Upper Rim Substitution of Calixarenes: Carboxylic Acids[1]

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Received 13 January 1997; revised 6 April 1997

The mono- **(5a)**, bis- **(4a** and **4b)**, and tetrakis **(1a)**-*p*-cyanomethylcalix[4]arenes as well as the bis(cyanomethyl)calix[6]arene **(6a)** have been transformed both by acid and base induced hydrolysis to the corresponding *p*-carboxymethylcalix[4]arenes **5b,4c,4d,2a**, and **6b** which, in turn, were converted to the methyl **(5c,4e,4f,2b)** and ethyl **(5d,4g,2c)** esters. The cyanomethyl groups in the sterically hindered compounds **7** and **8** and their corresponding monomers **10** and **11**, however, were inert to hydrolysis, even under strenuous conditions. The methyl ester **2b** can be converted to the 1,3-dibenzyl ether **(3b)** and the 1,3-dibenzoate **(3c)** as well as the tetrabenzyl ether **(3a)** and tetrabenzoate **(3d)**.

Calixarenes[2] carrying carboxyl groups directly attached to the upper rim have been synthesized in several ways. The earliest example involves lithiation of *p*-tetrabromocalix[4]arene tetramethyl ether followed by carbonation to yield the *p*-tetrakis(carboxy)calix[4]arene,[3] more recently also applied to the preparation of the mono- and dicarboxyl analogs.[4] The *p*-Claisen rearrangement route for making upper rim substituted calixarenes[5] has been adapted to carboxylation by catalyzed rearrangement of the 2-propenyl groups to 1-propenyl groups followed by ozonolysis to the aldehyde and oxidation to the carboxylic acid.[6] In a similar fashion, *p*-formylcalixarenes, obtained by direct formylation, are easily oxidized to the carboxylic acids.[7] *p*-Acetylcalixarenes undergo haloform oxidation to furnish carboxylic acids.[8] Application of the Heck reaction {CO, MeOH, $Pd[(PPh_3)]_2Cl_2$} to *p*-iodocalixarenes yields the methyl esters of *p*-carboxylic acids.[9]

The only procedure that has been published to date for the synthesis of calixarenes carrying carboxyl groups further removed from the *p*-position on the upper rim makes use of the *p*-quinonemethide route involving aminomethylation, quaternization by methylation, and treatment with a nucleophile.[10] By using diethyl sodiomalonate as the nucleophile followed by hydrolysis and decarboxylation of the resulting product the *p*-carboxyethylcalixarenes can be obtained. By using CN^- as the nucleophile the *p*-cyanomethylcalixarenes are produced in excellent yield, providing a potential route for synthesizing *p*-carboxymethylcalixarenes. These compounds are of interest, inter alia, for their ability to form intramolecular anhydrides, as will be discussed in a subsequent publication. Although reduction of the cyanomethyl groups to aminoethyl groups has been described,[10] hydrolysis to carboxymethyl groups has remained largely unattended until the present work which deals with this conversion.

Hydrolysis of the *p*-tetrakis(cyanomethyl)calix[4]arene **1a** proceeds smoothly under acidic conditions to afford the corresponding *p*-tetrakis(carboxymethyl)calix[4]arene **2a** in 84% yield. The tetrabenzyl ether **1b** also produced **2a** under these conditions, debenzylation occurring concurrently with hydrolysis. Base-induced hydrolysis of **1a**, on the other hand, gave a mixture of **2a** and the corresponding amide which could be converted to the methyl ester **2b** and ethyl ester **2c** by treatment with H_2SO_4/ROH. The same esters **(2b** and **2c)** can be easily prepared from the acid **2a**. Benzyloxy groups can be reintroduced into **2b** to give the 1,3-dibenzyl ether **3b** in 81% yield if a limiting amount of K_2CO_3 is used or the tetrabenzyl ether **3a** in 76% yield if a large excess of K_2CO_3 is used. Benzoyloxy groups can be introduced using benzoyl chloride in the presence of $AlCl_3$ to give the 1,3-dibenzoate **3c** in 86% yield. The 1,3-diether **3b** and diester **3c** exist in the flattened cone conformation,[11] while the tetrabenzyl ether **3a** and tetrabenzoyl ester **3d** (obtained using NaH as the base) exist in the 1,3-alternate conformation.[11]

Hydrolyses of the bis(cyanomethyl)calix[4]arene **4b**[12] and the bis(cyanomethyl)calix[6]arene **6a**[13] proceed under base-induced as well as acid-catalyzed conditions to produce the corresponding acids **4d** and **6b** in yields of 75–80%. The methyl and ethyl ethers **(4f** and **4g)** were prepared from the acid **4d** by treatment with H_2SO_4/ROH. It was surprising, therefore, to find that the acid-catalyzed hydrolyses of the mono- and bis(cyanomethyl)calix[4]arenes **4a**[12] and **5a**[14] do not yield products that could not be characterized as the acids **4b** and **5c**. Base-induced hydrolysis (8 h reflux), however, proceeds in a manner similar to that of **1a** to produce a mixture of the amide and acid which can be converted to the methyl and ethyl esters **4e,5c**, and **5d** by treatment with H_2SO_4/ROH. With longer reflux times (48 h) only the acids are produced.

