Dissymmetric Calix[4]arenes with C_4- and C_2-Symmetry. Synthesis, X-ray Structures, Conformational Fixation, and ^{1}H NMR Spectroscopic Studies

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Six dissymmetric calix[4]arenes with C_4 symmetry consisting of four 3,4-disubstituted phenolic units have been obtained by condensation of the respective 2- or 6-hydroxymethylated phenols. The regular incorporation of the phenolic units into the macrocycle was established on the basis of ^{1}H NMR spectra and in one case also by X-ray analysis. One example for a calixarene with C_2-symmetry consisting of *p*-cresol and 3,4-dimethylphenol units in alternating sequence was also prepared. Calixarene **4a** consisting of 3,4-dimethylphenol units shows a lower energy barrier ($\Delta G^{\ddagger}$ = 13.4 kcal/mol) for the cone-to-cone inversion in $CDCl_3$ than *p*-methylcalix[4]arene ($\Delta G^{\ddagger}$ = 14.6 kcal/mol). The dissymmetric calixarenes **4** could be conformationally fixed by alkylation of the phenolic hydroxyl group. Due to the equivalence of all four phenolic units, mono- and 1,3-di-derivatives could be obtained in addition to tetra derivatives. A tetraester derivative in the cone conformation, like the parent calix[4]arene, crystallizes as a racemate. In solution these tetraester derivatives exist in a distorted cone conformation with C_2 symmetry. Dynamic ^{1}H NMR spectra reveal an energy barrier of $\Delta G^{\ddagger}$ = 13.3-13.4 kcal/mol for the C_2-to-C_2 interconversion with the C_4-cone as transition state.

Calixarenes, usually easily available by well-established one-pot procedures,[1] are interesting either as host molecules themselves or as building blocks for the construction of more sophisticated host molecules[2] (e.g. calixcrowns,[3] calixspherands,[4] cavitands,[5] double-calixarenes,[6,7] double-cavitands,[8] hemicarcerands,[9] carcerands[10]).

This has led also to the study of the synthesis of chiral calixarenes, which as with all molecules is possible by the attachment of chiral residues to the calixarene framework.[11] More interesting, however, is the possibility to obtain "inherently" chiral calixarenes, due to the nonplanarity of the calix[4]arene molecule. Asymmetrical calix[4]arenes may be prepared from phenolic units differently substituted in the para position[12] or by the incorporation of a single meta-substituted phenol unit.[13] The rapid ring inversion of calix[4]arenes[2] renders the isolation of enantiomers impossible. After fixation of the cone-conformation by the attachment of suitable residues (larger than ethyl[14]) to the phenolic oxygens, a separation into the enantiomers was reported for one example.[15]

Two examples, in which chirality is created by the derivatization itself (although the residues introduced are achiral) should be also mentioned; 1,3-O-alkylated calix[4]arenes are easily prepared in a large variety, including compounds in which these positions are connected by an additional macrocycle.[3,4] By strating with a calix[4]arene

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of the type AABB, the resulting derivative is chiral.[16] 1,2-O-Alkylated calix[4]arenes[17] can be further alkylated with a different alkylating reagent. The resulting tri-*O*-alkyl derivatives[18] and the tetra-*O*-alkyl derivatives in the partial cone conformation[19] are chiral (while the cone conformation has a symmetry plane). Optical resolution has been reported for examples of the former type.[19]

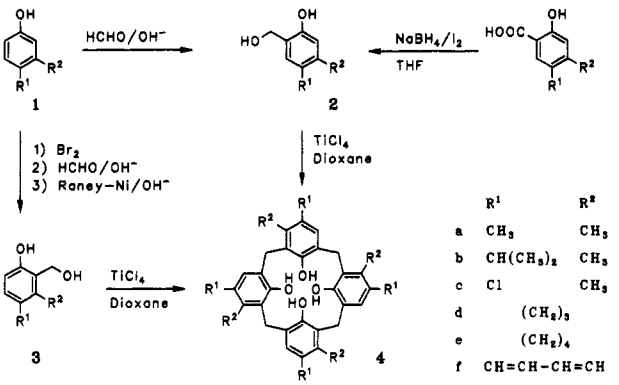
To obtain a conformationally pure tetra derivative in the cone conformation (both conditions must be fulfilled, not to end up with a complex mixture) turned out to be more difficult with assymmetrically substituted calix[4]-arenes than with symmetrical calix[4]arenes, a problem which is at least partly due to the asymmetry.[20] Therefore, dissymmetric calix[4]arenes consisting of *four* meta-substituted phenol units have some advantages.[21] Due to the homogeneity of the phenol units, not only tetra-O-alkylated derivatives obviously are easier to obtain in the cone conformation; there is also the rational possibility to synthesize 1,3-di-O-alkylated or mono-O-alkylated derivatives or even derivatives in the partial cone conformation, since only one constitutional isomer is possible in all these cases.

We describe in this publication the synthesis of several calix[4]arenes with C_4-symmetry and their conformational fixation by various derivatives. The optical resolution of some of these derivatives is reported elsewhere.[22]

Results and Discussion

Calix[4]arenes with C_4-Symmetry. Dissymmetric calix[4]arenes (**4**) are formed by the condensation of monohydroxymethyl derivatives of 3,4-disubstituted phenols (see Scheme I). Whether the 2-hydroxymethyl or the 6-hydroxymethyl derivative is used, mainly depends on the accessibility of these compounds. In the case of 3,4-dimethylphenol (**1a**), 3-methyl-4-*i*-propylphenol (**1b**), and 4-chloro-3-methylphenol (**1c**) conditions were found to prepare the corresponding 6-hydroxymethyl derivatives (**2a–c**) directly by reaction with the stoichiometric amount of formaldehyde in aqueous alkaline solution with a reasonable yield of 45–51% for **2a** and **2b**. An important feature obviously is that the sodium salt of the desired

Scheme I



product precipitates during the reaction; lithium hydroxide instead of sodium hydroxide was used to prepare **2c** (20%). This direct reaction with formaldehyde led in the case of 5,6,7,8-tetrahydro-2-naphthol (**1e**, 3,4-butanophenol) to the 1-hydroxymethyl derivative **3e** (3,4-butano-2-(hydroxymethyl)phenol) which was isolated in 20% yield. The direct pathway failed up to now for 5-indanol (**1d**, 3,4-propanophenol). However, in this case the selective substitution in the 6-position was possible by bromination (84%). Subsequent hydroxymethylation (70%) and debromination by hydrogenation (room temperature, normal pressure, alkaline medium, Raney nickel; 48%) finally gave the 2-hydroxymethylated phenol **3d**. This pathway would be possible (most probably) also starting with phenols **1a–c** and **1e**.

For the preparation of a suitable hydroxymethylated 2-naphthol, we first tried the hydrogenation of 2-hydroxy-1-naphthaldehyde. This resulted, however, in the isolation of more than 50% 1,1′-methylenebis(2-naphthol), which most probably is formed from the intermediate 1-hydroxymethyl compound **3f** by ipso substitution in the 1-position. This reaction would also interfere with the desired regular incorporation into the calix[4]arene. Therefore, we considered the 3-(hydroxymethyl)-2-naphthol (**2f**) to be a better educt. It was obtained by sodium borohydride reduction of the corresponding acid.

The condensation of the monohydroxymethylated precursors **2** or **3** was done in dioxane, using $TiCl_4$ as catalyst (and probably as template) similar to the conditions for the synthesis of calix[4]arene by 3 + 1,[12] 2 + 2,[12] or 2 × 1 + 2 × 1[23] approaches. The calix[4]arene formed was easily isolated and purified by flash column chromatography, due to the fact that it represents the compound migrating fastest. The yield of pure **4** varied between a reasonable 18–30% (**4a**, **4b**) and 5% (**4f**). It should be possible, however, to optimize the conditions for reaction and working up also in this latter case.

In principle higher members of the calixarene family could be formed also by condensation of the (hydroxymethyl)phenols **2** or **3**, but the calix[4]arenes **4**, unambiguously confirmed by mass spectrometry, are the only cyclic compounds we could isolate. The regular incorporation of the meta-substituted phenol units also is not self-evident, since it is known that $ArCH_2OH$ groups may react also to form dibenzyl ether structures ($ArCH_2OCH_2Ar$), which subsequently can lose formaldehyde[24] to form a product identical to the ipso-substitution product. The C_4-structure of **4** was demonstrated by the ^1H NMR spectra

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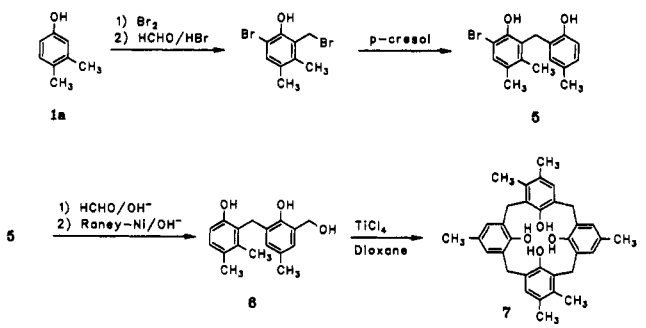
Scheme II



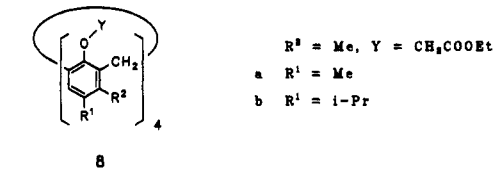
which showed single signals for all structural units, e.g. only one singlet for the ArH protons of the phenolic unit and one for the methyl groups in **4b** and **4c**, while two singlets for the methyl groups are found in **4a**. Only one signal is found for the $ArCH_2Ar$ protons, which splits into one pair of doublets at lower temperatures in all cases.

For **4a** and its tetraester derivative **8a**, the ring size as well as the regular incorporation of the 3,4-dimethylphenol units was shown also by single crystal X-ray analysis, which is discussed below.

