Tetrahedron Vol. 46, No. 2, pp. 671-682, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00
Pergamon Press plc

A STEPWISE SYNTHESIS OF FUNCTIONALIZED CALIX[4]ARENES AND A CALIX[6]ARENE WITH ALTERNATE ELECTRON-WITHDRAWING SUBSTITUENTS.

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(*Received in UK* 11 *September* 1989)

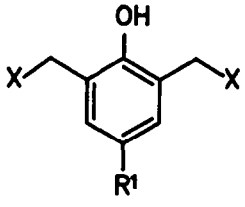
Abstract. Simple modifications of the $TiCl_4$-induced cyclocondensation of phenol derivatives raise the yields of pure calix[4]arenes, even in the presence of electron-withdrawing substituents. The first example of a calix[6]arene with alternate substituents is given.

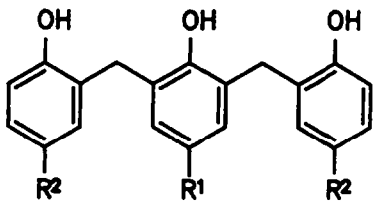
Most enzymic reactions take place inside highly hydrophobic cavities, where the substrate is fixed by non-covalent interactions in a well defined orientation with respect to the protein receptor. The discovery of new structures endowed with both hydrophobic cavities and functional groups to provide binding sites or to achieve chemical reactions is therefore a major goal in bio-organic chemistry.

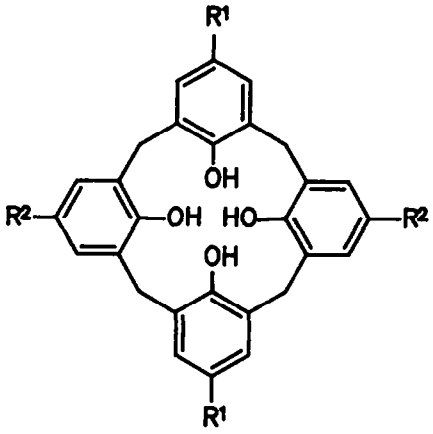
The cyclic array of aromatic rings in calix[n]arenes (n=4-8)[1] provides a cavity-shaped structure, well suited for inclusion of ionic or molecular guests. However, the use of calixarenes for bio-organic studies has been hampered by the lack of good synthetic methods for selectively functionalized derivatives, and most published work on the area is based on the step consumming chemical modification of the readily accessible 4-*tert*-butylcalix[4]arene, made in a one-pot reaction from 4-*tert*-butylphenol and formaldehyde.[2] Selective functionalization is difficult as well, and the routes developed so far to introduce functional groups at the phenol rings lead to tetrasubstituted derivatives, having the same substituents at all the *para* positions.[3,4] Among the alternative stepwise synthetic methods from 4-substituted phenols,[5] the titanium(IV)-induced cyclocondensation of linear trimers with a 2,6-bis-bromomethylated phenol (eq 1), described recently by Böhmer and coworkers,[6] can be considered as the most promising one.

Although many calix[4]arenes with four different substituents can be prepared by this unequivocal sequence, the yields after chromatographic purification are only moderate (12-14%) when the substituents are alkyl or phenyl groups, and deceptively poor (3-9%) in the more interesting cases when one of the substituents is an electron-withdrawing group, such as Cl or CO_2Et.[7] We describe herein the synthesis of the novel calix[4]arenes 13-18, containing at least two electron-withdrawing groups at alternate rings, from

the appropriate monomers 1-4 and trimers 5-12, as well as the first example of a calix[6]arene endowed with alternate substituents.







1 R^1 = ^{t}Bu
2 R^1 = Cl
3 R^1 = CO_2Et
4 R^1 = NO_2

a (X = OH)
b (X = Br)
c (X = Cl)

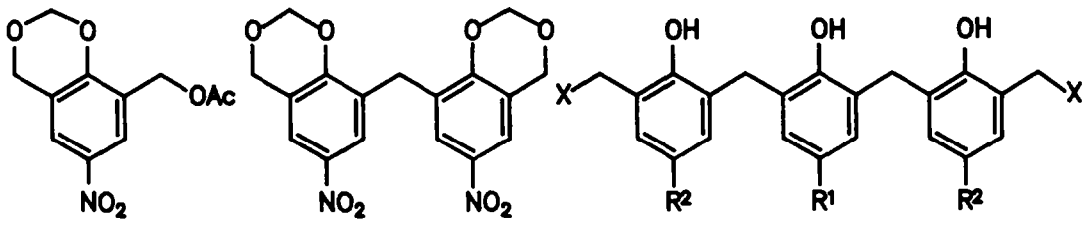
5 R^1 = ^{t}Bu; R^2 = Cl
6 R^1 = Cl; R^2 = ^{t}Bu
7 R^1 = R^2 = Cl
8 R^1 = Cl; R^2 = NO_2
9 R^1 = CO_2Et; R^2 = ^{t}Bu
10 R^1 = NO_2; R^2 = ^{t}Bu
11 R^1 = NO_2; R^2 = Cl
12 R^1 = NO_2; R^2 = CO_2Et

13 R^1 = ^{t}Bu; R^2 = Cl
14 R^1 = R^2 = Cl
15 R^1 = ^{t}Bu; R^2 = CO_2Et
16 R^1 = Cl; R^2 = NO_2
17 R^1 = ^{t}Bu; R^2 = NO2
18 R^1 = NO_2; R^2 = CO_2Et
21 R^1 = R^2 = H

