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Calixarene amino acids; building blocks for calixarene peptides and peptide-dendrimers

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Abstract—A modular strategy towards receptor macromolecules is presented, which combines synthetically diverse peptide synthesis with highly functional calixarene chemistry. The design and synthesis of calix[4]arene amino acids **1a**–**f**, calix-lysines, is described, which were used as construction blocks to assemble nanoscale, multivalent entities—calix–peptides **2** and calix–peptide-dendrimers **3**.

1. Introduction

Among the new challenges of chemistry are macromolecular entities composed of many identical components, arranged to serve as receptors for given binding units or ligands.[1] Multifunctionality of receptor molecules reflects a current trend of chemical sciences going towards 'smart' materials, informationally rich molecular devices, and nanofabrication.[2]

Through multiple, multivalent interactions macromolecular receptors display an increased affinity towards substrates, including biologically relevant ones. Such increase is due to either purely statistical reasons or positive cooperative effects. It is important, therefore, to harness the properties of compounds of intermediate size (e.g. 1–100 nm), somewhat between the molecular and solid state, and to create molecules that self-assemble into supramolecular structures, including solids, the properties of which surpass those of the molecular collection. This requires understanding the structure and dynamics of intra- and intermolecular interactions so that the properties of such molecular collections can be predicted and controlled. For some time, polymers have been offering effective routes towards such multifunctionality and multivalency, and more recently, dendrimers have entered the field.[3] While polymers, used for molecular recognition purposes, are often heterogeneous, linear, flexible, and not well defined, dendrimers tend to be monodisperse, globular, with defined size and shape. To build multivalent, functional nanostructures, polymers and dendrimers may be combined with calixarenes. Calixarenes are extremely popular building blocks in molecular recognition, and they have had a great impact in the history of supramolecular chemistry.[4] The three-dimensional surface, commercial availability and conformationally rigid structures make calixarenes most convenient for synthetic elaboration. Calixarene-based receptors are among the most effective and selective for cations; they are widely used to transport and extract various inorganic ions such as Na^+, K^+, and Cs^+,[5–7] lanthanides and actinides,[8] as well as organic cationic species.[9] Calixarene-based anion receptors show record thermodynamics and selectivities for phosphate, sulfate and chloride.[10,11] Calixarenes are also extremely important cavity-forming modules and have been employed for the construction of cavitands,[12,13] (hemi)carcerands[14] and self-assembling capsules.[15]

Existing syntheses of macromolecules that contain several identical or different binding sites typically require multiple steps for the preparation of monomers, thorough protection–deprotection strategy and are always time-consuming. Another issue is the potential application, which requires further synthetic planning and more experimental efforts. On the other hand, nature employs a limited number of construction blocks, modules, for instance amino acids, to assemble—quickly and effectively—a huge variety of proteins and enzymes. In this paper, we take advantage of this and introduce a general modular strategy towards multifunctional receptor macromolecules—calix–peptides and peptide-dendrimers (Fig. 1). This combines highly functional, receptor-oriented calixarene chemistry with synthetically diverse peptide synthesis. Namely, the design and synthesis of modules—calixarene amino acids is presented. Further, modular assembly of nanostructures—calixarene–peptides and calixarene–peptide-dendrimers is demonstrated. In general, presented here 'receptor–amino

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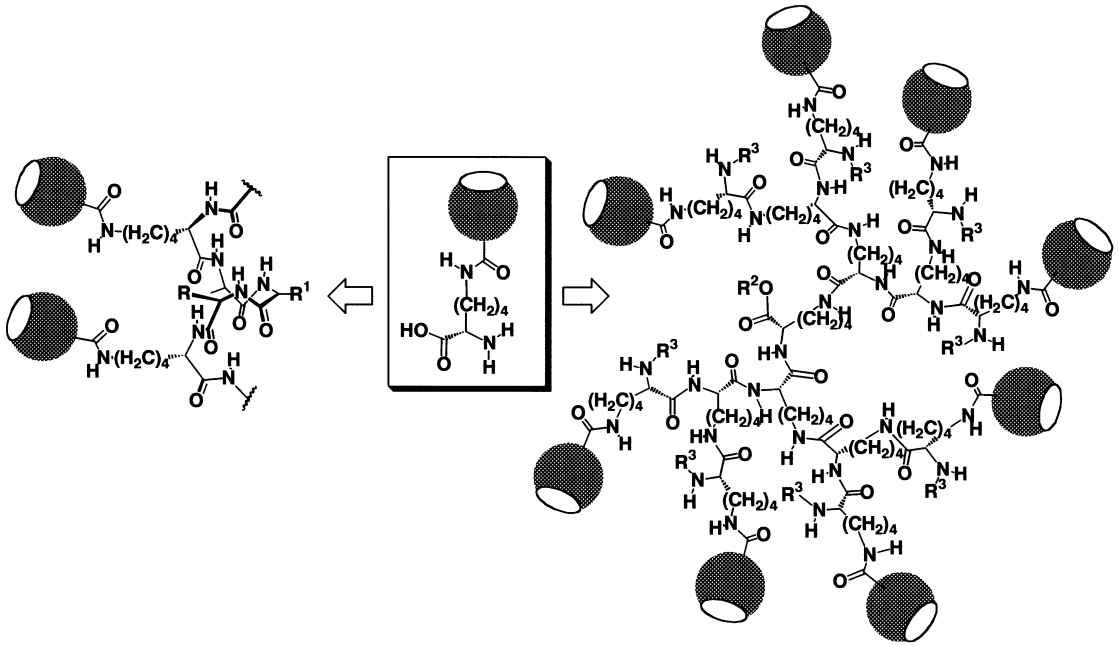


Figure 1. Calixarene amino acids as building blocks for multifunctional nanostructures—calix–peptides and calix–peptide-dendrimers. A modular approach.

acid' based modular approach may be useful for the construction of wide variety of multifunctional nanostructures.

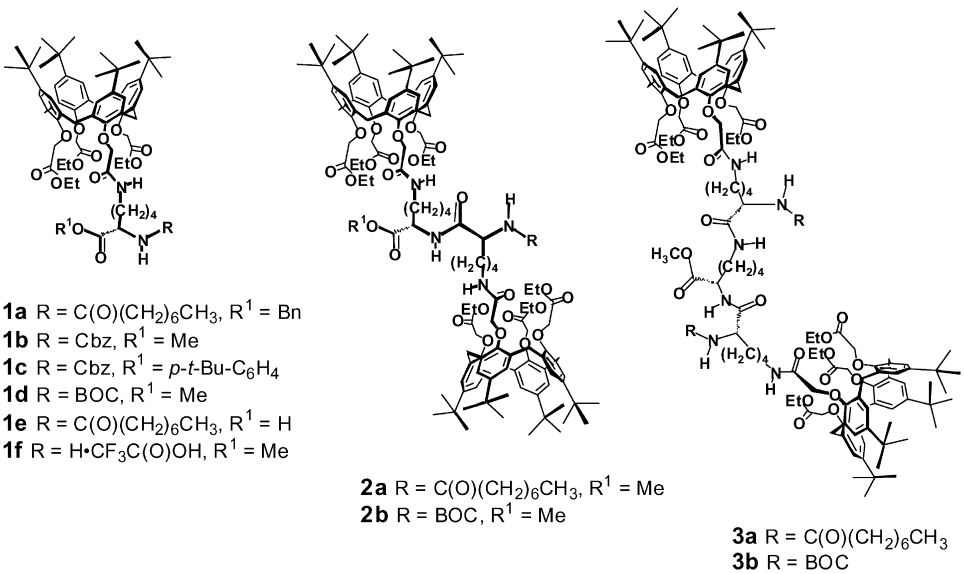
2. Results and discussion

2.1. Design

The proposed strategy is demonstrated for representative preparation of calix[4]arene amino acids **1**, calix[4]arene dipeptides **2**, and first generation of calix[4]arene peptide dendrimers **3** (Fig. 2).

In the synthesis of calix[4]arene amino acids, we took advantage of trifunctional lysine, which possesses a carboxylic group and two distant NH_2 groups of distinguishable reactivity. The ε-NH_2 group was attached to the calixarene fragment, while the α-NH_2 group was used in the coupling reactions with the other lysine C(O)OH group to form a peptide bond. This is an important feature of the proposed modular approach: both ends of amino acids are readily available for further peptide growth (Fig. 1). Notably, while a number of calix[4]arene–amino acid conjugates are known,[16] they are attached either via N- or C(O)O-terminus and, therefore, cannot be involved in the repetitive, multivalent peptide chain elongation.

The choice of the calixarene component for this project was justified by its strong affinity towards Na^+ cation.[5] It has been known for years that calix[4]arenes, functionalized with either ester or amide groups (or both) at the lower rim,



1a R = C(O)$(CH_2)_6CH_3$, R^1 = Bn
1b R = Cbz, R^1 = Me
1c R = Cbz, R^1 = *p*-*t*-Bu-C_6H_4
1d R = BOC, R^1 = Me
1e R = C(O)$(CH_2)_6CH_3$, R^1 = H
1f R = H•$CF_3C(O)OH$, R^1 = Me

2a R = C(O)$(CH_2)_6CH_3$, R^1 = Me
2b R = BOC, R^1 = Me

3a R = C(O)$(CH_2)_6CH_3$
3b R = BOC

Figure 2. Calixarene lysines **1a**–**f**, dipeptides **2a**,**b**, and tripeptides **3a**,**b**.

demonstrate a unique Na^+ selectivity, with the $K_{ass} \gg 10^6$ M^{-1} in apolar solvents. Moreover, the calixarene lower rim is relatively easy to functionalize. In our studies the calixarene Na^+ receptors were readily converted into the corresponding acids for the coupling with lysine derivatives.

