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SYNTHESIS AND CHARACTERIATION OF WATER SOLUBLE C_2 AND C_3 SYMMETRIC MULTI-CALIX[4]ARENE DENDRIMERS AND PILLARARENES A NOVEL CLASS OF MACROCYCLE IN SUPRAMOLECULAR CHEMISTRY

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PhD Thesis

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Water-soluble multi-calixarenes

1.1 Introduction

The research project on which this PhD work is based attempts to achieve non-covalent synthesis of supramolecular modular systems homo-and hetero-component, through the use of calixarenes coupled to porphyrins;in particular it was designed to the preparation of discrete assembled at the nanoscopic level, by means of hierarchical 'self-assembly' of organized systems governed by electrostatic interactions and host-guest inclusion in aqueous phase and in organic solvents. Moreover among the objectives is including the study of 'intelligent' chiral aggregates, obtained by inclusion of chiral centers in various structures.

The field of supramolecular chemistry[1] has been characterized to a large extent by research on macrocyclic molecules (crown ethers[2], cavitands/cryptands[3], cyclodextrins[4] and cucurbiturils[5]) able to act as artificial molecular receptors for neutral and charged species. The increasing understanding, and hence control, of non-covalent interactions (hydrogen bond, metal coordination, cation and van der Waals interactions) at a molecular level, has allowed chemists to optimize separation/extraction techniques and develop a wide range of sensors. From simple 1:1 host-guest complexes, thanks also to novel strategies of 'supramolecular (or non-covalent) synthesis' and self-assembly processes, more and more complex structures have been obtained, harnessing the

ability of molecules to interact with each other through weak forces. Nowadays, by approaching non-covalent synthesis via hierarchical self-assembly (the formation of an organized structure through different and distinct levels of self-assembly processes that decrease in strength[6]) it has become possible to create very sophisticated structures using as building blocks a large number of topologically and (stereo)electronically complementary molecules[7]. Thus the challenge for the future is shifting beyond simple host-guest binding, towards the construction of 'smart' supramolecular architectures performing specific tasks (e.g. nanoreactors, ion-selective channels, optoelectronic devices, antenna systems, etc.) following on from initial recognition processes between components.

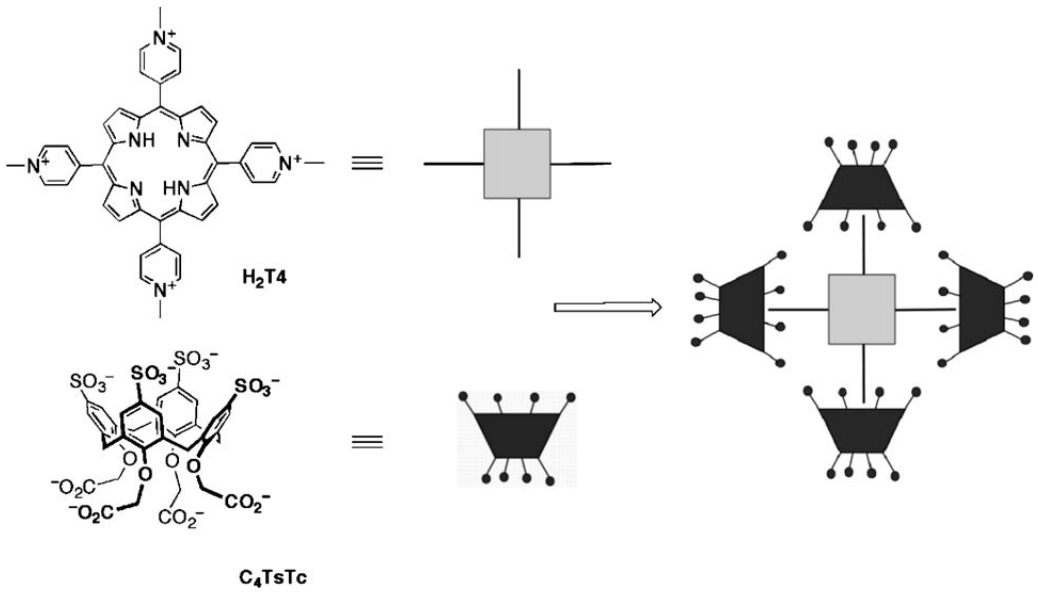
Calixarenes are good candidates to play a prominent role in this context [8]. They selectively recognize ionic and neutral species, including alkali-metal ions[9], alkane(di)ammonium ions[10], tetraalkylammonium ions[11], biogenic amines[12], amino acids[13] and fullerenes[14]. Their use in selective extraction processes and as sensors ranges from the analytical and environmental to the food and biomedical fields[15]. Furthermore, calixarenes self-assemble, in solution and in the solid state, by means of spontaneous and non-covalent association between two or even more molecules. This phenomenon is often promoted by the formation of hydrogen bonds[16], but can also be driven by halogen bonds[17], or by selective inclusion of a substrate[18]. Rosettes[19], capsules,[20] (pseudo)rotaxanes[21], multivalent ligands[22], nanoparticles and liquid crystals[23] are a few elegant examples of calixarene-based supramolecular systems, whose formation is controlled by non-covalent interactions.

Calixarenes may also act as templating agents for the assembly of hetero-component supramolecular species, a remarkable example being the organization of multi-porphyrin stacks in a programmable sequence[24]; in fact porphyrins are very attractive molecules because they have applications in many technological fields.[25] The synthesis of species with a designated sequence of given porphyrin(s) is, therefore, very desirable. To date, this goal has been targeted by means of classical covalent methods.[26] Only a few accounts dealing with species obtained by a non-covalent approach have hitherto been published.[26,27]

On the base of the enormous potential that an approach of non-covalent synthesis can still reserve in the emerging field of supramolecular polymers (adaptive materials, dynamers[28]), liquid crystals[29] and chiral memory aggregates[30], the research project we have done as part of the PhD thesis will cover the design, synthesis and study of multi-calixarederivatives that they can act in the presence of appropriate complementary modules (porphyrins), from templating agents and/or monomeric components of supramolecular architectures complex (mono-, bi-or three-dimensional).The general themes that were discussed during the studies concerned, the hierarchical self-assembly,chirality control and its amplification.It is well known that the action templating of calix[4]arenes against anionic water-soluble cationic porphyrins is able to promote the formation of hetero-aggregates component (calixarene / porphyrin) withpredeterminated stoichiometry and sequence [24].

It was recently reported a non-covalent synthesis of cationic porphyrin assemblies, in which it is possible to program both sequence and

stoichiometry.[24] The self-assembly of these multi-porphyrin systems relies on the templating role played by an octaanionic calix[4]arene (C4TsTc), which organizes the tetracationic porphyrins (H2T4) in a very stable 1:4 (porphyrin/calixarene) supramolecular core (Scheme 1). X-ray data have clearly shown that this multianionic synthon, in turn, acts as a template for the assembly of up to six additional cationic porphyrins, which stack above and below the mean plane containing the initially formed 1:4 core.[24a, c]

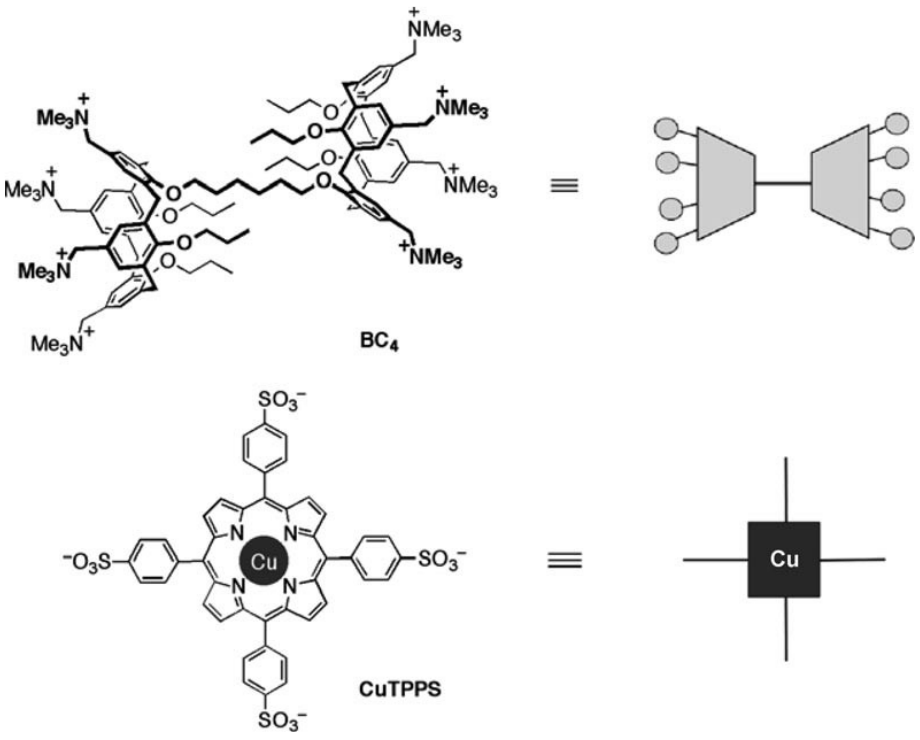


Scheme 1: Schematic representation of the 1:4 **H_2T4/C_4TsTc** supramolecular complex.

Diffusion NMR spectroscopy data have also shown that the different porphyrin/calixarene complexes synthesized are discrete species that do not self-aggregate. These species are kinetically inert, and as a result they

can form multiporphyrin supramolecular complexes with predetermined sequences.[24b]

In the context of a long term project aimed at investigating the design, structure and properties of new hybrid materials generated from the non-covalent assembly of tetracationic or tetraanionic porphyrins with appropriate complementary charged multi-calix[4]arene components in water solution, we have already shown that the templating action of a centrosymmetric water-soluble octacationic homoditopic bis-calix[4]arene with divergent cone cavities on a tetraanionic metallated porphyrin (scheme 2**),**makes it possible to exert control over the non-covalent synthesis of dendrimeric calix[4]arene/porphyrin assemblies by predetermining their sequence, stoichiometry, and dimensionality (2D or 3D).[31]



Scheme 2: Schematic representation of the octacationic bis-calix[4]arene BC_4 and the tetraanionic metalloporphyrin CuTPPS.

From an experimental viewpoint, the procedure for the synthesis of a target species is very simple: it requires only a titration in which the porphyrins are added to the calixarene.[32] Any break-point in the titration (that is, each slopechange observed on the absorption *vs* [porphyrin]×4/[calixarene] diagram (see below Figure 1) corresponding to the end-point for the formation of one complex and the starting point of the next one) indicates the concentration (molar ratio) at which a given species is formed.

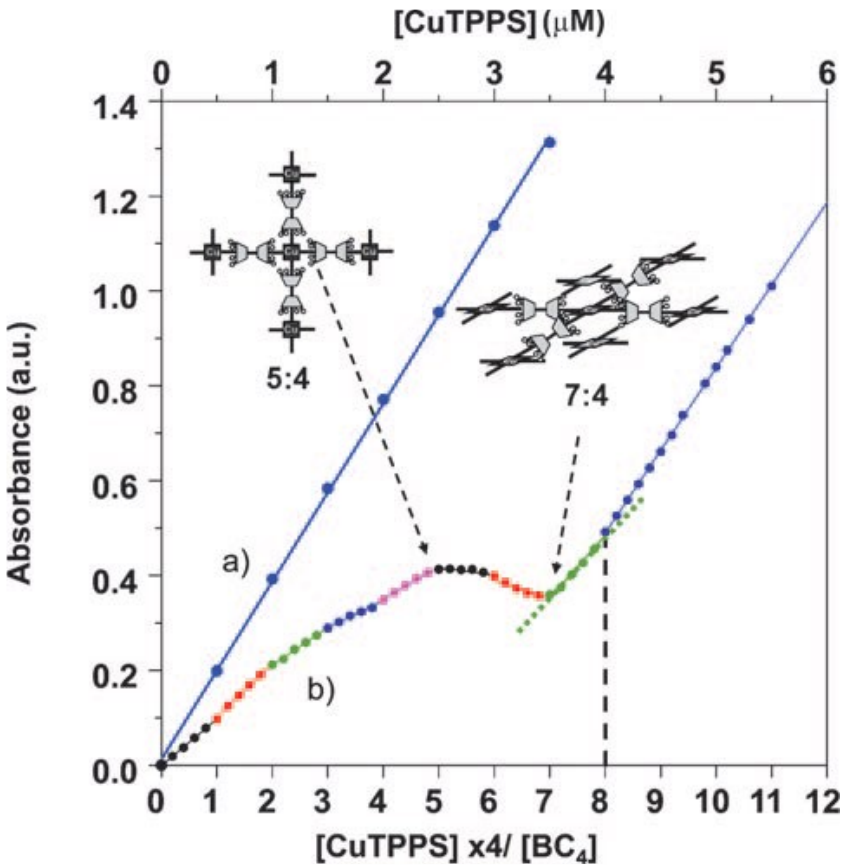
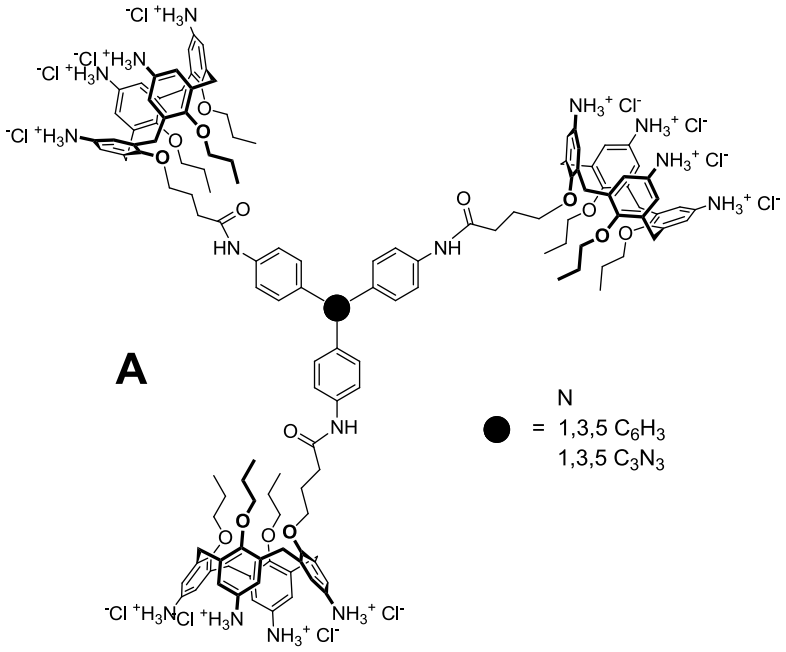


Figure 1: Absorbance variation (at 412 nm) for increasing concentrations of CuTPPS in aqueous solution: a) in the absence and b) in the presence of bis-calix[4]arene BC_4 (2 mM).

Addition of another (identical or different) porphyrin or metalloporphyrin to the previous complex leads to a new species, the formation of which will end at the successive break-point. The self-assembly of tetracationic porphyrins in the presence of octaanionic calixarenes occurs under hierarchical control and, therefore, the sequence and stoichiometry of such species can be controlled.[24c, 33] As a consequence of this hierarchical nature, the addition of calixarenes to porphyrins does not produce any species with higher porphyrin/calixarene ratios.[24 c]

Based on this knowledge, a part of this PhD work has been addressed to the synthesis and characterization of amino-surface functionalized tris(calix[4]arene), chiral tris(calix[4]arene) dendrons with rigid C_3 symmetric propeller cores (A and B) and water-soluble C_2-symmetrichomochiral biscalix[4]arene (C-G),with the later aim of developing new generations of non-covalent dendrimers by interaction with appropriate metalated porphyrins in water solution (Figure 2).


A
N
= 1,3,5 C6H3
1,3,5 C3N3

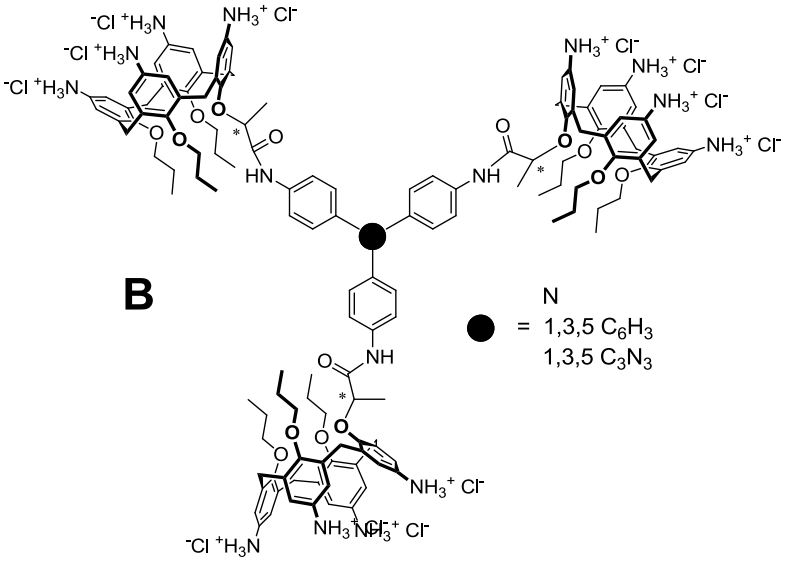

B
N
= 1,3,5 C6H3
1,3,5 C3N3

Figure 2: Amino-surface functionalized tris(calix[4]arene), chiral tris(calix[4]arene) dendrons with rigid C_3 symmetric propeller cores and water-soluble C_2-symmetrichomochiral biscalix[4]arene.

Dendrimers are key species in the ongoing evolution of macromolecular chemistry.[34] They contain three topologically different regions (core, branches and surface), each of which can be designed to encode specific functions and properties. The principles of symmetry have inspired and directed the design of molecules since earlier times, and still play a leading role in fields such as synthesis design[35] and supramolecular self-assembly.[36] Calixarenes,[37] by virtue of their unique three-dimensional topology, are attractive building blocks to use as potential dendrimer branching units via appropriate wide and narrow rim functionalization.

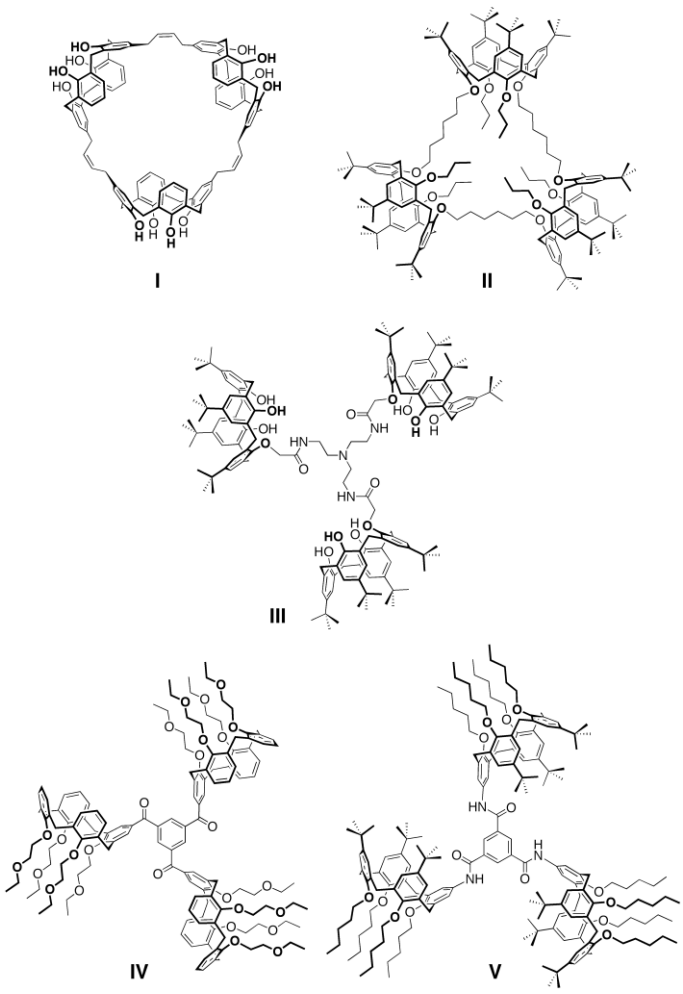
Owing to their easy and often selective chemical alteration at both rims, calixarenes can be covalently assembled in various ways to provide larger molecules (multi-calixarenes), consisting of three or more calixarene substructures linked together through appropriate spacer units in a linear, branched, or cyclic array.[38] Representative examples of C_3 symmetric cyclic covalent assembly of three calix[4]arene moieties with *inward*-oriented (**I**)[39] or *outward*-oriented (**II**)[40] cone cavities, respectively, are shown in Scheme 3. Also shown are star-like C_3 symmetric tris-calixarenes (**III**-**V**), where the macrocyclic substructures are connected via their narrow rim through amide bonds to a flexible "tren" (tris-(2-aminoethyl)amine) core (**III**),[41] or supported via their *inward*-oriented wide rims to a rigid trimesoyl keto (**IV**)[42] or amide (**V**)[43] core.

The incorporation of calixarenes into dendritic systems offers the potential of combining a high density of surface functionality, with an increased degree of preorganization, amphiphilic characteristics and a range of fixed three-dimensional architectures through the choice of the calixarene conformation.[44] In particular, suitably functionalized calixarenes have been demonstrated to act as templating units to build up multi-heterocomponent supramolecular assemblies with a programmed sequence of repeating units (non-covalent dendrimers).[24]

On the other hand, C_3 symmetric building blocks have been widely employed to prepare complex target molecules that have found application in areas as diverse as analytical chemistry,[45] molecular recognition,[46] materials science[47] and supramolecular chemistry.[48]Furthermore, they have also been used as central cores for the design of dendrimeric

frameworks with increased diversity.[49] A C_3 symmetric first-generation dendrimer, composed of three *outward*-oriented A,D-(1,10-phenanthrolino)-bridged calix[6]arene substructures, connected to a central benzene ring via 1,3,5-tris(ethynyl) bridges, is a typical example.[50]

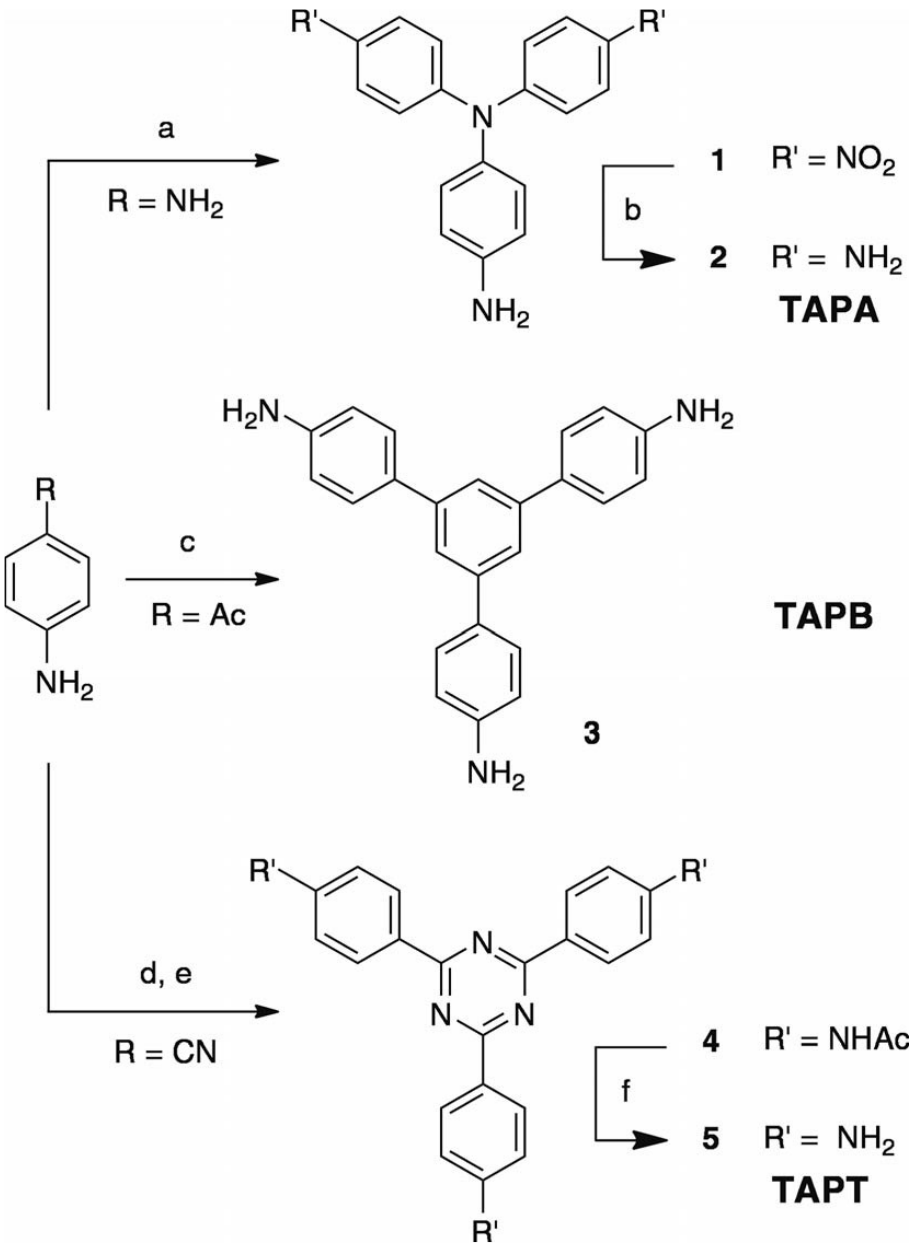
In the search for higher levels of structural order in the morphology of calix[4]arene dendrimers, here we report on the stepwise divergent synthesis of a variety of multivalent amphiphilic dendrons, consisting of amino-surface functionalized cone calix[4]arene subunits connected (via their narrow rims) to rigid C_3 symmetric tris-anilino cores by means of butanoylamido linkages (*vide infra*, Scheme 6, compds **12**, **14** and **16**). A specific orientation and spacing between the surface functional groups of the calixarene moieties in our dendrons are deemed essential for an ordered growth of subsequent generations of dendrimers achievable by a non-covalent synthetic approach.



Scheme 3. A selection of cyclic (**I–II**) and star-like (**III–V**) C_3-symmetric tris(calix[4]arene) covalent assemblies.

These requirements can be fulfilled by choosing rigid C_3 symmetric core building blocks, such as tris(4-aminophenyl) amine (**TAPA**), 1,3,5-tris(4-aminophenyl)benzene (**TAPB**) and 2,4,6-tris(4-aminophenyl)-*s*-triazine (**TAPT**), which are expected to minimize the entanglement of the peripheral aminocalix[4]arene moieties in the assembly process. A further point of interest of these central cores is their propeller-like conformation. The three anilino rings of these molecules are twisted in the same sense with respect to a reference plane, identified by the three carbon atoms attached to the central nitrogen atom (**TAPA**), or the plane of central benzene (**TAPB**) or *s*-triazine (**TAPT**) rings, respectively. Thus the

dendrons that can be derived from them are potentially chiral, and could ultimately instill helical growth in the aggregates that will become available.[51]



Scheme 4: Synthesis of C_3 symmetric tris-anilino cores **2**, **3** and **5**. Reagents and conditions: a) 4-fluoronitrobenzene, K_2CO_3, DMSO, 90 °C, 72 h, 90%; b) $H_2NNH_2 \cdot H_2O$, THF/EtOH, Pd/C, reflux, 16 h, 85%; c) $TsOH \cdot H_2O$, 145 °C, 16 h, 25%; d) Ac_2O, 0–25 °C; e) $ClSO_3H$, 0 °C, 24 h, 61%; f) 18 M HCl, reflux, 3 h, 48%.

Results and Discussion

The divergent synthetic approach to the target C_3 symmetric tris-calix[4]arene dendrons **12**, **14** and **16** starts with the syntheses of tripodal tris-anilino cores **TAPA** (**2**), **TAPB** (**3**) and **TAPT** (**5**), which are shown in Scheme 4. **TAPA** was prepared by the K_2CO_3-catalyzed S_NAr reaction of 4-fluoronitrobenzene on 1,4-phenylendiamine in dry DMSO to give *N*,*N*-di(4-nitrophenyl)-1,4-phenylendiamine **1**,[52] followed by reduction with $H_2NNH_2 \cdot H_2O$ and Pd/C[53] in refluxing THF/MeOH.

