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Self-Assembled Chiral Dimeric Capsules from Difunctionalized *N*,*C*-Linked Peptidocalix[4]arenes: Scope and Limitations

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Dedicated to Professor David N. Reinhoudt on the occasion of his 65th birthday

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In this paper we report the synthesis of the first examples of upper (wide) rim calix[4]arene amino acids **5** and **27**, together with the conformational, self-assembly and molecular inclusion properties of the *N*,*C*-linked peptidocalix[4]arenes obtained from them. Whereas the dipropyl derivative **5** readily undergoes peptide synthesis allowing a small library of calix[4]arene pseudopeptides **12**–**21** to be obtained, the tetrapropoxy compound **27** preferentially gives upper-rim-bridged derivatives (e.g., **28**) which are formed through an intramolecular condensation reaction. The tetrapropoxycalix[4]arene pseudopeptide **33** shows conformational and self-assembly properties quite different to those of the dipropoxy derivatives **12**–**21**. The observed differences are explained on the basis of the different conformational flexibilities of the two calix[4]arene scaffolds. Calixarene **5** is more rigid than **27** thanks to the presence of two OH groups at the lower (narrow) rim that are involved in strong intramolecular hydrogen bonds. Only peptidocalix[4]arenes **12**–**21** but not **33** form hydrogen-bonded dimeric capsules in which the two macrocycles approach each other face-to-face and rotated by 180° with respect to the other in order to allow hydrogen-bonding complementarity between the interacting peptide chains, which, in some cases (**17**–**19**), form an antiparallel β sheet enhancing the stability of the capsule. The structures of the chiral dimeric capsules were established by molecular modelling calculations and NOESY NMR experiments, which give consistent results, whereas their stability in $CDCl_3$ ($69 \leq K_{dim} \leq 950$ M^{-1}) was determined by dilution NMR experiments. Compound **12** forms both 1:1 and 2:1 [$K_{11} = (7.8 \pm 1.2) \times 10^2$ M^{-1}, $K_{21} = (1.8 \pm 0.2) \times 10^5$ M^{-2}] host:guest complexes with the methylpyridinium ($MePy^+$) cation in CD_2Cl_2/$CDCl_3$ (10:1, v/v). There is no evidence for a guest template effect in stabilizing the supramolecular capsule.

Introduction

The self-assembly of calix[4]arene derivatives in the cone conformation through the interaction of suitable functional groups on their upper (wide) rim may lead to the formation of a capsular structure whose interior can accommodate a guest.[1,2] Non-covalent interactions such as ion-pairing,[3–5] metal–ligand coordination,[6] hydrophobic interactions[7] and hydrogen bonding[8–10] have been exploited to obtain calixarene-based building blocks that self-assemble in supramolecular capsules upon face-to-face dimerization.

The self-assembly of homodimeric calixarene capsules through hydrogen bonding requires self-complementary subunits,[2] that is, the functionalization of the calixarene upper rim with appropriately positioned hydrogen-bonding donor and acceptor groups.[11] One famous example of a self-complementary calix[4]arene is Rebek's[8] and Böhmer's[9] tetraurea derivative. Among Nature's strategies to obtain self-assembled structures, peptides play a major role. In a reverse β sheet, for example, the amide groups are specifically oriented to display self-complementarity. The self-assembling propensity of peptides could be exploited to obtain supramolecular capsules based on calixarenes if the upper rim of the macrocycle could be functionalized with amino acids or peptides in an appropriate orientation. With the exception of a controversial and never confirmed preliminary report[12] and one example referring to a calix[6]arene derivative,[13,14] *C*- and *N*-linked peptidocalixarenes have not been exploited for the formation of chiral dimeric capsules. On the other hand, we have recently shown that difunctionalized *C*-linked peptidocalix[4]arenes form at the solid state open tubular structures by self-assembly through intermolecular hydrogen bonding.[15,16]

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A few years ago we reported in a short communication[17] the synthesis of a calix[4]arene amino acid which allowed, for the first time, the synthesis of *N,C*-linked peptidocalix[4]arenes able to form self-assembled dimeric capsules in a low polar medium. This paper provides a full account of a more extensive study on this new class of peptidocalix[4]arenes and illustrates the scope and limitations of their self-assembly properties, together with their inclusion properties towards the methylpyridinium cation.

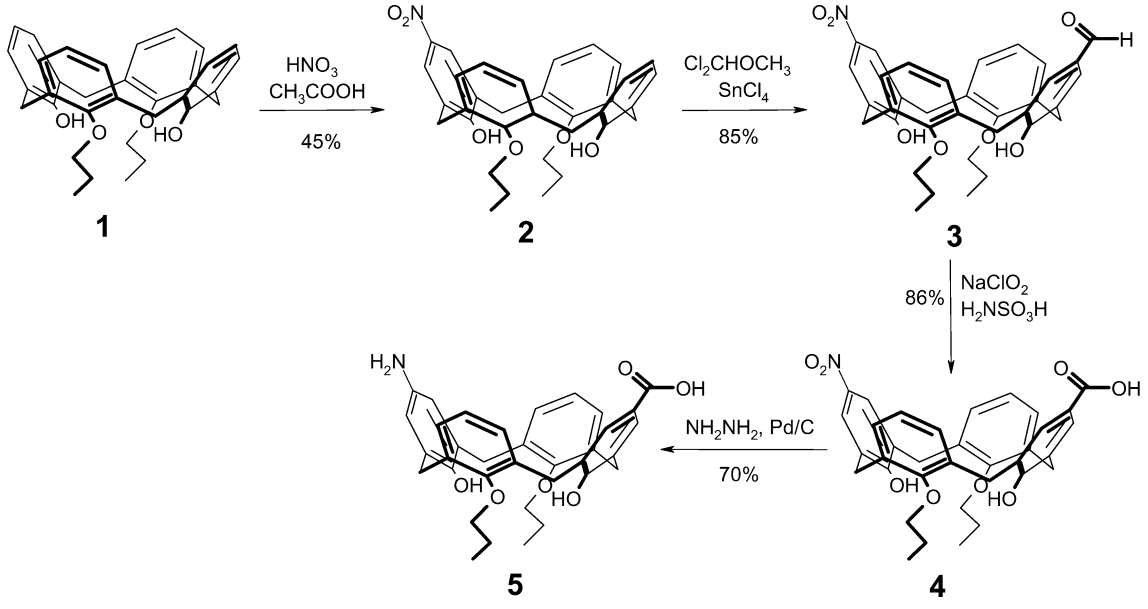
Results and Discussion

Synthesis of Calix[4]arene Amino Acids and *N,C*-Linked Peptidocalixarenes

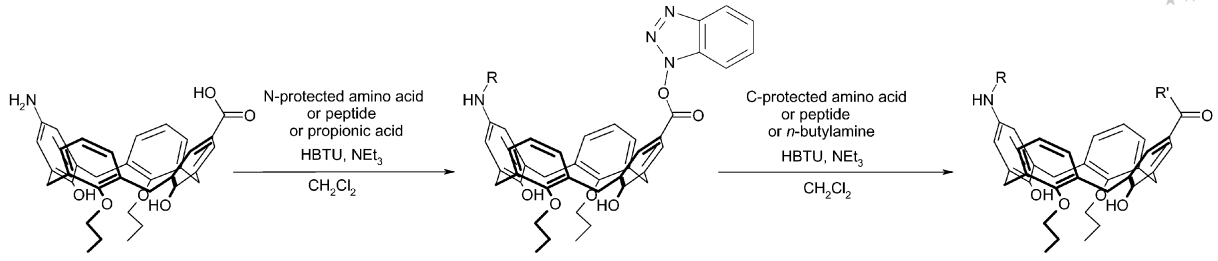
The synthesis of the calix[4]arene amino acid **5** derived from 1,3-dipropoxycalix[4]arene **1**[18] is depicted in Scheme 1.

This methodology exploits the higher reactivity of calixarene phenolic nuclei relative to those of aryl ethers in aromatic electrophilic substitution, which allows selectivity to be transferred from the lower (narrow) rim to the upper rim.[19] Compound **1** was first mononitrated by using a controlled excess of 65% HNO_3 (1.8 equiv.) and then formylated on the opposite phenolic nucleus with dichloromethyl methyl ether and $SnCl_4$. Subsequent oxidation of the formyl group of **3** to a carboxylic acid and reduction of the nitro group of **4** to an amine allowed the calix[4]arene amino acid **5** to be obtained in 23% overall yield from compound **1**. The mononitration of compound **1** is the step which reduces the yield of the whole process, all others giving very high yields. The acid/base properties of the calixarene amino acid **5** are rather different to those of the natural ones. In fact, IR spectroscopy reveals that **5** is not present in the zwitterionic form due to the lower basicity of the NH_2 group linked to the calixarene aromatic nucleus compared with the aliphatic amine of an α-amino acid. Nonetheless, **5** is quite stable both in the solid state and in solution at neutral or acidic pH and in mildly basic conditions. In contrast, a strongly basic solution leads to a slow degradation of the product, easily visualized by the appearance of a pink-red colour. The degradation is presumably due to the oxidation of the *p*-NH_2 aromatic nucleus to a benzoquinoneimine species which forms after the deprotonation of the phenolic OH. As a consequence, in the peptide synthesis (see below) the protection of the COOH group with an alkyl ester had to be avoided as the deprotection step in basic conditions leads to the formation of *p*-benzoquinoneimines.

The reaction of **5** with an *N*-protected amino acid/peptide or propionic acid in the presence of the coupling reagent HBTU leads to the formation of the intermediates **6**–**11** which are characterized by the presence of a benzotriazolyl active ester on the calixarene carboxylic acid (Scheme 2). During this coupling reaction no intra- or intermolecular condensation reactions between the $ArNH_2$ and the active ester take place. The former reaction is prevented by the presence of hydrogen bonds at the lower rim which do not allow flattening of the cone and the formation of an intramolecular amide bond (as was observed for the analogous tetrapropoxy derivatives, see below), while the latter is hindered by the low reactivity of the aromatic amine group. The resulting benzotriazolyl active ester of the carboxylic acid is also less reactive than the corresponding group derived from a natural amino acid, thus ensuring the stability of the intermediate during aqueous work-up and chromatography on silica gel. Addition of the *C*-protected amino acid/peptide in the presence of triethylamine and of another equivalent of the coupling reagent (not strictly necessary, but useful to improve the yield in case a small



Scheme 1.

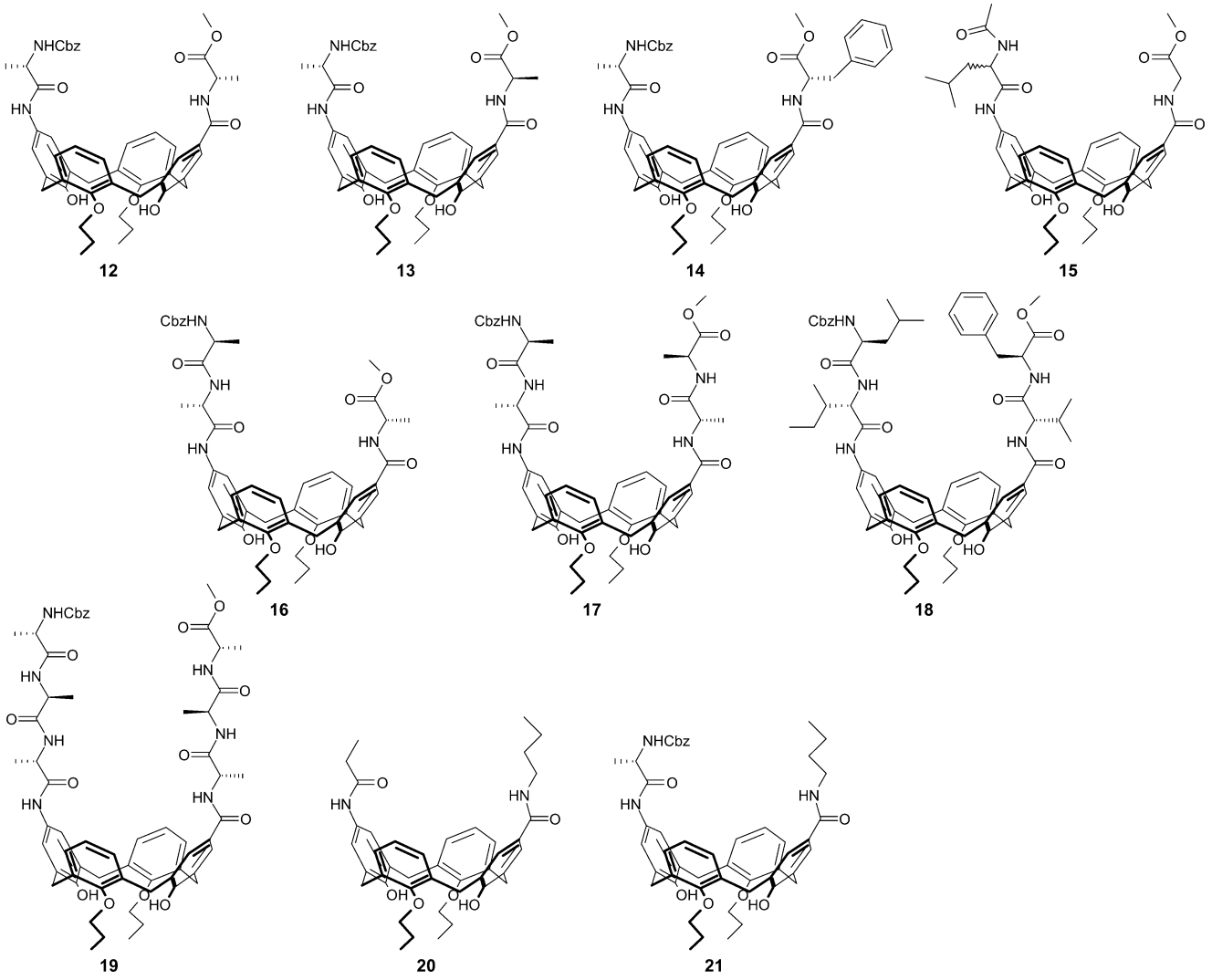


5

6 R = L-AlaNHCbz
7 R = (dl)-LeuNHAc
8 R = L-Ala-L-AlaNHCbz
9 R = L-Ile-L-LeuNHCbz
10 R = L-Ala-L-Ala-L-AlaNHCbz
11 R = C(O)Et

12 R = L-AlaNHCbz, R' = L-AlaOMe
13 R = L-AlaNHCbz, R' = D-AlaOMe
14 R = L-AlaNHCbz, R' = L-PheOMe
15 R = (dl)-LeuNHAc, R' = GlyOMe
16 R = L-Ala-L-AlaNHCbz, R' = L-AlaOMe
17 R = L-Ala-L-AlaNHCbz, R' = L-Ala-L-AlaOMe
18 R = L-Ile-L-LeuNHCbz, R' = L-Val-L-PheOMe
19 R = L-Ala-L-Ala-L-AlaNHCbz,
R' = L-Ala-L-Ala-L-AlaOMe
20 R = C(O)Et, R' = NH-*n*Bu
21 R = L-AlaNHCbz, R' = NH-*n*Bu

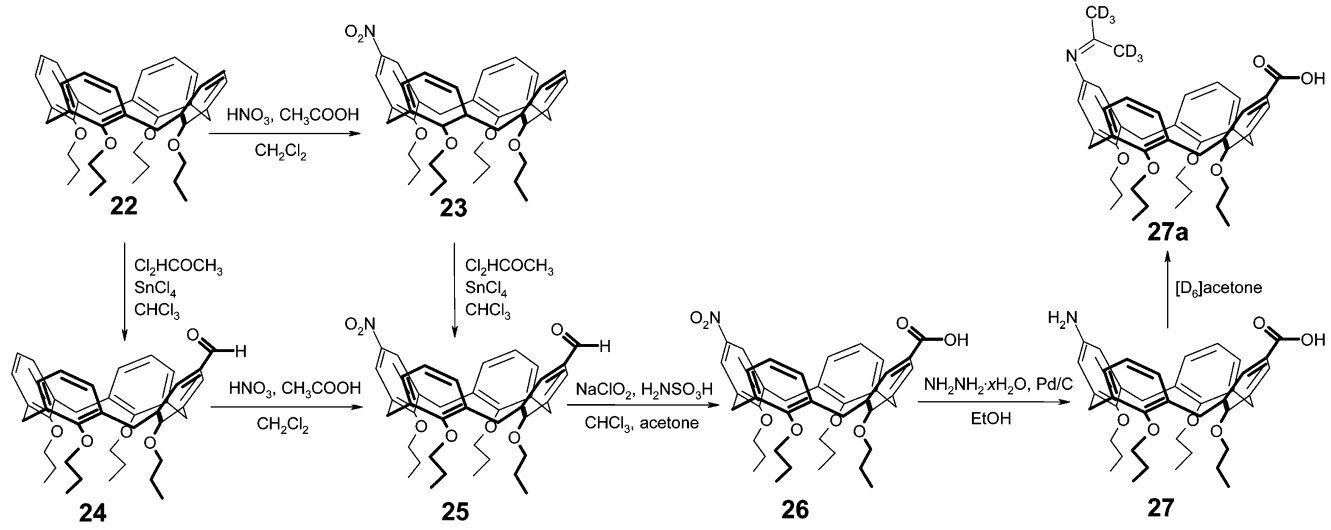
Scheme 2.



