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Novel Chiral Calix[4]arenes by Direct Asymmetric Epoxidation Reaction

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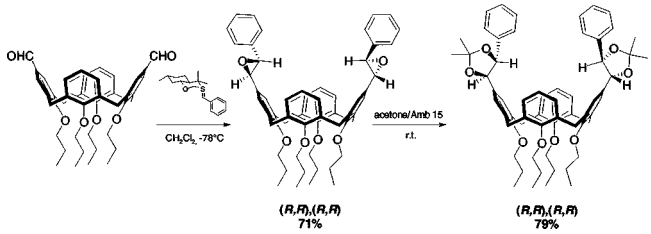

We report the first asymmetric synthesis of trans optically active (+) C_2 1,3-bisarylepoxide of calix[4]arene in excellent chemical yield and >99% ee, and its enantiospecific conversion to the corresponding bis-dioxolane

Calixarenes have attracted much attention in recent years for their unique structural/chemical properties, which allow their use in the synthesis of various molecular architectures. Since they are emerging as a new class of synthetic macrocycles possessing extensive host−guest chemistry,[1] chiral calixarenes are of particular importance for the enantioselective recognition and/or discrimination of chiral compounds. Chirality of calixarenes and, in particular, of the most studied calix[4]arenes has been generated by two different strategies. The first and most widely applied strategy usually requires the anchorage of the chiral constituents (mostly natural or commercially available compounds) at one rim of the calix[4]arenes. Among several examples, amino acids and small peptides[1c] were linked to the upper rim in the preparation of peptidocalixarenes, whose ability to bind different amino acids and other biological molecules was studied.[2] Recently, carbohydrates were also introduced,[3] and in such glycocalixarenes strong binding with certain proteins was detected.[4] Moreover, small molecules such as chiral epoxides[5] and, more recently, 1,2-amino alcohols[6] were anchored to the lower rim of calix[4]arenes. A drawback of this approach is the limited availability of the chiral fragments to be anchored to the macrocyclic platform.

The second strategy relies on the synthesis of "inherently" chiral calixarenes, in which the chirality is induced by an asymmetric substitution in the macrocycle, leading to the nonplanarity of the molecule.[7] This strategy appears more challenging, as there are always problems on regio- and stereoselectivity in the synthesis. Moreover, optical resolution of the racemates usually requires the use of HPLC methods.[8] In some cases, condensation with a chiral auxiliary allowed preparative TLC or conventional column chromatographic separation of diastereoisomers, whose cleavage afforded optically pure inherently chiral calixarenes.[9]

In principle, a third strategy for the preparation of chiral calixarenes could be easily expected via a "direct enantioselective reaction" on properly functionalized calixarenes. It is surprising to note that in spite of the significant number of reliable asymmetric reactions that have been developed so far, none of these has been applied on calixarenes. Our recent research was devoted to the synthesis of new calix[4]arenes possessing important chiral subunits on the upper rim (such as amino alcohols and related frameworks), which can be conveniently prepared by different enantioselective methods and subsequent elaboration of the chiral compounds.[10,11] In particular, we were interested in the more intriguing strategy with the direct generation of the appropriate functional groups.

Epoxides are among the most useful moieties in organic synthesis and, recently, 2,3-diaryloxiranes have been proved as versatile key intermediates.[12]

Most of the successful and widely applied asymmetric methods for their synthesis involve a transition metal-catalyzed

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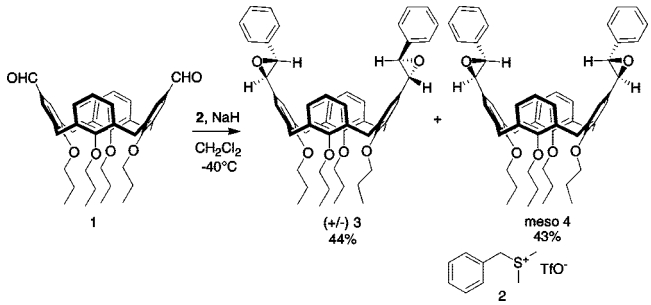
SCHEME 1. Synthesis of Calix[4]arene Bis-Epoxide in Achiral Conditions



reaction. However, the use of such metals appears, in principle, not to be compatible with substrates prone to coordination and/or complexation, like calixarenes. This can be, indeed, the main reason for the apparent lack of studies on direct asymmetric reactions on such macrocycles.

