Novel Upper Rim Functionalizations of Calix[4]arenes using the Tscherniac-Einhorn Amidomethylation Reaction

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Dedicated to Prof. Dr. F. Vögtle on the Occasion of his 60th Birthday

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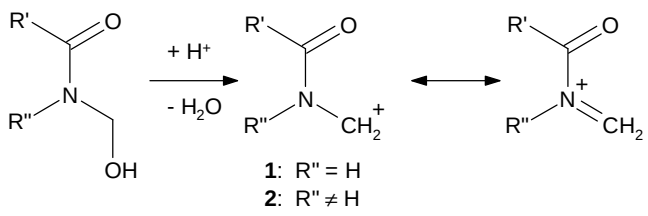
Abstract. A variety of novel upper rim functionalized calix[4]arenes have been synthesized, using the Tscherniac-Einhorn amidomethylation reaction. Partially or fully alkylated calix [4]arenes bearing propyl or ethoxyethyl substituents could be easily condensed with various *N*-methylol-amides and -imides under mild conditions. The resulting methylacetamido- (**4a**, **4b**, **7a**), methylchloroacetamido (**4c**, **4d**, **7b**, **7c**, **9** methylphthalimido (**4e**, **4f**, **4h**) and methylchloroacetamido methylphthalimido functionalized calix[4]arenes (**5**) were obtained in yields varying from 30 till 97%. The amidomethylation reactions were proven to be independent of the conformation of the calix[4]arene.

Calix[4]arenes are a well established building block in supramolecular chemistry [1], because they can be easily functionalized both at the phenolic OH groups (lower rim) or after (partial) removal of *tert*-butyl group at the *para* positions of the phenol rings (upper rim). The functionalization of the upper rim has been extensively studied, resulting in a wide range of methods for the introduction of a diversity of functional groups like allyl [2, 3], keto [4, 5], cyano [4], formyl [3, 6], nitro [7], *iso*(thio)cyanate [8], amino [9], carboxylic ester [9] or perfluorinated alcohol groups [10]. However, other functional groups like the aminomethyl moiety [11] or the more complex acetamido and chloroacetamido moieties can only be introduced *via* multi-step pathways, in often low yields.

The Tscherniac-Einhorn amidomethylation reaction [12], the condensation of *N*-methylol-amides and -imides with aromatic compounds under acidic conditions, has been used in different areas of organic chemistry [13–15] as a valuable alternative to the Mannich reaction. In general, the intermediate *N*-acylmethyleneimmonium ions are more electrophilic in the amidomethylation process than the aminomethylating agents used in the Mannich reaction. As a consequence also aromatics less reactive than phenol undergo amidomethylation [15a,c]. Whereas the Mannich reaction appears to occur with greater facility with the fully hydroxylated calixarenes [16], in this paper we demonstrate that the Tscherniac-Einhorn amidomethylation can easily be performed on partially and even fully alkylated calix[4]arenes. Furthermore, functionalities which are inaccessible using the Mannich reaction, can be introduced. The Tscherniac-Einhorn amidomethylation reaction allows the easy functionalization of calix[4]arenes with methylacetamido, methylchloroacetamido and methylphthalimido moieties or combinations thereof.

Results and Discussion

The methyleneimmonium ions **1** and **2**, formed from the corresponding amidoalkylation reagents in strong acids, are so reactive that they can react with a large variety of aromatics [15a,c]. The strong acid of choice for the reactions on the calix[4]arenes turned out to be TFA, and all reactions were carried out in 1:1 mixtures of TFA and chloroform [17].



Scheme 1 Formation and stabilization of the *N*-acylmethyleneimmonium ion **1** and methyleneimmonium ion **2**.

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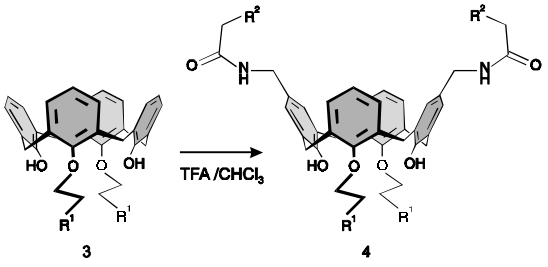
Tscherniac-Einhorn amidomethylation by reaction of one equivalent of the 1,3-dipropoxy- **3a** or bis(1-ethoxyethoxy)calix[4]arene **3b** with six equivalents of the commercially available *N*-(hydroxymethyl)acetamide at room temperature gave **4a** and **4b**, in yields of 85% and 95%, respectively. Mono-, tri- or tetrasubstituted products could not be detected [18]. In the ^{1}H NMR spectrum of **4a** the doublet at δ = 4.15 ppm (ArC$\underline{H}_2$NH) and the singlet at δ = 1.67 ppm (C(O)CH_3), together with the AB quartet that is characteristic for a symmetrically substituted calix[4]arene, clearly proved its formation (values for **4b**: δ = 4.11 and 1.42 ppm, respectively).

Introduction of the functional α-chloroacetamido substituents is also possible, using the commercially available *N*-(hydroxymethyl)-α-chloroacetamide. Both **4c** and **4d** were obtained in ≥95% yields. In the ^{1}H NMR spectrum, the ArC$\underline{H}_2$NH doublet at δ = 4.31 ppm **4c**, δ = 4.30 ppm **4d** and the C$\underline{H}_2$Cl singlet at δ = 4.04 ppm **4c**, δ = 3.89 ppm **4d** revealed the presence of the (2-chloroacetamido)methyl moieties. The resulting chloro substituent can be used for further functional group transformations [19]. These series of reactions prove that this type of reaction is not limited to either propoxy- or ethoxyethoxycalix[4]arenes, as is the case for some other reactions [20, 21].



