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KINETIC RESOLUTION OF RACEMIC 2-METHYL-1,2,3,4-TETRAHYDROQUINOLINE AND ITS STRUCTURAL ANALOGS BY USING 2-ARYLPROPIONYL CHLORIDES

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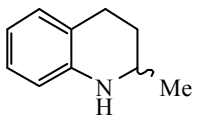
Acylation of 2-methyl-1,2,3,4-tetrahydroquinoline and 2-methylindoline with the acyl chlorides of naproxen, ibuprofen, and 2-phenylpropionic acid has been found to lead to efficient kinetic resolution with predominant formation of the (S,S)-(R,R)-diastereoisomers. The highest acylation stereoselectivity was found in toluene at -20°C. No significant kinetic resolution of N-(sec-butyl)aniline and 2-methylpiperidine was achieved by using 2-arylpropionyl chlorides.

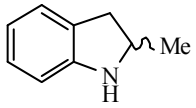
Keywords: 2-arylpropionic acids, 2-methylindoline, 2-methyl-1,2,3,4-tetrahydroquinoline, acyl chlorides, acylation, kinetic resolution.

Kinetic resolution (KR) [1], based on the difference in conversion rates of racemate enantiomers in reactions with asymmetric reagents or catalysts, has been used successfully to prepare optically pure biologically active compounds and synthetic intermediates [2-4]. Pure enantiomers of chiral amines are frequently isolated by KR as a result of an acylation reaction in the presence of either acylation enzymes [5,6] or synthetic catalysts of chiral acyl transfer [7-9]. In recent years, KR methods have also been intensively developed for the resolution of racemic amines through the action of chiral acylating agents [10-14].

We have proposed the use of chiral acyl chlorides, namely, 2-arylpropionyl chlorides and *N*-protected amino acyl chlorides, as resolving acylating agents for the KS of heterocyclic aromatic amines [15-22]. Of special interest among 2-arylpropionic acids is (*S*)-naproxen ((*S*)-2-(6-methoxynaphth-2-yl)propionic acid), since this acid is a nonsteroidal anti-inflammatory drug commonly used in clinical practice and available commercially as a pure enantiomer. Naproxen has a characteristic UV absorption maximum at 230 nm with a high molar extinction coefficient. This makes naproxen and its derivatives very convenient chiral derivatizing



1a



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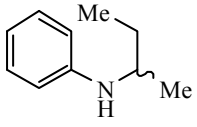

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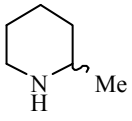

1d

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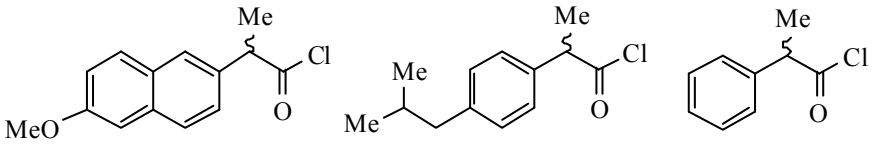
agents for determining the stereoisomeric purity of various optically active compounds by HPLC [23] and other methods [24]. The (*S*)-naproxen acyl chloride ((*S*)-**2a**) was first used in our laboratory for the preparative resolution of racemic amines, including 2-methyl-1,2,3,4-tetrahydroquinoline (**1a**) and 2-methylindoline (**1b**) [15, 16].

A serious problem hindering the common use of KR for obtaining optically pure compounds remains the impossibility of predicting the stereochemical result of the reaction from the structures of the amine and the resolving agent. Thus, it is quite important to obtain information on the results of KR using the broadest possible range of resolving agents and substrates. A possible approach to finding efficient resolving agents involves carrying out the reaction between a racemic amine and a racemic acylating agent. Such a reaction gives two racemic amides, namely, (*S,S*)(*R,R*) and (*R,S*)(*S,R*), whose ratio (*dr*) is equal to the selectivity factor $s = k_{fast}/k_{slow}$ [1, 25, 26]. In this case, the ratio of the concentrations of the diastereoisomeric products is independent of both the starting reagent ratio and the reaction time. We previously used this approach for evaluating the selectivity of acylating 3-methyl-2,3-dihydro-4*H*-[1,4]benzoxazines with 2-arylpropionyl chlorides [22].

In the present work, we studied kinetic resolution diastereoselectivity in the acylation of racemic amines **1a-d** with 2-arylpropionyl chlorides, derived from: naproxen **2a**, ibuprofen (2-(4-isobutyl-phenyl)propionic acid) **2b** and 2-phenylpropionic acid **2c**.

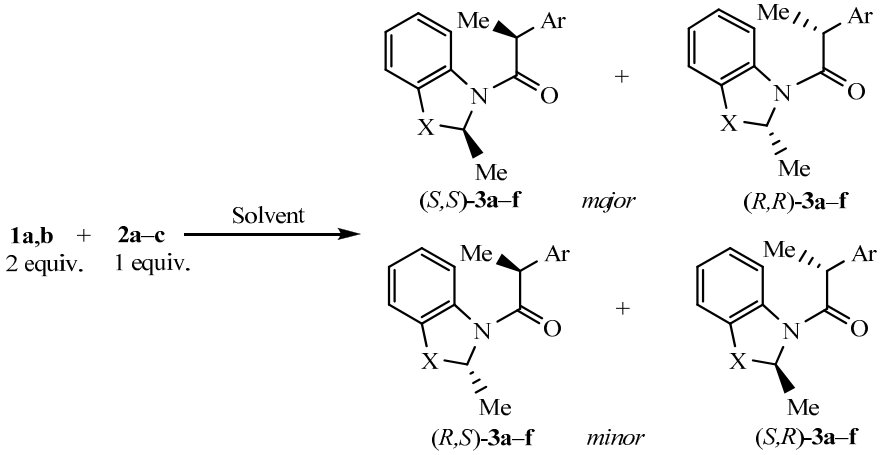


2a **2b** **2c**

Acyl chlorides **2a-c** were obtained by treating the corresponding 2-arylpropionic acids with oxalyl chloride in benzene at room temperature. The products were obtained in 95-97% yield and optical purity >98%, as indicated by ^{1}H NMR spectroscopy. The freshly prepared acyl chlorides were used in acylation reactions without further purification.

