Direct Regioselective Formylation of Tetraalkoxycalix[4]arenes Fixed in the Cone Conformation and Synthesis of New Cavitands

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Regioselectivity of the formylation of tetraalkoxycalix[4]arene fixed in the cone conformation has been studied. Direct, diametrical (1,3) diformylation of calix[4]arenes having four chelating chains at the lower rim has been achieved. Simple tetraalkoxycalix[4]arenes produce a mixture of diametrical (1,3) and proximal (1,2) diformylated products. The (1,3) functionalized compounds have been used for the synthesis of double calix[4]arenes **12a,d** linked *via* the upper rim. The residual mobility of these cone conformers is indicated by the X-ray crystal structure of compound **12d**, which shows a flattened cone conformation, and by the reactive behavior of 1,3-bis-(hydroxymethyl) derivatives **9a,d** which give very distorted 1,3-bridged compounds **11a,d**, through an intramolecular cyclization process.

Introduction

The selective binding of a substrate requires the design of receptors (hosts) having steric and electronic features complementary to those of the substrates (guests) to be bound. On the basis of these requirements, a great variety of receptor molecules have been designed for the selective recognition of ions and neutral molecules. In this area macropolycyclic (cage) hosts containing a cyclophane framework show interesting endoreceptor properties.[1] However, such host molecules are often structurally complex and can require elaborate syntheses using a stepwise assembly of several structural subunits.[2]

A complementary approach, which has been successfully used in the synthesis of cryptophanes[3] and hemicarcerands,[4] is that of assembling two rigid units facing each other. Also very recently a few calixarenes[5] have been used as building blocks for the construction of such cage molecules, through the linkage of two subunits *via* the upper rim (aromatic nuclei). In all double calixarenes known so far,[6] the two subunits either have free phenolic OH groups[7] or are completely functionalized at both rims.[8] It occurred to us that an attractive target would be the synthesis of double calix[4]arenes having the two subunits fixed in the cone conformation and the upper rim linked *via* a two-point diametrical (1,3) bridge. This would allow the synthesis of new cavitands in which the size of the apolar cavity can be modulated through the variation of the length of the bridge or the substituents on remaining aromatic nuclei. To reach this goal it was necessary to block the calix[4]arene in the cone conformation and then to selectively functionalize the upper rim at the 1,3-positions.

We report in this paper full details[9] of the first successful results in this direction together with their exploitation for the synthesis of two new 1,3-bridged double calix[4]arenes and the X-ray crystal structure of one such compound.

Results and Discussion

We and others have reported indirect methods for the regioselective 1,3-functionalization of calix[4]arene derivatives at the upper rim, most of them exploiting first the easier diametrical 1,3-alkylation of the phenolic oxygen atoms at the lower rim.[10] However, these methods cannot be applied to the tetraalkoxycalix[4]arenes **2**, because the *para*-positions in the aromatic nuclei of these compounds are equivalent. We tried to tackle this problem by introducing four chelating chains at the lower rim of the calix, hoping that they would not only block the calix in the cone conformation but eventually would interact with a cation or with a Lewis acid and induce selectivity in the functionalization at the upper rim.

It is known that the tetrafunctionalization of calix[4]-arenes at the lower rim with alkyl groups bulkier than ethyl blocks their conformational interconversion[11] and

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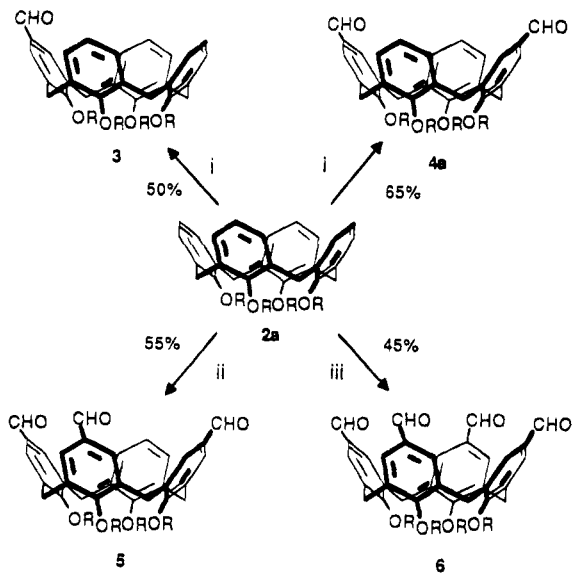
Scheme 1[a]



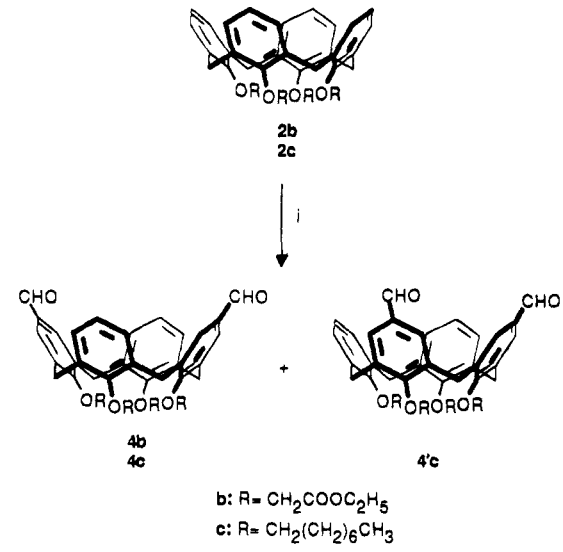
[a] (i) $SnCl_4$, Cl_2CHOCH_3, $CHCl_3$, $T = -10$ °C; (ii) $TiCl_4$, Cl_2CHOCH_3, $CHCl_3$, rt; (iii) $TiCl_4$, Cl_2CHOCH_3, $CHCl_3$, $T = 40$ °C.

that the alkylation using NaH in DMF is a general method to obtain calix[4]arenes in the cone structure.[12] By treating calix[4]arene **1a** with $CH_3CH_2OCH_2CH_2Br$ under these conditions we obtained the tetraalkylated compound **2a** in 75% yield.[13] The Gross formylation of aromatic compounds is a mild electrophilic reaction which uses Lewis acids as promoters.[14] By selecting suitable reaction conditions the formylation process on compound **2a** gives selectively the mono- **3**, di- **4a**, tri- **5**, and tetraformyl **6** derivatives (Scheme 1).

