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Preparation and behavior of (*R*)- and (*S*)-2,2,2-trifluoro-1-(1-pyrenyl)ethanol as chiral solvating agents: study of the diastereomeric association by Job's plots, intermolecular NOE and binding constants

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Abstract—Racemic 2,2,2-trifluoro-1-(1-pyrenyl)ethanol **2**, was prepared and the (*R*)- and (*S*)-enantiomers obtained by preparative chiral HPLC. The behavior of these compounds as chiral solvating agents is studied with mixtures of several enantiomeric aromatic alcohols and amines. The non-linear distribution of aromatic rings in the pyrene appears to enhance the enantiodiscrimination capacity. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

In organic chemistry, the determination of the enantiomeric composition of a compound by nuclear magnetic resonance (NMR) analysis is usually completed with the aid of an auxiliary as a chiral solvating agent. Pirkle's alcohol **1** is one of the most common chiral solvating agents[1] (CSAs) used in this field. Several structural modifications have been made on **1** in order to study the chiral recognition phenomena. For example, the introduction of a blocking group such as *tert*-butyl, allows us to study the diastereomeric complexes[2] through nuclear Overhauser effects, whilst the use of perdeutero derivatives allow the preparation of a CSA without proton NMR signals.[3] Moreover, increasing the number of stereogenic centers[4] affords an important increase in the enantiodiscriminating capacity of the CSA.

The work presented herein describes the modification of the aromatic part of **1**, changing the anthryl to a pyrenyl group and we analyze the behavior of this compound as a CSA. We have synthesized and studied the enantiomers of 2,2,2-trifluoro-1-(1-pyrenyl)ethanol **2**. Its capacity for chiral recognition has been tested in front of several racemic and non-racemic alcohol and amine derivatives. The study of the complex was carried out by determination of the stoichiometry, measurement of the binding constants and by observation of intermolecular NOE effects. In a previous work,[5] we described the preparation of the corresponding perdeuterio derivative of **2** (compound **3**) as the second case of 'chiral recognition between isotopomers'.

2. Results and discussion

Racemic 2,2,2-trifluoro-1-(1-pyrenyl)ethanol **2** was obtained by reducing 1-(trifluoroacetyl)pyrene **4**, which was prepared by acylation[6] of pyrene with trifluoroacetic anhydride (Scheme 1).

Preparative HPLC using a chiral (Whelk-O1) column made it possible to obtain the separated enantiomers. The absolute configuration was established by comparison of the specific rotation of each separated enantiomer with that described in the literature.[7]

The solvating experiments were carried out in the presence of racemic and non-racemic chiral compounds (1-phenylethan-1,2-diol **5**, 1-(1-naphthyl)ethanol **6**, 1-(1-phenyl)ethylamine **7** and 1-(1-naphthyl)ethylamine **8**) (Fig. 1) by addition of between one and two equivalents of one enantiomer of **2**. This mixture gave diastereomeric complexes where non-equivalence of the ^{1}H NMR chemical shift between each complex was observed.

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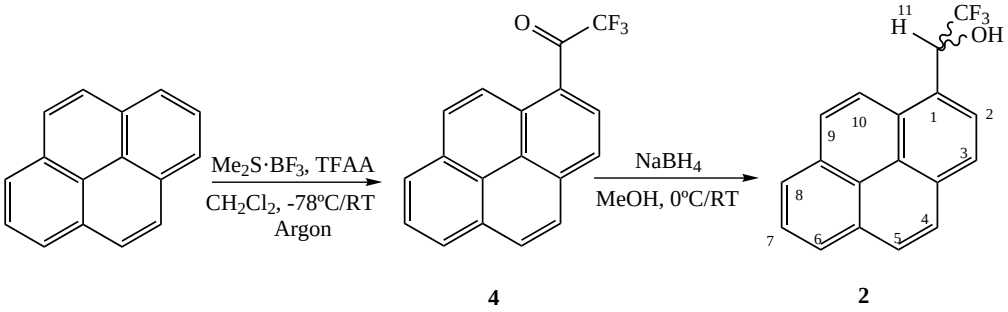

Scheme 1. Preparation of compound **2**.