2.2. Calixarene amino acids

First, we prepared a series of regioselectively protected lysine derivatives (Fig. 3). Thus, commercially available *N*-ε-BOC-*l*-lysine **4** was coupled with *n*-octanoyl chloride in the two-phase system EtOAc–H_2O, 1:1 in the presence of K_2CO_3 to afford *N*-α-acylated derivative **5** in 77% yield. The long aliphatic chain was used for solubility reasons. As followed from the absence of optical activity (see Section 4) and subsequent ^{1}H NMR analysis, compound **5** was obtained as a racemate. Apparently, base-catalyzed racemization[17] occurred as a result of rather basic conditions for acylation of enantiomerically pure **4**. The carboxylic group in **5** was then protected through benzylation. Namely, acid **5** was treated with benzyl alcohol and 1,3-dicyclohexylcarbodiimide (DCC) in CH_2Cl_2, containing catalytic quantities of 4-dimethylaminopyridine (DMAP) under nitrogen with the formation of benzyl ester **6** in 61% yield. Subsequently, the BOC protecting group in **6** was cleaved with TFA–THF, 1:4 mixture to afford the TFA salt of free amine **7** in a quantitative yield.

In another series of experiments, *N*-ε-BOC-*l*-lysine **4** was protected by a Cbz group (Cbz–Cl, Na_2CO_3) with the formation of *N*-α-Cbz-*N*-ε-BOC-*l*-lysine **8** in 65%.[18] Derivative **8** is optically active and, as will follow from the NMR analysis, enantiomerically pure. The carboxylic group in **8** was methylated (Cs_2CO_3, CH_3I, DMF) to form the corresponding ester **9** in 58% yield.[19] Reaction between **8**, 4-*t*-butylphenol, DCC and a catalytic amount of DMAP in CH_2Cl_2 afforded phenyl ester **10** in 62% yield. After the BOC deprotection with TFA, amine salts **11** and **12** were isolated in a quantitative yield.

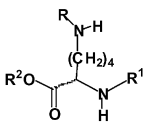
For *N*-α-BOC-*N*-ε-Cbz-*l*-lysine **13**, the carboxylic group was similarly methylated (Cs_2CO_3, CH_3I, DMF) to form the corresponding ester **14** in 65% yield.[20] The Cbz protection was then quantitatively cleaved with 10% Pd/C in CH_3OH to yield pure lysine **15**.[21] After the α-BOC protection in **14** was cleaved with TFA in THF, lysine derivative **16** was quantitatively isolated as a TFA salt.

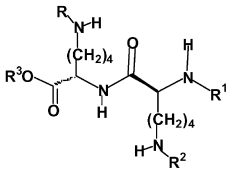
N-α-BOC-*N*-ε-BOC-*l*-lysine **17**[22] was methylated (CH_3I, Cs_2CO_3, DMF, 65%) and also benzylated (benzyl bromide, Cs_2CO_3, DMF, 68%) to afford *O*-benzyl esters **18** and **19**, respectively. Both the α- and ε-BOC groups in these were quantitatively cleaved with TFA in THF, yielding lysines **20** and **21** as TFA salts.

Finally, *N*-ε-Cbz-*l*-lysine **22**[23] was acylated with *n*-octanoyl chloride (K_2CO_3, EtOAc–H_2O, 1:1) to yield lysine acid **23** in 71% yield. The α-Cbz protection in **9** was quantitatively cleaved with 10% Pd/C in CH_3OH to yield pure **24**.[24]

In the coupling experiments between calixarenes and lysines, calix[4]arene acid chloride **25** was employed, which was prepared from the corresponding triester monoacid calix[4]arene and $SOCl_2$.[25] An equimolar amount of **25** in EtOAc was added to a solution of ε-deprotected lysines **7**, **11**, **12**, or **15** in EtOAc–H_2O, 1:1 and excess K_2CO_3. The reaction was complete in ~3 h and afforded calixarene lysines **1a–d** in 62–67% yield after column chromatography.

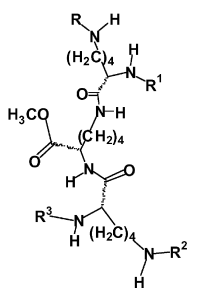
The structure of compounds **1a–d** was confirmed by high-resolution ^{1}H NMR spectroscopy, matrix-assisted laser desorption/ionization (MALDI) mass spectrometry and CHN elemental analysis. Typical ^{1}H NMR spectra are

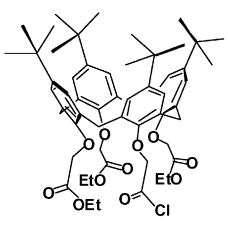




4 R = BOC, $R^1 = R^2 = H$
5 R = BOC, $R^1 = C(O)(CH_2)_6CH_3$, $R^2 = H$
6 R = BOC, $R^1 = C(O)(CH_2)_6CH_3$, $R^2 = Bn$
7 R = H•$CF_3C(O)OH$, $R^1 = C(O)(CH_2)_6CH_3$, $R^2 = Bn$
8 R = BOC, $R^1 = Cbz$, $R^2 = H$
9 R = BOC, $R^1 = Cbz$, $R^2 = Me$
10 R = BOC, $R^1 = Cbz$, $R^2 = p$-*t*-Bu-C_6H_4
11 R = H•$CF_3C(O)OH$, $R^1 = Cbz$, $R^2 = Me$
12 R = H•$CF_3C(O)OH$, $R^1 = Cbz$, $R^2 = p$-*t*-Bu-C_6H_4
13 R = Cbz, $R^1 = BOC$, $R^2 = H$
14 R = Cbz, $R^1 = BOC$, $R^2 = Me$
15 R = H, $R^1 = BOC$, $R^2 = Me$
16 R = Cbz, $R^1 = H•CF_3C(O)OH$, $R^2 = Me$
17 R = BOC, $R^1 = BOC$, $R^2 = H$
18 R = BOC, $R^1 = BOC$, $R^2 = Me$
19 R = BOC, $R^1 = BOC$, $R^2 = Bn$
20 R = H•$CF_3C(O)OH$, $R^1 = H•CF_3C(O)OH$, $R^2 = Me$
21 R = H•$CF_3C(O)OH$, $R^1 = H•CF_3C(O)OH$, $R^2 = Bn$
22 R = Cbz, $R^1 = R^2 = H$
23 R = Cbz, $R^1 = C(O)(CH_2)_6CH_3$, $R^2 = H$
24 R = BOC, $R^1 = H$, $R^2 = Me$

26 R = $R^2 = H•CF_3C(O)OH$, $R^1 = C(O)(CH_2)_6CH_3$, $R^3 = Me$
27 R = R^2 = BOC, $R^1 = C(O)(CH_2)_6CH_3$, $R^3 = Me$
28 R = R^2 = Cbz, R^1 = BOC, $R^3 = Me$
29 R = $R^2 = H$, R^1 = BOC, $R^3 = Me$





30 R = $R^2 = H$, $R^1 = R^3 = C(O)(CH_2)_6CH_3$ **25**
31 R = R^2 = Cbz, $R^1 = R^3 = C(O)(CH_2)_6CH_3$
32 R = $R^2 = H$, $R^1 = R^3$ = BOC
33 R = R^2 = Cbz, $R^1 = R^3$ = BOC

Figure 3. Building blocks for calixarene amino acids, dipeptides and tripeptides.

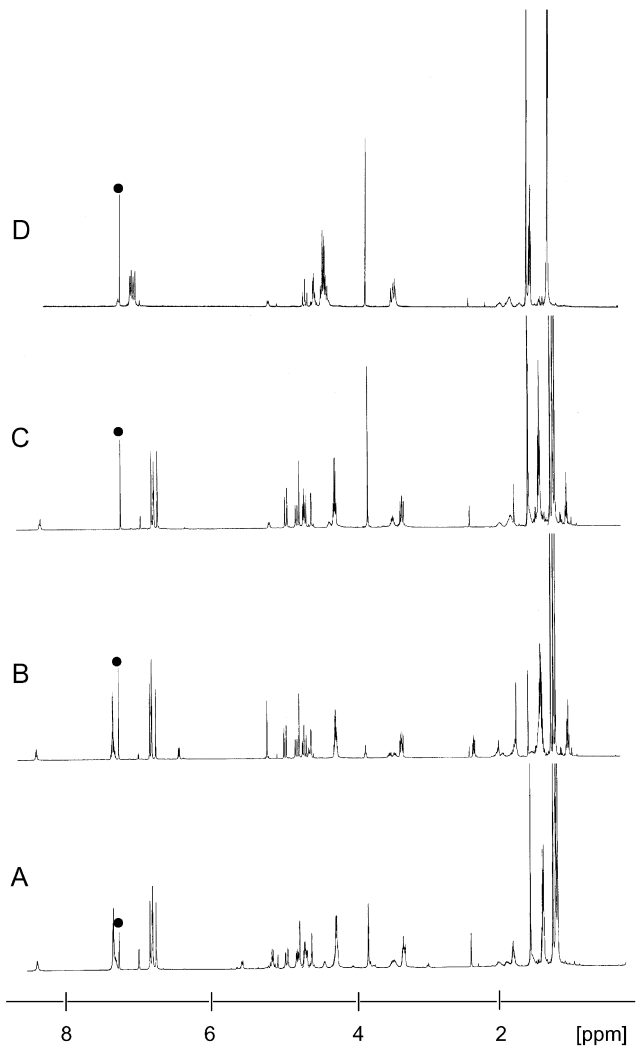


Figure 4. ^{1}H NMR spectra (500 MHz, $CDCl_3$, 295±1 K) of calixarene lysines: (a) **1b**, (b) **1a**, (c) **1d**, (d) **1d**·$Na^+ClO_4^-$. The residual $CHCl_3$ signals are marked '·'.

consistent with the monosubstituted calix[4]arene pattern, and contain in particular three calixarene aromatic (apparent) singlets in 1:2:1 ratio and three calixarene *t*-Bu singlets in 1:2:1 ratio ($CDCl_3$, 295 K) (Fig. 4). The ε-NH–C(O) amide proton is seen far down field as a triplet at ~8.4 ppm and apparently involved in the C═O···H–N hydrogen bonding with the calixarene lower rim carbonyl oxygens in apolar $CDCl_3$.[26]

This was additionally confirmed by molecular modeling.[27] The α-NH–C(O) proton is recorded as doublet and seen at ~5.5 ppm for carbamate derivatives **1b**–**d**, and at 6.4 ppm for amide derivative **1a**. As follows from molecular modeling (Fig. 5), the calix[4]arene fragment is positioned ~5–7 Å away from the amino acid fragment and should not sterically interfere with the peptide bond formation. It can also easily fit within the peptide/dendritic superstructures without disrupting hydrogen bonding and intramolecular folding processes.

