Synthesis and Structure of Chiral *Cone* Calix[4]arenes Functionalized at the Upper Rim with L-Alanine Units

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Synthetic routes were developed to link L-alanine methyl ester or L-alanyl-L-alanine methyl ester at the upper rim of calix[4]arenes blocked in the *cone* conformation. Several tetra- (**3** and **6**) and difunctionalized (**11** and **12**) amino acids containing macrocycles were obtained. Reaction of these compounds with hydrazine gave the corresponding hydrazido derivatives **4**, **13**, and **14**, while the hydrolysis of **3** with LiOH produced the tetraacid **5** whose lithium salt is water soluble at neutral pH. The structural properties of all amino acids containing calix[4]arenes were studied by mono- and bidimensional ^{1}H NMR experiments. The X-ray crystal structure of the difunctionalized receptor **11** shows three different conformations in the solid state, none of them having *intra-chain* hydrogen bonding.

Hybrid macrocyclic receptors, characterized by the presence of binding units of different nature, e.g. polar groups and hydrophobic cavities or surfaces, are receiving some attention in several areas of Supramolecular Chemistry[1]. Cholaphanes[2], glycophanes[3], or other macrocyclic compounds[4] have been used for the complexation of sugars and amino acids in different solvents. We linked carbohydrate units[5] at the upper and at the lower rim of calix[4]arenes[6], whereas (thio)urea derivatized calix[4]arenes have been widely exploited for the selective recognition of anions[7] or for the synthesis of *self*-aggregating molecular capsules[8]. Amino acid containing synthetic macrocycles have been studied to a minor extent, in spite of the important role played by amino acid units in several recognition processes of natural and artificial systems[9], in chiral discrimination[10] and stereoselective synthesis[11]. Only recently the synthesis of a few cavity containing macrocyclic compounds functionalized with amino acids were reported[12].

We have recently synthesised calix[4]arenes bridged at the upper rim with suitable peptide units, which showed promising antimicrobial activity towards Gram-positive bacteria in vitro as a result of their ability to bind D-alanyl-D-alanine residues[13].

As part of a general project aimed at the synthesis of *hybrid* calix[4]arene receptors containing amino acid residues, we report on the synthesis of calix[4]arene molecular clefts containing L-alanine units at the upper rim together with the X-ray crystal structure of one of such compounds.

To avoid the conformational problems connected with parent calixarenes[6], we decided to synthesise amino acid containing clefts on calix[4]arenes blocked in the *cone* conformation.

Tetrafunctionalized Receptors

The calix[4]arenetetracarboxylic acid **1** was obtained by oxidation of 5,11,17,23-tetraformyl-25,26,27,28-tetra-*n*-propoxycalix[4]arene[5b]. The condensation reaction of **1** with alanine methyl ester hydrochloride was performed via three different methods (Scheme 1). The direct procedure in the presence of *N*-hydroxybenzotriazole and DCC (Method A) afforded the tetrafunctionalized macrocycle **3** in 35% yield, while, using *O*-(benzotriazol-1-yl)-*N,N,N′,N′*-bis(pentamethylen)uronium tetrafluoroborate (TBPU) as coupling reagent[14] (Method B), the same product was obtained in 60% yield. Alternatively the acid **1** was first transformed into the acyl chloride **2** which was condensed with L-alanine methyl ester (Method C). The conversion of **1** in **2** was conveniently followed by IR spectroscopy, by taking samples at different times from the reaction mixture and observing the shift of the C=O stretching frequency from 1695 to 1730 cm^{-1}.

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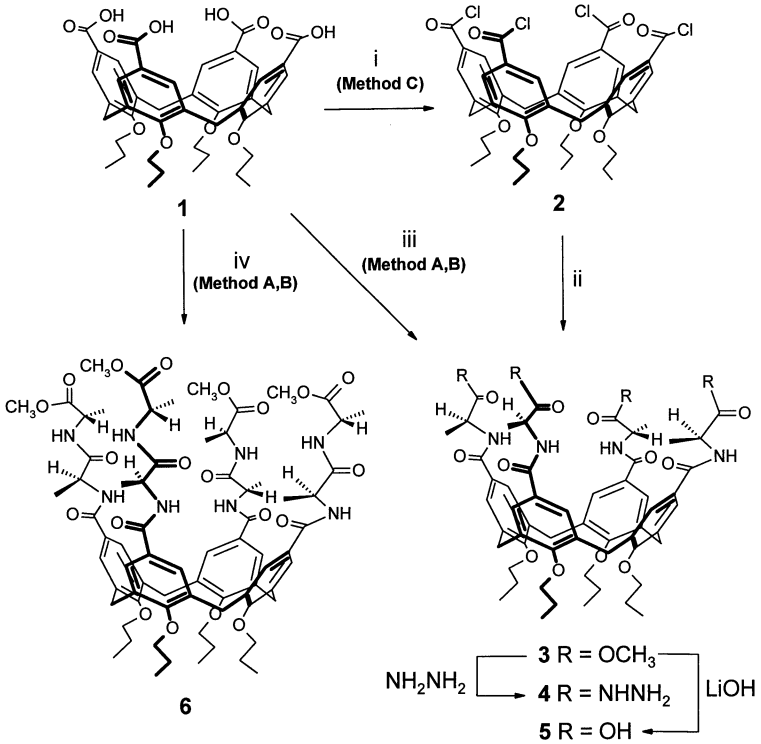
Scheme 1. Reagents and conditions: (i) oxalyl chloride, CH_2Cl_2, reflux; (ii) L-alanine methyl ester, NEt_3, CH_2Cl_2, room temp.; (iii) L-alanine methyl ester, coupling reagent, NEt_3, CH_2Cl_2, room temp.; (iv) L-alanyl-L-alanine methyl ester, coupling reagent, NEt_3, CH_2Cl_2, room temp.



This indirect procedure gave **3** in 60% overall yield which is comparable with that obtained using TBPU but it is more advantageous because of the lower cost of the reagents.

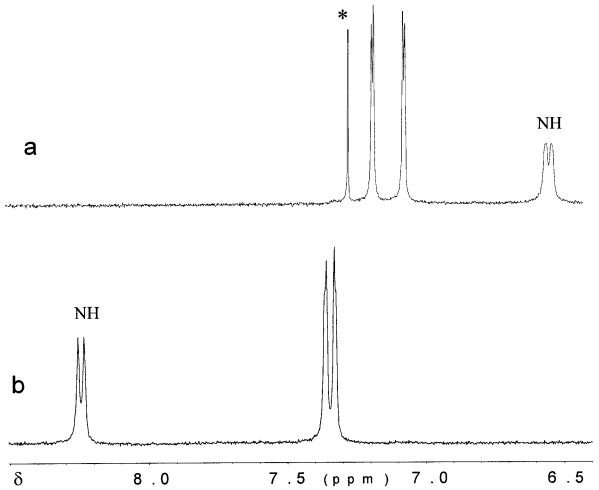
Compound **1** was then directly condensed, either in the presence of *N*-hydroxybenzotriazole or TBPU, with L-alanyl-L-alanine methyl ester hydrobromide, giving the desired product **6** in ca. 30% yield. The dipeptide was obtained by condensation of Cbz-L-alanine *N*-hydroxysuccinimide ester and L-alanine methyl ester hydrochloride and subsequent deprotection with HBr (33% in acetic acid)[15].

The conformational properties of compounds **3** and **6** were studied in solution by ^{1}H- and ^{13}C-NMR spectroscopy. The ^{1}H-NMR spectrum of **3** in $CDCl_3$ evidences the complete equivalence of the four alanine residues and shows two different signals for the aromatic protons (see Figure 1a). An analogous splitting of the aromatic protons was previously observed in tetraurea calix[4]arene derivatives and attributed to the formation of dimers (molecules capsules) via strong hydrogen bonds in $CDCl_3$[8]. We could rule out the formation of dimeric species in the case of compound **3** in $CDCl_3$ since its ^{1}H-NMR spectrum does not change by varying the concentration and because the splitting of the aromatic protons is also visible in [D_6]DMSO solution (see Figure 1b).

Therefore, this splitting must be attributed to the presence of the chiral amino acid unit on each aromatic nucleus.

