The Quinonemethide Route to Mono- and Tetrasubstituted Calix[4]arenes[1]

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p-tert-Butylcalixarenes have attracted widespread attention because of their ready availability from the base-induced condensation of *p-tert*-butylphenol and formaldehyde.[2] Although the parent calixarenes are of limited utility, compounds derived from them have found numerous applications for the binding of ions and molecules and as frameworks for building more complex structures.[3] Among the derivatization procedures that have been used, the quinonemethide route reported by Gutsche and Nam[4] has proved to be particularly useful. It involves aminomethylation followed by quarternization and treatment with a nucleophile which becomes attached to the *para*-position of the upper rim. Originally applied to calix[4]arene, it has subsequently been shown to work efficiently with calixarenes of any size[5] as well as with calix[4]resorcinarenes.[6] When the reaction is carried out in THF containing HOAc substitution occurs at all available *para*-positions of a calix[*n*]arene. For example, calix[4]arene (**1**) is converted to *p*-tetrakis[(dimethylamino)methyl]calix[4]arene (**2**) under these conditions. It has been discovered, however, that in the absence of HOAc the aminomethylation occurs at only a single position of calix[4]arene to give mono[(dimethylamino)methyl]calix[4]arene (**6**) in good yield. The present work provides several new examples of the use of the quinonemethide process for the synthesis of tetra-*para*-substituted calix[4]arenes along with examples of the synthesis of mono-*para*-substituted calix[4]arenes.

In the procedure described by Gutsche and Nam[2] the quaternary ammonium iodide **3**, obtained by treatment of **2** with MeI, was not isolated but was treated directly with the nucleophile. In the present work it was found that isolation of **3** increases the flexibility of the process, allowing the use of a wider range of nucleophiles such as aryl oxides and Grignard reagents. The earlier work showed that the simplest alkoxide MeO^- reacts smoothly with **3** to produce **4a**, and the present work extends this to include EtO^- and $C_6H_5CH_2O^-$ to produce **4b** and **4c**, respectively. Aryl oxides, on the other hand, failed in the earlier experiments but have now been shown to work if the aryl oxide is separately prepared and then allowed to react with **3**. Thus, compounds **4d**, **4e**, and **4f** can be prepared in 80–88% yield from phenoxide, *p-tert*-butylphenoxide, and *p*-methoxyphenoxide, these aryl oxides reacting as oxygen nucleophiles to give the *p*-[(aryloxy)methyl] derivatives of the calixarene. 2,6-Di-*tert*-butylphenoxide, on the other hand, is too hindered to react in this fashion and instead reacts as a carbon nucleophile to give the *p*-arylmethyl derivative **4g** in 29% yield. A similar product has been reported by Arduini et al.[7] in the reaction of *p*-(chloromethyl)calix[4]arene with 2,6-dimethylphenol.

The reaction of **3** with diethyl sodiomalonate, prepared from diethyl malonate and NaOEt, yields **4i** as described in the earlier work. The reaction of **3** with dimethyl sodiomalonate, prepared from dimethyl malonate and NaOMe, proceeds in comparable fashion to produce **4h**. When **3** is treated with dimethyl malonate and NaOEt in EtOH, however, the mixed ester **4j** is obtained, although when **3** is treated with diethyl malonate and NaOMe in EtOH only **4i** is obtained. The mixed ester **4j** has a sharp melting point, shows a single spot on TLC, and possesses ^1H NMR and ^{13}C NMR spectra that are generally well resolved and that contain the numbers and patterns of resonances expected for a pure compound (see Figures 1 and 2). In the ^{1} NMR spectrum only the quartet pattern for the $CO_2CH_2CH_3$ methyls and the doublet for the $ArCH_2$-CH methylenes are less well resolved than the other resonances. On the basis of these data it appears that **4j** may be a single entity in spite of the fact that it contains four stereogenic centers and could exist as a mixture of diastereoisomers. It is possible, of couse, that it is a mixture in which the diastereoisomers are so similar to one another that they travel together on TLC and show sharp composite NMR spectra. If **4j** is, indeed, a single diastereoisomer it might be the result of **3** existing in a symmetrical four-bladed propeller-like conformation in which one of the CO_2Et groups on each of the diethylmalonyl moieties projects outward from the upper rim and is more susceptible to methanolysis than the other CO_2Et group projecting inward. Compounds **4h**, **4i**, and **4j** all undergo hydrolysis and decarboxylation to yield the previously described *p*-(carboxyethyl)calix[4]arene (**4k**).

When a Grignard reagent was used as the nucleophile the result was different from what had been expected. Reaction of **3** with MeMgCl produces a 74% yield of *p*-triethylcalix[4]arene (**5b**) rather than the known *p*-tetraethylcalix[4]arene (**5a**).[7] The loss of a Me_3NCH_2 moiety might be the result of nucleophilic displacement of a Me group by MeMgCl (forming C_2H_6) to regenerate **2** followed by loss of Me_2NCH_2 to produce **1** by the reverse of the pathway of formation of **2** from **1**. Why only a single Me_3NCH_2 moiety is lost, however, is not understood.

