Synthesis of *Lower Rim* Polyhydroxylated Calix[4]arenes

Margarita Segura,[a] Francesco Sansone,[b] Alessandro Casnati,[b] Rocco Ungaro*[b]

[a] Departamento de Quimica Organica, Facultad de Ciencias, Universidad Autonoma de Madrid, Cantoblanco, 28049, Madrid, Spain

[b] Dipartimento di Chimica Organica e Industriale dell'Università, Parco Area delle Scienze 17/A, 43100, Parma, Italy
Fax +39(521)905472; E-mail: ungaro@unipr.it

Received 25 June 2001; revised 6 August 2001

Abstract: Several synthetic procedures were evaluated and a protective/deprotective method, which allows the introduction of two, three, and four amide-linked polyhydroxylated units (TRIS) at the *lower rim* of calix[4]arenes was developed. Di- and trifunctionalized derivatives are poorly soluble in water, whereas the solubility of calix[4]arene having four polyhydroxylated amide groups is good (6×10^{-3} M at 25 °C).

Key words: calixarenes, protecting groups, amides, supramolecular chemistry, water-soluble calix[4]arenes

In several classical applications of calixarenes[1] in Supramolecular Chemistry, e.g. in ionophore synthesis,[2] transition metal ion binding[3] and catalysis,[4] the *lower rim* is used as the recognition core, since the binding groups for cation complexation are introduced in this region via ether bonds. In this case, the *upper rim* usually bears substituents, which confer solubility to the ligands in the desired solvent. Water solubility[5] is achieved by attaching sulfonate,[6] phosphonate[7] or neutral hydroxylated groups.[8] Calix[4]arenes, especially when blocked in the *cone* conformation, possess, however, an apolar cavity of defined size which can take part in the recognition of neutral molecules,[9] quaternary ammonium cations[10] $(QUATS)^+$ and anions.[11]

More recently, we have been interested in the synthesis of *hybrid* receptors for anions,[12] amino acids[13,14] and carbohydrates,[15] which are characterized by the presence of polar groups at the *upper rim*, in close proximity to the calix[4]arene apolar cavity.

In order to enhance the potential of these receptors as biologically active compounds or as models for biological recognition processes, we needed to render them water soluble by attaching suitable solubilizing groups at the *lower rim*, while leaving the *upper rim* free for the introduction of polar binding groups. Water-soluble calix[4]arenes having anionic carboxylate[16] and sulfonate[17] or cationic tretralkylammonium[18] groups at the *lower rim* are known. However, charged groups can affect the binding properties of the receptors and, therefore, it was highly desirable to introduce at the *lower rim* neutral groups, which can eventually result in water-soluble receptors.

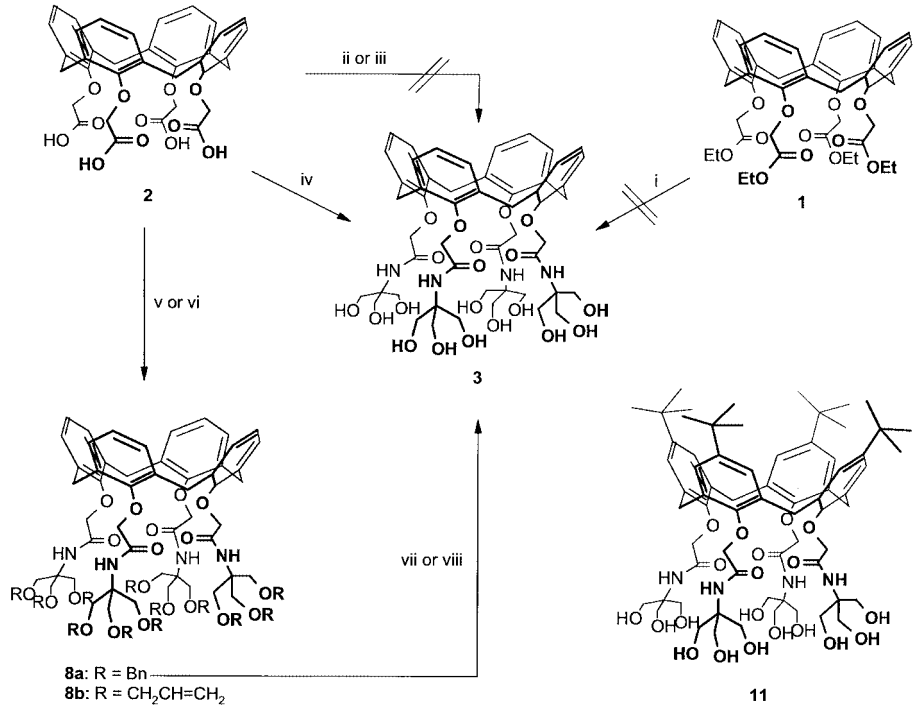
To the best of our knowledge, water-soluble calix[4]arenes bearing neutral polyhydroxylated groups at the *upper rim* are known,[8] but no example of this type exists for the *lower rim*.[19] We report in this paper the results of our systematic study aimed at attaching two, three, and four units of tris(hydroxymethyl)aminomethane (TRIS) at the *lower rim* of calix[4]arenes and the solubility properties of these compounds in protic solvents.

Using experimental conditions similar to those of a previously reported procedure,[8b] we first reacted the calix[4]arene tetraester **1**[20] with TRIS (**4**) in DMSO in the presence of K_2CO_3 (Scheme 1, i), but did not observe any substantial reactivity.

Negative results were also obtained in the reaction of TRIS (**4**) with the easily available calix[4]arene tetraacetic acid **2**[6d] as the starting material, activated as its acyl chloride or carrying out the reaction with 1,3-dicyclohexylcarbodiimide (DCC) in the presence of 1-hydroxy-1*H*-benzotriazole (HOBT)[21] (Scheme 1, ii and iii). The only positive result from a direct condensation was obtained by reacting **2** and **4,** in the presence of 1,1'-carbonyldiimidazole (CDI) in anhydrous DMF. This procedure gave the desired polyhydroxylated tetraamide **3** in 80% yield (Scheme 1, iv). Since this compound is water soluble, it was purified from imidazole by continuous liquid-liquid extraction of the aqueous solution with dichloromethane. The ^{1}H NMR spectrum of the product in DMSO-d_6 clearly showed the tetrafunctionalization because of its symmetrical pattern, typical of *cone* calix[4]arenes having a C_4 symmetry. The presence of a triplet (δ = 4.75), a doublet (δ = 3.59) and a broad singlet (δ = 7.32) corresponding to the OH, CH_2C and NH protons, respectively, ensured that the condensation had occurred with the amino group. Unfortunately, this procedure was not reproducible and, especially if the solvent contained traces of water, the tetraamide **3** was often obtained together with a mixture of partially condensed derivatives, which made the isolation of the compound in pure form difficult. To overcome this problem we resorted to an indirect protection/deprotection route. Reinhoudt and co-workers[8d] arrived at the same conclusion during their synthesis of neutral, water-soluble calix[4]arenes having polyhydroxylated groups at the *upper rim*. They used a TRIS derivative, which was protected at the hydroxyl groups with bulky *tert*-butyldimethylsilyl (TBDMS) moieties, obtained by reduction of the corresponding nitro derivative. We encountered some difficulties in the efficient reduction of this compound and moreover, the condensation of tetraacid **2**

Synthesis 2001, No. 14, 26 10 2001. Article Identifier:
1437-210X,E;2001,0,14,2105,2112,ftx,en;T05001SS.pdf.

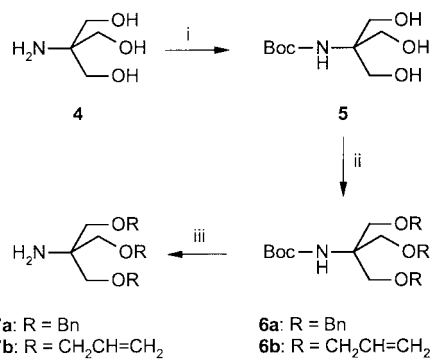
ISSN 0039-7881



Scheme 1 *Reagents and conditions*: i) TRIS (**4**), K_2CO_3, DMSO, 40 °C, 72–96 h; ii) 1. $(COCl)_2$, CH_2Cl_2, reflux, 6 h, 2. Et_3N, TRIS (**4**), DMF, r.t., 12 h; iii) HOBT, DCC, TRIS (**4**), DMF, –5 °C to r.t., 24 h; iv) CDI, TRIS (**4**), DMF, r.t., 48 h, 80%; v) 1. $(COCl)_2$, CH_2Cl_2, reflux, 6 h, 2. Et_3N, **7a** (or **7b**), CH_2Cl_2, r.t., 12 h, 75%; vi) HBTU, Et_3N, **7a** (or **7b**), THF, r.t., 12 h, 50%; vii) H_2 (2 bar), Pd/C, 2:1 EtOH/HOAc, r.t., 12 h, quantitative yield; viii) $Pd(OH)_2$, cyclohexene/EtOH (2:3), reflux, 24 h, quantitative yield

with TBDMS protected TRIS was not successful, probably because of the great steric bulk of this reagent.[8d] For these reasons we decided to use a TRIS derivative, which was *O*-protected with the less bulky allyl or benzyl groups.