The ^{1}H-NMR spectrum of **6** in $CDCl_3$ also shows the complete equivalence of the four dipeptide units and two different peaks for the aromatic protons. To assign the protons signals in compound **6**, and in particular to distinguish

Figure 1. ^{1}H NMR spectrum (300 MHz, 300 K) of aromatic and amide protons of compound **3** in (a): $CDCl_3$ and in (b): [D_6]DMSO; *$CHCl_3$



between those belonging to the two alanine units of the dipeptide, we used bidimensional experiments and combined information from COSY and NOESY maps. A COSY experiment allowed to assign the signals to each alanine unit. Two correlation peaks between the protons of the aromatic rings and the NH amide protons at higher field appeared from the map of the NOESY spectrum, showing that this signal is due to the NH amide proton of the alanine directly linked to the calixarene backbone.

The tetraester **3** was also converted in its tetrahydrazido derivative **4** with hydrazine and hydrolysed to the tetraacid

derivative **5** using LiOH at room temperature. It is interesting to observe that lithium salt of **5** is water soluble ($\leq 8 \times 10^{-3}$ M) at neutral pH.

Difunctionalized Receptors

We also synthesised molecular clefts having two amino acid or peptide units in diametrical position at the upper rim of the calix[4]arene. The reaction of 11,23-diformyl-25,27-dihydroxy-26,28-di-*n*-propoxycalix[4]arene[16] with methyl orthoformiate gave quantitatively the diacetal derivative **7**, which was subsequently alkylated to give, after deprotection, the *cone* diformyl derivative **8** (Scheme 2). By oxidation of **8** we obtained the diacid **9**; this compound is in the *cone* conformation and, as observed in other cases[16][17], shows solvent dependent ^{1}H-NMR spectra because of the formation of dimeric species in $CDCl_3$, which breaks down in more polar solvents like methanol or acetone.

To link amino acids or peptides to the calixarene **9**, we prepared the active ester **10**. This compound initially reacted with L-alanine methyl ester hydrochloride to give the calix[4]arene difunctionalized cleft **11** in 33% overall yield (Method D, Scheme 2). The same product was also obtained directly from **9** using *N*-hydroxybenzotriazole as coupling agent (Method A); in this case the reaction was significantly faster and **11** was obtained in higher yields (53%). However method D allowed to obtain the pure product **11** by simple recrystallization from methanol, whereas method A gave a crude product which had to be purified by column chromatography.

Compound **11** gave crystals (from methanol) suitable for X-ray analysis. It shows that three different conformations are present in the solid state (Figure 2).

All the three conformers adopt the classical "*flattened cone*" conformation of tetraalkoxycalix[4]arenes[6], even if slight but significant differences exist between the orientations of the phenolic units with respect to the reference molecular plane R, defined as least squares plane containing the carbon atoms of the CH_2 bridges[18] (see Table 1).

The Symbolic Representations of the molecular conformations[19] are C_1 +−, +−, +−, +− for the molecule A−B−C−D, and C_2 +−, +− for the molecules E−F−E′′F′ and G−H−G′−H′ which have a two-fold imposed molecular symmetry. The most significant differences between the three conformers concern the orientation of the amino acid units among themselves and with respect to the

Scheme 2. Reagents and conditions: (i) 1) 1-iodopropane, NaH, DMF, room temp.; 2) HCl; (ii) $NaClO_2$, NH_2SO_3H, $CHCl_3$/acetone, room temp.; (iii) *N*-hydroxysuccinimide, DCC, CH_2Cl_2, room temp.; (iv) DCC, *N*-hydroxybenzotriazole, L-alanine methyl ester, NEt_3, CH_2Cl_2/DMF, room temp.; (v) L-alanine methyl ester, NEt_3, CH_2Cl_2/DMF, room temp.; (vi) L-alanyl-L-alanine methyl ester, NEt_3, CH_2Cl_2/DMF, room temp.

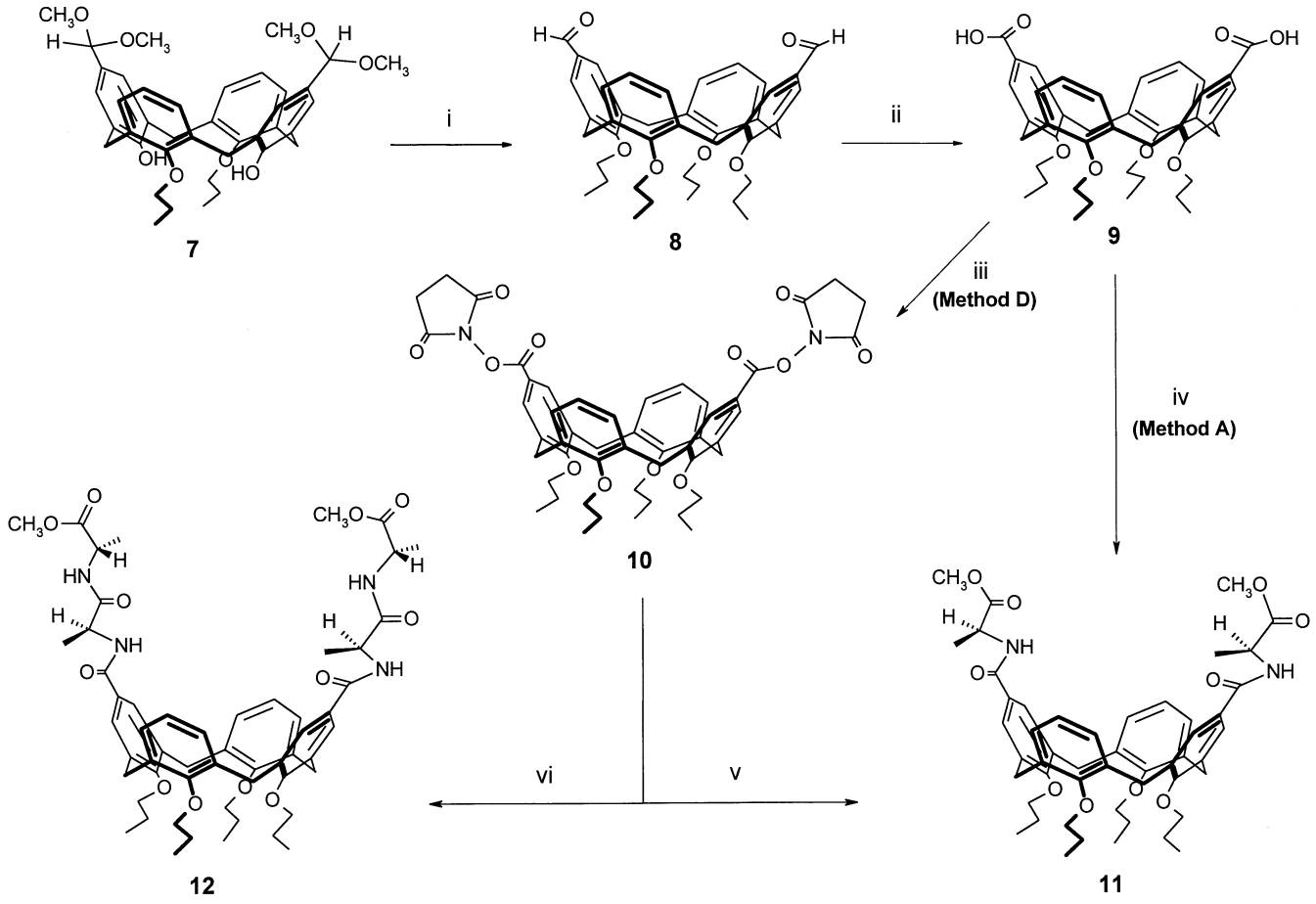


Figure 2. X-ray crystal structure of compound **11**: the three independent molecules found in the unit cell

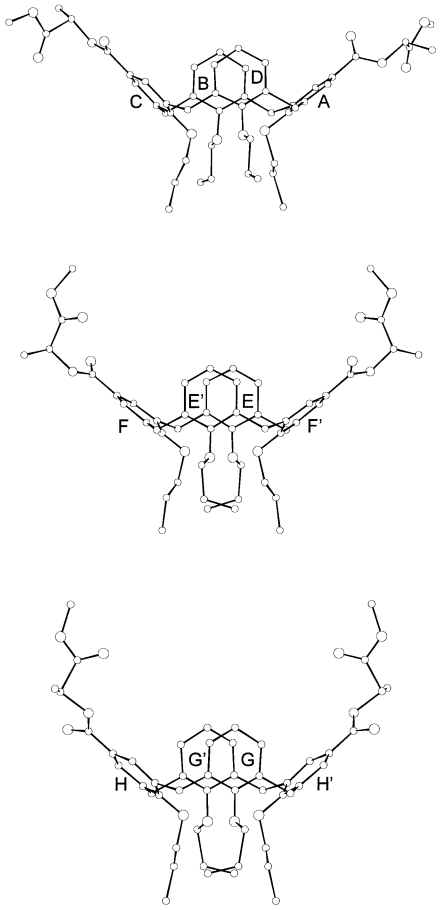


Table 1. Dihedral angles [°] between least-squares plane through the phenolic units and the reference plane R of the three conformers of **11**, according to ref.[18]

