The mixture was heated over 40°C for 40 min. After cooling the mixture was filtered through a short column of Celite and the filtrate was evaporated to dryness. The residue was purified by chromatography (CH₂Cl₂:MeOH 20:1) to afford pure **22**. Yield 62%; mp 298°C (dec.). Anal. calcd for C₆₆H₈₀N₂O₁₀·H₂O: C, 73.44; H, 7.65; N, 2.59. Found: C, 73.24; H, 7.58; N, 2.79. MS (FAB): *m/z* = 1062.0 [(M+H)⁺, 1061.6]. ¹H NMR (200 MHz, CDCl₃): δ = 7.99 (s, 2 H, ArH), 6.97 (d, *J* = 2.5 Hz, 2 H, ArH), 6.87 (br s, 2 H, ArH), 6.81 (br s, 4 H, ArH), 6.35 (s, 2 H, ArH), 3.87 and 3.82 (br s, 12 H, ArCH₂Ar), 3.22 (s, 12 H, OCH₃), 1.96 (s, 3 H, COCH₃), 1.58 (br s, 3 H, COCH₃) 1.15 [s, 18 H, C(CH₃)₃], 1.11 [s, 18 H, C(CH₃)₃]; ¹³C NMR (50 MHz, CDCl₃): δ = 169.9, 168.0 (s, CO), 153.8, 146.4, 145.9, 145.1, 143.7, 136.3, 134.6, 133.3, 132.9, 132.3, 130.5 (s, Ar), 127.3, 125.9, 125.5, 125.2, 124.1, 115.6 (d, ArH), 60.4, 60.3 (q, OCH₃), 34.7 [s, C(CH₃)₃], 31.9, 31.5 (t, ArCH₂Ar), 31.3 [q, C(CH₃)₃], 30.5 (t, ArCH₂Ar), 20.4, 19.9 (q, COCH₃).

37-Acetoxy-35-amino-5,11,17,23,29-penta-tert-butyl-38,39,40,41,42-pentamethoxycalix[6]arene (23)

A solution of calix[6]arene **17** (864 mg, 0.8 mmol) in THF (150 ml) 10% Pd(C) (1.2 g) was added and bubbled with a hydrogen stream at r.t. for 30 min. The mixture was stirred under H₂ at r.t. for 24 h. The mixture was filtered through Celite and the filtrate evaporated to dryness. The residue was triturated with hexane to afford pure **23**. Yield 76%; mp 197-201°C. Anal. calcd for C₆₉H₈₉NO₇: C, 79.34; H, 8.59; N, 1.34. Found: C, 79.04; H, 8.67; N, 1.27. MS (FAB): *m/z* = 1044.5 (M⁺, 1043.6). ¹H NMR (300 MHz, CDCl₃): δ = 7.09 (d, *J* = 2.5 Hz, 2 H, ArH), 7.08 (s, 2 H, ArH), 6.97 (t, *J* = 2.6 Hz, 4 H, ArH), 6.83 (d, *J* = 2.5 Hz, 2 H, ArH), 6.14 (s, 2 H, ArH), 3.95 (br s, 12 H, ArCH₂Ar), 3.30 (s, 6 H, OCH₃), 2.99 (s, 3 H, OCH₃), 2.88 (s, 6 H, OCH₃), 1.93 (s, 3 H, COCH₃), 1.23 [s, 18 H, C(CH₃)₃], 1.17 [s, 9 H, C(CH₃)₃], 1.09 [s, 18 H, C(CH₃)₃]; ¹³C NMR (75 MHz, CDCl₃): δ = 169.5 (s, CO), 154.1, 154.0, 153.8, 145.9, 145.7, 143.7, 139.3, 134.3, 133.6, 133.4, 133.3, 132.2 (s, Ar), 126.9, 126.4, 126.1, 125.44, 125.4, 114.6 (d, ArH), 60.1, 60.0 (q, OCH₃), 34.1, 34.07 [s, C(CH₃)₃], 31.42, 31.39, 31.25 [q, C(CH₃)₃], 31.2, 30.8, 30.5 (t, ArCH₂Ar), 20.3 (q, COCH₃).

General procedure for the synthesis of amides 24-26 from calix[6]arene 21

To a solution of calix[6]arene (**21**) (150 mg, 0.15 mmol) in THF (12ml) the corresponding anhydride (1.5 mmol) was added. After refluxing the mixture for 20 h, the solvent was removed under reduced pressure

and the residue was quenched with HCl and the resulting solid filtered and washed with H₂O.

39,42-Diacetoxy-11,17,29,35-tetra-tert-butyl-37,38,40,41-tetramethoxycalix[6]arene-5,23-disuccinamic diacid (24). Yield 77%; mp 198-200°C. Anal. calcd for C₇₄H₉₀N₂O₁₄·3 H₂O: C, 69.14; H, 7.53; N, 2.18. Found: C, 69.38; H, 7.30; N, 2.06. MS (FAB): *m/z* = 1232.2 [(M+H)⁺, 1231.7]. ¹H NMR (200 MHz, CDCl₃): δ = 7.39 (s, 2 H, NH), 7.03 (br s, 4 H, ArH), 6.94 (br s, 4 H, ArH), 6.86 (br s, 4 H, ArH), 4.83 (s, 4 H, ArCH₂Ar), 3.65 (br s, 8 H, ArCH₂Ar), 3.16 (s, 12 H, OCH₃), 2.7-2.6 (m, 4 H, CH₂CO), 2.65-2.5 (m, 4 H, CH₂CO), 1.68 (br s, 6 H, COCH₃), 1.11 [s, 36 H, C(CH₃)₃]; ¹³C NMR (50 MHz, CDCl₃): δ = 174.1, 170.3, 169.7 (s, CO), 152.9, 145.0, 135.4, 133.7, 131.8, 131.2 (s, Ar), 125.6, 124.4, 120.0 (d, ArH), 59.7 (q, OCH₃), 33.4 [s, C(CH₃)₃], 31.3, 31.0 (t, ArCH₂Ar), 30.6 [q, C(CH₃)₃], 29.4, 28.8 (t, COCH₂CH₂CO), 19.2 (q, COCH₃).