Standard manipulation with protecting groups afforded calixarene amino acids with free either NH_2 or C(O)OH ends. For example, removal the *O*-benzyl group in calixlysine **1a** was quantitatively accomplished by catalytic hydrogenolysis with 10% Pd/C in CH_3OH and afforded free acid **1e**. Cleavage of the BOC protection group in derivative **1d** was carried out with TFA in THF to give lysine **1f** with free amino group.

2.3. Calix peptides

Peptides have already been functionalized with binding and catalytic sites.[28–30] For example, metalloporphyrin-containing de novo designed proteins effectively mimic natural photosynthetic centers.[29] Peptide-based fluorescent metal ion sensors comprise a metal recognition domain and a signal transduction moiety that is triggered upon metal ion binding.[30] A number of selective sensors have been constructed which are based on naturally occurring zinc fingers, serum albumin proteins and siderophores. Another important area of application is based on the DNA binding ability of proteins and their assemblies.

In principle, any modified amino acid can be incorporated within the polymeric peptide sequence. Preparative organic chemistry of amino acids and peptide bond formation is well developed. Secondary and even higher order structures of peptides largely depend on the solvent, temperature, etc. and can be studied by standard spectroscopic techniques and also somewhat predicted by molecular modeling. As follows from our own molecular modeling, the calix[4]arene platform is ≤10 Å in its dimensions, so when incorporated within the peptide network it can easily fit there without disrupting important hydrogen bonding processes.

In the synthesis of calixarene peptides, standard peptide coupling was employed. Lysines **1f** and **1e**, possessing free amino and carboxylic groups, respectively, were mixed with equimolar amounts of DCC and HOBT in DMF and stirred at rt for 36 h. Standard workup and chromatography afforded calix dipepide **2a** in 46% yield. In the alternative procedure, 2.4 equiv. of calixarene acid chloride **25** were coupled with the ε-NH_2 groups of preformed bis-lysine derivative **26** (K_2CO_3, EtOAc–H_2O, 1:1) with the formation of **2a** in 49% yield after column chromatography. Bis-lysine **26** was prepared from bis-BOC derivative **27**, which itself was synthesized from amino acids **24** and **5** (DCC, HOBT, DMF, 64%). Both protocols gave comparable quantities of calyx dipeptide **2a**.

Similarly, bis-lysine **28**[31] was prepared from amino acids **13** and **16** (DCC, HOBT, DMF, 53%). This was then deprotected with Pd/C in CH_3OH resulting in **29**[32] in 94% yield. Bis-lysine **29** reacted with 2.4 equiv. of monoacid chloride **25** in presence of K_2CO_3 (EtOAc–H_2O, 1:1) with the formation of calixarene dipeptide **2b** in 45% yield after column chromatography.

The structure of calixarene dipeptides **2a**,**b** was confirmed by FTIR, ^{1}H and COSY NMR spectroscopy, MALDI mass spectrometry and CHN elemental analysis. Although the compounds were reasonably soluble in $CDCl_3$, the corresponding ^{1}H NMR spectra appeared to be rather broad, especially the amide/peptide NH signals, most probably due to noncovalent aggregation. Molecular modeling (MM2 and

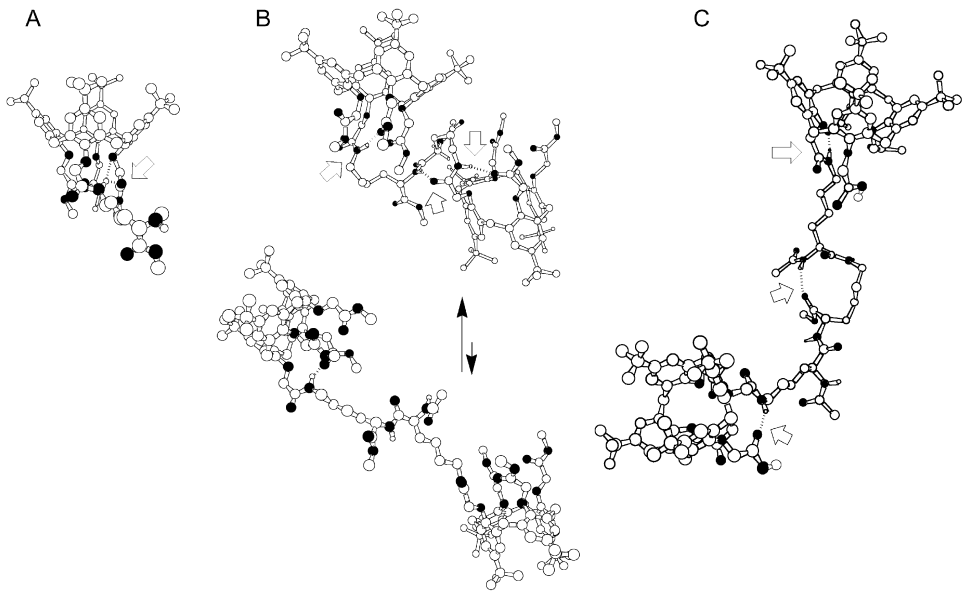


Figure 5. MacroModel 7.1 (Amber* ForceField) representation of calix[4]arene lysine **1** (A), calixarene dipeptide **2** (B), and calixarene dendritic structure **3** (C). Possible C═O···H–N hydrogen bonding is marked by arrows. For dipeptide **2**, both folded and unfolded structures are shown. The CH hydrogen and long alkyl chains are omitted for viewing clarity.

Amber Force Field)[27] suggests that not only the ε-NH–C(O) amide protons participate in the C═O···H–N hydrogen bonding with the calixarene lower rim carbonyl oxygens, but also the α-NH–C(O) proton is now involved in the intramolecular folding process (Fig. 5). The FTIR spectra of **2a**,**b** in KBr contain mostly associated NH stretching at ~3300 cm^{-1}.

In contrast, competitive and hydrogen bonding DMSO-d_6 produces sharp spectra. Typically, the ^{1}H NMR spectra are consistent with the monosubstituted calix[4]arene pattern. Dipeptide **2a** and also **26** and **27** exhibit two ~1:1 sets of signals for all groups of protons, indicating that pairs of diastereomeric products are formed in these cases. We attribute this to the base-catalyzed racemization of the amino acid precursor **5**, which was subsequently used in the preparation of racemic calixarene lysine **1e**, and also resulted in pairs of diastereomers for dipeptides **26** and **27**. This is not the case for dipeptides **2b**, **28**, and **29**, which were obtained enantiomerically pure (optical rotation, ^{1}H NMR analysis in different solvents).

2.4. Calix peptide dendrimers

Dendrimers have revolutionary entered supramolecular chemistry.[3] The layered, nanoscale architecture, globular shape, controlled nanomolar dimensions and easy modifications have made dendrimers unique carriers of supramolecular properties. Multivalent surfaces of dendrimers offer a unique opportunity for the substrate binding, providing strength and, often, cooperativity, with minimalized energy loses for reorganization and diffusion.

Surprising, that till now, only a limited progress has been reported in the literature on the preparation of calixarene dendrimers. For example, our recent search with SciFinder Scholar produced ~6000 references on dendrimers and ~5000 references on calixarenes, but less than 10 papers on calixarene-based dendrimers. A calix[4]arene platform was used as a core to which photochromic dyes and carbohydrate dendrons were attached.[33] This was relatively easy to achieve through standard, symmetrical tetrafunctionalization of calixarene. However, in two published examples,[34] involving calixarenes as branches and/or surface elements, the repetitive branching strategy for the preparation of higher dendritic generations was not clearly visible and had not been demonstrated. In a single report, Böhmer and co-workers postulated the divergent approach towards dendrimers, based on the multiple amide bond formation between appropriately functionalized calix[4]arene amines and calix[4]arene acid chlorides.[35] Experimentally, this had not been accomplished. Proposed here is the convergent[36] approach towards calixarene-containing dendrimers, which employs peptide chemistry. In such dendrimers, calixarene fragments are situated on the surface, thus providing the multivalency, and peptide groups serve as branching units.

In principle, peptide dendrimers are broadly defined as any dendrimer containing peptide fragments.[37] They are well suited for various biochemical and biotechnological applications, including diagnostic reagents, protein mimetics, anticancer and antiviral agents, vaccines, and drug delivery systems. Synthetically, amino acids are appealing building blocks because of well-developed peptide-coupling techniques. Polyamino acids consisting of branches of a trifunctional acid, especially lysine, represent the largest and most popular group of branching units being used today. The diamino nature of lysine creates a unique situation where each additional level of lysines effectively doubles the number of sites to which monomers are attached.

Two equivalents of calix amino acid **1e** were submitted to the coupling reaction with lysine methyl ester **20** in the presence of equimolar amounts of DCC and HOBT in DMF producing, after purification, 41% of dendritic bis-calixarene **3a**.

In the alternative procedure, triester monoacid chloride **25** was coupled with the preformed, first-generation lysine dendrimer **30** in presence of K_2CO_3 (EtOAc–H_2O, 1:1). This yields 47% of **3a** after column chromatography on silica gel. Bis-lysine **30** was prepared by the Pd/C hydrogenation of bis-Cbz derivative **31** in CH_3OH, which in its turn was obtained from amino acids **23** and *O*-methyl ester of *l*-lysine **20**. Accordingly, both procedures successfully yielded the same dendrimer. Since racemic lysine **5** was employed, dendrimer **3a** in our experiments was obtained as a mixture of diastereomers, which is highly difficult to separate. Similarly, calixarene acid chloride **25** was coupled with the preformed, first-generation lysine dendrimer **32** (K_2CO_3, EtOAc–H_2O) to afford optically pure dendrimer **3b** in 42% after column chromatography. Precursor dendrimer **32** was prepared by the Pd/C hydrogenation of bis-Cbz derivative **33**, which was obtained from amino acids **13** and **20**.