12 **13** **14** **15**

16 **17** **18**

19 **20** **21**



Scheme 3.

amount of active ester hydrolysis takes place in the basic reaction medium) results in the formation of the *N*,*C*-linked peptidocalix[4]arenes **12**–**19** in satisfying (40–70%) yields. Overall, the protection/deprotection of the carboxylic group, typical of classical peptide synthesis in solution, is not required and this is a big advantage of the described synthetic protocol, which was also followed in the synthesis of the amide derivatives **20** and **21**. All compounds were fully characterized by ^{1}H and ^{13}C NMR, ESI-MS and elemental analyses.

In order to avoid the oxidation reactions of the *p*-aminophenol rings in basic conditions and to evaluate the importance of the lower rim substitution on the self-assembly properties we also synthesized the calix[4]arene amino acid **27** having four propyl groups at the lower rim. After unsuccessful attempts to obtain compound **27** by alkylation of compound **4** by Mitsunobu reaction or of an *N*-protected derivative of **5** by direct reaction with *n*-propyl iodide in the presence of a base, we resolved to introduce the nitro and the formyl groups into the tetrapropoxycalixarene **22**. We explored the two possible pathways: first the nitration and then the formylation and vice versa (Scheme 3).

Mononitrotetrapropoxycalix[4]arene **23** is easily obtained in 55% yield by nitration of tetrapropoxycalix[4]-arene **22** following a literature procedure.[20] The pure product is obtained by crystallization from CH_2Cl_2/MeOH. The subsequent formylation yields a mixture of compounds whose separation by column chromatography is tricky. We succeeded in crystallizing the compound from the crude

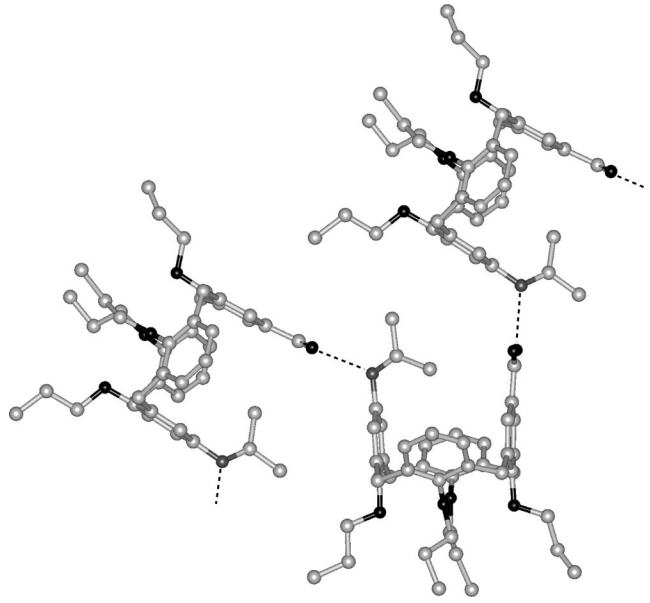


Figure 1. Ball-and-stick representation of the hydrogen-bonding motif in the crystal lattice of the imine derivative **27a** (solvent molecules and hydrogen atoms have been omitted for clarity; for a coloured picture see Figure S10 in the Supporting Information).

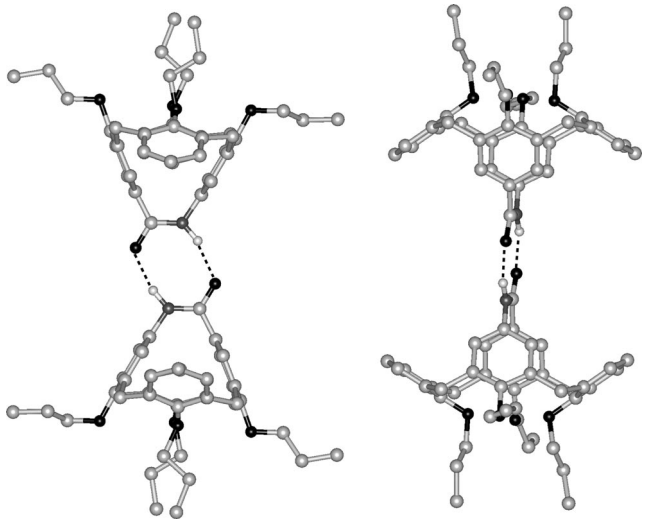
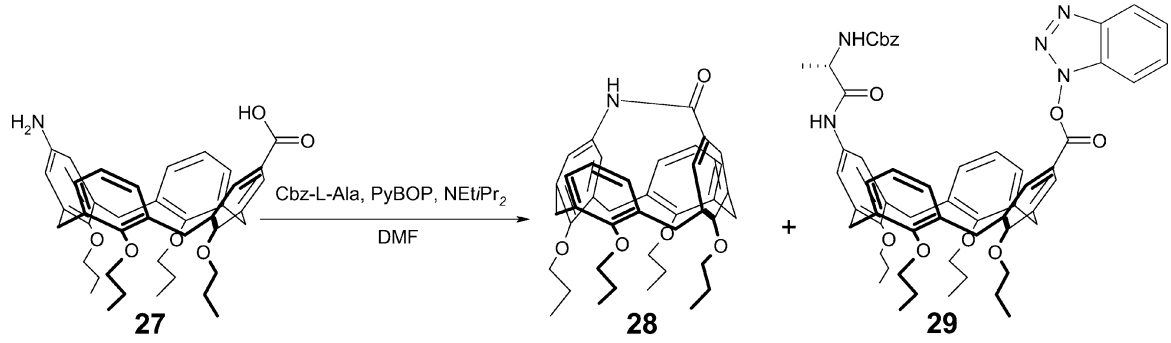
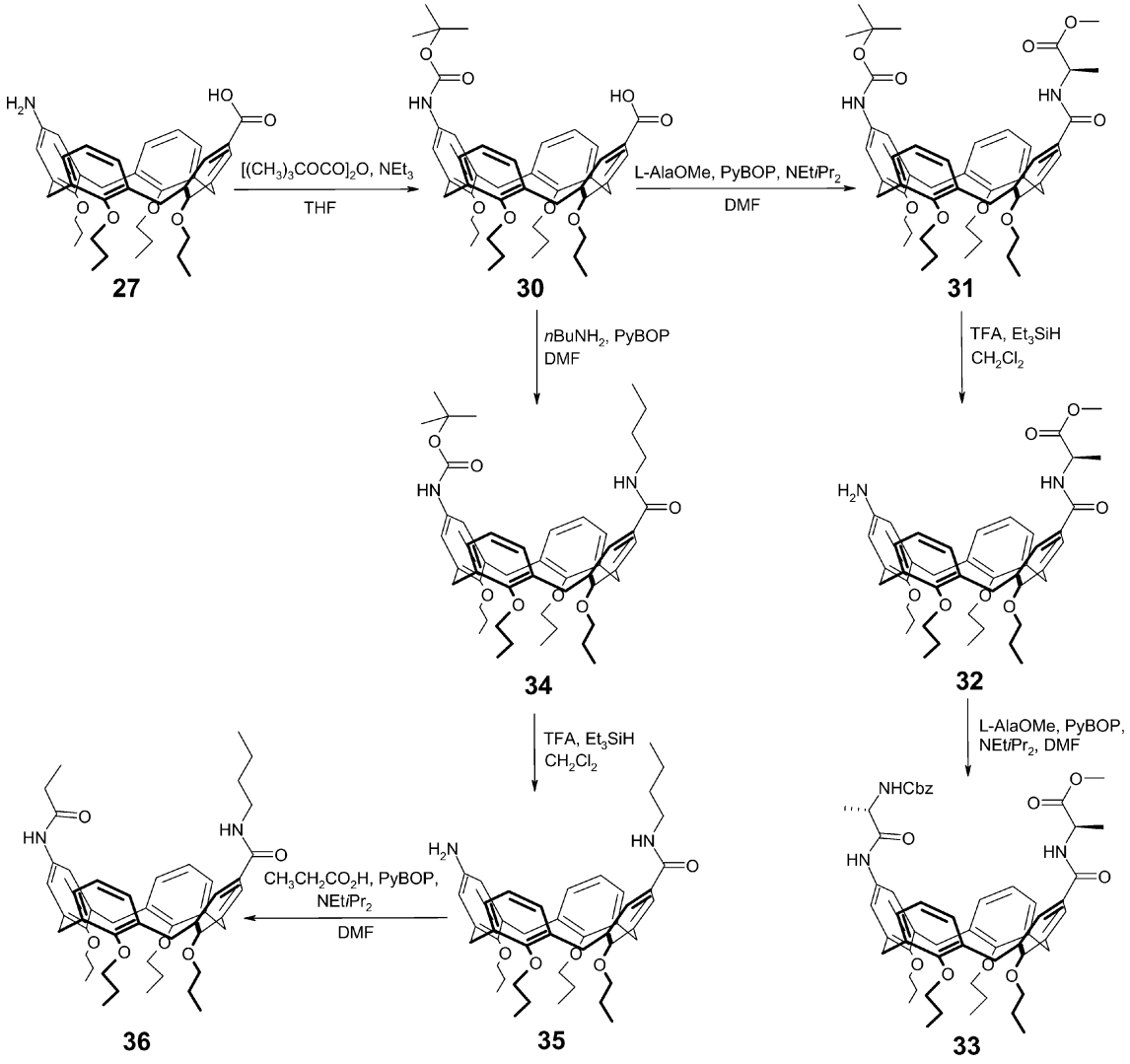


Figure 2. Ball-and-stick representation of the hydrogen-bonding motif in the crystal lattice of **28** (non-hydrogen-bonded H atoms have been omitted for clarity), viewed along two different directions (for a coloured picture see Figure S11 in the Supporting Information).

mixture with CH_2Cl_2/hexane in 14% yield but, unfortunately, the conditions for obtaining the selective crystallization of **25** are not easily reproducible. Therefore, even if the overall yield of this protocol is higher than the alternative procedure (see below), we do not recommend it. Alternatively, the monoformylation[21] of **22** yields pure **24** in 30% yield after column chromatography. During the reaction, 10–15% cleavage of the propyl groups of the starting material takes place. Nitration of **24** affords a crude mixture from which pure **25** can be isolated by column chromatography in 38% yield. The undesired 1,2-difunctionalized product is formed in 27% yield, and, considering that it has



Scheme 4.



Scheme 5.

a two-fold statistical factor, the formation of the 1,3-isomer is significantly favoured. The 1,3-disubstitution pattern of compound **25** is supported by ^{1}H and ^{13}C NMR spectroscopy and confirmed by X-ray diffraction studies (see below). The subsequent oxidation of the formyl group and reduction of the nitro group are carried out similarly to literature procedures in high yields. As expected, during these synthetic steps no oxidation of the aromatic nuclei takes place. Also compound **27**, like the calix[4]arene amino acid **5**, exists in a non-zwitterionic form.

A [D_6]acetone solution of compound **27**, upon standing in an NMR tube, formed crystals suitable for crystallographic studies. X-ray diffraction analysis[22] revealed that the crystallized compound was in fact the imine derivative **27a** which formed upon reaction with deuterated acetone (Figure 1). One and a half solvent molecules per calixarene unit are found in the crystal lattice, one of which is disordered. In the crystal, the calixarene scaffold adopts a closed flattened cone conformation with the Ar-imine and the Ar-COOH rings almost parallel and the unsubstituted aromatic nuclei pointing outwards. This conformation is quite unexpected since upper-rim 1,3-disubstituted calix[4]arenes usually adopt an open flattened cone conformation in order to reduce the steric hindrance between the two substituents.[23] No intramolecular hydrogen bonding is present to justify this conformation, which is probably induced by a combination of intermolecular hydrogen bonds formed between the COOH and the imine nitrogen atom of neighbouring molecules and crystal packing factors (Figure 1).

Functionalization of the tetrapropoxycalixarene amino acid **27** to obtain a pseudopeptide was first carried out following the same synthetic protocol developed for the dipropoxy derivative **5**. However, when **27** was treated with Cbz-alanine in the presence of PyBOP and a base, the major product was compound **28**, derived from the intramolecular reaction between the NH_2 group and the COOH activated by PyBOP (Scheme 4). The desired compound **29** was isolated only in trace amounts.

In the NMR spectrum of **28**, the aromatic protons *ortho* to the CO and NH groups resonate at unusually high fields (δ = 5.62 and 5.52 ppm, respectively) due to the highly flattened structure of the compound, which was confirmed by X-ray analysis.[22] In the crystal, thanks to the unusual *cis*-arrangement of the secondary amide bond, two molecules of **28** self-associate by means of two hydrogen bonds (Figure 2).

In contrast to the dipropoxy derivative **5**, whose structure is rigidified by the hydrogen bonds at the lower rim, the flexible scaffold of **27** allows the formation of the intramolecular condensation product even in the presence of the scarcely nucleophilic aromatic amine group.

To synthesize peptidocalixarene **33** and diamide **36**, the amino group of **27** had therefore to be protected. The Boc-protected calixarene amino acid **30** was then condensed with alanine methyl ester (or *n*-butylamine) in the presence of PyBOP, the protecting group was removed with TFA and, after reaction with Cbz-alanine (or propionic acid) in the presence of PyBOP, the final products **33** and **36** were obtained in good yields (Scheme 5).

Conformational and Self-Assembly Properties of *N*,*C*-Linked Peptidocalix[4]arenes

The two series of *N*,*C*-linked peptidocalix[4]arenes, one derived from dipropoxycalix[4]arene amino acid **5** and the other from the tetrapropoxy analogue **27**, show quite different conformational and self-assembly properties which highlight the important role played by hydrogen bonding at the lower rim of the calixarene.[24] Compounds **12**–**21** show concentration-dependent ^{1}H NMR spectra in $CDCl_3$. In the range 0.01–10 mM the largest shifts are observed for the ArN*H*, N*H*Cbz and Ar*H* (*meta* and *para* to the OPr group) protons. The NMR signals remain sharp and well-resolved within the whole concentration range explored and indicate the presence of a self-association equilibrium involving discrete entities in fast exchange on the NMR time-scale, ruling out the formation of disordered aggregates such as oligomers or polymers. The self-association behaviour of compounds **12**–**21** was therefore quantitatively investigated through ^{1}H NMR dilution experiments in $CDCl_3$. The shifts of several signals that could be easily followed during the dilution experiment were simultaneously fitted to the dimerization model by using the HypNMR program.[25,26] The non-linear regression analysis is in excellent agreement with the model for all the compounds (see Figure 3 as an example) and yielded the dimerization constants (K_{dim}) reported in Table 1, along with the dimerization-induced shifts ($\Delta\delta$) of selected protons. Attempts to fit the observed shifts to models including higher stoichiometry species were unsuccessful, failing to attain convergence. The values of the dimerization constants are in the range 10^2–10^3 M^{-1} and generally increase with the number of hydrogen-bonding groups present on the calixarene derivative. Moreover, in [D_6]DMSO the ^{1}H NMR spectra of compounds **12**–**21** are not concentration-dependent, while in [D_6]acetone smaller variations of the chemical shifts during the dilution experiments are observed.[27] These data suggest that in $CDCl_3$ the dimerization process is driven by the formation of hydrogen bonds, presumably involving the ArN*H* and N*H*Cbz hydrogen-bonding donor groups.

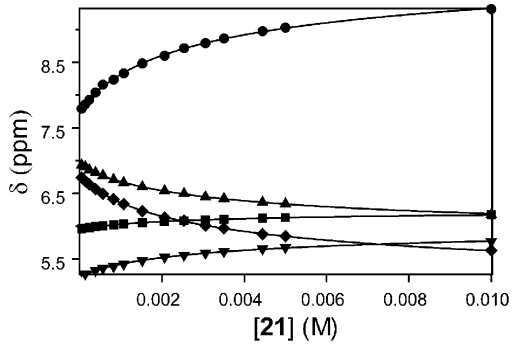


Figure 3. Plot of the experimental chemical shifts of the ArN*H* (●), Ar*H* (*meta* OPr) (▲), Ar*H* (*para* OPr) (♦), ArCON*H* (■) and N*H*Cbz (▼) resonances of **21** during the ^{1}H NMR dilution experiment ($CDCl_3$, 300 MHz, T = 298 *K*), along with the fitted curves (plain lines).

The ESI-MS spectra of 10^{-4} M solutions of compounds **12**–**21** in MeOH, both in the positive and in the negative mode, are characterized by the presence of a peak corresponding to the dimer with a relative abundance of 10–15% relative to the monomer peak.