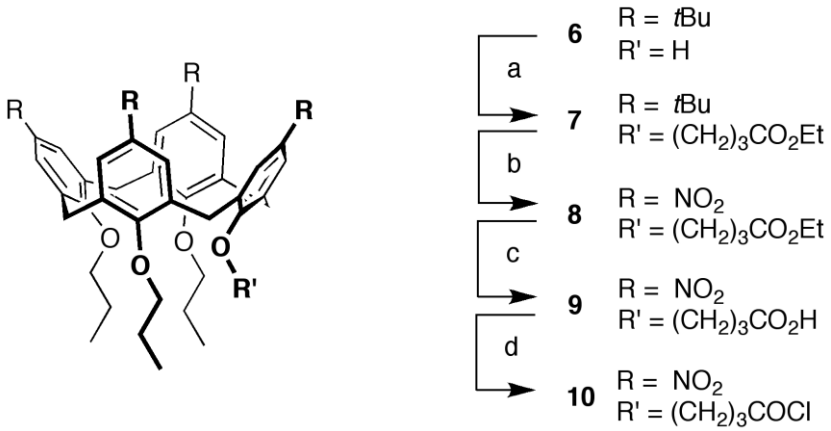
TAPB is usually obtained according to a straightforward two-step procedure, involving the acid-catalyzed ($SiCl_4$/EtOH,[54] CF_3SO_3H/toluene,[55] or $K_2S_2O_7/H_2SO_4$[56]) cyclo-trimerization of 4-nitroacetophenone to 1,3,5-tris-(4-nitrophenyl)benzene, and subsequent reduction (Sn/HCl,[55] Pd/C/$H_2NNH_2 \cdot H_2O$,[53b] active carbon, $FeCl_3 \cdot 6H_2O/H_2NNH_2 \cdot H_2O$[54] or $H_2NNH_2 \cdot H_2O$/Raney-Ni[57]) of the tris-nitro derivative formed to the corresponding tris-amine **3**. However, very recently **TAPB** has been prepared in a one-pot reaction by heating neat 4-aminoacetophenone at 142 °C for 16 h in the presence of $TsOH \cdot H_2O$ (0.1 equiv).[58] Although we could not reproduce the reaction in the claimed yield (71%), leading in our hands to minute amounts of product, we were able to obtain **TAPB** in a 25% isolated yield (after column chromatography) by raising the amount of the acid catalyst to at least one equivalent.

As far as the *s*-triazine core is concerned, **TAPT** has recently been prepared by coupling 2,4,6-tris(4-bromophenyl)-*s*-triazine with lithium

bis(trimethylsilyl)amide in the presence of a Pd(0) catalyst.[51a] A cheaper route to the symmetrical 2,4,6-triaryl-*s*-triazine systemcould in principle be offered by the direct trimerization of appropriate aromatic nitriles or their alkyl imidates under acid catalysis (Lewis acid/HCl,[59] triflic anhydride,[60] chlorosulfonic acid,[61] acetic or formic acid[62]). After trial and error, we have found that 4-acetamidobenzonitrile[63] could be efficiently converted into 2,4,6-tris(4-acetamidophenyl)-1,3,5-*s*-triazine **4** (61%) by treatment with $ClSO_3H$ at 0 °C for 2 d. Acid hydrolysis of this precursor, followed by base treatment, gave the desired **TAPT** in a 48% yield.

The stepwise synthesis of *p*-nitro-calix[4]arene butanoic acid fragment **9** from cone 5,11,17,23-tetra-*tert*-butyl-25-hydroxy-26,27,28-tripropoxycalix[4]arene **6**[64] is depicted in Scheme 5. Compound **6** is a pivotal building block that has found important applications in the synthesis of multivalent ligands,[65] supramolecular polymers,[66] and calixarene dendrimers.[67] Alkylation of the residual OH group of **6** with ethyl 4-bromobutyrate and NaH in refluxing THF gave ester **7** (82%), which upon exhaustive *ipso*-nitration[68] with fuming HNO_3 in CH_2Cl_2/AcOH at 0 °C afforded tetranitro derivative **8** (92%). Subsequent hydrolysis of the ester function with aqueous NaOH at room temperature in THF/MeOH gave acid **9** in 82% yield. Acid **9** was converted almost quantitatively (according to ^1H NMR spectroscopy) into the corresponding acid chloride **10** by treatment with an excess of thionyl chloride in refluxing toluene. ^1H and ^{13}C NMR spectra of calix[4]arene derivatives **7**–

10 are consistent with C_s symmetric structures locked in the cone conformation.[37c,[69]]

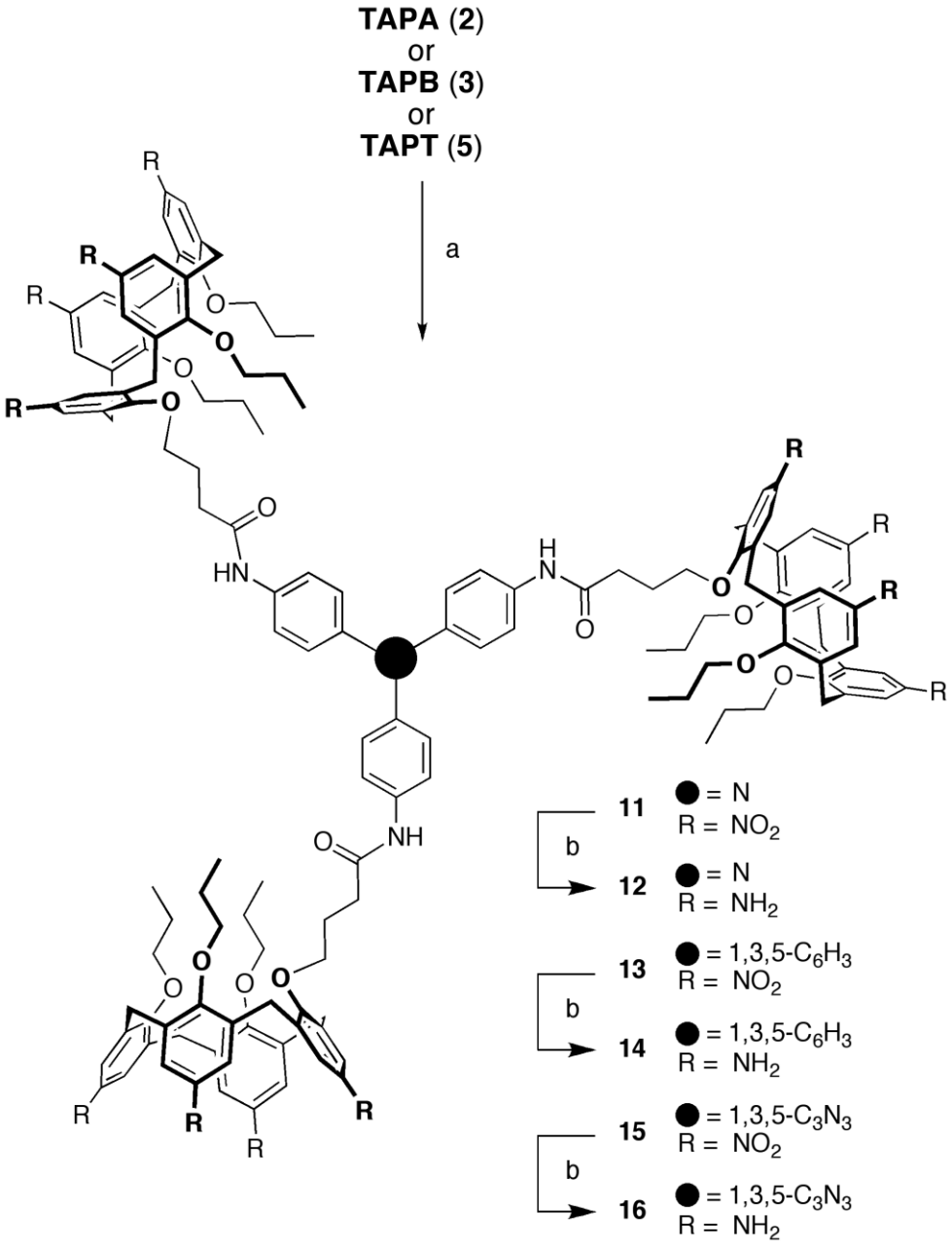


Scheme 5. Synthesis of *p*-nitrocalix[4]arene butanoic acid **9**. Reagents and conditions: a) $Br(CH_2)_3CO_2Et$, NaH, THF, 18 h, 82%; b) 100% HNO_3, AcOH, CH_2Cl_2, 0–25 °C, 92%; c) NaOH, THF/MeOH, r.t., 16 h, 82%; d) $SOCl_2$, toluene, reflux, 3 h, >98%.

The coupling of acid **9** via amide bond formation[[70]] with the rigid tris-anilino cores of **TAPA**, **TAPB**, and **TAPT** to produce the tris-calix[4]arene dendrons **11**, **13** and **15**, was initially carried out in dry *N*,*N*-dimethylformamide (DMF) in the presence of benzotriazol-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP®) catalyst and *i*Pr_2NEt at room temperature for 24 h (method A), as shown in Scheme 6. The reactions with **TAPA** and **TAPB** afforded the expected dendrons **11** and **13** in moderate yield, respectively, while the reaction with **TAPT** mostly gave unaltered **9** with no hint of the formation of the product of exhaustive amidation **15** (^{1}H NMR monitoring of the low-field resonance for the newly formed N–H amide bond). Higher temperatures (50–60 °C) and extended reaction times (up to 3 d) were attempted to no avail. ^{1}H

NMR analysis indicated the formation of mixtures of the mono- and di-amide (predominant), along with minute amounts of the desired tris-amide **15**. We reasoned that the low reactivity of **TAPT** is most likely due to the electron-withdrawming ability of the central *s*-triazine ring, which considerably reduces the nucleophilic character of the amino functionalities (conjugative effect). Hence we resorted to the 'classic' amidation procedure[69] using the much more reactive calix[4]arene acid chloride **10** (Scheme 5). The coupling reaction with the three aromatic tris-amino cores (**TAPA**, **TAPB**, and **TAPT**) was carried out in dry THF, at –10 °C, in the presence of *i*Pr$_2$NEt (method B). As a result, tris-amines were smoothly converted into the corresponding tris-amides in much higher yields(73–85%). Reaction times vary according to the nature of the central atom/ring of the C_3 symmetric core: the most reactive system is **TAPA** (reaction completed within 12 h), followed by **TAPB** (within 24 h) and **TAPT** (within 36 h and two equiv. of acid chloride for each amino group). The exhaustive reduction of the above dodecanitro intermediates with Raney-Ni catalyst[71]and H_2 (1 atm) at room temperature afforded the target amino-surface functionalized dendrons **12**, **14** and **16** in good yield. The reaction was conveniently monitored by ^{1}H NMR, following the appearance of a new broad resonance for the newly formed NH_2 groups at about 4.2 ppm, and consequential upfield shift (in the range 6.0–5.9 ppm) for the *ortho*-positioned aromatic hydrogen atom resonances of the calix[4]arene moieties. Dodecaamino compounds show a limited solubility in chlorinated solvents, but are quite soluble in aprotic dipolar solvents

such as DMF and DMSO. Upon acid treatment, clear aqueous solutions of protonated dodecaamino derivatives are obtained.



Scheme 6. Synthesis of tris-calix[4]arene dendrons **11**–**16**. Reagents and conditions: a) Method A: calix[4]arene **9**, PyBOP, *i*Pr$_2$NEt, DMF, r.t., 24 h, 48–51%; Method B: calix[4]arene **10**, *i*Pr$_2$NEt, THF, –10 °C, 12–36 h, 73–85%; b) Raney-Ni, DMF, H_2, 24–48 h, 53–88%.

^{1}H and ^{13}C NMR spectra are in full agreement with the proposed structures for all new compounds and in particular, dendrons **11–16**, because of their C_3 symmetry, display in [D_6]DMSO[72] relatively simple spectra (Figure 3). As far as their ESI mass spectra are concerned, they show the expected molecular ion peaks, with the exception of nitro-containing dendrons, which are characterized by an extensive fragmentation pattern and the absence of the parent peak under the experimental conditions used.

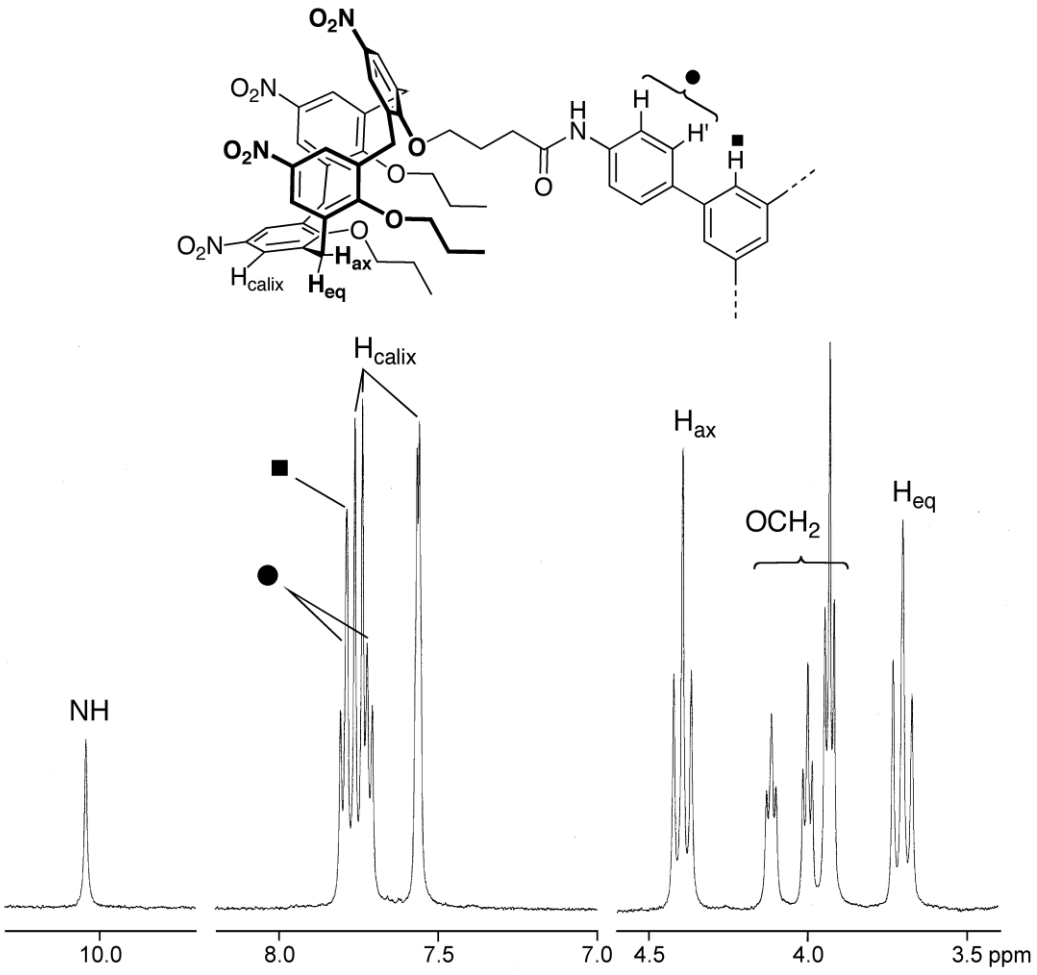


Figure 3. Sections of the ^{1}H NMR spectrum (500 MHz, 25 °C, [D_6]DMSO) of C_3 symmetric dendron **13**.

In order to demonstrate the utility of these system to act as templating units in the noncovalent synthesis of multi-heterocomponent supramolecular assemblies with a programmed sequence of repeating units (noncovalent dendrimers), in collaboration with the research group of Prof. R. Purrello, has been preliminarily chosen the water-soluble dodecacationic triscalix[4]arene with a **TAPA**core (compound **12)**as a templating agent for the assembly of tetraanionic porphyrin **CuTPPS** (see Scheme 2). pH titration experiments have shown that, at pH values <2, dodeca-amino triscalix[4]arene derivative **12** exists in the fully protonated form. When carrying noncovalent synthesis in aqueous solution, the protonation of amino-surface functionalized multi-cavity calix[4]arenes is a mandatory step not only for sample solubilization, but also because the formation of supramolecular assemblies with porphyrins is triggered by strong electrostatic interactions between oppositely charged **CuTPPS** and triscalix[4]arene **12** components. The results of an UV titration study of **12** with the **CuTPPS** are shown in Figure 4. As expected, Figure 4 shows a pronounced hypochromism resulting from the complexation of **CuTPPS** with the triscalix[4]arene, since the absorbance measured in the complexes is lower than that resulting exclusively by uncomplexed porphyrin molecules. Even though the three porphyrin moieties, accommodate one at a time inside the cavities of the triscalix[4]arene dendron, are spatially very far away from each other, the observed hypochromism is a mere consequence of a calixarene-mediated porphyrin-porphyrin electronic communication.

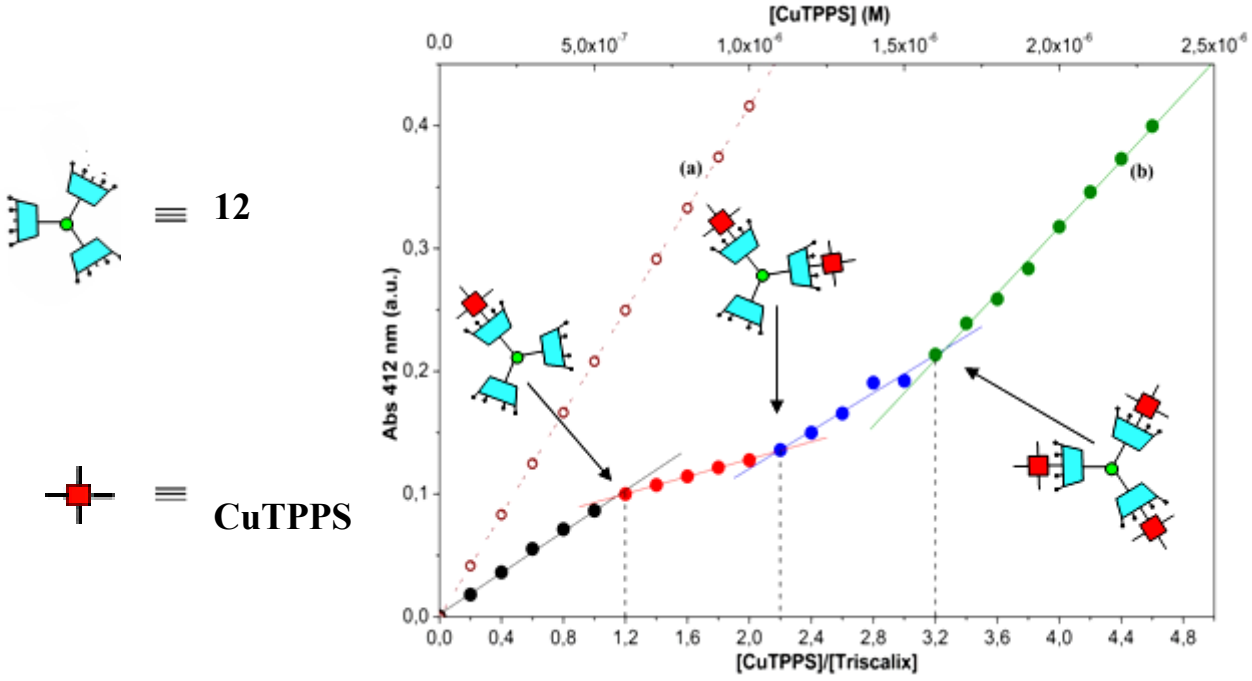


Figure 4: Absorbance variation (at 412 nm) for increasing concentrations of CuTPPS in aqueous solution: a) in the absence and b) in the presence of compound **12** (0.5 μM)

The breakpointsobserved upon addition of increasing ammount of porphyrin do not coincide exactlywith the expected 1:1, 2:1 and 3:1 ratios, but are shifted by about 20%, probably because of the hygroscopicity of the triscalix[4]arene.

Unlike previously investigated calixarene/porphyrin aggregates [24c,d], in this case we obtain the first breakpoint at a [**CuTPPS**]/[triscalix[4]arene] ratio equal to 1, which means that the first complex that is formed has a 1: 1 stoichiometry. By following the slope changes that generate the other breakpoints, we can deduce that subsequently added porphyrin molecules interact with the residual empty calix[4]arene cavitiesto sequentially form [**CuTPPS**]/[triscalix[4]arene] 2:1 and 3:1 complexes, respectively. Therefore, contrary to previously

investigated porphyrin/calixarene assemblies, obtained with mono- or bis-cavity calix[4]arenes through the intermediate formation of a cruciform 1:4 porphyrin/calixarene structure, here the core of the assembly is no longer a porphyrin unit, but the triscalix[4]arene itself.

The transfer of chiral information to achiral or dynamically racemic supramolecules and macromolecular helical systems from nonracemic guest molecules through non-covalent bonding interactions has attracted great interest in recent years.[73] This is because chirality-transfer phenomena can be used for sensing chirality for a wide range of chiral molecules, as well as for developing novel chiroptical devices and chiral materials as enantioselective adsorbents and catalysts.[74] In particular, when a receptor molecule is achiral, but chromophoric, the non-covalent bonding to an enantiomerically pure guest may provide a characteristic induced circular dichroism (ICD) in the absorption region of the receptor; the Cotton effect sign can be used to determine the absolute configuration of the guest.[30]

Recently, two different strategies have been elaborated by which chirality can be induced in porphyrin–biscalixarene supramolecular assemblies. The first, and more obvious one, makes use of chiral calixarenes whereas the second, which relies on a fully non-covalent approach, takes advantage of the ditopic nature of bis-calixarenes as non-covalent connectors between porphyrins and enantiomerically pure Δ- and Λ-tris-(1,10-phenanthroline) ruthenium(II) cations (Δ- and Λ-$[Ru(phen)_3]^{2+}$).[75] Some of the known assembly modes between porphyrin and (bis)calixarene molecules are sketched in Figure 5.[24] For

both systems, the first step involves the formation of a porphyrin–macrocycle (calixarene or bis-calixarene) species in a 1 : 4 molar ratio.

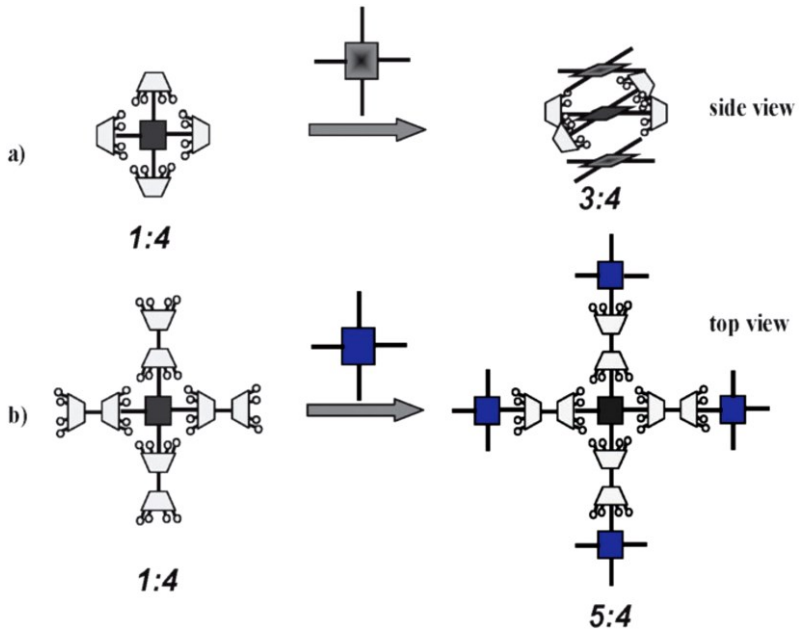
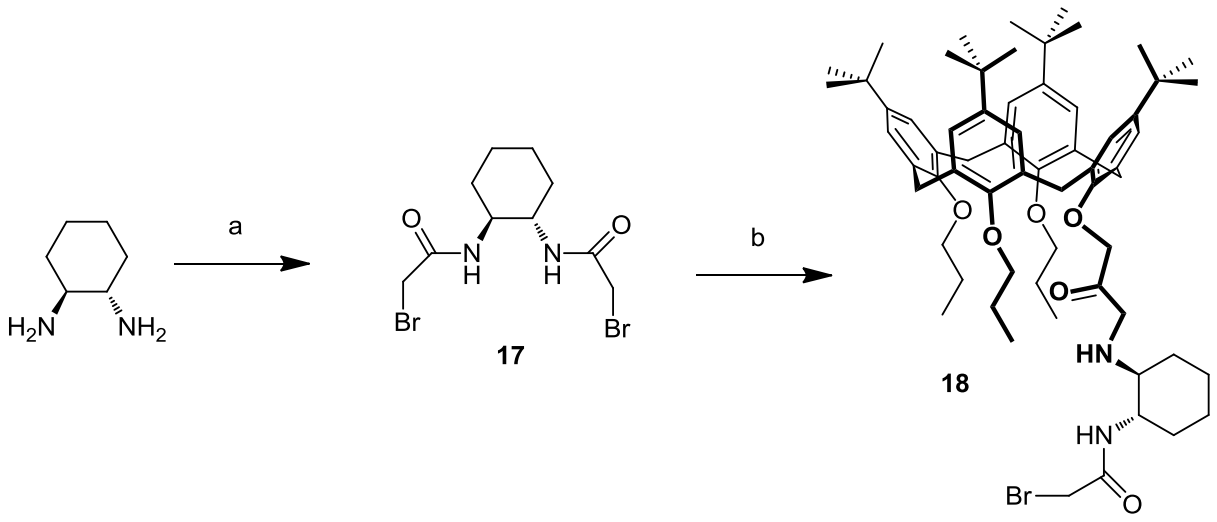


Figure. 5: Schematic representation of the 1 : 4 complexes formed by 1 mole of porphyrin and 4 moles of calix[4]arene (a) or biscalix[4]arene (b), and the two different assemblies (i.e. 3 : 4 and 5 : 4) subsequently derived from the relevant 1 : 4 species by further addition of porphyrin molecules

We have thus undertaken another synthetic project aimed at investigating the induction of chirality in calixarene-porphyrin self-assemblies by using chiral bis-cavity calix[4]arenes. To this end, the work has mainly been devoted to the design, synthesis and characterization of different pairs of water-soluble C_2-symmetrichomochiral biscalix[4]arene enantiomers and water-soluble C_3-symmetrichomochiral triscalix[4]arene enantiomers. The use of chiral templating agents in non-covalent synthesis is of great importance because these molecules not only organize the porphyrins in terms of sequence and stoichiometry, but also may impart to the resulting porphyrin/calixarene assemblies supramolecular properties (e.g., chirality,

amplification of chirality, chiral memory) that are not shown by the individual components.

Our initial attempts were focused on the use of chiral bis-electrophile **17** as a potential spacer to join two subunits of tripropoxycalix[4]arene **6** through a nucleophilic displacement reaction (Williamson synthesis of ethers). Compound **17** was synthesized, according to a literature procedure,[76] by reacting (1*S*,2*S*)-(+)-1,2-cyclohexanediamine with bromoacetyl bromide and triethylamine in CH_2Cl_2 at 0 °C for 12h(Scheme 7).



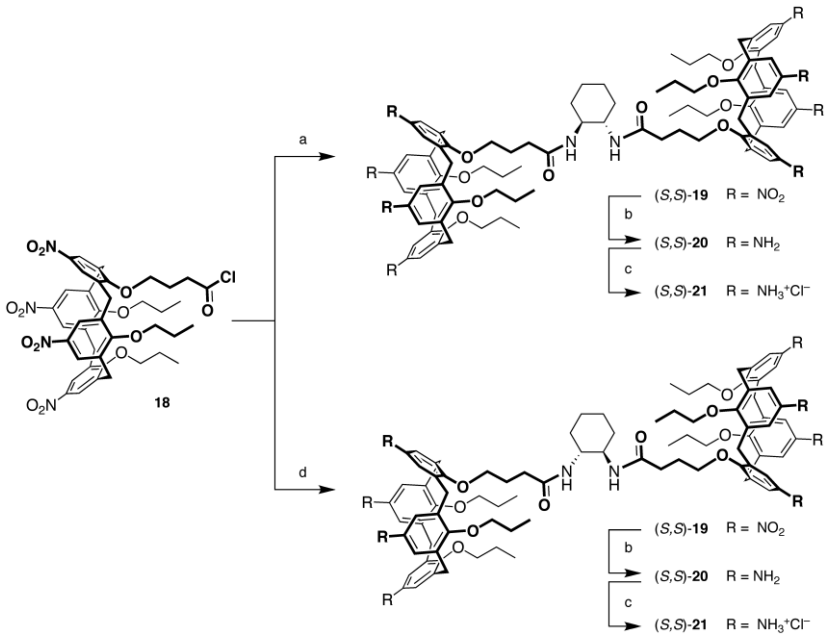
Scheme 7: Synthesis of *N,N*-bis(2-bromoacetyl)(1S,2S)-(1,2-cyclohexanediamide)**17**. Reagents and conditions: a)Bromoacetyl bromide, Et_3N, CH_2Cl_2, 0 °C, 12 h; b) 5,11,17,23-tetra-*tert*-butyl-25-hydroxy-26,27,28-tripropoxycalix[4]arene**6**, NaH, THF, reflux, 6 h.

