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Synthesis of Glycidyl Calixarenes, Versatile Substrates for the Preparation of Chiral Calixarene-Based Ligands

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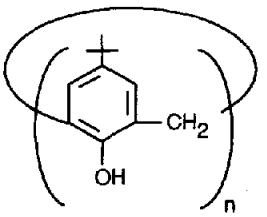
Abstract: The first calixarenes bearing chiral glycidyl groups at the lower rim have been obtained by treatment of *p-tert*-butylcalix[4]arene (**1a**) and *p-tert*-butylcalix[6]arene (**1b**) with glycidyl tosylate or 3-nitrobenzenesulfonate in the presence of a base. Their structure was established as *syn*-1,3-diglycidyl calix[4]arene **2**, tetraglycidyl calix[4]arene **3** (partial cone, 1,2-alternate and 1,3-alternate conformers), and 1,2,4,5-tetraglycidyl calix[6]arene **4**, respectively, by ^1H and ^{13}C NMR spectroscopy. Regio- and stereoselective epoxide ring-opening of **2** with amines led to chiral β-aminoalcohols (**5** and **6**).

Calixarene macrocycles (**1**) are the subject for increasing interest in the field of supramolecular chemistry or host-guest chemistry as basic skeletons for the synthesis of host compounds for ions or neutral molecules.[1] In this respect chiral calixarenes are of pivotal importance if enantioselective recognition or discrimination has to be exploited.[2] Chirality in calixarenes can be generated by either attaching chiral substituents at one of the rims (lower[3] or upper[4]) or synthetizing "inherently" chiral derivatives in which the nonplanarity of the molecule, in conjunction with an asymmetric substitution of the macrocycle, is exploited.[2,5] Despite its intellectual appeal, the inherent chirality suffers severe limitations, if homochiral compounds are required for practical applications, due to the difficulties met in the resolution of racemates.[5] Therefore, the former approach appears to be preferable when chiral derivatizing agents with high enantiomeric purity are available. Glycidyl arenesulfonates, commercially available in optically active form,[6] are a good example of such derivatizing agents. In fact, they may undergo nucleophilic attack at C-1 position with phenoxide anions leading to chiral glycidyl ethers.[6b] Then, the 2,3-epoxide ring can be opened by a regio- and stereoselective attack at C-3, thus allowing to introduce a variety of functionalities.[6,7]

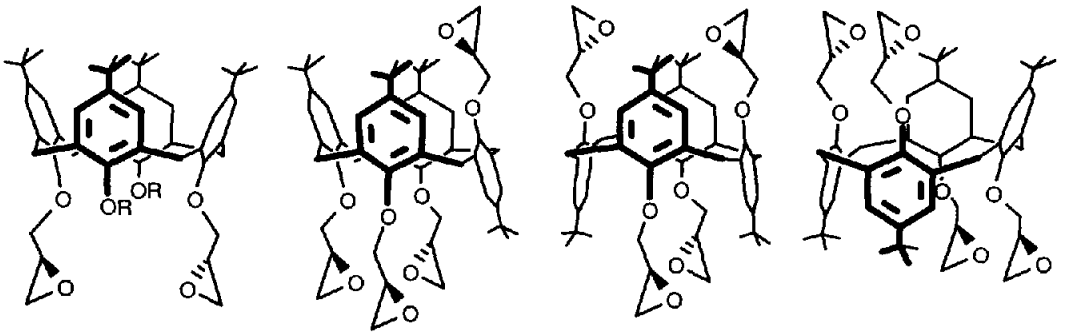


1a n = 4
1b n = 6

In the present paper we wish to report the synthesis of the first chiral calixarenes bearing glycidyl groups at the lower rim and examples of subsequent synthetic transformantions leading to compounds with potential applications as chiral auxiliaries.

