Calixarenes: Selective Functionalization and Bridge Building[1]

Suseela Kanamathareddy and C. David Gutsche*

Department of Chemistry, Texas Christian University, Fort Worth, Texas 76129

Received March 30, 1995[⊗]

The scope of the quinone methide method for introducing functional groups into the upper rim of calix[4]arenes has been expanded by taking advantage of selective esterification at the lower rim. A variety of calix[4]arenes carrying two functional groups on the upper rim have been prepared in this fashion, including compounds **12**–**25**. Compound **25**, containing a pair of propargyl groups, undergoes intramolecular oxidative coupling to yield the bridged compound **26**. In like fashion the tetrasubstituted propargyl compound **7b** undergoes both intramolecular and intermolecular oxidative coupling to give the doubly bridged calix[4]arene **27** and the doubly bridged bis-calix[4]-arene **28**.

The introduction of functional groups at the upper rim of calix[4]arenes has been studied in great detail in a number of laboratories during the past several years, and a variety of methods have been devised for this purpose.[2] Among these the quinone methide route[3] is particularly useful for upper rim functionalization (Scheme 1). It involves the de-*tert*-butylation of *p*-*tert*-butylcalix[4]arene (**1**)[4] to calix[4]arene (**2**), treatment of **2** with dimethylamine and formaldehyde to yield [*p*-(dimethylamino)-methyl]calix[4]arene (**3**), quaternization of **3** with MeI, and reaction of the quaternary salt with nucleophiles to yield products such as the previously reported[3] *p*-tetrakis-(cyanomethyl)calix[4]arene (**4**) and the tetrasubstituted acetylenic compound **6**, the latter prepared as a putative precursor to an intra- and/or intermolecularly bridged calixarene (*vide infra*). Compound **5**, also prepared for this purpose, was obtained more directly by treatment of **2** with $CH_3NHCH_2C{\equiv}CH$ and HCHO.

To expand the scope of the quinonemethide method, its applicability to the preparation of disubstituted calix-[4]arenes has been investigated. Employing a previously published procedure for selective O-aroylation,[5] **1** was converted to the diester **8** and treated with $AlCl_3$ to remove the *tert*-butyl groups *para* to the phenol groups to yield **9**, and **9** was hydrolyzed to 5,11-di-*tert*-butylcalix-[4]arene (**10**). Then, by means of the quinonemethide sequence, compounds **13**–**20** were prepared by treating the quaternary salt of **11** with the appropriate carbon nucleophile (to give **13**, **15**, **19**, and **20**) or oxygen nucleophile (to give **14**, **16**–**18**). Compound **14**, along with compound **12** which was prepared in a fashion similar to **5** by treatment of **10** with $CH_3NHCH_2C{\equiv}CH$, are potential precursors to intra- or intermolecularly bridged calixarenes (*vide infra*).

p-Tetrakis(cyanomethyl)calix[4]arene (**4**) has proved to be a useful starting material for further elaboration,[6] and **13** reacts in a comparable fashion. Treatment of **13** with benzyl bromide and K_2CO_3 in acetone at room temperature converts it to the 1,3-dibenzyl ether **22** (Scheme 2). Although two regioisomeric products can form in this case, only one product (82% yield) is obtained under these conditions. The position of the *tert*-butyl resonances in the ^1H NMR spectra of starting compound and product indicates that benzylation occurs on the phenolic moieties carrying the *p*-cyanomethyl groups. When benzylation occurs on rings carrying *p*-*tert*-butyl groups, the *tert*-butyl resonance generally moves upfield from its original position of δ 1.24. In the present case, however, the *tert*-butyl resonance of the product appears at δ 1.27, indicating a small downfield shift. This conclusion is further strengthened by the ^1H NMR spectrum of the product obtained when the benzylation is carried out at reflux temperature. In this case *tert*-butyl resonances at δ 1.26 and 1.06 are observed, the latter arising as the result of benzylation of one or more of the phenolic moieties carrying *p*-*tert*-butyl groups. In like fashion, the *tert*-butyl resonance of the fully O-benzylated compound **21**, prepared with benzyl bromide and NaH, appears upfield at δ 0.95. The regiochemical outcome of the dibenzylation of **13** is ascribed to the slightly greater acidity of the phenolic moieties carrying *p*-cyanomethyl groups as compared with *p*-*tert*-butyl groups.

The present work was undertaken not only to expand the scope of the quinonemethide sequence but also to explore the possibility of creating intra- and/or intermolecular diyne bridges across the upper rim of the calixarene. A number of upper rim bridge spanning moieties have already been reported, including $(CH_2)_n$,[7] $Hg(CH_2)_n$-Hg,[8] $CH_2CH_2COCH_2CH_2$,[9] CH_2ArCH_2,[9] $CH_2OArOCH_2$,[10,11] $CH_2O(CH_2CH_2O)_nCH_2$,[12] $CH_2OArCO_2CH_2$,[11] the bottom

⊗ Abstract published in *Advance ACS Abstracts,* August 15, 1995.

(1) Paper 42 in the series entitled Calixarenes. For paper 41, see: Sharma, S. K.; Alam, I.; Gutsche, C. D. *Synthesis* **1995**, in press.

(2) References to the numerous procedures used for introducing functional groups into the *para* positions can be found in review articles by the following: (a) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713. (b) Gutsche, C. D. *Aldrichimica Acta* **1995**, *28*, 3.

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

(4) The term "calixarene" is variously employed in different contexts. In colloquial usage (typically, in the discussion section), it implies the presence of hydroxyl groups groups at all of the lower rim positions and R groups (*i.e.* *tert*-butyl in **1**) at all of the *para* positions of the upper rim of the cyclic array. In some instances, however, it is helpful to indicate the number of such groups by the appropriate prefix (*i.e.* **1** as *p*-tetra-*tert*-butylcalix[4]-arene or even *p*-tetra-*tert*-butylcalix[4]-arenetetrol). This more explicit nomenclature is particularly applicable when fewer than the maximum number of positions at the upper and/or lower rims are occupied by R groups or OH groups, respectively. In the more precise and complete specification of a compound (typically, in the Experimental Section), the term "calixarene" implies only the basic skeleton to which the substituents, including the R and OH groups, are attached at positions designated by appropriate numbers.

(5) See, K. A.; Fronczek, F. R.; Watson, W H.; Kashyap, R. P.; Gutsche, C. D. *J.Org. Chem.* **1991**, *56*, 7256.