The quaternary salt obtained from mono[(dimethylamino)methyl]calix[4]arene (**6**) reacts with nucleophiles in a fashion comparable to **3**. Thus, CN^- yields **7a**, the alkoxides MeO^- and EtO^- yield **7c** and **7d**, the aryl oxides PhO^- and *p*-$PhPhO^-$ yield **7e** and **7f**, and diethyl sodiomalonate yields **7g**.[8]

Experimental Section

5,11,17,23-Tetrakis[(trimethylammonio)methyl]-25,26,27,28-tetra-hydroxycalix[4]arene Iodide (3). To a suspension of 40 g (0.06 mol) of 5,11,17,23-tetrakis[(dimethylamino)methyl]-25,26,27,28-tetrahydroxycalix[4]arene (**2**) in 120 mL of DMSO in an atmosphere of N_2 was slowly added a solution of 52 g (0.36 mol) of MeI in 50 mL of DMSO. The mixture was stirred for 3

(1) Calixarenes. 38. For part 37 cf. Sharma, S. K.; Gutsche, C. D. *Tetrahedron* **1994**, *50*, 4087.

(2) Gutsche, C. D.; Iqbal, M. *Org. Synth.* **1990**, *68*, 234. Gutsche, C. D.; Dhawan, B.; Leonis, M.; Stewart, D. *Org. Synth.* **1990**, *68*, 238. Munch, J. H.; Gutsche, C. D. *Org. Synth.* **1990**, *68*, 243.

(3) For comprehensive reviews covering the literature to 1989–90 cf. (a) Gutsche, C. D. Calixarenes. In *Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; Royal Society of Chemistry: London, 1989; *Calixarenes: A Versatile Class of Macrocyclic Compounds*, Böhmer, V., Vicens, J., Eds.; Kluwer Academic Publishers: Hingham, MA, **1991**.

(4) Gutsche, C. D.; Nam, K. C. *J. Am. Chem. Soc.* **1988**, *110*, 6153.

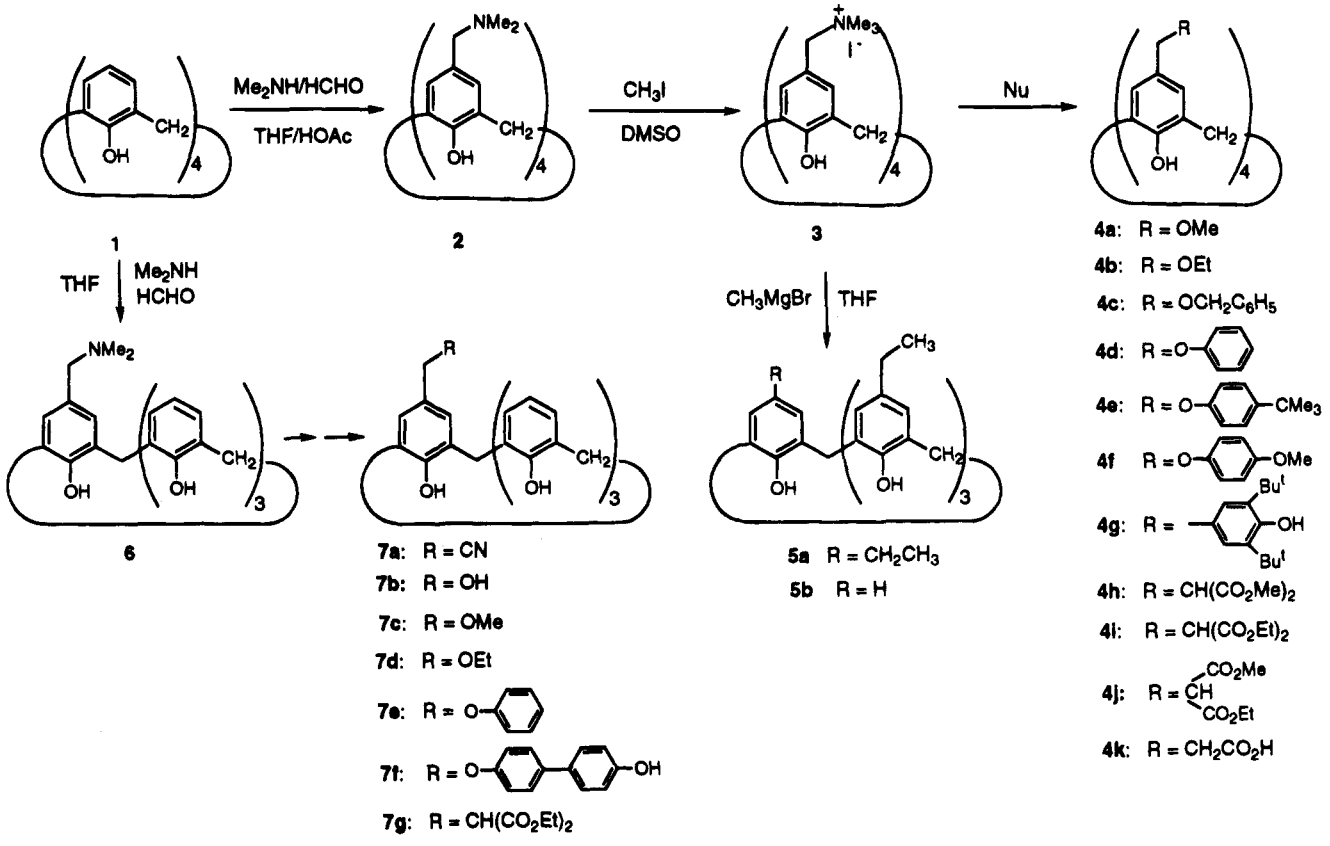
(5) Gutsche, C. D.; Alam, I. *Tetrahedron* **1988**, *44*, 4689.