Calix[4]arenes with C_2-Symmetry. In principle dissymmetric calix[4]arenes with C_2-symmetry are available in a similar way, outlined in Scheme II. Bromination of 3,4-dimethylphenol in the 6-position (76%), followed by bromomethylation in the 2-position (49%) and subsequent condensation with excess of *p*-cresol gave the dinuclear compound **5** (69%), which again was hydroxymethylated (72%) and finally debrominated by hydrogenation[25] (85%) to yield the mono(hydroxymethyl) dimer **6**. The yield for the cyclization to form the calix[4]arene **7** was again 20%. However, this synthesis involves more steps and consequently also a lower overall yield of 3% (not optimized for the single steps). As a result of this and also since these calixarenes with lower symmetry are less interesting with respect to a general derivatization, we have demonstrated this for one example only.

Derivatives of C_4-Calixarenes. O-Alkylation of calix[4]arenes in principle may fix any of the four possible conformations, provided the residues are bulky enough (larger than ethyl[14]) not to penetrate the annulus. One of the most frequently studied reagents is ethyl bromoacetate, which, in the presence of sodium or potassium ions, leads to tetraester derivatives[26] in the cone conformation, while the partial cone conformation predominantly is formed in the presence of cesium ions.[27]

We formerly faced many difficulties to obtain such tetraester derivatives conformationally pure in the cone conformation from asymmetrically substituted calix[4]arenes.[20] These problems did not arise to the same extent with C_4-calix[4]arenes, where for instance the tetra derivative **8a** in the cone conformation could be obtained



	R^1	R^2	Y
a	Me	Me	CH_2COOEt
b	i-Pr	Me	CH_2COOEt
c	$(CH_2)_3$		CH_2COOEt
d	Me	Me	n-Bu
e	Me	Me	Me
f	i-Pr	Me	n-Bu
g	Me	Me	$CH_2C_6H_4NO_2$
h	Me	Me	i-Pr

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	R^1	R^2	Y	Y'
a	Me	Me	H	n-Bu
b	Me	Me	H	$CH_2C_6H_4NO_2$
c	Me	Me	H	Me
d	Me	Me	H	i-Pr
e	i-Pr	Me	CH_2COOEt	H

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in yields up to 62% by reaction with ethyl bromoacetate in refluxing THF using NaH as a base. (The presence of the partial cone derivative in the mother liquors could be shown by ^1H NMR spectra.) When **4b** was reacted with excess ethyl bromoacetate in THF in the presence of excess NaH, 34% of **8b** in the cone conformation and 30% in the partial cone conformation could be isolated by column chromatography. On the other hand, reaction in refluxing acetone in the presence of K_2CO_3 gave 51% of the triester **10e**, the conformation of which cannot be unambiguously deduced from the ^1H NMR spectrum, since all four aromatic units and all three ester residues are different in all possible conformations (see below). The less reactive *n*-butyl bromide led only to the 1,3-diether derivative **9f**, even when applied in excess with excess NaH in DMF, while the tetramethyl ether was formed with methyl iodide in 50% yield under similar conditions.

In 1,3-derivatives[28] the symmetry is reduced from C_4 to C_2 and probably the preference of a conformation with C_2 symmetry found also for the tetraester derivatives (see later) is one of the factors favoring the formation of 1,3-derivatives. Thus, 1,3-diesters (**9a–c**) were obtained in high yield from **4a,b,d** as well as dimethyl (**9e**), dibutyl (**9d**, **9f**), and di-*i*-propyl (**9h**) ethers. In the case of *p*-nitrobenzyl bromide the 1,3-diether **9g** was obtained as a side product in the synthesis of the monoether **10b** (23%) using CsF as a weak base,[29] a procedure which was successfully used also to prepare the monomethyl (**10c**) or monobutyl ether (**10a**). Such mono-O-alkyl derivatives, which then are completely asymmetric, can be obtained also from 1,3-diether derivatives by partial cleavage of the ether links with iodotrimethylsilane.[30]

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NMR Studies. (a) Parent Calix[4]arenes. All calix[4]arenes **4** are flexible at room temperature but frozen[30] in the cone conformation (on the NMR time scale) at lower temperatures, as demonstrated by a pair of doublets (AB system) for the $ArCH_2Ar$ protons. The difference in chemical shifts for these protons is lower (~0.2 ppm) in comparison to calix[4]arenes without metasubstituents (~0.8 ppm). A coalescence temperature of T_c = 8 °C was found for **4a** in $CDCl_3$ (at 500 MHz) which with $\Delta\nu$ = 91 Hz and ^2J = 14.7 Hz leads to an energy barrier of $\Delta G^\ddagger$ = 13.4 kcal/mol for the ring inversion process. This is somewhat lower than $\Delta G^\ddagger$ = 14.6 kcal/mol which was found under identical conditions for the *p*-methylcalix[4]arene (T_c = 50 °C, $\Delta\nu$ = 374 Hz, ^2J = 13.9 Hz) which may be considered for comparison. (The difference of 42 °C in T_c does not account for this difference in $\Delta G^\ddagger$). Assuming energetically similar transition states and/or intermediates for the ring inversion in both cases,[31] this would mean that the ground state is energetically higher[15] (1.0–1.2 kcal/mol) in **4a** than in the analogous calix[4]arene with R_2 = H. However, no evidence for a conformation with C_2 symmetry (like in the crystalline state or for the tetraester derivatives, see below) is found down to −85 °C. On the other hand, for a calix[4]arene with methyl groups in *all* eight metapositions, the minimum energy conformation was found to have C_{2v}-symmetry ("pinched cone"), and the energy barrier for the formation of the corresponding equivalent C_{2v} conformation which takes place by ring inversion has a value of only $\Delta G^\ddagger$ = 10.7–10.9 kcal/mol.[32]

Regarding the ^1H NMR spectra in $CDCl_3$ the stabilization of the ground state in compounds **4** by intramolecular hydrogen bonds may be even stronger since the signals for the OH groups appear even at lower field (10.58–10.95 ppm) than in *p*-methylcalix[4]arene (10.12 ppm) or *tert*-butylcalix[4]arene (10.2 ppm). A slight exception is the *p*-chloro compound **4c** (10.17 ppm) which may be due to the higher acidity of the phenolic units. For comparison, the octamethylcalix[4]arene described by Biali et al. shows an OH signal at 8.19 ppm,[32] and calix[4]arenes with two opposite 4-chloro-3,5-dimethyl phenols units show signals at 10.38–10.45 ppm.[23] This would mean that the steric strain excerted by one methyl group for each pair of adjacent metapositions is not sufficient to compete with the cyclic array of intramolecular hydrogen bonds and to distort the 4-fold symmetry of the cone conformation to a measurable extent.

An interesting pattern is found for the *i*-propyl groups in **4b**. Well below the coalescence temperature, when the cone conformation is stable on the NMR time scale, each of the four equivalent *i*-propyl groups (indicating for instance the C_4-symmetry!) contains two different methyl groups. Due to the inherently chiral molecule, they are diastereotopic and appear as two doublets. Above the coalescence temperature, when the singlet for the $ArCH_2$-Ar protons indicates a rapid interconversion of the two enantiomers, these methyl groups are also equivalent and show just one doublet.

(b) Tetraester Derivatives. Surprisingly in the beginning, tetraester derivatives **8a** and **8b** showed a very broad signal for the aromatic protons, while a sharp singlet is found for the corresponding calix[4]arenes **4**, as well as for similar tetraester derivatives from e.g. *p-tert*-butylcalix[4]arene. At lower temperature this signal splits into *two* sharp singlets, indicating a conformation with two different aromatic units and hence with C_2 symmetry, a conformation which may be described as "pinched cone" (see Figure 1a). The remainder of the spectrum is in accordance with this interpretation and shall be discussed for **8b** as an example (see also Figure 1b,c). Not only are the aromatic protons different (two singlets at 7.016 and 5.758 ppm) but also the substituents at the aromatic moieties like the $ArCH_3$ groups. They appear as two singlets at 2.336 and 1.569 ppm. It seems reasonable to attribute the signal at higher field in both cases to the aromatic units being tilted into the cavity and thus being shielded by the adjacent aromatic units. Not only do two different pairs of *i*-propyl groups exist, but each i-propyl group being attached to a chiral skeleton also contains two diastereotopic methyl groups which appear as four doublets (vicinal coupling) at 1.20 (superimposed by one ester methyl group), 1.125, 0.712, and 0.449 ppm. The signals (heptets) of the *i*-propylmethine protons appear at 3.136 and 2.408 ppm, showing nearly the same difference in chemical shifts as the methyl singlets. Due to the pinched cone conformation, two different pairs of ether residues $OCH_2COCH_2CH_3$ exist, the CH_2 groups of which contain diastereotopic protons. The two AB systems (pairs of doublets) with geminal coupling (^2J = 16–17 Hz) for the OCH_2CO groups appear at 5.245/4.614 ppm and 4.452/4.238 ppm, respectively. It seems reasonable to attribute the pair with the larger difference in chemical shifts to the groups being closer to the chiral skeleton; this refers to those units where the ester groups are bent in and the parapositions are turned outwards. For the ethyl ester

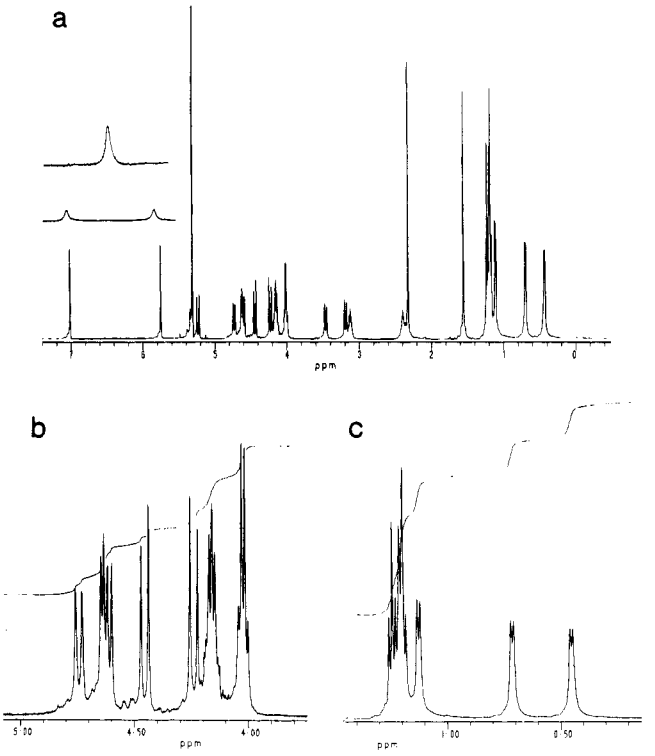

Figure 1. (a) ^1H NMR spectrum of **8b** (500 MHz, CD_2Cl_2, −77 °C). The aromatic region is also shown at −20 °C and 120 °C (200 MHz, $C_2D_2Cl_4$). (b) Section of the methylene protons. (c) Section of the methyl protons.