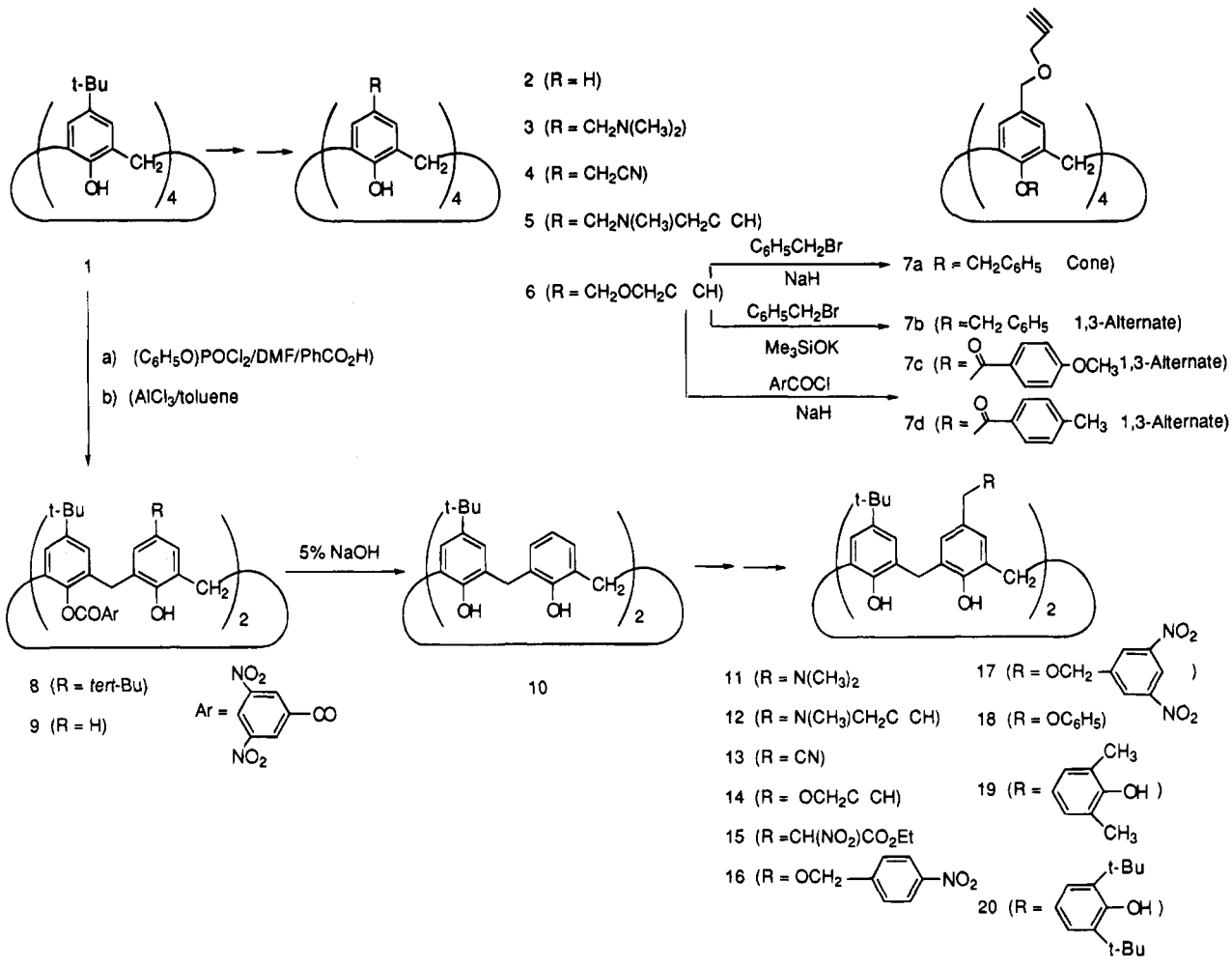
(6) Sharma, S. K.; Gutsche, C. D. *Tetrahedron Lett.* **1993**, 34, 5389. Sharma, S. K.; Gutsche, C. D. *Tetrahedron* **1994**, 50, 4087. Sharma, S. K.; Gutsche, C. D. *Synthesis* **1994**, 813. Sharma, S. K.; Gutsche, C. D. *J. Org. Chem.* in press. Alam, I.; Sharma, S. K.; Gutsche, C. D. *J. Org. Chem.* **1994**, *59*, 3716.

(7) Goldman, H.; Vogt, W.; Paulus, W.; Böhmer, V. *J. Am. Chem. Soc.* **1988**, *110*, 6811. Böhmer, V.; Vogt, W. *Pure Appl. Chem.* **1993**, *65*, 403.

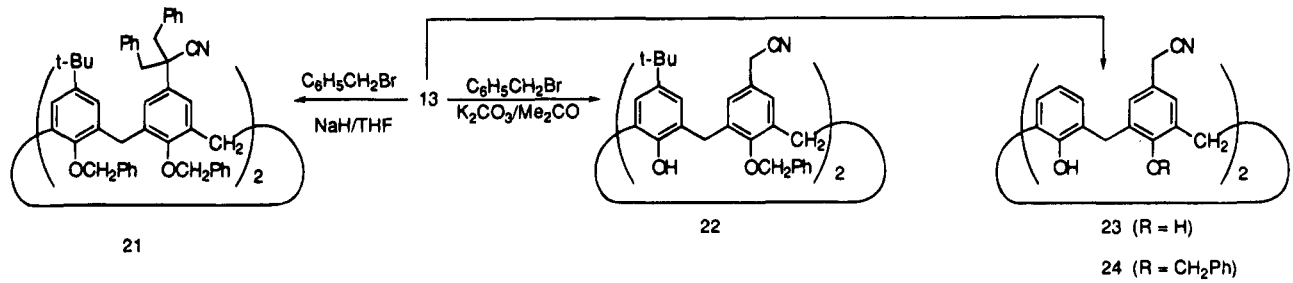
(8) Markowitz, M. A.; Janout, V.; Castner, D. G.; Regen, S. L. *J. Am. Chem. Soc.* **1989**, *111*, 8192.