(6) Matsushita, Y-i.; Matsui, T. *Tetrahedron Lett.* **1993**, *34*, 7433.

(7) Arduini, A.; Pochini, A.; Rizzi, A.; Sicuri, A. R.; Ugozzoli, F.; Ungaro, R. *Tetrahedron* **1992**, *48*, 905.

0022-3263/94/1959-3716$04.50/0

Scheme 1



h at rt and poured into 400 mL of Me_2CO. The taffy-like material that settled to the bottom of the flask was removed by filtration, thoroughly washed with Me_2CO, and then air dried. The crude product was ground to a fine powder, washed with THF, and again air dried to yield 66 g (88%) of a colorless powder: mp > 350 °C dec; ^{1}H NMR (DMSO-d_6) δ 7.35 (s, 8, ArH), 4.38 (s, 8, CH_2N), 3.42–4.02 (b, 8, $ArCH_2Ar$), 2.90 (s, 36, NMe_3).

5,11,17,23-Tetrakis(methoxymethyl)-25,26,27,28-tetrahydroxycalix[4]arene (4a). A mixture of 1.0 g (0.8 mmol) of quarternary ammonium salt **3** and 0.9 g (16 mmol) of NaOMe was stirred in 50 mL of MeOH (HPLC grade) at rt for 6 h in a N_2 atmosphere. The reaction mixture was acidified with 10% HCl, and the precipitate was removed by filtration and washed with ice-cold H_2O. Recrystallization from $CHCl_3$–CH_3OH (2:1) gave 0.37 g (77%) of **4a** as a white powder: mp 214–216 °C (lit.[4] mp 214–216 °C).

5,11,17,23-Tetrakis(ethoxymethyl)-25,26,27,28-tetrahydroxycalix[4]arene (4b). Following the procedure described above for **4a**, 1.0 g (0.8 mmol) of **3** and 1.1 g (16 mmol) of NaOEt were stirred in 50 mL of absolute EtOH for 6 h at rt to give 0.41 g (78%) of **4b** as a white powder after recrystallization from EtOH: mp 160–162 °C; ^{1}H NMR ($CDCl_3$) δ 10.13 (s, 4), 7.02 (s, 8), 4.28 (s, 8), 4.23 (bs, 4), 3.54 (bs, 4), 3.45 (q, 8, J = 6.90, 6.90, and 7.20 Hz), 1.19 (t, 12, J = 6.90 and 7.20 Hz); ^{13}C NMR ($CDCl_3$) δ 148.25, 132.19, 128.57, 128.12, 72.21, 65.48, 31.73, 15.24. Anal. Calcd for $C_{40}H_{48}O_8$: C, 73.15; H, 7.37. Found: C, 73.42; H, 7.35.

5,11,17,23-Tetrakis[(benzyloxy)methyl]-25,26,27,28-tetrahydroxycalix[4]arene (4c). A mixture of 1.0 g (0.8 mmol) of **3** and 2.16 g (20 mmol) of $PhCH_2OH$ in 100 mL of freshly distilled THF was treated slowly with 0.6 g (15 mmol) of NaH (60% in oil dispersion) in a N_2 atmosphere. The reaction mixture was refluxed for 6 h, excess solvent was removed under reduced pressure, and the residue was poured into a stirred mixture of MeOH and 1 N HCl (5:1 ratio) to give 0.63 g of crude product. Purification by flash chromatography on a silica gel column using Me_2CO–petroleum ether (3:7) as eluent afforded 0.43 g (59%) of **4c** as a white powder: mp141–143 °C; ^{1}H NMR ($CDCl_3$) δ 10.20 (s, 4),7.24 (s, 20), 6.96 (s, 8), 4.38 (s, 8), 4.24 (s, 8), 4.18 (bd, 4), 3.45 (bd, 4). Anal. Calcd for $C_{60}H_{56}O_8$: C, 79.62; H, 6.24. Found: C, 79.40; H, 6.25.

5,11,17,23-Tetrakis(phenoxymethyl)-25,26,27,28-tetrahydroxycalix[4]arene (4d). A mixture of 1.0 g (0.8 mmol) of **3** and 1.2 g (10 mmol) of sodium phenoxide (prepared by stirring a 1:1 mixture of phenol and NaOH in H_2O followed by removal of the H_2O) in 50 mL of DMSO was stirred at 70 °C in a N_2 atmosphere for 24 h. The precipitate obtained upon pouring the reaction mixture in 200 mL of 1 N HCl was crystallized from anhydrous Et_2O to give 0.6 g (88%) of **4d** as a colorless powder: mp 350 °C dec; ^{1}H NMR ($CDCl_3$) δ 10.17 (s, 4), 7.25 (m, 8), 7.12 (s, 8,), 6.92 (d+t, 12), 4.83 (s, 8), 4.26 (bd, 4), 3.51 (bd, 4); ^{13}C NMR ($CDCl_3$) δ 158.80, 148.64, 130.72, 129.50, 128.65, 128.29, 120.93, 114.82, 69.48, 31.78. An analytical sample was prepared by flash column chromatography using $CHCl_3$ as eluent. Anal. Calcd for $C_{56}H_{48}O_8$: C, 79.23; H, 5.70. Found: C, 79.01; H, 5.71.