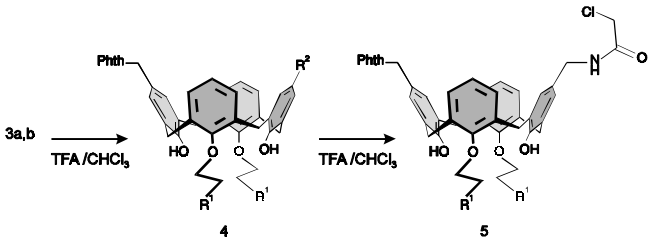
a $R^1 = CH_3$
b $R^1 = OCH_2CH_3$

a $R^1 = CH_3$, R^2 = H
b $R^1 = OCH_2CH_3$, R^2 = H
c $R^1 = CH_3$, R^2 = Cl
d $R^1 = OCH_2CH_3$, R^3 = Cl

Scheme 2 Synthesis of mono- and bis[(acetamido)methyl]- and -[(2-chloroacetamido)methyl]calix[4]arenes **4a**–**d**, starting from calix[4]arenes 3**a**–**b**.

N-(Hydroxymethyl)phthalimide as the amidomethylation reagent requires elevated temperatures, due to the lower electrophilic reactivity of the methyleneimmonium ion **2** [15b]. Reaction of calix[4]arene **3a** with 12 equivalents of the commercially available *N*-(hydroxymethyl)phthalimide at reflux temperature gave 47% of the monosubstituted **4e**, 17% of the disubstituted **4f**, and 25% of the calix[4]arene starting material **3a**. The double AB quartet for the methylene bridge protons, the two OH signals, and the signals corresponding to the phthalimide moiety in the ^{1}H NMR spectrum, prove the formation of monosubstituted **4e**. As expected, the spectrum of the disubstituted product **4f** only showed one OH signal and one AB quartet.

Reaction of calix[4]arene **3a** with 18 equivalents of *N*-(hydroxymethyl)phthalimide at 40 °C for 48 hours gave 25% of **4e**, 30% of **4f** and a mixture of other products in which one or both propoxy substituents are absent [22]. Reaction of the ethoxyethoxycalix[4]arene **3b** with 12 equivalents of *N*-(hydroxymethyl)phthalimide gave no dealkylation, and disubstituted **4h** was isolated in 49% yield [23, 24]. The synthesis of these protected amino substituted calix[4]arenes can be considered as a convenient alternative to presently used reactions [11]. The monosubstituted **4e** was used for further functionalization, using *N*-(hydroxymethyl)-α-chloroacetamide for a second amidomethylation step, to give the monophthalimido-mono(chloroacetamido) compound **5** in 60% yield.



e $R^1 = CH_3$, R^2 = H
f $R^1 = CH_3$, $R^2 = CH_2$Phth
g $R^1 = OCH_2CH_3$, R^2 = H
h $R^1 = OCH_2CH_3$, $R^2 = CH_2$Phth

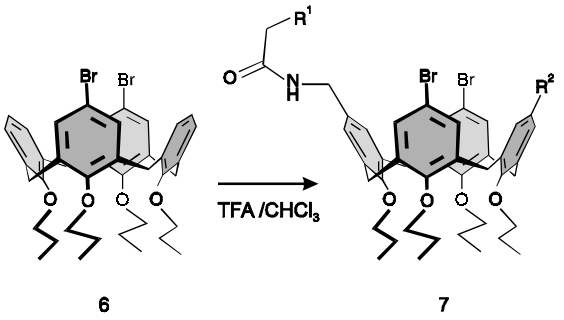
$R^1 = CH_3$

Scheme 3 Synthesis of mono- and bis(phthalimidomethyl) calix[4]arenes **4e**–**h**, and (2-chloroacetamido)methylphthalimidomethylcalix[4]arene **5**, starting from calix[4]arenes **3a**–**b**.

Reaction of 1,3-dibromocalix[4]arene 6 with six equivalents of *N*-(hydroxymethyl)acetamide for 36 hours, gave disubstituted **7a** in 83% yield. The same reaction with six equivalents of *N*-(hydroxymethyl)-α-chloroacetamide gave the monosubstituted product **7b** in 43% yield, with 27% recovered calix[4]arene starting material **6**. Using 12 equivalents of *N*-(hydroxymethyl)-α-chloroacetamide, both the monosubstituted **7b**, and disubstituted product **7c** were obtained in yields of 20% and 60%, respectively. The ^{1}H NMR spectrum of **7b** exhibits a double AB quartet for the methylene bridge protons, while the ArC$\underline{H}_2$NH doublet at δ = 4.03 ppm and the C$\underline{H}_2$Cl singlet at δ = 4.02 ppm clearly show the presence of the single (2-chloroacetamido)methyl moiety in **7b**. The spectrum of **7c** shows a single AB quartet and the expected ArC$\underline{H}_2$NH doublet at δ = 4.12 ppm and C$\underline{H}_2$Cl singlet at δ = 4.04 ppm.

This proves that the Tscherniac-Einhorn amidomethylation reaction is not limited to calix[4]arenes containing phenolic moieties, but can also take place on fully alkylated calix[4]arenes, which may even bear other upper rim substituents [25].

