Calixarenes. 8. Short, Stepwise Synthesis of *p*-Phenylcalix[4]arene, *p*-Phenyl-*p*-*tert*-butylcalix[4]arene, and Derived Products

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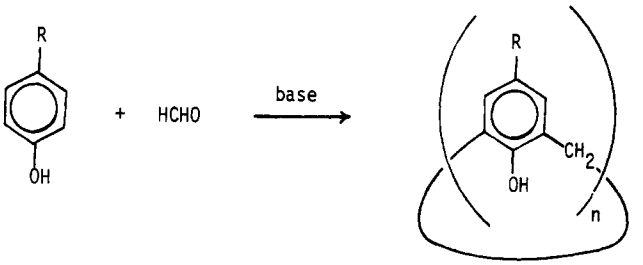
Calixarenes (Schemes I–IV) have been previously obtained by a one-flask process (Zinke synthesis) and by a multistep process (Hayes and Hunter synthesis). The former has the advantage of speed and simplicity but the disadvantage of difficult-to-separate product mixtures. The latter has the advantage of flexibility but the disadvantage of low yields and much effort. In an attempt to retain some of the flexibility of the Hayes and Hunter synthesis but to improve the yields and reduce the effort, we have devised a four-step synthesis of calixarenes. It involves the carefully controlled condensation of a para-substituted phenol with formaldehyde to give the bis(hydroxymethyl) linear dimer **2**, acid-catalyzed arylation of **2** to the linear tetramer **3**, selective hydroxymethylation of **3** to the monohydroxymethyl linear tetramer **4**, and acid-catalyzed cyclization of **4** to the calixarene **5**. The utility of the synthesis has been demonstrated in two cases, one leading to the symmetrically substituted *p*-phenylcalix[4]arene (**5a**) and the other to a compound of mixed function, di-*p*-phenyl-di-*p*-*tert*-butylcalix[4]arene (**5b**). The synthetic possibilitites of **5b** have been adumbrated by its conversion to the de-*tert*-butylated calixarene **11**, to the diacetyl calixarene **12**, and to the acetyl acetoxy calixarene **13** which, regardless of its conformation, possesses a chiral axis.

Calixarenes, which are [1_n]metacyclophanes comprising cyclic arrays of phenolic residues attached by methylene groups at the positions ortho to the hydroxyl groups, have been synthesized in two fundamentally different ways. One method, first reported by Zinke[1] and subsequently modified by others,[2–5] involves the treatment of para-substituted phenols with formaldehyde in the presence of base at temperatures of 140–220 °C, as illustrated in Scheme I. In the system that has been most carefully studied, viz., *p*-*tert*-butylphenol and formaldehyde,[6] the product of this "one-flask" method has been shown to be a mixture containing various cyclic oligomers whose relative amounts depend on the reaction conditions. By appropriate manipulation it is possible to obtain yields as high as 35% of *p*-*tert*-butylcalix[4]arene, 75% of *p*-*tert*-butylcalix[6]arene, and 65% or higher of *p*-*tert*-butylcalix[8]arene, making this the method of choice for the synthesis of these symmetrically substituted compounds. The several other para-substituted phenols that have been investigated, however, have afforded products that are more recalcitrant to purification and product manipulation, and the generality of this approach remains to be determined. The other method, first worked out by Hayes and Hunter[7] and more recently exploited and improved by Kämmerer and co-workers,[8–14] involves the sequential

Scheme I. One-Flack Synthesis of Calixarenes (Zinke Method)



addition of methylene groups and aryl functions to a para-substituted phenol "blocked" at one of the ortho positions by a halogen. In this fashion a linear oligomer can be elaborated which carries a hydroxymethyl group at one end and the halogen blocking group at the other. Removal of the halogen by hydrogenolysis followed by acid-catalyzed, high-dilution cyclization then gives the cyclic oligomer, as illustrated in Scheme II. This method is clearly superior to the first in affording products of unequivocal structure and in allowing synthetic flexibility with respect to the para-substituents; *i.e.*, calixarenes of mixed function can be prepared, as Kämmerer et al. have demonstrated with *p*-methyl and *p*-*tert*-butyl groups. However, it it long, tedious, and modest with respect to yields, typical examples being the ten-step sequences in which *p*-*tert*-butylphenol affords *p*-*tert*-butylcalix[4]arene in 10% overall yield[6] and *p*-phenylphenol affords *p*-phenylcalix[4]arene in 0.24% overall yield.[15] Recognizing the deficiencies in the Hayes and Hunter synthesis, Kämmerer and co-workers[12] have explored a more convergent approach which retains much of the flexibility of the sequential stepwise approach. It involves the condensation of a linear trimer with a 2,6-bis(halomethyl)-phenol, as illustrated in Scheme III. Although short, it suffers from quite low yields in the cyclization step, which range from 10–15% in the best cases to 2–7% in some of

(1) Zinke, A.; Ziegler, E. *Ber. Dtsch. Chem. Ges.* **1944**, *77*, 264.
(2) Cornforth, J. W.; D'Arcy Hart, P.; Nicholls, G. A.; Rees, R. J. W.; Stock, J. A. *Br. J. Pharmacol.* **1955**, *10*, 73.
(3) Buriks, R. S.; Fauke, A. R.; Munch, J. H. U. S. Patent 4 259 464, filed 1976, issued 1981.
(4) Gutsche, C. D.; Kung, T. C.; Hsu, M.-L. "Abstracts of Papers", 11th Midwest Regional Meeting of the American Chemical Society, Carbondale, IL, 1975; American Chemical Society: Washington, DC, 1975; No. 517.
(5) Patrick, T. B.; Egan, P. A. *J. Org. Chem.* **1977**, *42*, 382; **1977**, *42*, 4280.
(6) Gutsche, C. D.; Dhawan, B.; No, K. H.; Muthukrishnan, R. J. *J. Am. Chem. Soc.* **1981**, *103*, 3782.
(7) Hayes, B. T.; Hunter, R. F. *Chem. Ind. (London)* **1956**, 193; *J. Appl. Chem.* **1958**, *8*, 743.
(8) Kämmerer, H.; Happel, G.; Caesar, F. *Makromol. Chem.* **1971**, *162*, 179.
(9) Happel, G.; Mathiasch, B.; Kämmerer, H. *Makromol. Chem.* **1975**, *176*, 3317.
(10) Kämmerer, H.; Happel, G. *Makromol. Chem.* **1978**, *179*, 1199.
(11) Kämmerer, H.; Happel, G.; Böhmer, V.; Rathay, D. *Monatsh. Chem.* **1978**, *109*, 767.
(12) Böhmer, V.; Chhim, P.; Kämmerer, H. *Makromol. Chem.* **1979**, *180*, 2503.
(13) Kämmerer, H.; Happel, G. *Makromol. Chem.* **1980**, *181*, 2049.
(14) Kämmerer, H.; Happel, G.; Mathiasch, B. *Makromol. Chem.* **1981**, *182*, 1685.
(15) Gutsche, C. D.; No. K. H. *J. Org. Chem.*, previous paper in this issue.