The structure of compounds **3a**,**b** was confirmed by high-resolution ^{1}H and COSY NMR spectroscopy and MALDI mass spectrometry. With their nanoscale dimensions and masses of >2500 Da, the structural assignment of **3a**,**b** was heavily relayed on the spectral features of simpler precursors such as tripeptides **30**–**33** and also calix lysines **1a**–**f**. Although being soluble in $CDCl_3$, **3a**,**b** exhibit broad ^{1}H NMR spectra, probably due to noncovalent aggregation. As expected, DMSO-d_6 produces sharp spectra. Similar to dipeptides **2a**,**b**, molecular modeling suggests that not only the ε-NH–C(O) amide protons are involved in the C═O···H–N hydrogen bonding with the calixarene lower rim carbonyl oxygens, but also the α-NH–C(O) proton participates in the intramolecular folding process (Fig. 5). In the folded conformation, the calix[4]arene fragments are positioned ~15 Å away from each other. Such a long distance is important for building next generations of calix dendrimers.

Dendritic structures **3a**,**b** may be regarded as a first generation of more expanded peptide dendrimers with calixarene surfaces. Indeed, in the proposed here convergent strategy, the C(O)OMe group of the core may be deprotected,[38] activated (DCC, HOBT) and used in the coupling step with lysine ester **21**. This will result in calix peptide dendrimer **34** of a second generation (Fig. 6). Subsequently, the core Bn-ester group can be further deprotected (H_2, Pd/C), activated and coupled with **21**. This will result in the third generation dendrimer **35**. These steps can, in principle, be repeated. Molecular modeling, however, suggests that further generations of **35** may be rather sterically crowded. Accordingly, proposed here repetitive branching strategy would allow for the preparation of higher dendritic generations of calixarenes.

2.5. Preliminary complexation experiments

Calix[4]arene functionalized with C(O)OAlk ester and/or C(O)NHAlk/C(O)NAlk_2 amide groups at the lower rim demonstrate a unique affinity and selectivity towards Na^+ cation not only in single solvents, but also in extraction experiments from water to organic solvent and in the transport experiments through bulk liquid and supported liquid membranes.[5] Solid-state and NMR-derived structures showed perfect Na^+ coordination within the lower rim pocket, consisting of eight basic, ether and carbonyl oxygen atoms. Such complexes are kinetically stable on the NMR time scale (e.g. $K_{ass} \gg 10^6$ M^{-1}), and the exchange between free and complexes species is slow.

We found that calix amino acids **1a**–**d**, calix peptides **2a**,**b** and dendrimer **3a**,**b** strongly complex Na^+ cations within their binding pockets. In the preliminary experiments, extraction was studied from aqueous solution of $NaClO_4$ to CH_2Cl_2. Specifically, **1a**–**d**, **2a**,**b**, and **3a**,**b** were dissolved in CH_2Cl_2 and stirred overnight with equal volumes of saturated aqueous solution of $NaClO_4$. Organic layers were then separated, evaporated under reduced pressure, dried in vacuum and analyzed by high-resolution ^{1}H NMR spectroscopy in $CDCl_3$. The corresponding Na^+ complexes formed quantitatively. The NMR spectra changed dramatically and exhibited completely new sets of signals for all protons. Especially notable are ~0.3 ppm down field shift of the calixarene aromatic protons, and ~0.2 ppm down field shift of the OCH_2 ethyl ester protons (Fig. 4). This could be attributed to the electron-withdrawing nature of Na^+ cation. The methylene CH_2 protons next to the carbonyl at the lower rim are shifted up field, which has been observed for simpler calixarene–Na^+ complexes and is caused by complexation-induced fixation of the carbonyls. Also of interest, the ~1 ppm up field shift of the lower rim C(O)NH proton. Apparently, Na^+ cation disrupts the intramolecular C═O···H–N hydrogen bonding at the lower rim upon complexation. No residual uncomplexed receptors were detected (Fig. 7).

The efficiency of compounds **1a**–**d**, **2a**,**b**, and **3a**,**b** as Na^+ receptors was also evident in the MALDI mass spectra: exclusively $[M+Na]^+$ parent ions were observed. This behavior is in contrast to most MALDI mass spectra of peptides which yield predominantly $[M+H]^+$ parent ions. At the same time, decomplexation of Na^+ cation was readily achieved by an excessive washing with water.

While cooperativity in Na^+ binding is not expected for **2a**,**b**, and **3a**,**b**, the presence of (a) multiple binding sites on the periphery/surface of such nanoscale receptors and (b) unique, intramolecular hydrogen bonding within their peptide scaffolds may offer strong and specific affinity towards guests. In contrast to simple collections of small receptor-molecules, which might require prior assembly/reorganization for transport and delivery, nanostructures **2a**,**b**, and **3a**,**b** and especially their larger relatives can use intramolecular forces to arrange their multiple and interconnected components in ways that minimize free energy. Such intramolecular processes may lead to the shape changes, specific internal microenvironments, and cooperative organization of ion binding surfaces. We are currently exploring ion-complexing properties of calix–peptides **2a**,**b** and calix peptide dendrimers **3a**,**b** and report on this in the sequel.

3. Conclusions and outlook

A modular strategy towards multivalent, nanoscale receptor macromolecules—calix–peptides and peptide-dendrimers—has been introduced. This combines unique

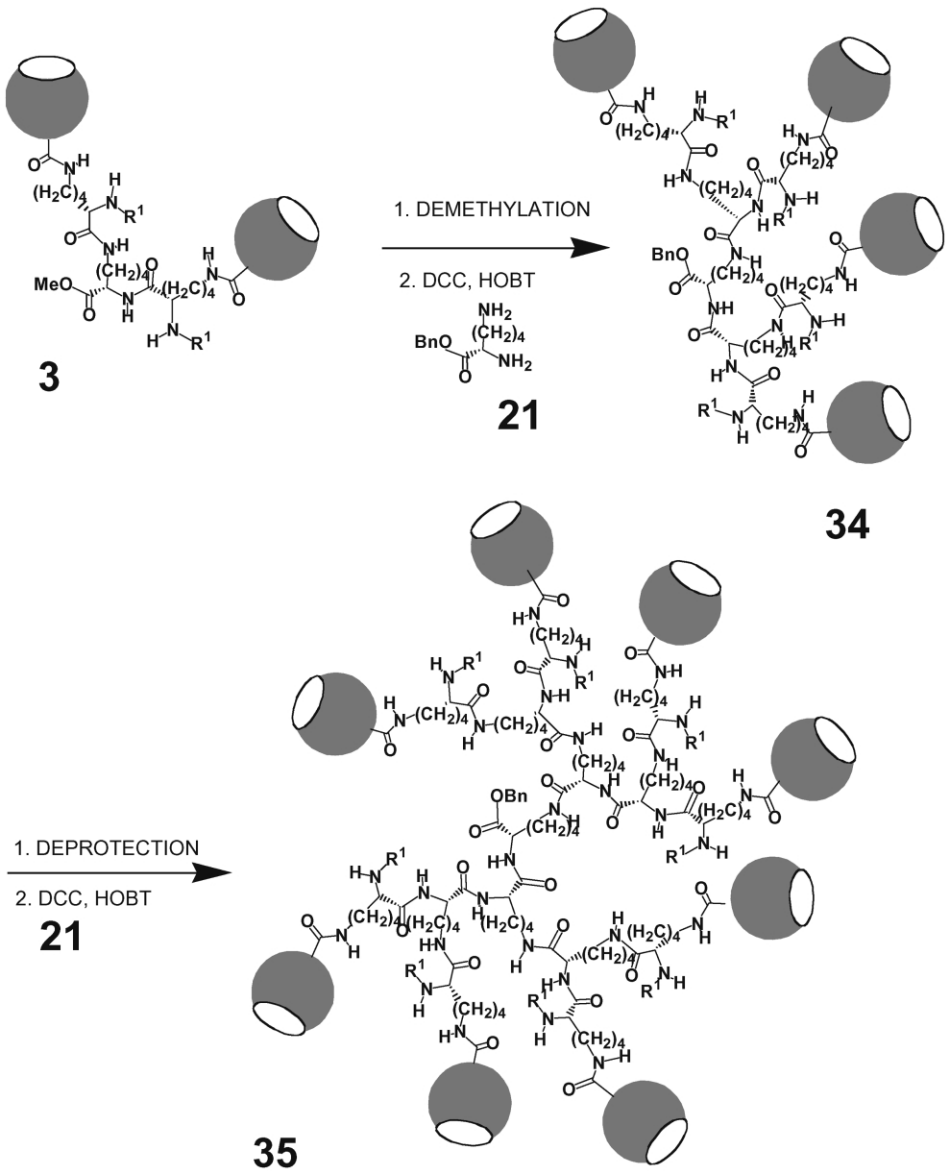


Figure 6. Towards higher generations of calix peptide dendrimers.

host–guest capabilities of calixarene chemistry with synthetically universal peptide synthesis. Calixarene amino acids are now available to be incorporated into peptide networks and nanostructured biological materials.