In this paper we report the first example of an efficient enantioselective preparation of a chiral calix[4]arene bis-epoxide via a direct asymmetric reaction on the parent 1,3-diformyl calix[4]arene.

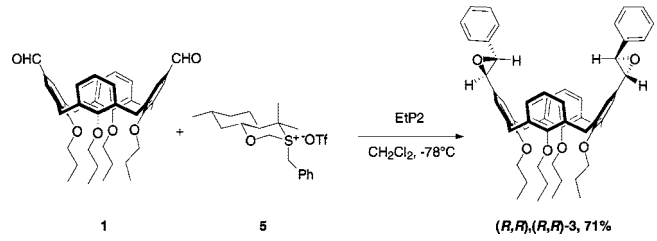
Our attention turned to the construction of a chiral epoxide fragment on the upper rim of the calix[4]arene with metal free methodologies.

Among the most successful ones, the Solladié−Cavallo preparation method of chiral trans biarylepoxides, which are usually obtained in high chemical yield and ee higher than 99%, seemed to be particularly appropriate.[13] In fact, this is a reaction between an appropriate aryl aldehyde and a chiral benzyliden sulfur ylide, which is derived from Eliel's oxathiane[14] and is generated in situ by deprotonation of the parent sulfonium salt with a strong base. Such an approach has proved to be general, allowing us to prepare, recently, new optically pure biarylepoxides, which were used as starting materials for the synthesis of functionalized 1,2-diarylethanols and acetonides.[15]

To test the reactivity of 1,3-diformyl calix[4]arene **1** toward sulfur ylides, the reaction was first performed with the achiral dimethyl benzyliden sulfur ylide (Scheme 1).

The bis-aldehyde **1** was easily prepared from commercial calix[4]arene by a slightly modified procedure[16] of the well-known approach,[17] in three steps by selective alkylation, formylation, and final exhaustive alkylation. The reaction on **1** was performed in homogeneous conditions, using benzyldimethylsulfonium triflate **2** as a soluble ylide precursor. The ylide was preformed in situ by deprotonation with NaH and after 15 h the reaction was complete toward two products (by TLC monitoring), which were obtained in 1:1 ratio and 87% overall yield, after chromatographic purification.

SCHEME 2. Synthesis of (*R*,*R*,)-(*R*,*R*)-Calix[4]arene Bis-Epoxide 3

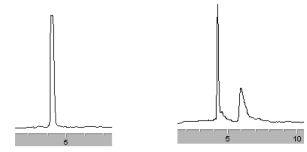


^{1}H and ^{13}C NMR analyses revealed the presence of two biaryl epoxides in both compounds. The coupling constant for the AB system of the oxiranyl protons appeared very small ($J_{AB} = 2.0$ Hz for one compound and $J_{AB} = 1.5$ Hz for the other one), confirming the expected trans,trans stereochemistry of the epoxides. Therefore, the two trans,trans stereoisomers were identified as the chiral C_2 compound **3** and the *meso* compound **4**, although we were unable, at that moment, to assign the correct structure of the two products. The complete stereoselectivity toward the trans,trans epoxides was delightfully unexpected, since the trans/cis ratio in model diarylepoxides bearing electron releasing groups on one aryl ring usually ranges between 2/1 and 4/1.[15b,18] This good preliminary result prompted us to attempt the asymmetric version of the reaction using the chiral sulfonium salt **5** derived from Eliel's oxathiane. After some attempts with different bases and conditions, the ylide was properly prepared with the phosphazene base EtP2 in dichloromethane at −78 °C under argon atmosphere and reacted immediately with the 1,3-diformyl calix[4]arene **1**. In this case a single product was detected and the reaction was completed in 6 h. After the usual workup and chromatographic purification, a single product was obtained in a gratifying 71% chemical yield (Scheme 2).

^{1}H and ^{13}C NMR analyses revealed the product as identical with one of the two (**3** or **4**) previously obtained via the achiral method (see Scheme 1). Moreover, the product appeared optically active, having a significant $[\alpha]^{25}_D$ value of +79.5 (*c* 1, $CHCl_3$). This strongly supported the formation of the chiral C_2 bis-epoxide **3**, which could be assigned to the structure previously described.

