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Preparation, conformational analysis and behaviour as chiral solvating agents of 9-anthrylpentafluorophenylmethanol enantiomers: study of the diastereomeric association

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Abstract—The synthesis, structure and behaviour as chiral solvating agents of the enantiomers of 9-anthrylpentafluorophenylmethanol is reported.

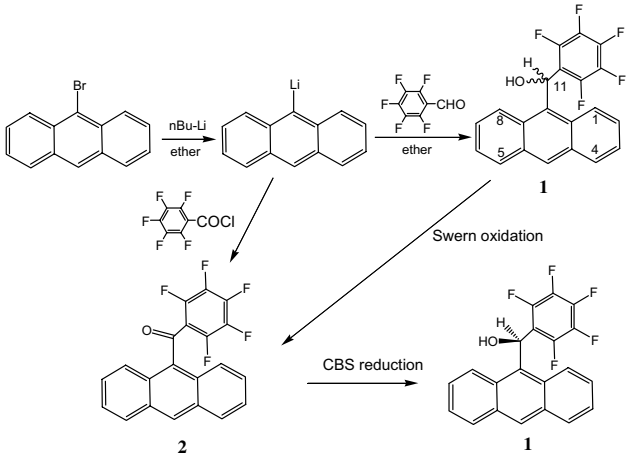
1. Introduction

Several alcohols containing anthracene and trifluoromethyl groups, such as Pirkle's alcohol[1] or α,α′-bis(trifluoromethyl)-9,10-anthracenedimethanol,[2] which are commercially available, are used as chiral solvating agents (CSA). The presence of a bulky group, such as *tert*-butyl[3] or adamantyl, transmits structural rigidity that compensates for the lack of acidity in the methinic proton. The presence of the aromatic group (anthracene) in the structure is one of the factors that allows the CSA to differentiate between enantiomers. Its proximity and relative position to the substrate affords an important and differential magnetic influence. The *per*-fluorophenyl group has a strong electron withdrawing character and its presence in the CSA could increase the zones around the enantiomers where the magnetic field of the NMR becomes modified by the presence of the anisotropic groups. The preparation of the enantiomers of 9-anthrylpentafluorophenylmethanol **1** gives us a novel CSA with new interactions and new associations that offer new possibilities for enantiodistinction.

2. Results and discussion

2.1. Preparation and characterization of 9-anthrylpentafluorophenylmethanol

The preparation of the enantiomers of 9-anthrylpentafluorophenylmethanol was proposed in two ways (Scheme 1): the preparation and separation of the racemic compound and the use of enantioselective reactions to prepare each of the enantiomers directly. In both cases the starting point would be the same intermediate, the lithium derivative of anthracene that is obtained via reaction of 9-bromoanthracene with



Scheme 1. Synthesis of 9-anthrylpentafluorophenylmethanol.

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n-BuLi. Racemic **1** was obtained by a subsequent reaction with pentafluorobenzaldehyde in a global yield of 60%. The enantioselective pathway was based on the enantioreduction of prochiral ketones with boranes catalyzed by chiral oxazaborazolidines (CBS reduction).[4] We prepared the 9-anthrylperfluorophenyl ketone **2** by reaction of anthryl-lithium with perfluorobenzoyl chloride in 55% yield. We also prepared compound **2** in an almost quantitative yield (95%), by the oxidation of alcohol **1** with dimethyl sulfoxide (Swern oxidation).[5] Although the CBS enantio- reduction of 9-anthryltrifluoromethyl ketone has already been described[6] with a very good yield and enantiomeric excess, which we have repeated with similar results, an analogous reaction with ketone **2** was not possible after testing different conditions. Moreover, the reduction of this compound with $NaBH_4$ or $LiAlH_4$ was not viable, thus showing the low electrophilic character of this ketone.

9-Anthrylpentafluorophenylmethanol **1** was characterized by NMR. At room temperature, the ^1H NMR spectrum showed well-resolved signals for all the protons of the molecule. Nevertheless, a significant shift of several peaks was observed when the concentration of the sample changed (Fig. 1). For example, methinic proton H_{11} shifts 0.13 ppm when the concentration of the sample decreases from 0.075 to 0.007 M possibly due to autoassociation processes.

The restricted rotation about the C_9–C_{11} (sp^2–sp^3) bond in (9-anthryl)carbinols derivatives[7] reflected in separated signals for absorption of H_1 and H_8 is well known. We have reported 13 kcal/mol for *tert*-butyl and 9.8 kcal/mol for the phenylderivatives. Nevertheless, in contrast to most of these molecules, the ^1H NMR spectrum of compound **1** only shows one doublet corresponding to the proton pair H_1 and H_8. After reducing the temperature to 190 K, the two protons were still indistinguishable, thus confirming that the rotational barrier about the sp^2–sp^3 bond is lower than 9 kcal/mol.