Acylation of racemic heterocyclic amines **1a,b** with the racemic acyl chlorides **2a-c** was carried out at a 2:1 reagent ratio in toluene, dichloromethane and acetonitrile at 20 and -20°C over 6 h. The initial concentration of the racemic amine was 0.1 mol/l.

The resulting mixture of diastereoisomeric amides was analyzed by HPLC and ^{1}H NMR spectroscopy. The (*S,S*)-amides **3c-f** were obtained by counter synthesis, starting from (*S*)-amines **1a,b** and (*S*)-acyl chlorides **2b,c**, in order to assign the configuration of the products. These (*S,S*)-amides correspond in their HPLC retention time and NMR spectra to the (*S,S*)- or (*R,R*)-diastereoisomers.



3 a,c,e X = $(CH_2)_2$, **b,d,f** X = CH_2; **3 a,b** Ar = 6-MeO-naphthalen-2-yl, **c,d** Ar = 4-(*i*-Bu)C_6H_4, **e,f** Ar = Ph

TABLE 1. Ratio of (*S,S*)(*R,R*)- and (*R,S*)(*S,R*)-Diastereoisomers **3a-f** in the Acylation Products

Amine	Acylation agent	Solvent	Product	*dr**	
				20°C	-20°C
1a	**2a**	PhMe	**3a**	97:3	98:2
		CH_2Cl_2		92:8	94:6
		MeCN		86:14	85:15
	2b	PhMe	**3c**	97:3	98:2
		CH_2Cl_2		92:8	94:6
		MeCN		87:13	89:11
	2c	PhMe	**3e**	96:4	98:2
		CH_2Cl_2		89:11	90:10
		MeCN		82:18	83:17
1b	**2a**	PhMe	**3b**	94:6	95:5
		CH_2Cl_2		92:8	93:7
		MeCN		76:24	80:20
	2b	PhMe	**3d**	95:5	96:4
		CH_2Cl_2		92:8	92:8
		MeCN		81:19	84:16
	2c	$PhCH_3$	**3f**	94:6	95:5
		CH_2Cl_2		89:10	91:9
		MeCN		80:20	80:20

*dr = (*S,S*),(*R,R*) / (*R,S*),(*S,R*) from HPLC data.

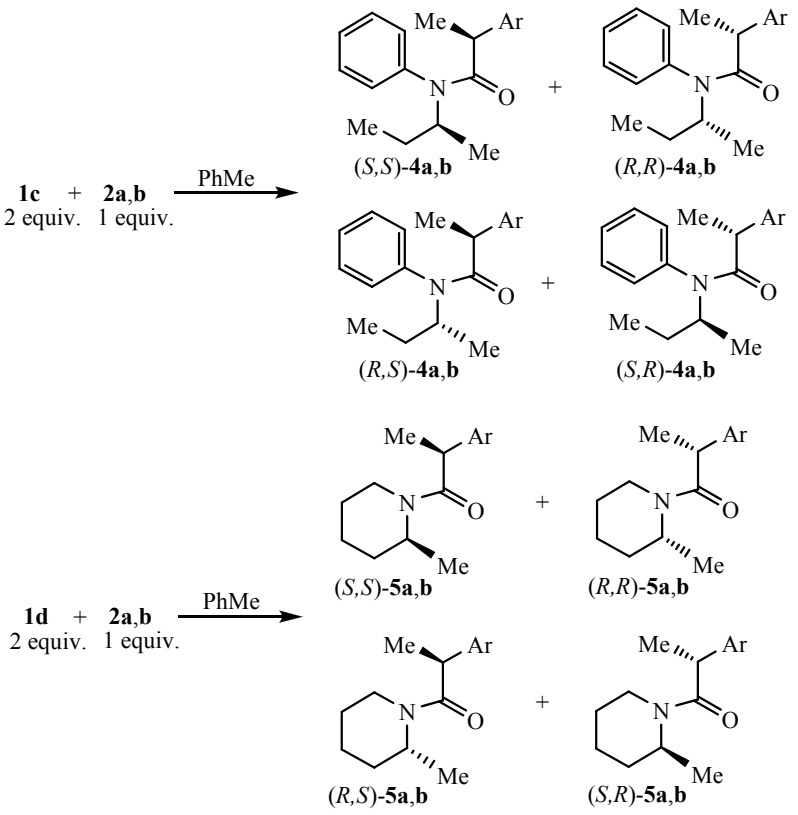
As in the acylation of racemic amines **1a,b** with the acyl chloride (*S*)-**2a** [21], the resulting amides **3c-f**, obtained by using the racemic acyl chlorides **2b,c**, were enriched in the (*S,S*),(*R,R*)-diastereoisomers, but contained a small amount (~10%) of (*R,S*),(*S,R*)-diastereoisomers. For an unequivocal assignment of the NMR signals and HPLC retention times, we synthesized mixtures of (*S,S*)- and (*S,R*)-amides **3c-f** containing up to 50% of the (*S,R*)-diastereoisomer, starting from (*S*)-amines **1a,b** and racemic acyl chlorides **2b,c** taken in a 2:1 ratio.