	A	B	C	D	E	F	G	H
R	142.0(3)	97.3(4)	135.5(3)	100.5(4)	96.6(3)	142.2(2)	96.4(3)	138.9(3)

calixarene cavity which can be established by examining the torsion angles and the intramolecular interatomic distances related to the alanine units reported in Tables 2 and 3. These values show that the two terminal $CHCH_3COOCH_3$ groups are oriented toward the inner side of the calixarene cavity in the two C_2 +−, +− conformers, whereas in the A−B−C−D conformer they point toward the outside. The amino acid chains occupy more efficiently the space in the conformer A−B−C−D, in which the shortest O2···O3 and O2···O4 intramolecular distances are observed, whereas a less efficient folding of the alanine units is obtained in the G−H−G′−H′ conformer which shows the longest O2···O3 and O2···O4 distances. Two water molecules are also present in the X-ray crystal structure; one of them in the equivalent position $-x-1, -y-1, z$, is hydrogen bonded to O3A [O3A···O1W 3.27(3) Å]. The second water molecule fills the intermolecular voids of the crystal lattice and is not involved in hydrogen bonding. Remarkably no *intrachain* hydrogen bond, which could cause the collapse of the binding cavity, is present in all three structures, thus indicating that in **11** the amino acid containing cleft is potentially available for the complexation of suitable complementary guests. Only one short intermolecular contact between N1C and O2F [2.87(2) Å] is evidenced in the X-ray crystal structure. A perspective view of the molecular packing is given in Figure 3.

Table 2. Torsion angles [°] in the alanine units at the upper rim of the three conformers of **11**

Solid angle	A	C	F	H
C3−C4−C10−O2	41(2)	−6(2)	164(1)	25(3)
C3−C4−C10−N1	−120(2)	−179(1)	−19(2)	−164(2)
C4−C10−N1−C11	176(1)	179(1)	−180(1)	−179(2)
C10−N1−C11−C13	−77(2)	−73(1)	−81(2)	−107(3)
N1−C11−C13−O3	−25(3)	−34(2)	−21(2)	−19(5)
N1−C11−C13−O4	156(1)	155(1)	127(1)	165(3)

Table 3. Interatomic distances [Å] involving the alanine units of compound **11**

Molecule A−B−C−D		C_1 +−, +−, +−, +−	
O2A···O2C	12.40(2)	O2A···O3A	3.27(2)
N1A···N1C	13.63(2)	O2A···O4A	3.65(2)
O3A···O3C	17.88(3)	O2C···O3C	3.43(2)
O4A···O4C	18.99(3)	O2C···O4C	3.60(1)
Molecule E−F−E′−F′		C_2 +−, +−	
O2F···O2F′	12.87(3)	O2F···O3F	3.59(2)
N1F···N1F′	13.73(2)	O2F···O4F	3.68(2)
O3F···O3F′	12.95(3)		
O4F···O4F′	15.74(3)		
Molecule G−H−G′−H′		C_2 +−, +−	
O2H···O2H′	13.50(3)	O2H···O3H	4.22(3)
N1H···N1H′	12.68(3)	O2H···O4H	4.37(3)
O3H···O3H′	11.41(2)		
O4H···O4H′	14.84(3)		

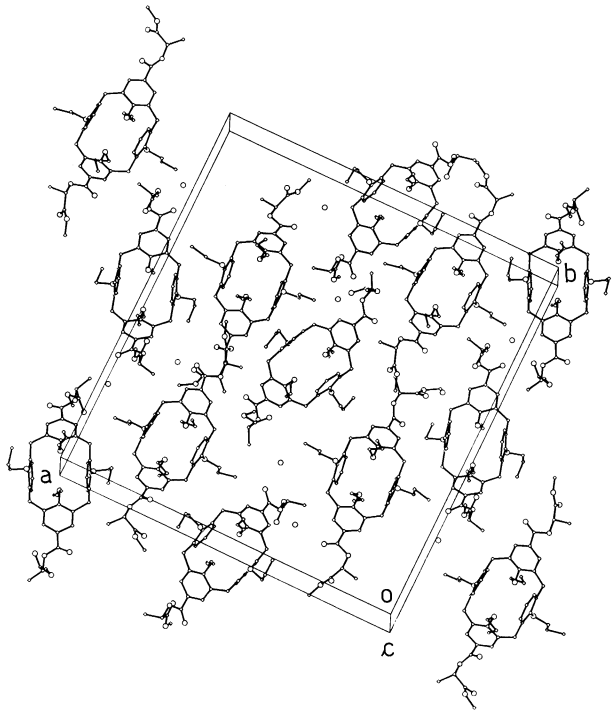
The active ester **10** was subsequently condensed with the dipeptide L-alanyl-L-alanine methyl ester hydrobromide, affording the peptidocalix[4]arene **12**. The reaction of the esters **11** and **12** with hydrazine hydrate gave the corresponding hydrazido derivatives **13** and **14** in high yield.

As for tetrafunctionalized compounds **3**−**6**, the structure of compounds **12**−**14** was established on the basis of mono and bidimensional NMR experiments.

Qualitative binding studies were performed to assess the complexation properties of the new receptors synthesized towards carboxylic acids, amino acids, small peptides, and ammonium salts. ^{1}H-NMR titration experiments for $CDCl_3$ soluble substrates and solid-liquid extractions for insoluble guests, were performed.

Whereas diesters **11** and **12** were not able to complex acetyl-D-alanine or acetyl-D-alanyl-D-alanine, the corresponding hydrazido derivatives **13** and **14** are able to dissolve these guests in $CDCl_3$ showing a guest/host ratio ≥ 1. The

Figure 3. PLUTO view of the molecular packing of compound **11** (the hydrogen atoms have been omitted for clarity)



^{1}H-NMR spectrum of ligand **13** changes substantially in the 1:1 complex with acetyl-D-alanyl-D-alanine showing, in particular, significant downfield shifts of NH protons. We are currently analysing these changes to obtain more quantitative information. Compound **3** is not able to extract acetyl-D-alanyl-D-alanine in $CDCl_3$. However in homogenous solution ($CDCl_3$) **3** is able to complex lauric acid (K_{ass} = 50 M^{-1}) and lauroyl-L-alanine (K_{ass} = 100 M^{-1}) but not their corresponding carboxylate anions.

In agreement with this observation, **3** is also able to interact with ammonium salts of primary amines and amino acids, showing a preference for linear over branched substrates.

In summary, several new chiral hosts, having two or four L-alanine or L-alanyl-L-alanine units at the upper rim of calix[4]arenes blocked in the *cone* conformation were synthesised. They have to be considered as a novel type of *hybrid* molecular receptors having polar binding groups organised on the periphery of an apolar cavity.

The X-ray crystal structure of the difunctionalized receptor **11** shows that the general preference of tetraalkoxycalix[4]arenes to assume a "*flattened cone*" conformation in the solid state[6], avoids the formation of intramolecular hydrogen bonding between the two amino acid chains, which are therefore free to interact with suitable guests. A water soluble tetrafunctionalized chiral receptor (**5**) potentially useful for the encapsulation of chiral guests was also obtained.

Preliminary binding studies indicate that the difunctionalized hydrazido derivatives **13** and **14** are able to extract in organic media acetyl derivatives of D-alanine and D-alanyl-D-alanine, whereas the tetrafunctionalized ester derivative **3** complex carboxylic acids (but not their carboxylate anions) and ammonium salts. Studies are in progress to understand more deeply the complexation properties of these chiral macrocycles.