Penta-pseudopeptides **17** and **18** and hepta-pseudopeptide **19**, having a higher number of hydrogen-bonding groups, show association constants higher than the tri-pseudopeptides **12**–**15**. However, among compounds having the same numbers of amino acids, significant variations in the association constants are observed. Comparison between the self-assembly properties of the different compounds of this small library, along with a careful analysis of the NMR spectra during the dilution experiments, proved helpful in investigating the structural features of the self-assembled dimers. Remarkably, the dimerization-induced shifts of the signals that experience the largest variations are generally conserved throughout the series (Table 1), indicating that the structure of the dimer is essentially the same for all the compounds. The amide groups directly linked to the aromatic nuclei (ArNHCO and ArCONH) are the only hydrogen-bonding groups that are present in all the compounds and must therefore be primarily responsible for the self-assembly. When other hydrogen-bonding groups are present they can contribute to the dimer stability through additional interactions. ArN*H* is the signal that undergoes the largest upfield shift upon dimer formation ($\Delta\delta$ in the range 2.0–2.9 ppm, Table 1), indicating that it is involved in a strong hydrogen bond. Therefore, the hydrogen-bond acceptor must be the Ar*CO* group. The small downfield shift (0.3–0.6 ppm) observed for the ArCON*H* protons is probably just a consequence of its proximity to the hydrogen-bonding acceptor Ar*CO* group. Besides ArN*H*, the second most shifted signals during the dilution experiments are those of the Ar*H* protons *meta* and *para* to the OPr groups, which are upfield-shifted ($\Delta\delta$ in the range –2.0 to –1.6 and –1.3 to –1.0 ppm for the *para* and *meta* protons, respectively). The upfield shift implies that the calixarene conformation in the dimer is more flattened than in the monomer, with the unfunctionalized aromatic rings pointing inwards into the shielding cone of the other two amide-functionalized phenolic nuclei. A minimized structure obtained is shown in Figure 4. Compound **20** is self-complementary in terms of its hydrogen-bonding donor and acceptor groups if two molecules approach each other "face-to-face", with the ArCO nucleus facing the ArNH one. In the dimer the flattening of the calixarene scaffold (open flattened cone conformation) is necessary to allow the hydrogen-bonding groups directly linked to the aromatic nuclei (ArN*H* and Ar*CO*) to get in close proximity to each other (Figure 4). This structure is in agreement with the observed dimerization-induced shifts and is also supported by the NOESY NMR spectrum of compound **20** at high concentrations ($>10^{-2}$ M) which shows the presence of an intense cross-peak between ArN*H* and the aromatic protons Ar*H*CO, together with a smaller correlation between the aromatic protons Ar*H*CO and Ar*H*NH which are held in close proximity by the ArNH···OCAr interaction (see Figure S3, Supporting Information).[28]

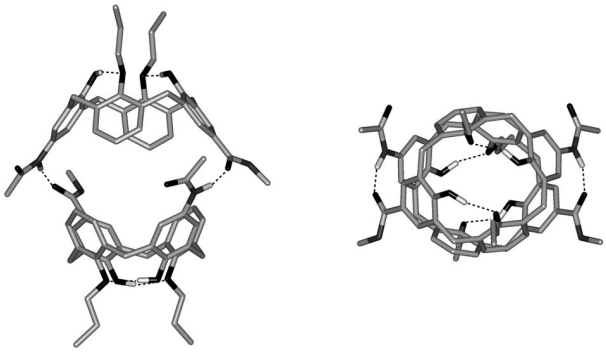


Figure 4. Lateral (left) and top (right) view of a molecular model (MMFF) of the self-assembled dimer of **20** (for a coloured picture see Figure S12 in the Supporting Information).

In peptidocalixarenes **12**–**15** and **21**, the significant downfield shift experienced by the N*H*Cbz (or the corresponding N*H*Ac for **15**) resonance upon dimerization ($\Delta\delta$ in the range 1.4–0.6 ppm) indicates that also this group acts as a hydrogen-bond donor, while the small downfield shift (0.6–0.3 ppm) observed for the NH of the *N*-linked amino acid (or amide) is probably just a consequence of its proximity to the hydrogen-bonding acceptor ArCO group. The temperature coefficients measured for the N*H* signals of

Table 1. Dimerization constants and dimerization-induced shifts ($\Delta\delta = \delta_{dimer} - \delta_{monomer}$) for the self-association of compounds **12**–**21**.[a]

Compound	K_{dim}[b] [M^{-1}]	$\Delta\delta$ [ppm]				
		ArN*H*	N*H*Cbz	ArCON*H*	Ar*H* (*p*-OPr)	Ar*H* (*m*-OPr)
12	105	2.3	0.8	0.4	–1.8	–1.2
13	115	2.6	0.9	0.3	–2.0	–1.3
14	69	2.5	0.8	0.4	–1.9	–1.2
15	79	2.0	0.8[c]	0.6	–1.6	–1.0
16	110	2.0	0.7[d]	0.4	–1.6	–1.0
17	788	2.0	n.d.	n.d.	n.d.	n.d.
18	466	n.d.	0.6	n.d.	n.d.	n.d.
19	950	1.5	0.8	n.d.	n.d.	–0.9
20	74	2.9	–	0.4	–1.8	–1.2
21	169	2.7	1.4	0.4	–2.0	–1.3

[a] Measured by ^{1}H NMR (300 MHz, $CDCl_3$) dilution experiments in the concentration range 10^{-2}–10^{-5} M at T = 298 K; n.d. = not determined because the proton signal is superimposed by others. [b] Errors between 2–15%. [c] $\Delta\delta$(N*H*Ac). [d] $\Delta\delta$[ArNHCOCH(CH_3)-N*H*].

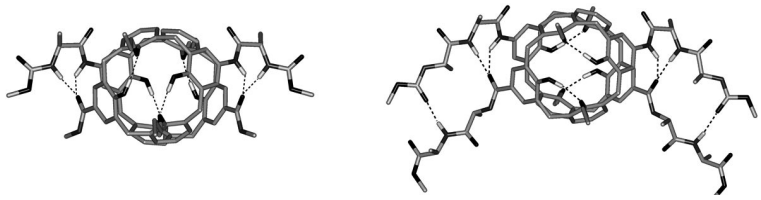


Figure 5. Top views of the molecular models (MMFF) of the self-assembled dimers of **21** (left) and **17** (right). The butyl chain and the benzyl group of **21** and the alanine methyl groups and the benzyl group of **17** have been omitted for clarity (for a coloured picture see Figure S13 in the Supporting Information).

compound **12** reflect the different degree of hydrogen-bonding involvement of these protons: ArN*H* (–17 ppb K^{-1}) > N*H*Cbz (–6.2 ppb K^{-1}) > ArCON*H* (–3.1 ppb K^{-1}).[29] Molecular modelling of compound **21** (Figure 5, left) and **12** (see Figure S4 in the Supporting Information) reveals that in both compounds only a bifurcated hydrogen bond between both N*H* donor groups of the *C*-linked amino acids and the ArCO acceptor unit is formed in spite of the fact that in the tri-pseudopeptide **12** a second CO acceptor group is also present. This explains the relatively high dimerization constant shown by **21** (nearly double that of **20**) and the large downfield shift $\Delta\delta$ = 1.4 ppm of the NHCbz proton observed upon $\mathbf{21}_2$ dimer formation.

The smaller dimerization constants of **12**–**15** compared with **21** (Table 1) confirm that the larger steric hindrance given by the *N*-linked amino acid side-chain disfavours self-assembly. The phenylalanine derivative **14**, in fact, displays the smallest dimerization efficiency among the tri-pseudopeptides. Also the NOESY NMR spectra of the peptidocalixarenes **12**, **15** and **21** show cross-peaks between the ArN*H* and Ar*H*CO protons and between the Ar*H*NH and Ar*H*CO aromatic protons (see Figures S5–S7, Supporting Information). The seven-fold increase in the association constant measured for the penta-pseudopeptide **17** with respect to **12** can be easily explained by an increase in the number of hydrogen-bonding interactions. Interestingly, the NOESY NMR spectrum of **17** shows a correlation peak between two CH protons, one belonging to the *N*-linked and the other to the *C*-linked peptide, in addition to the ArN*H*–Ar*H*CO cross-peak (see Figure S8, Supporting Information). A molecular modelling (MMFF) study yielded as the minimum energy conformer the dimer represented in Figure 5 (right) in which, in addition to the bifurcated interactions found in the pseudopeptides **12**–**15** and **21**, a hydrogen bond between the CO(Cbz) and the NH of the terminal alanine methyl ester is also present. This model substantiates the proximity of the two alanine CH protons of the two different chains and the resulting NOE correlations. Moreover, this additional interaction, together with the NH(alanine)···OCAr hydrogen bond, forms a 14-membered ring typical of a peptide β sheet. On the other hand, the tetra-pseudopeptide **16**, which lacks the second NH in the *N*-linked chain, self-assembles with the same efficiency as **12** and with a lower efficiency than **17** since it forms only two bifurcated hydrogen bonds. Even though it has the same number of amino acids as **17**, compound **18** self-assembles with less efficiency than **17** because of an increase in the steric hindrance of the lateral groups. The known higher tendency[30] for peptides having lipophilic side-chains to form β sheets in water cannot operate in chloroform and the steric hindrance predominates in this solvent. Finally, the longest member of this library, the hepta-pseudopeptide **19**, dimerizes with an association constant that is only 17% larger than the penta-pseudopeptide **17**, and it shows slightly broad NMR spectra even at low concentration. This indicates that by increasing the number of hydrogen-bonding groups, additional interactions, either intra- or intermolecular, take place and, besides the dimerization, oligomerization processes can also occur.

In contrast to the dipropoxy peptidocalixarenes described above, the tetrapropoxy derivatives **33** and **36** do not self-aggregate in the concentration range 0.01–10 mM. The ^{1}H NMR spectra of these compounds in fact are not dependent on the concentration. Instead, compound **33** adopts in $CDCl_3$ a closed flattened cone conformation with the substituted aromatic rings pointing inwards, as deduced from the relative position of the signals of the aromatic protons in the NMR spectrum: δ = 6.86 and 6.75 ppm for Ar*H*(CO), 6.39 and 6.28 ppm for Ar*H*(NH) and 6.80–6.70 ppm for the non-substituted Ar*H*. This structure is due to the formation of an intramolecular hydrogen bond which is confirmed by the presence in the NOESY spectrum of a cross-peak between the CH protons of the two alanine chains. In [D_6]acetone, on the other hand, the hydrogen bond is broken and the conformation adopted is an open flattened cone with the alanine chains pointing outwards [δ = 7.61 ppm for Ar*H*(CO), 7.27 and 7.22 ppm for the two signals of Ar*H*(NH) and 6.40–6.34 ppm for Ar*H*, Figure 6].

The diamide **36** in $CDCl_3$ also adopts a closed flattened cone conformation induced by the formation of an intramolecular hydrogen bond. The larger temperature coefficient[29] of the ArN*H* with respect to the ArCON*H* amide proton NMR chemical shifts (–4.7 vs. –2.2 ppb K^{-1}, respectively) and the presence of a cross-peak in the NOESY spectrum between COCH_2 and NHCH_2 and between ArN*H* and Ar*H*(CO) suggest that the intramolecular interaction is formed between ArN*H* as hydrogen-bond donor and ArCO as acceptor. In [D_6]acetone this hydrogen bond is broken, as deduced from the relative signal positions of the aromatic protons [Ar*H*(CO): 7.29, Ar*H*(NH): 6.89, Ar*H*: 6.50 ppm] in the ^{1}H NMR spectrum. The involvement of the hydrogen-bonding groups in intramolecular interactions therefore prevents the formation of self-assembled dimers, as observed for the dipropoxypeptidocalixarenes. In turn, the in-

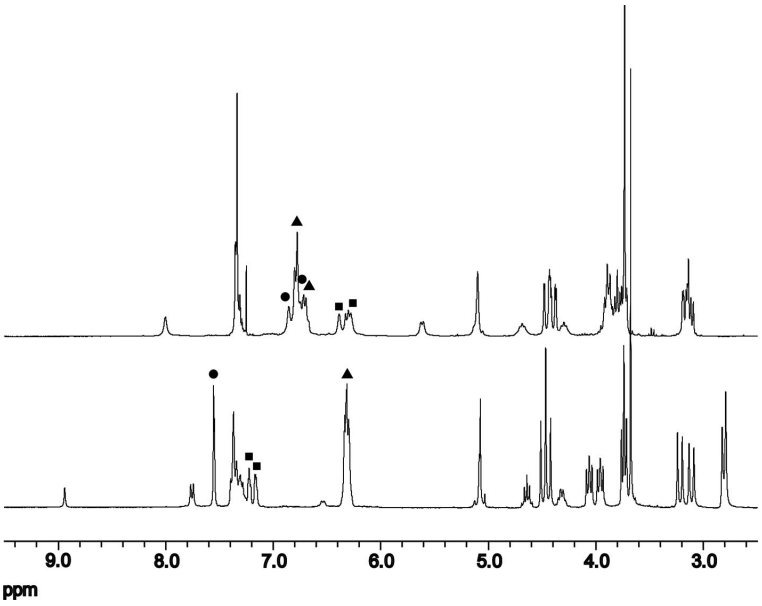


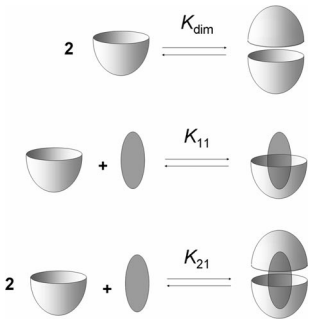
Figure 6. ^{1}H NMR spectra (top: 300 MHz, $CDCl_3$, T = 298 K; bottom: 300 MHz, [D_6]acetone, T = 298 K) of compound **33** showing the relative positions of the signals of the aromatic protons Ar*H*(CO) (●), Ar*H*(NH) (■) and Ar*H* (unsubstituted ring) (▲).

tramolecular interactions take place thanks to the tetrapropoxycalix[4]arene scaffold which is more flexible than those of the dipropoxy derivatives. For the latter compounds, in fact, the strong hydrogen bonds at the lower rim between the phenolic OH and O propoxy groups, impart sufficient rigidity on the calixarene scaffold to prevent the formation of intramolecular interactions.[24]

Complexation Properties

The molecular modelling studies performed on the self-assembled capsules derived from **12**–**21** reveal that they have an internal volume of around 150 Å^3.[17] To assess whether the inner cavity is available for guest encapsulation we studied the complexation ability of $\mathbf{12}_2$, $\mathbf{17}_2$ and $\mathbf{20}_2$ dimers towards the methylpyridinium ($MePy^+$) cation, a suitable guest in terms of size and electronic features for dimeric calixarene-based cages.[31,32] In order to follow the binding experiments by ^{1}H NMR in $CDCl_3$, we required a counterion which formed a loose ion-pair with the cation and whose resonances possibly did not interfere with the ^{1}H NMR spectra of the peptidocalixarenes. Therefore we initially evaluated whether concentrated $CDCl_3$ solutions of dimers $\mathbf{12}_2$, $\mathbf{17}_2$ and $\mathbf{20}_2$ were able to extract solid $MePyPF_6$, which is insoluble in this solvent. The ^{1}H NMR spectrum of a 10 mM $CDCl_3$ solution of **12** stirred for a few hours in the presence of solid $MePyPF_6$ and filtered to remove undissolved salt shows the presence of peaks belonging to the $MePy^+$ cation. The methyl group is clearly visible as a singlet at δ = 2.59 ppm ($\Delta\delta$ = –2.0 ppm), while the resonances of the pyridinium ring partly overlap the calixarene signals in the region 9.87–6.32 ppm, upfield-shifted by around 1.7–2 ppm with respect to free methylpyridinium tosylate [MePy(Tos)] in $CDCl_3$, thus indicating encapsulation of the guest. After the addition of 200 μL of [D_6]acetone to break down the cage and release the guest, all the signals of $MePy^+$ are clearly visible at lower fields. By integration of the signals of $MePy^+$ relative to the calixarene, 33% guest extraction (with respect to **12**) was determined. The ESI-MS spectra (both in methanol and dichloromethane) of the filtered solution showed the presence of peaks corresponding to both the complexes $\mathbf{12}_2{\cdot}MePy^+$ and $\mathbf{12}{\cdot}MePy^+$. The same experiment performed on compounds **17** and **20** yielded a 17% $MePyPF_6$ extraction in both cases. To measure the formation constants of the complexes a ^{1}H NMR titration was performed with methylpyridinium tetrakis(pentafluorophenyl)borate as the guest in $CD_2Cl_2/CDCl_3$ (10:1, v/v). The tetrakis(pentafluorophenyl)borate anion was chosen for solubility reasons, the absence of aromatic protons and because it forms a loose ion-pair with $MePy^+$. Upon addition of a concentrated solution of the guest to a 0.027 M solution of the host, complexation-induced shifts in the ^{1}H NMR spectra were observed for all the resonances of $MePy^+$ and for several of the host signals. In particular, all the signals of the guest were initially upfield-shifted with respect to their resonance in the absence of calixarene (δ = 2.15 vs. 4.40 ppm for the methyl group, 6.20 vs. 8.52 ppm for the PyH-*ortho* and 6.10 vs. 8.08 ppm for the PyH-*meta*), a clear indication of the binding of $MePy^+$ within the aromatic cavity of the dimeric capsule. During the titration their signals moved gradually to lower fields. Equilibrium is rapid on the NMR time-scale and the observed chemical shifts are a weighted average of the shifts of the nuclei in all the species present at equilibrium. The host and guest signals that were unequivocally identified were simultaneously fitted to the model in Scheme 6[33] using HypNMR.[25] The dimerization constant K_{dim} of **12** in $CD_2Cl_2/CDCl_3$ (10:1, v/v) was independently measured in a ^{1}H NMR dilution experiment and was found to be 38($\pm$0.4) M^{-1} (see Figure S9, Supporting Information). This

value was included as an invariant in the non-linear regression analysis which gave a good fit to the model (Figure 7), with errors in the calculated chemical shifts of the 1:1 and 2:1 complexes of <0.08 ppm. The calculated association constants K_{11} = (7.82±1.2)×10² M⁻¹ and K_{21} = (1.77±0.2)×10⁵ M⁻² allowed the species distribution during the ^{1}H NMR titration to be determined (Figure 7).