The diastereoisomeric ratio of the resulting amides **3a-f** was determined by HPLC, using the area ratio of the (*S,S*),(*R,R*)- and (*R,S*),(*S,R*)-amide peaks. Table 1 gives the mean values from two to four parallel determinations.

The highest acylation selectivity for all the investigated acyl chlorides was observed in toluene. Lower selectivity was found in the more polar solvents (Table 1). All the investigated acyl chlorides **2a-c** displayed high stereoselectivity in the acylation of heterocyclic amines **1a,b**. However, the selectivity in the acylation of amine **1b** was somewhat lower than in the acylation of amine **1a**. For example, the diastereoisomeric ratio of the amides formed in the acylation of amines **1a,b** with the acyl chloride **2a** in toluene at 20°C was 97:3 and 94:6, respectively. We should note that, in contrast to KR with *N*-protected amino acyl chlorides [20, 21], the reaction temperature in all cases had only a slight effect on the stereochemical result of the reaction.

Acylation of racemic *N*-(*sec*-butyl)aniline (**1c**) and 2-methylpiperidine (**1d**), which may be considered structural analogs of 2-methyl-1,2,3,4-tetrahydroquinoline (**1a**), using the acyl chlorides of naproxen (**2a**) and ibuprofen (**2b**), was carried out with a 2:1 reagent ratio in toluene at 20 and -20°C over 6 h; the initial concentration of the racemic amine was 0.1 mol/l. The resulting mixture of diastereoisomeric amides **4a,b** and **5a,b** was analyzed by HPLC and ^{1}H NMR spectroscopy (Table 2).

The stereoselectivity in the acylation of amines **1c,d** was considerably lower (the maximum *dr* was 66:34 in the amine **1d** acylation with acyl chloride **2b**) than for amines **1a,b**. Thus, we did not carry out assignment of the configuration of resulting amides **4a,b** and **5a,b**.



4, **5 a** Ar = 6-MeO-naphthalen-2-yl; **b** Ar = 4-(*i*-Bu)C_6H_4

The achievement of efficient KS apparently requires the amine to contain a heterocyclic fragment, whose conformational mobility is additionally limited by the condensed aromatic system.

Thus, we have shown that all the investigated 2-arylpropionic acid derivatives are capable of providing efficient kinetic resolution of racemic cyclic amines. At the same time, kinetic resolution of their acyclic structural analogs using 2-arylpropionyl chlorides proved impossible.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker DRX-400 spectrometer (400 MHz) in $CDCl_3$ at room temperature (acyl chlorides **2a-c**) and in DMSO-d_6 at 100°C (amides **3-5**) with TMS as internal standard. The

TABLE 2. Ratio of (*S,S*)(*R,R*)- and (*R,S*)(*S,R*)-Diastereoisomers **4a,b** and **5a,b** in the Acylation Products

Amine	Acylation agent	Product	*dr*	
			20 °C	-20 °C
1c	**2a**	**4a**	58:42*	60:40*
	2b	**4b**	60:40*	62:38*
1d	**2a**	**5a**	60:40*	62:38*
	2b	**5b**	65:35*[2]	66:34*[2]

*From HPLC data.

*[2]From ^{1}H NMR spectral data.

hydrogen atoms at the common carbon atom are designated as A and B. The high-resolution mass spectra were recorded on a Bruker Daltonics MicroOTOF-Q II mass spectrometer using electrospray ionization and direct sample inlet with flow rate 180 μl/h and positive ion mode in the mass range 50-800 Da at 250°C capillary temperature. The elemental analysis was carried out on a Perkin Elmer PE 2400 II analyzer. The HPLC analysis of the diastereoisomeric composition of amides **3d**, **4a,b**, and **5a,b** was carried out on a Knauer Smartline-1000 chromatograph using a 4.6×250-mm column packed with ReproSil 100 Si (5 μm). The elution rate was 1 ml/min with detection at 220 nm. The mobile phase was 80:1 hexane–2-propanol for amide **4a**, 160:1 hexane–2-propanol for amide **5a**, 250:1 hexane–2-propanol for amide **3d**, and 200:1 hexane–2-propanol for amide **4b**. The HPLC analysis of the diastereoisomeric content of amides **3c,e,f** was carried out on an Agilent-1100 chromatograph using a 4.6×250-mm Phenomenex Luna C18 column (5 μm). The elution rate was 0.8 ml/min with detection at 220 nm. The mobile phase was 90:10 acetonitrile–water for products **3c,e** and 65:35 acetonitrile–water for amide **3f**. Flash column chromatography was carried out on silica gel 60 (230-400 mesh) with benzene as the eluent. The melting points were determined on a Barloworld Scientific SMP3 instrument. The specific rotation was determined on a Perkin Elmer 341 polarimeter and given in (deg.·ml)/(g·dm); the solution concentration is given in g/100 ml.

(*RS*)-2-Methyl-1,2,3,4-tetrahydroquinoline (**1a**) [27], *N*-(*sec*-butyl)aniline (**1c**) [28], and (*RS*)-naproxen [29] were obtained by reported methods. (*S*)-2-Methyl-1,2,3,4-tetrahydroquinoline and (*S*)-2-methylindoline (**1b**) were obtained as described in our previous work [16]. Commercial samples of (*RS*)-2-methylindoline, (*RS*)-2-methylpiperidine (**1d**), (*S*)-naproxen, ibuprofen, (*S*)-ibuprofen, (*RS*)-2-phenylpropionic acid and (*S*)-2-phenylpropionic acid were used. All the solvents were purified by standard procedures immediately before use.