(30) Casnati, A.; Arduini, A.; Ghidini, E.; Pochini, A.; Ungaro, R. *Tetrahedron* **1991**, *47*, 2221–2228.

(31) Semiempirical calculations suggest the partial cone and the alternate conformations as intermediates for the ring inversion: Grootenhuis, P. D. J.; Kollman, P. A.; Groenen, L. C., Reinhoudt, D. N.; v. Hummel, G. J.; Ugozzoli, F.; Andreetti, G. D. *J. Am. Chem. Soc.* **1990**, *112*, 4165–4176.

(32) Dahan, E.; Biali, S. E. *J. Org. Chem.* **1991**, *56*, 7269–7274.

groups, we find a pair of quadruplets (4.164/4.153 ppm) (the diastereotopic character is just slightly visible for these two OCH_2CH_3 groups, which represent in principle an ABX_3 system) and a quadruplet (4.021 ppm) as well as two triplets (1.241/1.195 ppm). Distortion of the cone conformation of a calix[4]arene with C_{4v} symmetry to C_{2v} leaves the NMR pattern of the $ArCH_2Ar$ methylene protons unchanged. The analogous distortion from C_4 to C_2 creates two different $ArCH_2Ar$ groups. Consequently we find four doublets (^2J = 14 Hz) at 4.741, 4.630 ppm (axial protons) and 3.475, 3.203 ppm (equatorial protons). It has not been established which A-part belongs to which B-part, but it is evident that the difference in the equatorial protons is more pronounced than in the axial protons. This is reasonable again, since the equatorial protons are closer to the metamethyl groups, which originate the chirality of the whole molecule.

From the coalescence temperature T_c = 30 °C of the aromatic singlets (at 500 Hz in $CDCl_3$, see Figure 1) an energy barrier of $\Delta G^{\ddagger}$ = 13.4 and 13.3 kcal/mol, respectively, can be calculated for the tetraester derivatives **8a** ($\Delta\nu$ = 629 Hz) and **8b** ($\Delta\nu$ = 675 Hz), which belongs to the interconversion of the two equivalent "pinched cone conformations" with C_2-symmetry via the C_4-symmetrical cone conformation as the transition state. A distorted or pinched cone conformation has been found for all tetra-O-alkylated calix[4]arenes (with C_{4v} symmetry in the parent calixarene) in the crystalline state,[33] while the NMR spectra always suggest a 4-fold symmetry (see below). In the light of the present results the latter observation is most probably due to a time-averaged spectrum of the two identical conformations with C_2 symmetry. Obviously the steric strain between the *O*-alkyl residues and the lack of a cyclic array of intramolecular hydrogen bonds must combine with the steric strain due to the *m*-methyl groups, to observe this conformation also in solution. It should be noted that the analogous behavior with C_{2v} symmetry at lower temperature has been observed in solution for tetraoctyl ether derivatives with mutually attracting (hydrogen bonds) substituents like COOH or $CONH_2$ in the paraposition.[34] The $\Delta G^{\ddagger}$ values of 14.2 and 13.3 kcal/mol, respectively, for the interconversion C_{2v}-to-C_{2v} with the C_{4v}-symmetrical cone as transition state is of a comparable size.

From NMR relaxation time studies, a similar motion has been deduced for tetraester derivatives of *tert*-butylcalix[4]arene, which is strongly suppressed by the complexation of a sodium cation.[35] Similarly, **8a** forms in $CDCl_3$ solution a sodium complex (obtainable just by shaking with NaSCN), which again shows obviously C_4-symmetry, e.g. one (rather) sharp signal for the aromatic protons at 7.06 ppm, two singlets for the methyl groups at 2.36 and 2.04 ppm, and a triplet for the methyl groups of the ester residues at 1.37 ppm. In the methylene region a doublet for OCH_2CO at 4.24 ppm (A-part, ^2J = 16.0 Hz) and a doublet for $ArCH_2Ar$ at 3.70 ppm (B-part, ^2J = 13.0 Hz) is discernible, while the complementary doublets and the quadruplet(s) for OCH_2CH_3 merge to a multiplet between 4.36 and 4.21 ppm. The *m*-methyl groups make this Na^+ complex less stable, at least kinetically, than the complex with the corresponding tetraester derived from *tert*-butylcalix[4]arene, since addition of the free ligand **8a** leads to a broadening of all signals (exchange of the Na^+ cation) and not to the observation of the additional spectrum of **8a**.

(c) 1,3-Diether Derivatives. The introduction of two *O*-alkyl groups in 1,3-positions reduces the symmetry from C_4 to C_2. Consequently, in compounds **9** like in achiral calixarenes, the set of signals for the phenolic units is doubled, e.g. four singlets are found for the methyl groups and two singlets for the aromatic protons in 1,3-ethers derived from **4a**. Due to the intrinsic chirality and in contrast to the corresponding derivatives of "usual" calix[4]arenes (where C_{4v}-symmetry is reduced to C_{2v}-symmetry), two of the four $ArCH_2Ar$ groups differ from the other two and thus *two* pairs of doublets are observed. One singlet for the remaining OH groups and *one* set of signals for the residue attached to the phenolic oxygens in 1,3-positions are found. If this residue R is of the type CX_2Y, the two "groups" X again are diastereotopic. Thus, a pair of doublets (geminal coupling) is observed for the protons in OCH_2CO (**9a–c**) and two doublets (vicinal coupling with the methine proton) for the methyl groups in $OCH(CH_3)_2$ (**9h**).[36]

It is worth to note that the two isochronous $ArCH_2Ar$ groups are symmetry-related by a C_2 axis (the same is true for e.g. the equivalent $ArCH_3$ groups) and not by a symmetry plane, as for instance two pairs of the four NMR-equivalent methylene groups in a 1,3-derivative of *tert*-butyl calix[4]arene. The doubling of NMR signals observed in the presence of a chiral solvent therefore is due to enantiomers and not to enantiotopic groups in a molecule with a symmetry plane.[36]

(d) Monoether Derivatives. Attachment of only one residue to the phenolic oxygens leads to a totally asymmetric molecule, in which all aromatic units are different. Besides three singlets for the hydroxyl groups (9.581, 9.515, 9.308 ppm) and one set of signals for the butyl group, we thus observe in $CDCl_3$ four singlets for the aromatic protons (6.923, 6.905, 6.878, 6.796 ppm) and eight singlets for the methyl groups (2.399, 2.392, 2.244, 2.169, 2.151, 2.131, 2.015, 2.001 ppm) in the monobutyl ether **10a**, which is discussed here as an example.[38] All four $ArCH_2Ar$ groups are also different. Due to the superimposing OCH_2 signals, the resulting eight doublets are better discernible in pyridine-d_6 (4.762, 4.601, 4.551, 4.252, 3.981, 3.833, 3.688, 3.656 ppm) than in $CDCl_3$. The singlets of the aromatic protons (7.171, 7.143, 6.693, 6.636 ppm) are also spread over a larger range in pyridine in comparison to $CDCl_3$, and the same is true for the methyl singlets (2.491, 2.450, 2.293 (6H), 1.907 (6H), 1.334, 1.305), although two signals coincide here by chance. Obviously the cone conformation is more strongly deformed in pyridine than in $CDCl_3$.

Addition of Pirkle's reagent to such a monoether leads to an additional doubling of (in principle) all signals; also the complexity of such a spectrum may not allow observation of all different signals separately.

X-ray Structural Analysis. X-ray structures were obtained from **4a** and its tetraester derivative **8a**. Both compounds crystallize in the triclinic system (space group

(33) See for instance: Andreetti, G. D.; Ugozzoli, F. in reference 2b.
(34) Conner, M.; Janout, V.; Regen, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 9670–9671.
(35) Yamada, A.; Murase, T.; Kikukawa, K.; Matsuda, T.; Shinkai, S. *Chem. Lett.* **1990**, 455–458. Yamada, A.; Murase, T.; Kikukawa, K.; Arimura, T.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 2*, **1991**, 793–797.
(36) The multiplicity of signals corresponds in principle to the low temperature spectra of the tetraester derivatives.
(37) See, K. A.; Fronczek, F. R.; Watson, W. H.; Kashyap, R. P.; Gutsche, C. D. *J. Org. Chem.* **1991**, *56*, 7256–7268.
(38) An analogous pattern is found for instance for a triester (see **10d**) or a tetraester in the partial cone conformation (see **8b**).

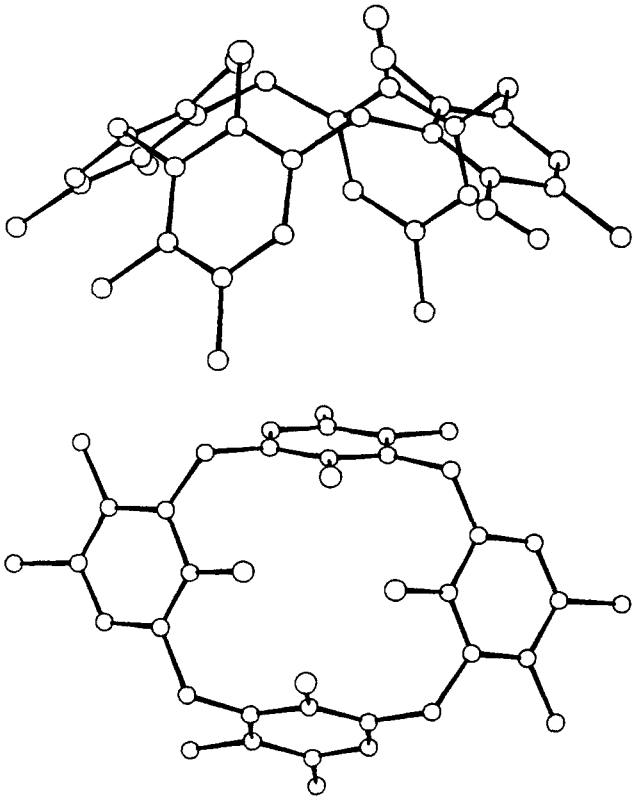

Figure 2. Molecular structure of **4a** seen from two different directions.