Particularly interesting and rather impressive is the regioselectivity observed in the diformylation: the diametrically (1,3) diformylcalix[4]arene **4a** is practically the sole reaction product while the proximal (1,2) isomer is present only in a small amount. A similar result is obtained in the formylation of the tetraester derivative **2b** which gives the (1,3) diformyl derivative **4b** in 45% yield.[15] On the contrary the same reaction performed on tetraoctyloxy derivative **2c** gives only a mixture of dialdehydes **4c** and **4'c** in 45:55 ratio and an overall yield of 25%[16] (Scheme 2).

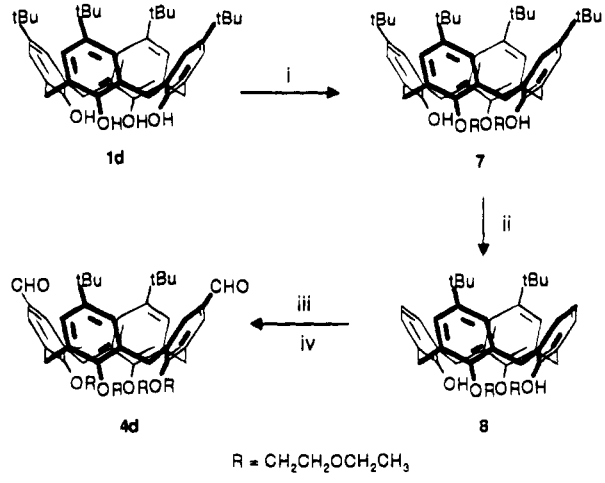
These results strongly indicate that the chelating chains at the lower rim of the calix play a very important role in determing the regioselectivity of this reaction.[17] Probably, after the first formylation, the acid catalyst

Scheme 2[a]



[a] (i) $SnCl_4$ or $TiCl_4$, Cl_2CHOCH_3, $CHCl_3$.

Scheme 3[a]



[a] (i) K_2CO_3, $BrCH_2CH_2OCH_2CH_3$, CH_3CN; (ii) $AlCl_3$, toluene; (iii) NaH, $BrCH_2CH_2OCH_2CH_3$, DMF; (iv) $SnCl_4$, Cl_2CHOCH_3, $CHCl_3$, rt.

coordinates preferentially to the two more basic ethereal chains in opposite position, thus producing a specific deactivation of the corresponding aromatic nuclei. The second formyl group is then forced to enter on the remaining site thus giving the process the diametrical (1,3) selectivity.

We have also synthesized another useful building block **4d** in the cone conformation by exploiting the recently reported[10a] selective removal of two *tert*-butyl groups from 1,3-dialkoxy-*p*-*tert*-butylcalix[4]arenes (Scheme 3).

The formyl group introduced selectively at the upper rim of conformationally rigid calix[4]arenes is very versatile, since it can be easily transformed into other functional groups: diol (**9a,d**), chloromethyl (**10a,d**), and carboxylic acid derivatives (**13** and **13'**). Calix[4]arene derivatives useful in host–guest chemistry have been

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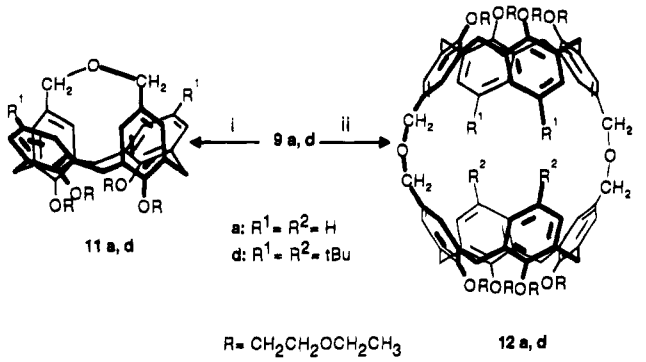
(15) Unpublished results from our laboratory.

(16) Attempts to separate the two isomers failed; therefore, they have been characterized as diesters, (**13** and **13'**, respectively) after oxidation, see Experimental Section.

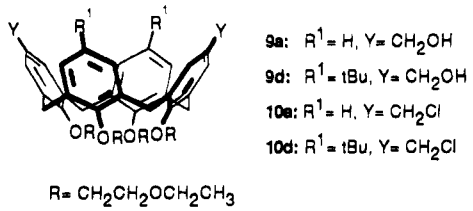
(17) Similar results were obtained by Reinhoudt et al. in the selective nitration of tetrakis(2-ethoxyethoxy)- and tetrapropoxycalix[4]arene in which the 1,3 (diametrical) dinitration was achieved only in the presence of chelating chains: Verboom, W.; Durie, A.; Egberink, R. J. M.; Asfari, Z.; Reinhoudt, D. N. *J. Org. Chem.* **1992**, *55*, 5639.

