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On the regioselectivity of the Friedländer reaction leading to huprines: stereospecific acid-promoted isomerization of *syn*-huprines to their *anti*-regioisomers

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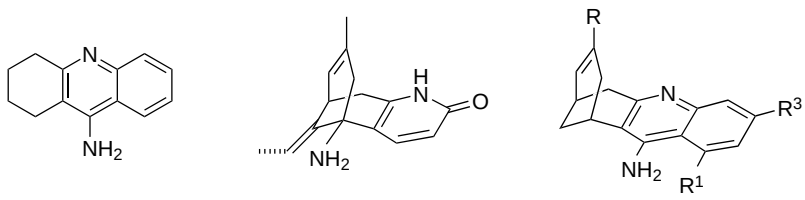
Abstract—Racemic 12-amino-6,7,8,11-tetrahydro-7,11-methanocycloocta[*b*]quinoline derivatives (*syn*-huprines) substituted at the 9-position with a methyl or ethyl group, and both enantioenriched forms of the 9-ethyl derivative, obtained by chiral MPLC resolution of the racemic mixture, were readily converted to the corresponding *anti*-isomers (huprines) by stereospecific acid-promoted ($AlCl_3$ or triflic acid) isomerization of the endocyclic C=C double bond from the 9(10)- to the 8(9)-position. These results support the hypothesis that the hitherto unseen *syn*-huprines are also formed under the usual acidic Friedländer reaction conditions used to prepare the known huprines, but rearrange in situ to the more stable *anti*-regioisomers (B3LYP/6-31G*).

1. Introduction

The huprines, **3**, are a new class of very potent, selective acetylcholinesterase (AChE) inhibitors of potential interest for the symptomatic treatment of Alzheimer's disease (AD),[1–6] that were designed through a conjunctive approach from the model AChE inhibitors, tacrine,[7] **1**, and (−)-huperzine A,[8] **2** (Fig. 1). They contain the 4-aminoquinoline substructure of tacrine and the carbobicyclic system of (−)-huperzine A.

From the synthetic point of view, (±)-huprines are easily available by Friedländer condensation of racemic enones[9] (±)-**4**, with 2-aminobenzonitriles **5** appropriately substituted at the 4-position and/or 6-position, in the presence of $AlCl_3$ as a Lewis acid catalyst in refluxing 1,2-dichloroethane (Scheme 1). More than thirty different huprines have been synthesized in racemic form by this methodology and interestingly in all cases only the aminoquinolines having the heterocyclic ring and the endocyclic C=C double bond in an *anti*-arrangement were obtained. This apparent *anti*-regioselectivity was initially explained on the basis of kinetic control during the Friedländer reaction (Scheme 1). The intermediate *syn*- and *anti*-enamines, *syn*- and *anti*-**6**, could be in equilibrium under the acidic reaction



Tacrine, **1** (−)-**Huperzine A**, (−)-**2** **Huprines**, (±)-**3**

Figure 1. Structures of huprines and their starting models.

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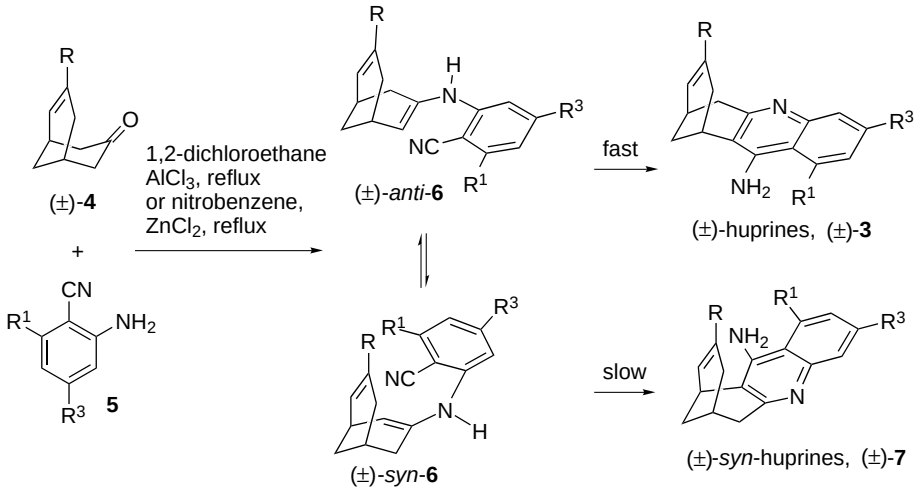


Scheme 1. A possible explanation of the regioselective Friedländer reaction leading to (±)-huprines, (±)-**3**, based on a kinetic control of the cyclization step.