To this end, we first protected the amino group of **4** as *tert*-butyl carbamate obtaining the compound **5** in 97% yield[22] (Scheme 2).



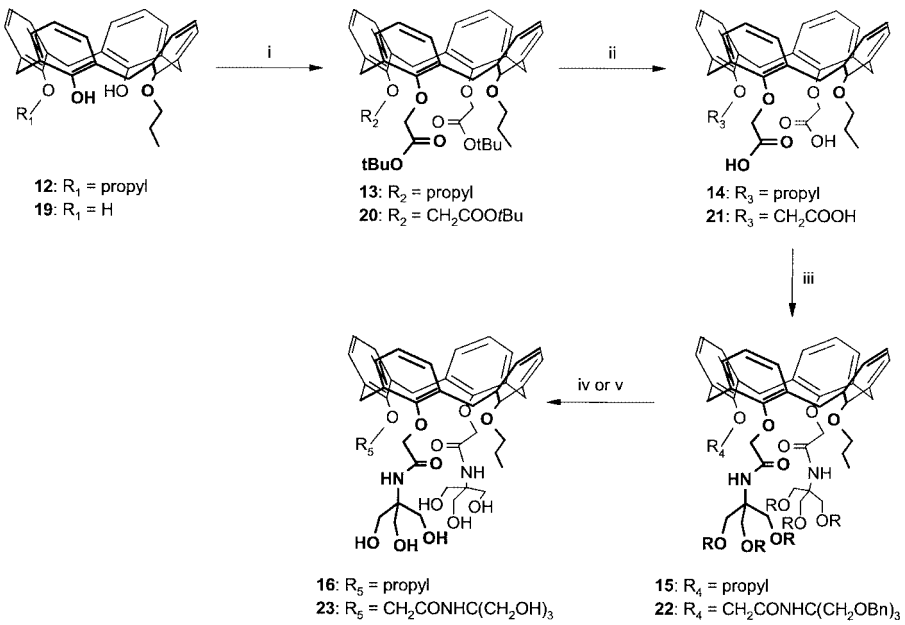
Scheme 2 *Reagents and conditions*: i) (*t*-BuOCO)$_2$O, MeOH–*t*-BuOH (3:2), r.t., 12 h, 97%; ii) BnBr (or allyl bromide), KOH, DMF, r.t., 2 h, 63–65%; iii) TFA, CH_2Cl_2, r.t., 4 h, 94–97%

O-Alkylation of **5** with benzyl or allyl bromide afforded the TRIS derivatives **6a** or **6b** in good yields, which were finally transformed into the *O*-protected amines **7a**,**b** in almost quantitative yields, by treatment with trifluoroacetic acid in dichloromethane. Condensation of **7a**,**b** with the calix[4]arene tetraacid **2**, activated as its acyl chloride or with *O*-benzotriazol-1-yl-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (HBTU),[23] which allows for milder reaction conditions, gave the amides **8a**,**b** in 50–75% yields (Scheme 1, v and vi). These protected compounds were easily purified by flash chromatography on silica gel and the benzyl derivative **8a** was quantitatively transformed into the polyhydroxylated tetraamide **3**, both using catalytic hydrogenation (Pd/C and H_2) in a 2:1 ethanol–acetic acid mixture or with palladium hydroxide and cyclohexene in ethanol[24] (Scheme 1, vii and viii). Surprisingly, the allyl protected derivative **8b** was quite stable in all tested classical deallylation procedures,[25] thus showing, once again, that multifunctional calixarene substrates often challenge well-established general synthetic procedures.

Therefore, the benzyl protection procedure was selected as the method for the synthesis of the other calix[4]arene derivatives **11** (Scheme 1), **16** and **23** (Scheme 3), having four, two and three polyhydroxylated amide functions at the *lower rim*, respectively.

All new compounds and intermediates were fully characterized by NMR (^{1}H and ^{13}C), mass spectrometry and elemental analyses.

While compounds **11**,**16** and **23** are soluble only in methanol–water mixtures, tetraamide **3** is soluble in water up to 6×10^{-3} M, as determined by NMR in D_2O at 300 K using potassium hydrogen phthalate as internal standard.



Scheme 3 *Reagents and conditions*: i) NaH, *t*-BuOCOCH$_2$Br, DMF, r.t., 5 h, 92% for **13** and 52% for **20**; ii) CF_3CO_2H, r.t., 3 h, quantitative yield; iii) 1. $(COCl)_2$, CH_2Cl_2, reflux, 6 h, 2. Et_3N, **7a**, CH_2Cl_2, r.t., 12 h, 77% for **15** and 54% for **22**; iv) H_2 (2 bar), Pd/C, EtOH–HOAc (2:1), r.t., 12 h, quantitative yield; v) $Pd(OH)_2$, cyclohexene–EtOH (2:3), reflux, 24 h, quantitative yield

The ^{1}H NMR spectrum is sharp at concentrations $< 2.5 \times 10^{-4}$ M, but becomes broad in the range of 2.5×10^{-4} to 6×10^{-3} M, indicating extensive aggregation under these conditions. This is also confirmed by UV/Vis experiments which show a linear dependence of the absorption only at concentrations $< 2.5 \times 10^{-4}$ M.

These data demonstrate that at least four polyhydroxylated amide units are needed to obtain water solubility in the case of de-*tert*-butylated calix[4]arene units **3**, but that the water solubility markedly decreases with *p-tert*-butylcalix[4]arenes.

We also checked the stability of compound **3** in water under different conditions. It has been observed, in fact, that α-phenoxyacetamides containing hydroxy groups in the *N*-alkyl residue undergo cleavage of the acetamide bonds in water at neutral pH on heating.[26] More recently,[19] in water-soluble cavitands bearing four polyhydroxylated residues R (Figure), the end groups rearrange from an amide to an ester-linked TRIS in the presence of dilute acids, forming an ammonium salt which enhances the water solubility of the receptors.

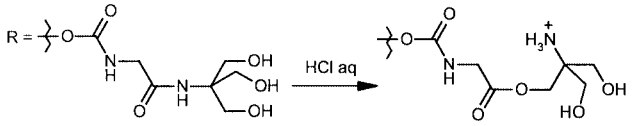


Figure Rearrangement of TRIS polyhydroxylated amides to ammonium esters

We found that tetraamide **3** is completely stable when warmed up to 65 °C at neutral pH for several hours, and under the acidic conditions (HOAc) used to debenzylate **8a** to **3**. Only when heated at 90 °C or treated with 12 N HCl, compound **3** decomposes, giving a complex mixture of products.

In conclusion, through a systematic study of the condensation reaction between activated calix[4]arene acetic acids and tris(hydroxymethyl)aminomethane (TRIS) units, we have developed both a direct and an indirect protection/deprotection method to link up to four TRIS units to the *lower rim* of calix[4]arenes. High yields in the deprotection step were obtained with benzyl derivatives, whereas no reaction was observed for allyl derivative **8b**. We have also shown that four TRIS moieties are needed to give a fair water solubility to calix[4]arenes without lipophilic substituents at the *upper rim*. However, we expect that the water solubility should increase for calixarenes bearing at the *upper rim* additional polar groups such as amino acids, peptides and carbohydrates.