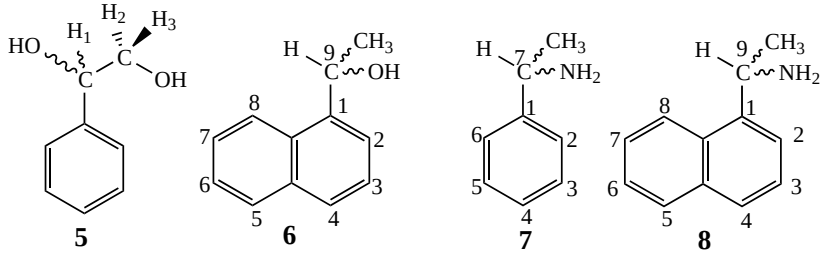

Figure 1. Chiral compounds used for discriminating experiments.

All experiments were compared with those achieved when Pirkle's alcohol **1** was used under the same conditions. The values of non-equivalence obtained when we studied the enantiodiscrimination of alcohols with **2** was lower than those obtained when we used compound **1**. Here, we only cite the values obtained when the dialcohol **5** was used (Table 1).

In the case of the amines, 1-(1-phenyl)ethylamine **7** or 1-(1-naphthyl)ethylamine **8**, the chemical shift changes that we observed when the CSA **2** was used were different if we employed Pirkle's alcohol **1**. As is shown in Table 2, the non-equivalence obtained in the methyl signal of both amines when compound **2** is used were larger than those obtained with Pirkle's alcohol **1**. On the other hand, when the observed signal was the methinic quartet, the differences were larger when **1** was applied.

The results indicate that the non-linear distribution of the aromatic rings increases the non-equivalence of the methyl groups. The influence of the magnetic anisotropy of the pyrene aromatic system must be very different for the two enantiomers, and this must be the cause of the important distinction between the methyl groups of amines **7** and **8**.

Table 1. Differences ($\Delta\delta = \delta - \delta_{R \text{ or } S}$) of the chemical shifts of the proton H_1 of two enantiomers of the compound **5** when several quantities of (*S*)-**2** or (*S*)-**1** were added

CSA [**5**]/[CSA]	(*S*)-**2** $\Delta(\Delta\delta)H_1$ (ppm)	(*S*)-**1** $\Delta(\Delta\delta)H_1$ (ppm)
0.5	0.003	0.007
1.0	0.005	0.009
1.5	0.006	0.010
2.0	0.007	0.012

Furthermore, the use of 2,2,2-trifluoro-1-(1-pyrenyl)-ethanol **2** allowed us to study the shift differences observed in the aromatic part of the amine **8** as well as the identification of the signals corresponding to each enantiomer (Fig. 2).

Knowledge of the stoichiometry of the complex in solution is basic data required for the study the geometry of the complex. As the chemical shift of a nucleus is a mean value of the several species presents in solution, when all components are completely dissolved, Job's method[8] can be applied to calculate the stoichiometry of the complex in solution.

The two complexes, (*S*)-**2**·(*R*)-**7** and (*S*)-**2**·(*S*)-**7**, were analyzed: 16 samples of a constant total concentration were prepared containing variable ratios of the two components. Only the complex (*S*)-**2**·(*S*)-**7** is fully described here.

The ^1H NMR spectra of these samples were recorded at 300 K and the chemical shift variations were observed for protons of amine **7** and the alcohol **2**. The plot of the variation of the chemical shift of amine protons CH_3 and $H_{7'}$ and H_2, H_{10}, H_4 and H_{11} of **2** versus the ratio between the concentration of each compound, **2** or **7**, and the total concentration (0.02 M) are reflected in Figs. 3 and 4. The maximum value of the parabolic curve in the X coordinate gives us the stoichiometry. In the six plots, a value of 0.5 was found, meaning that the stoichiometry of the complex is 1:1. The same results were obtained for the complex (*S*)-**2**·(*R*)-**7**.

We also studied the associates by observation of the intermolecular NOE effects obtained from the four

Table 2. Differences ($\Delta\delta=\delta-\delta_{R \text{ or } S}$) of the chemical shifts of protons of the enantiomers of compounds **7** and **8** when several quantities of (*S*)-**2** or (*S*)-**1** were added. The values in parentheses are those corresponding to the identical experiment when **1S** was added