The ultimate determination of the optical purity of compound **3** was not trivial and was achieved after numerous attempts by using different chiral stationary phases in the HPLC analysis. Nevertheless, the final result with CHIRALPAK IA was quite satisfactory, not only in terms of separation conditions (Figure 1) but also for the ee value for compound **3**, which was higher than 99%.

To unambigously determine the absolute configuration of (+)-**3**, the bis-epoxide was crystallized from *n*-hexane and its



a) b)

FIGURE 1. HPLC analysis using the chiral stationary phase: (a) racemic bis-epoxide (+/−)-**3** and (b) optically pure bis-epoxide (+)-**3**.

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(16) One equivalent of base (K_2CO_3) was used in the first dipropylation step, and the last exhaustive propylation was performed directly on the bis-aldehyde, obtaining the desired bis-aldehyde **1** in 60% overall yield from commercial calix[4]arene.

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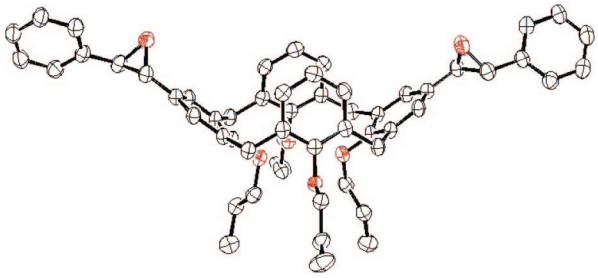
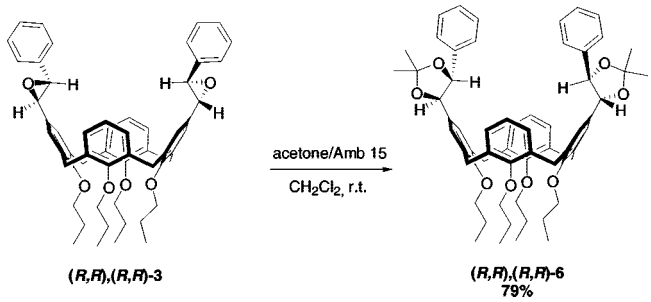


FIGURE 2. ORTEP plot of (+)-**3** with thermal ellipsoids drawn at 50% probability. Color code: red = O, black = C. Hydrogen atoms have been omitted for clarity.

SCHEME 3. Enantiospecific Conversion of Bis-Epoxide (*R*,*R*),(*R*,*R*)-3 to Bis-Acetonide (*R*,*R*),(*R*,*R*)-6



structure was determined by single-crystal X-ray analysis. Compound (+)-**3** crystallizes in monoclinic space group C2 and the crystal lattice comprises two inequivalent molecules with crystallographic C2 symmetry and identical absolute configuration. As shown in the representation, the calix[4]arene diepoxide adopts a "pinched cone" conformation and the oxiranyl carbon atoms have the (*R*,*R*)-(*R*,*R*) absolute configuration (Figure 2). This is the first direct confirmation of the general mechanistic model proposed for such reaction.[13a]

With these results in hand, we tried to stereoselectively transform such a diepoxide, in order to test its synthetic versatility as a chiral building block. Among our recent results on regio- and stereoselective ring-opening reactions of diaryl epoxides,[15] the direct conversion into 2,2-dimethyl-1,3-dioxolanes by the mild acetone/Amberlyst 15 system appeared very promising, on the way to the synthesis of diaryl glycols.[19] Thus, we submitted **3** to our conditions, and the corresponding trans,trans bis-acetonide **6** was obtained in excellent chemical yield (79%), with no loss of stereochemical integrity (Scheme 3).

^{1}H NMR analysis confirmed the trans,trans stereochemistry and HPLC analysis with the chiral stationary phase gave an ee value of 99%, which is identical with that of diepoxide **3**. The absolute configuration was assigned to be (*R*,*R*)-(*R*,*R*) by chemical correlation. On the basis of these data, the unprecedented diastereo- and enantioselective reaction on 1,3-diformylcalix[4]arene **1** to the corresponding 1,3-diepoxide (+)-**3**, coupled with the subsequent stereo- and enantiospecific conversion into 1,3-bisdioxolane **6** opens the way, currently under investigation in our laboratory, for further chiral functionalization of this important class of macrocycles via direct asymmetric reactions.

