Facile Synthesis of Calix[5]arenes with Three Different Upper Rim Substituents

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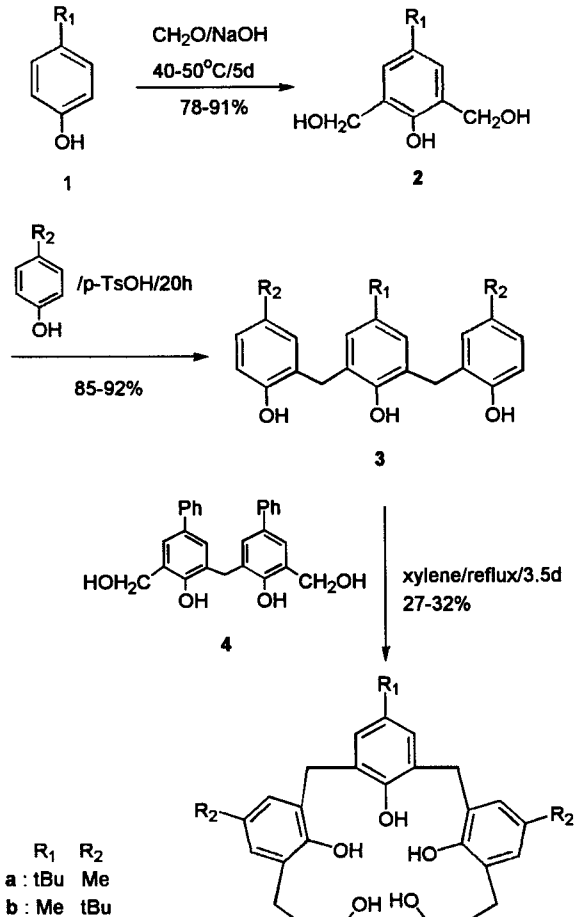
Four calix[5]arenes, which have three different substituents at the upper rim of calix, are synthesized by the '3+2' fragmentation condensation reaction. An equimolar mixture of *p*-substituted phenol trimer (BCB) and 2,2'-bishydroxymethyl *p*-substituted phenol dimer (AA) was refluxed for 3.5 days in xylene to produce calix[5]arenes **5a–d** in 27–32% isolated yield. The structure of the calix[5]arenes was established by elemental analysis and ^{1}H NMR/^{13}C NMR spectroscopy.

Calixarenes are macrocyclic compounds available in a variety of ring sizes and are of interest both as complexation hosts for ions and molecules and as frameworks for elaborating more complex structures.[1–3] The chemistry of calix[4]arenes has been extensively studied due to the ease with which these molecules can be synthesized, while that of calix[5]arenes is still relatively unexplored mainly because the odd membered calix[n]arenes can only be synthesized in relatively small yield. However they may possess a greater propensity to completely include small organic molecules than the analogous calix[4]arenes due to their larger cavity size.[4]

In 1982, Ninagawa and Matsuda[5] reported for the first time the one-step synthesis of *p-tert*-butylcalix[5]arene in 6% yield. The yield was recently increased to 15% by Steward and Gutsche[6] to allow its chemistry to be investigated with relative ease. However this method provides only the synthesis of calix[5]arenes with the same *para* substituents. The preparation of calix[5]arenes containing more than two different functional groups at the upper rim of calix is attractive because of the possibility of easily obtaining new host molecules. The stepwise route giving access to differently substituted calix[5]arenes was developed by Kämmerer and co-workers,[7] but the method has the weakness of a large number of steps and the subsequent lower overall yield. Gordon and co-workers[8] reported the synthesis of a calix[5]crown which has two arylazo groups at the upper rim of calix, starting from the attachment of the crown ether bridge at the lower rim of de-*tert*-butylated calix[5]arenes followed by diazo coupling. Very recently Haino and co-workers[9] reported the preparation of a calix[5]arene which has two different functional groups, methyl and *tert*-butyl, in 19% yield, however the experimental details were not described. We also explored the facile preparation of calix[5]arenes which have different substituents at the upper rim and here we describe our results. Calix[5]arenes are synthesized by '3+2' fragmentation condensation reaction between bishydroxymethyl dimer (AA) and *p*-substituted phenol trimer (BCB) as shown in following scheme. In the synthesis of trimers, we were concerned about the speed and simplicity. They should be synthesized by one- or two-step reactions. We were also concerned by the further functional group introduction at the upper rim of the calix directly or after removal of *t*-butyl groups. Therefore, bromine, *t*-butyl, methyl and phenyl groups were selected as *p*-substituents.