2-Arylpropionyl Chlorides 2a-c (General Method). Oxalyl chloride (175 μl, 2.0 mmol) was added to a stirred suspension of acid (1.0 mmol) in benzene (5 ml). The reaction mixture was stirred for 6 h at room temperature, evaporated in vacuum and dried over P_2O_5. Acyl chlorides **2a-c** were characterized in our previous work [22].

Kinetic Resolution (General Method). A solution of acyl chloride **2a-c** (0.15 mmol) in a solvent (toluene, methylene dichloride, or acetonitrile) (1.5 ml) was added in a single portion to a solution of amine **1a-d** (0.3 mmol) in the indicated solvent (1.5 ml). The reaction mixture was kept at constant temperature for 5 h and washed with 1 N hydrochloric acid (2×3 ml). (In the case of the reaction in acetonitrile, 1 N hydrochloric acid (5 ml) was added, and the amide was extracted with benzene). The organic layer was washed with saturated aqueous NaCl solution (4×3 ml), 5% aqueous sodium bicarbonate solution (2×3 ml), and water (2×3 ml), dried over magnesium sulfate, and evaporated to dryness in vacuum. The diastereoisomeric composition of amides **3c-f, 4a,b** and **5a,b** was determined by HPLC or ^{1}H NMR spectroscopy.

The mixtures of amides and pure (*S,S*)-diastereoisomers **3a,b** were described in our previous work [16].

Preparation of the (*S,S*)-Amides 3c-f. A solution of (*S*)-acyl chloride **2b** or **2c** (1 mmol) in toluene (10 ml) was added to a solution of (*S*)-amine **1a,b** (2 mmol) in toluene (10 ml). The reaction mixture was kept at constant 20°C temperature for 6 h, washed with 1 N hydrochloric acid (2×3 ml), saturated aqueous NaCl solution (4×3 ml), 5% aqueous sodium bicarbonate solution (2×3 ml) and water (2×3 ml), dried over magnesium sulfate and evaporated to dryness in vacuum. The (*S,S*)-amides **3c-e** were separated by flash chromatography. The (*S,S*)-amide **3f** was separated by recrystallization from ethanol–water.

***N*-[(2*S*)-2-(4-Isobutylphenyl)propionyl]-(2*S*)-2-methyl-1,2,3,4-tetrahydroquinoline ((*S,S*)-3c)**. Yield 0.242 g (72%). Colorless oil. $[\alpha]_D^{20}$ +129.7° (*c* 1.02, $CHCl_3$). *dr* ≥ 99.9% (HPLC: τ 12.2 min). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.81 (6H, d, *J* = 6.6, $CH_2CH(C\underline{H}_3)_2$); 0.91 (3H, d, *J* = 6.5, 2-CH_3); 1.16 (1H, dddd, *J* = 13.0, *J* = 10.1, *J* = 6.7, *J* = 5.3, H-3A); 1.36 (3H, d, *J* = 6.9, 2'-CH_3); 1.69-1.81 (1H, m, $CH_2C\underline{H}Me_2$); 1.86 (1H, ddd, *J* = 15.0, *J* = 10.1, *J* = 5.3, H-4A); 2.13 (1H, dddd, *J* = 13.0, *J* = 7.5, *J* = 5.3, *J* = 5.3, H-3B); 2.33 (1H, ddd, *J* = 15.0, *J* = 5.3, *J* = 5.3, H-4B); 2.34 (2H, d, *J* = 7.0, $C\underline{H}_2CHMe_2$); 4.24 (1H, q, *J* = 6.9, H-2'); 4.63 (1H, ddq, *J* = 7.5, *J* = 6.7, *J* = 6.5, H-2); 6.66-6.73 (2H, m, H Ar); 6.83-6.90 (2H, m, H Ar); 6.97-7.02 (1H, m, H-5); 7.10 (1H, ddd, *J* = 7.4, *J* = 7.4, *J* = 1.1, H-6); 7.18-7.26 (1H, m, H-7); 7.28-7.32 (1H, m, H-8). Found, *m*/*z*: 336.2322 $[M+H]^+$. $C_{23}H_{30}NO$. Calculated, *m*/*z*: 336.2327.

***N*-[(2*S*)-2-(4-Isobutylphenyl)propionyl]-(2*S*)-2-methylindoline ((*S*,*S*)-3d)**. Yield 0.257 g (80%). Colorless oil. $[\alpha]_D^{20}$ +63.7° (*c* 1.07, $CHCl_3$). *dr* ≥ 99.9% (HPLC: τ 4.9 min). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.85 (6H, d, *J* = 6.6, $CH_2CH(C\underline{H}_3)_2$); 0.92 (3H, d, *J* = 6.3, 2-CH_3); 1.43 (3H, d, *J* = 6.8, 2'-CH_3); 1.78-1.88 (1H, m, $CH_2C\underline{H}Me_2$); 2.43 (2H, d, *J* = 7.0, $C\underline{H}_2CHMe_2$); 2.55-2.60 (1H, m, H-3A); 3.36 (1H, dd, *J* = 15.7, *J* = 8.6, H-3B); 4.18 (1H, q, *J* = 6.8, H-2'); 4.75-4.84 (1H, m, H-2); 6.95-7.00 (1H, m, H-5); 7.06-7.11 (2H, m, H Ar); 7.11-7.16 (1H, m, H-6); 7.21 (1H, dd, *J* = 13.7, *J* = 7.7, H-4); 7.27-7.31 (2H, m, H Ar); 7.93-7.97 (1H, m, H-7). Found, %: C 81.95; H 8.57; N 4.08. $C_{22}H_{27}NO$. Calculated, %: C 82.20; H 8.47; N 4.36.

