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Fumarate of (*S*,*S*)-α,α′-Bis(trifluoromethyl)-1,8-anthracenedimethanol. A Chiral Macrocycle for the Diels−Alder Reaction with Cyclopentadiene

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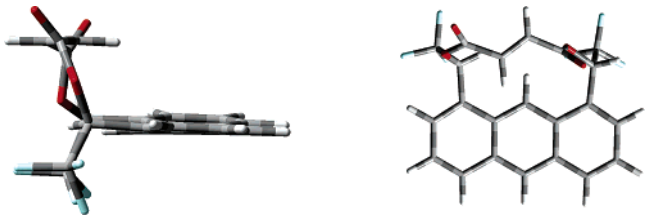

The synthesis and structural study of the fumarate of (*S*,*S*)-α,α′-bis(trifluoromethyl)-1,8-anthracenedimethanol by NMR spectroscopy are reported. The conformational study of the 13-membered macrocycle is presented. The cited alcohol is assayed as a chiral auxiliary in a Diels−Alder reaction with cyclopentadiene, and after methanolysis, provides the norbornene derivative with high enantioselectivity.

We have recently described the preparation of enantiomers (*S*,*S*)- and (*R*,*R*)-α,α′-bis(trifluoromethyl)-1,8-anthracenedimethanol **1**,[1] which were revealed as very active chiral solvating agents (CSAs), complementing the properties of α,α′-bis(trifluoromethyl)-9,10-anthracenedimethanol **2**.[2] The main characteristic of these two compounds is the presence of a double functionality (as with Pirkle alcohol)[3] that enables the formation of bidentate complexes with the examined substrates.[4] These structures are shown in Figure 1.

The possibility of using CSAs as chiral auxiliaries in such well-known organic reactions as Diels−Alder[5] and 1,3-dipolar cycloadditions[6] is of current interest to our laboratory.

The use of a CSA as a covalently bonded chiral auxiliary in an asymmetric synthesis can be justified by the fact that the noncovalent interactions governing chiral enantiorecognition

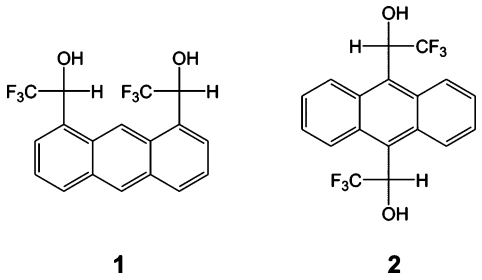

FIGURE 1. α,α′-Bis(trifluoromethyl)-1,8-anthracenedimethanol **1** and α,α′-bis(trifluoromethyl)-9,10-anthracenedimethanol **2**.

(steric hindrance, hydrogen bonds, π-stacking interactions, etc.)[7] are of a similar nature to the interactions that govern the stereoselectivity of the reactions used in asymmetric synthesis. Distinct examples are found in the literature, where recognized CSAs act as chiral auxiliaries in different organic reactions,[8] including Diels−Alder.[9]

The considerable capacity for enantiodiscrimination of a CSA and the spatial proximity of the hydroxyl groups of **1** led us to synthesize the fumarate of (*S*,*S*)-α,α′-bis(trifluoromethyl)-1,8-anthracenedimethanol **3**, an enantiopure thirteen-membered macrocycle, to be used as a chiral dienophile in an asymmetric Diels−Alder reaction with cyclopentadiene. Although there are an extensive number of publications on asymmetric Diels−Alder reactions, few works are found in which the asymmetric reaction of a chiral disubstituted fumaric chain occurs.[10]

Satisfactory preparation of (*S*,*S*)-**3** is achieved via a 1:1 diesterification reaction between fumaryl dichloride and (*S*,*S*)-**1**, using CH_2Cl_2 as a solvent in the presence of DMAP and Et_3N (75% yield after purification, Scheme 1).

The structural study of **3** was carried out by NMR. A prior and complete signals assignment was performed by NMR spectroscopic experiments (^{1}H, ^{13}C, COSY, HSQC, HMBC, and NOESY). The ^{1}H NMR spectra reveals that the molecule adopts an asymmetric conformation, spreading the fumarate chain onto one of the faces of the aromatic ring.