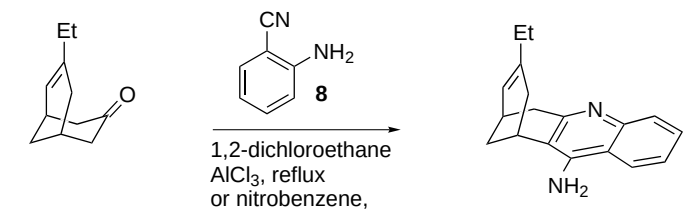
conditions. If the *anti*-aminoquinoline **3** was thermodynamically more stable than the corresponding *syn*-derivative **7**, this could also be reflected in the corresponding transition states, cyclization of *anti*-**6** to huprines **3** being faster than cyclization of *syn*-**6** to *syn*-huprines **7**.

Moreover, treatment of enantioenriched enones (−)-**4b** (79% e.e.) and (+)-**4b** (77% e.e.) with 2-aminobenzonitrile **8** under the usual Friedländer reaction conditions leads to the corresponding enantioenriched *anti*-aminoquinolines, huprines (+)-**3b** and (−)-**3b**, respectively, with significantly lower e.e.s (53% and 57% e.e., respectively),[5] (Scheme 2). Taking into account the apparent *anti*-regioselectivity of this cyclization, the partial racemization observed in these reactions might be due to partial racemization of the starting enones (−)-**4b** and (+)-**4b**, by isomerization of the C=C double bond under the acidic conditions of the reaction, which was also observed in the last step of the preparation of these enantioenriched enones, which involves the acid hydrolysis of their corresponding enantioenriched ethylene acetals.[5]

Alternatively, the decrease in enantiomeric excesses of the *anti*-aminoquinolines (+)- and (−)-**3b**, obtained from the enantioenriched enones (−)-**4b** and (+)-**4b**, respectively, could be explained as shown in Scheme 3, through a non-regioselective Friedländer reaction, followed by acid-promoted isomerization of the *syn*-aminoquinoline **7b**, to its *anti*-isomer **3b**. In this way, the *anti*-aminoquinoline obtained by isomerization of the *syn*-derivative, via migration of the endocyclic C=C double bond, would be enantiomeric with that directly obtained from the Friedländer reaction, thus decreasing the enantiomeric excess of the obtained product. As shown in Scheme 3, if the starting enone **4b** was enantiopure and assuming that the initial Friedländer cyclization gives X% ($X \leq 50$) of the *syn*-aminoquinoline, the e.e. of the final *anti*-aminoquinoline would be: (100−2X)%. Obviously, if the e.e. of the starting enone was lower, for example 80%, the e.e. of the final *anti*-aminoquinoline would be also lower: [0.8×(100−2X)]%.

This type of isomerization has also been observed in closely related systems and reflects the greater stability of the *anti*-arrangement for the C=C double bond and the heterocyclic ring in bicyclo[3.3.1]nonadiene derivatives.[10] Also, quantum mechanics calculations (B3LYP/6-31G*)[11] carried out on huprine **3** (R = Me, $R^1 = R^3 = H$) and *syn*-huprine **7** (R = Me, $R^1 = R^3 = H$) confirm the greater stability of the *anti*-derivative (2.4 kcal mol^{-1}).