As a first approach for the synthesis of glycidyl calixarenes, *p-tert*-butylcalix[4]arene (**1a**) was refluxed overnight with 2.2 equiv (*S*)-(+)-glycidyl toluensulfonate in CH_3CN, in the presence of K_2CO_3 as the base. Evaporation of the solvent under reduced pressure afforded a residue which was washed with water and then flash-chromatographed to give 1,3-diglycidyl calix[4]arene **2** in 78% yield.[8] The *syn*-distal disubstitution of **2** and its dissymmetry (due to the presence of a single C_2 axis of symmetry) was inferred from ^1H and ^{13}C NMR data. Thus, the presence in the ^1H NMR spectrum of two 1:1 resonances for *tert*-butyl groups at 0.98 and 1.30 ppm and two AX systems (δ 3.33 and 4.33, J = 13.0 Hz; 3.34 and 4.31, J = 13.0 Hz) for $ArCH_2Ar$ groups evidenced

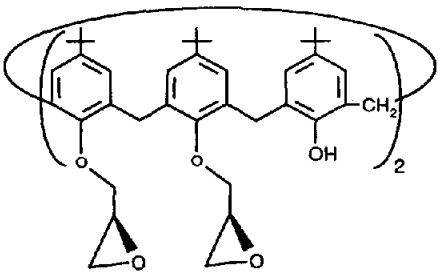
the 1,3-disubstitution of the macrocycle as well as its cone conformation. The ^{13}C NMR spectrum also agreed with the cone conformation[9] (two partially overlapped $ArCH_2Ar$ signals at 31.5 ppm in the DEPT experiment) as well as the equivalence of the two glycidyl groups [δ 44.6 (OCH_2), 50.2 (OCH) and 75.6 (OCH_2)].



2 R = H **3**-pc **3**-1,3-alt **3**-1,2-alt

A close scrutiny of the NMR spectra of samples of chromatographically purified **2** revealed the presence of small shoulders or satellite peaks attributable to the presence of the (*R,S*)-*meso*-diastereoisomer, the most probable by-product if non-enantiopure[6c] glycidyl tosylate is used or in the case of reduced regioselectivity in the nucleophilic attack at C-1 *vs* C-3 of the derivatizing agent.[6b] Integration of the pertinent signals in the ^1H NMR spectrum of **2** indicated a 9-12% abundance of the *meso*-isomer. The problem of the diastereomeric purity of **2** prompted us to use (*S*)-(+)-glycidyl 3-nitrobenzenesulfonate as the alkylating agent since this compound, available with high enantiomeric purity, undergoes displacement of the sulfonate group with better regioselectivity than glycidyl tosylate.[6b,c] In fact, compound **2** obtained in this case and isolated by chromatography had a diastereomeric purity higher than 97%.

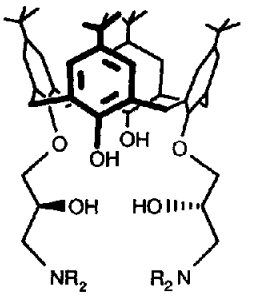
Exhaustive alkylation of **1a** using Cs_2CO_3 as base afforded tetraglycidyl calix[4]arene **3** in the three out of the four possible extreme conformations: partial-cone (**3**-pc, 24%), 1,2-alternate (**3**-1,2-alt, 18%) and 1,3-alternate (**3**-1,3-alt, 43%). The structure and conformation of these compounds[8] was established by their distinctive pattern in the ^1H and ^{13}C NMR[9] spectra, reflecting the molecular symmetry. Thus, the asymmetric **3**-pc was characterized by the presence of four *t*-Bu signals in the ^1H NMR spectrum (δ 1.03, 1.04, 1.34, 1.38) and four $ArCH_2Ar$ resonances in the ^{13}C NMR spectrum (δ 31.1×2C, 37.0, 37.7), while **3**-1,2-alt, possessing C_2-symmetry, gave two *t*-Bu and three $ArCH_2Ar$ signals (^1H NMR δ 1.24, 1.34; ^{13}C NMR δ 29.7, 38.6, 39.0). Compound **3**-1,3-alt with D_2-symmetry gave one *t*-Bu and two $ArCH_2Ar$ signals (^1H NMR δ 1.26; ^{13}C NMR δ 37.6, 38.1). To the best of our knowledge these tetraglycidyl derivatives are the first example of calix[4]arenes bearing chiral substituents in non-cone conformation.