Enantiomers of **1** were separated by Chiral HPLC. Compound **3**, the acetate derivative of **1**, was quantitatively prepared by treatment with acetyl chloride. The pure enantiomers (*R*)-**3** and (*S*)-**3** were separated on a semi-preparative Whelk-O1 (250 × 10 mm) and a preparative Whelk-O2 (250 × 25 mm) column using hexane/isopropyl alcohol (97/3, 3 mL/min) and (98/2, 12 mL/min, respectively), as the elution solvent. The first eluted compound was *dextro* and was further assigned to (+)-(*S*)-**3**. The second one was *laevo* and corresponded to (−)-(*R*)-**3**. Treatment of each isolated ester with KOH (0.05 M) gave the enantiomers (+)-(*S*)-**1** and (−)-(*R*)-**1**, respectively.

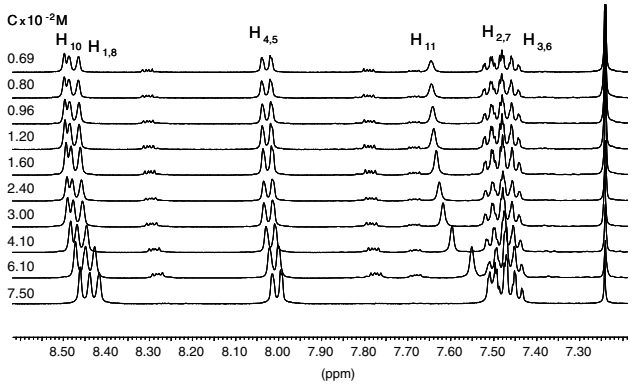


Figure 1. ^1H NMR spectra of **1** at several concentrations ($CDCl_3$).

The X-ray structure (Fig. 2)[8] of the first eluted isomer was obtained and provisionally assigned as the (*S*)-enantiomer. The asymmetric unit was composed by two molecules that show a parallelism between each anthracene and one of the perfluorophenyl rings. Two kinds of attractive π–π stacking interactions were seen:[9] one being a face to face parallel displaced between one anthracene ring and one perfluorophenyl ring, while the other being the edge to face showed by the two anthracene rings and between the two perfluorophenyl rings.

The absolute configuration of each enantiomer was deduced by the different ^1H NMR spectra of the diastereoisomeric (*S*)-α-methoxyphenylacetic acid esters as reported elsewhere.[10] The structural study[11] of these esters showed a conformational equilibrium between the *syn*-periplanar (*sp*) and *anti*-periplanar (*ap*) conformations of the α-carboxylic bond of the acid part. The first (*sp*) was more stable and was favoured by lowering the temperature. The absolute configuration of each isolated isomer was determined by considering the differences in the chemical shifts of the protons and the distribution of the groups around of the *sp* conformation of each diastereoisomer.

(*S*)-α-Methoxyphenylacetates of the enantiomers of 9-anthrylpentafluorophenylmethanol **1** were prepared by reaction of each enantiomeric alcohol (*R*)-**1** and (*S*)-**1** with the (*S*)-α-methoxyphenylacetyl chloride, obtaining the stereoisomers (*SR*)-**4** and (*SS*)-**4**. The same compounds were obtained by a similar preparation of the mixture from racemic **1** and subsequent separation by HPLC with the Whelk-O2 column using hexane/isopropyl alcohol (95/5, 10 mL/min).

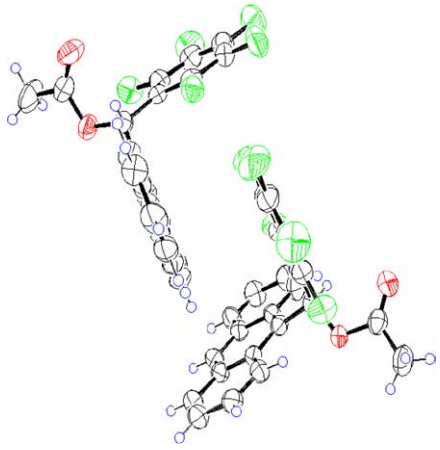


Figure 2. Ortep drawing of the X-ray diffraction analysis of acetate (*R*)-**3**.