***N*-[(2*S*)-2-Phenylpropionyl]-(2*S*)-2-methyl-1,2,3,4-tetrahydroquinoline ((*S*,*S*)-3e)**. Yield 0.218 g (75%). Colorless oil. $[\alpha]_D^{20}$ +190.2° (*c* 1.0, $CHCl_3$). *dr* ≥ 99.9% (HPLC: τ 6.2 min). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.92 (3H, d, *J* = 6.5, 2-CH_3); 1.16 (1H, dddd, *J* = 13.1, *J* = 10.0, *J* = 6.7, *J* = 5.1, H-3A); 1.39 (3H, d, *J* = 6.9, 2'-CH_3); 1.88 (1H, ddd, *J* = 15.0, *J* = 10.0, *J* = 5.6, H-4A); 2.14 (1H, dddd, *J* = 13.1, *J* = 7.0, *J* = 5.6, *J* = 5.4, H-3B); 2.37 (1H, ddd, *J* = 15.0, *J* = 5.4, *J* = 5.1, H-4B); 4.29 (1H, q, *J* = 6.9, H-2'); 4.63 (1H, ddq, *J* = 7.0, *J* = 6.7, *J* = 6.5, H-2); 6.79-6.84 (2H, m, H Ph); 7.02-7.06 (1H, m, H-5); 7.06-7.10 (3H, m, H Ph); 7.09-7.14 (1H, m, H-6); 7.20-7.25 (1H, m, H-7); 7.29-7.33 (1H, m, H-8). Found, *m*/*z*: 280.1696 $[M+H]^+$. $C_{19}H_{22}NO$. Calculated, *m*/*z*: 280.1701.

***N*-[(2*S*)-2-Phenylpropionyl]-(2*S*)-2-methylindoline ((*S*,*S*)-3f)**. Yield 0.207 g (78%). Colorless crystals, mp 115ºC (EtOH–H_2O). $[\alpha]_D^{20}$ +95.0° (*c* 1.0, $CHCl_3$). *dr* 99.9% (HPLC: τ 13.0 min). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.94 (3H, d, *J* = 6.4, 2-CH_3); 1.46 (3H, d, *J* = 6.9, 2'-CH_3); 2.56-2.62 (1H, m, H-3A); 3.36 (1H, dd, *J* = 15.8, *J* = 8.6, H-3B); 4.23 (1H, q, *J* = 6.9, H-2'); 4.77-4.86 (1H, m, H-2); 6.96-7.00 (1H, m, H-5); 7.11-7.16 (1H, m, H-6); 7.18-7.22 (1H, m, H-4); 7.22-7.42 (5H, m, H Ph); 7.93-7.97 (1H, m, H-7). Found, %: C 81.54; H 7.30; N 5.25. $C_{18}H_{19}NO$. Calculated, %: C 81.48; H 7.22; N 5.28.

Preparation of Amides 3c-f (Diastereoisomeric Mixture). A solution of the (*RS*)-acyl chloride **2b** or **2c** (1 mmol) in toluene (10 ml) was added to a solution of the (*S*)-amine **1a** or **1b** (2 mmol) in toluene (10 ml) at 20°C. The reaction mixture was kept at 20°C temperature for 6 h, washed with 1 N hydrochloric acid (2×3 ml), saturated aqueous NaCl solution (4×3 ml), 5% sodium bicarbonate solution (2×3 ml) and water (2×3 ml), dried over magnesium sulfate and evaporated to dryness in vacuum. Amides **3c-f** were purified by flash chromatography.