39,42-Diacetoxy-11,17,29,35-tetra-tert-butyl-37,38,40,41-tetramethoxycalix[6]arene-5,23 diglutaramic diacid (25). Yield 88%; mp 218°C. Anal. calcd for C₇₆H₉₄N₂O₁₄·2 H₂O: C, 70.45; H, 7.62; N, 2.16. Found: C, 70.13; H, 7.84; N, 1.95. MS (FAB): *m/z* = 1259.1 (M⁺, 1258.7). ¹H NMR (200 MHz, CDCl₃): δ = 7.18 (br s, 4 H, ArH), 6.96 (br s, 4 H, ArH), 3.88 (br s, 4 H, ArCH₂Ar), 3.72 (br s, 10 H, ArCH₂Ar and NH), 3.20 (s, 12 H, OCH₃), 2.45 (t, *J* = 2.8 Hz, 8 H, CH₂CO), 1.76 (br s, 6 H, COCH₃), 2.1-2.0 (m, 4 H, COCH₂CH₂CH₂CO), 1.17, [s, 36 H, C(CH₃)₃]; ¹³C NMR (50 MHz, CDCl₃): δ = 178.5, 170.8, 169.3 (s, CO), 146.0, 135.0, 134.7, 132.8, 131.7 (s, Ar), 126.4, 125.4, 125.2, 121.0 (d, ArH), 60.3 (q, OCH₃), 34.1 [s, C(CH₃)₃], 34.1 (t, COCH₂), 32.9 (t, ArCH₂Ar), 31.3 (t, ArCH₂Ar), 20.5 (t, COCH₂CH₂CH₂CO), 19.6 (q, COCH₃).

39,42-Diacetoxy-11,17,29,35-tetra-tert-butyl-37,38,40,41-tetramethoxycalix[6]arene-5,23 diglicolamic diacid (26). Yield 88%; mp 172°C. Anal. calcd for C₇₄H₉₀N₂O₁₆·3 H₂O: C, 67.44; H, 7.34; N, 2.12. Found: C, 67.48; H, 7.07; N, 1.97. MS (FAB): *m/z* = 1263.8 [(M+H)⁺, 1263.6]. ¹H NMR (200 MHz, CDCl₃): δ = 8.77 (s, 2 H, NH), 7.29 (s, 4 H, ArH), 6.86 (s, 8 H, ArH), 4.17 (s, 4 H, COCH₂O), 4.13 (s, 4 H, COCH₂O), 3.82 (s, 4 H, ArCH₂Ar), 3.69 (br s, 8 H, ArCH₂Ar), 3.15 (s, 12 H, OCH₃), 1.59 (br s, 6 H, COCH₃), 1.10 [s, 36 H, C(CH₃)₃]; ¹³C NMR (50 MHz, CDCl₃): δ = 172.4, 169.6, 168.0 (s, CO), 153.5, 146.3, 135.0, 134.2, 131.7 (s, Ar), 126.5 (d, ArH), 125.3 (s, Ar), 121.1 (d, ArH), 71.7 (t, COCH₂O), 68.9 (t, COCH₂O), 60.4 (q, OCH₃), 34.1 [s, C(CH₃)₃], 31.9 (t, ArCH₂Ar), 31.3 [q, C(CH₃)₃], 19.9 (q, COCH₃).

5,17,29-Tri-tert-butyl-37,39,41-tris(pentafluorobenzyloxy)-38,40,42-trimethoxycalix[6]arene (29)

To a suspension of **27** (500 mg, 0.59 mmol) and K₂CO₃ (330 mg, 2.4 mmol) in dry acetonitrile (50 ml) was added α-bromo-pentafluorotoluene (0.36 ml, 2.4 mmol). The mixture was refluxed for 18 h. The solvent was evaporated, and the residue was taken up in CH₂Cl₂ (100 ml), washed with 1 N HCl (2x25 ml), brine (1x25 ml) and dried over MgSO₄. The crude product was triturated with methanol and pure compound **29** filtered. Yield 740 mg (89%); mp 280°C. Anal. calcd for C₇₈H₆₉O₆F₁₅·3H₂O: C, 65.00; H, 5.24. Found: C, 65.03; H, 5.25. Karl Fischer: H₂O, 3.68. C₇₈H₆₉O₆F₁₅·3H₂O requires H₂O, 3.75. MS (FAB): *m/z* = 1386.4 (M⁺, 1386.5). ¹H NMR (250 MHz, CDCl₃): δ = 7.17 (s, 6 H, ArH), 6.72, 6.56 (m, 9 H, ArH), 4.96 (s, 6 H, OCH₂), 3.97 (br s, 12 H, ArCH₂Ar) 2.50 (s, 9 H, OCH₃), 1.31 [s, 27 H, C(CH₃)₃]; ¹³C NMR (62.5 MHz, CDCl₃): δ = 154.1, 153.1, 146.1, 134.8, 133.0 (s, Ar), 127.6, 124.2, 61.1 (t, OCH₂), 59.9 (q, OCH₃), 34.2 [s, C(CH₃)₃], 31.5 [q, C(CH₃)₃], 30.2 (t, ArCH₂Ar).

5,17,29-Tri-tert-butyl-37,38,39,40,41,42-hexamethoxycalix[6]arene (31)

To a stirring solution of calixarene **27** (140 mg, 0.16 mmol) in 25 ml of dry DMF, Cs₂CO₃ (320 mg, 1.0

mmol) and MeI (0.06 ml, 1.0 mmol) were added. The reaction mixture was heated at 90°C for 16 h and then quenched with 100 ml of 1N HCl and extracted with CH₂Cl₂ (2x40 ml). The combined organic extracts were washed with water (2x60 ml) and dried (Na₂SO₄). After evaporation the product was purified by column chromatography (silica gel, hexane/THF 8:2). Yield 136 mg (93%); mp 119-121°C. Anal. calcd for C₆₀H₇₂O₆: C, 81.05; H, 8.15. Found: C, 80.95; H, 8.22. MS (CI): *m/z* = 889.3 [(M+H)⁺, 889.5]. ¹H NMR (300 MHz, CDCl₃): δ = 7.01 (s, 6H, ArH), 6.87 (s, 9H, ArH), 3.92 (s, 12H, ArCH₂Ar), 3.19 (s, 9H, OCH₃), 2.99 (s, 9H, OCH₃), 1.16 [s, 27H, C(CH₃)₃]; ¹³C NMR (75 MHz, CDCl₃): δ = 156.1, 154.2, 145.9, 134.6, 133.5 (s, Ar), 128.6, 126.2, 123.3 (d, ArH), 60.1 (q, OCH₃), 34.1 [s, C(CH₃)₃], 31.5 [q, C(CH₃)₃], 30.6 (t, ArCH₂Ar).