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Experimental Section

General: Melting points were determined in sealed tube, under nitrogen atmosphere with Electrothermal apparatus. − ^{1}H and ^{13}C NMR spectra were recorded at 100, 300, 400 MHz and 25, 75 MHz respectively on a Bruker AC100, AC300, and AMX400 (TMS was used as internal standard). − IR spectra were recorded on a Perkin-Elmer 298. − Mass spectra were obtained in EI (70 eV) and CI (CH_4) modes on Finnigan Mat SSQ710. − Optical rotations were measured on a Autopol III Rudolph Research, using the wavelength of 589.3 nm. − TLC were performed on silica gel Merck 60 F_{254}, while flash chromatography using 230−240 mesh Merck 60 silica gel. − All the solvents were purified according to standard procedure; dry solvents were obtained according to literature methods and stored over molecular sieves. All reactions were carried out under nitrogen atmosphere. Amino acids and peptides were purchased from Sigma. *para-tert*-Butylcalix[4]arene[20], calix[4]arene[20], 25,27-dihydroxy-26,28-di-*n*-propoxycalix[4]arene[16], 11,23-diformyl-25,27-dihydroxy-26,28-di-*n*-propoxycalix[4]arene[16], 25,26,27,28-tetra-*n*-propoxycalix[4]arene[5b], 5,11,17,23-tetraformyl-25,26,27,28-tetra-*n*-propoxycalix[4]arene[5b] were synthesised according to literature procedures.

As verified also by other authors[21], the elemental analyses of calixarenes are very often incorrect because of inclusion of solvent molecules and can not considered an appropriate criterion of purity; nevertheless, the identity of the compounds reported has been proven by their spectral data.

25,26,27,28-Tetra-n-propoxycalix[4]arene-5,11,17,23-tetracarboxylic Acid (**1**): 25,26,27,28-Tetra-*n*-propoxycalix[4]arene-5,11,17,23-tetracarbaldehyde[5b] (2.4 g, 3.37 mmol) is dissolved in $CHCl_3$/acetone (1:1, v/v, 100 ml) and the solution cooled to 0°C. Aqueous solution (10 ml) of sulfamic acid (3.93 g, 40.47 mmol) and sodium chlorite (3.05 g, 33.73 mmol) is rapidly added. After 10 h at room temp. the organic solvents are distilled off and the residue is added of 2 N HCl (10 ml). The resulting precipitate is filtered and purified by trituration with CH_3OH to obtain the product as a white solid in 73% yield. − M.p. > 360°C. − ^{1}H NMR (300 MHz, CD_3OD): δ = 7.37 (s, 8 H, aromatic), 4.51 (d, J = 13.5 Hz, 4 H, H_{ax} of ArCH_2Ar), 3.95 (t, J = 7.3 Hz, 8 H, O$CH_2$$CH_2CH_3$), 3.31 (d, J = 13.5 Hz, 4 H, H_{eq} of ArCH_2Ar), 1.97−1.87 (m, 8 H, $OCH_2CH_2CH_3$), 1.03 (t, J = 7.4 Hz, 12 H, $OCH_2CH_2CH_3$). − ^{13}C NMR (75 MHz, $CDCl_3$/CD_3OD 9/1): δ = 169.5 (s, C=O), 161.7 (s, aromatic), 135.7 (s, aromatic), 131.3 (d, aromatic), 125.2 (s, aromatic), 77.9 (t, O$CH_2CH_2CH_3$), 31.8 (t, ArCH_2Ar), 24.2 (t, $OCH_2CH_2CH_3$), 10.9 (q, $OCH_2CH_2CH_3$). − IR (KBr): ν_{max} = 3050 cm^{-1} (OH), 1697 (C=O). − MS, CI(+), *m/z*: 752 (100) [M^+ − OH].

25,26,27,28-Tetra-n-propoxycalix[4]arene-5,11,17,23-tetracarbonyl Chloride (**2**): Oxalyl chloride (3 ml) is added to a stirring suspension of **1** (0.4 g, 0.52 mmol) in dry CH_2Cl_2 (30 ml) and the mixture is refluxed for 5 h. The solvent is removed at a Rotavapor and the product is obtained with satisfactory purity after 5 h under vacuum (0.1−0.5 mm Hg). − M.p. 160°C (dec.). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46 (s, 8 H, aromatic), 4.49 (d, J = 13.8 Hz,

4 H, H_{ax} of ArCH_2Ar), 3.95 (t, J = 7.4 Hz, 8 H, OCH_2CH$_2$CH$_3$), 3.36 (d, J = 13.8 Hz, 4 H, H_{eq} of ArCH_2Ar), 1.94−1.84 (m, 8 H, OCH$_2$CH_2CH$_3$), 1.01 (t, J = 7.4 Hz, 12 H, OCH$_2$CH$_2$CH_3). − ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.4 (s, C=O), 155.1, 135.7 (s, aromatic), 131.3 (d, aromatic), 125.2 (s, aromatic), 77.9 (t, OCH$_2$CH$_2$CH$_3$), 29.6 (t, ArCH$_2$Ar), 23.1 (t, OCH$_2$$CH_2CH_3$), 10.0 (q, OCH$_2CH_2$$CH_3$). − IR (KBr): ν_{max} = 1697 cm^{-1} (C=O). − MS, CI(+), *m/z*: 842 (10) [M$^+$], 807 (100) [M$^+$ − Cl].

11,23-Bis(1,1-dimethoxymethyl)-26,28-di-n-propoxycalix[4]arene-25,27-diol (**7**): Methyl orthoformate (4 ml, 30 mmol) and a catalytic amount of *p*-TsOH are added to a suspension of 25,27-dihydroxy-26,28-di-*n*-propoxycalix[4]arene-11,23-dicarbaldehyde[16] (1 g, 1.76 mmol) in CH_3OH (80 ml). The reaction is refluxed for 4 h, then quenched by addition of saturated $NaHCO_3$ (100 ml) and extracted with CH_2Cl_2 (250 ml); the organic layer is evaporated and the product obtained by crystallization from ethyl ether as white solid in 90% yield. − M.p. 214−215°C. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.44 (s, 2 H, OH), 7.12 (s, 4 H, aromatic), 6.94 (d, J = 7.4 Hz, 4 H, aromatic), 6.73 (t, J = 7.4 Hz, 2 H, aromatic), 5.27 (s, 1 H, ArCH), 4.30 (d, J = 12.9 Hz, 4 H, H_{ax} of ArCH_2Ar), 3.96 (t, J = 6.1 Hz, 4 H, OCH_2CH$_2$CH$_3$), 3.38 (d, J = 12.9 Hz, 4 H, H_{eq} of ArCH_2Ar), 3.27 (s, 12 H, OCH$_3$), 2.06−1.96 (m, 4 H, OCH$_2$CH_2CH$_3$), 1.31 (t, J = 7.3 Hz, 6 H, OCH$_2$CH$_2$CH_3). − ^{13}C NMR (25 MHz, $CDCl_3$): δ = 153.5, 151.9 (s, aromatic), 133.4, 129.0 (d, aromatic), 128.4, 127.8 (s, aromatic), 126.8, 125.3 (d, aromatic), 103.4 (d, ArCH), 78.3 (t, OCH$_2$CH$_2$CH$_3$), 52.6 (q, OCH$_3$), 31.5 (t, ArCH$_2$Ar), 23.5 (t, OCH$_2$$CH_2CH_3$), 10.9 (q, OCH$_2CH_2$$CH_3$). − MS, CI(+), *m/z*: 656 (10) [M$^+$], 625 (100) [M$^+$ − OCH$_3$].