The deshielding effect produced inside the macrocycle **3** by double-bond magnetic currents influences the chemical shift of the H_9 (9.48 ppm) 0.5 ppm downfield compared to the chemical shift of the same proton of **1**.[1] Deshielding is also observed in protons H_{11} and H_{14} compared with their homologues H_{16} and H_{13}, respectively, indicating that the former are located inside the macrocycle and the latter are placed outside. The one-

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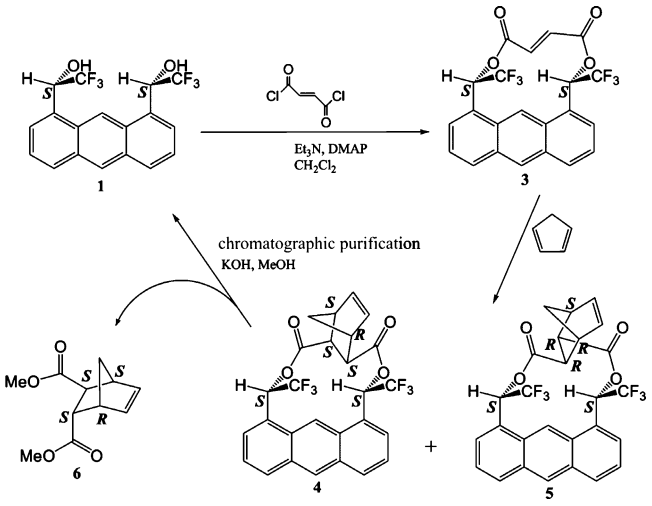
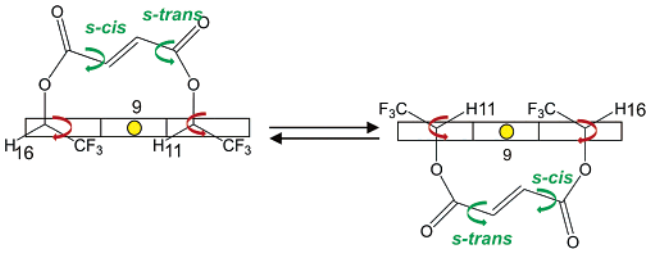
SCHEME 1. Preparation and Diels−Alder Reaction with the Cyclopentadiene of Macrocycle 3



SCHEME 2. Conformational Equilibrium of 3[a]



[a] H_9 is marked yellow, and bound rotations are marked red and green.

dimensional (1D)-NOE spectrum demonstrates the proximity of H_9 to H_{11} and the internal position of H_{14}. Moreover, H_2 and H_{16} are closer, as two-dimensional (2D) NOESY/EXSY shows (EXSY = exchange spectroscopy).

The presence of a positive H_{16} signal in the 1D-NOE spectrum is explained by the H_{11} versus H_{16} conformational exchange during H_9 saturation, and the corresponding NOE transmission. The degenerate equilibrium between two conformations is also studied by the 2D-NOESY/EXSY experiment, where phase-negative cross-peaks appear (green label). Four bond rotations are required for conformational exchange, which are represented in Scheme 2, where the olefinic system "jumps" over the anthracenic ring. C_8-C_{11} and C_1-C_{16} rotations (marked red) take place in the sense that CF_3 groups rotate outside the macrocycle, avoiding the inner macrocycle rotation as a result of the large steric hindrance that is produced by the presence of H_9 (marked yellow). $C_{12}-C_{13}$ and $C_{14}-C_{15}$ rotations (marked green) convert the s-cis conformation of the vinylic bond into an s-trans conformation and vice versa. Notice that the s-cis conformation of at least one vinylic bond is a geometric requirement for ring closure.

As no changes were observed in the ^1H NMR spectrum when the temperature was increased, we used the corresponding variation of the NOEDIFF (NOE-difference spectroscopy) with the temperature for protons H_{16} and H_{11} when H_9 is saturated.[11]

The equation $NOE(H_{16})/\Delta_{NOE}(H_{11}-H_{16}) = k/R_{16}$ allows us to obtain the kinetic constants at several temperatures and, consequently, using the Eyring equation to obtain the $\Delta G^{\ddagger}$ activation parameters at different temperature values (Table 1). By graphical representation, we obtain the enthalpy and entropy of the indicated conformational equilibrium ($\Delta H^{\ddagger} = 9.9 \pm 0.3$ kcal/mol and $\Delta S^{\ddagger} = 2.9 \cdot 10^{-2} \pm 0.3 \cdot 10^{-2}$ kcal/K·mol).

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TABLE 1. Variation of the NOEDIFF on H_{16} and H_{11} with Temperature Modification[a]

temp (K)	Δ NOE (%)	NOE_{16} (%)	R_{16} (s^{-1})	k (s^{-1})	$\Delta G^{\ddagger}$ (kcal/mol)
295	7.1	7.0	0.967	0.123	18.5 ± 0.3
305	12.2	6.6	0.975	0.207	18.8 ± 0.3
315	15.1	4.8	0.999	0.317	19.2 ± 0.3
325	17.9	3.8	1.055	0.571	19.4 ± 0.3
333	14.2	1.8	1.006	0.992	19.6 ± 0.3

[a] Relaxation was measured using the inversion−recovery method.