4

Analogous treatment of *p-tert*-butylcalix[6]arene (**1b**) with (*S*)-(+)-glycidyl toluensulfonate and Cs_2CO_3 as base afforded 1,2,4,5-tetraglycidyl calix[6]arene **4** in 45% yield.[8] Due to the presence of four chiral substituents, this structure is also dissymetric, with a single C_2 axis of symmetry, and therefore its ^1H NMR spectrum shows three 1:1:1 resonances for the *tert*-butyl groups at 1.08, 1.17 and

1.22 ppm. However, due to a partially reduced conformational mobility, a complete analysis of the spectrum requires heating at 330 K. Two sets of oxygen-bearing carbons [δ 44.2, 44.7 (t), 50.3x2C (d), 74.1 and 74.3 (t)] in the ^{13}C NMR spectrum (313 K) evidenced the presence of two non-equivalent glycidyl groups.



5 R = H
6 R = Me

The synthetic versatility of glycidyl derivatives in asymmetric synthesis, in particular for biologically relevant compounds, is well known.[7,10] In the case of glycidyl calixarenes this was tested subjecting them to ring-opening reactions using amines as nucleophiles.[10a,d] Thus, treatment of diglycidyl calix[4]arene **2** in acetonitrile with aqueous NH_3 at 50 °C afforded β-aminoalcohol **5** in 79% yield.[8] The nucleophilic attack at the 3 position of the 2,3-epoxide ring was firmly established by the presence, in its ^{13}C DEPT NMR, of a *C*HOH resonance at 68.8 ppm and a CH_2NH_2 signal at 54.9 ppm. The ring-opening reaction proceeded with very high stereoselectivity since no loss of diastereomeric purity of the starting **2** was observed in ^1H NMR analysis. Similarly, the *N,N*-dimethyl-β-aminoalcohol **6** was obtained using aqueous *N,N*-dimethylamine in 88% yield.[8] Compound **6** belongs to the general class of dialkylamino alcohols, which have found widespread use as chirality promoters in aldehydes alkylation with diorganozinc compounds.[11a] In accordance, preliminary results have shown that **6** possesses complexing property toward Zn^{2+} cation.

Since a large variety of nucleophiles can be used for the epoxide ring opening with regio- and stereoselectivity,[7,10] glycidyl calixarenes may be considered versatile substrates for the synthesis of numerous chiral analogs. The β-aminoalcohols **5** and **6**, here reported as examples, have structural features indicative of their potential use as ligand for chiral auxiliaries.[11] These aspects and other applications of glycidyl calixarenes are currently under investigation in our laboratory.

