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Diastereoselective Lower Rim (1*S*)-Camphorsulfonylation as the Shortest Way to the Inherently Chiral Calix[4]arene

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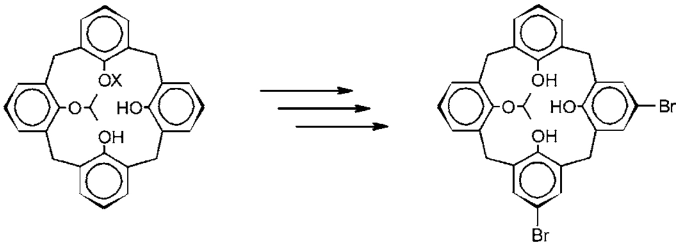
ABSTRACT



single enantiomer

A diastereomeric mixture of chiral 25-(1*S*)-camphorsulfonyloxy-26-isopropoxycalix[4]arene 2a (de 15%) and 25-isopropoxy-26-((1*S*)-10-camphorsulfonyl)calix[4]arene 2b has been obtained by asymmetrical lower rim (1*S*)-camphorsulfonylation of the monoisopropoxycalix[4]-arene. Pure diastereomer 2a has been obtained by simple crystallization, and its absolute configuration has been determinated by X-ray analysis. Enantiomerically pure inherently chiral 5,11-dibromo-26-isopropoxycalix[4]arene 4 has been synthesized by the upper rim dibromination of the diastereomer 2a followed by hydrolytical removal of the auxiliary camphorsulfonyl group.

Calixarenes are bowl-shaped macrocycles which are of great interest for the design of receptors of anions, cations, and neutral molecules.[1] Over the past few years, considerable efforts have been applied to the synthesis of chiral calixarenes and to the design of enantioselective sensors[2] and catalysts,[3] chiral stationary phases for chromatography,[4] and chiral solvating agents for NMR.[5] The unique cup-shaped architecture of calixarenes allows the synthesis of so-called *inherently chiral* species, in which the asymmetry is not connected with a chiral atom but with the asymmetric arrangement of substituents at the macrocyclic platform.

This could be done in two principal ways:[6] (1) fragment condensation and (2) substitution of the wide or/and narrow rims of the macrocyclic skeleton. Among the substitution

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(1) For reviews, see: (a) Gutsche, C. D. *Calixarenes Revisited*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambrige, 1998. (b) *Calixarenes 2001*; Asfari, Z., Bohmer, V., Harowfield, J., Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, 2001.

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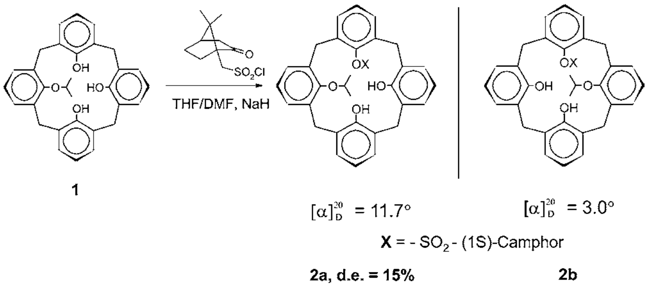
Scheme 1



patterns of the calix[4]arene lower rim,[7] the simplest one is the ABHH type possessing two different substituents in proximal position. Only a few examples of proximal heterodifunctionalization are known: all the compounds were obtained by multistep syntheses involving a protection and deprotection sequence[7b,8] or rearrangements.[9]

Most of the inherently chiral calixarenes were obtained as racemic mixtures or as mixtures of diastereomers in a 1:1 ratio.[10] Although a great number of such substances were obtained, only some of them were resolved into individual enantiomers[11] or diastereomers.[12] Herein, we report on the synthesis of an ABHH-substituted calix[4]arene via the lower rim asymmetrical (1*S*)-monocamphorsulfonylation of monoisopropoxycalix[4]arene and its transformation to optically pure, inherently chiral 5,11-dibromo-26-isopropoxy-25,27,-28-trihydroxycalix[4]arene.

The reaction of calix[4]arene monoisopropyl ether **1**[13] with 1.08 equiv of 1(*S*)-(+)-camphor-10-sulfonyl chloride in a THF/DMF (10/0.5) solution at room temperature in the presence of 1.1 equiv of sodium hydride gives a diastereomeric mixture of proximally substituted camphor derivatives **2a** and **2b** of the ABHH-type, inherently chiral calixarene with 85% total yield (Scheme 1).

The ^{1}H NMR spectrum of the crude product contains the superposition of the signals of the two diastereomers **2a** and **2b** (Figure 1b) with 15% diastereomeric excess of **2a**.