With these procedures in hand the hydrolysis of the cyano groups in the previously reported[15–17] calixarenes **7a,7b,8a**, and **8b** was undertaken. Unfortunately, all of these compounds proved to be completely inert to either base-induced or acid-catalyzed hydrolysis, starting material being recovered under the base-induced conditions and starting material or debenzylated starting material under the acid-catalyzed conditions. Even the use of NaOH in hot diethylene glycol (*ca.* 250 °C) or NaOH/H_2O_2 in hot ethylene glycol (*ca.* 180 °C) (to produce the amide) failed to alter the starting material. The hydrolysis of α,α-dimethyl-*p*-methoxybenzyl cyanide using H_2SO_4 at 100 °C has been reported,[18] but these conditions also failed in the present cases. To determine whether the calixarene moiety contributes to this unreactivity the corresponding monomeric compounds **10a,10b,11a**, and **11b** were prepared and subjected to comparable reaction conditions. Here also, all four of these compounds fail to undergo hydrolysis of the cyano group, leading to the conclusion that the resistance to hydrolysis is probably a function of the local environment around the cyano group with the calixarene ring playing, at most, a minor role.

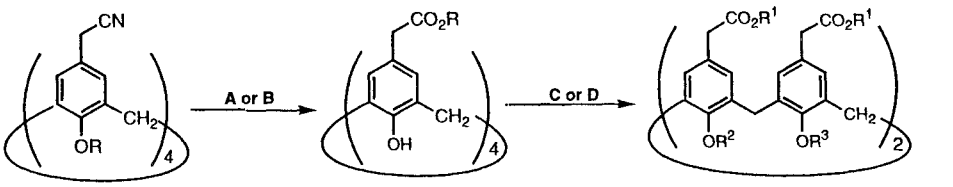
Table. Physical and Spectroscopic Data of the Hydrolysed Products and their Upper-Rim and Lower-Rim Ethers and Esters

