# Calix[4]arenes with Four Differently Substituted Phenolic Units

Volker Böhmer,*† Frank Marschollek,† and Lucia Zetta‡

*Institut für Organische Chemie, Universität Mainz, D-6500 Mainz, Germany, and Istituto di Chimica delle Macromolecole del CNR I-20133 Milano, Italy*

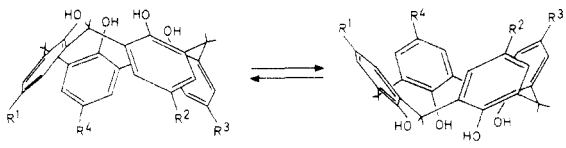
*Received November 14, 1986*

All three isomeric calix[4]arenes (**9a-c**) with the four different substituents $CH_3$, $C(CH_3)_3$, $C_6H_5$, and $COOC_2H_5$ in the para position were synthesized by an unequivocal reaction sequence. Starting with a para-substituted *o*-bromophenol it consists of two alternating bromomethylation (**1** → **2**, **3** → **4**) and condensation steps (**2** → **3**, **4** → **5**), followed by the hydrogenolytic elimination (**5** → **6**) of the protecting bromine atom. This linear trimer (**6**) with two reactive ortho positions is cyclized by condensation with a suitable bis(bromomethyl)phenol (**8**) in dioxane, using $TiCl_4$ as catalyst. In a similar way three further calix[4]arenes with four (**9d**) or three (**9e,f**) different phenolic units were prepared. The cone conformation of all these molecules is chiral, and thus, the separation into enantiomeric derivatives should be possible, if the cone conformation is fixed in a suitable way.

Cyclic compounds, consisting of several (usually four to eight) phenolic units which are connected by methylene bridges have attracted increasing interest during the last decade.[1] Since they have a cuplike conformation, which is confirmed by X-ray analysis for several examples with four[2-5] (and also one example with five[6]) phenolic units, they were named calixarenes by Gutsche.[1] This structure should enable them to include other molecules (or ions) in their cavity, making calixarenes or suitable derivatives potentially useful as enzyme mimics. Indeed the formation of inclusion complexes with neutral molecules like toluene[2] or anisole[5] was reported for the solid state, and the interaction of *p*-allylcalix[4]arene with *tert*-butylamine in acetonitrile obviously leads to complexation inside of the cavity, too.[7] Recently the first examples of an enzyme like catalysis by derivatives of calix[6]arenes were found.[8,9]

One of the most important features of enzymes is their ability to catalyze enantioselective reactions. The first step to imitate this behavior consists of chiral recognition. Therefore numerous examples of chiral macrocyclic host molecules have already been described. Mostly enantiomeric building blocks were used, which are incorporated as "chiral subunits" into the host molecule, e.g., amino acids,[10] tartaric acid derivatives,[11] binaphthyl[12] or biphenanthryl derivatives,[13] spiro compounds,[14] trans-substituted THF units,[15] and even more complicated fragments.[12,16] Thus, the chirality of the whole macrocyclic molecule is caused by a chiral part of its structure. However, a nonchiral linear molecule may become chiral in its cyclic analogue, too.[17] Such is the case with the calix[4]arenes, which are the subject of this paper.

The molecules of calix[4]arenes are not planar, rather they always exist (nearly) exclusively in the so-called cone conformation.[1] If calix[4]arenes consist of three different phenolic units in the order A-A-B-C or of four different phenolic units, the molecule has no symmetry plane, and the cone conformation (as well as any other potential conformation) is chiral. Temperature-dependent $^1H$ NMR spectra have shown that a rapid interconversion of the various conformers occurs at room temperature.[18] For chiral calix[4]arenes this means racemization, since one cone conformation is the mirror image of the other cone conformation (eq 1). Therefore a separation into enantiomers is impossible, unless the conformation is "fixed". This is possible by the introduction of bulky substituents at the phenolic hydroxy groups, which cannot penetrate through the annulus. Indeed the cone conformation is fixed in most of the known derivatives which are obtained by reaction of the phenolic hydroxy group, e.g., ethers[19] or esters.[19,20] (Only few examples are reported in which the partial cone[21] or the 1,3-alternate conformation[22] are fixed by derivatization.) Thus, it should be possible to obtain enantiomeric host molecules having an "enforced cavity"[23] from calix[4]arenes with differently substituted



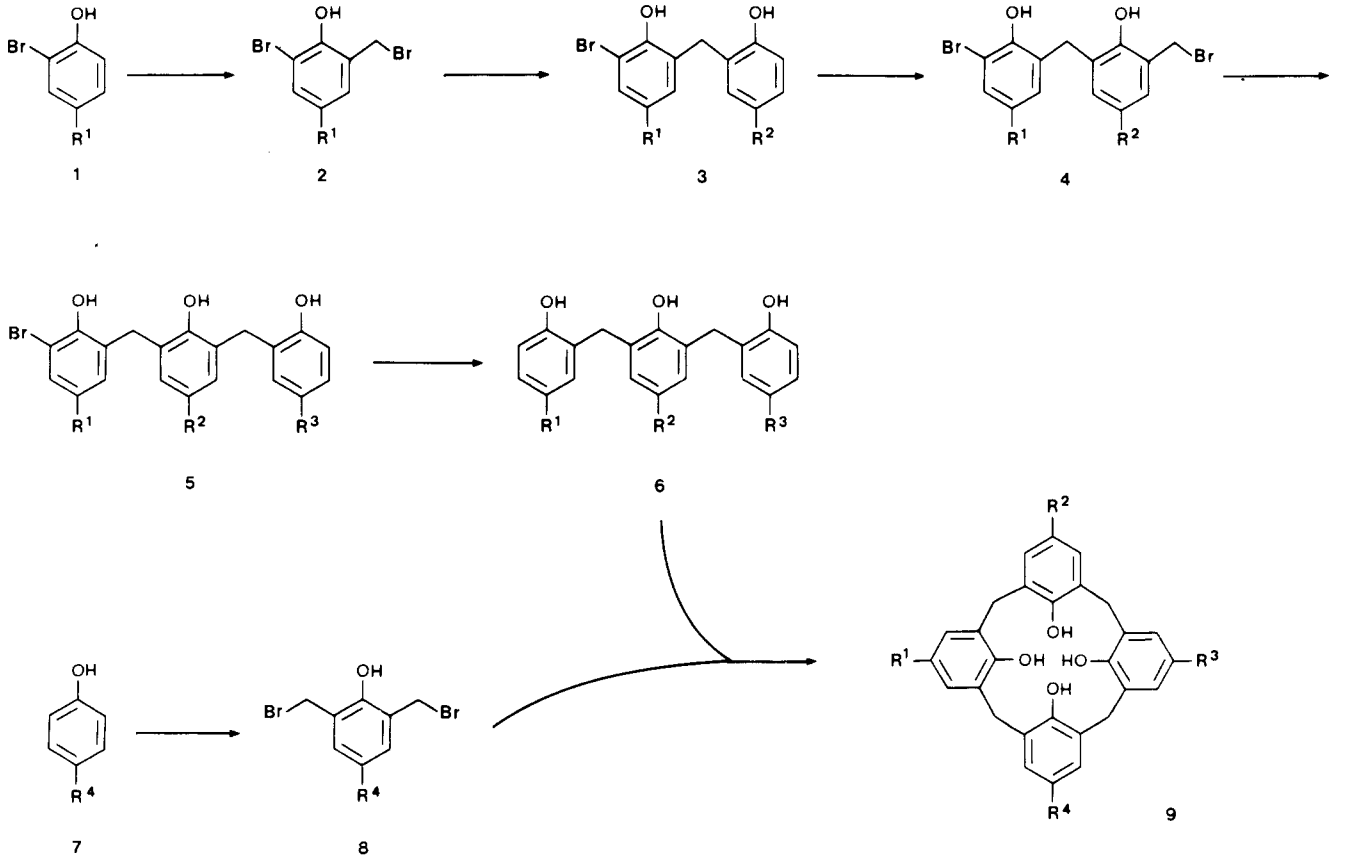

(1)

† Universität Mainz.
‡ Istituto di Chimica delle Macrmolecole del CNR.