Scheme 4[a]



[a] (i) NaH, TsCl, DMF/DME; (ii) **10a,d**, CsOH, DMF.

already synthesized from diametrically diformylated precursors prepared using this procedure.[18]



As further examples of the synthetic utility of these compounds we have synthesized the two upper rim bridged double calix[4]arenes **12a** and **12d**. First we reacted the ditosylate prepared "in situ" and the sodium salt of the diol **9a**, obtaining the double calixarene **12a** in very low yield (Scheme 4). The main product in this reaction (30%) is **11a**, which derives from an intramolecular cyclization process. This rather unexpected product represents the first example of a calix[4]arene bridged at the 1,3-positions of the upper rim with a very short chain. The rigid structure of this compound is evidenced by its ^{1}H NMR spectrum which shows two very broad signals for the CH_2OCH_2 bridges at room temperature and two doublets (3.54 and 4.59 δ) at −55 °C. Other broad signals, attributed to the protons of the two linked aromatic nuclei, are present at 5.6 and 5.9 ppm; the high field resonance shown by these protons is in agreement with a highly distorted flattened cone structure for this product.[19] The formation of **11a** also indicates that the introduction of four substituents at the lower rim of the calix blocks the ring inversion process but does not completely rigidify the macrocycle, thus justifing the need of exploring different strategies for calix[4]arene rigidification.[20]

In order to avoid the formation of product **11a**, the bis(chloromethyl) derivative **10a** was reacted with alkali metal salts of **9a** in different conditions. The best results have been obtained in DMF using the cesium salt which gives product **12a** in 50% yield. This compound shows a singlet at 3.42 ppm for the more mobile CH_2OCH_2 bridges and a singlet at 6.16 ppm for the protons of bridged aromatic nuclei, which show only a minor distortion from the cone structure. Similar results have been also

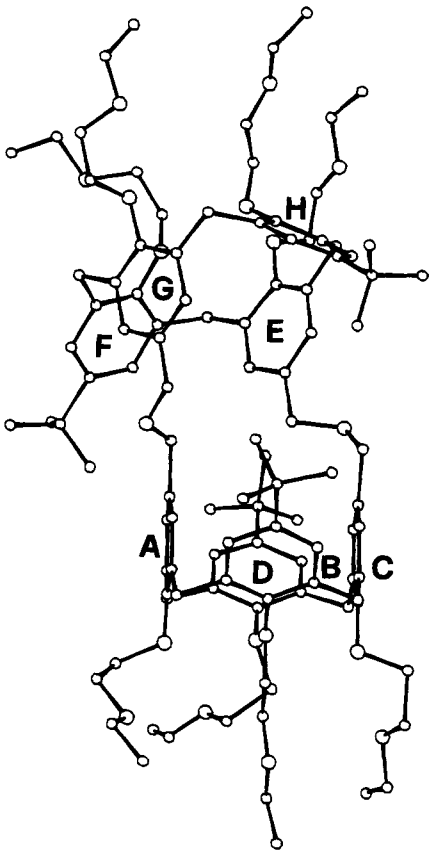


Figure 1. X-ray crystal structure of compound **12d**.

Table 1. Conformational Parameters (deg) in the Two Calix[4]arene Subunits[23]

	ϕ	χ		ϕ	χ
A–D	63(1)	−101(1)	E–F	61(1)	−107(1)
D–C	104(1)	−60(1)	F–G	106(1)	−54(1)
C–B	59(1)	−100(1)	G–H	58(1)	−104(1)
B–A	97(1)	−62(1)	H–E	101(1)	−57(1)

obtained with the bis(hydroxymethyl) derivative **9d**. Therefore, by choosing the reaction conditions, either the intramolecular **11a,d** or the intermolecular cyclization product **12a,d** can be prepared in good yield.

Figure 1 shows the X-ray crystal structure of compound **12d**.

In the host molecule **12d** each calix[4]arene subunit is in the typical "flattened cone" conformation (C_1+−, +−,+−,+−).[21] observed in other cone conformers of O-tetrafunctionalized calix[4]arenes,[22] in which two opposite aromatic units A,C (E,G) are almost parallel and the other two are almost perpendicular.

However, slight but significant differences, probably induced by the bridging groups, are observed in the conformations of the two calixarenes. In particular the dihedral angles between opposite phenolic units are: A–C 0.8(3)°, B–D 88.9(4)° in one calixarene and E–G 10.7(3)°, F–H 100.4(3)° in the other. A detailed list of the conformational parameters of the two calix[4]arenes are reported in Tables 1 and 2.

The flexibility of the bridges allows the host molecule to reach the minimum intramolecular energy by folding

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Table 2. Dihedral Angles (deg) Formed by the Least Squares Planes through the Phenolic Units and the Reference Planes R and R'

A–R	91.4(2)	E–R'	93.3(3)
B–R	133.8(3)	F–R'	142.3(3)
C–R	91.7(2)	G–R'	97.4(2)
D–R	137.3(3)	H–R'	138.2(3)

into the cavity. Less clear are the reasons for the bending of one calix[4]arene subunit with respect to the other, as shown by the dihedral angle of 23.8(2)° between their reference planes (the least-squares planes through the four CH_2 bridges). Probably this is imposed by the lattice energy minimization.