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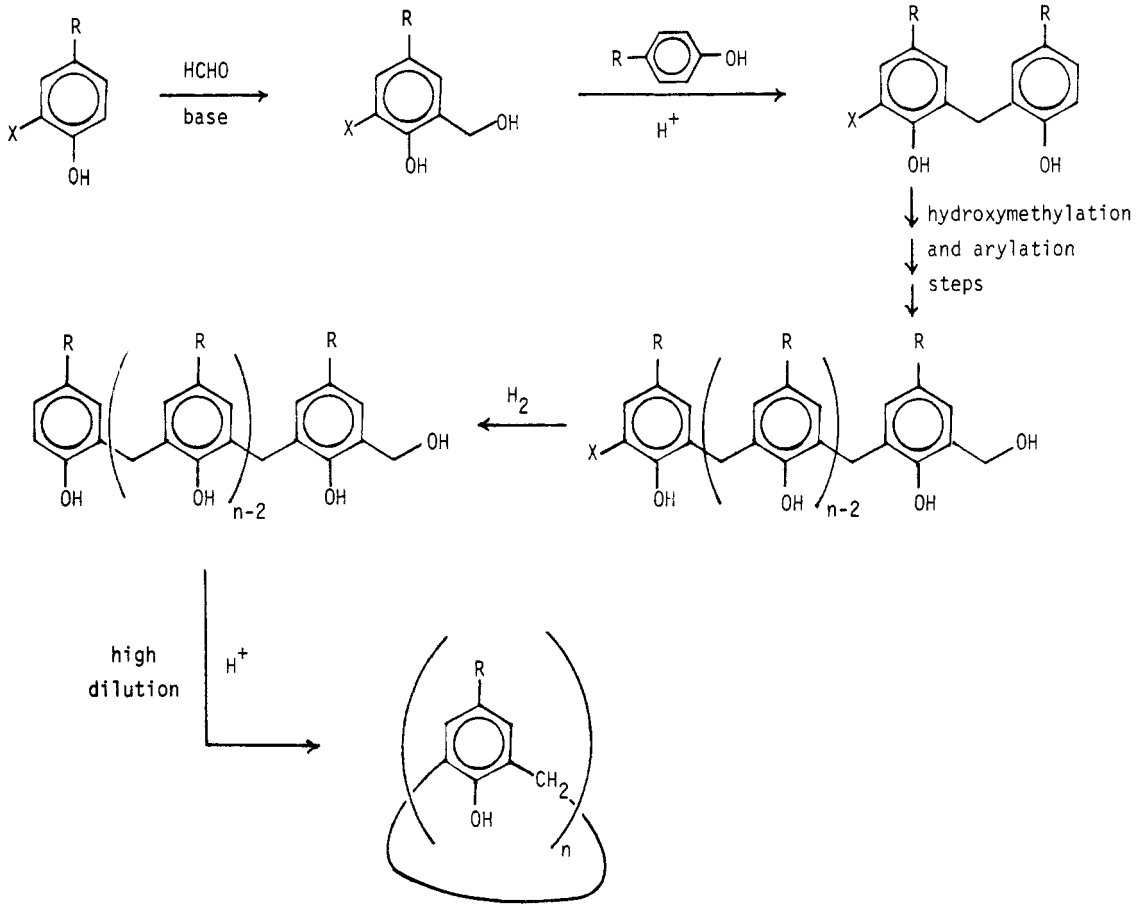
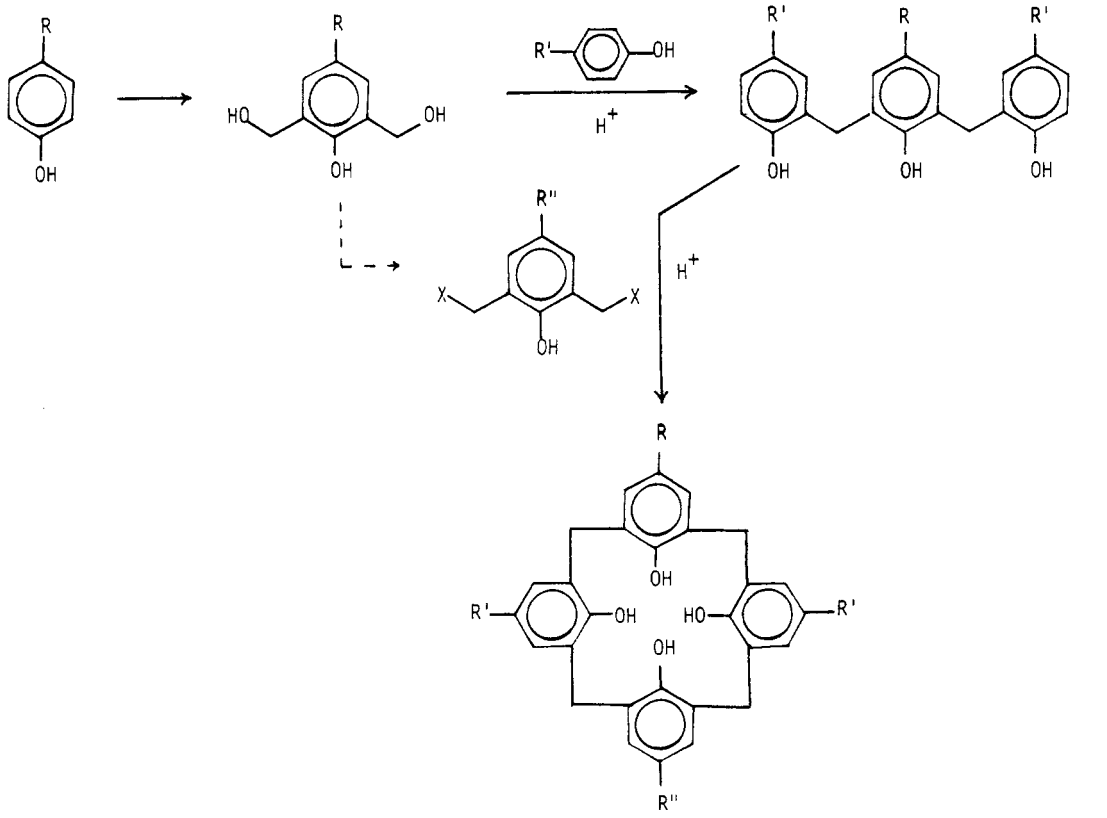
Scheme II. Sequential, Stepwise Synthesis of Calixarenes (Hayes and Hunter Method)