Synthesis of monomer and trimer precursors 1-12 and 22

Monomers **1b-3b** were obtained according to described procedures. Thus, **1b**[8] was prepared by a direct bromomethylation of 4-*tert*-butylphenol, whereas **2b** and **3b**,[6] carrying electron-withdrawing substituents, were obtained in two steps, *via* the corresponding 2,6-bis(hydroxymethyl) intermediates **2a**[9] and **3a**.[10] None of these methods was successful with 4-nitrophenol, but reaction with paraformaldehyde at 55-60°C under acidic conditions afforded the 1,3-benzodioxene derivative **19** in quantitative yield. Use of higher temperatures gave mixtures of **19** and the bis-benzodioxene **20**.[11] Treatment of **19** with the apropriate reagent (HCl/H_2O, HBr, HCl) afforded the respective substituted compounds **4a**, **4b**, and **4c**. Although the synthesis of **4c** by this method required two steps, the overall yield (73-81%) was higher than the yield reported by direct chloromethylation (40%).[12]

Trimers **5-12** were obtained in high yields from 2,6-bis(hydroxymethyl)phenols **1a-4a** and the appropriate 4-substituted phenol. Compounds **6**, **9**, **10**, and **12** were obtained by direct melting of both components, whereas compounds **5**, **8**, and **11** were prepared in acetic acid as solvent (H_2SO_4 catalysis). Significant improvement of the reported yields for **8**,[13] **11**,[14] and **6**,[15] was achieved. The bis(bromomethyl) derivative **22b** was obtained by hydroxymethylation of **5** to give **22a** followed by substitution with HBr.



19 20 22a (X = OH)
22b (X = Br)

Synthesis of calix[4]arenes 13-18 and calix[6]arene 23.

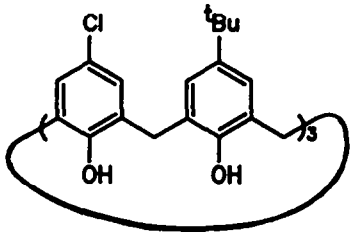
Typical Böhmer conditions are reflux (50-100 hours) of equimolecular amounts of monomer and trimer components in anhydrous dioxane (*ca.* 10^{-2} M in each component) in the presence of an excess of $TiCl_4$ (5-7 equiv.).[6,7] We found that crude reaction mixtures of most of these reactions showed NMR spectra corresponding to quasi-pure calixarenes, without significant traces of starting materials nor secondary products, especially when the reactions were carried out at higher dilution conditions (10^{-3} to $5x10^{-3}$ M) and with slow addition of both reactants (Table 1). Consequently, the low yields reported should be mainly due to a loss of compound during isolation or purification. For example, trimers **11** and **12** reacted with monomer **4b** under the conditions described above to give crude reaction mixtures whose NMR spectra were fully compatible with the expected calix[4]arenes **16** and **18**, but none of these compounds was isolated after the standard work-up (addition of silica gel, evaporation, extraction in a Soxhlet apparatus, further evaporation and purification by flash chromatography).[6] However, a proper choice of the work-up conditions, without adhering to silica gel chromatographic separation (see Table 1), gave a 27% yield of **16** and a 25% yield of **18**. The yield was even somewhat higher (30%) for calix[4]arene **13** (no NO_2 nor CO_2Et groups). It is noteworthy that **13** was also obtained in a 13% yield by direct reaction of trimer **5** with 4-*tert*-butyl-2,6-bis(hydroxymethyl)phenol (**1a**).

The synthesis of calix[4]arene **14** was claimed by Moshfegh *et al.* in 1982,[16] but this result was questioned by Gutsche, on the grounds of the low melting point described for this material (239-242°C).[17] We have now obtained **14** by two different ways. The Böhmer[3+1] approach, from **2b** and **7**, afforded a 12% yield, whereas direct chlorination of calix[4]arene **21**[18] with *N*-chlorosuccinimide gave a 38% yield of **14**.

Calix[6]arenes have been so far obtained by the one-step Gutsche procedure,[2a] or by the long stepwise [1+1+1+1+1+1] route described by Kämmerer.[5e] Only calix[6]arenes with the same substituent at each *para* position, were reported. We decided then to achieve a synthesis of a

calix[6]arene by a [3+3] Böhmermethodology.

Addition of **6** to a dioxane $TiCl_4$ solution followed by slow addition of **22b**, and heating for four days at 110°C afforded **23** in a 9% yield. To our surprise, use of the bis derivative **22a** instead of **22b**, or prolonged reaction times of more than six days afforded variable amounts of the calix[4]arene **13**, along with the expected compound **23**. The formation of **13** must be accounted in terms of a ring contraction of **23**, as soon as it is formed under the reaction conditions. This type of rearrangement has been precedented in the ring contraction of calix[8]arenes to calix[4]arenes under basic catalysis,[1] but no examples under acidic conditions, nor of a [6]-to-[4] shift are known.[19]



23

Run	Compd.	Reactants (conc.)	Conc. Ti^{4+}	Reflux	Work-up	Yield(%)
1	13	1a+5 (4.76×10^{-3}M)	3.65×10^{-2}M	120 hr	A (hexane)	13
2	13	1b+5 (5.16×10^{-3}M)	2.03×10^{-2}M	96 hr	A (hexane)	30
3	14	2b+7 (5.58×10^{-3}M)	3.36×10^{-2}M	120 hr	A (toluene)	3
4	14	2b+7 (5.58×10^{-3}M)	4.48×10^{-2}M	120 hr	A (toluene)	12
5	15	3b+9 (4.07×10^{-3}M)	4.56×10^{-2}M	80 hr	B	6
6	16	4b+11 (3.44×10^{-3}M)	4.30×10^{-2}M	96 hr	C	11
7	16	4b+11 (3.44×10^{-3}M)	5.10×10^{-2}M	96 hr	C	27
8	17	4b+10 (4.99×10^{-3}M)	4.66×10^{-2}M	60 hr	C	5
9	18	4b+12 (5.05×10^{-3}M)	4.56×10^{-2}M	192 hr	C	25

Table 1. Synthesis of calixarenes.
A: evaporation with SiO_2, Soxhlet extraction with indicated solvent (50-150 hr), evaporation and trituration with ether.
B: evaporation, trituration with CH_2Cl_2, filtration, evaporation with SiO_2, Soxhlet extraction with toluene (20 hr), evaporation and precipitation with CCl_4.
C: evaporation, trituration with CH_2Cl_2, filtration, evaporation and trituration with ether.