Compound	$\delta_{R,S}$ (ppm)	[CSA]/[**7** or **8**]	δ_R (ppm)	δ_S (ppm)	$\Delta(\Delta\delta)_{S,R}$ (ppm)
1-(1-Phenyl)ethylamine **7**		0.50	4.037	4.041	0.004 (0.023)
	H_7	1.00	4.008	4.015	0.007 (0.034)
	4.0984	1.50	4.006	4.014	0.008 (0.042)
		2.00	3.999	4.008	0.009 (0.046)
		0.50	1.354	1.349	−0.005 (0)
	CH_3	1.00	1.344	1.336	−0.008 (0)
	1.3736	1.50	1.343	1.334	−0.009(−0.002)
1-(1-Naphthyl)ethylamine **8**		2.00	1.340	1.331	−0.009 (−0.003)
		0.40	4.873	4.878	0.005 (0.018)
	H_9	0.80	4.832	4.841	0.009 (0.023)
	4.9491	1.20	4.806	4.817	0.011 (0.028)
		1.60	4.786	4.800	0.014 (0.045)
		2.00	4.777	4.792	0.015 (0.047)
		0.40	1.518	1.515	−0.003 (0)
	CH_3	0.80	1.502	1.497	−0.005 (0)
	4.0984	1.20	1.492	1.485	−0.007 (0)
		1.60	1.485	1.477	−0.008 (0)
		2.00	1.481	1.473	−0.008 (0)

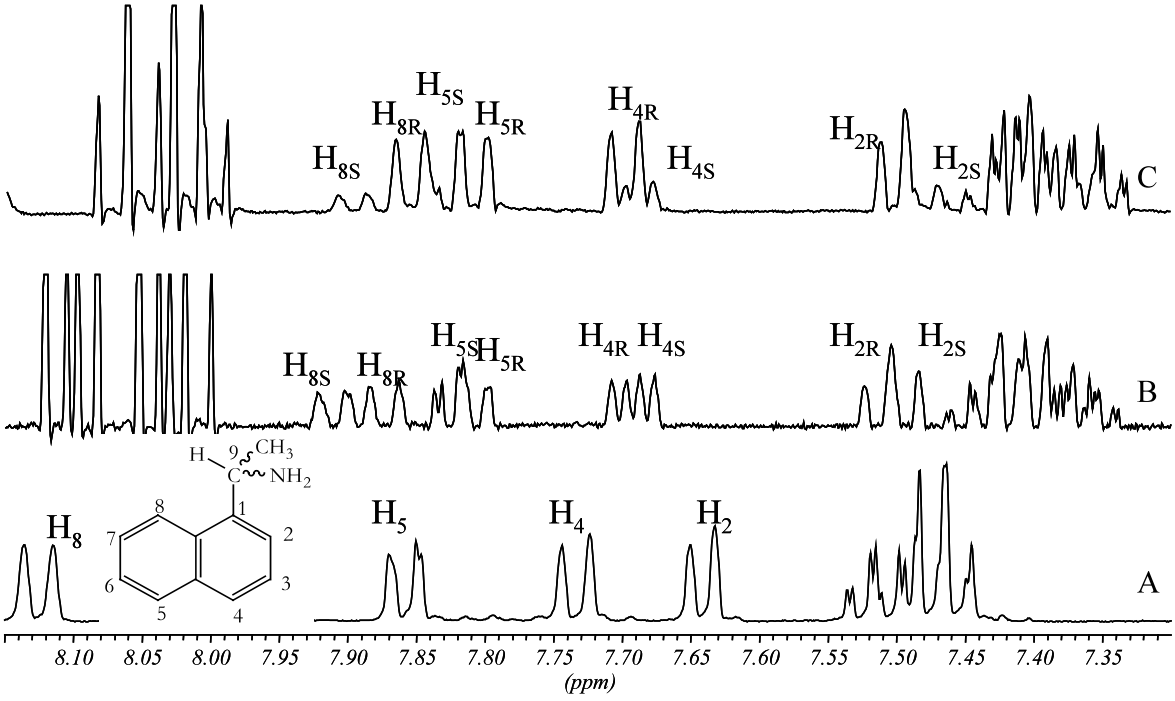

Figure 2. Aromatic part of the ^{1}H NMR spectra (298 K) of (a) racemic amine **8**. (b) Racemic amine **8** after addition of 1.6 equiv. of (*S*)-**2**. (c) An enriched mixture of enantiomers of amine **8** ($R/S=3/1$) after addition of 1.6 equiv. of (*S*)-**2**.

complexes (*S*)-**2**·(*R*)-**7**, (*R*)-**2**·(*S*)-**7**, (*S*)-**2**·(*S*)-**7** and (*R*)-**2**·(*R*)-**7**. We used the DPFGE–NOE methodology,[9] which achieves an optimal selected excitation and so avoids undesired magnetizations. All the samples were prepared in $CDCl_3$ using pure enantiomers **2** and **7** in degassed and sealed tubes under an argon atmosphere with 1.8 equiv. of CSA **2**. The results of the experiments were the same for all of the complexes.