(1) For reviews, see: Gutsche, C. D. *Acc. Chem. Res.* **1983**, *16*, 161; *Top. Curr. Chem.* **1984**, *123*, 1.
(2) Andreetti, G. D.; Ungaro, R.; Pochini, A. *J. Chem. Soc., Chem. Commun.* **1979**, 1005.
(3) Andreetti, G. D.; Pochini, A.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1773.
(4) Ungaro, R.; Pochini, A.; Andreetti, G. D.; Sangermano, V. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1979.
(5) Ungaro, R.; Pochini, A.; Andreetti, G. D.; Domiano, P. *J. Chem. Soc., Perkin Trans. 2* **1985**, 197.
(6) Coruzzi, M.; Andreetti, G. D.; Bocchi, V.; Pochini, A.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1133.
(7) Bauer, L. J.; Gutsche, C. D. *J. Am. Chem. Soc.* **1985**, *107*, 6063.
(8) Shinkai, S.; Koreishi, H.; Mori, S.; Sone, T.; Manabe, O. *Chem. Lett.* **1985**, 1033.
(9) Shinkai, S.; Mori, S.; Koreishi, H.; Tsubaki, T.; Manabe, O. *J. Am. Chem. Soc.* **1986**, *108*, 2409.
(10) DeVries, J. G.; Kellogg, R. M. *J. Am. Chem. Soc.* **1979**, *101*, 2759.
(11) Dhaenens, M.; Lacombe, L.; Lehn, J.-M.; Vigneron, J.-P. *J. Chem. Soc., Chem. Commun.* **1984**, 1097.
(12) Artz, S. P.; deGrandpre, M. P.; Cram, D. J. *J. Org. Chem.* **1985**, *50*, 1486.
(13) E.g.: Yamamoto, K.; Noda, K.; Okamoto, Y. *J. Chem. Soc., Chem. Commun.* **1985**, 1065.
(14) Dobler, M.; Dumic, M.; Egli, M.; Prelog, V. *Angew. Chem.* **1985**, *97*, 793.
(15) Naemura, K.; Ebashi, I.; Matsuda, A. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3057.
(16) Canceill, J.; Lacombe, L.; Collet, A. *J. Am. Chem. Soc.* **1985**, *107*, 6993.
(17) E.g.: Canceill, J.; Collet, A.; Gottarelli, G. *J. Am. Chem. Soc.* **1984**, 106, 5997 and references cited therein.
(18) (a) Happel, G.; Mathiasch, B.; Kämmerer, H. *Makromol. Chem.* **1975**, *176*, 3317. (b) Gutsche, C. D.; Bauer, L. J. *J. Am. Chem. Soc.* **1985**, 107, 6052.
(19) (a) Gutsche, C. D.; Levine, J. A. *J. Am. Chem. Soc.* **1982**, *104*, 2652. (b) Arduini, A.; Pochini, A.; Reverberi, S.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1984**, 981.
(20) Gutsche C. D.; Levine, J. A.; Sujeeth, P. K. *J. Org. Chem.* **1985**, *50*, 5802.
(21) Rizzoli, C.; Andreetti, G. D.; Ungaro, R.; Pochini, A. *J. Mol. Structure* **1982**, *82*, 133.
(22) Gutsche, C. D.; Dhawan, B.; Levine, J. A.; No, K. H.; Bauer, L. J. *Tetrahedron* **1983**, *39*, 409.
(23) Moran, J. R.; Karbach, S.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 5826.

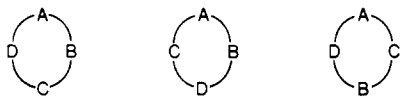
0022-3263/87/1952-3200$01.50/0 

**Scheme I**



**2a**, $R^1 = C_6H_5$
**3a**, $R^1 = C_6H_5$, $R^2 = C(CH_3)_3$
**4a**, $R^1 = C_6H_5$, $R^2 = C(CH_3)_3$
**4b**, $R^1 = CH_3$, $R^2 = C(CH_3)_3$
**5a**, $R^1 = C_6H_5$, $R^2 = C(CH_3)_3$, $R^3 = COOC_2H_5$
**5b**, $R^1 = C_6H_5$, $R^2 = C(CH_3)_3$, $R^3 = CH_3$
**5c**, $R^1 = CH_3$, $R^2 = C(CH_3)_3$, $R^3 = COOC_2H_5$
**5d**, $R^1 = CH_3$, $R^2 = C(CH_3)_3$, $R^3 = C_6H_{11}$
**6a**, $R^1 = C_6H_5$, $R^2 = C(CH_3)_3$, $R^3 = COOC_2H_5$
**6b**, $R^1 = C_6H_5$, $R^2 = C(CH_3)_3$, $R^3 = CH_3$
**6c**, $R^1 = CH_3$, $R^2 = C(CH_3)_3$, $R^3 = COOC_2H_5$
**6d**, $R^1 = CH_3$, $R^2 = C(CH_3)_3$, $R^3 = C_6H_{11}$
**6e**, $R^1 = CH_3$, $R^2 = CH_3$, $R^3 = C(CH_3)_2CH_2C(CH_3)_3$
**8a**, $R^4 = COOC_2H_5$
**8b**, $R^4 = C_6H_5$
**9a**, $R^1 = C_6H_5$, $R^2 = C(CH_3)_3$, $R^3 = COOC_2H_5$, $R^4 = CH_3$
**9b**, $R^1 = C_6H_5$, $R^2 = C(CH_3)_3$, $R^3 = CH_3$, $R^4 = COOC_2H_5$
**9c**, $R^1 = CH_3$, $R^2 = C(CH_3)_3$, $R^3 = COOC_2H_5$, $R^4 = C_6H_5$
**9d**, $R^1 = CH_3$, $R^2 = C(CH_3)_3$, $R^3 = C_6H_{11}$, $R^4 = C_8H_{17}$
**9e**, $R^1 = CH_3$, $R^2 = CH_3$, $R^3 = C(CH_3)_2CH_2C(CH_3)_3$, $R^4 = C_6H_{11}$
**9f**, $R^1 = CH_3$, $R^2 = CH_3$, $R^3 = C(CH_3)_2CH_2C(CH_3)_3$, $R^4 = Cl$

phenolic units. It is the aim of this paper to demonstrate a possible way to prepare calix[4]arenes built up by four different phenolic units. In this case there also exist three structural isomers:



There is evidence that during the usual "one-pot" synthesis of *tert*-butylcalix[4]arenes arylmethylene links are cleaved again;[24] the calix[4]arene may be obtained even from the calix[8]arene as starting material.[25] Any "exchange" of phenolic units (or substituents) during the synthesis, however, would lead to a mixture of these isomers, while the preparation of the different isomers (free from each other) proves the absence of those side reactions.

**Synthesis of Calixarenes.** The general principle of the synthetic pathway is illustrated in the Scheme I. It will be discussed in some detail for the preparation of **9a**.