***N*-[(2*RS*)-2-(4-Isobutylphenyl)propionyl]-(2*S*)-2-methyl-1,2,3,4-tetrahydroquinoline (3c)**. Yield 0.195 g (58%). Colorless oil. *dr* 0% (*S*,*S*/*R*,*S* 50:50) (HPLC: $\tau_{(S,S)}$ 12.2 min, $\tau_{(R,S)}$ 13.6 min). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.81 (3H, d, *J* = 6.6, $CH_2CH(C\underline{H}_3)_2$ (*S*,*S*)); 0.88 (3H, d, *J* = 6.6, $CH_2CH(C\underline{H}_3)_2$ (*R*,*S*)); 0.91 (1.5H, d, *J* = 6.5, 2-CH_3 (*S*,*S*)); 1.00 (1.5H, d, *J* = 6.7, 2-CH_3 (*R*,*S*)); 1.16 (1H, dddd, *J* = 13.0, *J* = 10.1, *J* = 6.7, *J* = 5.3, H-3A); 1.27 (1.5H, d, *J* = 6.7, 2'-CH_3 (*R*,*S*)); 1.36 (1.5H, d, *J* = 6.9, 2'-CH_3 (*S*,*S*)); 1.70-1.81 (1H, m, $CH_2C\underline{H}Me_2$); 1.86 (0.5H, ddd, *J* = 15.0, *J* = 10.1, *J* = 5.3, H-4A (*S*,*S*)); 2.13 (1H, dddd, *J* = 13.0, *J* = 7.5, *J* = 5.3, *J* = 5.3, H-3B); 2.33 (0.5H, ddd, *J* =15.0, *J* = 5.3, *J* = 5.3, H-4B (*S*,*S*)); 2.34 (1H, d, *J* = 7.0, $C\underline{H}_2CHMe_2$ (*S*,*S*)); 2.42-2.45 (0.5H, m, H-4A (*R*,*S*)); 2.45 (1H, d, *J* = 7.0, $C\underline{H}_2CHMe_2$ (*R*,*S*)); 2.62 (0.5H, ddd, *J* = 15.0, *J* = 5.3, *J* = 5.3, H-4B (*R*,*S*)); 3.70 (0.5H, q, *J* = 6.7, H-2' (*R*,*S*)); 4.24 (0.5H, q, *J* = 6.9, H-2' (*S*,*S*)); 4.63 (0.5H, ddq, *J* = 7.5, *J* = 6.7, *J* = 6.5, H-2 (*S*,*S*)); 4.72 (0.5H, ddq, *J* = 6.7, *J* = 6.7, *J* = 6.5, H-2 (*R*,*S*)); 6.67-6.72 (1H, m, C_6H_4 (*S*,*S*)); 6.85-6.90 (1H, m, C_6H_4 (*S*,*S*)); 6.98-7.02 (0.5H, m, H-5 (*S*,*S*)); 7.03-7.14 (3H, m, H-5 (*R*,*S*) + H-6 (*S*,*S*) + C_6H_4 (*R*,*S*)); 7.16-7.26 (2H, m, H-6 (*R*,*S*) + H-7 + H-8 (*R*,*S*)); 7.28-7.32 (0.5H, m, H-8 (*S*,*S*)). Found, %: C 82.50; H 8.99; N 4.15. $C_{23}H_{29}NO$. Calculated, %: C 82.34; H 8.71; N 4.17.

***N*-[(2*RS*)-2-(4-Isobutylphenyl)propionyl]-(2*S*)-2-methylindoline (3d)**. Yield 0.241 g (75%). Colorless oil. *dr* 10% (*S*,*S*/*R*,*S* 55:45) (HPLC: $\tau_{(R,S)}$ 4.1 min, $\tau_{(S,S)}$ 4.9 min). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.85 (6H, d, *J* = 6.6, $CH_2CH(C\underline{H}_3)_2$); 0.92 (1.65H, d, *J* = 6.3, 2-CH_3 (*S*,*S*)); 1.28 (1.35H, d, *J* = 6.3, 2-CH_3 (*R*,*S*)); 1.42 (1.35H, d, *J* = 6.8, 2'-CH_3 (*R*,*S*)); 1.43 (1.65H, d, *J* = 6.8, 2'-CH_3 (*S*,*S*)); 1.78-1.88 (1H, m, $CH_2C\underline{H}Me_2$); 2.41 (0.9H, d, *J* = 7.0, $C\underline{H}_2CHMe_2$ (*R*,*S*)); 2.43 (1.1H, d, *J* = 7.0, $C\underline{H}_2CHMe_2$ (*S*,*S*)); 2.55-2.61 (1H, m, H-3A); 3.11 (0.45H, dd, *J* = 16.0, *J* = 8.9, H-3B (*R*,*S*)); 3.36 (0.55H, dd, *J* = 15.7, *J* = 8.6, H-3B (*S*,*S*)); 4.03 (0.45H, q, *J* = 6.8, H-2' (*R*,*S*)); 4.18 (0.55H, q, *J* = 6.8, H-2' (*S*,*S*)); 4.55-4.62 (0.45H, m, H-2 (*R*,*S*)); 4.76-4.82 (0.55H, m, H-2 (*S*,*S*)); 6.95-7.00 (1H, m, H-5); 7.07-7.11 (2H, m, H Ar); 7.10-7.15 (1H, m, H-6); 7.21 (1H, dd, *J* = 13.7,

J = 7.7, H-4); 7.25-7.32 (2H, m, H Ar); 7.91-8.00 (1H, m, H-7). Found, %: C 81.91; H 8.54; N 4.07. $C_{22}H_{27}NO$. Calculated, %: C 82.20; H 8.47; N 4.36.

***N*-[(2*RS*)-2-Phenylpropionyl]-(2*S*)-2-methyl-1,2,3,4-tetrahydroquinoline (3e)**. Yield 0.182 g (65%). Colorless oil. *dr* 50% (*S*,*S*/*R*,*S* 75:25) (HPLC: $\tau_{(S,S)}$ 6.2 min, $\tau_{(R,S)}$ 6.5 min). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.92 (2.25H, d, *J* = 6.5, 2-CH_3 (*S*,*S*)); 1.01 (0.75H, d, *J* = 6.5, 2-CH_3 (*R*,*S*)); 1.16 (0.75H, dddd, *J* = 13.1, *J* = 10.0, *J* = 6.7, *J* = 5.1, H-3A (*S*,*S*)); 1.28 (0.75H, d, *J* = 6.9, 2'-CH_3 (*R*,*S*)); 1.27-1.35 (0.25H, m, H-3A (*S*,*S*)); 1.39 (2.25H, d, *J* = 6.9, 2'-CH_3 (*S*,*S*)); 1.88 (0.75H, ddd, *J* = 15.0, *J* = 10.0, *J* = 5.6, H-4A (*S*,*S*)); 2.14 (1H, dddd, *J* = 13.1, *J* = 7.0, *J* = 5.6, *J* = 5.4, H-3A); 2.37 (0.75H, ddd, *J* = 15.0, *J* = 5.4, *J* = 5.1, H-4B (*S*,*S*)); 2.42-2.50 (0.25H, m, H-4B (*R*,*S*)); 2.62 (0.75H, ddd, *J* = 15.0, *J* = 5.8, *J* = 5.7, H-4B (*R*,*S*)); 4.01 (0.25H, q, *J* = 6.9, H-2' (*R*,*S*)); 4.29 (0.75H, q, *J* = 6.9, H-2' (*S*,*S*)); 4.63 (0.75H, ddq, *J* = 7.0, *J* = 6.7, *J* = 6.5, H-2 (*S*,*S*)); 4.73 (0.25H, ddq, *J* = 6.9, *J* = 6.8, *J* = 6.7, H-2 (*R*,*S*)); 6.79-6.84 (2H, m, H Ph); 7.02-7.04 (1H, m, H-5); 7.06-7.10 (3H, m, H Ph); 7.09-7.14 (1H, m, H-6); 7.19-7.26 (1H, m, H-7); 7.29-7.33 (1H, m, H-8). Found, %: C 81.68; H 7.64; N 4.95. $C_{19}H_{21}NO$. Calculated, %: C 81.68; H 7.58; N 5.01.