Besides water solubility the successful introduction of polyhydroxylated functions at the *lower rim* of calix[4]arenes is attractive, because it offers the possibility of anchoring calix[4]arene receptors on hydroxylated solid surfaces (mica, glass, etc.) and studying the recognition process on monolayers.[27]

All solvents were dried and distilled according to standard procedures. Reagents were used as purchased. All air sensitive reactions were carried out under N_2. TLC was performed on silica gel 60-coated aluminum sheets (Macherey-Nagel) with detection by UV at 254 nm and by heating with H_2SO_4 (10% in MeOH). Flash chromatography was carried out on silica gel 60 (ICN, 32–63 mesh). Melting points were determined on a Gallenkamp apparatus in, under nitrogen sealed, capillaries. NMR spectra were recorded on a Bruker AC300 (^{1}H: 300 MHz; ^{13}C: 75 MHz) and AC100 (^{1}H: 100 MHz; ^{13}C: 25 MHz) spectrometers using partially deuterated solvents as

internal standards. Mass spectra by chemical ionization (CI) and electrospray ionization (ESI) methods were recorded on a Finnigan Mat SSQ 710 spectrometer. IR spectra were recorded on a Perkin-Elmer 298 spectrometer. Elemental analyses were obtained using a CHN 1106 Carlo Erba instrument. For reasons of clarity and in order to reduce space, the name calix[4]arene was used instead of the original IUPAC name: pentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecane.
25,26,27,28-Tetrakis(ethoxycarbonylmethoxy)calix[4]arene (**1**),[20] 25,26,27,28-tetrakis(carboxymethoxy)calix[4]arene (**2**),[6d] 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis(carboxymethoxy)-calix[4]arene (**9**),[16] 25,27-dihydroxy-26,28-dipropoxycalix[4]arene (**12**),[28] and 25,26,27-tribenzoyloxy-28-hydroxycalix[4]arene (**17**)[29] were synthesized according to previously described procedures.

25,26,27,28-Tetrakis{[tris(hydroxymethyl)methylamino]-carbonylmethoxy}calix[4]arene (3)

Direct Method: A solution of **2**[6d] (130 mg, 0.20 mmol), CDI (130 mg, 0.801 mmol) and **4** (96 mg, 0.792 mmol) in anhyd DMF (15 mL) was stirred at r.t. for 48 h. The solvent was removed at reduced pressure and the residue was dissolved in H_2O and purified by continuous liquid-liquid extraction with CH_2Cl_2 for 2 d. After concentration of the aqueous layer, compound **3** (670 mg, 80%) was obtained as a white solid; mp 120–125 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.18 (d, 4 H, *J* = 13.5 Hz, H_{eq} of ArC*H*$_2$Ar), 3.59 (d, 24 H, *J* = 5.6 Hz, C*H*$_2$OH), 4.50 (s, 8 H, OCH$_2$CO), 4.55 (d, 4 H, *J* = 13.5 Hz, H_{ax} of ArC*H*$_2$Ar), 4.75 (t, 12 H, *J* = 5.6 Hz, CH$_2$O*H*), 6.53 (br s, 12 H_{arom}), 7.32 (s, 4 H, NH).

^{1}H NMR (300 MHz, D_2O): δ = 3.49 (d, 4 H, *J* = 14.3 Hz, H_{eq} of ArC*H*$_2$Ar), 3.87 (s, 24 H, C*H*$_2$OH), 4.58 (d, 4 H, *J* = 13.3 Hz, H_{ax} of ArC*H*$_2$Ar), 4.75 (s, 8 H, OCH$_2$CO), 6.86 (br s, 12 H_{arom}).

^{13}C NMR (75 MHz, CD_3OD): δ = 32.3 (Ar*C*H$_2$Ar), 62.6 (CH$_2$OH), 63.6 [*C*(CH$_2$OH)$_3$], 74.9 (O*C*H$_2$CO), 124.1 (CH_{arom}), 129.9 (CH_{arom}), 135.9 (C_{arom}), 156.5 (C_{arom}), 172.5 (C=O).

IR (KBr): 1655 (C=O), 3395 cm^{-1} (OH).

ESI-MS: *m*/*z* [ion, % relative intensity] = 1090.9 [(M + Na)$^+$, 100], 969.9 {[M + Na – HNC(CH$_2$OH)$_3$]$^+$, 20}, 557.1 [(M + 2 Na)$^{2+}$, 55], 554.2 [(M + H + K)$^{2+}$, 70].

Anal. Calcd for $C_{52}H_{68}N_4O_{20}$ (1069.1): C, 58.42; H, 6.41; N, 5.24. Found: C, 58.25; H, 6.23; N, 5.07.

Compound **3** was also obtained in quantitative yield from **8a** (800 mg, 0.37 mmol) following the General Procedures C or D (*vide infra*).

***N*-(*tert*-Butyloxycarbonyl)tris(hydroxymethyl)aminomethane (5)**

A solution of di-*tert*-butyl dicarbonate (23.5 g, 107.0 mmol) in *t*-BuOH (100 mL) was added to a suspension of **4** (10.0 g, 82.0 mmol) in a 1:1 mixture of MeOH–*t*-BuOH (150 mL) and the mixture was stirred at r.t. for 18 h. The solvent was removed at reduced pressure to give a residue, which was purified by precipitation with cold EtOAc. Vacuum filtration afforded the pure compound **5** as a white solid (17.7 g, 97%) which showed the same spectroscopic properties as those previously reported.[22]

***N*-(*tert*-Butyloxycarbonyl)tris[(benzyloxy)methyl]amino-methane (6a); Typical Procedure**

A solution of **5** (10.0 g, 45.0 mmol) in anhyd DMF (100 mL) was stirred at r.t., with benzyl bromide (30 mL, 252.0 mmol). Portions of finely ground KOH (14.14 g, 252.0 mmol) were added over a period of 15 min. The mixture was stirred at r.t. for 2 h, concentrated to dryness and the residue partitioned between hexane (or CH_2Cl_2) (200 mL) and H_2O (200 mL). The organic layer was washed with brine, dried (Na_2SO_4) and the solvent removed at reduced pressure to give the crude product, which was purified by flash chromatography (hexane followed by hexane–EtOAc, 95:5); yield: 14.4 g (65%); colorless oil.

^{1}H NMR (100 MHz, $CDCl_3$): δ = 1.40 [s, 9 H, C(CH$_3$)$_3$], 3.78 [s, 6 H, C(CH$_2$O)$_3$], 4.49 (s, 6 H, OC*H*$_2$Ph), 4.92 (br s, 1 H, NH), 7.27 (br s, 15 H, C_6H_5).

^{13}C NMR (25 MHz, $CDCl_3$):δ = 28.4 [C(*C*H$_3$)$_3$], 58.7 [*C*(CH$_2$O)$_3$], 69.5 [C(*C*H$_2$O)$_3$], 73.4 (O*C*H$_2$Ph), 79.0 [*C*(CH$_3$)$_3$], 127.5 (CH_{arom}), 128.3 (CH_{arom}), 138.4 (C_{arom}), 154.9 (C=O).

ESI-MS: *m*/*z* = 514.1 [(M + Na)$^+$, 100%].

Anal. Calcd for $C_{30}H_{37}NO_5$ (491.6): C, 73.24; H, 7.59; N, 2.85. Found: C, 73.43; H, 7.49; N, 2.72.

***N*-(*tert*-Butyloxycarbonyl)tris[(allyloxy)methyl]aminomethane (6b)**

Synthesized from **5** (10 g, 45 mmol) and allyl bromide (21.8 mL, 252 mmol), according to the procedure used for preparing **6a**. Purified by flash chromatography (hexane–EtOAc, 95:5); yield: 14.98 g (63%); colorless oil. This product showed the same spectroscopic properties as previously reported.[22]

Tris[(benzyloxy)methyl]aminomethane (7a); Typical Procedure

To a solution of **6a** (7.66 g, 15.6 mmol) in CH_2Cl_2 (60 mL), cooled to 0 °C was added dropwise TFA (25 mL) over a period of 30 min and the mixture was stirred at r.t., for 4 h. The mixture was concentrated to dryness and the residue was partitioned between EtOAc (100 mL) and 5% aq Na_2CO_3 solution (100 mL). The organic layer was washed with brine, dried (Na_2SO_4), and the solvent removed under vacuum to give the product, which was not purified further; yield: 5.93 g (97%); yellowish oil.

^{1}H NMR (100 MHz, $CDCl_3$): δ = 3.47 [s, 6 H, C(CH$_2$O)$_3$], 4.50 (s, 6 H, OC*H*$_2$Ph), 7.29 (br s, 15 H, C_6H_5).

^{13}C NMR (25 MHz, $CDCl_3$): δ = 56.2 [*C*(CH$_2$O)$_3$], 72.6 [C(*C*H$_2$O)$_3$], 73.4 (O*C*H$_2$Ph), 127.5 (CH_{arom}), 128.3 (CH_{arom}), 138.5 (C_{arom}).

CI-MS: *m*/*z* [ion, % relative intensity] = 392.2 [(M + H)$^+$, 50], 270.2 [(M – CH$_2$OBn)$^+$, 100].

Anal. Calcd for $C_{25}H_{29}NO_3$ (391.5): C, 76.70; H, 7.47; N, 3.58. Found: C, 76.55; H, 7.41; N, 3.60.

Tris[(allyloxy)methyl]aminomethane (7b)

Synthesized from **6b** (4.27 g, 12.5 mmol), according to the procedure used for preparing compound **7a**; yield: 2.85 g (94%); yellowish oil.