Compound[a]	Yield (%)	mp (°C)	^{1}H NMR (300 MHz), ($CDCl_3$/TMS) δ, J (Hz)	^{13}C NMR (75 MHz), ($CDCl_3$/TMS) δ
2a[b]	84	310–312	12.20 (b, 4H, COOH), 9.60 (bs, 4H, Ar-OH), 6.95 (s, 8H, Calix-H), 3.82 (s, 8H, $ArCH_2Ar$), 3.27 (s, 8H, CH_2COO)	172.76 (CO), 148.25 (C-OH), 129.53, 129.25, 128.03 (ArC), 38.52 (CH_2COOH), 30.61 ($ArCH_2Ar$)
2b	93	164–165	10.12 (s, 4H, Ar-OH), 6.96 (s, 8H, Calix-H), 4.20 (bd, 4H, $ArCH_2Ar$), 3.66 (s, 12H, OCH_3), 3.50 (bd, 4H, $ArCH_2Ar$), 3.40 (s, 8H, CH_2COO)	172.11 (CO), 147.95 (C-OH), 129.85, 128.24, 127.50 (ArC), 50.05 (OCH_3), 40.31 (CH_2COO), 31.66 ($ArCH_2Ar$)
2c	89	202–203	10.15 (s, 4H, Ar-OH), 6.96 (s, 8H, Calix-H), 4.20 (bd, 4H, J = 13.53 Hz, $ArCH_2Ar$), 4.12 (q, 8H, J = 7.23 and 7.02 Hz, OCH_2CH_3), 3.49 (bd, 4H, J = 11.83 Hz, $ArCH_2Ar$), 3.38 (s, 8H, CH_2COO), 1.24 (t, 12H, J = 7.05 and 7.11 Hz, OCH_2CH_3)	171.68 (CO), 147.90 (C-OH), 129.84, 128.20, 127.63 (ArC), 60.82 ($COOCH_2CH_3$), 40.53 (CH_2COO), 31.71 ($ArCH_2Ar$), 14.23 (CH_3)
3a	76	255–256	7.41–7.39 (m, 12H, ArH), 7.08 (d, 8H, J = 6.0 Hz, ArH), 6.57 (s, 8H, Calix-H), 4.80 (s, 8H, OCH_2Ph), 3.63 (s, 8H, $ArCH_2Ar$), 3.54 (s, 12H, OCH_3), 2.89 (s, 8H, CH_2COO)	172.57 (CO), 155.02, 138.32, 133.98, 131.90, 128.08, 127.34, 127.01, 126.36 (ArC), 71.61 (OCH_2Ph), 51.73 (OCH_3), 40.00 (CH_2COO), 37.48 ($ArCH_2Ar$)
3b	81	165–166	7.97 (s, 2H, ArOH), 7.62–7.59 (m, 4H, ArH), 7.36–7.34 (m, 6H, ArH), 6.95 (s, 4H, Calix-H), 6.82 (s, 4H, Calix-H), 5.02 (s, 4H, OCH_2Ph), 4.24 (d, 4H, J = 13.5 Hz, $ArCH_2Ar$), 3.66 (s, 6H, OCH_3), 3.65 (s, 6H, OCH_3), 3.47 (s, 4H, CH_2COO), 3.32 and 3.28 (2 lines, 6H + 2H, $ArCH_2Ar$ and CH_2COO)	172.60 (CO), 172.25 (CO), 152.57, 151.36, 136.60, 133.32, 130.59, 130.07, 129.35, 128.77, 128.09, 127.87, 127.54, 124.11 (ArC), 78.48 (OCH_2Ph), 51.96 (OCH_3), 40.64 (CH_2COO), 40.40 (CH_2COO), 31.58 ($ArCH_2Ar$)
3c	86	234–235	8.24 (d, 4H, J = 7.5 Hz, ArH), 7.50–7.55 (m, 6H, ArH), 6.91 (s, 4H, Calix-H), 6.88 (s, 4H, Calix-H), 5.30 (b, 2H, Ar-OH), 3.88 (d, J = 14.1 Hz, $ArCH_2Ar$), 3.62 (s, 12H, OCH_3), 3.54 (d, 4H, J = 14.4 Hz, $ArCH_2Ar$), 3.39 (s, 4H, CH_2COO), 3.30 (s, 4H, CH_2COO)	172.29 (CO), 171.64 (CO), 164.50 (CO), 152.24, 133.92, 132.67, 132.07, 130.45, 130.45, 130.35, 130.28, 130.17, 128.95, 128.48, 128.05, 125.04 (ArC), 52.00 (OCH_3), 40.37 (CH_2COO), 40.18 (CH_2COO), 33.32 ($ArCH_2Ar$)
3d	78	350 (softening) 390–391	7.88–7.85 (m, 12H, ArH), 7.68–7.65 (m, 8H, ArH), 6.65 (s, 8H, Calix-H), 3.57 (s, 8H, $ArCH_2Ar$), 3.48 (s, 12H, OCH_3), 2.96 (s, 8H, CH_2COO)	171.31 (CO), 164.27 (CO), 147.96, 134.27, 134.02, 132.21, 131.09, 130.97, 130.05, 129.36, 129.00 (ArC), 52.31 (OCH_3), 40.64 (CH_2COO), 37.30 ($ArCH_2Ar$)
4c[b,e]	80	230 (dec.)	9.80 (bs, 4H, Ar-OH), 7.10 (d, 4H, J = 7.4 Hz, Calix-H), 6.96 (s, 4H, Calix-H), 6.64 (t, 2H, J = 7.4 Hz, Calix-H), 3.84 (bs, 4H, $ArCH_2Ar$), 3.41 (bs, 4H, $ArCH_2Ar$), 3.25 (s, 4H, CH_2COO)	172.6 (CO), 149.5 (C-OH), 147.7 (C-OH), 129.3, 128.6, 128.2, 127.5, 120.9 (ArC), 40.1 (CH_2COO), 30.5 ($ArCH_2Ar$)