Conformation of calixarenes 13-18 and 23

The new calixarenes showed typical ^{1}H-NMR spectra for the so-called cone conformations, although 1,3-alternate conformations could be possible as well, due to the alternate distribution of the substituents. Irradiation of each of the aromatic protons resulted in an increase in the signal intensity of the other aromatic proton (4-4.5%), as well as of methylene (6%) and *tert*-butyl (5%) signals. Although not conclusive, these NOE enhancements point to the cone conformation as the most likely. A more detailed study, including dipole moment measurements, is underway.

On the other hand, variable temperature NMR experiments on **13** and **18** showed typical splitting of the methylene singlets to doublets on cooling. Although these changes in the NMR spectra of calix[4]arenes have been

interpreted as shifts between cone and alternate conformations,[20] recent studies of activation parameters by Shinkai revealed that this conformational transition state does not exist, and that changes are due simply to a slow inversion of the cone conformation.[21] Our NMR results (Table 2) showed coalescence temperatures similar to other reported conformational barriers for calix[4]arenes in cone conformation.[20]

Compound	Solvent	Δ(Hz)	J(Hz)	T_c(K)	$G^{\neq}$(kcal/mol)
13	Chloroform	142.1	13.9	312	14.8
	Pyridine	281.7	12.7	270	12.4
18	Chloroform	104.5	14.2	299	14.3
	Pyridine	244.8	12.9	299	13.8
	Acetonitrile	90.8	13.7	250	12.0

Table 2. Coalescence temperatures and conformational barriers,[20] measured by ^{1}H-NMR on the methylene protons.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were registered on a Bruker WP 200 SY instrument, electron-impact mass spectra on a Hewlett-Packard 5985, and infrared spectra on a Philips PV-9700. Silica gel Merck 70-230 mesh, 230-400 mesh, and Alugram Sil G/UV$_{254}$ were used for conventional, flash, and analytical thin layer chromatography, respectively. T.l.c. plates were revealed by UV light and/or by iodine. Most chemicals were purchased from Aldrich Co., and used as received without further purification. Organic solvents were purified by standard procedures. Anhydrous dioxane was distilled from benzophenone and sodium under an argon atmosphere, immediately prior to use. Compounds **1a**,[22] **1b**,[8] **2a**,[9] **3a**,[10] **3b**,[6] and **7**[23] were obtained according to described procedures.

2,6-Bis(bromomethyl)-4-chlorophenol, (**2b**).

A mixture of 2,6-bis(hydroxymethyl)-4-chlorophenol (**2a**) (1.00 g, 5.3 mmole) and conc. hydrobromic acid (40 ml) was stirred at room temperature for 15 hours. Cold water (30 ml) was added and the mixture was filtered *in vacuo*. The collected solid was washed with cold water (3x30 ml) and dried, to give **2b** (1.63 g, 98%), m.p. 119-120°C (H_2O). IR (nujol): 3520 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 4.49 (s, 4H), 5.57 (s, 1H), and 7.26 (s, 2H) ppm. MS: *m/z* (relat. abund.) 314 (M^++2, 1.6), 312 (M^+, 1.4), 235 (18.5), 234 (3.3), 154 (14.9), 153 (100).

8-Acetoxymethyl-6-nitro-1,3-benzodioxene, (**19**).

4-Nitrophenol (13.9 g, 0.1 mole) was added over a hot mixture (55-60°C) of paraformaldehyde (12.0 g, 0.4 mole), acetic acid (50 ml), and concentrated sulfuric acid (21.9 ml), and the reaction was maintained at this temperature for 35 hours. Water (60 ml) was added at room temperature, and the mixture was neutralized by slow addition of solid K_2CO_3 (*ca.* 0.4 mole). The colorless solid was filtered and washed with cold water, dried and recrystallized from ethanol. Yield was 25.1 g (99%), m.p. 118°C (ethanol or acetic acid). IR (KBr): 1750, 1540, 1355, and 1260 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.17 (s, 3H), 4.97 (s, 2H), 5.16 (s, 2H), 5.38 (s, 2H), 7.90 (d, J=2.6 Hz, 1H), and 8.15 (d, J=2.6 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ 20.8, 59.8, 65.9, 91.9, 121.0, 121.3, 123.2, 125.3, 141.2, 155.2, and 170.5 ppm. MS: *m/z* (relat. abund.) 253 (M^+, 31.5), 223 (12.2), 210 (10.0), 181 (100), 180 (18.7), 164 (77.7), 134 (23.2). Variable amounts of dimer **20** were formed at

temperatures above 60°C, m.p. 216-218°C (lit.[11] 218°C). IR (KBr): 1520, 1350 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.99 (s, 2H), 4.96 (s, 4H), 5.37 (s, 4H), 7.84 (d, *J*=2.5 Hz, 2H), 7.93 (d, *J*=2.5 Hz, 2H) ppm. (Found: C 52.35, H 4.60, N 5.43. $C_{10}H_{11}NO_6$ requires C 52.18, H 4.38, N 5.53).

2,6-Bis(hydroxymethyl)-4-nitrophenol, (4a).