To investigate whether the amidomethylation reactions depend on the ability of the calix[4]arene to adapt the cone conformation, dipropoxycalix[4]arene **8**, fixed

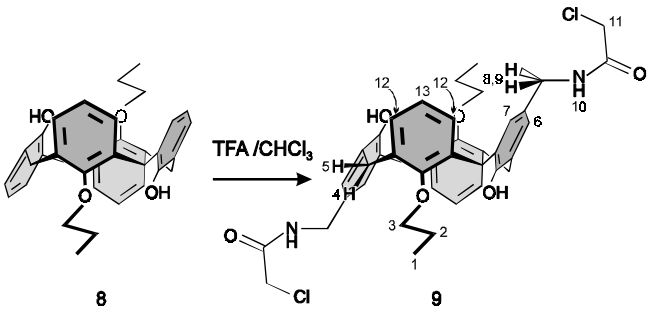


6 7

a R^1 = H, R^2 = $CH_2NHC(O)CH_3$
b R^1 = Cl, R^2 = H
c R^1 = Cl, R^2 = $CH_2NHC(O)CH_2Cl$

Scheme 4 Synthesis of bis[(acetamido)methyl]calix[4]arene **7a**, and mono- and bis[(2-chloroacetamido)methyl]calix[4]-arenes **7b**–**c**, starting from calix[4]arenes **6**.

in a so-called *anti* conformation, was reacted with *N*-(hydroxymethyl)-α-chloroacetamide to give disubstituted **9** in 95% yield. The ^{1}H NMR spectrum of **9** exhibits the C$\underline{H}_2$N signals around δ = 4.40 ppm and the CH_2Cl singlet at δ = 4.12 ppm. The spectrum furthermore shows only two types of methylene bridge protons (H_4 and H_5) and one type of propoxy substituent, indicating that in **9** there is a rapid exchange between the two 1,2 alternate conformations. Although the C$\underline{H}_2$N protons H_8 and H_9 (Scheme 4) are inherently non-equivalent, their splitting pattern (Figure 1) is more complex than expected, implying a hindered rotation around the Ar–CH_2N bond.



8 9

Scheme 5 Synthesis of *anti*-bis[(2-chloroacetamido)methyl] calix[4]arene **9**, starting from calix[4]arene **8**.

Temperature dependent measurements indicated that lowering of the temperature to approximately −30 °C did not show any changes except for small shifts in the absolute chemical shift. Raising the temperature showed the near collapse of the AB system, although the signals of H_8 and H_9 remain non-equivalent even at 60 °C [26].

The complex spectral outlook of the resonances of H_8 and H_9 was also simulated (Figure 1). The $^2J_{AB}$ coupling used for the simulation was obtained after irradiation of the H_{10} signal, yielding the AB system ($^2J_{AB}$ = 14.41 Hz). Using the input values for H_8 at δ = 4.315 ppm, H_9 at δ = 4.371 and H_{10} at δ = 6.690 ppm and a $^2J_{AB}$ = 14.41 Hz and J_{AX} = J_{BX} = 5.57 Hz, clearly revealed an ABX system that showed a nice correlation with the experimentally obtained data.

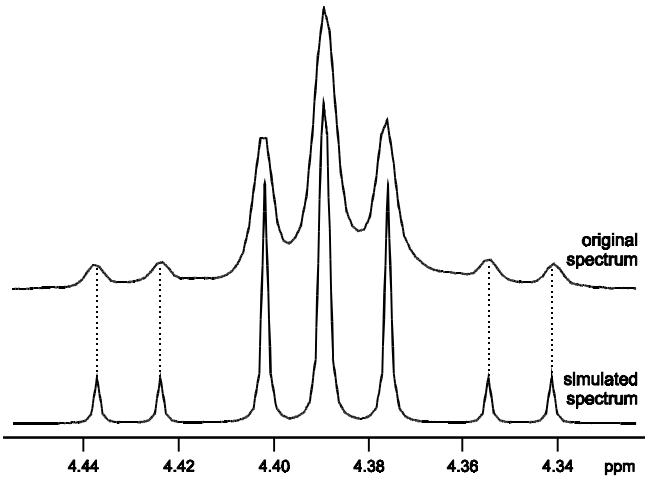


Fig. 1 Part of the ^{1}H NMR spectra of anti-5,17-bis[(2-chloroacetamido)methyl]-26,28-dihydroxy-25,27-di(1-propoxy)calix[4]arene (**9**) (simulated and original).

Conclusions

We conclude that the Tscherniac-Einhorn amidomethylation reaction provides easy access to a variety of novel upper rim functionalized calix[4]arenes. Methylacetamido, methylchloroacetamido, methylphthalimido, and combinations can be introduced under mild conditions on either partially or fully alkylated calix[4]-arenes. The calix[4]arene starting materials may bear propyl or ethoxyethyl substituents and may even be functionalized at the upper rim. The amidomethylation reactions are independent of the conformation of the calix[4]arene.

We are presently investigating the use of other amidomethylating agents, to further enlarge the scope of this reaction. Some of the compounds described here have been used as precursors for the synthesis of calix[4]arene based radiopharmaceuticals [27].

Experimental

General [28]

NMR experiments were performed using a Varian Unity 400 WB NMR spectrometer operating at 400 and 100 MHz for ^{1}H and ^{13}C, respectively. ^{1}H, ^{13}C, COSY [29], clean-TOCSY (MLEV17) [30], NOESY [31], and HMQC [32] experiments were used for the assignment of the ^{1}H and ^{13}C resonances.