4d[c]	77	360–361	10.20 (s, 4H, Ar-OH), 7.05 (s, 4H, Calix-H), 6.95 (s, 4H, Calix-H), 4.24 (bd, 4H, $ArCH_2Ar$), 3.51 (bd, 4H, $ArCH_2Ar$), 3.38 (s, 4H, CH_2COO), 1.22 (s, 18H, *tert*-Bu)	172.5 (CO), 147.3, 147.2, 143.2, 129.4, 128.5, 127.7, 127.4, 125.4 (ArC), 40.2 (CH_2COO), 33.6 (C-Bu^t), 31.2 (Bu), 30.9 ($ArCH_2Ar$)
4e	80	218–219	10.16 (s, 4H, Ar-OH), 7.05 (d, 4H, J = 7.5 Hz, Calix-H), 6.96 (s, 4H, Calix-H), 6.73 (t, 2H, J = 7.5 Hz, Calix-H), 4.20 (bs, 4H, $ArCH_2Ar$), 3.65 (s, 6H, OCH_3), 3.50 (bs, 4H, $ArCH_2Ar$), 3.38 (s, 4H, CH_2COO)	172.1 (CO), 148.8 (C-OH), 147.8 (C-OH), 129.7, 129.0, 128.0, 127.4, 122.2 (ArC), 52.0 (OCH_3), 40.3 (CH_2COO), 31.6 ($ArCH_2Ar$)
4f	85	251–252	10.23 (s, 4H, Ar-OH), 7.06 (s, 4H, Calix-H), 6.95 (s, 4H, Calix-H), 4.21 (bd, 4H, $ArCH_2Ar$), 3.65 (s, 6H, OCH_3), 3.49 (bd, 4H, $ArCH_2Ar$), 3.37 (s, 4H, CH_2COO), 1.22 (s, 18H, *tert*-Bu)	172.1 (CO), 147.8, 146.6, 144.6, 129.7, 128.5, 127.3, 125.9 (ArC), 51.9 (OCH_3), 40.4 (CH_2COO), 34.0 (C-Bu^t), 32.1 (Bu), 31.4 ($ArCH_2Ar$)
4g	85	238–239	10.22 (s, 4H, Ar-OH), 7.05 (s, 4H, ArH), 6.94 (s, 4H, ArH), 4.23 (bd, 4H, $ArCH_2Ar$), 4.10 (q, 4H, J = 7.0 Hz, OCH_2CH_3), 3.47 (bd, 4H, $ArCH_2Ar$), 3.34 (s, 4H, CH_2COO), 1.25 (t, 6H, J = 7.0 Hz, OCH_2CH_3), 1.23 (s, 18H, *tert*-Bu)	171.8 (CO), 147.8, 146.7, 144.6, 129.8, 128.5, 127.5, 127.3, 125.9 (ArC), 60.7 (OCH_2), 40.6 (CH_2COO), 34.1 (C-Bu^t), 32.1 (Bu), 31.4 ($ArCH_2Ar$), 14.2 (CH_3)
5c	79[d]	208–209	10.18 (s, 4H, Ar-OH), 7.07–7.04 (m, 6H, Calix-H), 6.97 (s, 2H, Calix-H), 6.76–6.70 (m, 3H, Calix-H), 4.20 (bs, 4H, $ArCH_2Ar$), 3.66 (s, 3H, OCH_3), 3.65 (bs, 4H, $ArCH_2Ar$), 3.39 (s, 2H, CH_2COO)	172.21 (CO), 148.82, 148.74, 147.96, 129.82, 129.00, 128.43, 128.28, 128.07, 127.43, 122.27 (ArC), 52.06 (OCH_3), 40.33 (CH_2COO), 31.71 ($ArCH_2Ar$)
5d	75[d]	255–257	10.19 (s, 4H, Ar-OH), 7.09–7.05 (m, 6H, Calix-H), 6.94 (s, 2H, Calix-H), 6.78–6.70 (m, 3H, Calix-H), 4.23 (bs, 4H, $ArCH_2Ar$), 4.10 (q, 2H, J = 6.45 and 7.01 Hz, OCH_2CH_3), 3.53 (bs, 4H, $ArCH_2Ar$), 3.38 (s, 2H, CH_2COO), 1.24 (t, 3H, J = 7.30 and 6.99 Hz, CH_2CH_3)	171.80 (CO), 148.85, 148.77, 147.91, 129.96, 129.85, 129.05, 128.39, 128.30, 128.15, 128.07, 127.63, 122.30 (ArC), 60.89 (OCH_2CH_3), 40.59 (CH_2COO), 31.74 ($ArCH_3Ar$), 14.23 (CH_3)
6b[b]	75	> 350 (dec.)	12.12 (bs, 2H, COOH), 8.71 (bs, 6H, Ar-OH), 7.03 (s, 4H, Calix-H), 6.96 (s, 4H, Calix-H), 6.85 (s, 4H, Calix-H), 3.76 (bs, 8H, $ArCH_2Ar$), 3.35 (bs, 4H, $ArCH_2Ar$), 3.28 (s, 4H, CH_2COO), 1.13 (s, 36H, *tert*-Bu)	
9b	86	60–61	7.46–7.30 (m, 5H, ArH), 7.24 (d, 2H, J = 8.4 Hz, ArH), 6.98 (d, 2H, J = 8.4 Hz, ArH), 5.07 (s, 2H, OCH_2Ph), 3.68 (s, 2H, CH_2CN)	158.40, 136.60, 130.41, 129.15, 128.67, 128.11, 127.48 (ArC), 115.51 (CN), 70.12 (OCH_2Ph), 22.83 (CH_2CN)