A mixture of 19 (2.0 g, 7.9 mmole), water (60 ml), and conc. hydrochloric acid (40 ml) was refluxed for 7 hours. After cooling, the solid was filtered and the filtrate was evaporated *in vacuo*, to give a yellow solid, which was purified by shaking with chloroform for 24 hours. The yield was 1.2 g (76%), m.p. 160°C (ethyl acetate). IR (nujol): 3500, 3410, 1520, 1340, 1220 cm^{-1}. ^1H NMR (*d*$_6$-acetone): δ 4.84 (d, *J*=5.0 Hz, 4H), 5.50 (t, *J*=5.0 Hz, 2H), 8.10 (s, 2H), and 9.72 (br s, 1H) ppm. ^{13}C NMR (*d*$_6$-acetone): δ 61.2, 122.4, 129.0, 141.4, and 160.0 ppm. MS: *m/z* (relat. abund.) 199 (M^+, 47.2), 181 (60.2). (Found: C 48.29, H 4.60, N 6.92. $C_8H_9NO_5$ requires C 48.24, H 4.55, N 7.03).

2,6-Bis(bromomethyl)-4-nitrophenol, (4b).

A mixture of 19 (2.00 g, 7.9 mmole) and 48% hydrobromic acid (60 ml) was refluxed for 6 hours. The reaction mixture was then filtered at room temperature, and the resulting solid was washed with cold water, dried and recrystallized from chloroform, to give 2.43 g (94%) of 4b, m.p. 146-147°C (dioxane or $CHCl_3$). IR (nujol): 3500-3200, 1525, 1340, 1255 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.57 (s, 4H), 6.50 (s, 1H), and 8.22 (s, 2H) ppm. ^{13}C NMR ($CDCl_3$ + *d*$_6$-acetone): δ 27.1, 125.8, 126.6, 140.0, and 158.4 ppm. MS: *m/z* (relat. abund.) 327 (M^++4, 6.6), 325 (M^++2, 10.9), 323 (M^+, 5.4), 246 (100), 244 (87.6), 165 (16.3), 164 (86.0). (Found: C 29.44, H 2.12, N 4.24. $C_8H_7Br_2NO_3$ requires C 29.57, H 2.17, N 4.31).

2,6-Bis(chloromethyl)-4-nitrophenol, (4c).

A mixture of 19 (2.00 g, 7.9 mmole) and conc. hydrochloric acid (65 ml) was heated under reflux for 7 hours. The resulting pale yellow solid was filtered at room temperature, washed with cold water, dried, and recrystallized from benzene, to give 1.74 g (94%) of 4c, m.p. 134°C (lit.[12] 134.2°C). IR (KBr): 3420, 1515, 1340, 1190 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.72 (s, 4H), 6.54 (s, 1H), and 8.28 (s, 2H) ppm. ^{13}C NMR (*d*$_6$-DMSO): δ 41.3, 126.3, 127.1, 139.3, and 159.8 ppm. MS: *m/z* (relat. abund.) 239 (M^++4, 4.0), 237 (M^++2, 13.7), 235 (M^+, 23.9), 200 (42.0), 199 (68.3), 164 (24.7), 165 (10.6), 91 (100).

4-tert-Butyl-2,6-bis[(5-chloro-2-hydroxyphenyl)methyl]phenol, (5).

A mixture of 4-*tert*-butyl-2,6-bis(hydroxymethyl)phenol (1a) (2.50 g, 11.9 mmole) and 4-chlorophenol (5.40 g, 29.8 mmole) was heated at 80-90°C and then a catalytic amount of conc. sulfuric acid was added. After 30 min, the mixture was cooled and filtered, and the solid collected was washed with cold water, and dried. Recrystallization in chloroform afforded 5 (4.44 g, 87%), m.p. 259°C. IR (nujol): 3200, 1605, 1490, 1225 cm^{-1}. ^1H NMR (*d*$_6$-DMSO): δ 1.18 (s, 9H), 3.81 (s, 4H), 6.80 (d, *J*=8.6 Hz, 2H), 6.90 (d, *J*=2.6 Hz, 2H), 6.99 (s, 2H), 7.02 (dd, *J*=8.6 and 2.6 Hz, 2H), 8.22 (s, 1H), and 9.84 (s, 2H) ppm. ^{13}C NMR (*d*$_6$-DMSO): δ 37.3, 117.0, 124.6, 126.6, 126.8, 127.4, 130.5, 143.4, 150.4, and 153.6 ppm. MS: *m/z* (relat. abund.) 432 (M^++2, 35.5), 431 (M^++1, 13.0), 430 (M^+, 49.7), 415 (96.6), 374 (46.0), 287 (25.8), 275 (24.9), 141 (100). (Found: C 66.29, H 5.80. $C_{24}H_{24}Cl_2O_3$ requires C 66.86, H 5.61).

2,6-Bis[(5-tert-butyl-2-hydroxyphenyl)methyl]-4-chlorophenol, (6).

A mixture of 4-*tert*-butylphenol (6.36 g, 42.4 mmole) and 2,6-bis(hydroxymethyl)-4-chlorophenol (2a) (2.00 g, 10.6 mmole) was heated at 120°C and then conc. hydrochloric acid (0.5 ml) was added. After 30 min, the reaction was allowed to cool down to room temperature, and most of the

unreacted 4-*tert*-butylphenol was removed by sublimation. Recrystallization in hexane of the residue afforded **6** (2.40 g, 50%), m.p. 181°C. IR (KBr): 3220, 1610, 1510, 1230, 820 cm^{-1}. ^1H NMR (*d*$_6$-DMSO): δ 1.18 (s, 18H), 3.80 (s, 4H), 6.73 (d, *J*=8.0 Hz, 2H), 6.76 (s, 2H), 7.04 (dd, *J*=8.0 and 1.9 Hz, 2H), 7.10 (d, 2H, *J*=2.1 Hz), 8.79 (s, 1H), and 9.39 (s, 2H) ppm. ^{13}C NMR (*d*$_6$-acetone): δ 30.2, 31.4, 33.6, 114.6, 122.7, 123.9, 125.2, 125.9, 127.5, 130.2, 140.8, 141.3, 151.2, and 152.4 ppm. MS: *m/z* (relat. abund.) 454 (M^++2, 6.0), 452 (M^+, 15.7), 302 (40.8), 287 (57.0), 247 (29.9), 221 (85.8), 163 (66.7), 147 (78.4), 53 (100). (Found: C 73.85, H 7.40. $C_{28}H_{33}ClO_3$ requires C 74.24, H 7.34).