By direct reaction of 2-bromo-4-phenylphenol with paraformaldehyde and gaseous hydrogen bromide in glacial acetic acid the bromomethyl derivative **2a** was obtained. The yield of 42% of pure product may be increased by a more careful elaboration of the reaction conditions.

Condensation of **2a** with an excess of *p-tert*-butylphenol to suppress the substitution of the second ortho position led to the methylenediphenol **3a** with 64% yield of the pure product. This condensation may be done without solvent or in toluene at temperatures of 70–90 °C and does not need a catalyst. The excess phenol is easily removed by steam distillation.

**3a** was bromomethylated again in acetic acid to give 71% of pure **4a**. (**4b** was obtained in the same way with 75% yield from the corresponding dimer.)

**4a** was reacted with an excess of molten *p*-hydroxybenzoic acid ethyl ester at 120 °C. After removal of the excess hydroxybenzoate by dissolution in boiling ethanol the trimer **5a** was obtained with 72% yield. (Condensation of **4a** with an excess of *p*-cresol led to **5b** and the reaction of **4b** with *p*-hydroxybenzoic acid ethyl ester or *p*-cyclohexylphenol to the trinuclear compounds **5c** and **5d**. The yield of 50–70% may be increased by optimizing the isolation and purification.)

The elimination of the bromine is possible by hydrogenolysis in a methanolic solution of potassium hydroxide under very smooth conditions (room temperature, normal

(24) Gutsche, C. D.; Iqbal, M.; Stewart, D. *J. Org. Chem.* **1986**, *51*, 742.
(25) Attempts to prepare calix[5]arenes by condensation of a trinuclear compound with a bisbromomethylated dinuclear compound under the reaction conditions described in this paper also led to the isolation of calix[4]arenes, indicating the cleavage of methylene bridges.

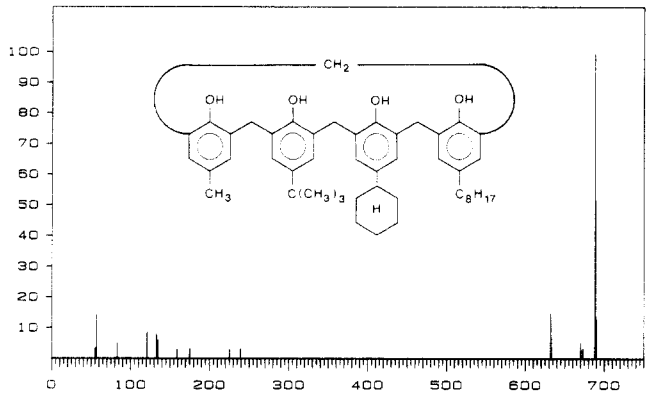



**Figure 1.** Electron impact mass spectrum (70 eV) of calixarene **9d**.

pressure).[26] Thus, **6a** is obtained in 75% yield from **5a**. (Compounds **6b–d** were prepared in the same way by hydrogenation of **5b–d**, the yield of pure product being generally in the range of 75–80%. **6e** was prepared directly by condensation of 3-(5-methylsalicyl)-2-hydroxy-5-methylbenzyl alcohol,[27] which was present from other experiments, with an excess of *p-tert*-octylphenol in 65% yield.)

This bisbromomethylated phenols **8** were usually prepared by direct bromomethylation[28] in acetic acid similar to the preparation of **2a**. This procedure failed in the preparation of **8a**, where only the monobromomethylated compound could be obtained. However, **8a** was obtained from the corresponding bishydroxymethylated compound[29] by reaction with HBr in acetic acid, a reaction also used in the synthesis of **8b**.

The ring-closure reaction of compound **8** with the trimer **6** was formerly carried out under high-dilution conditions in boiling acetic acid without catalyst.[30] Better yields were obtained now by condensation in boiling dioxane in the presence of $TiCl_4$,[31] and further optimization of the reaction conditions seems possible. The isolation and purification of the calixarenes was done by flash chromatography.[32] Thus, from bis(bromomethyl)-*p*-cresol and **6a** the calixarene **9a** was obtained in 6.4% yield.

Similarly the isomeric compounds **9b** and **9c** were obtained by condensation of **6b** with **8a** and **6c** with **8b**. The yield of pure product, 8.8% and 7.4%, respectively, was in the same range in these cases. A somewhat higher yield was achieved for **9d** (from **6d** and bis(bromomethyl)-*p*-octylphenol, 14% of pure product) and **9f** (from **6e** and bis(bromomethyl)-*p*-cyclohexylphenol, **12**% of pure product), while the condensation of **6e** with bis(bromomethyl)-*p*-chlorophenol yielded only 3% of pure **9e**. Although the isolation and purification procedure may influence the final yield, it seems that best results in the cyclization step are obtained in those cases where the parasubstituents of **8** and of the external rings of **6** are alkyl groups. Electron-withdrawing substituents like chlorine or carbethoxy probably decrease the yield.

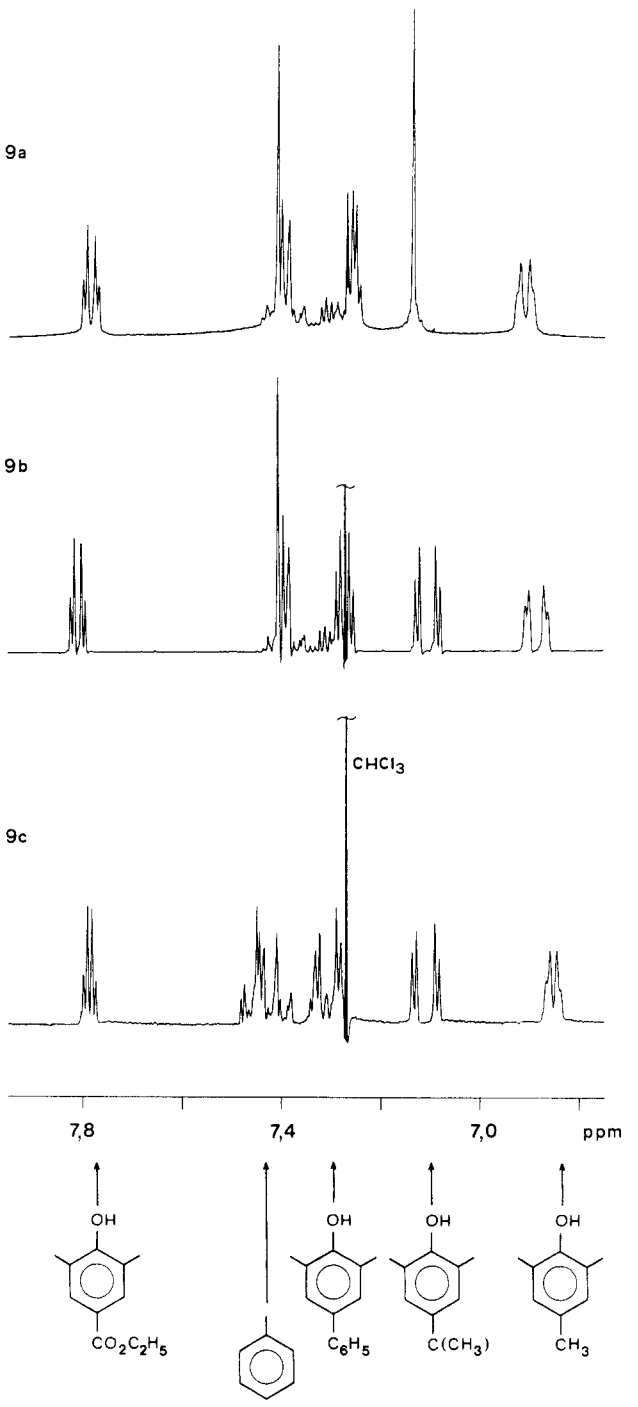



**Figure 2.** Aromatic region of the 270-MHz $^1H$ NMR spectra of the isomeric calixarenes **9a–c** in $C^2HCl_3$. The blackened signals are from the isotopic impurity $CHCl_3$.