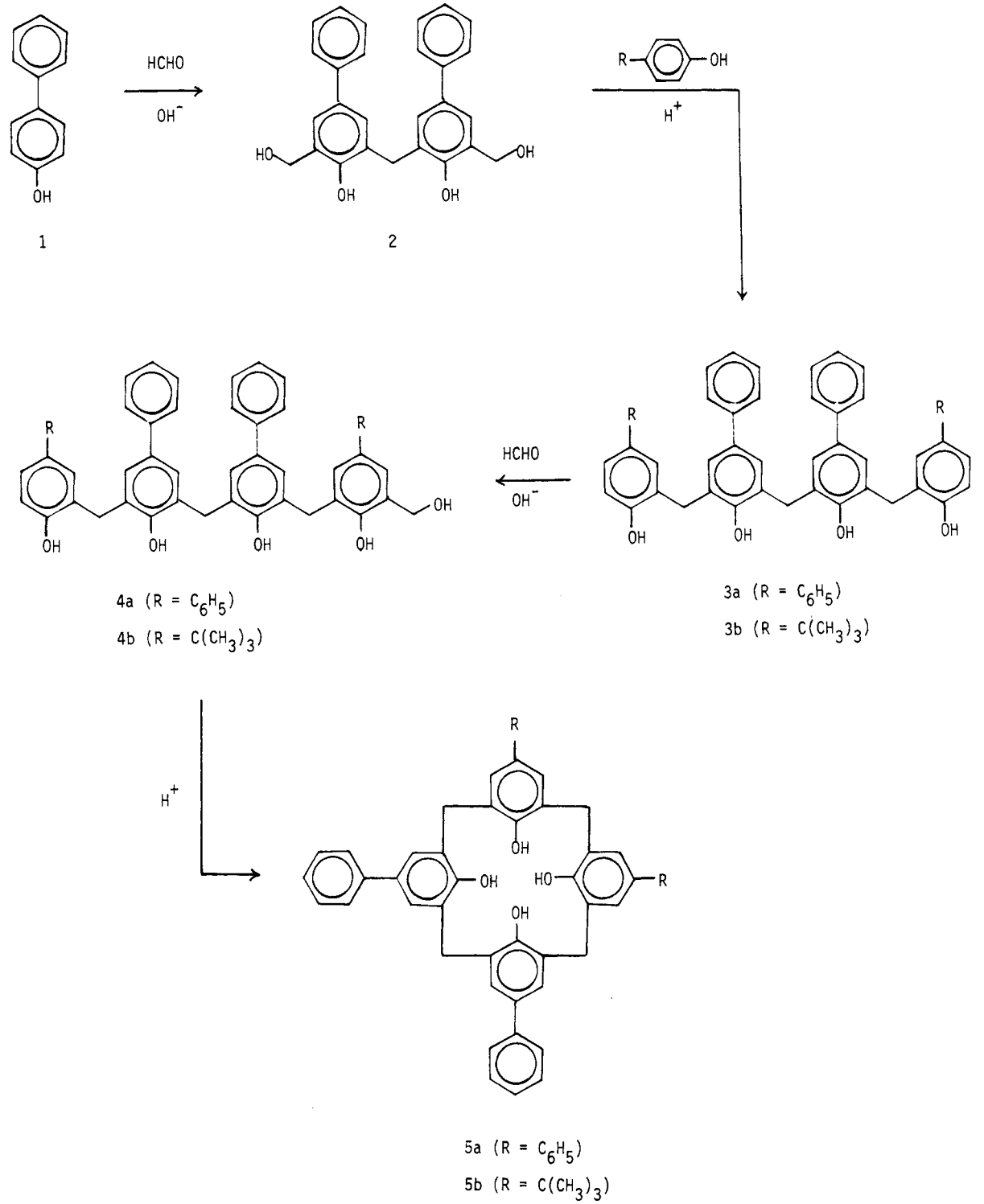


Scheme III. Convergent, Stepwise Synthesis of Calixarenes (Böhmer, Chhim, and Kämmerer Method)



the more interesting cases in which a mixture of alkyl, bromo, and nitro functions are incorporated as R groups. The purpose of the present work is to explore still another approach to a convergent synthesis which retains some of the functional group flexibility of the Hayes and Hunter method and which gives yields that are high enough to

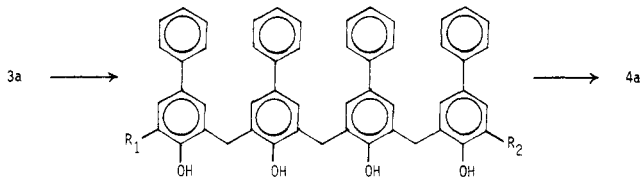
Scheme IV. Four-Step Synthesis of Calixarenes (No and Gutsche Method)



make the synthesis useful for the preparation of calixarenes in sufficient quantities to study their potentiality as enzyme models. It involves the four-step sequence in which a para-substituted phenol (1) is treated with formaldehyde under controlled conditions to yield the bis(hydroxymethyl) dimer (2), 2 is condensed with 2 equiv of a para-substituted phenol to yield the linear tetramer (3), 3 is monohydroxymethylated to 4, and 4 is cyclized to the calixarene (5), as outlined in Scheme IV.

Synthesis of 5,11,17,23-Tetraphenyl-25,26,27,28-tetrahydroxycalix[4]arene (5a). For reasons discussed in the accompanying paper,[15] *p*-phenylcalix[4]arene is of special interest; and so the sequence of reactions outlined in Scheme IV was first investigated in this system. The initial step, the conversion of *p*-phenylphenol to the bis(hydroxymethyl) dimer 2, was studied in some detail to maximize the yield. From a series of experiments at various temperatures, reaction times, and mole ratios of phenol to base, it was determined that the optimum conditions involve the action of aqueous formaldehyde on *p*-phenylphenol in fairly concentrated KOH for 8 days at 40 °C. These conditions give pure samples of 2 in yields as high as 47%, making this material easily preparable in large quantity. Reactions carried out under milder conditions contain larger amounts of 2-(hydroxymethyl)-4-phenol and 2,6-bis(hydroxymethyl)-4-phenol; reactions

Scheme V



6 (R_1 = Br, R_2 = H)

7 (R_1 = R_2 = Br)

8 (R_1 = Br, R_2 = CH_2OH)

9 (R_1 = R_2 = CH_2OH)

carried out under more strenuous conditions contain larger amounts of higher oligomers. The conversion of **2** to the linear tetramer **3a** by acid-catalyzed reaction with *p*-phenylphenol is straightforward, and when a large excess of *p*-phenylphenol is used, it affords **3** in 78% yield. The scale of operation at this point becomes a factor, however, because of the necessity of removing the excess *p*-phenylphenol first by fractional crystallization and then by flash chromatography,[16] reducing the amount of product that can be easily obtained to the level of a few grams per experiment. The step in the overall synthesis that appeared to be most dubious at the outset was the monohydroxymethylation of **3** to **4**. The initial experiments, in fact, were directed not to monohydroxymethylation but to monobromination of **3a** to **6** (Scheme V) which, following the Hayes and Hunter sequence at this point, would yield **4a** by hydroxymethylation to **8** followed by hydrogenolysis. Although unreacted starting material (**3a**) was easily separated from the bromination mixture, it proved to be exceedingly difficult to separate the monobromo tetramer (**6**) from the dibromo tetramer (**7**). Consequently, the mixture of these two compounds was hydroxymethylated, yielding a mixture of **7** and **8** which was hydrogenolyzed to yield a mixture of **3** and **4** that was easily separable by flash chromatography. The overall yield in this three-step sequence was only 12%, however, so direct hydroxymethylation of **3** was explored as an alternative. Various times, temperatures, and ratios of phenol to base were investigated, and it was determined that the optimum conditions involved treating **3** with aqueous formaldehyde and base for 5 days at room temperature with 4 molar equiv of KOH for each phenolic OH group. This gave a mixture from which starting material (**3a**), monohydroxymethyl tetramer (**4a**), and bis(hydroxymethyl) tetramer (**9**) were obtained as pure, crystalline compounds by flash chromatography in yields of 37%, 35%, and 15%, respectively. Since recovered **3a** can be used again, the yield of **4a** based on the amount of **3a** converted to product is 55%. Thus, the overall yield of **4a** from *p*-phenylphenol is 20%, which is considerably better than the 1.9% overall yield obtained via the nine-step route of Hayes and Hunter.[15] As discussed in the accompanying paper,[15] the acid-catalyzed cyclization of **4a** gives the calixarene **5a** in only 13% yield, two other products being formed in larger amounts. To determine whether this is due to the presence of the *p*-phenyl group on the terminus of the linear tetramer into which the cyclization is occuring, we undertook the reaction sequence outlined in the next section.