Scheme

Following the published procedure,[10,11] a mixture of *p*-substituted phenol, formaldehyde and NaOH was heated at 40 °C for 5 days to produce 2,6-bishydroxymethyl-4-substituted phenols **2a** and **2c**. Compound **2** was treated with excess *p*-substituted phenol in the presence of a catalytic amount of *p*-toluenesulfonic acid in benzene, the unreacted excess phenol and solvent were removed by steam distillation. The crude product was purified to afford the corresponding trimers **3a–c** in 85–92% yield. Dimer diol **4** was prepared in 55% yield by the treatment of *p*-phenylphenol with formaldehyde in the presence of KOH following the procedure published by our laboratory.[12] Using these trimers **3** and dimer diol **4** as coupling components, four calix[5]arenes **5a–d** were synthesized by a '3+2' fragmentation condensation route similar to

that developed by Böhmer and co-workers.[13,14] An equimolar mixture of trimer **3** and bishydroxymethyl dimer **4** in xylene was refluxed for 3.5 days under nitrogen atmosphere. After removal of solvent, the residue was purified to afford the calix[5]arenes **5** in 27–32% yield. When the same reaction was carried out in the presence of conc HCl or $TiCl_4$ as catalyst, the resulting product mixture was much more complicated and the isolation of pure calix[5]arenes was not successful. The structures of calix[5]arenes **5** were established by elemental analysis and ^1H NMR/^{13}C NMR spectroscopy. In the ^1H NMR spectrum of **5c**, the OH resonance peak appears as three singlets in the 1:2:2 ratio, and the resonances arising from the $ArCH_2Ar$ methylene hydrogens of the calix show temperature dependent spectral patterns. At room temperature the pattern is a broad singlet at around $\delta = 4.0$, while at lower temperature (−50 °C) it is three pairs of doublets in the 1:2:2 ratio. This pattern is compatible with the C_2 symmetry of proposed cyclic pentamer structure. The presence of three $ArCH_2Ar$ methylene carbon resonance peaks at $\delta = 32–31$ in the ^{13}C NMR spectrum of compound **5c** indicates a cone conformation,[15] but the confomational interconversion is fast on the ^1H NMR time scale at room temperature. Thus, we have provided an efficient method for the syntheses of calix[5]arenes which have three different substituents in AABCB pattern at the upper rim of the calix.

Melting points of all compounds were taken in sealed and evacuated capillary tubes on a Syblon thermolyne apparatus with polarizing microscope and were not corrected. IR spectra were determined on a Nicolet Impact 400 FT-IR spectrometer as KBr pellets. ^1H and ^{13}C NMR spectra were recorded on Varian Gemini 300 (300 and 75 MHz) and Bruker AMX 500 instrument. Chemical shifts are recorded as δ values in ppm relative to TMS as an internal standard. TLC analyses were carried out on silica gel plates (absorbent thickness 250 μm). Flash chromatography[16] was carried out with E. Merck silica gel (230–400 mesh ASTM). 2,6-Bishydroxymethyl-4-methylphenol (**2b**) was purchased from Aldrich and used without further purification.

2,6-Bishydroxymethyl-4-*tert*-butylphenol (2a):
This was synthesized by the published procedure.[10] *p-tert*-Butylphenol (15.0 g, 100 mmol), NaOH (4.0 g in 40 mL H_2O) and formaldehyde (15 mL, 35% aqueous solution) were stirred under N_2 for 5 days at 40 °C, and then brine (20 mL) was added. The precipitated sodium salt was collected by filtration, washed with brine (200 mL), dissolved in H_2O (50 mL) and then acidified with dil HCl (15 mL). The resulting yellow oil was extracted with CH_2Cl_2 (40 mL) and the organic layer was separated, washed with H_2O and dried ($MgSO_4$). Evaporation of solvent afforded 19.1 g (91%) of slightly waxy solid and showed one spot on TLC analysis. The crude product was used for the preparation of trimer without further purification A small amount of pure analytical sample was prepared by recrystallization from CCl_4, mp 75 °C (lit.[10] mp 74–75 °C).

4-Bromo-2,6-bishydroxymethylphenol (2c):
After the mixture of *p*-bromophenol (10.0 g, 57.8 mmol), NaOH (2.3 g in 32 mL H_2O) and 35% formaldehyde (9.2 mL) was heated for 5 days at 50 °C under N_2, the resulting paste was poured into 1% HCl solution (100 mL) and stirred for 2 h and then the precipitate was collected by filtration. After the crude product was decolorized by short column chromatography, a total of 10.5 g (78%) of the desired product was isolated by a recrystallization from acetone and hexane as a colorless crystalline solid: mp 178–179 °C.