$P\bar{1}$) with two enantiomeric molecules related to each other by the crystallographic center of symmetry.

As shown in Figure 2, **4a** exists in the cone conformation, which, however, is distorted with respect to 4-fold symmetry (Regen et al.[34] used the expression "pinched" cone conformation while boat conformation was used by Biali et al.[32] for the analogous distortion). The dihedral angles between the aromatic units and the best plane through the methylene (CH_2) carbons are 105.0(2), 145.9(2), 111.7(2), and 149.3(2)°, which is roughly in accordance with C_2-symmetry. The corresponding values observed for the *p-tert*-butyl[39] and the p-isopropyl calix[4]arene[40] are 123 to 126° (average value 124.5°), showing molecules with 4-fold symmetry in the crystalline state. This bending of two phenolic rings toward the cavity (by 19 and 13°) and consequently two toward the exterior (by 21 and 25°) leads also to a small but significant lengthening of the cyclic intramolecular O···O contacts, which are 2.742(6), 2.686(6), 2.692(6), and 2.699(6) Å (average 2.705 Å), while 2.671 Å was found for *tert*-butylcalix[4]arene. The torsion angles around the $ArCH_2Ar$ bonds strongly deviate from 90° whereas values close to 90° are observed in cases where 4-fold symmetry is present. A comparison of those torsion angles ϕ and χ, which especially in the case of higher homologues of the calixarene family are the most unambiguous parameters to characterize a conformation,[41] with the corresponding values for *tert*-butylcalix[4]arene and an octamethylcalix[4]arene where all metapositions are substituted by methyl[32] is given in Table I. It can be seen that the deviation from the 4-fold symmetry is less pronounced in **4a** than in the compound where two repulsive methyl groups are present in each pair of adjacent metapositions. The symbolic representation of the molecular conformation of **4a** according to the method proposed by Ugozzoli and Andreetti is C_1 +−,+−,+−,+−.

The conformational changes induced by the *m*-methyl groups seem less abrupt for the tetraester derivative **8a** in comparison to the corresponding derivative of *tert*-butylcalix[4]arene. This is due to the fact that the latter is already rather distorted with approximately 2-fold symmetry for the calixarene part. In fact the dihedral angles between the benzene rings and the best plane through the methylene carbons are 150.1(1), 93.55(8), 147.08(8), and 83.20(9)° in **8a** versus 135.9(2), 96.1(2), 135.8(1), and 93.3(2)° observed in the *p-tert*-butylcalix[4]arene tetraester. A comparison of both compounds in terms of the structural parameters ϕ and χ is found in Table II. Strong differences between both tetraesters are found for the conformation of the pendant ether ester chains, which, however, are caused most probably by packing effects, since the geometry of the basic frame of phenolic oxygens to which these groups are attached is very similar.

Experimental Section

Melting points above 300 °C were determined under argon using sealed capillary tubes. All melting points are uncorrected. All chromatographic separations were done using silica gel 60, particle size 0.040–0.063 mm (230–400 mesh ASTH), as stationary phase, and the eluent is indicated for the individual case.

Preparation of Monohydroxymethylated Phenols 2 or 3 via Direct Hydroxymethylation of 1. The phenol **1a–e**,**3** (0.1 mol) was dissolved in a solution of NaOH (0.1 mol) in water (40 mL) ($LiOH{\cdot}2H_2O$ in the case of **1c**) under an argon atmosphere. Aqueous formaldehyde (35%, 8.4 mL, 0.1 mol HCHO) was added and the reaction mixture stirred at room temperature. The resinous precipitate was collected by filtration, suspended in methanol or water, and then acidified with cold aqueous acetic acid. The white solid obtained after filtration and air drying usually was pure enough for further use. An analytical sample was recrystallized for further evaluation.

2a: Reaction time 1.5 h; yield 51%; mp 112–113 °C ($CHCl_3$/*n*-hexane); ^{1}H NMR (200 MHz, acetone-d_6) δ 8.05 (s, 1H, ArOH), 6.94 (s, 1H, ArH), 6.60 (s, 1H, ArH), 4.68 (d, 2H, $ArCH_2$), 4.30 (t, 1H, CH_2OH), 2.14 (s, 3H, $ArCH_3$), 2.13 (s, 3H, $ArCH_3$); EI-MS, *m/z* 152 (M^+, 54). Anal. Calcd for $C_9H_{12}O_2$: C, 71.00; H, 7.95. Found: C, 71.07; H, 7.85.

2b: Reaction time 1.5 h; yield 45%; mp 69–70 °C (CH_2Cl_2/*n*-hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.93, 6.87, 6.66 (s, 1H each, ArOH and ArH), 4.81 (d, 2H, $ArCH_2$), 3.06 (heptet, ^3J = 6.9 Hz, 1H, ArCH), 2.26 (s, 3H, $ArCH_3$), 2.14 (t, 1H, CH_2OH), 1.17 (d, ^3J = 6.9 Hz, 6H, $CH(CH_3)_2$); EI-MS, *m/z* 180 (M^+, 100). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.29; H, 8.95. Found: C, 73.38; H, 8.87.

2c: Reaction time 9 h; yield 23%; mp 123–125 °C (CH_2Cl_2); ^{1}H NMR (200 MHz, acetone-d_6) δ 8.54 (broad s, 1H, ArOH), 7.26 (s, 1H, ArH), 6.77 (s, 1H, ArH), 4.68 (d, 2H, $ArCH_2$), 4.47 (broad s, 1H, CH_2OH), 2.25 (s, 3 H, $ArCH_3$); EI-MS, *m/z* 172 (M^+, 58%).

3e: Reaction time 120 h; yield 20%; mp 64–66 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.84 (s, 1 H, ArOH), 6.89 (d, ^3J = 8.3 Hz, 1H, ArH), 6.63 (d, ^3J = 8.3 Hz, 1H, ArH), 4.85 (s, 2H, $ArCH_2$), 2.95 (broad s, 1H, CH_2OH), 2.68 (t, 2H, $ArCH_2$), 2.65 (t, 2H, $ArCH_2$), 1.77–1.66 (m, 4H, CH_2CH_2); EI-MS, *m/z* 178 (M^+, 33), 160 ($M^+ - H_2O$, 100).

Preparation of 3d Using Bromine as a Protecting Group. Bromination: To a ice-cooled solution of **1d** (0.25 mol, 33.55 g) in $CHCl_3$ (200 mL) was slowly added a solution of bromine (0.26 mol, 41.55 g) in $CHCl_3$ (50 mL) over a period of 1 h. The reaction mixture was stirred for a further 2 h at 5 °C. After evaporation of the solvent, the pure product was distilled under reduced pressure to give 84% of 6-bromo-3,4-propanophenol as a colorless

(39) Andreetti, G. D.; Ungaro, R.; Pochini, A. *J. Chem. Soc., Chem. Commun.* **1979**, 1005–1007.
(40) Perrin, M., Oehler, D. in reference 2b.
(41) Ugozzoli, F.; Andreetti, G. D. *J. Incl. Phenom. Molec. Recogn.* **1992**, *13*, 337–348.

Table I. Conformational Parameters[41] of Calixarene 4a in Comparison to *tert*-Butylcalix[4]arene (t-Bu-cal[4])[39] and a Calix[4]arene Having All Eight Meta Positions Substituted by Methyl Groups (octaMe-cal[4])[32]

t-Bu-cal[4] [C_4 +−]		4a [C_1 +−,+−,+−,+−]		octaMe-cal[4] [C_1 +−,+−,+−,+−][a]		octaMe-cal[4] [C_1 +−,+−,+−,+−][b]	
ϕ	χ	ϕ	χ	ϕ	χ	ϕ	χ
88.9(4)	−89.4(5)	71.6(8)	−108.5(7)	75 (1)	−122.3(9)	77 (1)	−123 (1)
		112.2(7)	−82.9(8)	121.1(9)	−78 (1)	121 (1)	−78 (1)
		75.6(8)	−104.6(8)	79 (1)	−115.9(9)	76 (1)	−121 (1)
		108.7(2)	−77.5(8)	119.4(9)	−78 (1)	121.9(9)	−77 (1)

[a] Recrystallized from DMF. [b] Recrystallized from pyridine.

Table II. Conformational Parameters[41] of Tetraester 8a in Comparison to the Analogous Tetraester Derivative of *tert*-Butylcalix[4]arene[33]

8a [C_1 +−,+−,+−,+−]		tetraester *t*-Bu-cal[4] [C_1 +−,+−,+−,+−]	
ϕ	χ	ϕ	χ
69.1(5)	−115.4(4	65.2(9)	−101.1(9)
105.1(4)	−46.6(5)	98.1(8)	−59.4(8)
66.1(5)	−119.2(4)	63.8(9)	−105.1(8)
108.6(4)	−50.9(5)	98.8(8)	−62.0(8)

oil: bp 60–62 °C (0.015); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.28 (s, 1H, ArH), 6.89 (s, 1H, ArH), 5.38 (s, 1H, ArOH), 2.83 (t, ^3J = 7.3 Hz, 4H, $ArCH_2$), 2.09 (q, ^3J = 7.4 Hz, 2H, CH_2CH_2); EI-MS, *m/z* 212 (M^+, 46), 133 (100).

Hydroxymethylation: A mixture of 6-bromo-3,4-propanophenol (0.2 mol, 42.50 g), a solution of NaOH (0.2 mol, 8 g) in water (50 mL), and aqueous formaldehyde 35% (67 mL, 0.78 mol HCHO) were stirred for 24 h under a nitrogen atmosphere. The yellow reaction mixture was acidified with 10% aqueous acetic acid (1 L) and the resinous oil thus obtained was partitioned between ether and water. The organic phase was separated, washed with water, dried ($MgSO_4$), and evaporated in vacuo. The resultant yellow oil was dissolved in CH_2Cl_2 and purified by column chromatography (silica gel, CH_2Cl_2) to yield 70% of 6-bromo-2-hydroxymethyl-3,4-propanophenol as a white crystalline solid: mp 65 °C (petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.24, 6.82 (s, 1H each, ArOH and ArH), 4.76 (s, 2H, $ArCH_2$), 2.6 (broad s, 1H, CH_2OH), 2.84–2.76 (m, 4H, CH_2), 2.12–2.00 (m, 2H, CH_2CH_2); EI-MS, *m/z* 242 (M^+, 23), 224 ($M^+ - H_2O$, 100). Anal. Calcd for $C_{10}BrH_{11}O_2$: C, 49.39; H, 4.56; Br, 32.88. Found: C, 49.26; H, 4.51; Br, 32.98.