0022-3263/95/1960-6070$09.00/0

Scheme 1



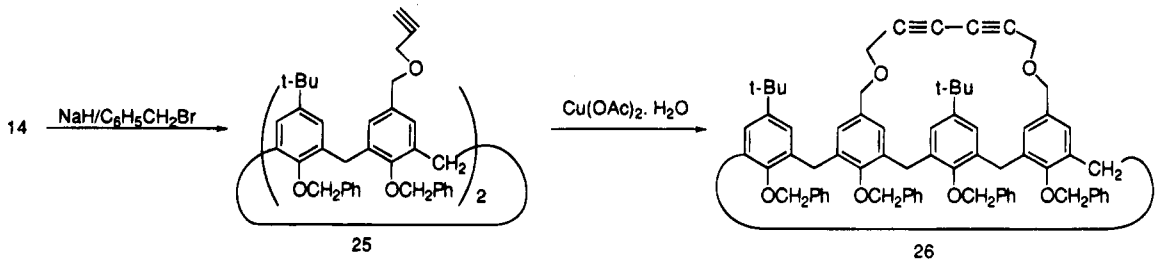
Scheme 2



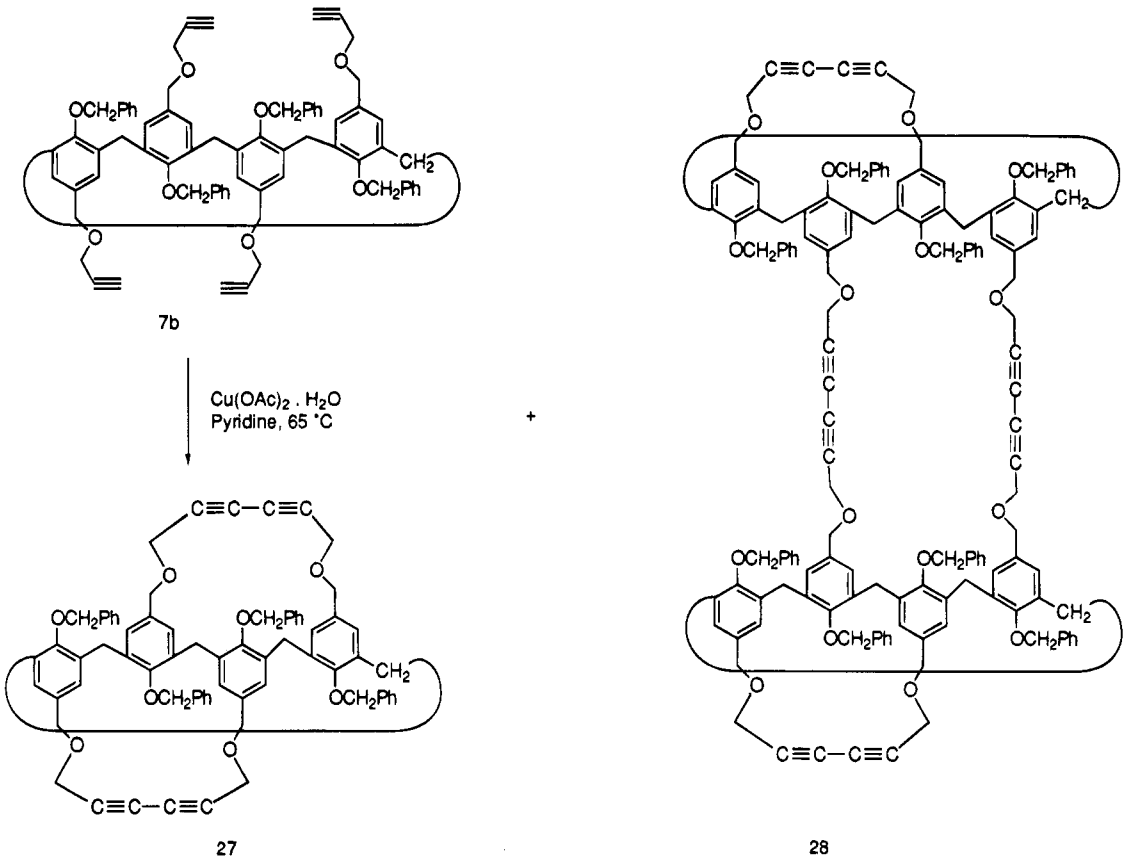
rim of a calixarene,[13] and a porphyrin.[14] This list has recently been expanded to include the $CH_2OCH_2C{\equiv}CC{\equiv}CCH_2OCH_2$ spanner,[15] identical with the one used in the present work. Our first attempts to install this bridge involved the action of Cu^{+2} on the free phenolic calixarenes **5**, **6**, **12**, and **14**, but no clean coupling products could be isolated. In the thought that the difficulty might arise from the free phenolic groups, **14** was converted with benzyl bromide and NaH to the cone conformer of the tetrabenzyl ether **25** (Scheme 3). Treatment of **25** with $Cu(OAc)_2{\cdot}H_2O$/pyridine in CH_3CN gives a 90% yield of the intramolecularly coupled product **24**, thus confirming that phenolic groups may, indeed, interfere with the oxidative coupling process. The structure of the coupling product **26** is based, *inter alia*, on the absence of a resonance at δ 2.36 (present in **25** and arising from the alkyne H), the change of the resonance at δ 3.90 arising from the $CH_2C{\equiv}C$ protons from a doublet (in **25**) to a singlet (in **26**), and a signal in the mass spectrum at *m/e* 1031, commensurate with an intramolecularly bridged compound. Shortly before the present work was completed, two papers by Arduini *et al.* described the intramolecular[15] and intermolecular[16]

(9) Berger, B.; Böhmer, V.; Paulus, E.; Rodriguez, A.; Vogt, W. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 96.
(10) Arduini, A.; Casnati, A.; Fabbi, M.; Minari, P.; Pochini, A.; Sicuri, A. R.; Ungaro, R. *Supramol. Chem.* **1993**, *1*, 235.
(11) Ikeda, A.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2671.
(12) van Loon; J.-D.; Groenen, L. C.; Wijmenga, S. S.; Verboom, W.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1991**, *113*, 2378.
(13) Beer, P. D.; Gale, P. A.; Hesek, D. *Tetrahedron Lett.* **1995**, *36*, 767.
(14) Asfari, Z.; Vicens, J.; Weiss, J. *Tetrahedron Lett.* **1993**, *34*, 627.
(15) Arduini, A.; Cantoni, M.; Graviani, E.; Pochini, A.; Secchi, A.; Sicuri, A. R.; Ungaro, R.; Vicenti, M. *Tetrahedron* **1995**, *51*, 599.
(16) Arduini, A.; Pochinii, A.; Sicuri, A. R.; Secchi, A.; Ungaro, R. *Gazz. Chim. Ital.* **1994**, *124*, 129.

Scheme 3



Scheme 4



oxidative coupling of a calix[4]arene tetraether carrying propargyloxy or ethynyl groups in the distal *para* positions on the upper rim. The propargyloxy groups were introduced via formlation, reduction to hydroxymethyl, and treatment with propargyl bromide.

On the basis of the success of the experiment described above for the calixarene carrying two propargyl groups on the upper rim, compound **6**, carrying four such groups, was converted with benzyl bromide and NaH to its tetrabenzyl ether in the cone conformation **7a.** However, in contrast to **25**, treatment of **7a** with $Cu(OAc)_2{\cdot}H_2O$ produced a mixture from which no pure compounds could be isolated and characterized. In the hope that a different conformer might behave more manageably, **6** was converted to its tetrabenzyl ether in the 1,3-alternate conformation **7b** using benzyl bromide with Me_3SiOK as the base.[17] This hope was realized, for the 1,3-alternate conformer **7b** produces a major product in 61% yield that was identified as the doubly intramolecularly bridged **27** (Scheme 4). Its structure was established in the manner described above for **26**, taking advantage of certain features of the ^1H NMR spectrum (*i.e.* no resonance at δ 2.38 for ≡CH; an eight-proton singlet at δ 4.40 for $CH_2C{\equiv}$) as well as the mass spectrum which showed a strong signal at *m/e* 1053. A few other examples of doubly bridged calixarenes have been reported,[11,18] the one most closely resembling **27** being the conformational mixture obtained from the tetramethyl ether of *p*-(chloromethyl)calix[4]arene and catechol or resorcinol.[11]

In addition to **27** another product was isolated in 7% yield for which structure **28** is proposed, based on a parent ion signal in the mass spectrum at *m/e* 2105, the appearance of four sets of resonances arising from the methylene hydrogens of the upper rim[19] $CH_2OCH_2C{\equiv}C$ moieties (δ 4.48, 4.40, 4.18, 4.14), ten signals in the δ 58–79 region of the ^{13}C NMR spectrum arising from methylene groups (78.5, 76.0, 73.6, and 73.0 for $ArCH_2O$,

(17) It should be noted that the different outcomes using NaH and Me_3SiOK as the bases provides a very useful method for exerting conformational control of the arylmethylation reaction.