All 2D spectra were collected as 2D hyper-complex data [33]. After weighting with shifted sine-bell functions, the COSY data were Fourier transformed in the absolute value mode while the clean-TOCSY (MLEV17) and HMQC data were transformed in the phase sensitive mode. All data processing was performed using standard Varian VnmrS/VnmrX software packages. COSY and TOCSY spectra were accumulated with 256 increments and 32 scans per increment, typically. In the clean-TOCSY experiments the mixing time of the MLEV17-pulse was arrayed between 30 and 100 ms; in the NOESY experiments mixing times of 30 to 90 ms were applied. – Routine experiments were recorded on a Varian Inova NMR spectrometer operating at 300 and 75.5 MHz for ^{1}H and ^{13}C, respectively. All spectra were recorded in $CDCl_3$ unless otherwise stated. Residual solvent protons were used as internal standard, and chemical shifts are given in ppm relative to tetramethylsilane (TMS). Fast atom bombardment (FAB) mass spectra were measured on a Finnigan MAT 90 spectrometer using *m*-nitrobenzyl alcohol (NBA) as a matrix. All solvents were purified by standard procedures. All other chemicals were analytically pure and were used without further purification. All reactions were carried out under an inert argon atmosphere. The presence of solvent in the analytical samples was confirmed by ^{1}H NMR spectroscopy. Melting points (uncorrected) of all compounds were obtained on a Reichert melting point apparatus. – The calix[4]arenes: **3a** [34], **3b** [35], **6** [11], **8** [36] were prepared according to literature procedures.

Amidomethylated calix[4]arenes 4, 5, 7, 9 (General Procedure)

The appropriate calix[4]arene and the amidomethylation reagent were dissolved in a mixture of $CHCl_3$ (20 mL) and trifluoroacetic acid (20 mL). The mixture was stirred overnight at room temperature (unless stated otherwise), after which it was poured onto ca. 50 grams of ice. Saturated $NaHCO_3$ solution (100 mL) was added, and the mixture was extracted with CH_2Cl_2 (100 mL). The organic layer was washed with a saturated $NaHCO_3$ solution (until no longer acidic), water, and brine, after which it was dried using $MgSO_4$. The solvent was removed *in vacuo* to give the crude product.

5,17-Bis[(acetamido)methyl]-26,28-dihydroxy-25,27-di(1-propoxy)calix[4]arene (**4a**)

Amounts used: 0.2 mmol (102 mg) of 3a and 1.2 mmol (107 mg) of *N*-(hydroxymethyl)-α-acetamide. A white solid was obtained which needed no further purification; Yield 85%; *m.p.* 146–148 °C. – ^{1}H NMR: δ/ppm = 8.42 (s, 2H, OH), 6.9 (m, 8H, ArH), 6.71 (t, 2H, J = 7.3 Hz, ArH), 5.57 (bm, 2H, NH), 4.24 and 3.26 (AB-q, 2 × 4H, J = 12.8 Hz, $ArCH_2Ar$), 4.15 (d, 4H, J = 5.1 Hz, CH_2N), 3.91 (t, 4H, J = 6.2 Hz, OCH_2), 2.01 (m, 4H, $C\underline{H}_2$-CH_3), 1.67 (s, 6H, $C(O)CH_3$), 1.24 (t, 6H, J = 7.3 Hz, CH_3). – ^{13}C NMR: δ/ppm = 169.5, 152.2, 151.4, 133.0, 128.4, 128.2, 127.9, 127.7, 124.7, 78.0, 52.9, 42.9, 30.8, 22.9, 10.4. – FAB-MS (*m/z*): 651.3 $(M+H)^+$.

$C_{40}H_{46}N_2O_6 \cdot 2.0\ CH_2Cl_2$	Calcd.:	C 61.47 H 6.14 N 3.41
(650.8)	Found:	C 61.46 H 5.95 N 3.45.

5,17-Bis[(acetamido)methyl]-26,28-dihydroxy-25,27-bis(1-ethoxyethoxy)calix[4]arene (**4b**)

Amounts used: 0.2 mmol (114 mg) of **3b** and 1.2 mmol (107 mg) of *N*-(hydroxymethyl)-α-acetamide. Purification using flash column chromatography (CH_2Cl_2 : MeOH = 96 : 4) gave a white solid; Yield 95%; *m.p.* 112–114 °C. – ^{1}H NMR: δ/ppm = 8.05 (s, 2H, OH), 6.85 (m, 8H, ArH), 6.69 (t, 2H, J = 7.3 Hz, ArH), 5.63 (bt, 2H, J = 5.1 Hz, NH), 4.36 and 3.27 (AB-q, 2 × 4H, J = 12.8 Hz, $ArCH_2Ar$), 4.1 (m, 8H, $ArOCH_2$, CH_2N), 3.87 (m, 4H, $ArOCH_2C\underline{H}_2$), 3.63 (q, 4H, J = 7.0 Hz, $C\underline{H}_2CH_3$), 1.42 (s, 6H, $C(O)CH_3$), 1.21 (t, 6H, J = 7.0 Hz, CH_3). – ^{13}C NMR: δ/ppm = 169.4, 152.2, 151.5, 133.1, 128.4, 127.9, 127.7, 124.8, 74.9, 68.6, 42.9, 30.6, 22.1, 14.7. – FAB-MS (*m/z*): 711.4 $(M+H)^+$.

$C_{42}H_{50}N_2O_8 \cdot 0.5CH_2Cl_2$	Calcd.:	C 67.76 H 6.82 N 3.72
(710.9)	Found:	C 67.58 H 6.82 N 3.40.