4-Chloro-2,6-bis[(5-nitro-2-hydroxyphenyl)methyl]phenol, (**8**).

2,6-Bis(hydroxymethyl)-4-chlorophenol (**2a**) (2.0 g, 10.6 mmole) was added over a solution of 4-nitrophenol (7.4 g, 56.0 mmole) in a mixture of acetic acid (8 ml) and sulfuric acid (2 ml), at 90-100°C. The reaction mixture was maintained at 100°C for 45 min, and then neutralized at room temperature with potassium carbonate (*ca.* 38 mmole). Water (70 ml) was added, and the solid which appeared was filtered and washed with cold water. The solid was finally shaked for 15-20 hours with acetic acid, filtered and recrystallized in acetic acid, to give **8** (4.0 g, 88%), m.p. 268°C (lit.[13] 270°C). IR (KBr): 3500-3000, 1510, 1340 cm^{-1}. ^1H NMR (*d*$_6$-DMSO): δ 3.91 (s, 4H), 6.91 (s, 2H), 6.98 (d, *J*=8.9 Hz, 2H), 7.89 (d, *J*=2.9 Hz, 2H), 8.01 (dd, *J*=8.9 and 2.9 Hz, 2H), 8.93 (br s, 1H), and 11.20 (br s, 2H) ppm. ^{13}C NMR (*d*$_6$-DMSO): δ 30.1, 115.3, 123.4, 124.4, 126.1, 127.8, 128.1, 129.3, 139.8, 152.1, and 162.1 ppm. MS: *m/z* (relat. abund.) 432 (M^++2, 22.3), 430 (M^+, 59.6), 395 (55.8), 384 (3.6), 349 (14.6), 338 (3.6), 278 (7.4), 152 (100).

4-Ethoxycarbonyl-2,6-bis[(5-tert-butyl-2-hydroxyphenyl)methyl]phenol, (**9**).

A mixture of 4-*tert*-butylphenol (12.60 g, 83.7 mmole) and 4-ethoxycarbonyl-2,6-bis(hydroxymethyl)phenol (**3a**) (1.00 g, 4.4 mmole) was heated at 100-110°C for 8 hours. The excess 4-*tert*-butylphenol was removed by steam distillation, and the resulting aqueous solution was extracted with ethyl acetate (3x20 ml). The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. Trituration of the residue with carbon tetrachloride afforded 1.45 g (67%) of **9**, m.p. 170°C (H_2O). ^1H NMR ($CDCl_3$): δ 1.26 (s, 18H), 1.39 (t, *J*=6.7 Hz, 3H), 3.94 (s, 4H), 4.34 (q, *J*=6.7 Hz, 2H), 6.74 (d, *J*=8.5 Hz, 2H), 7.08 (dd, *J*=8.5 and 2.0 Hz, 2H), 7.30 (d, *J*=2.0 Hz, 2H), 7.79 (br s, 2H), 7.91 (s, 2H), and 9.54 (br s, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ 14.2, 31.4, 33.9, 60.8, 115.4, 123.1, 125.0, 125.7, 127.5, 127.9, 130.8, 144.2, 149.8, 154.7, and 166.9 ppm. (Found: C 73.02, H 7.58. $C_{31}H_{38}O_5.2H_2O$ requires C 73.15, H 7.37).

2,6-Bis[(5-tert-butyl-2-hydroxyphenyl)methyl]-4-nitrophenol, (**10**).

A mixture of 4-*tert*-butylphenol (7.54 g, 50.2 mmole), 2,6-bis(hydroxymethyl)-4-nitrophenol (**4a**) (1.00 g, 5.0 mmole), and conc. hydrochloric acid (2.5 ml) was heated at 130°C for 10 hours. The excess 4-*tert*-butylphenol was removed by steam distillation, and the residue was filtered, washed with water, and dried. Purification was achieved by trituration with carbon tetrachloride. The yield was 2.14 g (92%), m.p. 210-212°C. ^1H NMR (*d*$_6$-DMSO): δ 1.19 (s, 18H), 3.90 (s, 4H), 6.75 (d, *J*=8.5 Hz, 2H), 7.07 (dd, *J*=8.5 and 2.6 Hz, 2H), 7.15 (d, *J*=2.6 Hz, 2H), 7.68 (s, 2H), 9.22 (br s, 1H), and 9.51 (br s, 2H) ppm. ^{13}C NMR (*d*$_6$-acetone): δ 31.2, 31.8, 34.4, 115.5, 124.6, 125.4, 125.6, 128.7, 129.7, 141.4, 143.7, 152.3, and 159.4 ppm. (Found: C 68.30, H 6.12, N 2.71. $C_{28}H_{33}NO_5.1/2CCl_4$ requires C 68.68, H 6.67, N 2.81).

2,6-Bis[(5-chloro-2-hydroxyphenyl)methyl]-4-nitrophenol, (**11**).

(**4a**) (1.00 g, 5.0 mmole) was added on a solution of 4-chlorophenol (3.15 g, 24.5 mmole) in a mixture of acetic acid (8.0 ml) and sulfuric acid (1.2 ml), maintained at 100°C. After 1.5 hours at 100°C, the reaction

mixture was allowed to cool at room temperature and potassium carbonate (3.2 g) was added slowly. The mixture was stirred for 30 min, cold water (60 ml) was added, and the stirring was continued for 2 hours more. The crude compound was filtered, washed with water, and dried. Purification was achieved by trituration with dichloromethane (30 ml), filtration, washing with a mixture of hexane-dichloromethane to remove last traces of 4-chlorophenol, and drying. The yield was 2.04 g (97%), m.p. 220°C (lit.[14] 218°C). IR (nujol): 3300-3100, 1550, 1370 cm^{-1}. ^1H NMR (*d*$_6$-DMSO): δ 3.89 (s, 4H), 6.81 (d, *J*=9.0 Hz, 2H), 7.09 (dd, *J*=9.0 and 2.6 Hz, 2H), 7.11 (d, *J*=2.6 Hz, 2H), 7.65 (s, 2H), and 9.99 (br s, 3H) ppm. ^{13}C NMR (CD_3OD): δ 31.1, 117.2, 125.1, 125.4, 128.4, 129.1, 129.3, 131.2, 141.6, 154.5, and 160.1 ppm. MS: *m/z* (relat. abund.) 423 (M^++4, 8.1), 421 (M^++2, 28.0), 419 (M^+, 47.8), 403 (8.7), 384 (28.0), 354 (17.4), 292 (16.1), 257 (26.1), 256 (17.4), 141 (100).

