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SYNTHESIS OF ENANTIOMERS OF 6-NITRO- AND 6-AMINO-2-METHYL-1,2,3,4-TETRAHYDROQUINOLINES

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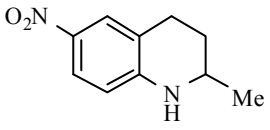
Enantiomers of 2-methyl-6-nitro-1,2,3,4-tetrahydroquinoline have been obtained by kinetic resolution of racemic 2-methyl-1,2,3,4-tetrahydroquinoline in acylation with acyl chlorides of N-protected amino acids followed by regioselective nitration of the diastereoisomeric amides and acidic hydrolysis. The introduction of a trifluoroacetyl protecting group into the position 1 of the enantio pure nitro compound followed by the reduction led to (S)-6-amino-2-methyl-1-trifluoroacetyl-1,2,3,4-tetra-hydroquinoline in a high yield.

Keywords: amides, diastereoisomers, enantiomers, kinetic resolution, nitration, reduction.

The enantiomers of 2-methyl-6-nitro-1,2,3,4-tetrahydroquinoline (**1**) and 6-amino-2-methyl-1,2,3,4-tetrahydroquinoline (**2**) are of interest as structural fragments of biologically active compounds [1-4].



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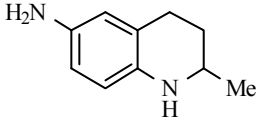

2

There are literature precedents for the preparation of racemic 2-methyl-6-nitro-1,2,3,4-tetrahydroquinoline (**1**) in the course of a tandem reductive amination and nucleophilic aromatic substitution of 4-(2-fluoro-5-nitrophenyl)-2-butanone [5] and also its (-)-enantiomer ((-)**1**) as a result of enantioselective catalytic hydrogenation of 2-methyl-6-nitroquinoline [6]. It is known that the regioselective introduction of a nitro group into the aromatic fragment of 1,2,3,4-tetrahydroquinolines is a complex problem, and previous investigations in this area have led to contradictory results [7-10]. Systematic study of the nitration of 1,2,3,4-tetrahydroquinoline and its derivatives has shown that in the presence of *N*-acyl substituents, the reaction proceeds selectively at the position 6 of the aromatic ring (the *para* position relative to the nitrogen atom) [11-16], while in the case of a bulky group (such as Fmoc) the regiodirected formation of the 6-nitro derivative was observed in 99% yield [16].

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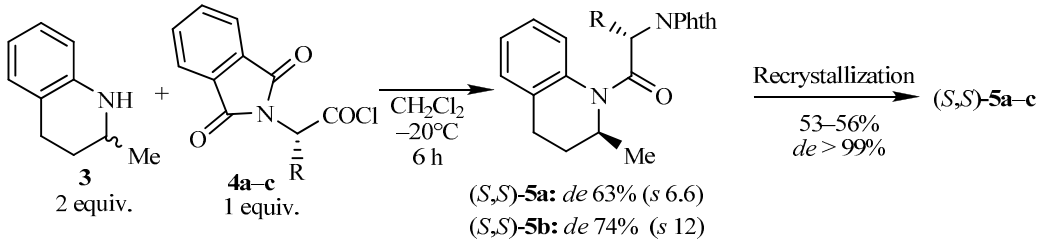
In the present work, we propose a new approach to the directed synthesis of the enantiomers of amines **1** and **2**, based on a kinetic resolution of racemic amines by acylation with acyl chlorides of chiral acids. Kinetic resolution (KR) is a method of resolution of optical isomers based on a difference in the conversion rate of the substrate enantiomers with a chiral reagent, or in the presence of a chiral catalyst [17, 18]. The effectiveness of KR is assessed according to the ratio of the rate constants for reactions of the substrate enantiomers, known as the selectivity factor (*s*). The value of *s* may be calculated from optical purity data for the reaction product and the unreacted substrate (*de* or *ee*) and the conversion (*C*) [17, 18].

$$C = \frac{ee_{\text{unreact}}}{ee_{unreact} + de_{\text{product}}}; \qquad s = \frac{\ln[(1-C)(1-ee_{\text{unreact}})]}{\ln[(1-C)(1+ee_{\text{unreact.}})]} \quad [17].$$

The KR process is considered to be adequate from a preparative point of view if $s > 10$ [19].

KR in acylation reactions is one of the most important methods for obtaining enantiomers of heterocyclic amines [18-22]. In our laboratory, a study on the KR of 2-methyl-1,2,3,4-tetrahydroquinoline (**3**) and other racemic heterocyclic amines on acylation with acyl chlorides of *N*-protected amino acids [23-26] and 2-arylpropionic acids [27-30] has been carried out. We have demonstrated that *N*-phthaloyl-(*S*)-amino acyl chlorides **4a,b** are efficient separating agents and may be used for obtaining (*S*)-enantiomers of heterocyclic amines [24, 25]. In particular, diastereoisomerically pure (*S,S*)-amides of *N*-phthaloyl-(*S*)-alanine (**5a**) and *N*-phthaloyl-(*S*)-phenylalanine (**5b**) with 2-methyl-1,2,3,4-tetrahydroquinoline were obtained in 54% and 53% yield, relative to racemic amine **3** [24, 25].



a R = Me, **b** R = CH_2Ph, **c** R = CH_2(*i*-Pr)

In the present work, we showed that *N*-phthaloyl-(*S*)-leucyl chloride (**4c**) is a more efficient resolving agent for amine **3**, compared to the reagents **4a** and **4b** studied previously (selectivity factor *s* was 6.6, 12 and 19 for the amine **3** reaction with acyl chlorides **4a-c** in CH_2Cl_2 at -20°C). The amide *(S,S)*-**5c** (*de* > 99.8%) was obtained after a single recrystallization of the KR product in 28% yield relative to racemic amine **3**. The absolute configuration of compound (*S,S*)-**5c** was determined on the basis of X-ray structural analysis data (Fig. 1) taking into account the known configuration of the acyl fragment.