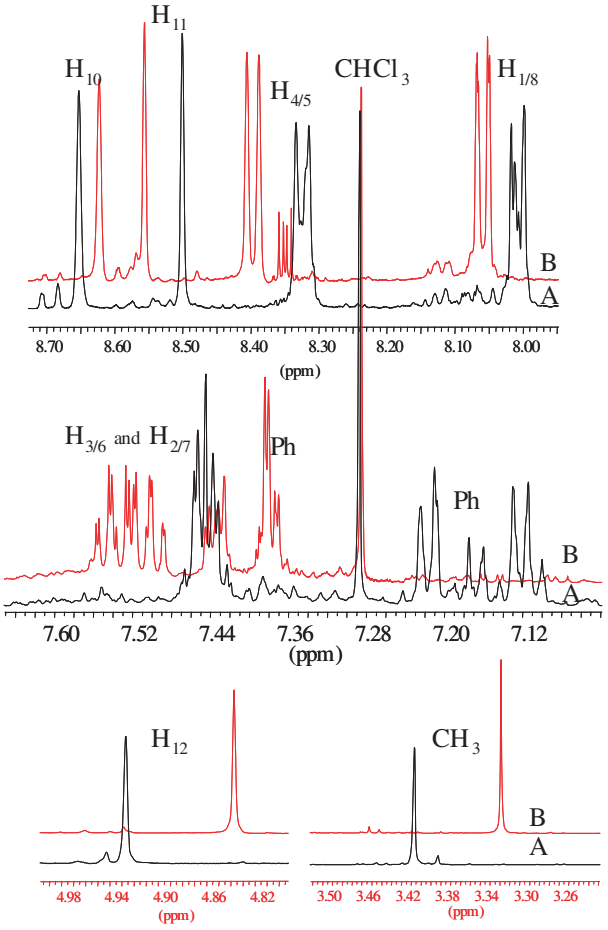


Figure 3. Portions of the ^{1}H NMR spectrum (at 300 K) of stereoisomers of (*S*)-α-methoxyphenylacetate of 9-anthrylpentafluorophenylmethanol **4**. (A) Ester of (−)-**1**, (*S,R*)-**4** and (B) ester of (+)-**1**, (*S,S*)-**4**.

Figure 3 shows the ^{1}H NMR spectra of both esters of **4** where very different chemical shifts for the same proton of each diastereoisomer are shown. The ester of *laevo* isomer (−)-**1** shows the H_{12} and CH_3 deshielded while the phenyl protons, H_{11} and the most anthracene protons are shielded in comparison with those of the *dextro* alcohol (+)-**1**. Low temperature ^{1}H NMR spectra showed greater differences.

The equilibrium between the *syn*-periplanar and *anti*-periplanar conformations for both stereoisomers is shown in Figure 4. The *syn* conformations are the most stable ones[11] and are favoured by the low temperatures.

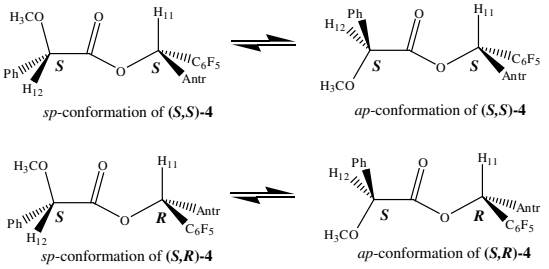
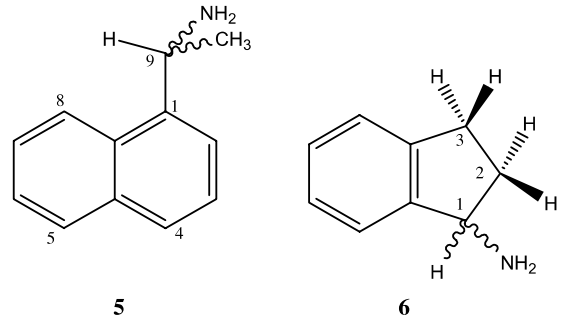


Figure 4. Conformational equilibrium of stereoisomers of (*S*)-α-methoxyphenylacetates of 9-anthrylpentafluorophenylmethanol **4**.

The anisotropy of the anthryl group determines the local magnetic fields nearby and the position of the peaks in the NMR spectra. Considering only the *syn* conformations, in the first case, the (*S,S*)-**4**, methoxy group and H_{12} are on the same side of the anthracene group being strongly shielded, corresponding to the NMR spectrum of ester of *dextro* alcohol (+)-(*S*)-**1**. In the (*S,R*)-**4** is the phenyl group that is influenced by the anisotropy of the anthracene ring being shielded to low frequencies and corresponding to the spectrum of the ester of *laevo* alcohol (−)-(*R*)-**1**.

2.2. Enantiorecognition activity

The activity as a chiral solvating agent of enantiomers of **1** was studied against racemic compounds 1-(1-naphthyl)ethylamine **5** and 1-aminoindane **6** (Fig. 5). In all cases, the presence of a basic group and the aromatic rings allowed the formation of an intermolecular hydrogen bond and a π-stacking stabilization interaction. The experiments were carried out in $CDCl_3$, adding portions of the CSA to a solution (0.05 M) of racemic substrate, until maximum differentiation of the corresponding enantiomer's signals occurred.



5 **6**

Figure 5. Substrates tested for the enantiodiscrimination.

In the case of substrate (*RS*)-**5**, the use of alcohol (*S*)-**1** as a chiral solvating agent afforded good results obtaining a good resolution of the signals corresponding to the H_9 and methyl group. This methyl group is only occasionally[12] separated.

