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Tetrahedron: *Asymmetry* 14 (2003) 1985–1988

TETRAHEDRON: *ASYMMETRY*

Kinetic resolution of (±)-2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine, (±)-2-methyl-1,2,3,4-tetrahydroquinoline and (±)-2-methylindoline using *N*-tosyl-(*S*)-prolyl chloride

Victor P. Krasnov,* Galina L. Levit, Iraida M. Bukrina, Irina N. Andreeva, Liliya Sh. Sadretdinova, Marina A. Korolyova, Mikhail I. Kodess, Valery N. Charushin and Oleg N. Chupakhin

Institute of Organic Synthesis of RAS (Ural Div.), S. Kovalevskoy St., 20, Ekaterinburg 620219, Russia

Received 27 March 2003; accepted 7 April 2003

Abstract—Acylation of racemic 2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine, 2-methyl-1,2,3,4-tetrahydroquinoline and 2-methylindoline with *N*-tosyl-(*S*)-prolyl chloride resulted in their kinetic resolution with the predominant formation of (*R*,*S*)-diastereoisomeric amides, des being 80, 66 and 38%, respectively. Recrystallisation of the amides followed by acid hydrolysis gave individual (*R*)-enantiomers of heterocyclic amines. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

High stereoselectivity in kinetic resolutions catalysed by enzymes is due to the specific spatial structure of biocatalyst–substrate complexes and this phenomenon excites envy in chemists involved in traditional organic synthesis. However, reasonably high enantiomeric excess of the products of kinetic resolutions could also be achieved using low-molecular weight chiral resolving agents. Thus, studying the effects of resolving agent structures and reaction conditions on stereochemical results of kinetic resolutions is of importance, and provides a powerful basis to choose the most appropriate agents.

Acylative kinetic resolutions have been reported to be carried out with a wide range of enzymes (amidases, proteases, esterases, lipases),[1] or chiral synthetic catalysts.[2] Recently we have developed efficient kinetic resolutions of racemic heterocyclic amines (Fig. 1), such as 2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine **1**, 2-methyl-1,2,3,4-tetrahydroquinoline **2** and 2-methylindoline **3** by use of (*S*)-naproxen chloride **4** (Fig. 2), a chiral resolving acylating agent, which afforded (*S*)-enantiomers of heterocyclic amines of high enantiomeric excess.[3]

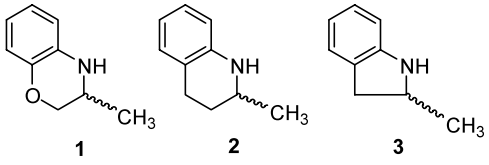


Figure 1. Heterocyclic amines.

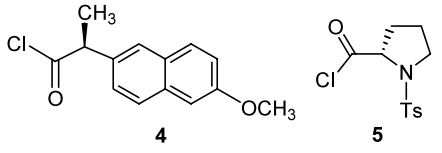


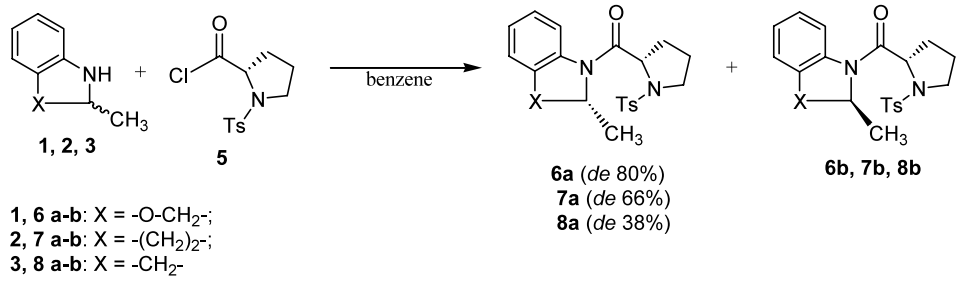
Figure 2. Chiral resolving agents.

Herein we wish to report that the use of another chiral agent, *N*-tosyl-(*S*)-prolyl chloride **5**,[4] for kinetic resolutions of the same heterocyclic amines **1**–**3** is a good complementary method enabling one to obtain the (*R*)-enantiomers of amines **1**–**3**.