In the acyl fragment of amide (*S,S*)-**5c**, there are no groups subject to nitration under mild conditions. Consequently this compound is of interest as an intermediate for obtaining optically pure nitro- and amino-substituted derivatives of 2-methyl-1,2,3,4-tetrahydroquinoline.

According to the known procedure [16], we carried out the nitration of amide (*S,S*)-**5c** with an equimolar mixture of KNO_3 and H_2SO_4 in CH_2Cl_2 at room temperature. After column flash chromatography, amide (*S,S*)-**6** was isolated in 77% yield. The composition, structure and purity of compound (*S,S*)-**6** were confirmed by NMR spectroscopy, HPLC, and elemental analysis. In the NMR spectra of amides containing a

residue of amine **1** or **3**, broadened signals for the majority of protons were observed at room temperature. On recording the ^{1}H NMR spectra at 100°C in DMSO-d_6, the signals became narrow and well resolved. A similar phenomenon was previously observed by us during investigation of structurally related amides [23-30].

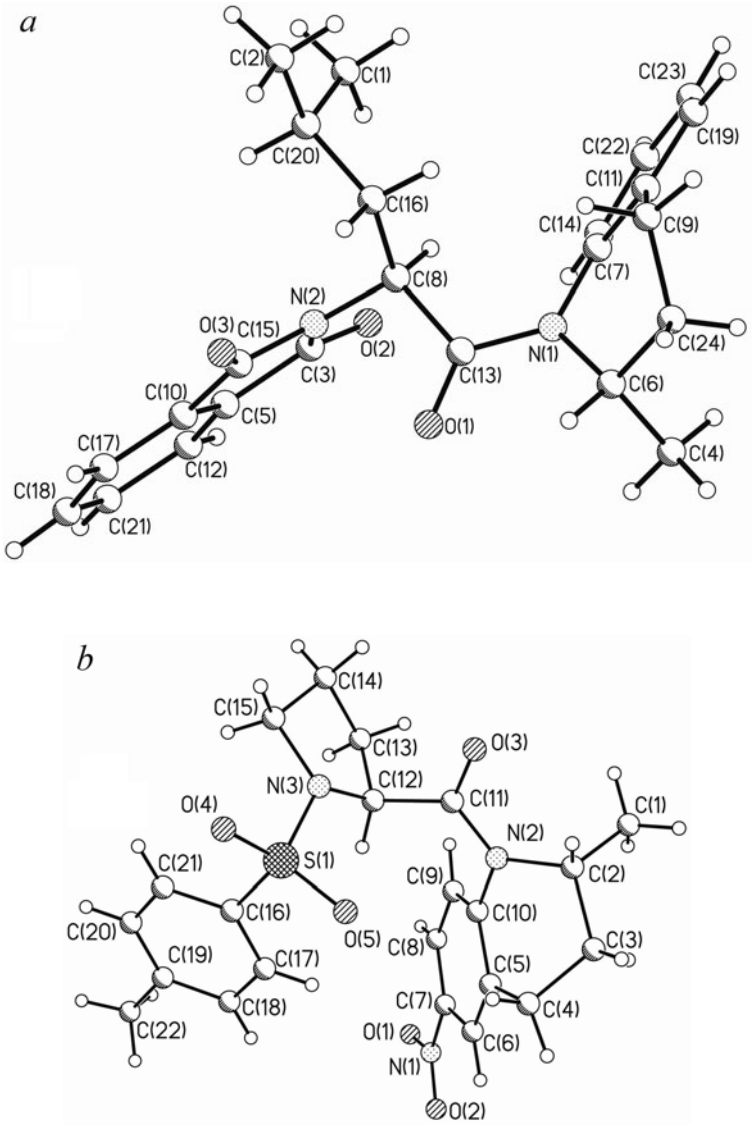
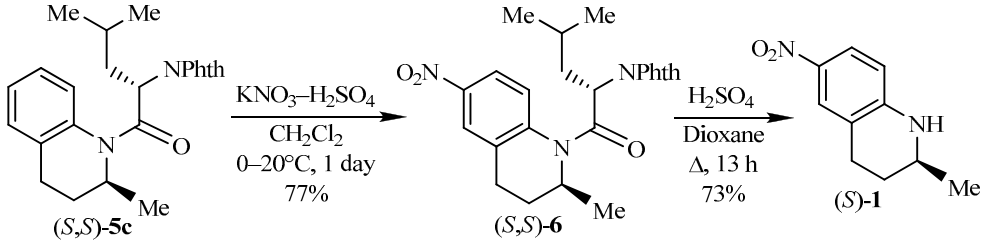
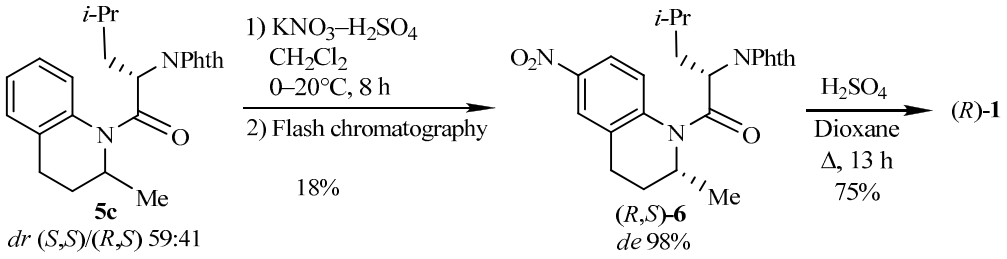


Fig. 1. Molecular structures of amides (*S*,*S*)-**5c** (*a*) and (*R*,*S*)-**8** (*b*), according to X-ray structural analysis data.