5,11,17,23-Tetrakis[(*p*-*tert*-butylphenoxy)methyl]-25,26,-27,28-tetrahydroxycalix[4]arene (4e). Following the procedure described above for **4d**, a mixture of 1.0 g (0.8 mmol) of **3** and 1.1 g (6.4 mmol) of sodium *p*-*tert*-butylphenoxide in 50 mL of DMSO gave 0.72 g (84%) of **4e** as a colorless powder after recrystallization from Et_2O–*n*-hexane (3:1): mp 151–153 °C; ^{1}H NMR ($CDCl_3$) δ 10.13 (s, 4), 7.28 (d, 8, J = 8.70 Hz), 7.13 (s, 8), 6.87 (d, 8, J = 9.0 Hz), 4.80 (s, 8), 4.26 (bd, 4), 3.56 (bd, 4), 1.28 (s, 36); ^{13}C NMR ($CDCl_3$) δ 156.70, 148.66, 143.62, 131.00, 128.71, 128.34, 126.29, 114.29, 69.71, 34.15, 31.76, 31.62. An analytical

(8) Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran (THF) was distilled over Na–benzophenone. Melting points were taken in sealed and evacuated melting point capillary tubes on a MEL-Temp apparatus (Laboratory Devices, Cambridge, MA) using a Fluka 51 K/J digital thermometer with a K-type thermocouple and are uncorrected. Column chromatography employed Aldrich 70–230 mesh, 60A silica gel, and flash chromatography used J. T. Baker silica gel with a 40-μm particle size. Thin-layer chromatography (TLC) was carried out on 250-μm Analtech silica gel plates and preparative thin-layer chromatography (PTLC) on 1000-μm silica gel plates containing a fluorescent indicator. ^{1}H NMR and ^{13}C NMR spectra were recorded at 20 ± 1 °C on a Varian XL-300 spectrometer with chemical shifts reported as δ values in parts per million (ppm). ^{1}H NMR spectra are referenced to tetramethylsilane (TMS) at 0.00 ppm as an internal standard, and ^{13}C NMR spectra are referenced either to $CDCl_3$ (77.00 ppm), DMSO (40.0 ppm), or TMS (0.00 ppm). Microanalytical samples were dried, in most cases, at least 48–72 h at 111 °C (toluene) or 140 °C (xylene) at 1–2 mm, and analyses were carried out by Desert Laboratories, Tucson, AZ.

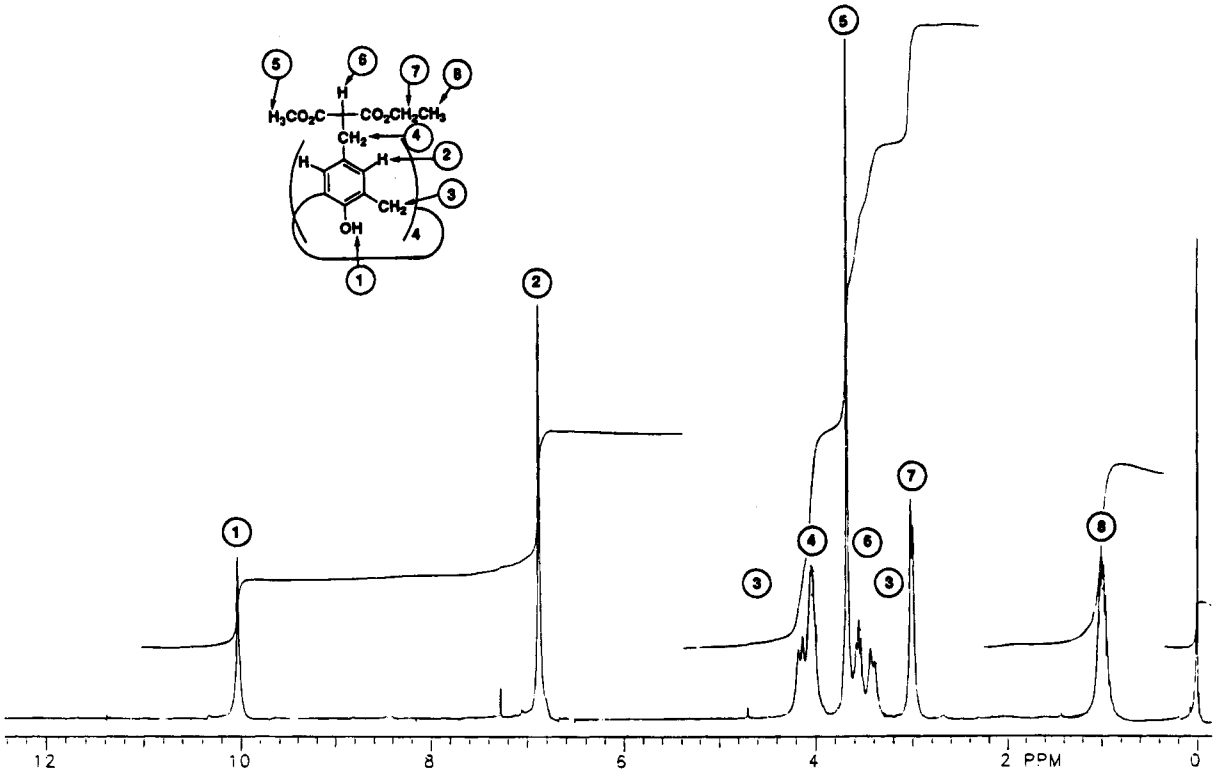


Figure 1. ^1H NMR spectrum of mixed ester **4j** in $CDCl_3$ solution at 300 MHz and 25 °C.