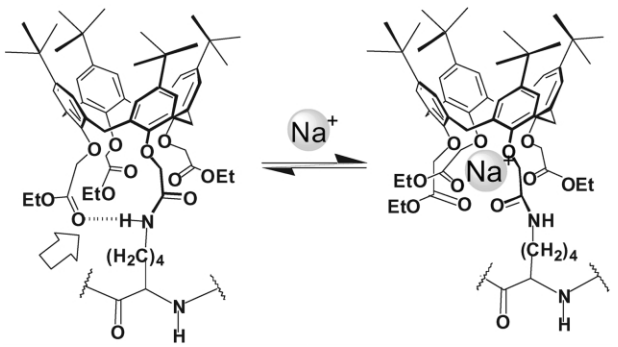


Figure 7. Complexation of Na^+ cation at the lower rims of multiple calix[4]arene fragments in amino acids **1** and peptides **2** and **3**. Addition of Na^+ disrupts intramolecular C═O···H–N hydrogen bonding. The ester C═O groups turn around to coordinate the cation.

Extended peptide dendrimers and dendritic polymers with calixarene surfaces can also be constructed. Through multiple, multivalent interactions such nanoscale receptors display a strong affinity towards substrates. Unique self-folding features of the incorporated peptide scaffolds offer an attractive opportunity to properly arrange and expose the multiple and interconnected receptor sites. This opens novel perspectives for the modular design of multifunctional receptors and sensors, multiply attached cavities and capsules, macromolecular devices and smart polymeric materials. We are currently working in these directions.

4. Experimental

4.1. General

Melting points were determined on a Mel-Temp apparatus (Laboratory Devices, Inc.) and a Buchi apparatus and are uncorrected. ^1H, ^{13}C and COSY NMR spectra were

recorded at 295±1°C on JEOL Eclipse 500 MHz spectrometer. Chemical shifts were measured relative to residual non-deuterated solvent resonances. FTIR spectra were recorded on a Bruker Vector 22 FTIR spectrometer. 337 nm MALDI mass spectrometry was performed on a Bruker BiFLEX I linear time-of-flight mass spectrometer operated in delayed extraction mode. Elemental analysis was performed on a Perkin–Elmer 2400 CHN analyzer. For column chromatography, Silica Gel 60 Å (Sorbent Technologies, Inc.; 200–425 mesh) was used. All experiments with moisture- or air-sensitive compounds were run in freshly distilled, anhydrous solvents under a dried nitrogen atmosphere. Molecular modeling was performed using MacroModel 7.1.[27]

4.1.1. *N*-α-(*n*-Octanoyl)-*N*-ε-BOC-(±)-lysine 5. A solution of *N*-ε-BOC-*l*-lysine **4** (0.50 g, 2 mmol) in mixture of H_2O (20 mL) and EtOAc (20 mL) was treated with *n*-octanoyl chloride (3.30 g, 20.3 mmol) and then stirred at rt for 3 h. The reaction mixture was diluted with aq HCl (5% vol, 50 mL) and CH_2Cl_2 (80 mL). The formed layers were separated. The aqueous layer was extracted by CH_2Cl_2 (3×30 mL), and the combined organic layer was then dried over anhydrous Na_2SO_4 and evaporated. The residue was solidified with hexane, yielding pure **5** (0.57 g, 77%) as a colorless solid: mp 115–116°C; $[\alpha]_D^{23}=0.0$ (c=0.02, EtOH); ^{1}H NMR (DMSO-d_6): δ 7.99 (d, J=7.8 Hz, 1H), 6.77 (t, J=7.1 Hz, 1H), 4.12 (dt, J=8.5, 7.8 Hz, 1H), 2.87 (dt, J=7.6, 7.1 Hz, 2H), 2.09 (dt, J=7.3, 2.5 Hz, 2H), 1.36 (s, 9H), 1.71–1.60, 1.60–1.40, 1.30–1.11 (3×m, 16H), 0.85 (t, J=6.6 Hz, 3H); ^{13}C NMR (DMSO-d_6): δ 174.5, 172.9, 156.1, 77.9, 52.2, 35.6, 31.8, 31.3, 29.6, 29.1, 29.0, 28.8, 25.8, 23.4, 22.6, 14.5; MS-EI m/z 371.9 (M^+, calcd for $C_{19}H_{36}N_2O_5$ 372.50).

4.1.2. *N*-α-(*n*-Octanoyl)-*N*-ε-BOC-(±)-lysine, *O*-benzyl ester 6. A solution of free acid **5** (0.37 g, 1.0 mmol) in THF (20 mL) was mixed with DCC (0.21 g. 1.0 mmol), catalytic amount of DMAP, and benzyl alcohol (0.13 g, 1.2 mmol). The solution was stirred at rt overnight, filtered, and concentrated in vacuo. Column chromatography on silica gel with EtOAc–CH_2Cl_2, 3:7 as an eluent afforded **6** (0.28 g, 61%) as a colorless oil: ^{1}H NMR ($CDCl_3$): δ 7.36 (m, 5H), 6.03 (d, J=7.8 Hz, 1H), 5.16, 5.12 (2×d, J=12.4 Hz, 2H), 4.64 (dt, J=7.8, 5.0 Hz, 1H), 4.51 (br s, 1H), 3.04 (dt, J=7.3, 6.0 Hz, 2H), 2.21 (t, J=7.3 Hz, 2H), 1.43 (s, 9H), 1.90–1.80, 1.72–1.58, 1.50–1.37, 1.37–1.18 (4×m, 16H), 0.87 (t, J=6.9 Hz, 3H); MS-EI m/z 461.8 (M^+, calcd for $C_{26}H_{42}N_2O_5$ 462.6).

4.1.3. *N*-α-(*n*-Octanoyl)-(±)-lysine, *O*-benzyl ester, TFA salt 7. A solution of **6** (0.46 g, 1.0 mmol) in THF (20 mL) was stirred with TFA (5 mL) at rt for 2 h. The reaction mixture was concentrated in vacuo to afford salt **7** (0.45 g, 94%), which was used without further purification. ^{1}H NMR ($CDCl_3$): δ 7.33 (m, 5H), 6.71 (d, J=7.8 Hz, 1H), 5.16, 5.12 (2×d, J=12.4 Hz, 2H), 4.55 (dt, J=8.3, 5.0 Hz, 1H), 2.93 (m, 2H), 2.23 (t, J=7.3 Hz, 2H), 2.0–1.0 (m, 16H), 0.87 (t, J=6.9 Hz, 3H).

4.1.4. *N*-α-Cbz-*N*-ε-BOC-*l*-lysine, *O*-(4-*tert*-butyl)phenyl ester 10. A solution of **8** (0.50 g, 1.3 mmol, $[\alpha]_D^{23}=-3.6$ (c=0.03, EtOH) in dry CH_2Cl_2 (20 mL) was stirred with DCC (0.27 g, 1.3 mmol), catalytic amount of DMAP, and 4-*t*-butylphenol (0.24 g, 1.6 mmol) at rt overnight. The reaction mixture was then filtered and concentrated in vacuo. Column chromatography with EtOAc–CH_2Cl_2, 2:8 as an eluent afforded phenyl ester **10** (0.41 g, 62%) as an oil: ^{1}H NMR ($CDCl_3$): δ 7.35 (m, 7H), 7.0 (d, J=8.7 Hz, 2H), 5.54 (d, J=7.3 Hz, 1H), 5.13 (s, 2H), 4.58 (m, 2H), 3.12 (m, 2H), 1.42 (s, 9H), 1.25 (s, 9H), 2.1–1.9, 1.9–1.8, 1.6–1.2 (3×m, 6H).

4.1.5. *N*-α-Cbz-*l*-lysine, *O*-methyl ester, TFA salt 11. A solution of **9** (0.39 g, 1.0 mmol) in THF (20 mL) was treated with TFA (5 mL) at rt for 2 h. The reaction mixture was concentrated in vacuo to afford pure salt **11** (0.38 g, 92%). ^{1}H NMR ($CDCl_3$): δ 7.30 (m, 5H), 5.74 (d, J=7.3 Hz, 1H), 5.06, 5.03 (2×d, J=11.9 Hz, 2H), 4.26 (m, 1H), 3.69 (s, 3H), 2.89 (m, 2H), 1.9–1.7, 1.7–1.5, 1.5–1.2 (3×m, 6H); ^{13}C NMR ($CDCl_3$): δ 173.0, 162.0 (q, J_{C-F}=37.9 Hz), 156.4, 136.2, 128.6, 128.3, 128.0, 127.8, 116.9 (q, J_{C-F}=308.1 Hz), 67.1, 53.7, 52.6, 39.5, 31.7, 26.8, 22.1.

4.1.6. *N*-α-Cbz-*l*-lysine, *O*-(4-*tert*-butyl)phenyl ester, TFA salt 12. Prepared analogously to compound **11** in a 95% yield. ^{1}H NMR ($CDCl_3$): δ 7.35 (m, 7H), 6.96 (d, J=8.3 Hz, 2H), 5.71 (d, J=7.3 Hz, 1H), 5.12, 5.07 (2×d, J=12.4 Hz, 2H), 4.50 (dt, J=8.3, 4.1 Hz, 1H), 2.92 (m, 2H), 1.27 (s, 9H), 2.0–1.0 (m, 6H).

4.1.7. *N*-ε-Cbz-*l*-lysine, *O*-methyl ester, TFA salt 16. A solution of **14** (0.2 g, 0.51 mmol) in THF (15 mL) was treated with TFA (4 mL) and then stirred at rt for 2 h. The reaction mixture was concentrated in vacuo to afford pure salt **16** (0.15 g, 95%). ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5H), 5.16 (br s, 1H), 5.05 (s, 2H), 3.98 (m, 1H), 3.76 (s, 3H), 3.13 (m, 2H), 2.0–1.8 (m, 2H), 1.6–1.3 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 170.2, 162.0 (q, J_{C-F}=36.0 Hz), 157.1, 136.6, 128.6, 128.2, 128.0, 127.9, 127.8, 116.4 (q, J_{C-F}=291.7 Hz), 62.7, 53.2, 53.1, 40.4, 29.8, 29.1, 21.8.