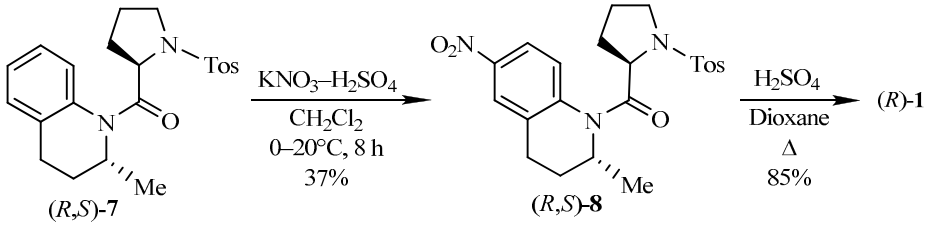


The hydrolysis of amide (*S,S*)-**6** under the conditions previously used by us for hydrolysis of other amides of *N*-phthaloyl-(*S*)-amino acids (heating in a mixture of conc. HCl and AcOH) [24, 25], was not successful. The (*S*)-enantiomer of 2-methyl-6-nitro-1,2,3,4-tetrahydroquinoline ((*S*)-**1**) was obtained by acidic hydrolysis of amide (*S,S*)-**6** on refluxing in 2 N H_2SO_4 in dioxane, in 56% overall yield, relative to amide (*S,S*)-**5c**.

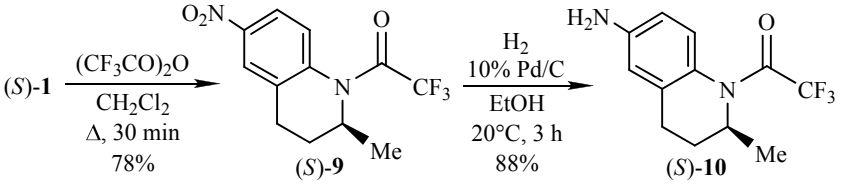
Nitration of the diastereoisomeric mixture **5c** led to a mixture of amides **6**, from which diastereoisomer (*R,S*)-**6** was isolated chromatographically. Hydrolysis of amide (*R,S*)-**6** (H_2SO_4 in dioxane) gave amine (*R*)-**1**. The optical purities of the enantiomers (*S*)-**1** and (*R*)-**1** were not less than 96% and 98%, respectively (according to chiral HPLC data).



We attempted to nitrate (*R,S*)-amide **7** (*de* > 99% according to HPLC data), obtained by KR of racemic amine **3** with *N*-tosyl-(*S*)-prolyl chloride according to a previously described procedure [23]. Nitration of amide (*R,S*)-**7** proceeded slower and led to the formation of a complex mixture with the predominant product due to nitration at the position 6 of the amine fragment. Amide (*R,S*)-**8** (purity 97% according to data of HPLC and ^{1}H NMR spectroscopy) was isolated by column flash chromatography in 37% yield, relative to amide (*R,S*)-**7**. The structure of (*R,S*)-amide **8** was confirmed by X-ray structural analysis (Fig. 1). Hydrolysis of amide (*R,S*)-**8** on refluxing in dioxane in the presence of conc. H_2SO_4 required more extended heating in comparison with the hydrolysis of amides of *N*-phthaloyl-(*S*)-amino acids. As a result, enantiomer (*R*)-**1** was obtained in 85% yield and *ee* 98% (according to chiral HPLC data).



Reduction of the nitro group of compound **1** was also studied. The reduction of amine (*S*)-**1** by the action of Sn in HCl led to amine **2** in 73% yield. However, compound **2** contained 20% of impurities (according to ^{1}H NMR spectroscopy data), and the purity was unaffected by recrystallization or chromatography. This is likely due to the readily oxidation of *p*-diaminobenzene system by the air oxygen. Consequently, to obtain derivatives of (*S*)-6-amino-2-methyl-1,2,3,4-tetrahydroquinoline we proposed an alternative route, involving introduction of a protecting group. It is known that trifluoroacetamides are readily hydrolyzed under mild alkaline conditions; therefore the use of a trifluoroacetyl group is a convenient method of temporarily blocking an amino group. Trifluoroacetamides are stable under conditions of catalytic hydrogenation [31]. Trifluoroacetylation of compounds (*S*)-**1** and (*R*)-**1** by the standard procedure led to amides (*S*)-**9** and (*R*)-**9**. Amine (*S*)-**10** was formed upon reduction of the nitro derivative (*S*)-**9** with hydrogen in the presence of Pd/C.



In the ^{1}H, ^{13}C, and ^{19}F NMR spectra of compound (*S*)-**10**, recorded at room temperature, double sets of signals were observed for the protons in positions 2, 3, 4, and 8, and also for the fluorine atoms of the CF_3 group. The ratio of conformers was 74:26. This is apparently associated to the hindered rotation about the amide bond. On heating to 100°C, merging of the conformer signals was observed in the NMR spectra, but even at this temperature some signals remained significantly broadened, in particular the signals of the CH_2 group protons and of H-8, and of the carbons of the methylene groups, and the nodal carbon C-8a.

Thus, we have proposed a new route for obtaining the enantiomers of 2-methyl-6-nitro-1,2,3,4-tetrahydroquinoline, reduction of which, after introducing the trifluoroacetyl protecting group, led to the enantiomers of 6-amino-1-trifluoroacetyl-2-methyl-1,2,3,4-tetrahydroquinoline.

EXPERIMENTAL

The ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded on a Bruker DRX-500 spectrometer (500, 470, and 125 MHz respectively) using TMS and hexafluorobenzene as internal standards. The NMR spectra of amides **5**, **6, 8-10** were recorded at 100°C, and of amines **1-3** at room temperature. The complete assignment of signals of compound (*R*,*S*)-**8** in ^{1}H and ^{13}C NMR spectra was carried out with the aid of two-dimensional NMR ^{1}H-^{1}H COSY, ^{1}H-^{13}C HSQC, and HMBC. The high-resolution mass spectra were obtained on a Bruker Daltonics series MicrOTOF-Q II mass spectrometer, electrospray ionization with direct sample inlet (flow rate 180 μl/h). The mass spectrometer was operated in the positive ionization mode in the mass range of 50-800 Da, at a capillary temperature of 250°C. Elemental analysis was carried out on Perkin Elmer 2400 II or Euro Vector EA3000 analyzers. Melting points were determined on a SMP3 instrument (Barloworld Scientific). Specific rotation was determined on a Perkin Elmer 341 polarimeter. HPLC analysis was performed on a Knauer Smartline-1100 chromatograph using ReproSil 100 Si column (250×4.6 mm, 5 μm for amides **5-8**) and Chiralcel OD-H column (250×4.6 mm, for amine **1** and amide **10**), detection at 220 nm, flow rate of 1 ml/min.