***N*-[(2*RS*)-2-Phenylpropionyl]-(2*S*)-2-methylindoline (3f)**. Yield 0.167 g (63%). Colorless oil. *dr* 20% (*S*,*S*/*R*,*S* 60:40) (HPLC: $\tau_{(S,S)}$ 13.0 min, $\tau_{(R,S)}$ 13.7 min). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.92 (1.8H, d, *J* = 6.3, 2-CH_3 (*S*,*S*)); 1.28 (1.2H, d, *J* = 6.3, 2-CH_3 (*R*,*S*)); 1.45 (1.2H, d, *J* = 6.8, 2'-CH_3 (*R*,*S*)); 1.46 (1.8H, d, *J* = 6.9, 2'-CH_3 (*S*,*S*)); 2.56-2.62 (1H, m, H-3A); 3.12 (0.4H, dd, *J* = 15.9, *J* = 8.9, H-3B (*R*,*S*)); 3.36 (0.6H, dd, *J* = 15.8, *J* = 8.6, H-3B (*S*,*S*)); 4.08 (0.4H, q, *J* = 6.8, H-2' (*R*,*S*)); 4.23 (0.6H, q, *J* = 6.9, H-2' (*S*,*S*)); 4.55-4.62 (0.4H, m, H-2 (*R*,*S*)); 4.78-4.85 (0.6H, m, H-2 (*S*,*S*)); 6.95-7.00 (1H, m, H-5); 7.10-7.16 (1H, m, H-6); 7.18-7.22 (1H, m, H-4); 7.22-7.42 (5H, m, H Ph); 7.93-7.97 (1H, m, H-7). Found, %: C 81.30; H 7.33; N 4.99. $C_{18}H_{19}NO$. Calculated, %: C 81.48; H 7.22; N 5.28.

Preparation of Amides 4a,b and 5a,b (Diastereoisomeric Mixtures). A solution of (*R,S*)-acyl chloride **2a** or **2b** (1 mmol) in toluene (10 ml) was added to a solution of (*R,S*)-amine **1c** or **1d** (2 mmol) in toluene (10 ml). The reaction mixture was kept at 20°C temperature for 6 h, washed with 1 N hydrochloric acid (2×3 ml), saturated aqueous NaCl solution (4×3 ml), 5% sodium bicarbonate solution (2×3 ml), and water (2×3 ml), dried over magnesium sulfate, and evaporated to dryness in vacuum. Diastereoisomers **4a,b** and **5a,b** were separated by flash chromatography.

(2*RS*)-*N*-(*sec*-Butyl)-*N*-[(2*RS*)-2-(6-methoxynaphthalen-2-yl)propionyl]aniline (4a). Yield 0.289 g (80%). Colorless oil. *major/minor* 60:40 (HPLC: τ_{maj} 4.2 min, $\tau_{min.}$ 4.5 min). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.83 (1.2H, dd, *J* = 7.4, *J* = 7.4, $CH_2C\underline{H}_3$ (*min.*)); 0.93 (1.8H, d, *J* = 6.8, $CHC\underline{H}_3$ (*maj.*)); 0.96 (1.8H, dd, *J* = 7.4, *J* = 7.4, $CH_2C\underline{H}_3$ (*maj.*)); 0.98 (1.2H, d, *J* = 6.8, $CHC\underline{H}_3$ (*min.*)); 1.13-1.30 (1H, m, NCH(Me)C<u>H</u>A (*min.*)); 1.35 (0.6H, dqd, *J* = 13.6, *J* = 7.4, *J* = 6.1, NCH(Me)C<u>H</u>B (*maj.*)); 1.41 (1.2H, d, *J* = 6.9, 2'-Me (*min.*)) and 1.42 (1.8H, d, *J* = 6.9, 2'-Me (*maj.*)); 1.51 (0.4H, dqd, *J* = 13.6, *J* = 7.4, *J* = 6.1, NCH(Me)C<u>H</u>B (*min.*)); 3.55 (1H, q, *J* = 6.9, H-2'); 3.90 (3H, c, OCH_3); 4.75-4.90 (1H, m, NC<u>H</u>(Me)Et); 7.00-7.62 (11H, m, H Ar + H Ph). Found, %: C 79.58; H 7.81; N 3.61. $C_{24}H_{27}NO_2$. Calculated, %: C 79.74; H 7.53; N 3.87.