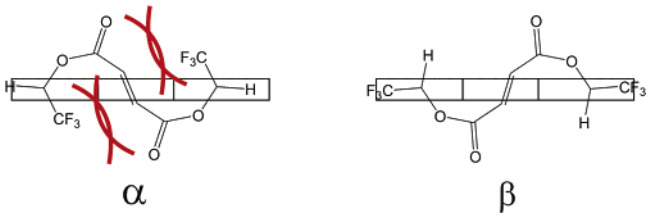

FIGURE 2. Possible transition states for the conformational equilibrium of Scheme 2.

The structure of compound **3**, where a considerable diastereotopic difference can be appreciated between the faces of the double bond, leads us to test its differentiating capacity in a concerted reaction such as the Diels−Alder. Given that the Diels−Alder stereocontrolled reactions intervening in the fumaric acid chain have only rarely been described, a simple and symmetrical diene was chosen as the cyclopentadiene; in this way, we were able to isolate and ascertain the influence of our dienophile 3.

The conformational analysis of compound **3** reveals two diastereotopic faces of the dienophile, whereas the two relative diene positions are equivalent by axial symmetry (Figure 3). While the reaction by the (si,si) face of the double bond, after hydrolysis, gives the (+)−(1*R*,2*S*,3*S*,4*S*)-dimethyl bicyclo[2.2.1]-hept-5-ene-2,3-dicarboxylate (+)-**6**, the (re,re) face generates the other enantiomer (−)-(1*R*,2*R*,3*R*,4*S*)-dimethyl bicyclo[2.2.1] hept-5-ene-2,3-dicarboxylate.

Compound **3** was treated with the diene under several conditions (Table 2), producing two diastereomeric adducts **4** and **5** that contain four new stereogenic centers. After the separation of the diastereoisomers by column chromatography, the major compound **4** was isolated and studied by NMR spectroscopy, showing four stable conformations at room temperature (see Supporting Information).

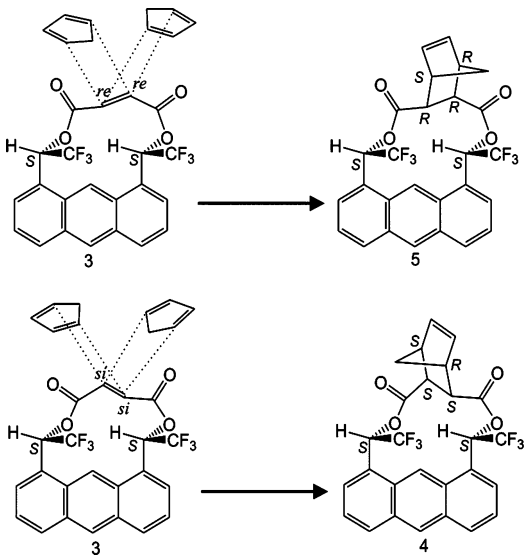

FIGURE 3. Geometry of the approach between diene and dienophile.

TABLE 2. Conditions of the Assayed Diels−Alder Reactions of (*S,S*-3) with Cyclopentadiene

cat.	*T* (°C)	solvent	time (h)	yield[a]	4/5
	−78	CH_2Cl_2	12		
	0	CH_2Cl_2	12		
	20	CH_2Cl_2	12		
	60	benzene	8	polymer	
$TiCl_4$	20	CH_2Cl_2	1	polymer	
$TiCl_4$	0	CH_2Cl_2	1	polymer	
$EtAlCl_2$	−78	CH_2Cl_2	3	100%	90/10
$EtAlCl_2$	0	CH_2Cl_2	1	100%	60/40

[a] Conversion determined by ^{1}H NMR.

The use of $EtAlCl_2$ as a catalyzer at low temperature gave **4** in a high diastereoselectivity (de = 80%), measured by ^{1}H NMR integration (see Supporting Information). After isolation and methanolysis, (+)−(1*R*,2*S*,3*S*,4*S*)-dimethylbicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate **6** was obtained and identified by comparing the measured specific rotation ($[\alpha]^{25}_D = +88.0$ (*c* 1, MeOH)) with the sign that is reported in the literature.[12] The auxiliary **1** was quantitatively recovered (Scheme 1).

We have described a new use for (*S,S*)-α,α′-bis(trifluoromethyl)-1,8-anthracenedimethanol **1** as a covalently bonded chiral auxiliary compound for an asymmetric Diels−Alder reaction of the fumaric chain with a high control of final enantiomers, and of no lesser importance, its recovery for further use has been quantitatively achieved. The structural study demonstrates that the si,si prochiral face of the double bond is available for a selective reaction with a diene. These primary results suggest good possibilities for new stereolective reactions, where **1** would be used as a chiral auxiliary bonded to a substrate by hydroxyl functions.