Acyl chloride **5** was described earlier as a chiral agent for the resolution of racemic 7,8-difluoro-2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine aimed at preparation of (*S*)-enantiomer which is the key intermediate in the synthesis of levofloxacin, one of the most efficient

* Corresponding author. Tel.: +7-3432-493057; fax: +7-3432-741189; e-mail: ca@ios.uran.ru

0957-4166/03/$ - see front matter
doi:10.1016/S0957-4166(03)00321-5



Scheme 1.

antibacterial drug.[5] Acylation was carried out with stoichiometric amounts of reagents, the resulting mixture of diastereoisomeric amides was resolved using column chromatography, and basic hydrolysis of (*S*,*S*)-amide gave the target (*S*)-enantiomer of 7,8-difluoro-2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine.

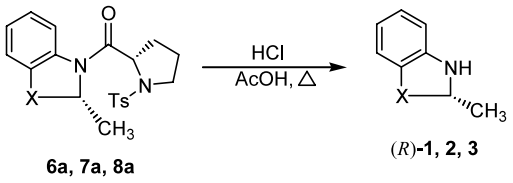
2. Results and discussion

The diastereomeric mixtures of amides **6a**,**b**, **7a**,**b** and **8a**,**b** were obtained by interaction of acyl chloride **5** with racemic amines **1**, **2** and **3** taken in the stoichiometric ratio in the presence of TEA (Scheme 1). In all mixtures **6a**,**b** (**7a**,**b** or **8a**,**b**) the ratio of diastereoisomers was 1:1 according to the ^{1}H NMR spectra and HPLC. The feature of the ^{1}H NMR spectra of amides **6a**,**b**, **7a**,**b** and **8a**,**b** measured at ambient temperature in $CDCl_3$ or DMSO-d_6 is broadening of the resonance signals of protons adjacent to stereogenic centres of both amine and proline moieties, whereas on heating solutions in DMSO-d_6 to 100°C the signals became sharp. This allows analysis of spectra of both diastereoisomeric mixtures and individual diastereoisomers to be performed.

When molar ratio of the starting amines **1**–**3** and acyl chloride **5** was 2:1, without any tertiary amine present in the reaction mixture, the resulting products **6a**,**b**, **7a**,**b** and **8a**,**b** were found to be significantly enriched with (*R*,*S*)-diastereoisomers **6a**, **7a** and **8a**, de values being 80, 66, and 38%, respectively. (*R*,*S*)-Diastereoisomers **6a**, **7a** and **8a** of high diastereoisomeric purity (de >99%) were obtained in yields from 28 to 48% after repeated crystallisation from a hexane–ethyl acetate mixture. (*S*)-Isomers of amines **1**–**3** could be isolated from acidic solutions on treatment of the reaction mixtures.

(*R*,*S*)-Amides **6a** (**7a** or **8a**) were hydrolysed on heating under reflux in a mixture of concentrated HCl and glacial acetic acid (Scheme 2) to give individual (*R*)-isomers of amines **1** (**2** or **3**) (ee about 97% by HPLC with pre-column derivatization using (*S*)-naproxen acyl chloride **4**[3]).

Unlike acidic hydrolysis of (*S*)-naproxen amides of heterocyclic amines, it took much more time (up to 40 h) to completely hydrolyse amides **6a** (**7a** or **8a**). Such prolonged exposure of the reaction mixture under acidic conditions resulted in an insignificant partial racemization of heterocyclic amines.



Scheme 2.

3. Conclusion

Thus, kinetic resolution of racemic amines **1**–**3** using *N*-tosyl-(*S*)-prolyl chloride as a chiral resolving agent results in predominant formation of (*R*,*S*)-amides and further acid hydrolysis of the latter makes it possible to obtain (*R*)-isomers of these amines in high enantiomeric excess.

4. Experimental

4.1. General

Solvents were purified according to standard procedures. Routine monitoring of reaction mixtures was carried out using Silufol UV 254 (Kavalier) TLC aluminium plated silica gel. Melting points were determined on a Boetius melting point apparatus and are uncorrected. ^{1}H NMR spectra were measured on a Bruker DRX 400 (400 MHz) spectrometer, spectra of amides **6a**,**b**, **7a**,**b** and **8a**,**b** (in DMSO-d_6 at 100°C), spectra of amines **1**–**3** (in DMSO-d_6 or $CDCl_3$ at ambient temperature). All signals are expressed in ppm (δ) with tetramethylsilane as an internal standard. 2D ^{1}H–^{1}H COSY spectra of **6a**, **7a** and **8a** were obtained to ease the proton chemical shifts assignment and interpretation of splitting patterns. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. The de values of amides **6a**, **7a** and **8a** were measured by HPLC on a Milichrom-4 chromatograph [Silasorb-600 column; mobile phase hexane:*i*-PrOH = 15:1 (A) and 20:1 (B); flow rate 0.1 ml/min; UV detection 230 nm; retention times: $\tau_{\mathbf{6a}}$ 7.3 min, $\tau_{\mathbf{6b}}$ 4.5 min (A); $\tau_{\mathbf{7a}}$ 5.7 min, $\tau_{\mathbf{7b}}$ 4.1 min (A); $\tau_{\mathbf{8a}}$ 6.2 min, $\tau_{\mathbf{8b}}$ 3.5 min (B). Microanalyses were carried out on a CHNS-O model EA-

1102 elemental analyser and were in good agreement with the calculated values.

