A New Route to Chiral Calix[4]arenes *via* 1,3-Derivatization

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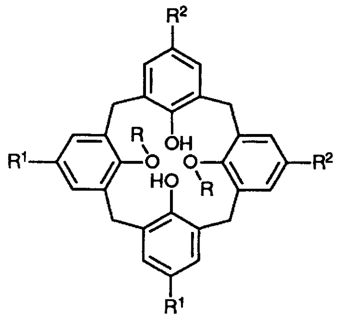
Alkylation of the phenolic hydroxy groups in the 1,3-position in calix[4]arenes consisting of two different phenolic units arranged in the order AABB leads to a new type of chiral calix[4]arenes in the cone conformation.

Calixarenes have attracted appreciable interest as potential host molecules, because of their easy accessibility and their large variety.[1] Chiral derivatives of calixarenes may be obtained by attaching chiral residues to the calixarene framework. Some of the many possible derivatives, which in principle can be obtained by this idea, have been synthesized and studied by Shinkai.[2]

In contrast, our interest was focussed on the synthesis of inherently chiral calix[4]arenes which are built up of non-chiral subunits and consequently owe their chirality only to the



a; $R^1 = Me, R^2 = Bu^t$
b; $R^1 = Ph, R^2 = Bu^t$

(**1**) R = H
(**2**) $R = CH_2CO_2Et$
(**3**) $R = Pr^i$

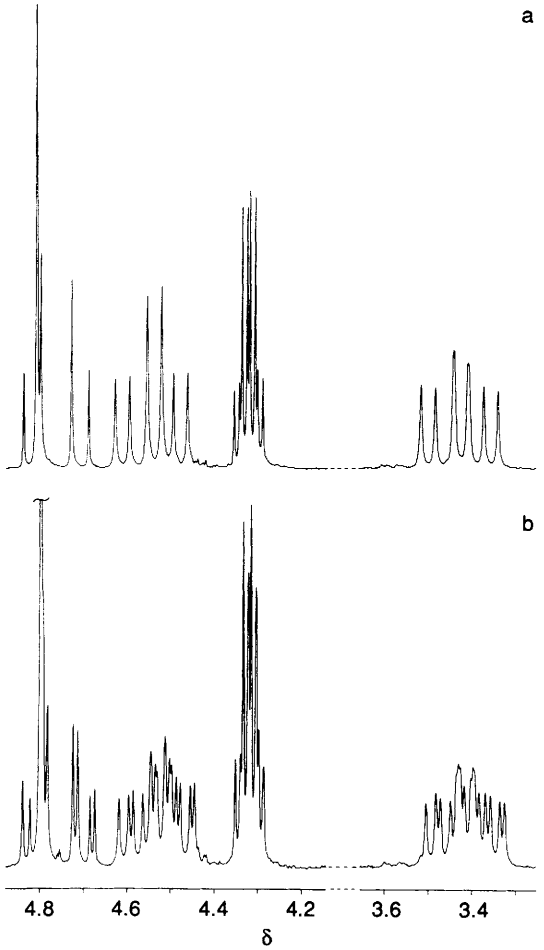


Figure 1. (a) Portions of the methylene proton resonances (Ar–CH_2–Ar, O–CH_2–CO, O–CH_2–Me) in the ^{1}H NMR spectrum ($CDCl_3$; 400 MHz) of (**2b**), and (b) the same spectrum in the presence of (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol.

fact that the calix[4]arene molecule is not planar. Asymmetric molecules of this type may be obtained if the calix[4]arene molecule is composed of three (in the order AABC) or four different *para*-substituted phenolic units,[3] or by the incorporation of a single *meta*-substituted phenolic unit.[4] Alternatively, dissymmetric calix[4]arenes with a C_2 or C_4 axis result if two or four *meta*-substituted phenolic units are incorporated in a definite way.[5]

To obtain stable enantiomers in any of the above arrangements it is necessary in all cases to fix the calix[4]arene in the cone conformation by the introduction of suitable residues on the phenolic hydroxy groups, which completely hinder the ring inversion.†[6] Recently several authors reported that *O*-alkylation or *O*-acylation of calix[4]arenes can be easily achieved at the 1,3-positions under carefully controlled conditions leading in high yields to the corresponding disubstituted derivatives.[7] If such a derivatization is carried out with a calix[4]arene consisting of two different phenolic units (in the order AABB) only *a single constitutional isomer is possible, and this derivative is chiral.* We describe here the first examples of this new type of chiral calix[4]arene, which are already fixed in the cone formation and which again owe their chirality to the non-planarity of the molecule as a whole and not to the presence of a chiral subunit or appendage.

Calix[4]arenes of the 'AABB-type' were first described by No and Gutsche.[8] They may be also prepared by the fragment condensation of a suitable dimer (AA) with a bisbromomethylated dimer (BB).[3a] Two compounds of this type, (**1a**) and (**1b**), were treated with ethyl bromoacetate (R–Br) in acetonitrile in the presence of potassium carbonate under conditions similar to those described by McKervey *et al.*[7b] [ratio (**1**) : R–Br : K_2CO_3 = 1 : 2 : 1; 4 h reflux], to yield the corresponding 1,3-derivatives after recrystallization from $CHCl_3$/ethanol: (**2a**) (82%; m.p. 108—110 °C) and (**2b**) (64%; m.p. 190—192 °C). The ^{1}H NMR spectra‡ of both compounds show two (but only two) singlets for the t-butyl groups [δ 1.08 and 1.24 for (**2a**) and 1.00 and 1.27 for (**2b**)] and two singlets for the methyl groups in the case of (**2a**) (δ 2.05 and 2.18) which is the most obvious proof that only the 1,3-derivatives were formed.‡

In a similar way by reaction of (**1a**) with a slight excess of isopropyl iodide [ratio (**1a**): R–I : K_2CO_3 = 1 : 3 : 3; 48 h reflux] compound (**3a**) could be obtained (the conversion was followed by TLC) in 54% yield (m.p. 172—174 °C) after recrystallisation from $CHCl_3$/ethanol.

The ^{1}H NMR spectra of these derivatives are rather complex, because all the functional groups are different. As an example, Figure 1(a) shows the methylene proton region (Ar–CH_2–Ar, O–CH_2–CO, and O–CH_2–Me) for compound (**2b**). The chirality is clearly demonstrated by the AB-system for the diastereotopic protons (–O–CH_2–CO–) of the residues attached to the phenolic oxygens. Interestingly two pairs of doublets are found for (**2a**), while in (**2b**) one methylene group gives a pseudo-singlet. Notwithstanding the complex spectra, the chirality could be further demonstrated by the addition of Pirkles reagent [1-(9-anthryl)-2,2,2-trifluoroethanol], which causes a doubling of peaks (ratio 1 : 1) in all cases [Figure 1(b)].

Since calix[4]arenes of the type AABB are now readily available, their 1,3-derivatization, including also more sophisticated derivatives such as calixcrowns,[7a,9] provides an easy access to a new type of chiral host molecules in which the remaining two hydroxy groups offer additional advantages. The recent discovery of a 1,2-derivatization of calix-

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† While these reactions caused no problems with calix[4]arenes having C_4 symmetry, many difficulties arose here with the totally asymmetric compounds.

‡ Satisfactory elemental analyses, ^{1}H NMR spectra, and electron impact mass spectra were obtained for all new compounds.

[4]arenes[10,11] should also be useful for a similar purpose, if calix[4]arenes of the 'ABAB-type' are used as the macrocyclic substructure.

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