IR(KBr) $\nu = 3410, 3310\ cm^{-1}$.

^1H NMR (acetone-d_6): $\delta = 7.50$ (s, 2H, ArH), 4.92 (s, 4H, CH_2), 2.91 (s, 3, OH).

Anal. Calcd. for $C_8H_9BrO_3$: C, 41.22; H, 3.90; Br, 34.28. Found: C, 41.18; H, 3.98; Br, 34.11.

2-[5-*tert*-Butylsalicyl-3-(5-methylsalicyl)]-4-methylphenol (3a):
After a mixture of compound **2a** (16.0 g, 68.6 mmol), *p*-cresol (59.4 g, 4 mole equivalent per hydroxymethyl group) and *p*-toluenesulfonic acid (100 mg) in benzene (250 mL) was refluxed for 20 h, excess *p*-cresol was removed by steam distillation. The resulting solid material was collected, washed with H_2O (100 mL), dried ($MgSO_4$) and then stirred with $CHCl_3$ (100 mL). $CHCl_3$ insoluble material was collected by filtration and recrystallized from acetone and hexane to afford 25.5 g (85%) of compound **3a** as a colorless crystalline solid: mp 242–243 °C (lit.[11] 242–243 °C).

4-*tert*-Butyl-2-[3-(5-*tert*-butylsalicyl)-5-methysalicyl]phenol (3b):
A mixture of compound **2b** (8.40 g, 50.0 mmol), *p-tert*-butylphenol (60 g, 4 mole equivalent per hydroxymethyl group) and *p*-toluenesulfonic acid (30 mg) in benzene (100 mL) was reacted by the same method as above. The resulting residue was triturated with hexane to afford 19.9 g (92%) of compound **3b** as a colorless crystalline solid: mp 226–227 °C (lit.[11] 226–227 °C).

2-[5-Bromosalicyl-3-(5-methylsalicyl)]-4-methylphenol (3c):
A mixture of compound **2c** (2.60 g, 11.1 mmol), *p*-cresol (9.6 g, mole equivalent per hydroxymethyl group) and *p*-toluenesulfonic acid (30 mg) in benzene (50 mL) was reacted by the same method as above. A recrystallization of crude product from acetone and hexane afforded 4.01 g (87%) of compound **3c** as a colorless crystalline solid: mp 250 °C.

IR (KBr): $\nu = 3180\ cm^{-1}$.

^1H NMR (acetone-d_6): $\delta = 7.17–6.81$ (m, 8H, ArH), 3.93 (s, 4H, CH_2), 2.93 (s, 2H, OH), 2.90 (s, 1H, OH), 2.22 (s, 6H, CH_3).

^{13}C NMR (acetone-d_6): $\delta = 152.73, 132.35, 132.22, 131.51, 131.39, 130.05, 128.94, 127.00, 115.84, 112.23$, (Ar), 30.45 ($CH_2$), 20.19 ($CH_3$).

Anal. calcd. for $C_{22}H_{21}BrO_3$: C, 63.92; H, 5.13; Br, 19.33. Found: C, 63.89; H, 5.05; Br, 19.10.

2-[5-Bromosalicyl-3-(5-*tert*-butylsalicyl)]-4-*tert*-butylphenol (3d):
A mixture of compound **2c** (4.00 g, 21.6 mmol), *p-tert*-butylphenol (32.4 g, 4 mole equivalent per hydroxymethyl group) and *p*-toluenesulfonic acid (30 mg) in benzene (80 mL) was reacted by the same method as above. The resulting residue was triturated with hexane to afford 7.28 g (90%) of compound **3d** as a colorless crystalline solid: mp 171–172 °C (lit.[11] 171–172 °C).

2-Hydroxy-3-(3-hydroxymethyl-5-phenylsalicyl)-5-phenylbenzylalcohol (4):
A mixture of *p*-phenylphenol (15.3 g, 90 mmol) and 35% formaldehyde (79 mL) was cooled in an ice bath, treated slowly with KOH (10.2 g) and then stirred for 4 days at 40 °C. The resulting yellow paste was suspended in ice-cold water, acidified with 10% HCl and the precipitate was collected by filtration. The crude product, which showed two major components on TLC, was heated with boiling $CHCl_3$ (100 mL), and the insoluble fraction was collected by filtration, washed twice with $CHCl_3$ (2 × 20 mL), hexane, (50 mL) and recrystallized from MeOH to yield 10.12 g (55%) of **4** as a powder; mp 128–129 °C (lit.[12] 128–129 °C).