As shown in Table 3, when the alcohol protons H_2 and H_{11}, were irradiated, we observed NOE effects for the CH_3 signal of 7 only. On the other hand, when the CH_3 proton signal of amine **7** was irradiated (Table 4) we observed NOE effects on H_2, H_{11} and H_{10} and only on H_{11} if the saturated peak was the one corresponding to the aromatic part. We want to emphasize the absence of NOE on H_7 when the alcohol protons are irradiated.

If we consider all the results obtained from the study of the amine **7**, recognition experiments, Job's plots, intermolecular NOE, and the possible formation of a hydrogen bond between the hydroxyl group of **2** and the

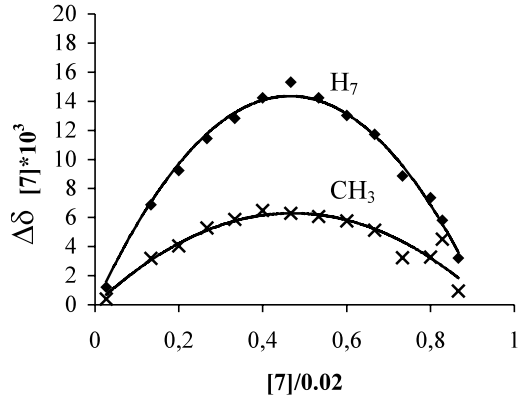

Figure 3. Job's plots of variation of chemical shift of protons, H_7 and CH_3 of amine **7**, in (*S*)-**2**·(*S*)-**7** complex.

amino group of **7** we can propose that the π-stacking interaction between two components is possible in two different approximations of the aromatics rings. In this case, the asymmetry of the pyrene group is responsible for the enantiodifferentiation of the methyl groups.

It is known that chemical shift differences observed when an association complex is formed could be a consequence of the different geometry of complexes, different binding constants (*K*) or a combination of both factors. In the case of amine **7**, we determined the binding constant of the complex with each enantiomer of **2** using the 'equimolar method'.[10] According to Bouquant and Chuche, could be applied this method if we supposed that the stoichiometry was 1:1. A sample of each complex ((*R*)-**2**·(*R*)-**7** and (*R*)-**2**·(*S*)-**7**) with an initial concentration of 0.053 M of each compound was prepared. We diluted (five times) these samples by additions of 0.1 ml of $CDCl_3$ and registered the ^1H NMR spectra at 298 K. The plot of the variation of the chemical shifts ($\Delta\delta$) of the amine protons (H_7 and CH_3) versus $(\Delta\delta/S_0)^{1/2}$, where S_0 is the initial concentration of the solute and δ_c is the chemical shift in the complex, are reflected in Fig. 5. From the plotted straight lines we determined the binding constant for every studied proton.

Finally, the mean constant of each complex, with the enantiomers (*R*)-**2** and (*S*)-**2** was 2.5±0.1 M^{-1} and 3.0±0.1 M^{-1}, respectively.

The same measures were carried out at lower temperatures, 275 and 260 K. We observed an increase in the values of *K* for each complex. We also determined the free enthalpies ($\Delta G°$) for each process at every temperature (Table 5).

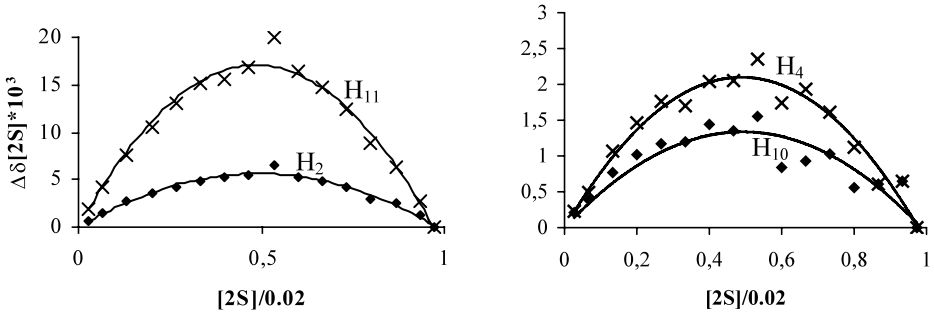

Figure 4. Job's plots of variation of chemical shift of protons H_2, H_{10}, H_4 and H_{11} of alcohol **2**, in the (*S*)-**2**·(*S*)-**7** complex.