Unfortunately, the subsequent condensation of calix[4]arene **6** with 0.5 equivalents of **17** and NaH, in anhydrous THF at reflux, produced monoether **18** as the sole reaction product (even after extended reaction times), along with unreacted**6**. Molecular model examination has shown

that the second etherification step to produce the desired biscalix[4]arene is likely precluded by the bulkiness of the calix[4]arene phenoxy nucleophile, and by severe steric repulsions resulting from two calixarene subunits linked at the 1,2-positions of the diaminocyclohexane ring.

In order to avoid the steric strain caused by the close proximity of two calix[4]arene moieties and facilitate the formation of C_2-symmetrichomochiral biscalix[4]arene enantiomers, we reasoned that the chiral *trans*-1,2-diaminocyclohexane core could span (via a bis-amidation procedure) two calix[4]arene subunits endowed with a longer butyric acid moiety at the lower rim. We have thus envisaged two complementary synthetic strategies, which rely on the incorporation –via amide-bond formation– of cheap chiral *trans*-1,2-diaminocyclohexane or lactic acid residues into the spacer connecting the two calix[4]arene subunits. More specifically, homochiral biscalix[4]arenes were synthesized by reaction of the achiral or chiral *p*-nitrocalix[4]arene butyric or lactic acid chloride, with the appropriate chiral (*trans*-1,2-diaminocyclohexane) or achiral primary (*p*-phenylendiamine, *trans*-1,4-diaminocyclohexane) or secondary (piperazine, *trans*-2,5-dimethylpiperazine) diamine, respectively.

The synthesis of bis-calix[4]arene enantiomers **21**/**24** fromacyl chloride **10**(see Scheme 5) is illustrated in Scheme 8.



Scheme 8. Synthesis of enantiomers (*R,R*)-/(*S,S*)-**21** Reagents and conditions: a) (1*S*,2*S*)-(+)-1,2-cyclohexanediamine, Et_3N, CH_2Cl_2, 0 °C, 12 h; b) Ni/Raney, THF, H_2, t.a., 18 h; c) HCl 4 M in dioxane; (1*R*,2*R*)-(−)-1,2-cyclohexanediamine, Et_3N, CH_2Cl_2, 0 °C, 12 h.

A solution of **10** in anhydrous CH_2Cl_2 was then reacted at –10 °C with a slight defect of enantiomerically pure (1*S*,2*S*)-(+)-1,2-cyclohexanediamine or (1*R*,2*R*)-(–)-1,2-cyclohexanediamine in the presence of triethylamine, to produce C_2-symmetricenantiomerically pure octanitro-biscalix[4]arene diamides (*R,R*)-**19** and(*S,S*)-**19**, respectively, in good yield, as shown in Scheme 8.Octa-nitro enantiomers were individually subjected to reduction with hydrogen and Raney/Ni catalyst in THF at room temperature to give octa-amino derivatives (*R,R*)-**20** and(*S,S*)-**20**, respectively. The corresponding octa-hydrochlorides (*R,R*)-**21** and(*S,S*)-**21** were obtained by treatment with 4M HCl in dioxane. As expected, the NMR spectra of enantiomers (*R,R*)-/(*S,S*)-**21**as well as those of the relevant precursors– are

superimposable, while their CD spectra, shown in Figure 6, are mirror images.

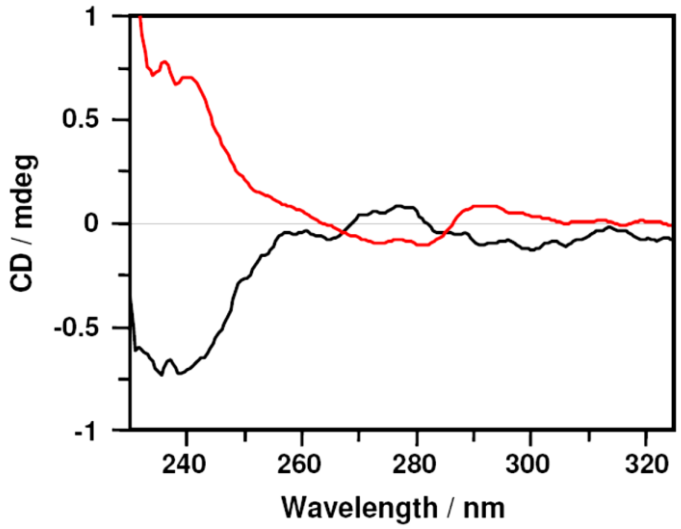
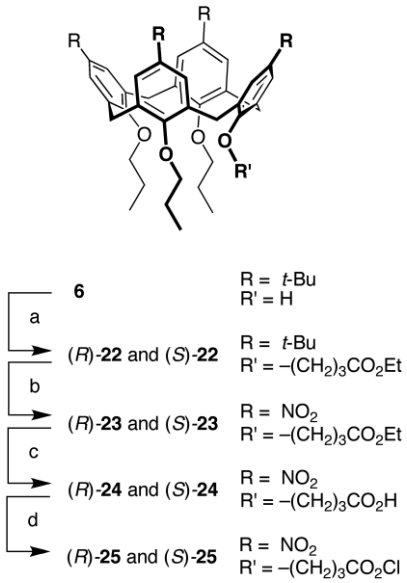


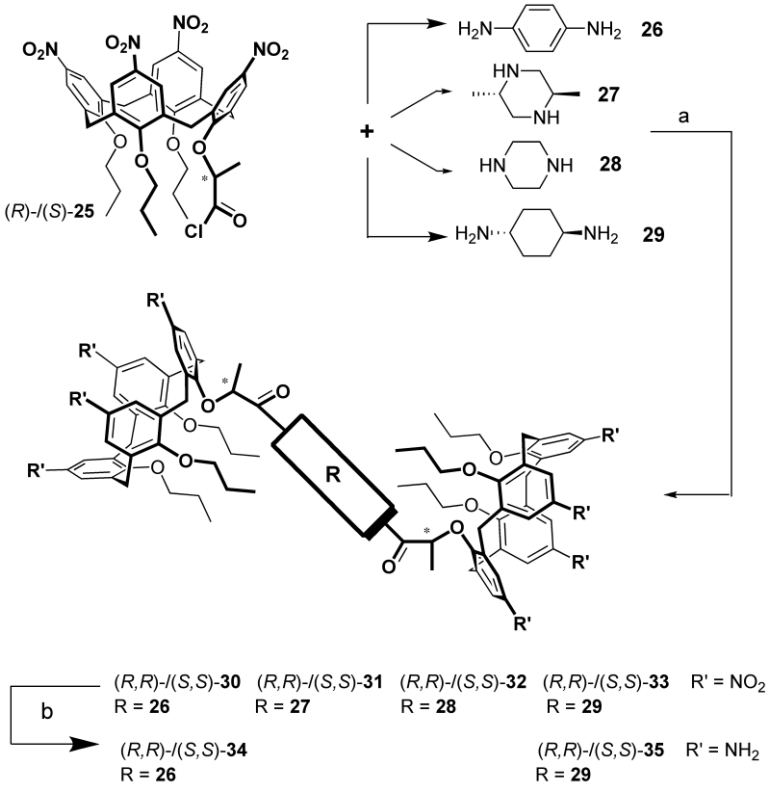
Figure 6. CD spectra of an aqueous solution of enantiomers (1*S*,2*S*)-**21**(50 μM) red trace and (1*R*,2*R*)-**21**(50 μM) black trace.

For the synthesis of the bis-calix[4]arene enantiomers bearing lactic acid residues in the connecting bridge, we firstly introduced the chiral methyl lactate moiety into the lower rim of the tris-propylated calix[4]arene building block **6**by the $MeO^{-}Na^{+}$-catalyzed alkylation with enantiomerically pure (*R*- or *S*-) *O*-tosylated methyl lactate electrophiles, synthesized by adapting a literature procedure for the structurally related ethyl ester.[[77]] The resulting enantiomerically pure *p-tert*-butylcalix[4]arene methyl esters were further derivatized according to the usual synthetic protocol outlined in Scheme 9 (upper rim *ipso*-nitration, followed by basic hydrolysis of the ester function and subsequent chlorination of the carboxylic acid intermediate) to ultimately provide (*R*)- and (*S*)-*p*-nitrocalix[4]arene lactic acid chloride enantiomers (*R*)-/(*S*)-**25**.



Scheme 9. Synthesis of compound (*R*)-/(*S*)-**25**. Reagents and conditiona) *R* and *S O*-tosylated methyllactate, MeONa, dry CH_3CN, 48 h; b) 100% HNO_3, AcOH, CH_2Cl_2, 0–25 °C; c) NaOH, THF/MeOH, r.t., 16 h; d) $SOCl_2$, toluene, reflux, 3 h.

Scheme 10shows the synthesis of the pairs of enantimeric bis-calix[4]arenes obtained by condensation of compound (*R*)-/(*S*)-**25**with *para*-phenylenediamine **26**, *trans*-2,5-dimethylpiperazine **27**, piperazine **28**, *trans*-1,4-cicloeasandiamine **29**. The reaction was carried out at–10 °C in CH_2Cl_2in the presence of triethylamineto give the respective octa-nitro biscalix (*R,R*)-/(*S,S*)-**30**,(*R,R*)-/(*S,S*)-**31**, (*R,R*)-/(*S,S*)-**32** and(*R,R*)-/(*S,S*)-**33**.Solutions of individual enantiomers in THF were subjected to reduction with hydrogen and catalyst Ni/Raney at room temperature to give the octa-ammonium pairs(*R,R*)-/(*S,S*)-**34** and (*R,R*)-/(*S,S*)-**35**, respectively. Reduction of compounds **31** and **32**has not yet been successful owing to their poor solubility.



Scheme 10. Synthesis of singly-bridged homochiral biscalix[4]arenes compounds **30–35**.Reagent and conditions: a) Et_3N, CH_2Cl_2, 0 °C, 12 h;

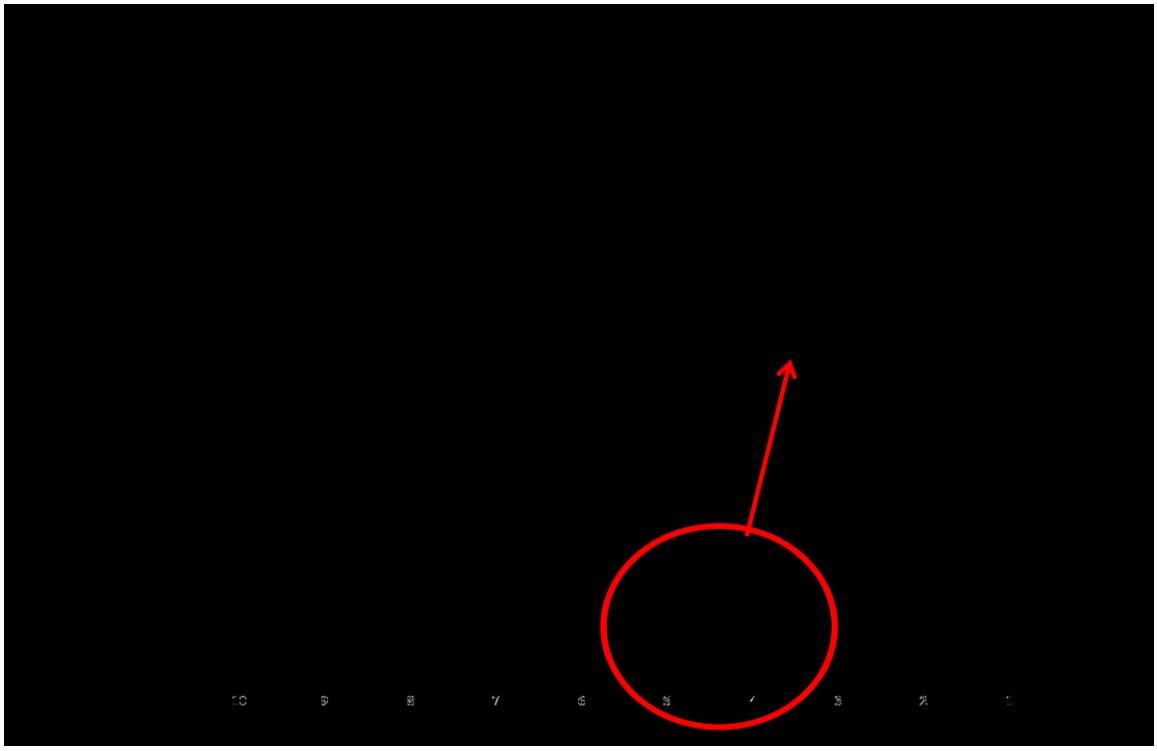


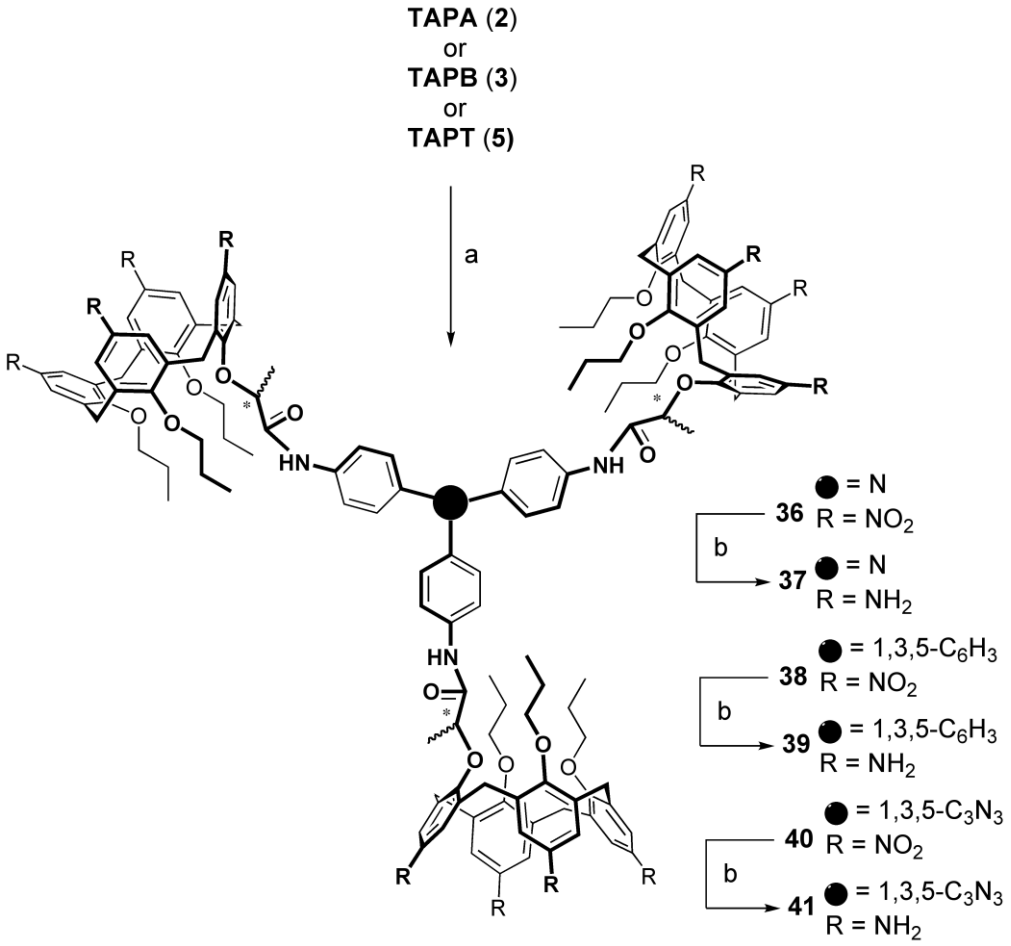
Figure 7. ^{1}H NMR spectrum (500 MHz, 25 °C, ([D_6] acetone) of C_2 symmetric dendron (*R,R*)-**30**.

Figure 7 shows the ^{1}H NMR spectrum of octanitro biscalixarenederivative(*R,R*)-**30**containing the*p*-phenylendiamine as a spacer.The C_2 symmetry of the molecule is demonstrated by the presence of the resonances of the amide proton at δ 9.72 ppm and spacer benzene ring protons atδ7.58 ppm that resonate as singlets.The aromatic rings of the calixarene moiety have a C_{2v} symmetry that is detectable from two sets of signals at δ 8.3 and 7.0 ppm that resonate as doublets and which belong to the inward and outward-oriented rings respectively.The insert of Figure 7 shows eight doublets for the methylene bridge protons and a quartet for the α-oxymethylene protonbelonging to the chiral proton of the lactic acid residue.

The data illustrated above have shown that it is possible to obtain dendrimeric structures through non-covalent assembly of water soluble C_3 symmetric tris-calix[4]arenes and porphyrins.So in order to observe the chirality induction in supramolecular assemblies consisting of multi-calixarenic and porphyrins structures, it were synthesized water soluble C_2 symmetry chiral bis-calix[4]arenes. However, a more comprehensive projects would provide a dendrimeric structure formed by a central hub characterized by water soluble C_3 symmetry chiral tris-calix[4]arene.This structure is a chirality inducer for porphyrins which can subsequently be extended by using chiral bis-calix[4]arenes in order to avoid the steric hindrance given by chiral tris-calix[4]arenes which have a C_3symmetry.For these reasons to conclude this project were designed, synthesized and characterized water soluble C_3 simmetry chiral tris-

calix[4]arenes in which the calix[4]arene has been functionalized at the lower rim with lactic acid residue to introduce a chiral center.

The synthesis of chiral triscalixarenes,from enantiomers (*R*)-**25** and (*S*)-**25** and bridging units**TAPA** (**2**), **TAPB** (**3**) and **TAPT** (**5**) is illustrated in Scheme 11. The reaction was carried out in CH_2Cl_2 containing triethylamine, and cooled to - 10 °C with ice bath and salt, to give the respective dodeca-nitro triscalix **41**R and S, **43** R and S, **45** R and S. The exhaustive reduction of the above dodecanitro intermediates with Raney-Ni catalyst[78]and H_2 (1 atm) at room temperature afforded the target amino-surface functionalized dendrons**39** and **41** in good yield. Unfortunately, the reduction of the dodeca-nitro derivative **36** has not provided the desired product dodeca-amino **37** due to the low solubility.



Scheme 11. Synthesis of tris-calix[4]arene dendrons **36**–**41**. Reagents and conditions: a) Method calix[4]arene (*R*)-**25** and (*R*)-**25**, TEA, CH_2Cl_2, –10 °C, 12–36 h, 73–85%; b) Raney-Ni, DMF, H_2, 24–48 h, 53–88%.

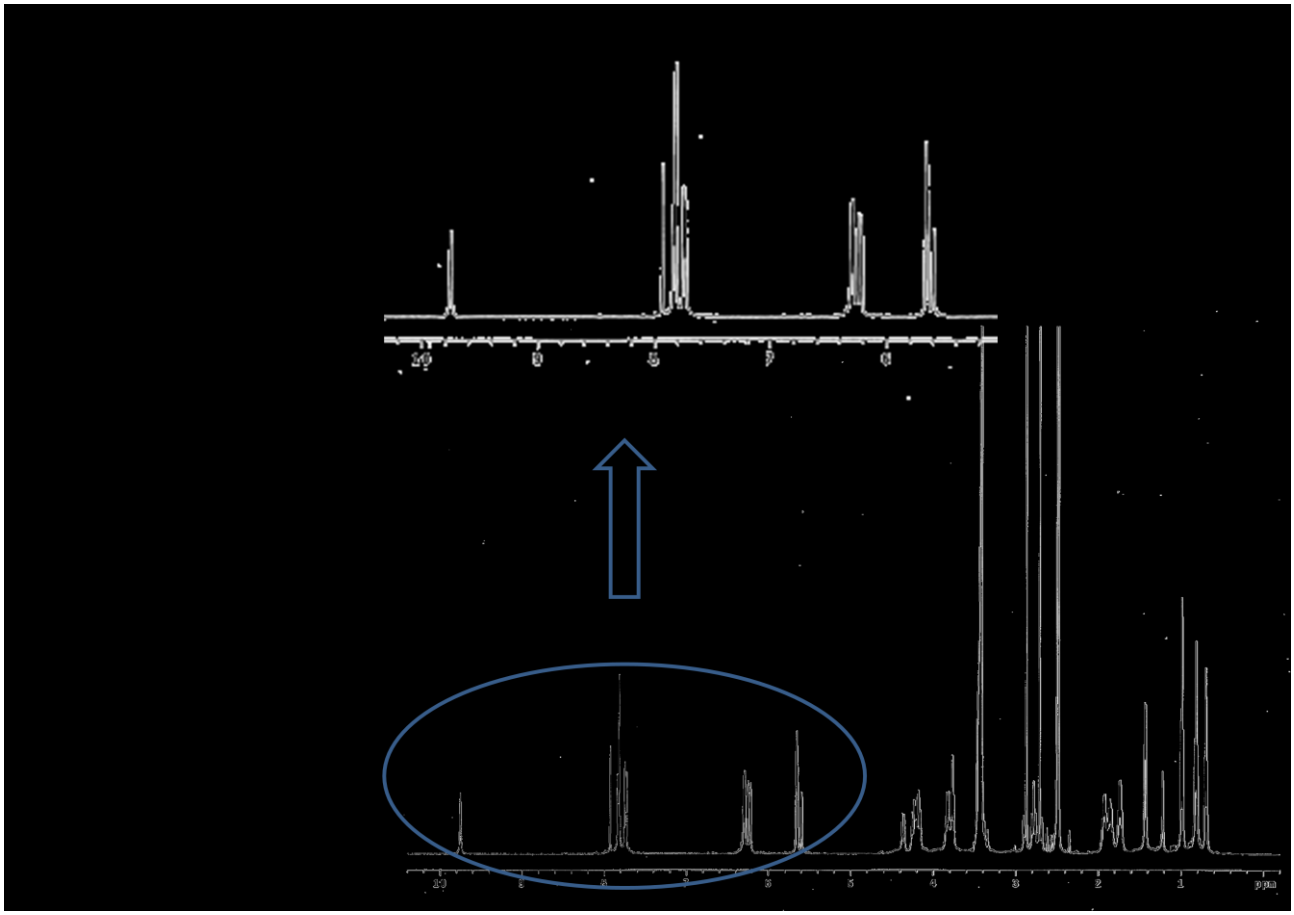


Figure 8. ^{1}H NMR spectrum (500 MHz, 25 °C, ([(D_6)DMSO]) of C_3 symmetric dendron **44**.

Figure 8 shows NMR spectrum of the dodeca-amino tris-calix[4]arene dendron **44**. Downfield region that is shown in the enlargement, it is indicative of the C_3 symmetry of the molecule and the C_{2v} symmetry of calixarenic moiety.Amide proton signals at δ 9.75 ppm and the proton of the benzene central ring atδ 7.82 ppm resonate as singlets which is in agreement with the C_3symmetry of the molecule. In addition, there is only one system AA'BB' at δ 7.8 and 7.7 ppm relative to the aniline ring doublets.The insert also shows the aromatic protons signals of calixarenic moiety that resonate as two sets of signals at up and down fields in accordance with the symmetry C_{2v}.

It was so realized the synthesis and NMR characterization of different pairs of enantiomers based calixarenic tris-cavity and bis cavity, these molecules have all the powers to be used in the near future as inductors chiral non-covalent in water in the synthesis of chiral supramolecular aggregates, in combination with modules achiral porphyrin tetra-anionic anionic (eg, the CuTPPS).

Experimental Section

***N*,*N*-Di(4-nitrophenyl)-1,4-phenylendiamine (1)**: Prepared by a slight modification of a known procedure.[[79]] A stirred mixture of 1,4-phenylendiamine (0.541 g, 5.00 mmol), 4-fluoronitrobenzene (1.411 g, 10.00 mmol) and anhydrous K_2CO_3 (2.764 g, 20.0 mmol) in dry DMSO (15 mL) was allowed to react at 90 °C for 3 d. Upon cooling, the mixture was poured into deionized water (200 mL) to give a precipitate. The solid was collected by suction filtration and then dissolved in AcOEt (150 mL). The organic solution was washed with brine, and dried over anhydrous Na_2SO_4. Concentration to dryness afforded the desired amine as a brown-red powder, (1.580 g, 90%) (R_f = 0.32, hexanes/AcOEt 2:1) mp 231–234 °C (ref.[51] mp 232–234 °C). ^{1}H NMR ([D$_6$]DMSO): δ = 8.15, 7.17 (2×d, J = 9.4 Hz, 8 H, Ar), 6.92, 6.65 (2×d, J = 9.0 Hz, 4 H, Ar), 5.41 (s, 2 H, NH_2) ppm. ESI MS m/z = 351.1 $[M + H]^+$.

Tris(4-aminophenyl)amine (2). Prepared by a slight modification of a known procedure.[80] Pd/C (10 wt %, 0.010 g) was added to a solution of amine **1** (0.210 g, 0.60 mmol) in THF/EtOH (2:1, 10 mL), followed by $H_2NNH_2 \cdot H_2O$ (0.1 mL). The mixture was heated at reflux for 16 h. After filtration through a celite pad, the filtrate was evaporated to dryness. The solid residue upon recrystallization from ethanol afforded the desired amine as blue-grey crystals (0.148 g, 85%), mp 240–242 °C (ref.[80] mp 246 °C. ^{1}H NMR ([D$_6$]DMSO): δ = 6.59, 6.43 (2×d, J = 9.0 Hz, 12 H, Ar), 4.68 (s, 6 H, NH_2) ppm. ESI MS m/z = 291.5 $[M + H]^+$.

1,3,5-Tris(4-aminophenyl)benzene (3). Prepared by a slight modification of a known procedure.[81] Equimolar amounts (1.6 mmol) of finely ground 4-aminoacetophenone and *p*-toluenesulfonic acid monohydrate were stirred and heated at 145 °C (oil bath) in a sealed 8 mL vial for 16 h. After cooling, the mixture was partitioned between CH_2Cl_2 and saturated aqueous $KHCO_3$. The organic extract was dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by CC (AcOEt/hexanes gradient, 1:1 to 3:2) to give yellow crystals of the triamine (0.047 g, 25%). ^{1}H NMR δ = 7.59 (s, 3 H, central benzene ring), 7.50, 6.78 (2×d, J = 8.5 Hz, 12 H, 1,4-phenylenes), 3.74 (br. s, 6 H, NH_2) ppm. ESI MS, m/z = 352.3 $[M + H]^+$.

2,4,6-Tris(4-acetamidophenyl)-*s*-triazine (4). Solid 4-acetamidobenzonitrile (0.976 g, 6.09 mmol) was added portion-wise to

chlorosulfonic acid (4 mL) at –15 °C under magnetic stirring. The temperature was kept at 0 °C for 24 h. The mixture was cautiously poured onto crushed ice to give a yellow precipitate. The solid was collected by filtration and washed with H_2O up to neutrality. The crude product was triturated with MeOH to give an off-white solid (0.595 g, 61%), which was used in the next step without further purification. Mp >250 °C; ^{1}H NMR ([D_6]DMSO): δ = 10.31 (s, 3 H, NH), 8.66, 7.84 (2×d, J = 9.0 Hz, 12 H, Ar), 2.11 (s, 9 H, CH_3) ppm. ^{13}C NMR ([D_6]DMSO): δ = 170.1, 169.0, 143.6, 129.9, 129.7, 118.7, 24.2 ppm. ESI MS, *m/z* = 481.5 $[M + H]^+$, 961.0 $(2M + H)^+$.

2,4,6-Tris(4-aminophenyl)-*s*-triazine (5). Prepared by a slight modification of a known procedure.[79a] A slurry of **4** (0.528 g, 1.10 mmol) in 18 M HCl (10 mL) was heated to reflux for 3 h. After cooling, the mixture was cautiously basified by addition of 20% NaOH (pH ~12). The precipitate obtained was collected by filtration and dissolved in AcOEt. The organic solution was dried over anhydrous Na_2SO_4 and concentrated to give tris-amine **5** as a pale yellow powder (0.187 g, 48%), mp >250 °C (ref.,[50a] mp 415–420 °C (dec.). ^{1}H NMR ([D_6]DMSO): δ = 8.34, 6.68 (2×d, J = 9.0 Hz, 12 H, Ar), 5.89 (br. s, 6 H, NH_2) ppm. ^{13}C NMR ([D_6]DMSO): δ = 169.5, 152.9, 130.1, 122.9, 113.1 ppm. ESI MS, *m/z* = 355.3 $[M + H]^+$.