(2*RS*)-*N*-(*sec*-Butyl)-*N*-[(2*RS*)-2-(4-isobutylphenyl)propionyl]aniline (4b). Yield 0.243 g (72%). Colorless oil. *major/minor* 60:40 (HPLC: $\tau_{min.}$ 4.4 min, $\tau_{maj.}$ 5.1 min). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.80 (1.2H, dd, *J* = 7.4, *J* = 7.4, $CH_2C\underline{H}_3$ (*min.*)); 0.86 (6H, d, *J* = 7.1, $CH_2CH(C\underline{H}_3)_2$); 0.87 (1.8H, d, *J* = 6.8, $CHC\underline{H}_3$ (*maj.*)); 0.95 (1.8H, dd, *J* = 7.0, *J* = 7.0, $CH_2C\underline{H}_3$ (*maj.*)); 0.96 (1.2H, d, *J* = 7.0, $CHC\underline{H}_3$ (*min.*)); 1.18-1.29 (1.4H, m) and 1.40-1.50 (0.6H, m, NCH(Me)C$\underline{H}_2$); 1.23 (1.2H, d, *J* = 6.9, 2'-CH_3 (*min.*)); 1.24 (1.8H, d, *J* = 6.9, 2'-CH_3 (*maj.*)); 1.77-1.87 (1H, m, $CH_2C\underline{H}Me_2$); 2.40 (2H, d, *J* = 7.0, $C\underline{H}_2CHMe_2$); 3.41 (1H, q, *J* = 6.9, H-2'); 4.45-4.58 (1H, m, NC<u>H</u>(Me)Et); 6.80-7.40 (9H, m, H Ar). Found, %: C 81.64; H 9.51; N 3.93. $C_{23}H_{31}NO$. Calculated, %: C 81.85; H 9.26; N 4.15.

(2*RS*)-2-Methyl-*N*-[(2*RS*)-2-(6-methoxynaphthalen-2-yl)propionyl]piperidine (5a). Yield 0.243 g (78%). Colorless oil. *major/minor* 60:40 (HPLC: $\tau_{min.}$ 19.8 min, $\tau_{maj.}$ 20.9 min). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.94 (1.8H, d, *J* = 6.9, 2-CH_3 (*maj.*)); 1.09 (1.2H, d, *J* = 6.9, 2-CH_3 (*min.*)); 1.39 (3H, d, *J* = 6.9, 2'-CH_3); 1.22-1.60 (6H, m, 3,4,5-CH_2); 2.68 (0.6H, ddd, *J* = 13.7, *J* = 12.7, *J* = 3.1, 6-CHA (*maj.*)); 2.86 (0.4H, ddd, *J* = 13.3, *J* = 12.9, *J* = 3.0, 6-CHA (*min.*)); 3.87 (3H, c, OCH_3); 3.96-4.07 (1H, m, 6-CHB); 4.11 (0.6H, q,

J = 6.9, H-2' (*maj.*)); 4.13 (0.4H, q, *J* = 6.9, H-2' (*min.*)); 4.48-4.57 (0.6H, m, H-2 (*maj.*)); 4.57-4.65 (0.4H, m, H-2 (*min.*)); 7.12 (1H, dd, *J* = 8.9, *J* = 2.6, H-7"); 7.23 (1H, d, *J* = 2.7, H-5"); 7.35 (0.6H, dd, *J* = 8.5, *J* = 1.9, H-3" (*maj.*)); 7.36 (0.4H, dd, *J* = 8.5; *J* = 1.9, H-3" (*min.*)); 7.62 (0.6H, d, *J* = 1.7, H-1" (*maj.*)); 7.64 (0.4H, d, *J* = 1.8, H-1" (*min.*)); 7.66-7.73 (2H, m, H-4",8"). Found, %: C 76.92; H 8.30; N 4.25. $C_{20}H_{25}NO_2$. Calculated, %: C 77.14; H 8.09; N 4.50.

***N*-[(2*RS*)-2-(4-Isobutylphenyl)propionyl]-(2*RS*)-2-methylpiperidine (5b)**. Yield 0.187 g (65%). Colorless oil. *major/minor* 65:35 (according to ^{1}H NMR spectroscopy). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.86 (6H, d, *J* = 6.6, $CH_2CH(C\underline{H}_3)_2$); 0.89 (1.95H, d, *J* = 5.2, 2-CH_3 (*maj.*)); 1.07 (1.05H, d, *J* = 5.4, 2-CH_3 (*min.*)); 1.28 (3H, d, *J* = 6.8, 2'-CH_3); 1.20-1.60 (6H, m, 3,4,5-CH_2); 1.78-1.88 (1H, m, $CH_2C\underline{H}Me_2$); 2.42 (2H, d, *J* = 7.1, $C\underline{H}_2CHMe_2$); 2.68 (0.35H, ddd, *J* = 13.2, *J* = 13.2, *J* = 3.0, 6-CHA (*min.*)); 2.75-2.85 (0.65H, m, 6-CHA (*maj.*)); 3.85-4.07 (1H, m, 6-CHB); 3.95 (1H, q, *J* = 6.8, H-2'); 4.35-4.50 (0.35H, m, H-2 (*min.*)); 4.50-4.60 (0.65H, m, H-2 (*maj.*)); 7.03-7.08 (2H, m, H Ar); 7.09-7.16 (2H, m, H Ar). Found, %: C 79.16; H 10.19; N 4.90. $C_{19}H_{29}NO$. Calculated, %: C 79.39; H 10.17; N 4.87.

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