**Properties.** The isomeric calixarenes **9a–c** show remarkable differences in their melting points, which range from 185–190 (**9c**) to 270 (**9b**) to 368 °C (**9a**). However, their chromatographic behavior is very similar. It was impossible to separate mixtures of them by TLC, and by HPLC a mixture of the three compounds was split only into two peaks, compounds **9b** and **9c** remaining unseparated.

The electron impact mass spectra are very suitable to prove the general composition of calixarenes, because in all cases (**9a–f**) the molecular ion is also the base peak and fragmentation is not often observed. Figure 1 shows for example the mass spectrum of **9d**, which has the highest molecular mass of all the calixarenes described here. Thus,

(26) Kämmerer, H.; Happel, G.; Böhmer, V. *Org. Prep. Proced. Int.* **1976**, *8*, 245.
(27) This compound can be obtained by hydrogenation of 3-(3-bromo-5-methylsalicyl)-2-hydroxy-5-methylbenzyl alcohol. Normally it would be preferable, however, to synthesize in the first step 2-[3-(3-bromo-5-methylsalicyl)-5-methylsalicyl]-4-*tert*-octylphenol by condensation with excess *p-tert*-octylphenol, which on hydrogenation gives **6e**.
(28) Bright, W. M.; Cammarata, R. *J. Am. Chem. Soc.* **1952**, *74*, 3690.
(29) Zinke, A.; Ott, R.; Leggewie, E.; Hassanein, A.; Zankl, G. *Monatsh. Chem.* **1956**, *87*, 552.
(30) Böhmer, V.; Chhim, Ph.; Kämmerer, H. *Makromol. Chem.* **1979**, *180*, 2503.
(31) Böhmer, V.; Goldmann, H.; Vogt, W. *J. Chem. Soc., Chem. Commun.* **1985**, 667.
(32) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Table I. $^1$H NMR Chemical Shifts (in ppm) of the Aromatic Protons in the Phenolic Rings, Substituted in the Para Position by X

| X | compound | | | |
|---|---|---|---|---|
| | $C_6H_5X$[35] | 9a | 9b | 9c |
| $CH_3$ | 7.06 | 6.90 | 6.88 | 6.84 |
| | | 6.93 | 6.91 | 6.86 |
| $C(CH_3)_3$ | 7.29 | 7.14 | 7.09 | 7.09 |
| | | | 7.13 | 7.13 |
| $C_6H_5$ | 7.48 | 7.25 | 7.27 | 7.29 |
| | | 7.26 | 7.29 | 7.33 |
| $COOC_2H_5$ | 7.97 | 7.78 | 7.81 | 7.78 |
| | | 7.80 | 7.83 | 7.79 |

if during the synthesis of a calixarene with four phenolic units ABCD a cleavage of methylene bridges and a regrouping of phenolic units occured, "wrong calixarenes" like AACD or BBCD would most probably be detected in the mass spectra.

However, the mass spectra cannot a priori distinguish the isomeric compounds **9a–c**. This can be done by their NMR spectra, especially in the aromatic region, which is shown in Figure 2. Owing to the intrinsic asymmetry of the three molecules, the two aromatic protons of each phenolic ring are magnetically nonequivalent. Hence, we find four AB systems at about 6.9, 7.1, 7.3, and 7.8 ppm. Only in compound **9a** does the AB system at 7.1 ppm become a "deceptively simple (single-line) AB spectrum". The resonance assignment of the four AB systems was obtained by using as reference the chemical shifts of the protons in ortho position to the substituent X in the model compounds $C_6H_5X$ (see Table I). The lines of the AB system around 6.9 ppm, deriving from the aromatic protons in ortho position to the methyl group, are broader than those of the other AB systems, owing to the extra splitting caused by the long-range coupling with the methyl protons ($^4J < 1$ Hz).[33] The spread multiplet at about 7.45 ppm (five-proton intensity) was assigned to the protons of the phenyl ring (X = $C_6H_5$).

Thus, by comparison of their $^1$H NMR spectra the three isomeric calixarenes can easily be distinguished among each other on the basis of the different chemical shifts. In addition, no contaminations are detected, especially no contaminations of one isomer by the other isomers.

The synthetic pathway, outlined in Scheme I therefore represents a general possibility to prepare asymmetrically substituted calix[4]arenes of the type AABC or ABCD in a definite way, while the only example known up to now (type AABC)[34] was obtained more or less fortuitously from AABB by incomplete conversion of the phenolic units B into C. Since already many different derivatives of calix[4]arenes with a fixed cone conformation are described, a large variety of chiral host molecules having an enforced cavity will be available in this way.

## Experimental Section

The melting points of calixarenes were taken in sealed capillary tubes under argon and all other melting points in the usual way. The values reported are uncorrected.

$^1$H NMR spectra normally were recorded on a Bruker WH-90 spectrometer (90 MHz). Those of the calixarenes **9a–f** were obtained with a Bruker AM 270 spectrometer (270 MHz), controlled by an Aspect 3000. The concentration of the solutions was in the range of 10–20 (90 MHz), and 1–2 mmol/L (270 MHz), respectively. Chemical shifts are reported as $\delta$ values in ppm relative to tetramethylsilane as an internal standard.

Electron impact mass spectra were recorded on a CH 7 A, Varian MAT, at 70 eV. Besides the molecular ion, only the most characteristic peaks are reported.

The calixarenes **9a–f** as isolated were not 100% combusted in elemental analysis, suggesting inorganic contaminants (2–3%) probably present from the chromatographic separation. When the combustion analysis is corrected for the noncombustibles, the calculated values for C, H, O and Cl are within the acceptable experimental error. No impurities could be detected by the NMR spectra and by TLC analyses.

Thin-layer chromoatographic analyses were carried out on silica gel plates of 0.25-mm thickness. For flash chromatography, silica gel (E. Merck, 230–400 mesh ASTM) was used in columns of 30 mm in diameter filled to a height of about 20 cm.

**2-Bromo-6-(bromomethyl)-4-phenylphenol (2a).** Gaseous hydrogen bromide was passed rapidly through a suspension of 19.5 g (78 mmol) of *o*-bromo-*p*-phenylphenol (1) and 2.7 g (90 mmol) of paraformaldehyde in 50 mL of acetic acid for about 20 min. With initial warming, a dark solution was formed, from which the reaction product slowly precipitated. After 20 h the whole mixture formed a crystalline slurry, which was filtered by suction. The product was dissolved in boiling toluene (with the addition of charcoal), filtered, and reprecipitated by addition of petroleum ether and cooling to yield 11.2 g (42%) of **2a**: mp 106 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.60–7.29 (m, 7, Ar H, 1, OH), 4.60 (s, 2, $CH_2Br$); MS, *m/e* 344, 342, 340 ($M^+$), 263, 261 ($M^+$ – Br). Anal. Calcd for $C_{13}H_{10}Br_2O$: C, 45.65; H, 2.95; Br, 46.72. Found: C, 45.60; H, 3.01; Br, 46.73.