Figure 6 shows the evolution of the ^{1}H NMR spectrum of the 1-(1-naphthyl)ethylamine **5** when the addition of CSA (*S*)-**1** was incremented. The doublet corresponding to the methyl group in the racemic compound appears as two completely separated doublets of the two enantiomers when 1.8 equiv (or more) of (*S*)-**1** are added. After the addition of an excess of one of the enantiomers of **5**, (*R*)-**5**, and considering the integration of the two signals, we confirmed that the methyl of the (*R*)-**5** enantiomer shifted to higher field than the methyl of the (*S*)-**5**. Similarly, at the same ratio, the quartet of the H_9 results in two quartets, one of each enantiomer, and in a similar arrangement than before.

The maximum separation obtained corresponded to the addition of 3.8 equiv of (*S*)-**1**. Further additions of

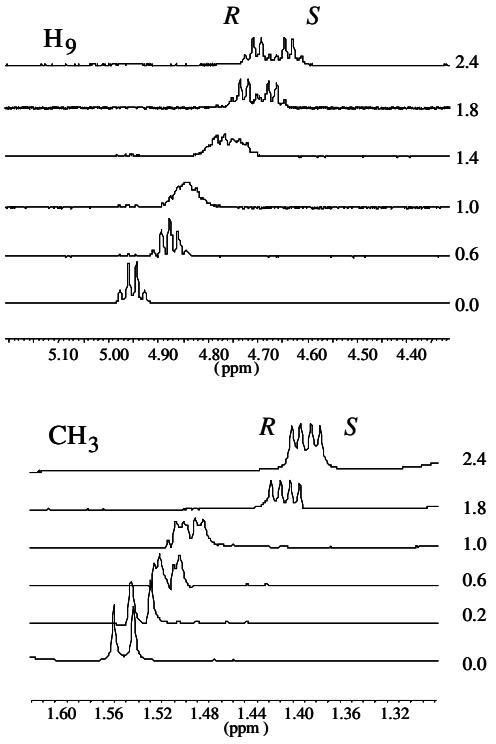


Figure 6. Aliphatic part of ^{1}H NMR spectrum of the enantiodiscrimination process of racemic **5** by the addition of several portions of (*S*)-9-anthrylpentafluorophenylmethanol (*S*)-**1**.

solvating agent precipitate of the components. Figure 7 shows the evolution of the difference obtained when portions of the (*S*)-**1** were added to a solution of racemic 1-(1-naphthyl)ethylamine **5**.

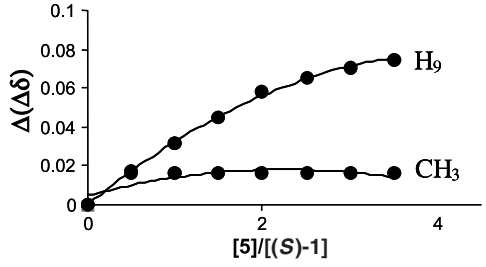


Figure 7. Evolution of the enantiodifferentiation of H_9 and CH_3 of *rac*-1-(1-naphthyl)ethylamine **5** when several quantities of (*S*)-**1** were added.

The distinction of the enantiomers of **6** could be followed in protons H_2, H_2', H_3 and H_3'. Figure 8 shows the enantiodiscrimination of these protons when (*S*)-**1** was added to a racemic mixture. Although the signals of aromatic protons of **6** also undergo a differentiating shift, it was impossible to follow because of its complexity.

Due to the quality of the results obtained in the enantiodiscrimination of (*RS*)-1-(1-naphthyl)ethylamine **5**, the complexes responsible for the phenomena were studied. Stoichiometry of the complex was the first parameter studied. As the chemical shift of a nucleus is a mean value of the several species present in solution,

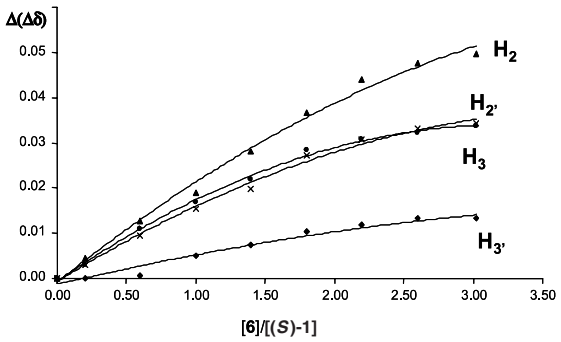


Figure 8. Evolution of the enantiodifferentiation of H_2, H_2', H_3 and H_3' of (±)-aminoindane **6** when several quantities of (*S*)-**1** were added.

when all components are completely dissolved, Job's method[13] can be applied to calculate the stoichiometry of the complex in solution. Complex (*S*)-**1**·(*S*)-**5** was analyzed: 10 samples of a constant total concentration were prepared containing variable ratios of the two components. ^{1}H NMR spectra of these samples were recorded at 300 K and the chemical shift variations were observed for several protons of compound (*S*)-**5**. The Job plot of the variation of the chemical shift of some amine protons H_2, H_8 and CH_3 versus the ratio between the concentration of amine (*S*)-**5** and the total concentration (0.01 M) is shown in Figure 9. The maximum value of the parabolic curve in the *X* coordinate gives us the stoichiometry. In the three plots, a value of 0.5 was found, meaning that the stoichiometry of the complex is 1:1.