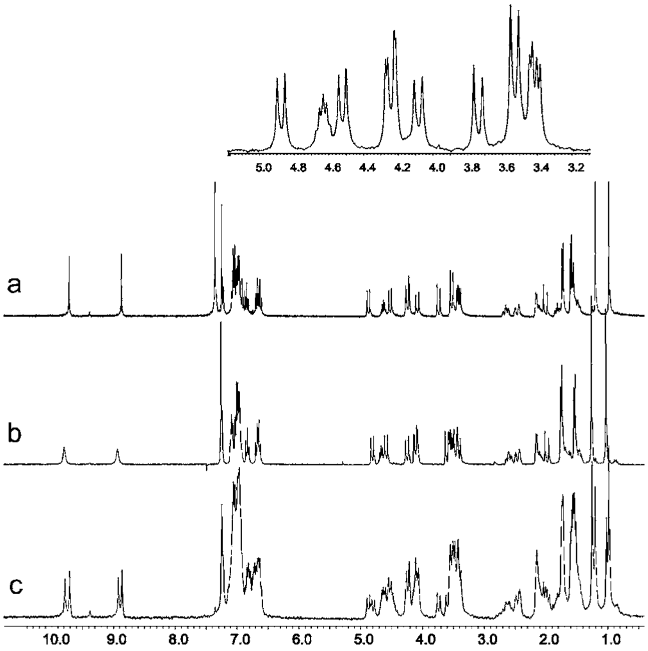


Figure 1. ^{1}H NMR spectra of diastereomer **2a** (a), diastereomer **2b** (b), and a diastereomeric mixture of **2a** and **2b** (c) at 300 MHz, in $CDCl_3$, at 298 K.

Diastereomer **2a** with 98% purity and 41% yield was obtained by simple crystallization from a mixture of benzene and hexane. The other diastereomer, **2b**, was also obtained by crystallization with 92% purity in 35% yield. Unexpectedly, the use in the sulfonylation reaction (Scheme 1) of a mild base K_2CO_3 in acetonitrile also leads to sulfonates **2a** (de 24%) and **2b** but in only 35% yield.[14]

The NMR spectrum of diastereomer **2a** provides some structural evidence. A set of 7 doublets at 4.88, 4.53, 4.23, 4.09 and 3.53, 3.43, 3.41 ppm corresponds to axial and

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[6] For general reviews on chiral calixarenes, see: Vysotsky, M. O.; Schmidt, C.; Bohmer, V. In *Advances in Supramolecular Chemistry*; Gokel, G., Ed.; JAI Press: Stanford, 2000; Vol. 7, pp 139−233.

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[10] (a) In the case of acetylation of tris(hydroxyethyl)calix[4]arenes with vinyl acetate using lipases as catalysts, a 100% enantiomeric excess of monoacetylated product was achieved with 19% yield. Browne, J. K.; McKervey, M. A.; Pitarch, M.; Russell, J. A.; Millership, J. S. *Tetrahedron Lett.* **1998**, *39*, 1787. (b) Assymetric induction was also applied for the synthesis of inherently chiral calix[4]arenes in high yields. Boyko, V. I.; Shivanyuk, A.; Pirozhenko, V. V.; Zubatyuk, R. I.; Shiskin, O. V.; Kalchenko, V. I. *Tetrahedron Lett.* **2006**, *47*, 7775.

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[13] 26-Monoisopropoxy-25,27,28-trihydroxycalix[4]arene was synthesized according to the litetrature but with sodium methylate (10% excess) as the base and a 5-fold excess of isopropyliodide. The reaction time was 15 h. The yield of compound **1** was 65%. Groenen, L. C.; Ruël, B. H. M.; Casnati, A.; Verboom, W.; Pochini, A.; Ungaro, R.; Reinhoudt, D. N. *Tetrahedron* **1991**, *47*, 8379.

[14] It is well known that the reactions performed in the presence of mild bases give exceptionally 1,3-disubstituted products, whereas 1,2-disubstituted products could be obtained with strong bases. For example, see: (a) Van Loon, J. D.; Arduini, A.; Coppi, L.; Verboom, W.; Rochini, A.; Ungaro, R.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1990**, *55*, 5639. (b) Groenen, L. C.; Ruel, B. H.; Casnati, A.; Timmerman, P.; Verboom, W.; Harkema, S.; Pochini, A.; Ungaro, R.; Reinhoudt, D. N. *Tetrahedron Lett.* **1991**, *32*, 2675. (c) Boyko, V. I.; Podoprigorina, A. A.; Yakovenko, A. V.; Pirozhenko, V. V.; Kalchenko, V. I. *J. Inclusion Phenom. Macrocyclic Chem.* **2004**, *50*, 193.