Syn-5,17-Bis[(2-chloroacetamido)methyl]-26,28-dihydroxy-25,27-di(1-propoxy)calix[4]arene (**4c**)

Amounts used: 0.2 mmol (102 mg) of **3a** and 1.2 mmol (148 mg) of *N*-(hydroxymethyl)-α-chloroacetamide. Purification using *p*-TLC (CH_2Cl_2 : MeOH = 96 : 4) gave a white solid; Yield 97%; *m.p.* 193–196 °C. – ^{1}H NMR: δ/ppm = 8.51 (s, 2H, OH), 6.98 (s, 4H, ArH), 6.94 (d, 4H, J = 7.5 Hz, ArH), 6.78 (t, 2H, J = 7.5 Hz, ArH), 6.69 (bs, 2H, NH), 4.31 (s, 4H, CH_2N), 4.30 and 3.37 (AB-q, 2 × 4H, J = 12.8 Hz, $ArCH_2Ar$), 4.04 (s, 4H, CH_2Cl), 3.98 (t, 4H, J = 6.5 Hz, OCH_2), 2.08 (m, 4H, CH_2–CH_3), 1.32 (t, 6H, J = 7.3 Hz, CH_3). – ^{13}C NMR: δ/ppm = 165.7, 153.1, 151.9, 133.3, 129.0, 128.5, 128.3, 127.4, 125.3, 78.4, 43.6, 42.6, 31.4, 23.4, 10.9. – FAB-MS (m/z, correct isotope pattern): 716.9 $(M-H)^-$.

$C_{40}H_{44}Cl_2N_2O_6 \cdot 0.8H_2O$	Calcd.:	C 65.44 H 6.26 N 3.82
(719.7)	Found:	C 65.44 H 6.37 N 3.63.

5,17-Bis[(2-chloroacetamido)methyl]-25,27-bis(1-ethoxyethoxy)-26,28-dihydroxycalix[4]arene (**4d**)

Amounts used: 0.2 mmol (114 mg) of **3b** and 1.2 mmol (148 mg) of *N*-(hydroxymethyl)-α-chloroacetamide. Purification using *p*-TLC (CH_2Cl_2 : MeOH = 96 : 4) gave a white solid; Yield 95%; *m.p.* 118–122 °C. – ^{1}H NMR: δ/ppm = 8.10 (s, 2H, OH), 6.97 (s, 4H, ArH), 6.93 (d, 4H, J = 7.3 Hz, ArH), 6.81 (bs, 2H, NH), 6.75 (t, 2H, J = 7.3 Hz, ArH), 4.43 and 3.35 (AB-q, 2 × 4H, J = 13.2 Hz, $ArCH_2Ar$), 4.30 (d, 4H, J = 5.5 Hz, CH_2N), 4.18 (t, 4H, J = 4.4 Hz, $ArOCH_2$), 3.93 (t, 4H, J = 4.4 Hz, $ArOCH_2CH_2$), 3.89 (s, 4H, CH_2Cl), 3.70 (q, 4H, J = 7.0 Hz, CH_2CH_3), 1.28 (t, 6H, J = 7.0 Hz, CH_3). – ^{13}C NMR: δ/ppm = 165.6, 152.9, 151.8, 133.3, 128.9, 128.3, 128.2, 127.3, 125.2, 75.4, 69.0, 66.8, 43.5, 42.4, 31.0, 15.1. – FAB-MS (m/z, correct isotope pattern): 777.3 $(M-H)^-$.

$C_{42}H_{48}Cl_2N_2O_8 \cdot 0.4H_2O$	Calcd.:	C 64.10 H 6.25 N 3.56
(779.8)	Found:	C 64.10 H 6.02 N 3.50.

26,28-Dihydroxy-5-(phthalimidomethyl)-25,27-di(1-propoxy)calix[4]arene (**4e**)

Amounts used: 0.2 mmol (102 mg) of **3a** and 2.4 mmol (425 mg) of *N*-(hydroxymethyl)phthalimide. The reaction was done at reflux temperature. Purification using flash column chromatography (CH_2Cl_2) first gave **3a** (Yield 25%) followed by **4e** as a white solid (Yield 47%) and finally **4f** as a white solid (Yield 17%); *m.p.* 118–120 °C. – ^{1}H NMR: δ/ppm = 8.34 (s, 1H, OH), 8.23 (s, 1H, OH), 7.7 (m, 2H, Phth), 7.5 (m, 2H, Phth), 7.13 (s, 2H, ArH–CH_2Phth), 6.95 (d, 2H, J = 7.4 Hz, ArH), 6.9–6.8 (m, 4H, ArH), 6.64 (t, 2H, J = 7.4 Hz, ArH), 6.54 (t, 1H, J = 7.4 Hz, ArH), 4.61 (s, 2H, CH_2Phth), 4.22 + 4.19 and 3.30 + 3.28 (2 × AB-q, 4 × 2H,

J = 12.9 Hz, $ArCH_2Ar$), 3.88 (t, 4H, *J* = 6.2 Hz, OCH_2), 1.97 (m, 4H, CH_2–CH_3), 1.22 (t, 6H, *J* = 7.3 Hz, CH_3). – ^{13}C NMR: δ/ppm = 168.5, 153.3, 151.8, 133.7, 133.5, 133.2, 132.2, 129.5, 129.0, 128.9, 128.4, 128.2, 128.1, 126.8, 125.3, 123.2, 119.0, 78.3, 41.3, 31.4, 23.5, 10.9. – FAB-MS (m/z): 667.3 (M^+).