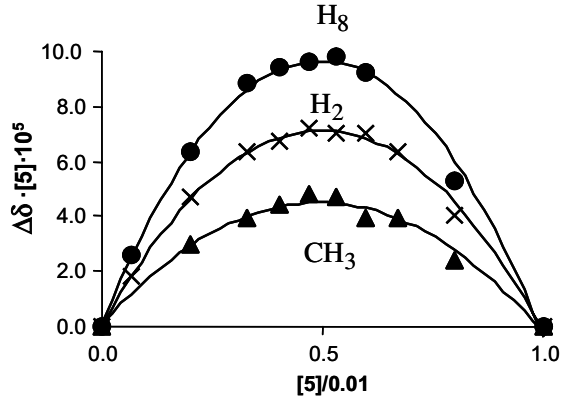


Figure 9. Job plot of the association of (*S*)-9-anthrylpentafluorophenylmethanol (*S*)-**1** with (*S*)-1-(1-naphthyl)ethylamine (*S*)-**5**.

As is well known, the chemical shift differences observed when an association complex is formed is a consequence of two factors, the difference in the chemical shift of the complexes (i.e., the different geometry of the association) and the different populations of the complex (i.e., the difference in the binding constants *K*.

Thus, the binding constant of each diastereomeric complex should be taken into account. The binding constants of the complexes formed between the enantio-

mers of amine **5** and alcohol (*S*)-**1** were determined using the equimolar method, which according to Bouquant and Chuche,[14] can be applied if the stoichiometry of the complex is 1:1.

A sample formed by a solution (0.05 M) of one of the enantiomers of **5** and (*R*)-**1** (0.05 M) was prepared in $CDCl_3$. This sample was diluted (four times) by additions of 0.1 mL of $CDCl_3$ and the ^1H NMR spectra registered at four temperatures. Figure 10 shows the plot of the variation of the chemical shifts ($\Delta\delta$) of the protons of amine **5** (H_2, H_9 and CH_3) versus $(\Delta\delta/S_0)^{1/2}$ at 285 K, where S_0 is the initial concentration of the solute and δc is the chemical shift of each proton in the pure complex. The binding constant for every proton studied was determined from the gradient $[(\delta c/K)^{1/2}]$ of the plotted straight lines. The average values and the free enthalpies obtained at several temperatures are expressed in Table 1.

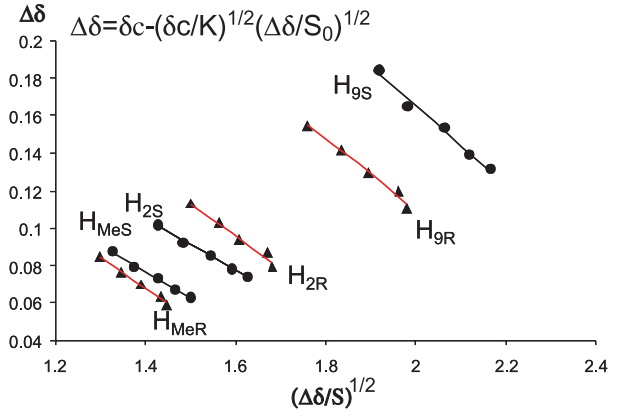


Figure 10. Straight lines obtained when an equimolar method is applied to the determination of the binding constant between each of the enantiomers of amine **5** with (*S*)-**1** at 285 K.

Table 1. Binding constants of the complex formation between each enantiomer of 1-(1-naphthyl)ethylamine **5** and (*S*)-9-anthrylpentafluorophenylmethanol (*S*)-**1**

T/K	(*R*)-**5**·(*S*)-**1**		(*S*)-**5**·(*S*)-**1**	
	K/M^{-1}	ΔG/kJ/mol	K/M^{-1}	ΔG/kJ/mol
300	7.4 ± 1.4	−5.0 ± 0.2	7.2 ± 0.7	−4.9 ± 0.4
285	12.3 ± 1.1	−6.0 ± 0.1	14.2 ± 0.9	−6.3 ± 0.2
270	30.9 ± 2.9	−7.7 ± 0.1	32.0 ± 2.3	−7.8 ± 0.2
255	72.1 ± 5.4	−9.1 ± 0.1	73.1 ± 3.9	−9.1 ± 0.2

The similarity of the constant values means that the enantiodiscrimination takes place because of the differences between the structures of the complexes of association; the factor of the concentration being a minor cause. As the process is exothermic, the binding constant increases when the temperature decreases. While with other chiral solvating agents,[2] when decreasing the temperature the difference between constants of the enantiomers increases considerably, in the present case the uniformity is maintained with low temperatures not enhancing the enantiodiscrimination.