Table. (continued)

Compound[a]	Yield (%)	mp (°C)	^{1}H NMR (300 MHz), ($CDCl_3$/TMS) δ, J (Hz)	^{13}C NMR (75 MHz), ($CDCl_3$/TMS) δ
10a	85	132–133	7.26–7.10 (m, 8H, ArH), 7.08–7.00 (m, 4H, ArH), 6.75 (d, 2H, J = 8.7 Hz, ArH), 5.10 (s, 1H, Ar-OH), 3.30 (d, 2H, J = 13.5 Hz, $[ArCH_2]_2CCN$), 3.24 (d, 2H, J = 13.5 Hz, $[ArCH_2]_2CCN$)	158.37, 135.05, 130.44, 128.96, 128.12, 127.29, 121.48 (ArC), 115.52 (CN), 50.57 ($[ArCH_2]_2CCN$), 46.62 ($[ArCH_2]_2CCN$)
10b	93	116–117	7.46–7.32 (m, 5H, ArH), 7.22–7.18 (m, 8H, ArH), 7.04–7.02 (m, 4H, ArH), 6.90 (d, 2H, J = 8.1 Hz, ArH), 5.04 (s, 2H, OCH_2Ph), 3.30 (d, 2H, J = 13.44 Hz, $[ArCH_2]_2CCN$), 3.25 (d, 2H, J = 13.5 Hz, $[ArCH_2]_2CCN$)	158.20, 136.66, 135.10, 130.45, 129.47, 128.62, 128.09, 128.04, 127.58, 127.24, 121.40 (ArC), 114.84 (CN), 70.04 (OCH_2Ph), 50.46 ($[ArCH_2]_2CCN$), 46.59 ($[ArCH_2]_2CCN$)
11a	76	200–201	9.39 (s, 1H, Ar-OH), 7.85 (d, 2H, J = 7.2 Hz, ArH), 7.53 (d, 2H, J = 8.7 Hz, ArH), 7.50–7.44 (m, 4H, ArH), 6.92 (d, 2H, J = 8.7 Hz, ArH)	
11b	85	122–123	7.86 (d, 2H, J = 7.8 Hz, ArH), 7.62 (d, 2H, J = 8.7 Hz, ArH), 7.46–7.38 (m, 9H, ArH), 7.04 (d, 2H, J = 8.4 Hz, ArH), 5.12 (s, 2H, OCH_2Ph)	159.94, 140.60, 136.83, 134.29, 130.53, 129.42, 129.26, 129.02, 128.52, 127.84, 127.70, 127.54, 118.49, 11.54 (ArC), 115.70 (CN), 70.49 (OCH_2Ph)

[a] Satisfactory microanalyses obtained: C ± 0.3, H ± 0.31.
[b] Recorded in DMSO-d_6.
[c] ^{1}H NMR recorded in $CDCl_3$ and ^{13}C NMR recorded in DMSO-d_6.
[d] Yield were calculated starting from cyanomethyl compound **5a**.
[e] Anal. calcd. for $C_{32}H_{28}O_8$, 1/2 $CHCl_3$, 1/2 H_2O[19]: C, 64.07; H, 4.88. Found: C, 64.10; H, 4.91. Drying the sample an additional 48 h at 140 °C resulted in only slightly lower values for carbon.

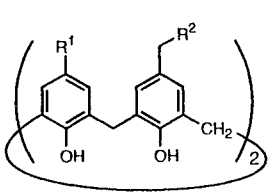


1a R = H
1b R = $CH_2C_6H_5$

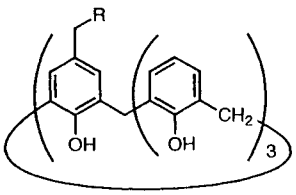
2a R = H
2b R = Me
2c R = Et

3a R^1 = Me, R^2 = R^3 = $CH_2C_6H_5$
3b R^1 = Me, R^2 = H, R^3 = $CH_2C_6H_5$
3c R^1 = Me, R^2 = H, R^3 = COC_6H_5
3d R^1 = Me, R^2 = R^3 = COC_6H_5