Table 3. Intermolecular NOEs observed when several protons of alcohol **2** were irradiated in the associated complex of one enantiomer of **7** with 1.8 equiv. of one enantiomer of **2**

Saturated proton of **2**	H_2		H_{11}	
NOE on **7**	((*S*)-**2**·(*S*)-**7**) ((*R*)-**2**·(*R*)-**7**)	((*S*)-**2**·(*R*)-**7**) ((*R*)-**2**·(*S*)-**7**)	((*S*)-**2**·(*S*)-**7**) ((*R*)-**2**·(*R*)-**7**)	((*S*)-**2**·(*R*)-**7**) ((*R*)-**2**·(*S*)-**7**)
Ar	–	–	–	–
H_7	–	–	–	–
CH_3	x	x	x	x

Table 4. Intermolecular NOE observed when several protons of amine **7** were irradiated in the associated complex of one enantiomer of **7** with 1.8 equiv. of one enantiomer of **2**

Saturated protons of **7**	Ar		H_7		CH_3	
NOE on **2**	((*S*)-**2**·(*S*)-**7**) ((*R*)-**2**·(*R*)-**7**)	((*S*)-**2**·(*R*)-**7**) ((*R*)-**2**·(*S*)-**7**)	((*S*)-**2**·(*S*)-**7**) ((*R*)-**2**·(*R*)-**7**)	((*S*)-**2**·(*R*)-**7**) ((*R*)-**2**·(*S*)-**7**)	((*S*)-**2**·(*S*)-**7**) ((*R*)-**2**·(*R*)-**7**)	((*S*)-**2**·(*R*)-**7**) ((*R*)-**2**·(*S*)-**7**)
H_2	—	—	—	—	x	x
H_{10}	—	—	—	—	x	x
H_{11}	x	x	—	—	x	x

Applied equation:

$$\Delta\delta \approx \delta_C - \sqrt{\frac{\delta_C}{K_1}}\sqrt{\frac{\Delta\delta}{S_0}}$$

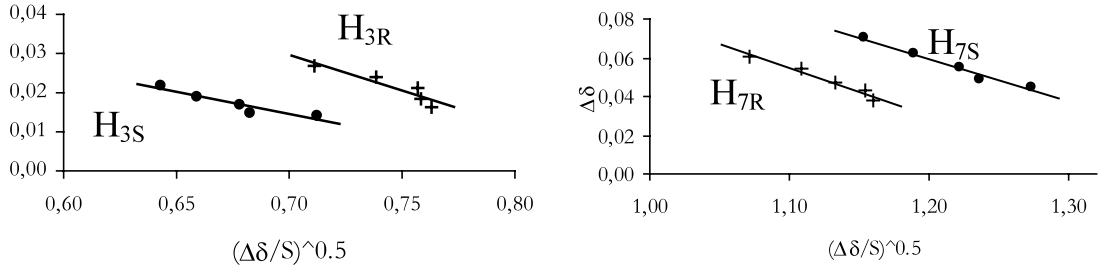

Figure 5. Plots obtained when the equimolar method is applied for the determination of binding constants of the complexes (*R*)-**2**·(*R*)-**7** and (*R*)-**2**·(*S*)-**7**.

Table 5. Binding constants and enthalpies of the association of each enantiomer of **8** with **2R** of at several temperatures

Temperature (K)	$K \pm 0.1$/ (M^{-1})		$\Delta G° \pm 0.1$/ (kJ mol^{-1})	
	(*R*)-**2**·(*R*)-**8**	(*R*)-**2**·(*S*)-**8**	(*R*)-**2**·(*R*)-**8**	(*R*)-**2**·(*S*)-**8**
298	2.5	3.0	−2.3	−2.7
275	20.1	13.0	−6.8	−5.9
260	47.2	29.3	−8.3	−7.3

The values of K increase as the temperature decreases. Moreover, the differences in $\Delta G°$ between enantiomers are larger while at room temperature there is practically no difference. One may suppose that at room temperature the observed chemical shift differences are only a consequence of the different geometries of both complexes. As the temperature decreases the differences in the stability are larger, meaning that at low temperatures the observed differentiation between enantiomers is the consequence of the addition of both factors, the geometry and the stability of each complex.

3. Experimental

^{1}H NMR spectra were recorded at 400.13 MHz. Chiral semipreparative HPLC was carried out using a (*R*,*R*) Whelk O1 column (250 mm×10 mm). Simple molecular mechanics calculations were carried out with CS Chem-3D Pro (v.5) program using the internal standard conditions.