Scheme 6. Model for the association of **12** with $MePy^+$.

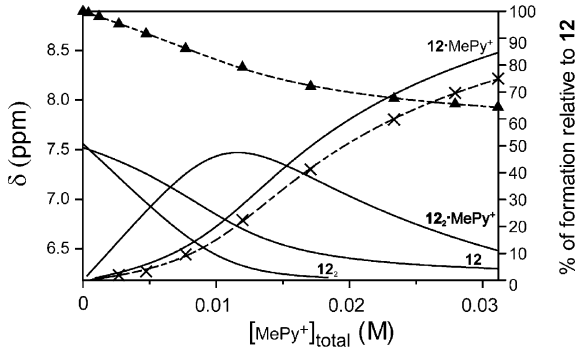


Figure 7. Complexation-induced shifts of the N*H*Ar (▲) and the Py*H-ortho* (×) resonances of **12** and $MePy^+$, respectively, together with the best fit curves obtained through nonlinear regression analysis (- - -) and the simulated concentration profiles (——) for the species involved in the equilibria of Scheme 6.

During the ^{1}H NMR titration, the maximum amount of the filled capsule $\mathbf{12}_2$·$MePy^+$ (47.5%, relative to **12**, Figure 7) is reached when the total concentrations of **12** and $MePy^+$ are 0.020 and 0.011 M, respectively. At this point, 6% of the empty dimer $\mathbf{12}_2$ is also present. In the absence of guest, at the same concentration of **12** (0.02 M), the amount of capsule $\mathbf{12}_2$ is 45%, as calculated from the K_{dim} of **12** in $CD_2Cl_2/CDCl_3$ (10:1, v/v) (see Figure S9, Supporting Information). This implies that the guest shows a good affinity towards the capsule enclosed space but does not display an important template effect on capsule formation as observed in other cases.[34–37]

Conclusions

Peptidocalix[4]arenes **12**–**21** are essentially pseudopeptides incorporating an unnatural calix[4]arene amino acid and therefore are intrinsically self-complementary in terms of hydrogen-bonding donor and acceptor groups if the structure assumes a pseudo-β-sheet conformation. Dimerization can thus be achieved when two molecules approach each other "face-to-face" and rotated by 180° with respect to the other. Upon hydrogen-bond formation, the aromatic cavities of the two calixarene molecules in the dimer are held in strong contact and surround an enclosed space, as proved by ^{1}H NMR and confirmed by the ability of the dimer to encapsulate a guest. The stability of the dimeric capsule increases by increasing the number of amino acid units up to a certain level when other intermolecular self-association motives leading to polymers prevail.

An interesting finding of this work is the disclosure of the important role played by the two OH groups at the lower rim of the calix[4]arenes which reduce the conformational flexibility of the macrocycle through hydrogen bonding thus controlling both the outcome of the synthetic transformations and the self-assembly properties of this new class of synthetic receptor.

The capsular supramolecular assembly formed through the action of enantiomerically pure peptide chains creates a partially enclosed chiral space[38] that is potentially capable of enantioselective recognition.[39] This possibility has not been investigated yet since our first aim was to learn about the molecular rules that regulate the self-assembly processes in *N,C*-linked peptidocalix[4]arenes. However, in order to investigate the chiral recognition properties of the capsule it will be necessary to enhance both its kinetic and thermodynamic stability and reduce the size of the openings which allow guests to escape from the interior. This will require, as in classical tetraurea calix[4]arenes, the synthesis of calix[4]arene subunits bearing four peptide chains at the upper rim, while maintaining two OH groups at the lower rim. The feasibility of such a synthesis is currently under study in our laboratory.

Experimental Section

General Methods: All reactions were carried out under nitrogen. Dry solvents were prepared according to standard procedures and stored over molecular sieves. Melting points were determined under nitrogen in sealed capillaries with an Electrothermal apparatus. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, on Bruker AV300 and AC300 spectrometers (partially deuteriated solvents were used as internal standard). Mass spectra were registered in ESI and CI (CH_4) mode with Micromass ZMD and Finnigan Mat SSQ710 spectrometers, respectively. Optical rotations were measured at 20 °C with a Perkin-Elmer 241 Polarimeter using a wavelength of 589 nm. $[a]_D$ values are given in 10^{-1}deg cm^2 g^{-1}. Elemental analyses were performed using a CHN 1106 Carlo Erba instrument and are reported as percentages. TLC was performed on silica gel Merck 60 F254 sheets and flash chromatography on 230–240 mesh Merck 60 silica gel. Amino acids were purchased from Sigma.

For reasons of clarity and in order to reduce space, the name calix[4]arene has been used instead of the full 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-dodecene.

^{1}H NMR Experiments for the Determination of the Dimerization Constant: ^{1}H NMR spectra were recorded for a series of samples of increasing concentrations of peptidocalixarene from 5×10^{-5} M up to 1.0×10^{-2} M.

^{1}H NMR Titration Experiment for the Determination of the Association Constants of 12 and 12_2 with $MePy^+$: A solution of methylpyridinium tetrakis(pentafluorophenyl)borate (41 mM, 1.5 mL) in $CD_2Cl_2/CDCl_3$ (10:1, v/v) was added in small aliquots to a 27 mM solution of **12** (0.5 mL) and the ^{1}H NMR spectra were recorded after each addition. Mathematical analysis of data and graphical presentation of results were performed using the program HypNMR2004 (v. 3.1.42).[40]

Extraction of Solid $MePyPF_6$: A solution of the peptidocalixarene [**12** (10 mM), or **17** (5 mM) or **20** (5 mM); 1 mL] in $CDCl_3$ was stirred overnight in the presence of $MePyPF_6$ (20 mg). The solution was filtered and the ^{1}H NMR spectrum of the filtrate was recorded using 0.5 mL of solution. A blank experiment in the absence of peptidocalixarene was performed to ensure the insolubility of $MePyPF_6$ in the solvent. The amount of $MePy^+$ extracted was determined by integration of the signals of $MePy^+$ with respect to the calixarene after addition of [D_6]acetone (0.2 mL).

11-Nitro-25,27-dihydroxy-26,28-dipropoxycalix[4]arene (2): HNO_3 (65% solution, 0.5 mL, 7.2 mmol) was added to a solution of 25,27-dihydroxy-26,28-dipropoxycalix[4]arene (**1**)[18] (2.0 g, 3.9 mmol) in CH_2Cl_2 (200 mL) and acetic acid (2 mL). The reaction mixture was stirred for 45 min at room temp., quenched by addition of a $NaHCO_3$ saturated solution (150 mL) and vigorously stirred for 10 min. The organic layer was separated, washed with distilled water (2×150 mL), dried with $MgSO_4$ and the solvents evaporated to dryness at reduced pressure. The crude was purified by flash chromatography (eluent: hexane/CH_2Cl_2, 2:1, v/v) to obtain the product as pale yellow solid. Yield 0.97 g, 1.8 mmol, 45%. M.p. 277–278 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.52 (s, 1 H, OH), 8.22 (s, 1 H, OH), 8.03 (s, 2 H, ArH), 7.06 (d, J = 7.5 Hz, 2 H, ArH), 6.98, 6.94 (2dd, J = 7.5, 1.5 Hz, ArH, 2H each), 6.79 (t, J = 7.5 Hz, 2 H, ArH), 6.66 (t, J = 7.5 Hz, 1 H, ArH), 4.31 (d, J = 13.2 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 4.30 (d, J = 13.0 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 4.07–3.93 (m, 4 H, $OCH_2CH_2CH_3$), 3.48 (d, J = 13.2 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 3.40 (d, J = 13.0 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 2.14–2.00 (m, 4 H, $OCH_2CH_2CH_3$), 1.32 (t, J = 7.4 Hz, 6 H, $OCH_2CH_2CH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.9, 153.2, 151.8, 139.6, 133.6, 131.6, 129.7, 128.8, 128.6, 128.5, 127.7, 125.5, 124.5, 114.1 (Ar), 78.5 (t, $OCH_2CH_2CH_3$), 31.3 (t, $ArCH_2Ar$), 23.4 (t, $OCH_2CH_2CH_3$), 10.8 (q, $OCH_2CH_2CH_3$) ppm. MS (CI-MS): calcd. for $C_{34}H_{35}NO_6$ 553.2; found 554.4 $[M + H]^+$. $C_{34}H_{35}NO_6$ (553.66): calcd. C 73.76, H 6.37, N 2.53; found C 73.82, H 6.21, N 2.42.

11-Nitro-23-formyl-25,27-dihydroxy-26,28-dipropoxycalix[4]arene (3): Cl_2CHOCH_3 (0.49 mL, 5.43 mmol) and $SnCl_4$ (2.12 mL, 18.1 mmol) were added to a solution of **2** (1 g, 1.81 mmol) in dry $CHCl_3$ (30 mL), cooled to –13 °C. The reaction was then stirred for 3 h at room temp., quenched by addition of 1 N HCl and vigorously stirred for 20 min. The organic layer was separated, washed with distilled water until neutral pH and the solvents evaporated to dryness under reduced pressure to achieve **3** as a solid. Yield 0.89 g, 1.5 mmol, 85%. All the spectroscopic data resulted in agreement with those previously reported.[41]

25,27-Dihydroxy-11-nitro-26,28-dipropoxycalix[4]arene-23-carboxylic Acid (4): A solution of **3** (1 g, 1.72 mmol) in $CHCl_3$/acetone (60 mL, 1:1, v/v) was cooled to 0 °C and treated with an aqueous solution (15 mL) of H_2NSO_3H (545 mg, 5.62 mmol) and $NaClO_2$ (342 mg, 3.78 mmol). The mixture was vigorously stirred at room temp. for 18 h and the solvent evaporated to dryness at reduced pressure. Then 1 N HCl (20 mL) was added to give **4** as a pale yellow solid which was crystallized from Et_2O. Yield 0.9 g, 1.48 mmol, 86%. M.p. 325–328 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.49 (s, 1 H, OH), 9.06 (s, 1 H, OH), 8.03 (s, 2 H, ArH), 7.86 (s, 2 H, ArH), 7.00 (dd, J = 7.5, 1.8 Hz, 2 H, ArH), 6.96 (dd, J = 7.5, 1.8 Hz, 2 H, ArH), 6.82 (t, J = 7.5 Hz, 2 H, ArH), 4.29 (d, J = 12.9 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 4.27 (d, J = 12.9 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 4.08–3.98 (m, 4 H, OCH_2), 3.49 (d, J = 12.9 Hz, 4 H, H_{eq} of $ArCH_2Ar$), 2.17–1.98 (m, 4 H, OCH_2CH_2), 1.32 (t, J = 7.2 Hz, 6 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.6 (s, CO), 159.7, 158.7, 151.7, 139.7, 132.7, 131.6, 131.1, 129.7, 129.1, 128.4, 127.8, 125.7, 124.5, 119.1 (Ar), 78.6 (t, OCH_2), 31.2 (t, $ArCH_2Ar$), 23.4 (t, OCH_2CH_2), 10.8 (q, CH_3) ppm. MS-CI: m/z (%)= 597.8 (80) $[M]^+$, 580 (100) $[M - OH]^+$. $C_{35}H_{35}NO_8$ (597.23): calcd. C 70.34, H 5.90, N 2.34; found C 70.51, H 6.01, N 2.28.

11-Amino-25,27-dihydroxy-26,28-dipropoxycalix[4]arene-23-carboxylic Acid (5): Hydrazine hydrate (0.40 mL, 8.36 mmol) and a catalytic amount of Pd/C (10%) were added to a suspension of **4** (250 mg, 0.418 mmol) in ethanol (25 mL). The mixture was stirred for 3 h at 60 °C, then the catalyst was filtered off rapidly under nitrogen. The organic solvent was evaporated under reduced pressure to obtain the product as a white solid, to be used without further purification. Yield 0.17 g, 0.30 mmol, 70%. ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 9.21 (s, 1 H, OH), 7.78 (s, 2 H, ArH), 7.62 (s, 1 H, OH), 7.04 (d, J = 7.8 Hz, 2 H, ArH), 7.02 (d, J = 7.8 Hz, 2 H, ArH), 6.80 (t, J = 7.4 Hz, 2 H, ArH), 6.38 (s, 2 H, ArH), 4.16 (d, J = 12.9 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 4.14 (d, J = 12.3 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 4.03–3.88 (m, 4 H, $OCH_2CH_2CH_3$), 3.56 (d, J = 12.9 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 3.24 (d, J = 12.3 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 2.09–1.91 (m, 4 H, $OCH_2CH_2CH_3$), 1.29 (t, J = 7.4 Hz, 6 H, $OCH_2CH_2CH_3$) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 167.2 (s, CO), 157.2, 151.7, 134.1, 133.1, 130.3, 129.0, 128.9, 128.2, 127.8, 125.3, 121.4, 115.9 (Ar), 78.1 (t, $OCH_2CH_2CH_3$), 30.6, 30.4 (t, $ArCH_2Ar$), 23.1 ($OCH_2CH_2CH_3$), 10.8 ($OCH_2CH_2CH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3358 (NH, OH), 1674 (CO) cm^{-1}. MS-ESI: m/z (%) = 590.3 (100) [M + Na]$^+$. $C_{35}H_{37}NO_6$ (567.26): calcd. C 74.05, H 6.57, N 2.47; found C 74.22, H 6.63, N 2.38.

General Procedure for the Synthesis of Intermediates 6–9 and 11: The calixarene **5** (100 mg, 0.18 mmol), the appropriate *N*-protected amino acid or dipeptide or propionic acid (0.35 mmol) and NEt_3 (1.2 mL, 0.88 mmol) were mixed in dry CH_2Cl_2 (10 mL). Then HBTU (240 mg, 0.63 mmol) was added and the reaction mixture was stirred at room temp. for 2–5 h. The reaction was quenched by addition of distilled water, the organic layer separated and the solvents evaporated to dryness at reduced pressure.

11-(*N*-Cbz-L-Alanyl)amino-23-benzotriazolyloxycarbonyl-25,27-dihydroxy-26,28-dipropoxycalix[4]arene (6): The crude was purified by flash column chromatography (eluent: hexane/AcOEt, 1:1) to obtain the product as a white solid. Yield 113 mg, 0.13 mmol, 72%. M.p. 170–173 °C. $[\alpha]_D^{20}$ = –17.7 (c = 0.84, in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.50 (s, 1 H, OH), 9.19 (s, 1 H, OH), 8.13 (br. s, 1 H, ArNH), 8.07 (d, J = 8.2 Hz, 1 H, ArH), 8.04 (s, 2 H, ArH), 7.51–7.37 (m, 3 H, ArH), 7.31–7.27 (m, 7 H, ArH), 6.88–6.95 (m, 4 H, ArH), 6.70 (t, J = 7.5 Hz, 2 H, ArH), 5.47 (br. s, 1 H, N*H*Cbz), 5.15 (d, J = 12.2 Hz, 1 H, CH_2Ph), 5.09 (d, J = 12.2 Hz, 1 H, CH_2Ph), 4.39 (br. s, 1 H, $CHCH_3$), 4.34 (d, J = 12.9 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 4.29 (d, J = 13.2 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 3.99 (br. s, 4 H, OCH_2CH_2), 3.51 (d, J = 13.2 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 3.35 (d, J = 12.9 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 2.05–2.15 (m, 4 H, OCH_2CH_2), 1.44 (d, J = 6.6 Hz, 3 H, $CHCH_3$), 1.25–1.40

(m, 6 H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 171.1, 163.5 and 161.5 (CO), 152.8, 150.5, 144.3, 134.7, 133.4, 132.3, 131.4, 131.3, 130.3, 130.0, 129.8, 129.6, 129.1, 128.7, 128.6, 126.2, 125.7, 121.2, 121.1, 120.8, 115.5 and 109.7 (Ar), 79.3 (OCH_2CH_2), 66.8 (CH_2Ph), 52.0 ($CHCH_3$), 31.8 and 31.4 ($ArCH_2Ar$), 24.2 (OCH_2CH_2), 18.8 ($CHCH_3$), 11.3 (CH_2CH_3) ppm. ESI-MS: *m*/*z* (%) = 912.3 (100) [M + Na]$^+$. $C_{52}H_{51}N_5O_9$ (889.37): calcd. C 70.18, H 5.78, N 7.87; found C 70.24, H 5.89, N 7.82.