2,6-Bis[(5-ethoxycarbonyl-2-hydroxyphenyl)methyl]-4-nitrophenol, (**12**).

A mixture of ethyl 4-hydroxybenzoate (15.0 g, 90.4 mmole) and **4a** (1.0 g, 5.0 mmole) was heated at 145°C for 8 hours. The excess ethyl 4-hydroxybenzoate was removed by sublimation. The yield of **12** was 1.9 g (76%), m.p. 229-230°C. IR (nujol): 3700-3200, 1695, 1520, 1350, 1295, 1230 cm^{-1}. ^1H NMR (*d*$_6$-acetone): δ 1.29 (t, *J*=7.1 Hz, 6H), 4.11 (s, 4H), 4.25 (q, *J*=7.1 Hz, 4H), 6.99 (d, *J*=8.6 Hz, 2H), 7.79 (dd, *J*=8.6 and 2.0 Hz, 2H), 7.92 (s, 2H), 7.93 (d, *J*=2.0 Hz, 2H), and 9.50 (br s, 2H) ppm. ^{13}C NMR (*d*$_6$-DMSO): δ 14.2, 30.2, 60.3, 115.3, 120.6, 123.5, 126.0, 128.4, 129.6, 132.1, 138.5, 160.1, 161.1, and 165.6 ppm. MS: *m/z* (relat. abund.) 450 (M^+-45, 4.5), 449 (M^+-46, 7.7), 357 (17.2), 121 (100). To have an analytical sample, **12** was acetylated with acetic anhydride. A 100% yield of the triacetyl derivative, m.p. 146°C (H_2O), was obtained. (Found: C 61.85, H 4.73, N 2.09. $C_{32}H_{31}NO_{12}$ requires C 61.83, H 5.02, N 2.25).

5,17-Di-tert-butyl-11,23-dichloro-25,26,27,28-tetrahydroxycalix[4]arene, (**13**).

Titanium(IV) chloride (1.0 ml, 9.1 mmole) was dissolved under argon in cold (0°C) dry dioxane (320 ml), the solution was heated to reflux and then a solution of **5** (1.00 g, 2.3 mmole) in dioxane (50 ml) was added slowly (*ca.* one hour). To the resulting dark brownish solution was added **1b** (0.78 g, 2.3 mmole) in dioxane (80 ml), during 16 hours. Heating of the mixture was pursued for four days, and then the solvent was evaporated, dichloromethane (100 ml) and silica gel (40 g) were added to the residue. The solvent was removed again, and the residue was extracted with hexane for six days in a Soxhlet apparatus. Evaporation of the solvent afforded **13** (0.42 g, 30%) as a solid of m.p.>300°C (ether-hexane). IR (KBr): 3130, 1650, 1490, 1210, 865 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.23 (s, 18H), 3.46 (d, *J*=13.8 Hz, 4H), 4.21 (d, *J*=13.8 Hz, 4H), 6.99 (s, 4H), 7.07 (s, 4H), and 10.09 (s, 4H) ppm. ^{13}C NMR (*d*$_6$-DMSO): δ 31.5, 32.2, 33.6, 120.7, 124.7, 126.9, 128.7, 132.6, 140.7, 151.1, and 153.4 ppm. MS: *m/z* (relat. abund.) 606 (M^++2, 5.4), 604 (M^+, 7.6), 548 (5.5), 533 (8.1), 492 (13.3), 474 (2.6), 153 (29.5), 57 (100). (Found: C 71.27, H 6.89. $C_{36}H_{38}Cl_2O_4$ requires C 71.40, H 6.32).

5,11,17,23-Tetrachloro-25,26,27,28-tetrahydroxycalix[4]arene, (**14**).

Method A: Titanium(IV) chloride (1.4 ml, 11.8 mmole) was dissolved under argon in cold (0°C) dry dioxane (25 ml), the solution was heated to reflux and a solution of a mixture of trimer **7** (0.65 g, 1.6 mmole) and monomer **2b** (0.50 g, 1.6 mmole) in dioxane (285 ml) was added slowly (24 hours). Heating was continued for 5 days and then the solvent was evaporated and dichloromethane (200 ml) was added on the residue. The solid was filtered and washed with dichloromethane. The combined filtrate and washings were treated with silica gel (16 g), the solvent removed, and the residue extracted in a Soxhlet with toluene for 48 hours. Elimination of the solvent afforded **14** (0.11 g, 12%), m.p.>300°C. ^1H NMR ($CDCl_3$): δ 3.47 (br s, AB

system, 4H), 4.15 (br s, AB system, 4H), 7.04 (s, 8H), and 9.90 (s, 4H) ppm. ^{13}C NMR ($CDCl_3$+*d*$_6$-DMSO): δ 28.5, 121.8, 126.2, 128.5, and 147.9 ppm. MS: *m/z* (relat. abund.) 564 (M^++4, 35.7), 562 (M^++2, 100), 560 (M^+, 67.9), 544 (35.7), 403 (39.3), 402 (53.6), 293 (39.3), 267 (57.1), 266 (53.6), 265 (75.0). (Found: C 62.03, H 4.48. $C_{28}H_{20}Cl_4O_4.1/2C_7H_8$ requires C 62.19, H 3.98).