Conclusions

A direct regioselective formylation of calix[4]arene tetraethers blocked in the cone conformation has been obtained for the first time. Particularly interesting is the diametrical (1,3) difunctionalization of substrates bearing chelating chains at the lower rim. Two of these chains are probably able to interact with the Lewis acid catalysts involved in the process and direct the formylation toward the other two opposite aromatic nuclei. This finding nicely complements the existing methodologies of selective diametrical functionalization of calix[4]arenes at the upper rim.[10]

Starting from 1,3-diformylcalix[4]arene derivatives, the synthesis of upper rim–upper rim double calix[4]arenes **12a,d** has been obtained in good yields. The X-ray crystal structure of the double calix[4]arene **12d** shows that the two macrocyclic subunits are present in a flattened cone conformation. These data, together with the observation that in certain conditions intramolecularly bridged compounds (**11a,d**) are formed, existing in a highly distorted flattened cone conformation, led to the general conclusion that tetraalkylation of calix[4]arenes at the lower rim with bulky groups hinders the ring inversion process, but is not sufficent to completely rigidify the calix. Preliminary results of a different strategy toward more rigid calix[4]arenes in the cone structure are reported in the following paper in this issue.[20]

Experimental Section

General. $CHCl_3$ was ethanol free, dried over $CaCl_2$, and used within a day after drying. DMF was freshly distilled under nitrogen and stored over molecular sieves (4 Å); CH_3CN, DME, and toluene were dried over molecular sieves (4 Å) for at least 3 h. ^1H NMR spectra were recorded in $CDCl_3$ (unless otherwise indicated) at 300 and 400 MHz. ^{13}C NMR were recorded at 25 and 75 MHz. Chemical shifts (δ) are expressed in ppm relative to the internal tetramethylsilane (TMS). Mass spectra were acquired in the CI (CH_4) mode unless otherwise indicated. Melting points are uncorrect. Elemental analyses were performed at Dipartimento di Chimica Generale ed Inorganica, Chimica Analitica, Chimica Fisica of the University of Parma.[23]

All reactions were carried out in a dry nitrogen atmosphere. Analytical TLC was performed on precoated silica gel plates (Merck, 60 F_{254}), and column chromatography was performed with silica gel (Merck, particle size 0.040–0.063 mm, 230–240 mesh). Calix[4]arenes **1d**,[24] **9a**,[13] and **2c**[25] were synthesized according to literature procedures.

5,17-Bis(1,1-dimethylethyl)-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene (2d). To a solution of **8** (0.70 g, 1.0 mmol) dissolved in DMF (60 mL) were added NaH (50% in oil, 0.10 g, 2.1 mmol) freed from protective oil by two hexane washings and 2-bromoethyl ethylether (0.47 g, 3.1 mmol) at room temperature. The reaction was vigorously stirred at 80 °C for 3 h, and then the solvent was evaporated under reduced pressure. The mixture was taken up with water (caution!) and extracted with ethyl acetate (100 mL). The organic layer was separated and washed with 0.01 N HCl (100 mL) and then twice with water, and the solvent was evaporated under vacuum to afford **2d** as a white solid. The reaction can be followed by TLC (hexane/ethyl acetate 85:15): yield 80%; mp 186–188 °C (lit. 188 °C).[17]

5-Formyl-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene (3). 1,1-dichloromethyl ether (1.13 g, 9.8 mmol) and **2a** (0.50 g, 0.70 mmol) were dissolved in chloroform (50 mL) and cooled at −10 °C, tin tetrachloride (2.55 g, 9.8 mmol) was added, and the reaction mixture was stirred for 30 min and then treated with water (100 mL). The organic layer was separated, washed twice with water, and dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. Purification by column chromatography (hexane/ethyl acetate 6:4) afforded 0.37 g of **3** as viscous oil (yield 50%): ^1H NMR (100 MHz) δ 1.12 and 1.27 (2t, 12H, J = 7.0 Hz), 3.14 and 3.22 (2d, 4H, J = 13.5 Hz), 3.53 (bq, 8H), 3.75–3.88 (m, 8H), 4.04–4.21 (m, 8H), 4.47 and 4.56 (2d, 4H, J = 13.5 Hz), 6.52 (bs, 3H), 6.65 (bs, 6H), 7.11 (s, 2H), 9.61 (s, 1H); ^{13}C NMR (25 MHz) δ 15.2, 30.8, 66.3, 69.6, 69.8, 73.2, 73.6, 122.2, 122.5, 128.1, 128.2, 128.6, 130.0, 131.1, 134.3, 135.3, 136.8, 156.7, 156.9, 162.6, 191.6; MS *m/e* 741 ($M + H^+$).

Bisformylation of 25,26,27,28-tetralkoxycalix[4]arenes. To a solution of the appropriate tetralkoxycalix[4]arene (**2a** or **2c**) (0.7 mmol) in $CHCl_3$ (35 mL) cooled at −10 °C were added 1,1-dichlorodimethyl ether (1.45 g, 12.6 mmol) and tin tetrachloride (3.28 g, 12.6 mmol). The reaction mixture was stirred at −10 °C for 30 min and then treated with water (100 mL). The organic layer was washed twice with water and dried (Na_2SO_4) and the solvent evaporated under reduced pressure.

5,17-Diformyl-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene (4a). Purification by column chromatography (hexane/ethyl acetate 1:1) afforded 0.35 g of **4a** (yield 65%): mp 64–66 °C; ^1H NMR (300 MHz) δ 1.17 and 1.20 (2t, 12H, J = 6.9 Hz), 3.26 (d, 4H, J = 13.7 Hz), 3.51 and 3.54 (2q, 8H, J = 6.9 Hz), 3.81–3.84 (m, 8H), 4.14 and 4.18 (2t, 8H, J = 5.3 Hz), 4.58 (d, 4H, J = 13.7 Hz), 6.68–6.76 (m, 6H), 7.05 (s, 4H), 9.48 (s, 2H); ^{13}C NMR (25 MHz) δ 15.3, 30.7, 66.3, 69.6, 69.7, 73.4, 73.6, 122.8, 128.5, 130.0, 131.2, 134.2, 136.4, 156.0, 162.3, 191.6; MS *m/e* 769 ($M + H^+$); IR (KBr): 2780, 1695 cm^{-1}.