4.2. *N*-[*N*′-Tosyl-(2*S*)-prolyl]-(3*RS*)-2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine 6a,b

Solution of *N*-tosyl-(*S*)-prolyl chloride **5** (0.29 g, 1.0 mmol) in benzene (1.5 mL) was added dropwise to a stirred solution of racemic **1** (0.15 g, 1.0 mmol) and TEA (0.14 mL, 1.0 mmol) in benzene (1.5 mL). The mixture was stirred at room temperature for 20 h, then washed consequently with 1N HCl, water, 5% $NaHCO_3$, water and dried ($MgSO_4$). The solution was evaporated in vacuum to dryness to give a yellow oily residue that was treated with hexane yielding amide **6a**,**b** as yellow crystals (0.28 g, 70%). ^{1}H NMR (DMSO-d_6): 1.12 d and 1.14 d (J=6.8 Hz, 3H, CH_3-benzoxazine); 1.6–2.1 (m, 4H, C^3H_2-C^4H_2-proline); 2.37 s and 2.39 s (3H, CH_3-C_6H_4); 3.3–3.5 (m, 2H, C^5H_2-proline); 4.2 (m, 2H, O-CH_2); 4.62 dd, J=8.2, 4.5 Hz, and 5.00 dd, J=8.4, 4.0 Hz (1H, C^2H-proline); 4.83 m and 4.81 m (1H, C^3H-benzoxazine); 7.7–6.9 (m, 8H, arom.).

4.3. *N*-[*N*′-Tosyl-(2*S*)-prolyl]-(2*RS*)-2-methyl-1,2,3,4-tetrahydroquinoline 7a,b

Following the above procedure, and starting with racemic amine **2** (0.15 g, 1.0 mmol) the title compound was obtained as yellow crystals (0.27 g, 66%). ^{1}H NMR (DMSO-d_6): 1.03 d and 1.04 d (J=6.5 Hz, 3H, CH_3-quinoline); 1.30 (m, 1H, C^3H-quinoline); 1.52 (m, 1H, C^4H-quinoline); 1.98 (m, 3H, C^3H_2-C^4H-proline,); 2.33 s and 2.38 s (3H, C**H**$_3$-C_6H_4); 2.38 (m, 1H, C^3H-quinoline); 2.68 (m, 2H, C^4H_2-quinoline); 3.33 (m, 2H, C^5H_2-proline); 4.28 dd, J=8.0, 4.7 Hz, and 4.89 dd, J=8.1, 4.5 Hz (1H, C^2H-proline); 4.66 ddq and 4.73 ddq (J=7.4, 6.8, 6.6 Hz, 1H, C^2H-quinoline); 7.7–7.0 (m, 8H, arom.).

4.4. *N*-[*N*′-Tosyl-(2*S*)-prolyl]-(2*RS*)-2-methylindoline 8a,b

Following the above procedure, and starting with racemic amine **3** (0.13 g, 1.0 mmol) the title compound was obtained as yellow crystals (0.26 g, 70%). ^{1}H NMR (DMSO-d_6): 1.24 d, J=6.5 Hz, and 1.31 d, J=6.5 Hz (3H, CH_3-indoline); 1.76 (m, 1H, C^4H-proline); 1.84–2.24 (m, 3H, C^3H_2-C^4H-proline); 2.34 s and 2.40 s (3H, C**H**$_3$-C_6H_4); 2.66 d, J=16.0 Hz, and 2.70 d, J=16.4 Hz (1H, C^3H-indoline); 3.40 (m, 3H, C^5H_2-proline and C^3H-indoline); 4.61 dqd, J=8.7, 6.3, 1.3 Hz, and 4.86 dqd, J=8.5, 6.5, 2.1 Hz (1H, C^2H-indoline); 4.68 dd, J=8.6, 3.4 Hz, and 4.70 dd, J=7.8, 4.1 Hz (1H, C^2H-proline); 7.00–7.90 (m, 8H, arom.).