4.1.8. *N,N*-α,ε-Bis-BOC-*l*-lysine, *O*-methyl ester 18. To a solution of *l*-lysine (2.0 g, 13.7 mmol) in water–dioxane, 1:1 (40 mL) were added BOC-anhydride (7.5 g, 34.3 mmol) and 1N NaOH (14 mL). The reaction mixture was stirred for 6 h at rt, then concentrated till 15 mL. The pH was adjusted to 2.4 by adding aqueous $NaHSO_4$, and the product was extracted with EtOAc (2×40 mL). The solvent was evaporated to give **17** (3.37 g, 71%) as an oil: ^{1}H NMR (DMSO-d_6): δ 6.98 (br s, 1H), 6.74 (br s, 1H), 3.83 (m, 1H), 2.86 (m, 2H), 1.35 (s, 18H), 1.7–1.1 (m, 6H). Diprotected derivative **17** (1.0 g, 2.9 mmol) was dissolved in THF (30 mL) and H_2O (6 mL), and the solution was neutralized till pH 7 with 20% aqueous Cs_2CO_3 and evaporated to dryness. The cesium salt was then stirred CH_3I (0.49 g, 3.5 mmol) in DMF (20 mL) for 2 h. Upon removal of the solvent by evaporation and treatment with H_2O (80 mL), the product was extracted with EtOAc (3×50 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to afford methyl ester **18** (0.68 g, 65%) as an oil: ^{1}H NMR ($CDCl_3$) δ 5.10 (br s, 1H), 4.59 (br s, 1H), 4.26 (m, 1H), 3.72 (s, 3H), 3.08 (m, 2H), 1.42 (s, 18H), 2.0–1.2 (m, 6H).

4.1.9. *N,N*-α,ε-Bis-BOC-*l*-lysine, *O*-benzyl ester 19. Free acid **17** (1.0 g, 2.9 mmol) was dissolved in CH_3OH (30 mL)

and H_2O (6 mL), and the solution was neutralized till pH 7 with 20% aqueous Cs_2CO_3 and evaporated to dryness. The resulting cesium salt was then stirred with benzyl bromide (0.60 g, 3.5 mmol) in DMF (20 mL) for 2 h. The solution was evaporated, and the product was partitioned between H_2O (60 mL) and EtOAc (120 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to afford ester **19** (0.86 g, 68%): ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 5H), 5.16, 5.10 (2×d, J=11.9 Hz, 2H), 5.10 (br s, 1H), 4.57 (br s, 1H), 4.28 (dt, J=7.8, 5.0 Hz, 1H), 3.04 (dt, J=6.9, 6.4 Hz, 2H), 1.43 (s, 18H), 2.0–1.0 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 172.8, 156.2, 155.6, 135.5, 128.6, 128.5, 128.3, 79.8, 79.1, 67.2, 53.3, 40.1, 32.1, 29.6, 28.5, 28.4, 22.5.

4.1.10. *l*-Lysine, *O*-methyl ester, bis-TFA salt 20. A solution of **18** (0.5 g, 1.4 mmol) in THF (20 mL) was treated with TFA (5 mL) and stirred at rt for 2 h. The reaction mixture was concentrated to afford pure **20** (0.51 g, 95%). ^{1}H NMR (DMSO-d_6): δ 4.03 (br s, 1H), 3.75 (s, 3H), 2.75 (m, 2H), 1.77 (m, 3H), 1.6–1.3 (m, 3H); ^{13}C NMR (DMSO-d_6): δ 170.6, 159.3 (q, J_{C-F}=31.7 Hz), 117.6 (q, J_{C-F}=298.5 Hz), 53.2, 52.3, 38.9, 30.0, 26.9, 21.8. Benzyl ester **21** was prepared analogously in 82% yield: ^{1}H NMR (DMSO-d_6): δ 7.37 (m, 5H), 5.20 (s, 2H), 4.06 (m, 1H), 2.70 (dt, J=8.3, 6.4 Hz, 2H), 1.78 (m, 2H), 1.50 (m, 2H), 1.37 (m, 1H), 1.26 (m, 1H); ^{13}C NMR (DMSO-d_6): δ 169.9, 159.3 (q, J_{C-F}=32.2 Hz), 135.7, 129.0, 128.8, 128.8, 117.6 (q, J_{C-F}=298.0 Hz), 67.6, 52.2, 38.9, 30.1, 26.9, 21.7.

4.1.11. *N*-α-(*n*-Octanoyl)-*N*-ε-Cbz-(±)-lysine 23. A solution of *N*-ε-Cbz-*l*-lysine **22** (0.50 g, 1.78 mmol) in water (20 mL) and EtOAc (20 mL) was treated with *n*-octanoyl chloride (2.46 g, 17.8 mmol) and stirred at rt for 3 h, after which 5% HCl (50 mL) and CH_2Cl_2 (80 mL) were added. After separation, the aqueous layer was extracted with CH_2Cl_2 (3×50 mL) times, and the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated. The residue was solidified in hexane to yield **23** (0.51 g, 71%) as a colorless solid: mp 119–120°C; $[\alpha]_D^{23}$=0.0 (c=0.02, EtOH); ^{1}H NMR (DMSO-d_6) δ 12.44 (s, 1H), 7.99 (d, J=7.8 Hz, 1H), 7.34 (m, 5H), 7.20 (t, J=5.3 Hz, 1H), 4.99 (s, 2H), 4.12 (m, 1H), 2.96 (m, 2H), 2.08 (m, 2H), 1.8–1.1 (m, 16H), 0.84 (t, J=6.6 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 174.5, 172.9, 156.6, 137.8, 128.9, 128.3, 128.2, 65.7, 52.2, 35.6, 31.8, 31.2, 29.6, 29.1, 29.0, 25.8, 23.4, 22.6, 14.5.

4.1.12. Dipeptide 26, two diastereomers. To a stirred and ice cooled solution of amine **24** (0.10 g, 0.38 mmol) in DMF (15 mL) was added carboxylic acid **5** (0.14 g, 0.38 mmol), HOBT (0.10 mg, 0.76 mmol), and DCC (0.16 g, 0.76 mmol). The reaction mixture was stirred for 30 min at 0°C and for 36 h at rt. The mixture was filtered, concentrated, diluted with EtOAc (200 mL) and washed successively with 1N $NaHSO_4$ (4×50 mL), water (3×50 mL), 1N $NaHCO_3$ (4×50 mL), and again water (3×50 mL). The organic layer was then dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed on silica gel eluting with THF–hexanes, 1:1 to afford dipeptide **27** (0.15 g, 64%) as an oil: ^{1}H NMR (DMSO-d_6, only one diastereomer is shown): δ 8.23 (d, J=7.80 Hz, 1H), 7.84 (d, J=8.0 Hz, 1H), 6.73 (m, 2H), 4.29 (m, 1H), 4.18 (dt, J=8.5, 5.5 Hz, 1H), 3.61 (s, 3H), 2.87 (m, 4H), 2.10 (m, 2H), 1.36 (s, 18H), 2.0–1.0 (m, 22H), 0.85 (t, J=6.6 Hz, 3H).

A solution of **27** (0.50 g, 0.81 mmol) in THF (20 mL) was treated with TFA (5 mL) and stirred at rt for 2 h. The reaction mixture was concentrated to afford pure **26** (0.50 g, 96%). ^{1}H NMR (DMSO-d_6, only one diastereomer is shown): δ 8.30 (d, J=7.6 Hz, 1H), 7.95 (d, J=7.8 Hz, 1H), 4.22 (m, 1H), 3.62 (s, 3H), 2.75 (m, 4H), 2.10 (m, 2H), 2.0–1.0 (m, 22H), 0.85 (t, J=6.6 Hz, 3H).

4.1.13. Tripeptide 30, a mixture of diastereomers. To a stirred and ice cooled solution of **20** (0.19 g, 0.50 mmol) in DMF (15 mL) was added Et_3N (0.14 mL, 1 mmol) and then acid **23** (0.42 g, 1 mmol), HOBT (0.28 g, 2 mmol), and DCC (0.43 g, 2 mmol). The reaction mixture was allowed to stir for 30 min at 0°C and for 36 h at rt, filtered, concentrated, diluted with EtOAc (200 mL), and washed successively with 1N $NaHSO_4$ (4×50 mL), water (3×50 mL), 1N $NaHCO_3$ (4×50 mL), and again water (3×50 mL). The organic layer was then dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed on silica gel eluting with $CHCl_3$–CH_3OH, 9:1 to afford bis-Cbz-protected trilysine **31** (0.21 g, 45%) as an oil: ^{1}H NMR(DMSO-d_6, only one diastereomer is shown): δ 8.20 (br s, 1H), 7.84 (m, 3H), 7.33 (m, 10H), 7.20 (t, J=5.5 Hz, 2H), 4.98 (s, 4H), 4.25 (m, 1H), 4.15 (m, 2H), 3.60 (s, 3H), 2.94 (m, 6H), 2.10 (m, 4H), 1.8–1.1 (m, 38H), 0.84 (t, J=6.4 Hz, 3H).

A solution of tripeptide **31** (0.15 g, 0.16 mmol) in CH_3OH (10 mL) was treated with 10% Pd/C (15 mg) and stirred under a hydrogen atmosphere for 6 h. The mixture was filtered through Celite and concentrated. The residue was dried under high vacuum to give **30** (0.10 g, 93%) as an oil: ^{1}H NMR (DMSO-d_6, only one diastereomer is shown) δ 8.20 (br s, 1H), 7.84 (m, 3H), 4.25 (m, 1H), 4.14 (m, 2H), 3.56 (s, 3H), 3.42 (m, 4H), 3.02 (m, 2H), 2.06 (m, 4H), 1.8–1.0 (m, 38H), 0.81 (t, J=6.9 Hz, 6H).