5,11,17,23-Tetra-*tert*-butyl-25-[3-(ethoxycarbonyl)propoxy]-26,27,28-tripropoxycalix[4]arene (7). A stirred mixture of calix[4]arene **6** (0.775 g, 1.00 mmol), NaH (0.072 g, 3.00 mmol) and ethyl 4-bromobutyrate (0.429 mL, 3.00 mmol) in anhydrous THF (20 mL) was refluxed for 18 h. A few drops of water were carefully added to the cooled mixture, and the solvent was evaporated under vacuum. The residue was partitioned between aqueous 1 M HCl and CH_2Cl_2. The organic layer was separated from the aqueous layer, washed with brine and dried over Na_2SO_4. Evaporation of the solvent left a solid, which upon recrystallization afforded ester **7** (0.734 g, 82%); mp 89–91 °C (MeCN); ^{1}H NMR: δ = 6.81, 6.77 (2×s, ratio 1:1, 8 H, Ar), 4.43 (d, J = 12.2 Hz, 2 H, $ArCH_2Ar$), 4.40 (d, J = 12.7 Hz, 2 H, $ArCH_2Ar$), 4.18 (q, J = 7.0 Hz, 2 H, OCH_2CH_3), 3.89 (t, J = 7.2 Hz, 2 H, OCH_2), 3.86–3.81 (m, 6 H, OCH_2), 3.134 (d, J = 12.7 Hz, 2 H, $ArCH_2Ar$), 3.126 (d, J = 12.2 Hz, 2 H, $ArCH_2Ar$), 2.53 (t, J = 7.5 Hz, 2 H, $CH_2C{=}O$), 2.35 (quintuplet, J = 7.6 Hz, 2 H, $CH_2CH_2C{=}O$), 2.05–1.99 (m, 6 H, $OCH_2CH_2CH_3$), 1.29 (t, J = 7.0 Hz, 3 H, OCH_2CH_3), 1.109, 1.104, 1.07 (3×s, ratio 1:1:2, 36 H, *t*-Bu), 1.01 (t, J = 7.3 Hz, 9 H, $OCH_2CH_2CH_3$) ppm; ^{13}C NMR: δ = 173.4, 153.7, 153.6, 153.5, 144.4, 144.18, 144.17, 133.9, 133.8, 133.7, 133.6, 125.0, 124.90, 124.88, 124.81, 76.9, 74.2, 60.2, 33.80, 33.77, 31.47, 31.45, 31.43, 31.40, 31.07, 31.03, 25.6, 23.29, 23.24, 14.3, 10.3 ppm. ESI MS, *m/z* 912.3 $(M + Na)^+$.

5,11,17,23-Tetranitro-25-[3-(ethoxycarbonyl)propoxy]-26,27,28-tripropoxycalix[4]arene (8). 100% HNO_3 (10.1 mL) was slowly added dropwise to a chilled solution of ester **7** (0.964 g, 1.08 mmol) in

CH_2Cl_2/AcOH (1:1, 40 mL). The reaction mixture was stirred at room temperature until the initial black purple color had turned orange (ca 2 h). The mixture was poured into water (50 mL), and extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with water (2×20 mL), dried over anhydrous Na_2SO_4 and concentrated. The solid residue was triturated with MeOH and collected by filtration (0.839 g, 92%). An analytical sample was obtained by recrystallization from CH_3CN/MeOH: beige needles, mp 223–225 °C. ^{1}H NMR: δ = 7.63 (br s, 4 H, Ar), 7.55 (br s, 4 H, Ar), 4.53, 4.51 (2×d, J = 14.0 Hz, 2 H each, $ArCH_2Ar$), 4.17 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.03 (t, J = 7.2 Hz, 2 H, OCH_2), 4.00–3.94 (m, 6 H, OCH_2), 3.43, 3.41 (2×d, J = 14.3 Hz, 2 H each, $ArCH_2Ar$), 2.46 (t, J = 7.5 Hz, 2 H, $CH_2C{=}O$), 2.22 (t, J = 7.4 Hz, 2 H, $CH_2CH_2C{=}O$), 1.94–1.88 (m, 6 H, $OCH_2CH_2CH_3$), 1.27 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.04, 1.02 (2×t, J = 7.5 Hz, ratio 1:2, 9 H, $OCH_2CH_2CH_3$) ppm; ^{13}C NMR: δ = 172.3, 161.6, 161.5, 161.2, 143.1, 142.9, 135.5, 135.34, 135.28, 135.23, 124.2, 124.1, 124.0, 123.9,77.7, 74.9, 60.7, 31.1, 30.4, 25.3, 23.2, 14.2, 10.2, 10.1 ppm. ESI MS *m/z* 862.3 $(M + NH_4)^+$.

5,11,17,23-Tetranitro-25-(3-carboxypropoxy)-26,27,28-tripropoxy-calix[4]arene (9). A suspension of nitro-ester **8** (0.719 g, 0.88 mmol) in THF/MeOH (4:3, 28 mL) was stirred for 24 h at room temperature in the presence of NaOH (0.280 g in 1.5 mL of water). After evaporation of volatiles under vacuum, the residue was acidified with aqueous 1N HCl, extracted with CH_2Cl_2 (3 × 20 mL), and dried over anhydrous Na_2SO_4. The solution was concentrated to dryness, and the residual solid was

purified by CC (AcOEt/cyclohexane gradient, 1:4 to 1:1) to afford acid **9** (0.593 g, 82% yield); mp 237–240 °C; ^{1}H NMR: δ = 7.63, 7.61 (2×d, J = 2.6 Hz, 4 H, Ar), 7.53, 7.52 (2×s, ratio 1:1, 4 H, Ar), 4.52 (d, J = 13.8 Hz, 2 H, ArC*H*$_2$Ar), 4.49 (d, J = 13.9 Hz, 2 H, ArC*H*$_2$Ar), 4.04 (t, J = 7.2 Hz, 2 H, OC*H*$_2$), 3.99–3.93 (m, 6 H, OC*H*$_2$), 3.42 (d, J = 14.0 Hz, 2 H, ArC*H*$_2$Ar), 3.41 (d, J = 14.1 Hz, 2 H, ArC*H*$_2$Ar), 2.53 (t, J = 7.3 Hz, 2 H, C*H*$_2$C=O), 2.23 (quintuplet, J = 7.3 Hz, 2 H, C*H*$_2$CH$_2$C=O), 1.94–1.86 (m, 6 H, OCH$_2$C*H*$_2$CH$_3$), 1.02, 1.01 (2×t, J = 7.5 Hz, ratio 1:2, 9 H) ppm; ^{13}C NMR: δ = 161.6, 161.5, 161.1, 143.1, 142.9, 135.5, 135.30, 135.27, 135.23, 124.2, 124.1, 124.0, 123.9, 77.7, 74.6, 31.1, 29.7, 25.0, 23.2, 10.2, 10.1 ppm. ESI MS *m/z* 839.1 $(M + Na)^+$.

5,11,17,23-Tetranitro-25-(3-chlorocarbonylpropoxy)-26,27,28-tripropoxycalix[4]arene (10). A stirred mixture of acid **9** (1.000 g, 1.22 mmol) and $SOCl_2$ (0.970 mL, 13.30 mmol) in dry toluene (1.4 mL) was heated at reflux for 3 h. Upon cooling, the mixture was concentrated to dryness under vacuum, and taken up in dry toluene (2 mL). Evaporation of the solvent afforded the $SOCl_2$-free acid chloride (99%), which was used for the next step without further purification. ^{1}H NMR: δ = 7.60 (br s, 8 H, Ar), 4.53, 4.47 (2×d, J = 14.0 Hz, 2 H each, ArC*H*$_2$Ar), 4.05 (t, J = 7.0 Hz, 2 H, OC*H*$_2$), 3.93–3.99 (m, 6 H, OC*H*$_2$), 3.45, 3.43 (2×d, J = 14.0 Hz, 2 H each, ArC*H*$_2$Ar), 3.09 (t, J = 7.2 Hz, 2 H, C*H*$_2$C=O), 2.30 (quintuplet, J = 7.2 Hz, 2 H, C*H*$_2$CH$_2$C=O), 1.94–1.88 (m, 6 H, OCH$_2$C*H*$_2$CH$_3$), 1.03 (t, J = 7.2 Hz, 9 H) ppm.

General Procedure for the Synthesis of Dodecanitro Tris-calixarene Dendrons. *Method A*. A solution of acid **9** (0.300 g, 0.37 mmol), PyBOP (1 equiv.) and *i*Pr_2NEt (1 equiv.) in dry DMF (3 mL) was stirred at room temperature for 10 min. Then a solution of tris-amino compound (0.26 equiv) in DMF (2 mL) was added, and stirring was continued for 1 d. After evaporation of the solvent, the residue was acidified with 0.1 M HCl (5 mL) and extracted with CH_2Cl_2 (3×5 mL). The organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. The solid residue after trituration with MeOH was collected by filtration, and further purified by CC.

Method B. Freshly prepared acid chloride **10**, generated from **9** (0.300 g, 0.37 mmol) was dissolved in dry THF (4.5 mL) and cooled to –10 °C. To this solution a mixture of tris-anilino compound (**TAPA** and **TAPB**: 0.26 equiv.;**TAPT**: 0.17 equiv.) and *i*Pr_2NEt (1 equiv.) in dry THF (3 mL) was added via cannula. The reaction mixture was stirred at room temperature for additional 12–36 h (^{1}H NMR monitoring) and concentrated. After evaporation of the solvent, the residue was acidified with 0.1 M HCl (5 mL) and extracted with CH_2Cl_2 (3×5 mL). The organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. The solid residue after trituration with MeOH (MeCN in the case of **15**) was collected by filtration, and further purified by CC.

TAPA Dodecanitro Tris-calixarene Dendron (11). CC ($CHCl_3$/acetone, 4:1) followed by trituration with MeOH afforded a brownish solid (Method A, 0.503 g, 51% yield; Method B, 0.838 g, 85% yield), mp 220–

223 °C; ^{1}H NMR ([D$_6$]DMSO): δ = 9.85(s, 3 H, NH), 7.75, 7.73, 7.55 (3×s, ratio 1:1:2, 24 H, ArH-calix), 7.47, 6.87 (2×d, J = 9.0 Hz, 6 H each, 1,4-phenylene core), 4.38, 4.37 (2×d, J = 13.5 Hz, 6 H each, axial ArCH_2Ar), 4.08, 3.98, 3.93 (3×t, J = 7.5 Hz, ratio 1:1:2, 24 H, OCH$_2$), 3.70, 6.68 (2×d, J = 13.5 Hz, 6 H each, equatorial ArCH_2Ar), 2.39 (t, J = 7.5 Hz, 6 H, CH_2CO), 2.14 (quintuplet, J = 7.5 Hz, 6 H, CH_2CH$_2$CO), 1.87–1.80 (m, 18 H, OCH$_2$CH_2CH$_3$), 0.94 (t, J = 7.5 Hz, 27 H, OCH$_2$CH$_2$CH_3) ppm; ^{13}C NMR ([D$_6$]DMSO): δ = 169.8, 161.9, 161.8, 161.6, 142.7, 142.1, 141.9, 135.9, 135.8, 135.7, 135.5, 134.1, 123.9, 123.8, 123.5, 120.2, 77.2, 77.1, 74.9, 32.3, 29.7, 25.3, 22.7, 10.0, 9.9 ppm.

TAPB Dodecanitro Tris-calixarene Dendron (13). CC (CH$_2$Cl$_2$/MeOH, 99:1), followed by trituration with MeCN gave a brown solid (Method A, 0.484 g, 48% yield; Method B, 0.736 g, 73% yield), mp 229–232 °C; ^{1}H NMR ([D$_6$]DMSO): δ = 10.06 (s, 3 H, NH), 7.81, 7.73 (2×d, J = 8.5 Hz, 6 H each, 1,4-phenylene core) 7.80 (s, 3 H, benzene core), 7.77, 7.75, (2×s, ratio 1:1, 12 H, ArH-calix), 7.57 (ill-resolved AB system, 12 H, ArH-calix), 4.41, 4.39 (2×d, J = 13.5 Hz, 6 H each, axial ArCH_2Ar), 4.13, 4.01, 3.96 (3×t, J = 7.5 Hz, ratio 1:1:2, 24 H, OCH$_2$), 3.73, 3.69 (2×d, J = 13.5 Hz, 6 H each, equatorial ArCH_2Ar), 2.48 (t, J = 7.5 Hz, 6 H, CH_2CO), 2.20 (quintuplet, J = 7.5 Hz, 6 H, CH_2CH$_2$CO), 1.92–1.84 (m, 18 H, OCH$_2$CH_2CH$_3$), 0.984, 0.976 (2×t, J = 7.5 Hz, ratio 1:2, 27 H, OCH$_2$CH$_2$CH_3) ppm; ^{13}C NMR ([D$_6$] DMSO): δ = 170.2, 162.0, 161.8, 161.7, 142.1, 142.0, 140.1, 138.9, 135.92, 135.88, 135.5, 127.3, 123.9,

123.8, 123.5, 119.3, 77.2, 77.1, 74.9, 32.4, 29.8, 25.2, 22.79, 22.75, 10.03, 9.98 ppm.

TAPT Dodecanitro Tris-calixarene Dendron (15). CC ($CHCl_3$/acetone, 10:1) provided a yellowish solid (Method A, 72 h, 50–60 °C, mixture of mono-, bis- and tris-amide; Method B, 0.828 g, 82%); mp >250 °C; ^{1}H NMR ([D_6]DMSO): δ = 10.32 (s, 3 H, NH), 8.67, 7.87 (2×d, J = 8.5 Hz, 6 H each, 1,4-phenylene core), 7.77, 7.74 (2×s, 6 H each, ArH calix), 7.559, 7.545 (2×d, J = 2.3 Hz, 12 H, ArH calix), 4.41, 4.38 (2×d, J = 14.0 Hz, 6 H each, axial ArCH_2Ar), 4.13, 4.00, 3.95 (3×t, J = 7.5 Hz, ratio 1:1:2, 24 H, OCH_2), 3.72, 3.68 (2×d, J = 14.0 Hz, 6 H each, equatorial ArCH_2Ar), 2.52 (t, J = 6.5 Hz, 6 H, CH_2C=O), 2.20 (quintuplet, J = 7.0 Hz, 6 H, C$H_2$$CH_2$C=O), 1.90–1.82 (m, 18 H, OCH_2C$H_2$$CH_3$), 0.971, 0.965 (2×t, J = 7.5 Hz, ratio 1:2, 27 H, OCH_2CH_2CH_3) ppm; ^{13}C NMR ([D_6]DMSO): δ = 170.8, 170.0, 162.0, 161.8, 161.7, 143.5, 142.1, 142.0, 135.94, 135.89, 135.5, 129.8, 123.9, 123.8, 123.5, 118.6, 77.2, 77.1, 74.8, 32.6, 29.7, 25.1, 22.8, 22.7, 10.04, 9.97 ppm.

General Procedure for the Synthesis of Dodecaamino Tris-calixarene Dendrons. A suspension of dodecanitro dendron (0.02 mmol) and Raney/Ni in DMF (4 mL) was stirred under H_2 at atmospheric pressure and room temperature for 24–48 h. After filtering on celite, the solvent was evaporated and the residue treated with the appropriate solvent system to obtain a precipitate.

TAPA Dodecaamino Tris-calixarene Dendron (12).Off-white powder from $CHCl_3$/petroleum ether (0.025 g, 53% yield), mp >250 °C; ^{1}H NMR ([D_6]DMSO): δ = (br s, 3 H, NH), 7.47, 6.87 (2×d, J = 8.8 Hz, 12 H, 1,4-phenylene-core), 6.00, 5.99, 5.90 (3×s, 24 H, ArH-calix, ratio 1:1:2),4.22 (br s, 24 H, NH_2), 4.17, 4.16 (2×d, J = 12.5 Hz, 12 H, $ArCH_2Ar$), 3.75, 3.65, 3.59 (3×t, J = 7.5 Hz, 24 H OCH_2, ratio 1:1:2), 2.78, 2.77 (2×d, J = 12.5 Hz, 12 H, $ArCH_2Ar$), 2.31 (t, J = 7.3 Hz, 6 H, CH_2CO), 2.15 (quintuplet, J = 7.3 Hz, 6 H, CH_2CH_2CO), 1.85–1.78 (m, 18 H, CH_2CH_3), 0.89, 0.88 (2×t, J = 7.3 Hz, 27 H, CH_3, ratio 1:2) ppm; ^{13}C NMR ([D_6]DMSO): δ = 170.4, 147.6, 147.4, 142.0, 134.6, 134.3, 134.1, 134.0, 123.5, 120.3, 114.2, 114.1, 76.4, 76.1, 73.9, 33.1, 30.9, 25.5, 22.6, 22.5, 10.3, 10.2 ppm. ESI MS *m/z* 1164.4 $(M + 2H)^{2+}$, 2358.5 $(M + H + MeOH)^+$.

TAPB Dodecaamino Tris-calixarene Dendron (14). Off-white powder from MeOH (0.035 g, 74% yield), mp >250 °C. ^{1}H NMR ([D_6]DMSO): δ = (br s, 3 H, NH), 7.80–7.68 (m, 15 H, ArH-core), 6.00, 5.99, 5.91 (3×s, ratio 1:1:2, 24 H, ArH-calix), 4.4–4.0 (hump, 24 H, NH_2), 4.19, 4.17 (2×d, J = 11.0 and 10.5 Hz, ratio 1:1, 12 H, axial $ArCH_2Ar$), 3.78, 3.66, 3.61 (3×t, J = 7.3 Hz, ratio 1:1:2, 24 H, OCH_2), 2.80, 2.78 (2×d, J = 12.1 Hz, ratio 1:1, 12 H, $ArCH_2Ar$), 2.39 (t, J = 7.3 Hz, 6 H, CH_2CO), 2.20 (quintuplet, J = 7.3 Hz, 6 H, CH_2CH_2CO), 1.85 (m, 18 H, $OCH_2CH_2CH_3$), 0.92, 0.91 (2×t, J = 7.3 Hz, ratio 1:2, 27 H, $OCH_2CH_2CH_3$) ppm; ^{13}C NMR ([D_6]DMSO): δ = 170.9, 147.6, 147.5, 142.3, 142.1, 142.0, 134.6, 134.14, 134.09, 127.3, 119.3, 114.2, 114.1, 76.4, 76.2, 73.9, 33.2, 30.9, 25.5, 22.7,

22.6, 21.1, 10.4, 10.3 ppm. ESI MS *m/z* 1205.7 $(M + H + Na)^{2+}$, 2421.2 $(M + H + MeOH)^{+}$, 2443.1 $(M + Na + MeOH)^{+}$.

TAPT Dodecaamino Tris-calixarene Dendron (16). Brownish-red powder from MeOH (0.042 g, 88% yield); mp >250 °C. ^{1}H NMR ([D_6]DMSO): δ = 10.28 (s, 3 H, NH), 8.68, 7.87 (2×d, J = 8.5 Hz, 6 H each, 1,4-phenylene core), 6.03, 6.01, 5.91 (3×s, ratio 1:1:2, 24 H, ArH calix), 4.24 (br s, 24 H, NH_2), 4.21, 4.18 (2×d, J = 12.2 Hz, 6 H each, axial $ArCH_2Ar$), 3.81, 3.68, 3.62 (3×t, J = 7.5 Hz, ratio 1:1:2, 24 H, OCH_2), 2.81, 2.79 (2×d, J = 12.2 Hz, 6 H each, equatorial $ArCH_2Ar$), 2.45 (t, J = 7.0 Hz, 6 H, CH_2C=O), 2.23 (quintuplet, J = 7.0 Hz, 6 H, CH_2CH_2C=O), 1.89–1.82 (m, 18 H, $OCH_2CH_2CH_3$), 0.926, 0.920 (2×t, J = 7.5 Hz, ratio 1:2, 27 H, $OCH_2CH_2CH_3$) ppm; ^{13}C NMR ([D_6]DMSO): δ = 171.4, 170.1, 147.6, 147.4, 143.6, 142.3, 142.1, 142.0, 134.7, 134.1, 134.0, 129.7, 129.6, 118.6, 114.2, 114.1, 76.4, 76.1, 73.8, 33.3, 30.8, 25.3, 22.7, 22.5, 10.4, 10.3 ppm. ESI MS *m/z* 1196.5 $(M + 2H)^{2+}$, 2392 $(M + H)^{+}$.

***N*,*N'*-Bis(2-bromoacetil)-(1*S*,2*S*)-1,2-cicloesandiammide (17).** This compound was synthesized by a slight modification of a known procedure.[[82]] To a chilled (–15 °C) solution of (1*S*,2*S*)-*trans*-1,2-cyclohexanediamine (380 mg, 3.33 mmoli) and triethylamine (674 mg, 6.66 mmoli) in dry CH_2Cl_2 (20 mL), bromoacetylbromide (1.35 g, 6.71 mmoli) in CH_2Cl_2 (1 mL) was added dropwise under stirring. The reaction mixture was allowed to warm slowly to room temperature, while stirring was continued for 12 h. The mixture was transferred into a separatory

funnel and extracted with 1N HCl, then with brine. The organic layer was then dried over anhydrous Na_2SO_4 and concentrated. The residue was triturated with a very little amount of CH_2Cl_2, and collected by filtration as a white solid (0.87 g, 75%); mp 236.1-236.8 °C;^{1}H NMR δ 6.62 (s, 2 H), 3.81 (s, 4 H), 3.72 (br s, 2 H), 2.07 (d, J = 10.2 Hz, 2 H), 1.80 (br s, 2 H), 1.33 (m, 4 H); ^{13}C NMR δ 166.4, 54.2, 32.0, 28.8, 24.5 ppm.

***N*-{p-tert-Butyl-25,26,27-tripropoxy-28(carbonylmethoxy)calix[4]arene}-*N′*-(2-bromoacetyl)-(1S,2S)-1,2-cyclohexanediamide (18).** A mixture of tripropoxycalix[4]arene (176 mg, 0.227 mmol) and NaH (10 mg, 0.455 mmoli) in dry THF (20 mL), was stirred at room temperature for 10 min. After addition of solid *N*,*N′*-bis(2-bromoacetyl)-(1*S*,2*S*)-1,2-cyclohexanediamide (40 mg, 0.112 mmoli), the mixture was heated to reflux for 36 h. Upon cooling, the solvent was evaporated to afford a residue, which was partitioned between 1 N HCl and $CHCl_3$. The organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography (SiO_2, eluent *n*-hexane/AcOEt (5:1 to 1:2, v/v), to give diamide as an off-white solid (67 mg, 50%). ^{1}H NMR ($CDCl_3$) δ6.81–6.71 (m, 8 H), 5.59 (s, 1 H), 4.89 (d, J = 13.5 Hz, 1 H), 4.68 (d, J = 2 Hz, 1 H), 4.66 (s, 1 H), 4.48 (d, J = 13.0 Hz, 1 H), 4.404, 4.396 (2×d, J = 12.5 Hz, ratio 1:1, 2 H), 4.31 (d, J = 15.5 Hz, 1 H), 3.90–3.80 (m, 6 H), 3.79–3.71 (m, 2 H), 3.49, 3.27 (dt, J = 10.7, 2.7 Hz, ratio 1:1, 2 H), 3.18, 3.17, 3.12, 3.11 (4×d, J = 12.0–13.0 Hz, ratio 1:1:1:1, 4 H), 2.51 (d, J = 12.6 Hz, 1 H), 2.09–1.97 (m, 8 H), 1.88–1.78 (m, 2 H), 1.51–1.36 (m, 4 H), 1.11, 1.09,

1.06, 1.03 (4×s, ratio 1:1:1:1, 36 H), 1.01, 0.99, 0.97 (3×t, J = 7.0 Hz, ratio 1:1:1, 9 H), ppm; ^{13}C NMR APT ($CDCl_3$) δ 169.6, 169.4 (C=O), 153.8, 153.7, 153.5, 152.9 (*ipso*-Ar), 144.7, 144.4, 144.3, 144.2 (*p*-Ar), 134.0 (×2), 133.9, 133.7, 133.64, 133.62, 133.4, 133.6 (*o*-Ar), 125.3, 125.2, 125.1, 125.0 (×3), 124.8 (×2) (*m*-Ar), 77.0, 76.8, 72.5 (OCH_2), 60.1, 54.1 (CH), 48.3 ($BrCH_2C$=O), 33.84, 33.82, 33.79, 33.77 ($C(CH_3)_3$), 31.7 ($ArCH_2Ar$), 31.49, 31.48, 31.42, 31.38 ($C(CH_3)_3$), 31.08, 31.06, 30.8 ($ArCH_2Ar$), 28.9, 24.5, 24.4 (cyclohexyl-CH_2), 23.39, 23.31, 23.30 ($OCH_2CH_2CH_3$), 10.41, 10.38, 10.31 ($OCH_2CH_2CH_3$), ppm.

***N,N′*-Bis{p-nitro-25,26,27-tripropossi-28-(3-carbonilpropossi) calix[4]arene)}-(1*R*,2*R*)-1,2-cicloesandiammide (19).** The acyl chloride **10** referred to the previous preparation was dissolved in anhydrous CH_2Cl_2 (5 mL) and cooled to -10 °C. To this solution was added via cannula a mixture of (1R,2R)-(-)-1,2-diaminocyclohexane (21 mg, 0.18 mmol) and triethylamine (38 mg, 0.37 mmol) in anhydrous CH_2Cl_2 (2 mL). The reaction mixture was kept stirring for overnight at ambient temperatures. After turning off the reaction by addition of water (5 mL), the product was extracted with CH_2Cl_2 and dried over Na_2SO_4. The solid obtained by evaporation of the solvent was redissolved in CH_2Cl_2 (5 mL) containing triethylamine (0.1 mL) and brought to dryness. The crude was then subjected to column chromatography (SiO_2, cyclohexane-AcOEt 2:1, v/v) to give the pure diamide in the form of a pale yellow solid (225 mg, 71%), mp 247-250 ° C. ^{1}H NMR δ 7.74 (s, 4 H),

7.72 (s, 4 H), 7.35 (s, 4 H), 7.29 (s, 4 H), 6.15 (bd, 2 H), 4.52 (d, J = 14.0 Hz, 4 H), 4.50 (d, J = 13.6 Hz, 2 H), 4.48 (d, J = 14.3 Hz, 2 H), 4.05-3.96 (m, 12 H), 3.90 (t, J = 7.2 Hz , 4 H), 3.60 (bt, 2 H), 3.41 (d, J = 14.4 Hz, 4 H), 3.39 (d, J = 14.0 Hz, 2 H), 3.38 (d, J = 13.5 Hz, 2 H), 2:22 to 2:11 (m, 8 H), 2.01 (d, J = 11.7 Hz, 2 H), 1.95-1.85 (m, 12 H), 1.76 (d, J = 7.7 Hz, 2 H), 1.32-1.18 (m, 4 H), 1.06 (t, J = 7.5 Hz, 6 H), 0.98 (t, J = 7.4 Hz, 12 H) ppm;^{13}C NMR APT ($CDCl_3$) δ 172.2 (C=O), 162.12, 162.10, 161.3, 161.1 (*ipso*-Ar), 142.76, 142.74 (*p*-Ar), 135.9, 135.8, 135.06, 135.02, 134.98 (*o*-Ar), 124.34, 124.26, 124.22, 123.60, 123.55, 123.49 (*m*-Ar), 77.8, 77.69, 77.65, 75.1 (OCH_2), 53.9 (CH), 32.4, 32.2, 31.1 ($ArCH_2Ar$), 25.9, 24.5 (cyclohexyl-CH_2), 23.3, 23.2 ($OCH_2CH_2CH_3$), 10.3, 10.0 ($OCH_2CH_2CH_3$) ppm.MALDI *m/z* = 1734.8 $[M+Na]^+$.

The (1S,2S)-1,2-enantiomeric cicloesandiammide **22** (mp 195-200 °C) was obtained in a similar manner, and with a yield comparable to amidation of '(1S,2S)-(+)-1,2-cyclohexanediamine. The NMR spectra of **19** are exactly similar to those of its mirror image **22**.

***N,N'*-Bis(5,11,17,23-tetra-amino-25,26,27-tripropoxy-28-[3-carbonylpropoxy]calix[4]arene)-(1R,2R)-1,2-cyclohexandiamide(20).**

A suspension of diamide **19** (50 mg, 0029 mmol) and Ni/Raney in THF (10 mL) was stirred at room temperature for 18 h under pressure of H_2 (1 atm), and then filtered over celite. The solvent was evaporated under reduced pressure, and the solid residue was triturated with cyclohexane and collected by filtration to the pump to obtain the octa-amine **20** (37 mg,

85%). ^{1}H NMR δ 6:09, 6.08, 6.03, 5.99 (4 × s, 4 H each), 5.80 (d, J = 7.3 Hz, 2 H), 4.30 (d, J = 13.3 Hz, 4 H), 4.27 (d, J = 13.2 Hz, 2 H), 4.26 (d, J = 13.2 Hz, 2 H), 3.78-3.69 (m, 16 H), 3.61 (bs, 2 H), 2.92 (d, J = 13.2 Hz, 8 H), 2.2-1.7 (m, 24 H), 1:33 to 1:18 (m, 4 H), 0.96, 0.94, 0.93 (3 × t, J = 7.0 Hz, 6 H each) ppm. MALDI *m/z* = 1495 $[M+Na]^{+}$.

The octa-enantiomeric amine **23** was obtained in a similar manner, and with a yield comparable to reduction of the precursor of the octa-nitro-(1S,2S)-1,2-cicloesandiammide. The NMR spectra of **20** are exactly similar to those of its mirror image **23**.