25,26,27,28-Tetra-n-propoxycalix[4]arene-5,17-dicarboxaldehyde (**8**): NaH (210 mg, 4.4 mmol, 50% oil dispersion) and 1-iodopropane (0.565 ml, 5.7 mmol) are added to a solution of **7** (950 mg, 1.44 mmol) in dry DMF (30 ml). The reaction is stirred for 16 h at room temp., then quenched with 1 N HCl (100 ml) and extracted with CH_2Cl_2 (150 ml). The organic layer is washed with saturated $Na_2S_2O_3$ × 5 H_2O (50 ml) and with water (50 ml), and distilled under reduced pressure. The crude product is purified by flash chromatography (hexane/ethyl acetate, 6:1) in order to obtain compound **8** in 70% yield. − M.p. 155−156°C. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.44 (s, 2 H, CHO), 6.98 (s, 4 H, aromatic), 6.75−6.70 (m, 6 H, aromatic), 4.46 (d, J = 13.6 Hz, 4 H, H_{ax} of ArCH_2Ar), 3.95−3.80 (m, 8 H, OCH_2CH$_2$CH$_3$), 3.22 (d, J = 13.6 Hz, 4 H, H_{eq} of ArCH_2Ar), 2.01−1.78 (m, 8 H, OCH$_2$CH_2CH$_3$), 1.09−0.88 (m, 12 H, OCH$_2$CH$_2$CH_3). − ^{13}C NMR (25 MHz, $CDCl_3$): δ = 191.6 (d, C=O), 161.9, 156.6, 135.9, 134.8, 131.1 (s, aromatic), 129.8, 128.8, 122.6 (d, aromatic), 77.0 (t, 2 OCH$_2$CH$_2$CH$_3$), 76.7 (t, 2 OCH$_2$CH$_2$CH$_3$), 30.9 (t, ArCH$_2$Ar), 23.4 (t, 2 OCH$_2$$CH_2CH_3$), 23.2 (t, 2 OCH$_2$$CH_2CH_3$), 10.4 (q, 2 OCH$_2CH_2$$CH_3$), 10.2 (q, 2 OCH$_2CH_2$$CH_3$). − MS, CI(+), *m/z*: 650 (100) [M$^+$+H].

25,26,27,28-Tetra-n-propoxycalix[4]arene-5,17-dicarboxylic Acid (**9**): Aqueous solution (2 ml) of sulfamic acid (383 mg, 4 mmol) and sodium chlorite (312 mg , 3.4 mmol) are rapidly added to a solution of **8** (560 mg, 1 mmol) in $CDCl_3$/acetone (1:1, v/v, 30 ml). The reaction is stirred at room temp. overnight, then quenched removing the organic solvents under reduced pressure and by addition of 1 N HCl (20 ml). The precipitate is collected on a Buchner and crystallized from methanol to obtain the compound **9** as a white solid in 90% yield. − M.p. 271−273°C. − ^{1}H NMR (100 MHz, $CDCl_3$): δ = 7.19−7.07 (m, 6 H, aromatic), 6.74 (s, 4 H, aromatic), 4.31 (d, J = 13.0 Hz, 4 H, H_{ax} of ArCH_2Ar), 3.98, 3.65 (t, J = 7.2 Hz, 4 H each, OCH_2CH$_2$CH$_3$), 3.80 (d, J = 13.0 Hz, 4 H, H_{eq} of ArCH_2Ar), 1.94−1.74 (m, 8 H, OCH$_2$CH_2CH$_3$), 1.08, 0.84 (t, J = 7.1 Hz, 6 H each, OCH$_2$CH$_2$CH_3). − ^{13}C NMR (25 MHz, $CDCl_3$): δ = 172.2 (s, C=O), 157.9, 136.9, 133.4 (s, aromatic), 129.8 (d, aromatic), 122.8 (s, aromatic), 77.1 (t, OCH$_2$CH$_2$CH$_3$), 31.2 (t, ArCH$_2$Ar), 23.8 (t, 2 OCH$_2$$CH_2CH_3$), 23.2 (t, 2 OCH$_2$$CH_2CH_3$), 11.1 (q, 2 OCH$_2CH_2$$CH_3$), 10.0 (q, 2 OCH$_2CH_2$$CH_3$). − IR (KBr): ν_{max} = 3500−3100 cm^{-1} (OH), 1690 (C=O). − MS, CI(+), *m/z*: 681 (65) [M$^+$ + H], 663 (100) [M$^+$ − OH].

5,17-Bis(succinimidoxycarbonyl)-25,26,27,28-tetra-n-propoxycalix[4]arene (**10**): A solution of **9** (0.800 g, 1.75 mmol), *N*-hydroxysuccinimide (0.340 g, 4.38 mmol), and DCC (0.605 g, 4.38 mmol) in dry CH_2Cl_2 (60 ml) is stirred at room temp. for 48 h. Then dicyclohexylurea is filtered off and CH_2Cl_2 removed on a Rotavapor; the product is obtained in 63% yield as a white solid by trituration with 2-propanol. − M.p. 248−249°C (dec.). − ^{1}H NMR (100 MHz, $CDCl_3$): δ = 7.96 (s, 4 H, aromatic), 6.29 (t, J = 7.6 Hz, 2 H, aromatic), 6.10 (d, J = 7.6 Hz, 4 H, aromatic), 4.47 (d, J = 13.0 Hz, 4 H, H_{ax} of ArCH_2Ar), 4.20, 3.67 (t, J = 7.2 Hz, 4 H each, OCH_2CH$_2$CH$_3$), 3.25 (d, J = 13.0 Hz, 4 H, H_{eq} of ArCH_2Ar), 2.93 (s, 8 H, CH_2 of succinimide), 1.93−1.84 (m, 8 H, OCH$_2$CH_2CH$_3$), 1.09, 0.90 (t, J = 7.1 Hz, 6 H each, OCH$_2$CH$_2$CH_3). − ^{13}C NMR ($CDCl_3$): δ = 169.7 (s, ArC=O), 164.4, 162.0 (s, aromatic), 155.0 (s, C=O of succinimide), 137.8, 131.9 (s, aromatic), 131.6, 128.0 (d, aromatic), 122.7 (s, aromatic), 118.1 (d, aromatic), 77.2 (t, 2 OCH$_2$CH$_2$CH$_3$), 76.9 (t, 2 OCH$_2$CH$_2$CH$_3$), 30.9 (t, ArCH$_2$Ar), 25.8 (t, CH_2 of succinimide), 23.5 (t, 2 OCH$_2$$CH_2CH_3$), 23.2 (t, 2 OCH$_2$$CH_2CH_3$), 10.8 (q, 2 OCH$_2CH_2$$CH_3$), 9.9 (q, 2 OCH$_2CH_2$$CH_3$). − IR (KBr): ν_{max} = 1770 cm^{-1} (C=O ester), 1750 (C=O imide). − MS, CI(+), *m/z*: 874 (35) [M$^+$], 761 (100) [M$^+$ − ONC$_4$H$_4$O$_2$].

General Procedures for Coupling of Amino Acid Units with Carboxy Derivatives of Calix[4]arenes. − Method A: Compound **1** or compound **9** (0.65 mmol) are dissolved in dry CH_2Cl_2/DMF (4:1, v/v, 25 ml) and then DCC (1.05 equiv. for each carboxy group), *N*-hydroxybenzotriazole (1.05 equiv. for each carboxy group), L-alanine methyl ester hydrochloride or L-alanyl-L-alanine methyl ester hydrobromide (6 equiv. for each carboxy group) and triethylamine (6 equiv. for each carboxy group) are added. The reaction mixture is stirred at room temp. (reaction time: see below), dicyclohexylurea is filtered off and the filtrate added of 0.5 N HCl (20 ml). The organic layer is separated, washed with water (2 × 20 ml) and CH_2Cl_2 is removed under reduced pressure. − *Method B.* L-alanine methyl ester hydrochloride or L-alanyl-L-alanine methyl ester hydrobromide (3.12 mmol) and triethylamine (0.78 mmol for each carboxy group) are added to a suspension of **1** (0.3 g, 0.39 mmol) in dry CH_2Cl_2 (30 ml). The solution is stirred at room temp. untill the complete solubilization of the amino acid, then *O*-(benzotryazol-1-yl)-*N,N,N′,N′*-bis(pentamethylene)uronium tetrafluoroborate (1.87 mmol) and triethylamine (2.88 mmol) are added. During the first 30 min pH is frequently checked and triethylamine is added to maintain it at ca. 8.5. After 4 h the reaction is quenched by addition of 1 N HCl (30 ml), then the organic layer is separated, washed with 5% $NaHCO_3$ (30 ml) and with water (30 ml) and evaporated to dryness under reduced pressure. − *Method C.* A solution of L-alanine methyl ester hydrochloride (1.71 mmol) and triethylamine (3.43 mmol) in dry CH_2Cl_2 (15 ml) is added to a solution of **2** (0.33 g, 0.39 mmol) in dry CH_2Cl_2 (20 ml). The reaction is stirred at room temp. for 4 h and then treated with 1 N HCl (30 ml). The organic layer is separated, washed with water (30 ml) and evaporated to dryness under reduced pressure. − *Method D.* Compound **10** (0.500 g, 0.57 mmol) is dissolved in dry CH_2Cl_2/DMF (4:1, v/v, 25 ml); L-alanine methyl ester hydrochloride or L-alanyl-

L-alanine methyl ester hydrobromide (6.86 mmol) and triethylamine (6.86 mmol) are added. The reaction is stirred at room temp. (reaction time: see below) and quenched by addition of 0.5 N HCl (20 ml). The organic layer is separated, washed with water (2 × 20 ml) and evaporated under reduced pressure.