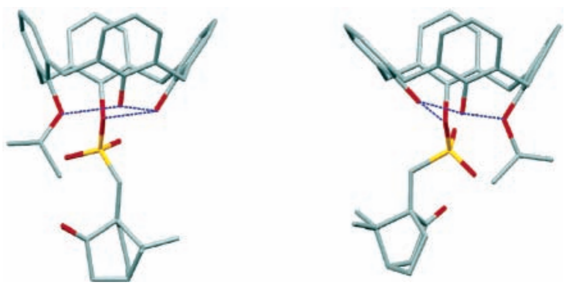


Figure 2. Molecular structure of diastereomers **2a** (left) and **2b** (right). Solvent molecules are omitted for clarity.

equatorial protons of the macrocyclic skeleton. This splitting pattern suggests that all the protons are different and corresponds to 1,2-heterodisubstituted calix[4]arene in a *cone* conformation. Two doublets at 4.25 and 4.24 ppm correspond to the AB spin system of the methylenesulfonate group. The methyl groups of isopropyl ether appear as two doublets at 1.74 and 1.60 ppm because of their diastereotopicity.

Diffraction quality crystals of both diastereomers have been grown from benzene−hexane (**2a**) and chloroform−hexane (**2b**) mixtures. X-ray analysis provides the absolute configuration of both species.

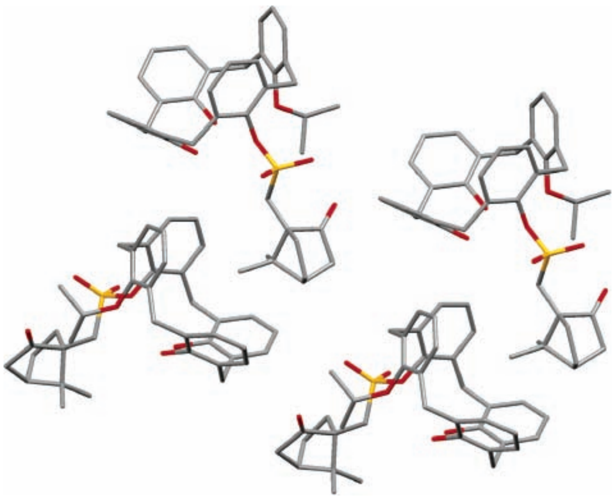


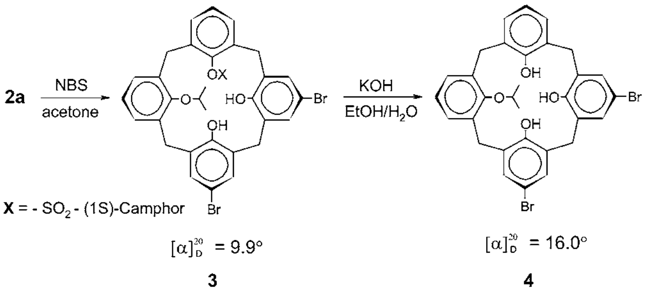
Figure 3. Packing of **2a** molecules in the crystal state.

Both calixarenes (Figure 2) are in a slightly distorted cone conformation. In diastereomer **2a**, the phenol ring opposite to the isopropyl-containing one is inclined. The angle between this ring and the main plain of the macrocycle, formed by the four carbons of the methylene bridges, is 141.7°. In diastereomer **2b**, the ring opposite the camphorsulfonyl-substituted one is inclined and the angle is 128.3°. In both cases, the conformation is stabilized with a network of hydrogen bonds (represented by dashed lines) at the narrow rim.

In the crystalline state, molecules are packed in chains. The camphor fragments of one chain are directed into the cavities of the macrocycles of another (Figure 3). The shortest distance between the carbon of one of camphor methyl group and the center of the aromatic ring of the macrocycle is 3.5 Å, suggesting a weak CH−π interaction, possibly guiding this inclusion pattern.

Chiral diastereomer **2a** was dibrominated at the upper rim with bromosuccinimide in acetone at room temperature yielding 94% of 5,11-dibromocalixarene **3**. The camphorsulfonyl group of **3** was removed under basic hydrolysis conditions yielding 73% of inherently chiral 5,11-dibromo-26-isopropoxycalix[4]arene **4** (Scheme 2).

Scheme 2



None of the reactions in Scheme 2 change the *inherent configuration* of compound **4**; consequently, it remains the same as in diastereomer **2a**.

In conclusion, in this research, we performed a simple and the shortest synthesis of chiral 25-((1*S*)-10-camphorsulfonyl)-26-isopropoxy-27,28-dihydroxycalix[4]arene **2a**, and the absolute configuration was determined by X-ray analysis. By simple reactions, inherently chiral 5,11-dibromo-26-isopropoxy-25,27,28-trihydroxycalix[4]arene has also been obtained. The calixarene possessing the reactive OH groups and bromine atoms could be used as a versatile platform in the design of chiral receptors or chiral advanced materials.

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Supporting Information Available: Experimental procedures for all the compounds, their characterization, and crystallographic details. This material is available free of charge via the Internet at http://pubs.acs.org.

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