(18) Ghidini, E.; Ugozoli F.; Ungaro, R.; Harkema, S.; El-Fadl, A. A.; Reinhoudt, *J. Am. Chem. Soc.* **1990**, *112*, 6979. Pappalardo, S.; Ferguson, G.; Gallagher, J. F. *J. Org. Chem.* **1992**, *57*, 7102. For a review, cf.: Asfari, Z.; Weiss, J.; Vicens, J. *Synlett* **1993**, 719.

70.8, 69.4, 58.7, and 57.2 for $OCH_2C\equiv$, 71.0 and 71.6 for $PhCH_2O$), and two signals at 156.4 and 154.8 in the ^{13}C NMR spectrum arising from the aromatic carbons carrying the benzyloxy moieties. In contrast, **27** has exactly half the number of resonances for the various moieties cited above for **28**. A double-calix[4]arene crown ether analogous to **28** but constructed with spanners engaging the lower rim functions has been described.[20]

The reaction described above, yielding **27** and **28**, was carried out at 65 °C. When the same reaction was carried out at room temperature, however, neither of these compounds was present, and the product consisted entirely of a material that appears to be polymeric. Conventional mass spectral techniques were unavailing in ascertaining the molecular weight range of this material.

Experimental Section[21]

5,11,17,23-Tetrakis[(*N*-methylpropargylamino)methyl]-calix[4]arene-25,26,27,28-tetrol (5) was prepared in 85% yield starting from calix[4]arene (**2**) and *N*-methylpropargylamine, following the procedure described below for **11**, and was purified by trituration with MeOH to give a white powder: mp >200 °C; ^1H NMR ($CDCl_3$) δ 7.00 (s, 8), 4.24 (bd, 4), 3.48 (bd, 4), 3.33 (s, 8), 3.23 (d, 8, J = 2.2 Hz), 2.29 (s, 12), 2.26 (t, 4, J = 2.4 Hz); ^{13}C NMR ($CDCl_3$) δ 148.6, 131.2, 129.5, 128.3, 78.5 (**C**≡CH), 73.3 (C≡**C**H), 59.3, 44.6, 41.6, 31.8; MS (FAB) $(M + H)^+$ 749. Anal. Calcd for $C_{48}H_{52}N_4O_4{\cdot}^1/_2H_2O$: C, 76.06; H, 7.05; N, 7.39. Found: C, 76.02; H, 6.92. N, 7.28.

5,11,17,23-Tetrakis[(propargyloxy)methyl]calix[4]arene-25,26,27,28- tetrol (6). A 0.65 g (1 mmol) of 5,11,17,23-tetrakis[(dimethylamino)methyl]calix[4]arene-25,26,27,28-tetrol (**3**) was dissolved in 10 mL of DMSO, 0.37 mL (6 mmol) of CH_3I was added, and the contents were stirred at rt for 30 min. In a separate round-bottomed flask 0.35 mL (6 mmol) of propargyl alcohol was dissolved in 10 mL of DMSO, and 0.4 g of 60% NaH was added at rt. The quarternary salt, prepared as described above, was added to this mixture, and the contents were heated at 85 °C for 3 h. The mixture was poured into 150 mL of cold H_2O, the solution was acidified with 2 N HCl, and the product was extracted into CH_2Cl_2. The CH_2Cl_2 extracts were mixed, washed with water and brine, and dried over Na_2SO_4. The residue was chromatographed over silica gel (70–230 mesh) to give 0.25 g (42%) of **6**. An analytical sample was obtained as a white powder by recrystallization from CH_2Cl_2–MeOH: mp 142–143 °C; ^1H NMR ($CDCl_3$) δ 10.13 (s, 4), 7.04 (s, 8), 4.39 (s, 8), 4.22 (bd, 4), 4.08 (d, 8, J = 2.4 Hz), 3.53 (bd, 4), 2.46 (t, 4, J = 2.5 Hz); ^{13}C NMR ($CDCl_3$) δ 148.5, 130.9, 128.9, 128.1 (ArC), 79.72 (**C**≡CH), 74.5 (C≡**C**H), 70.9, 56.8, 31.6. Anal. Calcd for $C_{44}H_{40}O_8$: C, 75.84; 5.79. Found: C, 75.47; H, 5.77.

5,11,17,23-Tetrakis[(propargyloxy)methyl]-25,26,27,28-tetrakis(benzyloxy)calix[4]arene (7a). A 0.7 g (1 mmol) sample of compound **6** was dissolved in 20 mL of THF–DMF (9:1), and to this solution was added 0.32 g (8 mmol) of NaH (60% dispersion in oil) at ice bath temperature. The contents were stirred for 15 min, and 1.34 g (8 mmol) of benzyl bromide dissolved in 5 mL of THF was added. The reaction mixture was warmed to rt, stirred for 2 h, and then heated at 75 °C for another 2 h. After cooling to rt a few drops of MeOH were added to decompose excess NaH, THF was removed under vacuum, cold H_2O was added, and the product was extracted into CH_2Cl_2 (3 × 25 mL). The combined organic layer was washed with H_2O and brine and dried over anhydrous Na_2SO_4. Removal of the solvent and recrystallization of the residue from CH_2Cl_2–MeOH gave 0.72 g (65%) of the tetrabenzyl ether **7a** as a white powder: mp 102–103 °C; ^1H NMR ($CDCl_3$) δ 7.28–7.18 (m, 20), 6.57 (s, 8), 4.91 (s, 8), 4.25 (s, 8), 4.14 (d, 4, J = 13.4 Hz), 4.01 (d, 8, J = 2.4 Hz), 2.88 (d, 4, J = 13.4 Hz), 2.46 (t, 4, J = 2.4 Hz); ^{13}C NMR ($CDCl_3$) δ 155.2, 137.5, 135.1, 130.6, 129.7, 128.5, 128.1, 127.9, 79.9, 76.5, 74.6, 71.4, 56.5, 31.3. Anal. Calcd for $C_{72}H_{64}O_8$: C, 81.79; H, 6.1. Found: C, 81.56; H, 5.94.

5,11,17,23-Tetrakis[(propargyloxy)methyl]-25,26,27,28-tetra(benzyloxy) calix[4]arene (7b) (1,3-Alternate Conformation). To a solution of 1.4 g of **6** in 20 mL of THF was added 1.28 g (10 mmol) of Me_3SiOK at ice bath temperature. The contents were stirred for 10 min, after which 1.2 g (10 mmol) of benzyl bromide in 2 mL of THF was added. The reaction mixture was stirred at rt for 16 h, solvent was removed under vacuum, and cold H_2O (50 mL) was added. The aqueous mixture was acidified with dilute HCl, and the product was extracted into CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with water and brine and dried over Na_2SO_4. The residue from evaporation of the solvent was passed over silica gel and recrystallized from CH_2Cl_2–MeOH to give 1.5 g (70%) of **7b** as a white powder: mp 181–182 °C; ^1H NMR ($CDCl_3$) δ 7.44–7.35 (m, 12), 7.26–7.12 (m, 8), 6.70 (s, 8), 4.79 (s, 8), 3.96 (s, 8), 3.94 (d, 8, J = 2.4 Hz), 3.59 (s, 8, $ArCH_2Ar$), 2.38 (t, 4, J = 2.4 Hz); ^{13}C NMR ($CDCl_3$) δ 155.8, 138.1, 133.8, 131.3, 130.4, 128.1, 127.2, 126.8, 80.0, 74.3, 72.1, 71.4, 56.8, 37.2. Anal. Calcd for $C_{72}H_{64}O_8$: C, 81.79; H, 6.10. Found: C, 81.59; H, 6.10.