Synthesis of 5,11-Diphenyl-17,23-di-*tert*-butyl-25,26,27,28-tetrahydroxycalix[4]arene (5b). The sequence illustrated in Scheme IV was again employed by starting with **2** which was prepared as described above. By use of *p-tert*-butylphenol both as reactant and solvent, **2** was converted to **3b** in 73% yield. In contrast to the previous case with *p*-phenylphenol, excess *p-tert*-butylphenol can be easily separated by steam distillation; thus, this step is less limited in the scale on which it can be conveniently carried out, and **3b** becomes a readily available material. Monohydroxymethylation of **3b** proceeded as described above for **3a** to give **4b** in 35% yield (46% based on recovered *3b*), and acid-catalyzed, high-dilution cyclization produced calixarene **5b** as the major product, isolable in yields as high as 96%. Thus, the low yields in the cyclization of **5a**[15] clearly are the result of the *p*-phenyl group on the terminal residue which affords alternative cyclization sites; when the phenyl is replaced by a *tert*-butyl group (i.e., **4b** instead of **4a**), the cyclization goes smoothly to a single product.

Products Derived from Calixarene 5b. The mixed calixarene **5b**, prepared from the readily available bis(hydroxymethyl) dimer **2** in ca. 30% overall yield, provides an attractive starting material for the preparation of functionalized calixarenes. The 4′-positions of the *p*-phenyl rings are potential sites for reaction, and removal of the *tert*-butyl groups from the *p-tert*-butylphenyl residues opens up these sites for reaction as well. Some preliminary experiments to demonstrate these potentialities have been undertaken.

The utility of the *tert*-butyl group as a blocking device is well-known,[17] and Kämmerer and co-workers[11] have already applied this technique to a dimethyl-di-*tert*-butylcalix[4]arene from which the two *tert*-butyl groups were removed to yield 45% of the dimethylcalix[4]arene. In similar fashion, **5b** was heated in toluene solution in the presence of $AlCl_3$ to produce a diphenylcalix[4]arene in 65% yield as a moderately high melting (mp 276–277 °C) solid that retains all of the analytical and spectral characteristics of a calixarene.

Prior to carrying out a Friedel–Crafts acetylation of **5b** to introduce keto functions, the hydroxyl groups were esterified by treatment with acetic anhydride. From the reaction mixture three isomeric acetates (**10**), Scheme VI were isolated in yields of 36% (mp 314–316 °C), 34% (mp 293–295 °C), and 6% (mp less well-defined). The structures of these conformational isomers as well as those of various other calixarenes will be discussed in a separate paper. When the highest melting of the acetate conformers was subjected to a Friedel–Crafts acetylation with acetyl chloride and $AlCl_3$ in CS_2, a 71% yield of the diketone **12** was isolated as a high-melting solid (mp 323–325 °C) which retains all of the analytical and spectral characteristics of

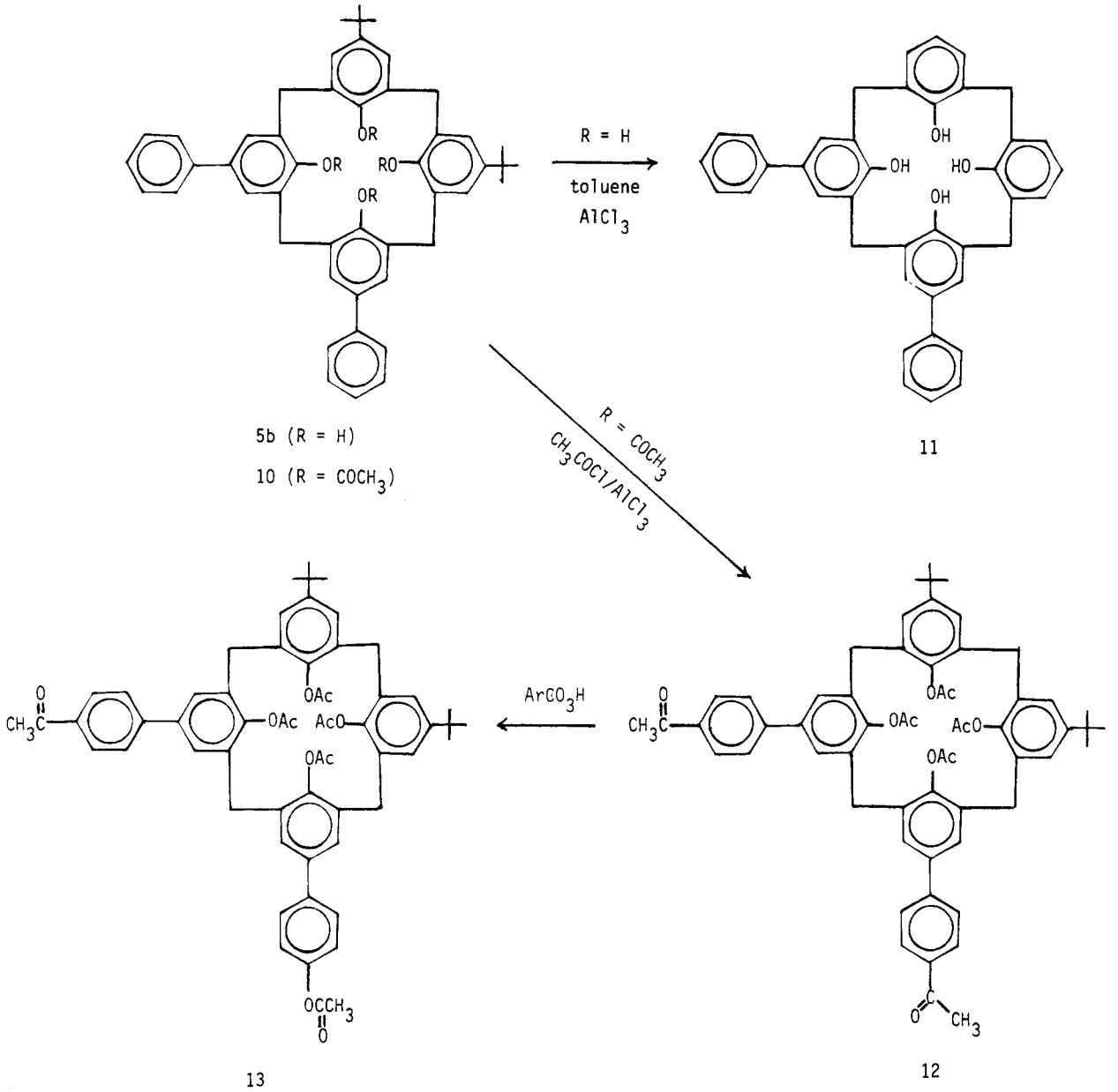
(16) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(17) Tashiro, M. *Synthesis* **1979**, 921.