Debromination: 3d was prepared by hydrogenation (Raney-Ni, room temperature, normal pressure) of this material (0.07 mol, 17.01 g) in alkaline methanol (0.16 mol KOH, 8.96 g, 500 mL). After complete hydrogen uptake, the mixture was filtered and cautiously acidified with dilute HCl. A red oil separated which was further purified by column chromatography (silica gel, $CHCl_3$/acetone 10:1) to yield (48%) a slightly reddish oil, pure enough for further reactions: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.45 (s, 1H, ArOH), 7.03 (d, ^3J = 8.1 Hz, 1H, ArH), 6.67 (d, ^3J = 8.1 Hz, 1H, ArH), 4.86 (d, 2H, $ArCH_2$), 2.86–2.66 (m, 4H, CH_2), 2.51 (t, 1H, CH_2OH), 2.13–1.98 (m, 2H, CH_2CH_2); EI-MS, *m/z* 164 (M^+, 26), 146 ($M^+ - H_2O$, 100). The above material solidified after several months but the crystalline material showed no sharp melting point (110–150 °C), probably due to condensation.

Preparation of 2f by Reduction: A solution of 2-hydroxy-3-naphthalenecarboxylic acid (0.1 mol, 18.82 g) in dry THF (200 mL) was added at room temperature to a suspension of $NaBH_4$ (0.12 mol, 4.54 g) in dry THF (200 mL) over 1.5 h and the mixture stirred until the evolution of gas ceased. Iodine (0.05 mol, 12.69 g) in THF (200 mL) was added slowly at 0 °C. The white suspension was further stirred at room temperature overnight. The mixture was treated with 3 M HCl (60 mL), diluted with water (300 mL), and extracted with ether (3 × 150 mL). The combined ether extracts were extracted with 3 M NaOH and the combined alkali extracts acidified with concentrated HCl to pH 6 to 7. The resultant pink solid was removed by filtration, washed with water, and dried. It was pure enough for further use. Slightly brown plates were obtained from acetone (60%): mp 185 °C; ^{1}H NMR (200 MHz, acetone-d_6) δ 8.80 (broad s, 1H, ArOH), 7.82–7.63 (m, 3H, ArH), 7.39–7.07 (m, 3H, ArH), 4.89 (s, 2H, $ArCH_2$), 4.52 (broad s, 1H, CH_2OH); EI-MS, *m/z* 174 (M^+, 29), 128 (100).

General Procedure for the Synthesis of Calix[4]arenes 4a–f. A solution (10–30 mmol) of the 2- or 6-hydroxymethylated phenol 2 or 3 was dissolved in dioxane (freshly distilled, 250–500 mL) and warmed to 60 °C under an argon atmosphere. $TiCl_4$ (10–30 mmol) was added and the reaction mixture refluxed for 96–120 h. After it was cooled, the solvent was removed and the resultant solid dissolved in CH_2Cl_2 (200–300 mL). After addition of silica gel (50 g), the solvent was evaporated again and the dry silica gel extracted with CH_2Cl_2 (750 mL) by means of a soxhlet apparatus (in the case of 4c with ethyl acetate and then CH_2Cl_2). After evaporation of the solvent, the crude product was purified as indicated below.

4a: Flash chromatography with $CHCl_3$ and subsequently with $CCl_4/CHCl_3$ (5:1); yield 17%; mp >450 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 10.61 (s, 4H, ArOH), 6.950 (s, 4H, ArH), 3.940 (broad s, 8H, $ArCH_2Ar$), 2.350 (s, 12H, $ArCH_3$), 2.093 (s, 12H, $ArCH_3$); ^{1}H NMR (500 MHz, $CDCl_3$, −50 °C) δ 10.75 (s, 4H, ArOH), 6.985 (s, 4H, ArH), 4.061 (d, ^2J = 14.7 Hz, 4H, $ArCH_2Ar$), 3.876 (d, ^2J = 14.7 Hz, 4H, $ArCH_2Ar$), 2.377 (s, 12H, $ArCH_3$), 2.107 (s, 12H, $ArCH_3$); EI-MS, *m/z* 536 (M^+, 100).

4b: Chromatography with $CCl_4/CHCl_3$ (5:1); white powder (17–29%); mp 291–293 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.79 (s, 4H, ArOH), 7.08 (s, 4H, ArH), 3.98 (broad s, 8H, $ArCH_2Ar$), 3.04–2.99 (heptet, ^3J = 6.5 Hz, 4H, ArCH), 2.45 (s, 12 H, $ArCH_3$), 1.11 (d, ^3J = 6.5 Hz, 24H, $CH(CH_3)_2$); ^{1}H NMR ($CDCl_2$, 500 MHz, −85 °C) δ 9.84 (s, 4H, ArOH), 6.96 (s, 4H, ArH), 3.98 (d, ^2J = 14.6 Hz, 4H, $ArCH_2Ar$), 3.79 (d, ^2J = 14.6 Hz, 4H, $ArCH_2Ar$), 2.94–2.92 (heptet, ^3J = 6.5 Hz, 4H, ArCH), 2.33 (s, 12H, $ArCH_3$), 1.06, 0.89 (2 d, ^3J = 6.5 Hz, 12H each, $CH(CH_3)_2$); EI-MS, *m/z* 648 (M^+, 88).

4c: Chromatography with $CHCl_3$ and subsequent trituration with chloroform/acetone; yield 6%; mp >450 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 10.17 (s, 4H, ArOH), 7.16 (s, 4H, ArH), 3.93 (s, 8H, $ArCH_2Ar$), 2.48 (s, 12H, $ArCH_3$); FD-MS, *m/z* 618 (M^+, 100).

4d: Flash chromatography with $CCl_4/CHCl_3$ (5:1); yield 12%; mp >470 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.58 (s, 4H, ArOH), 6.93 (s, 4H, ArH), 3.64 (broad s, 4H, $ArCH_2Ar$), 4.08 (broad s, 4H, $ArCH_2Ar$), 2.98 (broad s, 8H, $ArCH_2$), 2.71 (broad s, 8H, $ArCH_2$), 2.02 (broad d, 8H, CH_2); EI-MS, *m/z* 584 (M^+, 34), 83 (100).

4e: Flash chromatography with $CCl_4/CHCl_3$ (2:1) and trituration of the residue with *n*-hexane; yield 8%; mp >300 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 10.71 (s, 4H, ArOH), 6.87 (s, 4H, ArH), 3.87 (s, 8H, $ArCH_2Ar$), 2.87 (t, ^3J = 6.0 Hz, 8H, $ArCH_2$), 2.60 (t, ^3J = 6.1 Hz, 8H, $ArCH_2$), 1.78–1.64 (m, 16H, CH_2CH_2); FD-MS, *m/z* 640 (M^+, 100).

4f: Flash chromatography with $CHCl_3$ gave a slightly brown product (5%); mp 384–386 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.945 (s, 4H, ArOH), 8.359 (d, ^3J = 8.6 Hz, 4H, ArH), 7.838 (s, 4H, ArH), 7.587 (d, ^3J = 7.9 Hz, 4H, ArH), 7.483 (t, ^3J = 7.7 Hz, 4H, ArH), 7.217 (t, ^3J = 7.3 Hz, 4H, ArH), 4.559 (s, 8H, $ArCH_2Ar$); FD-MS, *m/z* 624 (M^+, 100).

Synthesis of Calix[4]arene 7. A solution of bromine (1.02 mol, 163 g) in $CHCl_3$ (200 mL) was added to a solution of 3,4-dimethylphenol (**1a**, 1 mol, 122.2 g) in $CHCl_3$ (600 mL) over a 2-h period at 5 °C. The mixture was stirred for a further 1 h, the solvent was evaporated, and the residue was recrystallized from $CHCl_3/CCl_4$ (2:1) to yield 6-bromo-3,4-dimethylphenol as white crystals (76%): mp 72–73 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.19 (s, 1H, ArH), 6.81 (s, 1H, ArH), 5.26 (s, 1H, ArOH), 2.16 (s, 6H, $ArCH_3$).

6-Bromo-3,4-dimethylphenol (0.2 mol, 40.2 g) and paraformaldehyde (0.22 mol, 6.6 g) were suspended in acetic acid (70 mL). A rapid stream of gaseous HBr was passed through this suspension

for 20 min, which afforded with warming a pink, viscous solution. After storage in a refrigerator, a white pinkish solid was formed, which was collected by filtration, washed with cold acetic acid, and dried over KOH. The crude product was recrystallized from CH_2Cl_2/petroleum ether to give colorless crystals of 6-bromo-2-(bromomethyl)-3,4-dimethylphenol (49%): mp 81–83 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.21 (s, 1H, ArH), 5.61 (s, 1H, ArOH), 4.65 (s, 2H, $ArCH_2$), 2.21 (s, 3H, $ArCH_3$), 2.16 (s, 3H, $ArCH_3$).

A solution of this compound (0.04 mol, 11.8 g) in CH_2Cl_2 (200 mL) was added dropwise to molten *p*-cresol (0.4 mol, 43.3 g) over a 30-min period under a nitrogen atmosphere. The reaction mixture was stirred at 60 °C for 5 h, when the evolution of HBr was complete. After addition of petroleum ether (80–100 °C, 100 mL), a white solid was formed, which was filtered and recrystallized from CH_2Cl_2/*n*-pentane to give 69% of **5** as colorless crystals: mp 168–170 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.17 (s, 1H, ArH), 6.95–6.65 (m, 3H, ArH), 6.20 (s, 1H, ArOH), 5.93 (s, 1H, ArOH), 4.00 (s, 2H, $ArCH_2Ar$), 2.21 (s, 3H, $ArCH_3$), 2.18 (s, 3H, $ArCH_3$), 2.16 (s, 3H, $ArCH_3$).