^{1}H NMR (100 MHz, $CDCl_3$): δ = 3.34 [s, 6 H, C(CH$_2$O)$_3$], 3.94 (dt, 6 H, *J* = 1.3, 5.3 Hz, OC*H*$_2$CH=CH$_2$), 5.07–5.34 (m, 6 H, OCH$_2$CH=C*H*$_2$), 5.89 (ddt, 3 H, *J* = 5.3, 10.1, 17.3 Hz, OCH$_2$C*H*=CH$_2$).

^{13}C NMR (25 MHz, $CDCl_3$): δ = 56.1 [*C*(CH$_2$O)$_3$], 71.9, 72.2 [OCH$_2$CH=CH$_2$, C(*C*H$_2$O)$_3$], 116.5 (OCH$_2$CH=*C*H$_2$), 134.7 (OCH$_2$*C*H=CH$_2$).

ESI-MS: *m*/*z* [ion, % relative intensity] = 264.1 [(M + Na)$^+$, 6], 242.1 [(M + H)$^+$, 42], 118.9 {[M + H – 3(CH$_2$CH=CH$_2$)]$^+$, 100}.

Anal. Calcd for $C_{13}H_{23}NO_3$ (241.3): C, 64.70; H, 9.61; N, 5.80. Found: C, 64.85; H, 9.73; N, 5.67.

Amides 8a,10,15,22; General Procedures

Method A: A mixture of the calix[4]arene acid **2**,**9**,**14**, or **21** (1 mmol) and oxalyl chloride (7.5 mL) in anhyd CH_2Cl_2 (60 mL) was refluxed for 6 h. After cooling, the solution was concentrated to dryness and the residue was dried under vacuum. The resulting acid chloride was dissolved in anhyd CH_2Cl_2 (20 mL) and a CH_2Cl_2 solution (25 mL) of **7a** (or **7b**) (1.5 equiv/COCl group) and Et_3N (2

equiv/COCl group) was added and the mixture was stirred at r.t. overnight. The solution was concentrated to dryness and the crude product **8a**,**10**,**15**,or **22**, respectively, was purified by flash chromatography.

Method B: To a solution of the calix[4]arene acid **2**,**9**,**14**,or **21** (1 mmol) in anhyd THF (20 mL) were added HBTU (1.5 equiv/CO_2H group), Et_3N (1.5 equiv/CO_2H group) and **7a** (or **7b**) (1.5 equiv/CO_2H group) and the mixture was stirred at r.t. overnight. The solvent was removed at reduced pressure and the residue was partitioned between CH_2Cl_2 and 5% aq HCl. The organic phase was washed with H_2O, dried ($MgSO_4$) and concentrated to dryness giving the crude product **8a**,**10**,**15**,or **22**, respectively, which was purified by flash chromatography.

Removal of Benzyl Protecting Groups from Amides 8a,10,15, 22; General Procedures

Method C: A suspension of benzyl derivative **8a**,**10**,**15**,or **22** (0.1 mmol) and 20% $Pd(OH)_2$ (50% w/w) in a mixture of cyclohexene (10 mL) and EtOH (15 mL) was refluxed until conversion was complete (TLC monitoring: hexane–EtOAc, 1:1 and EtOAc–*i*-PrOH–H_2O, 5:3:2). The mixture was cooled to r.t., filtered and the clear solution concentrated under vacuum to give the product **3**,**11**,**16**,or **23**, respectively, which was not purified further.

Method D: A solution of benzyl derivative **8a**,**10**,**15**,or **22**(0.1 mmol) in a 2:1 mixture of EtOH–HOAc (24 mL) containing 10% Pd/C was stirred under H_2 (pressure: 2 bar) at r.t. until conversion was complete (see above). The catalyst was filtered off and the filtrate was concentrated to dryness to give the product **3**,**11**,**16**,or **23**, respectively, which was not purified further.

25,26,27,28-Tetrakis{[tris(benzyloxymethyl)methylamino]-carbonylmethoxy}calix[4]arene (8a)

Prepared from **2** (100 mg, 0.15 mmol) and isolated in 75% yield (General Procedure A) or 50% (General Procedure B) after flash chromatography (hexane–EtOAc, 7:3); colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.00 (d, 4 H, *J* = 14.0 Hz, H_{eq} of ArCH_2Ar), 3.84 [s, 24 H, $C(CH_2O)_3$], 4.35 (s, 8 H, OCH_2CO), 4.37 (s, 24 H, OCH_2Ph), 4.39 (d, 4 H, *J* = 14.0 Hz, H_{ax} of ArCH_2Ar), 6.37 (br d, 8 H_{arom}, *J* = 7.2 Hz), 6.48 (br t, 4 H_{arom}, *J* = 7.2 Hz), 6.63 (br s, 4 H, NH), 7.10–7.20 (m, 60 H, C_6H_5).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.5 (ArCH_2Ar), 60.5 [$C(CH_2O)_3$], 68.7 [$C(CH_2O)_3$], 73.2 (OCH_2Ph), 74.6 (OCH_2CO), 122.6 (CH_{arom}), 127.3 (CH_{phenyl}), 127.4 (CH_{phenyl}), 128.1 (CH_{phenyl}), 128.4 (C_{arom}), 134.3 (CH_{arom}), 138.4 (C_{phenyl}), 155.8 (C_{arom}), 169.3 (C=O).

ESI-MS: *m*/*z* [ion, % relative intensity]= 2172.9 [$(M + Na)^+$, 100], 1094.7 [$(M + H + K)^{2+}$, 44].

Anal. Calcd for $C_{136}H_{140}N_4O_{20}$ (2150.6): C, 75.96; H, 6.56; N, 2.61. Found: C, 76.01; H, 6.74; N, 2.48.

25,26,27,28-Tetrakis{[tris(allyloxymethyl)methylamino]-carbonylmethoxy}calix[4]arene (8b)

Prepared from **2** (100 mg, 0.15 mmol) and isolated in 75% yield (General Procedure A) or 50% yield (General Procedure B) after flash chromatography (hexane–EtOAc, 6:4); colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.21 (d, 4 H, *J* = 14.1 Hz, H_{eq} of ArCH_2Ar), 3.78 [s, 24 H, $C(CH_2O)_3$], 3.94 (dt, 24 H, *J* = 1.3, 5.4 Hz, OCH_2CH=CH_2), 4.44 (s, 8 H, OCH_2CO), 4.53 (d, 4 H, *J* = 14.1 Hz, H_{ax} of ArCH_2Ar), 5.10 (ddt, 12 H, *J* = 1.3, 1.6, 10.3 Hz, $OCH_2CH=CH_2$), 5.20 (ddt, 12 H, *J* = 1.3, 1.6, 17.2 Hz, $OCH_2CH=CH_2$), 5.83 (ddt, 12 H, *J* = 5.4, 10.3, 17.2 Hz, $OCH_2CH=CH_2$), 6.56 (br s, 12 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.5 (ArCH_2Ar), 60.4 [$C(CH_2O)_3$], 68.2 [$C(CH_2O)_3$], 72.2 (OCH_2CH=CH_2), 74.7 (OCH_2CO), 116.5 ($OCH_2CH=CH_2$), 122.7 (CH_{arom}), 128.5 (CH_{arom}), 134.5 (C_{arom}), 135.0 ($OCH_2CH=CH_2$), 155.9 (C_{arom}), 169.2 (C=O).

ESI-MS: *m*/*z* [ion, % relative intensity]= 1571.9 [$(M + Na)^+$, 61], 794.5 [$(M + H + K)^{2+}$, 100].

Anal. Calcd for $C_{88}H_{116}N_4O_{20}$ (1549.9): C, 68.20; H, 7.54; N, 3.62. Found: C, 68.12; H, 7.38; N, 3.57.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrakis{[tris(benzyloxymethyl)methylamino]carbonylmethoxy}calix[4]arene (10)

Prepared according to the General Procedure A, from **9**[16] (300 mg, 0.34 mmol); flash chromatography (hexane–EtOAc, 8:2); yield: 510 mg (63%); white solid; mp 92–93 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 [s, 36 H, $C(CH_3)_3$], 3.08 (d, 4 H, *J* = 13.1 Hz, H_{eq} of ArCH_2Ar), 3.83 [s, 24 H, $C(CH_2O)_3$], 4.37 (s, 24 H, OCH_2Ph), 4.56 (d, 4 H, *J* = 13.1 Hz, H_{ax} of ArCH_2Ar), 4.60 (s, 8 H, OCH_2CO), 6.67 (s, 8 H_{arom}), 6.74 (br s, 4 H, NH), 7.12–7.25 (m, 60 H, C_6H_5).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.4 [$C(CH_3)_3$], 32.2 (ArCH_2Ar), 33.8 [$C(CH_3)_3$], 60.4 [$C(CH_2O)_3$], 68.8 [$C(CH_2O)_3$], 73.2 (OCH_2Ph), 74.5 (OCH_2CO), 125.3 (CH_{arom}), 127.3 (CH_{phenyl}), 127.4 (CH_{phenyl}), 128.2 (CH_{phenyl}), 133.2 (C_{arom}), 138.5 (C_{phenyl}), 144.8 (C_{arom}), 152.9 (C_{arom}), 169.7 (C=O).