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

To a vigorously stirred solution of **13** (2.0 g, 1.47 mmol) in dry toluene (22 ml), AlCl₃ (3.95 g, 29.60 mmol) was added. After 4 h the mixture was quenched with 1N HCl (20 ml) and the aqueous layer extracted with Et₂O (2x15 ml). The combined organic layers were washed with H₂O (3x20 ml) and dried (MgSO₄). After evaporation of the solvent the crude product was triturated with petroleum ether to afford pure **35**. Yield 1.16 g (62%); mp 134-136°C. Anal. calcd for C₇₈H₁₀₈O₁₄: C, 73.80; H, 8.57. Found: C, 73.71; H, 8.64. MS (CI): *m/z*: 1270.1 [(M+H)⁺, 1269.8]. ¹H NMR (400 MHz, CDCl₃): δ = 7.47 (br s, 2H, OH), 6.90 (br s, 12H, ArH), 6.65 (t, *J* = 7.2Hz, 2H, ArH), 3.80 and 3.50 (br s, 44H, ArCH₂Ar, OCH₂), 3.32 (s, 12H, OCH₃), 1.03 [s, 36H, C(CH₃)₃]; ¹³C NMR (25 MHz, CDCl₃): δ = 152.8, 151.9, 146.5, 132.9, 128.3 (s, Ar), 127.5, 126.2, 125.9, 119.6 (d, ArH), 72.6, 72.0, 70.4, 70.1 (t, OCH₂), 59.0 (q, OCH₃), 34.1 [s, C(CH₃)₃], 31.3 [q, C(CH₃)₃], 30.8 (t, ArCH₂Ar).

General Procedure for Formylation of Calix[6]arenes via Cl₂CHOCH₃ and TiCl₄ (SnCl₄) in CHCl₃

To a solution of calix[6]arene (0.40 mmol) in dry CHCl₃ (25 ml) at -15°C, was added dropwise a mixture of Cl₂CHOCH₃ and Lewis acid (Table 2). After 1-3 h stirring at r.t., the reaction mixture was quenched with 1N HCl (20 ml) and aqueous layer extracted with CH₂Cl₂ (2x15 ml). The combined organic phases were washed with H₂O (3x30 ml), dried (MgSO₄) and evaporated to dryness.

5,17,29-Tri-tert-butyl-37,39,41-tris(pentafluorobenzyloxy)-11,23,35-triformyl-38,40,42-trimethoxy-calix[6]arene (30).

Purified by column chromatography (CH₂Cl₂) and crystallized from CHCl₃/MeOH. Yield 18%; mp 252-253°C. Anal. calcd for C₈₁H₆₉O₉F₁₅·CHCl₃: C, 61.51; H, 4.55. Found: C, 61.91; H, 4.44. MS (FAB): *m/z* = 1471.7 [(M+H)⁺, 1471.5]. ¹H NMR (250 MHz, CDCl₃): δ = 9.53 (s, 3 H, CHO), 7.2-7.0 (br s, 12 H, ArH), 5.01 (s, 6 H, OCH₂), 4.5-4.0, 4.0-3.5 (br s, 6 H, ArCH₂Ar) 2.60 (s, 9 H, OCH₃), 1.31 [s, 27 H, C(CH₃)₃]; ¹³C NMR (62.5 MHz, CDCl₃): δ = 191.4 (d, CHO), 154.2, 146.8, 135.6, 134.5, 132.7, 132.2, 129.3, 129.0, 127.8, 127.6 (s, Ar), 59.9 (t, OCH₂), 53.4 (q, OCH₃), 34.2 [s, C(CH₃)₃], 31.4 [q, C(CH₃)₃], 30.5 (t, ArCH₂Ar).

5,17,29-Tri-tert-butyl-37,39,41-tris(pentafluorobenzyloxy)-11-moniformyl-38,40,42-trimethoxy-calix[6]arene (33) and 5,17,29-tri-tert-butyl-37,39,41-tris(pentafluorobenzyloxy)-11,23-diformyl-38,40,42-trimethoxycalix[6]arene (34).

Purified by column chromatography (CH₂Cl₂/hexane, 1:1) and crystallized from CHCl₃/MeOH. **33**: Yield 25%; MS (FAB): *m/z* = 1415.7 (M⁺, 1415.5). ¹H NMR (250 MHz, CDCl₃): δ = 9.37 (s, 1 H, CHO), 7.3-7.0 (m, 8 H, ArH), 6.65-6.5 (m, 6 H, ArH), 5.02 (s, 2 H, OCH₂), 4.90 (s, 4 H, OCH₂),

4.7-4.0, 4.0-3.40 (br s, 6 H, ArCH₂Ar), 2.70 (s, 6 H OCH₃), 2.38 (s, 2 H, OCH₃), 1.35 [s, 27 H, C(CH₃)₃]; ¹³C NMR (62.5 MHz, CDCl₃): δ = 190.8 (d, CHO), 158.5, 154.8, 154.7, 154.6, 153.1, 146.6, 146.1, 135.8, 134.7, 134.5, 133.2, 132.9, 132.5, 131.9, 129.0, 128.1, 127.6, 127.3, 127.2, 124.4 (s, Ar), 60.8, 60.7 (t, OCH₂), 34.22, 34.21 [s, C(CH₃)₃], 31.54, 31.51 [q, C(CH₃)₃], 30.7, 30.3, 30.2 (t, ArCH₂Ar). **34**: Yield 23%; mp 262-263°C. Anal. calcd for C₈₀H₆₉O₈F₁₅·2H₂O: C, 65.23; H, 4.62. Found: C, 64.95; H, 4.97. Karl Fischer: H₂O, 2.72. C₈₀H₆₉O₈F₁₅·2H₂O requires H₂O, 2.42. MS (FAB): *m/z* = 1443.4 [(M+H)⁺, 1443.5]. ¹H NMR (250 MHz, CDCl₃): δ = 9.50 (s, 2 H, CHO), 7.3-7.0 (m, 10 H, ArH), 6.8-6.5 (m, 3 H, ArH), 5.02 (s, 4 H, OCH₂), 4.96 (s, 2 H, OCH₂), 4.6-3.5 (br s, 12 H, ArCH₂Ar), 2.81 (s, 3 H OCH₃), 2.56 (s, 6 H, OCH₃), 1.32 [s, 27 H, C(CH₃)₃]. **11,17,29,35-Tetra-tert-butyl-5,23-diformyl-37,38,40,41-tetrakis[2-(2-methoxyethoxy)ethoxy]calix[6]arene-39,42-diol (36)**. The residue was purified by column chromatography (THF/hexane, 1:1.4). Yield 94%; mp 164-166°C. Anal. calcd for C₈₀H₁₀₈O₁₆: C, 72.48; H, 8.20. Found: C, 72.38; H, 8.28. MS (CI): *m/z*: 1325.6 [(M+H)⁺, 1325.8]. ¹H NMR (400 MHz, CDCl₃): δ = 9.69 (s, 2 H, CHO), 8.57 (br s, 2 H, OH), 7.50 (br s, 4 H, ArH), 7.1-6.8 (br s, 8 H, ArH), 4.2-3.30 (br s, 44 H, ArCH₂Ar, OCH₂), 3.27 (s, 12 H, OCH₃), 1.04 [s, 36 H, C(CH₃)₃]; ¹³C NMR (25 MHz, CDCl₃): δ = 191.3 (d, CHO), 158.9, 151.7, 147.0, 133.0, 131.9 (s, Ar), 130.9 (d, ArH), 128.8, 128.2 (s, Ar), 126.6, 125.9 (d, ArH), 72.6, 71.9, 70.4, 70.0 (t, OCH₂), 59.0 (q, OCH₃), 34.1 [s, C(CH₃)₃], 31.3 [q, C(CH₃)₃], 30.0 (t, ArCH₂Ar).