Hydroxymethylation of **5** (25 mmol, 8.03 g) was achieved by reaction with formaldehyde 35% (17 mL, 200 mmol HCHO) in aqueous NaOH (55 mmol, 2.2 g dissolved in 10 mL of water) at room temperature. Workups were as described for compound **2**. White crystals from $CHCl_3$/petroleum ether (60–80 °C, 72%): mp 145–147 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.82, (broad s, 1H, ArOH), 7.17 (s, 1H, ArH), 6.70 (s, 2H, ArH), 6.26 (s, 1H, ArOH), 4.77 (s, 2H, $ArCH_2$), 4.01 (s, 2H, $ArCH_2Ar$), 2.15 (m, 9H, $ArCH_3$), 1.90 (broad s, 1H, CH_2OH).

6 was obtained by hydrogenation of this hydroxymethylated dinuclear compound (0.01 mol, 3.51 g) in alkaline methanol (0.03 mol KOH, 1.79 g, 200 mL) as described for compound **3d**. The crude product (yield 85%) was pure enough for further use: mp 137–139 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 8.80–7.20 (broad s, 2H, ArOH), 7.04–6.54 (m 4H, ArH), 4.74 (s, 2H, $ArCH_2$), 3.95 (s, 2H, $ArCH_2Ar$), 2.90–2.40 (broad s, 1H, CH_2OH), 2.30 (s, 3H, $ArCH_3$), 2.17 (s, 6H, $ArCH_3$).

Calix[4]arene **7** was synthesized like compounds **4** with 8 mmol of compound **6** (2.18 g) and $TiCl_4$ (8 mmol, 1.52) in dioxane. Flash column chromatography with $CCl_4/CHCl_3$ (3:2) of the crude product afforded white crystals in 18% yield: mp >360 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.35 (s, 4H, ArOH), 6.96 (s, 2H, ArH), 6.85 (s, 2H, ArH), 6.82 (s, 2H, ArH), 3.96 (s, 4H, $ArCH_2Ar$), 3.79 (broad s, 4H, $ArCH_2Ar$), 2.34 (s, 6H, $ArCH_3$), 2.14 (s, 6H, $ArCH_3$), 2.10 (s, 6H, $ArCH_3$), (200 MHz, $CDCl_3$, −40 °C) δ 10.65 (s, 2H, ArOH), 10.35 (s, 2H, ArOH) 6.96 (s, 2H, ArH), 6.87 (s, 2H, ArH), 6.85 (s, 2H, ArH), 4.16 (d, ^2J = 13.4 Hz, 2H, $ArCH_2Ar$), 4.06 (d, ^2J = 14.5 Hz, 2H, $ArCH_2Ar$), 3.85 (d, ^2J = 14.5 Hz, 2H, $ArCH_2Ar$), 3.39 (d, ^2J = 13.4 Hz, 2H, $ArCH_2Ar$), 2.33 (s, 6H, $ArCH_3$), 2.14 (s, 6H, $ArCH_3$), 2.09 (s, 6H, $ArCH_3$); EI-MS, *m/z* 508 (M^+, 100).

Preparation of Calix[4]arene Tetraacetates 8a,b. The calix[4]arene **4a** or **4b** (0.3–0.4 mmol) was dissolved in dry THF (freshly distilled from sodium) under a nitrogen atmosphere. 97% NaH (40 mmol, 60% in the case of **4b**) was added in small portions to give a gray suspension. After the addition of ethyl bromoacetate (40–50 mmol), the mixture was refluxed following the progress of the reaction by TLC. After completion (6–11 h) the mixture was cooled and the THF removed in vacuo. The yellow solid residue was treated with water (50 mL, 2 M HCl in the case of **8b**) and extracted with $CHCl_3$ (2 × 20 mL). The organic phase was washed with water and dried ($MgSO_4$) and the $CHCl_3$ removed in vacuo to give a yellow brownish oil.

8a Cone: After three days, crystals formed which were filtered and washed with *n*-pentane; yield 62%; mp 178–180 °C; ^{1}H NMR (500 MHz, CD_2Cl_2, −60 °C) δ 6.974 (s, 2H, ArH), 5.624 (s, 2H, ArH), 5.224 (d, ^2J = 17.1 Hz, 2H, $ArOCH_2$), 4.728 (d, ^2J = 14.1 Hz, 2H, $ArCH_2Ar$), 4.670 (d, ^2J = 15.0 Hz, 2H, $ArCH_2Ar$), 4.505 (d, ^2J = 15.9 Hz, 2H, $ArOCH_2$), 4.494 (d, ^2J = 17.9 Hz, 2H, $ArOCH_2$), 4.178–4.188 (m, 6H, $ArOCH_2$ and CH_2CH_3), 4.039 (q, ^3J = 6.7 Hz, 4H, CH_2CH_3), 3.438 (d, ^2J = 14.6 Hz, 2H, $ArCH_2Ar$), 3.223 (d, ^2J = 14.6 Hz, 2H, $ArCH_2Ar$), 2.260 (s, 6H, CH_3), 2.250 (s, 6H, CH_3), 1.616 (s, 6H, CH_3), 1.461 (s, 6H, CH_3), 1.242 (t, ^3J = 6.9 Hz, 6H, CH_2CH_3), 1.195 (t, ^3J = 7.0, 6H, CH_2CH_3). FD-MS, *m/z* = 881 (M^+, 100).

8b was separated and purified by column chromatography (silica gel, eluent initially *n*-hexane, finally $CHCl_3$) and recrystallized from ethanol.

8b Cone: White needles (34%); mp 158–160 °C; ^{1}H NMR (500 MHz, CD_2Cl_2, −77 °C) δ 7.016 (s, 2H, ArH), 5.758 (s, 2H, ArH), 5.245 (d, ^2J = 17.0 Hz, 2H, $ArOCH_2$), 4.741 (d, ^2J = 14.1 Hz, 2H, $ArCH_2Ar$), 4.630 (d, ^2J = 14.4 Hz, 2H, $ArCH_2Ar$), 4.614 (d, ^2J = 17.0 Hz, 2H, $ArOCH_2$), 4.452 (d, ^2J = 16.1 Hz, 2H, $ArOCH_2$), 4.238 (d, ^2J = 16.1 Hz, 2H, $ArOCH_2$), 4.192–4.125 (m, 4H, CH_2CH_3), 4.024 (q, ^3J = 7.1 Hz, 4H, CH_2CH_3), 3.475 (d, ^2J = 14.1 Hz, 2H, $ArCH_2Ar$), 3.203 (d, ^2J = 14.1 Hz, 2H, $ArCH_2Ar$), 3.163–3.109 (m, 2H, ArCH), 2.421–2.396 (m, 2H, ArCH), 2.336 (s, 6H, CH_3), 1.569 (s, 6H, CH_3), 1.241 (t, ^3J = 7.1 Hz, 6H, CH_2CH_3), 1.210–1.181 (m, 12H, CH_2CH_3 and $CH(CH_3)_2$), 1.125 (d, ^3J = 6.4 Hz, 6H, $CH(CH_3)_2$), 0.712 (d, ^3J = 6.1 Hz, 6H, $CH(CH_3)_2$), 0.449 (d, ^3J = 6.4 Hz, 6H, $CH(CH_3)_2$); FD-MS, *m/z* = 994 (M^+, 100).

8b Partial Cone: Yield 30%; mp 160 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43, 7.17, 6.95, 5.98 (4 s, 1H each, ArH), 4.50–3.77 (m, 21 H, $ArCH_2Ar$, $ArOCH_2$ and CH_2CH_3), 3.55 (d, ^2J = 13.9 Hz, $ArCH_2Ar$), 3.21 (m, 3H, $ArCH_2Ar$ and ArCH), 2.75 (m, 2H, ArCH), 2.41, 2.36, 2.23, 1.68 (4 s, 3H each, $ArCH_3$), 1.33–1.09 (m, 24H, CH_2CH_3), 1.09 (d, ^3J = 6.8, 3H, $CH(CH_3)_2$), 1.02 (d, ^3J = 6.7, 3H, $CH(CH_3)_2$), 0.88 (d, ^3J = 6.7, 3H, $CH(CH_3)_2$), 0.69 (d, ^3J = 6.7, 3H, $CH(CH_3)_2$); FD-MS, *m/z* = 994 (M^+, 100).

General Procedure for the Synthesis of 1,3-Di-O-alkylated Calix[4]arenes 9a–h. A suspension of calix[4]arene **4** (0.5 mmol) and K_2CO_3 (0.55 mmol) in dry acetonitrile (10–30 mL) was refluxed for 0.5 h under argon atmosphere. The alkylating agent (1.1 mmol) was added and the reaction mixture refluxed for several hours. After evaporation of the solvent, the remaining solid was treated with 1 M HCl (20 mL) and CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with water and dried ($MgSO_4$) and the solvent evaporated in vacuo to give the crude product as a white solid, which was further purified either by recrystallization from $CHCl_3$/ethanol or by column chromatography.

9a: Reaction time 3.5 h; yield 86%; mp 233–234 °C ($CHCl_3$/ethanol); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.95, 6.88, 6.50 (3 s, 2H each, ArH and ArOH), 4.75 (d, ^2J = 15.5 Hz, 2H, $ArOCH_2$), 4.41 (d, ^2J = 14.4 Hz, 2H, $ArCH_2Ar$), 4.38 (d, ^2J = 15.5 Hz, 2H, $ArOCH_2$), 4.26 (d, ^2J = 14.0 Hz, 2H, $ArCH_2Ar$), 4.26 (q, ^3J = 7.0 Hz, 4H, CH_2CH_3), 3.66 (d, ^2J = 13.4 Hz, 2H, $ArCH_2Ar$), 3.46 (d, ^2J = 14.6 Hz, 2H, $ArCH_2Ar$), 2.39, 2.22, 2.01, 1.90 (4 s, 6H each, $ArCH_3$), 1.30 (t, ^3J = 7.2 Hz, 6H, CH_2CH_3); EI-MS, *m/z* 708 (M^+, 100); Calcd for $C_{44}H_{52}O_8$: C, 74.53; H, 7.40; O, 18.07. Found: C, 74.73; H, 7.49; O, 17.78.