3.1. 1-(Trifluoroacetyl)pirene, 4

At 195 K and under argon atmosphere a solution of trifluoroacetic anhydride (4.24 ml, 30 mmol) in anhydrous methylene chloride (4 ml) is added to a solution of boron trifluoride methyl sulfide complex ($Me_2S{\cdot}BF_3$, 3.16 ml, 30 mmol) in the same solvent (20 ml). After 10 min of gentle stirring, a solution of pyrene (2.02 g, 10 mmol) in anhydrous methylene chloride (6 ml) is added to the mixture. The resulting solution was stirred for an additional 15 min, and the mixture was allowed to warm to room temperature and stirred for 24 h. After a conventional workup ($NaHCO_3$ and CH_2Cl_2 extraction), the mixture was purified by flash chromatography. Ketone **4** (2.98 g, 65%) was obtained: mp 116–119°C;[6] IR (KBr) 2980, 2969, 2855, 1680, 1183, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm) 8.01 (H_4, d), 8.06 (H_7, dd), 8.12 (H_3, d), 8.18 (H_5, d), 8.25 (H_9, d), 8.26 ($H_{6,8}$, m) 8.50 (H_2, d) and 9.10 (H_{10}, d); ^{13}C NMR ($CDCl_3$) δ (ppm) 122.29 (C_1), 123.63 (C_{10c}), 123.80 (C_3), 123.95 (C_{10}), 124.85 (C_{10b}), 126.17 (C_7), 126.88 (C_4), 127.15 (C_8), 127.45 (C_6), 128.19 (C_2), 130.15 (C_{8a}), 130.74 (C_{5a}), 131.33 (C_5), 131.38 (C_9), 132.27 (C_{10a}), 135.86 (C_{3a}), 182.40 (C=O). MS (EI) *m*/*e* (%) 299 (M+1, 13), 298 (M, 49), 230 (17), 229 (M−69 (CF_3), 100), 202 (M+1−97 (C(CF_3)=O), 11), 201 (M−97 (C(CF_3)=O), 64), 200 (44), 100 (52).

3.2. 2,2,2-Trifluoro-1-(1-pyrenyl)ethanol 2

At 273 K a solution obtained ketone of (1 g, 3.36 mmol) in methanol (10 ml) is added to a solution of 175 mg (5.04 mmol) of sodium borohydride in 25 ml of the same solvent. The resulting mixture was allowed to warm to room temperature and stirred for 2–4 h. The solution was treated with a solution of NH_4Cl 5% and extracted with portions of ethyl acetate. The organic phase was washed with water and dried with Na_2SO_4, evaporated and purified by flash chromatography. A white solid was obtained (0.95 g, 95%). Mp 132–135°C;[7] IR (KBr) 3254, 1307, 1244, 1195 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm) 2.17 (OH, d), 6.18 (H_{11}, dq), 8.03 (H_7, dd), 8.06 (H_4, d), 8.11 (H_5, d), 8.15 (H_9, d), 8.21 ($H_{6,8}$, m), 8.23 (H_3, d), 8.26 (H_{10}, d), 8.32 (H_2, d); ^{13}C NMR ($CDCl_3$) δ (ppm) 69.25 (C_{11}), 121.94 (C_{10}), 124.89 (C_2), 124.52, 124.67, 125.56, 125.88 ($C_{3,6,8,10b}$),

126.20 (C_7), 126.98 (C_1), 127.28 (C_4), 128.31, 128.58 ($C_{5,9}$), 129.15 (C_{10a}), 130.37 (C_{8a}), 131.23 (C_{5a}), 132.07 (C_{3a}); MS (EI) *m*/*e* (%) 301 (M+1, 11), 300 (M, 53), 231 (M−69 (CF_3), 79), 203 (M−97 (C(CF_3)-O), 95), 202 (M−98 (C(CF_3)-OH), 100; (*R*)-**2** $[\alpha]_D^{20}=-16.8$; (*c* 0.48, CH_2Cl_2) and (*S*)-**2** $[\alpha]_D^{20}=+20.6$; (*c* 0.49, CH_2Cl_2).

Enantiopure samples of **2** were obtained by chiral HPLC (Welch-O1) using hexane/2-propanol 93/7 as liquid phase. $\lambda=290$ nm, flow 2.8 ml/min. $K_S=2.87$ and $K_R=3.85$, $\alpha=1.3$.

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