General Procedure for Formylation of Calix[6]arenes via HMTA in CF₃COOH

A mixture of calixarene (0.12 mmol) in 1.5 ml of CF₃COOH was added of HMTA and was refluxed for 17-36 h (Table 3). The reaction mixture was poured into 10 ml of ice-water and extracted twice with CH₂Cl₂ (2x10 ml). The organic layer was washed with H₂O (3x10 ml), dried (MgSO₄) and evaporated to dryness.

5,17,29-Tri-tert-butyl-11,23,35-triformyl-38,40,42-trimethoxycalix[6]arene-37,39,41-triol (28). Purified by preparative TLC (THF/hexane, 1:1.4). Yield 18%; mp 151-153°C. Anal. calcd for C₆₀H₆₆O₉: C, 77.40; H, 7.14. Found: C, 77.43; H, 7.21. MS (CI): *m/z*: 931.8 [(M+H)⁺, 931.5]. ¹H NMR (100 MHz, CDCl₃): δ = 9.79 (s, 3 H, CHO), 8.02 (s, 3 H, OH), 7.62 (s, 6 H, ArH), 6.96 (s, 6 H, ArH), 3.94 (s, 12 H, ArCH₂Ar), 3.56 (s, 9 H, OCH₃), 1.08 [s, 27 H, C(CH₃)₃].

5,17,29-Tri-tert-butyl-11,23,35-triformyl-37,38,39,40,41,42-hexamethoxycalix[6]arene (32). The residue was crystallized from cold MeOH. Yield 74%; 168-170°C. Anal. calcd for C₆₃H₇₂O₉: C, 77.75; H, 7.45. Found: C, 77.67; H, 7.51. MS (CI): *m/z* = 973.3 [(M+H)⁺, 973.5]. ¹H NMR (300 MHz, CDCl₃): δ = 9.74 (s, 3 H, CHO), 7.47 (s, 6 H, ArH), 6.99 (s, 6 H, ArH), 3.95 (s, 12 H, ArCH₂Ar), 3.30 (s, 9 H, OCH₃), 3.14 (s, 9 H, OCH₃), 1.19 [s, 27 H, C(CH₃)₃]; ¹³C NMR (75 MHz, CDCl₃): δ = 191.6 (d, CHO), 161.8, 154.1, 146.5, 135.7, 132.8, 131.9 (s, Ar), 130.5, 126.3 (d, ArH), 60.3, 60.1 (q, OCH₃), 34.2 [s, C(CH₃)₃], 31.4 [q, C(CH₃)₃], 30.6 (t, ArCH₂Ar).

11,17,29,35-Tetra-tert-butyl-5,23-diformyl-37,38,40,41-tetrakis[2-(2-methoxyethoxy)ethoxy]calix[6]arene-39,42-diol (36). The product was purified by column chromatography (THF/hexane, 1:1.4) in 44% yield, and showed the same physical and spectroscopic data as previously reported.

5,17,29-Tri-tert-butyl-37,39,41-tris(pentafluorobenzyloxy)-11,23,35-tris(hydroxymethyl)-38,40,42-trimethoxycalix[6]arene (37)

To a solution of compound **30** (41 mg, 28 μmol) in dry THF (7 ml) and MeOH (1 ml) was added NaBH₄

(16 mg, 0.42 mmol) and the mixture was refluxed for 2.5 h. After cooling, the reaction was quenched with a few drops of glacial acetic acid. CH_2Cl_2 was added and the organic layer was washed with 1 N NaOH (2x25 ml), brine (1x25 ml) and dried over MgSO_4 . Yield 41 mg (100%); mp > 300°C (dec.). Anal. calcd for $\text{C}_{81}\text{H}_{75}\text{F}_{15}\text{O}_9$, CH_2Cl_2 : C, 63.04; H, 4.97. Found: C, 63.11; H, 4.71. MS (FAB): $m/z = 1295.0$ [$(\text{M}-\text{CH}_2\text{C}_6\text{F}_5)^+$, 1295.5]. ^1H NMR (250 MHz, CDCl_3): $\delta = 7.14$ (s, 6H, ArH), 6.5-6.2 (br s, 6H, ArH), 4.96 (s, 6H, OCH_2), 4.5-4.2 (m, 9H, ArCH_2Ar , OH), 4.01 (s, 6H, CH_2OH), 3.5 (d, 6H, $J = 14$ Hz, ArCH_2Ar), 3.0-2.8 (s, 9H, OCH_3), 1.23 [s, 27H, $\text{C}(\text{CH}_3)_3$]; ^{13}C NMR (62.5 MHz, CDCl_3): $\delta = 154.3$, 154.1, 152.3, 147.1, 146.9, 137.5, 134.5, 132.7, 128.0, 127.9, 126.1, 126.0 (s, Ar), 77.2 (t, CH_2OH), 64.6 (t, OCH_2), 60.1 (q, OCH_3), 34.2 [s, $\text{C}(\text{CH}_3)_3$], 31.5 [q, $\text{C}(\text{CH}_3)_3$], 30.8 (t, ArCH_2Ar).