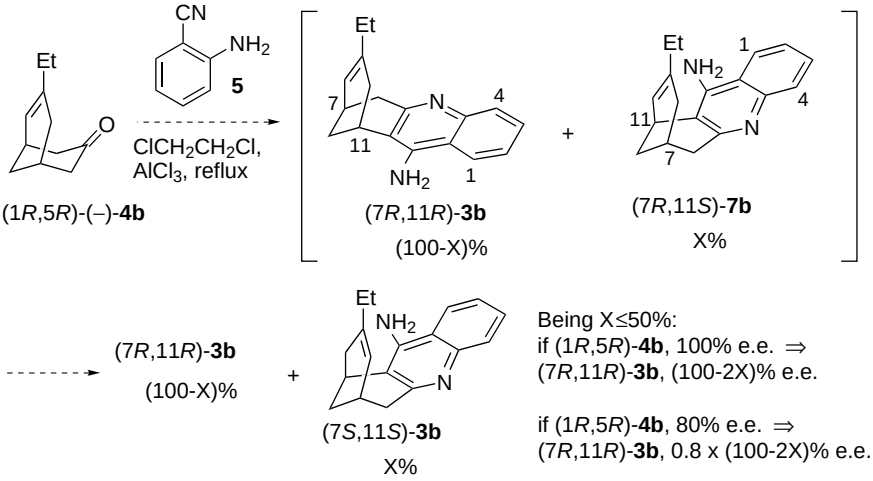
In order to check this hypothesis, we required the *syn*-huprines (±)-**7**. Compounds (±)-**7a** and (±)-**7b** were recently obtained by our research group[12] in a non-regioselective way by reaction of enones (±)-**4a** and



(−)-**4b** (79% e.e.)
[(+)-**4b** (77% e.e.)]

(+)-**3b** (75% yield; 53% e.e.)
[(−)-**3b** (80% yield; 57% e.e.)]

Scheme 2. Synthesis of enantioenriched huprines.



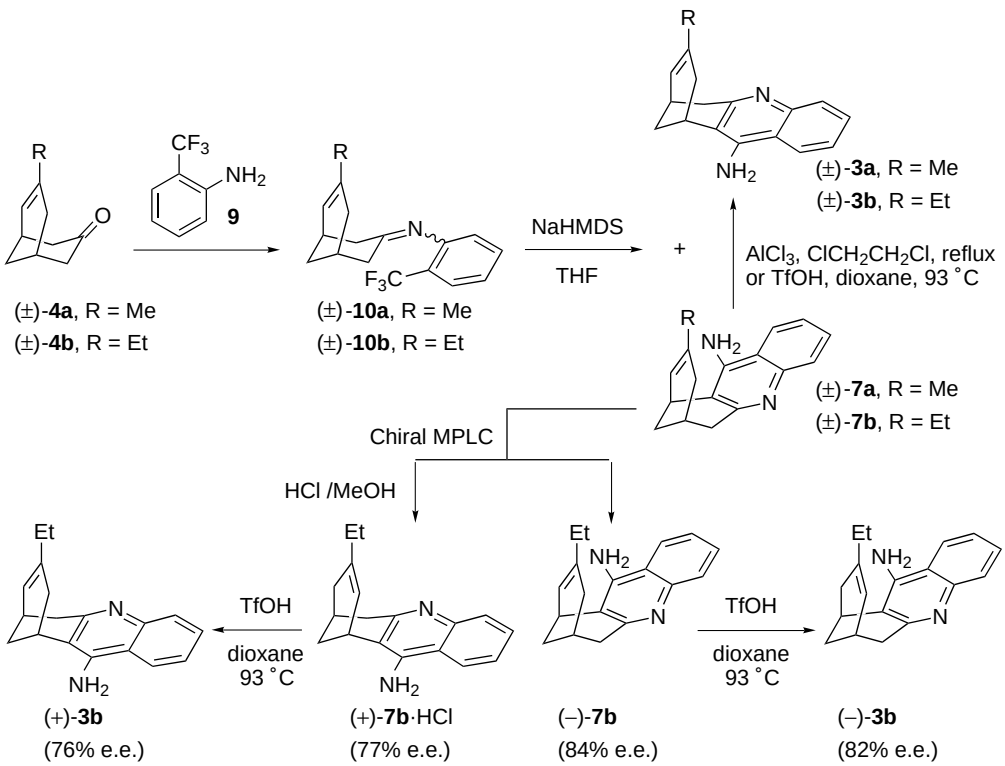
Scheme 3. An alternative explanation of the regioselective Friedländer reaction leading to enantioenriched huprines, **3b**, based on the conversion of the initially formed mixture of *syn*- and *anti*-products, **3b** and **7b**, to huprine **3b**.

(±)-**4b** with 2-(trifluoromethyl)aniline **9**, followed by treatment of the stereoisomeric mixture of imine products (±)-**10a** and (±)-**10b** with sodium hexamethyldisilazide,[13] and column chromatography separation of the *syn*- and *anti*-regioisomers (Scheme 4).