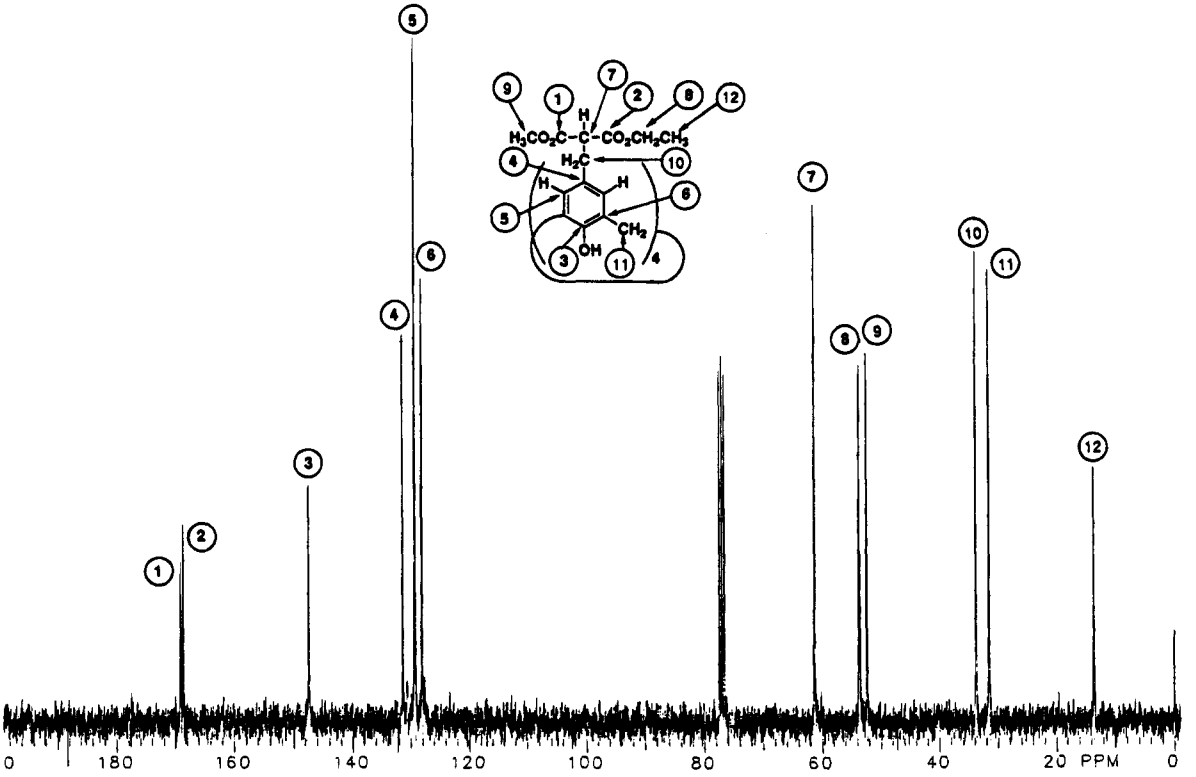


Figure 2. ^{13}C NMR spectrum of mixed ester **4j** in $CDCl_3$ solution at 75 MHz and 25 °C.

sample was prepared by flash chromatography on silica gel using $CHCl_3$ as eluent. Anal. Calcd for $C_{72}H_{80}O_8$: C, 80.56; H, 7.51. Found: C, 80.36; H, 7.24.

5,11,17,23-Tetrakis[(*p*-methoxyphenoxy)methyl]-25,26,-27,28-tetrahydroxycalix[4]arene (4f). Following the procedure described above for **4d**, a mixture of 1.0 g (0.8 mmol) of **3** and and 1.0 g (6.8 mmol) of sodium *p*-methoxyphenoxide in 50 mL of DMSO gave 0.62 g (80%) of **4f** as a colorless powder after recrystallization from CH_2Cl_2–CH_3OH (3:1): mp 196–198 °C; ^1H NMR ($CDCl_3$) δ 10.17 (s, 4), 7.11 (s, 8), 6.84 (2d, 16), 4.78 (s, 8), 4.27 (bd, 4), 3.75 (s, 12), 3.54 (bd, 4); ^{13}C NMR ($CDCl_3$) δ 153.94, 152.98, 148.58, 130.95, 128.61, 128.27, 115.78, 114.64, 70.24, 55.72, 31.76. An analytical sample was prepared by flash chromatography using $CHCl_3$ as eluent. Anal. Calcd for $C_{60}H_{56}O_{12}$: C, 74.36; H, 5.82. Found: C, 74.10; H, 5.81.

5,11,17,23-Tetrakis[(3′,5′-di-*tert*-butyl-4′-hydroxyphenyl)methyl]-25,26,27,28-tetrahydroxycalix[4]arene (4g). A mixture of 1.0 g (0.8 mmol) of **3**, 0.83 g (4.0 mmol) of 2,6-di-*tert*-

butylphenol, and 0.17 g (4.2 mmol) of NaH (60% in oil dispersion) in 70 mL of freshly distilled THF was refluxed for 18 h in an atmosphere of N_2. The THF was removed under reduced pressure, and the residue was washed with 1 N HCl solution. Purification by flash chromatography using petroleum ether-CH_2Cl_2 (3:2) as eluent gave 0.30 g (29%) of **4g**: mp 161–163 °C; ^{1}H NMR ($CDCl_3$) δ 10.22 (s, 4), 6.94 (s, 8), 6.82 (s, 8), 5.06 (s, 4), 4.18 (bd, 4), 3.40 (bd, 4), 3.69 (s, 8), 1.42 (s, 72); ^{13}C NMR ($CDCl_3$) δ 152.07, 146.99, 135.83, 135.19, 131.58, 129.21, 128.20, 125.41, 40.97, 34.38, 31.99, 30.45. Anal. Calcd for $C_{88}H_{112}O_8$: C, 81.44; H, 8.71. Found: C, 81.69; H, 8.90.