11-[*N*-Acetyl-(*dl*)-leucyl]amino-23-benzotriazolyloxycarbonyl-25,27-dihydroxy-26,28-dipropoxycalix[4]arene (7): The crude was purified by flash column chromatography (eluent: CH_2Cl_2/MeOH, 95:5) to obtain the product as a white solid. Yield 36 mg, 0.04 mmol, 24%. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.53 (s, 1 H, OH), 8.27 (s, 1 H, ArNH), 8.22 (s, 1 H, OH), 8.08 (d, *J* = 8.3 Hz, 1 H, ArH), 8.02 (s, 2 H, ArH), 7.52–7.39 (m, 3 H, ArH), 7.29 (d, *J* = 2.5 Hz, 1 H, ArH), 7.25 (d, *J* = 2.5 Hz, 1 H, ArH), 7.00–6.94 (m, 4 H, ArH), 6.81–6.75 (m, 2 H, ArH), 6.13 (br. s, 1 H, NH), 4.67–6.61 (m, 4 H, H_{ax} of $ArCH_2Ar$), 4.60 (br. s, 1 H, CH), 4.35–4.26 (m, 4 H, OCH_2CH_2), 3.49 (d, *J* = 13.2 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 3.36 (d, *J* = 13.0 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 2.11–2.00 (m, 4 H,OCH_2CH_2), 2.01 (s, 3 H, $COCH_3$), 1.67–1.51 (m, 3 H, CH and CH_2) 1.32 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), 0.95 (s, 6 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.7 (CO), 170.7 (CO), 169.4 (CO), 162.5, 160.6, 151.7, 150.09, 133.3, 131.3, 131.7, 129.5, 129.1, 128.9, 128.4, 128.1, 125.5, 124.6, 120.4, 108.6 (Ar), 78.5 (CH_2CH_3), 50.6, 41.6, 31.3 ($ArCH_2Ar$), 24.8, 23.4, 22.7, 21.9, 10.8 ppm. ESI-MS: *m*/*z* (%) = 759.7 (100), [$MOCH_3$ + Na]$^+$,[42] 862.7 (49) [M + Na]$^+$. $C_{49}H_{53}N_5O_8$ (839.39): calcd. C 70.06, H 6.36, N 8.34; found C 70.15, H 6.30, N 8.41.

11-(*N*-Cbz-L-Alanyl-L-alanyl)amino-23-benzotriazolyloxycarbonyl-25,27-dihydroxy-26,28-dipropoxycalix[4]arene (8): The crude was purified by flash column chromatography (eluent: CH_2Cl_2/MeOH, 20:1) to obtain the product as a white solid. Yield 59 mg, 0.06 mmol, 34%. M.p. 181–183 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.53 (s, 1 H, OH), 8.01 (s, 1 H, NH), 8.19 (s, 1 H, OH), 8.10–8.00 (m, 3 H, ArH), 7.53–7.42 (m, 2 H, ArH), 7.42–7.16 (m, 8 H, ArH), 7.06–6.83 (m, 5 H, 4 ArH and NH), 6.75–6.58 (m, 2 H, ArH), 5.68–5.55 (br. s, 1 H, NH), 5.13 (d, *J* = 15.0 Hz, 1 H, CH_2 Cbz), 5.05 (d, *J* = 15.0 Hz, 1 H, CH_2 Cbz), 4.68–4.55 (m, 1 H, CH), 4.41–4.17 (m, 5 H, CH and H_{ax} of $ArCH_2Ar$), 4.05–3.84 (m, 4 H, OCH_2), 3.49 (d, *J* = 17.5 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 3.34 (d, *J* = 12.9 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 2.14–1.95 (m, 4 H, OCH_2CH_2), 1.45–1.20 (m, 12 H, $CHCH_3$ and CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.6, 169.7, 162.6 and 160.6 (CO), 151.7, 150.1, 143.5, 135.9, 133.3, 131.9, 131.7, 129.4, 129.4, 129.2, 129.0, 128.9, 128.5, 128.2, 128.1, 128.0, 125.5, 124.7, 120.6, 120.4, 114.4 and 108.6 (Ar), 78.5 (OCH_2CH_2), 67.2 (CH_2), 51.1 and 49.5 (CH), 31.3 ($ArCH_2Ar$), 23.4 (OCH_2CH_2), 18.6 and 17.9 (CH_3), 10.8 ($OCH_2CH_2CH_3$) ppm. ESI-MS: *m*/*z* (%) = 983.6 (88) [M + Na]$^+$. $C_{55}H_{56}N_6O_{10}$ (960.40): calcd. C 68.73, H 5.87, N 8.74; found C 68.80, H 5.84, N 8.81.

23-Benzotriazolyloxycarbonyl-25,27-dihydroxy-11-(*N*-Cbz-L-leucyl-L-isoleucyl)amino-26,28-dipropoxycalix[4]arene (9): The crude was purified by flash column chromatography (eluent: CH_2Cl_2/MeOH, 95:5) to obtain the product as a white solid. Yield 96 mg, 0.09 mmol, 51%. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.55 (s, 1 H, OH), 8.24 (s, 1 H, OH), 8.08 (d, *J* = 8.2 Hz, 1 H, ArH), 8.02 (s, 2 H, ArH), 7.57–7.38 (m, 3 H, ArH), 7.35–7.24 (m, 8 H, ArH and NH), 6.96 (br. s, 4 H, ArH), 6.73 (t, *J* = 7.3 Hz, 2 H, ArH), 6.60 (br. s, 1 H, NHCbz), 5.10 (br. s, 2 H, CH_2Ph), 4.70–4.52 (m, 2 H, 2 CH), 4.32 (d, *J* = 13.2 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 4.28 (d, *J* = 12.9 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 3.99 (br. s, 4 H, OCH_2CH_2), 3.51 (d, *J* = 13.2 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 3.39 (d, *J* = 12.9 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 2.10–2.05 (m, 6 H, OCH_2CH_2, and 2 CH), 1.67 (br. s, 2 H, CH_2 Leu), 1.61–1.49 (m, 2 H, CH_2), 1.33 (t, *J* = 7.2 Hz, 6 H, CH_2CH_3), 0.96–0.83 (m, 12 H, CH_3) ppm. ESI-MS: *m*/*z* (%) = 965.1 (95) [$MOCH_3$ + Na]$^+$,[42] 1068.1 (100) [M + Na]$^+$. $C_{61}H_{68}N_6O_{10}$ (1044.50): calcd. C 70.10, H 6.56, N 8.04; found C 70.12, H 6.47, N 8.09.

23-Benzotriazolyloxycarbonyl-25,27-dihydroxy-11-propanoylamino-26,28-dipropoxycalix[4]arene (11): The crude was purified by flash column chromatography (eluent: hexane/AcOEt, 11:14) to obtain the product as a white solid. Yield 73 mg, 0.10 mmol, 55%. M.p. 191 °C (decomp.) ^1H NMR (300 MHz, $CDCl_3$): δ = 9.50 (s, 1 H, OH), 8.16 (s, 1 H, OH), 8.07 (d, *J* = 8.8 Hz, 1 H, ArH), 8.03 (s, 2 H, Ar), 7.54–7.36 (m, 3 H, ArH), 7.27 (s, 2 H, ArH), 7.12 (s, 1 H, NH), 7.03–6.88 (m, 4 H, ArH), 6.73 (t, *J* = 7.5 Hz, 2 H, ArH), 4.34 (d, *J* = 13.1 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 4.30 (d, *J* = 12.9 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 4.05–3.89 (m, 4 H, OCH_2CH_2), 3.51 (d, *J* = 13.1 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 3.37 (d, *J* = 12.9 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 2.34 (q, *J* = 7.5 Hz, 2 H, $COCH_2$), 2.16–2.02 (m, 4 H, OCH_2CH_2), 1.33 (t, *J* = 7.4 Hz, 6 H, $CH_2CH_2CH_3$), 1.24 (t, *J* = 7.7 Hz, 3 H, $COCH_2CH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.6 and 162.6 (CO), 160.6, 151.7, 150.0, 143.5, 133.3, 131.9, 131.7, 129.5, 129.4, 129.1, 129.0, 128.9, 128.5, 128.0, 125.5, 124.6, 120.5, 120.4, 114.4, 108.6, 78.5 (OCH_2CH_2), 31.3 and 30.5 ($ArCH_2Ar$), 23.4 (OCH_2CH_2), 14.1 ($COCH_2$), 10.8 ($OCH_2CH_2CH_3$), 9.6 ($COCH_2CH_3$) ppm. ESI-MS: *m*/*z* (%) = 763.8 (100) [M + Na]$^+$. $C_{44}H_{44}N_4O_7$ (740.32): calcd. C 71.33, H 5.99, N 7.56; found C 71.40, H 6.03, N 7.50.

General Procedure for the Synthesis of Peptidocalixarenes 12–18, 20 and 21: The appropriate *C*-protected amino acid or dipeptide or *n*-butylamine (0.13 mmol), NEt_3 (0.14 mL, 1.0 mmol) and HBTU (92 mg, 0.24 mmol) were added to a solution of intermediate **6**–**9** or **11** (0.07 mmol) in dry CH_2Cl_2 (5 mL). The reaction was stirred at room temp. for 5–10 h and then was quenched by adding distilled water (10 mL). The organic layer was diluted to 20 mL, separated and the solvents evaporated to dryness under reduced pressure.

11-(*N*-Cbz-L-Alanyl)amino-25,27-dihydroxy-23-(methoxy-L-alanyl)-carbonyl-26,28-dipropoxycalix[4]arene (12): The crude was purified by flash column chromatography (eluent: hexane/AcOEt, 1:1, v/v) to give the product as a white solid. Yield 52 mg, 0.06 mmol, 90%. M.p. 241.2–243.5 °C. $[\alpha]_D^{20}$ = –4.0 (*c* = 0.76, in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, *c* = 10^{-2} M): δ = 8.93 (br. s, 1 H, ArN*H*), 8.89 (s, 1 H, OH), 8.04 (s, 1 H, OH), 7.56 (s, 2 H, ArH), 7.32 (br. s, 7 H, ArH) 6.75 (d, *J* = 7.1 Hz, 1 H, ArCON*H*), 6.31 (br. s, 4 H, ArH), 5.80 (br. s, 2 H, ArH), 5.60 (br. s, 1 H, N*H*Cbz), 5.04–5.18 (m, 2 H, CH_2Ph), 4.91–4.78 (m, 1 H, C*H*$COOCH_3$), 4.40–4.56 (m, 1 H, C*H*NHCbz), 4.22 (d, *J* = 12.3 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 4.20 (d, *J* = 12.9 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 3.90 (t, *J* = 5.6 Hz, 4 H, OCH_2CH_2), 3.79 (s, 3 H, OCH_3), 3.32 (d, *J* = 12.9 Hz, 1 H, H_{eq} of $ArCH_2Ar$), 3.31 (d, *J* = 12.9 Hz, 1 H, H_{eq} of $ArCH_2Ar$), 3.24 (d, *J* = 12.9 Hz, 1 H, H_{eq} of $ArCH_2Ar$), 3.22 (d, *J* = 12.9 Hz, 1 H, H_{eq} of $ArCH_2Ar$), 2.11–1.95 (m, 4 H, OCH_2CH_2), 1.55 [d, *J* = 6.9 Hz, 3 H, $CH(CH_3)COOCH_3$], 1.50 [d, *J* = 7.2 Hz, 3 H, $CH(CH_3)NHCbz$], 1.29 (t, *J* = 7.3 Hz, 6 H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.9, 170.6, 167.3 and 157.8 (CO), 151.4, 150.0, 136.4, 131.8, 131.0, 129.6, 129.1, 128.8, 128.4, 128.3, 128.1, 127.9, 127.8, 127.7, 125.1, 122.6 and 120.0 (Ar), 77.9 (OCH_2CH_2), 66.8 (CH_2Ph), 52.5 (OCH_3), 48.7 and 51.6 ($CHCH_3$), 31.9, 31.7, 31.6 and 31.4 ($ArCH_2Ar$), 23.4 (OCH_2CH_2), 18.9 and 18.5 ($CHCH_3$), 10.7 (CH_2CH_3) ppm. ESI-MS: *m*/*z* (%) = 880.2 (100) [M + Na]$^+$. $C_{50}H_{55}N_3O_{10}$ (857.39): calcd. C 69.99, H 6.46, N 4.90; found C 70.14, H 6.51, N 4.79.

11-(*N*-Cbz-L-Alanyl)amino-25,27-dihydroxy-23-(methoxy-D-alanyl)-carbonyl-26,28-dipropoxycalix[4]arene (13): The crude was purified by flash column chromatography (eluent: CH_2Cl_2/MeOH, 40:1, v/v) to give the product as a white solid. Yield 46 mg, 0.05 mmol, 76%. M.p. 233–236 °C. ^{1}H NMR (300 MHz, $CDCl_3$, $c = 10^{-2}$ M): δ = 9.06 (br. s, 1 H, NH), 8.91 (s, 1 H, OH), 8.04 (s, 1 H, OH), 7.57 (s, 1 H, ArH), 7.55 (s, 1 H, ArH), 7.35–7.31 [m, 7 H, 2 ArH and 5 ArH(Cbz)], 6.75 (d, J = 7.2 Hz, 1 H, NH), 6.26 (br. s, 4 H, ArH), 5.71 (br. s, 1 H, NH), 5.66 (br. s, 2 H, ArH), 5.15–5.04 (m, 2 H, CH_2 Cbz), 4.83 [quint., J = 7.2 Hz, 1 H, CH(AlaOMe)], 4.49–4.45 [m, 1 H, CH(CbzAla)], 4.22–4.16 (m, 4 H, H_{ax} of $ArCH_2Ar$), 3.89 (br. s, 4 H, OCH_2CH_2), 3.79 (s, 3 H, OCH_3), 3.31 (d, J = 13.3 Hz, 1 H, H_{eq} of $ArCH_2Ar$), 3.30 (d, J = 13.3 Hz, 1 H, H_{eq} of $ArCH_2Ar$), 3.23 (d, J = 13.0 Hz, 1 H, H_{eq} of $ArCH_2Ar$), 3.21 (d, J = 12.9 Hz, 1 H, H_{eq} of $ArCH_2Ar$), 2.07–1.95 (m, 4 H, OCH_2CH_2), 1.56–1.44 [m, 6 H, $CHCH_3$ (AlaOMe) and $CHCH_3$ (CbzAla)], 1.26–1.25 (m, 6 H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.9, 170.5, 167.3 and 157.9 (CO), 151.4, 150.0, 136.4, 131.9, 130.9, 129.7, 129.0, 128.8, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 125.1, 122.6 and 119.9 (Ar), 77.9 (OCH_2CH_2), 66.7 (CH_2 Cbz), 52.5 (OCH_3), 51.5 and 48.6 (CH), 31.6 and 31.5 ($ArCH_2Ar$), 23.3 (OCH_2CH_2), 19.1 and 18.5 (CH_3), 10.7 ($OCH_2CH_2CH_3$) ppm. ESI-MS: m/z (%) = 880.5 (77) $[M + Na]^+$. $C_{50}H_{55}N_3O_{10}$ (857.39): calcd. C 69.99, H 6.46, N 4.90; found C 70.10, H 6.40, N 4.80.

11-(*N*-Cbz-L-Alanyl)amino-25,27-dihydroxy-23-(methoxy-L-phenylalanyl)carbonyl-26,28-dipropoxycalix[4]arene (14): The crude was purified by flash column chromatography (eluent: CH_2Cl_2/MeOH, 40:1, v/v) to give the product as a white solid. Yield 47 mg, 0.05 mmol, 76%. M.p. 217.5–220.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$, $c = 10^{-2}$ M): δ = 8.93 (s, 1 H, OH), 8.81 (br. s, 1 H, NH), 8.08 (s, 1 H, OH), 7.48 (s, 1 H, ArH), 7.46 (s, 1 H, ArH), 7.35–7.26 [m, 7 H, 5 Ar(Cbz) and 2 ArH], 7.16 (s, 1 H, ArH), 7.14 (s, 1 H, ArH), 6.57 (d, J = 7.5 Hz, 1 H, NH), 6.39 (br. s, 4 H, ArH), 5.91 (br. s, 1 H, NH), 5.55 (br. s, 2 H, ArH), 5.16–5.07 [m, 3 H, CH_2(Cbz) and CH(Phe)], 4.45 (m, 1 H, $CHCH_3$), 4.21 (d, J = 13.0 Hz, 4 H, H_{ax} of $ArCH_2Ar$), 3.90 (br. s, 4 H, OCH_2CH_2), 3.77 (s, 3 H, OCH_3), 3.33–3.22 (m, 6 H, H_{eq} of $ArCH_2Ar$ and $CHCH_2$), 2.05–1.98 (m, 4 H, OCH_2CH_2), 1.49 (d, J = 6.0 Hz, 3 H, $CHCH_3$), 1.24 (t, J = 7.3 Hz, 6 H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.3, 170.4, 167.1 and 157.7 (CO), 151.4, 150.1, 136.3, 135.9, 132.1, 131.1, 129.5, 129.3, 129.2, 129.1, 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 127.9, 127.7, 127.1, 125.1, 122.7 and 120.1 (Ar), 78.0 (OCH_2CH_2), 66.8 (CH_2 Cbz), 53.6 (OCH_3), 52.3 and 51.4 (CH), 37.9 (CH_2), 31.6, 31.5 and 31.4 ($ArCH_2Ar$), 23.4 (OCH_2CH_2), 18.9 (CH_3), 10.7 ($OCH_2CH_2CH_3$) ppm. ESI-MS: m/z (%) = 956.6 (48) $[M + Na]^+$. $C_{56}H_{59}N_3O_{10}$ (934.10): calcd. C 72.01, H 6.37, N 4.50; found C 72.15, H 6.28, N 4.64.