5,17,29-Tri-tert-butyl-11,23,35-tris(1,1-dimethoxymethyl)-37,38,39,40,41,42-hexamethoxycalix[6]arene (38)

To a sample of calixarene **32** (0.10 g, 0.103 mmol), dissolved in 5 ml of dry methanol was added a drop of CF_3COOH and heated at reflux for 2 h. Upon cooling product **38** precipitated as white crystals which were filtered. Yield 92 mg (81%); mp 199-201°C. Anal. calcd for $\text{C}_{69}\text{H}_{90}\text{O}_{12}$: C, 74.57; H, 8.15. Found: C, 74.46; H, 8.21. MS (CI): $m/z = 1034.8$ [$(\text{M}-\text{CH}(\text{OCH}_3)_2)^+$, 1035.6]. ^1H NMR (300 MHz, CDCl_3): $\delta = 7.17$ (s, 6H, ArH), 6.87 (s, 6H, ArH), 5.30 [s, 3H, $\text{CH}(\text{OCH}_3)_2$], 3.94 (s, 12H, ArCH_2Ar), 3.34 (s, 9H, OCH_3), 3.26 [s, 18H, $\text{CH}(\text{OCH}_3)_2$], 2.82 (s, 9H, OCH_3), 1.04 [s, 27H, $\text{C}(\text{CH}_3)_3$]; ^{13}C NMR (75 MHz, CDCl_3): $\delta = 156.5$, 153.4, 145.6, 134.1, 133.3, 132.5 (s, Ar), 127.9, 125.0 (d, ArH), 102.8 [d, $\text{CH}(\text{OCH}_3)_2$], 59.9 (q, OCH_3), 52.3 [q, $\text{CH}(\text{OCH}_3)_2$], 33.9 [s, $\text{C}(\text{CH}_3)_3$], 31.1 [q, $\text{C}(\text{CH}_3)_3$], 30.3 (t, ArCH_2Ar).

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

To a solution of **36** (115 mg, 0.09 mmol) in a mixture of acetone (10 ml) and CHCl_3 (10 ml) at 0°C were added sulfamic acid (36 mg, 0.37 mmol) and NaClO_2 (28 mg, 0.31 mmol) dissolved in a small quantity of H_2O . After stirring for 16 h the solvent was evaporated under reduced pressure and the residue was taken up in CH_2Cl_2 (50 ml). The organic layer was washed with 1N HCl (30 ml) and H_2O (4x30 ml). After evaporation of the solvent under reduced pressure the crude solid was triturated with acetone to give pure **39**. Yield 115 mg (97%); mp 274-276°C. Anal. calcd for $\text{C}_{80}\text{H}_{108}\text{O}_{18}$: C, 70.78; H, 8.01. Found: C, 70.67; H, 8.10. MS (CI): $m/z = 1357.5$ (M^+ , 1357.8). IR (KBr): 3340 cm^{-1} (OH), 3500-2500 cm^{-1} (COOH), 1660 cm^{-1} (C=O); ^1H NMR (400 MHz, CDCl_3): $\delta = 8.37$ (br s, 2H, OH), 7.67 (s, 4H, ArH), 7.1-6.7 (br s, 8H, ArH), 4.1-3.4 (br s, 44H, ArCH_2Ar , OCH_2), 3.29 (s, 12H, OCH_3), 0.96 [s, 36H, $\text{C}(\text{CH}_3)_3$]; ^{13}C NMR (25 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD} = 1/1$): $\delta = 169.7$ (s, COOH), 157.8, 152.2, 147.4, 133.6, 132.7 (s, Ar), 131.3 (d, ArH), 127.6 (s, Ar), 127.1, 126.4 (d, ArH), 121.8 (s, Ar), 73.1, 72.4, 70.7, 70.5 (t, OCH_2), 59.0 (q, OCH_3), 34.5 [s, $\text{C}(\text{CH}_3)_3$], 31.6 [q, $\text{C}(\text{CH}_3)_3$], 30.8 (t, ArCH_2Ar).

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

Method A: A suspension of calixarene **27** (200 mg, 0.24 mmol), NBS (192 mg, 1.08 mmol) in 2-butanone (5 ml) was stirred under argon at r.t. for 24 h. The mixture was extracted with CH_2Cl_2 , washed with $\text{Na}_2\text{S}_2\text{O}_5$ (10 ml), brine (3 x25 ml) and dried (Na_2SO_4). The solvent was eliminated and the residue was triturated with hexane to afford **40**. Yield 188 mg (70%).

Method B: To a stirred solution of **27** (600 mg, 0.71 mmol) in ethylacetate (50 ml), NBS (770 mg, 4.33 mmol) was added. The mixture was stirred for 18 h at room temperature under nitrogen. After quenching with 10% aq NaHSO₃ (50 ml) the organic layer was washed with 1N HCl (1x30 ml) and H₂O until neutral pH then dried (MgSO₄). Evaporation of the solvent under reduced pressure afforded a crude solid that gave **40** upon trituration with CH₂Cl₂/petroleum ether. Yield 370 mg (48%); mp 219-220°C. Anal. calcd for C₅₇H₆₃Br₃O₆: C, 63.17; H, 5.86. Found: C, 63.07; H, 5.99. MS (FAB): *m/z* = 1084.2 [(M+4)⁺, 1084.2]. ¹H NMR (250 MHz, CDCl₃): δ = 7.14 (s, 6H, ArH), 6.96 (s, 3H, OH), 6.94 (s, 6H, ArH), 3.85 (s, 12H, ArCH₂Ar), 3.50 (s, 9H, OCH₃), 1.12 [s, 27H, C(CH₃)₃]; ¹³C NMR (62.5 MHz, CDCl₃): δ = 152.1, 151.4, 147.7, 131.6 (s, Ar), 131.3 (d, ArH), 129.3 (s, Ar), 126.0 (d, ArH), 111.7 (s, Ar), 61.5 (q, OCH₃), 34.2 [s, C(CH₃)₃], 31.3 [q, C(CH₃)₃], 30.9 (t, ArCH₂Ar).