(18) Boiling points are uncorrected. 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 (accuracy ±1 °C). Infrared (IR) spectra were determined on a Perkin–Elmer 283B spectrometer. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Hitachi–Perkin Elmer R-24B spectrometer or a JEOL FX-100 spectrometer, and carbon nuclear magnetic resonance spectra (^{13}C NMR) were also obtained with the latter instrument. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.00) as an internal standard. Osmometric molecular weight determination[19] were made on Wescan Model 232A apparatus with concentrations of *ca.* 10^{-3} M in $CHCl_3$. Microanalyses were carried out by Industrial Testing Laboratories, St. Louis, MO. Thin-layer chromatographic (TLC) analyses were carried out on silica gel plates (absorbant thickness 250 μm). Flash chromatography[16] was carried out with E. Merck silica gel (230–400-mesh ASTM) on columns of diameters 80 mm (for more than 5 g of sample), 50 mm (for 1–5 g of sample), and 30 mm (for less than 1 g of sample) filled to a height of 6 in. Elution rates were 2 in./min; fractions of 125 mL were collected from the two larger columns and of 50 mL from the smallest column.

(19) We are indebted to Alice Gutsche for carrying out the osmometric molecular weight determinations.

Scheme VI



a calixarene and which shows the presence of two keto groups. Treatment of this material with *m*-chloroperbenzoic acid in sufficient quantity to oxidize both of the methyl ketone groups to acetoxy functions resulted in the conversion of only one, giving calixarene **13** in 35% yield. This calixarene of mixed function is interesting because the AABC pattern of arene moieties comprising the calix confers a chiral axis on the molecule.

Experimental Section[18]

Synthesis of 5,11,17,23-Tetraphenyl-25,26,27,28-tetrahydroxycalix[4]arene (5b) 3-[3-(Hydroxymethyl)-5-phenylsalicyl]-5-phenyl-2-hydroxybenzyl Alcohol (2). A mixture of 15.3 g of *p*-phenylphenol and 75 mL of 37% formaldehyde was cooled in an ice bath, treated slowly with 10.2 g of KOH, and then stirred for 8 days at 40 °C. The resulting yellow paste was suspended in ice-cold water and acidified with 10% HCl, and the precipitated solid collected by filtration. The crude product, which showed two major components by TLC analysis, was triturated with 100 mL of boiling $CHCl_3$, and the insoluble fraction was washed twice with 20 mL of $CHCl_3$ and once with 50 mL of hexane and recrystallized from CH_3OH to yield 8.7 g (47%) of **2** as a colorless powder: mp 127–128 °C; IR (KBr) 3340 (OH stretching), 880 cm^{-1} (1,2,3,5-tetrasubstituted Ar), ^1H NMR (acetone-d_6) δ 7.55–7.20 (m, 7, Ar H), 4.89 (s, 2, CH_2OH), 4.11 (s, 1, CH_2), 3.48 (br, 2, OH); R_f (ether/hexane, 7:3) 0.22.

Anal. Calcd for $C_{27}H_{24}O_4 \cdot 0.25CHCl_3$: C, 74.12; H, 5.50. Found: C, 74.34; H, 5.64.

Attempts to remove all of the $CHCl_3$ by heating the sample under vacuum resulted in decomposition of the product.

2-[3-[3-(5-Phenylsalicyl)-5-phenylsalicyl]-5-phenylsalicyl]-4-phenylphenol (3a). A mixture of 1.32 g (3.5 mmol) of **1** and 34 g (233 mmol) of *p*-phenylphenol in 200 mL of xylene was heated to 110 °C and treated with 5 mL of concentrated HCl. The solution was refluxed for 21 h, and at the 7- and 14-h intervals an additional 5 mL of concentrated HCl was added. To the cooled and acidified reaction mixture ether was added, and the xylene-ether solution was washed with water to remove HCl, dried over anhydrous $MgSO_4$, and concentrated in stages to effect fractional crystallization, yielding a total of seven fractions. The first two were pure *p*-phenylphenol, the third fraction was mainly *p*-phenylphenol, fractions 4–6 were mixtures of *p*-phenylphenol and **3a** and an unidentified compound, and fraction 7 was a rather complex mixture. Fractions 4–6 were combined and flash chromatographed (3:1 hexane/acetone as the eluent) to give a solid which, after recrystallization from $CHCl_3$/petroleum ether (bp 35–60 °C) consisted of 1.79 g (78%) of **3a** as a colorless powder: mp 182–184 °C dec; IR (KBr) 3260 (OH stretching), 878

(1,2,3,5-tetrasubstituted Ar), 820 cm^{-1} (1,2,4-trisubstituted Ar); ^1H NMR (acetone-d_6) δ 7.65–6.96 (m, 15, Ar H), 4.15 (s, 3, CH_2), 3.90 (br, 2, OH); R_f (acetone/petroleum ether, 1:2) 0.31.

Anal. Calcd for $C_{51}H_{40}O_4$: C, 85.45; H, 5.62. Found: C, 85.31; H, 5.80.

3-[3-[-3-(5-Phenylsalicyl)-5-phenylsalicyl]-5-phenylsalicyl]-5-phenyl-2-hydroxybenzyl Alcohol (4a). (A) Via Direct Hydroxymethylation of 3a. A suspension of 2.00 g (2.8 mmol) of **3a** in 30 mL of 37% formaldehyde cooled in an ice bath was treated with 2.50 g (45 mmol) of KOH. The mixture was stirred 5 days at room temperature (20–25 °C) and then acidified with cold 10% HCl to give a crude product containing unreacted **3a**, the desired compound **4a**, and the bis(hydroxymethyl) compound **9**. Separation by flash chromatography yielded pure fractions of **3a** and **4a** when hexane/acetone (5:2) was used as the eluent and **9** when this was followed with hexane/acetone (1:1) as the eluent. Evaporation of the solvent from the fraction containing **4a** followed by recrystallization from $CHCl_3$/hexane gave 0.725 g (35%) of **4a** as a colorless powder: mp 142–143 °C dec; identical in chemical, physical, and spectral properties with material prepared by hydrogenolysis of **8**.[15] Similar treatment of the fraction containing **3** gave 0.742 g (37%) of starting material, bringing the yield of **4a** to 55% based on starting material consumed. Evaporation of the third eluate followed by recrystallization from $CHCl_3$/hexane gave 0.335 g (15%) of 3-[3-[3-[3-(hydroxymethyl)-5-phenylsalicyl]-5-phenyl-salicyl]-5-phenyl-salicyl]-5-phenyl-2-hydroxybenzyl alcohol (**9**) as a colorless powder: mp 169–170 °C; IR (KBr) 3260 (OH stretching), 875 cm^{-1} (1,2,3,5-tetrasubstituted Ar); ^1H NMR (acetone-d_6) δ 7.58–7.20 (m, 14, Ar H), 4.88 (s, 1, CH_2OH), 4.11 (s, 3, CH_2), 3.40 (br, 3, OH); R_f (petroleum ether/acetone, 11:8) 0.18.