4.5. *N*-[*N*′-Tosyl-(2*S*)-prolyl]-(3*R*)-2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine 6a

Solution of *N*-tosyl-(*S*)-prolyl chloride **5** (0.89 g, 3.1 mmol) in benzene (20 mL) was added dropwise to a stirred solution of racemic **1** (0.93 g, 6.2 mmol) in benzene (20 mL). The mixture was stirred at room temperature for 20 h, then washed consequently with 1N HCl, water, 5% $NaHCO_3$, water and dried ($MgSO_4$). The solution was evaporated in vacuum to dryness to give an yellow oily residue which was recrystallized from hexane–ethyl acetate yielding amide **6a** as colourless crystals (0.48 g, 39%, de 99.2%). Mp: 158–60°C; $[\alpha]_D^{20}$ −330 (*c* 1.1, $CHCl_3$). Anal. calcd for $C_{21}H_{24}N_2O_4S$: C, 62.98; H, 6.04; N, 6.99; S, 8.01. Found: C, 62.78; H, 6.08; N, 6.99; S, 7.96. ^{1}H NMR (DMSO-d_6): 1.12 (d, J=6.8 Hz, 3H, CH_3-benzoxazine); 1.62 (m, 1H, C^4H-proline); 2.00 (m, 2H, C^3H-C^4H-proline); 2.11 (m, 1H, C^3H-proline); 2.36 (s, 3H, C**H**$_3$-C_6H_4); 3.29 (ddd, J=9.8, 7.2, 5.9 Hz, 1H, C^5H-proline); 3.44 (ddd, J=9.8, 7.1, 6.0 Hz, 1H, C^5H-proline); 4.17 (dd, J=10.7, 1.9 Hz, 1H, C^2H-benzoxazine); 4.21 (dd, J=10.7, 2.7 Hz, 1H, C^2H-benzoxazine); 4.61 (dd, J=8.2, 4.5 Hz, 1H, C^2H-proline); 4.82 (qdd, J=6.8, 2.7, 1.9 Hz, 1H, C^3H-benzoxazine); 6.88 (ddd, J=8.1, 7.3, 1.5 Hz, 1H, C^6H-benzoxazine); 6.94 (dd, J=8.2, 1.5 Hz, 1H, C^8H-benzoxazine); 7.14 (ddd, J=8.2, 7.3, 1.6 Hz, 1H, C^7H-benzoxazine); 7.25 (d, J=8.1 Hz, 3H, C^5H-benzoxazine and 2H-tosyl); 7.33 (d, J=8.1 Hz, 2H, tosyl).

4.6. *N*-[*N*′-Tosyl-(2*S*)-prolyl]-(2*R*)-2-methyl-1,2,3,4-tetrahydroquinoline 7a

Following the above procedure, and starting with racemic **2** (1.00 g, 6.8 mmol) and *N*-tosyl-(*S*)-prolyl chloride **5** (0.98 g, 3.4 mmol) the title compound was obtained as a yellowish residue (1.11 g, 82%) which was recrystallized from hexane–ethyl acetate yielding amide **7a** as colourless crystals (0.65 g, 48%, de 99.0%). Mp: 147–149°C; $[\alpha]_D^{20}$ −372 (*c* 2.0, $CHCl_3$). Anal. calcd for $C_{22}H_{26}N_2O_3S$: C, 66.30; H, 6.58; N, 7.03; S, 8.04. Found: C, 66.13; H, 6.63; N, 7.09; S, 8.17. ^{1}H NMR (DMSO-d_6): 1.04 (d, J=6.7 Hz, 3H, CH_3-quinoline); 1.30 (dddd, J=13.2, 9.2, 7.1, 6.2 Hz, 1H, C^3H-quinoline); 1.52 (m, 1H, C^4H-quinoline); 2.00 (m, 3H, C^3H_2-C^4H-proline,); 2.33 (s, 3H, C**H**$_3$-C_6H_4); 2.38 (m, 1H, C^3H-quinoline); 2.63 (ddd, J=14.6, 5.8, 5.3 Hz, 1H, C^4H-quinoline); 2.68 (ddd, J=14.6, 5.5, 4.8 Hz, 1H, C^4H-quinoline); 3.23 (ddd, J=9.9, 7.1, 5.9 Hz, 1H, C^5H-proline); 3.41 (ddd, J=9.9, 7.0, 6.2 Hz, 1H, C^5H-proline); 4.28 (dd, J=7.9, 4.8 Hz, 1H, C^2H-proline); 4.73 (ddq, J=7.5, 6.8, 6.7 Hz, 1H, C^2H-quinoline); 6.99 (dd, J=7.5, 1.3 Hz, 1H, C^5H-quinoline); 7.13 (d, J=8.2, Hz, 2H, tosyl); 7.19 (d, J=8.2, Hz, 2H, tosyl); 7.20 (ddd, J=7.5, 7.3, 2.1 Hz, 1H, C^6H-quinoline); 7.25 (ddd, J=7.3, 7.3, 1.3 Hz, 1H, C^7H-quinoline); 7.31 (dd, J=7.3, 2.1 Hz, 1H, C^8H-quinoline).