$C_{43}H_{41}NO_6 \cdot 0.6CH_2Cl_2$	Calcd.:	C 72.86	H 5.92	N 1.95
(667.8)	Found:	C 72.65	H 5.73	N 1.88.

26,28-Dihydroxy-5,17-bis(phthalimidomethyl)-25,27-di(1-propoxy)calix[4]arene (**4f**)

Amounts used: 0.2 mmol (102 mg) of **3a** and 3.6 mmol (638 mg) of *N*-(hydroxymethyl)phthalimide. The reaction was performed at 40 °C for 48 h. Purification using flash column chromatography (CH_2Cl_2) first gave **4e** as a white solid (Yield 25%), followed by **4f** as a white solid (Yield 30%) and finally a mixture of partially and fully depropylated products (not characterized); *m.p.* 140–142 °C. – ^1H NMR: δ/ppm = 8.43 (s, 2H, OH), 7.8 (m, 4H, Phth), 7.65 (m, 4H, Phth), 7.21 (s, 4H, ArH), 6.95 (d, 2H, *J* = 7.7 Hz, ArH), 6.73 (t, 2H, *J* = 7.7 Hz, ArH), 4.70 (s, 4H, CH_2Phth), 4.26 and 3.38 (AB-q, 2 × 4H, *J* = 12.8 Hz, $ArCH_2Ar$), 3.96 (t, 4H, *J* = 6.2 Hz, OCH_2), 2.05 (m, 4H, CH_2–CH_3), 1.30 (t, 6H, *J* = 7.3 Hz, CH_3). – ^{13}C NMR: δ/ppm = 167.6, 152.6, 151.2, 133.9, 133.2, 132.7, 129.0, 128.5, 127.7, 124.9, 123.2, 122.6, 77.8, 40.7, 30.8, 22.9, 10.4. – FAB-MS (m/z): 826.4 (M^+).

$C_{52}H_{46}N_2O_8 \cdot 0.35CH_2Cl_2$	Calcd.:	C 72.38	H 5.38	N 3.22
(827.0)	Found:	C 72.45	H 5.14	N 3.34.

26,28-Dihydroxy-25,27-bis(1-ethoxyethoxy)-5,17-bis(phthalimidomethyl) calix[4]arene (**4h**)

Amounts used: 0.4 mmol (228 mg) of **3b** and 7.2 mmol (1276 mg) of *N*-(hydroxymethyl)phthalimide. The reaction was performed at 40 °C. Purification using flash column chromatography (CH_2Cl_2 : MeOH = 99 : 1) first gave a mixture of **3b** and **4g**, followed by **4h** as a white solid (Yield 49%); *m.p.* 125–127 °C. – ^1H NMR: δ/ppm = 8.40 (s, 2H, OH), 7.8 (m, 4H, Phth), 7.65 (m, 4H, Phth), 7.17 (s, 4H, ArH), 6.93 (d, 2H, *J* = 7.3 Hz, ArH), 6.72 (t, 2H, *J* = 7.3 Hz, ArH), 4.71 (s, 4H, CH_2Phth), 4.40 and 3.32 (AB-q, 2×4H, *J* = 13.1 Hz, $ArCH_2Ar$), 4.20 (t, 4H, *J* = 4.4 Hz, $ArOCH_2$), 3.91 (t, 4H, *J* = 4.4 Hz, $ArOCH_2C\underline{H}_2$), 3.86 (s, 4H, CH_2Cl), 3.70 (q, 4H, *J* = 7.1 Hz, $C\underline{H}_2CH_3$), 1.27 (t, 6H, *J* = 7.1 Hz, CH_3). – ^{13}C NMR: δ/ppm = 167.7, 152.7, 151.6, 134.0, 133.5, 129.2, 128.8, 128.4, 128.2, 127.7, 127.1, 125.1, 75.5, 69.0, 66.6, 40.6, 31.2, 14.8. – FAB-MS (*m/z*): 886.2 (M^+).

$C_{54}H_{50}N_2O_{10}$	Calcd.:	C 73.12	H 5.68	N 3.16
(887.0)	Found:	C 72.89	H 5.55	N 3.20.

5-[(2-Chloroacetamido)methyl]-26,28-dihydroxy-17-(phthalimidomethyl)-25,27-di(1-propoxy)calix[4]arene (**5**)

Amounts used: 0.15 mmol (100 mg) of **4e** and 0.45 mmol (56 mg) of *N*-(hydroxymethyl)-α-chloroacetamide. Purification using *p*-TLC (CH_2Cl_2 : MeOH = 96 : 4) gave a white solid; Yield 60%; *m.p.* – 142 °C. – ^1H NMR: δ/ppm = 8.41 (s, 1H, OH), 8.37 (s, 1H, OH), 7.75 (m, 2H, Phth), 7.6 (m, 2H, Phth), 7.13 (s, 2H, $Ar\underline{H}$–CH_2Phth), 6.89 (d, 2H, *J* = 7.3 Hz, ArH), 6.89 (s, 2H, $Ar\underline{H}$–CH_2N), 6.84 (d, 2H, *J* = 7.5 Hz, ArH), 6.68 (t, 2H, *J* = 7.4 Hz, ArH), 6.53 (bs, 1H, NH), 4.61 (s, 2H, CH_2Phth), 4.22 + 4.18 and 3.30 + 3.27 (2 × AB-q, 4 × 2H, *J* = 13.2 and 12.8 Hz, $ArCH_2Ar$), 4.23 (d, 2H, *J* = 5.5 Hz, CH_2N), 3.99 (s, 2H, CH_2Cl), 3.88 (t, 4H, *J* = 6.4 Hz, OCH_2), 1.98 (m, 4H, $C\underline{H}_2$–CH_3), 1.22 (t, 6H, *J* = 7.2 Hz, CH_3). – ^{13}C NMR: δ/ppm = 168.2, 165.6, 156.2, 156.0, 153.1, 151.8, 137.7, 134.1, 133.8, 133.4, 133.1, 130.6, 129.5, 129.2, 128.9, 128.6, 128.3, 127.4, 125.4, 121.7, 114.6, 78.4, 77.2, 76.8, 42.6, 41.3, 31.3, 30.8, 23.4, 23.3, 23.0, 10.9, 10.4, 10.1. – FAB-MS (*m/z*, correct isotope pattern): 772.3 (M^+).