***N,N′*-Bis{p-amino-25,26,27-tripropossi-28-(3-carbonilpropossi)calix[4]arene)}(1*R*,2*R*)-1,2-cicloesandiammide otta-cloridrato (21).** The octa-hydrochloride **21** was prepared by addition of an excess of 4M HCl in dioxane to a solution of the octa-amine **20** in CH_2Cl_2, and subsequent evaporation of the solvent at low pressure. ^{1}H NMR (D_2O, dioxane (δ = 3.53 ppm) as an internal standard) δ 6.67, 6:47 (2 × s, 8 H each), 4.29 (d, J = 13.6 Hz, 2 H), 4.28 (d, J = 13.6 Hz, 2 H), 4.26 (d, J = 13.6 Hz, 2 H), 4.24 (d, J = 13.5 Hz, 2 H), 3.82-3.64 (m, 16 H), 3.39 (Br s, 2 H), 3.15 (d, J = 13.9 Hz, 8 H), 2.12 (m, 4 H), 2.00 (m, 4 H), 1.74-1.65 (m, 16 H), 1.54 (bs, 2 H), 1.10 (bs, 4 H), 0782 (t, J = 7.3, 6 H), 0775 (t, J = 7.3, 6 H), 0765 (t, J = 7.4, 6 H) ppm; ^{13}C NMR (D_2O, dioxane (δ = 66.3 ppm) as internal standard) δ 174.6, 156.6, 156.2, 156.09, 156.05, 136.6 (× 2), 136.52, 136.46, 136.14, 136.11, 135.92, 135.87, 124.2, 124.03, 124.00,

123.8, 122.4, 122.3 , 122.0, 121.8, 77.06, 77.01, 76.9, 74.1, 52.7, 32.4, 31.4, 30.0, 25.6, 23.9, 22.7, 22.6, 9.7, 9.5 ppm.

The enantiomeric octa-hydrochloride **24** was obtained in a similar manner starting from the octa-amine **23**. The NMR spectra of the enantiomers **21** and **24** are exactly superimposable, while their CD spectra are symmetrical and have opposite sign.

5,11,17,23-Tetra-*tert*-butyl-25-[(S)-(-)-ethoxycarbonyl-methoxy]-26,27,28-tripopoxycalix[4]arene (25). A suspension of 5,11,17,23-Tetra-*tert*-butyl-25,26,27-tripropoxy-28-hydroxy-calix[4]arene **6** (2 g, 2.58 mmol), methyl (R)-(+)-*O*-tosyl-lactate (2.67 g, 10.32 mmol) and NaOMe (0.54 g, 10 mmol) in dry MeCN (100 ml) was refluxed for 24 h. TLC analysis (cyclohexane-CH_2Cl_2 4:1, v/v) showed the disappearance of the starting calixarene while eluting with hexane/ethyl acetate 8:1, v/v was revealed the presence of a new spot due to the formation of the ester derivative. The solvent was evaporated and the residue was triturated with CH_2Cl_2, organic phase was filtered and evaporated under reduced pressure. The work-up without water is necessary to avoid the hydrolysys of the ester. The oily residue was purified by column chromatography (CC, SiO_2, hexane-ethyl acetate 99:1 to 95:5, v/v) to give ester as a white solid (1.76 g, 80% yield); mp 110-112 °C (MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.09−7.08 (m, 4 H), 6.57 (ABq, J = 2.7 Hz, 2 H), 6.53 (ABq, J = 2.7 Hz, 2 H), 4.64 (d, J = 13.0 Hz, 1 H), 4.48 (d, J = 12.5 Hz, 1 H), 4.47 (d, J = 12.5 Hz, 1 H), 4.43 (q, J = 7.0 Hz, 1 H), 4.42 (d, J = 12.0 Hz, 1 H), 4.05−3.96

(m, 4 H), 3.77−3.69 (m, 2 H), 3.73 (s, 3 H), 3.21 (d, *J* = 12.5 Hz, 1 H), 3.17 (d, *J* = 12.5 Hz, 1 H), 3.16 (d, *J* = 12.5 Hz, 1 H), 3.12 (d, *J* = 13.0 Hz, 1 H), 2.23−2.12 (m, 4 H), 1.98−1.91 (m, 2 H), 1.65 (d, *J* = 7.0 Hz, 3 H), 1.33 (s, 18 H), 1.09 (t, *J* = 7.0 Hz, 3 H), 0.999 (t, *J* = 7.0 Hz, 3 H), 0.996 (t, *J* = 7.0 Hz, 3 H) 0.94 (s, 9 H), 0.90 (s, 9 H); ^{13}C NMR APT ($CDCl_3$) δ 172.7, 154.5, 154.4, 152.9, 150.6, 144.4, 144.3, 143.8, 135.4, 135.2, 134.9, 132.6, 132.29, 132.21, 125.4, 125.38, 125.32, 125.2, 124.6, 124.5, 124.4, 124.3, 79.0, 77.4, 77.2, 77.0, 76.7, 76.54, 76.51, 51.5, 33.9, 33.6, 31.6, 31.4, 31.3, 31.2, 31.1, 31.0, 23.4, 23.05, 23.02, 22.6, 18.1, 14.0, 10.6, 10.0, 9.9 ppm.MALDI *m/z* = 883 $[M+Na]^+$.

5,11,17,23-Tetra-nitro-25-[(S)-(-)-ethoxycarbonyl-methoxy]-26,27,28-tripopoxycalix[4]arene (26). Fuming HNO_3 (18.1 mL) was lowly added dropwise to a chilled (–15 °C) and stirred solution of 5,11,17,23-Tetra-*tert*-butyl-25-[(S)-(-)-ethoxycarbonyl-methoxy]-26,27,28-tripopoxycalix[4]arene **25** (1.56 g, 1.81 mmol) in CH_2Cl_2/AcOH(1:1 v/v, 60 mL). The reaction mixture was allowed to slowly warm at room temperature, and stirring was continued for 12 h. The mixture was poured into water (100 mL), and extracted with CH_2Cl_2 (4 × 25 mL). The combined organic layers were washed with water (2 × 50 mL), then with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography (a gradient of hexane-CH_2Cl_2, 1:1 to 100% CH_2Cl_2, v/v, and CH_2Cl_2-EtOAc, 99:1, v/v) to give the tetra-nitro derivative as a pale yellow solid (1.082 g, 73%); mp 232-234 °C (MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.175 (AB q, *J* = 2.5 Hz, 2 H),

8.171, 7.01, 6.96 (3×s, 2 H each), 4.66 (d, J = 14.5 Hz, 1 H), 4.530 (d, J = 14.0 Hz, 1 H), 4.526 (d, J = 14.0 Hz, 1 H), 4.48 (d, J = 14.0 Hz, 1 H), 4.44 (q, J = 7.0 Hz, 1 H), 4.22–4.09 (m, 4 H), 3.77 (dt, J = 7.0 Hz, 2 H), 3.75 (s, 3 H), 3.47 (d, J = 15.0 Hz, 1 H), 3.41 (d, J = 14.5 Hz, 2 H), 3.40 (d, J = 13.5 Hz, 1 H), 1.97–1.85 (m, 6 H), 1.62 (d, J = 7.0 Hz, 3 H), 1.12, 0.93, 0.92 (3×t, J = 7.0 Hz, 3 H each) ppm; ^{13}C NMR APT ($CDCl_3$) δ 170.9 (C=O), 162.9, 160.3, 158.0 (Ar_{ipso}), 143.3, 143.0, 142.8 (Ar_{para}), 136.8, 136.7, 136.4, 134.8, 134.1, 134.0, 133.8 (Ar_{ortho}), 125.3, 125.2, 125.03, 124.99, 123.03 (×2), 122.98, 122.8 (Ar_{meta}), 79.2 (O*C*HCH$_3$), 78.0, 77.6, 77.4 (O*C*H$_2$CH$_2$CH$_3$), 52.4 (OCH$_3$), 31.7, 31.1 (ArCH$_2$Ar), 23.4, 23.2, 23.0 (OCH$_2$*C*H$_2$CH$_3$), 18.0 (OCH*C*H$_3$), 10.6, 9.65, 9.61 (OCH$_2$CH$_2$*C*H$_3$) ppm. MALDI m/z = 838 $[M+Na]^+$.

5,11,17,23-Tetra-nitro-25-[(S)-(-)-carboxyethoxy]-26,27,28-tripopoxycalix[4]arene (27). A suspension of the above ester (1.112 g, 1.32 mmol) in THF/MeOH (4:3, v/v, 34 mL) was stirred for 24 h at room temperature in the presence of NaOH (0.448 g in 3 mL of water). After evaporation of volatiles under vacuum, the residue was acidified with aqueous 1N HCl, extracted with CH_2Cl_2 (3 × 20 mL), and dried over anhydrous Na_2SO_4. The solution was concentrated to dryness to afford the desired acid (1.01 g, 92% yield); mp 235-238 °C (CH_2Cl_2/MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ= 8.084 and 8.072 (ABq, , J = 2.5 Hz, 2H), 8.067 and 8.053 (ABq, , J = 2.5 Hz, 2H), 7.12 (s, 2H), 7.08 (s, 2H), 4.62 (d, J = 14 Hz, 1H), 4.59 (q, J = 7.0 Hz, 1H), 4.54 (d, J = 14 Hz, 1H), 4.53

(d, *J* = 13.5 Hz, 1H), 4.49 (d, *J* = 13.5 Hz, 1H), 4.20-4.07 (m, 4H), 3.88-3.77 (m, 2H), 3.46 (d, *J* = 14 Hz, 1H), 3.44 (d, *J* = 13.5 Hz, 1H), 3.42 (d, *J* = 13.5 Hz, 1H), 3.41 (d, *J* = 14 Hz, 1H), 1.93-1.86 (m, 6H), 1.64 (d, *J* = 7.0 Hz, 3H), 1.10, 0.93, 0.91 (3xt, *J* =7.5 Hz, 3H each) ppm; ^{13}C NMR APT ($CDCl_3$) δ= 174.8, 162.5, 162.3, 160.6, 157.7, 143.4, 143.0, 142.9, 142.8, 136.61, 136.56, 136.4, 136.1, 134.9, 134.5, 134.3, 134.1, 125.2, 125.1, 125.0, 124.9, 123.3, 123.2, 123.1, 122.0, 78.5, 78.1, 77.8, 77.6, 31.71, 31.65, 31.1, 24.4, 24.3, 23.4, 23.1, 17.9, 10.5, 9.6 ppm.MALDI *m/z* = 824 $[M+Na]^+$.

General Procedure for the Synthesis of Octanitro Bis-calixarene. Freshly prepared acid chloride **28**, generated from **27** (0.250 g, 0.31 mmol) was dissolved in dry CH_2Cl_2 (4.5 mL) and cooled to –10 °C. To this solution a mixture of diamine compound **29**, **30**, **31**, **32** equiv.) and TEA (1 equiv.) in dry CH_2Cl_2 (3 mL) was added via cannula. The reaction mixture was stirred at room temperature for additional 12–36 h (^{1}H NMR monitoring) and concentrated. After evaporation of the solvent, the residue was acidified with 0.1 M HCl (5 mL) and extracted with CH_2Cl_2 (3×5 mL). The organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. The solid residue was further purified by CC.

(S,S)-*N,N′*-Bis(5,11,17,23-tetra-nitro-25,26,27-tripropoxy-28-(1-carbonyl-ethoxy)calix[4]arene)-1,4-phenylendiamide (33). CC (Hexane/EtOAc, gradient, 2:1 to 1:2) provided a brownish solid (128 mg 98% yield); mp >260 °C;^{1}H NMR ([D_6] acetone): δ= 9.72 (s, 2H, NH),

8.35 (d, *J* = 2.5 Hz, AB system, 2H, ArH-calix), 8.33 (2xd, *J* = 2.5 Hz, AB system, 4H, ArH-calix), 8.28 (d, *J* = 2.5 Hz, AB system, 2H, ArH-calix),7.58 (s, 4H, benzene core), 7.05-7.04 (3xd, *J* = 2.5 Hz, AB system, 6H, ArH-calix), 7.01 (d, *J* = 2.5 Hz, AB system, 2H, ArH-calix), 4.82 (d, *J* = 14.5 Hz, 2H, axial $ArCH_2Ar$), 4.71 (d, *J* = 14 Hz, 2H, axial $ArCH_2Ar$), 4.68 (q, *J* = 6.5 Hz, 2H, CH lactic acid), 4.63 (d, *J* = 14 Hz, 2H, axial $ArCH_2Ar$), 4.62 (d, *J* = 14 Hz, 2H, axial $ArCH_2Ar$), 4.38-4.27 (m, 8H, OCH_2), 3.90 (t, *J* = 6.5 Hz, 4H, OCH_2), 3.74 (d, *J* = 13.5 Hz, 2H, equatorial $ArCH_2Ar$), 3.71 (d, *J* = 13.5 Hz, 2H, equatorial $ArCH_2Ar$), 3.70 (d, *J* = 14 Hz, 2H, equatorial $ArCH_2Ar$), 3.58 (d, *J* =14.5 Hz, 2H, equatorial $ArCH_2Ar$), 2.09-1.96 (m, 12H, OCH_2CH_2), 1.71 (d, *J* = 6.5, 6H, CH_3 lactic acid), 1.48 (t, *J* = 7.5, 6H, $OCH_2CH_2CH_3$), 0.978 (t, *J* = 7.5, 6H, $OCH_2CH_2CH_3$), 0.878 (t, *J* = 7.5, 6H, $OCH_2CH_2CH_3$) ppm; ^{13}C ([D_6] acetone): δ= 169.6 (C=O), 164.8 , 164.7 , 162.3 , 160.1 (Ar_{ipso}), 144.8 , 144.47 , 144.43 , 144.3 (Ar_{para}), 138.0 , 138.96 , 138.82 , 138.63 , 137.0 , 136.8 , 136.2 , 136.1 (Ar_{meta}), 126.63 , 126.60 (x2), 126.5 , 124.39 , 124.30 (x2), 124.19 (Ar_{ortho}), 121.6 (benzene core), 83.30 (CH lactic acid), 79.4 , 79.06 , 79.04 (OCH_2), 32.87 , 32.73 , 32.06 , 32.01, ($ArCH_2Ar$), 24.77 , 24.73 , 24.60 (OCH_2CH_2), 18.98 (CH_3 lactic acid), 11.60 , 11,69 ($OCH_2CH_2CH_3$) ppm. MALDI *m/z* = 1701.3 $[M+Na]^+$.

Trans-(S,S)-*N,N'*-Bis(5,11,17,23-tetra-nitro-25,26,27-tripropoxy-28-(-1-carbonyl-ethoxy)calix[4]arene)-2,5.dimethyl-piperazinyldiamide (34).CC (Hexane/EtOAc, gradient, 1:1 to 1:4) provided a brownish solid (36 mg 25% yield); mp >260 °C; ^1H NMR (TCE): δ 8.12 (m, 8H, ArH

calix), 6.88 (m, 8H, ArH calix), 4.7 (m, 4H, axial $ArCH_2Ar$), 4.58 (m, 4H, axial $ArCH_2Ar$), 4.58 (m, 2H, CH lactic acid), 4.16-4.22 (m, 8H, OCH_2), 3.85 (m, 4H, OCH_2), 3.3-3.5 (m, 8H, equatorial $ArCH_2Ar$), 3.5 (m, 4, CH_2 piperazine), 3.3 (m, 2H, CH piperazine), 1.92 (m, 12 H, OCH_2CH_2), 1.64 (d, J = 6.5, 6H, CH_3 lactic acid), 1.16 (m, 6H, CH_3 piperazine), 1.04 (m, 6H, $OCH_2CH_2CH_3$), 0.98-0.95 (m, 12H, $OCH_2CH_2CH_3$) ppm;^{13}C NMR ($C_2D_2Cl_4$, 22 °C) δ 169.0, 167.9, 162.9, 160.4, 142.6, 142.3, 136.8, 136.6, 135.8, 133.9, 133.7, 124.9, 122.6, 77.9, 77.5, 77.3, 47.7, 43.7, 40.0 (broad, CH_2 piperazina), 31.0 (broad), 29.5, 23.2, 23.1, 22.8, 19.0 (broad), 10.5, 9.5 ppm. MALDI m/z = 1706.8 $[M+Na]^+$.

(S,S)-*N,N′*-Bis(5,11,17,23-tetra-nitro-25,26,27-tripropoxy-28-(-1-carbonyl-ethoxy)calix[4]arene)-piperazinyldiamide (35). CC (Hexane/EtOAc, gradient, 1:1 to 1:4) provided a brownish solid (42 mg 31% yield); mp>260 °C;^{1}H NMR (TCE): δ= 8.17 (d, J = 3.0 Hz, AB system, 2H, ArH-calix), 8.14 (d, J = 2.5 Hz, AB system, 2H, ArH-calix), 8.13 (d, J = 2.5 Hz, AB system, 2H, ArH-calix), 8.07 (d, J = 2.5 Hz, AB system, 2H, ArH-calix), 6.93 (d, J = 3.0 Hz, AB system, 2H, ArH-calix), 6.90 (d, J = 2.5 Hz, AB system, 2H, ArH-calix), 6.77 (d, J = 3.0 Hz, AB system, 2H, ArH-calix), 6.76 (d, J = 2.5 Hz, AB system, 2H, ArH-calix), 4.74-4.68 (m, 4H, axial $ArCH_2Ar$), 4.57-4.51 (m, 4H, axial $ArCH_2Ar$), 4.549, (q, J = 6.5 Hz, 2H, CH lactic acid), 4.23-4.15 (m, 8H, OCH_2), 3.848 (t, J = 6.5 Hz, 4H, OCH_2), 3.48-3.27 (m, 8H, equatorial $ArCH_2Ar$), 3.35 (s broad, 8H, CH_2 piperazine), 1.87-1.94 (m, 12H, OCH_2CH_2), 1.61 (d, J =

6.5, 6H, CH_3 lactic acid), 1.15 (t, J = 7.5, 6H, $OCH_2CH_2CH_3$), 0.98 and 0.95 (t, J = 7.5, 12H, $OCH_2CH_2CH_3$) ppm.MALDI m/z = 1678.8 $[M+Na]^+$.

(S,S)-N,N′-Bis(5,11,17,23-tetra-nitro-25,26,27-tripropoxy-28-(1-carbonyl-ethoxy)calix[4]arene)-trans-1,4-diaminocyclohexandiamide (36). CC (Hexane/EtOAc, gradient, 2:1 to 1:2) provided a brownish solid (77 mg 60% yield); mp>280 °C;^{1}H NMR ([D_6] acetone): δ= 8.33 (d, J = 2.5 Hz, AB system, 2H, ArH-calix), 8.32 (d, J = 2.5 Hz, AB system, 2H, ArH-calix), 8.29 (2xd, J = 2.5 Hz, AB system, 4H, ArH-calix), 7.15 (d, J = 7.5 Hz, 2H, NH), 7.07 (2xd, J = 2.5 Hz, AB system, 2H, ArH-calix), 7.02 (2xd, J = 2.5 Hz, AB system, 2H, ArH-calix), 4.76 (d, J = 14 Hz, 2H, axial $ArCH_2Ar$), 4.63 (d, J = 14 Hz, 2H, axial $ArCH_2Ar$), 4.62 (2xd, J = 14.5 Hz, 4H, axial $ArCH_2Ar$), 4.47 (q, J = 6.5 Hz, 2H, CH lactic acid), 4.34-4.26 (m, 8H, OCH_2), 3.90 (t, J = 6.5 Hz, 4H, OCH_2), 3.71 (d, J = 13.5 Hz, 2H, equatorial $ArCH_2Ar$), 3.70 (d, J = 13.5 Hz, 2H, equatorial $ArCH_2Ar$), 3.68 (d, J = 13.5 Hz, 2H, equatorial $ArCH_2Ar$), 3.60 (t, J = 6.5 Hz, 2H CHNH), 3.58 (d, J = 13.5 Hz, 2H, equatorial $ArCH_2Ar$), 1.96-2.1 (m, 12H, OCH_2CH_2), 1.92 (d, J = 8 Hz, 4H CH-cyclohexane), 1.82 (d, J = 8 Hz, 4H CH-cyclohexane), 1.57 (d, J = 6.5, 6H, CH_3 lactic acid), 1.14 (t, J = 7.5, 6H, $OCH_2CH_2CH_3$), 0.99 (m, 12H, $OCH_2CH_2CH_3$) ppm; ^{13}C ([D_6] acetone): δ170.3 (C=O), 164.75 , 164.72 , 162.3 , 160.35 (Ar_{ipso}), 144.5 , 144.4(x2) , 144.3 , (Ar_{para}), 139.0 , 138.9 , 138.8 , 138.6 , 137.0 , 136.8 , 136.2 , 136.1 (Ar_{meta}), 126.5 (x2) , 126.53 , 126.51 , 124.35 (x2) , 124.2 , 124.0 (Ar_{ortho}), 82.73 (CH lactic acid), 79.4 , 79.06 , 78.9 (OCH_2), 49.15

(CHNH) 32.87 , 32.70 , 32.65 , 32.57, ($ArCH_2Ar$), 32.057 , 32.018 (CH_2 cyclohexane) 24.77 , 24.71 , 24.56 (OCH_2CH_2), 19.11 (CH_3 lactic acid), 11.59 , 10,79 , 10.744 ($OCH_2CH_2CH_3$) ppm.MALDI *m/z* = 1706.8 $[M+Na]^+$.

General Procedure for the Synthesis of Octa-amino Bis-calixarene. A suspension of dodecanitro dendron (0.02 mmol) and Raney/Ni in DMF (4 mL) was stirred under H_2 at atmospheric pressure and room temperature for 24–48 h. After filtering on celite, the solvent was evaporated and the residue treated with the appropriate solvent system to obtain a precipitate.

(S,S)-*N,N′*-Bis(5,11,17,23-tetra-amino-25,26,27-tripropoxy-28-(1-carbonyl-ethoxy)calix[4]arene)-1,4-phenylendiamide (37).brownish solid;mp>280 °C;^{1}H NMR [CD_3OD] δ7.53 (s, 4 H), 6.54 (s, 4 H), 6.51, 6.46 (AB q, *J* = 2.4 Hz, 4 H), 5.74 (s, 4 H), 5.72 (s, 2 H), 5.69 (s, 2 H), 4.37–4.25 (m, 10 H), 4.01–3.82 (m, 8 H), 3.57 (t, *J* = 6.0 Hz, 4 H), 3.02 (d, *J* = 13.2 Hz, 2 H), 2.94–2.86 (overlapping d, 6 H), 1.98–1.78 (m, 12 H), 1.48 (d, *J* = 6.2 Hz, 6 H), 1.09 (t, *J* = 7.3 Hz, 6 H), 0.88 (t, *J* = 7.1 Hz, 6 H), 0.72 (t, *J* = 7.0 Hz, 6 H) ppm; ^{13}C NMR [CD_3OD] δ 172.5, 151.9 (×2), 150.6, 147.7, 142.1, 142.0, 141.9, 141.2, 138.60, 138.55, 138.48, 138.3, 138.2, 135.9, 135.6, 135.4, 134.9, 122.1, 118.0, 117.9, 117.4, 117.3, 117.0, 81.7, 78.0, 77.5 (×2), 32.9, 32.6, 32.2 (×2), 24.6, 24.2, 24.0, 17.9, 11.4, 10.5, 10.4 ppm.MALDI *m/z* = 1460.9 $[M+Na]^+$.

(S,S)-*N,N′*-Bis(5,11,17,23-tetra-amino-25,26,27-tripropoxy-28-(1-carbonyl-ethoxy)calix[4]arene)-trans-1,4-diaminocyclohexandiamide (40). mp>280 °C;^{1}H NMR [CD_3OD] δ 6.55, 6.54, 6.53, 6.51 (4×d, J = 2.7 Hz, 2 H each), 5.74 (s, 4 H), 5.65 (ABq, J = 2.7 Hz, 4 H), 4.33 (d. J = 13.0 Hz, 4 H), 4.27 (d. J = 13.2 Hz, 2 H), 4.26 (d. J = 13.3 Hz, 2 H), 4.07 (q, J = 6.5 Hz, 2 H), 3.97–3.82 (m, 4 H), 3.87 (t, J = 8.2 Hz, 4 H), 3.64 (bs, 2 H), 3.57 (t, J = 6.7 Hz, 4 H), 2.96 (d, J = 13.8 Hz, 2 H), 2.92 (d, J = 13.4 Hz, 2 H), 2.91 (d, J = 13.6 Hz, 2 H), 2.88 (d, J = 14.1 Hz, 2 H), 1.98–1.79 (overlapping m, 16 H), 1.35 (d, J = 6.5 Hz, 6 H), 1.28 (bs, 4 H), 1.11, 0.90, 0.87 (3×t, J = 7.5 Hz, 6 H each) ppm; ^{13}C NMR [CD_3OD] δ 173.8, 152.05, 152.03, 150.8, 147.9, 142.03, 141.97, 141.6, 140.6, 138.6 (×2), 138.4, 138.3, 135.8, 135.3, 135.0 (×2), 118.0, 117.4, 117.1, 81.1, 78.0, 77.5 (×2), 33.0, 32.7, 32.4, 32.2, 24.7, 24.3, 24.1, 18.0, 11.5, 10.07, 10.06 ppm.MALDI m/z = 1466.9 $[M+Na]^+$.

General Procedure for the Synthesis of Dodecanitro Tris-calixarene. Freshly prepared acid chloride **28**, generated from **27** (0.250 g, 0.31 mmol) was dissolved in dry CH_2Cl_2 (4.5 mL) and cooled to –10 °C. To this solution a mixture of triamine compound **2**, **3**, **5** (6 equiv.) and TEA (1 equiv.) in dry CH_2Cl_2 (3 mL) was added via cannula. The reaction mixture was stirred at room temperature for additional 12–36 h (^{1}H NMR monitoring) and concentrated. After evaporation of the solvent, the residue was acidified with 0.1 M HCl (5 mL) and extracted with CH_2Cl_2 (3×5 mL). The organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. The solid residue was further purified by CC.

TAPA-Dodecanitro-Tris(calyx[4]arene) Dendron (41)

CC (Hexane/EtOAc, gradient, 3:2 to 2:3) provided a brownish solid (66 mg 72% yield), mp 245-247 °C. ^{1}H NMR [$(CD_3)_2CO$] δ 9.30 (s, 3 H), 8.36-8.30 (m, 12 H), 7.55 and 6.94 (AX, J = 8.7 Hz, 12 H), 7.06-7.02 (m, 12 H), 4.86 (d, J = 14.3 Hz, 3 H), 4.73-4.69 (m, 6 H), 4.63 (d, J = 13.8 Hz, 6 H), 4.36 (dd, J = 9.3, 7.8 Hz, 6 H), 4.31 (t, J = 7.8 Hz, 6 H), 3.9 (t, J = 6.7 Hz, 6 H), 3.75, 3.72, 3.71, 3.61 (4xd, J = 14.0-14.3 Hz, 3 H each), 2.09-1.98 (m, 18 H), 1.73 (d, J = 6.4 Hz, 9 H), 1.15, 0.97, and 0.89 (3xt, J = 7.4 Hz, 9 H each) ppm; ^{13}C NMR [$(CD_3)_2CO$] δ 169.6, 169.5, 164.83, 164.79, 162.3, 160.3, 145.9, 144.46, 144.46, 144.43, 144.35, 139.02, 138.99, 138.8, 138.7, 137.0, 136.8, 136.24, 136.17, 135.04, 134.96, 126.63, 126.56, 125.5, 124.3, 124.2, 122.5, 122.4, 83.29, 83.25, 79.4, 79.1, 33.0, 32.8, 32.07, 32.02, 24.78, 24.75, 24.6, 19.1, 11.6, and 10.7 ppm. MALDI m/z = 2667 $[M+Na]^+$.

TAPB-Dodecanitro-Tris(calyx[4]arene) Dendron (43)

CC (Hexane/EtOAc, gradient, 3:2 to 1:4) provided a brownish solid (101 mg 77% yield), mp >280 °C. ^{1}H NMR [$(CD_3)_2CO$] δ9.43 (s, 3 H), 8.36, 8.34, 8.33, 8.30 (4xd, J = 2.8 Hz, 3 H each), 7.82-7.78 (m, 15 H), 7.06 (s, 6 H), 7.05, 7.03 (2xd, J = 2.6 Hz, 3 H each), 4.87 (d, J = 14.1 Hz, 3 H), 4.76 (bs, 3 H), 4.73 (d, J = 13.4 Hz, 3 H), 4.64 (d, J = 13.9 Hz, 3 H), 4.42 (d, J

= 13.8 Hz, 3 H), 4.40-4.30 (m, 12 H), 3.90 (t, *J* = 6.7 Hz, 6 H), 3.77 (d, *J* = 14.1 Hz, 3 H), 3.72 (d, *J* = 14.0 Hz, 3 H), 3.70 (d, *J* = 14.1 Hz, 3 H), 3.64 (d, *J* = 14.5 Hz, 3 H), 2.12-1.98 (m, 18 H), 1.76 (d, *J* = 6.5 Hz, 9 H), 1.15, 1.00, and 0.91 (3xt, *J* = 7.5 Hz, 9 H each) ppm; ^{13}C NMR [$(CD_3)_2CO$] δ 170.0, 169.9, 164.84, 164.81, 162.3, 160.2, 144.7, 144.47, 144.44, 144.35, 143.2, 139.7, 139.0, 138.8, 138.7, 138.1, 137.0, 136.9, 136.23, 136.18, 129.1, 126.65, 126.59, 125.3, 124.3, 124.2, 121.7, 121.6, 83.3, 79.4, 79.1, 32.9, 32.8, 32.1, 32.0, 24.8 (x2), 24.6, 19.1, 11.6, and 10.7 (x2) ppm. MALDI*m/z* =2728 $[M+Na]^+$.