**2-(3-Bromo-5-phenylsalicyl)-4-*tert*-butylphenol (3a). 2a** (10.0 g, 30 mmol) was added with stirring to a solution of 25.0 g (0.16 mol) of 4-*tert*-butylphenol in 100 mL of toluene at 70 °C during 1 h. The reaction was continued for 8 h at 90 °C. After steam distillation the residue was recrystallized from $CHCl_3$/petroleum ether, to yield 7.6 g (64%) of **3a** as white crystals: mp 116 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.57–6.74 (m, 10, Ar H), 6.56 (br s, 1, OH), 6.13 (br s, 1, OH), 4.02 (s, 2, $CH_2$), 1.20 (s, 9, $C(CH_3)_3$); MS, *m/e* 412, 410 ($M^+$), 397, 395 ($M^+ - CH_3$). Anal. Calcd for $C_{23}H_{23}BrO_2$: C, 67.16; H, 5.64; Br, 19.43. Found: C, 66.98; H, 5.74; Br, 19.45.

**2-(3-Bromo-5-phenylsalicyl)-4-*tert*-butyl-6-(bromomethyl)phenol (4a).** Gaseous hydrogen bromide was passed through a suspension of 12.0 g (30 mmol) of **3a** and 1.2 g (40 mmol) of paraformaldehyde in acetic acid for about 2 h. A solution was formed, which was extracted twice with 100 mL of boiling petroleum ether. After clarification with charcoal the etheral solution was evaporated and the residual red, viscous oil dissolved in 100 mL of cyclohexane. On cooling by an ice/salt mixture the product slowly separated in the form of white crystals, 10.8 g (71%): mp 89 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.57–6.92 (m, 9, Ar H), 6.56 (br s, 1, OH), 6.17 (br s, 1, OH), 4.58 (s, 2, $CH_2Br$), 4.02 (s, 2, $CH_2$), 1.27 (s, 9, $C(CH_3)_3$); MS, *m/e* 506, 504, 502 ($M^+$), 425, 423 ($M^+$ – Br). Anal. Calcd for $C_{24}H_{24}Br_2O_2$: C, 57.16; H, 4.80; Br, 31.69. Found: C, 57.32; H, 4.91; Br, 31.75.

**2-(3-Bromo-5-methylsalicyl)-4-*tert*-butyl-6-(bromomethyl)phenol (4b).** Gaseous hydrogen bromide was passed through a suspension of 16.9 g (50 mmol) of 2-(3-bromo-5-methylsalicyl)-4-*tert*-butylphenol and 2.0 g (67 mmol) of paraformaldehyde in 70 mL of acetic acid. From the dark solution a white precipitate finally separated, which was filtered by suction, washed with acetic acid, and recrystallized from toluene/petroleum ether to yield 16.6 g (75%) of **4b** in the form of white crystals: mp 117 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.24–6.80 (m, 4, Ar H), 4.50 (s, 2, $CH_2Br$), 4.25 (br s, 2, OH), 3.91 (s, 2, $CH_2$), 2.23 (s, 3, $CH_3$), 1.26 (s, 9, $C(CH_3)_3$; MS, *m/e* 444, 442, 440 ($M^+$), 363, 361 ($M^+$ – Br). Anal. Calcd for $C_{19}H_{22}Br_2O_2$: C, 51.61; H, 5.01; Br, 36.14. Found: C, 51.79; H, 4.80; Br, 36.16.

**2-[3-(3-Bromo-5-phenylsalicyl)-5-*tert*-butylsalicyl]-4-carbethoxyphenol (5a).** 4-Carbethoxyphenol (*p*-hydroxybenzoic acid ethyl ester) (20 g, 0.12 mol) was molten at 120 °C under argon. During 1 h, 10.1 g (20 mmol) of the bromomethyl compound **4a** was added with stirring, and the reaction was continued for 6 h

(33) Williamson, M. P.; Kostelnik, R. J.; Castellano, S. M. *J. Chem. Phys.* **1968**, *49*, 2218.
(34) No, K. H.; Gutsche, C. D. *J. Org. Chem.* **1982**, *47*, 2713. For further examples see also ref 36 and 37.
(35) Brügel, W. *Handbook of NMR Spectral Parameters*, Heyden: London, 1979; Vol. 1, p 33.
(36) Böhmer, V.; Merkel, L.; Kunz, U. *J. Chem. Soc., Chem. Commun.*, in press.
(37) Casabianca, H.; Satrallah, A.; Cortez-Tati, A.; Royer, J.; Vicens, J., submitted for publication in *Tetrahedron Lett.*

at 100 °C. The excess ester was removed by extracting the reaction mixture three times with boiling 20% ethanol. The residual mass solidified on cooling and was recrystallized from ethanol to yield 8.53 g (72%) of white crystals of **5a**: mp 180–182 °C; $^1$H NMR ($CDCl_3$) δ 8.01–6.80 (m, 12, Ar H, 3, OH), 4.29 (q, 2, $CH_2CH_3$, $J$ = 7 Hz), 3.99 (s, 2, $CH_2$), 3.94 (s, 2, $CH_2$), 1.35 (t, 3, $CH_2CH_3$, $J$ = 7 Hz), 1.25 (s, 9, $C(CH_3)_3$); MS, $m/e$ 590, 588 ($M^+$), 545, 543 ($M^+ - OC_2H_5$). Anal. Calcd for $C_{33}H_{33}BrO_5$: C, 67.23; H, 5.64; Br, 13.55. Found: C, 67.33; H, 5.78; Br, 13.42.

**2-[3-(3-Bromo-5-phenylsalicyl)-5-*tert*-butylsalicyl]-4-methylphenol (5b).** Bromomethyl compound **4a** (9.3 g, 18 mmol) was added during 1 h to a solution of 30 g (0.3 mol) of *p*-cresol in 100 mL of toluene at 80 °C. After 12 h at 100 °C (bath temperature), toluene and the excess *p*-cresol were removed by steam distillation. The residue was recrystallized from $CHCl_3$/petroleum ether to give 5.3 g (57%) of **5b**: mp 147–148 °C; $^1$H NMR ($CDCl_3$) δ 7.65–6.65 (m, 12, Ar H, 3, OH), 3.98 (s, 2, $CH_2$), 3.87 (s, 2, $CH_2$), 2.23 (s, 3, $CH_3$), 1.27 (s, 9, $C(CH_3)_3$); MS, $m/e$ 532, 530 ($M^+$), 517, 515 ($M^+ - CH_3$). Anal. Calcd for $C_{31}H_{31}BrO_3$: C, 70.06; H, 5.88; Br, 15.03. Found: C, 70.46; H, 6.16; Br, 15.60.

**2-[3-(3-Bromo-5-methylsalicyl)-5-*tert*-butylsalicyl]-4-carbethoxyphenol (5c).** Bromomethyl compound **4b** (6 g, 14 mmol) was added during 1 h to 25 g (0.15 mol) of molten 4-carbethoxyphenol at 120 °C. After 8 h at 120 °C the mixture was extracted three times by 100 mL of boiling ethanol (40%), and the residue was recrystallized twice from acetic acid/water to yield 3.72 g (50%) of **5c** as white crystals, mp 178 °C: $^1$H NMR ($CDCl_3$) δ 8.00–6.79 (m, 7, Ar H, 3, OH), 4.29 (q, 2, $CH_2CH_3$, $J$ = 7 Hz), 3.92 (s, 2, $CH_2$), 3.89 (s, 2, $CH_2$), 2.22 (s, 3, $CH_3$), 1.35 (t, 3, $CH_2CH_3$, $J$ = 7 Hz), 1.26 (s, 9, $C(CH_3)_3$); MS, $m/e$ 528, 526 ($M^+$), 483, 481 ($M^+ - C_2H_5$). Anal. Calcd for $C_{28}H_{31}BrO_5$: C, 63.76; H, 5.92; Br, 15.15. Found: C, 63.49; H, 5.88; Br, 14.89.