ESI-MS: *m*/*z* = 2396.4 [$(M + Na)^+$, 100%].

Anal. Calcd for $C_{152}H_{172}N_4O_{20}$ (2375.1): C, 76.87; H, 7.30; N, 2.36. Found: C, 76.79; H, 7.45; N, 2.24.

Tetrakis{[tris(hydroxymethyl)methylamino]carbonylmethoxy}calix[4]arene (3)

Prepared according to the General Procedure C or D from **8a** (800mg, 0.37 mmol); yield: quantitative; white solid; mp 120–125 °C.

The spectral data were identical with the product **3** obtained by the direct method (see above).

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrakis{[tris(hydroxymethyl)methylamino]carbonylmethoxy}calix[4]arene (11)

Prepared according to General Procedure D, from **10** (100 mg, 0.04 mmol); quantitative yield; white solid; mp 190–192 °C.

^{1}H NMR (300 MHz, CD_3OD): δ = 1.18 [s, 36 H, $C(CH_3)_3$], 3.42 (d, 4 H, *J* = 12.2 Hz, H_{eq} of ArCH_2Ar), 3.82 (s, 24 H, CH_2OH), 4.45 (d, 4 H, *J* = 12.2 Hz, H_{ax} of ArCH_2Ar), 4.56 (s, 8 H, OCH_2CO), 7.27 (br s, 8 H_{arom}).

^{13}C NMR (75 MHz, CD_3OD): δ = 31.3 (ArCH_2Ar), 31.7 [$C(CH_3)_3$], 35.2 [$C(CH_3)_3$], 62.7 (CH_2OH), 64.1 [$C(CH_2OH)_3$], 75.8 (OCH_2CO), 127.3 (CH_{arom}), 136.1 (C_{arom}), 149.5 (C_{arom}), 152.3 (C_{arom}), 172.3 (C=O).

ESI-MS: *m*/*z* (ion, % relative intensity] = 1315.9 [$(M + Na)^+$, 100], 1195.8 [$(M + Na - HNC(CH_2OH)_3)^+$, 25], 669.3 [$(M + 2\,Na)^{2+}$, 50], 666.5 [$(M + H + K)^{2+}$, 65].

Anal. Calcd for $C_{68}H_{100}N_4O_{20}$ (1293.6): C, 63.14; H, 7.79; N, 4.33. Found: C, 62.99; H, 7.62; N, 4.19.

25,27-Bis(*tert*-butyloxycarbonylmethoxy)-26,28-dipropoxycalix[4]arene (13); Typical Procedure

A mixture of dipropoxycalix[4]arene **12**[28] (800 mg, 1.57 mmol), NaH (502 mg, 12.56 mmol, 60% oil dispersion) and *tert*-butyl bromoacetate (3.48 mL, 23.55 mmol) in anhyd DMF (20 mL) was stirred at r.t. until the conversion was complete (TLC monitoring: hexane–EtOAc, 7:3 or 1:1). The solvent was removed at reduced pressure and the residue was partitioned between CH_2Cl_2 (25 mL) and 5% aq HCl (25 mL). The organic layer was washed with H_2O, dried ($MgSO_4$) and evaporated to dryness. The crude product was

purified by precipitation with cold MeOH; yield: 1.07 g (92%); white solid; mp 168–170 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (t, 6 H, *J* = 7.2 Hz, $OCH_2CH_2CH_3$), 1.42 [s, 18 H, $C(CH_3)_3$], 1.92 (sext, 4 H, *J* = 7.2 Hz, $OCH_2CH_2CH_3$), 3.20 (d, 4 H, *J* = 13.6 Hz, H_{eq} of $ArCH_2Ar$), 3.81 (t, 4 H, *J* = 7.2 Hz, $OCH_2CH_2CH_3$), 4.68 (d, 4 H, *J* = 13.6 Hz, H_{ax} of $ArCH_2Ar$), 4.71 (s, 4 H, OCH_2CO), 6.35 (t, 2 H_{arom}, *J* = 7.6 Hz), 6.37 (d, 4 H_{arom}, *J* = 7.6 Hz), 6.76 (t, 2 H_{arom}, *J* = 7.4 Hz), 6.87 (d, 4 H_{arom}, *J* = 7.4 Hz).

^{13}C NMR (25 MHz, $CDCl_3$): δ = 10.7 ($OCH_2CH_2CH_3$), 23.3 ($OCH_2CH_2CH_3$), 28.0 [$C(CH_3)_3$], 31.5 ($ArCH_2Ar$), 71.1 (OCH_2CO), 76.9 ($OCH_2CH_2CH_3$), 80.8 [$C(CH_3)_3$], 122.2, 122.3 (CH_{arom}), 127.8, 128.9 (CH_{arom}), 133.9, 135.8 (C_{arom}), 155.9, 156.1 (C_{arom}), 169.0 (C=O).

ESI-MS: *m*/*z* = 759.2 [$(M + Na)^+$, 100%].

Anal. Calcd for $C_{46}H_{56}O_8$ (736.9): C, 74.97; H, 7.66. Found: C, 75.02; H, 7.78.

25,27-Bis(carboxymethoxy)-26,28-dipropoxycalix[4]arene (14); Typical Procedure

A mixture of di-*tert*-butyl ester **13** (900 mg, 1.22 mmol) and TFA (10 mL) was stirred for 3 h at r.t. The solvent was removed at reduced pressure to give a residue which upon trituration with 5% aq HCl afforded a solid that was filtered, washed with water and dried under vacuum, to give 760 mg (quantitative yield) of pure **14**; white solid; mp 221–223 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, 6 H, *J* = 7.5 Hz, $OCH_2CH_2CH_3$), 1.91 (sext, 4 H, *J* = 7.5 Hz, $OCH_2CH_2CH_3$), 3.32 (d, 4 H, *J* = 13.4 Hz, H_{eq} of $ArCH_2Ar$), 3.84 (t, 4 H, *J* = 7.8 Hz, $OCH_2CH_2CH_3$), 4.34 (d, 4 H, *J* = 13.4 Hz, H_{ax} of $ArCH_2Ar$), 4.69 (s, 4 H, OCH_2CO), 6.38 (m, 6 H_{arom}), 7.03 (t, 2 H_{arom}, *J* = 7.4 Hz), 7.18 (d, 4 H_{arom}, *J* = 7.4 Hz).

^{13}C NMR (25 MHz, $CDCl_3$): δ = 10.0 ($OCH_2CH_2CH_3$), 22.5 ($OCH_2CH_2CH_3$), 30.8 ($ArCH_2Ar$), 71.7 (OCH_2CO), 78.9 ($OCH_2CH_2CH_3$), 123.4, 124.2 (CH_{arom}), 128.2, 129.4 (CH_{arom}), 132.6, 135.3 (C_{arom}), 152.5, 156.1 (C_{arom}), 171.4 (C=O).

ESI-MS: *m*/*z* = 645.1 [$(M + Na - 2H)^-$, 100%].

Anal. Calcd for $C_{38}H_{40}O_8$ (624.7): C, 73.06; H, 6.45. Found: C, 72.90; H, 6.55.

25,27-Bis{[tris(benzyloxymethyl)methylamino]-carbonylmethoxy}-26,28-dipropoxycalix[4]arene (15)

Prepared according to the General Procedure A, from **14** (200 mg, 0.32 mmol); flash chromatography (hexane–EtOAc, 7:3); yield: 335 mg (77%); colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.76 (t, 6 H, *J* = 7.4 Hz, $OCH_2CH_2CH_3$), 1.74 (m, 4 H, $OCH_2CH_2CH_3$), 3.23 (d, 4 H, *J* = 13.7 Hz, H_{eq} of $ArCH_2Ar$), 3.88 (t, 4 H, *J* = 7.7 Hz, $OCH_2CH_2CH_3$), 3.92 [s, 12 H, $C(CH_2O)_3$], 4.28 (s, 4 H, OCH_2CO), 4.36 (d, 4 H, *J* = 13.7 Hz, H_{ax} of $ArCH_2Ar$), 4.50 (s, 12 H, OCH_2Ph), 6.02 (d, 4 H_{arom}, *J* = 7.5 Hz), 6.25 (t, 2 H_{arom}, *J* = 7.5 Hz), 6.83 (br s, 2 H, NH), 6.93 (t, 2 H_{arom}, *J* = 7.4 Hz), 7.05 (d, 4 H_{arom}, *J* = 7.4 Hz), 7.24 (s, 30 H, C_6H_5).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.2 ($OCH_2CH_2CH_3$), 23.2 ($OCH_2CH_2CH_3$), 31.3 ($ArCH_2Ar$), 60.4 [$C(CH_2O)_3$], 68.4 [$C(CH_2O)_3$], 73.3 (OCH_2Ph), 74.4 (OCH_2CO), 75.8 ($OCH_2CH_2CH_3$), 121.9, 122.8 (CH_{arom}), 127.3 (CH_{phenyl}), 127.4 (CH_{phenyl}), 127.7 (CH_{arom}), 128.2 (CH_{phenyl}), 129.3 (CH_{arom}), 132.0, 136.4 (C_{arom}), 138.1 (C_{phenyl}), 154.7, 157.5 (C_{arom}), 168.9 (C=O).