TAPT-Dodecanitro-Tris(calyx[4]arene) Dendron (45)

CC (Hexane/EtOAc, gradient, 3:2 to 1:9) provided a brownish solid (98 mg 75% yield), mp >260 °C. ^{1}H NMR [$(CD_3)_2CO$] δ 9.71 (s, 3 H), 8.75 and 7.92 (AX, *J* = 8.8 Hz, 12 H), 8.36, 8.35, 8.33, 8.32 (4xd, *J* = 2.6 Hz, 3 H each), 7.064 (s, 3 H), 7.060 (s, 3 H), 7.04 and 7.03 (ABq, *J* = 2.8 Hz, 6 H), 4.87 (d, *J* = 14.2 Hz, 3 H), 4.81 (q, *J* = 6.5 Hz, 3 H), 4.75 (d, *J* = 14.1 Hz, 3 H), 4.64 (d, *J* = 14.2 Hz, 3 H), 4.63 (d, *J* = 14.2 Hz, 3 H), 4.41-4.30 (m 12 H), 3.90 (t, *J* = 6.7 Hz, 6 H), 3.78 (d, *J* = 14.3 Hz, 3 H), 3.72, (d, *J* = 14.5 Hz, 3 H), 3.70 (d, *J* = 14.3 Hz, 3 H), 3.67 (d, 3 H), 2.11-1.96 (m, 18 H), 1.77 (d, *J* = 6.5 Hz, 9 H), 1.15, 1.01, and 0.91 (3xt, *J* = 7.4Hz, 9 H each) ppm; ^{13}C NMR [$(CD_3)_2CO$] δ 172.3, 170.4, 164.8, 162.3, 160.1, 144.7, 144.45, 144.35, 144.2, 139.0, 138.8 138.7, 137.0, 136.9, 136.22, 136.18, 133.2, 131.4, 126.66, 126.61, 126.57, 124.38, 124.34, 124.2, 121.0,

120.9, 83.3, 83.2, 74.4, 79.11, 79.09, 32.9, 32.8, 32.07, 32.03, 24.8 (x2), 24.6, 19.0, 11.6, and 10.7 (x2) ppm. MALDI*m/z* = 2731 $[M+Na]^+$.

General Procedure for the Synthesis of Dodecaamino Tris-calixarene Dendrons.

A suspension of dodecanitro Dendron (0.02mmol) and Raney/Ni in DMF (4 mL) was stirred under H_2 at atmospheric pressure and room temperature for 24–48 h. After filtering on celite, the solvent was evaporated and the residue treated with the appropriate solvent system to obtain a precipitate.

TAPB-Dodecaamino-Tris(calyx[4]arene) Dendron (44)

Off-white powder from MeOH (0.035 g, 74% yield), mp >220 °C. ^{1}H NMR [(D_6)DMSO] δ 9.75 (s, 3 H), 7.83 (d, J = 8.5 Hz, 6 H), 7.82 (s, 3 H), 7.74 (d, J = 8.5 Hz, 6 H), 6.30, 6.29, 6.25, 6.22 (4xs, 3 H each), 5.66, 5.65, 5.60 (3xs, ratio 2:1:1, 12 H), 4.37 (d, J = 12.8 Hz, 3 H), 4.26-4.18 (m, 12 H), 3.85-3.80 (m, 6 H), 3.77 (t, J = 8.1 Hz, 6 H), 3.43 (m, 6 H), 2.89, 2.79, 2.77, 2.69 (4xd, partly overlapping to residual DMF resonances at δ2.88 and 2.72 ppm, 12 H), 1.95-1.90 (m, 6 H), 1.76-1.71 (m, 6 H), 1.43 (d, J = 5.9 Hz, 9 H), 0.98 (t, J = 7.3 Hz, 9 H), 0.81 (t, J = 7.5 Hz, 9 H), and 0.69 (t, J = 7.4 Hz, 9 H) ppm; ^{13}C NMR [(D_6)DMSO] δ 170.2, 148.4, 148.3, 146.9, 144.6, 142.5, 142.4, 142.3, 141.9, 141.1, 138.4, 136.4, 136.2, 136.1, 135.2, 133.7, 133.5, 132.9, 127.3, 120.0, 119.8, 114.7, 113.9, 80.1, 76.8, 75.9 (x2),

31.6, 31.5, 30.9 (x2), 23.0, 22.4, 22.2, 17.7, 10.8, 9.97, and 9.94 ppm. MALDI*m/z* = 2350 $[M+H]^+$.

TAPT-Dodecaamino-Tris(calyx[4]arene) Dendron (46)

Brownish-red powder from MeOH (0.042 g, 88% yield); mp 89-91 °C. ^{1}H NMR [(D_6)DMSO] δ 10.06 (s, 3 H), 8.70 and 7.91 (AX, J = 8.6 Hz, 12 H), 6.31, 6.29, 6.25, 6.22 (4xd, J = 2.2-2.6 Hz, 3 H), 5.67 (d, J = 2.6 Hz, 3 H), 5.66, 5.65 (sx2, 3 H each), 5.60 (d, J = 2.5 Hz, 3 H), 4.38 (d, J = 12.8 Hz, 3 H), 4.28-4.26 (m, 6 H), 4.20 (d, J = 11.8 Hz, 3 H), 4.17 (d, J = 11.7 Hz, 3 H), 3.86-3.75 (m, 12 H), 3.48 (t, J = 6.8 Hz, 6 H), 2.90, 2.80, 2.77, 2.70 (4xd, partly overlapping to residual DMF resonances at δ 2.88 and 2.72 ppm, 12 H) 1.96-1.91 (m, 6 H), 1.89-1.83 (m, 6 H), 1.77-1.72 (m, 6 H), 1.45 (d, J = 5.9 Hz, 9 H), 1.00 (t, J = 7.3 Hz, 9 H), 0.81 (t, J = 7.5 Hz, 9 H), and 0.68 (t, J = 7.5 Hz, 9 H) ppm; ^{13}C NMR [(D_6)DMSO] δ 170.6, 170.1, 148.3, 148.2, 146.8, 144.3, 143.0, 142.5, 142.3, 141.9, 137.4, 136.2, 135.9, 133.6, 133.4, 132.8, 130.2, 129.6, 119.2, 114.6, 114.1, 113.8, 76.8, 75.8 (x2), 31.5, 30.8, 22.9, 22.3, 17.5, 10.7, and 9.9 ppm. MALDI*m/z* = 2372 $[M+Na]^+$

The synthesis opposite enantiomers was carried out in a similar way. The NMR spectra of all enantiomers were superimposable.

Pillararenes

2.1 Introduction

Since the last century, one of the most intriguing challenges for organic chemists has been the design and synthesis of molecular receptors, which can somehow mimic the natural ones by interacting with complementary molecular guest, through a set of weak interactions. Cyclodextrins were observed for the first time by Villiers in 1891[83], and shortly after the metacyclophanes were reported by Pellagrin in 1899[84]. In 1905 cucurbiturils[85] were synthesized for the first time,whereas in 1967 the work of Pedersen led to the first report on crown ethers[86].

Even though their synthesis dates back to 1872, owing to the work of Baeyer,[87] calixarenes are molecular receptors whose chemistry has exploded much more recently, when David Gutsche[88] in 1975 became interested in these basket-shaped compounds, and their rediscovery has greatly influenced the field of supramolecular chemistry. The shape of calixarene cavity and the possibility to functionalize both rims of the macrocycle, the upper and the lower ones, has made these compounds good candidates for the production of capsules, nanotubes, dendrimeric systems, and receptors for a variety of organic and inorganic molecules.

In 2008 a new class of molecular receptors, named pillar[n]arenes, was reported for the first time by Ogoshi and Nakamoto.[89] Pillar[*n*]arenes are 1,4-disubstituted [1n]paracyclophanes derived from hydroquinones units

linked by methylene bridges at their 2,5-positions. Pillar[n]arenes differ from the [1n]paracyclophanes reported in 1985 by Gribble and Nutaitis[90] by virtue of having cleavable alkoxy groups in their 1,4-positions, a feature that makes them amenable to further functionalization in the manner of the calixarenes. Unlike calixarenes, formed composed of 4-substituted phenol moieties linked at the 2,6-positions, pillar[n]arenes are cylindrical rather than conical in shape (Figure 2.1), and more closely resemble the tubular geometry of the cucurbit[n]urils.

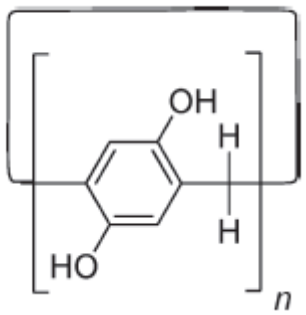


Figure 2.1: Schematic representation of a pillar[*n*]arene

Several papers dealing with pillar[*n*]arene synthesis report the isolation of the cyclopentamer only. Larger pillar[n]arenes require laborious syntheses and are obtained in very low yields. Cyclohexamers have been prepared, but always as minor products, and they have been isolated in approximately 10% yield[91]. The reason for the difference in yield between pillar[5]arene and pillar[*n*]arenes of larger size resides in the intrinsic structure of the pillar[5]arene. In fact, crystallographic evidence shows that the average bond angle for the methylene bridge in dimethoxypillar[5]arene (DMpillar[5]arene) is 111.3°, very close to the ideal 109.5° angle for sp^3 hybridized carbons (Figure 2.2).[90] A

cyclotetramer would impose an Ar–CH_2–Ar bond angle of 90°, whereas in the cyclohexamer the angle would be 120°. As a result, the cyclopentamer is the least strained of all the pillararenes, and it is therefore the main product obtained upon macrocyclisation reaction.

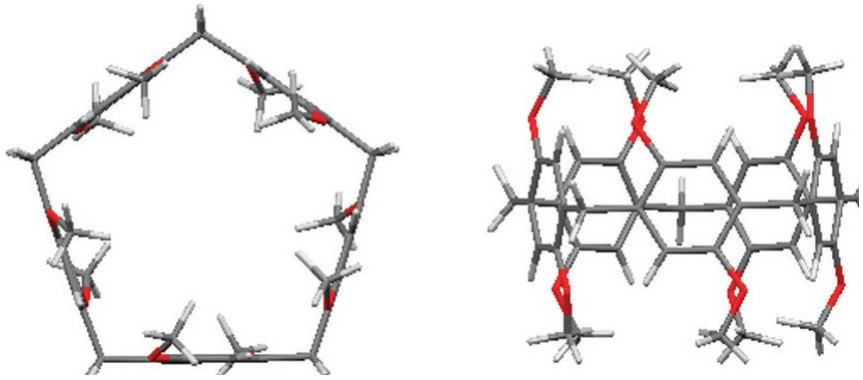
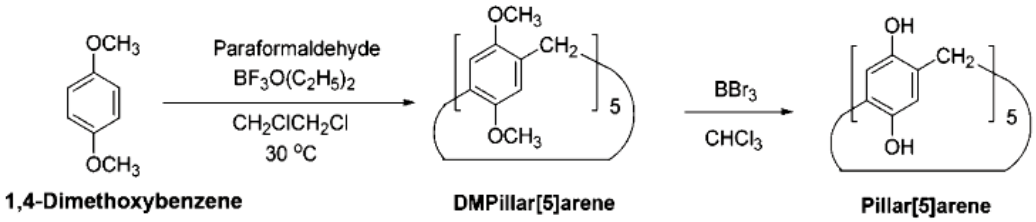


Figure 2.2: Representative structures of DMpillar[5]arene (left: top-view, right: side-view)

Contrary to the case of calix[*n*]arenes, that are generally prepared by base-catalyzed condensation of phenolic compounds and paraformaldehyde, pillar[*n*]arene synthesis requires a Lewis acid catalyst.

However, the use of inappropriate Lewis acids[7] such as $AlCl_3$, $FeCl_3$, $TiCl_4$ and $SnCl_4$ may result in the isolation of permethylated pillar[5]arene, along with a mixture of polymers. Based on several studies, the synthesis of peralkylated pillar[5]arenes is best carried out in 1,2-dichloroethane at 30 °C, using boron trifluoride diethyl etherate [BF_3•$O(C_2H_5)_2$] as the Lewis acid (Scheme 2.1). In the specific case of dimethoxy-pillar[5]arene the use of three equivalents of paraformaldehyde for each equivalent of 1,4-dimethoxybenzene, followed by quenching of the reaction with methanol results in a 71% yield of DMpillar[5]arene, along with a minimal

amount of polymers. Removal of the methoxy groups with BBr_3 in anhydrous chloroform provides perhydroxylated pillar[5]arene (**41**) in quantitative yield.



Scheme 2.1: Pillar[5]arene synthesis.

Dimethoxy-pillar[5]arene shows a D_5 symmetry and an internal diameter of the cavity, determined by X-ray analysis, of approximately 5 Å, similar to cucurbit[6]uril and α-cyclodextrins[92]. The cavity is therefore wide enough to accommodate an alkyl chain or a benzene ring.

Pillar[5]arenes have two interesting geometric properties. Firstly, the presence of substituents in the 1- and 4-positions leads to two possible planar chiral stereoisomers, *Rp* and *Sp* as shown in Figure 2.3, that arise through the spatial arrangement of the out-of-plane substituents. Secondly, rotation of one or more of the aromatic rings through the macrocyclic annulus generates the conformational isomers depicted in Figure 2.4. These conformers can be likened to those available to the better known calix[4]arenes. Therefore, it is possible to envisage conformers with all rings in the same orientation, one ring inverted, two adjacent rings inverted, and two non-adjacent rings inverted. By analogy with the

calixarenes, these can be described as *cone*, *partial cone*, 1,2-*alternate* and 1,3-*alternate*, respectively.

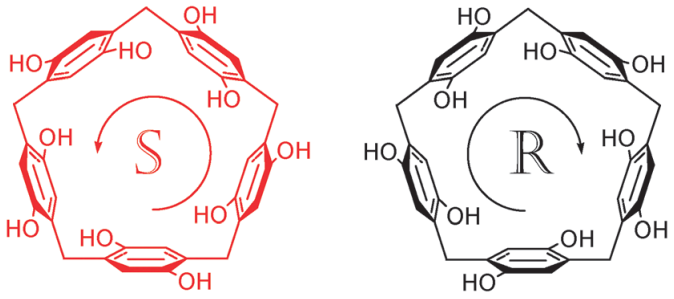


Figure 2.3: Planar chiral pillar[5]arenes: *Sp* (left) and *Rp* (right).

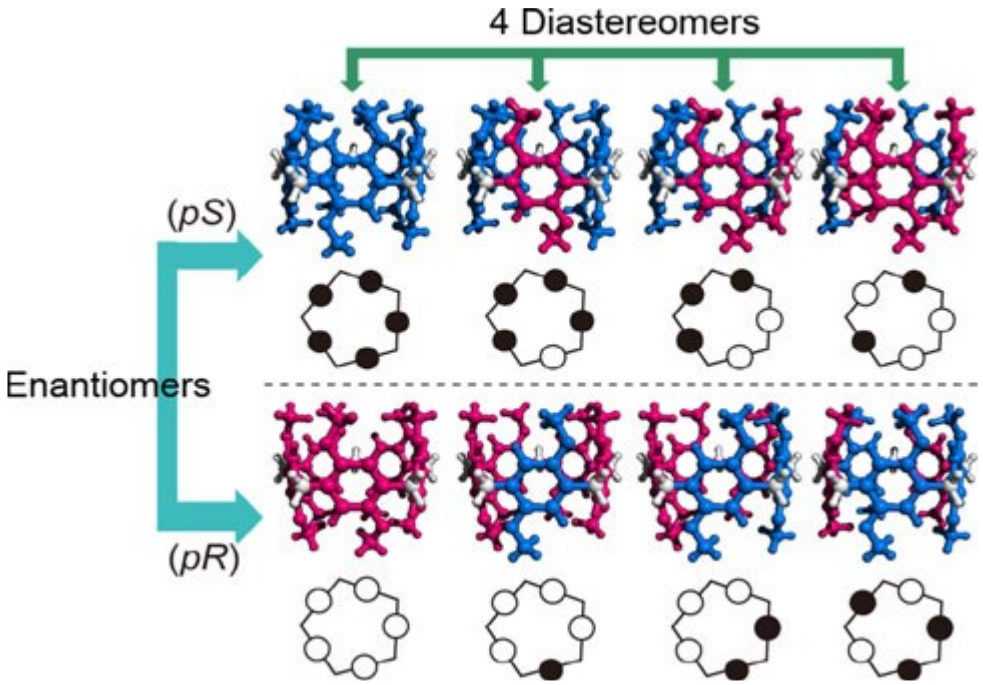


Figure 2.4: Conformers of DMpillar[5]arene

X-ray studies on dimethoxy-pillar[5]arene and pillar[5]arene (Figure 2.5) have shown that the former adopts in the solid state a D_5-symmetric *cone* conformation – actually, a racemic mixture of the two *Rp* and *Sp* enantiomers – while the latter seems to have lost this symmetry. Two of

the aryl rings have inverted with respect to the remaining three to give the 1,3-*alternate* conformer with a C_1 symmetry. Such a scrambling of the macrocycle units allows the formation of intramolecular hydrogen bonds.

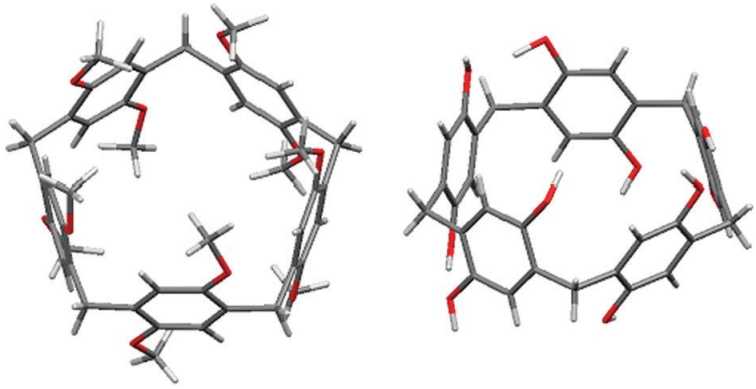


Figure 2.5: X-Ray structures of DMpillar[5]arene (left) and pillar[5]arene (right)

2.1 Results and Discussion

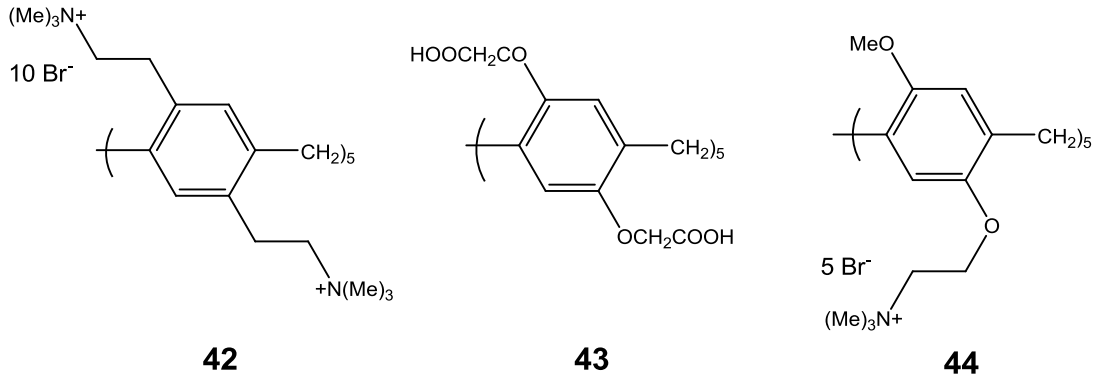
The structural features of this new class of compounds have attracted our attention. The combination of high yields, easy synthesis, cheap reagents and possibility of introducing different functionalities to one or both rims of the pillar[n]arenes, make these little-studied novel compounds an interesting alternative to the classical calixarenes, which are nowadays key players in supramolecular chemistry. Systems such as rotaxanes, pseudo-rotaxanes, nanotubes and other host-guest-derived supramolecular assemblies may be investigated by using suitably functionalized pillar[*n*]arenes and then compared with those obtained with other macrocyclic systems.

In the previous chapter we have reported the synthesis of (chiral) water-soluble multi-calixarenes. In the present one we have extended the studies

to anionic and cationic water-soluble pillar[*n*]arenes as potential templating agents for the formation of supramolecular assemblies together with oppositely charged porphyrins. In addition, we have also turned our attention to the formation of pillar[*n*]arene-based nanotubes and hybrid nanotubes composed of pillar[*n*]arene and calix[*n*]arene units (*vide infra*).

The vast majority of the studies carried out on the host–guest chemistry of pillar[5]arenes, have been carried out mainly in organic media, as a result of the poor solubility of pillar[5]arenes in aqueous media.

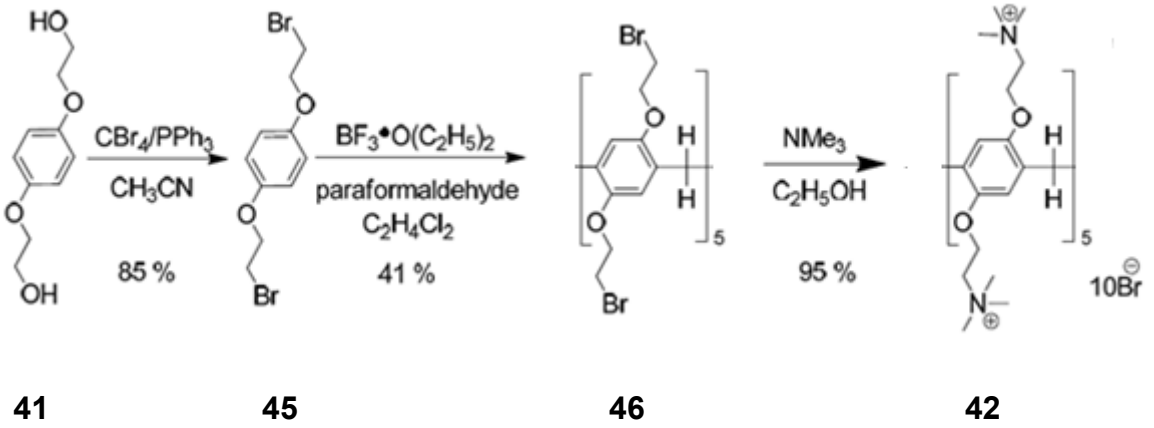
Water soluble pillar[5]arenes have been designed so as to introduce suitable functionalities at one or both rims, in order to obtain deca-cationic or anionic and penta-cationic pillar[5]arenes. Figure 2.6 shows the target compounds **42**, **43** and **44**. Compound **42** bears trimethylammonium groups at both rims, compound **43** is a pillar[5]arene bearing ten carboxylic units that can be converted into carboxylate group, and compound **44** is a pentacationic water-soluble pillar[5]arene characterized by five trimethylammonium groups.



42 **43** **44**

Figure 2.6: Schematic representation of the synthetic targets **42**, **43** and **44**.

Compound **42** was easily prepared in three steps starting from 1,4-bis(2-hydroxyethoxy)benzene (Scheme 2.2). The stepwise preparation of the key synthetic intermediate **46** has been recently reported by Hou et al.[93] However, their procedure involved several steps. In order to gain an easy access to **46**, a different synthesis was devised, with compound **45** being synthesized by the reaction of triphenylphosphine and tetrahalomethanes (CCl_4, CBr_4) with 1,4-bis(2-hydroxyethoxy)benzene, allowing the conversion of the alcohol groups to the corresponding alkyl halides under mild conditions and high yields. The cyclocondensation of monomer **45** with paraformaldehyde in the presence of boron trifluoride diethyl etherate ($BF_3{\cdot}(OC_2H_5)_2$) in 1,2-dichloroethane gave **46** in 41% yield.[94]



41 **45** **46** **42**

Scheme 2.2 Synthesis of the decacationic water-soluble pillar[5]arene **42**.

Treatment of **46** with excess of trimethylamine (30 equiv) in ethanol led to compound **42**, which was isolated as a colorless solid (95% yield). Pillar[5]arene **42** can be easily dissolved in water to give a colourless solution. Figure 2.7 shows the ^1H NMR spectrum of compound **42** in D_2O. The high symmetry of the molecule results in a very simple NMR

spectrum, displying a single resonance for the aromatic protons and, in the region between 3.5 and 4.5 ppm, four broad singlets assigned to the methylene bridges, the α and β oxymethylenes and the methyl hydrogen atoms of the trimethylammonium groups as singlet, indicative of the pillar[5]arene adopting in solution a cone conformation.

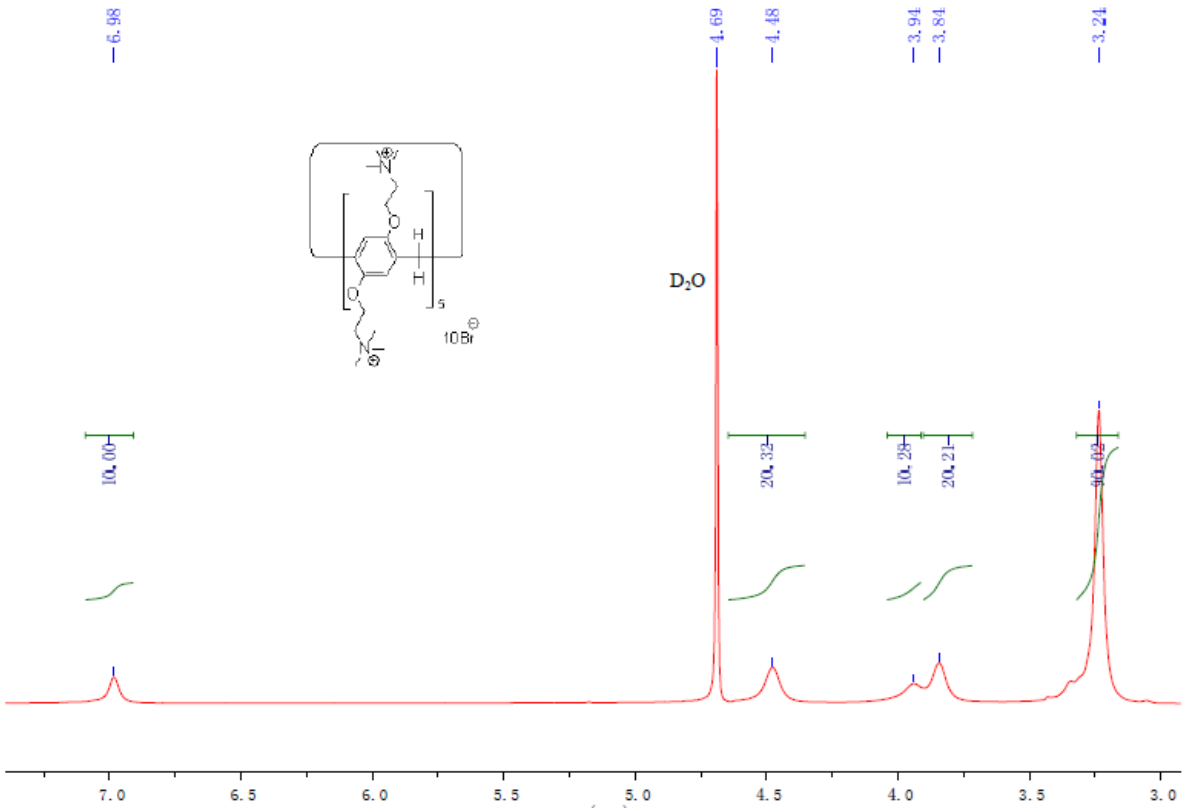
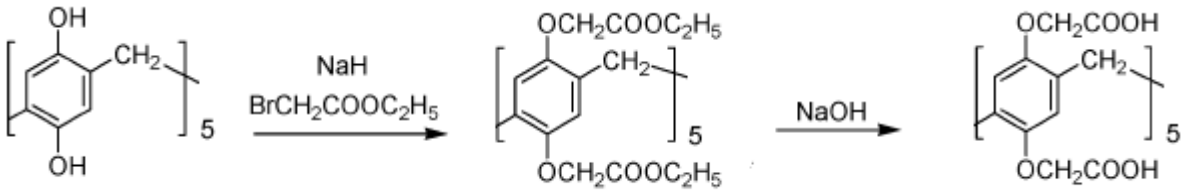


Figure 2.7: ^{1}H NMR spectrum (500 MHz, D_2O, 25 ° C) of **42**.