5,11,17,23-Tetrakis[2′,2′-bis(methoxycarbonyl)ethyl]-25,26,27,28-tetrahydroxycalix[4]arene (4h). To a solution of 1.0 g (0.8 mmol) of **3** in 50 mL of DMSO was added a well-stirred mixture of 1.32 g (10 mmol) of dimethyl malonate and 0.6 g (11 mmol) of NaOMe in 20 mL of HPLC-grade MeOH, and the reaction mixture was stirred for 18 h at rt in an atmosphere of N_2. Solvent was removed under reduced pressure, the residue was poured into ice-cold H_2O (250 mL) acidified with 2 N HCl, and the light yellow precipitate was removed by filtration and washed thoroughly with H_2O. The crude product was purified by flash chromatography using $CHCl_3$ as eluent followed by crystallization from $CHCl_3$–*n*-hexane (3:2) to yield 0.67 g (82%) of **4h** as a colorless powder: mp 145–146 °C; ^{1}H NMR ($CDCl_3$) δ 10.02–10.04 (bs, 4), 6.85 (s, 8), 4.13 (d, 4, J = 12.31 Hz), 3.65 (s, 24), 3.56 (t, 4, J = 7.64 and 6.98 Hz), 3.38 (d, 4, J = 12.06 Hz), 2.99 (d, 8); ^{13}C NMR ($CDCl_3$) δ 169.07, 148.20, 130.82, 128.96, 128.28, 53.79, 52.41, 33.97, 30.82. Anal. Calcd for $C_{52}H_{56}O_{20}$: C, 62.39; H, 5.64. Found: C, 62.67; H, 5.67.

5,11,17,23-Tetrakis[2′-(methoxycarbonyl)-2′-(ethoxycarbonyl)ethyl]-25,26,27,28-tetrahydroxycalix[4]arene (4j) was prepared by the procedure described above for **4h** by adding 1.0 g (0.8 mmol) of **3** in 50 mL of DMSO to a well-stirred mixture of 1.32 g (10 mmol) of dimethyl malonate and 0.7 g (11 mmol) of NaOEt in 20 mL of absolute EtOH and allowing the reaction mixture to stand 18 h at rt in an atmosphere of N_2. After removal of solvent, the residue was poured into 1 N HCl to give a light yellow semisolid that was washed with H_2O and flash chromatographed using $CHCl_3$ as eluant to yield 0.72 g (84%) of **4j** as a colorless powder which showed a single spot on silica gel TLC (R_f 0.75 with *n*-hexane/MeCN (3:1) as eluant; other eluants also showed only a single spot): mp 81–82 °C; ^{1}H NMR ($CDCl_3$) δ 10.02 (s, 4), 6.86 (s, 8), 4.14 (d, 4, J = 12.30 Hz), 4.03 (m, 8), 3.66 (s, 12), 3.54 (t, 4, J = 6.44 and 6.87 Hz), 3.40 (d, 4, J = 11.51 Hz), 2.99 (d, 8, J = 7.52 Hz), 1.77 (bs, H_2O), 1.00 (m, 12); ^{13}C NMR ($CDCl_3$) δ 169.21, 168.10, 148.17, 131.26, 129.12, 126.02, 61.34, 53.79, 52.52, 33.76, 31.27, 13.51. Anal. Calcd for $C_{56}H_{64}O_{20}\cdot H_2O$; C, 62.56; H, 6.19. Found C, 62.53; H, 6.03. The low mp of **4j** precluded drying the analytical sample at high temperature. The presence of H_2O was inferred from the broad resonance at δ 1.77 in the ^{1}H NMR. Chloroform solutions of calixarenes that do not show a proclivity to occlude H_2O show a sharp band at *ca.* δ 1.55 for H_2O in $CHCl_3$.

5,11,17-Triethyl-25,26,27,28-tetrahydroxycalix[4]arene (5b). A solution of 2.2 mL (6.6 mmol) of 3 M MeMgCl in THF diluted to 50 mL with dry THF was added dropwise from an addition funnel over a period of 3 h to a refluxing suspension of 1.0 g (0.8 m mol) of **3** in 100 mL of THF under N_2. After being refluxed for an additional 18 h, the reaction mixture was cooled, and 5 mL of saturated NH_4Cl solution was slowly added followed by 10 mL of dilute HCl. The THF was removed under reduced pressure, the residue was dissolved in $CHCl_3$, and the $CHCl_3$ solution was concentrated and treated with MeOH. The precipitate that formed was removed by filtration and then recrystallized from CH_2Cl_2–CH_3OH (2:1) to afford 0.3 g (74%) of **5b** as a colorless powder: mp 315–318 °C; ^{1}H NMR ($CDCl_3$) δ 10.20 (s, 4,), 7.03 (d, 2), 6.86 (s, 6), 6.71 (t, 1), 4.22 (bd, 4), 3.42 (bd, 4), 2.43 (q, 6, J = 7.50 Hz), 1.13 (t, 9, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ 148.99, 146.78, 146.23, 137.75, 137.68, 128.97, 128.48, 128.28, 128.20, 128.08, 122.18, 32.01, 31.93, 28.04, 15.68. An analytical sample was prepared by flash chromatography using CH_2Cl_2–petroleum ether (2:3) as eluent. Anal. Calcd for $C_{34}H_{36}O_4$: C, 80.28; H, 7.13. Found: C, 80.26; H, 7.25.