25,26,27,28-Tetra-n-propoxycalix[4]arene-5,11,17,23-tetrakis(carbonyl-N-L-alanine methyl ester) (**3**): Pure product is obtained by flash chromatography (CH_2Cl_2/acetone, 5:1, v/v). *Method A.* Reaction time: 48 h. Yield: 31%. *Method B.* Yield: 62%. *Method C.* Yield: 60%. − M.p. 110°C. − $[\alpha]^{25}_D$ = +50.5 (*c* = 1.05, EtOH). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.18, 7.07 (d, *J* = 2.0 Hz, 4 H each, aromatic), 6.64 (d, *J* = 7.0 Hz, 2 H, NH), 4.64−4.53 (m, 4 H, CH, alanine), 4.46 (d, *J* = 13.5 Hz, 4 H, H_{ax} of ArC*H*$_2$Ar), 3.88 (t, *J* = 7.3 Hz, 8 H, OC*H*$_2$CH$_2$CH$_3$), 3.74 (s, 12 H, OCH_3), 3.26 (d, *J* = 13.5 Hz, 4 H, H_{eq} of ArC*H*$_2$Ar), 1.97−1.87 (m, 8 H, OCH$_2$C*H*$_2$CH$_3$), 1.47 (d, *J* = 7.2, 12 H, CH_3, alanine), 0.99 (t, *J* = 7.3 Hz, 12 H, OCH$_2$CH$_2$C*H*$_3$). − ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8 (s, C=O ester), 167.1 (s, C=O amide), 159.4, 134.8, 128.3 (s, aromatic), 128.0, 127.0 (d, aromatic), 77.0 (t, O*C*H$_2$CH$_2$CH$_3$), 52.3 (q, OCH_3), 48.6 (d, CH, alanine), 31.0 (t, ArC*H*$_2$Ar), 23.2 (t, OCH$_2$*C*H$_2$CH$_3$), 16.1 (q, CH_3, alanine), 10.3 (q, OCH$_2$CH$_2$*C*H$_3$). − IR (CH_2Cl_2): ν_{max} = 1740 cm^{-1} (C=O ester), 1655 (C=O amide). − MS, CI(+), *m/z*: 1110 (100) [M$^+$].

25,26,27,28-Tetra-n-propoxycalix[4]arene-5,11,17,23-tetrakis(carbonyl-N-L-alanyl-L-alanine methyl ester) (**6**): Pure compound is obtained by flash chromatography (CH_2Cl_2/acetone, 1:1, v/v). − *Method A.* Reaction time: 48 h. Yield: 28%. − *Method B.* Yield: 35%. − M.p. 143°C. − $[\alpha]^{25}_D$ = +39.5 (*c* = 0.43, EtOH). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 7.1 Hz, 4 H, NH), 7.13, 7.00 (2 d, *J* = 2.0 Hz, 4 H each, aromatic), 6.79 (d, *J* = 7.9 Hz, 4 H, NH), 4.71−4.62 and 4.56−4.46 (m, 4 H each, C*H*, alanine), 4.44 (d, *J* = 13.6 Hz, 4 H, H_{ax} of ArC*H*$_2$Ar), 3.86 (t, *J* = 7.3 Hz, 8 H, OC*H*$_2$CH$_2$CH$_3$), 3.71 (s, 12 H, OCH_3), 3.22 (d, *J* = 13.6 Hz, 4 H, H_{eq} of ArC*H*$_2$Ar), 1.94−1.84 (m, 8 H, OCH$_2$C*H*$_2$CH$_3$), 1.39 (d, *J* = 7.2, 12 H, CH_3, alanine), 1.38 (d, *J* = 6.9 Hz, 12 H, CH_3, alanine), 0.98 (t, *J* = 7.3 Hz, 12 H, OCH$_2$CH$_2$C*H*$_3$). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.1 (s, C=O ester), 172.2, 166.4 (s, C=O amide), 159.4, 134.9, 134.6, 127.9 (s, aromatic), 127.7, 126.7 (d, aromatic), 76.9 (t, O*C*H$_2$CH$_2$CH$_3$), 52.2 (q, OCH_3), 48.9 (d, 4 CH, alanine), 48.2 (d, 4 CH, alanine), 30.8 (t, Ar*C*H$_2$Ar), 23.1 (t, OCH$_2$*C*H$_2$CH$_3$), 17.9 (q, 4 CH_3, alanine), 17.4 (q, 4 CH_3, alanine), 10.1 (q, OCH$_2$CH$_2$*C*H$_3$). − IR (KBr): ν_{max} = 1742 cm^{-1} (C=O ester), 1653 (C=O amide). − MS, CI(+), *m/z*: 1394 (100) [M$^+$].

25,26,27,28-Tetra-n-propoxycalix[4]arene-5,17-bis(carbonyl-N-L-alanine methyl ester) (**11**). − *Method A.* Reaction time: 6 h. The pure compound is obtained as a white solid in 56% yield by flash chromatography (hexane/THF 1:1, v/v). − *Method D.* Reaction time: 24 h. The pure compound is obtained in 53% yield by crystallization from CH_3OH as a white solid. − M.p. 143°C. − $[\alpha]^{25}_D$ = + 7.6 (*c* = 0.968, EtOH). − ^{1}H NMR (100 MHz, $CDCl_3$) δ 7.42, 7.39 (d, *J* = 2.0 Hz, 2 H each, aromatic), 6.66 (d, *J* = 7.0 Hz, 2 H, NH), 6.32−6.28 (m, 6 H, aromatic), 4.89−4.57 (m, 2 H, CH, alanine), 4.41 (d, *J* = 13.5 Hz, 4 H, H_{ax} of ArC*H*$_2$Ar), 3.99, 3.72 (t, *J* = 7.2 Hz, 4 H each, OC*H*$_2$CH$_2$CH$_3$), 3.78 (s, 6 H, OCH_3), 3.17 (d, *J* = 13.5 Hz, 4 H, H_{eq} of ArC*H*$_2$Ar), 1.98−1.78 (m, 8 H, OCH$_2$C*H*$_2$CH$_3$), 1.52 (d, *J* = 7.0 Hz, 6 H, CH_3, alanine), 1.05, 0.90 (t, *J* = 7.1 Hz, 6 H each, OCH$_2$CH$_2$C*H*$_3$). − ^{13}C NMR (25 MHz, $CDCl_3$): δ = 174.2 (s, C=O ester), 167.3 (s, C=O amide), 161.2, 155.6, 137.0, 133.2 (s, aromatic), 128.1, 127.9 (d, aromatic), 127.5 (s, aromatic), 122.6 (d, aromatic), 77.3 (t, 2 O*C*H$_2$CH$_2$CH$_3$), 76.9 (t, 2 O*C*H$_2$CH$_2$CH$_3$), 52.7 (q, OCH_3), 48.8 (d, CH, alanine), 31.2 (t, Ar*C*H$_2$Ar), 23.7 (t, 2 OCH$_2$*C*H$_2$CH$_3$), 23.4 (t, 2 OCH$_2$*C*H$_2$CH$_3$), 18.8 (q, CH_3, alanine), 10.9 (q, 2 OCH$_2$CH$_2$*C*H$_3$), 10.2 (q, 2 OCH$_2$CH$_2$*C*H$_3$). − IR (KBr): ν_{max} = 3370 cm^{-1} (NH), 1760 (C=O ester), 1660 (C=O amide). − MS, EI(+), *m/z*: 850 (25) [M$^+$], 748 (100) [M$^+$ − HNCH(CH$_3$)COOCH$_3$].