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Experimental Section

***trans*,*trans*-5,17-Bis(3′-phenyl-2′-oxiranyl)-25,26,27,28-tetrapropyloxycalix[4]arenes, 3 and 4.** To a suspension of NaH 97% (9.36 mg, 0.38 mmol) in CH_2Cl_2 (1.2 mL) a solution of 0.5 M benzyldimethylsulfonium triflate (**2**) in CH_2Cl_2 (0.64 mL) was added at 0 °C. After 1 h a solution of 5,17-diformyl 25,26,27,28-tetrapropyloxycalix[4]arene (**1**) (100 mg, 0.15 mmol) in CH_2Cl_2 (0.32 mL) was added and the mixture was stirred for 15 h at 0 °C. Once it reached room temperature, the mixture was quenched with 2 mL of H_2O and extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were dried over Na_2SO_4 and evaporated giving a residue that was purified on a silica gel column with hexane/diethyl ether (9:1) as eluent to afford **3** (55 mg, 44%) and **4** (53 mg, 43%).

(+/−)-**3** and (+)-**3**: ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 0.90 (m, 12H), 1.93 (m, 8H), 3.17 (d, 2H, J = 13 Hz), 3.21 (d, 2H, J =13 Hz), 3.68 (d, 1H, J = 1.5 Hz), 3.79 (d, 1H, J = 1.5 Hz), 3.87 (m, 8H), 4.48 (d, 2H, J = 13 Hz), 4.50 (d, 2H, J = 13 Hz), 6.55 (s, 2H), 6.59 (s, 2H), 6.62 (m, 6H), 7.31 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 10.2, 10.4, 23.2, 23.3, 29.7, 30.9, 31.1, 62.7, 62.9, 122.1, 123.4, 125.7, 127.9, 128.3, 128.4, 130.4, 134.8, 134.9, 135.1, 135.4, 137.6, 156.6, 156.7; mp 165−167 °C; MS ES+ (828) 851 $(M + Na)^+$. Anal. Calcd for $C_{56}H_{60}O_6$: C, 81.13; H, 7.29. Found: C, 80.0; H, 7.4.

4: ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 0.99 (t, 6H, J = 7.5 Hz), 1.04 (t, 6H, J = 7.5 Hz), 1.94 (m, 8H), 3.17 (d, 2H, J = 13 Hz), 3.20 (d, 2H, J = 13 Hz), 3.77 (t, 4H, J = 7 Hz), 3.79 (d, 1H, J = 2 Hz), 3.90 (d, 1H, J = 2 Hz), 3.99 (t, 4H, J = 7 Hz), 4.48 (d, 4H, J = 13 Hz), 6.34−6.40 (m, 6H), 6.95 (s, 2H), 6.96 (s, 2H), 7.37(m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 10.0, 10.6, 23.1, 30.9, 31.0, 62.5, 63.1, 76.7, 76.8, 122.2, 125.5, 126.6, 127.9, 128.1, 128.5, 130.1, 133.4, 133.6, 136.3, 136.7, 137.5, 155.6, 157.8; mp 194−199 °C; MS ES+ (828) 851 $(M + Na)^+$. Anal. Calcd for $C_{56}H_{60}O_6$: C, 81.13; H, 7.29. Found: C, 80.2; H, 7.2.

5,17-Bis((2′*R*,3′*R*)-3′-phenyl-2′-oxiranyl)-25,26,27,28-tetrapropyloxycalix[4]arene, (+)-3. To a solution of benzylic sulfonium salt **5** (190 mg, 0.43 mmol) in CH_2Cl_2 (2.5 mL) at −78 °C was added phosphazene base EtP2 (0.16 mL, 0.48 mmol) dropwise. After 10 min, a solution of 5,17-diformyl-25,26,27,28 tetrapropyloxy calix[4]arene (**1**) (127 mg, 0.19 mmol) in CH_2Cl_2 (0.35 mL) was added and the reaction was stirred for 6 h. The mixture was then warmed to rt, the reaction was quenched with H_2O (2 mL), and the organic phase extracted with CH_2Cl_2 (3 × 5 mL). The organic phases were collected, dried over anhydrous Na_2SO_4, and evaporated under vacuum. The crude residue was purified on silica gel column with *n*-hexane/CH_2Cl_2 (1:1) as eluent, to afford (+)-**3** (115 mg) as a white solid, in 71% yield. Mp 195−197 °C; $[\alpha]^{25}_D$ +79.5 (*c* 1 in $CHCl_3$); ee 99% (CHIRALPAK IA, hexane/2-propanol 95:5, flow rate 1 mL min^{-1}). Anal. Calcd for $C_{56}H_{60}O_6$: C, 81.13; H, 7.29. Found: C, 80.3; H, 7.1.