11,23,35-Tribromo-5,17,29-tri-tert-butyl-37,38,39,40,41,42-hexamethoxycalix[6]arene (41)

Method A: To a stirred slurry of **40** (400 mg, 0.37 mmol) and Cs₂CO₃ (720 mg, 2.21 mmol) in dry DMF (40 ml) MeI (0.28 ml, 4.50 mmol) was added. The reaction mixture was heated at 70°C for 16 h, the solvent was distilled off under reduced pressure and the residue was taken up in CH₂Cl₂ (60 ml). The organic solution was successively washed with 1N HCl (1x30 ml), H₂O (3x30 ml) and dried (MgSO₄). Evaporation of the solvent afforded the product **41**. An analytical sample was recrystallized from MeOH. Yield 291 mg (70%).

Method B: To a stirred slurry of NaH (60% oil dispersion, 100 mg, 2.49 mmol) in dry THF (20 ml) was added under argon a solution of calix[6]arene **40** (300 mg, 0.28 mmol) in dry THF (20 ml). The mixture was heated at reflux for 48 h, adding MeI (0.2 ml, 3.21 mmol) as soon as the reflux began. After cooling, 10% HCl (10 ml) was added, and the reaction mixture was stirred for 1h. The solvent was removed and the residue was extracted with Et₂O (3x50 ml), dried (Na₂SO₄), and evaporated to give a solid, which was purified by trituration in hexane. Yield 260 mg (83%); mp 186-188°C. Anal. calcd for C₆₀H₆₉Br₃O₆: C, 64.01; H, 6.18. Found: C, 64.12; H, 6.25. MS (FAB): *m/z*: 1125.9 [(M+4)⁺, 1126.5]. ¹H NMR (250 MHz, CDCl₃): δ = 7.03 (s, 12H, ArH), 3.89 (s, 12H, ArCH₂Ar), 3.30 (s, 9H, OCH₃), 3.07 (s, 9H, OCH₃), 1.22 [s, 27H, C(CH₃)₃]; ¹³C NMR (62.5 MHz, CDCl₃): δ = 155.1, 154.1, 146.3 (s, Ar), 137.0 (d, ArH), 132.9, 131.2 (s, Ar), 126.5 (d, ArH), 116.4 (s, Ar), 60.2, 60.1 (q, OCH₃), 34.2 [s, C(CH₃)₃], 31.5 [q, C(CH₃)₃], 30.5 (t, ArCH₂Ar).

11,23,35-Tribromo-5,17,29-tri-tert-butyl-38,40,42-trimethoxy-37,39,41-tris(4-methylbenzyloxy)calix[6]arene (42)

A suspension of calixarene **40** (80 mg, 0.07 mmol), Cs₂CO₃ (144 mg, 0.44 mmol) and of 4-methylbenzyl bromide (82 mg, 0.44 mmol) in dry DMF (10 ml) was heated at 80°C for 18 h. The mixture was extracted with Et₂O (50 ml), washed with 10% HCl (2x20 ml), brine (25 ml), dried (MgSO₄) and the solvent evaporated. The residue was crystallized in CHCl₃/MeOH to afford **42**. Yield 90 mg (87%); mp 122°C. Anal. calcd for C₈₁H₈₇Br₃O₆·MeOH: C, 68.96; H, 6.42. Found: C, 68.90; H, 6.34. MS (FAB): *m/z* = 1393.04 (M⁺, 1392.40). ¹H NMR (200 MHz, CDCl₃): δ = 7.43 and 7.08 (AA'BB' system, 12H, ArCH₃), 7.03 (s, 6H, ArH), 6.69 (br s, 6H, ArH), 4.72 (br s, 6H, OCH₂ArCH₃), 4.3-3.9 (br s, 6H, ArCH₂Ar), 3.7-3.2 (br s, 6H, ArCH₂Ar), 2.68 (s, 9H, OCH₃), 2.28 (s, 9H, ArCH₃), 1.20 [s, 27H, C(CH₃)₃]; ¹³C NMR (50 MHz, CDCl₃): δ = 154.6, 153.3, 146.3, 137.7, 137.0, 134.3, 132.6 (s, Ar), 130.2, 129.1, 128.2, 127.5 (d, ArH), 116.9 (s, Ar), 74.7 (t, OCH₂ArCH₃), 60.1 (q, OCH₃), 34.2 [s, C(CH₃)₃], 31.5 [q, C(CH₃)₃], 31.0 (t, ArCH₂Ar), 21.3 (q, ArCH₃).

5,23-Dibromo-11,17,29,35-tetra-*tert*-butyl-37,38,40,41-tetrakis[2-(2-methoxyethoxy)ethoxy]calix[6]arene-39,42-diol (43)

To a stirred solution of **35** (190 mg, 0.15 mmol) in ethyl acetate (10 ml) was added NBS (85 mg, 0.48 mmol). The mixture was stirred for 7 h at room temperature under nitrogen. After quenching with 10% aq NaHSO₃ (10 ml), the separated organic layer was washed with H₂O until neutral pH and dried (MgSO₄). Evaporation of the solvent afforded a crude product that was triturated with MeOH to give compound **43**. Yield 73 mg (34%); mp 218-220°C. Anal. calcd for C₇₈H₁₀₆Br₂O₁₄: C, 65.63; H, 7.49. Found: C, 65.56; H, 7.54. MS (CI): *m/z* = 1428.3 [(M+4)⁺, 1428.6]. IR (KBr): 3400 cm⁻¹ (OH); ¹H NMR (400 MHz, CDCl₃): δ = 7.24 (d, *J* = 2.4 Hz, 4H, ArH), 7.00 (d, *J* = 2.4 Hz, 4H, ArH), 6.63 (s, 4H, ArH), 5.48 (s, 2H, OH), 4.14 (ddd, *J* = 10.3, 4.2, 4.2 Hz, 4H, ArOCH₂HCH₂), 4.08 (d, *J* = 15.2 Hz, 4H, ArC₂HAr), 4.06 (s, 4H, ArCH₂Ar), 3.82 (ddd, *J* = 10.3, 4.2, 7.4 Hz, 4H, ArOCH₂HCH₂), 3.76 (d, *J* = 15.2 Hz, 4H, ArC₂HAr), 3.58 (ddd, *J* = 11.8, 4.2, 4.2 Hz, 4H, OCH₂CHH), 3.38 (ddd, *J* = 11.8, 4.2, 7.4 Hz, 4H, ArOCH₂CHH), 3.35-3.25 (m, 12H, OCH₂), 3.25-3.20 (m, 4H, OCH₂), 3.21 (s, 12H, OCH₃), 1.27 [s, 36H, C(CH₃)₃]; ¹³C NMR (25 MHz, CDCl₃): δ = 154.3, 148.3, 146.2, 133.6, 133.1, 130.3 (s, Ar), 127.4, 127.2 (d, ArH), 126.2 (s, ArBr), 124.2 (d, ArH), 71.8, 71.6, 70.4, 70.1 (t, OCH₂), 58.9 (q, OCH₃), 39.25 (t, ArCH₂Ar), 34.2 [s, C(CH₃)₃], 31.7 [q, C(CH₃)₃], 30.7 (t, ArCH₂Ar).