4.1.14. Tripeptide 32. To a stirred and ice cooled solution of **20** (0.17 g, 0.43 mmol) in DMF (20 mL) was added Et_3N (0.12 mL, 0.86 mmol) and then after 15 min, lysine **13** (0.33 g, 0.86 mmol), HOBT (0.24 g, 1.72 mmol) and DCC (0.35 g, 1.72 mmol).The mixture was allowed to stir for 30 min at 0°C and for 36 h at rt, then filtered, concentrated in vacuo, diluted with EtOAc (200 mL), and washed successively with 1N $NaHSO_4$ (4×50 mL), water (3×50 mL), 1N $NaHCO_3$ (4×50 mL), and again water (3×50 mL).The organic layer was then dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed on silica gel eluting with $CHCl_3$–CH_3OH, 9:1 to afford **33** (0.19 g, 50%): $[\alpha]_D^{23}$=−12.4 (c=0.02, EtOH); ^{1}H NMR (DMSO-d_6): δ 8.13 (br s, 1H), 7.75 (br s, 1H), 7.34 (m, 10H), 7.21 (t, J=6.0 Hz, 2H), 6.78 (d, J=6.4 Hz, 1H), 6.73 (d, J=7.8 Hz, 1H), 5.01 (s, 4H), 4.20 (m, 1H), 3.91 (m, 1H), 3.79 (m, 1H), 3.59 (s, 3H), 3.15 (m, 4H), 3.04 (m, 2H), 2.0–1.0 (m, 18H), 1.36 (s, 18H); MALDI-TOF MS, m/z 908 ([M+Na^+], calcd for $C_{45}H_{68}N_6O_{12}$ 908).

A solution of **33** (0.15 g, 0.17 mmol) in CH_3OH (10 mL) was treated with 10% Pd/C (15 mg) and stirred under a hydrogen atmosphere for 4 h. The mixture was filtered

through Celite and concentrated. The residue was dried under high vacuum to give tripeptide **32** (0.1 g, 95%): ^{1}H NMR (DMSO-d_6): δ 8.16 (br s, 1H), 7.80 (br s, 1H), 6.81 (d, J=8.3 Hz, 1H), 6.75 (d, J=7.1 Hz , 1H), 4.21 (m, 1H), 3.91 (m, 1H), 3.80 (m, 1H), 3.60 (s, 1H), 3.06 (m, 4H), 2.96 (m, 2H), 1.35 (s, 18H), 2.0–1.0 (m, 18H).

4.1.15. Preparation of calix[4]arene amino acids 1a–d. A typical protocol. A solution of calix[4]arene triester monoacid chloride **25** (0.49 g, 0.5 mmol) in EtOAc (10 mL) was added under vigorous stirring to a solution of TFA salt **7** (0.2 g, 0.42 mmol) and K_2CO_3 (0.58 g, 4.2 mmol) in EtOAc (10 mL) and H_2O (20 mL). The reaction mixture was stirred at rt for 3 h. The organic layer was separated and evaporated under reduced pressure. The residue was chromatographed on silica gel with THF–hexanes, 3:2 as eluents to afford **1a** (0.36 g, 65%) as a colorless solid: mp 69–70°C; IR (KBr): ν 3377, 2954, 2868, 1754, 1651, 1547, 1480, 1193, 1070; ^{1}H NMR ($CDCl_3$): δ 8.42 (t, J=6.4 Hz, 1H), 7.34 (m, 5H), 6.82 (s, 2H), 6.79 (s, 4H), 6.73 (s, 2H), 6.39 (d, J=7.3 Hz, 1H), 5.15 (s, 2H), 4.89 (d, J=13 Hz, 2H), 4.74 (d, J=13 Hz, 2H), 4.69 (s, 2H), 4.65–4.6 (m, 4H), 4.55 (m, 1H), 4.52 (m, 2H), 4.16 (m, 6H), 3.39 (m, 2H), 3.25, 3.21 (2×d, J=13 Hz, 4H), 2.20 (t, J=7.3 Hz, 2H), 1.85–1.50 (m, 6H), 1.25 (m, 19H), 1.11 (s, 9H), 1.07 (s, 18H), 1.03 (s, 9H), 0.85 (t, J=7.5 Hz, 3H); MALDI-TOF MS, m/z 1331.9 ([M+Na$^+$], calcd for $C_{79}H_{108}N_2O_{14}$ 1332.7). Anal. calcd for $C_{79}H_{108}N_2O_{14}$: C, 72.45; H, 8.31; N, 2.14. Found: C, 72.15, H, 8.67, N, 2.40. Calixarene **1b**: The product was purified by column eluting with THF–hexanes, 1:1. Yield 67%, mp 71–72°C; ^{1}H NMR ($CDCl_3$): δ 8.41 (t, J=6.0 Hz, 1H), 7.33 (m, 5H), 6.82 (s, 2H), 6.78 (s, 4H), 6.73 (s, 2H), 5.52 (d, J=8.3 Hz, 1H), 5.11, 5.06 (2×d, J=12.4 Hz, 2H), 4.90, 4.87 (2×d, J=16.0 Hz, 2H), 4.75, 4.73 (2×d, J=12.8 Hz, 2H), 4.70 (s, 2H), 4.63 (m, 4H), 4.50 (br s, 2H), 4.35 (m, 1H), 4.18 (m, 6H), 3.73 (s, 3H), 3.35 (m, 2H), 3.22 (m, 4H), 2.0–1.5 (m, 6H), 1.24 (m, 9H), 1.11 (s, 9H), 1.07 (s, 18H), 1.04 (s, 9H); MALDI-TOF MS, m/z 1265.2 ([M+Na$^+$], calcd for $C_{73}H_{96}N_2O_{15}$ 1264.6). Anal. calcd for $C_{73}H_{96}N_2O_{15}$: C, 70.62; H, 7.79; N, 2.26. Found: C, 70.81, H, 7.69, N, 2.53. Calixarene **1c** was chromatographed with THF–hexanes, 3:2. Yield 64%); mp 70–72°C; ^{1}H NMR ($CDCl_3$): δ 8.43 (t, J=6.0 Hz, 1H), 7.34 (m, 7H), 7.01 (d, J=8.7 Hz, 2H), 6.82 (s, 2H), 6.77 (s, 4H), 6.73 (s, 2H), 5.62 (d, J=8.3 Hz, 1H), 5.13, 5.09 (2×d, J=12.3 Hz, 2H), 4.91, 4.88 (2×d, J=12.4 Hz, 2H), 4.75, 4.73 (2×d, J=12.9 Hz, 2H), 4.70 (s, 2H), 4.62 (m, 4H), 4.55 (m, 1H), 4.52 (d, J=2.8 Hz, 2H), 4.17 (m, 6H), 3.44 (m, 2H), 3.24, 3.22 (2×d, J=13.2 Hz, 4H), 2.1–1.5 (m, 6H), 1.30 (s, 9H), 1.24 (m, 9H), 1.11 (s, 9H), 1.07 (s, 18H), 1.04 (s, 9H); MALDI-TOF MS, m/z 1382.9 ([M+Na$^+$], calcd for $C_{82}H_{106}N_2O_{15}$ 1382.7). Anal. calcd for $C_{82}H_{106}N_2O_{15}$: C, 72.43; H, 7.86; N, 2.06. Found: C, 72.12, H, 7.74, N, 1.94. Calixarene **1d** was chromatographed on silica gel eluting with THF–hexanes, 1:1. Yield 62%); mp 74–75°C; $[\alpha]_D^{23}$=−2.8 (c=0.02, EtOH); IR (KBr): ν 3382, 2961, 2869, 1755, 1720, 1673, 1480, 1363, 1194, 1128, 1069; ^{1}H NMR ($CDCl_3$): δ 8.40 (t, J=6.0 Hz, 1H), 6.82 (s, 2H), 6.78 (s, 4H), 6.73 (s, 2H), 5.13 (d, J=8.3 Hz, 1H), 4.89 (d, J=16.5 Hz, 2H), 4.74 (d, J=12.8 Hz, 2H), 4.70 (s, 2H), 4.63 (d, J=12.8 Hz, 2H), 4.62 (d, J=16.5 Hz, 2H), 4.53 (m, 2H), 4.28 (m, 1H), 4.19 (m, 6H),3.72 (s, 3H), 3.37 (m, 2H), 3.24, 3.21 (2×d, J=12.8 Hz, 4H), 1.42 (s, 9H), 2.0–1.3 (m, 6H), 1.28 (m, 9H), 1.11 (s, 9H), 1.07 (s, 18H), 1.01 (s, 9H); MALDI-TOF MS, m/z 1229.9 ([M+Na$^+$], calcd for $C_{70}H_{98}N_2O_{15}$ 1230.5). Anal. calcd for $C_{70}H_{98}N_2O_{15}$: C, 69.63; H, 8.18; N, 2.32. Found: C, 69.60, H, 8.28, N, 2.48.

4.1.16. Calixarene lysine 1e. A solution of benzyl ester **1a** (0.2 g, 0.15 mmol) in CH_3OH (10 L) was mixed with 10% Pd/C (20 mg) and stirred under a hydrogen atmosphere for 4 h. The reaction mixture was filtered through Celite and concentrated in vacuo to give pure **1e** (0.18 g, 98%) as a colorless solid: ^{1}H NMR ($CDCl_3$) δ 8.62 (t, J=6.4 Hz, 1H), 6.99 (d, J=5.0 Hz, 1H), 6.82 (s, 2H), 6.78 (s, 4H), 6.72 (s, 2H), 5.0–4.8 (m, 2H), 4.80–4.62 (m, 8H), 4.62–4.40 (m, 2H), 4.18 (m, 6H), 3.50 (dt, J=6.9, 6.4 Hz, 1H), 3.34 (m, 2H), 3.24, 3.22 (2×d, J=13.2 Hz, 4H), 2.26 (m, 2H), 2.0–1.8, 1.8–1.5, 1.5–1.15 (3×m, 25H), 1.11 (s, 9H), 1.07 (s, 18H), 1.04 (s, 9H), 0.85 (t, J=6.9 Hz, 3H).