Anal. Calcd for $C_{53}H_{44}O_6 \cdot 0.1CHCl_3$: C, 80.84; H, 5.64. Found: C, 80.95; H, 5.60.

When the reaction was carried out at 50 °C for 3 days the yield of **9** was increased to 33%.

(B) Via Bromination, Hydroxymethylation, and Debromination of 3a. A solution of 7.34 g (10.2 mmol) of **3a** in 160 mL of $CHCl_3$ was treated with 0.57 mL (11.2 mmol) of bromine in 60 mL of $CHCl_3$ at 30 °C. Stirring was continued for 24 h, and the yellow solution was then washed with water until free of Br_2 and HBr, dried over anhydrous $MgSO_4$, and evaporated to give a pale brown solid containing **3**, **6**, and **7**. Flash chromatography separated **3** from **6** and **7** but did not separate **6** from **7**, which consisted of 4.43 g of a colorless solid. A 3.55-g sample of this mixture was suspended in 150 mL of 37% formaldehyde, treated with 5.00 g of KOH, and stirred for 6 days at room temperature (20–25 °C) to give 3.30 g of a crude product containing **6–8**. A 3.27-g sample of this mixture was dissolved in 50 mL of CH_3OH, 10 mL of dioxane, and 5.5 mL of 20% aqueous KOH and subjected to hydrogenolysis in the presence of Raney nickel W-2 catalyst.[20] The crude product was flash chromatographed (2.4:1 petroleum ether (bp 35–60 °C)/acetone as the eluent) to yield **3a** and 0.724 g (12%) of **4a**, identical in chemical, physical, and spectral properties with material previously described.[15]

5,11,17,23-Tetraphenyl-25,26,27,28-tetrahydroxycalix[4]arene (5a) was obtained by the acid-catalyzed, high-dilution cyclization of **4a** in 13% yield, as described in the accompanying paper.[15]

Synthesis of 5,11-Diphenyl-17,23-di-*tert*-butyl-25,26,27,28-tetrahydroxycalix[4]arene and Derived Products. 2-[3-[3-(5-*tert*-Butylsalicyl)-5-phenylsalicyl]-5-phenylsalicyl]-4-*tert*-butylphenol (3b). A mixture of 10.0 g (26.3 mmol) of **2** and 150 g (1 mol) of *p*-*tert*-butylphenol was heated in an oil bath held at 120–125 °C until it started to melt and was then treated with 5 mL of concentrated HCl. The mixture was refluxed for 9.5 h, and excess *p*-*tert*-butylphenol was removed by steam distillation. The residue was dissolved in $CHCl_3$, washed with water, dried, and evaporated to give a crude product which was flash chromatographed (11:2 hexane/acetone as the eluent) and then recrystallized from hexane to give 12.11 g (73%) of a colorless powder: mp 177–178 °C; IR (KBr) 3220 (OH stretching), 878 (1,2,3,5-tetrasubstituted Ar), 820 cm^{-1} (1,2,4-trisubstituted Ar); ^1H NMR (acetone-d_6) δ 7.41–6.71 (m, 12, ArH and OH), 4.10 (s, 1, CH_2), 4.01 (s, 2, CH_2), 1.21 (s, 9, $C(CH_3)_3$); R_f (acetone/hexane, 1:3) 0.40.

3-[3-[3-(5-*tert*-Butylsalicyl)-5-phenylsalicyl]-5-phenylsalicyl]-5-*tert*-butyl-2-hydroxybenzyl Alcohol (4b). A solution of 3.00 g of **3b** in 10 mL of CH_3OH and 20 mL of dioxane was mixed with 5.7 mL of 20% aqueous KOH and 9 mL of 37% formaldehyde in an ice bath. The mixture was stirred at 40 °C for 30 h, diluted with 200 mL of ice-cold water, and acidified with cold, 10% HCl. The crude product was separated by filtration, washed with water until free of acid, dried, and subjected to flash chromatography to yield starting material **3b** and monohydroxymethyl compound **4b** with hexane/acetone (5:1) as the eluant followed by bis(hydroxymethyl) compound with hexane/acetone (2:1) as the eluant. The desired product **4b** was obtained as 1.11 g (35%) of a colorless powder after recrystallization from $CHCl_3$/petroleum ether (bp 35–60 °C): mp 132 ° dec; IR (KBr) 3220 (OH stretching), 875 (1,2,3,5-tetrasubstituted Ar), 818 cm^{-1} (1,2,4-trisubstituted Ar); ^1H NMR (acetond-d_6) δ 7.45–6.97 (m, 12, Ar H and OH), 4.85 (s, 1, CH_2OH), 4.08 (s, 1, CH_2), 1.22 (s, 9, $C(CH_3)_3$); R_f (acetone/pentane, 3:1) 0.58.

Anal. Calcd for $C_{48}H_{50}O_5$: C, 81.55; H, 7.13. Found: C, 81.31; H, 7.35.

3-[3-[3-(Hydroxymethyl)-5-*tert*-butylsalicyl]-5-phenylsalicyl]-5-phenylsalicyl]-5-*tert*-butyl-2-hydroxybenzyl alcohol, i.e., the bis(hydroxymethyl) analogue of **4b**, was obtained as 0.565 g (17%) of a colorless powder after recrystallization from $CHCl_3$/petroleum ether (bp 35–60 °C): mp 122–123 °C dec; IR (KBr) 3300 (OH stretching), 875 cm^{-1} (1,2,3,5-tetrasubstituted Ar); ^1H NMR (acetone-d_6) δ 7.41–7.03 (m, 12, Ar H and OH), 4.84 (s, 2, CH_2OH), 4.10 (s, 1, CH_2), 4.01 (s, 2, CH_2), 1.22 (s, 9, $C(CH_3)_3$); R_f (acetone/pentane, 3:7) 0.20.

Anal. Calcd for $C_{49}H_{52}O_6$: C, 79.86; H, 7.11. Found: C, 79.02; H, 7.04.

The trace of $CHCl_3$ responsible for the low C and H values could not be removed under vacuum, even at room temperature, without causing decomposition of the bis(hydroxymethyl) compound.