25,26,27,28-Tetra-n-propoxycalix[4]arene-5,17-bis(carbonyl-N-L-alanyl-L-alanine methyl ester) (**12**). − *Method D.* Reaction time: 72 h. The pure compound is obtained as a white solid in 43% yield by flash chromatography (ethyl acetate/hexane, 2:1, v/v). − $[\alpha]^{25}_D$ = +7.0 (*c* = 0.07, EtOH). − ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 8.16 (d, *J* = 7.9 Hz, 2 H, NH), 7.58 (d, *J* = 7.8 Hz, 2 H, NH), 7.24, 7.22 (d, *J* = 2.0 Hz, 2 H each, aromatic), 6.66−6.63 (m, 4 H. aromatic), 6.57 (t, *J* = 7.2 Hz, 2 H, aromatic), 4.75−4.67 (m, 2 H, CH, alanine), 4.49 (d, *J* = 13.6 Hz, 4 H, H_{ax} of ArC*H*$_2$Ar), 4.47−4.39 (m, 2 H, CH, alanine), 3.94, 3.88 (t, *J* = 7.2 Hz, 4 H each, OC*H*$_2$CH$_2$CH$_3$), 3.66 (s, 6 H, OCH_3), 3.23 (d, *J* = 13.6 Hz, 2 H, H_{eq} of ArC*H*$_2$Ar), 3.22 (d, *J* = 13.6 Hz, 2 H, H_{eq} of ArC*H*$_2$Ar), 2.00−1.93 (m, 8 H, OCH$_2$C*H*$_2$CH$_3$), 1.41, 1.28 (d, *J* = 7.1 Hz, 6 H each, CH_3, alanine), 1.06−0.96 (m, 12 H, OCH$_2$CH$_2$C*H*$_3$). − ^{13}C NMR (25 MHz, [D$_6$]acetone): δ = 173.7 (s, C=O ester), 172.8, 166.9 (s, C=O amide), 160.2, 157.2, 136.0, 135.8, 135.2 (s, aromatic), 129.1, 128.7, 127.8 (d, aromatic), 128.8 (s, aromatic), 122.8 (d, aromatic), 77.5 (t, 2 O*C*H$_2$CH$_2$CH$_3$), 77.4 (t, 2 O*C*H$_2$CH$_2$CH$_3$), 52.0 (q, OCH_3), 49.2 (d, 2 CH, alanine), 48.8 (d, 2 CH, alanine), 31.4 (t, Ar*C*H$_2$Ar), 23.9 (t, OCH$_2$*C*H$_2$CH$_3$), 17.8 (q, 2 CH_3, alanine), 17.6 (q, 2 CH_3, alanine), 10.6 (q, 2 OCH$_2$CH$_2$*C*H$_3$), 10.5 (q, 2 OCH$_2$CH$_2$*C*H$_3$). − IR (KBr): ν_{max} = 1750 cm^{-1} (C=O ester), 1650 (C=O amide). − FAB(+)-MS, *m/z*: 993 (100) [M$^+$ + H].

General Procedure for Hydrazinolysis: A solution of **3**, **11**, or **12** (0.15 mmol) in CH_2Cl_2 (10 ml) is added of 15 ml of a methanolic solution of hydrazine hydrate (5 equiv. for each ester group). The reaction mixture is stirred at room temp. for 18 h and then solvents removed under reduced pressure. The resulting solid is suspended in water and filtered on a Buchner to afford the pure compound as a white solid.

25,26,27,28-Tetra-n-propoxycalix[4]arene-5,11,17,23-tetrakis(carbonyl-N-L-alanine hydrazide) (**4**): Yield: 95%. − M.p. 168°C. − $[\alpha]^{25}_D$ = +183 (*c* = 1, EtOH). − ^{1}H NMR (300 MHz, CD_3OD): δ = 7.33, 7.28 (d, *J* = 2.0 Hz, 4 H each, aromatic), 4.53 (d, *J* = 13.1 Hz, 4 H, H_{ax} of ArC*H*$_2$Ar), 4.48 (q, *J* = 7.2 Hz, 4 H, CH, alanine), 3.95 (t, *J* = 7.4 Hz, 8 H, OC*H*$_2$CH$_2$CH$_3$), 3.33 (d, *J* = 13.1 Hz, 4 H, H_{eq} of ArC*H*$_2$Ar), 2.02−1.88 (m, 8 H, OCH$_2$C*H*$_2$CH$_3$), 1.39 (d, *J* = 7.2 Hz, 12 H, CH_3, alanine), 1.04 (t, *J* = 7.4 Hz, 12 H, OCH$_2$CH$_2$C*H*$_3$). − ^{1}H NMR ([D$_6$]DMSO) δ 9.05 (b, 4 H, N*H*NH$_2$), 8.07 (d, *J* = 6.9 Hz, 4 H, CONH), 7.48, 7.46 (d, *J* = 2.1 Hz, 4 H each, aromatic), 7.11 (b, 8 H, NHN*H*$_2$), 4.43 (d, *J* = 12.5 Hz, 4 H, H_{ax} of ArC*H*$_2$Ar), 4.37−4.30 (m, 4 H, CH, alanine), 3.89 (t, *J* = 7.6 Hz, 8 H, OC*H*$_2$CH$_2$CH$_3$), 3.36 (d, *J* = 12.5 Hz, 4 H, H_{eq} of ArC*H*$_2$Ar), 1.98−1.90 (m, 8 H, OCH$_2$C*H*$_2$CH$_3$), 1.26 (d, *J* = 7.1 Hz, 12 H, CH_3, alanine), 0.98 (t, *J* = 7.3 Hz, 12 H, OCH$_2$CH$_2$C*H*$_3$). − ^{13}C NMR (75 MHz, CD_3OD): δ = 171.9, 165.7 (s, C=O), 158.5, 133.9, 128.2 (s, aromatic), 128.1 (d, aromatic), 76.6 (t, O*C*H$_2$CH$_2$CH$_3$), 47.9 (d, CH, alanine), 30.4 (t, Ar*C*H$_2$Ar), 22.7 (t, OCH$_2$*C*H$_2$CH$_3$), 17.8 (q, CH_3, alanine), 10.1 (q, OCH$_2$CH$_2$*C*H$_3$). − IR (KBr): ν_{max} = 3283 cm^{-1} (NH$_2$), 1638 (C=O). − MS, CI(+), *m/z*: 1110 (100) [M$^+$ + H].

25,26,27,28-Tetra-n-propoxycalix[4]arene-5,17-bis(carbonyl-N-L-alanine hydrazide) (**13**): Yield: 87%. − M.p. 160−162°C. − $[\alpha]^{25}_D$ = +27.5 (*c* = 0.218, EtOH). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.60 (s, 2 H, N*H*NH$_2$), 6.96 (d, *J* = 7.4 Hz, 4 H, aromatic), 6.82 (t, *J* = 7.4 Hz, 2 H, aromatic), 6.79 (d, *J* = 2.0 Hz,

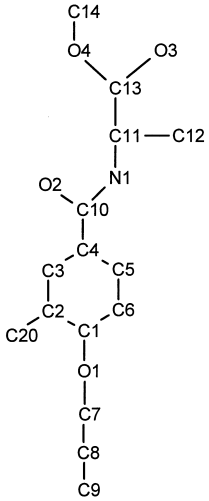
2 H, aromatic), 6.60 (d, J = 2.0 Hz, 2 H, aromatic), 6.48 (d, J = 7.1 Hz, 2 H, CONH), 4.60−4.45 (m, 2 H, CH, alanine), 4.46 (d, J = 13.6 Hz, 2 H, H_{ax} of ArCH_2Ar), 4.44 (d, J = 13.6 Hz, 2 H, H_{ax} of ArCH_2Ar), 3.95, 3.73 (t, J = 7.2 Hz, 4 H each, O$CH_2CH_2CH_3$), 3.16 (d, J = 13.6 Hz, 4 H, H_{eq} of ArCH_2Ar), 2.04−1.76 (m, 8 H, $OCH_2CH_2CH_3$), 1.35 (d, J = 7.1 Hz, 6 H, CH_3, alanine), 1.03, 0.91 (t, J = 7.2 Hz, 6 H each, $OCH_2CH_2CH_3$). − ^{13}C NMR (25 MHz, $CDCl_3$): δ = 173.1, 168.0 (s, C=O), 159.4, 157.2, 135.7, 135.6, 135.2, 134.8 (s, aromatic), 129.3, 129.1, 127.9, 126.5 (d, aromatic), 127.7 (s, aromatic), 122.6 (d, aromatic), 77.4 (t, 2 O$CH_2CH_2CH_3$), 76.9 (t, 2 O$CH_2CH_2CH_3$), 48.3 (d, CH, alanine), 31.2 (t, ArCH_2Ar), 23.6 (t, 2 $OCH_2CH_2CH_3$), 23.2 (t, 2 $OCH_2CH_2CH_3$), 18.1 (q, CH_3, alanine), 10.8 (q, 2 $OCH_2CH_2CH_3$), 10.3 (q, 2 $OCH_2CH_2CH_3$). − IR (KBr): ν_{max} = 3500 cm^{-1} (NH_2), 1650 (C=O). − MS, CI(+), *m/z*: 851 (40) [M^+ + H], 819 (100) [$M^+ - NHNH_2$].