The equimolar method also allows us to measure the chemical shift of several protons in the isolated associated state. The intersection of the straight lines of each proton and each enantiomer with the axis gives the corresponding δc. Figure 11 affords the plot corresponding to the proton H_9 of both enantiomers of **5** at several temperatures. The various lines (corresponding to one enantiomer at several temperatures) converge on a mean value of the chemical shift of the H_9 in the association complex. The values for various protons, together the experimental chemical shift for compound (±)-**5**, are presented in Table 2 meaning a standard and comparative value.

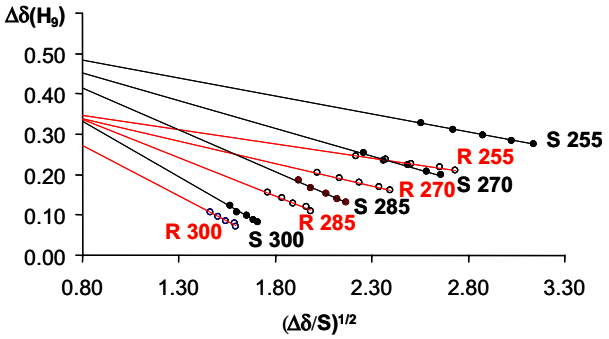


Figure 11. Measurement of the binding constant of the association between each enantiomer of 1-(naphthyl)ethylamine **5** and (*R*)-9-anthrylpentafluorophenylmethanol (*S*)-**1** measuring the variation of H_9 at 300, 285, 270 and 255 K.

Table 2. Extrapolated chemical shift of several protons of (*R*)-**5** and (*S*)-**5** of the complex formed with (*S*)-**1**

H	δH	(*S*)-**1**·(*S*)-**5**	(*S*)-**1**·(*R*)-**5**
H_9	4.960	4.513 ± 0.013	4.399 ± 0.012
H_4	7.750	7.672 ± 0.003	7.683 ± 0.007
H_2	7.652	7.278 ± 0.005	7.356 ± 0.021
CH_3	1.548	1.277 ± 0.006	1.265 ± 0.008

3. Experimental

NMR spectra were recorded at 400.13 and 500.13 MHz for ^1H. The temperature was controlled to 0.1 °C. The complete identification of the NMR signals was carried out with the aid of several 1D (NOE) and 2D (COSY, HMQC and HMBC) spectra.

The NMR titration method was carried out with 0.5 mL of a solution 0.05 M of the tested compounds **5** and **6**. After addition (at constant volume) of several portions of 0.2–0.5 equiv of CSA **1**, NMR spectra were measured and the variations of the chemical shifts calculated for each addition. The measurements were continued until maximum enantiodiscrimination (2.5–4.4 equiv).

Chiral semi-preparative HPLC was carried out using a (*R*,*R*)-Whelk-O1 (250 × 10 mm) column and a preparative HPLC using a (*R*,*R*)-Whelk-O2 (250 × 25 mm) column.

3.1. 9-Anthrylpentafluorophenyl ketone 2

Butyllithium (1.63 mL, 2.5 M in hexane) was slowly added to a solution of 9-bromoanthracene (0.700 g, 2.7 mmol) in anhydrous diethyl ether (30 mL) and in a stream of N_2. The mixture was stirred for 0.5 h and then added to a solution of pentafluorobenzoyl chloride (1.18 mL, 8.2 mmol in 15 mL of dried diethylether) at −78 °C. The resulting mixture was stirred at −78 °C for 5 h. The reaction was treated with a saturated solution of NH_4Cl (2×15 mL), a 10% NaOH solution (2×15 mL) and water (2×15 mL). The organic layer was dried over anhydrous $MgSO_4$, evaporated and then purified by flash chromatography (hexane/CH_2Cl_2, 8:2). Ketone **2** (0.55 g, 55%) was obtained: mp: 118–122 °C. IR (KBr) cm^{-1}: 2921, 1671–1650, 1518, 1490. EM *m/z* (%): 372 (100), 205 (58), 177 (72), 167 (8). ^1H NMR ($CDCl_3$, 300 K): δ (ppm) 8.65 (s, 1H, H_{10}), 8.10 (m, 2H, H_4 and H_5), 7.90 (m, 2H, H_1 and H_8), 7.54 (m, 4H, H_2, H_7, H_3 and H_6). ^{13}C NMR ($CDCl_3$, 300 K): δ (ppm) 133.4 (C_{8a} and C_{1a}), 131.0 (C_{4a} and C_{5a}), 130.9 (C_{10}), 129.1 (C_4 and C_5), 128.3 (C_9), 127.7 (C_2 and C_7), 125.6 (C_3 and C_6), 123.7 (C_1 and C_8). EM *m/z* (%): 372 (100), 205 (58), 177 (72), 167 (8). Anal. Calcd for $C_{21}H_9F_5O$: C, 67.75; H, 2.44. Found: C, 67.67; H, 2.51.