Calix[5]arenes 5; General Procedure:
A mixture of trimer **3** (1.95 g for **3a** 5.0 mmol) and dimer diol **4** (2.06 g, 5.0 mmol) in xylene (100 mL) was refluxed for 3.5 days under N_2. After removal of solvent, the residue was purified to afford the calix[5]arene **5**.

5-tert-Butyl-31,32,33,34,35-pentahydroxy-11,29-dimethyl-17,23-diphenylcalix[5]arene (**5a**):
The crude product was purified by the flash chromatography (eluent was 6:1 mixture of hexane and acetone) to afford **5a** (1.03 g, 27%) as a colorless crystalline solid: mp 332–333 °C.

IR (KBr): $\nu = 3260\ cm^{-1}$.

^{1}H NMR ($CDCl_3$): δ = 9.10 (s, 2H, OH), 8.89 (s, 1H, OH), 8.83 (s, 2H, OH), 7.55–7.03 (m, 20H, ArH), 3.88 (br, 10H, $ArCH_2Ar$), 2.25 (s, 6H, CH_3), 1.28 (s, 9H, But).

^{13}C NMR ($CDCl_3$): δ = 150.05, 148.01, 144.34, 135.01, 130.93, 129.89, 129.80, 128.80, 128.25, 128.10, 127.36, 127.13, 127.00, 126.92, 126.83, 126.31, 126.12 (Ar), 33.76 ($C(CH_3)_3$), 31.60, 31.45, 31.30 ($ArCH_2Ar$), 31,29 ($C(CH_3)_3$), 20.20 (CH_3).

Anal. calcd. for $C_{53}H_{50}O_5$: C, 82.99; H, 6.58. Found: C, 82.90; H, 6.62.

5,17-Di-tert-butyl-31,32,33,34,35-pentahydroxy-11-methyl-23,29-diphenylcalix[5]arene (**5b**):

The crude product was purified by flash chromatography (eluent was 6:1 mixture of hexane and acetone) to afford **5b** (1.29 g, 32%) as a colorless crystalline solid: mp 328–329°C.

IR (KBr): ν = 3250 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 9.11 (s, 2H, OH), 8.86 (s, 3H, OH), 7.51–7.01 (m, 20H, ArH), 4.16 (br, 5H, $ArCH_2Ar$), 3.72 (br, 5H, $ArCH_2Ar$), 2.26 (s, 3H, CH_3), 1.27 (s, 18H, *t*-Bu).

^{13}C NMR ($CDCl_3$): δ = 150.05, 148.07, 148.00, 144.67, 141.11, 135.06, 129.78, 128.83, 128.22, 128.12, 127.53, 127.13, 127.00, 126.92, 126.72, 126.25, 126.13, 125.89 (Ar), 33.81 ($C(CH_3)_3$), 31.67, 31.60, 31.46 ($ArCH_2Ar$), 31.34 ($C(CH_3)_3$), 20.28 (CH_3).

Anal. calcd. for $C_{56}H_{56}O_5$: C, 83.12; H, 6.99. Found: C, 83.14; H, 7.07.

5-Bromo-31,32,33,34,35-pentahydroxy-11,29-dimethyl-17,23-diphenylcalix[5]arene (**5c**):

The crude product was purified by column chromatography (eluent was 5:1 mixture of hexane and acetone) to afford **5c** (1.07 g, 27%) as a colorless crystalline solid: mp 257°C (dec).

IR (KBr): ν = 3250 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 9.12 (s, 1H, OH), 9.07 (s, 2H, OH), 8.70 (s, 2H,OH), 7.60–6.99 (m, 20H, ArH), 3.98 (br, 10H, $ArCH_2Ar$),[17] 2.25 (s, 6H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 149.97, 149.72, 147.88, 140.99, 135.15, 131.77, 131.26, 130.17, 129.95, 129.04, 128.83, 128.31, 128.17, 127.23, 127.14, 127.00, 126.42, 125.69, 113.33, (Ar), 31.53, 31.28, 30.96 ($ArCH_2Ar$), 20.17 (CH_3).

Anal. calcd. for $C_{49}H_{41}BrO_5$: C, 74.51; H, 5.24; Br, 10.12. Found: C, 74.48; H, 5.31; Br, 10.01.