25,26,27,28-Tetra-n-propossicalix[4]arene-5,17-bis(carbonyl-N-L-alanyl-L-alanine hydrazide) (**14**): Yield: 91%. − M.p. 214−216°C (dec). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.29 (s, 2 H, NHNH_2), 7.80 (d, J = 8.1 Hz, 2 H, CONHNH_2), 7.14 (d, J = 7.3 Hz, 2 H, aromatic), 7.10 (d, J = 7.3 Hz, 2 H, aromatic), 6.90 (t, J = 7.3 Hz, 2 H, aromatic), 6.65, 6.30 (d, J = 2.1 Hz, 2 H each, aromatic), 6.23 (d, J = 8.4 Hz, 2 H, ArCONH), 4.60−4.50 (m, 4 H), 4.48 (d, J = 13.4 Hz, 2 H, H_{ax} of ArCH_2Ar), 4.45 (d, J = 13.7 Hz, 2 H, H_{ax} of ArCH_2Ar), 3.99, 3.69 (t, J = 7.2 Hz, 4 H each, O$CH_2CH_2CH_3$), 3.18 (d, J = 13.7 Hz, 2 H, H_{eq} of ArCH_2Ar), 3.16 (d, J = 13.4 Hz, 2 H, H_{eq} of ArCH_2Ar), 1.95−1.85 (m, 8 H, $OCH_2CH_2CH_3$), 1.44, 1.28 (d, J = 7.1 Hz, 6 H each, CH_3, alanine), 1.11, 0.89 (t, J = 7.2 Hz, 6 H each, $OCH_2CH_2CH_3$). − ^{13}C NMR (25 MHz, $CDCl_3$): δ = 170.3, 168.9, 162.5 (s, C=O), 157.5, 156.1, 134.9, 133.0 (s, aromatic), 127.5, 126.0, 123.8 (d, aromatic), 126.1 (s, aromatic), 120.9 (d, aromatic), 75.6 (t, 2 O$CH_2CH_2CH_3$), 75.1 (t, 2 O$CH_2CH_2CH_3$), 47.3 (d, CH, alanine), 29.5 (t, ArCH_2Ar), 21.9 (t, 2 $OCH_2CH_2CH_3$), 21.4 (t, 2 $OCH_2CH_2CH_3$), 16.5 (q, 2 CH_3, alanine), 15.9 (q, 2 CH_3, alanine), 9.1 (q, 2 $OCH_2CH_2CH_3$), 8.3 (q, 2 $OCH_2CH_2CH_3$). − IR (KBr): ν_{max} 3320 cm^{-1} (NH_2), 1650 (C=O). − MS, CI(+), *m/z*: 993 (100) [M^+ + H].

25,26,27,28-Tetra-n-propoxycalix[4]arene-5,11,17,23-tetrakis-(carbonyl-N-L-alanine) (**5**): A solution of compound **3** (0.1 g, 0.09 mmol) in THF (14 ml) is cooled to 0°C. After addition of lithium hydroxide (0.008 g, 0.36 mmol) dissolved in water (3 ml), the mixture is stirred at room temp. for 6 h. The reaction is quenched by evaporation of the organic solvent and by addition of water (10 ml) and 4 N HCl until acidic pH. The product **5** is obtained as a white solid in quantitative yield. − M.p. 200°C. − $[\alpha]^{25}_D$ = +262 (c = 1.16, EtOH). − ^{1}H NMR (300 MHz, CD_3OD): δ = 7.34, 7.30 (d, J = 2.1 Hz, 4 H each, aromatic), 4.55 (d, J = 13.2 Hz, 4 H, H_{ax} of ArCH_2Ar), 4.47 (q, J = 7.3 Hz, 4 H, CH, alanine), 3.97 (t, J = 7.4 Hz, 8 H, O$CH_2CH_2CH_3$), 3.36 (d, J = 13.2 Hz, 4 H, H_{eq} of ArCH_2Ar), 2.03−1.96 (m, 8 H, $OCH_2CH_2CH_3$), 1.46 (d, J = 7.3 Hz, 12 H, CH_3, alanine), 1.08−1.02 (m, 12 H, $OCH_2CH_2CH_3$). − ^{13}C NMR (75 MHz, CD_3OD): δ = 175.2, 169.1 (s, C=O), 160.8, 136.1, 135.9, 129.8 (s, aromatic), 128.9, 128.8 (d, aromatic), 78.4 (t, O$CH_2CH_2CH_3$), 50.2 (d, CH, alanine), 32.0 (t, ArCH_2Ar), 24.5 (t, $OCH_2CH_2CH_3$), 17.2 (q, CH_3, alanine), 10.8 (q, $OCH_2CH_2CH_3$). − IR (KBr): ν_{max} = 3417 cm^{-1} (OH), 1730 (C=O acid), 1638 (C=O amide). − MS, CI(+), *m/z*: 1053 (100) [M^+ + H].

X-ray Structural Analysis of Compound **11**: $C_{50}H_{62}N_2O_{10}\cdot H_2O$, crystal system orthorhombic, system space group $P2_12_12$ with a = 31.592(4), b = 33.423(4), c = 9.414(2) Å, V = 9940(3) Å^3, D_{calcd} = 1.161 g/cm^3 and Z = 8. The data were measured at 295 K on a Siemens AED diffractometer using graphite monochromatized Cu-$K\alpha$ radiation (λ = 1.54178 Å). The intensities were determined by profile analysis according to the Lehmann and Larsen method[22]. During the data collection, one standard reflection collected every hundred showed a linear decay of 10% over the entire data collection. The intensities were corrected for Lorentz and polarization effects. A total of 16147 ± h, + k, + l reflections were measured and used in the solution of the phase problem by Direct Methods using SHELX86[23]. The best FOM E-map showed almost all the non-hydrogen atoms and revealed that the compound crystallizes with one independent molecule (A−B−C−D) and other two (E−F and G−H) half independent molecules disposed around the two fold crystallographic axes at −1/2, 0 and −1,0. The atomic numbering, identically repeated in each phenolic unit, is shown in Scheme 3.

Scheme 3. Atomic numbering scheme used for each phenolic unit in the three conformers of **11**



The 5915 unique observed reflections $I \geq 2\sigma$ (I) were used in the structure refinement which was carried out with the SHELX76 program[24]. The refinement was performed by chosing the (*S*) configuration of the calixarene derivative being (*S*) the stereochemistry of the alanine units. During the refinement two independent water molecules were found in the lattice. This leads to the 1:1 stoichiometry between calixarene derivative **11** and H_2O. The refinemet was done by blocked full matrix least-squares. Refined parameters refined were: the overall scale factor, the atomic coordinates, isotropic thermal parameters for all the non-hydrogen atoms. Due to the low number of observed reflections, only a limited number of atoms were treated with anisotropic thermal parameters. In particular for some of the aliphatic chains at the lower rim and for almost all the alanine units at the upper rim were allowed to undergo this treatment, even when in some case the enormous thermal motion at the terminal $COOCH_3$ group imposed to maintain isotropic temperature factors.

The hydrogen atoms, excepting those of the water molecules, were taken in their calculated positions with the geometrical constrain C−H = 0.96 Å and refined "riding" on the corresponding C atoms. The refinement was stopped at R = 0.099 (unit weights).

The atomic scattering factors of the non-hydrogen atoms were taken from Cromer and Waber[25], the values of Δf′ and Δf″ were those of Cromer and Ibers[26]. The geometrical calculations were obtained by PARST[27]. All the calculations were carried out on the Gould ENCORE91 at Centro di Studio per la Strutturistica Diffrattometrica of C.N.R in Parma.

A complete list of the atomic coordinates (table SI), thermal parameters (table SII), coordinates of H atoms (table SIII), a complete list of bond distances and angles (table SIV) and a full list of the experimental data for the X-ray experiment (table SV) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100915.

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