**2-[3-(3-Bromo-5-methylsalicyl)-5-*tert*-butylsalicyl]-4-cyclohexylphenol (5d).** **4b** (8 g, 18 mmol) and 53 g (0.3 mol) of *p*-cyclohexylphenol were reacted as described for **5c** (4–5 h, 130 °C). The excess of cyclohexylphenol was removed by sublimation under reduced pressure (bath temperature, 150 °C), and the residue was recrystallized from toluene to give 6.76 g (70%) of white crystals of **5d**: mp 134–135 °C; $^1$H NMR ($Me_2SO$-$d_6$) δ 7.2–6.7 (m, 7, Ar H), 3.88 (s, 2, $CH_2$), 3.81 (s, 2, $CH_2$), 2.10 (s, 3, $CH_3$), 1.8–1.2 (m, 11, $C_6H_{11}$), 1.12 (s, 9, $C(CH_3)_3$); MS, $m/e$ 538, 536 ($M^+$), 523, 521 ($M^+ - CH_3$). Anal. Calcd for $C_{31}H_{37}BrO_3$: C, 69.27; H, 6.94; Br, 14.87. Found: C, 68.90; H, 7.39; Br, 14.85.

The same condensation is possible, using instead of **4b** the corresponding hydroxymethylated compound and 10 mL of concentrated HCl as catalyst (compare the preparation of **6e**).

**2-[3-(5-Phenylsalicyl)-5-*tert*-butylsalicyl]-4-carbethoxyphenol (6a).** A suspension of Raney Ni in methanol was vigorously stirred in a two-necked flask under hydrogen at normal pressure. From a dropping funnel a solution of 13.4 g (23 mmol) of **5a** and 4.8 g (86 mmol) of KOH in 100 mL of methanol was added. When the hydrogen uptake was complete, the catalyst and precipitated KBr were filtered and washed with methanol. The filtrate was concentrated to about 100 mL and slowly dripped into ice-cold, aqueous HCl. Recrystallization of the precipitate from ethanol/water gave 8.9 g (75%) of white crystals of **6a**: mp 170–172 °C; $^1$H NMR ($CDCl_3$) δ 7.99–6.70 (m, 13, Ar H, 3, OH), 4.26 (q, 2, $CH_2CH_3$, $J$ = 7 Hz), 3.98 (s, 2, $CH_2$), 3.95 (s, 2, $CH_2$), 1.33 (t, 3, $CH_2CH_3$, $J$ = 7 Hz), 1.21 (s, 9, $C(CH_3)_3$); MS, $m/e$ 510 ($M^+$), 464 ($M^+ - OC_2H_5$). Anal. Calcd for $C_{33}H_{34}O_5$: C, 77.62; H, 6.71. Found: C, 77.84; H, 6.87.

**2-[3-(5-Phenylsalicyl)-5-*tert*-butylsalicyl]-4-methylphenol (6b).** Hydrogenation was carried out as described for the preparation of **6a**. Starting with 4.5 g (8.4 mmol) of **5b**, 3.13 g (73%) of **6b** was obtained as white crystals, mp 173 °C, after recrystallization from ethanol/water: $^1$H NMR ($CDCl_3$) δ 7.40–6.62 (m, 13, Ar H, 3, OH), 3.98 (s, 2, $CH_2$), 3.90 (s, 2, $CH_2$), 2.22 (s, 3, $CH_3$), 1.30 (s, 9, $C(CH_3)_3$); MS, $m/e$ 452 ($M^+$), 437 ($M^+ - CH_3$). Anal. Calcd for $C_{31}H_{32}O_3$: C, 82.27; H, 7.13. Found: C, 82.19; H, 7.15.

**2-[3-(5-Methylsalicyl)-5-*tert*-butylsalicyl]-4-carbethoxyphenol (6c).** Hydrogenation was carried out as described for the preparation of **6a**. Starting with 3.5 g (6.6 mmol) of **5c**, 2.3 g (78%) of **6c** was obtained, which after recrystallization from acetic acid/water formed white crystals: mp 198 °C; $^1$H NMR ($CDCl_3$) δ 7.98–6.61 (m, 8, Ar H, 3, OH), 4.31 (q, 2, $CH_2CH_3$, $J$ = 7 Hz), 3.92 (s, 2, $CH_2$), 3.87 (s, 2, $CH_2$), 2.22 (s, 3, $CH_3$), 1.35 (t, 3, $CH_2CH_3$, $J$ = 7 Hz), 1.28 (s, 9, $C(CH_3)_3$); MS, $m/e$ 448 ($M^+$), 402 ($M^+ - OC_2H_5$). Anal. Calcd for $C_{28}H_{32}O_5$: C, 74.98; H, 7.19. Found: C, 74.64; H, 7.21.

**2-[3-(5-Methylsalicyl)-5-*tert*-butylsalicyl]-4-cyclohexylphenol (6d).** Hydrogenation was carried out as described for the preparation of **6a**. Starting with 6.7 g (12.5 mmol) of **5d**, 4.3 g (75%) of **6d** was obtained as white crystals, mp 202–203 °C, after recrystallization from toluene: $^1$H NMR ($CDCl_3$) δ 7.25–6.64 (m, 8, Ar H, 3, OH), 3.88 (s, 4, $CH_2$), 2.28 (s, 3, $CH_3$), 2.3 (m, 1, $C_6H_{11}$), 1.8–1.3 (m, 10, $C_6H_{11}$), 1.30 (s, 9, $C(CH_3)_3$); MS, $m/e$ 459 ($M^+$), 444 ($M^+ - CH_3$). Anal. Calcd for $C_{31}H_{38}O_3$: C, 81.18; H, 8.34. Found: C, 80.86; H, 8.31.

**2-[3-(5-Methylsalicyl)-5-methylsalicyl]-4-*tert*-octylphenol (6e).** A mixture of 5.16 g (20 mmol) of 3-(5-methylsalicyl)-5-methylsalicyl alcohol and 61.8 g (0.3 mol) of *tert*-octylphenol was heated to 120 °C to give a homogeneous melt. After the addition of 5 mL of concentrated HCl the mixture was kept 6 h at this temperature. Excess octylphenol was removed by steam distillation, and the solid residue was recrystallized from toluene, to give 5.8 g (65%) of white crystals: mp 198 °C; $^1$H NMR ($Me_2SO$-$d_6$) δ 7.2–6.5 (m, 8, Ar H), 3.80 (s, 4, $ArCH_2Ar$), 2.13 (s, 3, $CH_3$), 2.03 (s, 3, $CH_3$), 1.61 (s, 2, $CH_2$), 1.25 (s, 6, $C(CH_3)_2$), 0.65 (s, 9, $C(CH_3)_3$); MS, $m/e$ 446 ($M^+$), 375 ($M^+ - CH_2C(CH_3)_3$). Anal. Calcd for $C_{30}H_{38}O_3$: C, 80.68; H, 8.58. Found: C, 80.74; H, 8.26.