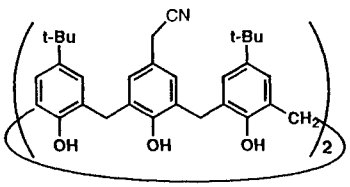
A = $AcOH/H_2SO_4/H_2O$ or $KOH/EtOH/H_2O$; **B** = H_2SO_4/ROH; **C** = $K_2CO_3/Me_2CO/NaI/C_6H_5CH_2Br$;
D = $AlCl_3$/ DMF-CH_2Cl_2/C_6H_5COCl or NaH/THF-DMF/C_6H_5COCl



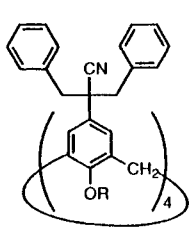
4a R^1 = H, R^2 = CN
4b R^1 = *tert*-Bu, R^2 = CN
4c R^1 = R^2 = CO_2H
4d R^1 = *tert*-Bu, R^2 = CO_2H
4e R^1 = H, R^2 = CO_2Me
4f R^1 = *tert*-Bu, R^2 = CO_2Me
4g R^1 = *tert*-Bu, R^2 = CO_2Et



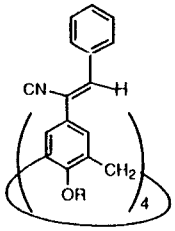
5a R = CN
5b R = CO_2H
5c R = CO_2Me
5d R = CO_2Et



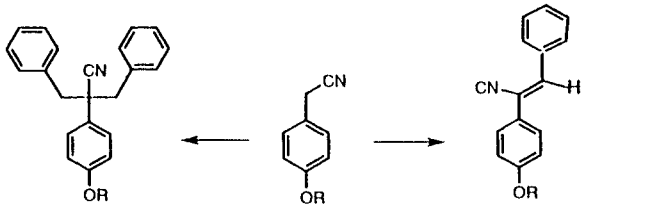
6a R = CN
6b R = CO_2H



7a R = H
7b R = $CH_2C_6H_5$



8a R = H
8b R = $CH_2C_6H_5$



10a R = H
10b R = $CH_2C_6H_5$

9a R = H
9b R = $CH_2C_6H_5$

11a R = H
11b R = $CH_2C_6H_5$

Attempts to reduce the cyano groups of calixarenes **7b** and **8b** as well as their monomeric counterparts **10b** and **11b** similarly met with failure. Reaction mixtures containing these compounds and B_2H_6 in THF solutions refluxed for 4 days yielded only recovered starting materials. Reaction mixtures containing **7b** or **10b** and $LiAlH_4$ in THF refluxed 10 hours likewise yielded only starting materials, while **8b** and **11b** under the same conditions produced mixtures of unidentified products still containing a CN group. As a check on the procedure the brosylate of **1** (R = *p*-bromobenzenesulfonyl) was successfully reduced with B_2H_6 to the corresponding tetraamine, as previously reported.[10]

Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. HPLC grade *N*,*N*-dimethylformamide (DMF), MeCN, and acetone were used. Tetrahydrofuran (THF) was dried over benzophenone/Na and distilled before using. Flash chromatography used J. T. Baker 40 mm silica gel, and column chromatography used Aldrich 70–230 mesh, 60 Å silica gel. Thin layer chromatography (TLC) was performed on 250 μm silica gel plates containing a fluorescent indicator. Melting points were taken in sealed and evacuated capillary tubes on a MEL-Temp apparatus (Laboratory Devices, Cambridge, MA) using a 400 °C thermometer and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian XL-300 spectrometer, and the chemical shifts are reported as δ values in ppm. ^{1}H NMR spectra are referenced to tetramethylsilane (TMS) at 0.00 ppm as an internal standard and recorded at room temperature (20 ± 1 °C) and ^{13}C NMR spectra are referenced to either $CDCl_3$ (77.00 ppm), DMSO-d_6 (40.0 ppm), or to TMS (0.00 ppm) and also recorded at 20 ± 1 °C. Microanalytical samples were dried for at least 48–72 h at 111 °C (toluene) or at 140 °C (xylene) at 1–2 Torr, and the analyses were carried out by Desert Laboratories, Tucson, AZ. Solvent of crystallization was retained in some of the analytical samples and affected the elemental analysis. In such cases, best fits between the analytical values and appropriate increments of the solvents were used.