The synthesis of pillararene **43** is outlined in Scheme 2.3. Alkylation of pillar[5]arene **41** led to the ethoxycarbonylmethoxy-substituted pillar[5]arene **47**. ^{1}H NMR inspection of the crude mixture showed the presence of a number of different compounds, which were tentatively identified as stable conformational isomers of compound **47**. This suggests that the ethoxycarbonylmethoxy substituents are sufficiently bulky to

inhibit, at room temperature, the rotational motion of the aryl moieties around the CH_2–Ar–CH_2 bonds.[95,96]



41 **47** **43**

Scheme 2.3: Synthesis of water-soluble pillar[5]arene **43**.

Column chromatography, followed by recrystallization, allowed us to isolate **43** in 27 % yield. The ^{1}H NMR spectrum of compound **47** (Figure 2.8) again shows high symmetry, with the singlets for the aromatic and bridging methylene hydrogen atoms (labeled in the figure as a and d, respectively) indicating that the macrocycle is adopting a regular C_5 symmetric *cone* conformation. In addition, close inspection of the spectrum shows that the resonance for the oxymethylene group is seen as an AB-system, being the two hydrogen atoms diastereotopic, as a result of the pillar[5]arene existing as a racemic mixture (*vide supra*). The CH_2 groups of the ethyl moieties also experience the same splitting into an AB-system.

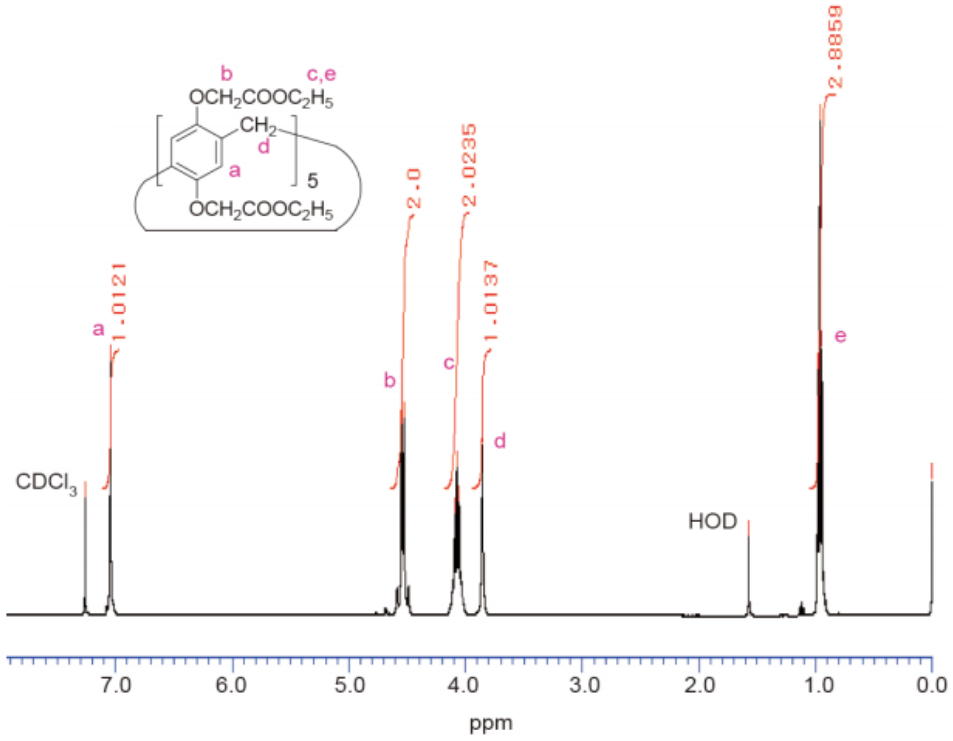


Figure 2.8: ^{1}H NMR spectra of **47** in $CDCl_3$.

The hydrolysis of **47** under basic conditions afforded the carboxylic acid-substituted pillar[5]arene **43**. Derivative **43** was found to be soluble in DMSO and DMF but insoluble in chloroform and water. Unlike **47**, the methylene protons at both rims were again seen as an AB-system (Figure 2.9 peak c). Due to the intra-molecular hydrogen bond between the carboxylic acid moieties, the mobility of the methylene protons is even more hindered than in the case of **47**. The interior of the cavity is electron-rich and, as a result, H_A and H_B (c and c', in the Figure) experience sensibly different environments, given that the methylene protons located in the inner and outer spaces are shielded and deshielded, respectively.

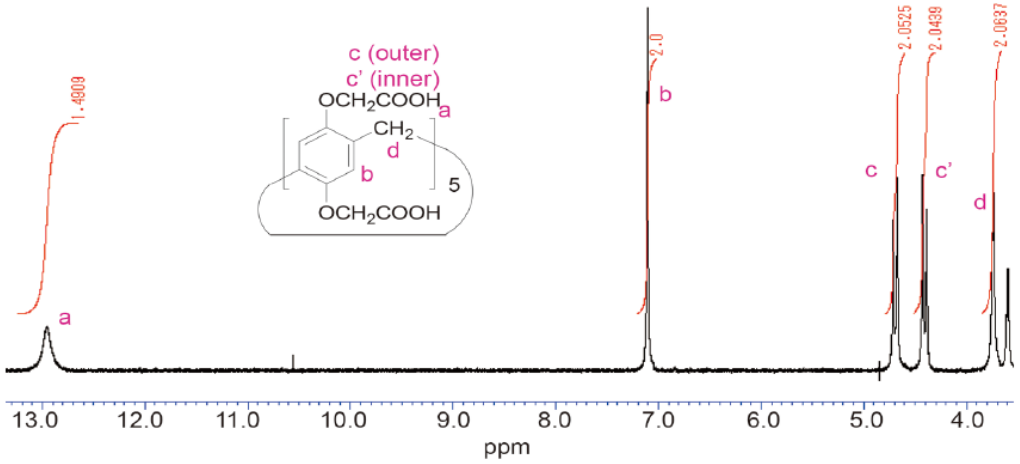
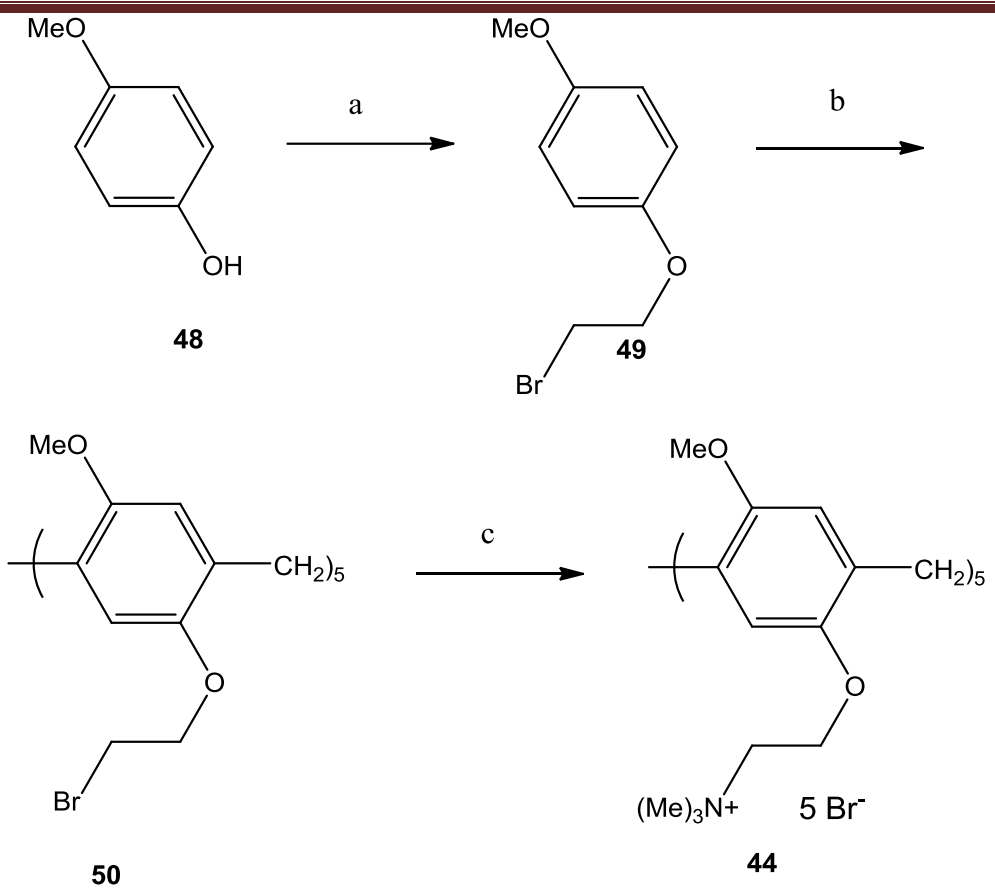


Figure 2.9: ^{1}H NMR spectra of **43** in DMSO-d_6.

The synthesis of penta-cationic pillar[5]arene **44** is outlined in Scheme 2.4. In this case, we chose compound **49** as the key precursor for the cyclocondensation Derivative **49** was obtained by alkylation of *p*-hydroxyanisole **48** in acetone in the presence of 1,2-dibromoethane. Cyclization of **49** was carried out under the typical conditions for pillar[*n*]arene synthesis, i.e., using paraformaldehyde in CH_2ClCH_2Cl and boron trifluoride diethyl etherate ($BF_3{\cdot}(OC_2H_5)_2$) as Lewis acid catalyst. The reaction provided compound **50** in the *cone* conformation in 45% yield, along with lower amounts of other conformers and polymerization products.



Scheme 2.4: Synthesis of penta-cationic pillar[5]arene **44**. a) $BrCH_2CH_2Br$, base, acetone; b) $(CH_2O)_n$, $BF_3{\cdot}(OC_2H_5)_2$, CH_2ClCH_2Cl; c)EtOH, $N(Me)_3$.

The ^1H NMR characterization of **50** at 25 °C is consistent with a low symmetry structure. The signals of the aromatic protons, the methylene bridge, the α and β oxymethylenes all resonate as multiplets whereas the methoxy groups, give rice to a singlet. This behavior may be due to a low conformational freedom of the cavity at room temperature.

Treatment of **50** with an excess of trimethylamine in ethanol gave penta-cationic pillar[5]arene **44** functionalized with trimethylammonium groups in good yield. Owing to the presence of five positive chargesat the upper rim, **44** is water soluble, but insoluble in organic solvents. The structure of

penta-cationic pillar[5]arene **44** was characterized byIn addition to ^{1}H NMR and MALDI-MS analysis, pillar[5]arene **44** was also characterized by 2D ROESY (Figure 2.10).

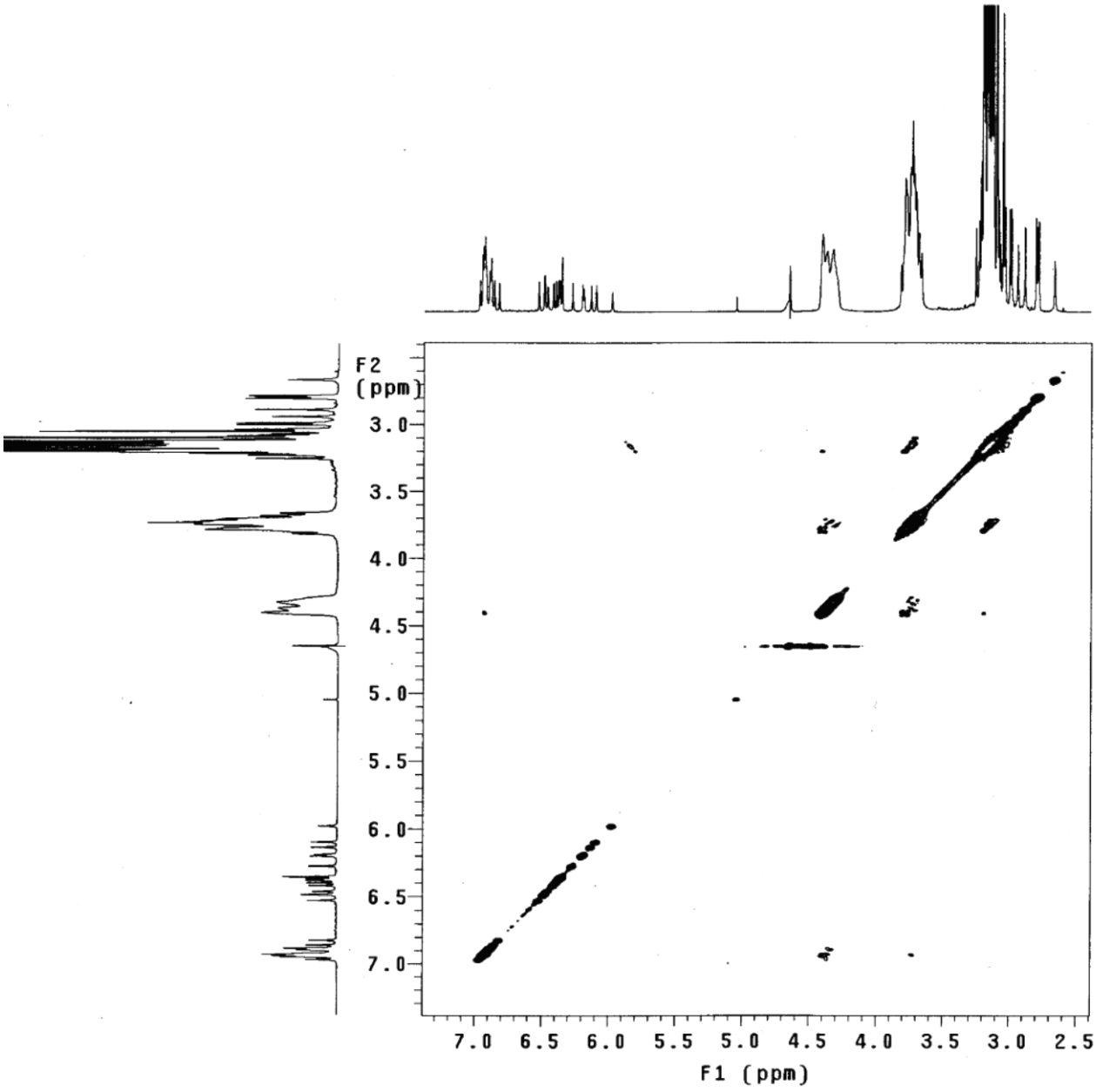


Figura 2.10 2D ROESY in D_2O compound **50.**

ROE correlations were observed between the protons from the α and β oxymethylenes moieties around 3.6-3.7 ppm and the phenyl protons

around 6.8-7.2 ppm, while other correlations were also found between the protons from the methoxy moieties around 2.8-3.3 ppm and the phenyl protons around 5.9-6.7 ppm. These observations indicate that the proton peaks around 6.8-7.2 ppm and 5.9-6.7 ppm were ascribed to the phenyl protons from the the α and β oxymethylene-side and methoxy-side, respectively. Correlations between the α and β oxymethylene-side phenyl protons and the methylene bridge proton were observed, whereas ROE correlations were observed between the methoxy-side phenyl protons and the methylene bridge proton (in the range of 2.6-3.3 ppm, methoxy and methylene bridge proton signals were overlapped).

2.3 Pillararene-based nanotubes

Tubular nanostructures based on molecular or supramolecular architectures are emerging as a novel type of molecular containers, able to transport ions or molecules, which may offer a variety of application in chemistry, nanotechnology and biology.

A number of synthetic procedures have recently been reported for the preparation of organic nanotubes. When the different subunits are linked by covalent bonds, the nanotube consists of a single, extended macromolecular entity; on the contrary, when subunits of the same or different type are held together by non-covalent interactions they form supramolecular tubular structures. Representative examples of the two cases are provided by the α-cyclodextrin polymeric nanotubes and the hydrogen-bonded cyclic oligopeptides nanotubes, respectively. The molecular properties of nanotubes can appropriately be adjusted by careful

selection of the starting molecules. For example, it is possible to synthesize peptide nanotubes with different inner diameters and with different chemical characteristics of the exposed surfaces. Thus, nanotubes with hydrophobic chemical groups on the surface can be inserted into a lipid barrier so as they may function as channels for the passage of ionic species, simulating what occurs in the lipid bilayer of the cell membrane. Nanotubes with slightly larger pores may instead act as transporters of neutral molecules of larger size, such as for example glucose. In contrast to self-assembled hollow structures, covalent organic synthesis may offer more robust tubes of various sizes and lengths.

Nanotubes assembled from pillar[5]arenes and hybrids nanotubes consisting of pillar[5]arene and calix[5]arene, were then foreseen as potential synthetic targets for this PhD work (Figure 2.11). To this end, two different synthetic strategies were envisaged. The first one consider the possibility of performing a templated "pillarization" reaction starting from a macrocycle (calix[5]arene or pillar[5]arene) endowed with 1,4-hydroquinone residues, which, under appropriate reaction conditions, should in principle undergo cyclization. The second strategy is based on the direct condensation of pre-formed macrocycles with suitable functionalities.

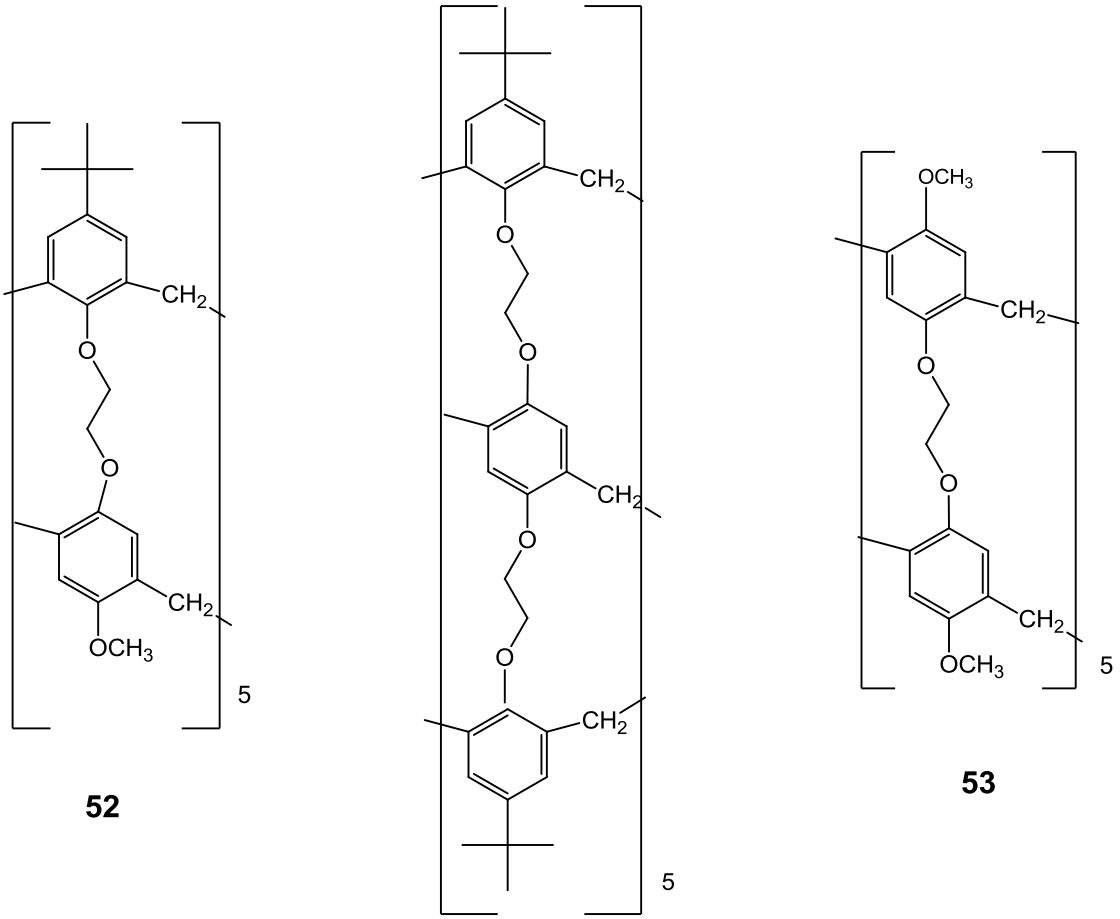
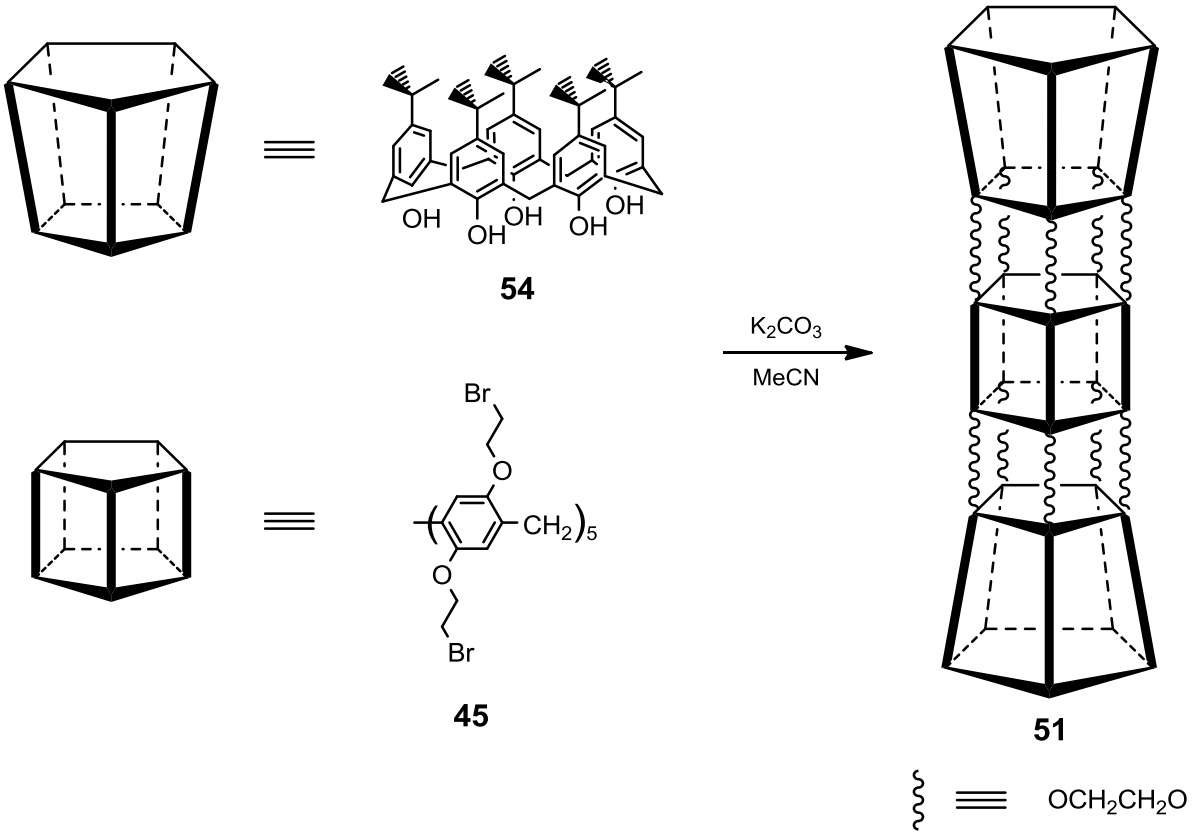


Figure 2.11: Structures of the nanotube targets **51, 52** and **53**.

Figure 2.11 shows the structure of the three molecular nanotubes synthesized. Compound **51** is a hybrid nanotube obtained by condensation of two *p-tert*-butylcalix[5]arene (**54**) molecules with pillar[5]arene **45** (Scheme 2.5).



Scheme 2.5: Synthesis of hybrid nanotube **51.**

The reaction involves the use of the previously described bi-functional pillar[5]arene derivative **45** alkylation in the alkylation of calix[5]arene **54**, using K_2CO_3 as a base, in refluxing CH_3CN (Scheme 2.5). The reaction was monitored by TLC over a period of seven days, until a less polar compound (relative to starting materials) formed. According to Maldi Ms data (Figure 2.13), hybrid nanotube **51** (Figure 2.12) was then recovered in 5% yield after column chromatography. Attempts to characterized derivative **51** by NMR spectroscopy have so far been unfruitful. In particular, the ^1H NMR spectrum of **51** shows very broad resonances even in the 0 – 100 °C temperature range. This is likely due to a reduced conformational freedom that makes the twisting motion of the oxyethylene

groups, connecting the pillar[5]arene and the two calix[5]arene molecules, slow compared to the NMR time scale.

To gain more detailed information on the structure of nanotube **51**, we are currently screening a number of different ions/molecules as potential guests, in an attempt to obtain an inclusion complex that would block the molecular motion.

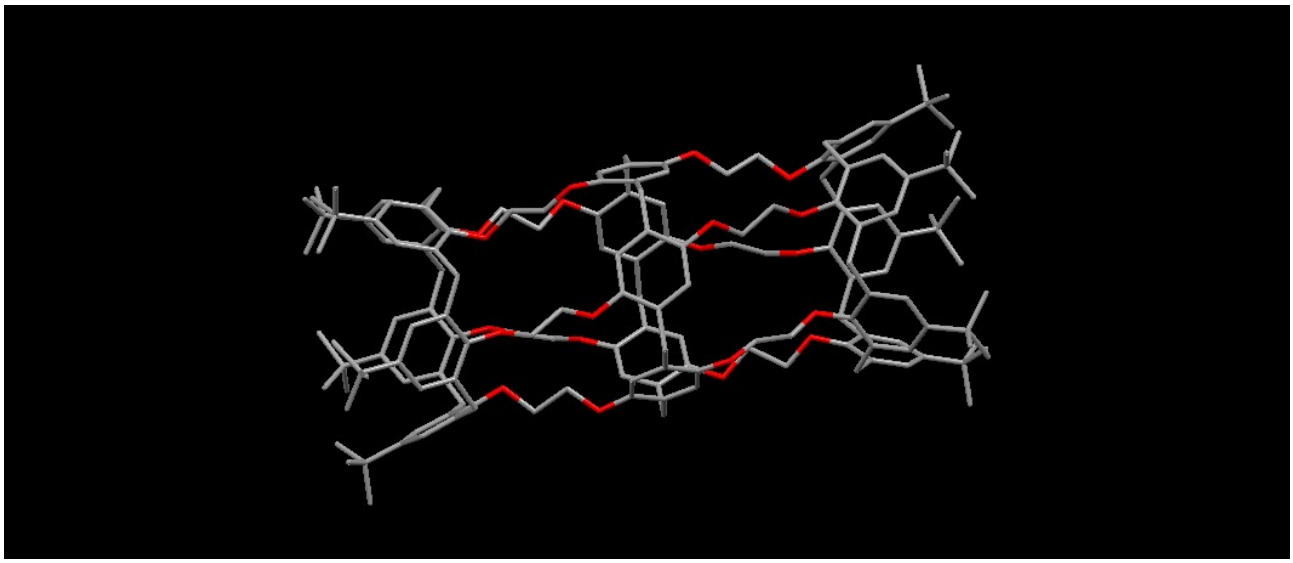


Figure 2.12: Molecular structure of nanotube **51**

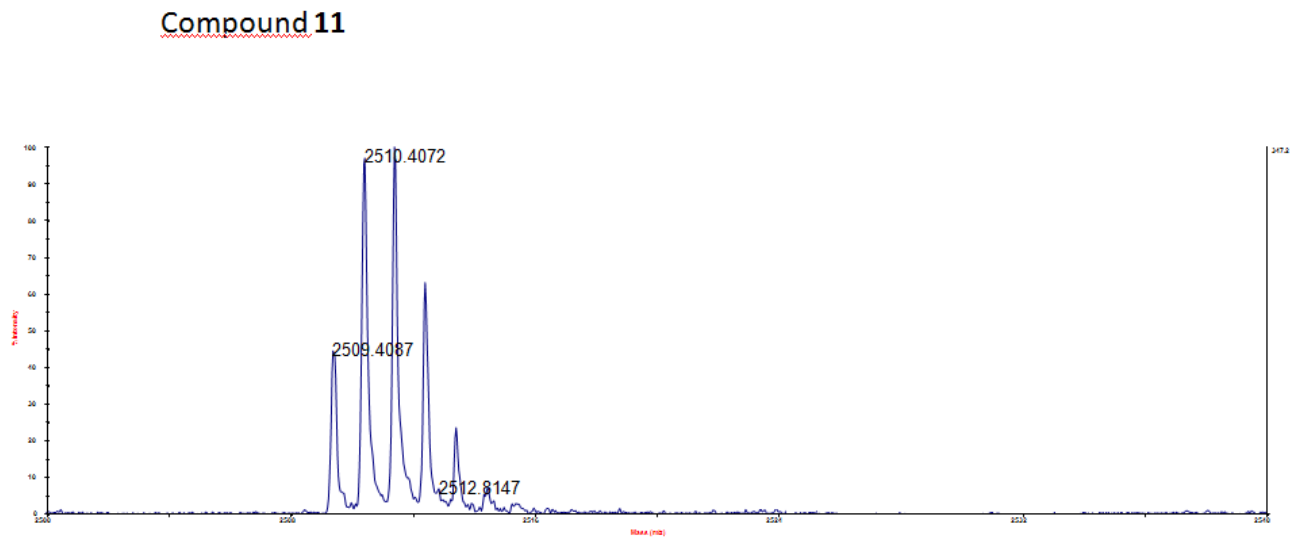
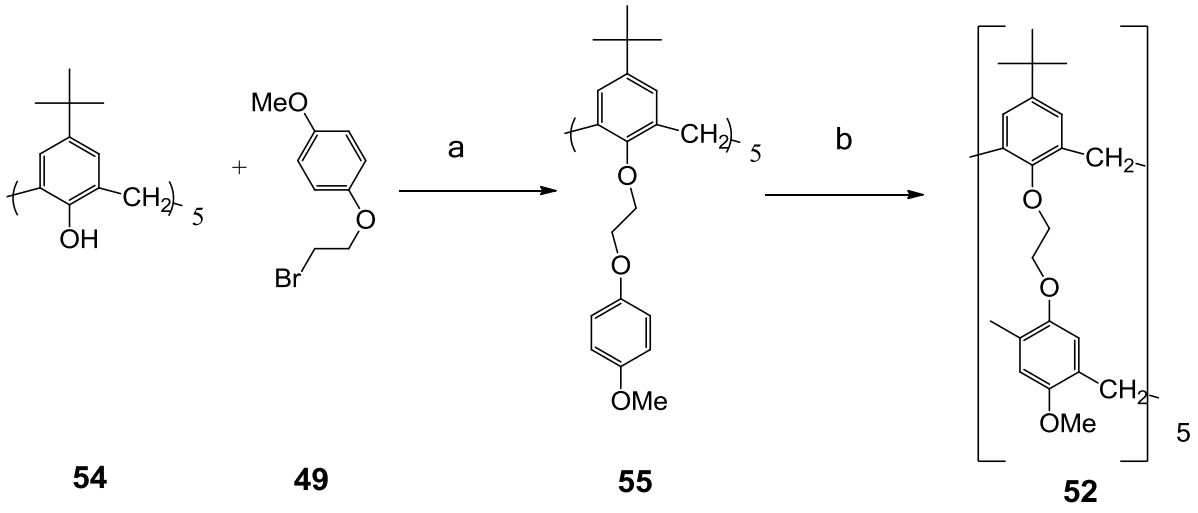


Figure 2.13: Section of the Maldi Ms spectrum of compound **51**.