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Experimental Section

(*S,S*)-α,α′-Bis(trifluoromethyl)-1,8-anthracenedimethanol.[3] Under a nitrogen atmosphere, (dimethylamino)pyridine (DMAP; 150 mg, 1.23 mmol) and triethylamine (1 mL, 7.17 mmol) were added to a solution of (*S,S*)-ABTE-18, **2**, (1 g, 2.67 mmol) in 500 mL of anhydrous dichloromethane. The mixture was stirred for 5 min, and then fumaryl dichloride (340 μL, 2.99 mmol) was slowly added over the mixture. The reaction was controlled by TLC. Once the reaction had finished (15 min), the reaction mixture was washed with 1 M HCl (100 mL), with a saturated solution of $NaHCO_3$ (100 mL), and with water (100 mL). The organic layer was dried over anhydrous Na_2SO_4 and then concentrated. The solid residue was purified by column chromatography on silica gel (hexane/dichloromethane, 8:2) to give compound (*S,S*)-**3** (0.85 g, 70% yield) as a white solid: $[\alpha]^{20}_D = +40$ (*c* = 1, CH_2Cl_2). IR (ATR, cm^{-1}): 3074, 1731, 1555, 1354, 1296, 1264, 1175, 1150, 1143. MS (MALDI-TOF, *m*/*z*, %, THF-cca): 454.0 (M^+, 11), 424.1 (50), 408.05 (100), 385.9 (14), 383.9 (33). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ 9.47 (s, 1H, H_9), 8.5 (s, 1H, H_{10}), 8.10 (d, $J_{4,3} = 8.4$ Hz, 1H, H_4), 8.04 (d, $J_{5,6} = 8.7$ Hz, 1H, H_5), 7.82 (2 × d, $J_{14,13} = 15.49$ Hz, $J_{7,6} = 6.91$ Hz, 2H, H_{14}, H_7), 7.67 (d, $J_{2,3} = 6.65$, 1H, H_2), 7.58 (q, $J_{11,F} = 6.65$ Hz, 1H, H_{11}), 7.49 (m, 2H, H_3, H_6), 7.18 (d, $J_{13,14} = 15.57$ Hz), 6.79 (q, $J_{16,F} = 7.96$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.7 (C═O, C_{12}), 163.1 (C═O, C_{15}), 136.2 (C−H_{ol}, C_{13}), 134.2 (C−H_{ol}, C_{14}), 132.6 (Cq_{ar}), 132.1 (2C, C−H_{ar}, C_2, C_4), 131.5 (Cq_{ar}), 131.1 (C−H_{ar}, C_5), 129.6 (Cq_{ar}), 129.2 (Cq_{ar}), 128.9 (C−H_{ar}, C_{10}), 128.2 (C−H_{ar}, C_7), 125.4, 125.0 (2C, C−H_{ar}, H_3, H_6), 77.0 (C−H, C_{11}), 66.8 (C−H, C_{16}).

Standard Experimental Procedure for the Diels−Alder Reaction and for Methanolysis. To a solution of **3** (100 mg, 23.25 mmol) in anhydrous dichloromethane (50 mL) at −78 °C kept under N_2 was added the catalyst, $EtAlCl_2$ (220 μL of 1 M in hexane, 0.22 mmol). The mixture was stirred for 15 min, and then cyclopentadiene (previously distilled from dicyclopentadiene) was slowly added (20 μL, 0.24 mmol). When the reaction was finished (3 h, TLC), it was washed with water (50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated, obtaining 109 mg (95% yield) of a mixture of diastereoisomers **4** (90%) and **5** (10%). The pure compound **4** (48 mg, 42% yield) was isolated by chromatography on silica gel (hexane/CH_2Cl_2, 9:1), which was hydrolyzed in a solution of MeOH (50 mL) containing KOH as a catalyst. After stirring (10 min), the solution was washed with 0.1 M HCl (2 × 50 mL), washed with a saturated solution of $NaHCO_3$ (3 × 50 mL), and then concentrated. The solid residue was purified by chromatography on silica gel (hexane/CH_2Cl_2, 7:3), obtaining the solid **6** (18.45 mg, 94.9% methanolysis yield, $[\alpha]^{25}_D = +88.0$ (*c* 1, MeOH)) and recovering the dialcohol **2** (33.56 mg, 96.7% hydrolysis yield).

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Supporting Information Available: Characterization data of compound **3** (^{1}H NMR, NOE, 2D NOESY/EXSY, COSY, HSQC, HMBC, inversion recovery, IR, and MALDI-TOF mass spectrum), stack plot of 1D-NOEDIFF experiments at several temperatures, ^{1}H NMR spectra of the crude Diels−Alder reaction and of compound **4**, as well as a structural study by NMR of **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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