5,11,17,23-Tetrakis[(propargyloxy)methyl]-25,26,27,28-tetrakis[(4-methoxybenzoyl)oxy)]calix[4]arene (7c) (1,3-Aternate Conformation). To a solution of 0.5 g of **6** in 15 mL of THF was added 0.32 g (8 mmol) of NaH (60% dispersion) at ice bath temperature. The contents were stirred for 10 min, after which 1.4 g (8 mmol) of *p*-anisoyl chloride in 5 mL of THF was introduced. The reaction was continued at rt for 16 h, the THF was removed under vacuum, and cold H_2O (50 mL) was added. The precipitate was collected by filtration, dried, and recrystallized from CH_2Cl_2–MeOH to give 0.85 g (78%) of **7c**: mp >380 °C; ^1H NMR ($CDCl_3$) δ 7.78 (8, d, J = 8.8 Hz), 7.11 (8, d, J = 8.8 Hz), 6.75 (s, 8), 4.07 (s, 8), 4.04 (s, 12), 3.90 (d, 8, J = 2.3 Hz), 3.59 (s, 8, $ArCH_2Ar$), 2.38 (t, 4, J = 2.3 Hz); ^{13}C NMR ($CDCl_3$) δ 164.0, 163.9, 148.1, 133.7, 133.0, 130.4, 121.3, 113.9, 79.5, 74.8, 70.7, 56.9, 55.7, 37.1. Anal. Calcd for $C_{76}H_{64}O_{16}$: C, 74.01; H, 5.23. Found: C, 74.61; H, 5.15.

5,11,17,23-Tetrakis[(propargyloxy)methyl]-25,26,27,28-tetrakis[(4-methylbenzoyl)oxy]calix[4]arene (7d) (1,3-alternate conformation) was prepared as described above for **7d** in 83% yield and was recrystallized from CH_2Cl_2–MeOH to give a white powder: mp >380 °C; ^1H NMR ($CDCl_3$) δ 7.72 (8, d, J = 8.0 Hz), 7.44 (8, d, J = 8.0 Hz), 6.73 (s, 8), 4.02 (s, 8), 3.86 (8, d, J = 2.3 Hz), 3.59 (s, 8, $ArCH_2Ar$), 2.62 (s, 12), 2.34 (t, 4, J = 2.3 Hz); ^{13}C NMR ($CDCl_3$) δ 164.3, 148.0, 144.3, 133.6, 133.0, 131.0, 130.5, 129.4, 126.3, 79.5, 74.5, 70.5, 56.8, 37.1, 22.1. Anal. Calcd for $C_{76}H_{64}O_{12}$: C, 78.06; H, 5.52. Found: C, 78.22; H, 5.49.

5, 17-Di-*tert*-butylcalix[4]arene-25,26,27,28-tetrol (10). A 4.62 g sample of diester **9**, prepared as previously described,[5] was added to 100 mL of a 5% NaOH solution (80:20 H_2O–EtOH), and the contents were boiled under reflux for 3 h. The dark brown reaction mixture was poured into 150 g of crushed ice, the precipitate after filtration was added to 150 mL of CH_2Cl_2 and treated with 100 mL of 2 N HCl, and the contents were stirred to bring the free calixarene into solution. The organic layer was separated, washed with water and brine,

(19) Although a calix[4]arene in the 1,3-alternate conformation cannot be said to have an upper and lower rim, these designations are retained for nomenclature purposes by employing the corresponding cone conformation as the referent (even though it might be an impossible structure).

(20) Asfari, Z.; Abidi;, R.; Arnaud, F.; Vicens, J. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1992**, *13*, 163. Asfari, Z.; Weiss, J.; Pappalardo, S.; Vicens, *Pure Appl. Chem.* **1993**, *65*, 585.

(21) Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. THF was freshly distilled from Na benzophenone. The melting points of all compounds melting above 250 °C were taken in sealed and evacuated capillary tubes on a Mel-Temp apparatus (Laboratory Devices, Cambridge, MA) using a 500 °C thermometer calibrated against a thermocouple. ^1H NMR spectra were recorded at 300 MHz. TLC analyses were carried out on Analtech silica gel plates (absorbant thickness 250 mm) containing a fluorescent indicator. Chromatography was carried out with J. T. Baker silica gel JT7042-2 (40 mm particles) on columns 50 mm in diameter filled to a height of *ca.* 7 in. Elution rates were 2 in./min; fractions of 50 mL were collected. Analytical samples were dried at least 36 h at 100–140 °C and 1–2 mm of pressure.

and dried over Na_2SO_4. The residue left after evaporation of the solvent was treated with MeOH to give 2.4 g (89%) of **10** as a white solid. An analytical sample was obtained as a white powder by crystallization from CH_2Cl_2–MeOH: mp 288–289 °C; ^1H NMR ($CDCl_3$) δ 10.26 (s, 4), 7.06 (s, 4), 7.01 (d, 4, J = 7.5 Hz), 6.70 (t, 2, J = 7.6 Hz), 4.24 (bd, 4), 3.50 (bd, 4), 1.22 (s, 18); ^{13}C NMR ($CDCl_3$) δ 148.6, 146.6, 144.5, 128.9, 127.4, 125.8, 122.3, 34.0, 32.1, 31.4. Anal. Calcd for $C_{36}H_{40}O_4$: C, 80.60; H, 7.50. Found: C, 81.19; H, 7.49.

5,17-Di-*tert*-butyl-11,23-bis[(dimethylamino)methyl]-calix[4]arene-25,26,27,28-tetrol (11). To a solution of 5.36 g (10 mmol) of **10** in 50 mL of THF were added 10 mL of AcOH, 3.38 mL (30 mmol) of 40% aqueous dimethylamine, and 2.44 mL (30 mmol) of 37% aqueous HCHO. The reaction mixture was stirred at rt for 24 h, the solvents were removed under vacuum, and the residue was dissolved in 100 mL of H_2O and neutralized with 10% K_2CO_3. The precipitate that formed was removed by suction filtration and recrystallized from $CHCl_3$–MeOH to give 6.0 g (92%) of **11** as a white powder: mp 263–265 °C; ^1H NMR ($CDCl_3$) δ 7.06 (s, 4), 6.95 (s, 4), 4.23 (bd, 4), 3.50 (bd, 4), 3.17 (s, 4), 2.18 (s, 12), 1.21 (s, 18). The compound was analyzed as a quarternary salt. Anal. Calcd for $C_{44}H_{60}N_2I_2O_4$: C, 56.54; H, 6.47; N, 2.99. Found: C, 56.72; H, 6.48; N, 2.99.