5,11,17,23-Tetrakis(carboxymethyl)calix[4]arene-25,26,27,28-tetrol (2a); (A) General Procedure for Acid-Catalyzed Hydrolysis:
To a 500-mL, round-bottomed flask was added **1a** (11.6 g, 20 mmol), followed by glacial HOAc (200 mL), water (20 mL), and conc. H_2SO_4 (30 mL) with stirring. The mixture was heated at reflux 6 h, cooled, and poured over crushed ice-cold water (800 mL) in a 2-L beaker which produced a precipitate, which was left overnight (18 h). The brownish precipitate was removed by filtration (very slow), and washed thoroughly with cold water. The product was dried in an oven at 80–90 °C and triturated with MeOH (3 × 150 mL) to furnish a white powder. Yield: 11.02 g. An analytical sample of **2a** was obtained by triturating again with MeOH.

In similar fashion **4b**[12] was hydrolyzed to **4d**; **10b** was hydrolyzed to **10b**; and **11b** was hydrolyzed to **11a**.

5,17-Bis(carboxymethyl)calix[4]arene-25,26,27,28-tetrol (4c); General Procedure for Base-Induced Hydrolysis:
A mixture of **4a**[12] (0.3 g, 0.59 mmol), KOH (0.25 g) in H_2O (10 mL) and abs. EtOH (10 mL) was heated at reflux under N_2 for 48 h. The mixture was cooled to r.t., poured over ice-cold H_2O with stirring, and neutralized with 20% HCl to give a white precipitate. This was removed by filtration, washed thoroughly with H_2O, and triturated with MeOH to leave **4c**. Yield: 0.26 g (80%).

In similar fashion **6a**[13] was hydrolyzed to **6b**.

5,11,17,23-Tetrakis(methoxycarbonylmethyl)calix[4]arene-25,26,27,28-tetrol (2b); General Procedure for Esterification:
A sample of **2a** (6.56 g, 10 mmol) was stirred in anhyd MeOH (100 mL) and treated with conc. H_2SO_4 (2 mL). The mixture was heated at reflux for 3 h, cooled, and the solvent removed under reduced pressure. Ice-cold water (100 mL) was added, the mixture was stirred for 30 min, and a grey precipitate was removed by filtration and triturated with MeOH (50 mL) for 1 h to give a white solid. This was purified by column chromatography (eluant $CHCl_3$), and an analytical sample was obtained by crystallization from *n*-C_6H_{14}/$CHCl_3$ (3:1) and trituration with MeOH to furnish **2b** as a powder. Yield: 6.62 g.

Compound **2b** was also obtained in 77% overall yield from **1a** by refluxing a mixture of acid **2a** and its amide (27.0 g; obtained by base-induced hydrolysis of **1a**) with H_2SO_4 (4 mL) and anhyd MeOH (200 mL) for 3 h.

In similar fashion the ethyl esters of **2a** and **4d** and the methyl esters of **4c** and **4d** were prepared.

5,11,17,23-Tetrakis(methoxycarbonylmethyl)-25,26,27,28-tetrakis(benzyloxy)calix[4]arene (3a) (1,3-Alternate Conformer):
Anhyd K_2CO_3 (69.0 g, 0.5 mol) and NaI (2.5 g) were suspended in Me_2CO (300 mL), and **2b** (7.0 g, 10 mmol) was added. The mixture was stirred for 5 min, BnBr (27.5 g, 0.15 M) was added, and stirring was continued for 6 days at r.t. The progress of the reaction was monitored by ^{1}H NMR spectral measurements. Solvents was removed by evaporation, and the residue was poured over ice-cold water and neutralized with 20% HCl to give a light yellow precipitate. This was removed by filtration and purified by column chromatography ($CHCl_3$ eluant) to afford **3a** as a white powder. Yield: 8.05 g (76%). With further eluting from CH_2Cl_2 compound **3b** was obtained in 6% yield.

5,11,17,23-Tetrakis(methoxycarbonylmethyl)-25,27-bis(benzyloxy)-calix[4]-arene-26,28-diol (3b) (Cone Conformer):
Anhyd K_2CO_3 (0.71 g, 5 mmol) and NaI (0.3 g) were suspended in Me_2CO (100 mL) in a 250-mL, round-bottomed flask. To this **2b** (0.71 g, 1 mmol) was added and the mixture stirred for 5 min. Benzyl bromide (0.3 g, 2.3 mmol) was added, and the mixture was stirred at r.t. (progress monitored by ^{1}H NMR). After completion (5 h) the mixture was filtered, the precipitate was washed thoroughly with Me_2CO (100 mL), and the combined filtrate concentrated and poured over hexane to give a white precipitate. This was separated by filtration, triturated with MeOH (50 mL), and purified by column chromatography (CH_2Cl_2) to give the product. Yield: 0.72 g.