**2,6-Bis(bromomethyl)-4-carbethoxyphenol (8a).** 2,6-Bis(hydroxymethyl)-4-carbethoxyphenol (5.7 g, 25 mmol) was added with stirring to 20 mL of a solution of hydrogen bromide in acetic acid (30 g of HBr per 100 mL). After 5 min, a clear solution was formed, from which after 7–10 min a white precipitate separated. The sticky mass was cooled, filtered by suction, and washed with petroleum ether to yield 7.5 g (85%) of crude **8a**, which on recrystallization from petroleum ether yielded a white powder: mp 155–157 °C; $^1$H NMR ($CDCl_3$) δ 7.99 (s, 2, Ar H), 6.22 (s, 1, OH), 4.58 (s, 4, $CH_2Br$), 4.36 (q, 2, $CH_2CH_3$, $J$ = 7 Hz), 1.39 (t, 3, $CH_2CH_3$, $J$ = 7 Hz); MS, $m/e$ 354, 352, 350 ($M^+$), 273, 271 ($M^+ - Br$). Anal. Calcd for $C_{11}H_{12}Br_2O_3$: C, 37.53; H, 3.44; Br, 45.40. Found: C, 37.32; H, 3.46; Br, 44.87.

**2,6-Bis(bromomethyl)-4-phenylphenol (8b).** Gaseous hydrogen bromide was passed rapidly through a suspension of 17.0 g (0.1 mol) of *p*-phenylphenol and 9.0 g (0.3 mol) of paraformaldehyde in 70 mL of acetic acid. With initial warming, a dark solution was formed, which finally solidified to a crystalline paste. After cooling, the precipitate was isolated by suction, washed three times with petroleum ether and recrystallized twice from toluene with the addition of charcoal. White crystals (14.8 g, 41%) of **8b** were obtained: mp 176–178 °C; $^1$H NMR ($CDCl_3$) δ 7.53–7.20 (m, 7, Ar H), 5.66 (s, 1, OH), 4.62 (s, 4, $CH_2Br$); MS, $m/e$ 358, 356, 354 ($M^+$), 277, 275 ($M^+ - Br$). Anal. Calcd for $C_{14}H_{12}Br_2O$: C, 47.23; H, 3.40; Br, 44.88. Found: C, 47.31; H, 3.51; Br, 44.52.

**5-Phenyl-11-*tert*-butyl-17-carbethoxy-23-methyl-25,26,27,28-tetrahydroxycalix[4]arene (9a).** In a 1-L three-necked flask equipped with condenser, dropping funnel, and mechanical stirrer a mixture of 400 mL of dry dioxane and 3.5 mL (32 mmol) of $TiCl_4$ was refluxed (bath temperature, 140 °C). During 6 h a solution of 2.56 g (5 mmol) of **6a** and 1.47 g (5 mmol) of 2,6-bis(bromomethyl)-4-methylphenol in 100 mL of dioxane was added. After the reaction was continued for 90 h, the solvent was evaporated in vacuo. The residue was respectively dissolved and suspended in $CH_2Cl_2$, and after addition of 40 g of silica gel, the solvent was evaporated again. The silica gel was extracted for 1 day with $CH_2Cl_2$ in a Soxhlet apparatus and the extract concentrated to few milliliters, and separated by flash chromatography with $CH_2Cl_2$. Two main fractions were isolated. The first fraction, a yellowish oil, could not be further identified. The second contained the desired calixarene **9a**, which was further purified by chromatography with $CHCl_3$. Finally the solid product was washed with warm petroleum ether, to yield 205 mg (6.4%) of slightly yellow crystals of **9a**: mp 368 °C; $^1$H NMR ($CDCl_3$) [aromatic region, see Table I and Figure 2] δ 4.3 (m br, 4, $ArCH_2Ar$, 2, $CH_2CH_3$), 3.6 (m br, 4, $ArCH_2Ar$), 2.12 (s, 3, $CH_3$), 1.34 (t, 3, $CH_2CH_3$), 1.25 (s, 9, $C(CH_3)_3$); MS, $m/e$ 642 ($M^+$). Anal. Calcd for $C_{42}H_{42}O_6$: C, 78.48; H, 6.59; O, 14.93. Found: C, 77.18; H, 6.49; O, 14.10.

**5-Phenyl-11-*tert*-butyl-17-methyl-23-carbethoxy-25,26,27,28-tetrahydroxycalix[4]arene (9b).** **6b** (2.65 g, 5 mmol)

and 1.76 g (5 mmol) of **8b** were reacted exactly as described for **9a**. The isolation and purification were done in the same way too. **9b** (283 mg, 8.8%) could be obtained as slightly yellow crystals: mp 268–270 °C; $^1$H NMR ($CDCl_3$) [aromatic region, see Table I and Figure 2] $\delta$ 4.3 (m br, 4, $ArCH_2Ar$, 2, $CH_2CH_3$), 3.6 (m br, 4, $ArCH_2Ar$), 2.15 (s, 3, $CH_3$), 1.36 (t, 3, $CH_2CH_3$), 1.25 (s, 9, $C(CH_3)_3$); MS, *m/e* 642 ($M^+$). Anal. Calcd for $C_{42}H_{42}O_6$: C, 78.48; H, 6.59; O, 14.93. Found: C, 76.50; H, 6.65; O, 14.20.

**5-Methyl-11-*tert*-butyl-17-carbethoxy-23-phenyl-25,26,27,28-tetrahydroxycalix[4]arene (9c).** **6c** (2.00 g, 4.4 mmol) and 1.59 g (4.4 mmol) of **8c** were reacted exactly as described for **9a**. The isolation and purification were done in the same way too. **9c** (210 mg, 7.4%) could be obtained as slightly yellow crystals: mp 185–188 °C; $^1$H NMR ($CDCl_3$) [aromatic region, see Table I and Figure 2] $\delta$ 4.3 (m br, 4, $ArCH_2Ar$, 2, $CH_2CH_3$), 3.6 (m br, 4, $ArCH_2Ar$), 2.12 (s, 3, $CH_3$), 1.33 (t, 3, $CH_2CH_3$), 1.24 (s, 9, $C(CH_3)_3$); MS, *m/e* 642 ($M^+$). Anal. Calcd for $C_{42}H_{42}O_6$: C, 78.48; H, 6.59; O, 14.93. Found: C, 77.15; H, 6.52; O, 13.70.

**5-Methyl-11-*tert*-butyl-17-cyclohexyl-23-octyl-25,26,27,28-tetrahydroxycalix[4]arene (9d).** To a boiling mixture of 300 mL of dry dioxane and 3 mL (27 mmol) of $TiCl_4$ was added a solution of 1.67 g (3.6 mmol) of **6d** and 1.43 g (3.6 mmol) of **8a** in 150 mL of dioxane during 6 h. The homogeneous solution was refluxed for further 50 h, filtered, and evaporated. The residue was extracted by three 20-mL portions of methylene chloride and the solution separated by flash chromatography ($CH_2Cl_2$/silica gel). Further chromatographic purification with carbon tetrachloride (monitored by TLC) finally led to the isolation of two fractions—174 mg of a viscous oil, the structure of which is still unknown, and 345 mg (14%) of **9d** in form of white crystals: mp 192 °C; $^1$H NMR ($CDCl_3$) $\delta$ 10.23 (s, 4, OH), 7.04 and 7.02 (d, 2, ArH(*tert*-butyl)), 6.86, 6.84, 6.82 (s br, 2, ArH-(cyclohexyl) 2, ArH(*n*-octyl), 2, ArH(methyl)), 4.25, 4.18 (m br, 4, $ArCH_2Ar$), 3.46 (m br, 4, $ArCH_2Ar$), 2.40 (t, 2, $ArCH_2C_7H_{15}$), 2.28 (m, 1, $C_6H_{11}$), 2.13 (s, 3, $CH_3$), 1.74 (m, 5, $C_6H_{11}$), 1.51 (m, 2, $ArCH_2CH_2C_6H_{13}$), 1.27 (m, 10, $C_8H_{17}$, 5, $C_6H_{11}$), 1.22 (s, 9, $C(CH_3)_3$), 0.87 (t, 3, $C_7H_{14}CH_3$); MS, *m/e* 689 ($M^+$). Anal. Calcd for $C_{47}H_{60}O_4$: C, 81.93; H, 8.78; O, 9.29. Found: C, 81.05; H, 8.74; O, 8.56.