5,17-Di-*tert*-butyl-11,23-bis[(*N*-methyl propargylamino)-methyl]calix[4]arene-25,26,27,28-tetrol (12) was prepared in 86% yield, starting from **10** and *N*-methylpropargylamine, using the same procedure as described above for **11**. An analytical sample was obtained as a white powder by recrystallization from $CHCl_3$–MeOH: mp 219–220 °C; ^1H NMR ($CDCl_3$) δ 10.29 (s, 4), 7.06 (s, 4), 6.98 (s, 4), 4.22 (bd, 4), 3.50 (bd, 4), 3.32 (s, 4), 3.24 (d, 4, J = 2.3 Hz), 2.29 (s, 6), 2.25 (t, J = 2.2 Hz, 2, C≡C**H**), 1.22 (s, 18); ^{13}C NMR ($CDCl_3$) δ 147.9, 146.6, 144.5, 131.6, 129.5, 128.2, 127.5, 125.8 (ArC), 78.6 (**C**≡CH), 73.3 (C≡**C**H), 59.4, 44.7, 41.7, 34.1, 32.1, 31.4; MS-(FAB) $(M + H)^+$ 699. Anal. Calcd for $C_{46}H_{54}N_2O_4$: C, 79.05; H, 7.79. Found: C, 79.02; H, 7.76.

5,17-Di-*tert*-butyl-11,23-bis(cyanomethyl)calix[4]arene-25,26,27,28-tetrol (13). A 6.5 g of (10 mmol) sample of **11** was dissolved in 50 mL of DMSO, and 1.62 mL of CH_3I was added. The contents were stirred for 30 min at rt, 2.45 g of NaCN was added, and the contents were heated at 100 °C for 15 h. The reaction mixture was cooled to rt, poured into 100 mL of cold water, and acidified with 2 N HCl, and the precipitate was removed by filtration and dried to give 5 g (81%) of product after trituration with MeOH. An analytical sample of **13** was obtained as a white powder by recrystallization from $CHCl_3$–MeOH: mp 304–305 °C; ^1H NMR ($CDCl_3$) δ 10.17 (s, 4), 7.08 (s, 4), 6.98 (s, 4), 4.25 (bd, 4), 3.54 (bd, 4), 3.51 (s, 4), 1.24 (s, 18); ^{13}C NMR ($CDCl_3$) δ 148.5, 146.6, 145.1, 129.3, 128.4, 127.1, 126.0, 123.2, 117.9, 34.2, 32.0, 31.5, 22.9. Anal. Calcd for $C_{40}H_{42}N_2O_4$: C, 78.20; H, 6.90. Found: C, 78.53; H, 7.04.

5,17-Di-*tert*-butyl-11,23-bis[(propargyloxy)methyl]calix-[4]arene-25,26,27,28-tetrol (14) was prepared in 33% yield from the amine **11**, following the procedure described above for **6**. An analytical sample was obtained by recrystllization from CH_2Cl_2–MeOH: mp 230–231 °C; ^1H NMR ($CDCl_3$) δ 10.25 (s, 4), 7.06 (s, 4), 7.01(s, 4), 4.37 (s, 4), 4.25 (bd, 4), 4.05 (d, 4, J = 2.3 Hz, C**H**$_2$C≡CH), 3.51(bd, 4), 2.43 (t, 2, J = 2.4 Hz, C≡C**H**), 1.22 (s, 18); ^{13}C NMR ($CDCl_3$) δ 148.5, 146.6, 144.7, 130.7, 128.9, 128.4, 127.3, 125.9, 79.7 (**C**≡CH), 74.4 (C≡**C**H), 70.9, 56.6, 34.1, 32.1, 31.4. Anal. Calcd for $C_{44}H_{48}O_6$: C, 78.54; H, 7.20. Found: C, 78.28; H, 7.34.

5,17-Di-*tert*-butyl-11,23-bis(2-nitro-2-carbethoxyethyl)-calix[4]arene-25,26,27,28-tetrol (15) was prepared in 77% yield from the reaction of the quarternary salt derived from **11** with ethyl nitroacetate in EtOH–NaOEt. An analytical sample was obtained as a pale yellow powder by recrystallization from CH_2Cl_2–MeOH: mp >160 °C (softens and melts with frothing); ^1H NMR ($CDCl_3$) δ 10.11 (s, 4), 7.04 (s, 4), 6.88 (s, 4), 5.12 (dd, 2, J = 6.5 Hz), 4.20 (bd, 4), 3.82 (q, 4, J = 7.0 Hz), 3.46 (bd, 4), 3.30 (m, 4), 1.24 (s, 18), 0.38 (t, 6, J = 7.0 Hz). Anal. Calcd for $C_{46}H_{54}N_2O_{12}$: C, 66.81; H, 6.58; N, 3.39. Found: C, 66.66; H, 6.53; N, 3.29.

5,17-Di-*tert*-butyl-11,23-bis[[(4-nitrobenzyl)oxy]methyl]-calix[4]arene-25,26,27,28-tetrol (16) was prepared in 40% yield from the reaction of the quaternary salt derived from **11** with 4-nitrobenzyl alcohol, as described above for **6**. An analytical sample was obtained as a pale yellow powder by recrystallization from CH_2Cl_2–MeOH: mp 211–212 °C; ^1H NMR ($CDCl_3$) δ 10.26 (s, 4), 8.18 (d, 4, J = 8.6 Hz), 7.47 (d, 4, J = 8.6 Hz), 7.05 (s, 4), 7.02 (s, 4), 4.55 (s, 4), 4.38 (s, 4), 4.25 (bd, 4), 3.54 (bd, 4), 1.20 (s, 18). Anal. Calcd for $C_{52}H_{54}N_2O_{10}$: C, 72.04; H, 6.28; N, 3.23. Found: C, 72.63; H, 6.25; N, 3.08.

5,17-Di-*tert*-butyl-11,23-bis[[(3,5-dinitrobenzyl)oxy]-methyl]calix[4]arene-25,26,27,28-tetrol (17) was prepared in 44% yield from the reaction of the quaternary salt derived from **11** with 3, 5-dinitrobenzyl alcohol, as described above for **6**. An analytical sample was obtained as a pale yellow powder by recrystallization from CH_2Cl_2–MeOH: mp 258–259 °C; ^1H NMR ($CDCl_3$) δ 10.28 (s, 4), 8.94 (m, 2), 8.50 (d, 4, J = 2.1 Hz), 7.05 (s, 4), 7.04 (s, 4), 4.61 (s, 4), 4.45 (s, 4), 4.25 (bd, 4), 3.53 (bd, 4), 1.17 (s, 18). Anal. Calcd for $C_{52}H_{52}N_4O_{14}$: C, 65.26; H, 5.48, N, 5.85. Found: C, 65.44; H, 5.51; N, 5.62.