5,11,17,23-Tetrakis(methoxycarbonylmethyl)-25,27-bis(benzoyloxy)-calix[4]arene-26,28-diol (3c) (Cone Conformer):
Anhyd $AlCl_3$ (1.33 g, 0.01 mol) was stirred with CH_2Cl_2/DMF (60 mL; 5:1) for 5 min (white fumes evolved), and **2b** (0.56 g, 0.5 mmol) was added. The mixture was stirred 10 min, benzoyl chloride (1.05 g, 15 mmol) was added at r.t., and stirring was continued for 8 h. The mixture was poured over ice-cold water, neutralized with 20% HCl, and the product extracted into CH_2Cl_2. The organic layer was concentrated and poured over 50 mL of MeOH to give a white precipitate which was removed, dried and purified by column chromatography (CH_2Cl_2 eluant). Yield: 0.39 g.

5,11,17,23-Tetrakis(methoxycarbonylmethyl)-25,26,27,28-tetrakis-(benzoyloxy)calix[4]arene (3d) (1,3-Alternate Conformer):
Compound **2b** (0.72 g, 1 mmol) was dissolved in a mixture of freshly distilled THF (50 mL) and DMF (10 mL) and treated with 1.0 g (25 mmol) of NaH (60% in oil dispersion). The mixture was stirred for 5 min, BzCl (1.40 g, 10 mmol) was added, and the mixture was stirred for 10 h at r.t. It was poured over ice-cold water and neutralized with 20% HCl to give a white semi-sold which was extracted with CH_2Cl_2. The organic layer was separated, solvent was removed under reduced pressure, and the concentrate was poured over *n*-hexane to give a white precipitate which was removed by filtration and triturated with MeOH (50 mL) to produce **3d**. Yield: 1.0 g (78%).

4-Benzyloxy-1-[α,α-dibenzyl]cyanomethylbenzene (10b):
NaH (4 g, 100 mmol; 60% in oil dispersion) was placed in a 250-mL, round-bottomed flask followed by freshly distilled THF (70 mL) and DMF (10 mL). To this was added **9a** (2.66 g, 10 mmol) and to the stirred mixture a solution of BnBr (17.0 g, 100 mmol) was added. The reaction mixture was heated at reflux for 18 h, the solvent was removed under reduced pressure, and the concentrated residue was neutralized with ice-cold 20% HCl to produce a light yellow semi-solid which was extracted with CH_2Cl_2. The organic layer was separated, concentrated, and triturated with hexane (50 mL) followed by MeOH (50 mL), and the product was purified by column chromatography ($CHCl_3$) to give **10b**. Yield: 7.5 g.

1-[4′-Benzyloxyphenyl]-1-cyano-2-phenylethene (11b):
Anhyd K_2CO_3 (13.8 g, 100 mmol) and NaI (0.2 g) were suspended in 100 mL of anhyd Me_2CO, 4-hydroxyphenylacetonitrile (**9a**, 4.0 g, 30 mmol) was added, and the mixture was stirred for 5 min. Benzyl bromide (15 g, 90 mmol) was added, the mixture was stirred for 24 h, and worked up according to above procedure to give a white powder which was purified by column chromatography ($CHCl_3$) to furnish 4-benzyloxyphenylacetonitrile (**9b**) as a powder. Yield: 5.82 g.

NaH (2.40 g, 60 mmol; 60% in oil dispersion) was placed in a 150-mL, round-bottomed flask followed by freshly distilled THF (60 mL). To this stirred solution 4-benzyloxyphenylacetonitrile (**9b**; 2.23 g, 10 mmol) followed by benzaldehyde (5.2 g, 50 mmol) were added. The reaction mixture was stirred for 24 h, the THF was removed under reduced pressure, and the concentrated residue was neutralized with 20% HCl to produce a light yellow, semi-solid material which was extracted with CH_2Cl_2. The organic layer was concentrated and triturated with hexane (50 mL) followed by MeOH (50 mL), and the residue was purified by column chromatography ($CHCl_3$) to furnish **11b**. Yield: 2.64 g.

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

(1) Paper 47 in the series entitled: "Calixarenes". For paper 46, see: Xie, D.J.; Gutsche, C.D. *J. Org. Chem.* **1997**, 62, 2280.
(2) For reviews see, *inter alia*, (a) Gutsche, C.D. Calixarenes, in *Monographs in Supramolecular Chemistry*, Stoddart, J.F., ed., Royal Society of Chemistry, London, 1989.
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