2. Results and discussion

Herein, we describe: (i) the chromatographic resolution of racemic *syn*-huprine (±)-**7b** by chiral medium pressure liquid chromatography (chiral MPLC), and (ii) the stereospecific acid-promoted isomerization of racemic and enantioenriched racemic-, (+)- and (–)-*syn*-huprines **7** to the corresponding *anti*-regioisomeric huprines (±)-, (+)- and (–)-**3**.

The enantiomers of **7b** were obtained from their racemic mixture by chiral medium pressure liquid chromatography (chiral MPLC) using microcrystalline cellulose triacetate (15–25 μm) as the chiral stationary phase and 96% EtOH as eluent, a method usually utilized for the preparative resolution of (±)-huprines.[1–5] The chromatographic fractions were analyzed by chiral HPLC, and combined conveniently, what allowed us to obtain (–)-**7b** (20 mg, 84% e.e.; 60 mg,



Scheme 4. Synthesis, chiral MPLC resolution, and acid-promoted isomerization of (±)- and enantioenriched *syn*-huprines.

62% e.e.) and (+)-**7b** (52 mg, 70% e.e.). A sample of (−)-**7b** (62% e.e.) and another of (+)-**7b** (70% e.e.) were transformed into the corresponding hydrochlorides to give, after washing with hot AcOEt, pure (−)-**7b**·HCl (60% e.e.) and pure (+)-**7b**·HCl (77% e.e.).

The studies on the isomerization of *syn*-huprines to their *anti*-regioisomers were first carried out under the usual Friedländer reaction conditions. Thus, treatment of a mixture of (±)-**7a**/(±)-**3a** in an approximate ratio of 2:1 with $AlCl_3$ in 1,2-dichloroethane under reflux for 24 h, afforded pure (±)-**3a**. Under the same reaction conditions, pure (±)-**7b** was completely isomerized to (±)-**3b**. Alternatively, (±)-**3b** was obtained quantitatively by isomerization of a mixture of (±)-**7b**/(±)-**3b** in an approximate ratio of 1:1 on reaction with triflic acid in dioxane at 93°C for 24 h.[14] Moreover, reaction of enantioenriched (+)-**7b**·HCl (77% e.e.) and (−)-**7b** (84% e.e.) with triflic acid in dioxane at 93°C proceeded stereospecifically to give (+)-**3b** (76% e.e.) and (−)-**3b** (82% e.e.), respectively. From the previously assigned absolute configurations of (+)- and (−)-huprines, (+)-**3b** and (−)-**3b**, the (7*S*,11*R*)- and (7*R*,11*S*)-configurations were assigned to the *syn*-huprines (+)-**7b** and (−)-**7b**, respectively.

3. Conclusion

In conclusion, these results suggest that the regioselectivity observed in the Friedländer reaction of enones **4** leading to the *anti*-aminoquinolines (huprines) may be due to the equilibration of the initially formed mixture of *syn*- and *anti*-regioisomeric products to the more stable *anti*-derivatives as shown in Scheme 3. The results obtained starting from enantioenriched huprines (Scheme 2) may be similarly explained by assuming that the initial cyclization reaction gives a mixture of the *anti*- and *syn*-derivatives in a ratio of about 86/14 ($X=14$ in Scheme 3).

4. Experimental

4.1. General methods

Melting points were determined in open capillary tubes with a MFB 595010 M Gallenkamp melting point apparatus. IR spectra were recorded on a FT/IR Perkin–Elmer spectrometer, model 1600. Absorption values are expressed as wave numbers (cm^{-1}). Optical rotations were measured on a Perkin–Elmer model 241 polarimeter. Chiral HPLC analyses were performed on a Waters model 600 liquid chromatograph provided with a Waters model 486 variable λ detector, using a CHIRALCEL OD-H column (25×0.46 cm) containing the chiral stationary phase cellulose tris(3,5-dimethylphenylcarbamate). Conditions A: mixture of hexane/EtOH/Et_2NH (90:10:0.1) as eluent, flow 0.20 mL/min, $\lambda=235$ nm. Chiral medium pressure liquid chromatography (chiral MPLC) separation was carried out on an equipment which consisted of a pump (Büchi 688), a variable λ UV detector (Büchi), and a column (25×2.5 cm) containing microcrystalline cellulose triacetate (15–25 μm) as the chiral stationary phase. High-resolution mass spectra were performed at the Mass Spectrometry Laboratory of the Departamento de Química Orgánica, Universidad de Santiago de Compostela, Spain. The ^1H and ^{13}C NMR data of compounds (+)-(7*S*,11*R*)- and (−)-(7*R*,11*S*)-**7b** coincide with those previously obtained for the racemic compound.[12] The rest of compounds have been previously described.[6] Ab initio calculations were performed with the Gaussian 98 program,[11] at the B3LYP/6-31G* level of theory.