5,17-Diformyl-25,26,27,28-tetrakis(n-octyloxy)calix[4]arene (4c) and 5,11-Diformyl-25,26,27,28-tetrakis(n-octyloxy)calix[4]arene (4'c). Purification by column chromatography afforded 0.163 mg (yield 25%) of bis aldehydes **4c** and **4'c**.[16] Oxidation: the aldehydes mixture (0.10 g, 0.11 mmol) was dissolved in a mixture of $CHCl_3$ (5 mL) and acetone (5 mL) and the solution cooled at 0 °C. Then a solution obtained dissolving $NaClO_2$ (tech, 80%, 0.04 g., 3.6 mmol) and H_2NSO_3H (0.04 g., 4.1 mmol) in H_2O (1 mL) was rapidly added and the reaction mixture stirred at room temperature for additional 3 h. The solvents were completely evaporated, the residue was taken up with 10% HCl (25 mL) and extracted with CH_2Cl_2 (2 × 30 mL), and the organic phase was dried over Na_2SO_4. After evaporation of the solvent, the mixture of the two acids was suspended in ethyl ether (30 mL), CH_2N_2 was added up to a persistent yellow color, the excess of diazomethane was eliminated with CH_3COOH, and the homogeneous solution was evaporated to dryness. Column chromatography separation (hexane/ethyl acetate 92:8) afforded the two diesters **13** and **13'** in 45% (from **4c**) and 55% (from **4'c**) as viscous oils. **13 (diametrical diester)**: ^1H NMR (400 MHz) δ 0.88 (m, 12H), 1.29–1.87 (m, 48H), 3.20 (d, 4H, J = 12.1 Hz), 3.75 and 4.03 (2t, 8H, J = 6.5 Hz), 3.86 (s, 6H), 4.42 (d, 4H, J = 12.1

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Hz), 6.33 (m, 6H), 7.61 (s, 4H); ^{13}C NMR (25 MHz) δ 51.87, 161.8; MS *m/e* 989 (M + H$^+$). **13′ (proximal diester)**: ^{1}H NMR (400 MHz) δ 0.88 (m, 12H), 1.28−1.85 (m, 48 H), 3.10−3.25 (m, 4H), 3.79 (s, 6H), 3.78−3.95 (m, 8H), 3.90−4.47 (m, 4H), 6.44−6.58 (m, 6H), 7.28 (s, 4H); ^{13}C NMR δ 51.99, 167.08; MS *m/e* 989 (M + H$^+$).

5,17-Diformyl-11,23-bis(1,1-dimethylethyl)-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene (4d). To a solution of **2d** (0.30 g, 0.36 mmol) in $CHCl_3$ (20 mL) were added 1,1-dichlorodimethyl ether (1.03 g, 9.0 mmol) and $SnCl_4$ (2.34 g, 9.1 mmol) at room temperature. The reaction was vigorously stirred at room temperature for 1 h and then quenched with 0.1 N HCl (50 mL). The organic layer was separated and washed twice with water and the solvent evaporated under vacuum to afford a white solid which, after column chromatography (hexane/ethyl acetate 8:2) gave **4d** yield 60%: mp 96−98 °C; ^{1}H NMR (300 MHz) δ 1.14 and 1.25 (m, 12H, *J* = 6.9 Hz), 1.31 (s, 18H) 3.17 (d, 4H, *J* = 13.5 Hz), 3.49 and 3.53 (2q, 8H, *J* = 6.9 Hz), 3.77−3.84 (m, 8H), 4.05−4.19 (2t, 8H, *J* = 5.3 Hz), 4.51 (d, 4H, *J* = 13.5 Hz), 6.70 and 7.04 (2s, 8H), 9.23 (s, 2H); ^{13}C NMR (25 MHz) δ 15.2, 31.1, 31.3, 34.1, 66.2, 66.5, 69.5, 69.6, 72.5, 73.8, 125.9, 129.3, 131.3, 134.7, 135.2, 145.5, 154.8, 191.4; MS *m/e* 881 (M + H$^+$).

5,11,17-Triformyl-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene (5). To a solution of **2a** (0.20 g, 0.28 mmol) and 1,1-dichlorodimethyl ether (1.61 g, 14.0 mmol) in $CHCl_3$ (20 mL) was added titanium tetrachloride (2.12 g, 11.2 mmol) at room temperature, the mixture stirred for 1.5 h, and then water (100 mL) added (caution!). The organic layer was separated, washed twice with water, and dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. Purification by column chromatography (hexane/ethyl acetate 4:6) gave 0.09 g of **5** (yield 40%): mp 58−60 °C; ^{1}H NMR (400 MHz) δ 1.14−1.22 (m, 12H), 3.24 and 3.33 (2d, 4H, *J* = 13.4 Hz), 3.4−3.5 (m, 8H), 3.7−3.8 (m, 8H), 4.05 (t, 2H, *J* = 5.3 Hz), 4.1−4.2 (m, 6H), 4.54 (d, 2H, *J* = 13.4 Hz), 4.63 (d, 2H, *J* = 13.4 Hz), 6.49−6.50 (bs, 3H), 7.08 (s, 2H), 7.22 (s, 4H), 9.61 (s, 1H), 9.63 (s, 2H); ^{13}C NMR (25 MHz) δ 15.1, 30.7, 66.3, 69.3, 69.5, 69.7, 73.4, 73.8, 74.0, 122.7, 128.4, 130.0, 130.1, 130.4, 131.2, 131.4, 134.0, 135.5, 136.0, 136.6, 156.0, 162.2, 191.2, 191.4; MS *m/e* 797 (M + H$^+$).