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8. Satifactory microanalytical and spectral data were obtained for compounds **2-6**. ^{1}H-NMR spectra were taken at 250 MHz in $CDCl_3$ at rt unless otherwise stated. Compound (*S,S*)-**2**: $[\alpha]^{25}_D$ +4.9 (*c* 6.6, $CHCl_3$); ^{1}H-NMR δ 0.98, 1.30 [s, $C(CH_3)_3$, 18H each], 2.99 (dd, *J* = 5.0, 4.2 Hz, 3-GlyH, 2H), 3.08 (dd, *J* = 5.0, 2.6 Hz, 3-GlyH, 2H), 3.33 and 4.33 (AX, *J* = 13.0 Hz, $ArCH_2Ar$, 4H), 3.34 and 4.31 (AX, *J* = 13.0 Hz, $ArCH_2Ar$, 4H), 3.56 (m, 2-GlyH, 2H), 4.07 (dd, *J* = 11.1, 4.9 Hz, 1-GlyH, 2H), 4.27 (dd, *J* = 11.1, 3.0 Hz, 1-GlyH, 2H), 6.82 and 6.83 (AB, *J* = 2.5 Hz, ArH, 4H), 7.06 and 7.07 (AB, *J* = 2.4 Hz, ArH, 4H), 7.21 (s, ArOH, 2H). Compound (*S,S,S,S*)-**3**-pc: $[\alpha]^{25}_D$ +4.7 (*c* 0.95, $CHCl_3$); ^{1}H-NMR δ 1.03, 1.04, 1.34, 1.38 [s, $C(CH_3)_3$, 9H each], 2.34 (dd, *J* = 4.8, 2.8 Hz, 3-GlyH, 1H), 2.47-2.59 (overlapped, 3-GlyH, 3H), 2.70 (dd, *J* = 4.6, 4.5 Hz, 3-GlyH, 1H), 2.86-2.91 (overlapped, 3-GlyH, 3H), 3.09 and 4.09 (AX, *J* = 12.9 Hz, $ArCH_2Ar$, 2H), 3.11 and 4.26 (AX, *J* = 12.7 Hz, $ArCH_2Ar$, 2H), 3.26 (m, 2-GlyH, 2H), 3.34-3.53 (overlapped, 1-GlyH, 2-GlyH, 7H), 3.69 and 3.80 (AB *J* = 13.8 Hz, $ArCH_2Ar$, 2H), 3.72 and 3.74 (AB, *J* = 12.4 Hz, $ArCH_2Ar$, 2H), 4.05-4.22 (overlapped, 1-GlyH, 3H), 6.57 and 7.07 (AB, *J* = 2.4 Hz, ArH, 2H), 6.59 and 6.94 (d, *J* = 2.5 Hz, ArH, 2H), 7.06 and 7.11 (AB, *J* = 2.2 Hz, ArH, 2H), 7.28 and 7.51 (AB, *J* = 2.5 Hz, ArH, 2H). Compound (*S,S,S,S*)-**3**-1,3-alt: $[\alpha]^{25}_D$ +9.2 (*c* 0.48, $CHCl_3$); ^{1}H-NMR δ 1.26 [s, $C(CH_3)_3$, 36H], 2.49 (dd, *J* = 5.0, 2.7 Hz, 3-GlyH, 4H), 2.80 (dd, *J* = 5.0, 4.4 Hz, 3-GlyH, 4H), 3.10 (m, 2-GlyH, 4H), 3.34 (dd, *J* = 11.2, 6.3 Hz, 1-GlyH, 4H), 3.68, 3.72 (s, $ArCH_2Ar$, 4H each), 3.92 (dd, *J* = 11.2, 2.6 Hz, 1-GlyH, 4H), 7.05 and 7.18 (AB, *J* = 2.4 Hz, ArH, 8H). Compound (*S,S,S,S*)-**3**-1,2-alt: $[\alpha]^{25}_D$ -28.1 (*c* 0.84, $CHCl_3$); ^{1}H-NMR δ 1.24, 1.34 [s, $C(CH_3)_3$, 18H each], 1.95 (dd, *J* = 4.9, 2.7 Hz, 3-GlyH, 2H), 2.22 (dd, *J* = 4.9, 2.7 Hz, 3-GlyH, 