5,17-Di-*tert*-butyl-11,23-bis[(phenyloxy)methyl]calix[4]-arene-25,26,27,28-tetrol (18) was prepared in 32% yield from the reaction of the quaternary salt derived from **11** with phenol, as described above for **6**. An analytical sample was obtained as a white powder by recrystallization from CH_2Cl_2–MeOH: mp 211–212 °C; ^1H NMR ($CDCl_3$) δ 10.24 (s, 4), 7.26 (m, 6), 7.10 (s, 4), 7.08 (s, 4), 6.95 (m, 4), 4.79 (s, 4), 4.28 (bd, 4), 3.53 (bd, 4), 1.23 (s, 18). Anal. Calcd for $C_{50}H_{52}O_6$: C, 80.18; h, 7.00. Found: C, 80.18; H, 6.99.

5,17-Di-*tert*-butyl-11,23-bis(3,5-dimethyl-4-hydroxy-benzyl)calix[4]arene-25,26,27,28-tetrol (19) was prepared in 60% yield from the reaction of the quaternary salt derived from **11** with 2, 6-dimethylphenol, as described above for **6**. An analytical sample was obtained by recrystallization from CH_2Cl_2–MeOH: mp 257–258 °C; ^1H NMR ($CDCl_3$) δ 10.24 (s, 4), 7.00 (s, 4), 6.80 (s, 4), 6.75 (s, 4), 4.49 (s, 2OH), 4.21 (bd, 4), 3.61 (s, 4), 3.44 (bd, 4), 2.20 (s, 12), 1.22 (s, 18). Anal. Calcd for $C_{54}H_{60}O_6$: C, 80.56; H, 7.51. Found: C, 80.31; H, 7.57.

5,17-Di-*tert*-butyl-11,23-bis(3,5-di-*tert*-butyl-4-hydroxybenzyl)calix[4]arene-25,26,27,28-tetrol (20) was prepared in 62% yield from the reaction of the quaternary salt derived from **11** with 2,6-di-*tert*-butylphenol, as described above for **6**. An analytical sample was obtained by recrystallization from CH_2Cl_2–MeOH: mp 275–276 °C; ^1H NMR ($CDCl_3$) δ 10.27 (s, 4), 7.00 (s, 4), 6.91 (s, 4), 6.81 (s, 4), 5.04 (s, 2OH), 4.22 (bd, 4), 3.64 (s, 4), 3.44 (bd, 4), 1.39 (s, 36), 1.20 (s, 18). Anal. Calcd for $C_{66}H_{84}O_6$: C, 81.44; H, 8.70. Found: C, 81.54; H, 8.77.

5,17-Di-*tert*-butyl-11,23-bis(α,α′-dibenzylcyanomethyl)-25,26,27,28-tetrakis(benzyloxy)calix[4]arene (21) (Cone Conformer). A 0.62 g (1 mmol) sample of **13** was added to 35 mL of THF containing 5 mL of DMF. The solution was cooled to ice bath temperature, and to this was added 0.8 g (20 mmol) of 60% NaH. The contents were stirred for 15 min, and 1.42 mL of benzyl bromide (12 mmol) in 5 mL of THF was introduced. The reaction mixture was warmed to rt and heated at 85 °C for 3 h. THF was removed under vacuum, 100 mL of cold H_2O was added, and the aqueous layer was acidified with dilute HCl. The product was extracted into CH_2Cl_2, washed with water and brine, and dried over Na_2SO_4. The residue from removing the solvent was passed over silica gel and recrystallized from CH_2Cl_2–MeOH to give **21** in 64% yield as a white powder: mp 224–225 °C; ^1H NMR ($CDCl_3$) δ 7.33–6.97 (m, 40), 6.92 (s, 4), 6.53 (s, 4), 5.05 (s, 4), 4.79 (s, 4), 4.07 (d, 4, J = 12.7 Hz), 3.03 (dd, 8, J =13.5 Hz), 2.77 (d, 4, J = 12.7 Hz), 0.95 (s, 18); ^{13}C NMR ($CDCl_3$) δ 177.6–121.2 (22 Ar signals), 77.1, 76.1, 49.9, 45.9, 33.8, 31.5, 31.3. Anal. Calcd for $C_{96}H_{90}N_2O_4$: C, 86.32; H, 6.79. Found: C, 86.38; H, 6.72.

5,17-Di-*tert*-butyl-11,23-bis(cyanomethyl)-25,27-bis-(benzyloxy)calix[4]arene-26,28-diol (22). A mixture of 1.28 g (2 mmol) of **13** and 0.55 g of K_2CO_3 (4 mmol) was added to 25 mL of acetone, and to this mixture was added 0.6 mL of benzyl bromide. The reaction mixture was stirred at rt for 24 h, K_2CO_3 was removed by filtration, the acetone was removed by evaportion under vacuum, and 20 mL of CH_2Cl_2 was added to the residue, which was then triturated with MeOH. The white precipitate was removed by filtration and dried to give

1.3 g (82%) of **22**. An analytical sample was obtained by recrystallization from CH_2Cl_2–MeOH: mp 304–305 °C dec; ^1H NMR ($CDCl_3$) δ 7.84 (s, 2), 7.60 (m, 5), 7.37 (m, 5), 7.04 (s, 4), 6.88 (s, 4), 5.04 (s, 4), 4.27 (d, 4, J = 13.0 Hz), 3.46 (s, 4), 3.30 (d, 4, J = 13.0 Hz), 1.27 (s, 18). Anal. Calcd for $C_{54}H_{54}N_2O_4$: C, 81.58; H, 6.85. Found: C, 81.70; H, 6.79.

5,17-Bis(cyanomethyl)calix[4]arene-25,26,27,28-tetrol (23). A 1.2 g (2 mmol) of **22** was dissolved in 100 mL of dry CH_2Cl_2, and 2.66 g (20 mmol) of $AlCl_3$ was added followed by 0.38 g (4 mmol) of phenol. The reaction mixture was stirred at rt for 5 h, 100 mL of cold H_2O was added, and the contents were acidified with dilute HCl. The organic layer was removed, and the aqueous layer was extracted with 25 mL of CH_2Cl_2. The combined organic layer was washed with water and brine and dried over Na_2SO_4. Evaporation of the solvent and trituration of the residue with MeOH gave 0.92 g (88%) of product. An anlytical sample was obtained by recrystallization from CH_2Cl_2–MeOH as a white powder: mp 322–323 °C; ^1H NMR ($CDCl_3$) δ 10.14 (s, 4), 7.08 (d, 4, J = 7.6 Hz), 6.98 (s, 4), 6.78 (t, 2, J = 7.5 Hz), 4.24 (bs, 4), 3.52 (s, 4), 3.50 (bs, 4); ^{13}C NMR ($CDCl_3$) δ 148.7, 148.5, 129.1, 129.0, 128.4, 127.7, 123.2, 122.4, 117.9, 31.6, 22.7. Anal. Calcd for $C_{32}H_{26}N_2O_4$: C, 76.49; H, 5.18; N, 5.58. Found: C, 76.10; H, 5.26; N, 5.47.