11-[*N*-Acetyl-(*dl*)-leucyl]amino-25,27-dihydroxy-23-(methoxy-L-glycyl)carbonyl-26,28-dipropoxycalix[4]arene (15): The crude was purified by flash column chromatography (eluent: CH_2Cl_2/AcOEt, 1:1, v/v) to give the product as a white solid. Yield 18 mg, 0.02 mmol, 31%. ^{1}H NMR (300 MHz, $CDCl_3$, $c = 10^{-2}$ M): δ = 8.92 (s, 1 H, OH), 8.82 (s, 1 H, NH), 8.12 (s, 1 H, OH), 7.57 (s, 2 H, ArH), 7.31 (s, 2 H, ArH), 6.75 (t, J = 3.9 Hz, 1 H, NH), 6.50 (br. s, 4 H, ArH), 6.18 (d, J = 9.0 Hz, 1 H, NH), 6.04 (br. s, 2 H, ArH), 4.64 (q, J = 8.1 Hz, 1 H, CH), 4.27–4.18 (m, 6 H, CH_2 and H_{ax} of $ArCH_2Ar$), 3.90 (br. s, 4 H, OCH_2CH_2), 3.79 (s, 3 H, CH_3), 3.35 (d, J = 12.9 Hz, 1 H, H_{eq} of $ArCH_2Ar$), 3.33 (d, J = 13.5 Hz, 1 H, H_{eq} of $ArCH_2Ar$), 3.25 (d, J = 13.2 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 2.05–1.98 (m, 4 H, OCH_2CH_2), 1.98 (s, 3 H, $COCH_3$), 1.82–1.71 (m, 3 H, CH and CH_2), 1.23 (t, J = 7.3 Hz, 6 H, CH_2CH_3), 0.91 (br. s, 6 H, CH_3) ppm. ESI-MS: m/z (%) = 816.4 (100) $[M + Na]^+$, 1668 (10) $[2M + 2Na + Cl]^+$. $C_{46}H_{55}N_3O_9$ (793.39): calcd. C 69.59, H 6.98, N 5.29; found C 69.67, H 7.09, N 5.25.

11-(*N*-Cbz-L-Alanyl-L-alanyl)amino-25,27-dihydroxy-23-(methoxy-L-alanyl)carbonyl-26,28-dipropoxycalix[4]arene (16): The crude was purified by flash column chromatography (eluent: CH_2Cl_2/MeOH, 30:1, v/v) to give the product as a white solid. Yield 30 mg, 0.03 mmol, 46%. ^{1}H NMR (300 MHz, $CDCl_3$, $c = 10^{-2}$ M): δ = 8.95 (br. s, 1 H, ArNH), 8.92 (s, 1 H, OH), 8.09 (s, 1 H, OH), 7.56 (s, 2 H, ArH), 7.41–7.28 (m, 7 H, ArH), 6.79 (br. s, 1 H, NH), 6.76 (br. s, 1 H, NH), 6.52 (br. s, 5 H, ArH and NH), 5.92 (br. s, 2 H, ArH), 5.35 (br. s, 1 H, CH), 5.11 (br. s, 2 H, CH_2Ph), 4.82 (quint., J = 6.9 Hz, 1 H, CH), 4.67 (quint., J = 6.6 Hz, 1 H, CH), 4.26–4.19 (m, 1 H, 4 H, H_{ax} of $ArCH_2Ar$), 3.91 (br. s, 4 H, OCH_2CH_2), 3.79 (s, 3 H, OCH_3), 3.37–3.22 (m, 4 H, H_{eq} of $ArCH_2Ar$), 2.05–1.98 (m, 4 H, OCH_2CH_2), 1.56 (d, J = 6.9 Hz, 3 H, CH_3), 1.47 (d, J = 6.6 Hz, 3 H, CH_3), 1.39 (d, J = 5.7 Hz, 3 H, CH_3), 1.27 (t, J = 7.2 Hz, 6 H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.9, 169.7, 167.0, 157.4 and 155.5 (CO), 151.5, 150.1, 132.4, 131.5, 129.3, 129.1, 128.8, 128.4, 128.2, 128.1, 127.9, 125.2, 120.3 and 120.2 (Ar), 78.1 (OCH_2CH_2), 67.1 (CH_2Ph), 52.5 (OCH_3), 50.8, 49.6 and 48.5 ($CHCH_3$), 31.5 ($ArCH_2Ar$), 23.4 (OCH_2CH_2), 18.5 and 18.3 ($CHCH_3$), 10.7 ($OCH_2CH_2CH_3$) ppm. ESI-MS: m/z (%) = 951.6 (100) $[M + Na]^+$, 1880.2 (10) $[2M + Na]^+$. $C_{53}H_{60}N_4O_{11}$ (928.42): calcd. C 68.52, H 6.51, N 6.03; found C 68.50, H 6.59, N 6.14.

11-(*N*-Cbz-L-alanyl-L-Alanyl)amino-25,27-dihydroxy-23-(methoxy-L-alanyl-L-alanyl)carbonyl-26,28-dipropoxycalix[4]arene (17): The crude was purified by flash column chromatography (eluent: CH_2Cl_2/MeOH, 20:1.5, v/v) to give the product as a white solid. Yield 26 mg, 0.03 mmol, 37%. M.p. 165.2–168.6 °C. $[\alpha]_D^{20}$ = –13.0 (c = 0.54, in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, $c = 4 \times 10^{-2}$ M): δ = 9.74 (br. s, 1 H, ArNH), 8.98 (s, 1 H, OH), 8.02 (s, 1 H, OH), 7.67–7.48 (m, 3 H, ArH and NH), 7.32 (br. s, 9 H, ArH and NH), 5.82 (br. s, 6 H, ArH), 5.73 (d, J = 7.6 Hz, 1 H, NHCbz), 5.20–5.06 (m, 2 H, CH_2Ph), 5.06–4.95 (m, 1 H, ArCONHCH), 5.00–4.85 (m, 1 H, ArNHCOCH), 4.61–4.49 (m, 1 H, $CHCOOCH_3$), 4.48–4.36 (m, 1 H, CHNHCbz), 4.25–4.01 (m, 4 H, H_{ax} of $ArCH_2Ar$), 3.83 (br. s, 4 H, OCH_2CH_2), 3.72 (s, 3 H, OCH_3), 3.36–3.03 (m, 4 H, H_{eq} of $ArCH_2Ar$), 2.08–1.80 (m, 4 H, OCH_2CH_2), 1.60 (d, J = 6.9 Hz, 3 H, $ArCONHCHCH_3$), 1.53 (d, J = 6.8 Hz, 3 H, $ArNHCOCHCH_3$), 1.43 [d, J = 6.5 Hz, 3 H, $CH(CH_3)$-NHCbz], 1.33 [d, J = 7.1 Hz, 3 H, $CH(CH_3)COOCH_3$], 1.23 (t, J = 7.2 Hz, 6 H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.1, 172.5, 171.8, 170.4 and 167. 6 (CO), 158.1 (Ar), 156.0 (CO), 151.5, 151.3, 150.4, 136.1, 131.7, 131.4, 130.5, 129.3, 129.1, 128.9, 128.8, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 125.2, 125.1, 122.3, 120.4 and 120.2 (Ar), 77.9 (OCH_2CH_2), 67.0 (CH_2Ph), 52.4 ($COOCH_3$), 50.0, 49.9, 49.4 and 49.2 ($CHCH_3$), 31.7 and 31.6 ($ArCH_2Ar$), 23.4 (OCH_2CH_2), 19.4, 18.9, 17.8 and 17.7 ($CHCH_3$), 10.8 ($OCH_2CH_2CH_3$) ppm. ESI-MS: m/z (%) = 1022.8 (100) $[M + Na]^+$. $C_{56}H_{65}N_5O_{12}$ (999.46): calcd. C 67.25, H 6.55, N 7.00; found C 67.32, H 6.51, N 6.89.

25,27-Dihydroxy-11-(*N*-Cbz-L-leucyl-L-isoleucyl)amino-23-(methoxy-L-phenylalanyl-L-valyl)carbonyl-26,28-dipropoxycalix[4]arene (18): The crude was purified by flash column chromatography (eluent: CH_2Cl_2/MeOH, 98:2, v/v) to give the product as a white solid. Yield 27 mg, 0.02 mmol, 32%. ^{1}H NMR (300 MHz, [D$_6$]acetone/MeOD, 8:2): δ = 7.75 (s, 1 H, ArH), 7.74 (s, 1 H, ArH), 7.41–7.26 (m, 10 H, ArH), 7.18 (s, 1 H, ArH), 7.17 (s, 1 H, ArH), 6.94 (d, J = 7.2 Hz, 2 H, ArH), 6.89 (d, J = 7.2 Hz, 2 H, ArH), 6.56 (t, J = 7.2 Hz, 2 H, ArH), 5.09 (br. s, 2 H, CH_2 Cbz), 4.67 (t, J = 6.3 Hz, 1 H, CH), 4.44 (t, J = 7.5 Hz, 1 H, CH), 4.38–4.24 (m, 6 H, 2 CH

and H_{ax} of $ArCH_2Ar$), 4.00 (t, J = 6.0 Hz, 4 H,OCH_2CH_2), 3.62 (s, 3 H, OCH_3), 3.50 (d, J = 12.9 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 3.36 (d, J = 12.6 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 3.10 (dd, J = 11.1, 6.0 Hz, 1 H, C*H*HPh), 2.99 (dd, J = 11.1, 8.1 Hz, 1 H, CH*H*Ph), 2.13–2.08 (m, 5 H, OCH_2CH_2 and CH), 1.90 (br. s, 1 H, CH), 1.75–1.68 (m, 1 H, CH), 1.57 (t, J = 7.5 Hz, 2 H, CH_2), 1.34 (t, J = 7.5 Hz, 6 H, CH_2CH_3), 1.20–1.08 (m, 2 H, CH_2), 0.95–0.83 (m, 18 H, CH_3). ESI-MS: m/z (%) = 1211.1 (100) $[M + Na]^+$. $C_{70}H_{85}N_5O_{12}$ (1187.62): calcd. C 70.74, H 7.21, N 5.89; found C 70.82, H 7.15, N 5.78.

23-Butylaminocarbonyl-25,27-dihydroxy-11-propanoylamino-26,28-dipropoxycalix[4]arene (20): The crude was purified by flash column chromatography (eluent: CH_2Cl_2/MeOH, 40:1, v/v) to give the product as a white solid. Yield 21 mg, 0.03 mmol, 45%. M.p. >300 °C. ^1H NMR (300 MHz, $CDCl_3$, $c = 10^{-2}$ M): δ = 8.84 (s, 1 H, OH), 8.19 (br. s, 1 H, ArNH), 8.01 (s, 1 H, OH), 7.52 (s, 2 H, ArH), 7.32 (s, 2 H, ArH), 6.43 (br. s, 4 H, ArH), 6.09 (br. s, 1 H, N*H*CH_2), 5.96 (br. s, 2 H, ArH), 4.24 (d, J = 13.2 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 4.22 (d, J = 13.2 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 3.91 (br. s, 4 H, OCH_2), 3.53–3.42 (m, 2 H, NHC*H*$_2$), 3.33 (d, J = 13.2 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 3.25 (d, J = 13.2 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 2.44 (q, J = 3.7 Hz, 2 H, $COCH_2$), 2.09–1.96 (m, 4 H, OCH_2CH_2), 1.68–1.51 (m, 2 H, $NHCH_2CH_2$), 1.49–1.36 (m, 2 H, $NHCH_2CH_2CH_2$), 1.35–1.19 (m, 9 H, $OCH_2CH_2CH_3$ and $NHCOCH_2CH_3$), 0.96 (t, J = 8.0 Hz, 3 H, $CONHCH_2CH_2CH_2CH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.6 and 156.9 (CO), 151.7, 149.9, 132.8, 132.1, 129.8, 129.2, 128.9, 128.2, 128.0, 127.6, 125.3 and 124.7 (Ar), 78.2 (OCH_2CH_2), 39.8 ($NHCH_2$), 32.0 and 31.5 ($ArCH_2Ar$), 29.7 ($NHCH_2CH_2$), 23.5 (OCH_2CH_2), 20.2 ($NHCH_2CH_2CH_2$), 15.4 ($COCH_2$), 13.8 ($NHCH_2CH_2CH_2CH_3$), 10.8 ($OCH_2CH_2CH_3$), 9.8 ($COCH_2CH_3$) ppm. ESI-MS: m/z (%) = 701.6 (100) $[M + Na]^+$. $C_{42}H_{50}N_2O_6$ (678.36): calcd. C 74.31, H 7.42, N 4.13; found C 74.37, H 7.38, N 4.05.

11-(*N*-Cbz-L-Alanyl)amino-23-butylaminocarbonyl-25,27-dihydroxy-26,28-dipropoxycalix[4]arene (21): The crude was purified by flash column chromatography (eluent: CH_2Cl_2/MeOH, 35:1, v/v) to give the product as a white solid. Yield 55 mg, 0.06 mmol, 94%. M.p. 195 °C (decomp.).^1H NMR (300 MHz, $CDCl_3$, $c = 10^{-2}$ M): δ = 9.31 (br. s, 1 H, NH), 8.90 (s, 1 H, OH), 8.05 (s, 1 H, OH), 7.53 (s, 2 H, Ar), 7.37–7.34 (m, 7 H, ArH), 6.17 (br. s, 5 H, NH and ArH), 5.77 (br. s, 1 H, NH Cbz), 5.62 (br. s, 2 H, ArH), 5.11 (m, 2 H, CH_2 Cbz), 4.55 (br. s, 1 H, CH), 4.25–4.18 (m, 4 H, H_{ax} of $ArCH_2Ar$), 3.90 (br. s, 4 H, OCH_2CH_2), 3.51 (br. s, 2 H, NHC*H*$_2$), 3.31 (d, J = 13.3 Hz, 1 H, H_{eq} of $ArCH_2Ar$), 3.30 (d, J = 13.4 Hz, 1 H, H_{eq} of $ArCH_2Ar$), 3.23 (d, J = 13.1 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 2.08–1.99 (m, 4 H,OCH_2CH_2), 1.75–1.55 (m, 2 H, $NHCH_2CH_2$), 1.53 (d, J = 6.8 Hz, 3 H, $CHCH_3$), 1.48–1.32 (m, 2 H, $NHCH_2CH_2CH_2$), 1.25 (t, J = 7.8 Hz, 6 H, $OCH_2CH_2CH_3$), 0.97 (t, J = 7.3 Hz, 3 H, $NHCH_2CH_2CH_2CH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.5, 167.8 and 157.3 (CO), 151.5, 150.0, 136.4, 132.2, 131.4, 129.6, 129.1, 128.8, 128.5, 128.2, 128.0, 127.0, 125.2, 123.8 and 120.1 (Ar), 78.1 (OCH_2CH_2), 66.9 (CH_2 Cbz), 51.5 (CH), 39.9 ($NHCH_2$), 31.9, 31.7 and 31.5 ($ArCH_2Ar$), 29.7 ($NHCH_2CH_2$), 23.5 (OCH_2CH_2), 20.2 ($NHCH_2CH_2CH_2$), 19.0 (CH_3), 13.9 ($NHCH_2CH_2CH_2CH_3$), 10.9 ($OCH_2CH_2CH_3$) ppm. ESI-MS: m/z (%) = 850.7 (100) $[M + Na]^+$. $C_{50}H_{57}N_3O_8$ (827.41): calcd. C 72.53, H 6.94, N 5.07; found C 72.65, H 7.02, N 4.95.