5,11-Diphenyl-17,23-di-*tert*-butyl-25,26,27,28-tetrahydroxycalix[4]arene (5b). To a 3-L, three-necked flask fitted with a condenser, addition funnel, and nitrogen/vacuum inlet was added a mixture of 1.5 L of acetic acid and 5 mL of concentrated HCl. The system was evacuated and filled with N_2, the contents were brought to reflux, and a solution of 1.300 g of **4b** in 125 mL of acetic acid was added dropwise (3 drops/min) over a period of 48 h. At intervals of 7 h an additional 5 mL of concentrated HCl was added until the reaction mixture contained a total of 20 mL. The mixture was refluxed for 66 h, and the acetic acid was then removed by distillation under reduced pressure. The pale colored residue was dissolved in 50 mL of $CHCl_3$ and decolorized with charcoal, and the $CHCl_3$ was removed by evaporation to give an almost pure product. Recrystallization from $CHCl_3$/petroleum ether (bp 35–60 °C) gave 1.23 g (96%) of **5b** as a colorless powder: mp 332–333 °C; IR (KBr) 3160 (OH stretching), 875 cm^{-1} (1,2,3,5-tetrasubstituted Ar); ^1H NMR ($CDCl_3$) δ 10.31 (s, 2, OH), 7.35 (m, 5, Ar H), 7.27 (s, 2, Ar H), 7.07 (s, 2, Ar H), 3.95 (br, 4, CH_2), 1.21 (s, 9, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 134.4 (10%, Ar), 132.5 (12%, Ar), 123.7 (10%, Ar), 119.0 (10%, Ar), 118.6 (24.5%, Ar), 118.3 (75%, Ar), 117.8 (55%, Ar), 117.6 (30%, Ar), 116.9 (71%, Ar), 116.8 (36%, Ar), 116.3 (25%, Ar), 116.1 (23%, Ar), 42.6 (10%, $C(CH_3)_3$), 41.3 (43%, CH_2), 40.5 (100%, $C(CH_3)_3$); osmometric mol wt ($CHCl_3$, 37 °C) 672 (calcd 688); R_f ($CHCl_3$/petroleum ether, 1:1) 0.61.

Anal. Calcd for $C_{48}H_{48}O_4$: C, 83.69; H, 7.02. Found: C, 84.03; H, 7.04.

5,11-Diphenyl-25,26,27,28-tetrahydroxycalix[4]arene (11). A solution of 0.250 g of **5b** in 10 mL of toluene was heated to 80 °C in an atmosphere of N_2. When all of the starting material had dissolved, 0.29 g (1.5 molar equiv/OH group) of $AlCl_3$ was added, and refluxing was continued 1 h to give a deep orange solution. This was poured into 25 mL of ice-cold 20% HCl and worked up in conventional fashion to give a pale yellow solid which was purified by flash chromatography (6:1 hexane/acetone as the eluent) followed by two recrystallizations from CH_2Cl_2/C_2H_5OH to give 0.136 g (65%) of a colorless powder: mp 276–277 °C (shrink at 180 °C); IR (KBr) 3180 (OH stretching), 875 (1,2,3,5-tetrasubstituted Ar), 755 cm^{-1} (1,2,3-trisubstituted Ar); ^1H NMR

(20) Mozingo, R. "Organic Syntheses"; Wiley: New York, 1955; Collect. Vol. 3; p 181.

($CDCl_3$) δ 10.23 (s, 2, OH), 7.32–6.80 (m, 9, Ar H), 3.95 (br, 4, CH_2); R_f (acetone/petroleum ether, 2:7) 0.55.

Anal. Calcd for $C_{40}H_{32}O_4$: C, 83.30; H, 5.60. Found: C, 83.47; H, 5.79.

5,11-Diphenyl-17,23-di-*tert*-butyl-25,26,27,28-tetraacetoxycalix[4]arene (10). A solution of 2.27 g of **5b** in 150 mL of acetic anhydride was treated with a small drop of concentrated H_2SO_4 and refluxed 5 h. The reaction mixture was poured into 800 mL of ice-cold water and kept in a refrigerator for 2 days, and the solid material was then separated by filtration, washed, and dried. The dark brown residue was dissolved in 50 mL of $CHCl_3$ and decolorized with charcoal, the $CHCl_3$ was then removed by evaporation, and the residue was submitted to flash chromatography (11:2 hexane/acetone as the eluent) to yield three isomers of **10**.

Isomer A of 10 was obtained as 1.016 g (36%) of a white powder after recystallization from 95% C_2H_5OH: mp 314–316 °C (shrinks at 263 °C); IR (KBr) 1750 cm^{-1} (C=O stretching); ^1H NMR ($CDCl_3$) δ 7.51–7.03 (m, 9, Ar H), 3.89–3.79 (m, 4, CH_2), 1.56 (s, 3, $OCOCH_3$), 1.38 (s, 3, $OCOCH_3$), 1.27 (s, 9, $C(CH_3)_3$); R_f (acetone/petroleum ether, 2:7) 0.61.

Anal. Calcd for $C_{56}H_{56}O_8$: C, 78.47; H, 6.60. Found: C, 78.78; H, 6.68.

Isomer B of 10 was isolated as 0.181 g (6%) of a white powder after recrystallization from aqueous ethanol: shrinks at 252 °C; turns orange at 260 °C, completely melts at 335 °C; IR (KBr) 1755 cm^{-1} (C=O stretching); ^1H NMR ($CDCl_3$) δ 7.48–7.07 (m, 18, Ar H), 3.90 (br, 4, CH_2), 3.61 (s, 2, CH_2), 3.47 (s, 2, CH_2), 1.66 (s, 3, $OCOCH_3$), 1.37 (s, 18, $C(CH_3)_3$), 1.32 (s, 6, $OCOCH_3$), 1.10 (s, 3, $OCOCH_3$); R_f (acetone/petroleum ether, 2:7) 0.55.

Anal. Calcd for $C_{56}H_{56}O_8 \cdot CH_3CO_2H$: C, 75.94; H, 6.61. Found: C, 75.90; H, 6.49.

Isomer C of 10 was isolated at 0.966 g (34%) of a white powder after recrystallization from 95% ethanol: mp 293–295 °C (shrink at 286 °C); IR (KBr) 3480 (OH stretching from occluded ethanol), 1755 cm^{-1} (C=O stretching); ^1H NMR ($CDCl_3$) δ 7.50–7.65 (m, 18, Ar H), 3.75–3.30 (m, 8, CH_2), 2.36 (s, 3, $OCOCH_3$), 2.24 (s, 3, $OCOCH_3$), 1.86 (s, 6, $OCOCH_3$), 1.41 (s, 9, $C(CH_3)_3$), 0.96 (d, 9, $C(CH_3)_3$); R_f (acetone/petroleum ether, 2:7) 0.51.

Anal. Calcd for $C_{56}H_{56}O_8 \cdot 0.5C_2H_5OH$: C, 77.78; H, 6.77. Found: C, 77.84; H, 6.78.

5,11-Bis(*p*-acetylphenyl)-17,23-di-*tert*-butyl-25,26,27,28-tetraacetoxycalix[4]arene (12). A mixture of 0.705 g of isomer A of **10** and 2.5 mL of acetyl chloride in 25 mL of CS_2 contained in a reaction flask filled with N_2 was treated with a total of 1.0 g of anhydrous $AlCl_3$, added in several portions. The mixture was refluxed overnight, and the red solution was then treated with 200 mL of cold, dilute HCl, and 200 mL of H_2O and worked up in conventional fashion to give 0.640 g (83%) of crude material as an orange powder. This was dissolved in a 2:1 mixture of $CHCl_3$/hexane, placed on a 20 × 40 mm column of silica gel, and eluted with a 3:1 mixture of petroleum ether (bp 35–60 °C) and acetone, and the residue from the evaporation of the eluate was then recrystallized from 95% ethanol to give 0.545 g (71%) of **12** as a very pale yellow powder: mp 323–325 °C (shrinks at 320 °C); IR (KBr) 3480 (ethanol OH stretching), 1740 ($OCOCH_3$ stretching, 1675 ($COCH_3$ stretching), 832 cm^{-1} (1,4-disubstituted Ar); ^1H NMR ($CDCl_3$) δ 8.08–7.02 (m, 168 Ar H), 3.83 (m, 8, CH_2), 2.61 (s, 6, $COCH_3$), 1.59 (d, 6, $OCOCH_3$), 1.37 (s, 6, $OCOCH_3$), 1.28 (s, 18, $C(CH_3)_3$); R_f (acetone/petroleum ether, 3:7) 0.40.