5,17,29-Tri-*tert*-butyl-11,23,35-tricyano-37,38,39,40,41,42-hexamethoxycalix[6]arene (44)

A mixture of **41** (90 mg, 0.08 mmol) and CuCN (4.5 mg, 0.50 mmol) in 3 ml of N-methylpyrrolidinone (NMP) was heated for 15 h under argon at 200°C. After cooling the reaction mixture to 100°C, a solution of 8.2 mg of FeCl₃·H₂O and 4 ml of 3N HCl was slowly added. Stirring was continued until the reaction mixture reached room temperature. The precipitate was filtered on a Buchner funnel, washed with H₂O and purified by column chromatography (silica gel, hexane/THF, 8:2) to give **44**. Yield 55 mg (78%); mp 256-258°C. Anal. calcd for C₆₃H₆₉N₃O₆: C, 78.48; H, 7.21. Found: C, 78.39; H, 7.27. MS (FAB): *m/z*: 964.6 [(M+H)⁺, 964.5]. IR (KBr): 2220 cm⁻¹ (CN); ¹H NMR (250 MHz, CDCl₃): δ = 7.22 (s, 6H, ArH), 7.00 (s, 6H, ArH), 3.92 (s, 12H, ArCH₂Ar), 3.45 (s, 9H, OCH₃), 3.07 (s, 9H, OCH₃), 1.21 [s, 27H, C(CH₃)₃]; ¹³C NMR (62.5 MHz, CDCl₃): δ = 159.8, 154.1, 146.7, 136.5 (s, Ar), 132.5, 126.6 (d, ArH), 119.2 (s, CN), 107.1 (s, ArCN), 60.6, 60.1 (q, OCH₃), 34.2 [s, C(CH₃)₃], 31.4 [q, C(CH₃)₃], 30.9 (t, ArCH₂Ar).

5,17,29-Tri-*tert*-butyl-11,23,35-trichloromethyl-37,38,39,40,41,42-hexamethoxycalix[6]arene (45)

A mixture of calixarene **31** (0.140 g, 0.16 mmol), chlorotrimethylsilane (0.3 g, 2.4 mmol) and paraformaldehyde (73 mg, 2.4 mmol) in 10 ml of dry CH₂Cl₂ was cooled at -15°C. A solution of SnCl₄ (0.28 ml, 2.4 mmol) in 4 ml of CH₂Cl₂ was slowly added. After 1.5 h at -15°C the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was poured into 15 ml of ice/water and extracted with 2x20 ml of CH₂Cl₂. The combined organic extracts were carefully washed with water to neutral pH and dried (Na₂SO₄). The product was crystallized from cold methanol. Yield 135 mg (81%); mp 150-152°C. Anal. calcd for C₆₃H₇₅Cl₃O₆: C, 73.14; H, 7.31. Found: C, 73.05; H, 7.40. MS (CI): *m/z* = 1034.8 [(M+2)⁺, 1034.6]. ¹H NMR (300 MHz, CDCl₃): δ = 7.00 (s, 6H, ArH), 6.83 (s, 6H, ArH), 4.24 (s, 6H, CH₂Cl), 3.92 (s, 12H, ArCH₂Ar), 3.40 (s, 9H, OCH₃), 3.04 (s, 9H, OCH₃), 1.15 [s, 27H, C(CH₃)₃]; ¹³C NMR (75 MHz, CDCl₃): δ =

154.0, 146.4, 135.0, 133.0, 132.6 (s, Ar), 128.8, 126.5 (d, ArH), 60.3, 60.2 (q, OCH₃), 46.5 (t, CH₂Cl), 34.1 [s, C(CH₃)₃], 31.4 [q, C(CH₃)₃], 30.6 (t, ArCH₂Ar).

5,17,29-Tri-tert-butyl-38,40,42-trimethoxy-37,39,41-tris(2-propenyloxy)calix[6]arene (46)

To a stirred slurry of **27** (400 mg, 0.47 mmol) and Cs₂CO₃ (930 mg, 2.85 mmol) in dry DMF (80 ml) allyl bromide (0.25 ml, 2.85 mmol) was added at 70°C. After stirring for 18 h the solvent was evaporated under reduced pressure and the residue taken up with CH₂Cl₂ (50 ml). The organic layer was washed with 1N HCl (3x30 ml), H₂O (1x30 ml), brine (1x30 ml) and dried (MgSO₄). Evaporation of the solvent afforded pure product **46**. Yield 380 mg (83%); mp 96-98°C. Anal. calcd for C₆₆H₇₈O₆: C, 81.95; H, 8.13. Found: C, 82.07; H, 8.27. MS (FAB): *m/z*: 966.7 (M⁺, 966.6). IR (KBr): 1647 cm⁻¹ (C=C); ¹H NMR (250 MHz, CDCl₃): δ = 7.14 (s, 6H, ArH), 6.9-6.6 (m, 9H, ArH), 6.0-5.8 (m, 3H, CH=CH₂), 5.19 (d, *J* = 17 Hz, 3H, CH=CHH), 5.04 (d, *J* = 10 Hz, 3H, CH=CHH), 4.10 (d, *J* = 3 Hz, 6H, OCH₂CH=CH₂), 3.93 (s, 12H, ArCH₂Ar), 2.79 (s, 9H, OCH₃), 1.25 [s, 27H, C(CH₃)₃]; ¹³C NMR (62.5 MHz, CDCl₃): δ = 154.6, 154.3, 145.9 (s, Ar), 134.8 (d, CH=CH₂), 134.0, 133.3 (s, Ar), 128.0, 126.9, 123.5 (d, ArH), 117.1 (t, CH=CH₂), 73.4 (t, OCH₂CH=CH₂), 60.1 (q, OCH₃), 34.2 [s, C(CH₃)₃], 31.5 [q, C(CH₃)₃], 30.7 (t, ArCH₂Ar).