11-(*N*-Cbz-L-Alanyl-L-alanyl-L-alanyl)amino-25,27-dihydroxy-23-(methoxy-L-alanyl-L-alanyl-L-alanyl)carbonyl-26,28-dipropoxycalix[4]arene (19): NEt_3 (250 μL, 1.8 mmol) and HBTU (490 mg, 1.3 mmol) were added to a solution of **5** (120 mg, 0.21 mmol) and tripeptide Cbz-NH-L-Ala-L-Ala-L-Ala (154 mg, 0.42 mmol) in a mixture of dry CH_2Cl_2 and dry DMF (20 mL, 3:1, v/v). The mixture was stirred for 72 h at room temp. The solvents were removed in vacuo and the residue was dissolved in CH_2Cl_2 (20 mL). The organic layer was washed with 0.01 M HCl (15 mL) and H_2O (15 mL) and the solvent evaporated to dryness. The crude was purified by flash chromatography (gradient from CH_2Cl_2 to CH_2Cl_2/MeOH, 9:1, v/v) to obtain intermediate **10**. Compound **10** (53 mg, 0.05 mmol) was dissolved in a mixture of dry CH_2Cl_2 and dry DMF (15 mL, 3:1, v/v) and the tripeptide L-Ala-L-Ala-L-AlaOMe (55 mg, 0.15 mmol), NEt_3 (150 μL, 1.1 mmol) and HBTU (150 mg, 0.40 mmol) were added to this solution. The mixture was stirred for 48 h at room temp. The solvents were removed in vacuo and the residue was dissolved in CH_2Cl_2 (15 mL). The organic layer was washed with 0.01 M HCl (10 mL) and H_2O (10 mL) and the solvents evaporated to dryness. After flash chromatography (gradient from CH_2Cl_2/MeOH, 20:1, v/v to CH_2Cl_2/MeOH, 15:1, v/v) pure **19** was obtained as a white solid. Yield 34 mg, 0.03 mmol, 14%. ^1H NMR (300 MHz, $CDCl_3$, $c = 10^{-2}$ M): δ = 9.28 (br. s, 1 H, NH), 8.95 (s, 1 H, OH), 8.06 (s, 1 H, OH), 7.73 (br. s, 1 H, NH), 7.58 (s, 2 H, ArH), 7.39 (br. s, 1 H, NH), 7.27 (br. s, 8 H, ArH and NH), 6.85 (br. s, 2 H, NH), 6.17 (br. s, 6 H, ArH), 5.82 (br. s, 1 H, NH), 5.07 (m, 2 H, CH_2Ph), 4.91 (br. s, 1 H, CH), 4.77 (br. s, 1 H, CH), 4.54–4.50 (m, 2 H, CH), 4.25 (br. s, 1 H, CH), 4.19–4.15 (m, 4 H, H_{ax} of $ArCH_2Ar$), 3.86 (br. s, 4 H, $OCH_2CH_2CH_3$), 3.67 (s, 3 H, OCH_3), 3.31–3.17 (m, 4 H, H_{eq} of $ArCH_2Ar$), 1.99 (br. s, 4 H, $OCH_2CH_2CH_3$), 1.71 (br. s, 6 H, CH_3), 1.50 (br. s, 6 H, CH_3), 1.35 (br. s, 6 H, CH_3), 1.24 (br. s, 6 H, $OCH_2CH_2CH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2, 172.8, 172.7, 171.8, 170.5, 167.6, 157.8, 156.2, 151.6, 150.3, 136.1, 133.9, 132.1, 131.2, 129.4, 129.1, 128.9, 128.8, 128.5, 128.4, 128.2, 128.0, 125.2, 120.5, 78.1, 67.1, 52.4, 51.1, 49.9, 49.5, 49.1, 48.1, 31.6, 29.7, 23.4, 19.2, 18.7, 18.5, 18.2, 18.0, 10.8 ppm. MS (ESI-MS): calcd. for $C_{62}H_{75}N_7O_{14}$ 1141.5; found 1164.6 (100, $[M + Na]^+$), 2306.1 (5, $[2M + Na]^+$). $C_{62}H_{75}N_7O_{14}$ (1141.53): calcd. C 65.19, H 6.62, N 8.58; found C 65.22, H 6.57, N 8.49.

5-Nitro-25,26,27,28-tetrapropoxycalix[4]arene-17-carbaldehyde (25): A solution of 65% HNO_3 (0.3 mL) was added to a solution of 5-formyl-25,26,27,28-tetrapropoxycalix[4]arene (**24**)[21] (450 mg, 0.72 mmol) in CH_2Cl_2 (10 mL) and acetic acid (1.0 mL). The reaction mixture was stirred for 3 h at room temp., quenched by addition of a $NaHCO_3$ saturated solution (10 mL) and vigorously stirred for 10 min. The organic layer was separated, washed with distilled water (2 × 10 mL), dried with Na_2SO_4 and the solvents evaporated to dryness at reduced pressure. The crude was purified by flash chromatography (eluent: hexane/ethyl acetate, 93:7, v/v) to obtain the product as a pale yellow solid. Yield 185 mg, 0.28 mmol, 39%. M.p. 121–122 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.47 (s, 1 H, CHO), 7.29 (s, 2 H, ArH), 6.98 (s, 2 H, ArH), 6.89–6.75 (m, 6 H, ArH), 4.47 (d, J = 13.8 Hz, 4 H, H_{ax} of $ArCH_2Ar$), 3.97–3.85 (m, 8 H, $OCH_2CH_2CH_3$), 3.24 (d, J = 13.8 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 3.22 (d, J = 13.8 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 2.00–1.87 (m, 8 H, $OCH_2CH_2CH_3$), 1.05 (t, J = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.04 (t, J = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 0.96 (t, J = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.7, 161.7, 156.5, 142.3, 136.1, 135.6, 135.0, 134.3, 129.6, 129.1, 128.7, 123.2, 122.8, 77.1, 76.9, 76.7, 31.0, 30.9, 23.3, 23.0, 10.3, 10.0 ppm. MS (ESI-MS): calcd. for $C_{41}H_{47}NO_7$ 665.3; found 688.7 $[M + Na]^+$. $C_{41}H_{47}NO_7$ (665.33): calcd. C 73.96, H 7.12, N 2.10; found C 74.05, H 7.20, N 2.03.

Alternative Procedure for the Synthesis of 25: $SnCl_4$ (0.17 mL, 1.41 mmol) was added to a solution of 5-nitro-25,26,27,28-tetrapropoxycalix[4]arene (**23**)[20] (300 mg, 0.47 mmol) and α,α-dichlo-

romethyl methyl ether (0.13 mL, 1.41 mmol) in dry $CHCl_3$ (20 mL) cooled to –12 °C with an ice/salt bath. The reaction mixture was stirred without making any addition to the cold bath, thus letting the temperature slowly increase. After 1.5 h the reaction was quenched by the addition of 1 M HCl (50 mL). The organic phase was washed with H_2O (2 × 30 mL), dried with Na_2SO_4 and the solvents evaporated to dryness under reduced pressure. Pure **25** was obtained after recrystallization from CH_2Cl_2/hexane (1:1, v/v). Yield 45 mg, 0.07 mmol, 14%.

5-Nitro-25,26,27,28-tetrapropoxycalix[4]arene-17-carboxylic Acid (26): A solution of **25** (165 mg, 0.25 mmol) in $CHCl_3$/acetone (10 mL, 1:1, v/v) was cooled to 0 °C and treated with an aqueous solution (1.5 mL) of H_2NSO_3H (80 mg, 0.82 mmol) and $NaClO_2$ (49 mg, 0.54 mmol). The mixture was vigorously stirred at room temp. for 4 h. Then the organic solvents were evaporated under reduced pressure and 1 N HCl (5 mL) was added to give **26** as a pale yellow solid. Yield 154 mg, 0.23 mmol, 92%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53 (s, 2 H, ArH), 7.39 (s, 2 H, ArH), 6.70–6.58 (m, 6 H, ArH), 4.48 (d, J = 13.6 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 4.45 (d, J = 13.6 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 3.96 (t, J = 7.2 Hz, 2 H, $OCH_2CH_2CH_3$), 3.92 (t, J = 7.5 Hz, 2 H, $OCH_2CH_2CH_3$), 3.91–3.76 (m, 4 H, $OCH_2CH_2CH_3$), 3.24 (d, J = 13.6 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 3.23 (d, J = 13.6 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 2.00–1.82 ($OCH_2CH_2CH_3$), 1.07–0.98 (m, 12 H, $OCH_2CH_2CH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.6, 162.3, 161.4, 156.2, 142.4, 136.5, 135.4, 134.6, 133.5, 130.5, 129.0, 128.3, 123.6, 122.8, 77.1, 76.9, 76.8, 31.5, 31.0, 23.3, 23.2, 10.3 ppm. MS (ESI-MS): calcd. for $C_{41}H_{48}NO_8$ 631.3; found 726.3 $[M - H + 2Na]^+$. $C_{41}H_{48}NO_8$ (681.33): calcd. C 72.22, H 6.95, N 2.05; found C 72.31, H 6.82, N 2.16.

5-Amino-25,26,27,28-tetrapropoxycalix[4]arene-17-carboxylic Acid (27): Hydrazine hydrate (54 μL, 176 mmol) and a catalytic amount of Pd/C (10%) were added to a suspension of **26** (150 mg, 0.22 mmol) in ethanol (10 mL). The mixture was heated at reflux for 4 h, then the catalyst was filtered off and the organic solvent was evaporated under reduced pressure to obtain the product as a white solid to be used without further purification. Yield 128 mg, 0.20 mmol, 90%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.06 (s, 2 H, ArH), 6.87 (d, J = 7.8 Hz, 4 H, ArH), 6.75 (t, J = 7.8 Hz, 2 H, ArH), 5.80 (s, 2 H, ArH), 4.45 (d, J = 13.4 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 4.36 (d, J = 13.5 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 4.25 (br. s, 2 H, NH_2), 3.94–3.80 (m, 6 H, $OCH_2CH_2CH_3$), 3.67 (t, J = 7.0 Hz, 2 H, $OCH_2CH_2CH_3$), 3.19 (d, J = 13.5 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 3.05 (d, J = 13.4 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 1.93–1.81 (m, 8 H, $OCH_2CH_2CH_3$), 1.07–0.89 (m, 12 H, $OCH_2CH_2CH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$/MeOD, 1:1, v/v): δ = 169.4, 159.4, 156.0, 153.4, 135.3, 134.5, 134.3, 133.8, 128.8, 128.2, 127.8, 127.7, 123.8, 121.5, 119.2, 76.2, 76.1, 75.8, 29.9, 22.5, 22.4, 22.2, 9.2, 8.8 ppm. $C_{41}H_{49}NO_6$ (651.35): calcd. C 75.55, H 7.58, N 2.15; found C 75.62, H 7.50, N 2.18.

Compound 28: $NEt(iPr)_2$ (53 μL, 0.31 mmol), *N*-Cbz-L-alanine (34 mg, 0.15 mmol) and PyBOP (140 mg, 0.27 mmol) were added to a solution of **27** (50 mg, 0.077 mmol) in dry DMF (3 mL). The mixture was stirred overnight at room temp. Upon addition of H_2O (3 mL) a precipitate formed which was collected by Büchner filtration. Column chromatography (eluent: hexane/AcOEt, 7:3, v/v) was carried out on the crude mixture and compound **28** was isolated as the more abundant component as a white powder. Yield 15 mg, 0.024 mmol, 31%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.14 (d, J = 7.4 Hz, 2 H, ArH), 7.12 (d, J = 7.4 Hz, 2 H, ArH), 6.98 (t, J = 7.4 Hz, 2 H, ArH), 6.80 (s, 1 H, NH), 5.62 (s, 2 H, ArH), 5.52 (s, 2 H, ArH), 4.43 (d, J = 14.4 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 4.42 (d, J = 14.5 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 3.82 (t, J = 8.4 Hz, 4 H, $OCH_2CH_2CH_3$), 3.69 (t, J = 6.4 Hz, 2 H, $OCH_2CH_2CH_3$), 3.68 (t, J = 6.5 Hz, 2 H, $OCH_2CH_2CH_3$), 3.17 (d, J = 14.4 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 3.15 (d, J = 14.5 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 1.83–1.69 (m, 8 H, $OCH_2CH_2CH_3$), 1.10 (t, J = 7.3 Hz, 3 H, $OCH_2CH_2CH_3$), 1.09 (t, J = 7.3 Hz, 3 H, $OCH_2CH_2CH_3$), 0.82 (t, J = 7.5 Hz, 6 H, $OCH_2CH_2CH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.2, 158.9, 155.4, 155.0, 137.8, 137.4, 135.3, 134.6, 131.1, 129.8, 129.7, 129.5, 129.4, 125.2, 121.8, 76.2, 76.1, 76.0, 31.2, 23.4, 23.3, 23.0, 10.8, 9.7 ppm. MS (ESI-MS): calcd. for $C_{41}H_{47}NO_5$ 633.3; found 656.6 $[M + Na]^+$. $C_{41}H_{47}NO_5$ (633.34): calcd. C 77.69, H 7.47, N 2.21; found C 77.75, H 7.40, N 2.28.

5-(Boc-Amino)-25,26,27,28-tetrapropoxycalix[4]arene-17-carboxylic Acid (30): Di-*tert*-butyl dicarbonate (154 mg, 0.70 mmol) was added to a solution of **27** (46 mg, 0.07 mmol) in a mixture of freshly distilled THF (5 mL), NEt_3 (1 mL) and H_2O (1 mL). The mixture was stirred for 7 h at room temp. The organic solvent was evaporated under reduced pressure and the residue was taken up in a mixture of Et_2O (5 mL) and 1 N NaOH (5 mL). The organic layer was separated, the aqueous phase was extracted with Et_2O (2 × 5 mL) and the combined organic layers were washed with 1 M NaOH (5 mL) and 1 N HCl (5 mL), dried with Na_2SO_4 and the solvents evaporated to dryness to obtain the product as a white solid to be used without further purification. Yield 50 mg, 0.066 mmol, 95%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.58 (br. s, 11 H, ArH and NH), 4.46 (d, J = 13.5 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 4.40 (d, J = 13.4 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 3.82 (br. s, 8 H, $OCH_2CH_2CH_3$), 3.20 (d, J = 13.5 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 3.11 (d, J = 13.4 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 1.94–1.85 (m, 8 H, $OCH_2CH_2CH_3$), 1.47 [s, 9 H, CH_3(Boc)], 1.04–0.88 (m, 12 H, $OCH_2CH_2CH_3$) ppm. $C_{46}H_{57}NO_8$ (751.41): calcd. C 73.47, H 7.64, N 1.86; found C 73.50, H 7.61, N 1.90.

5-(Boc-Amino)-17-(methoxy-L-alanyl)carbonyl-25,26,27,28-tetrapropoxycalix[4]arene (31): $NEt(iPr)_2$ (49 μL, 0.28 mmol), PyBOP (73 mg, 0.17 mmol) and L-alanine methyl ester hydrochloride (24 mg, 0.175 mmol) were added to a solution of **30** (50 mg, 0.07 mmol) in dry DMF (3 mL). The mixture was stirred for 24 h at room temp. Upon addition of H_2O (3 mL) the product was obtained as a white precipitate which was collected by Büchner filtration, washed with H_2O (2 × 2 mL) and used without further purification. Yield 45 mg, 0.05 mmol, 77%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.87 (s, 2 H, ArH), 6.76 (t, J = 6.4 Hz, 4 H, ArH), 6.71 (d, J = 6.4 Hz, 2 H, ArH), 6.44 (br. s, 1 H, NH), 6.38 (br. s, 1 H, NH), 6.33 (s, 2 H, ArH), 4.73 (br. s, 1 H, CH), 4.46 (d, J = 13.4 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 4.38 (d, J = 13.4 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 3.90–3.62 (m, 8 H, $OCH_2CH_2CH_3$), 3.77 (s, 3 H, OCH_3), 3.20–3.10 (m, 4 H, H_{eq} of $ArCH_2Ar$), 1.88 (br. s, 8 H, $OCH_2CH_2CH_3$), 1.44 [s, 9 H, CH_3(Boc)], 1.25 [br. s, 3 H, CH_3(Ala)], 1.05–0.85 (m, 12 H, $OCH_2CH_2CH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.5, 156.7, 153.9, 153.0, 152.9, 150.2, 135.4, 135.2, 134.8, 128.7, 128.6, 128.4, 126.8, 126.7, 122.1, 121.8, 79.8, 76.7, 76.6, 52.5, 48.3, 30.9, 29.6, 28.3, 23.2, 23.1, 18.5, 10.4, 10.1 ppm. MS (ESI-MS): calcd. for $C_{50}H_{64}N_2O_9$ 836.5; found 859.5 $[M + Na]^+$. $C_{50}H_{64}N_2O_9$ (836.46): calcd. C 71.74, H 7.71, N 3.35; found C 71.81, H 7.69, N 3.38.