5-[(*N*,*N*-Dimethylamino)methyl]-25,26,27,28-tetrahydroxycalix[4]arene (6). A solution of 85.0 g (0.2 mol) of 5,11,17,23-tetrahydroxycalix[4]arene (**1**), 32.5 g (0.4 mol) of 37% formaldehyde, and 46 g (0.41 mol) of 40% Me_2NH in 1.1 L of THF was stirred at rt for 2 h. The thick white precipitate was separated by filtration, washed throughly with ice-cold H_2O followed by MeOH, and then air dried and again triturated with Me_2CO to yield 92 g (95%) of **6** as a colorless solid: mp 350 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.16 (d, 6, J = 7.50 Hz), 6.98 (s, 2), 6.72 (t, 3, J = 7.5 Hz), 4.23 (bs, 4), 3.54 (bs, 4), 3.22 (s, 2), 2.19 (s, 6); ^{13}C NMR (DMSO-d_6) δ 157.67, 154.51, 153.78, 130.81, 130.70, 130.55, 130.26, 129.91, 127.65, 127.47, 118.27, 117.88, 60.23, 41.54, 32.69, 32.05, 28.04, 15.68. Anal. Calcd for $C_{31}H_{31}NO_4$: C, 77.31; H, 6.49, N, 2.91. Found: C, 77.56; H, 6.75, N, 2.84.

5-(Cyanomethyl)-25,26,27,28-tetrahydroxycalix[4]arene (7a). A solution of 5.0 g (10 mmol) of **6** and 2.1 g (15 mmol) of MeI in 100 mL of DMSO was stirred for 1 h under N_2, treated with 7.4 g (0.15 mol) of NaCN, and stirred 24 h at rt. The reaction mixture was poured into 400 mL of 1 N HCl and stirred and the precipitate removed by filtration and washed with H_2O and MeOH. Recrystallization from $CHCl_3$–CH_3OH (3:1) gave 4.1 g (88%) of **7a** as a colorless powder: mp 365–366 °C; ^{1}H NMR ($CDCl_3$) δ 10.16 (s, 4), 7.06 (bs, 6), 6.98 (s, 2), 6.75 (t, 3, J = 8.10 and 8.70 Hz), 4.24 (bs, 4), 3.53 (bs, 6); ^{13}C NMR (DMSO-d_6) δ 149.69, 149.19, 148.81, 129.11, 128.72, 128.63, 128.51, 128.42, 128.17, 128.12, 123.38, 121.11, 121.00, 119.22, 30.53, 30.47, 21.50. An analytical sample was prepared by flash chromatography using CH_2Cl_2 as an eluent followed by recrystallization from CH_2Cl_2. Anal. Calcd for $C_{30}H_{25}NO_4\cdot 1/10CH_2Cl_2$: C, 76.59; H, 5.38, N, 2.97; Cl, 1.50. Found: C, 76.69; H, 5.35, N, 2.91; Cl, 1.65.

5-(Hydroxymethyl)-25,26,27,28-tetrahydroxycalix[4]arene (7b). Following the procedure described above for **7a** and using 3.0 g (20 mmol) of CsOH, a crude product was obtained that was recrystallized from $CHCl_3$–CH_3OH (3:1) to give 0.83 g (48%) of **7b** as a colorless powder: mp 195–196 °C; ^{1}H NMR ($CDCl_3$) δ 10.20 (s, 4), 7.05 (m, 6), 7.00 (s, 2), 6.70 (m, 3), 4.26 (bs, 6), 3.52 (bs, 4); ^{13}C NMR ($CDCl_3$) δ 148.83, 148.75, 148.22, 131.97, 129.39, 129.01, 128.48, 128.25, 128.16, 122.29, 122.23, 70.40, 31.73. An analytical sample was prepared by flash chromatography using $CHCl_3$ as eluent. Anal. Calcd for $C_{29}H_{26}O_5$: C, 76.63; H, 5.77. Found: C, 77.59; H, 5.68.

5-(Methoxymethyl)-25,26,27,28-tetrahydroxycalix[4]arene (7c). Following the procedure described above for **7a** and using 2.7 g (50 mmol) of NaOMe, a crude product was obtained that was recrystallized from $CHCl_3$–CH_3OH (3:1) to yield 4.1 g (87%) of **7c** as a colorless powder: mp 229–231 °C; ^{1}H NMR ($CDCl_3$) δ 10.19 (s, 4), 7.06 (d, 4, J = 7.5 Hz), 7.04 (d, 2, J = 7.5 Hz), 7.01 (s, 2), 6.73 (2t, 3), 4.25 (bs, 4), 4.22 (s, 2), 3.56 (bs, 4), 3.31 (s, 3); ^{13}C NMR ($CDCl_3$) δ 148.91, 148.81, 148.34, 131.93, 129.08, 128.61, 128.32, 128.23, 122.32, 74.27, 58.06, 31.79. An analytical sample was prepared by flash chromatography using $CHCl_3$ as an eluent. Anal. Calcd for $C_{30}H_{28}O_5$: C, 76.90; H, 6.02. Found: C, 77.11; H, 5.99.