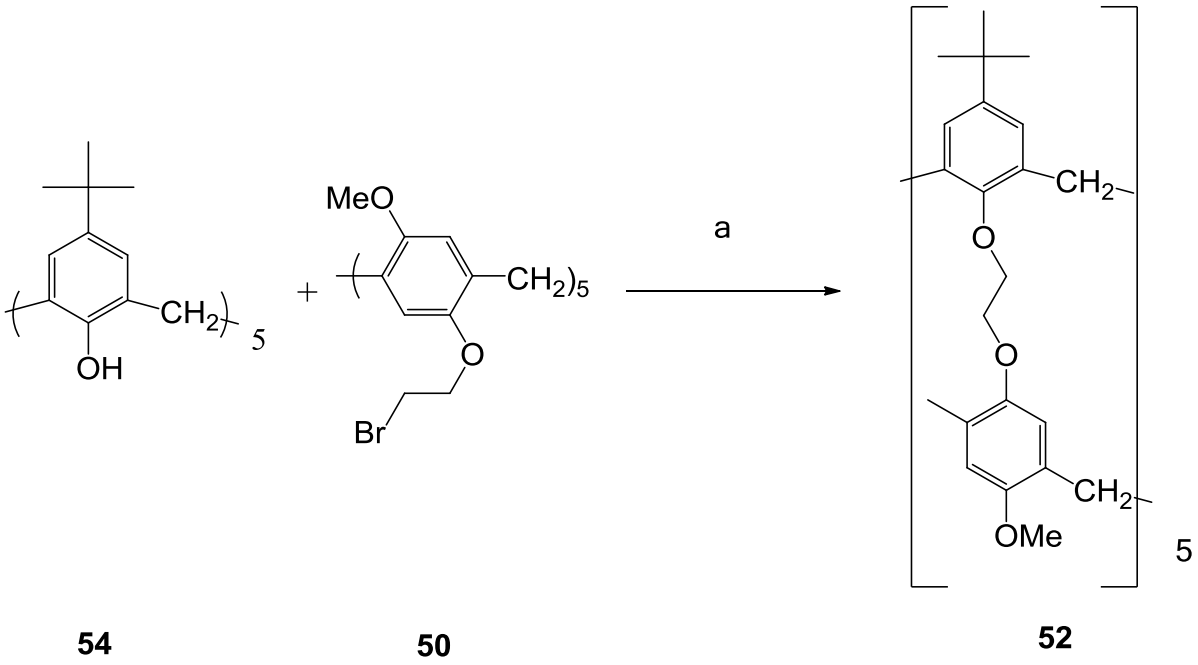
The strategy undertaken for the synthesis of compound **52** is an innovative method that exploits the preorganization of a macrocyclic structure to obtain the desired nanotubular product. In particular, alkylation of calix[5]arene **54** with bromo derivative **49** provides intermediate **55** that possesses at the lower rim the desired aromatic pendant functionalities which can undergo cyclization (Scheme 2.6). Cyclization of **55** carried out in CH_2ClCH_2Cl with paraformaldehyde and $(BF_3{\cdot}(OC_2H_5)_2)$ as a Lewis acid catalyst to gave **52** in high yield.



Scheme 2.6: Synthesis of hybrid nanotube **52**. Reagents and conditions: a) K_2CO_3 in anhydrous acetonitrile, 2 d, reflux. b) paraformaldehyde and $(BF_3{\cdot}(OC_2H_5)_2)$ in CH_2ClCH_2Cl, r.t., 2 h.

Similarly to the previously described nanotube **51**, the ^1H NMR spectrum of derivative **52** did not provide any conclusive structural information as a result of severe broadening of its signals. The mass spectrum, on the other hand, indicated the formation of nanotube **52**(Figure 2.14). Derivative **52** was also synthesized by an alternative strategy, starting from the two

preformed macrocycles, namely calix[5]arene **54** and pillar[5]arene derivative **50**. (Scheme 2.7).



54 **50** **52**

Scheme 2.7: Synthesis of hybrid dimer **52.** Reagents and conditions: a) K_2CO_3 in anhydrous acetonitrile, 3 d, reflux.

Interestingly, the ^1H NMR spectra of compound **12**, obtained by the two alternative synthetic routes, were found to be identical (Figure 2.15).

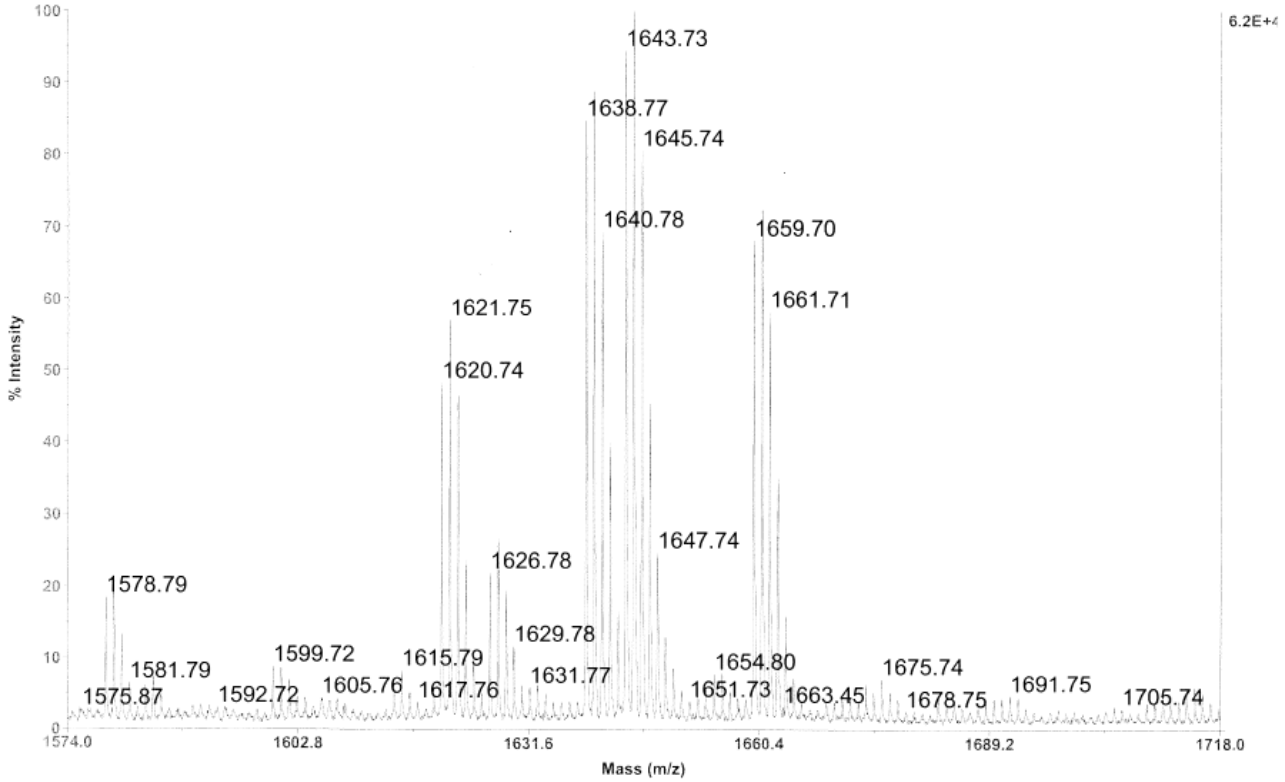


Figure 2.14: MALDI Ms spectrum compound **52.**

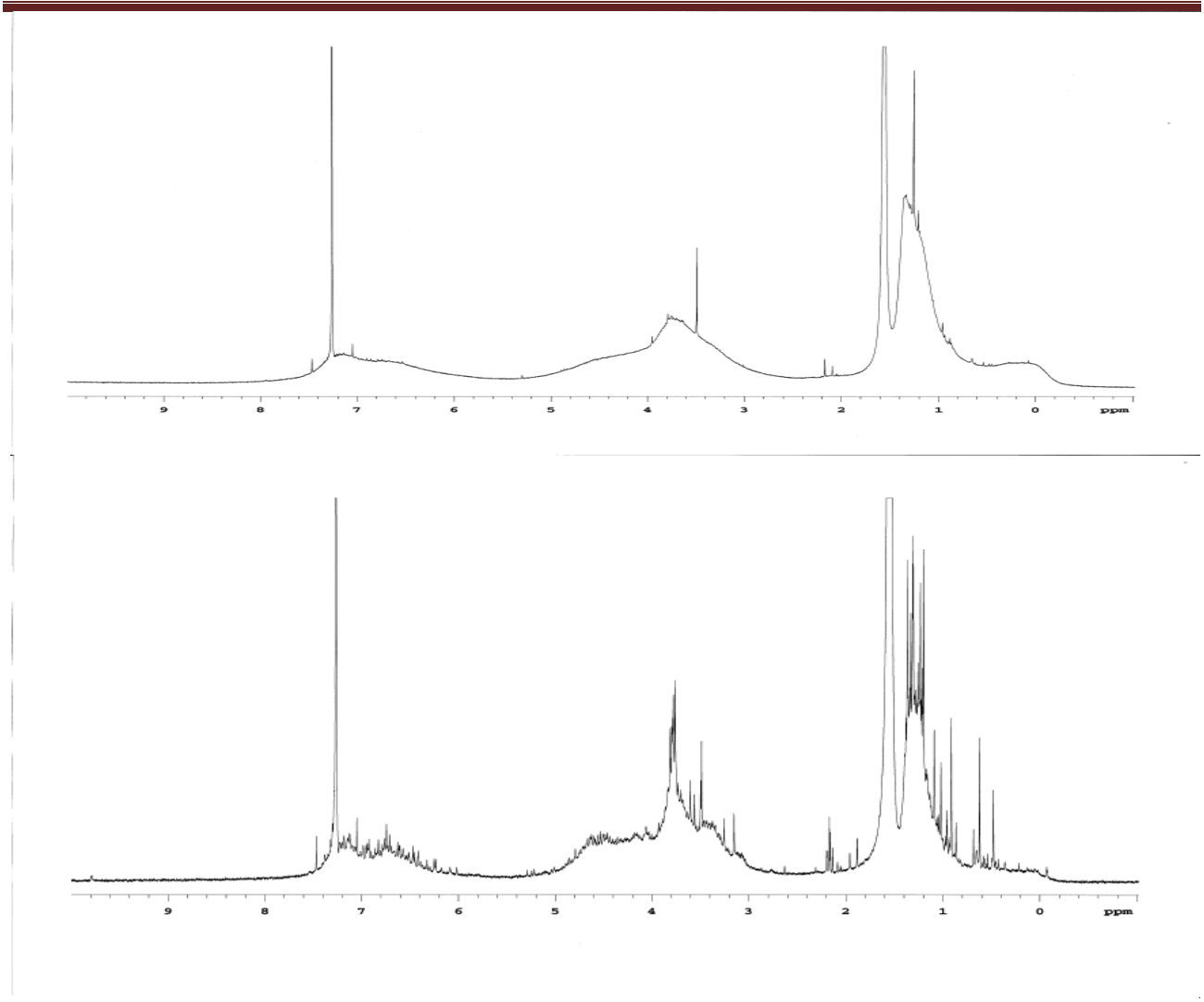
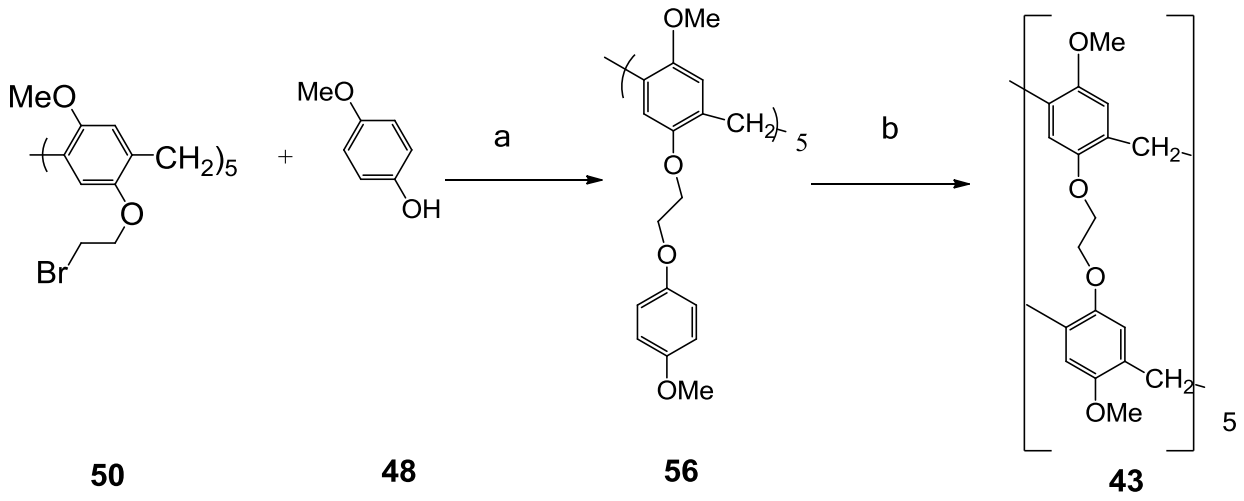


Figure 2.15: NMR spectrum compound **52** obtained by two different synthetic routes.

The synthesis of compound **53** relies on the same strategy used for **52**, that is to exploit the pre-organization of macrocyclic structure to induce cyclization, thus avoiding undesired products. Scheme 2.8 illustrates the method used for the synthesis of compound **53**. Pillar[5]arene derivative **50** and 4-methoxyphenol **48** undergo nucleophilic substitution reaction to give compound **56**. Macrocyclization of pillar[5]arene **56**, under the standard conditions employed so far (paraformaldehyde and $(BF_3 \cdot (OC_2H_5)_2$ in CH_2ClCH_2Cl), was not successful, on the other hand,

use of trifluoroacetic acid (TFA), as an alternative acid catalyst [97], provided the desired nanotube **53** in good yield, avoiding the formation of undesired polymerization by-products (Scheme 2.8).



50 **48** **56** **43**

Scheme 2.8: Synthesis of nanotube **53**. Reagents and conditions: a) K_2CO_3 in anhydrous acetonitrile, 2 d, reflux; b) paraformaldehyde and TFA in CH_2ClCH_2Cl, reflux, 2 d.

2.4 Experimental Section

1,4-bis(2-bromoethoxy)benzene (45).

Carbon tetrabromide (3.98 g, 12 mmol) was slowly added in small portions to a stirred solution of 1,4-bis(2-hydroxyethoxy)benzene (1.0 g, 5.04 mmol) and triphenylphosphine (3.15 g, 12 mmol) in 30 mL of dry acetonitrile at 0 °C. The reaction mixture was allowed to warm to room temperature, and the resulting clear solution was stirred for another 4 h under N_2. Then 20 mL of cold water were added to the reaction mixture, and product **45** precipitated as a white solid. The product was collected by vacuum filtration, thoroughly washed with methanol/water 60:40, and then recrystalized from methanol. The white flake-like crystals were dried under high vacuum (1.38 g, 85 %). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ (ppm): 6.89 (s, 4H), 4.27 (t, J = 6.3 Hz, 4H), 3.64 (t, J = 6.3 Hz, 4H).

Pillar[5]arene derivative (46).

To a solution of **45** (1.123 g, 3.83 mmol) in 1, 2-dichloroethane (70 mL), paraformaldehyde (116.3 mg, 3.83 mmol) was added under nitrogen atmosphere. Then boron trifluoride diethyl etherate ($BF_3{\cdot}(OC_2H_5)_2$, 0.54 g, 3.83 mmol) was added to the solution and the mixture was stirred at room temperature for 3 h. A green solution was obtained. After the solvent was removed, the crude solid was purified by column chromatography on SiO_2 with petroleum ether/dichloromethane (1:2 *v*/*v*) as the eluent to get a white powder (0.53g, 41 %). Mp: 95.0−97.0 °C) ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ (ppm): 6.93 (s, 10H), 4.25 (t, J = 5.7 Hz, 20H), 3.86 (s, 10H), 3.65 (t, J = 5.7 Hz, 20H).

Pillar[5]arene derivative compound (42).

Compound **45** (100 mg, 0.0595 mmol) and trimethylamine (33 % in ethanol, 3.22 mL, 2.38 mmol) were added to ethanol (10 mL) and the solution was refluxed overnight. After solvent evaporation, deionized water (10 mL) was added and the resulting suspension was filtered to obtain a clear solution. Water was then removed by evaporation to yield **42** as a colorless solid (130 mg, 95 %). ^{1}H NMR (500 MHz, D_2O, 25 °C) δ (ppm): 6.98 (s, 10H), 4.48 (s, 20H), 3.94 (s, 10H), 3.84 (s, 20H), 3.24 (s, 90H).

Ethoxycarbonylmethoxy-substituted pillar[5]arene (47).

Pillar[5]arene (**41**, 0.3 g, 0.5 mmol) was dissolved in MeCN (20 mL) under a nitrogen atmosphere. K_2CO_3 (0.82 g, 6 mmol) was added and the reaction mixture was stirred for 0.5 h. Then, an excess of ethyl bromoacetate (2.0 g, 12.5 mmol) was added and the reaction mixture was heated to reflux for 24 h. After removal of the solvent, the resulting solid was dissolved in CH_2Cl_2 and water. The organic layer was dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated to give a solid which was purified by column chromatography (SiO_2; CH_2Cl_2:acetone = 100:0 to 95:5). The product was finally crystallized from MeCN. (200 mg, yield: 27 %.). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 7.04 (s, 10H, ArH), 4.55 (dd, 20H, C*H*$_2$CH$_3$), 4.09 (m, 20H, ethyl protons), 3.86 (s, 10H, ArCH$_2$Ar), 0.96 (m, 30H, CH$_2$C*H*$_3$).

Carboxyl-substituted Pillar[5]arene (43).

Compound **47** (0.150 g, 0.102 mmol), NaOH (0.300 g), and THF (20 mL) were refluxed for 24 h. To the solution, diluted aqueous HCl was finally added. The precipitate was collected by filtration washed with water several times and dried under reduced pressure (0.110 g, yield: 91 %). ^{1}H NMR (DMSO-d_6, 500 MHz, ppm): δ 12.96 (br, 10H, CO_2H), 7.11 (s, 10H, ArH), 4.71 (d, 10H, CH_2CO), 4.42 (d, 10H, CH_2CO), 3.74 (s, 10H, $ArCH_2Ar$).

1-(2-Bromoethoxy)-4-methoxybenzene (49).

A solution of **48** (10.1 g, 81.3 mmol) in acetone (100 mL) was added over a 12 h period to a refluxed mixture of 1,2-dibromoethane (35 mL, 0.41 mol), finely powdered K_2CO_3 (35 g, 0.25 mol) and acetone (300 mL). The reaction was held at reflux for 125 h before the K_2CO_3 was removed by filtration. After solvent removal in vacuo, the remaining residue was combined with CH_2Cl_2, washed with 2.5 M NaOH, 1 M HCl, and brine, and dried over anhydrous Na_2SO_4. Evaporation of the volatiles in vacuo yielded an orange solid that was treated with a 10% CH_2Cl_2–90% hexanes solution (100 mL) to precipitate the dimeric material present.

After filtration, the filtrate was evaporated in vacuo and recrystallized from EtOAc/hexanes to yield 8.42 g (44.8%) of **49** as translucent sheet-like crystals with a ^{1}H NMR spectrum identical to that reported by literature.[98]

1-(2-Bromoethoxy)-4-methoxy-substituted pillar[5]arene (50).

To a solution of **49** (2.0 g, 8.6 mmol) in 1, 2-dichloroethane (120 mL), paraformaldehyde (258.2 mg, 8.6 mmol) was added under nitrogen atmosphere. Then boron trifluoride diethyl etherate ($BF_3 \cdot (OC_2H_5)_2$, 1.22 g, 8.6 mmol) was added to the solution and the mixture was stirred at room temperature for 3 h. A green solution was obtained. After the solvent was removed, the resulting solid was dissolved in CH_2Cl_2 and water. The organic layer was dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated to give a solid. The crude solid was purified by column chromatography (SiO_2; CH_2Cl_2:hexane = 50:50 to 65:35) to get a white powder (0.867 g, 44 %). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 6.70-6.89 (m, 10 H, ArH), 4.08-4.17(m, 10 H, OCH_2), 3.68-3.87 (m, 10 H, $ArHCH_2ArH$), 3.75 (s, 15 H, OCH_3) ppm. ^{13}C NMR: δ 151.3, 151.2, 128.9, 128.3, 115.8, 114.0, 69.1, 55.8, 30.3, 30.1 ppm. MALDI *m/z* = 1216 $[M]^+$

1-(2-trimethylammoniumethoxy)-4-methoxy-substituted pillar[5]arene (44).

Compound **50** (70 mg, 0.00576 mmol) and trimethylamine (33 % in EtOH, 1 mL, 0.73 mmol) were dissolved in ethanol (10 mL). The solution was refluxed for 48 h. The solvent was removed by evaporation and deionized water (10 mL) was added. After filtration, a clear solution was obtained. Water was evaporated and **44** was isolated as a colorless solid (78 mg, 89 %). ^{1}H NMR (500 MHz, D_2O, ppm) *δ* 6.8-7.0 (m, 5 H, ArH), 5.9-6.5 (m, 5 H, ArH), 4.2-4.5 (m, 10 H, OCH_2), 3.6-3.9 (m, 20 H, OCH_2CH_2 and $ArCH_2Ar$) 2.6-3.4 (m, 60 H, OCH_3 and $N(Me)_3$) ppm.

Nanotube derivative (51).

A suspension of *p-tert*-butylcalix[5]arene **54** (162 mg, 0.2 mmol), compound **4** (168 mg, 0.1 mmol) and K_2CO_3 (414 mg, 3 mmol) in dry MeCN (100 ml) was refluxed for 7 days. TLC analysis (cyclohexane-CH_2Cl_2-acetone 4:3:0.1, v/v) showed the disappearance of the starting calixarene and revealed the presence of a new derivative. The solvent was evaporated and the residue was triturated with CH_2Cl_2, organic phase was filtered and evaporated under reduced pressure. The solid residue was purified by column chromatography (SiO_2, cyclohexane-CH_2Cl_2-acetone 4:3:0.1, v/v) to give compound **54** as a white solid (10 mg, 80% yield). MALDI *m/z* =2511 $[M+NH_4]^+$.

p-tert-Butycalix[5]arene derivative (55).

A suspension of p-tert-butylcalix[5]arene **54** (150 mg, 0.18 mmol), 1-(2-bromoethoxy)-4-methoxybenzene **49** (427 mg, 0.18 mmol) and K_2CO_3 (255 mg, 1.80 mmol) in dry MeCN (15 ml) was refluxed for 48 h. TLC analysis (cyclohexane-CH_2Cl_2 2:3, v/v) showed the disappearance of the starting calixarene while eluting with CH_2Cl_2/ethyl acetate 10:1, v/v was revealed the presence of a derivative. The solvent was evaporated and the solid residue was treated with CH_2Cl_2 and HCl 1N. The organic layer was dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated under reduced pressure to give a white solid (225 mg, 78 % yield); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.95 (s, 10 H), 6.72 (d, J = 8.5 Hz, 10 H), 6.68 (d, J = 12 Hz, 10 H), 4.68 (d, J = 13.5 Hz, 5 H), 4.11 (t, J = 4.5 Hz, 10 H),

3.95 (t, *J* = 4.5 Hz, 10 H), 3.70 (s, 15 H), 3.29 (d, *J* = 13.5 Hz, 5 H), 1.05 (s, 45 H) ppm; ^{13}C NMR: δ 153.5, 153.1, 152.4, 145.1, 133.7, 125.5, 115.3, 114.5, 72.1, 68.1, 55.5, 34.0, 31.1, 29.4 ppm. MALDI *m/z* =1585 $[M+Na]^+$.

Nanotube derivative (52).

To a solution of **55** (0.2 g, 0.128 mmol) in 1, 2-dichloroethane (20 mL), paraformaldehyde (20 mg, 0.641 mmol) was added under nitrogen atmosphere. Then boron trifluoride diethyl etherate ($BF_3{\cdot}(OC_2H_5)_2$, (0.090 g, 0.641 mmol) was added to the solution and the mixture was stirred at room temperature for 2 h. A green solution was obtained. After the solvent was removed, the resulting solid was dissolved in CH_2Cl_2 and water. The organic layer was dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated to give a pale yellow solid. (0.165 g, 80 %). mp >260 °C. MALDI *m/z* =1643.7 $[M+Na]^+$.

Pillar[5]arene derivative compound (56).

Pillar[5]arene derivative **50** (150 mg, 0.123 mmol), 4-methoxyphenol **48** (152 mg, 1.23 mmol) and dry K_2CO_3 (339 mg, 2:46 mmol) were suspended in dry MeCN (20 mL), the reaction was kept at reflux for 48 h. After solvent removal in vacuo, the remaining residue was combined with CH_2Cl_2, washed with 2.5 M NaOH, 1 M HCl, and brine, and dried over anhydrous Na_2SO_4. The solid residue was purified by column chromatography (SiO_2, hexane/EtOAc, gradient, 5:1 to 3:2) to give compound **56** as a white solid (65 mg, 37 % yield) ^{1}H NMR ($CDCl_3$, 500

MHz) δ 6.93-6.77 (m, 30 H), 4.20 (m, 5 H), 4.10 (m, 5 H), 4.02 (m, 5 H), 3.96 (m, 5 H), 3.85-3.67 (m, 30 H), 3,55 (m, 10 H) ppm; ^{13}C NMR: δ 154.05, 153.07, 151.23, 149.78, 129.05, 128.29, 115.85, 115.83, 115.76, 115.68, 114.67, 114.63, 67.97, 67.82, 55.70, 55.64, 29.57 ppm. MALDI *m/z* =1432 $[M+H]^+$.

Nanotube derivative (53).

Pillar[5]arene derivative compound **56** (75 mg, 0.00524 mmol) and paraformaldehyde (7.86 mg, 2.62 mmol) were dissolved in 1,2-dichloroethane (19 mL). Then TEA (1 mL) was added to the solution and the mixture was stirred at reflux for 48 h. A green solution was got. After the solvent was removed, the resulting solid was dissolved in CH_2Cl_2 and $H_2O/NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated to give a pale yellowvsolid. (65 mg, 83 %). MALDI *m/z* =1514.6$[M+Na]^+$.

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