5,11,17,23-Tetraformyl-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene (6). A solution of **2a** (0.50 g, 0.7 mmol) in $CHCl_3$ (12 mL) and a solution of titanium tetrachloride (3.32 g, 17.5 mmol) in $CHCl_3$ (12 mL) were simultaneously added through dropping funnels to a stirred solution of 1,1-dichlorodimethyl ether (4.0 g, 35.0 mmol) in $CHCl_3$ (12 mL) at 40 °C over a period of 10 min. The reaction mixture was stirred for additional 20 min and then treated with water (150 mL) (caution!). The organic layer was separated, washed twice with water, and dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate 3:7) and gave 0.26 g of **6** as a viscous oil (yield 45%): ^{1}H NMR (300 MHz) δ 1.17 (t, 12H, *J* = 7.0 Hz), 3.33 (d, 4H, *J* = 13.9 Hz), 3.50 (q, 8H, *J* = 7.0 Hz), 3.78 (t, 8H, *J* = 4.7 Hz), 4.20 (t, 8H, *J* = 4.7 Hz), 4.62 (d, 4H, *J* = 13.9 Hz), 7.16 (s, 8H), 9.59 (s, 4H); ^{13}C NMR (25 MHz) δ 15.2, 30.8, 66.4, 69.6, 73.9, 130.2, 131.5, 135.7, 161.9, 191.2; MS *m/e* 825 (M + H$^+$).

5,11,17,23-Tetrakis(1,1-dimethylethyl)-25,27-bis(2-ethoxyethoxy)calix[4]arene (7). A mixture of **1d** (25.9 g, 40.0 mmol), K_2CO_3 (6.08 g, 44.0 mmol) and 2-ethoxyethyl tosylate (24.4 g, 100.0 mmol) in CH_3CN (1200 mL) was refluxed for 4 days. The solvent was then evaporated under reduced pressure and the solid residue was triturated with 1 N HCl (300 mL) and extracted with CH_2Cl_2 (300 mL). The organic layer was washed twice with water and evaporated under reduced pressure to give the crude compound **7** which upon recrystallization from petroleum ether afforded **7** as white needles. The reaction can be followed by TLC (hexane/ethyl acetate 8:2): yield 90%; mp 150−151 °C; (300 MHz) δ 0.96 and 1.31 (2s, 36H), 1.28 (t, 6H, *J* = 7.5 Hz), 3.30 (d, 4H, *J* = 13.0 Hz), 3.71 (q, 4H, *J* = 7.5 Hz), 3.93 (t, 4H, *J* = 5.2 Hz), 4.17 (t, 4H, *J* = 5.2 Hz), 4.39 (d, 4H, *J* = 13.0 Hz), 6.79 (s, 4H), 7.06 (s, 4H), 7.21 (s, 2H); ^{13}C NMR (25 MHz) δ 15.3, 31.1, 31.6, 33.6, 34.1, 66.7, 69.2, 75.2, 125.0, 125.6, 128.0, 133.5, 141.7, 147.5, 149.9, 150.3, 156.4, 156.5; MS (EI) *m/e* 793 (M$^+$ + 1).

11,23-Bis(1,1-dimethylethyl)-25,27-bis(2-ethoxyethoxy)calix[4]arene (8). A mixture of $AlCl_3$ (0.80 g, 6.0 mmol) in CH_2Cl_2 (8 mL) was stirred at room temperature for 15 min and then **7** (1.0 g, 1.26 mmol) dissolved in toluene (24 mL) was added. The reaction was vigorously stirred at room temperature for 3 h and then quenched with 1 N HCl (30 mL) and extracted with ethyl acetate (30 mL). The organic layer was separated, washed twice with brine, and evaporated under reduced pressure to give **8** which was recrystallized from methanol (white crystals). The reaction can be followed by TLC (hexane/ethyl acetate 7:3): yield 70%; mp 127−129 °C (CH_3OH); (300 MHz) δ 1.01 (s, 18H), 1.28 (t, 6H, *J* = 6.9 Hz), 3.34 (d, 4H, *J* = 13.2 Hz), 3.71 (q, 4H, *J* = 6.9 Hz), 3.93 (t, 4H, *J* = 5.4 Hz), 4.18 (t, 4H, *J* = 5.4 Hz), 4.41 (d, 4H, *J* = 13.2 Hz), 6.66 (t, 2H, *J* = 7.2 Hz), 6.82 (s, 4H), 7.05 (d, 4H, *J* = 7.2 Hz), 7.42 (s, 2H); ^{13}C NMR (75 MHz) δ 15.2, 31.1, 31.4, 34.0, 66.9, 69.2, 75.2, 118.9, 125.6, 128.2, 132.5, 147.0, 150.0, 150.2; MS (EI) *m/e* 681 (M$^+$ + 1).

5,17-Bis(hydroxymethyl)-11,23-bis(1,1-dimethylethyl)-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene (9d). To a solution of **4d** (0.20 g, 0.23 mmol) dissolved in absolute ethanol (20 mL) was added $NaBH_4$ (0.08 g, 2.1 mmol) at room temperature. The reaction was vigorously stirred for 2 h and then quenched with a saturated solution of ammonium chloride (50 mL). The solution was extracted with 100 mL of ethyl acetate, and the organic layer was separated and washed twice with water. The solvent was evaporated under vacuum to afford **9d** as white solid in quantitative yield: mp 140−142 °C; (400 MHz) δ 1.10 and 1.17 (2t, 12H, *J* = 7.0 Hz), 1.29 (s, 18H) 3.03 (d, 4H, *J* = 13.3 Hz), 3.45 and 3.51 (2q, 8H, *J* = 7.0 Hz), 3.71 and 3.85 (2t, 8H, *J* = 4.9 Hz), 3.86 and 4.20 (2t, 8H, *J* = 4.9 Hz), 3.94 (s, 4H), 4.40 (d, 4H, *J* = 13.3 Hz), 6.10 and 7.02 (2s, 8H);^{13}C NMR (25 MHz) δ 15.3 and 15.4, 31.2, 31.7, 34.2, 64.5, 66.5, 69.7, 72.3, 74.0, 125.8, 133.7, 135.6, 136.2, 143.2, 145.6, 154.3, 155.3; MS (EI) *m/e* 885 (M$^+$ + 1).