4.2. Preparative resolution of 12-amino-9-ethyl-6,7,8,11-tetrahydro-7,11-methanocycloocta[*b*]quinoline,[12] (±)-7b, by chiral MPLC: (+)-(7*S*,11*R*)-7b and (−)-(7*R*,11*S*)-7b

The chromatographic resolution of (±)-**7b**, obtained as described,[12] was carried out by using MPLC equipment as described in Section 4.1. The sample of (±)-**7b** was introduced as the free base in three portions (220 mg, 210 mg and 180 mg), using 96% EtOH (2.0–2.5 mL/min) as the sole eluent and solvent. The chromatographic fractions were analyzed by chiral HPLC under conditions A [(−)-**7b**, $t_R=35.43$ min, $K'_1=1.29$; (+)-**7b**, $t_R=43.91$ min, $K'_2=1.83$, $\alpha=1.42$, res.$=2.61$] and combined conveniently. In this way, (−)-**7b** (20 mg, 84% e.e.; 60 mg, 62% e.e.) and (+)-**7b** (52 mg, 70% e.e.) were obtained. The remaining product consisted of mixtures of both enantiomers with lower e.e.s.

A solution of (−)-**7b** (44 mg, 0.17 mmol, 62% e.e.) in MeOH (3 mL) was treated with a solution of HCl (1.49N solution in MeOH, 0.16 mL, 1.4 equiv.). The organic solvents were removed under reduced pressure, and the resulting yellowish solid residue was treated with hot AcOEt (3 mL), separated by filtration, and dried to afford (−)-**7b**·HCl {42.6 mg, $[\alpha]_D^{20}=-234$ ($c=0.29$, MeOH), 60% e.e. by chiral HPLC on the liberated base}: mp 136–137°C dec; IR 3500–2500 (max at 3356, 3225, 2962, 2928) (CH, NH, NH^+), 1649, 1637, and 1588 (ar-C-C and ar-C-N) cm^{-1}. Exact mass calcd for $C_{18}H_{20}N_2$ 264.1626, obsd 264.1619.

A solution of (+)-**7b** (52 mg, 0.20 mmol, 70% e.e.) in MeOH (5 mL) was treated with a solution of HCl (1.49N solution in MeOH, 0.4 mL, 3 equiv.). The organic solvents were removed under reduced pressure, and the resulting yellowish solid residue was treated with hot AcOEt (5 mL), separated by filtration, and dried to afford (+)-**7b**·HCl {43 mg, $[\alpha]_D^{20}=+302$ ($c=0.29$, MeOH), 77% e.e. by chiral HPLC on the liberated base}: mp 171–173°C (dec.); IR 3500–2500 (max at 3336, 3182, 2961, 2927, 2692) (CH, NH, NH^+), 1652, 1636, and 1588 (ar-C-C and ar-C-N) cm^{-1}. Exact mass calcd for $C_{18}H_{20}N_2$ 264.1626, obsd 264.1626.

4.3. Isomerization of (±)-12-amino-6,7,8,11-tetrahydro-9-methyl-7,11-methanocycloocta[*b*]quinoline,[12] (±)-7a, to (±)-12-amino-6,7,10,11-tetrahydro-9-methyl-7,11-methanocycloocta[*b*]quinoline,[6] (±)-3a

A solution of a mixture of (±)-**7a**/(±)-**3a**[12] (approximate ratio = 2:1, 270 mg, 1.08 mmol) in 1,2-dichloroethane (10 mL) was added dropwise to a suspension of $AlCl_3$

(214 mg, 1.60 mmol) in 1,2-dichloroethane (2 mL), and the reaction mixture was heated under reflux for 24 h. A mixture of THF (7 mL) and water (6 mL), and aqueous 0.5N NaOH (0.5 mL) were successively added to the resulting suspension, and the mixture was stirred at room temperature for 30 min. The organic solvents were evaporated at reduced pressure and the resulting aqueous suspension was filtered in vacuo. The solid residue was washed with water (2×5 mL), and dried to afford near pure (±)-**3a** (180 mg) (^{1}H NMR).