(+)-3: X-ray Crystallography. Single-crystal data were collected at 100(2) K with a single-crystal diffractometer (Cu Kα radiation, λ = 1.54184 Å). The SIR92 program was used for structure solution by direct method.[20] The SHELXL97 program package was used for full-matrix least-squares structure refinement.[21] ORTEP3 was used for molecular graphics.[22] All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included in the refinement at calculated positions by using a riding model included in the SHELXL program. Absolute configuration was determined by anomalous-dispersion effects in diffraction measurements. Data: monoclinic, *C*2, a = 25.7719(3) Å, b = 9.74588(16) Å, c = 18.1938(2) Å, β = 95.8354(12)°; Z = 4; F(000) = 1.776; V = 4546.05(10); 1.211 Mg/m^3; ϑ-range 4.02−72.15°; data/restraints/parameters: 7299/1/570; GOOF 1.094; R_1 0.0422;

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wR_2 0.1022 on all data. Flack parameter 0.04(15). The crystal structure has been deposited at the Cambridge Crystallographic Data Centre; Dep. no. CCDC 649979.

5,17-Bis((4′R,5′R)-2′,2′-dimethyl-5′-phenyl-1′,3′-dioxolyl)-25,26,27,28-tetrapropyloxycalix[4]arene, 6. To a solution of bis-epoxide **3** (34.5 mg, 0.04 mmol) in a 2:1 mixture of CH_2Cl_2/acetone (3 mL) at room temperature was added Amberlyst 15 (9 mg, 220 mg/mmol). After 1 h of stirring, the reaction was quenched by adding solid $NaHCO_3$, the solid residue was removed by filtration, and the solvent was evaporated. The crude product was purified on a silica gel column with petroleum ether:EtOAc 95:5 as eluent, to give pure compound **6** (30 mg) in 79% yield.

6: $[\alpha]^{20}_D$ +123 (*c* 0.63, CH_2Cl_2); ee 99% (CHIRALPAK IA; *n*-hexane/2-propanol 95:5; flow rate: 0.8 mL/min); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 0.83 (t, 6H, J = 7 Hz), 0.99 (t, 3H, J = 7 Hz), 1.35 (t, 3H, J = 7 Hz), 1.59 (s, 6H), 1.62 (s, 6H), 3.06 (d, 2H, J = 13 Hz), 3.14 (d, 2H, J = 13 Hz), 3.69 (t, 4H, J = 7 Hz), 3.98 (t, 4H, J = 7 Hz), 4.43 (2d, 4H, J = 13 Hz), 4.63 (d, 1H, J = 8.5 Hz), 4.79 (d, 1H, J = 8.5 Hz), 6.09 (d, 2H, J = 7.5 Hz), 6.22 (d, 2H, J = 7.5 Hz), 6.32 (t, 2H, J = 7.5 Hz), 6.83 (s, 2H), 7.03 (s, 2H), 7.20 (d, 4H, J = 8 Hz), 7.32 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 8.7, 9.9, 10.7, 23.0, 23.4, 27.1, 27.3, 29.7, 30.8, 30.9, 45.8, 76.5, 76.9, 85.4, 85.6, 109.1, 121.9, 126.4, 126.9, 127.4, 127.4, 128.0, 128.2, 129.4, 133.2, 133.3, 136.4, 136.9, 137.1, 155.3, 157.5. Anal. Calcd for $C_{62}H_{72}O_8$: C, 78.78; H, 7.68. Found: C, 78.5; H, 7.8.

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Supporting Information Available: Experimental procedures for compound **1**; ^{1}H and ^{13}C NMR of compounds **1**, **3**, **4**, and **6**; chiral HPLC spectra of compounds (+/−)-**3** and (+)-**3**; X-ray structure of (+)-**3** in CIF format, structure refinement details. This material is available free of charge via the Internet at http://pubs.acs.org.

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