$C_{46}H_{45}ClN_2O_7 \cdot 0.5CH_2Cl_2$	Calcd.:	C 68.46	H 5.68	N 3.43
(773.3)	Found:	C 68.30	H 5.51	N 2.99.

11,23-Bis[(acetamido)methyl]-5,17-dibromo-25,26,27,28-tetra(1-propoxy)calix[4]arene (**7a**)

Amounts used: 0.2 mmol (150 mg) of **6** and 1.2 mmol (107 mg) of *N*-(hydroxymethyl)-α-acetamide. The reaction mixture was stirred for 36 h at room temperature. Purification using flash column chromatography (CH_2Cl_2) gave a white solid; Yield 83%; *m.p.* 284–287 °C. – ^1H NMR: δ/ppm = 6.88 (s, 4H, ArH), 6.46 (s, 4H, ArH), 6.18 (bt, 2H, *J* = 5.8 Hz, NH), 4.39 and 3.10 (AB-q, 2 × 4H, *J* = 13.2 Hz, $ArCH_2Ar$), 4.13 (d, 2H, *J* = 5.8 Hz, CH_2N), 3.87 (t, 4H, *J* = 7.7 Hz, OCH_2), 3.78 (t, 4H, *J* = 7.7 Hz, OCH_2), 2.08 (s, 6H, $C(O)CH_3$), 1.91 (m, 8H, $C\underline{H}_2$–CH_3), 0.99 (m, 12H, CH_3). – ^{13}C NMR: δ/ppm = 169.6, 155.3, 154.0, 136.8, 133.6, 131.3, 130.3, 126.2, 114.1, 76.3, 42.1, 30.3, 22.7, 22.5, 9.8, 9.6. – FAB-MS (*m/z*, correct isotope pattern): 893.2 $(M+H)^+$.

$C_{46}H_{56}Br_2N_2O_6 \cdot 0.15CH_2Cl_2$	Calcd.:	C 61.22	H 6.27	N 3.09
(892.8)	Found:	C 61.22	H 6.06	N 2.87.

5,17-Dibromo-11-[(2-chloroacetamido)methyl]-25,26,27,28-tetra(1-propoxy)calix[4]arene (**7b**)

Amounts used: 0.2 mmol (150 mg) of **6** and 1.2 mmol (148 mg) of *N*-(hydroxymethyl)-α-chloroacetamide. The reaction mixture was stirred for 36 h at room temperature. Purification using flash column chromatography (CH_2Cl_2) gave a white solid; Yield 43%; *m.p.* 93–95 °C. – ^1H NMR: δ/ppm = 6.92 and 6.89 (2 × s, 2 × 2H, ArH–Br), 6.42 (s, 3H, ArH), 6.32 (bs, 1H, NH), 6.22 (s, 2H, ArH), 4.32 + 4.31 and 3.04 + 3.02 (2 × AB-q, 4 × 2H, *J* = 13.5 Hz, $ArCH_2Ar$), 4.03 (d, 2H, *J* = 6.5 Hz, CH_2N), 4.02 (s, 2H, CH_2Cl), 3.8 (m, 4H, OCH_2), 3.68 (t, 4H, *J* = 7.3 Hz, OCH_2), 1.81 (m, 8H, $C\underline{H}_2$–CH_3), 0.95 (m, 6H, CH_3), 0.87 (t, 6H, *J* = 7.7 Hz, CH_3). – ^{13}C NMR: δ/ppm = 165.1, 155.7, 155.5, 155.1, 137.5, 137.2, 133.6, 133.2, 130.6, 130.5, 130.1, 127.6, 126.5, 121.3, 114.1, 76.3, 42.7, 42.1, 30.3, 22.8, 22.5, 9.9, 9.5. – FAB-MS (*m/z*, correct isotope pattern): 855.3 (M^+).

$C_{43}H_{50}Br_2ClNO_5$	Calcd.:	C 60.33	H 6.00	N 1.64
(856.1)	Found:	C 60.51	H 5.77	N 1.72.