(*R*,*S*)-2-Methyl-1,2,3,4-tetrahydroquinoline (**3**) [32] and amide (*R,S*)-**7** [23] were obtained by known procedures. Compounds **4a,b** and **5a,b** were described previously [24, 25]. The remaining reactants were commercially available. Solvents were purified by traditional procedures.

***N*-Phthaloyl-(*S*)-leucyl Chloride (4c).** Oxalyl chloride (0.7 ml, 8.04 mmol) and DMF (5 μl) were added to a suspension of *N*-phthaloyl-(*S*)-leucine (1.00 g, 3.83 mmol) in a benzene–hexane 1:1 mixture (80 ml). The reaction mixture was stirred for 5 h and evaporated. The residue was dried in vacuum over P_2O_5. Yield 1.06 g (99%). Colorless oil. $[\alpha]_D^{20}$ -53.7° (*c* 1.4, C_6H_6). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.95 (3H, d, *J* = 6.6) and 0.97 (3H, d, *J* = 6.6, $CH(C\underline{H}_3)_2$); 1.47-1.57 (1H, m, $CHMe_2$); 2.05 (1H, ddd, *J* = 14.3, *J* = 10.0, *J* = 4.3) and 2.37 (1H, ddd, *J* = 14.3, *J* = 11.1, *J* = 4.3, $C\underline{H}_2CHMe_2$); 5.13 (1H, dd, *J* = 11.1, *J* = 4.3, CHCO); 7.77-7.82 (2H, m, H NPhth); 7.90-7.94 (2H, m, H NPhth). Found, %: C 60.29; H 5.04; N 4.94; Cl 12.15. $C_{14}H_{14}ClNO_3$. Calculated, %: C 60.11; H 5.04; N 5.01; Cl 12.67.

(*S*)-2-Methyl-1-[*N*'-phthaloyl-(*S*)-leucyl]-1,2,3,4-tetrahydroquinoline ((*S,S*)-5c). A solution of acyl chloride **4c** (4.20 g, 15 mmol) in CH_2Cl_2 (150 ml) was added to a solution of amine **3** (4.42 g, 30 mmol) in CH_2Cl_2 (150 ml) at -20°C under stirring. After 6 h the reaction mixture was washed with 1 N HCl (2×100 ml), NaCl solution (3×100 ml), 5% $NaHCO_3$ solution (2×100 ml), and water (2×100 ml). The organic layer was dried over $MgSO_4$ and evaporated. The residue was recrystallized from a hexane–EtOAc mixture, 2.5:1. Yield

3.28 g (56%). Colorless crystals, mp 168-169°C. $[\alpha]_D^{20}$ +447° (*c* 0.6, $CHCl_3$), *de* 99.8% (HPLC: hexane–2-PrOH, 80:1, τ 8.17 min). ^{1}H NMR spectrum (DMSO-d_6, 100°C), δ, ppm (*J*, Hz): 0.37 (3H, d, *J* = 6.6) and 0.63 (3H, d, *J* = 6.7, $CH(C\underline{H}_3)_2$); 0.89 (1H, ddd, *J* = 13.8, *J* = 9.7, *J* = 3.7) and 2.56 (1H, ddd, *J* = 13.8, *J* = 12.1, *J* = 3.9, $C\underline{H}_2CHMe_2$); 1.02 (3H, d, *J* = 6.6, 2-CH_3); 1.22-1.34 (2H, m, 3-CH_A, $C\underline{H}Me_2$); 2.36 (1H, dddd, *J* = 13.0, *J* = 7.9, *J* = 5.2, *J* = 4.6, 3-CH_B); 2.45 (1H, ddd, *J* = 14.9, *J* = 10.7, *J* = 5.1) and 2.69 (1H, ddd, *J* = 14.9, *J* = 4.8, *J* = 4.8, 4-CH_2); 4.59 (1H, ddq, *J* = 7.7, *J* = 6.9, *J* = 6.6, H-2); 5.55 (1H, dd, *J* = 12.1, *J* = 3.7, CHCO); 7.25 (1H, ddd, *J* = 7.5, *J* = 7.4, *J* = 1.2, H-6); 7.30-7.32 (1H, m, H-5); 7.33 (1H, ddd, *J* = 7.6, *J* = 7.4, *J* = 1.4, H-7); 7.48 (1H, dd, *J* = 7.6, *J* = 1.2, H-8); 7.83-7.88 (4H, m, H NPhth). ^{13}C NMR spectrum (DMSO-d_6, 100°C), δ, ppm: 19.5; 19.6; 21.9; 24.2; 25.0; 31.8; 34.1; 48.7; 51.9; 122.5; 124.7; 125.7; 126.2; 127.2; 131.0; 134.0; 135.6; 136.0; 167.8; 168.2. Found, %: C 73.82; H 6.94; N 7.18. $C_{24}H_{26}N_2O_3$. Calculated, %: C 73.82; H 6.71; N 7.17.