CI-MS: *m*/*z* = 1371.8 [$(M + H)^+$, 100%].

Anal. Calcd for $C_{88}H_{94}N_2O_{12}$ (1371.7): C, 77.06; H, 6.91; N, 2.04. Found: C, 77.18; H, 7.03; N, 1.95.

25,27-Bis{[tris(hydroxymethyl)methylamino]-carbonylmethoxy}-26,28-dipropoxycalix[4]arene (16)

Prepared from **15** (129 mg, 0.09 mmol) according to the General Procedure C or D; quantitative yield; white solid; mp 101–103 °C.

^{1}H NMR (300 MHz, CD_3OD): δ = 0.91 (t, 6 H, *J* = 7.5 Hz, $OCH_2CH_2CH_3$), 1.85 (m, 4 H, $OCH_2CH_2CH_3$), 3.19 (d, 4 H, *J* = 13.6 Hz, H_{eq} of $ArCH_2Ar$), 3.81 (s, 12 H, CH_2OH), 4.09 (t, 4 H, *J* = 7.7 Hz, $OCH_2CH_2CH_3$), 4.24 (s, 4 H, OCH_2CO), 4.44 (d, 4 H, *J* = 13.6 Hz, H_{ax} of $ArCH_2Ar$), 6.08 (d, 4 H_{arom}, *J* = 7.6 Hz), 6.25 (t, 2 H_{arom}, *J* = 7.5 Hz), 6.85 (t, 2 H_{arom}, *J* = 7.4 Hz), 7.01 (d, 4 H_{arom}, *J* = 7.4 Hz).

^{13}C NMR (75 MHz, CD_3OD): δ = 10.9 ($OCH_2CH_2CH_3$), 24.1 ($OCH_2CH_2CH_3$), 32.0 ($ArCH_2Ar$), 62.5 (CH_2OH), 63.5 [$C(CH_2OH)_3$], 74.9 (OCH_2CO), 77.1 ($OCH_2CH_2CH_3$), 123.0, 124.1 (CH_{arom}), 129.0, 130.2 (CH_{arom}), 134.2, 137.9 (C_{arom}), 155.4, 158.4 (C_{arom}), 172.0 (C=O).

ESI-MS: *m*/*z* [ion, % relative intensity] = 853.7 [$(M + Na)^+$, 100], 733.6 {$[M + Na - HNC(CH_2OH)_3]^+$, 30}.

Anal. Calcd for $C_{46}H_{58}N_2O_{12}$ (831.0): C, 66.49; H, 7.14; N, 3.37. Found: C, 66.31; H, 7.25; N, 3.28.

1,3-alternate-25,26,27-Tribenzoyloxy-28-propoxycalix[4]arene (18)

A mixture of tribenzoyloxy derivative **17**[29] (625 mg, 0.85 mmol), NaH (67.6 mg, 1.69 mmol, 60% oil dispersion) and propyl iodide (0.18 mL, 1.69 mmol) in anhyd DMF (10 mL) was stirred for 1 h at r.t. and poured into cold 5% aq HCl. The yellowish solid precipitate obtained was filtered, washed with H_2O and dried under vacuum to give **18** (605 mg, 91%) as a white solid; mp >300 °C (dec.).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10 (t, 3 H, *J* = 7.5 Hz, $OCH_2CH_2CH_3$), 1.92 (sext, 2 H, *J* = 7.5 Hz, $OCH_2CH_2CH_3$), 3.57 (d, 2 H, *J* = 14.5 Hz, H_{eq} of $ArCH_2Ar$), 3.60 (s, 4 H, $ArCH_2Ar$), 3.78 (t, 2 H, *J* = 7.5 Hz, $OCH_2CH_2CH_3$), 3.83 (d, 2 H, *J* = 14.5 Hz, H_{ax} of $ArCH_2Ar$), 6.42 (t, 1 H_{arom}, *J* = 7.4 Hz), 6.53–6.70 (m, 9 H_{arom}), 7.21 (dd, 2 H_{arom}, *J* = 1.4, 7.1 Hz), 7.34 (t, 2 H_{arom}, *J* = 7.2 Hz), 7.42 (d, 2 H_{arom}, *J* = 7.2 Hz), 7.55 (t, 3 H_{arom}, *J* = 7.7 Hz), 7.63 (t, 2 H_{arom}, *J* = 7.2 Hz), 7.75 (t, 2 H_{arom}, *J* = 7.4 Hz), 7.83 (d, 4 H_{arom}, *J* = 7.2 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.4 ($OCH_2CH_2CH_3$), 23.6 ($OCH_2CH_2CH_3$), 37.2, 37.4 ($ArCH_2Ar$), 73.0 ($OCH_2CH_2CH_3$), 122.1, 124.7, 125.0, 127.6, 128.1, 128.3, 128.9, 130.4, 130.5, 130.6, 131.3, 131.5, 132.0, 133.0, 133.4, 133.6, 133.9 (C_{arom}, CH_{arom}), 147.9 (C_{arom}), 157.0 (C_{arom}), 164.4 (C=O).

CI-MS: *m*/*z* = 778.3 [M^+, 100%].

Anal. Calcd for $C_{52}H_{42}O_7$ (778.9): C, 80.19; H, 5.43. Found: C, 80.27; H, 5.51.

25,26,27-Trishydroxy-28-propoxycalix[4]arene (19)

A solution of KOH (221 mg, 3.94 mmol) in H_2O (2 mL) was added to a suspension of **18** (550 mg, 0.76 mmol) in EtOH (20 mL) and the mixture was refluxed overnight. The solution was concentrated to dryness and the residue was partitioned between CH_2Cl_2 and 5% aq HCl. The organic phase was washed with 10% aq $NaHCO_3$ solution and H_2O, dried ($MgSO_4$) and concentrated at reduced pressure. The residue was purified by precipitation with cold Et_2O, affording the title compound (314 mg, 95%) as a white solid; mp 260–262 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, 3 H, *J* = 7.5 Hz, $OCH_2CH_2CH_3$), 2.19 (sext, 2 H, *J* = 7.2 Hz, $OCH_2CH_2CH_3$), 3.45 (d, 4 H, *J* = 13.5 Hz, H_{eq} of $ArCH_2Ar$), 4.12 (t, 2 H, *J* = 6.9 Hz, $OCH_2CH_2CH_3$), 4.27 (d, 2 H, *J* = 13.7 Hz, H_{ax} of $ArCH_2Ar$), 4.37 (d, 2 H, *J* = 13.0 Hz, H_{ax} of $ArCH_2Ar$), 6.66 (t, 2 H_{arom}, *J* = 7.5 Hz), 6.67 (t, 1 H_{arom}, *J* = 7.5 Hz), 6.86 (t, 1 H_{arom}, *J* = 7.5 Hz), 6.99 (d, 2 H_{arom}, *J* = 7.5 Hz), 7.01 (d, 2 H_{arom}, *J* = 7.5 Hz), 7.05 (d, 2 H_{arom},

J = 7.5 Hz), 7.07 (d, 2 H_{arom}, *J* = 7.5 Hz), 9.40 (s, 2 H, OH), 9.70 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.7 ($OCH_2CH_2CH_3$), 23.3 ($OCH_2CH_2CH_3$), 31.5, 31.9 ($ArCH_2Ar$), 79.0 ($OCH_2CH_2CH_3$), 120.9, 121.9 (CH_{arom}), 126.1, 128.4, 128.7, 128.8, 129.3, 134.2 (C_{arom}, CH_{arom}), 150.8 (C_{arom}), 151.4 (C_{arom}).

CI-MS: *m*/*z* [ion, relative intensity] = 466.1 [M^+, 100], 423.1 [$(M - Pr)^+$, 55].