Anal. Calcd for $C_{60}H_{60}O_{10} \cdot C_2H_5OH$: C, 75.42; H, 6.75. Found: C, 75.55; H, 6.31.

5-(*p*-Acetylphenyl)-11-(*p*-acetoxyphenyl)-17,23-di-*tert*-butyl-25,26,27,28-tetraacetoxycalix[4]arene (13). To a solution of 0.212 g (0.22 mmol) of **12** in 3 mL of $CHCl_3$ was added a solution of 0.160 g (0.93 mmol) of *m*-chloroperbenzoic acid in 4 mL of $CHCl_3$. The mixture was stirred for 24 h at 55 °C, washed with aqueous $NaHCO_3$ and water, dried, and evaporated to leave a solid which was subjected to flash chromatography (2:7 acetone/hexane as the eluent) followed by recrystallization from 95% ethanol to give 0.076 g (35%) of **13** as a colorless powder: mp 306–308 °C dec; IR (KBr) 1750 ($OCOCH_3$ stretching), 1680 cm^{-1} ($COCH_3$ stretching); ^1H NMR ($CDCl_3$) δ 8.10–7.03 (m, 16, Ar H), 3.81 (m, 8, CH_2), 2.61 (s, 3, $COCH_3$), 2.30 (s, 3, $OCOCH_3$), 1.55 (s, 6, $OCOCH_3$), 1.36 (s, 6, $OCOCH_3$), 1.27 (s, 18, $C(CH_3)_3$); R_f (acetone/hexane, 3:7) 0.46.

Anal. Calcd for $C_{60}H_{60}O_{11} \cdot 0.5C_2H_2OH$: C, 74.73; H, 6.49. Found: C, 74.60; H, 6.50.

Miscellaneous Experiments. 2-(5-Phenylsalicyl)-4-phenylphenol. A mixture of 20.0 g of *p*-phenylphenol and 1.76 g of paraformaldehyde in 200 mL of xylene was heated to 70 °C, treated with 15 mL of concentrated HCl, and heated for 15 h. To the cooled reaction mixture was added a small amount of ether to bring the contents into solution, and the xylene–ether solution was washed, dried, and concentrated to yield 5.0 g of *p*-phenylphenol. The remaining solvent was evaporated, and the residue was flash chromatographed (7:2 hexane/acetone as the eluent) to yield a fraction which, after recrystallization from toluene/petroleum ether (bp 35–60 °C), consisted of 6.35 g (41%) of product as a colorless powder: mp 157–158 °C; IR (KBr) 3260 (OH stretching), 880 (1,2,3,5-tetrasubstituted Ar), 820 cm^{-1} (1,2,4-trisubstituted Ar); ^1H NMR (acetone-d_6) δ 7.53–6.83 (m, 8, Ar H), 4.06 (s, 1, CH_2), 3.65 (br, 1, OH); osmometric mol wt ($CHCl_3$, 37 °C), 367 (calcd 352); R_f (petroleum ether/acetone, 3:1) 0.28.

Anal. Calcd for $C_{25}H_{20}O_2$: C, 85.20; H, 5.72. Found: C, 85.23; H, 5.67.

Also isolated from the flash chromatography was the corresponding linear trimer **2-[3-(5-phenylsalicyl)-5-phenylsalicyl]-4-phenylphenol** as a colorless powder after recrystallization from petroleum ether (bp 35–60 °C)/toluene: mp 193–195 °C; IR (KBr) 3210 (OH stretching), 880 (1,2,3,5-tetrasubstituted Ar), 820 cm^{-1} (1,2,4-trisubstituted Ar); ^1H NMR (acetone-d_6) δ 7.44–6.85 (m, 23, Ar H), 4.08 (s, 4, CH_2), 3.53 (br, 3, OH); osmometric mol wt ($CHCl_3$, 37 °C), 507 (calcd 534); R_f (petroleum ether/acetone, 3:1) 0.17.

Anal. Calcd for $C_{38}H_{30}O_3$: C, 85.37; H, 5.65. Found: C, 85.59; H, 5.68.

2-(Hydroxymethyl)-4-phenylphenol and 2,6-Bis(hydroxymethyl)-4-phenylphenol. A mixture of 15.32 g of *p*-phenylphenol and 150 mL of 37% formaldehyde was cooled, treated slowly with 20.4 g of KOH, and stirred for 1.5 days at room temperature. The crude product, a yellow waxy solid, was separated by flash chromatography into fractions containing *p*-phenylphenol, the monohydroxymethyl compound, and the bis(hydroxymethyl) compound. The former was obtained as 4.33 g (24%) of colorless needles after recrystallization from $CHCl_3$/hexane: mp 154–155 °C; IR (KBr) 3420 (OH stretching), 825 cm^{-1} (1,2,4-trisubstituted Ar); ^1H NMR (acetone-d_6) δ 7.56–6.83 (m, 4, Ar H), 4.81 (s, 1, CH_2), 3.45 (br, 1, OH); R_f (petroleum ether/acetone, 3:1) 0.20. The latter was obtained as 7.29 g (35%) of colorless needles: mp 116–117 °C; IR (KBr) 3360 (OH stretching), 873 cm^{-1} (1,2,3,5-tetrasubstituted Ar); ^1H NMR (acetone-d_6) δ 7.78–7.18 (m, 7, Ar H), 4.80 (s, 4, CH_2), 4.10 (br, 3, OH); R_f (ether/hexane, 7:3), 0.30.

Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 73.45; H, 6.20.

Registry No. 2, 81535-94-6; **3a**, 81535-95-7; **3b**, 81535-96-8; **4a**, 81535-91-3; **4b**, 81535-97-9; **5a**, 60705-63-7; **5b**, 81535-98-0; **6**, 81535-89-9; **7**, 81535-99-1; **8**, 81535-90-2; **9**, 81536-00-7; **10**, 81536-01-8; **11**, 81536-02-9; **12**, 81536-03-0; **13**, 81536-04-1; *p*-phenylphenol, 92-69-3; *p*-*tert*-butylphenol, 98-54-4; 3-[3-[3-[3-(hydroxymethyl)-5-*tert*-butylsalicyl]-5-phenylsalicyl]phenylsalicyl]-5-*tert*-butyl-2-hydroxybenzyl alcohol, 81536-05-2; 2-(5-phenylsalicyl)-4-phenylphenol, 7408-65-3; 2-[3-(5-phenylsalicyl)-5-phenylsalicyl]-4-phenylphenol, 81536-06-3; 2-(hydroxymethyl)-4-phenylphenol, 21140-36-3; 2,6-bis(hydroxymethyl)-4-phenylphenol, 3173-26-0; formaldehyde, 50-00-0.