2-Methyl-1-[*N*'-phthaloyl-(*S*)-leucyl]-1,2,3,4-tetrahydroquinoline (5c) (Mixture of Diastereoisomers). The mother liquor after recrystallization of amide (*S,S*)-**5c** was evaporated. The mixture of amides was purified by column flash chromatography on silica gel (eluent benzene → benzene–EtOAc, 95:5). Yield 1.87 g (32%). Amorphous powder, *dr* (*S,S*)/(*R,S*) 73:27 (HPLC: hexane–2-PrOH, 80:1, $\tau_{(R,S)}$ 6.1 min, $\tau_{(S,S)}$ 8.2 min). ^{1}H NMR spectrum (DMSO-d_6, 100°C), δ, ppm (*J*, Hz): 0.37 (2.19H, d, *J* = 6.6) and 0.63 (2.19H, d, *J* = 6.7), $CH(C\underline{H}_3)_2$ (*S*,*S*)); 0.87 (0.81H, d, *J* = 6.7) and 0.93 (0.81H, d, *J* = 6.5, $CH(C\underline{H}_3)_2$ (*R*,*S*)); 0.89 (0.73H, ddd, *J* = 13.8, *J* = 9.7, *J* = 3.7) and 2.56 (0.73H, ddd, *J* = 13.8, *J* = 12.1, *J* = 3.9, $C\underline{H}_2CHMe_2$ (*S*,*S*)); 0.98 (0.81H, d, *J* = 6.5, 2-CH_3 (*R*,*S*)); 1.02 (2.19H, d, *J* = 6.6, 2-CH_3 (*S*,*S*)); 1.08-1.17 (0.81H, m, $C\underline{H}_AC\underline{H}Me_2$, 3-$CH_B$ (*R*,*S*)); 1.22-1.34 (1.73H, m, 3-CH_A (*R*,*S*), 3-CH_B, $CHMe_2$ (*S*,*S*)); 1.46-1.56 (0.27H, m, 4-CH_B (*R*,*S*)); 2.08 (0.27H, ddd, *J* = 14.1, *J* = 8.6, *J* = 5.1, $C\underline{H}_BCHMe_2$ (*R*,*S*)); 2.17-2.39 (1H, m, 4-CH_A (*R*,*S*), 3-CH_A (*S*,*S*)); 2.45 (0.73H, m) and 2.69 (0.73H, ddd, *J* = 14.9, *J* = 4.8, *J* = 4.8, 4-CH_2 (*S*,*S*)); 4.54 (0.27H, ddq, *J* = 6.9, *J* = 6.6, *J* = 6.5, H-2 (*R*,*S*)); 4.59 (0.73H, ddq, *J* = 7.7, *J* = 6.9, *J* = 6.6, H-2 (*S*,*S*)); 5.20 (0.27H, dd, *J* = 9.1, *J* = 5.1, CHCO (*R*,*S*)); 5.55 (0.73H, dd, *J* = 12.1, *J* = 3.7, CHCO (*S*,*S*)); 6.71 (0.27H, d, *J* = 7.4, H-5 (*R*,*S*)); 6.82 (0.27H, ddd, *J* = 7.4, *J* = 7.4, *J* = 1.0, H-6 (*R*,*S*)); 7.03-7.06 (0.27H, m, H-7 (*R*,*S*)); 7.20-7.22 (0.27H, m, H-8 (*R*,*S*)); 7.25 (0.73H, ddd, *J* = 7.5, *J* = 7.4, *J* = 1.2, H-6 (*S*,*S*)); 7.30-7.32 (0.73H, m, H-5 (*S*,*S*)); 7.31-7.35 (0.73H, m, H-7 (*S*,*S*)); 7.48 (0.73H, dd, *J* = 7.6, *J* = 1.2, H-8 (*S*,*S*)); 7.60-7.65 (0.54H, m) and 7.70-7.75 (0.54H, m, H NPhth (*R*,*S*)); 7.83-7.88 (2.92H, m, H NPhth (*S*,*S*)). Found, %: C 73.72; H 6.87; N 7.08. $C_{24}H_{26}N_2O_3$. Calculated, %: C 73.82; H 6.71; N 7.17.

(*S*)-2-Methyl-6-nitro-1-[*N*'-phthaloyl-(*S*)-leucyl]-1,2,3,4-tetrahydroquinoline ((*S,S*)-6). Conc. H_2SO_4 (1.28 g, 12.8 mmol) and KNO_3 (1.29 g, 12.8 mmol) were added at 0°C to a solution of amide (*S,S*)-**5c** (1.00 g, 2.56 mmol) in CH_2Cl_2 (50 ml) with stirring. The reaction mixture was heated to room temperature and stirred for 1 day (until disappearance of the starting amide, monitoring by TLC). The solution was washed with water (3×40 ml), 5% $NaHCO_3$ solution (2×30 ml), and water (2×40 ml). The organic layer was dried over $MgSO_4$ and evaporated. The residue was subjected to column flash chromatography on silica gel (eluent hexane–EtOAc, 9:1). Yield 0.86 g (77%). Pale-yellow foam. $[\alpha]_D^{20}$ +634° (*c* 1.0, $CHCl_3$), *de* > 99% (HPLC: hexane–2-PrOH, 80:1, τ 10.18 min). ^{1}H NMR spectrum (DMSO-d_6, 100°C), δ, ppm (*J*, Hz): 0.53 (3H, d, *J* = 6.6) and 0.71 (3H, d, *J* = 6.6, $CH(C\underline{H}_3)_2$); 1.09 (3H, d, *J* = 6.5, 2-CH_3); 1.12 (1H, ddd, *J* = 13.9, *J* = 9.5, *J* = 4.2) and 2.60 (1H, ddd, *J* = 13.9, *J* = 11.7, *J* = 4.0, $C\underline{H}_2CHMe_2$); 1.35-1.44 (1H, m, $CHMe_2$); 1.44-1.52 (1H, m) and 2.25-2.33 (1H, m, 3-CH_2); 2.64 (1H, ddd, *J* = 15.8, *J* = 9.4, *J* = 5.8) and 2.91 (1H, dt, *J* = 15.8, *J* = 5.9, 4-CH_2); 4.60 (1H, tq, *J* = 6.6, *J* = 6.5, H-2); 5.47 (1H, dd, *J* = 11.7, *J* = 4.2, CHCO); 7.74 (1H, d, *J* = 9.5, H-8); 7.84-7.89 (4H, m, H NPhth); 8.14-8.17 (2H, m, H-5,7). ^{13}C NMR spectrum (DMSO-d_6, 100°C), δ, ppm: 19.0; 19.8; 21.8; 24.2; 24.3; 30.2; 35.0; 49.3; 51.8; 121.3; 122.6; 122.7; 125.4; 130.8; 134.1; 135.4; 142.3; 144.4; 167.5; 168.7. Found, %: C 66.19; H 5.93; N 9.28. $C_{24}H_{25}N_3O_5$. Calculated, %: C 66.19; H 5.79; N 9.65.