5,17-Bis(cyanomethyl)-26,28-bis(benzyloxy)calix[4]-arene-25,27-diol (24) was prepared according to the procedure described above for **22** and was isolated in 84% yield. An analytical sample was obtained by recrystallization from CH_2Cl_2–MeOH as a white powder: mp 285–286 °C; ^1H NMR ($CDCl_3$) δ 7.78 (s, 2), 7.57 (m, 4), 7.33 (m, 6), 7.06 (d, 4, J = 7.5 Hz), 6.82 (s, 4), 6.67 (t, 2, J = 7.5 Hz), 5.04 (s, 4), 4.28 (d, 4, J = 13.3 Hz), 3.37 (s, 4), 3.32 (d, 4, J = 13.3 Hz); ^{13}C NMR ($CDCl_3$) δ 153.3, 151.7, 136.2, 134.3, 128.8, 128.7, 128.6, 128.5, 128.2, 127.6, 127.5, 126.5, 119.3, 117.9, 78.6, 31.4, 22.9. Anal. Calcd for $C_{46}H_{38}N_2O_4$: C, 80.92; H, 5.61. Found: C, 80.67; H, 5.39.

5,17-Di-*tert*-butyl-11,23-bis[(propargyloxy)methyl]-25,-26,27,28-tetrakis(benzyloxy)calix[4]arene (25) was prepared in 78% yield following the procedure described above for **7a**. An analytical sample was obtained as a white powder by recrystallization from CH_2Cl_2–MeOH: mp 153–54 °C; ^1H NMR ($CDCl_3$) δ 7.32 (s), 7.21–7.09 (m), 6.94 (s, 4), 6.18 (s, 4), 5.04 (s, 4), 4.70 (s, 4), 4.15 (d, 4, J = 13.4 Hz), 3.93 (s, 4), 3.90 (d, 4, J = 2.4 Hz), 2.88 (d, 4, J = 13.2 Hz), 2.36 (t, 2, J = 2.4 Hz), 1.28 (s, 18); ^{13}C NMR ($CDCl_3$) δ 154.9, 153.3, 144.8, 138.0, 137.7, 135.5, 133.8, 130.2, 130.1, 129.2, 128.2, 128.0, 127.9, 127.6, 127.5, 125.6, 79.8, 77.1, 75.6, 74.2, 71.5, 56.4, 34.0, 31.6, 31.5. Anal. Calcd for $C_{72}H_{72}O_6$: C, 83.69; H, 7.02. Found: C, 83.33; H, 7.01.

Bridged Compound 26. A solution of 1.0 g (5 mmol) of $Cu(OAc)_2 \cdot H_2O$ in 40 mL of CH_3CN was heated to 65 °C, and to this was added a solution of 0.5 g (0.5 mmol) of the tetrabenzyl ether **25** in 10 mL of CH_3CN followed by 0.1 g of benzyl bromide (a catalyst for the reaction). The reaction mixture was stirred at 65 °C for 18 h, solvent was removed under vacuum, and 100 mL of cold H_2O was added to the residue, which was then acidified with dilute HCl. The pale yellow precipitate that separated was removed by filtration, dried, and passed through a small column of silica gel (70–200 mesh) using CH_2Cl_2. Evaporation of the solvent gave 0.45 g (90%) of the pure product. An analytical sample was obtained by recrystallization from hexane–CH_2Cl_2 as a colorless powder: mp 196–197 °C; MS(FAB) M^+ 1031; ^1H NMR ($CDCl_3$) δ 7.28–7.18 (m, 20), 7.00 (s,4), 6.32 (s, 4), 5.14 (s, 4), 4.60 (s, 4), 4.18 (s, 4), 4.11 (d, 4, J = 13.0 Hz), 4.08 (s, 4), 2.82 (d, 4, J = 13.0 Hz), 1.34 (s, 18); ^{13}C NMR ($CDCl_3$) δ 153.4, 153.2, 145.1, 138.5, 137.5, 135.6, 133.1, 131.5, 130.4, 129.5, 128.2, 127.9, 127.6, 127.5, 125.6, 124.8, 79.2, 77.6, 75.4, 72.6, 69.1, 58.4, 34.1, 31.6, 31.5. Anal. Calcd for $C_{72}H_{70}O_6$: C, 83.85; H, 6.84. Found: C, 83.73; H, 6.90.

Bridged Compounds 27 and 28. A solution of 0.2 g (0.19 mmol) of **7b** in 2–3 mL of pyridine was added to a solution of 0.5 g (2.5 mmol) of $Cu(OAc)_2 \cdot H_2O$ in 10 mL of pyridine at 65 °C. The reaction mixture was stirred at 65 °C for 4 h, pyridine was removed under vacuum, dilute HCl was added to the residue, and the product was extracted into CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with H_2O and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was chromatographed over silica gel (70–230 mesh). Elution with CH_2Cl_2 and recrystallization from $CHCl_3$–MeOH gave 120 mg (61%) of pure doubly bridged compound **27** as a white powder: mp > 250 °C dec; ^1H NMR ($CDCl_3$) δ 7.50–7.23 (m, 20), 6.73 (s, 8), 4.79 (s, 8), 4.48 (s, 8), 4.40 (s, 8), 3.33 (s, 8, $ArCH_2Ar$); ^{13}C NMR ($CDCl_3$) δ 155.1, 138.4, 133.5, 130.9, 128.3, 128.2, 127.9, 127.5, 127.4, 78.4, 73.5, 71.9, 69.4, 58.7, 37.2; FABMS (M^+, 1053, 30), [(M^+ – $CH_2C_6H_5$, 962, base peak]. Anal. Calcd for $C_{72}H_{60}O_8 \cdot {}^1/_2CH_2Cl_2$: C, 79.47; H, 5.61. Found: C, 79.27; H, 5.45.

Further elution with 2.5% EtOAc in CH_2Cl_2 gave 15 mg (7%) of a second fraction which was recrystallized from $CHCl_3$–MeOH to give **28** as a white powder: mp >250 °C dec; ^1H NMR ($CDCl_3$) δ 7.53–7.22 (m, 40), 6.73 (s, 8), 6.70 (s, 8), 4.81 (s, 8), 4.65 (s, 8), 4.48 (s, 8), 4.40 (s, 8), 4.18 (s, 8), 4.14 (s, 8), 3.37 (s, 16); ^{13}C NMR ($CDCl_3$) δ 156.4, 154.8, 138.2, 133.8, 133.5, 131.4, 131.2, 129.5, 128.4, 127.8, 127.7, 127.6, 127.3, 78.5, 76.0, 73.6, 73.0, 71.9, 71.6, 70.8, 69.4, 58.7, 57.2, 36.9; FABMS (M^+, 2105, base peak). Anal. Calcd for $C_{144}H_{120}O_{16} \cdot {}^1/_2$ $CHCl_3$: C, 80.12; H, 5.61. Found: C, 80.65; H:, 5.63.

When the reaction described above was carried out at room temperature, a complex mixture was produced from which neither of the bridged compounds **27** or **28** could be isolated. The material appears to be a polymer of sufficiently high molecular weight to make measurement by conventional mass spectral techniques unavailing.

Acknowledgment. We are indebted to the National Science Foundation and the Robert A. Welch Foundation for generous support of this research.

JO950617C