Synthesis of **2** from alcohol **1** was carried out by a Swern oxidation. To a solution of DMSO (0.50 mL, 7.05 mmol) in anhydrous dichloromethane (7 mL) at −78 °C and kept under N_2, trifluoroacetic anhydride (0.97 mL, 6.85 mmol) was added. After 15 min a solution of racemic 9-anthrylpentafluorophenylmethanol **1** (0.256 g, 0.68 mmol) and DMSO (1 mL, 14.09 mmol) in 4 mL of anhydrous dichloromethane was slowly added over the trifluoroacetic anhydride solution. The reaction mixture was stirred for 1 h and 25 min and then triethylamine (2.20 mL, 15.76 mmol) was added. The reaction mixture was still stirred for 1 h at −78 °C, washed with water (2×10 mL) and with a saturated solution of NaCl (2×10 mL) and the organic layer dried over anhydrous $MgSO_4$ and then concentrated. The solid residue was purified by column chromatography on silica gel (hexane/dichloromethane, 9:1) to give compound **2** (0.240 g, 95% yield).

3.2. (*RS*)-9-Anthrylpentafluorophenylmethanol 1

To a solution of 9-bromoanthracene (0.44 g, 1.7 mmol) in anhydrous diethyl ether (15 mL) and in a stream of N_2, butyllithium (1.60 mL, 1.6 M in hexane) was slowly added. The mixture was stirred for 0.5 h and then added to a solution of pentafluorobenzaldehyde (0.31 mL, 2.5 mmol in 15 mL of dried diethylether) at −78 °C. The resulting mixture was stirred at −78 °C for 2 h. The reaction was washed with a saturated solution of NH_4Cl (2×25 mL), a 10% NaOH solution (2×25 mL) and water (2×25 mL). The organic layer was dried over anhydrous $MgSO_4$, evaporated and then purified by flash chromatography (hexane/CH_2Cl_2 7:3). Alcohol (*RS*)-**1** (0.380 g, 60%) is obtained: mp: 168–170 °C. IR (KBr) cm^{-1}: 3308 (O–H, broad), 2963, 1524, 1498, 1112. EM *m/z* (%): 374 (26), 207 (8), 179 (100), 168 (5). UV λ_{max} (nm) (ethanol): 214, 248, 368. ^1H NMR ($CDCl_3$, 300 K, 400.13 MHz): δ (ppm) 8.46 (s, 1H, H_{10}), 8.43 (d, $J_{1,2} = J_{8,7} = 8.8$ Hz, 2H, H_1 and H_8), 8.00 (d, $J_{4,3} = J_{5,6} = 7.6$ Hz, 2H, H_4 and H_5), 7.51 (s, 1H, H_{11}), 7.49 (m, 2H, H_2 and H_7), 7.45 (m, 2H, H_3 and H_6), 3.28 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 300 K, 100.62 MHz): δ (ppm) 131.5 (C_9), 129.6 (C_{10}), 129.5 (C_4 and C_5), 126.5 (C_2 and C_7), 124.9 (C_3 and C_6), 123.9 (C_1 and C_8), 66.2 (C_{11}).

The pure enantiomers were obtained after hydrolysis of the isolated acetate derivatives **3**.

(+)-**1**: $[\alpha]_D^{25} = +32$ (*c* 2, ethyl acetate)
(−)-**1**: $[\alpha]_D^{25} = -32$ (*c* 2, ethyl acetate)

3.3. (*RS*)-9-Anthrylpentafluorophenyl acetate 3

Dimethylaminopyridine (DMAP) (107 mg, 0.87 mmol), triethylamine (4.26 mL, 30.7 mmol) and acetyl chloride (0.80 mL, 11.2 mmol) were added to a solution of **1** (822 mg, 2.20 mmol in 35 mL of anhydrous dichloromethane). After 3 h, the reaction had finished and the mixture washed with water (2×25 mL), HCl 1 M (2×25 mL) and a solution of 10% $NaHCO_3$ (2×25 mL). The organic layer was separated, dried and evaporated. The solid residue was purified by chromatography on silica gel (hexane/CH_2Cl_2 6:4). Acetate **3** (0.79 g, 86%) was obtained: mp: 154–158 °C. Anal. Calcd for $C_{23}H_{13}F_5O_2$: C, 66.35%; H, 3.15%. Found: C, 65.96%; H, 3.01%. IR (KBr) cm^{-1}: 2963, 2927, 2855, 2963, 1745, 1524, 1496, 1219. EM *m/z* (%): 416 (379),373 (117), 357 (206), 178 (365). UV λ_{max} (nm) (ethanol): 214, 250, 366. ^1H NMR ($CDCl_3$, 300 K, 400.13 MHz): δ (ppm) 8.61 (s, 1H, H_{11}), 8.52 (s, 1H, H_{10}), 8.45 (d, $J_{1,2} = J_{8,7} = 8.8$ Hz, 2H, H_1 and H_8), 8.03 (d, $J_{4,3} = J_{5,6} = 8.2$ Hz, 2H, H_4 and H_5), 7.54 (dd, $J_{2,1} = J_{7,8} = 8.8$ Hz, 2H, H_2 and H_7), 7.47 (dd, $J_{3,4} = J_{6,5} = 8.2$ Hz, 2H, H_3 and H_6), 2.18 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 300 K, 100.62 MHz): δ (ppm) 170.0 (C=O), 131.4 (C_9), 130.3 (C_{10}), 130.0 (C_{4a} and C_{5a}), 129.5 (C_4 and C_5), 127.0 (C_{1a} and C_{8a}), 126.9 (C_2 and C_7), 125.0 (C_3 and C_6), 123.7 (C_1 and C_8), 65.8(C_{11}), 20.8 (CH_3).