9b: Reaction time 21 h; yield 87%; mp 135–141 °C ($CHCl_3$/ethanol); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.96, 6.29, 6.11 (3 s, 2H each, ArOH and ArH), 4.80 (d, ^2J = 15.6 Hz, 2H, $ArOCH_2$), 4.63 (d, ^2J = 14.7 Hz, 2H, $ArCH_2Ar$), 4.39 (d, ^2J = 15.6 Hz, 2H, $ArOCH_2$), 4.26 (d, ^2J = 14.7 Hz, d, 2H, $ArCH_2Ar$), 4.30–4.18 (2 q, 2H each, CH_2CH_3), 3.65 (d, ^2J = 13.8 Hz, 2H, $ArCH_2Ar$), 3.41 (d, ^2J = 14.8 Hz, 2H, $ArCH_2Ar$), 3.18 (heptet, ^3J = 6.8 Hz, 2H, ArCH), 2.62 (heptet, ^3J = 6.7 Hz, 2H, ArCH), 2.46 (s, 6H, $ArCH_3$), 1.83 (s, 6H, $ArCH_3$), 1.29 (t, ^3J = 7.1 Hz, 6H, $CHCH_3$), 1.25 (d, ^3J = 6.8 Hz, 6H, $CH(CH_3)_2$), 1.19 (d, ^3J = 6.8 Hz, 6H, $CH(CH_3)_2$), 0.91 (d, ^3J = 6.7 Hz, 6H, $CH(CH_3)_2$), 0.49 (d, ^3J = 6.7 Hz, 6H, $CH(CH_3)_2$); FD-MS, *m/z* 820 (M^+, 100).

9c: Reaction time 6 h; yield 33%; mp 260–262 °C ($CHCl_3$/ethanol); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.31, 6.88, 4.71 (3 s, 2H each, ArOH and ArH), 4.71 (d, ^2J = 15.5 Hz, $ArOCH_2$), 4.51 (d, ^2J = 15.5 Hz, 2H, $ArOCH_2$), 4.40 (d, ^2J = 13.5 Hz, 2H, $ArCH_2Ar$), 4.29 (q, ^3J = 7.1 Hz, 4H, CH_2CH_3), 4.27 (d, ^2J = 14.0 Hz, 2H, $ArCH_2Ar$), 3.50 (d, ^2J = 13.2 Hz, 2H, $ArCH_2Ar$), 3.35 (d, ^2J = 13.8 Hz, 2H, $ArCH_2Ar$), 3.05 (t, ^3J = 7.2 Hz, 4H, $ArCH_2$), 2.83 (t, ^3J = 7.2 Hz, 4H, $ArCH_2$), 2.73–2.51 (m, 8H, CH_2CH_2), 2.12–1.82 (m, 8H, CH_2CH_2), 1.32 (t, ^3J = 7.1, 6H, CH_2CH_3); EI-MS, *m/z* 756 (M^+, 100).

9d: Reaction time 22 h; yield 89%; mp 264–265 °C (chromatography with $CCl_4/CHCl_3$ 2:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.06 (s, 2H, ArOH), 6.87 (s, 2H, ArH), 6.63 (s, 2H, ArH), 4.30 (d, ^2J = 13.1 Hz, 2H, $ArCH_2Ar$), 4.06 (d, ^2J = 14.2 Hz, 2H, $ArCH_2Ar$), 3.98–3.81 (m, 4H, $ArOCH_2$), 3.64 (d, ^2J = 13.0 Hz, 2H, $ArCH_2Ar$), 3.51 (d, ^2J = 14.3 Hz, 2H, $ArCH_2Ar$), 2.41 (s, 6H, $ArCH_3$), 2.21 (s, 6H, $ArCH_3$), 2.07 (s, 6H, $ArCH_3$), 1.94 (s, 6H, $ArCH_3$), 2.25–1.86 (m superimposed with 3 s from $ArCH_3$, 4H, CH_2CH_2), 1.83–1.64 (m, 4H, CH_2CH_2), 1.03 (t, ^3J = 7.2 Hz, 6H, CH_3); EI-MS, *m/z* 648 (M^+, 100).

9e: Chromatography with $CHCl_3/CCl_4$ (2:1); yield 87%; mp 296–297 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.43, 6.89, 6.55 (3 s, 2H each, ArOH and ArH), 4.25 (d, ^2J = 13.3 Hz, 2H, $ArCH_2Ar$), 4.17 (d, ^2J = 14.4 Hz, 2H, $ArCH_2Ar$, 3.87 (s, 6H, $ArOCH_3$), 3.67 (d, ^2J = 13.4 Hz, 2H, ArH_2Ar), 3.51 (d, ^2J = 14.4 Hz, 2H, $ArCH_2Ar$), 2.41 (s, 6H, $ArCH_3$), 2.23 (s, 6H, $ArCH_3$), 2.04 (s, 6H, $ArCH_3$), 1.92 (s, 6H, $ArCH_3$); EI-MS, *m/z* 564 (M^+, 100).

9f: Recrystallization of the crude product from CH_2Cl_2/methanol afforded white needles (84%); mp 178 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25, 6.89, 6.41 (3 s, 2H each, ArOH and ArH), 4.29 (d, ^2J = 13.4 Hz, 2H, $ArCH_2Ar$), 4.14 (d, ^2J = 14.4 Hz, 2H, $ArCH_2Ar$), 3.92–3.80 (m, 4H, $ArOCH_2$), 3.56 (d, ^2J = 13.4 Hz, 2H, $ArCH_2Ar$), 3.41 (d, ^2J = 14.5 Hz, 2H, $ArCH_2Ar$), 2.43 (s, 6H, $ArCH_3$), 3.11 (heptet ^3J = 6.8 Hz, 2H, ArCH), 2.65 (heptet, ^3J = 6.8 Hz, 2H, ArCH), 1.88 (s, 6H, $ArCH_3$), 1.90–1.82 (m superimposed with s from $ArCH_3$, 4H, CH_2CH_2), 1.66–1.58 (m, 4H, CH_2CH_2), 1.19 (d, *J* = 6.7 Hz, 6H, $CH(CH_3)_2$), 1.12 (d, ^2J = 6.7 Hz, 6H, $CH(CH_3)_2$), 0.96 (t, ^3J = 7.3 Hz, 6H, CH_2CH_3), 0.91 (d, ^2J = 6.7 Hz, 6H, $(CH(CH_3)_2)$, 0.54 (d, ^2J = 6.7 Hz, 6H, $CH(CH_3)_2$); FD-MS, *m/z* 761 (M^+, 100).

9g: This compound was isolated as a side product in the synthesis of **10b** by direct alkylation in 23% yield: mp 198 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 8.06 (d, ^3J = 8.7 Hz, 4H, $Ar(NO_2)H$), 7.88 (d, ^3J = 8.7 Hz, 4H, $Ar(NO_2)H$), 7.56, 6.91, 6.65 (3 s, 2H each, ArOH and ArH), 5.15 (d, ^2J = 13.4 Hz, 2H, $ArOCH_2$), 5.01 (d, ^2J = 13.5 Hz, 2H, $ArOCH_2$), 4.18 (d, ^2J = 13.3 Hz, 2H, $ArCH_2Ar$), 4.15 (d, ^2J = 14.3 Hz, 2H, $ArCH_2Ar$), 3.70–3.54 (t from 2 overlapped d, 4H, $ArCH_2Ar$), 2.39 (s, 6H, $ArCH_3$), 2.21 (s, 6H, $ArCH_3$), 2.09 (s, 6H, $ArCH_3$), 1.97 (s, 6H, $ArCH_3$); FD-MS, *m/z* 807 (M^+, 100).

9h: This product was obtained with excess of *i*-propyl iodide as alkylating agent; reaction time 47 h; chromatography with $CHCl_3$; yield 52%, white needles from acetonitrile; mp 310–312 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.662 (s, 2H, ArOH), 6.846, 6.569 (2 s, 2H each, ArH), 4.302 (d, ^2J = 13.3 Hz, 2H, $ArCH_2Ar$), 4.149 (d, ^2J = 14.4 Hz, 2H, $ArCH_2Ar$), 4.161 (heptet, ^3J = 6.1 Hz, 2H, OCH; superimposed with d from $ArCH_2Ar$), 3.585 (d, ^2J = 13.3 Hz, 2H, $ArCH_2Ar$), 3.470 (d, ^2J = 14.4 Hz, 2H, $ArCH_2Ar$), 2.392, 2.196, 2.043, 1.923 (4 s, 6H each, $ArCH_3$), 1.448 (d, ^3J = 6.1 Hz, 6H, $CH(CH_3)_2$), 1.407 (d, ^3J = 6.1 Hz, 6H, $CH(CH_3)_2$); EI-MS, *m/z* 620 (M^+, 3).

General Procedure for the Synthesis of Calix[4]arene Monoalkyl Ethers. To a solution of the calix[4]arene **4a** (0.3–0.5 mmol) and CsF (0.3–0.5 mmol) in dry DMF (20 mL, molecular sieve 4Å) was added an excess of alkylating agent. The reaction mixture was stirred at 40 °C for 42–96 h. After completion of the reaction the solvent was removed under reduced pressure. The workup was carried out as described for the synthesis of 1,3-derivatives **9**.

10a: Chromatography with $CHCl_3/CCl_4$ (2:1) and recrystallization from *n*-hexane afforded 60% of white needles: mp >260 °C; ^1H NMR (400 MHz, pyridine-d_5) δ 9.695 (broad s, 3H, ArOH), 7.171, 7.143, 6.693, 6.636 (4 s, 1H each, ArOH and ArH), 4.672 (d, ^2J = 14.5 Hz, 1H, $ArCH_2Ar$), 4.601 (d, ^2J = 14.1 Hz, 1H, $ArCH_2Ar$), 4.551 (d, ^2J = 13.1 Hz, 1H, $ArCH_2Ar$), 4.252 (d, ^2J = 14.3 Hz, 1H, $ArCH_2Ar$), 4.029–3.887 (m, 3H, $ArCH_2Ar$ and $ArOCH_2$), 3.833 (d, ^2J = 13.0 Hz, 1H, $ArCH_2Ar$), 3.688 (d, ^2J = 14.2 Hz, 1H, $ArCH_2Ar$), 3.656 (d, ^2J = 14.3 Hz, 1H, $ArCH_2Ar$), 2.491 (s, 3H, $ArCH_3$), 2.450 (s, 3H, $ArCH_3$), 2.293 (s, 6H, $ArCH_3$), 1.967–1.833 (m superimposed with s from $ArCH_3$, 2H, CH_2CH_2), 1.907 (s, 6H, $ArCH_3$), 1.696–1.628 (m, 2H, CH_2CH_2), 1.334 (s, 3H, $ArCH_3$), 1.305 (s, 3H, $ArCH_3$), 0.900 (t, ^3J = 7.4 Hz, 3H, CH_2CH_3); FD-MS, *m/z* 592 (M^+, 100).