Method B: A mixture of 25,26,27,28-tetrahydroxycalix[4]arene (21)[18] (0.50 g, 0.9 mmole), *N*-chlorosuccinimide (1.45 g, 10.4 mmole), and a catalytic amount of benzoyl peroxide was heated for 4 days at 85°C in carbon tetrachloride (30 ml). Evaporation of the solvent, and trituration of the residue with methanol (35 ml) afforded **14** (0.25 g, 38%), identical with the compound obtained by method A.

11,23-Di-tert-butyl-5,17-diethoxycarbonyl-25,26,27,28-tetrahydroxycalix[4]arene, (**15**).

To a solution of titanium(IV) chloride (1.0 ml, 9.1 mmole) in dry dioxane (20 ml), made as indicated above, was added under reflux, during 24 hours, a solution of a mixture of **9** (0.49 g, 1.0 mmole) and **3b** (0.35 g, 1.0 mmole) in dioxane (180 ml). After 80 hours of reflux, the solvent was evaporated and the residue triturated with dichloromethane (75 ml), filtrated *in vacuo*, and the solid washed with dichlorometane. Silica gel was added to the combined filtrates, the mixture was evaporated and the solid residue was extracted in a Soxhlet with toluene for 20 hours. The solvent was removed, carbon tetrachloride was added, and the solid formed was collected and dried. Yield was 0.04 g (6%), m.p.>310°C. ^{1}H NMR ($CDCl_3$): δ 1.23 (s, 18H), 1.28 (t, *J*=7.0 Hz, 6H), 3.59 (d, *J*=12.0 Hz, 4H), 4.25 (d, *J*=12.0 Hz, 4H), 4.25 (q, *J*=7.0 Hz, 4H), 7.14 (s, 4H), 7.74 (s, 4H), and 10.15 (br s, 4H) ppm. ^{13}C NMR ($CDCl_3$): δ 14.3, 31.4, 31.8, 34.1, 60.4, 124.5, 126.1, 127.0, 128.3, 130.7, 145.3, 146.2, 152.8, and 165.9 ppm. MS: *m/z* (relat. abund.) 681 (M^++1, 18.9), 637 (22.6), 636 (41.5), 635 (100). (Found: C 63.29, H 6.08. $C_{42}H_{48}O_8.CCl_4.1/4C_7H_8$ requires C 62.68, H 5.93).

5,17-Dichloro-11,23-dinitro-25,26,27,28-tetrahydroxycalix[4]arene, (**16**).

To a solution of titanium(IV) chloride (1.4 ml, 13.1 mmole) in dioxane (25 ml), prepared as indicated above, was added during 3 hours, under reflux, a solution of trimer **11** (0.36 g, 0.9 mmole) in dioxane (150 ml), and then a solution of monomer **4b** (0.28 g, 0.9 mmole) in dioxane (75 ml), during 20 hours. After 4 days of reflux, the solvent was evaporated, dichloromethane (150 ml) was added, and the solid was filtered and washed with dichloromethane. The combined filtrate and washings were evaporated, and the residue was triturated with ether, affording 0.13 g (27%) of **16**, m.p.>300°C (toluene). ^{1}H NMR (*d*$_6$-acetone): δ 4.10 (br s, 8H), 7.34 (s, 4H), and 8.21 (s, 4H) ppm. ^{13}C NMR (*d*$_6$-acetone+*d*$_6$-DMSO): δ 31.0, 123.3, 124.3, 128.0, 130.0, 131.0, 138.5, 151.2, and 162.3 ppm. MS: *m/z* (relat. abund.) 586 (M^++4, 13.0), 584 (M^++2, 68.0), 582 (M^+, 100), 566 (21.0), 552 (22.0), 554 (17.0), 549 (38.0), 547 (59.0). To have an analytical sample, **16** was acetylated with acetic anhydride. A 61% yield of the tetraacetyl derivative, m.p.>300°C (benzene), was obtained. (Found: C 57.61, H 3.78, N 3.56. $C_{36}H_{28}Cl_2N_2O_{12}$ requires C 57.53, H 3.75, N 3.72).

11,23-Di-tert-butyl-5,17-dinitro-25,26,27,28-tetrahydroxycalix[4]arene, (**17**).

To a solution of titanium(IV) chloride (2.3 ml, 21.1 mmole) in dioxane (110 ml), prepared as indicated above, were added simultaneously, during 36 hours and under reflux, two solutions of trimer **10** (1.04 g, 2.2 mmole) and monomer **4b** (0.73 g, 2.2 mmole) in 200 ml and 140 ml of dioxane, respectively. The mixture was maintained under reflux during 60 hours, and the solvent was evaporated *in vacuo*. The residue was triturated with dichloromethane (150 ml), filtered, and washed with the same solvent. Evaporation of the filtrate afforded 0.07 g (5%) of **17**, m.p.>340°C. ^{1}H NMR

($CDCl_3$): δ 1.25 (s, 18H), 3.64 (d, *J*=14.3 Hz, 4H), 4.28 (d, *J*=14.3 Hz, 4H), 7.23 (s, 4H), 7.98 (s, 4H), and 10.19 (s, 4H) ppm. MS: *m/z* (relat. abund.) 627 (M^++1, 56.5), 570 (56.5), 555 (100). (Found: C 67.98, H 5.91, N 3.92. $C_{36}H_{38}N_2O_8.H_2O.1/4C_7H_8$ requires C 67.90, H 6.34, N 4.19).

5,17-Diethoxycarbonyl-11,23-dinitro-25,26,27,28-tetrahydroxycalix[4]arene, (18).