3.4. (*S*)-α-Methoxyphenylacetate of anthrylpentafluorophenylmethyl 4

DMAP (0.004 g, 0.033 mmol in 2 mL of dried dichloromethane) was added all at once to a solution of 0.118 g (0.316 mmol) of the enantiopure alcohol (*R*)-**1**, 0.052 g (0.313 mmol) of (*S*)-α-methoxyphenylacetic acid and 0.065 g (0.315 mmol) of DCC in 8 mL of dried dichloromethane. After 24 h, the dicyclohexylurea was removed by filtration, the filter cake washed with three 3 mL portions of hexane and the combined filtrates washed with 2×2 mL cold 1 M aqueous hydrochloric acid, 2×2 mL saturated sodium bicarbonate and 2×2 mL saturated brine. The organic phase was then dried over $MgSO_4$ and filtered and the solvent removed to afford a yellow solid. The crude product was purified by flash chromatography (CH_2Cl_2/hexane, 9:1) to give compound (*S*,*R*)-**4** (0.11 g, 69%). (*S*,*R*)-**4**: ^1H NMR

($CDCl_3$, $T = 300$ K): δ (ppm) 8.66 (s, 1H, H_{10}), 8.50 (s, 1H, H_{11}), 8.33 (m, 2H, H_4 and H_5), 8.01 (m, 2H, H_1 and H_8), 7.44 (m, 4H, H_2, H_7, H_3 and H_6), 7.16 (m, 5H, phenyl group), 4.92 (s, 1H, H_{12}), 3.41 (s, 3H, CH_3).

Starting from the (*S*)-enantiomer of alcohol **1**, the (*S*,*S*)-**4** isomer was obtained. (*S*,*S*)-**4**: ^{1}H NMR ($CDCl_3$, $T = 300$ K): δ (ppm) 8.63 (s, 1H, H_{10}), 8.55 (s, 1H, H_{11}), 8.40 (d, $J_{4,3} = J_{5,6} = 8.7$ Hz, 2H, H_4 and H_5), 8.06 (d, $J_{1,2} = J_{8,7} = 8.2$ Hz, 2H, H_1 and H_8), 7.52 (m, 4H, H_2, H_7, H_3 and H_6), 7.40 (m, 5H, phenyl group), 4.84 (s, 1H, H_{12}), 3.32 (s, 3H, CH_3).

Both esters, (*S*,*R*)-**4** and (*S*,*S*)-**4**, could also be achieved starting from the racemic form of alcohol **1**. The reaction described above gives a mixture of the diastereomeric esters **4**, which are separated by HPLC (Welk-O1 column, 95% hexane-5% isopropanol). The first eluted ester was the (*S*,*R*)-**4** isomer while the second one was the (*S*,*S*)-**4** isomer, both of which were obtained with 100% ee.

3.5. Crystallography

A suitable crystal ($0.46 \times 0.42 \times 0.14$ mm^3) of (*R*)-**3** was selected for X-ray single crystal diffraction experiments and mounted at the tip of a glass fibre on an Enraf–Nonius CAD4 diffractometer producing graphite monochromated Mo Kα radiation. After the random search of 25 reflections, the indexation procedure gave rise to the cell parameters $a = 13.700(3)$, $b = 15.472(3)$ and $c = 17.466(3)$ Å. The cell volume was 3702.2(13) Å^3, the calculated density 1.49 g/cm^3 and the absorption coefficient 0.13 mm^{-1}. The assigned space group was $P2_12_12_1$ with $Z = 4$. Data were collected up to $2\theta = 60°$ in the ω–2ϑ scan mode resulting in 5922 reflections. Absorption correction was performed following the PSI-scan semi-empirical method. The structural resolution procedure was made using the WinGX package.[15] Solving for structure factor phases was performed by SIR2002[16] and the full-matrix refinement, by SHELXL97.[17] Non-H atoms were refined anisotropically and H-atoms were introduced in calculated positions and refined riding on their parent atoms. The final *R* indices were for $I > 2\sigma(I)$: $R1 = 0.0633$, $wR2 = 0.1218$ and for all data: $R1 = 0.2023$, $wR2 = 0.1535$. The largest difference Fourier peak and hole were 0.237 and -0.221 e Å^{-3}. Crystallographic data have been deposited with the been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 234752.

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