2H), 2.28 (dd, *J* = 4.9, 4.4 Hz, 3-GlyH, 2H), 2.39 (m, 2-GlyH, 2H), 2.53 (dd, *J* = 4.9, 4.5 Hz, 3-GlyH, 2H), 3.02 (m, 2-GlyH, 2H), 3.21 and 4.25 (AX, *J* = 12.3 Hz, $ArCH_2Ar$, 4H), 3.31 (dd, *J* = 10.3, 4.2 Hz, 1-GlyH, 2H), 3.44 (dd, *J* = 10.3, 5.0 Hz, 1-GlyH, 2H), 3.54 (dd, *J* = 11.0, 6.9 Hz, 1-GlyH, 2H), 3.82 (dd, *J* = 11.0, 3.4 Hz, 1-GlyH, 2H), 3.92 (s, $ArCH_2Ar$, 4H), 7.02 (d, *J* = 2.3 Hz, ArH, 2H), 7.10 (d, *J* = 2.3 Hz, ArH, 2H), 7.22 (d, *J* = 2.3 Hz, ArH, 2H), 7.26 (d, *J* = 2.3 Hz, ArH, 2H). Compound (*S,S,S,S*)-**4**: $[\alpha]^{25}_D$ -8.4 (*c* 0.98, $CHCl_3$); ^{1}H-NMR (334 K) δ 1.12, 1.19, 1.25 [s, $C(CH_3)_3$, 18H each], 2.25 (dd, *J* = 4.9, 2.7 Hz, 3-GlyH, 2H), 2.33 (dd, *J* = 4.9, 4.4 Hz, 3-GlyH, 2H), 2.40 (dd, *J* = 4.8, 2.6 Hz, 3-GlyH, 2H), 2.56 (dd, *J* = 4.8, 4.4 Hz, 3-GlyH, 2H), 2.92 (m, 2-GlyH, 2H), 3.16 (m, 2-GlyH, 2H), 3.43 (dd, *J* = 11.0, 5.9 Hz, 1-GlyH, 2H), 3.63 (dd, *J* = 11.0, 3.4 Hz, 1-GlyH, 2H), 3.67-4.10 (overlapped, $ArCH_2Ar$ and 1-GlyH, 16H), 6.30 (bs, ArOH, 2H), 6.90-7.12 (overlapped, ArH, 12H). (*S,S*)-**5**: $[\alpha]^{25}_D$ -2.2 (*c* 0.85, $CHCl_3$); ^{1}H-NMR δ 1.18, 1.23 [s, $C(CH_3)_3$, 18H each], 3.26 (dd, *J* = 12.4, 7.2 Hz, CH_2N, 2H), 3.38 and 4.53 (AX, *J* = 13.0 Hz, $ArCH_2Ar$, 4H), 3.43 and 4.20 (AX, *J* = 12.9 Hz, $ArCH_2Ar$, 4H), 3.45 (dd, *J* = 12.4, 7.9 Hz, CH_2N, 2H), 4.08 (dd *J* = 10.1, 5.4 Hz, OCH_2, 2H), 4.22 (bm, OCH_2, 2H), 4.24 (bm, C*H*OH, 2H), 7.03 and 7.05 (AB, *J* = 2.3 Hz, ArH, 4H), 7.06 and 7.07 (AB, *J* = 2.0 Hz, ArH, 4H). (*S,S*)-**6**: $[\alpha]^{25}_D$ +12.2 (*c* 1.03, $CHCl_3$); ^{1}H-NMR δ 1.15, 1.24 [s, $C(CH_3)_3$, 18H each], 2.38 [s, $N(CH_3)_2$, 12H], 2.56 (dd, *J* = 12.4, 6.3 Hz, CH_2N, 2H), 2.71 (dd, *J* = 12.4, 6.8 Hz, CH_2N, 2H), 3.35 and 4.48 (AX, *J* = 12.9 Hz, $ArCH_2Ar$, 4H), 3.43 and 4.24 (AX, *J* = 13.5 Hz, $ArCH_2Ar$, 4H), 3.94 (dd, *J* = 9.3, 7.8 Hz, OCH_2, 2H), 4.27 (dd, *J* = 9.3, 2.3 Hz, OCH_2, 2H), 4.50 (bm, C*H*OH, 2H), 7.00 and 7.01 (AB, *J* = 2.5 Hz, ArH, 4H), 7.05 and 7.06 (AB, *J* = 2.2 Hz, ArH, 4H), 8.78 (s, ArOH, 2H).

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