5,17-Bis(chloromethyl)-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene (10a). To a solution of **9a** (0.10 g, 0.13 mmol) in CH_2Cl_2 (2 mL) was added thionyl chloride (0.20 g, 1.7 mmol). The reaction was stirred for 2 h at room temperature and then treated with 10 mL of water (caution!) and extracted with 10 mL of CH_2Cl_2. The organic layer was separated and washed twice with water and the solvent evaporated under reduced pressure to afford in quantitative yield compound **10a**. The reaction can be followed by TLC (hexane/ethyl acetate 6:4): mp 111−113 °C; ^{1}H NMR (400 MHz) δ 1.20 and 1.21 (2t, 12H, *J* = 7.0 Hz), 3.15 (d, 4H, *J* = 13.5 Hz), 3.52 (q, 8H, *J* = 7.0 Hz), 3.81 (bt, 8H, *J* = 5.3 Hz), 4.12 (t, 8H, *J* = 5.3 Hz), 4.19 (s, 4H), 4.46 (d, 4H, *J* = 13.5 Hz), 6.59 (s, 4H), 6.62−6.65 (m, 6H); ^{13}C NMR (25 MHz) δ 15.3, 30.8, 46.6, 66.4, 69.6, 73.1, 73.4, 122.5, 128.4, 128.5, 130.9, 134.8, 135.3, 156.4, 156.5; MS *m/e* 809 (M + H$^+$).

5,17-Bis(chloromethyl)-11,23-bis(1,1-dimethylethyl)-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene (10d).[26] To a solution of **2d** (0.82 g, 1.0 mmol) in dichloromethane (100 mL) were added dimethoxymethane (0.86 g, 11.0 mmol), thionyl chloride (1.55 g, 13.0 mmol), and $SnCl_4$ (0.42 g, 1.6 mmol). The reaction was stirred for 1 h at room temperature and then treated with 100 mL of water (caution!). The organic layer was separated and washed twice with water and the solvent evaporated under reduced pressure. Purification by column chromatography (hexane/ethyl acetate 8:2) gave 0.587 g of **10d** (yield 63%): mp 101−103 °C; ^{1}H NMR (400 MHz) δ 1.17 and 1.23 (2t, 12H, *J* = 7.0 Hz), 1.30 (s, 18H), 3.09 (d, 4H, *J* = 13.2 Hz), 3.51 and 3.56 (2q, 8H, *J* = 7.0 Hz), 3.79 and 3.88 (2t, 8H, *J* = 5.0 Hz), 3.96 and 4.21 (2t, 8H, *J* = 5.0 Hz), 3.99 (s, 4H), 4.45 (d, 4H, *J* = 13.2 Hz), 6.27 and 7.00 (2s, 8H);^{13}C NMR (25 MHz) δ 15.7, 15.8, 31.5, 31.9, 34.5, 46.9, 66.6, 66.8, 69.8, 70.1, 72.9, 74.2, 126.1, 128.2, 131.2, 132.5, 133.9, 145.4, 154.8, 155.3; MS (EI) *m/e* 921 (M$^+$ + 1).

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Intramolecular Cyclization. A two-necked round-bottom flask, equipped with N_2 inlet and stirring bar, was charged with toluene (900 mL), DME (100 mL), the appropriate 5,17-bis(hydroxymethyl)calix[4]arene (**9a** or **9d**) (1.0 mmol), *p*-toluenesulfonyl chloride (0.19 g, 1.0 mmol), and NaH (50% in oil, 0.048 g, 1.0 mmol) freed from protective oil by two hexane washings. The solution was stirred at 60 °C for 48 h and then concentrated under vacuum. The residue was quenched with water (caution!) and extracted with ethyl acetate. The organic layer was separated, washed twice with water, and evaporated to afford a white solid which was further purified by column chromatography (hexane/ethyl acetate 7:3).

11a: yield 30%; ^{1}H NMR (400 MHz) δ 1.14 and 1.24 (2t, 12H, J = 7.0 Hz), 3.13 (d, 4H, J = 14.1 Hz), 3.51 and 3.59 (2q, 8H, J = 7.0 Hz), 3.67 and 3.82 (2t, 8H, J = 6.4 Hz), 3.90 and 4.16 (2t, 8H, J = 6.4 Hz), 4.47 (d, 4H, J = 14.1 Hz), 3.5 and 4.6 (2bs, 4H) 5.6 and 5.9 (2bs, 4H), 6.99 (t, 2H, J = 7.4 Hz), 7.15 (d, 4H, J = 7.4 Hz); ^{13}C NMR (25 MHz) δ 15.8, 31.4, 66.7, 67.1, 70.1, 70.3, 72.8, 74.0, 76.3, 122.4, 128.0, 129.6, 134.1, 137.9, 154.7, 157.9; MS *m/e* 755 (M + H$^+$).

11d: yield 40%; mp 90–91 °C; ^{1}H NMR (400 MHz) δ 1.07 and 1.17 (2t, 12H, J = 7.0 Hz), 1.35 (s, 18H), 3.02 (d, 4H, J = 14.0 Hz), 3.42 and 4.48 (2bs, 4H) 3.42 and 3.51 (2q, 8H, J = 7.0 Hz), 3.70 and 3.82 (2t, 8H, J = 5.16 Hz), 3.67 and 4.05 (2t, 8H, J = 5.16 Hz), 4.38 (d, 4H, J = 14.0 Hz), 5.7 (bs, 4H), 7.04 (s, 4H); ^{13}C NMR (25 MHz, $C_2D_2Cl_2$) δ 15.2, 31.7, 32.0, 33.9, 66.2, 66.4, 69.4, 70.0, 73.4, 125.8, 127.3, 132.9, 133.5, 136.3, 144.4, 154.2, 156.4; MS *m/e* 867 (M + H$^+$).