4.4. Isomerization of (±)-7b to (±)-12-amino-9-ethyl-6,7,10,11-tetrahydro-7,11-methanocycloocta[*b*]quinoline,[6] (±)-3b

4.4.1. Method 1. This reaction was carried out as described above for the isomerization of (±)-**7a** to (±)-**3a**, from a suspension of $AlCl_3$ (45 mg, 0.34 mmol) in 1,2-dichloroethane (2 mL), and a solution of (±)-**7b**[12] (60 mg, 0.23 mmol) in 1,2-dichloroethane (6 mL). The aqueous suspension, obtained after evaporation of the organic solvents, was extracted with CH_2Cl_2 (3×3 mL) and the combined organic extracts were dried with anhydrous Na_2SO_4 and evaporated at reduced pressure to give essentially pure (±)-**3b** (50 mg, 83% yield) (^{1}H NMR).

4.4.2. Method 2. Triflic acid (30 μL, 50.9 mg, 0.34 mmol) was added to a solution of a 1:1 mixture of (±)-**7b**/(±)-**3b** (50 mg, 0.19 mmol) in anhydrous dioxane (2.5 mL), and the reaction mixture was heated at 93°C for 24 h. The mixture was evaporated in vacuo and the resulting brown oily residue was partitioned between aqueous 10% $NaHCO_3$ (5 mL) and $CHCl_3$ (5 mL). The aqueous phase was extracted with $CHCl_3$ (2×5 mL), and the combined organic extracts were dried with anhydrous Na_2SO_4 and evaporated at reduced pressure to give essentially pure (±)-**3b** (50 mg, quantitative yield) (^{1}H NMR).

4.5. Isomerization of (+)-(7*S*,11*R*)-7b to (+)-(7*R*,11*R*)-3b[5]

This reaction was carried out as described before for the isomerization of (±)-**7b** to (±)-**3b** (Method 2), from triflic acid (26 μL, 44.1 mg, 0.29 mmol) and a solution of (+)-**7b**·HCl (21.8 mg, 0.08 mmol, 77% e.e.) in anhydrous dioxane (2.5 mL). After evaporation of the dried organic extracts, pure (+)-**3b** (15.2 mg, 70% yield, 76% e.e.) was obtained.

A solution of (+)-**3b** (13.0 mg, 49.2 μmol, 76% e.e.) in MeOH (2 mL) was treated with a solution of HCl (1.49N solution in MeOH, 0.10 mL, 3 equiv.). The organic solvents were removed under reduced pressure, and the resulting yellowish solid residue was treated with hot AcOEt (2×1 mL), separated by filtration, and dried to afford (+)-**3b**·HCl {12.6 mg, $[\alpha]_D^{20}=+185.5$ ($c=0.32$, MeOH), 72% e.e. by chiral HPLC on the liberated base}.

4.6. Isomerization of (−)-(7*R*,11*S*)-7b to (−)-(7*S*,11*S*)-3b[5]

This reaction was carried out as described for the isomerization of (±)-**7b** to (±)-**3b** (Method 2), from triflic acid (12.4 μL, 21.0 mg, 0.14 mmol) and a solution of (−)-**7b** (10.3 mg, 0.04 mmol, 84% e.e.) in anhydrous dioxane (1.3 mL). After evaporation of the dried organic extracts, pure (−)-**3b** (4.4 mg, 43% yield, 82% e.e.) was obtained.

A solution of (−)-**3b** (4.2 mg, 15.9 μmol, 82% e.e.) in MeOH (2 mL) was treated with aqueous HCl (1.49N solution in MeOH, 0.10 mL, 9 equiv.). The organic solvents were removed under reduced pressure, and the resulting yellowish solid residue was treated with hot AcOEt (2×1 mL), separated by filtration, and dried to afford (−)-**3b**·HCl {1.7 mg, $[\alpha]_D^{20}=-234.7$ ($c=0.16$, MeOH), 87% e.e. by chiral HPLC on the liberated base}.

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