(*R*)-2-Methyl-6-nitro-1-[*N*'-phthaloyl-(*S*)-leucyl]-1,2,3,4-tetrahydroquinoline ((*R,S*)-6). Conc. H_2SO_4 (1.35 g, 13.45 mmol) and KNO_3 (1.36 g, 13.45 mmol) were added at 0°C to a solution of amide **5c** ((*S,S*)/(*R,S*) 59:41) (1.05 g, 2.69 mmol) in CH_2Cl_2 (50 ml) under stirring. The reaction mixture was heated to room temperature and stirred for 8 h. The solution was washed with water (3×40 ml), 5% $NaHCO_3$ solution

(2×30 ml), and water (2×40 ml). The organic layer was dried over $MgSO_4$ and evaporated. The residue was subjected to column flash chromatography on silica gel (eluent hexane–EtOAc, 9:1), and amide (*R*,*S*)-**6** (0.199 g) was obtained as the fast eluting isomer (yield 41% calculated on (*R*,*S*)-**5c**). Yellow foam. $[\alpha]_D^{20}$ -402° (c 1.0, $CHCl_3$), *de* 98% (HPLC: hexane–2-PrOH, 80:1, τ 7.00 min). ^{1}H NMR spectrum (DMSO-d_6, 100°C), δ, ppm (*J*, Hz): 0.87 (3H, d, *J* = 6.6) and 0.94 (3H, d, *J* = 6.6, CH(C$\underline{H}_3$)$_2$); 1.00 (3H, d, *J* = 6.5, 2-CH_3); 1.31 (1H, dddd, *J* = 13.0, *J* = 8.9, *J* = 6.7, *J* = 5.7) and 2.27 (1H, dddd, *J* = 13.0, *J* = 6.7, *J* = 5.9, *J* = 5.9, 3-CH_2); 1.44-1.53 (1H, m, $CHMe_2$); 1.87 (1H, ddd, *J* = 14.3, *J* = 9.3, *J* = 4.8) and 2.08 (1H, ddd, *J* = 14.3, *J* = 8.8, *J* = 4.9, C$\underline{H}_2$CHMe$_2$); 2.35 (1H, ddd, *J* = 15.5, *J* = 8.9, *J* = 5.9) and 2.59 (1H, ddd, *J* = 15.5, *J* = 5.9, *J* = 5.7, 4-CH_2); 4.50 (1H, tq, *J* = 6.7, *J* = 6.5, H-2); 5.28 (1H, dd, *J* = 9.3, *J* = 4.9, CHCO); 7.58 (1H, d, *J* = 8.8, H-8); 7.60 (1H, d, *J* = 2.7, H-5); 7.64-7.67 (2H, m) and 7.72–7.76 (2H, m, H NPhth); 7.88 (1H, dd, *J* = 8.8, *J* = 2.7, H-7). ^{13}C NMR spectrum (DMSO-d_6, 100°C,), δ, ppm: 18.9; 21.2; 22.4; 23.7; 23.8; 29.9; 38.2; 49.4; 49.6; 121.6; 121.7; 122.2; 125.0; 130.1; 134.1; 134.2; 142.4; 143.6; 165.9; 168.0. Found, *m/z*: 436.1871 $[M+H]^+$. $C_{24}H_{26}N_3O_5$. Calculated, *m/z*: 436.1872.

(*R*)-2-Methyl-6-nitro-1-[*N*'-*p*-toluenesulfonyl-(*S*)-prolyl]-1,2,3,4-tetrahydroquinoline ((*R*,*S*)-8). Conc. H_2SO_4 (1.160 g, 11.6 mmol) and KNO_3 (1.17 g, 11.6 mmol) were added under stirring at 0°C to a solution of amide (*R*,*S*)-**7** (0.660 g, 1.66 mmol) in CH_2Cl_2 (40 ml). The reaction mixture was heated to room temperature and stirred for 1 day. The solution was washed with water (3×30 ml), 5% $NaHCO_3$ solution (2×25 ml), and water (2×30 ml). The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by column flash chromatography on silica gel (eluent hexane–EtOAc, 4:1). Yield 0.272 g (37%). Colorless powder, mp 180-181°C. $[\alpha]_D^{20}$ -527° (*c* 1.0, $CHCl_3$), *de* 98% (HPLC: hexane–2-PrOH, 20:1, τ 13.80 min). ^{1}H NMR spectrum (DMSO-d_6, 100°C), δ, ppm (*J*, Hz): 1.11 (3H, d, *J* = 6.6, 2-CH_3); 1.49 (1H, dddd, *J* = 13.9, *J* = 8.6, *J* = 6.4, *J* = 5.8) and 2.36 (1H, m, 3-CH_2); 1.58-1.66 (1H, m) and 1.98-2.15 (3H, m, 3,4-$(CH_2)_2$ proline); 2.34 (3H, s, $C_6H_4C\underline{H}_3$); 2.75 (1H, ddd, *J* = 15.7, *J* = 8.6, *J* = 5.8) and 2.88 (1H, ddd, *J* = 15.7, *J* = 6.1, *J* = 5.8, 4-CH_2); 3.30 (1H, ddd, *J* = 9.8, *J* = 7.3, *J* = 6.2) and 3.42 (1H, ddd, *J* = 9.8, *J* = 6.7, *J* = 6.5, 5-CH_2 proline); 4.34 (1H, dd, *J* = 8.1, *J* = 4.7, CHCO); 4.69 (1H, dqd, *J* = 6.6, *J* = 6.5, *J* = 6.4, H-2); 7.22 (2H, d, *J* = 8.4, H-3,5 Ts); 7.29 (2H, d, *J* = 8.4, H-2,6 Ts); 7.35 (1H, d, *J* = 8.8, H-8); 8.02 (1H, dd, *J* = 8.8, *J* = 2.7, H-7); 8.15 (1H, d, *J* = 2.7, H-5). ^{13}C NMR spectrum (DMSO-d_6, 100°C), δ, ppm: 18.9 (2-CH_3); 20.2 ($C_6H_4\underline{C}H_3$); 23.9 and 24.0 (C-4, C-4 proline); 29.7 (C-3); 30.6 (C-3 proline); 48.2 (C-2); 48.6 (C-5 proline); 57.4 (C-2 proline); 120.8 (C-7); 122.4 (C-5); 125.5 (C-8); 126.2 (*o*-C Ts); 128.9 (*m*-C Ts); 134.5 (*i*-C Ts); 135.2 (C-4a); 142.4 (C-8a); 142.7 (*p*-C Ts); 144.0 (C-6); 170.5 (CO). Found, %: C 59.28; H 5.66; N 9.52; S 7.44. $C_{22}H_{25}N_3O_5S$. Calculated, %: C 59.58; H 5.68; N 9.47; S 7.23.