5-Amino-17-(methoxy-L-alanyl)carbonyl-25,26,27,28-tetrapropoxycalix[4]arene (32): A sample of **31** (45 mg, 0.05 mmol) was dissolved in a CH_2Cl_2/TFA/triethylsilane/H_2O (3 mL, 47.5:47.5:2.5:2.5, v/v/v/v) solution and the mixture was stirred for 3 h at room temp. The solvents were evaporated in vacuo and the residue was dissolved in CH_2Cl_2 (3 mL). The organic phase was washed with 5% $NaHCO_3$ (2 mL) and H_2O (2 mL). The product was obtained as

a white solid and used without further purification. Yield 36 mg, 0.049 mmol, 98%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.08 (s, 1 H, ArH), 7.02 (s, 1 H, ArH), 6.70–6.58 (m, 6 H, ArH), 6.43 (d, J = 7.0 Hz, 1 H, NH), 5.83 (s, 2 H, ArH), 4.65 (quint., J = 7.1 Hz, 1 H, CH), 4.46 (d, J = 13.4 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 4.35 (d, J = 13.2 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 3.87–3.80 (m, 4 H, $OCH_2CH_2CH_3$), 3.76 (s, 3 H, OCH_3), 3.72–3.70 (m, 4 H, $OCH_2CH_2CH_3$), 3.18 (d, J = 13.2 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 3.02 (d, J = 13.4 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 1.93–1.81 (m, 8 H, $OCH_2CH_2CH_3$), 1.43 [d, J = 7.1 Hz, 3 H, CH_3(Ala)], 0.98–0.90 (m, 12 H, $OCH_2CH_2CH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.9, 167.2, 159.9, 157.0, 135.6, 135.5, 135.4, 135.3, 134.5, 128.7, 128.6, 128.2, 128.1, 127.2, 126.8, 122.1, 115.3, 77.1, 76.9, 52.5, 48.3, 31.9, 31.1, 23.3, 23.2, 18.6, 10.5, 10.4, 10.3 ppm. $C_{45}H_{56}N_2O_7$ (736.41): calcd. C 73.34, H 7.66, N 3.80; found C 73.35, H 7.54, N 3.95.

5-(*N*-Cbz-L-Alanyl)amino-17-(methoxy-L-alanyl)carbonyl-25,26,27,28-tetrapropoxycalix[4]arene (33): $NEt(iPr)_2$ (34 μL, 0.19 mmol), *N*-Cbz-L-alanine (27 mg, 0.12 mmol) and PyBOP (51 mg, 0.10 mmol) were added to a solution of **32** (36 mg, 0.05 mmol) in dry DMF (3 mL). The mixture was stirred for 6 h at room temp. Upon addition of H_2O (3 mL) the product was obtained as a white precipitate which was collected by Büchner filtration, washed with H_2O (2 × 2 mL) and purified by flash chromatography (hexane/ethyl acetate, 7:3, v/v). Yield 22 mg, 0.023 mmol, 48%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00 (s, 1 H, NH), 7.35–7.29 (m, 5 H, Ph), 6.86 (s, 1 H, ArH), 6.80–6.67 (m, 7 H, ArH), 6.39 (s, 1 H, ArH), 6.32 (d, J = 7.3 Hz, 1 H, NH), 6.28 (s, 1 H, ArH), 5.62 (d, J = 7.3 Hz, 1 H, NH), 5.10 (s, 2 H, CH_2Ph), 4.68 (br. s, 1 H, CH), 4.46 (d, J = 13.4 Hz, 1 H, H_{ax} of $ArCH_2Ar$), 4.45 (d, J = 13.5 Hz, 1 H, H_{ax} of $ArCH_2Ar$), 4.40 (d, J = 13.6 Hz, 1 H, H_{ax} of $ArCH_2Ar$), 4.39 (d, J = 13.4 Hz, 1 H, H_{ax} of $ArCH_2Ar$), 4.30 (br. s, 1 H, CH), 3.92–3.71 (m, 8 H, $OCH_2CH_2CH_3$), 3.76 (s, 3 H, OCH_3), 3.17 (d, J = 13.4 Hz, 1 H, H_{eq} of $ArCH_2Ar$), 3.16 (d, J = 13.5 Hz, 1 H, H_{eq} of $ArCH_2Ar$), 3.14 (d, J = 13.4 Hz, 1 H, H_{eq} of $ArCH_2Ar$), 3.11 (d, J = 13.6 Hz, 1 H, H_{eq} of $ArCH_2Ar$), 1.94–1.82 (m, 8 H, $OCH_2CH_2CH_3$), 1.39 [d, J = 6.9 Hz, 6 H, CH_3(Ala)], 1.05–0.99 (m, 6 H, $OCH_2CH_2CH_3$), 0.96–0.91 (m, 6 H, $OCH_2CH_2CH_3$) ppm. ^{1}H NMR (600 MHz, [D$_6$]acetone): δ = 9.02 (s, 1 H, NH), 7.84 (d, J = 7.2 Hz, 1 H, NH), 7.61 (s, 2 H, ArH), 7.44 (d, J = 7.8 Hz, 2 H, Ph), 7.40 (t, J = 7.8 Hz, 2 H, Ph), 7.34 (t, J = 7.8 Hz, 1 H, Ph), 7.27 (s, 1 H, ArH), 7.22 (s, 1 H, ArH), 6.61 (d, J = 7.2 Hz, 1 H, NH), 6.40–6.34 (m, 6 H, ArH), 5.15 (d, J = 12.6 Hz, 1 H, C*H*HPh), 5.11 (d, J = 12.6 Hz, 1 H, CH*H*Ph), 4.69 (quint., J = 7.2 Hz, 1 H, CH), 4.54 (d, J = 13.2 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 4.49 (d, J = 13.2 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 4.38 (quint., J = 7.2 Hz, 1 H, CH), 4.11 (t, J = 7.8 Hz, 2 H, $OCH_2CH_2CH_3$), 4.01 (t, J = 8.4 Hz, 2 H, $OCH_2CH_2CH_3$), 3.79 (t, J = 7.2 Hz, 4 H, $OCH_2CH_2CH_3$), 3.73 (s, 3 H, OCH_3), 3.27 (d, J = 13.2 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 3.18 (d, J = 13.2 Hz, 1 H, H_{eq} of $ArCH_2Ar$), 3.16 (d, J = 13.2 Hz, 1 H, H_{eq} of $ArCH_2Ar$), 2.06–1.94 (m, 8 H, $OCH_2CH_2CH_3$), 1.49 [d, J = 7.2 Hz, 3 H, CH_3(Ala)], 1.46 [d, J = 7.2 Hz, 3 H, CH_3(Ala)], 1.13 (t, J = 7.2 Hz, 6 H, $OCH_2CH_2CH_3$), 1.00 (t, J = 7.2 Hz, 6 H, $OCH_2CH_2CH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.7, 170.9, 168.8, 159.4, 156.9, 155.7, 154.1, 136.5, 135.6, 135.4, 134.9, 130.6, 128.9, 128.8, 128.5, 128.4, 128.3, 128.1, 128.0, 126.9, 126.2, 123.4, 122.9, 122.3, 77.3, 77.1, 66.8, 52.6, 50.6, 48.5, 31.0, 23.4, 23.3, 23.2, 19.5, 18.5, 10.6, 10.5, 10.1 ppm. MS (MALDI-MS): calcd. for $C_{56}H_{67}N_3O_{10}$ 941.5; found 964.4 $[M + Na]^+$, 980.4 $[M + K]^+$. $C_{56}H_{67}N_3O_{10}$ (941.48): calcd. C 71.39, H 7.17, N 4.46; found C 71.46, H 7.08, N 4.48.

5-(Boc-Amino)-17-butylaminocarbonyl-25,26,27,28-tetrapropoxycalix[4]arene (34): *n*-Butylamine (70 μL, 0.70 mmol) and PyBOP (91 mg, 0.17 mmol) were added to a solution of **30** (55 mg, 0.07 mmol) in dry DMF (3 mL). The mixture was stirred for 5 h at room temp. Upon addition of H_2O (3 mL) the product was obtained as a white precipitate which was collected by Büchner filtration, washed with H_2O (2 × 2 mL) and used without further purification. Yield 47 mg, 0.06 mmol, 84%. M.p. 93–95 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.82–6.65 (m, 8 H, ArH), 6.47 (br. s, 1 H, NH), 6.30 (s, 2 H, ArH), 5.68 (br. s, 1 H, NH), 4.46 (d, J = 13.5 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 4.38 (d, J = 13.4 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 3.92–3.79 (m, 6 H, $OCH_2CH_2CH_3$), 3.70 (t, J = 7.2 Hz, 2 H, $OCH_2CH_2CH_3$), 3.35 (q, J = 5.9 Hz, 2 H, $NHCH_2CH_2CH_2CH_3$), 3.17 (d, J = 13.4 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 3.12 (d, J = 13.5 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 1.93–1.84 (m, 8 H, $OCH_2CH_2CH_3$), 1.53–1.32 (m, 4 H, $NHCH_2CH_2CH_2CH_3$ and $NHCH_2CH_2CH_2CH_3$), 1.43 [s, 9 H, CH_3(Boc)], 1.03 (t, J = 7.7 Hz, 3 H, $NHCH_2CH_2CH_2CH_3$), 0.98–0.91 (m, 12 H, $OCH_2CH_2CH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.1, 159.0, 156.8, 154.1, 153.0, 135.6, 135.0, 134.7, 131.5, 128.7, 128.4, 126.5, 122.1, 79.3, 76.7, 76.6, 76.5, 39.5, 31.7, 30.9, 28.3, 23.3, 23.2, 23.0, 20.0, 13.8, 10.4, 10.0 ppm. MS (ESI-MS): calcd. for $C_{50}H_{66}N_2O_7$ 806.5; found 829.5 $[M + Na]^+$. $C_{50}H_{66}N_2O_7$ (806.48): calcd. C 74.41, H 8.24, N 3.47; found C 74.47, H 8.19, N 3.51.

5-Amino-17-butylaminocarbonyl-25,26,27,28-tetrapropoxycalix[4]-arene (35): Calixarene **34** (47 mg, 0.06 mmol) was dissolved in a CH_2Cl_2/TFA/triethylsilane/H_2O (3 mL, 47.5:47.5:2.5:2.5, v/v/v/v) solution and the mixture was stirred for 4 h at room temp. The solvents were evaporated in vacuo and the residue was dissolved in CH_2Cl_2 (3 mL). The organic phase was washed with 5% $NaHCO_3$ (2 mL) and H_2O (2 mL). The product was obtained as an oil and used without further purification. Yield 40 mg, 0.06 mmol, quantitative. ^{1}H NMR [300 MHz, $CDCl_3$/MeOD (4:1, v/v)]: δ = 6.90 (s, 2 H, ArH), 6.64 (d, J = 7.4 Hz, 4 H, ArH), 6.56 (t, J = 7.4 Hz, 2 H, ArH), 5.79 (s, 2 H, ArH), 4.39 (d, J = 13.4 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 4.29 (d, J = 13.4 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 3.80–3.62 (m, 8 H, $OCH_2CH_2CH_3$), 3.18 (t, J = 7.2 Hz, 2 H, $NHCH_2CH_2CH_2CH_3$), 3.10 (d, J = 13.4 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 2.96 (d, J = 13.4 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 1.86–1.75 (m, 8 H, $OCH_2CH_2CH_3$), 1.43–1.23 (m, 4 H, $NHCH_2CH_2CH_2CH_3$ and $NHCH_2CH_2CH_2CH_3$), 0.96–0.83 (m, 15 H, $OCH_2CH_2CH_3$ and $NHCH_2CH_2CH_2CH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3, 156.6, 149.9, 139.4, 135.5, 135.1, 134.6, 128.4, 128.0, 126.6, 121.8, 115.7, 76.7, 76.6, 76.5, 39.4, 31.4, 30.8, 23.1, 23.0, 20.0, 13.5, 10.2, 10.1, 10.0 ppm. $C_{45}H_{58}N_2O_5$ (706.43): calcd. C 76.45, H 8.27, N 3.96; found C 76.51, H 8.22, N 3.99.

17-Butylaminocarbonyl-5-propanoylamino-25,26,27,28-tetrapropoxycalix[4]arene (36): $NEt(iPr)_2$ (52 μL, 0.30 mmol), propionic acid (13 μL, 0.18 mmol) and PyBOP (62 mg, 0.12 mmol) were added to a solution of **35** (40 mg, 0.06 mmol) in dry DMF (3 mL). The mixture was stirred for 5 h at room temp. The reaction was quenched by the addition of 1 M HCl (3 mL). The mixture was extracted with AcOEt (2 × 3 mL) and the combined organic layers were washed with a saturated solution of Na_2CO_3 (3 mL) and H_2O, dried with Na_2SO_4 and the solvents evaporated to dryness. After flash chromatography (hexane/EtOAc, 7:3, v/v) pure **36** was obtained as a white solid. Yield 19 mg, 0.025 mmol, 42%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (s, 1 H, NH), 6.98 (d, J = 7.4 Hz, 4 H, ArH), 6.84 (t, J = 7.4 Hz, 2 H, ArH), 6.55 (s, 2 H, ArH), 6.07 (s, 2 H, ArH), 5.66 (t, J = 6.1 Hz, 1 H, NH), 4.46 (d, J = 13.5 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 4.39 (d, J = 13.5 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 4.00–3.90 (m, 4 H, $OCH_2CH_2CH_3$), 3.73 (t, J = 6.9 Hz, 2 H, $OCH_2CH_2CH_3$), 3.67 (t, J = 6.8 Hz, 2 H, $OCH_2CH_2CH_3$), 3.26 (q, J = 6.1 Hz, 2 H, $NHCH_2CH_2CH_2CH_3$), 3.15 (d, J = 13.5 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 3.14 (d, J = 13.5 Hz, 2 H, H_{eq} of $ArCH_2Ar$),

2.19 (q, J = 7.5 Hz, 2 H, $COCH_2CH_3$), 1.95–1.80 (m, 8 H, $OCH_2CH_2CH_3$), 1.47 (quint., J = 6.1 Hz, 2 H, $NHCH_2CH_2CH_2CH_3$), 1.30 (sext, J = 6.1 Hz, 2 H, $NHCH_2CH_2CH_2CH_3$), 1.13–1.03 (m, 9 H, $OCH_2CH_2CH_3$ and $COCH_2CH_3$), 0.93–0.86 (m, 9 H, $OCH_2CH_2CH_3$ and $NHCH_2CH_2CH_2CH_3$) ppm. ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 8.60 (s, 1 H, NH), 7.44 (br. t, 1 H, NH), 7.29 (s, 2 H, ArH), 6.89 (s, 2 H, ArH), 6.55–6.46 (m, 6 H, ArH), 4.49 (d, J = 13.8 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 4.45 (d, J = 13.8 Hz, 2 H, H_{ax} of $ArCH_2Ar$), 3.98 (t, J = 7.2 Hz, 2 H, $OCH_2CH_2CH_3$), 3.89 (t, J = 7.5 Hz, 2 H, $OCH_2CH_2CH_3$), 3.82 (t, J = 7.2 Hz, 4 H, $OCH_2CH_2CH_3$), 3.32 (q, J = 6.9 Hz, 2 H, $NHCH_2CH_2CH_2CH_3$), 3.20 (d, J = 13.8 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 3.11 (d, J = 13.8 Hz, 2 H, H_{eq} of $ArCH_2Ar$), 2.28 (q, J = 7.8 Hz, 2 H, $COCH_2CH_3$), 1.99–1.90 (m, 8 H, $OCH_2CH_2CH_3$), 1.55 (quint., J = 6.9 Hz, 2 H, $NHCH_2CH_2CH_2CH_3$), 1.36 (sext, J = 6.9 Hz, 2 H, $NHCH_2CH_2CH_2CH_3$), 1.10–0.90 (m, 18 H, $OCH_2CH_2CH_3$, $COCH_2CH_3$ and $NHCH_2CH_2CH_2CH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.7, 169.1, 158.4, 157.4, 153.2, 136.6, 135.6, 134.5, 133.9, 131.2, 129.2, 128.9, 128.6, 126.0, 123.5, 122.1, 76.9, 76.6, 76.5, 39.5, 31.6, 30.9, 29.6, 23.3, 22.9, 20.0, 13.7, 10.7, 10.6, 9.8 ppm. MS (ESI-MS): calcd. for $C_{48}H_{62}N_2O_6$ 762.5; found 785.5 $[M + Na]^+$. $C_{48}H_{62}N_2O_6$ (762.46): calcd. C 75.56, H 8.19, N 3.67; found C 75.68, H 8.07, N 3.74.

Molecular Modelling Studies: Molecular modelling was carried out at the molecular mechanics level using the MMFF94 force field[43] implemented in SPARTAN 06.[44] The conformational space of the molecule was first explored by a Monte Carlo method and then the dimer was constructed by placing two identical monomers in a mutual orientation suitable for intermolecular interactions to occur between the peptide chains. Then the molecular geometry of the whole dimer was allowed to relax without constraints. All the calculations were carried out on a Pentium IV PC (3.06 GHz).

Supporting Information (see also the footnote on the first page of this article): X-ray data for **27a** and **28**, 2D-NMR NOESY spectra of compounds **12**, **15**, **17**, **20** and **21**, molecular model (MMFF) of the self-assembled dimer $\mathbf{12}_2$, plot of the ^{1}H NMR spectroscopic data of **12** during the dilution experiment, colour version of Figures 1, 2, 4 and 5.

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