To a solution of titanium(IV) chloride (1.0 ml, 9.1 mmole) in dioxane (50 ml), prepared as indicated above, was added during 2 hours, under reflux, a solution of trimer 12 (0.50 g, 1.0 mmole) in dioxane (75 ml), and then a solution of monomer 4b (0.33 g, 1.0 mmole) in dioxane (75 ml), during 24 hours. After 8 days of reflux, the solvent was evaporated, dichloromethane (100 ml) was added, and the solid was filtered and washed with dichloromethane. The combined filtrate and washings were evaporated, and the residue was triturated with ether, affording 0.15 g (22%) of 18, m.p.>310°C (toluene). IR (nujol): 1720, 1530, 1350 cm^{-1}. ^1H NMR (CD_3CN): δ 1.27 (t, *J*=7.0 Hz, 6H), 4.05 (br s, 8H), 4.21 (q, *J*=7.0 Hz, 4H), 7.85 (s, 4H), 8.16 (s, 4H), and 9.56 (br s, 4H) ppm. MS: *m/z* (relat. abund.) 658 (M^+, 0.9), 628 (0.5), 613 (42.0), 612 (100). (Found: C 63.61, H 4.09, N 3.26. $C_{34}H_{30}N_2O_{12}.1/2C_7H_8$ requires C 63.87, H 4.86, N 3.97).

4-Tert-butyl-2,6-bis[(5-chloro-3-hydroxymethyl-2-hydroxyphenyl)methyl] phenol, (22a).

A mixture of trimer 5 (2.00 g, 4.64 mmole) and formaldehyde (8.8 ml of 40% solution in water, 116.0 mmole) in 25% aqueous sodium hydroxide (2.4 ml, 15.0 mmole) was heated at 50°C for 24 hours, under argon. An oil, which solidified on cooling, was formed. Water (25 ml) was added, and the solid was collected by filtration. Hot water (20 ml) was added to the solid and the mixture was acidified with 10% aqueous hydrochloric acid. Filtration and recrystalization from toluene afforded 1.69 g (75%) of 22a, m.p. 169-170°C. ^1H NMR ($CDCl_3$): δ 1.29 (s, 9H), 3.86 (s, 4H), 4.70 (s, 4H), 6.85 (d, *J*=2.7 Hz, 2H), 7.14 (s, 2H), 7.17 (d, *J*=2.7 Hz, 2H), 8.90 (s, 1H), and 9.15 (s, 2H) ppm. ^{13}C NMR (*d*$_6$-DMSO): δ 31.7, 32.0, 33.8, 59.9, 119.5, 122.1, 125.5, 126.9, 128.1, 130.9, 140.5, and 150.8 ppm. (Found: C 64.01, H 6.03. $C_{26}H_{28}Cl_2O_5$ requires C 63.55, H 5.74).

4-Tert-butyl-2,6-bis[(3-bromomethyl-5-chloro-2-hydroxyphenyl)methyl]phenol, (22b).

A suspension of 22a (0.50 g, 1.0 mmole) in acetic acid (2 ml) was stirred at room temperature for 35 hours with a 30% solution of hydrogen bromide in acetic acid (4 ml). The colorless solid which appeared was filtered and washed with hexane. Yield was 0.37 g (58%), m.p. 207-208°C. ^1H NMR ($CDCl_3$): δ 1.29 (s, 9H), 3.88 (s, 4H), 4.47 (s, 4H), 7.11 (d, *J*=2.6 Hz, 2H), 7.16 (s, 2H), 7.23 (d, *J*=2.6 Hz, 2H), and 7.90 (s, 2H) ppm. (Found: C 49.24, H 4.56. $C_{26}H_{28}Br_2Cl_2O_3$ requires C 50.47, H 4.27).

5,17,29-Tri-tert-butyl-11,23,35-trichloro-37,38,39,40,41,42-hexahydroxycalix[6]arene, (23).

To a solution of titanium(IV) chloride (0.8 ml, 6.9 mmole) in dioxane (150 ml), prepared as indicated above, was added during 2 hours, under reflux, a solution of trimer 6 (0.374 g, 0.83 mmole) in dioxane (25 ml), and then a solution of trimer 22b (0.510 g, 0.83 mmole) in dioxane (25 ml), during 20 hours. After 4 days of reflux, the solvent was evaporated, water was added, and the mixture was extracted with chloroform. The chlorofor m layer was dried over sodium sulfate, and the solvent was evaporated. The solid residue was dissolved in dichloromethane, silica gel (5.0 g) was added, and the solvent was removed. Extraction with hexane for 5 days in a Soxhlet apparatus, followed by evaporation afforded 0.090 g (9%) of calix[6]arene 23, m.p. >300°C. ^1H NMR ($CDCl_3$): δ 1.28 (s, 27H), 3.83 (br s, 12H), 7.13 (s, 6H), 7.15 (s, 6H), 10.14 (s, 3H), and 10.52 (s, 3H) ppm. ^{13}C

NMR ($CDCl_3$): δ 31.5, 32.4, 34.1, 125.9, 126.1, 126.7, 128.2, 128.7, 145.0, 147.1, and 148.4 ppm. MS: *m/z* (relat. abund.) 912 (M^++6, 2.9), 911 (M^++5, 10.3), 910 (M^++4, 29.4), 909 (M^++3, 39.7), 908 (M^++2, 100), 917 (M^++1, 42.6), 906 (M^+, 67.6), 891 (20.6), 852 (48.5), 850 (38.2), 796 (36.8), 794 (32.3). (Found: C 56.27, H 5.40. $C_{54}H_{57}Cl_3O_6$.5/2$CDCl_3$ requires C 56.11, H 4.73).

Acknowledgments. This research was supported by the "Comisiòn Interministerial de Ciencia y Tecnologia" (CICYT). One of us (C.S.) gratefully acknowledges a scholarship provided by "Caja Madrid". We are indebted to F. Fernåndez-Làzarand to Dr. A. Echavarren (CSIC, Madrid) for their participation during the early steps of this research.

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