5,17,29-Tri-tert-butyl-38,40,42-trimethoxy-11,23,35-tris(2-propenyloxy)calix[6]arene-37,39,41-triol (47)

A solution of **46** (480 mg, 0.50 mmol) in N,N-dimethylaniline (15 ml) was refluxed for 2h. The cooled reaction mixture was poured into a mixture of 12N HCl/ice (20 ml). The aqueous layer was extracted with CH₂Cl₂ (2x20 ml), washed with 1N HCl (1x20 ml), H₂O (3x30 ml), brine (1x20 ml) and dried (MgSO₄). After evaporation of the solvent the crude product was triturated with petroleum ether to afford pure **47**. Yield 200 mg (42%); mp 219-221°C. Anal. calcd for C₆₆H₇₈O₆: C, 81.95; H, 8.13. Found: C, 82.05; H, 8.21. MS (FAB): *m/z*: 966.2 (M⁺, 966.6). IR (KBr): 1638 cm⁻¹ (C=C); ¹H NMR (250 MHz, CDCl₃): δ = 6.91 (s, 6H, ArH), 6.83 (s, 6H, ArH), 6.74 (s, 3H, OH), 6.0-5.85 (m, 3H, CH=CH₂), 5.1-5.0 (m, 3H, CH=CHH), 4.95-4.90 (m, 3H, CH=CHH), 3.87 (s, 12H, ArCH₂Ar), 3.50 (s, 9H, OCH₃), 3.23 (d, *J* = 6 Hz, 6H, ArCH₂CH=CH₂), 1.05 [s, 27H, C(CH₃)₃]; ¹³C NMR (62.5 MHz, CDCl₃): δ = 152.3, 150.4, 147.0 (s, Ar), 138.3 (d, CH=CH₂), 132.3, 131.0, 129.0 (s, Ar), 127.3, 125.8 (d, ArH), 115.0 (t, CH=CH₂), 61.4 (q, OCH₃), 39.4 (t, ArCH₂CH=CH₂), 34.1 [s, C(CH₃)₃], 31.2 [q, C(CH₃)₃], 31.0 (t, ArCH₂Ar).

5,17,29-Tri-tert-butyl-38,40,42-trimethoxycalix[6]arene-11,23,35,37,39,41-hexaone (48)

To a solution of **27** (230 mg, 0.27 mmol) in CHCl₃ (27 ml) was added Ti(NO₃)₃·3H₂O (734 mg, 1.64 mmol) dissolved in a mixture of EtOH (90 ml) and MeOH (30ml) at room temperature. After stirring for 2h the reaction was quenched with 1N HCl (50ml) and the aqueous layer extracted with CH₂Cl₂ (2x60 ml). The organic phase was washed with H₂O until neutral pH and dried (Na₂SO₄). After evaporation of the solvent the crude product was purified by preparative plates (silica gel, hexane/CH₂Cl₂ 1/3) followed by trituration with n-hexane. Yield 59 mg (24%); mp 200-202°C. Anal. calcd for C₅₇H₆₀O₉: C, 77.00; H, 6.80. Found: C, 76.89; H, 6.88. MS (CI): *m/z*: 890.0 [(M+H)⁺, 889.4]. IR (KBr): 1670 cm⁻¹ (C=O), 1620 cm⁻¹ (C=C); ¹H NMR (100 MHz,

CDCl₃): δ = 7.07 (s, 6H, ArH), 5.98 (s, 6H, QH), 3.89 (s, 12H, ArCH₂Ar), 3.35 (s, 9H, OCH₃), 1.28 [s, 27H, C(CH₃)₃]; ¹³C NMR (25 MHz, CDCl₃): δ = 187.3, 186.6 (s, C=O), 176.2, 154.1, 148.6 (s, Ar), 132.3 (d, ArH), 130.7 (s, Ar), 127.7 (d, ArH), 60.5 (q, OCH₃), 34.3 [s, C(CH₃)₃], 31.5 [q, C(CH₃)₃], 30.6 (t, ArCH₂Ar).

37,38,40,41-Tetrabenzoyloxy-11,17,29,35-tetra-tert-butylcalix[6]arene-5,23,39,42-tetrone (50)

To a stirred solution of 38,39,41,42-tetrabenzoyloxy-5,11,17,23,29,35-hexa-tert-butylcalix[6]arene-37,40-diol **49** (200 mg, 0.14 mmol) in TFA (7 ml) at room temperature, was added Ti(CF₃CO₂)₃ (650 mg, 1.19 mmol). After 24 h, the solvent was evaporated and the residue was partitioned in CH₂Cl₂ and H₂O. The organic layer was dried (Na₂SO₄) and the solvent was eliminated. The residue was triturated with MeOH and the resulting solid was filtered and recrystallized (CHCl₃/MeOH) to give **50**. Yield 150 mg (80%); mp 260°C (dec.). Anal. calcd for C₈₆H₈₀O₁₂·2 H₂O: C, 76.99; H, 6.31. Found: C, 76.79; H, 5.96. MS (FAB): *m/z* = 1340.6 (M⁺, 1305.5). ¹H NMR (200 MHz, CDCl₃): δ = 8.03 (d, *J* = 8.4 Hz, 8H, ArH), 7.50 (t, *J* = 8.4 Hz, 4H, ArH), 7.31 (t, *J* = 8.4 Hz, 8H, ArH), 7.04 (d, *J* = 2.1 Hz, 4H, ArH), 6.80 (d, *J* = 2.1 Hz, 4H, ArH), 5.79 (s, 4H, QH), 4.17 (s, 4H, ArCH₂Ar), 3.70 and 3.48 (AB system, 8H), 0.84 [s, 36H, C(CH₃)₃]; ¹³C NMR (75 MHz, CDCl₃): δ = 188.0, 186.5 (s, CO), 163.8 (s, OCOAr), 150.0, 149.5, 145.7 (s, Ar), 133.4 (d, ArH), 133.1 (s, Ar), 131.9, 130.4, 128.6 (d, ArH), 128.5, 128.2 (s, Ar), 127.1, 126.7 (d, ArH), 39.4 (t, ArCH₂Ar), 34.0 [s, C(CH₃)₃], 30.7 [q, C(CH₃)₃], 30.2 (t, ArCH₂Ar).

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