(*S*)-2-Methyl-6-nitro-1,2,3,4-tetrahydroquinoline ((*S*)-1). Conc. H_2SO_4 (2 ml) was added to a solution of amide (*S*,*S*)-**6** (670 mg, 1.54 mmol) in 1,4-dioxane (15 ml). The obtained solution was heated for 13 h at 95-100°C. The reaction mixture was cooled to room temperature and poured into water (150 ml). Na_2CO_3 was added to the obtained suspension to pH 8.0-8.5, and the amine was extracted with $CHCl_3$. The organic layer was washed with water, dried over $MgSO_4$ and evaporated in vacuum. The residue was recrystallized from a 1:1 mixture of hexane and $CHCl_3$. Yield 216 mg (73%). Orange powder, mp 140-142°C (mp for (*R*,*S*)-**1** 135-137°C [5]). $[\alpha]_D^{15}$ -189° (*c* 0.59, $CHCl_3$), *ee* 96% (HPLC: hexane–2-PrOH–MeOH, 95:4:1, τ 20.0 min) ($[\alpha]_D^{20}$ -14.7° (*c* 0.50, $CHCl_3$) for (*S*)-**1**, *ee* 75% [6]). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.28 (3H, d, *J* = 6.4, 2-CH_3); 1.57 (1H, dtd, *J* = 13.1, *J* = 9.6, *J* = 6.3) and 2.00 (1H, dtd, *J* = 13.1, *J* = 4.4, *J* = 3.7, 3-CH_2); 2.77–2.83 (2H, m, 4-CH_2); 3.55 (1H, dqdd, *J* = 6.5, *J* = 6.4, *J* = 3.7, *J* = 3.2, H-2); 4.55 (1H, br. s, NH); 6.36 (1H, m, H-8); 7.87–7.90 (2H, m, H-5,7). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 22.2; 26.2; 28.8; 47.4; 112.1; 119.7; 124.2; 125.7; 137.4; 150.2. Found, %: C 62.17; H 6.59; N 14.25. $C_{10}H_{12}N_2O_2$. Calculated, %: C 62.49; H 6.29; N 14.57.

(*R*)-2-Methyl-6-nitro-1,2,3,4-tetrahydroquinoline ((*R*)-1) was obtained analogously to compound (*S*)-**1**, starting from amide (*R*,*S*)-**6** (121 mg, 0.28 mmol). Yield 40 mg (75%). Orange powder, mp 139-140°C (hexane–$CHCl_3$, 1:1). $[\alpha]_D^{20}$ +188° (*c* 0.55, $CHCl_3$), *ee* 98% (HPLC: hexane–2-PrOH–MeOH, 95:4:1, τ 18.22 min). The NMR spectra were analogous to the spectra of compound (*S*)-**1**. Found, %: C 62.63; H 6.37; N 14.40. $C_{10}H_{12}N_2O_2$. Calculated, %: C 62.49; H 6.29; N 14.57.

(*S*)-2-Methyl-6-nitro-1-trifluoracetyl-1,2,3,4-tetrahydroquinoline ((*S*)-9). Trifluoroacetic anhydride (315 mg, 1.5 mmol) was added to a solution of amine (*S*)-**1** (192 mg, 1 mmol) in CH_2Cl_2 (2.5 ml). The solution obtained was heated at 40°C for 30 min. The solution was then cooled to room temperature, washed with 5% $NaHCO_3$ solution (3×3 ml) and water (3×3 ml), dried over $MgSO_4$ and evaporated in vacuum. The residue was recrystallized from hexane. Yield 225 mg (78%). Pale-yellow needle-shaped crystals, mp 93-94°C (hexane). $[\alpha]_D^{20}$ +256° (*c* 0.62, $CHCl_3$). ^{1}H NMR spectrum (DMSO-d_6, 100°C), δ, ppm (*J*, Hz): 1.14 (3H, d, *J* = 6.5, 2-CH_3); 1.64 (1H, dddd, *J* = 13.6, *J* = 6.9, *J* = 6.8, *J* = 6.2) and 2.35 (1H, dddd, *J* = 13.6, *J* = 6.9, *J* = 6.8, *J* = 6.5, 3-CH_2); 2.80 (1H, dt, *J* = 16.4, *J* = 6.8) and 2.95 (1H, dt, *J* = 16.4, *J* = 6.9, 4-CH_2); 4.65 (1H, dqd, *J* = 6.5, *J* = 6.5, *J* = 6.2, H-2); 7.69 (1H, d, *J* = 8.9, H-8); 8.08 (1H, dd, *J* = 8.9, *J* = 2.7, H-7); 8.14 (1H, d, *J* = 2.7, H-5). ^{19}F NMR spectrum (DMSO-d_6, 100°C), δ, ppm: 95.9 (s, CF_3). ^{13}C NMR spectrum (DMSO-d_6, 100°C), δ, ppm (*J*, Hz): 18.0; 23.1; 28.7; 50.1; 115.7 (q, $^1J_{C–F}$ = 289, CF_3); 120.8; 122.8; 125.8; 134.6; 139.6; 145.0; 154.8 (q, $^2J_{C–F}$ = 36.2, CO). Found, %: C 49.98; H 3.95; F 19.56; N 9.63. $C_{12}H_{11}F_3N_2O_3$. Calculated, %: C 50.01; H 3.85; F 19.77; N 9.72.