5,17-Dibromo-11,23-bis[(2-chloroacetamido)methyl]-25,26,27,28-tetra(1-propoxy)calix[4]arene (**7c**)

Amounts used: 0.2 mmol (150 mg) of **6** and 2.4 mmol (296 mg) of *N*-(hydroxymethyl)-α-chloroacetamide. The reaction mixture was stirred for 36 h at room temperature. Purification using flash column chromatography (CH_2Cl_2) first gave **6** (Yield 15%) followed by **7b** as a white solid (Yield 20%) and finally **7c** as a white solid (Yield 60%); *m.p.* 105–108 °C. – ^1H NMR: δ/ppm = 6.79 (s, 4H, ArH), 6.43 (s, 4H, ArH), 6.40 (bs, 2H, NH), 4.32 and 3.03 (AB-q, 2 × 2H, *J* = 13.2 Hz, $ArCH_2Ar$), 4.12 (d, 4H, *J* = 5.5 Hz, CH_2N), 4.04 (s, 4H, CH_2Cl), 3.78 (t, 4H, *J* = 7.7 Hz, OCH_2), 3.71 (t, 4H, *J* =

7.3 Hz, OCH_2), 1.82 (m, 8H, $C\underline{H}_2-CH_3$), 0.92 (m, 12H, CH_3). – ^{13}C NMR: δ/ppm = 165.4, 155.2, 136.7, 133.9, 130.4, 130.3, 130.1, 126.4, 114.3, 76.1, 42.5, 42.2, 30.3, 22.7, 22.5, 9.8, 9.7. – FAB-MS (*m/z*, correct isotope pattern): 958.6 (M^-).

$C_{46}H_{54}Br_2Cl_2N_2O_6 \cdot 0.1\ CH_2Cl_2$
(961.7) Calcd.: C 57.07 H 5.63 N 2.89
Found: C 56.99 H 5.60 N 2.85.

Anti-5,17-Bis[(2-chloroacetamido)methyl]-26,28-dihydroxy-25,27-di(1-propoxy)calix[4]arene (**9**)

Amounts used: 0.2 mmol (102 mg) of **8** and 1.2 mmol (148 mg) of *N*-(hydroxymethyl)-α-chloroacetamide. Purification using flash column chromatography (CH_2Cl_2 : MeOH = 96 : 4) gave a white solid; Yield 95%; *m.p.* 245–248 °C. – ^1H NMR: δ/ppm = 7.37 (s, 2H, OH), 7.18 (d, 4H, J = 7.3 Hz, ArH), 7.03 (t, 2H, J = 7.3 Hz, ArH), 7.03 (s, 4H, ArH), 6.76 (bs, 2H, NH), 4.40 (m, 4H, CH_2N), 4.12 (s, 4H, CH_2Cl), 3.99 and 3.77 (AB-q, 2 × 4H, J = 15.4 Hz, $ArCH_2Ar$), 3.59 (t, 4H, J = 7.0 Hz, OCH_2), 1.19 (m, 4H, $C\underline{H}_2-CH_3$), 0.38 (t, 6H, J = 7.3 Hz, CH_3). – ^{13}C NMR: δ/ppm = 165.5, 153.2, 153.1, 133.2, 128.9, 128.1, 124.9, 75.3, 43.6, 42.7, 34.8, 22.1, 9.2. – FAB-MS (*m/z*, correct isotope pattern): 716.9 $(M-H)^-$.

$C_{40}H_{44}Cl_2N_2O_6 \cdot 0.2CH_2Cl_2$ Calcd.: C 65.54 H 6.07 N 3.80
(719.7) Found: C 65.56 H 5.96 N 3.87.
– ^1H NMR (400 MHz, $CDCl_3$, 30 °C): δ/ppm = 7.23 (bs, OH), 7.16 (d, $^3J_{AB}$ = 7.72 Hz, H_{12}), 7.01 (bs, H_6 and H_7), 7.01 (dd, $^3J_{AB}$ = 7.72 and 7.72 Hz, H_{13}), 6.69 (dd, br, ^3J = 5.57 and 5.57 Hz, H_{10}), 4.37 (dd, $^2J_{AB}$ = 14.41 Hz, ^3J = 5.57 Hz, H_9), 4.31 (dd, $^2J_{AB}$ = 14.41 Hz, ^3J = 5.57 Hz, H_8), 3.98 (d, $^2J_{AB}$ = 16.23 Hz, H_5), 4.10 (bs, H_{11}), 3.75 (d, $^2J_{AB}$ = 16.23 Hz, H_4), 3.59 (d, ^3J = 7.48 Hz, H_3), 1.21 (tq, ^3J = 7.48 and 8.14 Hz, H_2), 0.42 (t, ^3J = 8.14 Hz, H_1). At higher temperature H_6 and H_7 are slightly shifting, and the difference between H_6/H_7 and H_{13} becomes clear. At 30 °C, however, the chemical shifts are exactly the same. – ^1H NMR (400 MHz, DMSO-D_6, 30 °C): δ/ppm = 8.48 (dd, br, ^3J = 5.55 and 5.55 Hz, H_{10}), 7.18 (d, $^3J_{AB}$ = 7.46 Hz, H_{12}), 7.00 (bs, H_6 and H_7), 6.97 (dd, $^3J_{AB}$ = 7.46 and 7.46 Hz, H_{13}), 6.94 (bs, OH), 4.37 (dd, $^2J_{AB}$ = 14.70 Hz, ^3J = 5.52 Hz, H_9), 4.15 (dd, $^2J_{AB}$ = 14.70 Hz, ^3J = 5.52 Hz, H_8), 4.09 (bs, H_{11}), 3.92 (d, $^2J_{AB}$ = 15.55 Hz, H_5), 3.68 (d, $^2J_{AB}$ = 15.55 Hz, H_4), 3.55 (d, ^3J = 7.57 Hz, H_3), 1.16 (tq, ^3J = 7.57 and 7.58 Hz, H_2), 0.47 (t, ^3J = 7.58 Hz, H_1).

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