4.7. *N*-[*N*′-Tosyl-(2*S*)-prolyl]-(2*R*)-2-methylindoline 8a

Following the above procedure, and starting with racemic **3** (1.00 g, 7.5 mmol) and *N*-tosyl-(*S*)-prolyl chloride **5** (1.08 g, 3.8 mmol) the title compound was obtained as a yellowish residue (1.00 g, 69%) which was recrystallized twice from hexane–ethyl acetate yielding amide **8a** as colourless crystals (0.40 g, 28%, de 98.8%). Mp: 207–209°C; $[\alpha]_D^{20}$ −78 (*c* 1.1, $CHCl_3$). Anal. calcd for $C_{21}H_{24}N_2O_3S$: C, 65.60; H, 6.29; N, 7.29; S, 8.34. Found: C, 65.83; H, 6.27; N, 7.31; S, 8.34. ^{1}H NMR (DMSO-d_6): 1.31 (d, J=6.3 Hz, 3H, CH_3-indoline);

1.76 (m, 1H, C^4H-proline); 1.91 (m, 2H, C^3H-C^4H-proline); 2.19 (m, 1H, C^3H-proline); 2.40 (s, 3H, CH_3-C_6H_4); 2.66 (d, $J=16.1$ Hz, 1H, C^3H-indoline); 3.40 (m, 3H, C^5H_2-proline and C^3H-indoline); 4.61 (dqd, $J=8.7$, 6.3, 1.3 Hz, 1H, C^2H-indoline); 4.70 (dd, $J=8.6$, 3.4 Hz, 1H, C^2H-proline); 7.02 (td, $J=7.4$, 1.3 Hz, 1H, C^5H-indoline); 7.16 (ddd, $J=7.7$, 7.4, 2.3 Hz, 1H, C^6H-indoline); 7.25 (dd, $J=7.4$, 2.3 Hz, 1H, C^4H-indoline); 7.37 (d, $J=8.5$ Hz, 2H, tosyl); 7.69 (d, $J=8.5$ Hz, 2H, tosyl); 7.80 (bs, 1H, C^7H-indoline).

4.8. Isolation of (*S*)-amines 1–3: general procedure

The aqueous acid layers after washing the previous reaction mixtures was alkalised by 10N NaOH up to pH 8–9 under ice cooling, extracted by $CHCl_3$, washed with brine and dried over $MgSO_4$. Evaporation of the solvent in vacuum gave amines **1** (**2** and **3**) as yellow oils. (*S*)-**1**: 0.38 g (82%), ee 80% by HPLC (pre-column derivatization with acyl chloride **4**[3a]); (*S*)-**2**: 0.45 g (90%), ee 66% by HPLC (pre-column derivatization with acyl chloride **4**[3b]); (*S*)-**3**: 0.35 g (70%), ee 38% by HPLC (pre-column derivatization with acyl chloride **4**[3b]).