5-(Ethoxymethyl)-25,26,27,28-tetrahydroxycalix[4]arene (7d). Following the procedure described above for **7a** and using 2.2 g (32 mmol) of NaOEt for 36 h at rt, a light yellow semisolid material was obtained. It was extracted with $CHCl_3$, concentrated, poured over hexane to give a light yellow precipitate, and flash chromatographed using $CHCl_3$ as an eluent. Recrystallization from $CHCl_3$–CH_3OH (3:1) gave 0.97 g (80%) of **7d** as a colorless powder: mp181–182 °C; ^{1}H NMR ($CDCl_3$) δ 10.26 (s, 4), 7.08 (s, 2), 7.02 (m, 6), 6.78 (m, 3), 4.22–4.30 (bs, 6), 3.38–3.54 (m, 6), 1.28 (t, 3, J = 7.2 and 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 148.85, 148.80, 148.76, 129.44, 129.26, 129.01, 128.77, 128.61, 128.48, 128.25, 122.26, 72.26, 65.58, 31.74, 15.25. Anal. Calcd for $C_{31}H_{30}O_5$: C, 77.16; H, 6.27. Found: C, 77.15; H, 6.21.

5-(Phenoxymethyl)-25,26,27,28-tetrahydroxycalix[4]arene (7e). Following the procedure described above for **7a** and using 3.5 g (30 mmol) of sodium phenoxide a crude product was obtained that was recrystallized from $CHCl_3$–CH_3OH (2:1) to give 3.4 g (64%) of **7e** as a colorless powder: mp 145–146 °C; ^{1}H NMR ($CDCl_3$) δ 10.18 (s, 4), 7.28 (d, 2, J = 7.5 Hz), 7.07 (s, 2), 7.04 (2d, 6), 6.91 (d, 2, J = 7.5 Hz), 6.69 (t, 4, J = 7.5 and 7.5 Hz), 4.80 (s, 2), 4.24 (bd, 4), 3.56 (bd, 4); ^{13}C NMR ($CDCl_3$) δ 148.87, 148.75, 148.67, 130.80, 129.51, 129.44, 129.06, 128.64, 128.52, 128.32, 128.27, 128.08, 122.33, 120.94, 114.83, 69.61, 31.75, 31.65. An analytical sample was prepared by flash chromatography using $CHCl_3$ as eluent. Anal. Calcd for $C_{35}H_{30}O_5$: C, 79.23; H, 5.70. Found: C, 79.05; H, 5.65.

5-[[4′-(4″-Hydroxyphenyl)phenoxy]methyl]-25,26,27,28-tetrahydroxycalix[4]arene (7f). Following the procedure described above for **7a** and using 6.0 g (30 mmol) of sodium 4′-hydroxybiphenoxide, a crude product was obtained that was

recrystallized from $CHCl_3$–CH_3OH (3:1) to give 4 g (67%) of **7f** as a colorless powder: mp 145–146 °C; ^1H NMR ($CDCl_3$) δ 10.19 (s, 4), 7.42 (dd, 4, J = 8.7 and 6.9 Hz), 7.12 (s, 2), 7.04 (m, 5), 6.97 (d, 2, J = 8.4 Hz), 6.88 (d, 2, J = 8.4 Hz), 6.73 (dd, 4, J = 7.5 and 7.5 Hz), 4.84 (s, 2), 4.80 (bs, 1), 4.25 (bs, 4), 3.51 (bs, 4); ^{13}C NMR ($CDCl_3$) δ 148.86, 148.82, 148.76, 148.71, 129.47, 129.05, 128.85, 128.66, 128.57, 128.52, 128.33, 128.28, 128.19, 128.08, 127.97, 127.74, 122.35, 122.25, 115.70, 115.12, 69.83, 31.75. An analytical sample was prepared by flash chromatography using CH_2Cl_2 as eluent. Anal. Calcd for $C_{35}H_{30}O_5$: C, 79.08; H, 5.75. Found: C, 79.43; H, 5.61.

5-[2′,2′-Bis(ethoxycarbonyl)ethyl]-25,26,27,28-tetrahydroxycalix[4]arene (7g). A solution of 5.0 g (10 mmol) of **6** and 2.1 g (15 mmol) of MeI in 100 mL of DMSO was stirred for 1 h under N_2. Diethyl sodiomalonate, prepared from 9.6 g (60 mmol) of diethyl malonate and 4.4 g (65 mmol) of NaOEt in 40 mL of absolute EtOH, was added in portions, and the resulting mixture was allowed to stir at rt for 24 h. It was then poured into 400 mL of 1 N HCl and stirred and the precipitate removed by filtration and washed with H_2O and MeOH. Recrystallization from Et_2O–CH_3OH (4:1) gave 3.6 g (60%) of **7d** as a colorless powder: mp 138–139 °C; ^1H NMR ($CDCl_3$) δ 10.13 (s, 4), 7.04 (d, 6, J = 7.80 Hz), 6.89 (s, 2), 6.73 (m, 3), 4.26 (bs, 4), 3.94 (q, 4, J = 7.2, 6.9 and 7.2 Hz), 3.48 (bs, 4), 3.50 (t, 1, J = 7.8 Hz), 2.99 (d, 2, J = 7.2 Hz), 0.80 (t, 6, J = 7.28 and 6.90 Hz). An analytical sample was prepared by flash chromatography using $CHCl_3$ as eluent. Anal. Calcd for $C_{36}H_{36}O_8$: C, 72.47; H, 6.08. Found: C, 72.64; H, 5.85.

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