Synthesis of Double Calix[4]arenes 12a,d. A two-necked round-bottom flask was charged with 5,17-bis-(hydroxymethyl)calix[4]arene **9a** or **9d** (1.0 mmol) dissolved in DMF (2 mL) and $CsOH{\cdot}H_2O$ (0.33 g, 2.0 mmol). The mixture was stirred for 10 min and then evaporated to dryness under vacuum (high vacuum pump). The pale yellow solid was suspended in DMF (distilled, 80 mL), and the appropriate 5,-17-bis(chloromethyl)calix[4]arene **10a** or **10d** (1.0 mmol) was added. The mixture was stirred for 7 h at room temperature and then evaporated under reduced pressure. The solid was then taken up with 0.01 N HCl (100 mL) and extracted with ethyl acetate. The organic layer was separated, washed twice with water, and evaporated to afford a white solid which was further purified by column chromatography (hexane/ethyl acetate 8:2).

12a: yield 42%; mp 176–177 °C (MeOH); ^{1}H NMR (400 MHz) δ 1.18 and 1.25 (2t, 24H, J = 7.0 Hz), 3.15 (d, 8H, J = 13.0 Hz), 3.40 (s, 8H), 3.52 and 3.56 (2q, 16H, J = 7.0 Hz), 3.77 and 3.90 (2t, 16H, J = 5.2 Hz), 3.99 and 4.37 (2t, 16H, J = 5.2 Hz), 4.51 (d, 8H, J = 13.0 Hz), 6.16 (s, 8H), 6.98 (t, 4H, J = 7.2 Hz), 7.20 (d, 8H, J = 7.2 Hz); ^{13}C NMR (25 MHz) δ 15.2, 15.4, 31.0, 66.2, 66.5, 69.7, 69.7, 72.3, 74.2, 74.2, 122.4, 126.5, 128.9, 132.0, 133.0, 136.5, 153.7, 155.1; MS *m/e* 1509 (M + H$^+$).

12d: yield 38%; mp 208–210 °C (MeOH); ^{1}H NMR (400 MHz) δ 1.17 and 1.25 (2t, 24H, J = 6.9 Hz), 1.31 (s, 36H), 3.09 (d, 8H, J = 12.9 Hz), 3.41 (s, 8H), 3.52 and 3.56 (2q, 16H, J = 6.9 Hz), 3.74 and 3.96 (2t, 16H, J = 5.5 Hz), 3.87 and 4.29 (2t, 16H, J = 5.5 Hz), 4.45 (d, 8H, J = 12.9 Hz), 6.12 (s, 8H), 7.08 (s, 8H); ^{13}C NMR (25 MHz) δ 15.3, 31.7, 32.1, 34.3, 66.2, 66.5, 69.5, 69.6, 72.1, 72.8, 74.1, 125.5, 132.2, 132.9, 133.6, 144.8, 153.7, 155.1; MS *m/e* 1733 (M + H$^+$).

X-ray Structural Analysis of Compound 12d. Compound **12d** crystallized in the triclinic space group $P\bar{1}$ with a = 15.994(4), b = 17.168(4), c = 22.004(5) Å, α = 113.71(2), β = 105.13(2), γ = 80.02(2)°, V = 5308(2) Å^3, D_{calcd} = 1.085 g cm^{-3}, and Z = 2. the data were collected on a Siemens AED diffractometer using Ni-filtered Cu-K$_\alpha$ radiation (λ = 1.54178 Å), and the intensities were determined by profile analysis.[27] A total of 16260 $\pm$ h $\pm$ k + l reflections were measured and used in the structure solution by direct methods with SHELX86.[28] The 6303 unique observed reflections $I \geq 2\sigma(I)$ were used in the least-squares refinement which was carried out with SHELX76.[29] Parameters refined were the overall scale factor, the atomic coordinates, the anisotropic thermal parameters for all non H atoms with the exception of those of the *tert*-butyl groups at the B, D, H units and those of the ethereal chains at E, G, H units for which isotropic temperature factors were used. The H atoms were put in their calculated positions with the geometrical constraint C–H = –0.96Å and refined "riding" on the corresponding C atom.

The refinement was stopped at R = 0.076 (unit weights). No guest molecules were found neither in the intramolecular cavity nor in the lattice.

The atomic scattering factors of the non-hydrogen atoms were taken from Cromer and Waber,[30] the values of $\Delta f'$ and $\Delta f''$ were those of Cromer. The geometrical calculations were obtained by PARST.[32] All the crystallographic calculations were performed on the Gould 6040 Powermode of Centro di Studio per la Strutturistica Diffrattometrica del C. N. R., Parma, Italy.

A complete list of atomic coordinates (Table S 1), thermal parameters (Table S 2), coordinates of H atoms (Table S 3), a complete list of bond distances and angles (Table S 4), and a full list of the experimental data for the X-ray diffraction experiment (Table S5) have been deposited together with the list of the observed and calculated structure factors and are available on request.[33]

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Supplementary Material Available: ^{1}H NMR spectra of all new compounds **3, 4a, 4c, 4'c, 4d, 5, 6, 7, 8, 9a, 9d, 10a, 10d, 11a, 11d, 12a, 12d, 13, 13'** (18 pages). This material is contined in libraries on microfiches, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(33) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.