4.9. (*R*)-2,3-Dihydro-3-methyl-4*H*-1,4-benzoxazine (*R*)-1

Amide **6a** (0.60 g, 1.5 mmol) was heated under reflux in a mixture of glacial acetic acid (3 mL) and conc. HCl (3 mL) for 40 h. The reaction mixture was evaporated to dryness. Water (5 mL) was added to the residue, the precipitate was filtered off and washed with water. The combined aqueous filtrates were made alkaline with 10N NaOH to pH 9–10 at +5°C and extracted with $CHCl_3$ (3×5 mL). The organic layer was washed with brine, and dried ($MgSO_4$). The solution was evaporated to dryness to give amine (*R*)-**1** as a yellowish oil (0.17 g, 78%), ee 97.0% by HPLC (pre-column derivatization using (*S*)-naproxen acyl chloride **4**[3a]). $[\alpha]_D^{20}$ −19 (*c* 1.3, $CHCl_3$). [Lit.:[3a] (*S*)-**1**: $[\alpha]_D^{20}$ +19.8 (*c* 1.0, $CHCl_3$)]. Anal. calcd for $C_9H_{11}NO$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.35; H, 7.38; N, 9.43. ^{1}H NMR (DMSO-d_6): 1.11 (d, $J=6.3$ Hz, 3H, Me), 3.39 (dqd, $J=7.9$, 6.3, 2.8 Hz, 1H, C^3H), 3.61 (dd, $J=10.2$, 7.9 Hz, 1H, C^2H); 4.08 (dd, $J=10.2$, 2.8 Hz, 1H, C^2H); 5.46 (bs, 1H, NH), 6.41 (ddd, $J=7.8$, 7.1, 1.7 Hz, 1H, C^6H), 6.50 (dd, $J=7.8$, 1.6 Hz, 1H, C^5H), 6.56 (dd, $J=7.6$, 1.7 Hz, 1H, C^8H); 6.59 (ddd, $J=7.6$, 7.1, 1.6 Hz, 1H, C^7H).

4.10. (*R*)-2-Methyl-1,2,3,4-tetrahydroquinoline (*R*)-2

Following the above procedure, and starting with amide **7a** (0.60 g, 1.5 mmol) the title compound was obtained as a yellowish oil (0.19 g, 86%), ee 96.7% by HPLC (pre-column derivatization using (*S*)-naproxen acyl chloride **4**[3b]). $[\alpha]_D^{20}$ +84 (*c* 1.3, benzene). [Lit.:[6] (*R*)-**2**: $[\alpha]_D^{20}$ +85 (*c* 2.0, benzene)]. Anal. calcd for $C_{10}H_{13}N$: C, 81.59; H, 8.90; N, 9.51. Found: C, 81.37; H, 8.88; N, 9.46. ^{1}H NMR ($CDCl_3$): 1.20 (d, $J=6.2$ Hz, 3H, Me), 1.58 (dddd, $J=12.8$, 11.5, 9.8, 5.4 Hz, 1H, C^3H), 1.92 (dddd, $J=12.8$, 5.6, 3.5, 2.9 Hz, 1H, C^3H), 2.72 (ddd, $J=16.3$, 5.4, 3.5 Hz, 1H, C^4H); 2.83 (ddd, $J=16.4$, 11.5, 5.6 Hz, 1H, C^4H), 3.39 (dqd, $J=9.8$, 6.2, 2.9 Hz, 1H, C^2H), 3.63 (bs, 1H, NH), 6.46 (dd, $J=8.3$, 1.3 Hz, 1H, C^8H), 6.59 (td, $J=7.3$, 1.2 Hz, 1H, C^5H), 6.95 (m, 2H, C^5H and C^7H).

4.11. (*R*)-2-Methylindoline (*R*)-3

Following the above procedure, and starting with amide **8a** (0.58 g, 1.5 mmol) the title compound was obtained as a yellow oil (0.13 g, 65%), ee 97.2% by HPLC (pre-column derivatization using (*S*)-naproxen acyl chloride **4**[3b]). $[\alpha]_D^{20}$ +11 (*c* 2.0, benzene). [Lit.:[3b] (*S*)-**3**: $[\alpha]_D^{20}$ −12.2 (*c* 2.6, benzene)]. Anal. calcd for $C_9H_{11}N$: C, 81.16; H, 8.32; N, 10.52. Found: C, 81.22; H, 8.28; N, 10.42. ^{1}H NMR ($CDCl_3$): 1.28 (d, $J=6.2$ Hz, 3H, Me), 2.63 (dd, $J=15.4$, 7.7 Hz, 1H, C^3H), 3.14 (dd, $J=15.4$, 8.5 Hz, 1H, C^3H), 3.39 (bs, 1H, NH); 3.98 (ddq, $J=8.5$, 7.7, 6.2 Hz, 1H, C^2H); 6.60 (d, $J=7.8$ Hz, 1H, C^7H), 6.68 (ddd, $J=7.5$, 7.3, 1.1 Hz, 1H, C^5H); 7.00 (ddd, $J=7.7$, 7.5, 1.5 Hz, 1H, C^6H); 7.07 (dd, $J=7.3$, 1.5 Hz, 1H, C^4H).

Acknowledgements

This work was financially supported by the Russian Foundation for Basic Research (Grants No. 00-15-97390, No. 00-03-40139 and No. 03-03-33091).

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