(*R*)-2-Methyl-6-nitro-1-trifluoroacetyl-1,2,3,4-tetrahydroquinoline ((*R*)-9) was obtained analogously to compound (*S*)-**9**, starting from amine (*R*)-**1** (30.8 mg, 0.16 mmol). Yield 36.8 mg (80%). $[\alpha]_D^{20}$ -245° (*c* 0.54, $CHCl_3$). The NMR spectra were analogous to the spectra of compound (*S*)-**9**. Found, %: C 50.05; H 3.86; F 19.79; N 9.64. $C_{12}H_{11}F_3N_2O_3$. Calculated, %: C % 50.01; H 3.85; F 19.77; N 9.72.

(*S*)-6-Amino-2-methyl-1-trifluoroacetyl-1,2,3,4-tetrahydroquinoline ((*S*)-10). 10% Pd/C (16 mg) was added to a solution of amine (*S*)-**9** (161 mg, 0.56 mmol) in EtOH (10 ml). The suspension was stirred in an atmosphere of H_2 (3 bar) for 3 h. The solution was filtered, and the filtrate was evaporated. The residue was purified by column flash chromatography on silica gel (eluent: benzene). Yield 127 mg (88%). Colorless crystals, mp 65-66°C (hexane). $[\alpha]_D^{20}$ +266° (*c* 0.78, $CHCl_3$). HPLC: hexane–2-PrOH, 5:1, τ 18.90 min. ^{1}H NMR spectrum (DMSO-d_6, 100°C), δ, ppm (*J*, Hz): 1.05 (3H, d, *J* = 6.5, 2-CH_3); 1.22–1.43 (1H, br. m) and 2.29 (1H, ddt, *J* = 12.8, *J* = 6.6, *J* = 5.9, 3-CH_2); 2.37–2.46 (1H, m) and 2.52 (1H, dt, *J* = 15.1, *J* = 5.6, 4-CH_2); 4.57 (1H, ddq, *J* = 6.8, *J* = 6.6, *J* = 6.5, H-2); 4.87 (2H, br. s, NH_2); 6.44 (1H, dd, *J* = 8.4, *J* = 2.5, H-7); 6.46 (1H, d, *J* = 2.5, H-5); 6.93 (1H, br. d, *J* ≈ 8, H-8). ^{19}F NMR spectrum (DMSO-d_6, 100°C), δ, ppm: 96.4 (br. s, CF_3). ^{13}C NMR spectrum (DMSO-d_6, 100°C), δ, ppm (*J*, Hz): 18.6; 24.3; 30.4; 49.7; 111.2; 112.0; 116.2 (q, $^1J_{C–F}$ = 289.5, CF_3); 122.4; 125.2; 134.9 (br. s); 147.2; 154.1 (q, $^2J_{C–F}$ = 33.1, CO). Found, %: C 55.93; H 5.04; N 10.76. $C_{12}H_{13}F_3N_2O$. Calculated, %: C 55.81; H 5.07; N 10.85.

X-Ray Structural Investigation of Compounds (*S*,*S*)-5c and (*R*,*S*)-8 was carried out on an Xcalibur-3 X-ray diffractometer with a CCD detector according to the standard procedure (λMoKα, graphite monochromator, ω scanning). Fragments of colorless crystals of size 0.25×0.09×0.01 mm (compound (*S*,*S*-**5**)) and 0.22×0.15×0.09 mm (compound (*R*,*S*)-**8**) were used for analysis. Collection and processing of data were carried using the CrysAlis set of programs [33]. The structures of compounds were solved by a direct method with the SHELXS-97 program and were refined with the aid of the SHELXL-97 program [34] in an anisotropic (isotropic for hydrogen atoms) approximation. The positions of hydrogen atoms were solved partially and were refined independently, and partially including refinement according to the "rider" model with dependent thermal parameters. The X-ray structural analysis data are registered in the Cambridge Crystallographic Data Center (deposition CCDC 866868 and 866869).

Compound (*S*,*S*)-**5c** ($C_{24}H_{26}N_2O_3$, *M* 390.47). Orthorhombic, *a* 7.7347(6), *b* 12.9364 (10), *c* 22.1742(15) Å; β 90.00°, *V* 2218.7(3) Å^3; space group $P2_12_12_1$; *Z* 4; d_{calc} 1.169 g/cm^3; μ 0.077 mm^{-1}; *F*(000) 832. 2.79 < Θ < 26.39. Completeness for Θ 26.39° 95.6%. 9309 reflections were collected with $I > 2\sigma(I)$ (2492 independent, R_{int} 0.0516). *S* on F^2 was 0.987. Final probability factors R_1 ($I > 2\sigma(I)$) 0.0357, wR_2 ($I > 2\sigma(I)$) 0.0301. R_1 0.1353 (all data), wR_2 0.0336 (all data).

Compound (*R*,*S*)-**8** ($C_{22}H_{25}N_3O_5S$, *M* 443.52). Orthorhombic, *a* 8.5524(16), *b* 25.401(4), *c* 10.1677(18) Å; β 90.00°; *V* 2208.9(6) Å^3; space group $P2_12_12_1$; *Z* 4; d_{calc} 1.334 g/cm^3; μ 0.185 mm^{-1}; *F*(000) 936. 2.87 < Θ < 25.76. Completeness for Θ 25.76° 99.0%. 13896 reflections were collected with $I > 2\sigma(I)$ (4135 independent, R_{int} 0.0866). *S* on F^2 was 0.823. Final probability factors R_1 ($I > 2\sigma(I)$ 0.0425, wR_2 (I > 2σ(*I*)) 0.0311. R_1 0.1849 (all data), wR_2 0.0381 (all data).

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