**5,11-Dimethyl-17-*tert*-octyl-23-cyclohexyl-25,26,27,28-tetrahydroxycalix[4]arene (9e).** A solution of 2.23 g (5 mmol) of **6e** and 1.82 g (5 mmol) of 2,6-bis(bromomethyl)-4-cyclohexylphenol in 200 mL of dry dioxane was dropped slowly into a boiling mixture of 3.29 mL (30 mmol) of $TiCl_4$ in 400 mL of dioxane during 8 h. The whole mixture was refluxed under argon atmosphere for a further 24 h. Finally the dark red solution was evaporated, the residue was dissolved in $CHCl_3$ and after the addition of 50 g of silica gel evaporated to dryness again. The silica gel was extracted in a Soxhlet apparatus by boiling $CHCl_3$ for 16 h, and the extract was further purified by flash chromatography (silica gel/$CHCl_3$). From the first fractions, 750 mg of crude product was obtained, which on trituration with acetone gave 375 mg (12%) of pure **9e**: mp 238–239 °C; $^1$H NMR ($CDCl_3$) $\delta$ 10.14 (s, 4, OH), 7.01 and 6.97 (d, 2, ArH(*tert*-octyl)), 6.86, 6.84, 6.82 (s/d br, 6 Ar H), 4.18 (m, br, 4, $ArCH_2Ar$), 3.44 (m br, 4, $ArCH_2Ar$), 2.24 (m, 1, $C_6H_{11}$), 2.16 (s, 3, $CH_3$), 2.13 (s, 3, $CH_3$), 1.74 (m, 5, $C_6H_{11}$), 1.29 (m, 5, $C_6H_{11}$), 1.61 (s, 2, $C(CH_3)_2CH_2C(CH_3)_3$), 1.25 (s, 6, $C(CH_3)_2$), 0.66 (s, 9, $C(CH_3)_3$); MS, *m/e* 646 ($M^+$), 575 ($M^+ - C_5H_{11}$). Anal. Calcd for $C_{44}H_{54}O_4$: C, 81.69; H, 8.41; O, 9.89. Found: C, 79.40; H, 8.70; O, 8.85.

**5,11-Dimethyl-17-*tert*-octyl-23-chloro-25,26,27,28-tetrahydroxycalix[4]arene (9f).** **6e** (2.23 g, 5 mmol), 1.58 g (5 mmol) of 2,6-bis(bromomethyl)-4-chlorophenol, and 2.75 mL (25 mmol) of $TiCl_4$ were reacted exactly as described for **9e**. After evaporation of the reaction mixture, the residue was directly purified by flash chromatography ($CHCl_3$/silica gel). A crude product (200 mg) was isolated from the first fractions, which on trituration with acetone gave 80 mg (3%) of pure **9f**: mp 287 °C; $^1$H NMR ($CDCl_3$) $\delta$ 10.06 (s, 4, OH), 7.04 and 6.99 (d, 2, ArH(*tert*-octyl)), 6.98 (s, 2, ArH(Cl)), 6.87 and 6.84 (d br, 2, $ArH(CH_3)$), 6.81 (s, 2, $ArH-(CH_3)$), 4.16 (m br, 4, $ArCH_2Ar$), 3.42 (m br, 4, $ArCH_2Ar$), 2.17 (s, 3, $CH_3$), 2.11 (s, 3, $CH_3$), 1.62 (s, 2, $C(CH_3)_2CH_2C(CH_3)_3$), 1.27 (s, 6, $C(CH_3)_2$), 0.68 (s, 9, $C(CH_3)_3$); MS, *m/e* 598 ($M^+$), 527 ($M^+ - C_5H_{11}$). Anal. Calcd for $C_{38}H_{43}ClO_4$: 76.17; H, 7.23; Cl, 5.92; O, 10.68. Found: C, 73.67; H, 7.29; Cl, 6.33; O, 9.17.

# Synthesis of New Cyclopenta-Fused PAH Isomers of Cata-Annelated Benzenoid Systems

R. Sangaiah* and Avram Gold

*Department of Environmental Sciences and Engineering, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27514*

*Received July 7, 1986*

The syntheses of three new benz-annelated derivatives of aceanthrylene and acephenanthrylene are reported. These systems are of interest in studies on mechanisms of bioactivation and structure–activity correlations because of their predicted high level of biological activity. Of the three isomers, benz[*d*]aceanthrylene (**5**) has been synthesized by two routes involving Friedel–Crafts acylations of 1,2,3,4-tetrahydronaphthacene with chloroacetyl chloride or oxalyl chloride as the key step. The cyclic ketone product from each route has been successfully elaborated to **5**. Synthesis of benz[*k*]aceanthrylene (**9**) involves preparation of acenaphthene-3,4-dicarboxylic anhydride and its smooth conversion to **9**. A straightforward and high-yield synthesis of benz[*j*]acephenanthrylene (**27**) is described utilizing a Robinson annelation reaction of methyl vinyl ketone with a previously reported ketonic precursor of acephenanthrylene.

Cyclopenta-fused polycyclic aromatic hydrocarbons (PAH) are a unique class of PAH present in the environment. Initial biochemical studies have suggested that epoxidation of the cyclopenta ring is a major pathway of enzymatic transformation.[1–4] Resonance stabilization energy[5,6] ($\Delta E_{deloc}/\beta$), which has been shown to correlate with biological activity,[6] is in general larger for benzylic carbonium ions derived from ring-opened cyclopenta epoxides[7,8] than those derived from other peripheral arene

(1) Gold, A.; Nesnow, S.; Moore, M.; Garland, H.; Curtis, J.; Howard, B.; Graham, D.; Eisenstadt, E. *Cancer Res.* **1980**, *40*, 4482.

(2) Sangaiah, R.; Gold, A.; Ball, L. M.; Kohan, M.; Bryant, B. J.; Rudo, K.; Claxton, L.; Nesnow, S. In *Polynuclear Aromatic Hydrocarbons: Chemistry and* Carcinogenesis; Cooke, M., Dennis, A. J. Ed.; Battelle: Columbus, OH, 1985; p 795.

(3) Kohan, M. J.; Sangaiah, R.; Ball, L. M.; Gold, A. *Mutat. Res.* **1985**, *155*, 95.

(4) Nesnow, S.; Leavitt, S.; Easterling, R.; Watts, S. H.; Toney, S. H.; Claxton, L.; Sangaiah, R.; Toney, G. E.; Wiley, J.; Fraher, P.; Gold, A. *Cancer Res.* **1984**, *44*, 4993.

(5) Dewar, M. J. S.; Dougherty, R. C. *The PMO Theory of Organic Chemistry*; Plenum: New York, 1975; Chapter 4, pp 131–196.

(6) Jerina, D. M.; Lehr, R. E.; Yagi, H.; Hernandez, O.; Dansette, P. M.; Wislocki, P. G.; Wood, A. W.; Chang, R. L.; Levin, W.; Conney, A. H. In *In Vitro Metabolic Activation in Mutagenesis Testing*; DeSerres, F. J., Fouts, J. R., Bend, J. R., Philpot, R. M., Ed.; Elsevier North Holland Biomedical: Amsterdam, 1976; pp 159–177.

0022-3263/87/1952-3205$01.50/0 