10b: Chromatography with $CCl_4/CHCl_3$ (4:1) afforded a yellow powder (53%); mp 205 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 9.27, 9.20, 8.29 (3 s, 1H each, ArOH), 8.34 (d, ^3J = 8.4 Hz, 2H, $Ar(NO_2)H$), 7.93 (d, ^3J = 8.5 Hz, 2H, $Ar(NO_2)H$), 6.95, 6.92, 6.89, 6.78 (4 s, 1H each, ArH), 5.17 (d, ^2J = 12.5 Hz, $ArOCH_2$), 5.04 (d, ^2J = 12.5 Hz, 1H, $ArOCH_2$), 4.28 (d, ^2J = 13.2 Hz, 1H, $ArCH_2Ar$), 4.18 (d, ^2J = 14.6 Hz, 1H, $ArCH_2Ar$), 4.02 (d, ^2J = 14.3 Hz, 1H, $ArCH_2Ar$), 3.92–3.63 (m, 5H, $ArCH_2Ar$), 2.41 (s, 3H, $ArCH_3$), 2.39 (s, 3H, $ArCH_3$), 2.23 (s, 3H, $ArCH_3$), 2.17 (s, 9H, $ArCH_3$), 2.02 (s, 3H, $ArCH_3$), 2.01 (s, 3H, $ArCH_3$); EI-MS, *m/z* 671 (M^+, 59), 147 (100).

10c: Chromatography with $CCl_4/CHCl_3$ (2:1); yield 51%; mp >390 °C; ^1H NMR (500 MHz, $CDCl_3$, −50 °C) δ 9.452 (s, 1H, ArOH), 9.259 (s, 1H, ArOH), 9.213 (s, 1H, ArOH), 6.954, 6.938, 6.914, 6.827 (4 s, 1H each, ArH), 4.322 (d, ^2J = 13.4 Hz, 1H, $ArCH_2Ar$), 4.175 (d, ^2J = 14.6 Hz, 1H, $ArCH_2Ar$), 4.106 (d, ^2J = 14.0 Hz, 1H, $ArCH_2Ar$), 4.032 (s, 3H, $ArOCH_3$), 3.943 (d, ^2J = 14.0 Hz, 1H, $ArCH_2Ar$), 3.870 (d, ^2J = 14.7 Hz, 1H, $ArCH_2Ar$), 3.773 (d, ^2J = 13.4 Hz, 1H, $ArCH_2Ar$), 3.689 (d, ^2J = 14.0 Hz, 2H, $ArCH_2Ar$), 2.430, 2.415, 2.275, 2.215, 2.180, 2.169, 2.044, 2.037 (8 s, 3H each, $ArCH_3$); EI-MS, *m/z* 550 (M^+, 100).

10a and **10b** were obtained also in yields of 93 and 5%, respectively, by partial cleavage of the corresponding dialkyl ether **9** with 1 equiv of iodotrimethylsilane.[30]

10d: Obtained as side product of **9h**; yield 13%, white crystals from ethanol/CH_2Cl_2; mp 301–303 °C dec; ^1H NMR (400 MHz, $CDCl_3$) δ 9.616, 9.385, 9.353 (3 s, 1H each, ArOH), 6.919, 6.900, 6.880, 6.807 (4 s, 1H each, ArH), 4.356 (d, ^2J = 13.2 Hz, 1H, $ArCH_2Ar$), 4.360 (heptet, ^3J = 6.1 Hz, 1H, OCH; superimposed with d from $ArCH_2Ar$), 4.140 (d, ^2J = 14.4 Hz, 2H, $ArCH_2Ar$), 3.907 (d, ^2J = 14.6 Hz, 1H, $ArCH_2Ar$), 3.850 (d, ^2J = 14.6 Hz, 1H, $ArCH_2Ar$), 3.689 (d, ^2J = 13.1 Hz, 1H, $ArCH_2Ar$), 3.665 (d, ^2J = 14.5 Hz, 1H, $ArCH_2Ar$), 3.614 (d, ^2J = 14.3 Hz, 1H, $ArCH_2Ar$), 2.401, 2.391, 2.253, 2.173, 2.148, 2.129, 2.018, 2.000 (8 s, 3H each, $ArCH_3$), 1.561, 1.478 (2 d, ^3J = 6.2 Hz, 3H each, $CH(CH_3)_2$); EI-MS, *m/z* 578 (M^+, 6).

Triester 10e: Ethyl bromoacetate (2.4 mmol) was added to a suspension of calix[4]arene **4b** (0.3 mmol) and K_2CO_3 (2.4 mmol) in 20 mL of dry acetone. The mixture was refluxed for 12 h and worked up in the usual way (as described for instance for compounds **9**). Recrystallization from methanol/CH_2Cl_2 gave shining white crystals: yield 51%; mp 192–194 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.026, 6.931, 6.226, 5.994, 5.929 (5 s, 1H each, ArH and ArOH), 5.215 (d, ^2J = 17.0 Hz, 1H, $ArOCH_2$), 4.949 (d, ^2J = 14.2 Hz, 1H, $ArCH_2Ar$), 4.946 (d, ^2J = 17.1 Hz, 1H, $ArOCH_2$), 4.826 (d, ^2J = 14.0 Hz, 1H, $ArCH_2Ar$), 4.711 (d, ^2J = 15.5 Hz, 1H, $ArOCH_2$), 4.544 (d, ^2J = 15.7 Hz, 1H, $ArOCH_2$), 4.39–4.17 (m, 10H, $ArCH_2Ar$, $ArOCH_2$, CH_2CH_3), 4.060 (q, ^3J = 7.1 Hz, 2H, CH_2CH_3), 3.597 (d, ^2J = 14.0 Hz, 1H, $ArCH_2Ar$), 3.581 (d, ^2J = 14.0 Hz, 1H, $ArCH_2Ar$), 3.352 (d, ^2J = 14.5 Hz, 1H, $ArCH_2Ar$), 3.297 (d, ^2J = 14.5 Hz, 1H, $ArCH_2Ar$), 3.20–3.15 (m, 2H, ArCH), 2.608 (heptet, ^3J = 6.7 Hz, 1H, ArCH), 2.444 (s, 3H, $ArCH_3$, superimposed with heptet, 1H, ArCH), 2.393, 1.834, 1.572 (3 s, 3H each, $ArCH_3$), 1.294, 1.287 (2 t, ^3J = 7.1 Hz, 3H each, CH_2CH_3), 1.25–1.17 (m, 15H, CH_2CH_3 and $CH(CH_3)_2$), 0.896, 0.795, 0.623, 0.324 (4 d, ^3J = 6.7 Hz, 3H each, $CH(CH_3)_2$); FD-MS, *m/z* = 906 (M^+, 100).

X-ray Structures. Crystal data for **4a**: $C_{36}H_{40}O_4$, molecular weight 536.709 amu; triclinic, space group $P\bar{1}$, *a* = 12.344(3), *b* = 12.804(3), *c* = 10.331(3) Å, α = 96.32(2), β = 101.80(2), γ = 62.30(2), *V* = 1414.9(7) Å^3, *Z* = 2, ρ_{calcd} = 1.260 g cm^{-3}; *F*(000) = 576, (Cu K_α) 5.98 cm^{-1}.

X-ray diffraction experiments were carried out at *T* = 295 K on a Siemens A.E.D. diffractometer on line on a IBM PC using Ni-filtered Cu K_α radiation (λ = 1.54178 Å). The lattice parameters were determined by a least-squares fit of 30 $(\nu,\chi,\phi)_{hkl}$ reflections found in a random search on the reciprocal lattice in the range 30 < ν < 40°.

The systematic data collection was performed in the range 3 < ν < 70° with a scan width from [ν − 0.65] to [ν + 0.65 + Δλ/λtgν]. The intensities of the ±h,±k,+l reflections were determined by profile analysis according to the Lehman and Larsen procedure.[42] The intensity of one standard reflection, measured every 100 ones, showed no significant fluctuations. The intensities were corrected for Lorentz and polarization effects but not for absorption. A total of 5697 reflections were collected and the 4580 with $I > 2\sigma(I)$ were used in the refinement of the molecular model.

The structure was solved by direct methods, using the SHELX86 package,[43] which showed all the non-hydrogen atoms with the exception of one methyl group. The structure was completed by Fourier ΔF methods and refined by full-matrix least-squares methods with the SHELX76 package.[44] Some of

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(43) Sheldrick, G. M., SHELX86 Program for Crystal Structure Solution, 1986, University of Göttingen, Germany.
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the hydrogens were found in the Fourier map, the remaining ones were taken in their calculated positions with the geometrical constraint C–H 1.08 Å and refined "riding" on their C-atoms. In particular three of the four hydroxy hydrogens were found in the ΔF map. The hydrogen atoms of each methyl group were refined in a rigid group with a common isotropic temperature factor.

A total of 455 parameters were refined: the overall scale factor, the atomic coordinates, the anisotropic thermal parameters for all non-hydrogen atoms. The refinement was stopped at R = 0.0122 (unit weights). The highest peak in the final Fourier ΔF map was 0.46 e Å^{-3}.

The atomic scattering factors were obtained by analytical approximation according to the literature.[45] Geometrical calculations were performed by PARST.[46] Perspective plots of the molecule have been carried out by PLUTO.[47]

Crystal data for **8a** have been reported already.[21] Lists of fractional atomic coordinates of the non-hydrogen atoms of both compounds, as well as lists of the thermal parameters, fractional atomic coordinates for the hydrogen atoms, complete lists of bond distances and bond angles, and lists of the observed and calculated structure factors have been deposited at the Cambridge Crystallographic Data Centre.

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Supplementary Material Available: Proton NMR spectra (25 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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