Anal. Calcd for $C_{31}H_{30}O_4$ (466.6): C, 79.80; H, 6.48. Found: C, 79.82; H, 6.32.

25,26,27-Tris(*tert*-butyloxycarbonylmethoxy)-28-propoxycalix-[4]arene (20)

Synthesized from **19** (216 mg, 0.46 mmol) according to the procedure described for **13**; yield: 193 mg (52%); white solid; mp 230 °C (dec.).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, 3 H, *J* = 7.4 Hz, $OCH_2CH_2CH_3$), 1.44 [s, 18 H, $C(CH_3)_3$], 1.47 [s, 9 H, $C(CH_3)_3$], 1.91 (m, 2 H, $OCH_2CH_2CH_3$), 3.18 (d, 2 H, *J* = 13.4 Hz, H_{eq} of $ArCH_2Ar$), 3.22 (d, 2 H, *J* = 13.4 Hz, H_{eq} of $ArCH_2Ar$), 3.86 (t, 2 H, *J* = 7.3 Hz, $OCH_2CH_2CH_3$), 4.59 (s, 2 H, OCH_2CO), 4.62 (s, 4 H, OCH_2CO), 4.69 (d, 2 H, *J* = 13.5 Hz, H_{ax} of $ArCH_2Ar$), 4.81 (d, 2 H, *J* = 13.5 Hz, H_{ax} of $ArCH_2Ar$), 6.52–6.68 (m, 12 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.6 ($OCH_2CH_2CH_3$), 23.2 ($OCH_2CH_2CH_3$), 28.1 [$C(CH_3)_3$], 31.3, 31.6 ($ArCH_2Ar$), 71.7, 71.9 (OCH_2CO), 77.2 ($OCH_2CH_2CH_3$), 80.9 [$C(CH_3)_3$], 122.0, 122.4, 122.5 (CH_{arom}), 128.1, 128.3, 128.4 (CH_{arom}), 134.4, 134.8, 135.2 (C_{arom}), 155.9, 156.5 (C_{arom}), 169.1, 169.2 (C=O).

CI-MS: *m*/*z* [ion, % relative intensity] = 809.4 [$(M + H)^+$, 15], 640.4 {$M + H - 3$ [$(CH_3)_2C{=}CH_2]^+$, 100}.

Anal. Calcd for $C_{40}H_{60}O_{10}$ (809.0): C, 68.55; H, 8.63. Found: C, 68.69; H, 8.81.

25,26,27-Tris(hydroxycarbonylmethoxy)-28-propoxycalix-[4]arene (21)

Synthesized from **20** according to the procedure described for **14**; quantitative yield; white solid; mp 162–164 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.93 (t, 3 H, *J* = 7.4 Hz, $OCH_2CH_2CH_3$), 1.87 (sext, 2 H, *J* = 7.4 Hz, $OCH_2CH_2CH_3$), 3.23 (d, 4 H, *J* = 13.0 Hz, H_{eq} of $ArCH_2Ar$), 3.78 (t, 2 H, *J* = 7.4 Hz, $OCH_2CH_2CH_3$), 4.56 (d, 2 H, *J* = 13.4 Hz, H_{ax} of $ArCH_2Ar$), 4.64 (s, 6 H, OCH_2CO), 4.85 (d, 2 H, *J* = 13.0 Hz, H_{ax} of $ArCH_2Ar$), 6.50–6.59 (m, 4 H_{arom}), 6.70 (d, 4 H_{arom}, *J* = 7.2 Hz), 6.88 (d, 4 H_{arom}, *J* = 7.6 Hz), 10.9 (br s, 3 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.3 ($OCH_2CH_2CH_3$), 23.0 ($OCH_2CH_2CH_3$), 30.3, 30.8, 30.9 ($ArCH_2Ar$), 72.0, 72.2 (OCH_2CO), 78.6 ($OCH_2CH_2CH_3$), 123.2, 124.1, 124.2 (CH_{arom}), 128.3, 128.6, 129.1, 129.4 (CH_{arom}), 132.8, 133.4, 135.3, 135.9 (C_{arom}), 152.5, 153.4, 156.2 (C_{arom}), 170.5, 174.8 (C=O).

ESI-MS: *m*/*z* = 663.5 [$(M + Na)^+$, 100%].

Anal. Calcd for $C_{37}H_{36}O_{10}$ (640.7): C, 69.36; H, 5.66. Found: C, 69.24; H, 5.71.

25,26,27-Tris{[tris(benzyloxymethyl)methylamino]-carbonyl-methoxy}-28-propoxycalix[4]arene (22)

Prepared according to the General Procedure A, from **21** (130 mg, 0.20 mmol); flash chromatography (hexane–EtOAc, 8:2); yield: 192 mg (54%); colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.80 (t, 3 H, *J* = 7.3 Hz, $OCH_2CH_2CH_3$), 1.76 (m, 2 H, $OCH_2CH_2CH_3$), 3.06 (d, 2 H, *J* = 13.8 Hz, H_{eq} of $ArCH_2Ar$), 3.20 (d, 2 H, *J* = 13.8 Hz, H_{eq} of $ArCH_2Ar$), 3.78 [s, 6 H, $C(CH_2O)_3$], 3.92 [br s, 14 H, $C(CH_2O)_3$, $OCH_2CH_2CH_3$], 4.25 (d, 2 H, *J* = 14.5 Hz, H_{ax} of $ArCH_2Ar$), 4.37 (s, 6 H, OCH_2Ph), 4.41 (m, 4 H, OCH_2CO), 4.48 (s, 12 H, OCH_2Ph), 4.61 (s, 2 H, OCH_2CO), 6.15 (d, 2 H_{arom}, *J* = 7.4 Hz), 6.20 (d, 2 H_{arom}, *J* = 7.4 Hz), 6.31 (br s, 1 H, NH), 6.35 (t, 2 H_{arom}, *J* = 7.5 Hz), 6.75 (br s, 2 H, NH), 6.81–6.92 (m, 6 H_{arom}), 7.17–7.29 (m, 45 H, C_6H_5).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.4 ($OCH_2CH_2CH_3$), 23.0 ($OCH_2CH_2CH_3$), 31.2, 31.6 ($ArCH_2Ar$), 60.3, 60.4 [$C(CH_2O)_3$], 68.6, 68.8 [$C(CH_2O)_3$], 73.1, 73.2 (OCH_2Ph), 73.9, 74.4 (OCH_2CO), 76.2 ($OCH_2CH_2CH_3$), 122.0, 122.6, 122.8 (CH_{arom}), 127.3, 127.4 (CH_{phenyl}), 127.9, 128.0 (CH_{arom}), 128.2 (CH_{phenyl}), 128.9, 129.2 (CH_{arom}), 132.8, 133.0, 135.7, 136.0 (C_{arom}), 138.3 (C_{phenyl}), 154.7, 155.3, 157.1 (C_{arom}), 168.9, 169.0 (C=O).

ESI-MS: *m*/*z* = 1783.4 [$(M + Na)^+$, 100%].

Anal. Calcd for $C_{112}H_{117}N_3O_{16}$ (1761.2): C, 76.38; H, 6.70; N, 2.39. Found: C, 76.32; H, 6.63; N, 2.29.

25,26,27-Tris{[tris(hydroxymethyl)methylamino]-carbonyl-methoxy}-28-propoxycalix[4]arene (23)

Prepared according to General Procedure D, from **22** (120 mg, 0.12 mmol); quantitative yield; white solid; mp 132–134 °C.

^{1}H NMR (300 MHz, CD_3OD): δ = 0.92 (t, 3 H, *J* = 7.3 Hz, $OCH_2CH_2CH_3$), 1.87 (m, 2 H, $OCH_2CH_2CH_3$), 3.49 (d, 2 H, *J* = 12.2 Hz, H_{eq} of $ArCH_2Ar$), 3.51 (d, 2 H, *J* = 12.2 Hz, H_{eq} of $ArCH_2Ar$), 3.84 (s, 6 H, CH_2OH), 3.91 (d, 6 H, *J* = 11.4 Hz, CH_2OH), 3.98 (d, 6 H, *J* = 11.4 Hz, CH_2OH), 4.15 (m, 2 H, $OCH_2CH_2CH_3$), 4.41 (d, 2 H, *J* = 14.4 Hz, OCH_2CO), 4.49 (d, 2 H, *J* = 12.0 Hz, OCH_2CO), 4.61 (s, 2 H, OCH_2CO), 4.79 (d, 2 H, *J* = 14.9 Hz, H_{ax} of $ArCH_2Ar$), 6.87–6.94 (m, 4 H_{arom}), 7.24–7.28 (m, 8 H_{arom}).