4.1.17. Calixarene lysine 1f. A solution of **1b** (0.2 g, 0.16 mmol) in CH_3OH (10 mL) was treated with 10% Pd/C (20 mg) and stirred under a hydrogen atmosphere for 4 h. The mixture was filtered through Celite and concentrated in vacuo. The residue was dried under high vacuum to give 0.17 g (96%) of amine **1f**. ^{1}H NMR ($CDCl_3$): δ 8.47 (t, J=6.0 Hz, 1H), 6.77 (m, 8H), 4.95–4.80 (m, 2H), 4.80–4.65 (m, 4H), 4.65–4.52 (m, 4H), 4.52–4.45 (m, 2H), 4.15 (m, 6H), 3.72 (s, 3H), 3.60 (m, 1H), 3.35 (m, 2H), 3.22 (t, J=12.8 Hz, 4H), 2.0–1.5 (m, 6H), 1.24 (m, 9H), 1.12 (s, 9H), 1.07 (s, 9H), 1.04 (s, 9H), 1.02 (s, 9H).

4.1.18. Calixarene dipeptide 2a. *Procedure 1*. To a stirred and ice cooled solution of calix amino acid derivative **1e** (0.15 g, 0.14 mmol) in DMF (15 mL) was added successively **1f** (0.17 g, 0.14 mmol), HOBT (38 mg, 0.28 mmol), and DCC (58 mg, 0.28 mmol). The mixture was stirred for 30 min at 0°C and then for 36 h at rt. The mixture was filtered, concentrated, diluted with EtOAc (200 mL), and washed successively with 1N $NaHSO_4$ (4×50 mL), water (3×50 mL), 1N $NaHCO_3$ (4×50 mL), and again water (3×50 mL). The organic layer was then dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed on silica gel eluting with THF–hexanes, 7:3 to afford calix–peptide **2a** (two diastereomers, 0.15 g, 46%) as a colorless solid: mp 97–98°C; IR (KBr) ν_{max} 3378, 2959, 2868, 1752, 1671, 1540, 1474, 1369, 1297, 1191, 1124, 1066; ^{1}H NMR (DMSO-d_6, only one diastereomer is shown): δ 8.30 (d, J=7.8 Hz, 1H), 8.10 (m, 2H), 7.89 (d, J=8.0 Hz, 1H), 6.84 (m, 16H), 4.85–4.75 (m, 4H), 4.70–4.50 (m, 16H), 4.36 (m, 4H), 4.22 (m, 1H), 4.13 (m, 12H), 3.62 (s, 3H), 3.40–3.15 (m, 12H), 2.11 (m, 2H), 2.0–1.1 (m, 40H), 1.05 (m, 72H), 0.85 (t, J=7.7 Hz, 3H); MALDI-TOF MS, m/z 2332.6 ([M+Na$^+$], calcd for $C_{137}H_{190}N_4O_{26}$ 2332.0).

Procedure 2. A solution of acid chloride **25** (0.37 g, 0.38 mmol) in EtOAc (10 mL) was added to a vigorously stirred solution of dipeptide **26** (0.1 g, 0.16 mmol) and K_2CO_3 (0.53 g, 3.8 mmol) in EtOAc (10 mL) and H_2O (20 mL). The reaction mixture was stirred at rt for 6 h, and the organic layer was separated and evaporated. The residue was chromatographed on silica gel eluting with THF–hexanes, 7:3 to afford **2a** (0.18 g, 49%).

4.1.19. Calixarene dipeptide 2b. A solution of acid chloride **25** (0.61 g, 0.62 mmol) in EtOAc (10 mL) was added under vigorously stirring to a solution of dipeptide **29** (0.10 g, 0.26 mmol) and K_2CO_3 (0.86 g, 6.2 mmol) in EtOAc (10 mL) and H_2O (20 mL). The reaction mixture was stirred for 6 h at rt. The organic layer was separated and evaporated. The residue was chromatographed on silica gel eluting with THF–hexanes, 7:3 to afford calix dipeptide **2b** (0.27 g, 45%) as a colorless solid: mp 109–110°C; $[\alpha]_D^{23}=-5.1$ (c=0.02, EtOH); IR (KBr) ν_{max} 3333, 2959, 2864, 2358, 1752, 1673, 1540, 1475, 1368, 1300, 1190, 1125, 1056; ^{1}H NMR (DMSO-d_6): δ 8.16 (d, J=7.3 Hz, 1H), 8.11 (m, 2H), 6.96 (d, J=6.9 Hz, 1H), 6.85 (m, 16H), 4.78 (d, J=15.8 Hz, 4H), 4.7–4.5 (m, 16H), 4.37 (m, 4H), 4.25 (m, 1H), 4.2–4.0 (m, 12H), 3.96 (m, 1H), 3.60 (s, 3H), 3.22 (m, 12H), 1.38 (s, 9H), 2.0–1.1 (m, 30H), 1.1–0.9 (m, 72H); MALDI-TOF MS, m/z 2306.8 ([M+Na$^+$], calcd for $C_{134}H_{185}N_4O_{27}$ 2305.9). Anal. calcd for $C_{135}H_{184}N_4O_{27}$: C, 70.50; H, 8.12; N, 2.45. Found: C, 70.63, H, 8.19, N, 2.61.

4.1.20. Dendrimer 3a. *Procedure 1*. To a stirred and ice cooled solution of salt **20** (80 mg, 0.21 mmol) DMF (8 mL) was added Et_3N (0.06 mL, 0.42 mmol) and then after 15 min, calyx amino acid **1e** (0.51 g, 0.42 mmol), HOBT (0.11 g, 0.84 mmol), and DCC (0.17 g, 0.84 mmol). The mixture was allowed to stir for 30 min at 0°C and for 48 h at rt, then filtered, concentrated in vacuo, diluted with EtOAc (200 mL), and washed successively with 1N $NaHSO_4$ (4×50 mL), water (3×50 mL), 1N $NaHCO_3$ (4×50 mL), and again water (3×50 mL). The organic layer was then dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed on silica gel eluting with $CHCl_3$–CH_3OH, 9:1 to afford **3a** (0.22 g, 41%). ^{1}H NMR (DMSO-d_6, only one diastereomer is shown): δ=8.23 (br s, 1H), 8.10 (br s, 2H), 7.87 (m, 3H), 6.81 (m, 16H), 4.80 (m, 4H), 4.70–4.50 (m, 16H), 4.34 (s, 4H), 4.30 (m, 1H), 4.2–4.0 (m, 13H), 3.95 (m, 1H), 3.57 (s, 3H), 3.25–3.05 (m, 12H), 3.02 (m, 2H), 2.08 (m, 4H), 2.0–1.1 (m, 66H), 1.1–0.9 (m, 72H), 0.83 (m, 6H); MALDI-TOF MS, m/z 2588.7 ([M+Na$^+$], calcd for $C_{151}H_{216}N_6O_{28}$ 2586.4).

Procedure 2. A solution of acid chloride **25** (0.30 g, 0.30 mmol) in EtOAc (20 mL) was added to a vigorously stirring solution of tripeptide **30** (0.1 g, 0.15 mmol) and K_2CO_3 (0.41 g, 3.0 mmol) in EtOAc (10 mL) and H_2O (20 mL). The reaction mixture was stirred for 6 h at rt, the organic layer was separated and evaporated. The residue was chromatographed on silica gel eluting with $CHCl_3$–CH_3OH, 9:1 to afford **3a** (0.18 g, 47%).

4.1.21. Dendrimer 3b. A solution of monoacid chloride **25** (0.38 g, 0.38 mmol) in EtOAc (10 mL) was added to a vigorously stirred solution of **32** (0.1 g, 0.16 mmol) and K_2CO_3 (0.22 g, 1.6 mmol) in EtOAc (5 mL) and H_2O (15 mL). The reaction mixture was stirred for 6 h at rt. The organic layer was separated and evaporated under reduced pressure. The residue was chromatographed on silica gel with $CHCl_3$–MeOH, 9:1 as eluents to afford **3b** (0.17 g, 42%); $[\alpha]_D^{23}=-4.5$ (c=0.02, EtOH); IR (KBr): ν 3370, 2962, 2867, 1758, 1724, 1663, 1547, 1480, 1190, 1128, 1069; ^{1}H NMR (DMSO-d_6): δ 8.11 (m, 3H), 7.78 (t, J=6.0 Hz, 1H), 6.8 (m, 16H), 6.72 (m, 2H), 4.85–4.72 (m, 4H), 4.72–4.45 (m, 16H), 4.35 (m, 4H), 4.22 (m, 1H), 4.18–4.05 (m, 12H), 3.93 (m, 1H), 3.83 (m, 1H), 3.65 (s, 3H), 3.3–3.1 (m, 12H), 3.0 (m, 2H), 1.8–1.4 (m, 18H), 1.36 (s, 18H), 1.7–1.25 (m, 18H), 1.06 (s, 18H), 1.03 (s, 27H), 1.02 (s, 27H); MALDI-TOF MS, m/z 2532 ([M+Na$^+$], calcd for $C_{145}H_{204}N_6O_{30}$ 2534).

4.2. Liquid–liquid extraction experiments

Compounds **1a**–**d**, **2a**,**b**, and **3a**,**b** were dissolved in CH_2Cl_2 ($\sim 5\times10^{-3}$ M, 10 mL) and vigorously stirred overnight with saturated aqueous solution of $NaClO_4$ (10 mL) at rt. Organic layers were then separated, evaporated under reduced pressure, dried in vacuo and analyzed by high-resolution ^{1}H NMR spectroscopy in $CDCl_3$.

4.3. MALDI mass spectrometry measurements

Samples were initially reconstituted in acetone. A 2 μL aliquot of a given sample was deposited on the MALDI sample probe and the solvent was allowed to evaporate. A 2 μL aliquot of the MALDI matrix 2,5-dihydroxybenzoic acid (10 mg/mL) in MeOH (for compounds **1a**–**d** and **2a**,**b**) or a 2 μL aliquot of α-cyano-4-hydroxycinnamic acid (10 mg/mL) in MeOH–formic acid, 1:1 (for compounds **3a**,**b**) was deposited on the sample coated probe. Internal calibration was achieved by adding the peptide bradykinin ([M+H]$^+$ 1060.1 Da).

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