5-Bromo-31,32,33,34,35-pentahydroxy-11,29-di-tert-butyl-17,23-diphenylcalix[5]arene (**5d**):

The crude product was purified by column chromatography (eluent was 6:1 mixture of hexane and acetone) to afford **5d** (1.27 g, 29%) as a colorless crystalline solid: mp 289°C (dec).

IR (KBr): ν = 3260 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 9.16 (s, 1H, OH), 9.08 (s, 2H, OH), 8.77 (s, 2H, OH), 7.54–7.19 (m, 20H, ArH), 3.92 (br, 10H, $ArCH_2Ar$),[18] 1.30 (s, 18H, *t*-Bu).

^{13}C NMR ($CDCl_3$): δ = 149.96, 149.46, 147.88, 144.82, 141.05, 135.18, 131.77, 129.18, 128.86, 128.25, 128.18, 127.36, 127.12, 126.98, 126.75, 126.51, 126.22, 126.06, 125.28, 113.38 (Ar), 33.84, ($C(CH_3)_3$), 31.61, 31.54, 31.33 ($ArCH_2Ar$), 31.31 ($C(CH_3)_3$).

Anal. calcd. for $C_{55}H_{53}BrO_5$: C, 75.58; H, 6.12; Br, 9.14. Found: C, 75.49; H, 6.22; Br, 9.21.

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(1) Gutsche, C.D. *Calixarenes*, Stoddart, J.F.Ed.; Royal Society of Chemistry; London, 1989.
(2) Calixarenes: *A Versatile Class of Macrocyclic Compounds*, Vicens, J.; Böhmer, V. Eds.; Kluwer Academic Publishers: Dordrecht, 1991.
(3) Böhmer, V. *Angew. Chem. Int. Ed. Eng.* **1995**, *34*, 713.
(4) Gutsche, C.D.; Alam, I. *Tetrahedron* **1988**, *44*, 4689.
(5) Ninagawa, A.; Matsuda, H.; *Makromol. Chem. Rapid Commun.* **1982**, *3*, 65.
(6) Steward, D.R.; Gutsche, C.D. *Org. Prep. Proc. Int.* **1993**, *25*, 137.
(7) Kämmerer, H.; Happel, G.; Mathiasch, B. *Makromol. Chem.* **1981**, *182*, 1685.
(8) Gordon, J.L.M.; Böhmer, V.; Vogt, W. *Tetrahedron Lett.* **1995**, *36*, 2445.
(9) Haino, T.; Harano, T.; Matsumura, K.; Fukazawa, Y. *Tetrahedron Lett.* **1995**, *36* 5793.
(10) Hanus, F.; Fuch, E. *J. Prakt. Chem.* **1939**, *153*, 327.
(11) No, K.; Kim, J.E.; Kwon, K.M. *Tetrahedron Lett.* **1995**, *36*, 8453.
(12) No, K.; Hwang, K.L. *Bull. Korean Chem. Soc.* **1993**, *14*, 753.
(13) Böhmer, V.; Marschollek, F.; Zetta, L. *J. Org. Chem.* **1987**, *52*, 3200.
(14) Anreetti, G.D.; Böhmer, V.; Jordon, J.G.; Tabatabai, M.; Ugozzoli, F.; Vogt, W.; Wolff, A. *J. Org. Chem.* **1993**, *58*, 4023.
(15) Jaime, C.; de Mendoza, J.; Prados, P.; Nieto, P. M.; Sanchez, C.; *J. Org. Chem.* **1991**, *56*, 3372.
(16) Still, W.C.; Kahn, M.; Mitra, M. *J. Org. Chem.* **1978**, *43*, 2923.
(17) ^{1}H NMR (−50°C): δ = 4.24 (d, 1H, CH_2, J = 14.2), 4.17 (d, 2H, CH_2, J = 14.1), 4.08 (d, 2H, CH_2, J = 14.2), 3.70 (d, 1H, CH_2, J = 14.2), 3.60 (d, 2H, CH_2, J = 14.1), 3.46 (d, 2H, CH_2, J = 14.2).
(18) ^{1}H NMR (−50°C): δ = 4.28 (d, 1H, CH_2, J = 14.2), 4.22 (d, 2H, CH_2, J = 14.2), 4.13 (d, 2H, CH_2, J = 14.1), 3.72 (d, 1H, CH_2, J = 14.2), 3.65 (d, 2H, CH_2, J = 14.2), 3.53 (d, 2H, CH_2, J = 14.1).