^{13}C NMR (75 MHz, CD_3OD): δ = 9.8 ($OCH_2CH_2CH_3$), 22.8 ($OCH_2CH_2CH_3$), 30.7, 30.8 ($ArCH_2Ar$), 62.6, 62.8 (CH_2OH), 64.0, 64.2 [$C(CH_2OH)_3$], 75.2, 76.0 (OCH_2CO), 80.1 ($OCH_2CH_2CH_3$), 126.1, 126.9, 127.1 (CH_{arom}), 130.1, 130.3, 130.5, 130.6 (CH_{arom}), 136.7, 136.8, 137.0 (C_{arom}), 153.2, 153.7, 154.4 (C_{arom}), 171.5, 172.0 (C=O).

ESI-MS: *m*/*z* [ion, % relative intensity] = 972.7 [$(M + Na)^+$, 100], 852.7 {$[M + Na - HNC(CH_2OH)_3]^+$, 25}, 497.7 [$(M + 2Na)^{2+}$, 55], 494.6 [$(M + H + K)^{2+}$, 70].

Anal. Calcd for $C_{49}H_{63}N_3O_{16}$ (950.1): C, 61.95; H, 6.68; N, 4.42. Found: C, 61.87; H, 6.54; N, 4.39.

Acknowledgement

This work was partially supported by CNR (Programma M.U.R.S.T. - Chimica Legge 95/95) “Agenti di contrasto, di shift e sonde luminescenti”, M.U.R.S.T. (“Supramolecular Devices” Project) and EU (TMR grant FMRX-CT98-0231). We thank C.I.M. (Centro Interdipartimentale Misure) dell’Università di Parma for the NMR and Mass facilities.

References

(1) (a) Gutsche, C. D. *Calixarenes Revisited*, In *Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, **1998**. (b) *Calixarenes in Action*; Mandolini, L.; Ungaro, R., Eds.; Imperial College Press: Singapore, **2000**.

(2) Casnati, A.; Ungaro, R. In *Calixarenes in Action*; Mandolini, L.; Ungaro, R., Eds.; Imperial College Press: Singapore, **2000**, 62.

(3) Wieser, C.; Dieleman, C. B.; Matt, D. *Coord. Chem. Rev.* **1997**, *165*, 93.

(4) Cacciapaglia, R.; Mandolini, L. In *Calixarenes in Action*; Mandolini, L.; Ungaro, R., Eds.; Imperial College Press: Singapore, **2000**, 241.
(5) Casnati, A.; Sciotto, D.; Arena, G. In *Calixarenes 2001*; Asfari, Z.; Böhmer, V.; Harrowfield, J.; Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, **2001**, 440.
(6) (a) Shinkai, S.; Tsubaki, T.; Sone, T.; Manabe, O. *Tetrahedron Lett.* **1984**, *25*, 5315. (b) Shinkai, S.; Araki, K.; Tsubaki, T.; Arimura, T.; Manabe, O. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2297. (c) Scharff, J. P.; Mahjoubi, M. *New J. Chem.* **1991**, *15*, 883. (d) Casnati, A.; Ting, Y.; Berti, D.; Fabbi, M.; Pochini, A.; Ungaro, R.; Sciotto, D.; Lombardo, G. G. *Tetrahedron* **1993**, *49*, 9815.
(7) (a) Almi, M.; Arduini, A.; Casnati, A.; Pochini, A.; Ungaro, R. *Tetrahedron* **1989**, *45*, 2177. (b) Arimura, T.; Nagasaki, T.; Shinkai, S.; Matsuda, T. *J. Org. Chem.* **1989**, *54*, 3766.
(8) (a) Shinkai, S.; Araki, K.; Grootenhuis, P. D. J.; Reinhoudt, D. N. *J. Chem. Soc., Perkin Trans. 2* **1991**, 188. (b) Newkome, G. R.; Hu, Y.; Saunders, M. J.; Fronczek, F. R. *Tetrahedron Lett.* **1991**, *32*, 1133. (c) Grote Gansey, M. H. B.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron Lett.* **1994**, *35*, 7127. (d) Grote Gansey, M. H. B.; Steemers, F. J.; Verboom, W.; Reinhoudt, D. N. *Synthesis* **1997**, 643.
(9) Pochini, A.; Arduini, A. In *Calixarenes in Action*; Mandolini, L.; Ungaro, R., Eds.; Imperial College Press: Singapore, **2000**, 37.
(10) Mandolini, L.; Dalla Cort, A. In *Calixarenes in Action*; Mandolini, L.; Ungaro, R., Eds.; Imperial College Press: Singapore, **2000**, 85.
(11) Beer, P. D.; Cooper, J. B. In *Calixarenes in Action*; Mandolini, L.; Ungaro, R., Eds.; Imperial College Press: Singapore, **2000**, 111.
(12) (a) Pelizzi, N.; Casnati, A.; Ungaro, R. *Chem. Commun.* **1998**, 2607. (b) Casnati, A.; Pelizzi, N.; Pirondini, L.; Ungaro, R. *Supramol. Chem.* **2000**, *12*, 53.
(13) (a) Sansone, F.; Barboso, S.; Casnati, A.; Fabbi, M.; Pochini, A.; Ugozzoli, F.; Ungaro, R. *Eur. J. Org. Chem.* **1998**, 897. (b) Arena, G.; Contino, A.; Gulino, F. G.; Magrì, A.; Sansone, F.; Sciotto, D.; Ungaro, R. *Tetrahedron Lett.* **1999**, *40*, 1597.
(14) (a) Casnati, A.; Di Modugno, E.; Fabbi, M.; Pelizzi, N.; Pochini, A.; Sansone, F.; Tarzia, G.; Ungaro, R. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2699. (b) Frish, L.; Sansone, F.; Casnati, A.; Ungaro, R.; Cohen, Y. *J. Org. Chem.* **2000**, *65*, 5026.
(15) Dondoni, A.; Marra, A.; Scherrmann, M.-C.; Casnati, A.; Sansone, F.; Ungaro, R. *Chem. Eur. J.* **1997**, *3*, 1774.
(16) Arduini, A.; Pochini, A.; Reverberi, S.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1984**, 981.
(17) (a) Shinkai, S.; Kawabata, H.; Arimura, T.; Matsuda, T.; Satoh, H.; Manabe, O. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1073. (b) Shinkai, S.; Arimura, T.; Araki, K.; Kawabata, H.; Satoh, H.; Tsubaki, T.; Manabe, O.; Sunamoto, J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2039.
(18) (a) Shinkai, S.; Shirahama, Y.; Tsubaki, T.; Manabe, O. *J. Am. Chem. Soc.* **1989**, *111*, 5477. (b) Shinkai, S.; Shirahama, Y.; Tsubaki, T.; Manabe, O. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1859. (c) Arimori, S.; Nagasaki, T.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 2* **1995**, 679.
(19) Recently, Rebek and co-workers have reported on the synthesis of a resorcarene-based cavitand bearing polyhydroxylated functions on the alkylidene bridge: Haino, T.; Rudkevich, D. M.; Rebek, J. Jr. *J. Am. Chem. Soc.* **1999**, *121*, 11253.
(20) McKervey, M. A.; Seward, E. M.; Ferguson, G.; Ruhl, B.; Harris, S. J. *J. Chem. Soc., Chem. Commun.* **1985**, 388.
(21) Issberner, J.; Vögtle, F.; De Cola, L.; Balzani, V. *Chem. Eur. J.* **1997**, *3*, 706.
(22) We slightly modified the procedure reported by Seto, C. T.; Mathias, J. P.; Whitesides, G. M. *J. Am. Chem. Soc.* **1993**, *115*, 1321.
(23) Dourtoglou, V.; Gross, B. *Synthesis* **1984**, 572.
(24) Hanessian, S.; Liak, T. J.; Vanasse, B. *Synthesis* **1981**, 396.
(25) Greene, T. W. *Protective Groups in Organic Synthesis*; Wiley: New York, **1981**, 27.
(26) Anelli, P. L.; Brocchetta, M.; Canipari, S.; Losi, P.; Manfredi, G.; Tomba, C. *Gazz. Chim. Ital.* **1997**, *127*, 135.
(27) Messerschmidt, C.; Svenson, S.; Stocker, W.; Fuhrhop, J.-H. *Langmuir* **2000**, *16*, 7445.
(28) Arduini, A.; Fabbi, M.; Mantovani, M.; Mirone, L.; Pochini, A.; Secchi, A.; Ungaro, R. *J. Org. Chem.* **1995**, *60*, 1454.
(29) Gutsche, C. D.; Lin, L.-G. *Tetrahedron* **1986**, *42*, 1633.